New Methods and Recent Developments of the Stereochemistry of Ephedrine, Pyrrolizidine, Granatane and Tropane Alkoloids

by

G. FODOR D.Sc.

Relationships Between the Structure and Pharmacological Activity of Tropeines

by

K. NÁDOR D.Sc.

Achievements in the Total Synthesis of Natural Stereoids

by

I. V. TORGOV D.Sc.

AKADÉMIAI KIADÓ
PUBLISHING HOUSE
OF THE HUNGARIAN ACADEMY OF SCIENCES

This book contains three monographs in the field of carbon compounds occurring in nature.

G. Fodor presents an account of new methods and recent developments in the stereochemistry of ephedrine, granatoline, pyrrolizidine and tropane alkaloids. Detailed descriptions of stereochemical and synthetic investigations are given with special emphasis on work done by Hungarian chemists, largely by the author himself, and his former or present research teams. Informal discussions of unsolved or incompletely settled problems in this field are a feature of the presentation. Many details previously inaccessible to the English-speaking reader are included.

The part by K. Nádor interestingly completes the previous monograph by a systematic survey of the pharmacological actions of tropeines. Results in this field are fully utilized to point out relations between stereochemical structure and physiological properties, leading to several generalizations based on the author's research published here for the first time in English. A brief introduction to the necessary fundamental physiological con-

RECENT DEVELOPMENTS IN THE CHEMISTRY OF NATURAL CARBON COMPOUNDS

RECENT DEVELOPMENTS IN THE CHEMISTRY OF NATURAL CARBON COMPOUNDS

VOLUME I

AKADÉMIAI KIADÓ
PUBLISHING HOUSE OF THE HUNGARIAN ACADEMY OF SCIENCES
BUDAPEST 1965

NEW METHODS AND RECENT DEVELOPMENTS OF THE STEREOCHEMISTRY OF EPHEDRINE, PYRROLIZIDINE, GRANATANE AND TROPANE ALKALOIDS

by

G. FODOR D.Sc.

Member of the Hungarian Academy of Sciences
Stereochemical Research Laboratory
Hungarian Academy of Sciences

RELATIONSHIPS BETWEEN THE STRUCTURE AND PHARMACOLOGICAL ACTIVITY OF TROPEINES

by

K. NÁDOR D.Sc.

Institute for Experimental Medicine
Hungarian Academy of Sciences

ACHIEVEMENTS IN THE TOTAL SYNTHESIS OF NATURAL STEROIDS

by

I. V. TORGOV D.Sc.

Institute of Organic Natural Compounds
Academy of Sciences of the USSR

AKADÉMIAI KIADÓ

PUBLISHING HOUSE OF THE HUNGARIAN ACADEMY OF SCIENCES

BUDAPEST 1965

In memory of G. Zemplén

PREFACE

The Chemical Department of the Hungarian Academy of Sciences has decided on the publication of a series of monographs to give an account of researches in the field of naturally occurring organic compounds, dealing mainly with the elucidation of the structures of such substances.

Though books and monographs on natural products are abundant in the chemical literature, the individual feature of this series is that it collects for the first time the relevant work of Hungarian chemists which so far has been available only scattered throughout the pages of various journals.

Another object of the series is to give accounts on recent researches on natural carbon compounds carried out in both hemispheres; it is hoped that the English speaking reader will find here material of interest that has been heretofore accessible to him only with difficulty. The Hungarian Academy of Sciences and the Editorial Board want to thank here the foreign contributors to the series, whose monographs are very valuable in realizing this purpose.

G. Fodor

CONTENTS

⁂

K. NÁDOR

RELATIONSHIPS BETWEEN THE STRUCTURE AND PHARMACOLOGICAL ACTIVITY OF TROPEINES

⁂

I. V. TORGOV

ACHIEVEMENTS IN THE TOTAL SYNTHESIS OF NATURAL STEROIDS

CHAPTER VI

G. FODOR

NEW METHODS AND RECENT DEVELOPMENTS OF THE STEREOCHEMISTRY OF EPHEDRINE, PYRROLIZIDINE, GRANATANE AND TROPANE ALKALOIDS

FOREWORD

The present monograph deals with the stereochemical research carried out mostly in the Institute of Organic Chemistry of the University of Szeged, between 1945 and 1957, and in the Stereochemical Laboratory of the Academy of Sciences, Budapest, since 1958. It is natural that this treatise includes also relevant previous publications and recent achievements originating from other scientific institutes as the results of research carried out either in co-operation with our work, or independently.

As an introduction, it seems proper to give a short survey of the fairly strong background of the chemistry of alkaloids in Hungary. In theoretical respect, some interesting results had been achieved by the deceased Frigyes KONEK, associate professor of the University of Budapest, who worked as a pupil of professor EINHORN in Munich on the problem of the constitution of cocaine [20].

From the practical aspect of the chemistry of alkaloids, the work of the pharmacist János KABAY should be mentioned first, who developed the chemical technology of recovering morphine from ripe poppy-straw [40]. In spite of the opinion of Hungarian and foreign researchers and experts, he showed that no opium was necessary for the production of morphine. His revolutionary concepts and the corresponding experimental work formed the basis of establishing later the chemical factory Alkaloida in Büdszentmihály (present name Tiszavasvári). Considerable help has been offered for improving the technological processes of this factory by the research activity carried out since 1950 in the Institute of Organic Chemistry of the University of Debrecen under the leadership of academician Rezső BOGNÁR [8, 9, 10]. This work resulted in the possibility that today the Hungarian pharmaceutical industry manufactures the important by-alkaloids of morphine, such as thebaine, codeine and narceine, as well as a number of derived pharmaceuticals.*

In the field of the synthesis of alkaloids, mention must be made of the industrial researches concerning the syntheses of papaverine, ephedrine and novatropine. This work was carried out in the pharmaceutical factory Chinoin [18, 19], with the participation of Emil WOLF, Zoltán FÖLDI, Sándor HOFMANN and Rezső KŐNIG. At the same time other Hungarian researches concerning alkaloids with steroid skeleton, carried out by ZEMPLÉN and GERECS in the Institute of Organic Chemistry of the Technical University of Budapest, dealt with the constitution of solanine [56].

Valuable pharmacological studies were made between 1932 and 1935 in the Institute of Szeged by professor Béla ISSEKUTZ sen. concerning the spas-

* Cf. Acta Chim. Acad. Sci. Hung., *17*, 463 (1958).

molytic activity and chemical structure of papaverine and other compounds with an *iso*quinoline ring system. In the course of these investigations an exact connection was discovered between spasmolytic and capillary activity [39]. Preparation of similar synthetic 3-methyl *iso*quinoline derivatives of papaverine and tests of their activities were carried out also in the organic and pharmaceutical institutes of the University of Szeged in the years since 1935 till 1948, under the leadership of Victor BRUCKNER [16, 30]. At the same place, a detailed study was also made on the mechanism of the Pictet-Gams' ring closure of *iso*quinolines, both by spectroscopic [33] and chemical methods [15, 25, 44—46]. Intermediary products of this synthesis were the derivatives of 1-phenyl-2-amino-1-propanol [13, 14]. The same research group investigated the synthesis and pharmacological properties of new N-alkyl and aralkyl *nor-pseudo*ephedrines [17, 48, 53].

The mentioned successful researches give a general impression about the scope of investigations on alkaloids in Hungary. It is apparent that theoretical researches of structure, practical syntheses, as well as investigations concerning the relationship between physiological action and chemical structure have their traditions in Hungarian science.

As it is known, the definition of alkaloids is not exact at all; it denotes a very heterogeneous group of nitrogen-containing organic compounds of vegetable origin and of pharmacological action. An extensive research work has been in progress all over the world, among others in the Soviet Union, in the USA, with the purpose of isolating such compounds. The investigation of the active principles containing nitrogen produced by plants results in the daily discovery of new compounds. It is the task of the organic chemist to elucidate the structure of these materials. For the sake of an easy survey of this field, the relevant monographs employ various ways of dividing their material. Among these, the monograph series 'The Alkaloids' edited by MANSKE and HOLMES [47] may be regarded as the most complete and most modern treatise, which grew, within a few years, to seven volumes. This work comprises so far pyrrolidine, Senecio, pyridine, tropane, Strychnos, morphine, synomenine and colchicine alkaloids, Amarylidaceae, acridine, indole, Erythrina, Cinchona and the other quinoline alkaloids, quinazoline alkaloids, lupine, imidazole, Solanum and Veratrum alkaloids, β-phenylethylamine derivatives, Ephedra bases and finally Ipecac alkaloids. Thus, alkaloids of known constitution are discussed with the material being divided into some 20 groups, each listing compounds of common origin and similar structure. The classic alkaloid chemistry of HENRY [37] does the classification more strictly according to the carbon skeleton, and divides the very large material including more than a thousand compounds into the following groups: pyridine, tropane, lupinane, *iso*quinoline, phenanthridine, quinoline, indole, pyrrolidine, pyrrolizidine, quinazoline, and glyoxaline alkaloids, alkaloidic amines, and steroid alkaloids, i.e., 13 groups altogether. A summary of modern alkaloid chemistry was given by H. G. BOIT, assistant professor of the Humboldt University, Berlin, in 1950 [11]. Meanwhile a second volume appeared in 1961. Besides these works, a monograph of 433 pages was recently devoted to morphine alkaloids alone by BENTLEY [5]. Probably these few references are sufficient to demonstrate the scope and development of the chemistry of alkaloids in our days. The greatest part of reported researches deals with the isolation of new alkaloids, with the analytical and synthetic investigation of their constitution and, to a smaller extent, with their physiological

activity. When these monographs are surveyed, it may be surprising that up to 1955 they nearly completely omit the stereochemical formulas which would represent the steric structures of the compounds. It is interesting to note that the stereochemistry of materials containing nitrogen and that of alkaloids with saturated carbon ring system was so long a rather neglected field, whereas at the same time, the actual knowledge of the steric arrangement of homocyclic carbon compounds has been of very great assistance in interpreting reactivity; the concept of equatorial and axial bonds and their energetics has well been established in the chemistry of these latter compounds. In some cases the configuration of the alkaloids has been determined, but in a number of occasions also this problem has remained unsolved. In the past decades the configuration of quinine [51] and of a few other alkaloids was established. Nowadays, chemical literature reports an ever-increasing number of researches elucidating the stereochemical structures of alkaloids which have not been known before. A modern review is presented by A. R. BATTERSBY.* During the past decade several new methods [23, 32, 42b] were developed also in the former institute of the author for the purpose of determining the steric structure, i. e. configuration and conformation. Even these methods, of course, have not been sufficient to solve the problems in all of the above-mentioned 13 groups of alkaloids; however, some stereochemical questions, and through these the fine structures of the compounds have been successfully elucidated in the cases of tropanes, granatanes, pyrrolizidine alkamines and arylpropanolamines. The investigation of the configuration of the nitrogen atom in nicotine, and generally in alkaloids with pyrrolidine skeleton is under way. A pupil of the author, K. KOCZKA extended these studies to include codeine and tetrahydro*iso*quinoline alkaloids. A detailed report about this latter work may, however, be given only at some later date.

The primary purpose of stereochemical research, of establishing the steric configuration of alkaloids, is to obtain complete knowledge concerning the actual structure of the compound. Another aspect is that a controlled stereospecific synthesis, as it may be required in practical drug research, becomes possible only after the discernment of the stereochemistry of the compound. A third point is that the relationship between the stereochemical structure and physiological action can be stated only when the first property of the substance is completely known. These three aspects have governed the research work discussed in the following chapters.

* Tetrahedron, 141—149 (1961).

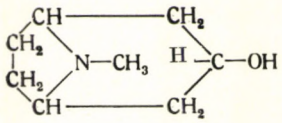
INTRODUCTION

SOME METHODS OF RESEARCH OF THE STERIC STRUCTURE OF ALKALOIDS

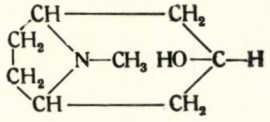
Stereochemical problems concerning organic compounds of known chemical structure can be of two kinds. One of the questions is *statical*, decision is required about the mutual relatiorship of isomers of number *n*, as they result from stereoisomerism, whether they are geometrical or optical ones. Even in the last case they can be either enantiostereomers or diastereomers. When these questions have been decided, the next endeavour is to find out the relative and absolute configurations. Thus, the establishment of the configurative *correlation* belongs to the statical problems. In the course of this work, it is attempted to find a relationship between the molecule of the alkaloid and one or more compounds of already known absolute configuration, by degrading the substance in question systematically, or by syntheses and other reactions, which leave the asymmetric carbon atom, or in the case of geometrical isomerism the double bonded carbon atom, unaffected. The other research problem of steric structure is of *dynamic* character. In this case the physical and chemical properties of two compounds, (e.g. those of alkaloids) having two or more flexible moieties of already known configuration are compared, in dependence on the steric structure. In this way, primarily the influence of the stereochemical structure on chemical reactivity is determined. The classic definition of alkaloids as "nitrogen-containing carbon compounds of base character and of marked physiological action" comprises also the idea of *pronounced physiological action*. It is apparent that this represents a dynamic stereochemical problem. Consequently, the interest of the chemist is focussed not only on the chemical reactivity exerted by a given alkaloid or by its various stereoisomeric modifications; his research must, to a certain extent, take into consideration also the action of these materials on the asymmetric receptors, on an asymmetric molecule of the living cell, or tissue. The organic chemist cannot undertake to do biochemical and pharmacodynamical research; thus, for the sake of successful work, co-operation with the scientists of these fields is absolutely necessary.

To decide between the cases and types of stereoisomerism, classical methods of stereochemistry, i.e. its physico-chemical procedures are employed in many cases. If it is known whether the isomerism is a geometrical or optical one, or if it is about a single modification of an asymmetric or mesoid system, the next task is the determination of the configuration. In the fields to be discussed in detail, the cases of geometrical and optical isomerism are about equally frequent; it is interesting that in several cases an overlapping is found between these two types. E.g. both tropine and *pseudo*tropine are pseudo-asymmetric molecules; they are optical isomers, but at the same time also geometrically isomeric with each other, if, e.g. the position of the hydroxyl

group — which is characteristic of the steric structure — is regarded in relation to any other point of the molecule (Fig. 1). As regards the chemistry of ephedrine, nature produces two diastereoisomeric (epimeric) modifications



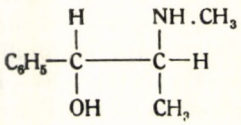
tropine



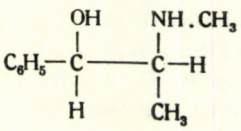
*pseudo*tropine

Fig. 1

(Fig. 2); thus, after having ascertained the steric structures of the compounds, the next problem is the determination of their relative and absolute configurations. In most cases, however, the main problem is the determination of the positions of two or more functional groups in relation to each other



(—)-ephedrine



(+)-*pseudo*ephedrine

Fig. 2

within the molecule of one and the same alkaloid. In theory, it appears very simple to solve this problem by physico-chemical methods. X-ray and electron diffraction methods developed nowadays to a high degree of perfection, permit the exact determination of the steric arrangement of alkaloids in crystallized form or in the vapour phase. However, the experiment must be followed by a vast amount of calculations, and considerable intuition and perseverance are necessary to obtain an absolutely exact evaluation of the diagrams, which may require the work of one or two years. In the case of alternative steric structures, naturally also other physical methods of measurement can give useful and essential clues; however, the stating of the alternatives remains the task of the organic chemist. The determination of the Raman and infrared spectra and that of the dipole moments supply all useful constants to decide about the relative steric position of the atomic groups, and to point out the real one of two or more possible alternative structures.

Organic preparative chemical methods in their classical form discovered the relative positions of two neighbouring groups by an intramolecular *ring closure* reaction, and the failure of this method was interpreted as an evidence that the groups in question were comparatively far from each other. Later researches succeeded in increasing the number of methods. The so-called method of lactone salt formation [42b] can extensively be used in the field of alkaloid chemistry, and it will be discussed later. The use of this method results in the fact that when the compound contains functional groups with nitrogen and oxygen, primary, secondary and tertiary amine molecules can be equally

well investigated, in the case of both 2-amino- or 3-amino-alcohols, and independently of the substituents of the nitrogen atom. In this way, the steric structure of the amine can be determined (Fig. 3). Namely, if a bridge is formed by a condensation reaction with ethyl iodo-acetate or bromo-acetate between the nitrogen-containing and oxygen-containing functional groups of the amine

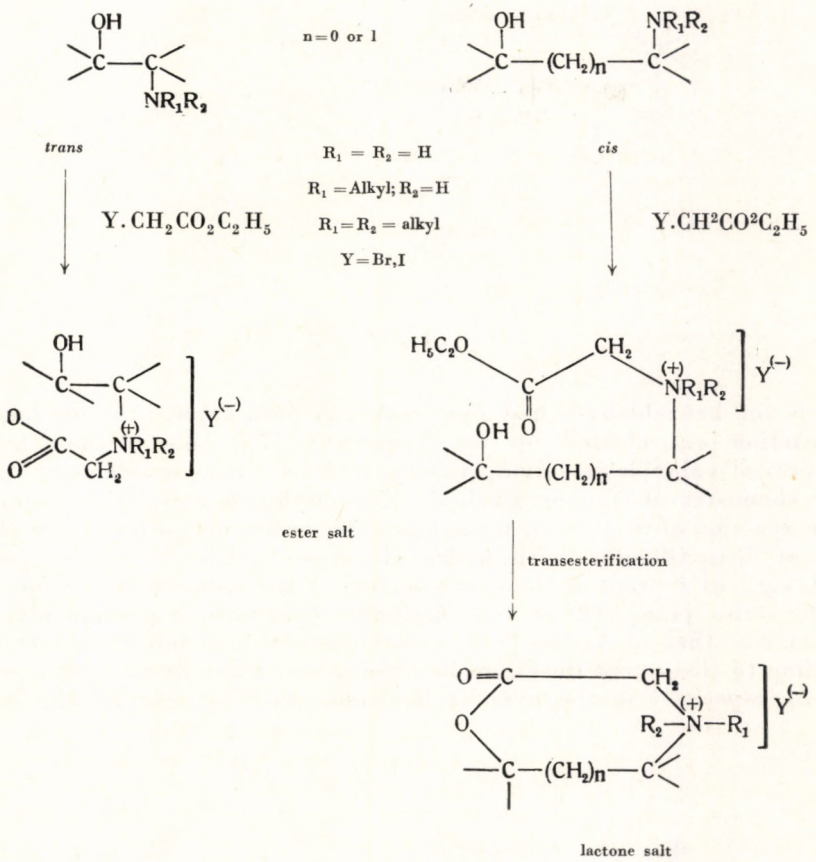


Fig. 3

(which groups are always present in these alkaloids), the occurrence of ring closure is a positive and unequivocal proof for the steric neighbourhood of the groups in question. Reversely, if two molecules, both having functional groups containing hydroxyl and nitrogen differ only as to the steric position of one single group, a positive reaction of lactone salt formation in one case, and the negative result in the other, i.e. the formation of an ester salt instead of a lactone salt, is an unambiguous evidence in deciding the problem of geometrical *(cis – trans)* isomerism, or epimerism in this pair of compounds.

Besides this novel reaction, also some new variations of the method of permanent ring formation are employed to form a bridge between two neighbouring

groups. Adopting the method of GOODSON and CHRISTOPHER [35], HARDEGGER and OTT [36] bridge over the distance between the nitrogen and $C_{(3)}$ oxygen atom by allowing the compound to react with *p*-nitrobenzaldehyde, which results in the formation of (4H)-meta-oxazine derivatives (Fig. 4). It is to be noted that the formation of an 1,3-oxazolidine ring between *cis* 1,2-amino

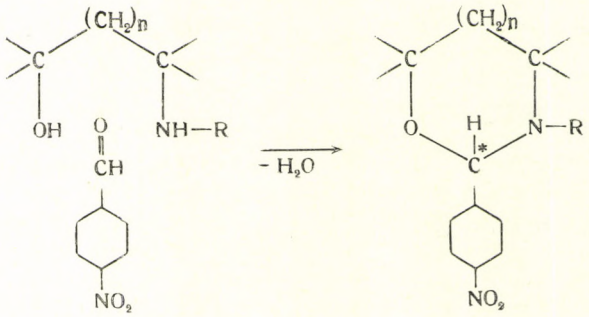


Fig. 4

alcohols and benzaldehyde had also previously been known; the mechanism of the reaction was cleared up by BERGMANN [7]. This method has also been proved valuable in solving various stereochemical problems in the field of the chemistry of tropane alkaloids. This method is again a variation of the classic reaction of ring acetal formation. The cyclic acetal formed in the presence of benzaldehyde with hydroxyl-oxygen atoms in *cis* position was useful, e.g., as a proof of the configuration of the epimeric ecgoninols in the tropane series [42b]. Other new methods of forming a permanently stable ring are, e.g., that of ADAMS [1, 3] as well as of HERZIG and EHRENSTEIN [38]; according to these procedures, cyclic sulphites of 1,2-diols have been prepared (Fig. 5), especially in the pyrrolizidine and steroid series [2]. This reaction

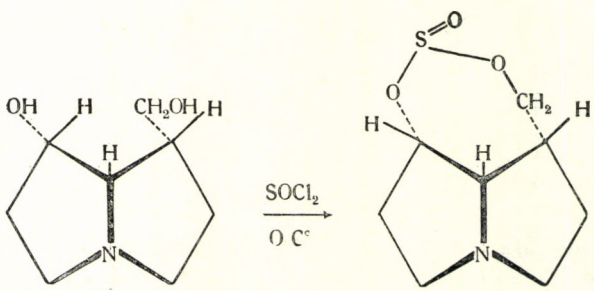


Fig. 5

could be generalized to include sesquiterpenes [43]. KOCZKA [31b, 42a] prepared 1,3-oxazolid-2-one- imide derivatives from *cis* 2-aminoalcohols with cyanogen bromide (Fig. 6).

Besides these methods of permanently stable ring closure, also reactions involving *transient ring formation* between two neighbouring groups

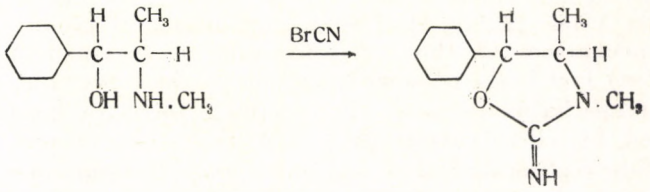


Fig. 6

have been developed. This process is principally based on the recognition of the stereospecifity of acyl migration [22] between the nitrogen and the oxygen atom. In addition to N $\rightleftharpoons$ O acyl migrations [4, 6, 12], such processes are also known between nitrogen and sulphur [55], as well as between two oxygen atoms [52]. If the process is intramolecular, and if the configuration is retained, the occurrence of the reaction indicates the *cis* position of the functional groups in question, and its failure is evidence for their being apart, i.e., in *trans* position. This reaction, which has been known for 70 years, was only lately employed as a means of determining the configuration [24, 27, 28, 29]. The reaction mechanism of acyl migration between oxygen atoms had been elucidated by German authors [52], and the formation of an intermediate of the orthodiester type was assumed [49] long ago. As regards the reversible N $\rightleftharpoons$ O acyl migration, there are two closely related hypotheses, one originating from WELSH [54], PHILLIPS and BALTZLY [50], and the other was proposed by Hungarian authors [22b, 23, 26]. Both representations agree in assuming intermediates with orthoester-amide ring system (Fig. 7); however,

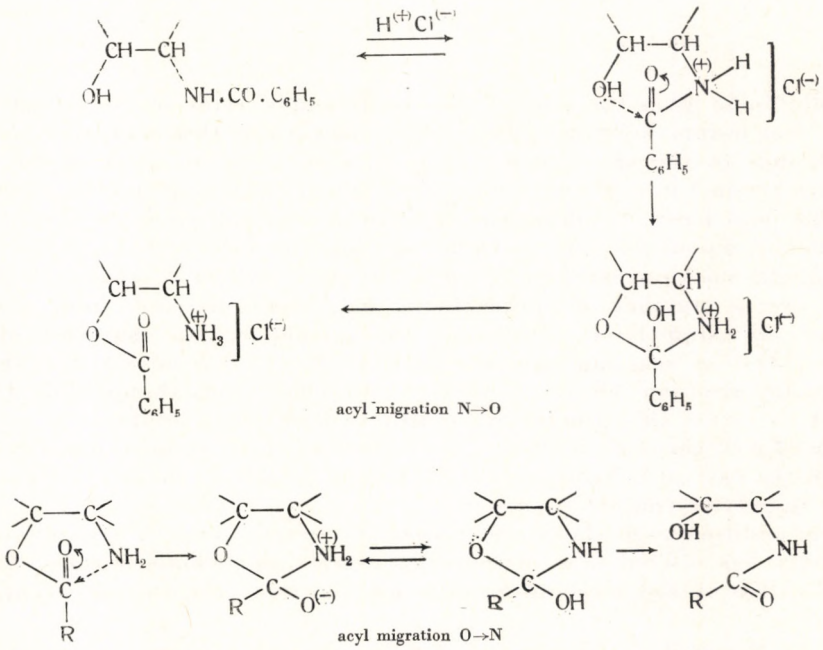


Fig. 7

these may be formed solely in the case when the two functional groups are near to each other [22b, 26]. Positive experimental proof for the intramolecular mechanism of the reaction could be obtained in two different fields. The first fact is the peculiar behaviour of the *trans*- and *cis*-2-benzoxycyclohexylamine bases. Namely, these bases, which are insoluble in water, are dissolved by excess alkali [26], and treatment of the alkaline solution with S-benzyl*iso*thiuronium chloride gives *iso*thiuronium salts of the orthoacids with the exact stoichiometric composition [23], which decompose then to yield N-benzoylaminocyclohexanol and benzylmercaptan. The other experimental evidence is that (±) *threo*-3,4-dimethyl-5-phenyl-

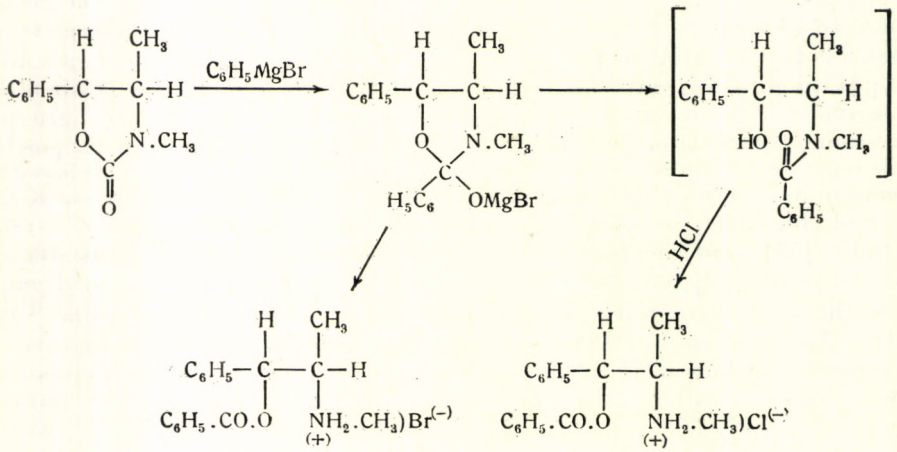


Fig. 8

oxazolid-2-one gives the salt of the ortho-amide ester on treatment with phenylmagnesium bromide [42b]. The structure of this compound exactly corresponds to the one which had previously been assumed as the intermediary product in acyl migration [22b]. When this compound is acted upon by acids and bases, it shows the same behaviour and gives the same O-acyl or N-acyl compounds, resp., as expected from the intermediate in the N⇄O acyl migration process (Fig. 8). Besides these synthetic chemical proofs, there are a number of other facts, e.g. those derived from reaction kinetics, to support the view of the intramolecular character of this process [34]*. A reaction closely related to N→O acyl migration is the stereospecific reaction of *cis*- and *trans*-2-ureido- and thioureido alcohols caused by acids; this process gives also two different products as a consequence of a distinct mechanism. The reaction has been so far studied in detail only in the case of ephedrine [42a, 31], thus it will be described more fully in the respective chapter (p. 45).

In addition to methods based upon cyclization, modern dynamic stereochemistry has offered new concepts in ascertaining configurations. So, reconsideration of the mechanism of some reactions clarifies the configura-

* Cf. Martin, R. R., Parcell, A., J. Am. Chem. Soc. *83*, 4835 (1961) and Porter, G. R., Rydon, H. N. Schofield, K., J. Am. Chem. Soc. *1960*, 2686.

tions which enable the reaction in question to occur at all, e.g., epoxide ring opening exclusively by a *trans*-placed hydroxyl group, as it occurs with scopine. Furthermore, the knowledge of the steric course of certain reactions, e.g. CURTIUS and HOFMANN degradations, (in terms of 1,2-shifts taking place always with the retention of the configuration within the migrating group, allowed also to ascribe definite configurations to the asymmetric carbon atom in tropic acid as well as to $C_{(2)}$ in the epimeric 2-amino-3β-tropanol arising from epimeric cocaines.

All that means a wide extension of the limits of the classic correlation methods which were strongly restricted to reactions involving no asymmetric centre.

REFERENCES

1. ADAMS, R., SHAFER, P. R., and BRAUN, B. H.: The Structure of Monocrotaline. XV. J. Am. Chem. Soc. *74*, 5612 (1952).
2. ADAMS, R., and VAN DUUREN, B. L.: Stereochemistry of the Pyrrolizidine Bases, J. Am. Chem. Soc. *76*, 6379 (1954).
3. ADAMS, R., and VAN DUUREN, B. L.: Riddeline, the Alkaloid from *Senecio riddellii*. II. The Structure of Riddellic Acid and the Total Structure of Riddeline, J. Am. Chem. Soc. *75*, 4638 (1953).
4. AUWERS, K.: Über molekulare Umlagerungen acylierter Amidooxyverbindungen, Liebig's Ann. Chem. *332*, 159 (1904).
5. BENTLEY, K. V.: The Chemistry of the Morphine Alkaloids, Oxford Univ. Press, London 1954, 1st ed.

6a BERGMANN, E., BRAND, E., and DREYER, F.: Synthese von α,β-Diglyceriden und unsymmetrischen Triglyceriden, Ber. dtsch. chem. Ges. *54*, 936 (1921).

b BERGMANN, E., ULPST, R., and CAMACHO, F.: Vermischte Notizen über die Aldehydverbindungen von Oxyaminen und über partielle Acylierung dieser Amine, Ber. dtsch. chem. Ges. *55*, 2796 (1922).

7. BERGMANN, E. D., GIL-AV, E., and PINCHAS, S.: Intramolecular Hydrogen Bonds in 2-Amino-alkanols and N-Alkylidene-2-aminoalcohols, J. Am. Chem. Soc. *75*, 68 (1953).
8. BOGNÁR, R.: Mákalkaloidok előállítása és kémiai átalakítása (The production and chemical conversion of poppy alkaloids.) Publications of the Chemical Dept. of the Hungarian Academy of Sciences *5*, 57 (1954).
9. BOGNÁR R.: Darstellung und einige Verwandlungen der Mohnalkaloide. Inaugural lecture at the Bulgarian Acad. of Sci., Sofia, March 23 (1953).
10. BOGNÁR, R., and SZABÓ, S.: A tebain hidrogénezéséről (Hydrogenation of thebaine). Magy. Kém. Foly. *59*, 321 (1953).
11. BOIT, H. G.: Fortschritte der Alkaloidchemie seit 1933, Akademie-Verlag, Berlin 1950.
12. BÖTTCHER, W.: Über eine Umlagerung vermittelst der Anhydroverbindung, Ber. dtsch. chem. Ges. *16*, 629 (1883).
13. BRUCKNER, V.: Über die Verwendung der Pseudo-nitrosite propenylhaltiger Phenoläther zur Synthese von α-arylierten β-Hydroxylamino- und β-Amino-propanolen. Neue Beiträge zur Kenntnis der Acylwanderungen, Liebig's Ann. Chem. *518*, 226 (1953).
14. BRUCKNER, V., and FODOR, G.: Über eine neue Synthese des α-3,4-Dioxy-phenyl-β-aminopropanols, Ber. dtsch. chem. Ges. *74*, 466 (1943).
15. BRUCKNER, V., FODOR, G., KOVÁCS, J., and KISS, J.: Synthetic and Degradative Studies in the *Iso*quinoline Series. III., J. Am. Chem. Soc. *70*, 2697 (1948); cf. BRUCKNER, V., KOVÁCS, J., and KOVÁCS, K.: Konstitutionsermittlung einiger synthetischer Isochinoline, Beitrag zur Kenntnis des Isochinolinringschlusses, Ber. dtsch. chem. Ges. *77*, 610 (1944); BRUCKNER, V., KOVÁCS, J., and NAGY, H.: Konstitutionsermittlung einiger synthetischer Isochinoline, Beitrag zur Kenntnis des Isochinolinringschlusses. II. Mitteilung, Acta Chim. Acad. Sci. Hung. *1*, 10 (1947).
16. BRUCKNER, V., FODOR, G., KISS, J., and KOVÁCS, J.: Synthesis of 6,7-Diethoxy-3-methyl-*iso*quinolines, J. Chem. Soc. *1948*, 885.
17. BRUCKNER, V. and KRÁMLI, A.: Über eine neue Synthese von Ephedrinabkömmlingen, Arch. Pharmaz. *273*, 372 (1935).

18. Chinoin, Pharmaceutical and Chemical Factory — WOLF, E.: Herstellung von Abkömmlingen des Benzylisochinolins, German Pat. 574, 676, and French Pat. 719, 638.
19. Chinoin Pharmaceutical and Chemical Factory — WOLF, E.: Darstellung eines Tetraäthoxybenzylisochinolins, Swiss Pat. 157, 186.
20. EINHORN, A., and KONEK DE NORWALL, F.: Über die Amide der Ecgonine, Ber. dtsch. chem. Ges. *26*, 962 (1893).
21. FODOR, G.: Synthese der Abkömmlinge des Isochinolins, Wiener Chem. Ztg. *45*, 241 (1942). A detailed survey of the field up to 1942. For additional publications cf. Nos. 16 and 30.
22a FODOR, G.: The Stereospecifity of Acyl Migration of Diastereomeric Aminoalcohols. Lecture presented at the public session of the Institute of Organic Chemistry of the University of Szeged, May 10, 1947.
b FODOR, G.: The Use of Acyl Migration in Separating Diastereoisomers, Budapest, Lecture held in the Chemical Division of the Free Trade-Union of Engineers and Technicians, June 17, 1948.
c FODOR, G., and KISS, J.: Separation of Diastereoisomeric Aminoalcohols, Nature *163*, 287 (1949).
23. FODOR, G.: The Steric Structure of Alicyclic Aminoalcohols and the Mechanism of the O → N Acyl Migration. Lecture held at the 1st Congress of the Hungarian Chemical Society, November 20, 1949.
24. FODOR, G., BRUCKNER, V., KISS, J., and KOVÁCS, J.: Use of Acyl Migration in Separating Diastereoisomeric Aminoalcohols, J. Org. Chem. *14*, 337 (1949).
25. FODOR, G., BRUCKNER, V., KISS, J., and KOVÁCS, J.: Synthetic and Degradative Studies in the *Iso*quinoline Series. IV. J. Am. Chem. Soc. *71*, 3694 (1949); cf. ELDERFIELD, R. C.: Heterocyclic Compounds, Vol. 4, John Wiley and Sons Inc., New York 1952, p. 369, 432, 435; cf. ADAMS, R.: Organic Reactions, Vol. 4, John Wiley and Sons Inc., New York 1948, pp. 77, 80—81.
26. FODOR, G., and KISS, J.: Acyl Migration in Diastereoisomeric 2-Aminocyclohexyl Benzoates, J. Am. Chem. Soc. *72*, 3495 (1950).
27. FODOR, G., and KISS, J.: Configuration of Alicyclic Aminoalcohols, Nature *164*, 917 (1949); cf.: Configuration of Diastereoisomeric 2-Amino-cyclohexanols and a Suggested Mechanism for Acyl Migration N → O, Acta Chim. Acad. Sci. Hung. *1*, 131 (1951).
28. FODOR, G., KISS, J., and SALLAY, I.: Configurational Correlation of Chloramphenicol and of *nor-pseudo*-Ephedrine, Nature *167*, 690 (1951).
29. FODOR, G., KISS, J., and SALLAY, I.: Configurational Correlation of Chloramphenicol with *pseudo-nor*-Ephedrine, J. Chem. Soc. *1951*, 1858.
30. FODOR, G., KISS, J., and SZEKERKE, M.: Attempts to find New Spasmolytics. VIII. The Synthesis of 6 : 7-Diethoxy-3-phenyl-*iso*quinolines, J. Chem. Soc. *1950*; cf. ELDERFIELD, R. C.: Heterocyclic Compounds, Vol. 4, John Wiley and Sons Inc., New York 1952, p. 367.
31a FODOR, G., and KOCZKA, K.: A Stereospecific Reaction of Diastereoisomeric Ureido-Alcohols, Research *4*, 381 (1951).
b The Stereochemical Course of the Conversion of 2-Ureido-Alcohols into Oxazolidones, J. Chem. Soc. *1952*, 850.
32. FODOR, G. and ÖTVÖS, L.: The Conformation of D-Glucosamine, Acta Chim. Acad. Sci. Hung. *5*, 205 (1954).
33. FODOR, G., and VARGA, É.: Az izokinolin gyűrű záródásának mechanizmusáról (The mechanism of *iso*quinoline ring closure), Magy. Kém. Foly. *44*, 65 (1938); cf. HOUBEN—WEYL: Die Methoden der Organischen Chemie, Vol. 4, Verlag Georg Thieme, Leipzig, 3. Aufl., p. 699.
34. FODOR-VARGA, É., FODOR, G. and FURKA, Á.: Kinetic Contribution to the Knowledge of Carbon Rings, Ružička-Festheft d. Croatica Chem. Acta, *29*, 303 (1957).
35. GOODSON, L. H., and CHRISTOPHER, H.: Diphenylethylamines. I. The Preparation of Tertiary Amines by the Grignard Reaction, J. Am. Chem. Soc. *72*, 358 (1950).
36. HARDEGGER, E., and OTT, H.: Beweis der Konfiguration des Pseudotropins, bzw. des Tropins, Helv. Chim. Acta *36*, 1186 (1953).
37. HENRY, T. A.: The Plant Alkaloids. Churchill, London (1949).
38. HERZIG, P. TH., and EHRENSTEIN, M.: Investigations on Steroids. XVIII. Chlorides and Cyclic Sulfites in the Series of 3β,5,19-Trihydroxyaetiocholanic Acid. A Case of Asymmetric Sulphur, J. Org. Chem. *17*, 724 (1952).
39. ISSEKUTZ, B., Sen., LEINZINGER, M., and DIRNER, Z.: Über die Wirkung der synthetischen Papaverinderivate, Arch. exp. Pathol. Pharmakol. *164*, 158 (1932).
40. KABAY, J.: Hungarian Pat. 109, 788; Brit. Pat. 406, 107; German Pat. 524, 964; U.S. Pat. 2,009,181

41a KÓBOR, J.: Lecture held at the Organic Chemical Congress in Debrecen, September 27, 1953; cf. KISS, J. and KÓBOR, J.: Adatok a tetralinváz sztereokémiájához (A contribution to the stereochemistry of the tetraline skeleton), Publications of the Industrial Chemical Research Institutes, (Hungary) *4*, 277 (1954).

b KISS, J., and KÓBOR, J.: Zur Kenntnis der Stereochemie des Tetralinringes, Acta Chim. Acad. Sci. Hung. *5*, 365 (1955).

42a KOCZKA, K.: Az aminoalkoholok sztereospecifikus reakciói. Újabb eredmények a tercier nitrogénatom térkémiájában (Stereospecific reactions of aminoalcohols. recent developments in the stereochemistry of the tertiary nitrogen atom). Thesis for candidature, Szeged, 1955; KOCZKA, K. and FODOR, G.: The Stereochemical Course of the Conversion of 2-Ureido Alcohols into Oxazolidones. II. Acta Chim. Acad. Sci. Hung. *13*, 89 (1958)

b FODOR, G.: Lecture held at the winter meeting of the Swiss Chemical Society, Zurich, February 28, 1954; cf. FODOR, G.: Neuere Ergebnisse auf dem Gebiet der Stereochemie der Tropanalkaloide, Chimia *8*, 179 (1954); KOCZKA, K. and FODOR, G.: Synthetic Confirmation of the Mechanism of Acyl Migration N$\rightleftarrows$O, Acta Chim. Acad. Sci. Hung. *13*, 83 (1958).

43. KOVÁCS, Ö., HEROUT, V., HORÁK, M., and ŠORM, F.: O terpenech. LXVII. Hidrogenacni produkty santoninu a alantolaktonu. Chemicke Listy, *21*, 225 (1956).

44. KRABBE, W.: Synthese von Isochinolin-Derivativen, Ber. dtsch. chem. Ges. *69*, 1569 (1936); KRABBE, W., BÖHLK, H. H., and SCHMIDT, K. H.: Synthese von Isochinolin-Derivaten (II. Mitteil.), Ber. dtsch. chem. Ges. *71*, 64 (1938).

45. KRABBE, W., POLZIN, E., and CULEMEYER, K.: Über die Darstellung einiger N-Acyl-vinylamine aus N-Acylaminoalkoholen (III. Mitteil. Über Synthese von Isochinolin-Derivaten), Ber. dtsch. chem. Ges. *73*, 652 (1940).

46. KRABBE, W., and SCHMIDT, K. H.: Über Vinylamine, Ber. dtsch. chem. Ges. *72*, 381 (1939).

47. MANSKE, R. F. H., and HOLMES, H. L.: The Alkaloids, Vol. 1—7. Academic Press Inc., New York, 1951—1960.

48. NEMES, G.: Vizsgálatok az oxi-aminoefedrin származékok szintézise köréből (Investigations relating to the synthesis of hydroxyaminoephedrine derivatives). Ph. D. thesis, Szeged, 1937.

49. PACSU, E.: Carbohydrate Orthoesters, in Vol. 1 of Advances in Carbohydrate Chemistry, Academic Press Inc., New York, 1945, pp. 78—124.

50. PHILLIPS, A. P., and BALTZLY, R.: Rearrangements between Primary Ethanolamides of Carboxylic Acids and the Corresponding Aminoethylesters, J. Am. Chem. Soc. *69*, 200 (1947).

51. PRELOG, V., and HÄFLIGER, O.: Über China-Alkaloide, 9. Mitteil. Über den Einfluss der Konfiguration auf die Basizität und über die relative Konfiguration an den Kohlenstoffatomen 8. und 9. Helv. Chim. Acta *33*, 202 (1950).

52. VARGHA, L.: Zur Kenntnis der Acylwanderungen in der Zuckergruppe, Ber. dtsch. chem. Ges. *67*, 1223 (1934); cf. OHLE, H.: Die Chemie der Monosaccharide und der Glykose, Berlin 1931, p. 92.

53. VAS, I.: Új efedrin származékok szintézise (Synthesis of new ephedrine derivatives). Ph. D. thesis, Szeged, 1937.

54. WELSH, L. H.: Mechanism and Stereochemical Course of Acyl Migrations in Derivatives of Ephedrine and ψ-Ephedrine, J. Am. Chem. Soc. *71*, 3500 (1949).

55. WIELAND, TH.: Peptidsynthesen. II. 9. Mitteil., Angew. Chem. *66*, 507 (1954).

56. ZEMPLÉN, G., and GERECS, Á.: Beiträge zur Konstitution des Solanins, Ber. dtsch. chem. Ges. *61*, 2294 (1928).

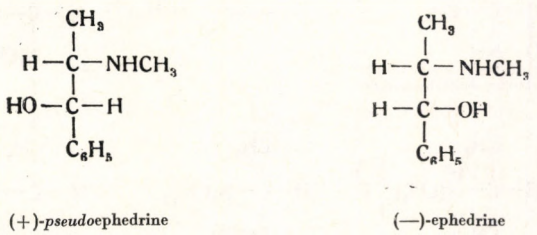
CHAPTER I

STEREOCHEMISTRY OF EPHEDRINE ALKALOIDS

(−)-Ephedrine and (+)ψ-ephedrine, the active principles of the Chinese drug *Ma Huang*, are classed among the alkaloids which have been known for a very long time, about five thousand years. It was recorded as early as in 1596 that an extract of this plant stimulated the blood circulation, and had diaphoretic, antipyretic, as well as cough-relieving actions. The drug was also employed as a medicine in other parts of the world. The active principle was isolated in 1885 by the Japanese researcher G. YAMANASHI in impure, and in 1887 by NAGAI [33] in pure state. The name ephedrine was given by this latter authorfor the substance occurs in *Ephedra vulgaris*. Details of determining the structure are described in the relating chapter written by L. RETI[36] in the monograph of MANSKE and HOLMES., mentioned in the Foreword (p 16).

CONFIGURATION OF EPHEDRINES

(+)-ψ-Ephedrine and (−)-ephedrine are not mirror-image isomers of each other, but they represent the two diastereoisomeric modifications of 2-methylamino-1-phenylpropan-1-ol (Fig. 9). The difference between their con-



(+)-*pseudo*ephedrine (−)-ephedrine

Fig. 9

figurations is clearly shown by the following two sequences of reactions carried out by FREUDENBERG et al. [23, 24]. The hydroxyl group of (+)-ψ-ephedrine and (−)-ephedrine can be removed by halogenation followed by reductive dehalogenation. The pair of 2-methylamino-1-phenylpropanes obtained in this way could be identified through the trimethylammonium compounds (Fig. 10). It follows from this reaction that (+)-ephedrine and (−)-ephedrine differ from each other only in the steric position of the $C_{(1)}$ hydroxyl group. The configuration of the $C_{(2)}$ carbon atom of both compounds was demonstrated by establishing the following relationship: L-(+)-alanine dimethylamide was

converted into the corresponding dimethylaminopropionic acid dimethylamide, and this compound was reacted with phenylmagnesium bromide to give α-dimethylamino-propiophenone. The catalytic reduction of the optically active ketone led to a mixture of (+)-N-methyl-ψ-ephedrine and (—)-N-methyl-

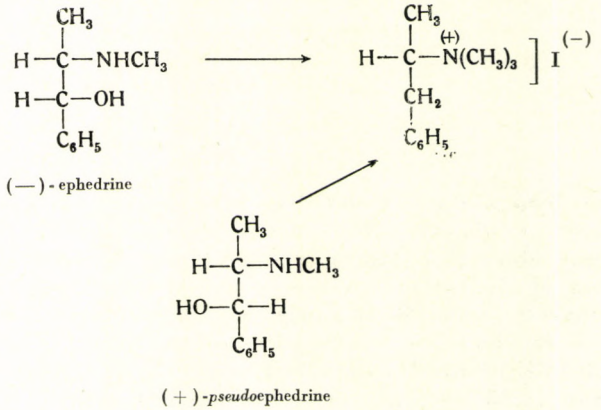


Fig. 10

ephedrine (Fig. 11). Elimination of the hydroxyl group in both compounds by the above-mentioned method, and subsequent quaternization on the dimethylamino group by methyl iodide gave the same quaternary salt of β-phenyl-*iso*-propylamine as the one prepared similarly from (—)-ephedrine and

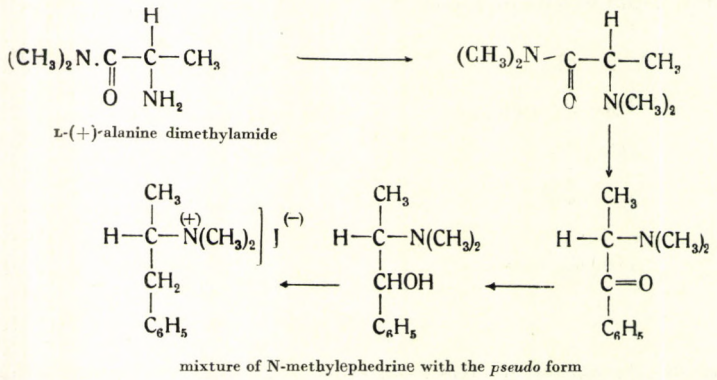


Fig. 11

(+)-ψ-ephedrine. Consequently, the absolute configuration of the carbon atom bearing the nitrogen in ψ-ephedrine and ephedrine was unequivocally shown to be identical with the configuration of L-(+)-alanine. The correlation between L-(+)-alanine and L-(+)-glyceraldehyde had been esta-

blished earlier by converting D-(+)-glucosamine into L-(+)-alanine [49]. Thus, the small capital roman letters D and L are used in the same meaning, and designate the same configuration in the groups of amino acids, sugars, as well as alkaloids [29]. The determination of the absolute configuration of the carbon atom bearing the hydroxyl in ephedrine was achieved in the following way [24]. The dimethylamide of D-(—)-mandelic acid was treated with methylmagnesium bromide to give rise to optically active phenylacetyl carbinol. Stereospecific reductive condensation by means of methylamine produced (—)-ephedrine (Fig. 12). Since MISLOW [32] established the exact configura-

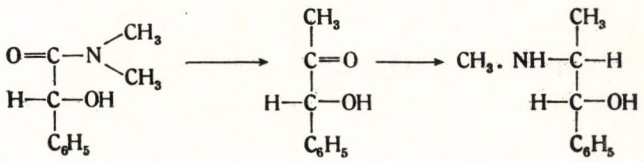


Fig. 12

tive correlation between D-(—)-mandelic acid and D-(—)-lactic acid, the absolute configuration of both carbon atoms of (—)-ephedrine became known. The absolute configuration of natural (+)-ψ-ephedrine can now logically be deduced from this result, since the only difference between these two compounds is in the position of the $C_{(1)}$ hydroxyl group. From experiments on the influence of substituents on the optical rotatory values of ephedrine and ψ-ephedrine, LEITHE [31] concluded identical configurations, shown in Fig. 13, to this pair of

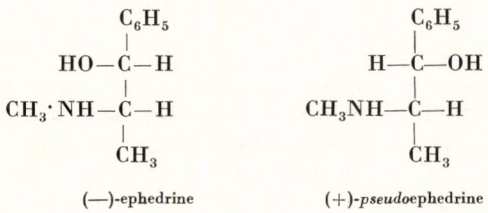


Fig. 13

epimers. As a consequence of the discussed results, the absolute configuration of both carbon atoms of natural ephedrine is expressed by the name D-(—)-*erythro*-1-phenyl-2-methylamino-propane-1-ol, whereas (+)-ψ-ephedrine should be considered as L-(+)-*threo*-1-phenyl-2-methylaminopropane-1-ol. This given designation, derived from the absolute configuration, as well as the molecular configuration obtained by planar projection according to Fischer's convention [25], are to be regarded as unambiguously determined facts. The doubt is expressed in the literature, originally put forward by JAROWSKI and HARTUNG [28], that the configuration of the β-carbon atom, i.e., that of $C_{(2)}$, has not been cleared up. Unfortunately, this point of view

is to be found also in the monograph of MANSKE and HOLMES [36]. According to WELSH [45], this state of affairs is due to a complete misinterpretation of clearly demonstrated experimental facts. It appears more probable to us that the explanation is in the arbitrary choice of the points of reference when describing the configuration of molecules with more than one asymmetric centres. Namely, the molecule of ephedrine can be regarded as a derivative of alanine, as well as an α-phenylethanol derivative; in the first case the molecule will be classed into the L-*erythro* series, and in the second into the D-*erythro* series. Just this fact gives great importance to the use of the CAHN—INGOLD—PRELOG convention* for describing the absolute configuration of compounds of this

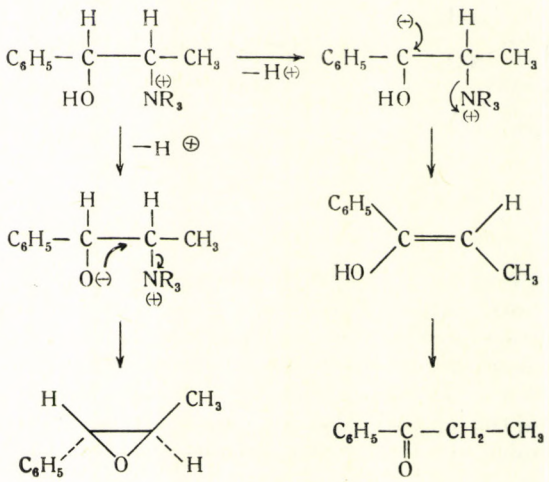


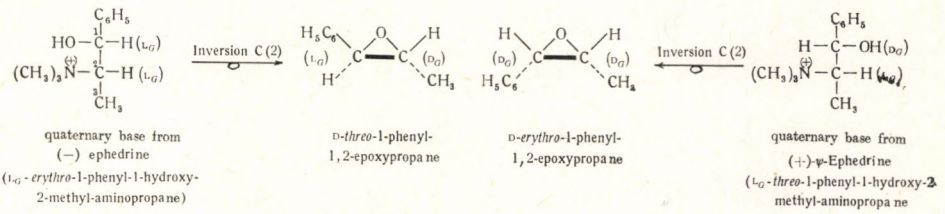
Fig. 14

kind. If the asymmetric centres in natural ephedrine are written in the order as required by this principle, the alkaloid will have the configuration of (—)-1*R* : 2*S* 1-phenyl-2-methylamino-1-hydroxy-propane, and (+)-*pseudo*ephedrine will be represented as the (+)1*S* : 2*S* modification of the same.

The stereochemistry of ephedrine and ψ-ephedrine has been discussed in a comprehensive and valuable study by WITKOP [48]. The Hofmann degradation of the quaternary ammonium hydroxide derived from ephedrine was carried out as early as in 1902 by SCHMIDT [17]. In the course of this process, an epoxide is formed. At those times, these reactions were not exactly and correctly formulated, which necessitated a repetition of this work interpreting the results in terms of modern stereochemistry. In the course of the elimination reaction, the proton of the propanol is apparently split off first; then the oxygen which has become an anion will substitute the trimethylamino group, provided oxygen and nitrogen assume the corresponding *anti*-configuration in the molecule. In this way *trans*-1-phenyl-2-methyl ethylenoxide

* J. Chem. Soc. *1951*, 612; Experientia *12*, 81 (1956).

is formed. The absolute configuration of ephedrine is, as it follows from the mentioned investigations of FREUDENBERG [23, 24], D$_G$-*erythro*-1-phenyl-1-hydroxy-2-methylaminopropane (Fig. 14). Unfortunately, WITKOP formulates ephedrine and pseudoephedrine directly with the opposite configuration as usual, as a consequence of the arbitrary choice of the points of reference criticized above. It was not possible here to rewrite all the tables of formulas of WITKOP in the opposite sense for the sake of unambiguous presentation. Therefore it is emphasized that Figs 17 and 18 will represent the *designations* of configuration in the sense as expressed by WITKOP and not by us. As a consequence of WITKOP's formulation and designation, the oxide formed from ephedrine must have



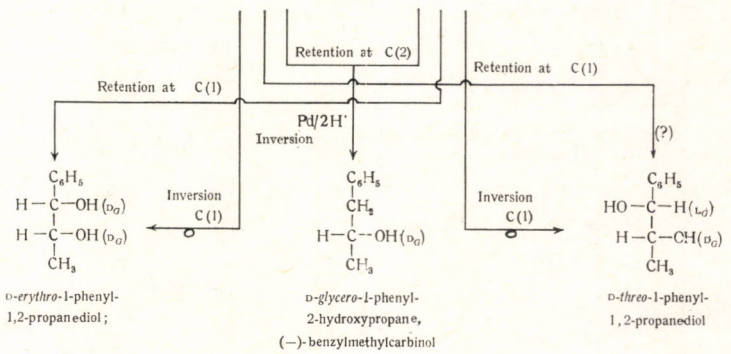


Fig. 15

the *trans*-structure. (+)-ψ-Ephedrine having a configuration (D$_G$) different from ephedrine only on C$_{(1)}$, gives the corresponding *cis*-epoxide as the *threo*-compound, when intramolecular S$_N$2-mechanism is taken into consideration, for which just the described elimination reaction is an example. The *trans*- and *cis*-epoxide was accompanied by a small amount of propiophenone. This may be explained by the fact that the action of alkali may set free a proton also from the carbon atom bearing the phenyl and hydroxyl groups. In this case the elimination involves the formation of a carbanion, which results in the formation of the enol form of propiophenone (Fig. 14).

The epimeric epoxides were subjected to catalytic hydrogenolysis. Both epoxides gave the same benzyl-methylcarbinol which was converted into the *p*-toluenesulphonate. This compound had been prepared previously by WINSTEIN et al. [47] and the configuration of D-*glycero*-1-phenyl-2-hydroxypropane was assigned to it (see Fig. 15). It is interesting that hydro-

genolysis with lithium aluminium hydride did not result in the formation of a uniform carbinol-toluenesulphonate; this fact shows that the metal hydride may attack on either pillar of the oxygen bridge of epoxides of asymmetric structure. In aqueous medium, in the presence of perchloric acid catalyst, the epoxides yield the corresponding diols. The free diols could not be crystallized. However, the dibenzoyl derivative of the diol from the *cis*-epoxide was a well-defined compound; the mother liquor of crystallization gave another dibenzoate which was found to be identical with the main product of the hydrolysis of the *trans*-epoxide. Consequently,

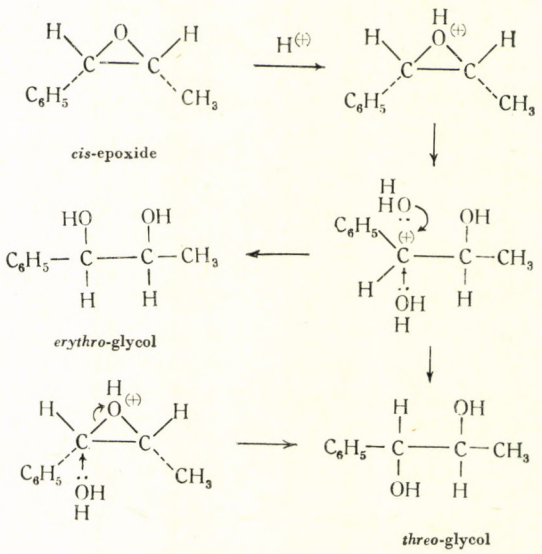


Fig. 16

in the case of the *trans*-epoxide, the inversion took place mostly on the $C_{(1)}$ carbon atom, whereas the S_N2 ring opening reaction of the *cis*-diol (which took place necessarily with the inversion from the corresponding protonated epoxide, i.e., from the conjugate acid) occurred by a monomolecular reaction with the retention of the configuration (Fig. 16).

The diols in question have also been synthesized by the authors in a stereochemically controlled way, as described below, and the products were identified with the compounds obtained from epoxide hydrogenolysis.

Cis-β-methylstyrene was prepared by partial hydrogenation of phenylmethyl-acetylene [22], then it was oxidized by potassium permanganate to give DL-*erythro*-1-phenylpropane-1,2-diol (*cis* hydroxyl addition). Furthermore, DL-*threo*-1-phenylpropane-1,2-diol was synthesized by means of the iodine silver benzoate complex, i.e. by the aid of Prévost's reaction. The two epimeric *threo* and *erythro* diols obtained from the acid hydrolysis of DL-*cis*-β-methylstyrene oxide were compared in the form of the dibenzoates (Fig. 17).

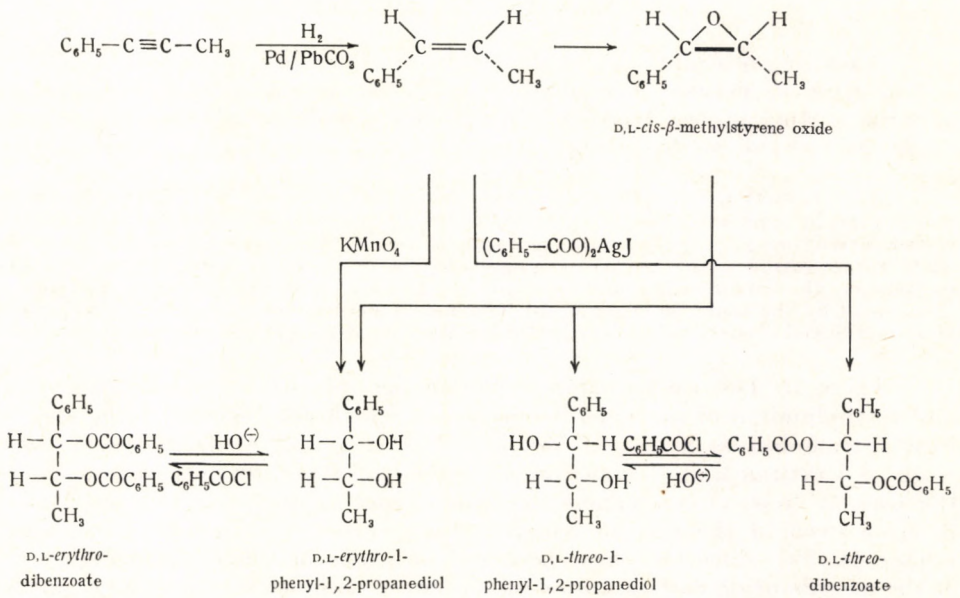


Fig. 17

Meanwhile WITKOP et al. prepared *α-iso*-ephedrine from the epoxide of already known absolute configuration; in this way also the absolute configuration of this compound became unambiguously defined* [22] (Fig. 18).

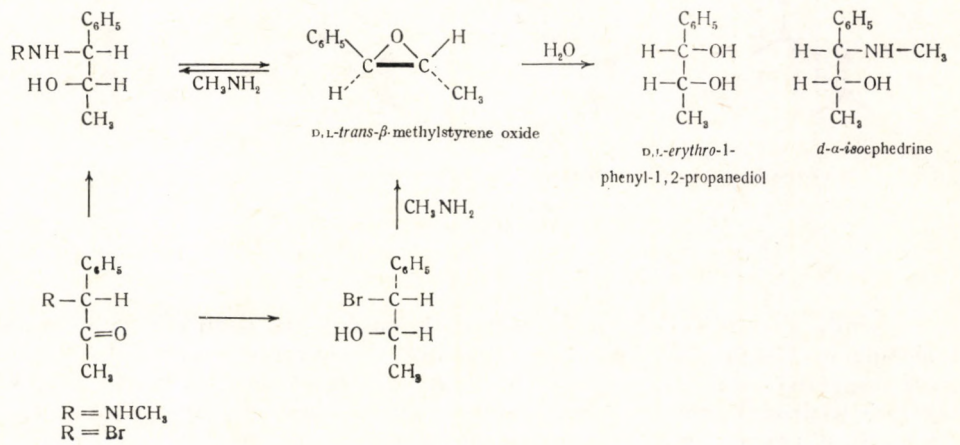


Fig. 18

* The author was informed by Dr FISCHER, Jena, about experiments showing that in the case of epoxides from ephedrine and pseudoephedrine, conclusions entirely different from those of WITKOP may be drawn. At the same time Dr FISCHER told that this study would be reported in Chemische Berichte. However, as far as the present author can judge, FISCHER and WITKOP were at variance only concerning the effect of PH upon the steric course of the *hydrolytic* cleavage of the epimeric methyl styrene oxides. That seems irrelevant as regards the configurational conclusions drawn from the *hydrogenolysis* of the epoxides and of the parent quaternary ammonium salts.

CONFORMATION OF EPHEDRINES

Another problem is the actual steric structure of ephedrine, regarded as a derivative of ethane. The question is the conformation of the compound, i.e., the stating of the relative position of the bulkier substituents, namely of the phenyl and methyl groups attached to the neighbouring carbon atoms.

As it is known, the mutual steric positions of the groups on the neighbouring carbon atoms may be expressed also with the notation of *constellation*, which is perhaps to a certain extent more tangible; this expression is used in the German scientific literature while the literature in the English language adopted the term of *conformation*. According to BARTON, the conformation, and especially the favoured conformation of a molecule is represented by the steric positions of all its atoms, if non-bonded interaction (interaction of atoms not linked directly to one another by covalent bonds) is also taken into consideration.

There are two conformable groups in the ephedrine molecule (hydroxyl and methylamino) of nucleophilic character, which are expected to be able to form intramolecular hydrogen bonding [15], as it follows from the classical work of LATIMER and RODEBUSH, as well as of HUGGINS [30]. According to the present views of stereochemistry, one cannot assume complete freedom of rotation even in the case of simple ethane derivatives, such as 1,2-dichloro ethane [4, 39], since the three favoured positions in which the substituents of the neighbouring carbon atoms do not cover each other cannot be regarded as equivalent ones from the aspect of internal energy contents [3].

According to S. MIZUSHIMA* the possible conformations of an ethane derivative can be pictured as shown in Fig. 19.

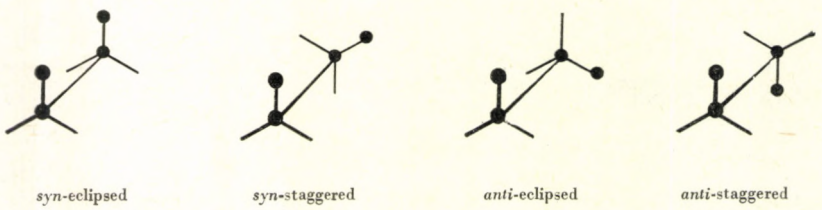


Fig. 19

Similar results have been obtained in the case of the comparatively simple molecule of butane-2,3-diol where the most favourable rotational position (*anti*-staggered) is determined by the relative bulk of the two methyl and of the two hydroxyl groups, resp., and by their mutual repulsive action. This does not, of course, mean the existence of rotational isomers (the so-called conformers or rotomers of simple ethane derivatives or of butane-2,3-diol). Nevertheless, it has been found as an experimental fact that the *meso*-modification of butane-2,3-diol cannot form cyclic acetals, whereas the optically active molecule as well as the racemic compound may be readily converted into it [40]. In the *meso*-configuration, both hydroxyl groups are *anti*staggered, as a consequence of the *anti*-staggered position of the two methyl groups,

* Structure of Molecules and Internal Rotation, N. Y., Academic Press (1954)

whereas in the active (and racemic) modifications, when the two hydroxyl groups are near to each other (skew), the alkyl groups will be *anti*-staggered, which results in the consequence that acetal rings are easily formed with *d*- and *l*-butane-2,3-diol, but not with the *meso*-compound. The three possible conformations of *meso*-butane-2,3-diol are, accordingly, not equivalent, except for the two mirror images.

The substituents of ephedrine have much greater requirement of space than *meso*-butane-2,3-diol. The Stuart — Briegleb scale models of (+)-ψ-ephedrine and of (—)-ephedrine show that the phenyl and methyl groups try to become arranged possibly far, *anti*-staggered from each other. Thus the hydroxyl and methylamino groups in (+)-ψ-ephedrine are directed sterically near to each other (skew) [13, 46] (Fig. 20).

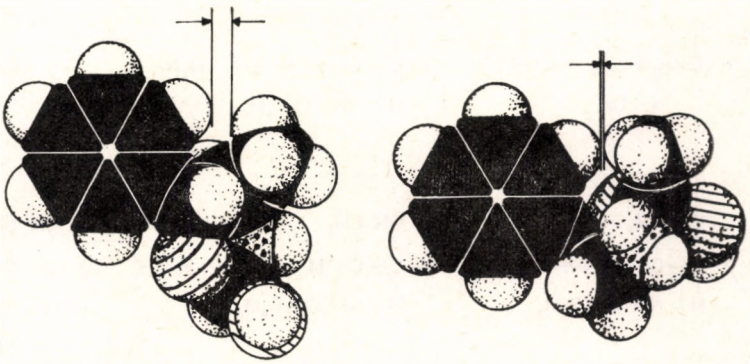


Fig. 20

If the electrostatic and steric repulsion of the phenyl and methyl groups are considered as the primary factor in the molecule of (—)-ephedrine, the spatial distance of the phenyl and methyl groups must involve also the distant arrangement of the hydroxyl and methylamino group. Consequently, the existence of a hydrogen bonding may be assumed in the ψ-ephedrine molecule, as it has been actually done [15], which is thus an *intra*molecular hydrogen bond. As contrasted with it, only an *inter*molecular hydrogen bond, namely in the form of hydration may be expected in the case of (—)-ephedrine. Indeed, according to the experimental facts, only (—)-ephedrine can bind hydrate water [8], whereas (+)-ψ-ephedrine cannot. The same holds true for the racemic modifications of these compounds.*

Thus the problem of the steric structure of β-aryl alkanolamines is not decided with the determination of the configuration, but immediately arises the next question as to the steric arrangement of the bulkiest substituents on the neighbouring carbon atoms, and consequently as to the steric positions i.e. conformation of the functional groups of the compound [10, 11]. Several attempts have been made to answer this question, first of all in connection with the arylpropanolamines of the ephedrine type. FODOR et al. demonstrated in a series of experiments begun in 1947 that the N-acyl deriva-

* The existence of the hydrogen bonding was demonstrated by infrared spectroscopy in the cases of both ψ-ephedrine and ephedrine by J. KANZAWA [Bull. Chem. Soc. Japan, *29*, 398, 479, 604 (1956)]. Intensity, however, was much greater in the case of ψ-ephedrine.

tives of ψ-ephedrine and ψ-*nor*-ephedrine readily undergo the reaction of N→O acyl migration [10, 11].

The process is reversible, and the configuration is retained. With N-acyl derivatives of 1-aryl-1-propanol-2-amines belonging to the ephedrine series, it was possible to perform a usually very slow reaction with the retention of

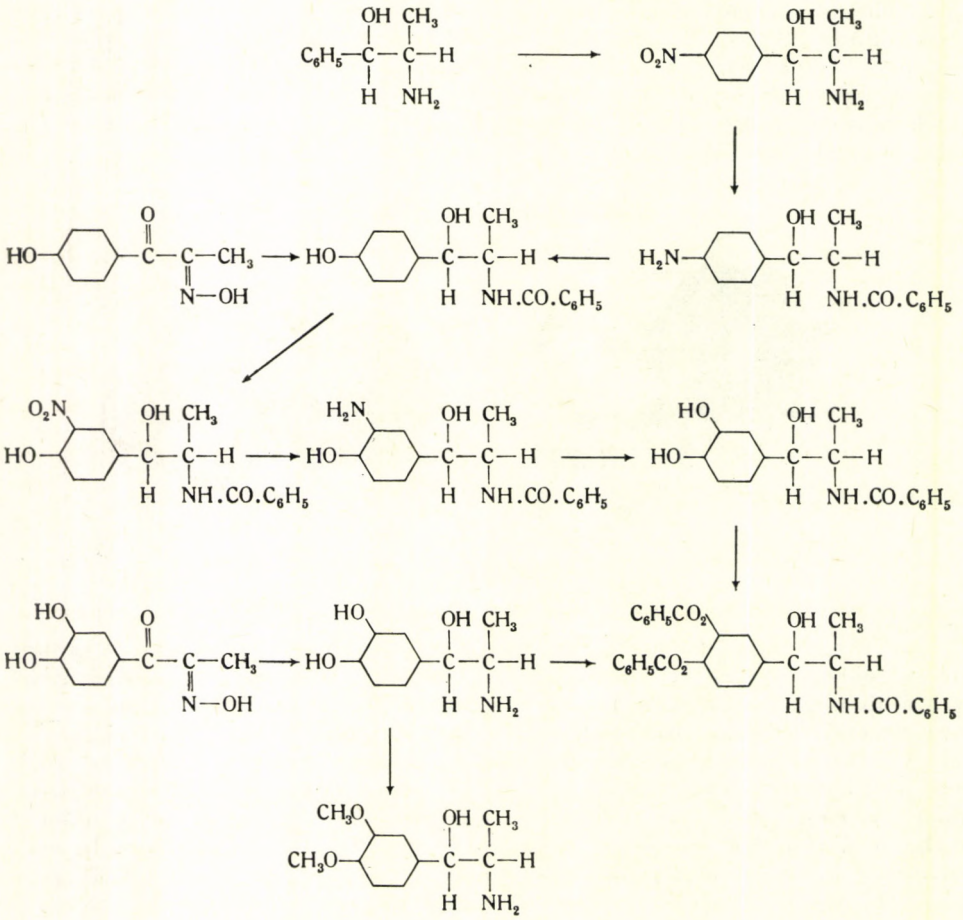


Fig. 21

the configuration [45], or with a quick process of acyl migration, accompanied by WALDEN inversion [15]. At the same time and independently, entirely consistent experimental results were reported by WELSH [43]. According to these, N-aroyl-ψ-ephedrine is capable of an acyl migration reaction in aqueous medium with a rate about 20 times greater than that of the corresponding N-aroyl-ephedrine derivative [45]. In the case of heating N-acetyl-ephedrine hydrochloride, WELSH found not only a different reaction rate, but also the change of configuration occurring at the same time. Since the mechanism of acyl migration is experimentally well established [16, 29, 45], as described in the introductory chapter, it is apparent that a positive occurrence of acyl migra-

tion (i.e., a process with the retention of configuration) indicates the steric neighbourhood of the groups containing oxygen and nitrogen; on the other hand, the delay in or the failure of this reaction — or even its occurrence with inversion — is a sign to show that the acylamino and hydroxyl groups were sterically apart from each other. On this basis, the *conformation* of ephedrine and ψ-ephedrine were given [12] in the same way as deduced by WELSH [45, 46] from the mutual repulsion of the phenyl and methyl groups. All these facts consistently prove that in the case of arylpropanolamines, where the

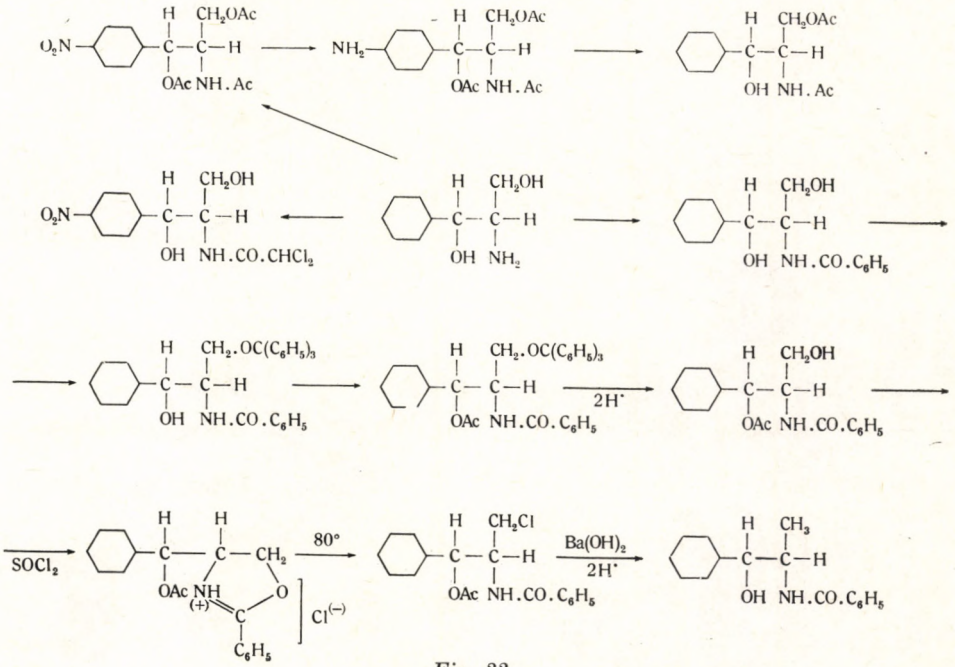


Fig. 22

probability of a preferred staggered conformation to eclipsed ones is higher in aqueous, alcoholic or dioxan solutions even at room temperature, the bulkier groups try to become arranged *anti*-staggered, or at least *skew*. These results rendered possible to decide by the aid of the N→O acyl migration about the relative distance of nitrogen and oxygen, i. e., the conformations of a number of ephedrine- and ψ-ephedrine derivatives could be determined. Series of systematic experiments revealed that physiologically active — pressor — representatives of arylpropanolamines had conformations and also configurations identical with ephedrine [2]. The configuration was proved by the reactions described below, employing the method of configurative correlation. In the course of the experiments, (±)-N-methyl-ephedrine was converted into (±)-ephedrine [21], *nor*-ephedrine into 4-hydroxy- [9] and 3,4-dihydroxy-*nor*-ephedrine [19], (Fig. 21) and (±)-chloramphenicol into (±)-N-benzoyl-ψ-*nor*-ephedrine [18] (Fig. 22). On the other hand, compounds which did not markedly influence the blood pressure of the experimental animals, and behaved like ψ-ephedrine in the course of the N→O acyl migration reaction, were all actually derivatives of ψ-ephedrine. This was proved first by acyl migration reaction, but these

statements were later confirmed also by the established configurative correlations [21, 9, 29, 19] mentioned previously. The analysis of this problem became finally completed by the X-ray diffraction studies of DUNITZ [35] on bromamphenicol, which proved in addition to the configuration of ψ-ephedrine (already known from other experiments*) that the $C_{(1)}$ hydroxyl and the acyl-

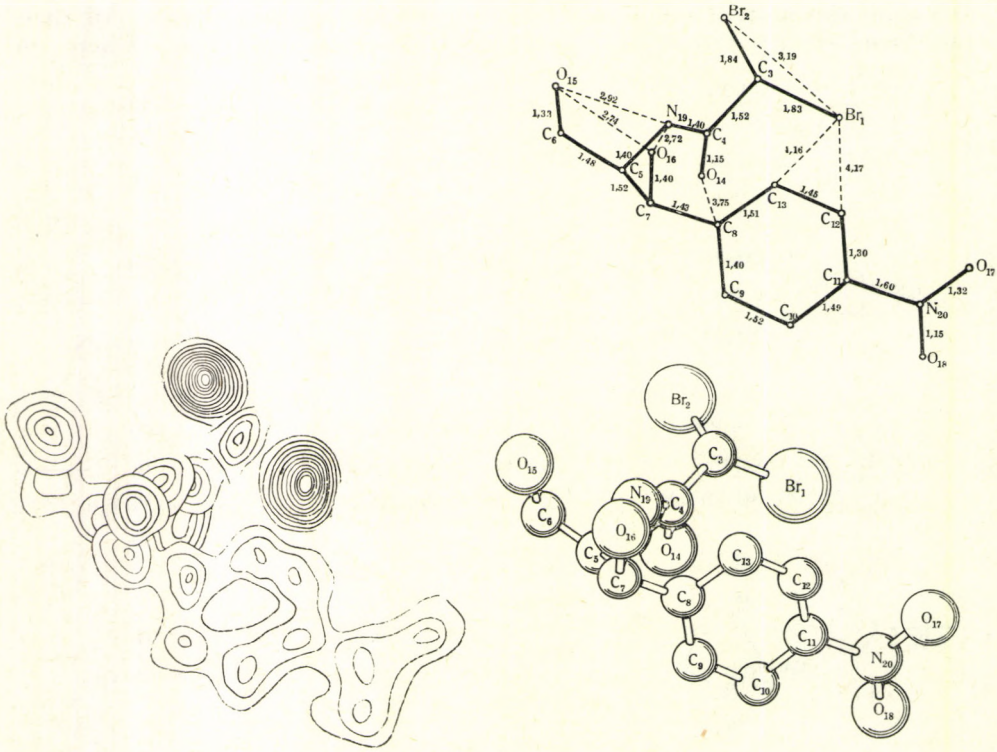


Fig. 23

ated amino-nitrogen of the crystals were, in fact, near to each other in space (skew) (Fig 23). In this connection reference should be made to the data of X-ray diffraction of crystalline ephedrine hydrochloride [34]. Ephedrine, in the form of its salts, shows the steric structure and conformation that corresponds to the classical projection formula. It should be emphasized, however, that it holds true only for ephedrine hydrochloride *crystals*. It is readily seen that repulsive and pulling forces entering the picture in the presence of an ammonium nitrogen are quite different from those present in molecules bearing no formal charge, or even from the case of an N-acylated amino alcohol. In HÜCKEL's opinion, this is the crucial circumstance [26].

The next problem is now the representation of the conformations of ephedrine bases which — if the configurations are given — correspond to all real facts. In this respect there are three possibilities. The first and the most

* M. C. REBSTOCK, H. M. CROOKS, JR., J. CONTROULIS and Q. R. BARTZ [J. Am. Chem. Soc., *71*, 2458 (1949)] arrived at the same conclusion on the basis of the values of optical rotatory power.

exact is the use of stereoformulas representing the actual steric structures of ephedrine and ψ-ephedrine. Another and simpler way is to use the so-called stellar formulas [4b, 6]. If the model of the ψ-ephedrine molecule, e.g., is represented so that the C—C bond of ethane is perpendicular to the plane of the paper, the substituents on the individual asymmetric carbons may be shown as situated on the vertices of two triangles. For energetic reasons, a condition of such arrangement is that the groups of identical character must not come near to each other, thus the two triangles cannot cover each other, they are just in a crossed position; in this way a stellar form will result. For ephedrine and ψ-ephedrine, the stellar formulas given by CLOSE [6], and shown in Fig. 24,

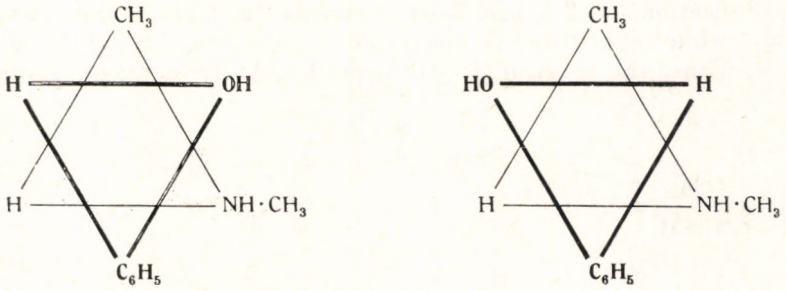


Fig. 24

are obtained. However, it must be noted here, that this way of projection is valid only as regards the conformations, while it may lead to mistakes concerning the configuration of the 'rear' carbon atom.

Another possibility of projection was suggested by FODOR et al. [15, 20]. Accordingly, in the classical projective formula of ephedrine and ψ-ephedrine, the carbon atom bearing the nitrogen is rotated, together with its substituents, by 60° around the axis connecting the two ethane carbon atoms; this conformation is projected on the paper. This results in a projection formula which truly pictures both configuration and conformation. Such formulas have been employed in the scientific literature by HÜCKEL [26, 27], SHEMYAKIN [38] and PREOBRAZHENSKI [35], and will also be used in the following parts of

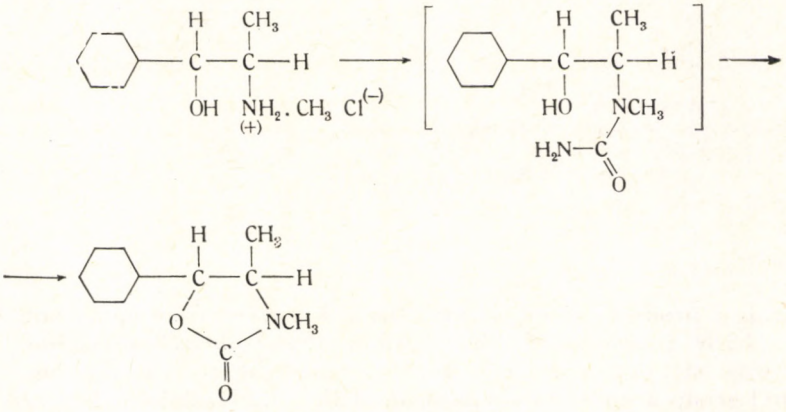


Fig. 25

this work. The assumption of hindered rotation around the C—C bond of ephedrine bases has been adopted by several text-books [41] and monographs [42]. In principle, these projection formulas are likewise obtained if the open-chain aldehydo-hexose formulas are translated into the cyclic semi-acetal formulas. In this case $C_{(6)}$ is imagined to be rotated by 60° around the axis connecting $C_{(4)}$ and $C_{(5)}$, as it must actually be done with the substituents of $C_{(5)}$ when assembling a model, because otherwise the conformation necessary for the cyclization cannot be achieved.

Ephedrine and *ψ*-ephedrine show thus a stereospecific behaviour in the course of the N→O acyl migration reaction. A similar stereospecifity is observed according to CLOSE [6], if the ephedrine epimers are melted with urea. By this reaction, a 2-oxazolidone derivative is formed from *ψ*-ephedrine (Fig. 25), while ephedrine is converted into a 2-imidazolidone derivative (Fig. 26). Thus, the reaction is stereospecific. At first, CLOSE assumed this

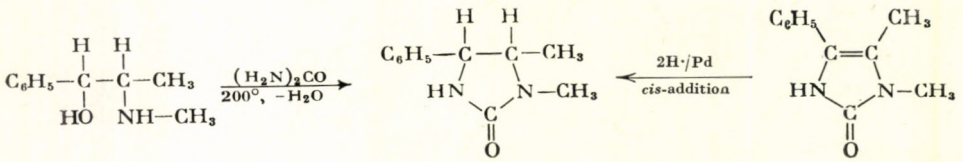


Fig. 26

iminazolidone to exist with the phenyl and methyl groups in the *trans*-position. We prepared N-ureido-ephedrine and supposed the formation of this compound as the primary product [20] which, with the *anti*-staggered conformation of the $N—CH_3$ and OH groups, suffers an intramolecular nucleophilic substitution ($S_N 2$) involving inversion on $C_{(1)}$, to give the *trans*-imidazolidone (Fig. 27). However, according to CLOSE, DUSCHINSKY [7] later succeeded

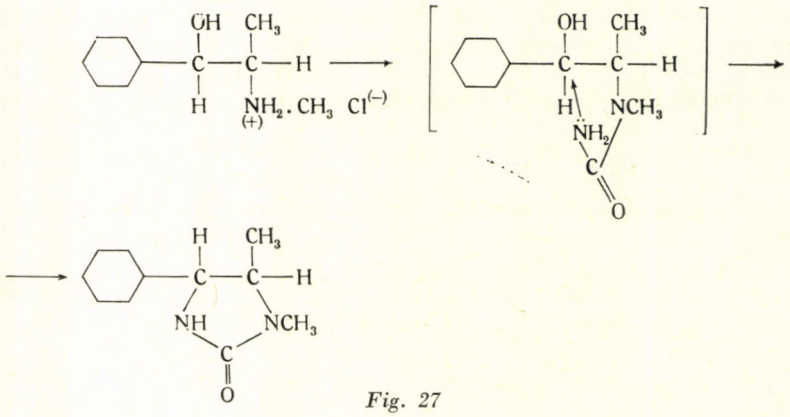


Fig. 27

in preparing a product, identical with the one derived from ephedrine, by the catalytic hydrogenation of the 3,4-dimethyl-5-phenylimidazoline which reaction was, of necessity, a *cis*-addition. Consequently, the $C_{(4)}$ methyl and $C_{(5)}$ phenyl group are also in *cis*-position in this imidazolidone derivative, and they have an *erythro*-configuration corresponding to ephedrine. It follows that

no change of configuration took place during the process of melting with urea. FODOR and KOCZKA [20] could, on the other hand, recover pseudoephedrine by the alkaline hydrolysis of 3,4-dimethyl-5-phenyloxazolidone which had been obtained from the urea melting reaction of ψ-ephedrine. This result showed that the melting of the *threo*-derivative with urea was not accompanied by inversion either, only the heterocycles formed from the two epimers were structurally different. Thus, the difference in the relative steric position of the hydroxyl group on a single carbon atom may result in diverse paths of reaction even under rather energetic reaction conditions, though the energies involved would be amply sufficient to efface both configurational and conformational differences. This fact indicates a definite stereospecifity, and confirms the experience that these two epimers profoundly differ, not only in their configuration, but also in their chemical reactivity.

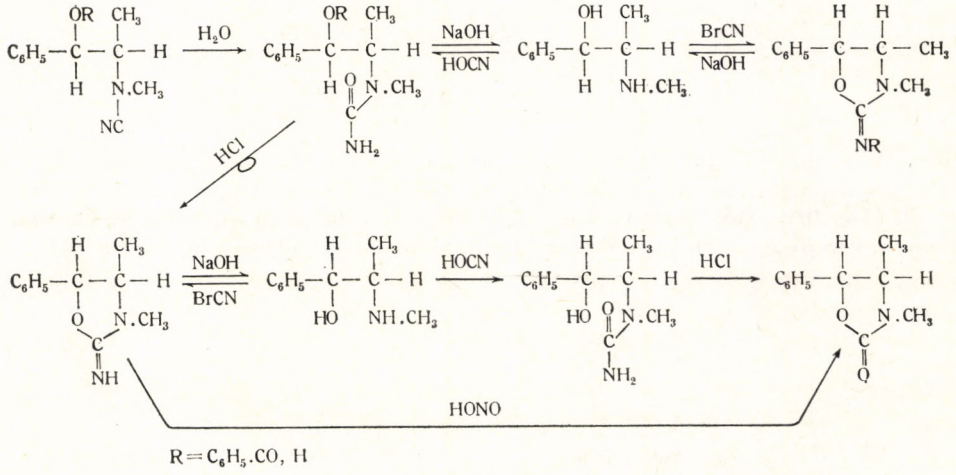


Fig. 28

The stereospecifity of ephedrine and ψ-ephedrine is not so marked in aqueous alkaline solutions. Both epimers, e.g., give rise with benzaldehyde [44] or with other aldehydes to the formation of diastereomeric phenyl-methyl-oxazolidine derivatives. As shown by FODOR and KOCZKA [29a, 20], the reaction with cyanogen bromide yielded the 2-imino derivatives of the corresponding oxazolidone in both cases (Fig. 6). The configurations of the compounds were clearly established as depicted in Fig. 28.

Another problem is the mechanism of the acyl migration reaction in N-acyl ephedrines with inversion (Fig. 29). According to FODOR and KISS this process is, in principle, exactly the same, as the N→O acyl migration of 2-amino cyclanols having a rigid ring system, e.g., 2-acylamino-cyclopentanols (Fig. 30). The generally known steric prerequisite of this reaction, occurring with S_N2 mechanism, is the *trans*-position of the atomic group split off from $C_{(1)}$ and of the new group which becomes attached to the same [1]. According to the studies of FODOR and KOCZKA, when N-carbamyl-ephedrine is acted upon by mineral acids, a 2-oxazolidone-imine derivative is formed, the process being accompanied by Walden inversion (Fig. 29). The hydrolysis of the product — which process does not affect the centres of asymmetry — affords ψ-ephed-

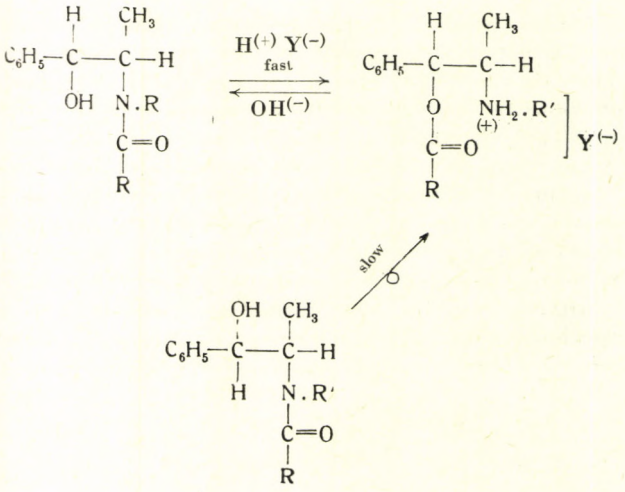


Fig. 29

rine, thus there is no doubt about the change of the configuration during the formation of the ring. According to the mechanism suggested by FODOR et al. [14, 20], the carbamyl-oxygen atom would push out the protonated propanol-hydroxyl, and so contribute to the formation of the ring [14].

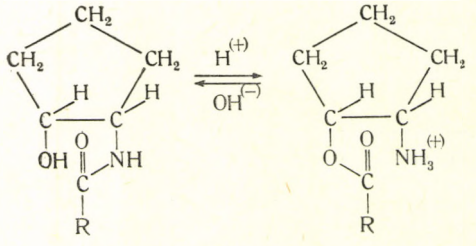


Fig. 30

FODOR and KOCZKA became aware of the parallelism between N→O acyl migration and the conversion of the ureido derivatives of the epimeric ephedrines under the influence of acids. They regarded the ureido rest as a special acyl group which permits the stabilization of the cyclic intermediate, and allows in this way a better insight into the mechanism of N→O acyl migrations accompanied by inversion. Consequently, it appeared desirable to prove exactly that when the oxazolidone-imide was formed from N-carbamyl ephedrine, it was actually the propanol-oxygen on $C_{(1)}$ which had to be driven out by the acyl-carbonyl-oxygen. Unequivocal proof could be offered by the use of carbonyl-O^{18} labelled N-ureido-ephedrine. Since methodical possibilities were lacking when this research was carried out, parallel experiments with N-thiocarbamyl-ephedrine were made as a first approximation to decide which atom (O or S) would enter the heterocycle to substitute the other. Final conclusions, of course, must be regarded always with reservation, as it is not sure that sulphur-isologues react completely the same way as the oxygen compounds.

KOCZKA and FODOR found [29c] (Fig. 31) that O-benzoyl-N-thiocarbamyl-ephedrine (II) gave under the action of acids an oxygen-free product, apparently a thiazoline derivative (V), with the elimination of benzoic acid. Thus, the question whether the thione-sulphur atom could expel the propanol-oxygen was answered in the affirmative.

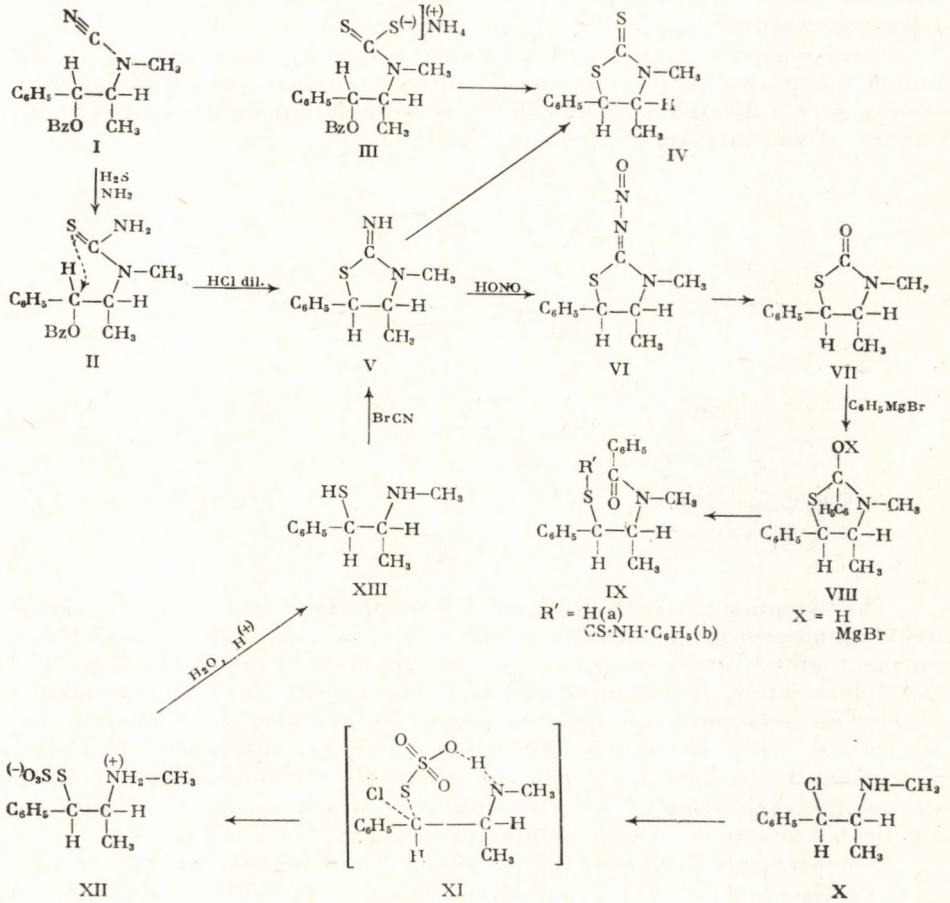


Fig. 31

A next task was to prove the configuration of the formed thiazolidone imide, and to decide in this way about the S_N1 or S_N2 mechanism of the process. For this purpose it appeared important to find a correlation between this thiazolidone imide and either thiol-ephedrine or thiol-ψ-ephedrine. For this purpose two ways were suggested. At first, (±)-thiazolidone imide (V) was converted by ring opening into a (±)-phenyl-methylamino-propane-thiol (IX); on the other hand, the L-*threo*-form of the same compound (XIII) was synthesized and transformed into the optically active imido-thiazolidone (V), and identified with the same. All these reactions are depicted in detail on the table of formulas (Fig. 31). The ring cleavage of V could not be effected either with acids or with alkalis; finally N-nitrosation and thermolysis of the nitrosimine (VI)

to the thiazolidone (VII) followed by ring opening by phenylmagnesium bromide was successful in obtaining N-benzoyl-thiol-ψ-ephedrine (IXa); this compound was identified in the form of its N-phenyldithiocarbamate (IXb). An analogous ring cleavage reaction was observed formerly in the case of the corresponding oxazolidone (Fig. 32). The first synthesis started with (±)-chloro-desoxy-*pseudo*ephedrine,* which was hydrolyzed through the thiosulphonate according to BRETSCHNEIDER's method with the retention of the configuration to give (±)-*threo*-1-phenyl-2-methylamino propanethiol (thiol-ψ-ephedrine) (XIII). This product was *p*-nitro-benzoylated on the nitrogen atom, and then oxidized; the reaction gave a disulphide (IXb) identical with the product prepared by ring cleavage of the racemic thiazolidone imide (V).

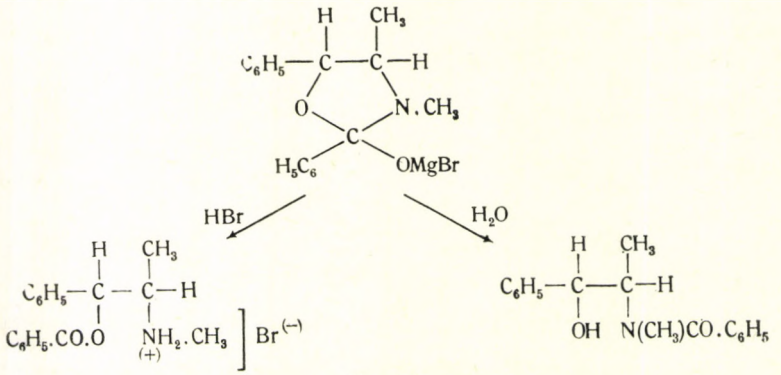


Fig. 32

The asymmetric synthesis from (+)-ψ-ephedrine gave L-*threo*-1-thiol-2-methylamino-propane practically in the same way: X→XI→XII→XIII; the treatment of the product with cyanogen bromide afforded the same (—)-thiazolidone imide as obtained also from the resolution of the racemate V. (—)-*Erythro*-thiolephedrine was prepared by reacting (+)-chloro-desoxy-ψ-ephedrine with potassium thiocyanate and by subsequent hydrolysis.

From these experiments one may deduce the intramolecular S_N2 mechanism for the cyclization of N-ureido-ephedrine which, in all probability, may be extended also to N→O acyl migrations occurring with inversion.

Independently from our studies, SICHER et al.* found a similar stereospecifity in the case of cyclisation of N-thiobenzoyl-2-aminoalcohols. *Erythro* derivatives gave Δ_2-thiazolines, while *threo* derivatives yielded Δ_2-oxazolines. All these results indicate the important influence of the conformation on the reactivity of ephedrine bases. The reactions mentioned here are stereospecific and cannot be interpreted in each case in terms of configurational differences. However, if the favoured conformations are taken into consideration, logical explanations are obtained.

Next, we should like to interpret the fact that the molecule of ephedrine behaves in some cases — especially in acidic medium — stereospecifically, while both ψ-ephedrine and ephedrine give the same type of products of ring closure without inversion when treated in alkaline medium. This experience is easily explained: in acidic medium not only the nucleophilic, but also the electrophilic prerequisite of the reaction of S_N2 type is given (push-pull reaction).

* H. BRETSCHNEIDER and W. KLÖTZER: Monatsh. Chem. *81*, 587 (1950).

It is admitted that, in principle, the possibility of a change in the conformation of the N-acyl-ephedrine compound is given, i.e., the hydroxyl and the acylated nitrogen groups may approach each other by rotation around the $C_{(1)}$—$C_{(2)}$ axis, thus intramolecular acyl migration might take place with the retention of the configuration; the probability of such a process is, however, not at all high. The competing reaction, namely the conversion *via* $S_N 2$ mechanism, is a process of higher reaction rate. The latter reaction is furthered not only by driving forces originating from within the molecule (presence of the nucleophilic oxygen), but in acidic medium also by the proton (or hydroxonium ion), which brings about a loosening of the propanol C—O bond. In alkaline medium, as it is easily seen, there is no electrophilic group present, thus splitting off of the oxygen atom in the form of water can be helped only by pushing forces from within the molecule; this effect in itself is not strong enough to bring the process to completion [20].

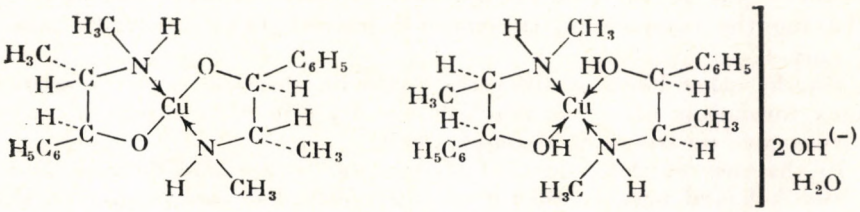


Fig. 33

An interesting example of the above statement may be given in the following: the same ureido-ephedrine gives under the conditions of neutral thermolysis an imidazolidone (Fig. 26), formed without inversion as a consequence of the lack of an electron-attracting group, e.g. a proton; however, when the compound is heated in aqueous hydrochloric acid, an oxazolidone imide is formed. On the other hand, if the *anti*-staggered conformation of the reacting groups is not given, like in the case of N-carbamyl-*pseudo*ephedrine, ring closure with the retention of the configuration takes place to give *trans*-3,4-dimethyl-5-phenyloxazolidone (Fig. 28).

A highly interesting new development in the field of determining the conformations of amino-alcohols was the striking observation of FÖLDI et al. [5d] in 1957. It was found that the *threo* and *erythro* forms of 2-aminoalcohols gave copper chelates of different structures. *Pseudo*ephedrine gave a true chelate, i.e., an uncharged intramolecular complex, while ephedrine afforded a positively charged complex ion. The derivative from *pseudo*ephedrine was shown to be entirely stable against the action of ammonium hydroxide, whereas the ephedrine derivative was readily decomposed by this reagent. This fact, that only the *threo* derivative, i.e., *pseudo*ephedrine gave a stable and genuine chelate, and the *erythro* derivative (i.e. ephedrine) did not, permitted the inference that the steric proximity of the amino and hydroxyl groups existed only in the molecule of the *threo* derivative (Fig. 33). This statement is in complete accordance with the conclusions of FODOR et al. drawn on the basis of stereospecific reactions. Had ephedrine, in accordance with the projection formula of FISCHER, the hydroxyl and methylamino groups in *cis*-position, chelation should give the result exactly opposite to that observed by FÖLDI.

* Coll. Czech. Chem. Comm., *20*, 1391, 1402, 1409.

Somewhat later, in 1958, DREFAHL and ZIMMERMANN observed a phenomenon similar to the one studied by FÖLDI, in the course of reacting diastereomeric amino-*cyclo*pentanols with cobaltous chloride in methanol [5a]. *Cis*-2-amino-cyclopentanol gave in anhydrous methanol a finely crystallized chelate, while practically no complex compound was formed with *trans*-2-amino-cyclopentanol. On the basis of this stereospecificity of chelate formation, DREFAHL and ZIMMERMANN could ascribe the same configurations to the two 2-amino-cyclopentanols as given previously by FODOR et al. as the result of considerations relating to the N→O acyl migration reaction [17].

In 1960 this method of complex formation was extended by DREFAHL et al. to studying the influence of the constellation of 1,2-disubstituted 2-amino-alcohols [5b]. They examined epimeric *nor*-ephedrine and *norpseudo*ephedrine. Two various cobaltous complexes of *nor-pseudo*ephedrine could be isolated in anhydrous methanol; one of them had the composition of (DL-*nor-pseudo*-ephedrine-H)$_3$Co. In the case of DL-*nor*-ephedrine, however, a single complex salt having the composition (DL-*nor*-ephedrine-H)$_6$CoCl$_2$ · 3 CH$_3$OH was isolated only.

On the other hand, a difference could be observed in the tendency of complex formation when the reaction was tried in 95% methanol: DL-*nor*-ephedrine gave no traces of a complex salt.

In the case of the N-methyl derivatives, DL-*pseudo*ephedrine and DL-ephedrine behaved perhaps even more differently. The first compound gave a brownish-violet chelate and an olive complex compound, while DL-ephedrine afforded no complex compound at all, apart from a transitory deepening of the colour when the base was added to a solution of cobaltous chloride in methanol; the hue, however, disappeared in a few minutes, with the precipitation of basic cobaltous chloride.

The experimental results were interpreted by DREFAHL as indicating a favoured steric proximity, i.e. *skew* conformation of the hydroxyl and amino groups with the staggered position of the bulky phenyl and methyl groups in *nor-pseudo*ephedrine and *pseudo*ephedrine. Anyhow, the behaviour of the epimeric *nor*-ephedrine shows at the same time that the energy barrier between the various possible conformations is not too high. It is possible, wrote DREFAHL, that the substituents leave the favoured staggered conformation and approach one another as near as it is allowed by the steric hindrance between the phenyl and methyl groups (*skew* orientation), and as it follows from the energetic factors of intramolecular interactions.

As a further approach, systematic investigations of the IR-spectra, of the dipole moments and conductivity measurements were undertaken by DREFAHL and HEUBLEIN [5c] in the series of 1,2-aminoalcohols including ethanolamine, *threo-* and *erythro*-3-aminobutan-2-ol, *nor*-ephedrine and *pseudo-nor*-ephedrine, *threo-* and *erythro*-2-amino-1,2-diphenylethanol, etc. In agreement with KANZAWA (p. 37), a considerable shift of the OH valency frequencies was observed throughout this series, pointing to the presence of relatively strong hydrogen bridges. However, this shift is much more significant in all cases with the *threo* derivatives. Similar parallelism (and discrepancy), though not so specific, has been observed in the dipole moment and molecular conductivity data. All these findings may be considered in favour of the afore-mentioned interpretation: the mutual repulsion of the bulkiest substituents is one of the main factors, while the attraction

between the OH and NH groups is the other. These two factors act in the same sense, in the *threo* derivatives while within the *erythro* forms they are competitive.

Recently HYNE* gave an account of an NMR study on the epimeric ephedrine bases. Based upon chemical shifts, he stated that none of the pure staggered conformations of the diastereoisomeric ephedrines could depict the real situation. (Fig. 34)

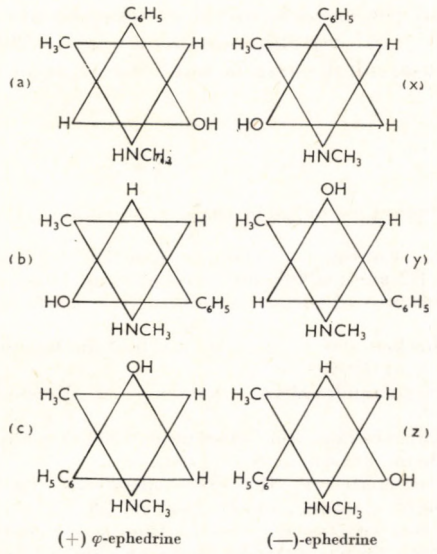


Fig. 34

Based upon chemical shifts, anisotropy effects, spin-coupling constants and upon hydrogen-bond phenomena, HYNE suggests the following preferred residence conformations to the diastereoisomers. Accordingly, the hydrogen bridge seems to be the preponderant factor in addition to the mutual repulsion between the methyl and the phenyl groups (Fig. 35).

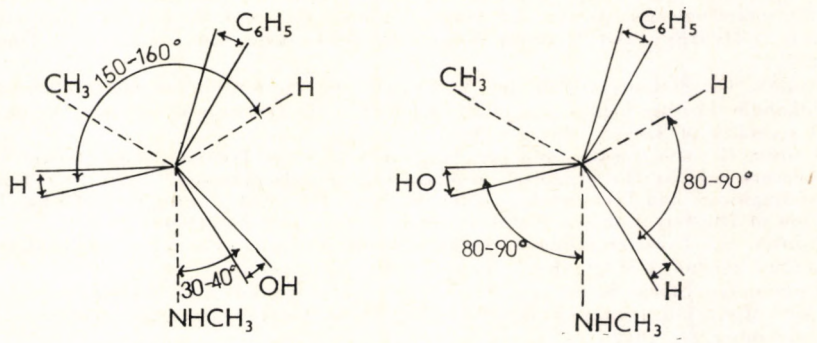


Fig. 35

*Canadian Journal of Chemistry *38*, 2536—2542 (1962)

However, the author of the same paper is at variance with this concept, suggesting the proportion of conformers to be $a:b:c = 62:30:8$ % for *pseudo*ephedrine while for ephedrine $x:y:z = 40:20:40$ % seems to account better for the chemical shift values observed. In both alternative interpretations the neglect of conformer *b* in the case of *pseudo*ephedrine seems to be rather surprising, since this form corresponds the best to both factors (i.e. H-bridge and non-bonded interaction) concerned.

Unfortunately, however, there are some limits as to the validity of the statements made upon physico-chemical measurements. In consequence, the picture concerning the real equilibrium between the different preferred conformations of 2-amino-alcohol *bases* is not quantitative as yet.

REFERENCES

1. Alexander, E. R.: Principles of Ionic Organic Reactions, J. Wiley, New York, 1950, p. 64.
2. Bánfi, D., Benke, G., Fodor, G., Kiss, J., Koczka, K., Sallay, I., and Szekeres, L.: Élettani hatású 1,2-aminoalkoholok térszerkezete közti összefüggés. (Relationship among the steric structures of physiologically active 1,2-aminoalcohols), Magy. Kém. Foly. *68*, 225 (1952).
3. Bier, G.: Die Drehbarkeit der C—C Bindung und die Gestalt der Kettenmoleküle in Lösung, Experientia *2*, 82 (1946).

4a Briegleb, G.: Zwischenmolekulare Kräfte und Molekülstruktur, Enke Verlag, Stuttgart, 1937, S. 863.

b Briegleb, G.: Wirkungsradien von Atomen in Molekülen (Atomkalotten und Molekülmodelle), Fortschr. Chem. Forsch. *1*, 642 (1950).

5a Drefahl, G. and Zimmermann, H.: Stereochemische Zuordnung von Aminocyclopentanolen durch Komplexbildung, Chem. Ber. *89*, 283 (1958).

b Drefahl, G. and Zimmermann, H.: Der Einfluss der Konstellation auf die Komplexbildung von 1,2-disubstituierten 2-Aminoalkoholen. Chem. Ber. *91*, 1809 (1960).

c Drefahl, G. and Heublein, G.: Konstellation acyclischer 1,2-Aminoalkohole, Chem. Ber. *94*, 922 (1961).

d Földi, Z., Földi, T. and Földi, A.: Conformation of *Pseudo*-Ephedrine. Copper Chelates of 2-Aminoalcohols, Acta Chim. Acad. Sci. Hung. *11*, 339 (1957).

6. Close, W. J.: The Conformation of the Ephedrines, J. Org. Chem. *15*, 1131 (1950).
7. Duschinsky, R.: Personal letter to W. J. Close; the latter informed G. Fodor (1950) also by way of letter.
8. Emde, H.: Über Diastereomerie I. Konfiguration des Ephedrins, Helv. Chim. Acta *12*, 369 (1929).
9. Fehér, É., Bánfi, D., Fodor, G., and Kiss, J.: Configurational Correlation of Pharmacologically Active 1,2-Aminoalcohols. III. Conversion of *dl-Nor*-Ephedrine into 4-Hydroxy and Methoxy-dl-*nor*-Ephedrine, Acta Chim. Acad. Sci. Hung. *1*, 385 (1951).
10. Fodor, G.: Stereospezifität der Acylwanderung im Kreise der diastereomeren Aminoalkohole. Lecture held at the public meeting of the Institute of Organic Chemistry of the University of Szeged, May 10, 1947.
11. Fodor, G.: Die Verwendung der Acylwanderung zur Trennung von Diastereoisomeren. Lecture held by the Organisation of the Chemical Department of the Free Trade Union of Engineers and Technicians, Budapest, June 17, 1948: Fodor, G. and Kiss, J.: Separation of Diastereoisomeric Aminoalcohols, Nature *163*, 287 (1949).
12. Fodor, G.: Diasztereoizomer aminoalkoholok kémiája. (Chemistry of diastereoisomeric amino alcohols.) Magy. Kém. Lapja, 1949, pp. 1—6.
13. Fodor, G.: Steric Structures of Alicyclic Aminoalcohols and Mechanism of the O→N Acyl Migration. Lecture at the First Congress of the Hungarian Chemical Society, Szeged, November 20, 1949.
14. Fodor, G.: Sztereospecifitás az aminoalkoholok kémiájában. (Stereospecifity in the chemistry of aminoalcohols.) Lecture at the session of the Hungarian Academy of Sciences, December 11, 1950; Publications of the VII. Dept. of the Hung. Acad. Sci., *1*, 1—10 (1952).

15. Fodor, G., Bruckner, V., Kiss, J., and Óhegyi, G.: Use of Acyl Migration in Separating Diastereoisomeric Aminoalcohols, J. Org. Chem., *14*, 337 (1949).
16. Fodor, G., and Kiss, J.: Acyl Migration O → N in the Diastereomeric 2-Aminocyclohexyl Benzoates, J. Am. Chem. Soc. *72*, 3495 (1950); Configuration of Diastereoisomeric 2-Amino-cyclohexanols and a Suggested Mechanism for Acyl Migration N→O, Acta Chim. Acad. Sci. Hung. *1*, 131 (1951).
17. Fodor, G., and Kiss, J.: Stereospecific Behaviour of the Diastereomeric 2-Acyl-amidocyclopentanols in Acyl Migration N→O, Research *4*, 382 (1951); The Stereochemistry of 2-Amino-cyclopentanols, J. Chem. Soc. *1952*, 1589.
18. Fodor, G., Kiss, J., and Sallay, I.: Configurational Correlation of Chloramphenicol and of *nor-pseudo*-Ephedrine, Nature *167*, 690 (1951); Configurational Correlation of Chloramphenicol with *pseudo-nor*-Ephedrine, J. Chem. Soc. *1951*, 1859.
19. Fodor, G., Kiss, J., and Bánfi, D.: Konfigurativer Zusammenhang zwischen (±) Corbasil und (±) nor-Ephedrin, Monatsh. Chem. *83*, 1146 (1952).
20. Fodor, G., and Koczka, K.: A Stereospecific Reaction of Diastereoisomeric Ureido-alcohols, Research *4*, 381 (1951); The Stereochemical Course of the Conversion of 2-Ureido-alcohols into Oxazolidones, J. Chem. Soc. *1952*, 850.
21. Fodor, G., Koczka, K., and Szekeres, L.: Configurational Correlation of Pharmacologically Active 1.2-Aminoalcohols. I. Conversion of N-Methyl-*dl*-Ephedrine into *dl*-Ephedrine and *Pseudo*-ephedrine, Acta Chim. Acad. Sci. Hung. *1*, 991 (1951).
22. Foltz, C. M., and Witkop, B.: The Stereochemistry of the 1-Phenyl-1,2-propanediol and of *α-Iso*-ephedrine, J. Am. Chem. Soc. *79*, 201 (1957).
23. Freudenberg, K., and Nikolai, F.: Die Konfiguration des Ephedrins, Liebigs Ann. Chem. *510*, 223 (1954).
24. Freudenberg, K., Schoeffel, E., and Braun, E.: Study on the Configuration of Ephedrine, J. Am. Chem. Soc. *54*, 234 (1932).
25. Hudson, C. S.: Historical Aspects of E. Fischer's Fundamental Conventions for Writing Stereoformulas in Plane. Advances in Carbohydrate Chemistry, Acad. Press. Inc., New York 1948, Vol. 2, pp. 1—21.
26. Hückel, W.: Der räumliche Bau von Ephedrin und Cocain, Deutsche Apoth. Ztg. *95*, 302 (1955).
27. Hückel, W.: Pharmazeutische Chemie. Organischer Teil, Enke Verlag, Stuttgart 1955, Vol. 2, pp. 317—318.
28. Jarowski, C., and Hartung, W. H.: Aminoalcohols XII. Optical Isomers in the Ephedrine Series of Compounds, J. Org. Chem. *8*, 564 (1943).
29a Koczka, K.: Az amino-alkoholok sztereospecifikus reakciói. Újabb eredmények a tercier nitrogén atom térkémiájában. (Stereospecific reactions of aminoalcohols. Recent developments in the stereochemistry of the tertiary nitrogen atom), Thesis for candidature, 1955.
b cf. Fodor, G.: Neuere Ergebnisse auf dem Gebiet der Stereochemie der Tropanalkaloide, Lecture in Zurich, February 28, and in Basel, March 2, 1954; Chimia *8*, 95 (1954).
c Koczka, K. and Fodor, G.: The Stereochemical Course of the Conversion of 2-Ureido Alcohols into Oxazolidones. II. Rearrangement of N-Thioureido-Alcohols; Acta chim. Acad. Sci. Hung. *13*, 89 (1958).
30. Latimer, W. M., and Rodebush, W. H.: Polarity and Ionization from the Standpoint of the Lewis Theory of Valence, J. Am. Chem. Soc. *42*, 1419 (1920); for aminoalcohols cf.: Huggins, M. L.: Hydrogen Bridges in Organic Compounds, J. Org. Chem. *1*, 407 (1936).
31. Leithe, W.: Die Konfiguration der Ephedrin-Basen, Ber. dtsch. chem. Ges. *65*, 660 (1932).
32. Mislow, K.: The Relative Configuration of (levo)-Mandelic Acid, J. Am. Chem. Soc. *73*, 3954 (1951).
33. Nagai, N.: Pharm. Ztg. *32*, 700 (1887).
34. Phillips, D. C.: Crystal and Molecular Structures of Ephedrine Hydrochloride, Acta Cryst. *7*, 159 (1954).
35. Преображенский, Н. А. — Денкин, Э. Н.: Химия Органических Лекарственных Веществ. Государст. научно-Техническое издательство, Москва (1953) 544—551 стр. cf.: Dunitz, J. D., and Leonhard, J. E.: X-ray Analysis of some Antibiotic Substances, J. Am. Chem. Soc. *72*, 4276 (1950).
36. Reti, L.: Ephedra Bases. Manske, R. F. H., and Holmes, H. L.: 'The Alkaloids', Acad. Press Inc., New York 1953, Vol. 3, p. 339—362.
37. Schmidt, E.: Über das Ephedrin und Pseudoephedrin, Arch. Pharmaz. *249*, 305—310 (1911).

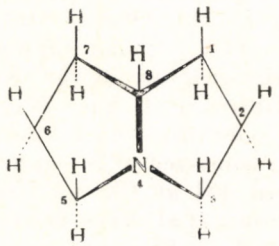
38. Шемякин, М. М. — Хохлов, А. С.: Химия Антибиотических Веществ. Государст. научно-техническое издательство. Москва (1953) 117—148 стр.
39. STUART, H. A.: Model Experiments on Fiber Molecules, Z. Elektrochem. *50*, 67 (1944).
40. TIPSON, R. S.: Presence of D-(levo)-2,3-Butanediol in the Mixed 2,3-Butanediols Produced by Normal Fermentation of Glucose with *Aerobacter aerogenes*, J. Am. Chem. Soc. *70*, 3610 (1948).
41. TURNER, R. B.: Organic Chemistry (Textbook), Longmans, Green and Co., London 1952, p. 811.
42. VELLUZ, L.: Substances naturelles de synthèse, Masson et Co., Paris 1951, Vol. 1. pp. 44—47.
43. WELSH, L. H.: The Constitution of Acetylephedrine and Acetyl-*pseudo*ephedrine, J. Am. Chem. Soc. *69*, 128 (1947).
44. WELSH, L. H.: Report on Ephedrine, J. Assoc. Offic. Agr. Chemists *31*, 528 (1948).
45. WELSH, L. H.: Mechanism and Stereochemical Course of Acyl Migration in Derivatives of Ephedrine and *Pseudo*-ephedrine, J. Am. Chem. Soc. *71*, 3500 (1949).
46. WELSH, L. H.: Letter to G. FODOR (June, 1950); (cf.: [45]).
47. WINSTEIN, S., BROWN, M., SCHREIBER, K. C., and SCHLESINGER, A. H.: Neighbouring Carbon and Hydrogen. IX. Neighbouring Phenyl in Benzyl-methylcarbinyl-*p*-toluenesulfonate, J. Am. Chem. Soc. *74*, 1140 (1952).
48. WITKOP, B., and FOLTZ, C. M.: Studies on the Stereochemistry of Ephedrine and *ψ*-Ephedrine, J. Am. Chem. Soc. *79*, 197 (1957).
49. WOLFROM, M. L., LEMIEUX, R. U., and OLIN, S. M.: Configurational Correlation of L-(levo)-Glyceraldehyde with Natural (dextro)-Alanine by a Direct Chemical Method, J. Am. Chem. Soc. *71*, 2870 (1949).

CHAPTER II

STEREOCHEMISTRY OF PYRROLIZIDINE ALKAMINES

OCCURRENCE

The basic ring system of this alkaloid group is the skeleton of pyrrolizidine, i.e., 1-mono*aza*[3.3.0]-octane (Fig. 36). In the naturally occurring representatives, one or more oxygen-containing functional groups, as well as a $C_{(1)}$ hydroxymethyl group are usually present. Esters with various mono- and dicarboxylic acids are wide-spread in nature. 1α-Methylpyrrolizidine is called heliotridane. Pyrrolizidine alkaloids are contained by certain genera of the plant families *Compositae*, *Boraginaceae*, and *Leguminosae*. In the family of *Compositae*, *Senecio* is the most important genus, comprising about one thousand species, all of them containing alkaloids of similar pyrrolizidine skeletons. This is the reason why natural esters of 1-hydroxymethyl-pyrrolizidine and its derivatives are often preferentially called '*Senecio*-alkaloids' [1, 5]. In the family of *Boraginaceae*, alkaloids of pyrrolizidine ring system are contained by the genera *Heliotridium*, *Trachelanthus*, and *Trichodesma*. Alkaloids of similar structure are found within the genus of *Crotalaria* of the family of *Leguminosae* [30].



pyrrolizidine
4-monoaza[3.3.0]octane

Fig. 36

ELUCIDATION OF THE CONSTITUTION

As it has been mentioned, the number of *Senecio* or pyrrolizidine alkaloids is very great, and ever increasing. Their isolation, and elucidation of the chemical constitution is discussed in detail, together with the analytical as well as synthetic aspects, by N. J. LEONARD [21a], in the monograph of MANSKE and HOLMES. Consequently, in the following part it will be dealt with stereochemical researches carried out since 1950 only, not reported in

that monograph, and with the stereochemical evaluation of earlier experimental results.*

The hydrolysis of all pyrrolizidine alkaloids results in the formation of two components: the alkamine part, known under the common name 'necine' and 'necinic acid', a mono- or dicarboxylic acid esterifying one or two hydroxyl groups of the alkamine.

Another limitation of the present review is that it can deal only with the stereochemistry of the alkamine component, i.e., with the heterocyclic nitrogen compound or compounds, as ascertainment of the steric structure of the corresponding carboxylic acids (by the synthetic and analytical methods of configurational correlations) falls beyond the scope of this work. Though the number of the alkaloids is high, only eight necines are known. Even among these, several bear the relationship of tertiary amine and amine oxide to one another; consequently, if the ring system is regarded, the number of primordial natural pyrrolizidine derivatives is even smaller. Necines known so far are the following: retronecine — which is the most common — and its N-oxide, isatinecine. The $C_{(7)}$ epimer of retronecine is heliotridine (Fig. 37). A desoxy compound is called trachelanthamidine which contains but one oxygen atom. Hastanecine and mikanecine (this latter is identical with platynecine) have the empirical formula of $C_8H_{15}NO_2$. The constitutions of hastanecine and otonecine have not been quite unequivocally elucidated yet. The structure of retronecine and platynecine are known for some time, but that of isatinecine was elucidated only recently [10]. Among the compounds containing three oxygen atoms, the structure of rosmarinecine became known recently; the compound is a hydroxy-platynecine. The structure of otonecine is, on the other hand, dubious, even the presence of a pyrrolizidine skeleton is uncertain [21]. In the field of isolating the *Senecio* alkaloids and ascertainment of their structure, an important part has been played by the Soviet school of alkaloid chemistry working in the ORDSHONIKIDSE Institute. Previously, OREKHOV and KONOVALOVA [19, 29] had supplied important data for the work of elucidating the steric structure of the necines which became known in those times; also MENSHIKOV et al. have been successful investigators of this field [24, 26]. The other scientific school which dealt with the same problem as their principal object, consisted of researchers forming a group around R. ADAMS and N. J. LEONARD [3] at Illinois University (USA). In Czecho-Slovakia, R. LUKEŠ and F. ŠORM et al. have been active workers of this field; the pupils of LUKEŠ published a fine and up-to-date monograph on the subject [11].

In connection with the analytical and synthetical progress of configurational research, also some earlier relating preparative results will be included here, because they may be of considerable assistance if stereochemical reactions and the work of determining the configuration are to be surveyed in their interdependence. Among the necines mentioned above, retronecine and heliotridine contain a double bond, which is comparatively readily saturated, e.g., by hydrogenating the material in the presence of Raney nickel catalyst [6, 28]. However, these unsaturated compounds can be subjected also

* In 1960 a new contribution by NELSON J. LEONARD [21b] in Vol. 6 of the work of MANSKE was published, where (on pages 56 and 62) he gave a detailed description and consideration *inter alia* of Hungarian results concerning the stereochemistry of pyrrolizidine alkamines.

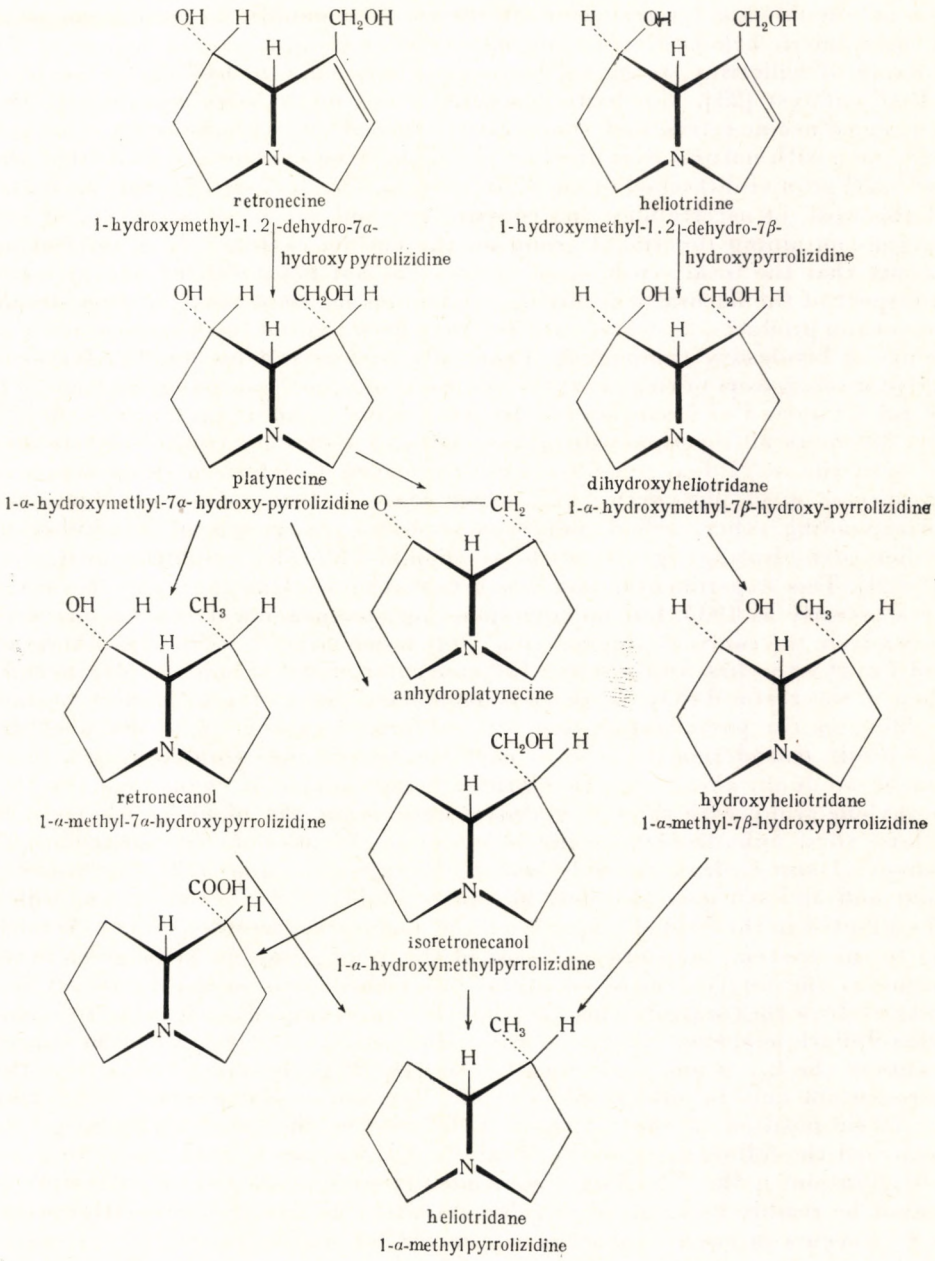

retronecine
1-hydroxymethyl-1.2-dehydro-7α-hydroxypyrrolizidine
heliotridine
1-hydroxymethyl-1.2-dehydro-7β-hydroxypyrrolizidine
platynecine
1-α-hydroxymethyl-7α-hydroxy-pyrrolizidine
dihydroxyheliotridane
1-α-hydroxymethyl-7β-hydroxy-pyrrolizidine
anhydroplatynecine
retronecanol
1-α-methyl-7α-hydroxypyrrolizidine
hydroxyheliotridane
1-α-methyl-7β-hydroxypyrrolizidine
isoretronecanol
1-α-hydroxymethylpyrrolizidine
heliotridane
1-α-methylpyrrolizidine

Fig. 37

to hydrogenolysis; in this case, with the loss of an oxygen atom and by saturation of a double bond, retronecine affords retronecanol [8]. Natural monoesters of the epimeric heliotridine become converted, e.g., in a way analogous to the reaction of heliotrine, to give 7-hydroxy-heliotridane on hydrogenation over a PtO_2 catalyst [23]. This hydrogenolysis, which occurs very readily with the mentioned necine esters, and among them especially so with the esters of necinic acid, i.e., with natural pyrrolizidine alkaloids, is an evidence to show that the hydroxyl group is attached to an allylic system. This fact significantly facilitated the work of ascertaining the constitution and the steric structure of the oxygen-containing functional group on the carbon skeleton. It is interesting to note that the total synthesis of necines has not been realized yet, at least, in respect of the naturally occurring compounds let alone some of their simple conversion products. Syntheses at first have been limited to the preparation of mono- or bis-desoxy compounds. Especially ADAMS and his pupils have been active investigators of this field; the synthesis of the stereoisomers of 1-methyl-pyrrolizidine and of 7-oxo-1-methyl-pyrrolizidine stand at their merits [3, 22]. Fig. 38 shows all reactions which have been of assistance to find correlations between the individual pyrrolizidine derivatives. Catalytic hydrogenation of retronecine gives platynecine [6], which may, in turn, be converted into the corresponding ether, called anhydroplatynecine by means of a number of various dehydrating agents, such as thionyl chloride, sulphuric acid, etc. [19, 29]. This experimental fact was established by OREKHOV and KONOVALOVA as early as 1935, but no corresponding stereochemical conclusions were drawn from the course of this reaction. Only much later, in 1950, were LEONARD and FELLEY the first to construct the molecular model of anhydroplatynecine. Then it was realized that the two five-membered rings of anhydroplatynecine, building up the pyrrolizidine ring system, formed an angle with one another; as a result, considering the relative configuration of anhydroplatynecine, there can be no doubt about the ether bridge being capable of connecting the $C_{(1)}$ methylene group with the $C_{(7)}$ hydroxyl only *below the plane of the ring*. It follows that anhydroplatynecine is undoubtedly one of the antipodes of anhydro-1-*anti*-hydroxymethyl-7-*anti*-hydroxypyrrolizidine [22]. The denotations *anti* and *syn* may also here be substituted by the α, β convention, which was adopted in the field of tropanes on the analogy of steroids [15, 16]. According to this system, the steric positions of the other groups must be given in relation to the tertiary nitrogen atom. From this steric model LEONARD and FELLEY draw the final inference [22] that the reagents used, such as thionyl chloride sulphuric acid etc., could in no way influence the steric position of the substituents of the $C_{(1)}$ atom, consequently the CH_2OH group must be far from the nitrogen not only in anhydroplatynecine, but also in platynecine. Concerning the steric position of the $C_{(7)}$ hydroxyl, however, the American investigators expressed the following opinion: "Nothing definite can be said concerning the configuration of the 7-hydroxyl as originally present in platynecine, since it cannot be readily ascertained whether retention or inversion of configuration at $C_{(7)}$ occurs in ether formation as effected by such a variety of reagents." At the same time they drew definite and final conclusions concerning the steric structure of some other natural pyrrolizidine derivatives and their conversion products, as follows: since platynecine can be converted into laevorotatory *iso*-retronecanol [2], i.e., into a modification of 1-hydroxymethylpyrrolizidine, by way of eliminating the $C_{(7)}$ hydroxyl group, the configuration of this compound is unequivocally given according to the above argumentation; conse-

quently, they regard the constitution, and the relative configuration, resp., of (—)-heliotridane, as the fundamental skeleton of platynecine to be also unambiguously determined [22].

Mention has been made above of trachelanthamidine, the only pyrrolizidine derivative containing a single oxygen. This compound is also a 1-hydroxymethyl-pyrrolizidine, however, it is not identical with the above-mentioned 1-*iso*-retronecanol and is not its mirror-image, either. It follows that trachelanthamidine can be but a mirror-image of 1-*syn*-hydroxymethylpyrrolizidine.

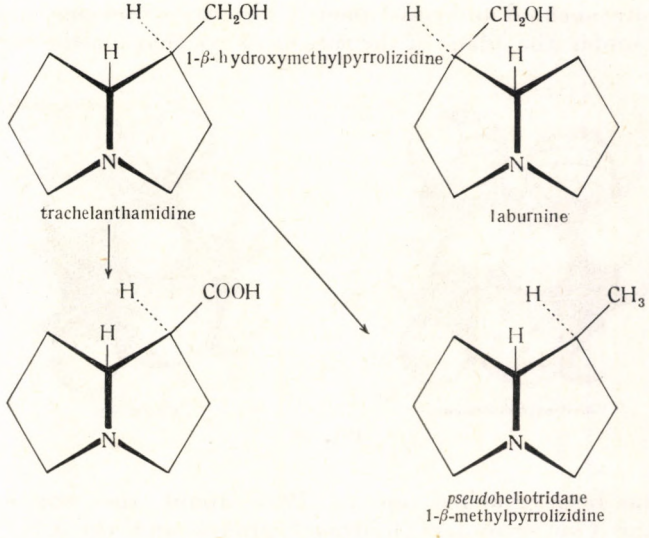
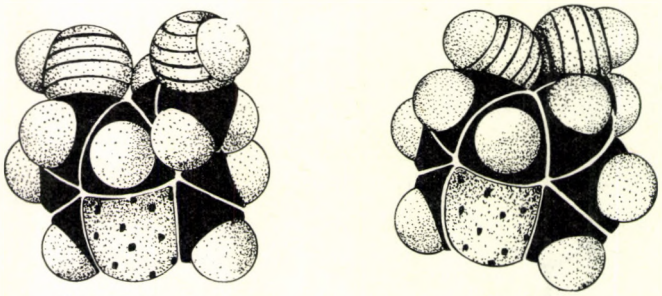


Fig. 38

Further, *pseudo*heliotridane, which represents the fundamental skeleton, can be nothing else except 1-*syn*-methylpyrrolizidine. Additional stereochemical achievements were that GALINOVSKY et al. isolated a pyrrolizidine alkamine called labournine [18] from *Cytisus laburnum*, the compound being identical in all its properties except the sense of optical rotation with trachelanthamidine which had been obtained by MENSHIKOV [25, 27]. Thus these two compounds are mirror images. Then again the two antipode pairs of 1-hydroxymethyl-pyrrolizidine were oxidized to give the four diastereomeric and enantiostereomeric pyrrolizidine-1-carboxylic acids and the correlation of the products with *iso*-retronecanol, lindelofidine, etc., was established through the work of ADAMS and HAMLIN [2a] as well as of MENSHIKOV et al. [20, 24]. All these results confirm the relative configurations shown in Figs 37 and 38.

The above reactions and their interpretation [22] give a rather clear-cut picture as regards the relative — let alone the absolute — configurations of the stereoisomeric modifications of 1-methyl- and 1-hydroxymethyl-pyrrolizidine (Fig. 37); however, they give no definite answer as to the configuration of the $C_{(7)}$ carbon atom of 7-hydroxypyrrolizidine derivatives most wide-spread in nature. In this respect it should be pointed out that heliotridine and retronecine are, in all probability, stereoisomers [21, 23]. Namely, satura-

tion of the double bond and reductive elimination of the oxygen-containing functional groups give the same fundamental compound, heliotridane, from both compounds [5, 26]. Elimination of the primary hydroxyl group by known methods and simultaneous saturation of the double bond resulted as shown by MENSHIKOV [23] and later by CULVENOR [9] in the formation of 1-methyl-7-hydroxypyrrolizidine, called 'oxyheliotridane'. This compound is the diastereoisomer of retronecanol (which latter can be obtained through the hydrogenolysis and hydrogenation of retronecine), however, the two compounds are not mirror images. Thus, these substances are necessarily the $C_{(7)}$ epimers of each other. Still, it remained undecided for a long period whether the $C_{(7)}$ hydroxyl in retronecanol and consequently also in retronecine and platynecine was situated under the plane of the ring or above that, on the 'top'. Similarly,



dihydroxyheliotridane platynecine

Fig. 39

no decision has been reached up to 1954 about the *syn* or *anti* steric positons of the two secondary hydroxyl groups and the CH_2OH group of rosmarinecine. The interpretation of the formation of anhydroplatynecine from platynecine permitted a deductive solution of this problem of configuration, whereas further researches relating to the configuration, partly by known and partly by new methods, made possible the complete elucidation of the relative configurations of these asymmetric compounds. In November, 1954, this author was the first to deduce the constitution of platynecine as 1-*anti*-hydroxymethyl-7-*anti*-hydroxypyrrolizidine [12], based on the fact of anhydroplatynecine formation and molecular scale models (Fig. 39.) The ring closure with the formation of the latter compound was interpreted by assuming that thionyl chloride as well as other electrophilic reagents attacked first the primary hydroxyl group, as a result of partly steric, partly electronic effects. This hydroxyl group is namely farther away from the electron-attracting nitrogen, thus its oxygen atom is more nucleophilic; on the other hand, it is sterically less shaded than the $C_{(7)}$ hydroxyl group which is to be found presumably under the plane of the ring. Another argument of the deduction was the fact, observed in connection with 2β-hydroxymethyltropane-3β-ol, that heating of the hydrochloride of this compound with thionyl chloride resulted in the selective substitution of the primary hydroxyl group by chlorine, and then the chloromethyl base underwent a spontaneous intramolecular ring closure to give the hydrochloride of a four-membered-ring ether [14]. Since the mechanism of this reaction was precisely elucidated [13], FODOR assigned a similar path to the formation of anhydro-

platynecine, too. On the other hand, if the chlorinated product of platynecine, isolated in impure state by KONOVALOVA and OREKHOV, suffered only ether ring closure when acted upon by sodium and amyl alcohol, i.e., under the action of a basic reagent [19] (the original purpose of the experiment was reductive dehalogenation), it is justified to assume that the primary product of chlorination had been 1-chloromethyl-7-*anti*-hydroxypyrrolizidine. This compound

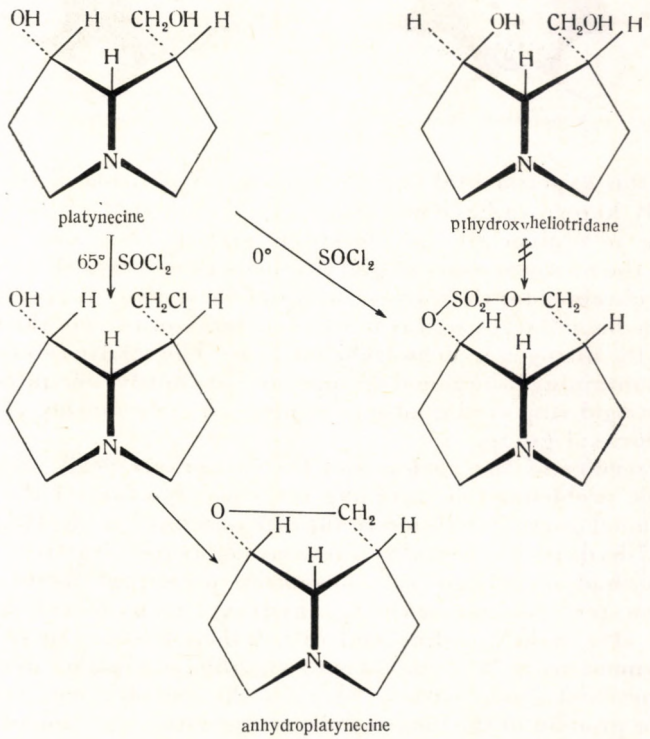
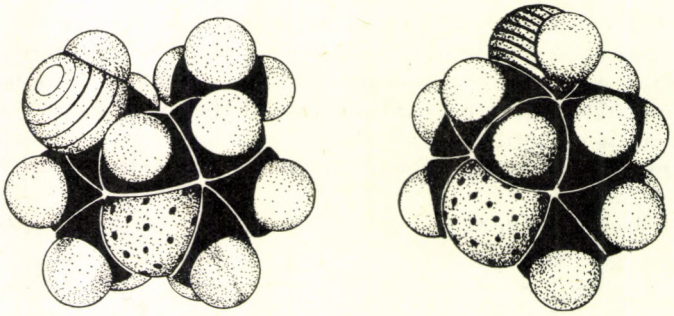


Fig. 40

could readily split off hydrochloric acid in alkaline medium, but presumably spontaneously as well ouring to its own basicity, to give anhydroplatynecine (Fig. 40). On this basis, the constitution of 1-*anti(α)*-hydroxymethyl-7-*anti(α)*-hydroxypyrrolizidine was suggested for platynecine. Consequently the $C_{(7)}$ epimeric dihydroheliotridine [28] should be regarded as 1-*anti(α)*-hydroxymethyl-7-*syn(β)*-hydroxypyrrolizidine. The same holds true for the relationship of the corresponding *dehydro* compounds, i.e., retronecine and heliotridine. Obviously, retronecanol and oxyheliotridane are also $C_{(7)}$ epimers (Fig. 41). This deduction represented a definite standpoint against the presented views of LEONARD and FELLEY [22a]. The prospect of an experimental solution of the problem was also held out by the author, but was realized sooner by ADAMS and VAN DUUREN [7a]. Both studies unequivocally confirmed the correctness of the above discussed working hypothesis. ADAMS and VAN DUUREN found that in concentrations as given by OREKHOV and KONOVALOVA, thionyl chloride and platynecine gave in the cold first a crystalline cyclic sulphite (see Fig. 5), while dihydroxyheliotridane was unable to give a similar cyclic



hydroxyheliotridane retronecanol

Fig. 41

product. By this experimental fact the mutual *cis*-position of the $C_{(1)}$ CH_2OH group (already known to have *anti*-configuration) to that of the $C_{(7)}$ hydroxyl group became unequivocally and definitely stated. Their *anti* steric position in relation to the nitrogen atom of platynecine was determined as well. Indirect evidence was obtained for the *trans*-position of these two groups in heliotridine and hydroxyheliotridine, as well as for the *syn*-configuration of the $C_{(7)}$ hydroxyl in relation to the nitrogen in dehydroheliotridine. The relative steric positions of the oxygen-containing functional groups are obviously unequivocally determined in this rigid ring system also as regards the relationship of the nitrogen atom and hydroxyl group.

Recent studies of the author and his co-workers dealt with the indirect solution of the problem of determining the steric position of the oxygen-containing functional group in relation to the nitrogen atom in the two $C_{(7)}$-epimers of 1-methyl-7-hydroxypyrrolizidine, retronecanol and 7-hydroxyheliotridane [17]. The method of lactone salt formation permitted further decision as regards the *syn* steric position of the $C_{(7)}$ hydroxyl in hydroxyheliotridane and consequently also in heliotridine and dihydroheliotridine; these experiments were in agreement with the behaviour of all tropane alkaloid derivatives containing a functional group with oxygen on the endoethylene bridge. At the same time, the product of the mentioned quaternization reaction of retronecanol

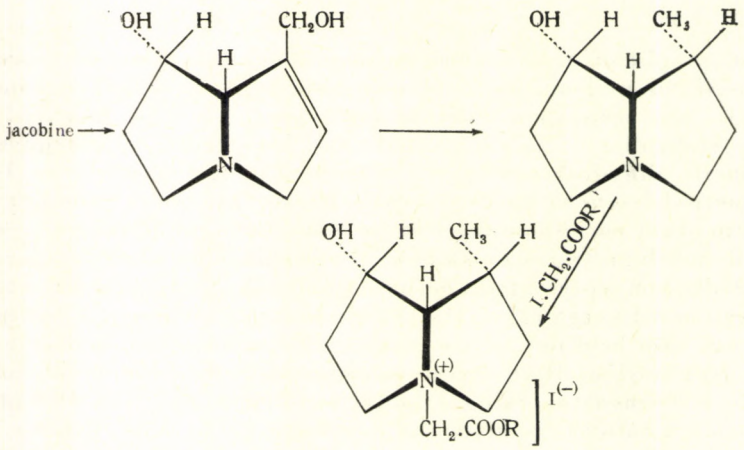


Fig. 42

gave further information concerning the *anti*-configuration of the $C_{(7)}$ hydroxyl group of retronecine and platynecine. In this way the steric structure of the most important necines were elucidated.

Use of the method of lactone salt formation for the epimeric pair of retronecanol and hydroxyheliotridane gave only negative evidences at first [16], since experiments in the Institute of the Szeged University showed that neither the ester salt prepared from retronecanol and ethyl iodoacetate, nor the betaine or N-acetic acid obtained from it, were capable to give a lactone salt by transesterification or direct esterification (Fig. 42).

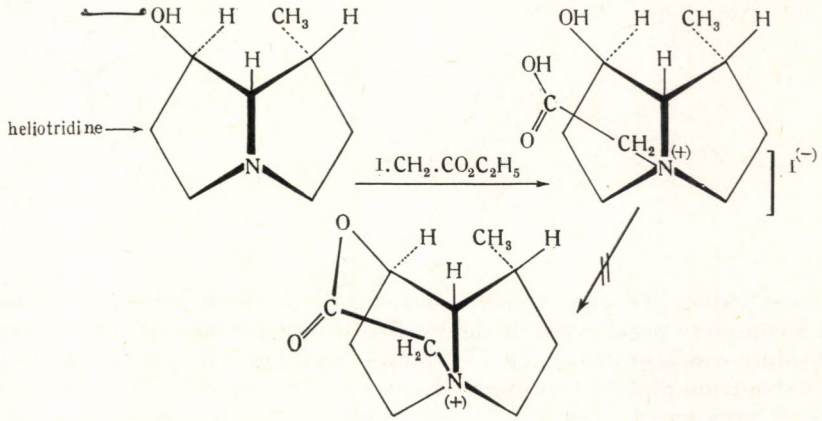


Fig. 43

However, in the case of hydroxyheliotridane, ring formation took place extremely difficultly and afforded a mixture (Fig. 43). That was the reason why FODOR et al. [17] chose later the reversed way of ring closure, i.e. esterification of the hydrobromide of the 7-epimeric aminoalcohols with bromoacetyl bromide, and then subjecting the O-bromoacetyl-retronecanol as well as the epimeric O-bromoacetyl-hydroxyheliotridane to an intramolecular quaternization. When the principle of high dilution and potassium acetate as a reagent were employed, the desired lactone was formed from the hydroxyheliotridane derivative, which was a positive evidence to show that the hydroxyl group of this molecule assumed *syn* (β) steric position in relation to the nitrogen atom (Fig. 44). This experimental result is in complete agreement with former deductive conclusions, and also with the statement of the configuration by ADAMS and VAN DUUREN on the basis of the experimental observations of sulphite ester formation.*

In this way, the relative configurations of the most important pyrrolizidine alkamines have been determined. A study of the absolute configuration of necines was reported recently by LEONARD [22b] (Fig. 46). The optical rotatory power of natural (—)-lupinine was compared with that of (—)-1-hydroxymethylpyrrolizidine; most natural *Senecio* alkaloids can be derived from the latter compound. The influence of esterification with organic and inorganic acids on the

* Suprisingly, O-bromoacetyl-retronecanol hydrobromide gave a lactone salt, too. In this case, however ring inversion took place, cf. Lecture by G. FODOR at the IUPAC Symposiom in Prague, August 1962.

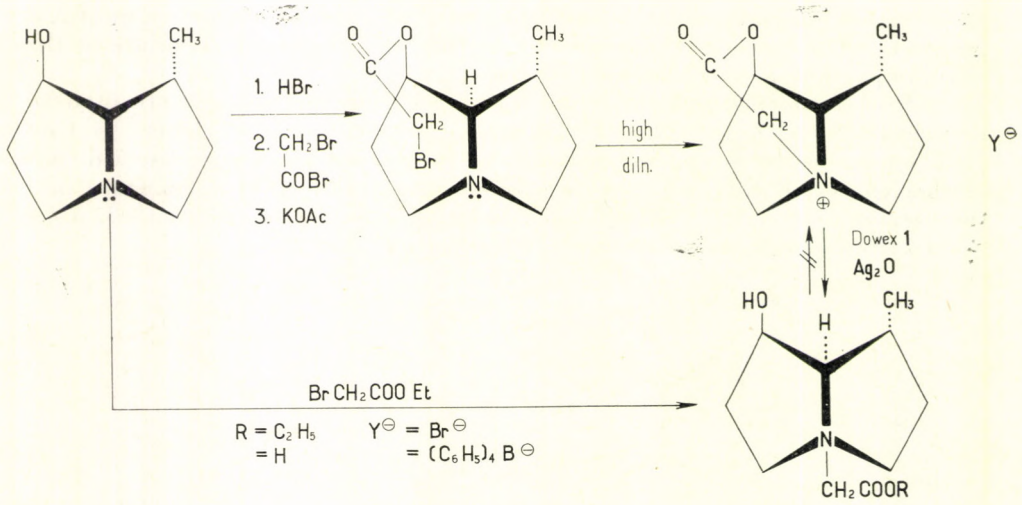


Fig. 44

rotational values was determined in the case of both methylol compounds. From a complete parallelism of the results of measurement it was inferred that the absolute configurations of (—)-lupinine and 1-hydroxymethylpyrrolizidine (obtainable from platynecine) were the same (Fig. 45). Since lupinine had been degraded previously to give (—)-4-methylnonane, and as a consequence of this correlation the absolute configuration of lupinine on $C_{(1)}$ can be taken for granted, one should not regard the mirror-images of the formerly arbitrarily chosen projection formulas of necines as the true representations of their absolute configurations.

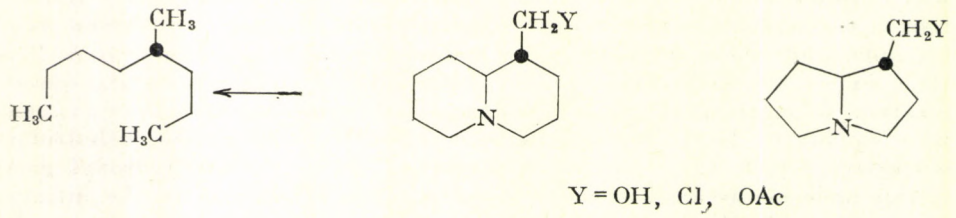


Fig. 45

Naturally, this evidence could gain final acceptance only after having found a direct chemical correlation between a natural necine and some other compound of known absolute configuration.

The absolute configuration of the $C_{(1)}$ atom of necines was determined by ADAMS and FLEŠ [7b] in retronecanone, and in 7-oxo-1-methylheliotridane; the latter compound is a dehydrogenation product of retronecanol, i.e., 1-deoxy-platynecine.

The stereospecific synthesis of retronecanone starts with (—)-β-methyl-δ-aminovaleric acid which is brominated in the α-position, then converted by intramolecular condensation into (—)-3-methylpyrrolidine carboxylic acid. Addition of ethyl acrylate, Dieckmann condensation, hydrolysis and decarb-

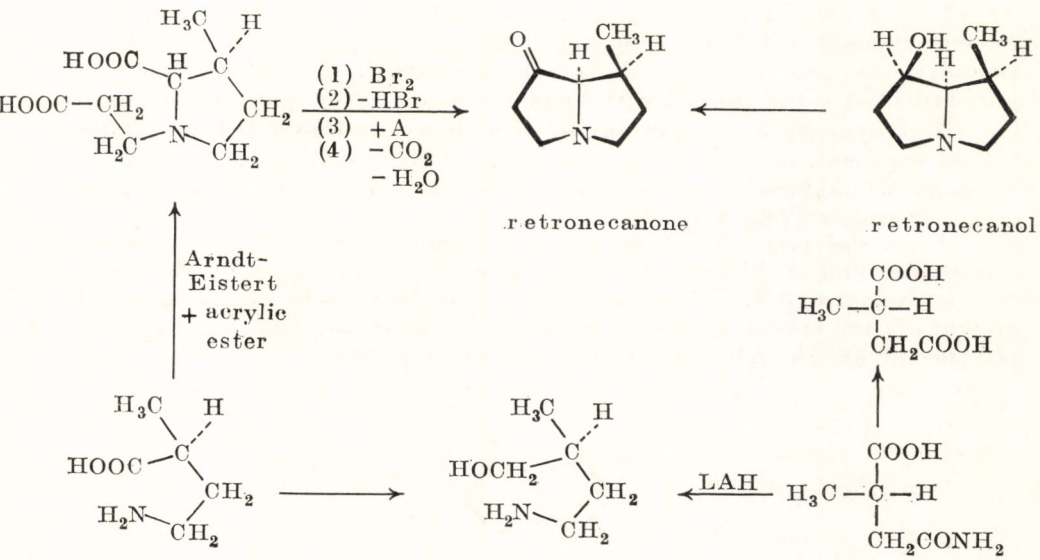


Fig. 46

oxylation yielded natural (—)-retronecanone. Since (—)-β-methyl-δ-aminovaleric acid can be synthesized from (+)-α-methyl-γ-aminobutyric acid by Arndt—Eistert's method, and since the antipodes of the latter compound may be prepared by the $LiAlH_4$ reduction of (—)-α-methylsuccinic-β-semiamide, the absolute configuration of the $C_{(1)}$ carbon atom of retronecanone which bears the methyl group is certain (Fig. 46). The next missing point was the absolute configuration of the $C_{(8)}$ hydrogen atom. This work was done by ADAMS and

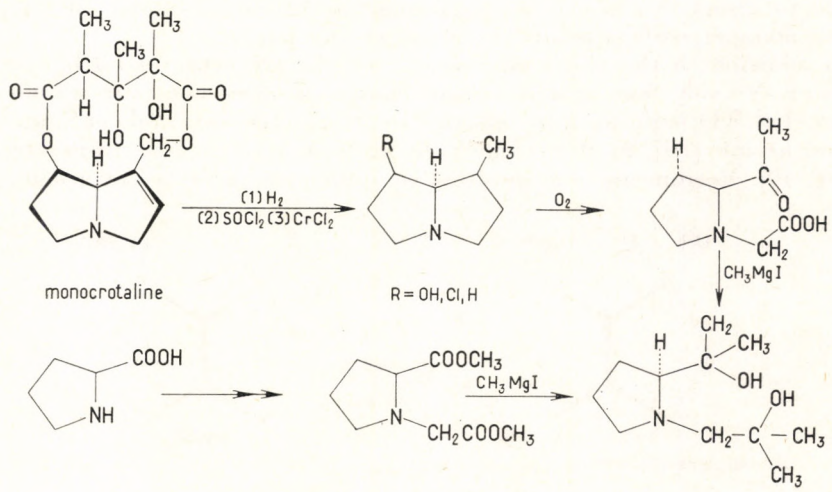
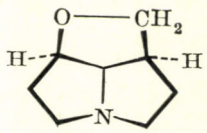


Fig. 47

FLEŠ [7c] in 1959. 1-Methyl-$\Delta_{1,2}$-dehydropyrrolizidine was obtained from the *Senecio* alkaloid called monocrotaline, and this compound was degraded by ozonolysis to give (—)-N-methoxycarbonylmethyl-2-acetylpyrrolidine. Grignard reaction of the product with 3 moles of methylmagnesium iodide afforded (—)-N-(2-hydroxy-2-methylpropyl)-2-(1-hydroxy-1-methylethyl)-pyrrolidine, which was identical with the product of the Grignard reaction of L-(—)-N-methoxycarbonylproline methyl ester, prepared, in turn, from the methyl ester of L-(—)-proline (Fig. 47).

From this fact follows the *R* configuration of the $C_{(8)}$ carbon atom in retronecine and in all related *Senecio* alkamines. Consequently, the projection formulas of pyrrolizidine alkamines published in literature up to the present are the mirror-images of the natural compounds. Thus, e.g., anhydroplatynecine has the following steric structure (Fig. 49).



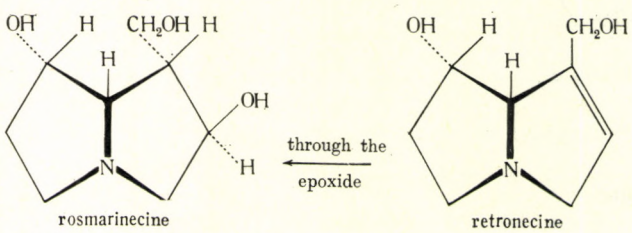
anhydoplatynecine

Fig. 48

One may use the convention of planar projection as suggested by ADAMS and FLEŠ; according to its principle the

bond must be thought laid in the plane of the paper with the two planes of the rings standing out in front. Unfortunately, this way of representation may lead to errors, because it was customary in literature so far to imagine both five-membered rings below the plane of the paper.

In addition to the above investigations, the structure of isatinecine as retronecine N-oxide was stated in the course of researches carried out by WARREN et al. The same authors reported the steric structure and configuration of rosmarinecine [10], as it became evident from its synthesis from retronecine (Fig. 49). Retronecine was oxidized by perbenzoic acid to isatinecine, fol-



rosmarinecine

1-α-hydroxymethyl-2β 7α-dihydroxy-pyrrolizidine

retronecine

Fig. 49

lowed by a separate step of oxidation on the $C_1—C_2$ double bond to epoxy-isatinecine. Selective reductive elimination of the oxygen attached to the nitrogen by means of zinc dust or by hydrogen activated with Adams Pt-catalyst, afforded epoxy retronecine. The latter product was hydrogenated over Raney nickel catalyst to rosmarinecine (Fig. 50). This experiment proves as a first step

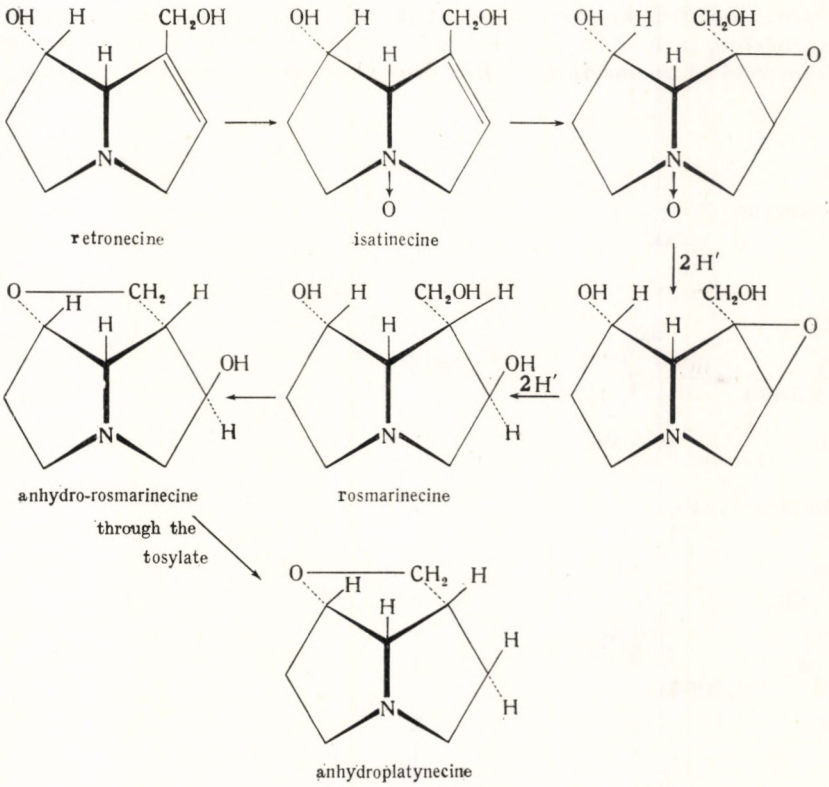


Fig. 50

only the identical steric positions of the $C_{(7)}$ hydroxyl groups in retronecine and in rosmarinecine; their *anti*-configuration can now definitely be stated today on the basis of the investigations of Adams [7] and Fodor [12, 16]. A further step was the dehydration of rosmarinecine to anhydrorosmarinecine in the

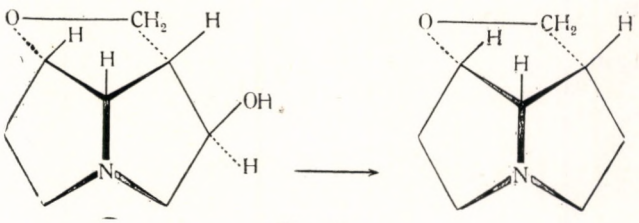


Fig. 51

same way as it had been done with platynecine. The hydroxyl group which had remained still free, was eliminated from the product by means of chlorination and subsequent reductive dehalogenation. The final product was anhydroplatynecine (Fig. 51). The following inferences may be drawn from this result: (i) The functional groups of rosmarinecine and platynecine are at $C_{(1)}$ and $C_{(7)}$ in identical steric positions. (ii) The $C_{(3)}$ hydroxyl which remained unbound has the opposite steric position to that of the CH_2OH group attached to $C_{(1)}$. Now, since it is known that the CH_2OH group has $C_{(1)}$ *anti* steric position in platynecine, in hydroxyheliotridane and in retronecanol, it follows that the $C_{(3)}$ hydroxyl of rosmarinecine has *syn*(β) steric position in relation to the

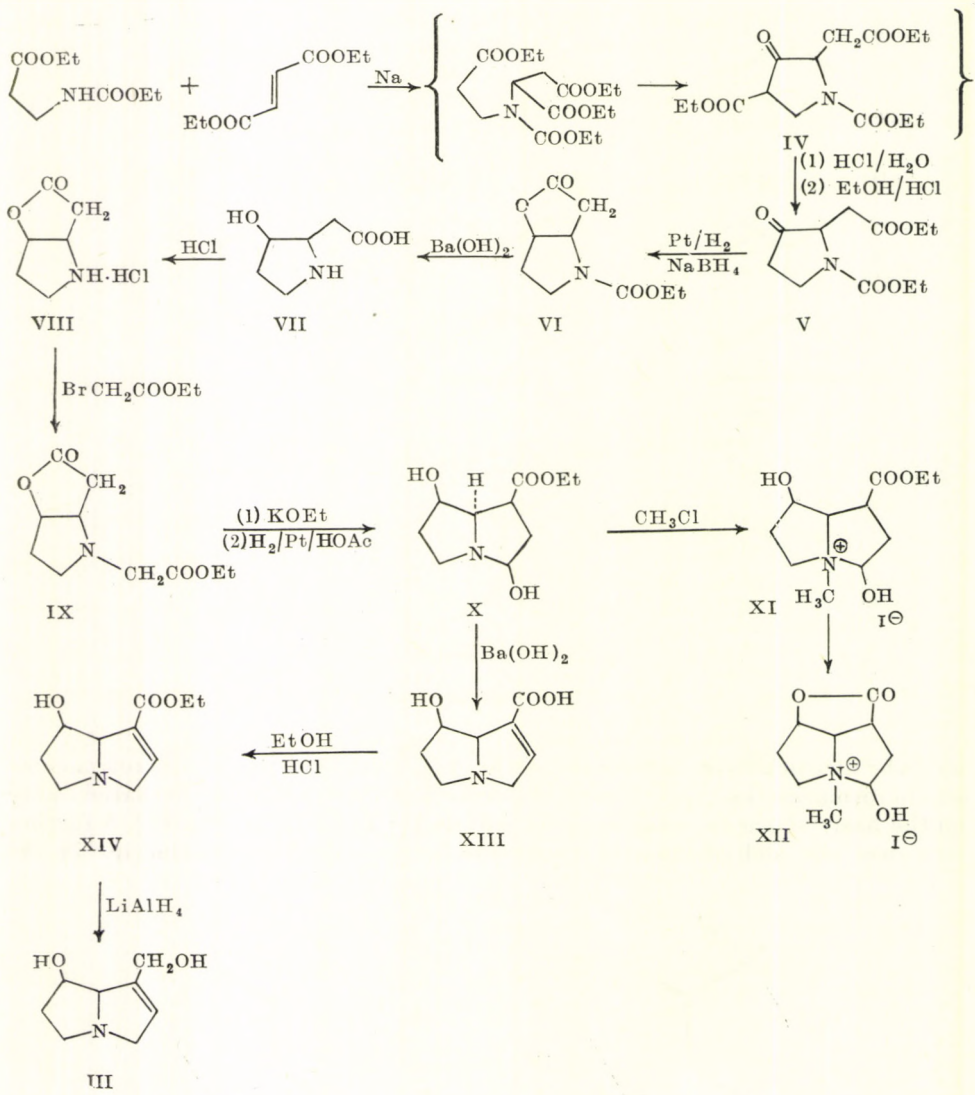


Fig. 52

nitrogen atom. The *syn (β)* steric position of the $C_{(3)}$ hydroxyl group standing out in front of the plane is unequivocally concluded from the stereochemical course of the hydrogenolysis (Fig. 50). Experiments have been begun, as a co-operation of FODOR and the Institute of Pietermaritzburg with the purpose of the direct determination of the relative relationship between the $C_{(3)}$ hydroxyl group and the nitrogen atom in rosmarinecine and anhydrorosmarinecine, respectively. The task is to attempt lactone salt formation from the anhydro derivative by means of ethyl iodoacetate; in this way the configurations stated by the methods of stereospecific synthesis and by configurational correlation could be confirmed also by direct experimental evidence.

The elucidation of the configurations of hastanecine and otonecine still await further investigations. This problem is presumably tackled simultaneously in several scientific institutes in Europe as well as overseas.

In January 1962 T. E. GEISSMAN and A. C. WAISS* reported on a total synthesis of (+)-retronecine as envisaged in the flow-sheet above (Fig. 52).

It is worth noticing that pyrrolizidines lacking the 7-hydroxy group, *inter alia iso*-retronecanol, trachelanthamidine and labournine, have been synthesized by KOCHETKOV et al.** and by BABOR et al.,*** respectively.

REFERENCES

1. ADAMS, R., and GIANTURCO, M.: Neues aus der Chemie der Pyrrolizidin Alkaloide, Angew. Chem. *69*, 5 (1957).
2a ADAMS, R., and HAMLIN, K. E.: Structure of Monocrotaline. VIII. Proof of Primary and Secondary Hydroxyl Groups in Retronecine. J. Am. Chem. Soc. *64*, 2597 (1942).
b ADAMS, R.: Über die Chemie der *Senecio* Alkaloide und verwandter Verbindungen. Angew. Chem. *65*, 433 (1953).
3. ADAMS, R., and LEONARD, N. J.: Structure of Monocrotaline. XI. Proof of the Structure of Retronecine. J. Am. Chem. Soc. *66*, 257 (1944).
4. ADAMS, R., and ROGERS, E. F.: The Structure of Monocrotaline, the Alkaloid in *Crotalaria Spectabilis* and *Crotalaria Retusa*. J. Am. Chem. Soc. *61*, 2815 (1939).
5. ADAMS, R., and ROGERS, E. F.: Structure of Monocrotaline. V. Retronecine, a Derivative of 1-Methylpyrrolizidine. J. Am. Chem. Soc. *63*, 228 (1941).
6. ADAMS, R., and ROGERS, E. F.: Structure of Monocrotaline. VI. The Structure of Retronecine, Platynecine and Retronecanol. J. Am. Chem. Soc. *63*, 537 (1941).
7a ADAMS, R. and VAN DUUREN, L.: Stereochemistry of the Pyrrolizidine Bases. J. Am. Chem. Soc. *76*, 6379 (1954).
b ADAMS, R. and FLEŠ, D.: The Absolute Configuration of the $C_{(1)}$-Atom in Retronecanone. J. Am. Chem. Soc. *81*, 4946 (1959).
c ADAMS, R. and FLEŠ, D.: The Absolute Configuration of the $C_{(8)}$-Atom in the Pyrrolizidine Moieties of the *Senecio* Alkaloids. J. Am. Chem. Soc. *81*, 5803 (1959).
8. BARGER, G., SESHADRI, T. R., WATT, H. E. and YABUTA, T.: Alkaloids of *Senecio*. I. Retrosine, J. Chem. Soc. (London) *1935*, 11.
9. CULVENOR, C. C. J., DRUMMOND, L. J. and PRICE, J. R.: The Alkaloids of *Heliotropium Europaeum* L. I. Australian J. Chem. *7*, 277 (1954).
10. DRY, L. J., KOEKEMOER, M. J. and WARREN, F. L.: *Senecio* Alkaloids. X. The Structure of Rosmarinecine and its Synthesis from Retronecine. J. Chem. Soc. *1955*, 59.
11. FERLES, M. and BLÁHA, K.: Alkaloidy s jádrem pyrrolizidinevym. Malé monográfie. Chemicke Listy *2*, 43 (1954).
12. FODOR, G.: Stereochemistry of Pyrrolizidine Alkaloids. Chem. and Ind. *1954*, 1424.

* J. Org. Chem. *28*, 139 (1963).
** Tetrahedron Letters, *3*, 92 (1961).
*** Chemicke Zvesti *13*, 163 (1959).

13. Fodor, G. et al. : Neuere Ergebnisse in der Stereochemie der Tropanalkaloide. Lecture at the Congress of the Chem. Ges. d. DDR in Leipzig, October 23, 1954, Tagungsberichte der DDR *1954*, pp. 137–157; cf. Kovács, Ö., Weisz, I., Zoller, P. and Fodor, G.: Über die Struktur des Vierringäthers aus Cocain 7. Mitteil. Über Stereochemie der Tropanalkaloide, Helv. Chim. Acta, *39*, 99 (1956).
14. Fodor, G., Kovács, Ö. and Weisz, I.: The Stereochemistry of Cocaine. Nature, *174*, 131 (1954); Kovács, Ö., Fodor, G. and Weisz, I.: Konfigurationsbeweis des Cocains, 4. Mitteil. Über Stereochemie der Tropanalkaloide. Helv. Chim. Acta *37*, 892 (1954).
15. Fodor, G. and Nádor, K.: Stereochemistry of the Tropane Alkaloids I. The Configurations of Tropine and *pseudo*-Tropine. J. Chem. Soc. *1953*, 721.
16. Fodor, G., Sallay, I. and Dutka, F.: The Configuration of Retronecine and of Related Compounds. (Stereochemistry of Pyrrolizidine Alkaloids. Part II.) Acta Phys. et Chem. Szeged, II: 30 (1956).
17. Fodor, G., Uresch, F., Dutka, F. and Széll, T.: Lactonization and Ring Inversion in the Pyrrolizidine Series. Collections 1963, in the press.
18. Galinovsky, F., Goldberger, H. and Pöhm, M.: Über das Laburnin, ein Alkaloid aus *Cytisus laburnum*. Monatsch. *80*, 550 (1949).
19. Konovalova, R. and Orekhov, A.: Über *Senecio* Alkaloide III. Mitteil. Abbau des Platynecins zum Heliotridan. Ber. dtsch. chem. Ges. *69*, 1908 (1936).
20. Лабенский А. С. — Серова, А. Н. — Меньшиков, Г. Л.: О стереоизомерных превращениах в рябу гелиотридана. Док. А. Н. *88*, 467 (1953).
21a Leonard, N. J.: *Senecio* Alkaloids, Manske, R. H. F. and Holmes, H. L.: 'The Alkaloids'. Acad. Press Inc., New York, 1951, Vol. I, pp. 107—164.
b Leonard, N. J.: *Senecio* Alkaloids, Manske, R. H. F.: 'The Alkaloids'. Acad. Press Inc., New York, 1960. Vol. 6, pp. 37—122.
22a Leonard, N. J. and Felley, D. L.: The Synthesis of Pyrrolizidines. VI. Stereochemical Correlation of 1-Methyl and 1-Hydroxymethyl-pyrrolizidine Isomers with Certain Alkaloid Products. J. Am. Chem. Soc. *72*, 2537 (1950).
b Leonard, N. J.: Absolute Configurations of the Necines, Chem. & Ind., *1957*, 1455.
23. Menschikov, G.: Über die Alkaloide von *Heliotropium lasiocarpum*. III. Mitteil. Über Oxy-heliotridan. Ber. dtsch. chem. Ges. *68*, 1051 (1935).
24. Меньшиков, Г. Л: Итоги равот советских исслебователей в области алкалоидов ряда 1-метилпирролизидина. Усп. Хим. *22*, 1153 (1953).
25. Меньшиков, Г.П.: Алкадоиды Trachelantus III. Строение трахелантамидына полученный при гидролиза трахеланталина. Ж. О. Х. *16*, 1311 (1946).
26. Menschikov, G.: Über die Alkaloide von *Heliotropium lasiocarpum*. II. Mitteil. Abbau des Heliotridins zum Heliotridan. Ber. dtsch. chem. Ges. *66*, 875 (1935).
27. Меньшиков. Г. П.—Бородина, Г.М.: Алкалоиды Trachelanthus Korolkovi. Ж. О. Х. *11*, 209 (1941).
28. Меньшиков, Г. П.—Кизов, А. Д. Исследование алкалоидов Heliotropium Lasiocarpium. Строение гелиотропиа. Ж. О. Х. *19*, 1702 (1949).
29. Orekhov, A. and Konovalova, R.: Über *Senecio* Alkaloide II. Mitteil. Zur Kenntnis des Platyphyllins. Ber. dtsch. chem. Ges. *68*, 1886 (1935).
30. Trautner, E. M. and Neufeld, O. E.: The Alkaloids of *Heliotropium europaeum* Growing in Australia. Australian J. Sci. *11*, 211 (1949).

CHAPTER III

STEREOCHEMISTRY OF GRANATOLINE ALKALOIDS

Ascertainment of the chemical constitution of ψ-pelletierine, the alkaloid of *Punica granatum* L. is described with proper fulness of details in the mentioned work of MANSKE and HOLMES, in the chapters about pyridine alkaloids by LEO MARION [22a]. However, the steric structures of the reduction products of ψ-pelletierine, i.e., of granatoline and ψ-granatoline have not been known until now. ALDER et al. succeded in 1953 to render glutaric dialdehyde a readily accessible compound by the reaction of acroleine with vinyl ethyl ether [1, 2; cf. 21, 25]; this compound was necessary as starting material for the synthesis of ψ-pelletierine, and afforded possibilities also for the study of the stereochemical course of the reduction of the alkaloid [1]. WILLSTÄTTER [29] and PICCININI [24] were the first to call attention to the close relationship between tropinone and ψ-pelletierine. As it is known, the 'chemical' reductions with sodium and alcohol or with sodium amalgam usually do not take a uniform course from the stereochemical point of view, and do not give a homogeneous product. Tropinone, e.g., reacted, according to WILLSTÄTTER, with sodium in alcohol as well as with sodium amalgam to give impure ψ-tropine [28]. Electrolytic reduction [4], or reduction of the ketone group with hydriodic acid [30] and with zinc, as well as the catalytic hydrogenation [18] with platinum, palladium or Raney nickel gave, however, tropine as the main product. The Indian investigator, MIRZA studied a few years ago the reduction of tropinone with lithium aluminium hydride [23] and reported that in this case quantitatively ψ-tropine was formed, independently of the concentration and temperature. This statement was based on the melting point measurement of the picrate of the end product only. Former colleagues of the author found [20], on the other hand, that this reduction process was far from following a homogeneous stereochemical course. Independently of the temperature, 50 % *syn*(β)- and 50 % *anti*(α)-3-tropanol could be obtained. This experience confirmed the statement of ALDER according to which endocyclic ketones of flexible molecule structure cannot be completely uniformly reduced by so-called chemical methods. The Hungarian investigators [20] carried out later the reduction of tropinone at various temperatures according to MEERWEIN—PONNDORF's method. Recently a detailed study was carried out by BECKETT, HARPER et al.* concerning the steric course of the reduction of tropinone by means of various metal hydrides. It was found that depending upon the temperature, a mixture of the two epimers was formed, but at higher temperatures mostly ψ-tropine could be obtained. Part of the chemical reactions discussed here were interpreted by ALDER [1] by assuming

* Chem. and Ind. *1957*, 663.

the *anti*(*endo*)-configuration of tropine [12]; consequently the formation of an alcohol with *anti*-configuration from the corresponding ketone is, as an *exo*-addition [3] in agreement with the stereochemical course of the catalytic hydrogenation of *nor*-camphor [19] and related bicyclic olefins [Fig. 53]. Perfectly similar conditions were found in the case of the reduction of ψ-pelletierine [1] which gave N-methylgranatoline on treatment with sodium and alcohol, and with sodium amalgam, respectively [5]. At the same time, catalytic hydrogenation [1] as well as reduction with hydriodic acid and zinc [27] resulted in the formation of N-methyl-ψ-granatoline as the main product. Electrolytic reduction gave a mixture [31]. On this basis ALDER and DORTMANN assumed that N-methylgranatoline was the *anti*, i.e., the *endo* form, while

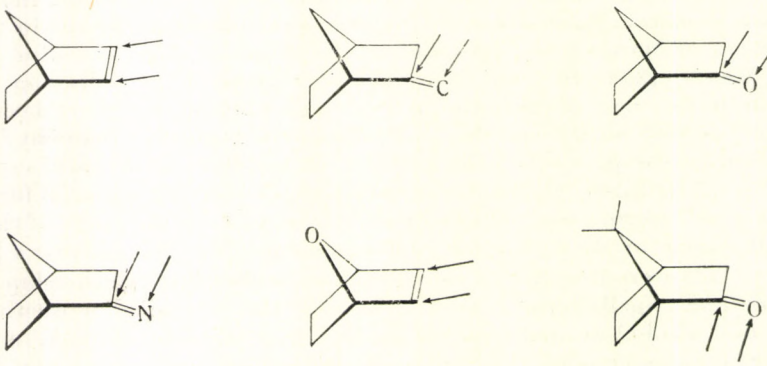


Fig. 53

N-methyl-ψ-granatoline the *syn*, thus the *exo*-modification. In the opinion of these authors, this is a general phenomenon, nearly independent from the character of the members of the ring as well as from the strain distance of the peripheral ring. Naturally, it should be taken into consideration that in the case of ψ-pelletierine, the N-methyl group does not behave identically with the isopropylidene bridge to be found in camphor derivatives. Besides the fact that the steric hindrance due to the methyl group cannot attain the same extent (as a consequence of the 7-membered peripheral carbocycle) in tropinone as in camphor, it is also to be considered that the methyl group on the ring nitrogen atom may swing over into a steric position distant from the ketone group. The problem of this overturn has been treated in detail in connection with the tropane alkaloids [6, 7, 8, 9, 14].

In order to confirm these deductions, ALDER et al. employed the method of acyl migration [cf. 6—13] (Fig. 54). N-methylgranatoline and ψ-granatoline were oxidized by alkaline potassium permanganate [5] to the corresponding *nor* compounds. These were acylated on the nitrogen atom by acetic anhydride or with benzoyl chloride, then stereospecific N→O acyl migration was attempted. In case of the ψ-granatoline both acetyl and benzoyl migration could be equally well realized in a reversible way, while no migration took place either from nitrogen to oxygen nor in the reverse direction with acyl granatolines. Comparison of these experimental facts with the infrared spectra of the isomeric N-methylgranatolines showed granatoline to be an α, *anti* and ψ-grana-

toline a β, *syn*-modification [1]. Besides, the condensation experiment with *p*-nitrobenzaldehyde [15, 17] gave also in the case of ψ-granatoline a cyclic tetrahydro-*meta*-oxazine derivative. The consequences of these experimental facts indicate in unison the analogous configuration of ψ-granatoline and ψ-tropine. Thus granatoline is rightly called as granatane-3α-ol, and ψ-granatoline as granatane-3β-ol.

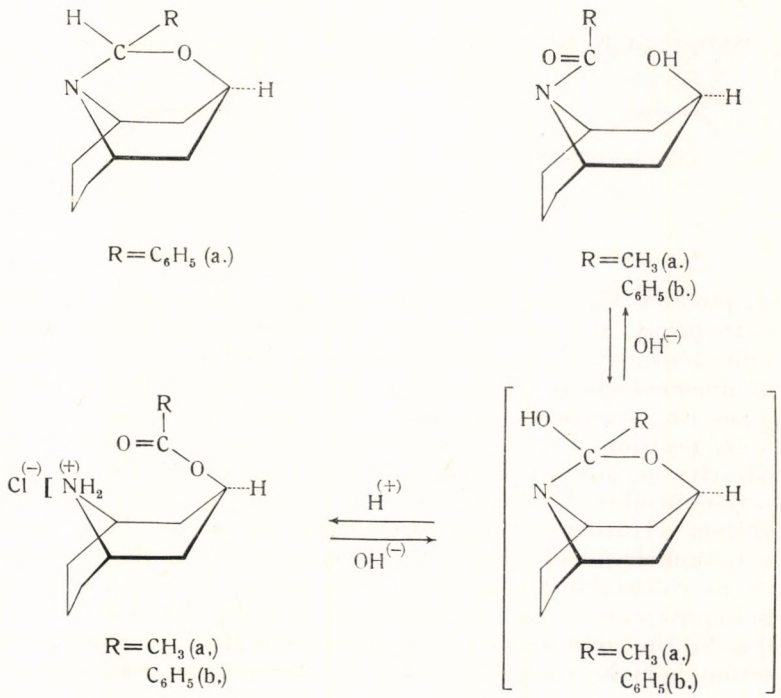


Fig. 54

In connection with the research relating to the stereochemistry of tropane compounds the possiblity of selective quaternarization was recognized in the cases of tropine [26], ψ-tropine [6, 7], 3α,6β-dihydroxytropane, and ecgoninol [9]. Regarding the similar structure of the two ring systems, it appeared promising to study the scope of the reaction of selective quaternization also in the case of 3β-granatols, epimeric on the nitrogen atom. HALMOS [16] introduced various groups in different sequence into the molecule of 3β-granatanole as the substituents *A* and *B*, employing the principle of reversed and normal quaternization given by FODOR and KOCZKA. Introduced groups were methyl and carbethoxymethyl; methyl and γ-cyanoethyl; methyl and γ-cyanopropyl. As contrasted with the striking selectivity of the reaction observed with tropane alkaloids, where the sequence of quaternization played a predominant part, the following statements could be made. In the case of the methyl and carbethoxymethyl groups, formation of the thermodynamically apparently most

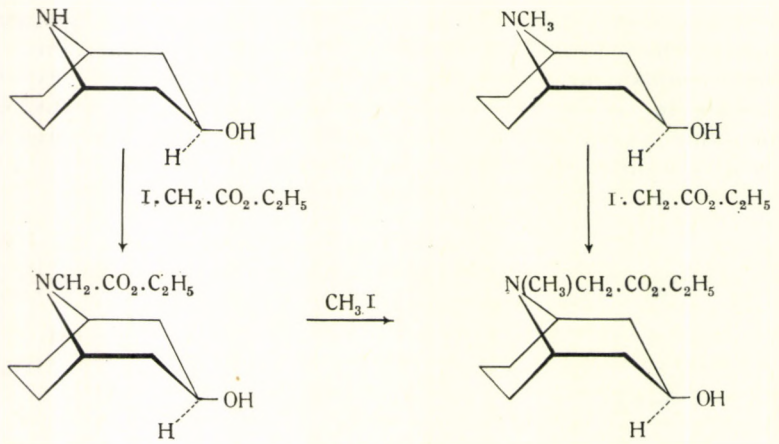


Fig. 55

stable end-product (Fig. 55) did not depend upon the sequence of alkylation. With γ-cyanopropyl and methyl groups, the reverse sequence of introduction gave *two* different γ-cyanopropyl-3β-granatolium iodides.

This phenomenon is rather readily interpreted. In the case of alkaloids with tropane ring system, it was shown by Hungarian investigators that the extent of deformation of the five-membered ring was of considerable influence on the selective occurrence or failure of this reaction. In the case of oscine, where the five-membered ring was nearest to the coplanar state, steric selectivity of the addition occurring on the nitrogen atom was smallest [14]. On the other hand, the 1,3-annelation of the two flexible ring systems in the granatane skeleton exerts no constraining condition in relation to the steric position of the methyl group attached to the nitrogen atom or being substituted there. Thus, a possibility for the methyl group to swing round is given, there are no preferred steric positions of higher probability (Fig. 56). Even if the probability of the two

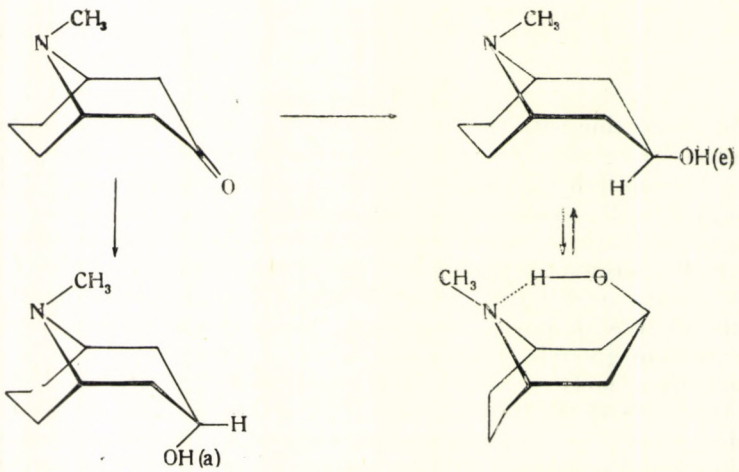


Fig. 56

steric positions in the direction of the substituted and not substituted piperidine ring, resp., is not the same, no fundamental difference can be found between the stability of these two arrangements. As it was pointed out in the mentioned paper of ALDER and DORTMANN [1], it is even probable that in this case the oxygen-containing functional group of 3β-*syn* steric position pushes the methyl group in the direction of the non-substituted piperidine ring. Unfortunately, these experiments have not made possible in any case so far the determination of the configuration of the nitrogen atom in the quaternary ammonium salts obtained. Thus, the question is not decided yet as regards the absolute steric positions of the groups attached to the nitrogen in the mentioned thermodynamically most stable compounds, or in products related with each other by way of kinetic probability. Investigations concerning this question require further experiments. However, as regards the fundamental question and the initial purpose of the experiments the answer has been obtained, namely, the problem whether the configurative stability of the tertiary nitrogen atom of the tropane skeleton was caused really by a pronounced Pitzer effect in the five-membered ring, appears to be solved. The question about the *meta*-annelation of two six-membered rings is beyond the scope of the selective quaternization reaction of cyclic bases.

REFERENCES

1. ALDER, K. and DORTMANN, H. A.: Über den sterischen Verlauf der Reduktion von *Pseudo*-Pelletierin. Die Konfiguration der N-Methyl-granatoline und ihrer Nor-Verbindungen. Chem. Ber. *86*, 1548 (1953).
2. ALDER, K., OFFERMANNS, H. and RÜDEN, E.: Zur Kenntnis der Polymerisationsvorgänge. IX. Mitteil. Über das dimere Methyl-vinyl-keton. Ber. dtsch. chem. Ges. *74*, 905 (1941).
3. ALDER, K. and STEIN, G.: Über den sterischen Verlauf von Additions- und Substitutionsreaktionen. VI. Liebigs Ann. Chem. *525*, 183, 221 (1936).
4. BARROWCLIFF, M. and TUTIN, F.: The Configurations of Tropine and ψ-Tropine and the Resolution of Atropine. J. Chem. Soc. *95*, 1970 (1909).
5. CIAMICIAN, G. and SILBER, P.: Über die Alkaloide der Granatwurzelrinde. Ber. dtsch. chem. Ges. *26*, 2738 (1893).
6. FODOR, G.: Lecture held at the Congress of Organic Chemistry, in Szeged, September 20, 1952. FODOR, G., KOCZKA, K. and LESTYÁN, J.: A Contribution to the Stereochemistry of the Trivalent Nitrogen (in Hungarian). Magy. Kém. Foly. *59*, 242 (1953).

7a FODOR, G.: Lecture held at the festive week of the Hungarian Academy of Sciences, Budapest, 1953.; FODOR, G.: New Studies Concerning the Stereochemistry of the Organically Bound Nitrogen Atom. (In Hungarian). Publications of the VIIth Dept. of the Hung. Acad. Sci. *3*, 311 (1953).

b FODOR, G., KOCZKA, K. and LESTYÁN, J.: Stereochemistry of the Tropan Alkaloids. Part IX. Selective Quaternization of Tropine and ψ-Tropine. J. Chem. Soc. 1956, 1411.

8. FODOR, G.; Über die Stereochemie der Alkaloide. Lecture at the 'Leipziger Hauptjahrestagung der Chem. Ges. d. DDR', October 23, 1954; cf.: Neuere Ergebnisse der Stereochemie der Alkaloide. Angew. Chemie *67*, 211 (1955); FODOR, G., KOVÁCS, Ö., TÓTH, J., WEISZ, I. and VINCZE, I.: Neuere Ergebnisse in der Stereochemie der Alkaloide. Tagungsber. 1955. d. Chem. Ges. d. DDR, p. 105.

9a FODOR, G.: Stereochemistry of the Tropane, Pyrrolizidine and Lupine Alkaloids Involving the Configuration of the Ring Nitrogen. Lecture at the IUPAC. Congress, Zurich, July 21, 1955.

b FODOR, G., KOVÁCS, Ö. and HALMOS, M.: The Stereochemistry of the Tropane Alkaloids. VIII. The Configuration of the Ring Nitrogen in Ecgoninol. J. Chem. Soc. *1956*, 873.

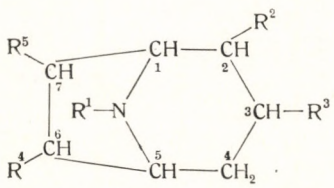
10. FODOR, G. and KISS, J.: Configuration of Alicyclic Aminoalcohols. Nature *164*, 917 (1949); FODOR, G. and KISS, J.: The Stereochemistry of 2-Aminocyclopentanols. J. Chem. Soc. *1952*, 1589.

11. Fodor, G., Kovács, Ö. and Weisz, I.: The Stereochemistry of Cocaine. Nature *174*, 131 (1954); Kovács, Ö., Fodor, G. and Weisz, I.: Konfigurationsbeweis des Cocains. 4. Mitteilung über Stereochemie der Tropanalkaloide. Helv. Chim. Acta *37*, 892 (1954).
12. Fodor, G. and Nádor, K.: Stereochemistry of Tropine and *Pseudo*-Tropine. Nature *169*, 462 (1952).
13. Fodor, G. and Nádor, K.: The Configurations of the Tropeines. J. Chem. Soc. *1953*, 721.
14. Fodor, G., Tóth, J. and Vincze, I.: The Stereochemistry of Tropane Alkaloids. VI. Configuration of Ring Nitrogen in Tropane-3α-6β-diol, Oscine and of Derived Quaternary Salts. J. Chem. Soc. *1955*, 3504.
15. Goodson, L. H. and Christopher, H.: Diphenyl-Ethylamines. I. The Preparation of Tertiary Amines by the Grignard Reaction. J. Am. Chem. Soc. *72*, 358 (1950).
16. Halmos, M.: The Direct and Reverse Quaternization of β-Methyl-granatanol and of β-Granatanol. (Unpublished.)
17. Hardegger, R. and Ott, H.: Beweis der Konfiguration des Pseudo-Tropins. bzw. des Tropins. Helv. Chim. Acta *36*, 1186 (1953).
18. Keagle, L. R. and Hartung, W. H.: Tropanone and its Homologues. J. Am. Chem. Soc. *68*, 1608 (1946).
19. Komppa, G. and Beckmann, S.: Über die Norcamphergruppe. I. Liebig's Ann. Chem. *512*, 172 (1934).
20. Kovács, Ö. and Weisz, I.: Reduction of Tropinone with Complex Metal Hydrides and by the Meerwein Method. (Unpublished.) cf. Fodor, G.: The Steric Structure of Tropane Alkaloids. Acta Chim. Acad. Sci. Hung. *5*, 396 (1955).
21. Longley, R. I. and Emerson, W. S.: The 1,4-Addition of Vinyl Ethers to α,β-Unsaturated Carbonyl Compounds. J. Am. Chem. Soc. *72*, 3079 (1950).
22a Manske, R. H. F. and Holmes, H. L.: The Alkaloids, Acad. Press Inc., New York 1951, Vol. 1, Chapter 5: Marion, L.: The Pyridine Alkaloids, 167—258, and within this: The Alkaloids of the Pomegranate Root Bark, 176—187.
b Manske, R. H. F.: The Alkaloids, Academic Press, New York 1960. Vol. 6, pp. 123—144: Marion, L.: The Pyridine Alkaloids.
23. Mirza, R.: Reduction of Tropinone with Lithium Aluminium Hydride. Nature *170*, 63 (1952).
24. Piccinini, A.: Studien betreffend die Konstitution der Alkaloide des Granatbaumes Gazz. Chim. Ital. *29*, I. 410, II. 104 (1899).
25. Smith, C. W., Norton, D. G. and Ballard, S. A.: Reduction of Acrolein and Related Compounds. I. Addition of Vinyl Ethers. J. Am. Chem. Soc. *73*, 5267 (1951).
26. Tóth, J.: Lecture held at the Organic Chemical Congress in Debrecen, September 27, 1953. See Fodor, G., Tóth, J., Lestyán, J. and Vincze, I.: The ascertainment of the absolute configuration of tropane alkaloids containing an oxygen-function on the pyrrolidine skeleton. (In Hungarian.) Publ. of the Hungarian Chem. Ind. *4*, 293 (1954).
27. Werner, L. F.: Analogues of Atropine and Homatropine. J. Am. Chem. Soc. *40*, 669 (1918).
28. Willstätter, R.: Über Pseudo-Tropin. II. Mitteilung über Ketone der Tropingruppe. Ber. dtsch. chem. Ges. *29*, 939 (1896).
29. Willstätter, R.: Über die Konstitution der Spaltungsprodukte von Atropin und Cocain. Ber. dtsch. chem. Ges. *31*, 1540 (1898).
30. Willstätter. and Iglauer, F.: Reduktion von Tropinon zu Tropin and Tropan. XV. Mitteil. Über Ketone der Tropingruppe. Ber. dtsch. chem. Ges. *33*, 1170 (1900).
31. Willstätter, R. and Veraguth, H.: Über einige Derivate des Pseudo-Pelletierins. Ber. dtsch. chem. Ges. *38*, 1989 (1905).

CHAPTER IV

STERIC STRUCTURE OF TROPANE ALKALOIDS

Alkaloids with tropane ring system occur in plants belonging to the botanical families of *Convolvulaceae*, *Solanaceae*, *Dioscoraceae* and *Erythroxylaceae*. By virtue of their strong physiological actions, the most important representatives of these compounds have long been in the foreground of interest. Such materials are atropine and hyoscyamine, cocaine, tropacocaine, as well as scopolamine and hyoscine. Their high physiological activity demanded an elucidation of the chemical structures. Other compounds, on the other hand, like oscine, valeroidine and meteloidine, were without effect. Common features in the chemical structure of tropane alkaloids originating from the manifold and various botanical families, were first discovered by the aid of hydrolysis.



R^1=H; CH_3 R^3=H; OH
R^2=H; COOH R^4=H; OH
R^5=H; OH

Fig. 57

Most compounds gave tropine, some afforded *nor*-tropine; *pseudo*tropine was obtained from tropacocaine, ecgonine from cocaine, oscine from scopolamine, 3,6-dihydroxytropane from valeroidine and 3,6,7-trihydroxytropane from meteloidine (Fig. 57). A common feature of the compounds is the presence of an ester bonding. Among the esterifying acids, mention should be made of *l*- and *dl*-tropic, *dl*-α-methylbutyric, tiglic, isovaleric, benzoic, veratric, cinnamic and truxillic acids. In the course of a thorough investigation, for which credit must be given primarily to WILLSTÄTTER, a number of the nitrogen-containing products of the hydrolysis were succesfully analyzed. The structures of other compounds, such as the fundamental skeleton of teloidine (component of meteloidine), were elucidated by the aid of synthesis. Particulars of these chemical investigations are described by F.R.H. MANSKE and H.L. HOLMES [125], where the elucidation of the chemical constitution of tropane alkaloids is discussed in detail, except for research concerning stereochemical

relationships. The fact that the greatest part of these compounds occur in nature in optically active form rendered necessary the study of their stereoisomeric relationships comparatively at an early date. However, complete study of this problem took actually place only recently. In the following part, research concerning the steric structures of the most important natural tropane alkaloids and of their conversion products will be discussed. Classification is done according to the tropane i.e. (alkamine) components.

Though the work of elucidating the relative configurations of natural tropane alkaloids was completed between 1951 and 1955, determination of the absolute configuration was carried out, both by physical and chemical methods, only in the latter years. Recently also the biogenesis of tropane alkaloids as well as their extensive interconversions *in vivo* has become the subject of vigorous studies. A very compressed summary of this researh is to be found in MANSKE's work*.

RESEARCHES RELATING TO THE STERIC STRUCTURES OF TROPINE, *PSEUDO*TROPINE AND THEIR ESTERS

Stereochemistry of Tropine

Hydrolysis of optically active hyoscyamine and inactive atropine both gave inactive tropine [77, 125, 141]. On the other hand, the isomeric *pseudo*tropine

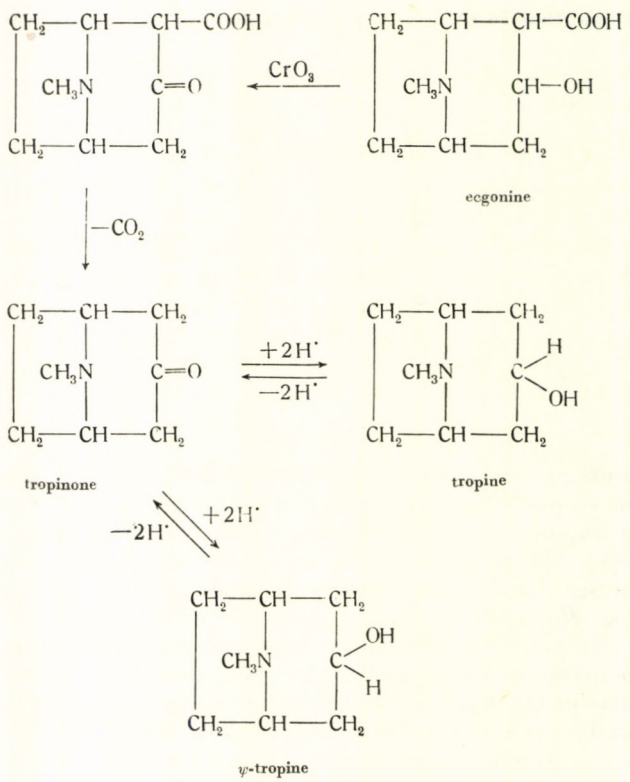


Fig. 58

* Vol. VI, pp 145—178 (1960).

was obtained from the hydrolysis of the alkaloid tropacocaine [117]. The relationship between these two compounds was cleared up by WILLSTÄTTER in 1894, at a time when even the constitutions of these compounds were not known. He converted tropinone, obtained from the oxidation of tropine [197], into *pseudo*tropine [198], and also succeeded in transforming tropine to *pseudo*-tropine by heating it with sodium amyloxide. Finally, he could reduce tropinone into a mixture of tropine and ψ-tropine [202] (Fig. 58). In this way he proved that these two compounds differed but in the relative steric position of the hydroxyl group. By these experiments the foundation of later stereochemical research was laid down. It is interesting to note that GADAMER held the view for a long time that the only difference between the two compounds was in the position of the methyl group attached to the nitrogen atom [77], and not in the steric position of the hydroxyl group. Later on, researches of Hungarian investigators suggested energy reasons for which the methyl group on the nitrogen had a more stable position in one direction than in the other [52], thus *two* tertiary amines, epimeric on the nitrogen atom, cannot exist in this group. (Cf. also [23]).

After having stated the constitution of tropine, WILLSTÄTTER pointed out in 1900 that though there were two asymmetric carbon atoms in both compounds, still no optical activity or possibility of resolution was to be expected, because steric causes permitted the existence of the *meso*-modifications only, which contained the nitrogen atom bridging over the distance between the two carbon atoms of the cycloheptane ring when in *cis*-position. Now for the *d*- and *l*-form to exist, a *trans* bonding would be required, between the $C_{(1)}$ and $C_{(5)}$ carbon atoms; however, as it can be seen even without a model, this is impossible [202]. Notwithstanding this logical argumentation, GADAMER regarded the tropine—ψ-tropine pair to be *dl*- and *meso*- diastereoisomers, and recognized the *meso*-configuration of both modifications only when he failed in resolving tropine into antipodes [77], whereas by way of repeating the experiments of MERLING [129] he split the piperidine ring, and prepared thus tropinic acid, which product did prove to be resolvable (Fig.

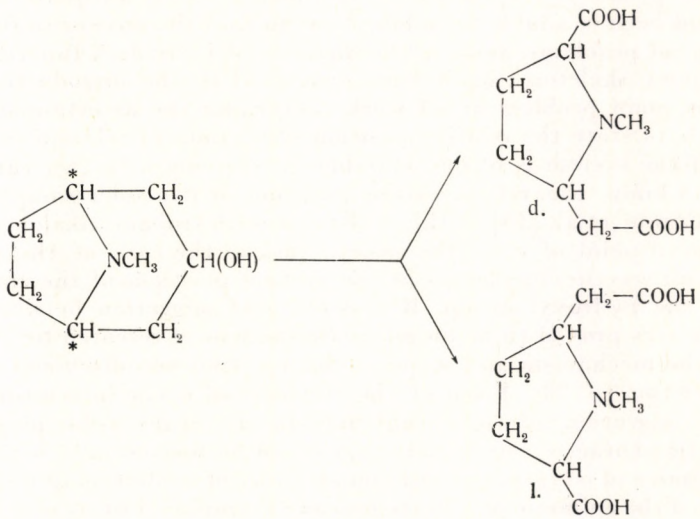


Fig. 59

59). It was in the same way that BARROWCLIFF and TUTIN [10] became convinced in 1909 about the *meso*-structure of the two stereoisomeric tropines, when resolution to antipodes had been unsuccessful. At the same time they succeeded in resolving atropine by *d*-camphorsulphonic acid into *d*- and *l*-hyoscyamine-*d*-camphorsulphonates (Fig. 60). In this way the isomeric relationship between atropine and hyoscyamine (the first being the tropine ester of (±)-tropic acid, the latter that of (−)-tropic acid) was successfully proved. *These investigations constitute an unequivocal proof that tropine and ψ-tropine are c i s - t r a n s isomeric m e s o - compounds on the* $C_{(3)}$ *carbon atom of the tropane skeleton.* These experiments [10, 77, 129] disproved the original assumptions of GADAMER as regards C_1-C_5 diastereoisomerism, as well as the possibility of N-diastereoisomerism. The steric position of the hydroxyl in relation

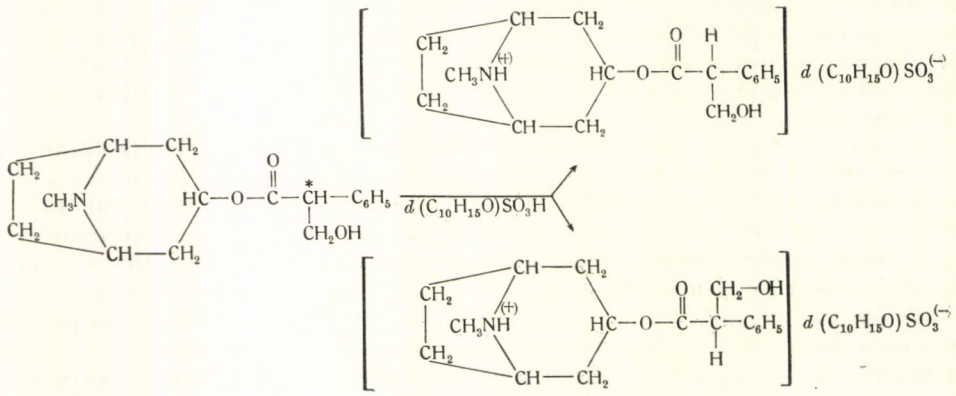


Fig. 60

to the N-methyl group as a whole, i.e. which of them had *syn*- or *anti*-orientation in the individual modifications, could not yet be decided by these studies.

Failure of early experiments to state the configuration of tropine and ψ-tropine is primarily explained by the fact that no adequate methods of research had been available for a long time to find the answer to fundamental stereochemical problems, such as the distance of individual functional groups in the tropane skeleton. As it was mentioned in the introductory chapter (p. 19), the main problem of all work concerning the ascertainment of configuration is to state the relative position of a group in relation to a point of reference if the system is of one variable; in systems with two variables it is necessary to know the relative steric positions of two such groups, and — as shown by FODOR et al. [49] — this is the case with tropane alkaloids. From the stereochemical point of view, the easiest task in the case of the tropine — ψ-tropine pair was the elucidation of the mutual positions of the ring nitrogen atom and the hydroxyl group. Reversible acyl migration between nitrogen and oxygen was proved to be an adequate method of research for solving this problem. The mechanism and scope of this reaction was discussed in detail in the Introduction (p. 23). Proof of the existence of cyclic intermediates in the O→N acyl migration reactions confirmed in case of reversible processes their stereospecific character, since such rings could be formed only with a relative steric proximity of oxygen and nitrogen, by way of mediation of a single atom. In the case of the epimeric pair of tropine and ψ-tropine, FODOR and NÁDOR [40, 41, 66] were the first to use this method of proving the structure (September,

1951), and independently, though later (June, 1952), NICKON and FIESER submitted the results of their acyl migration experiments also for publication. For this purpose, the former investigators oxidized tropine and ψ-tropine with

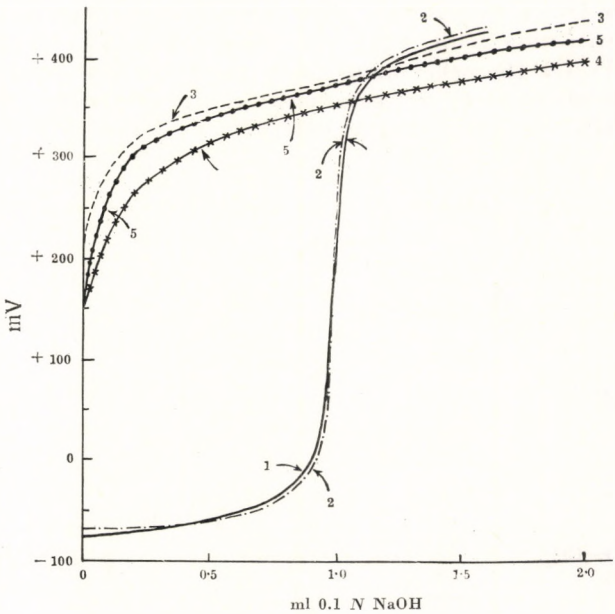


Fig. 61

potassium permanganate to *nor*-amines. FIESER and NICKON [135] achieved the same result by employing the technique of BRAUN's cyanogen bromide degradation; both epimeric *nor*-bases were acetylated and benzoylated.

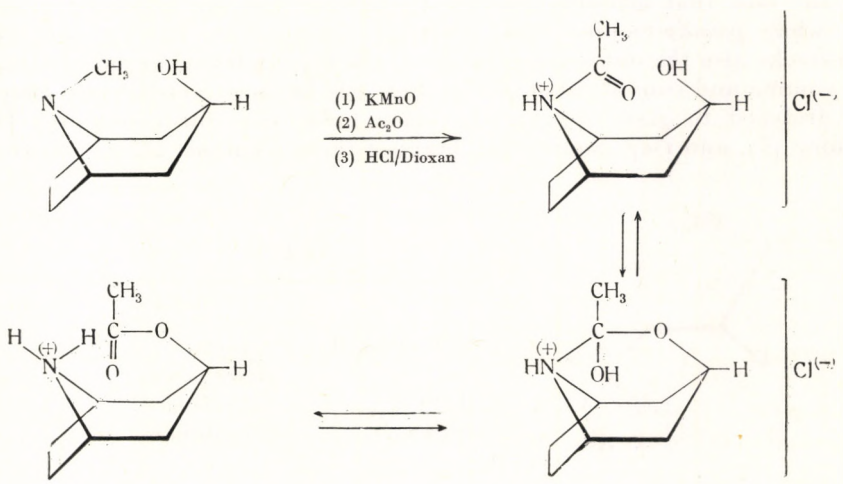


Fig. 62

N-Acetyl-*nor*-tropine as well as its epimeric pseudo-form could be converted into the comparatively stable amide salts. POLONOWSKI [149] prepared N-acetyl-*nor*-tropine hydrochloride, however, no study of its reactions was made. These compounds may be titrated potentiometrically as 'free hydrochloric acid', while O-acyl compounds show a buffering effect in the course of potentiometric titration [66b, 192], i.e., they behave like typical ammonium salts (Fig. 61). On the other hand, only the acyl (acetyl and benzoyl) derivatives of *pseudo-nor*-tropine can undergo a reversible N→O acyl migration (Fig. 62), but *nor*-tropine derivatives cannot (Fig. 63).

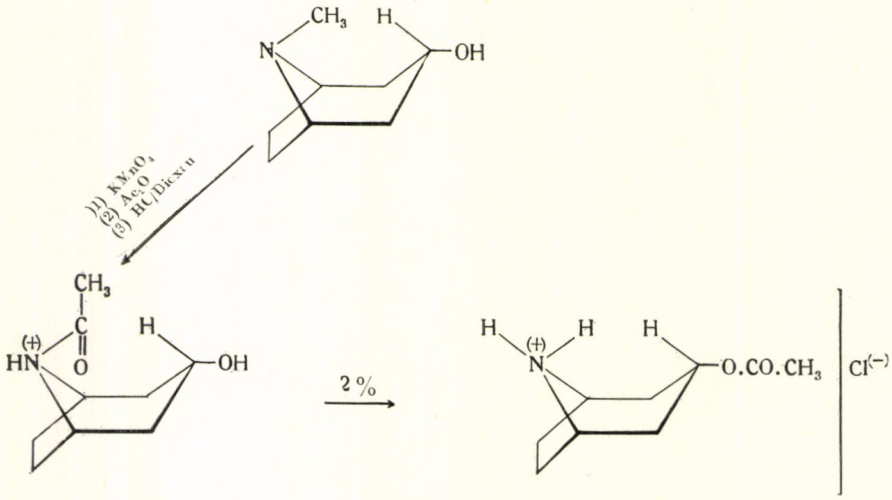


Fig. 63

This simple experimental fact was chronologically the first convincing proof to show that atropine and its derivatives had the hydroxyl group in *anti-*, while *pseudo*-tropine derivatives in *syn*-position. In this way, with a single stroke also the *anti*-configuration of the $C_{(3)}$ hydroxyl group of atropine, hyoscyamine and convolamine [137] (Fig. 64) became stated, since they can be hydrolyzed to give tropine; the same holds true for convolvine [137], poroidine [9], and *iso*poroidine [9], because these alkaloids afford *nor*-tropine

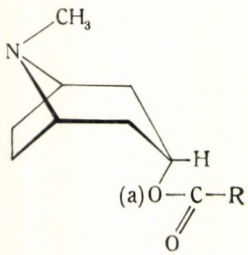


Fig. 64

Table I

R	Alkaloid
$CH(CH_2OH)C_6H_5$	Atropine
	Hyoscyamine
$C_6H_3(OCH_3)_2$	Convolamine
$CH(OH)C_6H_5$	Homatropine

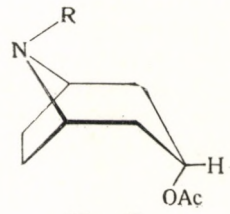


Fig. 65

Table II

R	Ac	Alkaloid
H	$CH_2CH(CH_3)_2$	Poroidine
H	$CH(CH_3)CH_2CH_3(d)$	Isoporoidine
H	$C_6H_3(OCH_3)_2$	Convolvine

on hydrolysis (Fig. 65). The *syn*-configuration of the esterified hydroxyl group of tropacocaine [117] and of tigloidine [8] became also ascertained (Fig. 66).

A little later after these acyl migration experiments, ZENITZ, MARTINI et al. [213] reported the same results, obtained by means of infrared spectroscopy and determination of the dipole moments of tropine and *pseudo*tropine. CLEMO and JACK, on the basis of their previous measurements of dipole

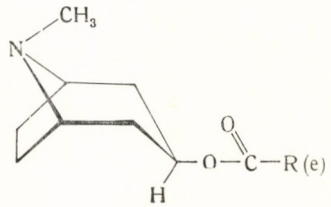
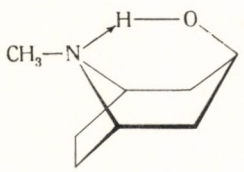


Fig. 66

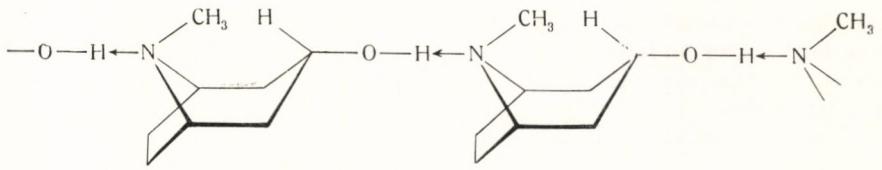
Table III

R	Alkaloid
$(H_3C)C = CH(CH_3)$	Tigloidine
C_6H_5	Tropacocaine

moments [22], also confirmed the issues of the chemical determination of the configuration. In the opinion of ZENITZ et al. both tropine and *pseudo*tropine have a well-defined hydrogen bonding. The band intensity, characteristic for the same is, however, somewhat more decreased by dilution in the case of tropine than with *pseudo*tropine. Spectral measurements carried out in three various concentrations gave the result interpreted as shown in Fig. 67.



pseudo-tropine



tropine

Fig. 67

As it is seen, it was concluded that ψ-tropine had an intramolecular hydrogen bonding besides an intermolecular one, as it remained unaffected even in case of dilution. This pseudoionic bond between the $C_{(3)}$ oxygen and the nitrogen atom could, however, exist only in the boat conformation of the molecule, being established by the unshared electron pair of the nitrogen. However, X-ray diffraction measurements of VISSER et al. [196] with tropine *hydrochloride* and tropine *hydrobromide crystals* showed (Fig. 68) that the

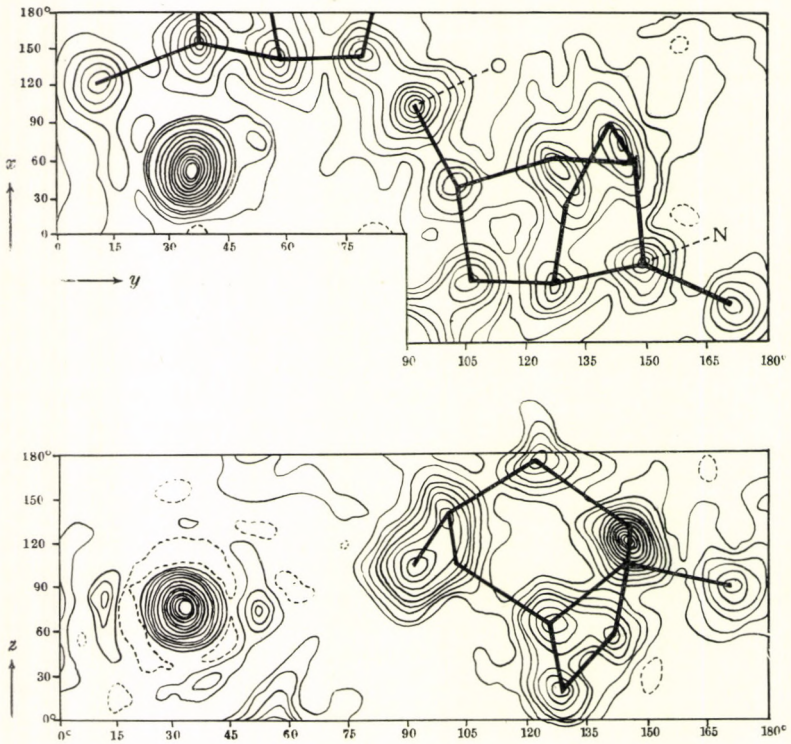


Fig. 68

chair conformation was in preponderance, whereas, as a consequence of the *anti*-orientation of the hydroxyl group of tropine, it could have been expected that this conformation was unfavoured. Unfortunately, the Dutch investigator did not examine ψ-tropine, thus there is no direct evidence for its chair conformation*; anyhow, on the strength of the above considerations, the latter may be regarded to be more probable also in this case than the boat form. On the other hand, most recent experiments of Hungarian researchers revealed that in several tropane derivatives the methyl group is preferably inclined toward the $C_{(3)}$ atom bearing the hydroxyl group [23, 44—54, 63, 162],

* This has been obtained now by Prof. MAC GILLAVRY according to our suggestion.

when formation of a hydrogen bond between the $C_{(3)}$ hydroxyl and nitrogen is less probable, since it would require just the opposite steric position of the methyl group. In this respect, however, the above experimental evidence is not convincing, because it shows no difference of quantitative character between the physical constants of the two epimeric compounds. It is interesting that in his new stereochemical monograph KLYNE [108] regarded this evidence from physico-chemical measurements as a *confirmation* of the results obtained in preparative chemical way. The situation may be different with β-granatoline ('ψ-granatol') which is formed by the *meta*-condensation of two six-membered rings; ALDER and DORTMANN [1] pointed out here that the existence of hydrogen bonding had been experimentally proved by SCHÄFER. Unfortunately, the curves and a promised detailed discusson have not been published so far. The fact that tropine was the *anti*-modification has recently also been proved for the hydrobromide in the above-mentioned X-ray diffraction studies of VISSER et al. [196]. Besides stating the chair conformation of the piperidine ring, it was also demonstrated that the N-methyl group was situated in the direction of the endoethylenic bridge (at least for the crystalline hydrobromide); see references [44—54] and the subsection titled "Configuration of the nitrogen atom in tropanes." The base has probably the N-epimeric, chair conformation (Fig. 68). HARTUNG and SMITH [91] in 1953 confirmed the *syn*-structure of ψ-tropine, based on a comparison of the p_k values. These investigators found, namely, a higher p_k value for ψ-tropine (3.67) than for tropine (2.98). This result was ascribed to an intramolecular hydrogen bonding in ψ-tropine. In addition, these authors also reported the fact that, during the same reaction time, benzoyl chloride gave 84.5% benzoyl tropine hydrochloride, while only 79.2% benzoyl ψ-tropine hydrochloride was formed, the result being again interpreted as a consequence of a hydrogen bond in the latter case. The same conclusion was drawn also from the relatively higher density of tropine. Later on, GEISSMAN et al. [84] stated that tropine was a by about 0.5 p_k units stronger base than ψ-tropine, at variance with the findings of HARTUNG. According to GEISSMAN "the differences between the basic strengths of tropine and pseudotropine cannot be based upon a consideration only of the configuration of the hydroxyl group"... "It is possible that the strain imposed upon the ring system by the ethylene bridge (i.e., on the piperidine skeleton)... is affected by the position of the hydroxyl group with respect to the bridge, and thus the tendency for the nitrogen atom to assume the tetrahedral form by ionization is affected by the configuration of the hydroxyl group." This debate does not justify the appraisement of KLYNE [108] as regards the high significance and reliability of the quoted physical measurements as a means of stating the configuration of rather complicated organic compounds.

If it is taken into consideration that the piperidine ring of the tropane skeleton can only in the boat conformation reach the state which permits the vicinity necessary for hydrogen bonding but, on the other hand, repulsive 'Pitzer strain' [15a] between the neighbouring $C_{(2)}$ and $C_{(3)}$ atoms would consequently acquire considerable values at the same time, it appears most probable that the *ground* state of the ψ-tropine molecule is predominantly the chair conformation (Fig. 68), and equilibrium with the boat form is brought about at very high temperatures only [196]. Naturally, O→N acyl migration would take place in the boat form. Nevertheless, it does not mean that our assumption of the boat configuration is the ground state of the molecule. In

fact, the experience that N→O acyl migration would occur in this system only when the reaction mixture is heated [40, 41, 66b], whereas aminoalcohols which have their groups in more favourable steric positions react istantaneously even at room temperature (see Chapter I p. 43), is an evidence to show that the boat configuration can be realized only in some excited state.

Final conclusions relating to the configurations of tropine and ψ-tropine, were erroneously drawn also from the measurements of other physical constants. Thus, e.g., SIXMA et al. studied in 1951 the rate of saponification of the epimeric benzoyl and *p*-nitrobenzoyl tropeines, and their methiodides [177]. Since tropine esters showed smaller *k*-values than ψ-tropeines, these investigators attributed this fact to an inhibited steric position of the hydroxyl group, and assuming boat conformation, they ascribed directly the opposite configurations to the epimers than those stated independently two months earlier in the experiments of Hungarian researchers of which SIEGMANN and his co-workers were unaware. In a later paper (in 1954) SIEGMANN et al. accepted [176] the presented additional evidence obtained by a preparative method [66b, 88, 135].

BEYERMANN, SIEGMANN, SIXMA and WISSER reported in 1957 further reaction kinetic measurements [17] in connection with the alcoholysis of benzoyltropeine, benzoyl-ψ-tropeine and their methiodides. The relative reaction rates found, completely supported the assumption that tropine and ψ-tropine had chair conformations, and their configurations corresponded to those given at first by the Hungarian research workers.

It was attempted also by HROMATKA et al. [97] to draw conclusions concerning the configuration from the rate differences of the saponification and acylation reactions of epimeric tropeines, as it was found that tropine benzilate could be prepared and hydrolyzed more difficultly than the corresponding ester of ψ-tropine.

When the above ascertainment of the chair conformations of tropine and ψ-tropine, as well as of their *anti*- and *syn*-configurations, resp., are considered, all these experiences become easily interpreted. Namely, in the chair conformation, just the hydroxyl group of *anti*-position is hindered, while the equatorial *syn*-hydroxyl group is free, thus easily esterified, and just as easily hydrolysed [49].

It was observed already by WILLSTÄTTER [198] that reduction of tropinone by sodium and alcohol gave predominantly *pseudo*tropine, according to our present knowledge *syn*-tropine. MIRZA reported the same final result of his experiments with lithium aluminium hydride [131]. However, probably because of isolating the final product as the picrate, he overlooked the fact that reduction by lithium aluminium hydride was not an absolutely stereospecific process,* thus also a considerable amount of tropine may have been formed, as it was proved indeed to be the case in the course of other investigations.**

As a consequence of an erroneous interpretation of the above experimental facts, also PADDOCK [139] became the victim of a similar mistake like the Dutch investigators. Assuming the boat conformation of tropinone, he

* Cf.: BECKETT et al. [15b]

** The best method of the stereospecific reduction of tropinone to *syn*-tropine is to use aluminium *iso*propoxide at 80°; at 20° a mixture of the epimers is formed [48a] [15b]

formulated tropine, the product of the catalytic reduction, with *syn*-hydroxyl groups, while ψ-tropine with *anti*-hydroxyl groups, since on the analogy of the conformational analysis of sterols [12], catalytic reduction results in the formation of an *axial*, and chemical reduction methods of an *equatorial* hydroxyl group. If the same system is deduced from the chair conformation, it is clear that we obtain directly the opposite, here and now right, result. In this respect the opinion of ALDER and DORTMANN [1], and that of FODOR [48] are in agreement. SPARKE [180] does not share PADDOCK's view either. Anyhow, it appears that some authors made conformational analysis overemphasized in that case since the configurations had been sufficiently elucidated — also according to ROBINSON [158] — already by the experiments of the acyl migration.

On the other hand, the studies of HARDEGGER and OTT [88] have been extremely useful. The Swiss investigators treated *nor*-tropine and *nor*-ψ-tropine with *p*-nitrobenzaldehyde under identical conditions, when the *syn*-modification gave, as expected, a cyclic tetrahydro-*m*-oxazine derivative (Fig. 69).

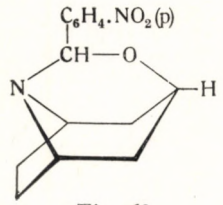


Fig. 69

This method and technique was first employed by GOODSON and CHRISTOPHER [85] for 3-amino-alcohols when condensing 2-(β-hydroxyethyl)-piperidine with benzaldehyde. Complex reactions occurred in the case of the *anti*-modification, which were also successfully elucidated by HARDEGGER [89]. One of the products was N-*p*-nitrobenzoyl-*nor*-tropine (Fig. 70).

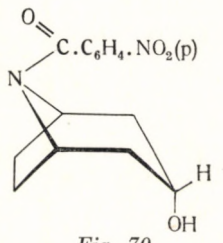


Fig. 70

In the course of these experiments also a μ-desoxy derivative was formed, which is a significantly more stable, closely related product to the intermediate in the acyl migration reaction, $N \rightleftarrows O$, i.e., to a μ-hydroxy-oxazidine (Fig. 57). Though in HARDEGGER's opinion early experiments afforded no "... incontestable proof", ("handfeste... unanfechtbare Beweise",) his results represent rather the *confirmation* of the question of configurations assigned by another method. He pointed out that the reaction of acyl migration has been tried *but in a few cases* for the purpose of determining the configuration; he

quoted the references [66a and b] and [135]; however this statement is hardly tenable, in view of this reaction having been successfully employed partly by Hungarian investigators in the study of various types of compounds such as β-aryl-alkanolamines, amino-cyclanols, amino-tetralinols and glucosamine (see [22—29, 32, 41] in Introduction, and [9—21] in Chapter I), and further by McCasland et al. [122] for epimeric inosamines, by Van Tamelen [190, 191] for amino borneols, and finally by Huisgen [99] in the research of the configuration of *anti*-diazoates.

With the above considerations, investigations concerning the proving of the *anti*-configuration of tropine and *syn*-configuration of ψ-tropine are completely concluded.

Nomenclature. The work of elucidating the configuration of a great number of tropane alkaloids, hydrolyzable to tropine, pseudotropine and their *nor* derivatives, presented the problem of nomenclature. In agreement with the editor of the J. Chem. Soc., also Hungarian authors [66b] regard the N-methyl bridge as the point of reference, and groups in relative *syn* steric positions are denoted by β, and those in distant position by α. This principle of nomenclature will consequently be applied throughout the following chapters discussing the derivatives of cocaine, scopolamine, valeroidine and teloidine.

Modern Syntheses of Tropeines

A modern variety of the synthesis of tropinone starts from furan. This compound is subjected to electrolytic (anodic) oxidation or to bromine in methanol to give dimethoxydihydrofuran [20, 21]; then the double bond is hydrogenated over Raney nickel catalyst which process results in the formation of succinic aldehyde dimethyl cyclic acetal. The product is treated with dilute acid, then acted upon by acetonedicarboxylic acid and methylamine in a suitable buffer solution (a modification by Hungarian authors [82]) to give 85—90% yield of tropinone (Fig. 71) within a few hours.

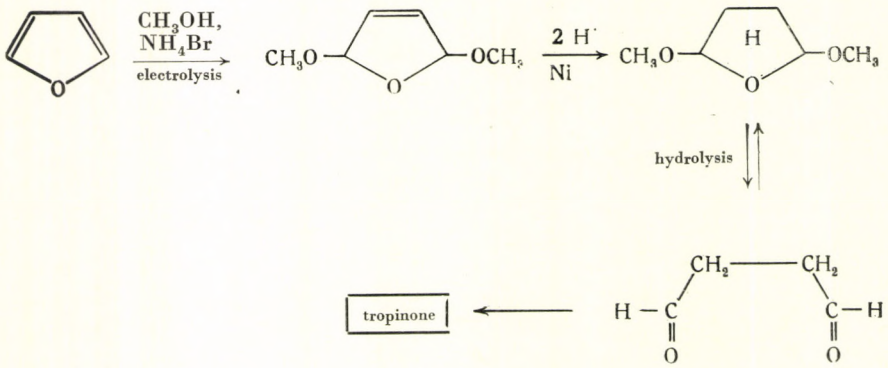


Fig. 71

The mechanism of the condensation as assumed by Schöpf [170], was recently experimentally confirmed by Galinovsky [80]. This investigator succeeded in reducing N-methylsuccinimide with lithium aluminium hydride

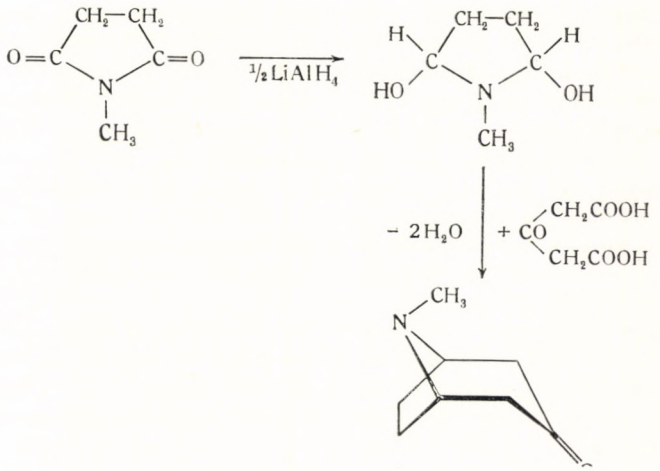


Fig. 72

to α,α-dihydroxy-N-methyl-pyrrolidine, which compound, in turn, gave tropinone when treated with acetonedicarboxylic acid, although the yields were low (Fig. 72). Anyhow, this is just one of the possible descriptions of the reaction mechanism; simultaneous attack of two nucleophilic centres on the oxo-carbon atom of the dialdehyde, i.e., a Mannich reaction, is also a feasible way; indeed, the low yield of the previously discussed

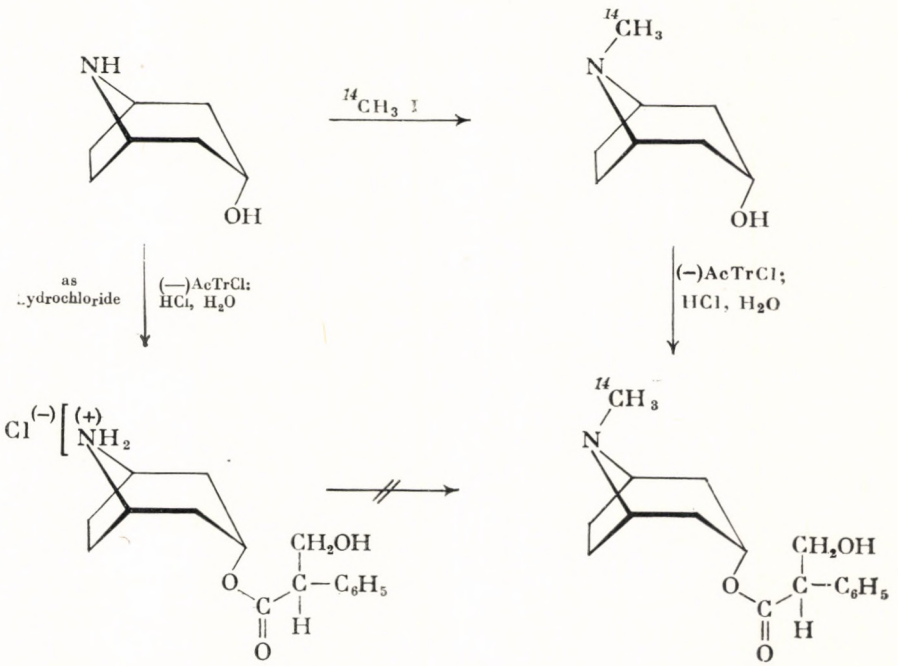


Fig. 73

two-step process is an indication in favour of this mechanism. The mechanism of the Mannich reaction was recently elucidated by CUMMINGS and SHELTON* by kinetic experiments. Accordingly, the methylolamine reacts with the carbanion at low pH values with $S_N 2$ mechanism. At higher pH values, however, the reaction appears to be trimolecular, just as it was assumed by the author et al. for the case of ROBINSON's tropinone synthesis.

The simplified practical synthesis of dimethoxydihydrofuran and its alkoxy derivatives recently rendered possible the development of syntheses of natural alkaloids of pharmacological importance on a semi-industrial scale. Thus, a direct and simple synthesis of *S*-(—)-hyoscyamine was realized by FODOR and RÁKÓCZI, after proper resolution of racemic tropic acid into the optically active components by means of (1*R* : 2*R*)-1-*p*-nitrophenyl-2-aminopropane-1,3-diol [57]. The synthesis of tropenol esters and the semitechnical utilization of the process were realized in a similar way. FODOR, JANZSÓ, ÖTVÖS and BÁNFI [59] described the synthesis of methyl-^{14}C-hyoscyamine in the way shown in Fig. 73.

An interesting tropinone synthesis starting with hexadiine-1,5 and involving the formation of N-methylpyrrolidine-2,5-diacetic ester was described by RAPHAEL et al.**

STUDIES ON COCAINE AND ITS EPIMERS

The determination of the isomerism of tropine and ψ-tropine, and oxidation of ecgonine to tropinone opened up the way also to the more complicated problem of the stereochemistry of cocaine. The acid hydrolysis of cocaine gives (—)-ecgonine [207] and this compound is decomposed by oxidation, with the formation of the intermediate β-keto acid, to tropinone [200, 203] (Fig. 58). On the other hand, when (—)-ecgonine is acted upon by alkalies [29—31], it

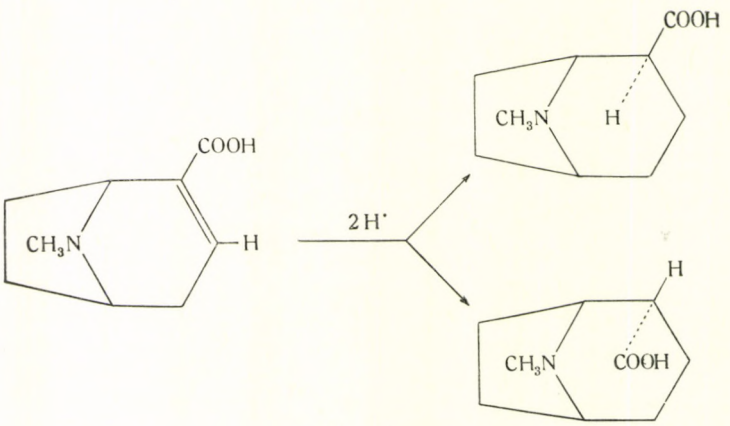


Fig. 74

* T. F. CUMMINGS and J. R. SHELTON: Mannich Reaction Mechanisms. J. Org. Chem *25*, 419—423 (1960).

** PARKER, W., RAPHAEL, R. A. and WILKINSON, D. I.: Acetylenic Routes to Tropinone *Pseudo*pelletierine and Lobelamine. J. Chem. Soc. *1959*, 2433.

is rearranged to (+)-ecgonine, which compound is not the enantiostereomeric, but the diastereomeric form of the starting material. Namely, these two compounds have not the same melting point, and also their absolute values of optical rotation are different. It was obvious to bring this fact into harmony with the irreversible isomerization of tropine to ψ-tropine [200, 201]. That was the reason why WILLSTÄTTER called the dextrorotatory ecgonine *d-pseudo*ecgonine as early as in 1900, without any evidence for the actual

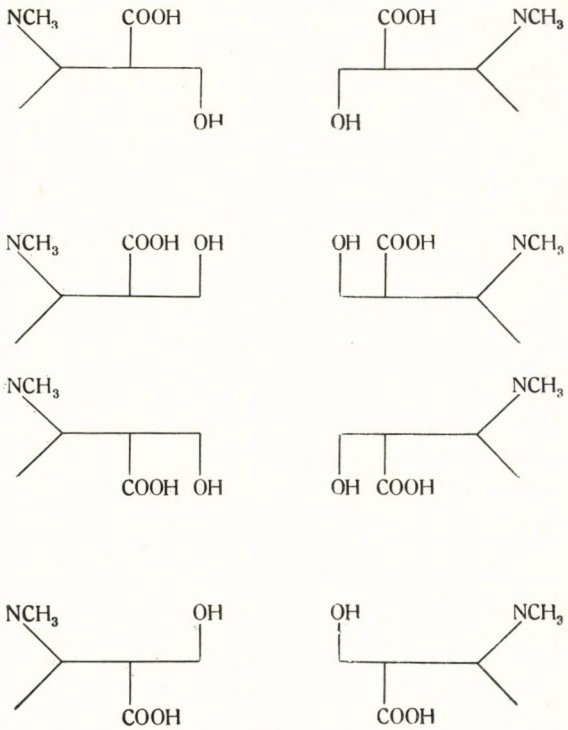


Fig. 75

$C_{(3)}$ epimerism of these two compounds. Ecgonine and *pseudo*ecgonine gave, even if under differently energetic conditions of treatment, the same anhydroecgonine [29, 30]. Hydrogenation of this product afforded, according to GADAMER, two dihydroanhydroecgonines [78, 79], epimeric on the $C_{(2)}$ carbon atom (Fig. 74). These experiments were later repeated by FINDLAY [34]. The early experiment of EICHENGRÜN and EINHORN [28] may serve as the basis to a new approach in elucidating the steric structure and the bond system of ecgonine. By way of brominating anhydroecgonine, these investigators prepared a dibromo derivative which was treated with potassium hydroxide to give an unstable lactone containing bromine. This compound could, as a β-lactone, possess only *cis*-configuration, according to our present knowledge. This experimental fact would be helpful for determining the steric positions of the $C_{(2)}$ and $C_{(3)}$ atoms, i.e., of the neighbouring ring carbon atoms bearing the functional groups in cocaine. However, since the correlation among ecgonine, ψ-ecgonine and the bromo-β-lactone has not been stated even until today,

this observation offers no sound basis for describing the relative steric positions of the functional groups either in ecgonine or in ψ-ecgonine [48a]. In 1922, WILLSTÄTTER and BOMMER realized the total synthesis of (+)-ecgonine, i.e., of ψ-ecgonine [201]. Two years later also natural cocaine was synthesized, starting with acetonedicarboxylic acid monomethyl ester [204]. The key-intermediate in this synthesis was methyl tropinone-2-carboxylate. Reduction

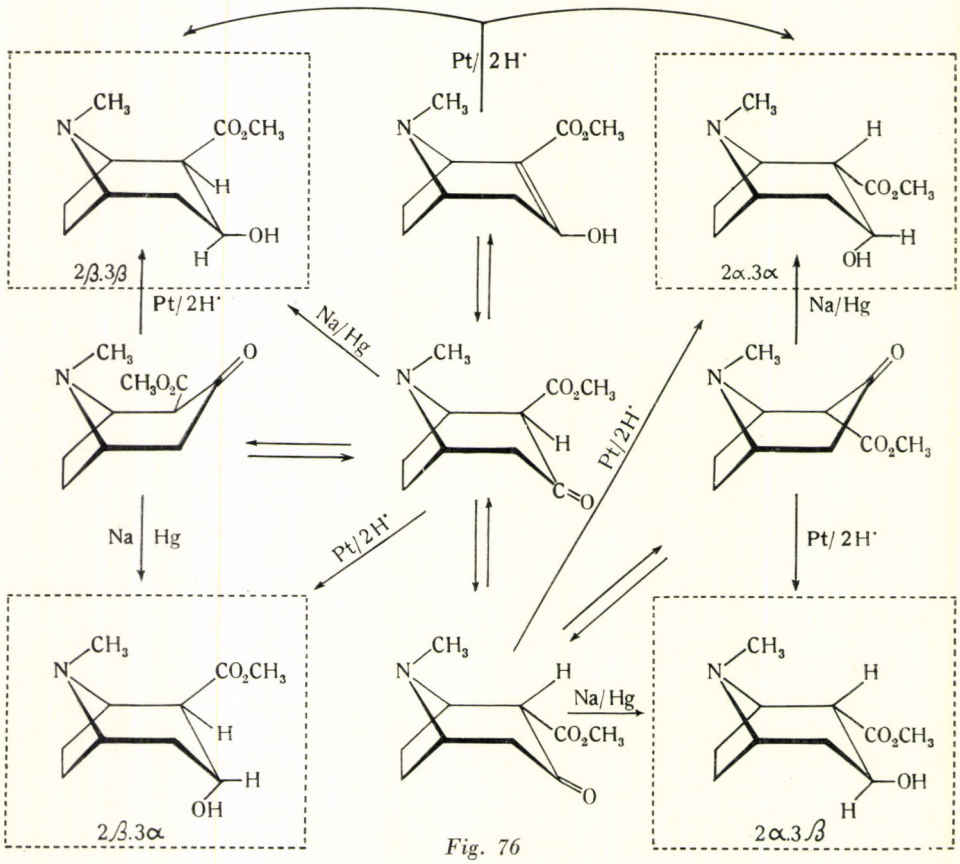


Fig. 76

of the latter afforded only three of the four possible racemates, mainly *dl-pseudoecgonine*, *dl-ecgonine* and a third pair of antipodes. Also this synthesis confirmed WILLSTÄTTER's belief that cocaine and *pseudo*cocaine originating from the reduction of the same oxo compound differed only as regards the steric position of the hydroxyl group of the $C_{(3)}$ carbon atom [201] (Fig. 75), although enolization of the oxocarboxylic ester might have considerably influenced the steric course of the reduction. *Cis*-hydrogen addition occurring on the enol form may lead, e.g., to the formation of modifications epimeric on both carbon atoms (Fig. 76). The author also omitted consideration of the fact that the β-hydroxycarboxylic ester is more capable of racemization on its carbon atom of α steric position, than on the β-carbon atom bearing the hydroxyl group. This problem was later studied in detail by FINDLAY [35] and Hungarian researchers [46b, 48a].

WILLSTÄTTER thus assumed that ecgonine and ψ-ecgonine were $C_{(3)}$ epimers only *per analogiam*, without having presented the proper experimental evidence.

Concerning the stereochemistry of cocaine, investigations reached this stage by 1951.

Establishment of the configuration of tropine and *pseudo*tropine encouraged FODOR and later his pupils to endeavour to determine the configuration of the cocaine epimers which is a far more intricate problem, for stereochemically it involves a system with two variables. One principle of the working hypothesis was the above finding of WILLSTÄTTER according to which cocaine or ecgonine could be isomerized under similar circumstances to give *pseudo*ecgonine [29], like *anti*-tropine to *syn*-tropine. This was the reason why he denoted the epimer of *l*-ecgonine as *d-pseudo*ecgonine [200], regarding both compounds to be $C_{(3)}$ epimers. The Hungarian investigators wanted to prove first the correctness of this assumption in an experimental way. The second part of the labour project consisted of the determination of the steric relationship of the groups at positions 2 and 3. The theoretical methods of conformational analysis were employed on one hand, and ring formation between the hydroxyl and carboxyl groups was attempted on the other. Since the possibility of failing with this experiment was taken into consideration, reactions of known stereochemical course occurring with the retention of the configuration were employed at the same time to convert the carboxyl group and prepare derivatives in which the neighbourhood or remoteness of the functional groups could easily be detected. A third task was the *direct* determination of the relative steric position of the carboxyl functional group at position 2 in relation to the ring nitrogen, by means of a cyclization reaction.

Determination of the Relative Steric Positions of the Nitrogen Atom and of the $C_{(3)}$ Hydroxyl Group in Cocaine Epimers

FODOR degraded cocaine through O-benzoylecgonine [31] to *nor*-ecgonine, and *pseudo*ecgonine by oxidation with $KMnO_4$ [30] to *nor-pseudo*ecgonine. In the course of these processes no change of the configuration could take place. Then the N-acetyl derivatives of the ethyl esters of these compounds were prepared, and comparative N→O acyl migration reactions were carried out in the presence of hydrogen chloride in dioxan. In this case, the ethyl ester of N-acetyl-*nor-pseudo*ecgonine was converted readily into the ethyl ester hydrochloride of O-acetyl-*nor-pseudo*ecgonine; however, when the *nor*-ecgonine derivative was reacted under comparatively mild conditions, though the starting material could not be recovered, no compound of salt character was formed either [43] (Fig. 77). When O-benzoyl-*nor*-ecgonine (the betaine) was liberated from O-benzoyl-*nor*-ecgonine hydrochloride [31], the product did not rearrange into the corresponding N-benzoyl derivative even if a prolonged period at pH 8 was assured. These experimental facts were interpreted in a way leading to the conclusion that they were in agreement with the assumption of WILLSTÄTTER [200] as regards the $C_{(3)}$ epimerism existing between (−)-ecgonine and (+)-ψ-ecgonine. It follows certainly only so much from these facts that *pseudo*ecgonine has a hydroxyl group in a steric position in *syn*-relation to the nitrogen atom [41, 43, 45a, 60]. The evidence produced in the case of ecgonine [41] needs further confirmation because of its negative charac-

ter regarding the *anti* steric position of the $C_{(3)}$ hydroxyl group, since the decision to be reached concerns *not* the configuration of *two* diastereomers, but *two among four* possible configurations. That was the reason why FODOR et al. set out in the autumn of 1952 to find another approach to the problem of the $C_{(2)}$ or $C_{(3)}$ epimerism of this epimeric pair, and to reach a final decision. The importance of further efforts was pointed out independently by G. STORK (November, 1952) and by W. HÜCKEL (January, 1953) in letters written to G. FODOR [100, 186]. First the elimination of the carboxyl group was attempted by treating the silver salt of ecgonine with bromine or iodine [48a]. The for-

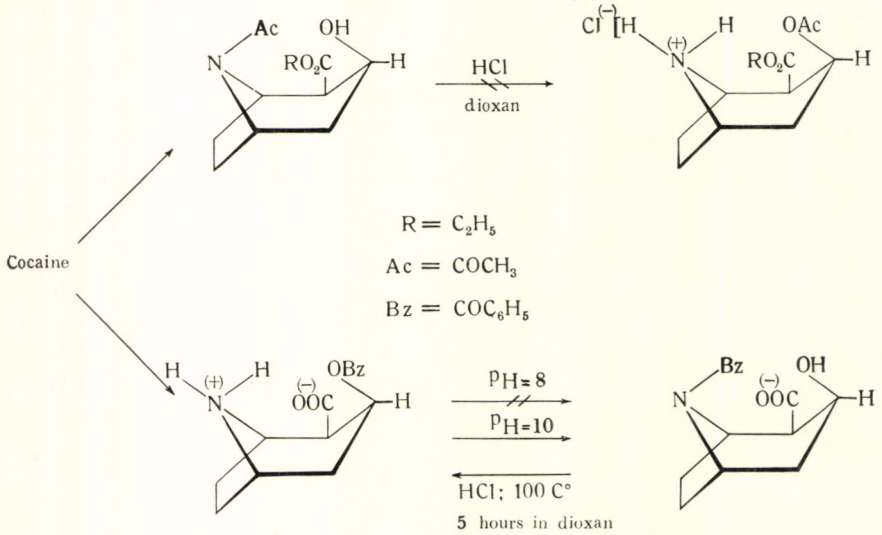


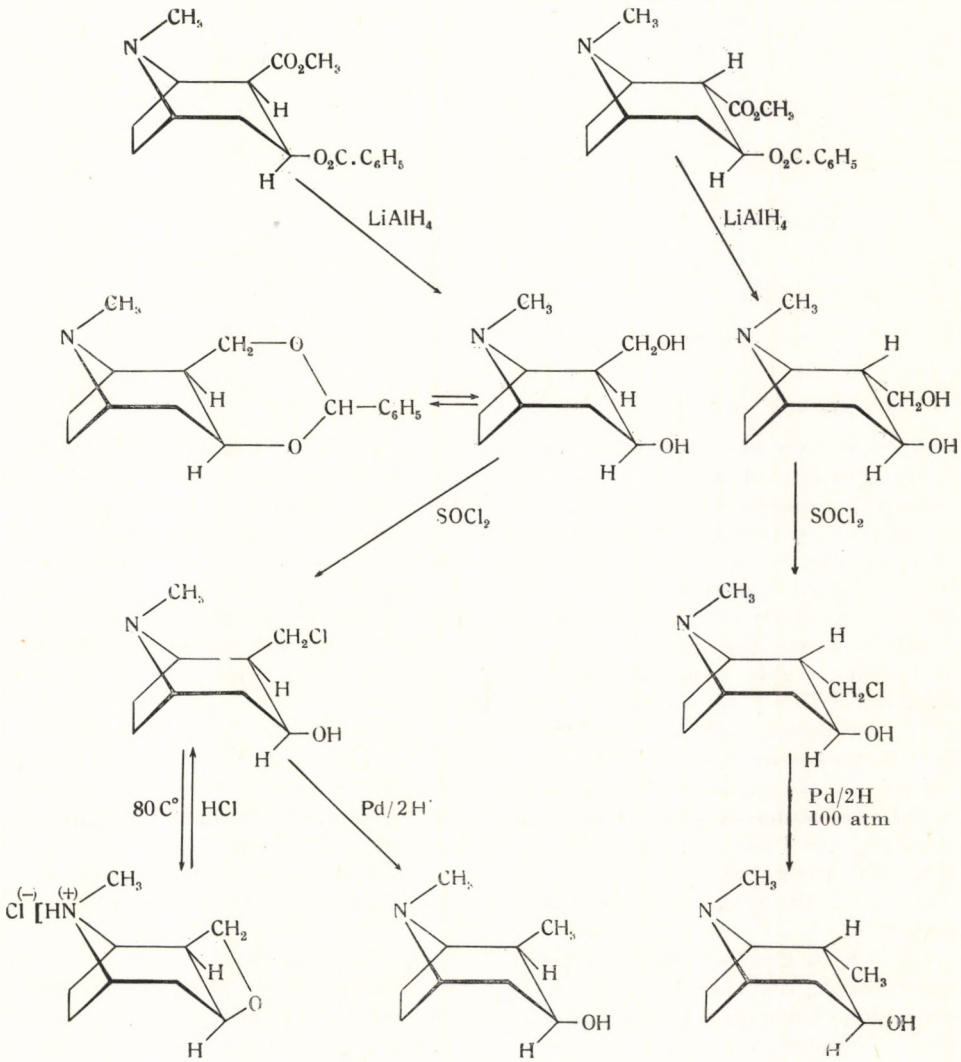
Fig. 77

mation of 2-bromo-3-tropanols was expected which on reductive dehalogenation would have given 3*α*- and 3*β*-tropanol in case of $C_{(3)}$ epimerism, and exclusively 3*β*-tropanol in case of $C_{(2)}$ epimerism. However, since the ecgonine—silver nitrate complex salt gave no well-defined product under such conditions and HUNSDIECKER's degradation reaction failed previously also with other hydroxy acids, first of all the $C_{(3)}$ hydroxyl was eliminated both from cocaine and *pseudo*-cocaine. For this purpose ecgoninol (prepared previously from cocaine [43, 60, 163]) and *pseudo*ecgoninol (prepared from *pseudo*ecgonine methyl ester by means of lithium aluminium hydride reduction) were converted into the corresponding 2-methyl-3-tropanol epimers [46a, 64]. It was done by chlorination with thionyl chloride and subsequent catalytic reduction (Fig. 78).

The hydrogenolysis of the chloro derivate from *pseudo*ecgoninol could successfully be carried out only under high pressure. On the other hand, the 2-chloromethyl-3-tropanol modification prepared from ecgoninol is extremely reactive, and this property will be discussed further also from other aspects (p. 106).

The stereospecific behaviour of the two different 2-methyl-3-tropanols was shown also in the course of oxidation. While the ecgonine derivative was readily oxidized by aluminium *iso*propoxide catalyst to give the corresponding

ketone, the desoxy compound obtained from *pseudo*ecgoninol proved to be completely resistant to this method of oxidation, though it could be oxidized with chromic acid. Both ketones, prepared in the spring of 1953, *gave the same oxime* which was found to be laevorotatory. FODOR and KOVÁCS regarded this common derivative as a decisive evidence [60]; the formation of identical oximes from both epimeric 2-methyltropanols seemed to confirm WILLSTÄTTER's statement [200] and his early findings, which made him declare that cocaine and *pseudo*cocaine were $C_{(3)}$ epimers. When the oxime in question obtained from 2-methyltropanol which, in turn, had been prepared from ecgonine, was successfully produced in larger amounts, and was carefully hydrolyzed by picric acid into the ketone, not the original *laevorotatory* ketone, but its



A *B*

Fig, 78

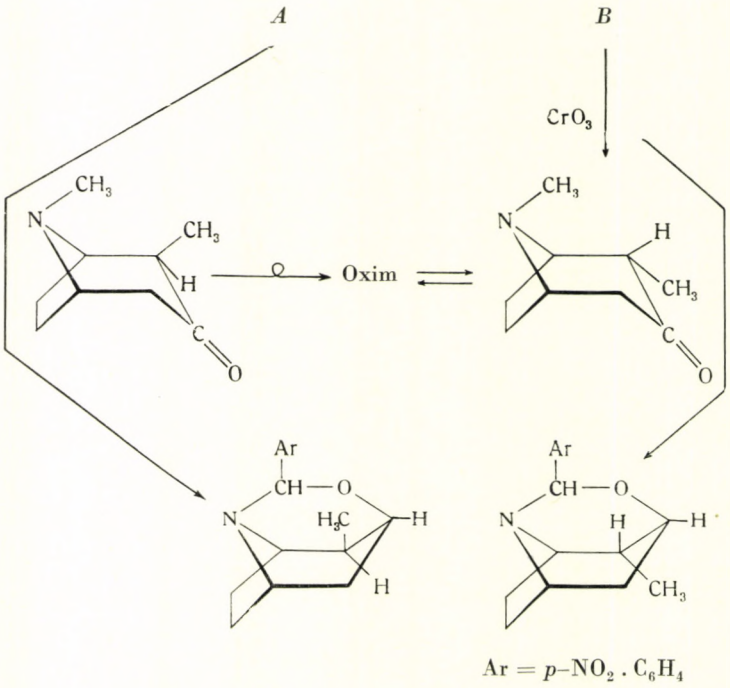


Fig. 78 (continued)

dextrorotatory isomer was obtained. The same ketone was isolated in the form of its crystallized salts in the course of later investigations, when 2-methyl-3-tropanol, obtained from *pseudo*ecgonine, was oxidized [46a,b, 64,] This ketone is reversibly converted into the above-mentioned oxime. By these experiments it was finally decided that the 2-methyl-3-tropanol epimers gave two different ketones; the ecgonine derivative undergoes inversion during alkaline oximation, while the ketone obtained from *pseudo*ecgonine can be converted into the oxime without change of configuration. This is the first and indisputable experimental evidence for the $C_{(2)}$ epimerism of the two compounds, i.e., of cocaine and *pseudo*cocaine.

Simultaneously with the final steps of this work (November, 1953), a preliminary note was published by FINDLAY [35a], stating the fact that he succeeded to convert O-benzoyl-*nor*-ecgonine into the N-benzoyl derivative *under the action of concentrated potassium carbonate solution* [60], notwithstanding previous experiments in mild alkaline medium which had failed (Fig. 77). From this fact the $C_{(2)}$ epimerism of cocaine and *pseudo*cocaine was concluded, the result being compared with former experimental evidences of FODOR.

It is interesting that no report about carrying out the counterpart of this experiment, i.e. the N→O acyl migration was made, although its *intramolecular* character had been proved much earlier [41, 46a] than that of the O→N migration, in which latter case also *intermolecular* ester amidation processes may not be excluded either. Having also the evidences obtained by way of oxidizing the two epimeric methyltropanols to the ketones, it is obvious

that FINDLAY's statements are sound. As an additional proof, the present author converted N-benzoyl-*nor*-ecgonine into the hydrochloride of the O-benzoyl derivative by means of hydrochloric acid in dioxan, under rather vigorous conditions [46a] (Fig. 77), and supplied in this way the complementary part of FINDLAY's experiment.

It was also stated by FINDLAY that while ecgonine could be epimerized to ψ-ecgonine only in the presence of concentrated potassium hydroxide [29], (—)-cocaine was converted into (+)-ψ-ecgonine methyl ester nearly completely within a short time when acted upon by 1/10 mol sodium methoxide, as a result of alcoholysis and epimerisation [35a] (Fig. 79). However, it is known

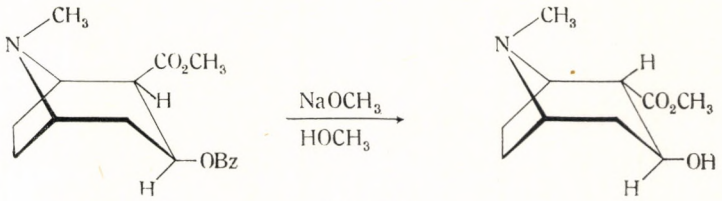


Fig. 79

that racemization of the α-carbon atom in carboxylic esters [3] does occur under such mild experimental conditions, while epimerization of mesoid alcohols, e.g. tropine to ψ-tropine [198], requires far more drastic conditions. This fact is also a proof by analogy for the $C_{(2)}$ epimerism of the pair of cocaine—ψ-cocaine.

As for additional evidence, FODOR, KOVÁCS and WEISZ [46b, 64] degraded both epimeric 2-methyl-3-tropanols *via* the N-cyano-compounds to the *nor* derivatives, and condensed them with *p*-nitrobenzaldehyde to two diastereomeric oxazine derivatives, using the method of GOODSON and CHRISTOPHER [85] applied by HARDEGGER and OTT [88] originally for *nor*-tropine (Fig. 78). It followed that both ecgonine and *pseudo*ecgonine had a secondary hydroxyl group in the *syn* position.

The steric neighbourhood of the nitrogen and oxygen atoms was proved in these epimeric *nor*-amines also by the reversibly and readily occurring

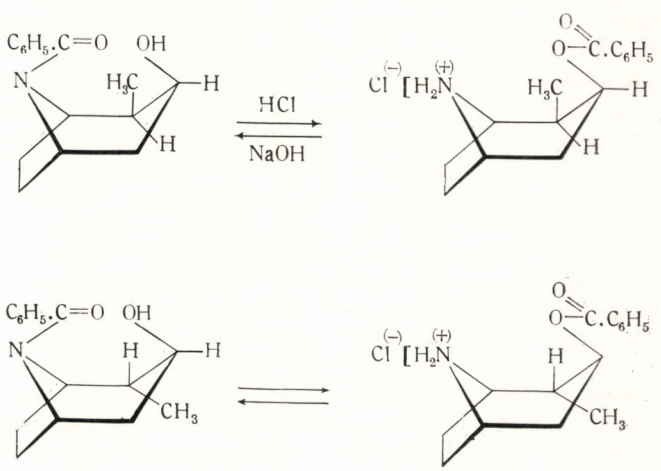


Fig. 80

O→N acyl migration of the benzoyl derivatives (Fig. 80). Thus the original names, given by WILLSTÄTTER [200] became to be modified, since both cocaine and *pseudo*cocaine are actually '*pseudo*'-derivatives, i.e., compounds derived from *pseudo*tropine [46a, 35a, 64].

The next problem was the explanation of the cause of failure of the acyl migration reaction in the case of N-acetyl-*nor*-ecgonine ethyl ester, in spite of the *syn* steric position of the hydroxyl group in relation to the nitrogen atom. HÜCKEL assumed that either the ethoxycarbonyl group suffered a screening effect from the $C_{(3)}$ hydroxyl group, or a hydrogen bond was formed (Fig. 81) between the nitrogen and ester-oxygen. The fact that FINDLAY [35a] found a

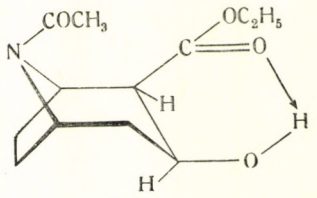


Fig. 81

hydrogen bridge between the OH and COOH oxygen atoms in the infrared spectra of benzoyl ecgonine is in agreement with this assumption. On the other hand, STORK pointed out that ecgonine and its derivatives, as it is known, became readily dehydrated under the action of acids, but *pseudo*ecgonine derivatives did not. He was of the opinion that when the ethyl ester of N-acetyl-*nor*-ecgonine was treated with hydrochloric acid in dioxan, elimination of the elements of water was brought about by the reagent, and the produced anhydro-compound suffered partial decomposition, since it was by no means capable of forming an O-acyl derivative. In our view, both factors may play a part, although a corresponding carboxylic *acid*, i.e. N-benzoyl-*nor*-ecgonine, undergoes the acyl migration process without dehydration. These facts confirm rather the assumption of a steric hindrance on part of the ester group. The above-mentioned researchers have not investigated, however, whether esters of this type are actually more readily dehydrated than carboxylic acids, although it seems probable that the electron withdrawing effect of the ethoxycarbonyl group is much greater than that of the carboxyl group, and splitting off of the proton from the carbon atom in α steric position (required for elimination) nvolves less prototropic work in this case than in that of the free acid [48a].

Relative Steric Positions of the Substituents of the $C_{(2)}$ *and* $C_{(3)}$ *Atoms in Cocaine Epimers*

In order to solve this problem, it should be considered first of all [41, 60] that ecgonine is converted into anhydroecgonine with extraordinary ease, while *pseudo*ecgonine can withstand dehydration by acids remarkably well, and is converted into the same olefine derivative only at 140° [29]. If the principle of *anti*-elimination [2] is combined with the assumption of the chair conformation of the tropane skeleton, one may expect an easy water elimination reaction of ecgonine, due to the presence of an *axially* bound hydroxyl on $C_{(3)}$, and of an equally *axial* hydrogen atom on $C_{(2)}$ (Fig. 82). In the case of ψ-ecgonine, however, the *equatorial* position of one group and the

axial of the other is less favourable for this elimination reaction. Since at the time of these final conclusions [41] ecgonine was still regarded by the author as a $C_{(3)}$-*α*-tropanol derivative, this inference appeared to be in agreement with former stereochemical concepts. Now it is known that the $C_{(3)}$ hydroxyl of the cocaine molecule assumes *syn* position — just like that of *pseudo-*

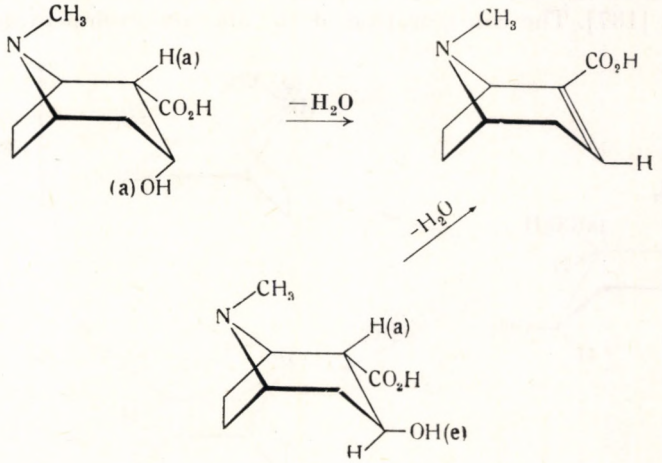


Fig. 82

cocaine — and this would mean together with the premise of the chair conformation that in ecgonine both the hydrogen to be split off as well as the hydroxyl group assume *axial* steric positions. In the boat form the situation is naturally the opposite (Fig. 83). However, the stereochemistry of *β*-hydroxy

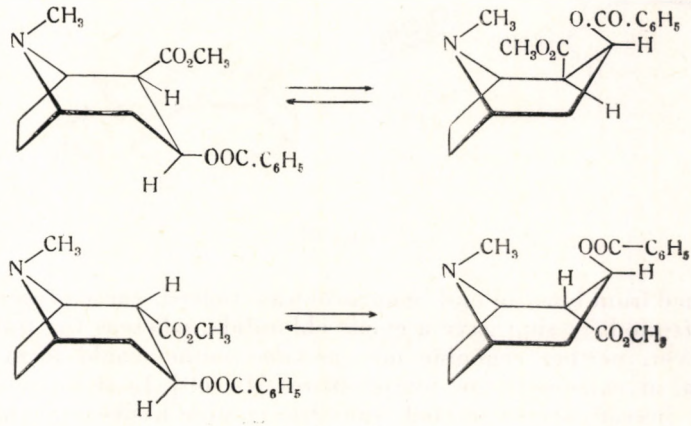


Fig. 83

acids and especially their elimination reactions have not been studied so far thoroughly enough to permit an *a priori* extension of principles [2], undoubtedly valid for the dehydration of simpler alcohols, to far more complicated systems, where conformations are in dynamic equilibrium, and the stability is modified by the presence of an endoethylenic bridge [49]. Namely, the tropane skeleton

can be regarded not simply as 2,6-endoethylene-piperidine, but also as 1,4-endomethylimino-*cyclo*heptane.

This was the reason why besides any evaluation of the facts reported in the literature also additional *experimental* evidence of various kinds were sought. In order to determine the steric proximity of the carboxyl and hydroxyl groups in β-hydroxy acids, TOIVONEN employed the method of condensation with chloral [187]. The configuration of the alkyloxycyclopentane carboxylic

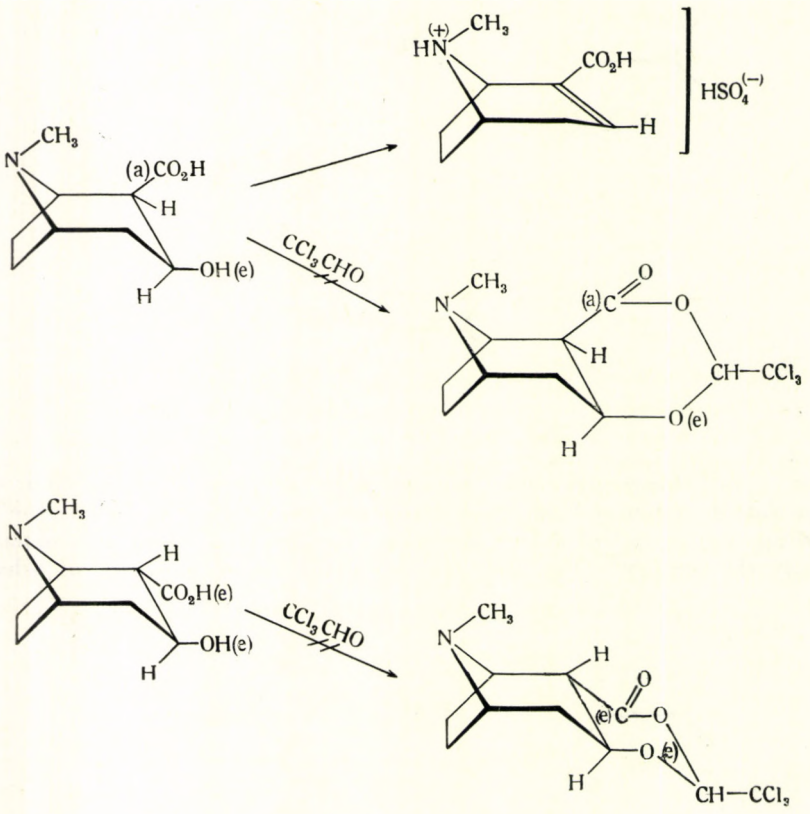


Fig. 84

acid obtained from borneol and *iso*borneol was, indeed, successfully elucidated, since the *cis*-modification gave a cyclic chloralide, whereas the *trans*-form did not. However, neither ecgonine nor *pseudo*ecgonine could form chloralides with chloral at extremely low temperatures [43, 60]. In the case of ecgonine, Hungarian investigators isolated anhydroecgonine hydrogen sulphate, while *pseudo*ecgonine gave the acid sulphate of the starting compound (Fig. 84). Thus, elimination of water occurred sooner than chloralide formation even in the case of ecgonine. Since these experiments and considerations gave no definite answer to the question of the steric position of the $C_{(2)}$ and $C_{(3)}$ functional groups in ecgonine, FODOR attempted to employ an alternative working hypothesis: the carboxyl group was converted into some other group which was expected to undergo a cyclization with the $C_{(3)}$ hydroxyl group in the case

of their steric neighbourhood. For this purpose, cocaine epimers were subjected to Curtius reaction, which — according to the literature — always took place, but for one exception [178], with the retention of configuration [3]. The result of the reaction was, in this case, the formation of the epimeric 2-amino-3-tropanols. These compounds were further studied by employing the method of acyl migration, which had been proved valuable, e.g., in the case of 2-amino-cyclanols (see introductory chapter; [27]). The 2-benzamino-3-tropanol prepared from cocaine, suffered quantitative N→O acyl migration under the action of hydrochloric acid, and gave the *bis*-hydrochloride of the

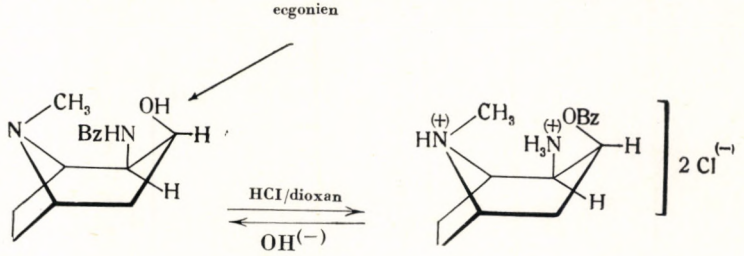


Fig. 85

O-benzoyl derivative (Fig. 85). With the N-benzoyl derivative of 2-amino-3-tropanol, obtained from ψ-ecgonine, no acyl migration reaction took place under identical circumstances (Fig. 86). The acyl shift was found to be reversible with the ecgonine derivative, thus the experiment confirmed the *cis*-configuration of the two functional groups in the case of this compound as well as for the original cocaine molecule [43, 60]. In order to obtain further confirmation of this statement, ecgoninol and *pseudo*ecgoninol were prepared by reduction with lithium aluminium hydride. During this process the asymmetric carbon atoms could not suffer any kind of attack. Then both 2-hydroxymethyl-3-

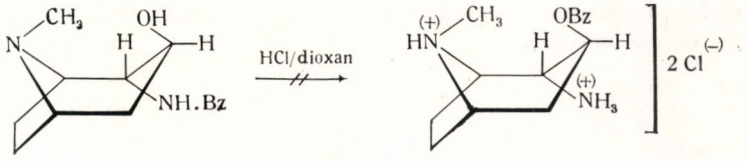


Fig. 86

tropanol epimers were subjected to acetylation in the presence of benzenesulphonic acid catalyst. This reaction took actually place only with ecgoninol (Fig. 87), while only the salt of the starting material with benzenesulphonic acid was obtained from ψ-ecgoninol (Fig. 88). Also this fact proved the proximity of the $C_{(2)}$ and $C_{(3)}$ groups of the cocaine derivative. The objection may be raised against this argument that when the piperidine ring in tropane is in its ground state in the chair conformation, the groups in question will be in *cis* steric position in cocaine, i.e. *equatorial, axial ;* but in *pseudo*ecgonine both groups of *trans* position will be *equatorial*, accordingly ring closure could not be excluded in the latter case, either. Thus the fact of cyclisation itself is not absolutely decisive. Indeed, formation of a ring is not conclusive if it may occur with either of the epimeric compounds, e.g., as a 4,6-benzal-

compound may be formed both from galactose [76a] and glucose [76b], i.e. from two $C_{(4)}$ epimeric hexoses. This analogy was pointed out by REICHSTEIN [155]. Another fact to be considered is that in the case of the tropane

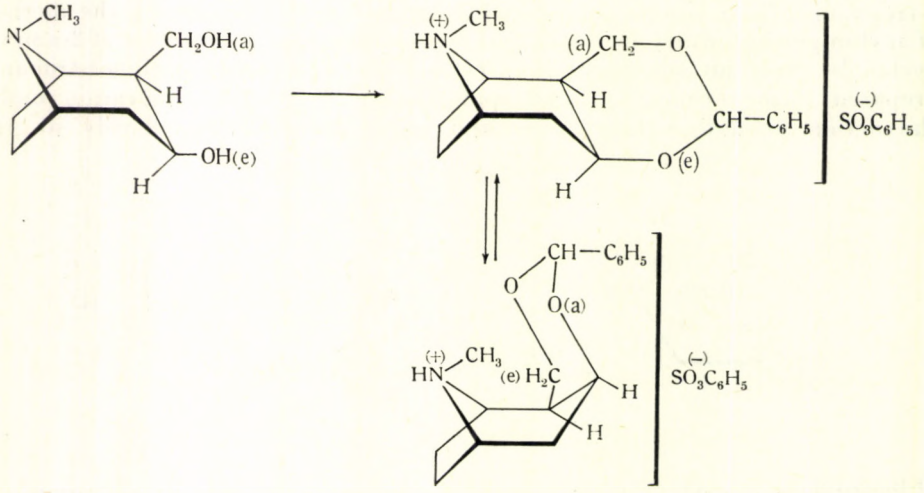


Fig. 87

skeleton — like in most similar systems — one should calculate with a dynamic equilibrium between the chair and boat configurations. This aspect is supported, e.g., by the tendency of the $C_{(3)}$ OH group to form a ring with the substituents of the nitrogen. However, if such an equilibrium does exist, it will *favour* the possibility of ring formation *equally* well in case of both sides of the *equatorial–axial*, *axial–equatorial* system if it is about a *cis*-modification. With *trans* modifications, on the other side, from between the two conformations, i.e., *axial–axial* and *equatorial–equatorial*, *only the latter state* will be preferred from the aspect of cyclization.

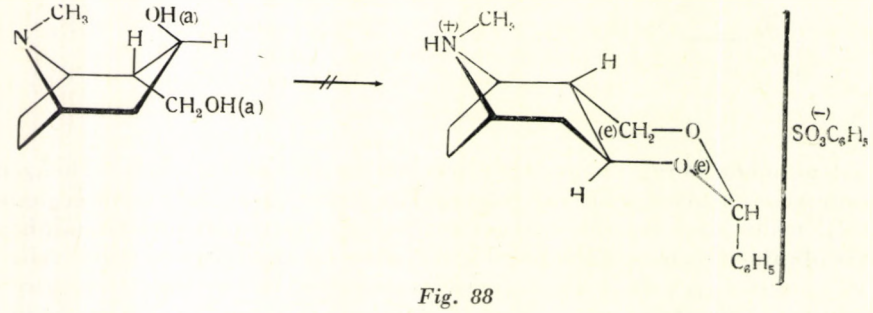


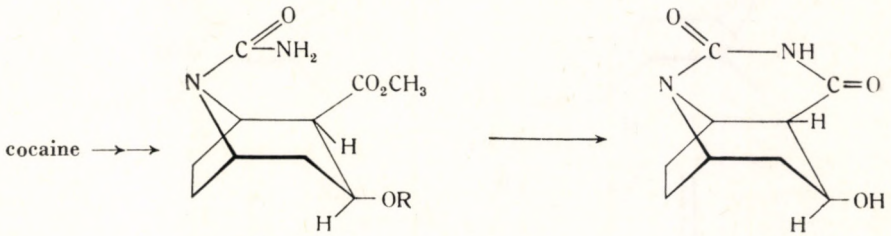
Fig. 88

Hence, from the experimental fact the straight statistical conclusion may be drawn that not necessarily only the presence of the chair conformation should be taken into consideration for the molecules of cocaine and ψ-cocaine. Under any circumstances, the *cis* steric position of the $C_{(2)}$ carboxyl and $C_{(3)}$ hydroxyl groups in the cocaine molecule, and their *trans* steric position in ψ-cocaine [48a, 49] should be regarded as definitely settled.

Direct Attachment of the Ring Nitrogen to the Carboxyl Group

For this purpose in 1954 FODOR synthesized N-cyano-*nor*-cocaine, known also previously, added the elements of water by treatment with sulphuric acid monohydrate, and the N-carbamyl-*nor*-cocaine obtained [59] was cyclized to the lactame by means of sodium methoxide at $-20°$ (Fig. 89).

On the basis of these experimental facts, cocaine should be characterized as 2β-carbomethoxy-3β-benzoyloxytropane, while ψ-cocaine is to be regarded as 2α-carbomethoxy-3β-benzoyloxytropane [48a, 49, 60]. From these results the steric structures of the esters of α- and β-truxillic acids formed with ecgonine methyl ester, of α- and β-truxilline, as well as that of cinnamyl ecgonine methyl ester follow automatically.



(a) R=COC_6H_5

(b) R=H

Fig. 89

Conformation of Cocaine

By employing the methods of conformational analysis, BOSE [18] ascertained that when methyl tropinone-2-carboxylate is hydrogenated, derivatives of most stable conformation must of necessity be formed, i.e., compounds which have *equatorial* (2α, 3β) functional groups both on the $C_{(2)}$ and $C_{(3)}$ carbon atoms. That is right if the ketone ester is in the chair conformation (Fig. 76). This prerequisite is given, however, only in the case of *pseudo*ecgonine ester. In *dl*-ecgonine and in the third racemate [204] these groups assume *equatorial–axial* (2β, 3β) or *axial–equatorial* (2α, 3α) steric positions, whereas in the fourth racemate they are of necessity *axial–axial* (2β, 3α). These statements are essentially in agreement with the above views, however, they are only the results of conformational analysis, and they can be consistent solely with the already proved [41, 42] configuration of ψ-ecgonine, while reservations are necessary concerning the decision between cocaine and the third racemate. The synthesis of the third and fourth epimer of cocaine has been realized by FINDLAY [36, 39], thus their stereochemical investigation is already in progress. However, so much is certainly known that an α hydroxyl group of *anti* steric position must be present in both compounds, while the carboxyl group is in *syn* (β) position in one compound, and in *anti* (α) in the other.

Predictions of conformational analysis are taken with special precaution in this case, since tropinone-2-carboxylate itself may occur as an enol-betaine, and even in its esters the 2β-methoxycarbonyl group may become easily rearranged into 2α steric position through the enol form. Besides, one must take into consideration a dynamic equilibrium between the chair and boat conformations of both epimeric (racemic) ketones. The table of for-

mulas in Fig. 76 lists all these possibilities, with regard to the fact that reduction of the enol form involves most probably *cis* hydrogen addition, and considering the predictions concerning the stereochemical course of the reduction of the carboxyl groups of cyclohexane ketones, according to which 'chemical' methods (e.g., use of sodium amalgam as done by WILLSTÄTTER) cause the formation of an *equatorial* hydroxyl group, and catalytic hydrogenation that of an *axial* one. Naturally, as a result of the relative stabilities of the end products, another problem is the possibility of their secondary interconversion (e.g. ecgonine ester into ψ-ecgonine ester) which makes the situa-

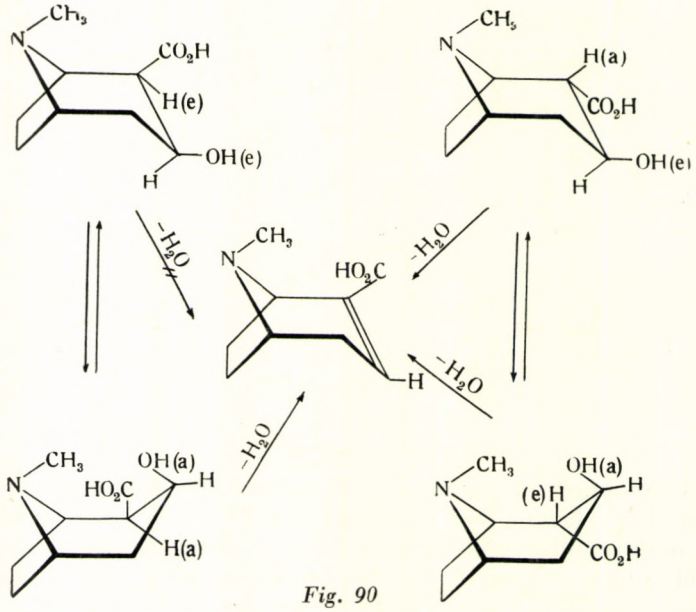


Fig. 90

tion even more complex. Thus, when 'chemical' methods are used, in principle all the four pairs of antipodes may be formed. It is necessary to presuppose that both epimeric ketones are in the chair form, in order that one may arrive at BOSE's final conclusions [18], i.e., formation of the $2\beta, 3\beta$-modification (ecgonine) and of the $2\alpha,3\beta$-epimer (ψ-ecgonine); in this case, however, the third epimer must be derived from the enol form of the ketoester or from one of the boat conformations.

The *third* ecgonine racemate, obtained by the reduction of methyl tropinone-2-carboxylate [204], becomes extremely easily dehydrated. While taking the mentioned restrictions into consideration, the above authors are nevertheless of the opinion, that the compound has functional groups of *anti* α steric position on $C_{(2)}$ as well as on $C_{(3)}$ [42, 48]. In this case both the hydrogen and hydroxyl are in *axial* position in the chair form and, consequently, according to the principle of *trans* elimination [2], it would favour the elimination of water (Fig. 90). For the synthesis of this pair of compounds, Hungarian investigators and FINDLAY carried out corresponding experiments (p. 108).

By means of the pressure hydrogenation of both epimeric modifications of 2-methyltropane-3-one, the third and fourth epimeric modifications of

2-methyl-3-tropanol were successfully prepared (Fig. 91). A study of the third and fourth epimers of cocaine is equally interesting also from the scientific i.e., pharmacological point of view. For this purpose the resolution of WILLSTÄTTER's 'third racemate' and the inversion of the antipodes at the $C_{(2)}$ carbon atom was attempted. On the other hand, FODOR wanted to proceed with the task of dehalogenating α-bromoecgonine-β-lactone, prepared by EICHENGRÜN and EINHORN [28], with the purpose of preparing the third epimer ($2\alpha,3\beta$-modification: *allo* ecgonine) by means of hydrolyzing the lactone

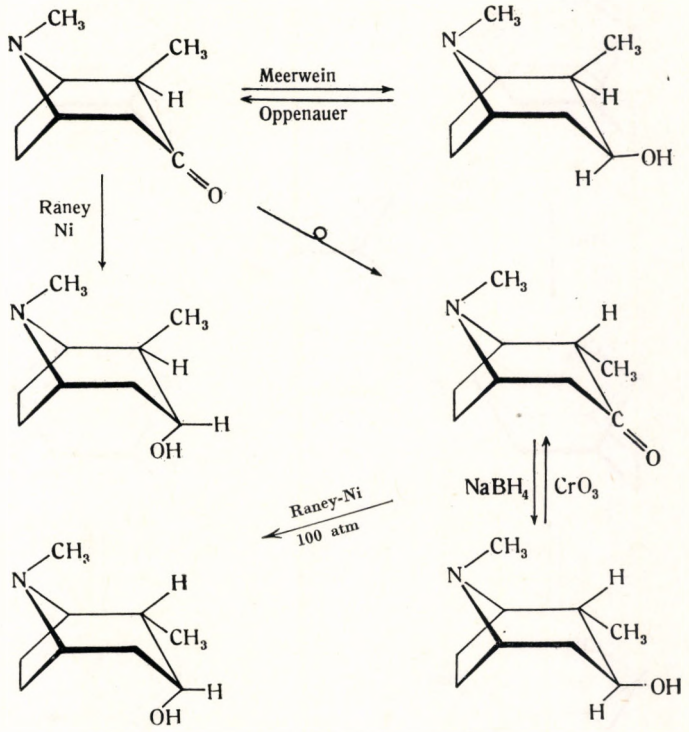


Fig. 91

bond [48] (Fig. 92). In principle, of course, it is possible that this experiment would represent merely a new way of formation of ecgonine. Unfortunately, however, preparation of α-bromoecgonine-β-lactone could not be reproduced so far, thus this way of approach has remained blocked.

However, it was successful to find a new possibility for the stereospecific synthesis of *all the four diastereomeric ecgoninols* [86, 111] by the use of the special conversions observed in the case of 2β-chloromethyl-3β-tropanol. When the hydrochloride of this compound was decomposed, e.g. by sodium ethoxide, the result was not the formation of the free base, but that of an ethoxyl derivative. This reaction was ascribed primarily to the great mobility of the chlorine atom, i.e., to its exchange with the ethoxide anion according to an $S_N 2$ mechanism. Later it was proved that this base could be isolated in crystalline form if extremely low temperatures were employed. A short period of warming in a neutral solvent, however, caused spontaneous conversion of

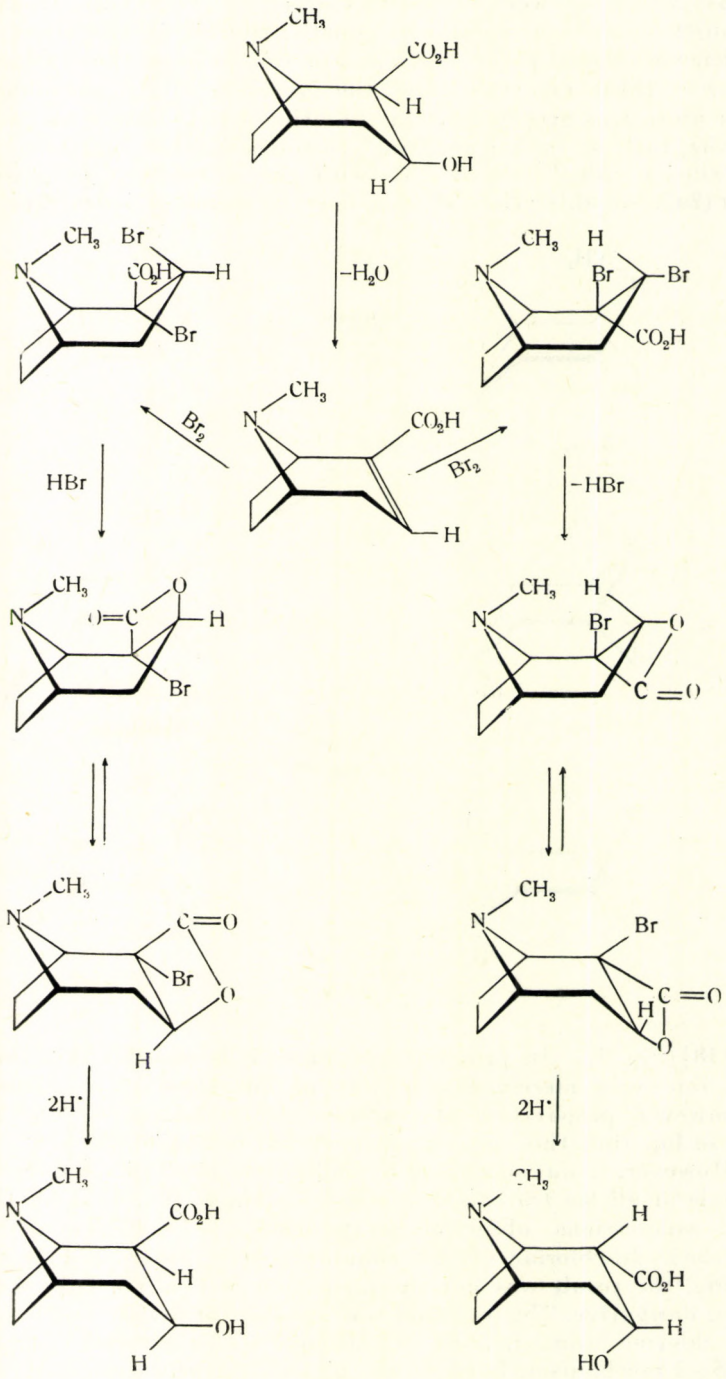

CH3
N
CO2H
H
OH
H
-H2O
CH3 Br
N
CO2H
H
Br
CH3 H
N
Br
Br
CO2H
Br2
CH3
N
CO2H
H
Br2
HBr
-HBr
CH3
N
O
O=C
H
Br
CH3 H
N
Br
O
C=O
CH3
N
C=O
Br
O
H
CH3
N
Br
C=O
H
O
2H·
2H·
CH3
N
CO2H
H
OH
H
CH3
N
H
CO2H
H
HO

Fig. 92

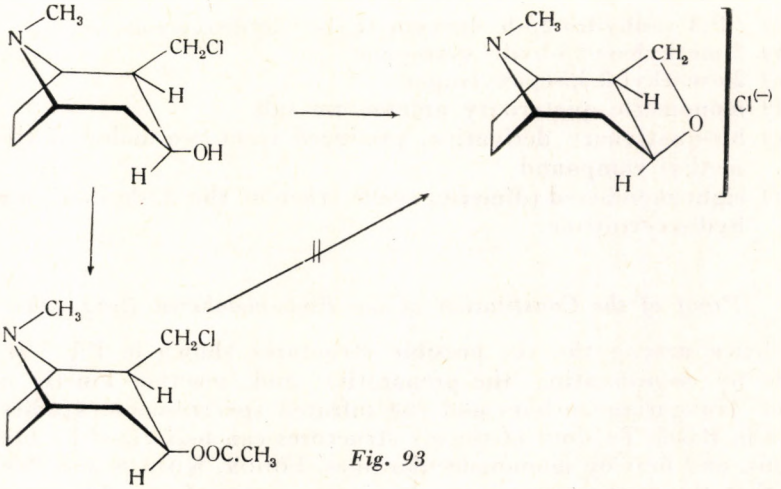


Fig. 93

the base into an isomeric compound containing chloride ions, and the melting point was raised to 140° (Fig. 93). As to the structure of this latter compound, there are six alternative possibilities (Fig. 94):

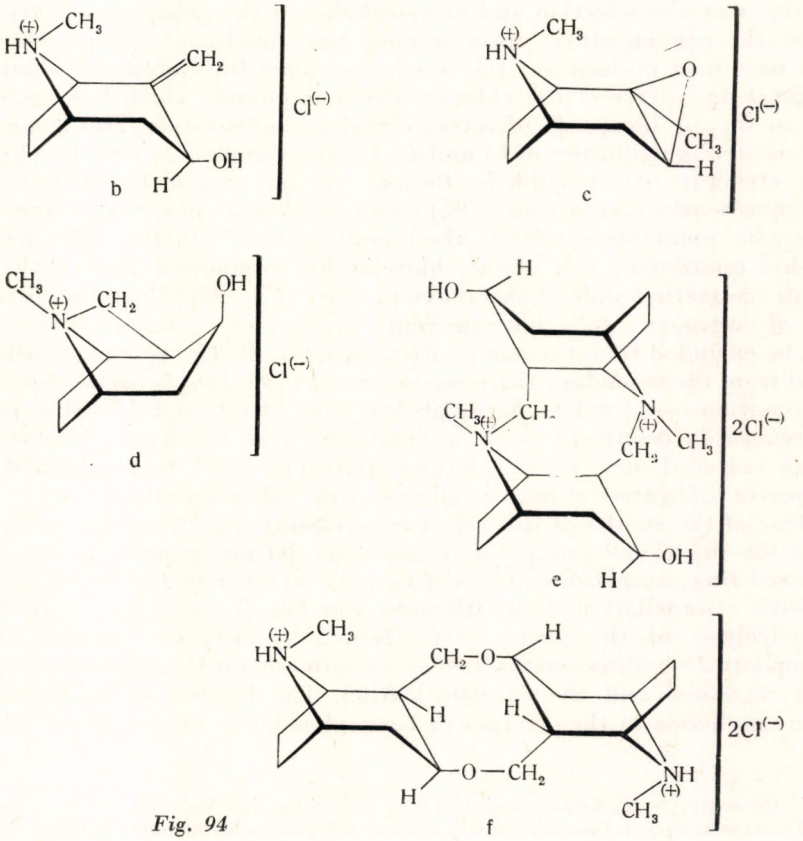


Fig. 94

a) ⟨2[1],3⟩-anhydro-2β-hydroxymethyl-3β-hydroxytropane
b) 2-methylene-3β-hydroxytropane
c) 2α-methyl-2,3β-epoxytropane
d) monomeric quaternary ammonium salt
e) bis-quaternary derivative, produced from two moles of the chloromethyl compound
f) eight-membered (dimeric) cyclic ether of the 2β-hydroxymethyl-3β-hydroxytropane.

Proof of the Constitution of the Four-membered Ring Ether

Choice among the six possible structures shown in Fig. 94 became possible by co-ordinating the preparative and reaction kinetic investigations of Hungarian authors and the infrared spectroscopic studies of Dr. ZOLLER in Basel. Two out of the six structures can be formed by bimolecular reactions, and four by monomolecular ones. FODOR, KOVÁCS and WEISZ [111] found that the spontaneous isomerization in water of the chloromethyl base to the hydrochloride of the final product revealed the occurrence of a monomolecular reaction. Consequently, the structures representing the dimeric quaternary salt (e) and the dimeric ether (f) can be excluded. Determination of the molecular weight also confirmed a 'monomolecular' constitution. The next step was the selection and identification of the groups necessary in any case for the condensation, from among the functional groups which may play a part in a cyclisation; this work was done by systematic elimination. The acetyl derivative of the chloromethyl compound, which has no free OH group on $C_{(3)}$, is incapable of intramolecular condensation. This fact excludes the alternative possibilities of *b)* and *d)*, i.e. the compounds with free hydroxyl group; structure *d)* is unlikely because of its extremely strained nature, although recently GALINOVSKY [81] could synthesize an extraordinary strained tricyclic ammonium salt in the lupinine series.* On the other hand, the N-methyl quaternary salt of the chloromethyl compound gave with 1 mole of alkali the methohalide of the above product (Fig. 95). Thus, the quaternary state of nitrogen does not prevent cyclization. Consequently, *d)* and *e)* can be excluded from the competition once for all. The epoxide constitution, derived from the secondary rearrangement of *b)* [39, 168] is impossible, because hydrogenation could not be accomplished even at 80° and 100 atm. pressure, and because on treatment with hydrochloric acid the hydrochloride of the starting material, i.e., of 2β-chloromethyltropan-3β-ol was obtained. Infrared spectra indicated a four-membered ring ether structure, too.

One of the results of this set of experiments was that the *cis* steric position of the functional groups of cocaine was definitely proved, since a four-membered ring can become attached to a six-membered one much more probably with *cis*-anellation than with *trans*. Further, it was shown that the alkaline hydrolysis of the cyclic ether afforded by way of a bimolecular S_N2 reaction, two 2β-hydroxymethyltropanols epimeric on $C_{(3)}$, namely the already known ecgoninol and the 3α-modification. The latter was epimerized with sodium amyloxide in the presence of benzophenone as an oxidation—reduction

* Recently, N. J. LEONARD [in MANSKE: The Alkaloids, Vol. VII. pp .265—266 (1961)] queried that structure in favour of a dimeric one, with an eight-membered ring.

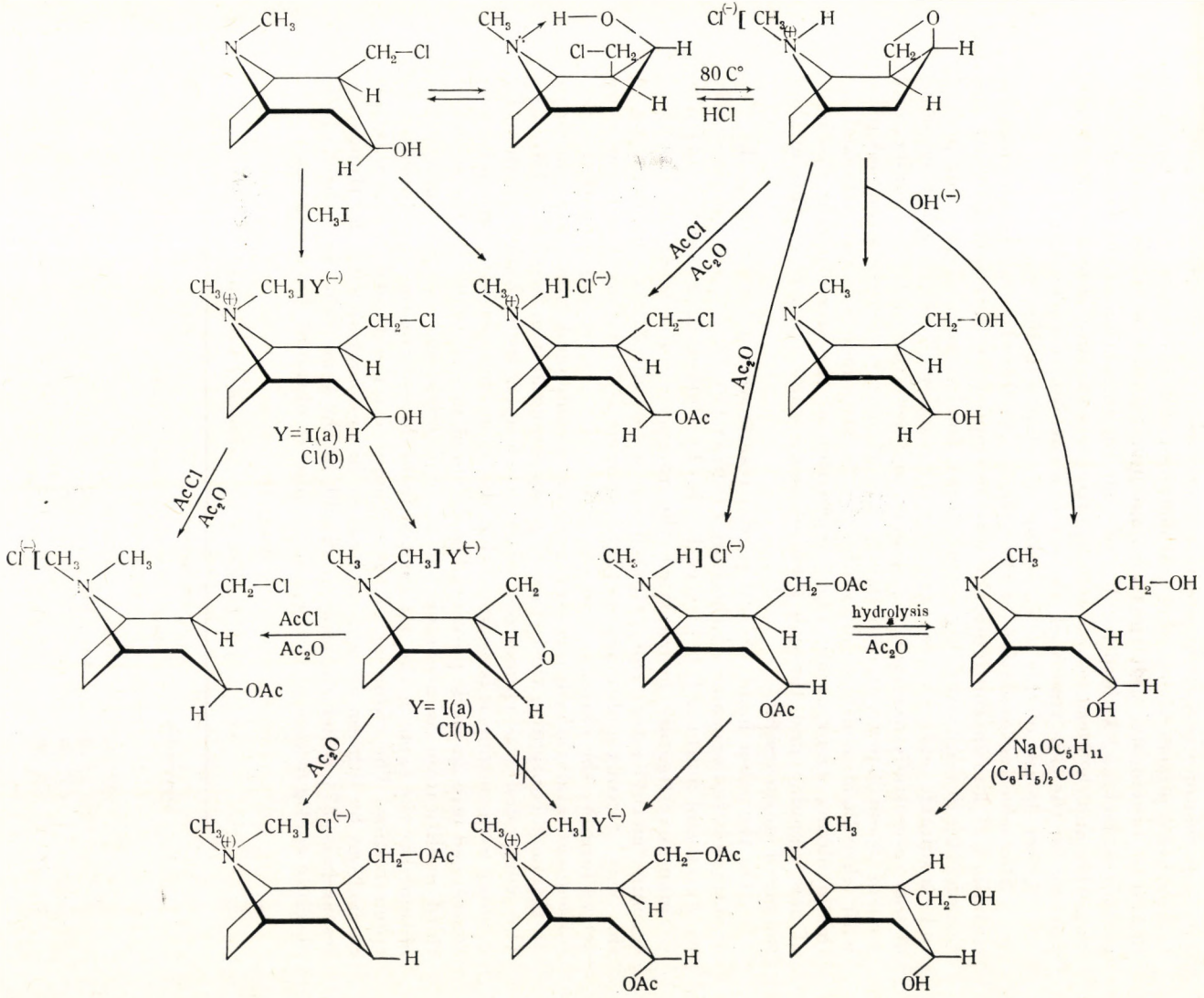

80 C°
HCl
CH3I
AcCl
Ac2O
OH(−)
Y= I(a) H
Cl(b)
hydrolysis
Ac2O
NaOC5H11
(C6H5)2CO
Y= I(a)
Cl(b)

Fig. 95

catalyst [27] to the diol of the fourth epimer, 2*a*-hydroxymethyl-tropane-3*a*-ol. The stereospecific synthesis of these two latter products opened up a way — in case of a successful selective oxidation of the CH_2OH group on $C_{(2)}$ — to two new epimers of ecgonine and consequently of cocaine, which had been unknown previously, and thus also an investigation of their physiological properties lacking. A third result was that the formation of the trimethylene ring ether and the steric course of its splitting was the subject of a detailed investigation for the first time with the use of a corresponding model.

Other details of this investigation are shown in Fig. 95.

The selective oxidation of the primary hydroxyl group of an epimeric ecgoninol of known configuration was attempted by HALMOS, KOVÁCS and FODOR [86]. Several oxidizing agents failed; finally moist silver oxide proved to be a suitable and selective reagent for the reaction. With this agent, ecgoninol was successfully oxidized to ecgonine, and ψ-ecgoninol to ψ-ecgonine, in a yield of 60 and 80 per cent, respectively. Unfortunately, overoxidation took place with the 2β,3*a*-modification, while the 2*a*,3*a*-epimer was not attacked by this oxidizing agent at all. Thus, realization of the stereospecific synthesis of new ecgonine and through them of new cocaine epimers by this method remained unsuccessful.

On the other hand, several partial results were achieved along the way of WILLSTÄTTER's cocaine synthesis by FINDLAY [36, 38, 39], and independently by ZEILE and SCHULTZ [211], recently also by PREOBRAZHENSKI [13, 14]. The German investigators benzoylated the racemate of WILLSTÄTTER's 'third ecgonine methyl ester' and prepared a new racemic cocaine modification in this way. FINDLAY obtained methyl tropinone-2(β?)-carboxylate in optically active form by the chromic acid oxydation of (+)-ψ-ecgonine methyl ester; subsequent catalytic hydrogenation gave a new compound, 2β-methoxycarbonyl-3*a*-tropanol, containing the hydroxyl group presumably in 3*a* position [36—39]. This compound was epimerized when acted upon by sodium ethoxide. By analogy with cocaine, it is assumed that the 2β-methoxycarbonyl group became rearranged into 2*a* steric position. The action of methyl iodide on the so-called third modification is accompanied by epimerization, and the methiodide obtained is the same as the one formed from the ester by the above-mentioned epimerization. The reduction of the ecgonine ester obtained in this way was carried out by lithium aluminium hydride in co-operation with the Hungarian researchers [37], which experiment should, at the same time, be a check of the absolute configuration of the ecgonine epimers obtained by synthesis.

Table IV

$C_{(2)}$ and $C_{(3)}$ *epimeric 2-hydroxymethyl-3-tropanols*

Configuration	Melting point		$[a]_{20}^{D}$	
	Base	Hydrochloride	Base	Hydrochloride
2β, 3β	oil	270—272°		—37.3°
2*a*, 3β	131—133°	232°	+58.3°	+46.3°
2β, 3*a*	139—141°	265°	+34.4°	—12.9°
2*a*, 3*a*	165—166°	172°	—11.8°	—13.7°

Corresponding to this labour plan, in October 1959 FINDLAY [39] reported the preparation of racemic *allo*cocaine and *allopseudo*cocaine. Finally, also the reduction of *allo*ecgonine methyl ester with lithium aluminium

hydride was described, in which case formation of 2α-hydroxymethyl-3α-tropanol was expected. This ecgoninol showed m.p. 202—202.8° and $[\alpha]_D^{20} =$ = 6.3°. These physical data correspond to none of those of the ecgoninols prepared previously by the Hungarian investigators (Table IV).

In this way the question remained undecided whether partial racemization took place during the reduction with lithium aluminium hydride, or the reaction course indicated previously by us in connection with the preparation of 2α-hydroxymethyl-3α-tropanol should be perhaps substituted, according to

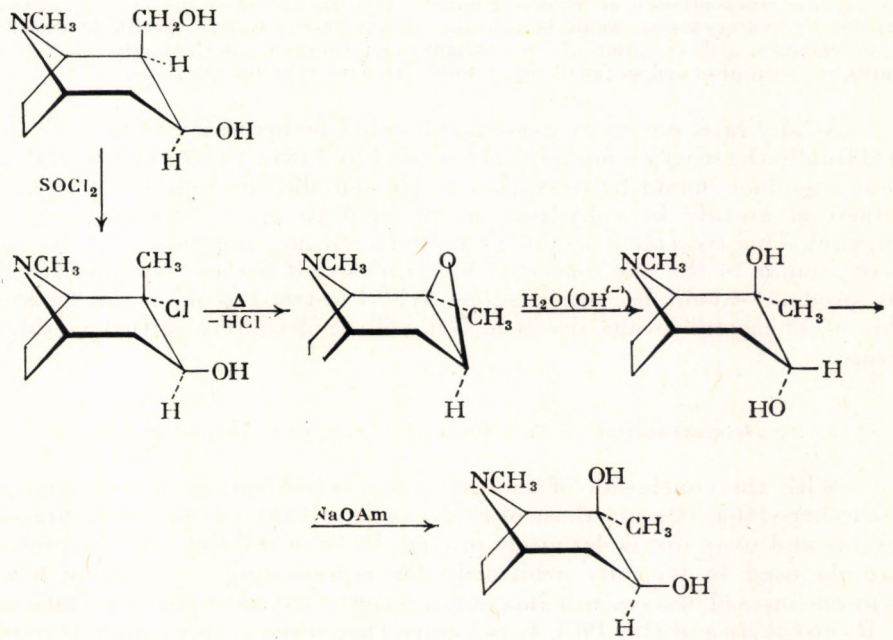


Fig. 96

FINDLAY, by the alternative route shown in Fig. 96. Essentially, FINDLAY assumed that treatment with thionyl chloride of 2β-hydroxymethyl-3β-tropanol, obtained from cocaine, was accompanied by a rearrangement, and consequently the product should not be formulated as 2β-chloromethyl-3β-tropanol, but as 2β-methyl-2α-chloro-3β-hydroxytropane. The latter product would become converted with the elimination of hydrogen chloride into 2α-methyl-2,3β-epoxytropane, and not into a four-membered ring ether. This compound, however, corresponds to the possible configuration of the conversion product from 'chloroecgoninol', formulated by us as *c)* in Fig. 94. FINDLAY suggested further that the hydrolysis of this epoxide gave 2α-methyltropane-2β,3α-diol and not 2β-hydroxymethyl-3β-tropanol. Epimerization with sodium amyloxide should give 2α-methyltropane-2β,3β-diol from this product, and not the fourth ecgoninol. This presentation, which was given also by FINDLAY himself only as an assumption, and not as a proved reaction sequence, can hardly be reconciled with the experimental results obtained by the author of present and his previous co-workers [111]. On the one hand, the ether proved to

be quite resistant to catalytic hydrogenation, which is in contrast with the behaviour of other epoxides of the tropane series, or with that of epoxides in general. On the other hand, infrared spectroscopy produced evidence also much more in favour of a strained trimethylene oxide ring than of a three-membered cyclic ether.

Both chloromethyltropanols (which were structural isomers according to FINDLAY) gave two epimeric 2-methyl-3-tropanols after hydrogenolysis, which were oxidized to two epimeric ketones; the products became, in turn, epimerized to the same ketoxime during the process of oximation. If the configuration of 2β-methyl-2α-chlorotropanol assumed by FINDLAY were a true representation of 'chloroecgoninol', then formation of the same 2β-methyl-3α-tropanol by hydrogenolysis would be probable only in case of a stereospecific hydrogenolysis of the chlorine, with retention of the configuration. However, no distinctly selective steric course has been observed so far in connection with such types of reactions.

At any rate, one more experiment would be necessary to be able to discard finally the reaction mechanism assumed by FINDLAY: the chloro-derivative from ecgoninol should be converted under non-alkaline conditions, e.g., with potassium acetate in anhydrous acetic acid to give 2β-acetoxymethyl-3α-tropanol. This treatment could, namely, by no means result in a rearrangement similar to the one indicated by FINDLAY; if his assumptions are right, the product should be either 2α-methyl-2β,3α-tropandiol, or the 2α,3β-diol. This problem still awaits decision, but will be definitely settled in the near future.

Determination of the Absolute Configuration of Cocaine

With the conclusion of the pertaining investigations of the Hungarian researchers [46a, 60] and those of FINDLAY [35b], the *relative* configuration of cocaine and ψ-cocaine is definitely proved. Proof of the fact that the projective formula used so far only arbitrarily for representing (—)-cocaine was the right one instead of its mirror-image, is a result of the most recent investigations of HARDEGGER and OTT [90]. It is known that when (—)-ecgonine is oxidized with chromic acid, also active 'ecgoninic' acid is formed in addition to inactive, 'tropinic' acid [118]. In the former compound only a single centre of asymmetry is retained from the cocaine skeleton, that of $C_{(5)}$. The absolute configuration of this atom was stated by Swiss investigators by correlation with L-(+)-glutamic acid: this latter compound was converted to L-N-methylpyrrolidonyl acetic acid (ecgoninic acid) *via* L-pyrrolidone carboxylic acid (Fig. 97). Identity of these two compounds proved unequivocally the complete similarity between the configuration of the $C_{(5)}$ atom of cocaine and that of the $C_{(2)}$ atom in D-glyceraldehyde. Therefore, the projection formulas of all cocaine derivatives, showing so far the relative configurations, can be accepted now as true representations of the absolute configuration.

In 1956 CAHN, INGOLD and PRELOG introduced a new convention for the unequivocal description of the configuration of organic compounds [19]. According to this principle, the absolute configuration of the centres of asymmetry are indicated not by the letters D and L, but by the notations *R* and *S*, which are independent of a reference compound. According to this convention, the steric structure of natural cocaine is described as (2*R* : 3*S*)-2-methoxycarbonyl-3-benzoxytropane; consequently, (+)-*pseudo*cocaine is (2*S* : 3*S*)-2-methoxycarbonyl-3-benzoxytropane. This convention assigns different classes

to carboxylic esters and to the primary alcohols obtained from them by reduction, thus *R* and *S* do not denote an 'optically active series'. In this way, (—)-ecgoninol, obtained from cocaine, is (2*S* : 3*S*)-2-hydroxymethyl-3-hydroxytropane [52, 56].

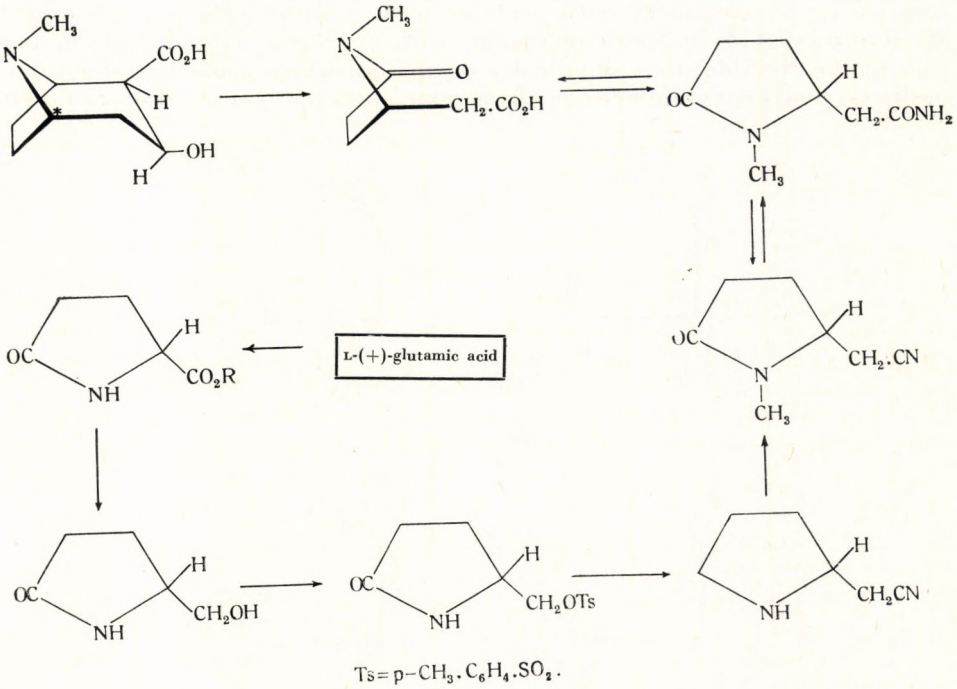


Fig. 97

STEREOCHEMISTRY OF SCOPOLAMINE AND VALEROIDINE

Scopolamine can be obtained from plants in two stereoisomeric forms: the optically active laevorotatory modification, hyoscine, from *Hyoscyamus muticus* [165, 167], and the racemic form from an extract of *Scopolia atropoides* Bercht and Presl [165]. Correct recognition of the constitution of scopolamine (hyoscine) was hindered for a long time by the fact that the primary isolated product of hydrolysis [106, 107, 165, 167] was not the actual alkamine component, i.e., scopine, which was obtained only much later [199], but oscine (termed generally scopoline in the German literature). However, acylation of this product did not regenerate scopolamine [166]. This fact indicated a fundamental change in the structure of the molecule during hydrolysis. Research work directed towards the elucidation of the chemical structure of oscine (scopoline), such as degradation and partial synthesis of the degradation products, primarily the experiments of SCHMIDT, HESS, KING et al. [167], established a connection between tropane and oscine. However, the use of structural formulas with planar six-membered rings did not give the obvious solution concern-

ing the steric relationships of the molecule, neither — by reasoning — for the original steric structure of scopolamine. Later WILLSTÄTTER and BERNER found that scopolamine could be split by way of mild enzymatic hydrolysis (with pancreatic lipase) or also by Sörensen buffer solution to give the native aminoalcohol, scopine [199]. Subsequently, scopine could easily be converted into oscine by treatment with acids or basic reagents. On the other hand, POLONOVSKY et al. reacted scopolamine with hydrogen peroxide, and in addition to the N-oxide, they obtained a compound which could be reduced to a hydroxyl derivative isomeric with scopine, but not convertible into oscine

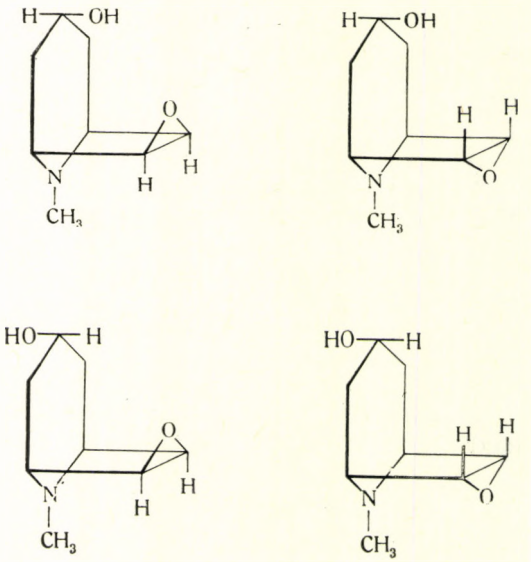


Fig. 98

[148]. Since this modification resisted the action of sodium amyloxide, POLONOVSKY assumed on the basis of analogous cases, but without an exact proof of the steric structure, that the product was a compound related to ψ-tropine, namely ψ-scopine, while scopolamine was regarded to correspond to tropine from the stereochemical point of view. Correct discovery of the steric structure was hindered in this phase of positive research results by the fact that the non-coplanar nature of six-membered hydroaromatic rings was not generally recognized yet, consequently no correct steric views could develop. At that time chemists dealing with the problems of tropane alkaloids did not apply for their own field of research the SACHSE—MOHR theory [134, 164] which had sound stereochemical aspects as its basis. An interesting document of this circumstance is the publication of WILLSTÄTTER and BERNER [199] from 1923, in which the four theoretically possible stereoisomeric forms of scopolamine are depicted with coplanar piperidine rings (Fig. 98). Just this was the reason which — after having learned the constitution of oscine — prevented the early investigators to decide which of the above structures should be

assigned to the natural alkaloid. In fact, WILLSTÄTTER, as a pupil of v. BAEYER, deliberately rejected SACHSE's theory in his early papers [199, 200], referring to the theory of strain.

When valeroidine is hydrolyzed, the product is 3,6-dihydroxytropane [8]. The latter compound can be found in the free state in Javanese Coca leaves [206]. Elucidation of the steric structure was promoted primarily by the accidental fact that potassium permanganate oxidation carried out by MITCHELL and TRAUTNER resulted in the formation of an urethane [132], presumably of cyclic nature, in addition to the expected *nor*-valeroidine (Fig. 99)

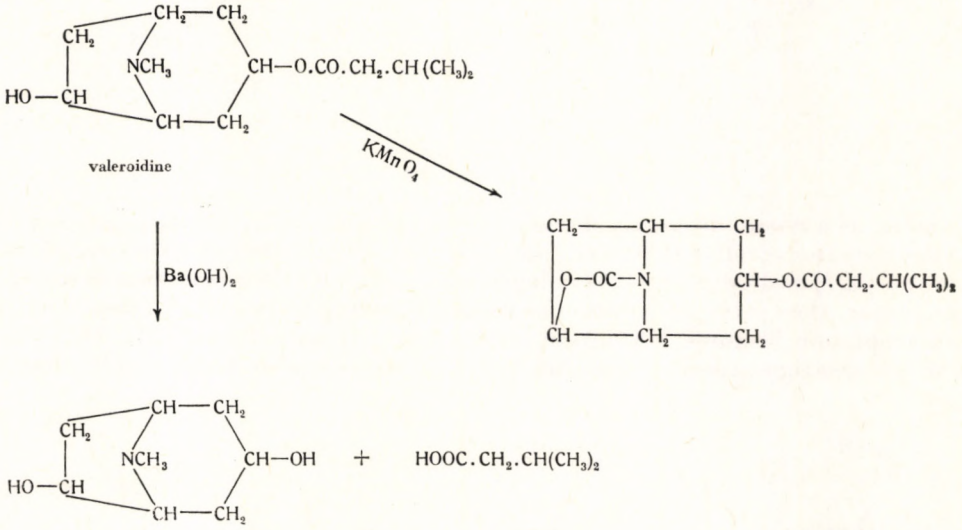


Fig. 99

This result made probable the *syn* steric position of one of the hydroxyl groups as compared to the nitrogen atom, although the 'urethane' constitution of the compound was based only on analytical figures. These investigations gave still nothing to go by concerning the steric position of the other acylated functional group of the molecule in relation to the nitrogen atom, and it was not decided either, which of the hydroxyl groups — that at $C_{(3)}$ or $C_{(6)}$ — assumed the *syn* steric position to nitrogen. Later stereochemical investigations proved the steric structure of scopolamine and valeroidine jointly just through the correlation of the two compounds.

The experimental fact of the conversion of scopolamine to oscine [166] was interpreted for the first time in modern stereochemical terms for the purpose of determining the configuration by FODOR [41], without bringing up any new experimental evidence (December, 1951). Accordingly, scopolamine or scopine, resp., can be transformed into oscine [199] only in that case, if the epoxide ring is in *syn* and the $C_{(3)}$ hydroxyl group in *anti* steric position as related to the nitrogen atom. Only under these conditions is given the possibility that the $C_{(3)}$ hydroxyl should be able to direct a nucleophilic attack from the opposite steric direction against one of the pillars of the epoxide bridge, i.e.,

against $C_{(6)}$ or $C_{(7)}$ (Fig. 100). As a result, the $C_{(6)}$ (or $C_{(7)}$) hydroxyl group of *dl*-oscine (scopoline) is formed. The reversed process, i.e., an attack of the epoxide oxygen against the $C_{(3)}$ hydroxyl being in *syn*-position, appeared for theoretical reasons from the beginning improbable. On this basis, the structural formula of 6,7-*syn*-epoxy-3-*anti*-tropoyloxytropane was assigned to scopol-

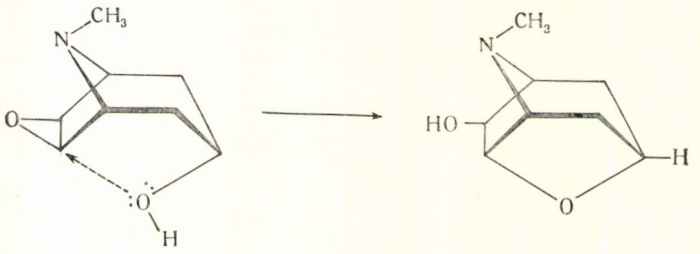


Fig. 100

amine, as a result of purely deductive considerations [41, 43]. It is interesting that the same result was attained within a year by two other researchers, MEINWALD [127] and COOKSON [24] independently. Besides the conversion of scopine to oscine, they interpreted also the reaction leading from scopolamine-N-oxide to scopinium bromide [148] from an up-to-date point of view (Fig. 101). The correct configuration of scopolamine was deduced also from these consid-

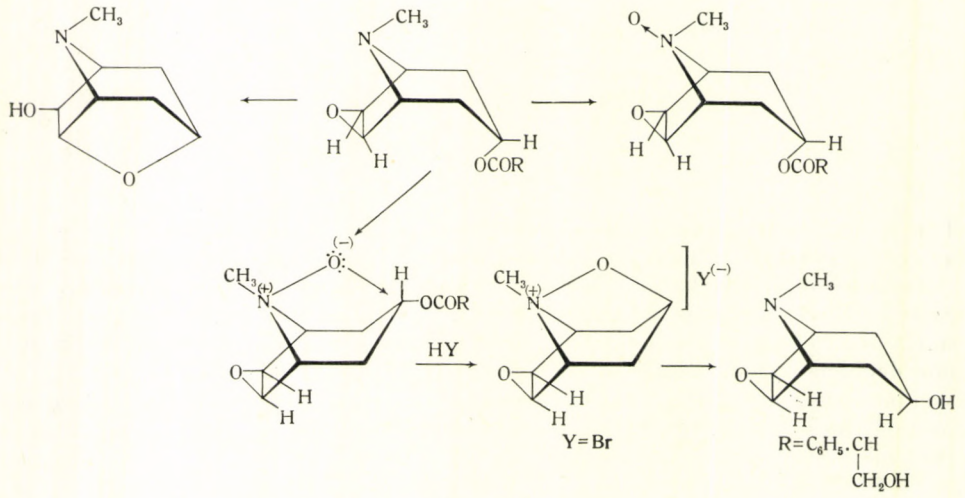


Fig. 101

erations, as from an auxiliary argument. Later FODOR found also convincing experimental proof for the correctness of his working hypothesis, when in the course of an investigation in common with KOVÁCS, the epoxide ring of scopolamine was subjected to hydrogenolysis; the reaction gave the *dl*-modification of 3,6-dihydroxytropane. The compound could be resolved [61a, b]; the

laevorotatory form was found to be identical with the 3,6-dihydroxytropane modification which had been prepared by BARGER, MARTIN and MITCHELL by hydrolyzing natural valeroidine [8], and had been isolated even earlier from Javanese Coca leaves by WOLFES and HROMATKA [206] (Fig. 102). It is an interesting coincidence that right in the days of realizing the above hydro-

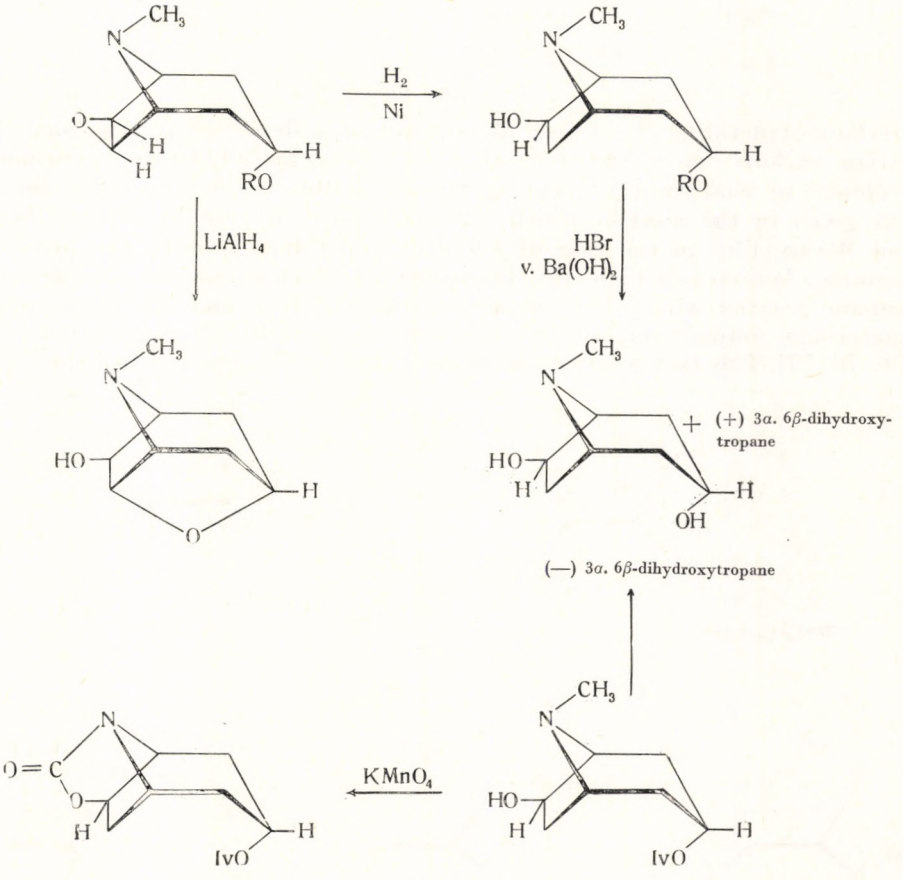


Fig. 102

genolysis, STOLL, JUCKER et al. reported the total synthesis of the same 3,6-dihydroxytropane [182]. Since oscine can be produced but from a 3*α(anti)*-hydroxytropane derivative, it follows that this hydroxyl group is in *α*, *anti* steric position not only in scopolamine, but also in valeroidine. On the other hand, information concerning the steric position of the $C_{(6)}$ hydroxyl of valeroidine had been supplied by the formation of the cyclic urethane in MITCHELL's and TRAUTNER's experiments [132]. This compound can be formed only in case of a *syn-(β)* position of the $C_{(6)}$ hydroxyl. Based on these evidences, FODOR declared valeroidine to be (—)-3-isovaleryl-3*α*,6*β*-dihydroxytropane [44], and confirmed at the same time the deduction of the configuration of scopolamine as 3*α*-tropoyloxy-6,7*β*-epoxytropane (Fig. 103). However, since the above cyclic

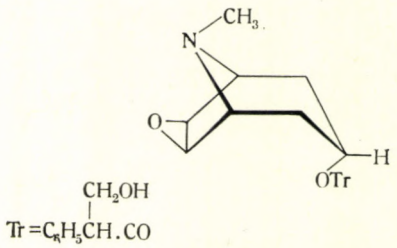


Fig. 103

urethane structure had not been the subject of a detailed investigation, Hungarian authors considered it worth while looking for additional experimental evidence to confirm these configurations definitely. A possibility for this was given in the method which had been tried in vain by MILLS, PARKIN and WARD [130] in the case of 4-hydroxypiperidine, namely the process of forming a lactone salt with ethyl bromoacetate. Both oscine and 3,6-dihydroxytropane reacted with ethyl iodoacetate equally well, and the corresponding quaternary ammonium salt lactones were successfully obtained in both cases [60, 70, 75]. This fact is an unambiguous proof for the β-position of the $C_{(6\ or\ 7)}$

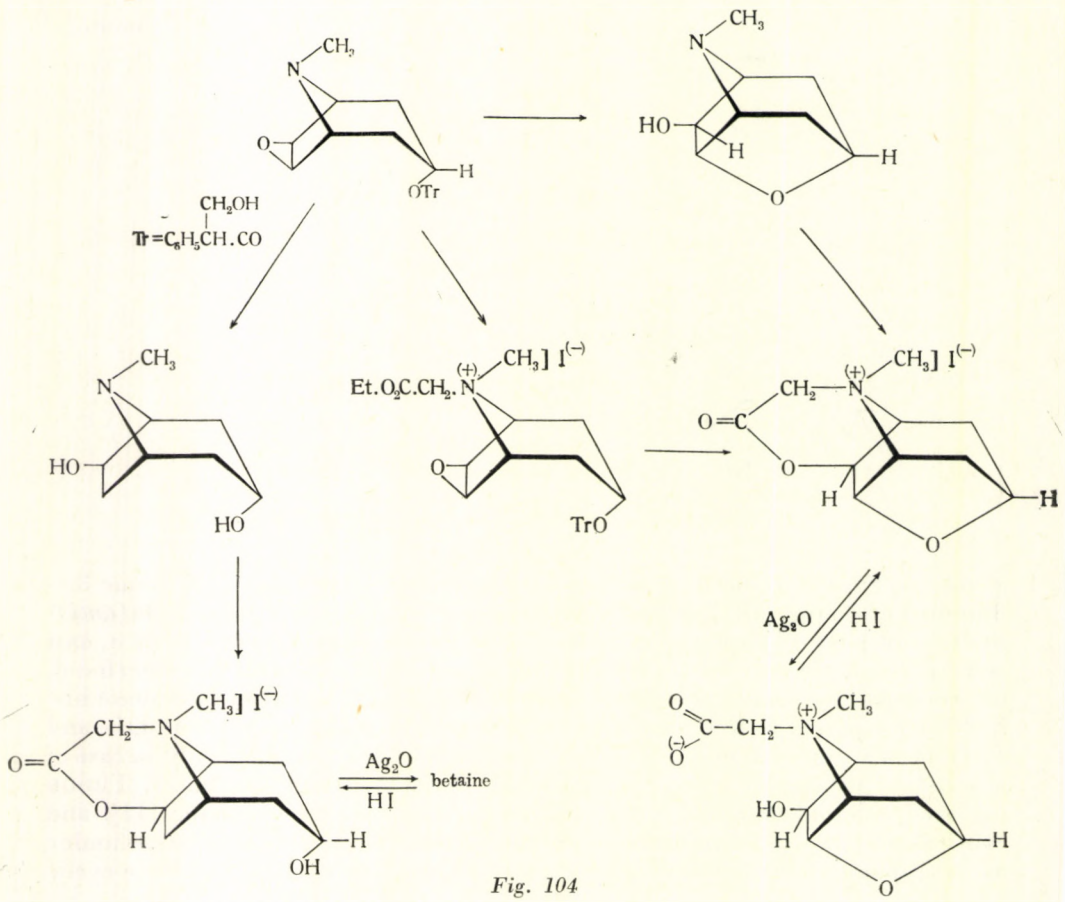


Fig. 104

hydroxyl related to the nitrogen atom, and even more so since the ring of this lactone could be opened again in a reversible way to give the betaine (Fig. 104).

Thus, the complete configuration of oscine is correctly given by the notation of *dl*-3*a*,6*a*-oxydo-7*β*-hydroxytropane, while valeroidine is (—)-3*a*-iso-

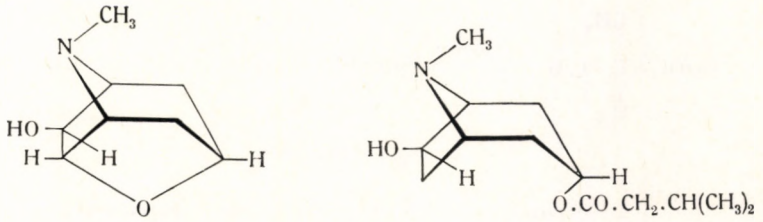


Fig. 105

valeroyloxy-6*β*-hydroxytropane (Fig., 105) and finally (—)-scopolamine can definitely be characterized by the structural formula of 3*a*-*S*(—)-tropoyloxy-6,7*β*-epoxytropane (Fig. 106).

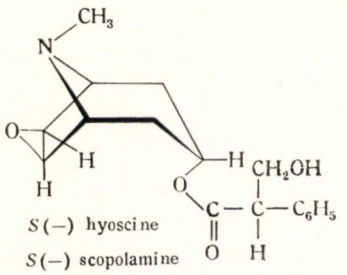


Fig. 106

Absolute Configuration of (—)-Tropic Acid

β-Chlorohydratropic acid was resolved into its antipodes by McKENZIE and STRATHERN [124] as early as in 1925, and the laevorotatory acid was subsequently hydrolyzed to natural tropic acid. On the other hand, in 1939 WHITMORE and BERNSTEIN succeeded in establishing a correlation between *α*-methyl-phenylacetic acid and dextrorotatory alanine by degrading the former compound to (—)-phenylethylamine, nitrating and reducing the benzoyl derivative of this product, and destroying the aromatic ring by oxidation to produce natural (+)-alanine (Fig. 107). When the unequivocal denotation of configuration of CAHN, INGOLD

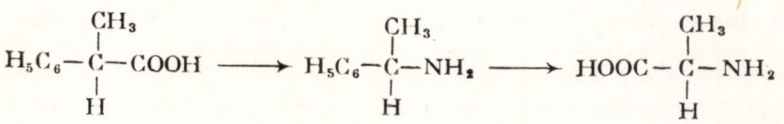


Fig. 107

and PRELOG is used, *S* configuration will be assigned to (+)-*α*-methyl phenylacetic acid (the absolute configuration of which had been previously ascertained), while the laevorotatory form has *R* configuration. In this way, the only missing link for correlating natural tropic acid with natural alanine was obviously the conversion of (—)-*β*-chlorohydratropic acid into *α*-methylphenylacetic acid of known absolute configuration. This work was recently accomplished by Hungarian investigators [58] by resolving the two optically active components of *β*-chlorohydratropic acid by means of codeine, and subjecting the laevorotatory form to

hydrogenolysis in ethyl acetate in the presence of palladium-charcoal and barium hydroxide. The product was $R(-)$-α-methylphenylacetic acid. Consequently, natural tropic acid is $S(-)$-tropic acid having the absolute configuration shown in Fig. 108. It follows that the configuration of (—)-hyoscyamine is to be given as $S(-)$-tropoyltropane-3α-ol, and (—)-hyoscine has the absolute configuration of $S(-)$-tropoyl-3α-hydroxy-6,7β-epoxytropane.

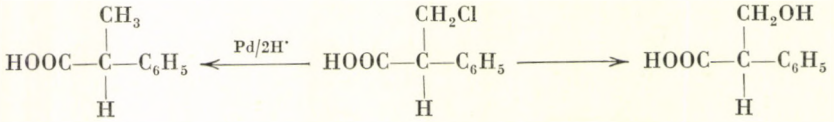


Fig. 108

Syntheses of Valeroidine and Scopolamine

Recognition of the steric structure of valeroidine and scopolamine rendered possible the stereospecific synthesis of these materials. Synthesis of the first compound was realized in June 1955 by Hungarian investigators [72]. STOLL et al. [184] after having accomplished the total synthesis of 3α,6β-dihydroxytropanes (Fig. 109), attempted after resolution of the ketone,

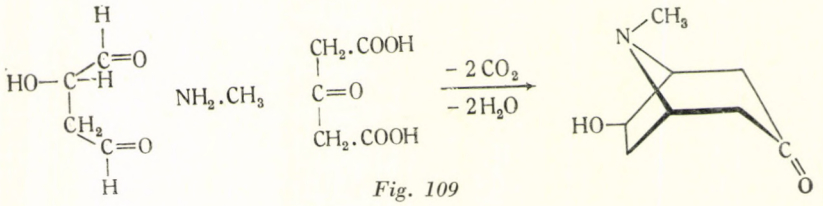


Fig. 109

the selective valeroylation of the (—)-modification at the $C_{(3)}$ carbon atom as early as in 1953. This experiment failed, and only a mixture was also obtained during the partial hydrolysis of the 3,6-divaleroyl derivative, which latter compound had been prepared from natural valeroidine and (—)-3α,6β-dihydroxytropane. The Hungarian authors succeeded later to realize the selective desacylation of the $C_{(6)}$ hydroxyl of tropane-3α,6β-diol-divaleroate [75].

As to the synthesis of scopolamine, only negative experiments had been known previously. Each investigator tried to achieve his purpose by the Robinson-condensation of epoxysuccinic dialdehyde. This difficultly accessible key-material was finally successfully prepared by SCHÖPF and SCHMETTERLING [171] however, the conversion product obtained from this substance under so-called physiological conditions was not scopinone, because the epoxide ring could not bear the action of two nucleophilic reagents, namely that of acetonedicarboxylic acid and methylamine (Fig. 110). PREOBRAZHENSKI [152, 153] wanted to synthesize scopine and thus scopolamine by reducing 6-tropene-3-one and subsequent epoxidation of the tropenol. However, after him also four other research laboratories (SCHÖPF, KARRER, STOLL and SHEEHAN) [105, 169] failed in preparing tropenone from maleic dialdehyde. SCHÖPF is of the opinion that during the hydrogenation of butynedial acetal, the produced but*ene*dial acetal becomes contaminated by but*ane*dial acetal, therefore what the above-mentioned author isolated was impure tropanone.*

* In 1962 FODOR and S. KISS succeeded in oxidizing tropenol into 6-tropene-3-one, a compound of considerable stability ; cf. Chem. & Ind. *1963*, 372.

FODOR and KOCZOR carried out the ring opening reaction of racemic 'tropene oxide' by means of acetyl bromide, to obtain 3α-acetoxy-6β-bromotropane; subsequently hydrogen bromide was split off by treating the product with collidine (and much better, later according to S. KISS, by piperidine), which reaction resulted in the formation of 3α-acetoxy-6-trop*ene* [51]. This compound, the acetate of tropenol, is a long presumed [25]

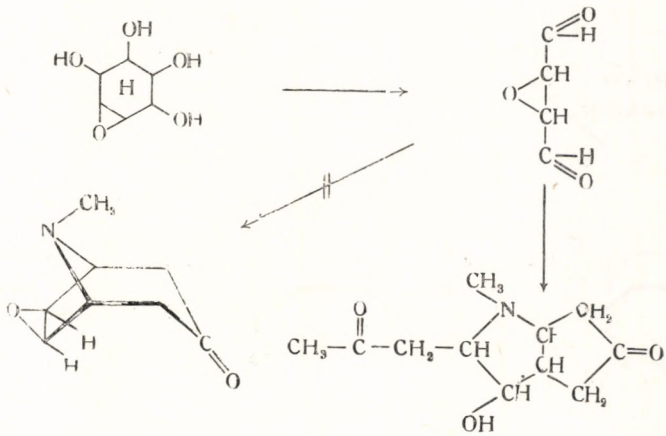


Fig. 110

intermediate of the biogenesis of tropane alkamines. FODOR, TÓTH, DOBÓ and VINCZE made tropenyl acetate even easier available by reducing 6β-phenyl carbamyloxy-3-tropanone to the 3α alcohol, acetylating the product, then carrying out a thermolysis to give tropane-3,6-diol monoacetate, and indirect water elimination from the latter compound. In the course of catalytic hydrogenation, tropenyl acetate became saturated to acetyltropine, which reaction was a definite proof of its structure [51, 69] (Fig. 111).

The reversible nature of phenylurethane formation has not been utilized so far as a preparative method for the transitory blocking of alcoholic (or phenolic) hydroxyl groups. About simultaneously with the observations of FODOR, also Japanese researchers studied the reaction kinetics of this process, with the use of simple models.*

Total Synthesis of Scopolamine

In the course of the hydrolysis of acetyltropenol by acids, Hungarian investigators isolated well-crystallized tropenol hydrochloride. For the purpose of epoxidation, acetyltropenol was acted upon by various organic peracids. Treatment with monoperphthalic acid in ether solution gave mainly the N-oxide [53, 72], however, with a great excess of the reagent also the N-oxide-epoxide was successfully prepared. Evidence for the structure of the latter product was obtained by hydrogenolysis, which gave the known 3α-acetoxy-

* MUHAYAMA TANAKI, MOTOKI SIMICHI and HAMADA YASUCHI, Bull. Chem. Soc Japan, *26*, 49 (1953).

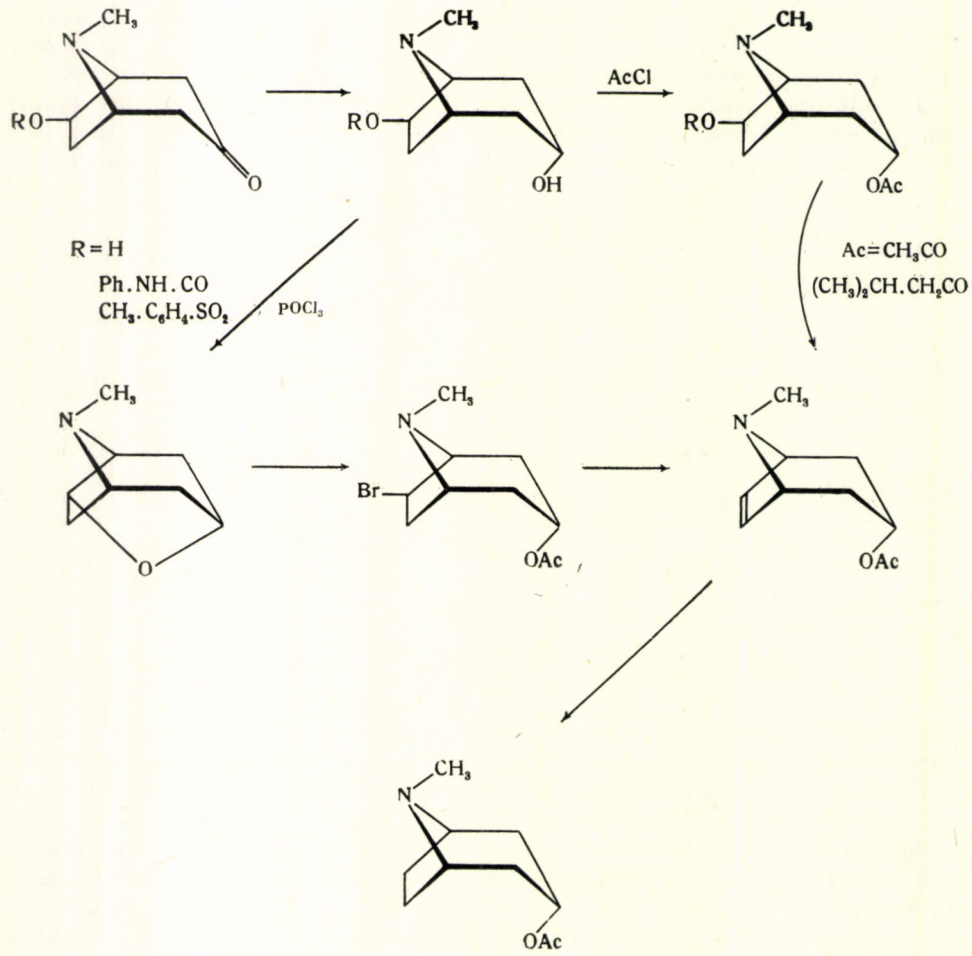


Fig. 111

6β-hydroxytropane [72]. However, the yield was extremely low, therefore new experiments were carried out with the more electrophilic trifluoroperacetic acid. Acetylscopine [53] was successfully prepared in this way (Fig. 112). Later on, studies by paper chromatography were carried out to investigate a number of organic acids (formic, acetic, trichloroacetic, trifluoroacetic acids) used together with 80—90% hydrogen peroxide, with the purpose of learning the best combination, i.e., to find the best peracid formed *in situ*, from the aspect of epoxidation. The use of formic acid and hydrogen peroxide was found to be the most advantageous; with this reagent N-oxide was not formed at all [53, 56]. Identification of acetylscopine was accomplished by converting scopine hydrochloride, obtained from scopolamine according to WILLSTÄTTER [199], or recently according to MEINWALD [128], into acetylscopine hydrochloride, by treating the compound with acetyl chloride.

MEINWALD's method essentially consists of subjecting N-methoxymethyl-scopolaminium chloride to alkaline hydrolysis, when no oscine is formed; the methoxymethyl group — as it is about an acetal bond — can readily be removed at the end of the process by dilute acids.

This method is analogus to the procedure of MOFFETT and GARRETT, who succeeded in hydrolyzing scopolamine methobromide to scopine methobromide under alkaline conditions [133].

The use of Kunz's method of hydrolysis (acetone + 0.1N NaOH) made possible to carry out also the reverse reaction: scopine base could be

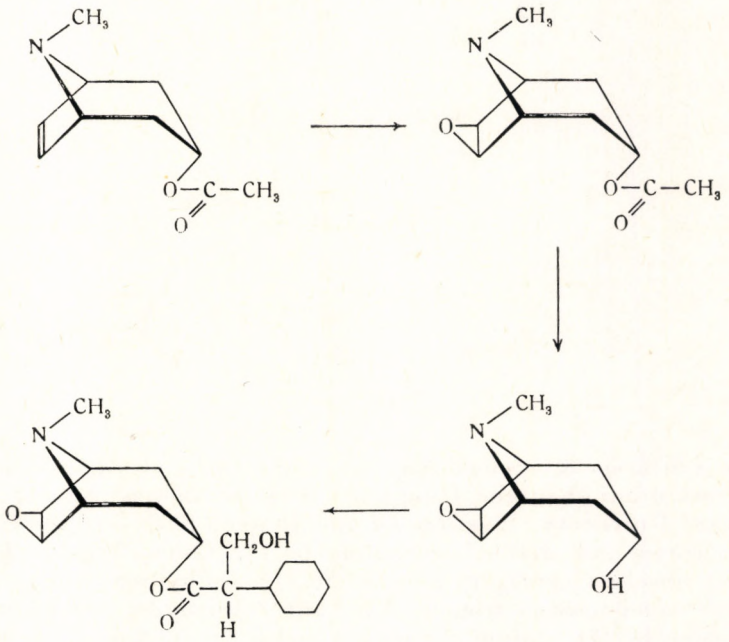


Fig. 112

isolated from acetylscopine [69]; the single further task for accomplishing the synthesis of scopolamine was the esterification of scopine with tropic acid. After innumerable unsuccessful experiments, scopine hydrochloride could finally be esterified with acetyltropoyl chloride at 65° in nitrobenzene solution. A number of by-products was formed, too, which were detected by paper chromatography; these products could be successfully separated by means of partition chromatography on cellulose powder, between butanol and 1N hydrochloric acid [69]. Eventually pure racemic scopolamine hydrochloride was obtained by hydrolysing acetyl-scopolamine with 2N hydrochloric acid, and repeating the chromatographic separation of the reaction product (Fig. 112) on a cellulose powder column several times [69]. Since (+)-hyoscine had been prepared from (+)-scopolamine by KING in 1919 [106, 107], and PREOBRAZHENSKI [173] could prepare also (—)-hyoscine by resolution, this synthesis is equal to the total synthesis of natural (—)-hyoscine.

A new variety of the synthesis [73] (Fig. 113) was the esterification of tropenol with (—)-acetyltropoyl chloride to give 6,7-dehydrohyoscyamine ace-

tate. This compound was found to be oxidable when reacted with formic acid and hydrogen peroxide, and even better by tungstic acid as a catalyst. In this way (—)-hyoscine could be prepared.

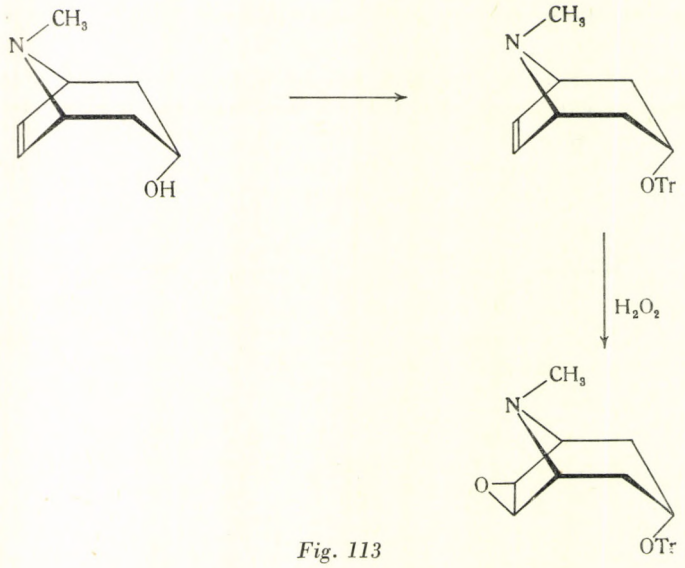


Fig. 113

The synthesis of scopolamine was the object of experiments also of investigators other than the Hungarian ones, in Zurich, New York and at the Harvard University. HARDEGGER and FURTER [87] were the first to prepare the compound defined according to the Cahn—Ingold—Prelog convention of absolute configurations as *S*(+)-6,7-dihydroxytropane-3-one, by ROBINSON's condensation from (+)-tartaric dialdehyde, which, in turn, had been prepared by the lithium aluminium hydride reduction of the corresponding dianilide. Preparation of the same ketone was reported by STERN and WASSERMAN [181]. On the other hand, the *racemic* ketone was obtained by SHEEHAN [174] in the following way: 2,5-dimethoxy-2,5-dihydrofuran was converted into the epoxide, then the ring opened with dilute acid to yield racemic tartaric dialdehyde. This compound was condensed according to

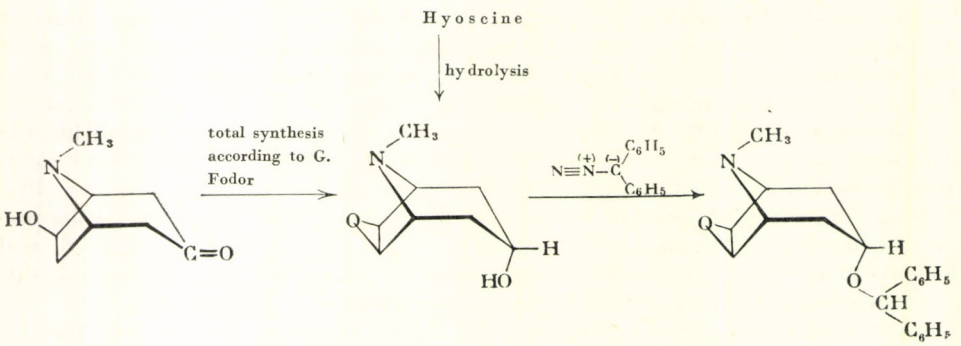


Fig. 114

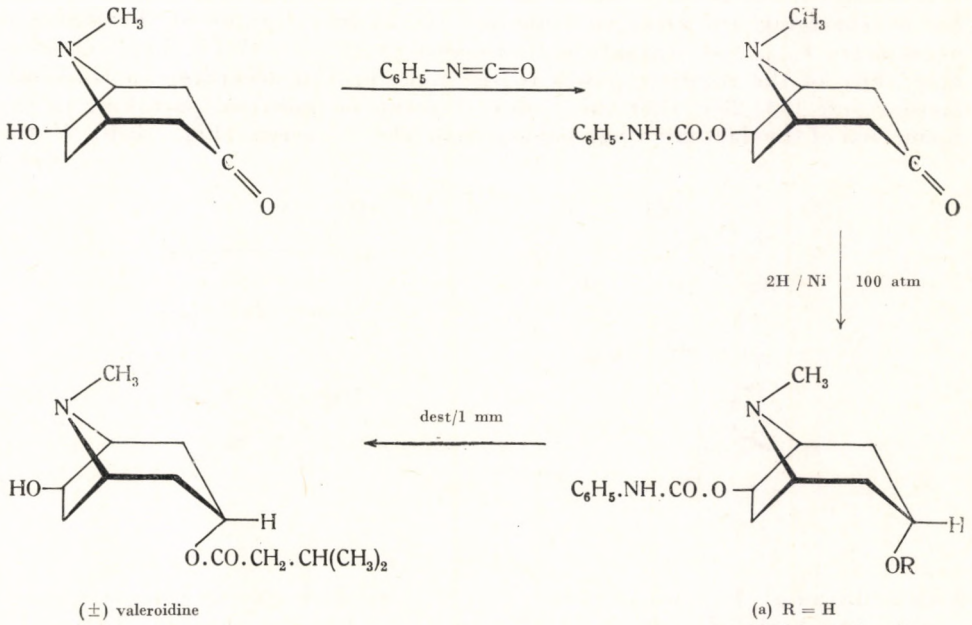
Robinson's method to give racemic 6α,7β-dihydroxytropane-3-one. Catalytic reduction of the product gave rise to tropane-3α,6α,7β-triol; however, selective dehydration of this compound resulted in the formation not of the expected scopine but of the undesired oscine.

Employing essentially the same course of synthesis as the Hungarian researchers in the case of scopolamine, LINDENMANN [119] prepared scopine benzhydryl ether (Fig. 114). 6-Hydroxytropinone was reduced through the phenylurethan, the resulting 6-phenylcarbamyl-oxytropane-3α-ol was etherified by treatment with benzhydryl bromide and diphenyl diazomethane, resp. and subjected to thermolysis (cf. Fig. 111). Tosylation of the diol-monoether and selective elimination of toluenesulphonic acid gave Δ_6-tropenyl-3-benzhydryl ether. Epoxidation of the latter compound by trifluoroperacetic acid in acetonitrile afforded scopine benzhydryl ether.

These scientific syntheses may after suitable modifications result later in the development of an economic synthesis of scopolamine. Scopinone was obtained recently according to MEINWALD and HEUSNER* by oxidizing scopine; reduction led to ψ-scopine, identical with that obtained from scopolamine-N-oxide [148].

Total Synthesis of Valeroidine and the Determination of its Absolute Configuration

As a branching off of scopolamine synthesis, in 1957 also the total synthesis of natural valeroidine was realized by Hungarian investigators [195].



(±) valeroidine

(a) R = H
(b) R = *iso*valeroyl

Fig. 115a

* Tetrahedron *3*, 311, 312 (1958).

Racemic 6β-phenylcarbamyloxy-3α-hydroxytropane was successfully resolved with (+)-tartaric acid into the antipodes, then both modifications were acylated with *iso*valeryl chloride, and finally both products were subjected to thermolysis to give (+)- and (−)-valeroidine (Fig. 115a). All the physical properties of the latter compound were identical with those of the authentic natural valeroidine obtained by MITCHELL [132].

The author of present and his previous co-workers [71] succeeded in realizing a simplified synthesis of valeroidine by the partial hydrolysis of the optically active (+)-3α,6β-diisovaleryloxytropane in acetone containing dilute sodium hydroxide.

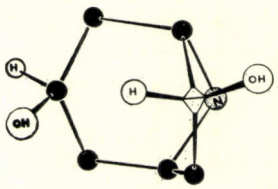


Fig. 115b

It was also successful to determine the absolute configuration of valeroidine with a high probability. FODOR, VINCZE and TÓTH [74, 75] quaternized the optically active alkamine of valeroidine, (−)-3α,6β-dihydroxytropane, with ethyl iodoacetate, when a highly *laevorotatory* ester salt ($[\alpha]_D^{20} = -23.7°$) was obtained. The lactone, which could be readily formed from this compound by overbridging the nitrogen atom and the hydroxyl group at the centre of asymmetry $C_{(6)}$, was strongly *dextrorotatory* ($[\alpha]_D^{20} = +37.5°$). This considerable shift of the rotatory power to the right proved according to Hudson's lactone rule [98, 205] that the hydroxyl group in question, partaking in the formation of the lactone ring, belonged to the D_G series (Fig. 115b). If the

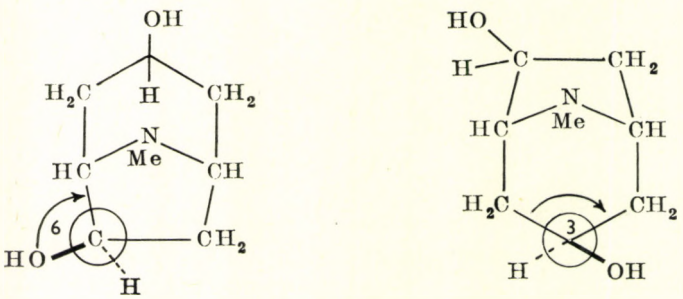


Fig. 115c

CAHN—INGOLD—PRELOG convention [19] is applied also in this case, valeroidine should be described as (3*R*:6*R*)(−)-3,6-dihydroxytropane-3-monoisovaleric ester (Fig. 115c). Establishment of the configurational correlation between valeroidine and some amino acid of known configuration is also in progress by SÓTI (Fig. 115d).

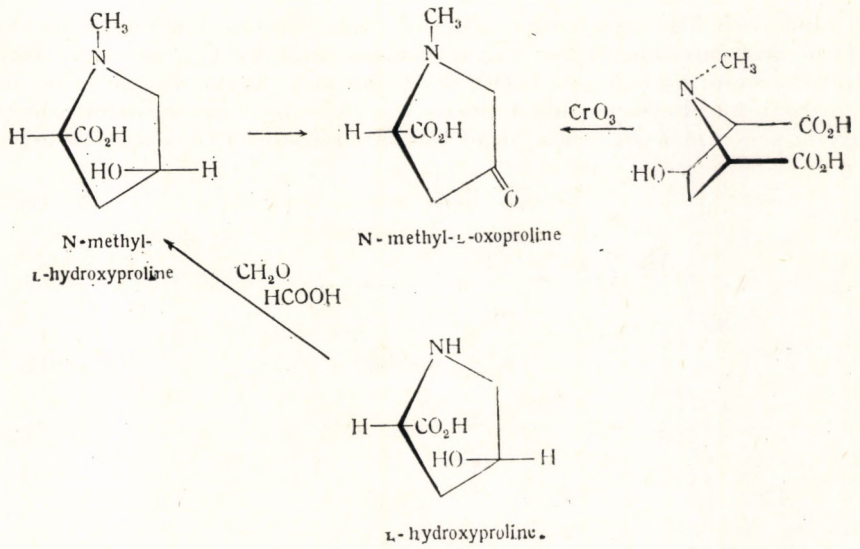


Fig. 115d

STERIC STRUCTURE OF METELOIDINE AND TELOIDINE

Meteloidine, an optically inactive minor alkaloid of *Datura meteloides* was isolated by PYMAN and REYNOLDS [154] besides scopolamine and atropine. KING ascertained [106] that similarly to tropine and ψ-tropine, it was a modification of 3-tigloyl-3,6,7-trihydroxytropane (tigloyl teloidine) having *mesoid* structure, for it cannot be resolved. This structure, based first on negative evidences, such as the all-*cis* steric position of both the $C_{(6)}$ and $C_{(7)}$ hydroxyl groups, was confirmed later by the synthesis of teloidine from *meso*tartaric dialdehyde, by SCHÖPF and ARNOLD [170] (Fig. 116). Recently SHEEHAN and BISSEL [174] achieved the synthesis of 3-(α-methylbutyryl)-teloidine, too.

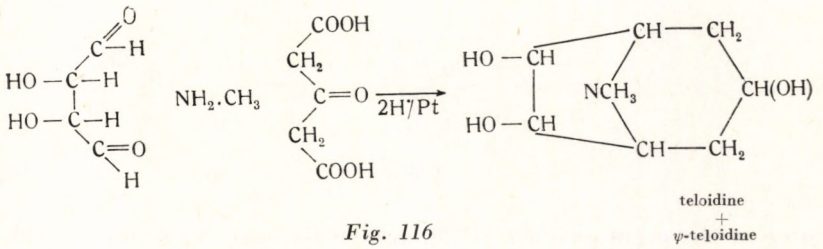
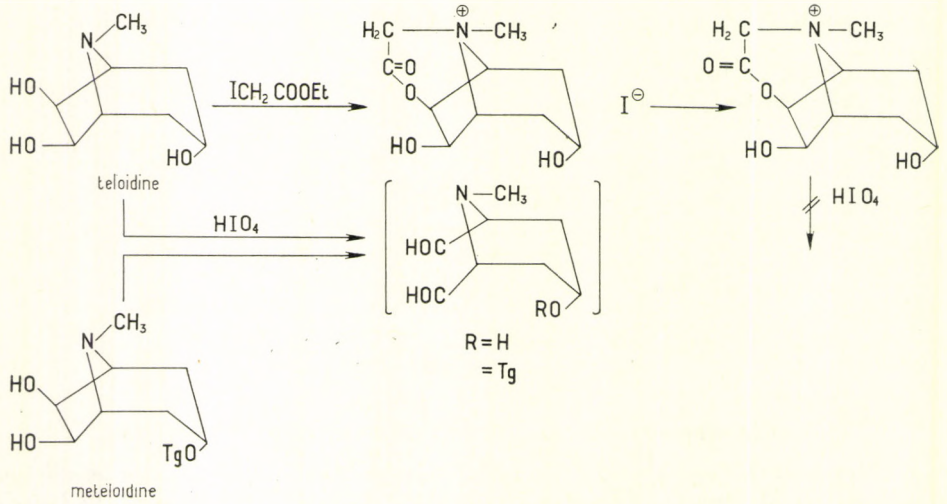


Fig. 116

These experimental data gave no exact answer as to the absolute configuration of teloidine, they established only so much that two of the three hydroxyl groups of teloidine were in *cis*-relationship with each other.

Early in 1954, the author and co-workers [46a, 70] proved the steric position of the $C_{(6)}$ and $C_{(7)}$ hydroxyl groups of teloidine in a similar way as it was done in the case of valeroidine alkamine. Namely, the action of ethyl iodoacetate caused conversion into a lactone salt also in this case. When this lactone iodide was converted into the corresponding chloride, this product was found to be entirely resistant to periodic acid, whereas both teloidine and teloidinone instantaneously consumed one mole of periodic acid

each [46a, 70]. This fact clearly showed that lactone formation took place with the participation of the nitrogen atom and the $C_{(6)}$ or equivalent $C_{(7)}$ hydroxyl group, and not with the hydroxyl at $C_{(3)}$; the *anti*-position of this latter group had been predicted previously only by way of analogy. Namely, catalytic pressure hydrogenation of teloidinone gave rise to the formation of



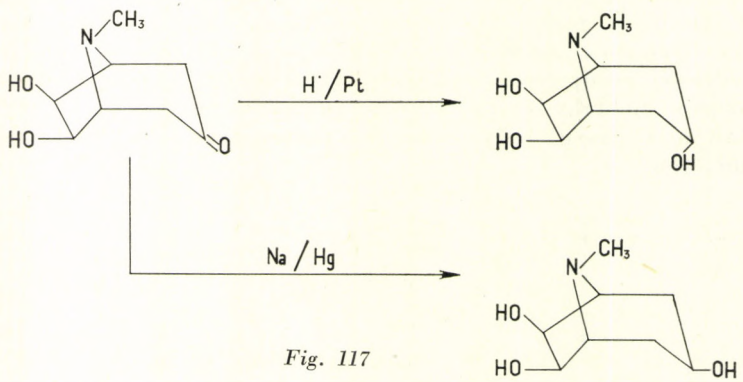


Fig. 117

teloidine as the main product [172], and under such conditions in the tropane series generally the formation of a hydroxyl of *anti*-position is favoured [18, 48].

Shortly after this work, *ψ-nor*-teloidine acetonide, obtained by hydrogenation from teloidine acetonide, was condensed by HEUSNER [92, 94] with *p*-nitrobenzaldehyde, to give an oxazidine. This constitutes further and final proof for the *syn*-position of the $C_{(3)}$ OH group of *ψ*-teloidine and in consequence for its *anti*-position in teloidine (Fig. 117). It was again HEUSNER [92, 93] who definitely proved the fact that tiglic acid was attached to the $C_{(3)}$ hydroxyl group of meteloidine. Namely, meteloidine gave an acetonide which on alkaline hydrolysis yielded the same teloidine acetonide which was also the main product

of the reduction of teloidine-3-one-6,7-acetonide. It is to be noted that also the synthesis of SHEEHAN and BISSEL [174] was based on the same principle: 6,7-benzalteloidine, prepared by the hydrogenation of 6,7-benzalteloidinone over Raney nickel catalyst, was acylated on the $C_{(3)}$ hydroxyl group by means of α-methylbutyric anhydride; the benzylidene group was then split off by hydrogenolysis (Pd in acetic acid) to give dihydrometeloidine.

Accordingly, the constitution of meteloidine is 3α-tigloyloxy-6β,7β-dihydroxytropane, and consequently teloidine will be described as 3α,6β,7β-trihydroxytropane.

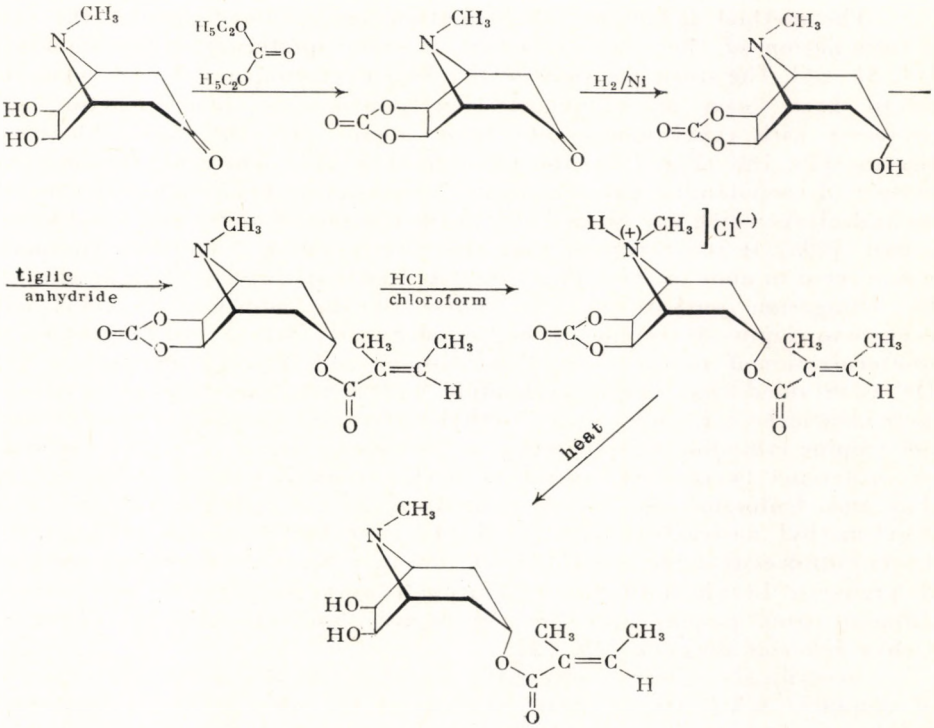


Fig. 118

Recently HEUSNER [95] succeeded in achieving the total synthesis of natural meteloidine (Fig. 118). Teloidinone was treated with diethyl carbonate and dispersed sodium to give teloidinone carbonate; this compound was catalytically hydrogenated to teloidine-6β,7β-carbonate, and then esterified with tiglic anhydride at carbon 3 to afford meteloidine-6β,7β-carbonate. Heating

Fig. 119

of this product in chloroform in the presence of hydrogen chloride resulted in the evolution of carbon dioxide, and the hydrochloride of the natural alkaloid was formed.

In 1957 a new alkaloid was isolated by EVANS [32] from *Datura* which gave meteloidine and tiglic acid on partial hydrolysis. Based on this evidence its constitution is (±)3α,6β-ditigloyloxy-7β-hydroxytropane (Fig. 119).

CONFIGURATION OF THE NITROGEN ATOM IN TROPANES

The method of lactone salt formation has rendered possible the exact determination of the steric structure of some quaternary tropanium salts [44, 51, 54]. The steric positions of the N-methyl group and N-carboxymethyl group have been unambiguously determined [48a] in the lactone salts prepared with ethyl iodoacetate from oscine [47, 70], 3α,6β-dihydroxytropane [70, 188] (Fig. 104), and teloidine (Fig. 117). The ethyl bromoacetate adduct of scopolamine gave the same N-carboxymethyloscinium lactone salt on hydrolysis which was formed also in the reaction of oscine and ethyl bromoacetate [48a]. It is interesting that the corresponding N-epimeric compound was formed in none of these four cases. A similar selectivity could be observed by Hungarian authors in the course of the addition of ethyl iodoacetate to tropine, ψ-tropine and ecgoninol. Shortly later FINDLAY studied the quaternization of tropine, N-ethyl-*nor*-tropine and N-propyl-*nor*-tropine [33]. He ascertained that tropine ethiodide and N-ethyl-*nor*-tropine methiodide were identical compounds, while N-ethyl-*nor*-tropine propiodide and N-propyl-*nor*-tropine ethiodide existed really as N-epimeric forms. FINDLAY confirmed the difference between the members of this epimeric pair by Debye-Scherrer diagrams. Unfortunately, however, he drew the conclusion in the case of the ethyl-methyl derivatives only on the basis of their identical melting points. Later FODOR et al. ascertained [48a, 49, 188] that N-ethyl-*nor*-tropine methiodide prepared in alcohol-benzene solution at room temperature was distinctly different from tropine ethiodide, as regards both the crystal system and Debye-Scherrer diagram [49, 62].

Accordingly, a steric selectivity was observed also in the quaternization of tropines. When tropine was acted upon by ethyl iodide, a quaternary iodide was formed at first, which was shown to be different from N-ethyl-*nor*-tropine methiodide, obtained by the N-ethylation of *nor*-tropine and subsequent quaternization of the product with methyl iodide (Fig. 120). According to the crystallographic studies of KOCH [109], the tropine ethiodide crystal belonged to the regular crystal system, while N-ethyl-*nor*-tropine methiodide was the member of a system lacking a principal axis of symmetry.

Quite recently both ethyl-methyl-*nor*-tropinium bromides were the subject of a detailed X-ray investigation in the Crystallographical Laboratory of the University of Amsterdam by Professor C. MACGILLAVRY in collaboration with present author (cf. Lecture No. A 2/31. by FODOR at the XIXth Congress of IUPAC, London, 15 July, 1963, Congress Abstracts A. 120). It was found that N-ethyl-*nor*-tropine methobromide has the ethyl group *axial*, the methyl *equatorial;* the opposite follows for the N-epimer (Fig. 121a,b,c). This case is of interest, because due to the lack of reactive functional groups, there is no possibility of bringing about a ring closure to ascertain the configurations of these epimers chemically.

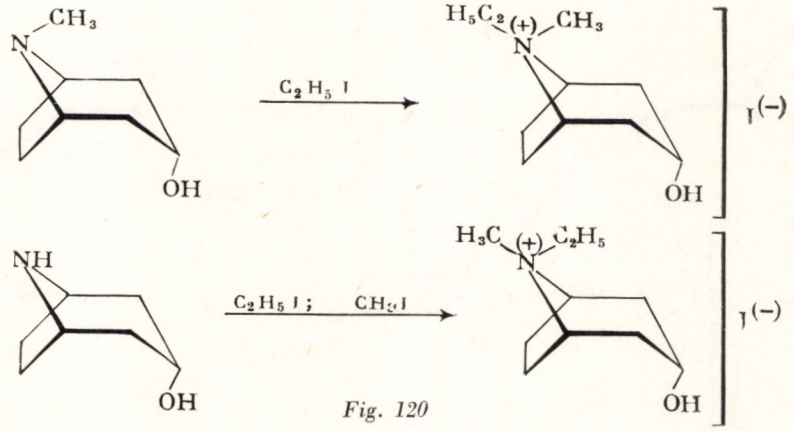
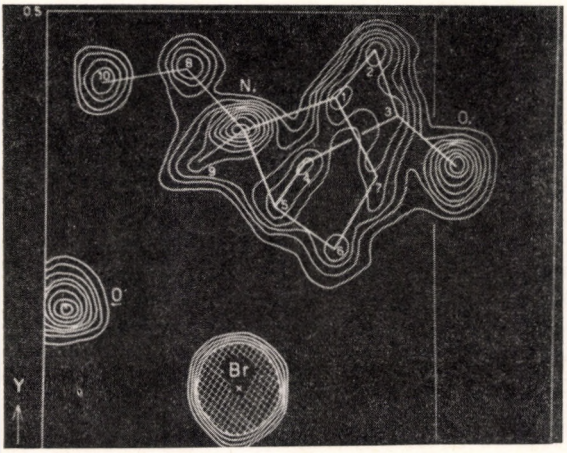
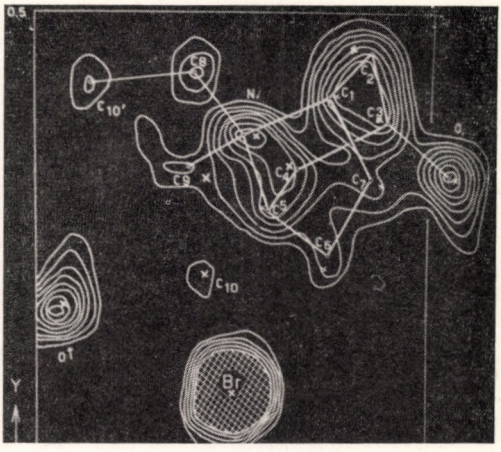


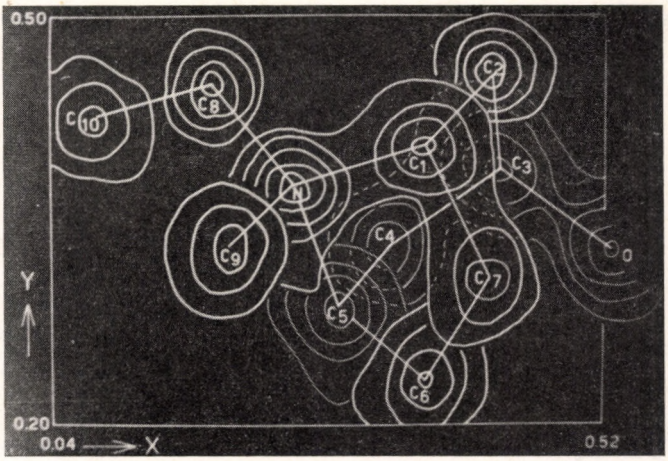
Fig. 120



a



b



c

Fig. 121a, b, c

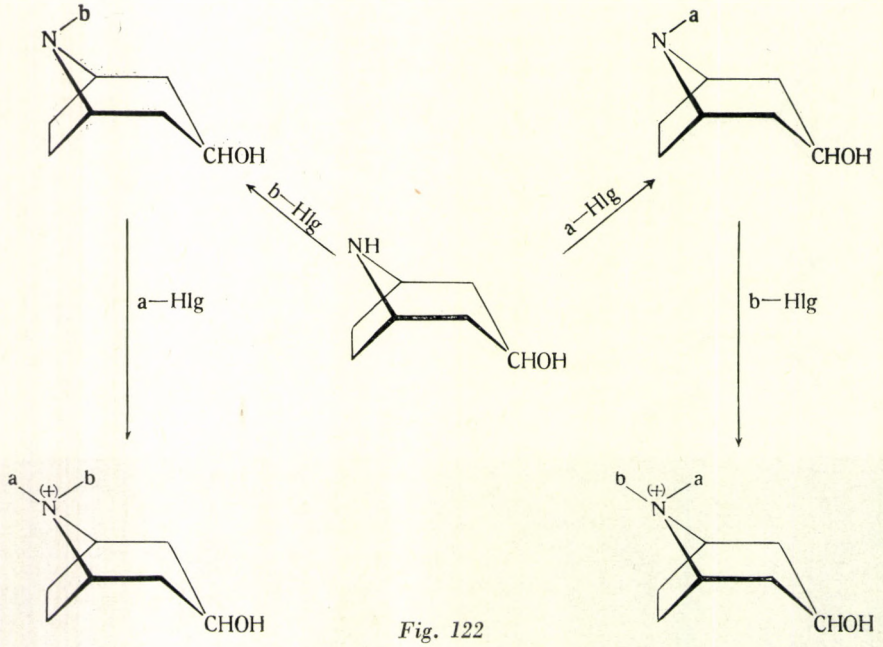


Fig. 122

Fodor et al. [44] found as a general rule that *nor*-tropane derivatives gave two different N-epimeric compounds, substituted on the nitrogen atom by groups *a* and *b*, depending upon the succession of the reaction with *a* halide and *b* halide. They called these two reaction sequences 'normal' and 'reversed' quaternizations (Figs 122 and 123).

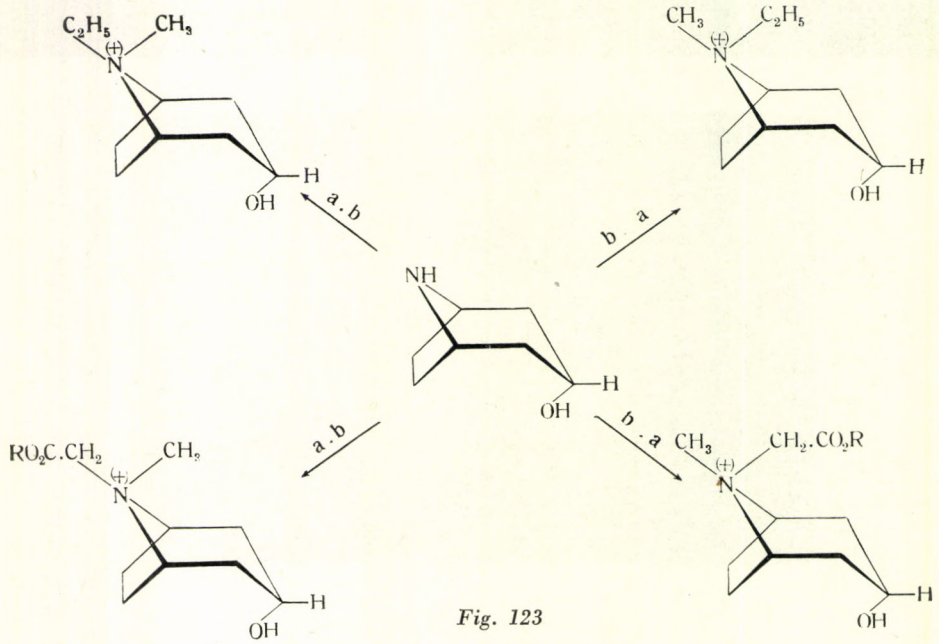


Fig. 123

The first series of experiments was carried out with *pseudo*tropine and N-ethoxycarbonylmethyl-*nor*-*pseudo*tropine. The used quaternizing agent was ethyl iodoacetate in the first case [44, 62], and methyl iodide in the second (Fig. 124).

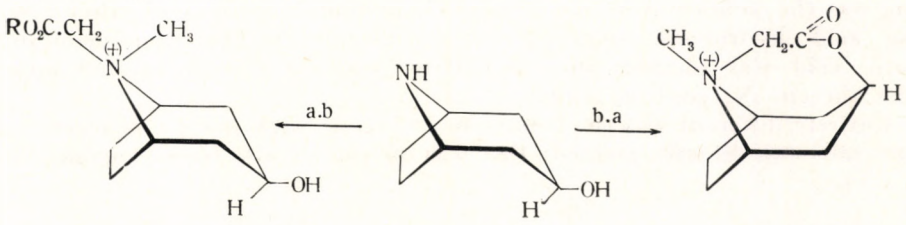


Fig. 124

The N-epimeric quaternary N-ethoxycarbonylmethyl-*pseudo*tropanium iodides gave two different betaines with moist silver oxide. The betaine prepared from *pseudo*tropine by means of ethyl iodoacetate contained 1 mole of crystal water, but the product obtained from N-ethoxycarbonylmethyl-*nor*-pseudotropine was found to be anhydrous. On this basis the author assigned N_a configuration to the carboxymethyl group in the second betaine; the opposite, N_b steric position of the CH_2COOR group in the quaternization product of *pseudo*tropine follows automatically.

The same conclusion was drawn from an examination of the IR spectrum of a product prepared from the 'anhydrous' betaine and hydrogen iodide. The maxima at 1750 and 1623 cm^{-1} should be ascribed according to PLIVA (Czecho-Slovak Academy of Sciences) to the presence of a lactone ring [45b].

The *thermolysis* of both N-epimeric esters resulted in a disproportionation, since the isolated main product was *pseudo*tropine methiodide [62].

Another series of experiments dealt with 3*α*,6*β*-dihydroxytropane, and N-ethoxycarbonylmethyl-3*α*,6*β*-dihydroxy-*nor*-tropane [70] (Fig. 125). The second compound failed to give a lactone either in its tertiary state or after being quaternized with methyl iodide; the first compound, on the other

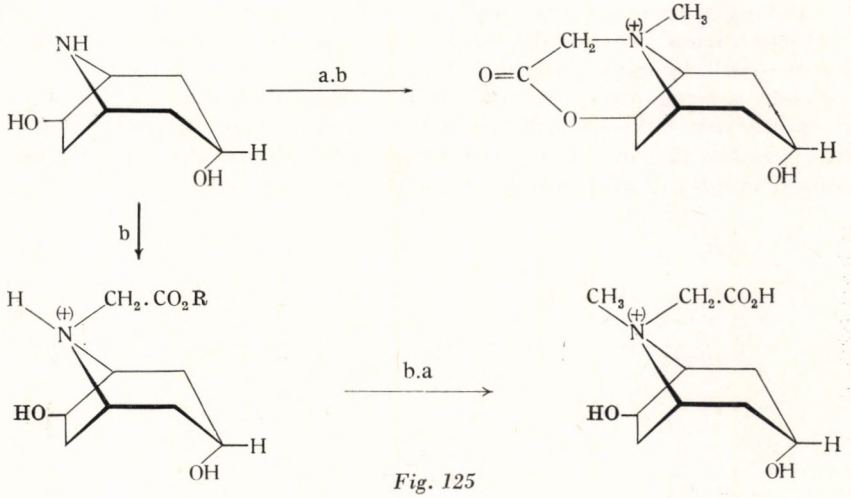


Fig. 125

hand, gave the lactone of N_b-carboxymethyl- 3,6-dihydroxytropanium iodide when treated with ethyl iodoacetate; the by-product was the corresponding quaternary ester salt. This ester salt could also be transformed into the same lactone by dissolving it in hot ethanol or heating above the melting point. Surprising was the behaviour of *nor*-tropane-3α,6β-diol-N-acetic acid ethyl ester during acid hydrolysis, since the hydrochloride of the corresponding N-acetic acid was formed; the CH_2COOH group of this compound must assume therein N_α configuration.

Entirely different was the behaviour of oscine: with ethyl iodoacetate a lactone salt was directly formed; this was obtainable also from scopolamine Fig. 126).

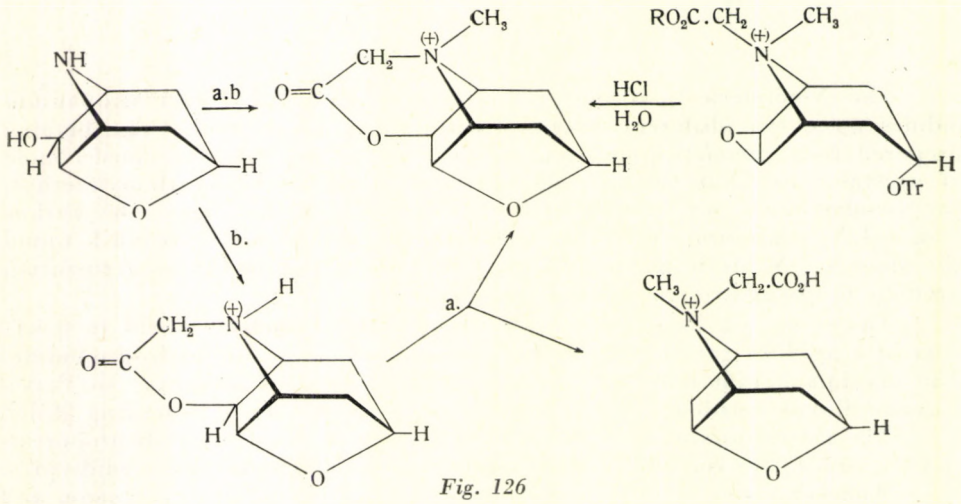


Fig. 126

N-ethoxycarbonylmethylation of *nor*-oscine gave a tertiary ester which afforded an ester salt, besides the N-epimeric lactone salt, on treatment with methyl iodide. Saponification of the tertiary ester salt yielded a trialkylammonium salt of the lactone. Thus, the stereospecifity of quaternization holds no longer true for the case of a tropane skeleton with a 3,6-bridge. The interpretation of this different behaviour in comparison with oscine derivatives will be given on p. 134.

When *nor*-ecgoninol was alkylated with ethyl iodoacetate and the tertiary aminoester subsequently methylated by means of methyl iodide, the product was the lactone of N_α-carboxymethyl-2β-hydroxymethyl-3β-hydroxytropanium iodide, in addition to the corresponding ester salt [63] (Fig. 127).

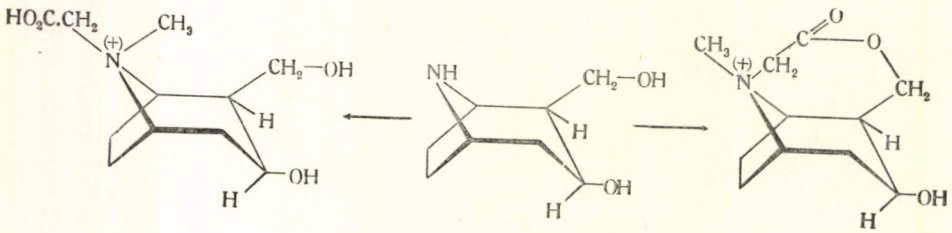


Fig. 127

Interestingly, the optical rotatory power of the lactone salt was $[\alpha]_D = \pm 0°$, while the betaine prepared from this compound by ring opening with moist silver oxide gave, after treatment with hydrochloric acid, a *highly laevorotatory* N-carboxymethochloride of ecgoninol. Direct quaternization of diacetylecgoninol by methyl iodide resulted in the formation of diacetylecgoninol-N-acetic ester methiodide, and the hydrolysis of this product yielded the *dextrorotatory* N_b-carboxymethochloride of ecgoninol.

From the above result, considering the already ascertained absolute 2*R* : 3*S* configuration of cocaine [86], the absolute configuration of the lactone

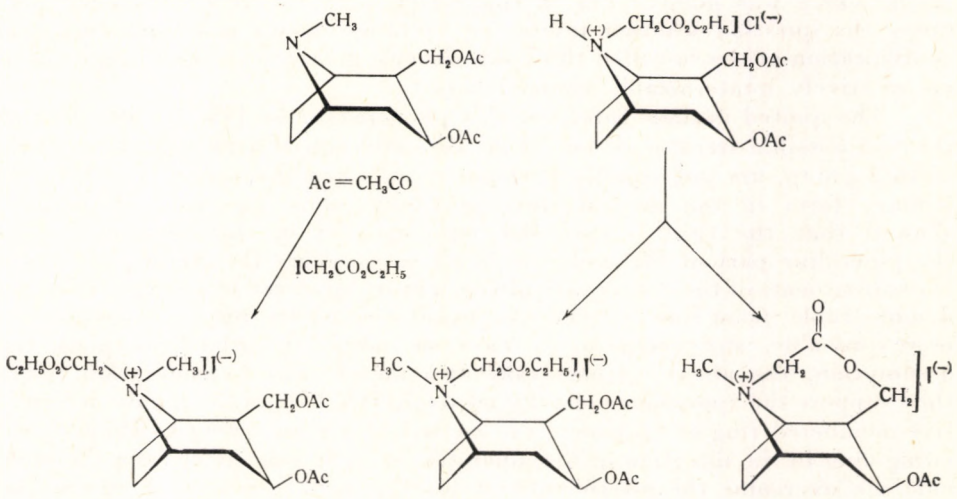


Fig. 128

salt could be given as (N*R* : 2*R* : 3*S*)-N-carboxymethyl-2-hydroxymethyl-3-hydroxytropanium iodide [52, 54] (Fig. 128).

The method of 'normal' and 'reverse' quaternization rendered possible also the preparation of the esters of N-epimeric carboxylic acids corresponding to the lactone salts; the configurations of the products (Figs 125—128) follow automatically. In the case of the quaternary salts of ecgoninol, wich is a cocaine derivative of already known absolute configuration [90], these configurations represent the absolute ones at the same time (Figs 127 and 128). The same holds true for the carboxymethylbetaine of teloidine (Fig. 117) having a *mesoid* structure. With the conclusion of the investigations begun by the Hungarian authors [75] for establishing a configurational correlation between 3*a*,6*β*-dihydroxytropane and oscine (deduction to the steric structure of *γ*-hydroxyproline), presently given relative configurations will automatically become equal either to the absolute ones or to their mirror-images.

These are the very first organic nitrogen compounds in which the absolute configuration of the asymmetric nitrogen atom is definitely known.

The preparation of these compounds and ascertaining of their steric structure presents a completely new problem of nomenclature. It was solved by the Hungarian researchers [71] in agreement with Dr R. S. Cahn (editor of J. Chem. Soc., London) as follows. Each compound having also a methyl

group on the nitrogen atom is a 'tropanium' salt; the steric position of a substituent present on the nitrogen atom in addition to the methyl group is denoted by *a*, if it is situated in the direction of the six-membered ring, and by index *b*, when it is in the direction of the five-membered ring. The adduct of (±)-3*a*,6*β*-dihydroxytropane with ethyl iodoacetate which is capable of forming a lactone (thus indicating the direction of its carboxymethyl group toward the pyrrolidine ring), e.g., is to be called (±)-N_b-ethoxycarbonylmethyl-3*a*,6*β*-dihydroxytropanium iodide, and to its N-epimer the name of (±)-N_a-ethoxycarbonylmethyl-3*a*,6*β*-dihydroxytropanium iodide will be assigned.

The fact of selective, stereospecific quaternization of tertiary amines [212], which was pointed out in connection with the tropane model [44], raises the question whether inferences could be drawn also concerning the configuration of the so-called third substituent, attached to the nitrogen atom of selectively quaternizable tropane bases.

The quoted authors interpret this phenomenon so [45, 48, 49, 52] that the two possible steric positions of an aliphatic substituent, e.g., that of the methyl group, are not equally probable even when the amine is still in the tertiary form in the ground state of the tropane skeleton. Experience showed that the third substituent was situated in the direction toward the piperidine part of the molecule in all cases where the steric positions of the substituents of the quaternary nitrogen atom appeared to be experimentally demonstrable; from this fact the conclusion was drawn that this position was more probable, and energetically more favoured. In order to explain this assumption, the above authors take two factors into consideration. First, they suppose the appearance of a Pitzer strain [15, 151] in the highly deformed five-membered ring of tropanes; the methyl group, in trying to shun it, will swing over in the direction of the piperidine ring. In this latter form the molecule can overcome the interference of the $C_{(3)}$ substituents with the methyl group by a clicking over of the six-membered ring into the chair conformation, since no considerable interaction can assert itself in this form between the methyl group and the hydrogen atoms, or the hydroxyl group of the ring. The other factor is the hydrogen bridge which can be formed especially in case of tropane derivatives containing a hydroxyl group on the endoethylene bridge, such as 3*a*,6*β*-dihydroxytropane, oscine and teloidine. This bond can obviously be established only by the unshared electron pairs of the nitrogen atom. That amounts to saying that the N-methyl group will be shoved away in the direction of the piperidine ring. With the mentioned tropane-6-ol derivatives these two effects appear parallel, and both promote the orientation of the nitrogen atom in the meaning described by the Hungarian authors.

On the other hand, the same phenomenon cannot be expected in the case of compounds containing a hydroxyl group of *syn* steric position in the piperidine ring, such as *syn*-3-tropanol or 2*β*-hydroxymethyltropane-3*β*-ol (ecgoninol): one should rather reckon here with the formation of a hydrogen bridge between the $C_{(2)}$ methylol group (or $C_{(3)}$ hydroxyl group) and the nitrogen atom. Consideration of the Pitzer strain prevailing in the five-membered ring, and of the hydrogen bond in the six-membered cycle result now in the anticipation of two different steric positions of the methyl group; the relative probability of the steric position of the substituents will be determined by the effect which is stronger than the other. Anyway, each experiment carried out in connection with the normal or reverse quaternization of ecgoninol and *nor*-ecgoninol

indicated the fact that the methyl group became more frequently situated over the piperidine ring (Fig. 121); this evidence shows [63] that the Pitzer strain is the prevailing factor also in this case. The third factor, which was pointed out to the author by BARTON [11], is the following: in the 1,3-diaxially substituted cyclohexane ring, the bulkiest substituent on $C_{(2)}$ is most stable when in *axial*, *trans* position in relation to the most voluminous neighbouring substituents. As regards the tropane derivatives, it means that when the endoethylene bridge is formally considered as a pair of *diaxial* substituents, an *axial* position (i.e., one in the direction of the piperidine ring) will be far more probable for the third substituent on the intermediate nitrogen atom than an *equatorial* configuration, i.e., inclination toward the pyrrolidine ring.

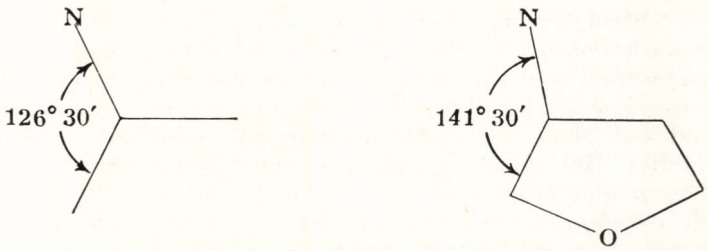


Fig. 129

The author and co-workers carried out an interesting series of experiments [71] with the purpose of demonstrating the appearance of the Pitzer strain. The molecular models of 3α,6β-dihydroxytropane and oscine were constructed according to the principles of descriptive geometry. It was shown that the pyrrolidine ring was much more distorted in the first case than in the second; although deformation of the whole molecule was increased by the oxygen bridge connecting $C_{(3)}$ with $C_{(6)}$ in oscine, still the angle α of the five-membered ring was by 15° smaller, and this moiety approached thus the coplanar state considerably better (Fig. 129). Consequently, it had to be taken into consideration that the method of reversed quaternization, which is based on the configurative stability of the tertiary amine, e.g. on that of 3,6-dihydroxytropane, can hardly hold true for the case of oscine. Indeed, in the course of this study it was shown that the N-carboxymethyl derivative of 3α,6β-dihydroxy-*nor*-tropane was not able at all to form a lactone when acted upon by mineral acids (Fig. 125). This is a proof for the N_a position of the carboxymethyl group in this compound, based upon the mentioned principles of nomenclature. In contrast with this, when the N-carboxymethyl derivative of *nor*-oscine is reacted with acids, the result is quantitative lactone formation (Fig. 126). Thus, in this case no difference can be found between the probability of one or the other orientation for the tertiary state of oscine, but the stability of the relatively most stable final product — the lactone salt — will decide on the most preferred steric position of the third substituent. These two related compounds are also different as regards their behaviour to methyl iodide. While the 3α,6β-dihydroxytropane derivative gives an ester- and carboxylic acid derivative incapable of lactone ring closure, N-carboxymethyl-*nor*-oscine affords two different methiodides [118] side by side, one of them capable of forming a lactone salt, whereas the other can give a carboxyammonium salt only. These facts confirmed the above working hypothesis, stating that the

extent of deformation of the pyrrolidine ring contributes to the configurative stability of the tertiary tropane nitrogen. For a further evaluation of the Pitzer strain, the author and K. KOCZKA have started experiments with pyrrolidine derivatives, primarily with γ-hydroxyproline.

The only possible dynamic alternative opposite to the above interpretation of the discussed experiments would be the following. The so-called third substituent, attached to the nitrogen atom, may assume in the ground state either position *a* or *b* (Fig. 122) with equal probability, however, the attack of the cation (or that of the molecule breaking off to afford the cation) effecting the quaternization may come only from the direction of the pyrrolidine ring. In this way, no decided orientation could be assigned to the third substituent of the nitrogen at the tertiary amine stage; solely the pyrrolidine ring would control the direction of the attack, but with no stable orientation of the unshared electron pair. However, it would follow from this alternative consideration that the cation to be introduced approaches the molecule from the direction of the pyrrolidine ring also in the cases of the so-called indirect quaternizations, e.g., with scopolamine, oscine, 3,6-dihydroxytropane or with teloidine. But in this direction the substituents already present — the epoxide oxygen of scopolamine or even more so the hydroxyls of teloidine bound with a hydrogen bridge to nitrogen — would at any rate give rise to a considerable steric hindrance against the approaching cation rather than facilitate its attack. The contradiction is especially obvious if the chair conformation of the piperidine ring in the tropane skeleton is taken into consideration, which — just in the case of scopolamine derivatives — is proved to be the far more probable state [45a].

In this configuration, namely, nothing would hinder the quaternizing cation to approach from the direction of the piperidine ring, and to compel the originally N_a situated methyl group to swing over into the steric position N_b. On the basis of all these considerations, the situation appears to be more plausible when interpreted according to the original version of FODOR et al. [45a, 51].

The configurational stability of the nitrogen atom of tertiary amines had been previously proved in a single case, by the example of the tricyclic Troeger base. In this case no possibility for turning inside out is given, thus the orientation of the *pyramidal* valency of tertiary nitrogen was proved by the resolvability of Troeger's base [150]. The configurational stability of the Troeger base gives still no clue for the oriented or non-oriented character of the unshared electron pair. The configurational stability of tertiary amines with tropane skeleton was interpreted by the cited authors by suggesting the tetrahedral orientation of the nitrogen atom in this case, too, i.e., by assuming that the latter was to be found in the hybridized [sp^3] state. Thus, the determined valency orientation [113] of the unshared electron pair of the tertiary tropane amines cannot be regarded simply as a *p*-orbital [151], but hybridized as a consequence of [sp^3] hybridization.

An interesting confirmation of the assumption that the unshared electron pair had well-defined steric orientation in tropane derivatives was recently contributed by LE FÈVRE and ARONEY as a result of studies concerning the polarizability of piperidine and morpholine [4, 5]. The Australian investigators determined the molecular Kerr constants, molecular refractions, and dipole moments. It was found that the N—H bonds had *axial* position in the piperidine ring (and also in morpholine), and out of the six possible

conformations of the piperidine ring (Fig. 130) chair form II was the most probable. With N-methylpiperidine, a nearly uniform statistic distribution of the methyl group between the *axial* (II) and *equatorial* (I) steric position was found. It was concluded from this finding that the space requirement of the unshared electron pair on the tertiary nitrogen was greater than that of a hydrogen atom, being in the order of magnitude of the space requirement of a methyl group.

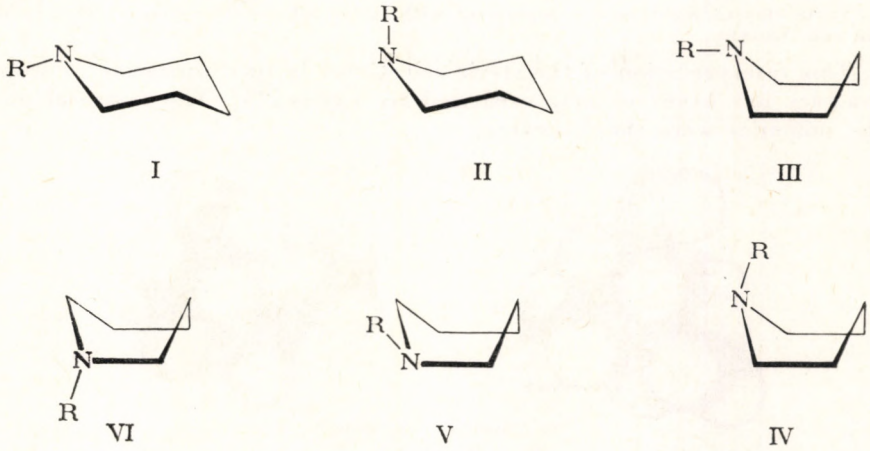


Fig. 130

One may refer here back to the paper of Fodor and Lestyán [65] who carried out dipole moment measurements in dioxan, and calculations concerning the six possible conformations as early as in 1952, using 4-hydroxy-piperidine. From these measurements and from the molecular refraction values, also the polarizability was concluded. The calculated dipole moments are given in Fig. 131. In order to determine the most probable conformations, the individual dipoles of the functional groups in the molecule were vectorially added, under consideration of the angle between the partial dipoles. The dipole

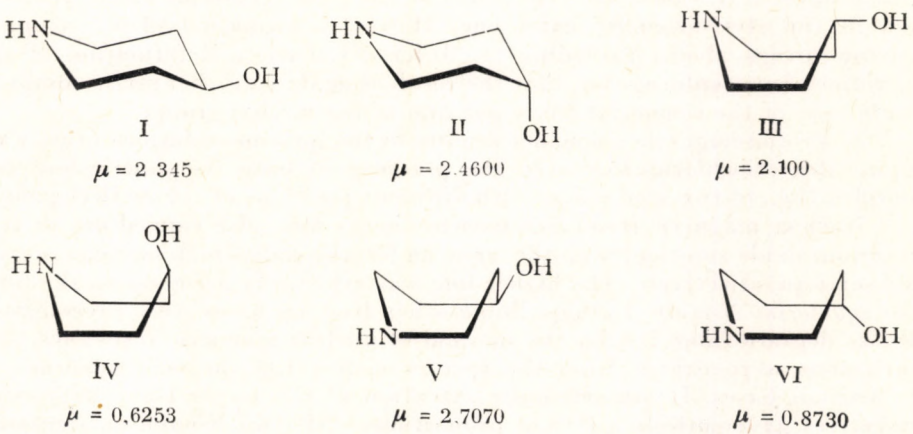


Fig. 131

moments calculated in this way should be regarded to be first approximations. Taking into consideration the dielectric constants, density, and the refractive indices measured for the D line of sodium, a dipole moment of 1.479 was established.

From these measurements and calculations, as well as on the basis of the fact that N-benzoyl-4-piperidinol undergoes N→O acyl migration (even if only at 150°), the Hungarian investigators concluded that in 4-hydroxypiperidine in any case the chair conformation must be present, and particularly that form (I) in which the functional groups are in *syn*, β position.

These measurements are in agreement with the results of the extensive studies of LE FÈVRE and ARONEY.

This interpretation of the steric selectivity in quaternization of tropane derivatives has been recently criticized by CLOSS [23]. The essential points of the polemics were the following.

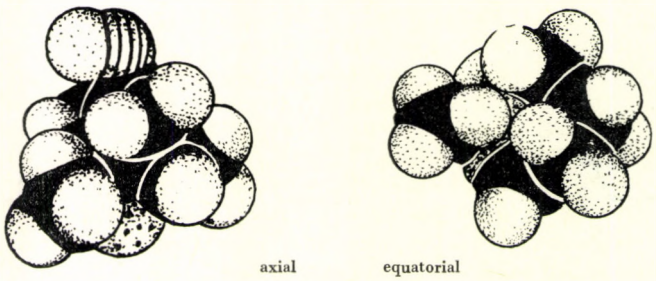


Fig. 132

1. The reaction rate of the quaternization should in any case be higher than the rate of the swinging over of the methyl group from *axial* position into the *equatorial* one. Consequently, the quaternization is controlled by kinetic factors.

2. According to the model studies of the American author, the Stuart—Briegleb model of tropane should reveal a greater steric compression in the case of the *equatorial* steric position of the methyl group than in the *axial* one (Fig. 132). This assumption was interpreted by MCKENNA [123] by stating that a group was, *in general*, more strongly shielded by two neighbouring *axial* groups of 1,3-position when it was in the *equatorial* steric position than in the stereoisomeric *axial* one. However, formation of the tropane skeleton brings about, according to MCKENNA, such a deformation of the piperidine chair conformation that the result is again a smaller steric compression in case of the *equatorial* steric position of the methyl group.

3. Protonmagnetic resonance studies of the aqueous solutions of pseudotropine deuteriochloride indicated the presence of both N-epimeric deuteriochlorides (i.e., of two stereomers with different positions of the methyl group).

Nuclear magnetic resonance measurements were also carried out in acid deuterium oxide solution, and the area under the individual maxima evaluated semi-quantitatively. The higher line was arbitrarily assigned to the form with *equatorial* N-methyl group. Some other tropane bases were investigated also, as deuteriochlorides, by the method of nuclear magnetic resonance, and conclusions were drawn from the spectra concerning the conformations of the original bases. It attracted the attention of the researchers that oscine derivatives gave entirely different proportions of the two N-epimeric deuteriochlorides in comparison with the bicyclic 'real' tropanes.

Our reflections as regards these arguments are as follows.

1. Neither the energy of activation nor the entropy of the process of swinging over of a methyl group above the tropane nitrogen atom firmly anchored by two valence bonds are known; consequently any *a priori* statements concerning their magnitude are arbitrary at present.

2. As it is shown in Fig. 132, the difference between the steric compressions and the two extreme positions of the *methyl* group is actually not too great. Existence of a Pitzer strain of five-membered rings could be denied only on this basis. In this case, however, there is no doubt about a Pitzer strain existing in the five-membered ring, which should be even higher in tropane than in cyclopentane, since the 1,3-annelation results in a distortion of the position of the, say, *equatorial* methyl group toward the ethylenic hydrogen atoms. Let alone this argument, Stuart—Briegleb models are at present hardly suitable for drawing quantitative conclusions concerning the interferences of bridged systems like tropane, because they are not designed with deformed valence angles calculated for this special purpose. Consequently, in this respect we can share McKenna's opinion: "If the work of Aroney and Le Fèvre is taken into account, and also the fact that with some types of space-filling models *there is not very much difference in steric compression between the two flanks of the heterocyclic nitrogen atom*, it is evident that assessment of the preferred conformation of tropane bases is a matter of some difficulty; the interesting general problem concerning stereochemical control in the quaternization of asymmetric bases should, however, be less intractable", i.e., even if the co-ordination of a stable configuration is disturbed to some extent by the kinetic control in the tertiary phase, the problem of the contribution of steric factors to the course of quaternization remains a question of general interest.

The objections of Closs gave furthermore no explanation for the complete disappearance of the stereospecifity of quaternization parallel with an obvious decrease of the Pitzer strain in the cases of oscine (see Figs 126 and 129) and the granatanols; in the latter case the thermodynamic factor becomes controlling.

3. The nuclear magnetic resonance spectra were taken not with the bases, but with the salts in acidic aqueous solution. In this case protons (or deuterons) are present in excess; consequently the exchange reaction on the nitrogen may proceed by electrophilic attack and substitution with the inversion of the methyl group.

In our opinion these conditions are not connected closely enough with the circumstances of quaternization in anhydrous medium to justify common conclusions.

Therefore, proton magnetic resonance, dipole moment and X-ray investigations with tropine and 6β-hydroxytropine including the corresponding ketones are carried on in collaboration with the Cambridge and Amsterdam Universities.*

To achieve final settlement of this problem, further investigations should be made in the future with the use of (—)-N-carboxymethyl-*nor*-3α,6β-dihydroxytropane. The racemate of this compound failed to lactonize [71]. It

* *Pseudo*tropine crystal has an equatorial methyl and intermolecularly H-bonded lone electron pair. Dipole moment measurements with α- and β-3-cyanotropane also support that configuration.

is intended now to attempt to force the lactonization of the compound at different temperatures under polarimetric control, and determine the activation energy of the configurational change of the carboxymethyl group from the kinetics of the reaction.

Aside from the result of further discussions concerning the conformation of the N-methyl group of *tertiary* tropane bases, there is no doubt about the fact that determination of the relative and also of absolute configurations of some quaternary ammonium bases was rendered possible *first* by the stereospecifity of the quaternization of tropane derivatives.

DIOSCORINE

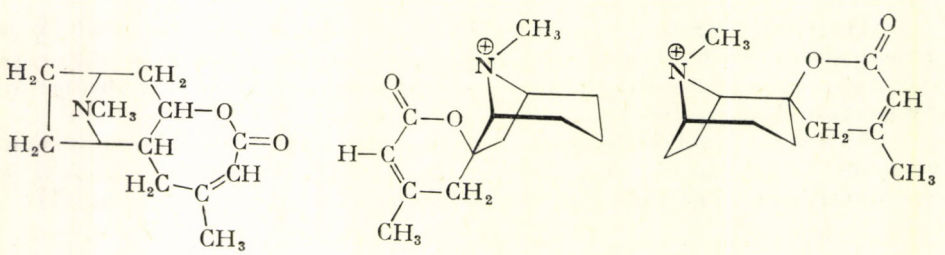
This tropane (?) alkaloid is today the last representative of the group which has not yet been made accessible by total synthesis. Its approximate constitution has been, however, made out with high probability of correctness by means of degradation reactions, and even the absolute configuration has been reported as ascertained by correlation. For a better understanding of the stereochemical correlations, constitution should be discussed briefly at first.

Elucidation of the Constitution and of the Configuration

The alkaloid of *Dioscorea hispida* Dennstedt, showed a positive Legal test, from which fact GORTER, as early as in 1911, concluded the presence of an α,β-unsaturated lactone group. Hofmann degradation of the alkaloid gave a base with the empirical formula of $C_{13}H_{21}N$ which product afforded trimethylamine on heating with palladium charcoal; other products were either *iso*butylbenzene or β,β-dimethylstyrene, depending upon the activity of the catalyst, and also an unknown base was isolated. Exhaustive methylation of the latter compound resulted in the formation of a hydrocarbon having the empirical formula $C_{11}H_{14}$, for which infrared spectral analysis indicated a constitution of *iso*butenyl-*cyclo*heptatriene. Hydrogenation gave $C_{11}H_{22}$, but the product did not appear to be identical with synthetic *iso*butyl*cyclo*heptane. Two synthetic stereoisomeric N,N-dimethyl-3- and 4-*iso*butyl*cyclo*heptyl amines were compared with, but found again to be different from the Hofmann base.

On the basis of this evidence, PINDER suggested first constitution *A* of a 2,3-annelated tropane-lactone for dioscorine [142] (Fig. 133).

Then BÜCHI et al. [6] showed that dioscorine gave a diol, 'dioscorinol' on hydrogenolysis; the ozonolysis of this compound produced glycollic aldehyde



A *B* *C*

Fig. 133

and a hydroxyketone [6, 146]. The latter suffered retro-aldol reaction on heating, and became decomposed to acetone and a ketone, $C_8H_{13}ON$, which was considered first to be 6-oxotropane, but identified (?) later as 2-oxotropane [16, 147].

The former assumption induced BÜCHI to form his working hypothesis involving a 6-*spiro*-tropanecarboxylic lactone (Formulae *B*), furthermore FODOR, HALMOS and SÓTI to synthesize* 6-oxotropane. This compound was prepared from 6β-hydroxytropinone by Clemmensen reduction and oxidation of the $C_{(6)}$ hydroxyl to an oxo-group. The ketone was not identical with the material described by BÜCHI. ARCHER [16] could degrade (—)-anhydroecgonine amide to L-(+)-2-oxotropane, and identify this product with the ketone, $C_8H_{13}ON$, obtained from dioscorine. Consequently, the natural base was believed to have a $C_{(2)}$ spirane structure (*C*) on the tropane skeleton, and the same absolute configuration as (—)-cocaine. Surprisingly, PINDER et al.** reported later

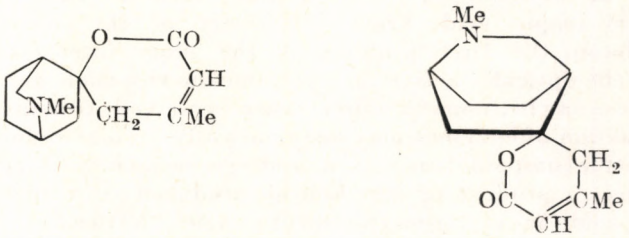


Fig. 134

that the keto base $C_8H_{13}NO$ from dioscorine was not identical with 2-oxotropane, so he withdrew his previous statement. Instead, the structure of 2-methyl-5-oxo-*iso*quinuclidine, based upon renewed Hofmann degradation of the same keto-base, has been suggested. In consequence, the structure suggested for dioscorine would be that shown in Fig. 134. Present author is extremely sorry to leave his readers in doubt since — owing to several changes in the concept on the structure of dioscorine — the last final decision seems to be taken with reservation and postponed till the total synthesis of dioscorine is achieved. Only that could rule out the possibility of a rearrangement of the original tropane skeleton into an *iso*quinuclidine *during degradation.*

STERIC STRUCTURE AND BIOGENESIS OF TROPANE ALKALOIDS

Since the time of ROBINSON's pioneering synthesis of tropinone [156] and his hypothesis concerning the biosynthesis of the tropane bases in plants, several investigators have dealt with the problem of the biogenesis of tropane alkaloids. ROBINSON was the first to synthesize tropinone [157] from succinic dialdehyde, methyl amine, and acetonedicarboxylic acid, a reaction similar to the so-called Petrenko—Kritschenko reaction [140] (cf. Figs 71 and 72). All these building-stones are simple, and they are presumably in direct connection with the carbohydrate and amino acid metabolism, consequently this way of formation of tropinone was accepted as the process which probably also occurs in the vegetal cell. Indeed, SCHÖPF succeeded in carrying out the same process under simulated physiological conditions, in dilute aqueous solution and at a pH value

* Unpublished.
** September 2nd, 1961; Chem. and Ind. *1961*, 1410.

tolerable for the plant [170]. The same experimental technique has so far proved successful in all known cases of employing Robinson's method to synthesize 3-tropanones. Thus, e.g., WILLSTÄTTER [201, 204] prepared in the same way the methyl ester of tropinone-2-carboxylic acid, which is the key-intermediate of the synthesis of cocaine and *pseudo*cocaine, starting with the monomethyl ester of acetonedicarboxylic acid, while STOLL, BECKER and JUCKER [182] condensed malic dialdehyde (2-hydroxybutane-1,4-dial) under similar conditions to give 6-hydroxytropinone. SCHÖPF and ARNOLD obtained 6,7-dihydroxytropane-3-one, i.e., teloidinone from *meso*tartaric dialdehyde [172] under physiological conditions. All these experiments show that the tropane skeleton can actually be built up under such circumstances. Another question is that in nature there occur not only optically inactive tropane derivatives, but also active modifications, such as cocaine, valeroidine etc., as well as esters of tropanols of *meso*structure (e.g. tropine) formed with optically active acids, such as tropic acid. From the aspect of the biogenesis of the tropane skeleton, the first problem is the more interesting: the way of formation of the optically active, i.e., asymmetric tropanols and tropane-diols. The second case can be, namely, fairly easily explained: tropane-3-one, formed without the action of enzymes may enzymatically become reduced to tropane-3α-ol. The latter compound may then undergo secondary esterification when acted upon by a product of metabolism produced in a different way, e.g. *S*(−)-tropic acid or (−)-α-methylbutyric acid. Naturally, one may also assume that in the case of the first type of formation the optically active malic dialdehyde produced in the course of the carbohydrate metabolism (or appearing as a decomposition product of aspartic acid), is converted into 6-hydroxytropane-3-one really under so-called physiological conditions, i.e., without the contribution of enzymes (Fig. 109). However, in the case of the cocaine skeleton one must of necessity consider an asymmetric synthesis, at least a stereospecific reduction of the tropane-3-one-2-carboxylic ester, because otherwise natural cocaine would be accompanied in the Coca leaf also by racemic cocaine or some ester of the (+)-modification [48, 49]. SCHÖPF et al. attempted to extend the spontaneous synthesis of tropane alkamines under physiological conditions also to epoxysuccinic dialdehyde. This reaction, however, resulted not in the formation of the expected scopine (6,7β-epoxytropane-3-one) but of a bicyclic hydroxypyrrolidine derivative [171] (Fig. 110). The result showed that, instead of Robinson condensation to give the expected ketone, the epoxide ring was opened at the pH values employed, as a result of the action of the highly nucleophilic acetonedicarboxylic acid.

KARRER and KEBRLE [105] making use of a former observation of ROBINSON, extended the method of synthesizing 1,4-dialdehydes also to α,δ-dioxocarboxylic acids. Therefore, it is conceivable that, instead of the unstable epoxysuccinic dialdehyde, its more stable derivative with one or two carboxylic substituents would serve as the key-intermediate for scopine, and the carboxyl group, becoming undesired after ring closure, could be removed either enzymatically or spontaneously.

All these working hypotheses are, of course, sound only if they can actually be verified by means of the isotope tracer technique. In this field the number of such experiments is increasing. It was shown first that the ^{14}C atom of putrescine did not become incorporated into the hyoscyamine or atropine molecule produced by *Datura stramonium* [101]. Another observation obtained not by radioactive tracer technique showed that feeding of orni-

thine, arginine [25, 26, 101] and also of putrescine [26] measurably increased the production of hyoscyamine in the living *Datura stramonium* plant. JAMES stated that ornithine was decomposed by a vegetable oxydase to δ-oxo-α-amino-valeric acid [102]. It was suggested that the amino-nitrogen of this compound supplied then the nitrogen atom of the tropane which subsequently underwent a 'transmethylation' by methionine to give tropinone. It should be mentioned that according to ROBINSON [157] α,α'-diaminoadipic acid and citric acid gave a small amount of *nor*-tropane-3-one under the action of hydrogen peroxide (Fig. 135). These acids can easily be produced *in vivo* from hexoses or C_3-sugars. In the light of this experiment, criticism may arise in connection with

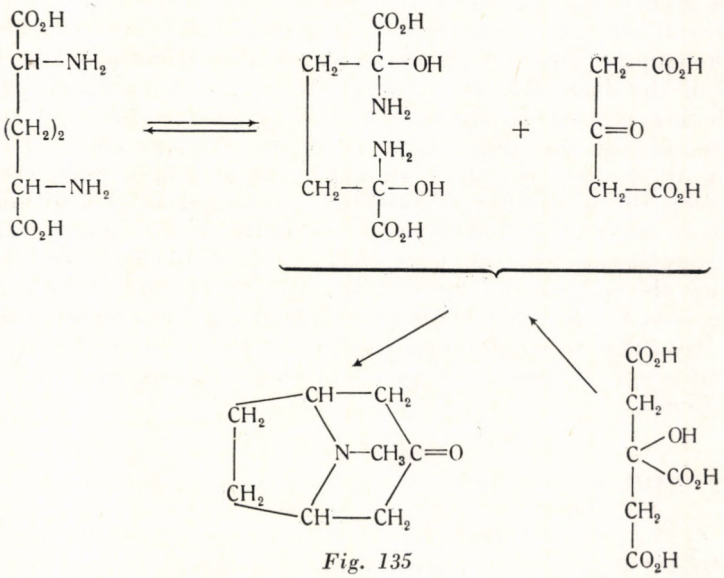


Fig. 135

the working hypothesis of CROMWELL [25, 26], according to which he regarded putrescine as the source of succinic dialdehyde, and supposed its formation through arginine and ornithine. The other alternative suggested by this author said that putrescine became converted into α-aminobutyraldehyde, and the geminal alkamine form of this compound was further oxidized to 2,5-dihydroxypyrrolidine, to be condensed finally with acetone into *nor*-tropanone (Fig. 136). For this working hypothesis there is absolutely no other sound basis than the mentioned feeding experiments. However, the question in which way ornithine becomes converted into succinic dialdehyde can be definitely answered only if it succeeds to obtain radioactive tropanol ester, e.g., scopolamine or atropine, from the leaves of *Atropa* or *Datura* fed with ^{14}C-labelled succinic dialdehyde.

Another important contribution to the knowledge of the formation of the tropane skeleton *in vivo* was supplied in 1960 by MOTHES, KACZKOWSKI and SCHÜTTE [103]. These investigators fed *Datura metel* with acetate-2-^{14}C and acetate-1-^{14}C. The rate of incorporation of 2-^{14}C acetic acid was about twice as high, from which fact it follows that the pyrrolidine ring underwent condensation with two molecules of acetate, with the loss of a carboxyl group. Since there is no doubt about the origin of the $C_{(1)}$ and $C_{(5)}$ carbon atoms of hyoscy-

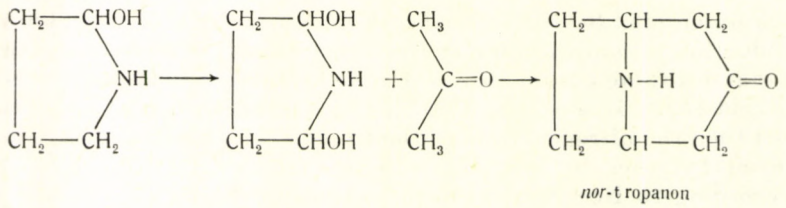


Fig. 136

amine (both are derived from the α-carbon atom of ornithine [114]), now it is known that atoms $C_{(2)}$, $C_{(3)}$ and $C_{(4)}$ originate from acetic acid *via* acetoacetic acid. This result indicates acetoacetic acid as one of the very probable building stones of the tropane skeleton. As to the way leading from ornithine to tropine we are still in the dark. MOTHES et al. [103] assume Δ_1-pyrroline as an intermediate which may take up acetoacetic acid to give pyrrolidinyl acetoacetic acid and this, in turn, by enzymatic dehydrogenation may yield *nor*-tropinone; methylation on the nitrogen atom should ensue at a later stage (Fig. 137).

However, the possibility of oxydative deamination of ornithine to succinic aldehyde as a step, followed by methylation and condensation with acetoacetic acid has not been ruled out either. In order to check the likelihood of this pathway, the author and his colleagues (URESCH and DUTKA) succeeded in preparing now $C_2 : C_3$ labelled succinic dialdehyde and employ it in co-operation with ROMEIKE, in feeding experiments on *Datura*, in order to arrive at a final settlement of this problem. No serious incorporation into hyoscyamine was found.

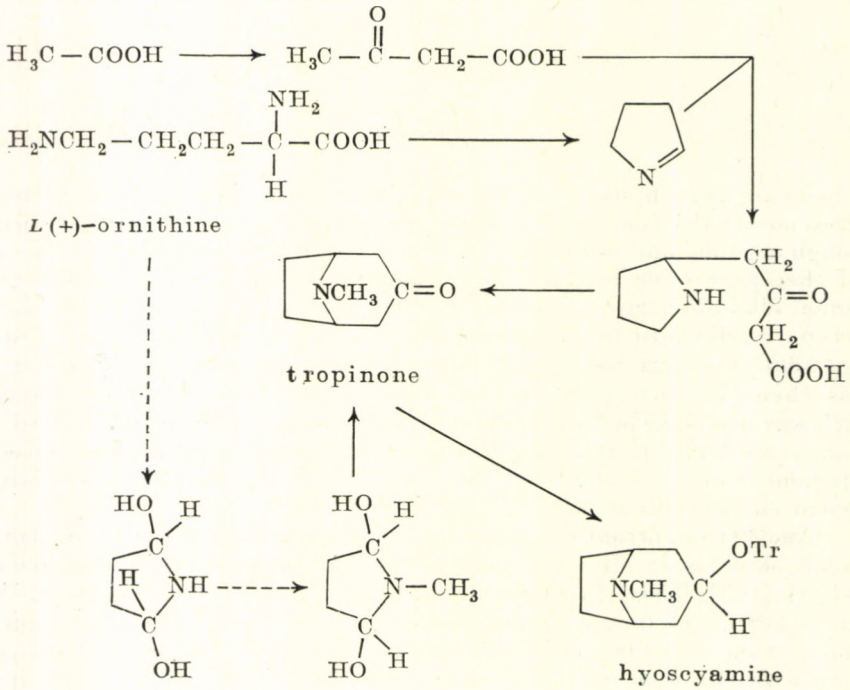


Fig. 137

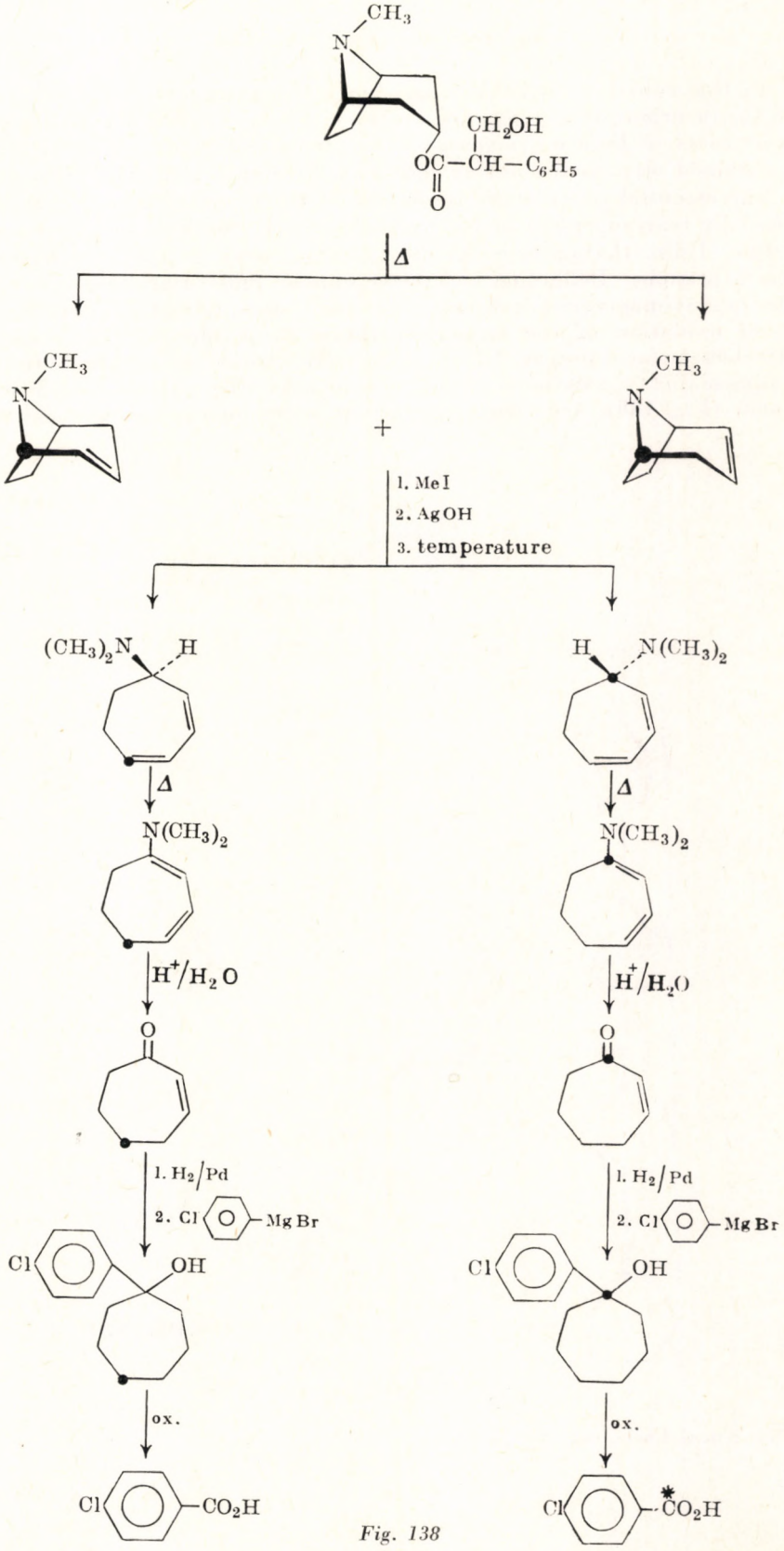

CH3
N
CH2OH
OC—CH—C6H5
O
Δ
CH3
N
+
CH3
N
1. MeI
2. AgOH
3. temperature
(CH3)2N
H
Δ
N(CH3)2
H+/H2O
O
1. H2/Pd
2. Cl
MgBr
Cl
OH
ox.
Cl
CO2H
H
N(CH3)2
Δ
N(CH3)2
H+/H2O
O
1. H2/Pd
2. Cl
MgBr
Cl
OH
ox.
Cl
*CO2H

Fig. 138

In this course of related experiments BOTHNER-BY et al.* had investigated the incorporation of labelled acetate-1-C^{14} into hyoscyamine biosynthesized by roots of *Datura stramonium*. The stepwise degradation of the alkaloid they obtained was carried out as shown in the flow sheet (Fig. 138).

The essential point is the resolution of the so-called *a*-methyl-tropidine followed by rearrangement of the optically active components into *β*-methyltropidine (1-dimethylamino*cyclo*hepta-1,3-diene) and, in turn, by hydrolysis to *cyclo*heptanone. Reduction to *cyclo*heptanone and Grignard reaction with *p*-chlorophenylmagnesium bromide were the consecutive steps. The last stage involved oxidation of the tertiary carbinol to *p*-chlorobenzoic acid. Only *p*-chlorobenzoic acid prepared from (+)*a*-methyltropidine contained the overwhelming majority of the label, while the acid derived from the (—)-modification had none (Fig. 138). Accordingly, an asymmetric incorporation of the radio-

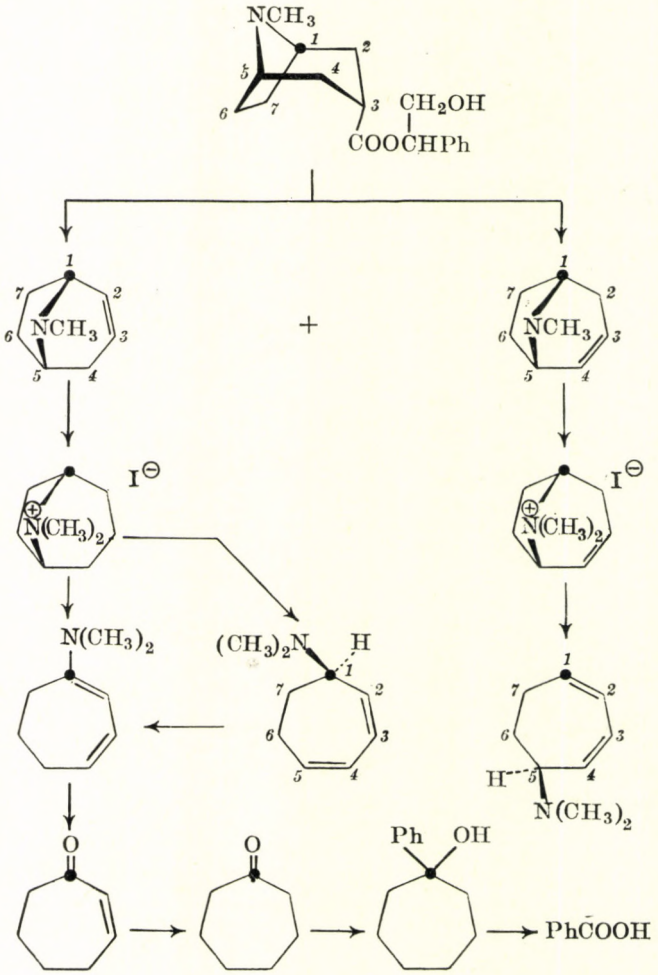


Fig. 139

* J. Amer. Chem. Soc. *84*, 53 (1962).

carbon took place. Taking into consideration that according to the Szent-Györgyi—Krebs cycle ^{14}C-labelled acetate must be metabolized to 5-^{14}C ornithine, one of the bridgeheads in the tropane skeleton must arise from that terminal carbon.

As a complementary piece of evidence, simultaneously with BOTHNER-BY, also LEETE succeeded in proving the stereospecific incorporation of *a*-^{14}C-ornithine into the tropine moiety of hyoscyamine.* Accordingly, there is serious likelihood of an asymmetrical intermediate in hyoscyamine biosynthesis, i. e. either Δ_1-pyrroline as suggested by analogy with nicotine biosynthesis by MOTHES, or succinic aldehyde as supposed by ROBINSON, SCHÖPF and lately by the present author (Fig. 139). The most striking observation is that even racemic ornithine is incorporated stereospecifically pointing strongly to an asymmetric step in the conversion of ornithine into tropine. In our opinion, Δ_1-dehydroproline** could be made responsible as an intermediate for this selective incorporation — an assumption to be checked in the near future (Fig. 140).

The biological interrelations among the individual tropane alkaloids may be represented in one possible way according to CROMWELL's assumptions as shown in Fig. 141. He considered 6-tropene-3-ol produced by the enzymatic dehydrogenation of tropine to be the presumable intermediate of all related tropane alkaloids, such as scopolamine, valeroidine, teloidine or meteloidine. This assumption would be supported primarily by the fact that it succeeded in identifying N-methyl-Δ_3-pyrroline as a component present in *Belladonna* [189]. All suggested conversions of tropenol can be understood with perfect easiness. The manifold transformations can be readily interpreted by simple reactions, like hydration, hydrogenation, peroxidation, and epoxidation, assuming

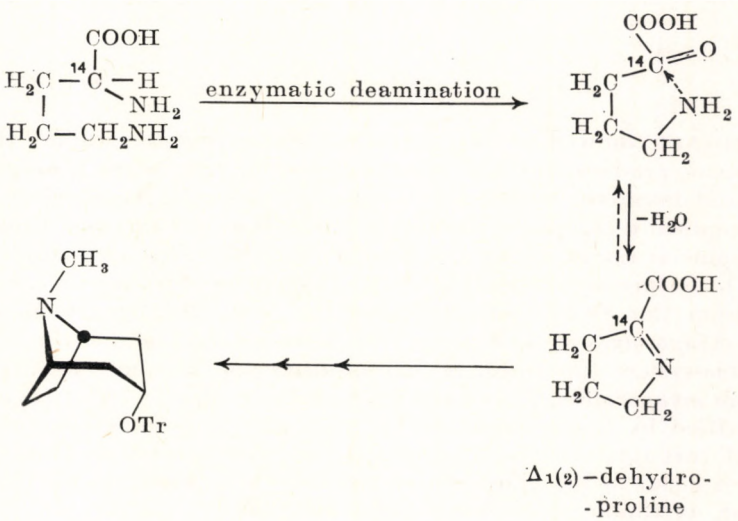


Fig. 140

* Amer. Chem. Soc. *84*, 55 (1962).

** This has been synthesized from *δ*-phtalimidomalonic ester *via* *α*-oxo-*δ*-phtalimido valerate by FODOR and URESCH, cf. Lecture A 6 at the XIXth Congress of IUPAC, London, July 12, 1963.

enzymatic actions at the same time. The scheme of PREOBRAZHENSKI's conception [153] (Fig. 141) is essentially the same; as it was mentioned, he reported the condensation of maleic dialdehyde to give tropenone [152], and hoped to be able to convert this compound into tropenol, then into the mentioned alkamines. However, tropenone could not be prepared sufficiently well in this way [105, 169, 185], thus PREOBRAZHENSKI has remained in debt for the subsequent conversions. The above-mentioned experiments of the Hungarian author led finally to the successful preparation of tropenol, the key to check the above hypothesis of biosynthesis [72]. Anyhow, *in vitro* conversions of this compound into tropane alkamines is in itself still not conclusive proof for its being the common intermediate of all tropane bases.*

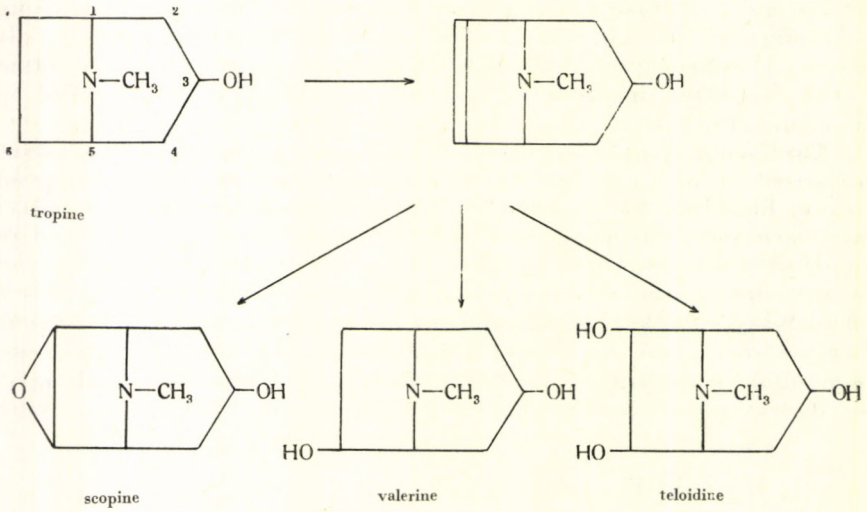


Fig. 141

TRAUTNER showed in the course of his systematic studies [189] that tropane bases produced by the vegetal family of *Solanaceae* belonged to two different and distinctly delimited systems of alkaloids. In the so-called *hyoscine-system* scopine, ψ-tropine, valerine and teloidine are formed. From among these, scopine is esterified by tropic acid, but the bases occurring in smaller amounts by isoprenoid carboxylic acids. Tropine itself is, however, completely missing from this system of alkaloids. The first alkaloid system occurs in *Duboisia myoporoides* as well as in *Datura meteloides*. In the other, so-called *hyoscyamine-system* (of *Duboisia Leichardtii)* and in some southern species of *Duboisia myoporoides*, TRAUTNER found only tropine and *nor*-tropine, which were esterified by tropic acid, atropic acid, and in smaller amounts also by isoprenoid carboxylic acids. The process of esterification is thus manifold. Some bases occur in the plant also in the free state. However, in these plants no scopine, ψ-tropine or hydroxy bases are found.

These two systems of alkaloids differ from each other not only as regards the degree of oxidation. All these facts contradict the statement of CROMWELL, according to which saturated bases, e.g. tropine, would be the

* In 1962 FODOR and S. KISS succeeded in oxidizing 6-tropen-3α-yl acetate into 3-acetylteloidine.

precursors of the oxidized and dehydrogenated ones [25, 26]. Even if it were successful to prove the fact of dehydrogenation occurring in the plant on the $C_{(6)}$ and $C_{(7)}$ carbon atoms of tropanol, this would not yet explain the formation of ψ-tropine containing a hydroxyl group of *syn* steric position on $C_{(3)}$. However, if one assumes that two different — even if related — mechanisms are in operation, the formation of all products becomes comprehensible.

Today it would be too early to accept the views of CROMWELL and PREOBRASHENSKI or, on the other hand, those of TRAUTNER as the final solutions of the problem. Namely, KOCZKA succeeded in 1955, following a suggestion of FODOR, in dehydrogenating N-benzylpyrrolidine to N-benzyl-$\Delta_{3,(4)}$-pyrroline, using diethyl azodicarboxylate, a reagent which does not occur in nature. One cannot exclude the possibility that some other naturally occurring compound, having an oxidation–reduction potential similar to that of diethyl azodicarboxylate, may be able to perform a similar dehydrogenation in the vegetal cell, and accomplish the tropine → tropenol (or hyoscyamine → dehydro-hyoscyamine) reaction in this way. The formation of ψ-tropine accompanying the oxygenated bases, is not readily explained by any of the mechanisms. However, it should also be considered that the irreversible conversion of tropine into ψ-tropine can be executed in the presence of a number of oxidation–reduction catalysts. Thus, disappearance of tropine from the plant does not exclude the possibility that *anti*-tropine was originally present in it, and became converted into *syn* (ψ)-tropine, because, even if only extremely rarely so far, it has been successful to detect free, not esterified tropine in the living *Atropa* plant [189].

Another interesting problem of the biogenesis of tropane alkaloids arose after the conclusion of the described stereochemical researches. Namely, it is remarkable that the oxygen-containing functional groups, either hydroxyl or epoxy, at $C_{(6)}$ and $C_{(7)}$ are contained in all tropane alkaloids occurring in nature always in *syn*, β position in relation to the nitrogen atom. It is interesting that in most synthetic 6(7)-hydroxy- or *presumably* 6(7)-alkoxytropane derivatives the steric position of this functional group is the same as in the natural product. As contrasted with this, STOLL, JUCKER et al. reported [182, 183] an occasion of condensing malic dialdehyde, when separation of the produced racemic 6-hydroxy-tropinone gave in addition to the (+)-6-hydroxy modification corresponding to natural (—)-valeroidine, also an epimeric (—)-modification, and not the laevorotatory mirror-image of the former compound. This compound was presumably 6α-hydroxytropane-3-one. A product of such structure has not occurred so far in nature according to our knowledge. As observed by STOLL and JUCKER [185], the ethers of 6-hydroxytropane possess extremely strong mydriatic action, therefore a number of compounds belonging to this type have been prepared [211] in the institute of STOLL, of KARRER, as well as in the *Boehringer* Laboratories. From a study of the models of these $C_{(6)}$- and $C_{(7)}$-substituted derivatives, KEBRLE and KARRER derived the final conclusion that the product obtained could be stable only if the oxygen-containing functional group was in *syn*, β steric position related to the nitrogen atom; this was the main reason to explain the frequent occurrence of the *syn*, β configuration of these hydroxyl derivatives, which latter fact was considered to be only probable at that time, but is proved since then [48a].

Long since has been a proof wanted concerning the identity of methoxy- and other alkoxy-derivatives with the alkamine components of valeroidine and

teloidine as regards the configuration of the $C_{6(7)}$ atom.* Decision of this problem in the affirmative appears to justify the assumption that naturally occurring and synthetically produced tropane alkaloids having $C_{6(7)}$ oxygen-containing functional groups are built up according to the same principle of synthesis.

If the view of KARRER [105] is accepted, it is supposed that the *syn*, β steric position of the C_6—C_7 oxygen function is predominant, because the opposite 6α configuration would result in an unstable molecular structure. In this respect reference should be made to a recent publication of ALDER and DORTMANN [1]; these authors, when supposing the *syn*-configuration of all 6(7)-hydroxytropanes and -tropanones, are of the opinion that this form is produced during the condensation reaction, because the intramolecular hydrogen bridge promotes this reaction as a stabilizing factor in the intermediate α,α-dihydroxypyrrolidine (cf. Fig. 72). However, if the *methoxyl* derivatives are also of the same configuration as the hydroxy compounds (as it is proved actually with the monomethoxy compound), the former assumption is hardly tenable, since the existence of a hydrogen bond is impossible in the case of ethers. For a final settlement of this problem it is necessary to ascertain the steric structure of the methoxy compounds exactly, by means of methylating 6β,7β-dihydroxytropane-3-one or by the acetolysis of 6,7-dimethoxytropane[48a]. Furthermore, the problem still remains to be solved whether the identical steric positions of the oxygen functions formed in these compounds are brought about by the requirements of stereochemical stability, or are these compounds built up from a common intermediate by stereospecific reactions.

The most recent results will shortly ensue. MARION et al. fed ornithine marked with ^{14}C on the α-carbon atom to *Datura* plant [114], and isolated radioactive atropine and radioinactive scopolamine. This tracer study concerning the biogenesis of tropane alkaloids indicates that we should suppose an independent way of formation of atropine and scopolamine in the plant. However, the more recent experiments of MOTHES and ROMEIKE [159, 160] in the Research Institute for Plant Physiology of the Academy of Berlin has thrown new light upon the problem of biogenesis. Namely, they found that with a young scission of *Datura* plant, on *Cyphomandra*, unable to produce alkaloids in itself, feeding of atropine or hyoscyamine resulted in the production of (—)-hyoscine. This product was detected in the leaves by paper chromatography [160, 162], and isolated later in the form of a crystalline picrate, which was identified in 1959 in the laboratory of the author by microanalysis and micropolarometry.** If we consider now that the biosynthesis of scopolamine takes place similarly as the chemical one by the oxidation of tropenol esters [69, 73], it can be justly assumed that when hyoscyamine is acted upon by any kind of vegetal dehydrogenase the compound is converted first into dehydrohyoscyamine, i.e. into tropenyl tropoylate, and then epoxidized by a peroxidase enzyme system. The experimental checking of this hypothesis consisted of feeding dehydrohyoscyamine to *Datura ferox* plants and, indeed, it has been successful to

* In 1958 FODOR and S. KISS succeeded in converting 6-methoxytropinone into 6β-acetoxytropinone, and 6-methoxytropine into 3α,6β-diacetoxytropane, by treatment with acetyl bromide; these experiments established the correctness of the above assumption. Lately 6-methoxytropine was converted by hydrobromic acid into methyl bromide and 3α, 6β-tropandiol.

** FODOR, G., ROMEIKE, A., JANZSÓ, G., and KOCZOR, I.: Epoxidation Experiments *in vivo* with Dehydrohyoscyamine and Related Compounds. Tetrahedron Letters 7, 16—18 (1959).

isolate (—)-scopolamine (hyoscine), which constitutes a proof for the possibility of converting tropic esters of tropenol into (—)-scopolamine in the plant. A next task is to investigate the enzymatic dehydration of *S*-atropine to *S*-(—)-dehydroatropine and obtain evidence for this reaction.

In further experiments, ROMEIKE could isolate two new alkaloids as intermediates, when cut-offs of *Datura* were fed to the alkaloid-free combination of *Datura ferox* scission of *Cyphomandra betacea*. One of the products was denoted as alkaloid 'U', the other as alkaloid 'V'. This latter compound was shown indeed to be an intermediate, since it could be converted further by

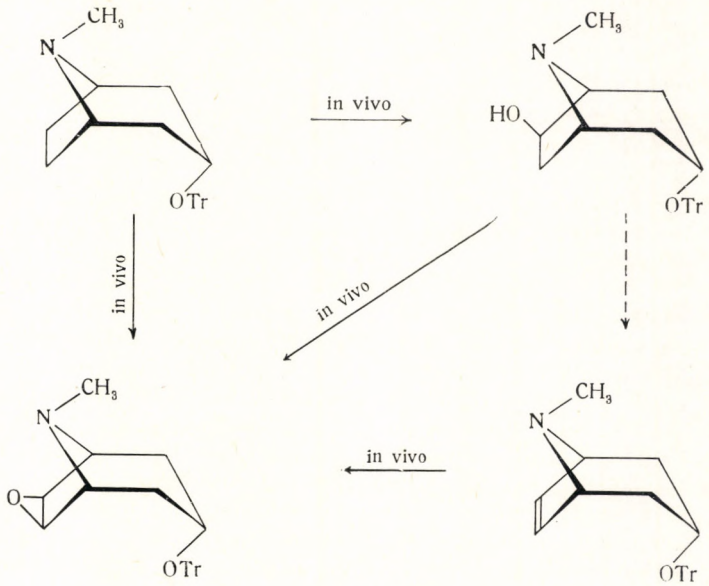


Fig. 142

continued feeding to give hyoscine. ROMEIKE could isolate 3,6-dihydroxytropane as the product of hydrolysis of alkaloid 'V' Furthermore, 6-hydroxyhyoscyamine, prepared recently by FODOR, KOCZOR and JANZSÓ by the hydrogenolysis of (—)-hyoscine, followed by separation of the two diastereoisomers *via* dibenzoyl tartarates was shown by paper chromatography to be identical with alkaloid 'V'. Accordingly, it appears that hyoscyamine is oxidized in the plant to hyoscine involving the intermediary formation of 6-hydroxyhyoscyamine, in which process also dehydrohyoscyamine may play the part of an intermediate, although this last product has not been found in the plant, perhaps because of its too quick metabolic decomposition. Moreover, it could be proved (August, 1960) in that when 'normal' *Datura stramonium* was fed with radioactive ^{14}C-marked *S*(—)-hyoscyamine, all the applied radioactivity became distributed between the hyoscine, alkaloid 'V' produced in the plant, and some hyoscyamine. Consequently, it can be stated that *oxidation of hyoscyamine to hyoscine follows the same route in the alkaloid-free plant as in the native one, and the intermediate is 6-hydroxyhyoscyamine in both cases* (Fig. 142). In the near future radioactive dehydrohyoscyamine and 6-hydroxyhyoscyamine will both be prepared and their behaviour investi-

gated by feeding experiments in the living plant. Feeding experiments with ^{14}C-formic acid gave methyl-^{14}C-marked hyoscyamine (70%) and hyoscine (30%). All these experiments were carried out on 2 months old plants, and former results obtained with older plants corrected accordingly [115].

The tracer studies of LEETE in 1960 ascertained that the whole radioactivity of 3-^{14}C-phenylalanine used in plant-feeding experiments was retained in the $C_{(2)}$ carbon atom of the tropic acid fragment of the hyoscyamine and hyoscine formed. It follows that tropic acid must be formed *in vivo* from phenylalanine, perhaps by the route leading through prephenic acid as assumed by WENKERT [193], and shown in Fig. 143.

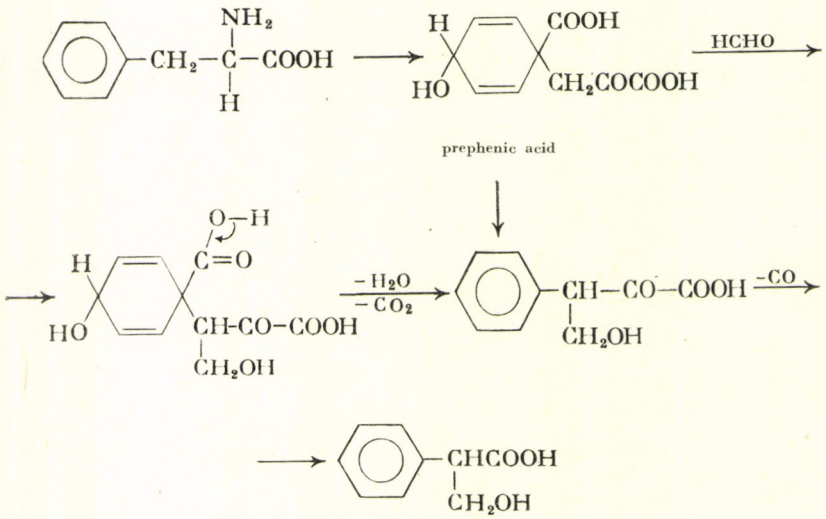


Fig. 143

Even though the steric structure of prephenic acid had been ascertained by PLIENINGER* this concept seems to be disapproved in view of some recent biogenetic experiments. First, GOODEVE and RAMSTAD** found that tryptophane-3-^{14}C was converted by *Datura stramonium* into tropic acid labelled on the carboxyl group. On the other hand, according to LEETE and LOUDEN*** *Datura stramonium* plants afforded tropic acid which contained the whole label in the methylol group. All these very divergent and even contradictory findings have been attempted to be united by LEETE in supposing carboxylation in the 3 position and reductive decarboxylation of the phenyloxalacetic acid on the terminal carbon to give tropic acid, labelled in the CH_2OH group. To get GOODEVE's findings with tryptophane into the picture, LEETE suggests oxidative metabolism of the tryptophane side chain followed by incorporation of the labelled carbon dioxide at the carbon atom next to the phenyl group. It is seen that all these biogenetic theories are still in need of experimental support as to their intermediates.

* Z. Naturforschung *1/6b*, No. 2, 81 (1961)
** Experientia *1961*, 1.24
*** Chem. and Ind. *1962*, 405

REFERENCES

1. ALDER, K. and DORTMANN, H. A.: Über den sterischen Verlauf der Reduktion von Pseudopelletierin. Die Konfiguration der N-Methyl-granatoline und ihrer *nor*-Verbindungen. Chem. Ber. *86*, 1544 (1953).
2. ALEXANDER, E. R.: Principles of Ionic Organic Reactions. J. Wiley, New York, 1950. p. 64.
3. ALEXANDER, E. R.: Principles of Ionic Organic Reactions. J. Wiley, New York, 1950. p. 111.
4. ARONEY, M. and LE FÈVRE, R. J. W.: The Conformations of Piperidine, Morpholine and Triethylamine. Proc. Chem. Soc. *1958*, 82.
5. ARONEY, M. and LE FÈVRE, R. J. W.: Molecular Polarisability. Application of the N—H and N—C Link Polarisabilities to the Conformation of Tertiary Amines, Piperidine and Morpholine. J. Chem. Soc. *1958*, 3002.
6. AYER, D. E., BÜCHI, G., REYNOLDS-WARNHOFF, P. and WHITE, D. M.: The Structure of Dioscorine. J. Am. Chem. Soc. *80*, 6146 (1958).
7. BÁCSKAY GY. Debye—Scherrer diagrams (Research Institute for Heavy Chemical Industries, Veszprém), February 9, 1954.
8. BARGER, G., MARTIN, WM. F. and MITCHELL, WM.: The Minor Alkaloids of *Duboisia myoporoides*. J. Chem. Soc. *1937*, 1820.
9. BARGER, G., MARTIN, WM. F. and MITCHELL, WM.: The Minor Alkaloids of *Duboisia myoporoides* II. Poroidine and *iso*-Poroidine. J. Chem. Soc. *1938*, 1685.
10. BARROWCLIFF, M. and TUTIN, F.: The Configuration of Tropine and *Pseudo*-Tropine and the Resolution of Atropine. J. Chem. Soc. *95*, 1966 (1909).
11. BARTON, D. H. R.: Letter of March 11, 1955 to G. FODOR; cf. BARTON, D. H. R.: Conformational Analysis of Substituted Cyclohexanes. Chem. and Ind. *1953*, 664.
12. BARTON, D. H. R. and ROSENFELDER, W. J.: The Stereochemistry of Steroids. IV. The Concept of Equatorial and Polar Bonds. J. Chem. Soc. *1951*, 1048.
13. М. С. Байнова. Г. И. Базилевская, К. М. Дюмаев, Н. А, Преобваженский: Синтез метилового эфира тропанон-3-карбиновой-2-кислоты, Ж. общей химми *30*, 1120 (1960)
14. Г. И. Базилевская, М. С. Байнова, К. Л. Дюмаев, Н. А. Преображенский: Синтетические исследования в области изомерних кокаинов, Ж. общей химии *30*, 1458 (1960)

15 a BECKETT, W., PITZER, S. and SITZER, R.: The Thermodynamic Properties and Molecular Structure of Cyclohexane, Methylcyclohexane, Ethylcyclohexane and the Seven Dimethylcyclohexanes. J. Am. Chem. Soc. *69*, 2488 (1947).

b. BECKETT, A. H., HARPER, N. J., BALON, A. D. J. and WATTS, T. H. E.: Reduction of Tropinone. Chem. and Ind. *1957*, 663.

16. BELL, M. R. and ARCHER, S.: L(+)-Tropinone. J. Am. Chem. Soc. *80*, 6147 (1958); *82*, 4642 (1960).
17. BEYERMAN, H. C., SIEGMANN, C. M., SIXMA, F. L. J. and WISSE, J. H.: The Sterical Structure of Tropinol and *Pseudo*tropinol. Rec. Trav. Chim. Pays-Bas, *75*, 1445 (1957).
18. BOSE, A. K. and CHAUDHURY, D. K. R.: Conformation of Tropane Alkaloids. Nature *171*, 652 (1952).
19. CAHN, R. S., INGOLD, C. K. and PRELOG, V.: The Specification of Asymmetric Configuration in Organic Chemistry. Experientia *12*, 81—94 (1956).
20. CLAUSON-KAAS, N., SI-OH-LI and ELMING, N.: The Preparation of 2,5-Diacetoxy-2,5-Dihydrofuran, 2,5-Diacetoxytetrahydrofuran and Pyridazine. Acta Chem. Scand. *4*, 1233 (1950).
21. CLAUSON-KAAS, N. and TYLE, Z.: Note on the Electrolytic Methoxylation of Furan. Acta Chem. Scand. *6*, 962 (1952).
22. CLEMO, G. R. and JACK, K. H.: The Configuration of Tropine and of *Pseudo*-Tropine. Chem. and Ind. *1953*, 195.
23. CLOSS, G. L.: The Configurational Equilibrium of the N-Methyl Group in Some Tropane Deuteriohalides. J. Am. Chem. Soc. *89*, 5456 (1959).
24. COOKSON, R. C.: The Stereochemistry of Alkaloids. Chem. and Ind. *1953*, 337.
25. CROMWELL, B. T.: Synthesis of Hyoscyamine in *Atropa belladonna* L. and *Datura stramonium* L. Biochemical J. *37*, 717 (1944).
26. CROMWELL, B. T.: The Role of Putrescine in the Synthesis of Hyoscyamine. Biochemical J. *37*, 722 (1944).
27. DOERING, W. v. E. and ASCHNER, T. C.: Mechanism of the Alkoxide-Catalyzed Carbinol-Carbonyl Equilibrium. J. Am. Chem. Soc. *75*, 393 (1953).

28. EICHENGRÜN, A. and EINHORN, A.: Über den Dihydrobenzaldehyd. Ber. dtsch. chem. Ges. *23*, 2870 (1890).
29. EINHORN, A. and MARQUARDT, A.: Über Rechtscocain. Ber. dtsch. chem. Ges. *23*, 468 (1890).
30. EINHORN, A.: Weitere Untersuchungen über das Cocain. Ber. dtsch. chem. Ges. *21*, 3029 (1888).
31. EINHORN, A. and FRIEDLAENDER, A.: Über Nor-Rechts-Ecgonin. Ber. dtsch. chem. Ges. *26*, 1482 (1893).
32. EVANS, W. C. and PARTRIDGE, M. W.: 7-Hydroxy-3:6-ditigloyloxytropane, a New Alkaloid Isolated from the Roots of Datura. J. Chem. Soc. *1957*, 1102.
33. FINDLAY, S. P.: Stereoisomeric Quaternary Ammonium Derivatives of Tropine Having a Pseudoasymmetric Nitrogen Atom. J. Am. Chem. Soc. *75*, 3204 (1953).
34. FINDLAY, S. P.: The Structure of Anhydroecgonine Ethyl Ester. J. Am. Chem. Soc. *75*, 1033 (1953).
35a FINDLAY, S. P.: The Three-Dimensional Structure of Cocaine. J. Am. Chem. Soc. *75* 4624 (1953).
b FINDLAY, S. P.: The Three-Dimensional Structure of the Cocaines. I. Cocaine and Pseudococaine. J. Am. Chem. Soc. *76*, 2855 (1954).
36. FINDLAY, S. P.: The Synthesis of Racemic Allococaine and Racemic Allopseudococaine. J. Org. Chem. *21*, 711 (1956).
37. FINDLAY, S. P.: Letter to the author (February 13, 1957).
38. FINDLAY, S. P.: Preparation and Properties of 2-Methoxycarbonyl-Tropinone. J. Org. Chem. *22*, 1385 (1957).
39. FINDLAY, S. P.: The Three-Dimensional Structures of the Cocaines. II. Racemic Allococaine and Racemic Allopseudococaine. J. Org. Chem. *24*, 1540 (1959).
40. FODOR, G.: Lecture at the Itinerary Congress of the Hungarian Physiological Society, Debrecen, September 6, 1951; FODOR, G., KISS, J., KOCZKA, K. and NÁDOR, K.: Neuere Ergebnisse in der Stereochemie der Amino-alkohole. Acta Physiol. Acad. Sci. Hung. *3*, 27 (1952).
41. FODOR, G.: Lecture at the festive week of the Hungarian Academy of Sciences in Budapest, December 11, 1951. FODOR, G.: New Research Methods of the Steric Structure of Organic Compounds. (In Hungarian.) Publ. of the VIIth Dept. of the Hung. Acad. Sci. *2*, 43 (1952).
42. FODOR, G.: Inaugural lecture at the Hungarian Academy of Sciences, Budapest, April 18, 1952. FODOR, G.: Proof of the Configuration of β-Hydroxy Acids. (In Hungarian.) Publ. of the VIIth Dept. of the Hung. Acad. Sci. *2*, 339 (1952).
43. FODOR, G.: Stereochemistry of the Tropane Alkaloids. Nature *170*, 278 (1952).
44. FODOR, G.: Lecture at the Congress of Organic Chemistry, Szeged, September 20, 1952.
45a FODOR, G., KOCZKA, K. and LESTYÁN, J.: A Contribution to the Stereochemistry of Trivalent Nitrogen. (In Hungarian.) Magyar Kémiai Folyóirat (Hung. Chem. Journ.) *59*, 242 (1953).
b FODOR, G.: A New Contribution to the Stereochemistry of Trivalent Nitrogen. (In Hungarian.) Publ. of the VIIth Dept. of the Hung. Acad. Sci. *3*, 311 (1953).
46a FODOR, G.: Lecture held at the Winter Meeting of the Swiss Chemical Society, Zurich, February 28, 1954, and at the Colloquy of the Institute of Organic Chemistry, University of Basel, March 2, 1954.; Chimia *8*, 179 (1954).
b KOVÁCS, Ö., FODOR, G. and WEISZ, I.: Konfigurationsbeweis des Cocains. Helv. Chim. Acta *37*, 892 (1954).
47a FODOR, G.: Über die Stereochemie der Alkaloide. Lecture held at the Leipziger Kongress der Chem. Ges. d. DDR, October 23, 1954; see: Neuere Ergebnisse der Stereochemie der Alkaloide, Angew. Chemie *67*, 211 (1954).
b FODOR, G., KOVÁCS, Ö., TÓTH, J., WEISZ, I. and VINCZE, I.: Neuere Ergebnisse der Stereochemie der Alkaloide. Tagungsber. d. Chem. Ges. d. DDR, 1954. pp 137–158 Akademie-Verlag Berlin (1955)
48a FODOR, G.: The Steric Structure of Tropane Alkaloids. Acta Chim. Acad. Sci. Hung. *5*, 379 (1955).
b The Steric Structure of Tropane Alkaloids (in Hungarian), Publ. of the VIIth Dept. of the Hung. Acad. Sci. *5*, 351 (1954).
49. FODOR, G.: Die Stereochemie der Tropanalkaloide. Experientia *11*, 129 (1955).
50. Г. Фодор: Пространственное строения тропановых алкалоидов, Успехи Химии, *23*, 264 (1954).
51. FODOR, G.: Stereochemistry of the Tropane, Pyrrolizidine and Lupine Alkaloids Involving the Configuration of the Ring Nitrogen. Lecture at the IUPAC Congress in Zurich, July 21, 1955.
52. FODOR, G.: Some Recent Development in the Synthesis and Stereochemistry of Tropane Alkaloids. Tetrahedron *1*, 86 (1957).

53. Fodor, G.: Über die Bestimmung der absoluten Konfiguration von quartären Ammoniumsalzen und über die Synthese des Acetylscopins. Lecture, November 3, 1955. Univ. of Münster. Angew. Chem. *68*, 188 (1956).
54. Fodor, G.: Détermination de la configuration de certaines amines tertiaires et de sels quaternaires d'ammonium organiques. Bull. Soc. Chim. France *1956*, 1032.
55. Fodor, G.: Sterische Probleme bei der Alkaloidsynthese. Lecture at the Arbeitstagung f. Biochemie und Physiologie d. Alkaloide, Quedlinburg, October 10, 1956. Abhandlg. Deutsch. Akad. Wiss. (Berlin) Kl. Chemie, Geologie, Biologie, *1956*, Heft 7, p. 93.
56. Fodor, G.: Tropane Alkaloids in Manske: The Alkaloids, Vol. 6, p. 145—178 (1960), London—N. Y. Academic Press (1960).
57. Fodor, G. and Csepreghy, Gy.: Method for Resolving Tropic Acid into the Optically Active Components. (In Hungarian.) Hungarian Pat. 146 013 (1958).
58. Fodor, G. and Csepreghy, Gy.: The Configuration of (—)Tropic Acid and of its Naturally Occurring Esters, Tetrahedron Letters No. 7, 16—18 (1959). J. Chem Soc. *1961*, 3222–3223.
59. Fodor, G., Janzsó, G., Ötvös, L. and Bánfi, D.: Synthese des *S*(—)-(Methyl ^{14}C)-Hyoscyamins, Chem. Ber. *93*, 2681 (1960).
60. Fodor, G. and (in part) Kovács, Ö.: The Stereochemistry of the Tropane Alkaloids. II. The Configurations of the Ecgonines and Cocaines. J. Chem. Soc. *1953*, 724.
61a Fodor, G., Kovács, Ö. and Mészáros, L.: The Stereochemistry of Scopolamine. Research *5*, 534 (1952).
b Fodor, G. and Kovács, Ö.: The Stereochemistry of the Tropane Alkaloids III. The Configurations of Scopolamine and of Valeroidine. J. Chem. Soc. *1953*, 2341.
62. Fodor, G., Koczka, K. and Lestyán, J.: The Stereochemistry of Tropane Alkaloids IX. Selective Quaternization of Tropines. J. Chem. Soc. *1956*, 1411.
63. Fodor, G., Kovács, Ö. and Halmos, M.: The Stereochemistry of Tropane Alkaloids. VIII. The Configuration of the Ring Nitrogen in Ecgoninols. J. Chem. Soc. *1956*, 873.
64. Fodor, G., Kovács, Ö. and Weisz, I.: The Stereochemistry of Cocaine. Nature *174*, 131 (1954).
65. Fodor, G. and Lestyán, J.: A piperidinváz térkémiájának vizsgálata. (An Investigation of the Stereochemistry of the Piperidine Skeleton.) Magyar Kémiai Folyóirat *59*, 240 (1953).
66a Fodor, G. and Nádor, K.: Stereochemistry of Tropine and *Pseudo*-Tropine. Nature *169*, 462 (1952).
b Fodor, G. and Nádor, K.: The Stereochemistry of Tropane Alkaloids I. The Configurations of the Tropines. J. Chem. Soc. *1953*, 721.
67. Fodor, G., Rákóczi, J. et al.: Über die technische Darstellung des Atropins und über die direkte Synthese von (—)Hyoscyamin. Angew. Chem. *72*, 139 (1960).
68. Fodor, G., Sallay, I. and Dutka, F.: The Configuration of Retronecine and of Related Compounds. (Stereochemistry of Pyrrolizidine Alkaloids. Part II.) Acta Phys. et Chem. Szeged, *II*, 80 (1956).
69. Fodor, G., Tóth, J., Koczor, I., Dobó, P. and Vincze, I.: The Total Synthesis of Scopolamine. Chem. and Ind. *1956*, 764; J. Chem. Soc. *1959*, 3461.
70. Fodor, G., Tóth, J. and Vincze, I.: Konfiguration der am Pyrrolidinring Sauerstoff-Funktion enthaltenden Tropanalkaloide. 5. Mitteilung über die Stereochemie der Tropanalkaloide. Helv. Chim. Acta *37*, 907 (1954).
71. Fodor, G., Tóth, J. and Vincze, I.: The Stereochemistry of Tropane Alkaloids. Part VI. Configurations of Ring Nitrogen in Tropane-3α,6β-diol, Oscine and of Derived Quaternary Salts. J. Chem. Soc. *1955*, 3504.
72. Fodor, G., Tóth, J., Koczor, I. and Vincze, I.: Synthesis of Tropenol, a Suggested Intermediate for Scopolamine. Chem. and Ind. *1955*, 1260.
73. Fodor, G., Tóth, J., Vincze, I., Dobó, P. and Romeike, A.: A Modified Synthesis of Scopolamine and its Biogenetic Relationships. Lecture read by A. Müller on behalf of G. Fodor at the XVIth IUPAC Congress, Paris, July 17, 1957. Angew. Chem. *69*, 678 (1957).
74. Fodor, G., Vincze, I. and Tóth, J.: The Absolute Configuration of Valeroidine, Experientia *13*, 183 (1957).
75. Fodor, G., Vincze, I. and Tóth, J.: The Absolute Configuration and a Simple Synthesis of (—)-Valeroidine. J. Chem. Soc. *1961*, 3219–3222.
76a Freudenberg, K., Toepffer, H. and Andersen, C. C.: Zur Kenntnis der Aceton-Zucker. XV. Versuche zur Synthese von Disacchariden. Ber. dtsch. Chem. Ges. *61*, 1750 (1928).
b Bacon, J. S. D., Bell, D. J. and Kosterlitz, H. W.: Acyl Migration in a Derivative of Galactose. J. Chem. Soc. *1939*, 1248.

77. GADAMER, J.: Die Beziehungen des Hyoscyamins zu Atropin und des Scopolamins zu i-Scopolamin. Arch. Pharmazie *239*, 294, 663 (1901).
78. GADAMER, J. and AMENOMIYA, T.: Über die optischen Funktionen der asymmetrischen Kohlenstoffatome in Ecgonin. Arch. Pharmazie *242*, 1 (1904).
79. GADAMER, J. and JOHN, C.: Beiträge zur Kenntnis des Ecgonins. Arch. Pharmazie *259*, 227 (1921).
80. GALINOVSKY, F.: Zur Chemie und Biosynthese der Pyrrolidin-Alkaloide Hygrin und Cuskhygrin und der Granatapfelbaum-Alkaloide. Lecture, Symposium on the Biochemistry of Alkaloids. Quedlinburg, October 8—12, 1956. Abhandlg. Deutsch. Akad. Wiss. Berlin, Kl. Chem., Geol. u. Biol. *7*, 98 (1959).
81. GALINOVSKY, F. and NESVABDA, H.: Über eine Umlagerung des Lupinin-p-toluolsulfonsäureesters. Die Konfiguration des Lupinins, Monatsh. *85*, 1300 (1954).
82. GÁL, Gy., SIMONYI, I., and TOKÁR, G.: Researches into the Synthesis and Determination of Tropinone. Acta Chim. Acad. Sci. Hung. *6*, 365 (1955).
83. GARRETT, E. R.: The Kinetics of Hydrolysis of Scopolamine Derivatives with an Unusual Elimination on Alkaline Hydrolysis. J. Am. Chem. Soc. *79*, 1071 (1957).
84. GEISSMAN, T. A., WILSON, B. T. and MEDZ, B.: The Base Strengths of *cis* and *trans*-1,2-Aminoalcohols. J. Am. Chem. Soc. *76*, 4182 (1954).
85. GOODSON, L. H. and CRISTOPHER, H.: Diphenylethylamines. I. The Preparation of Tertiary Amines by the Grignard Reaction. J. Am. Chem. Soc. *72*, 358 (1950).
86. HALMOS, M., KOVÁCS, Ö. and FODOR, G.: Oxidation of the Ecgoninol Epimers with Silver Oxide. J. Org. Chem. *22*, 1699 (1957).
87. HARDEGGER, E. and FURTER, H.: Synthese von *S*-(+)-6,7-Dihydroxy-3-tropanon. Helv. Chim. Acta *40*, 872 (1957).
88. HARDEGGER, E. and OTT, H.: Beweis der Konfiguration des Pseudotropins, bzw. des Tropins. Helv. Chim. Acta *36*, 1186 (1953).
89. HARDEGGER, E. and OTT, H.: Umsetzung von Norpseudo-tropin und Nor-tropin mit Aldehyden. Helv. Chim. Acta *37*, 685 (1954).
90. HARDEGGER, E. and OTT, H.: Konfiguration des Cocains und Derivate der Ecgoninsäure. Helv. Chim. Acta *38*, 312 (1955).
91. HARTUNG, W. H. and SMITH, P. F.: *cis* and *trans* Tropine (Tropanol). J. Am. Chem. Soc. *75*, 3859 (1953).
92. HEUSNER, A.: Zur Konstitution des Meteloidins. Chem. Ber. *87*, 1032 (1954).
93. HEUSNER, A.: Notiz zur Stereochemie des Meteloidins. Z. Naturforschung *9b*, 683 (1954).
94. HEUSNER, A., and ZEILE, K.: Stereochemie der im Pyrrolidinring substituierten Tropanderivate. Chem. Ber. *90*, 2114 (1957).
95. HEUSNER, A. and ZEILE, K.: Synthese des Meteloidins, Z. Naturforsch. *12b*, 661 (1957).
96. HEUSNER, A. and ZEILE, K.: Partialsynthese von Scopinon und Pseudoscopin, Chem. Ber. *91*, 2399 (1958).
97. HROMATKA, O., CSOKLICH, C. and HOFBAUER, I.: Über den Tropin-benzilsäureester. Monatsh. *83*, 1323 (1952).
98. HUDSON, C. S.: A Relation Between the Chemical Constitution and the Optical Rotatory Power of the Sugar Lactones. J. Am. Chem. Soc. *32*, 338 (1910).
99. HUISGEN, R.: Nitroso-acylamine und Diazo-ester. II. Acylwanderung und Acylablösung bei Nitrosoacylamiliden. Liebigs Annalen *573*, 163 (1951).
100.a HÜCKEL, W.: Private communication to G. FODOR, January 24, 1953.
b HÜCKEL, W.: Private communication to G. FODOR August 15, 1953.
101. JAMES, W. O.: Oxford Medicinal Plants Scheme Reports *1941*, 4 (1945); Biosynthesis of the Belladonna Alkaloids. Nature *158*, 654 (1946); see MANSKE, R. F. H. and HOLMES, H. L.: 'The Alkaloids.' Acad. Press. Inc. New York 1951, pp. 15—90.
102. JAMES, W. O. and BEEVERS, H.: Behaviour of Secondary and Tertiary Amines in the Presence of Catechol and Belladonna Catechol-Oxidase. Biochemical J. *43*, 636 (1948).
103. KACZKOWSKI, J., SCHÜTTE, H. R. and MOTHES, K.: Die Rolle des Acetats in der Biosynthese der Tropanalkaloide, Naturwiss. *47*, 304 (1960); Biophys. Biochem. Acta *46*, 588 (1961)
104. KEAGLE, L. C. and HARTUNG, W. H.: Tropanone and its Homologues. J. Am. Chem. Soc. *68*, 1608 (1949).
105. KEBRLE, J. and KARRER, P.: Synthesen von substituierten Tropinderivaten. Helv. Chim. Acta *37*, 484 (1954).
106. KING, H.: The Resolution of Hyoscine and its Components, Tropic Acid and Oscine. J. Chem. Soc. *115*, 476 (1919).
107. KING, H.: The Stereochemistry of Hyoscine. J. Chem. Soc. *1919*, 974.
108. KLYNE, W.: Progress in Stereochemistry. Butterworths Scientific Publ. London 1954. 1st ed., p. 171.

109. S. Koch and Gy. Grassely: Crystal diagrams (Dept. of Mineralogy and Petrology, the University of Szeged.)
110. Kovács, Ö., Fodor, G., Halmos, M.: The Absolute Configuration of the Nitrogen Atom in Some Optically Active Tropanols and Derived Quaternary Salts. J. Chem. Soc. *1956*, 873.
111. Kovács, Ö., Weisz, I., Zoller, P. and Fodor, G.: Konstitutionsbeweis eines Tropanvierringäthers. Synthese von zwei neuen epimeren Ecgoninolen. Helv. Chim. Acta *39*, 99 (1956).
112. Kraut, W.: Über das Atropin. II. Mittlg. Liebigs Ann. Chem. *133*, 87 (1865).
113. Lennard-Jones and Hall, G. G.: The Molecular Orbital Theory of Chemical Valency. VII. Molecular Structure in Terms of Equivalent Orbitals, Proc. Roy. Soc. (A) *205*, 357 (1951).
114. Leete, E., Marion, Z. and Spenser, I. D.: Biogenesis of Hyoscyamine. Nature *174*, 650 (1954).
115. Leete, E.: The Biogenesis of Tropic Acid and Related Studies on the Alkaloids of *Datura stramonium*. J. Am. Chem. Soc. *82*, 612 (1960).
116. Levene, P. A. and Simms, H. S.: Lactone Formation from Gluconic Acids and the Structure of Glucose. J. Biol. Chem. *68*, 737 (1926).
117. Liebermann, C.: Über das Benzoyl-pseudo-tropein, ein Nebenalkaloid der javanischen Cocablätter. Ber. dtsch. Chem. Ges. *24*, 2332 (1891).
118. Liebermann, C.: Über Tropinsäure und die Oxydation des Linksecgonins, Rechtsecgonins und Tropins. Ber. dtsch. Chem. Ges. *24*, 606 (1891); see [126.]
119. Lindenmann, A.: Über Synthesen von Scopin-benzhydryläthern, Chimia *13*, 114 (1959).
120. Lossen, W.: Über das Atropin. Liebigs Ann. Chem. *131*, 43 (1864).
121. Lossen, W.: Über das Cocain. Liebigs Ann. Chem. *133*, 351 (1865).
122. McCasland, G. E.: N→O Acyl Migration in Epimeric Acetyl-inosamines. J. Am. Chem. Soc. *73*, 2295 (1951).
123. McKenna, J.: Stereochemistry. Ann. Repts. *1959*, 196.
124. McKenzie, A. and Strathern, R. C.: Reactions of Displacement in the Tropic Acid Group. J. Chem. Soc. (London) *127*, 82 (1925).
125. Manske, F. R. H. and Holmes, H. L.: 'The Alkaloids' Acad. Press. Inc. New York, 1951.
126. Marion, L., Diaper, D. G. M. and Kirwood, S.: The Biogenesis of Alkaloids. III. A Study of Hyoscyamine Biosynthesis using Isotopic Putrescine. Canad. J. Chem. *29*, 964 (1951).
127. Meinwald, J.: The Stereochemistry of Scopolamine. J. Chem. Soc. *1953*, 712.
128. Meinwald, J. and Chapman, O. L.: The Alkaline Hydrolysis of Scopolamine Methoxy Methochloride: A New Route to Scopine. J. Am. Chem. Soc. *79* 665 (1957).
129. Merling, G.: Über Tropin. Liebigs Ann. Chem. *216*, 329 (1883); Über Tropin. Ber. dtsch. Chem. Ges. *24*, 318 (1891).
130. Mills, W. H., Parkin, J. D. and Ward, W. J. V.: The Configuration of the Ammonium Ion. II. Geometrically Isomeric Quaternary Ammonium Salts Derived from 4-Phenyl and 4-Hydroxy-piperidine. J. Chem. Soc. *1927*, 2625.
131. Mirza, R.: Reduction of Tropinone with Lithium Aluminium Hydride. Nature *170* 630 (1952).
132. Mitchell, Wm. and Trautner, E. M.: The Minor Alkaloids of *Duboisia myoporoides*. IV. Valeroidine. J. Chem. Soc. *1947*, 1330.
133. Moffett, R. B. and Garrett, E. R.: Alkaline Hydrolysis of Scopolamine Methyl Bromide and Other Esters of Quaternary Aminoalcohols. J. Am. Chem. Soc. *77*, 1245 (1955).
134. Mohr, E.: Die Baeyersche Spannungstheorie und die Struktur des Diamanten. J. prakt. Chem. (2) *98*, 315 (1918); Zwei spannungsfreie Cycloheptanmodelle. J. prakt. Chem. *103*, 316 (1922).
135. Nickon, A. and Fieser, L. F.: Configuration of Tropine and Pseudotropine. J. Am. Chem. Soc. *74*, 5566 (1952); received June 23, 1952.
136. Oldham, J. W. H. and Bell, D. J.: 2-Methyl and 2,6-Dimethyl Galactose. J. Am. Chem. Soc. *60*, 323 (1938).
137. Orechoff, A. and Konowalowa, R.: Über die Alkaloide von *Convolvulus-pseudo cantabricus*. III. Mitteilung. Konstitution des Convolvins und Isolierung von zwei neuen Basen. Ber. dtsch. Chem. Ges. *68*, 814 (1935).
138. Orville, L. Chapman. Letter to G. Fodor, November 8, 1955.
139. Paddock, N. L.: The Reduction of Tropinone with Lithium Aluminium Hydride. Nature *170*, 630 (1952).
140. Petrenko-Kritschenko and Zoneff, P. N.: Über die Kondensation von Acetondicarbonsäureestern mit Benzaldehyd unter Anwendung von Ammoniak. Ber. dtsch.

Chem. Ges. *39*, 1358 (1906); see ELDERFIELD, R. C.: Heterocyclic Compounds. J. Wiley, New York, 1950. Vol. I. p. 659.
141. PFEIFFER, E.: Über das Atropin. Liebigs Ann. Chem. *128*, 272 (1863).
142. PINDER, A. R.: An Alkaloid of *Dioscorea hispida*, Dennstedt, Part I. The Lactone Ring. J. Chem. Soc. *1952*, 2236.
143. PINDER, A. R.: An Alkaloid of *Dioscorea hispida*, Dennstedt. Part II. Hofmann Degradation. J. Chem. Soc. *1953*, 1825.
144. PINDER, A. R.: An Alkaloid of *Dioscorea hispida*, Dennstedt. Part. III. Further Investigations of the Hofmann Degradation. J. Chem. Soc. *1956*, 1577.
145. PINDER, A. R.: An Alkaloid of *Dioscorea hispida*, Dennstedt. Part IV. Further Investigations on the Lactone Ring. Tetrahedron *1*, 301 (1957).
146. PINDER, A. R., and JONES, J. B.: An Alkaloid of *Dioscorea hispida*, Dennstedt. Part V. The Degradation of Dioscorinol. J. Chem. Soc. *1959*, 615.
147. PINDER, A. R., DAVIES, W. A. M. and JONES, J. B.: An Alkaloid of *Dioscorea hispida*, Dennstedt, Part VI. Some Investigations on the Synthesis of Tropan-2-one. J. Chem. Soc. *1959*, 3504.
148. POLONOWSKI, M. and POLONOWSKI, M.: Sur les aminoxydes des alcaloides IV. Transformation du N-oxyde de scopolamine en un dérivé quaternaire scopinium. Bull. Soc. Chim. France (IV) *43*, 79 (1928).
149. POLONOWSKI, M. and POLONOWSKI, M., Bull. Soc. Chim. France (IV) *39*, 1147 (1926).
150. PRELOG, V. and WIELAND, P.: Über die Spaltung der Troeger'schen Base in optischen Antipoden, ein Beitrag zur Stereochemie des dreiwertigen Stickstoffs. Helv. Chim. Acta *27*, 1127 (1944).
151. Personal discussion between V. PRELOG and G. FODOR in Zurich on 26th February, 1954.
152. Преображенский, Н. А., Рубцов, И. А., Данкова, Т. Ф., Павлов, В. Л.: Синтез тропенона. II. Попытки синтеза алкалоида типа скополамина. Ж. О. Х. *15*, 952 (1945).
153. Преображенский, Н. А., Генки, Э. И.: Химия органических лекарственных веществ. Научно-Техническое издательство. Москва (1953).
154. PYMAN, F. L. and REYNOLDS, W. C.: Meteloidine. A New Solanaceous Alkaloid. J. Chem, Soc. *93*, 2077 (1908).
155. REICHSTEIN, T.: Comment to the lecture of G. FODOR, Basel, March 3, 1954.
156. ROBINSON, R.: A Synthesis of Tropinone. J. Chem. Soc. *111*, 762 (1917).
157. ROBINSON, R.: Synthesis in Biochemistry. J. Chem. Soc. *1936*, 1079.
158. ROBINSON, R.: Willstätter Memorial Lecture. J. Chem. Soc. *1953*, 1003.
159. ROMEIKE, A.: Über die Mitwirkung des Sprosses bei der Ausbildung des Alkaloidspektrums. Epoxydbildung beim Hyoscyamin durch *Datura ferox* L., Flora (Jena), *143*, 67 (1956).
160. ROMEIKE, A.: Zur Frage des Alkaloidtransports und der Alkaloidumwandlung bei *Datura*. Angew. Chem. *68*, 124 (1956).
161. ROMEIKE, A.: Über ein Zwischenprodukt bei der Epoxydierung des Hyoscyamins in der lebenden Pflanze. Naturwiss. *46*, 64 (1960).
162. ROMEIKE, A. and FODOR, G.: The Biogenesis of Hyoscine in *Datura stramonium* L. Tetrahedron Letters No. 22 p. 1 (1960).
163. ROSENMUND, K. W. and ZYMALKOWSKI, F.: Reduktion von Ecgonin, Ecgonidin und einigen Chinolincarbonsäuren mit Lithiumaluminiumhydrid, Chem. Ber. *85*, 152 (1952).
164. SACHSE, H.: Über die geometrischen Isomerien der Hexamethylenderivate. Ber. dtsch. Chem. Ges. *23*, 1363 (1890); Z. phys. Chem. *10*, 203 (1892).
165. SCHMIDT, E.: Über Scopolamin (Hyoscin). Arch. Pharmazie *230*, 207 (1892).
166. LUBOLDT, W.: Beiträge zur Kenntnis des Scopolamins und Scopolins. Arch. Pharmazie, *236*, 11 (1898).
167. SCHMIDT, E.: Über das Scopolamin. Arch. Pharmazie *232*, 409 (1894).
168. Private discussion between H. SCHMID and G. FODOR in Zurich, February 27, 1954.
169. SCHÖPF, CL.: Letter to G. FODOR on 27th April, 1955, stating that four different laboratories failed in reproducing the experiment.
170. SCHÖPF, CL., LEHMANN, G. and ARNOLD, W.: Die Synthese der Tropanalkaloide und des Pseudopelletierins unter physiologischen Bedingungen. Angew. Chemie *50*, 783 (1934).
171. SCHÖPF, CL. and SCHMETTERLING, A.: Versuche zur Synthese des Scopinons. Angew. Chemie *64*, 591 (1952).
172. SCHÖPF, CL. and ARNOLD, W.: Zur Frage der Biogenese des Meteloidins. Die Synthese des Teloidins unter zellmöglichen Bedingungen. Liebigs. Ann. Chem. *558*, 109 (1947).

173. Щукина, М. Н., Окун, С. С., Юрыкин, Д. Н., Преображенский, Н. А.: Разёл рацема скополамина в отрические антиподы. Ж. О. Х. *10*, 803 (1940).
174. SHEEHAN, J. C. and BISSEL, E. R.: The Synthesis of Dihydrometeloidine and Related Compounds. J. Org. Chem. *19*, 270 (1954).
175. SHEEHAN, J. C.: Letter to the author, 11th March, 1957.
176. SIEGMANN, C. M. and WIBAUT, J. P.: Synthesis and Some Pharmacological Properties of Esters of Some N-alkyl-homologues of Tropinol and *Pseudo*tropinol. Rec. Trav. Chim. Pays-Bas *73*, 203 (1954).
177. SIXMA, F. L. J., SIEGMANN, C. M. and BEYERMANN, H. C.: The Sterical Configuration of Tropine and *Pseudo*-Tropine. Proc. Acad. Amsterdam. B. *54*, 452 (1951).
178. SKITA, A. and RÖSSLER, R.: 1,3-Diaminocyclohexan. Ber. dtsch. chem. Ges. *72*, 461 (1939).
179. SMITH, P. and HARTUNG, W. H.: *cis* and *trans* Tropine (Tropanol). J. Am. Chem. Soc. *75*, 3859 (1953).
180. SPARKE, M. B.: Configuration of Tropine and *Pseudo*-Tropine. Chem. and Ind. *1953*, 749.
181. STERN, R. and WASSERMAN, H. H.: Lecture at the meeting of the ACS. April 8, 1957, The Synthesis of Optically Active *trans*-6,7-Dihydroxy-3-tropanone. Chem. Eng. News *35*, 98 (1957).
182. STOLL, A., BECKER, B. and JUCKER, E.: Synthese des Apfelsäure-dialdehyds und des 3,6-Dioxy-tropans. Helv. Chim. Acta *35*, 1263 (1952).
183. STOLL, A., LINDEMANN, A. and JUCKER, E.: Synthesen von O-Alkyl-äpfelsäure-dialdehyden. Helv. Chim. Acta *36*, 1500 (1953).
184. STOLL, A., LINDENMANN, A. and JUCKER, E.: Über zwei stereoisomere optisch aktive 3,6-Dioxytropane und die Identifizierung des Valeroidins. Helv. Chim. Acta *36*, 1506 (1953).
185. STOLL, A., JUCKER, E. and LINDENMANN, A.: Über Synthesen von neuartigen Verbindungen aus der 6-Alkoxy-tropan Reihe. Helv. Chim. Acta *37*, 495 (1954).
186. STORK, G.: Private communications to G. FODOR, September 4, and October 15, 1952.
187. TOIVONEN, N. J., HIRSJÄRVI, P., MELAJA, A., KAINULAINEN, A., HALONEN, A. and PULKKINEN, E.: Über die endo-exo-Isomerie bei Verbindungen vom Camphertypus. II. Die Konfiguration des Borneols und Isoborneols. Acta Chem. Scand. *3*, 991 (1949).
188. TÓTH, J.: Lecture at the Congress of Organic Chemistry in Debrecen, September 27, 1953; FODOR, G., TÓTH, J., LESTYÁN, J. and VINCZE, I.: Ascertainment of the Absolute Configuration of Tropane Alkaloides Having Oxygen-containing Functional Groups on the Pyrrolidine Ring. (In Hungarian). Publications of the Industrial Chemical Research Institutes, *4*, 293 (1954).
189. TRAUTNER, E. M.: Alkaloid Formations in *Duboisia myoporoides* and *D. Leichardtii*. The Australian Chem. Inst. Journ. and Proc. *1947*, 411.
190. VAN TAMELEN, E. E.: The Mechanism of Nitrogen-Oxygen Acyl Migration. J. Am. Chem. Soc. *73*, 5773 (1951).
191. VAN TAMELEN, E. E., TOUSIGNANT, W. F. and PECKHAN, P. E.: The Structure of Camphenamine. J. Am. Chem. Soc. *75*, 1297 (1953).
192. VARGA-FODOR, ÉVA (Faculty of Organic Chemistry, University of Szeged): Observations and measurements (in Hungarian).
193. WENKERT, E.: Alkaloid Biosynthesis, Experienta *19*, 165 (1959).
194. WERNER, G. and KASSNER, E.: Naturwiss. *46*, 649 (1959); WERNER, G. and MILTEN BERGER, K.: Zur Trennung der optischen Antipoden von Homatropin und Atropin, Liebigs Ann. Chem. *631*, 163 (1960).
195. VINCZE, I., TÓTH, J. and FODOR, G.: The Total Synthesis of Valeroidine. J. Chem. Soc. *1957*, 1349.
196. VISSER, W., MANASSEN, J. and DE VRIES, J. L.: The Structure of Tropine-Hydrobromide. Acta Cryst. *7*, 288 (1954).
197. WILLSTÄTTER, R.: Über das Tropinon. I. Mitteilung über Ketone der Tropingruppe. Ber. dtsch. chem. Ges. *29*, 393 (1896).
198. WILLSTÄTTER, R.: Über pseudo-Tropin. II. Mitteilung über Ketone der Tropingruppe. Ber. dtsch. chem. Ges. *29*, 936, 939 (1896).
199. WILLSTÄTTER, R. and BERNER, E.: Hydrolyse des Scopolamins. Ber. dtsch. chem. Ges. *56*, 1079 (1923).
200. WILLSTÄTTER, R. and BODE, A.: Über Alkalisalze von Amidoketonen. Ber. dtsch. chem. Ges. *33*, 416 (1900); see Synthese von r-Cocain. Liebigs Ann. Chem. *326*, 46 (1902).
201. WILLSTÄTTER, R. and BOMMER, M.: Eine vollständige Synthese von r-Ecgonin und von Tropinon. Liebigs Ann. Chem. *422*, 18 (1921).

202. WILLSTÄTTER, R. and IGLAUER, F.: Reduktion von Tropinon zu Tropin und Tropan. XV. Mitteilung über Ketone der Tropingruppe. Ber. dtsch. chem. Ges. *33*, 1170 (1900).
203. WILLSTÄTTER, R. and MÜLLER, W.: Über die Konstitution des Ecgonins XII. Mitteilung über Ketone der Tropingruppe. Ber. dtsch. chem. Ges. *31*, 2655 (1898).
204. WILLSTÄTTER, R., WOLFES, O. and MÄDER, O.: Synthese des natürlichen Cocains. Liebigs Ann. Chem. *434*, 111 (1923).
205. WITKOP, B.: The Application of Hudson's Lactone Rule to γ- and δ-Hydroxyamino Acids and the Question of the Configuration of Hydroxy-L-lysine from Collagen. Experientia *12*, 372 (1956).
206. WOLFES, O. and HROMATKA, O.: Über ein neues Tropanderivat aus Cocablättern. E. Merck's Jahresber. *47*, 45 (1933).
207. WÖHLER, F.: Fortsetzung der Untersuchungen über die Coca und Cocains. Liebigs Ann. Chem. *121*, 372 (1862); cf. LOSSEN, W. [120].
208. ZEILE, K. and HEUSNER, A.: Eine weitere Synthese des Scopolins. Darstellung einiger seiner Derivate. Chem. Ber. *90*, 2809 (1957).
209. ZEILE, K. and HEUSNER, A.: Darstellung von *cis*-6,7-Dimethoxytropinon und *dl-cis*-6-Oxy-7-methoxy-tropinon. Chem. Ber. *87*, 439 (1954).
210. ZEILE, K. and HEUSNER, A.: Synthese des Scopolins. Chem. Ber. *90*, 2800, 2809 (1957).
211. ZEILE, K. and SCHULTZ, W.: Über das dritte racemische Cocain. Chem. Ber. *89*, 678 (1956).
212. ZEILE, K. and SCHULTZ, W.: Über stereoisomere quartäre Ammoniumverbindungen des Tropins und Pseudotropins mit pseudoasymmetrischem Kohlenstoffatom. Chem. Ber. *88*, 1078 (1955).
213. ZENITZ, B. L., MARTINI, C. M., PRIZNAR, M. and NACHOD, C.: Stereochemistry of the Tropines. J. Am. Chem. Soc. *74*, 5564 (1952).

K. NÁDOR

RELATIONSHIPS BETWEEN THE STRUCTURE AND PHARMACOLOGICAL ACTIVITY OF TROPEINES

INTRODUCTION
PHARMACOLOGICAL FUNDAMENTAL NOTIONS

The relationship between chemical structure and physiological activity has long since continued to remain the central theoretical problem of drug research. The group of tropeines has been found to afford very useful model compounds for this work. The stereochemistry of this group was precisely established, which served as a firm basis for the chemist to start drawing conclusions between this property and physiological activity. Besides, special importance was given to this group of compounds by the fact that systematic modifications of the chemical structure within this type led to products having various effects on the vegetative nervous system. Thus a deep insight, never achieved heretofore, could be obtained concerning the relationship of activity and constitution, or even stereochemical structure. The discovery of Novatropin by ISSEKUTZ [58] opened up new possibilities for compounds belonging to the series of parasympatholytic alkyl monoquaternary tropeines. In the case of aralkyl monoquaternary tropeines it was found [39, 81, 84] that introduction of an aralkyl group suspended parasympatholytic activity, but a ganglion blocking effect appeared at the same time. Evaluation and utilization of this finding resulted in the discovery of Gastropin by NÁDOR and GYERMEK in 1954 [40, 82, 85]. N,N'-1,4-xylylen-bis-tropeines afforded, on the other hand, very active compounds possessing curare-like effect (NÁDOR, KÜTTEL, ISSEKUTZ) [38, 80, 90].

It were the first results of these investigations concerning the relationship between structure and activity which directed the attention to the stereochemical problems of the tropeines. The stereochemical structures of tropine and pseudotropine (FODOR and NÁDOR), of cocaine (FODOR and KOVÁCS) and of scopolamine (FODOR, KOVÁCS et al.) were elucidated first, which was followed by the determination of the spatial orientation of the pair of unshared electrons belonging to the nitrogen atom of the tropane skeleton (FODOR, LESTYÁN, KOCZKA and TÓTH). These important results were of great assistance in the course of further researches on physiologically active tropeines. Another reason to give special interest to tropeines in the last years was the fact that their exactly known stereochemistry made possible the collection of an amount of valuable data; these were obtained from investigations carried out with so-called model compounds possessing structures or activities similar to the above-mentioned substances. The most important theoretical question concerning model compounds is e.g., whether their activity is due to a structure or even spatial arrangement actually similar to that of the natural active agent, or should some other mechanism, quite independent of the former, be considered. For instance, it has not been determined so far whether the mydriatic activity of euphtalmine, the model of homatropine, is due to

common structural principles, and thus to reaction with the same receptors, or the same effect is obtained through influencing different receptors. Euphtalmine, like homatropine, is an ester of mandelic acid, namely that of 1,2,6,6-tetramethyl-4-hydroxypiperidine, which is a basic alcohol having the skeleton of piperidine; in this compound also the steric arrangements of the $N-CH_3$ and OH groups are probably, but not decidedly, the same. However, it is not known whether mydriasis is due to blocking of the parasympathetic nerve endings of the oculomotor nerve or to exciting the symphatetic mechanism of the eye. Similar but more complex problems arise in the case of compounds where structural analogies are not so simple as between homatropine and euphtalmine, and where there is only a theoretical similarity between the natural active agent and the model compound. One of the most interesting tasks of the research of tropeines is, e.g., the pharmacological study of the benzilic esters of homatropine and β-piperidinoethanol. Complete elucidation of the stereochemistry of homatropine would be of considerable assistance in solving this problem. Namely, that would render possible a search for the common mechanism of action by the aid of model compounds. An additional problem is then the research of the biochemical mechanism of action, which should also be considered by the pharmacologist as a question to be solved.

In the overwhelming majority of cases, tropeines exercise their physiological activity nearly exclusively on the vegetative nervous system. As a prerequisite of discussing relationships between structure and activity, it is absolutely necessary to get acquainted first with some pharmacological fundamental ideas connected with this problem.

From the morphological point of view, the vegetative nervous system can be divided into three parts. The central part may be listed first, which consists of the vegetative centres of the hypothalamus and the vegetative nuclei of medulla oblongata. Naturally, these centres are under a more constant and higher control, and they are in close functional relation with the higher cortical areas. The second morphological part of the vegetative nervous system is the centrifugal nerve-fibre system in which two types of nerves can be differentiated according to the place of exit: craniosacral nerves, which are also called parasympathetic nerves (from the brain and from the lower part of the spinal cord), and thoracolumbar or sympathetic nerves (from the dorsal and lumbar vertebrae). Both groups of nerves can be differentiated further, and it is customary to speak about medullary preganglionic, and non-medullary, so-called postganglionic fibres. The third morphological element is the vegetative ganglion, also called synapsis, which is to be found between the preganglionic and postganglionic fibres. Ganglia can be found exclusively in connection with the vegetative nerve fibres. According to localization, we may speak of parasympathetic and sympathetic ganglia. The parasympathetic ganglia are to be found in the effect organs, consequently the postganglionic fibre starting from the medulla is very short, whereas postganglionic fibres coming from sympathetic ganglia are long.

Highly important is the functional role of the terminal apparatus of the vegetative nervous system, i.e., the endings of the vegetative nerve fibres, where stimulations coming from the centre are transferred to the effect organs. In connection with the terminal apparatus and receptors, however, no differentiation of morphologically defined and specified elements can be made. GOODMAN and GILMAN [32] are of the opinion that the receptor or

effector character of a cell is determined by its physico-chemical conditions. According to ANITSCHKOW [2], functioning of vegetative receptors is in close alliance with the protein and carbohydrate metabolism of cells of certain parts of the organs.

From the functional point of view, the picture of the vegetative nervous system is quite different. Analysis of its function revealed that two stimulating agents are liberated in this system: acetylcholine and *nor*adrenaline or adrenaline (sympathin), resp. In this respect, it is customary to speak of parasympathetic and sympathetic nervous systems which are opposed to each other. At the endings of the parasympathetic nerves acetylcholine is liberated, whereas on sympathetic terminals *nor*adrenaline is produced. This is the reason why also the notions 'cholinergic' and 'adrenergic' are customarily used.

Thus, from the functional aspect, the vegetative nerve system can be divided into two parts. Both parts have their centres in the hypothalamus. According to DALE, KIBJAKOW and FELDBERG [14, 15, 16, 22, 23, 62] stimulation is transferred in the vegetative ganglia by a chemical stimulating agent, namely acetylcholine. However, one should also be aware of the fact that acetylcholine plays the part of the stimulant not only in the parasympathetic but also in sympathetic ganglia. Consequently, all preganglionic fibres are of cholinergic character, and only postganglionic sympathetic fibres are of the adrenergic type. On the terminal apparatus of these latter, not acetylcholine but the sympathetic stimulating agent is liberated.

The task of drugs acting on the vegetative nervous system is either to stimulate or hinder its functioning. Elucidation of the chemical structure of both stimulating and blocking agents has been of very considerable help in further research for drugs. The difficulty of researches of this kind for cholinergetic and anticholinergetic compounds was the property of acetylcholine to act as a stimulus transferring agent not only on the parasympathetic terminals, but also on the ganglia, and even on the motoric end plates of the cross-striped muscles. Consequently, three points of attack of acetylcholine should be distinguished. Drug research has the purpose to produce compounds having selective action possibly on only one of these points of attack. The effect of acetylcholine and other cholinergic stimulants on the parasympathetic terminal apparatus can be antagonized by tropeines, e.g., by atropine and its quaternary alkyl derivatives. This property is shown also by compounds consisting essentially of esters of aminoalcohols with aromatic carboxylic acids. The ganglionic function of acetylcholine can, on the other hand, be blocked by quaternary aralkyl esters of tropine. For the third point of attack of acetylcholine, namely in the motoric end plates of striped muscles, effective blocking agents have been found in the form of curare and similar bis-quaternary compounds.

As a result of common structural principles, parasympathomimetic and parasympatholytic compounds can mutually antagonize each other.

PFEIFFER [96] was the first to point out that the distance of the carbonyl oxygen from the nitrogen atom was the same in all of these compounds, a property which renders mutual antagonism possible. Between sympathomimetic or sympatholytic agents on one hand, and adrenaline on the other, no similar relationship has been found so far. The parasympatholytic activity of a compound is usually compared with that of atropine. To characterize ganglion-

blocking activity tetraethyl ammonium bromide, for ganglion stimulating agents tetramethyl ammonium bromide, and finally to compare curare-like activity, *d*-tubocurarine have been chosen as the reference standards. For an easy survey and study of the relationships between the structure and activity of these compounds, we have arranged available data in form of tables, and the intensity of pharmacological activity is given, wherever possible, characterized in relation to the standards indicated above.*

* This part of the monograph covers the literature of the field to 1960. More recent results are to be published in a forthcoming volume.

CHAPTER I

TROPEINES OF PARASYMPATHOLYTIC ACTIVITY

LADENBURG [66] was the first to denote the esters of tropine as 'tropeines' and laid down the following structural features as assumed prerequisites of mydriatic, i.e., a typical parasympatholytic action.

1. The acidic component to be esterified should contain a benzene ring and a hydroxyl group;
2. the hydroxyl group should be in that part of the chain which contains the carboxyl group.

However, investigations carried out by JOWETT and PYMAN [61] revealed that LADENBURG's rules could not be generalized. As shown by the experimental results of GOTTLIEB [33], tropine esters of aliphatic acids (which would be denoted today as tropan-3-ol esters) are not poisonous compounds. Thus, acetyl-, succinyl-, and lactyltropine are not toxic on cats even if given in large doses, such as 800 mg/kg.

Although topically applied tropine has no dilating effect on the pupil of the eye, tropeines prepared with aliphatic acids produce a rather marked and lasting mydriatic effect. A further characteristic of tropylacetate is that it considerably raises reflex excitability, and produces clonic-tonic spasm.

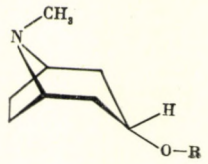
These symptoms are not brought about by the succinyl analogue; treatment with this compound results in the paralysis of the animal. The lactate has no other pharmacological effects worth mentioning.

Similar effects are produced by the above tropeines on the heart. Investigations concerning this point of action revealed that lactyl derivatives, being the esters of a hydroxycarboxylic acid, have a more pronounced parasympatholytic activity than tropeines derived from acids containing no hydroxyl group. Unfortunately, a great number of tropeines described in literature has not been subjected to comparative tests carried out simultaneously or, at least, by employing the same method. Thus, Table I shows a qualitative or partly quantitative picture about acylating groups (R), the introduction of which results in a mydriatic action of the 3α-tropine ester.

From among the various tropeines, undoubtedly atropine was the subject of the most detailed studies. The pharmacology of this compound was excellently reviewed by OETTINGEN [92] and PFANKUCH [95], respectively. Data are presented at the same place about the pharmacology of other formerly known tropeines. Unfortunately, these authors give no tables of properties for the comparison of these compounds.

However, the conclusion may be drawn also from this work that an effective mydriatic agent can be obtained in the series of tropan-3α-ol esters, if the esterifying acid is an aromatic hydroxycarboxylic acid. Since previous investigations had been only of informatory character, recently ENGELHARDT

Table I



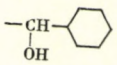
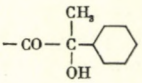
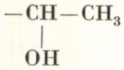
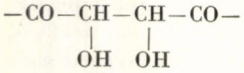
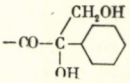
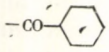
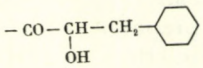
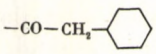
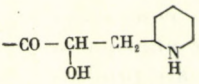
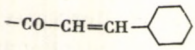
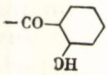
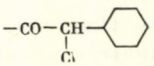
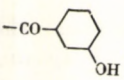
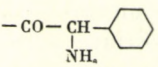
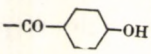
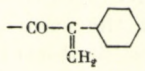
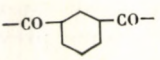
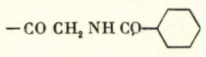
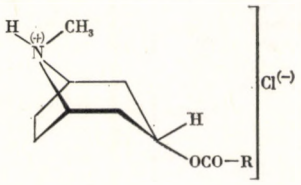
R	Mydriatic action	R	Mydriatic action
CH_3CO-	−		++
$-CO-C_2H_4-CO-$	−		
$-CO-CH=CH-CO-$	−		++
	(±)		
	−		+ (+)
	− (±)		++
	(±)		+ (+)
	(±)		
	−		+
	+		+
	−		(±)
	−		(±

Table II



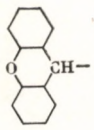
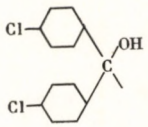
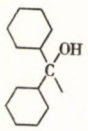
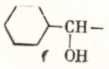
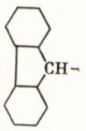
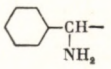
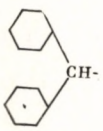
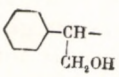
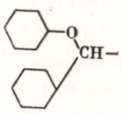
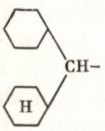
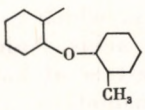
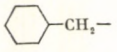
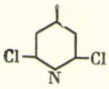
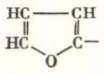
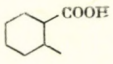
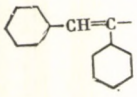
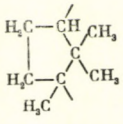
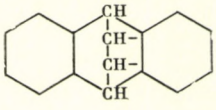
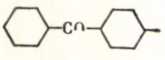
R	Spasmolytic action against acetylcholine on isolated rat and guinea-pig intestine, resp. Atropine = 1	R	Spasmolytic action against acetylcholine on isolated rat and guinea-pig intestine, resp. Atropine = 1
	1—15/10		1/10
	1—15/10		1/25
	1		1/25—1/100
			1/50—1/100
	1		1/100
	1		1/100
	1/8—1/10		1/100

Table II continued

R	Spasmolytic action against acetylcholine on isolated rat and guinea-pig intestine resp. Atropine = 1	R	Spasmolytic action against acetylcholine on isolated rat and guinea-pig intestine, resp. Atropine = 1
	1/200		1/1000—1/2500
	1/200		1/2000
	1/500		1/2500
	1/100		1/2000—1/4000
	1/100		< 1/5000
	<1/1000		1/10000

and WICK [19] carried out a comparative study of a great number of tertiary tropeines. The activity of the compound in question was always compared with that of atropine. The results of these experiments are given in Table II. It is also to be seen here that the highest parasympatholytic activity is associated with the esters of hydroxy acids. Further, it should be noted that esters with xanthene-9-carboxylic and benzilic acids are more potent agents than atropine. These investigations have somewhat modified the point of view held previously, which ascribed strong physiological action only to derivatives of hydroxy acids. Namely, as it is shown in Table II, the tertiary forms of the tropine esters of both fluorene-9-carboxylic acid and diphenyl acetic acid have a spasmolytic activity equal to that of atropine. Besides,

physiological action of a compound is decisively influenced by its steric structure, such as the position of the $C_{(3)}$—OH group in relation to the nitrogen atom; esters of *pseudo*tropine, e.g., of the following structure

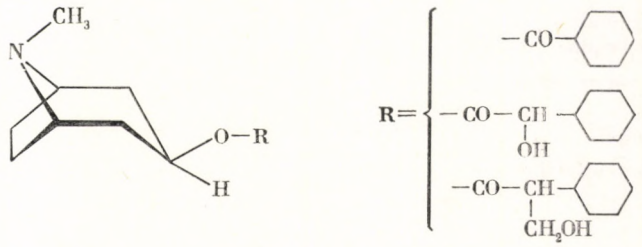


Fig. 1

have no mydriatic action at all. Thus, only tropeines having the N and O atoms in anti-(*a*) position can excercise an action on the parasympathetic terminal apparatus. That means that the action is stereospecific. The N—CH_3 group of tropeines has not been the subject of investigations from the aspect of structure–action relationship. However, from data available so far, there is good reason to doubt that optimum mydriatic activity, or, with aralkyl quaternary compounds, optimum ganglion blocking action is furnished by the substituents on the nitrogen atom. STOLL, LINDEMANN et al. [70, 109, 111, 112, 114] prepared several 6-alkoxytropeines bearing substituents on the nitrogen atom, but no detailed information has been published so far about the physiological action of these compounds. A new German patent [125] reports on *nor*tropines having a sulphur-containing substituent.

From among the *nor*compounds, only *nor*atropine has been investigated to a certain extent [11]. On the eye of the cat, the activity of these derivatives is shown to be one eighth of that of atropine. Another *nor*compound, *nor-l*-hyoscyamine has 1/4 activity in comparison with atropine. It might be concluded from this single result that optimum mydriatic action is furnished by the presence of an N-alkyl group. Relative activities of atropine and *d*- and *l*-hyoscyamine were studied by CUSHNY [12, 13] as well as by BARROWCLIFF and TUTIN [48]; the results are shown in Table III.

Even these few data are sufficient to indicate that optimum action does not depend solely on some definite constitution, but also on the given stereochemical arrangement. If the nitrogen atom of the N—CH_3 group of tropeines is quaternized with an alkyl group, parasympatholytic action remains nearly unchanged in comparison with the corresponding tertiary compound; central stimulating properties, however, which are especially strong in the case of atropine, will disappear. Indeed, a general rule of theoretical pharmaceutical chemistry is that quaternization by means of alkyl groups will reduce central actions. It is a general practice to choose and employ everywhere eumydrine [21, 36, 53] and novatropine [58] from among the parasympatholytic quaternary alkyl tropine salts. The first compound is the methonitrate of atropine and the second that of homatropine (tropine mandelate). Both derivatives are less toxic than the parent compounds. Previously also the use of genatropine (N-oxide of atropine) [43, 98, 116] was accepted, which is less poisonous than atropine.

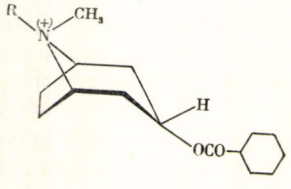
Table III

Parasympatholytic action	Atropine	*l*-Hyoscyamine	*d*-Hyoscyamine
Action against salivation caused by pilocarpine	5/10	1	1/12—1/40
Action against vagus stimulation		1	1/25—1/40
Action on the pupils	5/10	1	1/100
Action on isolated intestine	5/10	1	

According to LIEBERMANN and LIMPACH [69], *pseudo*atropine (tropoyl-3β-hydroxytropane) has no mydriatic action.

ENGELHARDT and WICK [19] published a detailed study on the influence of various alkyl groups used in forming quaternary derivatives. The investigation comprised esters of tropine with benzoic, xanthene-9-carboxylic, mandelic and tropic acids. (In the case of atropine also groups other than alkyl were studied.) The results of these experiments are summarized in Tables IV—IX. Compounds of very favourable action have been obtained

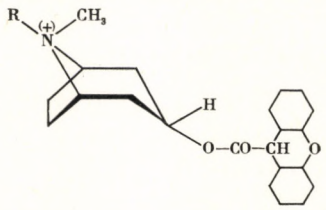
Table IV



	Spasmolytic action against acetylcholine on isolated rat and guinea-pig intestine, resp.	Mydriasis after subcutaneous injection on albino mice
	Atropine = 1	
R = H	1/100	< 1/100
CH_3	1/70	1/200
C_2H_5	1/100	—
C_3H_7 —*n*	1/500	—
C_4H_9 —*n*	1/2000	—
C_5H_{11}—*n*	1/2500	1/400
C_6H_{13}—*n*	1/2500	—
C_7H_{15}—*n*	1/150	—
C_8H_{17}—*n*	1/50—1/100	—
C_9H_{19}—*n*	1/50	—
$C_{10}H_{21}$—*n*	1/30	—
$C_{11}H_{23}$—*n*	1/10—1/25	< 1/1000
$C_{12}H_{25}$—*n*	1/100	< 1/1000

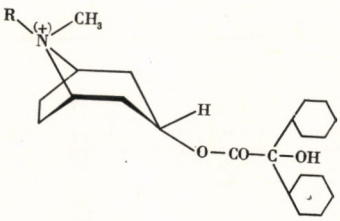
with xanthene-9-carboxylic acid and tropic acid, especially in the case of C_6 to C_8 alkyl groups; benzoic acid esters were useless. The activity of the above compounds attained or even surpassed that of atropine; at the same time, the mydriatic side effect, undesirable in this case, became very considerably reduced. A comparison of all properties indicates N-*n*-octyl-atropinium bromide to be the best; this compound proved to be the most favourable also from the

Table V



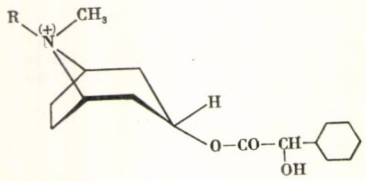
	Spasmolytic action against acetylcholine on isolated rat and guinea-pig intestine, resp.	Mydriasis after subcutaneous injection on albino mice
	Atropine = 1	
R = H	1—15/10	1/5—17/10
CH_3	15/10—2	1/500
C_2H_5	1—2	1/5
C_3H_7 —*n*	1/10—1/20	1/80
C_4H_9 —*n*	1/10	1/100—1/120
C_5H_{11}—*n*	5/6	1/100—1/120
C_6H_{13}—*n*	1/2—1	1/10
C_7H_{15}—*n*	1	1/1000
C_8H_{17}—*n*	3/4	< 1/1200
C_9H_{19}—*n*	1/10—1/15	< 1/1200

Table VI



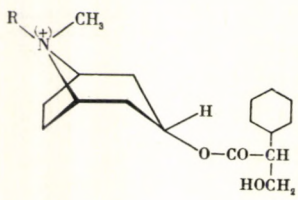
	Spasmolytic action against acetylcholine on isolated rat and guinea-pig intestine, resp.	Mydriasis after subcutaneous injection on albino mice
	Atropine = 1	
R = H	15/10	1/15
CH_3	12/10	12/10
C_2H_5	1/5—1/10	1/5—1/10
C_3H_7 —*n*	1/10	1/15
C_4H_9 —*n*	1/10	1/50—1/100
C_5H_{11}—*n*	1/50	1/100
C_6H_{13}—*n*	1/5—1/10	1/200
C_7H_{15}—*n*	1/4	1/100
C_8H_{17}—*n*	1/2	1/100
C_9H_{19}—*n*	1/3	< 1/1000
$C_{10}H_{21}$—*n*	1/5—1/10	< 1/1000

Table VII



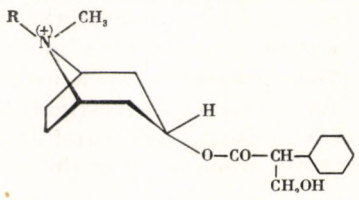
	Spasmolytic action against acetylcholine on isolated rat and guinea-pig intestine, resp.	Mydriasis after subcutaneous injection on albino mice
	Atropine = 1	
R = H	1/25	1/35
CH_3	1/5—1/10	1/7—1/10
C_2H_5	1/50	1/50
C_3H_7 —*n*	1/100	1/2000
C_4H_9 —*n*	1/2500	1/3000
C_5H_{11}—*n*	1/500	1/1000
C_5H_{11}—*n*	1/750	—
C_6H_{13}—*n*	1/500—1/1000	1/1000—1/2000
C_7H_{15}—*n*	1/10—1/20	1/500
C_8H_{17}—*n*	1/20—1/50	1/100
C_9H_{19}—*n*	1/25	< 1/1000
$C_{10}H_{21}$—*n*	1/10	< 1/1000
$C_{11}H_{23}$—*n*	1/10—1/20	< 1/1000
$C_{12}H_{25}$—*n*	1/10—1/15	< 1/1000

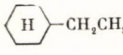
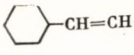
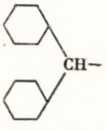
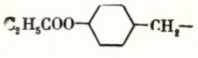
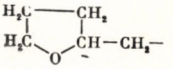
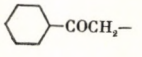
Table VIII



	Spasmolytic action against acetylcholine on isolated rat and guinea-pig intestine, resp.	Mydriasis after subcutaneous injection on albino mice	Spasmolytic action against pilocarpine on albino mice	Dose causing drooping of the head on rabbit, mg/kg	LD_{50} mg/kg subcutaneously on mice
R = H (Atropine)	1	1	1	—	735
CH_3	15/10	1,5	1/2—1/4	15	230
C_2H_5	1/3	1/2	1/6	12	103
C_3H_7 —*n*	1/20	1/20	1/20—1/40	4	180
C_4H_9 —*n*	1/50	1/50	1/50	3	51
C_5H_{11}—*n*	1/25—1/50	1/100	1/10	7	190
C_6H_{13}—*n*	1/10	1/20	1/7	4	175
C_7H_{15}—*n*	1/5	1/20	1/10	5	400
C_8H_{17}—*n*	1—5/10	1/50	1/5—1/10	5	330
C_9H_{19}—*n*	1/5	1/100	1/5	10	135
$C_{10}H_{21}$—*n*	1/10	1/150	1/10	—	—
$C_{11}H_{23}$—*n*	1/5	1/1000	—	—	—
$C_{12}H_{25}$—*n*	1/4	1/750	—	—	—
$C_{14}H_{29}$—*n*	1/20	—	—	—	—
$C_{16}H_{33}$—*n*	1/1000	—	—	—	—

Table IX

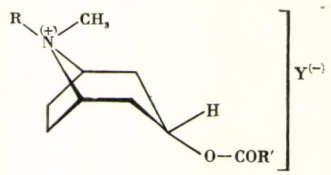


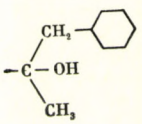
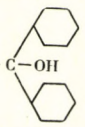
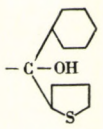
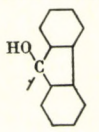
	Spasmolytic action against acetylcholine on isolated rat and guinea-pig intestine, resp.	Mydriasis after subcutaneous injection on albino mice
	Atropine = 1	
R = CH_3 / CH_3 >CH—	1/10—1/20	1/50
CH_3 / CH_3 >$CH-CH_2$—	1/50—1/100	1/1000
CH_3 / CH_3 >$CH-CH_2CH_2$—	1/150	1/30—1/40
$CH_3-(CH_2)_3-CH(C_2H_5)-CH$—	1/50	1/1000—1/2000
	1/5	—
$CH_2=CH-CH_2$—	1/5—1/10	1/5—1/10
$CH\equiv C-CH_2$—	1/2—1/4	1/2—2/3
$CH_3-(CH_2)_4-CH=CH-CH_2$—	1/3—1/4	1/3—1/4
$CH_3-(CH_2)_7-CH=CH-CH_2$—	1/10	1/40
$C_6H_5-CH_2$—	1/4	1/60—1/100
$C_6H_5-(CH_2)_2-CH_2$—	1/10—1/25	1/2—2/3
$C_6H_5-(CH_2)_4-CH_2$—	1/5—1/10	1/150—1/200
$C_6H_5-(CH_2)_6-CH_2$—	1/15—1/20	1/140
	1/3—1/4	1/10
	1/1000	—
	1/4	1/50—1/100
$C_4H_9COO-(CH_2)_4$—	1/50	—
$CH_3-(CH_2)_4-CHBr-CHBr-CH_2$—	1/10—1/15	1/60—1/100
	1/50—1/100	1/100
$HO-C_2H_4$—	1/4—1/10	1/100
	1/20—1/50	—
$BrCH_2-CHBr-CH_2$—	1/5—1/10	1/600
$CH_2=CBr-CH_2$—	1/10	1/100
$CH_3-CO-CH_2$—	1/10	1/10
$ClCH_2$—	1/5	—
$NH_2-CO-CH_2$—	1/2	—

therapeutic point of view. This medicine can be regarded as a selective neurotropic spasmolytic agent which is free of side-actions. It is to be noted that no pharmacological difference has been observed between the action of the N-diastereoisomers (also none in the case of N-*n*-octyl-noratropine methobromide) although these compounds differ in other properties, such as the melting points or infrared spectra. On the other hand, our own investigations [77] revealed a difference between the action of N-aralkyl-N-alkyl and di-N-aralkyl quaternary tropeines, which becomes especially pronounced in the case of the bisquaternary derivatives.

In the course of a search for new spasmolytic agents, ING et al. [28] prepared and studied various hydroxy esters of tropine and *pseudo*tropine. Even these few data were enough to draw the inference that the spasmolytic activity of 3β-acyloxytropanes (*pseudo*tropeines) is, in general, not lower than that of the analogous α-esters. This conclusion is supported also by the

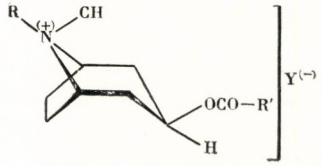
Table X

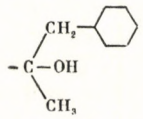
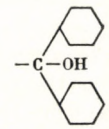
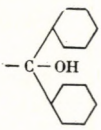


R	R'	Y	Spasmolytic action	Mydriatic action
			Atropine = 1	
H		ClO_4	0.2	0.1
CH_3		I	1	1
		Cl	0.01	—
H		Cl	1.5	0.4
CH_3			1	—
C_2H_5			1	—
CH_3		*)	0.7	—
CH_3		*)	0.3	—
		I	0.2	—

* The tertiary base was tested

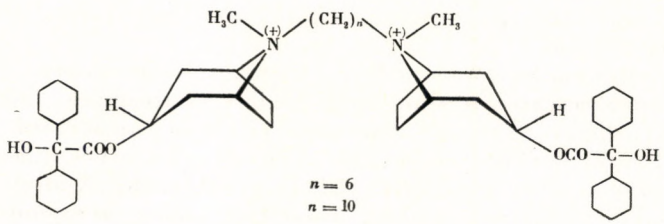
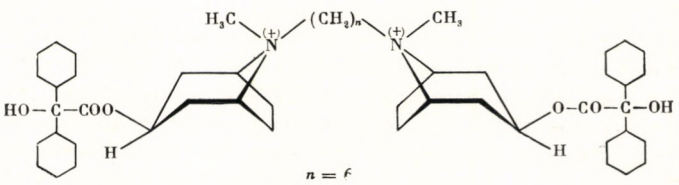
Table XI



R	R′	Y	Spasmolytic action	Mydriatic action
			Atropine = 1	
H		Cl	0.1	0
CH_3		I	1.5	0.25
		Cl	0.1	—
CH_3		*) I	0.15 0.4	— —
H		Cl	0.4	0.2
CH_3		I	1.0	—

* The tertiary base was tested

Table XII

Structural formula	Spasmolytic action	Mydriatic action
	Atropine = 1	
 $n = 6$ $n = 10$	0.2 0.1	0.1 —
 $n = 6$ $n = 10$	0.1 0.3	0.03 —

old experience that the benzil ester of *pseudo*tropine, described by HROMATKA and KREITMAIR [57, 65], proved to be a good spasmolytic agent. For the sake of an easy comparison of activities, tested compounds are listed in Tables X and XI. These studies permit drawing the highly important conclusion that the neurotropic spasmolytic actions of tropeines are not parallel. Consequently, one should not infer a spasmolytic action from a mydriatic effect. This fact necessitates also a revision of previous pharmacological data about tropeines, in order to obtain unequivocal conclusions concerning the relationship of structure and action.

The experiments of ING and his co-workers [28] also included several polymethylene-bisquaternary tropeines; however, they report only about spasmolytic and mydriatic activities, although it is known that compounds of this type are characterized not only by a parasympatholytic action, but also by a curare-like one. Structural formulas and activities of the two tested stereoisomeric pairs are shown in Table XII.

In the course of a search for mydriatic or cholinergic agents, STOLL, JUCKER and LINDEMANN [112] prepared a great number of 6-methoxytropeines and the corresponding quaternary derivatives. Unfortunately, the results of pharmacological tests with these compounds, carried out by ROTHLIN, TÄSCHLER, KONZETT and CERLETTI [103] are mentioned but very briefly. It appears that 6-methoxytropane-3α-ol benzoate and benzilate, or their methobromides, respectively, were especially active, since pharmacological results are given only for these compounds (cf. Tables XIII and XIV).

Data of these tables indicate that compound 'IV' is only twice as active as Buscopan (butylscopolaminium bromide), although the latter is listed among the less effective cholinolytic agents. A more detailed study of quaternizing groups would undoubtedly lead to additional useful results. It should be noted that compound IV was demonstrated to be *in vivo* more specific against neurogenous spasms than atropine. The corresponding 6-ethoxy derivative is less active and even more toxic. Publication of the detailed pharmacological results is necessary before it is possible to judge the value of the new evidence supplied by this group of compounds in substantiating conclusions drawn from the behaviour of other tropeines concerning the relationship of structure and action. Important is the observation that tropanyl esters with a hydroxyl group in β-position are practically ineffective, probably as a consequence of the formation of a hydrogen bond.

The property of N-allyl-*nor*morphine of being capable of antagonizing morphin effects prompted a research dealing with N-allyl-*nor*atropines and other N-allyltropeines. Syntheses of these compounds ran into considerable preparative difficulties, in spite of all experiences obtained with other analogous tropeines. Later, however, we succeeded [78] in synthesizing N-allyl-*nor*atropine. The compound has no antagonizing properties against atropine, and its parasympatholytic activity is not higher than 1/10 to 1/20 as compared with atropine.

Similar observations were also made by other researchers [30] in the course of a comparative investigation concerning tropine and N-allyl-*nor*tropine benzilates. For the sake of simplicity, results are summarized in Table XV. As it is seen, the parasympatholytic properties of the N-allyl compound cannot be compared with that of atropine or even less with the activity of the analogous $N-CH_3$ compound. On the other hand, the allyl compound has a potent local anaesthetic action, but it is extremely toxic at the same time.

Table XIII

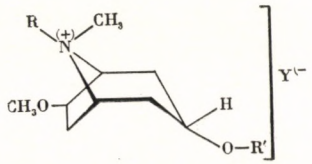
	Inhibition of isolated rabbit small intestine		Inhibition of intestine *in vivo* on cat and dog		Surface anaesthesia Cocain = 100	Mydriatic action	Inhibition of salivation	Toxicity LD_{50} intravenously on rabbit, mg/kg
	Acetylcholine	Pilocarpine	Vagus stimulation	Pilocarpine				
R = H; Y = Cl R′ = —CO— 	0.05	0.05	1	1	40	—	—	3— 5
R = CH_3; Y = Br R′ = —CO— 	0.05	0.05	3.5	2.8	0	—	—	10—15
R = H; Y = Cl R′ = —CO—C(OH) $(C_6H_5)_2$	0.6	2	1.5	1.5	150	—	—	5
R = CH_3; Y = Br R′ = —CO—C(OH) $(C_6H_5)_2$	4	3.3	21—28	21	0	4	5	20—25
Butylscopolaminium bromide (Buscopan)	2	2	14	14	—	2	—	—
Atropine	100	100	100	100	—	100	100	68

Table XIV

Quotient	Intestine *in vitro*		Intestine *in vivo*		Mydriasis	Salivation
	Acetyl-choline	Pilo-carpine	Vagus stimulation	Pilo-carpine		
Atropine / Compound IV	25	33	4	5	25	20
Atropine / Buscopan	55	55	7	7	50	—

Besides the various quaternary α-alkyl tropeines, the esters of N-alkoxy-carbonylmethyltropinium salts and quaternary scopolaminium salts are worth mentioning. These compounds were studied by ZEILE, ADICKER and WICK [123]. These derivatives are characterized by a considerable reduction of side-effects (such as mydriasis, tachycardia, dryness of mouth, etc.), with the spasmolytic

Table XV

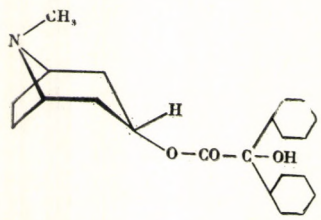
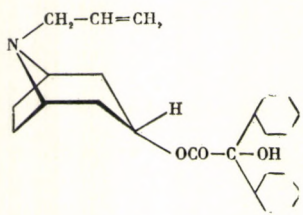
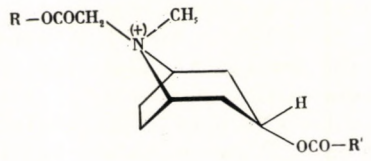
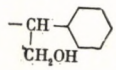
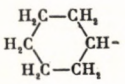
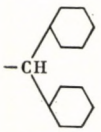
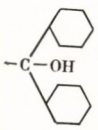
Structural formula	Parasympatholytic action	Antihistaminic action	Local anaesthetic action	Acute relative toxicity	Action on the central nervous system
	1.0—21,4	0.3	6.54	5.21	10
	0.03—7.0	0.03	11.67	12.2	10
Atropine	1.0	0.02—0.16	0.5	1.0	1
Diphenylhydramine	0.01	1.0	2.5—5.0	2.21	—
Procaine	0.0003—0.67	0.08	1.0	1.28	—

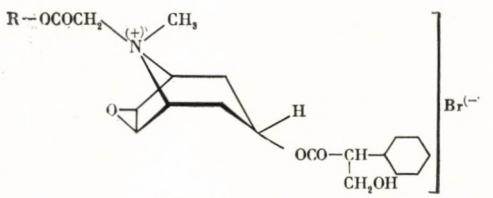
Table XVI



R	R′	Spasmolytic action (Atropine = 1)	Mydriatic action (Atropine = 1)
C_2H_5		1/75	1/75
C_7H_{15}		1	1/10
C_8H_{17}		1/5	1/1000
$C_{10}H_{21}$		1/50	1/1000
		1	1/10
C_3H_7		1/100	
C_3H_7		1/100	
C_4H_9		1/10	1/8
C_6H_{13}		1/2	1/100
C_7H_{15}		1	1/500
C_8H_{17}		5/10—1	1/1000
C_9H_{19}		1/2	1/400
$C_{10}H_{21}$		1/2	< 1/200

activity being unchanged (Tables XVI and XVII). Optimum action was found in compounds containing 6- to 8-membered carbon chains. The tropoyloxy group is, also in scopolamine, in *anti*-position in relation to the nitrogen atom.

Table XVII

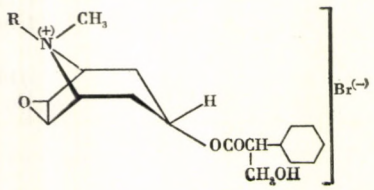


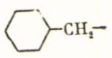
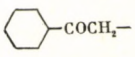
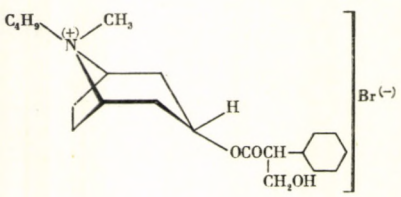
R	Spasmolytic action (Atropine = 1)	Mydriatic action (Atropine = 1)
C_6H_{13}	1/2	1/50
C_7H_{15}	1	1/10

Consequently, also this agent is expected to have very strong parasympatholytic and mydriatic action. Because of the high central activity (cf. Chapter VI), scopolamine is used almost exclusively for mydriatic purposes.

Some esters of scopoline have been known for a long time [6]. SCHILLER [105], however, dealt only with the acetate, benzilate and cinnamate in his pharmacological study. These compounds, particularly the cinnamate, caused the narcosis of frogs, and higher doses brought about paralysis. Mydriatic action was found in none of the cases. Later scopolylbenzoate was tried against seasickness [107]. MOFFETT and ASPERGREN [74] reported on

Table XVIII

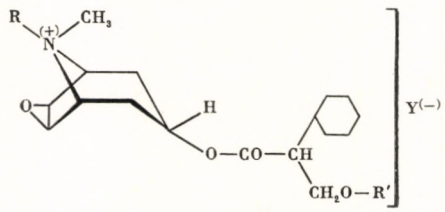


R	Spasmolytic action against pilocarpine on isolated rat and guinea-pig intestine, resp.	Cardiac action on frog against acetylcholine	Mydriasis on mice according to Pulewka	Toxicity on mice Subcutaneous injection, mg/kg
	Atropine = 1			
H	1	—	2.5	1600
C_4H_9-n	0.5—1.0	0.5—1.0	0.002	300
	0.2	0.2	0.25	300—450
	0.02	0.1—0.2	1.5	450—600
$C_2H_5-OCOCH_2-$	0.2	1.0	0.75	300—450
$C_4H_9-OCOCH_2-$	0.2	1.0	2.0	150—300
$CH_2=CH-CH_2-$	0.2	0.5—1.0	0.5	150—300
HOC_2H_4-	0.5—1.0	1.0	0.9	300—450
$(CH_3)_2CH-CH_2CH_2-$	0.01	1.0	0.001	300—450
$H_2N-CO-CH_2-$	0.5—1.0	1.0	0.8	450—600
	0.01	1.0	0.03	75—100

scopoline-phenylcyclopentyl acetate, and the methobromide of this compound. Both substances have but very slight anticholinergic action.

According to WICK [121], among recently studied quaternary scopolaminium derivatives, Buscopan is undoubtedly the most useful known spasmolytic agent. Tested compounds and their activities are shown in Table XVIII. Although Buscopan is considerably weaker than atropine or the other modern spasmolytic agents, it is generally accepted as a result of its much more restricted side-actions. Another most frequently used parasympatholytic tropeine is N-methylscopolaminium bromide (Pamin). MOFFETT and ASPERGREN [74] emphasized the advantageous properties of O-acetyl-methylscopolaminium bromide. The investigations of these researchers included, in addition to simple quaternary derivatives, and besides the hydrobromides and methobromides of the O-acyl derivatives, also some conversion products of scopolamine. It can be seen from Tables XIX and XX that neither the esters with atropic and hydratropic acids, nor the O-acyl-

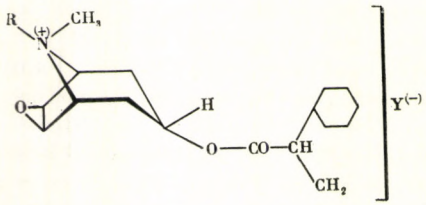
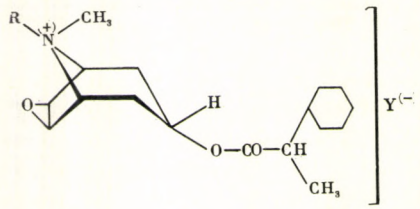
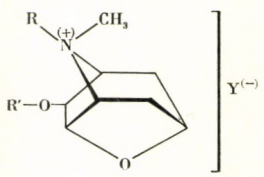
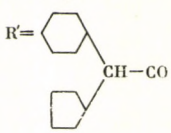
Table XIX



R	R′	Y	Toxicity on mice (intraperitoneal inj.) LD_{50} mg/kg	Spasmolysis on dog Atropine = 1	Inhibition of secretion on rats ED_{50}
CH_3	H	Br	150	6.0	0.003
C_2H_5	H	Br	200	3.0	0.02
$CH_2=CH-CH_2$	H	Cl	83	1.0	0.6
C_4H_9-n	H	I	200	0.2	0.05
C_2H_4OH	H	Br	233	2.0	0.5
	H	Cl	233	0.5	0.5—5.0
$(CH_2)_6$*	H	Br	5.3	0.2	0.2
→O**	H	Br	>1000	2.0	0.02
H	CH_3CO	Br	533	2.0	—
CH_3	CH_3CO	Br	167	6.0	0.004
→O***	CH_3CO	—	650	< 0.1	>1.0
H	$(CH_3)_3CCO$	Cl	767	4.0	—
CH_3	$(CH_3)_3CCO$	Br	77	2.0	0.005
H	$(CH_3)_2CHCH(C_2H_5)CO$	Br	838	< 1.0	—
CH_3	$(CH_3)_2CH \cdot CH(C_2H_5)CO$	Br	65	0.2	0.05
CH_3	$(CH_2)_4>CH-C_2H_4CO$	Br	167	0.3	0.007
CH_3	$C_2H_5-O-CH(CH_3)CO$	Br	200	2.0	0.008
H	C_6H_5NHCO	Cl	233	0.2	—
CH_3	C_6H_5NHCO	Br	200	0.2	0.05

Notes : * The compound is N,N'-hexamethylene-bis-scopolaminium dibromide
** Scopolamine-N-oxide-hydrobromide monohydrate
*** O-Acetylscopolamine-N-oxide

Table XX

Structural formula	Toxicity on mice, i.p., LD_{50}, mg/kg	Spasmolytic action on dogs	Inhibition of secretion* ED_{50} inactive
			
R = H Y = NO_3	650	< 0.1	> 2.0
R = CH_3 Y = Br	23	0.5	⩾ 1.0
			
R = H Y = Cl	1000	0.1	> 1.0
R = CH_3 Y = Br	30	1.0	—
			
R = CH_3 Y = Br			
R'= 	65	0.1	inactive

* The test was made on rats. Method of VISSHER et al. J. Pharmacol. Exp. Therap. *110*, 118 (1954)

tropyl derivatives show any special advantage in comparison with non-acylated tropic esters. From these data the conclusion may be drawn that the conversion products of scopolamine are, from the practical point of view, nearly of no value, furthermore they have rather unfavourable atropine indices and toxicity indices. The quaternary derivatives are, in general, considerably more toxic than the analogous tertiary compounds.

A great number of scopoline esters have been prepared by ZEILE and HEUSNER [124], and their pharmacological tests were made by WICK. These compounds, but for some benzilic esters, proved to be very feeble spasmolytic agents (Table XXI). These results also indicate that 3-acyloxy derivatives are necessary to obtain sympatholytic action.

Among some N-alkyl homologues of scopoline, ZIELE and HEUSNER [124] prepared also the N-propyl and N-*n*-butyl derivatives. The investigation included N-*n*-propyl-scopoline benzilate, too; the spasmolytic activity of the compound against acetylcholine was fairly weak, about 1/1000 of that of atropine. This result is worth consideration for future research, since it represents a decrease of activity to about 1/140 in comparison with the N-methyl analogues also shown in Table XXI. After administering non-toxic doses, no central actions could be observed either in the case of benzoate, O-ethyl-benzilate or phenylurethan and mandelate.

The benzhydryl ether of scopoline proved to be a rather inactive antihistaminic agent (about 20 times weaker than Benadryl), and its parasympatholytic activity against acetylcholine was not higher than 1/3 of the effect of atropine, either. However, the compound has a surprisingly strong local anaesthetic action which is 10 times greater than that of cocaine. No injurious effects on tissues were reported.

Also the O-acyl derivatives of atropine and scopolamine are powerful parasympatholytic agents. According to the studies of HERMAN, SHAW and ROSENBLUM [50], their antiacetylcholinic activity is hardly less than that of atropine. The action is lasting; this fact may be explained by the presence of the O-acyl group which is only slowly split off in the organism. Compounds of this type are shown in Table XXII.

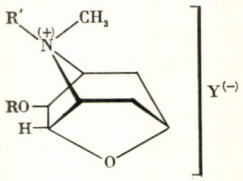
It can be seen from the Table that quaternization brings about a decrease of anti-acetylcholinic activity. Secretion-inhibiting activity, important from the aspect of practice, was studied on rats by analyzing the contents of the stomach 20 to 22 hours after administering a 350 mg/kg dose of the compound. If the amount and pH of the gastric juice was known, the acid contents could be expressed in milliequivalents/kg. The results of this work are summarized in Table XXIII. As regards the treatment of ulcers, the authors are of the opinion that O-propionylatropine methonitrate is the most valuable among the compounds listed in the Table. The oral toxicity of this agent is low, and favourable results have been obtained also in preliminary experiments on humans [4, 49].

The following conclusions may be drawn from the behaviour of parasympatholytic tropeines investigated so far.

a) Optimum activity is obtained if an $N-CH_3$ group is present.

b) The action marked with acyloxytropanes is shown in compounds having an aromatic ring. The α-position of the acyloxy group is more favourable. Besides xanthene-9-carboxylic acid, esterification with aryl-aliphatic hydroxy acids gave the most effective compounds; the OH group must be attached to the carbon atom between the ring and carboxyl group.

Table XXI



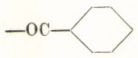
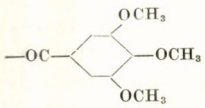
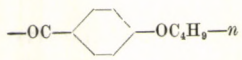
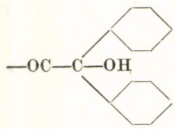
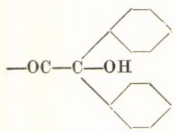
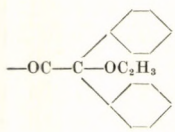
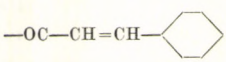
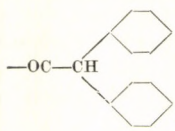
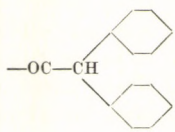
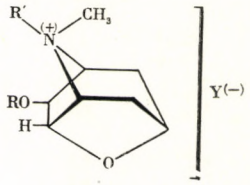
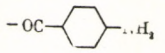
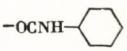
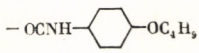
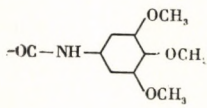
R	R′	Y	Spasmolytic action against acetylcholine	Mydriatic action	Surface anaesthesia tested with 1% solution
			Atropine = 1		Cocaine = 1
	H	Br	< 1/1000	—	0
	H	Cl	1/1000	—	0
	H	Cl	—	—	5
	H	Cl	1/7	1/125	5
	CH_3	Br	1/2—1/3	1	0
	H	Cl	< 1/1000	—	0
	H	Cl	< 1/1000	—	0
	H	Cl	1/800	—	15/10—2
	CH_3	Br	1/200	1/1000	0

Table XXI continued

			Spasmolytic action against acetylcholine	Mydriatic action	Surface anaesthesia tested with 1% solution
R	R′	Y	Atropine = 1		Cocaine = 1
	H	Cl	—	—	~ 1
	H	Cl	—	—	0
	H	Cl	—	—	5
	H	Cl	< 1/1000	—	0

c) Apart from the acyloxy group, no substituents of favourable action have been found.

d) Quaternization results in the disappearance of the central effects characteristic of the tertiary compounds. Vegetative effects are not, in general, decreased or, in each case, there can be found a quaternizing group which provides a compound attaining the vegetative activity of the tertiary base; most favourable groups are methyl, hexyl, heptyl and *n*-octyl. Some quaternary N-carboxymethyl derivatives are also active.

Table XXII

Name of compound	Antiacetylcholinic action on isolated intestine of guineapig
Atropine hydrobromide	0.5×10^{-8}
Atropine methobromide	0.6×10^{-8}
O-Acetylatropine hydrobromide	0.7×10^{-8}
O-Acetylatropine methobromide	0.5×10^{-7}
O-Propionylatropine hydrobromide	0.75×10^{-8}
O-Propionylatropine methobromide	0.2×10^{-7}
O-Valeroylatropine methobromide	0.2×10^{-8}

Table XXIII

Name of compound	Analysis of gastric juice		
	Total volume	pH	Milliequivalents of acid per kg weight of body
Blank experiment	9.7	< 2.0	2.541
Atropine hydrobromide	1.2	3.9	0.329
Atropine methobromide	1.7	3.8	0.420
O-Acetylatropine hydrobromide	0.95	4.0	0.480
O-Acetylatropine methobromide	0.48	5.2	0.277
O-Propionylatropine hydrobromide	1.54	5.8	0.227
O-Propionylatropine methonitrate	1.4	4.4	0.206
O-Valeroylatropine methonitrate	1.2	3.3	0.471
Scopolamine hydrobromide	2.2	2.9	1,201
Scopolamine methobromide	1.50	4.6	0.508
O-Acetylscopolamine hydrobromide	1.95	3.6	0.368
O-Propionylscopolamine hydrobromide	1.84	3.1	0.981
O-Butyrylscopolamine hydrobromide	2.3	3.5	0.662
O-Valeroylscopolamine hydrobromide	1.17	4.1	0.398
O-*iso*-Valeroylscopolamine hydrobromide	2.0	3.5	0.844
O-Benzoylscopolamine hydrobromide (dosis : 250 mg/kg)	1.6	5.6	0.507
O-Acetylscopolamine-N-oxyde hydrobromide	2.7	2.5	0.620
O-Acetylhomatropine hydrobromide	2.6	2.3	0.950
O-Benzoylhomatropine hydrobromide (dose : 200 mg/kg)	0.7	5.8	0.084

Spasmolytic and mydriatic actions are not parallel. Systematic variation of the structure, primarily that of the quaternary groups, can lead to spasmolytics which possess only minimal undesired mydriatic side-action. Marked mydriatic activity can be expected from tropeines derived from aromatic hydroxy acids and from the corresponding quaternary N-methyltropanium salts.

CHAPTER II

TROPEINES WITH GANGLIONIC ACTION

GANGLION BLOCKING AGENTS

Monoquaternary salts of tropeines, acting on the ganglia and antagonizing thus acetylcholine at the second point of its attack, became known through the researches of NÁDOR and GYERMEK [39, 81]. Ganglion blocking action itself was investigated in the exploratory experiments of GYERMEK and SZTANYIK [42], who found that this effect was hardly shown by tertiary tropeines, but markedly by the quaternary derivatives.

It was shown in previous experiments [79] that, in order to obtain optimum ganglion blocking action, the presence of the structural units (a) or (b)

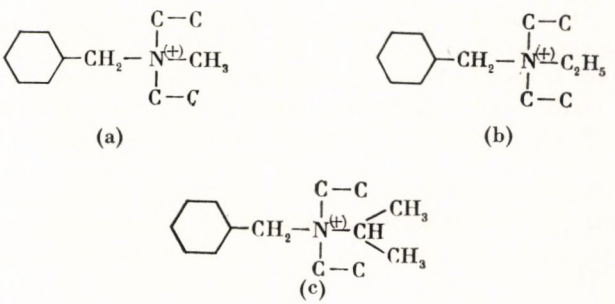


Fig. 2

or, according to our experiences the arrangement (c) (Fig. 2) was necessary. Studies with model compounds revealed that ganglion stimulating activity could be suspended by introducing an aralkyl group. To gather information, simple alkyl-*α*-tropinium ester salts were synthesized first. Pharmacological tests showed that although these compounds were 2 to 4 times as strong ganglion blocking agents as tetraethylammonium bromide (TEA), they had so strong parasympatholytic action at the same time that they could not be used in practice.

Very important for future research was the observation that the ganglion blocking activity of aralkyl-*α*-tropinium derivatives was not weaker, but mostly stronger than that of alkyl compounds. In addition, undesired parasympatholytic action of N-alkyl derivatives was reduced by this substitution to a minimum value. Consequently, instead of quaternary N-alkyltropeines, the *quaternary aralkyl* derivatives became the goal of synthetic work. *The parasympatholytic activity of tropeines can be reduced in this way much more effectively — and without decreasing the ganglion blocking properties — than by substituting*

the aromatic hydroxy acid, which forms the ester with the $C_{(3)}$ hydroxyl, by simpler aromatic carboxylic acids.

Accepted opinion until now has been (as mentioned in the case of 3-benzoyloxytropane) that α- and β-tropeines made with simple aromatic or alkylaromatic acids, such as benzoic, phenylacetic acid, etc., possess no useful parasympatholytic properties, however, these compounds have local anaesthetic action, especially when belonging to the β-series. On the other hand, tropine esters formed with alkylaromatic alcohol-carboxylic acids (e.g. tropic, mandelic acid, etc.), have strong parasympatholytic activity which, in general, is not decreased by N-alkylation, especially by N-methylation. Now it was found that, in case of tropeines made with simple aromatic acids, quaternization by an alkyl group resulted not in a parasympatholytic but in a well-defined ganglion blocking action. In this way, there are two possibilities to obtain a potent ganglion blocking agent in the series of tropeines:

a) From tropine esters of aromatic hydroxy acids, on the basis of the principle that parasympatholytic activity is markedly reduced by quaternization with an alkyl group, and a strong ganglion blocking action appears at the same time.

b) From tropeines made with simple aromatic acids, where undesired parasympatholytic blocking action need not be considered, by finding a quaternary α-aralkyl cationic substituent which can assuredly supply the desired ganglion blocking action.

Both possibilities have advantages and disadvantages. In the first case, it must be considered that the parasympatholytic action introduced by the presence of the aromatic hydroxy acid may not completely disappear. In case *b)*, i.e. with simple aromatic carboxylic acids this factor may be neglected; however, search for a highly active compound is less hopeful in this series.

A great number of quaternary tropeines was synthesized for the purpose of a careful analysis of this problem. Table XXIV shows the most important types within this series of compounds; other derivatives are described in the original paper [86].

An independent investigation was devoted to determine the influence of the steric position of the $C_{(3)}$ hydroxyl group on the activity. The results of these experiments are summarized in Table XXV. Concerning the relationship between chemical structure and pharmacological action, the Tables permit the following conclusions.

a) Quaternization with an aralkyl instead of a methyl group always results in the formation of a compound having considerably reduced parasympatholytic activity.

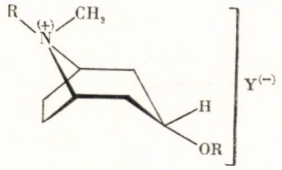
b) Quaternary N-benzyl-tropeines are, in general, at least as strong ganglion blocking agents as the quaternary methyl derivatives, and in several cases the former are even more effective.

c) Ganglion blocking action may considerably be increased by introducing a substituent — preferably halogene or phenyl — into *p*-position on the aralkyl group.

d) The aliphatic carbon atom must not be substituted, i.e. the nitrogen atom has to be attached to a CH_2 group. Substitution on this CH_2 group would extremely reduce ganglion blocking action.

e) If the N-aralkyl group is the same, tropeines made with aromatic hydroxy acids have stronger ganglion blocking action than benzoates.

Table XXIV



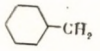
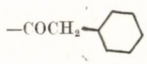
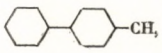
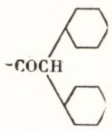
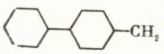
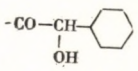
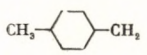
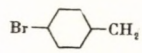
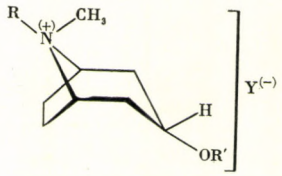
No.	R	R′	Ganglion blocking action TEA = 1	Parasympatholytic action Atropine = 1
N—131	CH_3	H	1	—
N—149	C_2H_5		1	—
N—192			1	—
N—180	CH_3	—$COCH_3$	< 0.3	—
N—228			2	< 0.005
N—308	CH_3		3	0.08
N—309			4.8	0.01
N—351			10	< 0.01
N—278	CH_3		5.3	0.05
N—299			2.0	0.01
N—350			10.0	0.01
Novatropine	CH_3		4.5	0.13
N—146	C_2H_5		2.2	0.15
N—190			3.0	0.004
N—272			14.0	0.01
N—239			19.0	0.015

Table XXIV continued



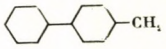
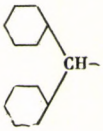
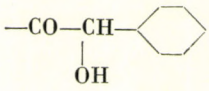
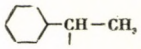
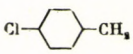
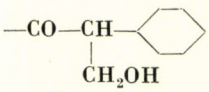
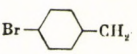
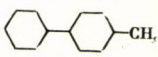
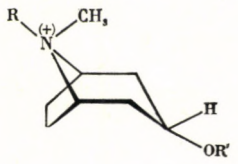
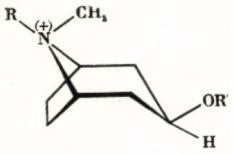
No.	R	R′	Ganglion blocking action TEA = 1	Parasympatholytic action Atropine = 1
N—310			40.0	0.01
N—241			0.7	—
N—271			1.6	—
Eumydrine			0.3	1.0
—			2.1	0.1
N—259			7.5	0.1
N—243			8.5	0.07
N—399 Gastropine			18.0	0.08

Table XXV



No.	R	R'	Ganglion blocking action TEA = 1	Parasympatholytic action Atropine = 1
N—160	CH_3—	—CO—	2	0.04
N—220	—CH_2—	—CO—	3	0.004



No.	R	R'	Ganglion blocking action TEA = 1	Parasympatholytic action Atropine = 1
N—293	CH_3—	—CO—	0.4	< 0.005
N—294	—CH_2—	—CO—	0.5	< 0.005

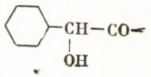
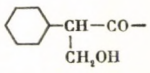
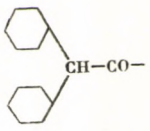
f) A consideration of the interaction of parasympatholytic and ganglion blocking factors leads to the conclusion that there are good prospects of finding highly active ganglion blocking agents derived from aromatic hydroxy acids.

g) In order to obtain strong ganglion blocking action, it is important to have the acyloxy group attached to $C_{(3)}$ in α-position compared with the nitrogen atom.

Ganglion blocking action of aralkyl tropeinium salts with bulkier acyl groups will become much less increased when the quaternary methyl is substituted by an aralkyl group (Table XXVI).

As a result of these considerations, the main subjects of our own experiments were quaternary derivatives of tropeines acylated with simple aromatic acids, mostly with benzoic and mandelic acids.

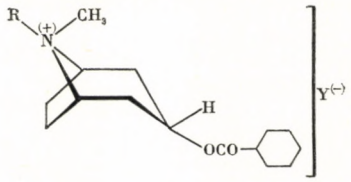
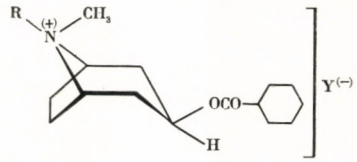
Table XXVI

Acyl group in the quaternary tropeine compound	Ganglion blocking action (TEA = 1) when the quaternary group is	
	methyl	benzyl
CH_3CO-	< 0.3	2.0
$(CH_3)_2CH-NCO-$	< 0.2	3.0
	2.0	3.0
	4.5	3.0
	4.0	2.1
	5.3	2.0

An independent study was devoted to the problem how suspension of the activity was influenced by the 3α- or 3β-position, resp., of the benzoxyl group. This pair of compounds proved, in fact, to be very suitable for investigating the relationship between steric structure and action. Various anticholinergic effects of these compounds were studied by GYERMEK [37], and are summarized in Table XXVII. As it is seen, members belonging to the α-series are more powerful parasympatholytic agents than the stereoisomeric β-compounds. Parasympathetic blocking action is, however, not in the same way influenced by the various quaternizing groups: activity is in the α-series essentially of a rather uniform value (with the single exception of the *n*-butyl compound), whereas parasympatholytic activities in the β-series are significantly different. On the other hand, N-alkylated members of the β-series are somewhat more potent ganglion blocking agents than the corresponding α-derivatives. Again, in the case of aralkyl substituents, α-derivatives are considerably more active.

As regards the relationship between structure and action, it may be concluded from these studies that most favourable ganglion blocking compounds are to be looked for among N-aralkyl-α-tropeinium salts which had been acylated with aromatic acids or aryl-hydroxyalkyl acids, such as benzoic or mandelic acid, having medium space requirement. Only a few derivatives were synthesized by us in the class of benzilates which, accidentally, are rather easy to obtain. However, it was inferred from the ideas mentioned above [75] that strong parasympatholytic agents may be found among those N-alkyl-α-tropeinium salts which had been acylated by aromatic hydroxy acids of higher requirement of space. This assumption was later justified by the preparation of various

Table XXVII

	Parasympatholytic action	Ganglion blocking action	Curare-like action
	Atropine = 1	TEA = 1	*d*-Tubocurarine = 1
R = H	0.01	0.1	0.0
CH_3	0.025	2.0	0.1
C_2H_5	0.02	3.0	0.25
C_3H_7—*n*	0.02	2.8	0.1
C_4H_9—*n*	0.005	6.0	0.25
$C_6H_5CH_2$	0.01	3.0	0.1
			
R = H	0.003	0.1	0.0
CH_3	0.002	0.2	0.07
C_2H_5	0.005	6.7	0.15
C_3H_7—*n*	0.003	6.0	0.10
C_4H_9—*n*	0.005	4.6	0.25
$C_6H_5CH_2$	0.005	0.5	0.10

tropine benzilates and the tropine ester of xanthene-9-carboxylic acid which has also great requirement of space [93].

However, by proper selection of the quaternary groups of a tropeine possessing sufficient primary activity, also compounds with considerable ganglion blocking action combined with increased instead of decreased parasympatholytic properties may be prepared. Such compounds are increasingly demanded in clinical practice, and by virtue of their having double point of attack, they can display very favourable therapeutic effects in case of vegetative disfunctions of the gastrointestinal canal. In the course of a research work carried out in co-operation with GYERMEK [83, 87] we succeeded in finding a compound of this type. The material was 4-diphenylmethyl-atropinium bromide which, after the favourable clinical experiences [104, 108, 117] has become accepted by practice under the name Gastropin (Equosanol) [20]. This compound is an 18 times stronger ganglion blocking agent than tetraethylammonium bromide, while its parasympatholytic activity is about 12 times smaller than that of atropine. In addition to these favourable therapeutic effects, also the resorption of the agent is good and quick. Since the compound is active in very small doses (2—5 mg in human therapy), undesired side-effects (such as mydriasis, dryness of the mouth, cardiac complaints etc.) hardly appear. The toxicity index is very favourable. The most important pharmacological properties of this medicine are contained in Table XXVIII, in comparison with other materials in the same field of application.

Table XXVIII

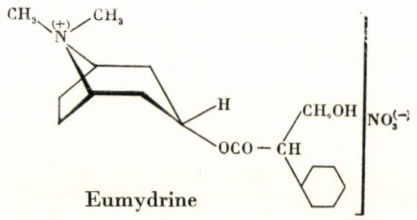
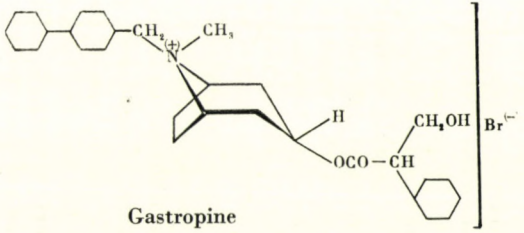
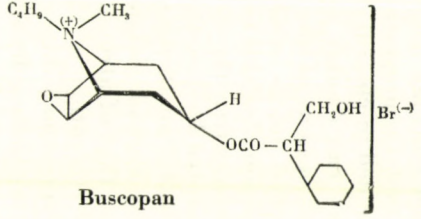
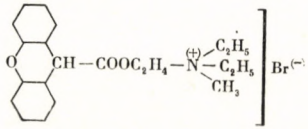
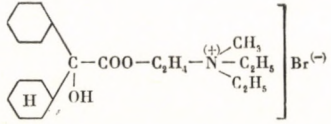
Structural formula	Spasmolysis *in vitro*	Spasmolysis *in vivo*	Inhibition of salivation	Bladderic action	Ganglion blocking action	Mydriatic action	Tachy-cardiac action	Relative toxicity
 Eumydrine	100	100	100	—	100	100	100	100
 Gastropine	22	95	10	>400	600	1.4	<20	83
 Buscopan	2.7	22	2	100	150	1.2	<20	56

Table XXVIII continued

 **Banthine**	200	90	40	<100	20	6	—	170
 **Anthrenyl**	100	—	>100	<100	<100	40	—	145

The O-acyl derivatives of atropine and scopolamine, as well as their methobromides, are comparatively weak ganglion blocking agents. Regarding this effect, HERMAN, SHAW and ROSENBLUM [50] found these compounds to be ranged between pentamethonium and butylscopolaminium bromide.

Asymmetric bis-quaternary tropinium derivatives were synthesized and tested by ARCHER, CAVALLITO and GRAY [3]. These compounds are summarized in Table XXIX. The object of these investigations was the preparation of a compound with hypotensive and ganglion blocking properties. In former studies, it was found by the same authors [34,35] that bis-quaternary compounds of the type

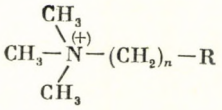


Fig. 3

where R is a bulky cationic group (e.g. tetrahydro*iso*quinoline), were very effective ganglion blocking agents; however, the duration of their action was very short. This fact called the attention to the tropane skeleton as to another bulky group. The table shows that when there is a trimethylammonium group at the end of the trimethylene chain, the duration of action is increased in the following order: tropinone — tropine — tropane. This fact was interpreted by assuming that the tropinone part suffers quick transformation in the organism, and it is converted through the corresponding tropanol derivative into the stable tropane compound. Thus most lasting action is shown by the tropane derivative. Unfortunately, these compounds have not been compared with known ganglion blocking agents so far.

Mention must be made also of Mydriasin and analogous derivatives prepared by v. BRAUN and MÜLLER [9] and by WICHURA [120] (Fig. 4).

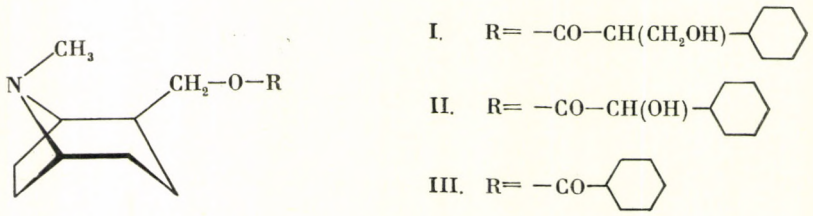
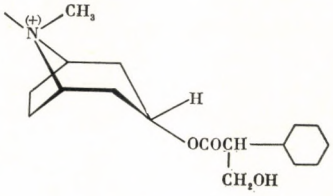
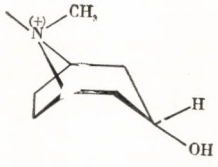
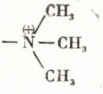
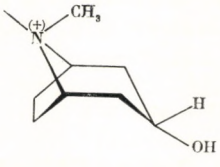
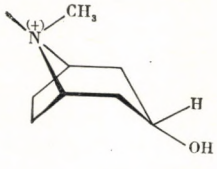
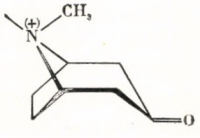
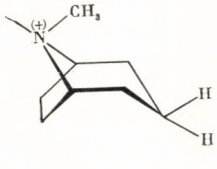
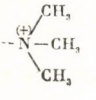


Fig. 4

Compound I brings about mydriasis in the manner like atropine, it has vagus inhibiting action, but no effect on accommodation; functioning of isolated rabbit intestine is stimulated by the compound, in this respect it may be regarded as an antagonist of atropine. On the other hand, II causes no mydriasis, it inhibits the cardiac vagus. The benzoate (III) brings about medium mydriasis only in 5% solution, it has no vagus inhibiting and local anaesthetic actions.

Table XXIX

R—$CH_2CH_2CH_2$—R′ · 2X−			Hypotensive action on dogs: dose in mg/kg /% blood pressure lowering/ duration of action in hrs
R	R′	X	
		Br	1/30/1
		Br	2/30/1.5
		Br	0.5/25/0.2—1 1/40/3.5
		Br	1/30—60/0.1—0.2
		Br	2/35/0.25
		Br	1/40/3

Among the tropic esters of N-alkylenoxy-*nor*-tropanes, also prepared by v. BRAUN [7], only the compound $n = 5$ has a moderate mydriatic action; in the case of the analogous tropeine derivatives, VII and VIII, this action is even less pronounced (Fig. 5).

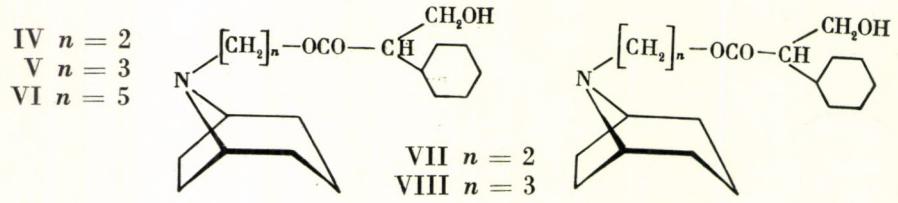


Fig. 5

Consequently, it seems that substitution on $C_{(3)}$ is the most favourable for obtaining an atropine-like action. Further substituents are not advantageous. This is also shown by the fact that meteloidine (ester of 6,7-dihydroxytropine with tiglic acid) has no action [99].

It is to be noted, on the other hand, that according to recent investigations of ALDER and DORTMANN [1], the tropic and mandelic esters of N-methyl-granatan-3α-ol possess strong mydriatic action, and the benzoate is a potent local anaesthetic. 3β-Diastereoisomers are, however, inactive [46, 118, 119].

TROPEINES WITH GANGLION STIMULATING ACTION

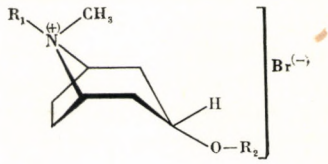
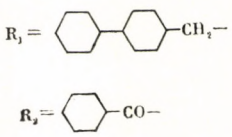
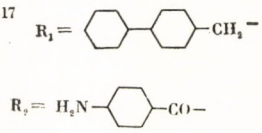
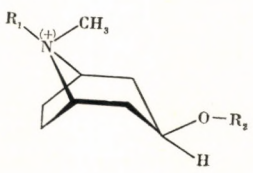
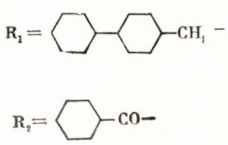
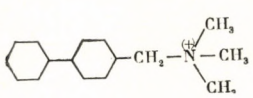
In the course of studying the role of bulky quaternizing groups, GYERMEK and NÁDOR succeeded in finding a new class of ganglion stimulating agents among the tropeines [41]. These findings can be regarded important also from the practical point of view, since compounds with respiration stimulating and hypertensive actions may find useful application in the collapsotherapy. For a reflexogenic stimulation of the respiratory centre only lobeline was used from among compounds of this type, which is a very powerful ganglion stimulant. Nicotine could not be used for this purpose, mostly because of its noxious side-actions on the heart and muscles. Most effective compounds are summarized in Table XXX.

Even these few compounds indicate that ganglion stimulating properties are possessed only by those members which bear the acyloxy group on the 3α-, i.e., in *trans*-position on the tropane skeleton. 3β-Acyloxy derivatives are practically inactive. It is also apparent that the $N-CH_3$ as well as the esterified hydroxyl groups *must occupy t r a n s - position both in ganglion blocking and ganglion stimulating compounds*. This relationship contributes important information to the elucidation of the structure of ganglionic receptors.

Besides, the presence of a simple aroyl group is also necessary to obtain ganglion stimulating action, because hydroxy esters studied in detail had just the opposite, i.e., ganglion blocking action, as discussed in the previous chapter.

Studies carried out with these compounds increased our knowledge as regards the mechanism of the action of ganglion stimulants, too. Like other ganglion stimulating agents, also these materials display their action in two steps: ganglia are first stimulated, then blocked by them. This fact leads to

Table XXX

	Activity of nicotine = 1			
	Ganglion stimulating action		Respiration stimulating action on cat	Toxicity, i.v. on mice, DL_{min} mg/kg
	on the blood tension of cat	on the nictitating membrane of cat		
				
N−361 	2.5		0.3	20
N−417 	60	15	13	1
				
N−406 	0.5		0.2	80
N−412 	0.2		0.1	—
Lobeline	0.1	0.2	0.2	15

the final conclusion that *in the strictest sense of the word one may not speak either of selective ganglion stimulants or of completely selective ganglion blocking agents.* Probably, the cholinergic receptor surfaces of the parasympathetic and sympathetic ganglia have similar but not identical structures, as it is the case also with parasympathetic terminals and with motor end plates, though both of the latter are of cholinergic character. Tropeines are exceptionally suitable for the purpose of further researches in this field, since the original action of these compounds can be influenced or even reversed by varying the individual substituents of the same primary structure.

CHAPTER III

BIS-QUATERNARY TROPEINES WITH CURARE ACTION

The observations of KIMURA, UNNA and PFEIFFER [63, 64] called the attention to the third point of attack of acetylcholine, which is on the motor end plates. It was found that 1,10-decamethylene-bis-atropinium bromide had a marked curare-like action. A suggestion for preparing such compounds could be derived also from the work of BARLOW and ING [5] as well as PATON and ZAIMIS [94], according to which 1,10-decamethylene-bis-trimethylammonium bromide (Decamethonium) possessed a very strong curare-like action. In connection with this compound the concept of interprosthetic distance was introduced, which denotes the distance in Å units of two pharmacologically active points of a molecule. In the case of curare-like action it was found to be 13—15 Å.

Simultaneously with the above research, experiments were carried out also by us [90] in the field of studying bis-quaternary compounds, primarily 1,4-xylylene-bis-quaternary tropeines of curare-like action. These compounds are shown in Table XXXI.

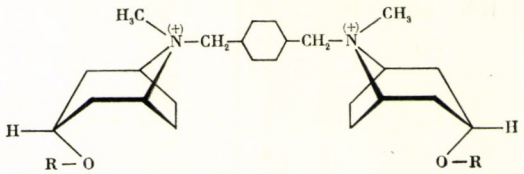
The preparation and pharmacological testing of such 1,4-xylylene-bis-tropeinium derivatives appeared all the more promising to us, since it could be presumed on the basis of the known antagonism between prostigmine and atropine that valuable compounds may be prepared if the structural prerequisite of capability for antagonism, i.e. the tropine skeleton, is introduced also into these bis-quaternary compounds of sufficient activity.

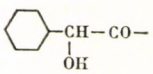
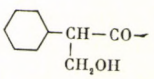
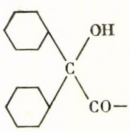
Even the first results of these investigations furnished important clues to decide about the structure and number of the compounds to be synthesized.

Table XXXI shows that 1,4-xylylene-bis-quaternary tropeines have very strong curare activity. Their effectivity is the same as that of *d*-tubocurarine. The action, however, is by no means selective, because these derivatives possess also a considerable parasympatholytic activity, thus they cannot be used in the therapeutic practice. On the other hand, these properties — including curare action — may be completely and at once counteracted by prostigmine.

When considering the preparation of other agents, we started with the known fact that there are considerable differences even among tertiary tropine esters; namely, parasympatholytic activity is found only with tropeines from aryl-aliphatic hydroxy acids (such as mandelic, tropic acid etc.), while the derivatives made with simple acids (e.g. benzoic, phenylacetic etc.) show but a very low activity. Thus, the synthesis of 1,4-xylylene-bis-quaternary tropeines derived from benzoic and phenylacetic acids appeared to be the most promising, since parasympatholytic action was undesired in this case. Table XXXII demonstrates that expectations were justified. Especially valuable is the benzoyl derivative which, besides a strong curare-like action, has also

Table XXXI

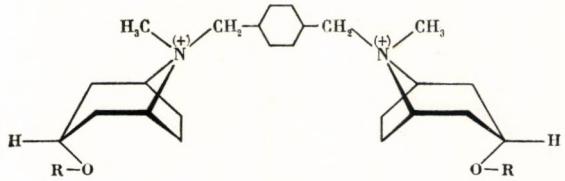


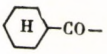
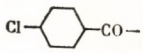
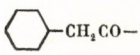
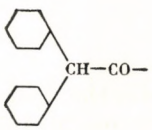
R	Curare-like action on frogs	Parasympatholytic action on cats
H	1/10	—
CH_3CO—	2/10	—
	1	1/50
	13/10	1/40
	5/10	1/40
d-Tubocurarine	1	—
Atropine	—	1

other favourable pharmacological properties [59, 60]. It is well worth mentioning that the action of this agent can instantly be counterbalanced by prostigmine, whereas its parasympatholytic action is practically negligible. Thus, an investigation of these 1,4-xylylene-bis-quaternary tropeines showed that the distance of the prosthetic groups of about 13—15 Å was not absolutely necessary: in these compounds this distance was considerably smaller. Nevertheless, the curare-like properties of these derivatives are very strong, in some cases attaining or even surpassing the activity of natural *d*-tubocurarine.

After the elucidation of the steric structure of tropine and ψ-tropine [25, 26], we considered it necessary to synthesize and also subject to a pharmacological study some derivatives of ψ-tropine (3β-hydroxytropane), defined now on an exact stereochemical basis. Thus, esters and corresponding 1,4-xylylene-bis-quaternary derivatives of ψ-tropine were synthesized. Pharma-

Table XXXII

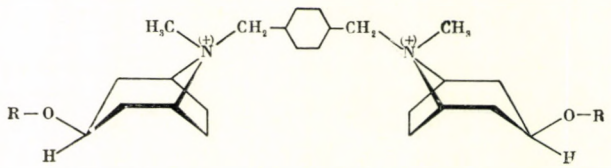


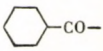
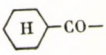
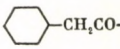
R	Curare-like action on frogs	Parasympatholytic action on cats
	2	1/75
	7/10	1/100
	65/100	1/75
	15/10	1/100
	65/100	1/50
d-Tubocurarine	1	—
Atropine	—	1

cologic tests with these compounds showed, however (see Table XXXIII) that 3β-acyl derivatives were much less active than the otherwise analogous 3α-acyloxy derivatives. A higher activity was thus exerted also here by an ester group in the α-(*anti*) position.

Similarly, curare activity was very considerably influenced also by N-diastereoisomerism. FODOR [24, 27] could demonstrate in the cases of several tropane derivatives that the N-methyl group of the tropane skeleton is to be found in much higher probability in the steric neighbourhood of the $C_{(3)}$

Table XXXIII



R	Curare-like action on frogs	Parasympatholytic action on cats
	6/10	1/150
	5/10	1/150
	2/10	1/100
d-Tubocurarine	1	—
Atropine	—	1

hydroxyl group. It follows from this statement that also the unshared electron pair of the nitrogen atom must have a definite steric orientation which will result in a predetermined configuration of the nitrogen atom in the tropanium derivative when quaternization with an alkyl- or aralkyl group establishes a co-ordinate bond.* Consequently, the quaternizing group, e.g., the 1,4-xylene group probably assumes, on the analogy of other groups, a steric position in the neighbourhood of the pyrrolidine ring (N_b position in FODOR's denotation), both in monoquaternary and bis-quaternary tropeines. The bis-quaternary tropeines were synthesized by reacting 2 moles of a tropeine with 1 mole of 1,4-xylylene dibromide.

However, if the 1,4-xylylene group is introduced first into the corresponding *nor*-compound in place of the $N-CH_3$ group of the tropine skeleton, i.e., if reversed quaternization is intended [24, 27], then this aralkylene group

* The author wishes to express also here his most sincere thanks to Prof. G. FODOR for the kind personal communication of the results of studies unpublished at that time, which made possible the preparation of compounds by 'reversed quaternization'.

will be in the steric vicinity of the hydroxyl group. If the bis-tertiary compound prepared in this way is subsequently quaternized with methyl bromide, the epimeric form of N,N'-xylylene-bis-(O-benzoyl)-α-tropinium bromide will be obtained.

These two different methods of preparation afford thus two diastereomers, just the way as expected; this pair of compounds is illustrated in Table XXXIV. These derivatives show also considerable structural differences, since one of them is almost linear, the other crescent-shaped and correspondingly also their physiologic action is fundamentally different. Namely, the linear compound is a very potent agent, more active than *d*-tubocurarine, while its diastereoisomer is forty times less effective.

Thus, the optimum structural conditions for a curare-like action can be characterized by saying that the $C_{(3)}$ atom of tropane should bear a benzoyloxy group in *a* steric position, while the xylylene group of the nitrogen atom must assume the so-called N_b stereo-arrangement.

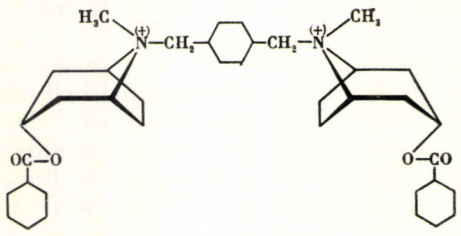
Similar detailed and precise analysis of the relationships of action, structure and configuration had not been made previously. The results of these investigations show unequivocally that modern drug research is hardly to be marked off from theoretical chemistry, and basically new results can be achieved in the field of investigating the structure–action relationship only in this way.

As it has been mentioned, monoquaternary tropeines have strong ganglion blocking action. From the theoretical point of view we considered it important to decide what kind of pharmacological action was possessed by the dicarboxylic esters of tropine: were they ganglion blocking agents or had they curare activity? This question was all the more interesting since from the already learned relationships between structure and activity the way of changing the otherwise ganglion blocking influence of aralkyl quaternization could not be foretold when this group was present twice in the molecule. A study of this type of compounds was also intriguing, because in this case good possibilities were given for synthesizing compounds having quaternary groups of discretionary composition. Namely, in the case of the above-mentioned 1,4-xylylene-bis-tropeinium salts, the structure and also the steric structure of the quaternizing group was decided from the beginning, although there was no proof whatever that it was the best quaternary group from the aspect of curare action. For the purpose of investigating this problem, the compounds summarized in Table XXXV were prepared and tested [38, 80].

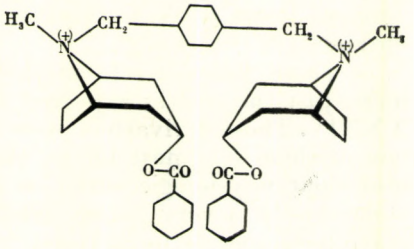
The Table shows that these derivatives are characterized by a strong curare action, while their ganglion blocking activity is hardly worth mentioning. The action can be promptly suspended by prostigmine. While showing weak parasympatholytic activity, these compounds were found to be rather toxic. Because of the strong curare-like action, it would be reasonable to carry out reversed quaternization experiments also with this type, since if the substituents are given, this is the only possibility for the variation of the steric position of the quaternary group and to clear up thereby the relationship between curare-like action and steric structure.

That was the motive of our efforts to prepare also other N-alkyl analogues besides the compounds containing the naturally given $N-CH_3$ group. In a paper [79] dealing with ganglion blocking agents, we gave an explanation for the different physiological behaviour of the homologous TMA and TEA (the first compound stimulates, the second paralyzes ganglia) by suggesting that

Table XXXIV

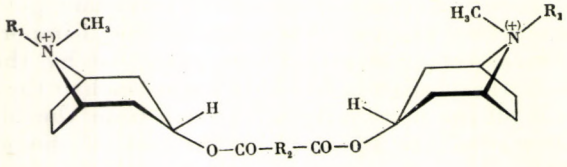


N—147. Activity on frogs : 2.5 γ/g



N—625. Activity on frogs: 90 γ/g

Table XXXV



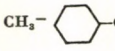
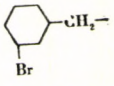
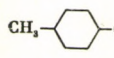
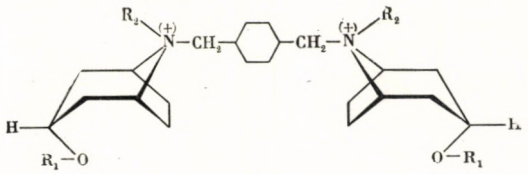
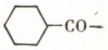
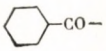
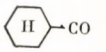
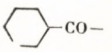
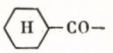
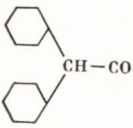
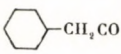
R_1	R_2	Curare-like action on frogs	Parasympatholytic action on cats	Ganglion blocking action
CH_3—		5/10	1/1000	51/10
	—CH_2CH_2—	1	1/500	2
		25/10	1/50	36/10
CH_3—		3/10	1/500	5/10
		5	1/20	18/10
d-Tubocurarine		1	—	—
Atropine		—	1	—
Tetraethylammonium bromide		—	—	1

Table XXXVI

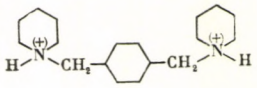
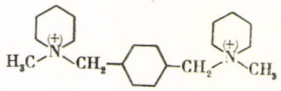
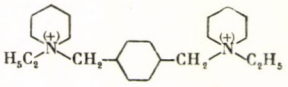


R_1	R_2	Curare-like action *d*-Tubocurarine = 1	Stereochemical relationship N/O
	C_2H_5—	0.65	*anti*
	C_2H_5—	0.50	*syn*
	C_2H_5—	0.35	*anti*
	nC_4H_9—	0.8	*anti*
	nC_4H_9—	0.6	*anti*
	nC_4H_9—	0.7	*anti*
	nC_4H_9—	0.4	*anti*

the well-known electron-releasing property of the methyl group gives rise to a relatively high electron density about the nitrogen atom of TMA, while the electron-withdrawing power of the ethyl group results in a relative deficiency of electrons. HOLMES [54] arrived at similar conclusions concerning the causes of curare-like action.

The investigation of the analogues of N-ethyl- and N-*n*-butyl-*nor*-tropines appeared to us to be of special interest. Table XXXVI shows that the N-*n*-butyl- and especially the N-ethyl analogues have much weaker curare activity than the N-methyl compound. Thus, the N-methyl group as a third

Table XXXVII

Structural formula	Curare-like action on frogs
	0.04
	0.15
	0.06
d-Tubocurarine	1

factor of determining the optimum structure should be ranged with the above-mentioned two.

Table XXXVII clearly demonstrates that curare-like and also ganglion blocking actions of a compound are very strongly influenced not only by structural elements, but also by the electron-attracting or electron-releasing effects present in the molecule.

As it is seen, the first compound, the bis-piperidinium derivative can hardly be regarded as an agent having curare-like action. This fact is probably in connection with the charge distributing property of the double-bond system. The different activities of N-methyl- and N-ethyl-bis-quaternary piperidinium derivatives were satisfactorily explained already on basis of the above interpretation.

As a result of the above experiences, the relationship between structure and effect can be summarized for the case of tropeinium salts with curare-like action as follows.

a) α-Acyloxy derivatives are considerably more active than the analogous β-compounds.

b) The most favourable α-acyl group is benzoyl. In the case of not simple aromatic acids, and particularly in case of arylaliphatic alcoholcarboxylic acids, possible appearance of a parasympatholytic side-effect should be taken into consideration.

c) The $N-CH_3$ group represents the optimum; this group must be in N_b steric position, i.e., near to the $C_{(3)}$ ester group.

d) An advantageous connecting linkage between the cationic groups is given by the 1,4-xylylene-chain. The interprosthetic distance be-

tween the two cationic groups need not necessarily be 13—14 Å, it may be shorter.

e) The quaternary derivatives of tropine esters with dicarboxylic acids are characterized by very strong curare-like action. In the case of these compounds, the introduction of an aralkyl group onto the nitrogen atom results in more potent derivatives than the substitution of the N-methyl group by an alkyl group. However, also the undesired parasympatholytic side-effect of aralkyl derivatives will be increased in this way.

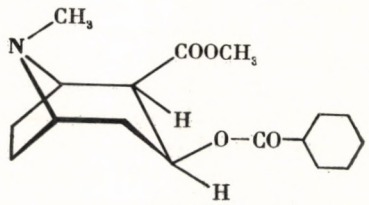
The clinical trial of 1,4-xylylene-bis-3α-benzoyltropinium bromide is in progress.

CHAPTER IV

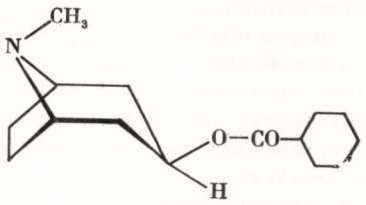
TROPEINES WITH LOCAL ANAESTHETIC ACTION

The relationship between structure and action in this class of compounds is much less known than in the case of the tropeines discussed above. This fact may be explained partly by the much smaller number of derivatives prepared in this group. Consequently, only a limited number of compounds having this physiological action could be investigated. Meanwhile modern synthetic local anaesthetics of very little toxicity have almost completely replaced cocaine and its formerly used substitutes. Another unfavourable circumstance was that no systematic comparative experiments with modern methods have been carried out, thus the comparison of pharmacological data relating to these compounds prepared on different occasions is only of partly-quantitative character.

The most significant representative of this group of compounds was cocaine, i.e., (—)-2α-carbomethoxy-3β-benzoyloxytropane (Fig. 6).



cocaine



3β-benzoyloxytropane

Fig. 6

In addition to the presence of a carbomethoxy group, cocaine differs from the above-mentioned tropeines also in having the benzoyloxy group in β-*syn* position related to the nitrogen atom. As it has been mentioned, tropeines and their quaternary derivatives belonging to the β-series are almost without any effect on the ganglia, whereas they have local anaesthetic action. A representative of 3β-acyloxytropanes with simpler structure is 3β-benzoyloxytropane, i.e. natural tropacocaine which is a local anaesthetic adopted also by medical practice. Also ψ-cocaine has an esterified 3β-hydroxyl group [10, 18, 56, 68, 122]; this agent shows definite advantages even over cocaine.

The basic compound of cocaine, ecgonine is completely ineffective as a local anaesthetic. A mydriatic action, characteristic again for cocaine, can be observed but when giving very large doses. Benzoylecgonine has similar characteristics.

However, a local anaesthetic action is observed with those analogues which contain either some other esterifying alkyl group instead of methyl (e.g., ethyl in cocaethylin, propyl, *iso*propyl etc.), or which have some other

acid radical (e.g. phthalic) on $C_{(3)}$. It is interesting that also *nor*-cocaine or the N-alkyl analogues are active [55, 73]. Thus it appears that stereochemical factors play a much more important part than the nature of the N or $C_{(3)}$ OH substituents in constituting a local anaesthetic action, and this feature is of considerably greater importance in the case of this pharmacological type than with tropeines with parasympatholytic action.

It can be regarded as a general rule that the presence of a 3β-benzoyl group is necessary to produce a definite local anaesthetic action in tropeines. Or even it can be stated that the given local anaesthetic action (e.g., that of cocaine, tropacocaine and ψ-cocaine) — where particulars of the mechanism have not been elucidated so far — is stereospecific; it should be borne in mind here that also among other local anaesthetics, such as α-eucaine (I) or 1-piperidino-methyl-2-benzoyloxycyclohexane (II), only one of the possible geometrical or optical isomers have local anaesthetic properties [72] (Fig. 7).

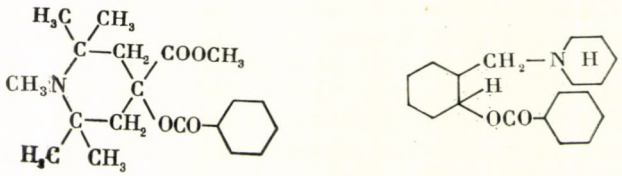


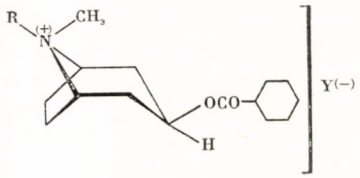
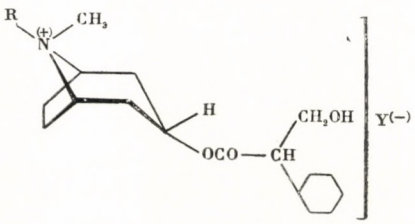
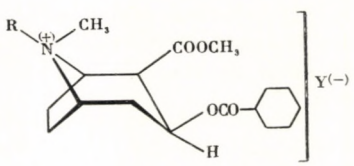
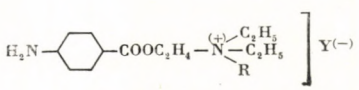
Fig. 7

Determination of the relative steric positions of the N and O atoms in these compounds is one of the next tasks; it will be attempted to correlate the results of these investigations with the character of the local anaesthetic action of these tropeines. It is to be noted that in the case of eucaine both the optically active and racemic modifications have almost the same physiological activity. This observation renders the above-mentioned correlations between steric structure and action open to discussion and permits also the conclusion that the tropane skeleton as a whole structural unit is not necessary for local anaesthetic action; another compound of definite steric structure, though different from the tropane skeleton, may have local anaesthetic properties as well.

Since data are rather limited concerning cocaine racemates, presently no more can be said about the connection of the configuration of the $C_{(2)}$ carboxyl group and the pharmacological action, than that the α steric position of this carboxyl is favourable for a local anaesthetic action.

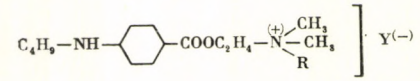
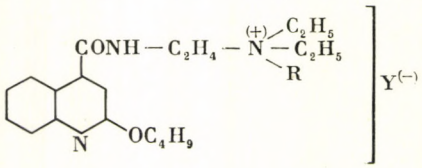
It was an accepted view in the field of local anaesthetics that they are active only when in the form of tertiary cyclic bases. The action is very quick, ensuing within a few minutes. It was stated about the prepared corresponding quaternary salts that they were ineffective as local anaesthetic agents, as a consequence of their insolubility in lipoids. A few years ago our research group [51, 89] succeeded in demonstrating that this view was erroneous, since also some quaternary ammonium salts had strong local anaesthetic action. Such compounds were in particular the N-methyl and N-benzylammonium derivatives; however, the action ensued here very slowly, only after 30 minutes. Being accustomed to expect a quick action, the activity of the quaternary compounds was apparently overlooked by some investigators. The duration of action is shown in Table XXXVIII.

*Table XXXVIII**

Structure of the quaternary compound		Conduction anaesthesia Procaine = 1	Infiltration anaesthesia Procaine = 1
	R = H, Y = Cl	2.6	2.2
	CH_3, Br	0.4	0.2
	$C_6H_5CH_2$, Br	2.0	2.2
	R = H, Y = 1/2 SO_4	0.6	0.6
	CH_3, NO_3	0.9	1.0
	$C_6H_5CH_2$, Br	2.7	3.6
	R = H, Y = Cl	7.3	9.7
	CH_3, I	1.5	15.8
	$C_6H_5CH_2$, Br	5.5	14.6
	R = H, Y = Cl	1·0	1.0
	CH_3, I	0.9	0.9
	C_6H_5, Br	2.4	6.5

* The table is compiled from data in References [37] and [89].

Table XXXVIII continued

Structure of the quaternary compound	Conduction anaesthesia Procaine=1	Infiltration anaesthesia Procaine=1
		
R = H X= Cl	6.4	8.6
CH_3 I	2.8	7.5
$C_6H_5CH_2$ Br	5.1	27.0
		
R = H Y = Br	16.0	21.4
CH_3 I	3.1	14.9
$C_6H_5CH_2$ Cl	11.7	15.6

The same observations were made also by GYERMEK [37] in connection with quaternary benzoyloxytropane derivatives (Table XXXIX). The previous inference, stating that a local anaesthetic action was characteristic of the members of the β-acyloxy series, holds true also of the corresponding quaternary compounds, in comparison with the analogous 3α-derivatives. The practical application of these agents is, however, considerably hindered by the fact that only a few from among a great number of investigated quaternary compounds were found to be free of deleterious effects on tissues.

Also eucaine, prepared by BRAUN [8], is worth mentioning. The compound is less toxic than cocaine, its activity is satisfactory, still it has not been used in practice. Analogous compounds such as the one shown in Fig. 8. are more or less active anaesthetic agents.

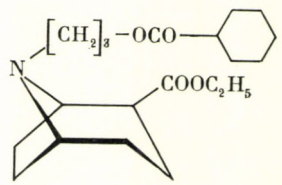
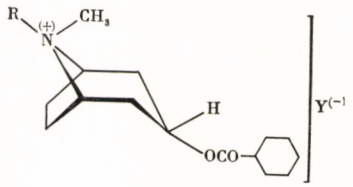
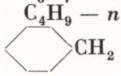
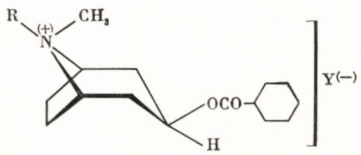
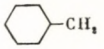


Fig. 8

The following conclusions can be drawn concerning the relationship between local anaesthetic action and the steric positions of the functional groups of the tropane skeleton.

a) Benzoylecgonine (Fig. 9) has no local anaesthetic properties.

Table XXXIX

	Local anaesthetic action on rats, infiltration method	Local anaesthetic action on frogs
	Procaine = 1	
R = H	0.5	—
CH_3	0.6	—
C_2H_5	1.4	—
$C_3H_7 - n$	1.2	—
$C_4H_9 - n$	0.6	—
	1.2	—
		
R = H	2.2	2.6
CH_3	0.25	0.4
C_2H_5	0.6	2.8
C_3H_7—n	0.8	3.0
C_4H_9—n	1.5	3.2
	2.2	2.0

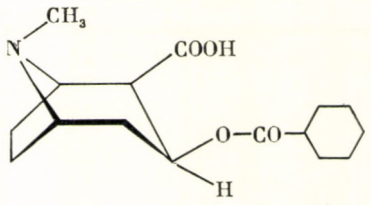


Fig. 9

However, esterification with alcohols re-establishes activity.

b) The methyl ester of ecgonine (Fig. 10) is also without action; however its esterification with benzoic acid or cinnamic acid gives again active derivatives.

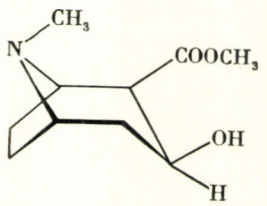


Fig. 10

Especially strong local anaesthetic action is observed only in the case of 3β-tropanols esterified with benzoic acid. From this observation the pharmacological statement has been derived that the benzoyl group is an 'anaesthesiophoric' one.

c) N-quaternization gave local anaesthetics which develop an effect only slowly, but the action is lasting.

d) The benzoic acid radical can be substituted by the isosteric thenoyl-2-carboxylic acid without any considerable change in the activity (cf. the analogy of benzene to thiophene).

CHAPTER V

TROPEINES WITH OTHER PHARMACOLOGICAL ACTIONS

NOR-TROPINE, TROPINE, TROPANE AND THEIR QUATERNARY DERIVATIVES

Nor-tropane-3α-ol and -3β-ol. — According to LEVY and HAZARD [67], a 1% solution of *nor*-tropine causes a 72% contraction of the pupil of the enucleated eye of the frog. Accordingly, the α-derivative has a miotic effect which is not shown by the β-compound. The α-derivative has no significant effect on the heart or blood vessels. Its parasympatholytic activity is also weak and uncertain [44]. On the other hand, the β-analogon (*nor-ψ*-tropine) strongly influences blood circulation, and unlike atropine, it increases blood pressure also in animals without suprarenal gland. Besides, it increases the frequency of the heart and the systolic power. According to HAZARD and POLONOWSKI [47] *nor-ψ*-tropine hinders the vagus effect of the heart both directly and also through reflector effects.

Tropane-3α-ol and -3β-ol. (Tropine and ψ-tropine.) — The α-compound has no mydriatic action [29]. Though an antimuscarine- (i.e. parasympatholytic) activity is detectable on the isolated frog heart, it is very feeble. Vagus inhibiting action is small. The compound counteracts the increased salivation of dogs produced by the administration of pilocarpine, however, large doses (100 mg/kg) are necessary for the purpose. Its actions on the heart and blood circulation are similar to those of atropine, though they are considerably weaker; best characterized is its hypotensive action. Intestinal tone is *in situ* increased by the α-compound on the intestine of dogs, while atropine has just the opposite action. This finding, together with the observation that acetylcholine retains its hindering action on the heart even after previous administration of tropine, indicates that tropine has no vagus blocking action [101].

β-Tropanol was much less investigated. In contrast with the α-compound, it contracts blood vessels and increases blood pressure in this way. This action is of the same character as that of nicotine. This derivative, just like the α-compound, shows no vagolytic activity on dogs [44].

As regards the α-type, consideration of the above facts allows the conclusion that the *nor*-compound has less marked vegetative action. While the *nor*-compound shows also a property (miosis) which is in contrast with the behaviour of atropine, α-tropanol, on the other hand, is rather similar to atropine as regards its actions. Though parasympathomimetic effects still occur, parasympatholytic properties become more and more pronounced. The structural prerequisite of parasympatholytic action is thus given by the presence of an $N-CH_3$ group in the tropane skeleton. No conclusions can be drawn concerning the β-series, because of the small number of respective investigations.

The quaternary salts of tropine [39, 81] are weak ganglion blocking agents without any practical significance. The same holds true for tropane-3β-ol.

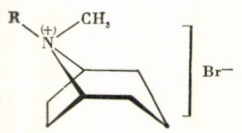
Among the homologues of tropine, 1-methyltropine was investigated by RAO [100]. This compound is a stimulant of the central nervous system and causes tremor as well as irregular tonoclonic spasms on mice, the final result being the paralysis of respiration and diastolic heart stoppage. In 4% solution the compound produces a transitory anaesthesia of the eye of the rabbit. It can stimulate rabbit intestine at a concentration of 1 : 20000.

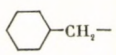
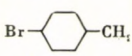
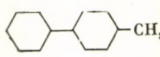
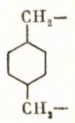
According to HAZARD [45], tropinone, the oxidation product of tropine differs but little from the pharmacological behaviour of the parent compound.

Also 3-chlorotropane was investigated by HAZARD. This compound paralyses the vagus and has no mydriatic action. It has probably ganglion stimulating properties of the character of nicotine.

The monoquaternary derivatives of tropane [88] are ganglion blocking agents, whereas the bis-quaternary compounds reveal curare-like activity.

Table XL

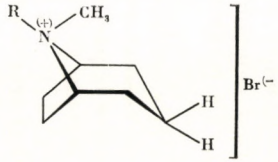
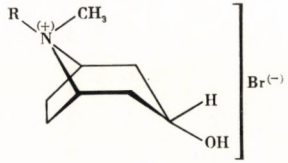
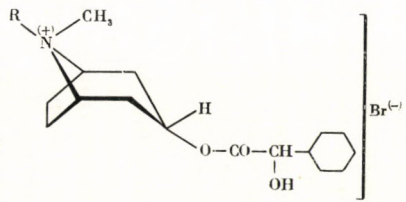
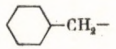
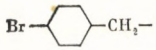
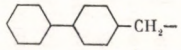


R	Ganglion blocking	Parasympatholytic	Anti-nicotinic*	Curare-like**
	action			
NA—85 CH_3—	3	1/200	10	80
N—415 	4	1/20	—	—
N—416 	15	1/15	2	30
N—421 	30	1/50	1/5	—
N—423*** 	< 2	1/60	> 20	7
N—426 $C_2H_5OCOCH_2$—	< 1	1/40	> 10	—
TEA	1	—	50	—
Atropine	—	1	—	—
Hexamethonium bromide	15	—	1	—
N—147 (cf. [90])	—	—	—	5

Notes:

* Antinicotinic action on intestine, γ/10 ml
** Curare-like action was tested on frogs. Action: γ/g
*** Compound N—423 is a bis-quaternary derivative

Table XLI

R			
	Ganglion blocking action is taken as unit if R = CH_3		
CH_3—	1.0	1.0	1.0
	1.3	1.0	0.7
	5.0	2.5	4.2
	10.0	8.0	8.8

Inferences concerning the relationship of action and the structure of the quaternary group can be drawn from Table XL. It is seen that the ganglion blocking activity is influenced by the introduction of a quaternary group to the same extent as it was already demonstrated for tropeines. This result also shows that appearance of a ganglion blocking action in tropeines is almost exclusively due to the presence of the quaternary ammonium group. The influence of the acyloxy group on this characteristic is only of secondary importance. Compounds listed in Table XLI afford still additional evidence for the correctness of this statement.

From a pharmacological study of these compounds it could be derived that the various quaternary groups influenced the ganglion blocking properties of the products in an almost identical way whether in tropane, tropane-3α-ol, or in the racemic 3α-mandelyloxytropane. As it is seen, the extent of the changes of activity is practically the same — except for *p*-bromobenzyl-α-tropinium bromide — and it is within the margin of error of biological methods. It was also ascertained that the exchange of the quaternizing methyl group against benzyl did not increase ganglion blocking activity. On the other hand, increased activity after substitution with *p*-bromobenzyl was 4.5 times, and with the *p*-phenylbenzyl group was 8 to 10 times as great as the original. A more detailed version of this Table, containing all the different main and side-effects was of considerable help to us in selecting the compounds with optimum properties, and among them Gastropine. Since this Table shows one of the most important connections between action and structure or steric structure, it should be developed further. For this purpose in the field of tropeines, the synthesis and pharmacological study of the quaternary derivatives of mandeloxytropane and of their N-diastereoisomers will be required.

TROPINE ETHERS WITH ANTIHISTAMINIC ACTION

Etherification of tropine, like that of 4-hydroxypiperidine, can be carried out with considerable difficulty. Consequently, the number of tropine ethers prepared is far less than that of the esters. The first compound of this type was the methyl ether of tropine [17]. However, this compound was not a pure and uniform product [52].

Recently the tropine ether of benzhydrol and its ring-substitution products have been described [91, 97, 113]. These compounds possess considerable antihistaminic activity. The reason for their preparation was partly that the basic alkyl ethers of benzhydrol had been known as strong antihistaminics (e.g. benadryl = β-dimethylaminoethylbenzhydryl ether) [71, 102]. Furthermore, these syntheses were forwarded also by the fact that tropine could be readily transformed into the benzhydryl ether by diphenyldiazomethane, prepared, in turn, from benzophenone in a convenient way [106]. Strong and long-lasting effects are shown especially by benzhydryl ethers chlorinated in the *para-* or *ortho*-positions [31]. E.g., tropine-*p*-chlorobenzhydryl ether is capable of saving guinea-pig as long as for 7 to 8 days from histamine bronchospasm. Even 0.1 g/kg of this compound is sufficient to protect the animal against a lethal dose of histamine. No report has been made so far about any detailed clinical study of the compound.

According to ZEILE and HEUSNER [124], the benzhydryl ether of scopoline shows no significant antihistaminic activity.

TROPEINES WITH ACTION ON THE CENTRAL NERVOUS SYSTEM

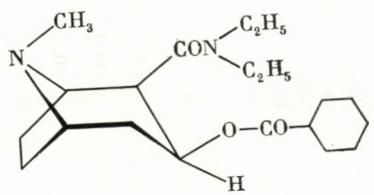
It has been known long since that atropine, besides its vegetative parasympatholytic effects, has a considerable central activity. Thus, higher doses of atropine bring about fits of rage, hallucination and, in general, a strong excitation of the central nervous system. Quaternization causes these effects to disappear, only the vegetative actions are retained. On the other hand, scopolamine has strong depressive action: once it was even employed as a basal narcotic. Even today this agent is used — although only to a limited extent — to calm raging patients suffering from mental disease. Scopolamine effects can also be eliminated by quaternization. Administration of large doses of cocaine result again in central reactions. All these central effects are, however, useless from the therapeutical point of view, except in the case of scopolamine. For the time being the question is not decided yet, whether the mentioned central actions are characteristic only of the tertiary tropeyl-tropeines, or also of other strongly parasympatholytic tertiary tropeines, such as the benzilic esters and xanthene-9-carboxylic esters. Besides, information should be obtained also concerning the central actions possessed by those parasympatholytic agents which are not of tropane structure, still have pharmacological characteristics similar to those of atropine.

In the course of a search after agents of central action, LONG, LANDS and ZENITZ [71a] prepared some *nor*-tropine derivatives, namely 9-phenothiazinyl-alkyl-*nor*-tropanes. On basis of the known central effects of chlorpromazine, it was assumed that the phenothiazine ring had *ab ovo* an important role in displaying the expected central actions of the drug. Studied compounds are summarized in Table XLII.

From the data shown in this Table it can be concluded that only those compounds will be characterized by a central stimulating action in which the phenothiazin ring is connected with the tropane skeleton through a propylene bridge. Longer or shorter carbon chains profoundly reduce activity.

Compounds containing an α-hydroxyl group at $C_{(3)}$ have higher activity than the otherwise analogous $C_{(3)}$ β-derivatives. Substitution of the hydroxyl group by hydrogen is unfavourable, while chloro-substitution in the phenothiazine ring results in increased activity. The presence of a trimethoxybenzoyl group is again detrimental, although this radical has a positive role in several compounds of central action, such as reserpine, mescaline, etc.

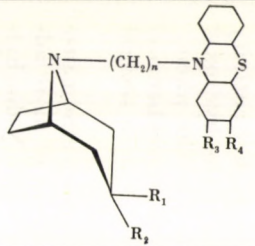
JORDAN et al., starting with the fact that higher doses of cocaine cause hallucinations, attempted to obtain some new cocaine derivatives of more advantageous actions. In the course of this investigation (+)-2-N,N-diethyl-

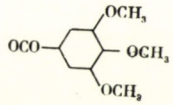
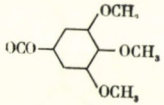


(+)-2-N,N-diethylcarboxamido-3β-benzoyloxytropane

Fig. 11

Table XLII



R_1	R_2	n	R_3	R_4	Central actions*		Adrenolytic activity** Dose necessary to reverse the action of adrenaline, mg/kg	
					Barbiturate potentiation	Rectal temperature	Mean value	Extreme values
H	OH	3	H	H	14.0	8.5	0.27	0.1 — 0.5
OH	H	3	H	H	6.5	6.0	0.58	0.2 — 1.6
H	OH +	3	Cl	H	100.0	100.0	0.24	0.1 — 0.6
OH	H	3	Cl	H	34.0	25.5	1.1	0.2 — 2.0
H	H	3	H	H	10.0	3.5	0.3	0.1 — 0.4
H	H	3	Cl	H	22.5	16.5	0.9	0.2 — 1.6
H		3	H	H	< 1.0	< 1.0	0.13	0.05— 0.2
	H	3	H	H	< 1.0	< 1.0	8.0	6.0 —10.0
H	OH	2	H	H	< 1.0	< 1.0	> 10.0	~
H	OH	4	H	H	< 1.0	< 1.0	4.5	2.0 — 8.0
H	OH	5	H	H	< 1.0	< 1.0	> 10.0	~
H	OH	3	H	Cl	8.0	3.0	0.4	0.2 — 0.8
H	OH	3	Br	H	100.0	94.0	0.26	0.1 — 0.4

* Activities for the individual compounds are given by regarding the activity of the compound marked with + to be 100%.

Barbiturate potentiation. The mean sleeping period produced on mice by the i.p. administration of 100 mg/kg Evipan *R* was taken as the standard. Potentiation was measured by giving subcutaneously 45 minutes earlier (before the Evipan) as much of the compound to be tested as to produce a 100% prolongation of sleep. With the compound marked by + this quantity was 1.7 mg/kg.

Rectal temperature was measured on mice in groups of 10 animals each. Subcutaneous doses were increased by the value of 0.3 log, and results obtained with the three last doses were taken as the extreme value of the effective dose. The quantity of compound (ED_{50}) necessary for decreasing the rectal temperature by 5 F° was graphically evaluated by the aid of the above data. With the compound marked by + this quantity was 1.3 mg/kg.

** Adrenolytic activity was measured on dogs, and the minimum dose necessary for reversing the hypertensive action of 1—5 γ/kg adrenaline was indicated. All the compounds tested were hydrochlorides except for the two trimethoxybenzoates which were employed as the acetate salts.

carboxamido-3β-benzoyloxytropane chlorohydrate was subjected to a very detailed pharmacological study.

On rabbits and mice, this compound showed much more pronounced central stimulating action than cocaine, however it was rather toxic. Interest in compounds with so-called psychotonic effect directed at the central nervous system gets today more and more in the foreground. Research on tropeines is expected to bring many more interesting results in this field.

CHAPTER VI

FUNDAMENTAL PROBLEMS OF STRUCTURE, ACTION AND OF ANTAGONISM

It is seen from the above discussion that tropeines, acting as antagonists on the three points of attack of acetylcholine, may differ from each other as regards their structure. It is a just assumption that these molecules still must contain a structural element or some characteristic which renders possible antagonism at all the three points of attack. PFEIFFER [96] was the first to point out that the interprosthetic distance between the nitrogen atom and the alcoholic and carbonyl oxygen was 5 to 7 Å, respectively, both in acetylcholine and atropine (Fig. 12). Furthermore, he argued that the same interprosthetic distances occur also in other parasympathomimetic compounds which can be antagonized by atropine (e.g. doryl, prostigmine, pilocarpine, etc.).

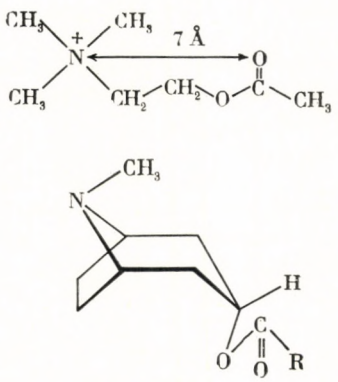


Fig. 12

According to this theory, the distance of 7 Å between N and the carbonyl oxygen of acetylcholine may permit attachment to the nerve terminals as well as to cholinesterase. The same structural attribute allows tropeines to become affixed; competitive antagonism is explained by the fact that the nitrogen of compounds with tropane skeleton is found in an 'umbrella' structure.

In testing this theory, we can start with the fact that if the interprosthetic distance of 5 and 7 Å, resp., is really a significant factor of parasympatholytic activity, this distance should occur only in the *anti*-tropeines of the α-series, but not in the β-compounds. It would appear that the *anti*-position of the hydroxyl group in atropine decides the possibility of a parasympatholytic action from the very beginning, so that this characteristic would hardly be subjected to any further influence by introducing different quaternary groups. In *syn-*

compounds, where the given structure *ab ovo* excludes the necessary and optimum distance of 5 and 7 Å, resp., no parasympatholytic action should occur. However, according to experimental evidence, the difference is not so marked. A more pronounced difference can be observed on the second point of attack of acetylcholine, i.e., on the vegetative ganglia. However, in this case the free or esterified hydroxyl group at $C_{(3)}$ has no decisive role, since, as it has been mentioned above, analogous quaternary tropanes derived from these 3-acyloxy compounds rather approach the same activity (Table XLI).

Consequently, the conclusion may be drawn that contrary to parasympatholytic activity, ganglionic effects of tropeines are determined not by the *syn-* or *anti*-position, or by the presence or absence of the $C_{(3)}$ hydroxyl group, but primarily by the nature and steric position of the substituents on the quaternary nitrogen atom. Members of the *syn-* and *anti*-series display no selective affinity for the receptors of vegetative ganglia, but they affect — mostly in the form of blocking — sympathetic and parasympathetic ganglia alike. The observation that the ethyl or even more the methyl group may be replaced by an N-benzyl group in quaternary tropinium salts appears to be true also in respect of ganglion blocking action. Thus the ganglion blocking activity of, e.g., N-benzyl-β-benzoyloxytropanium bromide is just as weak as that of the corresponding methyl analogon. Thus the situation is quite different from the case of higher alkyl derivatives, where the above structural change corresponds to an increase in activity by a factor of 3 to 6 as compared with TEA. In N-quaternary aralkyl salts, however, introduction of a *p*-substituent fundamentally changes the character of the compound, since tropeines with such quaternary groups are very effective cholinolytic agents. Probably, the cause of this difference between the two types is to be found in the relatively high or low electron density of the quaternary nitrogen atom, produced there by the substituents. According to present views, for obtaining a cholinergic action both on the parasympathetic terminal apparatus and on the vegetative ganglia, it is necessary to have such N-aralkyl quaternary ammonium compounds in which the preponderant alkyl group is methyl (e.g. acetylcholine, TMA, prostigmine etc.).

Least active ganglion blocking agents in the *syn*-series are the methyl and ethyl derivatives of the 3-benzoyloxytropanes, and the same holds true as regards activity on the myoneural ganglia. From the aspect of curare-like action, butyl derivatives were found to possess highest activity both in the *syn* and *anti* benzoyloxy series. Moreover, these compounds have also a considerable ganglion blocking action. Thus we could support our former observation also through results obtained in this series, according to which curare-like activity and ganglion blocking action run about parallel in the case of the monoquaternary compounds within one group of compounds, while with bisquaternary derivatives the activity is very much shifted toward curare-like activity.

A very important role is assigned to the 3α-acyloxy group in contributing to curare-like activity, since selectivity and consequently the therapeutical value of the compound critically depends upon the nature of this group (simple aromatic acid or arylaliphatic hydroxy acid). However, the presence of a 3α-acyloxy group is not a criterion of curare-like action, as it can be seen from a survey of the bis-tropinium compounds listed in Table XXXI; the activity of these derivatives is nearly as high as that of *d*-tubocurarine.

However, while the action of bis-acyltropinium derivatives can be antagonized by prostigmine, this is not so in the case of bis-tropanium salts containing no oxygen. This observation permits the conclusion that curare-like activity is such a two-phase process where the structural criteria of action and antagonizability are determined by the receptor surfaces themselves. There are good reasons to believe that drug research must proceed on the way indicated above to obtain a better knowledge of the structure of receptors and their function which follows from it.

REFERENCES

1. ALDER K., DORTMANN H. A.: Chem. Ber. *86*, 1544 (1953).
2. ANITSCHKOW, S. V.: Fiz. Zhurnal (in Russian) *36*, 64 (1950).
3. ARCHER, W. L., CAVALLITO, C. J., GRAY, A. P.: J. Am. Chem. Soc. *78*, 1227 (1956).
4. Austral. Patent: 23270/56.
5. BARLOW, R. B., ING, H. R.: Brit. Journ. Pharmacol. Chemother. *3*, 298 (1948).
6. BEILSTEIN's Handbuch der organischen Chemie, 4. Auflage Bd. *27*, 98; I. Erg: 246; II. Erg.: 62.
7. BRAUN, C. J., RÄTH, K.: Ber. dtsch. chem. Ges. *53*, 601 (1920).
8. BRAUN, V. J.: Ber. dtsch. chem. Ges. *53*, 235 (1918).
9. BRAUN, V. J., MÜLLER, E.: Ber. dtsch. chem. Ges. *51*, 235 (1918).
10. BRODT, K., KÜMMEL, W.: Münch. Med. Wschr.. *71*, 849, 851 (1924).
11. CARR, F. H., REYNOLDS, N. C.: J. Chem. Soc. *101*, 946 (1912).
12. CUSHNY, A. R.: J. Pharmacol. Exp. Ther. *15*, 105 (1920).
13. CUSHNY, A. R.: J. Physiol. *30*, 176 (1904).
14. DALE, H. H.: J. Physiol. *80*, 10 P (1933).
15. DALE, H. H.: Proc. Roy. Soc. Med. *28*, 319 (1935).
16. DALE, H. H., FELDBERG, W.: J. Physiol. *82*, 121 (1934); *86*, 353 (1936).
17. DRP. 106.492 (1900); C. 1900. I. 1082.
18. EINHORN, A., MARQUARDT, A.: Ber. dtsch. chem. Ges. *23*, 473, 981 (1890).
19. ENGELHARDT, A., WICK, H.: Arzneim. Forsch. *7*, 217 (1957).
20. EQUOSANOL, SCHWARZ, A. G.: Monheim/Düsseldorf.
21. ERBE, H.: Dissertation, München 1903. Quotation in [95] p. 185.
22. FELDBERG, W.: Brit. Med. Bull. *7*, 1531 (1950).
23. FELDBERG, W., GADDUM, J. H.: J. Physiol. *81*, 305 (1934).
24. FODOR, G., KOCZKA, K., LESTYÁN, J.: Magyar Kémiai Folyóirat *59*, 242 (1953); C. A. *48*, 10029.
25. FODOR, G., NÁDOR, K.: J. Chem. Soc. *1953*, 721.
26. FODOR, G., NÁDOR, K.: Nature *169*, 462 (1952).
27. FODOR, G., TÓTH, J., VINCZE, I.: J. Chem. Soc. *1955*, 3504.
28. FOSTER, R., GOODFORD, P. J., ING, H. R.: J. Chem. Soc. *1957*, 3575.
29. FRASER, T. R.: Proc. Roy. Soc. Edinburgh *1869*, 556.
30. FRIEDMANN, A. H., SMITH, C. M.: Arch. Int. Pharmacodyn. *120*, 160 (1959).
31. FROMMER, I.: DBP. 1,020.634.
32. GOODMAN, L. S., GILMAN, A.: The Pharmacological Basis of Therapeutics. McMillan, New York 1941.
33. GOTTLIEB, R.: Arch. Exp. Path. Pharm. *37*, 218 (1896).
34. GRAY, A. P., ARCHER, W. L., SCHLIEPER, D. C., SPINNER E. E., CAVALLITO, C. J.: J. Am. Chem. Soc. *77*, 3536, 3648 (1955).
35. GRAY, A. P., SPINNER, E. E., SCHLIEPER, D. C., CAVALLITO, C. J.: J. Am. Chem. Soc. *77*, 3533 (1955).
36. GRUBE: Dissertation, Göttingen 1905. Quotation in [95] pp. 185 and 397.
37. GYERMEK, L.: Nature *171*, 788 (1953).
38. GYERMEK, L., NÁDOR, K.: Acta Physiol. Acad. Sci. Hung. *4*, 159 (1953).
39. GYERMEK, L., NÁDOR, K.: Acta Physiol. Acad. Sci. Hung. *4*, 341 (1953).
40. GYERMEK, L., NÁDOR, K.: Arch. Int. Pharmacodyn *113*, 1 (1957).
41. GYERMEK, L., NÁDOR, K.: Pharmazie *10*, 485 (1955).
42. GYERMEK, L., SZTANYIK, L.: Acta Physiol. Acad. Sci. Hung. *2*, 41 (1951).
43. HAMET, R.: Rev. de pharmacol. *2*, 159 (1932).

44. Hazard, R.: Arch. Int. Pharmacodyn. *38*, 271 (1930).
45. Hazard, R.: Arch. Int. Pharmacodyn. *41*, 124 (1952).
46. Hazard, R., Polonowski, M.: Ber. gesamt. Physiol. *44*, 159 (1928); *50*, 142 (1929).
47. Hazard, R., Polonowski, M.: Compt. Rend. Acad. Sci. (Paris) *190*, 214 (1930).
48. Hefter's Handbuch, detailed data in Reference [92] p. 27.
49. Herman, L., Shaw, F. H.: J. Pharm. Pharmacol. *10*, 356 (1958).
50. Herman, L., Shaw, F. H., Rosenblum, E. I.: J. Pharm. Pharmacol. *10*, 348 (1958).
51. Herr, F., Nádor, K., Pataky, Gy., Borsy, J.: Arch. Exp. Path. Pharm. *217*, 447 (1953).
52. Heusner, A.: Personal communication in April, 1958.
53. Hildebrandt, H.: Arch. f. exp. Path. *53*, 76 (1905).
54. Holme, P. E., Jenden, D. J., Taylor, D. B.: Nature *159*, 86 (1947).
55. Huoben, J.: Fortschritte der Heilstoffchemie. Vol. III/2, p. 215.
56. Houben, J.: Fortschritte der Heilstoffchemie. Vol. III/2, p. 217.
57. Hromatka, O.: DRP. 655.404 (1938).
58. Issekutz, B.: Arch. Exp. Path. Ther. *19*, 99 (1917).
59. Issekutz, B.: Arch. Exp. Path. Pharmacol. *215*, 283 (1952).
60. Issekutz, B.: MTA. Orvosi Tud. Oszt. Közl. (in Hungarian) *3*, 61 (1952).
61. Jowett, H. A. D., Pyman, F. L.: J. Chem. Soc. *95*, 1020 (1909).
62. Kibjakow, A. W.: Pflüger's Archiv. *232*, 432 (1933).
63. Kimura, K. K., Unna, K. R.: J. Pharmacol. Exp. Therap. *98*, 286 (1950). .
64. Kimura, K. K., Unna, K., Pfeiffer, C. C.: J. Pharmacol Exp. Therap. *95*, 149 (1949)
65. Kreitmair, H.: Klin. Wochenschr. *15*, 676 (1936).
66. Ladenburg, A.: Ann. d. Chem. *217*, 82 (1883).
67. Levy, J., Hazard, R.: Arch. Int. Pharmacodyn. *36*, 26 (1930).
68. Liebermann, C., Giesel, F.: Ber. dtsch. chem. Ges. *23*, 508, 926 (1890).
69. Liebermann, C., Limpach, L.: Ber. dtsch. chem. Ges. *25*, 927 (1892).
70. Lindenmann, A.: Helv. Chimica Acta. *42*, 490 (1959).
71. Leow E. R., Kaiser, M. E., Moore, V.: J. Pharmacol. Exp. Therap. *83*, 120 (1945).
71a Long, J. P., Lands, A. M., Zenitz, B. L.: J. Pharmacol. Exp. Therap. *119*, 479 (1957).
72. Mannich C., Hönig, P.: Arch. Pharm. *265*, 598 (1927).
73. Merck, W., Ber. dtsch. chem. Ges. *18*, 2954 (1885); *21*, 48 (1888).
74. Moffett R. B., Aspergren, B. D.: J. Am. Chem. Soc. *78*, 3448 (1956).
75. Nádor, K.: MTA Kémiai Oszt. Közl. (in Hungarian) *4*, 1 (1954); C. A. *49*, 13598.
76. Nádor, K.: MTA Orvosi és Biológiai Oszt. Közl. (in Hungarian). *10*, 221 (1959); C. A. *54*, 3722.
77. Nádor, K.: Lecture, prepared for the Congress of the German Pharmacological Society in September, 1959.
78. Nádor, K.: Lecture, prepared for the Congress of the Hungarian Chemical Society, Budapest, May 14, 1958.
79. Nádor, K., Gyermek, L.: Acta Chim. Acad. Sci. Hung. *2*, 95 (1952).
80. Nádor, K., Gyermek, L.: Acta Chim. Acad. Sci. Hung. *2*, 369 (1952).
81. Nádor, K., Gyermek, L.: Acta Chim. Acad. Sci. Hung. *3*, 323 (1953).
82. Nádor, K., Gyermek, L.: Arzneim. Forsch. *8*, 336 (1958).
83. Nádor, K., Gyermek, L.: Orvosi Hetilap (in Hungarian) *1958*, 1504
84. Nádor, K., Gyermek, L.: Magyar Kémiai Folyóirat (in Hungarian) *57*, 349 (1951).
85. Nádor, K., Gyermek, L.: Hungarian Patent 144,335 (1958); USP 2,833.773.
86. Nádor, K., Gyermek, L.: Hungarian Patent 143,935 (1958).
87. Nádor, K., Gyermek, L.: Hungarian Patent 145,663 (1959).
88. Nádor, K., Gyermek, L., Markó, M.: Vegyipari Kutató Intézetek Közleményei (in Hungarian) *4*, 80 (1951); C. A. *52*, 16390.
89. Nádor, K., Herr, F., Pataky, Gy., Borsy, J.: Nature, *171*, 788 (1953)
90. Nádor, K., Küttelné-Issekutz L., Kovatsits, M.: Magyar Kémiai Folyóirat (in Hungarian) *56*, 440 (1950); C. A. *47*, 133.
91. Nield, C. H., Bosch, W. X. F.: USP. 2,782.200 (1956).
92. Oettingen, W. F.: Die Atropingruppe, in Hefter's Handbuch der experimentellen Pharmakologie. Erg. Werk. Band III. S. 1—47. Verlag Springer, Berlin 1937.
93. Ohnacker, G., Kottler, A.: DBP. 1,042.593 (1958).
94. Paton, W. D. M., Zaimis, E. J.: Brit. Journ. Pharmacol. Chemother. *4*, 381 (1949).
95. Pfankuch, E.: »Atropin« in Huoben, J.: Fortschritte der Heilstoffchemie. Band III/2. S. 323. Walter de Gruyter Verlag, Berlin 1939.
96. Pfeiffer, C. C.: Science *107*, 94 (1948).
97. Philips, R. F.: USP. 2,595.405 (1952).

98. Polonowski, M.: Compt. Rend. Acad. Sci. (Paris) *180*, 1755 (1925).
99. Pyman, F. L., Reynolds, W. C.: J. Chem. Soc. *1919*, 476.
100. Rao, G. R. R. Quart. Journ. Pharm. Pharmacol. 7, 227 (1934).
101. Raymond-Hamet, M.: Compt. Rend. Acad. Sci. (Paris) *188*, 820 (1929).
102. Rieveschl, G.: USP. 2,421.714.
103. Rothlin, E., Täschler, M., Konzett, H., Cerletti A.: Experientia, *10*, 142 (1954).
104. Sáry, B.: Orvosi Hetilap (in Hungarian) *1958*, 1508.
105. Schiller, A.: Arch. Exp. Path. Pharm. *38*, 71 (1897).
106. Smith, L. J., Howard, K. L.: Organic Syntheses. Coll. Vol. 3., p. 351. J. Wiley and Sons. Inc., New York, 1955.
107. Smith, P. K., Hemmingway, A.: Proc. Soc. Exp. Biol. Med. *63*, 206 (1946).
108. Somogyi, I., Kukor, I.: Gyógyszereink (in Hungarian) *1959*, No. 36. 15.
109. Stoll, A., Jucker, E.: Angew. Chem. *66*, 376 (1954).
110. Stoll. A., Jucker, E.: Chimia *9*, 25 (1955).
111. Stoll, A., Jucker, E., Ebnöther, A.: Helv. Chimica Acta, *38*, 559 (1955).
112. Stoll, A., Jucker, E., Lindemann, A.: Helv. Chimica Acta, *38*, 571 (1955).
113. Stoll, A., Jucker, E., Lindemann, A.: USP. 2,800.477 (1957); Belg. Pat. 545.227 (1957)
114. Stoll, A., Lindemann, A., Jucker, E.: Helv. Chimica Acta *36*, 1506 (1953).
115. Süess, R.: Helv. Chimica Acta *42*, 495 (1959).
116. Surmont, H., Polonowski, P.: Bull. Acad. Med. (Paris) *95*, 370 (1926).
117. Szécsi, K.: Orvosi Hetilap (in Hungarian) *1958*, 1954.
118. Tanret, G.: Ber. gesamt. Physiol. *22*, 14 (1924).
119. Werner, L. F.: J. Am. Chem. Soc. *40*, 669 (1918).
120. Wichura, W.: Z. Exp. Path. Ther. *20*, 1 (1919).
121. Wick, H.: Arch. Exp. Path. Pharm. *213*, 485 (1951).
122. Willstätter, R., Wolfes, O., Mäder, H.: Annalen der Chemie *434*, 111 (1923).
123. Zeile, K.: DBP. 1,010.070 (1957).
124. Zeile, K., Heusner, A.: Chem. Ber. *90*, 2809 (1957).
125. Zima, O., Seitz, G.: DBP. 1,034.183 (1958).

I. V. TORGOV

ACHIEVEMENTS IN THE TOTAL SYNTHESIS OF NATURAL STEROIDS

INTRODUCTION

The importance of total synthesis in organic chemistry is difficult to overestimate and it is still the crowning point of any endeavour in this field, including the area of steroids. It is therefore not surprising that work in this direction was begun immediately after the structure of the steroid skeleton had been established, although the stereochemistry of these compounds or even the location of some of their functional groups was still not known.

In a sense, the first steps towards the total synthesis of steroids may be considered to be the work by BARDHAN—SENGUPTA and RUZICKA devoted to the synthesis of cyclopentanophenanthrene derivatives. Of course the present successes owe their existence to the whole triumphant march of organic chemistry and it is very difficult to conceive a synthesis of even the simplest steroid hormones without, say, the ARNDT—EISTERT reaction, selective hydrogenation, or stereospecific reduction. The part played by the MANNICH—ROBINSON condensation has received universal acknowledgment, providing the means for building up the six-membered rings, and, what is especially valuable, the possibility of constructing polycyclic systems with angular methyl groups. The BIRCH reduction permitted JOHNSON to synthesize a number of steroids of the androstane group, and diene condensation was an initial stage in WOODWARD's and SARETT's syntheses. The seemingly simple method of protecting the carbonyl group by means of ethylene glycol made possible (or at least greatly facilitated) the synthesis of Δ^4-3-ketosteroids and sapogenins.

In the present review we have limited ourselves to an illustration of only those syntheses that have led to natural steroids or their racemic modifications. We have deliberately omitted (with few exceptions) the synthesis of compounds closely related to the natural products or the synthesis of their numerous isomers, in order to keep the survey within reasonable limits.

As in other branches of chemistry, the pace of total syntheses is ever accelerating. The period from 1940 to 1950 saw the preparation of only the simplest steroid hormones, equilenin and oestrone. In the succeeding decade the total synthesis of cholesterol, of all the sex and cortical hormones (including such complex products as cortisone and aldosterone), of the sapogenins and of a number of steroid alkaloids was accomplished. Ergosterol, the bile acids, the cardiac aglycones and other steroid alkaloids are all now "awaiting their turn". There is scarcely room for doubt that the present state of organic chemistry in general and of steroid chemistry in particular will permit these syntheses to be carried out within the next few years, or even months.

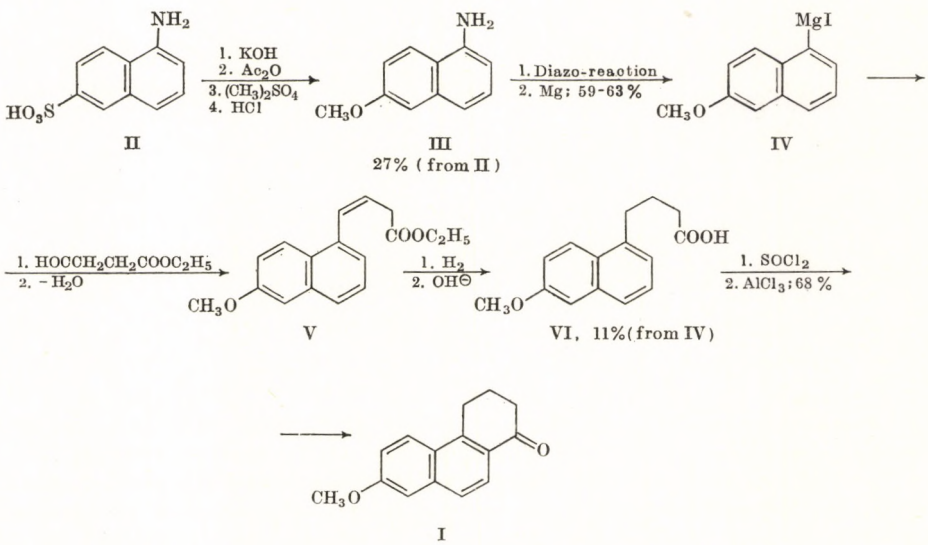
The total synthesis of the steroids has as yet received no applications of industrial importance, but the continuous improvement in techniques allows one to expect the achievement of methods for the practical synthesis not only of the relatively simple hormones, such as oestrone, but also of such complex compounds as cortisone or aldosterone.

CHAPTER I

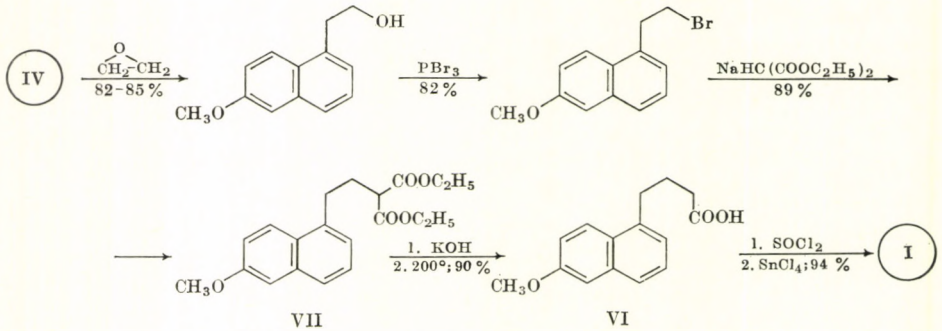
SYNTHESES OF EQUILENIN

SYNTHESIS ACCORDING TO BACHMANN

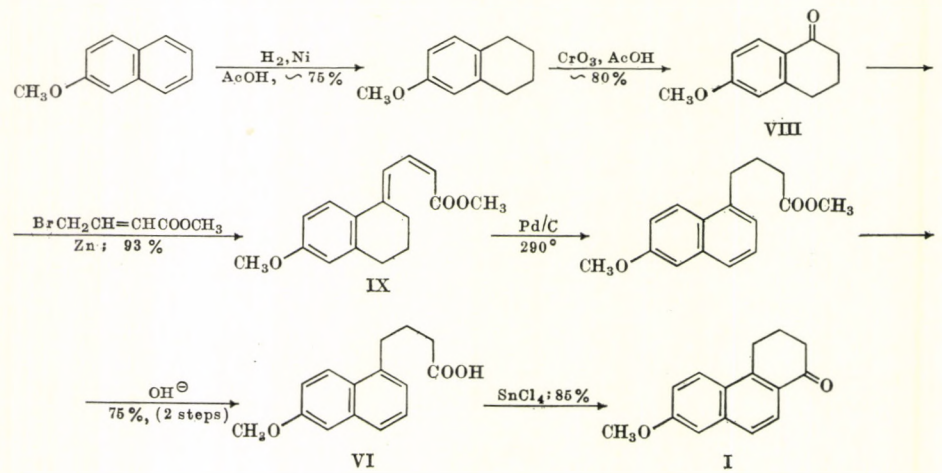
The preparation of equilenin by BACHMAN, COLE and WILDS [2, 3] in 1939—40 was the first total synthesis of a steroid hormone. BACHMANN started with the tricyclic ketone (I) prepared earlier by BUTENANDT and SCHRAMM [5] from CLEVE's acid (II). Fusion of the latter with potassium hydroxide yielded an aminonaphthol that on methylation with dimethyl sulphate gave 6-methoxy-1-aminonaphthalene (III). Iodine was introduced in place of the amino group by means of the diazo reaction, and the iodine derivative was converted to the organomagnesium compound (IV) which BACHMANN employed to react with succinic semialdehyde ester. The intermediate was easily dehydrated to the ester (V). Consecutive hydrogenation and hydrolysis of the latter produced the acid (VI), the chloride of which was converted by FRIEDEL—CRAFTS reaction to ketone I.



The process was improved by BACHMANN [2], COOK [7, 8] and WILDS [14], utilizing condensation with ethylene oxide and the malonic ester synthesis.



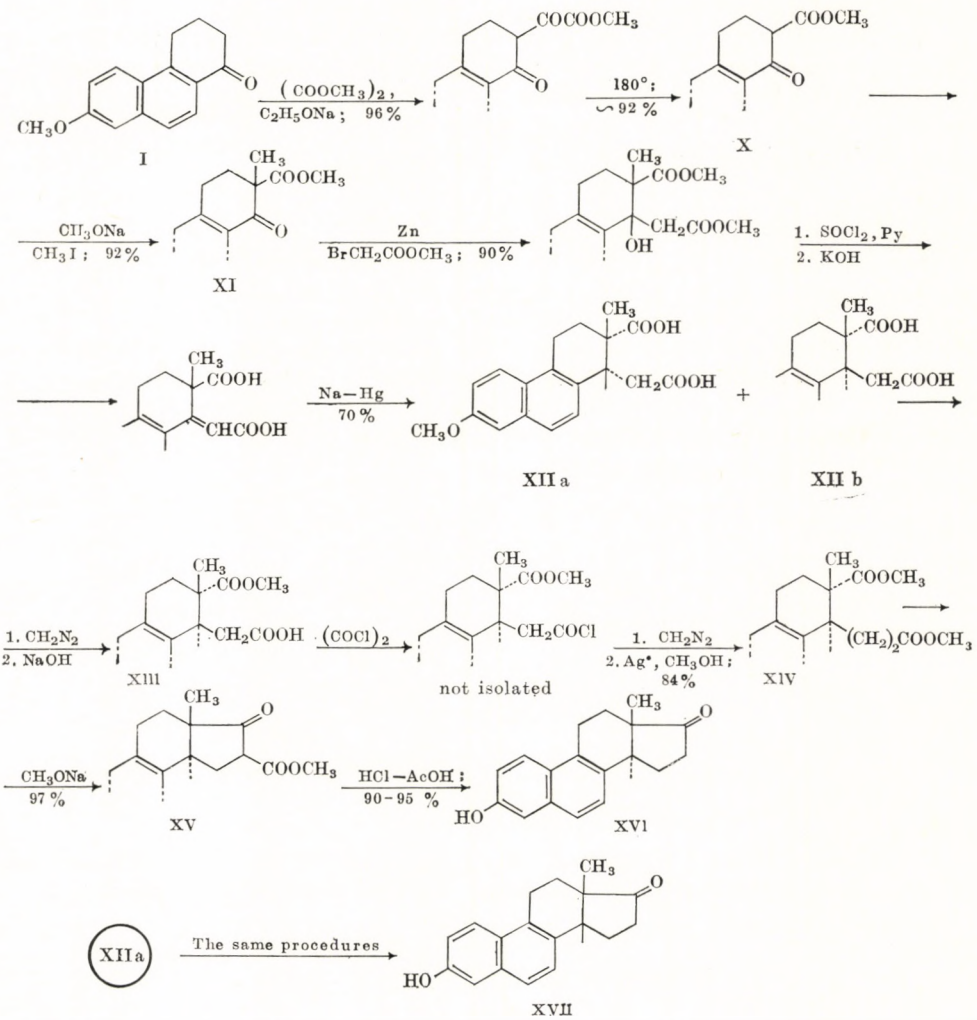
Later, STORK [13] proposed a much more convenient synthesis of the cyclic ketone I, starting with nerolin (β-methoxynaphthalene). Hydrogenation and subsequent oxidation of the latter gave 6-methoxytetralone-1 (VIII) (this compound was used later also by other workers in the synthesis of oestrone, see below). REFORMATSKY condensation of VIII with methyl γ-bromocrotonate was accompanied by elimination of water and gave the unsaturated ester (IX) that on heating with Pd/C underwent isomerization to the ester of the acid (VI) mentioned above.



Cyclization of VI gave the ketone I in an over-all yield of about 36% based on nerolin, or about 60% calculated for methoxytetralone (VIII).

In order to form ring D, BACHMANN first condensed the cyclic ketone I with oxalic ester. Pyrolysis of the produced glyoxylic ester in the presence of powdered glass yielded the keto-ester X, which was methylated to XI. Then BACHMANN introduced the side chain by REFORMATSKY reaction, obtaining, on dehydration through the chloride, alkaline hydrolysis and reduction, an approximately equal mixture of the two possible stereomeric *dl*-dicarboxylic acids (XIIa and XIIb). After their separation, esterification and selective hydrolysis, the half-ester XIII was converted by ARNDT—EISTERT reaction

to the diester XIV. DIECKMANN cyclization of the latter resulted in the β-keto-ester XV which on heating in a mixture of acetic and hydrochloric acids gave *dl*-equilenin (XVI).

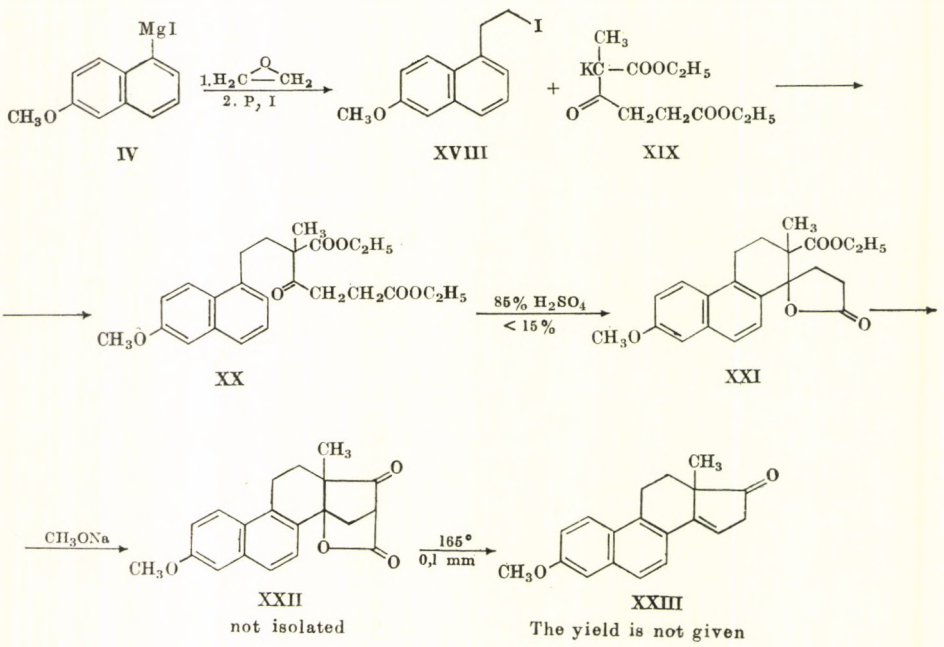


The yield was about 20% with respect to the ketone I and about 12% with respect to 6-methoxytetralone (VIII). The yield, bearing in mind the multiplicity of stages (13, when starting with ketone I, and 17, from ketone VIII), may indeed be considered as highly satisfactory. The racemic mixture was resolved by crystallization of the *l*-menthoxyacetates, yielding the naturally occurring *d*-equilenin and its *l*-isomer. *d*- and *l*-*Iso*equilenin (XVII) were obtained by an analogous route, starting with the dicarboxylic *dl*-acid XIIa.

In 1951 BACHMANN [4] reported a new, very original synthesis of equilenin, which, however, gave low yields and used less readily available compounds

as the starting materials, namely β-(6-methoxynaphthyl)-ethyl iodide (XVIII) (prepared from IV by condensation with ethylene oxide and conversion of the produced carbinol to the iodide) and ethyl 2-methyl-3-ketoadipate.

The potassio derivative of the β-keto-ester XIX on reaction with the iodide XVIII gives the keto-ester XX which cyclizes in 85% sulfuric acid to the lacto-ester XXI. Treatment of the latter with sodium methylate converts it to the keto-lactone XXII, yielding on pyrolysis the methyl ester of dehydro-equilenin (XXIII).



IV XVIII XIX

XX XXI

XXII
not isolated

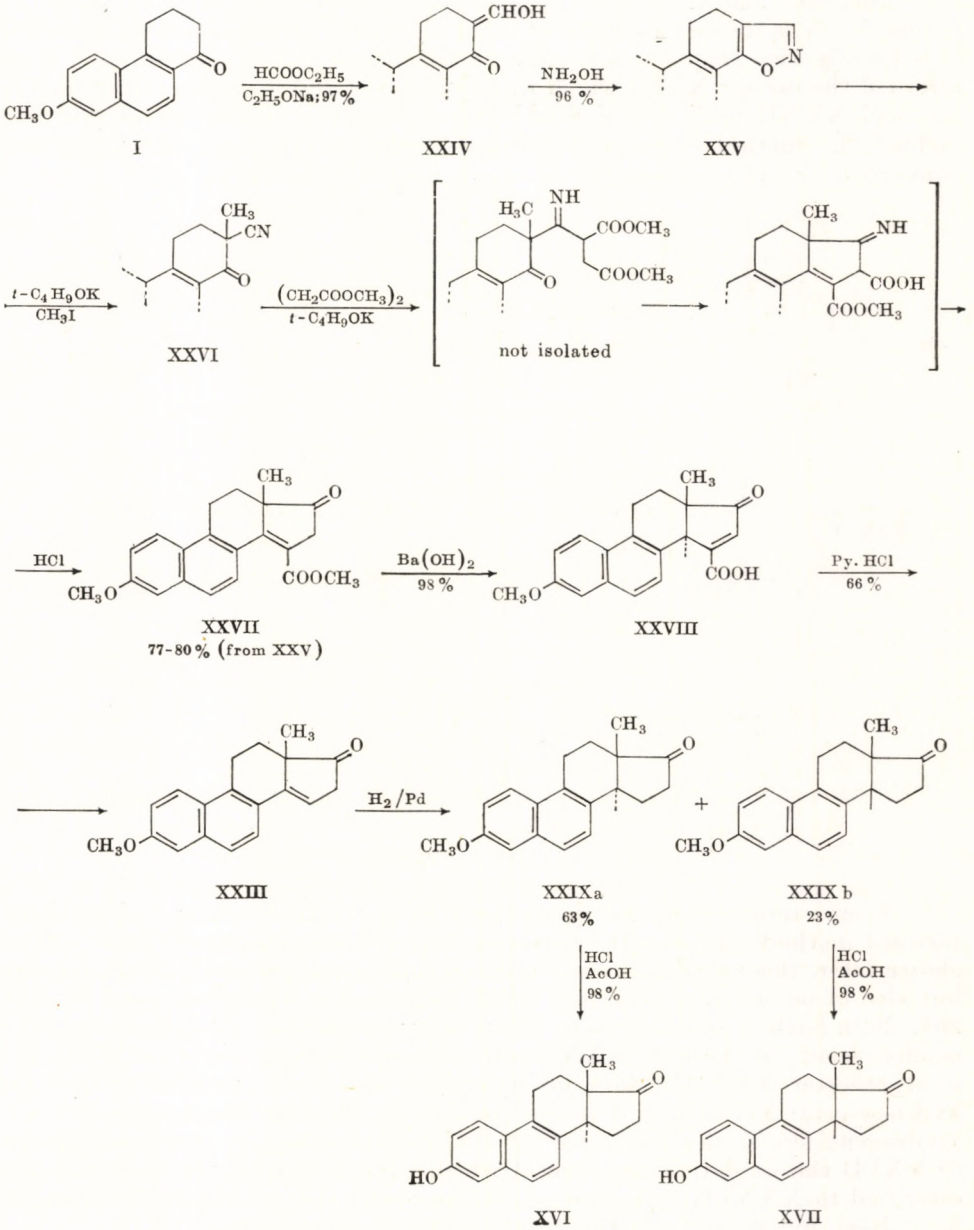
XXIII
The yield is not given

JOHNSON showed (see below) that ketone XXIII can be easily converted to *dl*-equilenin (XVI) by hydrogenation and subsequent demethylation.

SYNTHESIS ACCORDING TO JOHNSON

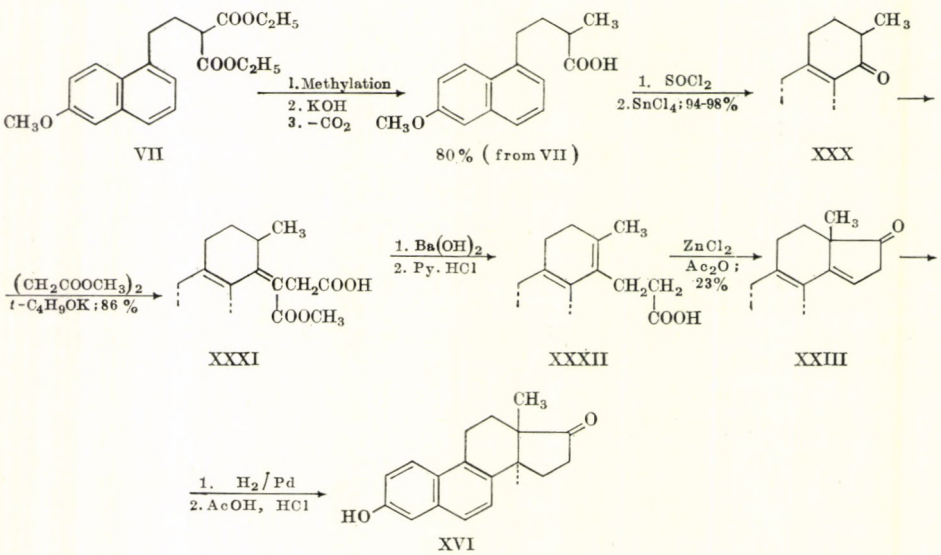
A simpler route to equilenin, with a much smaller number of stages than required for the BACHMANN synthesis was proposed in 1945 by JOHNSON, PETERSON and GUTSCHE [10, 11]. Like BACHMANN, JOHNSON started from the tricyclic ketone (I), but employed an entirely new reaction to build ring D. CLAISEN condensation of the ketone I with ethyl formate gave the keto-enol XXIV which yielded the isoxazole XXV on reaction with hydroxylamine. Treatment of the isoxazol (XXV) with methyl iodide in the presence of potassium *tert.*-butoxide led to its methylation with simultaneous opening of the hetero-ring, forming the cyano-ketone XXVI, similar to BACHMANN's keto-ester. One might have thought the synthesis would then be conducted along BACHMANN's scheme, namely REFORMATSKY reaction followed by

lengthening of the side chain, but JOHNSON chose a shorter, highly ingenious route. He carried out a succinic ester condensation with the objective of directly obtaining the required triatomic side chain. Actually, under the influence of potassium *tert.*-butoxide not only condensation, but cyclization took place, resulting in the keto-ester XXVII.



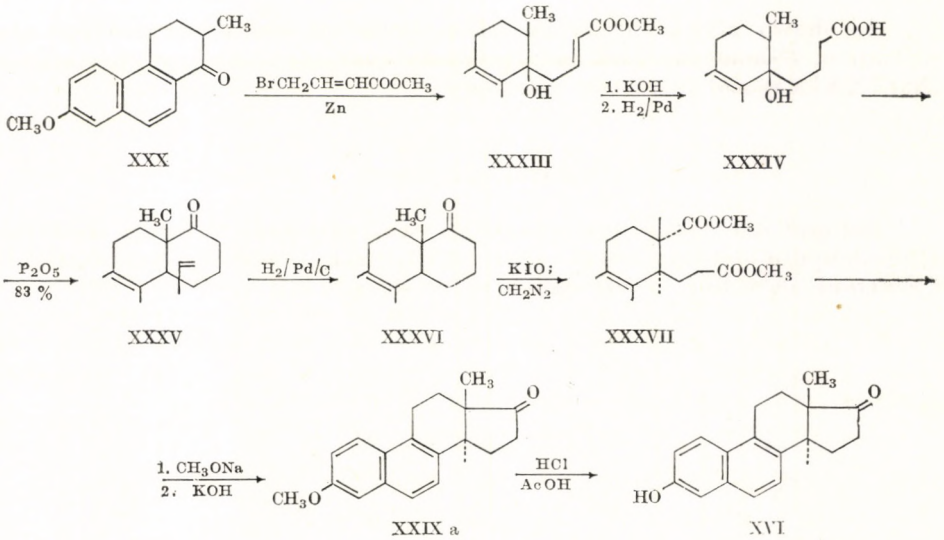
This keto-ester (XXVII) was then subjected to alkaline hydrolysis and the resultant keto-acid XXVIII on decarboxylation gave the methoxyketone XXIII. Hydrogenation of the latter led to a 2 : 1 mixture of equilenin and *iso*equilenin methyl ethers (XXIXa and XXIXb). Their separation and demethylation gave *dl*-equilenin (XVI) and *dl-iso*equilenin (XVII), and finally *d*-equilenin. The yield of *dl*-equilenin (XVI) was ca. 29% with respect to the ketone I and in all there were 8 operations.

JOHNSON also developed an alternative route [12], starting from the ketone XXX, a methyl analogue of I, that is readily obtainable from ester VII in a known way [14]. Condensation of the ketone XXX with succinic ester afforded the diester XXXI which was hydrolyzed and decarboxylated to give the acid XXXII with shifted double bond. DARZENS cyclization of this acid yielded the methyl ester of dehydroequilenin (XXIII) and the latter was converted into *dl*-equilenin in the manner described above.

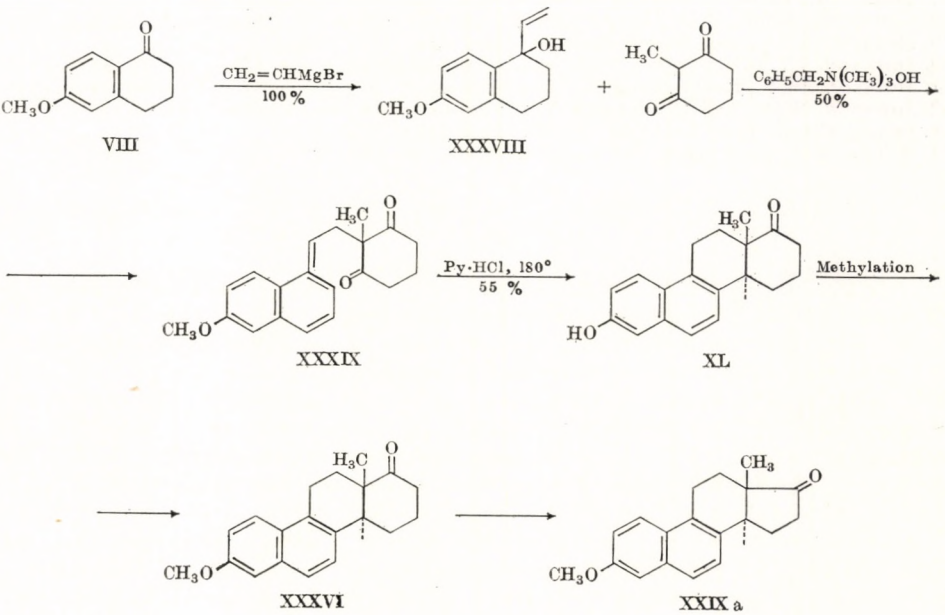


SYNTHESES VIA THE D-HOMOCOMPOUNDS

Some steroids may be synthesized by a relatively easy and straightforward method, utilizing the corresponding D-homocompound. As it will be shown later, this route has been used not only in the preparation of equilenin but also of oestrone, testosterone and 11-oxidized steroids (see pp. 248, 254, 267, 269). Such a synthesis was achieved by CHANG CHIN [6]. REFORMATSKY condensation of ketone XXX with γ-bromocrotonic ester afforded the hydroxy-ester XXXIII which on hydrolysis and hydrogenation yielded the hydroxy-acid XXXIV, and it was readily cyclized to the ketone XXXV. Hydrogenation of the latter led to the methyl ether of D-homo-equilenin (XXXVI) the oxidative cleavage of which gave a dicarboxylic acid that was esterified to XXXVII. Subsequent cyclization by the method of DIECKMANN, hydrolysis and decarboxylation gave equilenin methyl ether (XXIX).



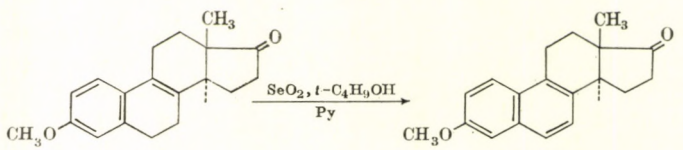
In another synthesis proposed by TORGOV and ANANCHENKO [1] the readily available 6-methoxytetralone-1 (VIII) served as the starting material. This was converted into the vinylcarbinol XXXVIII by the aid of vinylmagnesium bromide. In the presence of alkaline agents (best of all 'Triton B'), the vinylcarbinol underwent an interesting condensation with methyldihydroresorcinol to give the tricyclic diketone XXXIX. On heating the latter with pyridine hydrochloride three consecutive reactions took place, namely, cyclization, isomerization and demethylation, as a result of which D-homoequilenin (XL) was formed.



As shown above, by means of methylation, oxidative cleavage and cyclization, D-homoequilenin may be easily converted into equilenin methyl ether (XXIXa) and further to *dl*-equilenin.

OTHER SYNTHESES

dl-Equilenin methyl ether (XXIXa) was prepared [9] by the oxidation of 8(9)-dehydro-oestrone methyl ether (XLI), the intermediate in the synthesis of oestrone according to HUGHES—SMITH (see p. 252).



XLI XXIX a

REFERENCES

1. АНАНЧЕНКО, С. Н., ПЛАТОНОВА, А. В., ЛЕОНОВ, В. Н. и ТОРГОВ, И. В.: Известия АН СССР ОХН, *1961*, 1074.
2. BACHMANN, W. E., COLE, W., and WILDS, A. L.: *J. Am. Chem. Soc. 61*, 974 (1939).
3. BACHMANN, W. E., COLE, W., and WILDS, A. L.: *J. Am. Chem. Soc. 62*, 824 (1940).
4. BACHMANN, W. E., and HOLMEN, D. R.: *J. Am. Chem. Soc. 73*, 3660 (1951).
5. BUTENANDT, A., and SCHRAMM, G.: *Ber. 68*, 2083 (1935).
6. CHIN, CHANG: *Acta Chim. Sinica 21*, 190 (1955).
7. COHEN, A., COOK, J. W., and HEWETT, C. L.: *J. Chem. Soc. 1935*, 445.
8. COHEN, A., COOK, J. W., HEWETT, C. L., and GIRARD, A.: *J. Chem. Soc. 1934*, 653.
9. HUGHES, G. A., and SMITH, H.: *Chem. and Ind. 1960*, 1022.
10. JOHNSON, W. S., PETERSON, J. W., and GUTSCHE, C. D.: *J. Am. Chem. Soc. 67*, 2274 (1945).
11. JOHNSON, W. S., PETERSON, J. W., and GUTSCHE, C. D.: *J. Am. Chem. Soc. 69*, 2942 (1947).
12. JOHNSON, W. S., and STROMBERG, V. L.: *J. Am. Chem. Soc. 72*, 505 (1950).
13. STORK, G.: *J. Am. Chem. Soc. 69*, 576, 2936 (1947).
14. WILDS, A. L., and CLOSE, W. J.: *J. Am. Chem. Soc. 69*, 3079 (1947).

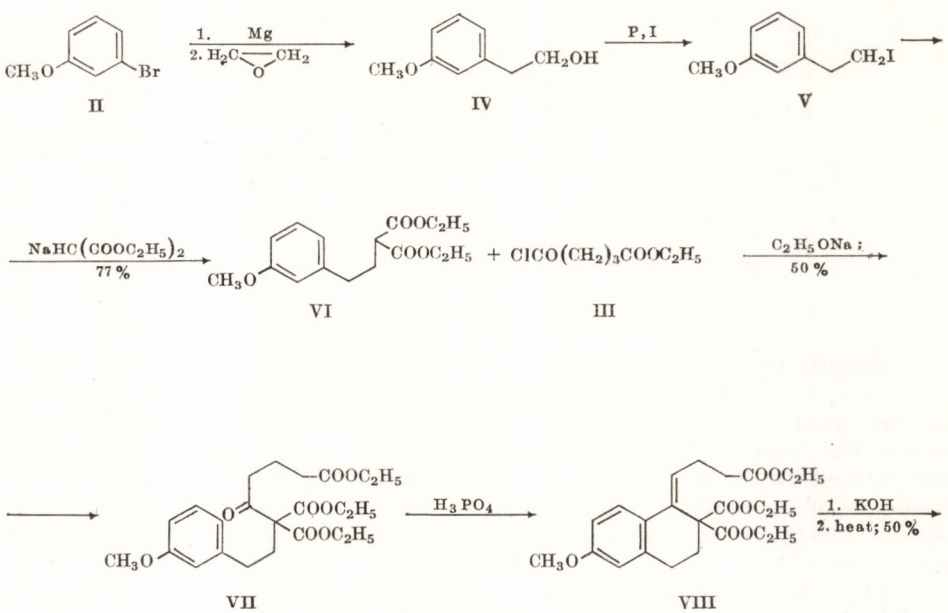
CHAPTER II

SYNTHESES OF OESTRONE AND ITS DERIVATIVES

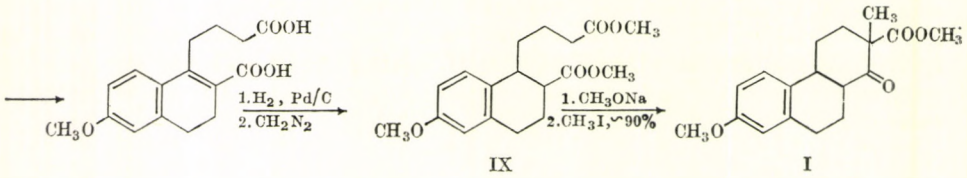
SYNTHESIS ACCORDING TO MIESCHER

The first synthesis of oestrone in 1948 by ANNER and MIESCHER [2, 3, 4] crowned a long series of investigations begun already by ROBINSON and continued by BACHMANN. The key intermediate was the so-called ROBINSON's ketone (I) prepared [18, 19, 5] from *m*-bromoanisole (II) and glutaric half-ester chloride (III).

Reaction of *m*-anisyl magnesium bromide with ethylene oxide gave the primary carbinol (IV) from which the corresponding iodide (V) was obtained. Condensation with sodiomalonate led to the diester VI, the sodium derivative of which on reaction with the chloride III gave the ketotricarboxylic ester VII. Cyclization of the latter with phosphoric acid yielded the bicyclic triester VIII which was transformed by consecutive alkaline cleavage, removal of one malonic type carboxylic group, hydrogenation, and esterification into the diester IX. DIECKMANN condensation followed by angular methylation gave ROBINSON's ketone (I).

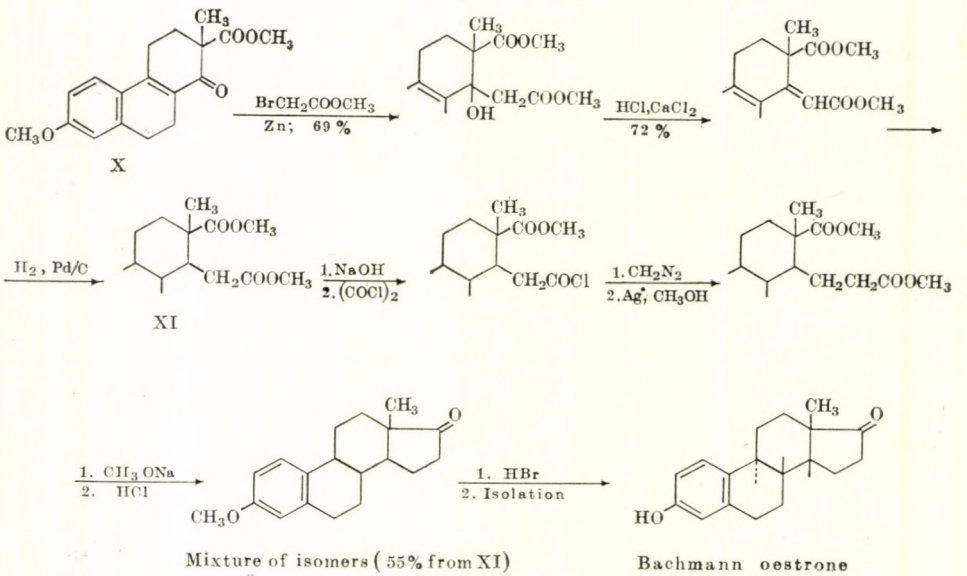


II IV V VI III VII VIII



Since structure I possesses three asymmetric carbon atoms, and the above reactions, in particular hydrogenation, are not stereospecific, the produced ketone (I) proved to be a mixture of stereoisomers. It was just because of this that ROBINSON was unable to complete the synthesis of oestrone.

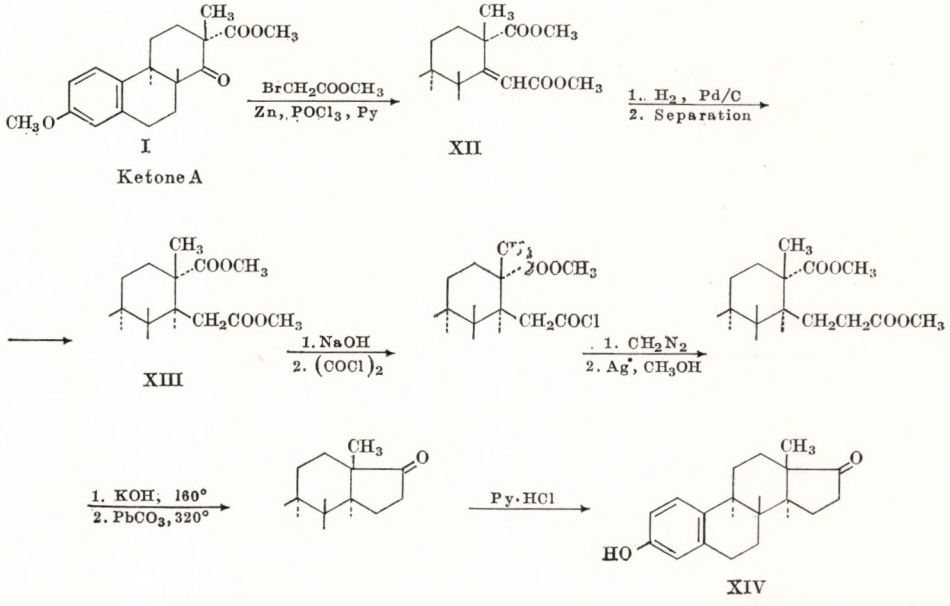
BACHMANN [5] made use of his method for constructing ring D (see p. 239) in the ketone X, and thus succeeded in preparing a mixture of tetracyclic compounds from which the so-called BACHMANN oestrone was isolated. However, it was found to differ from the natural product.



Despite the obvious difficulties, MIESCHER and ANNER decided to repeat this route. Working with larger quantities, they succeeded in isolating three isomers from 'ROBINSON's ketone'. One of them (ketone A) was found to possess the required 'natural' configuration, and another (ketone C) could be transformed to A on treatment with alcoholic alkali. This confirmed the existence of a *trans*-decalone system in ketone A. Following BACHMANN's scheme, the Swiss researchers were indeed able to obtain natural oestrone from ketone A.

The keto-ester (IA) was subjected to the REFORMATSKY reaction followed by dehydration to give the diester XII which on hydrogenation yielded a

mixture of isomers that was separated by crystallization. One of the isomers (XIII) was submitted to ARNDT—EISTERT reaction followed by cyclization, hydrolysis and demethylation to give *dl*-oestrone (XIV). The *d*- and *l*-isomers were obtained from the racemate by crystallization of the *l*-menthoxyacetates.

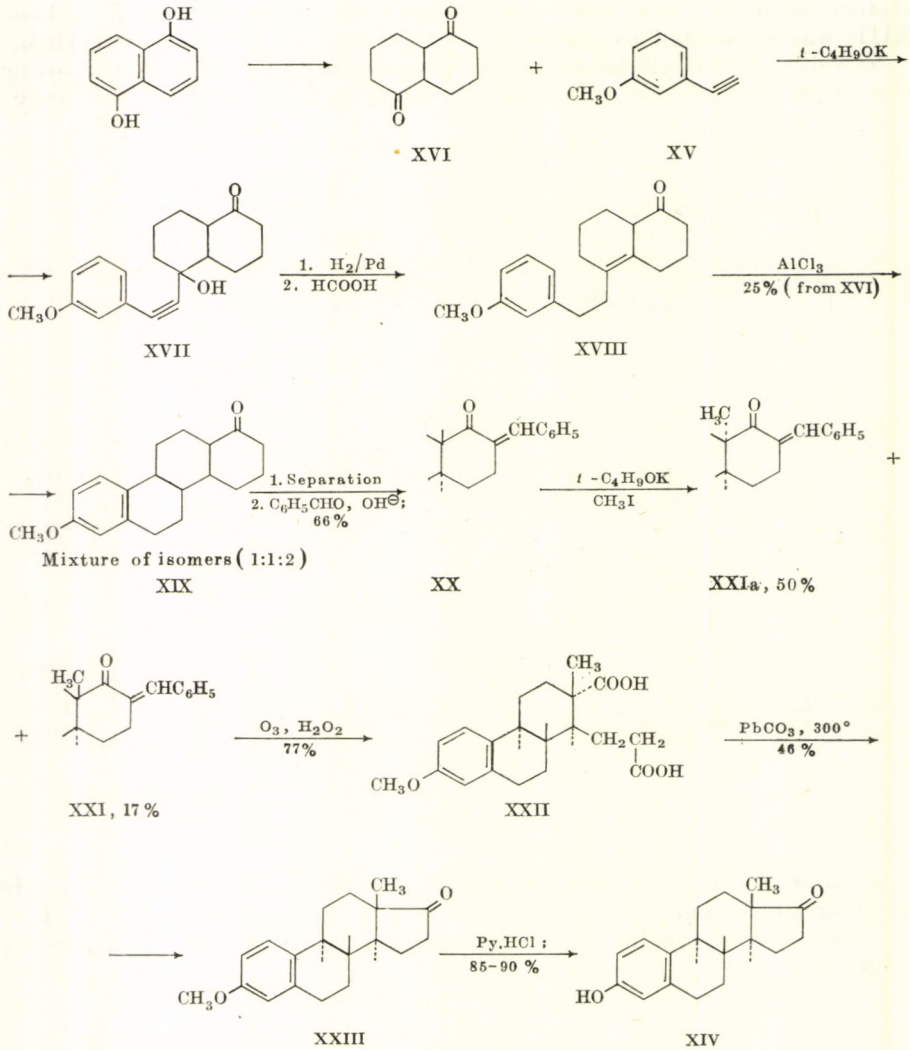


Later ANNER and MIESCHER prepared five isomers of oestrone from the other stereoisomers of the ketone I and of the diesters of type XIII.

The synthesis comparises 20 steps and is not characterized by stereospecificity.

SYNTHESIS ACCORDING TO JOHNSON

A novel, fundamentally different and shorter synthesis of oestrone was reported by JOHNSON and his group [12, 13]. The rather difficultly available *m*-methoxyphenylacetylene (XV) and decalin-1,5-dione (XVI) served as starting materials. These compounds were condensed to the tricyclic ketol XVII in the presence of potassium *tert.*-butylate. Exhaustive hydrogenation followed by dehydration led to the unsaturated ketone XVIII which, under the influence of $AlCl_3$, cyclized to a mixture of stereoisomeric ketones XIX. Three isomers were isolated from this mixture in 1 : 1 : 2 proportion, and subjected to further reaction involving the introduction of an angular methyl group and the conversion of a six to a five-membered ring. The procedure for this had been developed by JOHNSON earlier [11] on model compounds.



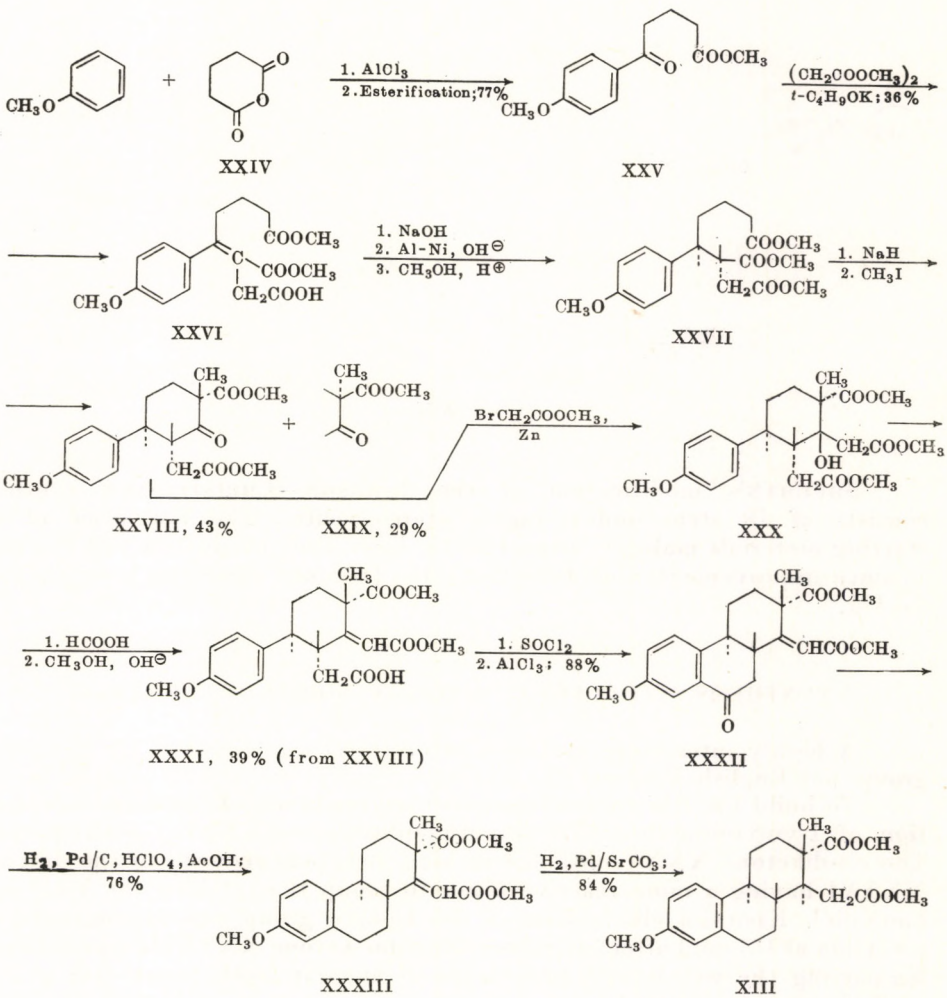
The benzal derivative was prepared from one of the less prevalent isomeric ketones (XIX), and on methylation this again yielded a mixture of isomers. Ozonization of one of them (XXI) led to the dicarboxylic acid XXII, pyrolysis of which afforded *dl*-oestrone methyl ether (XXIII). *dl*-Oestrone (XIV) was resolved by means of the menthoxyacetates.

Utilizing the other isomeric ketones (XIX and XXIa) JOHNSON accomplished the synthesis of all the 8 possible oestrone isomers; one of them proved to be identical with 'BACHMANN's oestrone'.

JOHNSON's synthesis is only partially stereospecific. It comprises 9 operations, the total yield of *dl*-oestrone amounts to 0.21%, based on diketone XVI. The method of forming the steroid molecule via D-homosteroids was also used by JOHNSON in other syntheses.

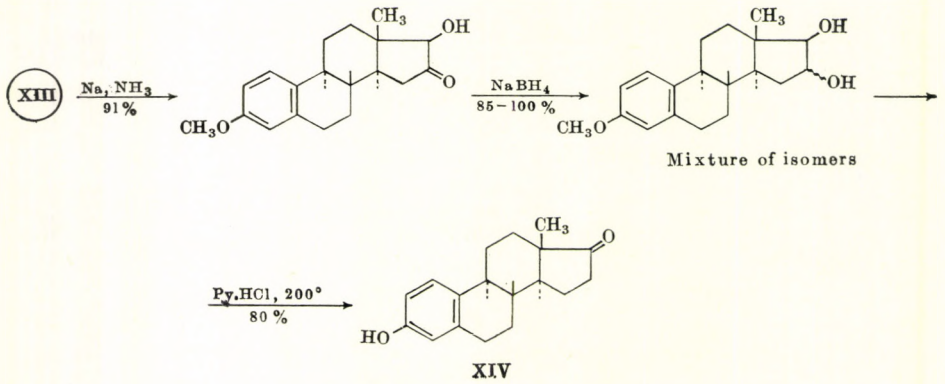
SYNTHESIS ACCORDING TO JOHNSON AND CHRISTIANSEN

Later JOHNSON and CHRISTIANSEN [14, 15] developed a route to oestrone, from more readily available products, namely, anisole and the acid chloride of ethyl hydrogen glutarate (III) or, better still, glutaric anhydride. The FRIEDEL—CRAFTS reaction was used to produce γ-anisoylbutyric ester (XXV) which was condensed with methyl succinate to the ester XXVI, then converted by saponification, reduction and esterification to the triester XXVII. DIECKMANN cyclization followed by methylation afforded the bicyclo keto-ester of the required configuration XXVIII as the predominant product, together with smaller amounts of its isomer (XXIX).



REFORMATSKY reaction converted the keto-ester (XXVIII) largely into the hydroxy-ester (XXX) accompanied by the formation of some lactones.

The crude mixture was treated with formic acid (dehydration), and then with an alcoholic alkali solution. This gave the acid XXXI. Intramolecular acylation by FRIEDEL—CRAFTS reaction led to the tricyclic keto-ester XXXII which on consecutive hydrogenation, first with palladized carbon in acidic medium and then with palladium on strontium carbonate in ethyl acetate, was converted into the methoxydiester XIII prepared first by MIESCHER (see p. 247). Conversion of this ester into *dl*-oestrone was carried out in two ways: according to BACHMANN—MIESCHER (see p. 247) and according to SHEEHAN [20]. The latter method involved the use of the acyloin condensation reaction to form ring D and then accomplished the synthesis of oestrone by a sequence of reactions: reduction, dehydration and demethylation.

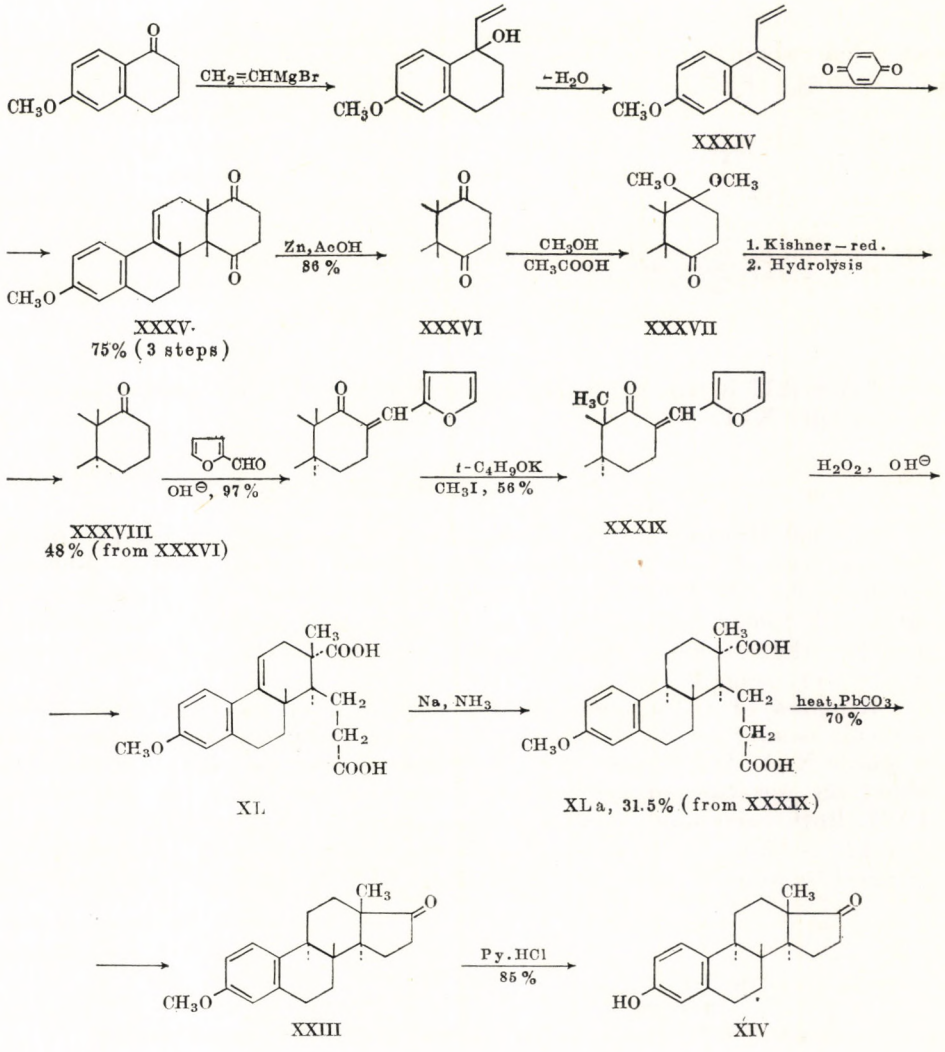


SHEEHAN's modification of the JOHNSON—CHRISTIANSEN synthesis consists of 18 steps and is highly stereospecific. The low price of the starting materials makes it attractive for large scale production, all the more so since improvements due to KIPRIANOV [16] can raise the over-all yield to 4%.

SYNTHESIS ACCORDING TO JOHNSON, ROBINS AND WALKER

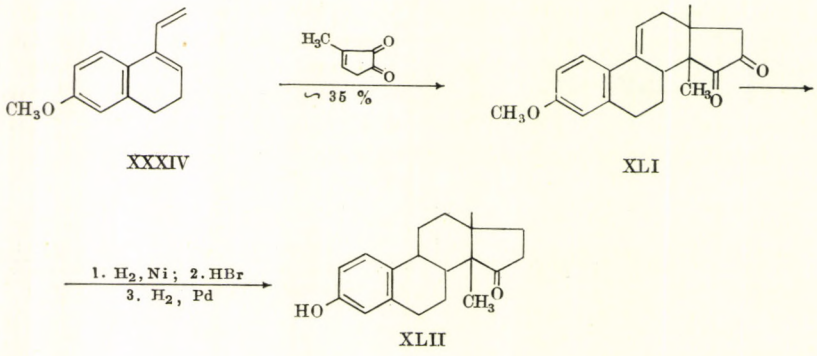
A highly interesting synthesis of oestrone was achieved by JOHNSON's group and English chemists [7].

To build the steroid arrangement they made use of the diene condensation of 1-vinyl-6-methoxy-3,4-dihydronaphthalene (XXXIV) with quinone. The *cis*-diketone XXXV obtained in high yield was reduced to the diketone XXXVI having a more reactive 17a-keto group that yielded the ketal with methanol. KISHNER elimination of the 15-keto group was accompanied by inversion at C_{14}, and after hydrolysis the *trans*-ketone XXXVIII was obtained. Employing the well-known procedures of angular methylation (see p. 248) (which gave the desired isomer in predominating amounts) and of ring D opening, the authors obtained the acid XL, which was reduced by sodium in liquid ammonia to the derivative of D-homomarrianolic acid (XLa).



Transformation of the latter into *dl*-oestrone methyl ether (XXIII) and then into *dl*-oestrone (XIV) was accomplished by conventional methods.

The entire synthesis from the initial 6-methoxytetralone involves 12 stages and the over-all yield with respect to the starting materials is about 3.2% (values for the individual yields have been taken from other sources [17]). The availability of the starting materials and the simplicity of the chemical operations makes this method highly promising even for commercial production. It should be noted that dienic condensation using the diene XXXIV with the objective of synthesizing steroids was first carried out in 1939 by DANE [8] who employed the reactive 3-methyl-Δ^3-cyclopentene-1,2-dione as the dienophil. The adduct XLI was converted by a series of reactions into compound XLII isomeric with oestrone, but the structure was not determined.



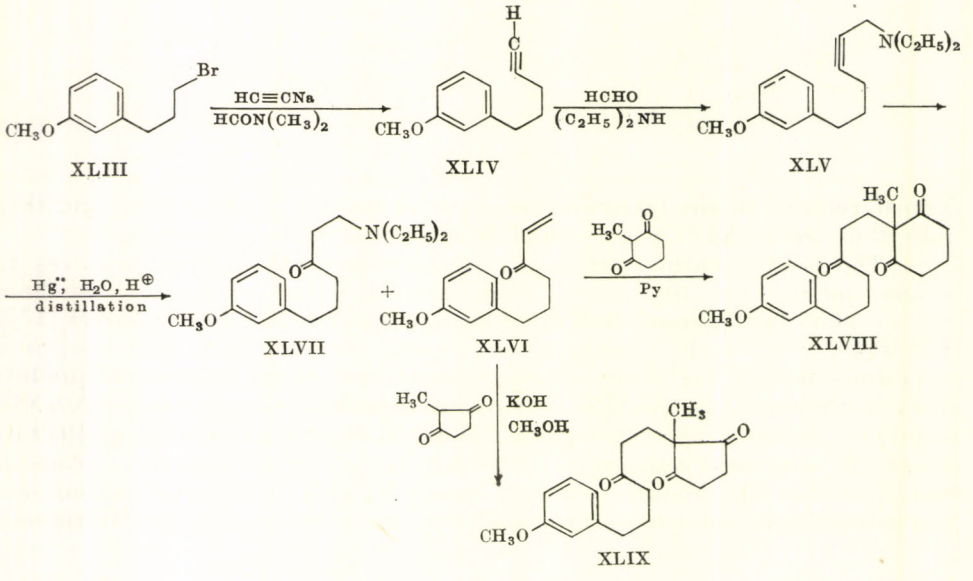
XXXIV XLI XLII

Later [21] it was definitely established that DANE's adduct possessed the structure XLI.

SYNTHESIS ACCORDING TO HUGHES AND SMITH

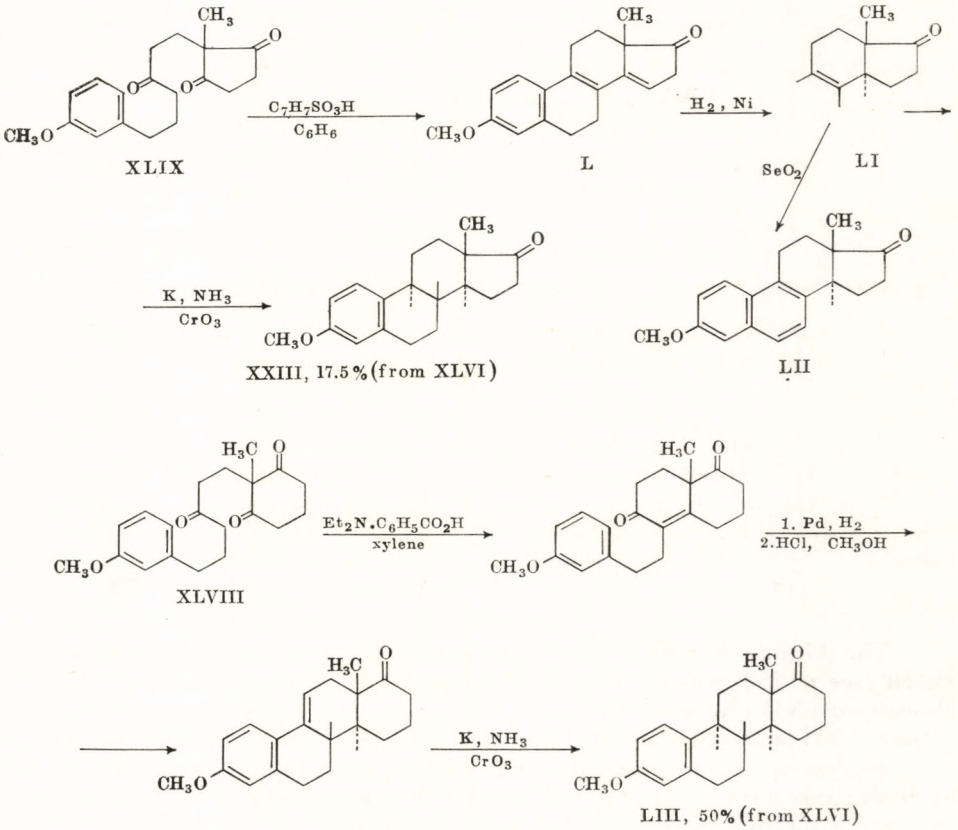
In 1960 HUGHES and SMITH described in two brief reports [9, 10] the total synthesis of D-homo-oestrone and oestrone, starting from *m*-(3-bromopropyl)anisole (XLIII) and methyldihydroresorcinol or 2-methylcyclopentane-1,3-dione, respectively. The MANNICH and MICHAEL reactions were utilized in the synthesis. Highly original was the double cyclization to form consecutively rings B and C.

Reaction of the bromide XLIII with sodium acetylide afforded the acetylenic compound XLIV which was converted by MANNICH reaction into the amine XLV. Distillation of the KUCHEROV hydration product of the latter yielded the unsaturated ketone XLVI contaminated with the β-ketoamine XLVII. Both compounds (actually the mixture is used) readily undergo the MICHAEL reaction with methyldihydroresorcinol, or with 2-methylcyclopentane-1,3-dione to give the triketones XLVIII or XLIX, respectively.



XLIII XLIV XLV XLVII XLVI XLVIII XLIX

The latter compound undergoes double cyclization when treated with *p*-toluenesulphonic acid to afford the steroid ketone L which is hydrogenated to ketone LI having *trans* C/D ring junction. Reduction with potassium in liquid ammonia followed by oxidation of the ketone–alcohol mixture leads to oestrone methyl ether (XXIII). Oxidation of the ketone LI with selenium dioxide gives equilenin methyl ether (LII).



XLIX L LI

XXIII, 17.5% (from XLVI) LII

XLVIII

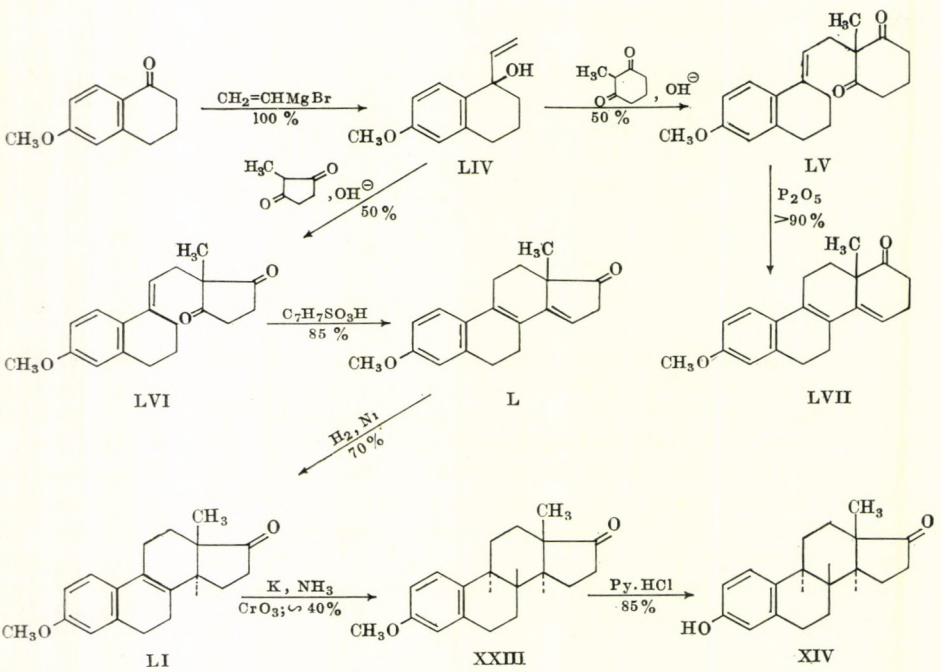
LIII, 50% (from XLVI)

Analogously, D-homo-oestrone (LIII) was obtained from the triketone XLVIII. The HUGHES—SMITH synthesis consists of 8 stages starting with the difficultly obtainable bromide XLIII.

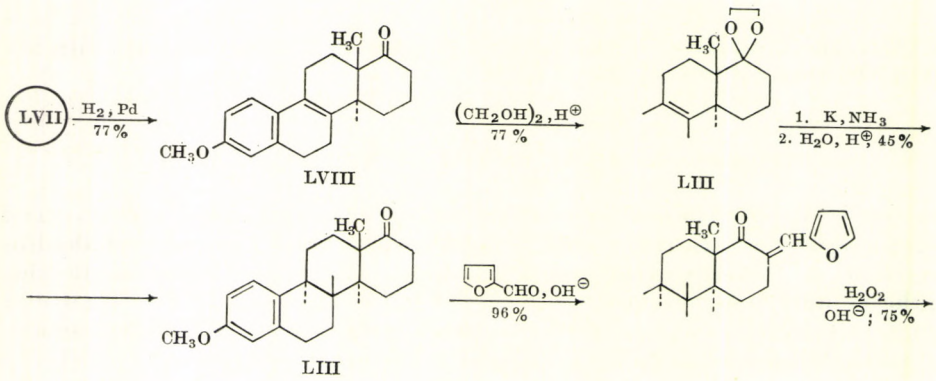
SYNTHESIS ACCORDING TO TORGOV AND ANANCHENKO

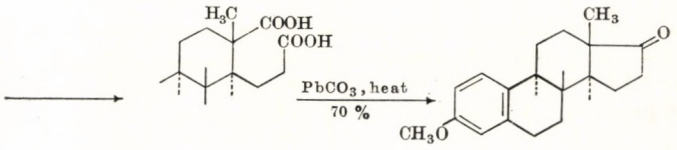
In 1960—62 TORGOV and ANANCHENKO [1] synthesized oestrone and D-homo-oestrone, starting with 6-methoxytetralone and methyldihydroresorcinol or 2-methylcyclopentane-1,3-dione. The basic reactions in this synthesis were condensation of 1-vinyl-6 methoxytetralol (LIV) (prepared from 6-methoxytetralone according to NORMAN) with methyldihydroresorcinol and methylcyclopentanedione, respectively. This interesting reaction is induced

by alkaline agents, such as potassium hydroxide, alcoholates, or, best of all, trimethylbenzyl ammonium hydroxide (Triton B), and leads to the tricyclic ketones LV and LVI which very readily undergo cyclization in acidic medium to the steroid ketones LVII and L.



The ketone L which had been previously obtained by HUGHES and SMITH (see p. 253) was converted into *dl*-oestrone methyl ether (XXIII) and *dl*-oestrone (XIV) by ordinary methods. The latter was also prepared from the ketone LVII and its dihydro derivative (LVIII). The ethyleneketal of the dihydro derivative on reduction with potassium in liquid ammonia followed by hydrolysis gave the methyl ether of D-homo-oestrone (LIII) which, using JOHNSON's method, was converted into *dl*-oestrone.



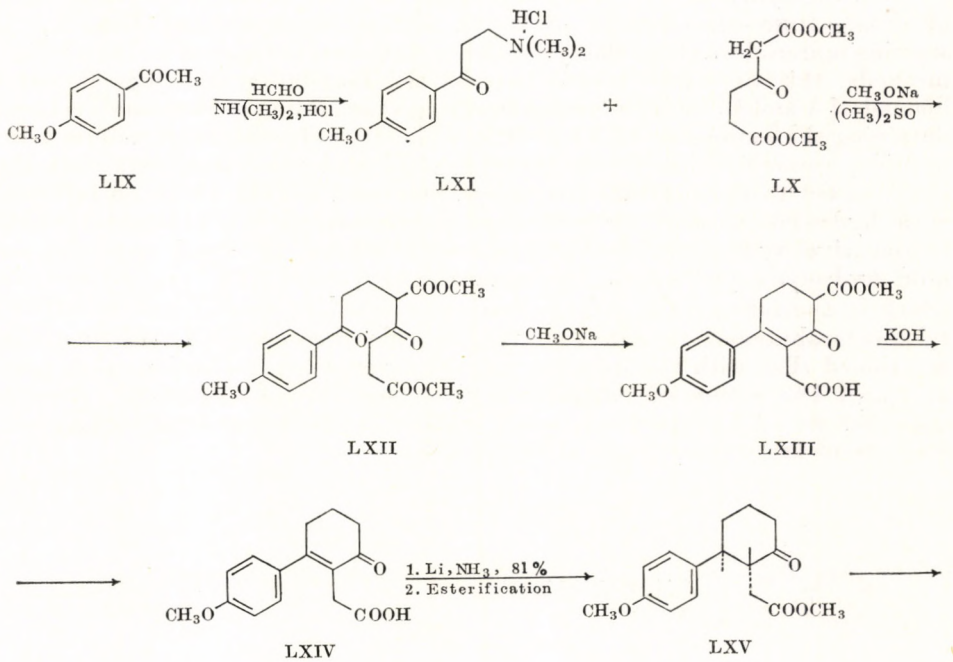


XXIII

The first route (via diketone LVI) comprises seven operations and is highly stereospecific. The yield of *dl*-oestrone (with respect to 6-methoxy-tetralone) exceeds 10%. The second route (via diketone LVII) is longer (10 stages), and the over-all yield is less (5.3%), but the starting material, methyl-dihydroresorcinol, is more readily available. Both alternatives are promising from an industrial standpoint.

SYNTHESIS ACCORDING TO BANERJEE

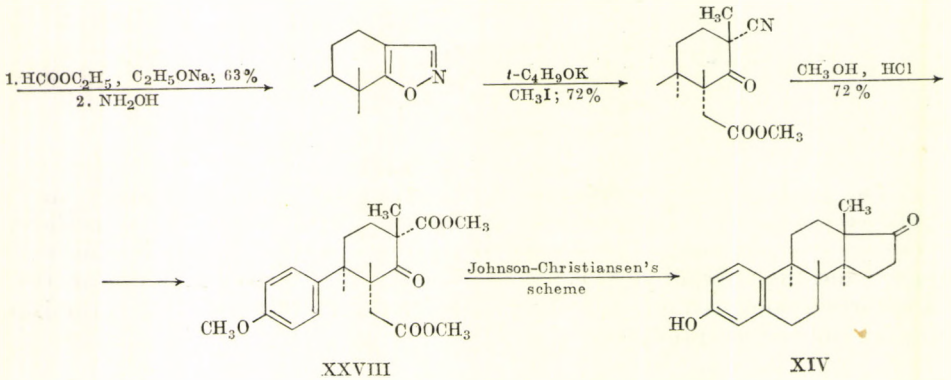
This synthesis was described [6] in a brief communication in 1960. The starting materials were the abundantly available *p*-methoxyacetophenone (LIX) and the less readily available dimethyl-3-ketoadipate (LX). The product obtained from LIX with formaldehyde and dimethylamine was condensed with the β-keto ester LX in the presence of dimethylsulphoxide and sodium methoxide to form the diketo-ester LXII. Treatment of the latter with sodium methoxide causes its saponification with simultaneous cyclization to the bicyclic half-ester LXIII, alkaline hydrolysis of which leads to the keto-acid LXIV. The double bond of the latter is readily and stereospecifically reduced by lithium in liquid ammonia.



LIX LXI LX

LXII LXIII

LXIV LXV

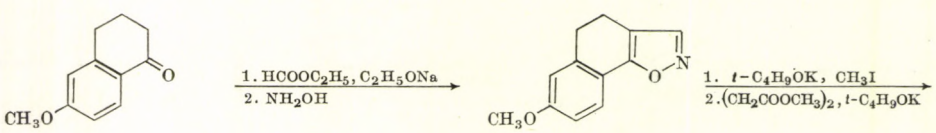


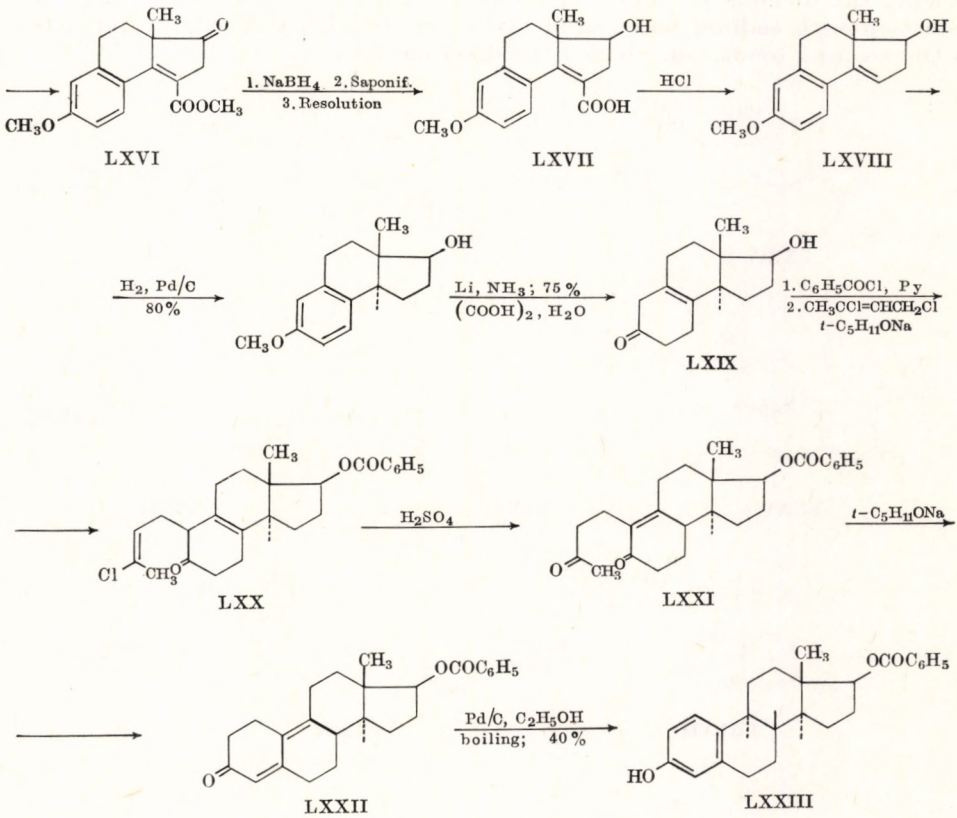
By a series of reactions described in the discussion of JOHNSON's synthesis of equilenin (see p. 241), the ester of the keto-acid LXV was converted to the keto-ester XXVIII from which *dl*-oestrone (see p. 249) had been synthesized earlier.

BANERJEE's synthesis involves 17 stages; it is very difficult to estimate the over-all yield.

SYNTHESIS ACCORDING TO VELLUZ

In the synthesis of VELLUZ published in 1960 [22, 23] just like in those of COLE—JOHNSON—ROBINS—WALKER and of ANANCHENKO—TORGOV, the starting material was 6-methoxytetralone. However, in contrast to the previous methods, this substance served here as the foundation for rings B and C instead of A and B. VELLUZ formed first ring D according to JOHNSON's scheme, obtaining the keto-ester LXVI in 50% yield. Its reduction with sodium borohydride, saponification to the hydroxy-acid and resolution with chloramphenicol led to the optically active hydroxy-acid LXVII which on refluxing with hydrochloric acid suffered decarboxylation to the carbinol LXVIII. Consecutive hydrogenation, reduction with lithium in liquid ammonia and mild hydrolysis yielded the β,γ-unsaturated ketol LXIX, the benzoate of which in the form of the sodium derivative could be readily condensed with 1,3-dichlorobutene-2 to give the tricyclic chloroketone LXX. (It should be mentioned that with the isomeric α,β-unsaturated ketol addition takes place at $C_{(11)}$.) The action of sulphuric acid on the chloroketone LXX afforded the diketone LXXI which was easily cyclized in the presence of sodium *tert.*-amylate to the tetracyclic dienone LXXII.





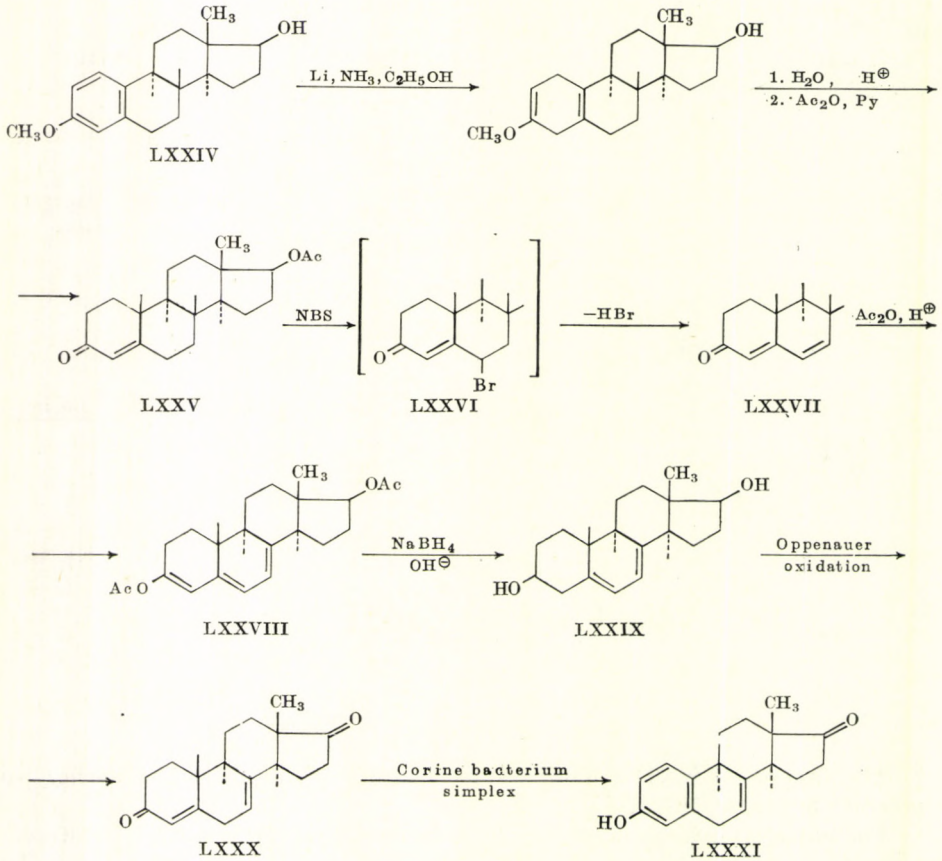
The dienone LXXII isomerizes on heating with palladized carbon to *d*-estradiol benzoate (LXXIII).

The entire synthesis involving 15 stages is characterized by high stereospecificity. It is noteworthy that the intermediate diketone LXXI may be utilized in the synthesis of dehydrotestosterone and adrenosterone, as will be shown in the following chapter (see p. 270).

SYNTHESIS OF EQUILIN ACCORDING TO DJERASSI

Equilin differs from oestrone only in the presence of a $\Delta^{7(8)}$-bond, but this seemingly small difference made its synthesis extraordinarily difficult, all attempts to introduce a double bond into ring B of oestrone invariably causing dehydrogenation with the formation of equilenin. Only in 1958, after much more complex steroids had been synthesized, could DJERASSI and collaborators [24] achieve the synthesis of equilin. They started with the methyl ether of oestradiol (LXXXIV) which on reduction with lithium and alcohol in liquid ammonia, followed by hydrolysis, gave 19-nortestosterone, the acetate of which (LXXV) was brominated with N-bromosuccinimide. The 6-bromo derivative (LXXVI) was formed, which was dehydrobrominated,

forming the dienone LXXVII. The enol acetate (LXXVIII) of the latter on reduction with sodium borohydride gave the diol LXXIX which, subjected to OPPENAUER oxidation, yielded the diketone LXXX.



LXXIV LXXV LXXVI LXXVII LXXVIII LXXIX LXXX LXXXI

The diketone (LXXX) already possessing the required $\Delta^{7(8)}$ bond was subjected to microbiological dehydrogenation with Corine bacterium simplex, resulting in the formation of a Δ-bond. The intermediate dienone spontaneously isomerized to equilin (LXXXI).

REFERENCES

1. АНАНЧЕНКО, С. Н., ЛЕОНОВ, В. Н., ПЛАТОНОВА, Д. В и ТОРГОВ, И. В.: *ДАН, 135,* 73 (1960).
2. ANNER, G., and MIESCHER, K.: *Helv. Chim. Acta 31,* 2173 (1948).
3. ANNER, G., and MIESCHER, K.: *Helv. Chim. Acta 32,* 1957 (1949).
4. ANNER, G., and MIESCHER, K.: *Helv. Chim. Acta 33,* 1379 (1950).
5. BACHMANN, W. E., KUSHNER, S., and STEVENSON, A. C.: *J. Am. Chem. Soc. 64,* 974 (1942).
6. BANERJEE, D. K., and SIVANANDAIAH, K. M.: *Tetrahedron Letters 5,* 20 (1960).
7. COLE, J. E. Jr., JOHNSON, W. S., ROBINS, P. A., and WALKER, J.: *Proc. Chem. Soc. 1958,* 114.

8. Dane, E., and Schmitt, J.: *Ann. 537*, 246 (1939).
9. Hughes, G. A., and Smith, H.: *Proc. Chem. Soc. 1960*, 75.
10. Hughes, G. A., and Smith, H.: *Chem. and Ind. 1960*, 1022.
11. Johnson, W. S.: *J. Am. Chem. Soc. 65*, 1317 (1943).
12. Johnson, W. S., Banerjee, D. K., Schneider, W. P., Gutsche, C. D., Shelberg, W. E., and Chinn, L. J.: *J. Am. Chem. Soc. 72*, 1426 (1950).
13. Johnson, W. S., Banerjee, D. K., Schneider, W. P., Gutsche, C. D., Shelberg, W. E., and Chinn, L. J.: *J. Am. Chem. Soc. 74*, 2832 (1952).
14. Johnson, W. S., and Christiansen, R. G.: *J. Am. Chem. Soc. 73*, 5511 (1951).
15. Johnson, W. S., Christiansen, R. G., and Ireland, R. E.: *J. Am. Chem. Soc. 79*, 1995 (1957).
16. Киприянов, Г. И. *Мед. Иромышленность* СССР, *1961*, 43.
17. Robins, P. A., and Walker, J.: *J. Chem. Soc. 1956*, 3264.
18. Robinson, R., and Walker, J.: *J. Chem. Soc. 1936*, 747.
19. Robinson, R., and Walker, J.: *J. Chem. Soc. 1938*, 183.
20. Sheehan, J. C., Erman, W. E., and Cruickshank, P. A.: *J. Am. Chem. Soc. 79*, 147 (1957).
21. Sighn, G.: *J. Am. Chem. Soc. 78*, 6109 (1956).
22. Velluz, L., Nominé, G., and Mathieu, J.: *Angew. Chem. 72*, 725 (1960).
23. Velluz, L., Nominé, G., Mathieu, J., Toromanoff, E., Bertin, N., Vignau, M., and Tessier, J.: *Compt. rend. 250*, 1510 (1960).
24. Zderic, J. A., Bowers, A., Carpio, H., and Djerassi, C.: *J. Am. Chem. Soc. 80*, 2596 (1958).

CHAPTER III

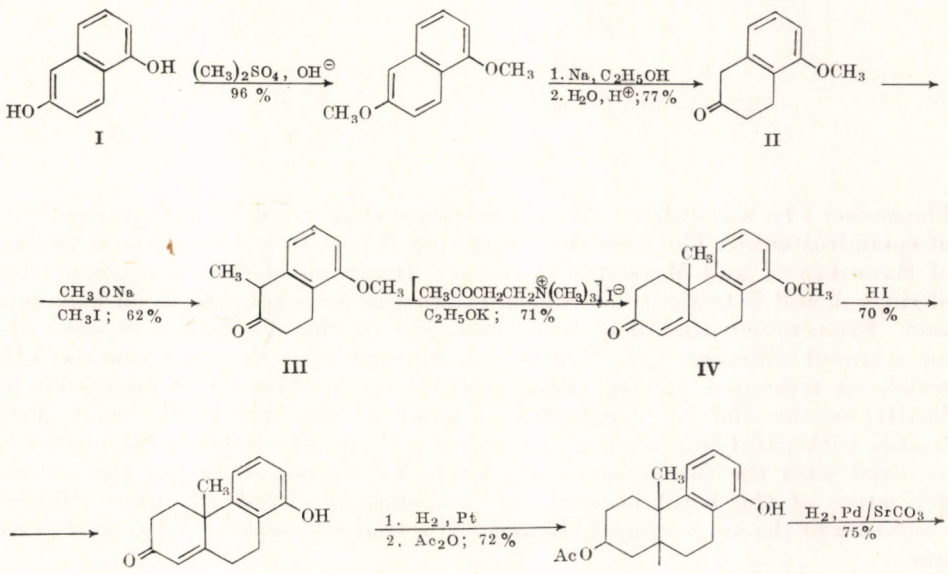
SYNTHESES OF ANDROSTANE DERIVATIVES

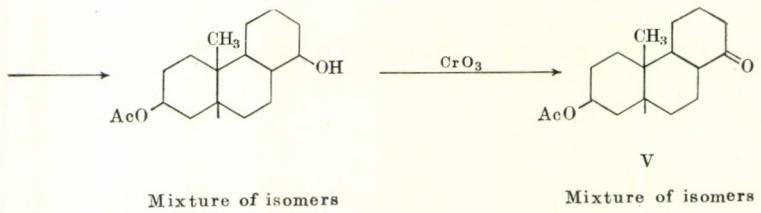
SYNTHESIS ACCORDING TO ROBINSON

The total synthesis of androstane proved to be a much more difficult task than that of oestrone, because special methods had to be devised for introducing the C_{10}-angular methyl group. In principle, this problem had been solved by ROBINSON [3, 15] as far back as in 1937, still much time was required before these studies ended in the total synthesis of natural steroids.

The total synthesis of androstane and pregnane derivatives was achieved almost simultaneously in 1951 by ROBINSON and WOODWARD using independent and entirely different methods. Since ROBINSON came to dehydroepiandrosterone we shall consider his synthesis in this section.

The starting material [1, 2] was 1,6-dihydroxynaphthalene (I), providing the basis of the ring system BC. Reduction of its methyl ether gave 5-methoxy-2-tetralone (II). Methylation in the 1-position led to 1-methyl-5-methoxy-2-tetralone (III). Ring A was then formed by MANNICH condensation and the resulting tricyclic ketone IV on demethylation, hydrogenation, selective acetylation, a second hydrogenation and oxidation afforded a mixture of the isomeric acetoxyketones V.



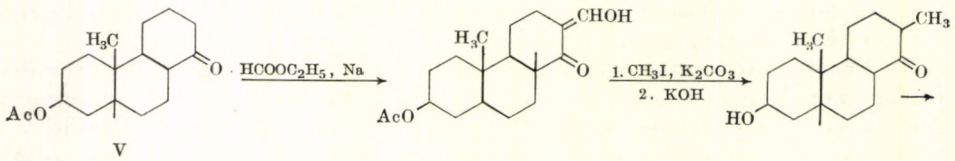


Mixture of isomers

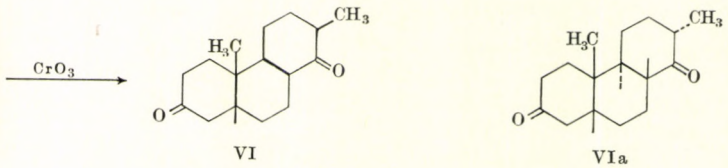
V

Mixture of isomers

This mixture was saponified and then separated by crystallization of the hydrogen succinates (yield for each isomer 5—10%). The fractionated isomeric half-esters were in turn resolved through the brucine salts (yield 30—40%). All the four optically active hydroxyketone acetates (V) were methylated, saponified and oxidized to the four diketones (VI). One of these stereoisomers (known as the REICH diketone), VIa, proved to be identical with the degradation product of cholesterol and desoxycholic acid.



V

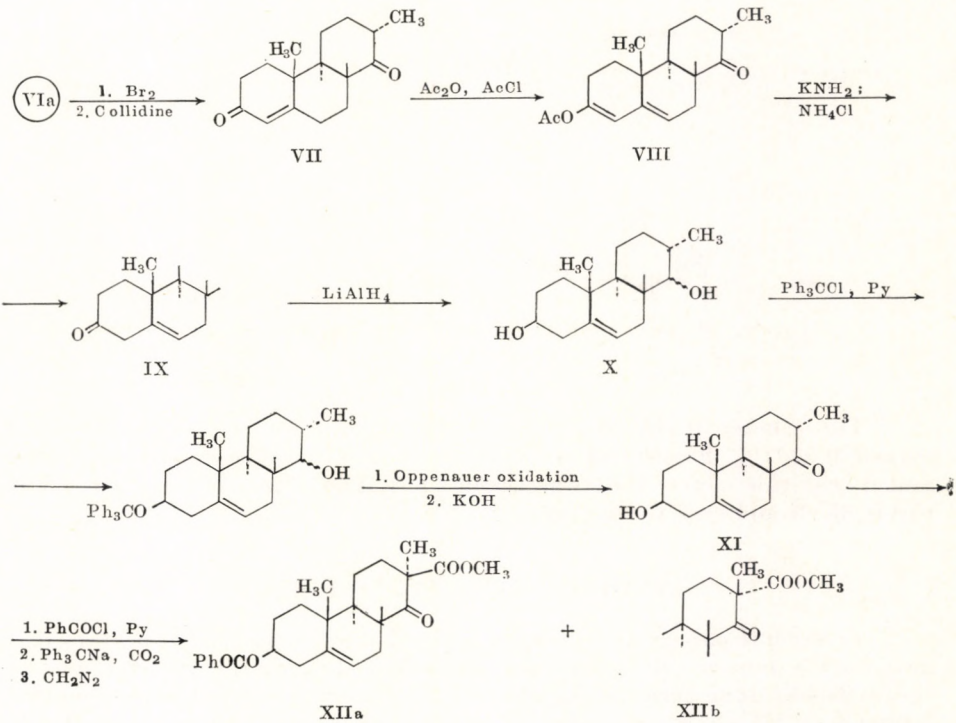


VI

27% (from V)

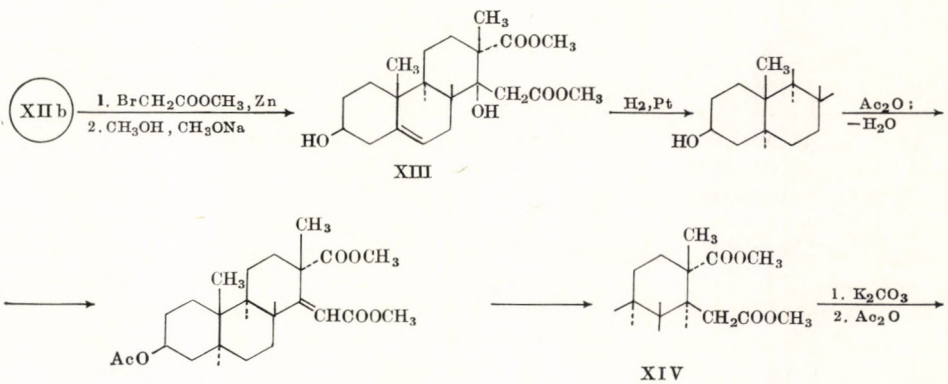
VIa

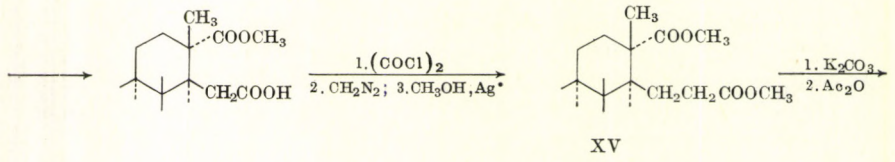
The isomer VI a was utilized in the further steps that ended in the total synthesis of epiandrosterone. The construction of ring D was, in general, similar to that of BACHMANN's and MIESCHER's schemes. Inversion of the *cis* configuration of rings A and B to the *trans* configuration was accomplished in an ingenious way. Bromination and dehydrobromination of the diketone VIa gave the unsaturated diketone VII, that was converted into the enol acetate VIII which on reduction yielded the diketone IX. The latter was converted by $LiAlH_4$ to the diol X. One hydroxyl group of this diol reacts much more readily with trityl chloride than the other, allowing the latter to be selectively oxidized with the formation of the ketol XI. Carboxylation of the sodium derivative of the ketol benzoate of XI followed by esterification afforded a mixture of the keto-esters XIIa and XIIb, that was separated by crystallization.



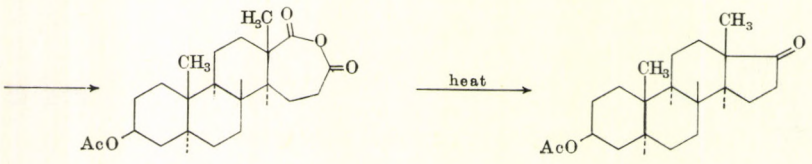
The isomer XIIb possessed the appropriate configuration of the CH_3 groups, and yielded on REFORMATSKY reaction followed by methanolysis the dihydroxydiester XIII. By succesive hydrogenation, acetylation, dehydration and again hydrogenation, the ester XIII afforded the diester XIV. The side chain was lengthened by ARNDT—EISTERT reaction. Hydrolysis and acetylation of the resulting ester XV gave the anhydride XVI, which on pyrolysis yielded epiandrosterone acetate (XVII).

Since epiandrosterone had been earlier converted to androsterone, testosterone, cholesterol and derivatives of pregnane, ROBINSON's synthesis was actually equivalent to the synthesis of the majority of steroid hormones and was an outstanding contribution to organic chemistry.





XV

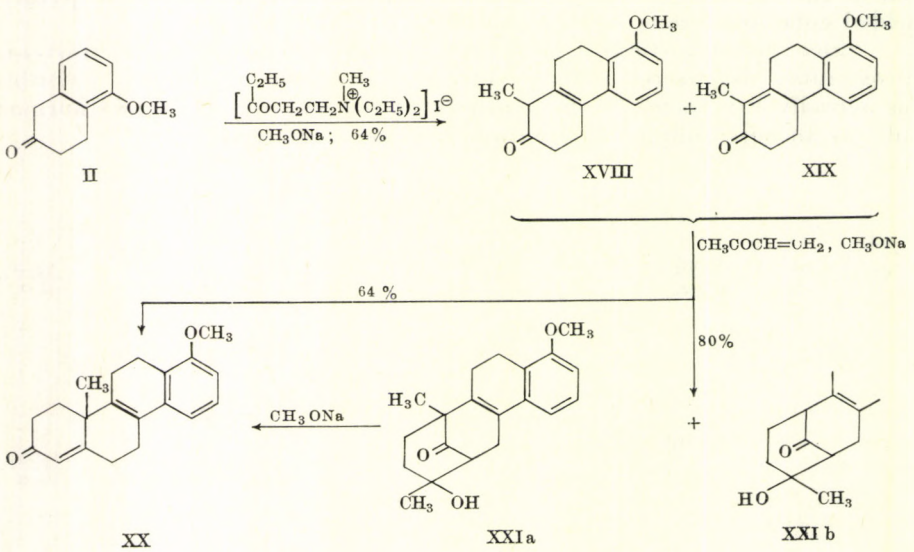


XVI XVII

The scheme involved about 40 stages, and the over-all yield did not exceed 0.0004%. Several of its operations may be shortened and modified, and it was this course that was taken by WILDS when carrying out his synthesis of etianic acid derivatives (see p. 277).

SYNTHESIS ACCORDING TO JOHNSON

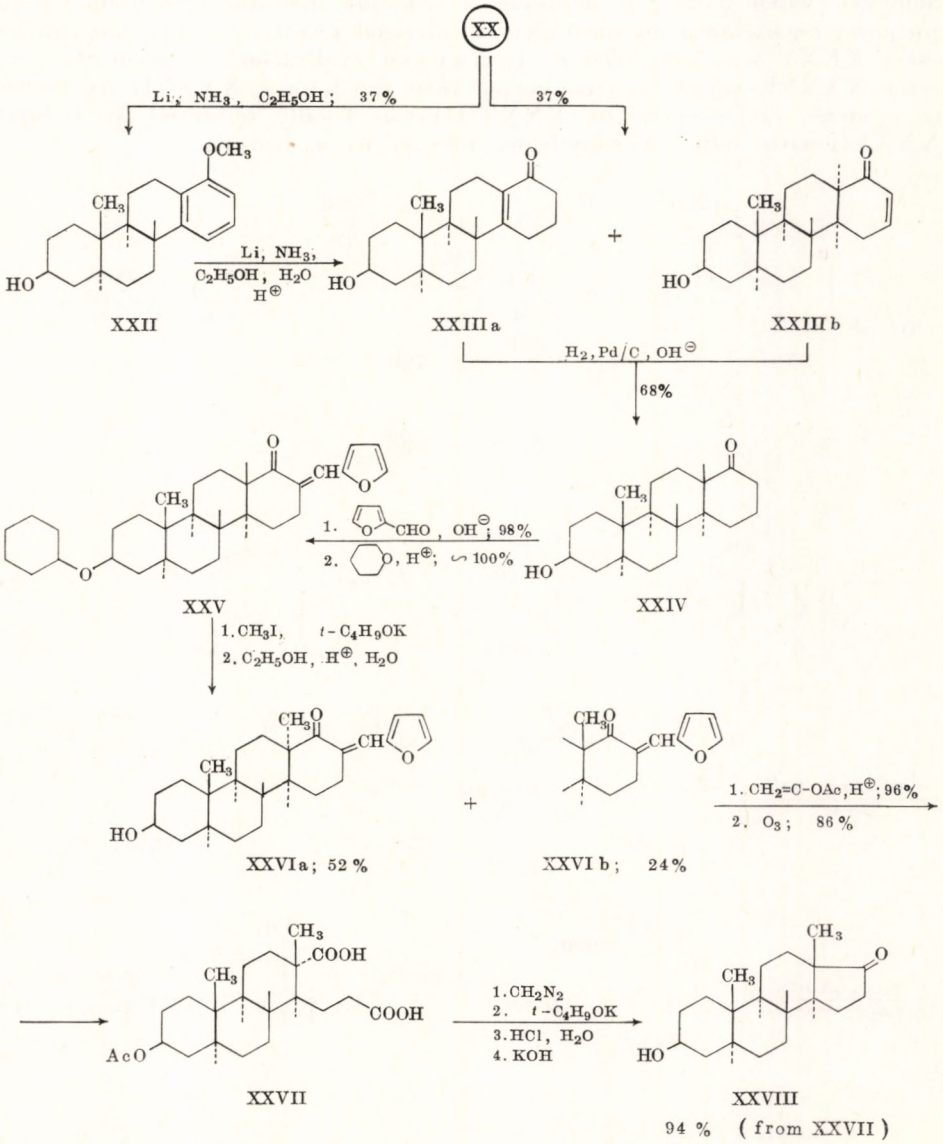
In several papers appearing in 1956, JOHNSON and collaborators [4, 13] described a number of routes to androstane derivatives via compounds of the hydrochrysene series. Like ROBINSON, JOHNSON started with 5-methoxy-2-tetralone (II) which on condensation with ethyl vinyl ketone (as its MANNICH base) underwent ring closure in position 1 as in ROBINSON's case (see p. 261), yielding a mixture of the tricyclic ketones XVIII and XIX. A second condensation of this mixture with methyl vinyl ketone, according to MICHAEL, gave the tetracyclic ketone XX. Under milder conditions, the ketol intermediates XXIa and XXIb could be isolated and their structures were established by a special investigation.



II XVIII XIX

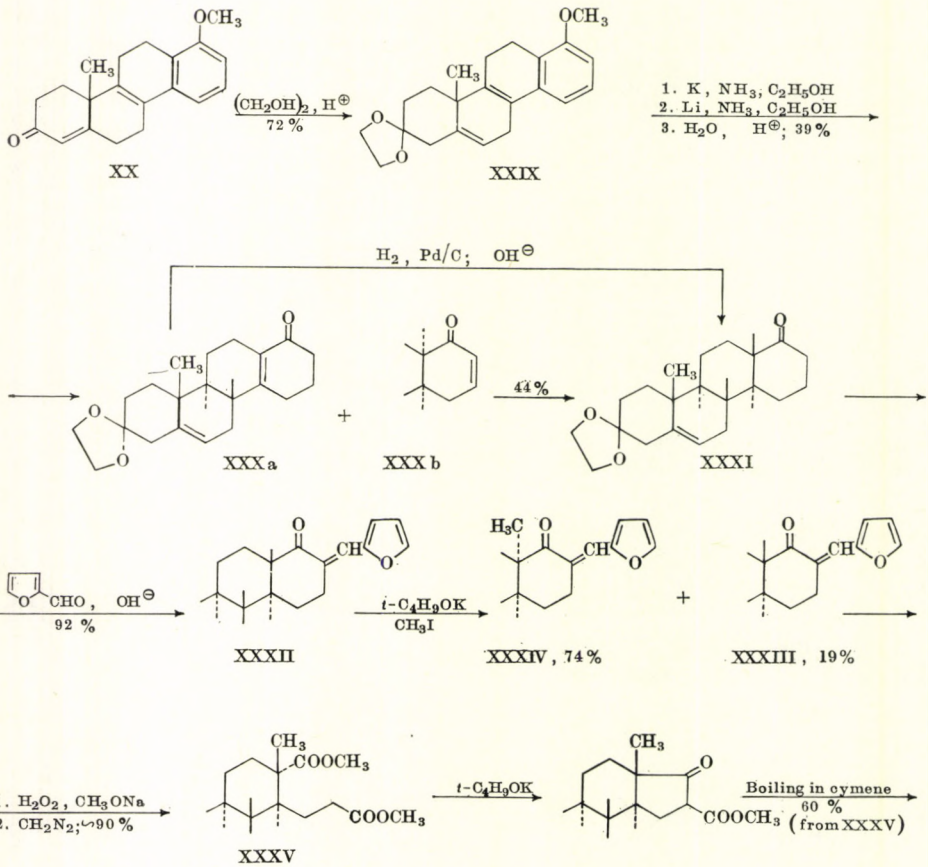
XX XXIa XXIb

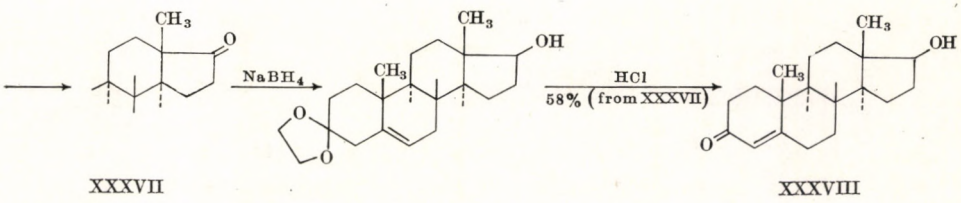
The ketone XX was reduced by lithium (or sodium) and alcohol in liquid ammonia, yielding the carbinol XXII. Subsequent reduction of the carbinol with a large excess of the same reducing agent afforded after hydrolysis a mixture of the ketols XXIIIa and XXIIIb that was subjected without separation to alkaline hydrogenation. As a result, the ketol XXIV was obtained with *trans* C/D ring junction. The ketone XX could also directly be reduced to the ketol mixture XXIIIa and XXIIIb under appropriate conditions [5, 6]. Subsequently, JOHNSON utilized the method described above for the degradation of a six-membered D-ring to a five-membered ring (see p. 248). Methylation of the furfurylidene derivative XXV gave a mixture of the 18-methyl compounds XXVIa and XXVIb, however, with the desired isomer (XXVIb) in the lower amounts. Ozonization of the acetate of XXVIb gave rise to the formation of the acid XXVII which on esterification, DIECKMANN cyclization, and hydrolysis afforded *dl*-epiandrosterone (XXVIII).



The complete synthesis involves 10 stages (several reactions being combined into a single step), if the starting material is 5-methoxy-2-tetralone (II), and 12 stages, if 1,6-dihydroxynaphthalene (I) is used. The over-all yield of *dl*-epiandrosterone (XXVIII) amounts to 1.5% with respect to I.

JOHNSON also achieved the synthesis of testosterone, starting from the ketone XX [7]. Its ketal (XXIX) was subjected to reduction in liquid ammonia, first by potassium and alcohol, and then by lithium and alcohol, both in a single operation. Hydrolysis of the products by oxalic acid gave a mixture of the unsaturated ketones XXX. XXXa was hydrogenated to the ketone XXXI. This reaction is accompanied by the partial hydrogenation of the $\Delta^{5(6)}$-bond, too, so that the yield of XXXI is not very high. The 1 : 4 proportion of the 18β-methyl compound XXXIII and its epimer XXXIV in the mixture as resulting from the methylation of the furfurylidene derivative XXXII is not very favourable either. Optimum opening of ring D could be achieved when hydrogen peroxide in alkaline medium was used for this purpose; ozonization did not give the desired result. The dicarboxylic acid ester XXXV was subjected to DIECKMANN cyclization, to form the keto-ester XXXVI, which was converted into the ketone XXXVII by heating in cymene. *dl*-Testosterone (XXXVIII) was finally obtained by reducing XXXVII with sodium borohydride, followed by hydrolysis.

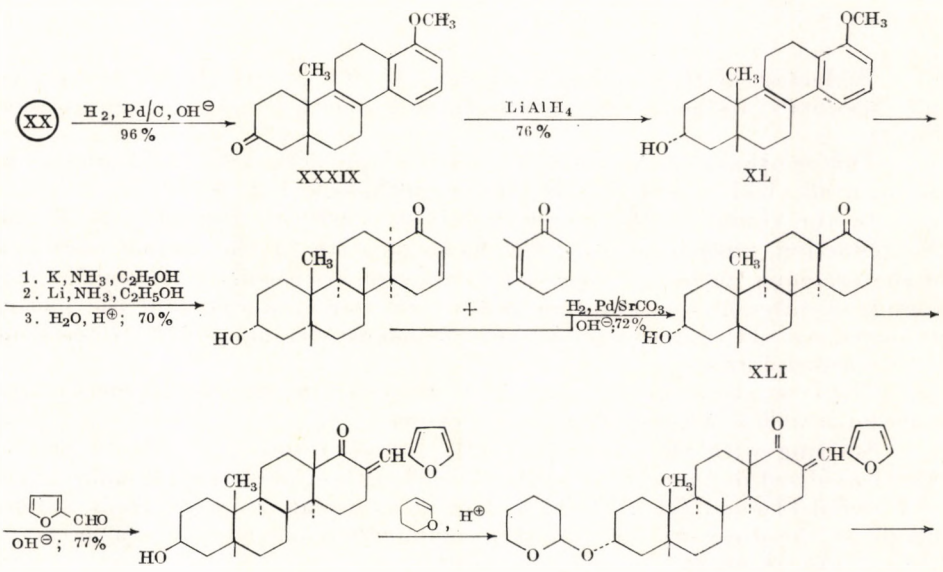


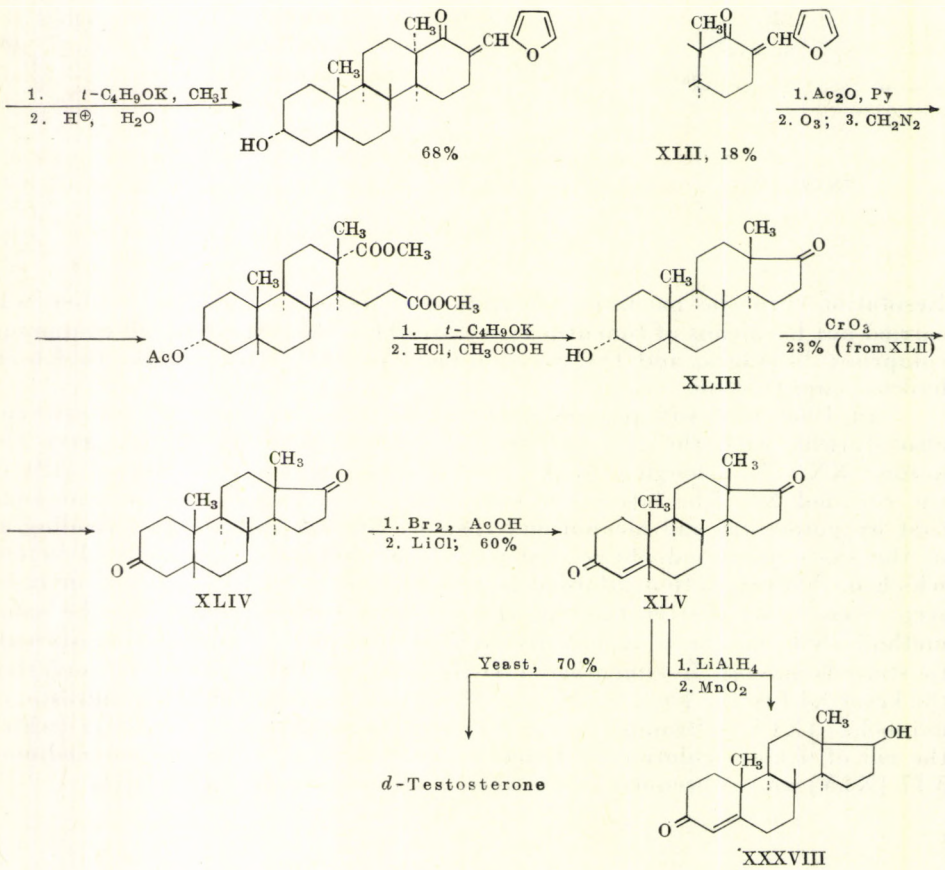


XXXVII XXXVIII

Resolution into the naturally occuring *d*-testosterone and its *l*-isomer was carried out by means of *l*-menthoxyacetate. The synthesis of the *dl*-compound comprises 14 stages, and the over-all yield is 0.2% with respect to 1,6-dihydroxynaphthalene.

In 1960 JOHNSON published [14] an alternative route to testosterone also starting with the Δ^4-3-ketone (XX). Hydrogenation of XX gave the ketone XXXIX belonging to the *cis*-AB series, which was reduced [12] to the carbinol XL. The latter was subjected to reduction in liquid ammonia, first by potassium and alcohol and then by lithium and alcohol, yielding as in the cases described above (see p. 266) a mixture of unsaturated ketons which on hydrogenation afforded largely the ketol XLI. The yields in these steps were much better than in the previous variant. Then, by the same method that had been repeatedly used to pass over from D-homosteriods to steroids having five-membered D-ring (see p. 248), JOHNSON converted the ketol XLI to the ketol XLIII which on oxidation yielded *dl*-5β-androstanedione-3,17 (XLIV). Bromination and dehydrobromination of the latter (whith the aid of lithium chloride in dimethylformamide) led to *dl*-androstenedione-3,17 (XLV) and subsequent reduction to *dl*-testosterone (XXXVIII).





Reduction of *dl*-Δ^4-androstenedione-3,17 (XLV) with the aid of fermenting (MAMOLI's method) gave *d*-testosterone, together with *l*-Δ^4-androstenedione.

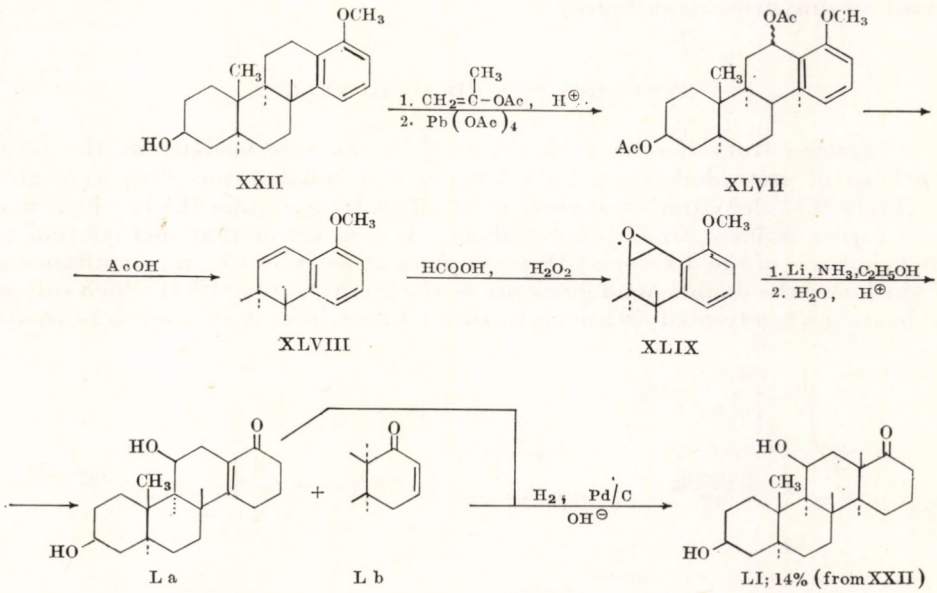
This synthesis of testosterone consists approximately of 18 stages and the over-all yield (based on dihydroxynaphthalene, I) is 0.15%.

In the course of the above described syntheses, JOHNSON, combining the reduction procedures with the hydrogenation of the double bond and of the aromatic nucleus, obtained a number of intermediate tetracyclic compounds of different configuration and several stereoisomerides of the natural products, e.g., of epiandrosterone (13-*iso*epiandrosterone) and of testosterone (13-*iso*testosterone).

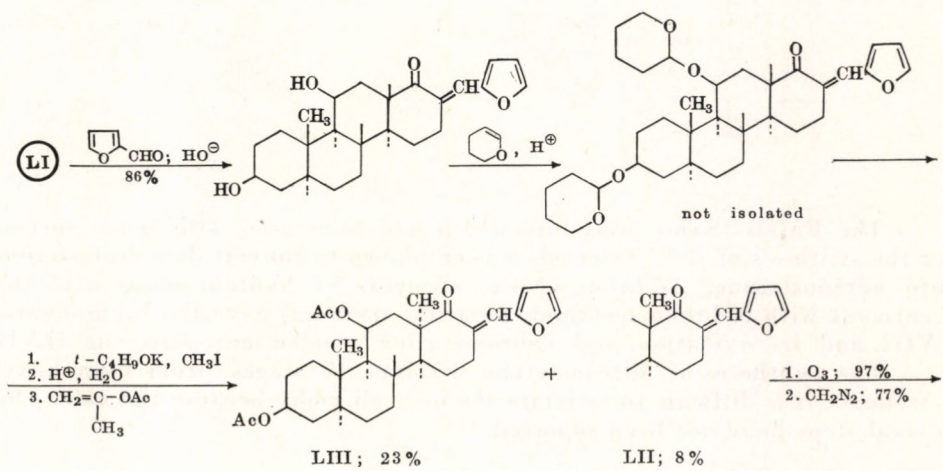
The least stereospecific stage of JOHNSON's syntheses is the methylation reaction which is accompanied by inversion at $C_{(13)}$.

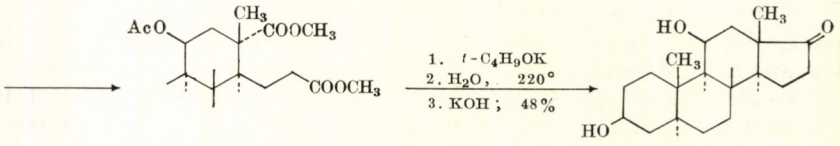
Starting with the carbinol XXII, JOHNSON was also able to prepare the 11-oxidized derivatives of androstane [8, 10], in particular, *dl*-androstane-3β,11β-diol-17-one (XLVI) which had been isolated earlier from adrenal glands as the *d*-isomer. Though this compound is inactive, it can be transformed into naturally occurring hormones.

Oxidation by lead tetra-acetate of the carbinol XXII afforded the diacetate XLVII which formed the $\Delta^{11(12)}$-compound (XLVIII) on heating with acetic acid. Reaction of XLVIII with a mixture of formic acid and hydrogen peroxide yielded the epoxide XLIX; the latter on reduction with lithium and alcohol in liquid ammonia followed by hydrolysis was transformed into a mixture of the unsaturated dihydroxyketones La and Lb. Alkaline hydrogenation of this mixture gave the dihydroxyketone LI possessing the configuration of the natural steroid.



Furthermore, JOHNSON applied the usual methods of angular methylation, opening of ring D, and cyclization to prepare *dl*-androstane-3β,11β-diol-17-one (XLVI). The largest losses were incurred during the methylation reaction when only 8% of the required isomer (LII) and 23% of the $C_{(13)}$-epimer (LIII) could be isolated.



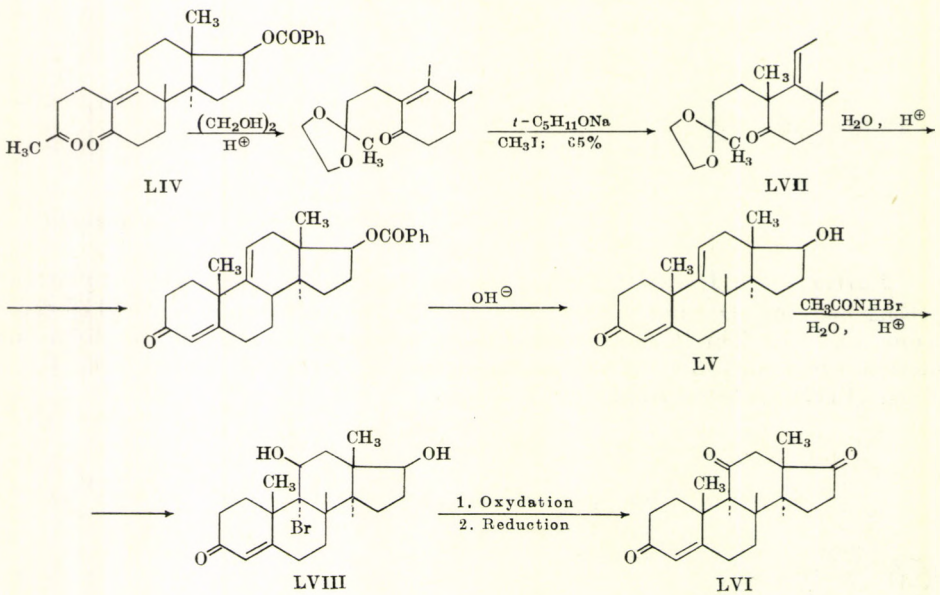


XLVI

The entire synthesis involves 16—18 steps; the yield is about 0.004% based on dihydroxynaphthalene (I).

SYNTHESIS ACCORDING TO VELLUZ

Starting from the tricyclic ketone LIV, an intermediate in the total synthesis of oestradiol (see p. 257), VELLUZ and collaborators [16] were able to obtain 9,11-dehydrotestosterone (LV) and adrenosterone (LVI) which had been earlier isolated from adrenal glands. It was found that methylation of the hemiketal of the diketone LIV takes place at position 10, and simultaneous migration of the double bond gives rise to the methylketone LVII which suffers cyclization when treated with acids to afford 9,11-dehydrotestosterone benzoate



The FRIED—SABO procedure which had been used with much success for the synthesis of $\Delta^{4,9(11)}$ steroids was employed to convert dehydrotesterone into adrenosterone. Addition of the elements of hydrobromous acid (by treatment with N-bromoacetamide in acidic medium) gave the bromohydrin LVIII, and its oxidation and debromination yielded adrenosterone (LVI).

The synthesis of adrenosterone involves 19 stages (from 6-methoxytetralone); it is difficult to estimate the over-all yield, because the values for several steps have not been reported.

REFERENCES

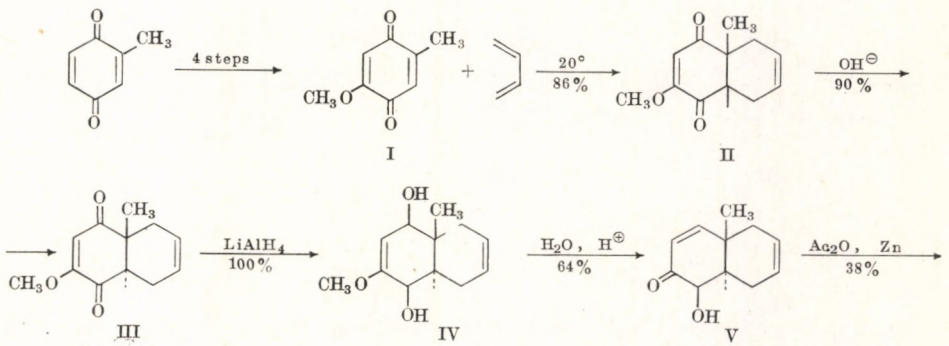
1. Cardwell, H. M. E., Cornforth, J. W., Duff, S. R., Holterman, H., and Robinson R.: *Chem. and Ind. 1951*, 389.
2. Cardwell, H. M. E., Cornforth, J. W., Duff, S. R., Holterman, H., and Robinson R.: *J. Chem. Soc. 1953*, 361.
3. Du Feu, E. C., McQuillin, F. J., and Robinson, R.: *J. Chem. Soc. 1937*, 53.
4. Johnson, W. S.: *J. Am. Chem. Soc. 78*, 6278 (1956).
5. Johnson, W. S., Ackerman, J., Eastham, J. F., and De Walt, H. A.: *J. Am. Chem. Soc. 78*, 6302 (1956).
6. Johnson, W. S., Bannister, B., and Pappo, R.: *J. Am. Chem. Soc. 78*, 6331 (1956).
7. Johnson, W. S., .Bannister, B., Pappo, R., and Pike, J. E.: *J. Am. Chem. Soc. 78*, 6354 (1956).
8. Johnson, W. S., Kemp, A. D., Pappo, R., Ackerman, J., and Johns, W. F.: *J. Am. Chem. Soc. 78*, 6312 (1956).
9. Johnson, W. S., Korst, J. J., Clement, R. A., and Dutta, J.: *J. Am. Chem. Soc. 82*, 614 (1960).
10. Johnson, W. S., Pappo, R., and Johns, W. F.: *J. Am. Chem. Soc. 78*, 6339 (1956).
11. Johnson, W. S., Rogier, E. R., and Ackerman, J.: *J. Am. Chem. Soc. 78*, 6322 (1956).
12. Johnson, W. S., Rogier, E. R., Szmuszkovicz, J., Hadler, H. I., Ackerman, J., Bhattacharya, B. K., Bloom, B. M., Stalmann, L., Clement, R. A., Bannister, B., and Winberg, H.: *J. Am. Chem. Soc. 78*, 6289 (1956).
13. Johnson, W. S., Szmuszkovicz, J., Rogier, E. R., Hadler, H. L., and Winberg, H.: *J. Am. Chem. Soc. 78*, 6285 (1956).
14. Johnson, W. S., Vredenburgh, W. A., and Pike, J. E.: *J. Am. Chem. Soc. 82*, 3409 (1960).
15. McQuillin, F. J., and Robinson, R.: *J. Chem. Soc. 1938*, 1097.
16. Velluz, L., Nominé, G., and Mathieu, J.: *Angew. Chemie 72*, 725 (1960).

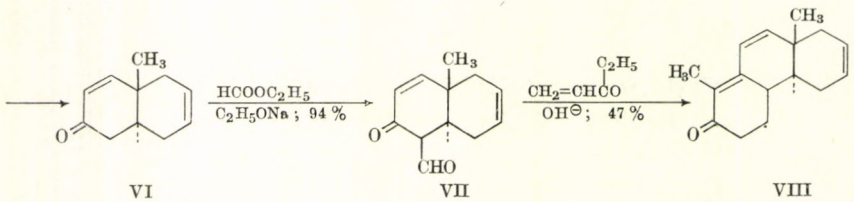
CHAPTER IV

SYNTHESIS OF 11-DESOXY COMPOUNDS OF THE PREGNANE SERIES

SYNTHESIS ACCORDING TO WOODWARD

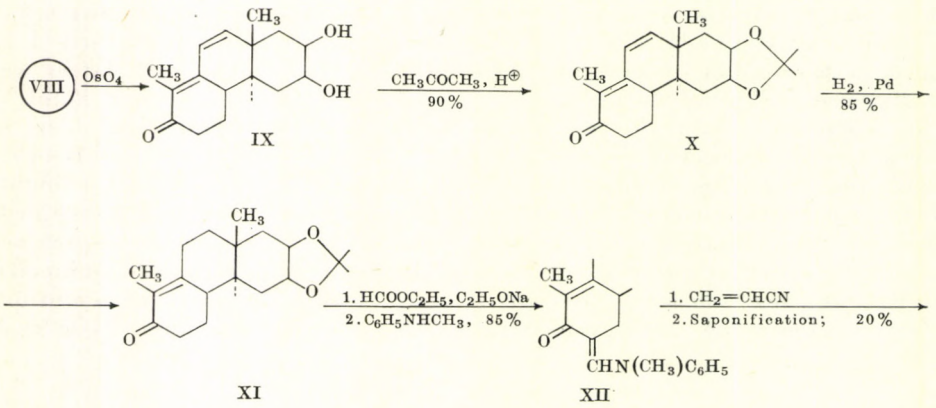
WOODWARD's syntheses [17, 18], published in 1951, were, together with the work of ROBINSON, the summit of achievements in steroid chemistry. They not only united various partial syntheses into a harmonious whole, but proved to be a mighty incentive to new explorations. WOODWARD's plan consisted in constructing first a *trans* decalone system (rings C and D) already containing the angular methyl group, and such functions that would permit subsequent formation of rings B and A; and the final task was the contraction of the six-membered D-ring to a five-membered one. WOODWARD started with the readily available methoxytoluquinone (I) and butadiene. These reacted to give the *cis*-diketone II, which was readily izomerized into the *trans* form (III). Lithium aluminium hydride reduction gave the diol IV, and the latter was hydrolyzed with acid to yield, after dehydration, the unsaturated ketol V. The remaining 'extra' hydroxyl was removed by treatment with zinc in acetic anhydride, and the resulting ketone VI now had all the desired requirements for completion of the steroid molecule: *trans* C/D-ring junction, a double bond to permit later contraction of ring D, and a keto group for attachment of ring B. Condensation of the ketone (VI) with ethyl formate in the presence of sodium ethylate afforded the formyl ketone VII, which was subjected to MICHAEL reaction with ethyl vinyl ketone. Under the reaction conditions CO was eliminated and cyclization to the tricyclic trienone (VIII) took place.



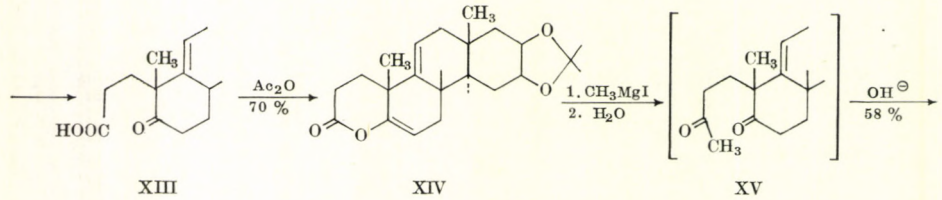


VI VII VIII

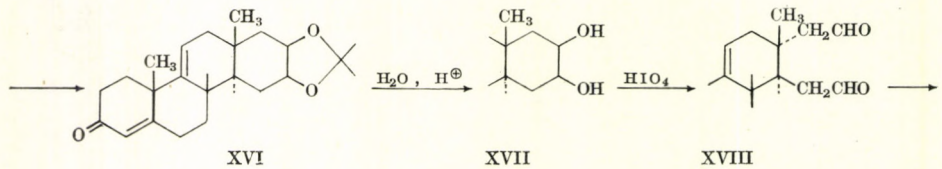
Before forming ring A, WOODWARD introduced hydroxyls into ring D by means of osmium tetroxide (acting, as is well known, mainly on the isolated double bond), then converted the glycol (IX) into the acetonide (X), a product which is stable towards alkaline agents. The 'extra' double bond in ring C was then eliminated by partial hydrogenation. Since, contrary to the ketone VI, there were two reaction centres in ketone XI, one of them had to be 'blocked', which was accomplished by formylation and subsequent treatment with methylaniline. Condensation of the methylanilinomethylene derivative (XII) with acrylonitrile, followed by alkaline hydrolysis gave a mixture of the epimeric keto-acids from which the required isomer (XIII) was isolated in a yield of 20%. All further work was now carried out with this compound. The lactone (XIV) was obtained by treatment with acetic anhydride, and was reacted successively with methyl magnesium iodide and with alkali. Under these conditions the intermediate diketone XV cyclized to the tetracyclic D-homosteroid ketone XVI.



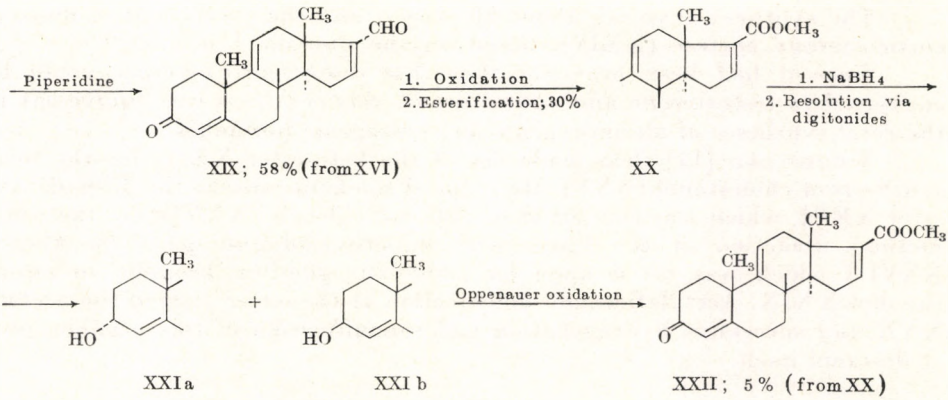
IX X XI XII



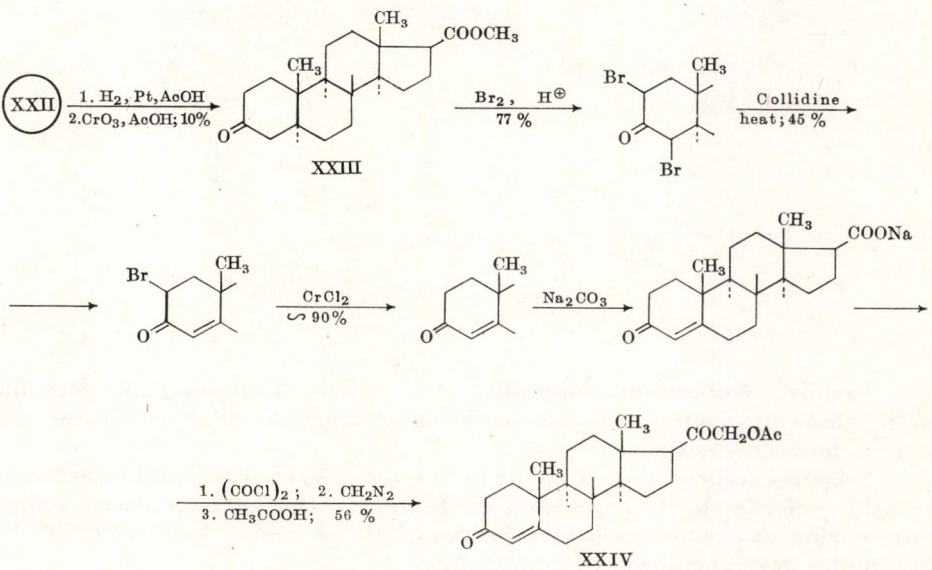
XIII XIV XV



XVI XVII XVIII



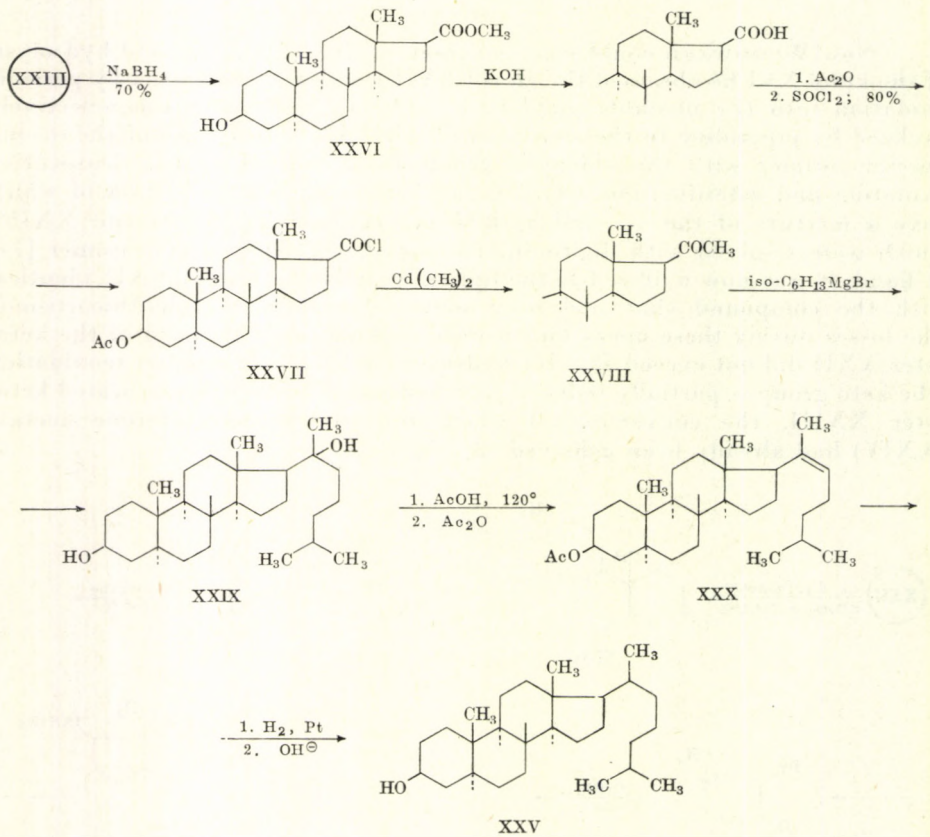
Now WOODWARD could start contracting ring D. By the acid hydrolysis of the ketol XVI he obtained the glycol XVII which was converted by periodic oxidation into the unstable dialdehyde (XVIII). The latter was selectively cyclized by piperidine to the steroid aldehyde XIX; hardly any of the second possible isomer with the aldehyde group at 15 was observed. Consecutive oxidation and esterification afforded the keto-ester XX, reduction of which gave a mixture of the 3α- and 3β-hydroxy compounds (XXIa and XXIb), which were resolved with digitonin. Having the optically active isomer [14] at hand, it was now oxidized to the optically active keto-ester XXII, identical with the compound that had been obtained earlier from hydrocortisone. The losses during these operations were very high, and the yield of the keto-ester XXII did not exceed 5%. Its hydrogenation and subsequent reoxidation (the keto group is partially reduced to a hydroxyl) yielded the saturated keto-ester XXIII, the conversion of which into desoxycorticosterone acetate (XXIV) had already been achieved [2, 13].



The synthesis involves about 30 stages, and the total yield of desoxycorticosterone acetate (XXIV), based on the quinone I is 0.00007%.

Since it had been proved earlier that desoxycorticosterone could be converted to testosterone and androsterone, this synthesis was equivalent to the total syntheses of all androgenic and gestagenic hormones.

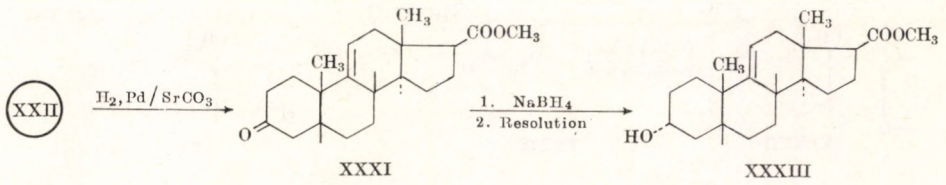
WOODWARD [14] then made use of the keto-ester XXIII for the total synthesis of cholestanol (XXV). He reduced the keto-ester to the 3β-hydroxy-ester XXVI, which was converted to the acid chloride (XXVII) by the usual method. Reaction of the latter with dimethylcadmium gave the ketone XXVIII which was acted upon by *iso*hexylmagnesium bromide to afford the diol XXIX. Acetylation and dehydration of the latter yielded the acetate XXX and successive hydrogenation and saponification of this product gave cholestanol itself.



XXVI XXVII XXVIII XXIX XXX XXV

Finally, WOODWARD succeeded [15, 16] in establishing the last link in the chain of reactions leading to the total synthesis of the major adrenocortical hormone, cortisone.

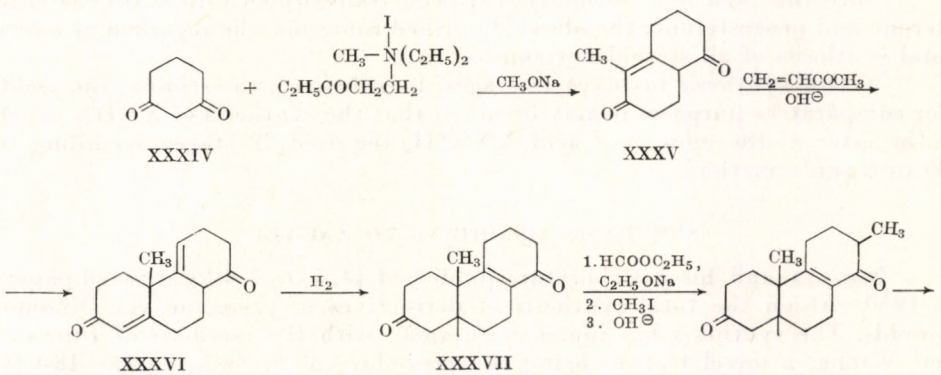
Selective hydrogenation of the keto-ester XXII led to XXXI containing a double bond in the 9(11)-position. Reduction of this keto-ester with sodium borohydride and subsequent resolution of the α and β isomerides as the digitonides gave the hydroxy-ester XXXII.

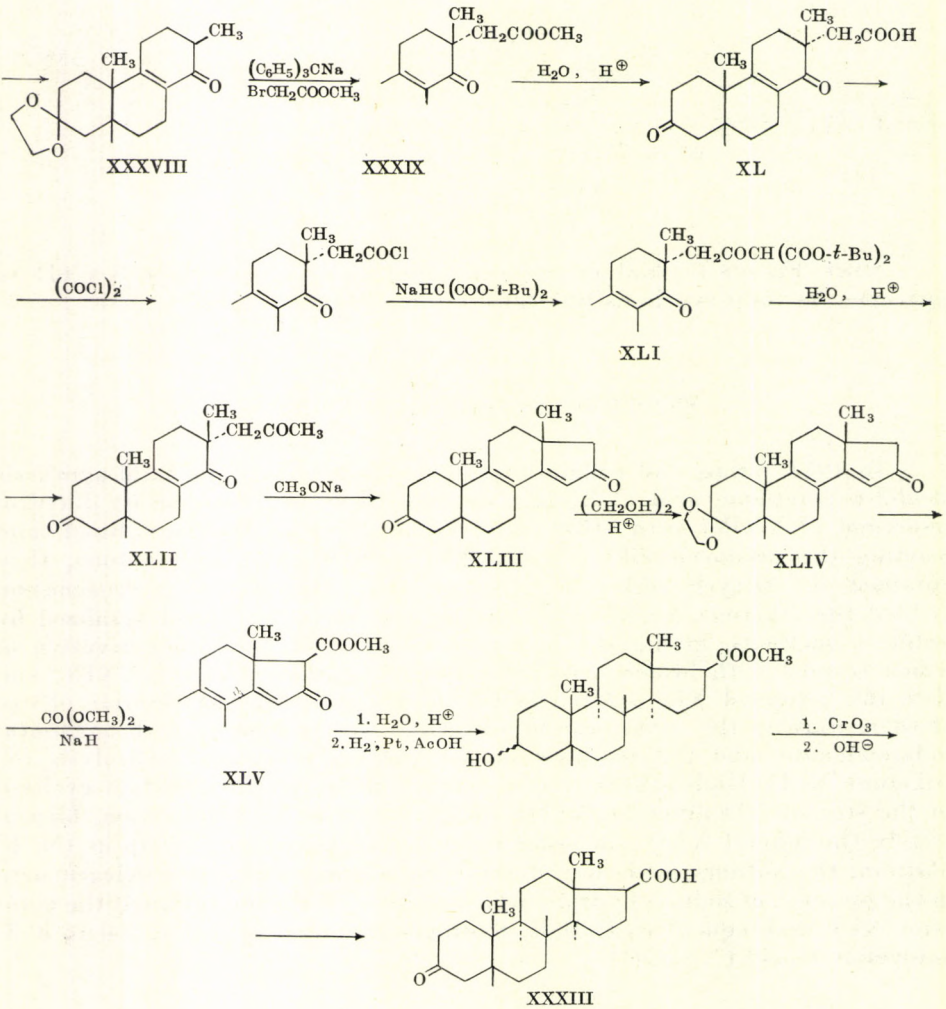


Since FIESER [3] had earlier converted the hydroxy-ester XXXII to cortisone, its total synthesis was thus accomplished.

SYNTHESIS ACCORDING TO WILDS

In 1953 WILDS and collaborators [11, 12] achieved the total synthesis of *dl*-3-ketoaetianic acid (XXXIII) via 16-ketosteroids. Condensing dihydroresorcinol (XXXIV) with ethyl vinyl ketone (as the MANNICH base), and reacting the produced diketone (XXXV) with methyl vinyl ketone, they obtained the tricyclic diketone XXXVI, that on selective hydrogenation yielded the diketone XXXVII. The latter was methylated and ketalized by ordinary methods, giving the ketone XXXVIII, the sodium derivative of which reacted with bromoacetic ester to yield the keto-ester XXXIX, and then the keto-acid XL, isolated in two isomeric forms. The chloride of one of them (having the configuration 18-β-CH_3) was condensed with *tert.*-butyl sodiomalonate, and the resultant ester (XLI) gave on acid hydrolysis the triketone XLII. Under the action of sodium methylate this product cyclized to the steroid 3,16-diketone XLIII which, subjected to ketalization, formed largely the 3-ketal XLIV. In order to introduce a carboxyl group at the 17 position, the authors made use of the condensation with dimethylcarbonate in the presence of sodium hydride, which resulted in the formation of the keto-ester XLV. Subsequent hydrolysis, hydrogenation and oxidation led to *dl*-3-ketoaetianic acid (XXXIII).





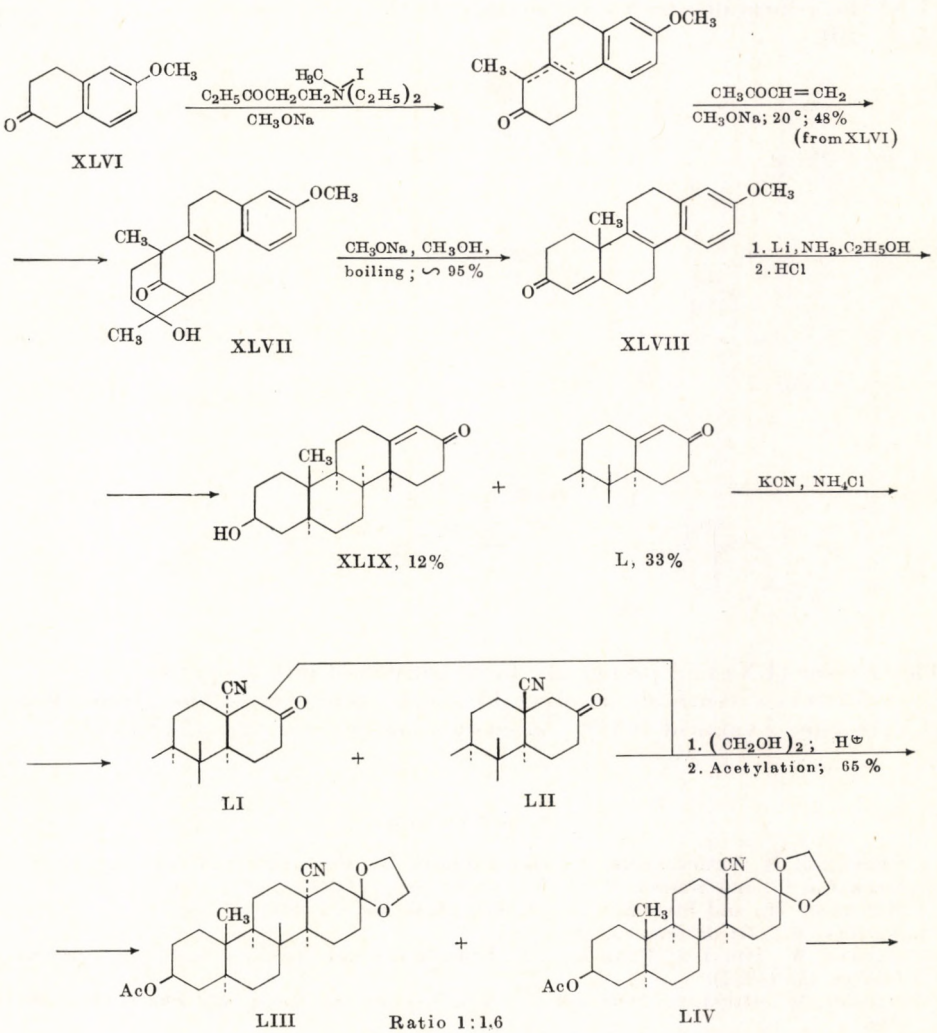
Since this acid had formerly [9] been transformed into desoxycorticosterone and progesterone, the above described route may be regarded as a new total synthesis of all steroid hormones.

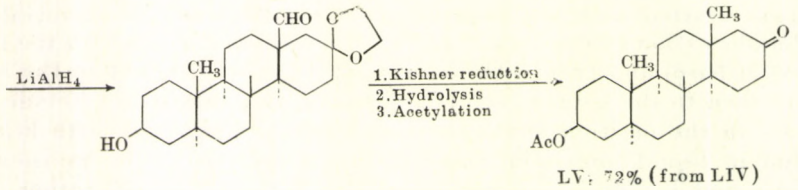
WILDS' synthesis involves 14 stages; it is difficult to estimate the yield. For comparative purposes it may be noted that the synthesis of XXIII, which is the ester of the epimer of acid XXXIII, required 22 stages according to WOODWARD's method.

SYNTHESIS ACCORDING TO NAGATA

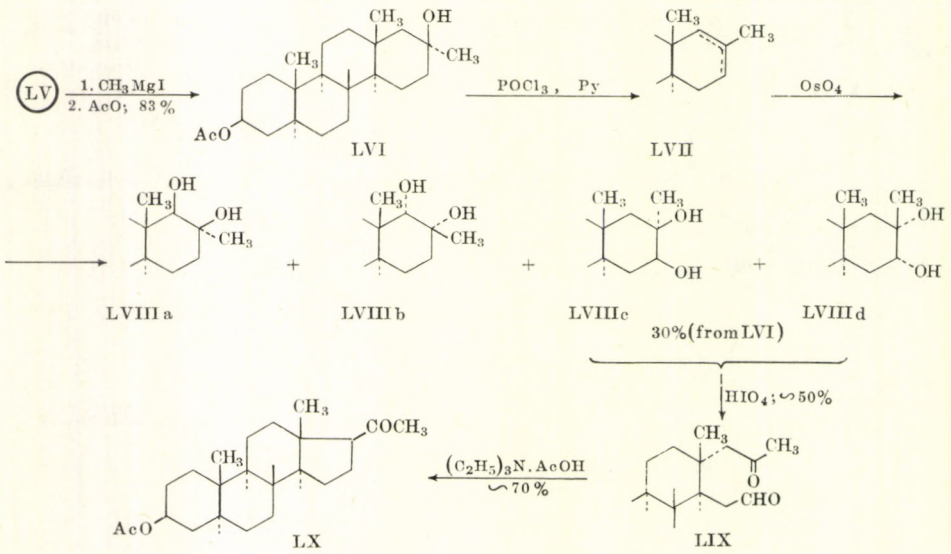
NAGATA and his collaborators published [4, 5, 6, 7, 8] a series of papers in 1960—61 on the total synthesis of derivatives of pregnane via D-homosteroids. The synthesis has much in common with the methods of JOHNSON and WILDS, a novel feature being the procedure of introducing the 18-CH_3 group, in a more stereospecific way than proposed by JOHNSON.

NAGATA started with the relatively well available 6-methoxytetralone-(XLVI). Condensation of this compound with ethyl vinyl ketone (in the form of a MANNICH base) and then with methyl vinyl ketone led first to the ketol XLVII and then to the ketone XLVIII, differing from JOHNSON's ketone (see p. 264) only in the position of the methoxyl group. Reduction with lithium and alcohol in liquid ammonia, followed by hydrolysis gave the isomeric ketols XLIX and L. The latter, possessing the 'natural' configuration, was obtained predominantly. Addition of hydrocyanic acid to (L) led to a mixture of the keto-nitriles LI and LII of which the ketal acetates, LIII and LIV, were separated by crystallization. (The 18β-isomer constituted more than 60% of the mixture.) The nitrile group was converted into a methyl group by a series of reductions, and the D-homosteroid 17-ketone (LV) was isolated on hydrolysis and acetylation.





Reaction of the ketone (LV) with methylmagnesium iodide yielded the carbinol (LVI), that was dehydrated to a mixture of Δ^{16}- and Δ^{17}-compounds (LVII). Oxidation of the mixture with osmium tetroxide led to a mixture of the four glycols LVIIIa—d which could be separated by crystallization and chromatography. Two glycols (isolated in an over-all yield of 30%) subjected to periodic acid oxidation gave the same unstable keto-aldehyde (LIX) that readily cyclized to the acetate of *dl*-Δ^{16}-5α-pregnene-3β-ol-20-one (LX) the *d*-form of which was obtained as the degradation product of tomatidine [10].



This ketone (LX) had previously been converted into progesterone [1].

NAGATA's synthesis involves 15 stages; the yield of the acetoxyketone (LV) reached a value of 0.35% based on 6-methoxytetralone-2 (XLVI).

REFERENCES

1. CAMERINO, B., VERCELLONE, A., and ALBERTI, G.: *Gaz. chim. italiana 83*, 795 (1953).
2. DJERASSI, C., and SCHOLZ, C.: *J. Am. Chem. Soc. 69*, 2404 (1947).
3. HEYMANN, H., and FIESER, L. F.: *J. Am. Chem. Soc. 73*, 4054 (1951).
4. NAGATA, W.: *Tetrahedron 13*, 268 (1961).
5. NAGATA, W., HIRAI, S., TERASAWA, T., KIKKAWA, I., and TAKEDA, K.: *Chem. and Pharm. Bull. 9*, 750 (1961).
6. NAGATA, W., HIRAI, S., TERASAWA, T., and TAKEDA, K.: *Chem. and Pharm. Bull. 9*, 769 (1961).

7. NAGATA, W., TERASAWA, T., AOKI, T., and TAKEDA, K.: *Chem. and Pharm. Bull. 9*, 783 (1961).
8. NAGATA, W., TERASAWA, T., HIRAI, S., and TAKEDA, K.: *Tetrahedron Letters 17*, 27 (1960).
9. REICHSTEIN, T., and FUCHS, H. G.: *Helv. Chim. Acta 23*, 658 (1940).
10. SATO, Y., KATZ, A., and MOSETTIG, E.: *J. Am. Chem. Soc. 73*, 880 (1951).
11. WILDS, A. L., RALLS, J. W., TYNER, D. A., DANIELS, R., KRAYCHY, S., and HARNIC, M.: *J. Am. Chem. Soc. 75*, 4878 (1953).
12. WILDS, A. L., RALLS, J. W., WILDMAN, W. C., and MCCALEB, K. E.: *J. Am. Chem. Soc. 72*, 5794 (1950).
13. WILDS, A. L., and SCHUNK, C.: *J. Am. Chem. Soc. 80*, 2427 (1948).
14. WOODWARD, R. B., SONDHEIMER, F., and TAUB, D.: *J. Am. Chem. Soc. 73*, 3547 (1951).
15. WOODWARD, R. B., SONDHEIMER, F., and TAUB, D.: *J. Am. Chem. Soc. 73*, 4057 (1951).
16. WOODWARD, R. B., SONDHEIMER, F., and TAUB, D.: *J. Am. Chem. Soc. 74*, 4223 (1952).
17. WOODWARD, R. B., SONDHEIMER, F., TAUB, D., HEUSSLER, K., and MCLAMORE, W.: *J. Am. Chem. Soc. 73*, 2403 (1951).
18. WOODWARD, R. B., SONDHEIMER, F., TAUB, D., HEUSSLER, K., and MCLAMORE, W.: *J. Am. Chem. Soc. 74*, 4223 (1952).

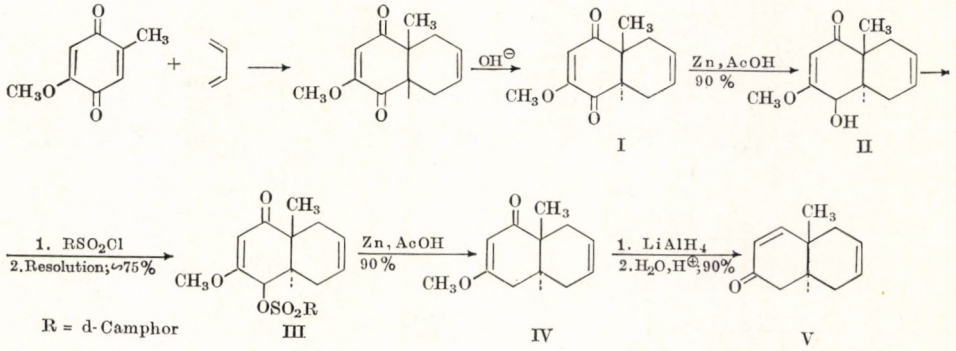
CHAPTER V

SYNTHESES OF 11-HYDROXY COMPOUNDS OF THE PREGNANE SERIES

In this section the total synthesis of derivatives of pregnane or closely related compounds will be described, by methods which involve the introduction of the oxygen function in the 11 position at the initial stages. It is for this distinction that WOODWARD's synthesis was discussed in the previous section (see p. 273), although it is not only a method for the preparation of 11-desoxypregnanes, but also of 11-oxidized pregnanes; the conversion of the former into the latter has been known for a long time.

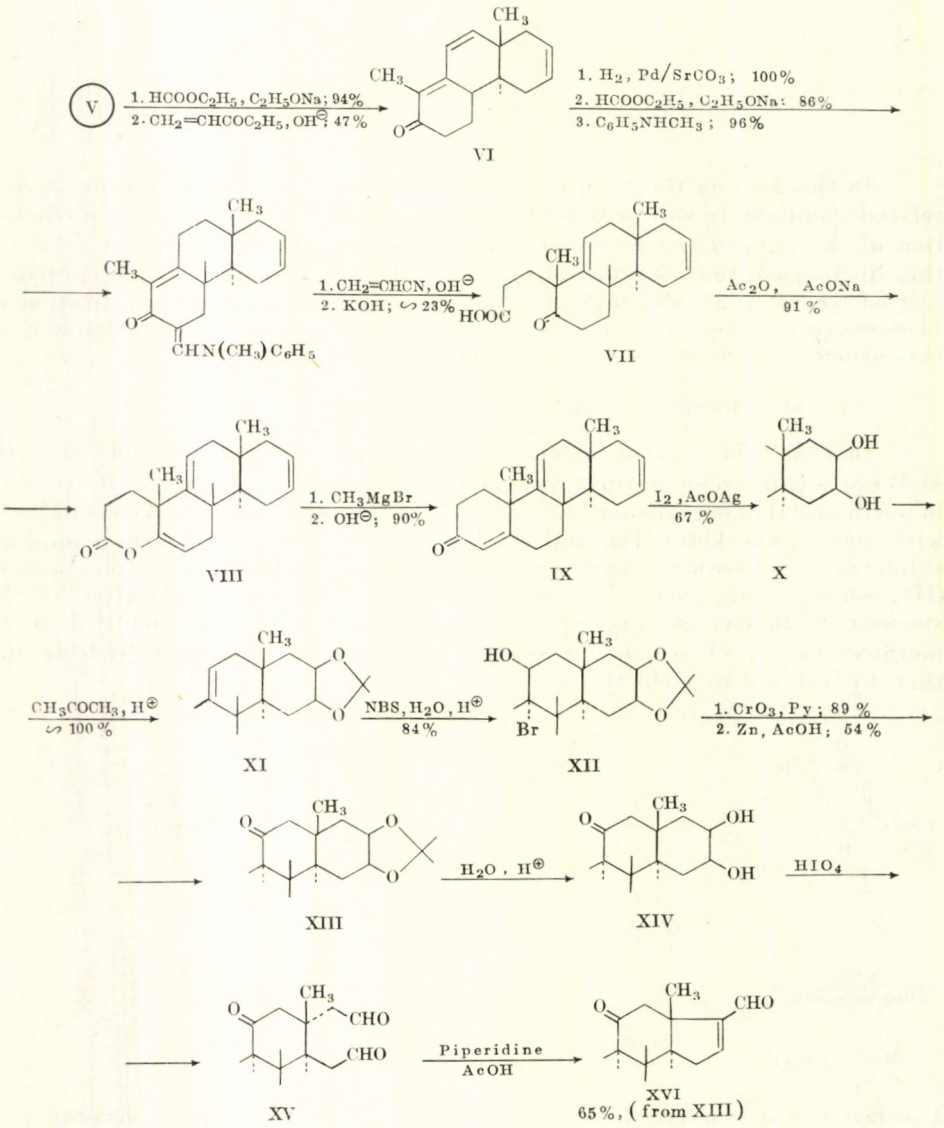
SYNTHESIS OF CORTISONE BY THE MONSANTO GROUP

In 1953—54 a group of chemists developed at Monsanto on the basis of WOODWARD's scheme their own modification for the synthesis of steroids, in particular that of cortisone [4, 5, 6, 34]. WOODWARD's diketone (I) was reduced with zinc to the ketol (II), and resolved by crystallization of the camphorsulphonate. Subsequent work was carried out with the laevorotatory isomer (III) whose configuration corresponded to the natural configuration of the steroids. Reductive cleavage of the ester III by zinc in acetic acid led to the methoxy ketone IV which was reacted with lithium aluminium hydride and then hydrolyzed to yield the dienone V.

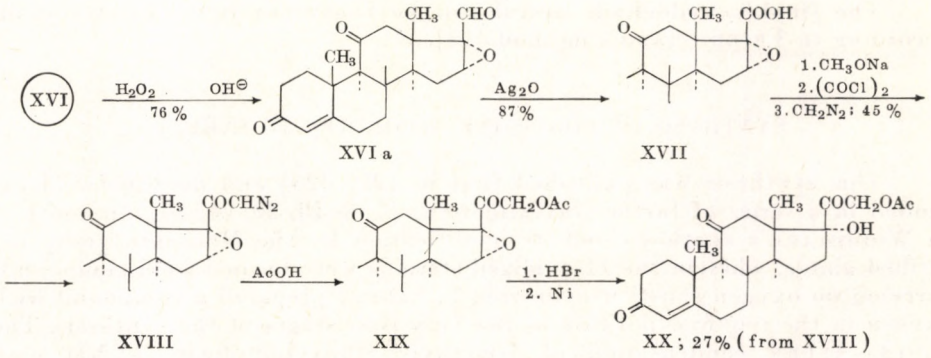


The latter was converted into the tricyclic ketone VI exactly according to WOODWARD's method and then, without any preliminary protection of the double bond in ring D, into the keto-acid VII and lactone VIII. Treatment of the lactone with methyl magnesium bromide at −50° and then with alkali afforded the tetracyclic ketone IX which (in the form of the racemate) was subjected to PREVOT oxidation (iodine and silver acetate) to give the 16,17-*cis*-diol X; the other double bonds were not affected. The acetonide of the diol

(XI) was converted by means of FRIED and SABO's method [10] into the bromohydrin XII which was then oxidized and debrominated, forming the diketone XIII. The acetonide protection was then removed, and the glycol (XIV) oxidized to the dialdehyde XV; the latter could be cyclized to the steroid diketo-aldehyde XVI.

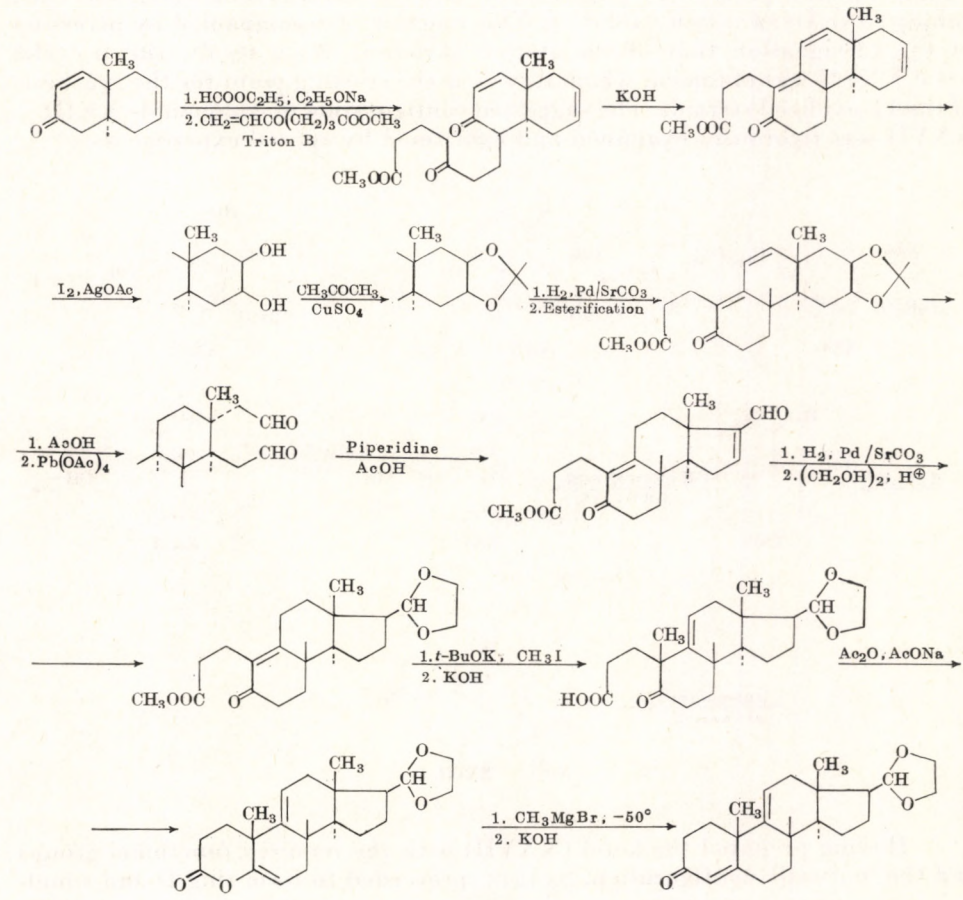


This was reacted with alkaline hydrogen peroxide, giving the epoxide (XVIa), which on oxidation yielded the acid (XVII). Its chloride was converted via the diazoketone XVIII into the acetoxyketone XIX and finally, by the action of hydrobromic acid followed by reduction in the presence of Raney nickel, into *dl*-cortisone acetate (XX).



Comprising 27 stages, the synthesis gave a 0.04% over-all yield of *dl*-cortisone acetate (XX), based on methoxytoluquinone. A notable feature of the synthesis is its high stereospecificity (except the preparation of the keto-acid VII).

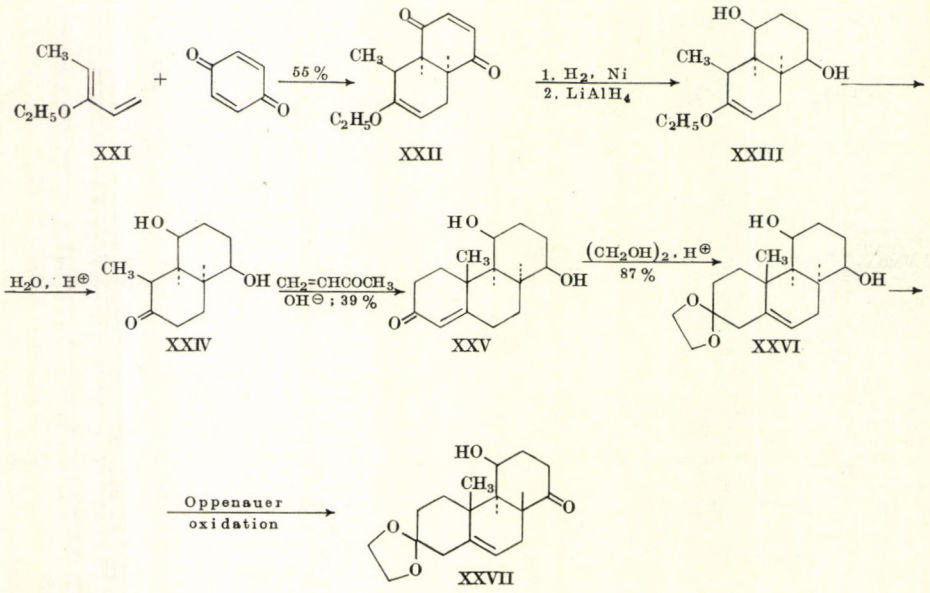
In another (incomplete) way described in a patent [3], methyl heptene-6-one-5-oate is used for constructing the rings A and B.



The final ketoaldehyde acetal can be converted into 11-ketosteroids according to FRIED—SABO's method [10].

SYNTHESIS OF CORTISONE ACCORDING TO SARETT

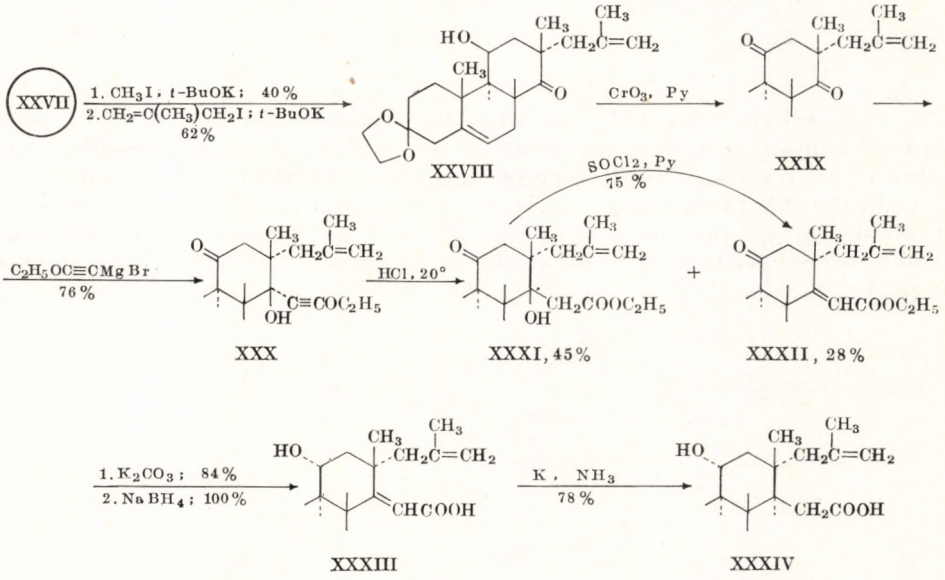
This synthesis was published first in 1952 [25] and modified and extended in a series of further investigations [7, 8, 19, 20, 26, 27]. In contrast to WOODWARD's synthesis and its modification by the Monsanto group described above, wherein the 11-oxidized steroids were formed from compounds carrying no oxygen substituent in ring C, SARETT prepared a compound with oxygen in the required position in the very first stages of the synthesis. The DIELS—ALDER condensation of 1-methyl-2-ethoxybutadiene (XXI) with quinone yielded the bicyclic *cis-cis* diketone XXII which, by selective hydrogenation and subsequent reduction with lithium aluminium hydride was converted into the diol XXIII. Acid hydrolysis of the latter led to the keto-diol XXIV, and this was condensed with methyl vinyl ketone in the presence of an alkaline agent (best of all trimethylbenzylammonium hydroxide, 'Triton B') to give the tricyclic keto-diol XXV. The keto group of this compound was now protected by conversion into the ketal XXVI which was then subjected to OPPENAUER oxidation. This reaction is accompanied by inversion at $C_{(8)}$ (designation that of the steroid skeleton). As a result, the tricyclic ketol XXVII was obtained, which served as the starting point for the synthesis of the 11-oxidized steroids. The suggested configuration of compounds XXIII—XXVII was rigorously examined and confirmed by special experiments.



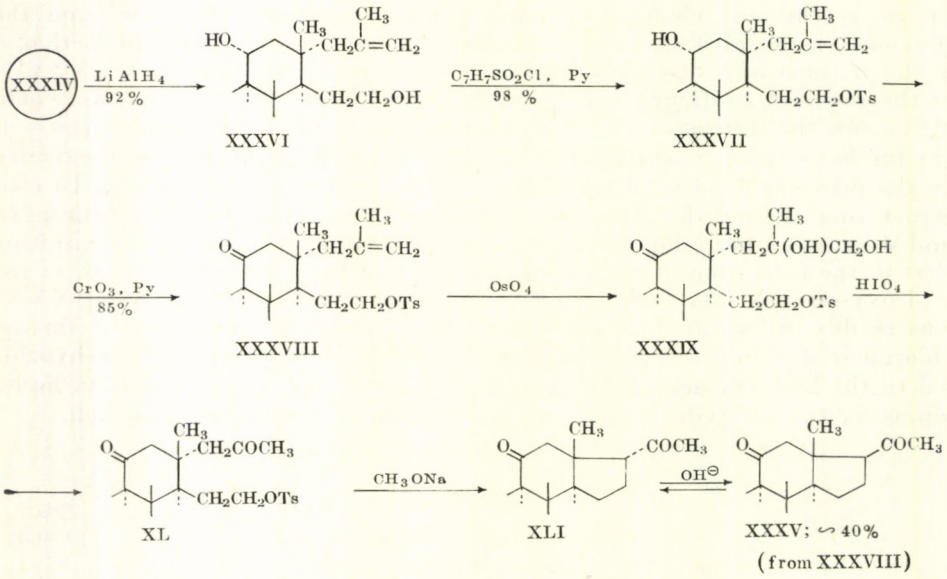
XXI XXII XXIII XXIV XXV XXVI XXVII

Having prepared the ketol (XXVII) with the required functional groups and the 'natural' configuration, SARETT proceeded to form ring D and simul-

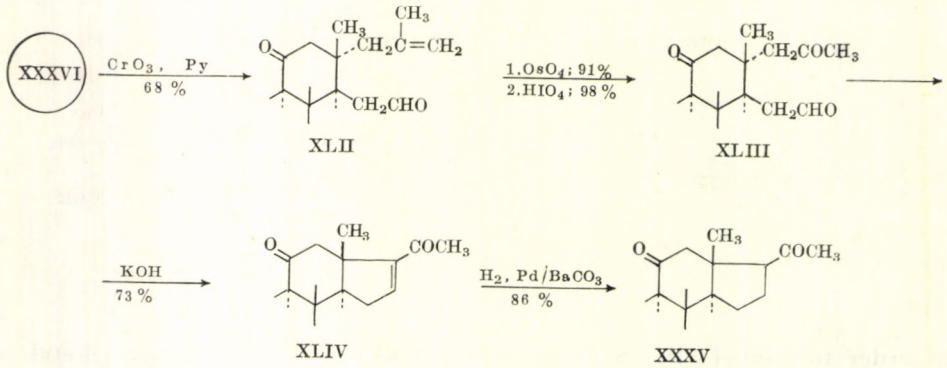
taneously the side chain, employing a method entirely different from the previous syntheses. Consecutive alkylation with methyl iodide and methallyl in the presence of potassium *tert.*-butoxide gave the substituted ketol XXVIII of the required configuration. Since the presence of the 11-OH group would affect now the stereospecificity of the reduction of the double bond adversely, the further steps were carried out after the ketol (XXVIII) had been oxidized to the diketone XXIX, in which the 11-keto group is very reactive. To construct ring B, not the REFORMATSKY reaction (cf. the work of BACHMANN and MIESCHER), but ethoxyethynylmagnesium bromide was used [1], resulting first in the formation of the carbinol XXX and then, after hydrolysis, of the hydroxy-ester XXXI and the unsaturated ester XXXII. Compound XXXI was readily dehydrated to the ester XXXII under the influence of thionyl chloride in pyridine. Alkaline hydrolysis and reaction with sodium borohydride led to the hydroxy-acid XXXIII which was reduced by potassium in liquid ammonia to the hydroxy-acid XXXIV of the required configuration.



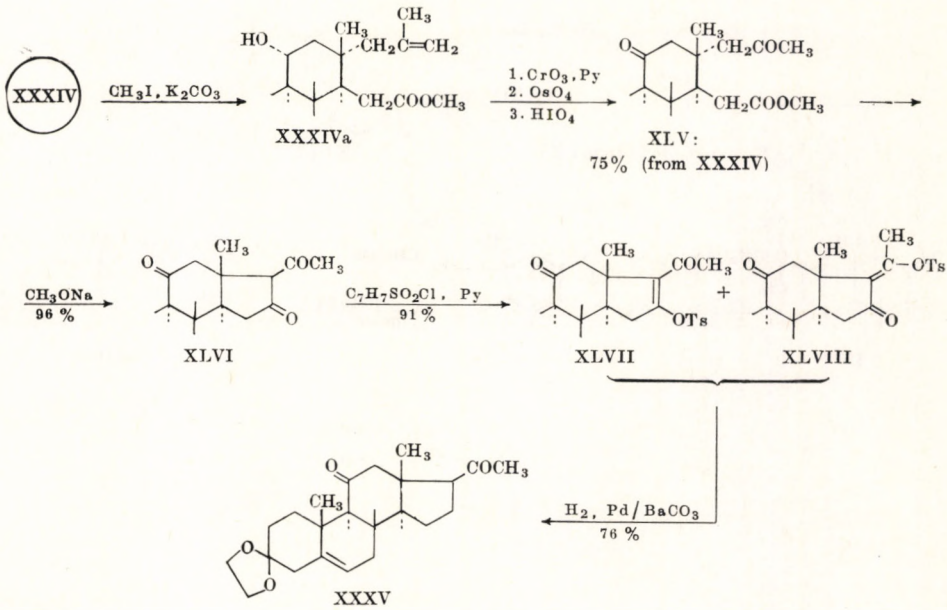
In order to convert the hydroxy-acid XXXIV into the 3-ethyleneketal of 11-ketoprogesterone (XXXV), an intermediate in the synthesis of cortisone, SARETT developed three methods. The first [14] consisted in reducing the acid XXXIV with lithium aluminium hydride to the diol XXXVI. The latter readily gave a monotosylate (XXXVII) which was then oxidized to the ketone XXXVIII. Treatment with 1 mole of osmium tetroxide led to the glycol XXXIX and this was subjected to periodic acid oxidation to give the diketone XL. Under the action of sodium methoxide, the diketone cyclized into diketone XLI, the epimer of XXXV. Compound XLI in alkaline medium yielded an easily separable equilibrium mixture of the diketones XLI and XXXV.



The second route [21] consisted in oxidizing the diol XXXVI with chromic anhydride in pyridine (SARETT's reagent) to the keto-aldehyde XLII followed by treatment with osmium tetroxide and then with periodic acid to yield the diketo-aldehyde XLIII. Cyclization of the latter in the presence of alkali led to the 3-ethyleneketal of 16,17-dehydro-11-ketoprogesterone (XLIV) which was hydrogenated to the 3-ethyleneketal of 11-ketoprogesterone (XXXV).



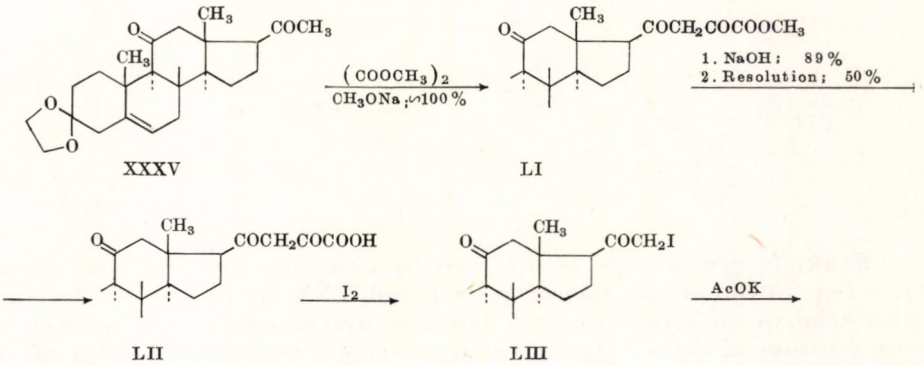
According to the third method [2], the acid XXXIV was esterified with the aid of methyl iodide and potassium carbonate in acetone. The resulting ester (XXXIVa) was oxidized in three subsequent steps by chromic anhydride in pyridine, osmium tetroxide, and periodic acid to give the diketo-ester XLV. When treated with sodium methodixe the latter cyclized almost quantitatively into the triketone XLVI. To remove the 16-keto group, SARETT transformed the triketone with the aid of *p*-toluenesulphochloride in pyridine into a mixture of the enolic tosylates XLVII and XLVIII, which on hydrogenolysis gave the 3-ethyleneketal of 11-ketoprogesterone (XXXV).

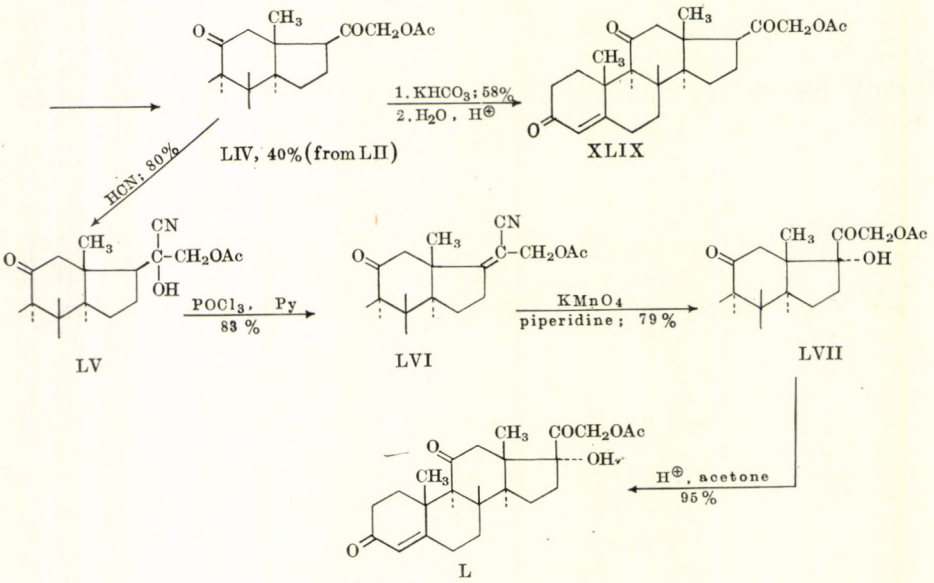


Of the three methods for preparation of the diketone XXXV, best results were obtained with the last (over-all yield 50% as compared with 31% in the first, and 36% in the second method, based on the acid XXXIV).

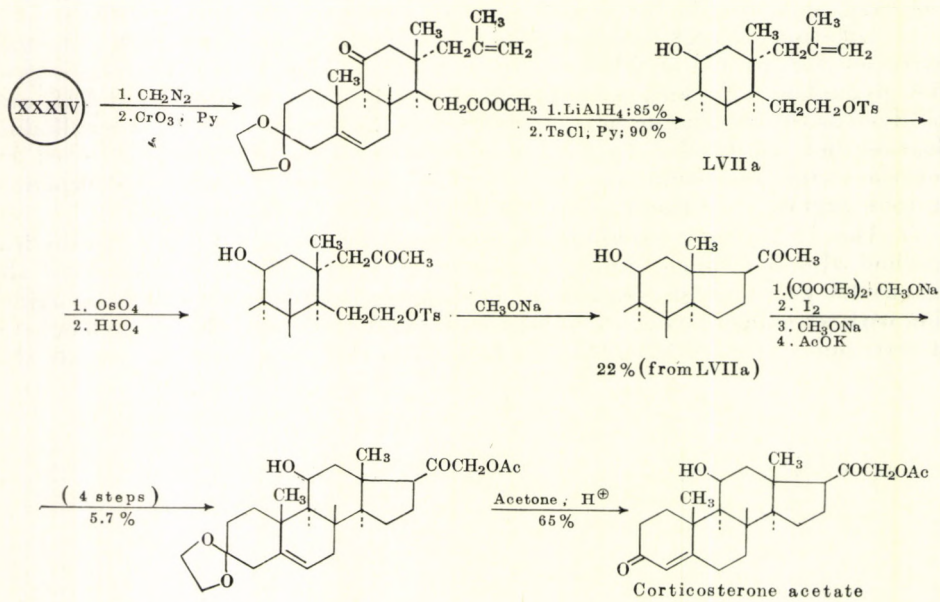
Diketone XXXV was converted to dehydrocorticosterone (XLIX) and cortisone acetate (L) as follows [22]. Condensation with methyl oxalate gave the glyoxalate LI which was saponified to the corresponding acid LII, and resolved as the strychnine salts. Iodination of the (+)-acid followed by alkaline degradation led to the 21-iodo compound (LIII) which was converted by reaction with potassium acetate into the 3-ethyleneketal of dehydrocorticosterone acetate (LIV) and then into dehydrocorticosterone (XLIX).

The 17-hydroxy group was introduced by means of the cyanohydrin method also developed earlier by SARETT [23, 24]. The cyanohydrin of the ketone LV gave on dehydration the unsaturated nitrile (LVI) which by oxidation with permanganate in the presence of pyridine yielded the 3-ethyleneketal of cortisone acetate (LVII). On acid hydrolysis this gave cortisone acetate (L).





Also corticosterone was synthesized [14, 22], starting from the epimer of the acid XXXIV.



Saretт's synthesis is highly stereospecific; the low yields at certain stages (e.g. in the preparation of the ketodiol XXV are due to side reactions rather than to the formation of undesirable stereoisomers. The presence and steric position of the substituent at C_{11} exerts a considerable effect on the

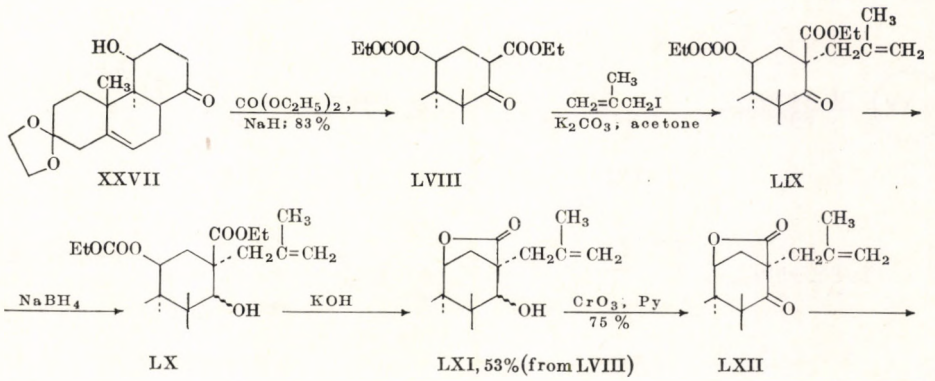
steric course of the reaction; thus, reduction of the 11-epimer of XXXIII gives largely the 14β-compound.

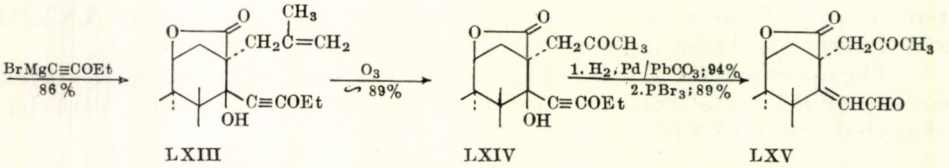
The optimum variant of SARETT's cortisone synthesis involves 28 stages, and the total yield of cortisone acetate is about 0.04% based on 1-methyl-2-ethoxybutadiene (XXI).

SYNTHESIS OF ALDOSTERONE ACCORDING TO WETTSTEIN (FIRST VARIANT)

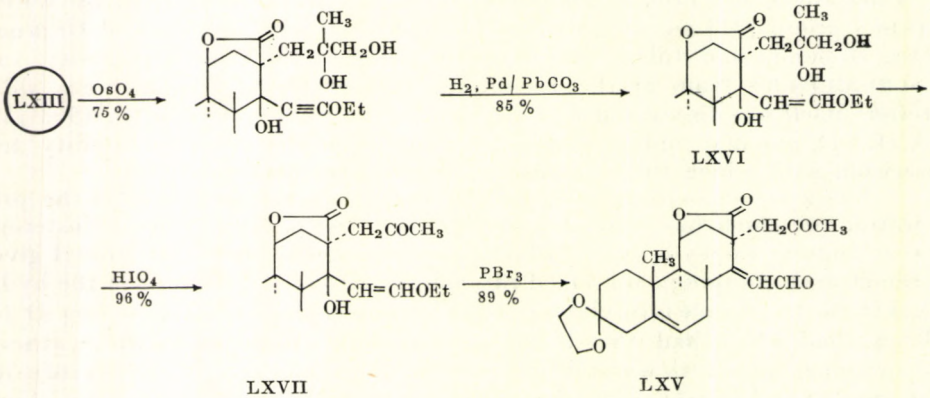
The synthesis of the powerful adrenal cortical hormone aldosterone was described in a brief communication for the first time in 1955 by WETTSTEIN's group [31] working in close co-operation with chemists of Organon (Oss, Holland) and Ciba, REICHSTEIN's group at the Basel University, and ESCHENMOSER's team at the Technische Hochschule of Zürich. Since aldosterone itself was discovered and isolated in the pure state only in 1953 [32, 33, cf. 11], one may only regard with admiration the amazing rapidity and precision with which these chemists achieved the total synthesis.

The starting material was SARETT's hydroxy-ketone (XXVII) the preparation of which has been described above (see p. 286). Since aldosterone has an angular aldehyde group (which, on reaction with the 11β-hydroxyl gives a semiacetal grouping), it seemed rational to introduce it at once in the hydroxyketone by simple formylation, with the project of forming then ring D by the method which had already been successfully employed in the synthesis of cortisone. Such work was indeed partially carried out [35, 39], but eventually the route via 18-carboxyl compounds proved to be more convenient. Condensation of the hydroxyketone XXVII with ethyl carbonate gave the keto-ester LVIII, alkylation of which with methallyl iodide yielded the substituted keto-ester LIX. Reduction with sodium borohydride resulted in the hydroxy-ester LX, and this, on alkaline hydrolysis, gave the hydroxylactone LXI, possessing the oxidized grouping of aldosterone [28]. In order to form ring D and the side chain, the authors in general followed SARETT's route. The hydroxylactone (LXI) was oxidized to the keto-lactone XLII, and the latter was reacted with ethoxyethynylmagnesium bromide to yield the comparatively stable ethynylcarbinol LXIII containing a small amount of the isomer. Its ozonization (without separation of the mixture) afforded the hydroxyketone LXIV. Consecutive selective hydrogenation and hydrolysis produced [29] the unsaturated keto-aldehyde LXV.

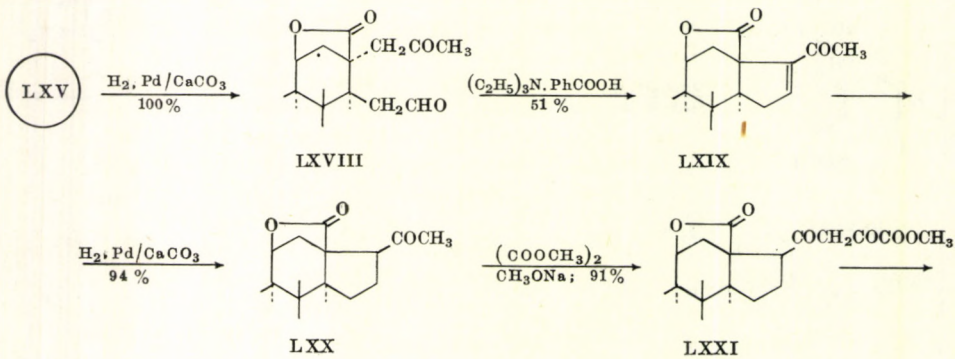


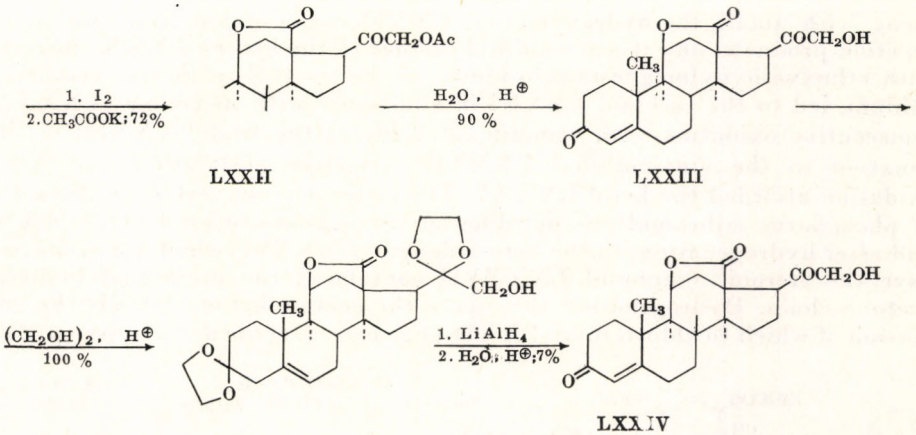


In an alternative method [29, 31], compound LXIII is oxidized with osmium tetroxide to the triol, and this is hydrogenated to the vinylcarbinol LXVI which, in turn, is subjected to cleavage by periodic acid, forming the ketol LXVII, finally, the latter is hydrolyzed to the keto-aldehyde LXV.



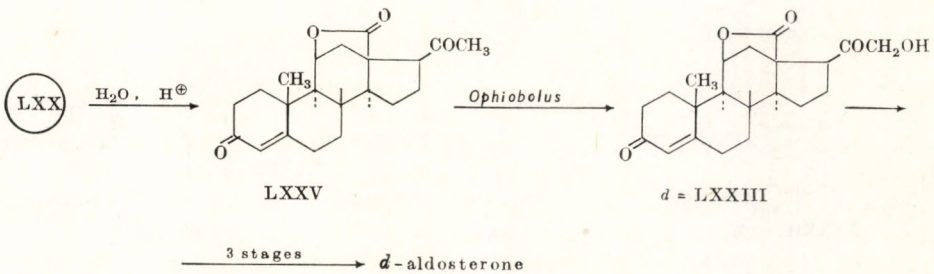
Hydrogenation of the α,β-unsaturated keto-aldehyde (LXV) took place stereospecifically, and the produced keto-aldehyde LXVIII was cyclized into the steroid ketone LXIX. A second hydrogenation gave the ketone LXX in almost quantitative yields. To introduce the 21-hydroxy group, LXX was condensed with oxalic ester to the glyoxalate (LXXI), with on consecutive iodination and treatment with potassium acetate was converted to the acetoxy-ketone LXXII. Hydrolysis of the latter gave the diketone LXXIII, differing from aldosterone only in the presence of an 18-CO instead of an OH group. After ethylene glycol protection of the side-chain keto group, reduction with lithium aluminium hydride and subsequent hydrolysis completed the synthesis of *dl*-aldosterone; the losses in the last stages were incongruously high [30].





The entire synthesis required 18 stages. The over-all yield of *dl*-aldosterone reached 0.23%, based on SARETT's hydroxyketone. With reference to 1-methyl-2-ethoxybutadiene (XXI), the number of stages is 25 and the yield 0.043%.

WETTSTEIN [38] also prepared the optically active *d*-aldosterone, starting with the intermediate LXX. When the micro-organism *Ophiobolus* was allowed to act on the diketone LXXV prepared from LXX, the *d*-isomer of the hydroxyketone LXXIII was formed and this could be converted by the usual means to *d*-aldosterone.

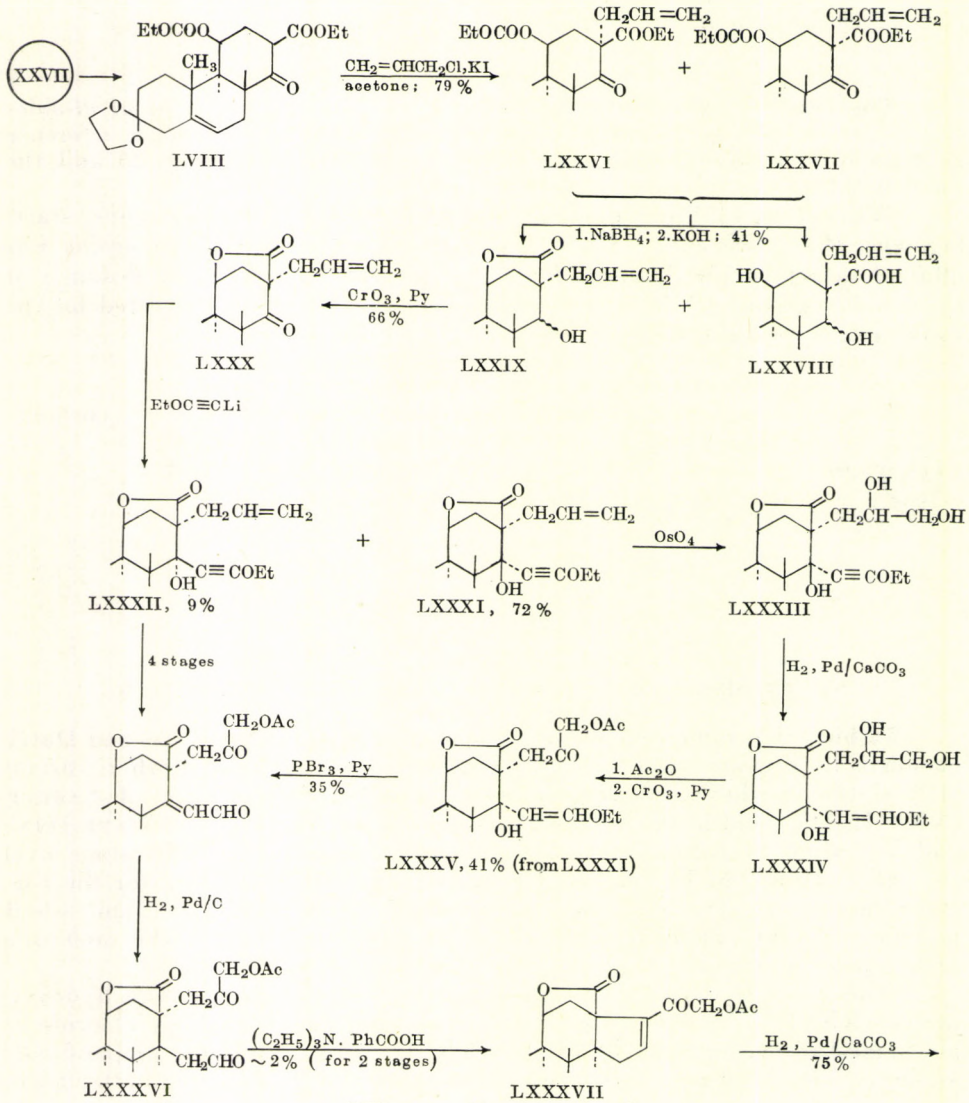


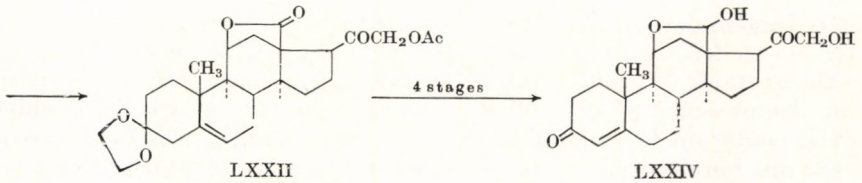
SYNTHESIS OF ALDOSTERONE ACCORDING TO REICHSTEIN

Within the framework of the co-operative effort of the Swiss and Dutch chemists to prepare aldosterone, REICHSTEIN carried out another variant [17] of the synthesis, starting from the same hydroxyketone of SARETT' (XXVII). The yield in this method was much lower than that of WETTSTEIN', and according to REICHSTEIN himself, the method had no advantage over the other. However, he employed a highly ingenious procedure for the construction of ring D containing the required hydroxyacetate chain, which possibly will find application in the further development of the molecular architecture of steroids.

The keto-ester LVIII obtained by the condensation of the hydroxyketone XXVII with ethyl carbonate, was alkylated with allyl chloride to give a mixture of isomers (LXXVI and LXXVII), with the latter in preponderant amounts. The mixture was reduced with sodium borohydride, and after treat-

ment with alkali, the hydroxylactone LXXIX was isolated from among the reaction products, and it was oxidized further to the ketone LXXX. Reaction with ethoxyethynylmagnesium bromide, or, better still, with ethoxyethynyllithium, led to the carbinol LXXXI in admixture with its isomer (LXXXII). Consecutive oxidation with osmium tetroxide to the triol LXXXIII, hydrogenation to the vinylcarbinol LXXXIV, selective acetylation and finally oxidation afforded the ketol LXXXV. The latter was converted by the action of phosphorus tribromide in pyridine to the α,β-unsaturated keto-aldehyde and after hydrogenation, to the keto-aldehyde LXXXVI, which by cyclization gave the steroid compound LXXXVII containing the preformed hydroxyacetone chain. Hydrogenation then gave the acetoxyketone LXXII the conversion of which to aldosterone (LXXIV) has been described above (see p. 293).





LXXII LXXIV

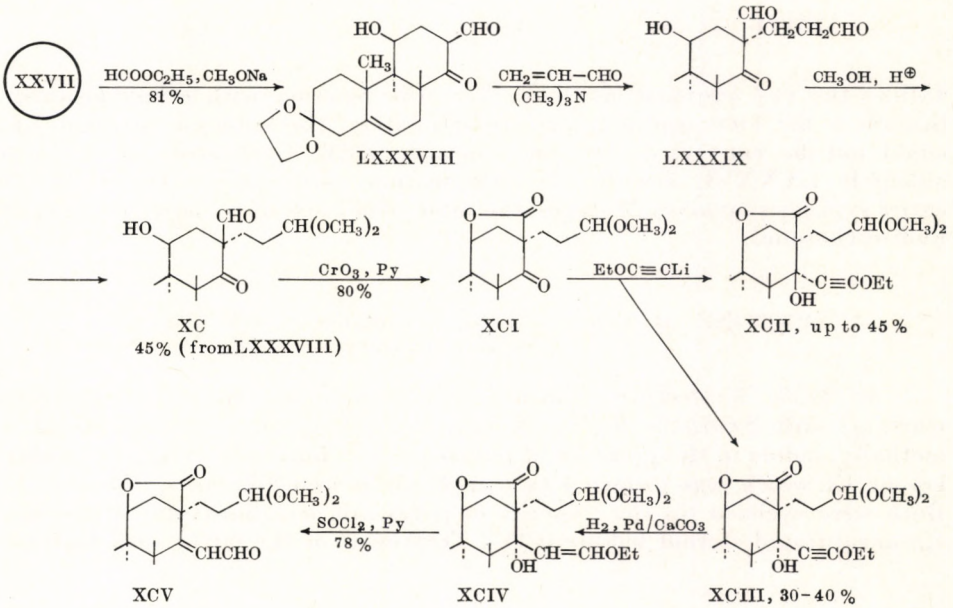
The weakest link in the synthesis is the cyclization to the acetoxyketone LXXXVII; the latter, moreover, can be purified only with much difficulty. Iti s noteworthy that REICHSTEIN and his collaborators worked with very small amounts of material, and finished the synthesis with as little as 3 mg of the acetoxyketone (LXXII).

SYNTHESIS OF ALDOSTERONE ACCORDING TO THE DUTCH GROUP

A third variant of the synthesis of aldosterone [9, 35, 36] was published in 1958 by a group of Dutch chemists of the Organon Company, working in close contact with the Swiss investigators.

This method differed from the previously described ones in that MICHAEL condensation with acrolein was carried out instead of alkylation. After a series of reactions a D-homosteroid was formed, which was further converted into aldosterone. The starting material was again the hydroxyketone XXVII, or to be more exact its formyl derivative (LXXXVIII) which had also been prepared earlier by SARETT [18].

Condensation of the formylketone LXXXVIII with acrolein takes place in the presence of trimethylamine and yields the keto-aldehyde LXXXIX. Methanol reacts with only one of the aldehyde groups [35] to give the mono-acetal XC which was oxidized to the keto-lactone XCI. The latter was converted with the aid of ethoxyacetylenelithium to a mixture of the carbinols XCII and XCIII, of which only the latter was used in the further stages. Selective hydrogenation led to the vinylcarbinol XCIV which on reaction with thionyl chloride in pyridine gave the unsaturated aldehyde XCV.



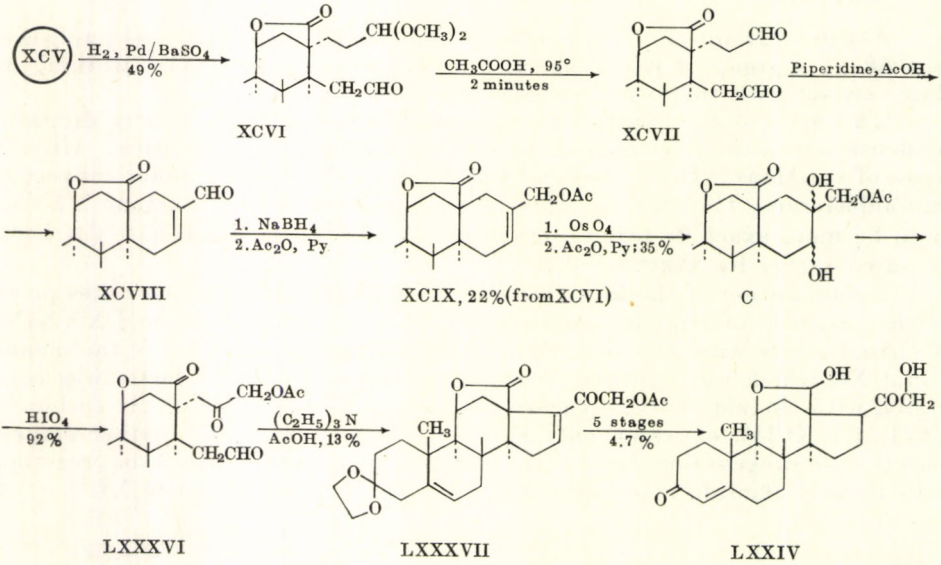
LXXXVIII LXXXIX

XC
45% (from LXXXVIII)

XCI XCII, up to 45 %

XCV XCIV XCIII, 30–40 %

Hydrogenation of the aldehyde (XCV) followed by hydrolysis under strictly controlled conditions (in order to avoid attack on the ketal group) led to the unstable dialdehyde XCVII, which was cyclized without any purification in the presence of piperidine acetate. Since the intermediate aldehyde (XCVIII) could not be isolated in the crystalline form, it was further reduced with sodium borohydride to the carbinol, the acetate of which (XCIX) could then be obtained pure [36]. The latter compound was oxidized in the usual way to the diol (C) and then to the keto-aldehyde (LXXXVI), prepared earlier by REICHSTEIN (see p. 294) as an oil. Cyclization of the pure crystalline aldehyde (LXXXVI) gave much better results than those obtained by REICHSTEIN (13% as compared to his 2%), and yielded the steroid acetoxyketone LXXXVII; the conversion of this product to aldosterone had been achieved earlier.

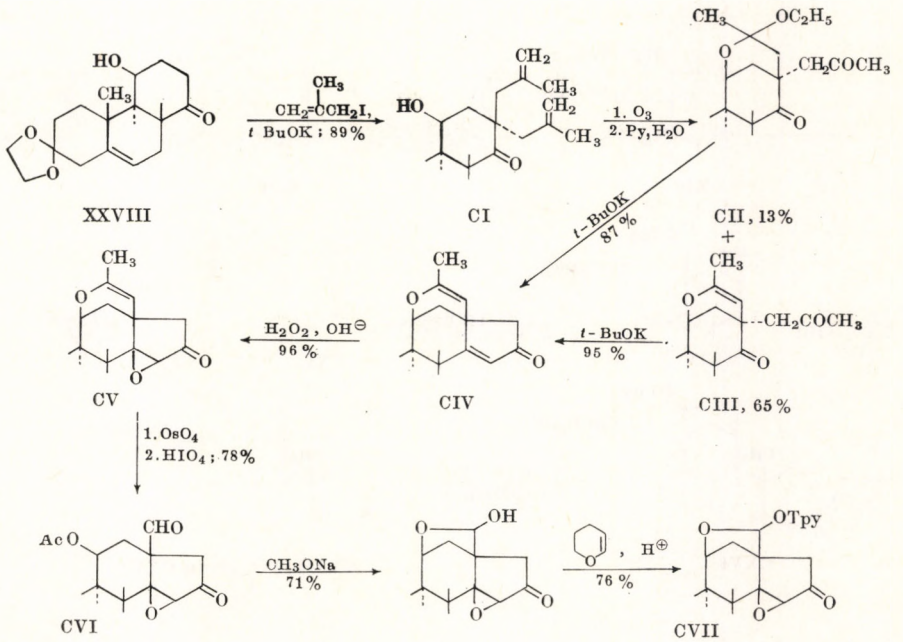


Unlike the two previous methods, here the reaction with ethoxyacetylene-lithium is not stereospecific, and unfortunately, the epimeric carbinol XCII could not be converted into the aldehyde XCV. Cyclization of the keto-aldehyde LXXXVI, despite the modifications, still gave a low yield. The entire synthesis involves 20 stages, the total yield is 0.0017%, based on SARETT's hydroxyketone.

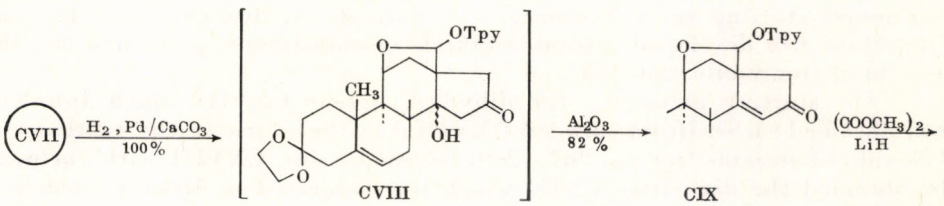
SYNTHESIS OF ALDOSTERONE ACCORDING TO WETTSTEIN (SECOND VARIANT)

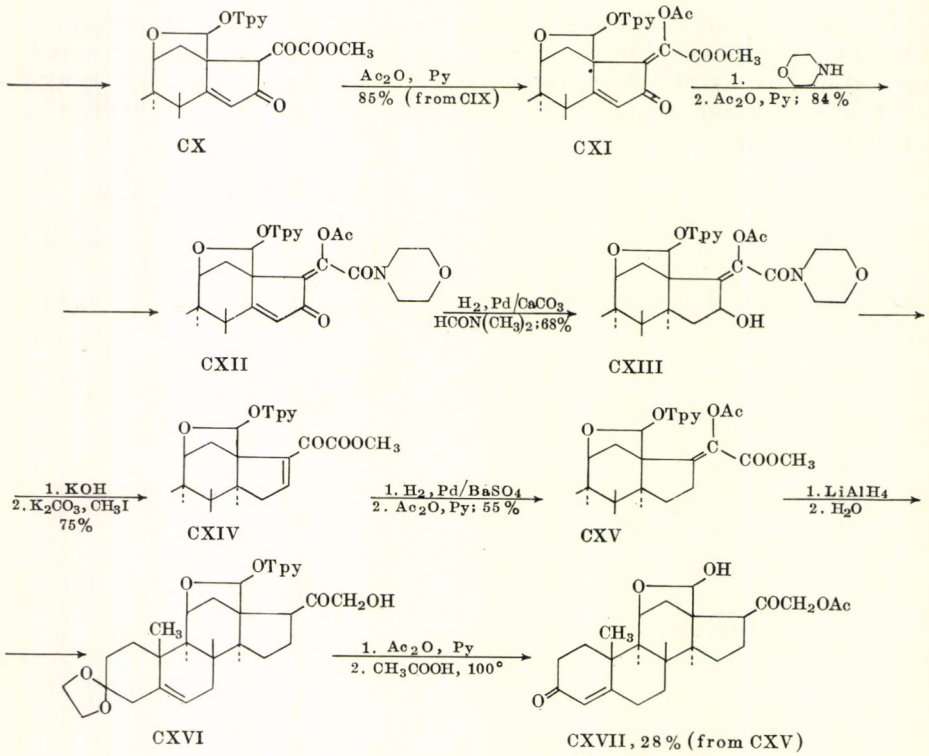
In 1959, WETTSTEIN published [13] an alternate route to aldosterone starting with SARETT's hydroxyketone (XXVII). This was alkylated by methallyl iodide in the presence of potassium *tert.*-butoxide, giving the dialkyl-ketone CI which was ozonized to a mixture of two diketones, CII and CIII. Both were cyclized (in the presence of potassium *tert.*-butoxide) to the same α,β-unsaturated steroid ketone (CIV). Treatment of the latter with hydrogen

peroxide in alkaline medium gave the epoxide CV, which was oxidized first by osmium tetroxide, then by periodic acid [40], to yield the acetoxy-keto-aldehyde CVI. Removal of the acetoxy group by means of sodium methoxide resulted in a semiacetal grouping retained till the final stage of the synthesis; the hydroxyl group was protected by conversion to the tetrahydropyranyl derivative (CVII).



Hydrogenation of compound CVII and dehydration of the resulting ketol (CVIII) gave unsaturated ketone CIX. In order to construct the side chain, the latter was condensed with dimethyl oxalate. Acetylation of the condensation product (CX) led to the enolacetate CXI, which was converted to the morpholide (CXII). These conversions were necessary, because on subsequent hydrogenation only the morpholide (CXII) gave the desired 16-hydroxy-derivative (CXIII) in high yield, compounds CX and CXI affording under these conditions only mixtures of various hydrogenation products [12]. Alkaline hydrolysis of the amide CXIII accompanied by dehydration and subsequent methylation yielded the unsaturated keto-ester CXIV which was hydrogenated and acetylated to the enol acetate CXV.





Reduction of the enol acetate (CXV) with lithium aluminium hydride followed by acetylation of the ketol CXVI and hydrolysis of the acetyl and ketal groups led to aldosterone acetate (CXVII).

The synthesis involved 20 stages, and the over-all yield of *dl*-aldosterone acetate reached a value of 1.2% based on SARETT's hydroxyketone.

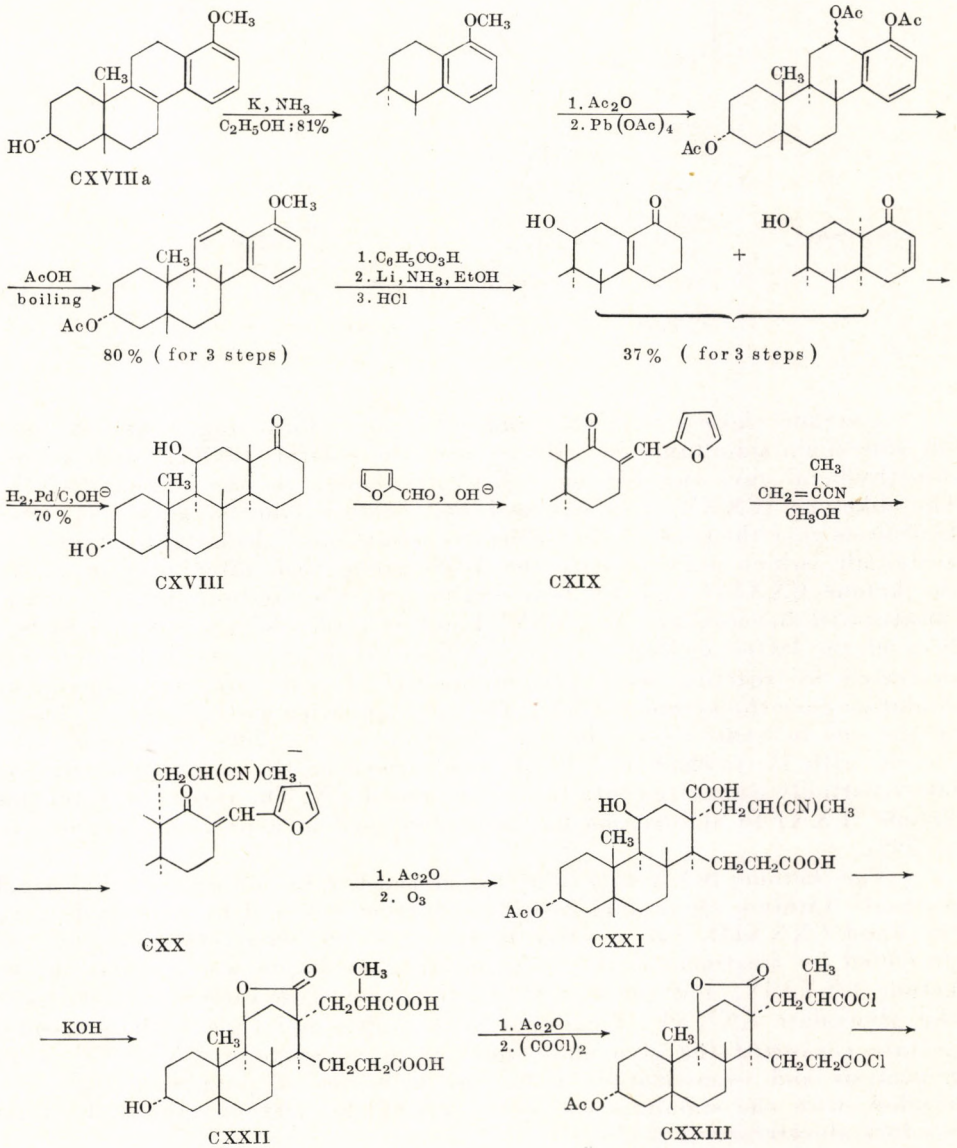
Thus, from among the four syntheses published by the Swiss—Dutch group, the second synthesis by WETTSTEIN proved to be the best; it has the distinction of being highly stereospecific.

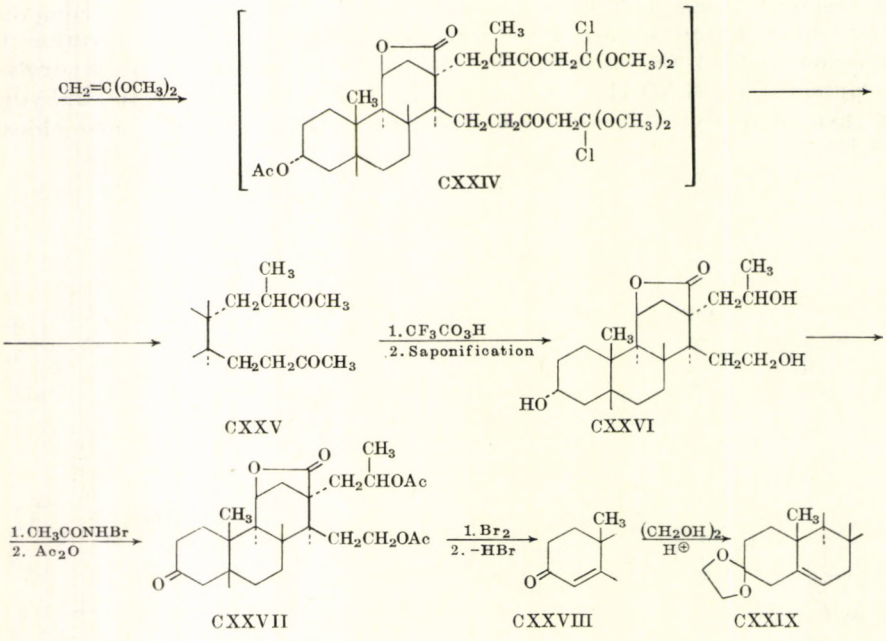
SYNTHESIS OF ALDOSTERONE ACCORDING TO JOHNSON

Besides the synthesis of testosterone, epiandrosterone and the cortical hormones, starting from hydrochrysene derivatives, JOHNSON and his collaborators also developed a total synthesis of aldosterone, published in 1958 as a brief communication [15].

The starting point was the dihydroxyketone CXVIII which JOHNSON had obtained earlier (from carbinol CXVIIIa) in the course of the synthesis of 11-oxidized steroids (see pp. 267—269).By condensing CXVIII with furfural, he obtained the derivative CXIX which was subjected to MICHAEL reaction

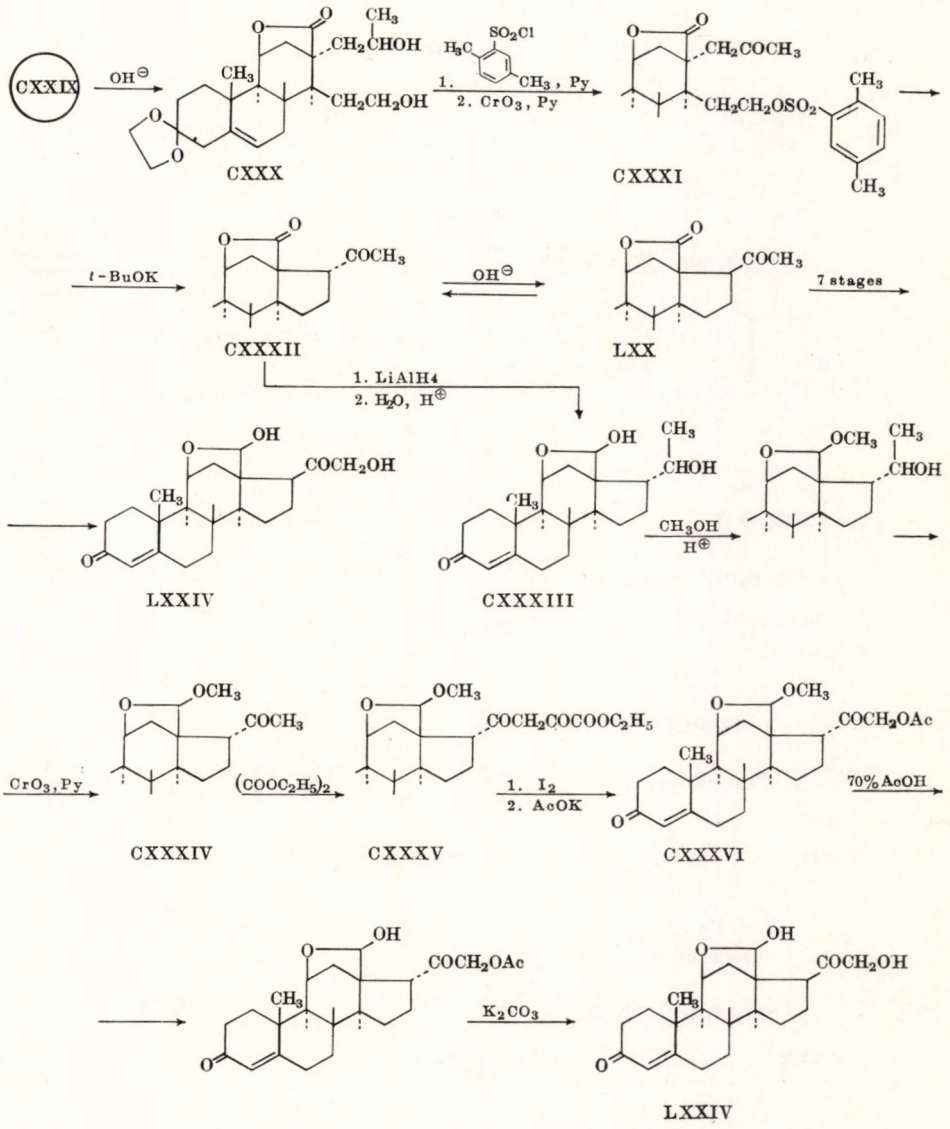
with methacrylonitrile. This resulted in the formation of compound CXX; the reaction occurred with inversion at $C_{(13)}$. On ozonization this compound yielded the dicarboxylic acid CXXI, and then, on hydrolysis, the lactone-acid (CXXII) was obtained. The action of acetic anhydride and then of oxalyl chloride converted this product into the acid chloride CXXIII.





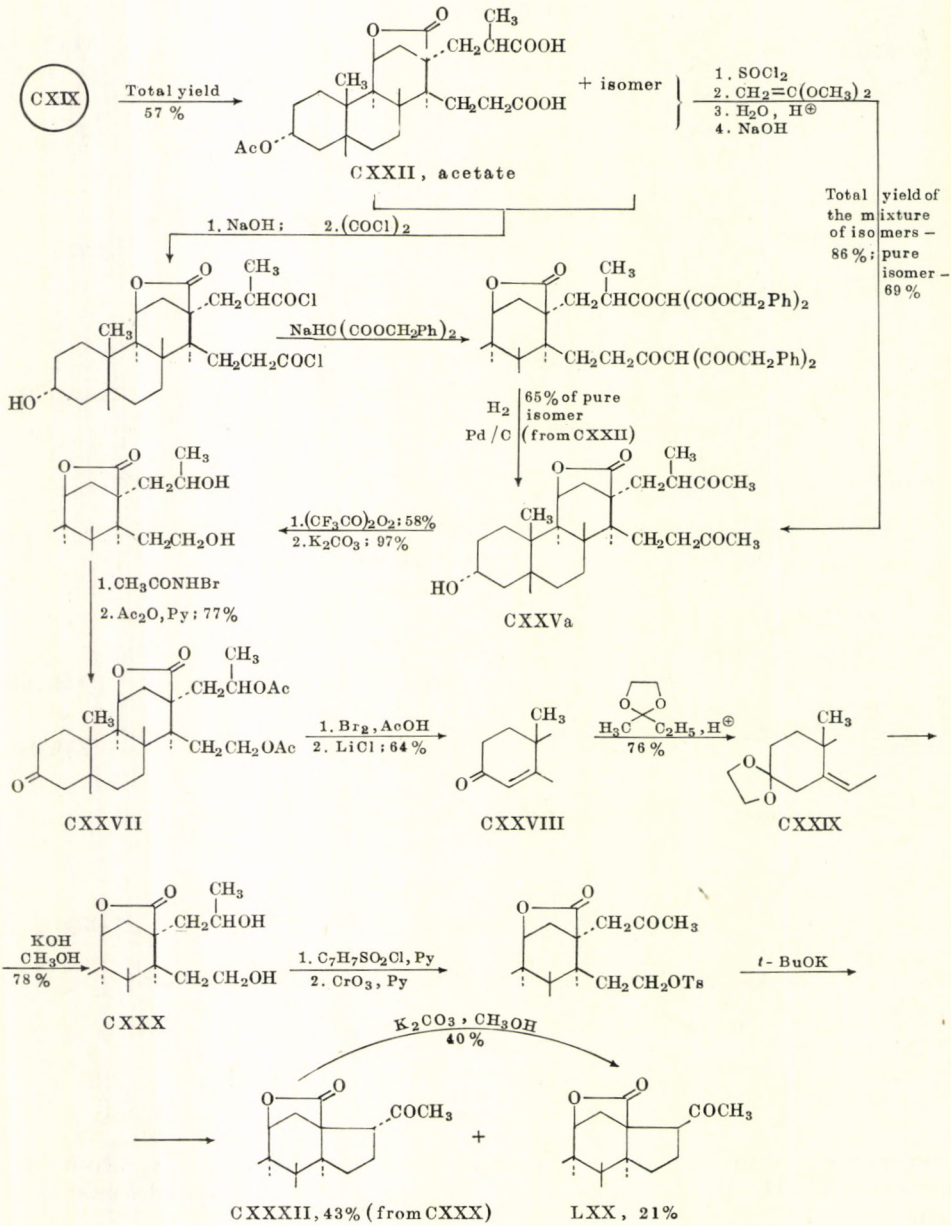
JOHNSON chose a somewhat unusual route to form ring D, and to build the side chain simultaneously. Reaction of the chloride CXXIII with ketene dimethylketal gave the diketone CXXV, evidently via the adduct CXXIV. The diketone (CXXV) was oxidized by trifluoroperacetic acid, and after hydrolysis gave the triol CXXVI. Selective oxidation of the latter by N-bromoacetamide (which oxidizes only the 3-OH group) led, after acetylation, to the ketone CXXVII and, on bromination and dehydrobromination, to the unsaturated diacetoxyketone CXXVIII and its ketal CXXIX. Alkaline hydrolysis of the latter yielded the diol CXXX; the primary alcohol group was protected by reaction with xylenesulphonyl chloride, so that subsequent oxidation gave the ketone CXXXI. The next operation was cyclization, similar to the one in SARETT's synthesis of cortisone (see p. 288): as a result, the steroid with 17-*iso*-chain (CXXXII) was formed as the major product. The latter partially isomerized into the 17β-epimer LXX. The transition from this ketone (LXX) to aldosterone has been described in a previous section (see p. 292).

The ketone (CXXXII) was transformed into aldosterone by usual methods. Lithium aluminium hydride reduction followed by hydrolysis gave the ketol CXXXIII. The reactive hydroxyl of the semiacetal grouping was protected by treatment with methanol; thus oxidation was possible to the ketone CXXXIV, and subsequent condensation with diethyl oxalate gave the glyoxalate CXXXV. Treatment with iodine and then with potassium acetate converted the glyoxalate into the acetoxyketone (CXXXVI). Acid hydrolysis and isomerization under the influence of potassium carbonate yielded, with the simultaneous hydrolysis of the acetoxy group, the final product aldosterone (LXXIV).

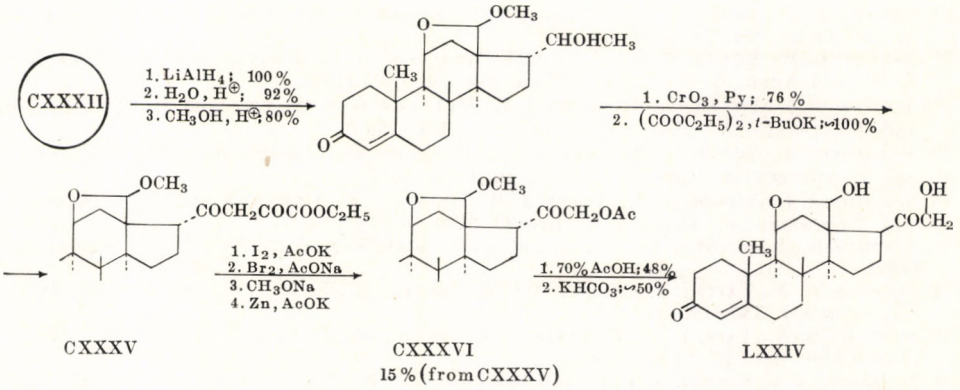


JOHNSON's synthesis involves 26 stages when starting with the dihydroxyketone CXVIII, or 38 stages if the starting point is 1,6-dihydroxynaphtalene.

JOHNSON reported the yields for the different stages in a corresponding patent [16] which differs a little from the preliminary communication [15]. For instance, besides the method using the ketene acetal (which was described above), the classical reaction with benzyl malonate was employed. Instead of xylenesulphonyl chloride, *p*-toluenesulphonyl chloride was employed for the protection of the primary hydroxyl group.



The conversion of the ketone CXXXII into aldosterone was carried out in the usual way; the greatest losses were involved in the step of introducing the 21-acetoxy group.



The total yield on *dl*-aldosterone is about 0.055% based on the dihydroxyketone CXVIII, or 0.002% calculated for 1,6-dihydroxynaphthalene.

REFERENCES

1. Arth, G. E., Poos, G. I., Lukes, R. M., Robinson, F. M., Johns, W. F., Feurer, M and Sarett, L. H.: *J. Am. Chem. Soc. 76*, 1715 (1954).
2. Arth, G. E., Poos, G. I., and Sarett, L. H.: *J. Am. Chem. Soc. 77*, 3834 (1955).
3. Barkley, L. B.: US Pat. 2,889,320 (1959); *C. A. 53*, 22, 094 (1959).
4. Barkley, L. B., Farrar, M. W., Knowles, W. S., and Raffelson, H.: *J. Am. Chem. Soc. 75*, 4110 (1954).
5. Barkley, L. B., Farrar, M. W., Knowles, W. S., and Raffelson, H.: *J. Am. Chem. Soc. 76*, 5017 (1956).
6. Barkley, L. B., Farrar, M. W., Knowles, W. S., Raffelson. H., and Thompson, Q. E.: *J. Am. Chem. Soc. 76*, 5011 (1954).
7. Beyler, R. E., and Sarett, L. H.: *J. Am. Chem. Soc. 74*, 1397 (1952).
8. Beyler, R. E., and Sarett, L. H.: *J. Am. Chem. Soc. 74*, 1406 (1952).
9. Burg, van der, W. J., Dorp, van, D. A., Schindler, O., Siegmann, C. M., and Szpilfogel, S. A.: *Rec. trav. chim. 77*, 171 (1958).
10. Fried, J., and Sabo, E. F.: *J. Am. Chem. Soc. 75*, 2273 (1953).
11. Harman, R. E., Ham, E. A., Brink, N. G., and Sarett, L. H.: *J. Am. Chem. Soc. 76*, 5035 (1954).
12. Heusler, K., Wieland, P., and Wettstein, A.: *Helv. Chim. Acta 41*, 997 (1958).
13. Heusler, K., Wieland, P., and Wettstein, A.: *Helv. Chim. Acta 42*, 1586 (1959).
14. Johns, W. F., Lukes, R. M., and Sarett, L. H.: *J. Am. Chem. Soc. 76*, 5026 (1954).
15. Johnson, W. S., Collins, J. C., Pappo, R., and Rubin, M. B.: *J. Am. Chem. Soc. 80*, 2585 (1958).
16. Johnson, W. S., Collins, J. C., Pappo, R., and Rubin, M. B.: US Patent 2,973,357 (1961); *C. A. 55*, 15,552.
17. Lardon, A., Schindler, O., and Reichstein, T.: *Helv. Chim. Acta 40*, 666 (1957).
18. Lukes, R. M., Poos, G. I., Beyler, R. E., Johns, W. F., and Sarett, L. H.: *J. Am. Chem. Soc. 75*, 1707 (1953).
19. Lukes, R. M., Poos, G. I., and Sarett, L. H.: *J. Am. Chem. Soc. 74*, 1401 (1952).
20. Poos, G. I., Arth, G. E., Beyler, R. E., and Sarett, L. H.: *J. Am. Chem. Soc. 75*, 422 (1953).
21. Poos, G. I., Johns, W. F., and Sarett, L. H.: *J. Am. Chem. Soc. 77*, 1026 (1955).
22. Poos, G. I., Lukes, R. M., Arth, G. E., and Sarett, L. H.: *J. Am. Chem. Soc. 76*, 5031 (1954).
23. Sarett, L. H.: *J. Am. Chem. Soc. 70*, 1454 (1948).
24. Sarett, L. H.: *J. Am. Chem. Soc. 71*, 2443 (1949).
25. Sarett, L. H., Arth, G. E., Lukes, R. M., Beyler, R. E., Poos, G. I., Johns, W. F., and Constantin, J. M.: *J. Am. Chem. Soc. 74*, 4974 (1952).

26. SARETT, L. H., JOHNS, W. F., BEYLER, R. E., LUKES, R. M., POOS, G. I., and ARTH, G. E.: *J. Am. Chem. Soc. 75*, 2112 (1953).
27. SARETT, L. H., LUKES, R. M., POOS, G. I., ROBINSON, J. M., BEYLER, R. E., VANDERGRIFT, J. M., and ARTH, G. E.: *J. Am. Chem. Soc. 74*, 1393 (1952).
28. SCHMIDLIN, J., ANNER, G., BILLETER, J. R., HEUSLER, K., UEBERWASSER, H., WIELAND, P., and WETTSTEIN, A.: *Helv. Chim. Acta 40*, 1034 (1957).
29. SCHMIDLIN, J., ANNER, G., BILLETER, J. R., HEUSLER, K., UEBERWASSER, H., WIELAND, P., and WETTSTEIN, A.: *Helv. Chim. Acta 40*, 1438 (1957).
30. SCHMIDLIN, J., ANNER, G., BILLETER, J. R., HEUSLER, K., UEBERWASSER, H., WIELAND P., and WETTSTEIN, A.: *Helv. Chim. Acta 40*, 2291 (1957).
31. SCHMIDLIN, J., ANNER, G., BILLETER, J. R., and WETTSTEIN, A.: *Experientia 11*, 365 (1955).
32. SIMPSON, S. A., TAIT, J. F., WETTSTEIN, A., NEHER, R., EUW, J. V., and REICHSTEIN, T.: *Experientia 9*, 333 (1953).
33. SIMPSON, S. A., TAIT, J. F., WETTSTEIN, A., NEHER, R., EUW, J. V., and REICHSTEIN, T.: *Helv. Chim. Acta 37*, 1163 (1954).
34. SPEZIALE, A. J., STEPHENS, J. A., and THOMPSON, Q. E.: *J. Am. Chem. Soc. 76*, 5011 (1954).
35. SZPILFOGEL, S. A., VAN DER BURG, W. J., SIEGMANN, C. M., and VAN DORP, D. A.: *Rec. trav. chim. 75*, 1043 (1956).
36. SZPILFOGEL, S. A., VAN DER BURG, W. J., SIEGMANN, C. M., and VAN DORP, D. A.: *Rec. trav. chim. 77*, 157 (1958).
37. VAN DER BURG, see BURG, VAN DER.
38. VISCHER, E., SCHMIDLIN, J., and WETTSTEIN, A.: *Experientia 12*, 50 (1956).
39. WETTSTEIN, A., HEUSLER, K., UEBERWASSER, H., and WIELAND, P.: *Helv. Chim. Acta 40*, 323 (1957).
40. WIELAND, P., HEUSLER, K., UEBERWASSER, H., and WETTSTEIN, A.: *Helv. Chim. Acta 41*, 74 (1958).

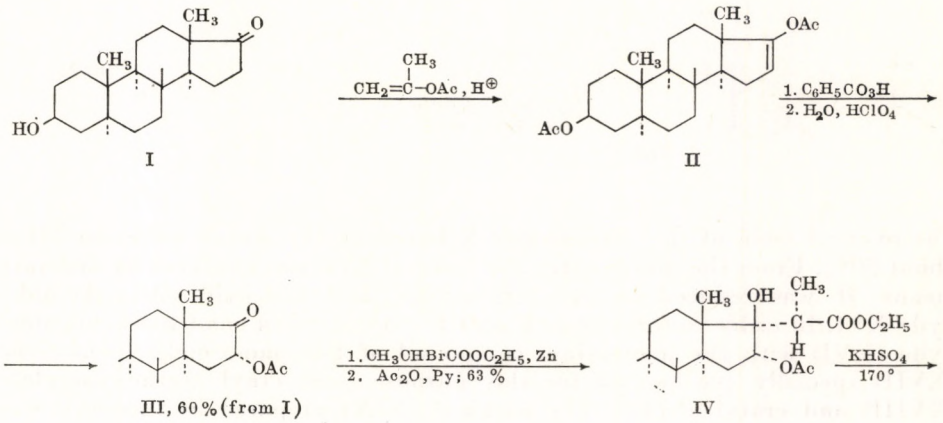
CHAPTER VI

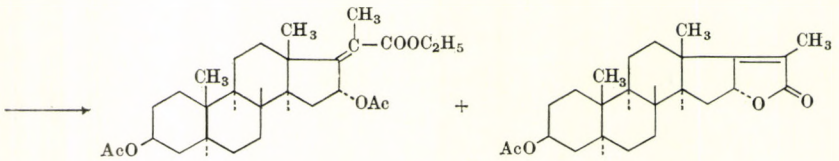
SYNTHESES OF OTHER STEROID COMPOUNDS

SYNTHESIS OF SAPOGENINS ACCORDING TO SONDHEIMER

The more important sapogenins (diosgenin, tigogenin, hecogenin and some others) have long been the object of investigation, mainly from the standpoint of their conversion into pregnane derivatives, and further into sex and adrenal cortical hormones. On the other hand, there was very little research for routes to the total synthesis of these compounds, despite their structural simplicity in comparison, for instance, with the corticoids. This gap has been aptly filled by the work of SONDHEIMER, MAZUR and DANIELLI who achieved [2, 8, 9] the total synthesis of tigogenin and neotigogenin in 1958—1959.

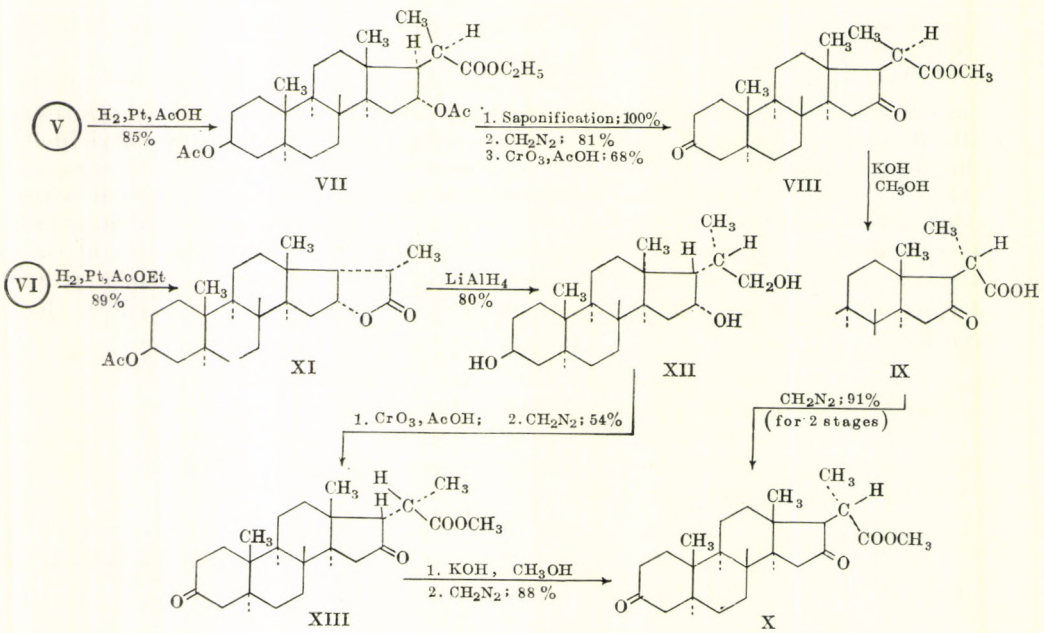
The starting material was epiandrosterone (I), the total synthesis of which has been described in an earlier section (see pp. 261, 265). Exhaustive acetylation afforded the enol acetate II, which, after epoxidation and hydrolysis, yielded the diacetoxyketone III. The next problem was to introduce an *iso*propyl chain in position 17. This was accomplished by REFROMATSKY reaction with ethyl α-bromopropionate, leading to a mixture of products, from which, after acetylation, the diacetate IV was isolated in 63% yield. Dehydration of the diacetate led to the unsaturated ester V and the lactone VI, which were despite the difference between their chemical structure both utilized in the synthesis.



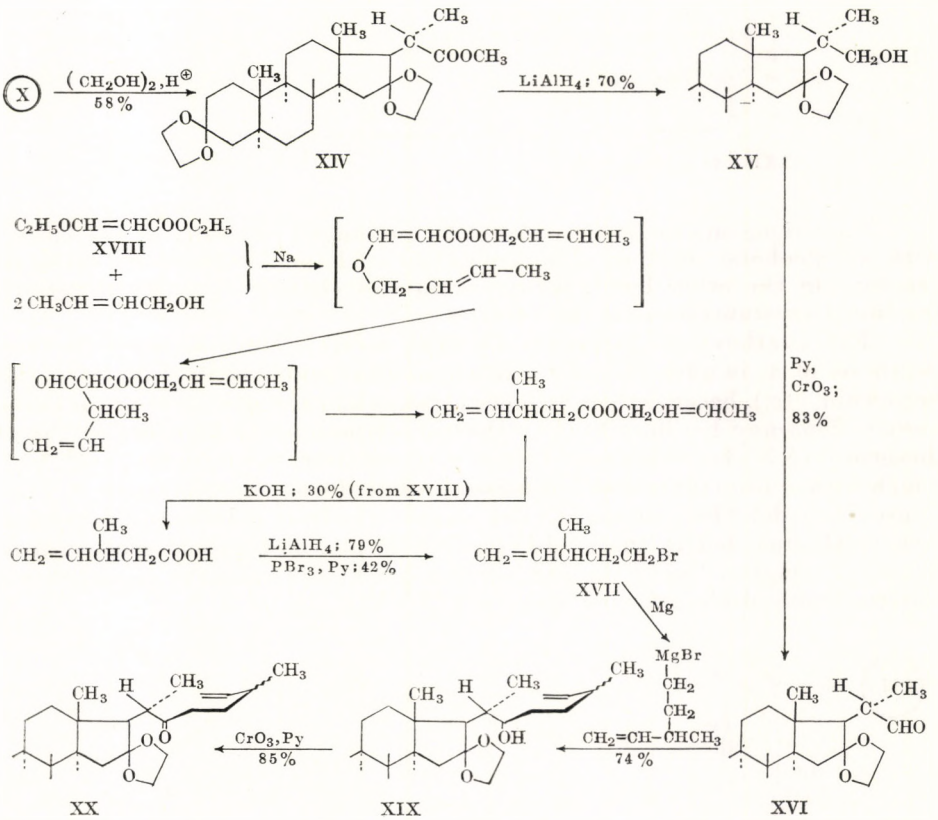


V, 40 % VI, 38 %

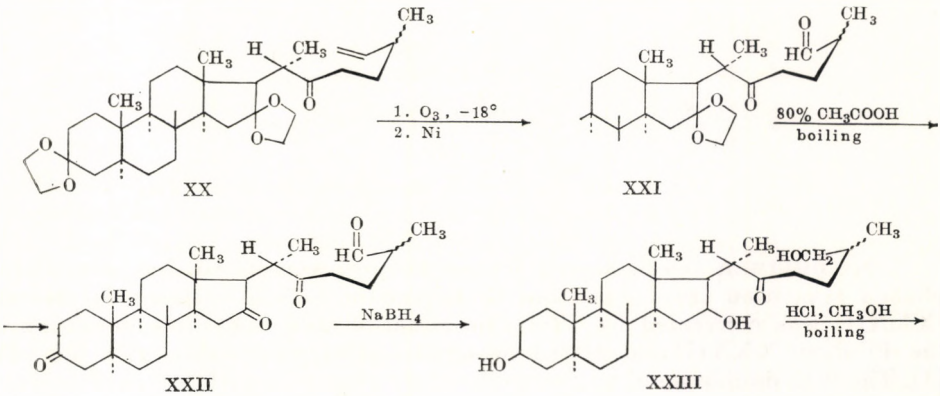
Hydrogenation of the unsaturated ester (V) gave the saturated compound VII having anomalous configuration at C_{20}. The saturated ester was subjected to the usual reactions (hydrolysis, esterification and oxidation) to prepare the diketo-ester VIII. The latter, in order to invert the configuration at C_{20}, was isomerized to the acid IX by heating with potassium hydroxide in methanol, and then methylated to the ester X. This compound also could be obtained from VI by hydrogenation to the lactone XI, reduction with lithium aluminium hydride to the triol XII, oxidation (and esterification) to the diketo-ester XIII, followed by isomerization and esterification.

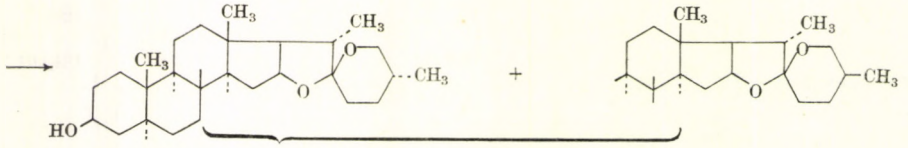


The over-all yield of the diketo-ester X based on the diacetoxyketone III is about 20%. From the diketo-ester the bisketal XIV was obtained by ordinary means; it was reduced to the carbinol XV, and then oxidized to the aldehyde XVI. In order to form rings E and F, SONDHEIMER condensed this aldehyde (XVI) with the magnesium compound of 1-bromo-3-methylpent-4-ene (XVII) specially synthesized for this purpose from ethyl β-ethoxyacrylate (XVIII) and crotyl alcohol. The carbinol (XIX) prepared in this way was oxidized to the ketone XX.



On ozonization of ketone XX and reductive degradation of the ozonide, the keto-aldehyde XXI was obtained, and this was hydrolyzed without purification to the triketo-aldehyde XXII. Sodium borohydride reduction of the latter proceeded selectively, the sterically hindered C_{22}-keto group was not affected. As a result, the keto-triol XXIII was formed, which on refluxing with hydrochloric acid in methanol gave an equimolecular mixture of tigogenin (XXIV) and neotigogenin (XXV).

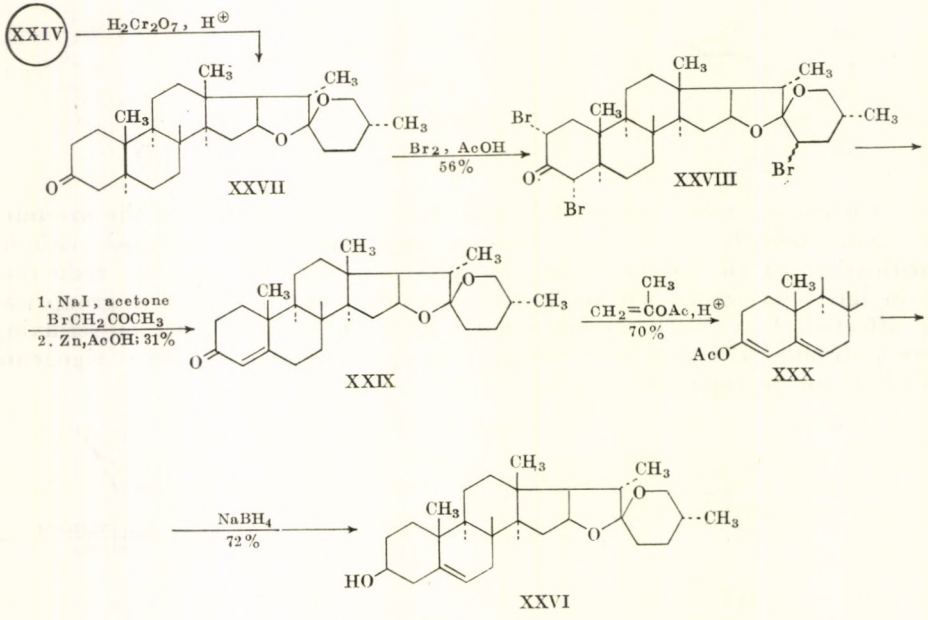




XXIV, 26 % (from XX) XXV

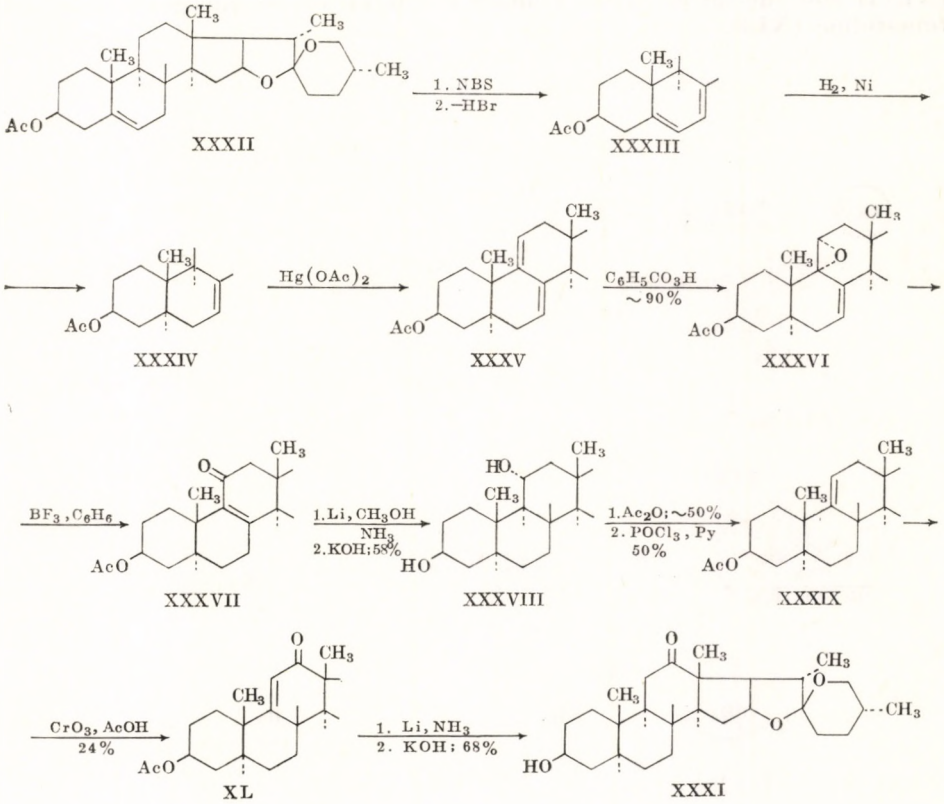
Pure tigogenin could be isolated by prolonged refluxing of the mixture with an alcoholic solution of hydrochloric acid and subsequent chromatography. On the other hand, neotigogenin was obtained (as the acetate) by fractional crystallization of the acetates.

The synthesis of tigogenin (XXIV) meant simultaneously the total synthesis of a number of other sapogenins (diosgenin, smilagenin, gitogenin, hecogenin, etc.), because their interconversions had already been accomplished earlier. This may be illustrated by the transformation of tigogenin (XXIV) into diosgenin (XXVI). Tigogenin (XXIV) is oxidized to tigogenone (XXVII) which is then brominated, the principal product being the tribromide XXVIII. Consecutive dehydrobromination (by means of sodium iodide) and debromination (with zinc) led to the Δ^4-3-ketone (XXIX) which was treated with isopropenyl acetate to yield the enol acetate XXX. Reduction of the latter with sodium borohydride afforded diosgenin (XXVI).



Sondheimer also achieved a previously contemplated, but not accomplished transition from diosgenin to hecogenin (XXXI). Diosgenin acetate (XXXII) was converted by allylic bromination and dehydrobromination to the $\Delta^{5,7}$-diene XXXIII and, after hydrogenation, to the Δ^7-compound (XXXIV) [3]. The 9,11 double bond was introduced by oxidation with mercuric acetate,

and the $\Delta^{7,9}$-diene XXXV was reacted with perbenzoic acid to give the epoxide XXXVI which [10, 11, 12] readily isomerized in the presence of boron trifluoride to the 11-ketone XXXVII. Reduction of the latter with lithium and alcohol in liquid ammonia gave the diol XXXVIII, from which the 11α-OH group could be readily removed by treatment with phosphoryl chloride. The resulting acetate of $\Delta^{9(11)}$-5α, 25D-spirostene-3β-ol (XXXIX) was oxidized by chromic acid to give a moderate yield of dehydrohecogenin acetate (XL) and finally hecogenin (XXXI).



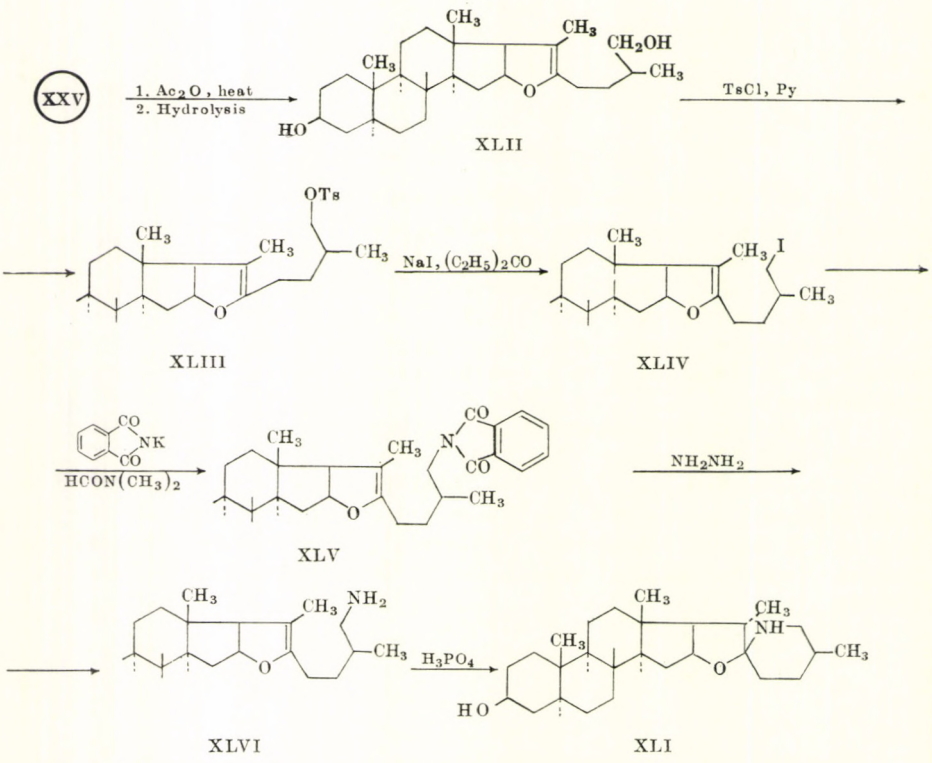
Starting with the sapogenins, one can, in turn, synthesize a number of steroid alkaloids (see below).

SYNTHESIS OF SOME STEROID ALKALOIDS

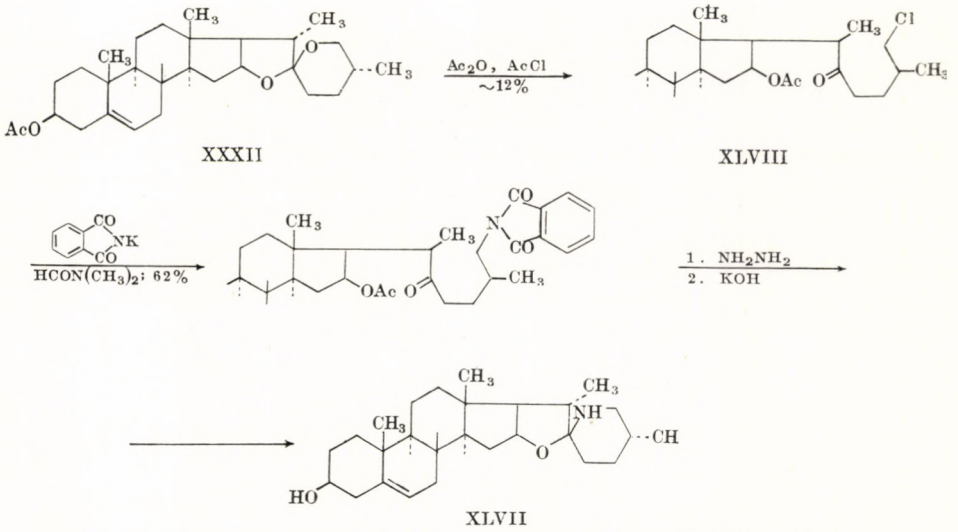
The interrelation between steroid sapogenins and certain alkaloids (tomatidine, solasodine), and the successful conversion of the former into the latter justifies the view that the total synthesis of these alkaloids has been achieved.

Synthesis of Tomatidine and Solasodine

Neotigogenin (XXV), the synthesis of which has been described above, was converted into tomatidine (XLI) by the following series of reactions [16]. The sapogenin was converted by ordinary means (heating with acetic anhydride and hydrolysis) into pseudoneotigogenin (XLII) from which the tosylate (XLIII) was prepared. The latter was heated with sodium iodide, yielding the unstable iodide XLIV which was acted upon by potassium phthalimide to give the derivative XLV. Its reaction with hydrazine yielded the amine (XLVI) and the latter cyclized under the influence of phosphoric acid into tomatidine (XLI).



In almost the same way [14, 15] solasodine was prepared from diosgenin, the only difference being the non-acidic cyclization of the intermediate amine (analogue of XLVI). The synthesis was developed in two variants. According to the shorter route, diosgenin acetate (XXXII) was transformed directly to the 26-chloro derivative XLVIII by heating with acetyl chloride and acetic anhydride, and this was then converted into solasodine via the phthalimide derivative.



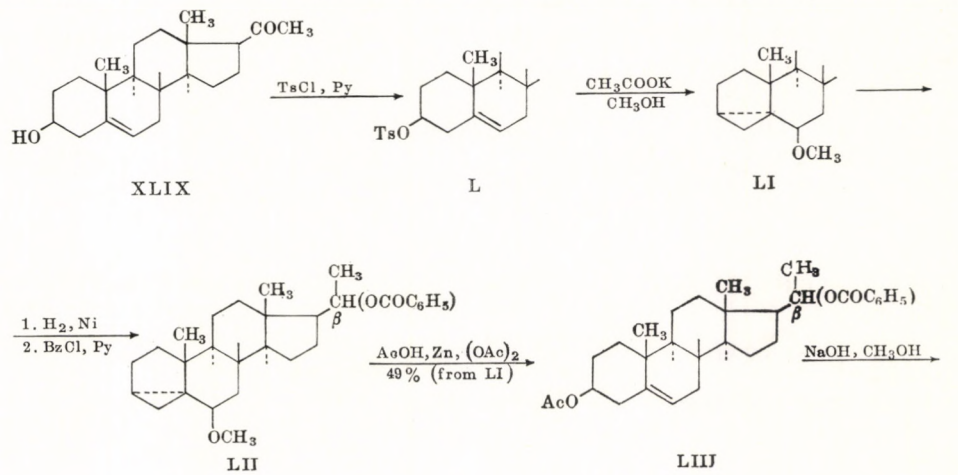
XXXII XLVIII XLVII

Synthesis of Conessine

In 1961 BARTON and MORGAN [1] described the synthesis of the steroid alkaloid conessine, the structure of which is interesting because of the presence of a nitrogeneous function at the C_{18} atom. The authors started with pregnenolone (XLIX), i.e. a steroid prepared by total synthesis, so that their work should be regarded as a total synthesis of conessine.

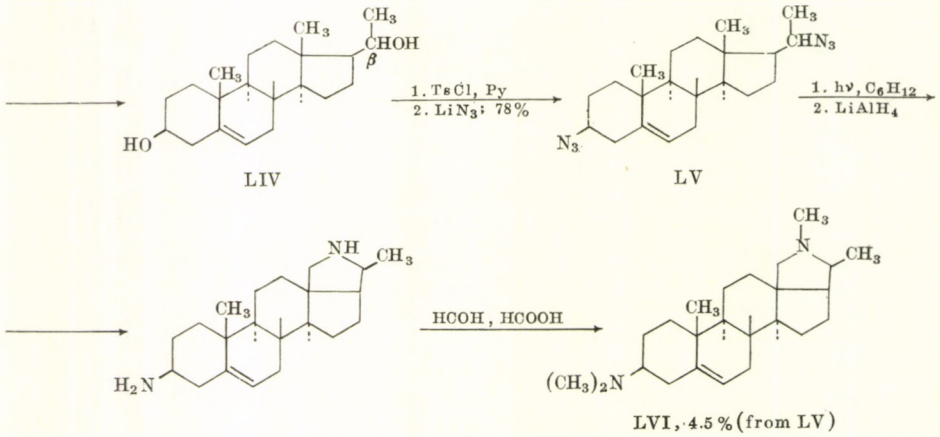
Solvolysis of pregnenolone tosylate (L) gave the isosteroid ketone (LI), which was hydrogenated to a mixture of 20-epimeric alcohols, resolved via the benzoates.

The 20β-epimer benzoate (LII) was transformed into Δ^5-pregnane-3β, 20β-diol-3-acetate-20-benzoate (LIII) by refluxing with acetic acid [13] and then hydrolyzed to the diol (LIV). The ditosylate of the latter was reacted with lithium azide to give the bisazide LV, which on irradiation yielded a mixture of amines. Consecutive reduction of this mixture with lithium aluminium hydride and finally methylation afforded conessine (LVI).



XLIX L LI

LII LIII



LIV LV

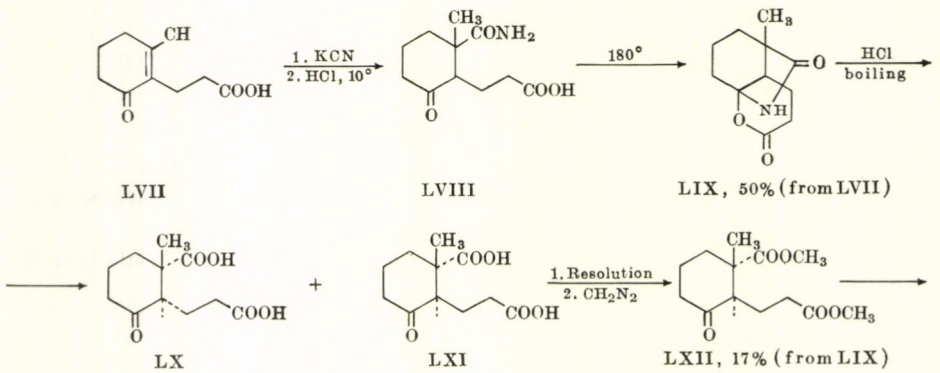
LVI, 4.5% (from LV)

SYNTHESIS OF VITAMIN D_3

Although vitamin D_3 is formally not a steroid, it is genetically very closely related to these compounds and on these grounds can be treated here.

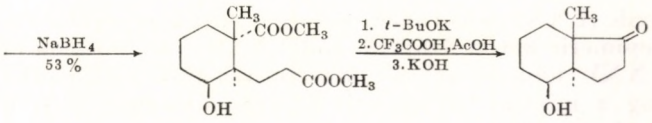
Vitamin D_3 is produced, even on industrial scale, from cholesterol synthesized earlier (see p. 276), and therefore its total synthesis may be considered to have been accomplished. However, the work of INHOFFEN and his group devoted to this problem is independent and it has considerable scientific interest, thus it deserves special detailed discussion.

The main starting material used by INHOFFEN for the total synthesis of vitamin D_3 was β-(3-methyl-Δ^2-cyclohexen-one-2-yl)-propionic acid (LVII). Addition of hydrogen cyanide to the double bond and hydrolysis of the resulting nitrile gave the amide LVIII, and this, on heating, yielded the lactone-lactam LIX. Acid hydrolysis of the latter afforded an equilibrium mixture of the *cis*- and *trans*-dicarboxylic acid LX and LXI. The *trans* isomer was resolved through the brucine salts to isolate the l-*trans*-acid, which was converted into the dimethyl ester (LXII). DIECKMANN cyclization of the latter gave, however, only the *cis*-indane derivative, so that it was found necessary to reduce first the keto group to hydroxyl. The resulting hydroxydiester (LXIII) was cyclized into a mixture of *cis*- and *trans*-isomeric β-keto-esters, from which, after hydrolysis and decarboxylation, the hydroxyketone LXIV was isolated in low yield [7].



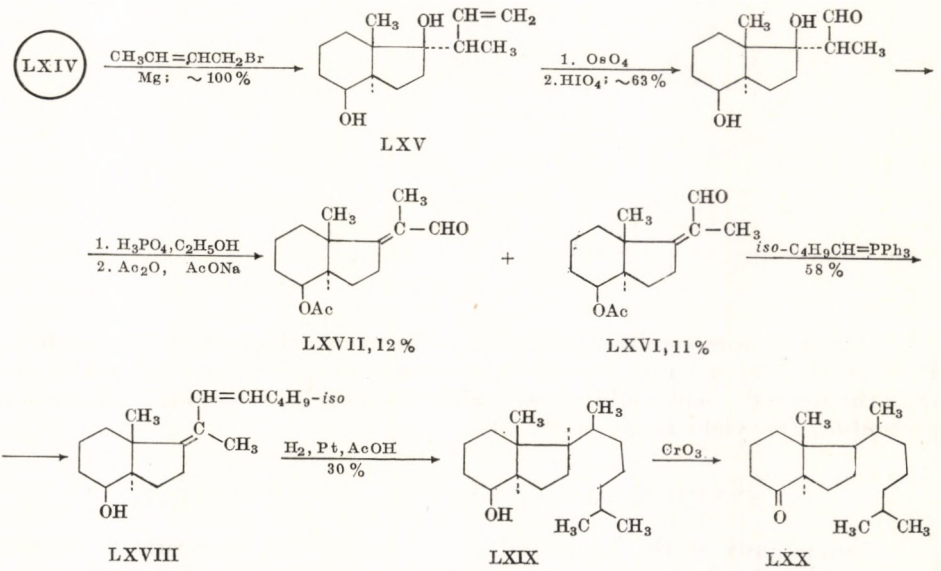
LVII LVIII LIX, 50% (from LVII)

LX LXI LXII, 17% (from LIX)

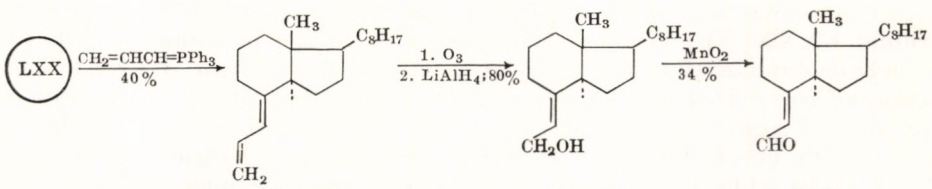


LXIII LXIV, ~ 4 % (for 3 steps)

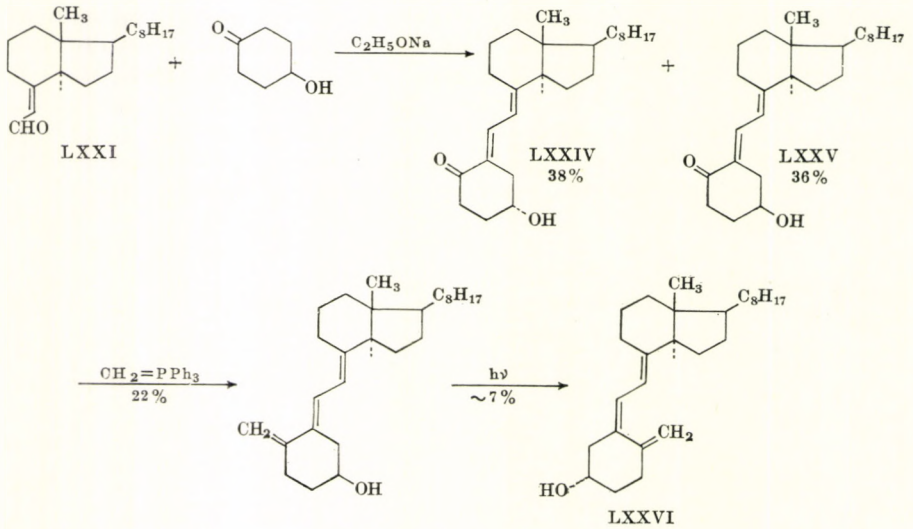
The condensation of this hydroxyketone (LXIV) with crotylmagnesium bromide was accompanied by allylic rearrangement, giving the diol LXV. Consecutive oxidation with osmium tetroxide and periodic acid converted the diol into a dihydroxyaldehyde, and the latter gave on dehydration and acetylation a mixture of the *cis*- and *trans*-isomeric acetoxyaldehydes, LXVI and LXVII, separated by crystallization. The *cis*-isomer (LXVI) was converted by means of the WITTIG reaction into the diene LXVIII which was hydrogenated to the carbinol (LXIX). The latter was oxidized to the ketone LXX, identical with the one isolated from the oxidation of vitamin D_3.



The next step was to prepare the C_{20}-aldehyde LXXI; it was again achieved by employing the WITTIG reaction [6]. The above ketone (LXX) with allylidenephosphorane gave the diene LXXII that was selectively ozonized. The ozonide was reduced with lithium aluminium hydride to the carbinol LXXIII, which could be oxidized by manganese dioxide to the C_{20}-aldehyde LXXI, isolated as the semicarbazone.



This aldehyde (LXXI) was condensed with *p*-hydroxycyclohexanone to a mixture of the epimeric ketols LXXIV and LXXV. The fraction enriched in the β-epimer LXXV underwent the WITTIG reaction with methylenephosphorane, yielding a mixture of trienols (5,6-*trans*-vitamin D_3), which was subjected to irradiation (quartz lamp) without separation. After treatment of the irradiation products with dinitrobenzoyl chloride in pyridine, pure vitamin D_3 (LXXVI) was isolated [5] by chromatography in a low yield.



Later it was established [4] that the *trans* aldehyde LXVII can also be converted by a series of reduction reactions into the carbinol LXIX, and thus the over-all yield could be somewhat improved. According to the scheme presented, the yield is about 10^{-6} %.

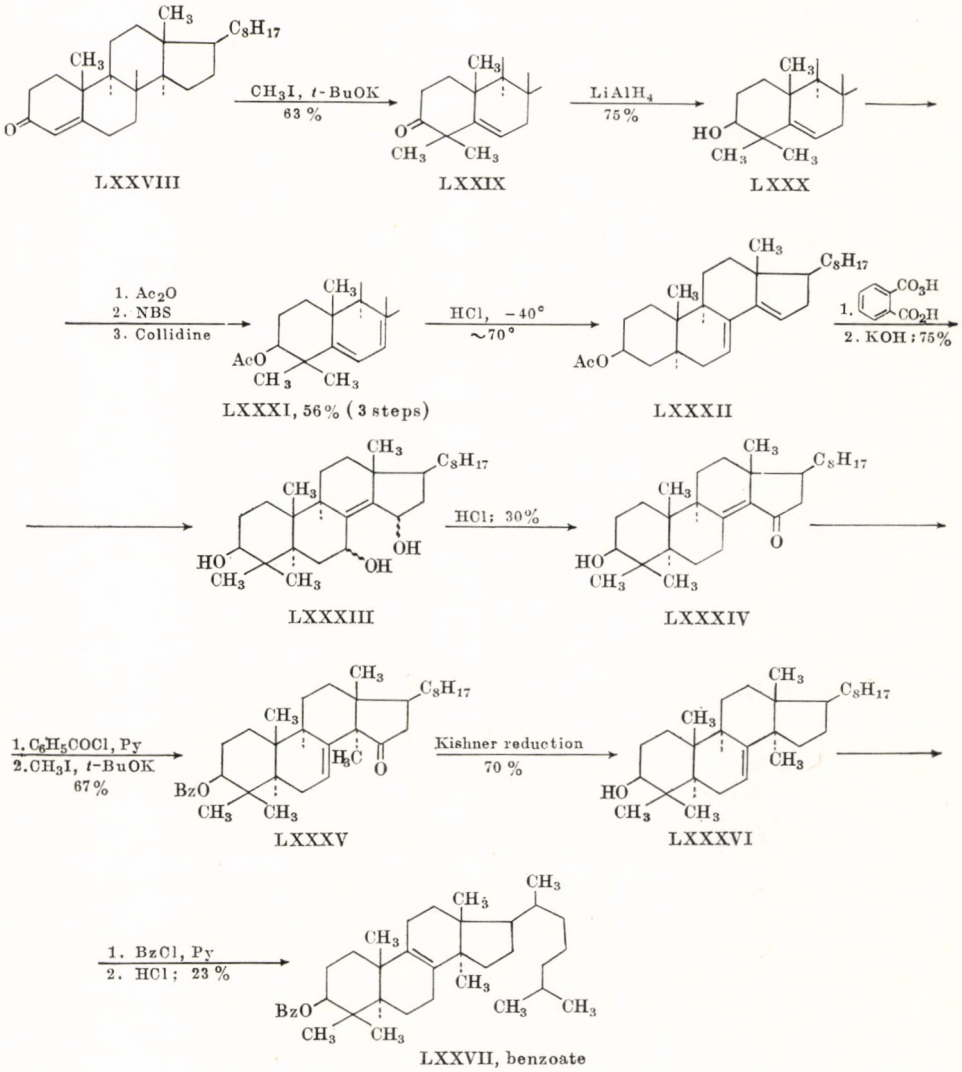
SYNTHESIS OF Δ^8-LANOSTENOL AND LANOSTEROL

Compounds of the lanosterol group possess the structure of steroids, but according to their composition and chemical properties they could also be classified as triterpenes. Hence, lanosterol is a sort of 'bridge' between two large classes of natural products, steroids and triterpenoids.

In 1954 WOODWARD, BARTON, and their collaborators [17] were able to 'take this bridge' by achieving the total synthesis of Δ^8-lanosterol (LXXIII) from cholestenone.

Methylation of cholestenone (LXXVIII) with methyl iodide in the presence of potassium *tert.*-butoxide yielded 4,4-dimethyl-Δ^5-cholestene-3-one (LXXIX), which was reduced with lithium aluminium hydride to give the carbinol LXXX. The acetate of the latter on allylic bromination followed by dehydrobromination was converted into the $\Delta^{5,7}$-diene LXXXI. This compound isomerized in the presence of hydrogen chloride (a reaction characteristic of ergosterol derivatives) to the $\Delta^{7,14}$-diene LXXXII, which was reacted with perphthalic acid to yield, after alkaline hydrolysis, the triol LXXXIII. In acidic medium the triol undergoes rearrangement with dehydra-

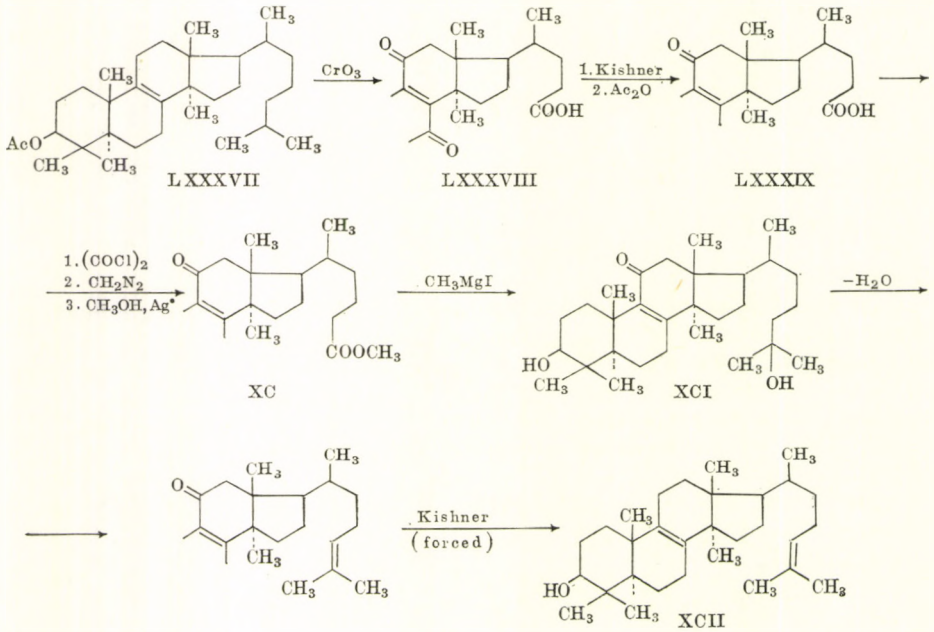
tion yielding $\Delta^{8(14)}$-15-ketone (LXXXIV). The benzoate of the latter on methylation with a large excess of methyl iodide gave a good yield of the 14-methyl-Δ^{7}-15-ketone LXXXV, which on KISHNER reduction afforded Δ^{7}-lanostenol (LXXXVI).



Treatment of Δ^{7}-lanostenol benzoate with hydrogen chloride led to a mixture of benzoates from which the benzoate of natural Δ^{8}-lanostenol was obtained in moderate yield.

Oxidation of Δ^{8}-lanostenol acetate (LXXXVII) gave the diketo-acid LXXXVIII in low yield. The KISHNER—HUANG—MINLON reduction under ordinary conditions removed the keto group (more drastic reaction resulted in the reduction of the Δ^{8}-bond). The acetate of the obtained 11-keto-acid (LXXXIX) was subjected to ARNDT—EISTERT reaction, yielding the homo-

acid methyl ester XC, and on further reaction with methylmagnesium iodide the keto-diol XCI was produced.



Dehydration of the latter (XCI) followed by KISHNER—HUANG—MINLON reduction [18] with anhydrous hydrazine at 230° led to natural lanosterol (XCII).

REFERENCES

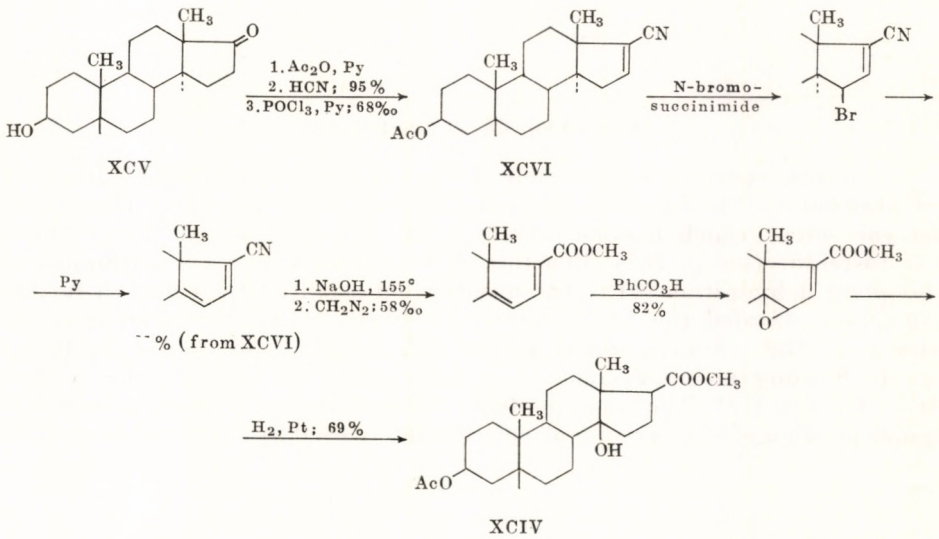
1. BARTON, D. N. R., and MORGAN, L. R.: *Proc. Chem. Soc. 1961*, 206.
2. DANIELLI, N., MAZUR, Y., and SONDHEIMER, F.: *Chem. and Ind. 1958*, 1724, 1725.
3. DJERASSI, C., ROMO, J., and ROSENKRANZ, G.: *J. Org. Chem. 16*, 754 (1951).
4. INHOFFEN, H. H., IRMSCHER, G., FRIEDRICH, G., KAMPE, D., and BERGES, O.: *Chem. Ber. 92*, 1772 (1959).
5. INHOFFEN, H. H., IRMSCHER, K., HIRSCHELD, H., STACHE, U., and KREUTZER, A.: *Chem. Ber. 91*, 2309 (1958).
6. INHOFFEN, H. H., QUINKERT, G., and SCHUTZ, S.: *Chem. Ber. 90*, 1283 (1957).
7. INHOFFEN, H. H., SCHUTZ, S., ROSSBERG, P., BERGES, O., NORDSIEK, K. H., PLENIO, H., and HOROLDT, E.: *Chem. Ber. 91*, 2626 (1958).
8. MAZUR, Y., DANIELI, N., and SONDHEIMER, F.: *J. Am. Chem. Soc. 82*, 5889 (1960).
9. MAZUR, Y., and SONDHEIMER, F.: *J. Am. Chem. Soc. 81*, 3161 (1959).
10. ROSENKRANZ, G., MANCERA, O., and SONDHEIMER, F.: *J. Am. Chem. Soc. 76*, 2227 (1954).
11. SONDHEIMER, F., MANCERA, O., ROSENKRANZ, J., and DJERASSI, C.: *J. Am. Chem. Soc. 75*, 1282 (1953).
12. SONDHEIMER, F., YASHIN, R., ROSENKRANZ, G., and DJERASSI, C.: *J. Am. Chem. Soc. 74*, 2696 (1952).
13. TURNER, R. B., and VOITLE, D. M.: *J. Am. Chem. Soc. 73*, 2283 (1951).
14. UHLE, F. C.: *J. Am. Chem. Soc. 76*, 4245 (1954).
15. UHLE, F. C.: *J. Org. Chem. 27*, 656 (1962).
16. UHLE, F. C., and MOORE, J. A.: *J. Am. Chem. Soc. 76*, 6412 (1954).
17. WOODWARD, R. B., PATCHETT, A. A., BARTON, D. N. R., IVES, D. A. J., and KELLY, R. B.: *J. Am. Chem. Soc. 76*, 2852 (1954).
18. WOODWARD, R. B., PATCHETT, A. A., BARTON, D. H. R., IVES, D. A. J., and KELLY, R. B.: *J. Chem. Soc. 1957*, 1131.

ADDENDA

SYNTHESIS OF DIGITOXIGENIN

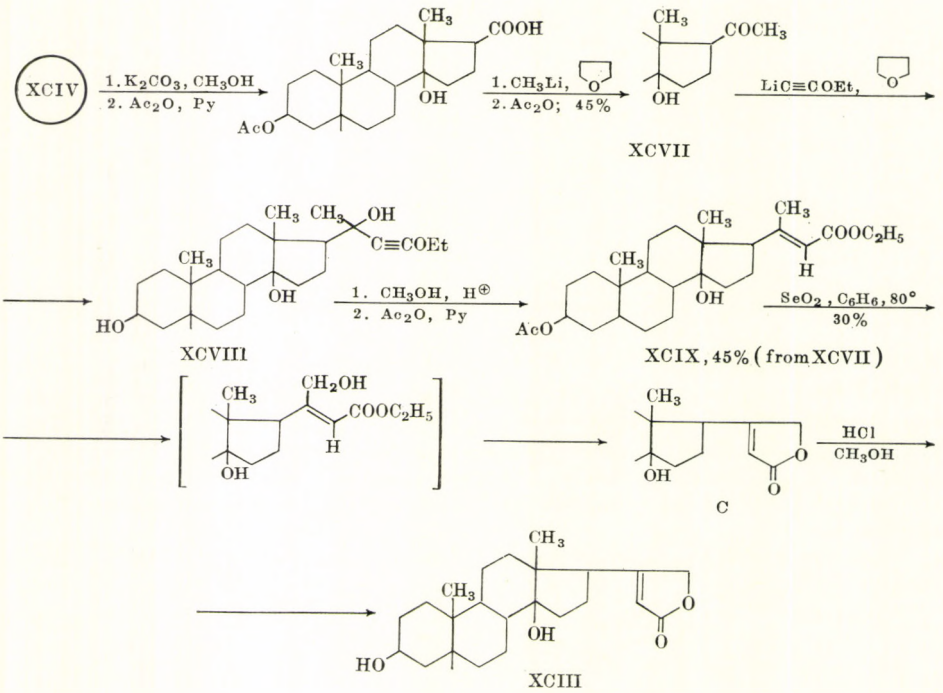
At the beginning of 1962 SONDHEIMER and his collaborators published [1] the first synthesis of the cardiac aglycone digitoxigenin (XCIII), starting from methyl 14β-hydroxy-3β-acetoxyaetianate (XCIV). Since the latter had been synthesized earlier [3] from 5β-androstane-3β-ol-17-one (XCV), the chain of the total synthesis (a rather long one, because the ketol XCV was obtained by the hydrogenation of dehydroepiandrosterone) has been completed.

The ester (XCIV) was prepared by RUZICKA according to the following scheme:



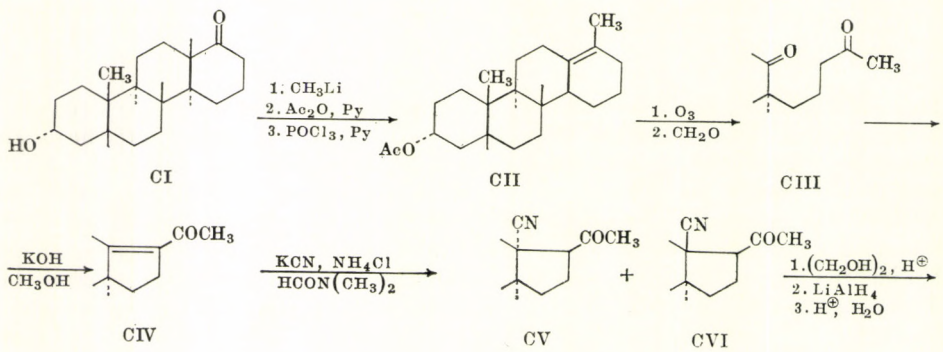
XCIV

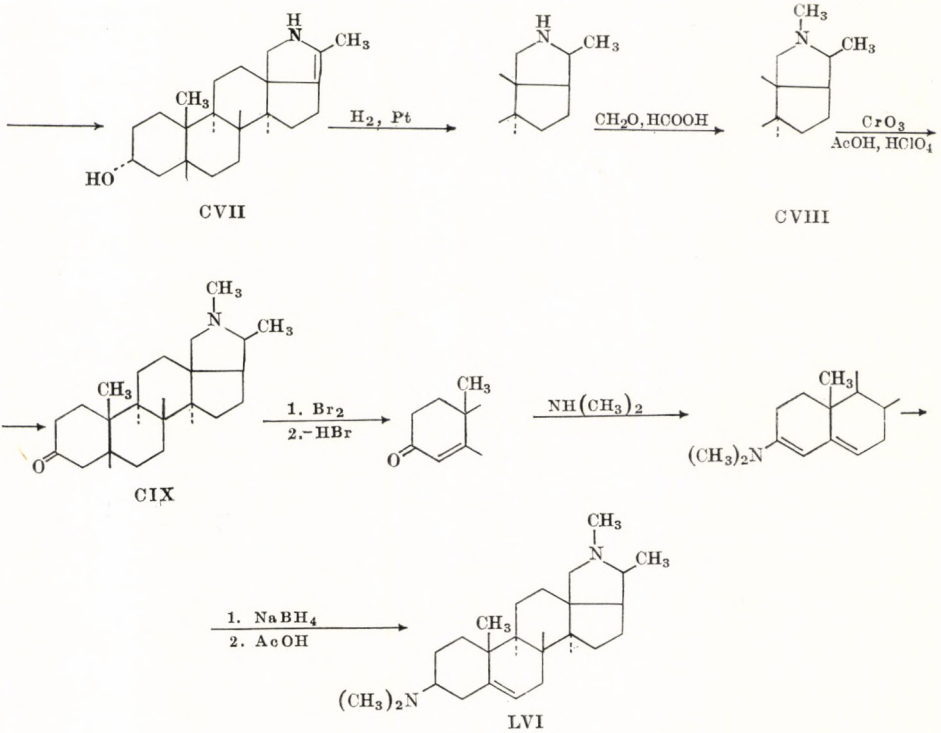
This ester (XCIV) was converted by SONDHEIMER into the pregnane derivative (pregnane-3β,14β-diol-20-one 3-acetate, XCVII) by a series of the usual reactions. Conversion with ethoxyethynillithium gave the carbinol XCVIII which was easily isomerized in acidic media to the α,β-unsaturated ester XCIX. The critical operation was the last step, when oxidation with selenium oxide succesfully introduced a hydroxyl group into position 21. Under the given reaction conditions the formed hydroxy-ester cyclized to digitoxigenin acetate (C) which was eventually saponified to digitoxigenin (XCIII).



SYNTHESIS OF *dl*-CONESSINE

The total synthesis of conessine (LVI) was achieved in 1962 by JOHNSON and MARSHALL [2]. The starting material was the ketol CI of the hydrochrysene series, which had already been the intermediate in the synthesis of testosterone (see p. 267). Reaction of this ketol with methyllithium and subsequent dehydration led to the unsaturated acetate CII, which on further ozonization afforded the 13,17-secosteroid diketone CIII. Cyclization of the latter gave the α,β-unsaturated ketone CIV which easily added hydrogen cyanide forming an approximately equal mixture of the epimeric γ-ketonitriles CV and CVI. The same method of introducing functional groups into angular position of the steroid molecule was lately used by NAGATA (see p. 279).





CVII CVIII CIX LVI

The further transformations were carried out with the 13β-isomer (CVI). Its ethyleneketal was reduced by lithium aluminium hydride to the intermediate aminoketale which was then hydrolized to the enamine CVII. Consecutive hydrogenation and methylation gave rise to the aminoalcohol CVIII which was oxidized to the aminoketone CIX. The latter was converted to *dl*-conessine by a series of the usual reactions.

REFERENCES

1. Danielli, N., Mazur, Y., and Sondheimer, F.: *J. Am. Chem. Soc. 84*, 877 (1962).
2. Marshall, J. A., and Johnson, W. S.: *J. Am. Chem. Soc. 84*, 1485 (1962).
3. Ruzička, L., Plattner, P. A., Heusser, H., and Meier, K.: *Helv. Chim. Acta 30*, 1342 (1947).

Responsible for publication: Gy. Bernát

Director of the Publishing House of the Hungarian Academy of Sciences
and of the Academy Press

Responsible Editor: E. K. Kállay-Tóth

Technical Editor: I. Farkas

Printed in Hungary at the Academy Press Budapest

cepts renders the monograph perfectly intelligible to the pure organic chemist.

I. V. Torgov presents a lucid and very concise monograph on the total synthesis of naturally occurring stereoids. This distinguished researcher covers the literature to about 1962, and arranges his material in a modern and interesting survey. All important achievements of this new and intriguing branch of steroid chemistry are condensed in charts of formulae, connected by a factual and extremely clear explanatory text.

AKADÉMIAI KIADÓ

Distributors:

KULTURA

Budapest 62, P.O.B. 149