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THE SYNTHESIS OF 5-HYDROXYBERBINE DERIVATIVES[1]

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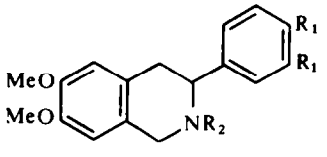
Abstract—The syntheses of 5-hydroxy-2,3,10,11-tetramethoxyberbine (**4**, R_1 = OMe; R_2 = OH) and 5-hydroxy-2,3-methylenedioxy-10,11-dimethoxyberbine (**4**, $R_1 + R_1 = CH_2O_2$; R_2 = OH) are described. The structures have been established by chemical and spectral methods and, in the former case, the relative stereochemistry has been elucidated. These are the first examples of 5-hydroxyberbine derivatives to be prepared.

RECENTLY[2] we described syntheses of tetrahydroberbering and tetrahydropalmatine based upon the cyclization of 2-β-arylethyl-1,2-dihydroisoquinolines. the route pioneered by Battersby *et al.*[3] This method together with the route developed by Bradsher *et al.*,[4] are now the ones of choice for syntheses[5] of berbine derivatives. especially those possessing the 2,3.9.10-tetra-oxygenation pattern. Another potential route to the berbine nucleus involves the addition of a two-carbon unit to a 3-aryl-1.2.3.4-tetrahydroisoquinoline (**1**).



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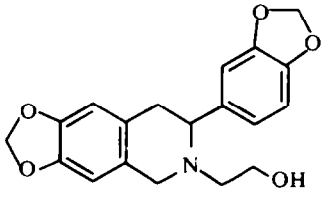
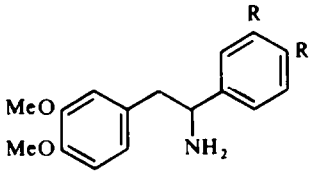


2

A previous attempt to cyclize the amino-alcohol (**2**) was unsuccessful,[6] but it seemed to us that cyclization of the corresponding aldehyde, or its dialkyl acetal should be feasible. Accordingly, a synthesis of (±)-norcoralydine was attempted from **1** (R_1 = OMe; R_2 = H).

Considerable improvements have been made (Experimental)[7] in the preparation of the known[7,8] amine **3** (R = OMe), which, when treated with HCHO/HCl under the conditions of the Pictet–Spengler reaction,[10] gave the required isoquinoline derivative **1** (R_1 = OMe; R_2 = H). The latter compound failed to react with chloracetal, in keeping with previous experience.[11,12] A convenient synthesis of substituted amino-acetaldehyde dialkyl acetals, originally devised by Frank and Purves,[13] and subsequently used by Bobbitt *et al.*[12] and by us,[2] was successful. The amine **1** (R_1 = OMe; R_2 = H) was reacted with glycidol to give the glycol **1** (R_1 = OMe; R_2 = —$CH_2CHOHCH_2OH$) which, without isolation, was oxidized with sodium periodate. Purification of **1** (R_1 = OMe; R_2 = —CH_2CHO) was achieved by



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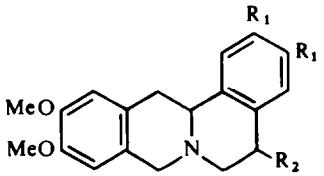

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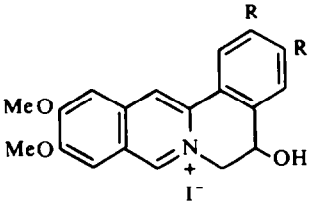
column chromatography, and the product, a yellow glass (IR band at 1730 cm^{-1}), was dissolved in 6N HCl, and the solution was left at room temperature overnight. A 70% yield of a base hydrochloride, $C_{21}H_{25}NO_5.HCl$ was obtained. The IR spectrum, which is devoid of absorption in the region 1800–1600 cm^{-1}, exhibits a strong band at 3300 cm^{-1}, which is shifted to 3500 cm^{-1} in the free base. The appearance of Bohlmann bands at 2760 cm^{-1} in the IR spectrum of the base indicated that the product is a berbine derivative with *trans*-fusion of the two central rings. The NMR spectrum of the base contains resonances associated with only 4 aromatic protons, 4 methoxyl groups, and a total of 9 aliphatic protons—reducing to 8 on deuteration. This evidence is compatible with structure **4** (R_1 = OMe; R_2 = OH) for the cyclization product. Dehydrogenation of this material with iodine afforded, in



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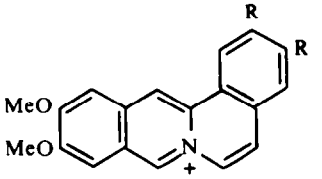
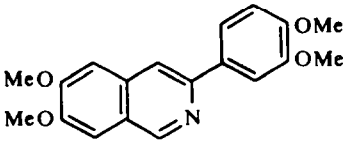


6

88% yield, a quaternary salt, the NMR spectrum of which is diagnostic for **5** (R = OMe). Brief treatment with 2N HCl caused dehydration of this salt to yield the known[14] iodide **6** (R = OMe). Reduction of **6** (R = OMe) with $NaBH_4$ gave norcoralydine **4** (R_1 = OMe; R_2 = H), identical with an authentic[15] specimen. The overall yield of norcoralydine from the 3-aryltetrahydroisoquinoline **1** (R_1 = OMe; R_2 = H) was 40%, and of the 5-hydroxyberbine **4** (R_1 = OMe; R_2 = OH), 63%. Recently[16] norcoralydine has been obtained, in 22·5% yield, by quaternization of **7** with bromoacetaldehyde, followed by cyclization to **6** (R = OMe) and catalytic hydrogenation.



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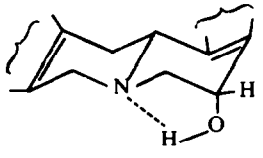
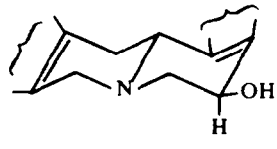
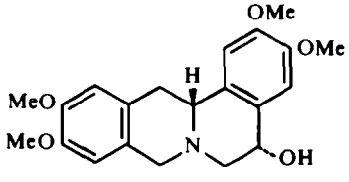
Fractional crystallization of the original cyclization product **4** (R_1 = OMe; R_2 = OH), eventually gave one pure diastereomorph, but it was not possible to isolate a second pure base. However, when the original mixture of diastereomorphs was treated with acetic anhydride, a separable mixture of two O-acetates resulted, O-*acetate A*, m.p. 188–189° (51% of the mixture) and O-*acetate B*, m.p. 162–163° (36%). Each O-acetate was then separately reduced with LAH to afford the hydroxy base A, m.p. 194–195° (identical with that obtained by fractional crystallization of the original basic product), and base B, m.p. 175–177°. The IR spectra of both O-acetates, and both bases exhibit the characteristic Bohlmann bands at *ca* 2800 cm^{-1}, and these compounds therefore exist in the *trans*-quinolizidine configuration. The IR spectrum of O-*acetate A* exhibits a band at 1715 cm^{-1} for the acetate carbonyl group, which is indicative of some interaction with the unshaired electron pair on the N atom. The OH band in the derived base A is a broad absorption in the region 3550–3450 cm^{-1}. In contrast, O-*acetate B* exhibits a CO frequency at 1735 cm^{-1}, typical of an acetate function, and the OH group of base B absorbs as a sharp band at 3540 cm^{-1}. An inspection of Dreiding models indicates that intramolecular H-bonding to the N atom can occur if the OH group of base A is axial (**8a**). The properties of base B are consistent with it possessing an equatorial OH group (**9a**). The NMR spectra of the O-acetates confirm these stereochemical assignments. The Me protons of the acetyl function in O-*acetate A*, because of the interaction with the N atom, resonate at higher field (2·10 δ) than the corresponding protons in O-*acetate B* (2·16 δ). The relative configurations of the two bases are then as depicted in **8b** and **9b**, respectively.



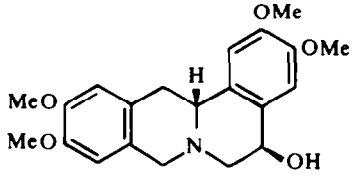
8a



9a

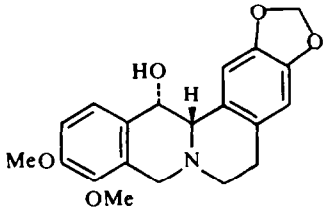


8b

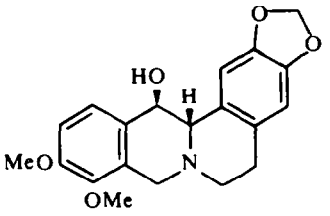


9b

An analogous situation exists in the 13-hydroxytetrahydroprotoberberines, where the OH group is also β to the N atom. Thus, the IR spectra of ophiocarpine **10a** and 13-epiophiocarpine **10b** show similar differences in the OH region.

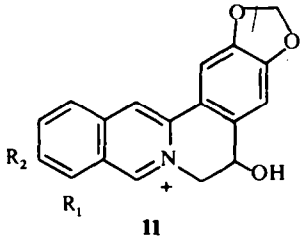


10a



10b

The reactions described above, which constitute the first synthesis of a 5-hydroxyberbine derivative, are significant in the light of the recent isolation of two alkaloids bearing this structural feature. Berberastine **11** ($R_1 = R_2 = OMe$) is a minor alkaloid of *Hydrastis canadensis*, and was first characterized by Nijland.[18] Thalidastine

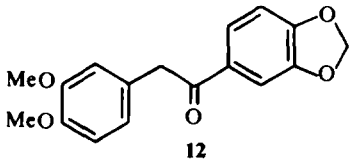


11

11 ($R_1 = OMe$; $R_2 = OH$), however, is one of the major alkaloids of *Thalictrum fendleri*; its structure was deduced[19] from the NMR spectrum of deoxythalidastine and from the mass spectrum of tetrahydrothalidastine. Deoxythalidastine has been synthesized.[20]

The mass spectrum of **4** ($R_1 = OMe$; $R_2 = OH$) shows marked differences in the relative abundances of the various fragment ion peaks from those reported[19] for tetrahydrothalidastine. Thus, the base peak of the spectrum of **4** ($R_1 = OMe$; $R_2 = OH$) at *m/e* 164 corresponds (Chart I) to ion (e) and is derived from the characteristic retro-Diels-Alder cleavage of ring C. This is typical of 10,11-dimethoxy-substituted berbines. The ion **d** is of very low abundance, in contrast to the spectrum of tetrahydrothalidastine in which the analogous ion is the base peak. This difference, which has been observed in the spectra of other tetrahydroprotoberberines,[21] and is associated with the presence of a phenolic OH group in ring D, may prove useful for distinguishing between differently substituted 5-hydroxyberbine derivatives.

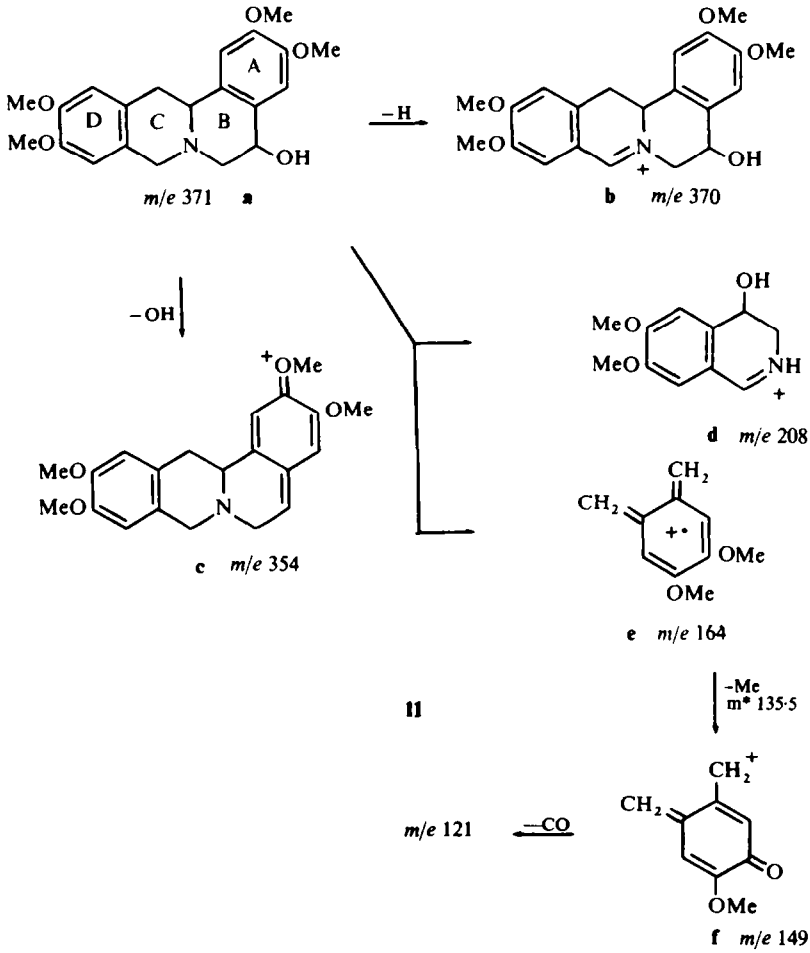
Since it is possible that a methylenedioxy group may be cleaved under the acid conditions that led to **4** ($R_1 = OMe$; $R_2 = OH$), we decided, before embarking upon a synthesis of berberastine, to repeat the sequence using the 3-aryl-1,2,3,4-tetrahydroisoquinoline **1** ($R_1 + R_1 = CH_2O_2$; $R_2 = H$) in place of **1** ($R_1 = OMe$; $R_2 = H$). The required benzyl ketone (**12**) was obtained, in 60% yield, by a Friedel–Crafts reaction between homoveratryl chloride and methylenedioxybenzene in the presence of $SnCl_4$ at $-10°$. Above this temperature cleavage of the methylenedioxy group occurred. The conversion of **12** to **3** ($R + R = CH_2O_2$) and thence to



12

1 ($R_1 + R_1 = CH_2O_2$; $R_2 = H$) was conducted as for **1** ($R_1 = OMe$; $R_2 = H$), and further elaboration to **4** ($R_1 + R_1 = CH_2O_2$; $R_2 = OH$) was achieved in 48% yield based upon the tetrahydroisoquinoline derivative **1** ($R_1 + R_1 = CH_2O_2$; $R_2 = H$). This time no attempt was made to separate the diastereomorphs of **4** ($R_1 + R_1 = CH_2O_2$; $R_2 = OH$); dehydrogenation gave **5** ($R + R = CH_2O_2$) in almost quantitative yield, and dehydration gave the known[14] benz[a]acridizinium ion **6** ($R + R = CH_2O_2$). Reduction of the latter with $NaBH_4$ provided tetrahydropseudoberberine[22] **4** ($R_1 + R_1 = CH_2O_2$; $R_2 = H$). The overall yield of tetrahydropseudoberberine from **1** ($R_1 + R_1 = CH_2O_2$; $R_2 = H$) was 32%.

CHART 1



EXPERIMENTAL

IR spectra were recorded for nujol mulls unless otherwise stated, in the case of solids, or for thin films in the case of liquids, using a Perkin–Elmer 237 spectrophotometer. UV spectra were recorded for solns in EtOH, unless otherwise stated, using a Perkin–Elmer 137 spectrophotometer. NMR spectra were determined using a Varian A60 spectrometer where absorptions are assigned to hydroxylic protons the assignments are confirmed by deuteration experiments. Mass spectra (70 eV) were obtained using an A.E.I. MS12 spectrometer. M.ps are uncorrected.

3,4-*Dimethoxyphenylacetyl chloride*. Thionyl chloride (38·0 g) was added to a soln of 3,4-dimethoxyphenylacetic acid (42·0 g) in dry benzene (500 ml) at 30° and the whole was allowed to stand for ¾ hr, then heated under reflux for 1½ hr. The solvent and excess $SOCl_2$ were evaporated under reduced pressure and the acid chloride distilled *rapidly* as a clear liquid (41·0 g). Bath temp 220°/0·13 torr ν_{max}. 1785 cm^{-1}.

3,4-*Dimethoxybenzyl*-3,4-*dimethoxyphenyl ketone*. Anhyd $AlCl_3$ (37 g) was added to a soln of 1,2-dimethoxybenzene (30·5 g) and 3,4-dimethoxyphenylacetyl chloride in CH_2Cl_2 (150 ml), and the mixture heated under reflux for 1¾ hr. The cooled soln was poured into a stirred mixture of water (70 ml), 12N HCl (150 ml), and ice (200 g). The organic phase was separated and the aqueous phase extracted (3 × 100 ml CH_2Cl_2). The combined extracts were dried and the solvent evaporated to yield an oil which solidified on cooling. Crystallization from aqueous EtOH gave the ketone as a white solid 25·0 g) m.p. 105–107° (Lit.[11] 103·5–104·5°).

3,4-*Dimethoxybenzyl*-3,4-*methylenedioxyphenyl ketone*. To a stirred mixture of methylenedioxybenzene (7·3 g) and $SnCl_4$ (18·4 g) in CH_2Cl_2 (50 ml) at −10°, was added a soln of homoveratryl chloride (13·0 g) in dry CH_2Cl_2 (50 ml). The mixture was allowed to attain room temp and stirred for a further 2 hr, then poured into 6N HCl (100 ml), and stirred for 16 hr. The product was worked up as the previous compound giving the *ketone* (10·8 g), m.p. 110–111° as cream prisms from EtOH. (Found: C, 68·1; H, 5·5. $C_{17}H_{16}O_5$ requires: C, 68·0; H, 5·3%).

Bis-1,2-(3,4-*dimethoxyphenyl*) *ethylamine* (3, R = OMe). A mixture of 3,4-Dimethoxybenzyl-3,4-dimethoxyphenyl ketone (25·0 g) ammonium formate (50·0 g), 98–100% formic acid (15 ml), and fermamide (15 ml) was heated at 185° for 3½ hr under N_2. The mixture at 60° was poured with stirring into ice cold water (100 ml) and the solid collected after 10 min. The solid was suspended in 5N H_2SO_4 (250 ml) and the mixture heated under reflux for 2½ hr. The resulting soln was cooled, extracted (1 × 50 ml CH_2Cl_2), and to the stirred aqueous phase was added charcoal (2·5 g). After filtration the soln was basified with 30% NaOH aq cooled to 10° and the base collected. This was washed with water and dried at 60° in a vacuum oven to give the amine as a white solid. (20·2 g) m.p. 106–107° (Lit.[8] 107°).

1-(3,4-*Methylenedioxyphenyl*)-2-(3,4-*dimethoxyphenyl*)-*ethylamine* (3, R = CH_2O_2), was prepared as the previous compound and obtained as a sticky brown solid (70%); characterized as the *amine hydrochloride*, m.p. 225–226°, which separated from EtOH as colourless prisms. (Found: C, 60·5; H, 6·1; Cl, 10·7; N, 4·0. $C_{17}H_{20}NO_4Cl$ requires: C, 60·45; H, 5·9; Cl, 10·5; N, 4·15%).

3-(3,4-*Dimethoxyphenyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (1, R_1 = OMe, R_2 = H). The appropriate ethylamine (5·0 g) and 18% aqueous formaldehyde (12 ml) were heated together on a steam bath for ¾ hr. 3N HCl (8·0 ml) was added and the mixture heated for a further ½ hr. On cooling the amine hydrochloride separated as white crystals (4·8 g), m.p. 278–280°, from which the free base was obtained m.p. 97–98° (EtOH). The methiodide was prepared in ether, m.p. 250° (EtOH). (Lit.[8] 250–252°).

3-(3,4-*Methylenedioxyphenyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroisoquinoline* (1, R_1R_1 = CH_2O_2, R_2 = H) was prepared similarly giving the crude base (4·5 g) m.p. 105–110° which was characterized as the *amine hydrochloride*, m.p. 261–263°, obtained as white prisms from EtOH. (Found: C, 61·5; H, 5·8; Cl, 10·4; N, 4·2. $C_{18}H_{20}NO_4Cl$ requires: C, 61·8; H, 5·7; Cl, 10·2; N, 4·0%).

2,3,10,11-*Tetramethoxy*-5-*hydroxyberbine* (4, R_1 = OMe, R_2 = OH). The isoquinoline 1 (R_1 = OMe, R_2 = H), (3·3 g), and glycidol (0·9 g) were heated together on a steam bath for 2 hr. The product was treated with chloroform (15 ml), and water (15 ml) and to the well stirred mixture at 0° was added dropwise sodium metaperiodate (2·2 g) in water (15 ml). After the addition the mixture was brought to pH8 using 1N NaOH and the whole stirred for 3 hr. The organic phase was separated, dried, and evaporated to give a yellow glass (ν_{max} cm^{-1} 1730) which did not crystallize. This product was purified by column chromatography using alumina packing and benzene:chloroform (1:1) as eluant, giving the *amino-aldehyde* (1, R_1 = OMe, R_2 = CH_2CHO) (3·35 g). This compound (3·3 g) was dissolved in 6N HCl (50 ml) and allowed to stand at room temp for 18 hr during which time the *hydrochloride of* 4 (R_1 = OMe, R_2 = OH) (2·52 g), m.p. 228–229° (EtOH) separated as white needles; ν_{max} cm^{-1} 3300 (OH), 2520 ($\overset{+}{N}H$). (Found: C, 61·5; H, 6·6; Cl, 8·7; N, 3·6. $C_{21}H_{26}NClO_5$ requires: C, 61·8; H, 6·4; Cl, 8·7; N, 3·4%). The *amine* (4, R_1 = OMe, R_2 = OH) was

obtained from its salt as white needles m.p. 194–195° after several recrystallizations (EtOH) λ_{max} (ε) nm. 227 sh (22.250). 284 (7770). ν_{max} cm^{-1}. 3500. 2760. 1610; NMR ($CDCl_3$); 2·5–4·0 (7H. m); 3·7 (1H. broad s. OH); 3·75–3·8 (12H. MeO groups); 4·45 (1H. m. CHOH); 6·5. 6·6. 6·75. 6·85 (each 1H. aromatic H's). *m/e* (Rel. int.) 371 (20). 354 (9). 165 (25). 164 (100). 149 (7). 121 (9). 47 (8). 46 (28). 45 (57). 44 (98). (Found: C. 67·6; H. 7·0; N. 3·9. $C_{21}H_{25}NO_5$ requires: C. 67·9; H. 6·8; N. 3·8%). The methiodide of **4** (R_1 = OMe. R_2 = OH) was prepared in acetone and obtained as cream coloured prisms m.p. 241–242° (EtOH); ν_{max} cm^{-1}. 3320. (Found: C. 51·3; H. 5·7; N. 2·8; I. 24·8. $C_{22}H_{28}NO_5I$ requires: C. 51·5; H. 5·5; N. 2·7; I. 24·7%).

2.3-*Methylenedioxy-5-hydroxy*-10.11-*dimethoxyberbine* (**4**. R_1R_1 = CH_2O_2. R_2 = OH) was prepared in the same way as its tetramethoxy-analogue. The *amino-aldehyde* **1** (R_1R_1 = CH_2O_2. R_2 = CH_2CHO) was obtained as a glass in 67% yield from **1** (R_1R_1 = CH_2O_2. R_2 = H). The *hydrochloride of* **4** (R_1R_1 = CH_2O_2. R_2 = OH) separated from the mixture as cream coloured needles (72%). m.p. 188–190°. ν_{max} cm^{-1}. 3430 (OH), 3290, (OH), 2660–2600 ($\overset{+}{N}H$). (Found: C, 60·4; H, 6·2; N, 3·8. $C_{20}H_{22}NO_5Cl.H_2O$ requires: C, 60·3; H, 6·4; N, 3·3%). The *amine* **4** (R_1R_1 = CH_2O_2; R_2 = OH) was obtained as pale yellow needles (EtOH, charcoal) m.p. 105–106° λ_{max}(ε) nm, 230 sh (20,800), 289 (7900), ν_{max} cm^{-1}, 3450–3350 (OH), 2790, 1610, *m/e* (Rel. int.), 355 (20), 338 (11), 165 (26), 164 (100), 149 (10), 121 (10), 63 (7), 46 (98), 45 (97), 44 (48). (Found: C, 66·7; H, 6·5; N, 3·7. $C_{20}H_{21}NO_5$ $\frac{1}{2}$ C_2H_5OH requires: C, 66·7; H, 6·4; N, 3·7%).

Dehydrogenation and dehydration of the 5-hydroxy berbines 2.3.10.11-*tetramethoxy-5-hydroxyberberinium iodide* (**5**. R = OMe). The berbine **4** (R_1 = OMe. R_2 = OH). (0·85 g). dissolved in EtOH (25 ml) was heated under reflux with AcOK (1·0 g) while a soln of I_2 (1·25 g) in EtOH (60 ml) was added over $\frac{1}{4}$ hr. The mixture was heated for a further $\frac{1}{2}$ hr after which time the periodide was collected. suspended in water and SO_2 passed through the suspension for $\frac{1}{2}$ hr. The berberinium iodide **5** (R = OMe_3), (0·99 g), m.p. 265–267°, was collected and recrystallized (water) giving yellow needles m.p. 243–245°. λ_{max} (ε) nm (90% aqueous EtOH). 240 sh (16.000). 265 (11.800). 291 (25.200). 311 sh (16.800). 340 (6700); ν_{max} cm^{-1}. 3530 (OH). 3400–3300 (OH). 1635. 1615. 1575; NMR (DMSO.d_6); 3·8–4·1 (12H. MeO groups); 4·85 (2H. d. J = 5·5 Hz. $C\underline{H}_2$ CH.OH); 5·1 (1H. broad. OH); 5·85 (1H. t. J = 5·5 Hz. $CH_2\underline{CH}$.OH); 7·15 (1H. s. 4-H); 7·7 (3H. broad s. 1-H. 9-H and 12-H); 8·95 (1H. s. 13-H); 9·7 (1H. s. 8-H). (Found: C. 50·0; H. 4·7; N. 3·0. $C_{21}H_{22}NO_5I$. $\frac{1}{2}$ H_2O requires: C. 50·0; H. 4·55; N. 2·8%).

2.3-*Methylenedioxy-5-hydroxy*-10.11-*dimethoxyberberinium iodide* (**5**. RR = CH_2O_2) was prepared from the berbine **4** (R_1R_1 = CH_2O_2. R_2 = OH) by the above method and obtained as yellow needles (92%) m.p. 220–222° (water); λ_{max} (ε) nm. 267 (26.700). 289 (33.900). 314 (19.600). 341 (9200); ν_{max} cm^{-1}. 3340. 1630. 1610. 1570; NMR (DMSO d_6); 4·05 and 4·15 (each 3H, s, OMe); 4·75–5·1 (2H. m. $C\underline{H}_2CH$.OH); 5·6 (1H, broad, OH); 5·95 (1H. broad t. $CH_2\underline{CH}$.OH); 6·2 (2H. s. CH_2O_2); 7·15 (1H. s. H-4); 7·75 (3H. broad s. 1-H. 9-H and 12-H); 8·85 (1H. s. 13-H); 9·4 (1H. s. 8-H). (Found: C. 50·2; H. 3·55; N. 3·2. $C_{20}H_{18}NO_5I$ requires: C. 50·1; H. 3·75; N. 2·9%).

2.3.10.11-*Tetramethoxybenz*[a] *acridizinium chloride* (**6**. R = OMe). The iodide **5** (R = OMe). (0·36 g) in 2N HCl (120 ml) was heated under reflux for $\frac{1}{4}$ hr. on cooling the product was collected and recrystallized (aqueous MeOH) giving yellow crystals (0·25 g) m.p. 242–244° dec. (sealed tube) (Lit.[14] m.p. 240–242°); λ_{max} (ε) nm (90% aqueous ethanol). 278 (18.300). 309 (23,100). 322 (15.400). 417 (2900) see Ref. 14; NMR (DMSO.d_6); 3·9. 3·93. 3·95. 4·0 (each 3H. s. OMe); 7·1 (4H. broad s. 1-H. 4-H. 9-H and 10-H); 7·5 (1H. d. J = 7·5 Hz. 5-H); 7·65 (1H. d. J = 7·5 Hz. 6-H); 8·8 (1H. s. 13-H); 9·5 (1H. s. 8-H).

2.3-*Methylenedioxy*-10.11-*dimethoxybenz*[a] *acridizinium chloride* (**6**. RR = CH_2O_2) was prepared from **5** (RR = CH_2O_2) by the above method and obtained as a yellow solid (92%). M.p. 242–245°; λ_{max} nm. 235. 281. 304. 313. 328. 422; λ_{min} nm. 255. 292. 309. 323. 372. This spectrum is identical to that described by Bradsher and Dutta.[14]

Reduction of the benzacridizinium salts (**6**) *with sodium borohydride* (±)-*norcoralydine*. A suspension of **6** (R = OMe). (0·25 g) in 2N HCl (120 ml) was neutralized with 0·880 ammonia soln. MeOH (50 ml) was added to the mixture and $NaBH_4$ (1·0 g) was added to the warm (50°) soln. The mixture was maintained at the same temp for $\frac{1}{2}$ hr. after which time the MeOH was evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 : ether (1 : 1). (4 × 25 ml). and the combined dried extracts evaporated to yield (±)-norcoralydine (0·18 g) m.p. 155–157° (EtOH). (Lit.[3] 157–158°). A mixed m.p. with authentic sample[15] was undepressed.

(±)-*Tetrahydro-ψ-berberine* was prepared from **6** (RR = CH_2O_2) by the above method and was obtained as a pale yellow solid (80%) m.p. 176–177° (EtOH). (Lit.[22] m.p. 177°); λ_{max} (ε) nm. 225 sh (6980). 289 (3200). ν_{max} cm^{-1}. 2780. 1610. *m/e* (Rel. Int.). 339 (20). 338 (6). 174 (9). 164 (100). 149 (11). 121 (14). (Found: C. 70·4; H. 6·4; N. 4·3. Calc. for $C_{20}H_{21}NO_4$: C. 70·8; H. 6·2; N. 4·2%).

Separation of the diastereomeric O-*acetates of* 2.3.10.11-*tetramethoxy-5-hydroxyberbine* (**4**. R_1 = OCH_3.

R_2 = OH). The crude base (0·3 g) m.p. 180–190° obtained by basification of an aqueous soln of its hydrochloride was dissolved in Ac_2O (3 ml) and stood for 24 hr at room temp. then at 0° for a further 24 hr. The mixture was diluted with water. and. on basification with 2N ammonia soln. a yellow solid (0·31 g) was deposited. The solid was dissolved in hot EtOH and on cooling O-*acetate A* (**8b**) separated as pale yellow needles (0·17 g). m.p. 188–189°; λ_{max} (ε) nm. 227 sh (20.650). 284 (6600); ν_{max} cm^{-1}. 1715 (C=O). 1605; NMR ($CDCl_3$); 2·1 (3H. s. CH_3CO); 2·7–4·1 (7H. m. aliphatic H's); 3·90 and 3·95 (each s. 6H. 2 × MeO); 5·95 (1H. t. J = 3·0 Hz. $CH_2\underline{CH}OAC$); 6·62. 6·72. 6·85. 6·95 (each 1H. s. aromatic H). *m/e* (Rel. Int.). 413 (7). 353 (18). 352 (10). 164 (100). 149 (7). 121 (8). (Found: C. 66·9; H. 6·8; N. 3·6. $C_{23}H_{27}NO_6$ requires: C. 66·8; H. 6·6; N. 3·4%). The mother liquors from which O-*acetate A* separated were concentrated and on cooling white needles (0·12 g). m.p. 162–163°. of O-*acetate B* were obtained; λ_{max} (ε) nm. 227 sh (21.000). 284 (6000). ν_{max} cm^{-1}. 1735 (C=O). 1610; NMR ($CDCl_3$); 2·16 (3H. s. CH_3CO); 2·5–4·0 (7H. m. aliphatic H's); 3·88 and 3·90 (each s. 6H. 2 × MeO); 6·1 (1H. m. $CH_2CH\underline{O}AC$); 6·60. 6·66. 6·75. 6·85 (each 1H. s. aromatic H). *m/e* (Rel. Int.). 413 (6). 353 (16). 352 (9). 164 (100). 149 (6). 121 (8). (Found: C. 66·8; H. 6·7. $C_{23}H_{27}NO_6$ requires: C. 66·8; H. 6·6%).

Reduction of the O-*acetates with lithium aluminium hydride.* A soln of O-*acetate A* (0·15 g) in THF:ether (1:1. 25 ml) was added to a stirred suspension of LAH (0·5 g) in ether (25 ml). The mixture was then stirred at room temp for 3 hr. heated for a further 1 hr and then cooled. The excess reagent was destroyed by the addition of 30% sodium potassium tartrate soln. the clear soln decanted. diluted with water (20 ml) and the organic solvents evaporated under reduced pressure. The residue was extracted with CH_2Cl_2:ether (1:1. 3 × 15 ml). the dried extracts combined dried and evaporated to yield 2.3.10.11-*tetramethoxy-5-hydroxyberbine A* (**8b**) (0·11 g). m.p. 194–195° (EtOH). The m.p. of a mixture of this compound and that obtained by repeated recrystallization of the mixture of enantiomers (**4**, R_1 = OMe, R_2 = OH) was undepressed; ν_{max} (10% soln in $CHCl_3$. 0·1 mm). 3580–3450. 2780. 1610 cm^{-1}.

2.3.10.11-*Tetramethoxy-5-hydroxyberbine B* (**9b**) was prepared from O-*acetate B* by the above method as colourless prisms (77%) m.p. 175–177° (MeOH). ν_{max} cm^{-1} (10% soln in $CHCl_3$. 0·1 mm). 3540. 2780. 1610 cm^{-1}. λ_{max} (ε) nm. 227 sh (22.300). 284 (7800). (Found: C. 67·8; H. 6·8. $C_{21}H_{25}NO_5$ requires: C. 67·9; H. 6·8%).

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