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Synthesis, characterization and biological evaluation of 3-alkyl-5(4-substituted benzene disulphonamido)-1, 2-benzisoxazoles and its derivatives

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ABSTRACT

The chlorosulphonic acid treated with 3-alkylbenzisoxazole to give [1A – 9A] which is concentrated with ammonia solution and further acidified with dil. H_2SO_4 we get sulphonamido derivatives [1B – 9B] which is on substituted with benzene sulphonyl chloride and pH adjusted to 10-11 by 50% NaOH solution to give Disulphonamido derivatives [1C-27°C]. The synthesized compounds characterized by spectral analysis like IR, NMR and Elemental Analysis. The synthesized compound screened by antibacterial activity.

Key words: Chlorosulphonic acid, substituted Benzisoxazole, NH_3, dil. H_2SO_4, NaOH sulphonamido, antibacterial activity.

INTRODUCTION

A heterocyclic compound promotes the life on earth[3]. They are widely distributed in nature and essential to life as they play vital role in metabolism of living cells. Heterocyclic ring system containing 'S' heteroatoms exhibited chemotherapeutic antituberculosis, antibacterial and other medicinal uses[3].

The literature survey of the Sulphonamide compounds showed that they are associated with physiological and biological properties and thus find importance in medicine.

Sulphadimethoxyne, Sulphamethoxy pyridoxine, Sulfoisoxazole and Sulpha-phenazole were found to be bactericidal. M-tert alkyl alkenes sulfonamides are used as antiknock agent for gasoline. Sulphonamide attached with heterocyclic ring is more potent than sulphonamide. For example Sulphapyridine was sulphadiazine is used to curve mild infections.

Disulphonamide compounds as a class behave as strong acids forming neutral sodium salts of the type $–SO_2–N–Na–$. These salts have high water solubility and are very stable to heat decomposing at temperature above 300^0C. However if the hydrogen of the disulphonamide is replaced by the alkyl the compound becomes water and alkali insoluble and is broken down more readily by strong acid or bases. Disulphonamide reacts with bases to form a series of neutral salts most of which are highly water soluble these compounds appear from preliminary experimental in mice to have high antistrepto coccal activity and in the case of the N^1-Methyl and N^1 – Ethyl disulphonamide have shown

promising result on infection caused by the Francis strain of influenza in mice. The results in mice again betahaemolytic streptococci indicate that these compounds as a class of low chemotherapeutic activity.

From the survey about the activity of benzisoxazole, sulphonamide and disulphonamide, they are found to posses various biological therapeutical and medicinal importance. Therefore it was thought worthwhile to prepare [1C-27°C] synthesized compounds [1C-27°C] characterized by means IR and elemental analysis.

In the biological investigation the compounds were screened for antibacterial activity against Bacillus subtilis (gram positive) and klebsiella (gram negative) bacteria by employing the food poison technique at 250 & 100 ppm.

EXPERIMENTAL

General procedure for the preparation of 3-alkyl-5-chlorosulphonyl-1, 2-benzisoxazole [1A-9A]

The chlorosulphonic acid (0.1 mol) was taken into flask and it was cooled. Then 3-alkyl benzisoxazole (0.01 mol) was added in portionwise to the cooled chlorosulphonic acid. The mix was then heated on oil bath at 120^{0}C for 4h, cooled and poured into crushed ice. It was stirred and solid separated was collected, washed with sodium bicarbonate solution and distilled water. It was crystallized from aqueous acetone which gives compounds [1A-9A].

General procedure for the synthesis of 3-alkyl-5-sulphonamido-1,2-benzisoxazoles [1A-9A]

The chlorosulphonic compounds [1A-9A] (0.1 mol) was treated with concentrated ammonia solution (1 mol). The reaction mixture was heated on water bath for one hour and acidified with dil. Sulphuric acid to congored and cooled. The precipitate was filtered, washed with cold water and crystallized from proper solvent [ethanol]. We get the synthesized comp. is [1B-9B].

General method for the synthesis of 3-alkyl-5-[4^1-substituted disulphanamido]-1,2-benzisoxazoles [1C-27C]

The comp. [1B-9B] (0.01 mole) was dissolved in 160 ml of distilled water containing 1.6 gm of anhydrous sodium carbonate and 3 gm of sodium hydroxide at 45^{0}C substituted benzene sulphonyl chloride (0.13 mole) was then added with vigorous agitation over one hour maintaining a PH of 10 to 11 by addition of 50% NaOH solution as required. After stirring for an hour the reaction mixture was cooled to 10^{0}C. The crude produce was filtered and dissolved in water where by the highly soluble sodium salt of the substituted disulphonamide wash out into solution.

The obtained product [1C-27°C] was then crystallized from concentrated aqueous solution adjusting the PH 6-7 by acetic acid.

Melting point were determined in open capillary tube and were found uncorrected. The purity of test compounds were determined by TLC on protected SiO_2 gel (HF_{254} 200 mesh). Aluminium plates (E-Merk). A single spot is obtained on TLC confirmed the purity of substituted disulphonamide benzisoxazoles and yield is calculated (w/w).

The melting points, percentage yields and elemental analysis [% of sulphur] of the synthesized compounds are given in table 1.

DISCUSSION

The IR spectra of some of the representative compound from the series were recorded on perkin-elmer infracourd in nujolrnull.

The absorption bands at 3400cm^{-1} and 1640cm^{-1} are due to secondary amine –NH– stretching and bending. The S = O grouping shows absorption band at 1330 cm^{-1} and 1160 cm^{-1} due to asymmetric and symmetric stretching. All the compound showed characteristic absorption of Benzisoxazole ring.

The absorption bands at 1530 cm^{-1}, 1220 cm^{-1} and 900 cm^{-1} are due to –C = N–, N–O–C and isoxazole ring respectively.

Biological Evaluation [Antibacterial screening]

The synthesized compounds were screened for antibacterial activity against *Bacillus subtilis* (Gram positive) and *Klebsiella* (Gram

negative) bacteria by employing the food poison technique at 250 and 100 ppm. The substituted benzisoxazole showed more activity at higher concentration. The aryl substituted disulphonamido benzoisoxazoles are relatively less active when compared with that of sulphonamido compounds.

Results and data are given in table 2(a), II(b) and II(c).

RESULTS AND DISCUSSION

All the synthesized compounds exhibit significant to moderate antibacterial activity. In present work substituted disulphonamide benzisoxazole and chlorosulphonic acid are key raw material compound.

The compound [1C-27C] are charactrised on the basis of spectral data and elemental analysis. Biological activities were carried out for above compounds.

Table 1: Physical data and elemental analysis [% of sulphur] of comp. [1C-27C]

S. No.	R_1	R_2	R_3	m.p. (^{0}C)	Yield (% w/w)	Sulphur % Found	Sulphur % Calculated
1C	Methyl	H	H	140	35	18.27	18.18
2C	Methyl	H	Methyl	105	40	17.36	17.48
3C	Methyl	H	Chloro	114	47	16.50	16.55
4C	Ethyl	H	H	125	38	17.41	17.48
5C	Ethyl	H	Methyl	120	40	16.73	16.84
6C	Ethyl	H	Chloro	152	40	15.86	15.98
7C	Propyl	H	H	159	35	16.92	16.84
8C	Propyl	H	Methyl	115	45	16.21	16.25
9C	Propyl	H	Chloro	127	30	15.47	15.44
10C	Methyl	5-Methyl	H	172	45	17.24	17.48
11C	Methyl	5-Methyl	Methyl	178	42	16.41	16.84
12C	Methyl	5-Methyl	Chloro	142	35	15.91	15.98
13C	Ethyl	5-Methyl	H	155	49	16.78	16.84
14C	Ethyl	5-Methyl	Methyl	139	42	16.27	16.24
15C	Ethyl	5-Methyl	Chloro	148	45	15.37	15.44
16C	Propyl	5-Methyl	H	129	46	16.29	16.24
17C	Propyl	5-Methyl	Methyl	137	49	15.59	15.68
18C	Propyl	5-Methyl	Chloro	165	35	14.87	14.93
19C	Methyl	7-Methyl	H	149	32	17.40	17.48
20C	Methyl	7-Methyl	Methyl	213	48	16.82	16.84
21C	Methyl	7-Methyl	Chloro	208	45	15.85	15.98
22C	Ethyl	7-Methyl	H	167	39	16.76	16.84
23C	Ethyl	7-Methyl	Methyl	137	31	16.34	16.24
24C	Ethyl	7-Methyl	Chloro	142	37	15.48	15.44
25C	Propyl	7-Methyl	H	128	40	16.29	16.25
26C	Propyl	7-Methyl	Methyl	170	45	15.77	15.68
27C	Propyl	7-Methyl	Chloro	163	45	14.87	14.92

Table 2(a): For compound 1A – 9A

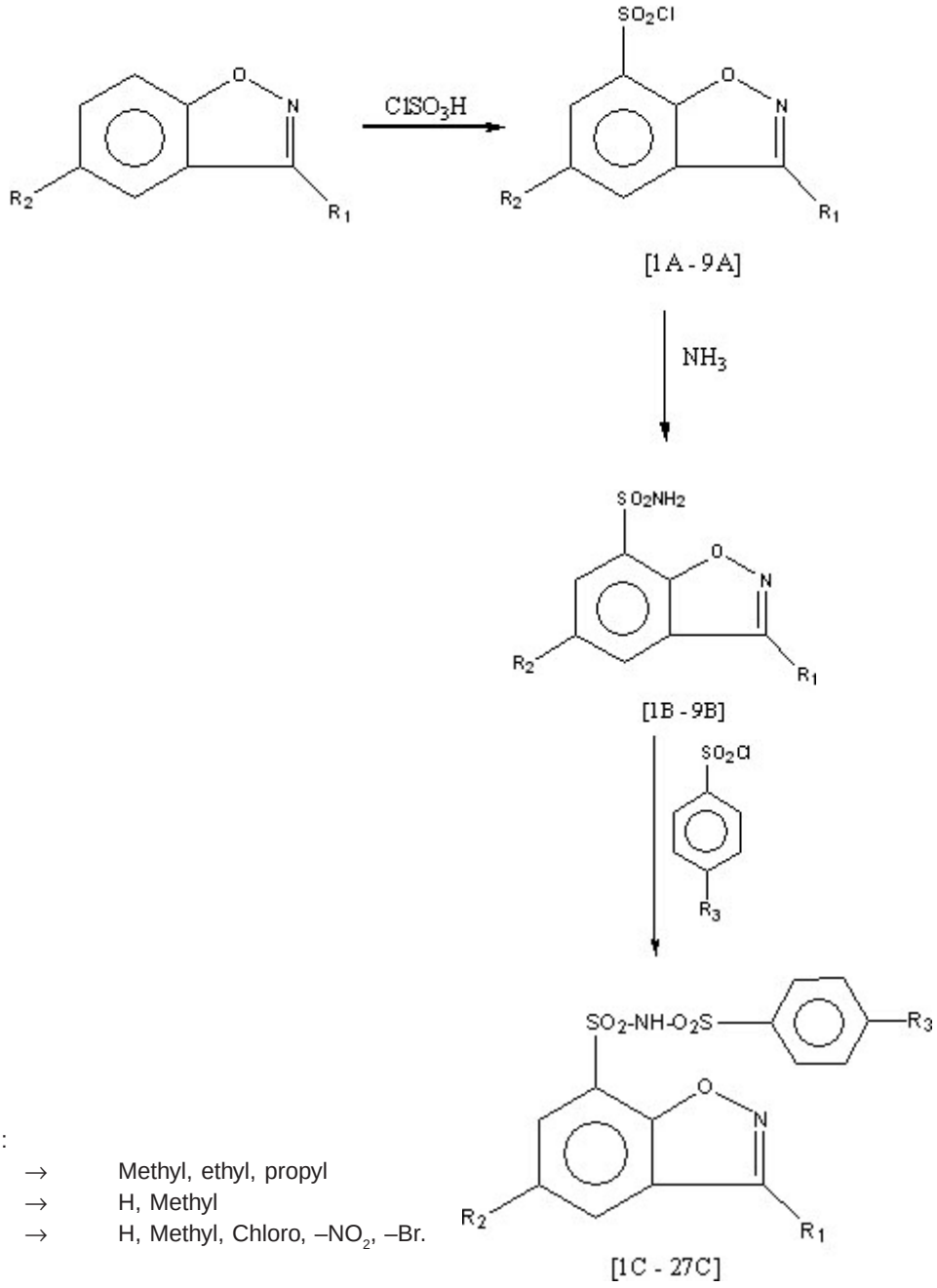
S. No.	R_1	R_2	*Bascillus subtilis*		*Klebsiella pneum*	
			250 ppm	100 ppm	250 ppm	100 ppm
1A	Methyl	H	++	+	-	-
2A	Methyl	5-Methyl	++	+	-	-
3A	Methyl	7-Methyl	-	-	-	-
4A	Ethyl	H	++	+	-	-
5A	Ethyl	5-Methyl	++	-	-	-
6A	Ethyl	7-Methyl	++	+	-	-
7A	Propyl	H	++	-	-	-
8A	Propyl	5-Methyl	-	-	-	-
9A	Propyl	7-Methyl	++	-	-	-

Table 2(c): For compound 1C-27°C

S. No.	R_1	R_2	*Bascillus subtilis*		*Klebsiella pneum*	
			250 ppm	100 ppm	250 ppm	100 ppm
1C	Methyl	H	H	++	+	+ --
2C	Methyl	H	Cl	++	+	+ --
3C	Methyl	H	$-CH_3$	+	+	-- --
4C	Ethyl	H	H	+	--	-- --
5C	Ethyl	H	Cl	++	++	+ --
6C	Ethyl	H	$-CH_3$	+	--	-- --
10C	Methyl	5-Methyl	H	++	+	+ --
11C	Methyl	5-Methyl	Cl	--	--	-- --
12C	Methyl	5-Methyl	$-CH_3$	++	+	-- --

Table 2(b): For compound 1B-9B

S. No.	R_1	R_2	*Bascillus subtilis*		*Klebsiella pneum*	
			250 ppm	100 ppm	250 ppm	100 ppm
1B	Methyl	H	H	+	+	- -
2B	Methyl	H	Cl	+	-	- -
3B	Methyl	H	Br	+	-	- -
4B	Methyl	H	$-CH_3$	-	-	- -
5B	Methyl	H	NO_2	-	-	- -
6B	Ethyl	5-Methyl	H	+	+	- -
7B	Ethyl	5-Methyl	Cl	+	-	- -
8B	Ethyl	5-Methyl	Br	+	-	- -
9B	Ethyl	5-Methyl	Methyl	-	-	- -



Where:

R_1 → Methyl, ethyl, propyl
R_2 → H, Methyl
R_3 → H, Methyl, Chloro, $–NO_2$, –Br.

CONCLUSION

Synthesized substituted disulphonamide benzisoxazoles and their derivatives are important class of heterocyclic compounds with a diverse medicinal use like antitubercular effect.

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