Reactions of Harmaline and its Derivatives, V
A one-Step Synthesis of Reserpine Analogues

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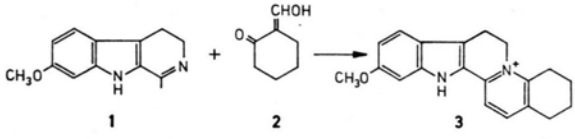
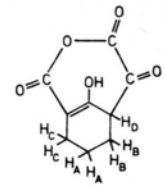
Harmaline, β-Carbolines, Indoles, Reserpine Analogues

The reaction of harmaline with the cyclohexanone derivative (**4**) affords the reserpine analogue (**5**) in high yields, thus providing a one step approach to such pharmacologically important substances.

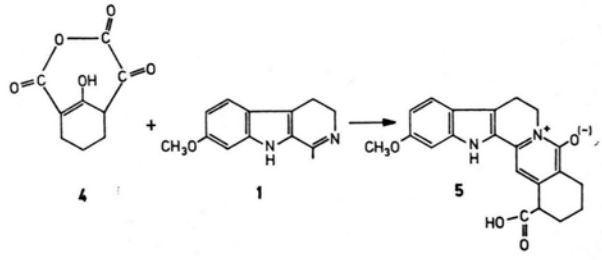
Our earlier studies[1–4] on the enamine chemistry of harmaline recently led us to report[5] the reactions of this alkaloid with formyl cyclohexanone (**2**) which afforded a ring system (**3**) isomeric to dihydrosempervirine instead of the desired reserpine skeletal system.



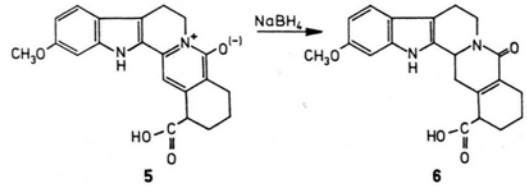
We now report the reaction of harmaline with the reaction product of cyclohexanone with oxalylchloride to afford the reserpinoid skeletal system. Equimolar amounts of cyclohexanone and oxalylchloride were refluxed in undried carbon tetrachloride or benzene for 2 hours. A white crystalline solid settled in the reaction mixture which was filtered and washed thoroughly with benzene. The substance, m.p. 240 °C, was found to be sparingly soluble in most solvents. Microanalysis indicated the absence of chlorine in the substance. The IR spectrum of the substance showed absorptions in the carbonyl region at 1782 cm^{-1}, 1685 cm^{-1} and 1665 cm^{-1}. The NMR spectrum in trifluoroacetic acid showed a two proton quintet at δ 1.96 (H_A, $J_{AB} = J_{AC} = 6$ H), a two proton quartet at δ 2.54 (H_B, $J_{ADB} = 5.5$–6.0 Hz), a two proton triplet at δ 2.84 (H_C, $J_{AC} = 6$ Hz), and a one proton triplet at δ 6.37 (H_D, $J_{BD} = 5.5$ Hz). The mass spectrum failed to afford the molecular ion in analogy with the mass spectra of other anhydrides[6], but afforded a



prominent M^+–OH and M^+–CO_2 peaks at $m/e = 179$ and 152 respectively. The loss of C=O from the fragment with $m/e = 152$ was confirmed by the presence of the corresponding metastable peak at $m/e = 101.1$. In view of these data the structure **4** was assigned to the product.



When harmaline was allowed to react with the substance **4** in methanol-benzene (1:1) for 24 hours at room temperature, a new slower running material was observed on t.l.c. The product crystallised as red crystals, m.p. 319 °C. The substance afforded a prominent peak at 1720 cm^{-1} in its IR spectrum. The ultra-violet spectrum afforded peaks at λmax 218 nm (εmax 20727), 267 nm (εmax 6182), 335 nm (εmax 13836), 455 (εmax 12364), λmin 370 nm (εmin 5818), 293 nm (εmin 5454) which shifted to λmax 220 nm (εmax 34545), 280 nm (εmax 9090), 335 nm (εmax 9455), 403 nm (εmax (13090); λmin 299 nm (εmin 6909), 370 nm (εmin 9090) on basification of the solution. This shift was found to be reversible, the original peaks appearing on acidification. The NMR spec-



trum of the substance in deuteromethanol showed the methoxyl group as a sharp 3-proton singlet at δ4.01. A one-proton double doublet was found to be centered at δ6.64 and was assigned to the proton B in ring A ($J_{AB} = 9$ Hz, $J_{BC} = 2.5$ Hz). A one-proton doublet centred at δ6.76 was assigned to the proton C ($J_{BC} = 2.5$ Hz). The proton A showed a clean doublet δat 7.38 ($J_{AB} = 9$ c/s). The aromatic proton in ring D was strongly deshielded by the quaternary nitrogen and appeared as a one-proton singlet at

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δ8.05. A two-proton triplet at δ4.47 ($J = 8$ c/s) was assigned to H_E, the methylene protons also being strongly deshielded by the adjacent quaternary nitrogen atom.

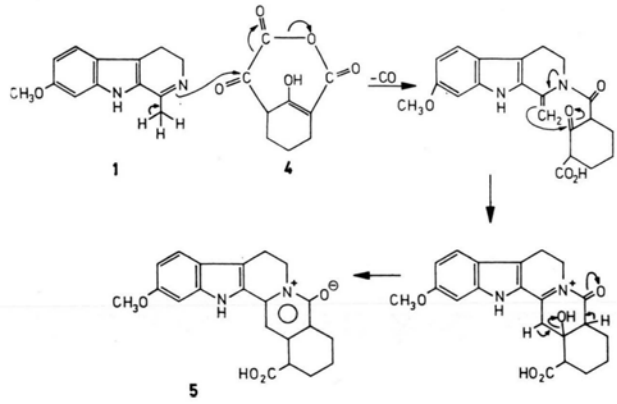
The mass spectrum of the red substance afforded the molecular ion at $m/e = 364$. The substance showed an initial loss of a methyl group (from the methoxyl) and subsequently underwent decarboxylation to afford a prominent peak at $m/e = 205$.

The substance **5** was reduced with sodium borohydride in ethanol for 5 minutes at room temperature to afford a major faster running colourless product m.p. 248–250 °C. The substance afforded a molecular ion at $m/e = 366$. The product showed the carbonyl absorption of the acid group at 1720 cm^{-1} and conjugated amide carbonyl at 1630 cm^{-1}. The structure of the reduced product is therefore assigned as **6**.

The mechanism of the reaction of harmaline with **4** involves the initial attack of the basic nitrogen on the carbonyl group followed by cyclization of the enamide and dehydration.

This procedure affords an easy one-step access to the pharmacologically important reserpine alkaloidal system. Reactions with suitably substituted cyclohexane derivatives should afford other interesting analogues of reserpine and such approaches are under investigation.

The authors wish to thank Dr. VIQAR UDDIN AHMAD for the microanalysis and NMR spectra of the substances **4** and **5**.



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