Studies on the Syntheses of Heterocyclic Compounds. Part 679.† A Stereoselective Total Synthesis of (±)-Ophiocarpine; a Simple Route to 13-Hydroxyberbines

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Phenolic cyclisation of (1*R**)-1-[(α*R**)-α,3-dihydroxy-4-methoxybenzyl]-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (21) gave 10-methoxy-2,3-methylenedioxy-13aα-berbine-9,13β-diol (33) and the isomeric 11,13β-diol (34). 9-*O*-Methylation of the diol (33) gave (±)-ophiocarpine (3). A general synthesis of 13-hydroxyberbines from 1,2,3,4-tetrahydro-α-hydroxybenzylisoquinolines by Mannich reaction and phenolic cyclisation is described.

OPHIOCARPINE (3),[1] the only known protoberberine alkaloid having an alcoholic hydroxy-group in ring C, was first synthesised by Govindachari[2] from the phthalidylisoquinoline (1) and then by Elliott[3] by hydroxylation[4] of dihydroberberine (2).

† Part 678, T. Kametani, H. Inoue, T. Honda, T. Sugahara, and K. Fukumoto, preceding paper.

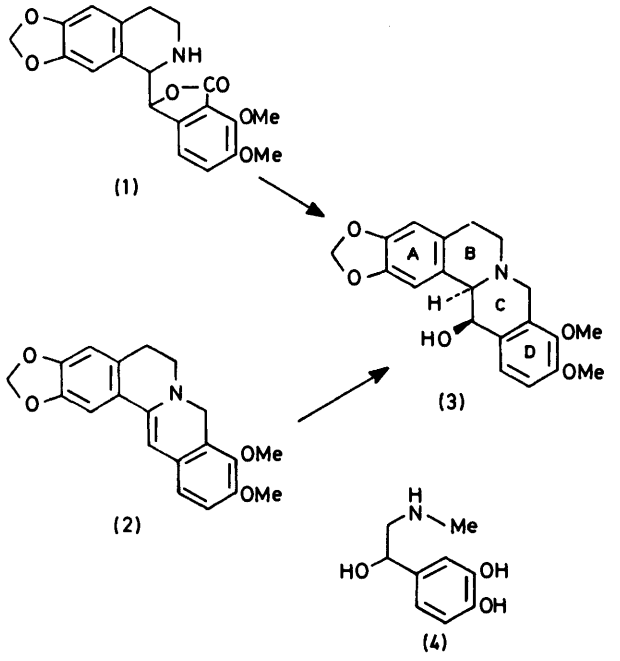
[1] T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids,' Hirokawa, Tokyo, and Elsevier, Amsterdam, 1968; 'The Chemistry of the Isoquinoline Alkaloids, Vol. 2,' The Sendai Institute of Heterocyclic Chemistry, Sendai, Japan, 1974.

[2] T. R. Govindachari and S. Rajadurai, *J. Chem. Soc.*, 1957, 557; T. R. Govindachari, S. Rajadurai, M. Sobramanian, and N. Viswanathan, *ibid*, 2943.

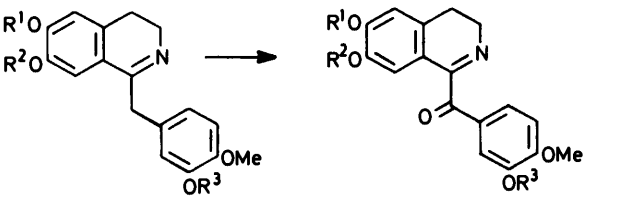
[3] I. W. Elliott, jun., *J. Heterocyclic Chem.*, 1967, **4**, 639.

[4] P. W. Jeffs and J. D. Scharver, *J. Org. Chem.*, 1975, **40**, 644.

In view of the structural similarity of 13-hydroxyberberines such as ophiocarpine (3) to adrenalin (4), we sought a simple synthesis of 13-hydroxyberbines.[5] We now report a general synthetic method and a total synthesis of ophiocarpine (3) by phenolic cyclisation.[6,7] We also describe an unusual reaction of a β-hydroxy-*N*-norlaudanosine in an attempted Mannich-type cyclisation.

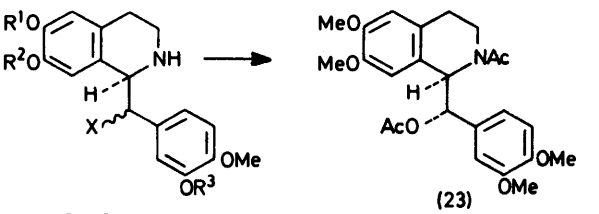


First we investigated the possibility of a berbine synthesis from non-phenolic α-hydroxybenzylisoquinolines by Mannich cyclisation. The key intermediates, the 1,2,3,4-tetrahydro-1-(α-hydroxybenzyl)isoquinolines (15)—(22), could be synthesised by a classical method:[8-13] oxidation of 3,4-dihydropapaverine (5)[8] in methanol by air at room temperature gave 3,4-dihydropapaveraldine (9),[8] which was reduced with sodium borohydride to afford (1*R**)-1,2,3,4-tetrahydro-1-[(α*S**)-α-hydroxy-3,4-dimethoxybenzyl]-6,7-dimethoxyisoquinoline (15). The presence of amino- and hydroxy-functions was proved by conversion of (15) into the *N*-acetyl acetate (23), which showed two i.r. carbonyl bands at 1 735 and 1 635 cm^{-1}.

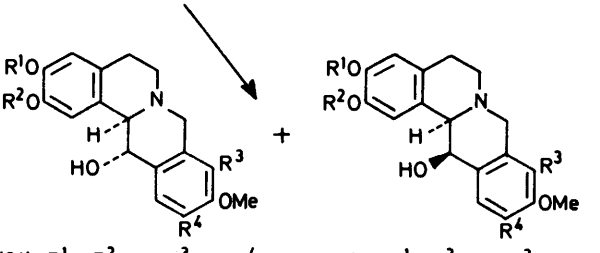


(5) $R^1 = R^2 = R^3 = Me$
(6) $R^1R^2 = CH_2$, $R^3 = Me$
(7) $R^1 = R^2 = Me$, $R^3 = CH_2Ph$
(8) $R^1R^2 = CH_2$, $R^3 = CH_2Ph$

(9) $R^1 = R^2 = R^3 = Me$
(10) $R^1R^2 = CH_2$, $R^3 = Me$
(11) $R^1 = R^2 = Me$, $R^3 = CH_2Ph$
(12) $R^1 = R^2 = Me$, $R^3 = H$
(13) $R^1R^2 = CH_2$, $R^3 = CH_2Ph$
(14) $R^1R^2 = CH_2$, $R^3 = H$

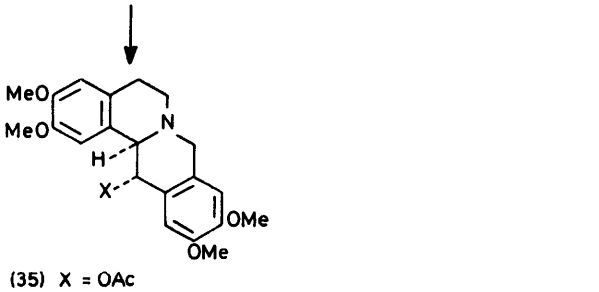


(15) $R^1 = R^2 = R^3 = Me$, X = ---OH
(16) $R^1R^2 = CH_2$, $R^3 = Me$, X = ---OH
(17) $R^1 = R^2 = Me$, $R^3 = H$, X = ---OH
(18) $R^1 = R^2 = Me$, $R^3 = CH_2Ph$, X = ---OH
(19) $R^1 = R^2 = Me$, $R^3 = H$, X = ◄OH
(20) $R^1R^2 = CH_2$, $R^3 = CH_2Ph$, X = ---OH
(21) $R^1R^2 = CH_2$, $R^3 = H$, X = ◄OH
(22) $R^1R^2 = CH_2$, $R^3 = H$, X = ---OH



(24) $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = OMe$
(25) $R^1R^2 = CH_2$, $R^3 = H$, $R^4 = OMe$
(26) $R^1 = R^2 = Me$, $R^3 = OH$, $R^4 = H$
(27) $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = OH$
(28) $R^1R^2 = CH_2$, $R^3 = OH$, $R^4 = H$
(29) $R^1R^2 = CH_2$, $R^3 = H$, $R^4 = OH$
(30) $R^1R^2 = CH_2$, $R^3 = OMe$, $R^4 = H$

(31) $R^1 = R^2 = Me$, $R^3 = OH$, $R^4 = H$
(32) $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = OH$
(33) $R^1R^2 = CH_2$, $R^3 = OH$, $R^4 = H$
(34) $R^1R^2 = CH_2$, $R^3 = H$, $R^4 = OH$



(35) X = OAc
(36) X = H

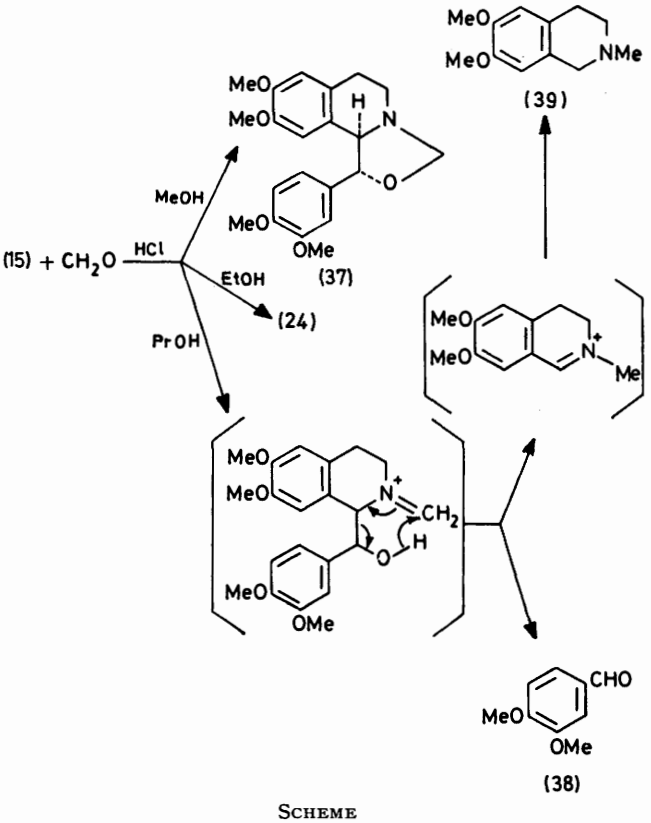
[5] M. Shamma, 'The Isoquinoline Alkaloids, Chemistry and Pharmacology,' Academic Press, New York, 1972.
[6] T. Kametani, K. Fukumoto, K. Kigasawa, M. Hiiragi, and H. Ishimaru, *Heterocycles*, 1975, **3**, 311.
[7] T. Kametani, K. Fukumoto, H. Agui, H. Yagi, K. Kigasawa, H. Sugawara, M. Hiiragi, T. Hayasaka, and H. Ishimaru, *J. Chem. Soc.* (*C*), 1968, 112.
[8] T. Kametani and K. Fukumoto, *J. Pharm. Soc. Japan*, 1963, **83**, 1031.
[9] J. A. Weisbach, J. L. Kirkpatrick, E. Macko, and B. Douglas, *J. Medicin. Chem.*, 1968, **11**, 760.
[10] J. S. Buck, W. H. Perkin, jun., and T. S. Stevens, *J. Chem. Soc.*, 1925, **127**, 675.
[11] R. H. Haworth, W. H. Perkin, jun., and J. Rankin, *J. Chem. Soc.*, 1925, **127**, 2020.
[12] J. S. Buck, W. H. Perkin, jun., and T. S. Stevens, *J. Chem. Soc.*, 1925, **127**, 1470.
[13] T. Kametani, M. S. Premila, S. Hirata, H. Seto, H. Nemoto, and K. Fukumoto, *Canad. J. Chem.*, 1975, **53**, 3824.

It was possible that the reduction of 3,4-dihydropapaveraldine-type compounds furnished mixtures of diastereoisomers. However, we found that the above reduction of (9) gave the (1*R**,α*S**)-isomer (15) in almost pure state and in high yield. The stereochemistry of this product (15) was determined by n.m.r. spectral analysis of the berbine (24) which was synthesised by Mannich cyclisation of (15) with formalin (see later). The preferential formation of the (1*R**,α*S**)-isomer (15) may be predicted on the basis of Cram's rule.[14] Similar phenomena have been reported by Shamma.[15]

Mannich cyclisation of the hydrochloride of (15) with 36% formalin was carried out in boiling ethanol for 2 h to give a moderate yield of 13α-hydroxyxylopinine (24), identified by spectroscopic and chemical methods. The presence of the *trans*-quinolizidine system was proved by Bohlmann bands,[16] and the mass spectrum revealed two characteristic fragment ions[5] at *m/e* 192 and 180. The latter ion showed the presence of the hydroxy-group on ring C, which was supported by the n.m.r. spectrum [δ 4.60 (C*H*·OH)] and the formation of an acetate (35). Catalytic hydrogenation of (35) gave (±)-xylopinine (36), identical with an authentic sample.[17] Thus, it was clear that the Mannich reaction product (24) possessed the 13-hydroxyberbine system. The relative configurations at C-13 and -13a were deduced from i.r. and n.m.r. spectra. The i.r. spectrum showed only free hydroxy-absorption at 3 580 cm^{-1}, and the *J* value of the methine proton at C-13 is 8 Hz, indicating the hydroxy group to be *trans* to the nitrogen lone pair and the hydrogen atoms at C-13a and -13 to be *trans* to each other;[18] in turn, the configuration of the reduction product (15) is therefore known with certainty.

Similarly, 3,4-dihydro-6,7-methylenedioxy-1-veratroylisoquinoline (10),[12] derived from (6), was reduced to the (1*R**)-1,2,3,4-tetrahydro-1-[(α*S**)-α-hydroxybenzyl]isoquinoline (16) with sodium borohydride, which was converted into the 13α-hydroxyberbine (25) in good yield by Mannich cyclisation.

Interestingly, Mannich cyclisation of the hydrochloride of (15) in boiling methanol or propan-1-ol gave other products in addition to the 13-hydroxyberbine (24). The reaction in methanol afforded the tetrahydrooxazole derivative (37), and the reaction in propanol yielded veratraldehyde (38) and the tetrahydroisoquinoline (39). The n.m.r. spectrum of (37) revealed methylene protons [δ 4.68 and 4.81 (AB-type quartet, *J* 12 Hz)] and two adjacent methine protons [δ 4.51 and 5.10 (as each d, *J* 8 Hz)] in addition to five aromatic protons and four protons on a tetrahydroisoquinoline ring. Treatment of (37) with acetic anhydride and pyridine gave the *NO*-diacetyl derivative (23). Veratraldehyde (38) and the tetrahydroisoquinoline (39) were identified by spectroscopic data and comparisons with the authentic samples.[19] The formation of these products can be explained by a retro-ene reaction[20] (Scheme).



SCHEME

Since the Mannich reaction of (15) under acidic conditions afforded abnormal products, we examined a synthesis of 13-hydroxyberbines in neutral medium by phenolic cyclisation.[6,7] Debenzylation of 1-(3-benzyloxy-4-methoxybenzoyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (11) [prepared from the 1-benzyl-3,4-dihydroisoquinoline (7)[7] by oxidation in air] with ethanolic hydrochloric acid under reflux gave the corresponding phenolic isoquinoline (12), which was reduced with sodium borohydride to afford a diastereoisomeric mixture of alcohols (17) and (19). Isolation of the (1*R**,α*R**)-isomer (19), the minor product, in a pure state could not be achieved, although purification of the (1*R**,α*S**)-isomer (17), the major component, was easy. Phenolic cyclisation of the (1*R**,α*S**)-alcohol (17) with formalin in boiling ethanol without acid for 2 h gave two products in the ratio 1 : 1, separable by chromatography on silica gel. Both products showed Bohlmann i.r. bands at 2 850—2 750 cm^{-1} and n.m.r. signal of the methine proton at C-13 as a doublet, *J* 9.0 Hz. One product showed n.m.r. signals for two neighbouring aromatic protons [δ 6.80 and 7.05 (each d, *J* 8 Hz)] and two isolated aromatic protons, and the other four

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[15] M. Shamma and C. D. Jones, *J. Amer. Chem. Soc.*, 1970, **92**, 4943.
[16] F. Bohlmann, *Chem. Ber.*, 1958, **91**, 2157.
[17] T. Kametani, Y. Kato, and K. Fukumoto, *J.C.S. Perkin I*, 1974, 1712.
[18] A. R. Battersby and H. Spencer, *J. Chem. Soc.*, 1965, 1087.
[19] T.-H. Yang and C.-M. Chen, *J. Chinese Chem. Soc.* (*Formosa*), 1970, **17**, 54.
[20] K. Alder and H. von Brachel, *Annalen*, 1962, **651**, 141.

isolated aromatic protons. Therefore, the first product was identified as 2,3,10-trimethoxyberbine-9,13α-diol (26) and the isomeric 11,13α-diol (27).

Direct reduction of the 1-benzoyl-3,4-dihydroisoquinoline (11) with sodium borohydride produced the (1*R**,α*S**)-alcohol (18), debenzylation of which with hot ethanolic hydrochloric acid afforded, surprisingly, the phenolic (1*R**,α*R**)-alcohol (19). Although the alcohol (19) was closely similar to its epimer (17) in i.r. spectra, the n.m.r. spectra showed a marked difference. Thus, the (1*R**,α*R**)-isomer (19) showed signals for an α-methine proton at δ 4.57 as a doublet (*J* 8 Hz) and five aromatic protons at δ 5.80 (1 H, s), 6.50 (1 H, s), 6.53 (2 H, s), and 6.95 (1 H, s), but the C-1 methine proton signal was obscured by overlapping with the other resonances. The (1*R**,α*S**)-isomer (17) showed C-1 and α-methine proton signals at δ 4.12 and 4.90, each as a doublet (*J* 5 Hz), in addition to signals for five aromatic protons at δ 6.55 (1 H, s), 6.65 (1 H, s), 6.73 (2 H, s), and 6.85 (1 H, s). The appearance of both methine proton signals of the (1*R**,α*S**)-isomer at lower field indicated that the α-hydroxy-group of the former was *cis* to the C-1 hydrogen atom, and the α-hydrogen atom was *cis* to the nitrogen lone pair.

Phenolic cyclisation of the (1*R**,α*R**)-alcohol (19) with formalin afforded two 13β-hydroxyberbines (31) and (32) in the ratio 1 : 1, separable by virtue of their different solubility in organic solvents. The product (31), soluble in ether, showed n.m.r. signals for the C-8 methylene protons at δ 3.46 and 4.22 as doublets (*J* 16 Hz), for the C-13 proton at 4.75 as a doublet (*J* 1.5 Hz),[18] and for the C-11 and -12 aromatic protons at 6.75 and 6.95 as doublets (*J* 8 Hz), in addition to signals for two isolated aromatic protons (6.43 and 6.60). Compound (32), insoluble in ether, showed four isolated aromatic proton signals at 6.55, 6.61, 6.79, and 6.98 in addition to a C-13 methine proton signal at 4.70 as a distorted doublet (*J* 1.5 Hz).

On the basis of the foregoing results, we attempted a total synthesis of ophiocarpine (3) as follows. Oxidation of 1-(3-benzyloxy-4-methoxybenzyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (8)[21] in methanol with air gave the 1-benzoyl derivative (13), reduction of which with sodium borohydride afforded the (1*R**,α*S**)-alcohol (20) showing n.m.r. signals for two methine protons at δ 4.10 and 4.84 as doublets (*J* 6 Hz). Debenzylation with hot ethanolic hydrochloric acid furnished the phenolic (1*R**,α*R**)-alcohol (21), which revealed an α-methine proton signal at δ 4.65 as a doublet, *J* 6 Hz; the 1-methine proton signal was obscured. Phenolic cyclisation of (21) with formalin in ethanol under reflux for 2 h gave the two phenolic 13-hydroxyberbines (33) and (34) in the ratio 1 : 1, which were separated by chromatography on silica gel. The product (33) in its n.m.r. spectrum showed signals for the C-8 methylene protons at δ 3.50 and 4.22, each as a doublet (*J* 16 Hz), the C-13 methine proton at 4.73 as a distorted doublet (*J* 2 Hz), and the two neighbouring aromatic protons at 6.75 and 6.95 as doublets (*J* 8 Hz), in addition to signals for two isolated aromatic protons (6.58 and 6.76). Compound (34) showed the C-13 proton signal as a doublet (*J* 1.5 Hz) at 4.70, and four isolated aromatic protons. Methylation of the 9,13β-diol (33) with diazomethane afforded (±)-ophiocarpine (3), m.p. 254—256°, whose i.r. and n.m.r. spectra were identical with those of authentic (±)-ophiocarpine provided by Professor Takemoto and Dr. Kondo.[22]

(±)-Epiophiocarpine (30) was also synthesised by our method; debenzylation of the 1-benzoylisoquinoline (13), followed by reduction with sodium borohydride of the resulting phenolic base (14), gave the (1*R**,α*S**)-alcohol (22), δ 4.15 and 4.86 (each d, *J* 5.5 Hz). Phenolic cyclisation with formalin as above afforded a mixture of the 9,13α-diol (28) [δ 3.5 (d, *J* 16 Hz, 8α-H), 4.03 (d, *J* 16 Hz, 8β-H), 4.58 (d, *J* 8 Hz, 13β-H), 6.35 (s, ArH), 6.73 (d, *J* 8 Hz, 11-H), 7.0 (d, *J* 8 Hz, 12-H), and 7.37 (s, ArH)] and 11,13α-diol (29) [δ 4.68 (d, *J* 8 Hz, 13β-H), and 6.53, 6.56, 7.03, and 7.40 (each s, ArH)]. Methylation of the product (28) with diazomethane gave (±)-epiophiocarpine (30), m.p. 175—177°, whose n.m.r. spectrum was in good accord with reported data.[23]

EXPERIMENTAL

I.r. spectra were measured with a Hitachi 215 spectrophotometer, u.v. spectra with a Hitachi 124 spectrophotometer, n.m.r. spectra with a JNM-PMX-60 spectrometer (tetramethylsilane as an internal standard), and mass spectra with a Hitachi RMU-7 spectrometer.

1-(3-*Benzyloxy*-4-*methoxybenzoyl*)-3,4-*dihydro*-6,7-*dimethoxyisoquinoline* (11).—A solution of 1-(3-benzyloxy-4-methoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (7)[7] (15.0 g) in methanol (250 ml) was stirred in air at room temperature for 2 weeks. The separated solid was collected by filtration and recrystallised from methanol to give the 1-*benzoylisoquinoline derivative* (11) (13.27 g, 93.1%) as needles, m.p. 126—128° (Found: C, 72.1; H, 5.85; N, 3.15. $C_{26}H_{25}NO_5$ requires C, 72.35; H, 5.85; N, 3.25%), $\nu_{max.}$ ($CHCl_3$) 1 660 cm^{-1} (C=O), δ (CCl_4) 3.70 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.83 (3 H, s, OMe), 5.09 (2 H, s, O·C*H*$_2$Ph), and 6.50—7.70 (10 H, m, ArH).

3,4-*Dihydro*-1-(3-*hydroxy*-4-*methoxybenzoyl*)-6,7-*dimethoxyisoquinoline* (12).—A mixture of the isoquinoline (11) (5 g), ethanol (100 ml), and concentrated hydrochloric acid (100 ml) was refluxed for 13 h, then the excess of reagent and ethanol were evaporated off *in vacuo*. The residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to give the *phenolic base* (12) (2.8 g, 70.9%) as needles, m.p. 167—168° (from ethanol) (Found: C, 66.25; H, 5.7; N, 3.8. $C_{19}H_{19}NO_5$,0.25H_2O requires C, 66.0; H, 5.7; N, 4.05%), $\nu_{max.}$ ($CHCl_3$) 3 550 (OH) and 1 660 cm^{-1} (C=O), δ ($CDCl_3$) 3.73 (3 H, s, OMe), 3.89 (6 H, s, 2 × OMe), and 6.65—7.61 (5 H, m, ArH), *m/e* 341 (M^+).

[21] T. Kametani, K. Fukumoto, T. Terui, K. Yamaki, and E. Taguchi, *J. Chem. Soc.* (*C*), 1971, 2709.

[22] T. Takemoto and M. Kondo, *J. Pharm. Soc. Japan*, 1962, **82**, 1413.

[23] M. Ohta, H. Tani, and S. Morozumi, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 1972.

1-(3-*Benzyloxy*-4-*methoxybenzoyl*)-3,4-*dihydro*-6,7-*methylenedioxyisoquinoline* (13).—A solution of 1-(3-benzyloxy-4-methoxybenzyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (8) (5.0 g) in methanol (75 ml) was treated and worked up as above to give the 1-*benzoyl*-3,4-*dihydroisoquinoline* (13) (3.74 g, 72.35%) as needles, m.p. 72—73° (from methanol) (Found: C, 72.1; H, 5.1; N, 3.3. $C_{25}H_{21}NO_5$ requires C, 72.3; H, 5.1; N, 3.35%), $\nu_{max.}$ ($CHCl_3$) 1 660 (C=O) and 1 630 cm^{-1} (C=N), δ (CCl_4) 3.83 (3 H, s, OMe), 5.07 (2 H, s, O·CH_2Ph), 5.87 (2 H, s, O·CH_2·O), and 6.58—7.57 (10 H, m, ArH).

3,4-*Dihydro*-1-(3-*hydroxy*-4-*methoxybenzoyl*)-6,7-*methylenedioxyisoquinoline* (14).—A mixture of the isoquinoline (13) (3.5 g), concentrated hydrochloric acid (80 ml), and ethanol (80 ml) was refluxed for 13 h and worked up as above to give the *phenolic isoquinoline* (14) (1.47 g, 53.65%) as needles, m.p. 211—212° (from methanol) (Found: C, 66.15; H, 4.9; N, 4.1. $C_{18}H_{15}NO_5$ requires C, 66.45; H, 4.65; N, 4.3%), $\nu_{max.}$ (KBr) 1 640 cm^{-1} (C=O), δ (CF_3·CO_2H) 4.10 (3 H, s, OMe), 6.18 (2 H, s, O·CH_2·O), and 6.93—7.70 (5 H, m, ArH).

(1R*)-1,2,3,4-*Tetrahydro*-1-[(αR*)-α-*hydroxy*-3,4-*dimethoxybenzyl*]-6,7-*dimethoxyisoquinoline* (15).—To a solution of the 1-benzoylisoquinoline (9) (20 g) in methanol (750 ml), sodium borohydride (12 g) was added in portions with stirring at room temperature, and the mixture was refluxed for 0.5 h. After evaporation of methanol, the residue was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to give the α-hydroxybenzylisoquinoline (15) as a syrup, characterised as *hydrochloride* (13.10 g, 58.75%), needles, m.p. 210° (from methanol–ether) (Found: C, 59.6; H, 6.55; N, 3.6. $C_{20}H_{25}NO_5$,HCl,0.5H_2O requires C, 59.35; H, 6.65; N, 3.45%), δ (free base in $CDCl_3$) 3.73 (6 H, s, 2 × OMe), 3.90 (6 H, s, 2 × OMe), 4.22 (1 H, d, *J* 4.4 Hz, 1-H), 4.99 (1 H, d, *J* 4.4 Hz, C*H*·OH), and 6.60—6.90 (5 H, m, ArH), *m/e* 360 ($M^+ - Cl^-$).

Acetylation of the Alcohol (15).—A mixture of (15) (100 mg), acetic anhydride (0.5 ml), and pyridine (0.5 ml) was stirred at room temperature overnight; the excess of reagent was then distilled off *in vacuo*. The residue was diluted with water and extracted with ether. The extract was washed with 5% sodium hydrogen carbonate, 10% hydrochloric acid, and water, dried (Na_2SO_4), and evaporated to give the NO-*diacetylisoquinoline* (23) (54 mg) as needles, m.p. 169—170° (from methanol) (Found: C, 65.0; H, 6.75; N, 3.15. $C_{24}H_{29}NO_7$ requires C, 65.0; H, 6.6; N, 3.15%), $\nu_{max.}$ ($CHCl_3$) 1 735 (C=O) and 1 635 cm^{-1} (N–C=O), δ ($CDCl_3$) 2.10 (6 H, s, COMe), 2.60—2.90 (2 H, m, 4-H_2), 3.25—3.60 (2 H, m, 3-H_2), 3.71 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.88 (6 H, s, 2 × OMe), and 6.15 (1 H, d, *J* 4.4 Hz, C*H*·OAc).

(1R*)-1,2,3,4-*Tetrahydro*-1-[(αR*)-α-*hydroxy*-3,4-*dimethoxybenzyl*]-6,7-*methylenedioxyisoquinoline* (16).—Sodium borohydride (800 mg) was added in small portions to a solution of the 1-benzoylisoquinoline (10) (900 mg) in methanol (50 ml). The mixture was worked up as above and the product recrystallised from methanol to give the *alcohol* (16) (672 mg, 73.8%) as needles, m.p. 148—150° (Found: C, 66.1; H, 6.2; N, 4.0. $C_{19}H_{21}NO_5$ requires C, 66.45; H, 6.15; N, 4.1%), δ ($CDCl_3$) 3.72 (3 H, s, OMe), 3.85 (3 H, s, OMe), 4.18 (1 H, d, *J* 4.4 Hz, 1-H), 4.90 (1 H, d, *J* 4.4 Hz, C*H*·OH), 5.85 (2 H, s, O·CH_2·O), and 6.42—6.80 (5 H, m, ArH).

(1R*)-1-[(αR*)-α,3-*Dihydroxy*-4-*methoxybenzyl*]-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (17).—To a solution of the phenolic isoquinoline (12) (500 mg) in methanol (30 ml) was added sodium borohydride (300 mg), and the mixture was worked up as above to give the *alcohol* (17) (390 mg, 77.2%) as needles, m.p. 142—143° (from ethanol) (Found: C, 65.85; H, 6.75; N, 3.85. $C_{19}H_{23}NO_4$ requires C, 66.05; H, 6.7; N, 4.05%), $\nu_{max.}$ ($CHCl_3$) 3 550 cm^{-1} (OH), δ ($CDCl_3$) 3.70 (3 H, s, OMe), 3.84 (6 H, s, 2 × OMe), 4.12 (1 H, d, *J* 5 Hz, 1-H), 4.90 (1 H, d, *J* 5 Hz, C*H*·OH), 6.55 (1 H, s, ArH), 6.65 (1 H, s, ArH), 6.73 (2 H, s, ArH), and 6.85 (1 H, s, ArH).

(1R*)-1-[(αR*)-3-*Benzyloxy*-α-*hydroxy*-4-*methoxybenzyl*]-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (18).—Sodium borohydride (340 mg) was added to a solution of the 1-benzoylisoquinoline (11) (500 mg) in methanol (30 ml) and the mixture was worked up as above to afford the alcohol (18), characterised as *hydrochloride* (364 mg, 66.8%), needles, m.p. 191—194° (from methanol–ether) (Found: C, 66.2; H, 6.65; N, 2.75. $C_{26}H_{29}NO_5$,HCl requires C, 66.15; H, 6.15; N, 2.95%), δ (free base in $CDCl_3$) 3.69 (3 H, s, OMe), 3.80 (6 H, s, 2 × OMe), 4.25 (1 H, d, *J* 5 Hz, 1-H), 4.88 (1 H, d, *J* 5 Hz, C*H*·OH), 4.97 (2 H, s, O·CH_2Ph), and 6.40—7.50 (10 H, m, ArH).

(1R*)-1-[(αS*)-α,3-*dihydroxy*-4-*methoxybenzyl*]-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (19).—A mixture of the non-phenolic (1*R**,α*R**)-alcohol (18) (2 g), concentrated hydrochloric acid (50 ml), and ethanol (50 ml) was refluxed for 7 h, and the reagent and ethanol were distilled off *in vacuo*. The residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to yield the *phenolic alcohol* (19) (1.2 g, 82.2%) as needles, m.p. 203—204° (from methanol) (Found: C, 65.2; H, 7.25; N, 3.95. $C_{19}H_{23}NO_5$,0.25CH_3OH requires C, 65.4; H, 6.85; N, 3.95%), $\nu_{max.}$ ($CHCl_3$) 3 550 cm^{-1} (OH), δ ($CDCl_3$) 3.43 (0.75 H, s, CH_3·OH), 3.79 (3 H, s, OMe), 3.85 (6 H, s, 2 × OMe), 4.57 (1 H, d, *J* 8 Hz, C*H*·OH), 5.80 (1 H, s, ArH), 6.50 (1 H, s, ArH), 6.73 (2 H, s, ArH), and 6.95 (1 H, s, ArH), *m/e* 345 (M^+).

(1R*)-1-[(αR*)-3-*Benzyloxy*-α-*hydroxy*-4-*methoxybenzyl*]-1,2,3,4-*tetrahydro*-6,7-*methylenedioxyisoquinoline* (20).—Sodium borohydride (800 mg) was added to a solution of the 1-benzoylisoquinoline (13) (1 g) in methanol (40 ml), and the mixture was worked up as above to give the alcohol (20), characterised as the *hydrochloride* (745 mg, 68.35%), needles, m.p. 189—192° (from ethanol) (Found: C, 65.55; H, 5.9; N, 3.25. $C_{25}H_{25}NO_5$,HCl requires C, 65.75; H, 5.75; N, 3.05%), δ (free base in $CDCl_3$) 3.82 (3 H, s, OMe), 4.10 (1 H, d, *J* 6 Hz, 1-H), 4.84 (1 H, d, *J* 6 Hz, C*H*·OH), 4.97 (2 H, s, O·CH_2Ph), and 6.43—7.48 (10 H, m, ArH).

(1R*)-1-[(αS*)-α,3-*Dihydroxy*-4-*methoxybenzyl*]-1,2,3,4-*tetrahydro*-6,7-*methylenedioxyisoquinoline* (21).—A mixture of the non-phenolic isoquinoline (20) (500 mg), concentrated hydrochloric acid (10 ml), and ethanol (10 ml) was refluxed for 5 h and worked up as above to give the phenolic *alcohol* (21) (220 mg, 59.6%) as needles, m.p. 130—131° (from ethanol) (Found: C, 65.25; H, 5.95; N, 3.9. $C_{18}H_{19}NO_5$ requires C, 65.65; H, 5.8; N, 4.25%), $\nu_{max.}$ ($CHCl_3$) 3 550 cm^{-1} (OH), δ ($CDCl_3$) 3.85 (3 H, s, OMe), 4.65 (1 H, d, *J* 6 Hz, C*H*·OH), 5.83 (2 H, s, O·CH_2·O), and 6.09—7.00 (5 H, s, ArH).

(1R*)-1-[(αR*)-α,3-*Dihydroxy*-4-*methoxybenzyl*]-1,2,3,4-*tetrahydro*-6,7-*methylenedioxyisoquinoline* (22).—To a solution of the phenolic 1-benzoylisoquinoline (14) (1.3 g) in

methanol (50 ml) was added sodium borohydride (800 mg), and the mixture was worked up as above to give the phenolic alcohol (22), whose hydrochloride afforded *needles* (691 mg, 47.3%), m.p. 232—234° (from ethanol) (Found: C, 56.2; H, 5.3; N, 3.6. $C_{18}H_{19}NO_5$,HCl,H_2O requires C, 56.35; H, 5.5; N, 3.65%), $\nu_{max.}$ ($CHCl_3$) 3 550 cm^{-1} (OH), δ (free base in $CDCl_3$) 3.87 (3 H, s, OMe), 4.15 (1 H, d, *J* 5.5 Hz, 1-H), 4.86 (1 H, d, *J* 5.5 Hz, C*H*·OH), 5.90 (2 H, s, O·CH_2·O), and 6.52—6.90 (5 H, m, ArH), *m/e* 330 (M^+ − Cl^-).

13α-*Hydroxyxylopinine* (24).—A mixture of the tetrahydroisoquinoline (15) hydrochloride (200 mg), 37% formalin (4 ml), and ethanol (8 ml) was refluxed for 2 h and then was evaporated *in vacuo*. The residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to give the *berbine* (24) (126 mg, 60%) as pale yellow needles, m.p. 158—160° (from benzene) (Found: C, 67.55; H, 6.8; N, 3.55. $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.8; N, 3.75%), $\nu_{max.}$ ($CHCl_3$) 2 850—2 750 (Bohlmann bands) and 3 580 cm^{-1} (OH), δ ($CDCl_3$) 3.83 (12 H, s, 4 × OMe), 4.60 (1 H, d, *J* 8 Hz, 13-H), 6.45 (1 H, s, ArH), 6.55 (1 H, s, ArH), 6.97 (1 H, s, ArH), and 7.52 (1 H, s, ArH), *m/e* 371 (M^+), 192, and 180.

13α-*Acetoxyxylopinine* (35).—A mixture of 13α-hydroxyxylopinine (24) (200 mg), acetic anhydride (1 ml), and pyridine (6 ml) was stirred overnight at room temperature. The excess of reagent was distilled off *in vacuo* and the residue was diluted with chloroform. The extract was washed with 5% sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated *in vacuo* to give 13α-*acetoxyxylopinine* (35) (170 mg, 76.2%) as needles, m.p. 181—183° (from methanol) (Found: C, 66.9; H, 6.9; N, 3.2. $C_{23}H_{27}NO_6$ requires C, 66.8; H, 6.6; N, 3.4%), $\nu_{max.}$ ($CHCl_3$) 1 720 cm^{-1} (C=O), δ ($CDCl_3$) 2.18 (3 H, s, OAc), 3.71 (3 H, s, OMe), 3.77 (9 H, s, 3 × OMe), 5.95 (1 H, d, *J* 8 Hz, 13-H), 6.40 (1 H, s, ArH), 6.43 (1 H, s, ArH), 6.60 (1 H, s, ArH), and 6.63 (1 H, s, ArH), *m/e* 413 (M^+), 371, 222, and 192.

Xylopinine (36).—A solution of 13-acetoxyxylopinine (35) (85 mg) in ethanol (30 ml) was shaken in hydrogen (90 atm) at 60 °C in the presence of 10% palladium–carbon (250 mg) for 5 h. After removal of the catalyst and solvent, the filtrate was evaporated, and the residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to give xylopinine (36) (17 mg, 23.3%) as needles, m.p. 151—153° (lit.,[17] 152—153°), identical [m.p. and i.r. spectrum (KBr)] with authentic (±)-xylopinine.[17]

Mannich Reaction of the Tetrahydroisoquinoline (15) *in Methanol*.—A solution of the tetrahydroisoquinoline (15) hydrochloride (200 mg) and 37% formalin (4 ml) in methanol (8 ml) was heated under reflux for 2 h, and the solvent was then distilled off *in vacuo*. The residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a syrup, which was chromatographed on silica gel (6 g). Elution with chloroform–methanol (99 : 1 v/v) gave 13α-hydroxyxylopinine (24) (26.5 mg, 14.1%), m.p. 158—160°, identical (i.r. and n.m.r. spectra) with an authentic sample. Elution with chloroform–methanol (98 : 2 v/v) then afforded the tetrahydro-oxazole (37), which was characterised as the *hydrochloride* (94.5 mg, 50.4%), needles, m.p. 178° (from methanol–ether) (Found: C, 61.5; H, 6.4; N, 3.45. $C_{21}H_{25}NO_5$,HCl requires C, 61.9; H, 6.4; N, 3.45), δ (free base in $CDCl_3$) 3.60 (6 H, s, OMe), 3.78 (6 H, s, OMe), 4.51 (1 H, d, *J* 8 Hz, 1-H), 4.68 and 4.81 (each 1 H, d, *J* 12 Hz, N·CH_2·O), 5.10 (1 H, d, *J* 8 Hz, C*H*·O), 6.21 (1 H, s, ArH), and 6.41—6.90 (4 H, s, ArH).

Mannich Reaction of the Tetrahydroisoquinoline (15) *in Propan-1-ol*.—A mixture of the tetrahydroisoquinoline (15) hydrochloride (800 mg), 37% formalin (16 ml), and propan-1-ol (32 ml) was refluxed for 2 h, cooled, and washed with ether. The ethereal layer was washed with water, dried (Na_2SO_4), and evaporated to give veratraldehyde (38) (195 mg, 58.1%), m.p. 43—44°, whose i.r. [$\nu_{max.}$ ($CHCl_3$) 1 670 cm^{-1} (C=O)] and n.m.r. spectra [δ ($CDCl_3$) 3.90 (6 H, s, 2 × OMe) and 9.70 (1 H, s, CHO)] were identical with those of authentic material. The aqueous layer was washed with ether, basified with 10% ammonia, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to leave 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (39) as a syrup, characterised as the *hydrochloride* (202 mg, 48.25%), needles, m.p. 218° (from methanol–ether) (Found: C, 58.05; H, 7.6; N, 5.6. $C_{12}H_{17}NO_2$,HCl,0.33H_2O requires C, 57.7; H, 7.55; N, 5.6%), δ (free base in $CDCl_3$) 2.47 (3 H, s, NMe), 2.67—2.90 (4 H, m, CH_2·CH_2), 3.43—3.60 (2 H, s, ArCH_2·N), 3.90 (6 H, s, 2 × OMe), 6.50 (1 H, s, ArH), and 6.59 (1 H, s, ArH), *m/e* 207 (M^+), identical (i.r. and n.m.r. spectra) with a sample prepared by an established method.[19]

10,11-*Dimethoxy*-2,3-*methylenedioxyberbine*-13α-*ol* (25).—A mixture of the tetrahydroisoquinoline (16) hydrochloride (200 mg), 37% formalin (4 ml), and ethanol (8 ml) was refluxed for 2 h, then evaporated *in vacuo*. The residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried (Na_2SO_4), and evaporated *in vacuo* to give the *berbine* (25) (139 mg, 67.2%) as needles, m.p. 119—121° (from methanol) (Found: C, 67.3; H, 6.25; N, 3.9. $C_{20}H_{21}NO_5$ requires C, 67.6; H, 5.95; N, 3.95%), δ ($CDCl_3$) 3.83 (6 H, s, OMe), 4.69 (1 H, d, *J* 9 Hz, C*H*·OH), 5.90 (2 H, s, O·CH_2·O), 6.49 (1 H, s, ArH), 6.53 (1 H, s, ArH), 6.99 (1 H, s, ArH), and 7.35 (1 H, s, ArH).

Phenolic Cyclisation of the 1-(α,3-*Dihydroxy*-4-*methoxybenzyl*)*isoquinoline* (17).—A solution of the phenolic isoquinoline (17) (100 mg) and 37% formalin (2 ml) in ethanol (4 ml) was refluxed for 2 h, then evaporated *in vacuo*. The residue was extracted with chloroform and the extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to give a syrup, which was chromatographed on silica gel (3 g). Elution with benzene–methanol (99 : 1 v/v) gave 2,3,10-*trimethoxyberbine*-9,13β-*diol* (26) (35.1 mg, 34.1%) as needles, m.p. 112—114° (from ethanol) (Found: C, 66.95; H, 6.75; N, 3.6. $C_{20}H_{23}NO_5$ requires C, 67.2; H, 6.5; N, 3.9%), $\nu_{max.}$ ($CHCl_3$) 3 550 (OH) and 2 850—2 750 cm^{-1} (Bohlmann bands), δ ($CDCl_3$) 3.86 (9 H, s, 3 × OMe), 4.73 (1 H, d, *J* 9 Hz, 13-H), 6.61 (1 H, s, ArH), 6.80 (1 H, d, *J* 8 Hz, 11-H), 7.05 (1 H, d, *J* 8 Hz, 12-H), and 7.46 (1 H, s, ArH). Elution with benzene–methanol (99 : 1 v/v) then afforded 2,3,10-*trimethoxyberbine*-11,13β-*diol* (27) (28.3 mg, 27.5%) as needles, m.p. 220—221° (from ethanol) (Found: C, 66.85; H, 6.7; N, 3.55. $C_{20}H_{23}NO_5$ requires C, 67.2; H, 6.5; N, 3.9%), $\nu_{max.}$ ($CHCl_3$) 3 550 (OH) and 2 850—2 750 cm^{-1} (Bohlmann bands), δ ($CDCl_3$) 3.83 (9 H, s, 3 × OMe), 4.60 (1 H, d, *J* 9 Hz, 13-H), 6.49 (1 H, s, ArH), 6.55 (1 H, s, ArH), 7.00 (1 H, s, ArH), and 7.4 (1 H, s, ArH).

Phenolic Cyclisation of the Phenolic Isoquinoline (22).—A solution of the isoquinoline (22) (250 mg) and 37% formalin (5 ml) in ethanol (10 ml) was refluxed for 2 h and worked up as above. Elution with benzene–methanol (99 : 1 v/v) from silica gel (7.5 g) afforded 10-*methoxy*-2,3-*methylenedioxyberbine*-9,13α-*diol* (28) (88 mg, 34%) as needles, m.p. 167—168° (from ethanol) (Found: C, 66.5; H, 5.6; N, 4.05. $C_{19}H_{19}NO_5$ requires C, 66.85; H, 5.6; N, 4.1%), $\nu_{max.}$ (KBr) 2 850—2 750 cm^{-1} (Bohlmann bands), δ ($CDCl_3$) 3.50 (1 H, d, *J* 16 Hz, 8α-H), 3.83 (3 H, s, OMe), 4.03 (1 H, d, *J* 16 Hz, 8β-H), 4.58 (1 H, d, *J* 8 Hz, 13-H), 5.88 (2 H, s, O·CH_2·O), 6.53 (1 H, s, ArH), 6.73 (1 H, d, *J* 8 Hz, 11-H), 7.0 (1 H, d, *J* 8 Hz, 12-H), and 7.37 (1 H, s, ArH). Further elution with benzene–methanol (99 : 1 v/v) gave 10-*methoxy*-2,3-*methylenedioxyberbine*-11,13α-*diol* (29) (79 mg, 30.5%) as needles, m.p. 200—201° (from ethanol) (Found: C, 66.55; H, 5.6; N, 3.95. $C_{19}H_{19}NO_5$ requires C, 66.85; H, 5.6; N, 4.1%), $\nu_{max.}$ (KBr) 2 850—2 750 cm^{-1} (Bohlmann bands), δ ($CDCl_3$) 3.89 (3 H, s, OMe), 4.68 (1 H, d, *J* 8 Hz, 13-H), 5.90 (2 H, s, O·CH_2·O), 6.53 (1 H, s, ArH), 6.56 (1 H, s, ArH), 7.03 (1 H, s, ArH), and 7.40 (1 H, s, ArH).

Phenolic Cyclisation of the Phenolic Isoquinoline (19).—A mixture of the phenolic isoquinoline (19) (450 mg), 37% formalin (9 ml), and ethanol (18 ml) was heated under reflux for 2 h. Ethanol was then removed by distillation *in vacuo* to leave a gum, which was extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated to give 2,3,10-trimethoxyberbine-9,13β-diol (31) as a syrup, characterised as the *hydrochloride* (114 mg, 24.5%), needles, m.p. 222—224° (from methanol–ether) (Found: C, 60.8; H, 6.4; N, 3.65. $C_{20}H_{23}NO_5$,HCl requires C, 61.0; H, 6.1; N, 3.55%), $\nu_{max.}$ (free base in $CHCl_3$) 3 550 (OH) and 2 850—2 750 cm^{-1} (Bohlmann bands), δ (free base in $CDCl_3$) 3.46 (1 H, d, *J* 16 Hz, 8α-H), 3.82 (9 H, s, 3 × OMe), 4.22 (1 H, d, *J* 16 Hz, 8β-H), 4.75 (1 H, d, *J* 1.5 Hz, 13-H), 6.57 (1 H, s, ArH), 6.75 (1 H, d, *J* 8 Hz, 11-H), 6.73 (1 H, s, ArH), and 6.95 (1 H, d, *J* 8 Hz, 12-H). The material undissolved during the above extraction with ether was dissolved in chloroform, and the solution was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to afford 2,3,10-*trimethoxyberbine*-11,13β-*diol* (32) (121 mg, 26%) as needles, m.p. 223—225° (from ethanol) (Found: C, 67.4; H, 6.75; N, 3.55. $C_{20}H_{23}NO_5$ requires C, 67.2; H, 6.5; N, 3.9%), $\nu_{max.}$ ($CHCl_3$) 3 550 (OH) and 2 850—2 750 cm^{-1} (Bohlmann bands), δ ($CDCl_3$) 3.85 (9 H, s, 3 × OMe), 4.70 (1 H, d, *J* 1.5 Hz, 13-H), 6.55 (1 H, s, ArH), 6.61 (1 H, s, ArH), 6.79 (1 H, s, ArH), and 6.98 (1 H, s, ArH).

Phenolic Cyclisation of the Phenolic Isoquinoline (21).—A solution of the isoquinoline (21) (50 mg) and 37% formalin (1 ml) in ethanol (2 ml) was refluxed for 2 h and the ethanol was distilled off *in vacuo*. A solution of the residue in chloroform was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to leave a syrup, which was chromatographed on silica gel (2 g). Elution with benzene–methanol (99 : 1 v/v) gave 10-*methoxy*-2,3-*methylenedioxyberbine*-9,13β-*diol* (33) (16.6 mg, 32%), needles, m.p. 222—224° (from ethanol) (Found: C, 66.35; H, 5.6; N, 4.1. $C_{19}H_{19}NO_5$ requires C, 66.85; H, 5.6; N, 4.1%), $\nu_{max.}$ (KBr) 2 850—2 750 cm^{-1} (Bohlmann bands), δ ($CDCl_3$) 3.50 (1 H, d, *J* 16 Hz, 8α-H), 3.90 (3 H, s, OMe), 4.22 (1 H, d, *J* 16 Hz, 8β-H), 4.73 (1 H, distorted d, *J* 1.5 Hz, 13-H), 5.90 (2 H, s, O·CH_2·O), 6.58 (1 H, s, ArH), 6.75 (1 H, d, *J* 8 Hz, 11-H), 6.76 (1 H, s, ArH), and 6.95 (1 H, d, *J* 8 Hz, 12-H), followed by 10-*methoxy*-2,3-*methylenedioxyberbine*-11,13β-*diol* (34) (19.2 mg, 37.1%), needles, m.p. 245—246° (from ethanol) (Found: C, 67.0; H, 5.85; N, 4.3. $C_{19}H_{19}NO_5$ requires C, 66.85; H, 5.6; N, 4.1%), $\nu_{max.}$ (KBr) 2 850—2 750 cm^{-1} (Bohlmann bands), δ ($CDCl_3$) 3.91 (3 H, s, OMe), 4.70 (1 H, d, *J* 1.5 Hz, 13-H), 5.92 (2 H, s, O·CH_2·O), 6.68 (2 H, s, ArH), 6.83 (1 H, s, ArH), and 7.03 (1 H, s, ArH).

(±)-*Ophiocarpine* (3).—An excess of diazomethane in ether was added to the 9,13β-dihydroxyberbine (33) (18 mg) in methanol (10 ml) and the mixture was set aside overnight at room temperature. Evaporation left (±)-ophiocarpine (3) (15 mg, 80.1%), needles, m.p. 254—256° (from chloroform–methanol) (Found: C, 66.55; H, 5.9; N, 3.8. Calc. for $C_{20}H_{21}NO_5$,0.33H_2O: C, 66.45; H, 5.95; N, 3.85%), $\nu_{max.}$ (KBr) 2 850—2 750 cm^{-1} (Bohlmann bands), δ ($CDCl_3$) 3.52 (1 H, d, *J* 16 Hz, 8α-H), 3.85 (3 H, s, OMe), 4.23 (1 H, d, *J* 16 Hz, 8β-H), 4.67 (1 H, d, *J* 1.5 Hz, 13-H), 5.80 (2 H, s, O·CH_2·O), 6.55 (1 H, s, ArH), 6.77 (1 H, s, ArH), 6.83 (1 H, d, *J* 8 Hz, 11-H), and 7.18 (1 H, d, *J* 8 Hz, 12-H), identical (i.r. and n.m.r. spectra and m.p.) with an authentic sample provided by Professor Takemoto and Dr. Kondo.[22]

(±)-*Epiophiocarpine* (30).—The 9,13α-dihydroxyberbine (28) (50 mg) in methanol (20 ml) was treated with an excess of diazomethane in ether and the product worked up as above to give (±)-epiophiocarpine (30) (42 mg, 80.7%) as needles, m.p. 175—176° (lit.,[3] 170—172°) (from methanol) (Found: C, 66.95; H, 5.8; N, 3.55. Calc. for $C_{20}H_{21}NO_5$,0.33H_2O: C, 66.45; H, 5.95; N, 3.85%), $\nu_{max.}$ (KBr) 2 850—2 750 cm^{-1} (Bohlmann bands), δ ($CDCl_3$) 3.57 (1 H, d, *J* 16 Hz, 8α-H), 3.80 (3 H, s, OMe), 4.07 (1 H, d, *J* 16 Hz, 8β-H), 4.60 (1 H, d, *J* 9 Hz, 13-H), 5.85 (2 H, s, O·CH_2·O), 6.53 (1 H, s, ArH), 6.78 (1 H, d, *J* 8 Hz, 12-H), and 7.33 (1 H, s, ArH). The n.m.r. spectrum of this product was in good accord with reported data.[23]

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