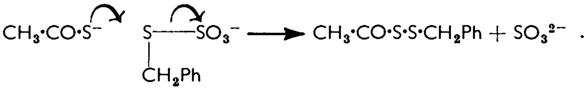
954. *New Syntheses of Trisulphides.*

By Brian Milligan, B. Saville, and J. M. Swan.

Trisulphides are obtained conveniently by the reaction of sodium alkyl thiolsulphates with sodium sulphide; the new method is illustrated by preparation of diethyl, diallyl, dibenzyl, diphenacyl, di-*p*-tolyl and di-(2-methylpent-2-enyl) trisulphide. Sodium benzyl thiolsulphate also yields dibenzyl trisulphide on reaction with thiolacetate in alkaline solution; in neutral solution is obtained the intermediate acetyl benzyl disulphide which yields the trisulphide on further reaction with sodium benzyl thiolsulphate and also on reaction with sulphide. Attempts to extend these new trisulphide syntheses were not always successful, the disulphide rather than the trisulphide being obtained.

Trisulphides are generally prepared by reaction of the corresponding thiols with sulphur dichloride in inert solvents, but this method is not readily applicable to complex water-soluble thiols. The method is also limited in the case of unsaturated trisulphides owing to possible side reactions of olefinic groups with sulphur dichloride. Thus, although attempts to prepare the trisulphide analogue of cystine, di-(2-amino-2-carboxyethyl) trisulphide, by several new methods now described have been unsuccessful, a number of other trisulphides were obtained in good yields under attractively mild conditions.

The essential discovery of these new synthetical methods resulted from an attempt to prepare acetyl benzyl disulphide through the action of sodium thiolacetate on sodium benzyl thiolsulphate according to an elementary substitution of the kind:



$$CH_3{\cdot}CO{\cdot}S^- \quad \underset{\displaystyle CH_2Ph}{S}{-}SO_3^- \longrightarrow CH_3{\cdot}CO{\cdot}S{\cdot}S{\cdot}CH_2Ph + SO_3^{2-} \quad \ldots\ldots \quad (1)$$

Finding the product of the above experiment to be dibenzyl trisulphide led us to suppose that the intermediate acetyl benzyl disulphide had rapidly undergone hydrolysis (cf. Böhme and Zinner [1]) to benzyl hydrogen disulphide which reacted with another molecule of sodium benzyl thiolsulphate as follows:

$$CH_3{\cdot}CO{\cdot}S{\cdot}S{\cdot}CH_2Ph + OH^- \longrightarrow CH_3{\cdot}CO_2H + Ph{\cdot}CH_2{\cdot}S{\cdot}S^- \quad \ldots\ldots \quad (2)$$

$$Ph{\cdot}CH_2{\cdot}S{\cdot}S^- + Ph{\cdot}CH_2{\cdot}S{\cdot}SO_3^- \longrightarrow Ph{\cdot}CH_2{\cdot}S{\cdot}S{\cdot}S{\cdot}CH_2Ph + SO_3^{2-} \quad \ldots\ldots \quad (3)$$

The formation of acetyl benzyl disulphide, as required by the above reaction sequence, was proved by allowing benzyl thiolsulphate to react with sodium thiolacetate in an aqueous buffer at pH 7·0 or in the presence of Ba^{2+} at pH 8·5. Under these conditions the chief product was indeed acetyl benzyl disulphide, which if further heated in suspension at 50° (as an emulsion) in a buffer at pH 8·5 gave some dibenzyl trisulphide. This points to an alternative trisulphide-forming reaction:

$$Ph{\cdot}CH_2{\cdot}S{\cdot}S^- + Ph{\cdot}CH_2{\cdot}S{\cdot}S{\cdot}CO{\cdot}CH_3 \longrightarrow Ph{\cdot}CH_2{\cdot}S{\cdot}S{\cdot}S{\cdot}CH_2Ph + CH_3{\cdot}CO{\cdot}S^- \quad \ldots \quad (4)$$

[1] Böhme and Zinner, *Annalen*, 1954, **585**, 142.

although the yield of trisulphide was much higher when sodium benzyl thiolsulphate was included with the intermediate acetyl benzyl disulphide. Heating acetyl benzyl disulphide in ethanol with cyclohexylamine as base gave *N*-cyclohexylacetamide, but no trisulphide could be isolated even when sodium benzyl thiosulphate was included in the mixture. The reason for this remains obscure.

Treatment of pyridinium *p*-tolyl thiolsulphate with sodium thiolacetate also afforded di-*p*-tolyl trisulphide, but sodium *o*-nitrophenyl thiolsulphate gave only di-*o*-nitrophenyl disulphide under a wide range of conditions. The presumed intermediate, acetyl *o*-nitrophenyl disulphide, obtained authentically by an independent method, likewise gave only di-*o*-nitrophenyl disulphide under conditions expected to yield trisulphide. Two explanations can be advanced: either the initially formed trisulphide is decomposed according to reactions (5) and (6) (cf. Minoura [2])

$$\mathrm{SO_3^{2-} + RS{\cdot}S{\cdot}SR \longrightarrow RS{\cdot}S{\cdot}SO_3^- + RS^-} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (5)$$

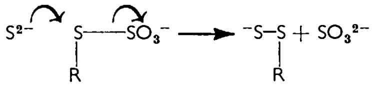
$$\mathrm{RS^- + RS{\cdot}S{\cdot}SO_3^- \longrightarrow RS{\cdot}SR + {}^-S{\cdot}SO_3^-} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (6)$$

or owing to parity in leaving-group propensities of thiolacetate and *o*-nitrobenzyl sulphide ($\mathrm{Ar{\cdot}CH_2{\cdot}S{\cdot}}$) the following reactions become important:

$$\mathrm{CH_3{\cdot}CO{\cdot}S^- + CH_3{\cdot}CO{\cdot}S{\cdot}SR \longrightarrow CH_3{\cdot}CO{\cdot}S{\cdot}S{\cdot}CO{\cdot}CH_3 + RS^-} \quad . \; . \; . \; . \; . \quad (7)$$

$$\mathrm{RS^- + CH_3{\cdot}CO{\cdot}S{\cdot}SR \longrightarrow RS{\cdot}SR + CH_3{\cdot}CO{\cdot}S^-} \quad . \; . \; . \; . \; . \; . \; . \quad (8)$$

Since our postulated mechanism for the successful production of trisulphides (reactions 1—3) is essentially dependent upon the intermediate existence of monoionised disulphide entities ($\mathrm{RS{\cdot}S^-}$) it was evident that the latter would also result from the action of sulphide ion on sodium alkyl thiolsulphates which might finally yield trisulphides according to reactions (9) and (10):



$$\mathrm{S^{2-}\quad \underset{\textstyle R}{\underset{|}{S}}\!-\!\!-\!SO_3^- \longrightarrow {}^-S\!-\!\underset{\textstyle R}{\underset{|}{S}} + SO_3^{2-}} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (9)$$

$$\mathrm{RS{\cdot}S^- + RS{\cdot}SO_3^- \longrightarrow RS{\cdot}S{\cdot}SR + SO_3^{2-}} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (10)$$

Experiments with benzyl, phenacyl, and *p*-tolyl thiolsulphates gave the corresponding trisulphides in good yield. Similarly, aqueous solutions of thiolsulphates prepared *in situ* from sodium thiosulphate and alk(en)yl halides (R = Et, allyl, or 2-methylpent-2-enyl) gave good yields of very pure trisulphides on treatment with sodium sulphide. However, reaction of sodium *N*-cyclohexylcarbamoylmethyl thiolsulphate, sodium phenoxycarbonylmethyl thiolsulphate, sodium *o*-nitrophenyl thiolsulphate, or the sodium salt of *S*-sulphocysteine (sodium 2-amino-2-carboxyethyl thiolsulphate) with sulphide ion gave only the corresponding disulphides.

EXPERIMENTAL

Light petroleum refers to the fraction of b. p. 55—70° uness stated otherwise.

Thiolsulphates.—Sodium benzyl thiolsulphate,[3] sodium phenacyl thiolsulphate,[4,5] sodium *N*-cyclohexylcarbamoylmethyl thiolsulphate,[6] sodium phenoxycarbonylmethyl thiolsulphate,[5] sodium *o*-nitrophenyl thiolsulphate,[7] and the sodium salt of *S*-sulphocysteine [8] were prepared by reported methods.

Pyridinium p-*Tolyl Thiolsulphate.*—*N*-Sulphopyridinium (kindly provided by Allied Chemical Corp., N.Y., U.S.A.) (1·66 g.) and toluene-*p*-thiol (1·29 g.) were heated together

[2] Minoura, *J. Soc. Rubber Ind. Japan*, 1950, **23**, 213; *Chem. Abstr.*, 1953, **47**, 7247.
[3] Purgotti, *Gazzetta*, 1890, **20**, 25.
[4] Baker and Barkenbus, *J. Amer. Chem. Soc.*, 1936, **58**, 262.
[5] Milligan and Swan, *J.*, 1961, 1194.
[6] Milligan and Swan, *J.*, 1959, 2969.
[7] Lecher and Hardy, *J. Org. Chem.*, 1955, **20**, 475.
[8] Sorbo, *Acta Chem. Scand.*, 1958, **12**, 1990.

on a steam bath for 15 min. according to the general method of Baumgarten.[9] Crystallisation of the resulting slurry from ethanol yielded the *product* (1·3 g., 44%) as plates, m. p. 128°. After several recrystallisations from methanol–ether the m. p. had fallen to 120° (Found: C, 50·7; H, 4·7; N, 4·9; S, 22·5. $C_{12}H_{13}NO_3S_2$ requires C, 50·9; H, 4·6; N, 4·9; S, 22·6%).

Reaction of Thiolsulphates with Thiolacetate.—(i) A solution of sodium benzyl thiolsulphate (4·5 g.) in water (20 ml.) and a solution (pH 8·5) of thiolacetic acid (0·77 g.) and tri(hydroxymethylamino)methane (2·5 g.) in water (30 ml.) were shaken together for 1·5 hr. The product (1·26 g.), isolated by extraction with ethyl acetate, crystallised from light petroleum, giving dibenzyl trisulphide (0·95 g., 34%), m. p. 49° (lit.,[10] 49°) (Found: C, 60·4; H, 5·3; S, 34·8. Calc. for $C_{14}H_{14}S_3$: C, 60·4; H, 5·0; S, 34·6%). When the reaction was carried out at pH 12, the yield was 65%.

(ii) A solution of thiolacetic acid (3·1 g.), tri(hydroxymethylamino)methane (10 g.), and barium acetate monohydrate (22 g.) in water (80 ml.) was adjusted to pH 8·5. To this solution was added a solution of sodium benzyl thiolsulphate (18 g.) in water (80 ml.) which caused the slow formation of an inorganic precipitate. The mixture was left overnight and the product was isolated by extraction with ethyl acetate. Crystallisation from light petroleum gave acetyl benzyl disulphide (5·7 g., 36%), m. p. 56—57° (lit.,[1] 58—59°) (Found: C, 55·1; H, 5·3; S, 32·1. Calc. for $C_9H_{10}OS_2$: C, 54·5; H, 5·1; S, 32·3%). Dibenzyl trisulphide was present in the mother liquors. Reaction at 50° gave mainly dibenzyl trisulphide.

(iii) Thiolacetic acid (1·3 g.) was shaken with a solution of sodium benzyl thiolsulphate (3·7 g.) in phosphate buffer (30 ml.; pH 7) for 1 hr., a crude product (1·46 g.) being precipitated. Crystallisation of this from light petroleum gave acetyl benzyl disulphide (1·1 g., 34%), m. p. 56—57°. However, when this experiment was repeated, mixtures of acetyl benzyl disulphide and dibenzyl trisulphide were obtained.

(iv) Pyridinium *p*-tolyl thiolsulphate (3·6 g.) was added to a solution of barium acetate monohydrate (3·4 g.), tri(hydroxymethylamino)methane (3·0 g.), and thiolacetic acid (0·5 g.) in water (40 ml.) at pH 9·2. After 3 hr. the pH had fallen to 6·8. The resulting precipitate was filtered off, dried, and extracted with ethyl acetate. Evaporation of the extract gave an oil (1·4 g.), which was chromatographed in light petroleum on alumina. Elution with this solvent gave a crystals (0·86 g.), m. p. 78° after crystallisation from methanol. The m. p. was undepressed on admixture with di-*p*-tolyl trisulphide, prepared by reaction of toluene-*p*-thiol with sulphur dichloride.[12]

Reactions of Acetyl Benzyl Disulphide.—(i) Acetyl benzyl disulphide (0·48 g.) was added to a solution of sodium benzyl thiolsulphate (0·54 g.) and tri(hydroxymethylamino)methane (5 g.) in water (30 ml.), adjusted to pH 8·5. One drop of a non-ionic detergent was added, and the mixture was shaken at 50° for 10 min. and then at room temperature for 2 hr. The product (0·36 g.), isolated by extraction with ethyl acetate, gave dibenzyl trisulphide (0·24 g., 36%), m. p. 48—49°, on crystallisation from light petroleum. Addition of an excess of sodium sulphite to the reaction mixture had no effect and a similar yield of trisulphide was obtained from an experiment at pH 12. When sodium benzyl thiolsulphate was omitted, the acetyl benzyl disulphide was recovered largely unchanged; a few hand-picked crystals were identified as dibenzyl trisulphide.

(ii) Tri(hydroxymethylamino)methane (5 g.) was dissolved in 0·1M-sodium sulphide (25 ml.) and the pH was adjusted to 8·5. Acetyl benzyl disulphide (1·0 g.) was added and the mixture was shaken at 50° for 30 min. and then set aside overnight. Extraction with ethyl acetate gave a product (0·78 g.), from which dibenzyl trisulphide (0·57 g., 78%), m. p. 49°, was obtained by crystallisation from light petroleum.

(iii) Acetyl benzyl disulphide (0·30 g.) and cyclohexylamine (0·2 g.) were heated under reflux in ethanol (10 ml.) for 15 min., and the mixture was then evaporated. The residue was partitioned between ethyl acetate and dilute hydrochloric acid. Evaporation of the ethyl acetate extract gave a residue (0·27 g.) from which *N*-cyclohexylacetamide, m. p. 104°, was obtained by crystallisation from light petroleum.

Acetyl o-*Nitrophenyl Disulphide.*—Thiolacetic acid (4 g.) in water (20 ml.) was titrated to pH 7 with 10N-sodium hydroxide, and the solution made into a slurry with *o*-nitrobenzenesulphenyl chloride (5·5 g.). After 5 min. the mixture was filtered and the precipitate

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[9] Baumgarten, *Ber.*, 1930, **63**, 1331.

[10] Smythe and Forster, *J.*, 1910, **97**, 1195.

fractionally crystallised from ethanol. *Acetyl* o-*nitrophenyl disulphide* (3·1 g., 46%) was obtained as yellow prisms, m. p. 77°, substantially free from di-*o*-nitrophenyl disulphide (Found: N, 5·7; S, 27·0. $C_8H_7NO_3S_2$ requires N, 6·1; S, 28·0%).

Reaction of Thiolsulphates with Sodium Sulphide.—0·1M-Sodium sulphide (100 ml.) was added to sodium benzyl thiolsulphate (4·5 g.) in M-phosphate buffer (50 ml.; pH 8·0) and, after 1 hr., the resulting precipitate of dibenzyl trisulphide (1·8 g., 65%) was filtered off and crystallised from ethanol (m. p. and mixed m. p. 49°). Likewise, sodium phenacyl thiolsulphate gave diphenacyl trisulphide (37%), m. p. 78° (lit.,[11] 85—86°) (Found: C, 57·1; H, 4·3; S, 29·3. Calc. for $C_{16}H_{14}O_2S_3$: C, 57·5; H, 4·2; S, 28·8%); and pyridinium *p*-tolyl thiolsulphate gave di-*p*-tolyl trisulphide, isolated by ethyl acetate extraction and recrystallisation from methanol, having m. p. and mixed m. p. 81° (lit.,[12] 76—77°). Similar reactions of sodium *N*-cyclohexylcarbamoylmethyl thiolsulphate, sodium phenoxycarbonylmethyl thiolsulphate, and sodium *o*-nitrophenyl thiolsulphate gave only the corresponding disulphides in yields of 76, 14, and 74%, respectively.

Preparation of Trisulphides from Unisolated Thiolsulphates.—A mixture of sodium thiosulphate pentahydrate (0·25 mole) and the appropriate alkyl or alkenyl halide (0·2 mole) in 60% v/v ethanol–water (100 ml.) was heated under reflux until the mixture was homogeneous, indicating substantially complete formation of the intermediate thiolsulphate. The mixture was then distilled at reduced pressure to remove most of the ethanol, cooled, extracted with light petroleum (b. p. 30—40°), and treated with sodium sulphide (0·09 mole) in water (200 ml.). The crude trisulphide, deposited as an oil, was then extracted with light petroleum, washed with water, and dried. Removal of solvent gave a residue further purified by vacuum distillation. Yields of 65—70% were obtained.

In this way allyl chloride gave diallyl trisulphide, b. p. 66—67°/0·8 $\times$ 10^{-3} mm., n_D^{20} 1·5896, shown to be 99% pure by gas–liquid chromatography (Found: C, 40·4; H, 5·6; S, 53·9. Calc. for $C_6H_{10}S_3$: C, 40·4; H, 5·6; S, 53·9%), together with a little fore-fraction, b. p. 60—95°/12 mm. Similarly, ethyl bromide gave diethyl trisulphide, b. p. 79·8—80·0°/11 mm., n_D^{20} 1·5657 (Found: C, 31·1; H, 6·4; S, 62·2. Calc. for $C_4H_{10}S_3$: C, 31·2; H, 6·5; S, 62·3%) (98—99% pure by gas–liquid chromatography), together with a small fraction (*ca.* 8% of total distillate) having b. p. 55—77°/11 mm. and containing some diethyl disulphide. The amount of this impurity was markedly reduced when the aqueous solution of the intermediate thiolsulphate was covered with a layer of light petroleum before addition of sodium sulphide. The procedure was designed to minimise disulphide formation by preventing reaction between sulphite and trisulphide (cf. reactions 9, 10, 5, and 6). This procedure applied in the case of 1-chloro-2-methylpent-2-ene (synthesis to be described later) gave the very involatile di-(2-methylpent-2-enyl) trisulphide which without further treatment was found by a combination of chemical and gas–liquid chromatographic analyses to be about 97·5% pure.

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[11] Bloch and Bergmann, *Ber.*, 1920, **53**, 968.

[12] Troeger and Hornung, *J. prakt. Chem.*, 1899, **60**, 134.