

Total synthesis of (\pm)-gigantine and its *O*-methyl ether

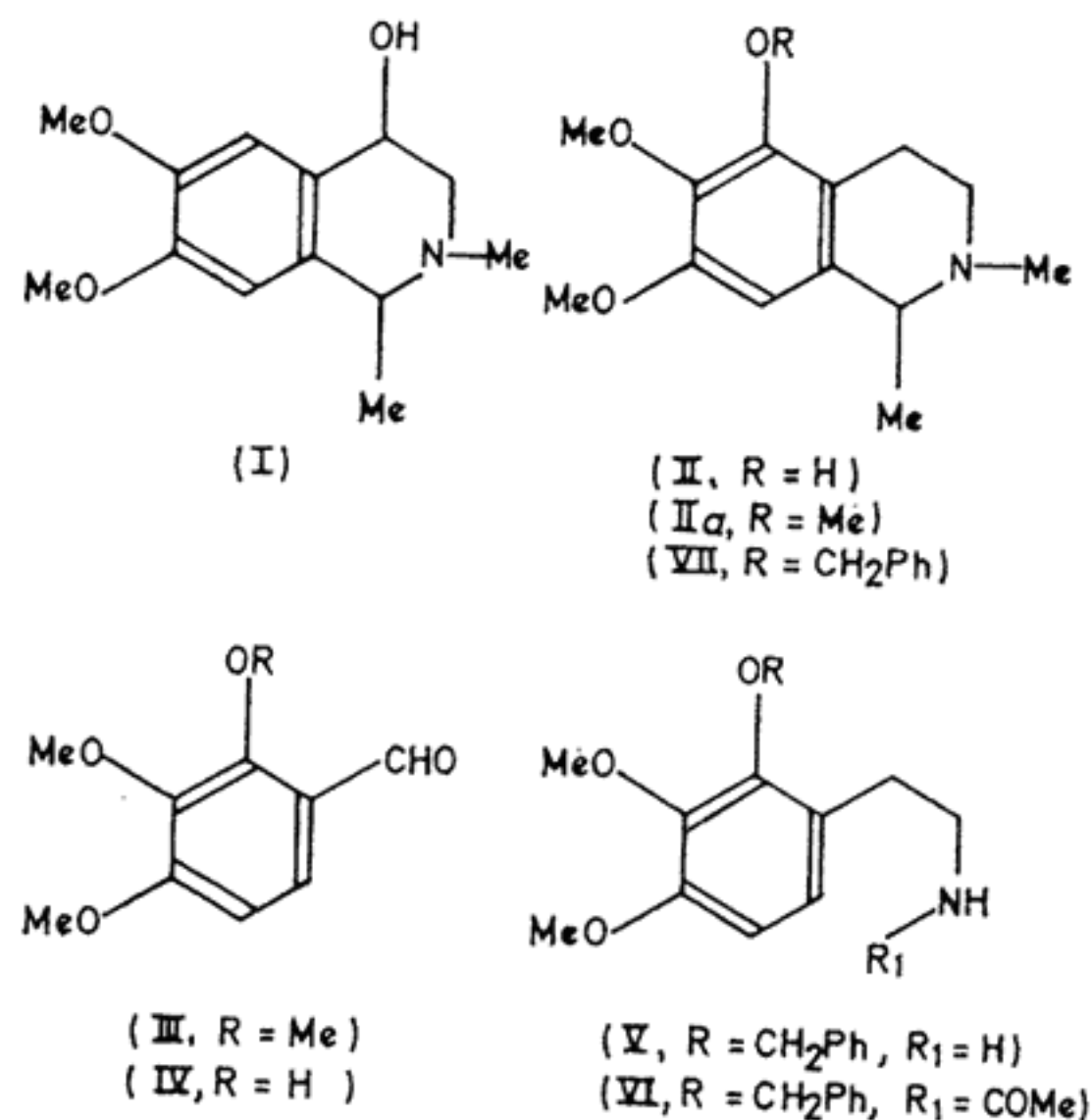
by A. M. Choudhury

University Chemical Laboratory, Lensfield Road, Cambridge, England

Gigantine, a 5,6,7-trioxygenated tetrahydroisoquinoline alkaloid isolated from the cactus *Cargenega gigantea* (Engelm.), was originally assigned the structure (I).¹ However, the position of the hydroxyl substituent was not firmly established and later Brossi *et al.*² rejected the structure because of its non-identity with both the synthetic *cis*- and *trans*-isomers of compound (I). Very recently Kapadia *et al.*³ have synthesised the tetrahydroisoquinoline (IIa) and have demonstrated its identity with *O*-methylated natural gigantine. Now the total synthesis of (\pm)-gigantine itself (II) and its *O*-methyl ether (IIa) have been accomplished as follows.

Selected demethylation of compound (III)⁴ with boron trichloride at -80°C gave the phenol (IV). The nitro-styrene of the benzyl ether of compound (IV) gave the known phenethylamine (V)⁵ on reduction with lithium aluminium hydride. Treatment of the phenethylamine (V) with acetyl chloride in anhydrous chloroform at room temperature afforded the amide (VI) as an oil. Bischler-Napieralski cyclisation, followed by *N*-methylation and reduction with sodium borohydride afforded compound (VII). Hydrogenolysis of compound (VII) with 10 per cent palladised charcoal in ethanol gave (\pm)-gigantine (II),⁶ mp $150-152^{\circ}\text{C}$ (Found: C, 65.7; H, 8.2; N, 5.95. Calc. for $\text{C}_{13}\text{H}_{19}\text{NO}_3$: C, 65.8; H, 8.1; N, 5.9 per cent). The overall yield from compound (III) was 20 per cent.

O-Methylgigantine (IIa),⁶ a brown oil, was synthesised in 38 per cent overall yield from 2,3,4-trimethoxyphenethylamine⁷ by a procedure similar to that outlined above and was identical in all respects with the product obtained by *O*-methylation of compound (II) with diazomethane. The picrate of compound (IIa) had mp $153-154^{\circ}\text{C}$.



References

- Hodgkins, J. E., Brown, S. D. & Massingill, J. L., *Tetrahedron Letters*, 1967, 1321
- Grethe, G., Usikokovic, M., Williams, T. & Brossi, A., *Helv. chim. Acta*, 1967, **50**, 2397
- Kapadia, G. J., Fayez, M. B. E., Smith, M. L. & Rao, G. S., *Chem. Commun.*, 1970, 856
- Ullmann, *Justus Liebigs Annln chem.*, 1903, **327**, 116; Papadakis, R. E. & Boand, W., *J. org. Chem.*, 1961, **26**, 2076
- Kametani, T., Kano, S., Watanabe, Y. & Kikuchi, T., *J. pharm. Soc. Japan*, 1967, **87**, 406; *Chem. Abstr.*, 1967, 82071u
- The infrared, n.m.r. and mass spectra of all the synthetic compounds were consistent with the structures shown. The spectra of synthetic gigantine were identical with those of natural gigantine.
- Kubota, S., Masiu, T., Fujita, E. & Kupchan, S. M., *J. org. Chem.*, 1966, **31**, 518