MONOGRAPHS ON THE
CHEMISTRY OF NATURAL PRODUCTS

General Editor: SIR ROBERT ROBINSON

THE CHEMISTRY OF THE MORPHINE ALKALOIDS

By

K. W. BENTLEY

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OXFORD
AT THE CLARENDON PRESS
1954

FOREWORD

In 1932 the U.S. Treasury Department (Public Health Service) published an excellent monograph, *Chemistry of the Opium Alkaloids*, by Professor Lyndon F. Small assisted by Associate Professor Robert E. Lutz.

The progress made in the last two decades has been so great, however, that a new work is required. This is all the more timely in that the formal synthesis of morphine by Professor M. Gates and his co-workers has finally established the validity of the constitutional formula proposed by Gulland and the writer in 1925.

The second volume of *The Alkaloids* (Academic Press) by R. H. F. Manske and H. L. Holmes, which contains three long chapters on morphine, thebaine, and sinomenine, appeared in 1952 whilst the present work was in preparation. The apparent duplication is not regretted partly on account of the new matter which it is now possible to include and partly because of the misunderstanding of the stages of development of the structural theory which does not show in true perspective some points where English chemists made a significant contribution.

Holmes (loc. cit., p. 26) remarks that the modern formulae (meaning our own) are but a small modification of those of Knorr and are based on Knorr's results together with a small further piece of evidence.

Again (p. 27) he states that Knorr's formula explained satisfactorily the complex rearrangements of morphine and thebaine. The first statement is misleading and the second will be seen to be incorrect on inspection of the details. For example, Knorr-codeinone to thebenine demands either a migration of carbonyl, or of the ethanamine chain, which cannot be theoretically justified, or based on analogy in any simple manner.

We allow no one to surpass us in respect for Knorr and Pschorr and other pioneers of morphine chemistry. They established the main facts, especially the constitutions of the phenanthrene degradation products, including morphenol and thebaol, and the very important transformation products thebenine, morphothebaine, and apomorphine. But until 1925 there was no consistent explanation of these degradations and transformations in terms of any acceptable structures for the parent bases. What appears to be a very small change in structure involved very great changes in the interpretations, and in fact proved the small key that unlocked a particularly massive door.

This is perhaps a suitable opportunity to recall the circumstances at that juncture, but in doing so it is far from the writer's wish to imply any comparison of the relative value of the key and the door.

In considering this stage of the development it is not difficult to confuse the issue by unduly meticulous attention to the formulae in

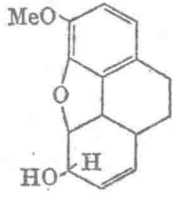
which codeine is represented as unsaturated, ignoring at the same time the equivalence of a bridged-ring structure for certain purposes.

Thus the allylic rearrangement of codeine to pseudocodeine was virtually recognized for the first time by Gulland and the writer in 1923.

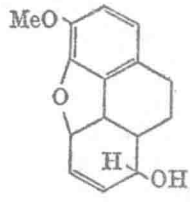
The swing of a bridge took the place of that of a bond. In that paper of 1923 the analogy of the process to the geraniol-linalol transformation was specifically indicated.

In 1925 we were sure that codeine is unsaturated, partly because we had made it into a glycerol by the action of very dilute potassium permanganate.

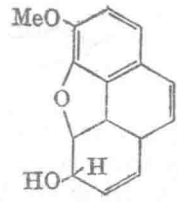
And in that year Wieland and Kotake, and Gulland and Robinson, simultaneously and independently, ascribed the correct positions of *sec*-hydroxyl and double bond to codeine (*iso*codeine) (I) and pseudocodeine (allopseudocodeine) (II). The existence of the oxide ring shown in these formulae had long been established.



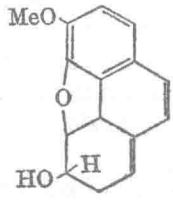
[I]



[II]



[III]



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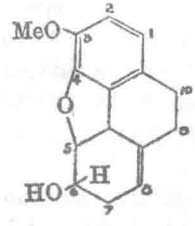


[V]

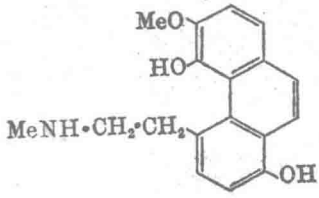
The position attributed to the oxygen was based on the conviction that a carbonyl oxygen (in codeinone and pseudocodeinone) would not migrate. Hence Pschorr's syntheses of 3:4:6-trimethoxyphenanthrene, obtainable from codeinone, and 3:4:8-trimethoxyphenanthrene, obtainable from pseudocodeinone, fixed the positions of the carbonyl group of the ketones, and therefore those of the *sec*-alcoholic groups of codeine and pseudocodeine also.

This led at once to the bis-ethenoid system of α-codeimethine (III) and β-codeimethine (IV).

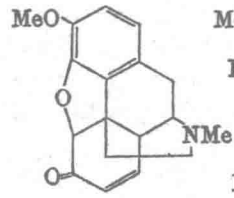
A year later van Duin, Robinson, and Smith found that neopine (q.v.) is β-codeine (V) and is directly convertible into β-codeimethine. [I to V inclusive are parts of the full structures.]

The appearance of a double bond in the 9:10 position during the formation of α-codeimethine was consistent with the attachment of the basic nitrogen to one of these carbon atoms. Position 9 was generally preferred by the early theorists, probably on conscious or subconscious biogenetic grounds, in that the other opium alkaloids are β-arylethylamine derivatives.

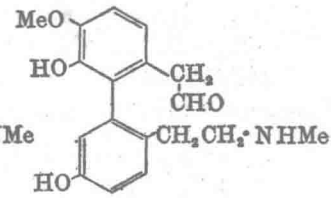
We selected position 9 not only on the basis of the structural relation with *iso*quinoline alkaloids, but also because it was the only position that allowed us to give an explanation of the formation of thebenine (VI) from codeinone (VII).



[VI]



[VII]



[VIII]

This theory is one to which the writer attaches considerable importance. It was advanced in 1923 on the bridge-ring basis, but is readily translated in terms of the 1925 formula.

We suggested that codeinone (VII) when treated with hot dilute hydrochloric acid undergoes hydrolysis and rearrangement to (VIII). There is then a swing about 180° and a natural type of condensation to give (VI). It will be seen that this scheme will not work plausibly enough if the nitrogen is attached to position 10 of the phenanthrene ring. This point is mentioned because it has been overlooked in subsequent comment.

In regard to the position of attachment of carbon of the ethanamine chain we were guided in 1923 and 1925 by three main considerations as follows:

(*a*) The view that the chain will not be displaced by C—C fission unless its removal is essential for formation of an aromatic nucleus.
(*b*) The mechanism of the codeinone to thebenine transformation.
(*c*) Biogenetic arguments.

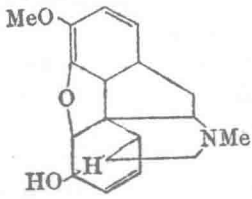
We came to the conclusion that C-13 was the only possible point of attachment.

Thus C-5 (Knorr formula) did not accommodate requirements under (*b*) and (*c*) and in a few cases (*a*) was also not satisfied.

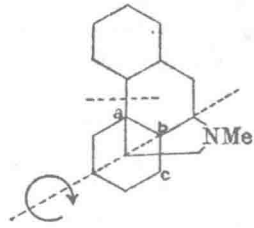
C-14 is excluded by β-codeimethine and C-8 by pseudocodeinone. Only C-13 survived all the tests.

Nevertheless, a tiny loophole existed, namely that the alkaloids might not be phenanthrene derivatives and the phenanthrene ring might

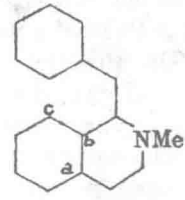
appear only in the course of degradation. Thus codeine might be (IX). This *punctilio* was disposed of by a study of the ultra-violet absorption of α- and β-codeimethines (1947). Naturally the Gates synthesis[1] has now made this matter still less worthy of further consideration. The biogenetic argument was always regarded as a guide to structure, but a conceivably unreliable one. In its simplest form we draw attention to the fact that the skeleton (X) is also that of laudanosine (XI). Fission and rotation of the lower ring, about the axis as indicated, equate the two part-structures.



[IX]



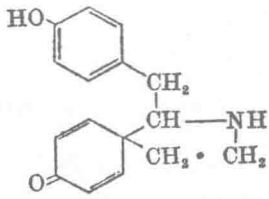
[X]



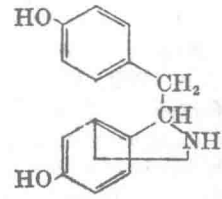
[XI]

The synthesis by Grewe of the morphinane ring system depends on a reversal of this process. As explained elsewhere, this scheme allows of a particularly close relation between sinomenine and a laudanosine derivative. The latter was synthesized and hopefully called protosinomenine, but it has not been available in sufficient amount to enable its properties and possible transformation to sinomenine to be thoroughly examined.

In the case of thebaine and morphine the oxygen atoms are not in the 3:4-position of the best known dihydroxyphenylalanine.



[XII]



[XIII]

In the Truman Wood Lecture of 1948 to the Royal Society of Arts the writer has suggested a mechanism of oxidative coupling of tyrosine which may be worthy of further study. It involved a migration at one stage and led to the thebaine structure. The usual coupling leading to laudanosine types is assumed to take place at the *p*-position to hydroxyl of tyrosine. This gives (XII) which suffers hemiquinone migration to

[1] A private communication (October 1953) discloses that morphine has also been synthesized by David Ginsburg and his colleagues at Rehovoth, Israel.

(XIII). Oxidation, oxidative ring coupling, and methylation can then give thebaine. As always, the order of the processes is undetermined, and as one example of this the starting-point could be 3:4-dihydroxyphenylalanine.

In the last decade the subject of rearrangements in the thebaine group has been twice awakened from sleep. The first occasion was signalled by elucidation of the constitution of phenyldihydrothebaine, discovered by Freund and carefully studied by Small.

It transpired that the final product of Hofmann degradation of this base contained no asymmetric carbon atom and owed its optical activity to restricted rotation of a heavily substituted diphenyl!

Dr. Bentley was associated with the writer in the performance of crucial experiments bearing on the validity of the rather surprising conclusion which we were forced to adopt.

The second occasion, also of great interest, was connected with the re-examination of Schöpf's flavothebaone by Dr. Bentley and Professor J. Dominguez. The complex results are still being scrutinized, but it is already clear that a double migration is involved and that a new and fascinating chapter of thebaine chemistry will be written.

Dr. Bentley has also elaborated the chemistry of the reduction products of thebaine in several directions.

In the volume which follows he has covered critically and exhaustively the whole field of the chemistry of these alkaloids and has thus performed a much needed service to the scientific world. He has carried out his task with remarkable skill backed by the enthusiasm which is felt by all who come into contact with this veritable Proteus among molecules.

R. ROBINSON

ADDENDUM. Kondo, Satomi, and Odera (Annual Reports of the I.T.S.U.U. Institute, 1951, 1952, 1953, Tokyo) have proved that *hasubanonine* from *Stephania japonica* Miers is 3:4:6:7-tetramethoxy-8-oxo-N-methylmorphinane as is suggested on p. 359 formula [CXIX]. Hasubanonine is a ketone and its methiodide affords a methine-base, which on acetolysis yields dimethylethylamine and 0-acetylhasubanol. Hasubanol methyl ether was identified with 3:4:6:8-tetramethoxyphenanthrene. Colour reactions indicate a free *p*-position with respect to the phenolic hydroxyl of hasubanol, which is accordingly sited at position-8. This is clearly a transform of the carbonyl group of the alkaloid. The methoxyl eliminated in the acetolysis of the methine must be at position-7, because hasubanonine was unchanged when an attempt was made to convert it into a hydroxymethylene derivative; sinomenine underwent this transformation with ease under the same conditions.

AUTHOR'S PREFACE

NEARLY a hundred and fifty years have elapsed since the first vegetable alkaloid was discovered, and only recently has the structure proposed for this base in 1925 been vindicated by the total synthesis of the alkaloid. It would seem that the 'morphine' chapter of organic chemistry is now all but closed and that all that remains is the filling in of details; but it would be rash to assert this, as one of the most interesting of molecular rearrangements in this field was only fully elucidated five years ago, while yet another received a credible solution only after the completion of the main text of this monograph. The moment seems opportune, however, for the presentation, in one volume, of a comprehensive survey of the chemistry of all the morphine alkaloids.

In this monograph each chapter is intended to be as far as possible a complete account of one section of the work, even though this has necessitated the duplication of certain parts. It is hoped that all papers relating to the chemistry of the morphine alkaloids published before 1 February 1953 are referred to in the monograph.

The compilation of this monograph has proved to be a more exacting task than was first anticipated and I wish to thank Professor Sir Robert Robinson, O.M., for his unfailing interest and constant encouragement at all stages of the work and for helpful discussion of all points of structural interest that have arisen.

I also wish to express my thanks to the following: Señor Justo Dominguez for his invaluable experimental assistance in the investigations related to flavothebaone; Dr. J. A. Barltrop for helpful discussion in relation to Chapter XXI; Dr. F. B. Strauss and Mr. F. H. L. H. Hastings for the preparation of all but one of the ultra-violet extinction curves embodied in the monograph; Messrs. A. F. Thomas, A. Marchant, and J. M. Swinstead for help with the checking of references and manuscripts; to my wife for her help in the equally laborious tasks of the reading of proofs and the preparation of the index; and finally to the officers of the Clarendon Press, for whom no trouble seems to be too great, for the courteous and efficient manner in which they have carried out their part of the work.

γηράσκω δ'ἀεὶ πολλὰ διδασκόμενος

THE DYSON PERRINS LABORATORY
OXFORD

THE CHEMISTRY DEPARTMENT
THE UNIVERSITY
ABERDEEN

March 1953

ABBREVIATIONS

Abderhalden's Hanb. biol. Arbeitsmethoden, Abderhalden's Handbuch der biologischen Arbeitsmethoden.

Acta Chem. Scand., Acta Chemica Scandinavica.

Acta Phytochim., Acta Phytochimica (Japan).

Allen's Comm'l Org. Anal., Allen's Commercial Organic Analysis.

Am. J. Pharm., American Journal of Pharmacy.

Anales Asoc. Quim. Argentina, Anales de la Asociación Química Argentina.

Anales Farm. Bioquím. (*Buenos Aires*), Anales de Farmacia y Bioquímica (Buenos Aires).

Anales real acad. farm., Anales de la real academia de farmacia.

Analyst, The Analyst.

Ann., Annalen der Chemie.

Ann. Chim., Annales de Chimie.

Ann. Chim. Anal., Annales de Chimie Analytique et de Chimie Appliquée et Revue de Chimie Analytique Réunies.

Ann. Chim. Farm., Annali di Chimica Farmaceutica.

Ann. Chim. Phys., Annales de Chimie et Physique.

Ann. Méd. Légale Criminol. Police Sci., Annales de Médecine Légale de Criminologie et de Police Scientifique.

Ann. pharm. Franç., Annales pharmaceutiques françaises.

Ann. Rep. Itsuu Lab., Annual Report of Itsuu Laboratory.

Ann. Sci. Univ. Jassy, Annales Scientifiques de l'Université de Jassy.

Ann. Suppl., Annalen der Chemie Supplement.

Apoth.-Ztg., Apotheker-Zeitung.

Arch. Exptl. Path. Pharmakol., Archiv für experimentelle Pathologie und Pharmakologie.

Arch. ges. Physiol., Archiv für gesamte Physiologie des Menschen und der Tiere.

Arch. Intern. Pharmacodynamie, Archives Internationales de Pharmacodynamie et de Thérapie.

Arch. Pharm., Archiv der Pharmazie und Berichte der deutschen pharmazeutischen Gesellschaft.

Arch. Sci. Biol., Archivio di Scienze Biologiche.

Arq. Biol. (*São Paulo*), Arquivos de Biologica (São Paulo).

Atti Accad. Gioenia Sci. Nat. Catania, Atti della Accademia Gioenia di Scienze Naturali di Catania.

Atti Accad. Lincei, Atti della Reale Accademia Nazionale dei Lincei.

Atti Soc. Medchir. Padova, Atti della Società Medico-chirurgica di Padova e Bolletino della Facoltà di Medicina e Chirurgica della r. Università di Padova.

Australian J. Pharm., Australian Journal of Pharmacy.

Ber., Berichte der deutschen chemischen Gesellschaft.

Ber. Deut. Pharm. Ges., Berichte der deutschen pharmazeutischen Gesellschaft.

Ber. ges. Physiol. expt. Pharmacol., Berichte über die gesamte Physiologie und experimentelle Pharmakologie.

Ber. Sächs. Akad. Wiss., Berichte über die Verhandlungen der Sächsischen Akademie der Wissenschaften zu Leipzig.

Ber. Ungar. Pharm. Ges., Berichte über die ungarische pharmazeutische Gesellschaft.

Biochem. Z., Biochemische Zeitschrift.

Boll. Chim.-Farm., Bollettino chimico-farmaceutico.

Boll. Soc. Ital. Biol. Sper., Bollettino della Società Italiana di Biologia Sperimentale.

Brit. Pat., British Patent.

Büchner's Rept. Pharmazie, Büchner's Repertorium der Pharmazie.

Bull. Acad. Sci. United Provinces, Agra, Oudh, Allahabad, Bulletin of the Academy of Sciences of the United Provinces of Agra and Oudh, Allahabad.

Bull. Biol. Pharm., Bulletin des Biologistes Pharmaciens.

Bull. Chem. Soc. Japan, Bulletin of the Chemical Society of Japan.

Bull. Health Org. League Nations, Bulletin of the Health Organisation of the League of Nations.

Bull. Hyg. Res. Inst. (Japan), Bulletin of the Hygenic Research Institute (Japan).

Bull. Sci. Pharmacol., Bulletin des Sciences Pharmacologiques.

Bull. Soc. Chim., Bulletin de la Société Chimique de France.

Bull. Soc. Chim. Belg., Bulletin de la Société Chimique de Belgique.

Bull. Soc. Chim. România, Bulletin de la Société Chimique de România.

Bull. Soc. Chim. Roy. Yougoslav., Bulletin de la Société Chimique du Royaume de Yougoslavie.

Bull. Soc. Pharm. Bordeaux, Bulletin des Travaux de la Société de Pharmacie de Bordeaux.

Bull. Soc. Roy. Sci. Liége, Bulletin de la Société Royale de Science de Liége.

Byull. Nauch.-Issl. Khim.-Farm. Inst., Byulleten Nauchno-Issledovatel'skogo Khimiko-Farmatsevicheskogo Instituta.

Can. J. Res., Canadian Journal of Research.

Časopis Českoslov. Lékárnictva, Časopis Československého Lékárnictva.

Chem. Abs., Chemical Abstracts.

Chemist and Druggist, Chemist and Druggist.

Chem. News, Chemical News.

Chem. Zent., Chemisches Zentralblatt.

Chem. Ztg., Chemiker-Zeitung.

Chimie et Industrie, Chimie et Industrie.

Chim. Anal., Chimie Analytique.

Chim. ind. agr. biol., La Chimica nell' industria, nell' agricoltura, nella biologia e nelle realizzazioni corporative.

Chûgai Iji Shimpo, Chûgai Iji Shimpo.

Compt. Rend., Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences.

Compt. Rend. Acad. Sci. U.S.S.R., Comptes Rendus de l'Académie des Sciences de l'U.R.S.S.

Compt. Rend. Soc. Biol., Comptes Rendus des Séances de la Société de Biologie et de ses filiales et associées.

Current Sci., Current Science.

Dansk Tids. Farm., Dansk Tidsskrift for Farmaci.

Deut. Med. Wochschr., Deutsche medizinische Wochenschrift.

D. R.-P., Deutsches Reichs-Patent.

Edinburgh New Phil. J., Edinburgh New Philosophical Journal.

Experientia, Experientia.
Farmatisiya, Farmatisiya.
Farm. Nueva, Farmacia Nueva (Madrid).
Farm. Zhur., Farmatsevtichnii Zhurnal.
Frdl., Friedlaender, Fortschritte der Teerfarben-fabrikation.
French Pat., French Patent.
Gazz. Chim. Ital., Gazzetta Chimica Italiana.
Gilbert's Ann. der Physik, Gilbert's Annalen der Physik.
Hanb. Krist.-Phys. Chem., Handbuch der kristall-physikalischen Chemie.
Helv. Chim. Acta, Helvetica Chimica Acta.
Ind. Eng. Chem. (*Anal. Edn.*), Industrial and Engineering Chemistry (Analytical Edition).
Indian J. Med. Res., Indian Journal of Medical Research.
Industria Chimica, Industria Chimica.
J.A.C.S., Journal of the American Chemical Society.
J. Agr. Soc. Japan, Journal of the Agricultural Society of Japan.
Jahresber. Chem., Jahresbericht der Chemie.
Jahresber. Chem. Tech., Jahresbericht der chemisch-technischen Reichsanstalt. Leipzig.
Jahresber. Fortschr. Chem., Jahresbericht über die Fortschritte der Chemie.
Jahresber. Fortschr. Phys. Wiss., Jahresbericht über die Fortschritte der physischen Wissenschaften.
Jahresber. Pharm., Jahresbericht der Pharmazie.
J. Am. Pharm. Assoc., Journal of the American Pharmaceutical Association.
J. Applied Chem. U.S.S.R., Journal of Applied Chemistry of U.S.S.R.
J. Assoc. Official Agr. Chem., Journal of the Association of Official Agricultural Chemists.
J. Biol. Chem., Journal of Biological Chemistry.
J. Chem. Ind. U.S.S.R., Journal of Chemical Industry of U.S.S.R.
J. Chem. Phys., Journal of Chemical Physics.
J. Chem. Soc. Japan, Journal of the Chemical Society of Japan.
J. Chim. Méd., Journal de Chimie Médicale.
J.C.S., Journal of the Chemical Society (London).
J. Gen. Chem. U.S.S.R., Journal of General Chemistry, U.S.S.R.
J. Indian Chem. Soc., Journal of the Indian Chemical Society.
J. Lab. Clin. Med., Journal of Laboratory and Clinical Medicine.
J. Org. Chem., Journal of Organic Chemistry.
J. Pharm., Journal de Pharmacie.
J. Pharm. Belg., Journal de Pharmacie de Belgique.
J. Pharm. Chim., Journal de Pharmacie et de Chimie.
J. Pharm. Elsass Lothr., Journal der Pharmazie von Elsass-Lothringen (Mülhausen).
J. Pharm. Pharmacol., Journal of Pharmacy and Pharmacology.
J. Pharm. Soc. Japan, Journal of the Pharmaceutical Society of Japan.
J. Phys. Chem., Journal of Physical Chemistry.
J. pr. Chem., Journal für praktische Chemie.
J. Soc. Chem. Ind., Journal of the Society of Chemical Industry.
J. Wash. Acad. Sci., Journal of the Washington Academy of Sciences.

Khim. Farm. Prom., Khimiko-Farmatsevticheskya Promyshlennost'.
Khim. Referat. Zhur., Khimicheskil Referativnyi Zhurnal.
Landwirtschaftl. Versuchsstationen, Die landwirtschaftlichen Versuchsstationen.
L'Orosi, L'Orosi, Bollettino di chimica farmacia e scienze affini.
Maanblad voor Naturwettenschappen (Amsterdam), Maanblad voor Naturwettenschappen (Amsterdam).
Mem. Proc. Manchester Lit. Phil. Soc., Memoirs and Proceedings of the Manchester Literary and Philosophical Society.
Mikrochemie, Mikrochemie.
Monatsh., Monatshefte für Chemie und verwandte Teile anderer Wissenschaften.
Mon. Prod. Chim., Moniteur des Produits Chimiques.
Münch. Med. Wochschr., Münchener medizinische Wochenschrift.
Nature, Nature.
Naturwiss., Naturwissenschaften.
Natuurw. Tijdschr., Natuurwettenschappelijk Tijdschrift.
Org. Chem. Ind. U.S.S.R., The Organic Chemical Industry (U.S.S.R.).
Pharm. Acta Helv., Pharmaceutica Acta Helvetiae.
Pharm. J. Trans., The Pharmaceutical Journal and Transactions.
Pharm. Monatsh., Pharmazeutische Monatshefte.
Pharm. Post, Pharmazeutische Post.
Pharm. Weekblad, Pharmazeutische Weekblad.
Pharm. Zentralhalle, Pharmazeutische Zentralhalle.
Pharm. Ztg., Pharmazeutische Zeitung.
Phil. Trans. Roy. Soc., Philosophical Transactions of the Royal Society.
Pogg. Ann. der Physik, Poggendorff's Annalen der Physik.
Proc. Chem. Soc., Proceedings of the Chemical Society.
Proc. Imp. Acad. (Tokyo), Proceedings of the Imperial Academy (Tokyo).
Proc. Ind. Acad. Sci., Proceedings of the Indian Academy of Science.
Proc. Jap. Pharmacol. Soc., Proceedings of the Japanese Pharmacological Society.
Proc. Soc. Exptl. Biol. Med., Proceedings of the Society for Experimental Biology and Medicine.
Quart. J. Pharm. Pharmacol., Quarterly Journal of Pharmacy and Pharmacology.
Quim. e ind., Química e industria.
Rec. Trav. Chim., Recueil des Travaux Chimiques des Pays-Bas.
Rept. Inst. Sci. Res. Manchoukuo, Report of the Institute of Scientific Research, Manchoukuo.
Rev. Faculté Sci. Univ. Istanbul, Revue de la Faculté des Sciences de l'Université d'Istanbul.
Russ. Pat., Russian Patent.
Schweiz. Apoth.-Ztg., Schweizerische Apotheker-Zeitung.
Schweiz. Wochschr., Schweizerische Wochenschrift.
Science, Science.
Science and Culture, Science and Culture.
Sci. Repts. Natl. Tsinghau Univ., Science Reports of the National Tsinghau University.
Semana Méd. (Buenos Aires), La Semana Médica (Buenos Aires).
Sitzber. Akad. Wiss. Wien, Sitzungsberichte der Akademie der Wissenschaften, Wien.
Süddeut. Apoth.-Ztg., Süddeutsche Apotheker-Zeitung.

Svensk Farm. Tids., Svensk Farmaceutisk Tidskrift.
Swed. Pat., Swedish Patent.
Swiss Pat., Swiss Patent.
Trans. Roy. Soc. Edinburgh, Transactions of the Royal Society of Edinburgh.
Trommsdorff's Journal der Pharmazie, Trommsdorff's Journal der Pharmazie.
Ukrain. Gosudarst. Inds. Eksptl. Farm., Ukrainskiĭ Gosudarstvennyi Institut Eksperimental'noĭ Farmatsii (Kharkov).
Univ. Calif. Pub. Pharmacol., University of California Publications in Pharmacology.
U.S. Pat., United States Patent.
U.S. Pub. Health Service Suppl., United States Public Health Service Supplement.
Virginia J. Sci., The Virginia Journal of Science.
Z. anal. Chem., Zeitschrift für analytische Chemie.
Z. angew. Chem., Zeitschrift für angewandte Chemie.
Z. anorg. Chem., Zeitschrift für anorganische Chemie.
Z. Elektrochem., Zeitschrift für Elektrochemie und angewandte physikalische Chemie.
Z. exptl. Path. Therap., Zeitschrift für experimentelle Pathologie und Therapie.
Z. Krist., Zeitschrift für Kristallographie.
Z. Krist. Mineral., Zeitschrift für Kristallographie und Mineralogie.
Z. phys. Chem., Zeitschrift für physikalische Chemie.
Z. physiol. Chem., Zeitschrift für physiologische Chemie.
Zeitschr. Chem., Zeitschrift für Chemie und Pharmazie.

CONTENTS

I

INTRODUCTION; HISTORICAL AND GENERAL DISCUSSION OF THE CONSTITUTION OF THE ALKALOIDS

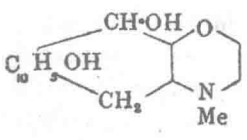
ALMOST a century and a half has elapsed since Sertürner isolated the first organic base clearly recognized as such, a crystalline substance that he obtained from the opium poppy, *Papaver somniferum*, and called morphine [1]. Largely on account of the migration phenomena encountered, the structural puzzle presented by morphine and related alkaloids has absorbed the interest of many chemists during this time, and in the case of scarcely any other natural product have so many constitutional formulae been proposed or such a volume of experimental work recorded. The fundamental researches of Hesse, Vongerichten, Knorr, and Pschorr established the alkaloid as a bridged-phenanthrene type, and the later work of Robinson and Schöpf resulted in the generally accepted structure for this group of bases.

That morphine is a phenol as well as a base was shown by its alkali-solubility [2], and codeine (discovered by Robiquet [3]) was subsequently shown by Grimaux [4–5] to be the methyl ether of morphine. Morphine yields a diacetyl-derivative [6–7] and codeine an acetyl-derivative [6] showing that these bases also contain an alcoholic group, and the hydroxyl of this is replaceable by chlorine when the alkaloids are treated with phosphorus pentachloride [8] or trichloride [9]. Oxidation of codeine with chromic acid affords a ketone, codeinone [10], which can also be obtained by the acid hydrolysis of a third alkaloid of this group, thebaine (discovered by Pelletier [11]), which was thus recognized as the methyl ether of an enolic form of codeinone [12]. The relationship between the three alkaloids was thus clear, and most of the evidence for the structure of the alkaloids of the morphine group is drawn from work on codeine and thebaine. These bases contain a third oxygen atom, which is inactive and was soon recognized as being part of an ether system.

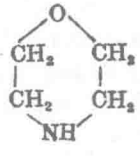
The mode of linkage of the nitrogen atom is clearly shown by the results of exhaustive methylation; with morphine the reaction is blocked by the formation of a phenol betaine [7, 13], but codeine methiodide on boiling with alkali is degraded to a base, α-codeimethine [14], showing that in codeine the nitrogen atom is part of a ring. Further degradation of α-codeimethine involves loss of the whole basic side-chain and formation of a fully aromatic phenanthrene derivative [15].

A similar reaction occurs when morphine methiodide [16] and thebaine methiodide [17] are heated with acetic anhydride, a process usually called acetolysis, and phenanthrene itself is obtained in low yield by the distillation of morphine with zinc dust [18]. These reactions and the empirical formula for codeine led to the conclusion that in the latter one NMe group and two carbon atoms were in some way attached to a partially hydrogenated phenanthrene skeleton.

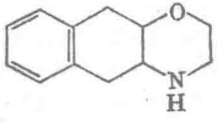
Initially various oxazine formulae for morphine were suggested, based on the theory that β-dimethylaminoethanol, frequently obtained during aromatizing degradations, was produced by the hydrolytic scission of an oxazine system, and Knorr [19] proposed the structure [I] for morphine. Numerous bases were subsequently prepared, all derived from [II], which was called 'morpholine' on account of its supposed relationship to morphine, and of these naphthalanmorpholine [III], a strong, synthetic, alkaloid-like base, was found to undergo exhaustive methylation with production of β-dimethylaminoethanol and naphthalene in the second step [20]. However, the extreme ease with which the last stage of the degradation occurred led Knorr to modify his morphine structure to [IV] [20].



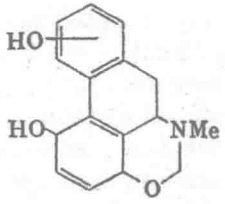
[I]



[II]



[III]



[IV]

In 1900 Pschorr and Sumuleanu [21] showed by synthesis that dimethylmorphol [V, R = Me] (obtained by hydrolysis and methylation of the product [V, R = Ac] of acetolysis of α-codeimethine [16] and codeine methiodide [16]) is 3:4-dimethoxyphenanthrene, and this was followed in 1902 by the identification of methylthebaol [VI, R = R′ = Me] (obtained by hydrolysis and methylation of the product [VI, R = Ac; R′ = Me] of acetolysis of thebaine [22] and of the product [VI, R = R′ = Ac] of acetolysis of codeinone [23]) as 3:4:6-trimethoxyphenanthrene [24]. In this way the location of oxygen substituents at positions 3:4 and 6 of the phenanthrene system in morphine was demonstrated, and Knorr's oxazine formula was modified to [VII] [23].

However, [VII] failed to explain the following facts.

(*a*) The isomerization of α-codeimethine to β-codeimethine on heating in alkaline solution [7].

(*b*) The formation of β-dimethylaminoethyl ethyl ether during some