Tetrahedron Letters No.1, pp. 11-13, 1964. Pergamon Press Ltd.
Printed in Great Britain.

THE STEREOCHEMISTRY AND ABSOLUTE CONFIGURATION OF NARCOTINE

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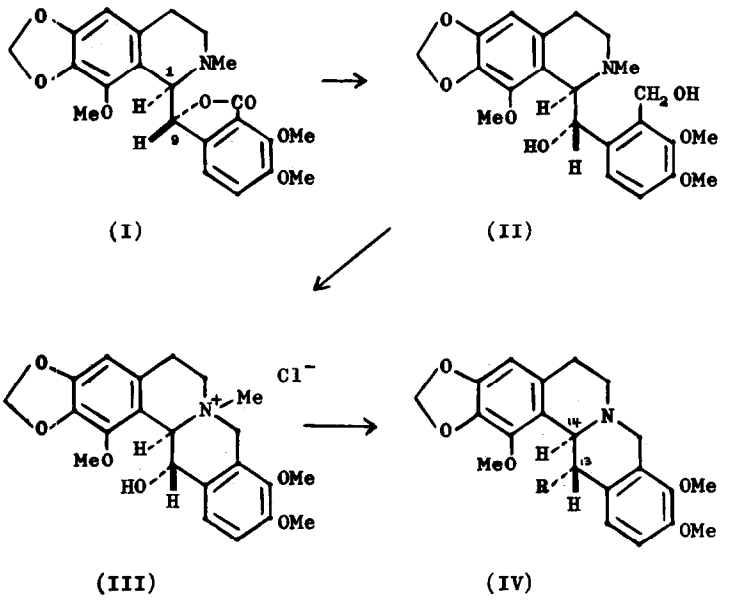
(Received 28 October 1963)

STRUCTURAL relations have a greater biogenetic interest when the natural products being considered are of known absolute stereochemistry. Our interest in the biosynthesis of narcotine (1) led to the following determination of its stereochemistry.

α-Narcotine (I) was reduced by lithium aluminium hydride to the α-diol (2) (II) which on treatment with methane sulphonyl chloride in pyridine gave the quaternary tetrahydroprotoberberine (III), isolated as the chloride, m.p. 220°. Pyrolysis yielded the corresponding base (IV, R=OH), m.p. 161° $[\alpha]_D$ −217° ($CHCl_3$) which underwent hydrogenolysis over palladised charcoal to yield the base (IV, R=H), m.p. 145°, with $[\alpha]_D$ −261° ($CHCl_3$). This product thus falls into that group of tetrahydroprotoberberines which Corrodi and Hardegger (3) have proved to possess the absolute configuration shown at position 14. It follows that α-narcotine (I), the naturally occurring alkaloid, has the illustrated configuration at position 1.

β-Narcotine (4) (I, opposite configuration at C-9) was carried through the same sequence of reactions to yield the base (IV, R=OH with opposite configuration at C-13), m.p. 185°,



(I) (II)

(III) (IV)

$[\alpha]_D$ -298^o ($CHCl_3$); this is referred to below as the β-base. Its NMR spectrum after D_2O exchange showed a partly resolved doublet corresponding to the C-13 proton (τ, 4.9, J, ca. 1.5 c./sec.) whereas the corresponding base in the α-series (IV, R=OH) showed a doublet with a large coupling (τ, 5.3, J, ca. 9 c./sec.). Both these bases possess the trans-quinolizidine system (infrared (6) bands near 2800 $cm.^{-1}$) and therefore the α-base is assigned the stereochemistry (IV, R=OH) with a dihedral angle (5) (Courtauld models) of ca. 160^o between the protons at 13 and 14. The epimeric β-base (IV, opposite C-13 configuration) has a dihedral angle of ca. 60^o and, further, the models show that its C-13 proton should be more affected than the α-isomer by long-range deshielding from the aromatic rings, in keeping with the

observed positions of the signals. There is considerable steric compression of the hydroxyl group in the α-base (IV, R=OH) and we find that this base is converted into the less-compressed β-base by vigorous treatment with methoxide. These results lead to the complete absolute stereochemistry (I) for natural α-narcotine, that is (7), 1R:9S.

It is pleasing that the absolute stereochemistry of the related phthalideisoquinoline alkaloid, hydrastine, recently determined (8), is the same as that of narcotine (I).

Satisfactory analyses and full spectral data consistent with the structures given have been obtained for all new compounds reported.

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1 A.R. Battersby and D.J. McCaldin, Proc. Chem. Soc., 365 (1962).

2 R. Mirza and R. Robinson, Nature 166, 271 (1950).

3 H. Corrodi and E. Hardegger, Helv. Chim. Acta 39, 889 (1956).

4 M.A. Marshall, F.L. Pyman and R. Robinson, J. Chem. Soc., 1315 (1934).

5 M. Karplus, J. Chem. Phys., 30, 11 (1959); L.M. Jackman, Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, p.84. Pergamon Press, London (1959).

6 F. Bohlmann, Chem. Ber., 91, 2157 (1958).

7 R.S. Cahn, C.K. Ingold and V. Prelog, Experientia 12, 81 (1956).

8 M. Ohta, H. Tani and S. Morosumi, Tetrahedron Letters No. 13, 859 (1963).