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SYNTHETIC APPLICATIONS OF 1,2-DIHYDROISOQUINOLINES

SYNTHESIS OF (±)-COREXIMINE

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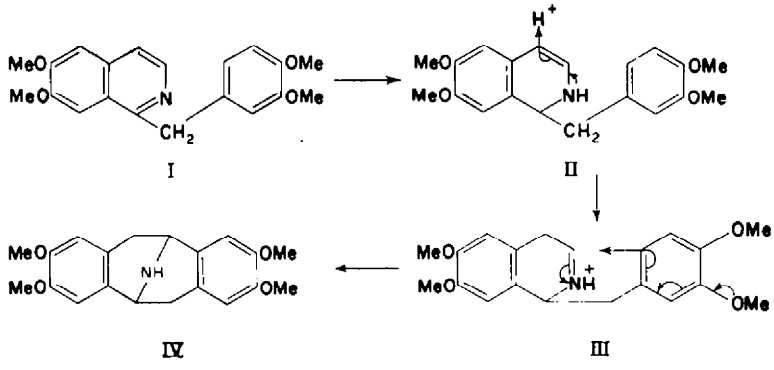
Abstract—1,2-Dihydroisoquinolines are shown to be useful synthetic intermediates and are employed here for the synthesis of (±)-norcoralydine (XIa) and (±)-coreximine (XIc).

ONE of the products formed during the reduction of papaverine (I) with tin and hydrochloric acid[1] is named pavine and it has been shown[2,3] to have the structure (IV). The formation of this compound is best explained[2,4] by a mechanism which involves protonation of 1,2-dihydropapaverine (II) produced initially by partial reduction of papaverine (I). It is known that enamines take up a proton to give the corresponding imine salts[5] and in this case the resultant salt (III) can cyclize as indicated to afford pavine (IV). The last step in this sequence seemed to be a potentially useful one for many syntheses in the field of isoquinoline alkaloids and its efficacy was demonstrated by the preparation of (±)-norcoralydine (XIa) by this method; a preliminary account



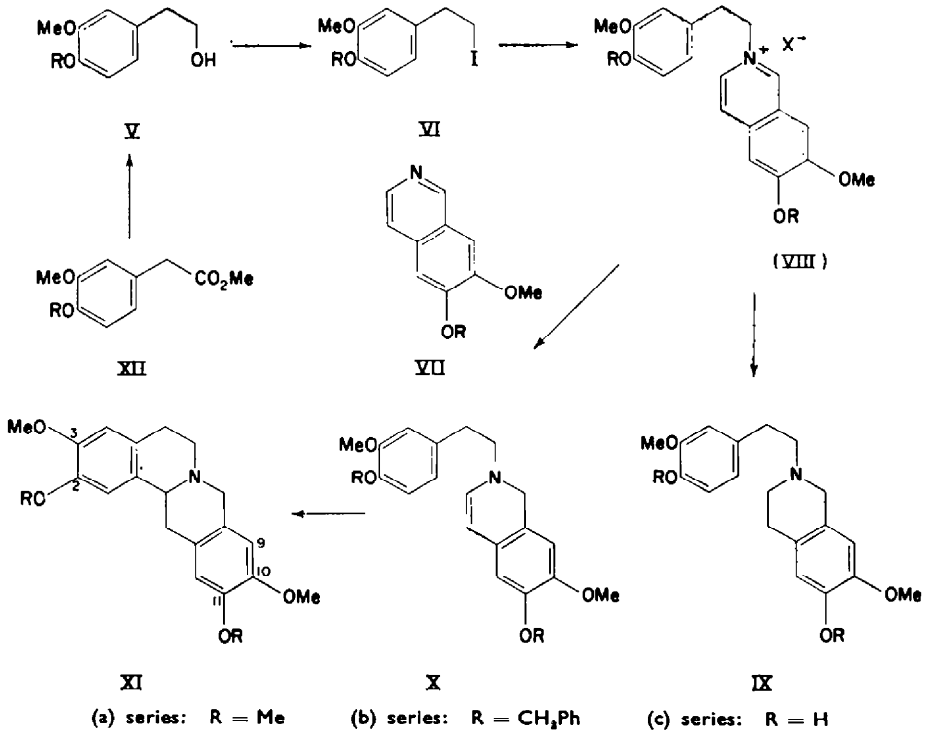
has been published.[6] Concurrently, several valuable syntheses involving 1,2-dihydroisoquinolines were carried out independently in the indole field[7] and there have been more recent applications.[8] The present paper will give a full account of our earlier work together with recent studies leading to the synthesis of (±)-coreximine (XIc).

The preparation of (±)-norcoralydine called for 3,4-dimethoxyphenylethyl iodide (VIa) which was derived from the corresponding alcohol (Va) by the method

[1] F. L. Pyman, *J. Chem. Soc.* **95**, 1610 (1909); F. L. Pyman and W. C. Reynolds, *Ibid.* **97**, 1320 (1910).
[2] A. R. Battersby and R. Binks, *Chem. & Ind.* 1455 (1954); A. R. Battersby and R. Binks, *J. Chem. Soc.* 2888 (1955).
[3] C. Schöpf, *Angew. Chem.* **62**, 453 (1950).
[4] E. Ochiai and K. Harasawa, *Pharm. Bull. Japan* **3**, 369 (1955).
[5] N. J. Leonard and V. W. Gash, *J. Amer. Chem. Soc.* **76**, 2781 (1954).
[6] A. R. Battersby, R. Binks and P. S. Uzzell, *Chem. & Ind.* 1039 (1955).
[7] K. T. Potts and R. Robinson, *J. Chem. Soc.* 2675 (1955); B. Belleau, *Chem. & Ind.* 229 (1955); *cf.* P. L. Julian and A. Magnani, *J. Amer. Chem. Soc.* **71**, 3207 (1949).
[8] R. C. Elderfield and B. A. Fischer, *J. Org. Chem.* **23**, 332 (1958); J. W. Huffman, *J. Amer. Chem. Soc.* **80**, 5193 (1958); D. R. Liljegren and K. T. Potts, *Proc. Chem. Soc.* 340 (1960).

using triphenylphosphite methiodide.[9,10] When the iodide (VIa) was heated with the known[11] 6,7-dimethoxyisoquinoline (VIIa), the quaternary salt (VIIIa; $X^- = I^-$) was obtained and attempts were made to reduce this partially to the 1,2-dihydroisoquinoline (Xa) over platinum in the presence of alkali.[12] However, two moles of hydrogen were absorbed without a break in the rate of uptake to yield a crystalline base having the ultra-violet absorption expected for the tetrahydroisoquinoline (IXa). Its structure was confirmed by showing that the same base was formed when the salt (VIIIa; $X^- = Cl^-$) was reduced with borohydride in methanol, a reagent which is known to reduce quaternized isoquinolines smoothly to 1,2,3,4-tetrahydroisoquinolines.[13]

Lithium aluminium hydride in ether has been used to reduce quaternized isoquinolines to 1,2-dihydroisoquinolines,[14] but because of the extremely low solubility of our salts in ether, the reaction was conveniently carried out at room temperature in tetrahydrofuran. Under these conditions, the salt (VIIIa; $X^- = I^-$) gave a high yield of an unstable base (Xa) which had an ultra-violet absorption spectrum corresponding closely with that of 2-methyl-1-phenyl-1,2-dihydroisoquinoline.[14] Our product, without purification or delay, was cyclized by being heated with a mixture of phosphoric and formic acids. Fractionation of the basic products gave (±)-norcoralydine (XIa), identical with an authentic specimen,[15] in 40 per cent overall yield from

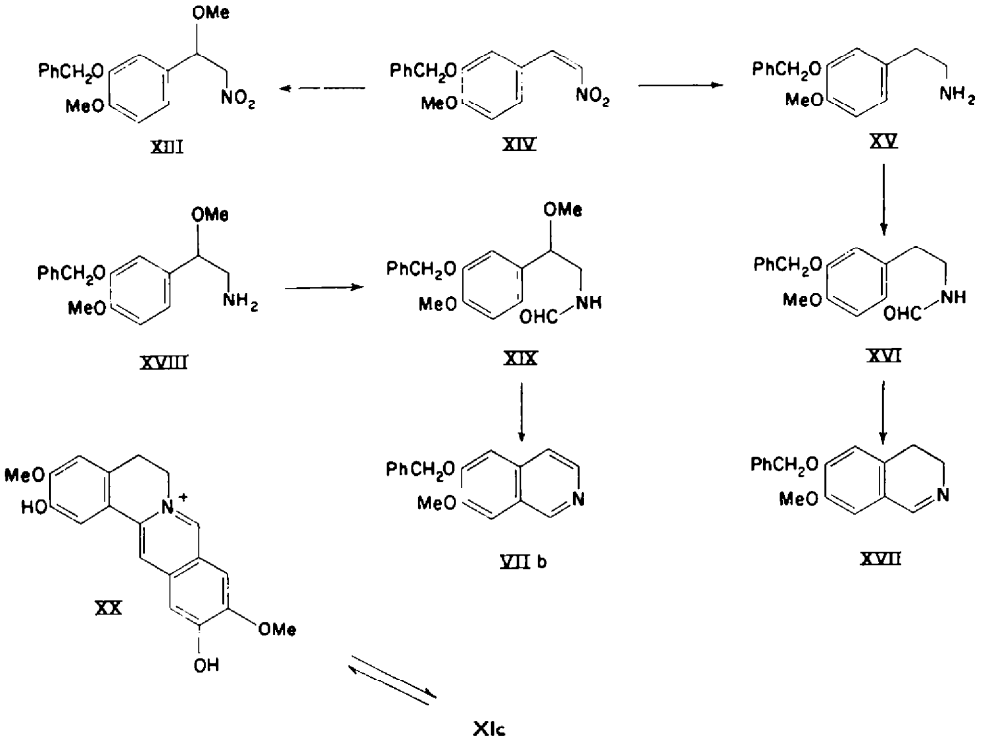


[9] S. R. Landauer and H. N. Rydon, *J. Chem. Soc.* 2224 (1953).
[10] *cf.* M. Barash and J. M. Osbond, *J. Chem. Soc.* 2157 (1959) where a different procedure is used.
[11] E. Späth and N. Polgar, *Monatsh.* **51**, 190 (1929).
[12] C. Schöpf, *Experientia* **5**, 201 (1949); C. Schöpf, G. Herbert, R. Rausch and G. Schröder, *Angew. Chem.* **69**, 391 (1957).
[13] R. Mirza, *J. Chem. Soc.* 4400 (1957); S. Cox, B.Sc. Thesis, Bristol (1956).
[14] H. Schmid and P. Karrer, *Helv. Chim. Acta* **32**, 960 (1949).
[15] A. Pictet and T. Q. Chou, *Ber. Dtsch. Chem. Ges.* **49**, 370 (1916).

the salt (VIIIa; $X^- = I^-$). A new route to the protoberberine alkaloids is thus available; the same method was used subsequently in similar work.[16]

In order to extend this procedure to a natural alkaloid, the synthesis of coreximine (XIc) was undertaken. This base, which has not previously been synthesized, occurs in *Dicentra eximia*[17] and until last year was the only protoberberine alkaloid having the 2,3,10,11 oxygenation pattern; all the many other alkaloids in this group carried oxygen functions at positions 2, 3, 9 and 10. However, *Xylopia discreta* (L. FIL.) Sprague and Hutchins has recently yielded xylopinine, which is (−)-norcoralydine (XIa), and discretinine, a closely related alkaloid.[18]

The iodide (VIb) necessary for the coreximine synthesis was readily prepared by the action of triphenyl phosphite methiodide[9] on the corresponding alcohol (Vb), which in turn was obtained by reduction of the ester (XIIb) with lithium aluminium hydride. Synthesis of the isoquinoline (VIIb), however, proved more difficult. The first route involved formylation of the known[19] phenethylamine (XV) by hot formic acid and Bischler–Napieralski ring-closure of the product (XVI) to give the 3,4-dihydroisoquinoline (XVII). These stages ran smoothly and the base (XVII) is now readily available. However, attempted dehydrogenation by several catalytic and chemical methods, under a variety of experimental conditions, failed to yield the desired isoquinoline (VIIb).



[16] J. W. Huffman and E. G. Miller, *J. Org. Chem.* **25**, 90 (1960).
[17] R. H. F. Manske, *Canad. J. Res.* **16B**, 81 (1938).
[18] J. Schmutz, *Helv. Chim. Acta* **42**, 335 (1959).
[19] R. Robinson and S. Sugasawa, *J. Chem. Soc.* 3163 (1931); E. Späth, A. Orechoff and F. Kuffner, *Ber. Dtsch. Chem. Ges.* **67**, 1214 (1934).

The successful route started with the addition of methoxide anion[20] to the nitrostyrene (XIV) to give the methoxynitro derivative (XIII). Lithium aluminium hydride reduction then yielded the oily methoxy amine (XVIII), which was purified as its crystalline picrolonate; the pure base was readily formylated by formic acetic anhydride to afford the amide (XIX). Attempted ring closure of this material under the usual conditions gave a negligible yield of basic material; only after careful study of experimental conditions was it possible to obtain the desired isoquinoline (VIIb). This reacted with the iodide (VIb) in boiling methanol and the resultant salt (VIIIb; $X^- = I^-$) was converted into the corresponding chloride by passage over IRA-400 resin in the chloride phase. Again catalytic hydrogenation of this material was unsatisfactory though the ultra-violet spectrum of the products suggested that some dihydroisoquinoline (Xb) had been formed; the corresponding tetrahydroisoquinoline (IXb) was prepared for comparison purposes from the quaternary salt (VIIIb; $X^- = Cl^-$) by borohydride reduction. Partial reduction of the chloride (VIIIb; $X^- = Cl^-$) was achieved at room temperature as before with lithium aluminium hydride in tetrahydrofuran and the ultra-violet spectrum of the unstable dihydroisoquinoline (Xb) so produced was very similar to that of the tetramethoxy analogue (Xa). Ring-closure of the dihydroisoquinoline (Xb) was carried out without delay in a mixture of phosphoric and formic acids and in this case, concomitant removal of the protecting benzyl groups occurred to yield (±)-coreximine (XIc) directly.

In order to provide a comparison sample, natural (−)-coreximine was dehydrogenated with mercuric acetate to a yellow product. This, by analogy with related cases,[21] is presumably the salt (XX), which without isolation was reduced by zinc and acid to afford (±)-coreximine (XIb). The synthetic material above and the sample prepared from natural coreximine were proved to be identical by melting point and mixed m.p. and their infra-red spectra were superimposable. The ultra-violet spectra of the two samples were identical in neutral and in alkaline solution. So far as we are aware, this represents the first synthesis of a naturally occurring alkaloid in either the isoquinoline or indole series by the 1,2-dihydroisoquinoline route.

Note added in proof: The paper by M. Tomita and J. Kunitomo [*J. Pharm. Soc. Japan* **80**, 1238 (1960)] has now become available to us in which the synthesis of (±)-coreximine by a different route is described.

EXPERIMENTAL

3,4-*Dimethoxyphenethyl iodide* (VIa)

Triphenyl phosphite (10·1 g), methyl iodide (3 ml) and 3,4-dimethoxyphenylethyl alcohol (5·4 g) were heated under reflux for 48 hr, further portions (1 ml) of methyl iodide being added after 4, 14 and 24 hr. The cooled reaction mixture in ether (150 ml) was then washed with 2 N-sodium hydroxide (18 ml) and with water (4 × 10 ml) and after being dried, the ether was evaporated. Distillation of the residue at 114–118°/0·05 mm gave a partially crystalline distillate from which the desired iodide (VIa) (2·4 g) was obtained by careful crystallization and recrystallization from methanol, m.p. 46–48° (Found: C, 41·0; H, 4·8. Calc. for $C_{10}H_{13}O_2I$: C, 41·1; H, 4·45%).

2-(3′,4′-*Dimethoxyphenethyl*)-6,7-*dimethoxyisoquinolinium iodide* (VIIIa; $X^- = I^-$)

A solution of the foregoing iodide (1·0 g) and 6,7-dimethoxyisoquinoline[11] (0·59 g) in methanol (7 ml) was heated under reflux for 8 hr. After the reaction mixture had been cooled, the *isoquinolinium*

[20] *cf.* K. W. Rosenmund, M. Nothnagel and H. Riesenfelt, *Ber. Dtsch. Chem. Ges.* **60**, 392 (1927).
[21] R. H. F. Manske, *J. Amer. Chem. Soc.* **72**, 4796 (1950).

iodide was collected (1·34 g; 89%) and recrystallized from aqueous methanol, m.p. 209–210° (decomp.). (Found: C, 52·2; H, 4·9; N, 2·9. $C_{21}H_{24}O_4NI$ requires: C, 52·4; H, 5·0: N, 2·9%).

2-(3′,4′-*Dimethoxyphenethyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (IXa)

(a) *By catalytic hydrogenation.* A solution of the foregoing quaternary iodide (0·75 g) in 50% aqueous acetone (500 ml) was passed through a column (8 in. × 0·7 in.) of "Amberlite" IRA-400, chloride phase. The main solution and washings were combined and evaporated to dryness to yield the quaternary chloride (VIIIa; $X^- = Cl^-$).

A portion (20 mg) of this was hydrogenated at room temperature and pressure over Adams' platinum in methanol (10 ml) containing 2 N-aqueous sodium hydroxide (0·3 ml). Hydrogen (2 moles) was absorbed smoothly over 2 hr and the solution was then filtered, diluted with water and freed from methanol by evaporation. Ether extraction of the aqueous suspension then yielded a crystalline base (16 mg) which was recrystallized from ethanol to yield the *tetrahydroisoquinoline* (IXa), m.p. and mixed m.p. with the product from (b), 113–114°.

(b) *Borohydride reduction.* An excess of sodium borohydride (0·2 g) was added portionwise to a solution of the above quaternary chloride (0·13 g) in methanol (10 ml). After being kept at room temperature for 2 hr, the solution was acidified, diluted with water and evaporated until free from methanol. The aqueous solution was then basified and worked up as in (a) to give the tetrahydroisoquinoline (IXa) (0·11 g), m.p. 113–114°. (Found: C, 70·4; H, 7·7. $C_{21}H_{27}O_4N$ requires: C, 70·55; H, 7·6%).

(±)-*Norcoralydine* (XIa)

A suspension of the quaternary iodide (VIIIa; $X^- = I^-$) (0·2 g) in anhydrous tetrahydrofuran (30 ml) was shaken with lithium aluminium hydride (0·2 g) at room temperature for 18 hr. Aqueous 33% (w/v) sodium potassium tartrate was then added carefully until the excess of hydride had been decomposed and a gelatinous precipitate had formed. The clear solution was decanted, the precipitate was washed with tetrahydrofuran (3 × 15 ml) and the combined organic solutions were diluted with water (50 ml). After the tetrahydrofuran had been evaporated under nitrogen, the aqueous suspension was rapidly extracted with ether (3 × 100 ml) and the extracts were evaporated to leave an unstable crystalline residue (qualitative ultra-violet absorption in ethanol, λ_{max} 256, 283, 331 mμ; λ_{min} 245, 270, 295 mμ). This material was dissolved in 5:1 by vol. 98% formic acid:phosphoric acid (12 ml) and heated in an evacuated sealed tube at 80° for 28 hr. The contents of the tube were poured into water (25 ml) and the solution was basified with sodium hydroxide. Ether extraction (3 × 75 ml) as usual gave a largely crystalline base which was fractionated in chloroform on Peter Spence Type "H" alumina to afford (±)-norcoralydine (60 mg), m.p. 157–158° unchanged on admixture with authentic material.[15] The infra-red spectra of the two samples were identical.

3-*Methoxy*-4-*benzyloxyphenethyl alcohol* (Vb)

Methyl 3-methoxy-4-benzyloxyphenylacetate was prepared from vanillin by the known stages of benzylation[22] followed by an azlactone synthesis.[23] In our experiments, the ester crystallized and had m.p. 60–63°.

This ester (5 g) in anhydrous ether (100 ml) was added dropwise over 1 hr to a stirred suspension of lithium aluminium hydride (0·68 g) in ether (100 ml). After the mixture had been heated under reflux for a further 1 hr, it was cooled and the excess of hydride was decomposed with water (5 ml). The ethereal solution was decanted and the inorganic residue was dissolved in hydrochloric acid. This solution was extracted with ether (2 × 50 ml) and the combined ethereal solutions were washed with aqueous potassium hydroxide and water before being dried and evaporated. The crystalline *phenethyl alcohol* (Vb) so obtained (4·0 g) was recrystallized from aqueous methanol, m.p. 70–70·5°. (Found: C, 74·8; H, 7·0. $C_{16}H_{18}O_3$ requires: C, 74·4; H, 7·0%).

3-*Methoxy*-4-*benzyloxyphenethyl iodide* (VIb)

The foregoing alcohol (3·5 g) was reacted with triphenylphosphite (4·7 g) and methyl iodide (1·3 ml) as for the analogue (VIa) above. Distillation of the products at 0·05 mm gave three fractions,

[22] J. Finkelstein, *J. Amer. Chem. Soc.* **73**, 550 (1951).
[23] H. R. Snyder, J. S. Buck and W. S. Ide, *Org. Synth.* **15**, 31 (1935); T. Kametani and J. Serizawa, *J. Pharm. Soc. Japan* **72**, 1081 (1952).

b.p. 135–143°, 143–160°, 160–180° of which the last two crystallized. Recrystallization of these two from aqueous methanol gave the *phenethyl iodide* (VIb) (2·5 g), m.p. 57– 57·7° (Found: C, 51·9; H, 4·7. $C_{17}H_{18}O_3N$ requires: C, 52·2; H, 4·65%).

3-*Benzyloxy-4-methoxy-ω-nitrostyrene* (XIV)

This material has been prepared previously,[19] but in our hands the ammonium acetate method[24] described below gave the best results.

A solution of 3-benzyloxy-4-methoxybenzaldehyde[19] (258 g) and ammonium acetate (78 g) in glacial acetic acid (770 ml) and nitromethane (128 ml) was heated under reflux for 1¾ hr. The yellow crystals which separated from the cooled solution were collected and washed with ethanol (3 × 10 ml). A second crop was obtained by addition of the acetic acid mother liquor to water (2·5 l) and recrystallization of the gummy precipitate from ethanol (charcoal). The combined crops of crystals were recrystallized from ethanol to give the nitrostyrene (XIV), m.p. 125–127° (200 g), λ_{max} 258, 365 mμ; λ_{min} 230, 286 mμ (log ε 4·0, 4·19, 3·87, 3·45 respectively) in EtOH.

N-(3-*Benzyloxy-4-methoxyphenethyl*) *formamide* (XVI)

The foregoing nitrostyrene was reduced by lithium aluminium hydride[25] in tetrahydrofuran to the known[19,25] amine (XI) in 61% yield; our distilled product, b.p. 170°/0·5 mm, crystallized and had m.p. 43–44°.

This amine (20 g) was heated under reflux in a bath at 150° for 5¼ hr with formic acid (8·2 g). After the mixture had been cooled, it was dissolved in ethyl acetate (150 ml) and the solution was shaken first with 0.5 N-sodium hydroxide (160 ml), then with N-hydrochloric acid (50 ml) and finally with water. Evaporation of the dried solution left a crystalline residue (22·6 g) which was recrystallized from methanol to yield the pure *formamide* (XVI), m.p. 101°. (Found: C, 71·0; H, 6·6. $C_{17}H_{19}O_3N$ requires: C, 71·55; H, 6·7%).

6-*Benzyloxy-7-methoxy*-3,4-*dihydroisoquinoline* (XVII).

A solution of the formamide (XVI) (1 g) in toluene (10 ml) was heated under reflux for 2¾ hr with freshly distilled phosphoryl chloride (5·9 g). The cooled mixture was treated with ice and water (20 g) and when the decomposition was complete, the toluene was shaken with the aqueous layer, separated and back-extracted with water. The combined aqueous solutions were extracted with ether (2 × 50 ml), basified strongly with sodium hydroxide and re-extracted with ether (3 × 50 ml). Evaporation of the combined ethereal solutions left a crystalline residue (0·52 g) which was sublimed in a short-path still to give the *dihydroisoquinoline* (XVII), m.p. 105° (Found: C, 76·7; H, 6·7; N, 5·2. $C_{17}H_{17}O_2N$ requires: C, 76·4; H, 6·4; N, 5·2%). λ_{max} 209, 232, 280, 313 mμ; λ_{min} 220, 250, 296 mμ (log ε 4·29, 4·42, 3·91, 3·85, 4·24, 3·37, 3·71 respectively) in EtOH.

The *picrate* of this base was prepared in methanol and was recrystallized from the same solvent m.p. 188–189° (Found: C, 55·8; H, 4·3; N, 11·0. $C_{23}H_{20}O_9N_4$ requires: C, 55·6; H, 4·1; N, 11·2%).

2-*Methoxy*-2-(3′-*benzyloxy-4′-methoxyphenyl*)-*nitroethane* (XIII)

The nitrostyrene (XIV) (14 g) was dissolved in hot anhydrous methanol (1·2 l) and the solution was cooled rapidly to room temperature to produce a fine suspension.[20] 2 N-Sodium methoxide (30 ml) was added and the mixture was shaken for 5 min before the reaction was quenched by the addition of glacial acetic acid (4·0 ml). Evaporation of the solution to dryness under reduced pressure left a gum which was partitioned between ether (250 ml) and water (250 ml). The ether layer was separated and the aqueous solution was extracted with more ether (2 × 250 ml). Evaporation of the dried ethereal solutions left a crystalline residue, m.p. 90·5–92·5° which was suitable for use in the next stage, but which was recrystallized from ether to afford the pure *nitroethane* (XIII), m.p. 102–104° (Found: C, 64·7; H, 6·4. $C_{17}H_{19}O_5N$ requires: C, 64·5; H, 6·1%). λ_{max} 232 (inflexion), 280 mμ; λ_{min} 254 mμ (log ε 3·94, 3·46, 3·05 respectively) in EtOH.

[24] L. C. Raiford and D. E. Fox, *J. Org. Chem.* **9**, 170 (1944).
[25] M. Tomita and T. Nakano, *J. Pharm. Soc. Japan* **72**, 1256 (1952); *Chem. Abstr.* **47**, 12288 (1953).

2-Methoxy-2-(3′-benzyloxy-4′-methoxyphenyl)-ethylamine (XVIII)

A solution of the foregoing nitroethane (10·5 g) in anhydrous ether (160 ml) was added over 30 min to a stirred suspension of lithium aluminium hydride (2·5 g) in ether (200 ml). The mixture was then stirred and heated under reflux for 4 hr. Water (5 ml) was added dropwise to the cooled mixture followed by 6 N-aqueous sodium hydroxide (4 ml) and more water (15 ml). After all reaction had subsided, the mixture was shaken for 15 min, kept for 1 hr, the ether was decanted and the inorganic residue was washed with ether (2 × 200 ml). Evaporation of the dried total ether solution gave a gum (7·9 g) suitable for use in the next stage. It was characterized as the *picrolonate* which was prepared in ethanol and recrystallized from the same solvent, m.p. 183·5–184° (Found: C, 59·1; H, 5·4. $C_{27}H_{29}O_8N_5$ requires: C, 58·8; H, 5·3%).

N-[2-*Methoxy*-2-(3′-*benzyloxy*-4′-*methoxyphenyl*) *ethyl*] *formamide* (XIX)

The crude amine (7·5 g) from the previous experiment was dissolved in formic acid (16 ml) and acetic anhydride (5·2 ml) was added. The solution was then heated at 38° for 45 min, cooled and mixed with ethyl acetate (300 ml). After this solution had been washed with 2 N-hydrochloric acid (2 × 50 ml), 5 N-sodium carbonate (2 × 50 ml), and water (2 × 50 ml), it was dried and evaporated to leave a gum (8·5 g). This, in chloroform (50 ml) was run onto a column of silica gel (200 g) and elution was continued with chloroform. The *formamide* (XIX) formed a middle crystalline fraction (5·0 g), m.p. 82–83° raised to 85° by recrystallization from ether (Found: C, 68·4; H, 6·9. $C_{18}H_{21}O_4N$ requires: C, 68·55; H, 6·7%). ν_{max} 3315 cm^{-1}, 1666 cm^{-1} (NH.CO).

6-Benzyloxy-7-methoxyisoquinoline (VIIb)

A solution of the foregoing amide (0·25 g) in anhydrous toluene (3 ml) was treated at room temperature with freshly distilled phosphoryl chloride (2 ml). The mixture was then slowly heated to the b.p. over 1½ hr and then under reflux for a further 1½ hr. In all, ten such experiments were carried out and they were combined into chloroform (100 ml). Ice-water (80 ml) was added cautiously followed by 2 N-hydrochloric acid (50 ml) and ether (300 ml). After being shaken and separated, the organic layer was washed with 2 N-hydrochloric acid (2 × 30 ml) and water (30 ml). The combined aqueous solutions were basified with potassium carbonate and extracted with ether (3 × 100 ml). Evaporation of the dried ethereal extracts left the crystalline *isoquinoline* (VIIb) which was dissolved in ethanol and treated with picric acid (1·2 equiv.). The precipitated *picrate* was collected and recrystallized from ethanol, m.p. 250° (decomp.) (Found: C, 60·0; H, 3·6. $C_{23}H_{18}O_9N_4$ requires: C, 55·9; H, 3·7%).

A solution of the picrate in the minimum volume of chloroform was passed down a column of alumina (Peter Spence, Type "H") and the colourless percolate was evaporated to yield the isoquinoline (VIIb) (0·6 g), m.p. 127–128°, λ_{max} 206, 236, 265, 312, 324; λ_{min} 214, 262, 302, 318 mμ (log ε 4·25, 4·73, 3·69, 3·46, 3·50, 4·19, 3·68, 3·33, 3·39 respectively) in EtOH.

2-(3′-Methoxy-4′-benzyloxyphenethyl)-6-benzyloxy-7-methoxyisoquinolinium iodide (VIIIb; $X^- = I^-$)

The pure isoquinoline (VIIb) (0·56 g) in methanol (5 ml) was heated under reflux with the iodide (VIb) (1 g) for 24 hr. The crystalline salt (0·73 g), m.p. 203–204°, was collected from the cooled solution and the mother liquor was evaporated to dryness. The residue was partitioned between ether (50 ml) and 2 N-hydrochloric acid (30 ml) and, after separation, the ether layer was extracted with more acid (2 × 30 ml). Basification of the combined aqueous solutions and ether extraction (3 × 50 ml) yielded unchanged isoquinoline (VIIb) (0·21 g). This was treated in methanol (2 5·ml) as before with the iodide (VIb) (0·5 g) to give a further quantity (136 mg) of the salt. The two crops were recrystallized together from methanol to give the *quaternary iodide* (VIIIb; $X^- = I^-$), m.p. 206–207° (Found: C, 61·0; H, 5·3. $C_{33}H_{32}O_4NI.H_2O$ requires C, 60·8; H, 5·3%). λ_{max} 258, 285, 318 λ_{min} 238, 278, 292 mμ (log ε 4·74, 3·76, 4·11, 4·39, 3·76, 3·74 respectively) in EtOH.

2-(3′-Methoxy-4′-benzyloxyphenethyl)-1,2,3,4-tetrahydro-6-benzyloxy-7-methoxyisoquinoline (IXb)

The iodide (VIIIb; $X^- = I^-$) was converted into the corresponding chloride (VIIIb; $X^- = Cl^-$) by ion-exchange as for the tetramethoxy analogue (VIIIa; $X^- = I^-$) above. Part of this chloride (63 mg) in methanol (10 ml) was reduced with sodium borohydride and worked up as for the tetramethoxy analogue (IXa) to yield the *tetrahydroisoquinoline* (IXb) (45 mg) which was recrystallized

from ether, m.p. 106–107° (Found: C, 77·9; H, 7·2. $C_{33}H_{35}O_4N$ requires C, 77·8; H, 6·9%). λ_{max} 227, 287 λ_{min} 223, 255 (log ε 4·31, 3·87, 4·28, 3·38 respectively) in EtOH.

(±)-*Coreximine* (XIc)

(a) *By synthesis.* Lithium aluminium hydride (0·5 g) was added to a suspension of the quaternary chloride (VIIIb; $X^- = Cl^-$) (0·5 g) in anhydrous tetrahydrofuran (35 ml) and the reactants were shaken at room temperature for 16 hr. The reaction mixture was worked up in the way used in the (±)-norcoralydine experiment above save that the 1,2-dihydroisoquinoline (Xb) was extracted into 3:1 ether–chloroform (3 × 60 ml). Evaporation of the dried extracts left an unstable gum (427 mg) which showed the following qualitative ultra-violet absorption spectrum λ_{max} 255, 280 (inflexion), 329 λ_{min} 245, 295 mμ in EtOH. This material was dissolved in 5:1 by vol. 98% formic acid : phosphoric acid (24 ml) and heated in an evacuated sealed tube at 90° for 24 hr. The contents of the tube were then poured into water (60 ml), the solution was adjusted to pH 9 with sodium carbonate, and then extracted with 3:1 ether–chloroform (3 × 100 ml). Evaporation of the dried extracts left a gum which crystallized on the addition of a few drops of methanol. Recrystallization of the solid from ethanol yielded (±)-*coreximine* (XIc) as colourless prisms (40 mg), m.p. 233–234° alone or on admixture with the material prepared from natural (−)-coreximine. (Found: C, 70·1; H, 6·6. $C_{19}H_{21}O_4N$ requires C, 69·7; H, 6·5%). λ_{max} 205, 223 (inflexion) 287 λ_{min} 253 mμ (log ε 4·84, 4·17, 3·88, 2·89 respectively) in EtOH. This spectrum was shifted by addition of 10 drops of 8 N-sodium hydroxide to 40 ml of solution to λ_{max} 246·5, 304 λ_{min} 272 mμ (log ε 4·16, 4·07, 3·40 respectively).

(b) *From* (−)-*coreximine.* A solution of (−)-coreximine (20 mg) in glacial acetic acid (8 ml) was heated on the steam bath with mercuric acetate (60 mg) for 5½ hr. The yellow solution was then diluted with 2 N-hydrochloric acid (2 ml), zinc dust (15 mg) was added and the mixture was heated until a colourless solution was obtained. Further portions (15 mg) of zinc dust were added from time to time to maintain a steady release of hydrogen. After the solution had been filtered, it was basified to pH 9 with sodium carbonate and extracted with 3:1 ether-chloroform (3 × 80 ml). The residue recovered from the extracts by evaporation was recrystallized from ethanol to yield (±)-coreximine (8 mg), m.p. 230–232°. The infra-red and ultra-violet spectra of this sample were identical with those of the synthetic base prepared under (a).

The two samples of (±)-coreximine were indistinguishable chromatographically on Whatman No. 1 paper in solvent system "C";[26] the spots were developed with diazotized *p*-nitraniline reagent.

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[26] H. Schmid, J. Kebrle and P. Karrer, *Helv. Chim. Acta* **35**, 1864 (1952).