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Synthesis and Antiinflammatory Activity of Aryl Sulphonanilides Structurally Related to Nimesulide

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Substituted sulphonanilides of diphenyl ether, benzyl phenyl ether and diphenylamine were synthesized which were structurally related to antiinflammatory drug nimesulide. Synthesized compounds displayed antiinflammatory activity comparable with that of nimesulide. From the result it can be concluded that the replacement of methane sulphonanilide group with other sulphonanilide and replacement of ether oxygen with -OCH_2-, -NH- decreases activity.

Aryl sulfonamides have a wide therapeutic application. They are known to exhibit antimicrobial[1], hypoglycemic[2], diuretic[3], antiviral[4], antitubercular, antifungal[5] and antiinflammatory[6] activities. Nimesulide is one of the sulphonanilide derivatives with antiinflammatory activity and have less gastric side effects because of weak acidic methane sulphonamido group and COX-2 selectivity[7]. Literature survey reveals that replacement of phenyl ring with any other heterocyclic rings like pyridine, pyridine N-oxide, 4(1-H-tetrazole-5-yl) phenyl results in inactive compounds[8]. So the present study was planned to synthesize compounds structurally related to nimesulide and to evaluate the structural requirement for activity. These analogues were synthesized as per Scheme 1.

Diphenyl ether, benzyl phenyl ether and diphenylamine (II) were synthesized by refluxing *o*-nitro chlorobenzene (I) with phenol, benzyl alcohol and aniline, respectively. Then compounds obtained were reduced to get amino derivatives (III) which on treatment with different sulphonyl chlorides offered sulphonanilides (IV). Finally all sulphonanilides were nitrated to yield final product (V).

MATERIALS AND METHODS

All melting points were determined in open glass capillaries in liquid paraffin bath and are uncorrected. TLC, using silica gel-G as an adsorbent, determined the purity of compounds and spots were viewed by exposure to iodine vapours. IR spectra were recorded on a Shimadzu-IR Spectrophotometer 408 in nujol mull or KBr, PMR spectra were recorded on a FX-90 QFT NMR Spectrophotometer (in δ ppm) using TMS as an internal standard. The structures of all compounds were consistent with their analytical and spectroscopic data.

Synthesis of *o*-nitro diphenyl ether (IIa)[9]:

Phenol (80 g, 0.85 mol) and potassium hydroxide (40 g, 0.715 mol) were heated to 130-140° until all alkali has been dissolved .The above mixture was cooled to 100-110° and 0.5 g copper catalyst and *o*-nitro chloro benzene (39.4 g, 0.25 mol) were added portion-wise and heated at 150-160° with stirring. At this temperature spontaneous reaction begins with ebullition and the separation of potassium chloride. Then heating was discontinued. To above reaction mixture was added *o*-nitro chloro benzene (39.4 g, 0.25 mol) and process was repeated. The temperature of mixture was then maintained at 150-160° for additional one and half h. The dark brown coloured melt was then poured into one liter of 2.5 % ice cold sodium hydroxide solution and stirred well to remove excess of phenol. The oily layer was separated and subjected to high vacuum distillation. The second fraction collected at 185-220°/20 mm yielded *o*-nitro diphenyl ether [Yield- 47%, B.P. 317-322°, IR (nujol, cm^{-1}) 3050 (aromatic C-H), 1550 (aromatic C=C), 1350 (aromatic- NO_2), 1240 (C-O), 1200, 1160 (aryl ethers C-O)].

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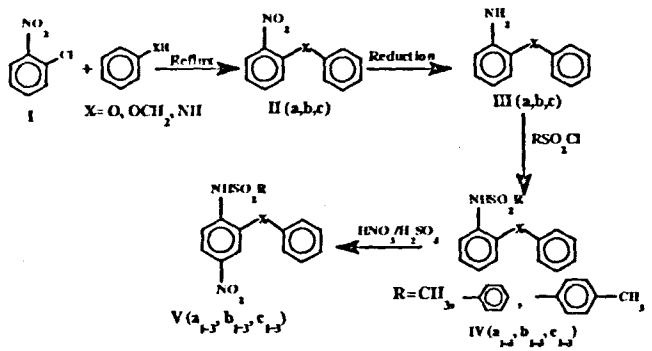

SUBSTITUENTS AT X AND R IN SCHEME 1.

Compound	X	R
IIIa	-O-	-
IIIa	$-OCH_2-$	-
IIIc	-NH-	-
IVa_1	-O-	$-CH_3-$
IVa_2	-O-	-Ph
IVa_3	-O-	$-PhCH_3$
IVb_1	$-OCH_2-$	$-CH_3-$
IVb_2	$-OCH_2-$	-Ph
IVb_3	$-OCH_2-$	$-PhCH_3$
IVc_1	-NH-	$-CH_3-$
IVc_2	-NH-	-Ph
IVc_3	-NH-	$-PhCH_3$

Synthesis of 2-phenoxy aniline (IIIa)[10]:

To *o*-nitro diphenyl ether (20 g, 0.093 mol) in 150 ml ethanol added 20 ml of hydrazine hydrate and 4.0 g of raney nickel portion wise. The air condenser was attached until evolution of hydrogen subsides. The reaction mixture was then refluxed for 10 h. The mixture was cooled to room temperature and raney nickel was filtered out. The excess of ethanol was distilled out and the concentrate was allowed to cool in refrigerator. The pinkish white solid was obtained which was recrystallized from ethanol. [Yield- 61.4%, M.P. 47-50°, IR (KBr, cm^{-1}), 3000 (aromatic C-H), 3450 (N-H), 1220,1080 (aryl ethers C-O)].

Synthesis of *o*-nitro phenyl benzyl ether (IIb)[9]:

Benzyl alcohol (46 ml, 0.425 mol) was added to sodium (11.5 g), copper (0.5 g) followed by *o*-nitro chloro benzene (20 g, 0.12 mol) in portions and heated to 150-160° with stirring. At this temperature spontaneous reaction begins with ebullition and separation of sodium chloride. Heating was then discontinued and to this mixture additional amount of *o*-nitro chloro benzene (20 g, 0.126 mol) was added and temperature was maintained at 150-160° for an additional 3 h. After cooling the mixture was extracted with 500 ml of petroleum ether. After removing petroleum ether the concentrate was subjected to high vacuum distillation. The second fraction was collected at 125-160°/20 mm, which contained *o*-nitro phenyl benzyl ether [Yield 52%, M.P.120-122°, IR (KBr, cm^{-1}), 3100 (aromatic C-H), 1610 (aromatic C=C), 1310 (aromatic-NO_2), 1150,1070 (aryl ethers C-O)].

Synthesis of 2-benzyloxy aniline (IIIb)[11]:

o-Nitro phenyl benzyl ether (28 g, 0.122 mol) in 250 ml ethanol was refluxed with stirring at 100-110°. To the mixture iron powder (44 g) was added in portions followed by concentrated HCl (3 ml) and heating was continued for about 18 h. Then reaction mixture was cooled and sodium carbonate was added till the pH becomes neutral. The reaction mixture was filtered, excess ethanol was distilled out and product was extracted with diethyl ether. Removal of ether by distillation yielded the product, which was recrystallized from ethanol. [Yield- 21.5%, M.P. 61-65°, IR (KBr; cm^{-1}), 3000 (aromatic C-H), 3200 (N-H), 1560, 1530 (C=C), 1200 (aryl ethers C-O)].

Synthesis of 2-nitro diphenyl amine (IIc)[12]:

Aniline (22 g, 0.23 mol) and potassium carbonate (3.0 g, 0.0217 mol) were refluxed with stirring. To this *o*-nitro chloro benzene (20 g, 0.126 mol) was added in portion wise over a period of one and half h while the temperature was maintained below 100° .The above reaction mixture was refluxed for additional 8 h and allowed to cool. The cold reaction mixture was then poured on crushed ice. The separated organic layer was subjected to high vacuum distillation, and the fraction collected at 180°/20 mm was solidified into 2-nitro-diphenylamine. It was recrystallized from chloroform [Yield 70.14%, M.P. 70°, IR (KBr; cm^{-1}), 3383 (N-H), 3000 (aromatic C-H), 1597 (C=C), 1520 (aromatic-NO_2)].

Synthesis of 2-amimo diphenylamine (IIIc)[13]:

A solution of 50 ml of sodium hydrogen sulphide (NaSH) [prepared from 10% sodium hydroxide (10 g, 0.025 mol) sulphur powder (3.2 g, 0.1 mol)] was added to a solution of 2-nitro-diphenylamine (18g, 0.084 mol) in 50 ml ethanol. The above mixture was refluxed for 2 h and allowed to cool. Excess ethanol was distilled out and crude 2-amino dipheny-

lamine obtained was recrystallised from chloroform. [Yield-64.64%, M.P. 80°, IR (KBr; cm^{-1}), 3383 (N-H), 3045 (aromatic C-H stretch), 773, 746 (aromatic C-H bending)].

Synthesis of 2-phenoxy methanesulphonanilide (IVa_1)[14]:

To a vigorously stirred mixture of 2-phenoxy aniline (1.18 g, 6.39 m mol) in 10 ml diethyl ether and 10 ml water basified with few drops of 10% sodium hydroxide at 0-3° methane sulphonyl chloride (7.0 g, 0.061 mol) was added drop wise under cold condition. The mixture was kept alkaline by addition of 10% sodium hydroxide. After additional stirring at room temperature for about 1h, the organic layer was separated and aqueous layer was adjusted to pH 7-8 with dilute HCl to separate pinkish white solid which was recrystallized from ethanol [Yield 48%, M.P. 75-78°, IR (nujol; cm^{-1}), 3200 (aromatic C-H), 1600 (C=C), 1160 (NH-SO_2), 1180 (C-O aryl ethers)]. Compounds IIIa, IIIb and IIIc were sulphonated using methane sulphonyl chloride, benzene sulphonyl chloride and *p*-toluene sulphonyl chloride with same procedure to yield $IVa_{1-3,}$ $IVb_{1-3\ and}$ IVc_{1-3}. All the compounds were characterized by IR peak at 1160 cm^{-1} (NH-SO_2).

Synthesis of 4-nitro-2-amino phenyl benzenenesulphonanilide (Vc_2)[15]:

To a solution of 2-amino phenyl benzenesulphonanilide (2.5 g, 0.0077 mol) in 5 ml of glacial acetic acid cooled to 0-5° in ice bath, cold nitrating mixture [nitric acid (0.2 ml), sulphuric acid (0.5 ml)] was added drop-wise with stirring over a period of 30 min. The reaction mixture was then poured into 100 ml of ice-cold water with stirring and white solid precipitated out was separated by filtration. The product was recrystallized from ethanol [Yield 68.25%, M.P. 147-150°, IR (KBr; cm^{-1}) 3474 (N-H), 667 (aromatic C-H), 1504 (aromatic-NO_2), 1149 (-NH-SO_2),PMR (δ ppm) 7.29(5H, s, Ar-H), 7.14 (3H, s, Ar-H), 7.60 (3H, s, Ar-H), %N_2 (calculated):11.3 %N_2(found):10.9]. Compounds IVa_{1-3}, IVb_{1-3} and IVc_{1-3} were nitrated by same procedure to yield Va_{1-3}, Vb_{1-3} and Vc_{1-3}. All the compounds were characterized by IR peaks 1530 cm^{-1} (C-NO_2), 1350 cm^{-1} (N-O stretch) and 1100 to1160 cm^{-1} (-NH-SO_2).

Antiinflammatory activity:

Antiinflammatory activity was determined by carrageenan-induced rat paw oedema method[16]. Groups of four male rats (Wistar, 150-160 g) were dosed (10 mg/kg) intra peritoneally with standard and test compounds one h before injection of 0.1ml of 1% suspension of carrageenan into sub-plantar region of right hind paw. The left paw received the same volume of saline. The paw volume was measured immediately and 15, 30, 60, 120, 150,180 min after carrageenan injection by plethysmometer (UGO-BASILE, Italy). The change in paw volume was compared with that in vehicle treated control animals and expressed as % inhibition of oedema, calculated as % inhibition=(1-Vt/Vc)x100. Where, Vt=volume of paw oedema in animals treated and Vc= vol-

TABLE 1: PHYSICAL PARAMETERS AND ANTIINFLAMMATORY ACTIVITY OF VARIOUS DERIVATIVES OF NIMESULIDE.

Compound No.	M.Wt.	M.P	Rf value	Average paw volume displaced in animals			% inhibition of rat paw oedema
				1 h	2 h	3 h	
Va_1	308	137-140	0.67[1]	0.21±0.012	0.18±0.018	0.16±0.012	70.49
Va_2	370	86-90	0.62[1]	0.28±0.010	0.20±0.008	0.94±0.007	63.50
Va_3	384	75-77	0.57[2]	0.28±0.008	0.21±0.013	0.16±0.009	62.20
Vb_1	322	129-132	0.50[2]	0.26±0.010	0.21±0.007	0.17±0.010	66.42
Vb_2	384	122-126	0.50[1]	0.26±0.011	0.25±0.030	0.19±0.009	62.50
Vb_3	398	119-123	0.59[2]	0.32±0.012	0.26±0.027	0.18±0.012	59.82
Vc_1	307	147-150	0.66[1]	0.22±0.014	0.20±0.004	0.17±0.008	65.22
Vc_2	369	108-110	0.70[1]	0.29!0.004	0.22±0.009	0.17±0.004	61.74
Vc_3	383	95-100	0.58[3]	0.27±0.091	0.26±0.004	0.21±0.004	59.08

Solvent systems for TLC: 1-chloroform, 2-Benzene, 3-Chloroform: Methanol (9:1).

ume of paw oedema in control animals. The Institutional Animal Ethics Committee (Registration No. 121/ 1999/ CPCSEA) approved the protocol of this study.

RESULTS AND DISCUSSION

The physical data like M.P., Rf value are reported in Table 1. All the compounds are consistent with their proposed structures. All the compounds showed characteristic IR peaks at 1100 to1160 cm^{-1} (secondary sulphonamide), 1530 and 1350 cm^{-1} (C-NO_2 and N-O stretch), 2950 (aromatic C-H), 1600 (C=C). The compounds Vc_{1-3} showed the characteristic N-H stretch at 3270 to3475 cm^{-1}. ^{1H} NMR showed characteristic peak at 7-8 δ ppm, which confirms presence of aromatic protons and peak at 1-2 δ ppm confirms presence of methyl protons.The synthesized compounds showed antiinflammatory activity comparable to standard drug nimesulide (85% inhibition in paw oedema). All the compounds showed more than 50% inhibition in paw oedema ($p<0.01$). Compound Va_2 is most active as compare to others. From the result it can be concluded that the replacement of methane sulphonanilide group with other sulphonanilide and ether oxygen with $-OCH_2-$, -NH- decreases antiinflammatory activity.

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