Synthesis of β-Amino-sulphones and αβ-Unsaturated Sulphones.

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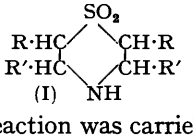
Arylsulphonylacetic acids have been condensed with aldehydes and bases. A number of *N*-substituted 2-aminoalkyl aryl sulphones (II) and 1-aryl-2-arylsulphonylethylenes (III) have been obtained. *p*-Tolylsulphonylacetic acid condenses with chloral, to give 3 : 3 : 3-trichloro-2-hydroxypropyl *p*-tolyl sulphone (IV).

The activating influence of a sulphonyl group on the hydrogen atoms attached to the adjacent carbon atom has been studied by a number of workers (see Suter, "The Organic Chemistry of Sulphur," Wiley, New York, 1944, p. 687; Gilman, "Organic Chemistry," Wiley, New York, 1943, p. 879). Most of the reactions involving activation by a sulphonyl group are undergone by alkyl- or aryl-sulphonylacetic acids, their derivatives, and keto-sulphones and disulphones. The Mannich reaction has not been applied to compounds containing reactive hydrogen atoms in a $\cdot CH_2 \cdot SO_2R$ group: Chodroff and Whitmore (*J. Amer. Chem. Soc.*, 1950, **72**, 1073) attempted to apply it to a series of α-arylsulphonyl-alkanecarboxylic acids in the presence of diethylamine but isolated only unsaturated sulphones of the type $C_6H_5 \cdot SO_2 \cdot CR{:}CH_2$. Having in view the somewhat similar condensations with ketones, aldehydes, and bases studied by Noller and Baliah (*ibid.*, 1948, **70**, 3853) we attempted to condense dimethyl, diethyl, dipropyl, and dibutyl sulphones with benzaldehyde and ammonia or amines to get compounds of the type (I), but failed. Benzyl phenyl sulphone and di- and tri-phenylsulphonylmethane also failed to condense. However, we found that arylsulphonylacetic acids undergo this type of reaction. Phenyl- and *p*-tolyl-sulphonylacetic acid condensed with aromatic aldehydes and ammonia or aliphatic primary amines to give the β-amino-sulphones (II), decarboxylation occurring during the reaction. Simultaneously αβ-unsaturated sulphones (III) were formed.



(I)

$R \cdot SO_2 \cdot CH_2 \cdot CHR' \cdot NHR''$ (II)

$R \cdot SO_2 \cdot CH{:}CHR'$ (III)

The reaction was carried out by refluxing the reagents in glacial acetic acid solution for 5—15 minutes. Longer times resulted in a lower yield of the amino-sulphone and a corresponding increase in the yield of the unsaturated sulphone. The latter type was produced exclusively when *p*-tolylsulphonylacetic acid was heated with benzaldehyde and ammonia in glacial acetic acid for 40 minutes; this suggests that the amino-sulphone initially formed decomposed to the unsaturated sulphone: indeed, 2-amino-2-phenylethyl *p*-tolyl sulphone, heated in glacial acetic acid under reflux for 30 minutes, gave 1-phenyl-2-*p*-tolyl-sulphonylethylene.

The condensation seems to be limited to aromatic aldehydes. Aliphatic aldehydes such as formaldehyde, acetaldehyde, and *n*- and *iso*-butyraldehyde failed to condense with *p*-tolylsulphonylacetic acid and ammonia. However, chloral underwent an aldol condensation :

$$p\text{-Me}\cdot C_6H_4\cdot SO_2\cdot CH_2\cdot CO_2H + CCl_3\cdot CHO \longrightarrow p\text{-Me}\cdot C_6H_4\cdot SO_2\cdot CH_2\cdot CH(OH)\cdot CCl_3 \quad (IV)$$

Of amines, ammonia and aliphatic primary amines condensed readily, but secondary amines failed to condense. For example, a mixture of *p*-tolylsulphonylacetic acid, benzaldehyde, and piperidine in acetic acid gave only 1-phenyl-2-*p*-tolylsulphonylethylene. When diethylamine was used in the place of piperidine, *p*-tolylsulphonylacetic acid was decarboxylated to methyl *p*-tolyl sulphone.

When arylsulphonylalkanecarboxylic acids are used in the place of arylsulphonylacetic acids, the condensation appears to proceed less readily; *e.g.*, α-*p*-tolylsulphonylpropionic acid condensed with ammonia and benzaldehyde or *m*-nitrobenzaldehyde only after 1 hour's refluxing. The yields were also poor in these cases.

Experimental

Triphenylsulphonylmethane.—Diphenylsulphonylmethane (Shriner, Struck, and Jorison, *J. Amer. Chem. Soc.*, 1930, **52**, 2060) (4·2 g.) and phenyl benzenethiolsulphonate (3·6 g.) were added to a solution obtained by dissolving sodium (0·4 g.) in ethanol (40 c.c.). The mixture was heated on a water-bath under reflux for 6 hr., poured into water (150 c.c.), and made alkaline with 10% sodium hydroxide solution. After removal of alkali-insoluble matter by ether, the solution was acidified with hydrochloric acid. The precipitated phenylthiobisphenylsulphonylmethane (3·8 g.) was obtained as colourless needles (from glacial acetic acid), m. p. 177·5—178·5°. Oxidation of this compound with hydrogen peroxide (30%) in acetic acid gave triphenylsulphonylmethane (64%), m. p. 215—217° (from acetic acid) (cf. Laves, *Ber.*, 1892, **25**, 347).

Condensation of Arylsulphonylacetic Acids with Aldehydes and Amines.—In general, a mixture of the arylsulphonylacetic acid (0·02 mole), the aldehyde (0·02 mole), and ammonium acetate or the aliphatic amine (0·02 mole) in glacial acetic acid (4 c.c.) was heated under reflux for 5—15 min. The reaction was stopped after the brisk evolution of carbon dioxide subsided. The resulting solution was cooled, mixed with ether (50 c.c.), and set aside for 1 hr. The ethereal layer was removed and on passage of dry hydrogen chloride into it, the β-amino-sulphone hydrochloride was obtained as needles either immediately or on short standing. In certain cases even a slight excess of hydrogen chloride coloured the product yellow or brown, and so the hydrochloride was precipitated by addition of sufficient ether saturated with hydrogen chloride. After complete separation of the hydrochloride (1—2 days), it was filtered off (filtrate A) and washed with ether and then with acetone. Crystallisation from ethanol or ethanol–ether gave needles. The data relating to these *hydrochlorides* are recorded in Table 1.

The αβ-unsaturated sulphone was obtained from the filtrate A. Evaporation of the ether left a residue which was a mixture of unchanged aldehyde, acetic acid, and unsaturated sulphone. Almost pure crystals of the last were obtained by shaking this mixture with a few c.c. of methanol. Crystallisation from ethanol or methanol gave the analytical sample.

The unsaturated sulphones derived from *m*-nitrobenzaldehyde were insoluble in ether. In these cases, after the addition of ether to the reaction mixture, the precipitated unsaturated sulphone was filtered off, and the filtrate treated as usual with hydrogen chloride to give the β-amino-sulphone hydrochloride. The unsaturated *sulphones* are listed in Table 2.

p-*Tolyl* 3 : 3 : 3-*Trichloro*-2-*hydroxypropyl Sulphone.*—A mixture of *p*-tolylsulphonylacetic acid (4·28 g.), ammonium acetate (1·54 g.), chloral (2·86 g.), and glacial acetic acid (4 c.c.) was heated under reflux for 30 min. The resulting brown solution was dissolved in ether (60 c.c.) and saturated with hydrogen chloride. The ammonium chloride that separated was filtered off. Removal of ether from the filtrate gave a liquid which gradually yielded crystals of the *sulphone*; colourless rhombic crystals (0·72 g.), m. p. 127—129° (Found : C, 37·9; H, 3·3. $C_{10}H_{11}O_3Cl_3S$ requires C, 37·8; H, 3·5%), were obtained from benzene.

2-*Amino*-1-*methyl*-2-*phenylethyl* p-*Tolyl Sulphone Hydrochloride.*—To a solution of α-*p*-tolylsulphonylpropionic acid (Chodroff and Whitmore, *loc. cit.*) (2·28 g.) and benzaldehyde (1·06 g.) in acetic acid (2 c.c.), ammonium acetate (0·77 g.) was added, and the mixture heated under reflux for 1 hr. After cooling, the product was extracted with ether and the *hydrochloride* (0·22 g., 7%) was precipitated. It was filtered off (filtrate B) and crystallised from ethanol–

TABLE 1. *β-Amino-sulphone hydrochlorides*, $R{\cdot}SO_2{\cdot}CH_2{\cdot}CHR'{\cdot}NHR'',HCl$.

No.	R′	R″	M. p.	Yield (%) *	Formula	Found, % C	H	Cl⁻	Required, % C	H	Cl⁻
				R = Phenyl.							
1	Ph	H	190—193°	27(21)	$C_{14}H_{15}O_2NS,HCl$	56·2	5·7	12·0	56·5	5·4	11·9
2	3 : 4-$(CH_2O_2)C_6H_3$	H	213—215(d)	30(19)	$C_{15}H_{15}O_4NS,HCl$	52·6	5·1	10·4	52·7	4·7	10·4
3	*o*-MeO·C_6H_4	H	211—213	20(28)	$C_{15}H_{17}O_3NS,HCl$	54·6	5·6	10·8	55·0	5·5	10·8
4	*p*-C_6H_4Cl	H	213—215	24(28)	$C_{14}H_{14}O_2NClS,HCl$	50·6	4·3	10·7	50·6	4·5	10·7
5	*o*-$NO_2{\cdot}C_6H_4$	H	225—228(d)	7(10)	$C_{14}H_{14}O_4N_2S,HCl$	49·4	4·5	10·4	49·1	4·4	10·4
6	*m*-$NO_2{\cdot}C_6H_4$	H	217—219	21(14)	$C_{14}H_{14}O_4N_2S,HCl$	48·8	4·6	10·2	49·1	4·4	10·4
7	2-Thienyl	H	210—212(d)	14 [a]	$C_{12}H_{13}O_2NS_2,HCl$	47·6	4·9	12·0	47·5	4·6	11·7
8	Ph	CH_2Ph	179—181	10(27)	$C_{21}H_{21}O_2NS,HCl$	64·9	5·5	9·4	65·0	5·7	9·2
9	*p*-C_6H_4Me	—	—	(17) [b]	—	—	—	—	—	—	—
				R = *p*-Tolyl.							
10	Ph	H	204—206	23(25)	$C_{15}H_{17}O_2NS,HCl$	58·1	5·6	11·3	57·8	5·8	11·4
11	3 : 4-$(CH_2O_2)C_6H_3$	H	213—214(d)	22(15)	$C_{16}H_{17}O_4NS,HCl$	53·8	5·1	10·1	54·0	5·0	10·0
12	*o*-MeO·C_6H_4	H	220—222	19(23)	$C_{16}H_{19}O_3NS,HCl$	56·1	6·0	10·6	56·2	5·8	10·4
13	*p*-MeO·C_6H_4	H	231—232	19(12)	$C_{16}H_{19}O_3NS,HCl$	56·0	6·1	10·6	56·2	5·8	10·4
14	*p*-C_6H_4Cl	H	206—209	19(31)	$C_{15}H_{16}O_2NClS,HCl$	52·1	5·2	10·2	51·9	4·9	10·2
15	*o*-$NO_2{\cdot}C_6H_4$	H	237—239(d)	18(5)	$C_{15}H_{16}O_4N_2S,HCl$	50·2	5·1	10·0	50·5	4·8	10·0
16	*m*-$NO_2{\cdot}C_6H_4$	H	219—220	25(20)	$C_{15}H_{16}O_4N_2S,HCl$	—	—	10·3	—	—	10·0
17	*p*-C_6H_4Me	H	195—197·5	25(22)	$C_{16}H_{19}O_2NS,HCl$	59·0	6·3	11·1	59·0	6·1	10·9
18	2-Thienyl	H	196·5—198·5(d)	15(20)	$C_{13}H_{15}O_2NS_2,HCl$	49·4	5·3	11·2	49·1	5·0	11·2
19	Ph	Me	185—188	8(35)	$C_{16}H_{19}O_2NS,HCl$	58·8	5·7	10·8	59·0	6·1	10·9
20	*m*-$NO_2{\cdot}C_6H_4$	Me	203—205	30(48)	$C_{16}H_{18}O_4N_2S,HCl$	—	—	9·4	—	—	9·6
21	Ph	Et	199—200	21(54)	$C_{17}H_{21}O_2NS,HCl$	60·1	6·7	10·6	60·1	6·5	10·4
22	*m*-$NO_2{\cdot}C_6H_4$	Et	208—210	23(41)	$C_{17}H_{20}O_4N_2S,HCl$	53·0	5·8	9·0	53·1	5·5	9·0
23	Ph	Allyl	177—178·5	13(43)	$C_{18}H_{21}O_2NS,HCl$	61·5	6·3	10·4	61·5	6·3	10·1
24	*m*-$NO_2{\cdot}C_6H_4$	Allyl	210—213	33(62)	$C_{18}H_{20}O_4N_2S,HCl$	54·5	4·9	9·1	54·5	5·3	8·9
25	Ph	Bu	185—188	9(60)	$C_{19}H_{25}O_2NS,HCl$	61·9	7·1	9·9	62·0	7·1	9·6
26	*m*-$NO_2{\cdot}C_6H_4$	Bu	195—198	14(70)	$C_{19}H_{24}O_4N_2S,HCl$	55·5	6·2	8·6	55·3	6·1	8·6
27	Ph	Octyl	169—171	11(61)	$C_{23}H_{33}O_2NS,HCl$	65·0	8·3	8·4	65·2	8·0	8·4
28	*m*-$NO_2{\cdot}C_6H_4$	Octyl	197—199	19(53)	$C_{23}H_{32}O_4N_2S,HCl$	58·7	6·6	7·6	58·9	7·0	7·6
29	Ph	CH_2Ph	194—195·5	36(64)	$C_{22}H_{23}O_2NS,HCl$	65·6	6·2	8·9	65·8	6·0	8·8
30	3 : 4-$(CH_2O_2)C_6H_3$	CH_2Ph	205—206	27(30)	$C_{23}H_{23}O_4NS,HCl$	61·8	5·4	8·3	61·9	5·4	8·0
31	*m*-$NO_2{\cdot}C_6H_4$	CH_2Ph	207—209·5	10(56)	$C_{22}H_{22}O_4N_2S,HCl$	59·2	5·2	8·0	59·1	5·2	7·9

* The percentage yields in parentheses are those of the αβ-unsaturated sulphones. The bases corresponding to Nos. 4, 16, and 20 were obtained by treatment of the corresponding hydrochlorides with aqueous ammonia in ethanol. *Base* from No. 4, colourless needles (ethanol–water), m. p. 98—99° (Found: C, 57·0; H, 5·0. $C_{14}H_{14}O_2NClS$ requires C, 56·9; H, 4·7%). *Base* from No. 16, yellow needles (methanol–water), m. p. 97—98° (Found: C, 56·3; H, 4·9. $C_{15}H_{16}O_4N_2S$ requires C, 56·3; H, 5·0%). *Base* from No. 20, colourless prisms (methanol), m. p. 108·5—109·5° (Found: C, 57·4; H, 5·4. $C_{16}H_{18}O_4N_2S$ requires C, 57·5; H, 5·4%).

[a] No unsaturated compound could be isolated. [b] No Mannich base could be isolated. (d) M. p. with decomp.

TABLE 2. *αβ-Unsaturated sulphones*, $R{\cdot}SO_2{\cdot}CH{:}CHR'$.

R′	M. p.	Formula	Found, % C	H	Required, % C	H
	R = Ph.					
Ph	74—74·5° [a]	$C_{14}H_{12}O_2S$	68·7	4·6	68·9	4·9
3 : 4-$(CH_2O_2)C_6H_3$	107—108	$C_{15}H_{12}O_4S$	62·4	4·5	62·5	4·2
o-MeO·C_6H_4	93—94	$C_{15}H_{14}O_3S$	65·6	4·9	65·7	5·1
p-ClC_6H_4	129·5—130	$C_{14}H_{11}O_2ClS$	60·3	4·2	60·3	4·0
o-$NO_2{\cdot}C_6H_4$	130—132	$C_{14}H_{11}O_4NS$	58·4	3·8	58·1	3·8
m-$NO_2{\cdot}C_6H_4$	145—146	$C_{14}H_{11}O_4NS$	57·8	4·1	58·1	3·8
p-C_6H_4Me	135·5—136·5	$C_{15}H_{14}O_2S$	70·1	5·6	69·8	5·4
	R = *p*-Tolyl.					
Ph	120·5—121 [b]	$C_{15}H_{14}O_2S$	69·8	5·4	69·8	5·4
3 : 4-$(CH_2O_2)C_6H_3$	114—114·5	$C_{16}H_{14}O_4S$	63·6	4·5	63·6	4·6
o-MeO·C_6H_4	81—82	$C_{16}H_{16}O_3S$	66·8	5·6	66·7	5·6
p-MeO·C_6H_4	100 (softens 88)	$C_{16}H_{16}O_3S$	66·4	5·6	66·7	5·6
p-$C_6H_4{\cdot}Cl$	151—153	$C_{15}H_{13}O_2ClS$	61·6	4·5	61·6	4·4
o-$NO_2{\cdot}C_6H_4$	158·5—160	$C_{15}H_{13}O_4NS$	59·3	4·5	59·4	4·3
m-$NO_2{\cdot}C_6H_4$	146—147	$C_{15}H_{13}O_4NS$	59·3	4·3	59·4	4·3
p-$C_6H_4{\cdot}Me$	154—155	$C_{16}H_{16}O_2S$	70·4	5·6	70·6	5·9
2-Thienyl	132·5—133·5	$C_{13}H_{12}O_2S_2$	59·4	4·7	59·1	4·6

[a] Field (*J. Amer. Chem. Soc.*, 1952, **74**, 3919) gives m. p. 74—75°. [b] Chodroff and Whitmore (*loc. cit.*) record m. p. 119·5—120°; Kohler and Potter (*J. Amer. Chem. Soc.*, 1935, **57**, 1316) give m. p. 121°.

ether as needles, m. p. 235—240° (decomp.) (Found: C, 58·9; H, 6·4; Cl^-, 10·9. $C_{16}H_{19}O_2NS,HCl$ requires C, 59·0; H, 6·3; Cl^-, 10·9%). Evaporation of the filtrate B yielded 1-*methyl*-2-*phenyl*-1-p-*tolylsulphonylethylene* (0·32 g., 11·8%), m. p. 118·5—119·5° (from ethanol) (Found: C, 70·5; H, 5·9. $C_{16}H_{16}O_2S$ requires C, 70·6; H, 5·9%).

2-*Amino*-1-*methyl*-2-m-*nitrophenylethyl* p-*Tolyl Sulphone Hydrochloride*.—By the same procedure as above, a mixture of α-*p*-tolylsulphonylpropionic acid (2·28 g.), *m*-nitrobenzaldehyde (1·51 g.), ammonium acetate (0·77 g.), and glacial acetic acid (2 c.c.) afforded the *hydrochloride* named (0·59 g., 16%), needles, m. p. 245—254° (decomp.) (from ethanol) (Found: C, 52·0; H, 5·3; Cl^-, 9·5. $C_{16}H_{18}O_4N_2S,HCl$ requires C, 51·8; H, 5·1; Cl^-, 9·6%). The ethereal solution gave 1-*methyl*-2-m-*nitrophenyl*-1-p-*tolylsulphonylethylene* (0·31 g., 10%), pale yellow plates (from methanol), m. p. 132—133° (Found: C, 60·4; H, 4·8. $C_{16}H_{15}O_4NS$ requires C, 60·6; H, 4·7%).

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