Supplementary Material Available: A listing of fractional coordinates and temperature factors (Table I), bond lengths (Table II), and bond angles (Table III) of dinosterol (6 pages). Ordering information is given on any current masthead page.

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Studies in Protoberberine Alkaloids. 14. Use of a Mixture of Phosphorus Pentabromide and Phosphorus Pentoxide As a Cyclizing Reagent in Protoberberine Synthesis

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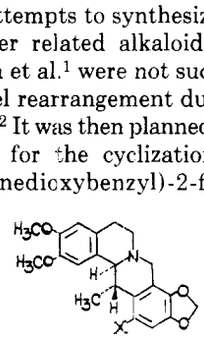
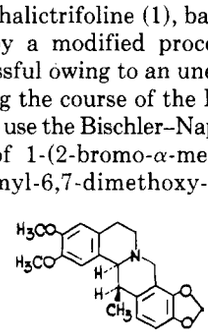
Cyclization of 1-(2-bromo-α-methyl-4,5-methylenedioxybenzyl)-2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**3**) with a mixture of PBr_5 and P_2O_5 (followed by reduction with $NaBH_4$ in MeOH) led to the formation of 13β-methyl-13aα*H*-tetrahydropseudoepiberberine (**7**), 4-bromo-13β-methyl-13aα*H*-tetrahydropseudoepiberberine (**17**), 13α-methyl-13aα*H*-tetrahydropseudoepiberberine (**8**), and 4-bromo-13α-methyl-13aα*H*-tetrahydropseudoepiberberine (**18**). Similarly the *N*-formyl derivative **4** gave 13β-methyl-13aα*H*-tetrahydropseudocoptisine (**9**), 13α-methyl-13aα*H*-tetrahydropseudocoptisine (**10**), 4-bromo-13α-methyl-13aα*H*-tetrahydropseudocoptisine (**19**), and 4-bromo-13α-methyl-13aα*H*-tetrahydropseudocoptisine (**20**).

Our attempts to synthesize thalictrifoline (**1**), base II (**2**), and other related alkaloids by a modified procedure of Shamma et al.[1] were not successful owing to an unexpected but novel rearrangement during the course of the Mannich reaction.[2] It was then planned to use the Bischler–Napieralsky reaction for the cyclization of 1-(2-bromo-α-methyl-4,5-methylenedioxybenzyl)-2-formyl-6,7-dimethoxy-1,2,3,4-



1 X = H
11 X = Br



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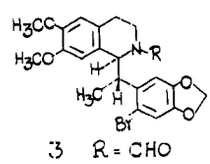
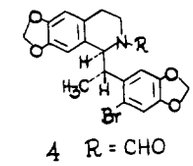
tetrahydroisoquinoline (**3**) and its bismethylenedioxy analogue **4** to get the required 13-methyltetrahydroprotoberberines.

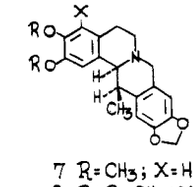
The tetrahydroisoquinolines **5** and **6** gave the corresponding *N*-formyl derivatives **3** and **4** when heated with formic acid and triethylamine. The *N*-formyl derivative **3** was then refluxed with freshly distilled phosphorus oxychloride in benzene and the quaternary salt formed was directly reduced with sodium borohydride in methanol. A mixture of two products was obtained the constituents of which were separated by chromatography and identified from their spectral, physical, and analytical data as the diastereoisomeric 13-methyltetrahydropseudoprotoberberines viz. 13β-methyl-13aα*H*-tetrahydropseudoepiberberine (**7**) and 13α-methyl-13aα*H*-tetrahydropseudoepiberberine (**8**). Similarly, when the *N*-formyl derivative **4** was cyclized using $POCl_3$, a mixture of two products was obtained and these were identified as 13β-methyl-13aα*H*-tetrahydropseudocoptisine (**9**) and 13α-methyl-13aα*H*-tetrahydropseudocoptisine (**10**). The structures of compounds **7**, **8**, **9**, and **10** were confirmed by comparison with authentic synthetic samples prepared as reported earlier.[1,3] Identical results were obtained when distilled $POBr_3$[4] was used for cyclization in the place of $POCl_3$.



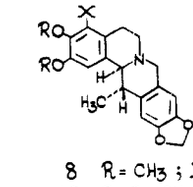
3 R = CHO
5 R = H



4 R = CHO
6 R = H



7 R = CH_3; X = H
9 R+R = CH_2; X = H
17 R = CH_3; X = Br
19 R+R = CH_2; X = Br



8 R = CH_3; X = H
10 R+R = CH_2; X = H
18 R = CH_3; X = Br
20 R+R = CH_2; X = Br

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Table I

Compd	Registry no.	TLC[a] R_f	Mp, °C	Chemical shift of the C-Me doublet δ, ppm	Rate of methiodide formation $k \times 10^{-4}$, s^{-1} (31.5 °C)	pK_a values
A (**17**)	65366-50-9	0.9	146	0.93	1.3	7.00 ± 0.05
B (**7**)	24306-61-4	0.8	197–198	0.93	1.2	
C (**18**)	65366-51-0	0.5	160	1.47	99.6	7.60 ± 0.05
D (**8**)	24314-69-0	0.4	132	1.48	60.3	
E (**19**)	65366-52-1	0.9	205–206	0.93	6.4	
F (**9**)	65391-28-8	0.8	195	0.94	9.5	
G (**20**)	65366-53-2	0.5	179	1.43	98.7	
H (**10**)	65391-29-9	0.4	131	1.44	69.00	

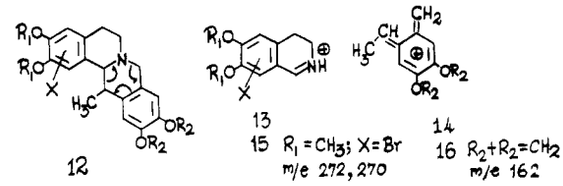
[a] Solvent system, $CHCl_3$/MeOH/EtOAc 40:1:2.5.

However, when an undistilled sample of $POBr_3$ was used for the cyclization of **3**, in addition to the two compounds **7** and **8**, a third compound was obtained in low yields. Analytical and NMR spectral data indicated this compound to be a bromo-substituted tetrahydroprotoberberine and structure **11** was tentatively assigned to it and it was expected to give thalictrifoline (**1**) on debromination. Hoping to improve the yield of this bromo compound a mixture of PBr_5 and P_2O_5 was employed in the cyclization step. When compound **3** was cyclized using this mixture and the resulting quaternary salts were reduced with $NaBH_4$ in MeOH four products were isolated. The mixture was separated by chromatography and the four products were designated as A, B, C, and D, respectively, in the order of their increasing polarity on TLC. (Compound C was found to be identical with the bromo compound obtained earlier during $POBr_3$ cyclization of **3**.) The *N*-formyl derivative **4** also under the same conditions of cyclization and reduction led to four products viz. E, F, G, and H. Some of the physical and spectral data of these compounds are given in Table I. Compounds B, D, F, and H were found to be identical with **7**, **8**, **9**, and **10**, respectively. Compounds A, C, E, and G gave **7**, **8**, **9**, and **10**, respectively, on reductive debromination.

Compounds A and C both analyzed well for the molecular formula $C_{21}H_{22}NO_4Br$ and this was confirmed by their mass spectra (M^+ at *m/e* 433 and 431). Their NMR spectra showed the presence of bromine in one of the two aromatic rings by showing signals for only three aromatic protons. The NMR spectrum in $CDCl_3$ (60 MHz) of compound A showed the following signals: δ 0.93 (3 H, d, J = 7 Hz, $CHCH_3$), 2.78–3.35 (5 H, m), 3.75 (2 H, bs, C_8H), 3.97 (6 H, s, $2OCH_3$), 6.08 (2 H, s, OCH_2O), 6.67 (1 H, s, ArH), 6.77 (1 H, s, ArH), 6.90 (1 H, s, ArH). The NMR spectrum of compound C in $CDCl_3$ (100 MHz) showed the following signals: δ 1.47 (3 H, d, J = 7 Hz, $CHCH_3$), 2.75–3.20 (5 H, m), 3.71 (1 H, d, J = 16 Hz, C_8H), 3.73 (1 H, s, $C_{13a}H$), 4.16 (1 H, d, J = 16 Hz, C_8H), 3.83 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 5.88 (2 H, s, OCH_2O), 6.52 (1 H, s, ArH), 6.69 (1 H, s, ArH), 6.76 (1 H, s, ArH). The chemical shift of the CCH_3 doublet[5] and the presence of a broad singlet in compound A and an AB quartet in compound C for the C_8-methylene protons[6] indicated the *trans*- and *cis*-quinolizidine geometry of compounds A and C, respectively. These assignments are supported by their TLC R_f values, rate of methiodide formation, and pK_a values (cf. ref 1).

The position of bromine in compounds A and C could be partially assigned from an inspection of their mass spectra. All 13-methyltetrahydroprotoberberines give rise to two intense characteristic fragments in their mass spectra arising out of a retro Diels–Alder type ring opening as shown.[7]

Thus compounds of the type **12** would give rise to ions **13** and **14**. Compounds A and C both exhibit prominent peaks at *m/e* 272, 270 and 162, which could be only due to ions **15** and **16**, indicating the presence of bromine in ring *A*.



Of the two possible positions 1 and 4 for bromine in ring *A* position 4 is preferred on stereochemical considerations and the most probable structure for compounds A and C could be represented by **17** and **18**. Compounds E and G, whose NMR and mass spectral data were similar to compounds A and C, were assigned structures **19** and **20**, respectively. X-ray crystallographic studies of these bromo compounds (which are in progress) will settle conclusively the position of bromine.

Experimental Section

Melting points are uncorrected. UV spectra were run on a Beckman DK2A spectrophotometer. EtOH (95%) solutions were used unless otherwise stated. IR spectra were run on a Perkin-Elmer Infracord and Model 421 IR spectrophotometers. Chemical shifts are quoted in ppm downfield from Me_4Si used as internal reference. Mass spectra are from a Varian Mat CH7 mass spectrometer. Elemental analyses were performed by Ciba-Geigy Research Centre, Bombay.

1-(2-Bromo-α-methyl-4,5-methylenedioxybenzyl)-2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (3). Anhydrous formic acid (3 g) was added to triethylamine (1.7 g) at 0 °C. To this mixture was added 1-(2-bromo-α-methyl-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline[2] (**5**) (3 g) and the mixture was refluxed at 145 °C for 2 h in an oil bath. The solution was cooled, poured into water, and extracted with chloroform. The $CHCl_3$ extract was washed with water, dried (Na_2SO_4), and distilled to yield a gum which was crystallized from ethyl acetate: 2.5 g; mp 205 °C; IR (KBr) 1670 cm^{-1} (CO); NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.17, 1.28 (2d, 3 H, $CHCH_3$), 3.89 (s, 6 H, 2 OCH_3), 6.00 (s, 2 H, OCH_2O), 6.65–7.00 (m, 4 H, aromatic protons). Anal. Calcd for $C_{21}H_{22}NO_5Br$: C, 56.24; H, 4.91; N, 3.13. Found: C, 56.43; H, 5.02; N, 3.32.

1-(2-Bromo-α-methyl-4,5-methylenedioxybenzyl)-2-formyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (4). This compound was prepared from 1-(2-bromo-α-methyl-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline[2] (**6**) by the procedure described above for compound **3**. It was crystallized from ethyl acetate: mp 195 °C; IR (Nujol) 1640 cm^{-1} (CO); mass spectrum *m/e* 229, 227, and 204. Anal. Calcd for $C_{20}H_{18}NO_5Br$: C, 55.55; H, 4.17; N, 3.24. Found: C, 55.81; H, 4.50; N, 3.30.

Cyclization of 3 Using a Mixture of PBr_5 and P_2O_5. To a solution of the *N*-formyl derivative **3** (2 g) in dry benzene (150 mL) was added PBr_5 (3 g) and P_2O_5 (6 g) and the mixture was shaken and left aside at room temperature overnight. It was then refluxed for 10 min and cooled. *n*-Hexane (100 mL) was added and after shaking and leaving for some time the clear supernatant liquid was decanted. The residue was dissolved in cold methanol (150 mL) and neutralized with aqueous sodium hydroxide solution (40%). $NaBH_4$ (1 g) was added in small portions. After 2 h the solvent was removed and the residue was treated with water (100 mL). The aqueous solution was then extracted with $CHCl_3$; the $CHCl_3$ extract was washed with water, dried (Na_2SO_4), and evaporated. The crude product was chromatographed over silica gel (30 g) and eluted with benzene. Fractions (20 mL) were collected and monitored by TLC on silica gel plates using $CHCl_3$/

MeOH/EtOAc (40:1:2.5) as the solvent system and the following compounds were isolated.

1. 4-Bromo-13β-methyl-13aα*H*-tetrahydropseudoepiberberine (17). Fractions 3–7 were combined and evaporated and the solid obtained was crystallized from benzene–hexane to yield pale yellow needles: 30 mg; mp 146 °C; IR (KBr) 2900–2750 cm^{-1} (Bohlmann bands); UV (EtOH) 288 nm (log ε 3.88); NMR data as given in the discussion; mass spectrum *m/e* 433 and 431 (M^+), 272, 270 and 162. Anal. Calcd for $C_{21}H_{22}NO_4Br$: C, 59.55; H, 5.08; N, 3.23. Found: C, 59.42; H, 5.05 N, 3.27.

2. 13β-Methyl-13aα*H*-tetrahydropseudoepiberberine (7). Fractions 9–16 were combined and evaporated to yield a solid which was crystallized from benzene as yellow needles: 300 mg; mp 197–198 °C; found to be identical (IR, mp, mmp, and spectra) with an authentic sample prepared as reported.[1]

3. 4-Bromo-13α-methyl-13aα*H*-tetrahydropseudoepiberberine (18). Fractions 20–30 were combined and evaporated to give a yellow residue. This was crystallized from benzene–hexane as yellow needles: 420 mg; mp 160 °C; UV (EtOH) 288 nm (log ε 3.88); NMR data as given in the discussion; mass spectrum *m/e* 433 and 431 (M^+), 272, 270, and 162. Anal. Calcd for $C_{21}H_{22}NO_4Br$: C, 59.55; H, 5.08; N, 3.23. Found: C, 59.34; H, 5.35; N, 3.22.

4. 13-α-Methyl-13aα*H*-tetrahydropseudoepiberberine (8). Fractions 31–34 gave a compound which was crystallized from benzene as colorless crystals: 60 mg; mp 132 °C; found to be identical with an authentic sample.[1]

Cyclization of 4 Using PBr_5 and P_2O_5. The *N*-formyl derivative **4** was cyclized as described above and the products were separated by chromatography.

1. 4-Bromo-13β-methyl-13aα*H*-tetrahydropseudocoptisine (19). Fractions 4–8 were combined and evaporated to give a colorless solid which was crystallized from benzene as colorless crystals: 55 mg; mp 205–206 °C; IR (Nujol) 2800–2700 cm^{-1} (Bohlmann bands); UV (EtOH) 292 nm (log ε 4.00); NMR ($CDCl_3$) δ 0.93 (d, 3 H, J = 7 Hz, $CHCH_3$), 2.20–4.20 (8 H), 5.93 (s, 2 H, OCH_2O), 6.05 (s, 2 H, OCH_2O), 6.57, 6.67, 6.70 (3s, 3 H, aromatic protons); mass spectrum, *m/e* 417, 415 (M^+), 256, 254, and 162. Anal. Calcd for $C_{20}H_{18}NO_4Br$: C, 57.70; H, 4.33; N, 3.36. Found: C, 57.81, H, 4.30; N, 3.36.

2. 13β-Methyl-13aα*H*-tetrahydropseudocoptisine (9). Fractions 10–16 were combined and crystallized from benzene as pale yellow crystals: 380 mg; mp 195 °C; identical with an authentic sample.[3]

3. 4-Bromo-13α-methyl-13aα*H*-tetrahydropseudocoptisine (20). Fractions 18–27 when combined and evaporated gave a yellow solid which was crystallized from benzene–hexane as yellow crystals: 400 mg; mp 179 °C; UV (EtOH) 291 nm (log ε 3.98); NMR ($CDCl_3$) δ 1.43 (d, 3 H, J = 7 Hz, $CHCH_3$), 2.57–3.00 (4 H), 3.30–4.35 (4 H), 5.92 (s, 2 H, OCH_2O), 6.01 (s, 2 H, OCH_2O), 6.52 (1 H, aromatic proton), 6.73 (s, 2 H, aromatic protons); mass spectrum *m/e* 417, 415 (M^+), 256, 254, and 162. Anal. Calcd for $C_{20}H_{18}NO_4Br$: C, 57.69; H, 4.33; N, 3.37. Found: C, 57.40; H, 4.30; N, 3.64.

4. 13α-Methyl-13aα*H*-tetrahydropseudocoptisine (10). Fractions 30–35 gave a compound which was crystallized from benzene–hexane as colorless needles: 75 mg; mp 131 °C. This compound was identical with an authentic synthetic sample.[3]

Catalytic Debromination of 17, 18, 19, and 20. The bromo compounds (250 mg each) were dissolved in methanol (75 mL) and Pd-C (10%, 150 mg) was added to the solution and hydrogenated at room temperature in a paar reduction apparatus for 5 h. The catalyst was then filtered off, the solution was neutralized with dilute NH_4OH solution, and the methanol was distilled off. The residue was then extracted with $CHCl_3$, and the $CHCl_3$ layer was washed with water, dried (Na_2SO_4), and evaporated. The solid residue was crystallized. Thus compounds **17**, **18**, **19**, and **20** gave **7**, **8**, **9**, and **10**, respectively.

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Registry No.—**3**, 65366-54-3; **4**, 65366-55-4; **5**, 65366-56-5; **6**, 65366-57-6; PBr_5, 7789-69-7; P_2O_5, 1314-56-3.

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Studies in Protoberberine Alkaloids. 15. Some Aspects on the Rate of Methiodide Formation in Protoberberine Chemistry

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The rates of methiodide formation of several synthetic tetrahydroprotoberberines and some 13-methyltetrahydroprotoberberines have been determined. The effect of the substitution pattern and the geometry of fusion of the **B/C** ring system on the rate constants of the compounds studied is briefly discussed. It is also observed that alkaloids having free phenolic hydroxyl groups have larger reaction rates when compared to their O-alkyl derivatives.

Two important methods being used at present to assign conformation to quinolizidine and indolizidine systems are a study of their NMR spectra[1] and determination of their rate of quaternization with methyl iodide.[2] In the course of our work on protoberberine alkaloids we had prepared a large number of synthetic tetrahydroprotoberberines and a few 13-methyltetrahydroprotoberberines. We established the structures and stereochemistry of these compounds on the basis of their IR, NMR, and mass spectral data. Thus a variety of substrates of known stereochemistry were readily available to us and we thought it worthwhile to study their rate of quaternization with a view to study the limitations of this

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