Tetrahedron Letters No.1, pp. 19-22, 1968. Pergamon Press Ltd. Printed in Great Britain.

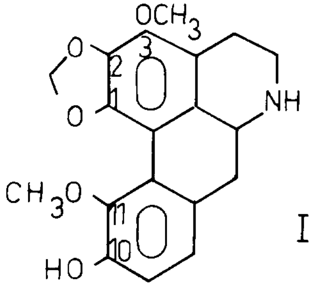
THE SYNTHESIS OF dl-HERNANDINE

K. S. Soh and F. N. Lahey

Department of Chemistry, University of Queensland, Brisbane,
Queensland, Australia.

(Received in US 26 September 1967)

Hernandine, the phenolic noraporphine alkaloid isolated from Hernandia bivalvis was recently shown(1) to have the structure(I). We have now confirmed this structure by synthesis.



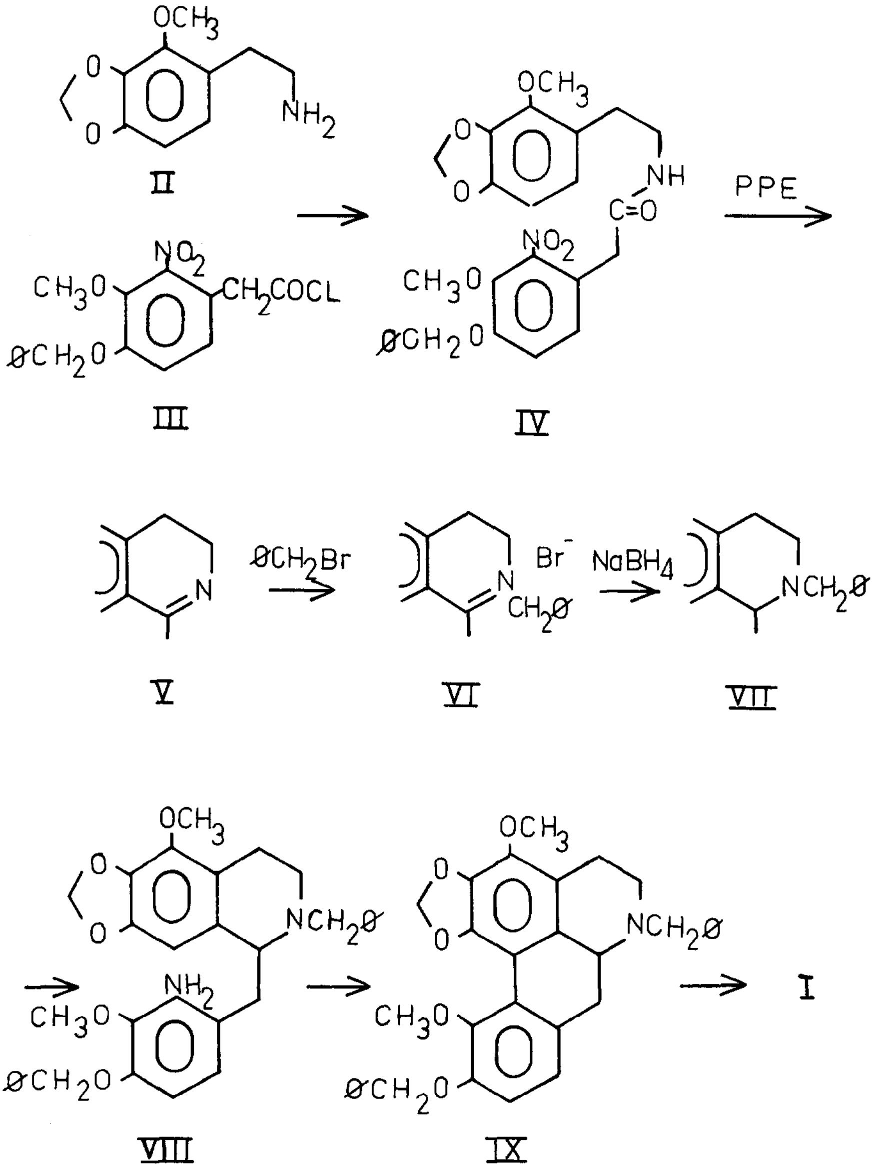
I

Few known naturally occurring aporphines have a substituent oxygen function at carbon 3 of the aporphine skeleton. The only other known examples are ocoteine(2), guatterine(3), cassyfiline(4) and cassythidine(5). Of these, only cassyfiline and hernandine are phenolic noraporphines. Ocoteine, a non-phenolic tertiary base, has been synthesised recently(6). The present synthesis of dl-hernandine thus represents the first synthesis of a phenolic noraporphine having a C3 oxygen substituent.

Effective use has been made of the benzyl group to protect both phenolic and secondary amine groups and polyphosphate ester (P.P.E.) has been confirmed as the reagent of choice for the

Bischler-Napieralski reaction.

The synthetic scheme for dl-hernandine is illustrated below:-



The amide (IV), m.p. 130-130.5°, was prepared in 76% yield by condensing 2-(2-methoxy-3,4-methylenedioxyphenyl) ethylamine (II) with 4-benzyloxy-3-methoxy-2-nitrophenylacetyl chloride (III) in the presence of alkali. Both (II) and (III) were synthesised by standard methods. The amide was cyclized smoothly in the presence of polyphosphate ester(7) to the base (V), m.p. 150-151°, which was isolated as the hydrochloride, m.p. 233-234°, in 76% yield. Refluxing the base (V) with benzyl bromide in benzene for twelve hours gave the dihydroisoquinolinium bromide (VI), m.p. 200-201° (dec.) in 72% yield. Sodium borohydride reduction of (VI) gave a quantitative yield of the tetrahydro-base (VII), m.p. 129.5-130°, and subsequent treatment with zinc and sulphuric acid afforded the amine (VIII), which was isolated as the dipicrolonate, m.p. 200-201° (dec.) in 45% yield. The free base was regenerated from the dipicrolonate with sulphuric acid and after removal of the picrolonic acid by filtration was diazotised without isolation.

A Pschorr ring closure was effected with this diazotised solution in the presence of freshly precipitated copper which gave the (dl) O,N-dibenzyl*nor*aporphine (IX) m.p. 126-127° in 10-15% yield. The infrared spectrum of (IX) was rich in detail, and identical in every respect with that of O,N-dibenzylhernandine, m.p. 118-119°, prepared by refluxing hernandine with two molar equivalents of benzyl bromide in acetone. The silica gel thin-layer Rf values of (IX) and O,N-dibenzylhernandine in four different solvent systems of different polarity were identical. The N.M.R. spectra of the two products were also identical.

Catalytic hydrogenolysis of the protecting benzyl groupings of (IX) with 5% palladium on carbon in dilute hydrochloric acid gave dl hernandine hydrochloride identified by comparison of the infrared spectrum with that of natural d-hernandine hydrochloride. Liberation of the base from the above hydrochloride afforded dl-hernandine; its infrared spectrum also was identical with that of the natural alkaloid, d-hernandine, m.p. 227-228° (dec.).

Satisfactory elementary analyses were obtained for the products described.

REFERENCES

1. K. S. Soh, F. N. Lahey and R. Greenhalgh, Tetrahedron Letters, 43, 5279, (1966).
2. M. J. Vernengo, Experientia, 19, 294 (1963).
3. W. M. Harris and T. A. Geissman, J.Org.Chem., 30, 432 (1965).
4. M. Tomita, Lu Sheng-Teh and Wang San-Jyi, Yakugaku Zasshi, 85, 827 (1965).
5. S. R. Johns and J. A. Lamberton, Aust.J.Chem., 19, 297 (1966).
6. T. R. Govindachari, B. R. Pai and G. Shanmugarundaram, Tetrahedron, 20, 2895 (1964).
7. Y. Kanaoka, E. Sato, O. Yonemitsu and Y. Ban, Tetrahedron Letters, 35, 2419 (1964).