475. *Emetine and Related Compounds. Part III.*[1] *The Stereospecific Synthesis of* (±)-*Emetine and* (±)-*Isoemetine.*

By D. E. Clark, R. F. K. Meredith, A. C. Ritchie, and T. Walker.

Stereospecific syntheses of (±)-emetine and (±)-isoemetine from intermediates of known stereochemical configuration are described.

In Part II [1] of this series we described the preparation of both diastereoisomeric forms, A and B, of the two pentacyclic bases (I) and (II).* This paper describes their stereospecific conversion into the corresponding diastereoisomers, (±)-isoemetine (III)A, and (±)-emetine (III)B.

The key stage was the introduction of the two remaining asymmetric centres of the emetine molecule, a process demanding *trans*-diaxial addition of hydrogen to the olefinic link of the conjugated ketone, with generation of the more stable conformation at each carbon atom.

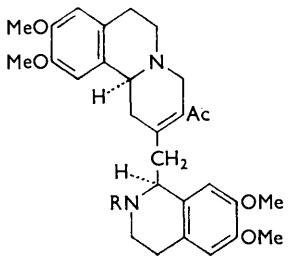
Barton and Robinson [2] have pointed out that reduction of the olefinic bond of αβ-unsaturated ketones, by means of an alkali metal in liquid ammonia, usually gives the stereochemically more stable configuration at the β-carbon atom. Although these authors made no specific generalisation about the stereochemistry of the α-carbon atom, the more stable configuration again resulted in the limited number of examples quoted.

Ketone (II)A with calcium in liquid ammonia gave *ca.* 48% of a crude base separable by fractional crystallisation into two isomers of the saturated ketone (VII), (a) (30%), and (b) (5%). Isomer (a) was converted by mineral acid at 100° into a third diastereoisomer (c); isomer (b) gave the remaining diastereoisomer (d) as an amorphous foam, characterised as its crystalline hydrobromide. These isomers could be readily distinguished by paper chromatography. The relation between isomers (a)—(d) is illustrated by the formulæ, from which it will be seen that, though the major reduction product had the more stable configuration at the β-carbon atom (2), the less stable configuration was obtained at

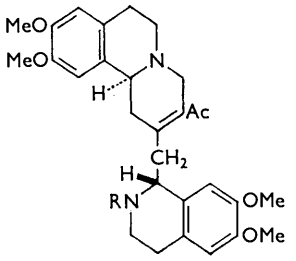
* Throughout this paper only one optical enantiomorph of each compound is shown.

[1] Part II, preceding paper.

[2] Barton and Robinson, *J.*, 1954, 3045.

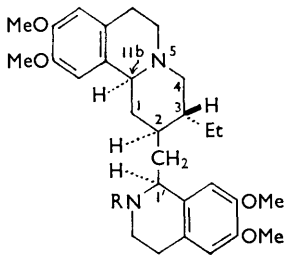


Series A



Series B

(I) R = $CH_2 \cdot CH_2Ac$
(II) R = CH_2Ph



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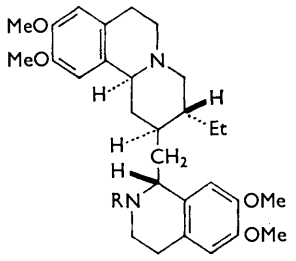
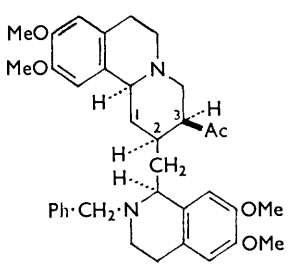


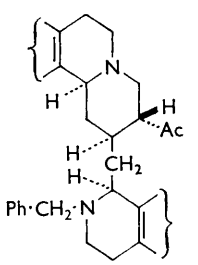
Series B

(III) R = H
(IV) R = $CH_2 \cdot CH_2 \cdot CHMe \cdot OH$
(V) R = CH_2Ph
(VI) R = $CH_2 \cdot CH_2Ac$

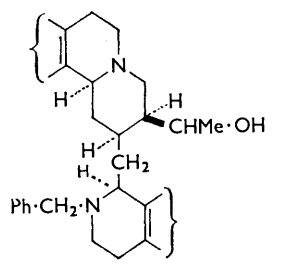
the α-position. This is in accord with the view [3,4] that protonation of the β-carbon atom in the intermediate dicarbanion is thermodynamically controlled and generates the more stable isomer, whereas kinetic control of protonation at the α-carbon atom may lead to the less stable configuration. The isolation of (VIIb) shows that the reduction was not completely stereoselective at the β-position.



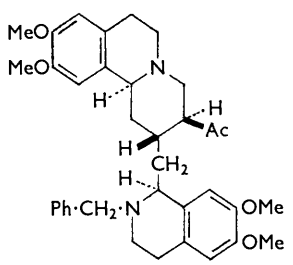
(VIIa) m.p. 161°



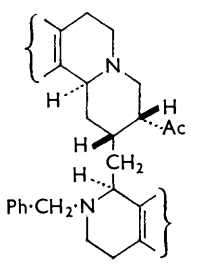
(VIIc) m.p. 109°



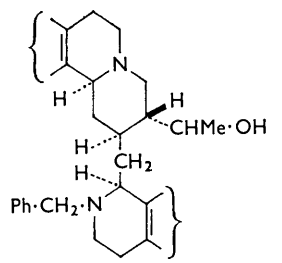
(VIIIa)



(VIIb) m.p. 186°



(VIId)



(VIIIc)

The isomeric ketones (a) and (c) gave different hydrazones and were reduced to the corresponding alcohols (VIIIa and c) with sodium borohydride, but they were converted

[3] Zimmerman, *J. Amer. Chem. Soc.*, 1956, **78**, 1168.
[4] Birch, Smith, and Thornton, *J.*, 1957, 1339.

into the same ethylene thioketal with ethane-1,2-dithiol in methanolic hydrogen chloride, the latter reagent causing inversion at the α-carbon atom (3) of (a).

The steric course of the reduction of ketone (II)A was unaffected by incorporation of a proton donor (ethanol) into the system, the product being the alcohol (VIIIa) in which the less stable conformation at the α-carbon atom was retained.

Reduction of ketone (II)B with lithium in liquid ammonia was not investigated in detail. Chromatography of the crude product and treatment with hot mineral acid to achieve equilibration gave the crystalline saturated ketone (IX)B.

Conversion of the acetyl substituent in the saturated ketones (IX)A [*i.e.*, (VIIc)] and (IX)B into an ethyl group was effected by desulphurisation of the ethylene thioketals with W4-Raney nickel. This reaction was slow in ethanol, but in boiling xylene [5] (±)-*N*-benzylisoemetine (V)A and (±)-*N*-benzylemetine (V)B resulted, respectively. In addition there was isolated a variable amount of a debenzylated product, whose infrared spectrum showed bands at 860 and 820 cm.$^{-1}$ for the CH=CH grouping of an aromatic system and the ultraviolet spectra of whose neutral and acid solutions closely resembled those of 6,7-dimethoxy-1-methylisoquinoline superimposed on a veratrole spectrum. The compound was accordingly formulated as (±)-emetamine (XII) and characterised as the hydrogen oxalate. This material could arise from hydrogenolysis of the benzyl group and subsequent dehydrogenation when the nickel catalyst had been degassed by prolonged heating in xylene.

(+)-*N*-Benzylemetine [obtained from (−)-emetine by benzoylation and reduction with lithium aluminium hydride] with Raney nickel in boiling xylene gave in 24 hr., in addition to unchanged starting material, a crystalline base whose elemental analysis was in agreement with structure (XII). The melting point and specific rotation of this base were close to the published values for (+)-emetamine. The R_F value and the infrared and ultraviolet spectra of this compound and of its hydrogen oxalate were identical with those of the racemic material from our synthetic intermediates. The crystalline (+)-base (XII) was obtained in good yield from (−)-emetine by means of Raney nickel in boiling xylene.

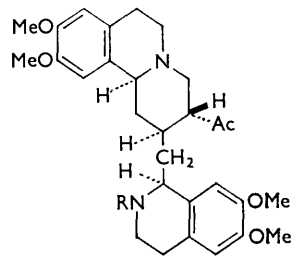
Ahl and Reichstein [6] have described the preparation of (+)-emetamine from (−)-emetine in low yield by dehydrogenation with palladised charcoal. Battersby and his co-workers,[7] however, found that in their hands this procedure gave, not emetamine, but a substance identical with it in all physical constants except specific rotation. We have been unable to effect a direct comparison between our material and natural emetamine but the agreement of their specific rotations as bases suggests identity, although the hydrogen oxalate of our base had a rotation rather less negative than that of the natural alkaloid (cf. ref. 7).

Removal of the *N*-benzyl group from bases (V)A and B was accomplished by catalytic hydrogenolysis with palladised charcoal. The A isomer gave (±)-isoemetine (III)A, isolated as the hydrochloride, whose melting point, mixed melting point, infrared spectrum, and R_F value were identical with those of an authentic specimen obtained by hydrogenation of (±)-*O*-methylpsychotrine hydrogen oxalate (kindly supplied by Dr. A. R. Battersby, The University, Bristol) in presence of Adams platinic oxide.[8] Similarly, the B isomer afforded (±)-emetine (III)B as the hydrobromide, with an infrared spectrum and R_F value indistinguishable from those of the natural alkaloid and showing at least half its activity against *Entamoeba histolytica* in rats.

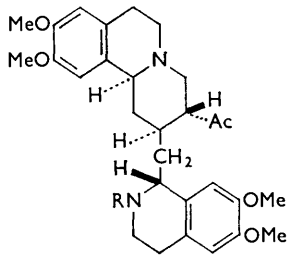
The conjugated ketones (I)A and B with lithium in liquid ammonia gave intractable mixtures of diastereoisomers (X). Equilibration with acid still afforded no crystalline

[5] Badger, Kowanko, and Sasse, *J.*, 1960, 1658.
[6] Ahl and Reichstein, *Helv. Chim. Acta*, 1944, **27**, 366.
[7] Battersby, *Chem. Soc. Special Publ.*, No. 3, 1955, 36; Battersby, Davidson, and Turner, *J.*, 1961, 3899.
[8] Cf. Karrer, Eugster, and Rüttner, *Helv. Chim. Acta*, 1948, **31**, 1219.

material, and isolation of the desired isomers (X)A and B was then best effected by treatment with ethane-1,2-dithiol and chromatography of the thioketals. The ethylene thioketal derivative of the keto-alcohol (X)B was thus obtained from the diketone (I)B in *ca.* 50% yield. An unexpected by-product was the di(ethylene thioketal) of ketone (XI) (*ca.* 12%), in which the carbonyl group of the *N*-3-oxo-n-butyl side-chain had been preserved. The structure assigned to this compound was based on analysis, the lack of hydroxylic absorption in the infrared spectrum, and hydrolysis to a product showing no ultraviolet absorption due to a conjugated carbonyl group. The peak intensity in the infrared spectrum at 1710 cm.$^{-1}$ of the carbonyl-stretching band was almost double that of ketone (X)B. The stereochemistry of this compound at $C_{(2)}$ and $C_{(3)}$ is uncertain.



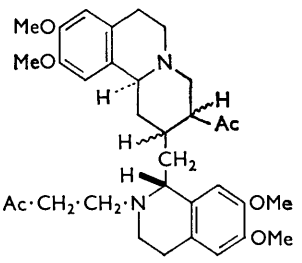
Series A



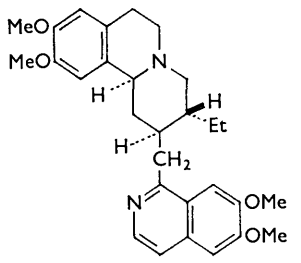
Series B

(IX) R = CH_2Ph

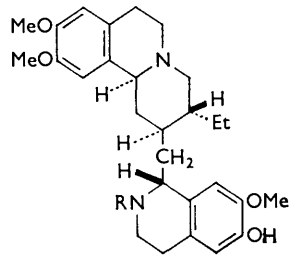
(X) R = $CH_2 \cdot CH_2 \cdot CHMe \cdot OH$



(XI)



(XII)



(XIII)

The ethylene thioketals of ketones (X)A and B were converted by hydrogenolysis at 50° with Raney nickel [9] into (±)-*N*-(3-hydroxy-n-butyl)-isoemetine (IV)A and -emetine (IV)B, respectively. The latter had an infrared spectrum and R_F value identical with those of material obtained by adding methyl vinyl ketone to (—)-emetine and reducing the adduct (VI)B with sodium borohydride.

Georgian and his co-workers [10] have described the desulphurisation of ethylene thioketals by alkali and hydrazine hydrate in ethylene glycol at 90—130°. The thioketal of ketone (X)B failed to undergo this reaction but was converted instead into the corresponding hydrazone, whose decomposition to the desired methylene compound (IV)B required the more drastic conditions of the Wolff–Kishner reaction (160—190°). In these circumstances extensive ether-fission to phenolic products was noted. Comparison of the intensity of the stretching-frequency band of the phenolic hydroxyl group at 3500 cm.$^{-1}$ for this material with that for (—)-*N*-(3-hydroxy-n-butyl)cephaeline (XIII; R = $CH_2 \cdot CH_2 \cdot CHMe \cdot OH$) suggested that demethylation of between one and two methoxyl groups had occurred.[11] Remethylation of the Wolff–Kishner product with trimethylanilinium chloride [12] gave (±)-*N*-(3-hydroxy-n-butyl)emetine (IV)B in good yield. The model compound (XIII; R = $CH_2 \cdot CH_2 \cdot CHMe \cdot OH$) was obtained by Michael addition of

[9] Shin Imaizumi, *Nippon Kagaku Zasshi*, 1957, **78**, 1396; *Chem. Abs.*, 1960, **54**, 1403.
[10] Georgian, Harrisson, and Gubisch, *J. Amer. Chem. Soc.*, 1959, **81**, 5834.
[11] Cf. Bible, *Tetrahedron*, 1960, **11**, 22.
[12] B.P. 291,088.

methyl vinyl ketone to (−)-cephaeline (XIII; R = H) and reduction of the resulting (−)-*N*-(3-oxo-n-butyl)cephaeline (XIII; R = $CH_2 \cdot CH_2Ac$) with sodium borohydride.

Battersby and Garratt [13] have recorded that (−)-emetine is substantially unchanged under anhydrous Wolff–Kishner conditions at 155° for 5 hours. In our hands treatment under similar but not identical conditions caused fission equivalent to *ca.* 75% of one methoxyl group. The resultant mixture of phenols could be remethylated to give (−)-emetine.

Final conversion of the alcohols (IV)A and B into (±)-isoemetine and (±)-emetine, respectively, was brought about by a modification [14] of the Oppenauer oxidation, in which the vigorous alkaline conditions caused the intermediate ketones (VI)A and B to undergo a retro-Michael reaction *in situ*. The compounds so produced were indistinguishable from those obtained as described above from the corresponding *N*-benzyl intermediates.

(±)-Emetine was resolved with *N*-acetyl-L-leucine,[15] and the (−)-base was shown to be identical with the natural alkaloid.

The stereospecific preparation of (±)-emetine and (±)-isoemetine from intermediates of known stereochemistry in the B and the A series, respectively, offers the first synthetic confirmation that the relative configurations of the asymmetric centres in the tetrahydroisoquinoline and the quinolizidine portion of the molecules are as illustrated. Indeed, taken in conjunction with the known stereochemical course of metal–ammonia reduction, our synthetic route completely defines the relative stereochemistry of all four asymmetric centres in emetine and isoemetine.

The annexed Table shows the activity, against *Entamoeba histolytica* in weanling rats,[16] of some of the compounds described above. The figures for the activity and toxicity of ketone (VI)B suggest that degradation to (−)-emetine is occurring *in vivo*. *N*-(3-Hydroxy-n-butyl)emetine shows a high degree of activity coupled with low toxicity, and further tests are being undertaken to evaluate this material as a potential amœbicide. None of the remaining intermediates described in this paper showed useful amœbicidal activity.

	Activity CD 100 (mg./kg.)	Oral toxicity LD 50 (mg./kg.)
(+)-Emetine HCl	2—4	10—25
(±)-Emetine HBr	<5	—
(+)-Emetine HBr, (III)B	2	—
(−)-Emetine HBr	>50	—
(−)-*N*-(3-Hydroxy-n-butyl)emetine HCl, (IV)B	2—5	>250
(±)-*N*-(3-Hydroxy-n-butyl)emetine	5—10	—
(−)-*N*-(3-Oxo-n-butyl)emetine HCl, (VI)B	2—4	10—25
(+)-*N*-Benzylemetine (V)B	>50	250—400

Experimental

Paper chromatography by the method of Barash *et al.*[17] and thin-layer chromatography [18] were used to ensure the homogeneity of the compounds described in this section (for general directions see Part II of this series).

3-*Acetyl*-2-(2-*benzyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolylmethyl*)-2,3,4,6,7,11b-*hexahydro*-9,10-*dimethoxy*-1H-*benzo*[a]*quinolizine* (VII) *and* (IX).—A *Series*. (i) Isomers (VIIa and b). Ketone (II)A (10 g.) in dried ether (100 ml.) and dried benzene (50 ml.) was stirred for 10 min. with calcium (1·6 g.) in refluxing ammonia (300 ml.). The blue colour was discharged with acetone, the ammonia evaporated, and the residue taken up in water (100 ml.) and benzene (50 ml.). After removal of insoluble material, the layers were separated and the aqueous phase was extracted with benzene (2 × 50 ml.). The combined organic layers were

[13] Battersby and Garratt, *J.*, 1959, 3512.
[14] Woodward, Wendler, and Brutschy, *J. Amer. Chem. Soc.*, 1945, **67**, 1425.
[15] Brossi, Baumann, and Schnider, *Helv. Chim. Acta*, 1959, **42**, 1515.
[16] Jones, *Ann. Trop. Med. Parasitol.*, 1956, **40**, 130.
[17] Barash, Osbond, and Wickens, *J.*, 1959, 3530.
[18] Stahl, *Chem. Ztg.*, 1958, **82**, 323.

washed 3 times with water, dried, and evaporated to a foam. Trituration with ether gave a pale solid (4·1 g.), m. p. 140—148°. The mother-liquor deposited a second crop (0·63 g.), m. p. 175—180°.

The first crop crystallised from ethanol as needles (2·9 g.), m. p. 160—161°, of the saturated *ketone* (VIIa) (Found: C, 72·0; H, 8·0; N, 4·9. $C_{36}H_{44}N_2O_5,H_2O$ requires C, 71·7; H, 7·7; N, 4·7%), $\lambda_{max.}$ (in EtOH–HCl) 232, 283 mμ (ε 16,200, 7600). The *hydrazone* separated from ether as a white amorphous solid, m. p. 117—119° (decomp.) (Found: C, 70·0; H, 8·0; N, 9·2. $C_{36}H_{46}N_4O_4,H_2O$ requires C, 70·1; H, 7·8; N, 9·1%).

Ketone (VIIa) with ethane-1,2-dithiol in saturated methanolic hydrogen chloride at room temperature for 3 hr. gave the ethylene thioketal (as a white foam) whose *dihydrochloride* crystallised from ethanol as prisms, m. p. 205—208° (decomp.) (Found: C, 57·1; H, 7·2; Cl, 8·9; N, 3·3; S, 8·2. $C_{38}H_{50}Cl_2N_2O_4S_2,5H_2O$ requires C, 57·3; H, 7·2; Cl, 8·9; N, 3·5; S, 8·1%).

The second crop from the reduction was leached with boiling ethanol (10 ml.) to give the *isomer* (VIIb) as a white powder (0·48 g.), m. p. 185—186° (Found: C, 74·0; H, 7·7; N, 4·8. $C_{36}H_{44}N_2O_5$ requires C, 73·9; H, 7·6; N, 4·8%), $\lambda_{max.}$ (in EtOH–HCl) 233, 283 mμ (ε 16,200, 7300). The *hydrazone* separated from ether as a powder, m. p. 175—179° (decomp.) (Found: C, 71·9; H, 7·8; N, 9·8. $C_{36}H_{46}N_4O_4$ requires C, 72·2; H, 7·7; N, 9·4%).

(ii) Isomer (VIIc). Isomer (a) of ketone (VII) (2 g.) was heated at 100° for 2 hr. in 12N-sulphuric acid. The solution was poured on ice, then neutralised with a solution of ammonia (*d* 0·88), and the basic product was extracted with benzene. Evaporation of the dried extract gave a foam, converted by trituration with ether into white crystals (1·6 g.), m. p. 107—109°. This was *isomer* (VIIc) (Found: C, 73·8; H, 7·8; N, 4·7. $C_{36}H_{44}N_2O_5$ requires C, 73·9; H, 7·6; N, 4·8%), $\lambda_{max.}$ (in EtOH–HCl) 232, 283 mμ (ε 16,400, 7300). The *hydrazone* was obtained from ether as an amorphous solid, m. p. 133—135° (Found: C, 71·8; H, 7·8; N, 9·4%). The *hydrochloride* crystallised from methanol–ether as pale yellow prisms, m. p. 206—208° (decomp.) (Found: C, 62·0; H, 7·3; Cl, 9·7; N, 3·9. $C_{36}H_{46}Cl_2N_2O_5,2H_2O$ requires C, 62·3; H, 7·3; Cl, 10·2; N, 4·0%).

The ethylene thioketal hydrochloride was obtained from methanol as colourless prisms, m. p. 205—207° (decomp.), alone or when mixed with a specimen of the hydrochloride from the ethylene thioketal of ketone (VIIa).

(iii) Isomer (VIId). Isomer (b) of ketone (VII) (0·3 g.) was treated with 12N-sulphuric acid as above, to give the isomer (VIId) as a pale foam (0·26 g.). The *hydrobromide* separated as white prisms, m. p. 207—210° (decomp.), from ethanol (Found: C, 53·3; H, 6·8; N, 3·5. $C_{36}H_{46}Br_2N_2O_5,3·5H_2O$ requires C, 53·4; H, 6·6; N, 3·5%).

B *Series* (IX)B. Ketone (II)B (2·57 g.) in tetrahydrofuran (150 ml.) was added to a refluxing solution of lithium (0·3 g.) in liquid ammonia (450 ml.). After 30 min. the excess of metal was destroyed with acetone, and the product was isolated and equilibrated with acid as described above. The resulting crude foam was eluted from a column of Florisil (45 g.) with ethyl acetate–benzene (1 : 4). Evaporation of the solvents and trituration with ether gave the *ketone* (IX)B (0·7 g.), m. p. 142—144° (Found: C, 72·5; H, 7·6; N, 4·4. $C_{36}H_{44}N_2O_5,0·5H_2O$ requires C, 72·8; H, 7·6; N, 4·7%). The *hydriodide* crystallised from water as pale yellow plates, m. p. 208—210° (decomp.) (Found: C, 49·5; H, 6·1; I, 29·8; N, 2·9. $C_{36}H_{46}I_2N_2O_5,2H_2O$ requires C, 49·3; H, 5·8; I, 30·0; N, 3·2%). The *perchlorate* separated from water as an amorphous solid, m. p. 180—181° (decomp.) (Found: C, 52·3; H, 6·2; Cl, 8·2. $C_{36}H_{46}Cl_2N_2O_{13},2H_2O$ requires C, 52·6; H, 6·1; Cl, 8·6%).

The ethylene thioketal was characterised as the *hydrobromide*, m. p. 212° (decomp.) (softening from 195°) (from ethanol–ether) (Found: C, 52·3; H, 6·3; Br, 18·0; N, 3·1; S, 7·5. $C_{38}H_{50}Br_2N_2O_4S_2,3H_2O$ requires C, 52·1; H, 6·4; Br, 18·2; N, 3·2; S, 7·3%).

2-(2-*Benzyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolylmethyl*)-2,3,4,6,7,11b-*hexahydro*-3-1′-*hydroxyethyl*-9,10-*dimethoxy*-1H-*benzo*[a]*quinolizine* (VIII).—*Isomer* (a). (i) Ketone (VIIa) (0·5 g.) and sodium borohydride (0·2 g.) in tetrahydrofuran (10 ml.) and water (2 ml.), with sufficient methanol to produce a single phase, were kept at room temperature for 24 hr. The solution was acidified with dilute hydrochloric acid, the organic solvents were removed by evaporation, and the residue was dissolved in water. Neutralisation with sodium carbonate and isolation of the basic product by extraction with benzene, as usual, gave a white foam. This was triturated with ether to produce the *alcohol* (VIIa) as a white powder (0·38 g.), m. p. 168—170°. Recrystallisation from ethanol afforded material, m. p. 170—172° (Found: C, 73·5; H, 8·0; N, 4·7. $C_{36}H_{46}N_2O_5$ requires C, 73·7; H, 7·9; N, 4·8%).

(ii) Ketone (II)A (0·58 g.) in tetrahydrofuran (35 ml.) containing ethanol (0·12 ml.) was added to a refluxing solution of lithium (0·07 g.) in liquid ammonia (100 ml.). After 30 min. the excess of lithium was destroyed by acetone, and the product isolated as before. The crude foam was eluted from Florisil (10 g.) with ethyl acetate–benzene (1 : 4). Removal of the solvents by evaporation, followed by crystallisation of the residue from ethanol, gave the alcohol (VIIIa) (0·12 g.), m. p. 164—165°, whose infrared spectrum and R_F value were identical with those of the specimen obtained as above.

Isomer (c). Ketone (VIIc) (0·5 g.) was reduced with sodium borohydride as above and the *alcohol* (VIIIc) isolated as a white amorphous solid (0·38 g.), m. p. 168—171°. Recrystallisation from ethanol gave material, m. p. 170—172°, differing in its infrared spectrum and R_F value from isomer (a) (Found: C, 73·9; H, 8·0; N, 4·8%).

(±)-N-*Benzylisoemetine* (V)A.—The ethylene thioketal (0·6 g.) of ketone (VIIc) was heated for 24 hr. in boiling xylene (50 ml.) with W4 Raney nickel catalyst (6 g.). When the catalyst had been filtered off the basic product was extracted from the xylene solution with 2N-hydrochloric acid. Neutralisation of the acidic fraction with sodium carbonate solution, extraction with ether, and evaporation of the dried extract gave a yellow foam (0·29 g.). This material was eluted from alumina (15 g.). (i) 1 : 9 Ethyl acetate–benzene (150 ml.) gave (±)-*N*-benzylisoemetine (0·13 g.); (ii) ethyl acetate (100 ml.) gave (±)-emetamine (XII) (0·16 g.) whose hydrogen oxalate, m. p. 168—171° (decomp.), crystallised from ethanol, $\lambda_{max.}$ (in H_2O) 237, 287, 318 mμ (ε 57,000, 7000, 8000).

(±)-N-*Benzylemetine* (V)B.—The ethylene thioketal (0·85 g.) of ketone (IX)B was treated with Raney nickel as in the preceding example. Elution of the crude base (0·42 g.) from alumina with 1 : 9 ethyl acetate–benzene gave (±)-N-*benzylemetine* (0·29 g.) as a pale froth. The *hydrobromide* separated from ethanol as white prisms, m. p. 211—213° (decomp.) (Found: C, 55·3; H, 6·7; Br, 19·7; N, 3·6. $C_{36}H_{48}Br_2N_2O_4,3H_2O$ requires C, 55·0; H, 6·9; Br, 20·3; N, 3·6%).

(+)-N-*Benzylemetine*.—*N*-Benzoylemetine [19] (1 g.) in ether (60 ml.) and tetrahydrofuran (40 ml.) was stirred, at the b. p., with lithium aluminium hydride (0·65 g.) for 3·5 hr. The suspension was cooled and water (0·65 ml.), 15% aqueous sodium hydroxide (0·65 ml.), and water (1·95 ml.) were added successively. The precipitate was filtered off and washed with benzene. Evaporation of the filtrate gave (+)-*N*-benzylemetine (1 g.) as a white foam, $[\alpha]_D^{20}$ +19° (*c* 1 in $CHCl_3$), whose infrared spectrum (in $CHBr_3$) and R_F value were identical with those of the racemic material obtained as above. The *hydrobromide* crystallised from water as needles, m. p. 204—206° (decomp.) (Found: C, 56·1; H, 6·9; Br, 21·0; N, 3·6. $C_{36}H_{48}Br_2N_2O_4,2H_2O$ requires C, 56·3; H, 6·8; Br, 20·8; N, 3·6%).

(+)-*Emetamine* (XII).—(*a*) *From* (+)-N-*benzylemetine*. (+)-*N*-Benzylemetine (1 g.) in xylene (50 ml.) was heated at the b. p. for 24 hr. with W4 Raney nickel catalyst (*ca.* 10 g.). The crude product was isolated as above and eluted from alumina (40 g.). (i) 1 : 9 Ethyl acetate–benzene (450 ml.) gave unchanged (+)-*N*-benzylemetine (0·41 g.); (ii) ethyl acetate (200 ml.) gave slightly impure (+)-emetamine (204 mg.). The pure base (120 mg.), m. p. 154—155°, was obtained by regeneration from the picrate and crystallisation from ether.

(*b*) *From* (−)-*emetine*. (−)-Emetine (1·59 g.) in xylene (40 ml.) was refluxed for 24 hr. with Raney nickel (*ca.* 12 g.) and worked up as above. The crude froth (0·94 g.) had the same R_F value and infrared spectrum as (+)-emetamine. Crystallisation from ether (15 ml.) gave the pure material as needles (0·53 g.), m. p. 156—157° (lit.,[20] 155—156°) (Found: C, 72·8; H, 7·5; N, 6·2. Calc. for $C_{29}H_{36}N_2O_4$: C, 73·1; H, 7·6; N, 5·9%), $[\alpha]_D^{22.5}$ +11·6° (*c* 1·98 in $CHCl_3$) [lit.,[20] +11·2° (*c* 6·1 in $CHCl_3$)], $\lambda_{max.}$ (in EtOH) 238, 279, 312, 324 mμ (ε 73,500, 7900, 3650, 4050), $\lambda_{max.}$ (in EtOH–HCl) 254, 288, 311 mμ (ε 69,000, 7600, 9700). The hydrogen oxalate, crystallised from slightly aqueous ethanol, had m. p. 171—172° (decomp.) [lit.,[20] 171° (decomp.)], $[\alpha]_D^{23}$ −1° (*c* 2 in H_2O) [lit., −6° (*c* 4 in H_2O)] (Found: C, 57·1; H, 6·6; N, 3·8. Calc. for $C_{33}H_{40}N_2O_{12},2H_2O$: C, 57·2; H, 6·4; N, 4·0%).

3-*Acetyl*-2,3,4,6,7,11b-*hexahydro*-9,10-*dimethoxy*-2-(1,2,3,4-*tetrahydro*-2-3′-*hydroxy*-*n*-*butyl*-6,7-*dimethoxy*-1-*isoquinolylmethyl*)-1H-*benzo*[a]*quinolizine* (X).—*Series* A. Ketone (I)A (5 g.) in tetrahydrofuran (150 ml.) was stirred for 30 min. with a refluxing solution of lithium (0·6 g.) in liquid ammonia (300 ml.). After an excess of acetone had been added, the crude product was isolated as a foam, heated with 5N-sulphuric acid for 2 hr. to effect equilibration, and

[19] Carr and Pyman, *J.*, 1914, **105**, 1591.
[20] Pyman, *J.*, 1917, **111**, 419.

converted into the ethylene thioketal (3·86 g.) as described above. This material was absorbed on alumina (100 g.; grade H) in benzene and eluted successively with 1 : 9 ethyl acetate–benzene (300 ml.), 1 : 3 ethyl acetate–benzene (400 ml.), 1 : 1 ethyl acetate–benzene (300 ml.), and ethyl acetate (1·4 l.). The last eluant gave the ethylene thioketal (1·8 g.) of ketone (X)A as a foam on evaporation of the solvent. The *hydrochloride* crystallised from methanol–ether as prisms, m. p. 215—220° (decomp.) (Found: C, 53·4; H, 7·4; Cl, 9·3; N, 3·5; S, 8·8. $C_{35}H_{52}Cl_2O_5S_2,4H_2O$ requires C, 53·3; H, 7·7; Cl, 9·0; N, 3·6; S, 8·2%).

Series B. Ketone (I)B (5 g.) was reduced as in the preceding example and the product, after equilibration with 5N-sulphuric acid, converted into the ethylene thioketal (5·42 g.). The crude foam in benzene was absorbed on silica gel (160 g.) and eluted with rigorously dried solvents; after preliminary elution with benzene (500 ml.) the following fractions were recorded: (i) 1 : 1 ethyl acetate–benzene (850 ml.) gave the *di(ethylene thioketal)* (0·73 g.) of ketone (XI). This material was homogeneous on a paper chromatogram and on a chromatostrip [17] of kieselgel G (Merck). The *hydrobromide* separated from water as an amorphous solid, m. p. 210—212° (decomp.) (Found: C, 48·6; H, 6·6; N, 2·9; S, 13·4. $C_{37}H_{54}Br_2N_2O_4S_4,2H_2O$ requires C, 48·7; H, 6·4; N, 3·1; S, 14·0%). (ii) Ethyl acetate (1·5 l.) gave the *ethylene thioketal* of (X)B (2·83 g.) as a pale homogeneous foam. Its *hydriodide* crystallised from ether–methanol as yellow plates, m. p. 207—209° (decomp.) (Found: C, 44·1; H, 5·9; I, 27·0; N, 2·7; S, 6·4. $C_{35}H_{52}I_2N_2O_5S_2,3H_2O$ requires C, 44·1; H, 6·1; I, 26·6; N, 2·9; S, 6·7%).

(±)-N-(3-*Hydroxy-n-butyl*)*isoemetine* (IV)A.—The ethylene thioketal (0·87 g.) of ketone (X)A in ethanol (30 ml.) was shaken under hydrogen at atmospheric pressure and 50° with W4 Raney nickel catalyst (*ca.* 6 g.) for 24 hr. Removal of the catalyst, followed by evaporation, gave (±)-*N*-(3-hydroxy-n-butyl)isoemetine as a white foam (0·46 g.). The amorphous *perchlorate* had m. p. 165—175° (resinous melt) (Found: C, 51·6; H, 6·8; Cl, 9·0; N, 3·3. $C_{33}H_{50}Cl_2N_2O_{13},H_2O$ requires C, 51·4; H, 6·8; Cl, 9·2; N, 3·6%).

(±)-N-(3-*Hydroxy-n-butyl*)*emetine* (IV)B.—(*a*) The ethylene thioketal (0·87 g.) of ketone (X)B, treated with Raney nickel as above, gave (±)-*N*-(3-hydroxy-n-butyl)emetine as a white foam (0·35 g.). The *hydrochloride* separated from methanol, after addition of ether, as a white amorphous solid, m. p. 212° (decomp.) (with previous sintering) (Found: C, 58·5; H, 8·2; Cl, 10·0; N, 3·9. $C_{33}H_{50}Cl_2N_2O_5,3H_2O$ requires C, 58·3; H, 8·3; Cl, 10·4; N, 4·1%).

(*b*) The ethylene thioketal (5 g.) of ketone (X)B was heated under nitrogen at 170° for 5 hr. in diethylene glycol (50 ml.) containing potassium hydroxide (10 g.) and anhydrous hydrazine (10 ml.). The mixture was cooled, then diluted with water (1 l.), and the pH adjusted to 8·0 by concentrated hydrochloric acid. Extraction with chloroform (6 × 80 ml.), followed by removal of the solvents from the washed and dried extracts, gave a yellow foam (3·64 g.) showing a strong phenolic hydroxyl-stretching band in its infrared spectrum. This material in xylene (50 ml.) was treated at 80° with 25% methanolic potassium hydroxide (9·2 ml.) and trimethylanilinium chloride (4·7 g.). The temperature was raised as rapidly as possible to 125° by distillation of the methanol and maintained at this temperature for 0·5 hr. The basic products were extracted in 2N-hydrochloric acid (40 ml.), and the pH of the acidic solution was then adjusted to 6·2. Extraction with ether (3 × 20 ml.) removed the dimethylaniline. The aqueous acidic solution was then made strongly alkaline and extracted with ether (4 × 50 ml.). Evaporation of the ether from the washed and dried extracts gave (±)-*N*-(3-hydroxy-n-butyl)-emetine (2·14 g.) as a pale foam.

Formation of the Hydrazone of Ketone (X)B *from its Ethylene Thioketal.*—The ethylene thioketal of ketone (X)B (1 g.) was heated for 1 hr. at 135—140° in diethylene glycol (10 ml.) containing potassium hydroxide (2 g.) and 95% hydrazine (2 ml.). Thin-layer chromatography showed that the thioketal had disappeared after *ca.* 10 min. After 1 hr. the solution was cooled, diluted with water (150 ml.), and extracted with benzene (4 × 50 ml.). The extracts were washed, dried, and evaporated, to give the *hydrazone* of ketone (X)B as a pale foam (0·55 g.). (Found: N, 8·5. $C_{33}H_{48}N_4O_5$ requires N, 8·75%). No phenolic material could be detected in this product. The *trioxalate* separated from ethanol–ether as an amorphous solid, m. p. 195—200° (softening from 180°) (Found: C, 53·6; H, 6·6; N, 5·9. $C_{33}H_{48}N_4O_5,3C_2H_2O_4,H_2O$ requires C, 53·9; H, 6·5; N, 6·4%).

Wolff–Kishner Reaction with (−)-*Emetine.*—(−)-Emetine (0·5 g.) was heated under nitrogen for 5 hr. at 155° ± 1° in dry diethylene glycol (5 ml.) containing potassium hydroxide (1 g.) and anhydrous hydrazine (1 ml.). When cool, the solution was diluted with water (100 ml.) and extracted with chloroform (6 × 30 ml.). The extracted material was isolated as usual, as

a yellow foam (0·35 g.) whose infrared spectrum showed a strong phenolic hydroxyl-stretching band. Thin-layer chromatography indicated the presence of emetine and several other components. Remethylation of this material (0·26 g.) with trimethylanilinium chloride gave (−)-emetine (0·183 g.), identified by its infrared spectrum and R_F value on paper and on a chromatostrip.

It was converted into (+)-emetine hydrobromide in 95·7% yield.

(±)-*Isoemetine* (III)A.—(*a*) (±)-*N*-Benzylisoemetine (V)A (0·5 g.) in water (100 ml.) containing 2N-hydrochloric acid (12·5 ml.) was shaken under hydrogen at room temperature and pressure with 10% palladium–charcoal for 18 hr. Removal of the catalyst, followed by neutralisation, extraction with ether, and evaporation, gave (±)-isoemetine (0·25 g.) as a foam whose infrared spectrum and R_F value were identical with those of an authentic specimen.

The hydrochloride separated from methanol–ether as crystals, m. p. 254—256° (decomp.) alone or mixed with an authentic specimen (Found: C, 59·2; H, 8·0; Cl, 12·2; N, 4·4. Calc. for $C_{29}H_{42}Cl_2N_2O_4,2H_2O$: C, 59·1; H, 8·2; Cl, 12·0; N, 4·9%).

(*b*) (±)-*N*-(3-Hydroxy-n-butyl)isoemetine (IV)A (0·149 g.) in benzene (5 ml.) containing benzophenone (0·41 g.) was heated at the b. p. under nitrogen for 24 hr. with a solution of potassium (0·052 g.) in t-butyl alcohol (2 ml.). The solution was cooled, an excess of ethanolic hydrogen chloride was added, and the solvents were removed by evaporation. The residue was taken up in water (20 ml.), and neutral material removed by extraction with benzene. Basification of the aqueous phase, followed by extraction and evaporation gave (±)-isoemetine (0·108 g.) as a white foam. The hydrochloride, m. p. 257—259° (decomp.), was identical with an authentic specimen.

(±)-*Emetine* (III)B.—(*a*) (±)-*N*-Benzylemetine (V)B (0·29 g.) in water (25 ml.) containing 2N-hydrochloric acid was shaken under hydrogen at room temperature and pressure with 10% palladium–charcoal (0·1 g.) for 5·5 hr., a second portion (0·1 g.) of catalyst being added after 2 hr. Removal of the catalyst, neutralisation, extraction with ether, and evaporation gave (±)-emetine (0·18 g.) as a pale foam. The *hydrobromide* separated from methanol as white crystals (0·13 g.), m. p. 228—232° (decomp.), whose infrared spectrum (in $CHBr_3$) and R_F value were identical with those of (+)-emetine hydrobromide from the natural alkaloid (Found: C, 50·1; H, 6·9; Br, 22·3; N, 4·1. Calc. for $C_{29}H_{42}Br_2N_2O_4,3H_2O$: C, 50·0; H, 6·9; Br, 22·9; N, 4·0%).

(*b*) (±)-*N*-(3-Hydroxy-n-butyl)emetine (IV)B (1·23 g.) was oxidised by the Oppenauer method described above. (±)-Emetine was isolated as a white foam (0·96 g.). The hydrobromide (0·67 g.), m. p. 230—232° (decomp.), separated from methanol.

Resolution of (±)-*Emetine.*—(−)-*Emetine.*[15] (±)-Emetine (1·32 g.) in methanol (10 ml.) was treated with *N*-acetyl-L-leucine (1 g.) in methanol (2 ml.), and ether (70 ml.) was added. The *N*-acetyl-L-leucine salt (1·04 g.) of (−)-emetine was collected after 1·5 hr. as white crystals, m. p. 163—165°, $[\alpha]_D^{22}$ −14·1° (*c* 6 in $CHCl_3$) {lit.,[15] m. p. 164—165°, $[\alpha]_D^{25}$ −17·2° (*c* 1 in $CHCl_3$)}. The corresponding salt of the natural alkaloid had m. p. 164—165° and $[\alpha]_D^{22}$ −13·9°.

Regeneration of the base with alkali and extraction with ether gave (−)-emetine (0·52 g.), $[\alpha]_D^{22}$ −47° ± 1° (*c* 2 in $CHCl_3$).

The hydrobromide, m. p. 232—234°, $[\alpha]_D^{24}$ +40·6° ± 1° (*c* 1 in $CHCl_3$), crystallised from methanol and was identical with the hydrobromide of the natural alkaloid.

(+)-*Emetine.* The mother-liquors after removal of the *N*-acetyl-L-leucine salt of (−)-emetine were evaporated to dryness, and the crude (+)-emetine was recovered by basification and extraction as usual. The crude (+)-base in methanol (2 ml.) was then treated with *N*-acetyl-D-leucine (0·54 g.) in methanol (1·5 ml.), and ether (40 ml.) was added. The N-*acetyl*-D-*leucine salt* of (+)-emetine rapidly separated as needles (1 g.), m. p. 164·5—166°, $[\alpha]_D^{21}$ +13·5° (*c* 6 in $CHCl_3$). Recrystallisation from methanol (5 ml.) and ether (50 ml.) gave the pure salt, m. p. 164—165°, $[\alpha]_D^{20}$ +14·3° (Found: C, 62·05; H, 8·6; N, 5·8. $C_{29}H_{40}N_2O_4,C_8H_5NO_3,3·5H_2O$ requires C, 62·0; H, 8·7; N, 5·9%).

Regeneration of the base from this salt gave (+)-emetine (0·53 g.), $[\alpha]_D^{24}$ +46·5° ± 1° (*c* 2 in $CHCl_3$).

The hydrobromide, m. p. 232—233°, $[\alpha]_D^{22}$ −40·6° ± 1° (*c* 1 in $CHCl_3$), crystallised from methanol (Found: C, 51·2; H, 6·7; Br, 23·6; N, 4·1. Calc. for $C_{29}H_{42}Br_2N_2O_4,2H_2O$: C, 51·3; H, 6·8; Br, 23·6; N, 4·1%).

(−)-N-(3-*Oxo-n-butyl*)*emetine* (VI)B.—(−)-Emetine (6·4 g.) in benzene (180 ml.) containing methyl vinyl ketone (3·6 ml.) was kept overnight at room temperature and the solvent then

removed *in vacuo*. The residual foam was dissolved in dilute hydrochloric acid, and an excess of aqueous sodium carbonate solution added. (−)-N-(3-*Oxo-n-butyl*)*emetine* was precipitated as a white amorphous solid (6·53 g.), m. p. 68—71° (with previous softening), $[\alpha]_D^{21}$ −46° (*c* 1 in $CHCl_3$). The hydrochloride separated from ethanol–ether as prisms, showing a double m. p., 217—220° and 245—250° (decomp.) (Found: C, 59·7; H, 8·1; Cl, 10·2; N, 4·1. $C_{33}H_{48}Cl_2N_2O_5,2H_2O$ requires C, 60·0; H, 8·0; Cl, 10·8; N, 4·2%).

(−)-N-(3-*Hydroxy-n-butyl*)*emetine* (IV)B.—(−)-*N*-(3-Oxo-n-butyl)emetine (2 g.) in methanol (40 ml.) was kept at room temperature with sodium borohydride (0·81 g.) in water (8 ml.) for 3 hr., then an excess of hydrochloric acid was added, and the organic solvents were evaporated. Dilution with water and neutralisation with sodium carbonate gave (−)-N-(3-*hydroxy-n-butyl*)*emetine* as a white amorphous solid (1·97 g.), m. p. 74—78° (with previous softening), $[\alpha]_D^{21}$ −37° (*c* 1 in $CHCl_3$). The *hydrochloride* was obtained from ether as a white amorphous powder, m. p. 190—196° (resinous melt decomposing at 215°) (Found: C, 58·6; H, 8·4; Cl, 10·4; N, 3·9. $C_{33}H_{50}Cl_2N_2O_5,3H_2O$ requires C, 58·3; H, 8·3; Cl, 10·4; N, 4·1%).

(−)-N-(3-*Oxo-n-butyl*)*cephaeline* (XIII; R = CH_2·CH_2Ac).—(−)-Cephaeline (XIII; R = H) (2 g.) and methyl vinyl ketone (1·2 ml.) in benzene (60 ml.) were kept at room temperature for 3 hr. The solvent was removed *in vacuo* and the residual foam dissolved in water (45 ml.) containing 2N-hydrochloric acid (9 ml.). Basification with 2N-sodium carbonate solution gave (−)-*N*-(3-oxo-n-butyl)cephaeline (XIII; R = CH_2·CH_2Ac) (2·14 g.) as an amorphous powder, m. p. 102° (softening from 85°), $[\alpha]_D^{21}$ −41·4° (*c* 1 in $CHCl_3$). The *hydrochloride* separated from ethanol–ether as an amorphous solid, m. p. 245—250° (resinous melt) (Found: C, 57·9; H, 7·8; N, 4·4; Cl, 10·4. $C_{32}H_{46}Cl_2N_2O_5,3H_2O$ requires C, 57·9; H, 7·9; N, 4·2; Cl, 10·7%).

(−)-N-(3-*Hydroxy-n-butyl*)*cephaeline* (XIII; R = CH_2·CH_2·CHMe·OH).—The ketone (XIII; R = CH_2·CH_2Ac) (1 g.) was reduced with sodium borohydride in aqueous methanol as above. (−)-*N*-(3-Hydroxy-n-butyl)cephaeline (0·86 g.) was obtained as an amorphous solid, m. p. 98—105° (with previous softening), $[\alpha]_D^{21}$ −28·8° (*c* 1 in $CHCl_3$). The *hydrochloride* was precipitated from ethanol–ether as an amorphous powder, m. p. 215° (decomp.) (Found: C, 57·2; H, 8·4; Cl, 10·2; N, 4·2. $C_{32}H_{48}Cl_2N_2O_5,3·5H_2O$ requires C, 57·0; H, 8·2; Cl, 10·5; N, 4·15%).

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