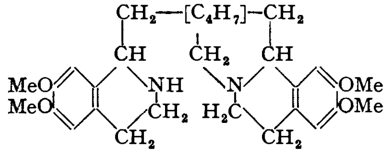
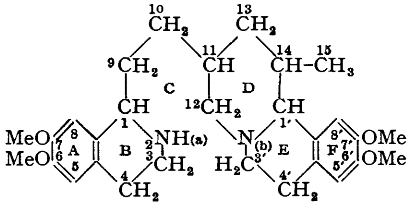
S 11. *Studies on the Structure of Emetine. Part I. The Hofmann Degradation.*

By A. R. BATTERSBY and H. T. OPENSHAW.

Emetine contains one *C*-methyl group, and may be represented by the partial structure (III). The methine base (IV), obtained from emetine by the exhaustive methylation procedure, is hydrogenated to N-*methylemetinetetrahydromethine* (V). This substance forms a *mono*- and a *di-methiodide*, both of which readily decompose on heating, with fission of trimethylamine hydriodide and formation of a tertiary *base* (XI) and its methiodide (IX, X = I) respectively. This decomposition has structural implications which support the assignment of the structure (IV) to the methine, and confirmation is obtained by oxidation of the base (XI) to 6-ethylveratric acid. The methiodide (IX, X = I) has been converted into a *dihydro*-derivative, which, as the corresponding chloride (XII), undergoes Emde's degradation to a tertiary *base* (XIV). Further degradation of this base by Hofmann's method leads to a nitrogen-free oil of the expected composition, together with a relatively larger amount of a base.

INVESTIGATIONS of the ipecacuanha alkaloids by Pyman *et al.* (*J.*, 1914, **105**, 1591; 1917, **111**, 419; 1918, **113**, 222; 1927, 1067), Karrer (*Ber.*, 1916, **49**, 2057; 1917, **50**, 582), Späth and Leithe (*Ber.*, 1927, **60**, 688), and others have established the interrelationships of the five alkaloids found in the root, and have determined the main features of their structures. The results have been reviewed by Henry (" The Plant Alkaloids," 3rd Edition, London, 1939, p. 324) and by Staub (" Ein Jahrhundert chemischer Forschung über Ipecacuanha-Alkaloide," Zurich, 1927). Emetine, the principal alkaloid, contains one secondary and one tertiary nitrogen atom [conveniently designated N(a) and N(b) respectively], each contained in a 6:7-dimethoxy-1:2:3:4-tetrahydro*iso*quinoline nucleus; these nuclei are linked together by a carbon chain attached at their 1-positions and at the tertiary nitrogen atom, N(b), which is common to two rings. Späth and Leithe (*loc. cit.*) expressed these findings by the partial structure (I). The more detailed structure (II) advanced by Brindley and Pyman (*J.*, 1927, 1067) rests on admittedly speculative considerations.


(I.)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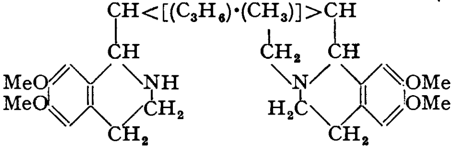

(III.)

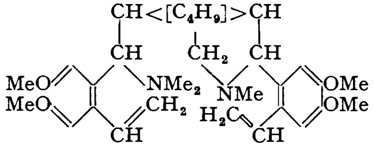
There is no evidence that the carbon atoms 9 and 14 each carry two hydrogen atoms, as shown in the structure (I); moreover, we have found that emetine contains one *C*-methyl group (Kuhn–Roth). We therefore prefer to represent the known facts by the partial structure (III), in which the placing of two hydrogen atoms on C_{12} is to be regarded as only tentative, as it depends on the acceptance of Pyman's interpretation of the formation of rubremetine (see Part II). In view of the importance of emetine in the treatment of amœbic dysentery, it is desirable that the structure of this alkaloid should be completely established.

The Hofmann degradation of emetine was first studied by Hesse (*Annalen*, 1914, **405**, 1), who obtained *N*-methylemetinemethine (IV) by the thermal decomposition of *N*-methylemetine dimetho-hydroxide. The methine was more fully characterised by Pyman (*J.*, 1917, **111**, 419; 1918, **113**, 222). The second stage of the Hofmann degradation, carried out by Karrer (*loc. cit.*) resulted in the loss of one nitrogen atom [N(a)] as trimethylamine; the retention of the second nitrogen atom [N(b)] shows that, in emetine itself, this atom is common to two rings. Neither the bismethine base nor any of its derivatives could be crystallised, and its further degradation was not studied. More recently, Ahl and Reichstein (*Helv. Chim. Acta*, 1944, **27**, 366) have carried out a complete series of Hofmann degradations on *N*(*a*)-acetylemetine; at the third stage, N(b) was split off as trimethylamine, confirming its linkage in two rings. Oxidation of the final product yielded 3:4-dimethoxyphthalimide, proving conclusively that the secondary nitrogen atom N(a) of emetine is contained in a dimethoxytetrahydro*iso*quinoline structure. By applying the same method, Brindley (Ph.D. Thesis, University of Manchester, 1927) eliminated N(b) from *N*(*a*)-benzoyl*iso*emetine, but the product was not further investigated.

Emde's method of degradation has been applied to emetine by Späth and Leithe (*loc. cit.*), the results being consistent with the structure (III). Reduction of *N*-methylemetine dimethochloride with sodium amalgam gave a tetrahydromethine, from which no crystalline derivatives were obtained. Reduction of the dimethochloride of this base caused fission of trimethylamine (40% of the theoretical) and gave an amorphous base. In the third treatment, trimethylamine was again evolved, but the product was a mixture containing 75% of a basic substance and only 25% of the expected nitrogen-free product, which was not characterised.

In planning the present series of investigations, we have had two principal aims in view; the degradation of emetine to a nitrogen-free product which, if structure (II) is correct, should be capable of synthesis, or of further degradation to recognisable products, and the determination of the size of the second ring (D) of which N(b) is a member. For both these purposes, a further study of the Hofmann degradation has been made. In order to avoid the difficulties often encountered in the conduct of multi-stage degradations of this type (see, for example, Ahl and Reichstein, *loc. cit.*), which are probably due to the accumulation of ethylenic linkages in the molecule, it was decided to hydrogenate the material at each stage (cf. Karrer *et al.*, *Helv. Chim. Acta*, 1928, **11**, 1062; 1930, **13**, 1292).

Catalytic hydrogenation of *N*-methylemetinemethine (IV) yielded N-*methylemetinetetrahydromethine* (V), characterised as the crystalline *perchlorate*. Isolation of this substance in 90% yield confirms the conclusion reached by Pyman (*J.*, 1917, **111**, 427) that the methine (IV) consists mainly, if not entirely, of an individual substance. Ring fission at N(a) can occur in two, and at N(b) in three possible ways, and the assignment of the structure (IV) to the methine involves the assumption that the ring fission has occurred between N and C_3 in each *iso*quinoline nucleus. This assumption is based mainly on the known ease with which 2-phenylethylamine derivatives undergo such fission; for example, the substance (VI) eliminates styrene in preference to ethylene (Hanhart and Ingold, *J.*, 1927, 997). Examples of the Hofmann degradation of tetrahydro*iso*quinolines to be found in the literature are concerned almost entirely with 1-benzyl derivatives, and in these cases ring-fission usually occurs at the alternative position N–C_1, presumably because this leads to conjugation of the newly formed double bond with *two* benzene nuclei. However, the dibenztetrahydropyrrocoline (VII) suffers fission of the N–C_3 bond of the *iso*quinoline system (Robinson and Sugasawa, *J.*, 1932, 789), and carnegine metho-hydroxide decomposes to a mixture of the two possible degradation products, one of which is formed by fission between N and C_3. A still closer analogy is provided by *lævo*canadine metho-hydroxide (VIII), which has been shown (Pyman, *J.*, 1913, **103**, 817) to decompose by two alternative routes, one of which (*a*) corresponds to fission of a N–C_3 bond. Moreover, the second mode (*b*) of ring-opening is reversible; a somewhat similar example of the reversibility of a Hofmann degradation has been encountered in the strychnidine series (Achmatowicz and Robinson, *J.*, 1934, 581). Since we have found no evidence of reversibility in the degradation of emetine, it is unlikely that the N(b)–C_1' bond is the point of fission. Further evidence in support of the structure (IV) for *N*-methylemetinemethine is adduced below.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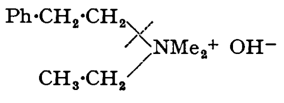
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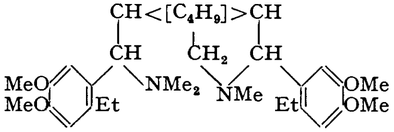
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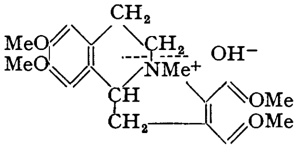
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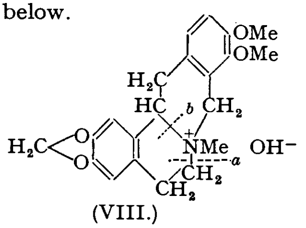
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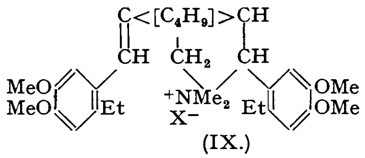
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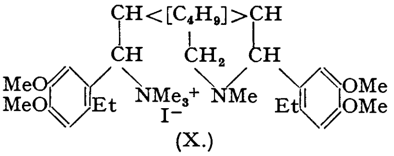
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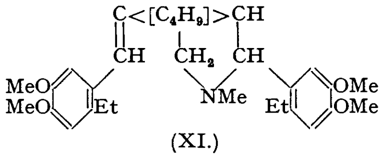
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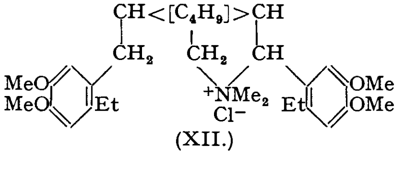
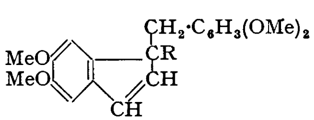

(XII.)

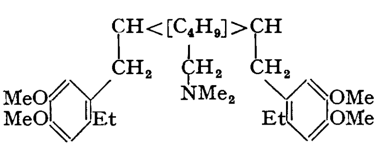
Initial attempts to convert the tetrahydromethine (V) into its dimethiodide, by treatment with methyl iodide in hot alcoholic solution, led to an unexpected result. The product obtained was a mixture of trimethylamine hydriodide (together with a little tetramethylammonium iodide) and a monomethiodide, designated des-*N*(*a*)-emetinetetrahydromethine methiodide (IX, X = I). When the methylation was conducted in ethereal solution at room temperature, the normal *dimethiodide* was obtained, together with a smaller amount of a monomethiodide, N-*methylemetinetetrahydromethine* N(a)-*methiodide* (X), isolated as its crystalline *hydriodide*. Separation of these products was facilitated by the discovery that the dimethiodide forms a crystalline complex with ethylene dichloride, very sparingly soluble in that solvent. Heating of a solution of the dimethiodide in water, or better in diethyl ketone, at 100° brought about decomposition to trimethylamine hydriodide and (IX, X = I). The monomethiodide (X) decomposed in a similar fashion to give a base, *des*-N(a)-*emetinetetrahydromethine* (XI), which was also obtained by thermal decomposition of its *methochloride* (IX, X = Cl), and was characterised as the crystalline *perchlorate* and *hydriodide*. The base was reconverted into (IX, X = I) by methyl iodide. The presence of an ethylenic linkage in (IX) was shown by the absorption spectrum of the iodide (see Table), and by hydrogenation of the chloride to des-*N*(*a*)-emetinehexahydromethine methochloride (XII), which gave a crystalline *iodide* and *platinichloride*. The position assigned to this double bond was confirmed by the oxidation of the base (XI) with barium permanganate; 6-ethylveratric acid was obtained, together with an amino-acid which has not yet been fully characterised.

The unusual and remarkably easy decomposition of the tetrahydromethine methiodides must be of structural significance. Two examples of somewhat similar reactions have been described in the literature. The alkaloid gramine (3-diethylaminomethylindole) yields trimethylamine and tetramethylammonium iodide when treated with methyl iodide in methyl alcohol (Madinaveitia, *J.*, 1937, 1927), and pavinemethine methiodide (XIII, R = NMe_3I) is decomposed by being heated with water or methyl alcohol to give trimethylamine hydriodide and the hydroxy- or methoxy-compound (XIII, R = OH or OMe) respectively (Pyman, *J.*, 1915, **107**, 176). Accordingly, we have ascribed the occurrence of this reaction to the presence of an activated benzylamine structure in (V), and this theory has been confirmed by a study of model substances (Norcross and Openshaw, forthcoming publication), hence providing further evidence for the position of ring-fission in the Hofmann degradation of emetine.

Since an odour of volatile amine was always observed during the handling of the tetrahydromethine (V), attempts were made to bring about its decomposition to (XI) and dimethylamine under a variety of conditions. In no case was any appreciable amount of dimethylamine liberated, and the material was usually recovered unchanged, except that partial demethylation of the methoxyl groups occurred when strongly acid conditions were employed. The tertiary base (XI) contains a single nitrogenous ring (ring D) and is of interest as a possible starting point for the determination of the size of this ring.



(XIII.)



(XIV.)

When treated with sodium amalgam and water, des-*N*(*a*)-emetinehexahydromethine methochloride (XII) underwent the Emde degradation. The resulting saturated, tertiary *base*, probably (XIV), has not so far yielded crystalline salts. A preliminary experiment on the Hofmann degradation of its amorphous methiodide gave a mixture containing a neutral *substance* of the expected composition, $C_{25}H_{30}(OMe)_4$, and a *base*. This result is similar to that obtained by Späth and Leithe (*loc. cit.*) and indicates that either the Emde degradation or the final Hofmann degradation did not proceed wholly in the desired direction. These reactions are being further investigated.

The ultra-violet absorption spectra of some emetine derivatives have been measured by Dr. A. E. Gillam, to whom we express our sincere thanks. In addition to rising absorption below 2250 A., each compound showed a well-defined maximum, as recorded in the Table. These measurements afford a clear differentiation between the saturated and the unsaturated compounds, the absorption of the latter closely resembling that of the similarly constituted stereoisomeric *O*-methyl*iso*eugenols.

Ultra-violet Absorption of Emetine Derivatives and Related Compounds in Alcoholic Solution.

Compound.	$\lambda_{max.}$	ϵ.
N-Methylemetine dimethiodide (β-form)	2840	6,350
Des-*N*(*a*)-emetinehexahydromethine methiodide (XII)	2860	6,800
Base (XIV)	2855	6,270
Des-*N*(*a*)-emetinetetrahydromethine methiodide (IX)	2660	15,900
	3030 *	7,240
cis-*O*-Methyl*iso*eugenol †	2600	13,400
trans-*O*-Methyl*iso*eugenol †	2630	14,500

* Inflexion.

† These compounds were prepared by Mr. F. Long, M.Sc., by the method of Boedecker and Volk (*Ber.*, 1931, **64**, 61).

Added in proof. The work described in this paper was begun in 1945 and completed in 1947. Since it was submitted for publication, the papers of Späth and Pailer (*Monatsh.*, 1948, **78**, 348; **79**, 127) have become available. These authors describe the degradation of emetine by essentially the same method, and they have carried the degradation further to obtain recognisable products. Of the various crystalline intermediates isolated by us, they obtained only the methiodide (IX) in a pure condition; their description of this substance agrees with ours. We defer detailed comment on the results of Späth and Pailer to a future communication.

EXPERIMENTAL.

C-*Methyl Determination*.—An ethereal solution of emetine, liberated from the commercial hydrochloride (1 g.), was shaken thrice with 10 c.c.-portions of 10% aqueous sodium hydroxide to remove traces of phenolic bases, dried (K_2CO_3), and evaporated at room temperature under reduced pressure. The residual amorphous glass was powdered, dried in a vacuum at 50°, and submitted to the Kuhn–Roth procedure (Found:* 0·94 mol. acetic acid).

N-*Methylemetinetetrahydromethine* (V).—Emetine hydrochloride was converted into a mixture of α- and β-*N*-methylemetine dimethiodides in 98% yield by a slight modification of the method of Pyman (*J.*, 1918, **113**, 222). Separation of the stereoisomers was unnecessary, since both forms give rise to the same methine. The anhydrous methiodide (22·52 g.) was converted into the methine base (14·07 g.; 93%) as described by Pyman (*J.*, 1917, **111**, 445), except that the heating of the quaternary hydroxide was continued for 2½ hours. The base was dissolved in pure alcohol (100 c.c.) and hydrogenated (PtO_2) at room temperature and pressure; 1·93 mols. of hydrogen were absorbed in 4 hours. The filtered solution was treated with a slight excess of dilute hydrochloric acid, the alcohol removed by distillation under reduced pressure, and the residual aqueous solution treated with excess of 20% perchloric acid. N-*Methylemetinetetrahydromethine perchlorate* separated as a gum which crystallised on standing or seeding. After recrystallisation from water it formed colourless needles, which were dried at 110° (16·25 g.); m. p. 183—184°. An additional quantity (1·28 g.) was obtained from the mother liquor by treatment with perchloric acid and recrystallisation; total yield, 90%. One further crystallisation raised the m. p. to 185—186°; $[\alpha]_D^{20^\circ}$ + 6·0° ± 0·2° (*c*, 5 in acetone) (Found, in air-dried substance: loss at 118°/1 mm., 2·50. $C_{32}H_{50}O_4N_2,2HClO_4,H_2O$ requires H_2O, 2·42%. Found*, in anhydrous substance: C, 52·7; H, 7·4; N, 4·0. $C_{32}H_{50}O_4N_2,2HClO_4$ requires C, 52·8; H, 7·2; N, 3·9%). The salt is readily soluble in cold acetone or chloroform, and in hot alcohol. Treatment with aqueous alkali liberates the base as a colourless, very viscous oil, which distils at 180—200° (bath)/5 × 10^{-4} mm.

Attempted Decomposition of N-*Methylemetinetetrahydromethine*.—The base was heated at 150°, alone or in admixture with a 5% solution of potassium hydroxide in ethylene glycol, while a stream of dry nitrogen was passed through it, and through dilute hydrochloric acid. In neither case was any dimethylamine found in the hydrochloric acid solution. After 4 hours' heating with 10% hydrochloric acid or 20% sulphuric acid, the base was shown, by reconversion into the perchlorate, to be largely unchanged, and no trace of the perchlorate of base (XI) (see later) could be obtained by fractional crystallisation. From a solution of the hydriodide of the base, which had been heated at 100° for 7 hours, the perchlorate was precipitated in an almost pure condition (m. p. 179—181°). When the base (0·68 g.) was heated under reflux with concentrated hydrochloric acid (20 c.c.) for 5 hours, some demethylation (phenolic fraction, 0·14 g.) and resinification occurred. The perchlorate, recovered from the non-phenolic material, consisted largely of a water-insoluble gum which could not be crystallised but did not appear to contain any of the perchlorate of the desired product (XI).

N-*Methylemetinetetrahydromethine Dimethiodide*.—Anhydrous tetrahydromethine perchlorate (1·5 g.) was suspended in water (15 c.c.) and treated with a slight excess of aqueous sodium hydroxide. The liberated base was isolated by extracting the mixture thrice with ether, drying the extract (K_2CO_3), and evaporating the ether under reduced pressure. The residue was dissolved in anhydrous ether (10 c.c.), and methyl iodide (1 c.c.) added. After 48 hours at room temperature, the colourless precipitate was collected, washed with ether, and dried in a vacuum (1·62 g.; 97%); microscopic needles, m. p. 125°. On addition to warm ethylene dichloride (10 c.c.) the *methiodide* dissolved, and rapidly crystallised again as small, irregular rhombs (1·61 g.), m. p. 130°, containing solvent of crystallisation. Recrystallisation from acetone gave clusters of colourless leaflets, which slowly redissolved with simultaneous deposition of compact rhombs, m. p. 135·5—136°. Owing to decomposition, the melting point is greatly dependent on the rate of heating; the melt quickly resolidifies and then melts at about 210—220°. After brief drying over calcium chloride in a vacuum, the composition approximates to that of a dihydrate (Found: C, 48·8; H, 7·0; I, 29·7; loss at 60°/1 mm., 3·8. $C_{34}H_{56}O_4N_2I_2,2H_2O$ requires C, 48·2; H, 7·1; I, 30·0; H_2O, 4·2%. Found, in anhydrous material: C, 50·4; H, 6·9. $C_{34}H_{56}O_4N_2I_2$ requires C, 50·4; H, 7·0%).

In another experiment, the base from 7·5 g. of perchlorate was treated as above. Crystallisation of the crude product from acetone gave a little tetramethylammonium iodide (88 mg.); on dilution of the mother liquor with ether, the dimethiodide (" sample *A* ", 3·28 g.) crystallised; m. p. 139—140° (sintered at 137°; melt resolidified). Concentration of the mother liquor at room temperature gave a crop of crystals (1·53 g.), m. p. 190—196° (decomp.). Washing with warm water raised the m. p. to 221—224° (1·27 g.), and crystallisation from alcohol gave colourless needles (1·06 g.), m. p. 232—232·5°, identified as (IX, X = I) (see below). The acetone mother liquor was diluted with ethylene dichloride, and on seeding yielded impure dimethiodide (0·926 g.), m. p. 128—130° (decomp.). Evaporation o the mother liquor left an amorphous residue (" gum *B* ", 1·74 g.), which after a lengthy crystallisation process gave a very small amount of the methiodide (IX).

N-*Methylemetinetetrahydromethine Monomethiodide Hydriodide* (X).—The tetrahydromethine base (4·837 g.) was dissolved in anhydrous, alkali-free ether (150 c.c.), and methyl iodide (1·4 c.c.; approx. 2·5 mols.) was added. After 40 hours at room temperature, the solid precipitate (1·55 g.) was collected and washed with ether. Treatment of the filtrate with further portions (1·5, 2·5, and 2·5 c.c.) of methyl iodide, and collection of the product before each fresh addition, at intervals of 2, 3, and 2 days, gave 3 further crops (1·54, 2·41, and 0·93 g. respectively). The first 2 crops were combined (3·09 g.) and crystallised from ethylene dichloride (25 c.c.) to yield the solvated dimethiodide (0·598 g.), m. p. 131—132° (sintered at 129°). The mother liquor was evaporated to dryness under reduced pressure, and the residual gum was crystallised from acetone to which a drop of concentrated hydriodic acid was added. The crystals (0·643 g.) were washed with acetone and dried in a vacuum; m. p. 143—144° (cloudy melt). Most of this material was subsequently lost in attempted purification, since it was not recognised at that time that the substance was a hydriodide. The third and fourth crops of crude methiodide gave, on treatment with ethylene dichloride, solvated dimethiodide (2·083 g.), m. p. 128—129° (decomp. and previous sintering). The mother liquors, treated as before, gave a crystalline solid (0·305 g.), m. p. 154—156° (cloudy melt). This material, together with a little of the earlier crop (0·34 g.), was suspended in water and made alkaline to phenolphthalein with sodium hydroxide; a clear solution was obtained. Extraction 4 times with ether removed only a trace (2 mg.) of non-quaternary material. After aspiration with air to remove ether and a trace of trimethylamine, the solution was extracted 4 times with chloroform. The extract was washed once with water, dried, and evaporated in a vacuum below room temperature. The residual yellow gum (0·336 g.) was dissolved in alcohol (5 c.c.); on addition of two drops of concentrated hydriodic acid crystallisation occurred. After being collected, washed with alcohol, and dried at room temperature, the product (0·262 g.) had m. p. 159—160° (cloudy melt), with previous sintering. A second crop (13 mg.; m. p. 160—162° with previous sintering) was obtained by concentrating the mother liquor in a vacuum desiccator. The first crop was recrystallised by dissolving it as rapidly as possible in warm alcohol, cooling immediately to room temperature and finally to 0°. The crystals (200 mg.) had m. p. 163—165° (cloudy melt). Half of this crop was dissolved in cold alcohol, shaken with charcoal, and filtered (" Filtercel "), and the filtrate was concentrated in a desiccator. The *hydriodide* (63 mg.) formed short, blunt-ended, colourless prisms, m. p. 162—164° (cloudy melt). For analysis, the substance was crystallised again in a similar fashion, and dried for 2 hours over phosphoric oxide in a vacuum at room temperature (23 mg., m. p. 163—164°, cloudy melt) (Found:* C, 49·8; H, 6·9; N, 3·2; I, 31·3. $C_{33}H_{53}O_4N_2I,HI$ requires C, 49·7; H, 6·8; N, 3·5; I, 31·8%).

Des-N(a)-*emetinetetrahydromethine Methiodide* (IX, X = I).—(a) *From* N-*methylemetinetetrahydromethine*. Anhydrous tetrahydromethine perchlorate (12 g.) was suspended in water (100 c.c.), aqueous sodium hydroxide (34 c.c. of N) was added, and the liberated base was recovered by extracting thrice with ether. The extract, after drying (K_2CO_3), was evaporated under reduced pressure at room temperature, and the residual clear, pale yellow oil (8·7 g.; 100%) was dissolved in anhydrous methyl alcohol (15 c.c.). Methyl iodide (5 c.c.) was added, and the mixture was heated under reflux; it quickly became golden yellow, and after 30 minutes separation of microscopic colourless crystals began. After 2 hours' boiling, the hot solution was filtered. The residue (0·34 g.) was washed with methyl alcohol, and crystallised from a small volume of water. It formed colourless octahedra, unmelted at 350°, and was identified as tetramethylammonium iodide (Found: N, 7·1. Calc. for $C_4H_{12}NI$: N, 7·0%).

The methanolic filtrate was treated with a further quantity of methyl iodide (2 c.c.) and refluxed for 3 hours. Methyl alcohol and excess of methyl iodide were removed on the steam-bath, and the syrupy residue was heated at 100° for an hour; it had then become partially crystalline. It was treated with boiling ethyl alcohol (30 c.c.) under reflux for 30 minutes, some of the crystalline material remaining undissolved. After cooling, the product (8·12 g.) was collected, washed with a little alcohol, and dried at 100°. The mother liquor (*A*) was treated as described below.

The pale yellow, crystalline material melted at 215—217° to a cloudy liquid. After being digested with warm water (two portions of 25 c.c.) and dried, it weighed 5·63 g. and had m. p. 226—227°. The aqueous washings were evaporated to dryness under reduced pressure, and the residue was crystallised from alcohol, giving colourless plates (1·9 g.), m. p. 264° (corr., decomp.), identified as trimethylamine hydriodide (recorded m. p. 263° corr.) (Found:* N, 7·8. Calc. for $C_3H_{10}NI$: N, 7·5%).

Recrystallisation of the water-insoluble material gave des-*N*(*a*)-emetinetetrahydromethine methiodide as colourless, long thin prisms (4·83 g.; 47%), m. p. 230°. Repeated recrystallisation from alcohol or acetone raised the m. p. to 233° (Found: C, 60·1; H, 7·7; N, 2·4; I, 20·6. Calc. for $C_{31}H_{46}O_4NI$: C, 59·7; H, 7·4; N, 2·3; I, 20·4%). $[\alpha]_D^{20^\circ}$ + 2° ± 0·3° (*c*, 3·1 in chloroform).

The alcoholic mother liquor *A* was refluxed for several hours, and concentrated to about 15 c.c. Only a very little material crystallised from the orange, viscous solution on cooling; this was redissolved by warming, and a solution of methanolic sodium methoxide (4·1 c.c. of 2N) added. On warming, trimethylamine was evolved (picrate, m. p. 217—218°, undepressed in admixture with an authentic specimen). The liquor was concentrated to 10 c.c. under reduced pressure and diluted with water; a viscous oil was precipitated. On shaking with ether, 3 layers were formed. These were separated, and both the bottom layer (*B*) and the aqueous layer were washed with ether. The ethereal extracts were washed with water, dried, and evaporated, yielding a pale yellow viscous oil (0·95 g.), which was subsequently shown to consist mainly of the tertiary base (XI), since it gave a perchlorate (0·76 g.), m. p. 132—134°, undepressed by admixture with a specimen of the material described below. The ether-insoluble syrup *B* (4 g.) on treatment with alcohol gave a crop of crystals (2·6 g.), m. p. 205°, which appeared to be a complex mixture and yielded very little pure material.

(b) *By decomposition of the dimethiodide in water.* *N*-Methylemetinetetrahydromethine dimethiodide (1 g., crystallised from ethylene dichloride) was dissolved in hot water (10 c.c.), and the solution, which became turbid after 30 minutes, was heated at 95° for 4 hours. After cooling, the yellow solid which had separated was collected, washed with water, and dried (0·68 g.; 92%); m. p. 222—223°. Recrystallisation from alcohol gave pale yellow needles (0·48 g.), m. p. 227°; recrystallised again from acetone, the product was colourless (0·42 g.; 57%), and had m. p. 232°, undepressed in admixture with material obtained as described above. The aqueous mother-liquor on evaporation and crystallisation of the residue from alcohol yielded trimethylamine hydriodide (0·12 g.).

(c) *By decomposition of the dimethiodide in diethyl ketone.* The dimethiodide (2·04 g.), crystallised from acetone to free it from ethylene dichloride, was dissolved in diethyl ketone (50 c.c.) and the solution heated at 100—110° for 3 hours. After standing overnight, the crystalline material was collected and washed once with diethyl ketone, twice with acetone, and thrice with water; the product (1·29 g.; 82%) had m. p. 229—229·5°, raised by one crystallisation from acetone to 233°. Evaporation of the diethyl ketone mother liquor gave only a brown gum (0·243 g.).

Des-N(a)-*emetinetetrahydromethine Methochloride* (IX, X = Cl).—A solution of the methiodide (4·64 g.) in warm 50% aqueous alcohol (150 c.c.) was stirred with freshly precipitated silver chloride (from 4·25 g. of silver nitrate) for 15 minutes. The filtered solution was evaporated to dryness, and the residue dissolved in hot acetone, treated with charcoal, filtered, and concentrated to 15 c.c. Ether was added to incipient turbidity; after cooling to 0°, the *methochloride* (3·58 g.; 90%), which formed almost rectangular, colourless plates, m. p. 147·5—148° (to a glass), was collected and dried at 100° in a vacuum (Found: C, 65·8; H, 8·9; N, 2·6. $C_{31}H_{46}O_4NCl,2H_2O$ requires C, 65·6; H, 8·9; N, 2·5%). On drying at 118° in a vacuum, the substance slowly lost weight (Found: 4·9. $2H_2O$ requires 6·3%) and turned brown; analysis indicated that it still contained water (Found: C, 68·9; H, 9·1; N, 2·4. Calc. for $C_{31}H_{46}O_4NCl$: C, 69·9; H, 8·6; N, 2·6%). The substance rapidly decolorised a dilute aqueous solution of permanganate.

Des-N(a)-*emetinetetrahydromethine* (XI).—The above methochloride (0·5 g.) was heated in a small retort at 180—185°/2 mm. The molten chloride effervesced steadily for 30 minutes. After a further 30 minutes, the pressure was reduced to *ca.* 10^{-5} mm.; all the material then distilled. The distillate, a colourless amorphous glass, m. p. 38—43°, was almost entirely soluble in ether. The ethereal solution was shaken with very dilute aqueous sodium hydroxide, which removed the insoluble material. After being dried (K_2CO_3), the ethereal solution was evaporated, and the residual pale yellow gum (0·330 g.) was distilled at 10^{-5} mm. (bath temp. 180—185°) (Found: C, 74·8; H, 8·9; N, 2·9. $C_{30}H_{43}O_4N$ requires C, 74·2; H, 8·8; N, 2·9%).

When the *base* was treated with dilute hydrochloric acid it formed a gummy hydrochloride, sparingly soluble in hydrochloric acid but readily soluble in water. Addition of perchloric acid to the aqueous solution precipitated the *perchlorate*, which was redissolved by warming and addition of acetone, and then crystallised on cooling (0·165 g.); m. p. 120—123°. After two recrystallisations from aqueous acetone (charcoal) it formed minute hexagonal prisms, m. p. 130—132°, which were dried to constant weight at 78° over phosphoric oxide in a vacuum (Found: C, 60·1; H, 7·8; N, 2·3; loss at 116° in a vacuum, 3·0. $C_{30}H_{43}O_4N,HClO_4,H_2O$ requires C, 60·3; H, 7·6; N, 2·2; H_2O, 3·0%). The anhydrous salt was a colourless glass.

The base (80 mg.) was allowed to react in ethereal solution with an excess of methyl iodide for 4 days. The crystalline precipitate (76 mg.; 73·5%), m. p. 226—228°, on recrystallisation from acetone had m. p. 232—233°, undepressed in admixture with the methiodide (IX).

Decomposition of N-*Methylemetinetetrahydromethine Methiodide Hydriodide.*—A solution of the salt (90 mg.) in diethyl ketone (4 c.c.) was heated in a bath at 100—110° for 3 hours, a slow stream of nitrogen being passed through the solution and then through a trap containing dilute hydrochloric acid. The contents of the trap were evaporated to dryness, and the small crystalline residue was identified as trimethylamine hydrochloride by conversion into the picrate (9 mg., m. p. and mixed m. p. 216—218°). The diethyl ketone solution was evaporated under reduced pressure, and the residue was dissolved in acetone (4 c.c.) and water (2 c.c.). By evaporation under reduced pressure the acetone was removed, leaving the product as a gum from which the water was decanted. The gum was dissolved in a little alcohol and the solution poured into aqueous sodium hydroxide. The liberated base was isolated by thorough extraction with ether; on evaporation, the base (54 mg.; 100%) remained as a clear yellow oil, which was characterised by conversion into the perchlorate (54 mg.), m. p. and mixed m. p. 128—130°, of the base (XI), and into the methiodide (IX, X = I), m. p. and mixed m. p. 230—231°.

Des-N(a)-*emetinetetrahydromethine Hydriodide.*—Impure *N*-methylemetinetetrahydromethine dimethiodide ("sample *A*", 3·15 g.), which had been isolated without the use of ethylene dichloride and probably contained monomethiodide hydriodide (X), was decomposed by heat in diethyl ketone as described above. The crude, dry product (2·13 g.), m. p. 211—216° (decomp.), on crystallisation from alcohol and then from acetone gave colourless needles (0·68 g.) of the methiodide (IX), m. p. 231—232°. The mother liquors from this material were combined with "gum *B*" (see above), and by a series of crystallisations gave a further quantity of less pure methiodide (0·6 g.), m. p. 227—228°, together with a fraction (0·358 g.), m. p. 129—133°, which was more soluble in acetone. Repeated recrystallisation of the latter from aqueous acetone and aqueous alcohol gave the *hydriodide* of base (XI) as colourless, hexagonal prisms, m. p. 132—134°, showing a slight but definite depression of m. p. in admixture with the dimethiodide (m. p. 136°). The material was dried in a vacuum over phosphoric oxide at room temperature (Found: loss at 100° in a vacuum, 2·6. $C_{30}H_{43}O_4N,HI,H_2O$ requires H_2O, 2·9%. Found in anhydrous substance: C, 59·3; H, 7·3; N, 2·5. $C_{30}H_{43}O_4N,HI$ requires C, 59·1; H, 7·3; N, 2·3%). The base was recovered from this salt and converted into the perchlorate which after a single crystallisation from aqueous acetone had m. p. 129·5—132°, undepressed by admixture with the perchlorate of des-*N*(*a*)-emetinetetrahydromethine (XI).

Oxidation of Des-N(a)-*emetinetetrahydromethine* (XI).—The base (0·89 g.), regenerated from the pure perchlorate, was dissolved in acetone (30 c.c.), and water (30 c.c.) was added. The mixture was cooled at 0° and stirred whilst aqueous barium permanganate (122·5 c.c. containing 4 atomic proportions of oxygen) was gradually added, the rate of addition being controlled so that no appreciable concentration of unreacted permanganate was present at any time. After the addition of the first quarter of the solution (15 minutes) a further quantity of acetone (20 c.c.) was added to maintain homogeneity. The total time of addition was 7 hours. After a further hour's stirring, by which time there remained no unchanged permanganate, the mixture was made alkaline to phenolphthalein by addition of barium hydroxide. The manganese dioxide was coagulated by heat and removed by filtration (" Filtercel "). The filter-cake was thoroughly extracted with boiling water (total, 350 c.c.) and boiling alcohol (400 c.c.). The alcoholic extract on evaporation left only a small residue, which was added to the combined aqueous solutions. After concentration to 150 c.c., a small quantity of insoluble material was removed by extracting 5 times with ether (total, 500 c.c.); evaporation of the ether left a brown gum (0·247 g.; " neutral and basic fraction ").

The aqueous solution was rendered acid to Congo-red with hydrochloric acid and extracted 6 times with ether. Evaporation of the extract, finally under reduced pressure, left a residue which largely crystallised on cooling. On crystallisation from hot water, colourless needles (124 mg.) were obtained, m. p. 142° after slight previous sintering. Small additional amounts were obtained from the mother liquors by evaporation and sublimation of the residue in a vacuum, and from the " neutral and basic fraction " where the acid was probably formed by atmospheric oxidation of the related aldehyde. The total yield was 172 mg. (44%). After further purification by sublimation at 0·05 mm. from a bath at 80—90°, the m. p. was 140·5—141·5°, undepressed in admixture with synthetic 6-ethylveratric acid of the same m. p. Before analysis, the acid was again crystallised from water and resublimed (Found:* C, 63·1; H, 6·65. Calc. for $C_{11}H_{14}O_4$: C, 62·8; H, 6·7%).

After removal of inorganic material and evaporation, the original aqueous liquor yielded a gum (0·5 g.) which had the properties of an amino-acid, and which is being further investigated.

6-*Ethylveratric Acid*.—(With Miss M. L. DONALDSON.) The following is a considerable improvement on the method described by Shinoda and Sato (*J. Pharm. Soc. Japan*, 1927, **548**, 860). 4-Ethylveratrole (5 g.) and pure, anhydrous benzene (20 c.c.) were stirred at room temperature with powdered aluminium chloride (3·5 g.), and a solution of acetyl chloride (3 g.) in benzene (5 c.c.) was added during an hour. After a further hour's heating under reflux, the aluminium chloride complex was decomposed in the usual manner. The benzene solution of the product was extracted twice with dilute sodium hydroxide solution, and the phenolic material thus removed was remethylated by shaking the alkaline extract with methyl sulphate (2 portions of 2 c.c.), and extracting with benzene the oil thus produced. The combined benzene extracts were dried and distilled, giving 5-acetyl-4-ethylveratrole (4·88 g.; 78%), b. p. 133—138°/1 mm., as a colourless oil which rapidly solidified. A sample, recrystallised from aqueous alcohol, formed rosettes of colourless needles, m. p. 62—63° (Shinoda and Sato, *loc. cit.*, give m. p. 63°).

The alkaline sodium hypochlorite solution obtained from aqueous sodium hydroxide (4·4 g. in 30 c.c.) and chlorine (3·2 g.) was heated to 55° and stirred, and the ketone (2·08 g.) was added. After reaction started, the temperature was kept at 60—70° by occasional warming for 30 minutes, and the mixture was stirred for a further 30 minutes without application of heat. Excess of hypochlorite was destroyed by adding sufficient sodium hydrogen sulphite, and the cooled solution was acidified with concentrated hydrochloric acid. The precipitated 6-ethylveratric acid (1·9 g.; 90%), m. p. 141—141·5° after slight previous sintering, was collected. After sublimation under reduced pressure it had m. p. 141·5° (Shinoda and Sato give m. p. 142°).

Des-N(a)-*emetinehexahydromethine Methiodide* (as XII).—Des-*N*(*a*)-emetinetetrahydromethine methiodide (IX, X = I) was unaffected by being shaken with hydrogen and platinic oxide, and was recovered unchanged when an aqueous-alcoholic solution was heated with excess of sodium amalgam for 40 hours.

A solution of the methochloride (IX, X = Cl) dihydrate (0·36 g.) in water (50 c.c.) was shaken with hydrogen and platinic oxide; absorption of hydrogen (97% of theoretical) ceased after 11 hours. The filtered solution was evaporated to dryness, but the residual gum did not crystallise. Its aqueous solution gave a pink precipitate (quaternary permanganate) when treated with potassium permanganate, which was stable for several minutes. No precipitate of base formed when the aqueous solution was treated with aqueous sodium hydroxide, confirming the quaternary nature of the product. The *methiodide* was precipitated by addition of sodium iodide to the aqueous solution of the chloride. It separated from aqueous alcohol as a hydrate, m. p. 128—129°. Recrystallisation from acetone–ether, followed by drying at 110°, gave a monohydrate, m. p. 170—171° (Found: C, 58·0; H, 7·7; loss at 118° in a vacuum over phosphoric oxide, 2·6. $C_{31}H_{48}O_4NI,H_2O$ requires C, 57·8; H, 7·8; H_2O, 2·8%. Found, in anhydrous substance: C, 59·1; H, 7·6; N, 2·1. $C_{31}H_{48}O_4NI$ requires C, 59·4; H, 7·7; N, 2·2%). The *platinichloride* formed orange leaflets from aqueous alcohol, m. p. 180—182° [Found: Pt, 13·6, 13·7. $(C_{31}H_{48}O_4N)_2PtCl_6$ requires Pt, 13·9%].

Des-N(a)-*emetineoctahydrobismethine* (XIV).—An aqueous solution (40 c.c.) containing des-*N*(*a*)-emetinehexahydromethine methochloride (2 g.) was treated with sodium amalgam (10 g. of 5%), and warmed under reflux for 10 minutes. An oil separated rapidly. After 48 hours, the oil was extracted with ether, and the aqueous layer was treated with a fresh portion (10 g.) of sodium amalgam; a further separation of oil then occurred. After several hours' warming, the oil was taken up in ether, and the combined ethereal extracts were shaken with 3 successive portions of N-hydrochloric acid (total, 7 c.c.; 2 equivs.) and once with water; the ethereal layer left no appreciable residue on evaporation. The acidic aqueous extract was made alkaline with aqueous sodium hydroxide and the liberated base isolated by means of ether as a pale yellow oil (1·25 g.). *Des*-N(a)-*emetineoctahydrobismethine* distilled under 4×10^{-4} mm. from a bath at 180° as a colourless, viscous oil, $[\alpha]_D^{20^\circ}$ + 1·2° ± 0·2° (*c*, 5·8 in acetone)

(Found: C, 74·3; H, 9·7; N, 3·3. $C_{31}H_{49}O_4N$ requires C, 74·5; H, 9·9; N, 2·8%). The base did not decolorise permanganate in acetone solution. The ultra-violet absorption (see Table) indicates the absence of a double bond conjugated with an aromatic nucleus.

Hofmann Degradation of the Base (XIV).—The above base (0·3 g.) was dissolved in anhydrous ether (10 c.c.) and treated with a small excess of methyl iodide. After 24 hours at room temperature, an amorphous precipitate formed and adhered to the sides of the flask. The liquor was decanted and the precipitate washed with ether. The product did not crystallise from acetone or from alcohol–ether. Its alcoholic solution was added to aqueous sodium hydroxide, and the mixture shaken with ether. The ethereal layer was discarded, and the oily methiodide was taken up in chloroform. Evaporation left the methiodide as a gum (0·39 g.) which failed to crystallise.

The methiodide (0·3 g.) was dissolved in aqueous alcohol and treated with silver oxide. A slight smell of trimethylamine was observed. The residue left by evaporation of the filtered solution was heated at 100° for 1½ hours under 15 mm., and extracted with boiling ether. Evaporation of the ether left a rather mobile oil (0·23 g.), which was redissolved in ether and shaken with dilute hydrochloric acid. The ethereal layer on evaporation gave a neutral, pale yellow oil (0·08 g.), which was distilled in a high vacuum from a bath at 165° and was then colourless (Found: C, 76·7; H, 9·3; N, <0·2; OMe, 26·8; 27·4. $C_{29}H_{42}O_4$ requires C, 76·6; H, 9·3; OMe, 27·3%). Attempts to prepare a picrate and a 1 : 3 : 5-trinitrobenzene adduct of this *substance* were unsuccessful.

The basic material was precipitated from the hydrochloric acid extract and isolated by means of ether. The substance (0·13 g.) distilled as an oil in a high vacuum from a bath at 175—180° (Found: C, 75·2, 75·2; H, 9·7, 10·0; N, 2·8%).

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UNIVERSITY OF MANCHESTER.
UNITED COLLEGE, UNIVERSITY OF ST. ANDREWS.

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