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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF 3-ALKYL-5-CHLOROSULPHONYL-1,2-BENZISOXAZOLES AND THEIR DERIVATIVES

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ABSTRACT

The chlorosulphonic acid was treated with 3-alkyl-benzisoxazole to give the product 3-alkyl-5-chloro sulphonyl-1,2-benzisoxazoles **(A1 – A9)**. The synthesized compounds are characterized by spectral analysis like IR, NMR and elemental analysis and also screened for antibacterial activity.

Key words: Chlorosulphonic acid, Substituted benzisoxazole, Sulphonamido, Antibacterial activity.

INTRODUCTION

Heterocyclic compounds promotes the life on earth[1]. These are widely distributed in nature and essential to life as they play important roles. Heterocyclic ring systems containing 'S' heteroatom exhibited chemotherapeutic, antituberculosis and other medicinal uses.

A number of benzisoxazoles show physiological activity and have been tested for pharmacological uses. The derivatives of 6-acetamidobenzisoxazole-3-acetic acid have been reported to have tuberculostatic activity[2]. Compounds belonging to 3-aminobenzisoxazole series have been shown to posses sedative and analgesic properties[3]. Some compounds have been found to posses trypanocidal activity[4]. 4,5,6,7-Tetrahydro derivatives were tested as analeptics[5]. Some derivatives of napthisoxazolyl phosphotioate have been used as acricides, insecticides and larvicides[6].

In the year 1972, Sounder[7] concluded that 3-phenyl-5-methyl-1,2-benzisoxazole

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derivatives were antiinflammator at 25 to 500 mg dose. Nishimura and others[8] synthesized a number of compounds having amidoxine substituent at 3-position and observed antidepressant, hypotensive and α-DOPA synergistic activities. The antifungal and antibacterial activities were observed by Thakar and coworkers[9,10] in the nitro substituted and formyl substituted 1,2-benzisoxazoles. Some of the 5-nitro derivatives show inhibitory action on phytophathogenic bacteria. Freedom and Jules[11] observed C.N.S. depressant effect and sedative effect in benzo thiapyrano isoxasoles.

Various methods are reported in literature for the synthesis of isoxazoles. Some of the important methods are given below -

(i) From O-halogeno-benzoyl compounds and hydroxyl amine,

(ii) From O-nitrobenzoyl compounds and hydroxylamine hydrochloride,

(iii) From other O-substituted benzoyl compounds and hydroxylamine,

(iv) From O-hydroxybenzoyl derivative,

(v) Miscellaneous (a) By hydrolysis of O-hydroxybenzal azides
(b) By bromination,

(vi) Closure of bond between 1-7a and 3-3a of 1,2-benzisoxazole and

(vii) Cyclising O-hydroxy benzoyl derivatives with pyridine.

It has been observed that neither cyclisation nor the methods mentioned above gives good yields and they are even tedious and time consuming. Thus, present work has been selected to synthesize benzisoxazole derivatives and also characterize them by means of IR, ^{1}H NMR and elemental analysis.

In the biological investigation, the compound were screened for antibacterial activity against *Bascillus subtilis* (gram positive) and *Klebsiella* (gram negative) bacteria by employing the food poison technique at 250 and 100 ppm.

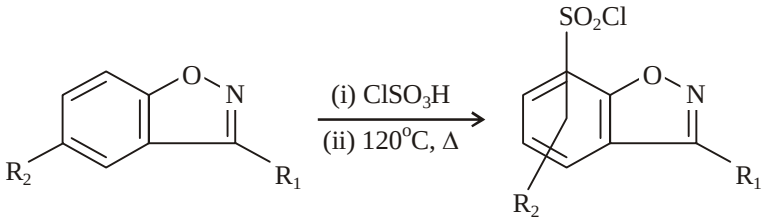
EXPERIMENTAL

General procedure for the preparation of 3-alkyl-5-chloro-sulphonyl-1,2-benzisoxazoles

The chlorosulphonic acid (0.1 mol) was taken into flask and it was cooled. Then the 3-alkyl-benzisoxazole (0.01 mol) was added portionwise to the cooled chlorosulphonic acid. The mixture was then heated on oil bath at 120^0C for 4 hours, cooled and poured on 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 **(A1 – A9)**.

Reaction Scheme



Where, R_1 = Me, Et, Pr.

R_2 = H, Me

Melting points were determined in open capillary tube and are uncorrected. The purity of test compounds were determined by TLC on protected SiO_2 gel (HF_{254} 200 mesh) on aluminium plates (E. Merck). A single spot was obtained on TLC, which confirmed the purity of substituted benzisoxazoles and yield was calculated (w/w).

The melting points, percentage yields and elemental analysis (% of sulphur) of the synthesized compounds are given in Table 1.

Table 1: Physical data and elemental analysis of compounds (A1 -A9)

Comp. No.	R_1	R_2	M.P. (°C)	Yield (%) (w/w)	Sulphur (%)	
					Found	Calculated
A1	Methyl	H	125	55	13.89	13.82
A2	Methyl	5-Methyl	110	52	12.93	13.03
A3	Methyl	7-Methyl	133	64	12.42	13.03
A4	Ethyl	H	108	55	13.11	13.07
A5	Ethyl	5-Methyl	95	60	12.26	12.38
A6	Ethyl	7-Methyl	103	45	11.79	12.33

Cont...

Comp. No.	R_1	R_2	M.P. (^oC)	Yield (%) (w/w)	Sulphur (%)	
					Found	Calculated
A7	Propyl	H	132	49	12.94	12.32
A8	Propyl	5-Methyl	120	54	12.42	11.71
A9	Propyl	7-Methyl	150	61	11.79	11.68

IR spectra

Infra red spectra of these compounds were taken in nujol mull using Perkin-Elmer infracord. The compounds show characteristic absorption of benzisoxazole molecules. The bands at 1530 cm^{-1}, 1220 cm^{-1}, 910 – 820 cm^{-1}, and 1620 cm^{-1} are due to –C = N–, N–O–C, isoxazole ring stretching and –C = C– of phenyl ring of isoxazole, respectively. The absorption bands at 1150 cm^{-1} and 1270 – 1315 cm^{-1} are characteristics of S = O symmetric and symmetric stretching.

^{1}H NMR spectra

The NMR spectra of few representative compounds were studied in TFAA on Varian T-60 spectrophotometer using TMS as an internal standard.

(A4): The compound was assigned the structure 3-ethyl-5-chlorosulphonyl-1,2-benzisoxazole from the following NMR data. Chemical shift in δ scale (ppm) are -

1.4 – 1.8 (t, 3H, CH_2-CH_3)

3.1 – 3.6 (q, 2H, CH_2-CH_3)

7.8 – 8.2 (d, J = 8 Hz, $1H_a$ aromatic)

8.3 – 8.6 (dd, J = 8 and 2 Hz, $1H_b$ aromatic)

8.6 – 8.85 (d, J = 1.5 Hz, $1H_C$ aromatic)

(A2): The NMR spectrum has the following data and chemical shifts in δ scale (ppm) are -

2.6 (S, 3H, 5-CH_3)

2.8 (S, 3H, 3-CH_3)

7.8 – 7.9 (d, J = 2 Hz, $1H_a$ aromatic)

8 – 8.1 (d, J = 1.5 Hz, $1H_b$ aromatic)

Thus, the structure of the compound is 3,5-dimethyl-5-chlorosulphonyl-1,2-benzisoxazole, which is consistent with the NMR data.

(A6): This compound was assigned the structure 3-ethyl-7-methyl-5-chlorosulphonyl -1,2-bensizoxazole, based on the following NMR data. Chemical shifts in δ scale (ppm) are -

1.5 – 1.8 (t, 3H, CH_2-CH_3)

2.8 (S, 3H, CH_3)

3.1 – 3.5 (q, 2H, CH_2-CH_3)

8.1 – 8.2 (d, J = 1.5 Hz, $1H_a$ aromatic)

8.4 – 8.5 (d, J = 1.5 Hz, $1H_b$ aromatic)

Biological evaluation (Antibacterial screening)

The synthesized compounds were screened for antibacterial activity against *Bascillus 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 concentrations. Results are given in Table 2.

Table 2

Comp. No.	R_1	R_2	*Bascillus subtilis*		*Klebsiella pneum.*	
			250 ppm	100 ppm	250 ppm	100 ppm
A1	Methyl	H	++	+	--	--
A2	Methyl	5-Methyl	++	+	--	--
A3	Methyl	7-Methyl	--	--	--	--
A4	Ethyl	H	++	+	--	--

Cont…

Comp. No.	R_1	R_2	*Bascillus subtilis*		*Klebsiella pneum.*	
			250 ppm	100 ppm	250 ppm	100 ppm
A5	Ethyl	5-Methyl	++	--	--	--
A6	Ethyl	7-Methyl	++	+	--	--
A7	Propyl	H	+	--	--	--
A8	Propyl	5-Methyl	--	--	--	--
A9	Propyl	7-Methyl	++	--	--	--

RESULTS AND DISCUSSION

All the synthesized compounds exhibited significant to moderate antibacterial activity. In the present work, substituted benzoxazole and chlorosulphonic acid were used as key raw material.

Compounds **(A1 – A9)** have been characterized on the basis of satisfactory analytical and spectral data.

CONCLUSION

Synthesized 3-alkyl-5-chlorosulphonyl-1,2-benzisoxazole and their derivatives form an important class of heterocyclic compounds with diverse medicinal uses.

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