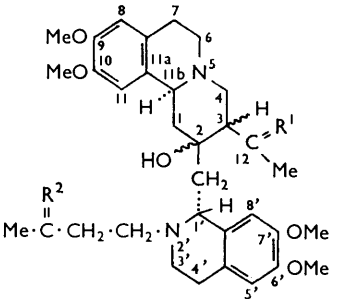
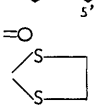
669. *Emetine and Related Compounds. Part IV.*[1] *Synthetic* N-*Substituted Derivatives of* (±)-*Emetine and* (±)-2,3-*Dehydroemetine.*

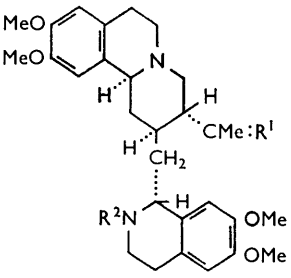
By A. C. Ritchie, D. R. Preston, T. Walker, and K. D. E. Whiting.

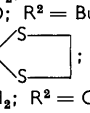
(±)-*N*-n-Butyl and (±)-*N*-(3-hydroxy-n-butyl) analogues of emetine and of 2,3-dehydroemetine have been prepared from intermediates previously used in the synthesis of the parent compounds.

In earlier parts of this series [1,2b] we described the preparation of the alcohol (I) and its conversion into (—)-emetine (VIII), an alkaloid widely used in the treatment of amœbic dysentery. An intermediate in this synthesis, (±)-*N*-(3-hydroxy-n-butyl)emetine (IX),* was also an active amœbicide. We have now studied the preparation, from the alcohol (I), of other *N*-substituted derivatives, both of (±)-emetine and of its more potent analogue (±)-2,3-dehydroemetine [2] (XIX), in the hope that these might prove of therapeutic value.



(I) $R^1 = R^2 = =O$
(II) $R^1 = R^2 =$ 
(III) $R^1 = O$; $R^2 = (S{\cdot}CH_2Ph)_2$
(IV) $R^1 = O$; $R^2 = H_2$
(V) $R^1 = H,OH$; $R^2 = H_2$
(VI) $R^1 = H,OH$; $R^2 = (S{\cdot}CH_2Ph)_2$
VII $R^1 = R^2 = H_2$



(VIII) $R^1 = H_2$; $R^2 = H$
(IX) $R^1 = H_2$; $R^2 = CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}OH$
(X) $R^1 = H_2$; $R^2 = Bu^n$
(XI) $R^1 = O$; $R^2 = Bu^n$
(XII) $R^1 =$  ; $R^2 = Bu^n$
(XIII) $R^1 = H_2$; $R^2 = CH_2{\cdot}CH_2{\cdot}COMe$
(XIV) $R^1 = H_2$; $R^2 = CH_2{\cdot}CH_2{\cdot}CMe$ 
(XV) $R^1 = H_2$; $R^2 = CH_2{\cdot}CH_2{\cdot}CMe(S{\cdot}CH_2Ph)_2$
(XVI) $R^1 = H_2$; $R^2 = COPr^n$
(XVII) $R^1 = O$; $R^2 = CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}OH$
(XVIII) $R^1 = H,OH$; $R^2 = CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}OH$

As the *N*-3-oxobutyl side-chain in the alcohol (I) could become the basis of *N*-butyl derivatives, our first objective was the preparation of *N*-n-butylemetine (X). If the pattern of our synthesis of emetine was to be followed, this would require selectively converting the carbonyl group of the oxobutyl side-chain into a methylene group, and leaving that at C-12 intact. This differentiation was effected by treatment of the alcohol (I) with toluene-ω-thiol, the monodithioketal (III) being obtained in high yield. In contrast, ethane-1,2-dithiol, having a smaller steric requirement, gave the bisethylene thioketal (II). The dithioketal (III) was refluxed in ethanol with W4 Raney nickel in the presence of acetone,[3] giving a high yield of the *N*-butyl ketone (IV). In the absence of acetone the alcohol (V) was the sole product, even at room temperature. The latter was obtained as a mixture of diastereoisomeric forms, one crystalline, the other

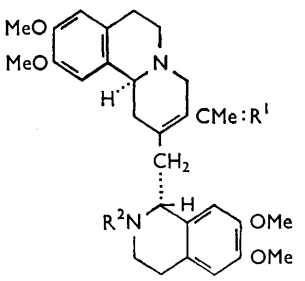
* Only one optical enantiomer is shown throughout this paper.

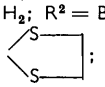
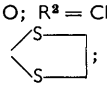
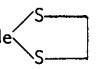
[1] Part III, Clark, Meredith, Ritchie, and Walker, *J.*, 1962, 2490.
[2] (*a*) Brossi, Baumann, Chopard-dit-Jean, Würsch, Schneider, and Schnider, *Helv. Chim. Acta*, 1959, **42**, 772; (*b*) Clark, Holton, Meredith, Ritchie, Walker, and Whiting, *J.*, 1962, 2479.
[3] Nazer and Issidorides, *J. Org. Chem.*, 1961, **26**, 839.

amorphous. These could not be distinguished by paper- [4] or thin-layer [5] chromatography and showed only very small differences in their infrared spectra. The amorphous isomer was the only detectable product when the alcohol (VI), obtained by reduction of the dithioketal (III) with sodium borohydride, was desulphurised with nickel or when the *N*-butyl ketone (IV) was reduced with sodium borohydride.

The remaining stages in the synthesis of (±)-*N*-butylemetine follow the path established for emetine.[1] The *N*-butyl ketone (IV) was dehydrated with 12N-mineral acid at 100° to the conjugated ketone (XX), and this was reduced with lithium in liquid ammonia to the saturated ketone (XI). Reductive desulphurisation of the ethylene dithioketal (XII) with hydrogen and W4 Raney nickel [6] at 50° then gave (±)-*N*-n-butylemetine (X), identical in its infrared spectrum in solution and R_F values on paper- and thin-layer chromatograms with the optically active enantiomorph made from (−)-emetine and with approximately half its amœbicidal activity.

(−)-*N*-Butylemetine (X) was obtained from (−)-emetine by addition of methyl vinyl ketone to give the adduct (XIII), whose ethylene thioketal (XIV) and benzyl thioketal (XV) were reduced with hydrogen over W4 nickel. Desulphurisation of the ethylene thioketal (XIV) to (−)-*N*-butylemetine (X) was also effected with hydrazine and alkali in ethylene glycol.[7] Alternatively, (−)-*N*-n-butyrylemetine (XVI) was reduced to this compound (X) with lithium aluminium hydride.



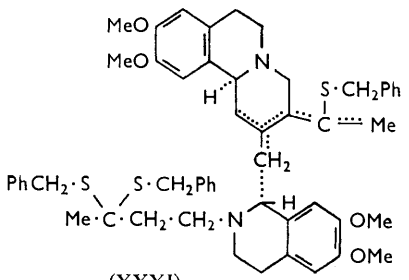
(XIX) $R^1 = H_2$; $R^2 = H$
(XX) $R^1 = O$; $R^2 = Bu^n$
(XXI) $R^1 = H_2$; $R^2 = Bu^n$
(XXII) R^1 =  ; $R^2 = Bu^n$
(XXIII) $R^1 = O$; $R^2 = CH_2{\cdot}CH_2{\cdot}COMe$
(XXIV) R^1 =  ; $R^2 = CH_2{\cdot}CH_2{\cdot}CMe$ 
(XXV) $R^1 = H_2$; $R^2 = CH_2{\cdot}CH_2{\cdot}CMe$
(XXVI) $R^1 = H_2$; $R^2 = CH_2{\cdot}CH_2{\cdot}COMe$
(XXVII) $R^1 = H_2$; $R^2 = CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}OH$
(XXVIII) $R^1 = H_2$; $R^2 = COPr^n$
(XXIX) $R^1 = H,OH$; $R^2 = CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}OH$
(XXX) $R^1 = O$; $R^2 = CH_2{\cdot}CH_2{\cdot}CMe(S{\cdot}CH_2Ph)_2$

The corresponding (±)-*N*-butyl-2,3-dehydroemetine (XXI) was synthesised by conversion of the conjugated ketone (XX) into the ethylene thioketal (XXII) and desulphurisation with sodium in liquid ammonia,[8] but it was thought that more convenient methods might originate from the conjugated ketone (XXIII).[2b]

The most direct approach was by reductive desulphurisation of the bisethylene thioketal (XXIV), but the vigorous conditions necessary for complete elimination of sulphur with hydrogen and W7 Raney nickel also caused non-stereoselective reduction of the 2,3-double bond, and thin-layer chromatography indicated that mixtures containing little of the desired product resulted. Under milder conditions, with hydrogen and W7 nickel at room temperature, selective hydrogenolysis of the allylic thioketal group occurred, to give a mixture consisting mainly of the monodithioketal (XXV) together with *ca.* 14% of (±)-*N*-butyl-2,3-dehydroemetine. As those were difficult to separate, the crude product was hydrolysed with acid and the (±)-*N*-n-butyldehydroemetine separated by chromatography from the ketone (XXVI). The latter was reduced with sodium borohydride to (±)-2,3-dehydro-*N*-(3-hydroxy-n-butyl)emetine (XXVII).

[4] Barash, Osbond, and Wickens, *J.*, 1959, 323.
[5] Stahl, *Chem. Ztg.*, 1958, **82**, 323.
[6] Shin Imaizumi, *Nippon Kagaku Zasshi*, 1957, **78**, 1396; *Chem. Abs.*, 1960, **54**, 1403.
[7] Georgian, Harrison, and Gubisch, *J. Amer. Chem. Soc.*, 1959, **81**, 5834.
[8] Ireland, Wrigley, and Young, *J. Amer. Chem. Soc.*, 1958, **80**, 4604.

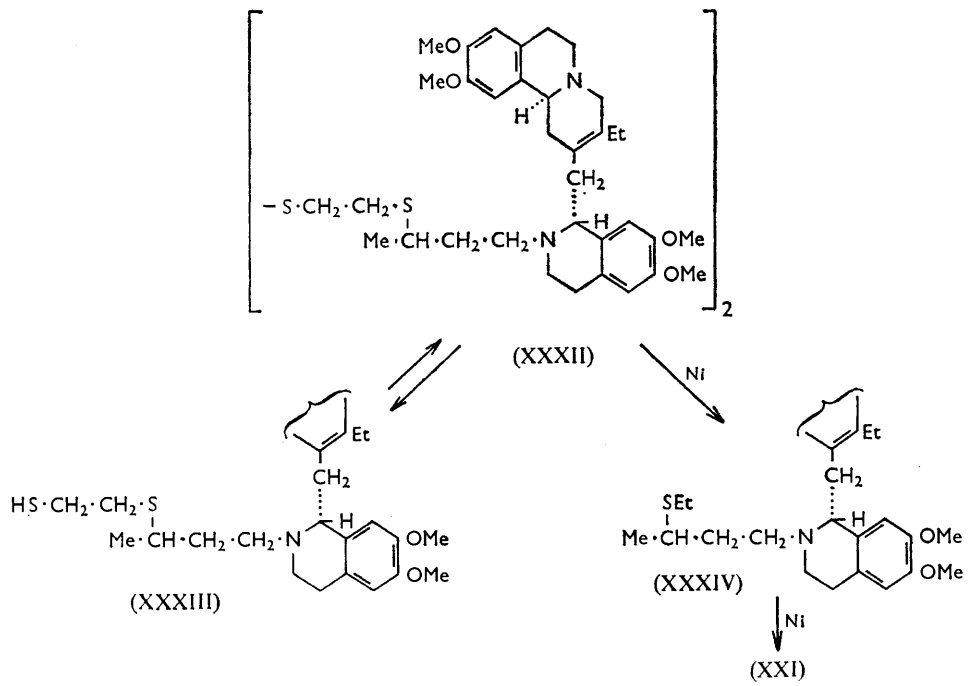
As we had previously shown that desulphurisation of the benzyl dithioketal (XV) was faster than that of the corresponding ethylene derivative, we hoped that the dibenzyl dithioketal of (XXIII) would react with nickel under milder conditions than those required for (XXIV) and so avoid saturation of the olefinic link. However, ketone (XXIII) with an excess of toluene-ω-thiol gave a mixture of the monodithioketal (XXX) and a non-ketonic product; this was not the desired bis-compound, but had three sulphur atoms per molecule. Its ultraviolet spectrum showed at 230 mμ an enhanced absorption (Δε 13,000) over that of (XXX). This material was formulated as a conjugated thioenol ether (XXXI), although the diene system could not be located. The difficulty in obtaining the diketal



(XXXI)

is again a reflection of the increased steric requirements of toluene-ω-thiol compared with ethane-1,2-dithiol.

Desulphurisation of the thioenol ether (XXXI) occurred under mild conditions with W7 nickel but gave only *ca.* 11% of (±)-*N*-butyl-2,3-dehydroemetine, and thin-layer chromatography showed the remainder of the material to be a mixture.



(XXXII) (XXXIII) (XXXIV) (XXI)

Complications due to the olefinic link of compound (XXIV) were avoided by the use of the bisethylene thioketal (II). This was reduced in good yield to the alcohol (VII) with hydrogen and W7 nickel at 60°. This alcohol was not dehydrated under conditions

effective for the related 2-hydroxy-12-ketone (IV), but was rapidly and completely converted into (±)-*N*-butyl-2,3-dehydroemetine with 10% of concentrated sulphuric acid in acetic anhydride at room temperature. The hydroxyl group in the alcohol (VII) was readily esterified with ethyl chloroformate and with acetic anhydride–perchloric acid. The acetate was unaffected by 10% of sulphuric acid in acetic anhydride at room temperature and was not, therefore, an intermediate in the dehydration of the alcohol.

A further alternative scheme to avoid difficulties caused by reduction of the olefinic link in the bisdithioketal (XXIV) envisaged desulphurisation with sodium in liquid ammonia. Though this would remove the allylic thioacetal group,[8] the effect on the unactivated thioacetal was uncertain. In model experiments, thioacetal (XIV) with sodium in refluxing ammonia gave crude unstable products and no *N*-butylemetine could be detected by paper chromatography. At −70° the thioacetal was recovered unchanged. The latter conditions produced from the bisdithioketal (XXIV), a substance whose elemental analysis corresponded to that of the expected monodithioketal (XXV), but it differed in R_F value from authentic material and failed to give a ketone on hydrolysis with acid. When a determination of the molecular weight showed the material to be dimeric and a positive test with sodium nitroprusside was obtained only in the presence of potassium cyanide, the compound was formulated as the disulphide (XXXII).

The reason for the attack on the unactivated thioketal group of (XXIV), and for the lack of attack on that of (XIV) under the same conditions, is not clear. The product from the reaction of mono-compound (XIV) with sodium in refluxing ammonia gave a positive test with sodium nitroprusside only in the presence of potassium cyanide and was probably a crude disulphide analogous to (XXXII).

The bisdithioketal (XXIV) was recovered unchanged after treatment with calcium hexammine in ether.[9]

Attempts to desulphurise the disulphide (XXXII) with alkali and hydrazine in ethylene glycol caused reduction to the thiol (XXXIII), which gave a positive test with sodium nitroprusside and was slowly re-oxidised to (XXXII) in the air.

In contrast to the monodithioketal (XXV), the disulphide (XXXII) was readily desulphurised with hydrogen and W7 nickel under mild conditions that left the olefinic linkage unaffected. The course of the reduction was followed by thin-layer chromatography and shown to proceed *via* the sulphide (XXXIV) to (±)-*N*-butyl-2,3-dehydroemetine (XXI).

The (±)-butyldehydroemetine produced by all these methods was identical with that obtained by butyrylation of (±)-2,3-dehydroemetine and reduction of the amide (XXVIII) with lithium aluminium hydride.

The annexed Table gives approximate values for the amœbicidal activity of some of

	(X) *	(X) †	(XIV) †	(XXI) *	(XXVII) *	(XXXIV) *
Oral activity CD 100 (mg./kg.)	10	5	5	10	10	10

* Racemic. † Optically active.

the compounds prepared as described above when they were tested in weanling rats by Jones's method.[10] The CD 100 for the hydrochloride of (−)-emetine is *ca.* 2 mg./kg. None of the remaining compounds showed useful activity, and the presence of oxygen at C-2 or C-12 strikingly reduced the potency. This was again illustrated by the 12-hydroxy-derivatives (XVIII) and (XXIX), which, in contrast to the very active parent compounds (IX) and (XXVII), showed feeble amœbicidal properties. These 12-alcohols were obtained by reduction of the corresponding ketones (XVII) [1] and (XXIII) with sodium borohydride. A full account of the biological properties will be submitted for publication elsewhere.

[9] Van Schooten, Knotnerus, Boer, and Duinker, *Rec. Trav. chim.*, 1958, **77**, 935.
[10] Jones, *Ann. Trop. Med. Parasitol.*, 1956, **40**, 130.

Experimental

For general directions see previous Parts of this series.

Reaction of 3-*Acetyl*-1,2,3,4,6,7-*hexahydro*-2-*hydroxy*-9,10-*dimethoxy*-2-[1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-(3-*oxo*-*n*-*butyl*)-1-*isoquinolyl*]*methyl*-11b[H]-*benzo*[a]*quinolizine* (I) *with Thiols.*—(*a*) *With ethane*-1,2-*dithiol.* The hydrochloride (18·2 g.) of ketone (I), suspended in anhydrous methanolic hydrogen chloride (200 ml.), was stirred for 3 hr. at room temperature with ethane-1,2-dithiol (7 ml.) till dissolution was complete. Removal of the solvent *in vacuo* and trituration of the residue with ethanol gave the ethylene dithioketal (II) as the *hydrochloride* (20·6 g.), m. p. 217—220° (decomp.). Recrystallisation from methanol–ether raised the m. p. to 226—227° (decomp.) (Found: C, 53·2; H, 7·2; Cl, 8·5; N, 3·3; S, 15·3. $C_{37}H_{54}Cl_2N_2O_5S_4,2\frac{1}{2}H_2O$ requires C, 53·2; H, 7·1; Cl, 8·5; N, 3·35; S, 15·4%). The free *base* crystallised from acetonitrile as prisms, m. p. 173—177° (Found: C, 60·2; H, 7·3; N, 3·6; S, 17·9. $C_{37}H_{52}N_2O_5S_4$ requires C, 60·6; H, 7·2; N, 3·8; S, 17·5%).

(*b*) *With toluene*-ω-*thiol.* The hydrochloride (20 g.) of ketone (I) was treated with toluene-ω-thiol (10 ml.) as in the previous example. After the solvent had been removed, the residue was dissolved in chloroform and neutralised with 2N-aqueous sodium hydroxide. The chloroform extract was washed with water, dried, and evaporated to dryness. Trituration with ether gave the crude *dibenzyl dithioketal* (III) (15·5 g.), m. p. 171—172°. Recrystallisation from acetonitrile afforded colourless crystals, m. p. 173—174° (Found: C, 69·6; H, 7·3; N, 3·5; S, 8·2. $C_{47}H_{58}N_2O_6S_2$ requires C, 69·6; H, 7·2; N, 3·5; S, 7·9%).

Reduction of the Dithioketal (III) *with Sodium Borohydride.*—The dithioketal (4 g.) in tetrahydrofuran (50 ml.) was treated at room temperature with sodium borohydride (1·6 g.) in water (16 ml.), sufficient methanol being added to achieve a homogeneous solution. After 4½ hr. the solution was acidified with hydrochloric acid, and the organic solvents were removed *in vacuo*. The residue was diluted with water, basified with sodium carbonate, and extracted with benzene. When the organic extract had been washed with water and dried, the solvent was removed and the residual foam triturated with ether. Insoluble material was filtered off and the ethereal filtrate evaporated to give the dihydroxy-dithioketal (VI) (3·3 g.) as a white foam. The *hydrochloride* separated from ethanol–ether as a granular powder, m. p. 182—185° (Found: C, 60·0; H, 7·4; Cl, 8·1; N, 2·7; S, 6·9. $C_{47}H_{62}Cl_2N_2O_6S_2,3H_2O$ requires C, 60·0; H, 7·3; Cl, 7·6; N, 3·0; S, 6·8%).

3-*Acetyl*-2-(2-*n*-*butyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*methyl*-1,2,3,4,6,7-*hexahydro*-2-*hydroxy*-9,10-*dimethoxy*-11b[H]-*benzo*[a]*quinolizine* (IV).—The dithioketal (III) (7·8 g.) in tetrahydrofuran (50 ml.), ethanol (200 ml.), and acetone (80 ml.) was refluxed for 3·5 hr. with W4 nickel (40 ml. of an ethanolic slurry). The catalyst was filtered off and washed with ethanol (200 ml.), and the filtrate and washings were evaporated *in vacuo* to a pink solid. Trituration with ether gave *ketone* (IV) as white crystals (3·75 g.), m. p. 190—193° (Found: C, 69·5; H, 8·3; N, 4·8. $C_{33}H_{46}N_2O_6,H_2O$ requires C, 69·7; H, 8·5; N, 4·9%).

2-(2-*n*-*Butyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*methyl*-1,2,3,4,6,7-*hexahydro*-2-*hydroxy*-3-(1-*hydroxyethyl*)-9,10-*dimethoxy*-11b[H]-*benzo*[a]*quinolizine* (V).—(*a*) *Desulphurisation of the dithioketal* (III). The dithioketal (1 g.) in tetrahydrofuran (5 ml.) and ethanol (25 ml.) was stirred at room temperature for 17 hr. with W4 nickel (4 ml. of slurry), then the catalyst was filtered off and washed with ethanol. Evaporation of the filtrate and washings gave a white foam, converted by trituration with ether into the crystalline *diastereoisomer* of the *alcohol* (V) (0·28 g.), m. p. 153—155° (Found: C, 69·4; H, 8·6; N, 5·0. $C_{33}H_{48}N_2O_6$ requires C, 69·7; H, 8·5; N, 4·9%).

Evaporation of the ethereal mother-liquors gave the second diastereoisomer of (V) as an amorphous foam (see below).

(*b*) *Desulphurisation of dithioketal* (VI). This compound (0·5 g.) with W4 nickel, as in the preceding example, gave the amorphous isomer of (V) as a white foam (0·23 g.).

The *hydriodide* was precipitated from water as an amorphous white powder, m. p. [softening 195]200—203° (Found: C, 46·3; H, 6·5; I, 29·2; N, 2·9. $C_{33}H_{50}I_2N_2O_6,2H_2O$ requires C, 46·0; H, 6·3; I, 29·5; N, 3·2%).

(*c*) *Reduction of the ketone* (IV) *with sodium borohydride.* The *N*-butyl ketone (IV) (0·25 g.) in tetrahydrofuran (2·8 ml.) was treated with sodium borohydride (0·1 g.) in water (1 ml.) at room temperature for 4 hr. with sufficient methanol present to ensure a homogeneous solution.

Isolation of the product as already described gave the amorphous isomer of (V) (0·23 g.) which gave the hydriodide, m. p. 198—203°.

3-*Acetyl*-2-(2-*n-butyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*methyl*-1,4,6,7-*tetrahydro*-9,10-*dimethoxy*-11b[H]-*benzo*[a]*quinolizine* (XX).—Ketone (IV) (3 g.) was heated at 100° for 5 hr. with 12N-sulphuric acid (15 ml.) under nitrogen. The solution was cooled, basified with ammonia solution (*d* 0·88), and extracted with benzene. Evaporation of the washed and dried extract and trituration of the residue with ether gave the conjugated *ketone* (XX) (1·86 g.) as a pale pink powder, m. p. 114—116° (Found: C, 71·9; H, 8·2; N, 5·1. $C_{33}H_{44}N_2O_5$ requires C, 72·2; H, 8·0; N, 5·1%).

The ethylene thioketal (XXII) gave a *hydrochloride* (from ethanol), m. p. 198—201° (decomp.) (Found: C, 58·6; H, 7·3; S, 9·5. $C_{35}H_{50}Cl_2N_2O_4S_2,H_2O$ requires C, 58·7; H, 7·3; S, 9·0%).

3-*Acetyl*-2-(2-*n-butyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*methyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-11b[H]-*benzo*[a]*quinolizine* (XI).—The conjugated ketone (XX) (5 g.) in benzene (50 ml.) and ether (50 ml.) was added in 5 min. to a refluxing solution of lithium (0·6 g.) in liquid ammonia (500 ml.) containing ether (100 ml.). After 30 min. the excess of lithium was destroyed with acetone, and the ammonia evaporated. The residue was diluted with water and extracted with benzene, and the crude product isolated by the usual procedure as a pale foam. This was heated at 100° for 1 hr. in 6N-sulphuric acid (40 ml.), then the solution was cooled, basified, and extracted with benzene. The crude saturated ketone (XI) was then obtained from the organic extract as a brown foam (4·69 g.). This material was converted into the ethylene dithioketal and eluted from a column of silica gel (150 g.) with benzene (500 ml.), followed by 1 : 9 ethyl acetate–benzene (1400 ml.). The latter eluant, after evaporation, gave the dithioketal (XII) (1·92 g.) as a homogeneous amorphous foam. Hydrolysis with 12N-sulphuric acid at 100° for 3 hr. afforded the ketone (XI) as a pale brittle foam whose infrared spectrum showed a carbonyl stretching band at 1720 cm.$^{-1}$ (in CS_2).

(±)-N-*n-Butylemetine* (X).—Compound (XII) (1·5 g.) in tetrahydrofuran (5 ml.) and ethanol (40 ml.) was stirred at 58° under hydrogen at atmospheric pressure with W7 nickel (20 ml. of slurry) for 24 hr. The catalyst was filtered off and the filtrate evaporated, to yield (±)-*N*-n-butylemetine as a pale foam (0·48 g.).

The hydrochloride separated from 2N-hydrochloric acid as white crystals, m. p. 231—234° (decomp.). The infrared spectra (in $CHBr_3$) and R_F values on a paper chromatogram or on thin-layer chromatography of both the bases and the hydrochloride were identical with those of (−)-*N*-n-butylemetine and its hydrochloride made from the natural alkaloid.

(−)-N-*n-Butylemetine* (X).—(*a*) *From* (−)-N-(3-*oxo-n-butyl*)*emetine* (XIII). (i) Ketone [1] (XIII) (6 g.) was converted as before into an amorphous dithioketal (XIV) whose *hydrochloride* (6 g.), m. p. 229—233° (decomp.), separated from ethanol–ether (Found: C, 55·9; H, 8·0; Cl, 9·7; N, 3·9; S, 8·7. $C_{35}H_{52}Cl_2N_2O_4S_2,3H_2O$ requires C, 55·9; H, 7·8; Cl, 9·4; N, 3·8; S, 8·5%). This derivative (0·55 g.), hydrazine hydrate (5 ml.), potassium hydroxide (5 g.), and 2-methoxyethanol (15 ml.) were heated at reflux for 5 hr. under nitrogen. The solution was cooled, poured into water, and extracted thrice with benzene. Isolation of the basic product from the extract by the usual method gave (−)-*N*-n-butylemetine as a homogeneous amorphous foam (0·22 g.). The hydrochloride (0·1 g.) separated slowly from 2N-aqueous hydrochloric acid as needles, m. p. 185—190°.

(ii) The thioketal (XIV) (0·53 g.) in ethanol (20 ml.) was stirred at 60° and atmospheric pressure with hydrogen and W4 nickel (3 ml. of slurry). The catalyst was filtered off and the solvent removed from the filtrate, to give (−)-*N*-n-butylemetine (0·22 g.). The hydrochloride (0·1 g.) had m. p. 186—192°.

(iii) The dibenzyl dithioketal (XV) (2·9 g.) [obtained as a froth from ketone (XIII) (2 g.) with toluene-ω-thiol (1 ml.) in methanolic hydrogen chloride (20 ml.)] was shaken in ethanol (180 ml.) with W4 Raney nickel (18 ml. of slurry) at 55° for 24 hr. under hydrogen at atmospheric pressure. Working-up in the usual manner gave chromatographically pure (−)-*N*-n-butylemetine (1·08 g.) whose hydrochloride (0·37 g.) had m. p. 187—190°.

(*b*) *From* (−)-N-*n-butyrylemetine* (XVI). Butyric anhydride (10 ml.) was added at 10° to (−)-emetine (2·9 g.) in ether (60 ml.) and 2N-aqueous sodium hydroxide (80 ml.). The mixture was shaken vigorously for a few minutes and then stirred at 20° for 45 min. The ethereal layer was washed with 2N-sodium hydroxide, and basic products were then extracted with 2N-hydrochloric acid (2 × 25 ml.). The acidic layers were made alkaline and extracted with ethyl acetate (4 × 40 ml.). These combined extracts, after being washed and dried, were evaporated.

to give (−)-*N*-n-butyrylemetine as a yellow foam (3·55 g.). The *hydrochloride* separated from ethanol–ether, and, after recrystallisation from the same solvent mixture, was obtained as plates (3·17 g.), m. p. 188—192° (decomp.), $[\alpha]_D^{22}$ −31·9° (*c* 1 in H_2O) (Found: C, 66·1; H, 8·4; Cl, 5·75; N, 4·65. $C_{33}H_{47}ClN_2O_5,C_2H_5{\cdot}OH$ requires C, 66·4; H, 8·4; Cl, 5·6; N, 4·6%). Neutralisation of an aqueous solution of the hydrochloride with aqueous sodium carbonate gave the free base as an amorphous powder, m. p. 80—90°, $[\alpha]_D^{20}$ −38° (*c* 1 in $CHCl_3$).

The amide (XVI) (7·8 g.) in 2 : 1 ether–tetrahydrofuran (80 ml.) was added in 30 min. to a stirred slurry of lithium aluminium hydride (3·2 g.) in the same solvent mixture (300 ml.). The suspension was heated under reflux for 5 hr. and then cooled. The excess of hydride was decomposed with ethanol, and the metal complexes were dissolved by addition of 2N-sodium hydroxide (500 ml.). The aqueous phase was extracted with ether (3 × 200 ml.) and the combined organic layers were washed, dried, and evaporated, to give (−)-*N*-n-butylemetine as a yellow froth. The *hydrochloride* (6·2 g.) separated slowly from N-hydrochloric acid (50 ml.) as needles, m. p. 188—192°, $[\alpha]_D^{23}$ +19·7° (*c* 1 in H_2O) (Found: C, 56·4; H, 8·6; Cl, 10·0; N, 3·7. $C_{33}H_{50}Cl_2N_2O_4,5H_2O$ requires C, 56·6; H, 8·6; Cl, 10·2; N, 4·0%). Neutralisation of an aqueous solution of the hydrochloride with aqueous sodium carbonate gave the free base as an amorphous powder, m. p. 60—80°, $[\alpha]_D^{22}$ −33·5° (*c* 1 in $CHCl_3$). The *hydrobromide* separated from water as prismatic needles, sintering at 205—207° and melting at 260° (decomp.), $[\alpha]_D^{22}$ +17·8° (*c* 1 in H_2O) (Found: C, 50·1; H, 7·6; Br, 20·3; N, 3·7. $C_{33}H_{50}Br_2N_2O_4,5H_2O$ requires C, 50·3; H, 7·7; Br, 20·3; N, 3·6%).

Reaction of 3-*Acetyl*-1,4,6,7-*tetrahydro*-9,10-*dimethoxy*-2-[1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-(3-*oxo*-*n*-*butyl*)-1-*isoquinolyl*]*methyl*-11b[H]-*benzo*[a]*quinolizine* (XXIII) *with Thiols.*—(*a*) *With ethane*-1,2-*dithiol.* Ketone (XXIII) [2b] (4 g.) in methanolic hydrogen chloride (40 ml.) was treated with ethane-1,2-dithiol (4 ml.), as described for ketone (I). The *hydrochloride* (5·32 g.) of the bisdithioketal (XXIV) separated from ethanol, and recrystallised from methanol–ether as prisms, m. p. 204—206° (decomp.) (Found: C, 54·8; H, 6·8; Cl, 9·0; N, 3·35; S, 16·5. $C_{37}H_{52}Cl_2N_2O_4S_4,H_2O$ requires C, 55·1; H, 6·8; Cl, 8·8; N, 3·5; S, 15·9%). The free *base* crystallised from acetonitrile as cubes, m. p. 160—162° (Found: C, 62·0; H, 7·2; N, 3·8; S, 18·4. $C_{37}H_{50}N_2O_4S_4$ requires C, 62·2; H, 7·1; N, 3·9; S, 17·9%).

(*b*) *With toluene*-ω-*thiol.* Ketone (XXIII) (15·2 g.) in saturated methanolic hydrogen chloride (350 ml.) containing toluene-ω-thiol (45 ml.) was kept at room temperature for 18 hr., and the solution then slowly evaporated *in vacuo* without external heating. The residual syrup in chloroform (100 ml.) was shaken with 5N-ammonia (150 ml.), and the aqueous phase extracted with chloroform (3 × 10 ml.). The combined organic extracts were washed, dried, and evaporated as usual, to give a red gum that was absorbed on silica gel (750 g.) and eluted successively with (1) benzene (2 l.), (2) 1 : 19 and 1 : 9 ethyl acetate–benzene (1 l. each), (3) 3 : 7 ethyl acetate–benzene (6 l.), and (4) 2 : 3 ethyl acetate–benzene (1 l.), followed by ethyl acetate (6 l.). Evaporation of fraction (3) gave the *thioenol ether* (XXXI) (12·9 g.) as a pale froth (Found: C, 71·25; H, 6·8; S, 10·4. $C_{56}H_{62}N_2O_4S_3,\frac{1}{2}H_2O$ requires C, 71·4; H, 7·0; S, 10·6%), $\lambda_{max.}$ (in EtOH–HCl) 286 mμ (ε 8450), $\lambda_{abs.}$ 230 mμ (ε 38,000). The *hydrobromide* separated from chloroform–ether as needles, m. p. 185—187° (decomp.) (Found: C, 59·9; H, 6·3; Br, 15·4; S, 8·8. $C_{54}H_{64}Br_2N_2O_4S_3,H_2O$ requires C, 60·1; H, 6·2; Br, 14·8; S, 8·9%). Evaporation of fraction (4) gave the dibenzyl dithioketal (XXX) as a foam (5·42 g.), $\lambda_{max.}$ (EtOH–HCl) 285 mμ (ε 7850), $\lambda_{infl.}$ 230 mμ (ε 24,800). The *hydrobromide* separated rapidly from chloroform–ethanol and recrystallised from nitromethane to give the homogeneous salt, m. p. 188—190° (decomp.) (Found: C, 59·4; H, 6·3; Br, 16·8; N, 3·0; S, 6·7. $C_{47}H_{58}Br_2N_2O_5S_2$ requires C, 59·2; H, 6·1; Br, 16·8; N, 2·9; S, 6·7%).

Desulphurisation of the Bisdithioketal (XXIV).—(*a*) *By means of Raney nickel.* The thioketal (1·5 g.) in tetrahydrofuran (20 ml.) and ethanol (50 ml.) was shaken under hydrogen at room temperature and pressure with fresh W7 Raney nickel (7 ml. of slurry). After 18 hr., more catalyst (5 ml.) was added and the reaction was allowed to continue till thin-layer chromatography showed that compound (XXIV) was absent (20—67 hr.). Removal of the catalyst and evaporation of the solvent gave a 2 : 1 mixture of the compound (XXV) and butyldehydroemetine (XXI) as a pale foam (0·82 g.). This mixture was hydrolysed at 90° in 12N-sulphuric acid for 24 hr., and the basic product was isolated by neutralisation with ammonia and extraction with benzene; this gave a crude foam (0·7 g.) that was absorbed on a column of silica gel. Evaporation of the fractions eluted with 50% ethyl acetate–benzene afforded crude (±)-*N*-n-butyl-2,3-dehydroemetine (XXI) (0·24 g.) that was converted into the homogeneous

hydrobromide (0·18 g.) identical with material described below. Further elution of the column with 3 : 7 methanol–ethyl acetate gave crude (±)-*N*-(3-oxo-n-butyl)-2,3-dehydroemetine (XXVI) as a yellow foam (0·4 g.).

(*b*) *By using sodium in liquid ammonia.* Sodium (1·5 g.) was added in 30 min. to a solution of bisdithioketal (XXIV) (5 g.) in tetrahydrofuran (65 ml.) and liquid ammonia (400 ml.) at −70°. After a further 45 min., ethanol was added to discharge the blue colour and the solution was evaporated. The residue was dissolved in water (50 ml.) and extracted with benzene (4 × 50 ml.). The *disulphide* (XXXII) was isolated as a crisp foam (4·06 g.) from the organic extracts (Found: S, 10·6%. *M*, 1200. $C_{70}H_{98}N_4O_8S_4$ requires S, 10·25%; *M*, 1252). The *hydrobromide* separated from ethanol–ether as a white powder, m. p. 190—195° (Found: C, 50·0; H, 6·7; Br, 19·2; N, 3·5; S, 7·8. $C_{70}H_{102}Br_4N_4O_8S_4,6H_2O$ requires C, 50·0; H, 6·7; Br, 19·0; N, 3·3; S, 7·6%).

(±)-2,3-*Dehydro*-N-(3-*hydroxy-n-butyl*)*emetine* (XXVII).—Ketone (XXVI) (1 g.) was reduced with sodium borohydride as described in previous examples, to give the alcohol (XXVII) as a pale foam (0·84 g.). The *hydrochloride* separated from ethanol–ether as a pale powder (Found: C, 58·9; H, 8·4; Cl, 10·9; N, 3·8. $C_{33}H_{48}Cl_2N_2O_5,3H_2O$ requires C, 58·5; H, 8·1; Cl, 10·5; N, 4·1%).

(±)-2,3-*Dehydro*-N-(3-*ethylthio-n-butyl*)*emetine* (XXXIV).—The disulphide (XXXII) (5 g.) in ethanol (200 ml.) was shaken under hydrogen at room temperature and pressure with fresh W7 nickel (50 ml.) for 18 hr. The product was isolated as a gum (2·68 g.) that was a 2 : 1 mixture of the sulphide (XXXIV) and butyldehydroemetine (XXI). Only partial separation of these was achieved on a silica column, but evaporation of several fractions eluted with 50% ethyl acetate–benzene, and shown to be homogeneous by thin-layer chromatography, gave the sulphide (XXXIV) as a yellow foam (0·5 g.). The *hydrochloride* crystallised from ethanol–ether as a pale yellow solid, m. p. 202—212° (with previous softening) (Found: C, 58·2; H, 7·9; Cl, 9·9; N, 4·0; S, 3·8. $C_{35}H_{52}Cl_2N_2O_4S,3H_2O$ requires C, 58·2; H, 8·1; Cl, 9·8; N, 3·9; S, 4·4%). This material gave no purple colour with sodium nitroprusside even in the presence of potassium cyanide and was unaffected by 12N-sulphuric acid at 100° after 24 hr.

(±)-2,3-*Dehydro*-N-[3-(2-*mercaptoethylthio*)-*n-butyl*]*emetine* (XXXIII).—The disulphide (XXXII) (0·51 g.) was heated under nitrogen for 4 hr. at 150° in diethylene glycol (10 ml.) containing 95% hydrazine (2 ml.) and potassium hydroxide (1 g.). Dilution with water and extraction with benzene gave the thiol (XXXIII) as a yellow homogeneous foam (0·38 g.) that gave a strong positive reaction with sodium nitroprusside. The hydrochloride (from ethanol–ether) had m. p. 202—215° (with previous softening). This material was not characterised since paper chromatography showed that recrystallisation caused regeneration of the disulphide (XXXII).

(±)-2-(2-*n-Butyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*methyl*-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-2-*hydroxy*-9,10-*dimethoxy*-11b[H]-*benzo*[a]*quinolizine* (VII).—The dithioketal (II) (2·55 g.) in tetrahydrofuran (7 ml.) and ethanol (63 ml.) was stirred for 44 hr. under hydrogen at 60°/1 atm. with fresh W7 nickel (40 g.), to give the *alcohol* (VII) as a foam (1·06 g.), that crystallised from ether–light petroleum as prisms, m. p. 142—144° (Found: C, 71·3; H, 8·7; N, 5·1. $C_{33}H_{48}N_2O_5$ requires C, 71·7; H, 8·8; N, 5·1%). The *hydrobromide* separated from aqueous hydrobromic acid as prisms, m. p. 218—221° (Found: C, 53·6; H, 7·1; Br, 22·1; N, 3·7. $C_{33}H_{50}Br_2N_2O_5,H_2O$ requires C, 53·4; H, 7·3; Br, 21·8; N, 3·8%).

The alcohol (0·46 g.) in methylene chloride (10 ml.) was heated at reflux for 30 min. with acetic anhydride (1 ml.) and 60% aqueous perchloric acid (0·5 ml.), and the cooled solution then poured on ice and 2N-sodium carbonate. Working-up of the organic layer as usual gave a foam that was digested with hot ether. When the ethereal solution was concentrated the *acetate* (0·27 g.) rapidly crystallised. Recrystallisation from ether–benzene gave prisms, m. p. 190—191° (Found: C, 70·3; H, 8·8; N, 4·5. $C_{35}H_{50}N_2O_6$ requires C, 70·1; H, 8·6; N, 4·8%).

The alcohol (1·02 g.) in benzene (10 ml.) was treated for 10 min. at room temperature with ethyl chloroformate. The basic fraction of the reaction product crystallised from ether, to give the *ethoxycarbonyl ester* (0·58 g.), m. p. 144—146°. Crystallisation from ethanol raised the m. p. to 149—150° (Found: C, 69·3; H, 8·6; N, 4·2. $C_{36}H_{52}N_2O_7$ requires C, 69·2; H, 8·4; N, 4·5%).

(±)-N-*n-Butyl*-2,3-*dehydroemetine* (XXI).—(*a*) *From* (±)-2,3-*dehydroemetine* (XIX). (±)-2,3-Dehydroemetine hydrochloride (0·6 g.) was shaken for 1½ hr. with 2N-sodium hydroxide (15 ml.), benzene (25 ml.), and butyric anhydride (2 ml.). The *butyryl* derivative (XXVIII)

was obtained from benzene–ether as a pale solid (0·45 g.), m. p. 159—160°. Recrystallisation from ethanol gave prisms, m. p. 164—165° (Found: C, 71·9; H, 7·9; N, 5·3. $C_{33}H_{44}N_2O_5$ requires C, 72·3; H, 8·1; N, 5·1%).

The amide (0·4 g.) in tetrahydrofuran (5 ml.) was stirred with a slurry of lithium aluminium hydride (0·2 g.) in 3 : 1 ether–tetrahydrofuran (24 ml.) for 6 hr. at the b. p. and then overnight at 20°. (±)-*N*-n-Butyl-2,3-dehydroemetine was obtained, after the usual treatment, as a pale homogeneous foam (0·36 g.). Its *hydrobromide* crystallised from aqueous ethanol as prisms, m. p. 188—195°, decomp. 225—230° (Found: C, 52·6; H, 7·2; Br, 21·5; N, 3·9. $C_{33}H_{48}Br_2N_2O_4,3H_2O$ requires C, 52·8; H, 7·25; Br, 21·3; N, 3·7%).

(*b*) *From the dithioketal* (XXII). The dithioketal (0·3 g.) in tetrahydrofuran (5 ml.) was added to sodium (0·1 g.) in refluxing liquid ammonia (25 ml.). After 30 min. the blue colour was discharged with ethanol and the product isolated as above. The crude base (XXI) gave the authentic homogeneous hydrobromide (0·18 g.), m. p. 190—195°.

(*c*) *From the thioenol ether* (XXXI). The thioenol ether (1 g.) in tetrahydrofuran (10 ml.) and ethanol (90 ml.) was stirred under nitrogen for 72 hr. with fresh W4 nickel (8 ml.). The gum (0·28 g.) obtained on removal of the catalyst and evaporation was heated with charcoal in 10% aqueous hydrobromic acid (4 ml.). When the charcoal was filtered off and the filtrate cooled, the hydrobromide (0·08 g.), m. p. 185—195°, of (XXI) slowly separated.

(*d*) *From the disulphide* (XXXII). The disulphide (0·95 g.) in ethanol (47·5 ml.) and tetrahydrofuran (7·5 ml.) was shaken under hydrogen at room temperature and pressure for 20 hr. with fresh W7 nickel (15 ml.). The compound (XXI) was isolated, as before, as a yellow foam (0·42 g.) that gave the hydrobromide (0·4 g.), m. p. 195—200°, decomp. 225—230°.

(*e*) *From the alcohol* (VII). The alcohol (0·52 g.) in acetic anhydride (10 ml.) was treated at 20° with sulphuric acid (2 ml.) in acetic anhydride (8 ml.). After 1 hr. the solution was poured on ice and 2N-sodium carbonate. Extraction with benzene and evaporation gave the product (XXI) as a pale gum (0·46 g.) that was converted into the homogeneous hydrobromide (0·42 g.), m. p. 188—200°, decomp. 225—230°.

1,4,6,7-*Tetrahydro*-3-(1-*hydroxyethyl*)-9,10-*dimethoxy*-2-[1,2,3,4-*tetrahydro*-2-(3-*hydroxy*-*n*-*butyl*)-6,7-*dimethoxy*-1-*isoquinolyl*]*methyl*-11b[H]-*benzo*[a]*quinolizine* (XXIX) (with Dr. D. E. Clark).—Ketone (XXIII) (20 g.) in methanol (25 ml.) and benzene (30 ml.) was stirred for 45 min. with sodium borohydride (7 g.) in water (60 ml.). The *diol* (XXIX), isolated by methods described above, separated from benzene–ether as crystals (13·93 g.), m. p. 128° (Found: C, 67·5; H, 8·3; N, 5·1. $C_{33}H_{46}N_2O_6$ requires C, 67·8; H, 8·3; N, 4·8%).

(±)-12-*Hydroxy*-N-(3-*hydroxy*-*n*-*butyl*)*emetine* (XVIII) (with Dr. D. E. Clark).—Ketone (XVII) [1] (1·32 g.) in methanol (30 ml.) was reduced, as before, with sodium borohydride (0·53 g.) in water (5 ml.). The alcohol (XVIII) was characterised as the *hydrochloride*, m. p. 210° (from ethanol–ether) (Found: C, 55·5; H, 8·2; Cl, 10·2; N, 4·0. $C_{33}H_{50}Cl_2N_2O_6,4H_2O$ requires C, 55·5; H, 8·2; Cl, 9·9; N, 3·9%).

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