

STRUCTURE OF DESMETHYLPSYCHOTRINE: A STEREOSELECTIVE SYNTHESIS
OF (+)-9-DEMETHYLPSYCHOTRINE

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With a view to establishing the structure of desmethylpsychotrine, one of the benzoquinolizidine alkaloids isolated from Alangium lamarckii Thw. (family Alangiaceae), the synthesis of (+)-9-demethylpsychotrine (VI) was achieved by employing the "cincholoipon-incorporating method".

Condensation of cincholoipon ethyl ester [(+)-X], prepared from the Cinchona alkaloid cinchonine (IX) by the known method, with 3-benzyloxy-4-methoxyphenacyl bromide furnished the amino ketone (+)-XI (71% yield), which was reduced with NaBH₄ to the amino alcohol XII (94% yield). The mercuric acetate-EDTA oxidation (1% aq. AcOH, reflux, 1.5 hr) of XII and column chromatographic separation of the products gave the 6-piperidone XIII (55% yield) and a mixture of the cis- and trans-2-piperidones XIV (20% yield). On catalytic hydrogenolysis (91% yield) followed by hydrolysis (97% yield), the 6-piperidone XIII produced the lactam acid (-)-XVI. When heated at 180° for 1.5 hr, the cis-acid (-)-XVI could transform into the trans-acid (+)-XVII (74% yield), which was esterified (96% yield) and then benzylated (98% yield) to provide the lactam ester (+)-XVIII. The Bischler-Napieralski cyclization of (+)-XVIII was effected with POCl₃ in boiling toluene and the resulting immonium salt was reduced to give the tricycle (-)-XIX in 73% overall yield. Conversion of (-)-XIX into the amide (-)-XXI was accomplished through the amino acid (-)-XX by alkaline hydrolysis (82% yield) followed by the condensation with 3-benzyloxy-4-methoxyphenethylamine (diethyl phosphorocyanidate, Et₃N, DMF, room temp., 87% yield). Ring closure of the amide (-)-XXI (POCl₃, boiling toluene) furnished the base (+)-XXII (81% yield), which was then debenzylated (10% aq. HCl-EtOH, reflux) to the desired phenolic base (+)-VI in 82% yield.

The UV, IR, and mass spectra of the phenolic base (+)-VI thus obtained were found to match those of natural desmethylpsychotrine, establishing the structure of this alkaloid as 9-demethylpsychotrine.