Studies on the Syntheses of Heterocyclic Compounds. Part CDLIII.† Total Synthesis of (±)-Ochrobirine ‡

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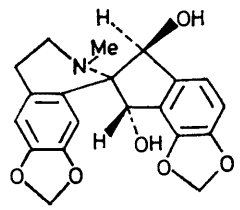
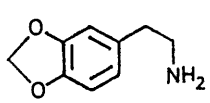
(±)-Ochrobirine (1) has been synthesised through a Pictet–Spengler reaction of 3,4-methylenedioxyphenethylamine (2) with 2,2-dihydroxy-6,7-methylenedioxyindane-1,3-dione (8), followed by *N*-methylation and stereoselective reduction with sodium borohydride.

OCHROBIRINE (1), $C_{20}H_{19}NO_6$, was first isolated in 1936 from *Corydalis sibirica* (L.) PERS. by Manske.[1-3] Its structure was elucidated [4] mainly on the basis of spectroscopic evidence. We hoped to achieve a total synthesis of ochrobirine which would confirm Manske's assignment.[4]

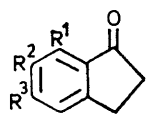
We have previously [5] reported the synthesis of 3-hydroxy-2-methoxyochotensinan-9,14-dione by condensation of ninhydrin with 3-hydroxy-4-methoxyphenethylamine. Recently Manske and Ahmed [6] reported the synthesis of an analogue of ochrobirine by a similar condensation. We have also reported [7] a mass spectral investigation of the ochotensinan-9,14-dione derivatives described in refs. 5 and 6.



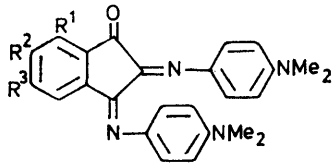
(1)



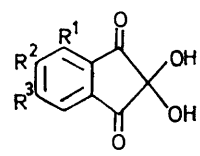
(2)



(3) R^1 = H, R^2 = R^3 = OMe
(4) R^1R^2 = O·CH_2·O R^3 = H

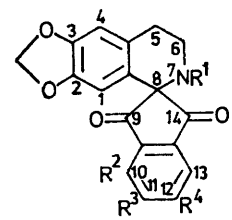


(5) R^1 = H, R^2 = R^3 = OMe
(6) R^1R^2 = O·CH_2·O, R^3 = H

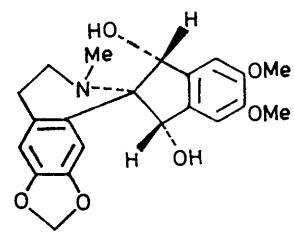


(7) R^1 = H, R^2 = R^3 = OMe
(8) R^1R^2 = O·CH_2·O, R^3 = H

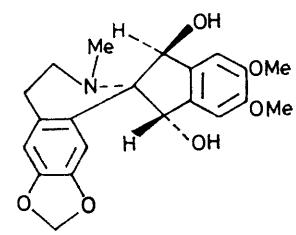
First, we prepared a model compound (9) from 5,6-dimethoxyindan-1-one (3) [8] in order to study the stereochemistry of the final reduction step. The ninhydrin analogue (7) was prepared according to Ruhemann's method [9] as follows. Treatment of the indanone (3) with *NN*-dimethyl-*p*-nitrosoaniline [10] in ethanol in the presence of a small amount of potassium hydroxide afforded the di-imine (5), and acidic hydrolysis of the product with dilute hydrochloric acid gave compound (7). A Pictet–Spengler reaction of 3,4-methylenedioxyphenethylamine (2) with compound (7) in ethanol in the presence of dry hydrogen chloride afforded the desired model compound (9). Treatment of (9) with a mixture of 95% formic acid and 35% formalin gave the *N*-methyl derivative (10). Reduction of compound (10) with sodium borohydride in methanol–chloroform yielded a mixture of stereoisomers (13) and (14) (1 : 2), and this result agreed with the report by Manske.[6] Thus the stereoselectivity of the reduction is not influenced by the substituents at C-11 and C-12 in compound (10).



(9) R^1 = R^2 = H, R^3 = R^4 = OMe
(10) R^1 = Me, R^2 = H, R^3 = R^4 = OMe
(11) R^1 = R^4 = H, R^2R^3 = O·CH_2·O
(12) R^1 = Me, R^2R^3 = O·CH_2·O, R^4 = H



(13)



(14)

In a similar manner, 6,7-methylenedioxyindan-1-one (4) [11] was treated with *NN*-dimethyl-*p*-nitrosoaniline to give the di-imine (6). Subsequent hydrolysis with dilute hydrochloric acid afforded the ninhydrin analogue (8), condensation of which with the amine (2) yielded the spiro-dione (11). Compound (11) showed spectroscopic

† Part CDLII, *Chem. and Pharm. Bull.* (*Japan*), T. Kametani and M. Ihara, 1971, **19**, 2256.

‡ Preliminary communication, T. Kametani, S. Hibino, and S. Takano, *Chem. Comm.*, 1971, 925.

[1] R. H. F. Manske, *Canad. J. Res.*, 1936, **14***B*, 354.
[2] R. H. F. Manske, *Canad. J. Res.*, 1939, **17***B*, 89.
[3] R. H. F. Manske, *Canad. J. Res.*, 1939, **17***B*, 95.
[4] R. H. F. Manske, R. G. A. Rodrigo, D. B. MacLean, D. E. F. Gracey, and J. K. Saunders, *Canad. J. Chem.*, 1969, **47**, 3589.
[5] T. Kametani, S. Takano, and S. Hibino, *J. Pharm. Soc. Japan*, 1969, **88**, 1123.
[6] R. H. F. Manske and Q. A. Ahmed, *Canad. J. Chem.*, 1970, **48**, 1280.
[7] T. Kametani, S. Hibino, S. Shibuya, and S. Takano, *J. Heterocyclic Chem.*, in the press.
[8] J. Koo, *J. Amer. Chem. Soc.*, 1953, **75**, 1891.
[9] S. Ruhemann, *J. Chem. Soc.*, 1910, 1438.
[10] G. M. Bennett and E. V. Bell, *Org. Synth.*, 1943, Coll. Vol. II, p. 223.
[11] T. Kishimoto and S. Uyeo, *J. Chem. Soc.* (*C*), 1969, 2600.

data characteristic of ochotensinan-9,14-dione derivatives.[5-7]

Treatment of compound (11) with a mixture of 95% formic acid and 35% formalin afforded the *N*-methyl compound (12) [δ 2·38 p.p.m. (3H, s, NMe)].

Reduction of compound (12) with sodium borohydride in methanol gave the expected (±)-ochrobirine through stereoselective reduction. The i.r. spectrum of the product showed the presence of two hydroxy-groups [$\nu_{max.}$ 3550 (sharp) and 3250 cm^{-1} (broad)]. The n.m.r. spectrum showed signals at δ 4·77 (sharp singlet, 1H) and 5·33 p.p.m. (broad singlet, 1H), assigned to the two methine protons at C-9 and C-14. All the spectroscopic data of the racemate of (1) were identical with those of natural ochrobirine, supporting the structure suggested by Manske.[4]

The stereochemistry of the two hydroxy-groups (C-9 and C-14) in natural ochrobirine was established as *trans* by Manske;[4] accordingly, it is obvious that the final reduction proceeded stereoselectively. However, Manske[6] reported that a mixture (1 : 2) of *cis*- and *trans*-isomers of demethylenedioxyochrobirine was obtained by reduction of 2,3-methylenedioxy-7-methylochotensinan-9,14-dione with sodium borohydride. We also obtained a similar result in the sodium borohydride reduction of compound (10) (see before). We suggest that this difference is due to steric hindrance by a methylenedioxy-group; *i.e.* substituents at C-10 and C-11 influence the stereoselectivity of the reduction of compound (12). Eliel and Haubenstock[12] have reported that use of methanol or ethanol as solvent results in an increase in stereoselectivity of the reagent used. We therefore consider that the initial attack of sodium borohydride on the diketone (12) occurs at the 14-carbonyl carbon atom from the less hindered side and that the *trans*-orientation of the two hydroxy-groups is then produced by intramolecular migration of hydride ion to the 9-carbonyl carbon atom from the hydroborate complex rather than by the attack of a second sodium borohydride molecule at the 9-carbonyl carbon atom.

EXPERIMENTAL

I.r. spectra were measured with a Hitachi EPI-3 recording spectrophotometer, u.v. spectra with a Hitachi EPS-3 recording spectrophotometer, and n.m.r. spectra with a Hitachi R-20 spectrometer with tetramethylsilane as an internal reference. Mass spectra were taken with a Hitachi RMU-7 spectrometer.

2,3-*Bis*-(p-*dimethylaminophenylimino*)-5,6-*dimethoxyindan*-1-*one* (5).—To a mixture of 5,6-dimethoxyindan-1-one (3) (2 g), *NN*-dimethyl-*p*-nitrosoaniline (8 g), and ethanol (20 ml) cooled in ice, ethanolic potassium hydroxide (0·056 g in 3 ml) was added dropwise. The mixture soon turned deep brown and a black solid was collected, washed with ethanol, and recrystallised from chloroform–hexane to give the *Schiff base* (5) (2·1 g) as black prisms, m.p. 205° (Found: C, 70·9; H, 5·85; N, 12·1. $C_{27}H_{28}N_4O_3$ requires C, 71·05; H, 6·2; N, 12·25%), $\nu_{max.}$ (KBr) 1687 cm^{-1} (C=O), *m/e* 456 (M^+).

2,2-*Dihydroxy*-5,6-*dimethoxyindane*-1,3-*dione* (7).—A mixture of compound (5) (1·6 g) and 18% hydrochloric acid (30 ml) was warmed on a water-bath, then left at room temperature overnight, and extracted with chloroform (100 ml × 10). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to yield the dione (7) (0·65 g) as a dark reddish solid. Recrystallisation from methanol afforded *prisms*, m.p. 214—217° (Found: C, 59·9; H, 3·8. $C_{11}H_8O_5$ requires C, 60·0; H, 3·65%), $\nu_{max.}$ (KBr) 1745 and 1705 cm^{-1} (C=O), δ($CDCl_3$) 3·96 (6H, s, 2 × OMe), 4·6br (2H, s, 2 × OH, exchanged by D_2O), and 7·24 p.p.m. (2H, s, ArH), *m/e* 220 ($M^+ - 18$).

11,12-*Dimethoxy*-2,3-*methylenedioxyochotensinan*-9,14-*dione* (9).—To an ice-cooled solution of compound (7) (0·35 g) in absolute ethanol (30 ml) a solution of 3,4-methylenedioxyphenethylamine (2) in absolute ethanol (5 ml) was added dropwise with stirring. After 10—15 min, a pale yellow precipitate separated, and the ice–water bath was then replaced by a solid carbon dioxide–acetone bath. Dry hydrogen chloride gas was bubbled over the surface of the mixture until all the precipitate had dissolved to form an orange solution. The solution was slowly warmed to 80—85° on a water-bath and kept at this temperature for 20 min. The solvent was removed under reduced pressure and the residue was suspended with chloroform. The suspension was shaken with an excess of dilute ammonia, washed with water, and dried (Na_2SO_4). Evaporation gave a solid, which afforded the *ochotensinan derivative* (9) (0·3 g) as yellowish-orange prisms, m.p. 259—260° (from chloroform–hexane) (Found: C, 65·0; H, 4·3; N, 4·1. $C_{20}H_{17}NO_6$ requires C, 65·4; H, 4·65; N, 3·8%), $\nu_{max.}$ (KBr) 1680 and 1730 cm^{-1} (C=O), $\lambda_{max.}$ ($CHCl_3$) 302 and 315 nm (log ε 4·12 and 4·09), *m/e* 367 (M^+).

11,12-*Dimethoxy*-2,3-*methylenedioxy*-7-*methylochotensinan*-9,14-*dione* (10).—A solution of the dione (9) (0·1 g) in 95% formic acid (1·2 ml) and 35% formalin (1·2 ml) was refluxed for 20 min, diluted with water, basified with concentrated ammonia, and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to dryness under reduced pressure. The residue was recrystallised from chloroform–hexane several times to give the N-*methyl derivative* (10) (56 mg) as yellow needles, m.p. 278—281° (Found: C, 66·1; H, 5·3; N, 3·2. $C_{21}H_{19}NO_6$ requires C, 66·5; H, 5·0; N, 3·65%), $\nu_{max.}$ (KBr) 1735 and 1690 cm^{-1} (C=O), $\lambda_{max.}$ (MeOH) 209·5, 258·5, 302, and 316 nm (log ε 4·80, 4·79, 4·16, and 4·10), δ($CDCl_3$) 2·36 (3H, s, NMe), 2·99 (2H, t, *J* 4·5 Hz, benzylic CH_2), 3·32 (2H, t, *J* 4·5 Hz, N·CH_2), 4·05 (6H, s, 2 × OMe), 5·80 (2H, s, O·CH_2·O), 5·90 (1H, s, 1-H), 6·63 (1H, s, 4-H), and 7·40 p.p.m. (2H, s, 10- and 13-H), *m/e* 381 (M^+).

11,12-*Dimethoxy*-2,3-*methylenedioxy*-7-*methylochotensinan*-9,14-*diol* [(13) *and* (14)].—Sodium borohydride (0·15 g) was added in portions to a stirred solution of compound (10) (0·05 g) in methanol (20 ml) and chloroform (5 ml). After stirring for about 1 h, more sodium borohydride (0·05 g) was added. After 24 h, the solution was acidified with acetic acid, and removal of the solvent left a semi-solid residue which was basified with concentrated ammonia. The mixture was extracted with chloroform (2 × 50 ml) and the extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to afford a mixture of isomers (13) and (14) (0·035 g). Recrystallisation from methanol–ether–hexane gave prisms, m.p. 175—179° (Found: C, 65·25; H, 6·15; N, 3·55. Calc. for $C_{21}H_{23}NO_6$: C, 65·45; H, 6·0; N, 3·65%), $\nu_{max.}$ (CCl_4) 3560sh and 3280br

[12] H. Haubenstock and E. L. Eliel, *J. Amer. Chem. Soc.*, 1962, **84**, 2368.

cm^{-1} (OH), $\lambda_{max.}$ (MeOH) 211, 236, and 289 nm (log ε 4·62, 4·05, and 3·96), δ($CDCl_3$) 2·64 (3H, s, NMe), 3·90 (6H, s, 2 × OMe), 4·71 (1H, s, 9-H), 5·25 [0·33H, s, 14-H of compound (13)], 5·47 [0·66H, s, 14-H of compound (14)], 5·80 (2H, s, O·CH_2·O), 6·02 (1H, s, 1-H), 6·62 (1H, s, 4-H), and 6·96 p.p.m. (2H, s, 10- and 13-H), *m/e* 385 (M^+).

2,3-*Bis*-(p-*dimethylaminophenylimino*)-6,7-*methylenedioxyindan*-1-*one* (6).—To a mixture of 6,7-methylenedioxyindan-1-one (1·5 g), *NN*-dimethyl-*p*-nitrosoaniline (6 g), and ethanol (15 ml), ethanolic potassium hydroxide (0·043 g in 3 ml) was added dropwise. The mixture was set aside for 1 day at room temperature and the black solid deposited was collected and washed with ethanol. Recrystallisation from chloroform–hexane gave the *Schiff base* (6) (1·2 g) as greenish-black prisms, m.p. 197—199° (Found: C, 70·65; H, 5·25; N, 12·7. $C_{26}H_{24}N_4O_3$ requires C, 70·9; H, 5·5; N, 12·7%), $\nu_{max.}$ (KBr) 1705 cm^{-1} (C=O), *m/e* 440 (M^+).

2,2-*Dihydroxy*-6,7-*methylenedioxyindane*-1,3-*dione* (8).—A mixture of compound (6) (0·8 g) and 18% hydrochloric acid (30 ml) was warmed on a water-bath, then set aside at room temperature overnight. The precipitate which separated was filtered off to give the dione (8) (0·22 g). The filtrate was extracted with chloroform (100 ml × 10). The extract was washed with water, dried (Na_2SO_4), and evaporated to give a dark red solid (8) (0·13 g). Recrystallisation from methanol yielded *prisms* of the dione (8), m.p. 221—223° (Found: C, 58·5; H, 2·25. $C_{10}H_4O_5$ requires C, 58·85; H, 2·0%), $\nu_{max.}$ (KBr) 1748 and 1716 cm^{-1} (C=O).

2,3:11,12-*Bismethylenedioxyochotensinan*-9,14-*dione* (11).—To a cooled solution of the dione (8) (0·306 g) in absolute ethanol (20 ml), a solution of the amine (2) (0·227 g) in absolute ethanol (5 ml) was added dropwise with cooling under a current of nitrogen. After stirring for 20 min, a colourless precipitate had separated. The ice–water bath was replaced by a solid carbon dioxide–acetone bath. Dry hydrogen chloride gas was bubbled over the surface of the mixture until all the precipitate had dissolved. The resulting solution was refluxed at 80—85° for 20 min on a water-bath. The solvent was removed under reduced pressure and the residue was dissolved in chloroform; the solution was shaken with an excess of dilute ammonia, washed with water, and dried (K_2CO_3). Removal of the solvent left a brown solid (0·45 g), which was recrystallised from ether or ether–hexane to give light brown *prisms* (11) (0·35 g), m.p. 167—171° (Found: C, 65·0; H, 3·85; N, 4·0. $C_{19}H_{13}NO_6$ requires C, 64·95; H, 3·75; N, 4·0%), $\nu_{max.}$ (KBr) 1740 and 1710 cm^{-1}, $\lambda_{max.}$ (MeOH) 212, 245, 297, and 348 nm (log ε 4·41, 4·56, 3·78, and 3·77), δ($CDCl_3$) 2·75 (2H, t, *J* 6·0 Hz, benzylic CH_2), 3·37 (2H, t, *J* 6·0 Hz, N·CH_2), 5·73 (2H, s, 2,3-O·CH_2·O), 5·94 (1H, s, 1-H), 6·20 (2H, s, 10,11-O·CH_2·O), 6·52 (1H, s, 4-H), and 7·13 and 7·53 p.p.m. (2H, AB-type q, *J* 7·5 Hz, 12- and 13-H), *m/e* 351 (M^+).

2,3:10,11-*Bismethylenedioxy*-7-*methylochotensinan*-9,14-*dione* (12).—A solution of compound (11) (0·1 g) in 95% formic acid (1·2 ml) and 35% formalin (1·2 ml) was refluxed for 20 min, diluted with water, basified with concentrated ammonia, and extracted with chloroform. The extract was washed with water, dried (K_2CO_3), and evaporated to dryness under reduced pressure. The residue was purified by chromatography on silica gel in chloroform to afford a red-brown solid (0·06 g). Recrystallisation from ether–hexane gave orange *prisms* of the *N*-methyl derivative (12), m.p. 118—122° (Found: C, 65·5; H, 4·2; N, 4·0. $C_{20}H_{15}NO_6$ requires C, 65·75; H, 4·15; N, 3·85%), $\nu_{max.}$ (KBr) 1738 and 1701 cm^{-1} (C=O), δ($CDCl_3$) 2·38 (3H, s, NMe), 2·96 (2H, t, *J* 4·5 Hz, benzylic CH_2), 3·29 (2H, t, *J* 4·5 Hz, N·CH_2), 5·78 (2H, s, 2,3-O·CH_2·O), 5·92 (1H, s, 1-H), 6·28 (2H, t, 10,11-O·CH_2·O), 6·59 (1H, s, 4-H), and 6·22 and 7·62 p.p.m. (2H, AB-type q, *J* 7·5 Hz, 12- and 13-H), *m/e* 365 (M^+).

(±)-*Ochrobirine* (1).—To a stirred solution of compound (12) (0·03 g) in methanol (10 ml) sodium borohydride (0·15 g) was added in portions. After stirring for about 1 h, more sodium borohydride (0·05 g) was added. Stirring was continued for 24 h, then the solution was acidified with acetic acid. Removal of the solvent left a semi-solid residue which was basified with concentrated ammonia. The mixture was extracted with chloroform (2 × 50 ml) and the extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to afford the racemate (1) (0·02 g). Recrystallisation from benzene gave (±)-*ochrobirine* (1) as prisms, m.p. 185—187° (Found: C, 65·15; H, 5·15; N, 3·75. $C_{20}H_{19}NO_6$ requires C, 65·05; H, 5·2; N, 3·8%), $\nu_{max.}$ (CCl_4) 3550sh and 3260br cm^{-1} (OH), $\lambda_{max.}$ (MeOH) 211, 242, and 291 nm (log ε 4·80, 3·94, and 3·91), δ($CDCl_3$) 2·61 (3H, s, NMe), 4·77 (1H, s, 9-H), 5·33br (1H, s, 14-H), 5·71 (2H, s, O·CH_2·O), 5·90 (2H, s, O·CH_2·O), 5·93 (1H, s, 1-H), 6·50 (1H, s, 4-H), and 6·72 p.p.m. (2H, s, 12- and 13-H), *m/e* 369 (M^+).

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