Intramolecular Thermal Rearrangement of Harmine Hydroiodide to a New Anhydronium Base, Methylharmol

Salimuzzaman Siddiqui*, Naheed Sultan, and Abdul Malik

H. E. J. Research Institute of Chemistry, University of Karachi, Karachi-32, Pakistan

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Harmine Hydroiodide, Thermal Rearrangement, Methylharmol, 1,2-Dimethyl-2H-pyrido[3,4-b]indol-7-ol

Thermal rearrangement of harmine hydroiodide (1) at 300 °C provided a new anhydronium base provisionally named as methylharmol (3). The structure was assigned on the basis of UV, IR and NMR spectral data of the base and its tetrahydro product (2). Nitration of methylharmol afforded 12-nitromethylharmol (4).

One of us has recently reported [1] that the alkaloids of Peganum harmala seeds are wholly located in the husk which forms about 50% of the seeds and that the kernel yields 20% of oil which is of edible quality. However, the economic viability of the harmful seeds as a new source of edible oil would considerably depend on the appropriate utilization of the alkaloids of the husk available in about 7% yield. Intensive structure activity correlation studies have therefore been undertaken on harmine series of alkaloids.

In an earlier communication Siddiqui and Sharma [2] had observed that thermal treatment of conessine and iso-conessine hydroiodides, the steroidal alkaloid of Holarrhena antidysenterica [3], results in the elimination of both the nitrogen atoms to form an steroidal hydrocarbon. These findings prompted us to carry out parallel studies on harmine hydroiodide where the nitrogen atoms form part of a highly stabilized β-carboline system. In this case both the nitrogen atoms remained intact on heating, while the π-electron system of the base underwent intramolecular rearrangement leading ultimately to the hydroiodide salt of a new quaternary base named as methylharmol (3).

Gradual heating of harmine hydroiodide to 300 °C resulted in a darkish brown mass which afforded methylharmol as lemon yellow shining rods. The procedure of its isolation as noted in the experimental was based on the sparing solubility of its hydroiodide in water and fair solubility of the free base in 3% ammonium hydroxide. It melted at 286 °C (decomp.) and analyzed for C_{13}H_{12}N_{2}O. The molecular formula was confirmed by high resolution mass spectrum, which showed molecular ion peak at m/z 212.0947 (calcd for C_{13}H_{12}N_{2}O 212.09458) and gave a fragmentation pattern similar to that of harmine [4].

The UV spectrum of methylharmol recorded in methanol showed maxima at 208, 252 and 336 nm, characteristic of β-carboline system [5]. The IR spectrum showed a broad band between 3400—3200 cm$^{-1}$ (NH/OH group). In addition there were peaks at 3100—2900 (C—H stretching) and 1610 cm$^{-1}$ (C=C vibration of the benzene ring). The peaks at 875 and 738 cm$^{-1}$ represented C—H bending of 1,2,4-trisubstituted benzene. There was no strong peak between 1800—1630 cm$^{-1}$, indicating the absence of a carbonyl group. The solubility of the base in warm alkaline solution indicated its acidic or phenolic nature and the absence of carboxylic group showed it to be a phenol. This was further confirmed by characteristic bathochromic shifts of UV maxima at pH 13. The completely dehydrated base in vacuum did not show the presence of NH group. This along with colour and UV spectrum, strongly suggested an anhydronium base structure for methylharmol.

On catalytic reduction methylharmol yielded tetrahydro derivative (2) C_{13}H_{16}N_{2}O, melting at 268—270 °C. The melting point and IR corresponded to those reported in the literature for N-methyltetrahydroharmol (6), isolated from Elaeagnus angustifolia. Final evidence for the structure 2 of tetrahydro derivative was provided through its mixed melting point with an authentic sample of N-methyltetrahydroharmol prepared according to the reported procedure [6].

* Reprint requests to Prof. Dr. S. Siddiqui.

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Keeping in view the fact that N-methyltetrahydroharmol is a reduction product of methylharmol and the relationship between serpencticine and its tetrahydro product [7], structure 3 has been assigned to methylharmol.

Conclusive support to this structure was provided by $^1$H and $^{13}$C NMR spectra of methylharmol. In $^1$H NMR (300 MHz) spectrum recorded in deuterated methanol, there were two singlets at $\delta$ 2.62 and 4.01 assignable to C—CH$_3$ and N$^+$—CH$_3$ respectively. The signal of H-8 appeared at $\delta$ 6.35 as a doublet ($J_{6,8} = 2.0$ Hz). The double doublet at $\delta$ 6.62 was assigned to H-6 ($J_{5,6} = 8.0$ and $J_{6,8} = 2.0$ Hz), while H-5 appeared as a doublet at $\delta$ 7.57 ($J_{5,6} = 5.9$ Hz). The relative assignments of the aromatic protons were confirmed by homodecoupling experiments and through comparison with the related peaks of harmine N-oxide isolated from Banisteriopsis caapi [8]. Irradiation of H-8 signal caused the double doublet of H-6 to collapse into a doublet with an ortho coupling of 8.9 Hz. On the other hand irradiation of H-6 signal converted the doublets of H-5 and H-8 each into singlets. H-3 and H-4 of the pyridine ring formed an AB system. The downfield doublet at $\delta$ 7.81 was assigned to H-4 which is alpha to nitrogen atom ($J_{3,4} = 6.6$ Hz), while H-6 was observed at $\delta$ 7.55 as a doublet ($J_{3,4} = 6.6$ Hz).

The assignments of various signals in the $^{13}$C NMR spectrum (75 MHz) of methylharmol recorded in DMSO were made through DEPT experiments (Table I) and supported by $^{13}$C NMR published data of harmine, harmol [9, 10] and N-methyltetrahydroharmine [11].

The formation of methylharmol can be accounted for as being due to internal rearrangement of $\pi$-electrons of harmine hydroiodide, catalyzed by the iodide ion when heated above its melting point (Scheme 1). Such a rearrangement had earlier been proposed by W. H. Perkin to explain the origin of N$_2$-methylharmine from harmine [12]. The hydrogen iodide formed in situ caused O-demethylation of the aromatic methoxy group to generate the phenolic function. The methyl iodide liberated during this step attacked the pyridine nitrogen, leading to the hydroiodide salt of methylharmol.

The participation of iodide ion in the rearrangement was evident from the observation that harmine did not undergo this type of rearrangement under similar experimental conditions. Parallel studies with harmaline and tetrahydroharmine in which the ring C is not aromatized, did not lead to any uniform product, thereby providing further support to the above mechanism.

As part of a general programme of studies in the correlation of structure and activity in $\beta$-carboline

### Table I. $^{13}$C NMR assignments of methylharmol (3).

<table>
<thead>
<tr>
<th>No. of carbon</th>
<th>Chemical shift$^a$</th>
<th>Multiplicity (DEPT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>141.73</td>
<td>C</td>
</tr>
<tr>
<td>3</td>
<td>137.62</td>
<td>CH</td>
</tr>
<tr>
<td>4</td>
<td>113.42</td>
<td>CH</td>
</tr>
<tr>
<td>4a</td>
<td>112.95</td>
<td>C</td>
</tr>
<tr>
<td>4b</td>
<td>128.28</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>122.99</td>
<td>CH</td>
</tr>
<tr>
<td>6</td>
<td>110.91</td>
<td>CH</td>
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<tr>
<td>7</td>
<td>155.72</td>
<td>C</td>
</tr>
<tr>
<td>8</td>
<td>99.28</td>
<td>CH</td>
</tr>
<tr>
<td>8a</td>
<td>130.69</td>
<td>C</td>
</tr>
<tr>
<td>8b</td>
<td>138.68</td>
<td>C</td>
</tr>
<tr>
<td>C—CH$_3$</td>
<td>14.26</td>
<td>CH$_3$</td>
</tr>
<tr>
<td>N$^+$—CH$_3$</td>
<td>42.98</td>
<td>CH$_3$</td>
</tr>
</tbody>
</table>

$^a$ All values are in ppm ($\delta$) with respect to TMS.
bases, nitration of methylharmol has also been carried out in the present work. As a result a mononitro derivative 4 was obtained as orange needles which decomposed at 334-335 °C. The molecular formula C_{13}H_{12}N_{2}O was confirmed by high resolution mass spectrum which showed M$^+$ peak at $m/z$ 257.080101. The IR spectrum showed intense peaks at 1510 and 1104 cm$^{-1}$ for the nitro group. The $^1$H NMR (300 MHz) spectrum in CD$_3$OD indicated the position of nitro group at C-8. In the aromatic region there were two doublets, each of one proton resonating at $\delta$ 6.32 ($J_{5,6} = 9.3$ Hz) and 7.7 ($J_{5,6} = 9.3$ Hz), which were assigned to H-6 and H-5 respectively.

**Experimental**

The melting points were recorded in glass capillary tubes and are uncorrected. UV (MeOH): Instrument Shimadzu 240 UV spectrometer. IR (KBr): Instrument Jasco A-302 infra red spectrometer. $^1$H and $^13$C NMR: Instrument Bruker AM-300 NMR spectrometer and TMS as internal reference; DEPT experiments were carried out at $\theta = 45^\circ$, 90$^\circ$ and 135$^\circ$. MS: Instrument Finnigan MAT 312. Elemental analysis: Instrument Carlo Erba Elemental Analyzer Mod. 1104.

**Thermal rearrangement of harmine hydroiodide to methylharmol (3)**

Harmine hydroiodide (5g, 14.7 mmol) was taken in a 50 ml Erlenmeyer flask immersed in a metal bath at 270 °C and the temperature was gradually raised to 300 °C. It was kept at this temperature with constant stirring till the mass completely melted. After cooling, the darkish brown solidified mass was repeatedly triturated with water to remove residual harmine hydroiodide. The residue was taken up in hot 3% ammonium hydroxide and a little quantity of insoluble blackish tarry residue was neglected. On cooling, the dilute ammonia solution gave methylharmol (3) as beautiful orange rectangular rods which on repeated crystallization from methanol-benzene (1:1) finally melted at 285-286 °C (yield 28%). It is soluble in methanol, sparingly soluble in ethyl acetate and water, insoluble in benzene and ether and analyzed for C$_{13}$H$_{12}$N$_2$O.

\[
C_{13}H_{12}N_2O \cdot H_2O
\]

Caled C 67.28 H 6.08 N 12.17 O 14.47.
Found C 67.96 H 6.02 N 12.13 O 13.89.

EIMS $m/z$ (rel. int. %): 212.09497 (M$^+$, 100), 197 (M$^+$-CH$_3$, 38.2), 183 (23.6) and 171 (58.3). - UV $\lambda_{max}$ (MeOH, nm): 205, 252 and 336. - IR $\nu_{max}$ (KBr, cm$^{-1}$): 3400-3200 (NH/OH), 3000-2900 (C-H stretching) and 1610 (C=C). - $^1$H NMR (90 MHz, CD$_3$OD): $\delta$ = 2.62 (3H, s, C-CH$_3$), 4.01 (3H, s, N$^-$-CH$_3$), 6.35 (1H, d, $J_{6,8} = 2.0$ Hz, H-8), 6.62 (1H, q, $J_{5,6} = 8.9$, $J_{6,8} = 2.0$ Hz, H-6), 7.55 (1H, d, $J_{3,4} = 6.6$ Hz, H-4), 7.57 (1H, d, $J_{5,6} = 8.9$ Hz, H-5) and 7.81 (1H, d, $J_{3,4} = 6.6$ Hz, H-3).

**Catalytic reduction of methylharmol to N-methyltetrahydroharmol (2)**

A solution of methylharmol in absolute methanol (100 ml) was brought to pH 10 with methanolic alkali and treated with hydrogen over platinum oxide (200 mg) for 10 h. The reduced product was taken up in ethyl acetate, filtered and the crystalline residue left on removal of the solvent from the filtrate was taken in a mixture of methanol-benzene (2:1) and kept in cold, when colourless plates of tetrahydro derivative (N-methyltetrahydroharmol) separated out 0.72 g (yield 70%) which melted at 268-270 °C. Its IR and mass spectral data are identical with that of N-methyltetrahydroharmol [6].

**Salts of methylharmol (3)**

The hydrochloride, hydrobromide, hydroiodide, nitrate and picrate salts of methylharmol were prepared by treating dilute acetic acid solution of the base with the aqueous solution of the corresponding alkali salts and picric acid respectively, followed by crystallization from methanol with the help of little water. The picrate melted at 283-284 °C while, all the other salts charred without melting above 360 °C.

**8-Nitromethylharmol (4)**

To a solution of 1g of methylharmol in 2 ml glacial acetic acid was added 2 ml of nitric acid (d = 1.4) at 10 °C under constant stirring. The initial yellow colour of the reaction mixture turned to reddish orange and finally to dark red. During the reaction period the temperature was not allowed to rise above 20 °C. After one minute a drop taken out from the reaction mixture was checked under UV light, which showed the absence of any unreacted methylharmol. At this stage the reaction mixture was poured into crushed ice and the resulting crystalline yellowish orange nitrate was filtered and washed with cold water. It was taken up in methanol from which it crystallized out as fine needles. On repeated crystallization from the same solvent it finally melted at 318-320 °C (de-
comp.). The liberated base, on recrystallization from a mixture of methanol-benzene (1:1) yielded 0.89 g (74%) 8-nitromethylharmol (4) which melted at 334–335 °C (decomp.) and analyzed for $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_3$.

$\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_3$

Calcd: C 60.81 H 4.31 N 16.34 O 18.54.
Found: C 60.68 H 4.31 N 16.33 O 18.69.

EIMS $m/z$ (rel. int. %): 257.080101 ($\text{M}^+$, 45.5), 227 ($\text{M}^+-\text{NO}_2$, 18.3), 212 ($\text{M}^+-\text{NO}_2$, 14.5). − IR $\nu_{\text{max}}$ (KBr, cm$^{-1}$): 3400–3200 (NH/OH), 3000–2900 (C–H stretching), 1610 (C=C), 1510 and 1350 (−NO$_2$). − $^1$H NMR (300 MHz, CD$_3$OD): $\delta = 6.32$ (1H, d, $J_{5,6} = 9.3$ Hz, H-6) and 7.7 (1H, d, $J_{5,6} = 9.3$ Hz, H-5).
