Intramolecular Sulphonyl-Amidomethylation. Part I [1,2]. Cyclization of Benzylsulphonamides

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Cyclization of benzylsulphonamides with aldehydes in strong acid media is a synthetically useful route to 3,4-dihydro-1*H*-2,3-benzothiazine 2,2-dioxides III. With insufficient acid strength or reaction time, kinetic products IV and VI are obtained; the latter compounds can be converted into the thermodynamic products III under stronger conditions. The reactions proceed *via* imine VII or iminium VIII compounds as common intermediates.

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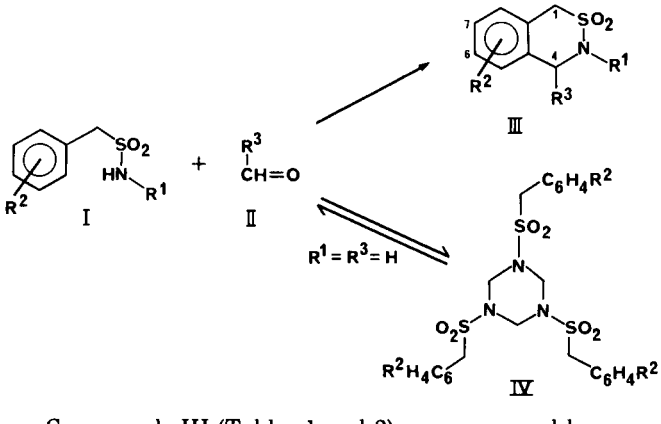
Acylamidomethylation [4,5] is a well-known and valuable electrophilic aromatic substitution. In this paper [1] we describe a closely related reaction, the intramolecular sulphonyl-amidomethylation at aromatic carbon which is applied here to the cyclization of benzylsulphonamides I to give 3,4-dihydro-1*H*-2,3-benzothiazine 2,2-dioxides III.

Only few examples of III are known (R^1 = H, Et, Ph; R^2 = R^3 = H) and they were synthesized by a different route [6]. Following our preliminary communication [1], another author [7] applied the above cyclization to related substrates to obtain intermediates for the synthesis of some compounds with useful biological activity, *e.g.* bacteriostatics.

Benzylsulphonamides I and aldehydes II give the thermodynamic products III under strong acid catalysis; with insufficient reaction time or acid strength the kinetic products, *e.g.* IV, are obtained (Scheme A).

Scheme A



Compounds III (Tables 1 and 2) were prepared by procedures A to D of increasing acidity using methanesulphonic acid (in procedure A, diluted with 1,2-dichloroethane; in B, plus trifluoroacetic acid; in C, plus trifluoromethanesulphonic anhydride) or trifluoromethanesulphonic acid (procedure D, plus trifluoromethanesulphonic anhydride). The aldehyde II used in most examples was formaldehyde generated *in situ* from *s*-trioxane although paraformaldehyde and dimethoxymethane were also useful sources especially for *N*-monosubstituted derivatives I (preparation of IIIa,b); the reaction failed with *s*-trithiane which was recovered unaltered (mp, mixed mp, and ir) in 85% yield.

By the milder procedures A or B, the benzylsulphonamide or its *N*-monosubstituted derivatives (Ia-i and formaldehyde led to the corresponding benzothiazines III which were isolated with moderate to high yields. There were two exceptions. The failure of Ig (R^1 = Ph; R^2 = H) is ascribed to intermolecular electrophilic attack at R^1 = Ph which is activated by the adjacent *N*-atom; accordingly, satisfactory results were obtained when an electron-attracting substituent was introduced at R^1 (Ih,i). From Ie (R^1 = *t*-Bu, R^2 = H) with procedure B, it was obtained a good yield of IIIa (R^1 = R^2 = R^3 = H) formed by removal of the *N*-*t*-butyl group in agreement with literature data [8] on acid cleavage of other *N*-*t*-butylsulphonamides; the milder procedure A furnished a complex mixture (tlc) which gave only one pure product (Ia, R^1 = R^2 = H) in low yield.

Benzylsulphonamides with a nuclear substituent that increases the electron density at ring-closure positions (Ij,k) also gave III by procedures A or B. In these substrates there are two non-equivalent ring-closure positions, *ortho* or *para* to the substituent; it was only isolated the *para*-cyclized product. However, a chromatographically homogeneous but low melting (112-114°) sample of IIIj (R^1 = R^3 = H, R^2 = 7-Me) showed small pmr peaks adjacent to those of the main component suggesting the presence of the *ortho*-cyclized isomer; this fact and crystallization losses to obtain pure IIIj account for the modest yield of this preparation. The structure of IIIj, supported here by pmr, was confirmed by single crystal X-ray diffraction [9].

Most benzylsulphonamides with an electron-attracting nuclear substituent (Iℓ-s) required stronger reaction conditions (procedures C or D) to yield III; Iq failed owing to decomposition and even procedures C or D were insufficient for Is which mainly gave the kinetic product VIs. Using

Table 1

Cyclization of Benzylsulphonamides I with formaldehyde (II, R^3 = H)

	R^1	R^2	Procedure [a]	Product	Yield (%)	Mp [b] (°C)	Calcd. %/(Found) C	H	N	S
Ia	H	H	A	IIIa [c]	68	142-143 (EtOAc)				
			B		66					
			B [d]		60					
			B [e,f]		41					
				Va	13	180-181 (EtOAc)	53.95 (53.70	4.80 5.00	7.40 7.50	16.94 16.90)
			C [d,f]	IIIa	56					
				Va	6					
Ib	Me	H	B	IIIb	78	74-75 (Pr^i_2O)	54.80 (55.10	5.62 5.79	7.10 7.28	16.26 16.22)
			B [d]		93					
			B [e]		90					
Ic	Et	H	B	IIIc [c]	88 (B-H)	70-71				
Id	*i*-Pr	H	B	IIId	90	90-91 (Pr^i_2O)	58.64 (58.75	6.71 6.82	6.22 6.18	14.23 14.22)
Ie	*t*-Bu	H	A	Ia [g]	9	99-100 (C_6H_6)				
			B	IIIa	63					
If	$PhCH_2$	H	B	IIIf [h]	58	84-85 (Pr^i_2O)	65.91 (66.07	5.53 5.74	5.12 5.43	11.73 11.51)
Ig	Ph	H	A or B	—						
Ih	*p*-ClC_6H_4	H	B	IIIh	70	142-143 (EtOH)	57.24 (57.28	4.12 4.16	4.77 4.88	10.91 11.09) [i]
Ii	*p*-$O_2NC_6H_4$	H	B	IIIi	48	154-155 (EtOAc)	55.25 (55.00	3.97 4.06	9.21 9.14	10.54 10.60)
			C		0					
Ij	H	*m*-Me	A	IIIj	44	118-119 (EtOH)	54.80 (54.80	5.62 5.89	7.10 7.26	16.26 16.18)
			B [f]		40					
Ik	H	*m*-AcNH	A [f,j]	IIIk	62	201-202 (MeOH)	49.99 (50.15	5.03 5.13	11.66 11.56	13.34 13.26)
			B [j]		55					
Iℓ	H	*o*-Cl	B [f]	IVℓ	70	254-255 (MeCN)	44.14 (44.06	3.70 3.96	6.44 6.63	14.73 14.57) [i]
				IIIℓ	1	165-166 (MeOH)	44.14 (44.37	3.70 4.00	6.44 6.48	14.73 14.65) [i]
			C		77					
Im	H	*m*-Cl	B	IIIm	49	119-120 ($CHCl_3$)	44.14 (44.02	3.70 3.89	6.44 6.68	14.73 14.68) [i]
			C		49					
In	H	*p*-Cl	B [k]	IVn	86	256-258 ($MeNO_2$)	44.14 (44.26	3.70 3.74	6.44 6.60	14.73 14.93) [i]
			C	IIIn	47	126-127 ($CHCl_3$)	44.14 (44.30	3.70 3.90	6.44 6.44	14.73 14.66) [i]
			D		85					

Table 1

(continued)

	R¹	R²	Procedure [a]	Product	Yield (%)	Mp [b] (°C)	Calcd. %/(Found) C	H	N	S
Io	Me	*p*-Cl	B	IIIo	78	71-72	46.65	4.35	6.05	13.84
						(Pr^i_2O)	(46.47	4.46	5.98	14.10) [i]
			C		80					
Ip	H	*p*-CO_2Me	A	IVp	77	204-209	49.78	4.60	5.81	13.29
						(AcOH)	(50.07	4.66	5.63	13.19)
			B		52					
			D	IIIp	52	208-209	49.78	4.60	5.81	13.29
						(EtOH)	(50.06	4.88	5.58	13.18)
Iq	H	*p*-CO_2H	B [k]	IVq	98	288-290	47.57	3.99	6.17	14.11
						(F-A)	(47.57	4.25	6.36	14.18)
			C [k]		17					
			D [k]		0					
Ir	H	*p*-O_2N	B or C [k]	IVr	68	293-294	42.10	3.53	12.27	14.05
						(DMF)	(42.27	3.80	12.10	13.90)
			D [f]	IIIr	31	222-223	42.10	3.53	12.27	14.05
						(MeCN)	(41.98	3.46	12.02	14.25)
				Vr	24	266-267	43.59	3.44	11.96	13.69
						(MeCN)	(43.86	3.60	12.11	13.50)
Is	Me	*p*-O_2N	B [*l*]	VIs	22	148-149	43.21	4.27	11.86	13.57
						(EtOAc)	(43.28	4.45	11.99	13.84)
			D [f,*l*]		44					
				IIIs [h]	1	167-168	44.62	4.16	11.56	13.24
						(EtOAc)	(44.49	4.29	11.70	13.41)

[a] *s*-Trioxan as HCHO source except otherwise specified. [b] Crystallization solvent in parentheses; for IIIc, benzene-hexane (B-H); for IVq, DMF-ethanol (F-A). [c] Known compound ref [5]; IIIc was also obtained by alkylation of IIIa as described. [d] Paraformaldehyde as HCHO source. [e] Methylal as HCHO source. [f] column chromatography of crude product on silica gel (for ir, alumina) prior to crystallization. [g] Extracted with 12% aqueous potassium hydroxide. [h] Identical to a sample obtained by alkylation (NaH/DMF and R¹X); IIIf and IIIs from IIIa and IIIr respectively. [i] Cl%: IIIh 12.07 (12.19); IV*l* 16.29 (16.43); III*l* 16.29 (16.46); IIIm 16.29 (16.55); IVn 16.29 (16.48); IIIn 16.29 (16.55); IIIo 15.30 (15.58). [j] Ethyl acetate was used instead of chloroform due to the low solubility of IIIk. [k] Work-up as for IVa in Experimental. For Iq sodium bicarbonate was omitted in the washings. [*l*] Is recovered extracting the crude product with aqueous potassium hydroxide; B, 49% (including Is insoluble in the work-up); D, 25%.

procedures A or B, this type of benzylsulphonamides (except Im,o) furnished the kinetic products IV in high yields.

The results obtained with other aldehydes (II, $R^3 \neq H$; Table 2) instead of formaldehyde indicate that an electron-attracting R^3 = substituent is required to yield III; apparently, the unfavorable steric effect of R^3 must be counterbalanced by a significant increase of the electrophilicity of the carbonyl carbon.

The intramolecular sulphonyl-amidomethylation of *N*-unsubstituted I ($R^1 = H$) can be interpreted as shown in Scheme B. The intermediate imines VII were not isolated but in one example (Ia with II, R^3 = Ph) the reaction stopped at this stage giving VIIa ($R^2 = H$, R^3 = Ph) in 44% yield; with a longer reaction time (24 hours), VIIa disappeared without formation of III ($R^1 = R^2 = H$, R^3 = Ph). This failure is ascribed to insufficient electrophilicity of the imino carbon. On this basis, the analogous VIIb ($R^2 = H$, $R^3 = p$-$O_2NC_6H_4$) was subjected to procedure C but omitting the aldehyde II, to give the corresponding IIIu in 46% yield; the latter was obtained from Ia ($R^1 = R^2 = H$) and *p*-nitrobenzaldehyde (II, $R^3 = p$-$O_2NC_6H_4$) in 34% yield.

The kinetically favored trimeric product IVa ($R^2 = H$) was obtained in 54% yield from Ia ($R^1 = R^2 = H$) and *s*-trioxane in methanesulphonic and acetic acids with a reaction time of two minutes; after three hours, 67% yield of compound IIIa ($R^1 = R^2 = R^3 = H$) was isolated instead. Furthermore, when IVa was subjected to the same conditions (without *s*-trioxane) for six hours gave 74% yield of IIIa. Table 1 contains several additional examples of isolation of compounds IV; one of them, IVp ($R^2 =$ *p*-CO_2Me), was converted in 72% yield to the correspond-

Scheme B

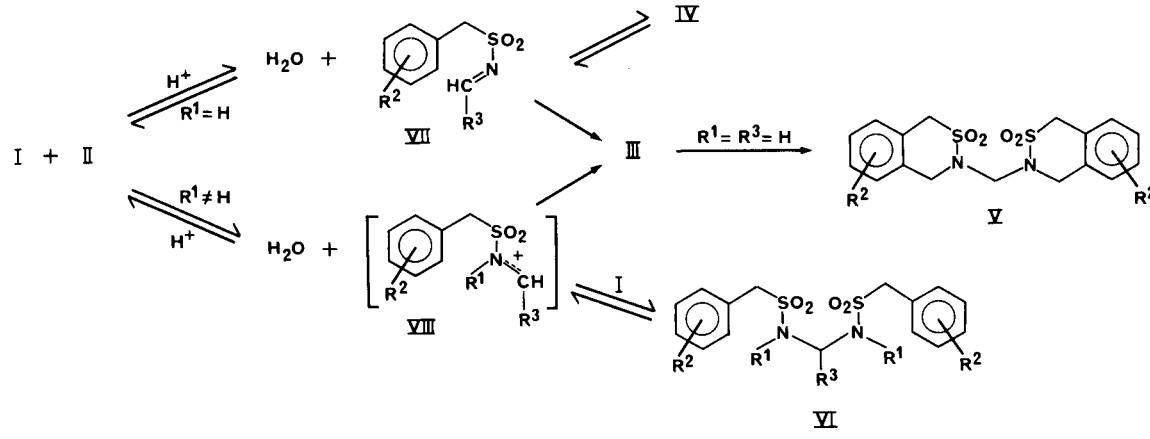


Table 2

Cyclization of Benzylsulphonamides I with aldehydes (II, $R^3 \neq H$)

	R^1	R^2	R^3	Procedure	Product	Yield (%)	Mp [a] (°C)	Calcd. % (Found) C	H	N	S
Ia	H	H	Me [b]	B-D	—						
Ia	H	H	CCl_3	B [c,d]	VIt	17	219-221	40.73	3.63	5.94	13.59
							(Pr^iOH	(40.74	3.75	6.20	13.37) [e]
					IIIt [f]	3	127-128	35.96	2.68	4.66	10.67
							(Pr^iOH)	(36.20	2.71	4.55	10.50) [e]
				C		58					
				D		44					
Ib	Me	H	CCl_3	B-D	— [g]						
Ia	H	H	Ph	B	—						
				D	VIIa [h]	44	94-95				
							(Pr^i_2O)				
Ia	H	H	p-$O_2NC_6H_4$	B [c,i]	IIIu	10	217-219	55.25	3.97	9.21	10.54
							(EtOAc)	(55.28	4.22	9.44	10.54)
				C [c,i]		34					

[a] Crystallization solvent in parentheses. [b] Paraldehyde as source of acetaldehyde. [c] Column chromatography of crude product on silica gel prior to crystallization. [d] Recovered Ia, 16%. [e] Cl%: VIt 22.54 (22.42), IIIt 35.38 (35.68). [f] Dimorphic; another sample melted at 143-144°; ir spectra of both samples in nujol showed some differences but were identical in chloroform solution. [g] Recovered Ib in procedure B or C, 80-85%. [h] Identified by mixed mp and ir with an authentic sample, see ref [21]. [i] Recovered % of p-nitrobenzaldehyde (procedure B, 58; C, 30) and Ia (B, 32; C, 16).

ing IIIp ($R^1 = R^3 = H$, $R^2 = 6\text{-}CO_2Me$) by increasing the acid strength of the reaction medium (procedure C without s-trioxane). In the case of Iq ($R^1 = H$; $R^2 = p\text{-}CO_2H$) the reaction did not proceed beyond the formation of IVq ($R^2 = p\text{-}CO_2H$). The higher thermodynamic stability of III with regard to IV is due to entropic (monomer versus trimer) and enthalpic (mainly C-C versus C-N bond) factors.

For N-monosubstituted I ($R^1 \neq H$) the common intermediate to the products is the iminium salt VIII (Scheme B). The kinetic products VI were isolated in two examples. Compound VIt obtained by procedure B, was converted (66% yield) into the thermodynamic product IIIt ($R^1 = R^2 = H$, $R^3 = CCl_3$) using the stronger procedure C without addition of II ($R^3 = CCl_3$).

The formation of III is favored (IIIa versus IIIb, and IIIn versus IIIo) or disfavored (IIIr *vs.* IIIs) by an alkyl at the N-atom ($R^1 = Me$). This different effect might be due to a change of the rate-determining-step of the reaction;

Table 3

New Benzylsulphonamides I

Compound	R^1	R^2	Yield (%)	Mp [a] (°C)	Calcd. % (Found) C	H	N	S
Id	*i*-Pr	H	86	101-102 (Pr^{i}OH)	56.31 (56.30	7.09 7.34	6.57 6.30	15.03 14.70)
Ik	H	*m*-AcNH	53	189-190 (MeOH)	47.36 (47.60	5.30 5.55	12.27 12.13	14.05 14.29)
Ip	H	*p*-CO_2Me	95	145-146 (MeOH)	47.15 (47.42	4.84 5.02	6.11 6.12	13.99 13.98)
Iq	H	*p*-CO_2H	96	274-275 (EtOH)	44.64 (44.62	4.22 4.50	6.51 6.62	14.90 15.05)
Iv [b]	H	*p*-$CONH_2$	47	243-244 (MeOH)	44.85 (45.12	4.70 5.00	13.08 13.37	14.97 14.91)

[a] Crystallization solvent in parentheses. [b] This benzylsulphonamide, an intermediate for the preparation of Iq, was not used in cyclization reactions.

the electron-donor alkyl group favors the formation of VIII but it disfavors the final cyclization to III.

EXPERIMENTAL

Melting points, determined in sealed capillaries, were not corrected; stirring was done magnetically and the extracts were dried (magnesium sulphate) and evaporated *in vacuo*. Analysis of crude products and column chromatography (silica gel 230-400 mesh or alumina, neutral, activity II) was done by thin layer chromatography (tlc) on silica gel or alumina (HF_{254}). The microanalyses were performed by UMYMFOR (University of Buenos Aires). The ir spectra (nujol) were recorded on a Perkin-Elmer 337E spectrometer. The pmr spectra were run on Varian EM-360A (LEA, University of San Luis), Bruker WP80 Sy (IQUIOS, University of Rosario), and Varian A60 spectrometers; δ in ppm relative to tetramethylsilane. The ms were taken at 70 eV (direct insertion) on Varian-MAT 112S (LEA) or Finnigan-MAT 8230 spectrometers (Department of Chemistry, Dortmund University, Germany).

Acids and acid anhydrides used in the cyclization reactions were of reagent grade; the latter compounds were distilled [10]. The reagent grade 1,2-dichloroethane was distilled and stored over 4 Å molecular sieves. Reagent grade aldehydes (II) or their polymeric precursors were used as such or after purification. Dimethoxymethane [11] was treated with sodium and distilled. Paraldehyde and benzaldehyde [12] were washed with aqueous sodium bicarbonate and sodium carbonate respectively, dried, and distilled. Trichloroacetaldehyde was prepared from its hydrate as described [13].

Benzylsulphonamides I (Tables 3 and 4).

These were usually prepared by a classical route [14] starting from benzyl halides and *via* the intermediate sodium benzylsulphonates and benzylsulphonyl chlorides. The benzyl halides were of commercial origin or they were obtained from the corresponding toluene derivatives by side-chain bromination with 1,3-dibromo-5,5-dimethylhydantoin [15]. Reaction [16] of the benzyl halides with aqueous sodium sulphite (10% excess) gave the sodium benzylsulphonates which were dried at 120° until no ir-absorption in the 3500 cm^{-1} region. For the new sodium *p*-carboxybenzylsulphonate double amount of sodium sulphite was used and, after reaction completion, the resulting solution was cooled and acidified to Congo Red to precipitate the crude product (100% yield) which was crystallized from 85% alcohol; ir: 1685 cm^{-1} (C=O).

Anal. Calcd. for $C_8H_7NaO_5S$: C, 40.34; H, 2.96; S, 13.46. Found: C, 40.37; H, 3.12; S, 13.70.

Treatment [16,17] of the sodium benzylsulphonates with phosphorus pentachloride (10% excess; for R^2 = *p*-CO_2H, 120% excess) and subsequent work-up led to the crude benzylsulphonyl chlorides which were used as such (R^2 = *o*-Cl, *m*-Cl, *m*-Me, *p*-ClCO from *p*-CO_2H) or after crystallization (R^2 = H, *p*-Cl, *m*-O_2N, *p*-O_2N). Reaction [14] of these chlorides in benzene-chloroform with aqueous ammonia or with a primary amine gave compounds I; the *p*-chlorocarbonylbenzylsulphonyl chloride furnished the diamide Iv (R^1 = H, R^2 = *p*-$CONH_2$).

A mixture of Iv (R^1 = H, R^2 = *p*-$CONH_2$, 10 mmoles) and 3*N* aqueous sodium hydroxide (15 ml) was heated at 80° for 24 hours; by acidification to Congo Red, crude Iq (R^1 = H, R^2 = *p*-CO_2H) was precipitated. The latter (3 mmoles), methanol (20 ml), and concentrated sulphuric acid (0.5 ml) were heated at 65° for 24 hours under exclusion of moisture; upon cooling, crystallized Ip out (R^1 = H, R^2 = *p*-CO_2Me) which was washed with methanol, 5% aqueous sodium bicarbonate, and water.

A mixture of I (R^1 = H, R^2 = *m*-O_2N, 15 mmoles), acetic acid (160 ml), acetic anhydride (16 mmoles), and 5% palladium-charcoal (160 mg) was hydrogenated [18] at 2 atmospheres (room temperature) in a Parr apparatus until the absorption of hydrogen ceased (1 hour); after centrifuging the supernatant solution was evaporated to give crude Ik (R^1 = H, R^2 = *m*-AcNH).

Known and new compounds I were crystallized to constant mp and they showed pmr spectra agreeing with their structures. The known Ij (R^1 = H, R^2 = *m*-Me, mp 163-164°) and Il (R^1 = H, R^2 = *o*-Cl, mp 108-109°) gave mps about 20° higher than those reported [19]; both were analyzed for C, H, and N, giving results within ± 0.3 of the calculated values.

Cyclization of Benzylsulphonamides I to 3,4-Dihydro-1*H*-2,3-benzothiazine 2,2-Dioxides III.

The reactions were performed at 35° in a Teflon stoppered reaction-tube with exclusion of moisture, and stirring during all the reaction period; 1 mmole each of I and the aldehyde II (or 1 equivalent of a precursor) were used. The following procedures were employed and the crude products were purified to consant mp. The results are summarized in Tables 1 and 2; spectral data of new products are given in Table 4.

Table 4

Spectral Data of New Benzylsulphonamides I and Reaction Products III-VII

Compound [a,b]	IR (nujol cm^{-1} [c] NH	SO_2	PMR δ [d,e]
Id	3280	1300; 1115	1.25 (d, 6H, gem-Me_2), 3.56 (m, 1H, CH), 4.40 (s, 2H, SCH_2), 7.29 (s, 5H, Ph)
Ik	3350; 3290; 3150	1315; 1150	2.05 (s, 3H, Me), 4.23 (s, 2H, SCH_2), 6.86 (s, 2H, NH_2), 7.0-7.76 (m, 4H, ArH), 10.02 (s, 1H, CNH)
Ip	3320; 3230	1345; 1140	3.87 (s, 3H, OMe), 4.35 (s, 2H, SCH_2), 6.92 (s, 2H, NH_2), 7.53 and 7.99 (two d, 2H each, ArH)
Iq	3330; 3230	1325; 1130	4.37 (s, 2H, SCH_2), 6.92 (s, 2H, NH_2), 7.51 and 7.97 (two d, 2H each, ArH), 13.1 (br , 1H, CO_2H)
Iv	[f]	1325; 1135	4.33 (s, 2H, SCH_2), 6.86 (s, 2H, SNH_2), 7.43 and 7.89 (two d, 6H, CNH_2 and ArH)
IIIb		1340; 1135	2.84 (s, 3H, Me), 4.30 (s, 2H, SCH_2), 4.54 (s, 2H, NCH_2), 7.0-7.4 (m, 4H, ArH)
IIId		1320; 1130	1.27 (d, 6H, gem-Me), 4.22-4.7 (m, CH) partially overlapped with 4.46 (s, SCH_2) and 4.61 (s, NCH_2) (total area 5H), 6.93-7.43 (m, 4H, ArH)
IIIf		1350; 1155	4.42 (s, 2H, SCH_2), 4.53 (br s, 4H, H_2CNCH_2), 7.0-7.35 (m, 9H, ArH)
IIIh		1355; 1140	4.61 (s, 2H, SCH_2), 5.11 (s, 2H, NCH_2), 7.08-7.62 (m, 8H, ArH)
IIIi		1345; 1165	4.30 (s, 2H, SCH_2), 5.13 (s, 2H, NCH_2), 7.0-7.56 (m, 6H, ArH), 8.17 (d, 2H, ArH *ortho* to NO_2)
IIIj	3275	1325; 1130	4.20 (s, 2H, SCH_2), 4.47 (s, 3H, NCH_2 overlapped in the base with NH), 6.81 (s, 1H, ArH-8), 7.00 (s, 2H, ArH-5 and H-6)
IIIk	3335; 3180	1320; 1125	2.02 (d, 3H, Me), 4.32 and 4.36 (s, and d, [g], partially overlapped, 4H, SCH_2 and NCH_2), 7.10 (d, 1H, ArH), 9.92 (s, 1H, OCNH), 7.20-7.50 (m, 3H, SNH and ArH)
IIIℓ	3285	1320; 1130	4.30 (s, 2H, SCH_2), 4.61 (distorted d, 2H, NCH_2), 6.50 (br s, 1H, NH), 7.23-7.50 (m, 3H, ArH)
IIIm [h]	3260	1350; 1125	4.50 (s, 2H, SCH_2), 4.68 (s, 2H, NCH_2), 6.93-7.44 (m, 3H, ArH)
IIIn	3270	1320; 1135	4.28 (s, 2H, SCH_2),4.40-5.05 (m, 3H, NCH_2 and NH [i]), 6.85-7.43 (m, 3H, ArH)
IIIo		1350; 1135	2.87 (s, 3H, NMe), 4.23 (s, 2H, SCH_2), 4.48 (s, 2H, NCH_2), 6.87-7.40 (m, 3H, ArH)
IIIp	3240	1320; 1130	4.07 (s, 3H, OMe), 4.60 (s, 2H, SCH_2), 4.76 (s, 2H, NCH_2), 7.27 (d, 1H, ArH-8), 8.00 (s, ArH-5) partially overlapped with 8.06 (d, ArH-7) (total area 2H)
IIIr	3230	1320; 1130	4.51 (s, 2H, SCH_2), 4.75 (d, 2H, NCH_2), 6.62 (br s, 1H, NH), 7.48 (d, 1H, ArH-8), 8.0-8.23 (m, 2H, ArH-5 and H-7)
IIIs		1340; 1160	2.92 (s, 3H, NMe), 4.38 (s, 2H, SCH_2), 4.64 (s, 2H, NCH_2), 7.30 (d, 1H, ArH-8), 8.09 (s, ArH-5) partially overlapped with 8.14 (d, ArH-7) (total area 2H)
IIIt	3240	1310; 1155	4.14 and 4.84 (two d, 1H each, SCH_2), 5.22 (s, 1H, Cl_3CCH), 5.68 (br s, 1H, NH), 7.00-7.90 (m, 4H, ArH)
IIIu	3310	1335; 1130	4.46 and 4.65 (two d, 1H each, SCH_2), 6.01 (d, 1H, NCH), 6.64-7.0 (m, 2H, ArH-5 and NH), 7.10-7.40 (m, 3H, ArH-6, H-7 and H-8), 7.73 (d, 2H, ArH *meta* to NO_2), 8.25 (d, 2H, ArH *ortho* to NO_2)

Table 4

(continued)

Compound [a,b]	IR (nujol cm^{-1}) [c] NH	SO_2	PMR δ [d,e]
IVℓ		1340; 1140	4.73 (s, 6H, SCH_2), 4.92 (s, 6H, NCH_2), 7.25-7.65 (m, 12H, ArH)
IVn		1340; 1155	4.56 (s, 6H, SCH_2), 4.95 (s, 6H, NCH_2), 7.46 (s, 12H, ArH)
IVp		1330; 1140	4.08 (s, 9H, OMe), 4.60 and 4.92 (two s, overlapped in the base, 6H each, SCH_2 and NCH_2), 7.54 (d, 6H, ArH), 8.16 (d, 6H, ArH *ortho* to CO_2Me)
IVq		1345; 1140	4.69 and 4.87 (two s, overlapped in the base, 6H each, SCH_2 and NCH_2), 7.48 (d, 6H, ArH), 8.02 (d, 6H, ArH *ortho* to CO_2H)
IVr		1355; 1140	4.78 (s, 6H, SCH_2), 4.89 (s, 6H, NCH_2), 7.62 (d, 6H, ArH), 8.26 (d, 6H, ArH *ortho* to NO_2)
Va		1345; 1130	4.55 (s, 4H, SCH_2), 4.63 and 4.67 (two s, 6H, NCH_2N and two NCH_2), 7.0-7.4 (m, 8H, ArH)
Vr		1340; 1140	4.67 (s, 4H, SCH_2), 4.92 and 4.96 (two s, overlapped in the base, 6H, NCH_2N and two Ar-CH_2N), 7.30-7.66 (m, 2H, ArH), 8.03-8.38 (m, 4H, ArH *ortho* to NO_2)
VIs		1330; 1145	2.87 (s, 6H, NMe), 4.33 (s, 2H, NCH_2N), 4.60 (s, 4H, SCH_2), 7.73 (d, 4H, ArH), 8.28 (d, 4H, ArH *ortho* to NO_2)
VIt	3270; 3200	1340; 1150	4.60 (s, 4H, SCH_2), 5.87 (br s, 1H, Cl_3CCH), 7.23-7.62 (m, 10H, ArH)

[a] For R^1, R^2 and R^3, see Tables 1-3. [b] Molecular weights of IIIb,f,j,n,r,u were determined by low resolution ms. [c] ν C=O: Ik, 1670; Ip, 1710; Iq, 1690; IIIk, 1660; IIIp, 1720; IVp, 1725; IVq, 1685. [d] Measured in trifluoroacetic acid (Id; IIId,f,h,m,p; IVp), DMSO-d_6 (Ik,p,q,v; IIIk; IVℓ,q,r; Va), deuteriochloroform (IIIb,i,j,n,o,s,t) and acetone-d_6 (IIIℓ,r,u; IVn; Vr; VIs,t). [e] NH and OH signals removed by deuterium oxide. [f] Several bands in the range 3390-3190 cm^{-1}. [g] After deuterium oxide, 4.35 (s). [h] The presence of a 1,2,4-trisubstituted benzene ring is supported by the ir (15 mg in 125 mg potassium bromide) absorption pattern in the range 2000-1650 cm^{-1} compared with those of IIIn and IIIℓ. [i] After deuterium oxide, 4.55 (s, 2H).

Procedure A.

To a solution or suspension of the reactants I and II in 1,2-dichloroethane (3.6 ml) were successively added with an interval of 15 minutes, methanesulphonic acid (0.4 ml) and acetic anhydride (1 mmole to remove the water formed). After 4 hours the mixture was cooled at 0°, diluted with chloroform (2-4 ml), washed with ice-water (2 × 5 ml) and 5% aqueous sodium bicarbonate (2 × 5 ml); the organic phase was dried and evaporated to give the crude product.

Procedure B.

To a solution or suspension of I in methanesulphonic acid (3 ml), a solution of II in trifluoroacetic acid (1 ml) was added dropwise. After 30 minutes the mixture was cooled at 0° and poured onto ice (20 g) and chloroform (10-20 ml); the organic phase was treated as in procedure A.

Procedure C.

To a solution of I in methanesulphonic acid (3.75 ml) were successively added trifluoromethanesulphonic anhydride (1 mmole) and a solution of II in 1,2-dichloroethane (0.25 ml); when paraformaldehyde was used, it was added as such after the solvent. After 3 hours the mixture was worked up as in procedure B.

Procedure D.

To a mixture of I, II, and 1,2-dichloroethane (3 ml) were successively added trifluoromethanesulphonic acid (1 ml) and its anhydride (1 mmole). After 3 hours the mixture was worked up as in procedure B.

Kinetic (IVa, R^2 = H) and Thermodynamic (IIIa, R^1 = R^2 = R^3 = H) Products from Benzylsulphonamide (Ia, R^1 = R^2 = H). Conversion of IVa into IIIa.

The experiments were run under exclusion of moisture.

The reaction of Ia (1 mmole) and *s*-trioxane (0.33 mmole) in acetic acid-methanesulphonic acid (4:1, 1.25 ml) at 35° was performed as described earlier [20] but reducing the reaction time to 2 minutes; the yield of 1,3,5-tris(benzylsulphonyl)hexahydro-1,3,5-triazine (IVa, R^2 = H), identified by mixed mp and ir, was increased to 54%.

The same reaction was performed extending the reaction time to 3 hours. After cooling, the mixture was added dropwise to ice (10 g) and chloroform (10 ml); the organic phase was washed with ice-water (5 ml) and 5% aqueous sodium bicarbonate (2 × 5 ml), dried, and evaporated. Crystallization from ethyl acetate gave 66% of 3,4-dihydro-1*H*-2,3-benzothiazine 2,2-dioxide (IIIa), mp 142-143° (ref [6], mp 142°); pmr (trifluoroacetic acid): δ 4.48 and 4.67 (two s, 2H each, two CH_2), 6.9-7.5 (m, 4H, ArH); ms: 183 (M^+).

Finely powdered trimer IVa (183 mg, 0.33 mmole) was vigorously stirred in a mixture of 100% acetic acid (0.25 ml) and methanesulphonic acid (1 ml) at 35° for 6 hours; the initially milky mixture became a clear liquid with some crystals in suspension. Work-up as in the preceding experiment furnished 74% yield of IIIa (ir) which after crystallization from ethyl acetate gave mp 142-143°, undepressed by admixture with the above sample of IIIa.

Cyclization of *N*-(*p*-Nitrobenzylidene)benzylsulphonamide (VIIb, R^2 = H, R^3 = p-$O_2NC_6H_4$).

The starting compound [21] was prepared by a general method [22] and it was crystallized from ethyl acetate (mp 174-176°, 66% yield).

Compound VIIb (1 mmole) was subjected to procedure C given above for the cyclization of benzylsulphonamides omitting the addition of aldehyde. Column chromatography of the crude product on silica gel using chloroform-alcohol 49:1 and 19:1 as eluants, gave the following com-

pounds: *p*-nitrobenzaldehyde, identified by mp and mixed mp (32%), benzothiazine (IIIu), crystallized from ethyl acetate (46%), mp 215-216°, undepressed by admixture with IIIu prepared from *p*-nitrobenzaldehyde (Table 2), benzylsulphonamide (Ia) identified by mp and mixed mp (18%).

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