Intramolecular Sulphonamidomethylation. Part II [1,2]. Fused Heterocycles from 2-Phenylethanesulphonamides

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1,2,4,5-Tetrahydro-3,2-benzothiazepine 3,3-dioxides **2**, with a variety of substituents on the nitrogen atom, can be easily obtained by the title reaction. The isomeric compounds **4-6** are also formed from sulphonamides bearing an *N*-aralkyl group with a chain of two or more carbon atoms. Activation of the ring closure-position or deactivation of the aromatic ring in the substituent can direct the reaction to give compounds **2**. Cyclization results are influenced by the size of the new heterocycle ring and by the predominant formation of derivatives with the SO_2 group outside the ring.

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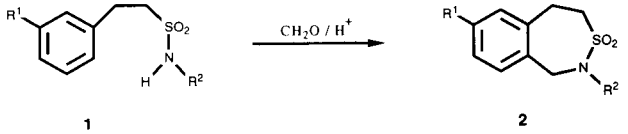
In a previous paper [1] we examined the cyclization of benzylsulphonamides with aldehydes in acid media through an intramolecular sulphonamidomethylation. Several derivatives of 3,4-dihydro-1*H*-2,3-benzothiazine 2,2-dioxide were obtained in good yields. It seemed interesting to know the applicability of the reaction on 2-phenylethanesulphonamides in order to obtain the homologues cyclic compounds, the 3,2-benzothiazepine 3,3-dioxides. Only two derivatives with this skeleton were reported in the literature; the 1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxide was described in our preliminary communication [1] and the 1-ethoxy-2,4,5-trihydro-3,2-benzothiazepine 3,3-dioxide which was obtained [5] in a poor yield by a synthesis with several steps.

We now examine the cyclization of the 2-phenylethanesulphonamide (**1a**, $R^1 = R^2 = H$) and its *N*-monosubstituted derivatives where R^2 on the nitrogen is an alkyl, aralkyl or functionalized group; only one example, (**1h**, $R^1 = MeO$, $R^2 = PhCH_2CH_2$) bears a nuclear substituent (Tables 1 and 2). Formaldehyde is formed from *s*-trioxane and the reaction media A and B were already used [1].

Scheme



1 **2**

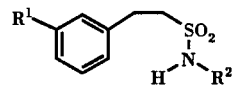
The cyclizations (Tables 3 and 4) of substrates with $R^2 = H$ or an alkyl group gave the correspondent compound **2** (Scheme) in high yields and steric effect of the group as in **1d** ($R^2 = Me_3CCH_2$) does not influence the results. The cyclizations were also successful when there was a substituent with an ester **1n** ($R^2 = EtO_2C$) and **1o** ($R^2 = EtO_2CCH_2$), with a ketone **1p** ($R^2 = PhCOCH_2$) or with an alcohol **1q** ($R^2 = HOCH_2CH_2$) function.

On the other hand, acyl groups do not withstand the reaction conditions. From **1s** ($R^1 = H$, $R^2 = MeCO$), the cyclization by procedure A gave the deacetylated product **2a** ($R^1 = R^2 = H$) in 64% yield. By procedure B, **2s** ($R^1 = H$, $R^2 = MeCO$) was obtained though only with low yield. However, it was proved that its formation was due to the presence of acetic anhydride in the reaction medium; by excluding the anhydride, the cyclization product was again **2a** ($R^1 = R^2 = H$). The cyclization of **1t** ($R^1 = H$, $R^2 = PhCO$) also failed to give **2t** ($R^1 = H$, $R^2 = PhCO$), whether by procedure A or B.

On the basis of our cyclization results [6] of sulphonamides with a deactivated aromatic ring, we expected the formation of heterocycles **2** and/or *N*-sulphonyl heterocycles **3-7** using substrates with an aralkyl group as *N*-substituent. The structure of the cyclization products depends on the length of the substituent alkyl chain and on the substitution on the two aromatic rings of the sulphonamide. Thus for the *N*-benzyl derivative **1f** ($R^1 = H$, $R^2 = PhCH_2$), **2f** ($R^1 = H$, $R^2 = PhCH_2$) was isolated in 73% yield whereas the isoindoline **3** could not be detected. The formation of the latter requires a 5-*endo-trig* cyclization, a disfavoured process according to the Baldwin rules [7]. On the contrary, when the *N*-substituent of the sulphonamide is the phenylethyl group as in **1g** ($R^1 = H$, $R^2 = PhCH_2CH_2$) the product was compound **4g** ($R^1 = R^3 = H$), isolated in high yield (90%); in this case ring closure to **4g** is a favourable 6-*endo-trig* process. However, cyclization of these *N*-aralkyl sulphonamides could be oriented to give compounds **2** by two ways. In one case, ring closure position in the reactant was activated by an appropriate nuclear substituent. Thus, **1h** ($R^1 = MeO$, $R^2 = PhCH_2CH_2$), bearing a methoxy group *para* to that position, afforded **2h** ($R^1 = MeO$, $R^2 = PhCH_2CH_2$) in 58% yield. On the other hand, cyclization to compounds **4** was reduced or avoided by introducing a deactivating group on the aromatic ring of the *N*-substituent. Starting from **1l** ($R^1 = H$, $R^2 = p\text{-}ClC_6H_4CH_2CH_2$), the cyclic **4l** ($R^1 = H$, $R^3 = Cl$) was obtained in a reduced yield (65%) and from **1m** ($R^1 =$

Table 1

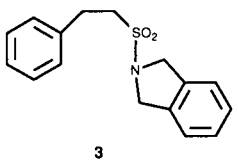
New 2-Phenylethanesulphonamides **1**



Compound	R^2 [a]	Yield %	Mp, °C [b]	Molecular Formula	Calculated % (Found) C	H	N	S
1b	Me	82	66-67 (i-Pr_2O)	$C_9H_{13}NO_2S$	54.26 (54.20	6.58 6.76	7.03 7.22	16.07 15.85)
1c	$Me(CH_2)_5$	99	78-79 (EtOH 80°)	$C_{14}H_{23}NO_2S$	62.42 (62.49	8.60 8.66	5.20 5.44	11.90 11.63)
1d	Me_3CCH_2	92	107-108 (EtOH 80°)	$C_{13}H_{21}NO_2S$	61.14 (61.18	8.29 8.41	5.48 5.63	12.56 12.44)
1e	Cyclohexyl	93	84-85 (i-Pr_2O)	$C_{14}H_{21}NO_2S$	62.89 (62.66	7.92 8.14	5.24 5.31	11.99 11.75)
1f	$PhCH_2$	75	137-138 (EtOAc)	$C_{15}H_{17}NO_2S$	65.44 (65.46	6.22 6.23	5.09 5.16	11.62 11.35)
1g	$Ph(CH_2)_2$	87	57-58 (EtOH)	$C_{16}H_{19}NO_2S$	66.42 (66.37	6.62 6.90	4.84 5.10	11.06 11.12)
1h [a]	$Ph(CH_2)_2$	63	69-70 (MeOH)	$C_{17}H_{21}NO_3S$	63.92 (63.98	6.63 6.53	4.38 4.68	10.04 9.97)
1i	$Ph(CH_2)_3$	99	80-81 (EtOH 60°)	$C_{17}H_{21}NO_2S$	67.29 (67.31	6.98 7.16	4.62 4.44	10.57 10.68)
1j	$Ph(CH_2)_4$	99	75-76 (i-PrOH)	$C_{18}H_{23}NO_2S$	68.11 (68.19	7.30 7.39	4.41 4.50	10.10 9.95)
1k	$Ph(CH_2)_5$	70	80-80.5 (EtOH)	$C_{19}H_{25}NO_2S$	68.85 (68.95	7.60 7.51	4.23 4.46	9.67 9.62)
1l [c]	p-$ClC_6H_4(CH_2)_2$	95	86-87 (EtOH)	$C_{16}H_{18}ClNO_2S$	59.34 (59.57	5.60 5.86	4.33 4.40	9.90 10.04)
1m	p-$O_2NC_6H_4(CH_2)_2$	80	99-100 (MeOH)	$C_{16}H_{18}N_2O_4S$	57.47 (57.21	5.42 5.61	8.38 8.20	9.59 9.47)
1n	EtO_2C	95	61-62 (CCl_4)	$C_{11}H_{15}NO_4S$	51.35 (51.51	5.88 5.87	5.44 5.58	12.46 12.22)
1o	EtO_2CCH_2	51	63-64 (i-Pr_2O)	$C_{12}H_{17}NO_4S$	53.12 (52.93	6.31 6.02	5.16 5.32	11.82 11.65)
1p	$PhCOCH_2$	49	103-104 (EtOAc)	$C_{16}H_{17}NO_3S$	63.34 (63.16	5.65 5.88	4.62 4.67	10.57 10.32)
1q	$HO(CH_2)_2$	52	[d]	$C_{10}H_{15}NO_3S$	52.38 (52.15	6.59 6.88	6.11 6.05	13.98 14.08)
1r	p-$MeC_6H_4SO_2$	79	98-99 (CCl_4)	$C_{15}H_{17}NO_4S_2$	53.08 (53.09	5.05 4.86	4.13 4.21	18.89 18.70)
1s	MeCO	92	75-76 (PhH)	$C_{10}H_{13}NO_3S$	52.85 (52.76	5.76 5.79	6.16 6.30	14.11 14.12)
1t	PhCO	80	112-113 (EtOH)	$C_{15}H_{15}NO_3S$	62.27 (62.41	5.22 5.35	4.84 4.86	11.08 11.20)

[a] R^1 = H except **1h**, R^1 = MeO. [b] Crystallization solvent in parentheses. [c] Cl% 10.95, (11.24). [d] Bp 150°/10^{-3} mm Hg.

H, R^2 = p-$O_2NC_6H_4CH_2CH_2$), only **2m** (R^1 = H, R^2 = p-$O_2NC_6H_4CH_2CH_2$), was produced (95% yield).



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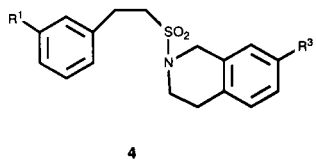

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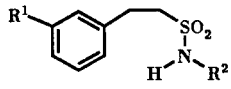
Cyclization of **1i** (R^1 = H, R^2 = $PhCH_2CH_2CH_2$), could anticipate the formation of two heterocycles, **2i** (R^1 = H, R^2 = $PhCH_2CH_2CH_2$) and **5**, both of them with a new seven members ring. Nevertheless, high yield (81%) of **5** indicated the preferred formation of a ring bearing the SO_2 group exocyclic to it. This preference might be ascribed to unfavourable interactions between S-O and C-H bonds when the SO_2 group is part of the ring.

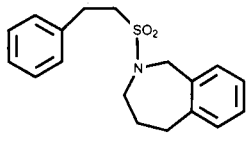
Table 2

Spectral Data of New 2-Phenylethanesulphonamides **1**



Compound	R^2 [a]	IR cm^{-1} [b] NH	CO	SO_2	^{1}H-NMR δ [c]
1b	Me	3260		1305 1145	2.70 (3H, d, NMe), 3.18 (4H, m, $S(CH_2)_2$), 4.55 (1H, c, NH), 7.25 (5H, s, ArH)
1c	$Me(CH_2)_5$	3265		1305 1120	0.85 (3H, t, Me), 1.28 (8H, s, $C(CH_2)_4$), 2.67-3.55 (6H, m, NCH_2 + $S(CH_2)_2$), 4.26 (1H, t, NH), 7.23 (5H, s, ArH)
1d	Me_3CCH_2	3270		1315 1145	0.85 (9H, s, Me), 2.70 (2H, d, NCH_2), 3.00-3.55 (4H, m, $S(CH_2)_2$), 4.27 (1H, t, NH), 7.27 (5H, s, ArH)
1e	Cyclohexyl	3250		1305 1145	0.9-2.1 (11H, m, C_6H_{11}), 3.00-3.55 (4H, s, $S(CH_2)_2$), 4.40 (1H, d, NH), 7.26 (5H, s, ArH)
1f	$PhCH_2$	3270		1300 1145	3.07 (4H, m, $S(CH_2)_2$), 4.17 (2H, d, NCH_2), 4.80 (1H, t, NH), 7.25 (10H, m, ArH)
1g	$Ph(CH_2)_2$	3240		1310 1125	3.07 (8H, m, $S(CH_2)_2$ + $N(CH_2)_2$), 4.33 (1H, t, NH), 7.18 (10H, m, ArH)
1h [a]	$Ph(CH_2)_2$	3255		1315 1125	2.60-3.50 (8H, m, $N(CH_2)_2$ + $S(CH_2)_2$), 3.76 (3H, s, MeO), 4.17 (1H, t, NH), 6.69-6.9 (3H, d, ArH), 7.0-7.4 (6H, m, ArH)
1i	$Ph(CH_2)_3$	3270		1300 1125	1.76 (2H, c, $NCCH_2C$). 2.40-3.40 (8H, m, NCH_2 + NC_2CH_2 + $S(CH_2)_2$), 4.38 (1H, t, NH), 7.20 (5H, s, ArH), 7.23 (5H, s, ArH)
1j	$Ph(CH_2)_4$	3265		1310 1135	1.18-1.92 (4H, m, $NC(CH_2)_2C$), 2.57 (2H, t, NC_3CH_2), 2.8-3.4 (6H, m, NCH_2 + $S(CH_2)_2$), 4.26 (1H, t, NH), 7.20 (5H, s, ArH), 7.25 (5H, s, ArH)
1k	$Ph(CH_2)_5$	3250		1310 1135	1.49 (6H, m, $C(CH_2)_3C$), 2.71 (2H, m, NCH_2), 3.31 (6H, m, $S(CH_2)_2$ + $ArCH_2$), 4.02 (1H, t, NH), 7.29 (10H, m, ArH)
1l	p-$ClC_6H_4(CH_2)_2$	3300		1320 1125	2.93-3.50 (6H, m, NCH_2 + $S(CH_2)_2$), 2.73 (2H, t, $NCCH_2$), 4.35 (1H, t, NH), 6.9-7.5 (9H, m, ArH)
1m	p-$O_2NC_6H_4(CH_2)_2$	3270		1340 1135	2.70-3.60 (8H, m, $N(CH_2)_2$ + $S(CH_2)_2$), 4.35 (1H, t, NH), 7.30 (5H, s, ArH), 7.35 (2H, d, ArH), 8.17 (2H, d, ArH o-NO_2)
1n	EtO_2C	3225	1755	1340 1135	1.25 (3H, t, Me), 2.90-3.40 (2H, m, $SCCH_2$), 3.42-3.90 (2H, m, SCH_2), 4.20 (2H, c, OCH_2), 7.25 (5H, s, ArH), 7.55 (1H, s, NH)
1o	EtO_2CCH_2	3310	1740	1310 1125	1.26 (3H, t, Me), 2.88-3.67 (4H, m, $S(CH_2)_2$), 3.90 (2H, d, NCH_2), 4.23 (2H, c, OCH_2), 5.05 (1H, t, NH), 7.25 (5H, s, ArH)
1p	$PhCOCH_2$	3260	1700	1340 1140	2.93-3.67 (4H, m, $S(CH_2)_2$), 4.60 (2H, d, NCH_2), 5.40 (1H, t, NH), 7.26 (5H, s, ArH), 7.35-7.70 (3H, m, ArH), 7.80-8.10 (2H, m, ArH, o-CO)
1q	$HO(CH_2)_2$	3265		1310 1140	2.77-3.53 (6H, m, $S(CH_2)_2$ + NCH_2), 3.71 (4H,t, OCH_2 + OH + NH), 6.87-7.67 (5H, s, ArH)
1r	p-$MeC_6H_4SO_2$	3180		1350 1155	2.40 (3H, s, Me), 2.90-3.40 (2H, m, $SCCH_2$), 3.50-4.00 (2H, m, SCH_2), 7.30 (8H, s, ArH + NH), 7.87 (2H, d, ArH, o-SO_2)
1s	MeCO	3150	1710 1685	1340 1150	1.95 (3H, s, Me), 2.9-3.3 (2H, m, $SCCH_2$), 3.5-3.9 (2H, m, SCH_2), 7.26 (5H, s, ArH), 8.75 (1H, s, NH)
1t	PhCO	3265	1690	1335 1165	2.90-3.30 (2H, m, $SCCH_2$), 3.70-4.10 (2H, m, SCH_2), 7.16 (5H, s, ArH), 7.30-7.90 (5H, m, ArH). 8.95 (1H, s, NH)

[a] R^1 = H except **1h**, R^1 = MeO. [b] In Nujol; ν OH: **1q**, 3260 cm^{-1}. [c] Deuteriochloroform as solvent. NH and OH signals removed by deuterium oxide.



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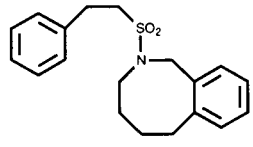

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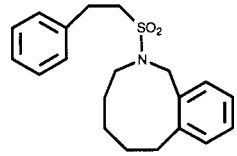

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Table 3

Reaction of Phenylethanesulphonamides **1** with Formaldehyde

Compound [a]	Procedure	Product	Yield %	Mp, °C [b]	Molecular Formula	Calculated % (Found) C	H	N	S
1a	A	**2a**	45	163-164 (MeOH)	$C_9H_{11}NO_2S$	54.80 (55.08	5.62 5.87	7.10 7.38	16.26 16.33)
	B		89						
1b	B	**2b**	78	175-176 (EtOAc)	$C_{10}H_{13}NO_2S$	56.86 (57.10	6.20 6.29	6.63 6.86	15.15 15.17)
1c	B	**2c**	73	45-46 (EtOH 80°)	$C_{15}H_{23}NO_2S$	64.02 (64.01	8.24 8.15	4.98 4.70	11.39 11.20)
1d	B	**2d**	80	119-120 (*i*-Pr_2O)	$C_{14}H_{21}NO_2S$	62.89 (63.16	7.92 8.19	5.24 5.35	11.99 12.19)
1e	B	**2e**	82	159-160 (EtOH)	$C_{15}H_{21}NO_2S$	64.48 (64.40	7.58 7.55	5.01 5.16	11.48 11.37)
1f	A	**2f**	73	138-139 (EtOAc)	$C_{16}H_{17}NO_2S$	66.87 (66.72	5.96 5.77	4.87 5.09	11.16 11.08)
	B	**2f**	12						
		2a	35						
1g	B	**4g** [c]	90	114-115 (EtOAc)	$C_{17}H_{19}NO_2S$	67.74 (67.97	6.35 6.23	4.65 4.36	10.64 10.41)
1h	A [d, e]	**2h**	58	140-141 (EtOH)	$C_{18}H_{21}NO_3S$	65.23 (65.26	6.39 6.54	4.23 4.14	9.67 9.45)
	B	–							
1i	B	**5**	81	103-104 (MeOH)	$C_{18}H_{21}NO_2S$	68.54 (68.38	6.71 6.87	4.44 4.53	10.16 9.90)
1j	A [d,e]	**2j**	28	63-64 (Et_2O)	$C_{19}H_{23}NO_2S$	69.27 (69.03	7.04 6.97	4.25 4.52	9.73 9.52)
		6	24	114-115 (MeOH)	$C_{19}H_{23}NO_2S$	69.27 (69.24	7.04 6.98	4.25 4.09	9.73 10.01)
	B	–							
1k	A [e]	**2k**	20	64-65 (MeOH)	$C_{20}H_{25}NO_2S$	69.94 (70.12	7.34 7.55	4.08 4.23	9.33 9.20)
1l	B [f]	**4l** [c,g]	65	121-122 (MeOH)	$C_{17}H_{18}ClNO_2S$	60.80 (60.53	5.40 5.39	4.17 4.25	9.54 9.32)
1m	A	**2m**	95	160-161 (EtOH)	$C_{17}H_{18}N_2O_4S$	58.95 (58.74	5.24 5.42	8.09 7.98	9.25 9.28)
	B		95						
1n	A [f]	**2n**	31	121-122 (MeOH)	$C_{12}H_{15}NO_4S$	53.52 (53.78	5.61 5.54	5.20 5.19	11.91 11.69)
1o	A	**2o**	70	66-67 (MeOH)	$C_{13}H_{17}NO_4S$	55.11 (55.22	6.05 6.13	4.94 4.70	11.31 11.18)
	B		84						
1p	A	– [h]							
	B	**2p**	66	149-150 (MeOH)	$C_{17}H_{17}NO_3S$	64.74 (64.80	5.43 5.54	4.44 4.35	10.17 10.05)
1q	B	**2q** [i]	68	101-102 (PhH)	$C_{11}H_{15}NO_3S$	54.75 (54.83	6.27 6.45	5.80 5.91	13.29 13.23)
1r	A [f]	**2r**	70	195-196 (EtOAc)	$C_{16}H_{17}NO_4S_2$	54.68 (54.40	4.88 4.82	3.99 4.04	18.24 18.16)

[a] For **1a**, $R^1 = R^2 = H$; for other compounds see Table 1. [b] Cyrstallization solvent in parentheses. [c] **4g**, $R^1 = R^3 = H$; **4l**, $R^1 = H$; $R^3 = Cl$. [d] Procedure A with five fold the volume of dichloromethane. [e] Column chromatography (silica gel) of the crude product before crystallization. [f] The crude pruduct was sublimed *in vacuo* prior to crystallization. [g] Cl% 10.56, (10.79). [h] Analysis (tlc) showed **2p** and unchanged **1p** but no pure derivative could be obtained. [i] The crude cyclization product was the *O*-trifluoroacetyl derivative of **2q**, ν CO: 1785 cm^{-1}, which by hydrolisis with potassium carbonate in aqueous methanol led to **2q**.

Table 4

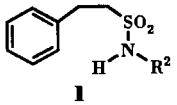
Spectral Data of Reaction Products **2**, **4-6**

Compound [a]	IR cm^{-1} [b] SO_2		^1H-NMR δ [c]
2a	1325	1130	3.22 (4H, s, $S(CH_2)_2$), 4.31(3H, s, NCH_2 + NH), 7.27 (5H, s, ArH)
2b	1330	1155	2.54 (3H, s, NMe), 3.15 (4H, s, $S(CH_2)_2$), 4.42 (2H, br s, NCH_2), 7.27 (5H, s, ArH)
2c	1330	1125	0.93 (3H, t, Me), 1.14-1.87 (8H, m, $C(CH_2)_4C$), 2.80 (2H, br s, NCH_2 exo), 3.16 (4H, br s, $S(CH_2)_2$), 4.40 (2H, s, NCH_2 endo), 7.30 (4H, s, ArH)
2d	1325	1150	0.96 (9H, s, Me), 2.53 (2H, s, NCH_2 exo), 3.16 (4H, s, $S(CH_2)_2$), 4.50 (2H, s, NCH_2 endo), 7.26 (4H, s, ArH)
2e	1320	1130	0.8-1.8 (11H, m, C_6H_{11}), 3.18 (4H, s, $S(CH_2)_2$), 4.36 (2H, s, NCH_2), 7.23 (4H, s, ArH)
2f	1330	1130	3.23 (4H, s, $S(CH_2)_2$), 4.00 (2H, br s, NCH_2 exo), 4.30 (2H, br s, NCH_2 endo), 6.90-7.80 (9H, m, ArH)
4g	1330	1140	2.93 (2H, t, NCH_2), 3.16 (4H, m, $S(CH_2)_2$), 3.60 (2H, t, $ArCH_2$), 4.48 (2H, s, NCH_2), 7.20 (9H, m, ArH)
2h	1330	1145	2.93 (4H, s, $N(CH_2)_2$), 3.10 (4H, s, $S(CH_2)_2$), 3.80 (3H, s, MeO), 4.23 (2H, br s, NCH_2 endo), 6.58-6.90 (2H, m, ArH *o*-MeO), 7.00 (1H, s, ArH, *m*-MeO), 7.23 (5H, s, ArH)
5	1325	1135	1.43-2.05 (2H, m, $NCCH_2C$), 2.70-3.15 (6H, m, $SCCH_2$ + $N(CH_2)_2$), 3.71 (2H, t, SCH_2), 4.48 (2H, s, NCH_2Ar), 6.75-7.42 (9H, m, ArH)
2j	1330	1140	1.60 (4H, m, $C(CH_2)_2C$), 2.64 (4H, m, $ArCH_2$ + NCH_2C), 3.15 (4H, br s, $S(CH_2)_2$), 4.37 (2H, s, NCH_2Ar), 7.22 (9H, m, ArH)
6	1325	1135	1.72 (4H, m, $C(CH_2)_2C$), 2.90 (2H, m, NCH_2C), 3.14 (4H, s, $ArCH_2$), 3.27 (2H, m, SCH_2), 4.52 (2H, s, NCH_2Ar), 7.25 (9H, s, ArH)
2k	1335	1130	1.45-1.59 (6H, m, $C(CH_2)_3C$), 2.50-2.80 (4H, m, $ArCH_2$ + NCH_2), 3.14 (4H, s, $S(CH_2)_2$), 4.40 (2H, br s, NCH_2Ar), 7.20 (9H, s, ArH)
4l	1315	1145	2.85 (2H, t, $SCCH_2$), 3.16 (4H, s, $N(CH_2)_2$), 3.53 (2H, t, SCH_2), 4.40 (2H, s, NCH_2), 7.06 (3H, s, ArH), 7.23 (5H, s, ArH)
2m	1340	1135	3.03 (4H, s, $N(CH_2)_2$), 3.18 (4H, s, $S(CH_2)_2$), 4.30 (2H, br s, NCH_2 endo), 7.00-7.68 (6H, m, ArH), 8.18 (2H, d, ArH *o*-NO_2)
2n	1350	1170	1.18 (3H, t, Me), 3.08-3.67 (4H, m, $S(CH_2)_2$), 4.10 (2H, c, OCH_2), 4.85 (2H, s, NCH_2), 7.30 (4H, s, ArH)
2o	1335	1145	1.20 (3H, t, Me), 3.28 (4H, s, $S(CH_2)_2$), 3.70 (2H, s, NCH_2 exo), 4.05 (2H, c, OCH_2), 4.50 (2H, s, NCH_2 endo), 7.00-7.52 (4H, m, ArH)
2p	1330	1135	3.27 (4H, s, $S(CH_2)_2$), 4.27 (2H, s, NCH_2 endo), 4.53 (2H, s, NCH_2CO), 7.00-7.68 (8H, m, ArH), 7.72-8.12 (2H, m, ArH *o*-CO)
2q	1315	1140	2.24 (1H, br s, OH), 2.97 (2H, t, NCH_2C), 3.18 (4H, s, $S(CH_2)_2$), 3.75 (2H, t, OCH_2), 4.50 (2H, br s, NCH_2Ar), 7.27 (4H, s, ArH)
2r	1360	1155	2.36 (3H, s, Me), 2.80-3.47 (4H, s, $S(CH_2)_2$), 5.00 (2H, s, NCH_2), 7.00-7.70 (8H, m, ArH)

[a] For R^1, R^2, and R^3, see Table 3. [b] In Nujol; ν CO: **2n**, 1740; **2o**, 1730; **2p**, 1680 cm^{-1}; νNH: **2a**, 3260 cm^{-1}; νOH: **2q**, 3520 cm^{-1}. [c] Deuteriochloroform as solvent.

Table 5

Competitive Cyclization Reactions



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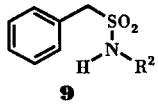

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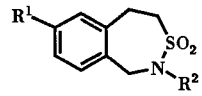
Sulphonamides [a]	Ring Size	Products Substitution on N	Yield [b] %
9a and **1a**	6	H	30
	7	H	30
9b and **1b**	6	Me	51
	7	Me	47
9a and **9b**	6	H	14
	6	Me	43
1a and **1b**	7	H	2.5
	7	Me	47.5

[a] 2-Phenylethanesulphonamide (**1a**, R^2 = H) and its *N*-methyl derivative **1b** (R^2 = Me), benzylsulphonamide (**9a**, R^2 = H) and its *N*-methyl derivative **9b** (R^2 = Me). [b] Of each product in the mixture after column chromatography.

Table 6

N-Substitution of 1,2,4,5-Tetrahydro-3,2-benzothiazepine 3,3-Dioxide (**2a**, $R^1 = R^2 = H$)



Compound [a]	X	Yield % [b]	Mp [c] °C	Molecular Formula	Calculated. % (Found) C	H	N	S	IR cm^{-1} SO_2 [d]	^1H-NMR δ [e]
2b	I	60	172-173 (EtOAc)							
2c	Br	49	45-46 (EtOH 80°)							
2f	Cl	72	138-139 (EtOAc)							
2g	*p*-$MeC_6H_4SO_3$	63	83-84 (MeOH)	$C_{17}H_{19}NO_2S$	67.74 (67.67	6.35 6.59	4.65 4.58	10.64 10.51)	1330 1155	2.93 (4H, s, $N(CH_2)_2$, partially overlapped with the next signal), 3.13 (4H, s, $S(CH_2)_2$), 4.30 (2H, br s, NCH_2Ar), 7.0-7.47 (9H, m, ArH)
2i	Br	92	110-111 (MeOH)	$C_{18}H_{21}NO_2S$	68.54 (68.54	6.71 6.96	4.44 4.18	10.16 10.03)	1330 1155	1.65-2.03 (2H, m, $NCCH_2$), 2.40-3.00 (4H, m, NCH_2CCH_2), 3.15 (4H, s, $S(CH_2)_2$), 4.40 (2H, br s, NCH_2Ar), 6.83-7.48 (9H, m, ArH)
2j	Br	74	62-63 (Et_2O)							
2l [f]	*p*-$MeC_6H_4SO_3$	49	89-90 (EtOH)	$C_{17}H_{18}ClNO_2S$	60.80 (61.06	5.40 5.67	4.17 4.02	9.54 9.66)	1335 1155	2.90 (4H, s, $N(CH_2)_2$, partially overlapped with the next signal), 3.15 (4H, s, $S(CH_2)_2$), 4.30 (2H, br s, NCH_2Ar), 6.90-7.65 (8H, m, ArH)
2m	Br	40	161-162 (EtOH)							
2n	Cl	61	121-122 (MeOH)							
2o	Br	84	66-67 (MeOH)							
2p	Br	89	149-150 (MeOH)							
2r	Cl	75	195-196 (EtOAc)							
2s	$MeCO_2$	67	127-128 (EtOAc)	$C_{11}H_{13}NO_3S$	55.21 (55.50	5.48 5.64	5.85 5.72	13.40 13.29)	1345 1155	2.30 (3H, s, Me), 3.26 (4H, s, $S(CH_2)_2$), 4.83 (2H, s, NCH_2), 7.10-7.67 (4H, m, ArH)
2t	Cl	72	179-180 (EtOAc)	$C_{16}H_{15}NO_3S$	63.77 (64.04	5.02 5.17	4.65 4.50	10.64 10.44)	1315 1160	3.10-3.40 (2H, m, $SCCH_2$), 3.43-3.70 (2H, m, SCH_2), 4.90 (2H, s, NCH_2), 6.40-7.90 (aprox 9H, m, ArH)

[a] For R^1 and R^2, see Table 1. [b] Procedure a) for **2b, c, f, g, i, j, l, m**; procedure b) for **2n-p**. [c] Crystallization solvent in parentheses. [d] In Nujol; ν CO: **2s**, 1690; **2t**, 1690 cm^{-1}. [e] Deuteriochloroform as solvent. [f] Cl% 10.56, (10.83).

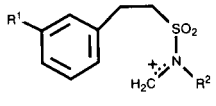
When the *N*-substituent is a 4-phenylbutyl group, as in **1j**, (R^1 = H, R^2 = $PhCH_2CH_2CH_2CH_2$) the reaction product was a mixture of **2j** (R^1 = H, R^2 = $PhCH_2CH_2CH_2CH_2$) and **6**. They were separated by column chromatography prior to crystallization giving 28% and 24% yield respectively. Probably, the expected major stability of the new ring associated to the exocyclic SO_2 group is here compensated by the larger size of that in compound **6**, (eight members), compared with **2j**, (seven members). This effect is more pronounced in the case of **1k** (R^1 = H, R^2 = $PhCH_2CH_2CH_2CH_2CH_2$); only a low yield (20%) of **2k** (R^1 = H, R^2 = $PhCH_2CH_2CH_2CH_2CH_2CH_2$) was obtained without detection of **7** with an unfavourable nine members ring.

Several competitive cyclization reactions were per-

formed in order to determine the easiness of formation of the heterocyclic ring and/or the relative stability of it in 3,4-dihydro-1*H*-2,3-benzothiazine 2,2-dioxide and in 1,2,4,5-tetrahydro-3,2-benzothiazepine 3,3-dioxide and in their *N*-methyl derivatives. The relative products yields (Table 5) were estimated by comparing the areas of the ^1H nmr signals assigned in unambiguously form to each compound.

The competitive cyclization between benzyl- and 2-phenylethanesulphonamides as well as between their *N*-methyl derivatives afforded in each case the two possible products in the same yield, showing a lack of preference for the formation of a particular ring size and a similar stability of both of them.

The competition between benzylsulphonamide and its *N*-methyl derivative, shows that the formation of the *N*-methyl substituted ring is clearly favoured over the unsubstituted one in a relation of 3 to 1. This favourable effect of an *N*-electron donor group on the cyclization may be ascribed to the stabilization of the intermediate electrophylic iminium ion **8**. This effect was even more pro nounced in the comparison of phenylethanesulphonamide and its *N*-methyl derivative. The *N*-methylated ring is favoured over the unsubstituted one in a relation of 19 to 1.



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For identification purposes, several *N*-substituted derivatives were prepared (Table 6) using general methods and starting from the parent benzothiazepine **2a** ($R^1 = R^2 =$ H). Most of compounds **2**,**4** and **6** were thus identified by direct comparison while the structure of **5** was proved by degradation.

EXPERIMENTAL

For general directions, see the preceding paper [1].

2-Phenylethanesulphonamides **1** (Tables 1 and 2).

All the 2-phenylethanesulphonamides are new except the unsubstituted compound, **1a** ($R^1 = R^2 =$ H). *N*-alkyl and *N*-aralkyl derivatives were prepared following general methods [8a] by reaction of 2-phenylethanesulphonyl chloride and the appropriate amine. The latter were pure commercial products or prepared according with the literature. The unknown 2-(*m*-methoxyphenyl)-ethanesulphonyl chloride was not isolated; it was used as a benzene solution of the crude product formed in the reaction of phosphorus pentachloride and *p*-toluidinium 2-(*m*-methoxyphenyl)ethanesulphonate; the latter is new (77% yield), mp 166-167° (from water).

Anal. Calcd. for $C_{16}H_{21}NO_4S$: N, 4.33. Found: N, 4.55.

Other sulphonamides were prepared by general methods in a different way. Compounds **1n** (R^1 = H, $R^2 = EtO_2C$) and **1r** (R^1 = H, $R^2 = p$-$MeC_6H_4SO_2$) were obtained from 2-phenylethanesulphonamide (**1a**) with ethyl chloroformate and tosyl chloride repectively, after refluxing 9 hours in acetone plus potassium carbonate. Acylation of **1a** with acetic anhydride (3 hours at 135°) and benzoyl chloride (in pyridine, 1 hour at 90°) furnished **1s** (R^1 = H, R^2 = MeCO) and **1t** (R^1 = H, R^2 = PhCO) respectively.

The *N*-phenacyl compound **1p** (R^1 = H, $R^2 = PhCOCH_2$) was prepared as described [9] for other examples. The required intermediate *N*-ethoxycarbonyl-*N*-phenacyl-2-phenylethanesulphonamide is new (93% yield), mp 90-91° (from alcohol); ir (Nujol): 1745 (ester C=O), 1700 cm^{-1} (phenacyl C=O), no NH absorption; ^1H nmr (deuteriochloroform): δ 1.23 (3 H, t, J = 7 Hz, CH_3), 3.23 (2 H, m, $C_6H_5CH_2$), 3.8-4.5 (4 H, m, CH_2SO_2 and CH_2CO_2), 5.20 (2 H, s, NCH_2), 7.1-7.7 (8 H, m, ArH), 7.8-8.1 (2 H, m, ArH *ortho* to C=O).

Anal. Calcd. for $C_{19}H_{21}NO_5S$: C, 60.78; H, 5.64; N, 3.73; S, 8.54. Found: C, 61.00; H, 5.72; N, 3.73; S, 8.29.

Reduction of **1o** (R^1 = H, $R^2 = EtO_2CCH_2$) with lithium aluminium hydride in tetrahydrofuran furnished **1q** (R^1 = H, $R^2 = HOCH_2CH_2$).

Reaction of 2-Phenylethanesulphonamides **1** with Formaldehyde (Tables 3 and 4).

The cyclizations were carried out in a tube with a Teflon stopper, at 35° with stirring and exclusion of humidity.

The two reaction media A and B were already detailed in the preceding paper [1]. In procedure A, the substrate **1** reacts with *s*-trioxane (as the formaldehyde source) in methanesulphonic acid and acetic anhydride diluted in 1,2-dichloroethane. The reaction medium of procedure B is a mixture of methanesulphonic and trifluoroacetic acids. Crude products were purified by crystallization directly or after chromatography or sublimation as indicated in Table 3.

Some cyclization derivatives were identified (mp, mixed mp and ir) with authentic samples prepared as described below. Thus, some compounds **2** were compared with the products of *N*-substitution of the benzothiazepine **2a** ($R^1 = R^2 =$ H). Compounds **4** and **6** were similarly identified with the products obtained by a general method [8b] from 1,2,3,4-tetrahydroisoquinoline and 1,2,3,4,5,6-hexahydrobenzazocine respectively. The structure of **5** was showed as follows. According to the literature [10] directions for similar compounds, a mixture of **5** (157 mg, 0.5 mmole), phenol (141 mg, 1.5 mmoles), propionic acid (0.2 ml) and freshly distilled aqueous 48% hydrobromic acid (1 ml) was heated at 128° for 2 hours under nitrogen. The mixture was basified with aqueous sodium hydroxide at room temperature and extracted with benzene; reaction [6] of this extract with *p*-toluenesulphonyl chloride in the presence of triethylamine gave *N*-(*p*-toluenesulphonyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine, mp 137-138°, (alcohol 80%), (lit [11] 135°).

Authentic Samples of Compounds **2**,**4** and **6**.

Using general methods, the sodium derivative of the benzothiazepine **2a** ($R^1 = R^2 =$ H) (reaction with oil dispersion of sodium hydride in anhydrous dimethylformamide; procedure a) or the potassium one (potassium carbonate in anhydrous acetone; procedure b), reacted with the appropriate R^2X(X = halogen; for **2g**, **l**, X = tosyl) to give authentic samples of the *N*-substituted

derivatives of **2a**.

Samples of **2s** (R^1 = H, R^2 = MeCO) and **2t** (R^1 = H, R^2 = PhCO) were obtained by heating a solution of **2a** (R^1 = R^2 = H) in dry pyridine with acetic anhydride and benzoyl chloride respectively during 6 hours at 115°.

Table 6 includes new compounds **2** prepared by this *N*-substitution of **2a**; some of them were not obtained by cyclization of sulphonamides **1**.

Compounds **4g** (R^1 = R^3 = H) and **6** were prepared by a general method [8b]. Reaction of tetrahydroisoquinoline and 2-phenylethanesulphonyl chloride in benzene with addition of triethylamine gave *N*-(2-phenylethanesulphonyl)-1,2,3,4-tetrahydroisoquinoline (**4g**, 42% yield), mp 112-113° (ethyl acetate). Similarly, from hexahydrobenzazocine resulted *N*-(2-phenylethanesulphonyl)-1,2,3,4,5,6-hexahydrobenzazocine (**6**, 71% yield), mp 114-115° (methanol).

Competitive Cyclization Reactions (Table 5).

A solution of *s*-trioxane (9 mg, equivalent to 0.3 mmole of formaldehyde) in trifluoroacetic acid (1 ml) was added to a solution of benzylsulphonamide (**9a**) and 2-phenylethanesulphonamide (**1a**) (1 mmole each) in methanesulphonic acid (3 ml). Following the cyclization procedure B [1], after 30 minutes at 35°, the reaction medium was cooled and added to a mixture of ice (20 g) and chloroform (10 ml). The organic phase was washed with 5% aqueous sodium bicarbonate (1 x 5 ml) and water (1 x 5 ml), dried (magnesium sulphate) and evaporated. The residue was chromatographed (silica gel 230-400 mesh) to separate the products from the unchanged sulphonamides. The analysis by ^{1}H nmr gave the percentages of the cyclization compounds formed.

Competitive reactions between the *N*-methyl derivatives of the above sulphonamides, **9b** and **1b** respectively, between benzylsulphonamide (**9a**) and its *N*-methyl derivative **9b** and between 2-phenylethanesulphonamide (**1a**) and its *N*-methyl derivative **1b** were similarly performed.

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REFERENCES AND NOTES

[1] O. O. Orazi, R. A. Corral and R. Bravo, *J. Heterocyclic Chem.*, **23**, 1701 (1986).

[2] This paper includes the results of the Doctoral Thesis of I. H. S. (Universidad Nacional de La Plata).

[3] Present address: Instituto de Química Orgánica de Síntesis, Universidad Nacional de Rosario, Casilla de Correo 991, (2000) Rosario, Argentina.

[4] Deceased.

[5] H. Bohme and F. Ziegler, *Liebigs Ann. Chem.*, 734 (1974).

[6] O. O. Orazi, R. A. Corral and H. Giaccio, *J. Chem. Soc., Perkin Trans. I*, 1977 (1986).

[7] J. E. Baldwin, R. C. Thomas, L. I. Kruse and L. Silberman, *J. Org. Chem.*, **42**, 3846 (1977) and previous refs cited.

[8a] M. Ouaedvlieg, "Houben-Weyl Methoden der Organischen Chemie", Vol **9**, 4th Ed, E. Müller, ed, G. Thieme Verlag, Stuttgart, 1955, Chapter 14; [b] F. Muth, "Houben-Weyl Methoden der Organischen Chemie", Vol **9**, 4th Ed, E. Müller, ed, G. Thieme Verlag, Stuttgart, 1955, Chapter 19.

[9] W. J. Gensler, F. J. Frank, S. K. Dheer and J. W. Lauher, *J. Org. Chem.*, **36**, 4102 (1971).

[10] J. Bornstein, S. C. Lashua and A. P. Boiselle, *J. Org. Chem.*, **22**, 1255 (1957).

[11] J. von Braun, G. Blessing and R. S. Cahn, *Ber.*, **57**, 908 (1924).