669. *Synthesis and Oxidation of Some 1-Benzylisoquinoline Derivatives*

By I. Baxter, L. T. Allan, and G. A. Swan

A number of new 1-benzylisoquinoline derivatives have been synthesised. Attempts to perform oxidative coupling with some of these were unsucessful.

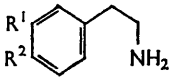
It has been suggested that the biosynthesis of aporphine alkaloids proceeds through intramolecular coupling of phenolic 1-benzylisoquinolines.[1] Early attempts to simulate this process in the laboratory using laudanosoline failed because carbon–nitrogen coupling occurred in preference to the desired carbon–carbon coupling.[2,3] It has been further suggested that the removal of the basic properties of the nitrogen atom in laudanosoline or its methyl ethers, by acylation or quaternisation, would prevent carbon–nitrogen interaction occurring and make carbon–carbon interaction more favourable.[2] No report of dehydrogenation experiments on any such modified materials had appeared and so it was decided to examine the action of various oxidising agents on a number of these compounds. The compounds chosen were of the first type and *N*-formyl was selected as the nitrogen blocking group.

The synthesis of the *N*-formyl-1,2,3,4-tetrahydroisoquinolines was achieved directly from the corresponding 3,4-dihydroisoquinolines by a one-stage process involving reductive formylation with a mixture of formic acid and formamide.[4] The yields obtained by this method were good and in most cases the products were obtained crystalline. It was essential to protect all hydroxyl groups by ether linkages because the presence of free hydroxyl groups appeared to inhibit the reduction completely.

[1] R. Robinson and S. Sugasawa, *J.*, 1931, 3163.
[2] R. Robinson and S. Sugasawa, *J.*, 1932, 789.
[3] C. Schöpf and K. Thierfelder, *Annalen*, 1932, **497**, 22.
[4] J. Gardent, *Bull. Soc. chim. France*, 1960, 118.

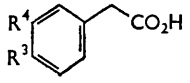
For the initial oxidation studies 2-formyl-1,2,3,4-tetrahydro-7-hydroxy-1-(3-hydroxybenzyl)-6-methoxyisoquinoline (Vh), 2-formyl-1,2,3,4-tetrahydro-1-(3-hydroxybenzyl)-6,7-dimethoxyisoquinoline (Vi) and 2-formyl-1,2,3,4-tetrahydro-7-hydroxy-1-(3-hydroxy-4-methoxybenzyl)-6-methoxyisoquinoline (Vj) were employed.

For the synthesis of these compounds we used the route shown in formulæ (I)—(V).



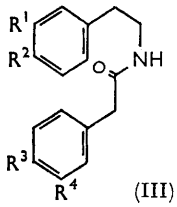
(I)

(Ia: $R^1 = OMe$, $R^2 = OCH_2Ph$)
(Ib: $R^1 = R^2 = OMe$)
(Ic: $R^1 = R^2 = OCH_2Ph$)

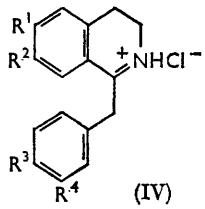


(II)

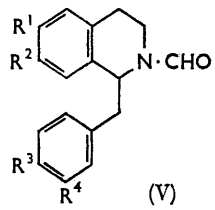
(IIa: $R^4 = OCH_2Ph$, $R^3 = H$)
(IIb: $R^4 = OCH_2Ph$, $R^3 = OMe$)
(IIc: $R^3 = R^4 = OCH_2Ph$)



(III)



(IV)



(V)

(IIIa, IVa, Va: $R^1 = OMe$, $R^2 = R^4 = OCH_2Ph$, $R^3 = H$)
(IIIb, IVb, Vb: $R^1 = R^2 = OMe$, $R^4 = OCH_2Ph$, $R^3 = H$)
(IIIc, IVc, Vc: $R^1 = R^2 = R^4 = OMe$, $R^3 = H$)
(IIId, IVd, Vd: $R^1 = R^3 = OMe$, $R^2 = R^4 = OCH_2Ph$)
(IIIe, IVe, Ve: $R^1 = R^2 = R^3 = R^4 = OMe$)
(IIIf, IVf, Vf: $R^1 = R^2 = R^4 = OCH_2Ph$, $R^3 = H$)
(IIIg, IVg, Vg: $R^1 = R^2 = R^3 = R^4 = OCH_2Ph$)

(Vh: $R^1 = OMe$, $R^2 = R^4 = OH$, $R^3 = H$)
(Vi: $R^1 = R^2 = OMe$, $R^4 = OH$, $R^3 = H$)
(Vj: $R^1 = R^3 = OMe$, $R^2 = R^4 = OH$)
(Vk: $R^1 = R^2 = R^4 = OH$, $R^3 = H$)
(Vl: $R^1 = R^2 = R^3 = R^4 = OH$)

4-Benzyloxy-3-methoxyphenethylamine (Ia) was prepared from the corresponding ω-nitrostyrene. Attempts to find a better route were unsuccessful. The reduction of 4-benzyloxy-3-methoxyphenylacetonitrile with lithium aluminium hydride or with hydrogen in the presence of 5% rhodium on alumina [5] gave only a 30% yield of the amine (Ia). 3-Benzyloxy-*N*-(4-benzyloxy-3-methoxyphenethyl)phenylacetamide (IIIa) was prepared by heating an equimolecular mixture of the amine (Ia) and 3-benzyloxyphenylacetic acid (IIa) at 180°. Bischler–Napieralski cyclisation then afforded the 3,4-dihydroisoquinoline hydrochloride (IVa). Reductive formylation of the latter, as described above, yielded the *N*-formyl compound (Va) which on treatment with acid, or better, hydrogen and palladium, was converted into the diphenol (Vh). In a similar way the monophenol (Vi) was prepared from 3,4-dimethoxyphenethylamine (Ib) and 3-benzyloxyphenylacetic acid. On methylation with dimethyl sulphate and aqueous sodium hydroxide both (Vh) and (Vi) gave the same syrupy trimethyl-*N*-formyl compound which had an infrared spectrum identical with that of the product from the reductive formylation of the hydrochloride (IVc) and must be 2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3-methoxybenzyl)isoquinoline (Vc).

2-Formyl-1,2,3,4-tetrahydro-7-hydroxy-1-(3-hydroxy-4-methoxybenzyl)-6-methoxyisoquinoline (Vj) was prepared from the amine (Ia) and the acid (IIb). The latter was obtained by a modification of Schöpf and Winterhalder's method.[6] On reduction with lithium aluminium hydride the *N*-formyl compound (Vj) was converted into a base which was identical with an authentic sample of *dl*-reticuline (VIa).[7]

Attempted oxidation of the *N*-formyl compounds (Vh), (Vi), and (Vj) with alkaline potassium ferricyanide at 0°, chloranil or tetrachloro-*o*-quinone in ethanol or acetic acid, manganese dioxide in chloroform, or horseradish peroxidase and hydrogen peroxide at pH 9·3 [8] yielded only unchanged starting material. The failure of these compounds to

[5] M. Freifelder, *J. Amer. Chem. Soc.*, 1960, **82**, 2386.
[6] C. Schöpf and L. Winterhalder, *Annalen*, 1940, **544**, 62.
[7] K. W. Gopinath, T. R. Govindachari, and N. Viswanathan, *Chem. Ber.*, 1959, **92**, 1657.
[8] A. J. Gross and I. W. Sizer, *J. Biol. Chem.*, 1959, **234**, 1611.

undergo coupling reactions prompted us to examine those compounds possessing more than two phenolic hydroxyl groups, namely (Vk) and (Vl), the latter being of particular interest in view of its close relationship to laudanasoline.

When isoquinoline was treated with a mixture of formic acid and formamide it was converted into 2-formyl-1,2,3,4-tetrahydroisoquinoline in 70% yield. A small quantity of a dihydrochloride of a base $C_{10}H_{14}N_2$,2HCl was also isolated which has been formulated as the dihydrochloride of 1,2,3,4-tetrahydro-4-methylaminoisoquinoline. In a similar manner papaverine (VIIa) was reduced by a mixture of formic acid and formamide to 2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline (Ve) in 50% yield. This material was identical with the compound obtained from the 3,4-dihydroisoquinoline salt (IVe) by reductive formylation. However papaveroline (VIIb) could not be reduced by formic acid and formamide to the *N*-formyl compound (Vl), a polymer being the sole product. The tri- and tetra-phenols (Vk) and (Vl) were eventually prepared by the scheme shown (I)—(V); both syntheses commenced from 3,4-dibenzyloxyphenethylamine (Ic). The synthesis of the latter base has been achieved from 3,4-dibenzyloxyphenylpropionhydrazide *via* a Curtius degradation.[9] Although the reduction of ω-nitrostyrenes by lithium aluminium hydride has been widely used for the preparation of phenethylamines we were unable to find an example of such a reaction being performed with 3,4-dibenzyloxy-ω-nitrostyrene. When this nitrostyrene was reduced with lithium aluminium hydride during 16 hr., using the Soxhlet procedure, a non-basic gum was obtained. Subsequent reduction of this gum with zinc dust and acetic acid gave a 38% yield of the amine (Ic). With a reaction time of 42 hr. no basic material was isolated even after treatment with zinc dust and acetic acid, presumably because the prolonged action of the reducing agent brought about hydrogenolysis of the benzyl ether groups. However when a slurry of the nitrostyrene and lithium aluminium hydride was stirred and refluxed for 12 hr. the amine (Ic) was isolated in 68% yield as its hydrochloride. Condensation of the free amine with the acid (IIa) gave the expected amide (IIIf) which was converted *via* the hydrochloride (IVf) into the *N*-formyl compound (Vf) which failed to crystallise. Catalytic debenzylation over palladium gave the crystalline triphenol (Vk). On methylation with dimethyl sulphate and alkali in the presence of sodium dithionite the trimethyl ether (Vc) was obtained.

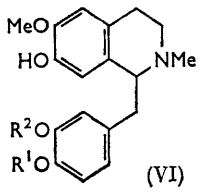
3,4-Dibenzyloxyphenylacetic acid (IIc) was prepared from 3,4-dibenzyloxybenzaldehyde. Reduction of the latter with sodium borohydride in methanol gave 3,4-dibenzyloxybenzyl alcohol which was converted by thionyl chloride into 3,4-dibenzyloxybenzyl chloride. Potassium cyanide in dry dimethyl sulphoxide converted the chloride into the related cyanide which was then hydrolysed by aqueous potassium hydroxide to the acid (IIc). 3,4-Dibenzyloxyphenethylamine and 3,4-dibenzyloxyphenylacetic acid condensed together at 180° to give the amide (IIIg) which was transformed in the normal way into the tetrahydroxy-compound (Vl). Methylation of (Vl) with dimethyl sulphate and sodium hydroxide in the presence of sodium dithionite gave the tetramethyl ether (Ve).

The action of various one-electron oxidising agents and high-potential benzoquinones in either ethanol or acetic acid on the *N*-formyl compounds (Vk) and (Vl) failed to bring about oxidative coupling. When our work was nearing completion, details appeared of some successful coupling experiments by Franck *et al.*[10] in which quaternary salts of phenolic 1-benzylisoquinolines had been employed. However these authors were unable to effect oxidative coupling of *N*-acyl-1,2,3,4-tetrahydroisoquinolines to aporphines.[11]

Attempts to convert the tertiary bases (VIa), (VIIIa), and (VIIIb) into aporphines by the action of alkaline potassium ferricyanide at 0° were unsuccessful. Part of the starting material was usually recovered unchanged and the ultraviolet spectra of the crude products

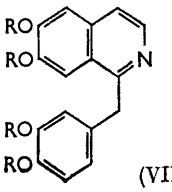
[9] E. J. Forbes, *J.*, 1955, 3926.
[10] B. Franck, G. Blaschke, and G. Schlingloff, *Tetrahedron Letters*, 1962, 439; B. Franck and G. Schlingloff, *Annalen*, 1962, **659**, 123.
[11] B. Franck and G. Blaschke, *Annalen*, 1963, **668**, 145.

suggested that aporphines could not be present in more than just traces. Horseradish peroxidase in the presence of hydrogen peroxide at pH 9—9·5 and 37° also failed to convert bases (VIIIa), (VIIIb), and (VIIIc) into aporphines. From (VIIIb) and (VIIIc) small



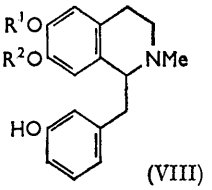
(VI)

(VIa: $R^1 = CH_3$, $R^2 = H$)
(VIb: $R^1 = H$, $R^2 = CH_3$)



(VII)

(VIIa: $R = CH_3$)
(VIIb: $R = H$)



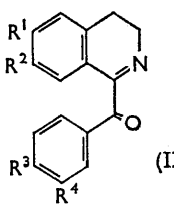
(VIII)

(VIIIa: $OR^1 = OR^2 = OH$)
(VIIIb: OR^1 and OR^2 replaced by $O{-}CH_2{-}O$)
(VIIIc: $OR^1 = OR^2 = OCH_3$)

amounts of *m*-hydroxybenzaldehyde were obtained as well as some unchanged starting material. 1,2,3,4-Tetrahydro-2-methylisoquinoline was recovered unchanged after treatment with horseradish peroxidase in the presence of hydrogen peroxide at pH 8·5 and 37°. The use of enzymic oxidations is limited by the poor water solubility of both the phenolic tertiary bases and *N*-formyl compounds in the pH range required. Recently Battersby and Brown [12] have successfully oxidised the tertiary base (VIb) with alkaline ferricyanide to give 4% yield of a mixture of coupled products.

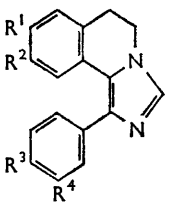
It has been shown that 1-benzyl-3,4-dihydroisoquinolines and to a less extent 1-benzylisoquinolines can be converted into 2-formyl-1,2,3,4-tetrahydroisoquinolines by the action of formic acid and formamide. It was of interest therefore to investigate the effect of this reagent on 1-benzoyl-3,4-dihydroisoquinolines. A mixture of formic acid and formamide converted the 3,4-dihydroisoquinoline (IXa) into a crystalline base, $C_{21}H_{22}N_2O_4$, which formed a mono-picrate, -hydrochloride, and -methiodide. The infrared spectrum of the base indicated that it contained no carbonyl group and that it was a derivative of tetrahydroisoquinoline. The ultraviolet spectrum indicated that a considerable change in the conjugation of the molecule had occurred. The base was not reduced by sodium borohydride or hydrogen and platinum and failed to undergo acetylation with acetic anhydride. It was unaffected by boiling hydrochloric acid but on heating with concentrated hydrochloric acid in a sealed tube was demethylated to give a tetrahydroxy-base isolated as its hydrochloride. The spectral evidence and the apparent inertness of the base are consistent with the substances being 5,6-dihydro-8,9-dimethoxy-1-(3,4-dimethoxyphenyl)imidazo-[5,1-*a*]isoquinoline (Xa). Thus the derived tetrahydroxy-base must be (Xb).

The analyses of the base (Xa) and its derivatives indicated that there was a tendency for solvation to occur. The picrate crystallised from acetone in needles containing one molecule of acetone of crystallisation which could not be removed even at 60° in a high vacuum. The acetone was detected by elemental analysis and the presence of a band at 1712 cm.$^{-1}$ in the infrared spectrum of the picrate corresponding to the band due to the carbonyl group in acetone.



(IX)

(IXa: $R^1 = R^2 = R^3 = R^4 = OCH_3$)
(IXb: $R^1 = R^2 = R^3 = OCH_3$, $R^4 = H$)

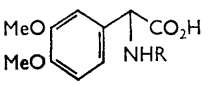


(X)

(Xa: $R^1 = R^2 = R^3 = R^4 = OCH_3$)
(Xb: $R^1 = R^2 = R^3 = R^4 = OH$)
(Xc: $R^1 = R^2 = R^3 = OCH_3$, $R^4 = H$)

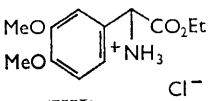
[12] A. R. Battersby and T. H. Brown, *Proc. Chem. Soc.*, 1964, 85.

In a similar way the 3,4-dihydroisoquinoline (IXb) was converted by formic acid and formamide into the base (Xc). The analyses of this base and its picrate indicated that solvation was not occurring in this case. As a proof of the structure an independent synthesis of the base (Xa) was performed. The method used was similar to that used by Child and Pyman [13] and more recently by Elliott [14] for the synthesis of 5,6-dihydro-8,9-dimethoxy-3-phenylimidazo[5,1-*a*]isoquinoline.

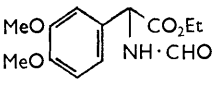


(XI)

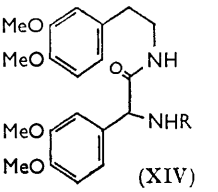
(XIa: R = H)
(XIb: R = CHO)
(XIc: $R = CO_2CH_2Ph$)



(XII)



(XIII)



(XIV)

(XIVa: $R = CO_2CH_2Ph$)
(XIVb: R = H)
(XIVc: R = CHO)

The initial aim was to synthesise the diamide (XIVc) because it was felt that this would readily undergo a double cyclodehydration to give the base (Xa). The first attempts to prepare the diamide (XIVc) were unsuccessful. Formylation of α-3,4-dimethoxyphenylglycine (XIa) with a mixture of formic acid and acetic anhydride gave the α-amido-acid (XIb) which, because of a marked tendency to undergo dehydration, failed to condense with 3,4-dimethoxyphenethylamine under a variety of conditions. The corresponding ester (XIII) was prepared *via* the salt (XII) but this also failed to condense satisfactorily with 3,4-dimethoxyphenethylamine.

A successful synthesis of the diamide (XIVc) was achieved in the following way. The amino-acid (XIa) reacted smoothly with benzyloxycarbonyl chloride to give the acid (XIc). Phosphorus pentachloride converted the acid (XIc) into its chloride which in turn reacted with 3,4-dimethoxyphenethylamine to yield the amide (XIVa). Catalytic hydrogenation of this amide over palladium gave the base (XIVb) which was converted by a mixture of formic acid and acetic anhydride into the diamide (XIVc). Phosphorus oxychloride in toluene converted the diamide into a red gum from which, by treatment with hydrochloric acid, a substance identical with the hydrochloride of the base (Xa) was isolated in low yield.

Experimental

Unless otherwise stated, light petroleum had b. p. 60—80°. Formic acid refers to 98—100% formic acid.

4-Benzyloxy-3-methoxyphenylacetonitrile.—A mixture of *O*-benzylvanillin [15] (17·5 g.), rhodanine (10 g.), fused sodium acetate (16 g.), and glacial acetic acid (54 ml.) was stirred and heated on a water-bath for 2·5 hr. After cooling, water (200 ml.) was added and the mixture stirred. The solid which was deposited was filtered off, washed with water, and dried. Recrystallisation from glacial acetic acid gave *5-(4-benzyloxy-3-methoxybenzylidene)rhodanine* (21·6 g.), m. p. 219° (Found: C, 60·25; H, 4·25. $C_{18}H_{15}NO_3S_2$ requires C, 60·50; H, 4·25%). The above rhodanine condensation product (21 g.) was suspended in 15% aqueous sodium hydroxide (120 ml.) and heated on a water-bath until all had dissolved. The solution was cooled in a freezing mixture and acidified by rapid addition of 10% hydrochloric acid. The solid which was deposited was collected, dried, and recrystallised from methanol, giving *β-(4-benzyloxy-3-methoxyphenyl)-α-thiopropionic acid* (16·2 g.) as a yellow crystalline solid, m. p. 155° (Found: C, 64·50; H, 5·15; S, 9·90. $C_{17}H_{16}O_4S$ requires C, 64·50; H, 5·10; N, 10·15%). To a hot solution of hydroxylamine hydrochloride (10·6 g.) in water (10 ml.) was added a solution of sodium (3·53 g.) in ethanol (100 ml.). The sodium chloride which was precipitated was filtered off and the filtrate added to the above thiopropionic acid (16 g.). The solution was heated on a water-bath for 20 min.

[13] R. Child and F. L. Pyman, *J.*, 1931, 36.
[14] I. W. Elliott, *J. Org. Chem.*, 1962, **27**, 3302.
[15] J. Finkelstein, *J. Amer. Chem. Soc.*, 1951, **73**, 550.

and kept at room temperature for 1·5 hr. The solution was evaporated to dryness (water-bath/reduced pressure) and the residue dissolved in 5% sodium hydroxide solution. After filtration, the solution was cooled and acidified cautiously with 10% hydrochloric acid. The product separated as a white solid and after recrystallisation from ethyl acetate containing a little light petroleum α-(*4-benzyloxy-3-methoxybenzyl*)-α-*oximinoacetic acid* (10 g.) was obtained as needles, m. p. 152° (Found: C, 64·45; H, 5·90; N, 4·65. $C_{17}H_{17}NO_5$ requires C, 64·75; H, 5·45; N, 4·45%). When this acid (5·7 g.) was warmed gently with acetic anhydride (40 ml.) a clear solution was obtained, which was evaporated to dryness and the residue dissolved in ether. The ethereal solution was washed with water and sodium hydrogen carbonate solution and dried (Na_2SO_4). Removal of the ether gave a solid residue which after crystallisation from ethanol gave 4-benzyloxy-3-methoxyphenylacetonitrile (2·5 g.) as long white needles, m. p. 67° (lit.,[16] 67—68°) (Found: C, 76·05; H, 5·95; N, 5·40. Calc. for $C_{16}H_{15}NO_2$: C, 75·90; H, 5·95; N, 5·55%).

4-Benzyloxy-3-methoxy-ω-nitrostyrene.—A mixture of *O*-benzylvanillin [15] (40 g.), ammonium acetate (11·6 g.), nitromethane (60 ml.), and glacial acetic acid (120 ml.) was refluxed for 1·5 hr. On cooling, the crystals which were deposited were collected and recrystallised from ethanol. The nitrostyrene (31 g.) formed yellow needles, m. p. 121° (lit.,[17] 122—123°).

4-Benzyloxy-3-methoxyphenethylamine (Ia). This was prepared by Hey and Palluel's method [18] and also as follows. A solution of 4-benzyloxy-3-methoxyphenylacetonitrile (2·4 g.) in dry ether (150 ml.) was added to a stirred solution of lithium aluminium hydride (0·55 g.) in dry ether (80 ml.) and the mixture then refluxed for 1 hr. The mixture was decomposed by the addition of water and 40% sodium hydroxide and the organic layer collected. The ether extract was washed with dilute hydrochloric acid and the acid solution basified with sodium hydroxide and extracted with ether. The latter (dried) ether extract was saturated with dry hydrogen chloride whereupon a solid was precipitated. Recrystallisation of the solid from a mixture of ethanol and ether gave the hydrochloride of the base (0·96 g.) as white needles, m. p. 171° (lit.,[19] 173—175°).

3-Benzyloxybenzaldehyde.—A mixture of *m*-hydroxybenzaldehyde (20 g.), benzyl chloride (21 ml.), 25% aqueous potassium hydroxide solution (25 ml.), and ethanol (100 ml.) was refluxed for 4 hr. The reaction mixture was cooled, filtered, concentrated, and poured into cold 2% sodium hydroxide solution (250 ml.). The benzyl ether (33 g.) separated as a cream solid, m. p. 50° (lit.,[20] 54°).

3-Benzyloxyphenylacetic Acid (IIa).—This, m. p. 126°, was prepared by Rapson and Robinson's method [20] or more readily as follows. Sodium borohydride (2·1 g.) was added to a solution of 3-benzyloxybenzaldehyde (20 g.) in a mixture of methanol (140 ml.) and water (10 ml.) and the solution kept overnight. A little glacial acetic acid was added to destroy the excess of borohydride and after neutralising with sodium hydrogen carbonate the reaction mixture was extracted with benzene (100 ml.). The dried extract was evaporated to dryness and the residue recrystallised from benzene–light petroleum. *3-Benzyloxybenzyl alcohol* (14 g.) separated in white needles, m. p. 48° (Found: C, 78·25; H, 6·85. $C_{14}H_{14}O_2$ requires C, 78·50; H, 6·60%). Phosphorus tribromide (2·3 ml.) was added to a solution of the foregoing alcohol (8·6 g.) in dry ether (60 ml.) and the solution kept at 4° for 2 days. The ethereal solution was extracted with water, dried, and evaporated to dryness. Recrystallisation of the residue from light petroleum gave 3-benzyloxybenzyl bromide (8·8 g.) in white needles, m. p. 55° (Found: C, 60·20; H, 4·60; Br, 29·20. $C_{14}H_{13}BrO$ requires C, 60·65; H, 4·70; Br, 28·85%). A mixture of the foregoing bromide (6·5 g.), sodium cyanide (1·8 g.), and dry dimethyl sulphoxide (50 ml.) was shaken at 27° for 24 hr. The reaction mixture was diluted with water and extracted with ether. Evaporation of the dried extract gave an oil which was disilled, b. p. 260°/20 mm. The oil was dissolved in ethanol (30 ml.) and refluxed with solution of potassium hydroxide (15 g.) in water (30 ml.) for 10 hr. The ethanol was distilled off and the solution acidified with 6N-hydrochloric acid. The precipitated solid was collected, dried, and recrystallised from dry benzene. 3-Benzyloxyphenylacetic acid (4·1 g.) formed white crystals, m. p. 124 (lit.,[20] 126°).

[16] I. T. Strukov, *Zhur. obshchei Khim.*, 1961, **31**, 2709.
[17] N. A. Lange and W. E. Hambourger, *J. Amer. Chem. Soc.*, 1931, **53**, 3865.
[18] D. H. Hey and A. L. Palluel, *J.*, 1957, 2926.
[19] S. Kobayashi, *Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1927, **6**, 149.
[20] W. S. Rapson and R. Robinson, *J.*, 1935, 1533.

3-Benzyloxy-N-(4-benzyloxy-3-methoxyphenethyl)phenylacetamide (IIIa).—A mixture of 3-benzyloxyphenylacetic acid (4·54 g.) and 4-benzyloxy-3-methoxyphenethylamine (4·75 g.) was heated at 180° for 45 min. On cooling, the residue was dissolved in hot benzene and washed first with dilute hydrochloric acid and then dilute sodium hydroxide solution. The benzene solution was dried, concentrated, and diluted with light petroleum. The precipitated solid was collected and recrystallised from ethanol. The *amide* (IIIa) separated on cooling in cream needles (6·3 g.), m. p. 110° (Found: C, 77·75; H, 6·95. $C_{31}H_{31}NO_4$ requires C, 77·35; H, 6·45%).

7-Benzyloxy-1-(3-benzyloxybenzyl)-3,4-dihydro-6-methoxyisoquinoline Hydrochloride (IVa).—A solution of the above amide (6·3 g.) in dry chloroform (28 ml.) was kept with phosphorus pentachloride (8 g.) for 5 days in the refrigerator. The resulting solid was filtered off, washed with cold chloroform then with ether, and treated with ethanol, yielding the hydrochloride. Dilution of the filtrate with ether yielded a further crop. This *hydrochloride* (3·9 g.) separated from a mixture of ethanol and dilute hydrochloric acid as a cream coloured solid, m. p. 201° (Found: C, 74·30; H, 6·40. $C_{31}H_{30}ClNO_3$ requires C, 74·45; H, 6·00%).

An alternative procedure was as follows. *Methyl β-(4-benzyloxy-3-methoxyphenyl)propionate* was prepared from hydroferulic acid by benzylation and esterification and separated from ethanol in needles, m. p. 54—55° (Found: C, 71·95; H, 7·1. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·65%). The ester (38·5 g.), amyl alcohol (13 ml.), and hydrazine hydrate (15 ml.) were refluxed for 5 hr. The solid which was deposited on cooling was collected, ground with ethanol, and recrystallised from ethanol. *β-(4-Benzyloxy-3-methoxyphenyl)propionhydrazide* (30·5 g.) separated as closely-packed needles, m. p. 122° (Found: C, 68·0; H, 6·8. $C_{17}H_{20}N_3O_3$ requires C, 68·0; H, 6·65%). A cooled solution of sodium nitrite (1·4 g.) in water (4·5 ml.) was added all at once to a stirred solution of the foregoing hydrazide (4 g.) in benzene (13·3 ml.) and acetic acid (13·3 ml.) at −5°. The mixture was stirred for a further 30 min. with cooling, diluted with benzene (88 ml.), and then run into a cooled, stirred 1·5N-sodium hydroxide solution (445 ml.). The benzene layer was collected, dried, and refluxed for 1 hr. 3-Benzyloxyphenylacetic acid (7 g.) was added and the mixture refluxed for 12 hr. The cooled solution was extracted with dilute sodium hydroxide (which led to the recovery of 6·14 g. of unchanged phenylacetic acid), washed with water, dried, and the benzene removed. Crystallisation of the gum from an ethanol–ether gave *NN′-di-[2-(4-benzyloxy-3-methoxyphenyl)ethyl]urea* (0·08 g.) in needles, m. p. 181° (Found: C, 73·35; N, 6·9. $C_{33}H_{36}N_2O_5$ requires C, 73·4; H, 6·7%). On another occasion *N-2-(4-benzyloxy-3-methoxyphenyl)ethylcarbamate*, m. p. 79°, was isolated at this stage (Found: C, 69·4; H, 6·9; N, 4·35. $C_{19}N_{23}NO_4$ requires C, 69·3; H, 7·05; N, 4·25%). Concentration of the mother-liquors gave a gum (2 g.) which slowly solidified to a white solid (1·17 g.). This was dissolved in dry chloroform (6 ml.) and treated with phosphorus pentachloride (1·4 g.) as described above. The hydrochloride (IVa; 0·48 g.) separated from ethanol–dilute hydrochloric acid as a cream coloured solid, m. p. 201°.

7-Benzyloxy-1-(3-benzyloxybenzyl)-2-formyl-1,2,3,4-tetrahydro-6-methoxyisoquinoline (Va).—A mixture of the foregoing hydrochloride (3·4 g.), formic acid (14 ml.), and formamide (70 ml.) was refluxed for 2·5 hr. The hot mixture was poured on crushed ice and the gummy precipitate collected and dissolved in dry ether. On standing a white solid crystallised. Recrystallisation from di-n-butyl ether gave the *isoquinoline* (2·9 g.) as white needles, m. p. 99° (Found: C, 77·85; H, 6·55. $C_{32}N_{31}NO_4$ requires C, 77·85; H, 6·35%).

2-Formyl-1,2,3,4-tetrahydro-7-hydroxy-1-(3-hydroxybenzyl)-6-methoxyisoquinoline (Vh).—The foregoing *N*-formyl compound (1·0 g.) was dissolved in glacial acetic acid (125 ml.) and shaken with palladium (from 0·7 g. of palladium oxide) in an atmosphere of hydrogen. When hydrogen uptake (2 mols.) had ceased, the catalyst was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in 4% sodium hydroxide solution and filtered. The filtrate was cooled in ice and saturated with carbon dioxide. The precipitated solid was collected and recrystallised from ethanol. The *isoquinoline* (0·55 g.) separated as a cream coloured solid, m. p. 258—260° (Found, for solid dried at 60°/1 mm. over P_2O_5: C, 67·35, 67·25; H, 6·8, 6·8. $C_{18}H_{19}NO_4$,0·5H_2O requires C, 67·1; H, 6·25%).

3-Benzyloxy-N-(3,4-dimethoxyphenethyl)phenylacetamide (IIIb).—Prepared from 3-benzyloxyphenylacetic acid (6·7 g.) and 3,4-dimethoxyphenethylamine (5·0 g.) as described for the amide (IIIa), it crystallised from ethanol in colourless needles (9·3 g.), m. p. 100—101° (Found: C, 74·05; H, 6·6; N, 3·65. $C_{25}H_{27}NO_4$ requires C, 74·05; H, 6·65; N, 3·45%).

1-(3-Benzyloxybenzyl)3,4-dihydro-6,7-dimethoxyisoquinoline Hydrochloride (IVb).—Prepared

from the preceding amide (9·3 g.) and phosphorus pentachloride (13·3 g.) in chloroform (25 ml.) as described for (IVa), the *hydrochloride* (8·95 g.) crystallised from a mixture of ethanol and dilute hydrochloric acid as cream coloured prisms, m. p. 202—203° (decomp.) (Found: C, 70·75; H, 6·5. $C_{25}H_{26}ClNO_3$ requires C, 70·85; H, 6·15%). A hot aqueous solution of the salt was cooled rapidly and basified with N-sodium hydroxide. The resulting gum crystallised when stirred with ether. The *base* was collected, dried, and recrystallised from benzene–light petroleum, when it had m. p. 82—84° (Found: C, 74·15; H, 6·6. $C_{25}H_{25}NO_3,H_2O$ requires C, 74·05; H, 6·65%).

1-(3-*Benzyloxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline*.—The foregoing hydrochloride (0·42 g.) absorbed 21·7 ml. of hydrogen (at 19° and 1 atm.) during 145 min. when shaken in acetic acid (15 ml.) in the presence of Adams catalyst (0·1 g.). Evaporation of the filtered solution gave a gum which crystallised from water. Recrystallisation from ethanol–ether gave the *hydrochloride* as needles, m. p. 170—171° (Found: C, 69·6; H, 6·25. $C_{25}H_{28}ClNO_3,0{\cdot}25H_2O$ requires C, 69·75; H, 6·65%).

1-(3-*Benzyloxybenzyl*)-2-*formyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (Vb).—Prepared from the hydrochloride (IVb; 6 g.), formic acid (24 ml.), and formamide (120 ml.) as described for (Va), the *amide* crystallised from di-n-butyl ether in colourless needles (4·8 g.), m. p. 101—102°, $\lambda_{max.}$ 283 mμ (log ε 3·79) (Found: C, 73·35; H, 6·65. $C_{26}H_{27}NO_4,0{\cdot}5H_2O$ requires C, 73·25; H, 6·55%). On reduction with an excess of lithium aluminium hydride in tetrahydrofuran it was converted into 1-(3-*benzyloxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-*methylisoquinoline* which was characterised as its *picrate*; recrystallisation from acetone–ethanol gave needles, m. p. 163—164° (Found: C, 60·3; H, 5·25. $C_{32}H_{32}N_4O_{10}$ requires C, 60·75; H, 5·05%). Alkaline hydrolysis of the amide (Vb) with 40% potassium hydroxide gave 1-(3-benzyloxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline which was characterised as its hydrochloride. Recrystallisation of the latter from ethanol–ether gave needles, m. p. 172—173° (Found: C, 69·95; H, 6·95. $C_{25}H_{28}ClNO_3$ requires C, 70·45; H, 6·6%).

2-*Formyl*-1,2,3,4-*tetrahydro*-1-(3-*hydroxybenzyl*)-6,7-*dimethoxyisoquinoline* (Vi).—To the foregoing *N*-formyl compound (4 g.) was added formic acid (45 ml.) and concentrated hydrochloric acid (21 ml.) previously saturated with hydrogen chloride at 0°. The solution was warmed on a water-bath for 45 min., refluxed for 10 min., and evaporated to dryness. The residue was dissolved in hot chloroform and the solution washed with dilute hydrochloric acid followed by dilute sodium hydroxide solution. The alkaline washings were saturated with carbon dioxide and the precipitate collected. Recrystallisation from ethanol gave the *phenolic* N-*formyl compound* (1·05 g.) as a cream coloured solid, m. p. 192—194° (Found for the material dried at 60°/1 mm. over P_2O_5; C, 69·2; H, 6·7. $C_{19}H_{21}NO_4$ requires C, 69·7; H, 6·5%).

Methylation of the Amides (Vh) *and* (Vi).—The method employed was the same for both compounds. The phenolic *N*-formyl compound (0·10 g.) was dissolved in dilute sodium hydroxide solution (5 ml.). Dimethyl sulphate (0·2 ml.) was added slowly with shaking and the mixture heated on a water-bath for 30 min. The mixture was extracted with chloroform and after drying the extract was evaporated to dryness under reduced pressure. The residue was chromatographed on alumina. Elution with benzene–chloroform (1 : 1) gave a syrup (Found: C, 68·5; H, 6·75. $C_{20}H_{23}NO_4,0{\cdot}5H_2O$ requires C, 68·55; H, 6·9%). The infrared spectrum of the syrup was identical with that of 2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3-methoxybenzyl)isoquinoline.

3,4-*Dihydro*-6,7-*dimethoxy*-1-(3-*methoxybenzyl*)*isoquinoline Hydrochloride* (IVc).—Prepared as for the hydrochloride (IVa) from 3-methoxy-*N*-(3,4-dimethoxyphenethyl)phenylacetamide (10·57 g.) and phosphorus pentachloride (21·1 g.) in chloroform (105 ml.), the hydrochloride (7·28 g.) crystallised from ethanol–ether in almost colourless crystals, m. p. 196° (Found: C, 65·2; H, 6·35. $C_{19}H_{22}ClNO_3$ requires C, 65·6; H, 6·35%).

2-*Formyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-(3-*methoxybenzyl*)*isoquinoline* (Vc).—Prepared from the above salt (0·36 g.), formic acid (1·5 ml.), and formamide (6 ml.) in the usual way, the product was a colourless syrup which failed to crystallise (Found: C, 69·5; H, 6·95. Calc. for $C_{20}H_{23}NO_4,0{\cdot}25H_2O$: C, 69·45; H, 6·85%).

3-*Benzyloxy*-4-*methoxybenzyl Alcohol*.—Prepared as for 3-benzyloxybenzyl alcohol from *O*-benzylisovanillin [1] (18 g.) by reduction with sodium borohydride (1·7 g.) in methanol (150 ml.), the alcohol (11·9 g.) crystallised from benzene–light petroleum in needles, m. p. 72° (lit.,[6] 73°).

3-*Benzyloxy*-4-*methoxybenzyl Chloride*.—To a solution of the foregoing alcohol (11·9 g.) in dry ether (200 ml.) containing pyridine (0·5 ml.) was added portionwise a solution of thionyl chloride

(7·9 ml.) in dry ether (50 ml.) during 30 min. The mixture was then kept for 10 min. and extracted with water. The ethereal solution was dried and evaporated to dryness. The residue crystallised from light petroleum giving the chloride (11·8 g.) as white needles, m. p. 77° (lit.,[6] 79°).

3-Benzyloxy-4-methoxyphenylacetonitrile.—The foregoing chloride (9·54 g.) was dissolved in dry dimethyl sulphoxide (100 ml.) and stirred after the addition of potassium cyanide (3·6 g.) at 37° for 8 hr. The mixture was diluted with water and extracted with ether. Evaporation of the dried extract gave a residue which on recrystallisation from benzene–light petroleum gave the nitrile (7·25 g.) as needles, m. p. 77° (lit.,[21] 79·5—80·5°).

3-Benzyloxy-4-methoxyphenylacetic Acid.—This was prepared by Robinson and Sugasawa's method [1] or from the preceding nitrile by the method of Schöpf and Winterhalder.[6]

3-Benzyloxy-N-(4-benzyloxy-3-methoxyphenethyl)-4-methoxyphenylacetamide (IIId).—Prepared from the foregoing acid (4·45 g.) and 4-benzyloxy-3-methoxyphenethylamine (6·2 g.) in the usual way, the amide crystallised from ethanol and had m. p. 138—140° (lit.,[7] 140—141°). An alternative procedure involved β-(4-benzyloxy-3-methoxyphenyl)propionhydrazide (5·35 g.) and 3-benzyloxy-4-methoxyphenylacetic acid (10 g.) as described for the preparation of 3-benzyloxy-*N*-(4-benzyloxy-3-methoxyphenethyl)phenylacetamide. The amide (6·95 g.) crystallised from ethanol and had m. p. 140° (Found: C, 74·95; H, 7·0. Calc. for $C_{32}H_{33}NO_5$: C, 75·15; H, 6·45%).

7-Benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline Hydrochloride (IVd).—Prepared from the above amide (8·08 g.) and phosphous pentachloride (10 g.) in chloroform (65 ml.) in the usual way, the hydrochloride (5·5 g.) crystallised from ethanol–ether as cream coloured needles, m. p. 203—205° (lit.,[7] 203—204°).

7-Benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-2-formyl-1,2,3,4-tetrahydro-6-methoxyisoquinoline (Vd).—This (1·75 g.) was prepared from the foregoing hydrochloride (1·96 g.), formic acid (7·8 ml.), and formamide (38 ml.) as described for the *N*-formyl compound (Va). The *amide* crystallised from di-n-butyl ether in needles, m. p. 106° (Found: C, 75·8; H, 6·1; N, 2·85. $C_{33}H_{33}NO_5$ requires C, 75·65; H, 6·35; N, 2·65%).

2-Formyl-1,2,3,4-tetrahydro-7-hydroxy-1-(3-hydroxy-4-methoxybenzyl)-6-methoxyisoquinoline (Vj).—The foregoing amide (1·65 g.) was debenzylated with hydrogen and palladium as described for the amide (Va). The *phenolic N-formyl compound* (0·88 g.) crystallised from ethanol and had m. p. 183° (Found: C, 65·9, 65·9; H, 6·2, 6·2. $C_{19}H_{21}NO_5,0{\cdot}25H_2O$ requires C, 65·6; H, 6·25. $C_{19}H_{21}NO_5$ requires C, 66·45; H, 6·2%).

7-Benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline.—A solution of the hydrochloride (IVd; 3·4 g.) in methanol (36 ml.) was treated, in nitrogen, first with sodium (0·15 g.) in methanol (10 ml.), then methyl iodide (15 ml.) and the mixture refluxed for 3 hr., then cooled, diluted with ether, and kept overnight in the refrigerator. The resulting solid was collected, washed with ether, and dried. Recrystallisation from methanol gave pale yellow crystals of the methiodide (3·8 g.), m. p. 196° (lit.,[7] 195—196°) (Found: C, 62·0; H, 5·25. Calc. for $C_{33}H_{34}INO_4$: C, 62·35; H, 5·35%). A hot solution of the methiodide (2·17 g.) in acetic acid (25 ml.) was treated with silver acetate (0·62 g.) in a mixture of acetic acid (13 ml.) and water (37 ml.). The resulting silver iodide was filtered off and washed with water. The combined filtrates were refluxed for 3 hr. with zinc dust (12 g.) and the hot mixture filtered. The cooled filtrate was basified with ammonium hydroxide and extracted with ether. Evaporation of the dried extract gave a residue which was recrystallised from benzene–light petroleum. The base (1·4 g.) formed needles, m. p. 89° (lit.,[22] 89°) (Found: C, 77·75; H, 6·75; N, 3·0. Calc. for $C_{33}H_{35}NO_4$: C, 77·75; H, 6·95; N, 2·75%). The picrate separated from ethanol as plates, m. p. 147° (lit.,[22] 149·5°) (Found: 62·75; H, 5·5. Calc. for $C_{39}H_{38}N_4O_{11},C_2H_6O$: C, 62·25; H, 5·6%).

1,2,3,4-Tetrahydro-7-hydroxy-1-(3-hydroxy-4-methoxybenzyl)-6-methoxy-2-methylisoquinoline (±-*Reticuline*; VIa).—The foregoing base (0·56 g.) was debenzylated with hydrogen and palladium (from 0·39 g. of palladium oxide) in glacial acetic acid (40 ml.). The catalyst was removed and the solution evaporated to dryness under reduced pressure. The residue was dissolved in 4% sodium hydroxide solution, extracted with ether, and saturated with carbon dioxide. The precipitate was collected with chloroform. After drying, the extract was

[21] A. R. Battersby, R. Binks, R. J. Francis, D. J. McCaldin, and H. Ramuz, *J.*, 1964, 3600.
[22] M. K. Jain, *J.*, 1962, 2203.

evaporated to dryness giving a brown solid, m. p. 69—71°. Recrystallisation of the crude solid from benzene–light petroleum gave ±-*reticuline* (0·3 g.), m. p. 144°, $\lambda_{max.}$ 284 mμ (log ε 3·93) (Found: C, 69·15; H, 6·95; N, 4·30. $C_{19}H_{23}NO_4$ requires C, 69·3; H, 7·05; N, 4·25%). This is the first reported crystalline sample of ±-reticuline. The *picrolonate* separated from ethanol and had m. p. 179—180° (Found: C, 58·85; H, 5·4. $C_{19}H_{23}NO_4,C_{10}H_8N_4O_5$ requires C, 58·6; H, 5·25%). The perchlorate crystallised from ethanol and had m. p. 108° (lit.,[7] 144°) (Found: C, 52·2; H, 5·8; N, 3·3. Calc. for $C_{19}H_{23}NO_4,HClO_4,0{\cdot}5H_2O$: C, 52·2; H, 5·75; N, 3·2%). The picrate was obtained in two forms. When a hot solution of picric acid in ethanol was added to a solution of the base in ethanol a sticky solid was deposited. Recrystallisation of the solid from ethanol containing a little acetone gave yellow needles, m. p. 191—192° (lit.,[22] 190—192°) (Found: C, 53·8; H, 4·7; N, 10·3. Calc. for $C_{25}H_{26}N_4O_{11}$: C, 53·9; H, 4·65; N, 10·0%). On standing the original ethanolic solution deposited a second yellow solid which crystallised from ethanol containing a little acetone and had m. p. 112° (Found: C, 51·25, 51·15; H, 5·3, 5·3; N, 9·6, 9·4. $C_{25}H_{26}N_4O_{11},1{\cdot}5H_2O$ requires C, 51·25; H, 5·0; N, 9·6%).

A mixture of the *N*-formyl compound (Vj; 34 mg.), lithium aluminium hydride (27 mg.), and dry tetrahydrofuran (12 ml.) was refluxed for 5 hr. The excess of hydride was decomposed with aqueous tetrahydrofuran and the product isolated by the method of Billek and Kratzl.[23] The oily product was converted into its picrate, m. p. 112°. No depression of m. p. was observed on admixture with the low-melting form of ±-reticuline picrate. Methylation of the base with ethereal diazomethane gave ±-laudanosine, m. p. 113° (lit.,[24] 115°).

Action of Formic Acid and Formamide on Isoquinoline.—A mixture of isoquinoline (4·77 g.), formic acid (14 ml.), and formamide (70 ml.) was refluxed for 8 hr. and poured into water. The aqueous solution (A) was extracted with ether (120 ml.). After drying, the extract was evaporated to dryness and the residue distilled. 2-Formyl-1,2,3,4-tetrahydroisoquinoline (3·74 g.) was obtained, b. p. 134°/0·8 mm. The *mercuric chloride derivative* prepared by the addition of the amide to a 5% aqueous solution of mercuric chloride crystallised from ethyl acetate–light petroleum in needles, m. p. 141° (Found: C, 21·15; H, 1·95; N, 2·35. $C_{10}H_{11}NO,1{\cdot}5HgCl_2$ requires C, 21·15; H, 1·95; N, 2·45%). The aqueous solution (A) was basified with sodium hydroxide solution and extracted with ether. Evaporation of the ether gave an oil which was dissolved in hydrochloric acid. Evaporation of the acid solution gave a white solid which was refluxed with ethanol and filtered. This solid, which was soluble in water and in methanol, when recrystallised from methanol gave 1,2,3,4-tetrahydro-4-methylamino-isoquinoline dihydrochloride (0·21 g.) as almost colourless needles, m. p. 318°, $\lambda_{max.}$ 255 mμ (log ε 2·55) (Found: C, 51·25; H, 6·85. $C_{10}H_{16}Cl_2N_2$ requires C, 51·05; H, 6·85%).

Action of Formic Acid and Formamide on Papaverine.—A mixture of papaverine (1·15 g.), formic acid (8 ml.), and formamide (40 ml.) was refluxed for 24 hr., poured into water, and extracted with chloroform. The extract was washed with dilute hydrochloric acid, dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed on alumina and elution with benzene–chloroform (4 : 3) gave 2-*formyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-1-(3,4-*dimethoxybenzyl*)*isoquinoline* (Ve; 0·57 g.), which separated from ethanol as needles, m. p. 136° (Found: C, 67·6; H, 6·65; N, 3·7. $C_{21}H_{25}NO_5$ requires C, 67·9; H, 6·8; N, 3·75%). This amide was also prepared from 3,4-dihydro-6,7-dimethoxy-1-(3-4-dimethoxybenzyl)isoquinoline hydrochloride [25] (1·07 g.), formic acid (6 ml.), and formamide (30 ml.) in the usual way.

3,4-*Dibenzyloxy*-ω-*nitrostyrene*.—A mixture of 3,4-dibenzyloxybenzaldehyde [26] (20 g.), ammonium acetate (4·7 g.), nitromethane (23 ml.), and glacial acetic acid (46 ml.) was refluxed for 3 hr. The solid which was deposited on cooling was collected and the filtrate diluted with water. The oil which was formed was collected by decantation and dissolved in the minimum of hot methanol, whence on cooling a further quantity of solid was obtained. Recrystallisation of the total solid product from methanol gave the nitrostyrene (18 g.) as yellow needles, m. p. 118° (lit.,[27] 118—119°).

3,4-*Dibenzyloxyphenethylamine* (Ic).—A mixture of the foregoing nitrostyrene (8 g.) and lithium aluminium hydride (4·5 g.) in ether (600 ml.) was stirred and refluxed for 12 hr. The excess of hydride was destroyed by the cautious addition of water and the mixture basified with

[23] G. Billek and K. Kratzl, *Monatsh.*, 1956, **87**, 106.
[24] G. A. Edwards, *J.*, 1926, 740.
[25] M. Onda, *J. Pharm. Soc. Japan*, 1954, **74**, 915.
[26] N. W. Bristow, *J.*, 1957, 513.
[27] K. E. Hamlin, U.S.P. 2,862,034 (*Chem. Abs.*, 1959, **53**, 7101).

sodium potassium tartrate solution. The organic layer was collected, dried (K_2CO_3), concentrated, and saturated with dry hydrogen chloride. The resulting solid was collected and recrystallised from ethyl acetate containing a little ethanol. The hydrochloride (5·49 g.) formed white closely-packed needles, m. p. 131° (lit.,[9] 133°).

3-Benzyloxy-N-(*3,4-dibenzyloxyphenethyl*)*phenylacetamide* (IIIf).—This was prepared from the above amine (4·4 g.), liberated from the hydrochloride as described by Forbes,[9] and 3-benzyloxyphenylacetic acid (3·25 g.). The *amide* crystallised from methanol in cream coloured needles (5·2 g.), m. p. 119° (Found: C, 79·55; H, 6·2; N, 2·55. $C_{37}H_{35}NO_4$ requires C, 79·7; H, 6·35; N, 2·5%).

6,7-Dibenzyloxy-1-(*3-benzyloxybenzyl*)-*3,4-dihydroisoquinoline Hydrochloride* (IVf).—Prepared from the preceding amide (4·8 g.) and phosphorus pentachloride (5·3 g.) as described for the hydrochloride (IVa), the *hydrochloride* (3·2 g.) crystallised from ethanol and had m. p. 146° (Found: C, 74·95; H, 6·0; N, 2·35. $C_{37}H_{34}ClNO_3,H_2O$ requires C, 74·8; H, 6·1; N, 2·3%).

2-Formyl-1,2,3,4-*tetrahydro*-*6,7-dihydroxy*-1-(*3-hydroxybenzyl*)*isoquinoline* (Vk).—The foregoing hydrochloride (3·0 g.) was treated with formic acid (12 ml.) and formamide (60 ml.) in the normal way to give the tribenzyl ether of the title compound, which failed to crystallise. This gum (2·73 g.) was dissolved in acetic acid and shaken with palladium (from 2·36 g. of palladium oxide) in hydrogen. When hydrogen uptake (3 mol.) ceased, the catalyst was filtered off and the filtrate evaporated to dryness under reduced pressure. Recrystallisation of the residue from ethanol gave the *trihydroxy*-N-*formyl compound* (1·2 g.) as white plates, m. p. 246°, $\lambda_{max.}$ 285 mμ (log ε 4·06) (Found: C, 67·7; H, 5·9. $C_{17}H_{17}NO_4$ requires C, 68·2; H, 5·75%). Methylation of the triphenol (0·25 g.) with dimethyl sulphate (2 ml.) and 20% sodium hydroxide solution (5·3 ml.) in the presence of sodium dithionite gave 2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3-methoxybenzyl) isoquinoline (0·14 g.). The infrared spectrum was identical with that of the amide (Vc).

3,4-Dibenzyloxybenzyl Alcohol.—3,4-Dibenzyloxybenzaldehyde (20 g.) was reduced by sodium borohydride (1·3 g.) as described for the preparation of 3-benzyloxybenzyl alcohol. The *alcohol* (15 g.) crystallised from ethyl acetate–light petroleum in white needles, m. p. 70° (Found: C, 78·5; H, 6·25. $C_{21}H_{20}O_3$ requires C, 78·7; H, 6·3%).

3,4-Dibenzyloxybenzyl Chloride.—The foregoing alcohol (13·5 g.) in ether containing a little pyridine was treated with thionyl chloride (7 ml.) in ether as described for the preparation of 3-benzyloxy-4-methoxybenzyl chloride. The *chloride* (10·6 g.) crystallised from light petroleum (b. p. 80—100°) containing a little benzene in needles, m. p. 40° (Found: C, 74·6; H, 5·65; Cl, 10·6. $C_{21}H_{19}ClO_2$ requires C, 74·75; N, 5·65; Cl, 10·35%).

3,4-Dibenzyloxyphenylacetonitrile.—This was prepared as for 3-benzyloxy-4-methoxyphenylacetonitrile, from the foregoing chloride (10·6 g.) and potassium cyanide (4·9 g.). The *nitrile* (8·3 g.) crystallised from benzene–light petroleum in needles, m. p. 70° (Found: C, 80·3; H, 5·9; N, 4·3. $C_{22}H_{19}NO_2$ requires C, 80·2; H, 5·8; N, 4·25%).

3,4-Dibenzyloxyphenylacetic Acid (IIc).—The preceding nitrile (7 g.) was hydrolysed with potassium hydroxide (21 g.) in a mixture of ethanol (40 ml.) and water (40 ml.) as described for the preparation of 3-benzyloxyphenylacetic acid. The acid (3·85 g.) crystallised from ethyl acetate–light petroleum (2 : 1) as almost white needles, m. p. 106° (lit.,[28] 108°).

3,4-Dibenzyloxy-N-(*3,4-dibenzyloxyphenethyl*)*phenylacetamide* (IIIg).—This (6·77 g.) was prepared from the foregoing acid (3·85 g.) and 3,4-dibenzyloxyphenethylamine (4·0 g.). The amide formed as a cream solid, m. p. 123° from ethanol (Found: C, 79·15; H, 6·5. $C_{44}H_{41}NO_5$ requires C, 79·05; H, 6·2%).

6,7-Dibenzyloxy-1-(*3,4-dibenzyloxybenzyl*)-*3,4-dihydroisoquinoline Hydrochloride* (IVg).—Prepared from the preceding amide (6·7 g.) and phosphorus pentachloride (6·7 g.) in chloroform (36 ml.), the *hydrochloride* crystallised from a mixture of ethanol and ether and had m. p. 198° (Found: C, 74·75; H, 6·1; N, 2·05. $C_{44}H_{40}ClNO_4,1{\cdot}5H_2O$ requires C, 74·5; H, 6·1; N, 2·0%).

6,7-Dibenzyloxy-1-(*3,4-dibenzyloxybenzyl*)-*2-formyl*-*1,2,3,4-tetrahydroisoquinoline* (Vg).—This (40·5 g.) was prepared from the foregoing hydrochloride (6·05 g.), formic acid (20 ml.), and formamide (100 ml.). The *tetrabenzyl ether* failed to crystallise even after chromatography on alumina (120 g.) (Found, for the oil dried to constant weight at 50°/2 mm.: C, 78·6; H, 6·3. $C_{45}H_{41}NO_5,0{\cdot}75H_2O$ requires C, 78·3; H, 6·2%).

[28] C. Schöpf, H. Perrey, and I. Jäckh, *Annalen*, 1932, **497**, 47.

2-*Formyl*-1,2,3,4-*tetrahydro*-6,7-*dihydroxy*-1-(3,4-*dihydroxybenzyl*)*isoquinoline* (VI).—The above tetrabenzyl ether (4·05 g.) was debenzylated by hydrogenation in the presence of a palladium catalyst (from 6·07 g. of palladium oxide) in glacial acetic acid. The catalyst was filtered off and the filtrate evaporated to dryness under reduced pressure. Recrystallisation of the residue from acetone–ethanol gave the *tetraphenol* (1·4 g.) as white plates, m. p. 247°, $\lambda_{max.}$ 285 mμ (log ε 4·03) (Found: C, 64·1; H, 5·6; N, 4·4. $C_{17}H_{17}NO_5$ requires C, 64·75; H, 5·45; N, 4·45%). The O-*tetrabenzoate* crystallised from ethanol and had m. p. 162° (Found: C, 74·0; H, 4·65; N, 2·3. $C_{45}H_{33}NO_9$ requires C, 73·85; H, 4·55; N, 1·9%). On methylation with dimethyl sulphate in 20% sodium hydroxide containing sodium dithionite, the tetraphenol was converted into 2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline.

1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1-(3-*methoxybenzyl*)-2-*methylisoquinoline*.—The hydrochloride (IVc, 8·47 c.) was converted into 3,4-*dihydro*-6,7-*dimethoxy*-1-(3-*methoxybenzyl*) *isoquinoline methiodide* which separated from a mixture of methanol and ether as prisms, m. p. 150° (Found: C, 52·2; H, 5·45. $C_{20}H_{24}INO_3,0{\cdot}5CH_4O$ requires C, 52·45; H, 5·55%). Reduction of the methiodide as described for the preparation of 7-benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline gave a gummy base (6·9 g.). The *picrate* crystallised from acetone–ethanol and had m. p. 170° (Found: C, 56·25; H, 5·2. $C_{26}H_{28}N_4O_{10}$ requires C, 56·1; H, 5·05%). On decomposition with lithium hydroxide this yielded the base as a gum from which the *hydrochloride* was prepared in benzene with dry hydrogen chloride. It crystallised from ethanol–ether and had m. p. 202° (Found: C, 62·45; H, 7·55. $C_{20}H_{26}ClNO_3,H_2O$ requires C, 62·9; H, 7·35%).

1,2,3,4-*Tetrahydro*-6,7-*dihydroxy*-1-(3-*hydroxybenzyl*)-2-*methyliosquinoline* (VIIIa).—The above base (5 g.), liberated from the picrate, was refluxed for 4 hr. in nitrogen with constant-boiling hydrobromic acid (60 ml.). The solution was evaporated to dryness (water-bath/reduced pressure) and an aqueous solution of the residue was treated with one of sodium picrate. The resulting *picrate* (4·5 g.) crystallised from acetone–ethanol and had m. p. 214° (Found: C, 53·35; H, 4·6. $C_{23}H_{22}N_4O_{10}$ requires C, 53·7; H, 4·3%). A column of Dowex 1 (approximately 65 × 11 mm.) was treated successively with 2N-hydrochloric acid, water, and acetone–water (1 : 1). The above picrate (0·4 g.) was dissolved in hot acetone (50 ml.), the solution mixed with water (50 ml.), cooled rapidly, and passed through the column. The column was further eluted with a mixture of acetone (50 ml.) and water (50 ml.). The combined eluates were evaporated to dryness and the residue was twice more evaporated after the addition of ethanol. The residual *hydrochloride* (0·24 g.) was a non-crystalline solid (Found: C, 60·0; H, 6·9. $C_{17}H_{20}ClNO_3,H_2O$ requires C, 60·1; H, 6·5%). An aqueous solution of the hydrochloride was treated with sodium hydrogen carbonate solution. The resulting precipitate was collected, washed with water, dried, and recrystallised from ethanol–light petroleum, giving the base, m. p. 165° (with softening for 20°) (Found: C, 68·4; H, 7·8. $C_{17}H_{19}NO_3,C_2H_6O$ requires C, 68·9; H, 7·55%).

3-*Benzyloxy*-N-(3,4-*methylenedioxyphenethyl*)*phenylacetamide*.—This was prepared from 3,4-methylenedioxyphenethylamine (3·2 g.) and 3-benzyloxyphenylacetic acid (4·9 g.) as described for the amide (IIIa). The *amide* (6·14 g.) crystallised from ethanol in shining plates, m. p. 98° (Found: C, 73·6; H, 6·35. $C_{24}H_{23}NO_4$ requires C, 74·05; H, 5·95%).

1-(3-*Benzyloxybenzyl*)-3,4-*dihydro*-6,7-*methylenedioxyisoquinoline Hydrochloride*.—This was prepared from the foregoing amide (6·14 g.) by reaction with phosphorus pentachloride (9·2 g.) in chloroform (28 ml.) in the usual way. The *hydrochloride* (4·0 g.) separated from ethanol–dilute hydrochloric acid and had m. p. 197°, for analysis dried for 4 hr. at 105°/1 mm. (Found: C, 68·95; H, 5·75. $C_{24}H_{22}ClNO_3,0{\cdot}5H_2O$ requires C, 69·15; H, 5·5%). The *methiodide* separated from methanol and had m. p. 213—214° (Found: C, 57·25; H, 4·8. $C_{25}H_{24}INO_3,0{\cdot}5H_2O$ requires C, 57·45; H, 4·8%).

1-(3-*Benzyloxybenzyl*)-1,2,3,4-*tetrahydro*-2-*methyl*-6,7-*methylenedioxyisoquinoline*.—The above methiodide (5·37 g.) was reduced as described for the preparation of 7-benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline. The crude base (1·72 g.) was a gum which was converted into its picrate. Recrystallisation from acetone–ethanol gave the *picrate* (2·1 g.) as prisms, m. p. 141° (Found: C, 60·1; H, 4·55. $C_{31}H_{28}N_4O_{10}$ requires C, 60·4; H, 4·55%). The *hydrochloride* crystallised from ethanol and had m. p. 107° (Found, for material dried for 5 hr. at 70°/1 mm.; C, 68·2; H, 6·75. $C_{25}H_{26}ClNO_3,H_2O$ requires C, 67·95; H, 6·35%).

1,2,3,4-*Tetrahydro*-1-(3-*hydroxybenzyl*)-2-*methyl*-6,7-*methylenedioxyisoquinoline* (VIIIb).—A solution of the foregoing base (3·18 g.) in acetic acid (160 ml.) and hydrochloric acid, saturated at 0° with hydrogen chloride (16 ml.), was heated on a water-bath for 30 min., then refluxed for 5 min. and evaporated to dryness (water-bath/reduced pressure). The residue was shaken with N-sodium hydroxide solution and ether and the aqueous layer saturated with carbon dioxide and extracted with chloroform. Evaporation of the dried (Na_2SO_4) chloroform extract gave a gum which yielded a *picrate* (2·65 g.), m. p. 207° (from acetone–ethanol) (Found: C, 55·7; H, 5·0. $C_{24}H_{22}N_4O_{10},C_2H_6O$ requires C, 55·45; H, 4·8%). This picrate (1·02 g.) was ground with concentrated hydrochloric acid, the picric acid was removed, and the filtrate diluted with water and evaporated to dryness (water-bath/reduced pressure, keeping the temperature as low as possible). The residue was treated with warm water and extracted with benzene. The aqueous solution was filtered and concentrated. On cooling, the *hydrochloride* (0·4 g.) separated and when recrystallised from ethanol had m. p. 220° (Found: 64·45; H, 6·4. $C_{18}H_{19}NO_3,HCl$ requires C, 64·8; H, 6·0%). The *base*, liberated from the hydrochloride with sodium hydrogen carbonate solution, crystallised from benzene–light petroleum and had m. p. 145° (Found: C, 71·85; H, 6·6. $C_{18}H_{19}NO_3,0{\cdot}25H_2O$ requires C, 71·65; H, 6·45%).

1-(3-*Benzyloxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-*methylisoquinoline*.—The hydrochloride (IVb; 2·45 g.) was converted into the *methiodide* (2·76 g.) as before, using sodium (0·14 g.) and methyl iodide (12 ml.). Crystallisation from methanol gave needles, m. p. 186° (Found: C, 58·0; H, 5·45. $C_{26}H_{28}INO_3,0{\cdot}5H_2O$ requires C, 58·0; H, 5·4%). The methiodide was reduced as for the preparation of 7-benzyloxy-1-(3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline to give a gummy base (1·86 g.). The *picrate* crystallised from acetone–ethanol in needles, m. p. 163—164° (Found: C, 61·05; H, 5·15. $C_{32}H_{32}N_4O_{10}$ requires C, 60·75; H, 5·05%).

1,2,3,4-*Tetrahydro*-1-(3-*hydroxybenzyl*)-6,7-*dimethoxy*-2-*methylisoquinoline* (VIIIc).—The foregoing base (1·8 g.) in glacial acetic acid (90 ml.) and concentrated hydrochloric aid, saturated at 0° with dry hydrogen chloride (9 ml.), was heated on a water-bath for 30 min., then refluxed for 15 min. The solution was evaporated to dryness (water-bath/reduced pressure) and the residue dissolved in dilute sodium hydroxide solution, extracted with ether and saturated with carbon dioxide. The precipitated solid was collected, dried, and recrystallised from benzene–light petroleum. The *base* formed cream coloured needles, m. p. 135° (Found: C, 73·0; H, 7·45. $C_{19}H_{23}NO_3$ requires C, 72·85; H, 7·3%). The *picrate* separated from acetone–ethanol and had m. p. 188° (Found: C, 55·6; H, 5·05. $C_{25}H_{26}N_4O_{10}$ requires C, 55·35; H, 4·8%).

Enzymic Oxidation of 1,2,3,4-*tetrahydro*-1-(3-*hydroxybenzyl*)-6,7-*dimethoxy*-2-*methylisoquinoline*.—The foregoing base (0·586 g.) was dissolved in water (630 ml.) containing N-sodium hydroxide solution (6·8 ml.). The pH was adjusted to 9 by the addition of 2N-hydrochloric acid. 0·29% Hydrogen peroxide (5 ml.) and horseradish peroxidase (6 mg.) were added and the mixture stored at 37° for 4 days. Every 24 hr. further quantities of 0·29% hydrogen peroxide (5 ml.) and horseradish peroxidase (6 mg.) were added. The solution was acidified with concentrated hydrochloric acid and continuously extracted with hot chloroform for 24 hr. Evaporation of the dried chloroform (Na_2SO_4) gave a gum (0·153 g.) which was refluxed with ether. The ether solution on evaporation gave a residue (0·08 g.) which crystallised from benzene to give *m*-hydroxybenzaldehyde (0·031 g.), m. p. 103—105°, mixed m. p. 104°. The ether-insoluble portion gave the hydrochloride of the starting base.

Action of Formic Acid and Formamide on 3,4-*Dihydro*-6,7-*dimethoxy*-1-(3,4-*dimethoxybenzoyl*)-*isoquinoline*.—A mixture of 3,4-dihydro-6,7-dimethoxy-1-(3,4-dimethoxybenzoyl)isoquinoline [29] (IXa; 1·11 g.), formic acid (6 ml.), and formamide (30 ml.) was refluxed for 2·5 hr. and poured into water. The solution was extracted with chloroform and the extract was evaporated to dryness (water-bath/reduced pressure) and the residue dissolved in the minimum of hot methanol. A grey solid was deposited which after four recrystallisations from benzene gave 5,6-*dihydro*-8,9-*dimethoxy*-1-(3,4-*dimethoxyphenyl*)*imidazo*[5,1-a]*isoquinoline* (0·37 g.) as needles m. p. 174—175°, $\lambda_{max.}$ 293, 320 mμ (log ε 4·25, 4·21) (Found: C, 66·85; H, 6·25; N, 7·45. $C_{21}H_{22}N_2O_4,0{\cdot}5H_2O$ requires C, 67·15; H, 6·2; N, 7·45%). The *methiodide* crystallised from water in pale yellow leaflets, m. p. 230° (Found: C,50·55; H, 5·35. $C_{22}H_{25}IN_2O_4,H_2O$ requires C, 50·2; H, 5·2%). The *picrate* crystallised from acetone as long brown needles, m. p. 230—231° (Found: C, 55·4; H, 4·65; N, 10·7. $C_{27}H_{25}N_5O_{11},C_3H_6O$ requires C, 55·1; H, 4·8; N,

[29] J. S. Buck, R. D. Haworth, and W. H. Perkin, *J.*, 1924, **125**, 2176.

10·7%). The *hydrochloride* crystallised from 10% hydrochloric acid as copper-coloured plates, m. p. 120—122°. After drying (P_2O_5) for 4 days at 56°/1 mm., the m. p. rose to 136° (Found: C, 54·3, 54·15; H, 6·45, 6·45. $C_{21}H_{23}ClN_2O_4,3·5H_2O$ requires C, 54·1; H, 6·5%). Demethylation of the base (92 mg.) with concentrated hydrochloric acid (2 ml.) in a sealed tube at 160° for 6 hr. gave 5,6-*dihydro*-8,9-*dihydroxy*-1-(3,4-*dihydroxyphenyl*)*imidazo*[5,1-a]*isoquinoline hydrochloride* (51 mg.) which crystallised from dilute hydrochloric acid and had m. p. 193°, $\lambda_{max.}$ 295, 310 mμ (log ε 4·29, 4·28) (Found: C, 56·0; H, 4·9. $C_{17}H_{15}ClN_2O_4,H_2O$ requires C, 55·95; H, 4·7%).

5,6-*Dihydro*-8,9-*dimethoxy*-1-(4-*methoxyphenyl*)*imidazo*[5,1-a]*isoquinoline* (Xc).—A mixture of 3,4-dihydro-6,7-dimethoxy-1-(4-methoxybenzoyl)isoquinoline [30] (IXb; 0·75 g.), formic acid (4 ml.), and formamide (20 ml.) was refluxed for 2·5 hr. The reaction mixture was poured into water and after filtration the solution was extracted with chloroform. The extract was washed with dilute hydrochloric acid, dried (K_2CO_3), and evaporated to dryness under reduced pressure. The residue (0·61 g.) was treated with a solution of picric acid (0·45 g.) in hot ethanol, whereupon a sticky brown solid was deposited. The supernatant liquid was decanted and the residue boiled for a short time with acetone. The hot solution was filtered and the insoluble material collected. Recrystallisation of the latter from glacial acetic acid gave the *picrate* as closely-matted needles, m. p. 218° (Found: C, 55·5; H, 4·05; N, 12·25. $C_{26}H_{23}N_5O_{10}$ requires C, 55·25; H, 4·1; N, 12·4%). Decomposition of the picrate in chloroform on an alumina column gave the *base* which crystallised from benzene–light petroleum in white prisms, m. p. 159°, $\lambda_{max.}$ 296, 317 mμ (log ε 4·23, 4·13) (Found: C, 71·3; H, 6·05; N, 8·3. $C_{20}H_{20}N_2O_3$ requires C, 71·4; H, 6·0; N, 8·35%).

N-*Formyl*-α-3,4-*dimethoxyglycine* (XIb).—A mixture of acetic anhydride (7·8 ml.) and formic acid (24 ml.) was heated at 60° for 2 hr. and then cooled to room temperature. α-3,4-Dimethoxyphenylglycine [31] (2·04 g.) was added and the mixture kept at room temperature for 24 hr. The solid which was deposited was filtered off and recrystallised from methanol. The original filtrate was evaporated to dryness under reduced pressure and the residue recrystallised from methanol. The crystalline solids from both stages were combined and recrystallised from methanol. The *acid* (2·06 g.) formed white rosettes, m. p. 217° (Found: C, 55·3; H, 5·5; N, 5·85. $C_{11}H_{13}NO_5$ requires C, 55·2; H, 5·50; N, 5·85%).

Ethyl α-3,4-*Dimethoxyphenylglycinate Hydrochloride* (XII).—This was prepared from α-3,4-dimethoxyphenylglycine (1·0 g.) and 10% ethanolic hydrogen chloride (30 ml.) in the normal way. The *hydrochloride* (0·98 g.) crystallised from ethanol–ether in needles, m. p. 235° (Found: C, 52·05; H, 6·55; N, 5·4. $C_{12}H_{18}ClNO_4$ requires C, 52·25; H, 6·6; N, 5·1%).

Ethyl N-*Formyl*-α-3,4-*dimethoxyphenylglycinate* (XIII).—A mixture of the above hydrochloride (0·43 g.), formic acid (6 ml.), acetic anhydride (2 ml.), and sodium formate (0·43 g.) was kept at room temperature overnight. After the addition of water the solution was evaporated to dryness under reduced pressure. The residue was refluxed with ethanol for 30 min. and concentrated whereupon a solid was deposited. Recrystallisation from benzene–light petroleum gave the *ester* (0·32 g.) as white needles, m. p. 85° (Found: C, 58·55; H, 6·25; N, 5·55. $C_{13}H_{17}NO_5$ requires C, 58·4; H, 6·45; N, 5·25%).

N-*Benzyloxycarbonyl*-α-3,4-*dimethoxyphenylglycine* (XIc).—Benzyloxycarbonyl chloride (10 ml.) and 4N-sodium hydroxide solution (10 ml.) were added during 30 min. to a cooled, stirred solution of α-3,4-dimethoxyphenylglycine (7·27 g.) in 4N-sodium hydroxide solution (20 ml.). The mixture was stirred for 2 hr., diluted with water, acidified with concentrated hydrochloric acid, and extracted with chloroform. Evaporation of the dried extract gave a residue which crystallised from benzene to give the *acid* (7·14 g.) as needles, m. p. 145° (Found: C, 62·25; H, 5·75; N, 4·05. $C_{18}H_{19}NO_6$ requires C, 62·6; H, 5·55; N, 4·05%).

α-*Benzyloxycarbamido*-3,4-*dimethoxy*-N-(3,4-*dimethoxyphenethyl*)*phenylacetamide*) (XIVa).—To a cooled stirred suspension of the foregoing acid (5·96 g.) in dry ether (60 ml.) was added phosphorus pentachloride (4·04 g.). When the solid had all dissolved, the solution was concentrated and diluted with dry benzene (80 ml.) and then added to a stirred solution of 3,4-dimethoxyphenethylamine (3·06 g.) in dry benzene (80 ml.). After 10 min., 10% sodium hydroxide solution was added and the mixture stirred for a further 60 min. The benzene layer was collected, concentrated under reduced presure, and diluted with light petroleum. The

[30] T. R. Govindachari and K. Nagarajan, *Proc. Ind. Acad. Sci.*, 1955, **42***A*, 261.
[31] A. Lawson and H. V. Morley, *J.*, 1957, 566.

gum which was deposited was recrystallised from methanol. The *amide* (5·64 g.) formed cream coloured needles, m. p. 93° (Found: C, 66·45; H, 6·65; N, 5·9. $C_{28}H_{32}N_2O_7$ requires C, 66·1; H, 6·35; N, 5·5%).

α-Formamido-3,4-dimethoxy-N-(3,4-dimethoxyphenethyl)phenylacetamide (XIVc).—A mixture of the foregoing amide (4·68 g.), palladium oxide (0·69 g.), acetic acid (3 ml.), and methanol (90 ml.) was shaken in hydrogen for 3 hr. The catalyst was removed and the solution evaporated to dryness. The residue was shaken with ammonium hydroxide and chloroform and the organic layer collected. Evaporation of the dried chloroform extract gave a basic gum (2·3 g.). The latter was dissolved with warming in a mixture of acetic anhydride (17·5 ml.) and formic acid (7·5 ml.), preheated to 60° for 1 hr., and the solution kept at room temperature for 24 hr. After dilution with water, the reaction mixture was extracted with chloroform. The extract was washed with dilute hydrochloric acid, potassium carbonate solution and water, dried, and evaporated to dryness under reduced pressure. The residue crystallised from methanol to give the *amide* (1·7 g.) as needles, m. p. 164°, $\lambda_{max.}$ 232, 280 mμ (log ε 4·26, 3·86) (Found: C, 62·5; H, 6·5; N, 6·95. $C_{21}H_{26}N_2O_6$ requires C, 62·65; H, 6·55; N, 6·95%).

5,6-Dihydro-8,9-dimethoxy-1-(3,4-dimethoxyphenyl)-imidazo[5,1-a]isoquinoline (Xa).—A mixture of the foregoing amide (0·58 g.), phosphorus oxychloride (1·5 ml.), and toluene (5 ml.) was heated at 120° for 20 min. The solution was cooled and diluted with a large volume of light petroleum (b. p. 40—60°). The supernatant liquid was decanted and the residue dissolved in hot water, filtered, cooled, and extracted with benzene. The aqueous solution was basified with ammonium hydroxide and extracted with benzene. After drying, the latter extract was evaporated to dryness and the residue chromatographed on alumina. Elution with benzene–chloroform (1 : 1) gave a red basic gum which was dissolved in a small volume of hot 10% hydrochloric acid. On cooling, the hydrochloride (0·02 g.) of the title compound was deposited and had m. p. 120—122°. On drying in a vacuum, the m. p. rose to 134°, alone or mixed with the hydrochloride of material from the reaction between 3,4-dihydro-6,7-dimethoxy-1-(3,4-dimethoxybenzoyl)isoquinoline, formic acid, and formamide. The infrared spectra were also identical.

3-Benzyloxy-N-(3-benzyloxy-4-methoxyphenethyl)phenylacetamide.—Prepared from 3-benzyloxy-4-methoxyphenethylamine [1] and 3-benzyloxyphenylacetic acid at 180°, the *amide* crystallised from ethanol and had m. p. 107—108° (Found: C, 77·5; H, 6·75. $C_{31}H_{31}NO_4$ requires C, 77·3; H, 6·5%).

6-Benzyloxy-1-(3-benzyloxybenzyl)-3,4-dihydro-7-methoxyisoquinoline Hydrochloride.—Prepared from the foregoing amide (1 g.) and phosphorus pentachloride (1·7 g.) in chloroform, the *hydrochloride* crystallised from ethanol–dilute hydrochloric acid in needles, m. p. 192—193° (Found: C, 74·4; H, 6·4. $C_{31}H_{31}ClNO_3$ requires C, 74·3; H, 6·25%).

6-Benzyloxy-1-(3-benzyloxybenzyl)-2-formyl-1,2,3,4-tetrahydro-7-methoxyisoquinoline.—Prepared from the foregoing salt (0·23 g.), formic acid (1 ml.), and formamide (5 ml.), it failed to crystallise even after chromatography on alumina (Found: C, 77·35; H, 6·75. $C_{32}H_{32}NO_4$ requires C, 77·85; N, 6·35%).

7-Benzyloxy-1-(3-benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinloine Methiodide.—The hydrochloride (IVa; 3·26 g.) was converted into *7-benzyloxy-1-(3-benzyloxybenzyl)-3,4-dihydro-6-methoxyisoquinoline methiodide* (3·49 g.). Recrystallisation from methanol gave needles, m. p. 198—199° (Found: C, 62·1; H, 5·9. $C_{32}H_{33}INO_3,CH_4O$ requires C, 62·05; H, 5·85%). Reduction of this with zinc dust in the normal manner gave the base as a gum. The *picrate* separated from ethanol and had m. p. 154—155° (Found: 64·5; H, 5·5. $C_{38}H_{36}N_4O_{10}$ requires C, 64·4; H, 5·1%). Decomposition of the picrate with lithium hydroxide gave the *base* which crystallised from benzene–light petroleum in needles, m. p. 110° (Found: C, 70·6, 70·6; H, 7·1, 6·95. $C_{32}H_{33}NO_3,3·5H_2O$ requires C, 71·0; H, 7·4%).

1,2,3,4-Tetrahydro-7-hydroxy-1-(3-hydroxybenzyl)-6-methoxy-2-methylisoquinoline.—The preceding base (1·86 g.) was debenzylated with acetic acid (17·5 ml.) and concentrated hydrochloric acid (8 ml.) pre-saturated with hydrogen chloride at 0° as described for the base (VIIIb). The *base* had m. p. 111—113° (Found: C, 69·55; H, 7·0. $C_{18}H_{21}NO_3,0·75H_2O$ requires C, 69·45; H, 7·2%).

2-Formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(4-methoxybenzyl)isoquinoline.—Prepared from 3,4-dihydro-6,7-dimethoxy-1-(4-methoxybenzyl)isoquinoline hydrochloride [30] (0·37 g.), formic acid, and formamide (10 ml.), the *amide* (0·15 g.) crystallised from methanol in prisms, m. p. 130° (Found: C, 70·35; H, 6·75; N, 4·45. $C_{20}H_{23}NO_4$ requires C, 70·35; H, 6·8; N, 4·1%).

3-*Methoxy*-N-(4-*methoxyphenethyl*)*phenylacetamide*.—This was prepared from *m*-methoxyphenylacetic acid and *p*-methoxyphenethylamine. When recrystallised twice from ethanol, then from benzene–light petroleum the *amide* formed colourless needles, m. p. 84° (Found: C, 72·2; H, 7·2. $C_{18}H_{21}NO_3$ requires C, 72·25; H, 7·0%). Attempts to cyclise this amide failed.

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