Synthesis of Fused Heterocycles: 1,2,3,4-Tetrahydroisoquinolines and Ring Homologues *via* Sulphonamidomethylation†

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The title heterocycles (3) have been obtained by a two-step synthesis; namely an initial intramolecular sulphonamidomethylation of *N*-aralkylsulphonamides (1) in acid media followed by desulphonylation of compounds (2) under moderate conditions, either by reduction or acid hydrolysis. Generally both steps gave good or high yields of compounds (3) variously substituted in the aromatic ring and with a six-, seven-, or eight-membered heterocyclic ring.

The Pictet-Spengler synthesis [1,2] of fused heterocycles has intramolecular electrophilic aromatic substitution as a final step; the synthesis is useful only when the ring-closure position is activated, *e.g.* by a *p*-methoxy group. An acyl substituent on the nitrogen (acylamidomethylation) [3,4] increases the reactivity of the electrophilic partner allowing the use of substrates with a non-activated aromatic moiety [4] although additional steps are required to introduce and to remove or reduce the acyl portion.

For a general synthesis (Scheme) including substrates with a deactivated aromatic ring, we now use the more electron-attracting sulphonyl group as the *N*-substituent (sulphonyl-amidomethylation); [5] a further key feature is the use of moderate conditions for the efficient removal of the sulphonyl group. A single example of an analogous synthesis (with an activated aromatic ring) has already been described [6] but removal of the sulphonyl group by lithium in liquid ammonia gave only a 29% yield of the tetrahydroisoquinoline; a related route developed by von Braun and others [7,8] starting with *N*-aralkylglycines used vigorous acid hydrolysis to remove the sulphonyl group.

2,2-dioxides [5] by intramolecular electrophilic attack at the phenyl ring of R^2. The cyclisation (procedure B) of (1i—l; $R^1 = H$, $R^2 = p\text{-ClC}_6\text{H}_4\text{CH}_2$) failed or gave mixtures which were difficult to purify; this lead to a low yield of (2j; $R^1 = H$, $R^2 = p\text{-ClC}_6\text{H}_4\text{CH}_2$, $n = 1$). This result indicates that under these conditions the deactivating effect of one chlorine atom is insufficient and, therefore, the group $R^2 = p\text{-ClC}_6\text{H}_4\text{CH}_2$ was abandoned.

The introduction of a second chlorine atom ($R^2 = 3,4\text{-}Cl_2C_6H_3CH_2$) or the use of an alternative R^2-substituent (alkoxycarbonylethyl, *o*-methoxycarbonylphenyl, phenacyl) gave much better results. Cyclisation of sulphonamides with non-activated, activated, and deactivated [*e.g.* (1c), (1e), and (1p) respectively] ring-closure positions were successful for the preparation of compounds (2; $n = 1$—3) with six-, seven-, and eight-membered rings; frequently, the milder procedures A or C furnished higher yields. The structure of the products, supported by analytical and spectral data, was confirmed for (2c, j, m, n, r) by their identity with samples obtained by sulphonylation of 1,2,3,4-tetrahydroisoquinoline.
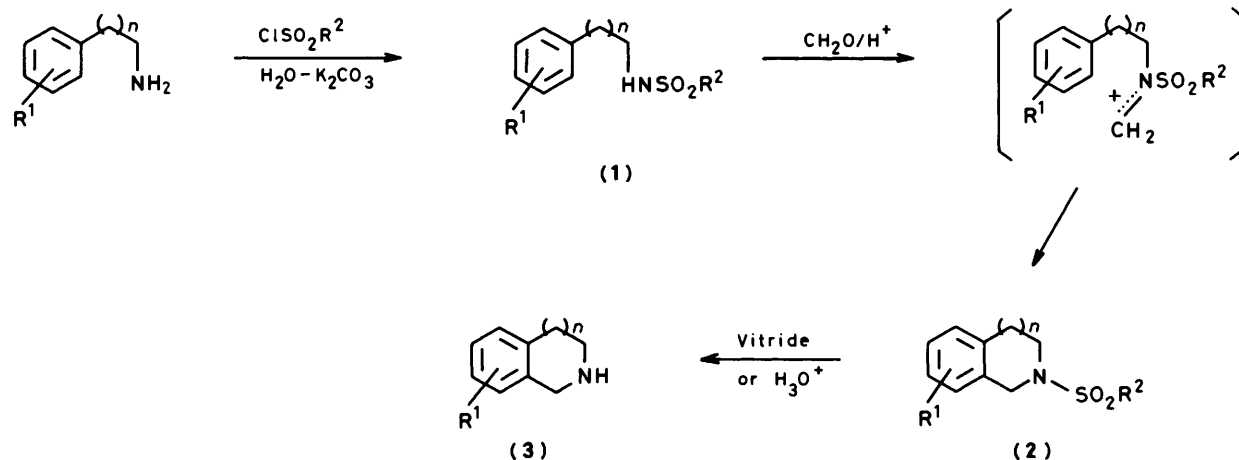
Scheme.

The intramolecular sulphonamidomethylation of compounds (1) with formaldehyde formed from *s*-trioxane was carried out by two procedures of increasing acidity, A and B, and by a third procedure, C, which is a variation of A (Tables 1 and 2).

The sulphonamides (1a—l) bear nuclear chloro substituents at R^2 to avoid cyclisation of 3,4-dihydro-1*H*-2,3-benzothiazines

Products (2; $n = 0, 4$) bearing five- or nine-membered rings were not formed. The difficulties associated with the latter case are well-known; the failure of the sulphonamidomethylation to give a 5-membered ring even in the presence of an activating group (1b; $R^1 = 3\text{-OMe}$) may be justified in terms of the Baldwin rule which states [9] that an *endo-trig* cyclisation is a disfavoured process.

Other authors [6] have carried out similar cyclisations using as a general procedure the reaction of an *N*-phenylethyltosyl amide (1; $n = 1$) with aqueous formaldehyde (slight excess

Table 1. New sulphonamides (1) and N-sulphonyl heterocycles (2; R^2 = 3,4-Cl$_2$C$_6$H$_3$CH$_2$)

Compd.	R^1	n	Cyclisation procedure	Yield (%)	M.p.[a] (°C)	ν_{max} (cm⁻¹)[b] NHSO$_2$	Found (%) (Required) C	H	N	Cl	S
(1a)	H	0		87	140—141	3 280 1 315, 1 142	50.9 (50.9)	4.1 (4.0)	4.3 (4.2)	21.65 (21.5)	9.5 (9.7)
(1b)	3-OMe	0		80	121—123	3 310 1 315, 1 142	50.1 (50.0)	4.35 (4.2)	3.95 (3.9)	19.6 (19.7)	9.1 (8.9)
(1c)	H	1		65	68—69	3 315 1 325, 1 135	52.4 (52.3)	4.55 (4.4)	4.0 (4.1)	20.6 (20.6)	9.3 (9.3)
(2c)	H	1	A B	92 83	191—193	1 335, 1 150	53.9 (53.9)	4.5 (4.2)	4.1 (3.9)	20.1 (19.9)	9.2 (9.0)
(1d)	4-OMe	1		74	98—99	3 230 1 314, 1 148	51.6 (51.35)	4.85 (4.6)	4.0 (3.7)	19.0 (18.9)	8.5 (8.6)
(2d)[c]	7-OMe	1	A B	40[d] 9	138—139	1 335, 1 155	53.0 (52.9)	4.6 (4.4)	3.8 (3.6)	18.6 (18.35)	8.0 (8.3)
(1e)	3,4-(OMe)$_2$	1		77	100—102	3 280 1 314, 1 143	50.6 (50.5)	4.9 (4.7)	3.6 (3.5)	17.6 (17.5)	7.75 (7.9)
(2e)	6,7-(OMe)$_2$	1	A B	80 63	172—173	1 340, 1 140	52.2 (51.9)	4.6 (4.6)	3.6 (3.4)	17.1 (17.0)	7.5 (7.7)
(1f)	H	2		93	112—113	3 250 1 310, 1 128	53.9 (53.6)	4.8 (4.8)	3.9 (3.9)	20.0 (19.8)	8.9 (8.95)
(2f)	H	2	A B	70 68	148—149	1 320, 1 127	55.0 (55.1)	4.8 (4.6)	3.7 (3.8)	19.4 (19.15)	8.7 (8.7)
(1g)	H	e		92	110—111	3 260 1 310, 1 153	54.8 (54.8)	5.2 (5.1)	3.6 (3.7)	19.1 (19.05)	8.3 (8.6)
(2g)	H	e	A B	92 71	137—139	1 325, 1 140	56.0 (56.25)	5.2 (5.0)	3.4 (3.65)	18.5 (18.45)	8.2 (8.3)
(1h)	H	3		89	80—81	3 260 1 325, 1 130	54.7 (54.8)	5.1 (5.1)	3.9 (3.8)	19.0 (19.05)	8.8 (8.6)
(2h)[c]	H	3	A B C	40 — 68	153—155	1 325, 1 140	56.15 (56.25)	5.1 (5.0)	3.75 (3.65)	18.4 (18.45)	8.4 (8.3)

[a] Crystallisation solvent: alcohol for (1a—h) and (2g,h); EtOAc for (2c,e,f); acetone for (2d). [b] In Nujol. [c] Column chromatography (SiO$_2$) before crystallisation. [d] Procedure C: 34%. [e] N-Substituent: 2-methyl-3-phenylpropyl group.

according to the Discussion section and apparently in small deficit in the Experimental section) in chloroform as solvent and a small amount of boron trifluoride–diethyl ether as acid catalyst. It seems to us that these conditions may be insufficient for those examples with a non-activated benzene ring, e.g. N-phenylethyltosylamide (1; R^1 = H, R^2 = p-MeC$_6$H$_4$, n = 1); according to the authors,[6] the latter substrate afforded 95.8% yield of N-tosyl-1,2,3,4-tetrahydroisoquinoline (2; R^1 = H, R^2 = p-MeC$_6$H$_4$, n = 1) when it was subjected to the general procedure. We have repeated this experiment and have obtained different results. With commercial chloroform as solvent and a 5% excess of formaldehyde none of expected compound (2; R^1 = H, R^2 = p-MeC$_6$H$_4$, n = 1) was formed (t.l.c.) and 48% of unchanged starting sulphonamide was recovered. A similar reaction in ethanol-free chloroform, gave negligible recovery of starting sulphonamide together with 10% of the cyclisation product (2; R^1 = H, R^2 = p-MeC$_6$H$_4$, n = 1) and 26% of compound (4) formed by addition of the starting sulphonamide to the intermediate of the reaction. The reaction with a 10% deficit of formaldehyde in commercial chloroform gave the starting sulphonamide (39%) and (4) (15%); compound (2; R^1 = H, R^2 = p-MeC$_6$H$_4$, n = 1) was absent according to t.l.c. On the other hand, reaction of the same sulphonamide with
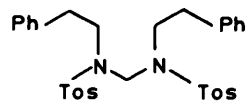
Ph—N(Tos)—CH$_2$—N(Tos)—Ph (4)

Tos = p-MeC$_6$H$_4$SO$_2$

s-trioxane using procedures A or B gave the desired compound (2) in 89 and 85% yields respectively.

For the final desulphonylation (2)→(3) a number of selected compounds (2) were treated with sodium bis(2-methoxyethoxy)-aluminum hydride (Vitride) in benzene at 80 °C in order to remove the 3,4-dichlorobenzylsulphonyl group; this method was previously used[10] for other sulphonamides in refluxing benzene or toluene. The yields of purified products (3) (Table 4) were >50% with the exception of that for [3e; R^1 = 6,7-(OMe)$_2$, n = 1] (36% yield). The latter result may be ascribed to the less facile desulphonylation of the parent compound [2e; R^1 = 6,7-(OMe)$_2$, R^2 = 3,4-Cl$_2$C$_6$H$_3$CH$_2$, n = 1] whose benzylic hydrogens adjacent to the N-atom possess a reduced acidity owing to the p-methoxy substituent; one path for the desulphonylation[11] starts with the abstraction by hydride ion of a proton α to the N-atom. A further limitation of this method may be Vitride attack on substituents (e.g. removal of R^1 = Cl) which prevents its use in the synthesis of (3p) and (3q) (R^1 = 6-Cl and 7-Cl respectively).

The classical acidic or basic hydrolysis of sulphonamides[12] is performed under very stringent conditions. Recent kinetic and mechanistic studies[13] have demonstrated that the acid hydrolysis is strongly accelerated by a neighbouring carboxy group, a finding we have applied in our synthesis. In a continous one-pot operation, the carboxylic function is generated from the alkyl ester and the sulphonyl group is removed under moderate conditions (10 h at 75 °C) in acidic (1.5M-HCl) aqueous t-butyl alcohol. This method was generally satisfactory, including those compounds for which Vitride gave a poor yield [2o; R^1 = 6,7-(OMe)$_2$, R^2 = EtO$_2$CCH$_2$CH$_2$, n = 1] or it is not suitable (2p) and (2q) (R^1 = 6-Cl and 7-Cl respectively, R^2 =

Table 2. New sulphonamides (1) and N-sulphonyl heterocycles (2)

Compd.	R^1	R^2	n	Cyclis-ation procedure	Yield (%)	M.p.ᵃ (°C)	ν_{max} NH	$(cm^{-1})^b$ SO₂	Found(%) (Required) C	H	N	Cl	S
(1i)	H	$p\text{-ClC}_6\text{H}_4\text{CH}_2$	0		56	176—177	3 280	1 303, 1 140	56.8 (56.85)	4.8 (4.8)	4.8 (4.7)	12.1 (12.0)	10.6 (10.8)
(1j)	H	$p\text{-ClC}_6\text{H}_4\text{CH}_2$	1		46	96—98	3 250	1 307, 1 120	58.3 (58.2)	5.5 (5.2)	4.7 (4.5)	11.6 (11.5)	10.2 (10.0)
(2j)	H	$p\text{-ClC}_6\text{H}_4\text{CH}_2$	1	B	21	191—193		1 335, 1 150	59.5 (59.7)	5.3 (5.0)	4.4 (4.35)	11.3 (11.0)	10.2 (10.0)
(1k)	H	$p\text{-ClC}_6\text{H}_4\text{CH}_2$	2		52	134—136	3 250	1 310, 1 130	59.5 (59.3)	5.9 (5.6)	4.4 (4.3)	11.2 (10.95)	10.05 (9.9)
(1l)	H	$p\text{-ClC}_6\text{H}_4\text{CH}_2$	3		63	112—114	3 295	1 302, 1 120	60.4 (60.4)	6.0 (6.0)	4.0 (4.1)	10.7 (10.5)	9.3 (9.5)
(1m)	H	$\text{C}_6\text{H}_5\text{COCH}_2$	1		21	88—90	3 230	1 320, 1 145	63.1 (63.3)	5.7 (5.65)	4.75 (4.6)		10.45 (10.6)
(2m)	H	$\text{C}_6\text{H}_5\text{COCH}_2$	1	B	56	82—84		1 340, 1 150	64.5 (64.7)	5.15 (5.4)	4.5 (4.4)		10.3 (10.2)
(1n)	H	$\text{EtO}_2\text{C(CH}_2)_2$	1		45	c	3 280	1 320, 1 130	54.8 (54.7)	6.9 (6.7)	5.2 (4.9)		11.1 (11.2)
(2n)	H	$\text{EtO}_2\text{C(CH}_2)_2$	1	A Bᵈ	90 67	81—82		1 330, 1 150	56.9 (56.55)	6.7 (6.4)	4.8 (4.7)		10.8 (10.8)
(1o)	3,4-(OMe)₂	$\text{EtO}_2\text{C(CH}_2)_2$	1		75	56—58	3 280	1 315, 1 135	52.1 (52.2)	6.6 (6.7)	4.1 (4.1)		9.3 (9.3)
(2o)	6,7-(OMe)₂	$\text{EtO}_2\text{C(CH}_2)_2$	1	A	85	85—86		1 340, 1 135	54.0 (53.8)	6.6 (6.5)	3.9 (3.9)		9.0 (9.0)
(1p)	3-Cl	$\text{MeO}_2\text{C(CH}_2)_2$	1		77	62—63	3 310	1 315, 1 130	47.2 (47.1)	5.5 (5.3)	4.6 (4.6)	11.8 (11.6)	10.7 (10.5)
(2p)	6-Cl	$\text{MeO}_2\text{C(CH}_2)_2$	1	A Bᵈ	67 22	81—82		1 325, 1 145	49.1 (49.1)	5.2 (5.1)	4.7 (4.4)	11.4 (11.2)	10.2 (10.1)
(1q)	4-Cl	$\text{MeO}_2\text{C(CH}_2)_2$	1		86	89—91	3 270	1 315, 1 135	47.4 (47.1)	5.2 (5.3)	4.5 (4.6)	11.7 (11.6)	10.3 (10.5)
(2q)	7-Cl	$\text{MeO}_2\text{C(CH}_2)_2$	1	A B	84 79	112—114		1 330, 1 160	49.3 (49.1)	5.1 (5.1)	4.5 (4.4)	11.45 (11.2)	10.4 (10.1)
(1r)ᵈ	H	$o\text{-MeO}_2\text{CC}_6\text{H}_4$	1		60	e	3 280	1 340, 1 165	60.4 (60.2)	5.35 (5.4)	4.6 (4.4)		10.1 (10.0)
(2r)	H	$o\text{-MeO}_2\text{CC}_6\text{H}_4$	1	B	49	96—97ᶠ		1 345, 1 165	61.4 (61.6)	5.4 (5.2)	4.4 (4.2)		9.5 (9.7)

ᵃ Crystallisation solvent: alcohol for (1i,j,q) and (2m—q); alcohol–water for (1l); MeOH for (1k), (2r); EtOAc for (2j); C_6H_6–hexane for (1m); Et₂O for (1o,p). ᵇ In Nujol; ν_{CO}: (1m), 1 670; (2m), 1 700 and 1 680; (1n), 1 740; (2n), 1 730; (1o), 1 720; (2o), 1 735; (1p), 1 740; (2p), 1 740, (1q), 1 735; (2q), 1 730; (1r), 1 725; (2r), 1 730 cm⁻¹. ᶜ B.p. 115—120 °C/1 Torr. ᵈ Column chromatography (SiO₂) before crystallisation. ᵉ B.p. 100—105 °C/10⁻³ Torr. ᶠ Dimorphic; second m.p. 84—86 °C.

$\text{MeO}_2\text{CCH}_2\text{CH}_2$, $n = 1$); however, the method failed with (2r; R^1 = H, $R^2 = o\text{-MeO}_2\text{CC}_6\text{H}_4$, $n = 1$) which was recovered (86%) unchanged. The latter compound was hydrolysed in alkaline medium to give the carboxy derivative (2; R^1 = H, $R^2 = o\text{-HO}_2\text{CC}_6\text{H}_4$, $n = 1$) which was desulphonated by acid hydrolysis to furnish 1,2,3,4-tetrahydroisoquinoline (as picrate) (72% overall yield). This desulphonation required a reaction time (24 h) longer than that of the other examples in agreement with the lower catalytic effect[13] of an aromatic carboxy group with regard to an aliphatic one.

Experimental

I.r. spectra (in Nujol unless otherwise stated) were taken on a Perkin-Elmer 337E. ¹H N.m.r. spectra were obtained at 60 MHz with a Varian A-60 and a Varian EM-360 (LEA, University of San Luis) and at 80 MHz with a Bruker WP80 Sy (University of Rosario); δ values in p.p.m. from internal SiMe₄. Elemental analyses were performed by UMYMFOR (University of Buenos Aires).

M.p.s and b.p.s are uncorrected. Magnetic stirring was used and evaporations were under reduced pressure. Thin-layer chromatography (t.l.c.) and column chromatography were performed on silica gel Merck 60F-254 and 230—400 mesh respectively.

Reagent grade solvents and acids for cyclisations were used; acetic anhydride and 1,2-dichloroethane were distilled and the latter was kept over molecular sieves.

Most of the aralkylamines were pure commercial products used as such or previously distilled. 3-Chloro- and 4-chloro-phenylethylamines were prepared from the corresponding nitriles using NaBH₄–SnCl₄;[14] the products were isolated as an acid oxalate[15] and a picrate[16] respectively.

The sulphonyl chlorides and the sodium sulphonates needed in their preparations were obtained by general methods.[17] All derivatives are known except the following: sodium 3,4-dichloro-toluene-α-sulphonate (80% yield), crystallised from water to constant i.r. absorption (Found: S, 11.9. $\text{C}_7\text{H}_5\text{Cl}_2\text{NaO}_3\text{S}$ requires S, 12.2%); ν_{max} 1 180 and 1 060 cm⁻¹ (SO₂). It was characterised as the S-benzylisothiouronium salt (82% yield), m.p. 178—181 °C (from 50% alcohol) (Found: N, 6.8. $\text{C}_{15}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_3\text{S}_2$ requires N, 6.9%). Sodium 2-ethoxycarbonylethanesulphonate (62% yield) crystallised from 90% alcohol to constant i.r. absorption (Found: S, 15.8. $\text{C}_5\text{H}_9\text{NaO}_5\text{S}$ requires S, 15.7%); ν_{max} 1 725 (C=O), 1 180 and 1 065 cm⁻¹ (SO₂). Ethyl 3-chlorosulphonyl-propanoate (68% yield), b.p. 85 °C/1 Torr (Found: Cl, 17.9. $\text{C}_5\text{H}_9\text{ClO}_4\text{S}$ requires Cl, 17.7%); ν_{max}.(neat) 1 740 (C=O), 1. 380 and 1 165 cm⁻¹ (SO₂); δ(CDCl₃) 1.30 (3 H, t, Me), 3.03 (2 H, t, CH_2CO), and 3.78—4.52 (4 H, m, OCH₂ and SCH₂).

Table 3. ^{1}H N.m.r. spectra of new sulphonamides (1) and N-sulphonyl heterocycles (2)

Compound[a]	δ/p.p.m.[b,c]
(1a)	4.23 (d,[d] NCH$_2$) partially overlapped with 4.33 (s, SCH$_2$) (total area 4 H), 6.70 (1 H, br, NH), 7.13—7.95 (8 H, m, ArH)
(1b)	3.80 (3 H, s, OMe), 4.23 (d,[d] NCH$_2$) partially overlapped with 4.33 (s, SCH$_2$), (total area 4 H), 6.33—7.90 (8 H, m, ArH and NH; after D$_2$O, 7 H)
(1c)	2.78 (2 H, distorted t, NCCH$_2$), 3.26 (2 H, q,[e] NCH$_2$), 4.03 (s, SCH$_2$) overlapped with 4.30 (t, NH), (total area 3 H), 6.88—7.73 (8 H, m, ArH)
(2c)	2.82 (2 H, t, NCCH$_2$), 3.48 (2 H, t, NCH$_2$C), 4.16 (2 H, s, SCH$_2$), 4.38 (2 H, s, ArCH$_2$N), 6.80—7.50 (7 H, m, ArH)
(1d)	2.65 (2 H, distorted t, NCCH$_2$), 3.17 (2 H, q,[e] NCH$_2$), 3.70 (3 H, s, OMe), 3.98 (3 H, s, SCH$_2$ and NH; after D$_2$O, 2 H), (7 H, m, ArH)
(2d)	2.73 (2 H, t, NCCH$_2$), 3.46 (2 H, t, NCH$_2$C), 3.75 (3 H, s, OMe), 4.13 (2 H, s, SCH$_2$), 4.30 (2 H, s, ArCH$_2$N), 6.33—7.67 (6 H, m, ArH)
(1e)	2.73 (2 H, distorted t, NCCH$_2$), 3.23 (2 H, q,[e] NCH$_2$), 3.86 (6 H, s, 2 × OMe), 4.07 (s, SCH$_2$) partially overlapped with 4.27 (t, NH), (total area 3 H; after D$_2$O, 2 H), 6.47—6.97 and 6.97—7.67 (each 3 H, dm, ArH)
(2e)	2.72 (2 H, t, NCCH$_2$), 3.46 (2 H, t, NCH$_2$C), 3.83 (6 H, s, 2 × OMe), 4.13 (2 H, s, SCH$_2$), 4.26 (2 H, s, ArCH$_2$N), 6.42 and 6.57 (each 1 H, ds, 5-ArH and 8-ArH), 7.00—7.67 (3 H, m, ArH)
(1f)	1.50—2.15 (2 H, m, NCCH$_2$), 2.63 (2 H, t, NC$_2$CH$_2$), 3.02 (2 H, q,[e] NCH$_2$), 4.13 (s, SCH$_2$) partially overlapped with 4.35 (t, NH), (total area 3 H; after D$_2$O, 2 H), 6.93—7.73 (8 H, m, ArH)
(2f)	1.10—1.80 (2 H, m, NCCH$_2$), 2.90 (2 H, distorted t, NC$_2$CH$_2$), 3.57 (2 H, t, NCH$_2$), 3.83 (2 H, s, SCH$_2$), 4.42 (2 H, s, ArCH$_2$N), 6.63—7.67 (7 H, m, ArH)
(1g)	1.17 (3 H, d, NCMe), 1.43—2.00 (2 H, m, NCCH$_2$), 2.62 (2 H, t, NC$_2$CH$_2$), 3.03—3.70 (1 H, m, NCH), 4.08 (3 H, br, SCH$_2$ and NH; after D$_2$O; 2 H, s), 6.87—7.77 (8 H, m, ArH)
(2g)	1.33 (d, NCMe) overlapped with 1.46—1.98 (m, NCCH$_2$) (total area 5 H), 2.30—3.33 (2 H, m, NC$_2$CH$_2$), 3.80 (2 H, s, SCH$_2$), 3.90—4.33 (1 H, m, NCH), 4.47 (2 H, s, ArCH$_2$N), 6.67—7.67 (7 H, m, ArH)
(1h)	1.32—1.93 (4 H, m, NCCH$_2$CH$_2$), 2.58 (2 H, distorted t, NC$_3$CH$_2$), 2.77—3.33 (2 H, m,[e] NCH$_2$), 4.10 (3 H, s, SCH$_2$ and NH; after D$_2$O, 2 H), 6.80—7.73 (8 H, m, ArH)
(2h)	1.32—1.97 (4 H, m, NCCH$_2$CH$_2$), 2.87 (2 H, distorted t, NC$_3$CH$_2$), 3.10 (2 H, distorted t, NCH$_2$C), 4.10 (2 H, s, SCH$_2$), 4.37 (2 H, s, ArCH$_2$N), 7.00—7.67 (7 H, m, ArH)
(1i)	4.10 (d,[d] 2 H, NCH$_2$), 4.31 (2 H, s, SCH$_2$), 7.67 (1 H, distorted t, NH), 7.31 and 7.38 (9 H, ArH)
(1j)	2.73 (2 H, distorted t, NCCH$_2$), 3.00—3.48 (2 H, q,[e] NCH$_2$), 4.08 (2 H, s, SCH$_2$), 4.27 (1 H, distorted t, NH), 6.90—7.44 (9 H, m, ArH)
(2j)	2.80 (2 H, t, NCCH$_2$), 3.43 (2 H, t, NCH$_2$C), 4.22 (2 H, s, SCH$_2$), 4.37 (2 H, s, ArCH$_2$N), 6.67—7.67 (8 H, m, ArH)
(1k)	1.47—2.10 (2 H, m, NCCH$_2$), 2.63 (2 H, t, NC$_2$CH$_2$), 3.00 (2 H, q,[e] NCH$_2$), 4.17 (3 H, SCH$_2$ and NH; after D$_2$O, 2 H), 6.87—7.65 (9 H, m, ArH)
(1l)	1.13—1.85 (4 H, m, NCCH$_2$CH$_2$), 2.53 (2 H, distorted t, NC$_3$CH$_2$), 2.93 (2 H, distorted, q,[e] NCH$_2$), 4.10 (SCH$_2$) overlapped with 4.25 (t, NH) (total area 3 H; after D$_2$O, 4.10, 2 H), 6.82—7.67 (9 H, m, ArH)
(1m)	2.87 (2 H, distorted t, NCCH$_2$), 3.47 (2 H, q, NCH$_2$), 4.47 (2 H, s, SCH$_2$), 4.95 (1 H, t, NH), 6.98—8.15 (10 H, m, ArH)
(2m)	2.90 (2 H, t, NCCH$_2$), 3.60 (2 H, t, NCH$_2$C), 4.53 and 4.63 (4 H, ds, SCH$_2$ and ArCH$_2$N), 6.87—8.83 (9 H, m, ArH)
(1n)	1.23 (3 H, t, Me), 2.48—3.03 (4 H, m, NCCH$_2$, and CH$_2$CO), 3.03—3.60 (4 H, m, NCH$_2$ and SCH$_2$), 3.87—4.67 (3 H, m, CH$_2$O and NH; after D$_2$O, 4.13, 2 H, q,), 7.23 (5 H, s, ArH)
(2n)	1.23 (3 H, t, Me), 2.53—3.13 (4 H, m, NCCH$_2$ and CH$_2$CO), 3.33 (2 H, t, SCH$_2$), 3.60 (2 H, t, NCH$_2$C), 4.10 (2 H, q, CH$_2$O), 4.46 (2 H, s, ArCH$_2$N), 6.97—7.43 (4 H, m, ArH)
(1o)	1.26 (3 H, t, CMe), 2.52—2.92 (4 H, m, NCCH$_2$ and CH$_2$CO), 3.13—3.46 (4 H, m, NCH$_2$C and SCH$_2$), 3.85 and 3.87 (6 H, ds, partially overlapped, 2 × OMe), 4.14 (2 H, q, CH$_2$O), 4.53 (1 H, t, NH), 6.62—6.89 (3 H, m, ArH)
(2o)	1.20 (3 H, t, CMe), 2.62—3.05 (4 H, m, NCCH$_2$ and CH$_2$CO), 3.26 (2 H, distorted t, SCH$_2$), 3.53 (2 H, t, NCH$_2$C), 3.80 (6 H, s, 2 × OMe), 4.08 (2 H, q, CH$_2$O), 4.36 (2 H, s, ArCH$_2$N), 6.51 and 6.57 (2 H, ds, partially overlapped, 5-ArH and 8-ArH)
(1p)	2.55—3.07 (4 H, m, NCCH$_2$ and CH$_2$CO), 3.07—3.60 (4 H, m, NCH$_2$ and SCH$_2$), 3.70 (3 H, s, OMe), 4.60 (1 H, t, NH), 7.23 (4 H, ArH)
(2p)	2.33—3.07 (4 H, m, NCCH$_2$ and CH$_2$CO), 3.07—3.63 (m, NCH$_2$ and SCH$_2$) partially overlapped with 3.67 (s, OMe) (total area 7 H), 4.57 (2 H, s, ArCH$_2$N), 6.67—7.53 (3 H, m, ArH)
(1q)	2.58—2.96 (4 H, m, NCCH$_2$ and CH$_2$CO), 3.12—3.52 (4 H, m, NCH$_2$C and SCH$_2$), 3.70 (3 H, s, OMe), 4.57 (1 H, t, NH), 7.02—7.37 (4 H, m, ArH)
(2q)	2.66—3.02 (4 H, m, NCCH$_2$ and CH$_2$CO), 3.18—3.58 (m, NCH$_2$C and SCH$_2$) overlapped with the base of 3.66 (s, OMe) (total area 7 H), 4.44 (2 H, s, ArCH$_2$N), 6.94—7.29 (3 H, m, ArH)
(1r)	2.77 (2 H, distorted t, NCCH$_2$), 3.23 (2 H, q, NCH$_2$), 3.86 (3 H, s, OMe), 5.95 (1 H, t, NH), 6.77—7.37 (5 H, m, ArH), 7.37—8.23 (4 H, m, ArH)
(2r)	2.83 (2 H, t, NCCH$_2$), 3.50 (2 H, distorted, t, NCH$_2$), 3.87 (3 H, s, OMe), 4.37 (2 H, s, ArCH$_2$N), 6.67—8.00 (8 H, m, ArH)

[a] For R^1, R^2, and n, see Tables 1 and 2. [b] CDCl$_3$ as solvent except for (1a,b), (CD$_3$)$_2$CO and for (1i), (CD$_3$)$_2$SO. [c] NH signal removed by D$_2$O. [d] After D$_2$O, s. [e] After D$_2$O, t.

Preparation of N-*Aralkylsulphonamides* (1) (Tables 1—3).—
We have used several slightly modified classical methods;[17] the preferred procedure was as follows: the appropriate sulphonyl chloride (1 mmol) was added to a cold (0 °C) and stirred solution (3.3 ml) of the aralkylamine (1 mmol) in benzene–toluene (9:1); aqueous potassium carbonate (2 mmol in 1 ml) was then added over 30 min. After being stirred for 24 h at 35 °C, the mixture was acidified (Congo Red) with aqueous HCl and extracted with CHCl$_3$; the organic phase was dried (MgSO$_4$) and evaporation of the solvent gave the crude sulphonamide which was purified by crystallisation or distillation.

The N-benzyl-4-chlorobenzylsulphonamide (1i) was prepared following literature directions[18] for other examples. The intermediate *ethyl* N-(4-*chlorobenzylsulphonyl*)*carbamate* is new and was obtained as other analogues[19] (80% yield), m.p. 119—120 °C (from CCl$_4$) (Found: C, 43.3; H, 4.4; Cl, 13.0; N, 5.3; S, 11.7. C$_{10}$H$_{12}$ClNO$_4$S requires C, 43.25; H, 4.4; Cl, 12.8; N, 5.0; S, 11.5%); $\nu_{max.}$ 3 120 (NH), 1 710 (C=O), and 1 350 and 1 167 cm^{-1} (SO$_2$); δ(CDCl$_3$) 1.31 (3 H, t, Me), 4.24 (2 H, q, OCH$_2$), 4.58 (2 H, s, SCH$_2$), and 7.33 (5 H, s, ArH and NH; after D$_2$O: 4 H).

Also the *ethyl* N-*benzyl*-N-(4-*chlorobenzylsulphonyl*)*carbamate* is new; (70% yield), m.p. 106—107 °C (from MeOH) (Found:

Table 4. Desulphonylation of compound (2) to the heterocycles (3)

Compound (2)[b]	Procedure	Yield (%)	M.p.[c] (°C)	Heterocycles (3)[a]
(2c)	a	58	202—206[e] (H₂O)	
(2d)	a	53	206—209 (EtOH)	2.93 (2 H, dist. t, NCCH₂), 3.33 (s, NCH₂C, partially overlapped with H₂O of the solvent; after D₂O, 2 H, t), 3.73 (3 H, s, OMe), 4.23 (2 H, s, ArCH₂N), 6.53—7.37 (3 H, m, cation ArH), 8.63 (4 H, s, anion ArH overlapped in the base with NH₂; after D₂O, 2 H, s), 8.93 (br s, NH₂)
(2e)	a	36	197—199 (EtOH)	2.90 (dist. t, NCCH₂), 3.33 (dist. t, NCH₂C, partially overlapped with H₂O of the solvent), 3.73 (6 H, s, 2 × OMe), 4.17 (2 H, s, ArCH₂N), 6.80 (2 H, s, cation ArH), 8.63 (4 H, s, anion ArH overlapped with NH₂; after D₂O, 2 H, s), 8.93 (br s, NH₂)
(2f)	a	61	181—184[f,g] (EtOH)	3.13 (2 H, dist. t, NC₂CH₂), 3.73 (2 H, dist. t, NCH₂C), 4.60 (2 H, s, ArCH₂N), 7.26 (4 H, m, cation ArH), 8.70 (2 H, s, anion ArH)
(2g)	a	68	173—175[h] (EtOH)	1.23 (3 H, d, Me), 1.45—2.33 (2 H, m, NCCH₂), 2.93 (2 H, dist. t, NC₂CH₂), 3.23—3.87 (br, CH), 4.30 (2 H, s, ArCH₂N), 7.33 (4 H, s, cation ArH), 8.63 (4 H, s, anion ArH overlapped in the base with NH₂; after D₂O, 2 H, s)
(2h)	a	59	176—178 (EtOH)	1.33—2.17 (4 H, NCCH₂CH₂), 2.83 (2 H, dist. t, NC₃CH₂), 3.20 (2 H, dist. t, NCH₂C), 4.67 (2 H, s, ArCH₂N), 7.07—7.87 (m, cation ArH, NH₂ and solvent),[i] 9.03 (2 H, s, anion ArH)
(2n)	b	53	203—205[e] (H₂O)	
(2o)	b	65	197—199 (EtOH)	
(2p)	b	62	189—191 (EtOH)	3.00 (2 H, dist. t, NCCH₂), 3.40 (dist. t, NCH₂C overlapped with H₂O of the solvent; after D₂O, 2 H, t), 4.27 (2 H, s, ArCH₂N), 7.33 (3 H, s, cation ArH), 8.65 (2 H, s, anion ArH), 9.02 (2 H, br s, NH₂)
(2q)	b	60	214—217[j] (EtOH)	
(2r)	b[k]	72	203—206[e] (H₂O)	

[a] As picrate salt. [b] For R¹, R², and n, see Tables 1 and 2. [c] Crystallisation solvent in parentheses. M.p.s from literature: (2d), 207—208 °C; (3e) = (3o), 202—203 °C; (3h), 175 °C; (3p), 191—192 °C. [d] (CD₃)₂SO as solvent except (CD₃)₂CO for (3f) and [²H₅]pyridine for (3h); NH₂ signals removed by D₂O. [e] Identified by m.p., mixed m.p., and i.r. absorption with an authentic sample of 1,2,3,4-tetrahydroisoquinoline picrate. [f] Found: C, 51.2; H, 4.5; N, 15.1. C₁₆H₁₆N₄O₇ requires C, 51.1; H, 4.3; N, 14.9%. [g] The picrate was converted into the known N-tosyl-2,3,4,5-tetrahydro-1H-2-benzazepine, m.p. 137—138 °C (lit.,[7] m.p. 135 °C). [h] Found: C, 52.6; H, 4.45; N, 14.4. C₁₇H₁₈N₄O₇ requires C, 52.3; H, 4.65; N, 14.35%. [i] In (CD₃)₂CO, 7.00—7.83 (4 H, m, cation ArH). [j] Found: C, 45.7; H, 3.35; N, 14.1; Cl, 9.0. C₁₅H₁₃N₄ClO₇ requires C, 45.4; H, 3.3; N, 14.1; Cl, 9.0%. [k] 24 h at 75 °C after alkaline hydrolysis. Direct acid hydrolysis failed, 86% of (2r) being recovered.

N, 4.1. C₁₇H₁₂ClNO₄S requires N, 3.8%); ν_max. 1 725 (C=O), and 1 375 and 1 155 cm⁻¹ (SO₂); δ(CDCl₃) 1.33 (3 H, t, Me), 4.33 (2 H, q, OCH₂), 4.55 and 4.64 (each 2 H, 2 × s, NCH₂ and SCH₂), and 7.00—7.38 (9 H, m, ArH).

Cyclisation of N-*Sulphonyl Heterocycles* (2) (Tables 1—3).— The solution or suspension of the reactants [(1) and s-trioxane, 1 mmol and 1 equiv. respectively] in the reaction medium was kept at 35 °C in a Teflon stoppered tube with stirring and under exclusion of moisture.

Procedure B has already been described;[5] in procedure A, the reaction medium was formed by methanesulphonic acid (0.4 ml) and acetic anhydride (1 mmol) diluted in 1,2-dichloroethane (3.6 ml); procedure C was the same as A but with a five-fold increase in the volume of 1,2-dichloroethane. After the reaction time (procedure A, 4 h; B, 30 min; C, 15 h), the mixture was cooled at 0 °C and diluted with CHCl₃. The organic phase was washed with ice—water and aqueous NaHCO₃, dried (MgSO₄), and evaporated to leave the crude products. These were purified to constant m.p. by crystallisation, directly or after column chromatography. Compounds (2c, j, m, n, r) were identified by direct comparison (m.p., mixed m.p. and i.r.) with a sample obtained by a general method[17] from 1,2,3,4-tetrahydro-isoquinoline and the appropriate aralkylsulphonyl chloride dissolved in benzene–CHCl₃ (4:1) and in the presence of pyridine or triethylamine.

Bis-[N-*(2-phenylethyl)tosylamido]methane.*—To a solution of N-phenylethyltosylamide (275 mg, 1 mmol) in chloroform (13 ml; stirred 48 h with molecular sieves 4 Å) was added boron trifluoride–ether (8 drops) and titrated aqueous formaldehyde (0.1 ml, 1.05 mmol). After being stirred for 15 min at room temperature, the mixture was diluted with water (5 ml) and basified with 10% aqueous ammonia; the organic layer was separated and the aqueous phase extracted with CHCl₃. The residue from the combined organic extracts (washed with water and dried) was chromatographed on silica gel (benzene–CHCl₃, 1:1). First fractions gave the crude title *compound* which was crystallised from alcohol (73 mg, 26%), m.p. 160—161 °C (Found: 66.1; H, 6.3; N, 4.9; S, 11.1. C₃₁H₃₄N₂O₄S₂ requires C, 66.2; H, 6.1; N, 5.0; S, 11.4%); ν_max. no NH absorption, and 1 330 and 1 150 cm⁻¹ (SO₂); δ(CDCl₃) 2.42 (6 H, s, 2 × Me), 2.80 (4 H, distorted t, 2 × ArCH₂), 3.51 (4 H, distorted t, 2 × ArCCH₂), 4.93 (2 H, s, NCH₂N), 7.20 ca. 10 H, s, partially overlapped with the solvent and ArH from tosyl, 2 × Ph), 7.27 and 7.66 (each 4 H, dd, ArH *ortho* to Me and *ortho* to SO₂ respectively). Evaporation of the later eluates followed by crystallisation from benzene afforded N-tosyl-1,2,3,4-tetra-hydroisoquinoline (29 mg, 10%), m.p. 144—146 °C, identified by mixed m.p. and i.r. absorption with an authentic sample. Final elution of the column with CHCl₃ gave a small amount (5%) of the starting tosylamide.

Removal of the N-*Sulphonyl Group from Compounds* (2) *to give the Fused Heterocycles* (3) (Table 4).—(a) *Reduction with sodium bis(2-methoxyethoxy)aluminium hydride* (*Vitride*). With exclusion of moisture, a benzene solution of Vitride (7 mmol)

was added to a solution or suspension of the *N*-sulphonyl derivative (2) (1 mmol) in anhydrous benzene (10 ml). When gas evolution had ceased, the mixture was heated for 10 h at 80 °C. The mixture was then cooled to room temperature, when ethanol (1 ml) and 10% aqueous NaOH (5 ml, to remove the excess of Vitride) were added and stirring maintained for a further 2 h. The aqueous phase was extracted with benzene and the combined benzene phases were washed with water, dried (MgSO₄), and concentrated to 5 ml. Addition of a benzene solution (5 ml) of picric acid (1.1 mmol) precipitated the crude picrate which was filtered off and recrystallised.

(b) *Acid Hydrolysis.* The *N*-sulphonyl compound (2) (1 mmol) in a mixture (1:1; 6 ml) of t-butyl alcohol and aqueous 3M-HCl was heated for 10 h at 75 °C in a reaction tube with a Teflon stopper. After the mixture had cooled to room temperature it was washed (2 × 5 ml) with benzene–CHCl₃ (4:1) and the aqueous phase, after basification with 10% aqueous sodium carbonate, was repeatedly extracted with the same solvent mixture. The organic extract was worked up as above to give crude picrates which were purified by crystallisation.

N-(o-*Carboxyphenylsulphonyl*)-1,2,3,4-*tetrahydroisoquino-line.*—*N*-(o-Methoxycarbonylphenylsulphonyl)-1,2,3,4-tetra-hydroisoquinoline (331 mg, 1 mmol) in ethanol (5 ml) and aqueous 2.5M-NaOH (8 ml) were heated in a Teflon stoppered tube at 75 °C. After a few minutes dissolution occurred and the heating was continued for 10 h. The solution was allowed to cool to room temperature when it was acidified with aqueous 3M-HCl and extracted (2 × 10 ml) with benzene–CHCl₃ (4:1); the organic phase was washed with water, dried (MgSO₄), and evaporated to leave a residue which was crystallised from MeOH to give the title *compound* (254 mg, 80%), m.p. 154—155 °C (Found: C, 60.8; H, 5.0; N, 4.3. C₁₆H₁₅NO₄S requires C, 60.6; H, 4.8; N, 4.4%); $v_{max.}$ 3 270 (OH), 1 730 (OH and C=O of monomeric acid), and 1 330 and 1 170 cm⁻¹ (SO₂); δ(CD₃COCD₃) 2.87 (2 H, t, ArCH₂C), 3.56 (2 H, t, ArCCH₂), 4.42 (2 H, s, ArCH₂N), 7.12 (4 H, s, ArH from tetrahydroiso-quinoline), and 7.33—8.20 (4 H, m, ArH fro PhSO₂).

References
1 W. M. Whaley and T. R. Govindachari, *Org. React. (N.Y.)* or *(USSR)*, 1951, 6, 151.
2 M. R. Euerby and R. D. Waigh, *J. Chem. Soc., Chem. Commun.*, 1984, 127.
3 R. R. Wittekind and S. Lazarus, *J. Heterocycl. Chem.*, 1971, 8, 495.
4 N. M. Mollov and A. P. Venkov, *Synthesis*, 1978, 62.
5 O. O. Orazi and R. A. Corral, *J. Chem. Soc., Chem. Commun.*, 1976, 470.
6 K. Ito and H. Tanaka, *Chem. Pharm. Bull.*, 1977, 25, 1732.
7 J. von Braun, G. Blessing, and R. S. Cahn, *Ber. Dtsch. Chem. Ges.*, 1924, 57, 908.
8 J. von Braun and O. Bayer, *Ber. Dtsch. Chem. Ges.*, 1927, 60, 1257.
9 J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Silberman, *J. Org. Chem.*, 1977, 42, 3846 and previous refs. cited.
10 E. H. Gold and E. Babad, *J. Org. Chem.*, 1972, 37, 2208.
11 E. Negishi and A. R. Day, *J. Org. Chem.*, 1965, 30, 43 and refs. cited.
12 S. Searles and S. Nukina, *Chem. Rev.*, 1959, 59, 1077.
13 T. Graafland, A. Wagenaar, A. J. Kirby, and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, 1979, 101, 6981.
14 S. Kano, Y. Yuasa, and S. Shibuya, *J. Chem. Soc., Chem. Commun.*, 1979, 796.
15 R. Huisgen and H. König, *Chem. Ber.*, 1959, 92, 203.
16 F. C. Brown, C. K. Bradsher, E. C. Morgan, M. Tetenbaum, and P. Wilder, *J. Am. Chem. Soc.*, 1956, 78, 384.
17 Houben-Weyl's Methoden der Organischen Chemie, ed. E. Müller, G. Thieme Verlag, Stuttgart, 1955, vol, 9.
18 W. J. Gensler, F. J. Frank, S. K. Dheer, and J. W. Lauher, *J. Org. Chem.*, 1971, 36, 4102.
19 F. J. Marshall and M. V. Sigal, *J. Org. Chem.*, 1958, 23, 927.