Reactions of Harmaline and its Derivatives, IV Synthesis of a Pentacyclic System Isomeric with 11-Methoxy-5,6-dihydrosempervirine

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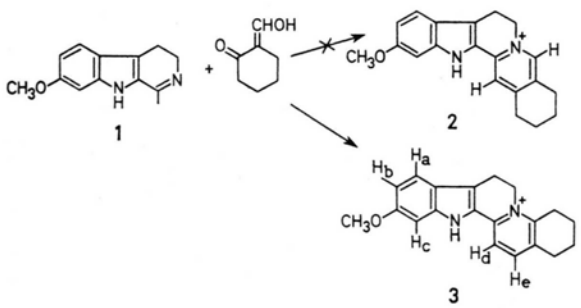
Reaction of harmaline with formyl cyclohexanone has afforded methoxyisosempervirine.

We have previously demonstrated that harmaline (**1**), a major indole alkaloid from the seeds of *Peganum harmala*[1], can serve as a versatile starting material for the synthesis of indoloquinolizidines and pharmacologically interesting indole alkaloidal systems bearing a methoxyl group at the 11-position[2–4]. Since there is a rapid equilibrium between the imine and the enamine forms of harmaline[5] both N- and C-alkylations were found to occur.

In continuation of these studies harmaline was allowed to react with 2-formycyclohexanone in refluxing 1:1 methanol-benzene. After 3 hours harmaline was found to be converted to a new slower moving material in about 70% yield. The product crystallised from a mixture of acetone, methanol and pet. ether as yellow needles, m.p. 200–202 °C. The two likely structures for the product are **2** and **3** depending on whether N-alkylation or C-alkylation preceded cyclization.



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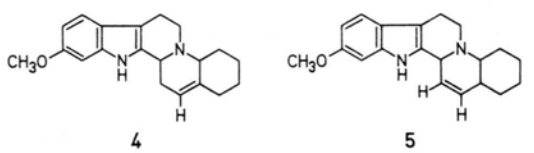
The NMR spectrum of the product in CD_3OD immediately ruled out **2** as the two aromatic protons H_d and H_e in ring D resonated as two doublets of an AB system centered at δ 7.74 and δ 7.96 respectively (J = 8 c/s). The two vicinal aromatic protons H_a and H_b in ring A also appeared as two doublets of another AB system centered at δ 6.60 and δ 7.42 respectively (J = 8.2 c/s). H_b also showed meta coupling with H_c (J = 2 c/s). The methylene protons adjacent to the quaternary nitrogen were found significantly deshielded and resonated as a triplet at δ 4.5 (J = 7.8 c/s). The methoxyl group afforded a sharp singlet at δ 3.8.

The IR spectrum showed the absence of any carbonyl group in the substance. The UV spectrum in methanol afforded λ maxima at 221, 264 (shoulder), 280, 322 and 413 nm (ε max 22250, 5230, 7417, 12160, 17025 respectively) λ min 245, 288, and 355 nm (ε min 3040, 4985 and 7990 respectively), and no shifts were observed in acidic or basic solutions.

Reduction of the yellow crystals in aqueous ethanol with sodium borohydride afforded a new faster running product which was crystallised as colourless needles from ethylacetate, m.p. 240–42 °C. The NMR spectrum of the product was in agreement with structure **4**. The alternative structure **5** was ruled out on the grounds of the presence of only one olefinic proton in the molecule at δ 5.53.



This procedure offers an alternative route to such pentacyclic heterocycles[6] isomeric with the pharmacologically interesting yohimbine, reserpine and alstonine skeletal systems. Extensions to other indole alkaloidal systems are currently under investigation.

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