# An Aryne Route to Laureline, and Related Topics

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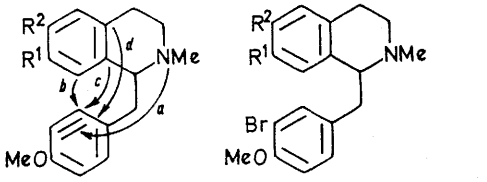
A route to laureline (IX), involving as key steps treatment of 1-(3-bromo-4-methoxybenzyl)-1,2,3,4-tetrahydro-2-methyl-6,7-methylenedioxyisoquinoline (IIa) with potassamide in liquid ammonia followed by Pschorr ring-closure, is described, together with details of the synthesis of compound (IIa) and related compounds from the appropriate phenethylamines and 3-bromo-4-methoxyphenylacetic acid.

The problem of polymerisation which supervenes in amine-catalysed condensation of aromatic aldehydes with nitromethane contaminated with methyl nitrite is noted.



THERE are a number of possible transformations which arynes of type (I),[1] generated from bromo-alkaloids of type (II), could undergo. These include the formation of new carbon–nitrogen bonds, by external addition of amide ion or by internal addition of the nitrogen of the heterocyclic ring [arrow *a* in (I)]. The former course,



(I) (II) a; $R^1R^2$ = O·$CH_2$·O
b; $R^1$ = PhC$H_2$·O, $R^2$ = MeO
c; $R^1$ = HO, $R^2$ = MeO
d; $R^1$ = H, $R^2$ = PhC$H_2$·O

through cine-substitution, would lead predominantly to a 1-(2-amino-4-methoxybenzyl)isoquinoline derivative [2] suitable for elaboration by Pschorr synthesis to an aporphine; the latter would lead in the first instance to a dibenzotetrahydroindolizinium ion. Other possible transformations of such arynes include the formation of new carbon–carbon bonds,[3] as indicated by arrows *b*—*d* in (I). Routes indicated by arrows *b* and *d* would lead directly to an aporphine and to a morphinandienone respectively and might be expected, for example, where the substituent $R^1$ is hydroxy; [3] path *c* would lead to an alternative type of dienone, interesting in connection with recent discussion of *Erythrina* alkaloid biosynthesis.[4] We now report syntheses of the bromo-alkaloids (IIa—d) and the conversion of (IIa) into the aporphine alkaloid, laureline.[5] The formation [arrow *a* in (I)] and transformation of a dibenzotetrahydroindolizinium ion have been noted in this work, but the reactions indicated by arrows *b*—*d* in (I) have not been realised.

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[1] R. W. Hoffmann, 'Dehydrobenzene and Cycloalkynes,' Academic Press, New York, 1967, ch. 2, and references there cited.

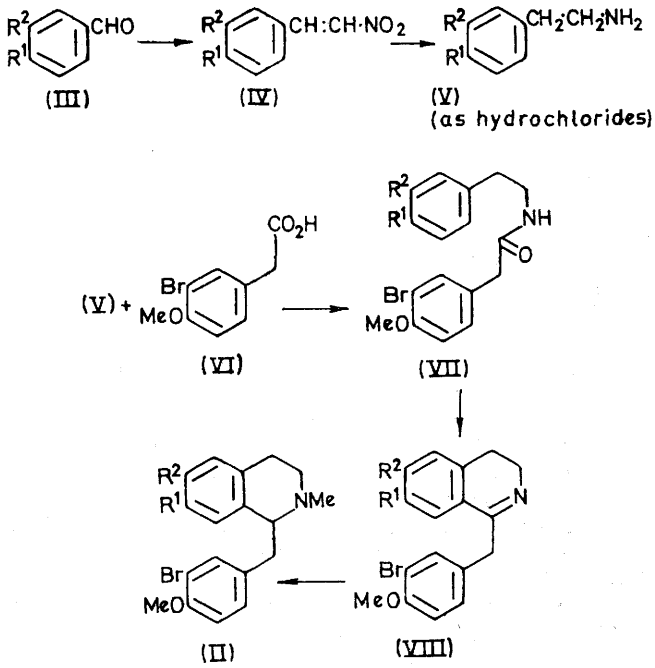
[2] *Cf.* R. A. Benkeser and W. E. Buting, *J. Amer. Chem. Soc.*, 1952, **74**, 3011.

[3] D. H. Hey, J. A. Leonard, and C. W. Rees, *J. Chem. Soc.*, 1963, 5266.

[4] D. H. R. Barton, R. James, G. W. Kirby, D. W. Turner, and D. A. Widdowson, *J. Chem. Soc.* (*C*), 1968, 1529.

[5] Preliminary communication, M. S. Gibson and J. M. Walthew, *Chem. and Ind.*, 1965, 185.

The syntheses of compounds (IIa, b, and d) are set out in the Scheme; compound (IIc) is derived from (IIb) by debenzylation.



(III) (IV) (V) (as hydrochlorides)

(V) + (VI) (VII) (VIII) (II)

The aldehydes (IIIa, b, and d) were condensed with nitromethane to give the corresponding nitrostyrenes (IVa, b, and d). No problems were encountered when sodium hydroxide was the condensing agent,[6] but with methylamine or ethylamine (directly or generated *in situ* from their hydrochlorides),[7] the success of the operation was conditional upon the absence of methyl nitrite in the samples of nitromethane employed. The presence of methyl nitrite leads to extensive formation of polymeric material, a problem which has been encountered by other workers.[8,9] Methyl nitrite may be removed from nitromethane by distillation prior to use, or alternatively, by hydrolysis if sodium hydroxide is the condensation agent. The nitrostyrenes were reduced

[6] N. A. Lange and W. E. Hambourger, *J. Amer. Chem. Soc.*, 1931, **53**, 3865.

[7] (*a*) S. Kobayashi, *Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1927, **6**, 149; (*b*) W. J. Gensler and C. M. Samour, *J. Amer. Chem. Soc.*, 1951, **73**, 5555; (*c*) D. H. Hey and A. L. Palluel, *J. Chem. Soc.*, 1957, 2926, and references cited.

[8] *Cf.* M. S. Gibson and J. M. Walthew, *Chem. and Ind.*, 1963, 1520.

[9] F. Bennington and R. D. Morin, *J. Org. Chem.*, 1967, **32**, 1050.

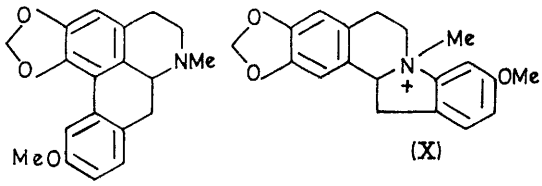
with lithium aluminium hydride (Erne–Ramirez or Finkelstein procedures [10] with modified work-up) to the amines which were isolated as hydrochlorides (Va, b, and d).

3-Bromo-4-methoxyphenylacetic acid (VI) was prepared by bromination of *p*-methoxyphenylacetic acid or, at earlier stages of this work, from 3-bromo-4-methoxybenzaldehyde. Two routes were explored from the aldehyde: one proceeded *via* the oxazolone [ArCHO ⟶ ArCH=C·CO·O·CPh:N ⟶ $ArCH_2$·CO·$CO_2H$ ⟶ (VI)]; the other was the method, with improvements, adopted previously by Naik and Wheeler [ArCHO ⟶ $ArCH_2$·OH ⟶ $ArCH_2Cl$ ⟶ $ArCH_2$·CN ⟶ (VI)].[11]

The acid (VI) was converted into the acyl chloride with thionyl chloride or, for reaction with (Vd), oxalyl chloride; treatment with the amines, generated *in situ* from the hydrochlorides (Va, b, and d) by use of sodium hydroxide in tetrahydrofuran, gave the amides (VIIa, b, and d). Alternatively, the acid (VI) was treated with *NN'*-dicyclohexylcarbodi-imide, followed immediately by a solution of the amine [12] in chloroform. The latter method was satisfactory for preparing the amides (VIIb and d), but the former method was preferable for (VIIa). The amides (VIIa, b and d) were then converted into the corresponding dihydroisoquinolines (VIIIa, b and d) with phosphoryl chloride in tetrahydrofuran. Other normal procedures for Bischler–Napieralski cyclisation, including the use of phosphorous pentachloride in chloroform reported for (VIIb),[13] were less satisfactory. The three bases (VIIIa, b, and d) were treated with methyl iodide and the resulting methiodides were then reduced with sodium borohydride to the corresponding (±)-tetrahydroisoquinolines (IIa, b, and d).

Reaction of the bromo-alkaloid (IIa) with potassamide in liquid ammonia, followed by treatment of ether-soluble products with dry hydrogen chloride, allowed the separation of (±)-1-(2-amino-4-methoxybenzyl)-1,2,3,4-tetrahydro-2-methyl-6,7-methylenedioxyisoquinoline (as the dihydrochloride [14]) and other basic material [fraction *A*] from feebly basic or non-basic products [fraction *B*]. Diazotisation of the former fraction followed by Pschorr ring-closure gave (±)-10-methoxy-1,2-methylenedioxyaporphine (IX) (laureline); this was isolated as the hydrochloride [3·7K overall yield from (IIa)] which, like (±)-corydine hydrochloride,[7c] crystallised as a monohydrate. The i.r. spectra (mulls) of the natural and synthetic laureline hydrochlorides showed minor differences; in particular, the latter showed a peak at 3333 $cm^{-1}$ (O–H), absent from the former. However, identity was established by correspondence of u.v. and mass spectra, and of colour reactions.[15] Fraction *B* provided a compound isomeric with laureline. This would most reasonably seem to be formed through intramolecular capture of the aryne by the tertiary nitrogen (>NMe) [arrow *a* in (I)] to give the dibenzotetrahydroindolizinium ion (X), followed by Hofmann elimination. Recent syntheses of substances closely related to (X) have involved similar internal capture of an aryne, with quaternisation as a subsequent step.[9,16]

Attempts to generate arynes and derived products [arrows *b* and *c* (I)] from compounds (IIc and d) under similar conditions were unsuccessful, bromo-alkaloids being recovered, though in diminished amount.




(IX) (X)

EXPERIMENTAL

The normal chromatographic and spectroscopic methods, and mixed m.p. determinations where appropriate, were used to establish purity and identity.

*Nitrostyrenes* (IV).—Sodium hydroxide (18·11 g) in ethanol (150 ml) was added during 50 min to a stirred solution of *m*-benzyloxybenzaldehyde [17] (37·8 g) and nitromethane (21·75 g) in ethanol (120 ml) at 10°; a thick white precipitate formed. After a further 2 h at 10°, water (750 ml) was added, a small amount of insoluble material was discarded, and the solution was acidified (in portions) with 2N-hydrochloric acid with stirring to give m-*benzyloxy*-β-*nitrostyrene* (IVd) as yellow needles (25·3 g, 56%), m.p. 90—91° (from ethanol) (Found: C, 70·8; H, 5·1; N, 5·6. $C_{15}H_{13}NO_3$ requires C, 70·6; H, 5·0; N, 5·4%).

The nitrostyrenes (IVa) and (IVb) were similarly prepared.[6] These nitrostyrenes were also prepared by use of pure nitromethane in the presence of ethylamine,[7] but if traces of methyl nitrite were present, only polymers were produced.

β-*Phenethylamine Hydrochlorides* (V).—*m*-Benzyloxy-β-nitrostyrene (10 g) in dry tetrahydrofuran (150 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (3·8 g) in tetrahydrofuran (50 ml) under nitrogen so that the mixture boiled gently. The mixture was then maintained at reflux for 1 h, cooled, and the excess of lithium aluminium hydride was destroyed by cautious addition of saturated aqueous sodium sulphate. Sufficient anhydrous sodium sulphate was then added to form a filterable cake. This was filtered off and washed well with dry ether. The combined filtrate and washings were dried ($MgSO_4$) and saturated with dry hydrogen chloride. The precipitated solid (7·3 g) was collected and washed with dry ether, and excess of hydrogen chloride was removed *in vacuo* (KOH

[10] (*a*) M. Erne and F. Ramirez, *Helv. Chim. Acta*, 1950, **33**, 912; (*b*) J. Finkelstein, *J. Amer. Chem. Soc.*, 1951, **73**, 550; (*c*) D. H. R. Barton, D. S. Bhakuni, G. M. Chapman, and G. W. Kirby, *J. Chem. Soc.* (*C*), 1967, 2134.

[11] R. G. Naik and T. S. Wheeler, *J. Chem. Soc.*, 1938, 1780, and references cited.

[12] J. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.*, 1955, **77**, 1067; H. G. Khorana, *Chem. and Ind.*, 1955, 1087; *cf.* F. Kurzer and K. Douraghi-Zadek, *Chem. Rev.*, 1967, **67**, 107.

[13] W. M. Whaley and C. N. Robinson, *J. Org. Chem.*, 1954, **19**, 1029.

[14] E. Schlittler, *Helv. Chim. Acta*, 1932, **15**, 394.

[15] F. Faltis, G. Wagner, and E. Adler, *Ber.*, 1944, **77**, 689.

[16] T. Kametani and K. Ogasawara, *J. Chem. Soc.* (*C*), 1967, 2208.

[17] I. Baxter, L. T. Allen, and G. A. Swan, *J. Chem. Soc.*, 1965, 3645.

pellets). Crystallisation from n-propanol gave m-*benzyloxy-β-phenethylamine hydrochloride* (Vd) as plates (6·1 g, 59%), m.p. 184—185° (Found: C, 68·1; H, 7·0; N, 5·5. $C_{15}H_{17}NO,HCl$ requires C, 68·3; H, 6·8; N, 5·3%).

The nitrostyrenes (IVa) and (IVb) were reduced by the Erne–Ramirez procedure [10a] and the reaction mixtures were worked up as for (Vd) to give (Va) (42%) and (Vb) * (47%) respectively. β-(4-Benzyloxy-3-methoxyphenyl)-propionic acid was also converted by successive reaction with oxalyl chloride (rather than thionyl chloride) and then ammonia into the amide,[7a] but satisfactory conditions were not determined for converting the latter into (Vb).

3-*Bromo-4-methoxyphenylacetic Acid* (VI).—(a) *From p-methoxyphenylacetic acid.* Bromine (5 g) in glacial acetic acid (25 ml) was added to a stirred solution of *p*-methoxyphenylacetic acid (5 g) in acetic acid (50 ml) during 30 min at room temperature; hydrogen bromide was evolved. After a further 30 min, the temperature was raised to 70° and the solution was poured into water with stirring. The recovered solid yielded 3-bromo-4-methoxyphenylacetic acid (5 g, 67%) as plates, m.p. 114—115° (from aqueous ethanol), raised by recrystallisation from benzene to 117—118° (lit.,[18] 118°).

(*b*) *From 3-bromo-4-methoxybenzaldehyde.* Bromine (160 g) was added during 1 h to a stirred solution of anisaldehyde (136 g) in 90% acetic acid (300 ml) containing a trace of iodine. The temperature of the mixture rose to *ca.* 45°. When cool, the solution was poured into water, sodium sulphite was added, and the mixture was extracted with ether. The extracts were washed with sodium carbonate solution and with water, dried, and evaporated. Distillation gave 3-bromo-4-methoxybenzaldehyde (71 g, 33%), b.p. 158—162° at 15 mm, m.p. 49·5° (lit.,[19] 51—52°); the fraction, b.p. 130—150° at 15 mm, mainly anisaldehyde, was recycled, giving an overall yield of 66%.

(i) A stirred mixture of 3-bromo-4-methoxybenzaldehyde (70 g), benzoylglycine (64·4 g), acetic anhydride (161 ml), and anhydrous sodium acetate (80 g) was heated on a steam-bath for 2 h. Excess of acetic anhydride was decomposed by careful addition of water and the mixture was then poured into water. The recovered solid yielded 4-(3-*bromo-4-methoxybenzylidene*)-2-*phenyloxazol-5-one* (85·9 g, 74%), m.p. 185—186° (from acetone) (Found: C, 57·1; H, 3·5; N, 3·9. $C_{17}H_{12}BrNO_3$ requires C, 57·0; H, 3·4; N, 3·9%).

A stirred suspension of the oxazolone (76 g) in 10% aqueous sodium hydroxide (500 ml) was heated under reflux for 3 h. The solution was cooled in ice and aqueous hydrogen peroxide (20% w/w; 250 ml) was added during 75 min. Next day, the solution was acidified with conc. hydrochloric acid, and benzoic acid was removed by distillation in steam. When cool, the residual solid was collected, dried, and crystallised from benzene to give 3-bromo-4-methoxyphenylacetic acid (25·5 g, 51%). The intermediate 3-*bromo-4-methoxyphenylpyruvic acid* (1·43 g, 94%), obtained from the oxazolone (2 g) by a similar procedure from which the hydrogen peroxide treatment was omitted, formed needles, m.p. 172—173° (from chloroform) (Found: C, 43·8; H, 3·2. $C_{10}H_9BrO_4$ requires C, 43·9; H, 3·3%).

(ii) Sodium hydroxide (67·5 g) in water (50 ml) was added with shaking to 3-bromo-4-methoxybenzaldehyde (106 g) and 40% aqueous formaldehyde (120 ml) in methanol (120 ml) at 60° during 30 min. The solution was boiled under reflux for 30 min.[20] Recovery in the normal way furnished 3-bromo-4-methoxybenzyl alcohol (65·4 g, 61%), b.p. 150—160° at 14 mm, m.p. 61—62° (lit.,[11] 63—64°).

The alcohol (76 g) in dry ether (320 ml) and olefin-free light petroleum (b.p. 40—60°; 220 ml) was treated with dry hydrogen chloride,[21] as described for a similar case, to give 3-bromo-4-methoxybenzyl chloride (77·5 g, 92%), m.p. 46—48° (lit.,[11] 51—52°).

A mixture of the chloride (66 g) and powdered potassium cyanide (36·2 g) in dry acetonitrile (200 ml) was boiled under reflux for 21 h.[22] The insoluble residue was filtered off and washed with ether. The filtrate and washings were combined and washed with water, dried, and evaporated to give 3-bromo-4-methoxybenzyl cyanide (54 g, 86%), m.p. 54—60° (lit.,[11] 56—57°).

Alkaline hydrolysis of the nitrile (54 g) gave 3-bromo-4-methoxyphenylacetic acid (42 g, 72%).[11]

N-(3,4-*Methylenedioxyphenethyl*)-2-(3-*bromo-4-methoxyphenyl*)*acetamide* (VIIa) *and Related Amides* (VIIb and c).—(i) 3-Bromo-4-methoxyphenylacetyl chloride, from the acid (VI) (1 g), in dry tetrahydrofuran (10 ml.) was added during 15 min to a mixture of 3,4-methylenedioxyphenethylamine hydrochloride (Va) (0·82 g) and aqueous sodium hydroxide solution (40% w/v; 1 ml) in tetrahydrofuran (30 ml) with vigorous shaking. After a further 15 min, the mixture was poured into water (500 ml) and the pH was adjusted to 10. The solid was filtered off, washed with water, and dried. N-(3,4-*Methylenedioxyphenethyl*)-2-(3-*bromo-4-methoxyphenyl*)*acetamide* (VIIa) (1·33 g, 83%) crystallised from benzene as needles, m.p. 144—145° (Found: C, 55·2; H, 4·4; N, 3·8. $C_{18}H_{18}BrNO_4$ requires C, 55·1; H, 4·6; N, 3·6%).

The acid (VI) (2 g) and the amine hydrochloride (Vb) (2·6 g) were similarly converted into the amide (VIIb) (2·1 g, 53%), which formed needles, m.p. 128·5—129·5° (from aqueous ethanol) (lit.,[13] 127—128°) (Found: C, 62·0; H, 5·4; N, 2·9. Calc. for $C_{25}H_{26}BrNO_4$: C, 62·0; H, 5·4; N, 2·9%).

The acid (VI) (4·9 g) and *m*-benzyloxyphenethylamine hydrochloride (Vc) (5·37 g) were similarly converted into N-(m-*benzyloxyphenethyl*)-2-(3-*bromo-4-methoxyphenyl*)*acetamide* (VIId) (6·0 g, 65%) which formed needles, m.p. 91—92° (from n-butanol) (Found: C, 63·6; H, 5·0; N, 3·3. $C_{24}H_{24}BrNO_3$ requires C, 63·4; H, 5·2; N, 3·0%).

N-*Benzyl-3-bromo-4-methoxyphenylacetamide* (0·58 g, 85%), similarly prepared from benzylamine (0·5 g), formed needles, m.p. 119—119·5° [from benzene–light petroleum (b.p. 60—80°)] (Found: C, 57·4; H, 4·9; N, 4·3. $C_{16}H_{16}BrNO_2$ requires C, 57·5; H, 4·8; N, 4·2%).

(ii) A solution of the acid (VI) (6·76 g) in dry chloroform (100 ml) was added to a solution of *NN'*-dicyclohexylcarbodiimide (5·68 g) in chloroform (500 ml); 4-benzyloxy-3-methoxyphenethylamine, from the hydrochloride (Vb) (8·1 g), in chloroform (100 ml), was then quickly added, and the volume of the solution was reduced to *ca.* 200 ml by distillation. The mixture was cooled in ice and the crystalline *NN'*-

* The hydrochloride (Vb) had m.p. 176—178° (from n-butanol).[10c]

[18] H. Kondo and S. Uyeo, *J. Pharm. Soc. Japan*, 1933, **53**, 557 (*Chem. Abs.*, 1933, **27**, 4223).

[19] O. L. Brady and L. B. Manjunath, *J. Chem. Soc.*, 1924, **125**, 1063.

[20] *Cf.* A. Ahmed, K. S. Narang, and J. N. Ray, *J. Indian Chem. Soc.*, 1938, **15**, 152.

[21] *Cf.* M. S. Gibson and J. M. Walthew, *J. Chem. Soc.*, 1963, 4603.

[22] *Cf.* G. Stork, S. S. Wagle, and P. C. Mukharji, *J. Amer. Chem. Soc.*, 1953, **75**, 3197.

dicyclohexylurea (5·8 g, m.p. 226°) was filtered off. The filtrate was evaporated to give the amide (VIIb) as a gum which crystallised from aqueous ethanol as needles (12·4 g, 93%), m.p. 127·5—128·5°.

The amide (VIIa) (5·0 g, 50%) was similarly prepared from the acid (VI) (6·24 g) and the amine hydrochloride (Va) (6·0 g); in like manner, the acid (VI) (1·08 g) and the amine hydrochloride (Vc) (1·16 g) gave the amide (VIIc) (1·4 g, 70%).

1-(3-*Bromo*-4-*methoxybenzyl*)-3,4-*dihydro*-6,7-*methylenedioxyisoquinoline* (VIIIa); *Hydrochloride and Methiodide.*—A solution of (VIIa) (1·0 g) and freshly distilled phosphoryl chloride (1 ml) in dry tetrahydrofuran (25 ml) was heated under reflux for 45 min. The mixture was poured into water (250 ml), basified with aqueous sodium hydroxide solution, and extracted with ether. The ether solution was extracted with 2N-hydrochloric acid and the ether layer was discarded. The acidic extract was then basified and extracted with ether. After being washed with water and dried ($Na_2CO_3$), the final ether solution was saturated with dry hydrogen chloride. The precipitated solid gave 1-(3-*bromo*-4-*methoxybenzyl*)-3,4-*dihydro*-6,7-*methylenedioxyisoquinoline hydrochloride monohydrate* as pale greenish-yellow needles (0·75 g, 69%), m.p. 250° (from water) (decomp.) after loss of water of crystallisation at 142° (Found: C, 50·2; H, 4·2; N, 3·2. $C_{18}H_{16}BrNO_3,HCl,H_2O$ requires C, 50·4; H, 4·4; N, 3·3%).

The free *base* (VIIIa) (needles, m.p. 46—48°), from the hydrochloride (0·96 g), was heated under reflux with methyl iodide (10 ml) for 2 h and the resulting solid (1·19 g) was collected and washed with ether. Crystallisation from ethanol gave 1-(3-*bromo*-4-*methoxybenzyl*)-3,4-*dihydro*-2-*methyl*-6,7-*methylenedioxyisoquinolinium iodide* as golden-yellow needles (0·95 g, 79%), m.p. 203·5—204° (Found: C, 44·0; H, 3·6; N, 2·9. $C_{19}H_{19}BrINO_3$ requires C, 44·2; H, 3·7; N, 2·7%).

The methiodide (57% overall) may also be prepared directly from the crude base produced in the cyclisation reaction.

(±)-1-(3-*Bromo*-4-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-2-*methyl*-6,7-*methylenedioxyisoquinoline Hydrochloride.*—Sodium borohydride (2 g) was added during 15 min to a suspension of the foregoing methiodide (2·43 g) in ethanol (50 ml) at room temperature giving a colourless solution. On the following day, the solvent was removed *in vacuo* and the gummy residue was treated with water and extracted with ether. The dried ethereal solution of (IIa) was treated with dry hydrogen chloride and the precipitated solid was then crystallised from water to give (±)-1-(3-*bromo*-4-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-2-*methyl*-6,7-*methylenedioxyisoquinoline hydrochloride monohydrate* (1·63 g, 78%) as plates, m.p. 197—199° (Found: C, 51·4; H, 5·3; N, 3·1. $C_{19}H_{20}BrNO_3,HCl,H_2O$ requires C, 51·3; H, 5·2; N, 3·15%).

7-*Benzyloxy*-1-(3-*bromo*-4-*methoxybenzyl*)-3,4-*dihydro*-6-*methoxyisoquinoline* (VIIIb); *Hydrochloride and Methiodide.*—A solution of (VIIb) (3·4 g) and freshly distilled phosphoryl chloride (1·5 ml) in dry tetrahydrofuran (25 ml) was heated under reflux for 1 h. Following work-up [as for (VIIIa)], extraction (2N-HCl) of the ethereal solution containing basic and neutral materials led to precipitation of 7-benzyloxy-1-(3-bromo-4-methoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline hydrochloride, which crystallised from water as pale greenish-yellow needles of the *monohydrate* (1·77 g, 48%), m.p. 175—180° (decomp.) [lit.,[13] (for the sesquihydrate) 194—196°] (Found: C, 57·6; H, 5·2; N, 2·7. $C_{25}H_{24}BrNO_3,HCl,H_2O$ requires C, 57·7; H, 5·1; N, 2·7%).

The free base (VIIIb) (needles, m.p. 89—92°), from the hydrochloride (1·08 g), was treated with methyl iodide as for (VIIIa). The *methiodide* * crystallised from n-butanol as yellow needles (1 g, 79%), m.p. 200—201·5° (Found: C, 51·2; H, 4·3; N, 2·0. $C_{26}H_{27}BrINO_3$ requires C, 51·3; H, 4·4; N, 2·3%).

(±)-7-*Benzyloxy*-1-(3-*bromo*-4-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-6-*methoxy*-2-*methylisoquinoline* (IIb) *and its Debenzylation.*—The foregoing methiodide (1·3 g) was reduced with sodium borohydride (1 g) as previously described and the resulting oily tetrahydro-base (IIb) (0·82 g, 80%) was characterised as the *picrate*, yellow needles, m.p. 179—181° (from aqueous acetone) (Found: C, 53·2; H, 4·1; N, 8·0. $C_{32}H_{31}BrN_4O_{10}$ requires C, 53·3; H, 4·3; N, 7·8%).

The crude base (0·75 g) in aqueous acetic acid (20 ml, 50%) was added to boiling 25% aqueous hydrochloric acid, the odour of benzyl chloride soon becoming apparent in the distillate. After 1 h, the solution was cooled, treated with an excess of aqueous sodium hydrogen carbonate and extracted with ether. The dried extract provided (±)-1-(3-bromo-4-methoxybenzyl)-7-hydroxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (IIc) (0·45 g, 76%), which crystallised from light petroleum (b.p. 60—80°) as needles, m.p. 85—86°.

The picrate crystallised from aqueous acetone as yellow needles, m.p. 193—194° (lit.,[13] 200—201°) (Found: C, 48·1; H, 3·8; N, 9·2. Calc. for $C_{25}H_{25}BrN_4O_{10}$: C, 48·3; H, 4·0; N, 9·0%).

6-*Benzyloxy*-1-(3-*bromo*-4-*methoxybenzyl*)-3,4-*dihydroisoquinoline* (VIIId); *Hydrochloride and Methiodide.*—A solution of (VIId) (4·54 g) and freshly distilled phosphoryl chloride (2·8 ml) in dry tetrahydrofuran (50 ml) was heated under reflux for 1 h, and the mixture was worked up as for (VIIIa). 6-*Benzyloxy*-1-(3-*bromo*-4-*methoxybenzyl*)-3,4-*dihydroisoquinoline hydrochloride* (3·1 g, 66%) crystallised from n-butanol as pale yellow platelets, m.p. 205—206° (Found: C, 61·0; H, 4·9; N, 2·9. $C_{24}H_{22}BrNO_2,HCl$ requires C, 60·9; H, 4·8; N, 2·9%).

The free base (VIIId) (needles, m.p. 118—123°), from the hydrochloride (1 g), was treated with methyl iodide as for (VIIIa). The *methiodide* (1·1 g, 86%) crystallised from n-propanol as orange rhombs, m.p. 146—147° (decomp.) (Found: C, 52·0; H, 4·5; N, 2·4. $C_{25}H_{25}BrINO_2$ requires C, 51·9; H, 4·3; N, 2·4%).

(±)-N-*Methyl*-6-*benzyloxy*-1-(3-*bromo*-4-*methoxybenzyl*)-1,2,3,4-*tetrahydroisoquinoline* (IId).—The foregoing methiodide (1·1 g) was reduced with sodium borohydride (0·5 g) as previously described and the resulting gummy tetrahydro-base (IId) (0·81 g, 90%) (hydrochloride, m.p. 100—106°) was characterised as the *picrate*, which formed orange plates, m.p. 123—125° (from benzene) (Found: C, 54·4; H, 4·3; N, 8·2. $C_{31}H_{29}BrN_4O_9$ requires C, 54·6; H, 4·3; N, 8·2%).

(±)-10-*Methoxy*-1,2-*methylenedioxyaporphine* (IX) (*Laureline*).—A solution of the base (IIa), from the hydrochloride (1 g), in dry ether (25 ml) was added to a stirred solution of potassamide, from potassium (0·35 g), in redistilled anhydrous ammonia (75 ml). The resulting dark reddish-brown solution was stirred for 30 min, and ammonium chloride and ether were then added. The ammonia was evaporated off, and the ether solution was

* This compound has been reported but not characterised.[13]

washed with 2N-aqueous sodium hydroxide solution (5 ml.) and with water. The ethereal extract was dried and treated with dry hydrogen chloride; an amorphous solid *A* (0·33 g), m.p. 200—220°, separated. Evaporation of the residual ether solution provided an amorphous solid *B* (0·13 g), m.p. 90—98° [from light petroleum (b.p. 100—120°)].

Fraction *A* (0·33 g) was basified with aqueous 2N-sodium hydroxide and extracted with ether (2 × 25 ml). The ethereal solution was extracted with aqueous 2N-sulphuric acid (2 × 25 ml). The acidic extract was diazotised at *ca.* 0° by addition of aqueous sodium nitrite solution and the resulting solution was heated at 80° for 20 min. A red colouration was produced. Zinc dust (1 g) and conc. hydrochloric acid (2 ml) were then added and the solution was heated at 80° for a further 5 min. After filtration and cooling, the solution was washed with ether. The aqueous phase was then basified with aqueous sodium hydroxide and extracted with ether (3 × 10 ml); the ether extract was washed with water, dried ($MgSO_4$), and treated with dry hydrogen chloride; a lilac solid separated. Crystallisation from aqueous 0·01N-hydrochloric acid gave (±)-10-methoxy-1,2-methylenedioxyaporphine hydrochloride monohydrate [(±)-laureline hydrochloride monohydrate] as colourless needles (30 mg, 3·7%), m.p. 230° (decomp.) (Found: C, 62·5; 62·3; H, 6·0; 5·7; N, 4·2. Calc. for $C_{19}H_{19}NO_3,HCl,H_2O$: C, 62·7; H, 6·0; N, 3.8; Cl, 9·8%); a sample of the hydrochloride, after being dried in high vacuum, was found to be hygroscopic (Found: Cl, 10·0%). Recrystallised (−)-laureline hydrochloride had m.p. 229—232° (decomp.); mixed m.p. 225—230° (decomp.). (±)-Laureline hydrochloride monohydrate showed $\nu_{max.}$ (Nujol) 3333, 1610, 1577, 1290, 1221, 1041, and 942 $cm^{-1}$; the first absorption band was missing from the corresponding spectrum of (−)-laureline hydrochloride, and certain other bands were slightly displaced. However, the u.v. absorption spectra were identical: $\lambda_{max.}$ (water) 222 (log ε 4·25), 264 (3·97), 273 (4·01), and 304—308 nm (3·68). Identity of the (−)- and (±)-bases was established by correlation of mass spectra: *m/e* 309 ($M^+$), 308 ($M^+ - 1$), 294 ($M^+ - 15$), and 266 ($M^+ - 43$).

Substance *B* was soluble in cold conc. hydrochloric acid but apparently insoluble in 2N-hydrochloric acid. It gave a purple colouration with aqueous ferric chloride solution, and decolourised a solution of bromine in carbon tetrachloride. Spectroscopic data: $\nu_{max.}$ (Nujol) 2786, 1616, 1250, 1190, 1161, 1120, 1042, 1011, 991, 941, 899, and 812 $cm^{-1}$; $\lambda_{max.}$ (ethanol) 257—260 (log ε 4·09) and 304 nm (3·99); *m/e* 309 ($M^+$), 294 ($M^+ - 15$), and 266 ($M^+ - 43$).

*Treatment of Bases* (IIc and d) *with Amide Ion.*—Bases (IIc and d) were recovered in diminished yield from treatment with potassamide under the foregoing conditions, possibly because of limited solubility. In neither case was there definitive evidence (diazo-coupling test) of primary aromatic amine formation, nor from (IIc) of aporphine formation (u.v. spectrum). Base (IIc) was also recovered from attempted conversion into the aporphine by use of lithium diethylamide in ether.

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