# ALKYL ANHYDRONIUM BASES OF HARMALINE -- A β-CARBOLINE ALKALOID OF *PEGANUM HARMALA*

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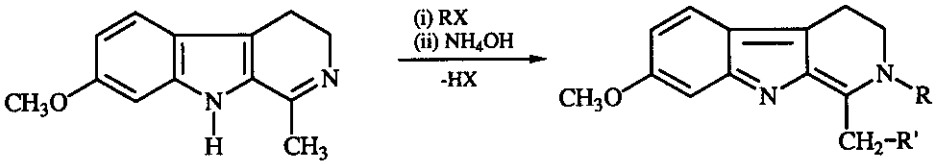
**Abstract**-This paper reports the synthesis of alkylanhydronium bases from harmaline on its reaction with different alkyl halides. There is no earlier procedure of formation of alkylharmaline with anhydronium skeleton, with these or any other reagent.

In harmaline (**1**), a simple major β-carboline alkaloid of *Peganum harmala,*[1,2] the existence of imine-enamine equilibrium[3] was established[4,5] through $^1$H-nmr studies. Through this tautomerism various *C*- and *N*-alkylated and acylated products have been communicated earlier by various groups of workers.[6,7] In these products indole nucleus remains intact. Robinson obtained methylharmine with anhydronium skeleton from the corresponding metho salt under drastic conditions.[8] However, there is no report in literature on the formation of any alkylharmaline with anhydronium skeleton.

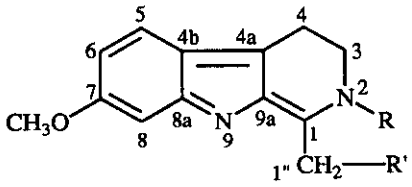
In the present studies formation of a series of *N*-alkylated harmaline with anhydronium skeleton has been achieved under mild reaction conditions. On treatment of harmaline with various alkyl halides, these derivatives have been obtained in moderate yields with the loss of indolic *N*-H hydrogen. Thus, when reaction of harmaline was carried out with amyl bromide, butyl bromide, propyl bromide, ethyl iodide and allyl bromide in methanol at room temperature for 1 month the corresponding *Py N*-alkyl derivatives (**2-6**) with anhydronium skeleton have been obtained. Under same reaction conditions methyl iodide does not react with harmaline. However, when reaction was attempted with the sodium salt of harmaline in methanol under reflux for two h, the corresponding *Py-N,C*-dimethylanhydronium base (**7**) was obtained in 79.8 % yield. All these derivatives were characterized through various spectroscopic methods (Table 1-7) including 1D and 2D nmr studies (COSY-45, NOESY, *J*-resolved and hetero-COSY) .

An alternative structure A was also considered for these bases in which the benzene ring is not dearomatized as in anhydronium bases (**2-7**). However the $^{13}$C-nmr favoured the anhydronium




**1** **2-7**

Scheme




**2** R = $CH_3$-$CH_2$-$CH_2$-$CH_2$-$CH_2$-$CH_2$—, R' = H

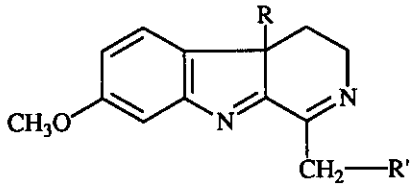
**3** R = $CH_3$-$CH_2$-$CH_2$-$CH_2$—, R' = H

**4** R = $CH_3$-$CH_2$-$CH_2$—, R' = H

**5** R = $CH_3$-$CH_2$—, R' = H

**6** R = $CH_2$=CH-$CH_2$—, R' = H

**7** R = $CH_3$ R' = $CH_3$




Structure A

structure since it showed six quarternary $sp^2$ carbons : (*i.e.* C-1, C-4a , C-4b, C-7, C-8a and C-9a), while the alternative srtucture A would have only five such carbons ( *i.e.* C-1, C-4b, C-7, C-8a and C-9a). Moreover, structure A would also have a quarternary $sp^3$ carbon (*i.e.* C-4a) which was also not observed. Another evidence in support of the anhydronium structure came from the downfield chemical shifts of the protons at C-1' being substituted on the N atom which is a usual observation in N-alkyl derivatives.[10] In the alternate structure A the alkyl groups would be at a saturated quarternary carbon (*i.e.* at C-4a) and hence the chemicl shifts of the protons at C-1' must be at upfield region. In view of these observations the anhydronium structures of **2-7** were decided.

## EXPERIMENTAL

Melting points are uncorrected. Mass spectra were recorded on a Finnigan MAT 112 and 312 double focussing mass spectrometers connected to a PDP 11/34 computer system; nmr spectra ($CDCl_3$): Bruker 400 MHz for $^1H$ and 75 MHz for $^{13}C$. The chemical shifts are reported in $\delta$ (ppm) and the coupling constants are in Hz. The $^{13}C$-nmr spectral assignments (Table 2-7) have been made partly through a comparison of the chemical shifts with the published data for similar compounds[9,10] and partly through the appearance of signals in DEPT and HMQC spectra.

## EXPERIMENTAL PROCEDURE FOR ALKYLATION OF HARMALINE:

To a solution of harmaline (1 mmol; 214 mg) in 50 ml of methanol, alkyl halide (1.2 mmol) was added and the reaction mixture was kept in dark at the temperature of $25^0C$ for 1 month during which the reaction was regularly monitored by tlc. The solvent was removed under reduced pressure to give a brownish mass which was basified with 30% aqueous ammonia and extracted out with EtOAc. The EtOAc layer was repeatedly washed with water, dried ($Na_2SO_4$) and freed of the solvent under reduced pressure. Tlc of the residue showed two spots which were separated through chromatography on chromatotron model 7924T ($CHCl_3$:MeOH, 19:1) and characterized as alkylharmaline (**2-6**) and unreacted harmaline (35-50 mg).

2-Amyl-2,4-dihydro-7-methoxy-1-methyl-3*H*-pyrido[3,4-*b*]indole (**2**): Needles (204.5 mg) from methanol. mp $176\text{-}178^0C$. Ms *m/z* (rel. int.) : 284.1856 $M^+$ (calcd for $C_{18}H_{24}N_2O$, 284.1888) (10), 269 (6) and 213 (18); uv $\lambda_{max}$ (MeOH) nm: 391, 254 and 204; ir $\nu_{max}$ ($CHCl_3$) $cm^{-1}$: 3150, 2900, 1640, 1560, 1520, 1460, 1150 and 1135; $^1H$ and $^{13}C$-nmr (Table 1).

2-Butyl-2,4-dihydro-7-methoxy-1-methyl-3*H*-pyrido[3,4-*b*]indole (**3**): Needles (194.5 mg) from methanol. mp 180-182$^0$C. Ms *m/z* (rel. int.) :270.1692 $M^+$ (calcd for $C_{17}H_{22}N_2O$, 270.1732) (45), 255 (30), 241 (28) and 213 (52); uv $\lambda_{max}$ (MeOH) nm: 390, 253, 217 and 205; ir $\nu_{max}$ ($CHCl_3$) $cm^{-1}$: 3140, 2920, 1640, 1600, 1520, 1460, 1140 and 1135 ; $^1$H and $^{13}$C-nmr (Table 2).

2,4-Dihydro-7-methoxy-1-methyl-2-propyl-3-*H*-pyrido[3,4-*b*]indole (**4**): Needles (165 mg) from methanol. mp 206-208 $^0$C. Ms *m/z* (rel. int.) :256.1560 $M^+$ (cacld for $C_{16}H_{20}N_2O$, 256.1575) (58) , 241 (22) and 213 (44); uv $\lambda_{max}$ (MeOH) nm: 391, 254 and 204; ir $\nu_{max}$ ($CHCl_3$) $cm^{-1}$:3150, 2900, 1640, 1560, 1520, 1460, 1150 and 1135; $^1$H and $^{13}$C-nmr (Table 3).

2,4-Dihydro-2-ethyl-7-methoxy-1-methyl-3*H*-pyrido[3,4-*b*]indole (**5**): Needles (163.5 mg) from methanol. mp 236-238$^0$C. Ms *m/z* (rel. int.) :242.1451 $M^+$ (calcd for $C_{15}H_{18}N_2O$, 242.1419) (24) , 227 (18) and 213 (22); uv $\lambda_{max}$ (MeOH) nm: 391, 259 and 218; ir $\nu_{max}$ ($CHCl_3$) $cm^{-1}$:3150, 2950, 1625, 1580, 1560, 1440, 1150 and 1105; $^1$H and $^{13}$C-nmr (Table 4).

2-Allyl-2,4-dihydro-7-methoxy-1-methyl-3*H*-pyrido[3,4-*b*]indole (**6**): Needles (184.5 mg) from methanol. mp 200-202$^0$C. Ms *m/z* (rel. int.) :254.1408 $M^+$ (calcd for $C_{16}H_{18}N_2O$) (42), 239 (28), 223 (10) and 213 (20); uv $\lambda_{max}$ (MeOH) nm: 392, 254, 217 and 205; ir $\nu_{max}$ ($CHCl_3$) $cm^{-1}$: 3140, 2900, 1610, 1595, 1580, 1440, 1150 and 1135; $^1$H and $^{13}$C-nmr (Table 5).

**PREPARATION OF DIMETHYLHARMALINE:**

To a freshly prepared solution of sodium ethoxide (Na 500 mg ; EtOH 50 ml), harmaline (1 mmol; 214 mg) and methyl iodide (1.2 mmol ; 0.075 ml) were added and the reaction mixture was refluxed for 2 h. The reaction mixture was then poured into water and shaken out with EtOAc. The EtOAc phase on usual work up showed two spots on tlc, which were separated using chromatotron model 7924T ($CHCl_3$:MeOH, 9:1) and characterized as dimethylharmaline (**7**) (193 mg) and unreacted harmaline (30 mg).

2,4-Dihydro-1-ethyl-7-methoxy-2-methyl-3*H*-pyrido[3,4-*b*]indole (**7**) Needles (193 mg) from methanol. mp 144-146$^0$C. Ms *m/z* (rel. int.) :242.1429 $M^+$ (calcd for $C_{15}H_{18}N_2O$, 242.1419) (100) , 227 (18), 213 (20) and 199 (34); uv $\lambda_{max}$ (MeOH) nm: 385, 252 and 208; ir $\nu_{max}$ ($CHCl_3$) $cm^{-1}$: 3140, 2910, 1610, 1580, 1560, 1400, 1150 and 1125; $^1$H and $^{13}$C-nmr (Table 6).

**Table1.** $^{1}H$ and $^{13}C$-Nmr values of **2.**

| C | $\delta_C$ | H | $\delta_H$ |
|---|---|---|---|
| 1 | 164.00 | - | - |
| 3 | 51.37 | 3 | 3.94 *t* (8.1) |
| 4 | 28.81 | 4 | 3.18 *t* (8.1) |
| 4a | 118.94 | - | - |
| 4b | 127.12 | - | - |
| 5 | 121.97 | 5 | 7.30 *d* (9.0) |
| 6 | 116.20 | 6 | 6.71 *dd* (9.0, 2.0) |
| 7 | 162.13 | - | - |
| 8 | 94.25 | 8 | 7.10 *d* (2.0) |
| 8a | 145.04 | - | - |
| 9a | 124.20 | - | - |
| 1' | 54.75 | 1' | 3.77 *t* (7.7) |
| 2' | 28.22 | 2' | 1.76 *quintet* (7.7) |
| 3' | *22.50 | 3' | 1.36 *m* |
| 4' | *28.50 | 4' | 1.36 *m* |
| 5' | 13.62 | 5' | 0.92 *t* (7.7) |
| 1" | 19.00 | 1" | 2.96 *s* |
| $OCH_3$ | 55.84 | $OCH_3$ | 3.81 *s* |

* Values may be interchanged

**Table 2.** $^{1}H$ and $^{13}C$-Nmr values of **3.**

| C | $\delta_C$ | H | $\delta_H$ |
|---|---|---|---|
| 1 | 164.17 | - | - |
| 3 | 51.38 | 3 | 3.93 *t* (8.2) |
| 4 | 20.72 | 4 | 3.18 *t* (8.2) |
| 4a | 118.96 | - | - |
| 4b | 127.24 | - | - |
| 5 | 121.88 | 5 | 7.33 *d* (9.0) |
| 6 | 116.39 | 6 | 6.75 *dd* (9.0, 2.0) |
| 7 | 162.26 | - | - |
| 8 | 94.44 | 8 | 7.15 *d* (2.0) |
| 8a | 145.34 | - | - |
| 9a | 124.16 | - | - |
| 1' | 54.45 | 1' | 3.78 *t* (7.5) |
| 2' | 30.59 | 2' | 1.76 *quintet* (7.5) |
| 3' | 20.05 | 3' | 1.45 *sextet* (7.5) |
| 4' | 13.67 | 4' | 1.00 *t* (7.5) |
| 1" | 19.16 | 1" | 3.00 *s* |
| $OCH_3$ | 55.88 | $OCH_3$ | 3.85 s |

**Table 3.** $^{1}H$ and $^{13}C$-Nmr values of **4.**

| C | $\delta_C$ | H | $\delta_H$ |
|---|---|---|---|
| 1 | 164.77 | - | - |
| 3 | 41.82 | 3 | 3.86 *t* (8.5) |
| 4 | 19.87 | 4 | 3.10 *t* (8.5) |
| 4a | 119.10 | - | - |
| 4b | 125.61 | - | - |
| 5 | 122.27 | 5 | 7.39 *d* (8.9) |
| 6 | 115.71 | 6 | 6.78 *dd* (8.9, 2.0) |
| 7 | 161.94 | - | - |
| 8 | 94.12 | 8 | 7.02 *d* (2.0) |
| 8a | 144.16 | - | - |
| 9a | 125.01 | - | - |
| 1' | 41.82 | 1' | 3.79 *t* (7.2) |
| 2' | 29.72 | 2' | 1.85 *sextet* (7.2) |
| 3' | 16.53 | 3' | 1.06 *t* (7.2) |
| 1" | 19.15 | 1" | 2.94 *s* |
| $OCH_3$ | 55.74 | $OCH_3$ | 3.82 s |

**Table 4.** $^{1}H$ and $^{13}C$-Nmr values of **5.**

| C | $\delta_C$ | H | $\delta_H$ |
|---|---|---|---|
| 1 | 162.34 | - | - |
| 3 | 50.93 | 3 | 3.94 *t* (8.2) |
| 4 | 20.85 | 4 | 3.23 *t* (8.2) |
| 4a | 119.17 | - | - |
| 4b | 124.61 | - | - |
| 5 | 122.31 | 5 | 7.41 *d* (9.0) |
| 6 | 116.27 | 6 | 6.79 *dd* (9.0, 2.1) |
| 7 | 163.82 | - | - |
| 8 | 94.41 | 8 | 7.11 *d* (2.1) |
| 8a | 145.23 | - | - |
| 9a | 127.27 | - | - |
| 1' | 49.95 | 1' | 3.85 *q* (7.2) |
| 2' | 13.71 | 2' | 1.44 *t* (7.2) |
| 1" | 18.74 | 1" | 2.98 *s* |
| $OCH_3$ | 55.84 | $OCH_3$ | 3.82 *s* |

**Table 5.** $^{1}H$ and $^{13}C$-Nmr values of **6.**

| C | $\delta_C$ | H | $\delta_H$ |
|---|---|---|---|
| 1 | 164.8 | - | - |
| 3 | 51.2 | 3 | 3.95 *t* (8.4) |
| 4 | 20.5 | 4 | 3.14 *t* (8.4) |
| 4a | 119.1 | - | - |
| 4b | 127.0 | - | - |
| 5 | 122.1 | 5 | 7.27 *d* (9.0) |
| 6 | 116.0 | 6 | 6.68 *dd* (9.0, 2.1) |
| 7 | 162.1 | - | - |
| 8 | 94.2 | 8 | 7.06 *d* (2.1) |
| 8a | 145.0 | - | - |
| 9a | 124.5 | - | - |
| 1' | 56.9 | 1' | 4.48 *d* (5.2) |
| 2' | 129.4 | 2' | 5.88 *ddd* (15.6,10.4,5.2) |
| 3' | 120.2 | 3'a | 5.37 *d* (15.6) |
| | | 3'b | 5.30 *d* (10.4) |
| 1'' | 18.8 | 1'' | 2.92 *s* |
| $OCH_3$ | 55.8 | $OCH_3$ | 3.80 *s* |

**Table 6.** $^{1}H$ and $^{13}C$-Nmr values of **7.**

| C | $\delta_C$ | H | $\delta_H$ |
|---|---|---|---|
| 1 | 169.42 | - | - |
| 3 | 53.25 | 3 | 3.95 *t* (8.5) |
| 4 | 20.38 | 4 | 3.17 *t* (8.5) |
| 4a | 119.05 | - | - |
| 4b | 124.11 | - | - |
| 5 | 121.83 | 5 | 7.29 *d* (8.9) |
| 6 | 116.21 | 6 | 6.74 *dd* (8.9, 2.0) |
| 7 | 162.04 | - | - |
| 8 | 94.30 | 8 | 7.13 *d* (2.0) |
| 8a | 145.18 | - | - |
| 9a | 125.86 | - | - |
| 1' | 41.33 | 1' | 3.58 *s* |
| 1'' | 24.70 | 1'' | 3.41 *q* (7.0) |
| 2'' | 12.24 | 2'' | 1.35 *t* (7.0) |
| $OCH_3$ | 55.86 | $OCH_3$ | 3.85 *s* |

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