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A SHORT ROUTE TO THE PHTHALIDEISOQUINOLINES AND THE 13-HYDROXYLATED PROTOBERBERINES[1]

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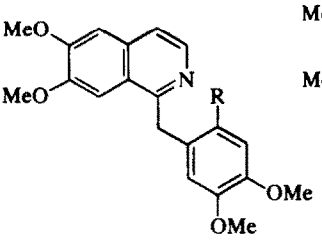
Abstract—CrO_3 oxidation of 2'-hydroxymethylpapaverine (**2**) yields the aromatic phthalideisoquinoline **3**. Catalytic reduction of **3** gives the *erythro*-norphthalideisoquinoline **7** and the *threo* analog **9**. Respective N-methylation furnishes the *erythro*-phthalideisoquinoline **8**, and the *threo* isomer **10**. The nor compounds **7** and **9** can be converted in hydroxylic base to the lactam alcohols **11** and **12**, respectively; but **12** tends to dehydrate to the oxyprotoberberine **15**. LAH reduction of **11** and **12** affords in turn the 13-hydroxyprotoberberines **13** and **14**. Three factors affect the conformation of the phthalideisoquinolines, namely the relative stereochemistry at C-1 and C-9, substitution on nitrogen, and substitution at C-8.

The classical phthalideisoquinoline alkaloids possess a tetracyclic nucleus incorporating a γ-lactone ring such as in (−)-α-narcotine or (−)-β-hydrastine.[2] All of the synthetic routes to the phthalideisoquinolines available at the inception of the present work required the use of the somewhat inaccessible meconine or one of its analogs.[2,3] It seemed to us that a practical route to this series could proceed from the readily available 2'-hydroxymethylpapaverine (**2**), itself derived from the plentiful papaverine (**1**).[4] It is well established that the benzylic α position in papaverine is activated and lends itself to facile oxidation,[2] and by extension it was now determined that controlled chromium trioxide in HOAc–H_2SO_4 oxidation of **2** led in 75% yield to the aromatic phthalideisoquinoline **3**. Catalytic reduction of **3** with Adams catalyst in ethanol containing perchloric acid afforded in near quantitative yield and in almost equal proportions a mixture of the diastereoisomeric norphthalideisoquinolines **7** and **9** which could be separated chromatographically. Subsequent N-methylation of each of the two racemates by the formaldehyde-borohydride method furnished the required phthalideisoquinolines **8** and **10**, respectively. Alternatively, the mixture of the diastereoisomeric norphthalideisoquinolines could be N-methylated first, and then separated chromatographically into **8** and **10**. The norphthalideisoquinolines **7** and **9** were further characterized by means of their crystalline N-acetyl amides.



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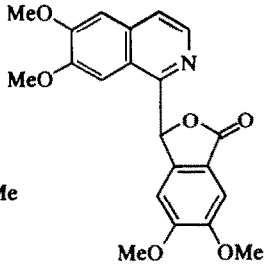

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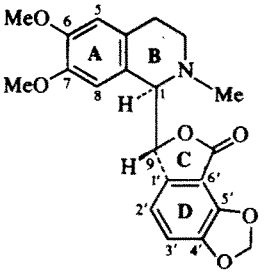

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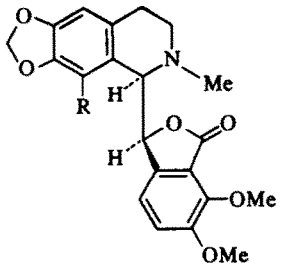


5: R = H
6: R = OMe

The relative stereochemistry and some aspects of the conformation of the phthalideisoquinolines were initially considered by Safe and Moir who correctly established (+)-adlumine (**4**) to be *threo* and (−)-β-hydrastine (**5**) and (−)-α-narcotine (**6**) to be *erythro* on the basis of conclusions derived from NMR data.[5] One of their significant observations was that the low coupling constant for H-1 and H-9 ($J_{1,9}$ = 3·4–4·3 Hz) indicates a dihedral angle of about 50° between these two hydrogens. Another was that the chemical shift of H-2' can be used to differentiate between the *threo* and *erythro* series.

The fact that pairs of diastereoisomeric norphthalideisoquinolines as well as phthalideisoquinolines were now available to us has allowed for a firm establishment of conformations and explicit assignments of chemical shifts. A convenient starting point at this stage was the observation that, in the tetrahydrobenzylisoquinoline series, ring C lies close to the N atom if that N is secondary, but that following N-methylation ring C is found in the proximity of ring A and away from the relatively bulky N-Me group.[6] Presently, this same steric factor, i.e. N-methylation, has also been found to prevail in the phthalideisoquinolines, so that N-methylation forces rings C and D away from the N and into proximity with ring A.

Of the four aromatic protons present in each of species **7–10**, the hydrogen most distant from the γ-lactone ring, and whose chemical shift would be least subject to stereochemical or conformational considerations is H-5, and it can be seen (Table 1) that the chemical shift for H-5 remains nearly constant around δ6·6.†‡ Furthermore, the

†This conclusion requires an exchange in the assignments of the chemical shifts for H-5 and H-8 in corlumine and bicuculline made in Ref. 5. A similar change is also necessitated for cordrastine I in Ref. 3.

‡The fact that H-5 always appears near δ6·6 allows assignments for the chemical shifts of this proton in bicuculline, cordrastine II, capnoidine and cordrastine I which now become δ6·64, 6·65, 6·64 and 6·66, respectively.[7] Bicuculline and cordrastine II belong to the *erythro* series and must be represented by a conformation similar to **8B**. Capnoidine and cordrastine I are *threo* bases which exist in conformation **10B**. The conformation of the alkaloid adlumine, belonging to the *threo* series, is also as in **10B**.

Table 1. NMR chemical shifts of phthalideisoquinolines (δ,$CDCl_3$)‡

Compound	O-CH_3	N-H	N-CH_3	H-5	H-8	H-1	H-9	H-2'	H-5'
Nor-erythro 7	3.62, 3.87, 3.87, 3.90	2.06	-	6.65	6.76	4.74	5.69	5.84	7.25
Erythro 8	3.75, 3.78, 3.87, 3.92	-	2.60	6.62	6.20	4.08	5.55	6.47	7.25
Nor-threo 9	3.78, 3.82, 3.89, 3.92	1.90	-	6.67	6.52	4.58	5.61	7.01	7.18
Threo 10	3.72 3.77, 3.82, 3.90	-	2.69	6.65	6.32	4.09	5.62	7.00	7.17

‡$J_{1,9}$ = 3.5 Hz. H-5 and H-8 are slightly split (≤1 Hz) by interaction with H-4 and H-1, respectively, H-9 is further split (≤1 Hz) by H-2', and vice versa.

most downfield aromatic signal may be assigned in each case to H-5' which falls within the deshielding zone of the lactone carbonyl. The chemical shift for H-1 is affected by methylation on nitrogen, in both the *erythro* and *threo* series, with a resulting upfield shift of ~0·6 ppm (Table 1).

As observed by Safe and Moir, the signals for H-1 and H-9 may be readily recognized because of their low coupling constant, $J_{1,9} = 3{\cdot}5$ Hz (Table 1), so that the dihedral angle ϕ is close to 50°.[5] In each of the four compounds, **7–10**, considered here, there are only two staggered conformations (A and B) which fit this requirement.

If one considers the nor-*erythro* **7** and *erythro* **8** series first, it can be seen that the H-8 signal in *erythro* **8** appears upfield at δ6·20 due to shielding by ring D, so that conformation **8B** must prevail. In the nor-*erythro* base **7**, it is the H-2' and 3'-MeO signals, at δ5·84 and 3·62, respectively, that are upfield (Table 1), due to ring A shielding, and conformation **7A** predominates.

The chemical shift of H-8 can also be used as a probe in establishing conformation in the nor-*threo* **9** and *threo* **10** series. This signal is relatively upfield, at δ6·32, in the case of *threo* **10** because of shielding by the lactone carbonyl, thus leading to the assignment of conformation **10B**. It is further downfield at δ6·52 in the nor-*threo* base **9**; no shielding is involved in this instance, and conformation **9A** is paramount.

An interesting case is that of the *erythro* alkaloid narcotine (**6**) which incorporates a methoxyl at C-8, thus forcing the molecule into a **7A** type conformation.[5] Two opposing steric factors, namely N-methylation and substitution at C-8, can therefore influence the conformation of the phthalideisoquinoline bases. N-Methylation tends to move rings C and D towards ring A, while substitution at C-8 forces rings C and D towards the nitrogen atom, even when this nitrogen is methylated.

The realization that we had on hand the two diastereisomeric norphthalideisoquinolines **7** and **9** meant that a new route to the 13-hydroxyprotoberberines was now possible. Earlier syntheses of 13-hydroxyprotoberberines had involved either hydroboration of a 7,8-dihydroprotoberberine or LAH reduction of a phthalideisoquinoline followed by recyclization and N-demethylation.[8,9]

When *erythro*-norphthalideisoquinoline **7** was refluxed for 5 hr with methanolic KOH, a 90% yield of the corresponding lactam alcohol **11** was obtained. Alternatively, when the *threo*-norphthalideisoquinoline **9** was treated with the same base under milder conditions, i.e. for 24 hr at room temperature, again a high yield of the diastereoisomeric lactam alcohol **12** was generated. If tougher conditions were used in the lactamization of **9**, namely refluxing in methanolic KOH for 20 hr, a high yield of the corresponding oxyprotoberberine **15** was obtained, resulting from facile dehydration of lactam alcohol **12** where the C-13 hydroxyl is *trans* to the C-14 hydrogen. No such dehydration was observed from the lactamization of **7**.

LAH reduction of **11** and **12** yielded the required 13-hydroxyprotoberberine bases **13** and **14** respectively. Consonant with its relative stereochemistry, the 13-hydroxyprotoberberine **13** showed an NMR spectrum with H-13 at δ4·76, $J_{13,14} = 9$ Hz. This large coupling constant is in accordance with a *trans* relationship between H-13 and H-14.[10]

In conclusion, it can be stated that the three factors that affect the conformation of phthalideisoquinolines are (a) the relative stereochemistry at C-1 and C-9, (b) the substitution on nitrogen and (c) the substitution at C-8. The present sequence also affords a relatively short route to lactam alcohols of type **11** and **12**, as well as to 13-hydroxylated tetrahydroprotoberberines.

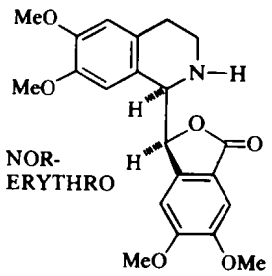
EXPERIMENTAL

Standard experimental procedures. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis. M.ps are uncorrected. The NMR data is at 60 MHz in $CDCl_3$; and TMS was the internal standard. Mass spectra were obtained on an AEI MS-902 spectrometer. All TLC was on Merck Silica Gel-254 plates.

2'-Hydroxymethylpapaverine (**2**). Paraformaldehyde (6 g) was dissolved with slight heating in a mixture containing 600 ml AcOH and 40 ml conc HCl. Papaverine (20 g, 0·06 mol) was added and the mixture heated 15 hr at 60°. A large volume (600 ml) water was added, and the soln neutralized with $NaHCO_3$, and extracted with $CHCl_3$. Work-up gave 17·2 g of colorless crystals, m.p. 172–174° (benzene).[4]

Aromatic phthalideisoquinoline **3**. Compound **2** (5 g, 0·013 mol) was dissolved in 80 ml of a soln of AcOH–H_2SO_4–H_2O (5:1:2), and a soln of CrO_3 (6 g, 0·06 mol) in 40 ml of AcOH–H_2O (1:1) was added dropwise with stirring and cooling (ice-water). The dark brown mixture was stirred and cooled for an additional 20 min until the soln became dark green. The mixture was diluted with 400 ml H_2O, and 20 g of $NaHSO_3$ was added portionwise with slight heating (60°). After cooling, the mixture was extracted with chloroform. The organic extract was washed with a soln of sat $NaHCO_3$, and then H_2O. Work up gave a dark yellow solid which was recrystallized from EtOH, 3·8 g colorless crystals (76%), m.p. 190–192°; $\nu_{max}^{CHCl_3}$ 1760 cm^{-1}; λ_{max}^{EtOH} 233 sh, 248, 300 and 335 nm (log ϵ 3·79, 3·93, 3·10 and 2·84). High resolution mass measurement, M^+, Found: *m/e* 381·1227. Calcd. for $C_{21}H_{19}NO_6$: 381·1211.

Catalytic reduction of aromatic phthalideisoquinoline **3**. A soln of **3** (200 mg, 0·52 mmol) in 50 ml EtOH containing 20 drops of 70% $HClO_4$ was hydrogenated over PtO_2 (50 mg) at 30 psi for 3 hr. The catalyst was removed and the solvent evaporated in *vacuo*; water was added and the soln neutralized with dil NH_4OH. Extraction with $CHCl_3$ and work-up gave a mixture of the diastereoisomeric racemic **7** and **9**. Preparative TLC using benzene-MeOH (4:1) afforded the nor-*erythro* isomer **7** (65 mg, R_f 0·41) and the nor-*threo* isomer **9** (60 mg, R_f 0·60).



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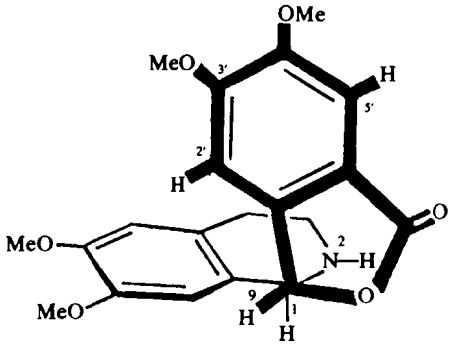
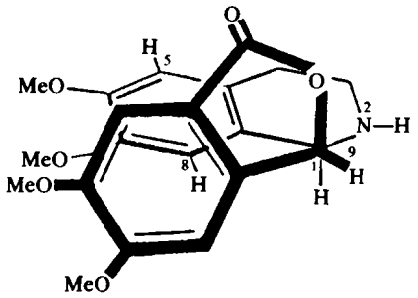
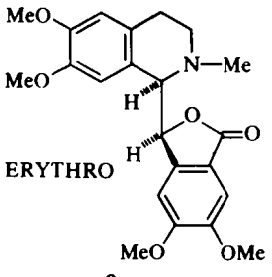


7A



7B



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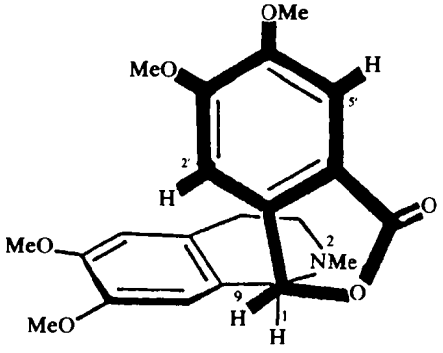
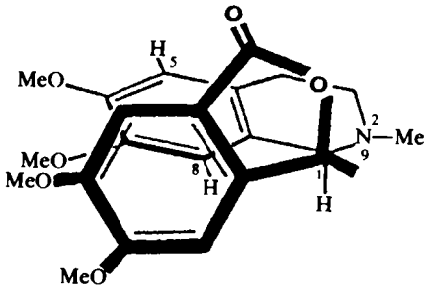
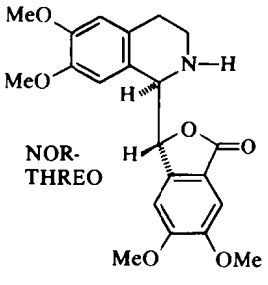


8A



8B



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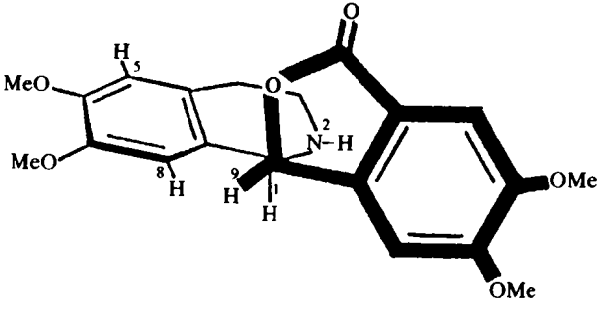
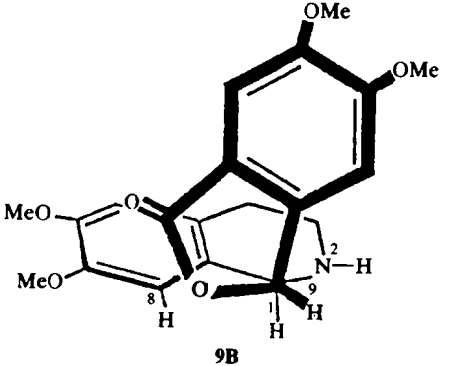
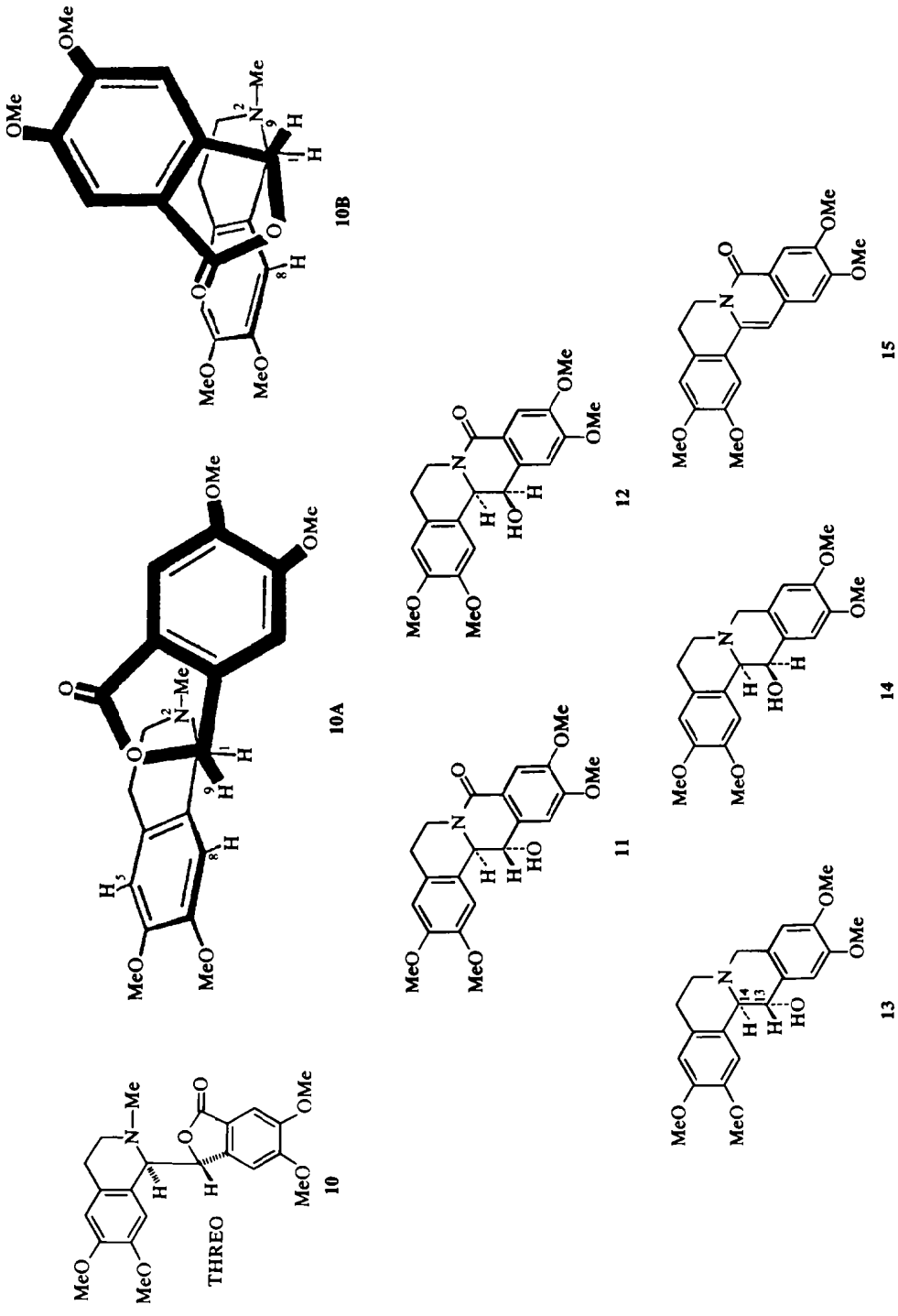


9A



9B


THREO
10
10A
10B
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12
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14
15

Recrystallization of **7** from EtOH gave colorless crystals, m.p. 183–185°; $\nu_{max}^{CHCl_3}$ 1750 cm^{-1}; λ_{max}^{EtOH} 212, 227, 262, 295 and 310 sh nm (log ϵ 3·88, 3·82, 3·27, 3·19 and 2·98). (Found: C, 65·27; H, 6·12. Calcd. for $C_{21}H_{23}NO_6$: C, 65·44; H, 6·02%).

Recrystallization of **9** from EtOH yielded colorless crystals, m.p. 205–207°; $\nu_{max}^{CHCl_3}$ 1750 cm^{-1}; λ_{max}^{EtOH} 215, 228, 263, 295 and 308 sh nm (log ϵ 4·03, 4·08, 3·58, 3·57 and 3·38). (Found: C, 64·70; H, 6·10. Calcd. for $C_{21}H_{23}NO_6 \cdot 1/2\ C_2H_5OH$: C, 64·70; H, 6·37%).

N-Methylation of diastereoisomeric mixture of norphthalideisoquinolines **7** *and* **9**. The diastereoisomers **7** and **9** (170 mg, 0·44 mmol) obtained from the catalytic reduction of **3** were dissolved in 2 ml of 37% aq. formaldehyde, and the soln heated for 2 hr at 110°. Evaporation of the solvent in *vacuo* left a solid which was dissolved in hot MeOH. The soln was cooled in an ice bath, and excess $NaBH_4$ (35 mg, 0·9 mmol) was added cautiously. Stirring was continued for an additional 15 min at 0°. The mixture was then diluted with water and extracted with $CHCl_3$. After drying and evaporation of the solvent, the residue was separated by TLC using benzene-MeOH (4:1). The two components isolated were *erythro*-**8** (62 mg, R_f 0·54), and *threo*-**10** (58 mg, R_f 0·67).

Erythro **8**, m.p. 157–159° (EtOH); $\nu_{max}^{CHCl_3}$ 1750 and 2780 cm^{-1}; λ_{max}^{EtOH} 218 sh, 230, 262, 295 and 307 sh nm (log ϵ 4·20, 4·25, 3·95, 3·89 and 3·73). (Found: C, 65·90; H, 6·20. Calcd. for $C_{22}H_{25}NO_6$: C, 66·15; H, 6·31%).

Threo **10**, m.p. 115–117° (EtOH), $\nu_{max}^{CHCl_3}$ 1750 and 2780 cm^{-1}; λ_{max}^{EtOH} 230, 262, 296 and 307 sh nm (log ϵ 4·13, 3·97, 3·89 and 3·78). (Found: C, 65·89; H, 6·80. Calcd. for $C_{22}H_{25}NO_6 \cdot 1/2C_2H_5OH$: C, 65·54, H, 6·63%).

N-Methylation of erythro-*norphthalideisoquinoline* **7** *and of* threo-*norphthalideisoquinoline* **9**. Nor-*Erythro* **7** (20 mg, 0·05 mmol) was N-methylated using aq. formaldehyde (1 ml), MeOH (10 ml) and $NaBH_4$ (8 mg, 0·2 mmol) as above to give 18·2 mg of **8**. Similarly 20 mg of **9** yielded 19·2 mg of **10**.

(±)-erthro-6, 7, 3', 4'-*Tetramethoxy*-N-*acetyl*-1, 2, 3, 4-*tetrahydronorphthalideisoquinoline*. A soln of nor-*erythro* **7** (20 mg, 0·05 mmol) in one ml Ac_2O containing 8 drops of pyridine was stored for 20 hr at room temp. The solvent was evaporated, and water and $CHCl_3$ added. Work-up of the organic layer gave 18 mg of *erythro*-6,7,3',4'-tetramethoxy-N-acetyl-1,2,3,4-tetrahydronorphthalideisoquinoline, m.p. 204–205° (EtOH); $\nu_{max}^{CHCl_3}$ 1750 and 1625 cm^{-1}; λ_{max}^{EtOH} 215, 230, 265, 295 and 305 sh nm (log ϵ 4·46, 4·43, 3·90, 3·86 and 3·73); NMR δ2·27 (3H, s, CH_3CO). (Found: C, 64·28; H, 5·98. Calcd. for $C_{23}H_{25}NO_7$: C, 64·62; H, 5·90%).

(±)-threo-6, 7, 3', 4'-*Tetramethoxy*-N-*acetyl*-1, 2, 3, 4-*tetrahydronorphthalideisoquinoline*. The above procedure was followed. From 20 mg of **9**, 17 mg of the corresponding acetamide was obtained, m.p. 230–231° (EtOH); $\nu_{max}^{CHCl_3}$ 1750 and 1635 cm^{-1}; λ_{max}^{EtOH} 215, 228, 265, 295 and 305 sh nm (log ϵ 4·53, 4·48, 3·91 and 3·86); NMR δ1·90 (3H, s, CH_3CO). (Found: C, 64·25; H, 6·18. Calcd. for $C_{23}H_{25}NO_7 \cdot 1/2C_2H_5OH$: C, 64·00; H, 6·22%).

(±)-trans-2,3,10,11-*Tetramethoxy*-8-*oxo*-13-*hydroxyberbane* (**11**). *Erythro*-**7** (70 mg, 0·18 mmol) was dissolved in 10 ml of MeOH, and 15 mg of KOH added. The soln was refluxed for 5 hr. AcOH was added, and the soln evaporated. The residue was taken up in $CHCl_3$. Work-up gave 63 mg (90%) of a solid which was recrystallized from EtOH, m.p. 210–212°; $\nu_{max}^{CHCl_3}$ 1630 cm^{-1}; λ_{max}^{EtOH} 213, 230, 270, 295 and 307 sh nm (log ϵ 4·28, 4·38, 3·81, 3·43 and 3·22). (Found: C, 65·62; H, 6·21. Calcd. for $C_{21}H_{23}NO_6$: C, 65·44; H, 6·02%).

(±)-cis-2, 3, 10, 11-*Tetramethoxy*-8-*oxo*-13-*hydroxyberbane* (**12**). *Threo*-**9** (50 mg, 0·13 mmol) was dissolved in 10 ml of MeOH, and 11 mg of KOH added. The soln was left at room temp for 24 hr. Work-up gave 44 mg (89%) of colorless crystals, m.p. 209–211° (EtOH); $\nu_{max}^{CHCl_3}$ 1645 cm^{-1}; λ_{max}^{EtOH} 212, 230, 275, 297 and 306 sh nm (log ϵ 3·93, 3·96, 3·34, 3·30 and 3·11). (Found: C, 65·24; H, 6·00. Calcd. for $C_{21}H_{23}NO_6$: C, 65·44; H, 6·02%).

(±)-trans-2, 3, 10, 11-*Tetramethoxy*-13-*hydroxyberbane* (**13**). Lactam **11** (20 mg, 0·05 mmol) in 3 ml THF was refluxed with LAH for 8 hr to yield 15 mg (78%) crystals, m.p. 197–199° (MeOH); λ_{max}^{EtOH} 212, 230 and 290 nm (log ϵ 4·17, 3·93 and 3·48). (Found: C, 66·60; H, 6·68. Calcd. for $C_{21}H_{25}NO_5 \cdot 1/2CH_3OH$: C, 66·66; H, 6·97%).

(±)-cis-2, 3, 10, 11-*Tetramethoxy*-13-*hydroxyberbane* (**14**). Lactam **12** was reduced as above in 81% yield to give crystals, m.p. 198–200° (MeOH-ether); λ_{max}^{EtOH} 213, 233 sh and 288 nm (log ϵ 4·07, 3·56 and 3·17). (Found: C, 67·68; H, 6·95. Calcd for $C_{21}H_{25}NO_5$: C, 67·90; H, 6·78%).

Oxyprotoberberine **15**. (±)-*cis*-**12** (20 mg, 0·5 mmol) was dissolved in 10 ml of MeOH containing 4 mg of KOH, and the soln refluxed 20 hr under N_2. AcOH was added, the solvent evaporated, and the residue extracted with benzene. Work-up gave nearly colorless prisms, 15 mg (78%), m.p. 195–197° ($CHCl_3$–ether); $\nu_{max}^{CHCl_3}$ 1635 cm^{-1}; λ_{max}^{EtOH} 232, 265, 338 and 350 sh nm (log ϵ 3·90, 3·73, 3·59 and 3·46); NMR δ2·92 (2H, t, J = 6 Hz, CH_2), 3·93 (3H, s, OCH_3), 3·97 (3H, s, OCH_3), 4·00 (6H, s, 2OCH_3), 4·37 (2H, t, J = 6 Hz, CH_2N), five arom. H s at 6·72, 6·82, 6·92, 7·25 and 7·80.

High resolution mass measurement, M^+: Found: *m/e* 367·1397. Calcd. for $C_{21}H_{21}NO_5$: 367·1420.

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