Stereospecific Total Synthesis of (±)-Ochrobirine

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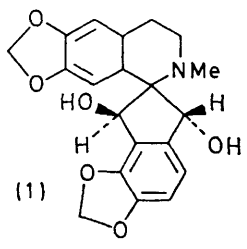
Summary (±)-Ochrobirine (*trans*-oriented) has been synthesised *via* stereoselective reduction.

OCHROBIRINE (1), $C_{20}H_{19}NO_6$, was first isolated in 1936 from *Corydalis sibirica* (L). Pers. by Manske,[1] who elucidated the structure mainly on the basis of spectroscopic evidence.[2]

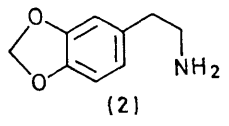
Previously we reported[3] the synthesis of 1-spiroisoquinoline derivatives by condensation of ninhydrin with phenethylamine derivatives. Recently, Manske and Ahmed[4] reported the synthesis of an analogue of ochrobirine by the reaction of ninhydrin with homopiperonylamine (2). We now report the total synthesis of ochrobirine by the Pictet–Spengler reaction to give (10), followed by reduction of (11) with sodium borohydride.

5,6-Dimethoxyindanone (3)[5] and 6,7-methylenedioxyindanone (4)[6] were each treated with *p*-nitrosodimethylaniline in ethanol in the presence of a small amount of potassium hydroxide to give the Schiff bases (5), m.p. 205°, and (6), m.p. 197—199°, respectively. Acid hydrolysis of (5) and (6) (dilute hydrochloric acid) gave the compounds (7), m.p. 214—217°, and (8), m.p. 208—210°. The Pictet–Spengler reaction of 3,4-methylenedioxyphenethylamine (2) with (7) in ethanol, with cooling, in the presence of HCl gas gave the compound (9) as yellow prisms (from chloroform–hexane), m.p. 259—260°. The same reaction of (2) with (8) gave the compound (10) as pale brown prisms (from ether–hexane), m.p. 167—171°. *N*-Methylation of (10) with a mixture of 95% formic acid and 35% formalin afforded the *N*-methyl compound (11) as yellowish orange prisms (from ether–hexane), m.p. 118—122°.

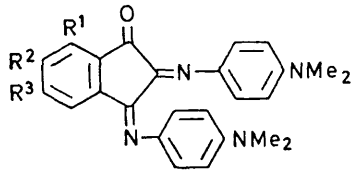
Reduction of the compound (11), having two carbonyl groups at C-9 and C-14, with sodium borohydride in methanol, afforded the expected (±)-ochrobirine (1) as



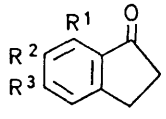
(1)



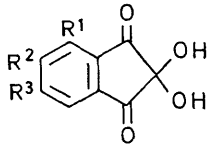
(2)



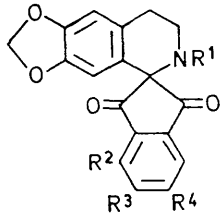
(5) R^1 = H; R^2 = R^3 = OMe
(6) R^1,R^2 = OCH_2O; R^3 = H



(3) R^1 = H; R^2 = R^3 = OMe
(4) R^1,R^2 = OCH_2O; R^3 = H



(7) R^1 = H; R^2 = R^3 = OMe
(8) R^1,R^2 = OCH_2O; R^3 = H



(9) R^1 = R^2 = H; R^3 = R^4 = OMe
(10) R^1 = R^4 = H; R^2,R^3 = OCH_2O
(11) R^1 = Me; R^2,R^3 = OCH_2O; R^4 = H

crystals (benzene–hexane), m.p. 185—187°, through stereoselective reduction, because of the presence of a methylenedioxy-group at the 10- and 11-positions. Manske and Ahmed[4] reported that a mixture of *cis/trans* (1 : 2) isomers of demethylenedioxyochrobirine was obtained by reduction of ochotensinan-9,14-dione with sodium borohydride. In our case, the *trans*-orientation of the two hydroxy-groups was assigned on the basis of spectral properties. The i.r., u.v., and n.m.r. spectra of the racemate of (1) were identical with those of natural ochrobirine, and R_F values of the synthetic product were in agreement with those of a natural sample in various solvent systems.

We therefore consider that the initial attack by sodium borohydride on the diketone (11) occurs at C-14 from the less hindered side, and then the attack of the second hydride ion occurs at C-9 from the opposite side.

This constitutes the first total synthesis of (±)-ochrobirine.

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[1] R. H. F. Manske, *Canad. J. Res.*, 1936, **14B**, 354; 1939, **17B**, 89; 95.
[2] R. H. F. Manske, R. G. A. Rodrigo, D. B. MacLean, D. E. F. Gracey, and J. K. Saunders, *Canad. J. Chem.*, 1969, **46**, 3589.
[3] T. Kametani, S. Takano, and S. Hibino, *J. Pharm. Soc. Japan*, 1969, **88**, 1123; T. Kametani, S. Hibino, and S. Takano, to be published.
[4] R. H. F. Manske and Q. A. Ahmed, *Canad. J. Chem.*, 1970, **48**, 1280.
[5] J. Koo, *J. Amer. Chem. Soc.*, 1953, **75**, 1891.
[6] T. Kishimoto and S. Uyeo, *J. Chem. Soc.* (*C*), 1969, 2600.