Cyclic Products from Sulphonamides and Formaldehyde

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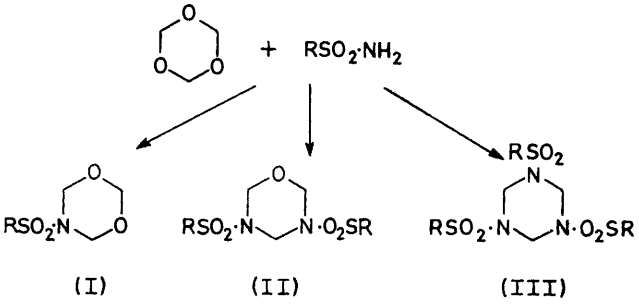
N-Sulphonyldihydro-1,3,5-dioxazines (I) and di-*N*-sulphonyltetrahydro-1,3,5-oxadiazines (II) can be obtained by the reaction of sulphonamides with trioxan (as source of formaldehyde) in a strong organic acid medium at 35°. Under analogous conditions, a new procedure of wide scope leads to tri-*N*-sulphonylhexahydro-1,3,5-triazines (III).

THE *N*-sulphonyl derivatives (I)—(III) can be formally regarded as the result of replacement of oxygen atoms in trioxan by sulphonamide groups (Scheme). Compounds of types (I) and (II) have not been reported previously, but a few of type (III) have been prepared by heating a sulphonamide with formaldehyde or trioxan in a solvent containing an acid catalyst at *ca.* 100°; this method gave good yields [1] but failed [2] with several sulphonamides. Some examples of type (III) have also been obtained (unspecified yields) either by melting a mixture of a sulphonamide with paraformaldehyde [3] or by reaction of the latter with *N*-sulphinyltoluene-*p*-sulphonamide.[4]

This paper reports the synthesis of compounds of type (I) and (II) and a general procedure for the preparation of those of type (III).

Compounds (I) were obtained by reaction of sulphonamides with an excess of trioxan (as source of formaldehyde) at 35° in a mixture of methanesulphonic and acetic acids (2 : 1). This procedure generally affords high yields with either alkane- or arene-sulphonamides (Table 1). The low yield of (If) from *p*-acetamidobenzenesulphonamide is ascribed to the formation of secondary products by attack of formaldehyde on the acetamido-substituent. Trifluoroacetic acid can also be used as reaction medium but yields are significantly lower. Compounds (I) and (III) can be interconverted; however, transformations of this sort seem of limited preparative value.



SCHEME

Compounds (II) were similarly prepared from sulphon-

[1] (*a*) A. Magnus-Levy, *Ber.*, 1893, **26**, 2148; (*b*) L. McMaster, *J. Amer. Chem. Soc.*, 1934, **56**, 204; (*c*) C. D. Egginton and A. J. Lambie, *J. Chem. Soc.* (*C*), 1969, 1623; (*d*) E. E. Gilbert, *Synthesis*, 1972, 30.

[2] E. Hug, *Bull. Soc. chim. France*, 1934, [5] **1**, 990; see also Table 3, compound (IIIl).

[3] W. Scheele and L. Steinke, *Kolloid-Z.*, 1941, **97**, 176; 1942, **100**, 361.

[4] R. Albrecht, G. Kresze, and B. Mlakar, *Chem. Ber.*, 1964, **97**, 483.

amides and trioxan (molar ratio 2 : 1) in trifluoroacetic acid; as shown in Table 2 the yields are very low. This is due to losses during isolation and especially to the formation of substantial amounts of compounds (III); the latter were isolated (35—60% yield) and identified by comparison with authentic samples. Attempts to improve the yields by varying the molar ratio of reactants, the reaction time, and the medium (*e.g.* by using methanesulphonic and acetic acids), or by treating compound (I) with the parent sulphonamide, were unsuccessful.

The molecular formulae of (I) and (II) were ascertained from elemental analyses and low resolution mass spectrometry. The compounds are devoid of i.r. absorption in the N–H and O–H regions with the exception of (If) [ν_{AcNH} 3342 cm^{-1} (Nujol)]. The n.m.r. spectra (Tables 1 and 2) established the structures. The resonances of the ring methylene groups appear as sharp singlets; this 'averaging' of axial and equatorial protons is caused by fast ring inversion on the n.m.r. time-scale. The methylene groups at positions 4 and 6 in (I) and at 2 and 6 in (II) give coincident signals, resulting in each case in a sharp, four-proton singlet. A different situation has been encountered [5] in the 100 MHz spectrum of the 5-(2,4-dinitroanilino)dihydro-1,3,5-dioxazine, which shows two separated broad doublets assigned to the 4- and 6-protons.

The condensation of sulphonamides with trioxan in molar ratio 3 : 1 in methanesulphonic and acetic acids (4 : 1) at 35° led to compounds (III). The procedure was applied to alkane- and arene-sulphonamides bearing a variety of substituents, generally giving high yields (Table 3). The reaction can also be performed in trifluoroacetic acid but the yields are usually lower; in this solvent the preparation of (IIIj) failed, *NN'*-methylenebis-(*p*-nitrobenzenesulphonamide) being obtained instead.

EXPERIMENTAL *

Analytical data for the new compounds (all within ±0·4%) referred to in Tables 1—3 are available as Supplementary Publication No. SUP 21271 (4 pp.).†

TABLE 1

5-Sulphonyldihydro-1,3,5-dioxazines (I)

	R	Yield (%)	M.p. (°C)	Cryst. solvent	δ [a] 2-H_2 (2H, s)	δ [a] 4- and 6-H_2 (4H, s)	δ [a] R
(Ia)	Me	78	123—125	MeOH	5·20	5·24	3·25 (3H, s, Me)
(Ib)	Ph	71	158—159	AcOEt	4·88	5·23	7·4—8·2 (5H, aromatic)
(Ic)	*p*-MeC_6H_4	74	139—140	EtOH	4·90	5·22	2·45 (3H, s, Me), 7·2—8·0 (4H, aromatic)
(Id)	*p*-ClC_6H_4	74	140—141	Bu^nOH	4·90	5·22	7·4—8·1 (4H, aromatic)
(Ie)	*m*-$NO_2{\cdot}C_6H_4$	66	139—140	EtOH	4·85	5·25	7·6—9·0 (4H, aromatic)
(If)	*p*-$AcNH{\cdot}C_6H_4$	27	210—212	EtOH	4·85	5·17	2·08 (3H, s, Me), 7·75 (4H, s, aromatic)
(Ig)	*p*-$MeO_2C{\cdot}C_6H_4$	47	156—157	MeEtCO	4·88	5·25	3·98 (3H, s, Me), 7·9—8·4 (4H, aromatic)
(Ih) [b]	2-Naphthyl	84	208—210	$AcOBu^n$	4·83	5·27	7·5—8·7 (7H, aromatic)

[a] Solutions in $CDCl_3$ except for the less soluble (If and h), for which $(CD_3)_2SO$ was used. [b] Owing to its low solubility in chloroform, (Ih) was isolated by the procedure used for compounds (III).

TABLE 2

3,5-Disulphonyltetrahydro-1,3,5-oxadiazines (II)

	R	Yield (%)	M.p. (°C)	Cryst. solvent	δ [a] 2- and 6-H_2 (4H, s)	δ [a] 4-H_2 (2H, s)	δ [a] R
(IIa)	Me	9	157—158	AcOEt	5·18	5·20	3·12 (6H, s, Me)
(IIb)	Et	18	110—111	$MePr^iCO$	5·03 [b]	5·03 [b]	1·37 (6H, t, *J* 7, Me), 3·34 (4H, q, *J* 7, CH_2)
(IIc)	$PhCH_2$	15	186—187	Me_2CO	4·50	4·88 [c]	4·93 [c] (4H, s, $PhCH_2$), 7·37 (10H, s, aromatic)
(IId)	*o*-MeC_6H_4	11	134—135	AcOEt	4·94	4·85	2·50 (6H, s, Me), 6·9—7·9 (8H, aromatic)
(IIe) [d]	*p*-MeC_6H_4	10	158—159	AcOEt	4·81	4·93	2·45 (6H, s, Me), 7·2—7·9 (8H, aromatic)

[a] $CDCl_3$ as solvent except for (IIc), measured in $(CD_3)_2SO$; *J* in Hz. [b] Superposed. [c] Partially superposed. [d] This compound was formerly obtained (with Dr. H. Schuttenberg) by melting a mixture of the sulphonamide and paraformaldehyde but the preparation could not be reproduced.

M.p.s were determined for samples in sealed capillary tubes. Reactions were carried out in a flask with ground-glass joint and Teflon stopper; evaporations were performed under reduced pressure. I.r. spectra (Nujol mulls) were recorded with a Perkin-Elmer 337E spectrophotometer and n.m.r. spectra (60 MHz) with a Varian A-60 instrument (standard internal tetramethylsilane). Microanalyses were performed by Dr. B. B. de Deferrari (University of Buenos Aires).

5-Sulphonyldihydro-1,3,5-dioxazines (I).—To a stirred solution of trioxan (180 mg, 2 mmol) in acetic acid (0·5 ml), the sulphonamide (1 mmol) was added; after 5 min methanesulphonic acid (1 ml) was added dropwise during 80—90 s. Stirring was continued at 35° for 15 min. The mixture, cooled in ice, was then diluted with chloroform

* Some of the reactions in trifluoroacetic acid were performed in collaboration with Dr. I. A. Benages.

† For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1974, Index issue.

[5] S. R. Johns, J. A. Lamberton, and E. R. Nelson, *Austral. J. Chem.*, 1973, **26**, 1297.

(10 ml), washed with ice–water (2 × 10 ml) and aqueous 5% sodium hydrogen carbonate (2 × 10 ml), dried ($MgSO_4$), and evaporated and the *product* was crystallized (Table 1).

3,5-*Disulphonyltetrahydro*-1,3,5-*oxadiazines* (II).—The sulphonamide (0·01 mol) and trioxan (450 mg, 5 mmol) in trifluoroacetic acid (10 ml) were heated for 2 h at 35° with stirring. Chloroform (50 ml) was added to the ice-cooled mixture, followed by ice–water (25 ml). In some cases (IIa, c, and d) a solid remained undissolved; it was separated and identified (mixed m.p. and i.r. spectra) as the corresponding 1,3,5-trisulphonylhexahydro-1,3,5-triazine (III).

The chloroform phase was separated, washed with ice–water (25 ml) and aqueous 5% sodium hydrogen carbonate (2 × 25 ml), dried ($MgSO_4$), and evaporated. The residue was heated with ethanol (4 × 10 ml); after cooling at room temperature the alcoholic phase was separated. The insoluble material was identified as compound (III).

The combined alcoholic solutions were evaporated and the residue was crystallized from methanol to give crude *product* (II); this was recrystallized as indicated in Table 2. Fractionation with ethanol was omitted for (IIa) (all the material dissolved).

1,3,5-*Trisulphonylhexahydro*-1,3,5-*triazines* (III).—A solution of trioxan (30 mg, 0·33 mmol) in acetic acid (0·25 ml) was added dropwise with stirring to the sulphonamide (1 mmol) in methanesulphonic acid (1 ml); the mixture was stirred for a further 15 min at 35°. After cooling at 0°, crushed ice (10 g) was added and the mixture was maintained for 1—2 h in an ice-bath with occasional shaking. The precipitate was filtered off and washed with ice–water, aqueous 5% sodium hydrogen carbonate, and water. The dried crude product (III) was crystallized (Table 3).

Interconversion of 5-(p-*Tolylsulphonyl*)*dihydro*-1,3,5-*dioxazine* (Ic) *and* 1,3,5-*Tris*-(p-*tolylsulphonyl*)*hexahydro*-1,3,5-*triazine* (IIIg).—(*a*) A solution of (Ic) (24 mg, 0·1 mmol) and toluene-*p*-sulphonamide (68 mg, 0·4 mmol) in trifluoroacetic acid (0·2 ml) was maintained at 35° for 3 h. After dilution with chloroform (1 ml), the cooled solution was washed with ice–water (2 × 1 ml) and aqueous 5% sodium hydrogen carbonate (2 × 1 ml), dried ($MgSO_4$), and evaporated; the residue was crystallized from ethanol to give (IIIg), m.p. and mixed m.p. 169—170° (36%).

(*b*) A solution of trioxan (135 mg, 1·5 mmol) and (IIIg) (275 mg, 0·5 mmol) in trifluoroacetic acid (3 ml) was heated at 35° for 15 h. Chloroform (10 ml) was added to the cooled solution, which was then washed with ice–water (2 × 10 ml) and aqueous 5% sodium hydrogen carbonate (2 × 10 ml), dried ($MgSO_4$), and evaporated. The residue was crystallized from ethanol to give compound (Ic), m.p. and mixed m.p. 136—139° (16%).

NN′-*Methylenebis*-(p-*nitrobenzenesulphonamide*).—To a solution of trioxan (0·36 g, 4 mmol) in trifluoroacetic acid (25 ml), *p*-nitrobenzenesulphonamide (2·42 g, 12 mmol) was added. The mixture was stirred during 24 h at 35°, then slowly poured on crushed ice (100 g) and left for several hours at 0—5°. The precipitate was filtered off and washed with ice–water, aqueous 5% sodium hydrogen carbonate, and water. Crystallizations from nitromethane gave the *product*, m.p. 204—206° (36%), $\nu_{max.}$ 3290 cm^{-1} (NH), δ [$(CD_3)_2SO$] 4·37 (2H, distorted d, CH_2), 7·7—8·4 (8H, m, aromatic), and 8·8br (NH) (after addition of D_2O the doublet coalesced to a singlet and the signal at δ 8·8 disappeared) (Found: C, 37·55; H, 3·0; N, 13·65; S, 15·4. $C_{13}H_{12}N_4O_8S_2$ requires C, 37·5; H, 2·9; N, 13·45; S, 15·4%).

TABLE 3

1,3,5-Trisulphonylhexahydro-1,3,5-triazines (III) [a,b]

	R	Yield (%)	M.p. (°C)	Cryst. solvent [c]	δ [d] Ring CH_2 (6H, s)	δ [d] R
(IIIa) [e]	Me	74	290—291 (decomp.)	A	4·89	3·06 (9H, s, Me)
(IIIb)	Et	73	219—220	B	4·92	1·22 (9H, t, *J* 7, Me), 3·18 (6H, q, *J* 7, CH_2)
(IIIc)	n-C_5H_{11}	91	117—118	C	4·98	0·6—2·2 (27H, Bu^n), 3·18 (6H, distorted t, S·CH_2)
(IIId)	$PhCH_2$	45	276—278 (decomp.)	D	4·73	4·50 (6H, s, $PhCH_2$), 7·30 (15H, s, aromatic)
(IIIe) [f]	Ph	76	219—221	E	4·63	7·3—8·0 (15H, aromatic)
(IIIf) [g]	*o*-MeC_6H_4	85	250—251 (decomp.)	A	4·85	2·48 (Me) [h] 7·2—7·9 (12H, aromatic)
(IIIg) [i]	*p*-MeC_6H_4	87	169—170	F	4·57	2·43 (9H, s, Me), 7·2—7·8 (12H, aromatic)
(IIIh)	*p*-ClC_6H_4	93	228—230	F	5·08	7·9—8·5 (12H, aromatic)
(IIIi)	*m*-NO_2·C_6H_4	68	238—240	G	4·88	7·8—8·7 (*ca.* 12H, aromatic)
(IIIj)	*p*-NO_2·C_6H_4	70	248—251 (decomp.)	D	4·82	8·0—8·5 (*ca.* 12H, aromatic)
(IIIk)	*p*-AcNH·C_6H_4	75	242—244	F	4·50	2·08 (9H, s, Me), [h] 7·65 (12H, s, aromatic)
(IIIl) [j]	*p*-MeO_2C·C_6H_4	69	201—202	H	4·73	3·97 (9H, s, Me), 7·7—8·2 (12H, aromatic)
(IIIm)	1-Naphthyl	55	262—264 (decomp.)	A	5·05	7·4—8·7 (21H, aromatic)
(IIIn)	2-Naphthyl	67 [k]	243—244 (decomp.)	G	4·70	7·4—8·6 (*ca.* 21H, aromatic)

[a] Molecular weights of (IIIa—n) were determined by low resolution mass spectrometry except (IIIk) which decomposed. [b] Compound (IIIk) shows several i.r. bands in the 3600—3100 cm^{-1} region (NH); the others do not absorb in this range. [c] A = *NN*-dimethylformamide; B = isobutyl methyl ketone; C = methanol; D = nitromethane; E = ethyl methyl ketone; F = n-butanol; G = acetonitrile; H = n-butyl acetate. [d] *J* in Hz; compounds (IIIc, e, g, k, and l) in $CDCl_3$, (IIIh) in $(CD_3)_2CO$, and the remainder in $(CD_3)_2SO$ solutions. [e] After the characterization of (IIIa) was completed, it was obtained by another procedure (ref. 1*d*). [f] Lit.,[1a] m.p. 217°. [g] Lit.,[1b] m.p. 245·5—246·5°. [h] Partially superposed with residual solvent signals. [i] Lit.,[1b] m.p. 169·5°. [j] The preparation of this compound by the procedure given in ref. 1*d* was unsuccessful. [k] Double volumes of methanesulphonic and acetic acids were used.

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