Studies on Tetrahydroisoquinolines. Part 15.[1,2] Lead Tetra-acetate Oxidation of Four Hydroxytetrahydroprotoberberines, (±)-Govanine, (±)-Discretine, (±)-Corytencine, and (±)-10-Hydroxy-2,3,11-trimethoxytetrahydroprotoberberine

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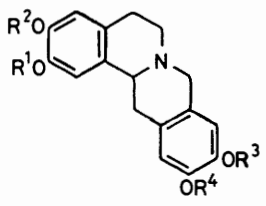
Lead tetra-acetate oxidation of (±)-2- (1) and (±)-10- (2) hydroxytetrahydroprotoberberines afforded the *p*-quinol acetates (5) and (6), which on treatment with acetic anhydride–concentrated sulphuric acid gave (±)-2,5β- (35), and (±)-10,13α- (40) and (±)-10,13β- (41) diacetoxytetrahydroprotoberberines respectively. Alkaline hydrolysis of the diacetate (35) produced the (±)-5α- (38) and (±)-5β- (39) methoxy-compounds, whereas similar treatment of the diacetates (40) and (41) produced the same (±)-13α-methoxy-derivative (42). While oxidation of (±)-3-hydroxytetrahydroprotoberberine (3) gave directly the (±)-5α- (7) and (±)-5β- (8) acetoxy-derivatives, oxidation of the (±)-11-hydroxy-congener (4) produced the unexpected rearranged product, the (±)-12-acetoxy-9-hydroxy-derivative (18), together with a small amount of (±)-13β-acetoxytetrahydroprotoberberine (17). A discussion of the stereochemistry of the reactions is presented.

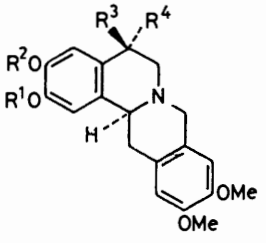
FROM previous studies of the lead tetra-acetate oxidation

Oxidation of (4)[9] produced the (±)-13β-acetoxy-11-

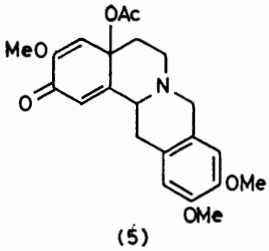
quinoline (30) (85.6% yield), was determined analogously to that of (18). Namely, the pentamethyl ether (31) was unequivocally identical with authentic (±)-3-(2-ethyl-4,5-dimethoxyphenyl)-5,7,8-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline derived from the methiodide of (23).



	R^1	R^2	R^3	R^4
(1)	H	Me	Me	Me
(2)	Me	Me	H	Me
(3)	Me	H	Me	Me
(4)	Me	Me	Me	H
(29)	Me	Me	Me	CH_2Ph



	R^1	R^2	R^3	R^4
(7)	Me	H	H	OAc
(8)	Me	H	OAc	H
(9)	Me	Ac	H	OAc
(10)	Me	Ac	OAc	H
(11)	Me	Me	H	OAc
(12)	Me	Me	OAc	H
(13)	Me	H	OH	H
(14)	Me	H	H	OH
(15)	Me	Me	OH	H
(16)	Me	Me	H	OH
(35)	Ac	Me	OAc	H
(36)	H	Me	OH	H
(37)	Me	Me	OAc	H
(38)	H	Me	H	OMe
(39)	H	Me	OMe	H



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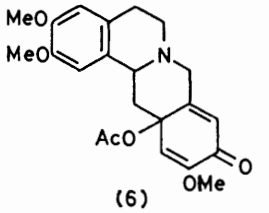

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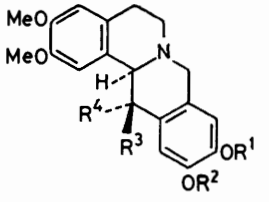
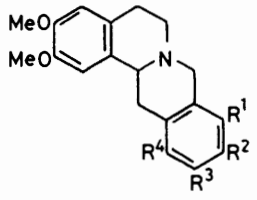
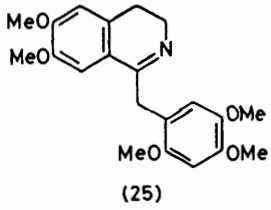


	R^1	R^2	R^3	R^4
(17)	Me	H	OAc	H
(19)	Me	Me	OH	H
(40)	Ac	Me	H	OAc
(41)	Ac	Me	OAc	H
(42)	H	Me	H	OMe

stereospecifically (±)-2,5β-diacetoxy-3,10,11-trimethoxytetrahydroprotoberberine (35), in 90.9% yield, the configuration of the aliphatic acetoxy-group being assigned on the basis of the one-proton triplet (J 2.5 Hz) at δ 6.00 in the n.m.r. spectrum. Hydrolysis of (35) gave the diol (36), and since (35) was reconverted on acetylation of (36), it was demonstrated that no configurational change had occurred during hydrolysis. Methylation of (36) with diazomethane afforded the monohydroxy-compound (15), which on acetylation yielded the known (±)-5β-acetoxy-2,3,10,11-tetramethoxytetrahydroprotoberberine (37).[8] Hydrolysis of (35) with aqueous KOH–MeOH furnished a mixture of (±)-2-hydroxy-3,5α,10,11-tetramethoxy- (38) and (±)-2-hydroxy-3,5β,10,11-tetramethoxy- (39) tetrahydroprotoberberines in the ratio 1 : 1.



	R^1	R^2	R^3	R^4
(18)	OH	OMe	H	OAc
(20)	OAc	OMe	H	OAc
(21)	OMe	OMe	OMe	H
(22)	H	OMe	OMe	OMe
(23)	OMe	OMe	H	OMe
(24)	OMe	H	OMe	OMe



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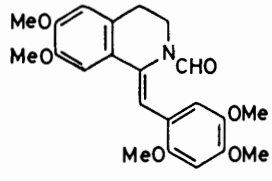

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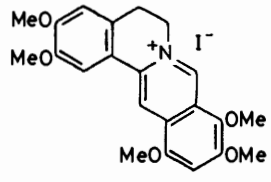


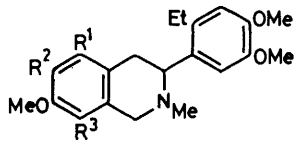
(27)

On the other hand, similar treatment (Ac_2O–concentrated H_2SO_4) of p-quinol acetate (6) afforded (±)-10,13α-diacetoxy- (40) and (±)-10,13β-diacetoxy- (41) 2,3,11-trimethoxytetrahydroprotoberberines in the ratio 1 : 3. Hydrolysis of either (40) or (41) with aqueous KOH–MeOH gave the same (±)-10-hydroxy-2,3,11,13α-tetramethoxytetrahydroprotoberberine (42), with the stereochemistry being assigned on the basis of the one-proton doublet (J = 9 Hz) at δ 4.64 in the n.m.r. spectrum. Synthesis of 13-acetoxytetrahydroprotoberberines in the manner described above may be regarded as biomimetic.[13]

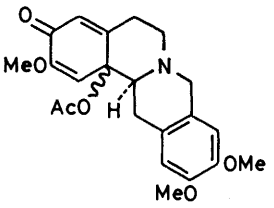
At present the most probable mechanistic reaction pathway appears to be as follows. Stereoselective formation of (35) may be due to attack of acetic acid that is strongly hydrogen-bonded to the β-oriented electron pair of the nitrogen in the quinone methide (43) which has an adjacent secondary carbon. The quinone

In accord with earlier observations, the 7-phenolic tetrahydroisoquinolines (1) and (2) were oxidized to the isolable p-quinol acetates (5) and (6), while the 6-phenolic counterparts (3) and (4) afforded the non-isolable or transient p-quinol acetates (32) and (33), and (34) respectively. The acetates (5) and (6) were treated with Ac_2O–concentrated H_2SO_4 in order to produce rearrangement. Thus the acetate (5) furnished

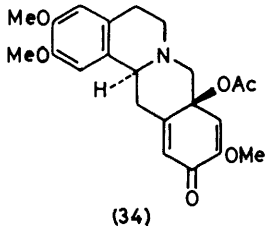
methide (44), with an adjacent tertiary carbon, presents a somewhat convex α-face giving rise to less stereoselectivity and allowing the 13α-acetate (40) to be produced to the extent of one quarter of the total product.



	R^1	R^2	R^3
(28)	H	OH	H
(30)	OAc	H	OH
(31)	OMe	H	OMe



(32) α – OAc
(33) β – OAc



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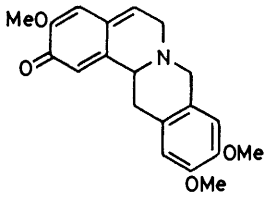

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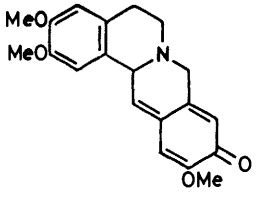

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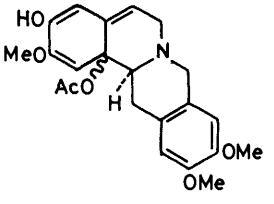
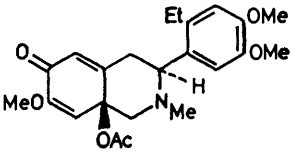
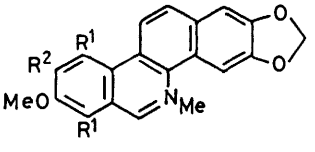


(45) α – OAc
(46) β – OAc



(47)



(48) R^1 = H, R^2 = OMe
(49) R^1 = OMe, R^2 = H

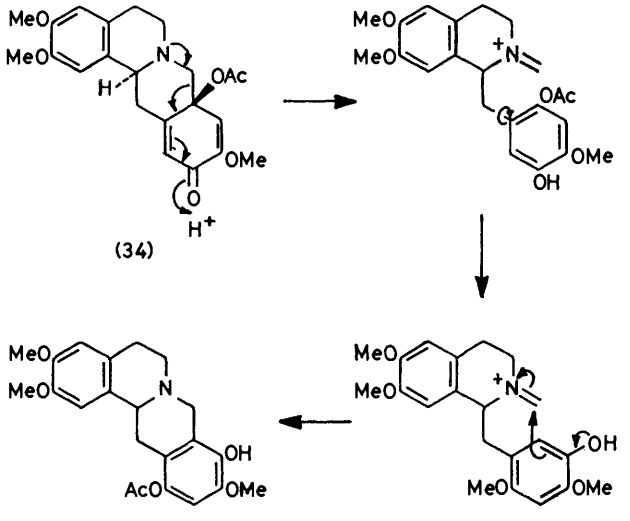
Since the hydrogen bond between methanol and the nitrogen atom is weaker than that between acetic acid and nitrogen, and since in an alkaline medium methanol must preferentially hydrogen bond to hydroxide ion rather than nitrogen, all stereochemical control is lost during the hydrolysis, resulting in the formation of equimolar quantities of the 5α- (38) and 5β- (39) methyl ethers. On the other hand, absence of hydrogen bonding to the nitrogen atom, together with the inherent stereostructure of (44), as already mentioned, must be responsible for stereoselective formation of the 13α-methyl ether (42).

As a result of these hydrogen-bonding effects in combination with a slightly convex structure for (3), the transient *p*-quinol acetates (32) and (33) undergo preenolization, forming (45) and (46), with concurrent internal 1,3-shift of the acetoxy-group, culminating in formation of the 5α- (7) and 5β- (8) acetates.

The other transient *p*-quinol acetate (34), derived from (4), must be formed as a single stereoisomer to furnish the 13β-acetate (17). The acetate (34), however, is a vinylogous Mannich base, and retro-Mannich opening of ring C with concomitant Mannich recyclization takes place to produce (18).

Although the same vinylogous Mannich base moiety is present in both *p*-quinol acetates (32) and (33), similar ring opening and recyclization do not occur. The observation that acetoxy-migration to the 5-position is preferred to retro-Mannich reaction may be explained by the fact that the carbon adjacent to the reaction centre is secondary and does not hinder migration. Since such carbon in (34) is tertiary, acetoxy-migration is heavily hindered, thereby allowing the retro-Mannich reaction to occur. In support of this proposal, it is observed that no migration product is obtained in the reaction of (47), where the reaction terminus is completely blocked by the adjacent tertiary carbon carrying a freely rotating benzene ring.

Although no direct information concerning the stereochemical formation of *p*-quinol acetates has been available until now, it appears that the carbon adjacent to the carbon bearing the acetoxy-group plays a dominant role. Namely, when the former carbon is secondary, the *p*-quinol acetate is formed as a single isomer with the acetoxy-group in a β-configuration as evidenced in (5)



(34) (18)

and in the 13β-acetate (17), a migration product of (34). On the other hand, when it is tertiary, *p*-quinol acetates are formed as pairs of isomers containing an appreciable amount of the α-isomer.

Since the net change during the novel reaction mentioned above can be viewed as a rearrangement *via* oxidation, such reaction may be adequately described by the term ' tetrahydroisoquinoline oxidative rearrange-

ment,' * and may have certain implications concerning isoquinoline alkaloid biogenesis. A related precedent for the creation of a similar oxygenation pattern has been reported in the conversion of nitidine (48) sulphate to chelilutine (49).[14]

EXPERIMENTAL

All melting points were measured on a Büchi melting point apparatus. N.m.r. spectra were taken with a JEOL model JNR-4H-100 spectrometer (100 MHz) in $CDCl_3$ solution (5—10%) with Me_4Si as internal standard, unless otherwise noted. I.r. spectra were run on a Hitachi model 215 ($CHCl_3$). Mass spectra were measured with a Hitachi model RMU-6E mass spectrometer. Preparative t.l.c. was performed on silica gel HF_{254} (Merck). Microanalytical data for all new compounds are shown in Table 1. Spectral data for tetrahydroprotoberberines and 3-phenyltetrahydroisoquinolines are shown in Tables 2 and 3, respectively.

(±)-2-*Hydroxy*-3,10,11-*trimethoxytetrahydroprotoberberine* [(±)-*Govanine*] (1).—A stirred solution of 3,4-dihydroisoquinoline hydrochloride [5] (454 mg) in MeOH (20 ml) was treated with $NaBH_4$ (76 mg) at room temperature for 1 h to give (±)-7-benzyloxy-6-methoxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (383 mg, 91.4%) as prisms, m.p. 105.5—107.5° (acetone) (Found: C, 74.1; H, 6.98; N, 3.3. $C_{26}H_{29}NO_4$ requires C, 74.45; H 6.95; N 3.35%); δ 3.76 (3 H, s, OMe), 3.78 (6 H, s, 2 × OMe), and 5.03 (2 H, s, OCH_2Ph). A mixture of the 7-benzyloxy-compound (419 mg), 87% formic acid (1.5 ml), and 37% formalin (1.5 ml), was heated on a boiling water-bath for 3 h. After basification with saturated aqueous $NaHCO_3$, the product was taken up in $CHCl_3$. Usual work-up gave (±)-2-*benzyloxy*-3,10,11-*trimethoxytetrahydroprotoberberine* (427 mg, 99.1%) as plates, m.p. 154—155° (from Pr^iOH) (Found: C, 74.9; H, 6.8; N, 3.3. $C_{27}H_{29}NO_4$ requires C, 75.15; H, 6.75; N, 3.25%); δ 3.83 (3 H, s, OMe), 3.86 (6 H, s, 2 × OMe), 5.13 (2 H, s, OCH_2Ph), and 6.56, 6.62, 6.63, and 6.77 (each 1 H, s, ArH). Hydrogenolysis of the 2-benzyloxy-compound (7.45 g) with 10% palladium–charcoal gave (1) (5.5 g, 94.6%) as prisms, m.p. 157—158° (from Pr^iOH) (lit.,[5] 170—172°).

Oxidation of (±)-*Govanine* (1), (±)-10-*Hydroxy*-2,3,11-*trimethoxytetrahydroprotoberberine* (2), (±)-*Discretine* (3) *and* (±)-*Corytencine* (4).—(i) The oxidation of (1) (400 mg) with $Pb(OAc)_4$ (572 mg) in AcOH (4 ml) was carried out in the manner [15] described previously to give quantitatively the *p*-quinol acetate (5).

(ii) Similar oxidation as noted above of (2) (400 mg) and $Pb(OAc)_4$ (624 mg) in AcOH (4 ml) gave quantitatively the *p*-quinol acetate (6).

(iii) Similar oxidation as noted above of (3) (100 mg) with $Pb(OAc)_4$ (156 mg) in AcOH (1 ml) gave an oil (105 mg), which was separated by preparative t.l.c. ($CHCl_3$–MeOH, 24 : 1 v/v) into a mixture of (±)-5α- (7) and (±)-5β-acetoxy-3-hydroxy-2,10,11-trimethoxytetrahydroprotoberberine (8) (35 mg, 30%) and (3) (25 mg, 25%). The former (7 + 8) (300 mg) [δ 1.98 and 2.05 (3 H, each s, 5 : 1)] was hydrolysed with concentrated HCl (7.5 ml) at room temperature for 2 h to give an amorphous mass (219 mg), which was separated by preparative t.l.c. ($CHCl_3$–MeOH, 15 : 1 v/v) into (±)-3,5β-*dihydroxy*-2,10,11-*trimethoxytetrahydroprotoberberine* (13) (129 mg, 48%) as scales, m.p. 192—193° (transition at 109—111°) (from MeOH), and the (±)-3,5α-*isomer* (14) (54 mg, 20%) as scales, m.p. 135—138° (transition at 120—122°) (from MeOH). Methylation of (13) (58 mg) with CH_2N_2 gave (±)-5β-*hydroxy*-2,3,10,11-*tetramethoxytetrahydroprotoberberine* (15) (60 mg, 100%) as prisms, m.p. 182—185° (from EtOH) (lit.,[8] 194—195°), whose n.m.r. and i.r. spectral data were well consistent with those of an authentic sample derived from (35). Similar methylation of (14) (17 mg) afforded (±)-5α-hydroxy-2,3,10,11-tetramethoxytetrahydroprotoberberine (16) (16 mg, 90.4%) as prisms, m.p. 177—182° (from MeOH) (lit.,[8] m.p. 175—177°).

(iv) Similar oxidation as noted above of (4) [9] (300 mg) with $Pb(OAc)_4$ (468 mg) in AcOH (3 ml) gave an oil (412 mg), which was separated by preparative t.l.c. ($CHCl_3$–MeOH, 20 : 1 v/v) into (±)-13β-acetoxy-11-hydroxy- (17) (50 mg, 12.5%), m.p. 104—114°, and (±)-12-*acetoxy*-9-*hydroxy*-2,3,10-*trimethoxytetrahydroprotoberberine* (18) (207 mg, 51.9%) as prisms, m.p. 172—179° (from MeOH). Hydrolysis of (17) (20 mg) with concentrated HCl (0.2 ml) and H_2O

TABLE 1

Microanalytical data for new compounds

Compound	Formula (mol. wt.)	Calc. (%) C	Calc. (%) H	Calc. (%) N	Found (%) C	Found (%) H	Found (%) N
(1)	$C_{20}H_{23}NO_4$ (341.39)	70.36	6.79	4.10	70.15	6.9	3.8
(13)	$C_{20}H_{23}NO_5$		357.1576			357.1566 [a]	
(14)	$C_{20}H_{23}NO_5$		357.1576			357.1589 [a]	
(15)	$C_{21}H_{25}NO_5 \cdot 0.25H_2O$ (375.92)	67.09	6.84	3.72	67.1	7.0	3.65
(18)	$C_{22}H_{25}NO_6$ (399.43)	66.15	6.31	3.51	66.2	6.3	3.5
(20)	$C_{24}H_{27}NO_7$ (441.46)	65.29	6.16	3.17	65.05	6.25	3.05
(23)	$C_{22}H_{27}NO_5$ (385.44)	68.55	7.06	3.63	68.6	6.95	3.65
(25)	$C_{21}H_{25}NO_5 \cdot HCl$ (407.90)	61.84	6.43	3.43	61.85	6.45	3.5
(26)	$C_{22}H_{25}NO_6$ (399.43)	66.15	6.31	3.51	66.1	6.35	3.55
(27)	$C_{22}H_{24}NO_5I \cdot H_2O$ (527.35)	50.10	4.97	2.66	49.85	4.9	2.4
(28)	$C_{21}H_{27}NO_4$ (357.43)	70.56	7.61	3.92	70.5	7.55	3.9
(30)	$C_{23}H_{29}NO_6$ (415.47)	66.49	7.04	3.37	66.45	7.15	3.35
(31)	$C_{23}H_{31}NO_5 \cdot 0.5H_2O$ (410.50)	67.29	7.85	3.41	67.0	7.9	3.5
(35)	$C_{24}H_{27}NO_7$ (441.46)	65.29	6.16	3.17	65.45	6.25	3.2
(38)	$C_{21}H_{25}NO_5$ (371.42)	67.90	6.78	3.77	67.75	7.0	3.75
(39)	$C_{21}H_{25}NO_5$ (371.42)	67.90	6.78	3.77	68.05	6.85	3.7
(40)	$C_{24}H_{27}NO_7$ (441.46)	65.29	6.16	3.17	65.4	6.25	3.25
(41)	$C_{24}H_{27}NO_7$ (441.46)	65.29	6.16	3.17	65.4	6.3	3.2
(42)	$C_{21}H_{25}NO_5$ (371.42)	67.90	6.78	3.77	67.85	6.85	3.8

[a] High resolution mass spectral data.

* The authors thank Professor M. Shamma for this terminology.

TABLE 2

Spectral data for tetrahydroprotoberberines

Compound	$\nu_{max.}$/cm^{-1}	δ ArH	δ 5-H	δ 13-H	δ OMe	δ Others	m/e M^+	m/e Base peak
(*a*) 5-Oxygenated tetrahydroprotoberberines								
(13)	3 530 (OH)	6.58, 6.67, 6.72, 6.92	4.48 (br s, $W_{\frac{1}{2}}$ 6 Hz)		3.87 (6 H), 3.90		357	164
(14)	3 540 (OH)	6.52, 7.04, 6.60 (2 H)	4.80 (dd, *J* 4 and 8 Hz)		3.83 (9 H)		357	164
(15)		6.55, 6.62, 6.71, 6.81	4.49 (m)		3.84, 3.89, 3.86 (6 H)			
(16)		6.58, 6.62, 6.70, 7.10	4.85 (dd, *J* 4 and 8 Hz)		3.86 (9 H), 3.90			
(35)	1 760, 1 725 (OAc)	6.62, 6.70, 7.06, 7.08	6.00 (t, *J* 2.5 Hz)		3.87 (9 H)	2.12 (5β-OAc) 2.33 (2-OAc)		
(36) [a]	3 540 (OH)	6.68 (2 H), 7.18 (2 H)	4.84 (t, *J* 2.5 Hz)		3.72, 3.78 (6 H)			
(37)	1 715 (OAc)	6.64, 6.75, 6.85, 6.95	5.97 (t, *J* 3 Hz)		3.88, 3.89, 3.91, 3.95	2.12 (5β-OAc)		
(38)	3 540 (OH)	6.61, 6.57, 6.74, 6.96	4.58 (dd, *J* 5 and 10 Hz)		3.79 (6 H), 3.83	3.51 (5α-OMe)	371	164
(39)	3 540 (OH)	6.49, 6.57, 6.75, 6.83	4.20 (t, *J* 2.5 Hz)		3.78 (6 H), 3.82	3.43 (5β-OMe)	371	164
(*b*) 13-Oxygenated tetrahydroprotoberberines								
(17)	3 530 (OH) 1 720 (OAc)	6.57, 6.59, 6.72, 7.00		6.53 (d, *J* 2.5 Hz)	3.85 (9 H)	1.71 (13β-OAc)		
(19)		6.57, 6.61, 6.78, 6.93		4.80 (br s, $W_{\frac{1}{2}}$ 4 Hz)	3.85 (6 H), 3.88 (6 H)			
(40)	1 760, 1 730 (OAc)	6.61, 6.76, 6.78, 6.83		6.14 (d, *J* 8 Hz)	3.76, 3.83, 3.85	2.24 (13α-OAc) 2.31 (10-OAc)		
(41)	1 765, 1 730 (OAc)	6.58, 6.70, 6.80, 7.03		6.54 (d, *J* 2.5 Hz)	3.76, 3.83 (6 H)	1.72 (13β-OAc) 2.27 (10-OAc)		
(42)	3 530 (OH)	6.59 (2 H), 6.90, 7.42		4.64 (d, *J* 9 Hz)	3.81, 3.83, 3.87	3.32 (13α-OMe)	371	180
(*c*) Other tetrahydroprotoberberines								
(1)	3 540 (OH)	6.52 (2 H), 6.59, 6.74			3.74, 3.78 (6 H)			
(18)	3 530 (OH) 1 760 (OAc)	6.50, 6.60, 6.70			3.78, 3.85 (6 H)	2.27 (12-OAc) 3.03 (d, 8α-H) [b] 4.20 (d, 8β-H) [b]		
(20)	1 760 (OAc)	6.61 (2 H), 6.67			3.76, 3.85 (6 H)	2.27, 2.30 (9- and 12-OAc) 3.46 (d, 8α-H) [b] 3.99 (d, 8β-H) [b]		
(23)		6.38, 6.59, 6.78			3.78, 3.79, 3.85 (6 H), 3.88	3.33 (d, 8α-H) [b] 4.21 (d, 8β-H) [b]	385	194

[a] N.m.r. spectrum run in [$^2H_5$]pyridine solution. [b] *J* 16 Hz.

TABLE 3

Spectral data for 3-phenyltetrahydroisoquinolines

Compound	$\nu_{max.}$/cm^{-1}	δ ArH	δ OMe	δ NMe	δ Others	m/e M^+	m/e Base peak
(28)	3 540 (OH)	6.55, 6.57, 6.68, 7.04	3.81, 3.83, 3.87	2.16	1.19 (3 H, t) [a] 2.67 (2 H, q) [a]		
(30)	3 530 (OH) 1 755 (OAc)	6.50, 6.68, 7.05	3.82, 3.85, 3.87	2.19	1.19 (3 H, t) [a] 2.19 (5-OAc) 2.67 (2 H, q) [a] 3.36 (d, 1α-H) [b] 4.31 (d, 1β-H) [b]	415	208
(31)		6.21, 6.48, 6.78	3.59, 3.64, 3.71 (9 H)	2.08	4.25 (d, 1β-H) [b]		

[a] *J* 7.5 Hz. [b] *J* 16 Hz.

(0.1 ml) at room temperature for 1 h furnished (±)-10,13β-dihydroxy-2,3,11-trimethoxytetrahydroprotoberberine (17 mg, 95%) as an oil, which was methylated with CH_2N_2–MeOH to yield an oil (quantitative), purification of which on preparative t.l.c. ($CHCl_3$–MeOH, 24 : 1 v/v) afforded (±)-13β-hydroxy-2,3,10,11-tetramethoxytetrahydroprotoberberine (19) [7 mg, 37.6% from (17)] as prisms, m.p. 200—203° (from MeOH–ether) (lit.,[10] 198—200°).

Acetylation of (18) (200 mg) with Ac_2O–pyridine gave an oil (290 mg), which was purified on preparative t.l.c. ($CHCl_3$–MeOH, 32 : 1 v/v) to yield (±)-9,12-*diacetoxy*-2,3,10-*trimethoxytetrahydroprotoberberine* (20) (188 mg, 85.1%) as prisms, m.p. 164—169° (from benzene). Methylation of (18) (50 mg) with CH_2N_2–MeOH gave (±)-2,3,9,10,12-*pentamethoxytetrahydroprotoberberine* (23) (quantitative) as prisms, m.p. 187—189° (from MeOH), which was identical

in all respects with an authentic specimen (see later).

(Z)-6,7-*Dimethoxy*-1-(2,4,5-*trimethoxybenzylidene*)-1,2,3,4-*tetrahydroisoquinoline*-2-*carbaldehyde* (26).—A mixture of β-(3,4-dimethoxyphenyl)ethylamine (4.0 g) and methyl 2,4,5-trimethoxyphenylacetate (4.4 g) was heated at 160° for 3 h. Usual work-up gave *N*-β-[(3,4-dimethoxyphenyl)ethyl]-2,4,5-trimethoxyphenylacetamide (5.6 g, 75.7%) as needles, m.p. 118.5—119° (from EtOH) (Found: C, 64.8; H, 7.05; N, 3.65. $C_{21}H_{27}NO_6$ requires C, 64.76; H, 6.99; N, 3.60%); $\nu_{max.}$ 1 655 cm^{-1} (NHCO). A solution of the amide (4.5 g) and $POCl_3$ (21 ml) in CH_2Cl_2 (80 ml) was refluxed for 2.5 h. Usual work-up afforded 3,4-*dihydro*-6,7-*dimethoxy*-1-(2,4,5-*trimethoxybenzyl*)*isoquinoline* (25) *hydrochloride* (4.7 g, quantitative) as prisms, m.p. 229—232° (from MeOH).

A mixture of (25) (1.66 g), fused AcONa (2.64 g), and acetic formic anhydride (13 ml) was stirred at room temperature for 3 h. The mixture was poured into MeOH (20 ml) and the whole allowed to stand at room temperature for 30 min. Removal of the solvent under reduced pressure gave a residue which was taken up in $CHCl_3$. Usual work-up gave the *aldehyde* (26) (1.54 g, 99.4%), m.p. 143—143.5° (from MeOH); $\nu_{max.}$ 1 660 cm^{-1} (NCHO); δ 3.80, 3.86, and 3.96 (each 3 H, s, OMe), 3.90 (6 H, s, 2 × OMe), 6.51, 6.60, and 7.25 (each 1 H, s, ArH), 6.87 (2 H, s, 2 × ArH), and 8.10 (1 H, s, NCHO).

Alternative Synthesis of (23).—A mixture of the enamide (26) (150 mg), dioxan (60 ml), Bu^tOH (20 ml), and 47% HI (1 ml) was irradiated with a 400 W high-pressure mercury lamp (Pyrex filter) under a current of argon for 5 h to precipitate crystals, which were collected and dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with brine, saturated aqueous Na_2SO_3, and further brine. Removal of the solvent gave 2,3,9,10,12-*pentamethoxyprotoberberine iodide* (27) (125 mg, 65.4%) as plates, m.p. 230—234° (from MeOH); δ (CF_3CO_2D) 4.06 and 4.13 (each 3 H, s, OMe), 4.22 (9 H, s, 3 × OMe), and 7.04, 7.36, 7.64, 8.85, and 9.51 (each 1 H, s, ArH).

$NaBH_4$ reduction of (27) (50 mg) in MeOH at room temperature for 2 h gave an oil, which was purified by preparative t.l.c. ($CHCl_3$–MeOH, 26 : 1 v/v) yielding (23) (31 mg, 81.6%) as prisms, m.p. 185—188° (MeOH).

(±)-3-(2-*Ethyl*-4,5-*dimethoxyphenyl*)-6-*hydroxy*-7-*methoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (28).—Treatment of (±)-11-benzyloxytetrahydroprotoberberine (29) [16] (4.3 g) with MeI (60 ml) in MeOH (50 ml) at room temperature for 3 days and evaporation of the excess of MeI precipitated crystals. A mixture of the collected crystals, KOH (80 g), and MeOH (600 ml) was refluxed for 4 h. Work up as usual gave (±)-6-benzyloxy-3-(4,5-dimethoxy-2-vinylphenyl)-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (4.3 g, 96.6%) as prisms, m.p. 102—104° (n-hexane–acetone) (Found: C, 75.35; H, 6.85; N, 3.1. $C_{28}H_{31}NO_4$ requires C, 75.48; H, 7.01; N, 3.14%); δ 2.16 (3 H, s, NMe), 3.84 (6 H, s, 2 × OMe), 3.89 (3 H, s, OMe), 5.06 (2 H, s, OCH_2Ph), 5.18 (1 H, dd, *J* 2.5 and 11 Hz), 5.48 (1 H, dd, *J* 2.5 and 17 Hz), 6.58 and 6.61 (each 1 H, s, ArH), and 6.97 (2 H, s, ArH). Catalytic hydrogenation of the vinyl compound (4.0 g) over 10% palladium–charcoal gave the *tetrahydroisoquinoline* (28) (3.0 g, 93%), m.p. 139—139.5° (from benzene).

Oxidation of (28).—The same oxidative procedure as noted earlier [(28) (800 mg), $Pb(OAc)_4$ (1.192 g), AcOH (8 ml)] gave an oil (1.109 g), which was purified by preparative t.l.c. ($CHCl_3$–MeOH 22 : 1 v/v) to afford (±)-5-*acetoxy*-3-(2-*ethyl*-4,5-*dimethoxyphenyl*)-8-*hydroxy*-6-*methoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (30) (794 mg, 85.6%) as prisms, m.p. 167—168° (from EtOH); the *diacetate* had m.p. 140—141° (from EtOH) (Found: C, 65.5; H, 6.85; N, 3.0. $C_{25}H_{31}NO_7$ requires C, 65.62; H, 6.83; N, 3.06%); $\nu_{max.}$ 1 760 cm^{-1} (OAc); δ 2.09, 2.14, and 2.26 (each 3 H, s, NMe + 2 × OAc), 4.20 (1 H, d, *J* 16 Hz, 1β-H), and 6.49, 6.53, and 6.87 (each 1 H, s, ArH). Methylation of (30) (143 mg) with CH_2N_2–MeOH gave an amorphous mass (124 mg), which was purified by preparative t.l.c. ($CHCl_3$–MeOH 20 : 1 v/v) to yield (±)-3-(2-*ethyl*-4,5-*dimethoxyphenyl*)-5,7,8-*trimethoxy*-2-*methyl*-1,2,3,4-*tetrahydroisoquinoline* (31) (80 mg, 58%) as prisms, m.p. 80—81° (from MeOH), identical with an authentic sample obtained in the following manner.

Alternative Synthesis of (31).—A mixture of the methiodide (100 mg) (m.p. 260—264°) of (23) and KOH (4 g) in MeOH (13 ml) was refluxed for 3 h. Usual work-up gave (±)-3-(4,5-dimethoxy-2-vinylphenyl)-5,7,8-trimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (80 mg, quantitative) as prisms, m.p. 86—87° (from EtOH) [Found: M^+, 399.202 5. $C_{23}H_{29}NO_5$ requires *M* 399.204 6]; δ 2.14 (3 H, s, NMe), 4.22 (1 H, d, *J* 16 Hz, 1β-H), 5.12 (1 H, dd, *J* 2.5 and 11 Hz), 5.42 (1 H, dd, *J* 2.5 and 17 Hz), 3.69, 3.74, and 3.85 (each 3 H, s, OMe), 3.79 (6 H, s, 2 × OMe), and 6.32, 6.91, and 6.94 (each 1 H, s, ArH). Catalytic hydrogenation of the vinyl compound (76 mg) over 10% palladium–charcoal gave (31) (72 mg, 94.7%), m.p. 80—81°.

Treatment with Ac_2O–*Concentrated* H_2SO_4 *of the* p-*Quinol Acetates* (5) *and* (6).—*Compound* (5). Concentrated H_2SO_4 (0.8 ml) was added dropwise to a stirred, ice-cooled solution in Ac_2O (4 ml) of the acetate (5) obtained from (1) (400 mg) and stirring was continued at room temperature for 1 h. Usual work-up followed by chromatography of the product (468 mg) on silica gel (eluant $CHCl_3$) gave (±)-2,5β-*diacetoxy*-3,10,11-*trimethoxytetrahydroprotoberberine* (35) (330 mg, 64.1%) as needles, m.p. 150—151° (from acetone–light petroleum). Hydrolysis of (35) (200 mg) with concentrated HCl (4 ml) at room temperature for 1 h gave an oil, which was purified by preparative t.l.c. ($CHCl_3$–MeOH 20 : 1 v/v) to yield (±)-2,5β-dihydroxy-3,10,11-trimethoxytetrahydroprotoberberine (36) (103 mg, 63.6%), m.p. 165—170°, reacetylation of which afforded (35). Methylation of (36) (92 mg) with CH_2N_2 furnished (±)-5β-hydroxy-2,3,10,11-tetramethoxytetrahydroprotoberberine (15) (80 mg, 83.3%) as needles, m.p. 189—190° (from CH_2Cl_2–acetone) (lit.,[8] 194—195°); the (±)-5β-acetate (37) had m.p. 184—186° (lit.,[8] 188—189°).

Compound (6). Similar treatment with Ac_2O–concentrated H_2SO_4 of (6) obtained from (2) (400 mg) gave an oil (538 mg), which was chromatographed on silica gel (eluant $CHCl_3$) to give (±)-10,13β-*diacetoxy*-2,3,11-*trimethoxytetrahydroprotoberberine* (41) (183 mg, 35%) as prisms, m.p. 166—167° (from acetone–light petroleum), and the (±)-10,13α-*isomer* (40) (61 mg, 12%) as needles, m.p. 168—169° (from acetone–light petroleum), respectively.

Treatment with Aqueous KOH (5% *w/v*)–MeOH *of the* (±)-*Diacetates* (35), (41), *and* (40).—*Diacetate* (35). A mixture of (35) (200 mg), 5% w/v aqueous KOH (6 ml), and MeOH (6 ml) was stirred at room temperature for 1 h. The residue obtained after removal of the solvent was dissolved in H_2O and to the whole was added NH_4Cl (excess). The product was taken up in $CHCl_3$. Usual work-up gave an oil (260 mg), which was separated by preparative t.l.c. ($CHCl_3$–MeOH, 30 : 1 v/v) into (±)-2-*hydroxy*-3,5α-10,11-*tetramethoxytetrahydroprotoberberine* (38) (70 mg, 33%) as prisms, m.p. 179—

181° (decomp.) (from acetone), and (±)-2-*hydroxy*-3,5β,10,11-*tetramethoxytetrahydroprotoberberine* (39) (73 mg, 34.8%) as needles, m.p. 137.5—138° (from acetone–cyclohexane) [moving rate: (38) > (39)], respectively.

Diacetate (41). Similar treatment of (41) (250 mg) gave an oil (200 mg), which was purified by preparative t.l.c. ($CHCl_3$–MeOH, 20 : 1 v/v) yielding (±)-10-*hydroxy*-2,3,11,13α-*tetramethoxytetrahydroprotoberberine* (42) (61 mg, 29%) as needles, m.p. 146—148° (from acetone).

Diacetate (40). Similar treatment of (40) (84 mg) gave (42) (20 mg, 28.2%), m.p. 141—143°, identical (n.m.r. and i.r. spectra) with the sample obtained from (41).

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