STUDIES ON SOME DEHYDROGENATION PRODUCTS OF EMETINE

by

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ACKNOWLEDGEMENT

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INTRODUCTION

Emetine is the principal one of five closely related alkaloids which have been isolated from the Ipecacuanha root. Because of its toxic effect on Entamoeba Histolytica it has been used extensively in the treatment of amoebic dysentery, but for this purpose it has been replaced to a great extent in recent years by less toxic synthetic drugs. As its name suggests it can also be used as an emetic.

Emetine was first isolated as a crude product in 1817 by Pelletier and Magendie, but the first pure sample was not obtained until 1894 by Paul and Cownley (1), who were also successful in isolating the alkaloids cepheline and psychotrine. The two remaining alkaloids of the group were isolated several years later by Pyman (2).

It was not until 1948 that Pailer and coworkers (11)(12)(13)(14) published a series of articles in which the complete proof of structure of emetine was described. With its structure known, most of the chemical research which has been carried out on the alkaloid during the past five years has involved two different lines of approach. These are (1) attempts at total synthesis, and (2) a study of some dehydrogenation products obtained by mild oxidation of emetine.

Numerous research groups throughout the world have been attacking the problem of total synthesis, and a considerable degree of success has already been attained. Battersby and Openshaw (20) were almost immediately successful in synthe-

sizing d,l-rubremetinium bromide, the racemic form of a mild oxidation product of emetine. More recently, Evstigneeva and coworkers (24) have been successful in synthesizing the gross emetine structure, and have indicated methods of separating emetine from the resulting mixture of isomers.

The new work contained in this thesis is concerned chiefly with the second line of approach mentioned above. The primary aim was to obtain information about some of the dehydrogenation products of emetine which would permit elucidation of their structures. Attempts to prepare new diastereoisomers of emetine by reduction of the unsaturated derivatives have also been made. Results of this work have provided valuable information of use in proposing structures for tetradehydroemetine and isotetradehydroemetine. In addition, a diastereoisomer of emetine heretofore unreported has been isolated and characterized.

Some additional work has been concerned with dehydrohalorubremetine, a compound derived from rubremetinium chloride, and significant information about its structure has been secured.

BACKGROUND AND HISTORICAL REVIEW

A. Interrelationships of the Ipecac Alkaloids.

Although Paul and Cownley were successful in isolating three of the Ipecac alkaloids in 1894, it was not until 1914 that the first really fruitful research was begun by Pyman and coworkers (2)(3)(4). It was principally their work which produced the correct molecular formulas and methods of interconversion.

Carr and Pyman (2) accurately determined the molecular formulas for emetine, psychotrine, and cepheline, the three alkaloids which had been isolated by Paul and Cownley. Later, Pyman (3) reported the isolation of O-methylpsychotrine and emetamine, and their molecular formulas were likewise determined. The results are shown in the following table.

Alkaloid	Molecular Formula
Emetine	$C_{29}H_{40}O_4N_2$
Cepheline	$C_{28}H_{38}O_4N_2$
Psychotrine	$C_{28}H_{36}O_4N_2$
O-methylpsychotrine	$C_{29}H_{38}O_4N_2$
Emetamine	$C_{29}H_{38}O_4N_2$

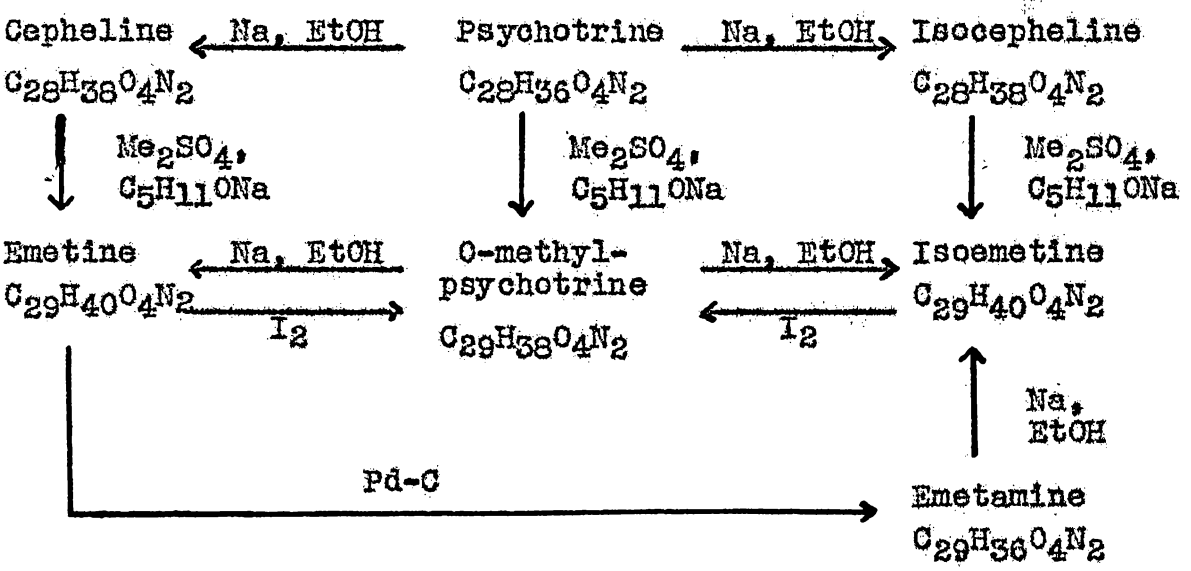
It was found that in emetine, O-methylpsychotrine, and emetamine all four oxygen atoms are part of methoxyl groups (2). In both cephaline and psychotrine there are three methoxyl groups and a phenolic group. In all cases the nitrogen atoms possess a basic function.

Emetine and cepheline both give the same compound, $C_{25}H_{32}N_2O_4$, on demethylation (2). By treating cepheline with methyl sulfate and sodium amyl oxide, emetine is obtained (3). Therefore, the two must have the same basic structure with the only difference lying in the one phenolic functional group.

Methylation of psychotrine gives O-methylpsychotrine, while reduction with sodium and alcohol gives cepheline and a diastereoisomer, isocepheline (3). A similar reduction of O-methylpsychotrine gives emetine and isoemetine (4). It is therefore apparent that psychotrine differs from cepheline only in having an additional double bond. The same must be true for O-methylpsychotrine and emetine. The fact that emetine and isoemetine are diastereoisomers was further demonstrated when emetine and isoemetine both gave O-methylpsychotrine on oxidation with one mole of iodine in alcohol (4). The extra double bond occurring in psychotrine and O-methylpsychotrine must therefore involve a carbon atom which is asymmetric in emetine.

In emetamine both nitrogen atoms were found to be tertiary, whereas the other four alkaloids had been shown to contain one secondary and one tertiary nitrogen (4). Reduction with sodium in alcohol gives isoemetine. Emetamine can be produced by a palladium-charcoal dehydrogenation of emetine (5). In neither case is any O-methylpsychotrine produced, so it appears likely that emetamine is not a further oxidation product of O-methylpsychotrine.

The following diagram summarizes the results just discussed.

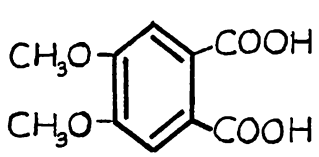


B. Proof of Structure of Emetine.

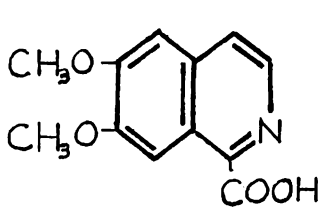
It has already been mentioned that emetine contains one secondary and one tertiary nitrogen, and that all four oxygen atoms occur in methoxyl groups. The first statement concerning the nitrogen atoms was shown to be true when benzoylation of emetine gave a mono-benzoyl derivative which still contained a basic nitrogen (2).

Karrer (6) found that a single Hofmann degradation of emetine gave a methine base which still contained both nitrogen atoms. On a second degradation one of the nitrogens split off as trimethylamine. This indicated that one nitrogen is a member of a single ring, while the other is a common member of two rings.

Oxidation of emetine with potassium permanganate in acetone (2) was found to yield m-hemipinic acid (I) and 6,7-dimethoxyisoquinoline-1-carboxylic acid (II). This showed that an isoquinoline nucleus was present, and probably linked to the rest of the molecule at the 1-position. Spath and Leithe (7) on using a slightly alkaline permanganate solution obtained corydaldine (III) in addition to the two products already mentioned, and from oxidation of the ethyl ether of

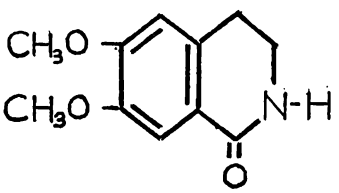


I

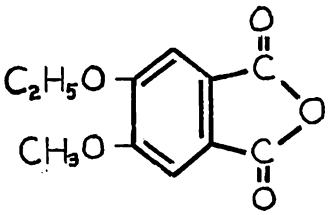


II

cepheline they isolated m-hemipinic acid (I) and 4-methoxy-5-ethoxyphthalic anhydride (IV). Their results proved that the group V occurs twice in the emetine molecule. In addition, the yield of compounds containing the isoquinoline nucleus on oxidation of emetine led Spath and Leithe to believe that two isoquinoline groupings were present.



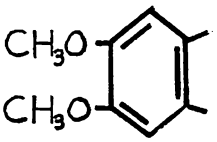
III



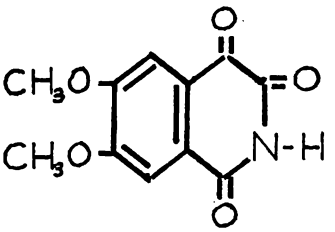
IV

With the information obtained up to this point, Brindley and Pyman (8) and Staub (9) proposed complete structures for emetine, despite the fact that little was known about the inner part of the molecule. Their structures were later proved to be incorrect.

No further work on the structure of emetine was reported until 1944 when Ahl and Reichstein (5) carried out a 3-fold Hofmann degradation on N-acetylemetine. The resulting neutral product was then oxidized with permanganate in sulfuric acid solution, yielding 4,5-dimethoxyphthalonimide (VI), the same product which had previously been obtained by chromic acid oxidation of emetine (10). Since the same product was also obtained by chromic acid oxidation of 6,7-dimethoxytetrahydroisoquinoline it was concluded that the secondary nitrogen



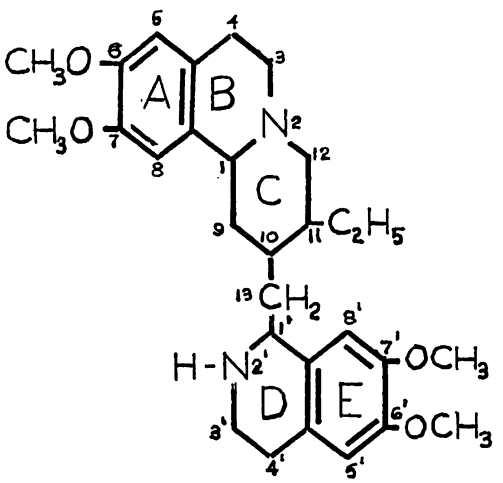
V



VI

in emetine must be part of such a grouping.

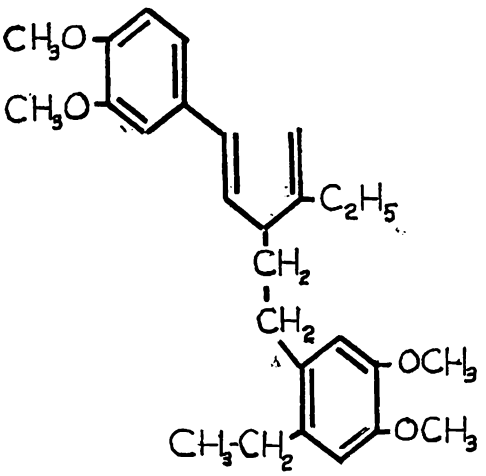
This summarizes most of the information available when Pailer and coworkers began a series of systematic Hofmann degradation studies which were to result in a conclusive proof of the structure VII for emetine.



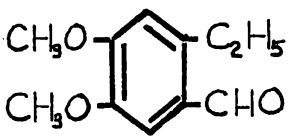
VII

Spath and Pailer (11) first subjected emetine to a 3-fold Hofmann degradation with catalytic hydrogenation of the resulting olefin after each of the first two degradations, and obtained the olefin VIII. Ozonolysis of VIII afforded 2-ethyl-

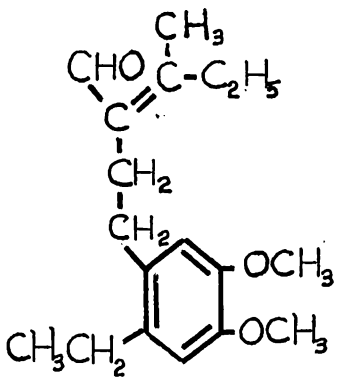
4,5-dimethoxybenzaldehyde (IX) and an unsaturated aldehyde (X), which on catalytic hydrogenation gave the aldehyde XI. The structure of XI was proved by an independent synthesis (12).



VIII



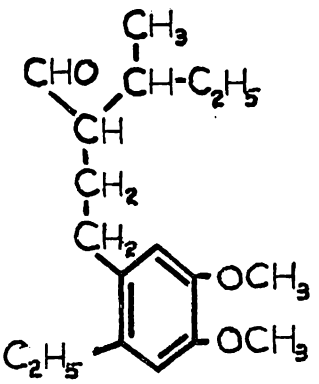
IX



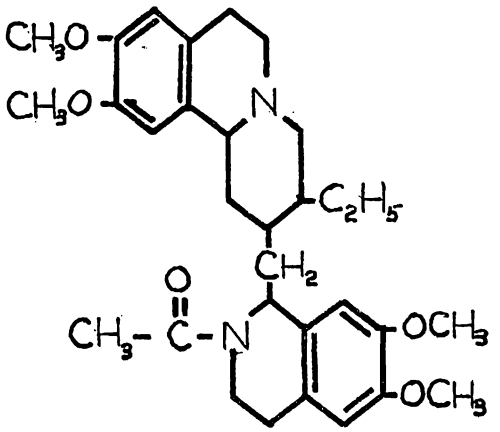
X

A 3-fold Hofmann degradation of N-acetylemetine (XII) with catalytic hydrogenation following each step gave, after removal of the acetyl group, the compound XIII. A 2-fold Hofmann degradation of XIII with catalytic hydrogenation after the first step gave the olefin XIV. Ozonolysis of XIV yielded IX and XI, the same products obtained from the previous series of degradations (13).

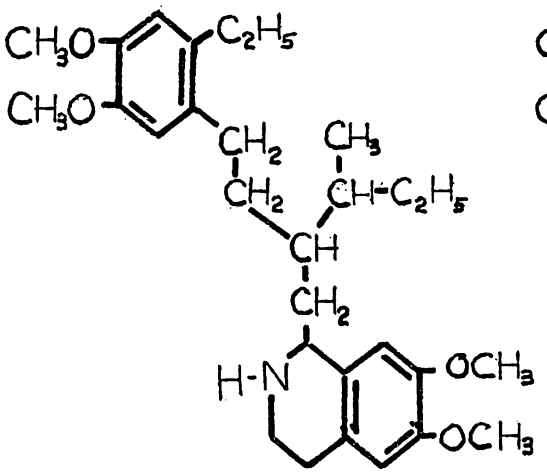
Following these two series of degradations the only possibilities remaining for the inner structure of emetine were XV, XVI, and XVII. A final series of reactions carried out by Pailer and Porschinski (14) correctly determined the nature of ring C.



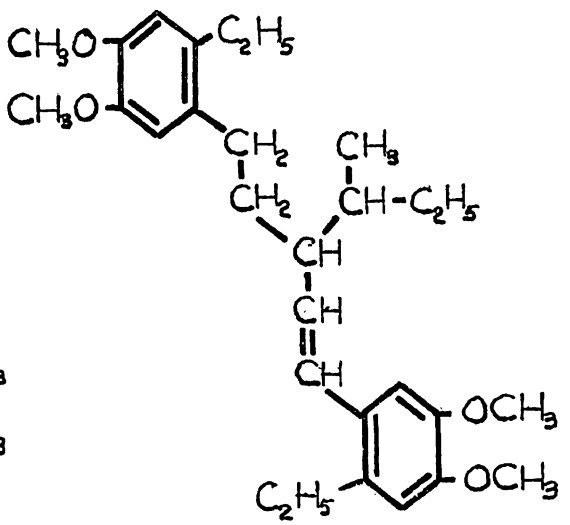
XI



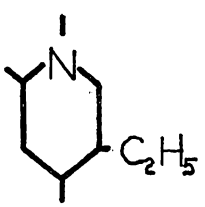
XII



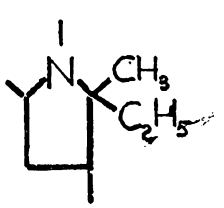
XIII



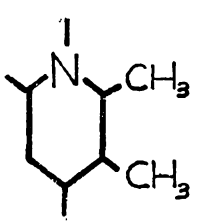
XIV



XV



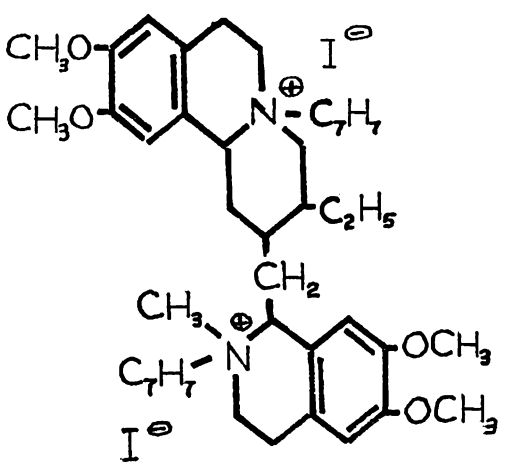
XVI



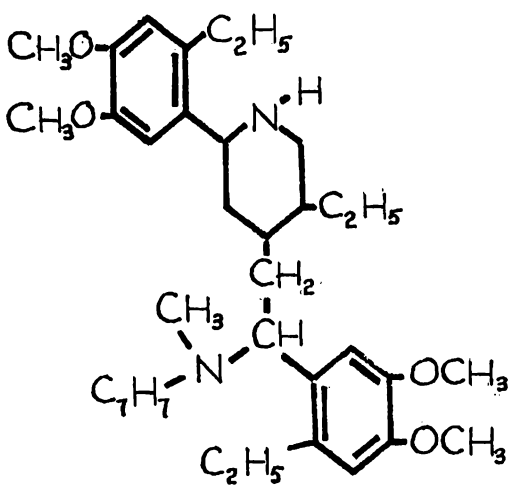
XVII

On reaction with benzyl iodide, N-methylemetine was converted to the diiodobenzylate (XVIII). This was reacted with silver oxide giving an olefin which on catalytic hydrogenation yielded the compound XIX. A palladium dehydrogenation of XIX gave β-collidine (XX). These results definitely proved that ring C is six-membered and has an ethyl substituent beta to the nitrogen, leaving XV as the only possibility and concluding the proof of structure VII for emetine.

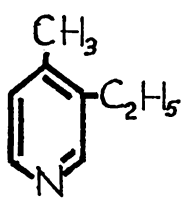
Battersby and Openshaw (15), using a completely independent approach, have confirmed the structure for ring C of emetine.



XVIII



XIX

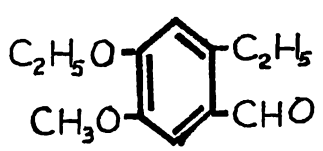


XX

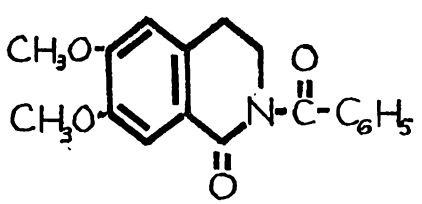
C. Structure of the Other Ipecac Alkaloids.

Since the interrelationships among the five Ipecac alkaloids were already known, the structures of the remaining four followed almost directly from the known emetine structure. The principal problem remaining was to determine the position of the phenolic group in cepheline and psychotrine. This was accomplished by Pailer and Porschinski (16) who first carried out a 2-fold Hofmann degradation on O-ethylcepheline. The resulting olefin was cleaved with ozone, giving an aldehyde whose semicarbazone was found to be that of 2-ethyl-4-ethoxy-5-methoxybenzaldehyde (XXI). This result definitely proved that the hydroxyl group is located at the 6'-position in cepheline. From known relationships it followed that the hydroxyl group in psychotrine must be located at the same position.

In order to determine the position of the double bond in psychotrine and O-methylpsychotrine, Karrer, Eugster, and Ruttner (17) oxidized N-benzoyl-O-methylpsychotrine with perphthalic acid and isolated a product believed to be N-benzoyl corydaldine (XXII). The identity of this product was later



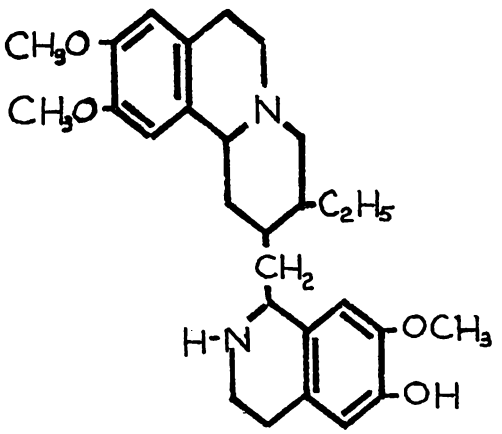
XXI



XXII

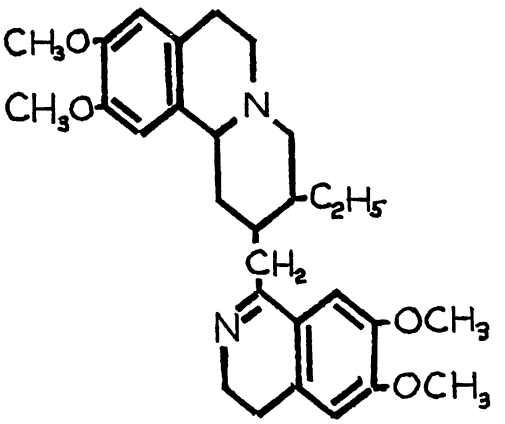
proved by an independent synthesis (18). This result coupled with the fact that two diastereoisomers are obtained by reduction of O-methylpsychotrine must place the double bond at C_1,-C_{13}. However, it is known that the double bond in similar tetrahydroisoquinoline derivatives can easily be shifted to the endocyclic position, and in some cases it is even possible to obtain an equilibrium mixture under certain conditions. It is therefore entirely possible that the double bond in O-methylpsychotrine itself could occur at position C_1, -N_2, . Evidence for such a structure has been reported recently by Openshaw and Wood (19), who base their conclusion on a study of the ultraviolet absorption spectrum of O-methylpsychotrine hydrogen oxalate. This point will be discussed further in a later section.

The fact that both nitrogens in emetamine are tertiary and that emetine and isoemetine are both obtained on sodium and alcohol reduction indicates the structure XXVI for emetamine.



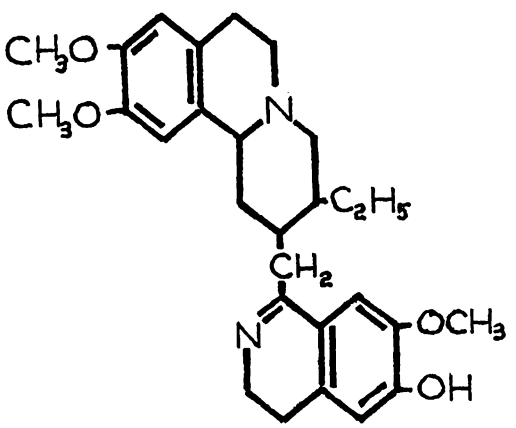
CEPHELINE

XXIII



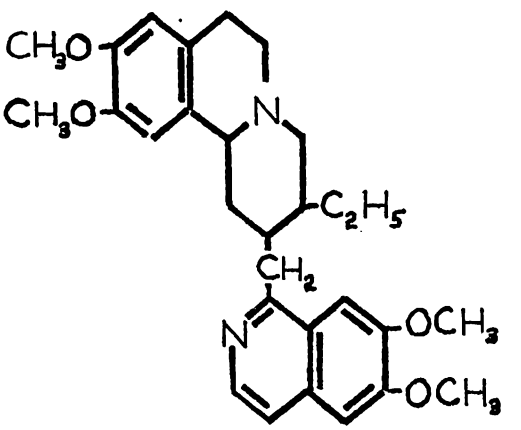
O-METHYLPSYCHOTRINE

XXIV



PSYCHOTRINE

XXV



EMETAMINE

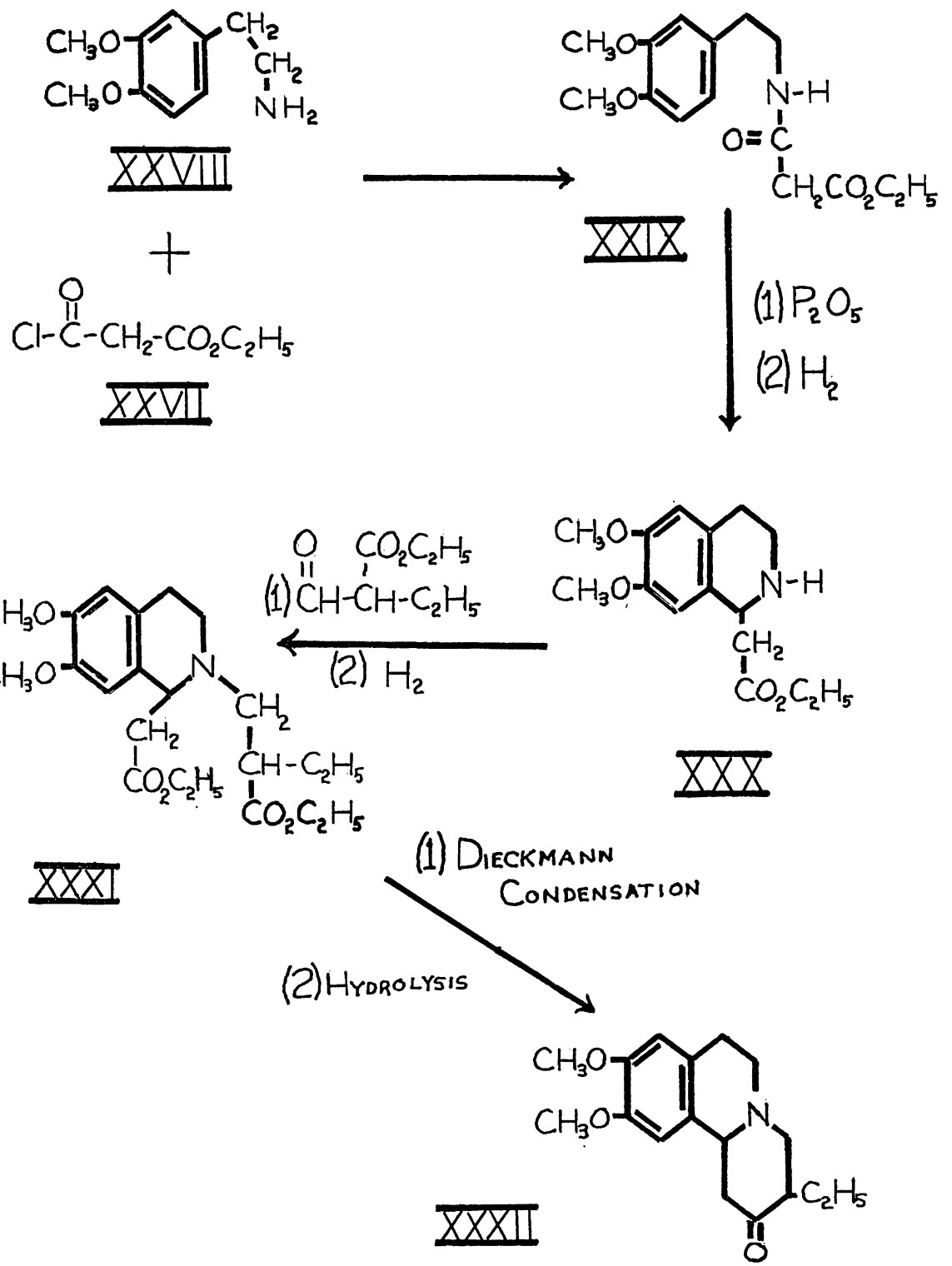
XXVI

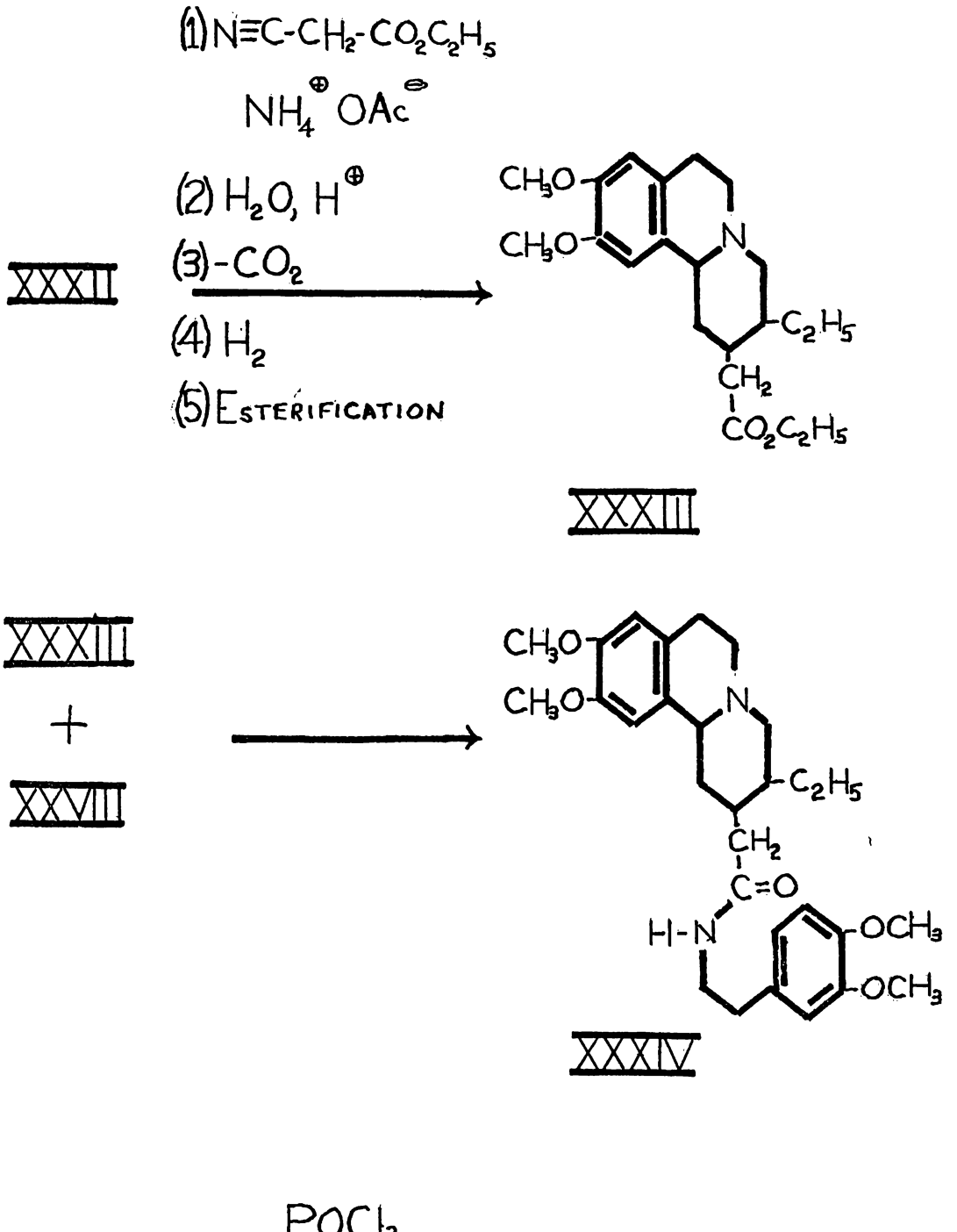
CONTRIBUTIONS TO THE TOTAL SYNTHESIS OF EMETINE

Up to the present time there have been four studies reported which are of primary significance in the problem of totally synthesizing emetine. Two of these were directed toward attainment of the actual emetine structure, while the others were involved with the syntheses of C-noremetine, which differs from emetine only in that the side-chain ethyl group is missing.

The first study directed toward the total synthesis of emetine was that reported by Battersby and Openshaw (20), who succeeded in obtaining a product having the structure assigned to O-methylpsychotrine (XXIV). The product which they obtained was probably a mixture of stereoisomers. It was later oxidized to d,l-rubremetinium bromide, which possessed ultraviolet and visible absorption spectra identical with those of the optically active rubremetinium bromide obtained by oxidation of natural emetine.

The synthesis was carried out as follows: Carbethoxyacetyl chloride (XXVII) and homoveratrylamine (XXVIII) were reacted to yield the amide XXIX, which underwent a Bischler-Napieralski ring closure with phosphorus pentoxide to give a dihydroisoquinoline derivative. Catalytic hydrogenation converted it to the corresponding tetrahydroisoquinoline derivative XXX. This was treated with ethyl α-formylbutyrate and the resulting crude product was catalytically hydrogenated to give the di-ester XXXI. A Dieckmann condensation of XXXI


XXVIII
XXVII
XXIX
(1) P_2O_5
(2) H_2
XXX
(1) $CH(CO_2C_2H_5)-CH-C_2H_5$
(2) H_2
XXXI
(1) Dieckmann Condensation
(2) Hydrolysis
XXXII


(1) N≡C-CH2-CO2C2H5
NH4⊕ OAc⊖
(2) H2O, H⊕
(3) -CO2
(4) H2
(5) ESTERIFICATION
XXXII
CH3O
CH3O
N
C2H5
CH2
CO2C2H5
XXXIII
XXXIII
+
XXVIII
CH3O
CH3O
N
C2H5
CH2
C=O
H-N
OCH3
OCH3
XXXIV
POCl3
XXIV

followed by hydrolysis gave the ketone XXXII. Condensation with ethyl cyanoacetate, followed by hydrolysis, decarboxylation, catalytic hydrogenation, and re-esterification afforded the ester XXXIII, which was condensed with homoveratrylamine to give the amide XXXIV. Ring closure with phosphorus oxychloride then gave a product having structure XXIV. The oxidation to d,l-rubremetinium bromide was accomplished with mercuric acetate.

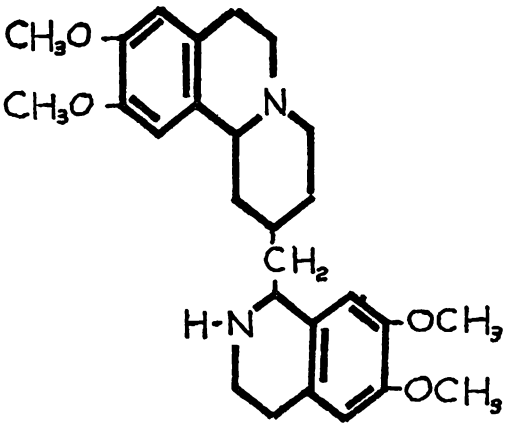
Although there has not as yet been any report concerning reduction of the synthetic O-methylpsychotrine isomers, it seems almost certain that such a reduction should result in the formation of a mixture of emetine isomers, which may or may not contain emetine itself.

The two syntheses of C-noremetine (XXXV), both reported by Pailer and coworkers (21)(22)(23), were accomplished by using two entirely different methods of approach. The first followed the same general pattern used by Battersby and Openshaw, involving condensation of homoveratrylamine with a suitable intermediate followed in order by closures of rings B and C. The second, however, started with ring C intact and the homoveratryl group was added with subsequent closure of ring B.

The first synthesis of XXXV was published by Pailer and Strohmayer (21) in 1951. The starting material, γ-phenoxypropyl-malonic acid (XXXVI), was brominated to give γ-phenoxypropyl-bromomalonic acid (XXXVII). Decarboxylation of XXXVII afforded α-bromo-δ-phenoxyvaleric acid (XXXVIII), which was

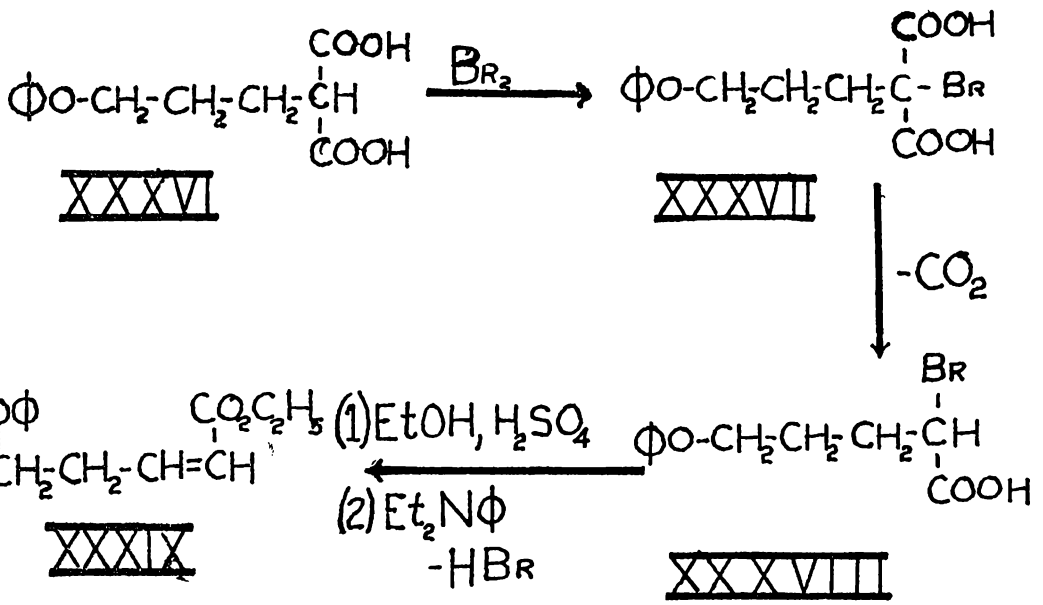
esterified with ethanol and sulfuric acid. Dehydrobromination of the ester was effected by treatment with diethyaniline, yielding ethyl 5-phenoxy-2-penteneoate (XXXIX). Ethyl malonate was condensed with XXXIX by a Michael type addition to give the tri-ester XL, which underwent hydrolysis and decarboxylation to give β-phenoxyethyl-glutaric acid (XLI). Reaction of XLI with concentrated hydrobromic acid yielded β-bromoethyl-glutaric acid (XLII). This was esterified with diazomethane, and the resulting methyl ester was condensed with homoveratrylamine. Heating the condensation product afforded the lactam XLIII. Ring closure with phosphorus oxychloride in toluene gave a product which was isolated as the quarternary ammonium iodide (XLIV). Reaction with silver chloride converted XLIV to the quarternary ammonium chloride from which the hydrochloride XLV was produced by catalytic hydrogenation. Acid hydrolysis of XLV was followed by conversion of the acid to the acid chloride by means of thionyl chloride. Condensation of the acid chloride with homoveratrylamine gave the maide XLVI, which underwent ring closure with phosphorus oxychloride to give dehydro-C-noremetine (XLVII). Catalytic hydrogenation of XLVII yielded C-noremetine.

A simpler method of preparing the intermediate, β-bromoethylglutaric acid (XLII) was reported later by Pailer and Strohmayer (22). Condensation of β-methoxypropionaldehyde (XLVIII) with cyanoacetamide (XLIX) using piperidine as cat-

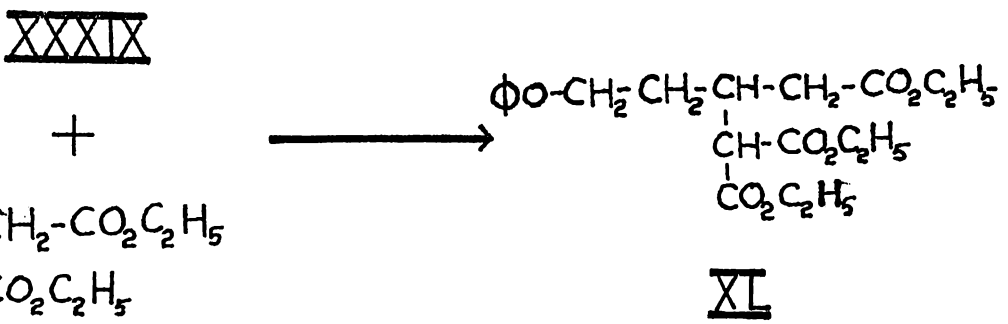


C-NOREMETINE

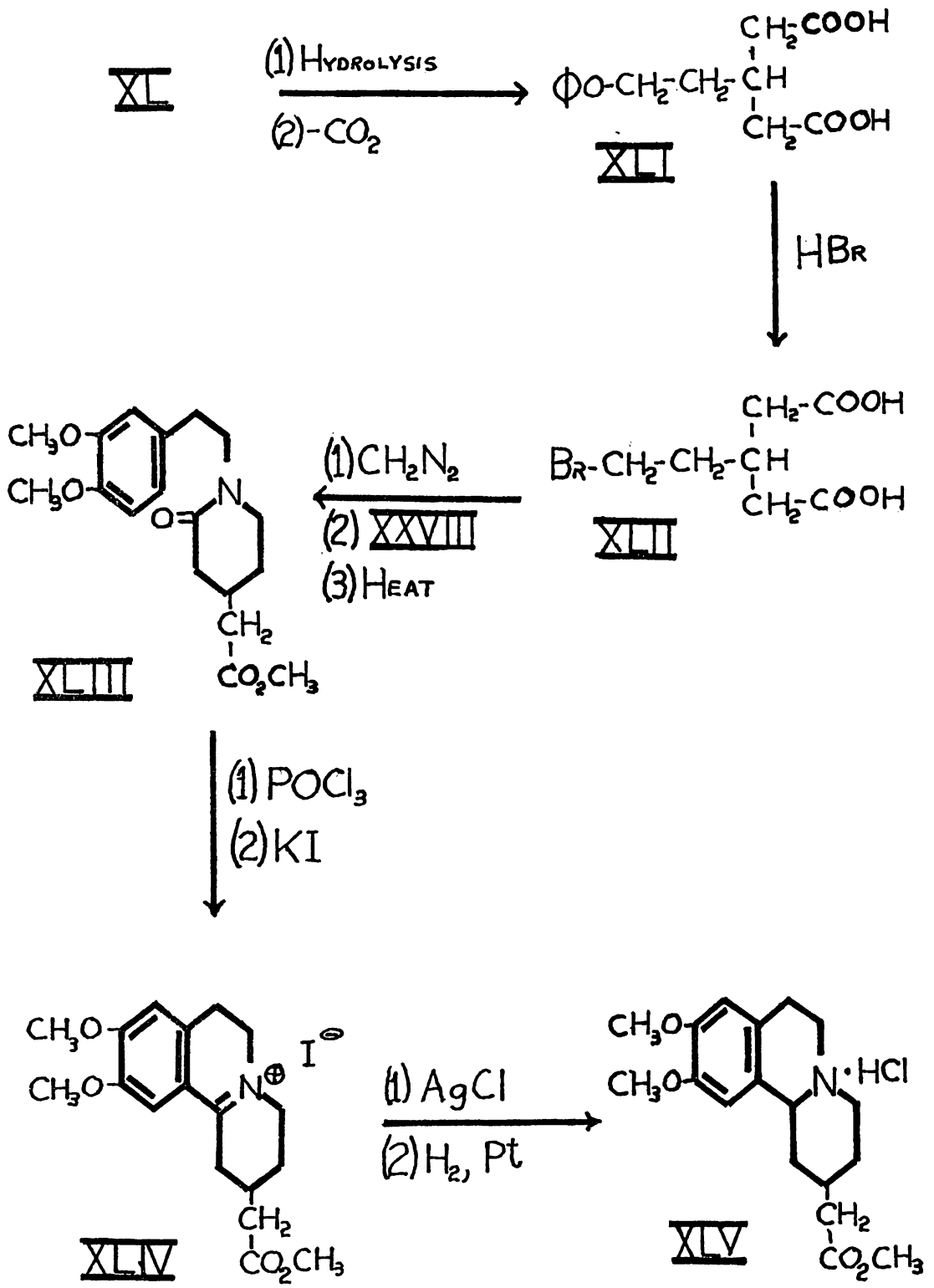
XXXV

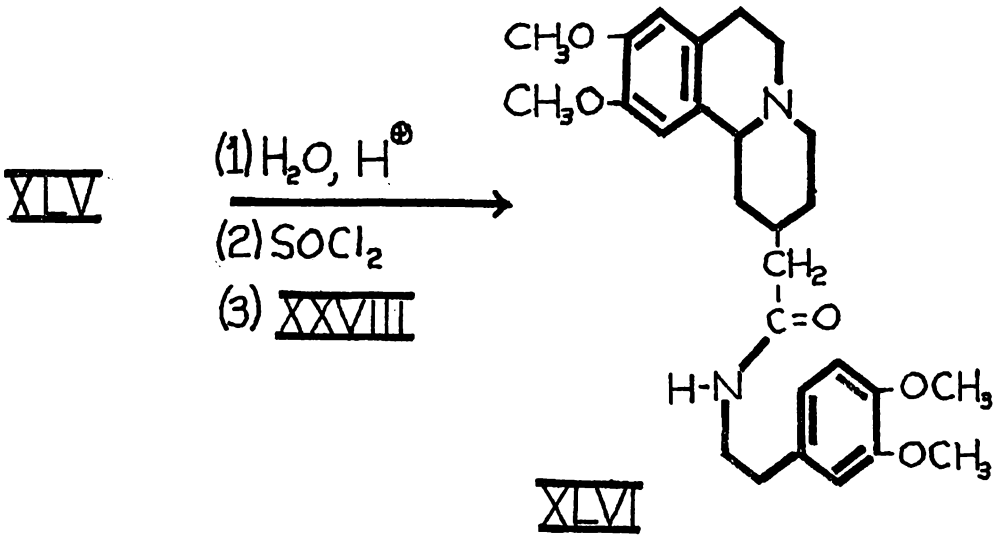


XXXVI XXXVII XXXVIII XXXIX

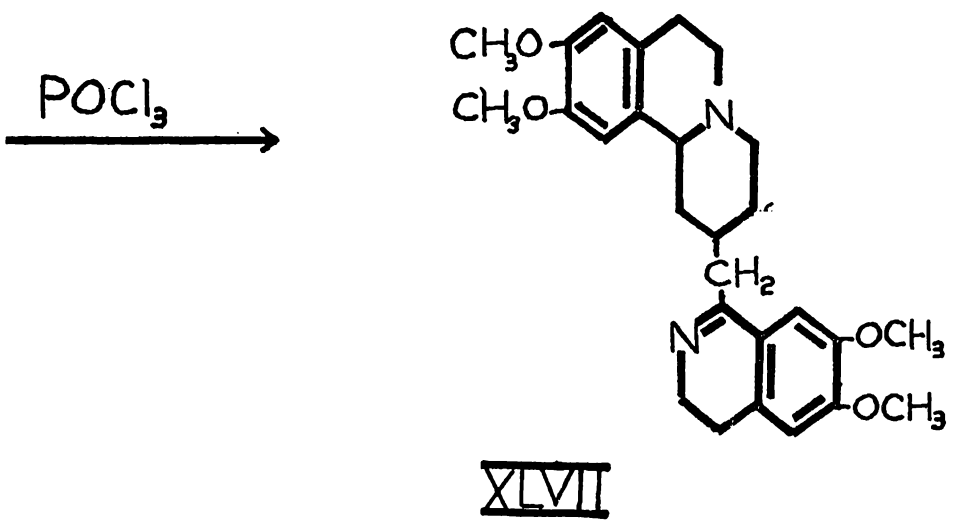


XXXIX XL

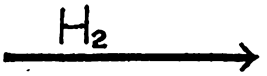

XL
(1) Hydrolysis
(2) -CO2
φO-CH2-CH2-CH(CH2-COOH)-CH2-COOH
XLI
HBr
Br-CH2-CH2-CH(CH2-COOH)-CH2-COOH
XLII
(1) CH2N2
(2) XXVIII
(3) Heat
CH3O
CH3O
O
N
CH2
CO2CH3
XLIII
(1) POCl3
(2) KI
I⊖
N⊕
XLIV
(1) AgCl
(2) H2, Pt
N·HCl
XLV



XLVI

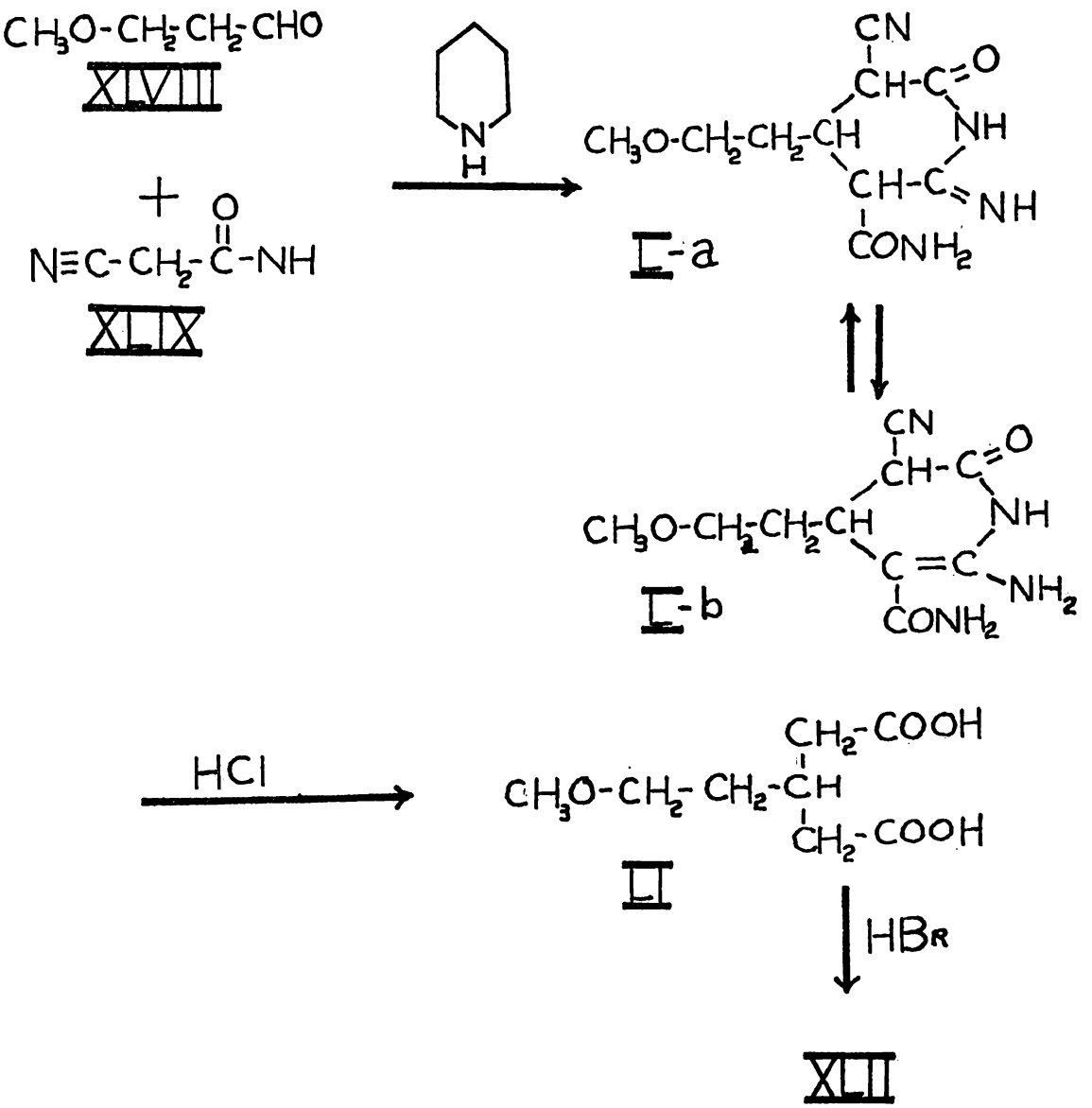


XLVII



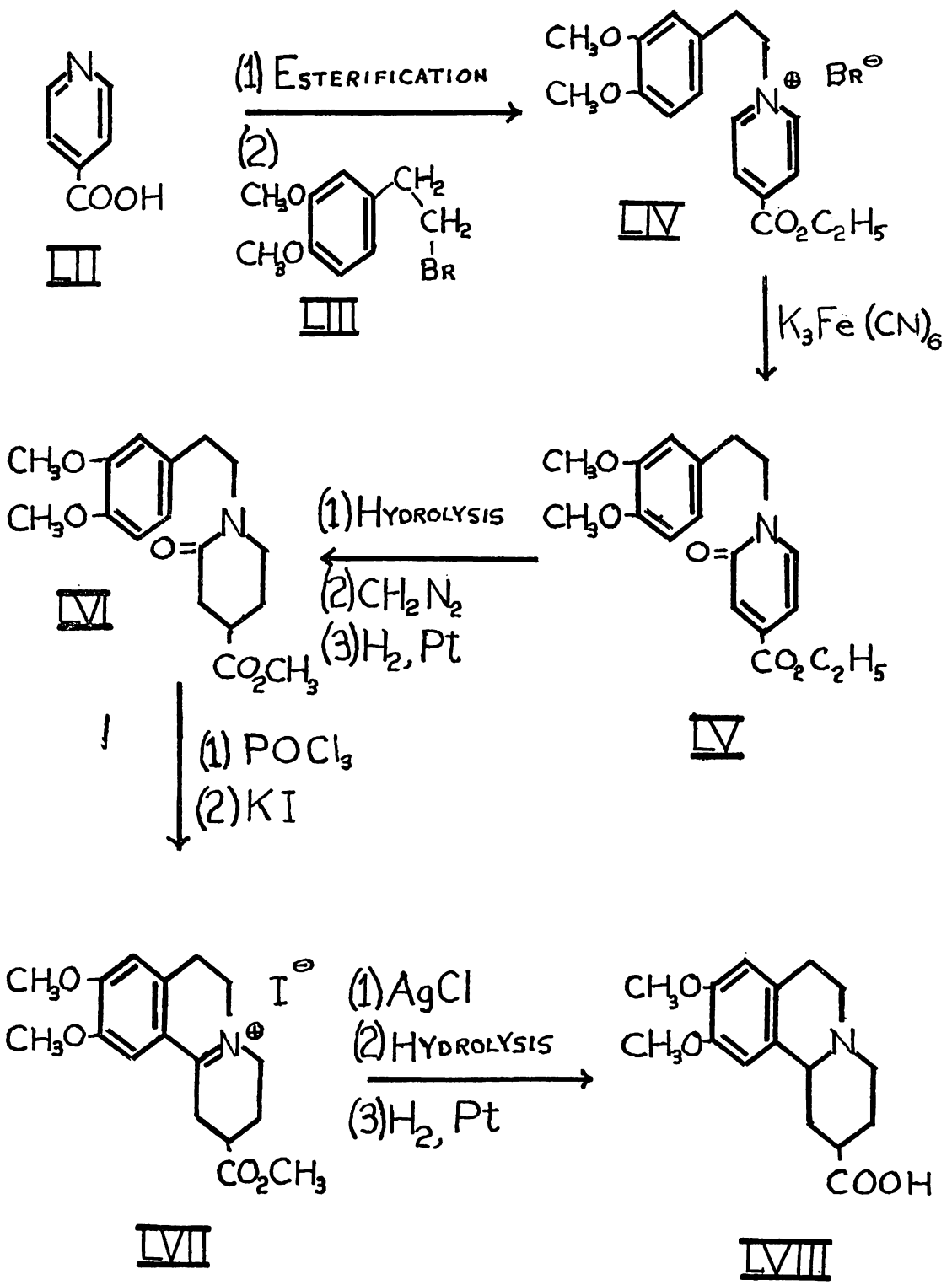
XXXV

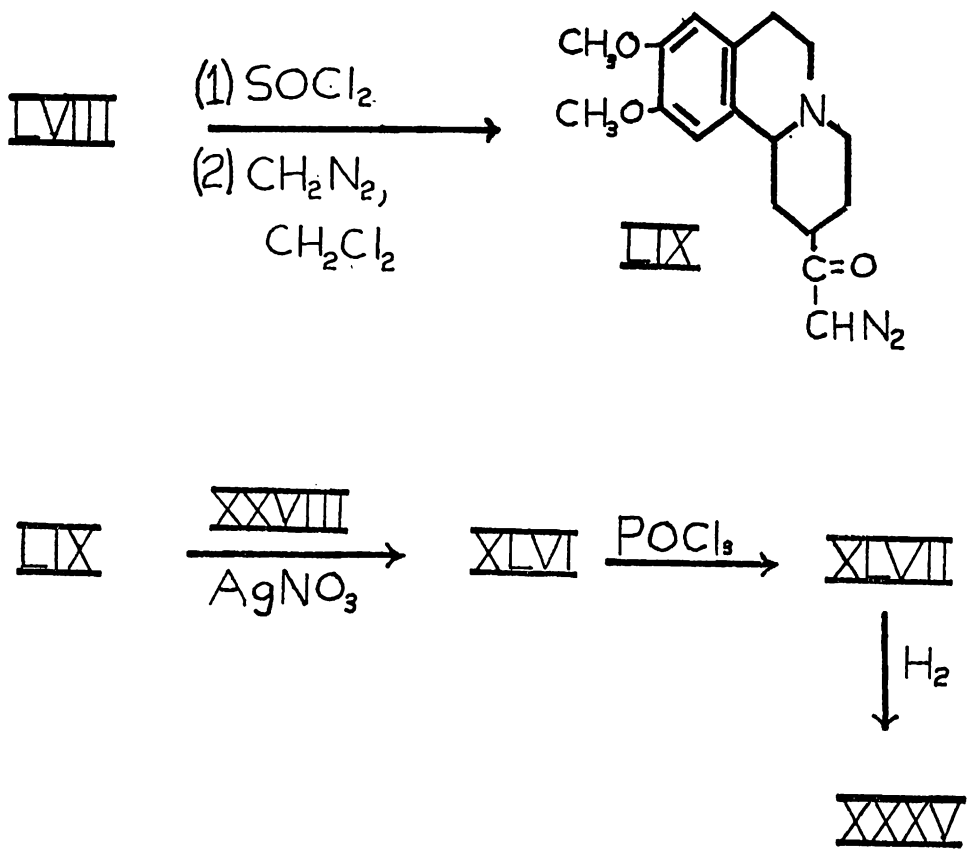
alyst gave a substituted lactam which was found to exist as an equilibrium mixture of two tautomeric forms, La and Lb. Hydrolysis with concentrated hydrochloric acid yielded 3-(β-methoxyethyl)-glutaric acid (LI), which was converted to XLII by treatment with concentrated hydrobromic acid.



The second synthesis of C-noremetine was reported in 1952 by Pailer et al. (23). An azeotropic esterification of isonicotinic acid (LII) and ethanol formed the ethyl ester which was reacted with homoveratryl bromide (LIII), giving the N-substituted pyridinium bromide (LIV). Oxidation to the pyridone (LV) was accomplished with potassium ferricyanide. Alkaline hydrolysis of LV was followed by esterification with diazomethane, and the resulting methyl ester on catalytic hydrogenation yielded the piperidone LVI. Ring closure was effected with phosphorus oxychloride, and the ring closed product was isolated as the quarternary ammonium iodide, LVII. This was converted to the chloride, which was first hydrolyzed, then catalytically hydrogenated to give the acid LVIII. Treatment with thionyl chloride converted LVIII to the acid chloride which, on reaction with diazomethane in methylene chloride, was converted to the diazoketone LIX. In an Arndt-Eistert reaction, LIX was reacted with homoveratryl-amine in the presence of silver nitrate to give the amide XLVI. Ring closure with phosphorus oxychloride followed by catalytic hydrogenation yielded C-noremetine.

In neither of these two reported syntheses of C-noremetine was any mention made of an attempt to separate diastereoisomers. However, the hexachloroplatinate of both final products was prepared and the two were found to be identical. Such a result is somewhat surprising in view of the fact that three asymmetric centers are present in the molecule, making four racemates theoretically possible.


(1) Esterification
(2)
II
III
IV
V
VI
VII
VIII
$K_3Fe(CN)_6$
(1) Hydrolysis
(2) CH_2N_2
(3) H_2, Pt
(1) $POCl_3$
(2) KI
(1) AgCl
(2) Hydrolysis
(3) H_2, Pt



Evstigneeva et al. (24) have recently reported a total synthesis of emetine in which they have not only attained the gross emetine structure but have also succeeded in isolating emetine itself from the final product by isolation and resolution of d,l-emetine. At one point in the synthesis the diastereoisomers present were separated and subsequent steps carried out on each of the racemates.

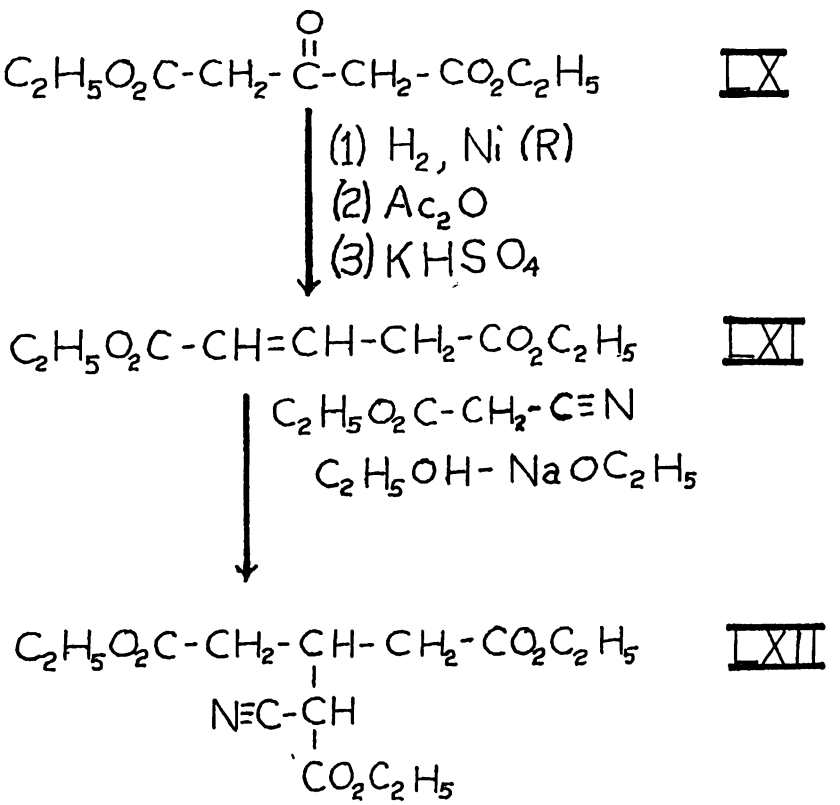
Diethyl-β-ketoglutarate (LX), the starting material, was hydrogenated under pressure over Raney nickel to give diethyl-β-hydroxyglutarate. This was then refluxed with

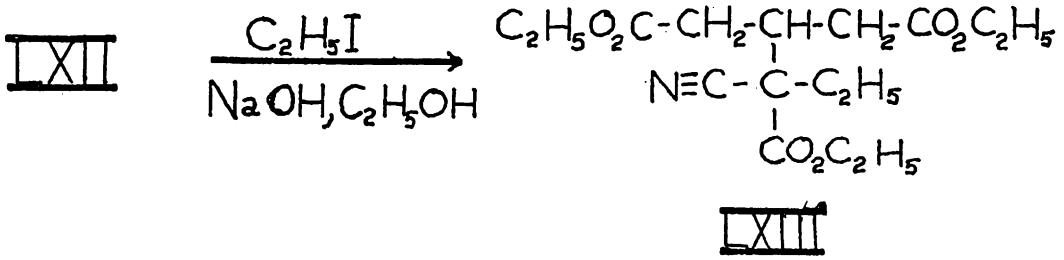
acetic anhydride to form the β-acetoxy derivative, which lost acetic acid on treatment with potassium bisulfate solution to give diethyl glutaconate (LXI). Reaction of LXI with ethyl cyanoacetate in the presence of sodium ethoxide afforded the compound LXII. By treating LXII with ethyl iodide in basic solution the alkylated product LXIII was obtained. Mild hydrolysis using ethanolic sodium hydroxide at room temperature selectively hydrolyzed the ester group alpha to the cyano group, and on refluxing the mixture the resulting product was decarboxylated to give the diester LXIV. Condensation of LXIV with homoveratrylamine was carried out simultaneously with catalytic hydrogenation under pressure to yield the ring-closed product LXV.

At this point the diastereoisomers of LXV were separated by crystallization from toluene, isomer A being soluble and isomer B insoluble. Ring closure with phosphorus oxychloride in toluene was carried out separately on LXV-A and LXV-B to give the hydrochlorides LXVI-A and LXVI-B respectively. LXVI-B was characterized as the hydrogen iodide, m.p. 257-258°. The free base from LXVI-A was catalytically hydrogenated under pressure to give VII-A, which failed to yield a crystalline hydrochloride. The base from LXVI-B, m.p. 60-63°, was similarly converted to VII-B, which gave a hydrochloride with m.p. 145-146°. On oxidation with alcoholic iodine both VII-A and VII-B afforded rubremetinium iodide, m. p. 178.5-181°, which possessed an identical ultraviolet and

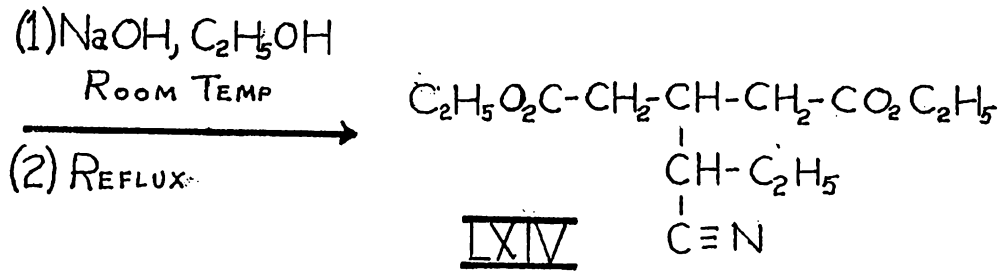
visible spectrum with the product obtained by a similar oxidation of natural emetine.

VII-B gave a d-camphorsulfonate which showed a m.p. of 238.5-240° after crystallization from ethanol. Hydrolysis of the VII-B d-camphorsulfonate yielded a base, m.p. 71.5-72.5°. The d-camphorsulfonate from natural emetine, m.p. 222-223°, gave, on hydrolysis, a base showing the same melting point. The hydrochloride of synthetic emetine melted at 243-255° and that of natural emetine at 235-255°. No explanation was given for some of the discrepancies in melting points.

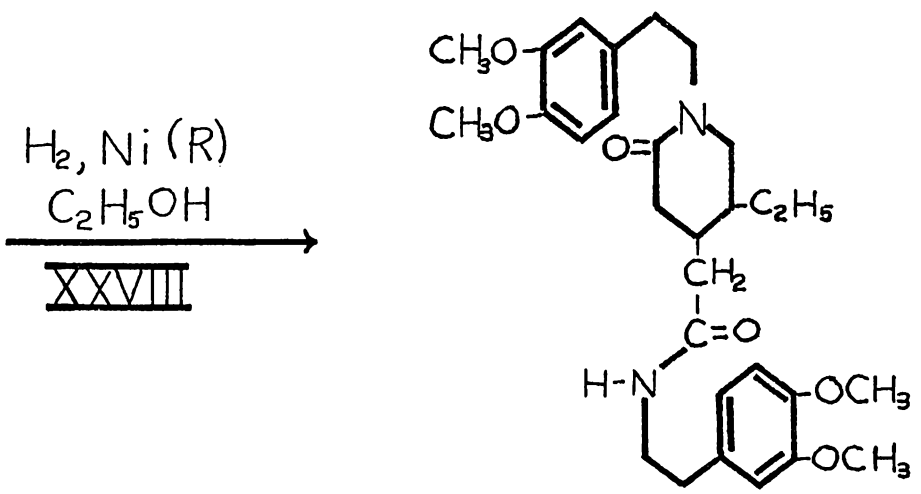




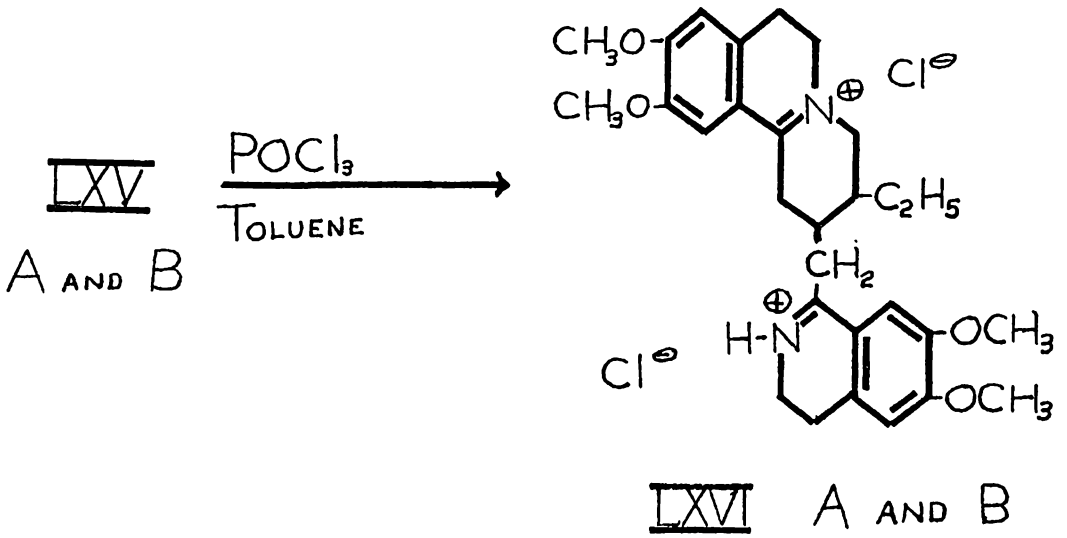
LXIII



LXIV



LXV A AND B


LXV
A AND B
POCl3
TOLUENE
CH3O
CH3O
Cl⊖
N⊕
C2H5
CH2
H-N⊕
OCH3
OCH3
Cl⊖
LXVI A AND B

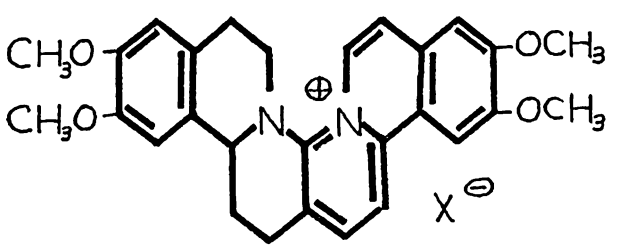

H2, Ni (R)
VII A AND B

STUDIES ON RUBREMETINIUM SALTS

The highly colored rubremetinium cation was first obtained by Carr and Pyman (2), who oxidized emetine with ferric chloride and isolated rubremetinium chloride. Since then, rubremetinium salts have been formed by oxidation of emetine with a variety of mild oxidizing agents, such as bromine (9), iodine (6), and mercuric acetate (25). In addition to emetine, the related compounds O-methylpsychotrine (3), tetradehydroemetine (25), and isotetradehydroemetine (26) are readily converted to rubremetinium salts. Emetamine, however, gives a colored product which is similar to but not identical with a rubremetinium salt.

The molecular formula of rubremetinium chloride has been reported to be $C_{29}H_{33}N_2O_4Cl$ (2)(6). The fact that it behaves as a monoacidic, quaternary base was first determined by Carr and Pyman and later confirmed by Battersby and Openshaw (25), who potentiometrically titrated a solution of rubremetinium chloride against 0.01 N sodium hydroxide solution.

In view of this behavior, Brindley and Pyman (8) proposed the structure LXVII for rubremetinium salts. This proposal,



LXVII

however, was based on an incorrect emetine structure and must therefore be rejected.

Karrer, Eugster, and Ruttner (17) later reported that reduction of rubremetinium bromide with zinc and acetic acid gave tetrahydrodehydroemetine*, m.p. 134°, $[\alpha]_D^{18} = +42°$, an optically active tetrahydro derivative which resisted catalytic hydrogenation. Since it was already known that quaternary isoquinolinium systems could be reduced easily and that non-quaternary systems resisted reduction, these workers believed that rubremetinium salts must possess the structure LXVIII**, and that tetrahydrodehydroemetine must therefore have the structure LXIX. Since the latter is identical with the structure of emetamine, the two compounds were considered to be stereoisomers.

As further evidence in favor of structure LXVIII, Karrer and Ruttner (27) reported that rubremetinium bromide could be reduced by lithium aluminum hydride to give an unstable dihydro derivative, o-dihydrodehydroemetine, which analyzed as $C_{29}H_{34}O_4N_2$. This product was found to absorb one mole of hydrogen on catalytic hydrogenation to give tetrahydrodehydroemetine and an isomer, isotetrahydrodehydroemetine, m.p. 194°

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*Karrer preferred to use the term "dehydroemetine" rather than "rubremetine" as a basis for his nomenclature.

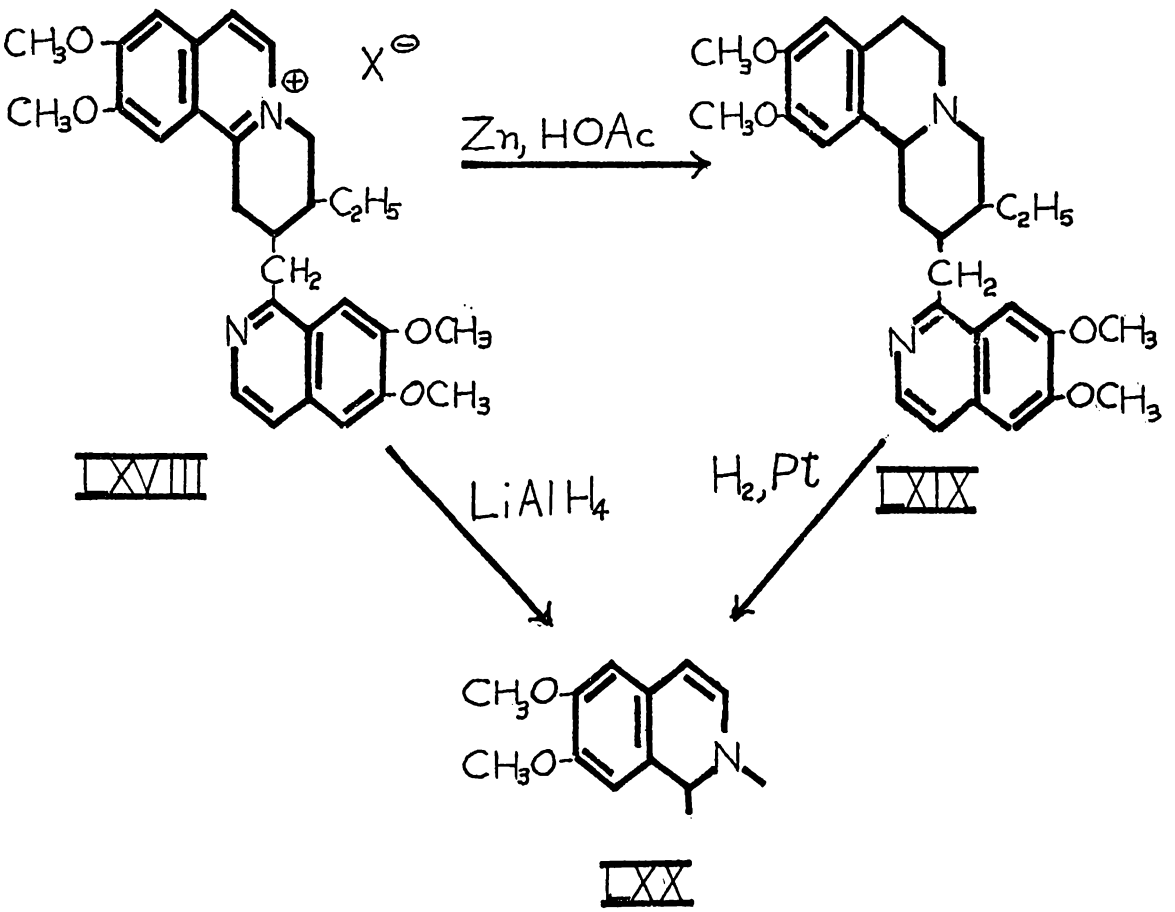
**This proposal was actually in the form of a partial structure since the correct emetine structure was not yet known. However, since the inner part of the molecule is not involved, it can be applied to the known emetine structure to give LXVI.

$[\alpha]_D^{18} = -380°$. On the basis of previous results from reduction of isoquinoline systems, o-dihydrodehydroemetine was considered to have the partial structure LXX.

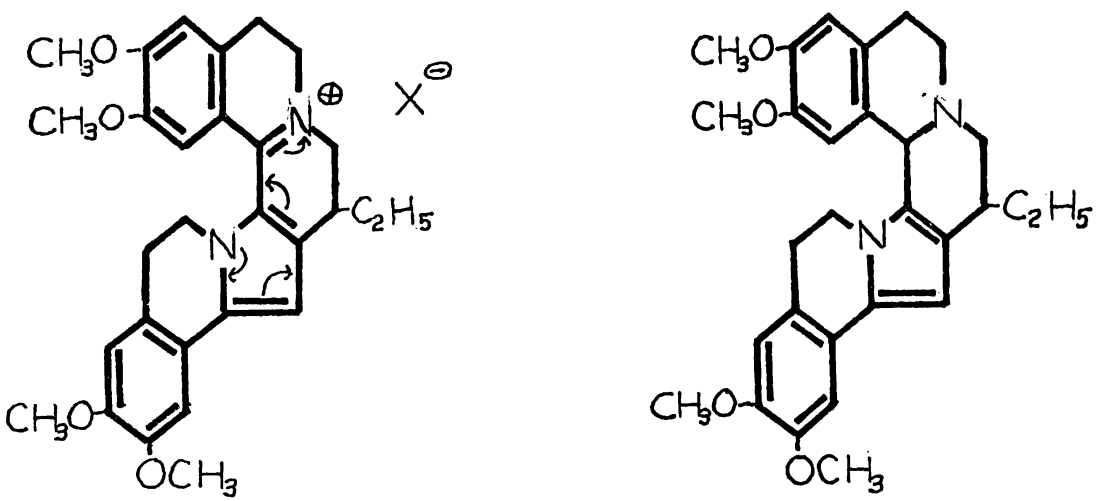
There are, however, numerous arguments against structure LXVIII. It does not explain the lack of basicity of the non-quaternary nitrogen, nor the intense color of rubremetinium salts. In addition, emetamine, if it were an isomer of tetrahydrodehydroemetine, should give a rubremetinium salt on mild oxidation. A different product is obtained, however, as has already been mentioned.

Further arguments against LXVIII have recently been provided by Openshaw and Wood (19). These workers have pointed out that reduction of the rubremetinium cation with lithium aluminum hydride to the dihydro derivative should produce two isomers, since an asymmetric center is created. Moreover, further reduction of a single dihydro derivative would not be expected to give two tetrahydro isomers, since there would not be a new center of asymmetry formed in this step.

In an attempt to overcome the various objections to structure LXVIII, Battersby, Openshaw, and Wood (28) have suggested that rubremetinium salts could have the structure LXXI. This mesomeric structure, similar to that of a cyanine dye, would account for the intense color and its behavior as a monoacidic base. It would also explain the fact that emetamine does not give rubremetinium salts on oxidation. In addition, these workers found that a crude reduction product



LXVIII LXIX LXX



LXXI LXXIII

of rubremetine gave color reactions which indicated the presence of a pyrrole ring.

Karrer and Ruttner have objected to the structure LXXI on the grounds that it contains two dihydropyridine rings (D and E), and should therefore be oxidized further quite readily. The validity of this objection was questioned by Openshaw and Wood, who pointed out that ring E could be considered as part of a 3,4-dihydroisoquinoline system, which is known to possess considerable stability. Furthermore, the molecule should be resonance stabilized to a large degree.

Structure LXXI would not be consistent with the hydrogenation data obtained by Karrer and Ruttner. It has been pointed out (26) that absorption of two moles of hydrogen would necessarily result in the formation of a pyrroline structure, and it is known that such a structure will readily undergo hydrogenation.

Openshaw and Wood (19), however, have further investigated the reduction of rubremetinium salts, and have reported results which are not in agreement with those obtained by Karrer and Ruttner. They found that on catalytic hydrogenation of rubremetinium chloride in ethanol solution only one mole of hydrogen was taken up, and the product consisted of two stereoisomeric dihydrorubremetines. The α-isomer was found to be strongly levorotatory, m.p. 198°, $[\alpha]_D^{15} = -395°$, while the β-isomer was even more strongly dextrorotatory, m.p. 202°, $[\alpha]_D^{16} = +406°$. On crystallization of the original mixture from meth-

anol, a product, m.p. 128°, $[\alpha]_D^{18} = +21°$, separated which was believed to be a complex containing one molecule of each isomer and two molecules of methanol. The pure α-isomer was isolated from the mother liquor. On crystallization from ethanol, the complex was found to split up, with the less soluble β-isomer separating first. When methanol solutions of the two isomers were mixed, the "partial racemate" was again produced.

These results are consistent with structure LXXI since absorption of one mole of hydrogen would result in the formation of LXXII, which contains a stable pyrrole nucleus and should not be hydrogenated further at atmospheric pressure. Openshaw and Wood found that both of the dihydrorubremetine isomers gave pyrrole color reactions and that both were converted back to the rubremetinium cation by oxidation with mercuric acetate. The formation of two stereoisomers was attributed to the introduction of an asymmetric center at $C_{1'}$.

In an effort to resolve some of the apparently conflicting data on the reduction of rubremetinium salts, Tietz and McEwen (29) have recently reinvestigated the reduction procedures which had been used by earlier workers. On hydrogenation of rubremetinium chloride, according to the method of Openshaw and Wood (19), they found that two moles of hydrogen were absorbed, with the second mole being taken up at a much slower rate than the first. Two products were obtained from the reaction mixture. One of them, m.p. 196.2-197.2°, $[\alpha]_D^{20} = -392°$

was similar in properties to both α-dihydrorubremetine and isotetrahydrodehydroemetine. The other, m.p. 132.0-132.8°, $[\alpha]_D^{20}$ = +41.9°, corresponded to tetrahydrodehydroemetine. No product with the properties of β-dihydrorubremetine was isolated. However, when a similar hydrogenation was stopped after absorption of one mole of hydrogen, a compound, m.p. 201.5-202.5°, $[\alpha]_D^{20}$ = +402°, which appeared to be β-dihydrorubremetine, was obtained. This product was found to consume one mole of hydrogen on catalytic hydrogenation.

These results indicated that β-dihydrorubremetine is actually a dihydro derivative, but that α-dihydrorubremetine must be a tetrahydro derivative, identical with isotetrahydrodehydroemetine. Moreover, the complex reported by Openshaw and Wood must consist of a molecule each of β-dihydrorubremetine and isotetrahydrodehydroemetine plus the two molecules of methanol.

On treatment of rubremetinium chloride with lithium aluminum hydride followed by catalytic hydrogenation, Tietz and McEwen (29) isolated two products which correspond in psycical properties to the isotetrahydrodehydroemetine and tetrahydrodehydroemetine obtained by Karrer and Ruttner. A mixed melting point test and identical ultraviolet absorption spectra confirmed the fact that isotetrahydrodehydroemetine and the previously obtained " -dihydrorubremetine" are the same compound. Similarly, the product corresponding to tetrahydrodehydroemetine was found to be identical with the like

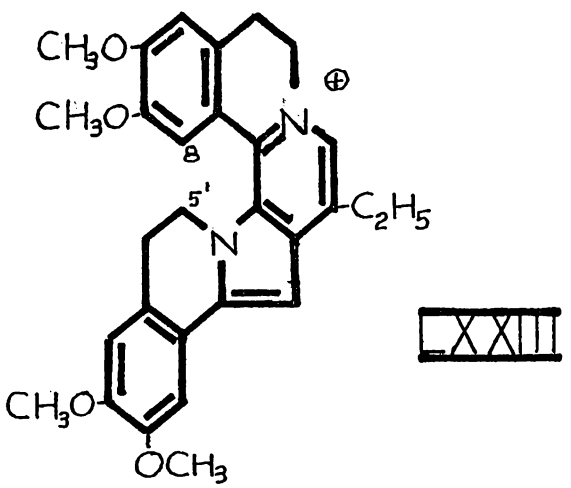
substance obtained by direct hydrogenation of rubremetinium chloride.

Although their results seemed to confirm those reported by Karrer and Ruttner, there was one point of disagreement mentioned by Tietz and McEwen. The product resulting from treatment of rubremetinium chloride with lithium aluminum hydride was observed to take up two moles of hydrogen, whereas Karrer and Ruttner had reported absorption of only one mole. This indicates that "o-dihydrodehydroemetine" is actually not a dihydro product, and that some type of reaction other than reduction must have taken place in the lithium aluminum hydride reaction.

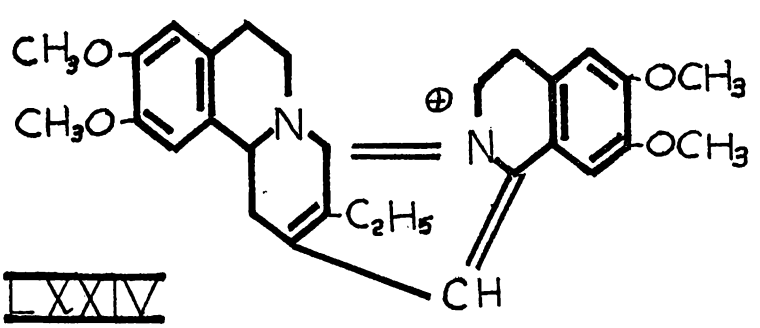
The results just discussed not only indicate the data of Openshaw and Wood to be in error, but at the same time provide strong argument against structure LXXI for rubremetinium compounds. As was mentioned previously, LXXI is capable of accounting for absorption of only one mole of hydrogen in a low pressure catalytic hydrogenation. Woodward (30) has proposed a structure (LXXIII) for the rubremetinium cation which not only overcomes this objection, but also accomodates other experimental facts. It can easily account for the absorption of two moles of hydrogen since the resulting tetrahydro derivative would have the structure LXXII with the pyrrole nucleus still intact. The optical activity of the rubremetinium cation can be explained by molecular dissymmetry resulting from steric interference at positions C_3, and C_8.

On the basis of structure LXXIII, however, rubremetinium chloride would have the molecular formula $C_{29}H_{31}N_2O_4Cl$, instead of the previously accepted value, $C_{29}H_{33}N_2O_4Cl$.

Another structure (LXXIV) has been advanced by Evstigneeva et al. (31), but there have been no experimental facts reported which would provide evidence for it. Such a structure would appear to be incapable of existence since it contains a three-member bridge across the meta-positions of a pyridine ring, and such a system should be quite highly strained.



LXXIII



LXXIV

DIASTEREOISOMERS OF EMETINE

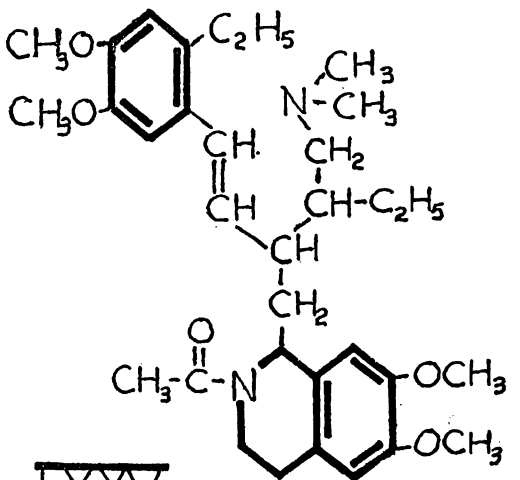
An investigation of the emetine structure reveals the presence of four asymmetric centers. Emetine, an optically active compound, must therefore by one of sixteen theoretical stereoisomers. Isoemetine, which has already been mentioned, was the first diastereoisomer of emetine to be isolated. Since it is prepared by reduction of O-methylpsychotrine, it must differ from emetine in the configuration of C_1.

The first experimental work directed toward the preparation of new diastereoisomers of emetine was that reported by Hazlett and McEwen (26), who worked with some degradation products of emetine. It was believed that the results of such experiments would have considerable value in the event of a total synthesis of emetine, which would probably involve the formation of two or more isomers. A previous knowledge of the properties of the various diastereoisomers would be expected to facilitate their separation and identification.

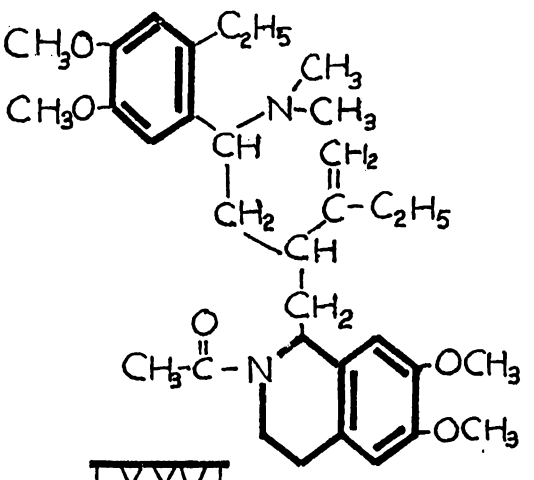
In an attempt to prepare the diastereoisomer of emetine differing in the configuration of C_1, Hazlett and McEwen (26) subjected N-acetylemetine (XII) to a series of degradation reactions which were intended to eliminate asymmetry at that point. This was to be followed by a resynthesis of the emetine structure, with the probable formation of two isomers.

XII was converted to the iodomethylate, which was subjected to a Hofmann degradation, then catalytic hydrogenation and reacetylation. A second Hofmann degradation, however,

did not give the expected results. Instead of the desired compound LXXV, the reaction product after acetylation was found to consist of two isomers, LXXV and LXXVI. The evidence for the formation of LXXV was indirect. Since the substance could not actually be isolated in pure form, the scheme was abandoned.



LXXV



LXXVI

Battersby and Openshaw (25), on studying the oxidizing action of mercuric acetate on emetine hydrochloride, isolated in addition to rubremetinium chloride a small amount of a previously unreported substance. This new compound, isolated as the hydrogen oxalate, was found on analysis to contain four fewer hydrogen atoms than emetine, and was designated as tetradehydroemetine. When four molar proportions of mercuric acetate were used for the oxidation, a much higher yield of tetradehydroemetine was obtained. Absorption of two moles of hydrogen on catalytic hydrogenation confirmed the presence of two ethylenic bonds, and on further dehydrogenation with

mercuric acetate the substance was converted to rubremetinium chloride, indicating that it must be an intermediate in the formation of rubremetinium salts. Its ultraviolet absorption spectrum indicated that the two double bonds were in conjugation with each other and with a benzene ring.

Since the formation of such a compound must result in the removal of two or more asymmetric centers present in emetine, Hazlett and McEwen (26) considered the possibility that hydrogenation of tetradehydroemetine might result in the production of some new emetine diastereoisomers. When a suspension of tetradehydroemetine hydrogen oxalate in ethanol solution was catalytically hydrogenated, four products were obtained. In addition to emetine, isolated as the hydrobromide, and isoemetine, isolated as the benzoyl derivative, two new diastereoisomers of emetine, neoemetine and emetine-IV, were isolated as their hydrogen oxalates. Neoemetine was further characterized as the hydrobromide.

On dehydrogenation of emetine with four moles of mercuric acetate (26), the procedure for working up the reaction mixture was varied slightly and a second tetradehydro product was obtained. This new compound, isotetradehydroemetine, was isolated in crystalline form as the free base and further characterized as the hydrogen oxalate, N-methyl dimethiodide, and N-benzoylmethiodide. Further oxidation with mercuric acetate gave the rubremetinium cation. Therefore, isotetradehydroemetine, like tetradehydroemetine, must be an intermediate in the formation of rubremetinium salts.

Catalytic hydrogenation of isotetradehydroemetine in 50% acetic acid solution resulted in the absorption of two moles of hydrogen (26). Emetine, isolated as the hydrobromide and further identified as the benzoyl derivative, was the only product obtained. A catalytic hydrogenation of isotetradehydroemetine hydrogen oxalate in ethanol also proceeded with absorption of two moles of hydrogen, and once again emetine, isolated as both the hydrogen oxalate and hydrobromide, was the only isolable product.

Reduction of isotetradehydroemetine with sodium and alcohol:

It has been shown that on reduction of a double bond by means of sodium and alcohol the hydrogen atoms are generally added at "trans" positions, while on catalytic hydrogenation the addition is predominantly "cis". In view of this fact it seemed desirable to try to reduce isotetradehydroemetine with sodium and alcohol, since the different mode of hydrogen addition should result in the formation of isomers other than emetine, the only product obtained on catalytic hydrogenation.

When eight molar proportions of sodium was reacted with a solution of isotetradehydroemetine in absolute ethanol, a new substance, isolated as the hydrogen oxalate, m.p. 207° (dec), was obtained in small yield. This compound showed no observable rotation in water solution (c = 2.0). Analysis of the hydrogen oxalate indicated a molecular formula of $C_{29}H_{40}O_4N_2$ for the free base, and on attempted catalytic hydrogenation no uptake of hydrogen was observed. The compound was therefore

assumed to be a new diastereoisomer of emetine and was designated as emetine-V. The similarity of the infrared absorption spectrum of its hydrogen oxalate with those of the known emetine isomers served to confirm this view (fig. 1). Furthermore, oxidation of emetine-V hydrogen oxalate with excess mercuric acetate, with subsequent treatment of the product with hydrobromic acid solution, gave a good yield of a red crystalline material, which showed a melting point behavior similar to that described for rubremetinium bromide (25).

Emetine-V was further characterized as the hydrobromide, m.p. 221-224°, with no observable rotation in water solution (c = 1.0). The benzoyl derivative of emetine-V could not be isolated in crystalline form, but treatment of an ether solution of benzoylemetine-V with dilute hydrochloric acid resulted in the formation of an insoluble hydrochloride derivative, $C_{36}H_{44}O_5N_2 \cdot HCl$, m.p. 190-195°, $[\alpha]_D^{23} = -14.0$ (c = 1.64 in chloroform). The definite levorotation provides evidence that emetine-V is not a racemic compound.

On further investigation of the reaction mixture from the sodium reduction, a second product was also isolated as the hydrogen oxalate, m.p. 157-184°, $[\alpha]_D^{24} = +22.0$ (c = 1.41 in water). There was no absorption of hydrogen observed on attempted catalytic hydrogenation, and the rubremetinium cation was obtained on oxidation with excess mercuric acetate.

Although the optical rotation of the hydrogen oxalate was close to that reported for emetine-IV hydrogen oxalate, the

melting point behavior was quite different (26). In order to establish its identity as emetine-IV it was necessary to compare other derivatives. Emetine-IV hydrobromide, m.p. 212-217°, $[\alpha]_D^{28} = +8.0$ (c = 1.04 in water) was prepared from an authentic sample of emetine-IV, which in turn was prepared according to the procedure used by Hazlett and McEwen (26). A mixed melting point of the two hydrobromides showed no depression. Further evidence that the two must be identical was provided by the similarity of infrared absorption spectra of the hydrogen oxalates and also the free bases. (fig.2) (fig. 3). In addition, identical behavior was noted on attempted preparation of the benzoyl derivatives. It was therefore concluded that the second compound obtained from sodium reduction of isotetradehydroemetine must be emetine-IV hydrogen oxalate.

Since the reaction time was quite short and a considerable proportion of isotetradehydroemetine was recovered, it was felt that a much larger excess of sodium should be used in the reduction. When sodium was added until reaction had practically ceased, a much larger yield of both emetine-V and emetine-IV resulted. On carrying out a number of reactions it was found that the presence of water in the ethanol had a marked effect on the resulting proportions of the two isomers. Completely anhydrous conditions seemed to favor the formation of emetine-V, but when a small amount of water was present in the alcohol the ratio of emetine-IV to emetine-V

was increased. This is shown by Table I, which gives yields of the two products under various conditions.

Table I

Amount of iso-TDE reacted	% alcohol/100	Emetine-IV HOx	Emetine-V HOx
10 g.	anhydrous	3.6 g.	5.1 g.
10	95	3.1	2.3
10	90	2.4	1.1
17.5*	**	9.6	---

*This consisted of the isotetradehydroemetine which had been recovered from previous reactions.

**It was known that the alcohol which was used contained an appreciable amount of water, although the percentage was not determined.

Treatment of emetine-V with four equivalents of mercuric acetate gave a gum which could not be crystallized and also could not be converted to either a hydrogen oxalate or hydrobromide derivative. Catalytic hydrogenation of the crude material yielded emetine-V and emetine-IV, both isolated as the hydrogen oxalate. The emetine-IV was further identified as the hydrobromide. It was significant that the aqueous solution from the mercuric acetate oxidation was found to have a definite rotation. This fact supplied further evidence that emetine-V is not racemic.

One attempt was made to reduce tetradehydroemetine with sodium and absolute ethanol. A small amount of emetine-V was isolated as the hydrogen oxalate, but the major portion

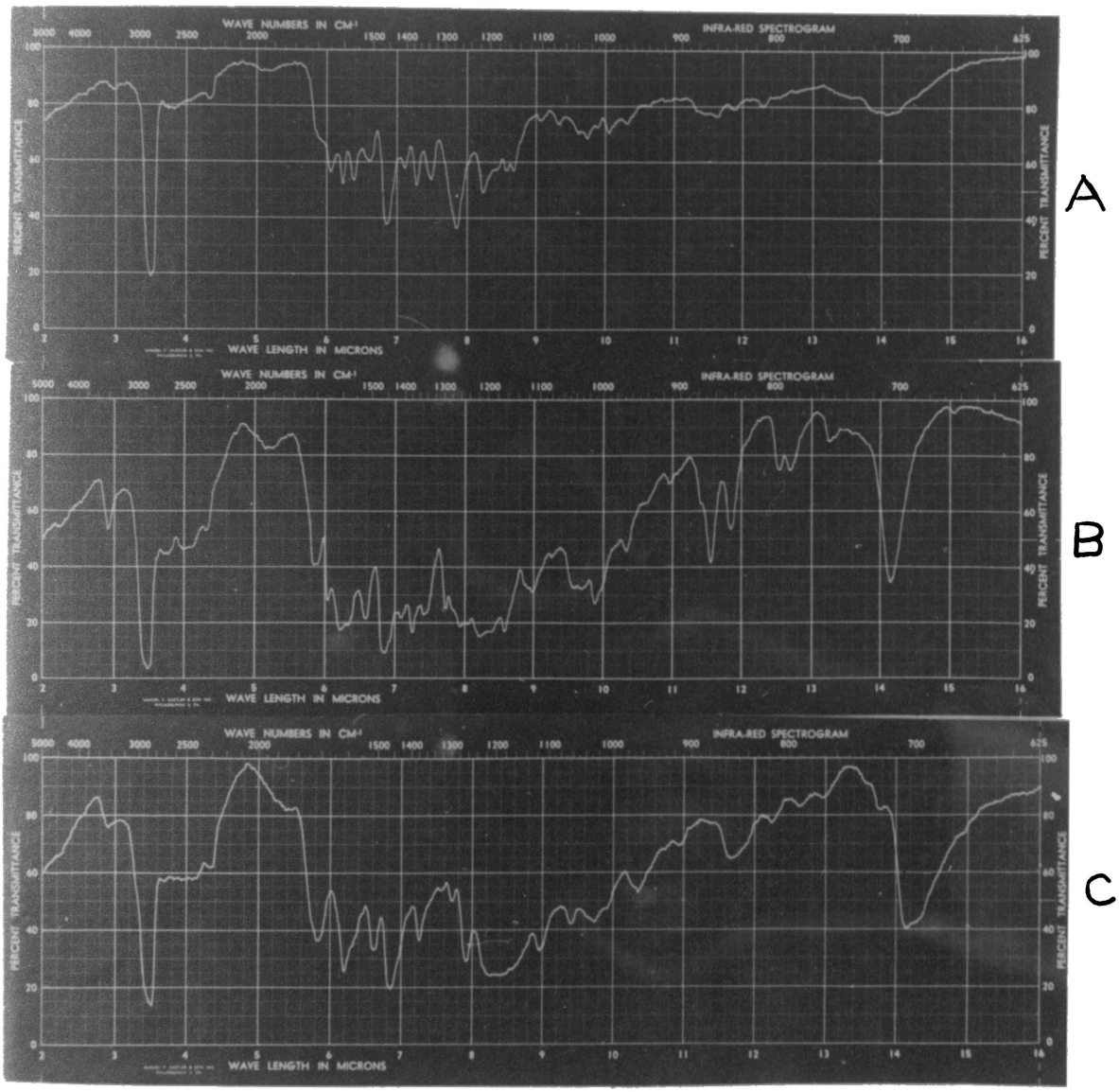
of the reaction product consisted of what seemed to be a mixture of other substances.

Fig. 1. Infrared absorption spectra in nujol suspension:

A. Emetine-V hydrogen oxalate.

B. Tetradehydroemetine hydrogen oxalate.

C. Isotetradehydroemetine hydrogen oxalate.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WAVE LENGTH IN MICRONS
A
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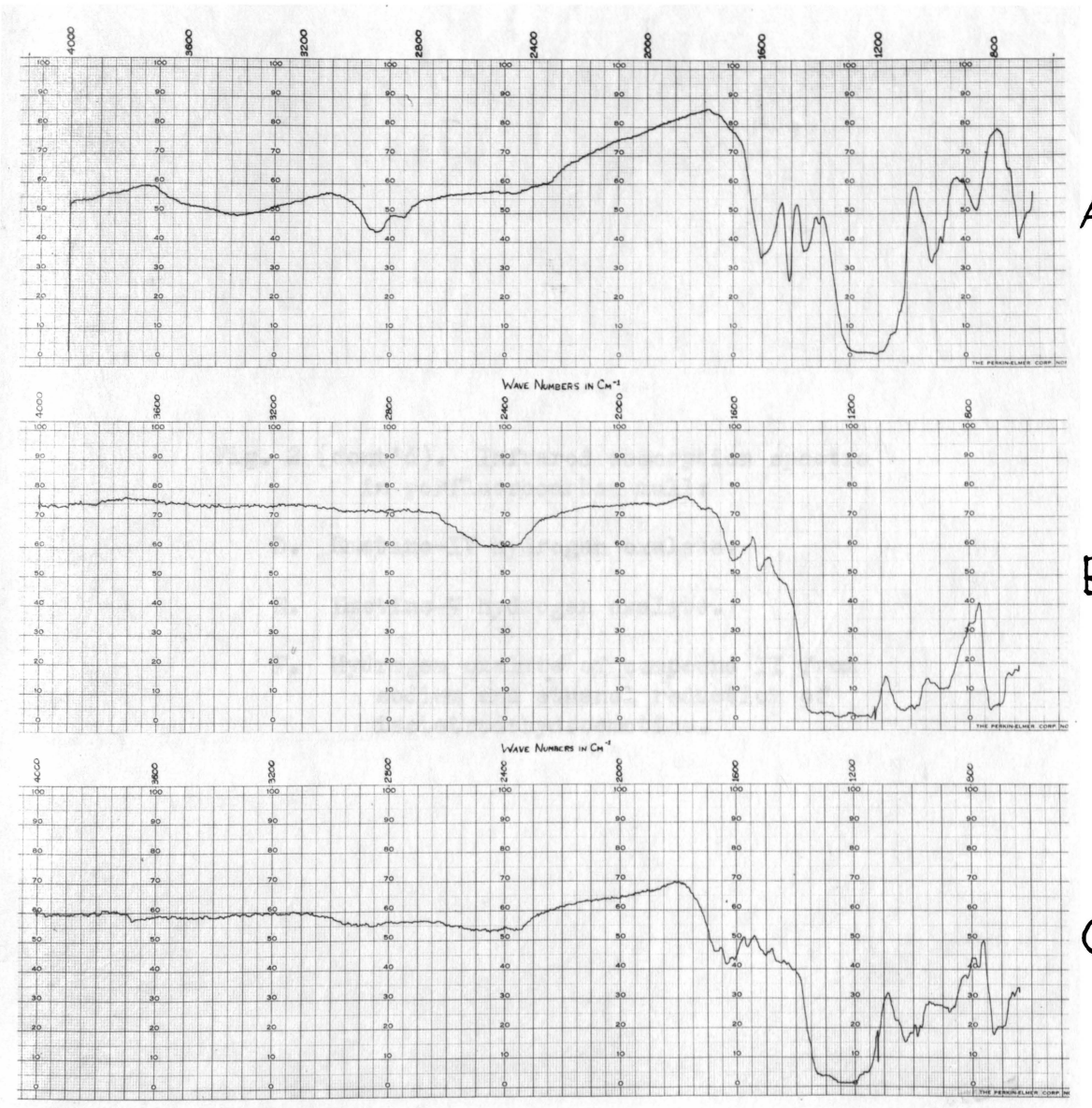
Fig. 2. Infrared absorption spectra in perfluorocarbon mull:

A. Emetine hydrogen oxalate.

B. Isoemetine hydrogen oxalate.

C. Neoemetine hydrogen oxalate.


A
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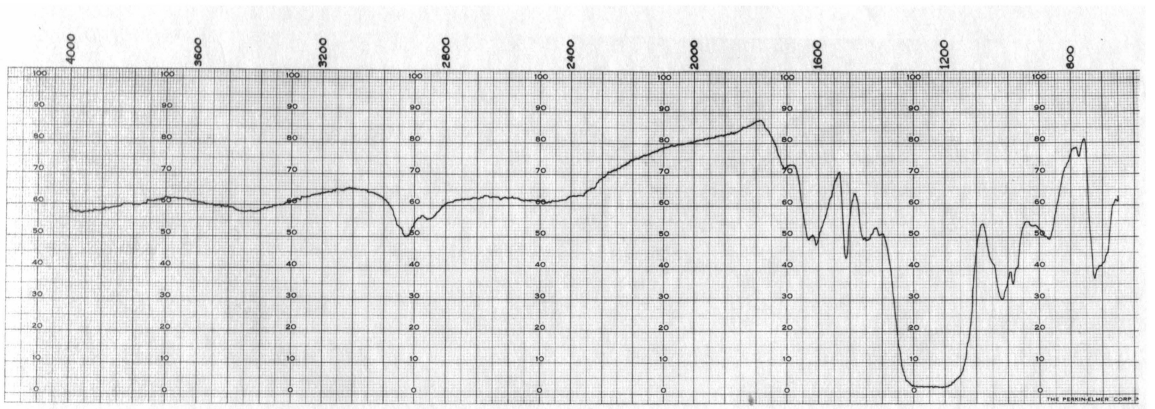
WAVE NUMBERS IN CM⁻¹

Fig. 2 (cont'd). Infrared absorption spectra in perfluorocarbon mull:

D. Emetine-IV hydrogen oxalate.

E. Emetine-V hydrogen oxalate.

F. Hydrogen oxalate of compound II from sodium and ethanol reduction of isotetradehydroemetine.



D

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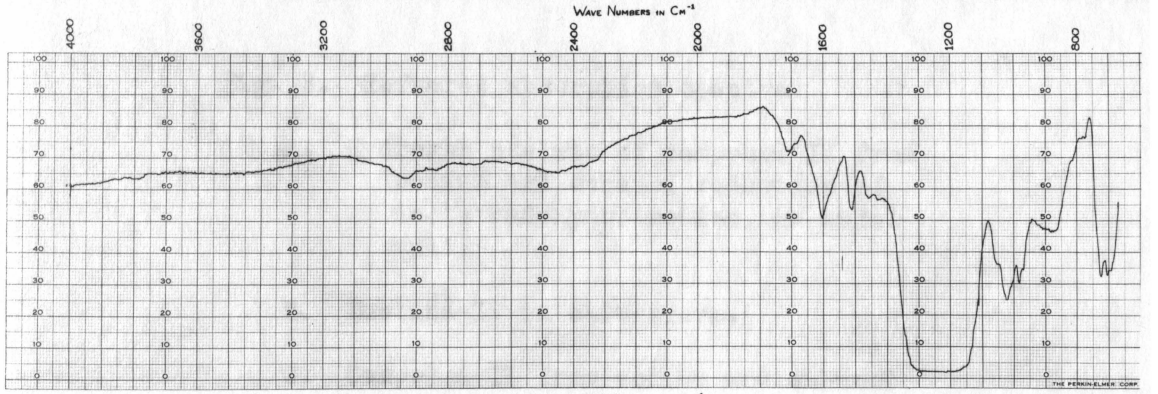

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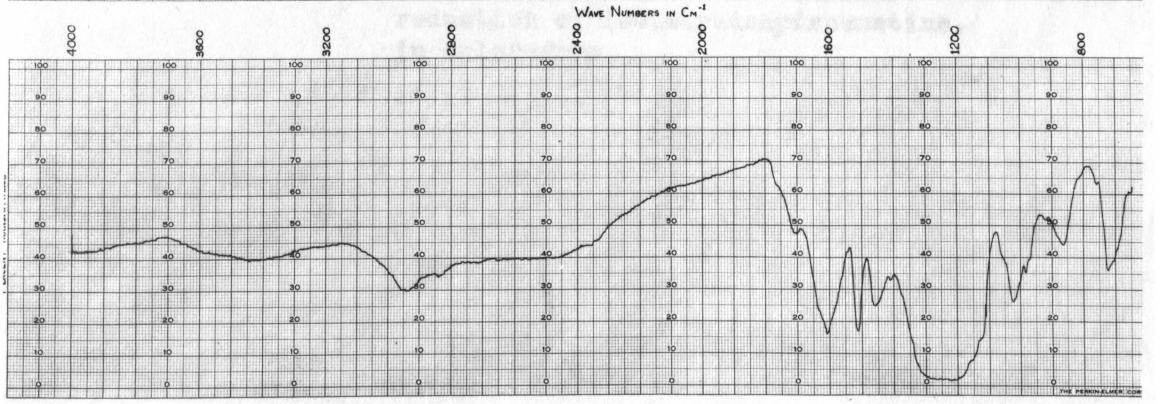
Wave Numbers in Cm^{-1}



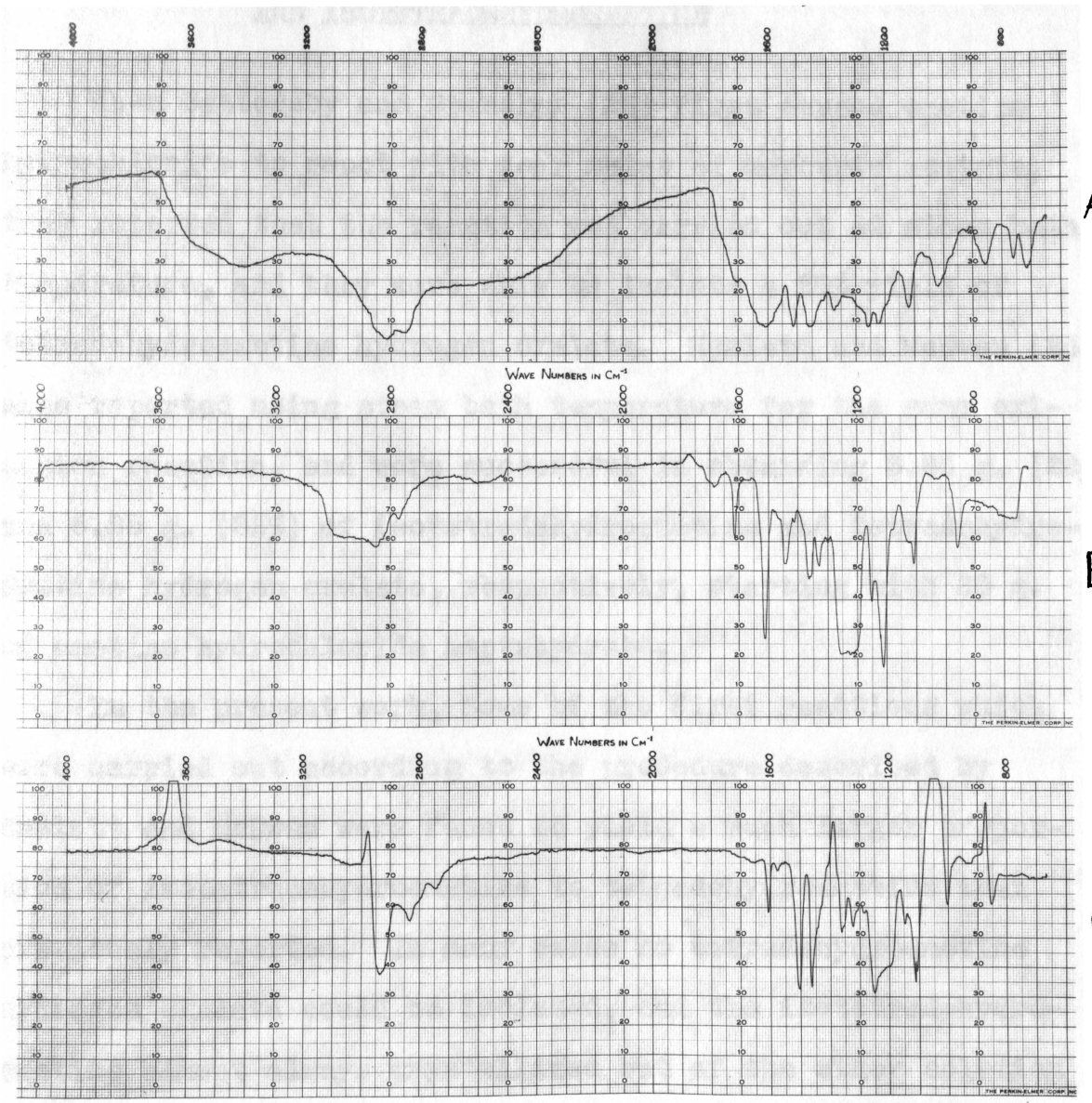
F

Fig. 3. Infrared absorption spectra:

A. Hydrogen oxalate of compound II from sodium and ethanol reduction of isotetradehydroemetine, in nujol mull.

B. Emetine-IV in chloroform.

C. Compound II from sodium and ethanol reduction of isotetradehydroemetine, in chloroform.


A
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B
WAVE NUMBERS IN CM⁻¹
C

FURTHER STUDIES ON TETRADEHYDROEMETINE AND ISOTETRADEHYDROEMETINE

When Battersby and Openshaw (25) first caused emetine hydrochloride to react with four moles of mercuric acetate, they reported that the reaction was carried out at steam bath temperature, and they were able to isolate a 28% yield of tetradehydroemetine hydrogen oxalate. Hazlett and McEwen (26) also reported using steam bath temperature for the same oxidation reaction, and were successful in obtaining 3.86 g. (28%) and 6.25 g. (32%) of isotetradehydroemetine and tetradehydroemetine hydrogen oxalate, respectively, starting with 20 g. of emetine hydrochloride heptahydrate.

In the present work, some of the first reactions which were carried out according to the procedure described by Hazlett and McEwen were found to yield a much larger proportion of isotetradehydroemetine to tetradehydroemetine than previously reported. In many cases no tetradehydroemetine hydrogen oxalate could be isolated, and the isotetradehydroemetine almost always crystallized out of the ether solution during extraction of the aqueous solution of the reaction products. It was believed that the reaction temperature might be an important factor; therefore, in all succeeding preparations of the two tetradehydro compounds the temperature was kept fairly constant and was recorded for each reaction. When different reaction temperatures were employed, it was found that the resulting proportion of the two isomers varied con-

siderably. Lower temperatures definitely favored the formation of isotetradehydroemetine, with a 90% yield being obtained in one case. Some of the results are shown in Table II.

Table II

Reaction Temp.	Reaction Time	Yield from 20 g. Em·2HCl·$7H_2O$ iso-TDE	TDE Hydrogen Ox.
55-60°	5 hrs.	6.8, 8.2 g.	0 g.
60-65	6	12.1	0
65-70	5	10.5	0
70-75	7	8.5	0.5
75-80	7	6.5	2.6
	5	6.1	2.2
100	4	4.1	4.0

The above results are not in agreement with the observations of Openshaw and Wood (19). These workers reported that they were unable to isolate isotetradehydroemetine after any of the numerous mercuric acetate oxidations which they had carried out. Furthermore, in some of their later experiments they were able to account for almost all of the original emetine as tetradehydroemetine hydrogen oxalate and rubremetinium chloride.

Several attempts were made to interconvert the two tetradehydro isomers. Each was subjected to various experimental conditions, including those of the mercuric acetate oxidation, but in no case could one isomer be converted to the other. Such results indicate that the two isomers do not arise from any process involving initial formation of one with subsequent partial conversion to the other, but that both must be formed independently.

When emetine-V hydrogen oxalate was first isolated after sodium and alcohol reduction of isotetradehydroemetine, it was thought that the compound might be racemic, since no rotation could be observed in aqueous solution. This brought up the possibility that isotetradehydroemetine might have been racemized under the basic reaction conditions before being reduced to emetine-V. Some attempts were therefore made to racemize isotetradehydroemetine by heating it in an alcoholic sodium ethoxide solution. The results of these experiments showed that a definite decrease in specific rotation did occur, but there was never complete loss of optical activity. In addition, a slight increase in the melting point of the recovered crystalline material was observed. It was therefore concluded that epimerization must be taking place at one of the asymmetric centers in isotetradehydroemetine. Table III summarizes the results of these experiments, in which approximately 2% alcoholic sodium ethoxide solution was used at the reflux temperature.

Table III

Time reacted	Specific rotation	Melting point
0 hrs.	-20.2	153-55°
2½	- - -	154-58
7	-10.2	159-65
30	- 5.6	158-61

A similar experiment was carried out with tetradehydroemetine, the free base being liberated from the hydrogen ox-

alate and refluxed for three hours in alcoholic sodium ethoxide solution. After reconversion of the base to tetradehydroemetine hydrogen oxalate, however, there was no change observed in either melting point or specific rotation.

In the case of isotetradehydroemetine, a definite decrease in specific rotation was also observed when the free base was recovered from the hydrogen oxalate salt.

Structures of tetradehydroemetine and isotetradehydroemetine:

Battersby and Openshaw (25), in discussing the properties of tetradehydroemetine hydrogen oxalate, reported that its ultraviolet absorption spectrum indicated the presence of two double bonds in conjugation with each other and with a benzene ring. On the basis of their interpretation it followed that position C_1, must be involved in one of the double bonds, since isoemetine was obtained on catalytic reduction of tetradehydroemetine hydrogen oxalate (19)(26). The second double bond would then occur at either position C_9-C_{10} or C_{10}-C_{11}.

The ultraviolet absorption spectrum of isotetradehydroemetine hydrogen oxalate was later found to be quite similar to that of tetradehydroemetine hydrogen oxalate (Fig. 4), indicating that there could be no major difference in the conjugated systems of the two isomers. Since emetine was produced by catalytic hydrogenation of both compounds (26), it would not be possible for them to be optical isomers, differing in

the configuration of a remaining asymmetric center. Hazlett and McEwen (26) considered two possibilities for their structures: (1) the isomers might be represented by structures LXXVII and LXXVIII, or (2) they could be geometrical isomers about the double bond at $C_{1'}$-C_{13}.

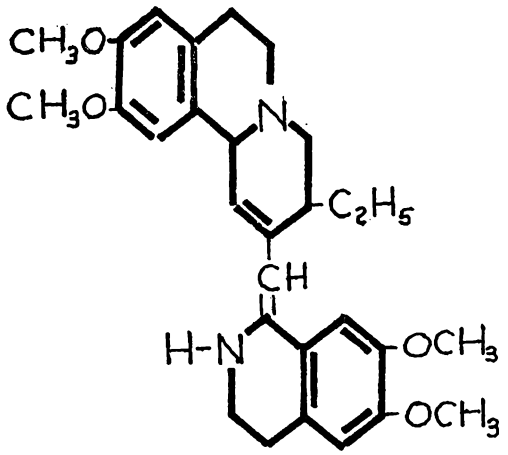
The recent work by Openshaw and Wood (19) has provided additional information which has a direct bearing on the structure of tetradehydroemetine. These workers found that the ultraviolet absorption spectrum of tetradehydroemetine hydrogen oxalate was almost identical with that of compound LXXIX, which is known to contain two 6,7-dimethoxy-3,4-dihydroisoquinoline nuclei. It was therefore believed that tetradehydroemetine hydrogen oxalate might have the structure LXXX. The free base would then have either structure LXXXI or LXXXII in which one or both of the double bonds have shifted to a position exocyclic with respect to the isoquinoline nuclei. Such a phenomenon has already been mentioned in the discussion of O-methylpsychotrine, and there is considerable evidence to show that such a shifting of double bonds can occur (32)(33).

The problem of assigning structures to the two tetradehydro isomers was somewhat complicated by further spectral studies. Although the ultraviolet absorption spectra of tetradehydroemetine hydrogen oxalate and isotetradehydroemetine hydrogen oxalate are almost identical, it has been found that there is very little similarity in the spectra of the free bases (Fig. 5). There must then be a distinct difference in

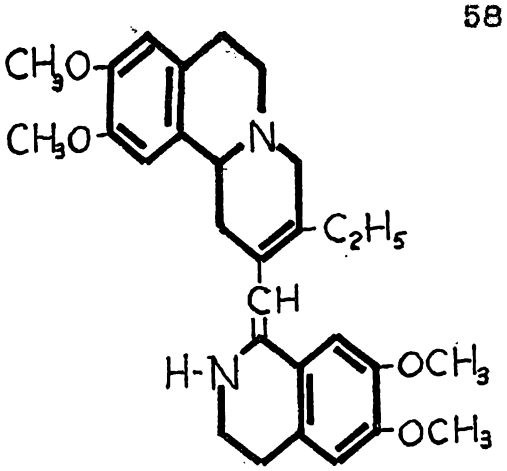
the conjugated systems of the two bases, but the olefinic linkages must be capable of shifting into similar types of conjugation on conversion to the hydrogen oxalates.

Bills and Noller (32), who studied the ultraviolet absorption spectra of some 3,4-dihydroisoquinoline derivatives, have reported some information which has been found useful in interpreting the results of the spectral studies made on tetradehydroemetine and isotetradehydroemetine. They obtained the spectra of 1-methyl- (LXXXIII), 1-benzyl- (LXXXIV), and 1-(α-picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (LXXXV). It was found that the spectra of the 1-methyl and 1-benzyl derivatives were almost identical, but that of the 1-(α-picolyl) derivative was somewhat different from the other two. (Fig. 6). Since its peaks occurred at longer wavelengths, indicating a greater degree of conjugation, it was concluded that the 1-(α-picolyl) derivative must actually have the exocyclic structure LXXXVI. The hydrochlorides of the three compounds were found to have quite similar spectra, however, (Fig.7) suggesting that on formation of the hydrochloride, the double bond in the 1-(α-picolyl) derivative must shift back to the endocyclic position, giving all three hydrochlorides a similar conjugated system as shown by structures LXXXVII, LXXXVIII, and LXXXIX.

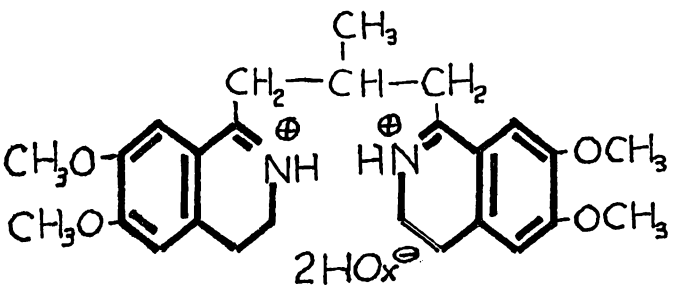
It should be noted that a considerable shift in absorption peaks occurs in going from the free base to the hydrochloride in the case of the 1-methyl and 1-benzyl derivatives. Bills and Noller have attributed this to the fact that a formal



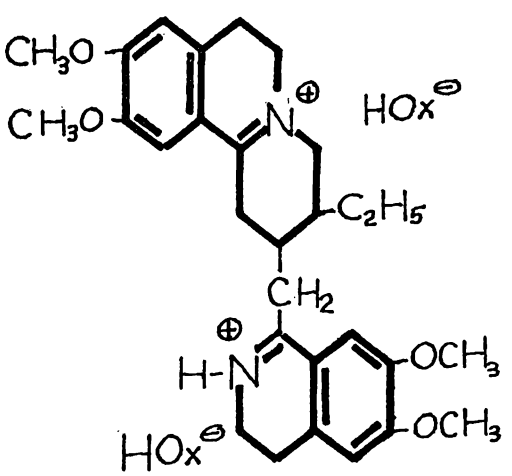
LXXVII



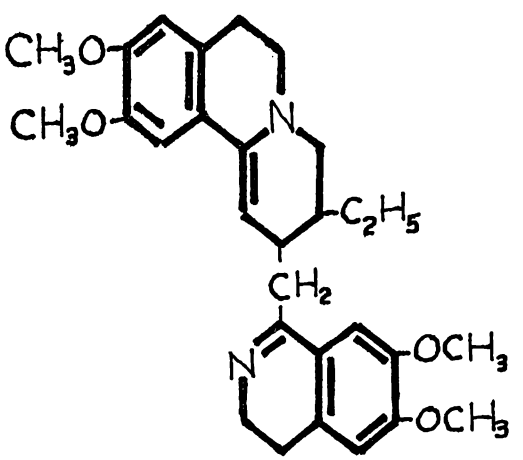
LXXVIII



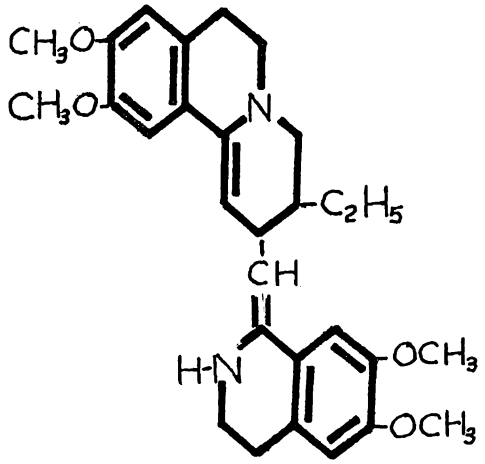
LXXIX



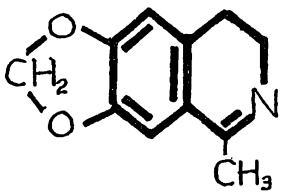
LXXX



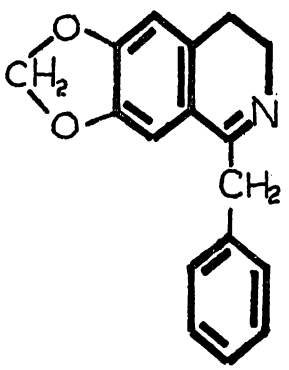
LXXXI



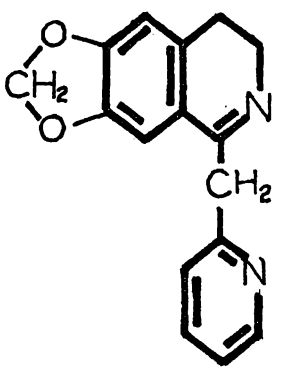
LXXXII



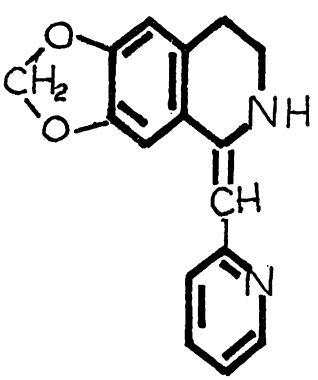
LXXXIII



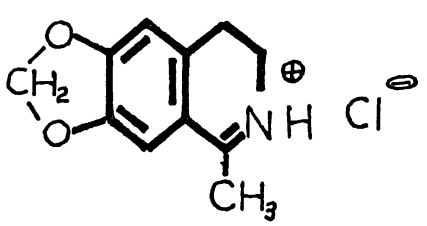
LXXXIV



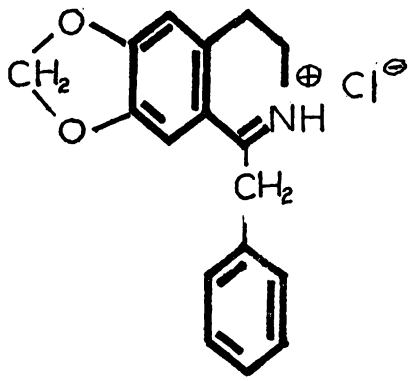
LXXXV



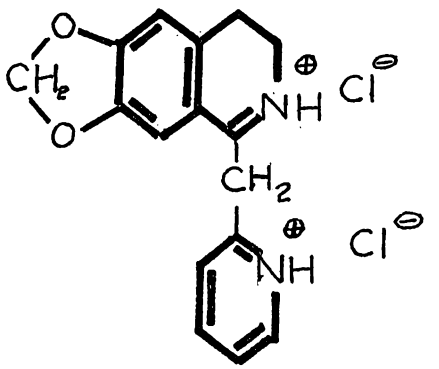
LXXXVI



LXXXVII

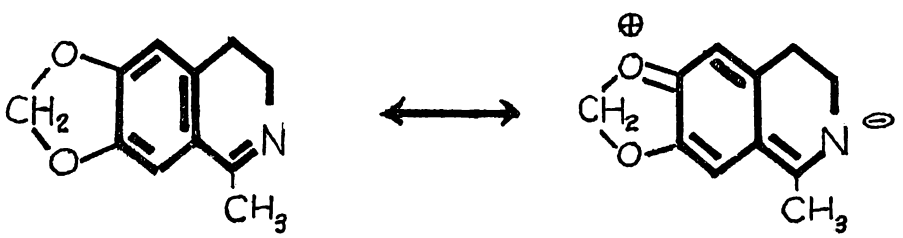


LXXXVIII



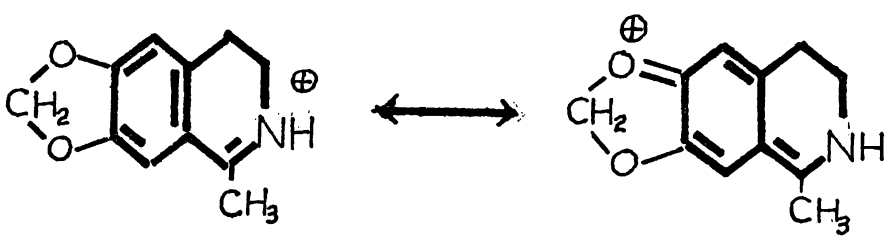
LXXXIX

charge separation would be involved in the resonance structures of the free base (LXXXIII-a), while this would not be true in the case of the hydrochloride, which should therefore absorb light of longer wavelength (lower energy).



LXXXIII

LXXXIII - a



LXXXVII

LXXXVII - a

The ultraviolet absorption spectra of tetradehydroemetine hydrogen oxalate and isotetradehydroemetine hydrogen oxalate are quite similar to those of the three hydrochlorides studied by Bills and Noller. This supports the possibility that tetradehydroemetine hydrogen oxalate might have the structure LXXX porposed by Openshaw and Wood. The situation with respect to the structure of isotetradehydroemetine, however, is not clarified by this observation. Since the spectra of the free bases possess little similarity, it follows either that some fundamental difference must exist in the positions of the double bonds in the two hydrogen oxalates, at the same time the types of conjugation being similar in the two compounds, or else a complex isomerization occurs to give geometrically isomeric hydrogen oxalate salts.

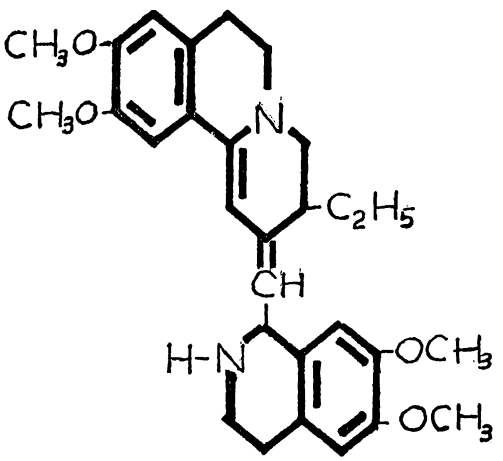
One possibility which would be consistent with the first argument is that isotetradehydroemetine have the structure XC, with isotetradehydroemetine hydrogen oxalate being represented by XCI. Structure XCI would be expected to have an ultraviolet absorption spectrum similar to that of LXXX since the only type of conjugation present in the molecule would be the $\rangle C = \overset{\oplus}{N}\langle$ group in conjugation with a benzene ring. The extra conjugated double bonds in structure XC could account for the absorption peaks of isotetradehydroemetine lying further toward the visible than those of tetradehydroemetine (LXXXI or LXXXII). In addition, the spectrum of isotetradehydroemetine is somewhat similar to that of LXXXVI except that the two peaks do not

lie as far toward the visible. This would be expected since fewer double bonds are in conjugation with a benzene ring.

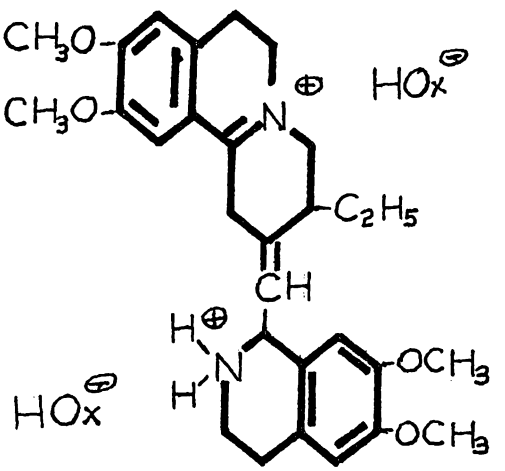
The infrared absorption spectra of tetradehydroemetine and isotetradehydroemetine have also furnished some significant information. The spectra of the two free bases have been found to be similar in many respects (Fig. 8). There is, however, one notable difference. A moderately strong peak occurring at 1570 cm^{-1} in the case of tetradehydroemetine is not found in the spectrum of isotetradehydroemetine. This peak lies in a region where absorption due to a ring $>C = N-$ grouping is known to occur (34). Although this observation does not supply absolute proof that such a group is present in the molecule, it can be used as evidence strongly in favor of structure LXXXI for tetradehydroemetine.

Although it does not appear in Fig. 8, the spectrum of isotetradehydroemetine at a higher concentration in chloroform solution shows a definite peak at 3560 cm^{-1}, which lies in the N-H absorption region. The presence of such a peak would be expected for structure XC. Further argument for the presence of an N-H group in isotetradehydroemetine is the fact that the molecule possesses one active hydrogen as shown in a Zerewitinoff determination.

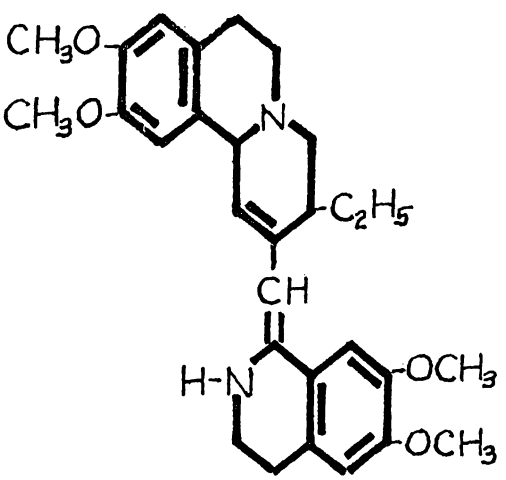
There is another possible structure for isotetradehydroemetine which is consistent with all the arguments which have so far been presented. Structures XCII and XCIII for isotetradehydroemetine and isotetradehydroemetine hydrogen oxalate,



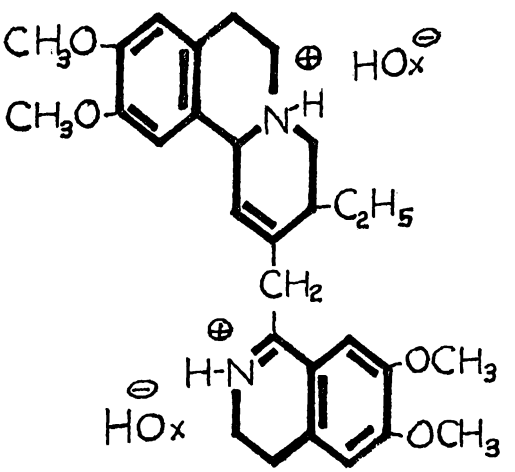
XC



XCI



XCII



XCIII

respectively, would be possibilities in view of the interpretations made from their spectra. However, there are some experimental results which seem to favor XC and XCI.

First, the fact that no isoemetine has been obtained from either catalytic hydrogenation or sodium and alcohol reduction of isotetradehydroemetine strongly indicates that C_1, is not involved in a double bond. Isoemetine is formed quite readily from reduction of both O-methylpsychotrine and tetradehydroemetine hydrogen oxalate, and it seems likely that it would also be formed in an appreciable amount by reduction of isotetradehydroemetine if a double bond were present at C_1,- C_{13}.

A second argument in favor of XC arises from the fact that no O-methylpsychotrine is obtained on mercuric acetate oxidation of emetine. The first double bond formed in such a dehydrogenation would most likely be in conjugation with one of the benzene rings. If it were formed at C_1,- N_2, or C_1,-C_{13}, it is quite probable that some O-methylpsychotrine would be isolated from the reaction mixture, especially at the milder conditions. The fact that none is obtained indicates that the first double bond is probably formed at C_1 - N_2 or C_1-C_9, and this would not be consistent with structure XCII.

The epimerization of isotetradehydroemetine in sodium ethoxide solution would be expected of XC. The removal of a proton from C_1, would leave an anion which would be stabilized by resonance. The epimerization which occurs on formation

of the hydrogen oxalate, however, cannot be explained by any means consistent with the interpretation of the spectra of isotetradehydroemetine and isotetradehydroemetine hydrogen oxalate. It is possible that the double bond at C_{10}-C_{13} in isotetradehydroemetine could shift to the conjugated position at C_{11}-C_{13} on formation of a salt, but under such circumstances the ultraviolet spectra of tetradehydroemetine hydrogen oxalate and isotetradehydroemetine hydrogen oxalate would not be similar, since different types of conjugated systems would be present in the two molecules. Furthermore, it seems likely that it would be possible to convert isotetradehydroemetine into tetradehydroemetine if such a shift were to occur.

It must also be noted that structure LXXXI for tetradehydroemetine is not obviously capable of explaining the formation of a total of five different diastereoisomers of emetine by the two methods of reduction which have been used. Since only two asymmetric centers are created by saturation of the two double bonds, it should be possible to obtain only four diastereoisomers. Also, it has been found that no change takes place in tetradehydroemetine on refluxing in alcoholic sodium ethoxide solution. During a sodium and alcohol reduction the reaction conditions are somewhat more vigorous, however, and it is possible that some form of isomerization might take place.

FURTHER INVESTIGATION OF DEHYDROHALORUBREMETINE

Hazlett and McEwen (26), on studying the effect of alkali on rubremetinium chloride, found that heating the substance with an aqueous alcoholic solution of sodium hydroxide gave an unstable crystalline product, $C_{29}H_{32}O_4N_2$, which no longer contained chlorine and was believed to result from an overall dehydrochlorination reaction. The new compound, called dehydrohalorubremetine, failed to give back rubremetinium chloride on being heated with hydrochloric acid solution. On low pressure catalytic hydrogenation, the crude material readily absorbed two moles of hydrogen, and from the mixture of products, a pure crystalline, optically inactive substance was obtained by fractional crystallization. The compound was called tetrahydrodehydrohalorubremetine, although it was admitted that the apparent absorption of two moles of hydrogen did not necessarily signify that the crystalline product obtained contained four hydrogen atoms more than dehydrohalorubremetine, particularly since the hydrogenation was carried out on crude material.

The hydrogenation product would not form an acyl derivative with either benzoyl chloride or p-toluenesulfonyl chloride. Its ultraviolet absorption spectrum was found to be almost identical with that of isotetrahydrodehydroemetine, and it was considered possible that tetrahydordehydrohalorubremetine might actually be racemic isotetrahydrodehydroemetine.

Openshaw and Wood (19), in agreement with their arguments concerning the structure of rubremetinium salts, considered the compound to be racemic dihydrorubremetine. They further believed that dehydrohalorubremetine possessed the structure XCIV which contains no centers of asymmetry.

Tietz and McEwen (29) have repeated the hydrogenation of dehydrohalorubremetine and found the crude material to absorb 1.8 moles of hydrogen. They were able to isolate, in addition to the racemic tetrahydrodehydrohalorubremetine, a small amount of a lower melting crystalline base which possessed a definite dextrorotation. Both compounds analyzed correctly for $C_{29}H_{34}N_2O_4$, had identical infrared absorption spectra and similar ultraviolet spectra, and both gave an analysis for slightly more than one terminal methyl group. It was believed that the two compounds were the optically active and inactive forms of the same substance.

Tietz and McEwen (29) have further pointed out the possibility that dehydrohalorubremetine is a Hofmann degradation product of the rubremetinium cation, as evidenced by three facts: (1) There is a considerable amount of racemization during formation of dehydrohalorubremetine. (2) In the case of the racemic tetrahydrodehydrohalorubremetine, one active hydrogen was found by a Zerewitinoff determination. (3) Although both racemic and active hydrogenation products gave a test for slightly more than one terminal methyl group, it is known that such a determination usually gives considerably

less than the theoretical value. Therefore, it appears that the two substances possess two C-CH_3 groups.

It was noted, however, that the hydrogenation data was not consistent with a Hofmann degradation product. On the basis of Woodward's structure (LXXIII) for the rubremetinium cation, ring opening might be expected to occur at C_3-N_2, resulting in XCV as the structure for dehydrohalorubremetine. This would be expected to add three moles of hydrogen in a low pressure catalytic hydrogenation to give XCVI.

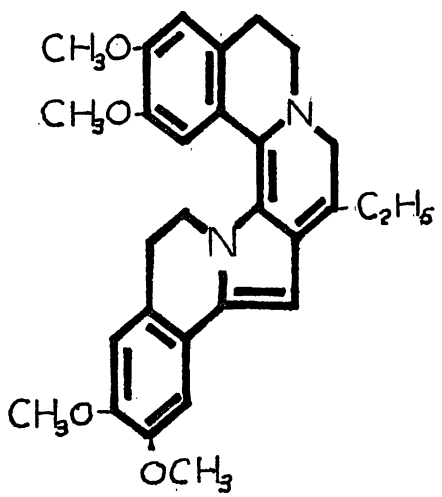
The hydrogenation of dehydrohalorubremetine has been studied further in order to determine whether the compound might take up three moles of hydrogen under different conditions from those used by previous workers. It was considered that an acid medium might be more favorable for the hydrogenation of such a substance than the neutral alcohol solution used previously. When a solution of dehydrohalorubremetine was hydrogenated in glacial acetic acid solution, a considerable amount of tarry material was formed, and the hydrogenation data was not considered to be significant. However, when an alcohol solution of dehydrohalorubremetine was kept only slightly acidic by dropwise addition of acetic acid during the hydrogenation, it was found that 2.7 moles of hydrogen were absorbed, and over half of the starting material was accounted for as either the active or racemic "tetrahydrodehydrohalorubremetine". This result strongly indicates that the hydrogenation product of dehydrohalorubremetine is actually

a hexahydro derivative, and that dehydrohalorubremetine itself must arise from a Hofmann degradation reaction of the rubremetinium cation. As a result, this observation provides further evidence for Woodward's proposed structure.

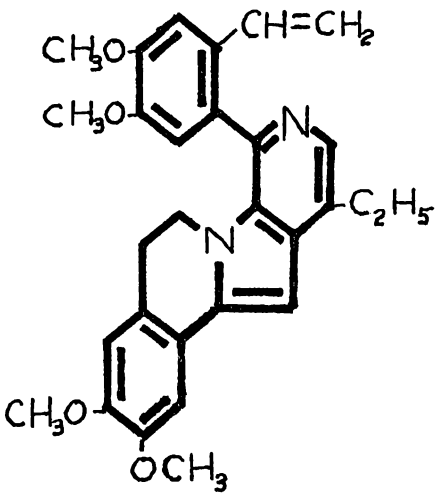
Additional evidence for the occurrence of a ring opening reaction has been supplied by an oxidation study on dehydrohalorubremetine. Oxidation of the compound with an acidic permanganate solution resulted in the production of an appreciable amount of formic acid, identified as the p-bromophenacyl ester. The formation of formic acid indicates the presence of a terminal methylene group in dehydrohalorubremetine.

Although there is strong evidence that a Hofmann degradation reaction does take place in the formation of dehydrohalorubremetine, it has not yet been possible to determine conclusively whether the ring opening occurs at C_3-N_2 or $C_{3'}$-$N_{2'}$, since a break at $C_{3'}$-$N_{2'}$ would result in formation of XCVII, which would also take up three moles of hydrogen to give XCVIII, and would give formic acid on oxidation. If opening occurred at C_3-N_2, it should be possible to prepare an acyl derivative of the hydrogenation product (XCV), providing that the acyl group is not so large that steric hindrance would prevent its formation. However, no such derivative could be formed from either the racemic or optically active "tetrahydrodehydrohalorubremetine", even on using acetyl chloride as the acylating agent. In all attempts at acylation

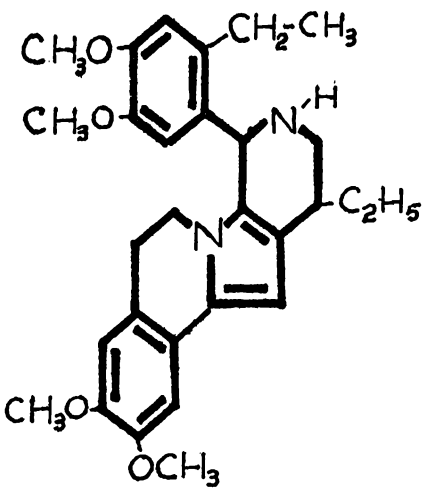
the starting material was recovered unchanged. Although this strongly points to a ring opening at $C_{3'}$- $N_{2'}$, it cannot be considered as conclusive evidence, and further information will have to be obtained in order to definitely distinguish between the two possibilities.



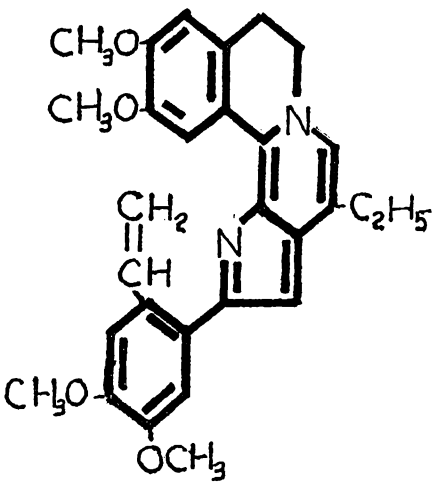
XCIV



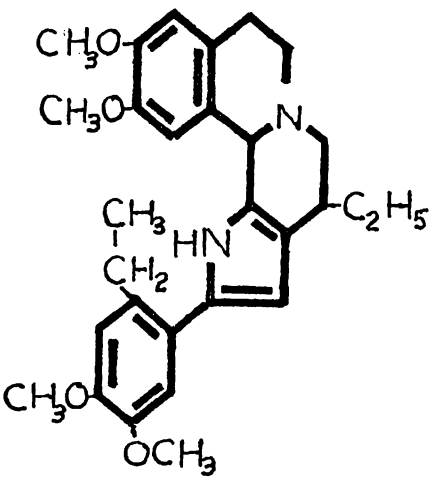
XCV



XCVI



XCVII



XCVIII

Fig. 4. Ultraviolet absorption spectra:

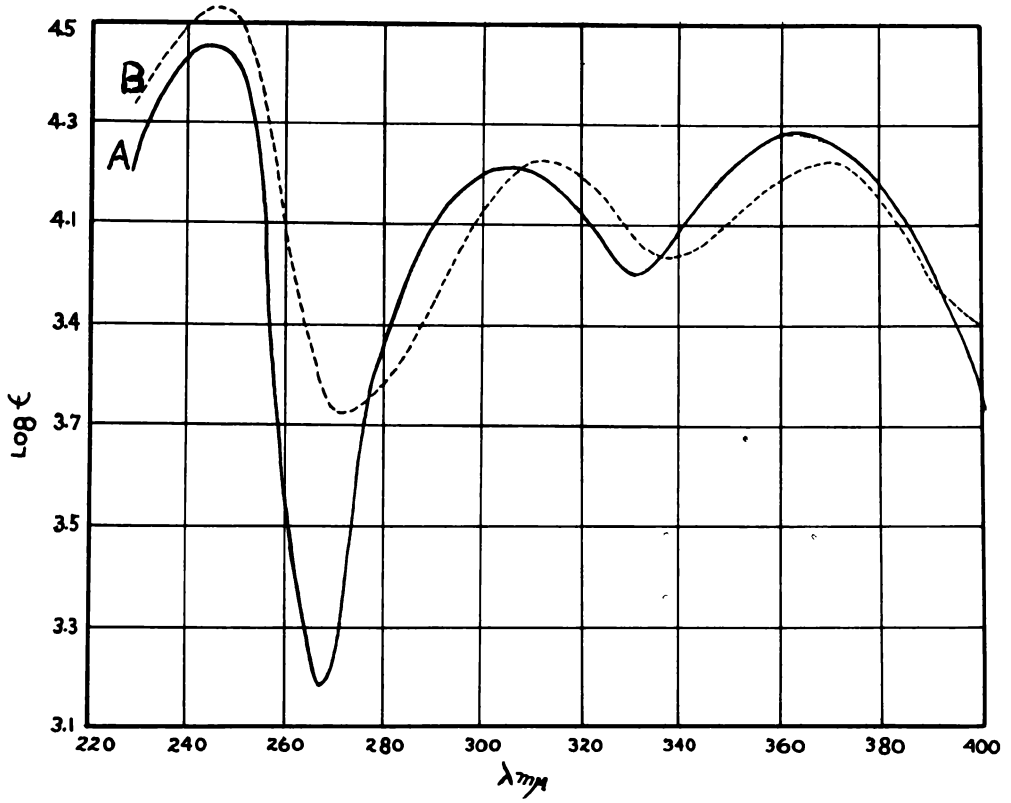
A. Isotetradehydroemetine hydrogen oxalate in water.

B. Tetradehydroemetine hydrogen oxalate in water.

Fig. 5. Ultraviolet absorption spectra:

A. Tetradehydroemetine in alcohol.

B. Isotetradehydroemetine in alcohol.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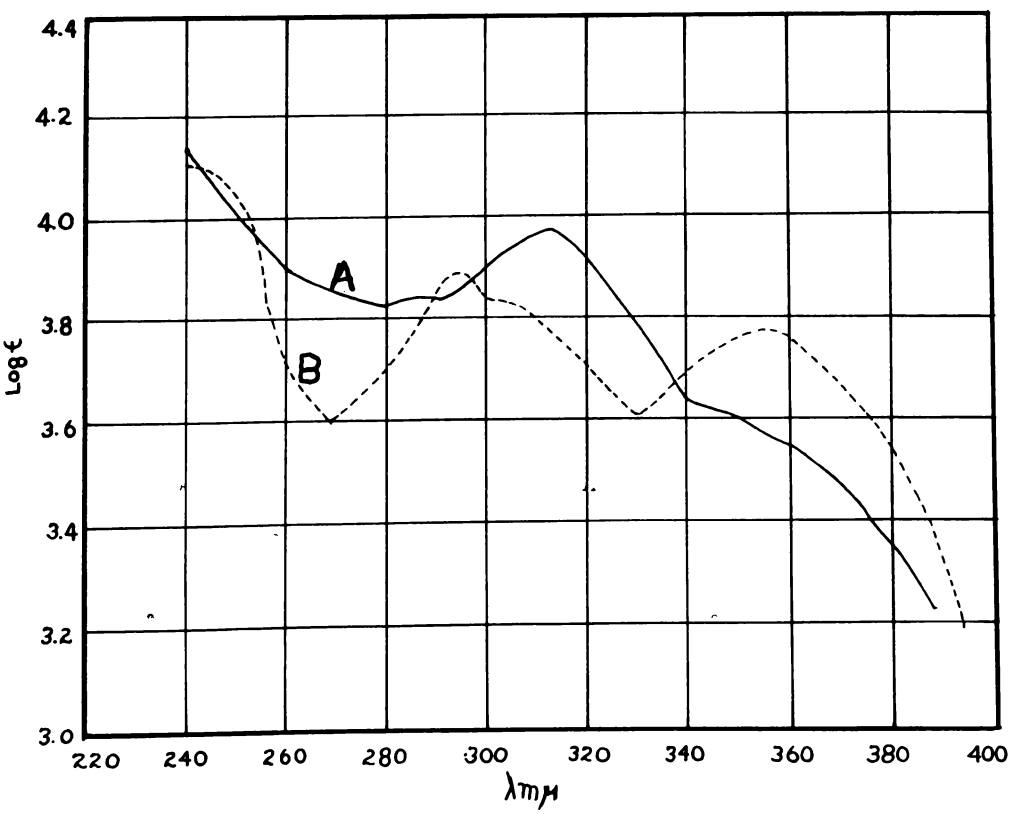
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λmμ

Fig. 6. Ultraviolet absorption spectra:

A. Structure LXXXIII in alcohol.

B. Structure LXXXIV in alcohol.

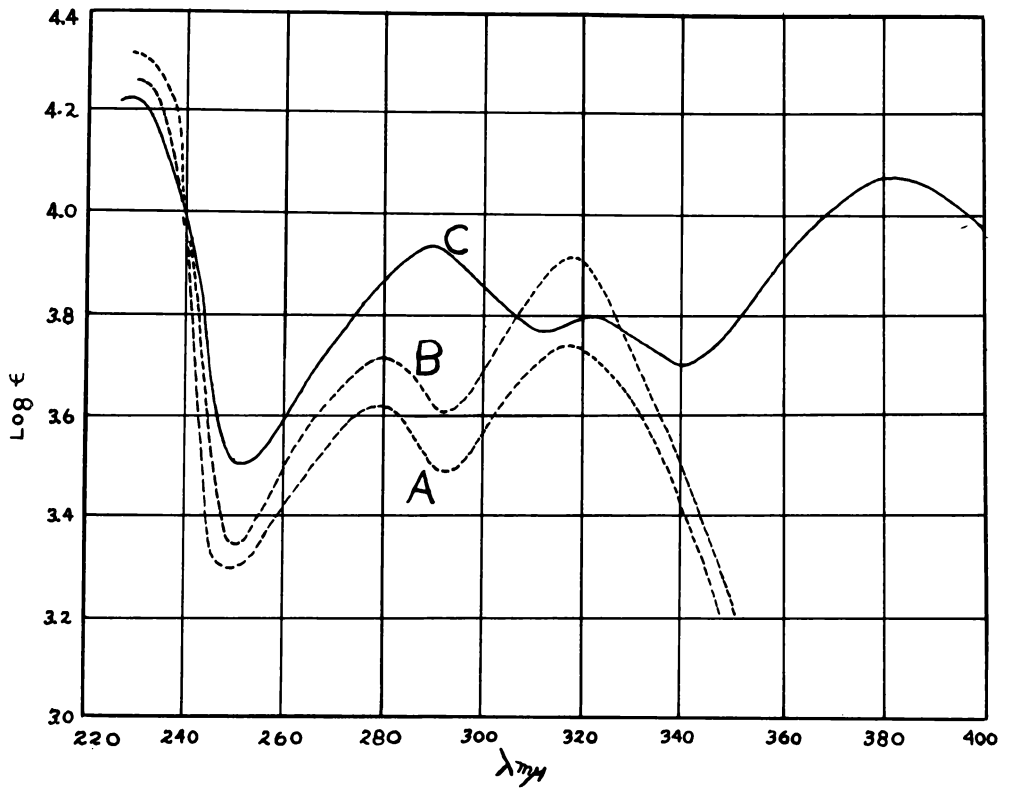
C. Structure LXXXVI in alcohol.

Fig. 7. Ultraviolet absorption spectra:

A. Structure LXXXVII in alcohol.

B. Structure LXXXVIII in alcohol.

C. Structure LXXXIX in alcohol.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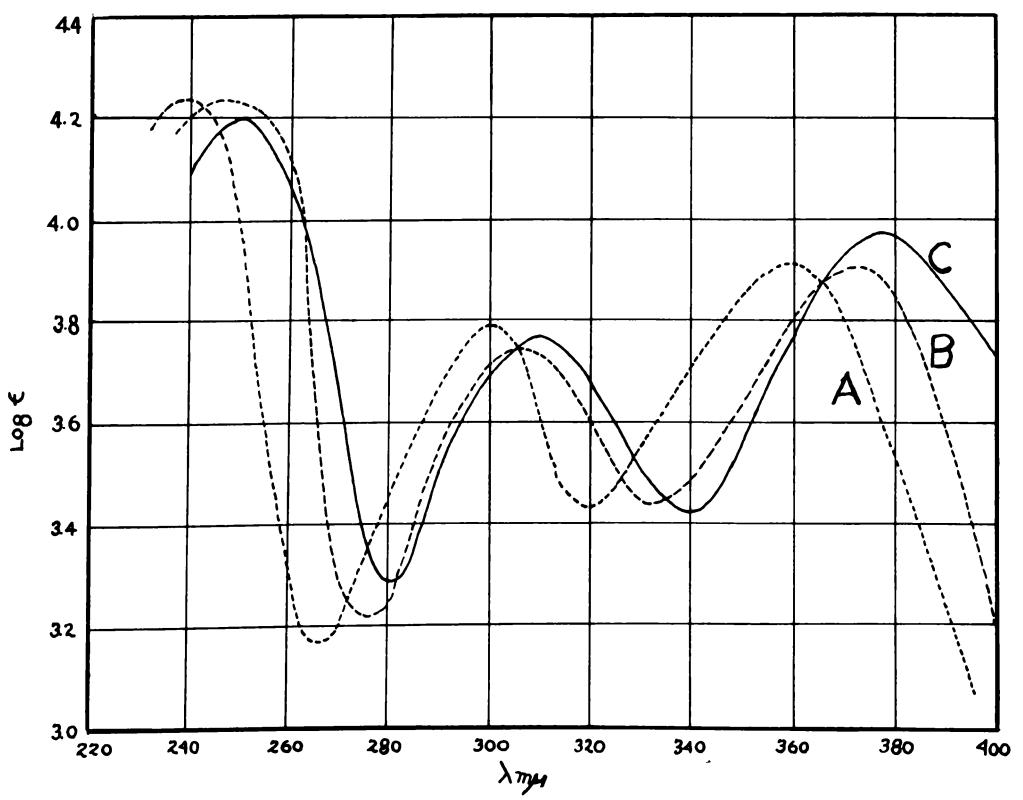
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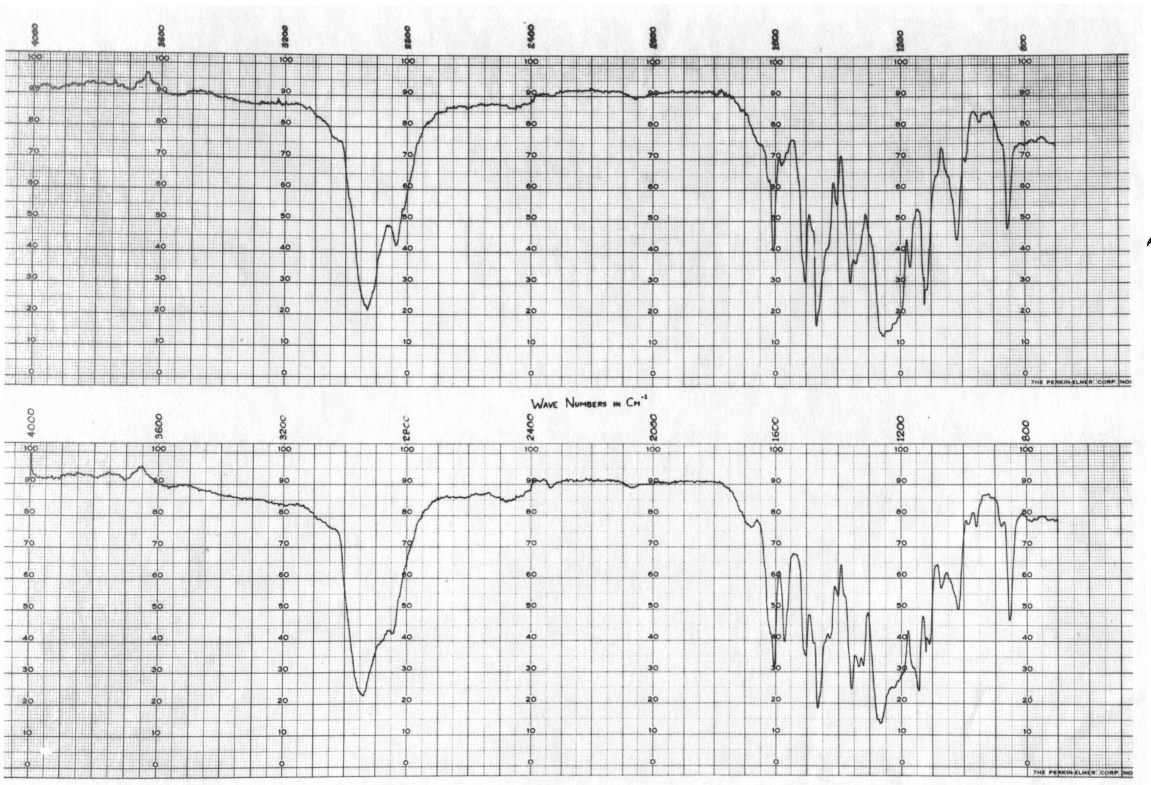
Fig. 8. Infrared absorption spectra:

A. Isotetradehydroemetine in chloroform.

B. Tetradehydroemetine in chloroform.


A
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WAVE NUMBERS IN CM⁻¹
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1200
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THE PERKIN-ELMER CORP. INC.

EXPERIMENTAL

Reduction of Isotetradehydroemetine with 8 Equivalents of Sodium and Ethanol:

To 2.40 g. of isotetradehydroemetine, prepared according to the method of Hazlett and McEwen (26), dissolved in 25 cc. of hot absolute ethanol, was added 1.00 g. of finely divided sodium. The mixture was refluxed until all the sodium had been consumed, then an additional 25cc. of ethanol was added. The solution was cooled and unreacted isotetradehydroemetine (1.2 g.) crystallized and was filtered from the mixture. About 20 cc. of water was added to the filtrate, which was then concentrated to 10 cc. to insure complete removal of the alcohol. The liberated base was taken up in five 5 cc. portions of ether and the combined ether extracts dried over anhydrous potassium carbonate. Evaporation of the ether left a yellow gum which was dissolved in hot ethanolic oxalic acid solution. On cooling, colorless crystals of emetine-V hydrogen oxalate readily formed, 0.30 g., m.p. 201-205°. Recrystallization from ethanol raised the m.p. to 206-207°. No rotation could be observed (c = 1.9 in water).*

Anal: Calculated for $C_{29}H_{40}N_2O_4 \cdot 2C_2H_2O_4$: C, 59.98; H, 6.71; N, 4.24. Found: C, 59.91, 59.77; H, 6.92, 6.92; N, 3.98, 4.13.

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* On one occasion a small positive rotation was observed with a more concentrated solution. However, after further recrystallization the substance did not give an observable rotation, indicating that the previously observed rotation was due to impurities.

Emetine-V was recovered unchanged after attempted catalytic hydrogenation over platinum. This proves that both the ethylenic linkages of isotetradehydroemetine were saturated in the sodium and ethanol reduction.

Emetine-V Hydrobromide:

A solution of 1.2 g. emetine-V hydrogen oxalate in water was made basic by addition of 10% sodium hydroxide solution. The liberated base was taken up in ether and the ether extract dried over anhydrous potassium carbonate. Evaporation of the ether left a clear gum which was dissolved in 5 cc. of 5% hydrobromic acid. After long standing, white crystals of emetine-V hydrobromide formed (0.35 g.). On concentration of the filtrate to 5 cc, an additional 0.12 g. was obtained. The m.p., after two recrystallizations from water, was 221-224°. No rotation could be observed (c=1.00 in water).

Anal: An air-dried sample lost 8.96% of its weight on being heated in vacuo. $C_{29}H_{40}O_4N_2 \cdot 2HBr \cdot 3\frac{1}{2}H_2O$ requires 8.94%. Calculated for $C_{29}H_{40}O_4N_2 \cdot 2HBr \cdot 3\frac{1}{2}H_2O$: N, 3.97; Br, 22.66. Found: N, 4.35; Br, 23.25.*

Benzoylemetine-V Hydrochloride:

A solution of 2.0 g. of emetine-V hydrogen oxalate in

---

* The carbon and hydrogen analyses were carried out on a different sample of emetine-V hydrobromide, and the results indicate that the state of hydration was different in this case.

Calculated for $C_{29}H_{40}O_4N_2 \cdot 2HBr \cdot 1\frac{1}{2}H_2O$: C, 52.0; H, 6.77. Found: C, 52.27; H, 6.85.

water was made basic with 10% sodium hydroxide solution. The mixture was extracted with ether, and the combined extracts were thoroughly dried over two successive portions of anhydrous potassium carbonate. The ether solution was concentrated to about 60 cc. and 1.3 g. of freshly purified benzoic anhydride was added. The mixture was refluxed for 3 hours, then concentrated to about 25 cc. and refluxing continued for an additional 2 hours. After addition of 20 cc. of ether, the solution was washed with dilute hydrochloric acid. The orange-yellow gummy precipitate which immediately formed was removed and washed thoroughly with ether and dilute hydrochloric acid. On drying, the gum crystallized to give 1.1 g. benzoylemetine-V hydrochloride, m.p. 190-195° with previous sintering, $[\alpha]_D^{23} = -14.0°$ (c = 1.64 in chloroform). Concentration of the ether solution afforded an additional 0.25 g. The total yield amounted to 65%.

Anal: An air-dried sample lost 2.97% of its weight on being heated in vacuo at 100°. $C_{36}H_{44}O_5N_2 \cdot HCl \cdot H_2O$ requires 2.82%. Calculated for $C_{36}H_{44}O_5N_2 \cdot HCl \cdot H_2O$: N, 4.39; Cl, 5.56. Found: N, 4.33; Cl, 5.86.

Oxidation of Emetine-V Hydrogen Oxalate with Excess Mercuric Acetate:

A solution of 0.125 g. emetine-V hydrogen oxalate in 2.0 cc. of water was mixed with a solution of 0.5 g. mercuric acetate, 0.03 g. potassium acetate, and 0.2 cc. acetic acid

in 3.0 cc. of water, and the mixture heated on a steam bath for one hour. An additional 0.2 g. mercuric acetate was added and heating continued for one hour. The cooled solution was filtered and the precipitate washed with water. The combined filtrate and washings were heated to boiling and treated with hydrogen sulfide. After filtration, the precipitate was washed thoroughly with boiling water and alcohol, and the combined filtrate and washings concentrated under reduced pressure to about 2 cc. Five drops of concentrated hydrobromic acid was added and rubremetinium bromide (0.035 g.) crystallized on standing. After two recrystallizations from water-acetone it showed a m.p. of 180-185°. Battersby and Openshaw (20) reported 195-205°. The ultraviolet and visible spectrum was identical with that reported by Battersby and Openshaw.

Reduction of Isotetradehydroemetine with Excess Sodium and Ethanol:*

To 10.0 g. of isotetradehydroemetine dissolved in 150 cc. of absolute ethanol was added finely divided sodium in small portions until it no longer reacted. An additional 60 cc. of absolute ethanol was added and the solution heated to reflux temperature. More sodium was added in small amounts for about 2½ hours. To the warm reaction mixture was added 50 cc. of

*The same procedure was used for all reactions indicated in Table I, with the reaction conditions varied as shown.

95% alcohol, followed by addition of 200 cc. of water. The solution was concentrated under reduced pressure to about 100 cc., and the liberated bases were taken up in ether. The combined ether extracts were dried over anhydrous potassium carbonate and evaporated, leaving a yellow gum. This was dissolved in hot ethanolic oxalic acid solution, and, on cooling to room temperature, emetine-V hydrogen oxalate (5.1 g., 38%), m.p. 205-207°, crystallized and was filtered from the solution.

The ethanol mother liquor from the emetine-V hydrogen oxalate was placed in an ice-salt bath and a gummy precipitate formed. The mother liquor was decanted and the precipitate recrystallized twice from ethanol. On filtration the crystals readily turned to a gum, but solidified again on drying <u>in vacuo</u>; 2.8 g. of the hydrogen oxalate was obtained m.p. 157-184°, $[\alpha]_D^{28} = +27^\circ$ (c = 1.26 in water).

A solution of 2.0 g. of the hydrogen oxalate in water was made basic with 10% sodium hydroxide solution. The base was taken up in ether and the combined extracts dried over anhydrous potassium carbonate. Evaporation of the ether left a red gum which was dissolved in 20 cc. of hot 5% hydrobromic acid solution. The gummy precipitate which readily formed on cooling was recrystallized from water giving 0.30 g. of white crystals, m.p. 212-217°. After an additional recrystallization from water the compound showed a m.p. of 214-217°, $[\alpha]_D^{24} = +7.1^\circ$ (c = 1.83 in water). These values correspond to those found for authentic emetine-IV hydrobromide (see below).

Next, 1.0 g. of the hydrogen oxalate was treated with excess mercuric acetate using the same procedure that was used for emetine-V hydrogen oxalate. Treatment of the resulting aqueous solution with concentrated hydrochloric acid gave 0.1 g. rubremetinium chloride which showed a m.p. behavior similar to that described by Battersby and Openshaw (25).

Emetine-IV Hydrobromide:

A solution of 0.30 g. of emetine-IV hydrogen oxalate, prepared according to the procedure used by Hazlett and McEwen (26), was made basic with 5% sodium hydroxide solution. The base was extracted with ether and the extracts dried over anhydrous potassium carbonate. Evaporation of the ether left a clear gum, which was dissolved in hot 3% hydrobromic acid. The gummy precipitate which first formed was recrystallized twice from water giving 0.07 g. colorless crystals of emetine-IV hydrobromide, m.p. 214-219°, $[\alpha]_D^{28} = +8.0°$ (c = 1.04 in water). On concentration of the filtrate an additional 0.05 g. was obtained.

Anal: An air-dried sample lost 11.42% of its weight on being heated in vacuo at 110°. $C_{29}H_{40}O_4N_2 \cdot 2HBr \cdot 4\frac{1}{2}H_2O$ requires 11.20%. Calculated for $C_{29}H_{40}O_4N_2 \cdot 2HBr \cdot 4\frac{1}{2}H_2O$: N, 3.87; Br, 22.09. Found: N, 4.05; Br, 22.1.*

*The carbon and hydrogen analyses were carried out at a different time from the other analyses, and the results indicate that the hydrobromide had a different state of hydration. Calculated for $C_{29}H_{40}O_4N_2 \cdot 2HBr \cdot \frac{1}{2}H_2O$: C, 53.45; H, 6.65. Found: C, 53.37; H, 7.01.

Oxidation of Emetine-V Hydrogen Oxalate with 4 Equivalents of Mercuric Acetate:

A solution of 4.0 g. emetine-V hydrogen oxalate in 50 cc. of water was treated dropwise with a solution of 7.8 g. mercuric acetate, 0.5 g. potassium acetate, and 5.0 cc. glacial acetic acid in 100 cc. of water for 1½ hours at about 70° on a steam bath. The mixture was heated for an additional 15 minutes after addition of mercuric acetate was complete. The cooled solution was filtered and the precipitate of mercurous acetate washed thoroughly with water. The filtrate was treated with hydrogen sulfide and the insoluble sulfides removed by filtration and washed with hot water. The combined filtrate and washings were made basic with 10% sodium hydroxide solution, and the mixture extracted with ether. The ether solution was dried over anhydrous potassium carbonate and evaporated, leaving a red gum which was dissolved in 5% ethanolic oxalic acid. No precipitate formed, even on long standing or cooling in dry ice-acetone. The ethanol solution was evaporated to dryness under reduced pressure. The residue was dissolved in water and the solution made basic with 10% sodium hydroxide solution. The free base was isolated as before and dissolved in hot 5% hydrobromic acid. A gummy precipitate formed on standing, but it could not be converted to a crystalline form, even after attempted recrystallization from water.

One gram of the crude base was dissolved in 25 cc. of 50% acetic acid solution and hydrogenated at atmospheric

pressure over 0.1 g. platinum oxide catalyst; 71 cc. (STP) (0.93 moles) of hydrogen was absorbed in one hour. The catalyst was filtered from the reaction mixture and washed with water. The combined filtrate and washings were made basic with 10% sodium hydroxide solution and extracted with ether. The ether solution was dried over anhydrous potassium carbonate and evaporated, leaving a yellow gum which was dissolved in 5% ethanolic oxalic acid. Emetine-V hydrogen oxalate (0.25 g.) m.p. 207° crystallized and was filtered from the solution.

The mother liquor was concentrated, but no precipitate formed on cooling. The base was recovered as before and dissolved in hot 5% hydrobromic acid. Emetine-IV hydrobromide (0.12 g.), m.p. 211-217° was obtained. A mixed melting point determination with an authentic sample of emetine-IV hydrobromide showed no depression.

Oxidation of Emetine-IV Hydrogen Oxalate with Excess Mercuric Acetate:

One gram of emetine-IV hydrogen oxalate was oxidized with mercuric acetate according to the same procedure which was used for emetine-V hydrogen oxalate. Treatment of an aqueous solution of the product with concentrated hydrochloric acid gave 0.1 g. of rubremetinium chloride.

Oxidation of Neoemetine Hydrogen Oxalate with Excess Mercuric Acetate:

A solution of 0.25 g. neoemetine hydrogen oxalate in 5 cc. of water was treated with a solution of 1.0 g. mercuric acetate, 0.05 g. potassium acetate, and 5.0 cc. glacial acetic acid in 10 cc. of water, and the mixture refluxed for two hours. An additional 0.5 g. of mercuric acetate was added and refluxing was continued one hour. The reaction mixture was worked up using the same procedure as for the oxidation of emetine-IV hydrogen oxalate. Rubremetinium chloride (0.06 g.) was obtained.

Attempted Benzoylation of Emetine-IV:

The base recovered from 1.2 g. of emetine-IV hydrogen oxalate was reacted with 0.8 g. of benzoic anhydride according to the procedure used by Pyman (3) for the benzoylation of isoemetine. On treatment of the resulting ether solution with dilute hydrochloric acid, a gummy material formed in a manner similar to the formation of benzoylemetine-V hydrochloride. The substance hardened on drying, but could not be purified. It showed a definite dextrorotation in chloroform solution.

Attempted Benzoylation of Neoemetine:

The base recovered from 0.3 g. of neoemetine hydrogen oxalate was reacted with 0.24 g. benzoic anhydride, using Pyman's method of benzoylation (3). No crystalline material

could be isolated from the ether solution after treatment with dilute hydrochloric acid. The aqueous layer was made basic with 10% sodium hydroxide solution and extracted with ether. After drying over anhydrous potassium carbonate, the ether was evaporated and the resulting gum dissolved in ethanolic oxalic acid. Neoemetine hydrogen oxalate, (0.15 g.) m.p. 155-157°, formed immediately.

Reduction of Tetradehydroemetine with Excess Sodium and Ethanol:

Tetradehydroemetine was liberated from an aqueous solution of 2.0 g. tetradehydroemetine hydrogen oxalate by treatment with 5% sodium hydroxide solution, then extracted with ether. The combined extracts were dried over anhydrous potassium carbonate and the bum remaining after evaporation of the ether was dissolved in 40 cc. of absolute ethanol. Finely divided sodium was added in small portions until there was no further reaction, then an additional 30 cc. of absolute ethanol was added. The solution was heated to reflux temperature and the addition of sodium continued in small portions for about 2½ hours. To the warm reaction mixture was added 25 cc. of 95% alcohol, followed by 100 cc. of water. The resulting solution was concentrated under reduced pressure to remove alcohol and the liberated bases taken up in ether. The combined ether extracts were dried over anhydrous potassium carbonate and evaporated, and the resulting yellow gum dissolved in 5% ethanolic oxalic acid solution. On standing at room

temperature, a precipitate readily formed. Emetine-V hydrogen oxalate (0.1 g.), was obtained, m.p. 206-207° after one recrystallization from ethanol.

The mother liquor from the emetine-V hydrogen oxalate was cooled and a small amount of precipitate formed. This was filtered and again dissolved in ethanol, and allowed to stand at room temperature. The crystals which formed were filtered and dried in vacuo, m.p. 168-174°. There was insufficient material for further determinations.

The combined mother liquors were concentrated and cooled. The precipitate which formed (1.1 g.) readily turned to a gum when exposed to air, but solidified on drying. The substance showed a wide melting point range and appeared to be impure, $[\alpha]_D^{26} = +45.0^\circ$ (c = 2.0 in water).

Reaction of Isotetradehydroemetine with Sodium Ethoxide Solution:*

An alcoholic solution of sodium ethoxide was prepared by adding 1.0 g. of sodium to 50 cc. of absolute ethanol. To the solution was added 1.0 g. of isotetradehydroemetine, and the mixture was refluxed for 30 hours. The precipitate which formed on cooling the reaction mixture was filtered and recrystallized from ethanol, giving 0.65 g. of white crystalline material, m.p. 158-161°, $[\alpha]_D^{28} = +5.6^\circ$ (c = 2.72 in benzene).

*The same procedure was followed for all the reactions shown in Table III.

Oxidation of Emetine with 4 Equivalents of Mercuric Acetate:

The procedure used was essentially the same as that described by Hazlett and McEwen (26), except that the reaction temperature, which was regulated by use of a heating mantle, and the reaction time were varied as shown in Table II. Also, the isotetradehydroemetine, which crystallized from the ether during continuous extraction, was filtered directly from the ether solution and recrystallized from absolute ethanol.

Isotetradehydroemetine was found to contain one active hydrogen by a Zerewitinoff determination. Calculated for $C_{29}H_{36}O_4N_2$: 0.21. Found: 0.15, 0.16.

Reaction of Tetradehydroemetine with Sodium Ethoxide Solution:

Tetradehydroemetine was liberated by treatment of an aqueous solution containing 1.4 g. of tetradehydroemetine hydrogen oxalate with 5% sodium hydroxide solution. The base was taken up in ether and the combined extracts dried over anhydrous potassium carbonate. The ether was evaporated and the resulting gum dissolved in 10 cc. of absolute ethanol. This was added to a sodium ethoxide solution which had been prepared by adding 1.0 g. sodium to 50 cc. absolute ethanol. The mixture was refluxed for 3 hours, then 100 cc. of water was added and the alcohol removed by concentrating the solution to 50 cc. under reduced pressure. The free base was extracted with several portions of ether, and the combined

extracts dried over anhydrous potassium carbonate. Evaporation of the ether left a gum which was dissolved in 5% ethanolic oxalic acid. Tetradehydroemetine hydrogen oxalate (1.1 g.), m.p. 152-154°, $[\alpha]_D^{34}$ = +85° (c = 1.14 in water), was obtained. (Reported, m.p. 151-153°, $[\alpha]_D^{18}$ = +84.5° (c = 1.9 in water)(25).

Recovery of Isotetradehydroemetine from the Hydrogen Oxalate:

An aqueous solution containing 0.4 g. of isotetradehydroemetine hydrogen oxalate, prepared as described by Hazlett and McEwen (26), was made basic with 10% sodium hydroxide solution to liberate the free base. On extraction with ether, the resulting base readily dissolved in the ether layer. The aqueous layer was further extracted with several portions of ether, and the combined ether extracts evaporated, leaving 0.25 g. of colorless crystals, m.p. 150-154°, $[\alpha]_D^{32}$ = +4.4° (c = 1.12 in benzene).

Hydrogenation of Dehydrohalorubremetine:

Dehydrohalorubremetine was prepared from rubremetinium chloride according to the procedure described by Hazlett and McEwen (26).

A. A solution of 1.85 g. of crude dehydrohalorubremetine in 50 cc. of glacial acetic acid was hydrogenated at atmospheric pressure over 0.1 g. platinum oxide catalyst. After 72 hours, the solution had absorbed 283 cc. (STP)(3.0 moles) of hydrogen. The catalyst was filtered from the reaction mixture and the acetic acid solution concentrated almost to dryness

under reduced pressure. Sodium bicarbonate solution (10%) was added until the solution was made basic. The mixture was filtered and the precipitate found to consist of a small amount of amorphous material which showed a wide melting range under 100°.

The filtrate was extracted with ether and the material obtained on evaporation of the ether behaved similarly. No material corresponding to either the optically active or racemic form of tetrahydrodehydrohalorubremetine could be isolated.

B. In a second hydrogenation of dehydrohalorubremetine, 1.1 g. of the crude material was dissolved in 40 cc. of absolute ethanol and hydrogenated over 0.10 g. of platinum oxide catalyst for about 2 hours, at which time the rate of hydrogen absorption became much slower. Two drops of glacial acetic acid was added, and the hydrogenation resumed. After 12 hours, two more drops of glacial acetic acid was added along with 0.10 g. of fresh catalyst. Hydrogenation was continued for an additional period of 24 hours, then two drops of acetic acid and 0.05 g. of catalyst were added. After a total of 108 hours reaction time, the hydrogenation was stopped. During this time there was absorption of 189 cc. (STP)(2.7 equivalents) of hydrogen. A thick suspension which first formed became somewhat thinner as the hydrogenation progressed. The catalyst and some suspended material were filtered from the reaction mixture and the organic material extracted with

hot ethanol. On cooling the ethanol solution, 0.20 g. of white crystals separated, m. p. 176-177°.* The mother liquor was combined with the original filtrate and concentrated under reduced pressure to about three-fourths the original volume. The precipitate which formed was recrystallized from ethanol, giving 0.10 g. of white crystals, m. p. 179-180°.* The mother liquor was again combined with the original filtrate and the same procedure repeated to give two additional fractions on concentration to one-half and one-fourth the original volume; (1) 0.14 g., m.p. 174-175°; (2) 0.19 g., m.p. 168-170°.* Further concentration of the mother liquor gave only low-melting amorphous material.

Oxidation of Dehydrohalorubremetine with Potassium Permanganate:

The procedure used for the reaction was similar to that described by Folkers and Koniuszy (35). To a solution of 0.32 g. dehydrohalorubremetine in 20 cc. of 2 N sulfuric acid was added dropwise a 2% solution of potassium permanganate until the purple color persisted. The excess permanganate was removed by addition of a few drops of hydrogen peroxide solution. The mixture was filtered and the precipitate washed thoroughly with 2 N sulfuric acid and water. The combined filtrate and

*Tietz and McEwen report a m.p. of 180.2-181.8° for the racemic and 165.8-166.0° for the optically active tetrahydrodehydrohalorubremetine. In this case the total yield of products falling in this m.p. range is 62%.

washings were distilled until the residual volume was about 20 cc., then an additional 10 cc. of water was added to the residue. Distillation was again continued until the volume of the residue had decreased to about 20 cc. The same procedure was repeated once more, then the collected distillates neutralized to approximately pH 7 with dilute sodium hydroxide solution. About 25 cc. of methanol and 0.10 g. p-bromophenacyl bromide were added and the mixture refluxed for 3 hours. The solution was evaporated to dryness under reduced pressure, and the residue treated with 10 cc. of hot methanol. On cooling, 35 mg. of p-bromophenacyl bromide separated from the methanol solution. The filtrate was concentrated to about 5 cc., and 30 mg. of white crystals were obtained, m.p. 131-133°. One recrystallization from methanol raised the m.p. to 133-134°. The value reported for the m.p. of the p-bromophenacyl ester of formic acid is 134-135° (35). A mixed melting point with an authentic sample showed no depression.

SUMMARY

Reduction of isotetradehydroemetine with sodium and ethanol has been found to give emetine-IV and emetine-V. Completely anhydrous conditions favor the formation of emetine-V, while the presence of moisture increases the proportion of emetine-IV to emetine-V.

Emetine-V has been characterized as the hydrogen oxalate, the hydrobromide, and as benzoylemetine-V hydrochloride. Emetine-IV has been further characterized as the hydrobromide.

Oxidation of emetine-V hydrogen oxalate with four equivalents of mercuric acetate gave a gum which could not be converted to a crystalline derivative. Hydrogenation of the crude product gave emetine-IV and emetine-V.

Neoemetine, emetine-IV, and emetine-V have all been converted to the rubremetinium cation by oxidation with mercuric acetate.

Reduction of tetradehydroemetine with sodium and ethanol gives a small amount of emetine-V plus a mixture of other isomers.

In the oxidation of emetine with four equivalents of mercuric acetate, it has been found that (1) low temperature favors the formation of isotetradehydroemetine, with the maximum yield being produced at 60-65°, and (2) approximately equal amounts of tetradehydroemetine and isotetradehydroemetine are produced when the reaction is carried out at reflux temperature.

Isotetradehydroemetine shows a decrease in rotation and an increase in melting point on being heated in alcoholic sodium ethoxide solution. The base recovered from isotetradehydroemetine hydrogen oxalate also possesses a lower rotation than the original isotetradehydroemetine.

Ultraviolet and infrared spectral studies on tetradehydroemetine, isotetradehydroemetine, and their salts, together with the known chemical properties of the substances, permit the assignment of highly probable structures to these compounds.

On catalytic hydrogenation under mildly acidic conditions, dehydrohalorubremetine has been found to absorb 2.7 moles of hydrogen to give the previously reported optically active and inactive forms of "tetrahydrodehydrohalorubremetine". The result is consistent with structure LXXIII for rubremetinium salts and is in agreement with the possibility that a Hofmann degradation occurs on formation of dehydrohalorubremetine.

Oxidation of dehydrohalorubremetine with potassium permanganate gives some formic acid, characterized as the p-bromophenacyl derivative. This result indicates that a terminal methylene group is present in dehydrohalorubremetine.

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