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Synthesis and Analgesic Activity of Some New Phenyl Sulfonyl Derivatives

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(±) Menthol (**1**) was oxidized to menthone (**2**) which was reacted with hydroxyl amine hydrochloride to yield menthone oxime (**3**). Menthone oxime (**3**) was converted to (2s,5r)-(±)-2-isopropyl-5-methyl-1-azacycloheptan-7-one (**4**) *via* Schmidt reaction, which was reacted with various substituted phenyl sulfonyl chlorides in alkaline medium to yield 7-isopropyl-4-methyl-1-(substituted phenyl sulfonyl)azepan-2-one (**5a-g**). The structure of all synthesized compounds have been established by analytical and spectral methods. These compounds have also been screened for analgesic activity.

Key Words: Synthesis, Analgesic activity, Phenyl sulfonyl derivatives.

INTRODUCTION

Phenyl sulfonyl derivatives possess varying degree of antibacterial[1] and antifungal[2] activity. Recently, pyrazole benzene sulfonyl derivatives were evaluated[3] for their ability to block COX-2. Further, lactam derivatives constitute an important class of compounds possessing diverse biological activities such as antibacterial, antifungal and analgesic activities. Therefore, it was thought of interest to combine above mentioned moieties together in a molecular framework to see additive effect of these moieties towards biological activities. In addition, the compacteness and planarity of such ring systems may be an additional factor for enhancing biological activities. Thus synthesis of series of systems containing sulfonyl and lactam moiety was attempted and the synthesized compounds were screened for analgesic activity.

EXPERIMENTAL

All the melting point were taken in open capillaries and are uncorrected. IR spectra (KBr, cm^{-1}) were recorded on Shimadzu 8400-S FTIR spectrophotometer. ^1H NMR spectra were recorded on Bruker 300 MHz

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NMR spectrometer using $CDCl_3$ as solvent and TMS as internal standard (chemical shift in δ ppm). The course of all reactions and purities of products were checked by means of TLC, carried out on silica gel G. Chromatograms were developed with mixtures of carbon tetrachloride and chloroform. Crystalline samples of sulfonyl derivatives were grown from ethanol.

Synthesis of menthone (2): Chromic acid solution was made using potassium permanganate (60 g), water (300 mL) and sulphuric acid (27 mL). Menthol (100 g) was dissolved in chromic acid solution by continuous stirring till fumes subsided. This reaction mixture was extracted with ether 2-3 times and ether layer was separated. The separated ether layer was shaken with 5% NaOH, then NaOH layer was discarded and same procedure was repeated until green colour in NaOH layer disappeared. The ethereal layers were taken in beaker and evaporated to yield menthone[4].

Synthesis of (1E)-2-isopropyl-5-methylcyclohexanone oxime (menthone oxime) (3): A mixture of menthone (7 mL, 0.05 mol), sodium hydrogen carbonate (6.00 g, 0.07 mol) and hydroxyl amine hydrochloride (4.48 g, 0.07 mol) in 40 mL methanol and 5 mL distilled water was heated to 65ºC for 3 h. After completion of the reaction the mixture was diluted with 50 mL distilled water and then extracted three times with hexane. The extract was washed successively with 5% $NaHCO_3$ and saturated NaCl solution. After evaporation of solvent, the crude product was distilled under reduced pressure. Distillation *in vacuo* gave 0.04 mol (76%) of appropriate oxime[5]; m.p. 54-56°C; IR (KBr, cm^{-1}): 3205 ν(O-H), 2995 ν(C-H), 1610 ν(C=N), 820-1180 ν(C-C); ^1H NMR ($CDCl_3$) δ: 0.93 (2d, 6H at C-8 and C-9), 1.03 (d, 3H at C-10), 1.16-1.47 (m, 2H at C-5 and C-7), 1.23 (S, 1H, OH), 1.67-2.01 (m, 4H at C-3 and C-4), 2.22-2.50 (d, 2H at C-6), 3.12-3.22 (m, 1H at C-2).

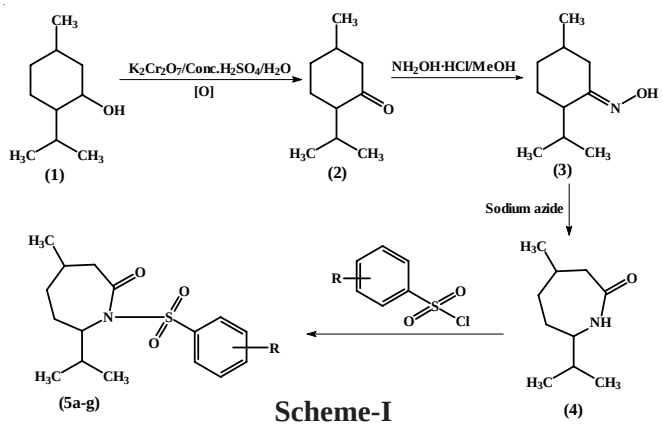
Synthesis of (2s,5r)-(±)-2-isopropyl-5-methyl-1-azacycloheptane-7-one (4): To a solution of oxime (0.08 mol) in chloroform (100 mL) maintained at -5ºC, was added dropwise with stirring conc. H_2SO_4 (25 mL). The addition was carried out at such a rate, so that temperature did not rise above 15ºC. After the addition, the temperature was brought down to 5ºC and sodium azide (10.4 g) was added in portions maintaining the temperature below 35ºC. The addition required about 2 h, next the reaction mixture was stirred at 50ºC for 2 h. It was then poured in to crushed ice and stirred till clear solution resulted. The mixture was made alkaline with 60% aqueous KOH. The precipitate was filtered and filtrate was extracted with chloroform. The chloroform extract was then evaporated to yield (2s,5r)-(±)-2-isopropyl-5-methyl-1-azacycloheptane-7-one[5]; m.p. 121-122°C; IR (KBr, cm^{-1}) : 3271 ν(-NH), 2993 ν(C-H), 1661 ν(C=O), 820-1180 ν(C-C); ^1H NMR ($CDCl_3$) δ: 0.91 (6H at C-9 and C-10), 1.01 (3H at

C-11), 1.17-1.45 (2H at C-5 and C-8), 1.68-2.03 (4H at C-3 and C-4), 2.23-2.51 (2H at C-6), 3.10-3.20 (1H at C-2), 5.95 (1H from -NH, D_2O exchangeable).

Synthesis of 7-isopropyl-4-methyl-1-(substituted phenyl sulfonyl)-azepan-2-one (5a-g): Compound **4** (1 mL) was reacted with 10 % KOH solution (4 mol) to which substituted phenyl sulphonyl chloride (1.5 mol) was added in small portions with constant shaking. This was acidified with dil. HCl, filtered and finally the product was recrystallized from ethanol[6]; (**5a**) IR (KBr, cm^{-1}): 2987 ν(C-H), 1664 ν(C=O), 1327 ν(C=C, aromatic), 1000-1087 ν(SO_2), 825 ν(C-H, aromatic), 569 ν(C-Br); ^{1}H NMR ($CDCl_3$) δ : 0.93 (6H at C-9 and C-10), 1.05 (3H at C-11), 1.15-1.47 (2H at C-5 and C-8), 1.65-2.01 (4H at C-3 and C-4), 2.25-2.57 (2H at C-6), 3.16-3.28 (1H at C-2), 7.23-8.05 (d, 4H, Ar-H); (**5g**) IR (KBr, cm^{-1}): 2981 ν(C-H), 1669 ν(C=O), 1320 ν(C=C, aromatic), 1000-1087 ν(SO_2), 827 ν(C-H, aromatic); ^{1}H NMR ($CDCl_3$) δ : 0.90 (6H at C-9 and C-10), 1.04 (3H at C-11), 1.15-1.48 (2H at C-5 and C-8), 1.65-2.00 (4H at C-3 and C-4), 2.22-2.51 (2H at C-6), 3.17-3.25 (1H at C-2), 7.20-8.10 (m, 4H, Ar-H).

RESULTS AND DISCUSSION

(±)-Menthol (**1**) was reacted with chromic acid solution to give menthone (**2**). The menthone (**2**) was reacted with hydroxylamine hydrochloride in presence of sodium bicarbonate using methanol as solvent to give menthone oxime (**3**). The menthone oxime was converted to (2s,5r)-(±)-2-isopropyl-5-methyl-1-azacycloheptane-7-one (**4**), a seven membered lactam *via* Schmidt reaction. The compound **4** was reacted with various substituted phenyl sulfonyl chloride in alkaline media to give 7-isopropyl-4-methyl-1-(substituted phenyl sulfonyl)azepan-2-one (**5a-g**) (**Scheme-I**). The compounds were found to be soluble in common organic solvents (*e.g.*, DMSO, ethanol and chloroform). The characterstic properties of compounds (**5a-g**) are presented in Table-1.



Scheme-I

TABLE-1
PHYSICAL DATA OF COMPOUNDS (**5a-g**)

Compd.	R	m.f. / m.w.	m.p./b.p. (ºC)	$^{\dagger}R_f$	Yield (%)
5a	4-Bromo	$C_{16}H_{22}NO_3SBr$ (388.31)	155	0.577	72
5b	4-Methyl	$C_{17}H_{25}NO_3S$ (323.45)	50	0.446	83
5c	4-Acetamido	$C_{18}H_{26}N_2O_4S$ (366.47)	180	0.330	79
5d	4-Chloro	$C_{16}H_{22}NO_3SCl$ (343.86)	75	0.322	63
5e	2-Chloro-3,5-dinitro	$C_{16}H_{20}N_3O_7SCl$ (433.86)	38	0.588	95
5f	3-Nitro	$C_{16}H_{22}N_2O_5S$ (354.42)	b.p.-123	0.320	87
5g	-H	$C_{16}H_{23}NO_3S$ (309.42)	b.p.-112	0.420	83

$^{\dagger}CCl_4(1):CHCl_3(1)$

Screening for analgesic activity

The analgesic activity of compounds (**5a-g**) were determined by hot plate method[7] using wister mice of either (25-30 g) of either sex. The animals were selected by random sampling technique and were divided into group of three animals each. The time taken by each animal to show paw licking response was recorded by placing animal on a hot plate maintained at a temperature of 55 ± 0.50ºC before administration of compounds. This data was used as control reading. The test compounds at three dose levels of 2.5, 5.0 and 10.0 mg/Kg were administered intraperitonially by solubilizing compounds in DMSO, while one group received piroxicam as a standard at dose of 4 mg/Kg body weight. After 1 h interval, the time taken for paw licking responses was recorded for all animals and percent analgesic activity was determined. The results of analgesic activity are summarized in Table-2.

TABLE-2
ANALGESIC ACTIVITY DATA OF SYNTHESIZED COMPOUNDS (**5a-g**) USING HOT PLATE METHOD

Comp.	Mean increase in latency period			Analgesic activity* (%)			ED_{50}
	2.5 mg	5.0 mg	10.0 mg	2.5 mg	5.0 mg	10.0 mg	
5a	0.6 ± 0.40	2.2 ± 0.30	5.9 ± 0.40	5.20	19.13	51.30	9.84
5b	0.5 ± 0.26	2.3 ± 0.20	5.9 ± 0.47	4.10	20.0	51.30	9.78
5c	3.2 ± 0.17	8.0 ± 0.83	13.2 ± 0.62	27.82	69.56	114.7	3.98
5d	3.7 ± 0.18	9.6 ± 0.10	12.8 ± 0.66	32.10	83.47	111.3	3.23
5e	1.5 ± 0.09	9.8 ± 0.23	11.6 ± 0.50	13.00	85.21	108.6	4.20
5f	0.8 ± 0.06	3.6 ± 0.21	8.8 ± /0.72	6.95	31.30	76.52	7.10
5g	1.6 ± 0.30	5.5 ± 0.23	8.1 ± 0.50	13.91	47.82	70.43	6.67

*Standard used is piroxicam at a dose of 4mg/ Kg 11.50 $\pm$ 0.9 sec

The writhing method[8] was based on acetic acid induced writhing in mice. Group of three mice were administered with test compounds, control and standard. The test compound and standard compound (piroxicam) were used at dose of 2.5 and 4 mg/Kg body weight intraperitonially, respectively. The results of analgesic activity are summarized in Table-3.

TABLE-3
ANALGESIC ACTIVITY DATA OF SYNTHESIZED COMPOUNDS (**5a-g**) USING WRITHING METHOD

Compound	Number of writhings in 15 min	Writhing inhibition (%)
5a	62	13.88
5b	61	15.27
5c	41	43.05
5d	42	41.66
5e	45	37.5
5f	52	27.77
5g	54	25
Control	72	-
Piroxicam (Standard)	31	56.94

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