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THE SYNTHESIS OF BERBERASTINE[1]

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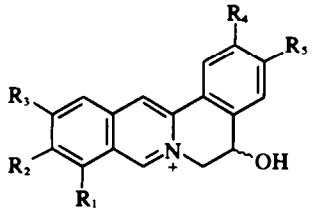
Abstract—The structure of berberastine iodide (**1a**) has been confirmed by a synthesis of its racemate. The key intermediate is the 7,8-dimethoxy-3-arylisoquinoline derivative (**3a**) and several methods for its formation were studied.

Berberastine (**1a**) was the first of three 5-hydroxyberbine alkaloids to be reported, and it was isolated[2] from *Hydrastis canadensis* L. Dehydration of **1a** gave the known[3] dehydroberberine, whereas reduction with zinc and sulphuric acid led to 5-hydroxytetrahydroberberine (tetrahydroberberastine; **2a**) itself a minor alkaloid[4] of *H. canadensis*. Since tetrahydroberberastine does not exhibit the properties of a pseudobase, the hydroxyl was assumed to be located at C_5 rather than at C_6, but definitive proof is lacking. The absolute configuration at C_5 in berberastine (**1a**), tetrahydroberberastine (**2a**) and thalidastine[5] (**1b**) is not known.

The first synthesis of 5-hydroxyberbine derivatives[6] involved the initial preparation of the 3 - aryl - 1,2,3,4 - tetrahydroisoquinolines (**3c**, $R_6 = H$ and **3d**, $R_6 = H$). Each was condensed with glycidol and the intermediate glycols (**3c**, $R_6 = CH_2CHOHCH_2OH$ and **3d**, $R_6 = CH_2CHOHCH_2OH$) were oxidised with periodic acid to the aminoaldehydes (**3c**, $R_6 = CH_2CHO$ and **3d**, $R_6 = CH_2CHO$), respectively, which were cyclised with 6N HCl to the 5-hydroxyberbines (**2c** and **2d**). Dehydrogenation with iodine then gave the quaternary salts (**1c** and **1d**), respectively. In an alternative procedure[7] the β-diketones (**6a** and **6b**) were arylated with *o*-iodobenzoic acid in the presence of copper and NaOEt to yield the isocoumarins (**5e** and **5f**), respectively. Reaction with aminoacetal gave the isocarbostyrils (**4e** and **4f**), which were reduced to (**3e**, $R_6 = CH_2CH(OMe)_2$ and **3f**, $R_6 = CH_2CH(OMe)_2$), then cyclised to (**2e** and **2f**), respectively.

For the synthesis of berberastine (**1a**), the key intermediate is 3 - (3,4 - methylenedioxy)phenyl - 7,8 - dimethoxy - 1,2,3,4 - tetrahydroisoquinoline (**3a**, $R_6 = H$). The general problem of the synthesis of 3 - substituted - 7,8 - di - oxyisoquinoline derivatives is probably the most



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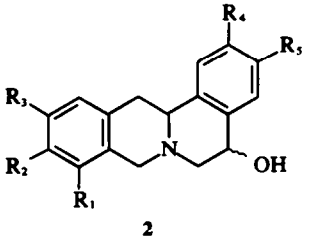

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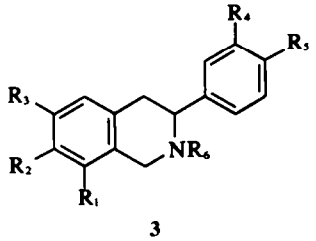

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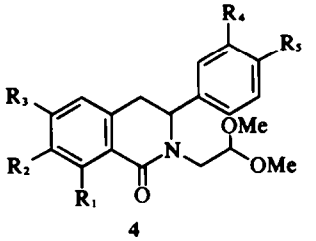

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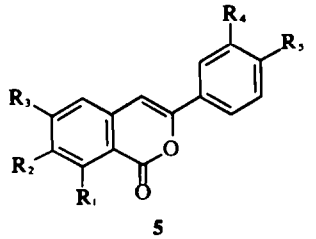

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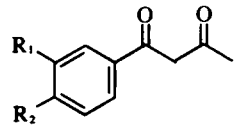
	R_1	R_2	R_3	R_4	R_5
a:	OMe	OMe	H	O—CH_2—O	
b:	OMe	OH	H	O—CH_2—O	
c:	H	OMe	OMe	OMe	OMe
d:	H	OMe	OMe	O—CH_2—O	
e:	H	H	H	OMe	OMe
f:	H	H	H	O—CH_2—O	
g:	OH	OMe	H	O—CH_2—O	
h:	H	OMe	OH	O—CH_2—O	



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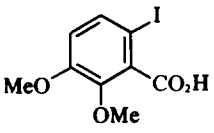
a: $R_1 = R_2 = OMe$
b: $R_1 + R_2 = CH_2O_2$



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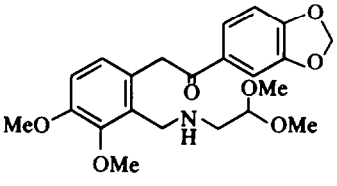
difficult remaining task in synthetic isoquinoline chemistry. We chose initially the isocoumarin route outlined above since the starting materials seemed to be readily accessible.

6 - Iodo - 2,3 - dimethoxybenzoic acid (7) had been prepared previously[8] by a 5-step sequence from 2,3-dimethoxybenzoic acid. A considerable improvement was achieved by utilising the thallation reaction,[9] when the required acid (7) was obtained in 83% in one isolated step from 2,3-dimethoxybenzoic acid. Unchanged 2,3-dimethoxybenzoic acid was easily separated by esterification of the reaction mixture with methanol and hydrogen chloride; under these conditions (7) did not react. Methylenation of catechol was accomplished by essentially a known procedure,[10] with minor modifications to avoid the need for special equipment (Experimental). Acetylation to 3,4-methylenedioxyacetophenone[11] and conversion to **6b**[7,12] were carried out as previously described.

All attempts to arylate **6b** with **7**, under the conditions previously[7] used, failed; the major products were 3,4 - methylenedioxyacetophenone and 2,3 - dimethoxy - 6 - ethoxybenzoic acid. Eventually it was found that by using NaH/DMF the phenolic isocoumarin (5g) was formed and it was isolated in 60% yield. Methylation with methyl iodide in DMF then resulted in almost quantitative conversion to the required isocoumarin (**5a**). However, when, the latter was reacted with aminoacetal, the product proved to be **8**, and not the expected isocarbostyril (**4a**). Our attempts to cyclise **8** to **4a** failed; it was not possible to use acidic reagents due to the acid-labile nature of the dimethyl acetal function. Reduction of **8** gave the amido alcohol **9**, which also resisted attempts at cyclisation. Hauser *et al*[13] reported that amidoalcohols of type **9** can be cyclised to dihydroisocarbostyrils, although Bailey and DeGrazia[14] found that in some cases the products are more correctly formulated as 1-alkyliminoisochromans. Attempts at reduction of the amide function in **9** with LAH and with B_2H_6 were also unsuccessful, and no further progress was possible with these intermediates.

A versatile synthesis of 7,8-dioxyisoquinolines involves[15] the acid-catalysed cyclisation of 2,3-dioxybenzylaminoacetaldehyde dialkylacetals, although the method has not been applied yet to the preparation of 3-arylisoquinoline derivatives. The required precursor of **3a**, (R_6 = H) is the acetal (**10**) and several attempts have been made[16,17] to prepare it. Eventually it was obtained in acceptable yield by condensing 2,3-dimethoxybenzylamine with the ketoacetal (**11**), followed by reduction of the imine function formed. The glyoxal derivative (**11**) was produced in high yield by Pummerer rearrangement[18] of **12**, itself obtained from ethyl 3,4-methylenedioxybenzoate and dimsyl sodium.[19] Ring-



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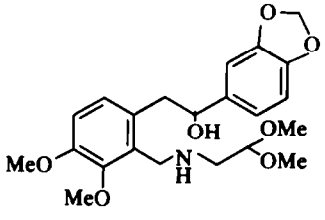

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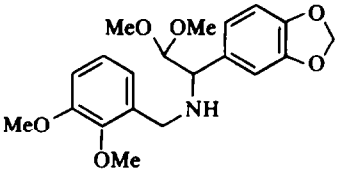

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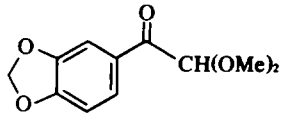

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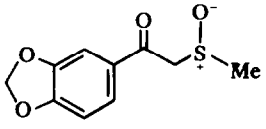

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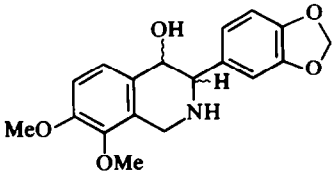

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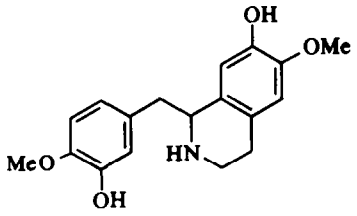

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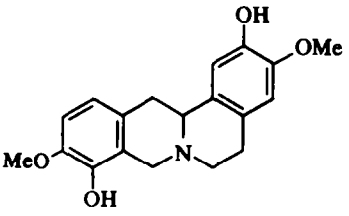

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closure of **10** was effected with 6N HCl, but the 4 - hydroxy - 1,2,3,4 - tetrahydroisoquinoline (**13**) was isolated in only 18% yield. Furthermore it was not possible to remove the C_4-OH group by dehydration or reduction, neither was aromatisation of the heterocyclic ring accomplished. The synthesis was, therefore, not carried beyond this point.

It has been found by Kametani *et al*[20] and by Battersby *et al*[21] that when 1 - benzyl - 1,2,3,4 - tetrahydroisoquinolines such as **14** are treated with formaldehyde, the cyclisation ortho to the phenolic OH group to give **15** is strongly dependent upon pH of the reaction medium. The extrapolation of these considerations to the preparation of 3-arylisoquinoline derivatives[22] has now provided the

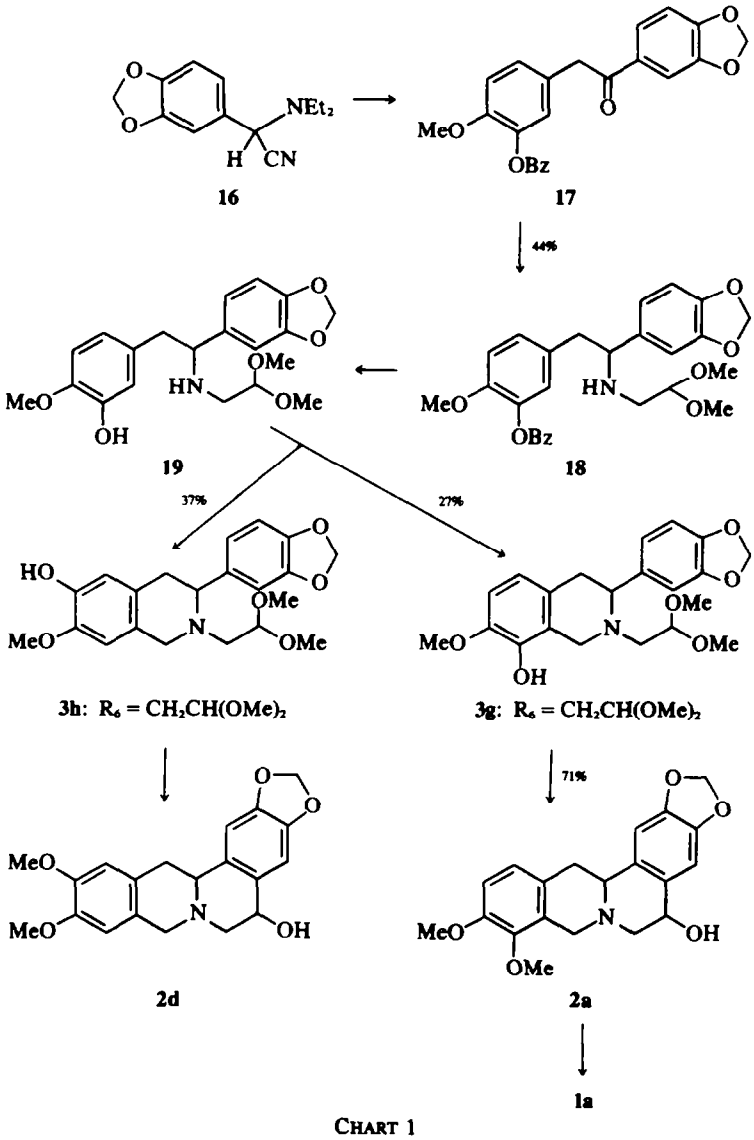

CHART 1

basis for the successful synthesis of berberastine, and it is summarised in Chart 1.

The α-aminoitrile (**16**) was alkylated[23] with 3-benzyloxy - 4 - methoxybenzyl chloride in the presence of NaH/DMF and the deoxybenzoin (**17**) was isolated after acid work-up. Condensation of **17** with aminoacetal, followed by reduction ($NaBH_4$) gave the aminoacetal derivative (**18**). Unchanged deoxybenzoin was re-cycled. The phenol (**19**) was treated with 37% aqueous formaldehyde in methonol and the mixture of **3g** ($R_6 = CH_2CH(OMe)_2$; 27%) and **3h** ($R_6 = CH_2CH(OMe)_2$; 37%) was separated by preparative-scale TLC. The structures were assigned on the basis of subsequent experiments, although NMR and IR spectral differences were apparent. The same isomer (**3h**, $R_6 = CH_2CH(OMe)_2$) was obtained when **19** was treated with $HCHO/H{\cdot}CO_2H$, when it is known that cyclisation para to phenolic OH occurs. Even here, however, TLC examination of the product indicated the presence of a small amount of **3g** ($R_6 = CH_2CH(OMe)_2$). Both isomers (**3g**, $R_6 = CH_2CH(OMe)_2$ and **3h**, $R_6 = CH_2CH(OMe)_2$) were *O*-methylated with CH_2N_2 to **3a** ($R_6 = CH_2CH(OMe)_2$) and **3d** ($R_6 = CH_2CH(OMe)_2$), respectively, and when the latter was treated with 6N HCl, the 5-hydroxyberbine (**2d**) was obtained, identical with the compound obtained previously[6] from **3d** ($R_6 = H$) and glycidol. With the identities of the isomeric tetrahydroisoquinolines established, **3g** ($R_6 = CH_2CH(OMe)_2$) was cyclised with 6N HCl/EtOH to give tetrahydroberberastine (**2a**). A partial separation of the diastereomorphic mixture was achieved on TLC. A third component was identified as 5-ethoxytetrahydroberberine.

Tetrahydroberberastine (**2a**) was dehydrogenated with iodine to yield (±)-berberastine iodide. Unfortunately an authentic sample of berberastine iodide was not available for comparison, but the spectral characteristics of the synthetic material were virtually identical with those published[2,24] for berberastine iodide. In addition the NMR and mass spectral data are entirely compatible with structure **1a**, and correlate well with the other 5-hydroxyberbine derivatives reported.[6]

EXPERIMENTAL

2,3 - *Dimethoxy* - 6 - *iodobenzoic acid* (**7**). Thallium (III) oxide (42·0 g, 0·184 mole) was dissolved in trifluoroacetic acid (200 ml) by heating at reflux for 2 days. To the cooled soln was added dimethoxybenzoic acid (20·0 g, 0·11 mole) and the resultant soln was heated under reflux for 5 h. The solvent was removed by distillation and the residual oil was stirred with dichloromethane (200 ml) and 2N KI (500 ml) for *ca* 0·5 h. $NaHSO_3$ was added to the red mixture until a light yellow colour was obtained. The mixture was filtered and the residue was washed with dichloromethane and the filtrates were combined. The organic phase was separated and washed successively with water (100 ml) and brine (100 ml), dried (Na_2SO_4), and evaporated to dryness to obtain a pale red oil (*ca* 34 g), crystallisation of which from chloroform/petrol gave **7** (28·1 g, 83%) as an off-white solid, m.p. 136–137°, analytical sample (from chloroform/petrol) m.p. 137–138° (lit.[8] m.p. 137–138°); ν_{max} ($CHBr_3$) (cm^{-1}): 1715 (CO·O), 810 (1,2,3,4 - tetra - substituted benzene); NMR ($CDCl_3$): 3·85 (3H, s, $\underline{CH_3}O$–C_3); 3·90 (3H, s, CH_3O–C_2); 6·71 (1H, d, J = 8·5 Hz, C_4–$\underline{H}$); 7·50 (1H, d, J = 8·5 Hz, C_5–$\underline{H}$); 9·6 (1H, s, removed by D_2O, –CO_2–$\underline{H}$) (Found: C, 34·8; H, 3·4; I. 42·0 Calc. for $C_9H_9IO_4$: C, 35·1; H, 3·0; I, 41·2%).

Methyl 2,3 - *dimethoxy* - 6 - *iodobenzoate*. Ethereal diazomethane was added to a soln of 2,3 - dimethoxy - 6 - iodobenzoic acid (11·0 g, 36 mmole) in MeOH (100 ml) and the yellow soln was kept at ambient temp for 16 h purged with N_2 for 1 h, and evaporated to dryness. The residue was dissolved in ether (200 ml) and washed successively with sat $NaHCO_3$ aq (2 × 50 ml), water (50 ml), brine (2 × 50 ml) and dried (Na_2SO_4) and evaporated to dryness to afford *methyl* 2,3 - *dimethoxy* - 6 - *iodobenzoate* (11·0 g, 95%), m.p. 57–59°; λ_{max} (nm) (ε) (EtOH): 236 (12,500), 290 (2,300); ν_{max} (cm^{-1}) (nujol): 1725; NMR ($CDCl_3$) 3·83 (3H, s, C_3–$\underline{OCH_3}$); 3·93 (3H, s, C_2–$\underline{OCH_3}$); 6·69 (1H, d, J = 8·5 Hz, C_4–$\underline{H}$); 7·42 (1H, d, J = 8·5 Hz, C_5–$\underline{H}$) (Found: C, 37·0; H, 3·2; I, 39·0. $C_{10}H_{11}IO_4$ requires: C, 37·3; H, 3·4; I, 39·4%).

Methylenedioxybenzene. A soln of catechol (220 g, 2·00 mole) in DMSO (180 ml), total volume 360 ml, was added in eighteen 20 ml portions, at 4 min intervals, with simultaneous addition of NaOH pellets (9·2 g portions, total 165·6 g, 4·14 mole), to a stirred soln of dichloromethane (200 ml) in DMSO (400 ml) heated to reflux (105°) under N_2. Dichloromethane (50 ml) was added after reaction time of 75 min, and again (50 ml) after a further 20 min. Water was then added in portions (100 ml) with concurrent distillation (b.p. *ca* 110°) such that the total volume of the mixture remained approximately constant. After 1·4 litres of colourless distillate was collected, the organic phase in the distillate was separated and the aqueous phase was extracted with ether (1 × 200 ml, 2 × 100 ml). The combined organic phases, derived from the distillate, were dried ($MgSO_4$), and ether was removed by distillation under reduced pressure (water pump) at 21°. The colourless residual oil was distilled to afford methylenedioxybenzene (210 g, 86%), b.p. 62°/11 mm Hg (lit.[10] b.p. 74°/22 mm Hg).

8 - *Hydroxy* - 7 - *methoxy* - (3,4 - *methylenedioxyphenyl*)*isocoumarin* (**5g**). Sodium hydride (50% oil dispersion, 2·38 g, 49·5 mmole) was washed with petrol (60–80°, 3 × 100 ml) under N_2. Dry DMF (150 ml) was added, followed by 3,4 - methylenedioxyphenylbutan - 2,4 - dione (9·70 g, 47·1 mmole), 2,3 - dimethoxy - 6 - iodobenzoic acid (13·80 g, 44·8 mmole) and Cu powder (0·50 g). The mixture was heated under reflux for 7·5 h, stood at 21° for 16 h, and evaporated to dryness. The resultant black oil was stirred with dichloromethane (1·5 litres) and 0·5N HCl (1 litre) and filtered. The organic phase was washed with 0·2M K_2CO_3 (500 ml), dried (Na_2SO_4), and evaporated to dryness to afford a black tar (*ca* 20 g). Extraction of the tar with hot petrol (60–80°, 3 × 200 ml) left a gummy dark solid which was stirred with CCl_4 (200 ml), filtered, and the residue was washed with more CCl_4 and dried to obtain crude (**5g**) (suitable for subsequent reactions) (8·76 g, 28·1 mmole, 62·8%) as a pale brown solid. Sublimation of the crude product at 206°/0·07 mm Hg gave 8 - *hydroxy* - 7 - *methoxy* - 3 - (3,4 - *methylenedioxyphenyl*) - *isocoumarin* (**5g**) (75% recovery) as a very pale green solid, m.p. 217–218°; λ_{max} (nm) (ε) MeOH) 231 (29,500), 323 (22,900), 377 (13,500); λ_{max} (nm) (ε) (CH_2Cl_2) 238 (25,500), 327 (21,200), 378 (13,500); ν_{max} (KBr) (cm^{-1}) 1670 (CO·O), 930 (OCH_2O), ν_{max} ($CHBr_3$) 2840 (OMe), 1655 (CO·O), 940 (OCH_2O); NMR (DMSO-d^6) (100 MHz) 3·86 (3H, s, Ar$\underline{OCH_3}$); 6·10 (2H, s, –$\underline{OCH_2}$O–); 7·03 (1H, d, J = 9 Hz, C_6–$\underline{H}$ or C_5'–$\underline{H}$); 7·08 (1H, d, J = 9 Hz, C_5'–$\underline{H}$ or C_6–$\underline{H}$); 7·30 (1H, s, C_2'–$\underline{H}$); 7·33 (1H, d of d, J = 9 and 2·5 Hz, C_5–$\underline{H}$); 7·37 (1H, d, J = 2·5 Hz, C_4–$\underline{H}$); 7·53 (1H, d, J = 9 Hz, C_6'–$\underline{H}$) (Found: C, 65·6; H, 4·1. $C_{17}H_{12}O_6$ requires C, 65·4; H, 3·9%).

7,8 - *Dimethoxy* - 3 - (3,4 - *methylenedioxyphenyl*)*isocoumarin* (**5a**). Pure sublimed 8 - hydroxy - 7 - methoxy - 3 - (3,4 - methylenedioxyphenyl)isocoumarin (5g; 0·250 g, 0·80 mmole), K_2CO_3 (0·280 g, 2·00 mmole) and idomethane (2 ml) in DMF (25 ml) was stirred for 2 days at 21° and the mixture was evaporated to near dryness. The residue was shaken with dichloromethane (60 ml)

and washed with water (4 × 20 ml) and brine (20 ml), dried (Na_2SO_4), and evaporated to dryness. The residue was washed thoroughly with dry ether and dried to afford 7,8 - *dimethoxy* - 3 - (3,4 - *methylenedioxyphenyl*)*isocoumarin* (**5a**) (0·260 g, 99·5%) as a pale yellow solid, m.p. 216–217°; λ_{max} (nm) (ϵ) (MeOH) 228·5 (29,200), 320·5 (24,000), 371·5 (11,200); ν_{max} (cm^{-1}) ($CHBr_3$) 2845 (OMe), 2780, 1725 (CO·O), 940 (OCH_2O); NMR (DMSO-d^6) (100 MHz) 3·84 (3H, s, C_7–OCH_3); 3·90 (3H, s, C_8–OCH_3); 6·05 (2H, s, $-OCH_2O-$); 6·97 (1H, d, J = 9 Hz, C_5'–H); 7·10 (1H, s, C_2'–H); 7·2–7·45 (2H, m, C_6–H and C_6'–H); 7·32 (1H, s, C_4–H); 7·57 (1H, d, J = 9 Hz, C_5–H) (Found: C, 66·1; H, 4·6. $C_{18}H_{14}O_6$ requires: C, 66·3; H, 4·3%).

N - (2,2 - *Dimethoxyethyl*) - 2,3 - *dimethoxy* - 6 - (3,4 - *methylenedioxyphenacyl*)*benzamide* (**8**). A suspension of **5a** (15·7 g, 48·2 mmole) in aminoacetal (20 ml) and DMSO (150 ml) was stirred for 2 weeks at *ca* 20°. The light red soln was poured into water (2 litres) and extracted with ether (3 × 300 ml). The combined ethereal extracts were stood for 1 h and filtered. The residue was washed with dry ether (2 × 10 ml) and dried to obtain N - (2,2 - *dimethoxyethyl*) - 2,3 - *dimethoxy* - 6 - (3,4 - *methylenedioxyphenyacyl*)*benzamide* (**8**) (5·60 g, 13·0 mmole, 27%) m.p. 132·5–133·5°. The ethereal filtrate was evaporated to dryness and the residue was washed with dry ether (2 × 10 ml) and dried to afford **8** (2·30 g, 5·3%) as an off-white solid, m.p. 129–130°. The aqueous DMSO soln was extracted with dichloromethane (3 × 300 ml) and the combined extracts were washed with water (1 × 2 litres, 2 × 1 litre) and dried (Na_2SO_4) and evaporated to dryness. The residue was triturated with ether to obtain a further sample of **8** (2·20 g, 5·1%) as a very pale brown solid, m.p. 129–130° (total yield 10·1 g, 23·5 mmole, 48·7%), analytical sample, m.p. 132·5–133·5°; λ_{max} (nm) (ϵ) (EtOH) 205 (48,800), 230 (29,700), 278 (9,150), 314 (9,150); ν_{max} (cm^{-1}) ($CHBr_3$) 3420 broad, m. NH); 2850 (OCH_3); 1690–1650 (carbonyls); 940 (OCH_2O); NMR ($CDCl_3$) 3·32 [6H, s, $CH(OCH_3)_2$]; 3·37 (2H, apparent t, J ≃ 5·5 Hz, –NH CH_2–CH–); 3·86 (6H, s, 2 × $ArOCH_3$); 4·30 (2H, s, $ArCH_2CO$); 4·38 [1H, t, J = 5·5 Hz, $CH_2CH(O\cdot CH_3)_2$]; 6·02 (2H, s, $-OCH_2O-$); 6·54 (1H, broad t, J ≃ 5·5 Hz, –NH); 6·86 (1H, d, J = 8 Hz, C_5'–H); 6·89 (2H, s, C_4–H and C_5–H); 7·50 (1H, d, J = 1·5 Hz, C_2'–H); 7·68 (1H, d of d, J = 1·5 and 8 Hz, C_6'–H) (Found: C, 61·3; H, 5·8; N, 3·2. $C_{22}H_{25}NO_8$ requires: C, 61·25; H, 5·8; N, 3·25%).

N - (2,2 - *Dimethoxyethyl*) - 2,3 - *dimethoxy* - 6 - [2 - *hydroxy* - 2 - (3,4 - *methylenedioxyphenyl*)*ethyl*]*benzamide* (**9**). To a soln of **8** (2·69 g, 6·44 mmole) in 95% EtOH (80 ml) was added $NaBH_4$ (2·0 g) and the soln was stirred for 2 h, then evaporated to near dryness. Chloroform (50 ml) and water (60 ml) were added and the organic phase was washed with water (2 × 30 ml) and dried (Na_2SO_4) and evaporated to dryness to give a pale yellow gum. Crystallisation from benzene (50 ml) and petrol (60–80°, 60 ml) gave N - (2,2 - *dimethoxyethyl*) - 2,3 - *dimethoxy* - 6 - [2 - *hydroxy* - 2 - (3,4 - *methylenedioxyphenyl*)*ethyl*]*benzamide* (**9**) (2·53 g, 94%), m.p. 121–122°; λ_{max} (nm) (ϵ) (EtOH) 205 (57,700), 287 (6,340); ν_{max} (cm^{-1}) ($CHBr_3$) 3420 (s, sh, NH), 3300 (broad, s, OH), 2850 (w, OMe), 2790 (w), 1645 (CONH), 940 (OCH_2O); NMR ($CDCl_3$) 3·86 (6H, s, 2 × $ArOCH_3$); 4·0–4·3 (1H, broad, removed by D_2O, OH); 4·50 (1H, t, J = 5 Hz, –CH–OH); 4·74 (1H, broad t, J ≃ 7 Hz, NHCH_2CH–); 5·95 (2H, s, $-OCH_2O-$); 6·63 (1H, broad t, J ≃ 7 Hz, –NH); 6·75–7·0 (5H, m, aromatics) (Found: C, 61·05; H, 6·1; N, 3·4. $C_{22}H_{27}NO_8$ requires: C, 61·0; H, 6·3; N, 3·2%).

2,3-*Dimethoxybenzylamine*. A soln of hydroxylammonium chloride (10·5 g, 0·15 mole) in water (12·5 ml) was added to a soln of 2,3-dimethoxybenzaldehyde (20·75 g, 0·125 mole) in warm EtOH (50 ml), followed by a soln of NaOH (7·5 g, 0·19 mole) in water (10 ml) The resultant white mixture was stood at 21° for 20 h, then crushed ice (80 g) was added. The mixture was saturated with CO_2, filtered, and the residue was washed with water (3 × 30 ml), and dried to obtain 2,3-dimethoxybenzaldoxime (20·02 g, 89%), ν_{max} (cm^{-1}) (nujol) 3200 (OH), 1655 (–C=N–); NMR ($CDCl_3$) 3·87 (6H, s, 2 × $-OCH_3$); 6·8–7·5 (3H, m, aromatics); 8·5 (s, 1H, Ar–CH=N); 9·3 (1H, broad s, removed on deuteration, =N–OH).

Zn powder (50 g) was added portionwise over 0·75 h to a stirred soln of 2,3-dimethoxybenzaldoxime (32·3 g, 0·178 mole) in glacial AcOH (200 ml) at 55 to 70°. After stirring for a further 0·75 h the mixture was filtered, the residue was washed with hot AcOH, and the combined filtrates were evaporated to near dryness under reduced pressure. The residue was basified with aqueous ammonia and extracted with chloroform (1 × 150 ml, 2 × 50 ml). The combined extracts were then extracted with 2N HCl (1 × 250 ml, 1 × 100 ml) and the combined aqueous acid extracts were basified with aqueous ammonia and extracted with chloroform (1 × 200 ml, 2 × 50 ml), washed with water, dried (Na_2SO_4) and evaporated to dryness to obtain 2,3-dimethoxybenzylamine as a yellow oil (24·67 g, 83%). Treatment of an ethereal soln of 2,3-dimethoxybenzylamine with HCl chloride gas afforded 2,3 - *dimethoxybenzylammonium chloride* as a white solid (quantitative conversion), m.p. 157–159°; λ_{max} (nm) (ϵ) 278 (2,100); ν_{max} (cm^{-1}) 3200–2500 (br, mult), 2010, 1970, 1900, 1800 (1,2,3 - trisubstituted benzene), 805 (s), 768 (s), 738 (s), 700 (m); NMR (DMSO-d^6) 3·78 (6H, s, 2 × OCH_3); 2·9 (2H, broad s, $ArCH_2$–NH_2^+)' 6·95–7·2 (3H, m, aromatics); 8·3–9·0 (3H, broad, –NH_3^+); after D_2O, 3·75 and 3·82 (6H, d, 2 × OCH_3); 4·01 (2H, s, $ArCH_2$–NH_3^+); 7·10 (3H, s, aromatics (Found: C, 52·8; H, 6·7; N, 6·6; Cl, 17·6. $C_9H_{14}ClNO_2$ requires C, 53·0; H, 6·9; Cl, 17·4%).

3,4 - *Methylenedioxyphenacyl methylsulphoxide* (**12**). Sodium hydride (29·6 g, 50% oil suspension, 0·616 mole) was washed with petrol (40–60°) (3 × 200 ml) under N_2, then dry DMSO (600 ml) was added and the effervescent mixture was stirred at ≤ 68° for 2 h to obtain a light grey soln. Dry THF (300 ml) was added and the soln was cooled to *ca* 6°. A soln of methyl 3,4-methylenedioxybenzoate (54·0 g, 0·300 mole) in dry THF (180 ml) was added with stirring over 10 min, temp ≤ 15°. The soln was stirred for 1·3 h at 15°, poured into water (4 litres), acidified with conc HCl (100 ml) and extracted with chloroform (4 × 500 ml). The combined extracts were washed with water (1 litre), dried (Na_2SO_4) and evaporated to small volume when a white solid began to precipitate. The mixture was diluted with ether (1·3 litres), stood for 2 h at 21°, filtered, washed with ether and dried to obtain 3,4 - *methylenedioxyphenacyl methylsulphoxide* (**12**) (57·0 g, 84%), m.p. 112–113°, λ_{max} (nm) (ϵ) (EtOH) 206 (14,100), 234 (16,100), 281 (6,550), 318 (8,820); ν_{max} (cm^{-1}) (nujol) 1665; NMR ($CDCl_3$) 2·71 (3H, s, O=S–CH_3); 4·15 and 4·43 (2H, d of d, J = 14 Hz, $-COCH_2-$); 6·04 (2H, s, $-OCH_2O-$); 6·85 (1H, d, J = 8 Hz, C_5–H); 7·40 (1H, d, J = 2 Hz, C_2–H); 7·56 (1H, d of d, J = 8 Hz and 2 Hz, C_6–H) (Found: C, 53·1; H, 4·5; S, 13·8. $C_{10}H_{10}O_4S$ requires; C, 53·1; H, 4·5; S, 14·1%).

ω,ω - Dimethoxy - 3,4 - *methylenedioxyacetophenone* (**11**). A soln of **12** (33·9 g, 150 mmole) and I_2 (24 g, 94 mmole) in MeOH (300 ml) was heated under reflux for 2 h, then cooled, and evaporated to dryness. The residue was dissolved in dichloromethane (300 ml), washed with aqueous sodium thiosulphate soln, $NaHCO_3$ aq, dried (K_2CO_3) and evaporated to dryness to obtain *ω,ω - dimethoxy* - 3,4 - *methylenedioxyacetophenone* (**11**) (32·10 g, 95·5%) as a pale yellow oil. Distillation of a sample (4·7 g) afforded a pale yellow oil (3·0 g, 64% recovery), b.p. 112–116°/0·07 mm Hg; λ_{max} (nm) (ϵ) (EtOH) 232·5 (15,700), 277·5 (6,700), 314·5 (8,160); ν_{max} (thin film) 2825 (sharp), 1670 (C=O), 930 ($-OCH_2O-$); NMR ($CDCl_3$) 3·44 (6H, s, 2 × $-OCH_3$); 5·08 (1H, s, CO–CH–); 6·00 (2H, s, $-OCH_2O-$); 6·80 (1H, d, J = 8 Hz, C_5–H);

7·53 (1H, d, J = 1·5 Hz, C_2–H); 7·75 (1H, d of d, J = 8 Hz and 1·5 Hz, C_6–H) (Found: C, 59·1; H, 5·2. $C_{11}H_{12}O_5$ requires: C, 58·9; H, 5·4%).

α - (2,3 - Dimethoxybenzylamino) - 3,4 - methylenedioxyphenylacetaldehyde dimethylacetal (**10**). A soln containing 2,3-dimethoxybenzylamine (28·3 g, 169 mmole), *ωω* - dimethoxy - 3,4 - methylenedioxyacetophenone (35·0 g, 156 mmole) and *p*-toluenesulphonic acid (0·1 g) in toluene (500 ml) was heated under reflux for 24 h under a Dean and Stark head. The light red soln was evaporated to dryness and the residue was dissolved in MeOH (500 ml), cooled to *ca.* 5°, and $NaBH_4$ (20 g) was added in portions over 20 min with stirring. The soln was stirred at 21° for 1·5 h then evaporated to near dryness. The residue was shaken with ether and water and ice-cold ethereal soln was extracted with ice-cold 2N H_2SO_4 (1 × 150 ml, 3 × 50 ml). The combined acid extracts were basified with aqueous ammonia (*d* 0·88) with ice-cooling, extracted with ether (1 × 300 ml, 2 × 100 ml) and the combined ethereal solns were washed with water (200 ml), brine (2 × 200 ml), dried (Na_2SO_4) and evaporated to dryness. The resultant light red oil (44 g) was chromatographed on neutral alumina (2·5 kg), eluting with 33% chloroform in petrol (60–80°). The first 3 litres of eluate were discarded and the following 9 litres (monitoring by TLC) were evaporated to dryness. The resultant oil was dissolved in ether, ice-cooled, and extracted with ice-cold 2N H_2SO_4. The aqueous acid soln was basified with aqueous ammonia (*d* 0·88) with cooling and extracted with ether. The ethereal extract was washed with water, brine, dried (Na_2SO_4) and evaporated to dryness to obtain *α - (2,3 - dimethoxybenzylamino) - 3,4 - methylenedioxyphenylacetaldehyde dimethylacetal* (**10**) (20·8 g, 55·8 mmole, 36%) as a viscous pale yellow oil, λ_{max} (nm) (ε) (EtOH) 281 (5,070); ν_{max} (cm^{-1}) (thin film) 3400 (NH), 2850 (OCH_3), 935 (OCH_2O); NMR ($CDCl_3$) 2·7 (1H, broad s, –NH); 3·13, 3·23, 3·29, 3·40 (6H, singlets, 2 × CHOCH_3); 3·54 (1H, d, J = 5·5 Hz, ½ of Ar–CH_2–N–); 3·7–3·9 (7·5 H, m, 2 × ArOCH_3, ½ of Ar–CH_2–N, ½ of Ar–CH–CH–); 4·22 (0·5 H, d, J = 7·0 Hz, ½ of CH–OCH_3); 4·48 (0·5 H, d, J = 6·3 Hz, ½ of CH_3O–CH–OCH_3); 5·87 (2H, s, –OCH_2O–); 6·6–7·1 (6H, m, aromatics) (Found: C, 63·7; H, 6·5; N, 3·7. $C_{20}H_{23}NO_6$ requires: C, 64·0; H, 6·7; N, 3·7%).

7,8 - Dimethoxy - 4 - hydroxy - 3 - (3,4 - methylenedioxyphenyl) - 1,2,3,4 - tetrahydroisoquinoline (**13**). A soln of *α - (2,3 - dimethoxybenzylamino) - 3,4 - methylenedioxyphenylacetaldehyde dimethyl acetal (4·20 g, 11·2 mmole) in MeOH (100 ml) was cooled in an ice bath and 36% HCl (100 ml, A.R) was added and the light red soln was kept at room temp for 2 days. The soln was evaporated to small bulk under reduced pressure, temp ≯40°, and filtered. The solid was washed with a small amount of water and shaken with 2N ammonia (50 ml) and chloroform (50 ml). The organic phase was washed with water (50 ml), brine (50 ml), dried (Na_2SO_4) and evaporated to dryness. The resultant off-white solid (0·620 g) was triturated with ether and dried to afford 7,8 - dimethoxy - 4 - hydroxy - 3 - (3,4 - methylenedioxyphenyl) - 1,2,3,4 - tetrahydroisoquinoline* (**13**) as a white solid (0·600 g, 16·3%), m.p. 162–164°, λ_{max} (nm) (ε) (EtOH) 205 (58,000), 283 (6,170); ν_{max} (cm^{-1}) ($CHBr_3$) 3530 (OH), 3200 (NH), 930 (OCH_2O), no change in absorption positions above 3000 cm^{-1} on dilution; NMR ($CDCl_3$) 2·32 (2H, s, removed on deuteration, –OH and –NH); 3·8–3·9 (7H, s, 2 × ArOCH_3 and ArCH–CHOH); 3·92 (1H, d, J = 15 Hz, ArCH(H)–NH–); 4·32 (1H, d, J = 15 Hz, ArCH(H)–NH–); 4·49 (1H, s, ArCH–OH); 5·91 (2H, s, –OCH_2O–); 6·75–7·24 (5H, m, aromatics) (Found: C, 65·7; H, 4·3. $C_{18}H_{19}NO_5$ requires C, 65·6; H, 4·3%).

α - Cyano - N,N - diethyl - 3,4 - methylenedioxybenzylamine (**16**). A soln of piperonal (32·9 g, 0·219 mol) in MeOH (130 ml) was added to a soln of diethylammonium chloride (31·9 g, 0·33 mole) and NaCN (24 g, 0·49 mole) in water (150 ml) and stirred for 18 h at 19°. The pale red two-phase soln was diluted with water (800 ml) and extracted with ether (1 × 500 ml, 1 × 150 ml) and the combined ethereal extracts were washed with aqueous sodium metabisulphite (6 × 150 ml), water (150 ml), brine (2 × 150 ml) and dried ($MgSO_4$). Evaporation of the ethereal soln gave *α - cyano - N,N - diethyl - 3,4 - methylenedioxybenzylamine* (**16**) as a red oil (41·25 g, 81%); NMR ($CDCl_3$) 1·07 (6H, t, J = 7·5 Hz, 2 × CH_2CH_3); 2·53 (2H, q, J = 7·5 Hz, CH_2CH_3); 2·61 (2H, q, J = 7·5 Hz, CH_2CH_3); 4·92 (1H, s, CH–CN); 5·99 (2H, s, –OCH_2O–); 6·80 (1H, d, J = 8 Hz, C_5–H); 7·02 (1H, s, C_2–H); 7·06 (1H, d, J = 8 Hz, C_6–H) (Found: C, 65·3; H, 7·0; N, 11·6. $C_{12}H_{16}N_2O_2$ requires: C, 65·5; H, 7·3; N, 12·7%).

3 - Benzyloxy - 4 - methoxybenzyl - 3,4 - methylenedioxyphenyl ketone (**17**). Sodium hydride (7·5 g, 60% suspension in oil, 0·187 mole) was washed with petrol (30–40°) under N_2 then a soln of **16** (41·2 g, 0·177 mole) in DMF (200 ml) was added. The resultant red-brown suspension was stirred under N_2 for 3 h at 23° and 3-benzyloxy-4-methoxybenzyl chloride (38·3 g, 0·146 mole) was added and the mixture was stirred for a further 16 h. The solvent was removed by evaporation under reduced pressure and the residue was stirred with dichloromethane (400 ml) and 1N H_2SO_4 (400 ml) for 20 h. The aqueous phase was extracted with more dichloromethane (100 ml) and the combined organic extracts were washed with sat $NaHCO_3$ aq (2 × 200 ml), brine (2 × 200 ml), and dried ($MgSO_4$). Evaporation afforded a red oil, which, on trituration with ether gave *3 - benzyloxy - 4 - methoxybenzyl - 3,4 - methylenedioxyphenyl ketone* (**17**) (24·68 g, 45%) m.p. 110°, analytical sample m.p. 113° (from EtOH); λ_{max} (nm) (ε) (EtOH) 204 (66,400), 230 (29,800), 280 (8,800), 315 (8,500); ν_{max} (cm^{-1}) ($CHBr_3$) 2840 (OCH_3), 2785 (w), 1670 (C=O), 940 (OCH_2O); NMR ($CDCl_3$) 3·80 (3H, s, ArOCH_3); 4·02 (2H, s, COCH_2Ar); 5·08 (2H, s, Ph–CH_2–O); 5·95 (2H, s, –OCH_2O–); 6·78 (1H, d, J = 10 Hz, C_5–H on piperonoyl); 6·82 (3H, s, aromatics on dialkoxybenzyl); 7·2–7·5 (5H, m, C_6H_5–CH_2–); 7·35 (1H, d, J = 2 Hz, C_2–H on piperonoyl); 7·53 (1H, d of d, J = 2 Hz and 10 Hz, C_6–H on piperonoyl) (Found: C, 73·7; H, 5·5. $C_{23}H_{20}O_5$ requires: C, 73·4; H, 5·4%).

N - (2,2 - Dimethoxyethyl) - 2 - (3 - benzyloxy - 4 - methoxyphenyl) - 1 - (3,4 - methylenedioxyphenyl)ethylamine (**18**). A soln of **17** (18·1 g, 48·2 mmole), *p*-toluene–sulphonic acid (*ca* 60 mg) and aminoacetal (30 ml) in toluene (250 ml) was heated under reflux under a Dean and Stark head for 20 h. Evaporation of the solvent gave a pale red oil which was dissolved in EtOH (350 ml) and treated with $NaBH_4$ (12 g) with stirring. After 1·5 h the soln was evaporated to near dryness and the residue was shaken with ether (400 ml) and water (400 ml). The ethereal soln was cooled by addition of ice and extracted with ice-cold 2N HCl (3 × 50 ml). The combined extracts were basified with aqueous ammonia (*d* 0·88) and extracted with 10% chloroform in ether (1 × 200 ml, 2 × 100 ml). The combined extracts were washed with water (100 ml), brine (100 ml), dried ($MgSO_4$) and evaporated to dryness. The resultant pale red oil was extracted with hot petrol (80–100°, 400 ml, 2 × 100 ml) and the extracts were combined, cooled to about 25°, and decanted from a trace of yellow oil. The colourless soln was kept at 4° for 20 h, filtered, and the residue was dried to give *N - (2,2 - dimethoxyethyl) - 2 - (3 - benzyloxy - 4 - methoxyphenyl) - 1 - (3,4 - methylenedioxyphenyl)ethylamine* (**18**) (9·82 g, 44%) m.p. 65–66°; λ_{max} (nm) (ε) (EtOH) 205 (86,900), 286 (6,300); ν_{max} ($CHBr_3$) 3220 (NH), 2850 (OCH_3), 2790 (w), 940 (OCH_2O); NMR ($CDCl_3$) 2·0 (1H, broad s, removed by deuteration, —NH); 2·50 (2H, d, J = 5·5 Hz, CH_2NH); 2·76 (2H, d, J = 7 Hz, ArCH_2CH);

3·25 (6H, s, 2×CH–O–CH_3); 3·65 (1H, t, J = 7 Hz, ArCH–CH_2); 3·82 (3H, s, Ar–OCH_3); 4·34 (1H, t, J = 5·5 Hz, $CH_2CH(OCH_3)_2$); 5·07 (2H, s, PhCH_2–); 5·92 (2H, s, –OCH_2O—); 6·6–7·0 6H, m, aromatics); 7·3–7·5 (5H, m, C_6H_5–CH_2) (Found: C, 69·9; H, 6·7; N, 3·1. $C_{27}H_{31}NO_6$ requires: C, 69·7; H, 6·7; N, 3·0%).

N - (2,2 - *Dimethoxyethyl*) - 2 - (3 - *hydroxy* - 4 - *methoxyphenyl*) - 1 - (3,4 - *methylenedioxyphenyl*)*ethylamine* (**19**). Hydrogenolysis of **18** (9·82 g, 21·1 mmole) in EtOH (300 ml) containing 10% Pd–C (0·40 g) at atmospheric pressure and crystallisation from petrol (80–100°) gave N - (2,2 - *dimethoxyethyl* - 2 - (3 - *hydroxy* - 4 - *methoxyphenyl*) - 1 - (3,4 - *methylenedioxyphenyl*)*ethylamine* (**19**) (6·89 g, 87%) m.p. 85–86°; λ_{max} (nm) (ϵ) (EtOH) 232 (11,300), 284·5 (8,030); ν_{max} ($CHBr_3$) 3520 (OH, strong), 3300 (NH, weak), 2840 (OCH_3), 2780 (w), 940 (OCH_2O); NMR ($CDCl_3$) 2·51 (2H, d, J = 5·5 Hz, –NHCH_2–); 2·7 (2H, m, ArCH_2CH–); 3·22 (6H, s, 2×–CHOCH_3); 3·6 (1H, m, ArCHNH); 3·80 (3H, s, Ar–OCH_3); 3·90 (2H, s, removed on deuteration, –OH and –NH); 4·37 (1H, t, J = 5·5 Hz, CH_2CH–OCH_3); 5·90 (2H, s, –OCH_2O–); 6·6–7·0 (6H, m, aromatics) (Found: C, 64·2; H, 6·7; N, 3·8. $C_{20}H_{25}NO_6$ requires: C, 64·0; H, 6·7; N, 3·7%).

N - (2,2 - *Dimethoxyethyl*) - 8 - *hydroxy* - 7 - *methoxy* - 3 - (3,4 - *methylenedioxyphenyl*) - 1,2,3,4 - *tetrahydroisoquinoline* (**3g**, $R_6 = CH_2CH(OMe)_2$). A soln of **19** (3·01 g, 8·03 mmole) in MeOH (60 ml) and 36% aqueous formaldehyde (25 ml) was stood at 21° for 5 h, then at 4° for 20 h. The soln was evaporated to near dryness and the residue was shaken with water and ether. The ethereal soln was ice-cooled and extracted with ice-cold 1N HCl (2×60 ml). The combined acid extracts were basified by addition of solid $NaHCO_3$ and the mixture was extracted with ether (3×100 ml). The combined ethereal extracts were washed with brine, dried ($MgSO_4$), and evaporated to dryness to afford a pale yellow-green oil (2·56 g). Separation of the two major components was achieved by preparative layer chromatography on alumina (Merck) with two elutions using 50% chloroform in petrol (60–80°).

Fraction A, (TLC R_f 0·53, alumina, chloroform) was N - (2,2 - *dimethoxyethyl*) - 8 - *hydroxy* - 7 - *methoxy* - 3 - (3,4 - *methylenedioxyphenyl*) - 1,2,3,4 - *tetrahydroisoquinoline* (**3g**, $R_6 = CH_2CH(OMe)_2$) (0·85 g, 27%). The hydrochloride salt was obtained in ether and crystallised from water, m.p. 195–196° (dec); λ_{max} (nm) (ϵ) (EtOH) 205 (63,000), 233 (19,900), 286 (8,800); λ_{max} (cm^{-1}) ($CHBr_3$) 3290 (OH), 2490, 2440, 2380 (NH^+); NMR (free base) ($CDCl_3$) 2·46 and 2·63 (2H, doublets, J = 5 Hz, –NCH_2CH–); 2·95 (2H, broad d, J ~ 7 Hz, C_4–H); 3·28 (3H, s, –CH–OCH_3); 3·31 (3H, s, –CHOCH_3); 3·73 (1H, broad s, removed on deuteration, Ar–OH); 3·3–4·15 (2H, m, CH_2 at C_1); 4·3–4·7 (2H, m, –N–CH–Ar and CH_2CH–OCH_3); 5·91 (2H, s, –OCH_2O–); 6·62 (1H, s, C_5–H); 6·68 (1H, s, C_8–H); 6·73–6·80 (2H, m, C_2'–H and C_5'–H); 6·90 (1H, m, C_6'–H) (Found: C, 59·1; H, 6·1; N, 3·2. $C_{21}H_{25}NO_6$·HCl requires: C, 59·5; H, 6·2; N, 3·3%).

Fraction B, an oil (TLC R_f 0·47, alumina, chloroform) was N - (2,2 - *dimethoxyethyl*) - 6 - *hydroxy* - 7 - *methoxy* - 3 - (3,4 - *methylenedioxyphenyl*) - 1,2,3,4 - *tetrahydroisoquinoline* (**3h**, $R = CH_2CH(OMe)_2$) (1·15 g, 37%). The hydrochloride salt was obtained in ether and crystallised from water, m.p. 204–207°; λ_{max} (nm) (ϵ) (EtOH) 205 (61,400), 291 (7,500); ν_{max} (cm^{-1}) ($CHBr_3$) 3520 (OH), 2840 (OCH_3), 2520 (NH^+), 940 (OCH_2O); NMR (free base) ($CDCl_3$) 2·35 to 2·75 (2H, m, –N–CH_2–CH–); 2·90 (2H, broad 'd', J ~ 7 Hz, ArCH_2CH); 3·28 (3H, s, –CH–OCH_3); 3·31 (3H, s, –CH–OCH_3); 3·3–4·0 (2H, m, ArCH_2N–); 3·83 (3H, s, Ar–OCH_3); 4·2–4·7 (2H, m, $ArCH_2CH$Ar and –$CH_2CH(OCH_3)_2$); 4·60 (1H, s, removed on deuteration, Ar–OH); 5·93 (2H, s, –OCH_2O–); 6·54 (1H, s, C_8–H); 6·64 (1H, s, C_5–H); 6·60–6·83 (2H, m, C_2'–H and C_5'–H); 6·88–6·92 (1H, m, C_6'–H) (Found: C, 58·3; H, 6·2; N, 3·2. $C_{21}H_{25}NO_6$·HCl·½H_2O requires: C, 58·3; H, 6·1; N, 3·2%).

N - (2,2 - *dimethoxyethyl*) - 6 - *hydroxy* - 7 - *methoxy* - 3 - (3,4 - *methylenedioxyphenyl*) - 1,2,3,4 - *tetrahydroisoquinoline* (**3h**, $R_6 = CH_2CH(OMe)_2$). A soln of **19** (0·518 g, 1·38 mmole) in MeOH (12 ml), formic acid (98–100%, 8 ml) and 37% formaldehyde (6 ml) was stood at 21° for 5 h, then at 4° for 22 h, and evaporated to near dryness. The residue was shaken with ether (50 ml) and $NaHCO_3$ aq (50 ml) and the ethereal soln was washed with water, cooled with ice, and extracted with ice-cold 1N HCl (2×30 ml). The combined acid extracts were basified with solid $NaHCO_3$ and the mixture was extracted with dichloromethane (3×20 ml). The combined extracts were washed with water (30 ml), brine (30 ml), dried ($MgSO_4$) and evaporated to dryness. Trituration of the oil with ice-cold 0·5N HCl (5 ml) gave an off-white solid which was crystallised from water to afford **3h**, ($R_6 = CH_2CH(OMe)_2$; 0·402 g, 67%), m.p. 204–207°, mixed m.p., with sample obtained by chromatographic separation, 204–207°. Both NMR and IR spectra were superimposable with those of sample obtained by chromatography (Found: C, 58·2; H, 6·2; N, 3·2. Calcd for $C_{21}H_{25}NO_6$·HCl·½H_2O: C, 58·3; H, 6·1; N, 3·2%).

N - (2,2 - *Dimethoxyethyl*) - 7,8 - *dimethoxy* - 3 - (3,4 - *methylenedioxyphenyl*) - 1,2,3,4 - *tetrahydroisoquinoline* (**3a**, $R_6 = CH_2CH(OMe)_2$). A soln of **3g** ($R_6 = CH_2CH(OMe)_2$; 0·679 g, 1·75 mmole) in ether (100 ml) was added to a soln of diazomethane (~3 g) in ether (120 ml) and the soln was stood for 3 days at room temp. The soln was concentrated to 0·25 volume, washed with water (20 ml) and extracted with 1N NaOH (2×20 ml), then with water (20 ml). The combined aqueous extracts were treated with gaseous CO_2 to obtain a milky suspension, which was extracted with dichloromethane (3×20 ml). The combined organic extracts were washed with water (20 ml), brine (20 ml), dried ($MgSO_4$) and evaporated to dryness to recover **3g** ($R_6 = CH_2CH(OMe)_2$; 0·273 g, 39%). The ethereal soln was ice-cooled and extracted with ice-cold 1N HCl (3×12 ml) and the combined aqueous acid extracts were basified with aqueous ammonia (*d* 0·88) and extracted with dichloromethane (3×20 ml). The combined organic extracts were washed with water (20 ml), brine (20 ml), dried ($MgSO_4$), and evaporated to dryness to afford an oil (0·384 g). The oil was extracted with hot cyclohexane and decanted from a trace of dark red-brown tar. The cooled cyclohexane solution was treated with HCl gas then degassed with N_2 and filtered. The residue was washed with dry ether and crystallised from water to obtain N - (2,2 - *dimethoxyethyl*) - 7,8 - *dimethoxy* - 3 - (3,4 - *methylenedioxyphenyl*) - 1,2,3,4 - *tetrahydroisoquinoline hydrochloride* **3a** ($R_6 = CH_2CH(OMe)_2$; 0·347 g, 45% conversion, 74% yield), m.p. 130–132°; λ_{max} (nm) (ϵ) (EtOH) 205 (62,000), 289 (10,500); ν_{max} (cm^{-1}) ($CHBr_3$) 2850 (OCH_3), 2800 (w), 2500–2000 (NH^+), 940 (OCH_2O); NMR (free base) ($CDCl_3$) 2·48 and 2·67 (2H, doublets, J = 5 Hz, –NCH_2CH–); 2·98 (2H, broad d, J ~ 7 Hz, $ArCH_2CH$Ar); 3·28 (3H, s, –CH–OCH_3); 3·32 (3H, s, CHOCH_3); 3·45–4·0 (2H, m, ArCH_2N–); 3·86 (6H, s, 2×Ar–OCH_3); 4·1–4·7 (2H, m, Ar–CH–N– and CH_2–CH–OCH_3); 5·95 (2H, s, –OCH_2O–); 6·6–7·0 (5H, m, aromatics) (Found: C, 59·0; H, 6·5; N, 3·1. $C_{22}H_{28}ClNO_6$·½H_2O requires: C, 59·1; H, 6·5; N, 3·1%).

Similarly was prepared:

N - (2,2 - *Dimethoxyethyl*) - 6,7 - *dimethoxy* - 3 - (3,4 - *methylenedioxyphenyl*) - 1,2,3,4 - *tetrahydroisoquinoline hydroch-*

loride **3d**, (R_6 = $CH_2CH(OMe)_2$), 81% conversion, 92% yield, m.p. 159–160° (aqueous n-PrOH), λ_{max} (nm) (ε) (EtOH) 206 (61,500), 290 (10,000); ν_{max} (cm^{-1}) ($CHBr_3$) 2850 (OCH_3), 2790 (w), 2500–2000 (NH^+), 940 (OCH_2O); NMR (free base) ($CDCl_3$) 2·44 and 2·62 (2H, doublets, J = 5·5 Hz, $-N-\underline{CH_2}-CH-$); 2·94 (2H, broad d, J~7 Hz, $Ar\underline{CH_2}CHAr$); 3·26 (3H, s, $-CHO\underline{CH_3}$); 3·31 (3H, s, $-CHO\underline{CH_3}$); 3·5–3·9 (2H, m, $Ar-\underline{CH_2}-N-$); 3·93 (6H, s, 2 × $Ar-O\underline{CH_3}$); 3·95–4·30 (1H, m, $Ar-\underline{CH}-CH_2$); 4·49 (1H, t, J = 5 Hz, $CH_2\underline{CH}-OCH_3$); 5·93 (2H, s, $-O\underline{CH_2}O-$); 6·60 (2H, broad s, $C_5-\underline{H}$ and $C_8-\underline{H}$); 6·70 (2H, broad s, $C_2'-\underline{H}$ and $C_5'-\underline{H}$); 6·81 (1H, m, $C_6'-\underline{H}$) (Found: C, 57·0; H, 6·7; N, 3·0. $C_{22}H_{27}NO_6\cdot HCl\cdot 1\frac{1}{2}H_2O$ requires: C, 56·8; H, 6·7; N, 3·0%).

Tetrahydroberberastine hydrochloride (**2a**). Compound **3a** (R_6 = $CH_2CH(OMe)_2$; 203 mg, 0·454 mmole) was dissolved in 6N HCl (5 ml) and kept at 32° for 18 h. The mixture was filtered and the residue was washed with water (2 × 2 ml) and dried to afford *tetrahydroberberastine hydrochloride* (**2a**; 127 mg, 71%) as an off-white solid, m.p. 202–203°; λ_{max} (nm) (ε) (EtOH) 205 (62,600), 287 (5,700); ν_{max} (cm^{-1}) ($CHBr_3$) 3550 (broad, OH), 2850 (OCH_3), 2780 (w), 2900–2700 (m, NH^+), 945 (OCH_2O); NMR (DMSO-d^6) 2·9–4·0 (8H, m, $-\underline{NH}$, $-\underline{OH}$, $\underline{CH_2}$ at C-6, CH_2 at C-8, CH_2 at C-13); 3·79 (3H, s, $ArO\underline{CH_3}$); 3·80 (3H, s, $ArO\underline{CH_3}$); 4·4–4·9 (2H, m, $C_5-\underline{H}$ and $C_{13}'-\underline{H}$); 6·02 (2H, s, $-O\underline{CH_2}O-$); 6·9–7·15 (4H, m, aromatics) (Found: C, 61·2; H, 5·8; N, 3·4. $C_{20}H_{21}NO_5\cdot HCl$ requires: C, 61·3; H, 5·7; N, 3·6%).

5 - *Ethoxy* - 8,9 - *dimethoxy* - 2,3 - *methylenedioxyberbine.* Compound **3d** (R_6 = $CH_2CH(OMe)_2$; 203 mg, 0·454 mmole) was dissolved in EtOH (7·0 ml) and 36% HCl (7·0 ml) and kept at 38° for 12 h, then at 21° for 10 h. The mixture was evaporated to near dryness at ≯40°, and 2N NaOH was added and extracted repeatedly with chloroform. The combined extracts (50 ml) were washed with water (2 × 20 ml), dried ($MgSO_4$) and evaporated to dryness to obtain a buff gum (170 mg), which was separated into 3 components by PLC (alumina, Merck) with 3 elutions using 40% chloroform in petrol (60–80°). *Fraction A*, (R_f 0·75, alumina, chloroform) (84 mg) was dissolved in cyclohexane, treated with gaseous HCl, "degassed" with N_2, filtered, dried, and crystallised from water to afford 5 - *ethoxy* - 8,9 - *dimethoxy* - 2,3 - *methylenedioxyberbine hydrochloride* (61 mg, 32%) as a buff solid, m.p. 180–182°; NMR ($CDCl_3$) 1·21 (3H, t, J = 7 Hz, $-OCH_2\underline{CH_3}$); 2·5–4·0 (6H, m, $\underline{CH_2}$ at C-6, $\underline{CH_2}$ at C-8, $\underline{CH_2}$ at C-13); 3·64 (2H, q, J = 7 Hz, $-O\underline{CH_2}CH_3$); 4·1–4·4 (2H, m, $C_5-\underline{H}$ and $C_{13}'-\underline{H}$); 5·92 (2H, s, $-O\underline{CH_2}O-$); 6·6–7·0 (4H, m, aromatics) (Found: C, 59·9; H, 6·2. $C_{22}H_{25}NO_5\cdot HCl\cdot H_2O$ requires: C, 60·3; H, 6·4%).

Fractions B (R_f 0·33) *and C* (R_f 0·19), mutually contaminated (by TLC) were apparently samples of tetrahydroberberastine. IR spectra ($CHBr_3$) were identical except for B, 3250 cm^{-1} (broad, weak) and 3560 (m, sharp); for C, 3250 (broad, strong) and 3560 (weak, sharp).

Berberastine iodide (**1a**). A boiling soln of **2a** (100 mg, 0·255 mmole) and potassium acetate (300 mg, 3 mmole) in hot EtOH (3 ml) was treated with a soln of I_2 (180 mg, 0·71 mmole) in EtOH by dropwise addition over 10 min, with immediate precipitation of a yellow solid. After boiling for a further 10 min the mixture was cooled, filtered, and the residue was washed with EtOH (2 × 1 ml), water (2 ml) and dried to obtain *berberastine iodide* (**1a**; 97 mg, 80%) as a yellow solid, m.p. ≮300°, λ_{max} (nm) (log ε) (H_2O) 228 (4·61), 265 (4·41), 345 (4·37), 4·26 (3·71); λ_{min} 211 (4·33), 251 (4·28), 304 (3·84), 376 (3·46); $\lambda_{infl.}$ 273 (3·36) [lit.[2] λ_{max} (log ε) (H_2O) 228 (4·63), 265 (4·41), 344 (4·35), 424 (3·77); λ_{min} 212, 250, 302·5, 377]; ν_{max} (KBr) 3240 (strong, OH), 1660–1620 (C=$\overset{+}{N}$) [spectrum of synthetic **1a** very similar to that published for **1a**]; NMR (100 MHz) (DMSO-d^6) 4·08 (3H, s, $C_9-O\underline{CH_3}$); 4·12 (3H, s, $C_{10}-O\underline{CH_3}$); 4·7–5·3 (3H, m, $C_5-\underline{H}$ and $\underline{CH_2}$ at C-6); 5·95–6·05 (1H, m, removed on deuteration, $-\underline{OH}$); 6·20 (2H, s, $-O\underline{CH_2}O-$); 7·16 (1H, s, C_4-H); 7·83 (1H, s, $C_1-\underline{H}$); 8·02 (1H, d, J = 9 Hz, $C_{11}-\underline{H}$); 8·24 (1H, d, J = 9 Hz, $C_{12}-\underline{H}$); 9·01 (1H, s, $C_8-\underline{H}$); 9·98 (1H, s, $C_{13}-\underline{H}$) (Found: C, 50·4; H, 3·7; N, 2·8. $C_{20}H_{18}INO_5$ requires: C, 50·1; H, 3·8; N, 2·9%).

10,11 - *Dimethoxy* - 5 - *hydroxy* - 2,3 - *methylenedioxyberbine hydrochloride* (**2d**). N - (2,2 - Dimethoxyethyl) - 6,7 - dimethoxy - 3 - (3,4 - methylenedioxyphenyl) - 1,2,3,4 - tetrahydroisoquinoline hydrochloride (319 mg, 0·68 mmole) was added to 6N HCl (8 ml) and the suspension was stirred at 21° for 18 h. The mixture was filtered and the residue was washed with water (3 × 2 ml) and dried to afford **2d** (149 mg, 56%) as a pale buff solid, m.p. 191–193° (lit.[6] m.p. 188–190°) mixed m.p. 190–192° (Found: C, 60·4; H, 6·3; N, 3·4. Calcd for $C_{20}H_{21}NO_5\cdot HCl\cdot H_2O$: C, 60·3; H, 6·4; N, 3·3%).

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