Some Heterocyclic Sulfonyl Derivatives

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2,3-Diphenylpyrazine, 3,4-diphenylfurazan and 2-methyl-4,5-diphenyl oxazole react with chlorosulfonic acid to give the sulfonyl chlorides Ia, IIa, IIIa. The chlorides were condensed with nucleophiles to give thirteen derivatives. 4',4''-bis-Dimethylsulfamoyl-2-methyl-4,5-diphenyloxazole (IIIb) was oxidized with bromine to give 4,4'-bis-dimethylsulfamoylbenzil (IV), which by heating with ethylenediamine afforded the 4',4''-bis-dimethylsulfamoylpyrazine (V). The spectral data of the various compounds are briefly discussed.

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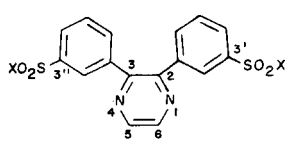
The work described forms part of our general program on the chemistry and biological activity of aromatic sulfonyl compounds [1-5], but in particular extends our studies [6-8] on heterocyclic sulfonyl derivatives.

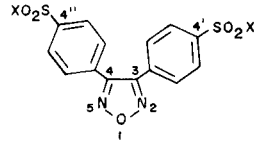
Previous work [9] showed that benzil with chlorosulfonic acid undergoes an interesting cyclisation to form 3-chloro-2-phenylbenzofuran-6,4'-bis-sulfonyl chloride; this process probably involves the 1,2-dicarbonyl system. In order to test this hypothesis, the carbonyl groups were removed by condensation with ethylenediamine and with hydroxylamine-acetic anhydride to give, 2,3-diphenylpyrazine [10] and 3,4-diphenylfurazan [11] respectively.

2,3-Diphenylpyrazine reacted with chlorosulfonic acid (6 moles) under forcing conditions (170°) and gave mainly the 3',3''-bis-sulfonyl chloride (Ia). The compound Ia was characterized by condensation with dimethylamine, sodium azide and hydrazine to give the derivatives (Ib, Ic, Id) (Table 1). The azide Ic by heating with triethyl phosphite afforded the phosphinimine (Ie) and the hydrazide Id was reacted with acetone to give If. The nmr spectrum of the dimethylamine Ib showed two resonances for the methyl protons (δ 2.72, 2.6); the pyrazine-5,6 hydrogens appeared as a low field singlet (δ 8.7) and the phenyl protons as a complex multiplet (δ 7.9-7.4) with no AA'BB' pattern. The fact that two different resonances appear for the methyl protons suggest that Ib contains a small quantity of an isomeric dimethylsulfonamide since the product gave the correct analytical and mass spectral data (Table 1).

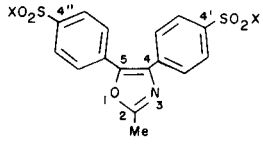
3,4-Diphenylfurazan reacted with chlorosulfonic acid (6 moles) at 85° to give the 4',4''-bis-sulfonyl chloride IIa; this was reacted with dimethylamine and sodium azide to give the derivatives IIb, IIc. The nmr spectrum of the dimethylamide IIb showed the phenyl protons as a multiplet (δ 8.2-7.8) with the AA'BB' pattern indicative of *p*-disubstitution and the methyl protons appeared as a sharp singlet (δ 2.8). The observed *p*-sulfonation is in agreement with previous observations [12] on the nitration of phenylfurazan and is probably due to the mesomeric stabilization of the Wheland intermediates by electron-donation from the hetero oxygen atom. The formation of the 4',4''-derivative IIb is contrary to our previous report [9] when the compound was assigned as the 3',3''-isomer, but repetition gave a product whose nmr spectrum showed a well-defined AA'BB' pattern for the aromatic resonances which supports the structure given here.



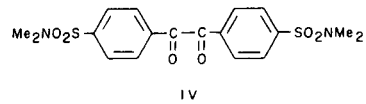
	X
Ia	Cl
Ib	NMe_2
Ic	N_3
Id	$NHNH_2$
Ie	$N{=}P(OEt)_3$
If	$NHN{=}CMe_2$



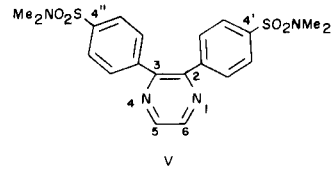
	X
IIa	Cl
IIb	NMe_2
IIc	N_3



	X
IIIa	Cl
IIIb	NMe_2
IIIc	NH_2
IIId	morpholino
IIIe	N_3
IIIf	$NHNH_2$
IIIg	$NHN{=}CMe_2$



IV



V

2-Methyl-4,5-diphenyloxazole, prepared by reaction of benzoin acetate and ammonia [13] on heating with chlorosulfonic acid (13 moles) at 85° gave the 4',4''-bis-sulfonyl chloride IIIa. The chloride IIIa reacted with nucleophiles to give the derivatives IIIb-IIIg (Table 1). The nmr spectrum of the dimethylamide IIIb showed the phenyl protons as a multiplet (δ 8.3-7.7, 8H), with the AA'BB' pattern. Compound IIIb was oxidized by bromine to give 4',4''-bis-dimethylsulfamoylbenzil (IV) which was condensed with ethylenediamine to give the pyrazine V. The intermediate dihydropyrazine was not isolated due to facile oxidation. The ir spectrum of the dimethylsulfamoyl compound (IV) showed the carbonyl absorption (1780 cm^{-1}) and in the

Table 1

Heterocyclic Sulfonyl Derivatives

Compound No.	Yield (%)	Mp, (°C)	Molecular Formula	Analysis % Found/(Calcd.) C	H	N	Mass Spectra (M^+)
Ia	83	90-92	$C_{16}H_{10}Cl_2N_2O_4S$	44.5 (44.7)	2.2 (2.3)	6.6 (6.5)	428
Ib	85	69-70	$C_{20}H_{22}N_4O_4S_2$	53.5 (53.8)	5.1 (4.9)	12.3 (12.5)	446
Ic	92	148-150	$C_{16}H_{10}N_8O_4S_2$	43.2 (43.4)	2.5 (2.3)	25.4 (25.3)	442
Id	56	221-223	$C_{16}H_{16}N_6O_4S_2$	45.8 (45.7)	3.9 (3.8)	20.2 (20.0)	—
Ie	79	266-268	$C_{28}H_{40}N_4O_{10}P_2S_2$	47.0 (46.8)	5.4 (5.6)	8.0 (7.8)	—
If	77	199	$C_{22}H_{24}N_6O_4S_2$	52.8 (52.8)	4.6 (4.8)	17.0 (16.8)	—
IIa	30	136-138 [a]	$C_{14}H_8Cl_2N_2O_5S_2$	39.9 (40.1)	2.0 (1.9)	6.8 (6.7)	418
IIb	71	161	$C_{18}H_{20}N_4O_5S_2$	49.3 (49.5)	4.8 (4.6)	12.5 (12.8)	436
IIc	37	101-102	$C_{14}H_8N_8O_5S_2$	38.6 (38.8)	1.7 (1.8)	25.6 (25.9)	432
IIIa	97	89-91	$C_{16}H_{11}Cl_2NO_5S_2$	44.5 (44.4)	2.6 (2.5)	3.2 (3.2)	431
IIIb	89	198-199	$C_{20}H_{23}N_3O_5S_2$	53.3 (53.5)	5.1 (5.1)	9.2 (9.4)	449
IIIc	72	245	$C_{16}H_{15}N_3O_5S_2$	48.7 (48.9)	3.9 (3.8)	10.9 (10.7)	393
IIId	81	234-235	$C_{24}H_{27}N_3O_7S_2$	54.3 (54.0)	4.8 (5.1)	8.0 (7.8)	533
IIIe	73	140-141	$C_{16}H_{11}N_7O_5S_2$	43.4 (43.1)	2.4 (2.5)	22.3 (22.0)	445
IIIf	92	209-211	$C_{16}H_{17}N_5O_5S_2$	45.3 (45.4)	4.1 (4.0)	16.7 (16.5)	—
IIIg	75	159-161	$C_{22}H_{25}N_5O_5S_2$	52.8 (52.5)	5.1 (4.9)	13.6 (13.9)	—
IV	62	227-228	$C_{18}H_{20}N_2O_6S_2$	50.6 (50.9)	4.6 (4.7)	6.5 (6.6)	—
V	73	182-183	$C_{20}H_{22}N_4O_4S_2 \cdot \frac{1}{2}H_2O$	52.6 (52.7)	5.2 (5.1)	12.5 (12.3)	446

[a] Lit [9] mp 132-138°.

nmr spectrum the phenyl protons resonated as a multiplet (δ 8.3-7.8, 8H), with a typical AA'BB' pattern and a singlet (δ 3.2, 12H), for the methyl protons. The mass spectrum of IV did not give the molecular ion, but fragmentation occurred indicating cleavage of the dicarbonyl group. The nmr spectrum of the bis-dimethylsulfamoylpyrazine V showed the phenyl protons (δ 7.9-7.6) with the AA'BB' pattern indicative of *p*-disubstitution. The conversion of IV to V provides an unambiguous preparation of the 4',4''-bis-dimethylsulfamoylpyrazine (V). This compound has mp 182-183° and is clearly different from the isomer Ib, mp 69-70°, and it therefore supports the nmr evidence that the latter is mainly the 3',3''-derivative. The *para*-product with the greater symmetry may be expected to have the higher mp.

The mass spectra of the heterocyclic sulfonyl derivatives generally showed the molecular ions (M^+) with subsequent fragmentation of the sulfonyl moieties to give the parent heterocycles which suffered further degradation.

The general pattern of behaviour is illustrated by the mass spectra of the pyrazine sulfonyl azide Ic and the furazan dimethylsulfonamide IIb.

In contrast, the mass spectra of the hydrazides and acetone hydrazones (Table 1) did not give the molecular ions in agreement with previous observations [2].

The heterocycles in which the 1,2-dicarbonyl group had been removed by condensation reacted normally with chlorosulfonic acid and no cyclisation to the benzofuran ring system was observed. It therefore seems certain that the presence of the 1,2-dicarbonyl system is necessary for benzofuran formation.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. The ir spectra were measured as Nujol mulls unless otherwise stated with a Unicam SP-300 spectrophotometer. The uv spectra were determined with a Unicam SP-1800 spectrophotometer. The nmr spectra were recorded with a Bruker WP 80 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained with a VG Micromass V 15 instrument. The tlc were carried out using Camlab 'Polygram' silica gel plates sensitized to UV 254 nm. Microanalyses were by ICI Ltd (Pharmaceuticals Division, Cheshire, England).

2,3-Diphenylpyrazine-3',3''-bis-sulfonyl Chloride (Ia).

2,3-Diphenylpyrazine (10 g, 0.043 mole) was heated with chlorosulfonic acid (32 g, 0.027 mole) at 170° for 75 minutes. The cooled solution was poured onto ice (200 g) and the precipitate was filtered off, washed with water (3 × 50 ml) and dried to give the bis-sulfonyl chloride Ia (15.3 g); ir (potassium bromide): ν max 1600 (arom C=C), 1360, 1140 (SO_2) cm^{-1}; ms: 432, 430, 428 (M^+), 395, 393 (M-Cl), 358 (M-2Cl); tlc (ethyl acetate-cyclohexane 2:3) showed one spot, R_f 0.30.

3,4-Diphenylfurazan-4',4''-bis-sulfonyl Chloride (IIa).

3,4-Diphenylfurazan (10 g, 0.045 mole) was heated with chlorosulfonic acid (32 g, 0.3 mole) at 85° for 2 hours to give IIa (5.4 g); ir (potassium bromide): ν max 1600 (arom C=C), 1340, 1160 (SO_2) cm^{-1}; tlc (ethyl acetate-petroleum 2:3) showed one spot, R_f 0.25.

2-Methyl-4,5-diphenyloxazole-4',4''-bis-sulfonyl Chloride (IIIa).

2-Methyl-4,5-diphenyloxazole (50 g, 0.2 mole) was heated with chlorosulfonic acid (297 g, 2.6 moles) at 85° for 7 hours to give IIIa (90 g); ir (potassium bromide): ν max 1600 (arom C=C), 1345, 1160 (SO_2) cm^{-1}; tlc (ethyl acetate-cyclohexane 2:3) showed one spot, R_f 0.40.

General Procedures for the Preparation of Derivatives of the bis-Sulfonyl Chlorides Ia, IIa, IIIa.

(a) bis-Dimethylsulfonimides Ib, IIb, IIIb.

To the bis-sulfonyl chloride (0.005 mole) in methanol (15 ml) was added dimethylamine (40% aqueous solution, 0.02 mole) and the mixture was left at room temperature for 2 hours. The precipitate was filtered off, washed with water (2 × 25 ml) and purified by recrystallization from aqueous methanol.

Compound Ib.

This compound had ir (potassium bromide): ν max 1600 (arom C=C), 1340, 1160 (SO_2) cm^{-1}; nmr (DMSO-d_6): 8.7 (s, pyrazine-5.6H, 2H), 7.90-7.50 (m, phenyl H, 8H), 2.72, 2.6 (s, NMe_2, 12H).

Compound IIb.

This compound had ir (potassium bromide): ν max 1600 (arom C=C), 1360, 1120 (SO_2) cm^{-1}; nmr (deuteriochloroform): δ 8.2- 7.8 (m, aromatics, 8H), 2.8 (s, NMe_2, 12H); ms: 436 (M^+), 392 (M-NMe_2), 328 (M-SO_2NMe_2), 220 (M-2SO_2NMe_2), 144 (2-phenylfurazan), 102 (PhCN), 76 (C_6H_4).

Compound IIIb.

This compound had ir: ν max 1600 (arom C=C), 1360, 1140 (SO_2) cm^{-1}; nmr (deuteriochloroform): δ 8.3-7.75 (m, aromatics, 8H), 2.9 (s, Me, 3H), 3.2 (s, NMe_2, 12H).

(b) bis-Sulfonylazides Ic, IIc, IIIc.

To a solution of the sulfonyl chloride (0.01 mole) in acetone (30 ml) was added a solution of sodium azide (0.03 moles) in water (15 ml). The suspension was stirred for 4 hours and poured onto ice-water (150 ml); the precipitate was filtered off and recrystallized from aqueous acetone.

Compound Ic.

This compound had ir (potassium bromide): ν max 3000 (C-H), 1590 (arom C=C), 2100 (N_3), 1340, 1160 (SO_2) cm^{-1}; ms: 442 (M^+), 358 (M-2N_3), 294 (M-N_3, -SO_2N_3), 230 (2,3-diphenylpyrazine), 102 (C_6H_4CN), 76 (C_6H_4).

Compound IIc.

This compound had ir (potassium bromide): ν max 2100 (N_3), 1600 (arom C=C), 1340, 1165 (SO_2) cm^{-1}.

Compound IIIe.

This compound had ir (potassium bromide): ν max 2100 (N_3), 1600 (arom C=C), 1340, 1135 (SO_2) cm^{-1}.

(c) bis-Sulfonohydrazides and Acetone Hydrazones.

Hydrazine hydrate (98%, 0.04 mole) was added to the bis-sulfonyl chloride (0.01 mole) in methanol (20 ml) and the mixture was left for 5 hours. Addition of ice-water (200 ml) gave a precipitate which was filtered off, washed with water (2 × 20 ml) and dried to give the bis-sulfonohydrazides Id, IIIf. These were characterized by warming with acetone (10 ml) for 15 minutes; on cooling the solution (0°) the pure acetone hydrazones If, IIIg crystallized out.

Compound Id.

This compound had ir (potassium bromide): ν max 3400, 3250 (NH), 1600 (arom C=C), 1360, 1140 (SO_2) cm^{-1}.

Compound IIIf.

This compound had ir (potassium bromide): ν max 3450, 3300 (NH), 1595 (arom C=C), 1365, 1160 (SO_2) cm^{-1}.

Compound If.

This compound had ir (potassium bromide): ν max 3200 (NH), 1600 (arom C=C), 1355, 1140 (SO_2) cm^{-1}.

Compound IIIg.

This compound had ir (potassium bromide): ν max 3225 (NH), 1590 (arom C=C), 1345, 1140 (SO_2) cm^{-1}.

4,4'-bis-Dimethylsulfamoylbenzil (IV).

To a solution of 2-methyl-4',4''-bis-dimethylsulfamoyl-4,5-diphenyloxazole (IIIb) (10 g, 0.2 mole) in glacial acetic acid (100 ml) was added bromine (3.5 g, 2 moles). The mixture was refluxed for 1 hour and poured onto ice (250 g); the precipitate was filtered off, washed with water (4 × 50 ml) and dried. Recrystallization from aqueous ethanol gave IV (7.2 g); ir: ν max 1780 (C=O), 1320, 1140 (SO_2) cm^{-1}; nmr (deuteriochloroform): δ 8.3-7.8 (m, aromatics, 8H), 3.2 (s, NMe_2, 12H), ms: no M^+ ion, fragment ions at 212 ($COC_6H_4SO_2NMe_2$), 168 ($COC_6H_4SO_2$), 140 ($C_6H_4SO_2$), 104 (C_6H_4CO), 76 (C_6H_4), 28 (CO).

2,3-bis(4',4''-Dimethylsulfamoylphenyl)pyrazine (V).

4,4'-bis-Dimethylsulfamoylbenzil (IV) (3 g, 0.007 mole) was refluxed with ethylenediamine (2.5 g, 0.04 mole) for 4 hours. The cold solution was poured onto ice (100 g) and the precipitate filtered off and washed with water. Recrystallization from ethanol gave the pyrazine V as yellow needles (2.3 g); ir: ν max 1600 (arom C=C), 1335, 1140 (SO_2) cm^{-1}; nmr (deuteriochloroform): δ 8.8 (s, pyrazine-5,6H, 2H), 7.9-7.5 (q, phenyl H, 8H), 2.8 (s, NMe_2, 12H); ms: 446 (M^+), 402 (M-NMe_2), 338 (M-SO_2NMe_2), 294 (M-SO_2, 2NMe_2), 230 (diphenylpyrazine), 78 (pyrazine), 76 (C_6H_4).

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