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Synthesis, Characterization and Antimicrobial Activity Studies of 1- & 2-[{2-(3,4-Dimethoxyphenyl)ethyl}-methylamino]sulphonyl Naphthalenes

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Two isomeric naphthalene sulphonyl compounds *viz.*, 1- & 2-[{2-(3,4-dimethoxyphenyl)ethyl}methylamino] sulphonyl naphthalenes (**I** and **II**) were synthesized from 3,4-dimethoxybenzyl chloride (homo veratryl chloride, HVC) and naphthalene as the main starting materials and characterized by spectral methods. Their antimicrobial activities were also studied.

Key Words: Sulphonyl naphthalenes, Homo veratryl chloride, Antibacterial activity.

INTRODUCTION

Compounds having sulphonyl group have been shown to have various pharmacological activities[1,2] and serve as useful intermediates in organic synthesis[3]. 3,4-Dimethoxy-N-methyl benzene ethanamine [methylveratryl amine (MeVA)] has been prepared[4] by different methods and has been used as the key intermediate for the synthesis of verapamil, a well known antiarrhythmic and angina drug.

However, the above compound (MeVA) has been found occur in nature and has been isolated from epithelantha micromeres and turbinicarpus alonsoi[5,6]. The same intermediate has been coupled with different moieties to get compounds having calcium antagonist activity[7] in rats and negative chronotropic activity[8].

Verapamil biotransformation to metabolite by microorganism in mammalian body occurs by cleavage of C–N or C–O bonds. Besides O-demethylation and N-demethylation were the main metabolic pathways of verapamil in rat liver microsomes[9,10]. Moreover, the intermediate, MeVA, has been shown[11] to exhibit genotoxicity due the presence of secondary amino group in it.

This report is a synthesis of the drug intermediate (MeVA) by modified methods and its reaction with α- and β-sulfonyl naphthalenes to give compounds similar to verapamil which are expected to have properties common to verapamil and sulfa drugs.

EXPERIMENTAL

Commercial grade samples of homo veratryl chloride and naphthalene supplied by Aldrich were used as the primary starting materials for the synthesis of the sulphonyl naphthalenes and all other chemicals used were commercial grade samples obtained from SD-Fine chemicals. The compounds were prepared by several modified steps (9 steps) as detailed below.

Step-1: Preparation of homo veratryl nitrile (HVN): The conversion of veratryl chloride in to veratryl nitrile was effected by a modified method of phase transfer catalysis[12,13]. A mixture of 0.32 g (0.001 mol) of tetra butyl ammonium bromide (TBAB) and 1.95 g (0.039 mol) of sodium cyanide was dissolved in 2.6 mL of water at 25 ºC. To this, 6.75 g (0.04 mol) of homo veratryl chloride (HVC) dissolved in 20 mL of toluene, was added drop wise for a total period of 1 h. The reaction mixture was stirred for 4 d at 25-30 ºC. The completion of reaction was tested by TLC with hexane and ethyl acetate in the ratio 1:1 as mobile phase. About 5 mL of water was added and stirred for 15 min. The solid mass formed at this stage was filtered and the organic layer was separated, washed to neutral pH and distilled completely to get the crude product of homo veratryl nitrile.

About 6.4 g of homo veratryl nitrile (HVN) was dissolved in 9.6 mL of methanol, heated to 60-65 ºC for 0.5 h and then cooled to 25 ºC followed by the addition of 9.6 mL of water drop wise for a period of 0.5 h. The reaction mixture was further cooled slowly to 0-5 ºC and stirred for 0.5 h. The pure HVN thus separated was filtered and dried at 35 ºC for 4 h. Yield *ca.* 85 %; m.p. 63-64 ºC.

Step-2: Preparation of homo veratryl amine (HVA): About 13.5 mL of methanol was cooled to 0-5 ºC in an autoclave and saturated with ammonia gas. To this 5 g (0.028 mol) of HVN and 0.3 g of raney nickel were added and the temperature was maintained at 55 ºC with 6 kg hydrogen gas pressure for 20 h. The reaction mixture was cooled to 25 ºC and filtered. The filtrate was concentrated and distilled at 120-140 ºC and 1 mm Hg pressure to get the required product[14,15] homo veratryl amine, HVA.Yield: *ca.* 60 % ; b.p. 125-135 ºC (at 1 mm).

Step-3: Preparation of 3,4-dimethoxy-N-methyl benzene ethanamine (MeVA): About 4.5 g (0.025 mol) of homo veratryl amine in 12.5 mL of toluene was mixed with 3.2 g (0.03 mol) of benzaldehyde. Azeotropically, water was removed slowly in 24 h. The reaction mixture was cooled to 45 ºC and mixed with 4.1 g (0.033 mol) of dimethyl sulphate (DMS) in 4.03 mL of toluene for 15 min. The temperature of the reaction mixture was raised to *ca.* 85 ºC and maintained for 1.5 h. The

reaction mass was cooled to 20-25 ºC and mixed with 12.5 mL of water and stirred for 0.5 h. The aqueous layer was washed with 2.5 mL of toluene and distilled up to 80 %, cooled to 5-10 ºC and mixed with 5.5 g of sodium hydroxide, dissolved in 2.4 mL of water. The product in the aqueous medium was extracted with 2.5 mL of toluene. The toluene layer was adjusted to neutral pH by washings with water and dried over anhydrous sodium sulphate. It was then distilled to remove toluene completely to give the required product *viz.*, 3,4-dimethoxy-N-methyl benzeneethanamine (MeVA). The product was further distilled at 125-130 ºC and 1 mm Hg pressure. Yield: *ca.* 80 %; b.p. 125-130 ºC.

Step-4: Preparation of α-sodium naphthalene sulfonate (α-NaNS)[16,17]: About 10 g (0.078 mol) of naphthalene in 11.9 g (0.117 mol) of acetic anhydride was stirred to dissolve at 20 ºC and treated with 7.72 g (0.078 mol) of conc. sulphuric acid drop wise below 25 ºC for a period of 1 h and then distilled slowly under 1 mm Hg pressure for a period of 3 h at 40 ºC. The reaction mass was quenched in lye solution (12 g sodium hydroxide in 50 mL of water) at 40-60 ºC under stirring. The mass was cooled to 30 ºC, filtered after 1 h; bed washed with 15 mL of isopropyl alcohol followed by 15 mL of hexane and dried in 1 mm Hg pressure for 6 h at 50 ºC. Yield *ca.* 85 %.

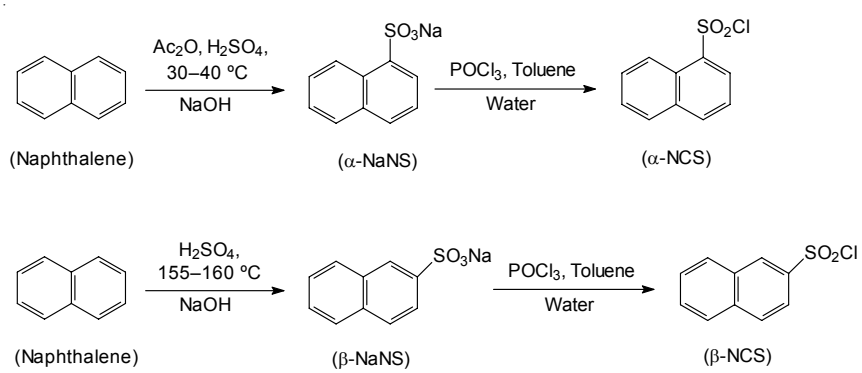
Step-5: Preparation of α-naphthalene sulfonyl chloride (α-NSC)[18-21]: About 10 g (0.04 mol) of α-NaNS was added to 6.6 g (0.04 mol) of phosphorous oxychloride and heated to 110-115 ºC for 3 h. The reaction mixture was cooled to 60 ºC, distilled out excess $POCl_3$ and mixed with 40 mL of toluene. Reaction mass further cooled to 20 ºC followed by the addition of 20 mL of cold water at 20 ºC and stirred for 20 min. The toluene layer was washed to pH-7 with water, dried over anhydrous sodium sulphate and distilled out completely under1mm Hg pressure at 60-65 ºC. The compound was re-crystallized in 100 mL of hexane. Yield *ca.* 50 %; m.p. 69-71.5 ºC.

Step-6: 1-[{2-(3,4-Dimethoxy phenyl)ethyl}methyl amino]sulphonyl naphthalene (compound-I): To about 3.4 g (0.017 mol) of MeVA 4.0 g (0.017 mol) of α-NSC, dissolved in 20 mL of dichloro methane, was added slowly followed by the addition of 2.6 g (0.027 mol) of tri ethyl amine (TEA), at 20 ºC.The reaction mixture was warmed to 40 ºC and maintained at the same temperature for 4 h. The completion of the reaction was checked by TLC with 1:1 hexane and ethyl acetate as mobile phase. The reaction mixture was cooled to 15 ºC and mixed with 50 mL of DCM & 50 mL of water. The DCM layer was separated, washed to neutral pH with 5 % aqueous sodium bicarbonate solution, dried over anhydrous sodium sulphate and concentrated. The crude compound was crystallized in 10 volumes of isopropyl alcohol. Yield: *ca.* 35 %; m.p. 78.2-79.6 ºC.

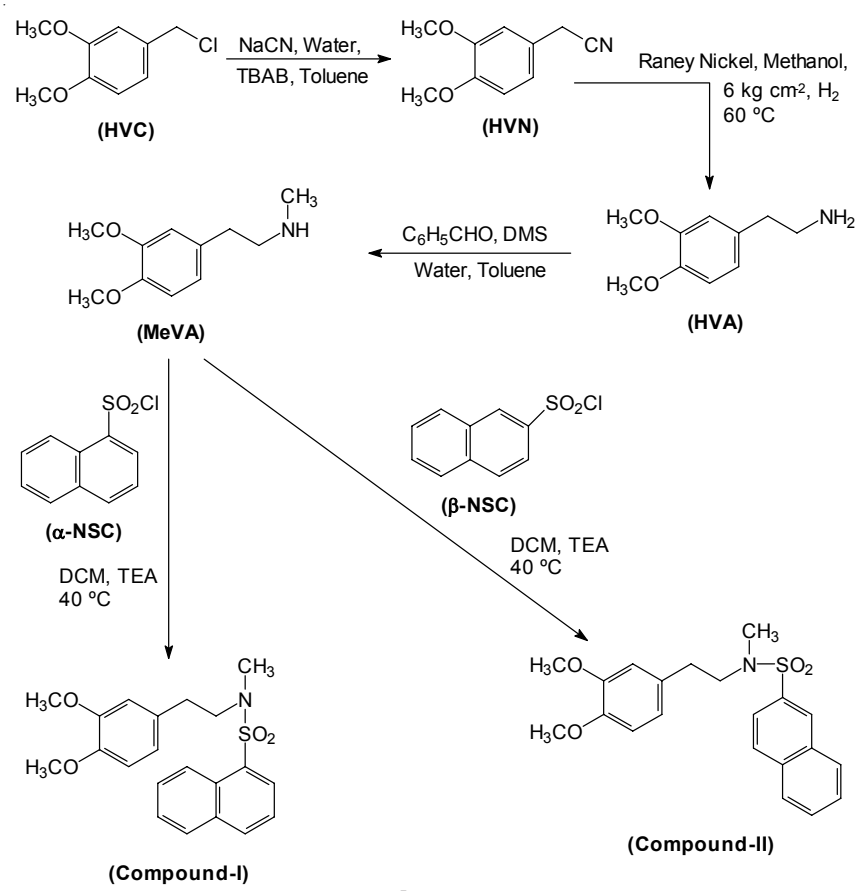
Step-7: Preparation of β-sodium naphthalene sulphonate: About 2.5 g (0.02 mol) of naphthalene was taken in 2.0 g (0.02 mol) of sulphuric acid and heated to 165 ºC for 15 h. The reaction mass was cooled to 80 ºC, quenched over sodium hydroxide solution (0.4 mol), further cooled to 20 ºC and filtered. The bed was washed with 50 mL of isopropyl alcohol (IPA) and 50 mL of hexane. The product *viz.*, β-sodium naphthalene sulphonate (β-NaNS) formed was dried under 1 mm Hg pressure at 60 ºC for 4 h. Yield 80 %.

Step-8: Preparation of β-naphthalene sulfonyl chloride (β-NSC): About 10 g (0.04 mol) of β-NaNS was added to 6.6 g (0.04 mol) of $POCl_3$ and heated to 110-115 ºC for 3 h. The reaction mixture was cooled to 60 ºC, distilled out excess of $POCl_3$ and mixed with 40 mL of toluene. Reaction mass further cooled to 20 ºC followed by the addition of 20 mL cold water at 20 ºC and stirred for 20 min. The toluene layer was washed to pH-7 with water, dried over anhydrous sodium sulphate and distilled out completely under reduced pressure at 60-65 ºC. The compound was purified in 100 mL of hexane. Yield *ca.* 50 %; m.p. 74-76 ºC.

Step-9: 2-[{2-(3,4-Dimethoxy phenyl)ethyl}methylamino]sulphonyl naphthalene (Compound-II): To 4.0 g (0.017mol) of β-NSC, 3.4 g (0.017 mol) of MeVA, dissolved in 20 mL of dichloro methane, was added slowly followed by the addition of 2.6 g (0.027 mol) of tri ethyl amine at 20 ºC. The reaction mixture was warmed to 40 ºC and maintained at the same temperature for 4 h. The completion of the reaction was checked by TLC with 1:1 hexane and ethyl acetate as mobile phase. The reaction mixture was cooled to 15 ºC and mixed with 50 mL of DCM and 50 mL of water. The DCM layer was separated, washed to neutral pH with 5 % aqueous sodium bicarbonate solution, dried over anhydrous sodium sulphate and concentrated. The crude compound was crystallized in 10 volumes of isopropyl alcohol. Yield *ca.* 35 %.



Scheme-I. Preparation of naphthalene sulphonyl chlorides



Scheme-II

Elemental analysis was done at SAIF, Central Drug Research Institute, Lucknow, India. The mass spectral pattern of the compounds were obtained on a Shimadzu-QP-2010 mass spectrometer, UV-visible spectra were recorded on Lambda-25 spectrophotometer in methanol (2.60×10^{-5} M) using matched quartz cells of path length 1 cm. The IR spectra in KBr pellets were obtained on Perkin-Elmer IR Spectrum-1 spectrophotometer. ^{1}H and ^{13}C NMR spectra in $CDCl_3$ were recorded using Jeol 300 MHz NMR spectrophotometer.

Antimicrobial activity studies: The antimicrobial activity tests were performed using Bauer[22] disc diffusion method. The test concentrations of the compounds prepared were 25, 50, 75 and 100 mM in ethyl alcohol. Each disc was impregnated with 50 µL of each of the solutions. The pure cultures were stored in nutrient agar. All the antimicrobial activities were determined by using Mueller Hinton Agar [MHA] (Himedia, Bombay). The MHA plates were prepared by pouring 15 mL of molted medium (pH

= 7.2) and allowing it to set for solidification. The 24 h old bacterial cultures were swabbed on the agar plate forming a uniform culture. Different concentrations of the compound disc were placed on the surface of the agar medium aseptically. Streptomycin (Himedia, Chemical Ltd., Mumbai) served as control. Each concentration was tested in triplicates. The plates were evaluated after incubation at 37 ºC for 24 h and the zones of inhibitions were measured at the end of 24 h period.

RESULTS AND DISCUSSION

Elemental analysis: Anal. calcd. for compounds **I** & **II** (%) for $C_{21}H_{23}NO_4S$: C, 65.46; H, 5.97; N, 3.64; S, 8.31. Found; Compound-**I**: C, 65.16; H, 6.07; N, 3.24; S, 8.11; Compound-**II**: C, 65.36; H, 5.77; N, 3.34; S, 8.21.

Mass spectra: Both compounds (**I** & **II**) showed similar peaks such as the molecular ion peak at m/z = 385 and base peak at m/z = 234, which may arise due to the fragmentation of 3,4-dimethoxy benzyl group. The moderate intense peak at m/z = 355 can be accounted for the loss of methoxy group from the parent ion. The medium intense peak at 191 and 127 can be assigned to the formation of naphthalene sulfonyl and naphthalene cations respectively. The weak intense peak at 91 and 77 may be due to the formation of tropylium and phenyl cations.

Electronic spectra: The electronic spectra of compound-**I** showed three prominent peaks in the UV region: The intense high energy absorptions at λ_{max} = 205 nm ($€_{max}$ = 63,800 M^{-1} cm^{-1}) and λ_{max} = 225 nm ($€_{max}$ = 55,140 M^{-1} cm^{-1}) may be attributed to the allowed $\pi\rightarrow\pi^*$ transition of dimethoxy benzene and naphthalene moieties, respectively; whereas, the low intense and low energy transition at λ_{max} = 285 nm ($€_{max}$ = 9,780 M^{-1} cm^{-1}) may be assigned to $n\rightarrow\pi^*$ transitions centered around $–SO_2–$ group.

The electronic spectra of compound **II** also showed three prominent peaks in the same wave length range in the UV region: The intense high energy absorptions at λ_{max} = 210 nm ($€_{max}$ = 55,065 M^{-1} cm^{-1}) and λ_{max} = 230 nm ($€_{max}$ = 63,650 M^{-1} cm^{-1}) may be attributed to the allowed $\pi\rightarrow\pi^*$ transition of dimethoxy benzene and naphthalene moieties, respectively. The intensity of these two bands are found to be reverse compared to compound **I**. Another low intense and low energy transition at λ_{max} = 280 nm ($€_{max}$ = 9,195 M^{-1} cm^{-1}) may be assigned to $n\rightarrow\pi^*$ transitions centered on $–SO_2–$ group.

IR spectra (KBr); Compound I: Medium intense peaks at 1159 and 1261 cm^{-1} may be attributed to C–N and to O-aryl stretching respectively; whereas the peaks at 1593 and 1518 cm^{-1} may be assigned to aromatic stretching. The N-CH_3 stretching is observed at 3435 cm^{-1}.

Compound II: The isomer of compound **I** *viz.*, compound **II** also showed similar peaks at 1158 cm^{-1} (C-N stretching); 1263 cm^{-1} (O-aryl); 1590 and 1516 cm^{-1} (aromatic stretching); 3435 cm^{-1} (N-CH_3 stretching).

NMR spectra ($CDCl_3$): The proton and carbon ^{13}NMR spectra of the compounds prepared greatly support the structure of the compounds proposed as detailed below.

^{1}H NMR (δ): Compound I: 2.81 (Triplet, 2H, Ar-CH_2-); 2.86 (singlet, 3H, N-CH_3); 3.44 (triplet, 2H, -CH_2-N); 3.80 (singlet, 6H, -OCH_3); 6.6 (multiplet, 3H, aromatic protons); 6.7 - 8.63 (multiplet, 7H, aromatic protons).

Compound II: 2.80 (Triplet, 2H, Ar-CH_2-); 2.86 (singlet, 3H, N-CH_3); 3.32 (triplet, 2H, -CH_2-N); 3.84 (singlet, 6H, -OCH_3); 6.75 (multiplet, 3H, aromatic protons); 6.7-8.63 (multiplet, 7H, aromatic protons). The proton NMR of both compounds (**I** & **II**) show triplets amounting a total of 4H which can be attributed to the two non equivalent -CH_2- protons (2H at δ = 2.81 to Ar-CH_2- and 2H at δ = 2.86 -CH_2-N). Similarly, peaks at δ = 2.86 (singlet, 3H, N-CH_3) and δ = 3.84 (singlet, 6H, -OCH_3) may be assigned to the methyl protons.

For compound **I**, the multiplets at down field δ = 6.6 (3H) and δ = 6.7-8.63 (7H) and for compound **II**, the multiplets at 6.75 (3H); 6.7-8.63 (multiplet, 7H) may be assigned to the aromatic protons.

The magnified aliphatic proton NMR shows the non-equivalent nature of -OCH_3 protons as doublet peak at δ = 3.80 & 3.83 in the high-resolution spectrum. The triplet peak of the -CH_2- protons and singlet peak of -NCH_3 protons appear in a magnified form at δ = 2.78, 3.44 and 2.86, respectively.

^{13}C NMR (δ): Compound I: 34.23 (Ar-CH_2), 34.53 (N-CH_3), 51.39 (N-CH_2), 55.77 (O-CH_2), 55.79 (O-CH_2), 111.12-134.14 (aromatic carbons), 134.35 (C-SO_2), 147.55 (C-OMe), 148.79 (C-OMe).

Compound II: 34.44 (Ar-CH_2), 35.14 (N-CH_3), 51.89 (N-CH_2), 55.81 (O-CH_2), 55.83 (O-CH_2), 111.24-134.68 (aromatic carbons), 134.88 (C-SO_2),147.67 (C-OCH_3), 148.92 (C-OCH_3).

^{13}C DEPT NMR (δ): To asses the nature of carbon atom (1º, 2º, 3º and 4º), a Distortion less Enhancement Polarization Transfer (DEPT) ^{13}C NMR was recorded. In the DEPT ^{13}C NMR of Compound **I**, the -O-CH_3 primary carbon appears up with more intensity and at more down field at δ = 55.77 and 55.79 than the -N-CH_3 1º carbon (δ = 34.53) which appears with less intensity and at high field. The secondary carbon appears as inverse peak with equal intensity. The down field peak at δ = 51.39 can be attributed to -N-CH_2- where as the up field peak at δ = 34.23 can be attributed to Ar-CH_2-. The peaks characteristic of tertiary carbon at δ = 111.12 to134.14 appear above as it is. The peak characteristics of quaternary carbon are found to be disappearing in the DEPT ^{13}C NMR.

In the DEPT ^{13}C NMR of Compound **II**, the -O-CH_3 primary carbon appears up with more intensity and at more down field at δ = 55.81 and 55.83 than the -N-CH_3 1o carbon (δ = 35.14) which appears with less intensity and at high field. The secondary carbons appear as inverse peak with equal intensity. The down field peak at δ = 51.89 can be attributed to -N-CH_2- where as the up field peak at δ =34.44 can be attributed to Ar-CH_2-. The peaks characteristic of tertiary carbon at δ = 111.24 to134.68 appear above as it is. The peak characteristics of quaternary carbon are found to be disappearing in the DEPT ^{13}C NMR.

Antimicrobial studies: Both compounds (**I** & **II**) were tested for their activities against the bacteria such as *Proteus vulgaris*, *Proteus mirabilis*, *Escherchina coli* and *Pseudomonas aureginosa* at different concentrations of the compounds. Both compounds are found to be active against *Proteus vulgaris*. Compound **II** *viz.*, 2-[{2-(3,4-dimethoxy phenyl)ethyl}methyl amino]sulphonyl naphthalene is found to be active against both *Proteus vulgaris* and *Pseudomonas aureginosa*. Its activity against *Proteus vulgaris* is almost comparable with the standard *viz.*, tetracycline. Compound **II** 2-[{2-(3,4-dimethoxy phenyl)ethyl}methyl amino]sulphonyl naphthalene is found to be more active even at low concentration than compound-**I** *viz.*, 1-[{2-(3,4-dimethoxy phenyl)ethyl}methyl amino]sulphonyl naphthalene, the latter being active only at moderately higher concentrations.

TABLE-1
ANTIBACTERIAL ACTIVITY OF 1- & 2-[{2-(3,4-DIMETHOXY PHENYL)ETHYL}METHYL AMINO]SULPHONYL NAPHTHALENES AGAINST HUMAN PATHOGENS

Compd.‡	†Diameter of zone of inhibition in human pathogen (mm)															
	E. coli				*P. vulgaris*				*P. mirabilis*				*P. aeruginosa*			
	25	50	75	100	25	50	75	100	25	50	75	100	25	50	75	100
I	0	0	0	0	6	10	12	14	0	0	0	0	0	0	0	0
II	0	0	0	0	5	8	16	20	0	0	0	0	4	6	10	10
TE*	2	14	20	26	8	20	26	30	16	18	24	32	16	28	30	34

*TE = Tetracycline; †Values are mean of three replicates; ‡Volume of each solution (mm) of the compound used 50 µL.

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