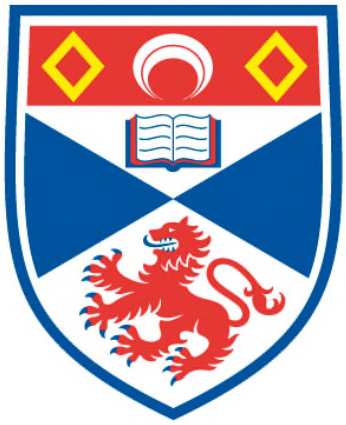
PART I
SOME METHYL ETHERS OF MANNITOL

PART II
THE STRUCTURE OF RUBREMETINE

Hamish Christopher Swan Wood

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1950

Part I

SOME METHYL ETHERS OF MANNITOL

Part II

THE STRUCTURE OF RUBREMETINE

A Thesis

presented by

HAMISH CHRISTOPHER SWAN WOOD, B.Sc.,

to the

UNIVERSITY OF SAINT ANDREWS

in application for the

Degree of

DOCTOR OF PHILOSOPHY.

April, 1950.

MS 1055

DECLARATION.

I hereby declare that the following Thesis is a record of experiments carried out by me, that the Thesis is my own composition and has not previously been presented for a Higher Degree.

The investigation was carried out in the Chemical Research Laboratory of the United College, under the direction of John Dewar, B.Sc., Ph.D., and H.T. Openshaw, M.A., D.Phil.

24th. April, 1950.

CERTIFICATE.

I hereby certify that Mr. Hamish C.S. Wood, B.Sc., has spent nine terms at Research Work in the Chemical Research Laboratory of United College, that he has fulfilled the conditions of Ordinance No. 16 (St. Andrews), and that he is qualified to submit the accompanying Thesis for the Degree of Ph.D.

UNIVERSITY CAREER AND RESEARCH EXPERIENCE.

I entered the University of St. Andrews in October, 1943, pursuing the course of study leading to the Degree of B.Sc., which I obtained in June, 1946. In June, 1947, I was awarded First Class Honours in Chemistry.

I was admitted as a Research Student of the University of St. Andrews in October, 1947, and for a period of one year carried out Research Work on the Methyl Ethers of Mannitol under the supervision of Dr. John Dewar. From October, 1948, until the present date, I have been engaged on research into the structure of Rubremetine under the direction of Dr. H.T. Openshaw.

In October, 1947, I obtained a D.S.I.R. Grant, which I still hold, and in October, 1949, was awarded an Honorary Post-Graduate Scholarship by the University of St. Andrews.

CONTENTS

Part I

SOME METHYL ETHERS OF MANNITOL

Part II

THE STRUCTURE OF RUBREMETINE

PART I

A Contribution

to the Study of the Methyl Ethers of Mannitol

with Special Reference to Optical Rotatory

Power

INTRODUCTION

The investigation of the relationship between the chemical constitution of a compound and the optical activity which it exhibits has been the subject of numerous researches during the past sixty years. Despite the large amount of experimental data which has been accumulated the problem has not yet been solved.

The first workers to attempt to infer the degree, and the sign, of the optical activity of a compound by a quantitative evaluation of the asymmetry of the molecule were Crum Brown (1) and Ph. A. Guye (2). This theory had to be abandoned, however, as it failed to take into account many factors which influence optical activity. Further molecular theories of optical rotatory power were developed in subsequent years by Gray (3), de Malleman (4), and Boys (5) and it is possible to calculate the approximate specific rotation of simple molecules by such methods.

Kuhn (6) and Born (7), on the other hand, attempted to explain the origin of optical rotatory power on the basis of the elementary physical processes occurring in the molecule and have developed an explanation of optical activity which forms the keystone of most modern theories. The problem is essentially one of quantum optics and the position today is best summarised/

summarised in the words of Professor T.M. Lowry in an address to the British Association (8).

"The real theory of optical rotatory power may be found by the mathematician, but is concealed from the chemist, in the papers of Born....."

The experimental work referred to above included an extremely detailed and systematic study of the molecular rotations of several homologous series of secondary alcohols and esters, which was carried out, from 1911 onwards, by Pickard and Kenyon (9). A similar investigation was made by Levene and his coworkers (10) on the optical rotatory powers of fatty acids, and Rule (11) has carefully studied the effect on the molecular rotation of changes in the polarity of substituent groups. These attempts to correlate the degree of optical activity with the structure of the molecule have not led to the discovery of any definite relationships.

In 1909, however, C.S. Hudson (12), in a series of instructive papers, demonstrated that important quantitative relationships may be traced in the optical rotatory power of members of the sugar group. This unique quality of the sugars is attributed, by Lowry, to the simple and constant type of rotatory dispersion exhibited by many members of the group.

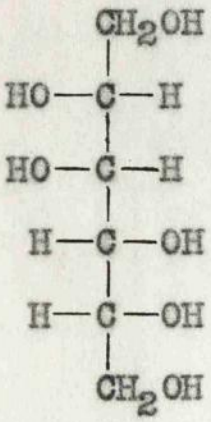
Several years later, Irvine and Patterson (13), working in this laboratory, published a paper dealing with the optical effect/

effect of successive substitution in the hexahydric alcohol, mannitol. Confirmation of this work came from a subsequent paper communicated by Irvine and Steele (14) in the following year.

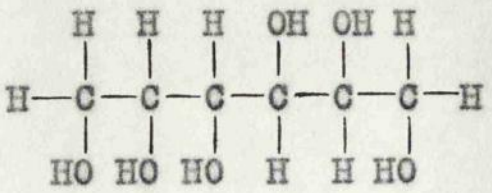
The present research has as its object a further study of the methyl ethers of mannitol and also a review of the optical effect of successive methylation in the mannitol molecule.

Mannitol was first isolated by Proust (15) in 1806 from the dried juice of the manna ash, Fraxinus ornus, and since that date it has been found to a varying extent in many different plants, especially fungi and algae. This wide distribution in nature has been attributed to its formation from sugars by bacterial action.

Mannitol crystallises in beautiful needles or prisms, melting at 166°, and having a specific rotation of $[\alpha]_E^{25} = -0.24°$ in water. The configuration (I) is now generally accepted for d-mannitol though it has been suggested by McCrea (16) that the structure in the crystal is best represented by (II).



I



II

The/

The methyl ethers of mannitol are prepared by the methods normally employed for such syntheses in the carbohydrate field, and employing the elegant methylation technique evolved by Purdie and Irvine. In the synthetic work to be discussed, the hexahydric alcohol was condensed with either acetone or benzoyl chloride to give a series of intermediates of known constitution. The free hydroxyl groups in these substances were methylated in the usual manner and subsequent hydrolysis led to the partially alkylated mannitols which were required.

A complete study of the optical effect of successive methylation in the mannitol molecule can be achieved only by preparing all the possible methyl ethers of mannitol, and by ascertaining the true specific or molecular rotation of these compounds.

Developments in the technique of sugar chemistry make it possible that the complete series of methylated mannitols may ultimately be prepared and, until this has been accomplished, it would be premature to speculate freely on the optical results which have been obtained. With the addition of the new compounds now described to those which are already known, certain deductions of a qualitative nature may be drawn.

The measurement of the true molecular rotation of these derivatives is a more difficult problem because the optical rotation exhibited by a solution of an optically active substance depends/

depends on the concentration of the substance and on the nature of the solvent. A procedure which has been adopted by several authors, in an endeavour to eliminate this effect, is extrapolation of the rotation to a concentration of 100%. This method is only reliable, however, if a sufficient number of measurements are made at high concentrations and it is perhaps more significant to use the reverse procedure of an extrapolation to infinite dilution.

The determination of the optical rotatory powers of pure liquid substances would thus appear to offer the best opportunity for a comparative study. In the present research it was impossible to do more than to ascertain the molecular rotations of the mannitol ethers in solution as several exist in the crystalline state and others are syrups of varying degrees of viscosity. Comparison has been preserved by using approximately the same concentration throughout and the same or similar solvents.

A knowledge of the character of the dispersion of the rotatory power is also advisable when a comparative study of optical rotations is to be made. As has already been mentioned, many members of the sugar group appear to exhibit a remarkably simple type of rotatory dispersion and the measurements of specific rotation to be described have been confined to light of one wave length.

ACETONE DERIVATIVES OF MANNITOL

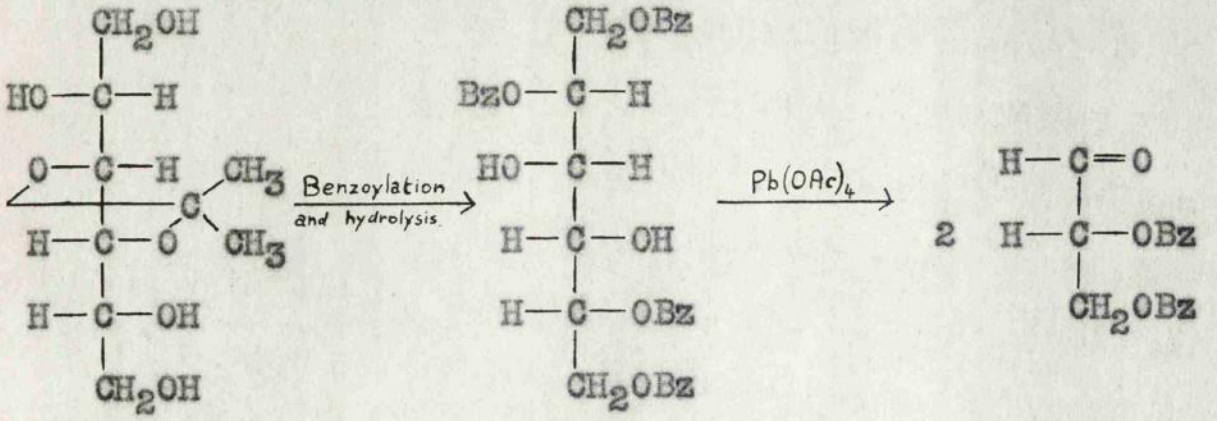
The reaction between acetone and the polyhydric alcohols or members of the sugar group was first investigated by Fischer (17), though he dismissed the resulting compounds as of little interest. The value of these derivatives in carbohydrate chemistry was not fully realised until their constitution was studied by Irvine and his collaborators. Perhaps the most outstanding property of these compounds is the instability exhibited in the presence of even dilute acids and this facile hydrolysis makes them admirable intermediates for many syntheses in the field of sugar chemistry.

Triacetone-mannitol was first prepared by Fischer (17), in 1895, by shaking dry powdered mannitol with acetone containing hydrogen chloride as a condensing agent. The constitution of this compound was not investigated until 1914 when Irvine and Patterson (13) undertook a detailed study of the acetone derivatives of mannitol. These workers carried out a graded hydrolysis of triacetone-mannitol and obtained both a diacetone-mannitol and a monoacetone derivative from the reaction mixture. The former was called α-diacetone-mannitol to distinguish it from the β-diacetone compound isolated by Fischer as a by-product in the acetonation of mannitol and which was later shown to be 1:2-5:6-diacetone-mannitol (18, 19). Irvine

and/

and Patterson assigned a symmetrical 1:2-3:4-5:6 structure to the triacetone-mannitol and the hydrolysis products were designated 1:2-3:4-diacetone-mannitol and 1:2-monoacetone-mannitol respectively.

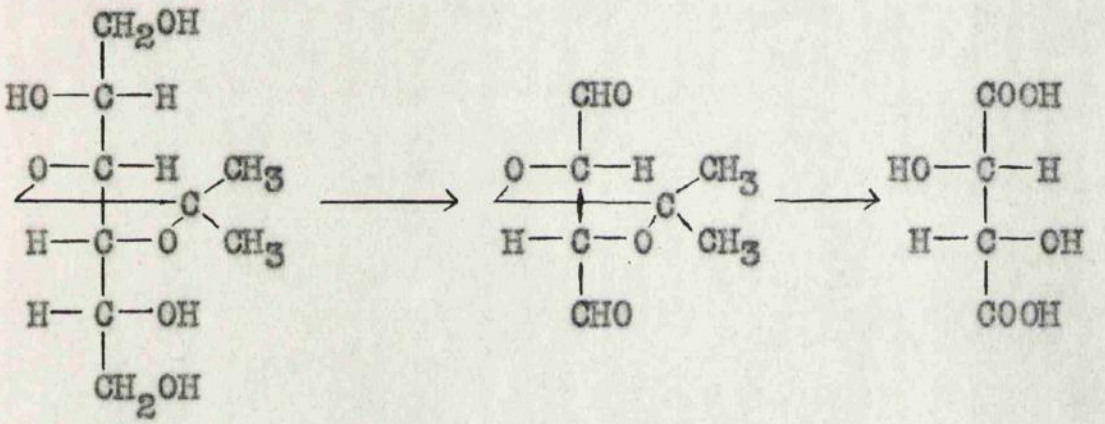
That the latter structure was incorrect was pointed out by Müller (20), who showed that this monoacetone derivative could be obtained by the debenzoylation of 1:6-dibenzoyl-monoacetone-mannitol and that it gave a ditrityl derivative. The acetone residue, therefore, could not possibly engage a primary hydroxyl group and Müller suggested that it was attached to carbon atoms 3 and 4 (III). This assumption was proved correct by Brigl and Grüner (21) who oxidised the tetrabenzoyl-mannitol (IV), which Fischer (22) had prepared from the monoacetone-mannitol of Irvine and Patterson, with lead tetraacetate and obtained dibenzoyl-d-glyceraldehyde (V).



III IV V

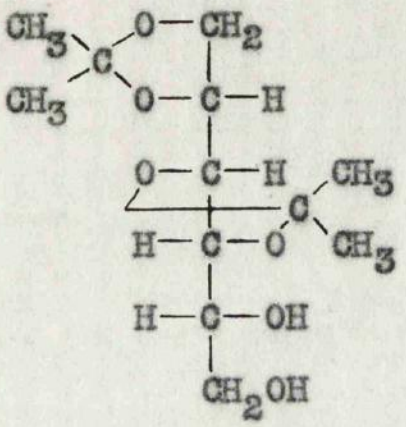
Further/

Further confirmation came from the work of H.O.L. Fischer and Appel (19) who oxidised monoacetone-mannitol to acetone-dihydroxysuccinic-dialdehyde (VI), which they later converted to l-tartaric acid (VII).

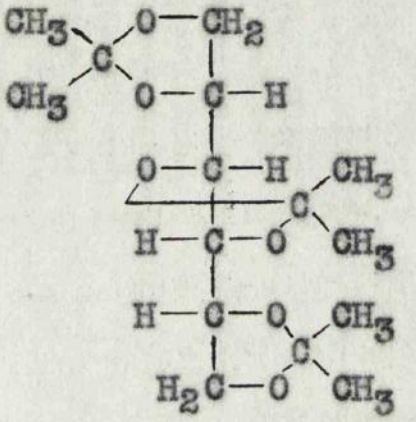


III VI VII

∝-Diacetone-mannitol has not been studied so extensively and support for the structure proposed by the original workers has come from experiments carried out recently by Wiggins (23). The latter oxidised ∝-diacetone-mannitol to diacetone-aldehydo-d-arabinose which was subsequently hydrolysed to give d-arabinose identical with an authentic specimen. The acetone residues, therefore, must be attached to carbons 1, 2, 3 and 4 and, as hydrolysis of ∝-diacetone-mannitol gives the 3:4-monoacetone compound, the former is correctly represented as 1:2-3:4-diacetone-mannitol (VIII). These results further prove that the original triacetone derivative must be 1:2-3:4-5:6-triacetone-mannitol (IX).



VIII



IX

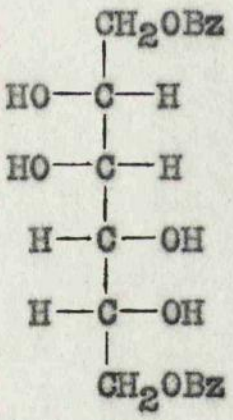
To conform to the normal mode of writing the mannitol molecule, the formulations above may seem to involve a trans ketal linkage. There is now a considerable weight of evidence to show that rotation can occur about any of the bonds in the mannitol molecule and hence cis ketal formation is always possible (23).

DI - AND TRIBENZOATES OF MANNITOL

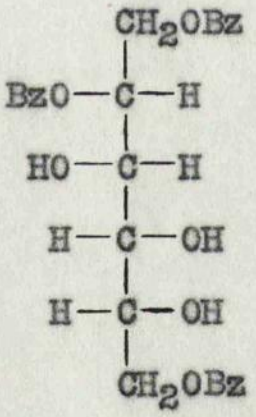
In 1898, Einhorn and Hollandt (24) prepared a dibenzoyl-mannitol by the action of a limited amount of benzoyl chloride on mannitol in pyridine solution. Some years later, Brigl and Grüner (25) modified this method by diminishing the amount of pyridine and simplifying the extraction of the product. As a result of reducing the volume of pyridine, most of the mannitol was undissolved initially, but, by vigorous stirring and regulation of the rate of addition of benzoyl chloride, a smooth reaction was brought about.

The structure of dibenzoyl-mannitol has been the subject of much controversy in the past. Ohle and his coworkers (26) described it as the 2:3 or 4:5 dibenzoyl derivative of mannitol. This conclusion was based on the result of the oxidation of dibenzoyl-mannitol with potassium permanganate and the isolation of what was believed to be dibenzoyl-meso-tartaric acid. Brigl and Grüner (25) showed that this identification was erroneous and that the oxidation product was benzoyl-glycollic acid. Not only was the product compared directly with synthetic benzoyl-glycollic acid but crystalline glycollic acid was isolated by saponification under the proper conditions. The benzoyl groups, therefore, are not adjacent and it was suggested that they had entered the two primary or 1:6-hydroxyl groups. Recently, Haworth and Wiggins (27) have made a study of/

of the dimethylene derivatives of dibenzoyl-mannitol and these researches prove conclusively that the dibenzoyl compound is 1:6-dibenzoyl-mannitol (X). This structure implies that the primary hydroxyl groups are acylated much more rapidly than the more numerous secondary ones, an observation which is entirely in accord with many others to the same effect which have been made in recent years (28).



X



XI

Ohle and his collaborators (26) noted that the dibenzoyl-mannitol of Einhorn and Hollandt was contaminated with a tribenzoate, with solubilities similar to those of the dibenzoyl-mannitol. The alcoholic mother liquors from the recrystallisation of the dibenzoate contain this tribenzoyl-mannitol and it is best obtained by concentrating the solution and cooling in the refrigerator (29).

This compound was considered by Brigl and Grüner (21) to be/

be 1:2:6-tribenzoyl-mannitol (XI). It combined with acetone to give a syrupy monoacetone derivative which was benzoylated to give the known 1:2:5:6-tetrabenzoyl-3:4-monoacetone-mannitol. The structure of the latter was proved by its synthesis from 1:2:5:6-tetrabenzoyl-mannitol (IV) and acetone, the configuration of the tetrabenzoate being deduced as described in the previous chapter. These results have been fully confirmed by Hockett and Fletcher (29) who subjected tribenzoyl-mannitol to lead tetraacetate oxidation, the oxidation curve showing unequivocally that the 1:2:6 formulation is correct.

The di- and tribenzoates of mannitol, which have been discussed, have been used in the present work as intermediates in the preparation of a further series of methylated mannitols. The removal of the benzoyl groups, subsequent to methylation, has presented more difficulty than the hydrolysis of the corresponding acetone residues, though catalytic cleavage with sodium methoxide has proved effective in most cases.

THE PREPARATION OF METHYL ETHERS OF MANNITOL

The synthesis of 3:4-dimethyl-mannitol.

Methylation of 1:2:5:6-tetrabenzoyl-mannitol (IV) and subsequent debenzoylation appeared to offer an easy route to the 3:4-dimethyl derivative of mannitol. Moreover, a quantity of this tetrabenzoyl-mannitol had been prepared in a high degree of purity during preliminary experiments, and confirmation of the structure by Brigl and Grüner (21) left no doubt that the methyl groups would, in fact, enter the 3 and 4 positions. The synthesis of 3:4-dimethyl-mannitol from the 3:4-monoacetone-mannitol of Irvine and Patterson may be represented diagrammatically as follows.

3:4-monoacetone-mannitol

↓

1:2:5:6-tetrabenzoyl-3:4-monoacetone-mannitol

↓

1:2:5:6-tetrabenzoyl-mannitol

↓

1:2:5:6-tetrabenzoyl-3:4-dimethyl-mannitol

↓

3:4-dimethyl-mannitol

Monoacetone-mannitol, prepared by the graded hydrolysis of triacetone-mannitol, was converted to the tetrabenzoyl derivative according to the directions given by Fischer (22), using benzoyl chloride in dry quinoline. Removal of the acetone residue was also carried out as described by Fischer, the/

the hydrolysis being effected with fuming hydrochloric acid in ethyl acetate solution. The subsequent methylation of the tetrabenzoate was accomplished in the usual manner with methyl iodide and dry silver oxide, to yield a clear, viscous syrup.

Some difficulty was experienced in the removal of the benzoyl groups from 1:2:5:6-tetrabenzoyl-3:4-dimethyl-mannitol : the method employed involved a catalytic cleavage with a small quantity of sodium methoxide. This method of hydrolysis of an ester, now in general use in sugar chemistry, was introduced by Fischer and Bergmann (30) in 1919 for the removal of acetyl groups, and it has since been shown by Zemplén (31) that 1/600 th. of the theoretical amount of sodium methoxide is sufficient to catalyse the reaction.

The debenzoylation was first attempted at room temperature by shaking a methyl alcoholic suspension of tetrabenzoyl-dimethyl-mannitol with a trace of sodium. This method led to complete hydrolysis of the benzoyl groups when applied to 1:6-dibenzoyl-dimethylene-mannitol by Haworth and Wiggins (27). Debenzoylation did not appear to be complete in this instance, however, as the product, which was obtained as a clear syrup, had a methoxyl value much below the theoretical amount.

The saponification was next attempted at 100°, the tetrabenzoyl-dimethyl-mannitol being dissolved in dry methanol and a small quantity of sodium methoxide added. The experimental details were those given by Dewar and Fort (32) for/

for the debenzoylation of 2-benzoyl-6-trityl-3:4-dimethyl-β-methylglucoside. The reaction went quite smoothly, no discolouration occurring, and the product was obtained as a clear syrup which crystallised after some time. Recrystallisation of the dimethyl-mannitol from ethanol gave fine white needles melting at 143-144°.

As the result of an accident, the product was lost before an analysis could be carried out and the characterisation of this dimethyl derivative is therefore not complete. The mode of synthesis, however, leads to an unambiguous structure and an identical product should be obtained by the methylation of 1:2-5:6-diacetone-mannitol (18,19) and subsequent deacetonation.

The synthesis of 1:2-dimethyl-mannitol.

The 1:2-dimethyl ether of mannitol was prepared as directed by Irvine and Patterson (13) and the synthesis may be summarised thus.

α-diacetone-mannitol

↓

1:2-dimethyl-diacetone-mannitol

↓

1:2-dimethyl-mannitol

Methylation of α-diacetone-mannitol was carried out in the normal manner to yield 1:2-dimethyl-diacetone-mannitol as a neutral/

neutral, colourless liquid. Subsequent deacetonation was readily effected by acid hydrolysis to give crystalline 1:2-dimethyl-mannitol, melting sharply at 93°.

The attempted synthesis of 1:2:3:4-tetramethyl-mannitol.

In the course of a further series of preliminary experiments, concerned with the action of benzoyl chloride on the acetone compounds of mannitol, the 1:2-dibenzoyl derivative of α-diacetone-mannitol was prepared. Removal of the acetone residues by acid hydrolysis yielded 1:2-dibenzoyl-mannitol as a crystalline compound, melting at 151-152°. Methylation of the latter and subsequent debenzoylation would appear to furnish a possible means of synthesising 1:2:3:4 (or 3:4:5:6)-tetramethyl-mannitol. The projected synthesis may be represented, in outline, thus.

α-diacetone-mannitol

↓

1:2-dibenzoyl-diacetone-mannitol

↓

1:2-dibenzoyl-mannitol

↓

1:2-dibenzoyl-3:4:5:6-tetramethyl-mannitol

↓

1:2:3:4 (or 3:4:5:6)-tetramethyl-mannitol

α-Diacetone-mannitol was treated with benzoyl chloride in pyridine and the mixture allowed to stand overnight. Benzoylation occurred/

occurred readily and 1:2-dibenzoyl-diacetone-mannitol was isolated in the normal way. The acetone residues were removed by acid hydrolysis in acetone solution, the progress of the reaction being followed polarimetrically. A constant value for the rotation was attained after six hours and crystalline 1:2-dibenzoyl-mannitol was obtained from the reaction mixture.

The 1:2-dibenzoate was subjected to four successive treatments with methyl iodide and silver oxide, the theoretical yield of methylated product being obtained. A methoxyl determination on the resulting syrup, however, gave a value of 19.3%, the calculated figure for 1:2-dibenzoyl-tetramethyl-mannitol being 27.8% ; further treatment with the alkylating agents produced no increase in methoxyl content. Moreover, an estimation of the benzoyl content, also carried out on the crude product, revealed the presence of three benzoyl groups in the molecule. A repeat experiment again gave a syrup with identical values for methoxyl and benzoyl content. The molecular weight of the syrup, as determined by the cryoscopic method, was approximately 400, the theoretical value for dibenzoyl-tetramethyl-mannitol being 445, thus no intermolecular condensation can have taken place. No explanation can be offered, at present, for these analytical results, and it will be shown later (p.20) that a similar anomaly occurs in the methylation of the 1:6-dibenzoyl derivative of mannitol.

1:2-diacetyl-mannitol was considered a suitable alternative

to/

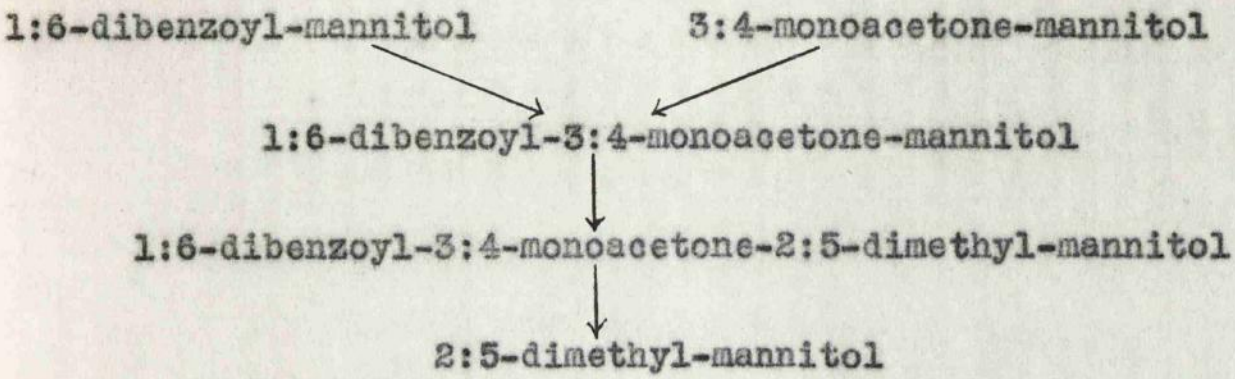
to the 1:2-dibenzoyl compound as the essential intermediate in the synthesis. The 1:2-diacetyl derivative of ∝-diacetone-mannitol was prepared in a crystalline state but a preliminary study of the acid hydrolysis of this compound revealed that both the acetyl and acetone residues were removed by this procedure.

It has been found, however, by v. Vargha (33) that, although both the acetyl and acetone residues of 1:2-5:6- diacetone-diacetyl-mannitol were removed by acid hydrolysis, it was possible, by a polarimetric study, to arrest the reaction at such a point that cleavage of the acetone residues alone had occurred.

A further study of the hydrolysis of 1:2-diacetyl-diacetone-mannitol would thus prove of interest.

The synthesis of 2:5-dimethyl-mannitol.

1:6-Dibenzoyl-mannitol condenses with acetone, in the presence of concentrated sulphuric acid, to give the known 1:6-dibenzoyl-monoacetone-mannitol (26). Crystallisation of the latter compound yields long prismatic needles, identical with those obtained from the treatment of 3:4-monoacetone-mannitol with a limited amount of benzoyl chloride in pyridine. The intermediate is thus 1:6-dibenzoyl-3:4-monoacetone-mannitol and methylation will result in the formation of the corresponding 2:5-dimethyl ether. The synthesis of 2:5-dimethyl-mannitol, therefore, may be summarised as follows.



Methylation of 1:6-dibenzoyl-3:4-monoacetone-mannitol was achieved by the method of Purdie and Irvine, the theoretical yield of alkylated product being obtained after three treatments with methyl iodide and silver oxide.

As the result of trial experiments it was found advantageous to remove the benzoyl groups from 1:6-dibenzoyl-3:4-monoacetone-2:5-dimethyl-mannitol before hydrolysis of the acetone residue. Debenzoylation was effected by treatment of the methylated syrup, in methyl alcoholic solution, with a small amount of sodium methoxide, 3:4-monoacetone-2:5-dimethyl-mannitol being isolated in 94% yield.

Deacetonation was readily accomplished by refluxing an aqueous acetone solution of the 3:4-monoacetone-2:5-dimethyl derivative with dilute hydrochloric acid. The course of the reaction was followed with the aid of the polarimeter, a constant value for the rotation being attained after three hours. 2:5-Dimethyl-mannitol was isolated from the reaction mixture as a colourless syrup which, on distillation and solution in benzene, deposited crystals, melting at 58.5 - 60°.

The/

The attempted synthesis of 2:3:4:5-tetramethyl-mannitol.

It was anticipated that methylation of 1:6-dibenzoyl-mannitol and subsequent debenzoylation would provide a method for the synthesis of 2:3:4:5-tetramethyl-mannitol. The alkylation, however, did not proceed in the usual manner, and the partially methylated product, when analysed, had a methoxyl content of 25.2%, as compared to the theoretical value of 27.8%. Further, an estimation of the number of benzoyl groups revealed the presence of three such groups in the molecule. This anomaly is similar to that observed in the methylation of 1:2-dibenzoyl-mannitol.

The crude product is evidently a mixture and a separation was attempted by fractional distillation of the syrup under reduced pressure. The lower boiling fraction was obtained as a clear, water-white liquid and the higher fraction as a brown viscous gum. A preliminary examination of these distillates indicated that no significant separation had been achieved and the problem remains unsolved.

DISCUSSION OF RESULTS

The preparation of two new dimethyl ethers of mannitol has been discussed fully in the preceding chapters and a study has also been made of other derivatives of the hexahydric alcohol with a view to the synthesis of further methylated mannitols. In the present chapter it is intended to review the optical effect of successive methylation in the mannitol molecule.

The original investigation of this problem was carried out in 1915 by Irvine and Patterson (13). The results of this research, however, were based on the information available at that time and, in the subsequent years, much work has been done on the chemistry of mannitol derivatives. In particular, different structures have been assigned to several of the compounds which were utilised by the original workers, and their generalisations concerning the optical effect of successive substitution in the mannitol molecule, which are reported below, are in some cases incorrect.

Irvine and Patterson based their conclusions on the values of the optical rotatory powers of four methyl ethers of mannitol. The first of these compounds was the dimethyl-mannitol (A) obtained from α-diacetone-mannitol by methylation and subsequent deacetonation. A tetramethyl-mannitol (B) was prepared from monoacetone-mannitol, and a further tetramethyl derivative (C) by the reduction of tetramethyl-mannose. The remaining compound was

a/

a pentamethyl ether of mannitol (D), obtained from (A) by exhaustive treatment with methyl iodide and silver oxide. The structures of these compounds, as formulated by Irvine and Patterson, and the values recorded for the specific rotations are given below.

	A	B	C	D
1.	CH_2OCH_3	CH_2OCH_3	CH_2OCH_2	CH_2OCH_3
2.	$CH.OCH_3$	$CH.OCH_3$	$CH.OCH_3$	$CH.OCH_3$
3.	$CH.OH$	$CH.OCH_3$	$CH.OH$	$CH.OCH_3$
4.	$CH.OH$	$CH.OCH_3$	$CH.OCH_3$	$CH.OCH_3$
5.	$CH.OH$	$CH.OH$	$CH.OCH_3$	$CH.OCH_3$
6.	CH_2OH	CH_2OH	CH_2OH	CH_2OH
	$[\alpha]_D$ -8.8°	-12.5°	+39.8°	+9.8°

The deductions made by Irvine and Patterson concerning the optical effect of methylation in the mannitol molecule were summarised as follows.

"Comparing B with D : Methylation in position 5 results in marked exaltation of the dextrorotation.

Comparing C with D : Substitution in position 3 has a strong laevorotatory effect.

Comparing A with C, and A with B : Confirms the dextro effect of methylating position 5 and indicates that methylation in position 4 also increases the dextrorotation.

Comparing/

Comparing A with mannitol : Alkylation in positions 1 and 2 has a laevorotatory effect. Previous experience has shown that methylation in a terminal hydroxyl group has little effect on the rotation of an alkylated sugar and thus the methyl group in position 2 is chiefly responsible for the laevorotation of dimethyl-mannitol."

Irvine and Patterson also state that the optical effect of methylation in the sugar group, is to increase the rotation of the asymmetric system into which the alkyl group is directly introduced. They thus claim that it is possible to ascribe a direction to the optical effect of each of the asymmetric systems present in the mannitol molecule, viz. that the asymmetric systems 4 and 5 are dextro, and the systems 2 and 3 are laevo. They also state that these conclusions are in agreement with the configuration assigned to mannitol as the groups in question are situated on opposite sides of the carbon chain.

Nine methyl ethers of mannitol are now known, and although the problem cannot be solved in its entirety until the complete series of methylated mannitols has been prepared, the results of the present research justify a review of the work carried out by Irvine and Patterson.

Details of the optical rotatory power exhibited by the known methyl ethers of mannitol are given in table 1., and it will be apparent that the measurements of specific rotation have been carried out under a variety of conditions which would normally preclude/

Table 1.

	Mol.Wt.	Specific Rotation	Molecular Rotation	Symbol	Solvent	Ref.
Mannitol	182	-0.24°	-0.4°		H_2O	(34)
3 (or 4)-methyl-mannitol	196	+16.7°	+32.7°	+2A	H_2O	(35)
1:2(or 5:6)-dimethyl-mannitol	210	-7.47°	-15.7°	-A	EtOH	
1:6-dimethyl-mannitol	210	+17.0°	+35.7°	+2A	$CHCl_3$	(36)
2:5-dimethyl-mannitol	210	-32.7°	-68.7°	-4A	EtOH	
3:4-dimethyl-mannitol	210					
1:2:5:6-tetramethyl-mannitol	238	-12.6°	-30.0°	-2A	EtOH	
1:3:4:5(or 2:3:4:6)-tetramethyl-mannitol	238	+20.7°	+49.3°	+3A	EtOH	(37)
1:2:3:4:5(or 2:3:4:5:6)--pentamethyl-mannitol	252	+8.9°	+22.4°	+A	EtOH	(13)
1:2:3:4:5:6-Hexamethyl-mannitol	266	+12.5°	+33.3°	+2A	Nil	(37)

preclude any accurate comparative study. A survey of the literature, however, has revealed that the optical rotation of mannitol derivatives is not greatly affected by a change of solvent, provided that the latter is of an essentially neutral character, or by small variations in the concentration of the solution. As the following discussion is intended to be qualitative rather than quantitative in nature, the values quoted in table 1. for the molecular rotations of the methylated mannitols have been used throughout. Nevertheless, determinations of optical rotatory power in the course of the present research were carried out under carefully regulated conditions (table 2.) which, if extended to the complete series of methylated mannitols, would provide data for an accurate quantitative study.

Table 2.

Solvent : Absolute ethyl alcohol, magnesium dried.
Temperature : 17° C.
Wavelength of light : Sodium doublet (D line, 5890,5896 Å)
Concentration : c 1.27-1.65 g. per 100 cc.
Polarimeter tube : Two decimetre.

In an endeavour to clarify the discussion and to further emphasise the qualitative aspect of the results, it is not intended to compare the numerical values of the molecular rotations/

rotations given in table 1., but to express these rotations as multiples of the symbol A, where A represents approximately 16°. The symbols are entered in table 1. along with the corresponding molecular rotations, the error introduced by this approximation being of the order of 4% in all cases save one, where it is somewhat greater.

By comparing the rotation of 1:3:4:5-tetramethyl-mannitol with that of 1:2:3:4:5-pentamethyl-mannitol we find that methylation in position 2 has a laevorotatory effect to the extent of -2A. Similarly, a study of the rotations of 1:2:3:4:5-pentamethyl-mannitol and the 1:2:3:4:5:6-hexamethyl derivative reveals that alkylation in position 6 increases the dextrorotation of the molecule by +A. Finally, by a comparison of the rotation of 3-monomethyl-mannitol with that of mannitol itself, we find that methylation in position 3 results in dextro-rotation to the extent of + 2A. These results are summarised in table 3.

Table 3.

1. Methylation in the 1 or 6 positions results in dextrorotation to the extent of +A.
2. Methylation in the 2 or 5 positions results in laevorotation to the extent of -2A.
3. Methylation in the 3 or 4 positions results in dextrorotation to the extent of +2A.

An/

An application of these results to the remaining methyl ethers of mannitol in table 1. can now be made. Thus, we would expect that methylation in the 1 and 2 positions would be accompanied by laevorotation to the extent of -A, and this deduction is confirmed by the experimental value for the molecular rotation of 1:2-dimethyl-mannitol. In a similar fashion, it is possible to predict that the optical effect produced by methylating the 1 and 6 positions will be dextrorotatory in character, and of the order of +2A. This is borne out by the value of the molecular rotation of 1:6-dimethyl-mannitol. Calculations of the optical effect of methylating positions 2 and 5, and positions, 1, 2, 5 and 6, can be made, and the results confirmed by the experimental values for the molecular rotations of 2:5-dimethyl-mannitol and 1:2:5:6-tetramethyl-mannitol respectively.

It thus appears possible to attribute a qualitative value to the optical effect of methylating selected hydroxyl groups in the mannitol molecule and to predict the order of magnitude of the change in rotation. Interesting confirmation of this theory has come from subsequent work carried out by Mr. J.A. Fewster, B.Sc.[*] The latter isolated a substance, claimed to be 5-monomethyl-mannitol, which had a molecular rotation of -31.3°, this rotation agreeing closely with the predicted value of -2A.

The/

[*] I am indebted to Mr. Fewster for permission to use this result.

The optical results which have been obtained are based, in part, on an extension of the theory of optical superposition. The validity of the latter has been the subject of much controversy, but it would appear from the work of C.S. Hudson (12) that an extended version of the theory can be applied to certain members of the sugar group, provided that the results so obtained are not in conflict with those arrived at by other physical or chemical methods. The deductions which have been made concerning the optical properties of the methyl ethers of mannitol are in agreement with the known experimental data and a limited application of the theory of optical superposition would thus seem justified.

In conclusion, it must be emphasised that the present research formed the initial stages only, of what was intended to be a complete study of the optical properties of the methyl ethers of mannitol. The results which have been obtained, therefore, are not conclusive in themselves and form the basis for a future investigation.

SUMMARY

The preparation of various acetone derivatives of mannitol has been carried out and the structures, which were assigned to these compounds by previous workers, have been examined in some detail.

1:2:5:6-Tetrabenzoyl-mannitol has been prepared from the 3:4-monoacetone derivative of mannitol, and methylation of the tetrabenzoate has given 1:2:5:6-tetrabenzoyl-3:4-dimethyl-mannitol. Subsequent debenzoylation yielded the new 3:4-dimethyl-mannitol, which was obtained in the crystalline state. A specimen of the known 1:2-dimethyl ether of mannitol has been prepared from α-diacetone-mannitol, and the properties of this compound agree with those given in the literature. The action of benzoyl chloride on α-diacetone-mannitol has been investigated and 1:2-dibenzoyl-diacetone-mannitol, has been obtained as a crystalline compound, which on hydroysis yielded crystalline 1:2-dibenzoyl-mannitol. The methylation of this dibenzoate has been studied in an attempt to prepare 1:2:3:4 (or 3:4:5:6)-tetramethyl-mannitol. The preparation of 1:2-diacetyl-diacetone-mannitol, in the crystalline state, is also described.

Previous work on the constitutions of 1:6-dibenzoyl-mannitol and 1:2:6-tribenzoyl-mannitol is described, and the preparation/

preparation of these two compounds has been carried out. 1:6-Dibenzoyl-mannitol has been condensed with acetone to give the known 1:6-dibenzoyl-3:4-monoacetone-mannitol, and the latter has also been obtained by the action of a limited amount of benzoyl chloride on 3:4-monoacetone-mannitol. Methylation of the dibenzoyl-monoacetone derivative has given 1:6-dibenzoyl-3:4-monoacetone-2:5-dimethyl-mannitol and subsequent debenzoylation has afforded crystalline 3:4-monoacetone-2:5-dimethyl-mannitol. Removal of the acetone residue from the latter was achieved by acid hydrolysis and 2:5-dimethyl-mannitol was obtained in the crystalline state. The methylation of 1:6-dibenzoyl-mannitol has also been studied and some interesting results have been obtained.

The investigation, which was carried out by Irvine and Patterson in 1914, on the optical effect of successive substitution in the mannitol molecule is described. The optical rotatory powers of the new methyl ethers of mannitol have been determined, and the values of the optical rotations of the other known methylated mannitols are recorded. A study of these optical rotatory powers has shown that certain deductions of a qualitative nature concerning the optical effect of successive methylation in the mannitol molecule can be made, and the results, which are summarised in table 3 on page 26, constitute a review of the work originally carried out by Irvine and Patterson.

Compounds/

Compounds which have been prepared for the first time in the course of the present research are underlined in the above summary and also in the Experimental Section.

General Information

1. All melting points are uncorrected unless stated otherwise.
2. Determinations of methoxyl and benzoyl content were carried out by the author; all other analyses are by Drs. Weiler and Strauss, Oxford.
3. Light petroleum employed for recrystallisations boils over the range, 60° - 80°.

EXPERIMENTAL SECTION

Preparation of Triacetone-mannitol.

Triacetone-mannitol was prepared as described by Fischer (17), from 120 g. of dry powdered mannitol. The product melted at 68° and had a specific rotation of $[\alpha]_D^{20}$ +12.5° (EtOH; c=9.58). Fischer gives the melting point as 68-70° and the specific rotation as $[\alpha]_D^{20}$ +12.5° (EtOH; c=9.05).

The acetonation was carried out three times in all; the duration of the period of initial shaking being respectively (A) one hour, (B) two hours, and (C) four hours. The yields were compared and were found to have increased from 26% in (A) to 95% in (B). This was probably due to the fact that, after shaking for one hour, a large proportion of the mannitol remained undissolved in the acetone, and was filtered off. Only a negligible quantity remained undissolved when the shaking was continued for four hours.

Partial Hydrolysis of Triacetone-mannitol.

A solution of triacetone-mannitol (45g.) in 480 c.c. of acetone, containing water (90 c.c.) and 0.1 $\overline{N}$ hydrochloric acid (30 c.c.), was heated on the water bath, under reflux, for thirty minutes. The reaction was immediately arrested by the addition of an excess of aqueous ammonia (9 c.c. of 2 $\overline{N}$) and the hydrolysis products were isolated as directed/

directed by Irvine and Patterson (13). The hydrolysis was repeated several times, the average yields being:-

Unchanged triacetone-mannitol	16.3 g.	m.p. = 67-68°
Diacetone-mannitol	9.9 g.	n_D = 1.4638
		$[\alpha]_D^{20}$ +15.70° (EtOH; c=2.63)
Monoacetone-mannitol	6.0 g.	m.p.=85°
		$[\alpha]_D^{20}$ +23.0° (EtOH; c=2.63)
Mannitol	1.2 g.	

Irvine and Patterson state that α-diacetone-mannitol has a specific rotation of $[\alpha]_D^{20}$ +15.75°(EtOH; c=2.60) and that monoacetone-mannitol melts at 85° and has a specific rotation of $[\alpha]_D^{20}$ +23.2°(EtOH; c=2.6).

Benzoylation of 3:4-Monoacetone-mannitol.

1:2:5:6-Tetrabenzoyl-monoacetone-mannitol was prepared by the action of benzoyl chloride on monoacetone-mannitol in dry quinoline. The experimental details were those given by Fischer (22), the tetrabenzoate being obtained in 76% yield. The product, after recrystallisation from ethanol, melted at 122-123° and had a specific rotation of $[\alpha]_D^{20}$ +27.16° (Acetone; c=1.03). Fischer gives m.p.=122-123°(corr.) and $[\alpha]_D^{20}$ +0.60° (acetylene tetrachloride).

Deacetonation of 1:2:5:6-Tetrabenzoyl-monoacetone-mannitol.

The hydrolysis was effected in ethyl acetate solution with/

with fuming hydrochloric acid, as described by Fischer (22), a slight modification being introduced in the extraction of the product. It was found that the tetrabenzoyl-mannitol crystallised with benzene of crystallisation and this was removed by heating on the water bath in vacuo. Recrystallisation from ethanol yielded colourless needles, melting at 121-122° and with a specific rotation of $[\alpha]_D^{21}$+8.79°(Acetone; c=1.59). The product obtained by Fischer melted at 122-123°(corr.) and had a specific rotation of $[\alpha]_D^{21}$+7.83° (acetylene tetrachloride).

Methylation of 1:2:5:6-Tetrabenzoyl-mannitol.

Tetrabenzoyl-mannitol (23g.) was dissolved in the minimum quantity of hot dry acetone, with the careful addition of methyl iodide (36 c.c.) and dry silver oxide (36g.). (See Irvine and Purdie (38) for the preparation of silver oxide). The mixture was refluxed gently for six hours and the product extracted with a large excess of ether. The silver oxide was filtered off through a silica bed, washed well with ether, and the combined extracts were taken to dryness under reduced pressure.

The methylation was repeated using the same quantities of the alkylating agents and the theoretical yield (24.1g.) of tetrabenzoyl-dimethyl-mannitol was obtained. The use of acetone, as an extraneous solvent, was not necessary in the second alkylation as the partially methylated product was soluble/

soluble in methyl iodide.

Methoxyl estimation. Found : 10.0%

$C_{34}H_{28}O_8(OCH_3)_2$ requires : 9.9%

Benzoyl group estimation. Found : 4.05 groups/molecule

Tetrabenzoyl-dimethyl-mannitol requires : 4.00 groups/mol.

Debenzoylation of 1:2:5:6-Tetrabenzoyl-3:4-dimethyl-mannitol.

1. Tetrabenzoyl-dimethyl-mannitol (7.5g.) was suspended in dry methanol (100 c.c.), 0.15g. of sodium added, and the mixture shaken overnight in a small, glass-stoppered bottle. The clear solution thus obtained was evaporated to dryness under reduced pressure and the residue extracted with ether to remove methyl benzoate. The crude product (2.1g.-84%) was distilled at 160° and a pressure of 8.0×10^{-5} mm. of Hg. to give a clear syrup which could not be induced to crystallise. A portion of the syrup was redistilled and sent for analysis.

Found : C. 49.0% H. 8.16% OCH_3. 18.7% *

$C_8H_{18}O_6$ requires : C. 45.7% H. 8.57% OCH_3. 29.5%

The product is obviously not a pure dimethyl-mannitol and the low methoxyl content suggests that debenzoylation is probably not complete. A more drastic method for the removal of the benzoyl groups was thus employed.

2./

* Carried out by Drs. Weiler and Strauss, Oxford.

2. Tetrabenzoyl-dimethyl-mannitol (0.941g.) was dissolved in dry methanol (25 c.c.) by refluxing at 100° for several minutes. To this solution was added 0.099g. of sodium in 5 c.c. of dry methanol and the mixture was refluxed for a further five minutes. Water (10 c.c.), and the calculated quantity (0.216 c.c.) of glacial acetic acid required to neutralise the sodium, were then added. The methanol was removed by evaporation under reduced pressure and the residual aqueous solution extracted three times with chloroform to remove unchanged material. The aqueous solution was filtered and taken to dryness in vacuo. The residue was extracted with hot, dry acetone by refluxing for ten minutes, and the insoluble material, consisting of sodium acetate, filtered off. The acetone solution was taken to dryness under reduced pressure and yielded a colourless gum (0.245g.). The latter was distilled at 150° and 2.0×10^{-5} mm. of Hg. to give a clear viscous syrup, which crystallised on standing. Recrystallisation from ethanol gave 0.24g. (76%) of slender needles, melting at 143-144°.

Analyses ?

Methylation of ∝-Diacetone-mannitol.

The methylation was carried out as directed by Irvine and Patterson (13), 1:2-dimethyl-diacetone-mannitol being obtained as a colourless liquid boiling at 140-141°/13 mm. The product, obtained in 75% yield, had a specific rotation of/

of $[\alpha]_D^{20}$ +21.8° (EtOH); the original workers quote: $[\alpha]_D^{20}$ +21.9° (EtOH).

Deacetonation of 1:2-Dimethyl-diacetone-mannitol.

The hydrolysis of dimethyl-diacetone-mannitol was also carried out as directed by Irvine and Patterson (13). Recrystallisation of the product from benzene gave 57% of 1:2-dimethyl-mannitol, melting sharply at 93° and with a specific rotation of $[\alpha]_D^{20}$ -7.47° (EtOH; c=1.47). Irvine and Patterson give m.p.=93° and $[\alpha]_D^{20}$ -8.85° (EtOH).

Benzoylation of α-Diacetone-mannitol.

Diacetone-mannitol (14.4g.) was dissolved in dry pyridine (40 c.c.), 40 c.c. of benzoyl chloride added, and the mixture allowed to stand overnight in a tightly corked flask. The product was extracted by shaking thoroughly with benzene, and the benzene solution washed in turn with water, dilute hydrochloric acid, sodium hydroxide solution, and finally with distilled water. After drying over anhydrous sodium sulphate, the solution was evaporated to dryness under reduced pressure to give a clear syrup which crystallised partially on the addition of light petroleum. The crystalline product was filtered off, washed with light petroleum, and recrystallised several times from methanol, to give 14.1g. (55%) of 1:2-dibenzoyl-diacetone-mannitol. The product melted at 90-92° and/

and had a specific rotation of $[\alpha]_D^{21}$ +20.7° ($CHCl_3$; c=2.7).

Found : C. 66.3% H. 6.4%

$C_{26}H_{30}O_8$ requires: C. 66.4% H. 6.4%

Deacetonation of 1:2-Dibenzoyl-diacetone-mannitol.

Dibenzoyl-diacetone-mannitol (20g.) was dissolved in acetone (140 c.c.) and 20 c.c. of 2 N sulphuric acid in 40 c.c. of water were added. The mixture was refluxed at 100° and the progress of the reaction followed polarimetrically, a constant value for the rotation being attained after six hours. The solution was neutralised by the addition of excess barium carbonate, filtered, and evaporated to dryness under reduced pressure. The resulting crystalline mass was extracted with ethanol, filtered, and the alcohol extract taken to dryness. Recrystallisation from ethanol gave 14.0g (85%) of 1:2-dibenzoyl-mannitol, melting at 151-152° and exhibiting a specific rotation of $[\alpha]_D^{20}$ -22.3° (Acetone; c=0.85).

Found : C. 61.7% H. 5.5%

$C_{20}H_{22}O_8$ requires : C. 61.5% H. 5.6%

Methylation of 1:2-Dibenzoyl-mannitol.

Dibenzoyl-mannitol (12g.) was methylated by the usual procedure using methyl iodide (57 c.c.) and dry silver oxide (57g.), the dibenzoyl-mannitol being dissolved initially in the minimum quantity of hot dry acetone. The alkylation was allowed/

allowed to proceed for four hours and the product extracted in the normal manner.

After six such methylations, the methoxyl content of the molecule had reached a value of 19.3%, as compared to the theoretical 27.8% for dibenzoyl-tetramethyl-mannitol. An estimation of the benzoyl content was carried out and revealed the presence of approximately three benzoyl groups per molecule. (For details of these analytical methods see Mann and Saunders' "Practical Organic Chemistry," 2nd. edition, p.342).

The methylation was repeated using a fresh sample of dibenzoyl-mannitol, and determinations of methoxyl and benzoyl content were carried out after four treatments with the alkylating agents. The analysis figures again revealed a methoxyl content of 19.3% and a benzoyl content of three groups per molecule.

The molecular weight of the crude syrups resulting from these methylations was determined by the Cryoscopic method, and was found to be approximately 400. The molecular weight of a dibenzoyl-tetramethyl-mannitol should be 445, and thus it would not appear that any intermolecular condensation had taken place.

Preparation of 1:2-Diacetyl-diacetone-mannitol.

∝-Diacetone-mannitol (55g.) was dissolved in dry pyridine (60 c.c.),60 c.c. of acetic anhydride added, and the/

the mixture allowed to stand overnight in a tightly corked flask. The contents of the flask were transferred to a dry separating funnel and shaken thoroughly with benzene (400 c.c.). The benzene solution was washed twice with water, with dilute hydrochloric acid to remove the pyridine, with dilute sodium hydroxide solution to remove traces of acid, and finally with distilled water. After drying over anhydrous sodium sulphate, the benzene solution was filtered, and the solvent removed by distillation under reduced pressure. The product crystallised in the flask and recrystallisation from ethanol yielded 45g. (62%) of needles, melting sharply at 58° and having a specific rotation of $[\alpha]_D^{20}$ +29.48° ($CHCl_3$; c=4.39).

Found : C. 55.4% H. 7.6%

$C_{16}H_{26}O_8$ requires : C. 55.4% H. 7.5%

Preparation of 1:6-Dibenzoyl and 1:2:6-Tribenzoyl-mannitol.

50g. of mannitol, suspended in dry pyridine (152 c.c.), were treated with benzoyl chloride, as directed by Brigl and Grüner (25), and 1:6-dibenzoyl-mannitol was isolated from the reaction mixture in 42% yield. The dibenzoate melted at 179-180° and had a specific rotation of $[\alpha]_D^{19}$ +16.35°(Py.; c=3.15). Brigl and Grüner quote the melting point as 181-182°(corr.) and the specific rotation as $[\alpha]_D^{20}$ +16.2°(Py.; c=3.21).

The alcoholic mother liquors from the recrystallisation of/

of the dibenzoate were treated as described by Hockett and Fletcher (29), and 1:2:6-tribenzoyl-mannitol was obtained, in 14% yield, as uniform needles melting at 163-164°, and with a specific rotation of $[\alpha]_{,}^{19}$-42.3°(Py.; c=1.49). Hockett and Fletcher give m.p. =166-167°(corr.) and $[\alpha]_{D}^{20}$-43.7°(Py.; c=1.00).

Acetonation of 1:6-Dibenzoyl-mannitol.

The acetonation of 1:6-dibenzoyl-mannitol was carried out according to the instructions of Ohle and his coworkers (26), the 1:6-dibenzoyl-3:4-monoacetone derivative being obtained in 57% yield as long prismatic needles, melting at 95.5-96.5° and with a specific rotation of $[\alpha]_{D}^{13}$+40.5° (Acetone; c=0.59). Ohle gives the melting point as 96.5° and the specific rotation as $[\alpha]_{D}^{20}$+41.36°(Acetone ; c=0.44).

Benzoylation of 3:4-Monoacetone-mannitol.

Monoacetone-mannitol (10g.) was dissolved in a mixture of pyridine (63c.c.) and benzoyl chloride (6.3 c.c.), and the solution was kept at 37° for twenty four hours. The solution was then poured, with vigorous stirring, into 500 c.c. of 5% sulphuric acid, when the product was thrown out as an oil. The latter was taken up in ether and the ethereal solution shaken in turn with dilute sulphuric acid, sodium hydroxide solution, and distilled water. After drying over anhydrous sodium sulphate and filtering, the ethereal solution was evaporated to dryness under/

under reduced pressure. The syrupy residue was dissolved in the minimum amount of hot benzene and precipitated by the careful addition of light petroleum. The product (1.5g.=8%) was recrystallised from a mixture of benzene and light petroleum and finally obtained as prismatic needles melting at 94-95°.

A mixed melting point with 1:6-dibenzoyl-3:4-monoacetone-mannitol obtained from the 1:6-dibenzoate showed no depression and the substances are thus identical.

Methylation of 1:6-Dibenzoyl-3:4-Monoacetone-mannitol.

1:6-Dibenzoyl-3:4-monoacetone-mannitol (3.0g.) was treated, in the usual manner, with methyl iodide (15 c.c.) and dry silver oxide (15g.), the mixture being refluxed gently for six hours and the product finally extracted with ether. After three such methylations, the theoretical yield of product was obtained, as a clear syrup which could not be induced to crystallise. A sample was distilled at 125° and 4.0×10^{-5} mm. of Hg. and sent for analysis.

Found : C. 64.73% H. 6.17%

$C_{25}H_{30}O_8$ requires : C. 65.50% H. 6.55%

Debenzoylation of Dibenzoyl-monoacetone-dimethyl-mannitol.

Dibenzoyl-monoacetone-dimethyl-mannitol (1.205g.) was dissolved in dry methanol (25 c.c.), 0.066 g. of sodium in dry/

dry methanol (5 c.c.) added, and the mixture refluxed at 100° for ten minutes. Water (10 c.c.) and the calculated quantity of glacial acetic acid (0.165 c.c.) were added and the solution evaporated to dryness under reduced pressure to remove the alcohol and methyl benzoate. The residue was extracted with dry, acid-free acetone by refluxing for ten minutes, the insoluble sodium acetate filtered off, and the acetone solution taken to dryness under diminished pressure leaving a clear gum which crystallised on standing overnight. The product (0.62g.=94%) was recrystallised several times from a mixture of benzene and light petroleum and 3:4-monoacetone-2:5-dimethyl-mannitol was obtained as rhombic plates melting at 62-63° and with a specific rotation of $[\alpha]_D^{20}$ +35.75° (EtOH; c=2.57).

Found : C. 53.06% H. 8.71%

$C_{11}H_{22}O_6$ requires : C. 52.80% H. 8.80%

Deacetonation of 3:4-Monoacetone-2:5-dimethyl-mannitol.

Monoacetone-dimethyl-mannitol (0.44g.) was dissolved in a mixture of acetone (20 c.c.) and water (4 c.c.), and 4 c.c. of 2 N hydrochloric acid added. The mixture was refluxed gently at 100° on the water bath and the course of the reaction followed polarimetrically, a constant value for the rotation being attained after three hours. The hydrochloric acid was neutralised by the careful addition of barium carbonate, the solution/

solution filtered, and evaporated to dryness under reduced pressure. The syrupy residue was dissolved in absolute ethanol, a small white precipitate of barium chloride filtered off, and the solution taken to dryness. The resulting clear syrup was distilled twice at 130° and 5.0 x 10^{-4} mm. of Hg, the distillate crystallising on the addition of benzene. Recrystallisation from ethyl acetate gave 2:5-dimethyl-mannitol monohydrate, (0.33g.=79%), melting at 58.5-60° and with a specific rotation of $[\alpha]_D^{17}$ -30.1° (EtOH ; c=0.48)

Found : C. 42.9% H. 8.66%

$C_8H_{18}O_6.H_2O$ requires : C. 42.2% H. 8.86%

Methylation of 1:6-Dibenzoyl-mannitol.

Dibenzoyl-mannitol (8.0g.) was dissolved in hot, dry methanol (100 c.c.) with the addition of methyl iodide (38 c.c.) and dry silver oxide (38g.). The mixture was refluxed gently for six hours and the product extracted as usual with ether. Evaporation to dryness gave an orange syrup which was soluble in methyl iodide, and this was subjected to the normal methylation technique without the use of methyl alcohol as a solvent. After four such treatments with the alkylating agents the methoxyl content of the syrup was determined and found to be 25.2% as compared to the theoretical 27.8% calculated for dibenzoyl-tetramethyl-mannitol. Further methylation did not increase/

increase the methoxyl content and an estimation of the benzoyl content revealed the presence of three benzoyl groups per molecule.

A sample of the crude syrup was distilled at a pressure of 2.0×10^{-4} mm. of Hg. and two fractions were taken. The first, a clear limpid liquid, boiled between 95° and 115°. The second was a brown viscous gum distilling at over 115°. The benzoyl content of these syrups was investigated but no satisfactory results could be obtained.

BIBLIOGRAPHY

(1)	Crum Brown	Proc. Roy. Soc. Edin. 1890 17 181.
(2)	Ph. A. Guye	Comptes rendus, 1890 714 110.
(3)	Gray	Phys. Rev. 1916 7 472.
(4)	De Malleman	Trans. Faraday Soc. 1930 26 281.
(5)	Boys	Proc. Roy. Soc. 1934 A144 655.
(6)	Kuhn	Z. Physik. Chem. 1929 B4 14.
		Trans. Faraday Soc. 1930 26 293.
		Ber. 1930 63 190.
(7)	Born	Physikal. Zeit. 1915 16 251.
		Ann. der Physik. 1918 55 177.
		Proc. Roy. Soc. 1935 A150 84.
(8)	Lowry	Reports, British Assoc. 1934 43.
(9)	Pickard and Kenyon	J.C.S. 1911 99 45 et seq.
(10)	Levene et al	J. Biol. Chem. 1924-1936.
		J. Org. Chem. 1937 1 76.
(11)	Rule et al	J.C.S. 1924 125 2155 et seq.
		J.C.S. 1931 674 et seq.
(12)	Hudson	J.A.C.S. 1909 31 66 et seq.
(13)	Irvine & Patterson	J.C.S. 1914 105 898, 915.
(14)	Irvine & Steele	J.C.S. 1915 107 1221.
(15)	Proust	Annales de Chimie 1806 57 143.
(16)	McCrea	Nature, 1931 127 162.
(17)	Fischer	Ber. 1895 28 1145.

(18)/

(18)	Baer & H.O.L. Fischer	J.Biol. Chem. 1939 128 463.
(19)	H.O.L. Fischer & Appel	Helv. Chim. Acta. 1934 17 1574.
(20)	Müller	Ber. 1932 65 1055.
(21)	Brigl & Grüner	Ber. 1933 66 931.
(22)	Fischer	Ber. 1915 48 266.
(23)	Wiggins	J.C.S. 1946 13.
(24)	Einhorn & Hollandt	Ann. 1898 301 95.
(25)	Brigl & Grüner	Ber. 1932 65 641.
(26)	Ohle et al	Ber. 1929 62 2982.
(27)	Haworth & Wiggins	J.C.S. 1944 58.
(28)	Compton	J.A.C.S. 1938 60 395.
	Cramer & Purves	J.A.C.S. 1939 61 3458.
	Hockett & Downing	J.A.C.S. 1942 64 2463.
(29)	Hockett & Fletcher	J.A.C.S. 1944 66 469.
(30)	Fischer & Bergmann	Ber. 1919 52 830.
(31)	Zemplén & Pascu	Ber. 1929 62 1613.
(32)	Dewar & Fort	J.C.S. 1944 496.
(33)	v. Vargha	Ber. 1933 66 1394.
(34)	Braham	J.A.C.S. 1919 41 1707.
(35)	Haskins, Hann & Hudson	J.A.C.S. 1943 65 70.
(36)	Wiggins	J.C.S. 1946 384.
(37)	Freudenberg & Sheehan	J.A.C.S. 1940 62 558.
(38)	Irvine & Purdie	St. Andrews University Memorial Volume of Scientific Papers - 'A general review of Purdie's reaction.'

PART II

Investigations

on the Structure of Rubremetine

INTRODUCTION

Emetine is the principal member of the group of alkaloids obtained from the roots of Cephaelis Ipecacuanha and related plant species.

The first crude preparation of the alkaloid was obtained by Pelletier and Magendie (1) in 1817, and since that date, the chemistry of emetine has been the subject of numerous researches. Despite these many investigations, it is only recently that conclusive proof of the structure of emetine has been forthcoming, as the result of systematic degradative work.

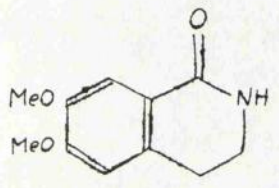
Oxidation techniques have played a large part in the study of the problem and the isolation of a brilliant red substance, by the gentle oxidation of the parent alkaloid, has proved to be of considerable interest. Any structure proposed for emetine must be able to account for the formation of this highly coloured dehydro derivative, which has been termed rubremetine, and an examination of the constitution of the latter compound is thus advisable.

The present research is part of a general investigation which is being carried out in St. Andrews on the emetine problem, and it deals in particular with the structure of rubremetine and related topics.

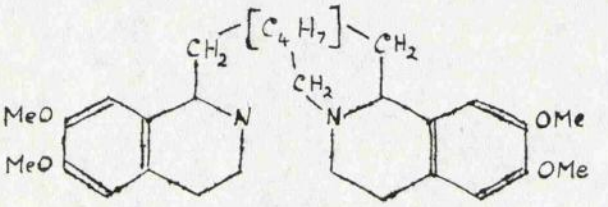
INVESTIGATIONS ON THE STRUCTURE OF EMETINE AND RELATED ALKALOIDS.

The early investigations on the chemistry of emetine did not give a great deal of information concerning the detailed structure of the alkaloid. The painstaking researches of Pyman and his coworkers (2, 3, 4, 5) established the molecular formulae of the bases derived from ipecacuanha, and demonstrated the relationships which exist between emetine and its congeners. The nature of the functional groupings present in the molecule was investigated by several workers (6, 7), and the results of oxidative degradation, combined with spectroscopic studies, indicated the presence of two tetrahydroisoquinoline residues (2,8).

The first direct chemical evidence for this latter hypothesis came from the work of Späth and Leithe (9) who isolated corydaldine (I) from the mild potassium permanganate oxidation of emetine in alkaline solution. On the basis of their results, they put forward the partial structure (II) for emetine, and conjectured that the tertiary nitrogen atom was part of a piperidine ring.

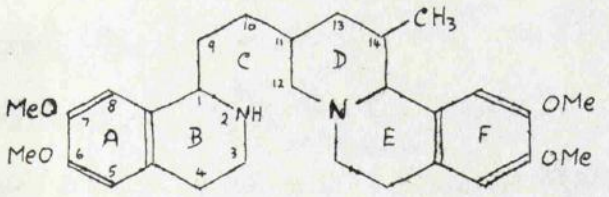


I

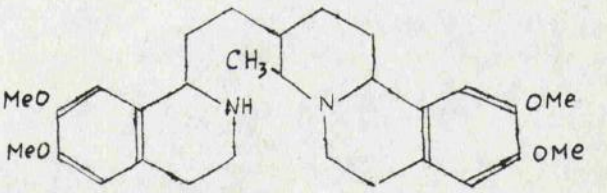


II

Following the publication of this work, Brindley and Pyman (5) presented the first complete proposals for the constitution of emetine and the related alkaloids. They suggested that emetine should be represented by structure (III), this formulation being derived from an earlier proposal (IV) made by Robinson on biogenetic grounds. This structure (III) could explain all the known chemical properties of emetine and it also afforded an ingenious explanation of the formation of rubremetine, which will be discussed in the following chapter.



III

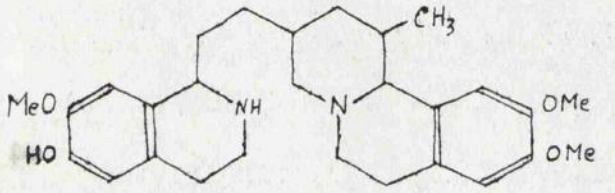


IV

This new formula for emetine permitted the deduction of intelligible formulae for the subsidiary alkaloids of ipecacuanha, of which some mention might be made.

Cephaeline, $C_{28}H_{38}O_4N_2$, was known to contain one phenolic hydroxyl group and to yield emetine on methylation. Moreover, on oxidation with ferric chloride it gave a base, $C_{20}H_{27}O_3NCl_2$, and not the anticipated, rubremetine-like, substance. As the result of a study of this oxidation product, Brindley and Pyman concluded that the phenolic group must be in ring A, and suggested that it occupies position 6. Thus, on the basis of their formula for/

for emetine, they assigned structure (V) to cephaeline. This proposal was given strong support by the researches of Späth and Leithe (9).



V

The constitutions assigned to psychotrine, $C_{28}H_{36}O_4N_2$, and O-methylpsychotrine, $C_{29}H_{38}O_4N_2$, may now be considered in some detail, as the nature of the latter compound will be shown to have a bearing on the structure of rubremetine.

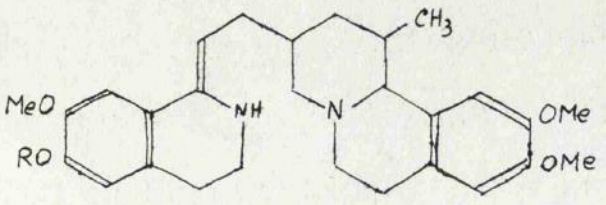
It was known that psychotrine, on reduction by chemical methods, yielded a mixture of bases from which cephaeline and a stereoisomer, isocephaeline, could be isolated. Similar reduction of O-methylpsychotrine gave a mixture of emetine and isoemetine. Recently it has been shown by Karrer (10), that the catalytic hydrogenation of O-methylpsychotrine yields either emetine or isoemetine according to the conditions employed. It is thus apparent that both psychotrine and O-methylpsychotrine contain one olefinic linkage and reduction creates at least one new asymmetric centre.

Brindley and Pyman suggested that the double bond lay between C_1 and C_9 and based this proposal on the following observations.

They/

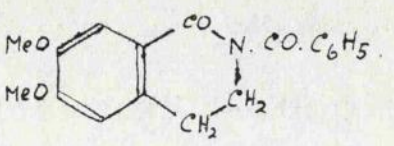
They showed that O-methylpsychotrine gave a good yield of psychotrine on partial hydrolysis with one mole of acid. As psychotrine, like cephaeline, appears to possess the phenolic hydroxyl group at position 6 in ring A, they argue that the demethylation of this particular hydroxyl is due to the activating effect of the substituted vinyl group in the <u>para</u> position.

It was also known that the chemical reduction of O-methylpsychotrine afforded a third product, in addition to emetine and <u>iso</u>emetine. This substance, $C_{28}H_{38}O_3N_2$, which contained only three methoxyl groups, was assumed to have arisen from O-methylpsychotrine by replacement of one methoxyl group by a hydrogen atom, and saturation of the olefinic linkage. There is evidence (11) that such replacements of alkoxy groups by hydrogen are facilitated by a substituted vinyl group in the <u>para</u> position, and support is thus given to the structures proposed for psychotrine (VI) and O-methylpsychotrine (VII).



VI , R = H

VII , R = Me.

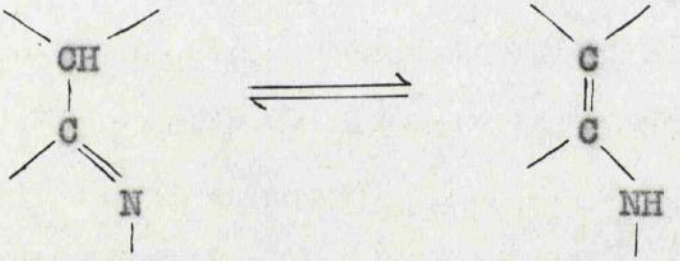


VIII

Further support for the above structures came from the work/

work of Carr and Pyman (2) who claimed to have shown that O-methylpsychotrine is a secondary-tertiary base by the isolation of its N-monobenzoyl derivative. Confirmation of this proposal came from later work carried out by Karrer (10), who oxidised N-benzoyl-O-methylpsychotrine and obtained N-benzoylcorydaldine (VIII).

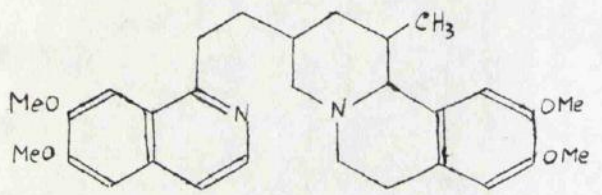
It is known, however, that tautomerism exists in the system



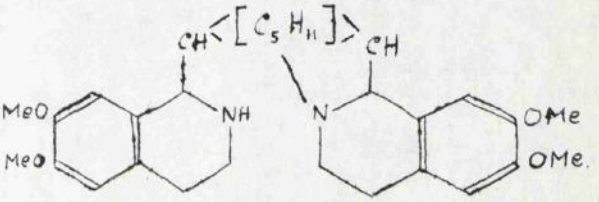
and thus, if the double bond in O-methylpsychotrine should normally lie between C_1 and N_2, the formation of the N-monobenzoyl derivative would still be possible by migration of the double bond out of the ring. Examples of this type of migration are known in the chemistry of the alkaloids (12), and it seems possible that the double bond in O-methylpsychotrine might occupy the C_1 to N_2 position. Further evidence relating to this point will be presented later.

Finally, the structure proposed for <u>emetamine</u>, $C_{29}H_{36}O_4N_2$, may be studied. This substance is a ditertiary base which, on reduction, yields a small quantity of <u>iso</u>emetine. Emetamine is more feebly basic than O-methylpsychotrine, and Brindley and Pyman formulate the base as containing one unreduced 6:7-dimethoxy<u>iso</u>quinoline residue (IX). This proposal has

received support from work carried out recently by Ahl and Reichstein (13), who isolated emetamine from the complex mixture of substances produced by the catalytic dehydrogenation of emetine.



IX



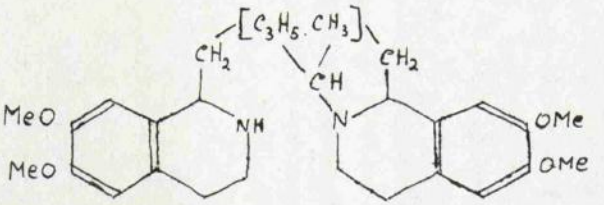
X

These detailed structures, advanced by Brindley and Pyman, for the ipecacuanha alkaloids, were based on admittedly speculative considerations, and while they provided a satisfactory basis for further research, the known facts, at that time, were more accurately represented by the partial structure (X) for the parent alkaloid.

The only work of interest to be published during the subsequent twenty years was a study of the partial Hofmann degradation of N-acetylemetine, carried out by Ahl and Reichstein (13). These workers succeeded in eliminating the tertiary nitrogen atom from the molecule, and by oxidation of the final product, obtained 4:5-dimethoxyphthalonimide, thus proving conclusively that the secondary nitrogen atom of emetine is part of a 6:7-dimethoxytetrahydroisoquinoline structure. They also investigated the catalytic dehydrogenation of emetine; further consideration/

consideration of this work will be given in the Theoretical Section.

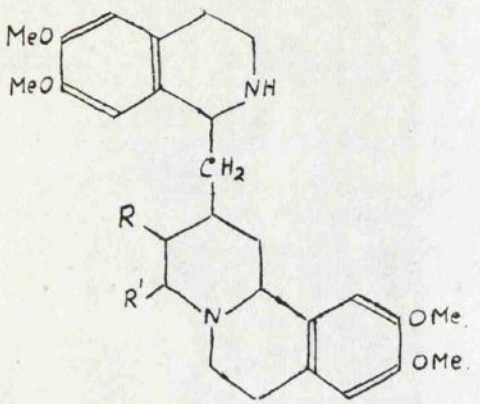
During recent years, work has been carried out, in this laboratory, on the structure of emetine, by Dr. A.R. Battersby and Dr. H.T. Openshaw (14,15). A careful study of the Hofmann degradation of emetine was made by these workers, and the results indicated that the partial structure (XI) could be assigned to emetine. It was now apparent that the structure (III), put forward by Brindley and Pyman, could no longer be accepted.



XI

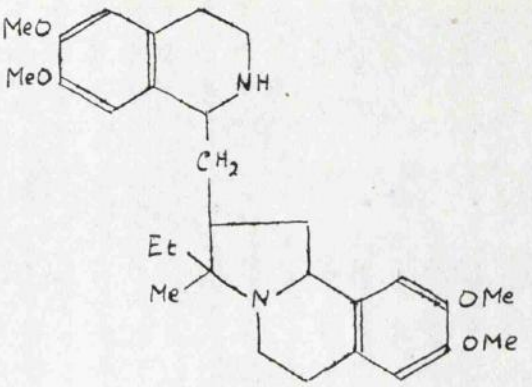
A series of papers were published, at this point, by Späth and Pailer (16), who had also investigated the Hofmann degradation of emetine. The results obtained by the Austrian workers were in complete agreement with the partial structure (XI) and they led to three possible formulae (XII, XIII, XIV) for emetine.

(OVER).



XII ; R = Et, R' = H

XIII ; R = R' = Me.



XIV

Robinson (17) has pointed out that structures (XII) is satisfactory on biogenetic grounds; structure (XIII) and (XIV), on the other hand, cannot be readily reconciled with theories of biogenesis.

In a more recent paper, Pailer and Porschinski (18) described the isolation of 4-methyl-3-ethylpyridine (β-collidine) from the drastic dehydrogenation of two degradation products of emetine, and claimed that this strongly supports structure (XII). The formation of β-collidine, however, involves a far reaching decomposition and the authors themselves admit that the possibility of molecular rearrangement cannot be entirely excluded.

By a continuation of their systematic degradative study, Battersby and Openshaw (15) have now obtained conclusive experimental evidence for the structure of emetine, and there is no doubt that the alkaloid is correctly represented by formula (XII).

RESEARCHES INTO THE STRUCTURE OF RUBREMETINE.

The results obtained by a study of the oxidative degradation of emetine, and the related alkaloids, may be conveniently grouped in two sections. Firstly, there are those methods which involve an extensive breakdown of the molecule and the isolation of small fragments, and secondly, those which leave the carbon skeleton of the alkaloid intact, and are more correctly termed dehydrogenations.

Reagents such as potassium permanganate and chromic acid are typical of the first category of oxidising agent, and treatment of emetine with these substances has given products such as 6:7-dimethoxy*iso*quinoline-1-carboxylic acid, *m*-hemipinic acid (2), and 4:5-dimethoxyphthalonimide (8). These, and related observations, established the presence of two 1-substituted-6:7-dimethoxytetrahydro-*iso*quinoline units in emetine, but gave no information regarding the central part of the molecule.

Oxidation with mild acidic oxidising agents, on the other hand, effects a dehydrogenation to give a highly coloured derivative. Thus, when Carr and Pyman (2) treated emetine hydrochloride with a large excess of aqueous ferric chloride, and extracted the product with chloroform, they obtained a new scarlet hydrochloride, which was deposited as minute *red needles* on crystallisation from water. This substance, which was formed in about 35% yield, was designated *rubremetine hydrochloride*, from the/

the parent base rubremetine. No further crystalline products could be obtained from the remainder of the oxidised material, which was dark brown in colour, and of a resinous character.

The melting point of the air-dried salt, which contains six molecules of water of crystallisation, varies greatly with the rate of heating, but 127-128°(corr.) may be taken as an average figure for the melting and effervescing point. After drying at 100°, the salt, when placed in the bath at 150°, sinters from 166° and melts and effervesces at 173°(corr.). After drying at 100°, it suffers a further loss at 110-120°, and undergoes some change, becoming insoluble in water but soluble in dilute hydrochloric acid.

The salt is readily soluble in alcohol or chloroform, sparingly so in cold, but more readily in hot water, moderately soluble in cold acetone and more readily in the hot solvent, and insoluble in ethyl acetate. With Frohde's reagent, a sherry colour changing to magenta is produced first, but almost immediately becomes sage-green.

The corresponding hydrobromide and hydriodide were prepared by double decomposition with potassium bromide and iodide, and the analyses of these salts led to the general formula, $C_{29}H_{33}O_4N_2X$ (X = Halogen). The substance is incapable of forming diacidic salts and one nitrogen atom has therefore been rendered either non-basic or only feebly basic. That the former was correct was shown by Brindley (19), who found that the salt was sparingly soluble/

soluble in concentrated hydrochloric acid, and the solution deposited the original material on cooling.

Carr and Pyman were somewhat uncertain as to the nature of the second nitrogen atom in rubremetine, but in view of the strength of the base, and its facility for decomposition, they suggested that this nitrogen atom was quaternary in character, and in subsequent publications (5) the salt was referred to as rubremetinium chloride.

Confirmation of the quaternary nature of this second nitrogen atom has come from the work of Battersby and Openshaw (20), who carried out a potentiometric titration using 0.01$\bar{N}$ sodium hydroxide solution and obtained a curve for 'rubremetine hydrochloride' which was almost identical with that for an equimolar solution of potassium chloride; the curve for a similar solution of ammonium chloride differed considerably. Moreover, the alkaline solution showed no fall in pH on standing and this would seem to indicate that no appreciable quantity of pseudo-base is formed under these conditions.

The action of silver oxide on rubremetinium chloride had also been investigated by Carr and Pyman, and a further study was made by Battersby and Openshaw, the results confirming the earlier observations. A deep red, halogen-free solution was obtained on treating an aqueous solution of rubremetinium chloride with silver oxide, and acidification of a sample of this strongly alkaline solution gave rubremetinium chloride in 88% yield.

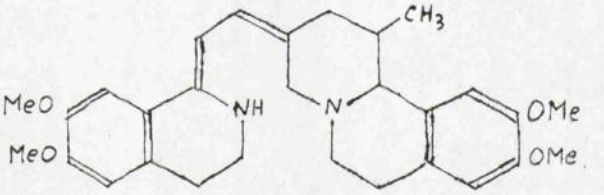
When/

When the solution was evaporated to dryness two products were obtained. One, a bright red, micro-crystalline solid was evidently the quaternary hydroxide, since it dissolved in water to give an alkaline solution from which the chloride could be recovered by the addition of hydrochloric acid. The second substance was an orange-yellow gum, insoluble in water, but soluble in ether. It dissolved in dilute hydrochloric acid, but no rubremetinium chloride could be isolated from the resulting dark red solution. This second substance was probably a pseudo-base or an anhydro-base, as it was observed that its solutions were very unstable and rapidly darkened and resinified on standing.

Pyman (3) also investigated the oxidation of emetine by members of the halogen group. Employing iodine in alcoholic solution as the oxidising agent, he isolated rubremetine together with an interesting by-product which proved to be O-methylpsychotrine (VII). Pyman also observed that O-methylpsychotrine can be dehydrogenated by bromine in chloroform to give rubremetinium bromide, and this base must therefore be an intermediate in the oxidation of emetine to rubremetine.

A second intermediate in the latter oxidation was isolated by Battersby and Openshaw (20). These workers treated emetine hydrochloride with mercuric acetate in boiling, aqueous acetic acid and isolated rubremetine in 45% yield. A second product of this oxidation was a base, isolated as its crystalline hydrogen oxalate/

oxalate. Analysis indicated the formula, $C_{29}H_{36}O_4N_2$, and since micro-hydrogenation confirmed the presence of two ethylenic linkages, the base was termed tetradehydroemetine. A spectroscopic study suggested that the double bonds were conjugated with one another and with a benzene nucleus, and the tentative formula (XV), based on Brindley and Pyman's structure for emetine, was therefore put forward.

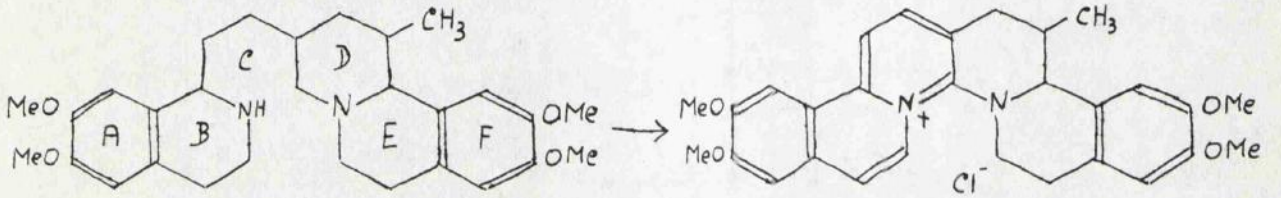


XV

Further properties of this interesting substance, and alternative proposals for its structure, will be examined in the Theoretical Section. Battersby and Openshaw found, however, that tetradehydroemetine was converted to rubremetine on further treatment with mercuric acetate, and thus it represents a second intermediate stage in the dehydrogenation of emetine.

In the formation of rubremetinium chloride from emetine hydrochloride, eight atoms of hydrogen are eliminated from the molecule, one nitrogen atom becomes quaternary, and the other loses its basic character. Brindley and Pyman (5) were the first workers to put forward a tentative structure for rubremetine, and they suggested that the change from emetine (III) to rubremetinium chloride/

chloride (XVI) involved an oxidative ring closure between carbon atom 12 and nitrogen atom 2. The loss of basicity of one of the nitrogen atoms was attributed to the resulting amidine formation. Aromatisation of rings B and C was also postulated to account for the colour of the product.



III XVI

Brindley and Pyman (5) further investigated the chemistry of rubremetine, and noted that it could not be obtained either from the oxidation of N-methylemetine, or from the oxidation of emetamine.

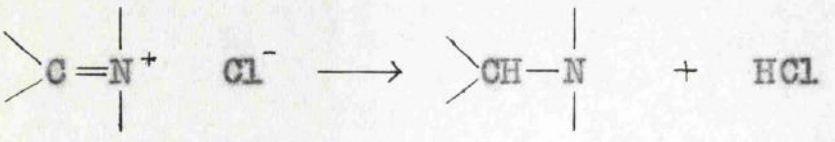
Treatment of the latter alkaloid with bromine in chloroform gave a small amount of a red micro-crystalline solid, which resembled rubremetinium bromide in colour and solubility, but differed in melting point. The non-identity of these two oxidation products has recently been confirmed by Karrer (10) who studied the absorption spectra of the compounds.

The oxidation of N-methylemetine has been studied in the course of the present research and the results, which confirm those of Brindley and Pyman, will be discussed fully in the Theoretical Section.

It/

It was pointed out by Staub (21), that the structure (XVI), proposed for rubremetine, contains two hydrogen atoms fewer than are required by the analytical results. This is not a serious objection, however, as the necessity for careful drying of rubremetinium salts before analysis, and their high molecular weight, make the exact hydrogen content of the molecule rather uncertain. In view of this uncertainty regarding the degree of unsaturation of rubremetinium salts, Battersby and Openshaw carried out an investigation of their catalytic reduction. This study did not yield the desired information but some interesting results were obtained; an extension of this work forms part of the present research.

The original workers found that hydrogenation of an alcoholic solution of rubremetinium chloride, using Adam's platinum catalyst, was very slow, and ceased when about 0.6 moles of hydrogen had been absorbed. In the presence of three moles of sodium acetate, however, a rapid uptake of one mole of hydrogen occurred, complete in five hours, the solution becoming almost colourless. Battersby and Openshaw suggested that the beneficial effect of the sodium acetate indicated that the quaternary nitrogen atom was involved.



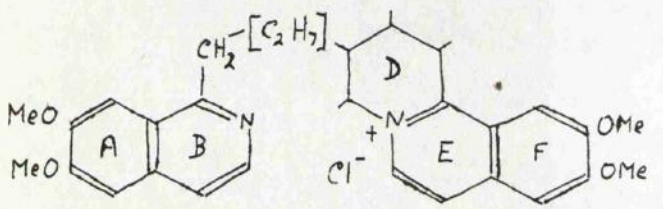
No/

No reduction product could be isolated by these workers as the solution was rapidly reoxidised by atmospheric oxygen in the presence of the catalyst, with the formation of orange-red rubremetinium chloride.

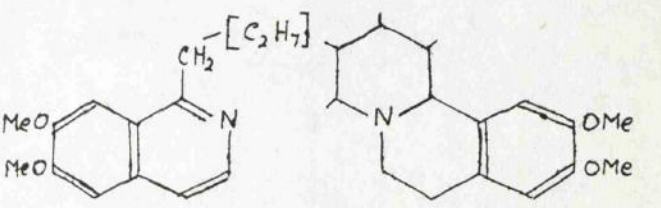
Carr and Pyman (2) investigated the chemical reduction of rubremetine, and found that rubremetinium chloride was unaffected by boiling with tin and hydrochloric acid for two days; reduction with sodium and alcohol, on the other hand, appeared to effect some change.

The chemical reduction of rubremetine was also investigated by Karrer, Eugster and Rüttner (10), who treated rubremetinium bromide with zinc dust and acetic acid. These workers isolated a crystalline base from the reaction mixture, and analysis indicated the molecular formula, $C_{29}H_{36}O_4N_2$. Karrer and his collaborators also reported that a solution of this tetrahydro derivative, which was optically active, was not reduced by hydrogen in the presence of platinum black. With methyl iodide, the reduction product gave a crystalline monomethiodide.

On the basis of this work, Karrer, Eugster and Rüttner proposed the partial structures (XVII) and (XVIII) for rubremetine and its reduction product, respectively.



XVII



XVIII

The structure (XVII), proposed for rubremetine, does not explain satisfactorily several properties of rubremetinium salts, and there is no doubt that it is incorrect. The nitrogen atom in ring B of formula (XVII) must have the normal basic character, whereas the non-quaternary nitrogen atom in rubremetine has lost its basic function completely. There is also no apparent reason why the structure (XVII) should be deep red in colour. Karrer claims that the rings E and F form the chromophore system found in the berberis alkaloids and dehydrocorydaline, but as these substances are either colourless or pale yellow, the explanation is far from satisfactory. Also, the proposed structure cannot explain the catalytic hydrogenation of rubremetine to a dihydro derivative which is resistant to further reduction. Moreover, if Karrer's proposal is correct, it would be expected that the product obtained by the oxidation of emetamine (IX, p.54), in which ring B is already aromatic, would be identical with rubremetine, and Karrer (10) shows that this is not the case. Finally, although emetine can be oxidised to rubremetine by mercuric acetate, it has been found that this reagent is incapable of dehydrogenating 1-n-butyl-3:4-dihydroisoquinoline under similar conditions (22).

The question of providing a satisfactory structure for rubremetine on the basis of the established formula (XII) for emetine still remains, and the present research has been directed towards the solution of this problem.

THEORETICAL SECTION

STUDY OF THE DEHYDROGENATION OF EMETINE

The dehydrogenation of emetine has been investigated by two distinct methods in the course of the present research, and the results which have been obtained have given considerable information concerning the nature of rubremetine. A further study was made of the oxidation of the alkaloid with mercuric acetate, and the work of Battersby and Openshaw (20) has been confirmed and extended. The catalytic dehydrogenation of emetine has also been investigated and some interesting results have been obtained.

In mercuric acetate, the organic chemist possesses a mild oxidising agent which is of considerable value, since any excess can be readily removed from the reaction mixture by treatment with hydrogen sulphide. This reagent has been used for the dehydrogenation of hydroaromatic nitrogenous rings (23), and the work of Battersby and Openshaw has shown that it provides a very convenient method for the preparation of rubremetine.

The mercuric acetate oxidation of emetine has been repeated using five molecular proportions of mercuric acetate. In an endeavour to take the reaction more nearly to completion, the heating of the mixture at 100°, after the addition of the oxidising solution, was extended from half an hour to two hours, and increased/

increased yields of the two main oxidation products were obtained. Tetradehydroemetine was isolated as the crystalline hydrogen oxalate in 45% yield, and rubremetinium chloride in 19% yield. A subsequent oxidation on a larger quantity of emetine, using six moles of mercuric acetate, gave 43% of tetradehydroemetine hydrogen oxalate and 46% of rubremetinium chloride. These yields are higher than any previously recorded for this oxidation.

It has already been mentioned that Battersby and Openshaw carried out a micro-hydrogenation of tetradehydroemetine hydrogen oxalate and confirmed the presence of two ethylenic linkages in the molecule. The small quantity of material involved, however, precluded any attempt to isolate crystalline products from the reaction mixture.

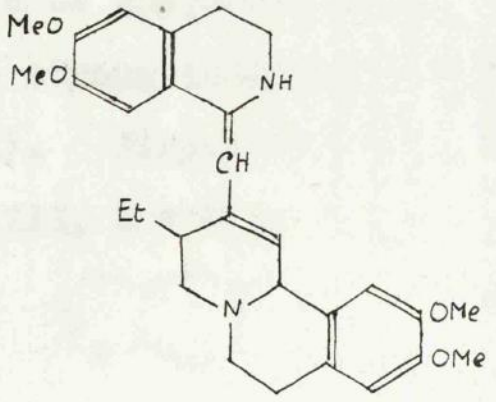
The catalytic reduction of tetradehydroemetine hydrogen oxalate, in aqueous solution, has been repeated on a somewhat larger scale. No trace of emetine could be detected in the resulting mixture of substances, but <u>iso</u>emetine was obtained in 78% yield as the crystalline N-monobenzoyl derivative.

At least two new asymmetric centres are created in the reduction of tetradehydroemetine, and the formation of four stereoisomeric 'emetines' is thus possible. It was thought that the slightly acidic conditions, under which the hydrogenation of the hydrogen oxalate had been carried out, might affect the stereochemistry of the reduction. A sample of the free base in

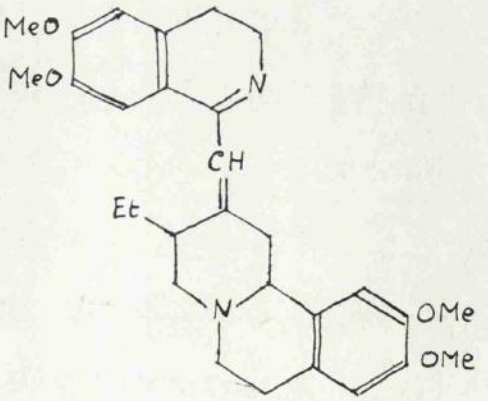
alcoholic/

alcoholic solution was therefore reduced under similar conditions. Attempts to isolate emetine from the reaction mixture again proved abortive, and the yield of N-monobenzoyl<u>iso</u>emetine was only 36%. The remainder of the benzoylated material was a dark yellow resin from which no further crystalline products could be isolated.

The structure (XV), suggested by Battersby and Openshaw for tetradehydroemetine, may now be modified to (XIX) on the basis of the established formula for emetine. In view of the discussion on page 53 concerning the position of the double bond in O-methylpsychotrine, which is also an intermediate in the oxidation of emetine to rubremetine, it would seem reasonable to suggest structure (XX) as a further possibility for tetradehydroemetine.



XIX

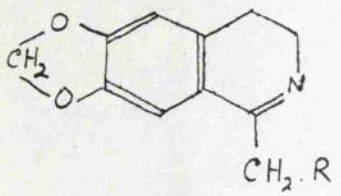


XX

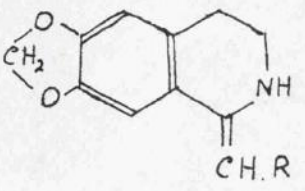
The absorption spectrum of a specimen of tetradehydroemetine hydrogen oxalate in aqueous solution has been determined in an endeavour to obtain further information concerning the position of/

of the ethylenic linkages, and the curve is given in figure 1. The maxima of this light extinction curve coincide almost exactly with those obtained by Battersby and Openshaw for tetradehydroemetine hydrogen oxalate, but there is some discrepancy as to the intensity of the absorption. These intensities have therefore been carefully checked using a fresh sample of tetradehydroemetine hydrogen oxalate and the results confirm the values given in figure 1.

Within recent years, a paper has been published by Bills and Noller (24) on the absorption spectra of dihydro<u>iso</u>quinolines. These workers studied the light extinction curves of substances of the type (XXI, R = H or C_6H_5) and have shown that they exist in this form and not as the alternative structure (XXII, R = H or C_6H_5), even though the double bond in (XXII), when R = C_6H_5, would be conjugated with two benzene nuclei. There appears to be a strong tendency for the double bond to be <u>endocyclic</u> as in (XXI). Figure 1. gives the 'averaged' curve of the hydrochlorides of (XXI, R = H or C_6H_5).



XXI



XXII

The similarity between this curve and that for tetradehydroemetine hydrogen oxalate will at once be apparent, and this is evidence in favour of structure (XX) for tetradehydroemetine/

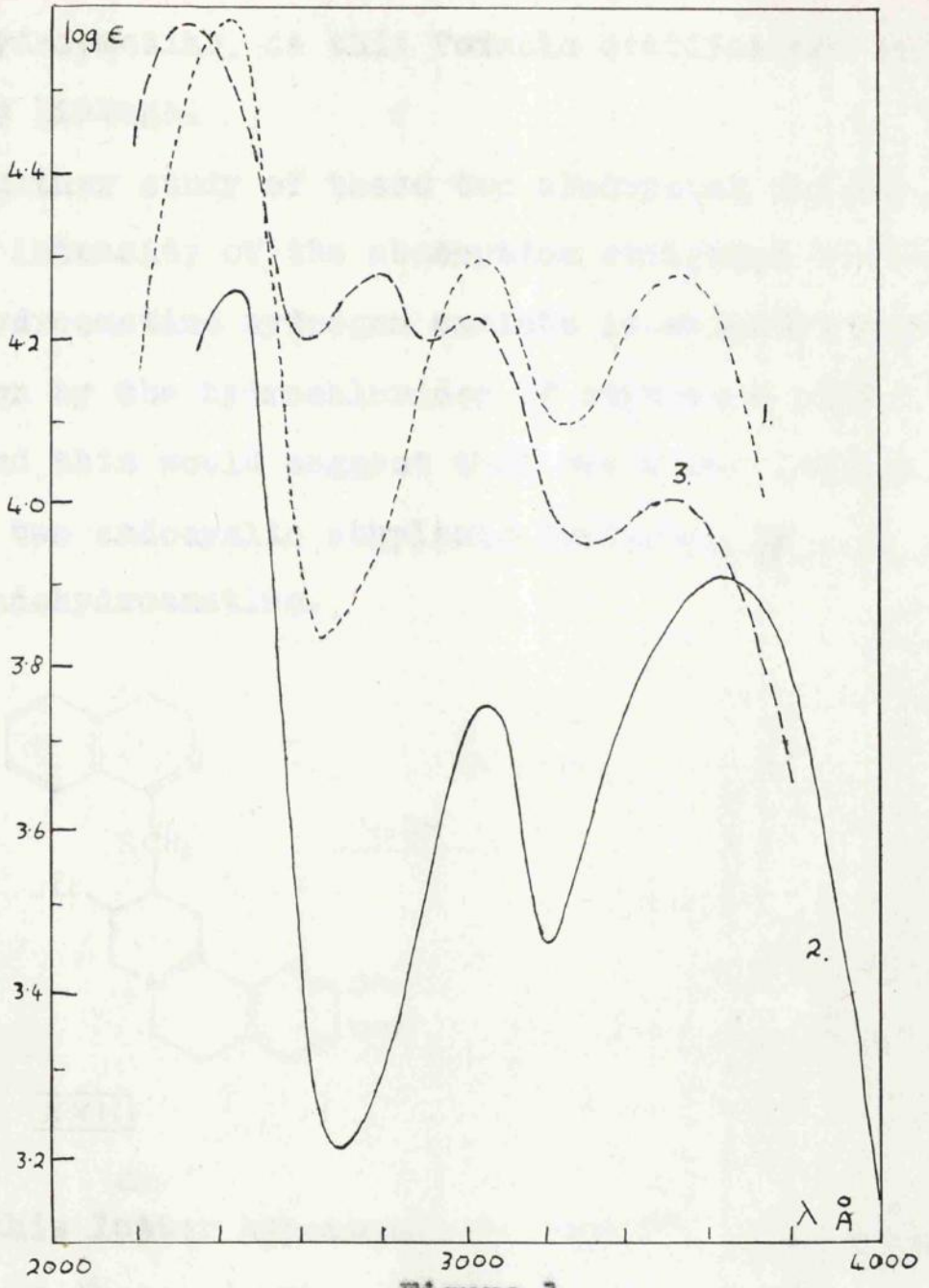
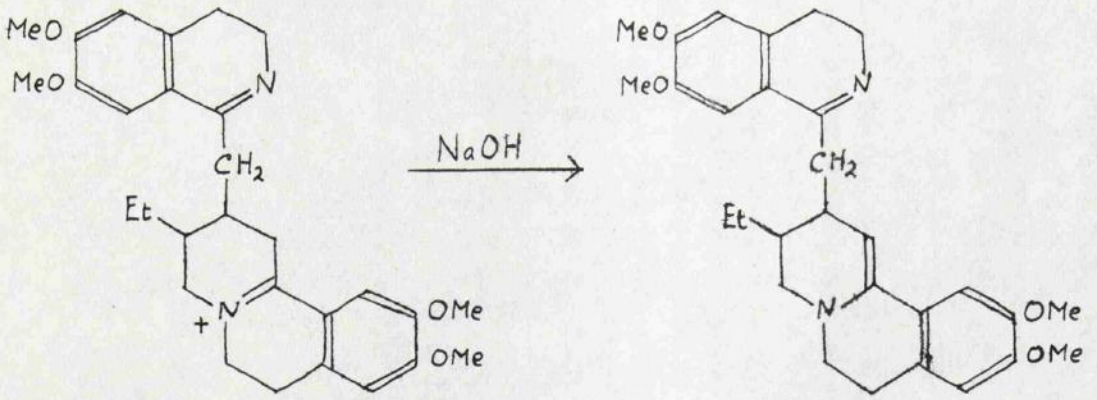


Figure 1.

		$\lambda_{max.}$	ϵ
Curve 1.	Tetradehydroemetine hydrogen oxalate.	2450 3050 3550	36,920 19,060 18,700
Curve 2.	Hydrochlorides of (XXI, R = H or C_6H_5).	2450 3050 3650	16,980 5,650 7,920
Curve 3.	Tetradehydroemetine hydrogen oxalate plus excess alkali.	2300 2800 3020 3510	38,110 19,050 16,940 10,060

tetradehydroemetine, as this formula contains one endocyclic ethylenic linkage.

A further study of these two absorption spectra has shown that the intensity of the absorption exhibited by the tetradehydroemetine hydrogen oxalate is slightly more than twice that shown by the hydrochlorides of structure (XXI, R = H or C_6H_5), and this would suggest that structure (XXIII), which contains two endocyclic ethylenic linkages, is also a possibility for tetradehydroemetine.



XXIII

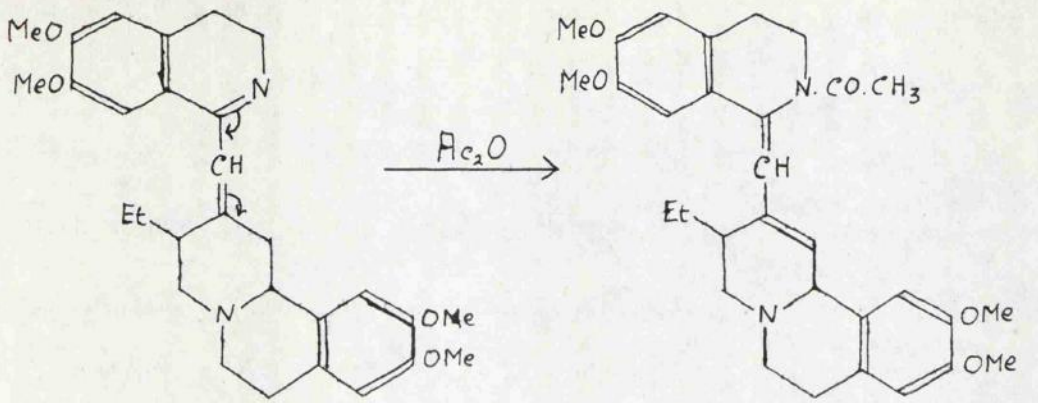
If this latter hypothesis is correct, there will probably be a marked change in the absorption spectrum of tetradehydroemetine hydrogen oxalate when measured in alkaline solution, as the result of a migration of the double bond out of the ring. The light extinction curve of a specimen of tetradehydroemetine hydrogen oxalate has therefore been determined in the presence of excess aqueous alkali, and the resulting curve is given in figure 1.

Comparison/

Comparison of this latter curve with the absorption spectrum of tetradehydroemetine hydrogen oxalate reveals that some change has taken place, although the magnitude of the change does not appear to be as great as is known to exist for a similar migration of an ethylenic linkage (24). The evidence, however, is not conclusive and the structure (XXIII) must remain as a possibility for tetradehydroemetine.

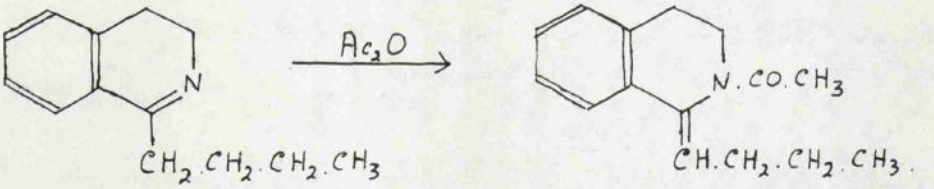
In an endeavour to obtain further information concerning the structure of tetradehydroemetine, an attempt was made to acetylate the compound. The method employed was that used by Ahl and Reichstein (13) for the acetylation of emetine, and involved shaking the base with acetic anhydride and 10% potassium hydroxide solution. The product was found to contain 85% of the starting material and a more vigorous acetylation was attempted, the tetradehydroemetine being heated with acetic anhydride and a few crystals of sodium acetate in an atmosphere of carbon dioxide. The product now contained only a negligible quantity of the starting material, but the N-acetyltetradehydroemetine (XXIV) could not be induced to crystallise, and decomposed on attempted distillation.

N-Acetyltetradehydroemetine appeared to be very unstable, and on exposure to air and light underwent changes which rendered it much darker in colour and insoluble in ether.



XX XXIV

Acetylation of the model substance, 1-n-butyl-3:4-dihydroisoquinoline (XXV), under similar conditions, gave a 94% yield of a pale brown gum which distilled to give a water-white product. No sign of instability or decomposition was apparent.

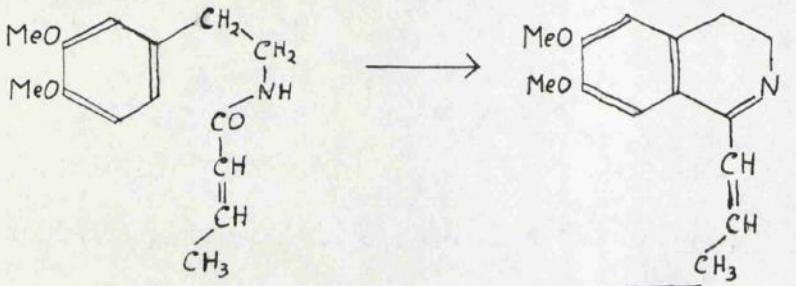


XXV XXVI

The stability of this model substance to light and air, and to distillation, lends support to the structure (XX) for tetradehydroemetine. Acetylation of the alternative (XXIII) would involve a shift of one unsaturated linkage similar to that observed with the model substance, and the product would likewise be expected to be stable.

A second model substance (XXVIII) has also been prepared, and it was intended to compare its absorption spectrum with that of tetradehydroemetine. Crotonyl chloride in ether was added dropwise/

dropwise to a solution of two molecular proportions of homoveratrylamine in ether. The resulting amide (XXVII) was obtained in the crystalline state, and ring closure was achieved by the Bischler-Napieralski reaction to give the corresponding dihydroisoquinoline (XXVIII).

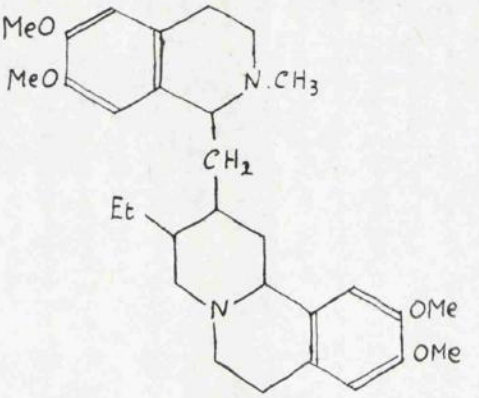


XXVII XXVIII

This compound was extremely unstable, and all attempts to prepare crystalline derivatives have so far proved fruitless. The product decomposed on attempted distillation in a high vacuum and a large proportion appeared to polymerise to give a dark brown resin. The behaviour of this model substance was very similar to that observed with the free base, tetradehydroemetine, and this would also seem to give support to structure (XX) for the latter compound.

No experimental details were given by Brindley and Pyman (5) for the oxidation of N-methylemetine (XXIX), though they stated that treatment of this base with bromine did not give rubremetine. In view of the importance of this observation, it was deemed advisable to repeat the oxidation of N-methylemetine, and a new method for its preparation was also undertaken. This method was first employed by Craig and Tarbell (25) for the methylation of a secondary/

secondary nitrogen atom in the conversion of tetrahydropapaverine to laudanosine.



XXIX

Emetine, in alcoholic solution, was shaken with excess formaldehyde and hydrogen at a pressure of two to three atmospheres in the presence of Raney nickel catalyst. The shaking was continued for five hours and, after filtering off the catalyst and evaporating to dryness, the product was obtained as a clear red gum. Separation of the unchanged secondary-tertiary base from the ditertiary base was achieved by preparation of the acidic succinyl derivative of the former and its removal by extraction with sodium hydroxide solution. This method of separation was first employed by Karrer and his coworkers (10) for the isolation of emetamine from a mixture of emetine and emetamine. N-methylemetine (XXIX) was obtained in 19% yield as the crystalline hydrobromide. This yield compares favourably with that obtained by Carr and Pyman (2) using a more tedious methylation procedure involving dimethyl sulphate and sodium methoxide.

Oxidation/

Oxidation of N-methylemetine was carried out in the usual manner using four moles of mercuric acetate, in an endeavour to obtain a product analogous to tetradehydroemetine. A crystalline base was isolated from the reaction mixture, but it was not present in sufficient quantity for analysis. Most of the product was non-basic in character, and although the solution was red in colour, no rubremetinium bromide could be obtained on the addition of concentrated hydrobromic acid.

The extraction of a quantity of ipecacuanha root was undertaken to furnish samples of the minor alkaloids of the plant. In particular, a specimen of O-methylpsychotrine was required for a study of the position occupied in the molecule by the unsaturated linkage.

The extraction of the root was carried out according to the method evolved by Pyman and his collaborators (2), as being the most suitable for application on the laboratory scale. All the known alkaloids, except psychotrine, were obtained in the crystalline state either as the free base or as a salt. The emetamine, however, was present in such small amount that the isolation of the alkaloid in any degree of purity was impossible.

The catalytic dehydrogenation of emetine with palladium, as described by Ahl and Reichstein (13), has been carried out in an endeavour to furnish a pure specimen of emetamine. These workers isolated emetamine from the reaction mixture along with a fission product, which was shown to be 1-methyl-6:7-dimethoxyisoquinoline.

The/

The experimental details given by Ahl and Reichstein were followed closely by the present author, with one slight exception. The palladised charcoal catalyst, used by the original workers, was prepared by the reduction of palladium chloride with formaldehyde and alkali, in the presence of the charcoal support; the catalyst used in the present research was also prepared from palladium chloride but the reduction was carried out by shaking with hydrogen in a glass hydrogenation apparatus.

This slight modification appears to have had a profound effect upon the course of the reaction as no emetamine could be isolated from the mixture of products. O-methylpsychotrine was obtained, however, in approximately the same yield along with 1-methyl-6:7-dimethoxyisoquinoline. Great care has been taken in the characterisation of this O-methylpsychotrine and its identity has been confirmed beyond any doubt. The melting points of the free base, the picrate, and the hydrogen oxalate, agreed with those given in the literature, and the latter salt in dilute aqueous solution exhibited the blue fluorescence characteristic of salts of O-methylpsychotrine. After drying in vacuo, the hydrogen oxalate melted at 154-157°, and no depression of this melting point was evident in admixture with O-methylpsychotrine hydrogen oxalate obtained from ipecacuanha root. The specific rotation of the hydrogen oxalate was also in agreement with the recorded value for O-methylpsychotrine hydrogen oxalate.

A/

A sample of the O-methylpsychotrine obtained by the catalytic dehydrogenation of emetine was oxidised with mercuric acetate, and rubremetinium bromide was isolated from the reaction mixture. The absorption spectrum of this rubremetinium bromide has been determined and the light extinction curve is given in figure 2. This curve is identical with that measured for authentic rubremetinium bromide, and differs from the curve obtained by Karrer (10) for the oxidation product of emetamine.

The catalytic reduction of this rubremetinium bromide was carried out in a glass micro-hydrogenation apparatus, and the reduction products have been shown to be identical with those obtained from an authentic specimen of rubremetine.

There is no doubt that the dehydrogenation product is, in fact, O-methylpsychotrine, and the discrepancy between the results of the present research and those obtained by Ahl and Reichstein may be attributed to a difference in the activity of the catalyst employed. A comparison of the most probable structures for O-methylpsychotrine (XXX) and emetamine (XXXI) indicates that the former may be regarded as an intermediate in the formation of emetamine by the catalytic dehydrogenation of emetine, and the present research has shown that it can be isolated under certain conditions.

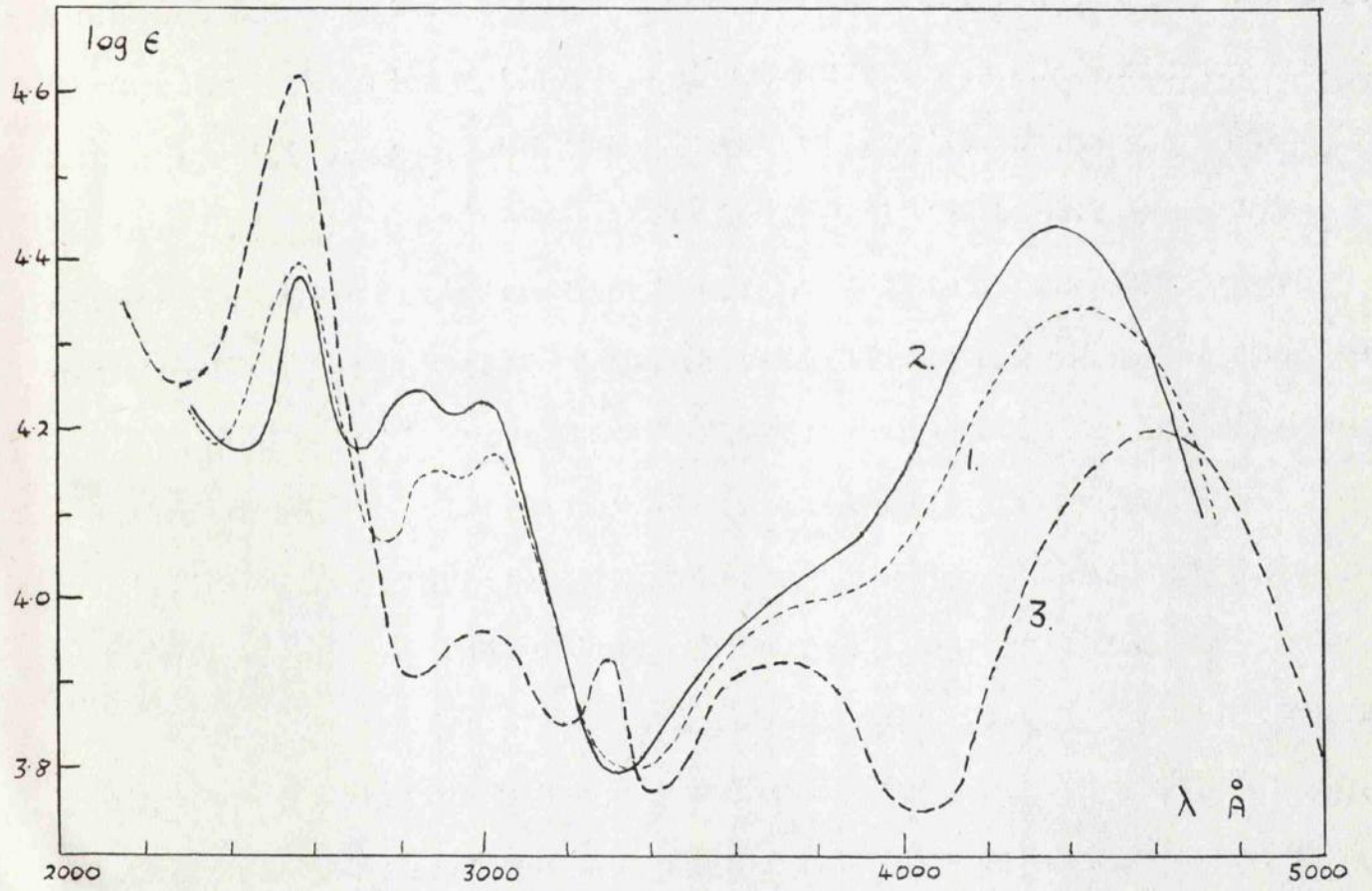
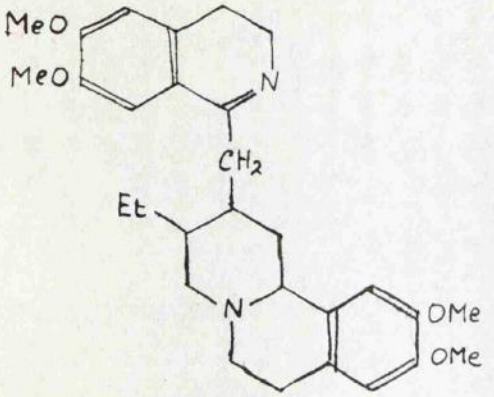


Figure 2.

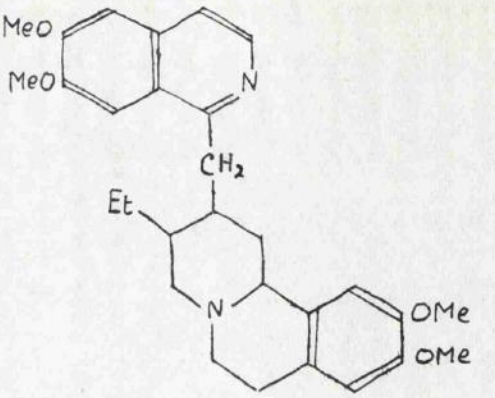
Curve 1. Rubremetinium bromide obtained by oxidation of O-methylpsychotrine.

Curve 2. Rubremetinium bromide obtained by oxidation of emetine.

Curve 3. Oxidation product of emetamine.

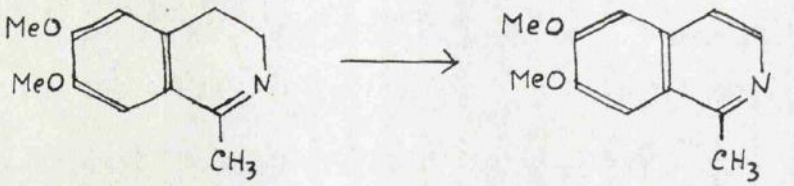


XXX



XXXI

It is interesting to note, however, that the catalyst which was used in the dehydrogenation of emetine was sufficiently active to dehydrogenate a sample of 1-methyl-6:7-dimethoxy-3:4-dihydroisoquinoline (XXXII) to 1-methyl-6:7-dimethoxyisoquinoline (XXXIII) under similar conditions.



XXXII XXXIII

The absorption spectrum of a specimen of O-methylpsychotrine hydrogen oxalate has been determined in order to obtain further evidence concerning the position of the double bond in the molecule, and the light extinction curve is given in figure 3. This curve is very similar to the absorption spectra exhibited by compounds of the type (XXI, R = H or C_6H_5) and which have been shown by Bills and Noller (24) to contain an endocyclic double bond. This result gives considerable support to the structure (XXX), which has been suggested for O-methylpsychotrine.

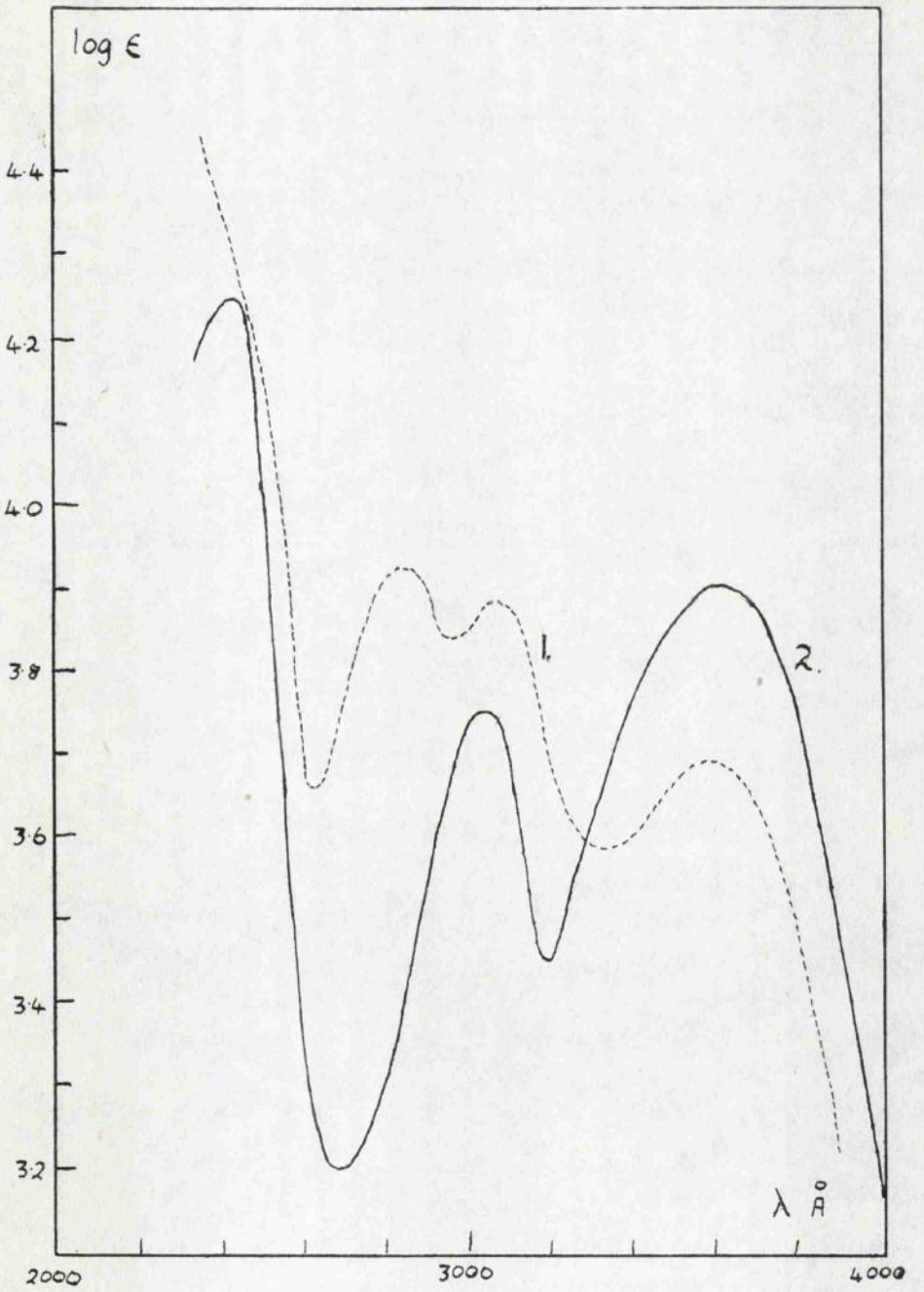


Figure 3.

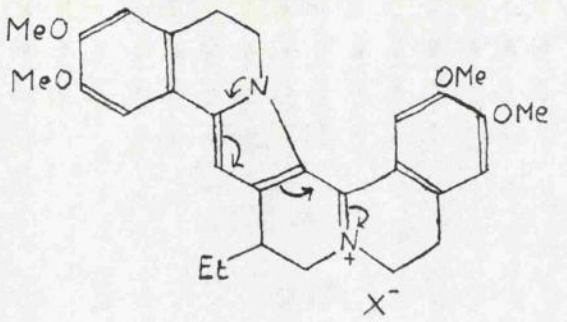
		$\lambda_{max.}$	ϵ
Curve 1.	O-methylpsychotrine hydrogen oxalate.	2840	8,453
		3070	7,691
		3570	5,070
Curve 2.	Hydrochlorides of (XXI, R = H or C_6H_5)	2450	16,980
		3050	5,650
		3650	7,920

EXAMINATION OF RUBREMETINE

The isolation of an optically active tetrahydro derivative, by Karrer and his collaborators (10), from the zinc dust and acetic acid reduction of rubremetine has already been mentioned, and it follows that rubremetine must contain at least one asymmetric centre. No value has been recorded in the literature, however, for the optical rotation of any rubremetinium salt, and accordingly, the specific rotation of rubremetinium chloride in aqueous solution has been determined. A value for the specific rotation of $[\alpha]_{D}^{15} + 52.0^{\circ}$ has been obtained, after correcting for the water of hydration in the sample of rubremetine.

The preparation of some diastereoisomeric salts of rubremetine has also been carried out. The relative solubilities of these salts have been studied, as they may be of assistance in the separation of the stereoisomers of a synthetic rubremetine. The salts which have been prepared were the dextro- and laevo- camphor-π-sulphonates, and the dextro- and laevo-α-bromocamphor-π-sulphonates of rubremetine.

It was shown in an earlier chapter that the formula for rubremetine, suggested by Karrer (10), must be rejected as completely unsound. A structure (XXXV) for rubremetine has recently been put forward by Battersby, Openshaw and Wood (22), and this new formulation appears to be capable of explaining all the known chemistry of rubremetinium salts.



XXXV

This is a resonance hybrid structure similar to that of a cyanine dye, and the positive charge is shared between the two nitrogen atoms as indicated by the curved arrows. This structure is formed from emetine by the loss of eight atoms of hydrogen, oxidative ring closure taking place as shown, to give a five-membered nitrogenous ring. The intense red colour of rubremetinium salts is thus accounted for, and like the cyanine dyes, one nitrogen atom will be apparently quaternary and the other non-basic. The structure (XXXV) could not be obtained by the oxidation of N-methylemetine or emetamine, and this is also in accordance with the known facts. The catalytic reduction of rubremetine to a mixture of stereoisomeric dihydrorubremetines will be described later in the present chapter, and this observation can also be explained by structure (XXXV) for rubremetine.

On the basis of this proposal for rubremetine, it seemed possible that the resistance of Karrer's tetrahydro derivative to catalytic hydrogenation could be due to the presence of an intact/

intact pyrrole nucleus in the molecule. The reduction of rubremetine with zinc dust has been carried out as described by Karrer (10), and the product was obtained as a clear yellow gum. Karrer stated that his product "crystallised after some time", but all attempts by the present author to obtain either the free base or a derivative in the crystalline state have so far proved fruitless. The crude reduction product, however, gave a red pine shaving reaction and with Ehrlich's reagent it gave an intense blue-green colour, which changed to red on the addition of excess reagent. This result confirms the presence of a five-membered nitrogenous ring in rubremetine and affords strong support for structure (XXXV). The crude zinc dust reduction product has also been oxidised with six moles of mercuric acetate, and a small amount of rubremetinium chloride was isolated from the reaction mixture. Further evidence in support of structure (XXXV) for rubremetine is presented below.

The catalytic hydrogenation of rubremetinium chloride has been examined. Working in alcoholic solution with Adam's platinum catalyst, and in the presence of three moles of sodium acetate, a rapid uptake of one mole of hydrogen took place, complete in thirty minutes. The beneficial effect of sodium acetate on the reduction is thus confirmed, and it is also significant that, working in glacial acetic acid solution, the reduction was extremely slow with no definite end point, even in the presence of fused sodium acetate. Battersby and Openshaw (20)/

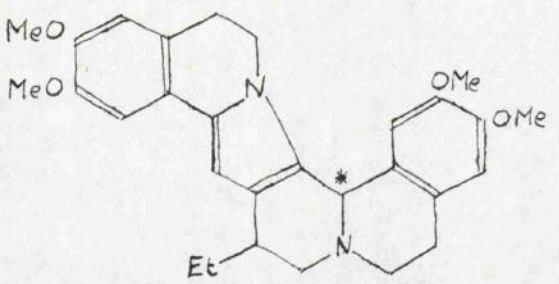
(20) stated that the reduction product was rapidly re-oxidised by atmospheric oxygen in the presence of the catalyst. Nevertheless, it has been found by the present author that it was possible to isolate a crystalline base from the reaction mixture if the catalyst was filtered off extremely rapidly. This was at first thought to be a single substance but subsequent examination revealed that the product was a mixture of two stereoisomeric dihydrorubremetines.

The lower melting form, which was designated α-dihydrorubremetine analysed correctly for $C_{29}H_{34}O_4N_2$, and was found to possess the unusually high specific rotation of $[\alpha]_D^{15}$ -395.0° in acetone. The separation of the remaining isomer, β-dihydrorubremetine, was facilitated by the fact that it forms a crystalline complex with methanol which is very sparingly soluble in that solvent. Analysis of this complex showed that it possessed the formula, $C_{29}H_{34}O_4N_2.CH_3OH$. Recrystallisation from ethanol decomposed this addition compound, and β-dihydrorubremetine was obtained as fine feathery needles which analysed correctly for $C_{29}H_{34}O_4N_2$, and exhibited a specific rotation of $[\alpha]_D^{15}$ +22.2° in acetone.

Both isomers gave a red pine shaving reaction and an intense green colour with Ehrlich's reagent which changed to red on the addition of excess reagent. Moreover, both α- and β-dihydrorubremetine coupled with diazotised sulphanilic acid to give a brilliant red azo dye. The latter test was repeated under/

under the same conditions using emetine hydrochloride and tetradehydroemetine hydrogen oxalate in place of the dihydrorubremetine and no coupling took place in either case. These results confirm the presence in the molecule of a pyrrole nucleus with at least one unsubstituted position, and give very strong support to structure (XXXV) for rubremetine.

On the basis of this structure for rubremetine, it would seem possible that dihydrorubremetine can be represented by structure (XXXVI). The α- and β-forms of the base will result from the creation of a new asymmetric carbon atom marked *



XXXVI

In support of this theory, it has been found that both α- and β-dihydrorubremetine can be readily oxidised to rubremetine on treatment with two molecular proportions of mercuric acetate, under the normal mild conditions.

The nature of the nitrogen atoms in dihydrorubremetine has also been investigated and a potentiometric titration using α-dihydrorubremetine has been carried out with this object in view. α-dihydrorubremetine was dissolved in a known amount of standard/

standard acid and the excess acid titrated against standard alkali. The resulting curve indicated that α-dihydrorubremetine is to be regarded as a monoacidic base, and the same must also be true for its stereoisomer, β-dihydrorubremetine. These results are again in full accord with (XXXVI) since one of the nitrogen atoms is incorporated in a pyrrole nucleus in this structure, and will therefore be non-basic in character.

A sample of α-dihydrorubremetine has been dehydrogenated with palladised charcoal at a temperature of about 200°, and in an atmosphere of carbon dioxide. Approximately one mole of hydrogen was evolved and the crude product was obtained as a bright red gum. This was separated into neutral, acidic and basic fractions and attempts were made to isolate crystalline products. The neutral and acidic fractions have not yielded any crystalline material, but a new crystalline base has been obtained in the form of pale yellow needles, melting at 185-186° after recrystallisation from methanol.

A similar dehydrogenation of β-dihydrorubremetine again afforded a mixture of products from which a crystalline base could be isolated. This was shown to be identical with the base obtained from α-dihydrorubremetine by determining the melting point in admixture with the former substance.

This base gave a brilliant orange colour with one drop of Ehrlich's reagent and must therefore contain a five membered nitrogenous ring. Analysis indicated that it possesses the approximate/

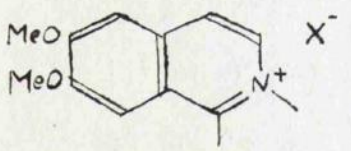
approximate molecular formula, $C_{29}H_{30}O_4N_2$, but the oxygen:nitrogen ratio is not completely satisfactory. Since the same base is obtained from both α- and β-dihydrorubremetine, the asymmetry of the carbon atom marked * in structure (XXXVI) must have been destroyed in the dehydrogenation, which involves the elimination of approximately four atoms of hydrogen. It is difficult to see how this change has occurred to give a product which would exhibit the properties of the "dehydrogenation base", and no structure has been suggested as yet for the latter substance.

A second dehydrogenation of α-dihydrorubremetine has been carried out under much more drastic conditions, the temperature being maintained at 300° for almost two hours. This was done in an endeavour to obtain some relatively simple heterocyclic base from dihydrorubremetine. As in the previous dehydrogenations, the product was separated into neutral, acidic and basic fractions, but no crystalline materials could be isolated. The neutral fraction was subjected to chromatographic analysis on an alumina column, and although some degree of separation was achieved, no crystalline products have been obtained.

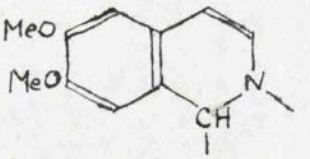
Within the past month, a further paper has been published by Karrer and Rüttner (29) on the chemistry of rubremetine. They claim to have carried out the reduction of rubremetine with lithium aluminium hydride and obtained a crystalline o-dihydro derivative. The latter compound was reduced catalytically to give a mixture of two stereoisomers, claimed to be tetrahydro derivatives of rubremetine/

rubremetine. One of these substances was identical with the tetrahydro derivative which Karrer had previously obtained by the zinc dust reduction of rubremetine (10). The second product, after crystallising from ether, melted at 194° and exhibited a specific rotation of $[\alpha]_D^{18}$ -380° in ethanol. These constants suggest that this latter derivative is identical with α-dihydrorubremetine (XXXVI).

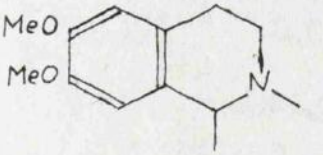
Karrer claims that the isolation of these reduction products confirms the presence of the grouping (XLI) in rubremetine. The α-dihydro derivative was represented by the partial structure (XLII) and the tetrahydro derivatives by the partial formula (XLIII). On the basis of these results, Karrer and Rüttner state that structure (XXXV) can no longer be accepted for rubremetine.



XLI



XLII



XLIII

Detailed comment on these recent proposals is not possible in the present dissertation, but several discrepancies are apparent in Karrer's paper, and these may be mentioned briefly.

A new asymmetric centre is created in the change from (XLI) to (XLII), yet only one crystalline derivative has been obtained. In the second reduction, which involves the formation of (XLIII), no new asymmetric centres are formed, but the isolation of two stereoisomeric derivatives is reported. The authors give no explanation/

explanation of this unusual observation.

It is intended to make a detailed investigation of these reduction products of rubremetine, and an endeavour will be made to correlate the work carried out by Karrer with the results of the present research.

DEGRADATION OF N-ACETYLEMETINE

One section of the researches which are being carried out in St. Andrews on the emetine problem, is concerned with the synthesis of compounds which might be of use in the treatment of amoebic dysentery.

Recent developments in the chemotherapy of the disease, which is caused by the parasite Entamoeba histolytica, have aimed at reducing to a minimum the nausea and vomiting which accompany the use of emetine. The alkaloid is normally employed as the hydrochloride for hypodermic injection, although a double iodide of emetine and bismuth has been used for oral administration in an attempt to overcome the emetic properties of the drug.

The first synthetic work on amoebicidal agents was carried out by Pyman and his collaborators (26) who synthesised various substances structurally related to emetine. These workers finally prepared a compound which was at least as active as emetine in vitro, but it was clinically useless because of the intense irritation produced on injection.

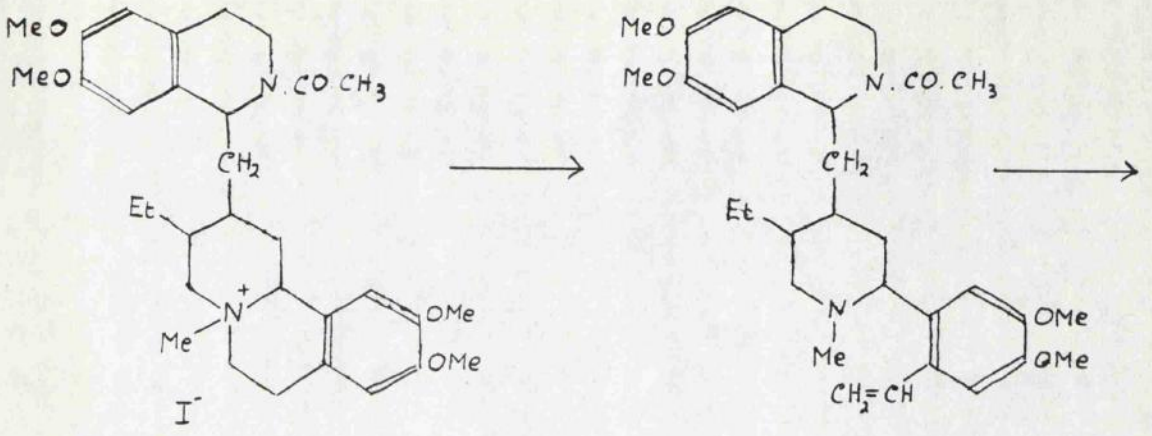
The present degradation of N-acetylemetine has been carried out to furnish a compound closely related to emetine but of a type which should prove amenable to synthesis.

A study of the Hofmann degradation of N-acetylemetine was first carried out by Ahl and Reichstein (13), and the results of this investigation gave important information concerning the structure/

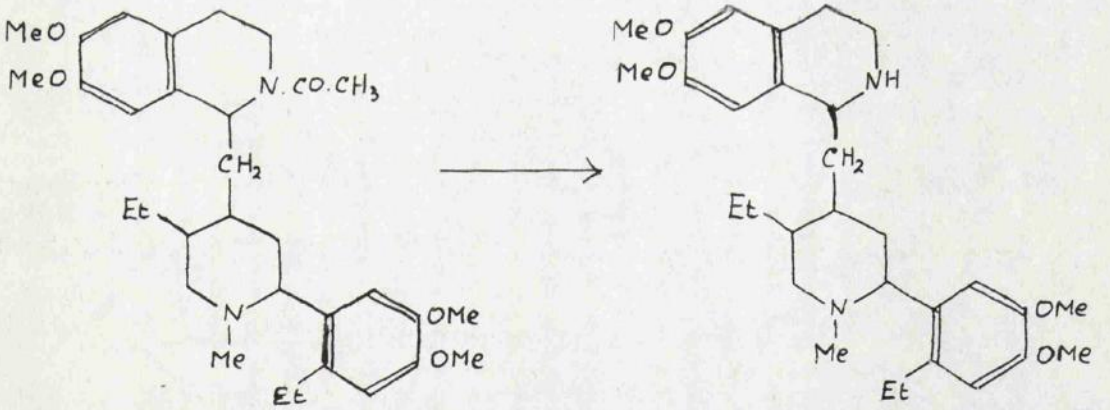
structure of emetine. The first stage of this Hofmann degradation has been repeated in the course of the present research and a new derivative of emetine has been obtained. It is intended to test the pharmacological activity of this compound against Entamoeba histolytica.

N-acetylemetine was prepared by shaking emetine, in ethereal solution, with acetic anhydride and 10% potassium hydroxide solution, as described by Ahl and Reichstein (13). The product was isolated as a clear, water-white gum which was converted to the crystalline N-acetylemetine methiodide (XXXVII) by treatment with methyl iodide. This methiodide was then degraded by the normal Hofmann procedure, solid potassium hydroxide being added to the quaternary hydroxide before evaporating to dryness, and the resulting methine (XXXVIII) was obtained as a pale pink glass. This methine was hydrogenated, using Adam's platinum catalyst to N-acetylemetinedihydromethine (XXXIX), which was purified by means of the crystalline hydrogen oxalate.

Ahl and Reichstein were of the opinion that the above treatment with solid potassium hydroxide removed the acetyl group from the secondary nitrogen atom, since the product was reacetylated at this stage. It has been found by the present author that the acetyl group is apparently unaffected by treatment with potassium hydroxide, as analyses of the N-acetylemetine-:dihydromethine (XXXIX) and its hydrogen oxalate revealed that the acetyl group had not been removed.



XXXVII XXXVIII



XXXIX XL

In an attempt to bring about cleavage of the acetyl group, a variation of Grignard's reaction was employed. Dry methyl iodide in ether was added dropwise to the theoretical quantity of magnesium turnings suspended in ether, and the mixture was refluxed for six hours. N-acetylemetinedihydromethine (XXXIX), in ethereal solution, was added dropwise to the Grignard reagent, with vigorous stirring. An immediate white precipitate was formed; this was allowed to stand overnight and then refluxed for

a/

a further nine hours. The addition compound was decomposed with ammonium chloride and the basic product extracted directly into ether. Investigation of this base, however, revealed that it was identical with the starting material.

The acetyl group was finally removed by employing the method used by Pailer (16) for the deacetylation of a derivative of N-acetylemetine. N-acetylemetinedihydromethine (XXXIX) was dissolved in methanol and heated with 10% hydrochloric acid in a sealed tube, at 130-135°, for six hours. The basic product was distilled at 200° and 5.0×10^{-6}mm. and was obtained as a pale yellow glass. No crystalline derivatives of this dihydromethine (XL) have yet been prepared, but a sample has been reacetylated and N-acetylemetinedihydromethine (XXXIX) was obtained in good yield as the crystalline hydrogen oxalate.

SUMMARY

The chemical dehydrogenation of emetine, using mercuric acetate, has been studied in some detail and improved experimental techniques have given high yields of rubremetine and tetradehydroemetine. An investigation of the chemical constitution of this latter intermediate has been carried out by several methods. The catalytic reduction of tetradehydroemetine has been shown to give rise to isoemetine, and the yield of the latter substance was found to depend on the conditions employed. The ultra-violet absorption spectrum of tetradehydroemetine has also been determined, and the resulting light extinction curve has given some indication of the position of the ethylenic linkages in the molecule. Acetylation of tetradehydroemetine and of a model substance, and a study of the properties of a second model substance, have also given information concerning the structure of tetradehydroemetine.

A new method for the preparation of N-methylemetine has been carried out, and the mercuric acetate oxidation of this base has been studied. The extraction of a quantity of ipecacuanha root has also been undertaken to furnish samples of the minor alkaloids of the plant.

The catalytic dehydrogenation of emetine with palladised charcoal has been investigated, and O-methylpsychotrine, together with a fission product, has been isolated from the reaction mixture. A careful examination of the properties of this O-methylpsychotrine has/

has been made, and a study of the ultra-violet absorption spectrum has given support to the structure proposed for this alkaloid.

The specific rotation of a sample of rubremetinium chloride has been determined, and a series of diastereoisomeric salts of rubremetine has also been prepared.

A new structure of the cyanine dye type, containing a five membered nitrogenous ring, has been suggested for rubremetine, and evidence is brought forward in support of this proposal. The zinc dust reduction of rubremetine has been repeated and the presence of a pyrrole nucleus in the crude reduction product has been confirmed. The oxidation of this crude product with mercuric acetate has also been carried out.

The catalytic reduction of rubremetine has been examined and a mixture of two crystalline dihydrorubremetines has been obtained. Both these stereoisomers were readily oxidised with mercuric acetate to give rubremetine, and by means of a potentiometric titration, they have been shown to be monoacidic bases. The catalytic dehydrogenation of both α- and β-dihydrorubremetine has been carried out, and the same crystalline base has been obtained from both experiments.

N-acetylemetine has been prepared from emetine, and the corresponding methiodide has been subjected to a Hofmann degradation. The resulting methine was hydrogenated to give N-acetylemetinedihydromethine, which was characterised as the crystalline hydrogen oxalate. The acetyl group was removed by heating/

heating with alcoholic hydrochloric acid in a sealed tube, and it is intended to test the pharmacological activity of the resulting dihydromethine against the parasite Entamoeba histolytica.

General Information

1. All melting points are uncorrected.
2. Analyses were carried out by Drs. Weiler and Strauss, Oxford.
3. All solids were dried at room temperature *in vacuo*, over phosphoric oxide, unless otherwise stated.
4. Solutions in ether were dried over anhydrous sodium sulphate.

EXPERIMENTAL SECTION

Extraction of ipecacuanha root.

The powdered root (1.5 kg) was suspended in 2000 c.c. of warm ethanol, and heated with constant stirring for three hours. The solution was filtered and the filtrate was evaporated to dryness to give a dark brown gum. This was extracted with 300 c.c. of $\bar{N}$ hydrochloric acid, the mixture being warmed on the steam bath. After cooling, the solution was filtered ("Filtercel") and the filtrate was extracted with ether (4 x 150 c.c.) to remove non-basic material.

The aqueous acid solution was treated with concentrated ammonia (100 c.c.) and the bases, which separated as a dark brown tar, were extracted with ether (7 x 200 c.c.). 16.1 g. of a light brown resin were obtained, after drying and evaporating to dryness. Continued ether extraction (4 x 200 c.c.) of the basic solution gave a further 1.2 g. of resin.

The ipecacuanha root was extracted five times in all, using 2000 c.c. of ethanol for each extraction, and the extracts were worked up as above. The ether extraction of these bases was carried out by adding the acidic solution dropwise to a mixture of ether and ammonia with very vigorous stirring. During the ether extraction of the bases from the second and third alcohol extractions, an emulsion formed which could not be broken. This was probably due to some impurity introduced as the result of an accident, and these extracts were put to one side. The total

basic material from the fourth and fifth extractions weighed 4.1 g.

In the course of the fourth extraction, crystals separated during the evaporation of the alcoholic extract. These were filtered off and subjected to a preliminary examination. The substance melted at 178-183°, was insoluble in ether, but dissolved readily in water, dilute sodium hydroxide and dilute hydrochloric acid. An attempt was made to prepare the S-benzylthiourea salt, but no derivative was formed, and the crystals were not examined further.

The combined aqueous ammoniacal solutions were extracted with chloroform (4 x 200 c.c.) to remove psychotrine. Evaporation of the chloroform extract gave a brown gum which was dissolved in sodium hydroxide, filtered, and extracted with ether to remove non-phenolic material. The alkaline layer was re-extracted with chloroform (3 x 60 c.c.) and was evaporated to dryness to give a brown gum (1.3 g). This was dissolved in moist acetone and allowed to stand, but no crystallisation of the free base took place. The solvent was evaporated and the residue dissolved in chloroform which was then extracted with dilute hydrochloric acid (3 x 30 c.c.). Excess sodium hydroxide was added to the acid extract, and the psychotrine was extracted with chloroform (2 x 30 c.c.). Evaporation to dryness gave a brown gum (0.9 g), which was dissolved in dilute hydrochloric acid, and strong potassium iodide solution added. Amorphous psychotrine hydriodide was filtered off and redissolved in water, but it could not be induced to crystallise.

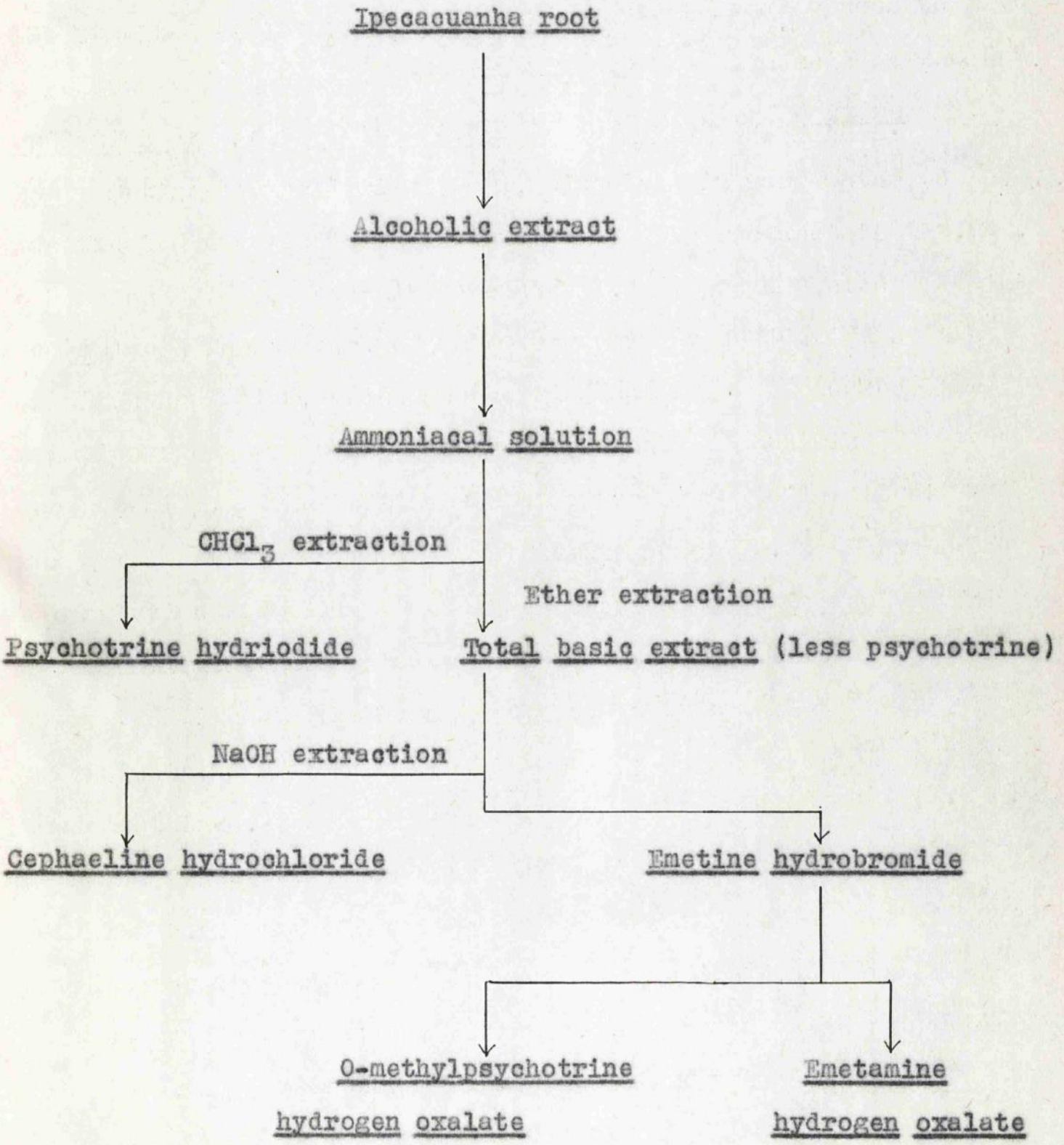
The/

The total basic extracts (21.4 g), from the three successful alcohol extractions of the root, were dissolved in ether and extracted with $\overline{N}$ sodium hydroxide (3 x 100 c.c.) to remove phenolic material. After washing with distilled water, the ethereal solution was dried and evaporated to dryness to give a yellow resin (9.8 g). 50 c.c. of $\overline{N}$ hydrobromic acid were added and the solution was warmed gently. On cooling, emetine hydrobromide crystallised as fine needles (10.0 g), which sintered at 242° and melted from 247-262°.

Excess ammonium chloride (50 g) was added to the alkaline solution to precipitate the phenolic alkaloids, and the mixture was extracted with ether (8 x 150 c.c.). The ether extract was dried, evaporated to dryness, and the residue dissolved in dilute hydrochloric acid. Cephaeline hydrochloride (9.9 g) crystallised on cooling and seeding with an authentic specimen; the product sintered at 231° and melted gradually up to 260°.

The mother liquors, after removal of the emetine hydrobromide, were basified and extracted with ether, evaporation of the extract giving 1.4 g. of a pale yellow gum. This was dissolved in ethanol (8 c.c.) and a solution of hydrated oxalic acid (1.0 g) in ethanol (4 c.c.) was added. Crystals separated on standing and, after collecting and drying, sintered at 150° and melted at 153°. The product was recrystallised from ethanol and it was found that a portion was much less soluble in this solvent. The less soluble material was probably emetamine hydrogen oxalate but it was not present/

EXTRACTION SCHEME



present in sufficient quantity for complete identification. The more soluble portion was recrystallised several times from ethanol, and O-methylpsychotrine hydrogen oxalate was finally obtained as rosettes of fine white needles, which sintered at 151°, melted at 153-154°, and effervesced at 156°.

Oxidation of emetine with five moles of mercuric acetate.

Emetine hydrochloride (5 g), dissolved in warm water (60 c.c.), was treated dropwise with a solution of mercuric acetate (12.9 g. = 5 moles + 10%), potassium acetate (1.2 g) and 6 c.c. of glacial acetic acid in 120 c.c. of water. During the addition of the oxidising solution, which was carried out over 60 minutes, the reaction flask was warmed on the steam bath and swirled occasionally. The heating was continued in an oil bath at 100° for a further two hours to complete the reaction. After cooling, the solution was filtered and the mercurous acetate washed with water until the washings were colourless. The filtrate was saturated with hydrogen sulphide, warmed to coagulate the precipitate, and filtered ("Filtercel"); a clear orange solution A was obtained.

The filter cake was extracted with boiling ethanol (4 x 150 c.c.) and the extract was evaporated to low bulk. This extract was added to the main aqueous solution A, and the whole was evaporated to a volume of 100 c.c. Concentrated hydrochloric acid (5 c.c.) was added to the solution and rubremetinium chloride (XXXV, $X^- = Cl^-$)/

XXXV, $X^- = Cl^-$) separated as very fine needles. The solution was warmed to dissolve the crystals and allowed to cool slowly overnight, yielding (XXXV, $X^- = Cl^-$) as beautiful scarlet needles (0.67 g). After washing with distilled water and drying, the product sintered at 99°, and effervesced and melted at 140-144°.

The clear orange filtrate was made strongly alkaline with saturated sodium carbonate solution and extracted with ether (5 x 50 c.c.), yielding a clear green gum B (2.74 g) after drying and evaporating to dryness.

Concentrated hydrochloric acid was added to the aqueous alkaline solution, which was then taken to dryness under reduced pressure. The last traces of water were removed by the addition of absolute ethanol (50 c.c.) and re-evaporating to dryness. The residue was extracted with acetone and absolute ethanol until the final extract was colourless. Evaporation of the solvents gave a red brown resin which was dissolved in water, concentrated, and on cooling deposited crystals of rubremetinium chloride (0.17 g), melting at 141-142°.

The gum B was dissolved in absolute ethanol (14 c.c.) and a solution of hydrated oxalic acid (1.8 g) in ethanol (7 c.c.) was added. Crystallisation occurred immediately and tetradehydroemetine hydrogen oxalate (2.32 g) was obtained as faintly pink crystals, m.p. = 150-152°. Recrystallisation from ethanol (100 c.c.) yielded very pale yellow needles (1.9 g), melting at 152-153°.

Total/

Total yield of rubremetinium chloride = 0.84 g. (19% calculated as the hexahydrate)

Total yield of tetradehydroemetine hydrogen oxalate = 2.32 g. (45% calculated as the trihydrate)

A second oxidation, carried out on 10 g. of emetine hydrochloride using five moles of mercuric acetate, yielded 3.57 g. (39%) of rubremetinium chloride, melting at 122° with previous sintering, also 4.31 g.(41%) of tetradehydroemetine hydrogen oxalate, m.p. = 148-150°, with sintering at 140°. Recrystallisation of the tetradehydroemetine hydrogen oxalate from ethanol (200 c.c.) gave pale yellow crystals (2.17 g) which sintered at 151°, and melted at 153-154°.

A third oxidation, carried out on 20 g. of emetine hydrochloride using six moles of mercuric acetate, yielded 8.28 g. (46%) of rubremetinium chloride, melting at 140° with sintering at 112°, also 8.95 g.(43%) of tetradehydroemetine hydrogen oxalate, which sintered at 151° and melted at 153-154°.

0.5 g. of rubremetinium chloride were dissolved in the minimum amount of hot water, and 1 c.c. of concentrated hydrobromic acid was added. Rubremetinium bromide (XXXV, $X^- = Br^-$) crystallised on cooling. The solution was warmed to dissolve the crystals, and allowed to cool slowly overnight, yielding (XXXV, $X^- = Br^-$) as beautiful scarlet needles, melting at 115° when air-dried.

Catalytic reduction of tetradehydroemetine hydrogen oxalate.

Tetradehydroemetine hydrogen oxalate (1.0 g) was dissolved

in/

in distilled water (30 c.c.), 100 mg. of Adam's PtO_2 catalyst were added and the mixture was shaken with hydrogen at room temperature. Reduction ceased after 35 minutes, when 63 c.c. (2 moles) of hydrogen had been absorbed.

The catalyst was filtered off ("Filtercel"), and washed well with hot distilled water. Evaporation of the filtrate *in vacuo* gave 0.95 g. of a clear yellow gum. This was dissolved in a small amount of water and 15 c.c. of 2N hydrobromic acid were added, but no crystallisation took place even on seeding with emetine hydrobromide.

The free base (0.72 g) was recovered as usual, dissolved in ether, and treated with 0.15 g. of benzoic anhydride. The mixture was heated for 45 minutes on the water bath, allowing the ether to evaporate. The residue was dissolved in ether, and the ethereal solution shaken with very dilute hydrochloric acid. After washing with ether, the acid extract was treated with excess ammonia and the basic material extracted into ether. Crystals were deposited on evaporating the ether extract to low bulk, and, after standing overnight, these were collected and dried. Recrystallisation from acetone gave 0.67 g. (78%) of N-monobenzoylisoemetine, as white hexagonal prisms, melting at 202-203°.

Pyman (3) gives the melting point of N-monobenzoylisoemetine as 207-208° (corr.).

Catalytic/

Catalytic reduction of tetradehydroemetine.

Tetradehydroemetine hydrogen oxalate (1.0 g) was converted to the free base (0.75 g) in the usual manner. The base was dissolved in 40 c.c. of Mg dried ethanol and was hydrogenated as above, two moles of hydrogen being absorbed.

No trace of emetine hydrobromide could be detected in the resulting mixture of products, and only 36% of N-monobenzoylisoemetine was isolated after treatment with benzoic anhydride. The ethereal mother liquors from the crystallisation of the N-monobenzoylisoemetine deposited a dark brown gum on evaporation to dryness, but no crystalline material could be isolated from the latter.

Acetylation of tetradehydroemetine.

Tetradehydroemetine hydrogen oxalate (0.7 g) was converted to the base as usual, the latter being obtained as a green gum (0.68 g). The gum was dissolved in ether (20 c.c.), 12 c.c. of 10% potassium hydroxide solution and 1.2 c.c. of acetic anhydride were added, and the mixture was shaken for ten minutes. The ether layer was washed twice with dilute potassium hydroxide, and the aqueous phase, which was still acid to litmus at this stage, was extracted once with ether. Evaporation of the combined ether extracts gave a yellow gum A (0.06 g).

The aqueous phase was made alkaline with potassium hydroxide solution and the pale brown precipitate which appeared was taken up/

up in ether (3 x 25 c.c.). After drying, the ethereal solution was evaporated to dryness in vacuo and yielded 0.57 g of a green gum which, on treatment with hydrated oxalic acid (0.35 g) in ethanol (4 c.c.) gave 0.4 g. of crystals, identical with tetradehydroemetine hydrogen oxalate, m.p. and mixed m.p. with authentic specimen = 149-151°.

The free base (0.28 g) was recovered as usual, treated with acetic anhydride (2 c.c.) and a few crystals of sodium acetate, and heated on the water bath at 100° for 30 minutes in an atmosphere of carbon dioxide. The residue was dissolved in 20 c.c. of 10% potassium hydroxide and the aqueous phase was extracted with ether (3 x 30 c.c.), washing each ether layer with water; the aqueous phase was acid to litmus at this stage. The combined ether extracts were washed with dilute potassium hydroxide, dried, and evaporated to dryness giving a clear gum B (0.06 g).

A and B were combined and distilled at 145° and 5.0×10^{-6} mm. giving a pale yellow gum. This was dissolved in N/4 hydrochloric acid (4 c.c.) and excess 20% perchloric acid was added. The perchlorate was filtered off and dissolved in acetone, but the product could not be induced to crystallise and darkened appreciably on standing.

Excess potassium hydroxide was added to the aqueous phase and the mixture was extracted with ether, to yield a gum C (0.18 g) after drying and evaporating to dryness. The ethereal solution was unstable to light at this stage and darkened on standing overnight/

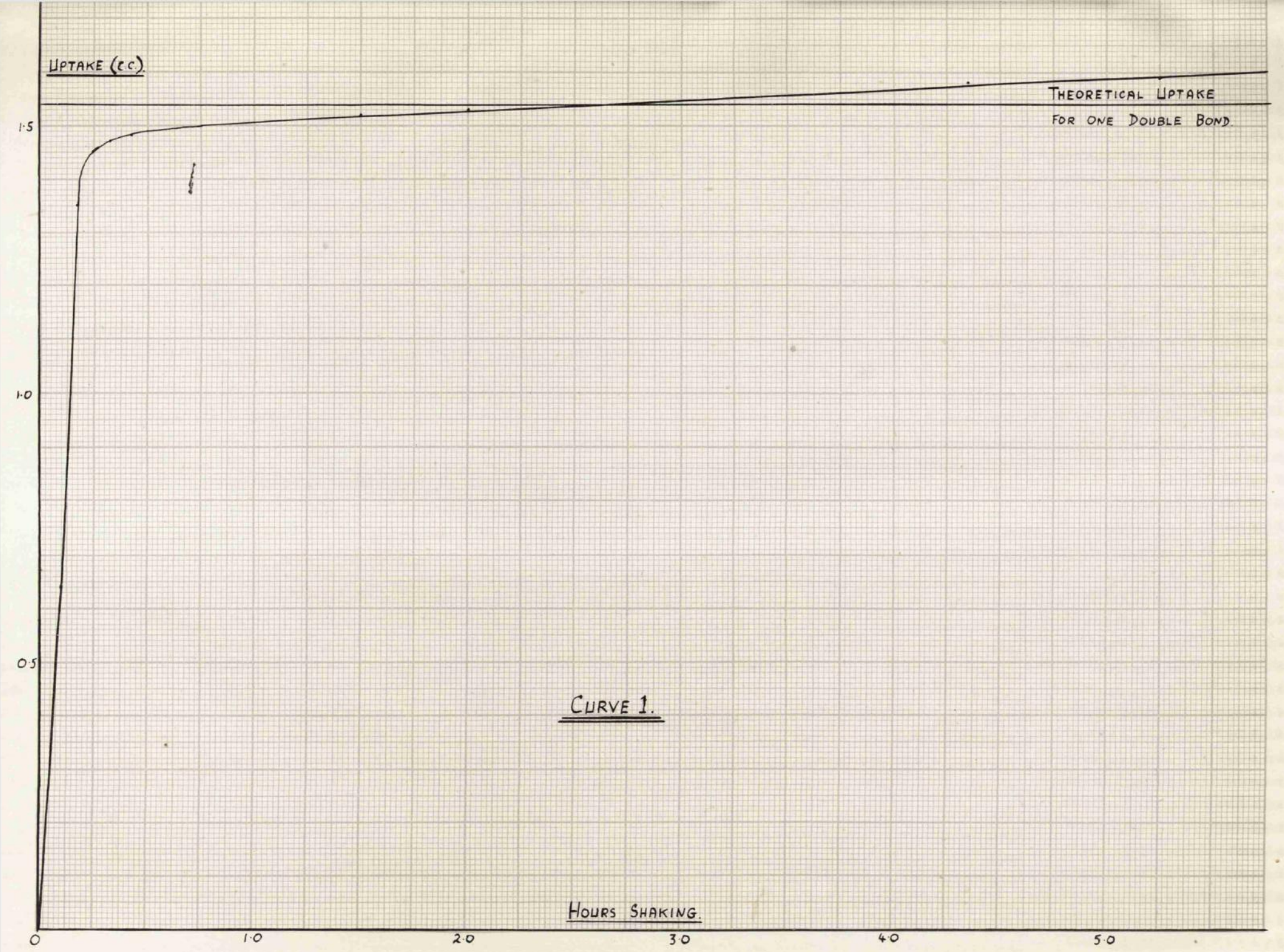
overnight. The gum C was dissolved in ethanol (1.5 c.c.) and treated with a solution of hydrated oxalic acid (0.12 g) in ethanol (0.75 c.c.). On seeding with tetradehydroemetine hydrogen oxalate, a few crystals formed and these were filtered off. The mother liquors were concentrated, basified, and extracted with ether. The ethereal solution (40 c.c.), which was still unstable to light, was extracted with 7 c.c. of N/100 hydrochloric acid to remove the more basic material, washed with water, and dried; the solution was still unstable to the action of light. After evaporating to dryness and distilling at 155° and 4.0×10^{-5} mm., a clear yellow gum was obtained which turned brown rapidly on exposure to light and air. The gum was dissolved in a small amount of ether but the N-acetyltetradehydroemetine (XXIV) could not be induced to crystallise. It appeared to be very unstable, and underwent changes which rendered it much darker in colour and also made it insoluble in ether.

The above acetylation was repeated on a further 1.2 g. of tetradehydroemetine hydrogen oxalate with similar results.

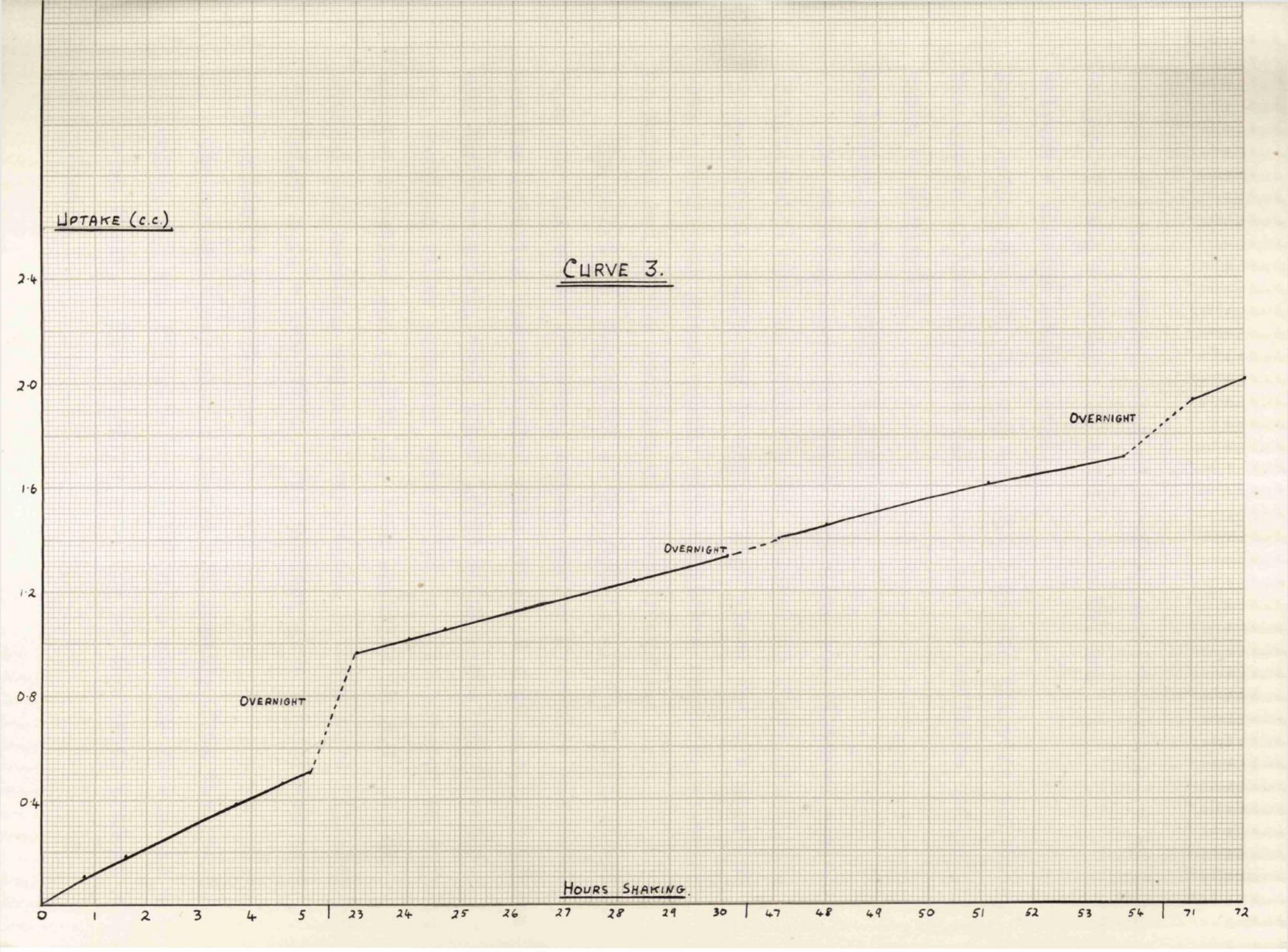
Acetylation of 1-n-butyl-3:4-dihydroisoquinoline (XXV).

1-n-butyl-3:4-dihydroisoquinoline (0.5g) was treated with acetic anhydride (5 c.c.) and a few crystals of sodium acetate, and heated on the water bath at 100° in an atmosphere of carbon dioxide for thirty minutes. The colour of the solution changed from yellow to bright green during this period.

Excess/


UPTAKE (c.c.)
THEORETICAL UPTAKE
FOR ONE DOUBLE BOND.
1·5
1·0
0·5
0
1·0
2·0
3·0
4·0
5·0
HOURS SHAKING.

CURVE 1.


UPTAKE (c.c.)
CURVE 3.
2·4
2·0
1·6
1·2
0·8
0·4
OVERNIGHT
OVERNIGHT
OVERNIGHT
HOURS SHAKING.
0 1 2 3 4 5 23 24 25 26 27 28 29 30 47 48 49 50 51 52 53 54 71 72

Curve 3.

Weight of rubremetinium chloride = 32.6 mg. (containing 3.4% water)

Weight of PtO_2 = 20 mg. t = 17° p = 747 mm.

Solvent = Glacial acetic acid.

Fused sodium acetate (20 mg) was added to the chloride solution. The uptake of hydrogen was very slow, and no definite end-point could be discerned.

Isolation of the reduction product.

The solution from the first reduction was filtered rapidly ("Filtercel") and the filtrate was allowed to stand overnight. No appreciable darkening in colour took place and the solution gave a brilliant green colour with Ehrlich's reagent, changing to bright red on the addition of excess reagent.

The solution was evaporated to dryness to give a resinous solid. This was dissolved in water, excess sodium hydroxide was added, and the solution was extracted with ether (2 x 50 c.c.) to remove any basic material, each ether layer being washed with water. The combined ether extracts were dried, and evaporated to dryness to give a yellow gum (0.032 g). On solution in 0.5 c.c. of ethanol and cooling, crystals separated. These were filtered off and dried, m.p. = 173-178°. The product gave a positive test with Ehrlich's reagent.

The catalyst was also filtered off rapidly from the second reduction, and the filtrate was diluted to exactly 20 c.c. in a graduated flask. The specific rotation of the crude product was determined/

white needles, which darkened at 175° and melted at 198-199°. β-dihydrorubremetine (1.27 g), with one molecule of methanol of crystallisation, was obtained as white prisms, melting at 127-128°, with sintering at 125°.

Examination of dihydrorubremetine (XXXVI).

1. Analyses.

(a) Mixture of α- and β-dihydrorubremetine.

Found : C. 72.93% H. 7.49%

$C_{29}H_{34}O_4N_2$ requires : C. 73.4% H. 7.24%

(b) α-dihydrorubremetine.

Found : C. 73.1% H. 7.40% N. 5.99%

$C_{29}H_{34}O_4N_2$ requires : C. 73.4% H. 7.24% N. 5.92%

(c) β-dihydrorubremetine (methanol complex)

Found : C. 71.1% H. 7.5%

$C_{29}H_{34}O_4N_2.CH_3OH$ requires : C. 71.2% H. 7.5%

(d) β-dihydrorubremetine.

Found : C. 73.5% H. 6.84% N. 6.07%

$C_{29}H_{34}O_4N_2$ requires : C. 73.4% H. 7.24% N. 5.92%

2. Optical rotation.

(a) α-dihydrorubremetine.

c = 0.1645 l = 2 dm. α_D -1.300° solvent = acetone

$[\alpha]_D^{15}$ -395.0°

(b)/

in distilled water (30 c.c.), 100 mg. of Adam's PtO_2 catalyst were added and the mixture was shaken with hydrogen at room temperature. Reduction ceased after 35 minutes, when 63 c.c. (2 moles) of hydrogen had been absorbed.

The catalyst was filtered off ("Filtercel"), and washed well with hot distilled water. Evaporation of the filtrate in vacuo gave 0.95 g. of a clear yellow gum. This was dissolved in a small amount of water and 15 c.c. of 2N hydrobromic acid were added, but no crystallisation took place even on seeding with emetine hydrobromide.

The free base (0.72 g) was recovered as usual, dissolved in ether, and treated with 0.15 g. of benzoic anhydride. The mixture was heated for 45 minutes on the water bath, allowing the ether to evaporate. The residue was dissolved in ether, and the ethereal solution shaken with very dilute hydrochloric acid. After washing with ether, the acid extract was treated with excess ammonia and the basic material extracted into ether. Crystals were deposited on evaporating the ether extract to low bulk, and, after standing overnight, these were collected and dried. Recrystallisation from acetone gave 0.67 g. (78%) of N-monobenzoylisoemetine, as white hexagonal prisms, melting at 202-203°.

Pyman (3) gives the melting point of N-monobenzoylisoemetine as 207-208° (corr.).

Catalytic/

Excess 10% potassium hydroxide (100 c.c.) was added and the solution was extracted with ether (4 x 50 c.c.), washing each ether extract with water. The combined ether extracts were shaken with $\overline{N}$-hydrochloric acid (3 x 25 c.c.) to remove unchanged material. Evaporation to dryness gave a pale brown gum (0.57 g = 94%). This product dissolved cleanly in ether, and a portion was distilled at 115° and 8.0×10^{-5} mm. to give a water white gum. No sign of instability or decomposition was apparent.

Preparation of the dihydroisoquinoline (XXVIII).

1. Preparation of the amide (XXVII).

4.13 g. of homoveratrylamine were dissolved in 60 c.c. of dry ether in a reaction flask protected against the entry of moisture. 1.3 g. of crotonyl chloride (1 mole = 1.2 g) in 40 c.c. of dry ether were added dropwise with continuous shaking. A white precipitate separated and this was allowed to stand for several days. 40 c.c. of distilled water were added to the mixture whereupon the original white precipitate dissolved, and large yellow needles (1.74 g) of (XXVII) separated in the aqueous phase. These were filtered off and after drying, melted at 82-84°.

The mother liquors, which consisted of a mixture of ethereal and aqueous solutions, were saturated with solid ammonium sulphate and extracted thoroughly with ether (3 x 100 c.c.). Evaporation of the ethereal extract gave 1.2 g. of a yellow gum. This was dissolved/

dissolved in hot water, and on cooling, a further 1.1 g. of (XXVII) separated, melting at 84-85°.

The total yield of (XXVII) was 2.8 g.(98%), and after two recrystallisations from water, the melting point was 85-86°.

2. Ring closure.

1.0 g. of the amide (XXVII) was dissolved in 20 c.c. of dry toluene, which had been distilled from phosphorus pentoxide. 2.5 g. of phosphorus pentoxide were added to the solution of the amide, and the mixture was refluxed for 10 minutes, the phosphorus pentoxide becoming yellow and sticky. A further 2.5 g. of phosphorus pentoxide were added and the refluxing was continued for a total of 25 minutes. A final portion of 2.0 g. of phosphorus pentoxide was then introduced and the mixture was refluxed for 45 minutes in all.

The reaction mixture was cooled and 20 c.c. of water were added cautiously, followed by 10 c.c. of 2 N hydrochloric acid. After shaking thoroughly, the toluene layer was separated and extracted twice with 2 N hydrochloric acid (20 c.c. portions). The acid extracts were combined, treated with excess sodium hydroxide solution and extracted with ether (3 x 50 c.c.). The ethereal solution, which became cloudy on exposure to air and darkened appreciably, was dried and evaporated to dryness. The dihydroisoquinoline (XXVIII) was obtained as a yellowish-red gum (0.87 g. = 94%), which could not be induced to crystallise.

Attempts were made to prepare the picrate, the hydrogen oxalate./

oxalate, and the hydrobromide of the dihydroisoquinoline, but no crystalline materials could be isolated. Solutions of (XXVIII) and its salts darkened very rapidly on exposure to light and air and appeared to undergo some polymeric change. A sample of the base was distilled at 190° and 2.0×10^{-5} mm; the distillate was a dark brown resinous material, and a large portion of the residue polymerised to give a hard black resin.

Preparation of N-methylemetine (XXIX).

Emetine hydrochloride (2.0 g) was converted to the free base (1.65 g) as usual. The latter was dissolved in ethanol (50 c.c.) and excess dry formaldehyde (four moles) was introduced into the solution by passing a stream of dry hydrogen over dry paraformaldehyde (0.5 g) heated in a flask at 180-190°, and then into the cooled solution. About 0.5 g. of freshly prepared Raney nickel catalyst (27) were added and the solution was shaken with hydrogen for five hours at 2.5 atmospheres. The catalyst was filtered off ("Filtercel") and the solution was evaporated to dryness to give a clear red gum (1.77 g).

This gum was dissolved in dry pyridine, succinic anhydride (0.6 g) added, and the solution was boiled under reflux for two hours. Evaporation of the pyridine in vacuo gave a dark brown gum, which was treated with sodium hydroxide (20 c.c.) and extracted thoroughly with chloroform (4 x 30 c.c.). The chloroform solution was dried, evaporated to dryness, and the residue/

residue mixed with 0.6 g. of succinic anhydride. After heating the mixture at melting point for two hours, the residue was dissolved in chloroform and extracted with sodium hydroxide. Evaporation of the chloroform solution in vacuo gave 1.55 g. of a dark brown gum.

The gum was dissolved in the minimum quantity of hot ethanol, added to a mixture of water (200 c.c.) and ether (100 c.c.) in a separating funnel, and shaken thoroughly. The solution was extracted a further twice with ether (2 x 70 c.c.), washing each ether layer with water. This ethereal solution was extracted with N hydrochloric acid (3 x 25 c.c.), the combined acid extracts being shaken with ether to remove non-basic material. Excess sodium hydroxide was added to the acid solution and the basic material was extracted into ether. After drying and evaporating to dryness, 0.62 g. of a yellow gum were obtained.

The product was distilled at 155° and 5.0×10^{-6} mm. to give a yellow glass (0.46 g). This was dissolved in 2 N hydrobromic acid (5 c.c.) and crystallisation took place after some time. N-methylemetine (XXIX) hydrobromide was obtained as fine white needles (0.39 g = 19%), which sintered at 208° and melted gradually up to 230°. The product was recrystallised from water (5 c.c.) and the melting point remained unchanged.

A second methylation was carried out on 7.1 g. of emetine hydrochloride and yielded 0.85 g.(12%) of N-methylemetine hydrobromide, which sintered at 209-210° and melted gradually up to 230°.

Oxidation/

Oxidation of N-methylemetine with four moles of mercuric acetate.

N-methylemetine hydrobromide (0.3 g) was dissolved in warm water (5 c.c.) and treated dropwise with a solution of mercuric acetate (0.594 g. = 4 moles + 10%), potassium acetate (0.06 g), and 0.5 c.c. of glacial acetic acid in 10 c.c. of distilled water. During the addition of the oxidising solution, which was carried out over fifteen minutes, the reaction flask was warmed on the steam bath and swirled occasionally. When the addition of the oxidising solution was complete, the reaction flask was heated in an oil bath at 100° for two hours to complete the reaction. The solution was cooled and filtered, the mercurous acetate being washed with water until the washings were colourless. The filtrate was saturated with hydrogen sulphide, and filtered ("Filtercel") to yield a clear, pale orange solution.

Excess sodium carbonate was added to this solution which was then extracted with ether (4 x 50 c.c.). The colourless ether extract was dried and evaporated to dryness to give a yellow gum (0.03 g). This crystallised on standing but the crystalline material was not present in sufficient quantity for analysis.

On acidification of the aqueous alkaline solution with concentrated hydrochloric acid, the colour changed to a very pale yellow. The solution was evaporated to dryness, and to ensure the complete absence of water, 30 c.c. of ethanol were added and the whole re-evaporated to dryness. Extraction of the residue with acetone and ethanol, and evaporation of the extract gave 0.38 of gum.

The/

The gum was dissolved in water and excess (7 c.c.) concentrated hydrobromic acid was added. Crystals of sodium bromide separated on concentrating the solution, and allowing to cool. These were filtered off and the mother liquors taken to dryness. Absolute ethanol (3 c.c.) was added, the solution filtered, and the mother liquors were concentrated. No crystalline product separated, even on seeding with rubremetinium bromide.

Catalytic dehydrogenation of emetine.

2.0 g. of emetine (from the purified hydrochloride) were mixed with 1.5 g. of 10% palladised charcoal. The palladised charcoal catalyst was prepared from palladium chloride as described by Adkins, Richard and Davies (28). The mixture was heated for one hour at 180-190° in an atmosphere of carbon dioxide and the hydrogen evolved was collected over 50% potassium hydroxide solution. After 30 minutes, 150 c.c. (1.7 moles) of hydrogen had been evolved and gas evolution ceased.

The reaction flask was cooled, the contents were dissolved in boiling ethanol (50 c.c.) and the solution was filtered ("Filtercel") to remove the catalyst. The filter cake was extracted thoroughly with boiling ethanol (3 x 50 c.c.) and the extract was added to the main alcohol solution.

The above dehydrogenation was repeated using a further 2.0 g. of emetine, the alcoholic extracts being combined and evaporated to dryness/

dryness to give a red gum (3.54 g.).

50 c.c. of 20% potassium hydroxide solution were added to the gum, and the mixture was extracted thoroughly with ether (6 x 60 c.c.). The ether extracts, which were bright red in colour, were dried and evaporated to dryness in vacuo. A reddish-yellow thick oil was obtained and this was divided into two fractions in a molecular still. The first, distilling up to 115° at 2.0×10^{-3} mm., was a pale yellow oil (0.62 g). Crystals separated on the addition of ether, and after collecting and drying, they melted at 97°. Recrystallisation from light petroleum gave yellow needles, melting at 102°. The mixed melting point with 1-methyl-6:7-dimethoxyisoquinoline (m.p. = 106°) was 104°.

The second fraction was a red oil which distilled up to 210° (mainly 185-200°) at 2.0×10^{-3} mm. This oil was dissolved in ether, filtered, and evaporated to dryness to give 1.98 g. of syrup. The latter was redissolved in ether (30 c.c.) and the solution was extracted with N hydrochloric acid (3 x 30 c.c.). Excess sodium hydroxide was added to the acid extract, and the bases were taken up in ether (3 x 50 c.c.). After drying and evaporating to dryness, 1.77 g. of a clear yellow gum were obtained. This was dissolved in ether (15 c.c.) and 1.77 g. of picric acid in ether were added slowly with scratching; 2.9 g. of a yellow crystalline powder separated after some time. After recrystallisation from acetone (20 c.c.), O-methylpsychotrine picrate (1.68 g) was obtained as octagonal plates, melting at 147-149°. Pyman (5) gives/

gives the melting point as 142-175°.

The picrate was suspended in 20 c.c. of water, excess sodium hydroxide solution was added, and the free base was extracted with ether (4 x 50 c.c.). The ether extract was freed from picric acid by shaking with small portions of 20% potassium hydroxide solution until the extracts were colourless. After drying, the ethereal solution was taken to dryness under reduced pressure. The resulting gum, on solution in a mixture of ether and light petroleum, deposited O-methylpsychotrine as white crystals, melting at 115-120°. Recrystallisation from hot dry ether gave beautiful white prisms, melting at 124-125°. Pyman (5) quotes 123-124° (corr.) for the melting point of O-methylpsychotrine.

0.4 g. of the free base were dissolved in ethanol (8 c.c.) and a solution of hydrated oxalic acid (0.24 g) in 5 c.c. of ethanol was added. O-methylpsychotrine hydrogen oxalate (0.64 g) crystallised on cooling, and after collecting and drying, it melted at 152-156°. Recrystallisation from acetone gave rosettes of needles, sintering at 149°, and melting at 154-157°. The mixed melting point with O-methylpsychotrine hydrogen oxalate (m.p. = 151-154°) from ipecacuanha root was 152-155°.

The specific rotation of this O-methylpsychotrine hydrogen oxalate was measured in aqueous solution and a value of $[\alpha]_D^{15}$ +47.1° (H_2O ; c = 0.3) was obtained. Pyman (3) gives $[\alpha]_D$ +45.9° for the anhydrous salt.

Oxidation/

Oxidation of O-methylpsychotrine with mercuric acetate.

O-methylpsychotrine (0.344 g), recovered from the crystalline hydrogen oxalate, was dissolved in 10 c.c. of $\overline{N}$ acetic acid. A solution of mercuric acetate (1.52 g. = 6 moles + 10%), potassium acetate (0.27 g), 1 c.c. of glacial acetic acid and 10 c.c. of water, was added, washing in with 5 c.c. of water. The mixture was heated under reflux at 110-120° for five hours and then cooled thoroughly. The mercurous acetate was filtered off and washed with water until the washings were colourless.

After saturating the clear orange filtrate with hydrogen sulphide, the solution was heated to boiling to coagulate the precipitate and filtered ("Filtercel"). The filter cake was extracted thoroughly with boiling ethanol (3 x 50 c.c.), the extract being taken to small bulk and added to the main aqueous solution.

Concentrated hydrobromic acid was added to the solution after evaporating to small volume (10 c.c.), and a fine crystalline precipitate separated. This was redissolved and the solution was allowed to cool slowly. The resulting red needles of rubremetinium bromide (0.183 g = 42%) were collected and air-dried. This product melted at 123-124° with effervescence, and the melting point in admixture with air-dried rubremetinium bromide (m.p. = 115°), obtained from emetine, was 117-122°.

The identity of this oxidation product with rubremetinium bromide was confirmed by a comparison of the absorption spectra of these two substances (Figure 2, p.79), and by the results of

the/

the following catalytic reduction.

Micro-hydrogenation of rubremetinium bromide from O-methylpsychotrine.

68.6 mg. of rubremetinium bromide were dissolved in 5 c.c. of purified ethanol. Crystalline sodium acetate (70 mg. = 3 moles) and 34 mg. of Adam's PtO_2 catalyst were added, and the mixture was shaken with hydrogen in a glass micro-hydrogenation apparatus. One mole of hydrogen was absorbed during a period of one hour, and the products were isolated as in the reduction of rubremetinium chloride on p. 127.

α-dihydrorubremetine was obtained as woolly white needles which melted at 197-198° with previous sintering. The mixed melting point with an authentic specimen of α-dihydrorubremetine (m.p. = 198-199°) was 197-198°. β-dihydrorubremetine was also isolated as the crystalline methanol complex, melting at 124-126°. The mixed melting point with an authentic specimen (m.p. = 127-128°) was 125-126°.

Catalytic dehydrogenation of 1-methyl-6:7-dimethoxy-3:4-dihydroisoquinoline (XXXII).

1.0 g of 1-methyl-6:7-dimethoxy-3:4-dihydroisoquinoline (XXXII) was mixed with 1.0 g. of 10% palladised charcoal. The mixture was heated at 200° in an atmosphere of carbon dioxide for one hour, and the hydrogen evolved was collected over 50% potassium/

potassium hydroxide. 70 c.c. (0.65 moles) of hydrogen were collected, and gas evolution ceased. The dehydrogenation was repeated on a further 1.0 g. of the dihydroisoquinoline.

The products from these two dehydrogenations were combined and dissolved in boiling ethanol (50 c.c.), the catalyst being filtered off through a pad of Filtercel. The filter cake was extracted with boiling ethanol (3 x 50 c.c.) and the extracts were added to the main bulk of the solution. Evaporation to dryness *in vacuo* gave a clear gum (1.4 g). This was extracted repeatedly with light petroleum, and on concentrating the petrol solution, pale yellow needles (0.7 g. = 35%) of 1-methyl-6:7-dimethoxyisoquinoline (XXXIII) were obtained, melting at 99-102°. Several recrystallisations from light petroleum gave 0.45 g. of fine white needles which melted at 106°. The mixed melting point with an authentic specimen was 105-106°.

The residue which remained after the petrol extraction was dissolved in excess ammonium hydroxide, and shaken thoroughly with chloroform (3 x 40 c.c.). After drying over anhydrous sodium sulphate, the chloroform extracts were evaporated to dryness to give a very small quantity of a dark resin. No further crystalline material could be isolated.

Spectroscopic measurements.

The absorption spectra which are given in the Theoretical Section were determined using a "Unicam" quartz spectrophotometer. 1 cm. quartz cells were used throughout, and the light sources

were/

were respectively a hydrogen lamp, for wavelengths below 3300 Å, and a tungsten filament lamp for wavelengths above 3300 Å.

Specific rotation of rubremetinium chloride in aqueous solution.

1. c = 0.4265 l = 2 dm. α_D + 0.416° $[\alpha]_D^{15}$ + 48.8°

Correcting for the water of hydration (5.85%) in the sample used $[\alpha]_D^{15}$ + 52.0° for the anhydrous material.

2. c = 0.4265 l = 2 dm. α_{5461} + 0.204° $[\alpha]_{5461}^{15}$ + 23.9°

Correcting as before for water of hydration (5.85%) $[\alpha]_{5461}^{15}$ + 25.4° for the anhydrous salt.

Preparation of the camphor-π-sulphonates of rubremetine.

1. d-camphor-π-sulphonate of rubremetine.

Rubremetinium chloride (0.2 g) was dissolved in 2 c.c. of hot water and added to a solution of the sodium salt of d-camphor-π-sulphonic acid (0.08 g) in 1 c.c. of hot water. Crystallisation occurred on cooling and the resulting d-camphor-π sulphonate of rubremetine was obtained as red leaflets (0.214 g = 94% calculated as the anhydrous salt). After recrystallising from 10 c.c. of water, the salt melted at 183-184° and effervesced at 186°.

2. l-camphor-π-sulphonate of rubremetine.

This salt was prepared in a similar manner using 0.2 g. of rubremetinium chloride and 0.075 g. of l-camphor-π-sulphonic acid./

acid. The l-camphor-π-sulphonate of rubremetine was obtained as red leaflets (0.20g = 88%). The product, on recrystallisation from 10 c.c. of water, melted at 176-177°, with effervescing at 183°.

The solubilities of these two salts were almost identical. Both were easily soluble in ethanol and acetone, soluble in hot water, and almost insoluble in ethyl acetate.

Preparation of the α-bromocamphor-π-sulphonate of rubremetine.

1. d-α-bromocamphor-π-sulphonate of rubremetine.

Rubremetinium chloride (0.2 g) was dissolved in 2 c.c. of hot water and a solution of the ammonium salt of d-α-bromocamphor-π-sulphonic acid (0.1 g) in 1 c.c. of hot water was added. Crystallisation occurred on cooling and the resulting d-α-bromocamphor-π-sulphonate of rubremetine was filtered off. The product was obtained as orange-red leaflets (0.255 g = 100%), melting at 214-215° with effervescing at 216-217°.

The salt was recrystallised from 15 c.c. of water, and the recrystallised material sintered at 237°, melted at 239° and effervesced at 240°.

2. l-α-bromocamphor-π-sulphonate of rubremetine.

This salt was prepared as above using 0.2 g. of rubremetinium chloride and 0.1 g. of the ammonium salt of l-α-bromocamphor-π-sulphonic acid. The salt was obtained as orange-red leaflets (0.255 g = 100%), melting at 199-200° with effervescing/

effervescing at 201-202°.

After recrystallisation from 10 c.c. of water, the product sintered at 213°, melted at 217° and effervesced from 220-221°.

The solubilities of these two salts were compared. It was found that the salt prepared from the dextro acid was slightly less soluble in water than that from the laevo acid. Both were easily soluble in ethanol and acetone, and almost insoluble in ethyl acetate.

Zinc dust reduction of rubremetinium chloride.

0.81 g. of rubremetinium chloride were reduced with zinc dust and acetic acid as described by Karrer and his collaborators (10). The tetrahydro derivative was obtained as a pale brown resin A, which could not be induced to crystallise.

A portion of this gum (0.14 g) was dissolved in ethanol (0.8 c.c.), and a solution of hydrated oxalic acid (0.1 g) in ethanol (0.5 c.c.) was added. A small quantity of a green solid separated and was filtered off. Recrystallisation from ethanol (0.5 c.c.) gave a product which sintered at 167°, and melted from 171-176°. A marked depression of this melting point was evident in admixture with tetradehydroemetine hydrogen oxalate. The free base was recovered into ether as usual and evaporation gave a gum B (0.014 g) which did not appear to be identical with A, as will be shown later.

The mother liquors from the hydrogen oxalate were basified with/

sodium hydroxide, extracted with ether (3 x 20 c.c.) and dried. Evaporation gave a clear pale brown gum (0.09 g) which could not be obtained in the crystalline state.

The presence of a pyrrole nucleus in the products of the zinc dust reduction of rubremetine was shown by the following two tests which were carried out on A. Neither test was given by gum B.

1. A minute portion of A was dissolved in a drop of ethanol and a few drops of Ehrlich's reagent (p-dimethylamino-benzaldehyde in hydrochloric acid) were added. An intense emerald green colour was produced, which changed to bright red on the addition of excess reagent.

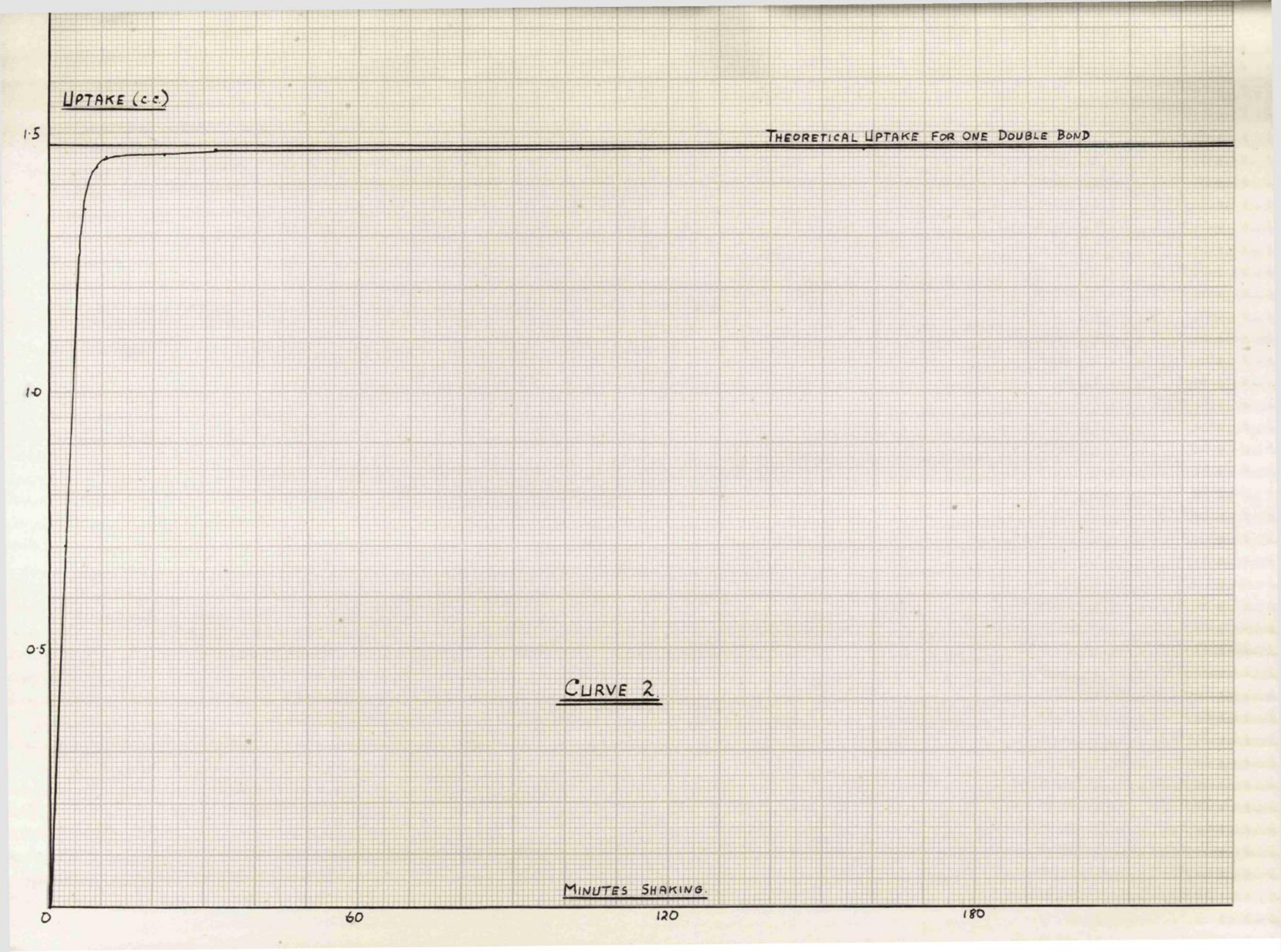
2. Vapour from the destructive distillation of A imparted a carmine colour to a pine splint moistened with concentrated hydrochloric acid.

The zinc dust reduction was repeated on a fresh sample of rubremetinium chloride (1.0 g). The specific rotation of the crude product was measured in alcoholic solution, and a value of $[\alpha]_D^{17} + 14^\circ$ (c = 0.5) was obtained.

An attempt was made to prepare the 2:4-dinitro-1-naphthol-7-sulphonate of the reduction product. 0.18 g. of gum A were dissolved in 2 c.c. of hot ethanol and added to a solution of 0.234 g. of 2:4-dinitro-1-naphthol-7-sulphonic acid in 2 c.c. of hot ethanol. A gum was formed and solidified on cooling, but it could not be induced to crystallise.

A further sample (0.11 g) of gum A was dissolved in 5 c.c. of

N/


UPTAKE (c.c.)
1·5
1·0
0·5
THEORETICAL UPTAKE FOR ONE DOUBLE BOND
0
60
120
180
MINUTES SHAKING.

CURVE 2.

determined in alcoholic solution $[\alpha]_D^{17}$ -140° (c = 0.168).

The product from the third reduction was worked up in a similar manner to that from the first reduction. Ehrlich's test when applied to the acid solution was only faintly positive. No crystalline base was isolated from this reduction.

Catalytic reduction of rubremetinium chloride.

Rubremetinium chloride (0.5 g) was dissolved in 30 c.c. of magnesium dried ethanol. Adam's PtO_2 catalyst (0.1 g) and crystalline sodium acetate (0.45 g) were added, and the mixture was shaken with hydrogen at room temperature and atmospheric pressure in a glass hydrogenation apparatus. The uptake of hydrogen was rapid, and ceased when one mole had been absorbed.

The catalyst was filtered off rapidly ("Filtercel") and the clear yellow filtrate was evaporated to dryness in vacuo. Excess sodium hydroxide was added to the residue and the mixture was extracted with ether, washing each ether layer with water. The combined ether extracts were dried and evaporated to dryness to give a yellow gum. This was dissolved in 5 c.c. of ethanol and, on cooling, crystallisation occurred. The product (XXXVI) was obtained as pale yellow needles (0.23 g), which darkened at 169° and melted at 180-183°. A second crop (0.05 g), melting at 177-180°, was obtained from the mother liquors.

The two crops were recrystallised from ethanol (8 c.c.) and a mixture of α- and β-dihydrorubremetines was obtained as fine white/

(b) β-dihydrorubremetine.

c = 0.1755 l = 2 dm. α_D +0.078° solvent = acetone

$[\alpha]_D^{15}$ +22.2°

3. Ehrlich's test.

A minute portion of α-dihydrorubremetine was dissolved in ethanol and one drop of Ehrlich's reagent was added. An intense green colour was formed which changed to red on the addition of excess reagent.

The test was repeated on a sample of β-dihydrorubremetine with a similar result.

4. Pine shaving reaction.

A pine shaving moistened with hydrochloric acid was held in the vapour from the destructive distillation of α-dihydrorubremetine. A bright carmine colour was imparted to the shaving.

The test was repeated using β-dihydrorubremetine and a positive result was obtained.

5. Diazo-coupling.

0.1 g. of sulphanilic acid was dissolved in 2 c.c. of N sodium hydroxide and a solution of 0.05 g. of sodium nitrite in 1 c.c. of water was added. The mixture was cooled in ice and poured into 1 c.c. of 2 N hydrochloric acid.

Excess/

Excess sodium carbonate solution was added to neutralise the acid, and the diazonium solution was added to a solution of 0.05 g. of α-dihydrorubremetine in 1 c.c. of dilute acetic acid. Coupling took place, and a brilliant red azo dye was formed.

The test was repeated using β-dihydrorubremetine, with an identical result.

The test was also carried out, exactly as above, using samples of emetine hydrochloride and tetradehydroemetine hydrogen oxalate in place of the dihydrorubremetine. No coupling took place in either case.

Mercuric acetate oxidation of α-dihydrorubremetine.

α-dihydrorubremetine (0.1 g) was dissolved in 2 c.c. of dilute acetic acid. A solution of mercuric acetate (0.148 g = 2 moles + 10%), potassium acetate (0.025 g), 2 c.c. of water and 0.2 c.c. of glacial acetic acid was added, washing in with 1 c.c. of water.

After heating for three to three and a half hours at 110-120° under reflux, there was a slight deposit of mercurous acetate, and a small quantity of metallic mercury was also formed. The solid material was filtered off, washed well with water, and the filtrate was saturated with hydrogen sulphide. After heating to boiling three times, the solution was filtered ("Filtercel") to give a clear red solution. The filter cake was thoroughly extracted with hot ethanol, the extract evaporated to low bulk and added to the main solution. After evaporating to about 5 c.c., concentrated hydrochloric/

hydrochloric acid (2 c.c.) was added, and rubremetinium chloride crystallised out as beautiful scarlet needles (0.028 g. = 21%). The product sintered at 114°, and melted and effervesced at 126-127° both alone, and in admixture with an authentic specimen.

Mercuric acetate oxidation of β-dihydrorubremetine.

The oxidation was carried out exactly as above using 0.1 g. of β-dihydrorubremetine. 0.028 g. (21%) of rubremetinium chloride was obtained, melting with effervescence at 123-125°. The mixed melting point with an authentic specimen was 123-125°.

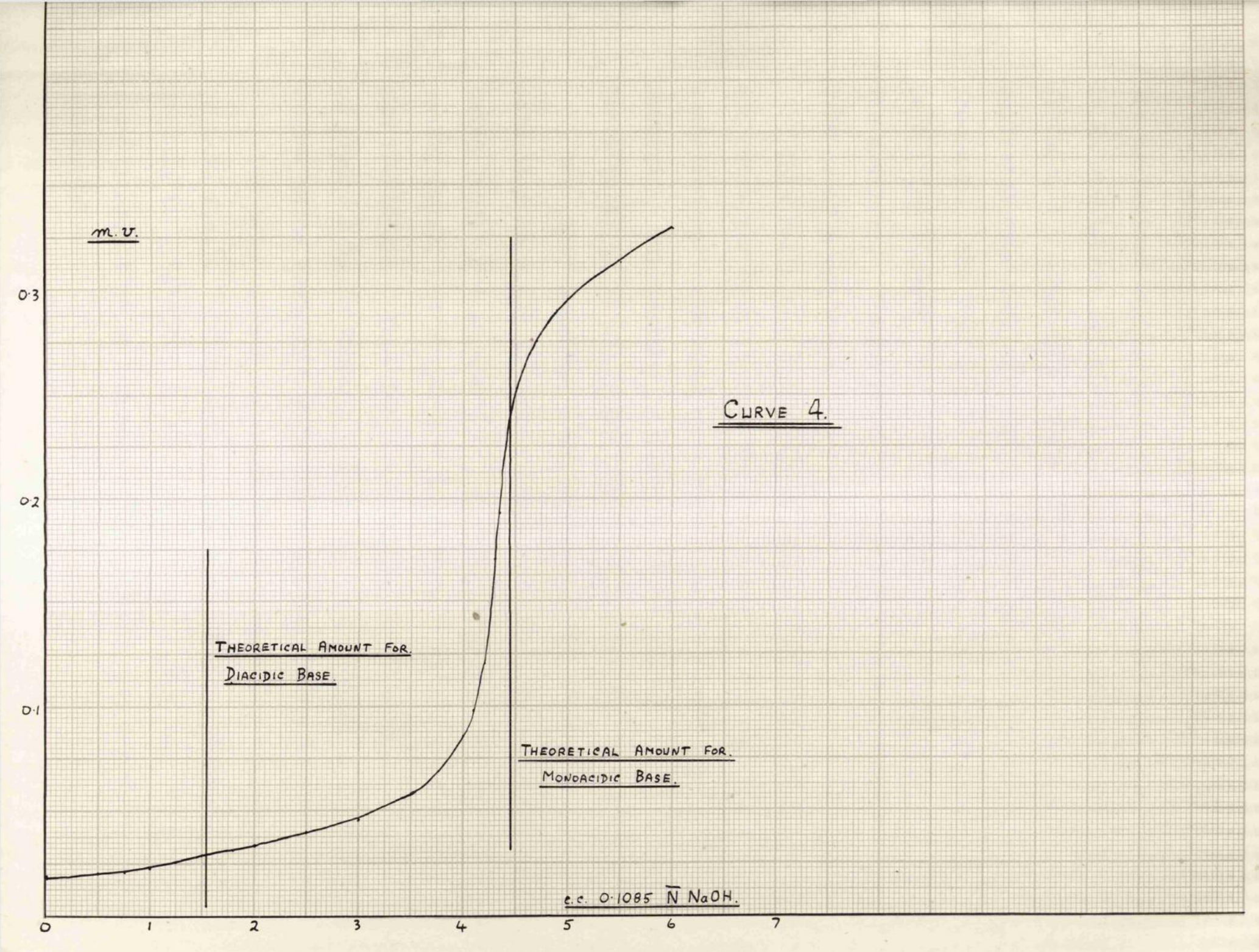
Potentiometric titration of α-dihydrorubremetine.

The apparatus used in this experiment was a Marconi pH meter, in conjunction with the glass and calomel electrodes. As the titration was to be carried out in 50% alcohol solution, a trial experiment was performed using standard acid and standard alkali in 50% alcohol solution. The resulting curve indicated that the glass electrode does function correctly in this concentration of alcohol.

0.15 g. of α-dihydrorubremetine was dissolved in 8.00 c.c. of 0.1 N hydrochloric acid. The excess acid was titrated against 0.1085 N sodium hydroxide solution with constant stirring. The resulting curve 4. shows that α-dihydrorubremetine is to be regarded as a monoacidic base.

Dehydrogenation of α-dihydrorubremetine.

α-dihydrorubremetine/


m.v.
0·3
0·2
0·1
0
1
2
3
4
5
6
7
THEORETICAL AMOUNT FOR DIACIDIC BASE.
THEORETICAL AMOUNT FOR MONOACIDIC BASE.
c.c. 0·1085 N NaOH.

CURVE 4.

α-dihydrorubremetine (0.25 g) was mixed with 0.25 g. of 10% palladised charcoal and heated at 200-210° for 40 minutes in an atmosphere of carbon dioxide. The hydrogen evolved (12 c.c. = 1 mole) was passed through a trap at -50° and collected over 50% potassium hydroxide at room temperature and pressure. The contents of the reaction flask were dissolved in boiling ethanol (50 c.c.) and filtered ("Filtercel") to remove the catalyst. Evaporation of the bright orange filtrate gave 0.22 g. of a red resin.

This resin was dissolved in excess sodium hydroxide solution and extracted with ether A (3 x 25 c.c.). The aqueous layer was acidified and extracted with chloroform to remove quaternary matter. Evaporation of the chloroform solution gave a reddish-brown resin (0.11 g), which could not be induced to crystallise.

The ether solution A was extracted with $\overline{N}$ hydrochloric acid (3 x 25 c.c.) to remove basic material, the acid extract being bright red in colour. The ether layer was washed with water, dried, and evaporated to dryness yielding a pale yellow gum (0.015 g). This gum was dissolved in ethanol and a solution of picric acid in ethanol was added. An amorphous solid was formed which could not be obtained in the crystalline state.

The acid extract was basified and extracted with ether (3 x 50 c.c.). After drying, the extract was evaporated to dryness to give 0.171 g. of a brown gum. This was dissolved in a small amount of an ethanol-ether mixture, and crystallisation occurred/

occurred after standing overnight. A small amount of crystalline material, melting at 174-178° was obtained, and recrystallisation from methanol gave pale yellow needles, melting at 185-186°. The base, in alcoholic solution, gave a brilliant orange colour with Ehrlich's reagent.

Dehydrogenation of β-dihydrorubremetine.

0.4 g. of β-dihydrorubremetine was dehydrogenated as above, using 0.4 g. of palladised charcoal catalyst. A crystalline basic fraction was again isolated, and after several re-:crystallisations from methanol, pale yellow needles were obtained melting at 184-185°. There was no depression of this melting point when determined in admixture with the base obtained from α-dihydrorubremetine. A specimen of the base was purified carefully, and after drying for 48 hours over phosphorus pentoxide at room temperature, it was sent for analysis.

Found : C. 72.1% H. 6.38% N. 5.88%

Further dehydrogenation of α-dihydrorubremetine.

α-dihydrorubremetine (0.25 g) was mixed with 10% palladised charcoal (0.25 g) and heated at the temperatures shown below. The reaction was carried out in an atmosphere of carbon dioxide as before, and the hydrogen evolved was collected over 50% potassium hydroxide solution.

Time/

Time	Temperature	Vol. of hydrogen.
20 minutes at	180-190°	-
30 " "	205-210°	-
60 " "	210-220°	12 c.c.
20 " "	245-250°	-
30 " "	270-275°	-
95 " "	300-305°	32 c.c. approx.

The reaction mixture was worked up and separated into neutral, basic and acidic fractions as in the previous dehydrogenations. No crystalline materials could be isolated however.

The neutral fraction (0.026 g) was dissolved in a mixture of light petroleum (90%) and benzene, and passed down a six inch column of activated alumina. 10 c.c. samples of the eluting solvent, composition as shown below, were taken, and each was evaporated to dryness to give small varying amounts of a colourless gum. A drop of alcoholic picric acid solution was added to each of these extracts, but no crystalline product was obtained.

Weight of gum	Composition of eluting solvent
2.0 mg.	50% benzene, 50% light petroleum
1.0 mg.	" "
1.7 mg.	" "
0.8 mg.	100% benzene
0.2 mg.	"
0.5 mg.	"
0.1 mg./	

Weight of gum	Composition of eluting solvent
0.1 mg.	100% benzene
3.5 mg.	100% ethanol
3.0 mg.	"

Preparation of N-acetylemetine methiodide (XXXVII).

10.0 g. of emetine hydrochloride were converted to amorphous N-acetylemetine (7.92 g) according to the instructions of Ahl and Reichstein (13). The crude N-acetylemetine was treated with methyl iodide in benzene, and N-acetylemetine methiodide (XXXVII) was obtained as yellow prisms (10.08 g = 100%), melting at 208-211°. Further recrystallisation from ethanol gave 9.7 g. of product melting at 211-213°.

Hofmann degradation of N-acetylemetine methiodide.

5.0 g. of N-acetylemetine methiodide were degraded by the Hofmann procedure, as described by Ahl and Reichstein (13), and the resulting N-acetylemetine methine (XXXVIII) was obtained as a pale yellow glass. This was dissolved in 50 c.c. of ether and shaken with $\overline{N}$ hydrochloric acid (3 x 30 c.c.). The acid extract was treated with excess sodium hydroxide solution and extracted thoroughly with ether (3 x 50 c.c.). After drying and evaporating to dryness, 3.57 g. (96%) of a water-white gum were obtained.

This methine was dissolved in 50 c.c. of dry ethanol, 100 mg. of/

of platinic oxide were added, and the mixture was shaken with hydrogen. Uptake of hydrogen ceased after 30 minutes, when 162 c.c. (1 mole) of hydrogen had been absorbed.

The catalyst was filtered off ("Filtercel") and the filtrate was evaporated to dryness in vacuo to give a clear gum (3.65 g). This was dissolved in 25 c.c. of ethanol, and 1.8 g. of hydrated oxalic acid in 25 c.c. of ethanol were added. Crystallisation occurred on cooling, and 4.6 g. of white needles were obtained. After several recrystallisations from ethanol, N-acetylemetinedihydromethine hydrogen oxalate was obtained as fine white needles, melting at 200-201° with previous sintering. A specimen was dried at 100° in vacuo over phosphorus pentoxide for five hours, and analysed.

Found: C. 59.8% H. 6.94% N. 3.43%

$C_{32}H_{46}O_5N_2.2\ C_2H_2O_4$ requires : C. 60.1% H. 7.02% N. 3.90%

0.4 g. of the hydrogen oxalate were converted to the free base as usual, and the resulting gum was distilled at 180° and 5.0×10^{-6} mm. A sample of the distillate was sent for analysis.

Found: C. 71.4% H. 8.78% N. 5.65%

$C_{32}H_{46}O_5N_2$ requires : C. 71.3% H. 8.62% N. 5.20%

Deacetylation of N-acetylemetinedihydromethine.

Method 1.

0.12 g. of dry magnesium turnings were suspended in 5 c.c. of dry ether, and 0.55 g. of dry methyl iodide in 5 c.c. of dry ether/

ether were added dropwise with vigorous stirring. The reaction flask carried a reflux condenser and was protected against the entry of moisture.

The mixture was refluxed on the water bath for 6 hours, and 0.422 g. of N-acetylemetinedihydromethine in 10 c.c. of dry ether were added dropwise. An immediate white precipitate formed; this was allowed to stand overnight and then refluxed for a further 9 hours on the water bath.

The mixture was poured into a concentrated solution of ammonium chloride in ice-water to decompose the addition compound, and the base was extracted with ether (3 x 50 c.c.), washing each ether layer with water. After drying and evaporating to dryness, a yellowish-brown glass (0.371 g = 95%) was obtained.

0.2 g. of this glass were dissolved in 4 c.c. of ethanol, and a solution of hydrated oxalic acid (0.15 g) in ethanol (3 c.c.) was added. The crystalline material, after filtering off and drying, melted at 201-202°. There was no depression of this melting point in admixture with N-acetylemetinedihydromethine hydrogen oxalate.

Method 2.

N-acetylemetinedihydromethine (0.22 g) was dissolved in 5 c.c. of methanol, and 4.5 c.c. of 10% hydrochloric acid were added. The mixture was heated for 6 hours at 130-135° in a sealed tube, 2 hours being required to attain this temperature. After cooling overnight, the tube was opened carefully. The methyl/

methyl chloride and methanol were evaporated under reduced pressure, leaving 5 c.c. of aqueous solution which was extracted with ether (10 c.c.). Excess sodium hydroxide was added, and the basic material was extracted with ether (3 x 30 c.c.). The ethereal solution was dried and evaporated to dryness to give 0.19 g. (94%) of a yellow gum (XL). This dihydromethine (XL) was distilled at 180° and 5.0×10^{-6} mm. and was finally obtained as a clear yellow glass (0.18 g).

Acetylation of the dihydromethine (XL).

0.36 g. of the dihydromethine (XL) were dissolved in 5 c.c. of ether, and shaken for a few minutes with 10 c.c. of 10% potassium hydroxide and 1 c.c. of acetic anhydride. The ether layer was separated and the aqueous phase was extracted thoroughly with two further portions of ether. After drying, the ethereal extracts were evaporated to dryness to give 0.27 g. of a colourless gum. This was dissolved in 2 c.c. of ethanol, and 0.9 g. of hydrated oxalic acid in 2 c.c. of ethanol were added. Crystallisation occurred after some time, and fine white needles, melting at 198-199° were obtained. There was no depression of this melting point in admixture with N-acetylemetinedihydromethine (XXXIX) hydrogen oxalate.

BIBLIOGRAPHY

(1)	Pelletier and Magendie.	Ann. Chim. Phys. 1817(2) 4 172.
	Pelletier and Dumas.	Ann. Chim. Phys. 1823(2) 24 180.
(2)	Carr and Pyman.	J.C.S. 1914 105 1591.
(3)	Pyman.	J.C.S. 1917 111 419.
(4)	Pyman.	J.C.S. 1918 113 222.
(5)	Brindley and Pyman.	J.C.S. 1927 1067.
(6)	Hesse, Paul and Cownley.	Pharm. J. 1898(4) 7 98.
	Hesse.	Ann. 1914 405 1.
	Keller.	Arch. Pharm. 1911 249 512.
(7)	Karrer.	Ber. 1916 49 2057.
(8)	Windaus and Hermanns.	Ber. 1914 47 1470.
	Dobbie and Fox.	J.C.S. 1914 105 1639.
(9)	Späth and Leithe.	Ber. 1927 60 688.
(10)	Karrer, Eugster & Rüttner.	Helv. Chim. Acta. 1948 31 1219.
(11)	Semmler.	Ber. 1908 41 2556.
	Salway.	J.C.S. 1910 97 2413.
(12)	Barrett, Perkin & Robinson.	J.C.S. 1929 2942.
	Nishikawa, Perkin & Robinson.	J.C.S. 1924 125 657.
(13)	Ahl and Reichstein.	Helv. Chim. Acta. 1944 27 366.
(14)	Battersby and Openshaw.	J.C.S. 1949 S 59.
(15)	Battersby and Openshaw.	J.C.S. 1949 3207.
(16)	Späth and Pailer.	Monatsh. 1948 78 348.
	Pailer.	Monatsh. 1948 79 127.
	Pailer.	Monatsh. 1948 79 331.

(17)	Robinson.	Nature. 1948 162 524.
(18)	Pailer and Porschinski.	Monatsh. 1949 80 94.
(19)	Brindley.	Ph.D. Thesis, Manchester. 1927.
(20)	Battersby and Openshaw.	J.C.S. 1949 S 67.
(21)	Staub.	Helv. Chim. Acta. 1927 10 826.
(22)	Battersby, Openshaw & Wood.	Experientia. 1949 V/3 114.
(23)	Tafel.	Ber. 1892 25 1622.
	Gadamer.	Arch. Pharm. 1915 253 281.
		Arch. Pharm. 1924 262 452.
	Legerlotz.	Arch. Pharm. 1918 256 123.
(24)	Bills and Noller.	J.A.C.S. 1948 70 957.
(25)	Craig and Tarbell.	J.A.C.S. 1948 70 2783.
(26)	Child and Pyman.	J.C.S. 1929 2010.
		J.C.S. 1931 36.
	Coulthard, Levene & Pyman.	Biochem. J. 1933 27 727.
		Biochem. J. 1934 28 264.
	Pyman.	Chem. & Ind. 1937 56 789.
(27)	Covert and Adkins.	J.A.C.S. 1932 54 4116.
(28)	Adkins, Richard & Davies.	J.A.C.S. 1941 63 1320.
(29)	Karrer & Rüttner.	Helv. Chim. Acta.1950 33 291.

In conclusion, I wish to express very sincere thanks to Dr. John Dewar, and to Dr. H.T. Openshaw, for their valuable advice and kindly criticism throughout the conduct of these researches.

I am also most grateful to the Department of Scientific and Industrial Research for the provision of a Maintenance Grant.