Total Synthesis of (−)-Discretine (2,10,11-Trimethoxy-13aα-berbin-3-ol)

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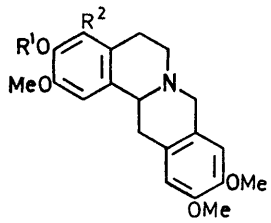
(±)-Discretine (1) was obtained by a Mannich reaction of 1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-6-hydroxy-7-methoxyisoquinoline with formalin. Optical resolution of (±)-discretine could not be achieved. (±)-*O*-Benzyldiscretine (3), which was synthesised by a Mannich reaction of 6-benzyloxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-methoxyisoquinoline (14) with formalin, was resolved to give (−)-*O*-benzyldiscretine through its di-*p*-toluoyltartrate; debenzylation then afforded (−)-discretine, which was identical with the natural base.

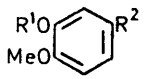
(−)-DISCRETINE (1) is an alkaloid isolated from *Xylopia discreta*; its structure was originally proposed by Schmutz.[1] Bernoulli and his co-workers [2] later assigned its structure on the basis of the results of permanganate oxidation of *O*-ethyldiscretine. We now describe the total synthesis of (−)-discretine.

Condensation of 3-hydroxy-4-methoxyphenethylamine (6) [3] with sodium 3,4-dimethoxyphenylglycidate (8) (36·4%) or 3,4-dimethoxyphenylacetaldehyde (7) [4] (21·8%) by phenolic cyclisation [5] afforded the tetrahydroisoquinoline (13) as a key intermediate. (±)-Discretine (1) was prepared from compound (13) and 37% formalin in the presence of formic or acetic acid by a Mannich reaction. A by-product, isolated in about 15% yield, was identified by mass and n.m.r. spectra as (±)-4-hydroxymethyldiscretine (2). The position of the hydroxymethyl group was supported by the fre-

[1] J. Schmutz, *Helv. Chim. Acta*, 1959, **42**, 335.
[2] F. Bernoulli, H. Linde, and K. Meyer, *Helv. Chim. Acta*, 1963, **46**, 323.
[3] (*a*) M. Ernz and F. Ramirez, *Helv. Chim. Acta*, 1950, **33**, 912; (*b*) J. Finkelstein, *J. Amer. Chem. Soc.*, 1951, **73**, 550.
[4] Y. Ban and T. Oishi, *Chem. and Pharm. Bull.* (*Japan*), 1958, **6**, 574.
[5] T. Kametani, T. Kobari, K. Fukumoto, and M. Fujihara, *J. Chem. Soc.* (*C*), 1971, 1796.

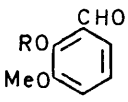
quencies of the aldehyde carbonyl absorptions in the i.r. spectra ($CHCl_3$) of the hydroxy-aldehyde (4) (1630 cm^{-1}) [derived by oxidation of (2) with manganese dioxide [6]] and its *O*-acetyl derivative (5) (1692 cm^{-1}). These were





(1) $R^1 = R^2 = H$
(2) $R^1 = H$, $R^2 = CH_2{\cdot}OH$
(3) $R^1 = CH_2Ph$, $R^2 = H$
(4) $R^1 = H$, $R^2 = CHO$
(5) $R^1 = Ac$, $R^2 = CHO$

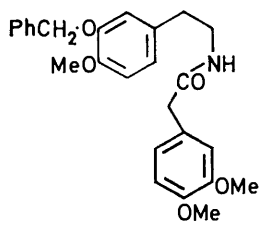
(6) $R^1 = H$, $R^2 = [CH_2]_2{\cdot}NH_2$
(7) $R^1 = Me$, $R^2 = CH_2{\cdot}CHO$
(8) $R^1 = Me$, $R^2 =$ 
(9) $R^1 = CH_2Ph$, $R^2 = [CH_2]_2{\cdot}NH_2$
(10) $R^1 = Me$, $R^2 = CH_2{\cdot}CO_2H$



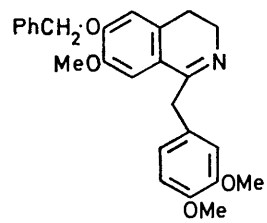
(11) R = H
(12) R = Ac

(13) $R^1 = R^2 = H$
(14) $R^1 = CH_2Ph$, $R^2 = H$
(15) $R^1 = CH_2Ph$, $R^2 = Me$

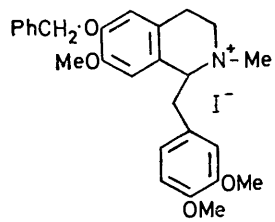
analogous to the corresponding absorptions of *o*-vanillin (11) (1650 cm^{-1}) and *O*-acetyl-*o*-vanillin (12) [7] (1700 cm^{-1})



(16)



(17)



(18)

Attempted optical resolution of (±)-discretine by means of (−)-di-*p*-toluoyltartaric acid resulted in failure; another attempt to achieve a total synthesis of (−)-discretine was carried out as follows. The amide (16) prepared from the 3-benzyloxy-4-methoxyphenethylamine (9) and 3,4-dimethoxyphenylacetic acid (10) was cyclised by a Bischler-Napieralski reaction to give the 3,4-dihydroisoquinoline (17), which was reduced with sodium borohydride to give the corresponding 1,2,3,4-tetrahydroisoquinoline derivative (14). Heating compound (14) with 37% formalin in acetic or formic acid gave the (±)-*O*-benzyldiscretine derivative (3) in addition to the isoquinoline (15). Optical resolution [8] of (±)-*O*-benzyldiscretine was achieved efficiently by use of (−)-di-*p*-toluoyltartaric acid to afford optically active *O*-benzyldiscretine. Debenzylation with ethanolic hydrochloric acid gave (−)-discretine (1), the spectroscopic data of which were identical with those of natural discretine donated by Professor Bernoulli.

EXPERIMENTAL

M.p.s were determined with a Yanagimoto micro-apparatus. I.r. and u.v. spectra were taken with Hitachi EPI-3 and EPS-3 recording spectrophotometers, respectively. Mass spectra were measured with a Hitachi RMU-7 spectrometer. N.m.r. spectra were measured with a Hitachi R-20 spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal standard. Optical rotations were measured with a JASCO PIP-SL automatic polarimeter.

1-(3,4-*Dimethoxybenzyl*)-1,2,3,4-*tetrahydro*-6-*hydroxy*-7-*methoxyisoquinoline* (13).—To a solution of sodium glycidate (8) (250 mg) in water was added a solution of the phenethylamine (6) (300 mg) in ethanol (15 ml), and the mixture was adjusted to pH 2·4 with 10% hydrochloric acid (0·6 ml) and acetic acid (0·4 ml). The mixture was then heated under reflux for 72 h and set aside overnight at room temperature. After being basified with 10% ammonia, the mixture was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to afford the *tetrahydroisoquinoline* (13) (163 mg, 36·4%) as needles (from benzene), m.p. 144—145° (decomp.) (Found: C, 69·0; H, 7·0; N, 4·25. $C_{19}H_{23}NO_4$ requires C, 69·3; H, 7·05; N, 4·25%), $\nu_{max.}$ ($CHCl_3$) 3460 cm^{-1} (OH, NH); τ ($CDCl_3$) 6·27, 6·19, and 6·16 (9H, each s, 3 × OMe), 5·68 (1H, t, *J* 6·2 Hz, 1-H), and 3·49 (1H), 3·29 (1H), and 3·19 (3H) (each s, ArH).

Mannich Reaction of the Isoquinoline (13) *with Formalin and Acetic Acid.*—A mixture of compound (13) (750 mg), 37% formalin (75 ml), and acetic acid (4 ml) was heated under reflux (125—135°) for 3 h, basified with 10% ammonia, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a brown syrup, which was chromatographed on silica gel (25 g). Elution with chloroform gave a yellow syrup, which was recrystallised from methanol or acetone–ether to give (±)-*discretine* (1) (528 mg) as a powder, m.p. 182—184° (decomp.) (Found: C, 69·95; H, 6·4; N, 4·3. $C_{20}H_{23}NO_4$ requires C, 70·35; H, 6·8; N, 4·1%), $\nu_{max.}$ ($CHCl_3$) 3560 (OH) and 2690—2930 cm^{-1} (*trans*-quinolizidine), τ ($CDCl_3$) 3·32 (1H), 3·38 (2H), and 3·41 (1H) (each s, ArH), and 6·18 (9H, s, 3 × OCH_3), *m/e* 341 (M^+), 176 and 164.

[6] T. Kametani, K. Fukumoto, T. Terui, K. Yamaki, and E. Taguchi, *J. Chem. Soc.* (*C*), 1971, 2709.
[7] W. Davies, *J. Chem. Soc.*, 1921, **123**, 1584.
[8] (*a*) T. Kametani, H. Sugi, and S. Shibuya, *Tetrahedron*, 1971, **27**, 2409; (*b*) T. Kametani, K. Sakurai, S. Kano, and H. Iida, *J. Pharm. Soc. Japan*, 1967, **87**, 822.

Elution with chloroform–methanol (99 : 1) afforded 4-*hydroxymethyl*-2,10,11-*trimethoxyberbin*-3-*ol* (2) (113 mg) as a powder, m.p. 148° (from benzene–hexane) (Found: C, 67·0; H, 6·6; N, 3·4. $C_{21}H_{25}NO_5$,0·25H_2O requires C, 67·0; H, 6·8; N, 3·7%), $\nu_{max.}$ ($CHCl_3$) 3450 cm^{-1} (OH), τ ($CDCl_3$) 3·40 (2H), and 3·49 (1H) (each s, ArH), 5·37 (2H, s, CH_2·OH), and 6·18 (9H, s, 3 × OCH_3), *m/e* 371 (M^+), 190, and 164.

N-(3-*Benzyloxy*-4-*methoxyphenethyl*)-3,4-*dimethoxyphenylacetamide* (16).—A mixture of 3-benzyloxy-4-methoxyphenethylamine (9) (1 g) and 3,4-dimethoxyphenylacetic acid (10) (0·8 g) was heated at 180° for 3 h and then extracted with chloroform. The extract was washed with hydrochloric acid, water, 5% sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and evaporated to give the *amide* (16) (1·1 g) as a powder (from benzene), m.p. 133—135° (Found: C, 71·75; H, 6·4; N, 3·5. $C_{26}H_{29}NO_5$ requires C, 71·7; H, 6·7; N, 3·2%), $\nu_{max.}$ 3330 (NH) and 1648 cm^{-1} (CO).

6-*Benzyloxy*-1-(3,4-*dimethoxybenzyl*)-3,4-*dihydro*-7-*methoxyisoquinoline* (17).—A mixture of the amide (16) (1·1 g), phosphoryl chloride (4 ml), and dry benzene (30 ml) was refluxed for 2 h. The solvent was evaporated off and the residue was washed with n-hexane and recrystallised from methanol–ether to give the *hydrochloride* (916 mg) of (17) as pale yellow grains, m.p. 145° (Found: C, 68·5; H, 6·3; N, 3·15. $C_{26}H_{27}NO_4$,HCl requires C, 68·8; H, 6·7; N, 3·1%), $\nu_{max.}$ 2710—2150 (=$\overset{+}{N}$H) and 1614 cm^{-1} (>C=$\overset{+}{N}$H).

6-*Benzyloxy*-1-(3,4-*dimethoxybenzyl*)-1,2,3,4-*tetrahydro*-7-*methoxyisoquinoline* (14).—To a solution of the hydrochloride of (17) (916 mg) in methanol (20 ml), sodium borohydride (0·48 g) was added in small portions with stirring at room temperature during 30 min. The mixture was refluxed for 30 min, the solvent was removed, and the residue was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a brown gum (900 mg), recrystallisation of which from methanol–ether afforded the *hydrochloride* of (14) as grains, m.p. 128° (Found: C, 68·4; H, 6·4; N, 3·1. $C_{26}H_{30}ClNO_4$ requires C, 68·5; H, 6·6; N, 3·1%), τ ($CDCl_3$) 2·68 (5H, s, ArH), 3·27 (3H), 3·38 (1H), and 3·42 (1H) (each s, ArH), 4·97 (2H, s, CH_2Ph), 6·23 (9H, s, 3 × OCH_3), and 7·29br (1H, s, NH).

3-*Benzyloxy*-2,10,11-*trimethoxyberbine* (3).—A mixture of compound (14) (500 mg), 37% formalin (13 ml), and acetic acid (13 ml) was refluxed for 3 h at 125—135°, then basified with 10% ammonia, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated, and the residue was subjected to column chromatography on silica gel (25 g). Elution with chloroform gave a yellow gum, which crystallised from ethanol to give O-*benzyldiscretine* (3) (320 mg) as yellow needles, m.p. 159—160° (320 mg) (Found: C, 75·35; H, 6·75; N, 3·4. $C_{27}H_{29}NO_4$ requires C, 75·15; H, 6·75; N, 3·25%), τ ($CDCl_3$) 2·58—2·72br (5H, ArH), 3·27 (1H), 3·38 (2H), and 3·48 (1H) (each s, ArH), 4·92 (2H, s, CH_2Ph), and 6·13 (3H) and 6·16 (6H) (each s, 3 × OCH_3). Elution with chloroform–methanol (99 : 1) afforded a pale yellow gum, which crystallised from ethanol to give (15) (695 mg) as a *powder*, m.p. 79—80° (Found: C, 73·2; H, 7·2; N, 2·95. $C_{27}H_{31}NO_4$,0·5H_2O requires C, 73·3; H, 7·3; N, 3·15%), τ ($CDCl_3$) 2·70—2·74br (5H, s, CH_2·C_6H_5), 3·40 (2H) and 3·47 (2H) (each s, ArH), 3·90 (1H, s, 8-H), 5·05 (2H, s, CH_2Ph), 6·20, 6·33, and 6·48 (9H, each s, 3 × OCH_3), and 7·53 (3H, s, NCH_3), *m/e* 431 (M^+ − 2), 282, and 151.

Optical Resolution of 3-*Benzyloxy*-2,10,11-*trimethoxyberbine* (3).—To a solution of compound (3) (100 mg) in acetone (3 ml) was added a solution of (−)-di-*p*-toluoyltartaric acid (115 mg). The mixture was set aside overnight at room temperature. The precipitate was collected and recrystallised from methanol to give (−)-O-*benzyldiscretine* (−)-*di*-p-*toluoyltartrate* (45 mg) as needles, m.p. 183—185° (Found: C, 70·0; H, 6·2; N, 2·4. $C_{27}H_{29}NO_4$,0·5$C_{22}H_{18}O_8$,0·5H_2O requires C, 70·1; H, 6·05; N, 2·2%), $[\alpha]_D^{20}$ −136° (*c* 0·100 in $CHCl_3$).

(−)-*Discretine* (1).—A suspension of the foregoing tartrate (45 mg) in an excess of saturated sodium hydrogen carbonate solution was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated. A solution of the residue in concentrated hydrochloric acid (13 ml) and ethanol (8 ml) was refluxed for 6 h under a current of nitrogen. The solvent was removed and the residue was extracted with chloroform; the extract was washed with 10% ammonia and water, dried (Na_2SO_4), and evaporated to give compound (1) as a powder (from methanol or acetone–ether), m.p. 182—183°, $[\alpha]_D^{20}$ −297·6° (*c* 0·1008 in $CHCl_3$) (lit.,[2] m.p. 180—181°, $[\alpha]_D$ −300°), the i.r. spectrum of which was identical with that of natural discretine. The *hydrochloride* was a powder, m.p. 212—213° (from ethanol) (Found: C, 63·45; H, 6·25; N, 3·65. $C_{20}H_{23}NO_4$,HCl requires C, 63·25; H, 6·31; N, 3·7%).

6-*Benzyloxy*-1-(3,4-*dimethoxybenzyl*)-1,2,3,4-*tetrahydro*-7-*methoxy*-2-*methylisoquinoline* (15).—A mixture of compound (17) (250 mg), methanol (10 ml), and methyl iodide (3·2 g) was refluxed for 1 h. The solvent was distilled off, and the residue was recrystallised from methanol to give 6-*benzyloxy*-1-(3,4-*dimethoxybenzyl*)-3,4-*dihydro*-7-*methoxyisoquinoline methiodide* (18) (261 mg) as yellow needles, m.p. 200—202° (Found: C, 57·65; H, 5·55; N, 2·25. $C_{27}H_{30}INO_4$ requires C, 57·95; H, 5·4; N, 2·5%).

To a solution of the methiodide (18) (261 mg) in methanol (50 ml), sodium borohydride (500 mg) was added in small portions with stirring. Stirring was continued for 30 min at room temperature and the solvent was then removed under reduced pressure. The residue was diluted with water, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a gum, which crystallised from ethanol to give a powder (15) (200 mg), m.p. 79—80° (decomp.), identical with an authentic sample.

Oxidation of the Hydroxymethyl Derivative (2).—Manganese dioxide (1·12 g) was added to a suspension of compound (2) (280 mg) in chloroform (150 ml). The mixture was refluxed for 8 h, filtered, and concentrated to dryness, and the residue was chromatographed on silica gel (11 g). Elution with chloroform–methanol (99·5 : 0·5) gave 3-hydroxy-2,10,11-trimethoxyberbine-4-carbaldehyde (4) (38 mg) as a brown syrup, $\nu_{max.}$ ($CHCl_3$) 1630 (CHO) and 3410—2940 cm^{-1} (hydrogen bond), τ ($CHCl_3$) −0·27 (CHO), 6·18 (6H) and 6·11 (3H) (each s, 3 × OCH_3), and 3·45, 3·37, and 3·04 (3H, each s, ArH), *m/e* 369 (M^+) and 164.

Acetylation of the Aldehyde (4).—A mixture of compound (4) (38 mg), acetic anhydride (3 ml), and pyridine (1 drop) was set aside for 2·4 h, and then poured into water. The separated oil was extracted with chloroform. The extract was washed with water, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated to give 3-acetoxy-2,10,11-trimethoxyberbine-4-carbaldehyde (5) as a brown syrup, $\nu_{max.}$ 1692 (CHO) and 1765 cm^{-1} (C=O), τ ($CDCl_3$) −0·30 (1H, s, CHO), 7·63 (3H, s, Ac), 6·18

(9H, s, 3 × OCH_3), and 3·45, 3·39, and 2·95 (3H, each s, ArH).

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