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N-SULPHONYLFORMAMIDRAZONES; PREPARATION AND STRUCTURE

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Abstract—Potentially tautomeric N-sulphonylformamidrazones and models with fixed amide-hydrazone and hydrazide-imide structure have been prepared. The compounds with tautomeric possibilities have been shown to exist only in the amide-hydrazone form by ^{13}C and ^{1}H NMR spectroscopy. The same compounds exist as two rotamers in solution arising from hindered rotation around the N=CH–N single bond.

N-Sulphonylformamidrazones have been prepared and their structure investigated by ^{13}C and ^{1}H NMR spectroscopy as an extension of our investigations on the structure of sulphonylformamidine[1] and sulphonylformamidrazone[2,3] systems. For the new N-sulphonylformamidrazones it was especially interesting to compare the actual tautomeric and isomeric species present in solution with those found for similar N″-sulphonylformamidrazones[2] and N,N″-substituted formamidrazones.[4] This could give information on the influence of the sulphonyl group on the position of the C=N double bond and on the actual rotamers, in compounds with the possibility of existence in tautomeric species. Furthermore interest has been displayed on N″-sulphonylformamidrazones as potential antitumor agents[5] why their N-isomers might be of interest in similar investigations.

Few N-sulphonylformamidrazones have appeared in the literature[6] and their structure has been quoted as arylsulphonylhydrazide-imides **B**, which is in contrast to findings for N,N,N″-trisubstituted formamidrazones[4] where the tautomeric species found was the amide-hydrazone **A**. N″-sulphonyl substituted formamidrazones, however, have been shown to exist in the hydrazide imide form **B**.[2]

$R^1SO_2NR^2N{=}CH{-}NHR^4$ $\qquad$ $R^1SO_2NR^2NH{-}CH{=}NR^4$

A $\qquad$ **B**

RESULTS

The synthesis of N-sulphonylformamidrazones **1** proceeds easily by reacting equimolar amounts of sulphonohydrazide and imidate (Method A), or from equimolar amounts of amine and sulphonylhydrazidate (Method B). Yields range from 30 to 77%; data are given in Table 1 (satisfactory microanalytical data were obtained for new compounds).

$$R^1SO_2NR^2NH_2 + R^4NCHOEt \rightarrow R^1SO_2NR^2NCHNHR^4$$

1f–j, l–n

(Method A)

$$R^1SO_2NR^2NCHOEt + R^3R^4NH \rightarrow R^1SO_2NR^2NCHNR^3R^4$$

1a–e, k, o

(Method B)

The preparation of compounds **2** with fixed hydrazide imide structure was carried out by sulphonylation of N,N′,N″-trisubstituted formamidrazone by means of methanesulphonyl chloride or *p*-toluenesulphonyl chloride, with excess triethylamine.

$$PhNCHNMeNHMe + RSO_2Cl \rightarrow RSO_2NMeNMeCHNPh$$

2a–b

a R = Me; **b**, R = *p*-MeC_6H_4

Compounds **2** were found unstable, decomposing after a few days at room temperature, in contrast to compounds **1** which were stable for long time. The decomposition of **2** proceeds with the scission of the C=N double bond as seen from the distillation of decomposed **2a** which gave N²-sulphonylated formohydrazide in addition to unidentified residue.

$$MeSO_2NMeNMeCHNPh \rightarrow MeSO_2NMeNMeCHO$$

To clarify which of the tautomers **A** or **B** was present in solution the ^{1}H and ^{13}C NMR spectra of compounds **1a–d, o** with fixed amide hydrazone structure **A**, and compounds **2a–b** with fixed hydrazide imide structure **B**, were compared to those from compounds **1e–n**, having the possibility of tautomerism. (Tables 2 and 3). For compounds **1e** and **1k** the estimation of the tautomeric form as A was simple from the $NHCH_3$ coupling observed in the ^{1}H spectra (the coupling disappeared on shaking with D_2O). For the other compounds the ^{1}H NMR spectra gave no conclusive evidence, the R^4 group being an aryl group. For these compounds the ^{13}C chemical shift values of C-1 in the R^4 substituent were especially valuable in the estimation of the tautomeric form present, together with the signal pattern for the C-2 to C-4 carbon atoms. The chemical shift values of the N=CH–N carbon atom were of no value being much influenced by the kind of substituents attached to the neighbouring N atoms.

The C-1 chemical shift values in the R^4 substituent were found at 143.9–144.3 for the phenyl group in the tautomer **A** models, the corresponding values being 139.9–140.3 for phenyl substituents and 137.5–140.4 for tolyl substituents for compounds **1f–j, l–n**. The observed upfield shift of around 4 ppm on going from the model compounds to **1e–n** is in accordance with the influence of an N-methyl group found for other systems.[3,7] The

Table 1. $R^1SO_2NR^2N{=}CHNR^3R^4$

Compound	R^1	R^2	R^3	R^4	Yield/ Method %	M.p.(B.p./mmHg) °C	Mass Spectrum m/e (% of base peak)
1a	Me	H	Me	Ph	55/B	122	227(M^+)(17), 148(65), 107(24), 106(100), 104(10), 77(35), 51(14), 42(23)
1b	Me	Me	Et	Et	77/B	(110-116/0.7)	
1c	Me	Me	Me	Ph	76/B	117	242(M^+)(7), 162(83), 120(91), 106(100), 104(22), 77(64), 42(34)
1d	Me	Me	Et	Ph	22/B	86	225(M^+)(13), 176(71), 134(28), 121(23), 120(100), 106(18), 104(17), 77(47)
1e	Me	Me	H	Me	42/B	82	165(M^+)(12), 85(80), 43(100), 42(20), 41(32)
1f	Me	Me	H	Ph	30/A	119	227(M^+)(14), 148(100), 106(98), 104(62), 77(52), 41(79)
1g	Me	H	H	Ph	50/A	158	213(M^+)(0.3), 121(71), 93(100), 92(20), 77(15), 66(57), 65(34)
1h	Me	H	H	p-MeC_6H_4	39/A	135	227(M^+)(22), 149(14), 148(100), 133(61), 118(55), 106(18), 91(59), 77(12), 65(20)
1i	Me	Me	H	p-MeC_6H_4	50/A	124	241(M^+)(15), 162(100), 148(29), 120(83), 118(78), 91(58), 67(25)
1j	Ph	H	H	p-MeC_6H_4	64/A	150	289(M^+)(13), 148(100), 133(35), 118(35), 106(19), 91(40), 77(29), 51(17)
1k	p-MeC_6H_4	H	H	Me	62/B	162	229(M^+)(19), 92(13), 91(37), 74(100), 65(29), 63(11), 43(36), 42(97)
1l	p-MeC_6H_4	H	H	Ph	61/A	157	289(M^+)(18), 134(100), 104(44), 92(18), 91(28), 77(48), 65(16), 51(18)
1m	p-MeC_6H_4	H	H	p-MeC_6H_4	39/A	140	303(M^+)(13), 148(100), 133(34), 118(34), 107(23), 106(27), 91(57), 77(18), 65(20)
1n	p-MeC_6H_4	Me	H	p-MeC_6H_4	67/A	153	317(M^+)(6), 163(13), 162(100), 147(20), 120(50), 118(57), 92(10), 91(58), 65(17)
1o	p-MeC_6H_4	H	Me	Ph	71/B	161	303(M^+)(18), 148(94), 107(31), 106(100), 91(27), 77(42), 42(24)

Table 2. ^{13}C NMR chemical shift values in DMSO-d_6 solution

Compound		N = CH-N	R^1 C1	R^1 C2	R^1 C3	R^1 C4	R^1 p-CH_3	R^2	R^3	R^4 C1	R^4 C2	R^4 C3	R^4 C4	R^4 p-CH_3
1a		155.2	36.6						33.7	144.3	118.7	129.5	123.4	
1b		162.1	40.6					29.6	40-42,13.2	40-42[b]	13.2			
1c		160.2	40.3					30.2	33.9	143.9	119.3	129.4	124.0	
1d		159.6	40.3					30.3	41.8,12.0	142.8	120.3	129.4	124.3	
1e	cis[a]	161.3	40.7					29.6		27.6				
	trans	157.2	38.2					29.8		31.3				
1f	cis[a]	157.7	40.3					30.4		140.0	117.1	129.0	122.0	
	trans	150.5									116.4		122.4	
1g		152.6	36.9							140.1	115.5	129.3	121.8	
										140.3	116.6	129.1	121.5	
1h	cis[a]	153.1	36.8							138.0	116.8	129.7	130.6	20.2
	trans									140.4	115.6			
1i	cis[a]	157.8	40.4					30.3		137.5	117.2	129.4	131.0	20.2
	trans	150.6									116.5		131.3	
1j		152.4[b]	140.1	127.6	128.8	132.5				139.2	115.5	129.7	130.7	20.2
										137.8	116.5	129.4	130.3	
1k	cis[a]	158.4	136.4	127.7	129.0	142.5	21.0			27.7				
	trans	149.2								31.3				
1l		151.5	136.2	127.7	129.2	142.9	20.9			140.4	116.3	129.2	121.3	
		139.2								140.2	115.3	127.7	121.7	
1m		152.1	136.3	127.6	129.2	142.8	20.9			137.7[b]	116.5	129.7	130.6	20.2
		139.7									115.4	129.4	130.2	
1n	cis[a]	157.5	137.6	129.1	129.4	143.6	21.1	40.4		137.6	117.3	129.4	130.9	20.3
	trans	150.5						38.6			116.5			
1o		154.3	136.1	127.7	129.2	142.9	20.9		33.5	144.2	118.5	129.4	123.3	

[a] Assigned from the intensities and the coupling constants in the ^1H NMR spectra.

[b] Broad.

Table 3. ^{1}H NMR chemical shift values[a] in DMSO-d_6 solution

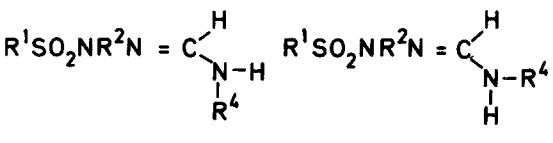
Compound	N = CH-N		R^1	R^2	R^3		R^4	J_{NH-CH} Hz		Ratio
	cis	trans			cis	trans		cis	trans	cis/trans
1a	8.35(s)		2.98(s)	9.33(s)	3.30(s)		6.9-7.5(m)			
1b[b]	7.93(s)		2.88(s)	2.82(s)	1.08(t) 3.28(q)		1.08(t) 3.28(q)			
1c[c,d]	8.48(s)		3.02(s)	2.85(s)	3.35(s)		7.0-7.5(m)			
1d[d]	8.28(s)		2.96(s)	2.88(s)	1.15(t) 3.87(q)		7.1-7.5(m)			
1e	7.53(d)	6.78(d)	2.80(s)	2.73(s)	6.3(m)		2.60(d)	5	12	6/1
1f	8.32(d)	7.97(d)	2.97(s)	2.88(s)	9.67(d)	9.42(d)	6.9-7.5(m)	6	12	7/3
1g[e]	8.07(d,b)	7.57(d)	3.02(s) 2.98(s)	9.3(b)	9.28(b)	8.92(b)	6.8-7.6(m)	5	12	1/1
1h	7.97(d)	7.43(d)	2.97(s) 2.90(s,b)	8.77(b)	9.10(b)	8.67(d)	7.0-7.2(b) 2.22(s)	6	12	3/4
1i	8.23(d)	7.88(d)	2.93(s)	2.85(s)	9.55(d)	9.33(d)	7.0-7.4(m) 2.22(s)	7	11	6/3
1j	[f]		7.3-8.0(m)	9.5(b)	8.0-9.3(b)		7.0(s,b) 2.23(s) 2.20(s)			1/1
1k	7.8[g]	6.8[h]	7.1-7.8(m) 2.38(s)	9.1(b)	6.4-6.8(b)		2.48(b)[g,i] 2.70(b)[g,j]			5/1
1l	8.30(d)	[f]	7.0-7.7(m) 2.33(s)	9.5(b)	9.26(d)	8.70(d)	7.0-7.7(m)	8	12	1/1
1m	7.93(d)	[f]	7.0-7.8(m) 2.37(s)	9.53(b)	9.12(d)	8.56(d)	6.9(b) 2.22(s)	8	12	1/1
1n	8.25(d)	7.73(d)	7.0-8.0(m) 2.43(s)	2.77(s)[i] 2.67(s)[j]	9.53(d)	9.37(d)	7.0-8.0(m) 2.26(s)	8	12	5/1
1o	8.28(s)		7.0-7.8(m) 2.43(s)	9.78(s)	3.18(s)		7.0-7.8(m)			

[a] Centers of multiplets, multiplicity given in paranthesis. [b] Collaps of the CH_2CH_3 quartets at 273 K in $CDCl_3$ solution. [c] Data for $CDCl_3$ solution. [d] No changes on cooling to 223 K in $CDCl_3$ solution. [e] The Me signals collapsed on heating. [f] Partly concealed by the aromatic protons. [g] Concealed by the DMSO-d_6 signal. [h] Concealed by the NH signal. [i] cis. [j] trans.

influence of the *p*-methyl group was also of the expected magnitude.[8]

C-2 chemical shift values for the model **1a, c–d, o** are found at 118.5–120.3 while the corresponding values in compounds **1f, j, l–n** are found from 115.4 to 117.3 ppm. Tautomer **B** models **2a–b** showed chemical shift values of C-1 149.9, C-2 121.0, C-3 128.8 and C-4 123.1. These values especially for C-1 and C-2 clearly indicate the existing tautomeric species as the amide hydrazone **A**.

While the model compounds for both **A** and **B** tautomers exhibits only one set of signals in the ^{13}C spectra, compounds **1e–n** showed doubling of some of the signals, often of different intensities. The position of these signals clearly indicates that these isomers are not tautomers and therefore the existence of different rotamers seems straightforward. From the shift values it is clear that it is the $CHNR^3R^4$ moiety of the molecule which exhibits the doubling, which consequently can be assigned to hindered rotation around the $CH-NR^3R^4$ bond. Combination of the ^{1}H and ^{13}C data gave in some cases the structural assignment to *cis* and *trans* isomers.



cis *trans*

As for the ^{13}C spectra the ^{1}H spectra of compounds **1a–e** only showed one set of signals for the R^3R^4 groups at room temperature. On cooling **1b–d**, no changes were seen except for compound **1b** for which the CH_2-quartets broadened indicating hindered rotation around the $CH-NR^3R^4$ bond. Similarly heating a DMSO-d_6 solution of **1g** caused collapse of the two CH signals around 373 K, and collapse of the methyl signals.

The mass spectral and the IR spectral data (not given) were in accordance with the proposed composition of the compounds although they did not give information on the actual tautomeric form.

DISCUSSION

As found in other amidrazone systems[2–4] ^{13}C NMR spectra provides an easy way for structural estimation of the actual tautomeric species present in solution. For the N-sulphonylformamidrazones investigated here the species turned out to be the formamide-hydrazone in accordance with results for N,N'N''-trisubstituted formamidrazones without sulphonyl groups,[4] but in contrast to findings for N''-sulphonylated formamidrazones[2] and earlier reports on N-sulphonylated formamidrazones.[6] No sign of mixtures of the two tautomers was found. A reasonable explanation for the differences between the N and the N''-sulphonylated compounds seems to be the electron-attracting sulphonyl group, able to change the unsulphonylated formamide-hydrazone structure to formhydrazide-imide structure in the N''-sulphonylated

compounds, and stabilising the formamide hydrazone structure in the N-sulphonylated formamidrazones.

No clear results regarding the structure around the C=N double bond were found but the existence of appreciable amounts of the *cis* isomer, regarding the structure at the N=CH–N single bond, indicate the structure at C=N double bond to be the *E* form as the *Z* form would be sterical unfavorable.

The estimation of the rotamers as arising from N=CH–N single bond hindered rotation and not N–N hindered rotation or *Z*/*E*-isomerism at the C=N double bond, is based on the evidence that the chemical shift difference in the ^{13}C NMR spectra for the two rotamers is found only in the $CHNR^3R^4$ moiety of the molecule. It is known that the magnitude of chemical shift differences is dependent on the distance from the centre of isomerism.[10,11] The assignment is also in accordance with investigations on the conformational status of tosylhydrazides ($RSO_2NR'NR''COCH_3$) where hindered rotation was found to arise from C–N and not N–N restricted rotation.[9] The position of the N=CH–N ^{13}C signal at lower field in the *cis* than in the *trans* form is also in accordance with results for tosylhydrazides, for which the carbonyl carbon signal is found at lowest field for the most sterical hindered conformer. The presence of only one rotamer of compounds **1a, c–d** and **2** is probably best explained from sterical reasons the less hindered rotamer being favoured in the solvent investigated.

EXPERIMENTAL

The equipment was reported earlier.[2] ^{13}C NMR spectra were recorded broad band noise decoupled on c. 1M Solutions on a JEOL FX 90 Q apparatus. When doubt in assignments also undecoupled spectra were obtained. The IR data was in accordance with the proposed structures. Elemental analysis were satisfactory (C,H,N,S) for all new compounds except **2a** and **2b**, due to their fast decomposition.

General procedure for the preparation of **1**

Method A. Sulphonohydrazide[12] (0.05 mol) and imidate[13] (0.05 mol) were stirred in dry ether (100 ml) for 1–7 days, the ppt was filtered off and recrystallized from ethanol giving **1**.

Method B. Amine (0.05 mol) and N^2-sulphonyl-*O*-ethylformohydrazonate[14] (0.05 mol) were refluxed in toluene (50 ml) for 2–3 hr. The solvent was evaporated and the residue recrystallized from ethanol giving compounds **1a–d**.

Compounds **1e** and **1k** were prepared by stirring the formohydrazonate with excess methylamine in methanol solution for 1 week.

N^1,N^2 - *Dimethyl* - N^2 - *methylsulphonylformohydrazide phenylimide* **2a**

N^1,N^2-Dimethylformohydrazide phenylimide (0.02 mol) methanesulphonyl chloride (0.02 mol) and triethylamine (0.04 mol) were stirred in benzene (50 ml) for 36 hr at room temperature. The ppt was filtered off, the filtrate evaporated and recrystallized from ethanol. M.p. 76°, yield 52%. MS *m/e* (% of base peak): 241(8)M^+, 162(25), 104(47), 93(8), 77(43), 59(100), 51(17), 43(8), 42(13). ^{13}C NMR (DMSO-d_6): Ph C1 150.0, C2 121.0, C3 128.9, C4 123.2; CH=N 153.8; CH_3SO_2 38.5; $CHNCH_3$ 33.6; SO_2NCH_3 34.6. ^1H NMR (DMSO-d_6): CH 7.60 (s, 1H), Ph 7.3–6.3 (m, 5H), Me 3.12 (s, 6H), Me 3.08 (s, 3H).

N^1,N^2 - Dimethyl - N^2 - (4 - *methylphenylsulphonyl*)*formohydrazide phenylimide* **2b**

Prepared analogously to **2a**. M.p. 83°, yield 69%. MS *m/e* (% of base peak): 317(8)M^+, 162(32), 104(27), 93(20), 91(22), 87(20), 77(32), 65(11), 59(100). ^{13}C NMR (DMSO-d_6): N=CH–N 153.7; arylSO_2 C1 133.9, C2 128.2, C3 130.1, C4 144.7, *p*-Me 21.0; SO_2NCH_3 35.5; $CHNCH_3$ 32.2; CHNPh C1 149.9, C2 120.9, C3 128.8, C4 123.2. ^1H NMR (DMSO-d_6): Aryl and CH=N 7.9–6.6 (m, 10H), *p*-Me 2.45 (s, 3H), SO_2NCH_3 2.73 (s, 3H), $CHNCH_3$ 3.17 (s, 3H).

Decomposition of **2a**

Partly decomposed **2a** was distilled b.p. 62–84°/0.15 mm Hg, the distillate crystallized on cooling and was recrystallized from ethanol giving N^1,N^2-dimethyl-N^2-methylsulphonylformohydrazide, m.p. 71°, MS *m/e* (% of base peak): 166(1)M^+, 87(100), 59(64), 43(22), 42(14). ^1H NMR ($CDCl_3$): 8.27 (s, 0.5H), 8.15 (s, 0.5H) 3.25 (s, 1.5H), 3.21 (s, 1.5H), 3.15 (s, 1.5H), 3.12 (s, 1.5H), 3.07 (s, 1.5H), 3.02 (s, 1.5H).

N^1,N^2-*Dimethylformohydrazide phenylimide*

1,2-Dimethylhydrazine dihydrochloride (0.12 mol), O-ethyl-N-phenylformimidate[13] (0.12 mol) and triethylamine (0.48 mol) were stirred at room temperature in ether (100 ml) for 24 hr. The ppt was filtered off and washed, the filtrate evaporated and distilled twice. B.p. 60–70°/0.1 mm Hg, yield 20%. ^{13}C NMR (DMSO-d_6): CH 153.5 Ph C1 151.8, C2 120.9, C3 128.8, C4 121.9; CH_3 35.7 and 33.6. ^1H NMR (DMSO-d_6): CH 7.55 (s, 1H), Ph 7.2–6.3 (m, 5H), NH 4.9 (b, 1H), NCH_3 3.00 (s, 3H), $NHCH_3$ 2.43 (d, 3H). $J_{NHCH} = 5$ Hz.

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