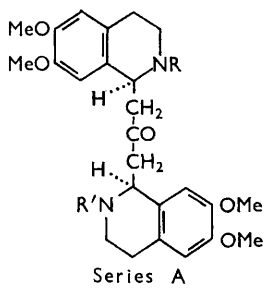
474. *Emetine and Related Compounds. Part II.*[1] *The Stereospecific Synthesis of* (±)-2,3-*Dehydroemetine and* (±)-2,3-*Dehydroisoemetine.*

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

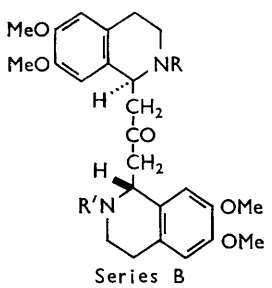
The diastereoisomers of the ketones (XXII) and (XXIII) have been synthesised stereospecifically and their configurations assigned. The isomers of ketone (XXIII) have been converted severally into (±)-2,3-dehydroemetine and (±)-2,3-dehydroisoemetine.

In Part I [1] we described the synthesis of the tetrahydroisoquinolyl ketones (I)—(IV),* each in both diastereoisomeric forms, A and B. This paper describes attempts to complete the ring skeleton of emetine (VII) from these intermediates.

Preliminary efforts to prepare condensation products of the type (VIII), with the

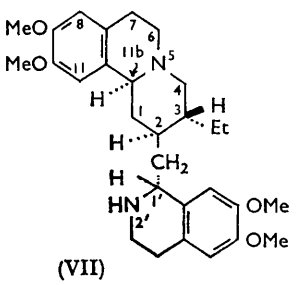


Series A

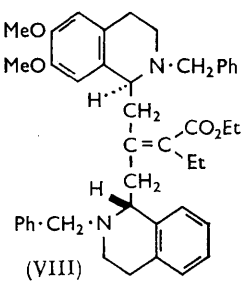


Series B

(I) R = R′ = H
(II) R = H, R′ = CH_2Ph
(III) R = R′ = CH_2Ph
(IV) R = R′ = $COPr^n$
(V) R = R′ = $CH_2 \cdot CH_2Ac$
(VI) R = $CH_2 \cdot CH_2Ac$, R′ = CH_2Ph



(VII)



(VIII)

$[Ph_3P \cdot CHR \cdot CO_2Et]^+ \quad Br^-$

(IX)

object of subsequent ring closure on to the nitrogen atom, were frustrated by the low reactivity of the carbonyl group to nucleophilic reagents. For instance, attempted Reformatsky reactions between ethyl bromoacetate or ethyl α-bromobutyrate and the

* Throughout this paper, where optical enantiomorphs are possible only one is shown.

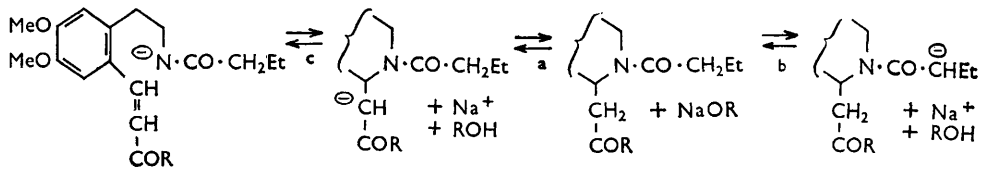
[1] Part I, Chapman, Holton, Ritchie, Walker, Webb, and Whiting, preceding paper.

ketone (III)B gave back the latter unchanged, as the only identifiable product, even when the preformed zinc complex of ethyl bromoacetate [2] was used to avoid difficulties associated with the use of basic ketones in this reaction.[3]

The Wittig reagent [4] (IX; R = H) from ethyl bromoacetate failed to react with the dihenzyl ketone (III)B under conditions that furnished good yields of ethyl cinnamate [5] and cyclohexylidene acetate from benzaldehyde and cyclohexanone, respectively. Both cyclohexanone and the ketone (III)B were unaffected by the Wittig reagent (IX; R = Et) from ethyl α-bromobutyrate. Attempted condensations of this ketone (III)B with ethyl cyanoacetate (Knoevenagel), with ethyl α-chloro- and α-bromo-acetate (Darzens),[6,7] or with sodium acetylide in liquid ammonia, were unsuccessful, recoveries of starting material being high.

An alternative route for construction of the quinolizidine ring-system lies in the intramolecular cyclisation of compounds of the type (IV) and (V), in which the ring formation might act as a driving force for the attack on the carbonyl group.

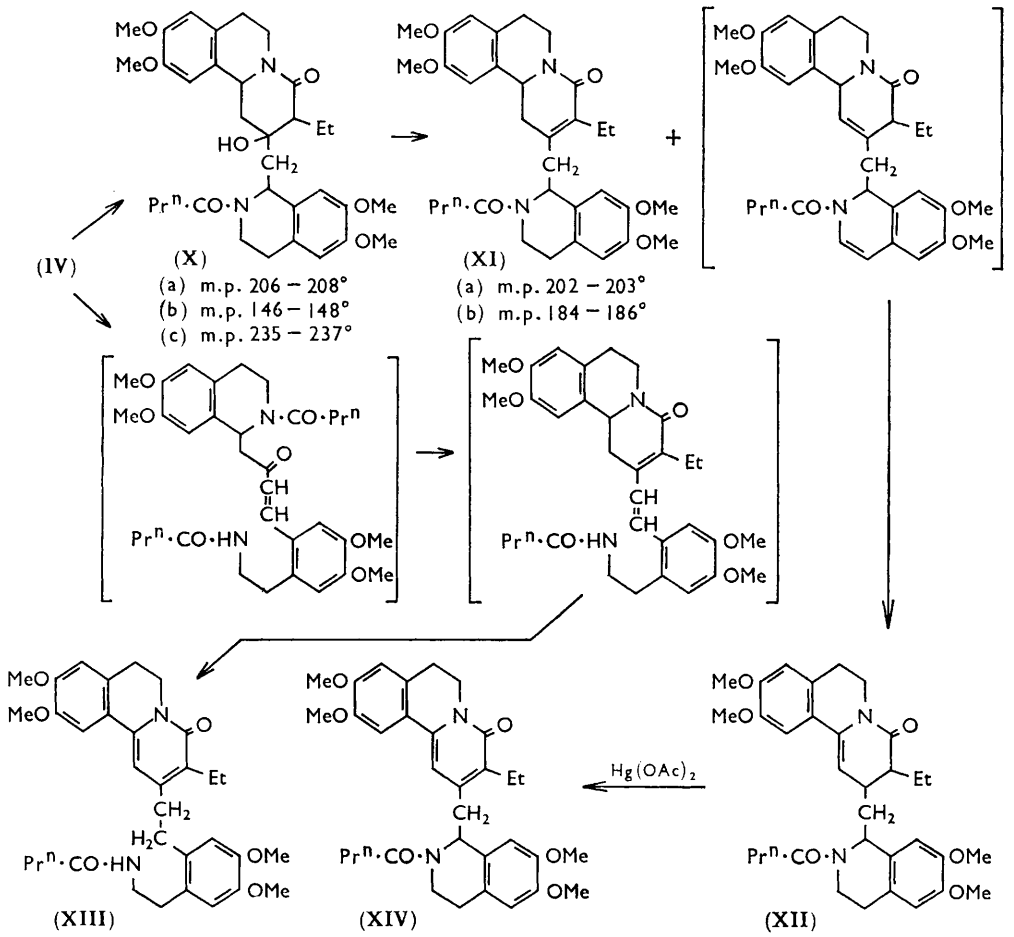
Alkaline condensing agents that caused irreversible carbanion formation, *e.g.*, triphenylmethylsodium, sodium hydride, and sodamide in benzene, gave no cyclisation products



(IV)

from the dibutyryl ketone (IV), but brought about inversion of both A and B isomers into an equilibrium mixture of the two. However, heating with alkali-metal alkoxides in the presence of the corresponding alcohol effected the desired cyclisation, although this also was preceded by inversion and equilibration. Clearly the preferred site of carbanion formation is the methylene group adjacent to the ketonic carbonyl group. The desired carbanion, adjoining the carbonyl group of the amide, will exist only when anion formation is reversible, since $k(a) \gg k(b)$. Step (c) represents a possible course for the equilibration of the diastereoisomeric ketones. The vigorous conditions necessary to effect cyclisation resulted in a multiplicity of products. These were separated by chromatography on neutral alumina and are rationalised in the annexed chart. Three alcohols (X), two αβ-unsaturated lactams (XI), and one γδ-unsaturated lactam (XII) were characterised. Their ultraviolet and infrared spectra were in agreement with the assigned structures. As equilibration preceded cyclisation, no conclusions on their stereochemistry could be reached. The alcohols (Xa and b) were dehydrated to the corresponding αβ-unsaturated lactams (XIa and b). The structure of the unexpected pyridone (XIII) is deduced from the ultraviolet spectrum ($\lambda_{max.}$ 268, 347 mμ; ε 11,000, 22,000) and the presence in the infrared spectrum of absorption bands at 3420, 1663, and 1630 cm.$^{-1}$ for >NH, NH·CO and >N·CO, respectively. The pyridone (XIV), prepared by oxidation of the γδ-unsaturated lactam with mercuric acetate, had an identical ultraviolet spectrum, but the bands for >NH and NH·CO were absent from the infrared spectrum. One suggested mechanism for the formation of the pyridone (XIII) is indicated in the chart. This proliferation of products and the loss of stereospecificity in the cyclisation made the dibutyryl ketone (IV) unsuitable for the synthesis of emetine.

[2] Evans, *Diss. Abs.*, 1958, **18**, 1252.
[3] Grob and Brenneisen, *Helv. Chim. Acta*, 1958, **41**, 1184.
[4] Wittig and Schöllkopf, *Chem. Ber.*, 1954, **87**, 1318.
[5] Wittig and Haag, *Chem. Ber.*, 1955, **88**, 1654.
[6] Newman, " Organic Reactions," Wiley and Sons, Inc., New York, 1949, Vol. V, p. 413.
[7] Johnson, Belew, Chinn, and Hunt, *J. Amer. Chem. Soc.*, 1953, **75**, 4995.

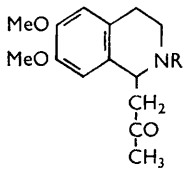


In compounds of the type (V), the $-CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_3$ side chain should readily give a reactive anion at the methylene group adjacent to its carbonyl group and thus offer the possibility of cyclisation under milder conditions. The diastereoisomeric ketones (I)A and (I)B combined rapidly with methyl vinyl ketone to give the adducts (V)A and (V)B, respectively, isolated as their crystalline hydrochlorides. Of the free bases, only (V)A was obtained as a solid. The bases underwent stereochemical inversion in solution to an equilibrium mixture containing *ca.* 75% of A. Because of this inversion, the Michael reaction from either of the pure isomers of (I) could give some of the adduct (V) of the second isomer. Though equilibration of (V)A was rapid, isomer B required *ca.* 24 hr. to attain equilibrium. When Michael condensations of this duration were performed, a mixture of the adducts (V)A (*ca.* 65%) and (V)B (*ca.* 15%) was obtained, regardless of the isomer of (I) employed. The hydrochlorides did not undergo equilibration.

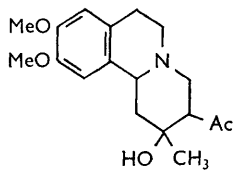
The diastereoisomeric bases (V) cyclised rapidly at room temperature when one mol. of sodium methoxide was used in benzene–methanol, giving, stereospecifically, the alcohols (XIX)A and (XIX)B in 50—60% yield. The purity of these compounds (and of the other bases described in this paper) was established by paper chromatography.[8] Nuclear magnetic resonance measurements clearly showed the presence of two $CO{\cdot}CH_3$ groups, thus eliminating the alternative structure (XXI). In cyclisations of the triketone (V)A

[8] Barash, Osbond, and Wickens, *J.*, 1959, 3530.

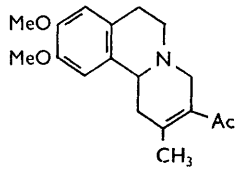
with sodium hydride in benzene *ca.* 10% of a second isomer of (XIX)A resulted, and the yield of the isomer obtained previously was reduced to *ca.* 30%. The alcohols were dehydrated in high yield, without inversion, at 100° with 12N-sulphuric acid or concentrated hydrochloric acid, to the corresponding diastereoisomeric conjugated ketones (XXII)A and B. Again the structure of the latter was confirmed by nuclear magnetic resonance spectroscopy.



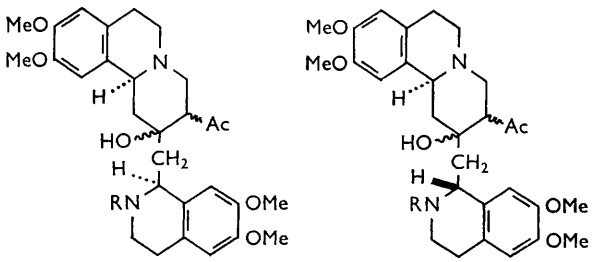
(XV) R = H
(XVI) R = $CH_2 \cdot CH_2Ac$



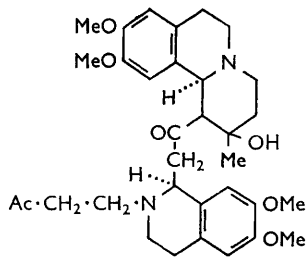
(XVII)



(XVIII)

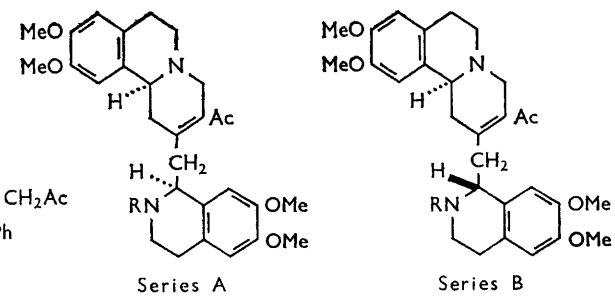


(XIX) R = $CH_2 \cdot CH_2Ac$ (XX) R = CH_2Ph



(XXI)

By a similar sequence the methyl ketone (XV) was converted, through the adduct (XVI), into the tricyclic keto-alcohol (XVII). Cyclisation was effected at room temperature with concentrated hydrochloric acid or with ethanolic solutions of sodium methoxide or hydrogen chloride. Dehydration occurred smoothly when these solutions were heated, and the conjugated tricyclic ketone (XVIII) could be obtained directly from the bicyclic ketone (XV) in high yield. Acid-catalysed cyclisations of this type failed with ketone (V), which was recovered unchanged.



(XXII) R = $CH_2 \cdot CH_2Ac$
(XXIII) R = CH_2Ph

The unsymmetrical *N*-benzyl ketones (II)A and B reacted with methyl vinyl ketone to produce, stereospecifically, the adducts (VI)A and B, which cyclised in good yield, with alkali, to single crystalline isomers of the alcohols (XX)A and B. These, on dehydration with mineral acid, gave the two pure diastereoisomeric forms of the conjugated ketones (XXIII)A and B, respectively.

The *N*-3-oxo-n-butyl compound (XIX)B could be converted in high yield into the

corresponding *N*-benzyl compound (XX)B by formation of the quaternary salt (XXVI) with benzyl bromide and a mild Hofmann degradation.

The spectral properties of the conjugated bases (XVIII), (XXII), and (XXIII) are summarised in Table 1. In the tricyclic ketone (XVIII) the wavelength of the ultraviolet absorption maximum of the $>C{:}\overset{|}{C}\cdot CO\cdot CH_3$ chromophore showed a hypsochromic shift from the calculated value of 247 mμ, as a result of transannular interaction with the nitrogen atom.[9] In contrast, the pentacyclic bases in ethanol showed only enhanced

TABLE 1.

Light absorption of the conjugated ketones.

Base	Δε* (EtOH)	ν(C=O) (cm.$^{-1}$)	Salt	Δε* (EtOH)	ν(C=O) (cm.$^{-1}$)
(XVIII)	10,000	1678	HCl	9000	1675
(XXII)A	5000	1680	HCl	5100	1692
	5000 †	—	HI	6600	1690
(XXII)B	5000	1680	—	—	—
	4000 †	—	HCl	4300	—
(XXIII)A	4900	1680	HI	4500	1692
	4700 †	—	HBr	5000	1694
(XXIII)B	5000	1680	HI	4500	1692
	6000 †	—	HCl	5000	1694

* This figure is the difference between the ε value at 232 mμ of the conjugated ketone or its salt and that of the corresponding alcohol or its salt before dehydration. † The solvent was 0·001N-ethanolic hydrogen chloride.

rising end-absorption, although maxima at 232 mμ were observed in approximately 0·001N-ethanolic hydrogen chloride. Measurements indicated that the absorbing species in the acidic ethanol were still the free bases and not the hydrochlorides, suggesting that, in weakly acidic solution, the bases were resistant to protonation because of steric hindrance to solvation of the cation.[10] The absorption intensities of the pentacyclic compounds and of their salts were approximately half that of the tricyclic ketone (XVIII). In addition the frequency of the carbonyl stretching band in the salts was significantly higher than in the free bases, a feature absent from the spectrum of compound (XVIII). These effects are probably caused by the steric interaction of the carbonyl group with the tetrahydroisoquinoline system, with resulting distortion of the former from coplanarity with the double bond.[11,12]

Complete steric inhibition of conjugation was shown in the semicarbazone of the diketone (XXII)A, whose ultraviolet spectrum was identical with that of the semicarbazone of the saturated ketone (XIX)A. Even the semicarbazone of the unsaturated tricyclic compound (XVIII) was not entirely free from strain, since, although the expected bathochromic shift of 20—25 mμ from the absorption maximum (226 mμ) of the semicarbazone of the saturated compound (XVII) was shown, the absorption intensity was reduced and enhancement at the lower frequency was still apparent (Table 2).

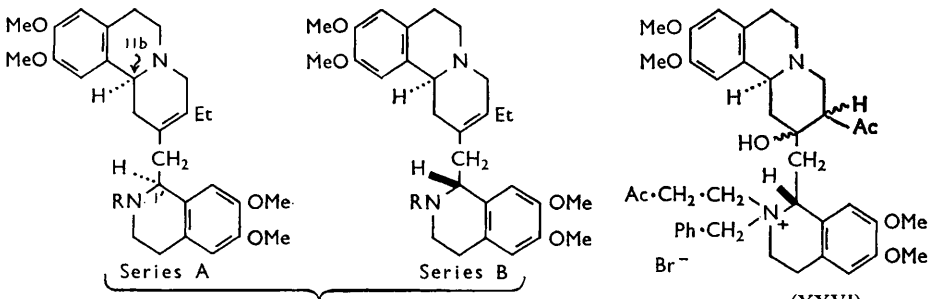
TABLE 2.

Ultraviolet absorption of semicarbazones.

	(XVII)	(XVIII)	(XIX)A	(XXII)A
Δε* at 226—233 mμ (max.)	25,400	8600	24,000	24,700
Δε* at 250 mμ (inflection)	—	13,000	—	—

* This is the difference in the ε values of the semicarbazone and the ketone.

[9] Georgian, *Chem. and Ind.*, 1954, 930; 1957, 1480.
[10] Robinson and Smith, *J.*, 1960, 4574.
[11] Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890; Braude and Timmons, *ibid.*, 1955, 3766.
[12] Turner and Voitle, *J. Amer. Chem. Soc.*, 1951, **73**, 1403.



(XXIV) R = CH_2Ph (XXV) R = H (XXVI)

The carbonyl group in the *N*-benzyl ketones (XXIII)A and B was eliminated by desulphurisation of the ethylene thioketal with sodium in liquid ammonia,[13] to give the corresponding methylene compounds (XXIV)A and B, respectively, and the benzyl groups were finally removed by catalytic hydrogenolysis with palladium. (±)-2,3-Dehydroisoemetine (XXV)A and (±)-2,3-dehydroemetine (XXV)B were obtained stereospecifically from the respective diastereoisomers of (XXIV). Brossi and his co-workers [14] separated (±)-2,3-dehydroemetine and (±)-2,3-dehydroisoemetine from mixtures of the two compounds prepared by a non-stereospecific synthesis, and showed that the former had an amœbicidal activity *in vivo* in rats similar to that of (—)-emetine. The infrared and ultraviolet spectra and the R_F values of the hydrochlorides of our compounds were identical with those recorded by Brossi *et al.* Our stereospecific synthesis of each isomer from compounds of known configuration affords a direct confirmation of their relative stereochemistry at $C_{(1')}$ and $C_{(11b)}$.

In tests against *Entamoeba histolytica* in weanling rate by Jones's method,[15] all the compounds described in the present paper were inactive, with the exception of (±)-2,3-dehydroemetine (XXV)B. This showed an activity approximately equal to that of (—)-emetine (cf. Brossi *et al.*).

Experimental

Nucleophilic Attack on the Dibenzyl Ketone (III)B.—(a) *Reformatsky reaction.* Ethyl bromoacetate (1·05 ml.) in benzene–ether (1 : 1) (10 ml.) was added to a refluxing suspension of activated zinc wool (1·5 g.) in dried benzene–ether (1 : 1) (20 ml.), followed by further portions of zinc (2 × 1 g.) after 1·5 hr. and 3 hr. After 4 hr., ketone (III)B (3 g.) in benzene–ether (20 ml.) was added and the reaction was continued at the b. p. for 4 hr. and then at room temperature overnight. The product was isolated by acidification with acetic acid, extraction with chloroform, and removal of zinc salts by washing with water. Evaporation of the solvent gave a dark gum which was absorbed on neutral alumina. The fraction (1 g.) eluted with chloroform–benzene (1 : 1) was converted into a picrate, m. p. 91—93° alone or mixed with the picrate of (III)B.

(b) *Wittig reaction.* Triphenylphosphine (2·62 g.), ethyl α-bromobutyrate (1·48 ml.), ethanol (2 ml.), and benzene (13 ml.) were heated under reflux for 2 days. Removal of the solvent *in vacuo* and trituration with ether gave (*1-ethoxycarbonylpropyl*)*triphenylphosphonium bromide* (IX; R = Et) (2·33 g.), m. p. 146—147° (decomp.). Several recrystallisations from ethyl acetate–ethanol–ether raised the m. p. to 158° (decomp.) (Found: C, 62·5; H, 5·9; Br, 17·3; P, 7·1. $C_{24}H_{26}BrO_2P$ requires C, 63·0; H, 5·7; Br, 17·5; P, 6·8%).

This salt (0·74 g.), ketone (III)B (1 g.), and 1·41N-ethanolic sodium ethoxide (1·14 ml.) were kept in benzene (15 ml.) for 5 days at room temperature and then refluxed for 3 hr. Dilution with benzene, followed by washing with water and evaporation of the solvent, gave a

[13] Ireland, Wrigley, and Young, *J. Amer. Chem. Soc.*, 1958, **80**, 4604.
[14] Brossi, Baumann, Chopard-dit-Jean, Würsch, Schneider, and Schnider, *Helv. Chim. Acta*, 1959 **42**, 772.
[15] Jones, *Ann. Trop. Med. Parasitol.*, 1956, **40**, 130.

yellow gum. Elution of this from neutral alumina with benzene–ethyl acetate gave unchanged material (III)B (0·73 g.), identified as the picrate, m. p. 87—88°.

(c) *Darzens reaction.* Ethyl chloroacetate (0·396 g.) and ketone (III)B (1 g.) were left at room temperature for 18 hr. in benzene (5 ml.) containing potassium t-butoxide in t-butyl alcohol (0·32N; 10·75 ml.). The solution was diluted with chloroform and the extract washed several times with water. The residue, after evaporation of the solvent, crystallised from ethanol to give unchanged material (III)B (0·7 g.), m. p. 126—128°.

Cyclisation of the Dibutyryl Ketone (IV).—Ketone (IV)B (30 g.) in dried benzene (500 ml.) containing sodium ethoxide [from sodium (6·25 g.) in ethanol (100 ml.)] was heated at the b. p. for 5 hr. The cooled solution was washed with water, dried, and evaporated. The residue was heated in boiling ethanol (300 ml.) with Girard's reagent P (30 g.) and glacial acetic acid (30 ml.) for 1·5 hr., and the solution then concentrated to half its volume by evaporation *in vacuo*. 2N-Sodium hydrogen carbonate (500 ml.) was added and the mixture extracted with benzene (3 × 350 ml.). The benzene solution was washed with water, dried, and evaporated to a yellow, non-ketonic foam (22 g.). Acidification of the aqueous phase with concentrated hydrochloric acid and extraction with chloroform gave a mixture (5·9 g.) of the ketones (IV)A and B. The non-ketonic product was absorbed on alumina (2·5 kg.), deactivated by the addition of 10% aqueous acetic acid (125 ml.) to a stirred suspension in benzene. The column was developed with benzene and eluted with ethyl acetate–benzene mixtures. The following results were recorded.

(i) Fractions 1—90 eluted with 1 : 10 ethyl acetate–benzene. Evaporation to dryness and trituration with ether gave *isomer* (a) (3·4 g.) of 2-(2-*n-butyryl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*methyl*-3-*ethyl*-4,6,7,11b-*tetrahydro*-9,10-*dimethoxy*-4-*oxo*-1H-*benzo*[a]*quinolizine* (XI), m. p. 185—190°. Recrystallisation from ethanol raised the m. p. to 202—203° (Found: C, 70·4; H, 7·7; N, 5·0. $C_{33}H_{42}N_2O_6$ requires C, 70·4; H, 7·5; N, 5·0%), $\lambda_{max.}$ (in EtOH) 258, 281 mμ (ε 5700, 9300).

From the ethereal mother-liquor the γδ-unsaturated lactam (XII) (0·56 g.) separated gradually. Recrystallisation from ethyl acetate gave pure 2-(2-*n-butyryl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolylmethyl*)-3-*ethyl*-3,4,6,7-*tetrahydro*-9,10-*dimethoxy*-4-*oxo*-2H-*benzo*[a]*quinolizine*, m. p. 169—171°, $\lambda_{max.}$ (in EtOH) 250, 282, and 310 mμ (ε 16,600, 12,600, and 9500) (Found: C, 70·4; H, 7·3; N, 5·2. $C_{33}H_{42}N_2O_6$ requires C, 70·4; H, 7·5; N, 5·0%).

(ii) Fractions 90—120, eluted with 1 : 5 ethyl acetate–benzene. Evaporation of the solvent and trituration of the residue with ethyl acetate–ether gave *isomer* (b) of the alcohol (X). Recrystallisation from ether afforded pure 2-(2-*n-butyryl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolylmethyl*)-3-*ethyl*-2,3,4,6,7,11b-*hexahydro*-2-*hydroxy*-9,10-*dimethoxy*-4-*oxo*-1H-*benzo*[a]-*quinolizine*, m. p. 146—148°, $\lambda_{max.}$ (in EtOH) 282 mμ (ε 8300) (Found: C, 68·4; H, 7·6; N, 4·7. $C_{33}H_{44}N_2O_7$ requires C, 68·3; H, 7·6; N, 4·8%).

(iii) Fractions 120—150, eluted with 2 : 5 ethyl acetate–benzene. The material contained in these fractions crystallised from ethanol to give *isomer* (a) of the alcohol (X) (1·2 g.), m. p. 202—204°. Recrystallisation from ethanol gave the pure alcohol, m. p. 206—208°, $\lambda_{max.}$ (in EtOH) 283 mμ (ε 8000) (Found: C, 68·5; H, 7·7; N, 4·8%).

From the mother-liquor, *isomer* (c) (70 mg.) of the alcohol (X) separated. This had m. p. 235—237° after crystallisation from ethanol–chloroform, and $\lambda_{max.}$ (in EtOH) 282 mμ (ε 8100) (Found: C, 67·0; H, 7·7; N, 4·4. $C_{33}H_{44}N_2O_7,C_2H_5{\cdot}OH$ requires C, 67·0; H, 8·0; N, 4·5%).

(iv) Fractions eluted with ethyl acetate. The material present in these fractions crystallised from ethyl acetate to give the pyridone (XIII). Recrystallisation from the same solvent afforded pure 2-(2′-*n-butyrylaminoethyl*-4,5-*dimethoxyphenethyl*)-3-*ethyl*-6,7-*dihydro*-9,10-*dimethoxy*-4-*oxo*-4H-*benzo*[a]*quinolizine*, m. p. 174—175°, $\lambda_{max.}$ (in EtOH) 268, 347 mμ (ε 11,000, 22,000) (Found: C, 70·3; H, 7·5; N, 5·0. $C_{33}H_{42}N_2O_6$ requires C, 70·4; H, 7·5; N, 5·0%).

Dehydration of the Alcohols (X).—*Isomer* (a). The alcohol (0·1 g.), pyridine (1 ml.), and phosphorus oxychloride (0·2 ml.) were heated under reflux for 3 hr. The solution was poured on ice, and the product was isolated by extraction with benzene, washing with water, 2N-hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and evaporation of the solvent. Trituration of the residual oil with ether gave isomer (a) (30 mg.) of the αβ-unsaturated lactam (XI), m. p. 202—203°.

Isomer (b). The alcohol (88 mg.) in pyridine (2 ml.) and thionyl chloride (0·1 ml.) was left at room temperature for 0·5 hr. and then worked up as above. Isomer (b) of the lactam (XI) separated from ether as scaly crystals (24 mg.), m. p. 184—186°, $\lambda_{max.}$ (in EtOH) 257, 281 mμ

(ε 6200, 9400). The presence of this material in the cyclisation products of ketone (IV) was indicated by infrared spectroscopy.

2-(2-*n*-*Butyryl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolylmethyl*)-3-*ethyl*-6,7-*dihydro*-9,10-*dimethoxy*-4-*oxo*-4H-*benzo*[a]*quinolizine* (XIV).—The γδ-unsaturated lactam (XII) (0·11 g.) and mercuric acetate (0·25 g.) were heated in 95% acetic acid at 100° for 3 hr., then the mixture was cooled, the suspended solid removed, and the filtrate evaporated to dryness. The residue, in chloroform, was washed with 5% acetic acid, water, dilute sodium hydroxide solution, and water again. Evaporation gave a yellow solid which was absorbed on neutral alumina and eluted with chloroform. Trituration of the crude oil (95 mg.) with ether yielded a solid that crystallised from ethyl acetate–ether to give the *pyridone* (XIV) (12 mg.), m. p. 169—172°, $\lambda_{max.}$ (in EtOH) 270, 347 mμ (ε 11,200, 21,600) (Found: C, 70·3; H, 7·3; N, 4·8. $C_{33}H_{40}N_2O_6$ requires C, 70·7; H, 7·2; N, 5·0%).

1,3-*Bis*-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-3′-*oxo*-*n*-*butyl*-1-*isoquinolyl*)*acetone* (V).—*Isomer* A. (*a*) Ketone (I)A (1 g.) in methylene chloride (25 ml.) was kept at room temperature for 2 hr. with methyl vinyl ketone (0·35 g.), and the solvent was then evaporated *in vacuo*. The residue was taken up in ethanol, and ethanolic hydrogen chloride added. The white precipitate was filtered off after 15 min., to give the *hydrochloride* of the *adduct* (V)A (0·95 g.), m. p. 188—191° (decomp.) (Found: C, 57·7; H, 7·1; Cl, 9·9; N, 3·9. $C_{33}H_{46}Cl_2N_2O_7,2H_2O$ requires C, 57·5; H, 7·3; Cl, 10·3; N, 4·1%).

Concentration of the mother-liquor *in vacuo* at room temperature gave a fine white precipitate of the hydrochloride of the isomer (V)B (0·21 g.), m. p. 120—124° (decomp.).

(*b*) Ketone (I)B (1 g.), in methylene chloride (25 ml.), was allowed to react for 24 hr. with methyl vinyl ketone (1·05 g.) and worked up as above, to give the hydrochloride (0·9 g.), m. p. 188—191° (decomp.), of (V)A and the hydrochloride (0·31 g.), m. p. 122—125° (decomp.), of (V)B.

The free *base* (V)A was obtained from the hydrochloride (0·5 g.) by basification and extraction into benzene. After the benzene extract had been washed with water and evaporated, the residue was triturated with ether to give a crystalline precipitate (0·155 g.), m. p. 101—103°. Two crystallisations from ether afforded material, m. p. 105—107° (Found: C, 67·8; H, 7·6; N, 5·1. $C_{33}H_{44}N_2O_7$ requires C, 68·2; H, 7·6; N, 4·8%).

Isomer B. Ketone (I)B (20 g.) in methylene chloride (250 ml.), with methyl vinyl ketone (20 ml.) for 2 hr. at room temperature, gave the *hydrochloride* (5·3 g.), m. p. 187—188° (decomp.), of (V)A, and that (20·6 g.), m. p. 121—123° (decomp.), of (V)B when worked up as above (Found: C, 53·4; H, 7·4; Cl, 10·2; N, 3·6. $C_{33}H_{46}Cl_2N_2O_7,5H_2O$ requires C, 53·3; H, 7·6; Cl, 9·5; N, 3·8%).

Equilibration of the Isomers (V)A *and* (V)B.—The hydrochloride (2 g.) of each isomer was neutralised and the base extracted into benzene (80 ml.). The dried solution was kept at room temperature, aliquot parts being removed at intervals and re-converted into the hydrochlorides as described above. The results are in the annexed Tables (a) and (b).

(a) *Isomer* (V)A.

Time	(V)A, HCl		(V)B, HCl	
(hr.)	g.	m. p. (decomp.)	g.	m. p. (decomp.)
0·5	0·33	186—188°	0·11	127—132°
3·5	0·4	187—189	0·09	126—129
6·5	0·31	185—187	0·05	125—128
22	0·31	186—188	0·06	125—129

(b) *Isomer* (V)B.

Time	First crop, hydrochloride			(V)B, HCl	
(hr.)	g.	m. p. (decomp.)	Compn.*	g.	m. p. (decomp.)
0·5	0·24	121—123°	>90% B	0·11	123—127°
3·5	0·25	125—180	50% A	0·16	125—129
6·5	0·25	176—182	80% A	0·12	126—129
19	0·21	186—187	A	0·12	122—125

* The composition of this material was determined by infrared analysis.

Similar results were obtained when methylene chloride was used as the solvent.

3-*Acetyl*-2,3,4,6,7,11b-*hexahydro*-2-*hydroxy*-9,10-*dimethoxy*-2-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-3′-*oxo*-*n*-*butyl*-1-*isoquinolylmethyl*)-1H-*benzo*[a]*quinolizine* (XIX).—*Isomer* A. (*a*)

Cyclisation with sodium methoxide. The hydrochloride (1·5 g.) of base (V)A was neutralised and the base extracted into benzene (45 ml.). Sodium methoxide (0·15 g.) in methanol (3 ml.) and ethanol (3 ml.) was added and the solution stirred at room temperature for 5 min. The alkali was removed by washing with water, and the solvent evaporated. Trituration of the residue with ethanol gave the crystalline free *base* (XIX)A (0·78 g.), m. p. 158—159° (Found: C, 68·1; H, 7·7; N, 5·0. $C_{33}H_{44}N_2O_7$ requires C, 68·3; H, 7·6; N, 4·8%). The *hydrochloride* crystallised from ethanol as prisms, m. p. 200° (decomp.) (Found: C, 58·8; H, 7·3; Cl, 10·4; N, 4·3. $C_{33}H_{46}Cl_2N_2O_7,H_2O$ requires C, 59·0; H, 7·2; Cl, 10·6; N, 4·0%). The *perchlorate*, after being leached with hot methanol, had m. p. 219—221° (decomp.) (Found: C, 46·1; H, 6·0; Cl, 8·6; N, 3·3. $C_{33}H_{46}N_2Cl_2O_{15},4H_2O$ requires C, 46·2; H, 6·3; Cl, 8·3; N, 3·3%). The *semicarbazone*, crystallised from ethanol, had m. p. 189—190° (Found: C, 58·9; H, 7·2; N, 15·7. $C_{35}H_{50}N_8O_7,H_2O$ requires C, 59·0; H, 7·4; N, 15·7%), $\lambda_{max.}$ (in EtOH) 227, 283 mμ (ε 41,500, 7600).

(*b*) *Cyclisation with sodium hydride.* Ketone (V)A, from the hydrochloride (4 g.), was stirred in benzene (100 ml.) with sodium hydride (0·24 g.) at room temperature for 6 hr. After the unchanged hydride had been filtered off, the solution was worked up as above. The material which separated from ethanol was an *isomer* (0·3 g.), m. p. 177—179°, of the alcohol (XIX)A. This crystallised from acetone as needles, m. p. 186° (Found: C, 66·3; H, 7·7; N, 4·4. $C_{33}H_{44}N_2O_7,H_2O$ requires C, 66·2; H, 7·7; N, 4·7%).

Acidification of the ethanolic mother-liquor with ethanolic hydrogen chloride gave the hydrochloride (1·34 g.), m. p. 199—200° (decomp.), of the isomer of (XIX)A obtained above.

Isomer B. Ketone (V)B, from the hydrochloride (2 g.), was allowed to react with sodium methoxide (0·9 g.) in benzene (34 ml.) containing methanol (12 ml.) and ethanol (12 ml.), as above. The *keto-alcohol* (XIX)B separated from ethanol as pale crystals (0·82 g.), m. p. 156—157° (Found: C, 68·3; H, 8·0; N, 5·0. $C_{33}H_{44}N_2O_7$ requires C, 68·3; H, 7·6; N, 4·8%). The *hydrochloride* separated from ethanol as colourless plates, m. p. 192—193° (decomp.) (Found: C, 56·3; H, 7·3; Cl, 10·2; N, 3·7. $C_{33}H_{46}Cl_2N_2O_7,3H_2O$ requires C, 56·0; H, 7·4; Cl, 10·0; N, 4·0%). The *perchlorate*, after being leached with hot methanol, had m. p. 238—240° (decomp.) (Found: C, 50·5; H, 5·8; Cl, 9·6; N, 3·7. $C_{33}H_{46}Cl_2N_2O_{15}$ requires C, 50·8; H, 5·9; Cl, 9·1; N, 3·6%).

3-*Acetyl*-4,6,7,11b-*tetrahydro*-9,10-*dimethoxy*-2-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-3′-*oxo*-*n*-*butyl*-1-*isoquinolylmethyl*)-1H-*benzo*[a]*quinolizine* (XXII).—*Isomer* A. The hydrochloride (6·59 g.) of alcohol (XIX)A was heated at 100° for 3 hr. in 12N-sulphuric acid (33 ml.). The solution was cooled and basified with a solution of ammonia (*d* 0·88). Extraction with benzene, then washing and evaporation of the solvent, gave a foam that was converted by trituration with ether into pale pink crystals of the conjugated *ketone* (XXII)A (4·5 g.), m. p. 131—132°, λ (in EtOH) 230 mμ (ε 22,100), $\lambda_{max.}$ 282 mμ (ε 9900), $\lambda_{max.}$ (in EtOH–HCl) 232, 284 mμ (ε 22,400, 8400) (Found: C, 68·1; H, 7·6; N, 4·9. $C_{33}H_{42}N_2O_6,H_2O$ requires C, 68·25; H, 7·6; N, 4·8%). The *hydriodide* crystallised from water as pale yellow plates, m. p. 168° (decomp.), λ (in EtOH) 230 mμ (ε 32,800), $\lambda_{max.}$ 284 mμ (ε 7900) (Found: C, 47·6; H, 5·4; I, 30·0; N, 3·0. $C_{33}H_{44}I_2N_2O_6,H_2O$ requires C, 47·4; H, 5·5; I, 30·3; N, 3·3%). The *semicarbazone* separated from ethanol as a pale amorphous powder, m. p. 209—210°, $\lambda_{max.}$ 226, 283 mμ (ε 46,000, 8600) (Found: C, 61·4; H, 7·3; N, 16·8. $C_{35}H_{48}N_8O_6$ requires C, 61·2; H, 7·1; N, 16·8%).

Isomer B. The hydrochloride (10·21 g.) of the alcohol (XIX)B, treated as above, gave the conjugated *ketone* (XXII)B as pale crystals (5·7 g.), m. p. 126—128° (Found: C, 70·0; H, 7·6; N, 4·9. $C_{33}H_{42}N_2O_6$ requires C, 70·4; H, 7·5; N, 5·0%), λ (in EtOH) 230 mμ (ε 21,000), $\lambda_{max.}$ 242 mμ (ε 9400), $\lambda_{max.}$ (in EtOH–HCl) 232, 282 mμ (ε 20,600, 7600). The *hydriodide* separated from water as pale yellow plates, m. p. 190° (decomp.), $\lambda_{max.}$ (in EtOH) 225, 281 mμ (ε 44,000, 9000) (Found: C, 47·6; H, 5·6; I, 29·6; N, 3·1. $C_{33}H_{44}I_2N_2O_6,H_2O$ requires C, 47·4; H, 5·5; I, 30·3; N, 3·3%).

1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-2-3′-*oxo*-*n*-*butyl*-1-*isoquinolylacetone* (XVI).—Ketone (XV) (from 1·4 g. of the hydrochloride) in methylene chloride (25 ml.) was kept at room temperature with methyl vinyl ketone (0·35 g.) for 19 hr. After the solvent had been removed *in vacuo*, the residue was converted into the hydrochloride. This separated from ethanol–ether as a white amorphous powder (1·01 g.), m. p. 65—68°, decomp. *ca.* 95° (Found: C, 52·4; H, 8·1; N, 3·6. $C_{18}H_{26}ClNO_4,3H_2O$ requires C, 52·6; H, 7·9; N, 3·4%).

3-*Acetyl*-2,3,4,6,7,11b-*hexahydro*-2-*hydroxy*-9,10-*dimethoxy*-2-*methyl*-1H-*benzo*[a]*quinolizine* (XVII).—(*a*) *Cyclisation with ethanolic hydrogen chloride.* The hydrochloride (2·85 g.) of ketone

(XVI) was taken up in saturated ethanolic hydrogen chloride. After 2·5 hr. at 0°, the crystals (1·85 g.) were collected. This material had m. p. 231° (decomp.), raised to 234° (decomp.) by crystallisation from ethanol–ethyl acetate, and was the *hydrochloride* of the tricyclic alcohol (XVII) (Found: C, 60·8; H, 7·2; Cl, 10·2; N, 4·1. $C_{18}H_{26}ClNO_4$ requires C, 60·8; H, 7·4; Cl, 10·0; N, 3·9%).

(*b*) *Cyclisation with concentrated hydrochloric acid.* The hydrochloride (2·6 g.) of ketone (XVI) was left in concentrated hydrochloric acid (15 ml.) for 22 hr. at room temperature. The base, which was isolated by neutralisation and extraction in the usual manner, gave the hydrochloride (1·08 g.) of the alcohol (XVII), m. p. 235° (decomp.) (from ethanol).

(*c*) *Cyclisation with sodium methoxide.* The hydrochloride (1 g.) of ketone (XVI) was neutralised and the base extracted into benzene (25 ml.). The dried solution was treated at room temperature for 18 hr. with a solution of sodium methoxide (0·3 g.) in methanol (5 ml.) and ethanol (2 ml.). Removal of the alkali by washing with water, and evaporation of the solvent, gave the alcohol (XVII) as an amorphous foam which was converted into the hydrochloride (0·6 g.), m. p. 235° (decomp.), in ethanol.

3-*Acetyl*-4,6,7,11b-*tetrahydro*-9,10-*dimethoxy*-2-*methyl*-1H-*benzo*[a]*quinolizine* (XVIII).—(*a*) *Dehydration with ethanolic hydrogen chloride.* The hydrochloride (2·6 g.) of the methyl ketone (XVI) was heated under reflux with saturated ethanolic hydrogen chloride (15 ml.) for 1 hr. The *hydrochloride* (1·31 g.) of the conjugated ketone (XVIII) separated on cooling and had m. p. 221° (decomp.), $\lambda_{max.}$ (in EtOH) 232, 282 mμ (ε 17,500, 5200) (Found: C, 63·8; H, 7·5; Cl, 9·9; N, 3·9. $C_{18}H_{24}ClNO_3$ requires C, 64·0; H, 7·2; Cl, 10·5; N, 4·1%).

(*b*) *Dehydration with sodium methoxide.* The hydrochloride (1·2 g.) of the tricyclic alcohol (XVII) was neutralised, and the base was extracted into benzene (35 ml.). The dried solution was heated under reflux for 2 hr. with sodium methoxide (0·17 g.) and methanol (1 ml.), and was then left overnight at room temperature. The crude base, isolated in the usual manner, gave the hydrochloride (0·75 g.), m. p. 221° (decomp.), of the conjugated ketone (XVIII). The *semicarbazone* crystallised from ethanol as a pale powder, m. p. 221—223°, $\lambda_{max.}$ (in EtOH) 233 mμ (ε 16,000), $\lambda_{infl.}$ 250 mμ (ε 13,000) (Found: C, 60·7; H, 7·3; N, 14·5. $C_{19}H_{26}N_4O_3,H_2O$ requires C, 60·6; H, 7·5; N, 14·9%).

1-(2-*Benzyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)-3-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-3′-*oxo*-*n*-*butyl*-1-*isoquinolyl*)*acetone* (VI).—*Isomer* A. The hydrochloride (3 g.) of the unsymmetrical ketone (II)A was neutralised and the base extracted into benzene (45 ml.). The dried solution was kept at room temperature overnight with methyl vinyl ketone (0·825 ml.), then the crude adduct (VI)A was isolated, by procedures described above, as a yellow foam (2·78 g.). The *hydrochloride*, deposited from 2N-hydrochloric acid, had m. p. 162—165° (decomp.) (Found: C, 62·1; H, 7·1; Cl, 10·3; N, 3·9. $C_{36}H_{46}Cl_2N_2O_6,H_2O$ requires C, 62·5; H, 7·0; Cl, 10·3; N, 4·0%).

Isomer B. The hydrobromide (1 g.) of ketone (II)B was converted into the free base in benzene solution (15 ml.) and kept at room temperature with methyl vinyl ketone (0·27 ml.). After 2 hr. the solvent was evaporated *in vacuo* and the residue taken up in 2N-hydrochloric acid. The *hydrochloride* (0·76 g.) of (VI)B separated as an amorphous hydrate, m. p. 132—134° (decomp.) (Found: C, 56·3; H, 7·2; Cl, 9·9; N, 3·6. $C_{36}H_{46}Cl_2N_2O_6,5H_2O$ requires C, 56·5; H, 7·4; Cl, 9·3; N, 3·7%).

3-*Acetyl*-2-(2-*benzyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolylmethyl*)-2,3,4,6,7,11b-*hexahydro*-2-*hydroxy*-9,10-*dimethoxy*-1H-*benzo*[a]*quinolizine* (XX).—*Isomer* A. The adduct (VI)A (2·78 g.) in benzene (70 ml.) was stirred for 15 min. at room temperature with sodium methoxide (0·29 g.) in methanol (5·5 ml.). The alkali was removed by washing with water, and the benzene was removed *in vacuo* to give a crude froth, which was treated with ethanolic hydrogen chloride. The *hydrochloride* of (XX)A was precipitated as plates (1·93 g.), m. p. 198° (decomp.) (Found: C, 61·2; H, 7·1; Cl, 9·6; N, 3·5. $C_{36}H_{46}Cl_2N_2O_6,2H_2O$ requires C, 61·0; H, 7·1; Cl, 10·0; N, 4·0%). The free *base* crystallised from ethanol as plates, m. p. 148—149° (Found: C, 71·9; H, 7·3; N, 4·4. $C_{36}H_{44}N_2O_6$ requires C, 72·0; H, 7·4; N, 4·7%).

Isomer B. (*a*) The adduct (VI)B (8·06 g.) was cyclised as above. The *hydrochloride* of the alcohol (XX)B was obtained from ethanol as plates (4·93 g.), m. p. 187—189° (decomp.) (Found: C, 62·6; H, 7·4; Cl, 10·0; N, 3·8. $C_{36}H_{46}Cl_2N_2O_6,H_2O$ requires C, 62·5; H, 7·0; Cl, 10·2; N, 4·0%). The free *base* crystallised from ethanol as prisms, m. p. 178—179° (Found: C, 71·9; H, 7·6; N, 4·5%).

(*b*) The alcohol (XIX)B (2·15 g.), in methylene chloride (50 ml.) containing redistilled

benzyl bromide (1·0 ml., 5 mol.), was kept at room temperature overnight. Evaporation *in vacuo* and addition of an excess of ether (50 ml.) gave the quaternary *salt* (XXVI) as an amorphous powder (2·82 g., 95%), m. p. 150—155° (decomp.). Crystallisation from 2-methoxyethanol and then from chloroform–ether gave needles, m. p. 155—160° (decomp.) (Found: C, 61·1; H, 6·9; N, 3·5; Br, 10·75. $C_{40}H_{51}O_7N_2Br,2H_2O$ requires C, 60·9; H, 6·9; N, 3·5; Br, 10·2%).

This salt (2·17 g.) in aqueous dioxan (90 ml., 50%) was treated with a saturated solution of sodium hydrogen carbonate (10 ml.) at room temperature for 1½ hr. The solution was concentrated *in vacuo*, and the residual aqueous suspension was extracted with chloroform (4 × 50 ml.). The extract was dried ($MgSO_4$) and evaporated *in vacuo*, and the residue was treated with ethanolic hydrogen chloride, to give the hydrochloride (1·29 g., 68%), m. p. 185—187° (decomp.), of the alcohol (XX)B. The regenerated base, m. p. 177—179°, crystallised from alcohol, was identical with (XX)B made as in (*a*) above.

3-*Acetyl*-2-(2-*benzyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolylmethyl*)-4,6,7,11b-*tetrahydro*-9,10-*dimethoxy*-1H-*benzo*[a]*quinolizine* (XXIII).—*Isomer* A. The hydrochloride (13·58 g.) of alcohol (XX)A was heated at 100° for 2·5 hr. with 12N-sulphuric acid (70 ml.). Neutralisation of the cooled solution with ammonia solution (*d* 0·88) was followed by extraction with benzene, washing, and evaporation to dryness *in vacuo*. The residual foam crystallised on trituration with ether, to give the conjugated *ketone* (XXIII)A (7·6 g.), m. p. 148—149° (decomp.), λ (in EtOH) 230 mμ (ε 22,000), $\lambda_{max.}$ 283 mμ (ε 10,400), $\lambda_{max.}$ (in EtOH–HCl) 232, 283 mμ (ε 22,100, 8400) (Found: C, 73·2; H, 7·2; N, 4·5. $C_{36}H_{42}N_2O_5,\frac{1}{2}H_2O$ requires C, 73·1; H, 7·3; N, 4·7%). The hydrochloride was deposited from ethanol as colourless crystals, m. p. 173—176° (decomp.), $\lambda_{max.}$ (in EtOH) 230, 283 mμ (ε 21,300, 8400). The hydrobromide was obtained from aqueous acid solution as an amorphous powder, m. p. 176—177° (decomp.), $\lambda_{max.}$ (in EtOH) 232, 283 mμ (ε 21,600, 8900). The hydriodide separated from water as a pale yellow powder, m. p. 168—170° (decomp.), λ (in EtOH) 230 mμ (ε 31,000), $\lambda_{max.}$ 285 mμ (ε 7900).

Isomer B. The hydrochloride (4·93 g.) of alcohol (XX)B was dehydrated as above. The free *base* (XXIII)B separated from ether as white crystals (2·73 g.), m. p. 132—134°, λ (in EtOH) 230 mμ (ε 22,000), $\lambda_{max.}$ 282 mμ (ε 10,200), $\lambda_{max.}$ (in EtOH–HCl) 232, 284 mμ (ε 23,400, 8200) (Found: C, 74·0; H, 7·0; N, 4·6. $C_{36}H_{42}N_2O_5$ requires C, 74·2; H, 7·3; N, 4·8%). The hydriodide was precipitated from aqueous solution as an amorphous yellow powder, m. p. 174—175° (decomp.), λ (in EtOH) 230 mμ (ε 31,000), $\lambda_{max.}$ 284 mμ (ε 7600).

(±)-N-*Benzyl*-2,3-*dehydroisoemetine* (XXIV)A.—Ketone (XXIII)A (3·7 g.) was kept at room temperature overnight with ethane-1,2-dithiol (4 ml.) in saturated methanolic hydrogen chloride (75 ml.). Concentration of the solution *in vacuo* gave the *ethylene thioketal hydrochloride* of compound (XXIII)A as colourless plates (4·33 g.), m. p. 200—203° (decomp.). Recrystallisation from ethyl acetate–2-methoxyethanol gave prisms of unchanged m. p. (Found: C, 58·1; H, 7·0; Cl, 8·5; N, 3·2; S, 8·1. $C_{38}H_{48}Cl_2N_2O_4S_2,3H_2O$ requires C, 58·1; H, 6·9; Cl, 9·0; N, 3·6; S, 8·2%). The free *base* crystallised from acetonitrile as prisms, m. p. 153—154° (Found: C, 69·2; H, 7·1; N, 3·9; S, 9·6. $C_{38}H_{46}N_2O_4S_2$ requires C, 69·3; H, 7·0; N, 4·3; S, 9·7%).

A solution of this base (1·05 g.) in dried tetrahydrofuran (10 ml.) was added dropwise to a stirred solution of sodium (0·4 g.) in refluxing liquid ammonia (75 ml.). After 30 min. the blue colour was discharged with ethanol, and the excess of ammonia evaporated. Benzene (100 ml.) was added and inorganic salts were removed by washing with water. Evaporation of the solvent afforded a foam which, with ethanolic hydrogen bromide, gave the *hydrobromide* of compound (XXIV)A as pale prisms (0·96 g.), m. p. 204—206° (decomp.) (Found: C, 55·9; H, 6·6; Br, 21·2; N, 3·4. $C_{36}H_{46}Br_2N_2O_4,2H_2O$ requires C, 56·3; H, 6·6; Br, 20·9; N, 3·6%).

(±)-N-*Benzyl*-2,3-*dehydroemetine* (XXIV)B.—Ketone (XXIII)B (2·01 g.) with ethane-1,2-dithiol (2 ml.) in methanolic hydrogen chloride (50 ml.) for 19 hr. at room temperature gave the ethylene thioketal as a foam (2·03 g.). The *hydrobromide* was deposited from ethanol as a fawn microcrystalline solid, m. p. 195—200° (decomp.) (Found: C, 51·5; H, 6·4; Br, 17·8; N, 3·0; S, 7·5. $C_{38}H_{48}Br_2N_2O_4S_2,4H_2O$ requires C, 51·0; H, 6·3; Br, 17·9; N, 3·1; S, 7·2%).

The thioketal (2·5 g.) in tetrahydrofuran (10 ml.) was reduced with sodium (1 g.) in liquid ammonia (150 ml.) as above. (±)-*N*-Benzyl-2,3-dehydroemetine was obtained as a pale foam (1·7 g.), whose *hydrogen oxalate* separated from acetone as a buff powder that crystallised from water as monoclinic prisms, m. p. 140—145° (Found: C, 60·5; H, 7·2; N, 3·6. $C_{38}H_{46}N_2O_8,5H_2O$ requires C, 60·8; H, 7·5; N, 3·7%).

(±)-2,3-*Dehydroisoemetine* (XXV)A.—(±)-*N*-Benzyl-2,3-dehydroisoemetine hydrobromide (0·289 g.) in 50% aqueous ethanol (10 ml.) was hydrogenated at room temperature and pressure for 3·5 hr. with three portions (50 mg. each) of 10% palladium–charcoal. Removal of the catalyst, concentration of the solution, and basification with ammonia solution (*d* 0·88), gave chromatographically pure (±)-2,3-dehydroisoemetine as a colourless amorphous powder (0·141 g.), m. p. 80—84°. The crystalline hydrochloride (80 mg.) separated from ethanol–ether as prisms, m. p. 220—225° (decomp.). The R_F value and the infrared spectrum (of a bromoform solution) were identical with those of an authentic specimen, m. p. 220—225° (decomp.) (lit.,[14] 223—225°).

(±)-2,3-*Dehydroemetine* (XXV)B.–(±)-*N*-Benzyl-2,3-dehydroemetine hydrogen oxalate (0·44 g.) was hydrogenated in aqueous ethanol, and worked up as above. The free base (XXV)B was obtained as a buff solid (0·13 g.), the hydrochloride of which separated from ethanol–ether as colourless crystals (0·07 g.), m. p. 230—232° (decomp.). The R_F value and infrared spectrum of this compound were identical with those of an authentic specimen, m. p. 235° (decomp.) (lit.,[14] 248—250°).

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