DAVID GINSBURG

THE OPIUM ALKALOIDS

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Preface

There lived in Troyes, district of Champagne, during the latter part of the eleventh century one of the great commentators on the Bible, Rabbi Shlomo Yitshaki, better known by his abbreviated name, Rashi. Whereas many other commentators believed their potential greatness to bear a direct relationship to the esotericity of their writings, Rashi was a master of simplicity in exposition and explanation. And when he did not know the meaning of a phrase he admitted his ignorance.

This small monograph is an attempt to present a didactic Rashi-like commentary (admittedly hampered by lesser talent) on a field which has been my first love, the opium alkaloids (fortunately of less moment than the Bible). It is aimed primarily at graduate students and is far from being encyclopedic. There are, indeed, in the chemical literature volumes and chapters in volumes which are infinitely more comprehensive than the present book, for example, Small's *Chemistry of the Opium Alkaloids*, Bentley's *Chemistry of the Morphine Alkaloids*, and the chapters by Holmes and by Stork in *The Alkaloids*. To these the reader is referred for a vast amount of additional detail and for all documentation.

The present book grew out of a series of lectures given at different times during the academic year 1960–61 for graduate students at Harvard and Brandeis Universities and at the University of Zürich. My thanks are due to the John Simon Guggenheim Memorial Foundation for the award of a fellowship which permitted me to rediscover the joys of the laboratory and of tranquil days of reading and thinking after an all too long period of allegedly important administration. I am grateful also to Professors R. B. Woodward, S. G. Cohen, and H. Schmid for their kind hospitality and to colleagues too numerous to mention for their intellectual stimulation during my sabbatical year. It appears to be a fact that the 365 days of a sabbatical year are shorter than those of an ordinary year.

I am particularly grateful to my first reader, Dr. Tom Mabry, whose careful and critical reading of the manuscript not only aided in weeding out minor errors but in addition forced me to improve the lucidity of a number of points in the text. I have not accepted the view of a group of colleagues at the University of Zürich that it might be better first to present the reader with the correct structures of papaverine and its degradation products and then to show, as I have, the "comedy of

errors" which actually developed during the elucidation of the papaverine structure. Since I am convinced that the errors of others can be most instructive, I have, rather, retained the "mystery story" approach but have shifted the papaverine chapter to the last part of the book. Thus, if the reader is of the kind that enjoys mystery stories, he will discover the correct solution, as is customary, in the closing pages of the book.

I am greatly indebted to Dr. André Dreiding for a number of constructive suggestions and for several steric representations in the book. In the main, the steric formulae of the morphine alkaloids present a clearer picture than those of the hexagonal projection type which appear in most of the books on the subject. In specific cases the more schematic steric representations have been replaced by those observed from such perspective so as to better illustrate the point under discussion.

Haifa DAVID GINSBURG
August, 1961

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CHAPTER I

Introduction

When the unripe seed capsule of the opium poppy, *Papaver somniferum*, is cut or pricked, a viscous liquid is exuded. After the exudate dries and darkens with exposure to air, a hard but still partly sticky mass is obtained. This is opium, which has been used for many centuries by some for medicinal purposes and by others to smoke in their pipes, reaching, we are told, most pleasant Elysian fields of sensation, albeit addicting and enslaving.

The pharmacologically active constituents of opium have been employed in medicine for many thousands of years in the form of a highly colored tincture. During the nineteenth century these constituents were isolated as pure chemical entities.

Papaverine, the simplest structurally, is used with excellent results as a muscle relaxant. Morphine is used as an analgesic which even today has no peer in controlling severe pain. Codeine is used as a more specialized analgesic and as an effective agent for the control of the cough reflex. Thebaine is too toxic to be used as such but has served as a starting material for the synthesis of more specific analgesics which have rather limited medicinal uses.

The organic chemist of the present generation is armed with many physical tools which may be employed and, indeed, which have been very helpful in the relatively rapid elucidation of the structures of complex natural products. Relatively, that is, to his pioneering predecessors of the heroic period of organic chemistry. It would be interesting to speculate how different might have been the approaches of a Fischer or a Willstätter if they had had at their disposal the present routine tools of ultraviolet and infrared spectroscopy, chromatography in all its forms, optical rotatory dispersion, mass spectroscopy and nuclear magnetic resonance, and the tools of the X-ray crystallographer. To all of these we must, of course, add the present more solidly grounded theoretical structure of organic chemistry as a whole. Indeed, many of the pioneers in the field of natural products contributed much to the creation of a firmer theoretical basis of the field as a whole through the stimulation of fundamental researches on the structures of complex natural substances.

There is little doubt, for example, that the impetus for the study of phenanthrene chemistry was given first by the interest in the structures of several of the opium alkaloids, and later by the interest in steroids. The development of the chemistry of larger alicyclic rings was stimulated by the interest in the natural perfumery agents muscone and civetone, whilst there is little doubt that steroids are again responsible for the development of conformational analysis and for the fact that the stereochemistry of the cyclohexane ring is better understood today than that of either smaller or larger alicyclic rings. And knowledge of the chemistry of the cycloheptane ring is growing at least partly because azulenes, "pro"-azulenes and various tropolones exist in Nature.

The same is true for quinoline and isoquinoline chemistry. The interest in the structure of papaverine led to increased research on the behavior of compounds embodying these ring systems.

CHAPTER II

Morphine and Codeine

Morphine is the major constituent of opium, constituting about 10% (and sometimes up to 20%) of its weight. Although its medicinal value was recognized by the ancients, it was not until 1805 that Sertürner, a German apothecary, described its isolation in pure form from an opium extract.

If we compare the empirical formula, $C_{17}H_{19}O_3N$, of morphine, which contains no methoxyl groups, with that of papaveroline (completely demethylated papaverine), $C_{16}H_{13}O_4N$ (p. 97), we immediately make the qualitative observation that morphine is more highly reduced than papaverine. Further, when we consider that morphine contains one *N*-methyl group which is absent in papaverine, we are tempted to look for an intimate structural relationship between morphine as a C_{17} compound and the papaverine skeleton as a C_{16} unit. We shall find, however, in spite of the fact that both morphine and papaverine are produced by the same plant, and notwithstanding certain botanical-chemical investigations which apparently indicate the formation of one at the expense of the other at certain stages of plant development, that the relationship between the two alkaloids, although logical, is not quite so obvious chemically. Indeed, the early structural work on morphine showed rather quickly that morphine is quite different from papaverine in skeletal structure.

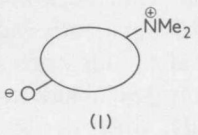
Sir Robert Robinson has waxed poetical when describing the place of morphine in organic chemistry. He has called it the Proteus among molecules, the star performer among molecular acrobats. We shall see that these statements are amply justified, although thebaine, a close relative of morphine, has perhaps surpassed it on the molecular trapeze. In any case the man responsible for the first correct formulation of the morphine structure is certainly permitted poetic licence.

It was shown through acetylation that morphine has two hydroxylic functions. One of these appeared to be phenolic since a monomethyl ether could readily be formed by methylation. Morphine methyl ether proved to be the same as codeine, another alkaloid present in opium to the extent of 0.2–0.8%.

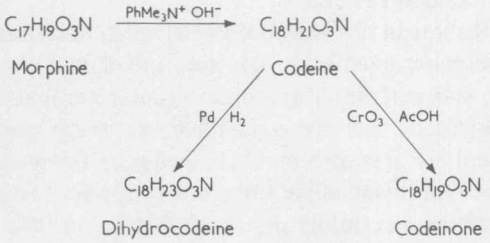
Codeine was obviously a more suitable starting material for degradative reactions than morphine with its free phenolic group. Quite often

in structural studies of natural products, the phenolic functions were stabilized towards oxidative degradation in particular by methylation or by blocking with some other group. Most of the degradative work on morphine was, therefore, carried out on codeine. The data collected applied equally well to morphine, as soon as the simple relationship between the two alkaloids was known. It very soon became apparent in the case of morphine (which, of course, contains a basic nitrogen atom along with the free phenolic group) that codeine was a more suitable starting material not only in reactions which involved oxidation, in order to avoid unwanted damage to the molecule, but also in reactions which were complicated by the betaine-like behavior of certain morphine derivatives.

One of the important reactions which was used to elucidate the structure of morphine was the Hofmann exhaustive methylation and degradation procedure. When, however, morphine methiodide was subjected to this degradation, no reaction occurred because the phenolic betaine (I) was formed under the alkaline conditions of the reaction. Such a problem did not exist in codeine, where the phenolic character of the parent had been removed by methylation.



(I)



Codeine could be oxidized to codeinone, which has two hydrogen atoms less than the starting material and corresponds to a ketone in its properties. This means that codeine contains a secondary alcoholic hydroxyl group and that the second of the two hydroxylic functions of morphine is also that of a secondary alcohol.

Codeine absorbed one mole of hydrogen when reduced catalytically

in the presence of palladium, indicating that it (as well as morphine) contains one isolated double bond.

The ready bromination of both codeine and morphine, in which one atom of bromine is introduced into the molecule with concurrent formation of one mole of hydrogen bromide, notwithstanding the presence of an isolated double bond, indicates that an aromatic ring is present in both alkaloids and that the hydroxyl group in morphine which could be readily methylated is indeed phenolic. The relative stability of codeine to acid treatment rules out the possibility of the methyl ether being merely an enol ether.

$$\underset{\text{Codeine}}{C_{18}H_{21}O_3N} \xrightarrow[(-HBr)]{Br_2} \underset{\text{Bromocodeine}}{C_{18}H_{20}O_3NBr} \xrightarrow[H_2]{Pd} \underset{\text{Bromodihydrocodeine}}{C_{18}H_{22}O_3NBr} \xrightarrow[H_2]{Pd} \underset{\text{Dihydrocodeine}}{C_{18}H_{23}O_3N} + HBr$$

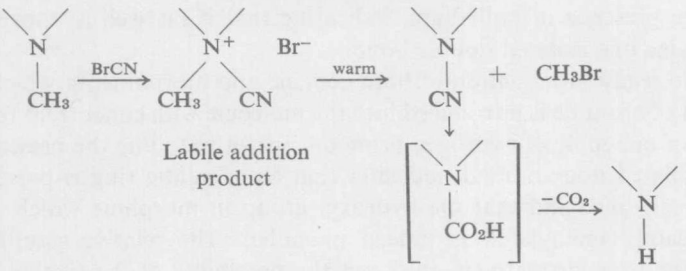
The ease of bromination might be explained by the presence of the methoxyl group in the aromatic ring, but perhaps another factor may be responsible. We shall be in a position to determine this point when we are able to define the position of the entering bromine atom.

Bromocodeine may be reduced stepwise in the presence of palladium, first to bromodihydrocodeine and thence to the same dihydrocodeine which is obtained by reducing codeine directly. In the latter step, the hydrogenolysis of the C—Br bond is again an indication that the bromine atom is a substituent in an aromatic nucleus.

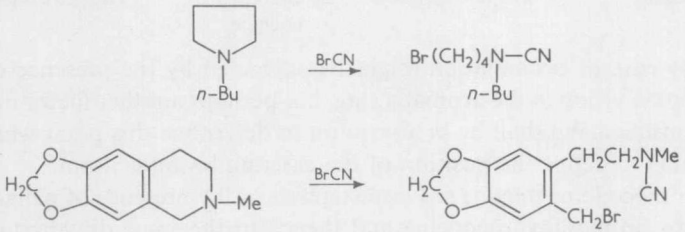
We have seen that morphine contains one phenolic function and one secondary alcoholic group. The third oxygen function in morphine and in codeine, because of its inertness to the various hydroxylic or carbonyl reagents, was considered by elimination to be an ether oxygen.

Early investigation of the character of the nitrogen atom showed it to be tertiary and attached to a methyl group. Codeine forms an *N*-oxide when it is treated with 30% hydrogen peroxide. Reduction of the *N*-oxide with sulfurous acid gives codeine. Morphine and codeine both form crystalline hydrochlorides, sulfates, phosphates, etc., as well as methiodides. There was therefore no doubt as to the basic, amine nature of the nitrogen atom.

The von Braun degradation is a useful tool in the study of alkaloid structure; it is a fairly general reaction. In the simplest case, a tertiary amine which has a methyl group attached to nitrogen is cleaved by means of cyanogen bromide to give the corresponding cyanamide and methyl bromide. Acid treatment of the cyanamide gives the unstable carbamic acid, which decarboxylates spontaneously and affords the corresponding secondary amine.



The reaction may take another course as exemplified in the following cases:



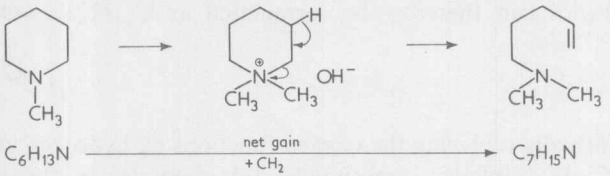
In the case of codeine, cyanogen bromide effects the net empirical change of adding one nitrogen atom and subtracting three hydrogen atoms. This is exactly what we expect for the change $\backslash N—CH_3 \rightarrow$ $\backslash N—CN$.
/ /

$$\underset{\text{Codeine}}{C_{18}H_{21}O_3N} \xrightarrow{BrCN} C_{18}H_{18}O_3N_2$$

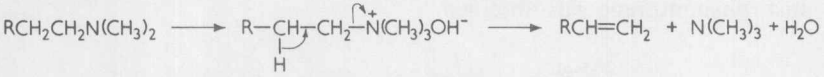
Further evidence as to the nature of the nitrogen atom in morphine and in codeine was accumulated from the results of the Hofmann exhaustive methylation and degradation of codeine. The fact that only one mole of methyl iodide is required to form the quaternary salt shows that codeine is a tertiary amine.

$$\underset{\text{Codeine}}{C_{18}H_{21}O_3N} \xrightarrow{1\text{ mole } CH_3I} \underset{\substack{\text{Codeine}\\\text{methiodide}}}{C_{19}H_{24}O_3NI^-} \xrightarrow{OH^-} \underset{\alpha\text{-Codeimethine}}{C_{19}H_{23}O_3N}$$

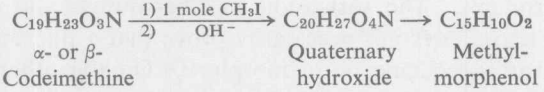
The net empirical result is the addition of CH_2 to codeine. This is exactly what we would expect for a *cyclic* tertiary amine, for example in the case of *N*-methylpiperidine, $C_6H_{13}N$.



This is, of course, in contradistinction to the case of an open chain, tertiary, aliphatic amine, where the bimolecular elimination leads to the net *loss* of carbon from the aliphatic chain, e.g.,



It must be noted that heating of α-codeimethine converts it into an isomeric compound, β-codeimethine, but either of these methines on further methylation and heating with alkali gives the nitrogen-free product methylmorphenol, $C_{15}H_{10}O_2$.



This is certainly far from being an ordinary reaction. If we return to our general aliphatic case, we see that the tertiary amine adds one carbon atom after reacting with methyl iodide and then loses three carbon atoms in the form of trimethylamine, a net loss of two carbon atoms by the starting material.

In the case of the codeimethines, however, the net loss based on the starting material is four carbon atoms. The quaternary hydroxide loses not three but *five* carbon atoms, a C_{20} compound giving the C_{15} methylmorphenol! Only three of these five carbons are accommodated by the formation of trimethylamine. It was, indeed, eventually found that the other two carbon atoms appear as ethylene. There must be something extraordinary about the morphine and the codeine structure which leads to the extrusion of a chain containing five carbon atoms by the quaternized methines. Why should such a five-carbon loss occur?

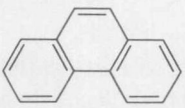
A step towards arriving at the explanation may be made by studying the chemistry of methylmorphenol.

Methylmorphenol, $C_{15}H_{10}O_2$, has one methoxyl group, since demethylation by heating with hydrobromic acid gives a phenolic product, morphenol, $C_{14}H_8O_2$, which forms a monoacetate or a monobenzoate. In view of the inertness of the second oxygen atom in the molecule, it was assumed to be an ether.

Morphenol can therefore be formulated as $C_{14}H_7$—|—OH ≡ 1H
O ≡ 2H

and by formally replacing the oxygen functions by hydrogen atoms, we obtain $C_{14}H_{10}$, which corresponds, for example, to the empirical formula of a tricyclic aromatic hydrocarbon such as anthracene or phenanthrene.

When either methylmorphenol or morphenol was distilled with zinc dust, phenanthrene was obtained.

$C_{15}H_{10}O_2$ or $C_{14}H_8O_2$ —Zn dust, Δ→ 

Now, zinc-dust distillation is a brutal reaction in which linearly annelated compounds often give the angularly annelated polycyclic aromatic products. The formation of phenanthrene in this brutal reaction therefore does not necessarily prove that a phenanthrene-like skeleton exists in codeine or in morphine. On the other hand, the formation of a linear polycyclic hydrocarbon in a zinc-dust distillation constitutes good evidence for the presence of a similar linear skeleton in a natural product. The formation of naphthacene in such a reaction carried out on terramycin was indeed taken to mean that a linear tetracyclic system was present in the antibiotic. Although in the case of morphenol and its methyl ether the evidence is equivocal, we should remember that methylmorphenol was formed in the Hofmann degradation. If it is shown that it contains a phenanthrene skeleton, it is most improbable that the phenanthrene formed in the zinc-dust distillation is an artifact.

The structure of methylmorphenol was investigated in order to fix the positions of two of the three oxygen functions in codeine.

$C_{15}H_{10}O_2$ Methylmorphenol —Na, alcohol (+2H)→ $C_{15}H_{12}O_2$ Methylmorphol —HBr (−CH_2)→ $C_{14}H_{10}O_2$ Morphol

Methylmorphenol ↓ HBr → $C_{14}H_8O_2$ Morphenol ↓ Acetyl or benzoyl morphenol ↓ CrO_3, AcOH → An acetyl or benzoyl quinone

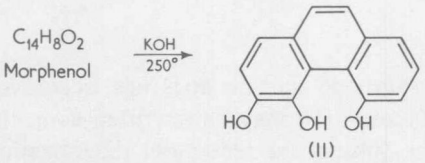
Methylmorphol ↓ Acetyl or benzoyl methylmorphol ↓ CrO_3, AcOH → An acetyl or benzoyl quinone

Reduction of methylmorphenol, $C_{15}H_{10}O_2$ (which contains one methoxyl group and one disubstituted ether oxygen), with sodium and alcohol gave methylmorphol, $C_{15}H_{12}O_2$, which still contained the methoxyl group but in which a phenolic function appeared, as evidenced by the formation of a monoacetate or a monobenzoate. Demethylation of methylmorphol with hydrobromic acid led to morphol, a diphenol.

Demethylation of methylmorphenol with hydrobromic acid led to morphenol, in which the disubstituted ether oxygen is still present together with one free phenolic group; a monoacetate or a monobenzoate could be derived from this substance.

A significant result was obtained by oxidation of the acetyl or of the benzoyl derivatives of either morphenol or of methylmorphol, respectively. In each case a quinone was obtained and this contained the same number of carbon atoms as the starting material. Had the acetoxy or the benzoyloxy group been attached to the 9- or to the 10-position of either an anthracene or a phenanthrene nucleus, this group would have been lost in the oxidation and the quinone produced would have contained a lesser number of carbon atoms than the starting material. The 9- and 10-positions are thus eliminated as points of attachment for one of the oxygen functions (or both) in methylmorphenol.

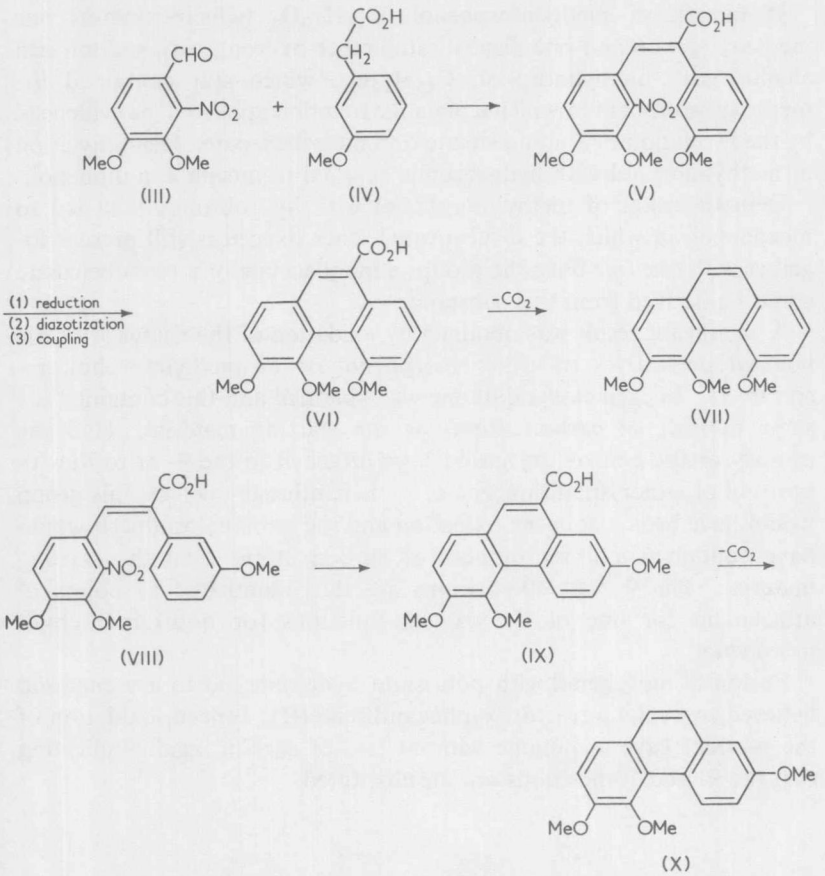
Fusion of morphenol with potassium hydroxide led to a compound believed to be 3,4,5-trihydroxyphenanthrene (II). Indeed, oxidation of the product gave a quinone without loss of carbon, again indicating that the 9- and 10-positions are unsubstituted.



(II)

The structure of (II) was proven by a synthesis of the type which came to be known as the Pschorr phenanthrene synthesis. The synthetic sequence was indeed designed owing to Pschorr's interest in morphine chemistry.

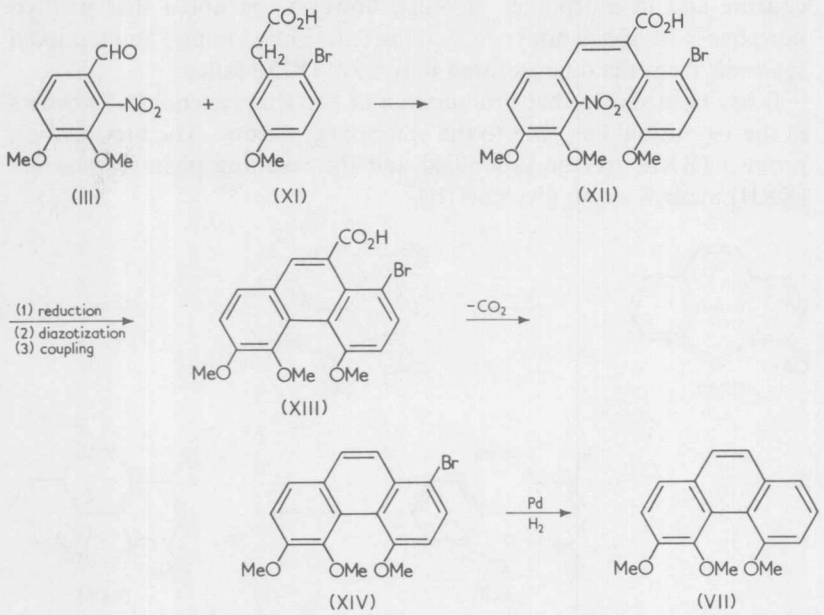
2-Nitro-3,4-dimethoxybenzaldehyde (III) was condensed with *m*-methoxyphenylacetic acid (IV). Reduction of the nitro group in the product (V), followed by diazotization and intramolecular coupling, led to the trimethoxyphenanthrenecarboxylic acid (VI). This was decarboxylated to give 3,4,5-trimethoxyphenanthrene (VII), which was identical to the trimethyl ether of (II).



However, this synthetic scheme does not unequivocally prove the structure of (II) because (V) may be rewritten as in the conformation (VIII), so that the subsequent reduction, diazotization and coupling steps might lead to an isomeric trimethoxyphenanthrenecarboxylic acid (IX). This, in fact, was formed as a by-product in the Pschorr synthesis. Decarboxylation of (IX), of course, gives 2,5,6-trimethoxyphenanthrene (X).

To complete the synthetic proof, the same aldehyde (III) was therefore condensed with a substituted phenylacetic acid (XI) in which blocking one of the positions *ortho* to the aliphatic side chain by a bromine atom rendered cyclization in the sense (VIII)→(IX) impossible.

The condensation product (XII) was reduced; diazotization and coupling then gave the only possible phenanthrene derivative (XIII).



Decarboxylation to (XIV) followed by hydrogenolysis of the carbon–bromine bond gave (VII), identical to the major product of the previous synthetic sequence.

These reactions prove the structures of morphenol (XVI) and of the related degradation products, methylmorphenol (XV), methylmorphol (XVII) and morphol (XVIII). Since methylmorphenol is obtained from codeine via the Hofmann exhaustive methylation and degradation, a phenanthrene ring system in a lower oxidation state must be present in