

THE ALKALOIDS

Chemistry and Physiology

Edited by

R. H. F. MANSKE

*Dominion Rubber Research Laboratory
Guelph, Ontario*

H. L. HOLMES

*Riker Laboratories, Inc.
Los Angeles, California*

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PREFACE

It is the fond hope of the editors and contributors of this volume that the excellent reception accorded Volume I will be extended to Volume II. We are apprehensive of the chief criticism of Volume I, namely that some of the chapters were already out of date at the time of printing. Progress in certain of these fields, particularly in those of strychnine and morphine, has been so rapid, and even spectacular, that changes in page proof would not adequately have circumvented this deficiency. Accordingly, supplementary chapters have been added to this volume to bring the information in these fields and the others presented herein up to date.

We have been able to secure the cooperation of a number of competent pharmacologists to contribute chapters on a variety of physiological and pharmacological responses and these are scheduled to appear in Volume V. The intervening Volumes, III and IV, will deal with alkaloids containing the quinoline, the isoquinoline, the glyoxaline, the quinuclidine, and the steroid nuclei, as well as several other groups not so specifically characterized.

We do not agree with the criticism that the order of the chapters is not a preferred one. Plants do not elaborate alkaloids, nor do chemists determine their structure in accordance with a scheme which has its genesis in the five membered heterocycles and its apodosis in the complex polynuclear systems. The sequence of the chapters in the present and the proposed volumes is therefore often dependent upon their accessibility although whenever possible, closely related fields will be placed in sequence. It is our aim to provide a readable and comprehensive work which will include all matters of importance in alkaloid chemistry.

R. H. F. M.

H. L. H.

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PART I

The Morphine Alkaloids. I

H. L. HOLMES

*University of British Columbia
Vancouver, Canada*

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I. Introduction

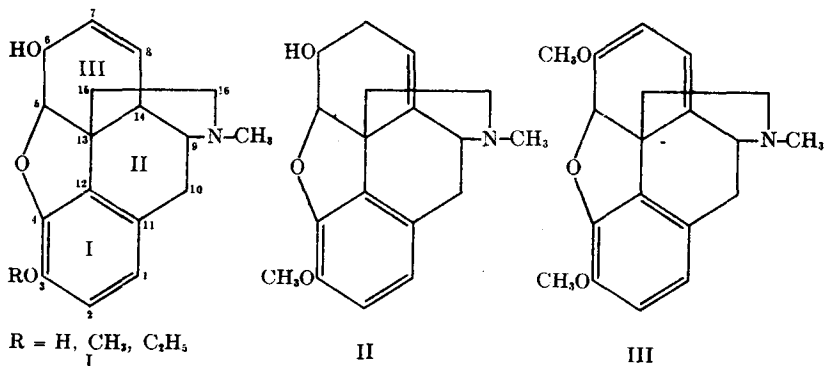
The interest in the opium alkaloids dates back to the seventeenth century, when attempts were made to isolate from opium the principle to which it owes its activity. During the course of these experiments many extracts were obtained and employed in medicine under the name, *Magisterium opii*.

The isolation of a constituent of opium in crystalline form was first attained, in 1803, by Derosne (47); an apothecary practicing in Paris. He diluted his sirupy extract of opium with water and precipitated the "salt of opium" with potassium carbonate. Séguin, in 1804, read a paper (48) to the Institute of France "Sur l'opium," in which he described the isolation of morphine, and the following year Sertürner (304, 305, 306) isolated both morphine and meconic acid from opium. In subsequent work (49, 52, 53, 54) he recognized the ability of morphine to neutralize acids. This "vegetable alkali" was the first member of a large group of naturally occurring substances, which later became known as the alkaloids.

Since Sertürner's characterization of morphine as a vegetable alkali, codeine, thebaine, and neopine have been isolated from the same source, while isothebaine, an aporphine base, has been found to occur in *Papaver orientale* during the flowering season. Since Derosne's time, the structures of morphine (I, R = H), codeine (I, R = CH₃), neopine (II), and thebaine (III) have been established except for the location of the ethanamine

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 (-CH₂-CH₂-N-CH₃) chain, a number of degradations to, and the synthesis

of phenanthrene and various hydroxylated and alkoxyated derivatives have been effected. However, attempts to degrade these alkaloids to hydrophenanthrenes, which still retain at least part of the ethanamine chain, and to establish their structures by synthesis have failed. Until such a



time as the constitution of morphine is finally settled it is obviously impractical to attempt the complete synthesis of these alkaloids or to embark on a study of the stereochemical problem. Hence it would appear that the most direct route to a knowledge of the chemistry of these interesting bases would be to examine the analytical evidence which has led to the structure accepted today, followed by a study of their reactions and rearrangement products. This will be followed in turn by a review of the attempts to synthesize various hydrophenanthrenes which might prove to be degradation products of morphine and the related bases. Finally, the physical constants of the various products of transformation and degradation, not listed elsewhere (331), have been tabulated, followed by a bibliography of the more readily available papers on the subject.

II. Elucidation of the Structure of Morphine, Codeine, and Thebaine

1. THE PHENANTHRENE NUCLEUS OF MORPHINE

Many of the early workers sensed a close relationship between morphine, codeine, and thebaine; however, little progress was made towards the elucidation of the structure of these alkaloids until about the year 1880. The first elementary analysis of morphine was reported in 1831 by Liebig (50) who considered that the base was represented by the formula $C_{34}H_{36}O_4N_2$. This was subject to much revision until 1847 when Laurent (51) arrived at the formula $C_{34}H_{38}O_4N_2$ which subsequently was shown, by molecular weight determinations (329, 330) to be the dimeric form of that accepted today, $C_{17}H_{19}O_2N$. The early work clearly demonstrated

that of the three oxygen atoms of morphine, two are in hydroxyl groups (diacetyl (276) and dibenzoyl (66, 279) derivatives), and one is phenolic (ferric chloride test, precipitation of the alkaloid from its alkaline solution by carbon dioxide and the formation of monoalkyl ethers). This phenolic hydroxyl has been alkylated by a number of methods (the monomethyl ether (I, $R = CH_3$) of morphine is codeine (13, 227, 233)), and several of the less familiar reagents which have proved useful for this purpose are the arylsulfonic esters (188) and trimethylphenylammonium hydroxide (227).

Methylation of morphine (227). The methohydroxide of dimethylaniline is prepared by adding 55.0 g. of the methyl benzenesulfonate of dimethylaniline to an ethanolic solution of sodium ethylate (4.5 g. sodium in 45 cc. ethanol) and removal of the sodium benzenesulfonate by filtration. The methylation of morphine is effected by adding 42.0 g. of the base to the alcoholic solution of the methohydroxide and heating the reaction mixture in an oil bath until all the ethanol is expelled and the temperature of the reaction mixture has risen to 110° , at which temperature it is maintained for 1 hour. The mixture is acidified with 15% acetic acid and the dimethylaniline removed by steam distillation.

Codeine is then liberated from its acetate by the addition of a large excess of 20% sodium hydroxide solution and the oily base (23.5 g.), which first separates, soon crystallizes. An additional 6.0 g. is recovered from the aqueous alkaline solution by extraction with benzene. Based on the amount of morphine used (9.0 g. of morphine may be recovered from the alkaline solution) the conversion to codeine is 85%.

Replacement of the second hydroxyl group by halogens and the oxidation of codeine ($C_{18}H_{21}O_3N$) to a ketone, codeinone ($C_{18}H_{19}O_3N$), amongst other reactions has clearly diagnosed the alcoholic nature of this group. The third oxygen atom is very unreactive and appears to be present in an ether type of linkage (76).

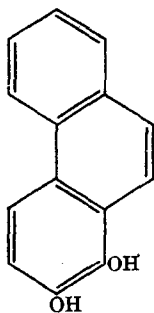
Several reactions, although quite drastic in nature, indicate that in all probability the morphine alkaloids contain a phenanthrene skeleton while the relatively high percentage of hydrogen in these bases has led to the presumption that the phenanthrene system is partially hydrogenated. The recovery of 3-4% of phenanthrene (characterized through its picrate and by its conversion to phenanthrenequinone which in turn was oxidized to diphenic acid) (12) from the zinc dust distillation of morphine can hardly be construed as direct evidence for the presence of the phenanthrene system in morphine owing to the poor yield and because of the possible secondary origin of this hydrocarbon under these pyrogenic conditions. Even the improvement in the yield of phenanthrene to 19-20% (86) through the conversion of morphine to des-*N*-methylcodeine (13, 233) prior to pyrolysis with zinc dust does not remove the second of these objections. Another phenanthrene derivative, $C_{14}H_7O \cdot OCH_3$, was obtained by heating acetylmethylmorphimethine (acetyl-des-*N*-methylcodeine) to 120° (13). Modification and extension of this reaction afforded a phenanthrene deriva-

tive (72) in moderate yield by other than pyrolytic methods. Furthermore, when morphine methiodide was boiled with acetic anhydride, a nitrogen-free, water- and alkali-insoluble phenanthrene derivative ($C_{18}H_{14}O_4$) was obtained. Hydrolysis of this nitrogen-free product with alcoholic ammonia at an elevated temperature removed two acetyl residues with the formation of morphol ($C_{14}H_{10}O_2$), a new dihydroxyphenanthrene (methylmorphol, the monomethyl ether of morphol, results in a similar fashion from the acetolysis of codeine methiodide (76) and subsequent hydrolysis (72) of the acetyl group of the resulting acetylmethylmorphol).

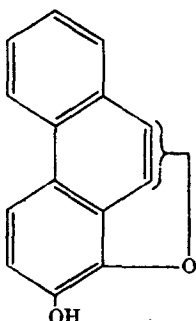
Morphol and methylmorphol are both soluble in alkali and give a positive color reaction with ferric chloride solution, thus indicating the phenolic nature of the two hydroxyl groups of morphol. Methylation of both morphol ($(CH_3)_2SO_4$) (285) and methylmorphol ($CH_3I + C_2H_5ONa$) (97a) yields the dimethyl ether, dimethylmorphol ($C_{16}H_{14}O_2$). Dimethylmorphol has been oxidized to a quinone (97a) but morphol itself proved to be too sensitive to air and other oxidants to undergo a similar oxidation. This difficulty was circumvented by the oxidation (H_2CrO_4) (72, 92) of diacetylmorphol and the subsequent removal (alcoholic ammonia) (72) of the two acetyl groups from the resulting diacetylmorpholquinone. The formation by diacetylmorpholquinone of a crystalline azine (with *o*-toluylenediamine) (92) would suggest that this quinone is an *ortho*-quinone of the phenanthrenequinone type. Since morpholquinone ($C_{14}H_8O_4$) contains two more oxygens than morphol ($C_{14}H_{10}O_2$) it may safely be inferred that neither of the two hydroxyls of morphol occupy positions C_9 or C_{10} . Furthermore, the oxidation ($KMnO_4$) of morpholquinone to phthalic acid (92, 93) locates the two hydroxyls in one of the terminal rings of morphol. Then the observation that morpholquinone, like alizarin, has pronounced properties as a dye for mordanted fabrics prompted early workers to conclude that the two hydroxyls of morphol occupy vicinal positions in the phenanthrene nucleus (92) (the isolation of protocatechuic acid (322) from the alkali fusion of morphine supports this conjecture). From these data morphol was considered to be IV.

The study of methylmorphenol, a second nitrogen-free cleavage product from codeine, went hand in hand with that of morphol. Codeine (I, $R = CH_3$) and codethylene (I, $R = C_2H_5$), when exhaustively ethylated and then heated with alcoholic potash, yielded methylmorphenol ($C_{15}H_{10}O_2$) and ethylmorphenol ($C_{16}H_{12}O_2$), respectively (68, 69, 85). That these two products were ethers of a phenanthrene derivative was established by removal of the alkyl groups to give the phenolic parent substance morphenol ($C_{14}H_8O_2$) (69, 88, 95) and the zinc dust distillation of these to phenanthrene (68, 69, 81, 88). Although one of the oxygen atoms of morphenol is present as an ether, yet a close relationship was sensed between morphenol and

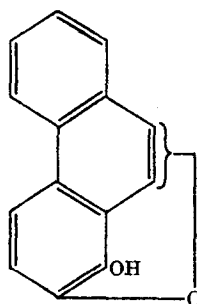
morphol (85, 86, 87, 88, 92, 95). This conjecture proved to be well founded since morphenol was later reduced to morphol by sodium and ethanol (88), from which it would appear that the degradation process has been carried one step further in morphol than in morphenol. This relation of morphenol



IV

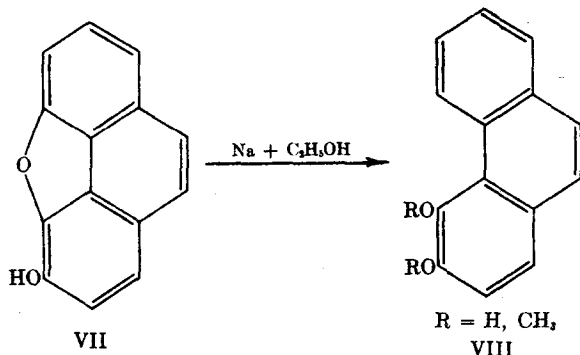


V



VI

to morphol (IV) finds expression only when morphenol is represented by V or VI. Oxidative experiments, however, demonstrated that such formulas were untenable for both morphol and morphenol since acetylmorphenol yields a quinone in which the oxide ring is still intact. This leaves only a phenanthrylene oxide of structure VII as the plausible structure for morphenol. Furthermore, on these grounds, the reduction of morphenol to morphol necessitates a relocation of the hydroxyl groups of the latter at C₃ and C₄ as in VIII (R = H). (While the marked stability of diphenylene oxide prejudiced the early workers against a structure such as VII for morphenol (9), yet the failure to isolate phthalic acid from its oxidation



VII

VIII

(95) (KMnO_4 or H_2CrO_4) appears to be significant in the light of this formula.) While this oxide bridge proved to be quite resistant to many hydrolytic agents it did, in the case of morphenol methyl ether, yield to the action of fused potassium hydroxide (131). The resulting trihydroxy-

phenanthrene, when methylated (131), proved to be identical with synthetic 3,4,5-trimethoxyphenanthrene (Pschorr synthesis-2-nitro-3,4-dimethoxybenzaldehyde + sodium 3-methoxyphenylacetate) (28). This combined with the characterization of dimethylmorphol as 3,4-dimethoxyphenanthrene (97) served to locate the hydroxyls of morphol at C₃ and C₄ (VIII) and the oxide bridge of morphenol at C₄-C₅ (VII).

The hydrophenanthrene nucleus of morphine is not completely saturated but must contain one isolated ethylenic double bond since codeine decolorizes bromine slowly, is quantitatively reduced to a dihydro derivative by the absorption of one mole of hydrogen (PdCl₂) (173, 320) and is oxidized by potassium permanganate (291) to a dihydroxydihydrocodeine.

2. OXAZINE AND ISOQUINOLINE FORMULAS FOR MORPHINE

The nature of the nitrogen complex of morphine and its mode of attachment to the hydrophenanthrene nucleus has proved to be the major problem in this field. The basic nitrogen of morphine and codeine is tertiary and a component of a ring since both bases react with molar proportions of methyl iodide (13, 78, 233) to give quaternary salts, while codeine methohydroxide (Ag₂O, (233) NaOH or KOH (13) on the methiodide) when heated does not lose the nitrogen atom but is converted to a new tertiary amine, des-*N*-methylcodeine (morphine methiodide does not undergo a similar Hofmann reaction when heated with alkali which may probably be attributed to phenolbetaine formation (13, 83)). This des-*N*-methylcodeine or α -methylmorphimethine contains one more center of unsaturation (76) than codeine.

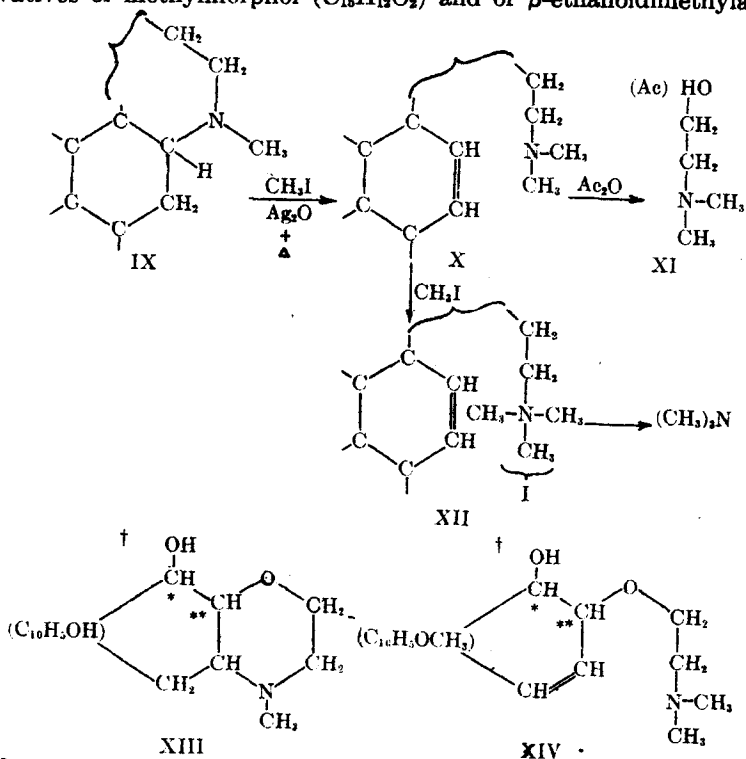
α -Methylmorphimethine (256). Three hundred and three grams of morphine is added to a methanolic solution of sodium methylate (24.0 g. sodium in 1 l. methanol) to which 250 g. dimethyl sulfate is added dropwise. When about one-quarter of the dimethyl sulfate has been added the heat of reaction becomes apparent and the remainder is added at such a rate that the reaction mixture boils gently. When the reaction subsides the mixture is heated on a steam bath for 3-4 hours. Removal of the methanol (vacuum) leaves a residue of codeine methomethyl sulfate. The salt may be degraded to α -methylmorphimethine by boiling for 10 minutes with aqueous sodium hydroxide solution (125 g. sodium hydroxide in 1500 cc. water).

The α -methylmorphimethine, which separates as a brown oil, is recovered by decantation and is washed with water. Recrystallization from toluene yields 210-225 g. (67-70%) of the base.

Elimination of the nitrogen atom was first achieved by exhaustively methylating des-*N*-ethylcodeine and degrading it by the method of A. W. Hofmann. The basic cleavage product was characterized as its chloroplatinate and regarded, at that time, as methylethylpropylamine (68, 69). The characterization of this base as methylethylpropylamine must have been a question of mistaken identity for the subsequent degradation of

des-*N*-methylcodeine methiodide (XII) has been demonstrated (75) to yield trimethylamine (characterized as its aurichloride and chloroplatinate). Such a series of reactions can only be explained if the nitrogen complex of codeine is a component of a ring as in part formula IX and bears a methyl group (75) (demethylation of codeine to norcodeine, which in contrast to the former yields a nitrosamine (179), supports the previous conclusion).

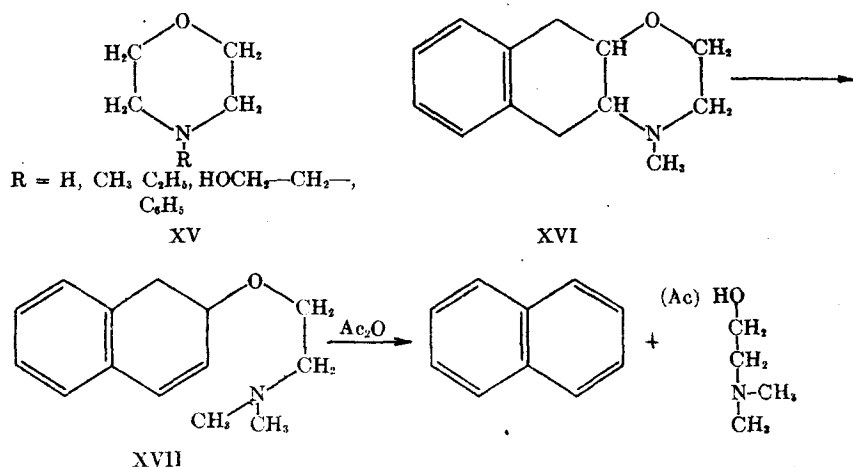
The most fruitful experiment, yet equally as misleading, in exposing the nature of the nitrogen chain of morphine was a modification of the earlier acetolysis experiments on the methiodide of morphine and codeine. It was found that acetic anhydride cleaved the nitrogen chain of des-*N*-methylcodeine (α -methylmorphimethine) $C_{15}H_{23}O_2N$, to give the acetyl derivatives of methylmorphol ($C_{15}H_{13}O_2$) and of β -ethanoldimethylamine



\dagger Knorr was in doubt as to the location of the alcoholic hydroxyl offering ** as an alternative position to *.

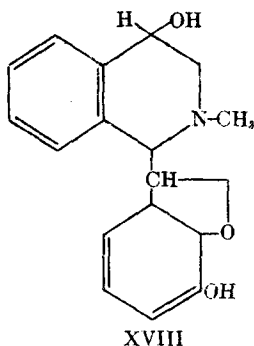
($C_4H_{11}ON$) (XI) (67, 72, 75), the latter being characterized as its aurichloride and chloroplatinate salts. Under the above conditions 50% of the α -methylmorphimethine is isomerized to a β -isomer (78), while some dimethylamine is also formed in the process (75). It is to be seen that

(a) these cleavage products account for all of the carbon atoms of α -methylmorphimethine and (b) only two of the three morphine-oxygen atoms appear in methylmorphol; a third appearing in β -ethanoldimethylamine. Hence the early workers (76) inferred that the carbon skeleton and the ethanamine chain of α -methylmorphimethine were mutually linked through the inert oxygen atom. From a consideration of the evidence so far discussed Knorr (76) proposed the first of his formulas (1889) for morphine (XIII) and methylmorphimethine (XIV). The incorporation of a hydrogenated oxazine ring in his formula for morphine led Knorr to develop a good synthesis for the morpholines (XV) (17, 77) with the view of studying the products of their degradation for comparison with those obtained from morphine under similar conditions. His greatest contribution to the support of his formula for morphine, and at the same time to its



ultimate downfall, was the synthesis and degradation of naphthalanemorpholine (XVI) (91). Under conditions of acetolysis similar to those used on α -methylmorphimethine, des-*N*-methylnaphthalanemorpholine (XVII) yielded naphthalene and the acetyl derivative of β -ethanoldimethylamine. This would be striking evidence in favor of such an oxazine formula if it had not been for the marked difference in the ease of formation of this basic cleavage product from α -methylmorphimethine and the naphthalanemorpholine analog. Knorr regarded this difference as due to the great tendency of such hydroaromatic systems as the methine base (XVII) to attain a completely aromatic structure. Such a condition on the other hand was not to be found in α -methylmorphimethine where more vigorous conditions were necessary for the extrusion of the ethanamine chain.

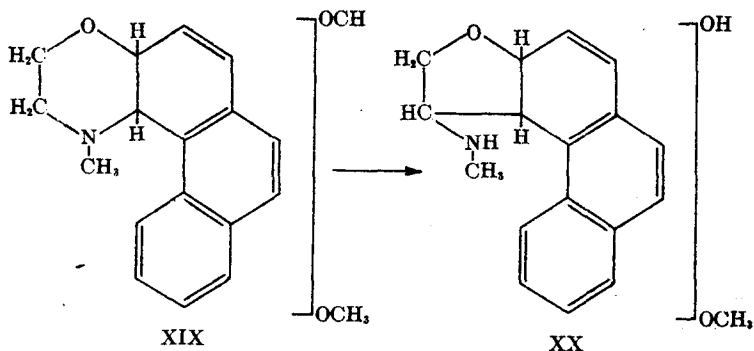
At about the same time that Knorr published his formula for morphine, Goldschmiedt completely elucidated the structure of papaverine so that at this time it was the natural tendency to interpret all difficult structural problems of alkaloid chemistry on an isoquinoline system. Vis (317) pointed out that there was no unequivocal evidence to prove that morphine contained a phenanthrene nucleus which could not equally well be interpreted on his benzylisoquinoline structure (XVIII) as the result of a rearrangement. The one piece of evidence which tended to support such a structure



for morphine, namely, the formation of triacetyl (235) and tribenzoyl (66) derivatives (cleavage of the oxide bridge), was later discredited (164). Furthermore, since α - and β -methyilmorphimethine are not antipodes (78), it was concluded that this necessitated the existence, in these bases, of two asymmetric centers. This could only be interpreted on the Vis formula as a cleavage of the oxide bridge and subsequent closing of this linkage in the alternate steric position, which appears highly improbable. If Knorr's assumption of a morpholine ring were correct, then hydrogen chloride should cleave the ether linkage of α -methyilmorphimethine with the formation of a phenanthrene derivative. His isolations of morphol in good yield (a demethylation has occurred (78, 115)) as well as secondary products resulting from the action of alkali upon β -chloroethyldimethylamine (117) critically disposed of Vis's benzylisoquinoline formula.

Freund (79, 80, 84) attacked the problem by a study of the closely related base, thebaine ($C_{19}H_{21}O_3N$), which was also considered to contain a morpholine ring system. Many of the reactions of thebaine mirror those of morphine and codeine but proceed with much greater facility and it also appears to be more subject to rearrangement by acid than the latter bases. In contrast to codeine, thebaine (β -ethanolmethylamine being the other cleavage product (80)) as well as its methiodide (β -ethanoldimethylamine being the other cleavage product (84)) is converted by boiling acetic

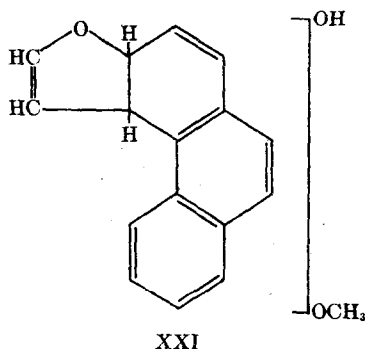
anhydride to the *O*-acetyl derivative of thebaol ($\text{CH}_3\text{O}(\text{C}_{14}\text{H}_9\text{O})\text{OCH}_3$) (it is to be noted that thebaol, in contrast to methylmorphol, retains all three oxygens of thebaine and that two of them are present in methoxyl groups). Acetylthebaol may be considered as the thebaine analog of acetylmethylmorphol and like the latter may be oxidized (CrO_3) to a quinone, acetylthebaolquinone ($\text{CH}_3\text{O}(\text{C}_{16}\text{H}_9\text{O}_4)\text{OCH}_3$) (84), which gives a crystalline azine with *o*-toluylenediamine. Freund centered his attention upon the acid rearrangement products, morphothebaine and thebenine. Morphothebaine ($\text{C}_{18}\text{H}_{19}\text{O}_3\text{N}$) was first considered to be an intermediate in the formation of thebenine ($\text{C}_{18}\text{H}_{19}\text{O}_3\text{N}$). This concept, however, was later abandoned when morphothebaine could not be converted to thebenine under the conditions of the above rearrangement and when it was demonstrated that thebenine was a secondary amine (two moles of ethyl iodide are required for ethiodide formation, which on degradation afforded methyl-diethylamine (84)). It must be accepted that these two bases result by different mechanisms. Thebenine contains two phenolic hydroxyls which, when protected by acetyl groups, can be oxidized to a quinone. In 1897 Freund proposed his first formula for thebaine but did not attempt to locate the methoxyl groups, although by oxidation (KMnO_4) of thebaolquinone (saponification of acetylthebaolquinone with sodium ethylate (84)) a product considered to be 3(?) -methoxyphthalic acid (84) was isolated. Hence one methoxyl must be in ring I and the other in ring III. The conversion of the tertiary base, thebaine, to the secondary amine, thebenine, which involved a demethylation as well, was represented by XIX and XX. Formula XX adequately accommodated the conversion of thebenine to trimethylamine and thebenol (XXI) by exhaustive methylation (two moles



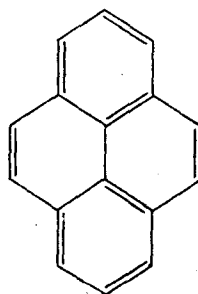
of CH_3I) and degradation of the methiodide. This formula also accommodated the erroneous statement (14, 84) that diacetylthebeninequinone was a naphthoquinone and not a phenanthrenequinone. Moreover the conversion of thebenol to pyrene (XXII) (zinc dust (84, 100) or hydriodic

acid and phosphorus (84)) was readily understandable on these formulas.

In 1899 Knorr (90, 91) revised his earlier formula for morphine but clung to his original concept of an oxazine ring system in this base. Follow-

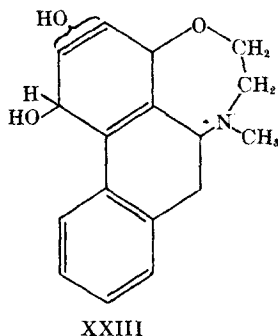


XXI

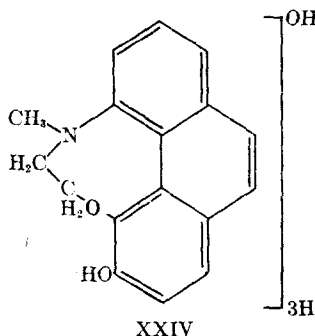


XXII

ing the trend of opinion of the time he modelled his oxazine formula XXIII in close analogy to that of papaverine, a formula having little in its favor. It could not be made to represent the conversion of thebaine to pyrene without an attendant shift of the ethanamine chain. This structure was completely disproved in the next four years.



XXIII



XXIV

Von Gerichten, basing his speculations largely upon observations made during a study of the morphenol degradation of the morphine alkaloids, made two tentative proposals, XXIV and XXV in 1900. In neither formula was any conjecture made as to the location of the alcoholic hydroxyl group or the saturated portion of the nucleus. While the first was but a slight modification of the Knorr formula (91, 95, note 1), the second was an entirely new innovation in the oxazine formulas for morphine. In formula XXV he expressed his belief that the phenanthrylene oxide of morphenol was of primary origin and an inherent part of the structure of morphine. It was so ingeniously fabricated that it also included a morpho-