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STUDIES IN HARMINE SERIES OF ALKALOIDS

Part I. Derivatives of Tetrahydroharmine

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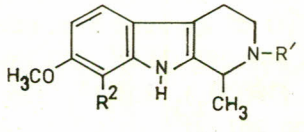
As part of studies in structure activity relationship in β-carboline bases, a series of N-substituted and benzene ring substituted derivatives of tetrahydroharmine have been prepared in high yields and characterised through chemical and spectral studies.

INTRODUCTION

Taking into account a recent finding [1] at the Institute that the kernels of the seeds of *Peganum harmala*, a wild growing plant in Pakistan and neighbouring countries, may provide a large scale commercial source of edible oil, extensive pharmacochemical studies are being carried out on the two alkaloidal harmala bases harmine and harmidine/harmaline available from the seed husk in 7 % yield. A number of synthetic analogues of tetrahydroharmine have been reported in an earlier communication [2]. As a part of studies in this direction the following new derivatives of tetrahydroharmine have been prepared according to the procedures described in the experimental. Their structures have been established through chemical and spectral studies and they have further characterized through their various salts:



Tetrahydroharmine, $R^1 = R^2 = H$

1) N-allyltetrahydroharmine
   $R^1 = -CH_2 - CH = CH_2$, $R^2 = H$
2) N-amyltetrahydroharmine
   $R^1 = -(CH_2)_4 - CH_3$, $R^2 = H$
3) N-crotonoyltetrahydroharmine
   $R^1 = -\overset{O}{\overset{\|}{C}} - CH = CH - CH_3$, $R^2 = H$
4) N-nitrosotetrahydroharmine
   $R^1 = -NO$, $R^2 = H$
5) N-benzenesulfonyltetrahydroharmine
   $R^1 = -SO_2C_6H_5$, $R^2 = H$
6) 8-aminotetrahydroharmine
   $R^1 = H$, $R^2 = -NH_2$
7) py-N, 8-N-diacetylaminotetrahydroharmine
   $R^1 = -COCH_3$. $R^2 = -NH\text{-}COCH_3$
8) py-N, 8-N-dibenzoylaminotetrahydroharmine
   $R^1 = -COC_6H_5$, $R^2 = -NHCOC_6H_5$
9) 8-N-benzenesulfonylaminotetrahydroharmine
   $R^1 = H$, $R^2 = -NHSO_2C_6H_5$
10) 8-N-benzenesulfonylaminotetrahydroharmine - diacetate
    $R^1 = -COCH_3$, $R^2 = -N(SO_2C_6H_5)(COCH_3)$
11) py-N, 8-N-dibenzenesulfonylaminotetrahydroharmine
    $R^1 = SO_2C_6H_5$, $R^2 = -NHSO_2C_6H_5$
12) py-N, 8-N-dibenzenesulfonylaminotetrahydroharmine - monoacetate
    $R^1 = -SO_2C_6H_5$, $R^2 = -N(SO_2C_6H_5)(COCH_3)$

Reaction of allyl bromide and crotonoyl chloride with tetrahydroharmine in chloroform afforded corresponding N-allyl and N-crotonoyl derivatives at room temperature in about theoretical yields. On the other hand N-amyltetrahydroharmine could be obtained by refluxing amylbromide and tetrahydroharmine in methanol at 60 – 70° for 10 hr in 85 % yield.

Nitrosation of terahydroharmine afforded N-nitroso derivative under mild reaction conditions as described in experimental (yield 75 %). Action of benzene sulfonyl chloride on the base in 10 % aqueous alkali afforded N-benzene sulfonyltetrahydroharmine at room temperature in almost theoretical yield.

It may be noted that reduction of 8-nitroharmidine with Zn/HCl yields 8-aminotetrahydroharmine under highly critical conditions. It was isolated as its crystalline hydrochloride (yield 90 %). The position of amino group was ascertained at C-8 by proton NMR studies. Its acetylation with acetic anhydride/sodium acetate and benzoylation with benzoyl chloride in aqueous alkali

afforded diacetate and dibenzoate derivatives respectively.

On treatment with benzene sulfonyl chloride the amino base gave corresponding mono-and di-N-benzene sulfonyl derivatives in high yields. It was confirmed through spectral studies and formation of the diacetate that substitution in mono-N-benzene sulfonyl amino tetrahydroharmine has taken place at the amino group in the benzene ring at position 8.

EXPERIMENTAL

Melting points were recorded in glass capillary tubes and are uncorrected. IR spectra were measured on a Unicam SP 200 G spectrometer. Proton NMR spectra were determined on JEOL PMX-60 instrument with TMS as internal reference. Mass spectra were recorded on MAT 112 with GC/MS with computer MAT 188. The purity of the samples was checked on TLC. (silica gel).

N-Allyltetrahydroharmine:- Allyl bromide (1 ml) was added to a solution of tetrahydroharmine (1 g) in 50 c.c. of chloroform. After keeping in dark over night at room temperature a cream coloured crystallizate of tetrahydroharmine hydrobromide settled out, which was filtered, and washed with little chloroform. The chloroform mother liquor was repeatedly washed with water, dried (Na_2SO_4) and freed of the solvent under reduced pressure. The bright red transparent residue was taken up in moist ethyl acetate and charcoaled after drying (Na_2SO_4). A colourless crystalline residue was obtained on removal of the solvent on water bath, which formed colourless needles from methanol-benzene, melting at 128 – 30°.

IR spectrum of the allyl base in $CHCl_3$ showed a strong peak at 3400 cm^{-1} (indolic N – H) and 1640 (C=C). The mass spectrum exhibited molecular ion peak at *m/e* 256 in agreement with the moleculer formula $C_{16}H_{20}N_2O$ for N-allyltetrahydroharmine. The presence of N-allyl group was shown by diagnostic fragments at *m/e* 216 and 215 which result from the loss of allyl group with and without transfer of one hydrogen atom to indole moiety. Other prominent peaks are at 241 = $(M\text{-}CH_3)^+$, 200 = $(M\text{-}CH_3 + CH_2\text{-}CH = CH_2)^+$, 186 (retro-Diels Alder fragment) [3].

The ^1H -NMR spectrum showed a three-protons doublet at δ1.40 ($CH_3\text{-}C_1$), a three-protons singlet at δ3.83 ($CH_3\text{-}O$), a one-proton singlet at δ 7.66 (indolic N-H), a two-protons doublet at δ3.3, ($N\text{-}\underline{CH_2}\text{-}CH = CH_2$), a one-proton multiplet at δ6.00 ($N\text{-}CH_2\text{-}\underline{CH} = CH_2$) and a two-protons multiplet at δ5.30 ($\text{-}CH = \underline{CH_2}$).

Salts of N-Allyltetrahydroharmine: – Hydrochloride and hydroiodide were prepared by bringing the components together in acetonic medium. On crystallization from mixture of acetone and ethylacetate the hydrochloride formed shining rectangular colorless plates melting at 215 – 16°, the hydroiodide formed prismatic rods melting at 140 – 42°. Both of these are soluble in water, methanol and acetone.

– Pictrate, m.p. 169 – 70°, came out in the form of orangish yellow needles on adding aqueous picric acid solution to the dilute acetic acid solution of the base, and cooling overnight. It is soluble in methanol and insoluble in water.

– Chloroplatinate, prepared by adding 3 % solution of chloroplatinic acid to the aqueous solution of the hydrochloride, formed a yellow powder. It did not melt up to 360°. It is insluble in water, methanol and ethanol.

N-Amyltetrahydroharmine:- To a solution of tetrahydroharmine (1 g) in methanol (40 c.c.), 2 c.c. of amyl bromide were added. The reaction mixture was refluxed for 10 hr on water bath at 60 – 70°. On removal of the solvent under reduced pressure a reddish transparent mass was obtained which was partitioned between ethyl acetate and water. The aqueous phase after basifying with ammonia and extraction with ethyl acetate yielded tetrahydroharmine. The ethyl acetate layer was repeatedly washed with water, dried and freed of the solvent. N-amyltetrahydroharmine was obtained as a cream colored transparent residue. On crystallization from methanol-benezene (9:1) it came out as colorless needles (0.5 g), melting at 66 – 68°. It is hygroscopic in nature.

The IR spectrum ($CHCl_3$) showed a strong peak at 3400 cm^{-1} (indolic N-H) while absorption of py N-H was not observed. The mass spectrum showed molecular ion at *m/e* 286, which was in agreement with the molecular formula $C_{18}H_{26}N_2O$ of the amyl base; other diagnostic peaks appeared at *m/e* 285 $(M\text{-}1)^+$, 271 $(m\text{-}CH_3)^+$, 255 $(M\text{-}OCH_3)^+$, 229 $[M\text{-}(CH_2)_3\ CH_3]^+$, 186 (retro-Diels Alder fragment(, 200, 201 [3].

Salts of Amyltetrahydroharmine: – Hydrochloride was obtained as white amorphous powder on addition of etheral hydrochloric acid to an ethereal solution of the base. On crystallization from methanol it came out as fine needles melting at 196°. It is readily soluble is water.

– Picrate separated out as yellow needles on adding aqueous picric acid to a dilute acetic acid solution of the base m.p. 158 – 60°. It is insoluble in water and soluble in methanol and acetone.

N - Crotonyltetrahydroharmime:- Freshly distilled crotonoyl chloride (0.2 ml) was added to a solution of tetrahydroharmine (0.4 g) in 50 ml of chloroform. On

keeping the reaction mixture at room temperature for a few minutes tetrahydroharmine hydrochloride separated out as colourless needles. The crystallizate was filtered and washed with chloroform. The combined light violet coloured chloroform filterate and washings were repeatedly washed with water, dilute ammonia, again with water and dried over Na_2SO_4, filtered and freed of the solvent under reduced pressure. The crotonoyl derivative was obtained on rubbing up the residue with ether as a colourless crystalline powder, which melted at 162 – 64°. It is soluble in chloroform, ethyl acetate, methanol, and benzene, and insoluble in petroleum ether and ether.

The IR spectrum in $CHCl_3$ showed peaks at 3400 cm^{-1} (indolic N-H), 1660 (C = O), 1625 (C=C) and 1150 (C-0). The mass spectrum exhibited molecular ion at *m/e* 284 which was in agreement with the molecular formula $C_{17}H_{20}N_2O_2$ for the N-crotonoyltetrahydroharmine; other diagnositic peaks appeared at 269 $(M\text{-}CH_3)^+$, 215 $(M\text{-}O{=}C\text{-}CH{=}CH\text{-}CH_3)^+$, 199, 200, 201 [3] and 69 $(O{\equiv}C\text{-}CH{=}CH\text{-}CH_3)^+$. ^1H NMR spectrum ($CDCl_3$) showed a one-proton quartet at δ 5.73 (C_1-H), a one-proton broad signal at δ 8.7 (indolic N-H), a three-protons doublet at δ 1.5 (C_1-CH_3), a three-protons singlet at δ 3.83 (O-CH_3), a three-protons doublet at δ 1.93 (=CH-CH_3), a one-proton doublet at δ 6.33 (O=C-CH=CH-CH_3), a one-proton multiplet is hidden under the signal of aromatic protons between δ 6.6 to δ 7.5 (-HC=CH-CH_3).

N-Nitrosotetrahydroharmine:- To a solution of tetrahydroharmine (1 g) in 1 % acetic acid, an aqueous solution of sodium nitrite (1.2 mole) was added in cold. N-nitrosotetrahydroharmine came out as yellow precipitate, which was taken in slightly diluted acetone and kept in the cold overnight. The light yellow crystallizate thereby obtained was recrystallized from acetone-water, when it formed flowers of slender needles melting at 156°.

The IR spectrum showed the absence of N-H stretching vibration frequency. A strong band appeared at 3400 cm^{-1} (indolic N-H), 1530 (N=O). The mass spectrum exhibited the molecular ion peak at *m/e* 245 in agreement with the molecular formula $C_{13}H_{15}N_3O_2$ for N-nitrosotetrahydroharmine. Other diagnostic fragment ion peaks appeared at *m/e* 215 (23.58 %) = $(M\text{-}NO)^+$, 200 (26. 35 %) = $[M\text{-}(CH_3 + NO)]^+$ (3) 199 (24.47 %) = $[M\text{-}(CH_3{+}NO)^+\text{-}1H]^+$[3] 201 (9.36 %) = $[M\text{-}(CH_3{+}NO) +1H]^+$[3] 186 (16.19 %) = (retro-Diels Alder fragment) [3], 58 (100 %).

N-Benzenesulfonyltetrahydroharmine:- To a suspension of tetrahydroharmine (2 g) in 10 % aqueous sodium hydroxide (30 ml), 3 ml of benzenesulfonyl chloride was gradually added with constant shaking. On keeping the reaction mixture at room temperature for about 45 min a thick crop of cream coloured crystallizate settled out, which was filtered after dilution, and washed thoroughly with water, then with little dilute hydrochloric acid, and again with water. On keeping the solution of the product in dilute acetone over night in the cold benzenesulfonyl derivative was obtained as bright colurless rods which when recrystallized from acetone-water (9:1) melted at 276-78°. It is insoiuble in petroleum ether, sparingly soluble in ether and soluble in other organic solvents.

In the IR spectrum ($CHCl_3$) the N-H absorption was not observed. It showed peaks at 3400 cm^{-1} (indolic-N-H), 1630 (indolic N-H bending), 1600 and 1565 (aromatic C = C), 1140 and 1320 (O = S = O), 1100 (C-O), while in the mass spectrum molecular ion was observed at *m/e* 356 (44 %) in agreement with the molecular formula $C_{19}H_{20}N_2O_3S$. Other prominent fragments were observed at *m/e* 341 (65.20 %) = $(M\text{-}CH_3)^+$, 215 (54.83 %) = $(M\text{-}SO_2C_6H_5)^+$, 200 (100 %) [3] = $[M\text{-}SO_2C_6H_5 + CH_3]^+$, 199 (47.61 %) = $[M\text{-}(SO_2C_6H_5 + CH_3)\text{-}1H]^+$, 141 (4 %) = $(SO_2C_6H_5)^+$, 77 (44 %) = $(C_6H_5)^+$.

Aminotetrahydroharmine :- 8-nitroharmidine (2 g) prepared according to the method reported by Siddiqui and Saira [4] was dissolved in 150 ml of 30 % aqueous hydrochloric acid and zinc dust was gradually added with occasional shaking. The reaction mixture was heated on the water bath till the yellow colour disappeared, care being taken that the temperature did not exceed above 60-70°. Unreacted zinc was filtered off and the colourless filterate after cooling down to 40° ws treated with small portions of sodium chloride till the solution turned turbid. On keeping it in the cold overnight aminotetrahydroharmine hydrochloride was obtained as colourless crystallizate. The crystallizate was washed with small quantities of saturated saline. On recrystallization from methanol it formed colourless slender needles melting at 270-74° (decomp).

An additional quantity of the hydrochloride was obtained on working up the filterate (Total yield 90 %). It is readily soluble in water. The hydrochloride analysed for $C_{13}H_{17}N_3O$. 2HCl H_2O (Found: C, 48.46; H, 6.65; N, 13.03; 0, 9.81; Cl, 22.09 %. Calculated for $C_{13}H_{17}N_3O$. 2HCl. H_2O: C, 48.45; H, 6.52; N, 13.04; O, 9.94; Cl, 22.05 %).

The free amino base was obtained as rectangular plates by treating a concentrated aqueous solution of the hydrochloride with a few drops of concentrated ammonia in the cold. On recrystallization from benzene it melted at 120°. (yield 80 %). It is sparingly soluble in ether and ethyl acetate, soluble in hot benzene and readily soluble in methanol.

The IR spectrum ($CHCl_3$) showed strong peaks at 3430 cm^{-1} (indolic N-H), 3200-3400 cm^{-1} (broad; -NH_2, and py-N-H), 1630 cm^{-1} (indolic N-H bending), 1610 cm^{-1} (N-H bending) and 1120 cm^{-1} (C-O). The mass spectrum showed the molecular ion peak at *m/e* 231 which was in agreement with the molecular formula $C_{13}H_{17}N_3O$ for the 8-amino-tetrahydroharmine and other prominent peaks appeared at 230 = $(M-1)^+$, 216 (B.P.) = (M-CH3)+, 199,200,201,186 (retro-Diels Alder fragment) [3].

The NMR spectrum ($CDCl_3$), showed doublet at δ1.38 (3H, C_1-CH_3), singlet at δ8.03 (1H, indolic N-H), singlet at δ 3.92 (3H, OCH_3), multiplet at δ3.73- 4.16 (IH, C_1-H), multiplet extending from δ 2.5 - 3.33 (7H, NH_2, py-N-H, N-CH_2, and -CH_2 overlap), a doublet at δ6.76, J = 8 cps (1H C_6-H), doublet at δ 6.96 J = 8 cps (1H, C_5-H).

Salts of Aminotetrahydroharmine: – Hydroiodide was obtained on treating the aqueous solution of the hydrochloride with potassium iodide. On recrystallization with methanol it formed fine needles, m.p. 270° (decomp.). It is soluble in methanol and acetone, sparingly soluble in water.

– Picrate came out as yellow crystallizate on adding a concentrated aqueous solution of picric acid to the aqueous solution of the hydrochloride. It formed fine needles on recrystallization from methanol and melted at 180°. It is soluble in methanol and acetone, and insoluble in water.

– Succinate, m.p. 274-76° (decom.). separated out as colourless flowers of needles on dissolving the hydrochloride in fairly concentrated aqueous solution of succinic acid and keeping the solution in cold overnight. It is soluble in methanol,, acetone and water, insoluble in ethyl acetate, benezene, chloroform, ether and petroleum ether.

– Oxalate, m.p. 178-80°, was prepared following the procedure of succinate. It crystallized from water as elongated rods. It is soluble in methanol and water and insoluble in other organic solvents.

– Nitrate was prepared by rubbing the hydrochloride with concentrated aqueous solution of potassium nitrate. On recrystallization from methanol, it formed colourless prismatic rods, m.p. 206 (decomp.) It is soluble in water and methanol and insoluble in other organic solvents.

py-N, 8-N-Diacetylaminotetrahydroharmine: To a suspension of aminotetrahydroharmine hydrochloride (0.2 g) in acetic anhydride (1 c.c.) sodium acetate (0.5 g) was added and kept at room temperature for 2 hr. On working up the reaction mixture in the usual manner, the diacetyl derivative was obtained in the form of colourless needles, melting at 138-40° (yield 0.18 g). It is insoluble in petroleum ether and ether and soluble in other organic solvents.

The IR spectrum in $CHCl_3$ showed bands at 3430 cm^{-1} (indolic N-H), 3320 (amide N-H), 1680 cm^{-1} and 1640 (amide C=O), 1180 (C-O). The mass spectrum showed the molecular ion at *m/e* 315 (51.12 %), which was in agreement with the molecular formula $C_{17}H_{21}N_3O_3$ for the diacetyl derivative. Other important fragments were observed at 314 (1.03 %) = (M-1)+, 300 (60. 09 %) = $(M-CH_3)^+$, 272 (10. 28 %) =(M-$COCH_3$)+, 258 (100 %), 229 (11.87 %) = [M-2($COCH_3$)]$^+$, 43 (70 %) = $(O{\equiv}C\text{-}CH_3)^+$.

py N,&N-Dibenzoylaminotetrahydroharmine: A suspension of aminotetrahydroharmine hydrochloride (0.5 g) in 10 % aqueous solution of sodium hydroxide (20 ml) was treated with freshly distilled benzoyl chloride (2.5 ml) with constant shaking. On working up the reaction mixture the dibenzoyl derivative was obtained in the form of colourless needles from 1:1 methanol-benzene melting at 228-30°. It is soluble in chloroform, methanol, acetone, sparingly soluble in ether and benzene.

IR spectrum in $CHCl_3$ showed absorption at 3410 cm^{-1} (indolic N-H), 333o (amide N-H), 1660 and 1650 (amide C=O),1620 (indolic N-H bending), 4 peaks between 1415 and 1600 (aromatic C=C), 1180 = (C-O), the mass spectrum exhibited molecular ion at *m/e* 439 (15.74 %), in agreement with the molecular formula $C_{27}H_{25}N_3O_3$ for the dibenzoyl derivative and other peaks at *m/e* 424 (12.88 %) = $(M-CH_3)^+$, 334 (8.55 %) = $(M-COC_6H_5)^+$, 306 (3.25 %) = $(M-COC_6H_5+CO)^+$, 186 (2.59 %) = (Indole moiety after RDA cleavage [3], 105 (100 %) = $(O{\equiv}C\text{-}C_6H_5)^+$, 77 (78 %) = $(C_6H_5)^+$, 199(1.97%)[3].

8 N- Benzenesulfonylaminotetrahydroharmine : To a suspension of aminotetrahydroharmine hydrochloride (0.25 g) was added 1.2 moles (0.3 ml) of benzene sulfonyl chloride and kept at room temperature for 2 hr. The reaction mixture was then poured into cold water (20 ml) and shaken up with a little ether, when after standing for about 10 min, 8-N-benzene sulfonyl derivative of the amino tetrahydroharmine separated out from the aqueus phase in colourless bunches of needles. On recrystallization from methanol-benzene (1:1) it melted at 266-68°.

A small quantity of the dibenzene sulfonyl derivative was obtained on working up the ether phase. The preparation of this product in good yield is described later.

Characterization of 8-N-Benzene sulfonylamino tetrahydroharmine: IR. spectrum in KBr showed peaks at 3370 cm^{-1} (indolic N-H), 3140 (broad, N-H), 1630 (indolic N-H bending), 1400-1600 cm^{-1} (4 peaks, aromatic C=C), 1160 and 1340 (symmetric and asymmetric O=S=Ostretch-

ing respectively) and 1090 (C-O).

The mass spectrum showed the molecular ion at *m/e* 371 (38.75 %), which was in agreement with the molecular formula $C_{19}H_{21}N_3O_3S$ and other diagnostic fragments at 370 (3.25 %) = $(M-1)^+$, 356 (60.03 %) = $(M-CH_3)^+$, 230 (24.71 %) = $(M-SO_2C_6H_5)^+$, 215 (87.77 %) = $(M-SO_2C_6H_5 + CH_3)^+$, 201 (100 %), = $[M-(HNSO_2C_6H_5 + CH_3)+H]^+$, 141 (2.42 %) = $(SO_2C_6H_5)^+$, 77 (19.22 %) = $(C_6H_5)^+$

The ^1H -NMR spectrum (DMSO-d_6) showed a one-proton singlet at 10.73 (O_2S-N-H at C-8), a one proton broad signal at 9.5 (indolic N-H), a five-protons singlet at 7.56 (SO_2-C_6H_5), a one-proton doublet at 6.56 J=8 cps (H-6), a one-proton doublet at 7.26 J-8 cps (H-5), a one-proton quartet at 4.59 (H-1), a three-protons single at 3.07 (OCH_3), a five-protons multiplet at 2.66-4.1 signals for CH_2, N-CH_2 and py-N-H overlap). a three-protons doublet at 1.66 J=7 cps (C_1-CH_3).

Acetylation of 8 N-Benzenesulfonylamino tetrahydroharmine:- Acetylation of 8-N-benzenesulfonyl aminotetrahydroharmine. (250 mg) was performed with acetic anhydride (2 ml) and pyridine (1 ml) by keeping the reaction mixture overnight at room temperature. On working up the reaction mixture in the usual manner the diacetyl derivative was obtained as colourless crystalline mass in nearly theoretical yield which formed bunches of needles from methanol meling at 254-56°. It is soluble in ethyl acetate, chloroform and methanol and insoluble in petroleum ether and ether.

IR spectrum in KBr showed absorption frequency at 3340 cm^{-1} (indolic N-H), 1700 (SO_2-N-C-CH_3), 16 40 (carbonyl absorption of acetyl group at py-N), 1630 (indolic N-H bending , aromatic C=C), 1180 and 1360 (symmetric and asymmetric O=S=O stretching respectively), 1090 (C-O).

The mass spectrum showed the molecular ion peak at *m/e* 455 (1.63 %) which was in agreement with the molecular formula $C_{23}H_{25}N_3O_5S$ for the 8N-benzenesulfonylaminotetrahydroharmine-diaceate. Other important peaks appeared at *m/e* 413 (5.14 %) = (M-loss of acetyl group with transfer of one hydrogen to the indole moiety)$^+$, 398 (4.77 %) = $[M-(COCH_3+CH_3)+H]^+$, 272 (5.4 %) = $[M-(COCH_3+SO_2C_6H_5)+1H]^+$, 43 (100 %) = $(O\equiv C-CH_3)^+$.

py N,8N-Dibenzenesulfonylaminotetrahydroharmine:- 1 ml (2.4 mole) of benzene sulfonylchloride was added to a suspension of aminotetrahydroharmine hydrochloride (0.25g) in dry pyridine (2 ml). The reaction mixture was kept at room temperature for 2 hr, diluted with water, basified with ammonia and extracted out with ethyl acetate. The ethyl acetate extract was repeatedly washed with water, dried and freed of the solvent. On keeping a solution of the residue in methanol overnight in the cold, a colourless crystallizate separated out. On recrystallization from methanol-benzene (1:1) the dibenzene sulfonyl derivative of aminotetrahydroharmine was obtained in fine needles melting at 196-7° in nearly theoretical yield (0.36 g).

Characterization of py N,8N-Dibenzenesulfonyl-aminotetrahydroharmine: The IR spectrum in $CHCl_3$ showed a strong absorption at 3400 cm^{-1} (indolic N-H), 3310 ($C_6H_5SO_2$N-H), 1630 (indolic NH bending), 1600 (aromatic C=C), 1140 and 1340 (symmetric and asymmetric O=S=O stretching respectively), 1080 (C-O stretching).

Mass spectrum afforded the molecular ion at *m/e* 511 (38.51 %) which was in agreement with the molecular formula $C_{25}H_{25}N_3O_5S_2$ for the dibenzenesulfonyl derivative and other important fragments at 496 (23.12 %) = $(M-CH_3)^+$, 370 (22.47 %) = $(M-SO_2C_6H_5)^+$, 369 (22.47 %) = $[M-(SO_2C_6H_5+H)]^+$, 335 (28.06 %) = $(M-SO_2C_6H_5 + CH_3)^+$, 214 (89.4 %) = $[(M-2\ (SO_2C_6H_5) + CH_3)]^+$, 77 (100 %) = (C_6H_5)+, and 58 (99.65 %). The ^1H -NMR spectrum ($CDCl_3$) showed a one-proton singlet at δ 9.0 (-O_2-S-N-H at C-8), a one-proton broad signal at δ 8.0 (indolic N-H), twelve-protons multiplet at δ 6.5-7.86 (aromatic protons), a one-proton quartet at δ 5.4 (C_1-H), a one-proton multiplet at δ 4.26 (H-3e), a one-proton multiplet at δ 3.60 (H-3a) [5] a two-protons multiplet at δ 2.66 (C-4 methylene protons), a three-protons doublet at δ 1.56 J=7 cps (C_1-CH_3), a three-protons singlet at δ 3.36 (OCH_3).

Acetylation of py N, 8N-(Dibenzenesulfomylaminotetrahydroharmine: py N,8N-dibenzensulfonylaminotetrahydroharmine (250 mg) was dissolved in dry pyridine (1 ml) and acetic anhydride (2 ml) was added. The reaction mixture was left overnight at room temperature. The monoacetyl derivative was obtained as colourless crystalline residue on working up the reaction mixture in the usual manner. It crystallized out from methanol-benzene as fine needles and melted at 245-46° It is insoluble in petroleum ether and ether and soluble in ethyl acetate, chloroform and methanol.

IR spectrum showed strong peak at 3340 cm^{-1} (indolic N-H) and other peaks at 1700 (-OS_2-N-C(=O)-CH_3), 1630 (indolic N-H bending), 1160, and 1360 (symmetric and asymmetric SO_2 stretching respectively), 1080 (C-O). The mass spectrum exhibited the molecular ion peak at *m/e* 553 (27.99 %) which was in agreement with the molecular formula $C_{27}H_{27}N_3O_6S_2$ for the py N,8N-

dibenzenesulfonylaminotetrahydroharmine – monoacetate. Other diagnostic fragment ion peaks were observed at *m/e* 538 (6.99 %) = $(M\text{-}CH_3)^+$, 511 (35.44 %) = (M-loss of acetyl group with transfer of one hydrogen atom to the indolic moiety)$^+$, 510 (0.6 %) = $(M\text{-}COCH_3)^+$, 496 (27.62 %) = $[M\text{-}(COCH_3+CH_3)+H]^+$, 412 (4.88 %) = $(M\text{-}SO_2C_6H_5)^+$, 369 (22.26 %) = $(M\text{-}SO_2C_6H_5+COCH_3)^+$, 228 (42.19 %) = $(M\text{-}2.\ SO_2C_6H_5+COCH_3)^+$, 77 (100 %) = $(C_6H_5)^+$, 43 (70.60 %) = $(O\equiv C\text{-}CH_3)^+$.

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