Pergamon

Tetrahedron Vol. 50, No. 18, pp. 5425-5438, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0199-4

Reaction of Normal and Pseudo 2-Formylbenzenesulfonyl Chlorides with Amines: Experimental and Theoretical Studies on the Structure of 2-Formyl benzenesulfonamides in Solid, Solution and Gas Phases#.

Kallanthottathil G. Rajeev[a], Srikantiah M. Shashidhar *[a], Kuruvilla Pius[b] and Vivekananda M. Bhatt[c]

[a]Division of Organic Chemistry (Synthesis), Bioorganic Chemistry Unit, National Chemical Laboratory, Pune 411 008, India

[b]School of Chemical Sciences, Mahathma Gandhi University, Priyadarshini Hills, Kottayam 686 560, India

and

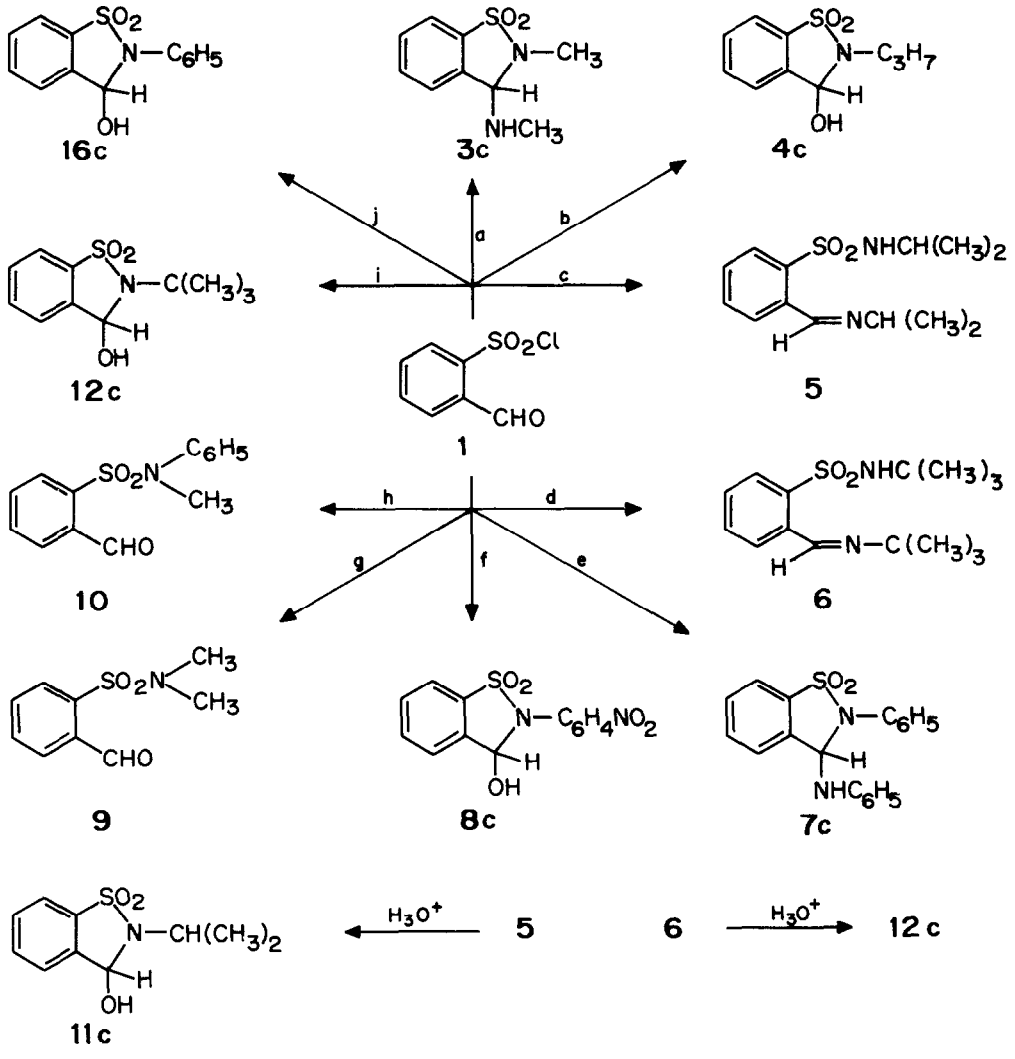
[c]The Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India.

Abstract: *The reaction of 2-formylbenzenesulfonyl chloride 1 and its pseudo isomer 2 with primary amines give either the corresponding sulfonamido Schiff bases or the corresponding 2-formylbenzenesulfonamide depending on the concentration of the amine used. These derivatives exist as an equilibrium mixture of the corresponding sulfonamide and 2-alkyl-3-hydroxy(or 3- aminoalkyl)-benzisothiazole-1,1-dioxide. Spectroscopic studies suggest that 2-formylbenzenesulfonamides exist as benzisothiazole-1,1-dioxides in the solid state, as a mixture of 2-formylbenzenesulfonamide and the corresponding benzisothiazole-1,1-dioxide in solution and as 2-formyl-benzenesulfonamides in the gas phase.*

The influence of one functional group on the reactions of another in the same molecule is well documented in the literature. Such effects have been categorized as electronic, steric, field and proximity effects. There are a large number of reports on the intramolecular catalytic reactions[1,2] and ring-chain tautomerism in small organic molecules.[3] These studies fall into the purview of proximity effects. Most of these studies concern the effect of a carbonyl group on the behavior of a neighboring carboxylic acid or its derivative.[1,4,5] However, there are few systematic studies with sulfonic acids or their derivatives.[6-12] We had earlier reported[13] the catalysis of sulfonate ester hydrolysis by a neighboring carbonyl group. Herein, we report a systematic study on the reactions of 2-formylbenzenesulfonyl chloride **1** and its pseudo isomer **2** with amines and on the structure of the corresponding sulfonamides (**3-12**) in solid, solution and gas phases.

Reactions of the normal sulfonylchloride **1** with amines are summarized in **Scheme 1**. The reaction of **1** with excess of methylamine and aniline yielded the corresponding 3-amino benzisothiazole-1,1-dioxides, **3c** and **7c** respectively. iso-Propylamine and t-butylamine on the other hand gave the corresponding imino sulfonamides **5** and **6** respectively. On reacting **1** with excess of n-propylamine, 3-hydroxy-benzisothiazole-1,1-dioxide, **4c** was

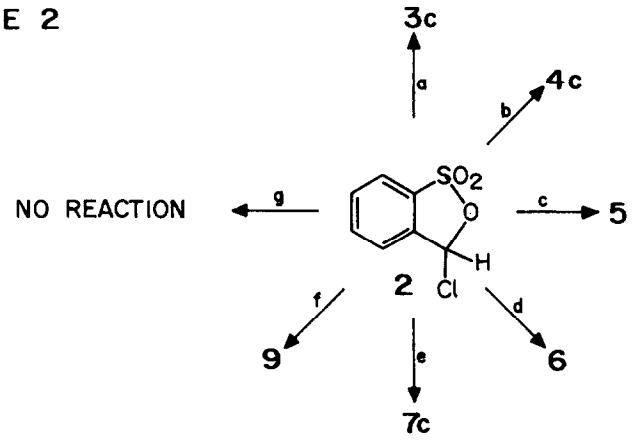
SCHEME 1



a) Ether/aq. CH_3NH_2 b) CH_2Cl_2/ n-$C_3H_7NH_2$ c) CH_2Cl_2/ iso-$C_3H_7NH_2$
d) CH_2Cl_2/ t-$BuNH_2$ e) CH_2Cl_2/ $C_6H_5NH_2$ f) CH_2Cl_2/ p-$NO_2C_6H_4NH_2$/ pyridine g) CH_2Cl_2/ aq. $HN(CH_3)_2$ h) CH_2Cl_2/ $H_3CNHC_6H_5$
i) CH_2Cl_2/ NEt_3/ 1eq. t-$BuNH_2$ j) $CHCl_3$/ NEt_3/ 1eq. $C_6H_5NH_2$

obtained. Similarly the reaction of **1** with p-nitroaniline afforded the benzisothiazole-1,1-dioxide **8c**. As expected the reaction of N,N-dimethylamine and N-methylaniline resulted in the formation of the corresponding benzenesulfonamides **9** and **10**. When **1** was allowed to react with one equivalent of the primary amine (e.g. t-butylamine), in presence of triethylamine, the only isolable product was the corresponding benzisothiazole-1,1-dioxide (**12c**). The nature of the product obtained depends on the amine used as well as its concentration. Benzisothiazole-1,1-dioxides **11c** and **12c** could also be obtained by the mild acid hydrolysis of the corresponding Schiff bases **5** and **6**.

SCHEME 2



a) CH_2Cl_2/CH_3NH_2 b) $CH_2Cl_2/n\text{-}C_3H_7NH_2$ c) $CH_2Cl_2/i\text{-}C_3H_7NH_2$
d) $CH_2Cl_2/t\text{-}BuNH_2$ e) $C_6H_5NH_2$ f) $CH_2Cl_2/(CH_3)_2NH$
g) $C_6H_5NHCH_3$

The reaction of amines with the pseudo sulfonyl chloride **2** (**Scheme 2**) was similar to that of its normal isomer except that the reaction was very sluggish. When **2** was treated with an aqueous solution of methylamine, a very low yield of the benzisothiazole-1,1-dioxide **3c** was obtained. Most of the sulfonyl chloride **2**, presumably underwent base catalyzed hydrolysis to 2-formylbenzenesulfonic acid. However, a good yield of the benzisothiazole-1,1-dioxide **3c** was obtained on using methylamine in non aqueous medium. n-Propylamine, iso-propylamine, aniline and dimethylamine reacted with **2** at ambient temperature to give **4c**, **5**, **7c** and **9** in moderate to good yields. t-Butylamine, on the other hand, reacted only when heated with **2** in a sealed tube to yield **6** as the only isolable product. The reaction of stoichiometric amounts of the amines with **2** was too slow and in most reactions major amount of the pseudo sulfonylchloride was recovered.

2-Formylbenzenesulfonamides: In principle, 2-formylbenzenesulfonamides can exist either in the open form or as the corresponding benzisothiazole-1,1-dioxides (**Scheme 3**). The IR spectrum (nujol and KBr disc) of the N,N-disubstituted sulfonamide **10**, in which case there is no possibility of cyclization, showed a strong peak at 1700 cm^{-1} as expected. The infrared spectra (nujol and KBr disc) of the sulfonamides **4**, **8**, **11** and **12** did not show any absorption around 1700 cm^{-1}. However, when the IR spectra (of **11** and **12**) were recorded in chloroform solution a relatively strong peak around 1695 cm^{-1} was observed, whereas, in the case of the n-propylamino

derivative **4** a very weak peak was observed at 1695 cm^{-1}. These results indicated that the N-substituted 2-formylbenzenesulfonamides under scrutiny might exist in the cyclic form in the solid state and as a mixture of open and cyclic forms in solution, in varying amounts. Thus, these compounds were rigorously examined by NMR spectroscopy.

Table 1. ^{13}C NMR chemical shifts for saturated carbons of 2-formylbenzenesulfonamides in solid and solution[a] states.

Compound #	State	δC_3[b]	δC_2	δC_1	δC(OH)	δCHO
4⇔4c	Solid	11	22	43	84	--
	Soln.	10.8[c],11.2	21.5,22.8[c]	42.9,44.9[c]	81.7	191.0[c]
11⇔11c	Solid	--	21,23	46	80	--
	Soln.	--	20.5,23.1,23.8[c]	45.9,46.4[c]	79.6	191.0[c]
12⇔12c	Solid	--	28	57	80	--
	Soln.	--	29.2,30.0[c]	55.0[c],57.7	80.3	191.0[c]

a: In $CDCl_3$. b: C_1, C_2 and C_3 represent alkyl carbons that are one, two and three bonds away from nitrogen respectively. c: Peaks arising from the open form, assigned on the basis of relative intensities of the signals.

The ^1H NMR spectra (in $CDCl_3$) of 2-formylbenzenesulfonamides showed signals characteristic of 2-formylbenzenesulfonamides as well as the corresponding 3-hydroxy benzisothiazole-1,1-dioxides. The benzylic hydrogen (of the cyclic form) appeared between 5.7 and 6.4 ppm and the aldehydic hydrogen (of the open form) appeared at about 10.3 ppm. In the case of n-propyl, iso-propyl and t-butyl derivatives **4 ⇔ 4c, 11 ⇔ 11c** and **12 ⇔ 12c** two sets of signals were observed for alkyl hydrogens (see experimental for details). The ^{13}C NMR spectra (in $CDCl_3$ solution) of these derivatives also showed carbons characteristic of both the open and cyclic forms. The benzylic carbon of the cyclic form appeared at about 80 ppm and the aldehydic carbon appeared at 191 ppm (the carbonyl carbon of the commercially available sodium 2-formylbenzenesulfonate appears at about 194 ppm in the solid state). The signals due to the alkyl carbons could be assigned to the open and cyclic forms based on the relative intensities of the peaks (see **Table 1**, aromatic carbons are not listed in this table since assignments could not be made based on the relative intensities of the peaks due to the small differences in chemical shifts). However, the ^{13}C NMR spectra (CP/MAS) of the same samples in the solid state showed signals characteristic of only the cyclic form and no peak due to the aldehydic carbon was observed. Also, only one set of signals, arising due to the cyclic form, was observed for the alkyl carbons (two signals were observed for the iso-propyl methyl group, probably due to the nonequivalence of the two methyl groups in the cyclic form). All the observed chemical shifts in the solid state are in close agreement with those in solution. These results clearly show that 2-formylbenzenesulfonamides exist in the cyclic form in the solid state and as a mixture of the open and cyclic forms in solution.

The amount of open and cyclic forms present in solution could be estimated from the integrals of the corresponding peaks in the ^1H NMR spectra of the derivatives under scrutiny. The chemical shift values and the amounts of the open and cyclic forms of 2-formylbenzenesulfonamides as well as the corresponding Schiff bases present in solution are tabulated in **Table 2**.

Table 2. Amount of cyclic and open forms of 2-formylbenzensulphonamides and the corresponding Schiff bases present in solution[a].

Compound#	δ Open	% Open	δ Cyclic	% Cyclic
4 ⇔ 4c	10.38	04	5.71	96
8 ⇔ 8c	10.29	19	6.34	81
11 ⇔ 11c	10.39	30	5.94	70
12 ⇔ 12c	10.45	63	6.02	37
3 ⇔ 3c	--	00	5.22	100.0
7 ⇔ 7c	08.85	05	6.44	95
5 ⇔ 5c	08.47	93	5.48	07
6 ⇔ 6c	08.52	100.0	--	00

a: Determined by ^1H-NMR spectroscopy at ambient temperature in $CDCl_3$. The concentration of the compounds was about 0.08M.

SCHEME 3

3	X = NR	R = CH_3	**3c**
4	= O	= n-C_3H_7	**4c**
5	= NR	= $CH(CH_3)_2$	**5c**
6	= NR	= $C(CH_3)_3$	**6c**
7	= NR	= C_6H_5	**7c**
8	= O	= p-$C_6H_4NO_2$	**8c**
11	= O	= $CH(CH_3)_2$	**11c**
12	= O	= $C(CH_3)_3$	**12c**
13	= NH	= CH_3	**13c**
14	= NH	= C_6H_5	**14c**
15	= O	= CH_3	**15c**
16	= O	= C_6H_5	**16c**

The n-propyl derivative **4** ⇔ **4c** exists mainly as benzisothiazole-1,1-dioxide (thus a very weak carbonyl peak in the IR solution spectrum), whereas, an appreciable amount of the open form is present in the case of the iso-propyl derivative **11** ⇔ **11c**. The t-butylamine derivative **12** ⇔ **12c** exists largely in the open form (thus a strong carbonyl peak in the IR solution spectrum). The amount of the open and cyclic forms present in solution was independent of the concentration of the compound being examined in the range 0.04M to 0.18M.

Next, the t-butylamine derivative **12** ⇔ **12c** was chosen to examine the effect of the solvent on the ring-chain equilibrium, as appreciable amounts of both open and cyclic forms are present in solution, in this case. ^{1}H NMR spectra of **12** ⇔ **12c** were recorded in various solvents and the amount of the open and cyclic forms present in solution was determined by peak integrals. From the results tabulated in **Table 3**, it is clear that the equilibrium **12** ⇔**12c** shifts towards the cyclic isomer **12c** as the polarity of the solvent increases. It is likely that water being a protic solvent favours the cyclization of 2-formylbenzenesulfonamides to the corresponding 3-hydroxy-benzisothiazole-1,1-dioxides, due to the formation of hydrogen bond with the resulting hydroxy group. Similar results were obtained in the case of iso-propylamine and n-propylamine derivatives. For instance, iso-propylamine derivatives **11** ⇔ **11c** existed in the ratio 3:7 in chloroform-d and about 1:99 in acetone-d_6. The n-propyl derivative **4** ⇔ **4c** consisted of about 95% of the cyclic form in chloroform and it was completely cyclic in acetone-d_6.

Table 3. Effect of solvents[a] on the equilibrium **12** ⇔ **12c**.

Solvent	δ 12	% 12	δ 12c	% 12c
Chloroform	10.45	63	6.02	37
Acetone	10.76	43	6.12	57
Acetone-Water 9:1	10.78	26	6.14	74
DMSO	10.74	22	6.05	78
Acetone-Water 7:3	10.78	19	6.14	81
Acetone-Water 1:1	10.57	08	6.08	92

a: Determined by ^{1}H-NMR spectroscopy at ambient temperature. The concentration of **12** was about 0.08M.

The effect of temperature on the sulfonamide ⇔ benzisothiazole-1,1-dioxide equilibrium in solution (DMSO-d_6) was examined by VT-NMR. The iso-propylamine derivative **11** ⇔ **11c** consisted of about 2% **11** at 30°C which increased to about 11% on raising the temperature to 80°C. Similarly, in the case of the t-butylamine derivative **12** ⇔ **12c** the amount of the open form increased with temperature. However, the effect of temperature on the sulfonamide ⇔ benzisothiazole equilibrium is not profound, as an increase of about 50°C only increases the open form by about 10%.

The major peaks observed in EI-MS of benzisothiazole-1,1-dioxides **3c, 4c, 7c, 8c, 11c** and **12c**, Schiff bases **5** and **6** as well as N-phenyl N-methyl 2-formylbenzenesulfonamide (**10**) are shown in **Table 4**. The fragmentation pattern of the n-propyl derivative **4** ⇔ **4c** is shown in **Scheme 4** as an example. Mass spectra of **4c, 8c, 11c** and **12c** show S-N bond cleavage to yield m/z 169 as the base peak. The ion with m/z 169 further undergoes loss of sulfur dioxide and carbon monoxide consecutively giving rise to peaks at m/z 105 and 77. If these derivatives existed as 3-hydroxy benzisothiazole-1,1-dioxides in the gas phase, it would be reasonable to

expect the loss of the tertiary hydroxy group from the molecular ion. However, no such prominent peak at m/z 289, 210 or 224 was observed in the mass spectra of **8c, 11c** or **12c** respectively. The mass spectrum of the n-propyl derivative **4c** does show a very small peak (about 5%) at m/z 210. This perhaps indicates the presence of a small fraction of the cyclic isomer under mass spectral conditions (preferential evaporation of one of the tautomers due to melting of the sample on the heated probe cannot be ruled out). Also, it is important to note that the fragmentation pattern of these 3-hydroxy benzisothiazole-1,1-dioxides closely resemble the fragmentation pattern of **10**, in which there is no possibility of cyclization. On the other hand, the mass spectra of **3c** and **7c** (which are completely cyclic in solution, see below) show base peaks at m/z 182 and 244 respectively, due to the loss of the 3-amino group.

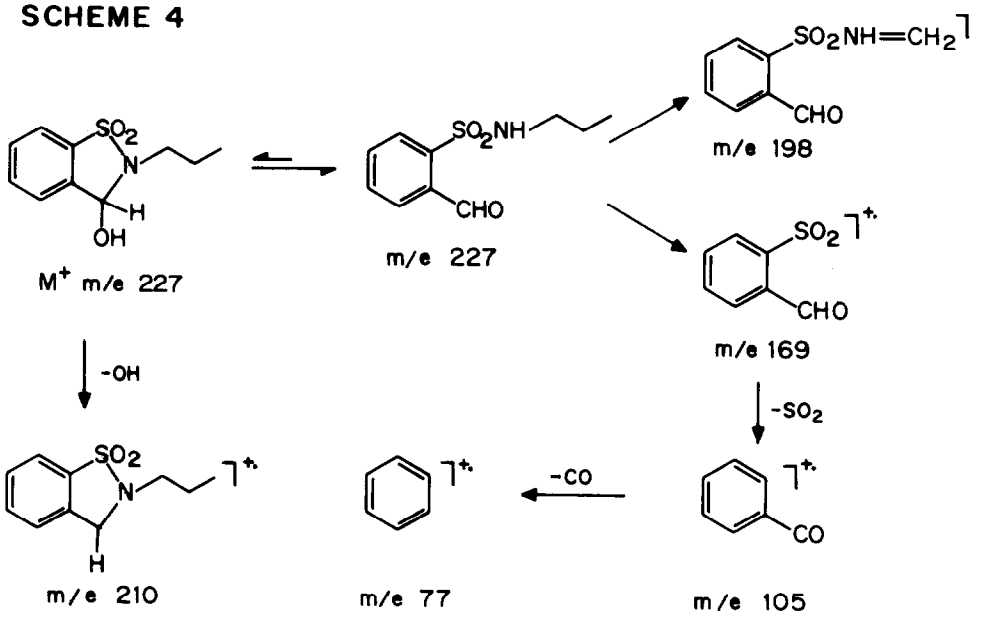
Table 4. EI-MS Fragmentation of benzisothiazole-1,1-dioxides.

Compound#	**m/z (Relative intensity)**
4c	M+ 227(6), 210(5), 198(46), 169(100), 168(71), 105(30), 77(44).
11c	M+ 227(1), 212(43), 169(100), 105(17), 77(8).
12c	M+ 241(<1), 226(63), 169(100), 168(43), 105(60), 77(38).
8c	M+ 306(9), 169(100), 138(46), 105(58), 77(69).
10	M+ 275(4), 169(14), 107(100), 106(56), 105(19), 104(22), 77(12).
3c	M+ 212(<2), 182(100), 118(20), 117(25), 91(15).
7c	M+ 336(<2), 244(100), 180(35), 179(20), 178(15), 153(15), 152(50), 151(15).
5	253(40), 210(20), 168(100), 146(5). 145(55), 104(35), 103(85), 77(55).
6	281(12), 224(2), 168(100), 159(40), 104(15), 57(15).

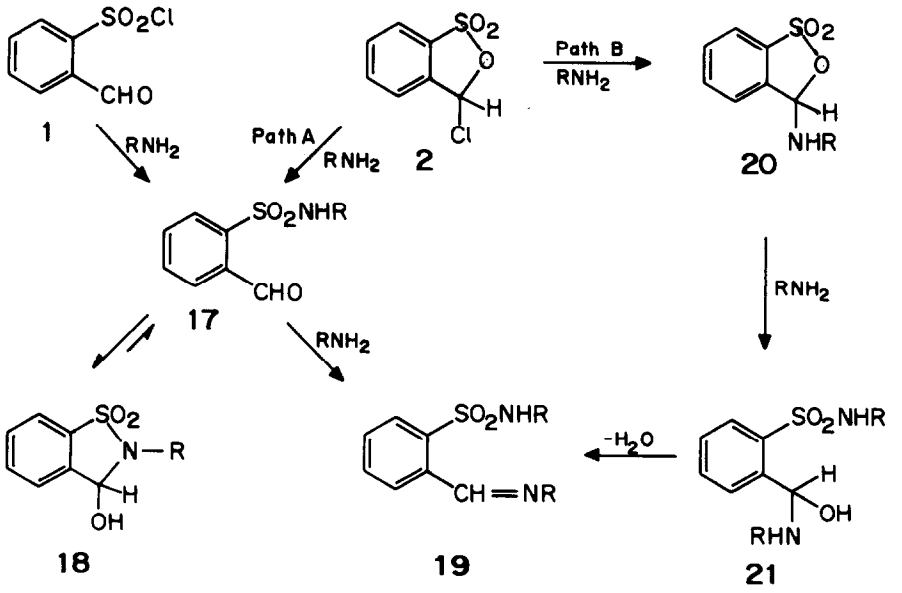
Thus, these results indicate that sulfonamides **4c, 8c, 11c** and **12c** exist more or less completely in the open form in the gas phase. This is in contrast to the corresponding carboxylic acid derivatives viz., 2-formylbenzoic acid amides, which are completely cyclic (ie., exist as 3-hydroxy-iso-indolenones) in solid, solution and gas phases.[14,15] It is not surprising to see that benzisothiazole-1,1-dioxide ⇔ 2-formylbenzenesulfonamide equilibrium is shifted completely towards the open form in the gas phase, as the polarity (dielectric constant) of the medium is very low. Furthermore, benzisothiazole-1,1-dioxides lack additional stabilization due to intermolecular hydrogen bonding or hydrogen bonding with the solvent molecules (see **Tables 2** and **3**) when present in the gas phase.

A theoretical approach to the study of equilibria involving tautomeric systems of the type discussed in the present work would serve to complement as well as supplement the experimental methods. The semi-empirical SCF-MO method[16] **AM1** has been used in the present investigation to obtain the standard heats of formation of model systems. It is reasonable to assume that **15** (see **Scheme 3**) would serve as a model for the systems **4, 11** and **12**. The model system employed for the cyclic counterparts of these three species is **15c**. Calculations have also been carried out on the species **16** and **16c** in order to model the phenyl derivatives. Similarly to obtain the relative stabilities of Schiff bases like **3** and their cyclic analogs **3c**, the heats of formation of model systems **13** ⇔ **13c** and **14** ⇔ **14c** have been computed. The **AM1** heats of formation values of all these species (in kcal/mol) are as follows: **13** (127.8), **13c** (123.9), **14** (163.5), **14c** (160.2), **15** (76.9), **15c** (77.5), **16** (110.4) and **16c** (113.8).

SCHEME 4



SCHEME 5



Computational studies with **AM1** method reveal that **15** is more stable than the heterocyclic system **15c** by 0.6 kcal/mol. Similarly the phenyl derivative **16c** is computed to be less stable than its acyclic counterpart **16** by 3.4 kcal/mol. In the case of Schiff bases the acyclic form **13** is less stable than its cyclic tautomer **13c** by 3.9 kcal/mol. The phenyl derivatives too follow the same trend; the cyclic tautomer **14c** is computed to be more stable than **14** by 3.3 kcal/mol. Thus, the present investigation leads to the suggestion that an acyclic sulfonamide structure is intrinsically preferable to its isomeric 3-hydroxy isothiazole structure. These results are in close agreement with the experimental studies in the gas phase. The reversal of the order of stability on going from the gas phase to the condensed phases is probably due to intermolecular interactions and medium effects. The present calculations do not include intermolecular or solvent interactions and hence the results are not valid in solution.

Thus, from the results discussed above, it is clear that 2-formylbenzenesulfonamides exist (a) in the cyclic form in solid state, (b) as a mixture of open and cyclic forms in solution and (c) more or less completely in the open form in the gas phase and (d) under a given set of conditions (phase, solvent, temperature etc.) the open form is favoured as the steric bulk on the nitrogen increases.

It is pertinent to comment on the mechanism of formation of 3-hydroxy benzisothiazole-1,1-dioxides from the normal and pseudo sulfonylchlorides **1** and **2**. The mechanism of formation of benzisothiazole-1,1-dioxides **18** and Schiff bases **19** from the normal sulfonyl chloride **1** is straight forward (**Scheme 5**). It involves the reaction of **1** with two molecules of the amine successively. The initial formation of **17** is obvious since an amine is expected to react with the sulfonyl chloride much faster than with an aldehyde. This is evident from experiments in which **1** was allowed to react with one equivalent of n-propylamine and t-butylamine in the presence of triethylamine. The only isolable product was the isothiazole-1,1-dioxide **18**. 2-Formylbenzenesulfonamide present in equilibrium with **18** further reacts with excess of the amine (when present) to yield the corresponding Schiff base **19**.

For the reaction of the pseudo sulfonyl chloride **2** (**Scheme 5**) with amines there are two sites for initial attack *viz.*, the sulfonyl sulfur (path A) and the benzylic carbon (path B). It is interesting to note that all the primary amines except n-propylamine, when used in excess, react with **2** to give **19** as the only isolable product. The reaction of **2** with n-propylamine leads to the formation of **18** exclusively. This is possible only if the initial attack is on sulfonyl sulphur (path A) to produce **17** which then undergoes cyclization to **18**. The possibility of hydrolysis of the Schiff base **19** (derived from n-propylamine) to **17** during work-up can be ruled out since the reaction mixture showed the presence of only **18** (by TLC), even before the work-up. Also the reaction of dimethylamine with **2** affords a respectable yield of the sulfonamide **9**, which is possible only when the initial attack by the amine is on the sulfonyl sulfur. Thus, it can be concluded that the reaction of **2** with amines proceeds through path A.

Schiff bases: The reaction of normal **1** or pseudo **2** sulfonylchloride with primary amines, except n-propylamine, resulted in the formation of the corresponding Schiff bases. As mentioned earlier, the Schiff bases **5** and **6** could be easily hydrolyzed to the corresponding sulfonamides **11** and **12** by the treatment with aqueous acetic acid. However, the Schiff bases **3c** and **7c** did not undergo hydrolysis under similar conditions, and they were recovered unaffected. These experiments suggested the possibility of a cyclic structure for the methyl and phenyl derivatives **3** and **7**.

^{1}H and ^{13}C NMR spectra of the Schiff bases (see **Table 2** and experimental part for details) showed that the methylamino derivative **3** ⇔ **3c** exists completely in the cyclic form and the t-butylamino derivative **6** ⇔ **6c**

completely in the open form, in solution. However, the iso-propyl derivative showed signals characteristic of both the open and cyclic forms. These results show that, in solution, the sulfonamide (open form) is favoured as the steric bulk of the substituent on the nitrogen increases. Similar results have been reported in the case of the Schiff bases obtained from 2-benzoylbenzenesulfonic acid derivatives.[6-9] It is evident from the mass spectra of the Schiff bases (see **Table 3**) that **3c** and **7c** are completely cyclic in the gas phase. The IR and mass spectra the iso-propyl and t-butyl derivatives **5** and **6** are more complex and definitive conclusions regarding their structure in the solid phase and the gas phase could not be arrived at. Thus, further experimental studies (such as solid state ^{13}C NMR spectroscopy and X-ray crystallography) and theoretical studies are necessary to establish the structure of **5** and **6** in the solid phase and the gas phase.

In conclusion, 2-formylbenzenesulfonyl chloride **1** and its pseudo isomer **2** react with amines to yield the corresponding sulfonamides which cyclize to the corresponding benzisothiazole-1,1-dioxides. The ratio of the sulfonamide to that of benzisothiazole-1,1-dioxide present depends on the steric bulk of the substituent on the nitrogen and also on the polarity of the medium. This route might provide a method for the synthesis of various 3-substituted benzisothiazole-1,1-dioxides which are known to possess antibacterial and antihirbicidal activities.[17] As to how the equilibrium between the open and cyclic forms might affect their biological activity remains to be seen.

Acknowledgment: *The authors would like to thank Drs. S. Rajappa and K.N. Ganesh for their encouragement. KGR thanks CSIR, New Delhi and MSS thanks the Director, NCL, Pune, for fellowships. Assistance of Dr. R. Krishna Kumar in VT-NMR studies is gratefully acknowledged. We thank Dr. Ganapathy and his colleagues for recording solid state ^{13}C NMR spectra. We would like to thank the referee for some helpful suggestions.*

Experimental:-

All the melting points are uncorrected and were recorded using an electrothermal melting point apparatus. All the solvents and amines used were purified according to the literature procedures.[18] TLC was performed on Merck pre-coated 60 F_{254} plates and the spots were rendered visible by UV light. Loba silica gel (100-200 mesh) was used for column chromatography. Preparative TLC was performed using Merck Kieselgel 60 F_{254} plates. Infrared spectra were recorded on a Perkin Elmer 599B or model 1620 instruments. NMR spectra in solution, were recorded on a Brucker ACF 200 spectrometer and all the chemical shifts are referred to internal TMS. Solid state ^{13}C NMR spectra (CP/MAS) were recorded on a Brucker MSL 300 spectrometer, operating at 75.476 MHz. Recording conditions were: spectral width, 400 ppm; pulse angle, 90°; width, 5.3 μs; repetition time, 4 sec; CP-contact time, 1 msec; spinning frequency, 2-3.5 kHz. Electron impact mass spectra were recorded on an automated Finnigan MAT 1020 mass spectrometer. The source conditions were as follows: temperature range, 150-200°C; ionizing energy, 70 ev; pressure, 10^{-6}mm Hg (1mm Hg = 133.3Pa). The samples were introduced into the source by direct insertion probe. Normal and pseudo 2-formylbenzenesulfonyl chlorides were prepared as reported earlier.[19,20] Usual "work-up" implies washing of the organic extract with water followed by brine, drying over anhydrous sodium sulfate and evaporation of the solvent in vacuum.

Reaction of normal 2-formylbenzenesulfonyl chloride (1) with excess of amines:

Methylamine: The sulfonyl chloride **1** (0.205g, 1mmol) was dissolved in ether (10ml) and 40% aqueous solution of methylamine (1ml) was added and stirred at ambient temperature for 6h and then worked-up as usual. The product was recrystallized from benzene-petroleum ether (40-60°C) to obtain 2,3-dihydro-2-methyl-3-methylamino-benzisothiazole-1,1-dioxide (**3c**) as a colorless solid (0.019g, 9%), m.p. 89-90°C. IR (Nujol): 3300-3400cm^{-1}. IR (KBr disc): 3390cm^{-1}. ^{1}H-NMR, δ($CDCl_3$): 2.20(s, 3H), 2.94(s, 3H), 4.81-4.84(d, 1H, exchangeable with D_2O) 5.22(s, 1H), 7.62-7.86(m, 4H). ^{13}C-NMR δ($CDCl_3$): 26.5, 27.7, 76.8, 121.2, 125.3, 130.3, 133.2, 136.4. HRMS. Calcd. for $C_8H_8NO_2S$ (M^+-CH_3NH) = 182.0276; Found, M^+-CH_3NH = 182.0275

n-Propylamine: The sulfonyl chloride **1**, (0.103g, 0.5mmol) was dissolved in dry dichloromethane (2ml), n-propylamine (1ml) was added and stirred at ambient temperature for 3 hours. Solvent and excess of the amine were removed in vacuum. The residue was taken in dichloromethane (6ml) and worked-up as usual. 2,3-Dihydro-2-n-propyl-3-hydroxy benzisothiazole-1,1-dioxide (**4c**) was purified by column chromatography; eluent: 10% ethylacetate-petroleum ether (0.080g, 72%), m.p. 99-100°C. IR (Nujol): 3550-3300 cm^{-1}. IR (KBr disc): 3550-3350cm^{-1}. IR ($CHCl_3$): 3440, 1699(w) cm^{-1}. ^{1}H-NMR, δ($CDCl_3$): 0.83-0.90(t, 3H, CH_3 of **4**), 0.99-1.05(t, 3H, CH_3 of **4c**), 1.45-1.55(m, 2H, CH_2 of **4**), 1.73-1.91(m, 2H, CH_2 of **4c**), 2.91-3.01(q, 2H, NCH_2 of **4**), 3.20-3.49(m, 3H, NCH_2 of **4c** and -OH), 5.68-5.73(s, 1H, C(H)OH of **4c**), 7.58-8.12 (m, 4H, open and cyclic), 10.38(s, 1H, CHO of **4**). ^{13}C-NMR, δ($CDCl_3$): 10.8, 11.2, 21.5, 22.8, 42.9, 44.9, 81.7, 120.7, 121.0, 125.1, 129.7, 130.6, 132.3, 132,5, 133.1, 133.4, 134.9, 136.6, 191.0. ^{13}C NMR, δ(solid): 11, 22, 43, 84, 120, 131, 134, 138. MS: M^+ = 227. Analysis: Calcd. For $C_{10}H_{13}NO_3S$ C 52.86%, H 5.73%, N 6.18%: Found: C 52.36%, H 5.75%, N 6.19%.

iso-Propylamine: The sulfonyl chloride **1** (0.30g, 1.47mmol) and iso-propylamine (1ml) were used and the reaction was carried out as above to obtain N-iso-propyl 2-[(isopropylimino)methyl]benzensulfonamide (**5**) as a viscous liquid, (0.36g, 53%). IR (Neat): 3200-3400, 1630 cm^{-1}. ^{1}H-NMR, δ($CDCl_3$): 1.01(d, 6H), 1.25(d, 6H), 3.27-3.40(m, 1H), 3.47-3.59(m, 1H), 7.23(s, 1H, -NH- proton, exchangeable with D_2O) 7.41-7.56(m, 3H), 8.02-8.05(m, 1H), 8.47(s, 1H). ^{13}C-NMR, δ($CDCl_3$): 23.8, 24.0, 46.6, 62.1, 129.9, 130.0, 132.3, 132.6, 133.7, 139.9, 157.8.

t-Butylamine: The sulfonyl chloride **1** (0.25g, 1.2mmol) was reacted with t-butylamine (1ml) as above. The product was crystalized from benzene-petroleum ether mixture to obtain N-t-butyl 2-[(t-butylimino)-methyl]benzenesulfonamide (**6**) (0.27g, 75%), m.p. 131-132°C. IR (Nujol): 2500-3250, 1620 cm^{-1}. ^{1}H-NMR, δ($CDCl_3$): 1.23(s, 9H), 1.35(s, 9H), 7.52-7.65(m, 4H, ArH and -NH-), 8.15(d, 1H), 8.53(s, 1H). ^{13}C-NMR, δ($CDCl_3$): 29.6, 30.5, 54.9, 58.9, 129.3, 130.0, 131.9, 132.5, 134.1, 142.2, 155.6. MS: M^+ = 296. Analysis: Calcd. For $C_{15}H_{24}N_2O_2S$ C 60.81%, H 8.11%, N 9.46%; Found: C 61.51%, H 8.18%, N, 9.11%.

Aniline: The reaction was carried out as above, using normal sulfonyl chloride **1** (0.55g, 2.68mmol) and aniline (1.2ml). The reaction mixture was worked up as usual (except that dilute HCl wash was included to remove aniline). The product, 2,3-dihydro-2-phenyl-3-phenylamino benzisothiazole-1,1-dioxide (**7c**) was crystallized from benzene-petroleum ether, (0.54g, 60%), m.p. 135°C. IR (Nujol): 3380, 1600 cm^{-1}. IR (KBr disc): 3380, 1610 cm^{-1}. ^{1}H-NMR, δ($CDCl_3$ + D_2O): 6.44(s, 1H, C(H)NHC_6H_5 of **7c**), 6.53-6.54(q, 2H), 6.57-6.77(m, 1H), 7.09-7.30(m, 2H), 7.35-7.50(m, 5H), 7.67-7.94(m, 3H), 7.94-7.96(m, 1H), 8.85(s, 1H, C(H)=NC_6H_5 of **7**) . ^{13}C-NMR δ($CDCl_3$): 72.5, 115.3, 120.0, 121.3, 121.6, 122.8, 125.1, 125.8, 128.3, 128.5, 129.4, 129.7, 130.8, 132.8, 133.5, 134.0, 135.6, 136.4, 144.1. MS: M^+ = 336. Analysis calcd. For $C_{19}H_{16}N_2O_2S$: C 67.86,%, H 4.76%,

N 8.33%; Found C 67.22%, H 4.51%, N 7.72%.

p-Nitroaniline: The sulfonyl chloride **1** (0.31g, 1.5mmol) was dissolved in dry dichloromethane (3ml) and a solution of p-nitroaniline (0.09g, 0.65mmol) and pyridine (two drops) in dichloromethane (5ml) was added and the mixture was stirred at ambient temperature for 12h. The reaction mixture was evaporated to dryness in vacuum. Residue was chromatographed over a column of silica gel; eluent: dichloromethane. The solid obtained was further purified by preparative TLC (dichloromethane, three elutions). The fraction with R_f value 0.4 was collected. 2,3-Dihydro-2-p-nitrophenyl-3-hydroxy benzisothiazole-1,1-dioxide (**8c**) was obtained as a yellow solid (0.075g, 38%), m.p. 182°C (dec). IR (Nujol): 3200-3500, 1590 cm^{-1}. IR (KBr disc): 3450, 1610 cm^{-1}. ^{1}H-NMR, δ(DMSO-d_6 + D_2O): 6.78(s, 1H), 7.67-7.87(m, 5H), 8.00-8.04(d, 1H), 8.33-8.37(d, 2H). ^{13}C-NMR, δ(DMSO-d_6): 80.6, 119.1, 121.1, 125.7, 126.4, 131.9, 133.5, 135.0, 135.8, 142.3, 143.2. MS: M^+ = 306.

Dimethylamine: The reaction was carried out as in the case of methylamine, using **1** (0.204g, 1mmol) and 40% aqueous dimethylamine (1mL). N,N-dimethyl 2-formylbenzenesulfonamide (**9**) was obtained as a viscous liquid. It was purified by filtering through a short column of silica gel, eluent: chloroform, (0.165g, 77%). IR (Neat): 1690, 1580cm^{-1}. ^{1}H-NMR, δ($CDCl_3$): 2.81(s, 6H), 7.74-7.82(m, 2H), 7.95-7.99(m, 1H), 8.09-8.14(m, 1H), 10.86(s, 1H). ^{13}C-NMR, δ($CDCl_3$): 37.3, 129.4, 129.9, 133.2, 133.3, 135.4, 138.7, 190.7.

N-Methylaniline: The sulfonyl chloride **1** (1.3g, 6.36mmol) was reacted with N-methylaniline (2ml) as in the case of aniline. N-Methyl N-phenyl 2-formylbenzenesulfonamide (**10**) (1.3g, 74%) was obtained as colorless needles m.p. 67-68°C. IR (Nujol): 1700, 1600 cm^{-1}. IR (KBr disc) 1700, 1600 cm^{-1}. ^{1}H-NMR δ($CDCl_3$): 3.24(s, 3H), 7.07-7.15(m, 2H), 7.18-7.37(m, 3H), 7.73-7.81(m, 2H), 7.97-8.07(m, 2H), 9.86(s, 1H). ^{13}C-NMR ($CDCl_3$): 38.5, 127.4, 128.5, 129.2, 129.5, 130.5, 133.3, 135.0, 137.3, 140.3, 189.8. HRMS: Calcd. for $C_{14}H_{13}NO_3S$, M^+ = 275.0616; Found, M^+ = 275.0641. Analysis: Calcd. For $C_{14}H_{13}NO_3S$: C 61.09%, H 4.73%, N 5.09%; Found C 61.72%, H 4.85%, N 5.11%.

Reaction of 1 with stoichiometric amount of amines:

t-Butylamine: The sulfonyl chloride **1** (0.24g, 1.17mmol) was dissolved in dry dichloromethane (12ml). A solution of t-butylamine (0.085g, 1.16mmol) and triethylamine (0.17g, 1.75mmol) in dichloromethane (12ml) was added drop-wise. The progress of the reaction was followed by TLC (eluent, dichloromethane). After the addition of 9ml of the amine solution TLC showed the formation of the Schiff base **6**. The addition of the amine was stopped and the reaction mixture was worked up as usual. The product was crystallized from benzene-petroleum ether mixture to obtain 2,3-dihydro-2-t-butyl-3-hydroxybenzisothiazole-1,1-dioxide (**12c**) as a colorless solid (0.2g, 95%), m.p. 120-121°C. IR (Nujol): 3370-3500 cm^{-1}. IR (KBr disc): 3510-3360 cm^{-1}. IR ($CHCl_3$): 3440, 3285, 1695cm^{-1}. ^{1}H-NMR, δ($CDCl_3$): 1.23(s, 9H, CH_3 of **12**), 1.66(s, 9, CH_3 of **12c**), 2.96-3.04(d, 1H, -OH of **12c**, exchangeable with D_2O), 5.67(s, 1H, -NH- of **12**, exchangeable with D_2O) 6.02(d, 1H, C(H)OH of **12c**, collapses to singlet on D_2O exchange), 7.62-7.80(m, 2H), 8.01-8.08(m, 1H), 8.21-8.26(m, 1H), 10.45 (s, 1H, CHO of **12**). ^{13}C-NMR, δ($CDCl_3$): 29.2, 30.0, 55.0, 57.7, 80.3, 120.2, 124.9, 129.2, 130.5, 132.2, 132.4, 133.0, 133.5, 135.7, 136.1, 143.6, 191.0. ^{13}C NMR, δ(solid): 28, 57, 80, 121, 126, 131, 134, 136. HRMS: Calcd. for $C_{10}H_{12}NO_3S$ (M^+-CH_3) = 226.0538; Found, M^+-CH_3 = 226.0523.

Aniline: Aniline was reacted with the normal sulfonyl chloride **1** as above, to obtain 2,3-dihydro-2-phenyl-3-hydroxy benzisothiazole-1,1-dioxide (**16c**) (81%) as colorless powder m.p. 147-148°C. However, this reaction was not very reproducible and often resulted in the formation of the corresponding Schiff base **7c** exclusively. The yield reported here represents the best yield obtained among several trials. IR (Nujol):

3450, 1500 cm^{-1}. ^{1}H-NMR, δ($CDCl_3$): 3.17-3.25(s, 1H, -OH of **13c**, exchangeable with D_2O) 6.34(s, 1H, C(H)OH of **13c**), 7.10-8.09(m, 9H, aromatic H of **13** and **13c**), 10.29(s, 1H, CHO of **13**). MS: M^+ = 261. Analysis calcd. For $C_{13}H_{11}NO_3S$: C 59.77%, H 4.21%, N 5.36%; Found C 59.37%, H 4.21%, N 5.27%. HRMS: Calcd. for $C_{13}H_{11}NO_3S$ M^+ = 261.0459; Found, M^+ = 261.0450.

Hydrolysis of Schiff bases:

Hydrolysis of the Schiff base 5: The Schiff base **5** (0.18g, 0.67mmol) was dissolved in dichloromethane (2ml), a mixture of water and acetic acid (2:1, 1ml) was added and the mixture was stirred at ambient temperature for 4h. The reaction mixture was diluted with dichloromethane (12ml), washed with sodium bicarbonate solution and worked up as usual. The solid obtained was crystallized from benzene-petroleum ether (40-60°C) mixture to obtain 2,3-dihydro-2-isopropyl-3-hydroxy benzisothiazole-1,1-dioxide (**11c**) as colorless crystals, (0.15g, 98%), m.p. 85-86°C. IR (Nujol): 3400-3500 cm^{-1}. IR (KBr disc): 3510-3480 cm^{-1}. IR ($CHCl_3$): 3440, 3320, 1695 cm^{-1}. ^{1}H-NMR, δ($CDCl_3$): 1.09-1.12(d, 6H, CH_3 of 11), 1.50-1.53(d, 6H, CH_3 of **11c**), 2.94-3.00(d, 1H, exchangeable with D_2O), 3.50-3.6(m, 1H, CH of **11**), 4.09-4.23(m, 1H, CH of **11c**), 5.56(d, 1H, -NH- of **11**, exchangeable with D_2O), 5.94(d, 1H, C(H)OH of **11c**, collapses to singlet on D_2O exchange), 7.62-8.18(m, 4H, aromatic H of **11** and **11c**), 10.39(s, 1H, CHO of **11**). ^{13}C-NMR, δ($CDCl_3$): 20.5, 23.1, 23.8, 45.9, 46.4, 79.6, 120.9, 125.4, 129.2, 130.9, 132.8, 133.5, 133.8, 135.5, 136.9, 191.0. ^{13}C NMR, δ(solid): 20, 24, 43, 78, 120, 125, 131, 132, 135, 138. HRMS: Calcd. for $C_9H_{10}NO_3S$ (M^+-CH_3) = 212.0381; found, M^+-CH_3 = 212.0358.

Hydrolysis of the Schiff base 6: The Schiff base **6** (0.13g, 0.44mmol) was hydrolyzed as above, to obtain **12c** as white crystals (0.10g, 94%), m.p. 120-121°C

Reaction of 3-chloro benzisoxathiole-1,1-dioxide 2 with amines:

Methylamine: The pseudo sulfonyl chloride **2** (0.41g, 2mmol) was dissolved in dry dichloromethane (5ml). Methylamine gas generated from a 40% aqueous solution was dried over solid potassium hydroxide and bubbled through the sulfonyl chloride solution. The reaction was complete in about one hour (as shown by TLC). The reaction mixture was diluted with dichloromethane (10ml) and worked-up as usual. The residue was crystallized from benzene-petroleum ether (40-60°C), to obtain **3c** as colorless crystals (0.37g, 87.0%), m.p. 89-90°C.

n-Propylamine: The pseudo sulfonyl chloride (**2**) (0.205g, 1mmol) was dissolved in chloroform (5ml) and stirred at ambient temperature, after the addition of n-propylamine (0.6ml) for 20h. The reaction mixture was diluted with chloroform (15ml) and worked-up as usual: The residue was crystallized from benzene- n-pentane mixture to obtain **4c** as colorless crystals (0.136g, 60%), m.p. 100°C.

iso-Propylamine: The pseudo sulfonyl chloride **2** (0.308g, 1.5mmol) and iso-propylamine (3ml) were mixed and stirred at ambient temperature for 4h. The reaction mixture was diluted with dichloromethane (10ml) and worked-up as usual to obtain **5** as an oil (0.29g, 74%).

t-Butylamine: The pseudo sulfonyl chloride **2** (0.205g, 1mmol) and t-butylamine (0.5ml) were heated in a sealed tube at 60°C for 12hrs. It was then cooled to 0°C and opened carefully. The solid obtained was suspended in water, extracted with ether and worked up as usual to obtain **6** as a white solid, (0.038g, 13%), m.p. 131-132°C.

Aniline: The pseudo sulfonyl chloride **2** (0.205g, 1mmol) and aniline (0.7ml) were used and the reaction was carried out as in the case of n-propylamine. Products were separated by column chromatography. Fraction 1: eluent, 50% benzene-petroleum ether, pseudo sulfonyl chloride was recovered (0.06g, 29%). Fraction 2: eluent,

benzene, **7c** was obtained as a colorless solid (0.2g, 59%), m.p. 135°C.

Dimethylamine: The reaction was carried out as above. The sulfonamide **9** was obtained as a viscous liquid, (65%)

References:-

*NCL Communication No. *5840*

1. Bowden, K. *Adv. Phy. Org. Chem.* **1993**, *28*, 171-206.
2. Menger, F.M.; Venkataram, U. V. *J. Am. Chem. Soc.* **1985**, *107*, 4706-4709.
3. Valters, E. R.; Flitsch, W. **1985**, *Ring-Chain Tautomerism*, Plenum Press, NY.
4. Bhatt, M. V.; El Ashry S. H.; Somayaji, V. *Ind. J. Chem.* **1980**, *19B*, 473-486
5. Bhatt, M. V.; Ravindranathan, M. *J. Chem. Soc.* **1973**, 1160-1166.
6. Watanabe, H.; Mao, C-L.; Barnish, I. T,; Hauser, C. R. *J. Org. Chem.* **1969**, *34*, 919-926.
7. Balode, D.; Valters, R.; Valtere, S. *Khim. Geterotsikl Soedin.* **1978**, 1632- 1635 CA *90*, 120792q.
8. Balode, D.; Valters, R. *Latv. PSR. Zinat. Akad. Vestis. Khim. Ser.* **1980**, 227-230, CA *93* 168175e.
9. Valters, R.; Balode, D.; Kampare, R.; Valtere, S. *Khim. Geterotsikl Soedin.* **1981**, 1209-1213 CA *95*, 203048f.
10. Thea, S.; Guanti, G.; Hopkins, A. R.; Williams, A. *J. Org. Chem.* **1985**, *50*, 3336-3341.
11. Wagenaar, A.; Engberts, B. F. N. *J. Org. Chem.* **1988**, *53*, 768-772.
12. Fulop, F.; Mattinen, J.; Pihlaja, K. *Tetrahedron*, **1990**, *46*, 6545-6552.
13. Bhatt, M. V.; Shashidhar, M. S. *Tetrahedron Lett.* **1986**, *27*, 2165-2166.
14. Hendi, M. S.; Natalie Jr., K. J.; Hendi, S. B.; Campbell, J. A.; Greenwood, T. D.; Wolfe, J. F. *Tetrahedron Lett.* **1989**, *30*, 275-278.
15. Luzzio, F. A.; O'Hara, L. C. *Synth. Commun.* **1990**, *20*, 3223-3234.
16. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902-3909.
17. Bronsdijk, J.M.; Praetorius, H.A. *EP 162,494* CA *104* P148864w, **1986**.
18. Perrin, D.D.; Armarego, W. L. F. **1988**, *Purification of Laboratory Chemicals*. Second edition, Pergamon Press.
19. Shashidhar, M.S., Bhatt, M. V. *Proc. Ind. Acad. Sci. (Chem. Sci.)*, **1989**, *101*, 319-326.
20. King, J. F.; Hawson, A.; Huston, B. L.; Danks, L. J.; Komery, J. *Can. J. Chem.* **1971**, *49*, 943-955.

(*Received in UK* 19 *August* 1993; *revised* 28 *February* 1994; *accepted* 4 *March* 1994)