The Synthesis of Indospicine, a Hepatotoxic Amino-acid

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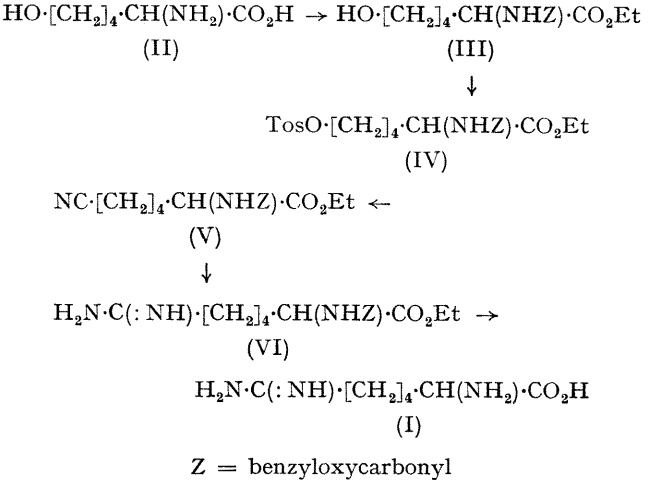
Summary *N*-Benzyloxycarbonyl-6-hydroxynorleucine is converted, *via* the 6-cyano-derivative, into indospicine.

INDOSPICINE (I), the hepatotoxic constituent of *Indigofera spicata* Forsk, [1,2] is remarkable among plant amino-acids for its amidine grouping as well as for its hepatoxicity. As further confirmation of the structure previously suggested by one of us (M.P.H.)[1] and with the aim of making this unusual substance more readily available, a total synthesis has been carried out.

6-Hydroxynorleucine (II)[3] was prepared from 5-hydroxyvaleraldehyde by a standard hydantoin synthesis. The amino-acid functions were blocked as the ethyl ester and *N*-benzyloxycarbonyl derivative (III), and the resulting compound was tosylated and converted into the nitrile (V) with potassium cyanide. Reaction of (V) with hydrogen chloride followed by ammonia in ethanol gave the amidine (VI). Removal of the amino-acid blocking groups from (VI) by heating under reflux in 2N-HCl for 4 hr. gave DL-indospicine (65% yield) which was separated from other products by chromatography on Zeokarb 226 (NH_4) cation-exchange resin.[1] It was crystallized as the sparingly soluble orange flavianate and converted into the monohydrochloride. This crystallized from aqueous ethanol as the hemihydrate m.p. 195—197°.

Apart from physical properties involving optical activity, the racemate proved (chromatographic behaviour and colour reactions on paper and thin-layer chromatography, high-voltage ionophoresis at pH 10·1, peak effluent volume on amino-acid analyser, n.m.r., and mass spectra‡) to be identical with the natural indospicine. The synthetic material inhibits the incorporation of [^{14}C]arginine into protein in a rat-liver cell-free system, with half the activity of natural L-indospicine.[4]



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† The natural isolate crystallized as the monohydrate m.p. 131—134°. Rigorous drying did not completely remove this water of crystallization from either sample.

‡ The mass spectrum of indospicine shows no reproducible peaks of higher mass number than *m/e* 111; a peak of *m/e* 156 ($M - NH_3$) has been observed on one occasion only. The ethyl esters of both natural and synthetic indospicine were prepared and showed peaks of *m/e* 184 but no parent ion.

[1] M. P. Hegarty and A. W. Pound, *Nature*, 1968, **217**, 354.
[2] G. S. Christie, N. P. Madsen, and M. P. Hegarty, *Biochem. Pharmacol.*, 1969, **18**, 693.
[3] R. Gaudry, *Canad. J. Res.*, 1948, **B**, **26**, 387.
[4] N. P. Madsen, G. S. Christie, and M. P. Hegarty, unpublished results.