CCCLXVIII.—*Trisulphonylmethanes.*

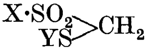
By DAVID T. GIBSON.

IN his presidential address to the Chemical Society (J., 1913, **103**, 724), Frankland raised the interesting question whether " optical activity can be preserved in the case of an asymmetric system becoming ionised at the central atom " (compare Kenyon and Phillips, *Trans. Faraday Soc.*, 1930, 458; Kuhn and Albrecht, *Ber.*, 1927, **60**, 1297; Shriner and Young, *J. Amer. Chem. Soc.*, 1930, **52**, 3332). Accordingly, as some of the trisulphonylmethanes (V) are comparable in strength with monochloroacetic acid, it seemed worth while attempting the resolution of one suitably asymmetrically constituted.

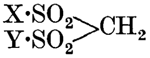
The preparation of such test compounds has been rendered possible by the discovery that the process devised by Brooker and Smiles (J., 1926, 1723) can be extended to compounds containing $\cdot SO_2\cdot CH_2\cdot CO_2Et$, $\cdot SO_2\cdot CH_2\cdot CO\cdot CH_3$, and $\cdot SO_2\cdot CH_2\cdot SO_2\cdot$ groups; and that alkylthiol groups can also be introduced into the reactive methylene, illustrating, incidentally, the similarity between thiolsulphonic alkyl esters and aromatic disulphoxides (J., 1924, **125**, 176; 1925, **127**, 224, 1821). Further, it is often possible to use solid sodium carbonate instead of sodium ethoxide as condensing agent. In introducing an alkylthiol group into a sulphonylacetone, $R\cdot SO_2\cdot CH_2\cdot CO\cdot CH_3$, it is advisable to use a thiolsulphonic ester, $R\cdot SO_2\cdot SAlkyl$, derived from the same sulphinic acid, as evidence of a partial exchange of $R\cdot SO_2$ groups was once obtained.


$X\cdot SO_2\cdot \underset{YS}{CH}\cdot CO\cdot CH_3$

(I.)

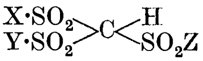

$\begin{matrix}X\cdot SO_2\\ YS\end{matrix}\!>\!CH_2$

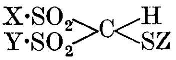
(II.)


$\begin{matrix}X\cdot SO_2\\ Y\cdot SO_2\end{matrix}\!>\!CH_2$

(III.)

(V.)


$\begin{matrix}X\cdot SO_2\\ Y\cdot SO_2\end{matrix}\!>\!C\!<\!\begin{matrix}H\\ SO_2Z\end{matrix}$


$\begin{matrix}X\cdot SO_2\\ Y\cdot SO_2\end{matrix}\!>\!C\!<\!\begin{matrix}H\\ SZ\end{matrix}$

(IV.)

The acetyl or ester group can be readily hydrolysed, and the resulting sulphide-sulphone (II) oxidised to a mixed disulphone of type (III). The disulphones (III) were first obtained more directly by Posner's method (*Ber.*, 1903, **36**, 200) with the important improvement of fractionating the disulphide mixture before oxidising it. Thus a good yield of pure disulphone was easily obtained; but the odours evolved during the process are so offensive that the more circuitous method may be preferable. The disulphones can then be condensed afresh with a disulphoxide, and the resulting disulphonethiolmethane (IV) oxidised to trisulphone.

On these lines three unsymmetrical trisulphonylmethanes were prepared (III $\longrightarrow$ IV $\longrightarrow$ V) : *phenylsulphonylmethylsulphonylethylsulphonylmethane* (V; $X = Ph$, $Y = Et$, $Z = Me$), from either *methylsulphonylethylsulphonylmethane* and diphenyl disulphoxide or *phenylsulphonylethylsulphonylmethane* and methyl *p*-toluenethiolsulphonate; *phenylsulphonyl*-p-*tolylsulphonylmethylsulphonylmethane* (V; $X = Me$, $Y = Ph$, $Z = C_6H_4Me$), also in two ways; and *phenylsulphonyl*-3 : 5-*dichlorophenylsulphonylmethylsulphonylmethane* (V; $X = Me$, $Y = Ph$, $Z = C_6H_3Cl_2$).

The extensive work of Tröger (*J. pr. Chem.*, 1920, **101**, 126, *et seq.*) has shown that the $SO_2{\cdot}CH_2$ group imitates $CO{\cdot}CH_2$ closely in reaction, and Aschan, discussing the bromination of acid chlorides ("Terpene und Campher," p. 107), suggests that the sulphonyl chlorides might react in the form $R{\cdot}CH{:}SOCl{\cdot}OH$. These trisulphones may therefore be capable of existing in a symmetrical enolic form, though no suggestion of such enolisation is actually made by Tröger, or by Schroeder and Herzberg (methionic acid; *Ber.*, 1905, **38**, 3391), and it has been definitely rejected by Hückel ("Theoretische Grundlagen der Organischen Chemie"). Shriner, Struck, and Jorison (*J. Amer. Chem. Soc.*, 1930, **52**, 2060) say that it "violates the principles of the octet theory." The last authors consider that alkaline solutions of bis(phenylsulphonyl)methane (III; $X = Y = Ph$) constitute "the first case in which the position of one of the negative charges is unquestionably on the methylene carbon atom."

Preliminary attempts to resolve the disulphonylethanes $(R{\cdot}SO_2)_2CH{\cdot}CH_3$ showed that they are too weakly acidic to form salts.

The trisulphonylmethanes are slightly soluble in hot water, but do not separate, when the solution is cooled, until a few drops of mineral acid are added. They are extremely soluble in solutions of organic bases, but only the first of them formed well-defined crystalline salts with brucine and hydroxyhydrindamine. With them no sign of resolution could be detected, and while this may be due to enolisation, it is more probable that ionisation has rendered the activity too fugitive to be observed.

EXPERIMENTAL.

The disulphones (III) were prepared by shaking the less reactive mercaptan with the calculated amount of 40% formalin solution (estimated by Romijn's method, *Z. anal. Chem.*, 1897, **36**, 18) and warming the mixture till a homogeneous liquid was obtained. The more reactive mercaptan was then added, and the whole agitated with concentrated hydrochloric acid. Even when preparing the symmetrical disulphones (X = Y) it is advantageous to add the mercaptan thus in two stages, lest the heat generated cause loss (methyl mercaptan, b. p. 6°). The oil which separated was fractionated with a Widmer column, and the appropriate fraction oxidised with permanganate.

The disulphoxide and the compound containing the $SO_2\cdot CH_2\cdot SO_2$ or $SO_2\cdot CH_2\cdot CO\cdot$ group were warmed in alcoholic solution for several hours with sodium ethoxide (calc. amount); or with solid anhydrous sodium carbonate until it had all dissolved. The alcohol was evaporated, the solution made alkaline if necessary, any insoluble impurity removed with ether, and the required product precipitated from the aqueous solution with acetic acid. If desired, the sulphinic acid which was simultaneously formed could be removed from the filtrate with mineral acid. The oxidations were conducted by shaking with cold acid $2\frac{1}{2}$% permanganate solution, or with perhydrol in acetic acid. In the latter case any excess was destroyed with sulphurous acid before the product was worked up.

The Disulphones.—Bis(ethylthio)methane was prepared by Claesson (*J. pr. Chem.*, 1877, **15**, 176) from methylene iodide, and by Baumann (*Ber.*, 1886, **19**, 2813) from chloroform, and sodium mercaptide, but it is much more satisfactorily obtained from 40% formalin (20 c.c.) and ethyl mercaptan (25 g.). The first runnings are ethyl disulphide, evidently produced by the reaction : $CH_2O + 2C_2H_5\cdot SH = CH_3\cdot OH + C_2H_5\cdot S\!:\!S\cdot C_2H_5$. The main fraction, b. p. 182—184°, is the required disulphide (yield, 75%).

The corresponding disulphone, m. p. 104°, was obtained in practically theoretical yield by oxidation with 1% permanganate solution. The dibromo- and the dichloro-derivative, m. p. 131° and 98° respectively, were obtained as described by Baumann.

Bis(methylsulphonyl)methane also has been obtained by Baumann (*Ber.*, 1890, **23**, 1875) in a circuitous way from formaldehyde and hydrogen sulphide. It is much more easily obtained by condensing methyl mercaptan with formaldehyde and oxidising the product (b. p. 145—150°) as above. The disulphone, m. p. 142°, and its dibromo-derivative, m. p. 234°, as Baumann states, were obtained; the *dichloro*-derivative melts at 152° (Found : Cl, 29·7. $C_3H_6O_4Cl_2S_2$ requires Cl, 29·4%).

Bis(methylsulphonyl)ethane was obtained from methyl mercaptan and acetaldehyde. The *disulphide* boils at 156—158° (Found : C, 39·2; H, 8·05. $C_4H_{10}S_2$ requires C, 39·4; H, 8·2%). The disulphone (permanganate) has m. p. 122° (Found : C, 25·9; H, 5·4. $C_4H_{10}O_4S_2$ requires C, 25·8; H, 5·4%). The *monoiodo*-derivative was obtained by treatment of the disulphone with potassium iodide and iodate in acetic acid; m. p. 225° (Found : I, 41·1. $C_4H_9O_4IS_2$ requires I, 40·7%).

Methylthioethylthiomethane was prepared from ethyl mercaptan, formaldehyde, and methyl mercaptan; the main fraction had b. p. 163—167° (Found : C, 39·3; H, 8·2. $C_4H_{10}S_2$ requires C, 38·8; H, 8·2%). The *disulphone* (permanganate), purified by sublimation in a vacuum at 110°/11 mm., melted at 94—95° (Found : C, 26·6; H, 5·8. $C_4H_{10}O_4S_2$ requires C, 25·8; H, 5·4%) : a mixture with bis(ethylsulphonyl)methane, m. p. 102°, melted below 75°.

Phenylthioethylthiomethane was obtained from phenyl mercaptan, formaldehyde, and ethyl mercaptan; b. p. 147—151°, $n_D^{18^\circ}$ 1·598 (Found : C, 59·0; H, 6·9. $C_9H_{12}S_2$ requires C, 58·7; H, 6·6%). It gave a much better yield (65%) of the disulphone than Posner (*loc. cit.*) obtained, who did not isolate the intermediate disulphide. The same disulphone was also obtained from ethyl phenylsulphonylacetate and ethyl *p*-toluenethiolsulphonate by oxidising the oil which separated when an aqueous extract of the reaction mixture was warmed. The mother-liquor deposited *sodium phenylsulphonylacetate*, indicating considerable loss of ester by hydrolysis (Found : Na, 10·3. $C_8H_7O_4SNa$ requires Na, 10·3%).

α-Phenylsulphonyl-α-methylsulphonylethane. From phenyl mercaptan, acetaldehyde, and methyl mercaptan, *α-phenylthio-α-methylthioethane*, b. p. 140—145°/10 mm., was obtained (Found : C, 58·5; H, 6·6. $C_9H_{12}S_2$ requires C, 58·7; H, 6·5%). This was oxidised to the *disulphone*, m. p. 104° after recrystallisation from benzene (Found : C, 43·7; H, 4·9. $C_9H_{12}O_4S_2$ requires C, 43·6; H, 4·9%). The disulphone was not readily soluble in alkali, and showed no tendency to form a salt with hydroxyhydrindamine.

Methyl p-*toluenethiolsulphonate* was obtained by methylating sodium *p*-toluenethiolsulphonate with methyl iodide (25% yield) or methyl sulphate (65% yield). Unlike the ethyl ester (Otto, *Ber.*, 1882, **15**, 129), it is a crystalline solid, m. p. 58°, b. p. 193°/10 mm. (decomp.) (Found : C, 47·4; H, 4·9. $C_8H_{10}O_2S_2$ requires C, 47·5; H, 4·95%).

Phenylsulphonylmethylsulphonylmethane. Condensation of phenyl mercaptan, formaldehyde, and methyl mercaptan gave the *disulphide*, b. p. 148—152°/11 mm. (Found : C, 56·8 ; H, 5·9. $C_8H_{10}S_2$ requires C, 56·5 ; H, 5·9%). The *disulphone* had m. p. 147° (Found : C, 41·1 ; H, 4·7. $C_8H_{10}O_4S_2$ requires C, 41·0 ; H, 4·4%). Attempts to obtain it from phenylsulphonylacetone and methyl *p*-toluenethiolsulphonate gave a *compound* (a), m. p. 77° (Found : C, 51·4 ; H, 5·5 ; S, 24·9. $C_{11}H_{14}O_3S_2$ requires C, 51·2 ; H, 5·4 ; S, 24·8%). This was easily soluble in alkali, and when the solution was warmed, the acetyl group was hydrolysed, and a *compound* (b) precipitated, m. p. 80° (Found : C, 50·3 ; H, 5·8 ; S, 29·5. $C_9H_{12}O_2S_2$ requires C, 50·0 ; H, 5·6 ; S, 29·6%). On oxidation, (b) gave a disulphone, melting at about 146° but not identical with phenylsulphonylmethylsulphonylmethane (147°), α-phenylsulphonyl-α-methylsulphonylethane (104°), or phenylsulphonylethylsulphonylmethane (112°). The extra methylene group must therefore be in the phenyl nucleus.* Compounds (a) and (b) are accordingly derivatives of *p*-tolylsulphonylmethane, and this is confirmed by the fact that the disulphone from (b), after recrystallisation from benzene, melts at 154°. p-*Toluenesulphonylmethylsulphonylmethane*, prepared directly from the respective mercaptans, melts at 158°, and a mixture of the two between 154° and 158°.

Phenylsulphonyl-p-*tolylsulphonylmethane* (III ; X = Ph, Y = C_7H_7). Phenylsulphonylacetone (10 g.), *p*-tolyl disulphoxide (15 g.), and sodium ethoxide gave *α-phenylsulphonyl-α-*p-*tolylthioacetone* (12 g.), m. p. 99° (from alcohol) (Found : S, 20·1. $C_{16}H_{16}O_3S_2$ requires S, 20·0%). When this was warmed for a few minutes in alkaline solution, the acetyl group was removed and *phenylsulphonyl*-p-*tolylthiomethane* was precipitated, m. p. 85° (alcohol) (Found : C, 60·5 ; H, 5·2. $C_{14}H_{14}O_2S_2$ requires C, 60·5 ; H, 5·05%). It gave the *disulphonylmethane*, on oxidation with perhydrol, in practically theoretical yield ; m. p. 115° (alcohol) (Found : C, 54·3 ; H, 4·7. $C_{14}H_{14}O_4S_4$ requires C, 54·3 ; H, 4·5%).

Trisulphones.—Bis(ethylsulphonyl)phenylthiomethane (IV ; X = Y = Et, Z = Ph) was obtained by Fromm's method (*Annalen*, 1889, **253**, 166) in 30% yield (m. p. 83°) and from bis(ethylsulphonyl)-methane, phenyl disulphoxide, and sodium ethoxide in 65% yield (m. p. 88°). Either sample gave the same trisulphone (V) with alkaline permanganate in 80% yield (m. p. 165°) ; the bromo-derivative had m. p. 134° (compare Laves, *Ber.*, 1892, **25**, 361). The use of excess of disulphoxide gave no sign of the disubstitution which Smiles (*loc. cit.*) found with $CO{\cdot}CH_2{\cdot}CO$ compounds. An attempt to obtain (V) directly from bis(ethylsulphonyl)methane and benzenesulphonyl chloride gave unexpectedly *bis*(*ethylsulphonyl*)-

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* Mr. J. D. Louden's suggestion.

chloromethane, m. p. 96° (Found: C, 26·3; H, 4·0. $C_5H_{11}O_4ClS_2$ requires C, 25·8; H, 4·7%).

Methylsulphonylethylsulphonylphenylthiomethane (IV; X = Me, Y = Et, Z = Ph) was obtained from methylsulphonylethylsulphonylmethane and phenyl disulphoxide, purified by sublimation, and recrystallised from benzene; m. p. 126° (Found: C, 40·5; H, 5·0; equiv., 284. $C_{10}H_{14}O_4S_3$ requires C, 40·8; H, 4·8%; equiv., 294).

Phenylsulphonylethylsulphonylmethylthiomethane (IV; X = Ph, Y = Et, Z = Me), obtained from phenylsulphonylethylsulphonylmethane, methyl *p*-toluenethiolsulphonate, and sodium ethoxide, had m. p. 98° (methyl alcohol) (Found: C, 40·8; H, 4·85. $C_{10}H_{14}O_4S_3$ requires C, 40·8; H, 4·8%).

Phenylsulphonylmethylsulphonylethylsulphonylmethane (V) was obtained by oxidation of either of the two preceding compounds. The product from the former melted at 216°, that from the latter at 216—219°, and a mixture of the two at the same temperature (Found: C, 37·3; H, 4·7; equiv., 316, 319, 321. $C_{10}H_{14}O_6S_3$ requires C, 36·9; H, 4·3%; equiv., 326). It is sparingly soluble in all the usual cold solvents, but does not separate from pure water until a few drops of a mineral acid are added. It is acid to thymol-blue, and as it is not precipitated from its salts by acetic acid, it can thus be conveniently freed from any unoxidised generator. The *bromo*-derivative has m. p. 141° (Found: C, 29·8; H, 3·4. $C_{10}H_{13}O_6BrS_3$ requires C, 29·7; H, 3·2%).

The *brucine* salt of the trisulphone was obtained by crystallising the substances in the requisite proportion from a mixture of alcohol (2 parts) and chloroform (1 part). It separated in stout prisms, m. p. 140—150° (efferv.), and had $[\alpha]_{5461}$ − 25·7° ($l = 1$) in 3·5% aqueous alcohol solution (Found: equiv., 747. $C_{35}H_{46}O_{11}N_2S_3$ requires equiv., 766). The rotation and m. p. were unaltered by repeated recrystallisation, and when the salt was carefully decomposed with ammonia, the ammonium salt was inactive.

The two active hydroxyhydrindamines were obtained as described by Pope and Read (J., 1912, **101**, 764). The trisulphone (2·1 g.) and *d*-hydroxyhydrindamine (1·0 g.) were refluxed with ethyl acetate (80 c.c.) till all had dissolved. On cooling, 85% of the salt crystallised, m. p. 159° (Found: N, 2·85. $C_{19}H_{25}O_7NS_3$ requires N, 2·95%). It is very readily soluble in alcohol, water, and acetone. $[\alpha]_{5461}$ = + 17·3° in water (3·3 g. in 100 c.c.), + 18·5° in dry alcohol (7·25 g. in 100 c.c.), + 33·2° in pure acetone (6·39 g. in 100 c.c.), changing to + 31·7° after 24 hours, and + 24·5° in pure dry acetone (4·265 g. in 100 c.c.), changing to + 33·2° after 4 hours. When, however, the trisulphone was liberated from the salt, its solutions were inactive. Even by adding the calculated quantity of *lævo*-hydroxyhydrindamine to a solution containing the salt from the *d*-base, an inactive solution was obtained, and there was no sign of any fugitive activity.

Phenylsulphonyl-p-*tolylsulphonyl*-3 : 5-*dichlorophenylthiomethane*, obtained from phenylsulphonyl-*p*-tolylsulphonylmethane, 3 : 5 : 3′ : 5′-tetrachlorodiphenyl disulphoxide, and sodium ethoxide in 90% yield, and recrystallised from alcohol, sintered at 123° and melted at 145° (Found : Cl, 14·6. $C_{20}H_{16}O_4Cl_2S_3$ requires Cl, 14·6%).

Phenylsulphonyl-p-*tolylsulphonylmethylthiomethane*, obtained from the same disulphonylmethane, methyl *p*-toluenethiolsulphonate, and sodium carbonate in 60% yield, had m. p. 105° (Found : C, 50·7; H, 4·75. $C_{15}H_{16}O_4S_3$ requires C, 50·6; H, 4·5%).

Phenylsulphonylmethylsulphonyl-p-*tolylthiomethane*, obtained from phenylsulphonylmethylsulphonylmethane and di-*p*-tolyl disulphoxide, had m. p. 169° (Found: C, 50·3; H, 5·1. $C_{15}H_{16}O_4S_3$ requires C, 50·5; H, 4·5%).

Phenylsulphonyl-p-*tolylsulphonylmethylsulphonylmethane*, obtained from either of the two preceding compounds by means of perhydrol, melted at 174°, and a mixture at the same temperature (Found : C, 46·9; H, 4·9. $C_{15}H_{16}O_6S_3$ requires C, 46·4; H, 4·1%). Its salts with cinchonine, brucine, and *d*-hydroxyhydrindamine showed no tendency to crystallise.

Phenylsulphonylmethylsulphonyl - 3 : 5 - *dichlorophenylthiomethane*, obtained from the disulphonylmethane and the tetrachlorodiphenyl disulphoxide, had m.p. 147° (Found : C, 40·8; H, 3·0. $C_{14}H_{12}O_4Cl_2S_3$ requires C, 40·8; H, 2·9%). With perhydrol, it gave the *trisulphone*, m. p. 208° (becoming blue) (Found : C, 38·4; H, 3·3. $C_{14}H_{12}O_6Cl_2S_3$ requires C, 38·0; H, 2·7%). No crystalline salts were obtained from this trisulphone.

Analytical Note.—As the halogenated sulphones $\cdot SO_2\cdot CX_2\cdot SO_2\cdot$ were sometimes difficult to decompose by the usual Carius method, they were warmed till dissolved with alkaline sulphite solution. The solution was cooled, and the halide precipitated in the usual way with silver nitrate. In addition to those cited above, the method was tried with 2 : 2-*dichloro*-1 : 3-*dithiolan dioxide*, m. p. 233° (water) (Found : Cl, 29·5. $C_3H_4O_4Cl_2S_2$ requires Cl, 29·8%), and 2-*bromo*-2-*methyl*-1 : 3-*dithiolan dioxide*, m. p. 248° (Found : Br, 30·0. $C_4H_7O_4BrS_2$ requires Br, 30·3%).

Tetrabromomethyl-1 : 3 : 5-*trithian* 1 : 3-*Dioxide.*—By methylating 1 : 3 : 5-trithian 1 : 3-dioxide in the cold with methyl sulphate, the *monomethyl* derivative was obtained (Found : C, 22·2; H, 3·9; S, 44·6. $C_4H_8O_4S_3$ requires C, 22·2; H, 3·7; S, 44·4%). The *tetrabromo*-derivative, obtained by bromination below 50°, had

m. p. 205° [Found (by Carius method at 310°): S, 17·6; Br, 59·3, 59·5. Found (by alkaline sulphite method): Br, 60·0. $C_4H_4O_4Br_4S_3$ requires Br, 60·1; S, 18·0%].

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