## 473. *Emetine and Related Compounds. Part I. The Synthesis of Tetrahydroisoquinolyl Ketones.*

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The bistetrahydroisoquinolyl ketones (II)B and (V)B have been prepared and their configurations established. Their role in the synthesis of emetine is discussed.

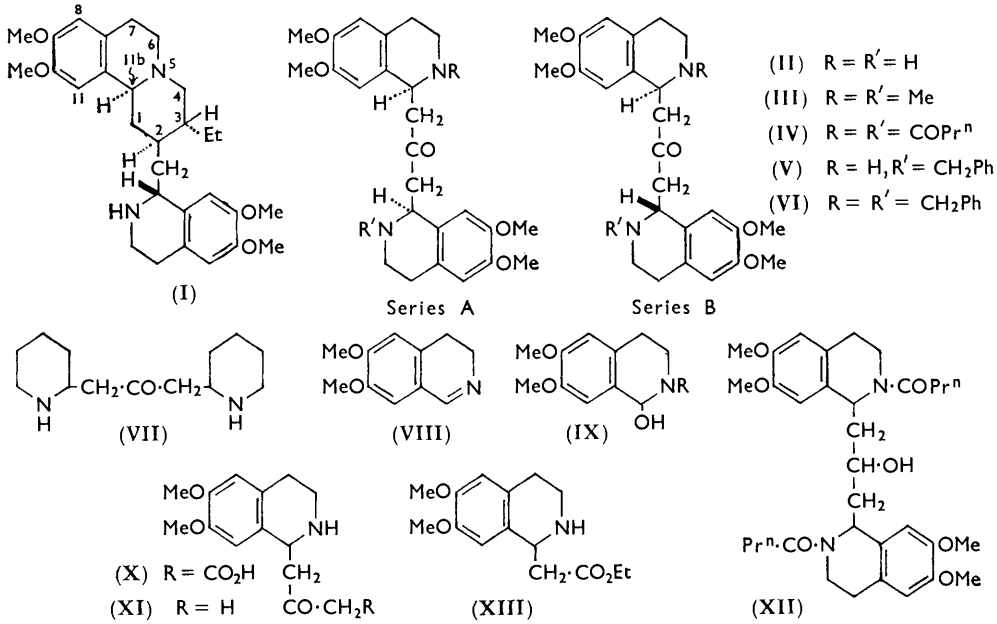
Although the absolute configurations of the benzoquinolizidine and the tetrahydroisoquinoline fragments of the emetine molecule have been separately determined, thus enabling the natural alkaloid to be formulated as (I),[1] the chemical syntheses so far published [2] have not provided any confirmation of the relation between the stereochemistry at $C_{(1')}$ and that at any of the three remaining asymmetric centres. This is primarily because the tetrahydroisoquinoline system, containing the asymmetric centre at $C_{(1')}$, was formed only after the benzoquinolizidine portion had been separately synthesised. It is then difficult to correlate the stereochemistry of these portions by conformational arguments. Moreover, even in Battersby's elegant synthesis, the generation of the asymmetric centre at $C_{(1')}$ resulted in a loss of stereospecificity and the production of a mixture of emetine and its epimer isoemetine. In contrast, in bistetrahydroisoquinolyl ketones of type (II) the asymmetric centres corresponding to $C_{(1')}$ and $C_{(11b)}$ are already present. Professor D. H. R. Barton, F.R.S., for whose invaluable aid and advice throughout this work we are deeply grateful, suggested that if ketone (II)B could be prepared and its stereochemistry established, then constructing the final ring of emetine would afford direct evidence about the relative stereochemistry at these positions in the alkaloid and would make possible a completely stereospecific synthesis.

Related *NN'*-dimethyl ketones are well known as products of the reaction, in alkaline solution, between acetone and a pseudo-base such as (IX; R = Me).[3] In this case the

[1] Battersby, Binks, and Edwards, *J.*, 1960, **3474** and references therein.
[2] Battersby and Turner, *J.*, 1960, 717, and references therein.
[3] Pyman, *J.*, 1909, **95**, 1266.

symmetrical ketone (III) results. A closely analogous *NN'*-dimethyl ketone can be obtained from the dihydroisoquinoline alkaloid cotarnine.[4,5] Nothing is known about the stereochemistry of these compounds.

In a related reaction, Schöpf and his co-workers[6] isolated the two diastereoisomers of the symmetrical ketone (VII) by treating 2,3,4,5-tetrahydropyridine with acetonedicarboxylic acid in aqueous alkali.




We have found that the nature of the condensation of acetonedicarboxylic acid and 3,4-dihydro-6,7-dimethoxyisoquinoline (VIII) varies with the solvent used. In aqueous solution equimolar quantities of the reactants gave the keto-acid (X) as an unstable solid, readily decarboxylated to the methyl ketone (XI).[7] With two mol. of the base and one of the acid a mixture of the two diastereoisomeric ketones (II)A * and (II)B resulted in *ca.* 60% yield. Their *NN'*-dibutyryl derivatives (IV) were separated by fractional crystallisation into compounds with m. p. 175° and 136° severally, the latter being converted into a polymorph, m. p. 163°, in ethyl acetate.

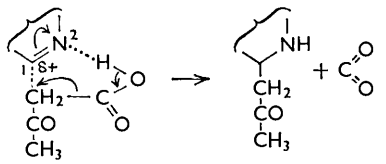
Stereoselective synthesis of either diastereoisomer of the ketone (II) could be achieved by modifying the reaction conditions to ensure that the product is an insoluble salt of the isomer required. The position of equilibrium between the ketones is thereby shifted by a mass-action effect and the pure salt of a single isomer is precipitated. Thus, when the hydrochloride of the dihydroisoquinoline (VIII) reacted with acetonedicarboxylic acid in ethanol containing pyridine, the ketone (II)A, which separated in 60% yield as the hydrochloride, was shown to be stereochemically pure by conversion into the butyryl derivative, m. p. 175°. In contrast, from condensations performed in aqueous solutions containing *ca.* 0·7 equivalent of sulphuric acid, the sulphate of (II)B crystallised in 54% yield and gave only the butyryl derivative, m. p. 136°. In the same concentration of aqueous sulphuric acid, ketone (II)A was inverted, in good yield, into the insoluble sulphate of (II)B.

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

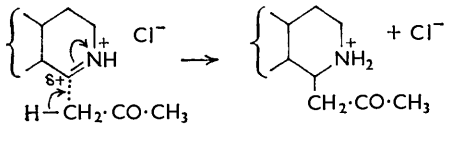
[4] Cf. Dey and Kantam, *J. Indian Chem. Soc.*, 1935, **12**, 430.
[5] Cf. Beke and Harsányi, *Acta Chim. Acad. Sci. Hung.*, 1957, **11**, 349.
[6] Schöpf, Benz, Braun, Hinkel, and Rokohl, *Angew. Chem.*, 1953, **65**, 161.
[7] Cf. Itoh, *Chem. and Pharm. Bull.* (*Japan*), 1960, **8**, 441.

The ketones (II)A and (II)B decomposed in methylene chloride at room temperature into the methyl ketone (XI) and the dihydroisoquinoline (VIII).

The dibutyryl derivative (IV), m. p. 136°, gave, on reduction of the ketone group with sodium borohydride, two stereoisomeric alcohols (XII), thus showing that the parent ketone was the *meso*-form (II)B. The butyryl compound, m. p. 175°, gave only a single alcohol (XII) and was therefore derived from the racemic ketone (II)A. The stereochemistry of our products is thus clearly established, and the asymmetric centres in ketone (II)B have the same relative configuration as those at $C_{(1')}$ and $C_{(11b)}$ in emetine. Ketone (II)A is likewise related to isoemetine.



Scheme (a)



Scheme (b)

Schöpf *et al.*,[8] on studying the mechanism of the condensation, concluded that, in aqueous alkaline or buffered solution (pH 6—12), the reaction is essentially the elimination of water from a pseudo-base and the active methylene group of the undissociated β-keto-acid. Participation of the pseudo-base seems less likely under our conditions, when aqueous solutions containing mineral acid (pH 3·5) are used.

That direct (possibly concerted)[9] attack on an azomethine link may occur was demonstrated by the vigorous reaction of the dihydroisoquinoline (VIII) and acetoacetic acid in anhydrous acetone to give the methyl ketone (XI) in high yield [scheme (a)].

The same product, accompanied by *ca.* 10—15% of the symmetrical ketone (II)A, resulted when acetonedicarboxylic acid was substituted for acetoacetic acid. In this instance the ketone (II)A was isolated as an insoluble salt-like complex of unknown constitution, from which the parent compound was obtained by treatment with alkali.

When the electrophilic power of the carbon atom at position 1 of the dihydroisoquinoline (VIII) was increased by formation of the hydrochloride, reaction with relatively weak nucleophiles occurred in non-aqueous solvents. As the base was now completely protonated, the usual self-catalysis of the condensation could not occur, and the addition of a second base, *e.g.*, pyridine, was necessary to promote anion formation [scheme (b)]. Acetone gave a good yield of the methyl ketone (XI) as the hydrochloride under these conditions. This, in its turn, condensed with a second mol. of the dihydroisoquinoline hydrochloride to produce, stereoselectively, the hydrochloride of the symmetrical ketone (II)A. Similarly, no reaction was observed between the dihydroisoquinoline hydrochloride and acetonedicarboxylic acid in ethanol until after the addition of pyridine. The hydrochloride of the ketone (II)A was then rapidly precipitated, with vigorous evolution of carbon dioxide.

These findings suggest that under our conditions condensation does not proceed *via* the undissociated acid, but by a base-catalysed nucleophilic attack on the carbon atom of the azomethine link. Beke *et al.*[10] recently postulated the formation of intermediates of the type shown in scheme (b), to explain the acid-catalysed acceleration of nucleophilic attack on a pseudo-base.

An additional example of this type of reaction was the condensation of potassium ethyl malonate with the dihydroisoquinoline (VIII) in acetic acid to give the well-known ester (XIII).

In an alternative synthetic scheme, it was hoped to establish the potential secondary

[8] Schöpf, Braun, Burkhardt, Dummer, and Müller, *Annalen*, 1959, **626**, 123.
[9] Cf. van Tamelen and Knapp, *J. Amer. Chem. Soc.*, 1955, **77**, 1860.
[10] Beke, Szántay, and Bárczai-Beke, *Annalen*, 1960, **636**, 150.

amino-group of emetine as an *N*-benzyl derivative that would be stable throughout later stages of the synthesis but would permit final regeneration by hydrogenolysis. For this the unsymmetrical ketone (V)B was required.

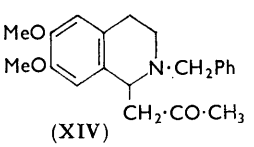
The pseudo-base (IX; R = $CH_2Ph$) with the keto-acid (X) gave a mixture of the two diastereoisomeric ketones (V)A and (V)B, which were separated by fractional crystallisation of the hydrochlorides. Catalytic hydrogenolysis of these salts with palladium in aqueous acidic solution gave the symmetrical ketones (II)A and (II)B, respectively, in good yield, thereby establishing the configurations of our diastereoisomers. A similar stereoisomeric mixture of (V)A and (V)B resulted from the reaction of the pseudo-base (IX; R = $CH_2Ph$) with the methyl ketone (XI) in presence of alkaline catalysts.

With benzyl bromide in *NN*-dimethylformamide each isomer of the ketones (V) and (II) yielded the insoluble hydrobromide of the symmetrical ketone (VI)B, thereby again demonstrating that inversion between the A and the B series can be brought about by a mass-action effect. Reactions in other solvents gave mixtures from which the two diastereoisomeric bases (VI)A and (VI)B were separated by fractional crystallisation. The pseudo-base (IX; R = $CH_2Ph$), with acetone and an aqueous alkaline catalyst or with acetonedicarboxylic acid, gave the isomer (VI)B as the major product. When a large excess of acetone was used in the former reaction, the methyl ketone (XIV) resulted. This condensed with a further mol. of the pseudo-base (IX; R = $CH_2Ph$) to give mainly the isomer (VI)B. The stereochemistry of these diastereoisomers was established by hydrogenolysis with palladium in aqueous acidic solution to the symmetrical ketones (II)A and (II)B, respectively.

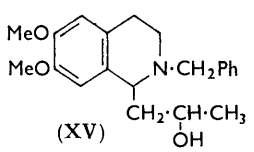
Hydrogenolysis of ketone (VI)B in acetic acid with two mol. of hydrogen caused fission at $C_{(1)}$. Use of palladium catalysts gave the tetrahydroisoquinoline (XVI), and use of Adams platinic oxide gave a mixture of this with the alcohol (XV). When the methyl ketone (XIV) was hydrogenated with Adams catalyst in acetic acid, this alcohol again resulted, but, with palladium, debenzylation to the secondary base (XI) occurred. The tetrahydroisoquinoline (XVI) was prepared by catalytic hydrogenation of the quaternary salt (XVII) with Adams catalyst in aqueous solution and could be debenzylated to 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline by further reaction of the hydrobromide under these conditions or by hydrogenolysis of the free base in acetic acid with palladium.

The lability of the *N*-benzyl ketones (XIV) and (VI) was also shown by the decomposition of their acid salts in warm ethanol to salts of the dihydroisoquinoline (XVII), and by their reaction with hydroxylamine to give the hydroxyamino-compound (XVIII), identical with that obtained in the same fashion from the pseudo-base (IX; R = $CH_2Ph$).[11]

None of the compounds described showed appreciable activity against *Entamoeba histolytica*, when tested on weanling rats by Jones's method.[12]



(XIV)



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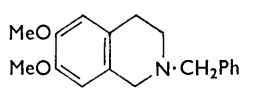
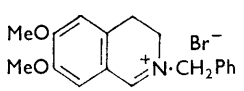
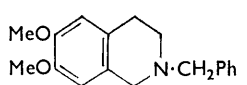


(XVI)



(XVII)



(XVIII)

## Experimental

1,3-*Bis*-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*acetone* (II).—*Mixed isomers.* 3,4-Dihydro-6,7-dimethoxyisoquinoline [13] (VIII) (10 g.) in methanol (20 ml.) and water (80 ml.)

[11] Cf. Beke and Harsányi, *Acta Chim. Acad. Sci. Hung.*, 1957, **11**, 303.
[12] Jones, *Ann. Trop. Med. Parasitol.*, 1956, **40**, 130.
[13] Späth and Epstein, *Ber.*, 1926, **59**, 2791; Späth and Polgar, *Monatsh.*, 1929, **51**, 190.

was allowed to react for 2·75 hr. with acetonedicarboxylic acid (4 g.) in water (20 ml.). An excess of aqueous sodium carbonate was added and the solution extracted with methylene chloride (3 times). The combined extracts were washed three times with water, dried, and evaporated to a gum that yielded a pale solid on trituration with ether. Recrystallisation from acetone gave the mixed diastereoisomers of the ketone (II) (6·36 g.), m. p. 140—142°.

*Isomer A.* (*a*) Ethanolic hydrogen chloride was added to 3,4-dihydro-6,7-dimethoxyisoquinoline (VIII) (15 g.) in ethanol (178 ml.) to pH 5·8, followed by acetonedicarboxylic acid (5·89 g.) and pyridine (15 ml.). After 1 hr. the crystalline *hydrochloride* (11·6 g.), m. p. 204—205° (decomp.), of ketone (II)A was collected (Found: C, 58·05; H, 6·6; Cl, 13·5; N, 5·5. $C_{25}H_{34}Cl_2N_2O_5$ requires C, 58·45; H, 6·7; Cl, 13·8; N, 5·5%).

The free *base*, recrystallised from acetone, had m. p. 143—144° (Found: C, 68·0; H, 7·5; N, 6·2. $C_{25}H_{32}N_2O_5$ requires C, 68·15; H, 7·3; N, 6·4%). The NN′-*dibutyryl derivative* (IV) was prepared in butyric anhydride–pyridine and recrystallised from ethyl acetate as prisms, m. p. 173·5—175° (Found: C, 68·4; H, 7·5; N, 4·9. $C_{33}H_{44}N_2O_7$ requires C, 68·3; H, 7·6; N, 4·8%). The NN′-*diacetyl derivative*, prepared in acetic anhydride–pyridine, had m. p. 201—202°, after recrystallisation from methanol containing a little chloroform (Found: C, 66·4; H, 7·0; N, 5·2. $C_{29}H_{36}N_2O_7$ requires C, 66·4; H, 6·9; N, 5·3%).

(*b*) The hydrochloride (0·4 g.) of the dihydroisoquinoline (VIII) in ethanol (20 ml.) and pyridine (4 ml.) was kept at 20° with the hydrochloride (0·5 g.) of the methyl ketone (XI). A portion of the latter (0·2 g.), which separated after 2 days, was removed. After 7 days the crystalline hydrochloride (0·17 g.), m. p. 203° (decomp.), of ketone (II)A was collected.

*Isomer B.* The dihydroisoquinoline (VIII) (18 g.) in water (180 ml.) containing methanol (36 ml.), concentrated sulphuric acid (1·8 ml.), and acetonedicarboxylic acid (7·2 g.) gave the *sulphate* (15·2 g.) of the ketone (II)B as a white amorphous solid, m. p. 140—142° (decomp.), after 18 hr. at 20° (Found: C, 50·5; H, 6·8; N, 4·9; S, 5·1. $C_{25}H_{34}N_2O_9S,3H_2O$ requires C, 50·7; H, 6·8; N, 4·7; S, 5·4%).

The free *base* crystallised from acetone as prisms, m. p. 144—145° (Found: C, 67·8; H, 7·5; N, 6·3. $C_{25}H_{32}N_2O_5$ requires C, 68·15; H, 7·3; N, 6·4%). The amorphous NN′-*dibutyryl derivative* (IV), precipitated from butyric anhydride–pyridine with an excess of aqueous sodium carbonate solution, had m. p. 134—136° (Found: C, 68·2; H, 7·4; N, 4·5. $C_{33}H_{44}N_2O_7$ requires C, 68·3; H, 7·6; N, 4·8%). Recrystallisation from ethyl acetate, with an added seed, gave a polymorphic form, m. p. 161·5—163° (Found: C, 68·0; H, 7·6; N, 4·4%). The infrared spectra of these two forms were identical in bromoform solution.

*Conversion of the Base* (II)A *into* (II)B.—Ketone(II)A (1 g.) was left at room temperature for 20 hr. in water (12 ml.) and concentrated sulphuric acid (0·12 ml.). The precipitate was dried and washed with methylene chloride (10 ml.). The residual solid (0·9 g.) [m. p. 141—142° (decomp.)] was the sulphate of ketone (II)B and gave the *NN′*-dibutyryl derivative (0·85 g.), m. p. 133—136°.

*Decomposition of the Bases* (II)A *and* (II)B.—Ketone (II)B (0·5 g.) was left overnight at room temperature in methylene chloride (10 ml.). Removal of the solvent and treatment of the residue with ethanolic hydrogen chloride gave the crystalline hydrochloride (0·17 g.) of the methyl ketone (XI), m. p. 181—183° (decomp.). Evaporation of the mother-liquor gave a gummy solid identified as the crude dihydroisoquinoline (VIII) by its infrared and ultraviolet spectra.

Ketone (II)A behaved similarly.

1,3-*Bis*-(2-*butyryl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*propan*-2-*ol* (XII).—*Reduction of ketone* (IV)A. The *NN′*-dibutyryl-ketone A (0·8 g.) in ethanol (15 ml.) was treated with sodium borohydride (0·7 g.) in water (8 ml.) at room temperature for 72 hr. The mixture was acidified with 2N-hydrochloric acid and extracted with benzene (2 × 50 ml.). The combined extracts were washed with water, dried, and evaporated to a froth. Trituration with ether afforded colourless crystals (0·7 g.), m. p. 177—180°. Recrystallisation from ethyl acetate–isopropyl ether gave the *alcohol* (XII), m. p. 179—181° (Found: C, 68·0; H, 8·0; N, 4·7. $C_{33}H_{46}N_2O_7$ requires C, 68·0; H, 8·0; N, 4·8%).

*Reduction of ketone* (IV)B. The *NN′*-dibutyryl derivative B (1 g.) in ethanol (20 ml.) was treated with sodium borohydride (0·8 g.) in water (10 ml.), and worked up as above. The crude solid (0·8 g.) after trituration with ether had m. p. 140·5—143° (cloudy melt). Two crystallisations from ethyl acetate–isopropyl ether gave a second *isomer* of the alcohol (XII) (0·37 g.), m. p. 159—160° (Found: C, 68·0; H, 8·1; N, 4·5%).

From the mother-liquors, by precipitation with isopropyl ether and recrystallisation from isopropyl ether–ethyl acetate, a third *isomer* (0·27 g.), m. p. 153—154°, was obtained (Found: C, 67·7; H, 8·2; N, 4·8%). The mixed m. p. of these last two isomers was 138—141°.

*γ-(1,2,3,4-Tetrahydro-6,7-dimethoxy-1-isoquinolyl)-β-oxobutyric Acid* (X).—The dihydroisoquinoline (VIII) (24 g.) in water (192 ml.) and methanol (48 ml.) was treated with acetonedicarboxylic acid (18·5 g.) in water (48 ml.) at 15° for 2·5 hr. The *acid* (X) (22 g.) was filtered off and washed successively with water, ethanol (3 times), and ether, to give a fine amorphous powder, m. p. 107—110° (decomp.) (Found: C, 61·0; H, 6·6; N, 4·6. $C_{15}H_{19}NO_5$ requires C, 61·4; H, 6·5; N, 4·8%).

The *ethyl ester hydrochloride* separated from ethanolic hydrogen chloride at room temperature as prisms, m. p. 173—174° (decomp.) (Found: C, 56·8; H, 6·7; N, 3·8. $C_{17}H_{24}ClNO_5$ requires C, 57·1; H, 6·8; N, 3·9%).

After several days at room temperature, the acid (10 g.) decomposed to a dark gum from which the hydrochloride (5·5 g.), m. p. 181°, of the methyl ketone (XI) was isolated.

*1,2,3,4-Tetrahydro-6,7-dimethoxy-1-2′-oxopropylisoquinoline* (XI).—(*a*) Ethyl acetoacetate (4·48 ml.) was hydrolysed overnight at room temperature with sodium hydroxide (1·39 g.) in water (35 ml.). Concentrated hydrochloric acid (2·56 ml.) was added, followed by the dihydroisoquinoline (VIII) (6 g.) in water (13 ml.) and methanol (12 ml.). After 18 hr. the solution was basified with sodium carbonate and extracted with methylene chloride (3 times). The dried extracts were evaporated and the residual gum was taken up in ethanolic hydrogen chloride. The *hydrochloride* (7·14 g.) of the methyl ketone (XI) separated as prisms, m. p. 180° (decomp.) (Found: C, 58·6; H, 6·8; Cl, 12·3; N, 4·8. $C_{14}H_{20}ClNO_3$ requires C, 58·8; H, 7·0; Cl, 12·4; N, 4·9%).

The N-*acetyl derivative*, crystallised from ethyl acetate–ether, had m. p. 98—100° (Found: C, 65·7; H, 7·1; N, 4·7. $C_{16}H_{21}NO_4$ requires C, 66·0; H, 7·1; N, 4·8%).

(*b*) The dihydroisoquinoline (VIII) (6 g.) in acetone (30 ml.) was treated with acetoacetic acid (4·8 g.) in acetone (30 ml.). After 1·5 hr. at room temperature the solvent was removed and the hydrochloride (5 g.), m. p. 177° (decomp.), of the methyl ketone (XI) isolated as above.

(*c*) The hydrochloride (0·5 g.) of the dihydroisoquinoline (VIII) in ethanol (10 ml.), acetone (10 ml.), and pyridine (1 ml.) was kept at room temperature for 3 days. The hydrochloride (0·33 g.), m. p. 181° (decomp.), of ketone (XI) was gradually deposited.

(*d*) The dihydroisoquinoline (VIII) (30 g.) and acetonedicarboxylic acid (23 g.) were stirred in acetone (300 ml.) for 4 hr. The salt-like solid (5·9 g.) which separated was of unknown composition but gave the hydrochloride, m. p. 205°, and the butyryl derivative, m. p. 175°, derived from ketone (II)A, with ethanolic hydrogen chloride and butyric anhydride, respectively. Reaction with sodium hydroxide gave ketone (II)A, m. p. 140°.

The acetyl derivative of the methyl ketone (XI) (18·6 g.), m. p. 98—100°, was obtained from the filtrate by evaporation and acetylation.

*Ethyl 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-isoquinolylacetate* (XIII).—The dihydroisoquinoline (VIII) (1·91 g.) and potassium ethyl malonate (1·7 g.) were heated in glacial acetic acid at 100° for 3·5 hr. The gum obtained after removal of the solvent *in vacuo* was basified, and extracted twice with ethyl acetate. Evaporation of the washed and dried extracts gave a crude oil, which, on trituration with ether, yielded the crystalline ester (XIII) (1·07 g.), m. p. 72—76°.[14]

*2-Benzyl-1,2,3,4-tetrahydro-1-hydroxy-6,7-dimethoxyisoquinoline* (IX; R = $CH_2Ph$).—The dihydroisoquinoline (VIII) (50 g.) in ethanol (250 ml.) with benzyl bromide (33·5 ml.) at room temperature for 1·5 hr. gave *2-benzyl-3,4-dihydro-6,7-dimethoxyisoquinolinium bromide* (XVII) (43·7 g.) as pale crystals, m. p. 192—195° (decomp.) (from *NN*-dimethylformamide–ethanol) (Found: C, 60·3; H, 5·5; Br, 21·9; N, 3·8. $C_{18}H_{20}BrNO_2$ requires C, 59·7; H, 5·5; Br, 22·1; N, 3·9%). The derived *picrate*, m. p. 157—159° (decomp.), crystallised from *NN*-dimethylformamide–ethanol (Found: C, 56·3; H, 4·3; N, 11·2. $C_{24}H_{22}N_4O_9$ requires C, 56·5; H, 4·3; N, 11·0%).

The quaternary bromide (15·6 g.), after 1 hr. at room temperature in aqueous trimethylamine (25% w/v; 100 ml.), was converted into the *pseudo-base* (IX; R = $CH_2Ph$) (11·58 g.) that separated, on scratching, as a fine white powder, m. p. 112—115° (decomp.) (Found: C, 72·0; H, 7·1; N, 5·0. $C_{18}H_{21}NO_3$ requires C, 72·2; H, 7·1; N, 4·7%). It gave a picrate [m. p. 157—159° (decomp.)] identical with that from the compound (XVII) above.

[14] Cf. Battersby, Openshaw, and Wood, *J.*, 1953, 2463.

1-(2-*Benzyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)-3-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*acetone* (V).—(*a*) The keto-acid (X) (9·2 g.) was added to the pseudo-base (IX; R = $CH_2Ph$) (10·8 g.) in ethanol (54 ml.) at room temperature. After 1·5 hr., the solution was treated with ethanolic hydrogen chloride to pH 1 and left overnight in the refrigerator. The *hydrochloride* (6·6 g.) of ketone (V)A separated as plates, m. p. 150—152° (decomp.) (Found: C, 59·8; H, 6·8; Cl, 10·9; N, 4·0. $C_{32}H_{40}Cl_2N_2O_5,2H_2O$ requires C, 60·1; H, 6·9; Cl, 11·1; N, 4·4%). The ethanolic mother-liquor was evaporated, the residue taken up in water (200 ml.), and ammonium bromide added. The precipitate was dried, and was then dissolved in ethanol (25 ml.). The *hydrobromide* of isomer (V)B (4·1 g.) separated, after 18 hr. in the refrigerator, as fine crystals, m. p. 152—155° (decomp.) (Found: C, 54·9; H, 6·2; Br, 22·5; N, 4·1. $C_{32}H_{40}Br_2N_2O_5,2H_2O$ requires C, 54·8; H, 5·9; Br, 22·8; N, 4·0%).

(*b*) The pseudo-base (IX; R = $CH_2Ph$) (10·9 g.) and the methyl ketone (XI) (10·47 g.) were kept in ethanol (100 ml.) with sodium carbonate (0·25 g.) for 12 hr. at room temperature, and then for 2 days in the refrigerator. The product was isolated as an oil (18·02 g.) by addition of water, extraction with benzene, and evaporation. The hydrochloride (4·56 g.) of (V)A and the hydrobromide (4·48 g.) of (V)B were obtained as above.

*Hydrogenolysis of the Stereoisomeric Ketones* (V).—*Isomer A*. The hydrochloride (4·59 g.) of (V)A in water (125 ml.) was shaken under hydrogen at room temperature and pressure with 10% palladised charcoal (1 g.) until uptake ceased (48 min.). Removal of the catalyst and basification with 2N-sodium carbonate gave ketone (II)A (2·13 g., 70%), m. p. 140—143° (butyryl derivative, m. p. 173—176°).

*Isomer B*. The hydrobromide (5 g.) of (V)B in water (125 ml.), ethanol (25 ml.), and concentrated hydrobromic acid (0·5 ml.) was hydrogenated as above with 10% palladised charcoal (1 g.). Ketone (II)B (1·95 g., 62%) resulted; it had m. p. 138—140° (butyryl derivative, m. p. 135—137°).

1-*Acetonyl*-2-*benzyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (XIV).—(*a*) Acetoacetic acid (8 g.) was added to the pseudo-base (IX; R = $CH_2Ph$) (10 g.) in acetone (20 ml.). After 1 hr. the solvent was removed and the residue crystallised from ethanol–light petroleum (1 : 1), to give *ketone* (XIV) (8·84 g.) as prisms, m. p. 90—91° (Found: C, 74·1; H, 7·6; N, 4·1. $C_{21}H_{25}NO_3$ requires C, 74·3; H, 7·4; N, 4·1%). The *picrate* had m. p. 150—151° (decomp.) (from chloroform–ethanol) (Found: C, 56·7; H, 5·0; N, 9·9. $C_{27}H_{28}N_4O_{10}$ requires C, 57·0; H, 5·0; N, 9·9%).

(*b*) The pseudo-base (IX; R = $CH_2Ph$) (3 g.) with 2N-aqueous sodium carbonate (0·15 ml.) in refluxing acetone (20 ml.) for 4 hr. gave the ketone (XIV), which was isolated as the picrate (2·6 g.), m. p. 148—150° (decomp.). The free base was generated from a solution of the picrate in chloroform by passage through a column of alumina and had m. p. 85—87°.

1,3-*Bis*-(2-*benzyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*acetone* (VI).—*Isomer B*. (*a*) Ketone (II)A (2 g.) in *NN*-dimethylformamide (50 ml.) and benzyl bromide (7 ml.) was kept overnight at room temperature. The *hydrobromide* (2·18 g.) of the symmetrical ketone (VI)B separated as an amorphous powder, m. p. 156—157° (decomp.) (Found: Br, 20·0; N, 3·9. $C_{39}H_{46}Br_2N_2O_5$ requires Br, 20·4; N, 3·6%). The free *base* (1·1 g.) had m. p. 125—127°. Crystallisation from chloroform–ether (1 : 4) gave needles (0·9 g.), m. p. 130—131° (Found: C, 75·2; H, 7·2; N, 4·6. $C_{39}H_{44}N_2O_5$ requires C, 75·45; H, 7·1; N, 4·5%).

Repetition of the experiment, but with ketone (II)B (2 g.), gave the hydrobromide (2·1 g.), m. p. 156—157° (decomp.), having an infrared spectrum in Nujol identical with that of the preceding specimen.

(*b*) Ketone (V)A, from the hydrochloride (2 g.), was kept overnight at room temperature in *NN*-dimethylformamide (20 ml.) with benzyl bromide (0·365 ml.). Addition of ethanolic hydrogen bromide to pH 1 gave the hydrobromide (0·4 g.), m. p. 156—157° (decomp.), of base (VIB).

The hydrobromide (2 g.) of ketone (V)B also yielded the hydrobromide (0·36 g.), m. p. 156—157° (decomp.), of (VI)B when treated similarly.

(*c*) Ketone (XIV) (1 g.) in ethanol (20 ml.) was kept for 72 hr. at 40° with the pseudo-base (IX; R = $CH_2Ph$) (0·88 g.) and 2N-aqueous sodium carbonate (0·5 ml.). The yellow oil was dissolved by the addition of chloroform. Ketone (VI)B (1·36 g.), m. p. 126—128°, slowly separated.

(*d*) The pseudo-base (IX; R = $CH_2Ph$) (3 g.), acetone (1 ml.), ethanol (25 ml.), and sodium carbonate (0·1 g.) were allowed to react for 2 days at room temperature. The gum, obtained

after removal of the solvents and the inorganic salts, crystallised from ethanol to give ketone (VI)B (0·6 g.), m. p. 126—128°.

*Isomer A.* (*a*) The hydrobromide (5 g.) of the ketone (V)B was converted into the base and treated in benzene (50 ml.) with benzyl bromide (1 ml.) for 20 hr. at room temperature. The product was isolated as a crude base (3 g.), and converted in ethanol into a crystalline hydrobromide (2·46 g.), m. p. 143—145° (decomp.). The free ditertiary base (1·2 g.), isolated from the hydrobromide and crystallised from ether, was a diastereoisomeric mixture of ketones (VI)A and (VI)B, m. p. 118—123°. Ketone (VI)B slowly separated as plates (0·3 g.), m. p. 128—131°, from a solution of this mixture in chloroform–ether (1 : 4). Addition of ether to the mother-liquor gave the *isomer* (VI)A (0·6 g.), m. p. 112—113°; recrystallisation from chloroform–ether raised the m. p. to 113—115° (Found: C, 75·7; H, 7·1; N, 4·8. $C_{39}H_{44}N_2O_5$ requires C, 75·45; H, 7·1; N, 4·5%).

The *hydrochloride* separated from ethanol as fine needles, m. p. 134—136° (decomp.) (Found: Cl, 10·1; N, 4·3. $C_{39}H_{46}Cl_2N_2O_5$ requires Cl, 10·2; N, 4·0%).

(*b*) Ketone (V)A (from 5 g. of the hydrochloride), treated as above with benzyl bromide (1 ml.) in benzene (50 ml.), gave 0·2 g. of ketone (VI)B, m. p. 130—131°, and 0·6 g. of (VI)A, m. p. 110—112°.

*Hydrogenolysis of the* NN′*-Dibenzyl Ketones* (VI)A *and* (VI)B.—*Aqueous solvents.* (*a*) The hydrochloride (0·195 g.) of ketone (VI)A in water (5 ml.) and ethanol (2 ml.) was shaken with 10% palladised charcoal (0·031 g.) under hydrogen at room temperature and pressure for 1·5 hr. Basification, after removal of the catalyst and evaporation of the ethanol, gave crude base (II)A (0·038 g.), m. p. 135—139°, identified by its infrared spectrum.

(*b*) The hydrobromide (0·16 g.) of ketone (VI)B, treated in a similar manner, gave crude (II)B (0·025 g.), m. p. 131—132°, identified by its infrared spectrum.

*Acetic acid as solvent.* (*a*) Hydrogenation of ketone (VI)B (5 g.) in acetic acid (75 ml.) with Adams catalyst (0·25 g.) at room temperature and pressure was stopped after an uptake of 2 mol., and the catalyst was filtered off. Dilution with water, followed by basification, extraction with chloroform, and evaporation, gave a brown oil. Elution of this from alumina with benzene–chloroform (19 : 1) yielded 2-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (XVI) (1 g.), m. p. 85—88°. Further elution with chloroform gave 1-(2-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl)propan-2-ol (XV) as a brown gum [*hydrobromide*, yellow prisms, m. p. 146—148° (decomp.), from ethanol–ether (Found: C, 59·4; H, 6·7; Br, 19·2; N, 3·7. $C_{21}H_{28}BrNO_3$ requires C, 59·7; H, 6·6; Br, 19·0; N, 3·3%)].

(*b*) Ketone (VI)B (3 g.) in acetic acid (50 ml.) was hydrogenated at room temperature and pressure with 20% palladised charcoal (0·4 g.) until 2 mol. of hydrogen had been absorbed. The crude base, isolated as above, afforded the hydrochloride (0·8 g.) of the tetrahydroisoquinoline (XVI) from ethanol, as plates, m. p. 230—232° (decomp.).

*Hydrogenolysis of Ketone* (XIV).—(*a*) The ketone (2 g.) in acetic acid (20 ml.) was hydrogenated at room temperature and pressure with 20% palladised charcoal (0·25 g.). The uptake was 1·2 mol. The crude base, isolated as above, gave the hydrochloride (0·45 g.) of the acetonyl base (XI) from ethanol as prisms, m. p. 180—182°.

(*b*) The ketone (3 g.) in acetic acid (50 ml.) was shaken with Adams catalyst (0·19 g.) at room temperature and pressure under hydrogen until the uptake was 1·5 mol. The crude base, isolated as above, afforded the hydrobromide (1·6 g.) of the alcohol (XV) from ethanol, as prisms, m. p. 146—148° (decomp.).

2-*Benzyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (XVI).—The quaternary bromide (XVII) (1 g.) in water (20 ml.) was shaken with Adams catalyst (0·1 g.) at room temperature and pressure under hydrogen until one mol. was absorbed. The crude basic product, in benzene–light petroleum, deposited the *tetrahydroisoquinoline* (XVI) as needles (0·54 g.), m. p. 88—90° (Found: C, 76·3; H, 7·8; N, 4·9. $C_{18}H_{21}NO_2$ requires C, 76·3; H, 7·5; N, 4·9%), that gave a *picrate*, prisms (from *NN*-dimethylformamide–ethanol), m. p. 174—176° (decomp.) (Found: C, 56·2; H, 4·7; N, 11·1. $C_{24}H_{24}N_4O_9$ requires C, 56·25; H, 4·7; N, 11·1%), and a hydrochloride (from ethanol) as plates, m. p. 235—237° (decomp.).

2-*Benzyl*-1,2,3,4-*tetrahydro*-1-*hydroxyamino*-6,7-*dimethoxyisoquinoline* (XVIII).—(*a*) The pseudo-base (IX; R = $CH_2Ph$) (2 g.) in ethanol (20 ml.) was heated at reflux for 10 min. with hydroxylamine hydrochloride. Evaporation of the solvent and addition of aqueous sodium carbonate gave the *hydroxyamino-compound* (XVIII) (1·8 g.), m. p. 172—174°. Recrystallisation from *NN*′-dimethylformamide–ethanol gave prisms, m. p. 173—174° (Found: C, 69·2; H, 7·3; N, 8·9. $C_{18}H_{22}N_2O_3$ requires C, 68·8; H, 7·1; N, 8·9%).

(*b*) Ketone (VI)B (0·62 g.), treated as above, gave (XVIII) (0·44 g.), m. p. 172—174°.

(*c*) Ketone (XIV) (0·5 g.) similarly gave (XVIII) (0·4 g.), m. p. 173—174°.

*Hydrogenolysis of the Benzyl Base* (XVI).—The tetrahydroisoquinoline (XVI) (0·3 g.) in acetic acid (10 ml.) was hydrogenated with 10% palladised charcoal (0·1 g.) as above. The crude product (0·2 g.) gave 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, characterised as the picrate, m. p. 203—205° (decomp.) [lit.,[15] 202—203° (decomp.)], and the hydrochloride, m. p. 258—262° (lit.,[15] 262°).

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[15] Forsyth, Kelly, and Pyman, *J.*, 1925, **127**, 1659.