1140. *Unsymmetrical Dialkyl Disulphides from Bunte Salts.*

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Simple unsymmetrical dialkyl disulphides can be obtained in a state of high purity by reaction of the appropriate thiol and sodium *S*-alkyl thiosulphate (Bunte salt) at pH 8, provided the reaction time is short. Disproportionation of these unsymmetrical disulphides is catalysed by thiols and by sulphite; the disproportionation by thiols can be inhibited by formaldehyde. The yield of ethyl methyl disulphide was not increased by addition of formaldehyde, and the disulphide could then not be separated from the accompanying monothiohemiacetal, formed from ethanethiol and formaldehyde. However, the use of sodium *m*-formylbenzenesulphonate instead of formaldehyde gave ethyl methyl disulphide in good yield.

Simple unsymmetrical dialkyl disulphides have been prepared by fractional distillation of the products obtained by ultraviolet irradiation of a mixture either of two dialkyl disulphides or of a thiol and a disulphide.[1-3] Related methods involve heating similar mixtures with small amounts of sodium sulphide [4] or iodine,[5] or oxidation of mixtures of the appropriate thiols.[2, 6] A more direct route to these compounds, requiring, however, anhydrous conditions, is the reaction of thiols with alkanesulphenyl thiocyanates which, because they are unstable, are generally prepared *in situ*.[7]

A simpler route, namely, reaction of thiols with Bunte salts (reaction 1) was therefore investigated. Footner and Smiles [8] first examined this reaction, using various arylalkyl or aryl thiosulphates and thiols in strongly alkaline solution, but found that the product

$$\mathrm{RS^- + R'S{\cdot}SO_3^- \rightleftharpoons RS{\cdot}SR' + SO_3^{2-}} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (1)$$

was generally a mixture of the two symmetrical disulphides rather than the expected unsymmetrical disulphide. Good yields of pure unsymmetrical disulphides related to

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[1] McAllan, Cullum, Dean, and Fidler, *J. Amer. Chem. Soc.*, 1951, **73**, 3627.

[2] Birch, Cullum, and Dean, *J. Inst. Petroleum*, 1953, **39**, 206.

[3] Kleiman, U.S.P. 2,474,849/1949 (*Chem. Abs.*, 1950, **44**, 653).

[4] Proell, U.S.P. 2,521,870/1950 (*Chem. Abs.*, 1951, **45**, 8027); Kleiman U.S.P. 2,510,893/1950 (*Chem. Abs.*, 1951, **45**, 637).

[5] Kleiman, U.S.P. 2,510,894/1950 (*Chem. Abs.*, 1951, **45**, 637).

[6] Carson and Wong, *J. Org. Chem.*, 1959, **24**, 175.

[7] Hiskey, Carroll, Babb, Bledsoe, Puckett, and Roberts, *J. Org. Chem.*, 1961, **26**, 1152.

[8] Footner and Smiles, *J.*, 1925, **127**, 2887.

cysteine have been obtained by conducting the reaction in weakly alkaline solution,[9] especially in the presence of strontium ions,[10] or at pH 5 in a stream of nitrogen to remove sulphur dioxide.[10] In these cases, moreover, disproportionation is minimized by the insoluble nature of the products.

Disproportionation of unsymmetrical disulphides in alkaline solution is known to be catalysed by thiols,[11] and probably also by sulphite, which can give rise to thiol by reaction with the unsymmetrical disulphide reverse of reaction (1)]. Methanethiol caused disproportionation of ethyl methyl disulphide at pH 8, giving after 3 hours a mixture of dimethyl, ethyl methyl, and diethyl disulphide in the molar ratio 32 : 55 : 13, as estimated by gas–liquid chromatography (g.l.c.). Sodium sulphite, in the same conditions, gave the same products in the ratio 26 : 46 : 28. It is therefore not surprising that, when methanethiol and sodium *S*-ethyl thiosulphate were allowed to react at pH 8 for 3 hours, a mixture of dimethyl, ethyl methyl, and diethyl disulphide was obtained (molar proportions 16 : 74 : 10, respectively). When the reaction time was reduced to 15 minutes, much purer ethyl methyl disulphide was obtained (ratio 3 : 96 : 1), without markedly affecting the total yield. Similar results were obtained for the alternative reaction of ethanethiol with sodium *S*-methyl thiosulphate, and in the syntheses of methyl n-propyl disulphide, ethyl n-propyl disulphide, and allyl ethyl disulphide. Reaction conditions, yields, and purities of products (estimated by g.l.c.) are shown in Table 1. While the yields of unsymmetrical disulphides were not high (10—42%), the shorter reaction time is recommended for products of highest purity, although this is less important for disulphides of higher molecular weight. Evans *et al.*[12] recently prepared 1,3-dimethylbut-2-enyl 2-methylpent-2-enyl disulphide (40% yield, 96% purity) by reaction of the appropriate thiol and Bunte salt at 0° for only 8 minutes.

TABLE 1.

Products obtained by reaction of thiols (RSH) and Bunte salts ($R'S{\cdot}SO_3Na$) according to the general method.

				Molar ratios of products		
R	R′	Reaction time (min.)	Yield of (%) *	RS·SR	RS·SR′	R′S·SR′
Me	Et	180	50	16	74	10
		60	55	7	90	3
		15	42	3	96	1
Et	Me	60	40	5	85	10
		15	21 †	1·5	97	1·5
Me	Pr	60	37 ‡	2	98	0
		15	31	1	98	1
Pr	Me	60	23	0·5	97	2·5
		15	10	0	98·5	1·5
Et	Pr	60	21 ‡	1·5	98·5	0·5
		15	18	0·4	99·4	0·2
Pr	Et	60	18 §	3	94	3
		15	16	0·5	96·5	3
Et	Allyl	60	43 ¶	0·5	99·5 **	0

* Yields refer to distilled material and were calculated on Bunte salt; when this salt was prepared *in situ*, yields were calculated from the corresponding alkyl halide used as starting material. † Based on methyl iodide. ‡ Based on propyl bromide. § Based on ethyl bromide. ¶ Based on allyl chloride. ** The product contained 2% of an unidentified contaminant of low retention volume.

In attempts to improve yields of unsymmetrical disulphides while retaining high purity, other variants of the reaction were explored. Addition of strontium or barium ions to a mixture of ethanethiol and sodium *S*-methyl thiosulphate at pH 8, in an attempt to displace

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[9] Schöberl and Bauer, *Angew. Chem.*, 1957, **69**, 478; *Fette u. Seifen*, 1958, **60**, 1061.

[10] Swan, *Nature*, 1957, **180**, 643; Stapleton and Swan, *Austral. J. Chem.*, 1962, **15**, 570.

[11] See, *e.g.*, Parker and Kharasch, *Chem. Rev.*, 1959, **59**, 583.

[12] Evans, Higgins, Saville, and Watson, *J.*, 1962, **5045**.

the equilibrium by precipitation of sulphite, gave surprisingly low yields (8—20%). Reaction at pH 5 also gave very low yields. In a recent synthesis of trisulphides from Bunte salts, Milligan, Saville, and Swan [13] used formaldehyde to eliminate sulphite (as its bisulphite addition compound) from reaction mixtures. Reaction of ethanethiol and sodium *S*-methyl thiosulphate in the presence of formaldehyde gave ethyl methyl disulphide contaminated with only a trace of diethyl disulphide, but containing relatively large amounts of (ethylthio)methanol, $EtS{\cdot}CH_2{\cdot}OH$, formed by reaction of thiol with formaldehyde.[14,15] Formaldehyde was also found to inhibit the disproportionation of ethyl methyl disulphide by methanethiol but, surprisingly, was less effective in inhibiting disproportionation by sulphite (see Table 4).

(Ethylthio)methanol was prepared by reaction of ethanethiol with formaldehyde at pH 8, and its structure and purity were confirmed by proton magnetic resonance spectroscopy. On gas–liquid chromatography or attempted distillation at atmospheric pressure, partial disproportionation to formaldehyde, and bisethylthiomethane, $CH_2(SEt)_2$, occurred. It could not be separated from ethyl methyl disulphide by distillation, by washing the crude mixture with lead acetate solution, or by treatment with iodoacetate, and a pure sample reacted only slowly with iodine–potassium iodide solution. The chemical stability was unexpected in view of the results obtained with more complex thiols.[15]

Contamination of unsymmetrical disulphides by compounds such as (ethylthio)-methanol and bisethylthiomethane could be avoided by using sodium *m*-formylbenzenesulphonate in place of formaldehyde. By this technique any mono- or di-thioacetals remain in the aqueous phase. Ethyl methyl disulphide was thus obtained from methanethiol or ethanethiol in 60% yield and 95% purity, the only impurities being the two symmetrical disulphides.

EXPERIMENTAL

Analysis of Products.—Mixtures of symmetrical and unsymmetrical disulphides were separated by g.l.c. on an F and M chromatograph (model 500). Operational details were as follows: carrier gas, helium, 28 lb./in.^{2}, flow rate 50—60 c.c./min.; 8 ft. stainless-steel column (¼″ outside diameter), packed with Silicone oil 550 (20%) on Chromosorb P; thermal conductivity detector, bridge power 150 mA, block temperature 250°; injection port temperature 170°. Mixtures of disulphides were generally separated by isothermal operation; but, when (ethylthio)methanol and bisethylthiomethane were also present, temperature programming was necessary.

The retention volumes, adjusted for dead space in the column, for isothermal operation at 150°, and flow rate 58 c.c./min., for dimethyl, ethyl methyl, methyl n-propyl, diethyl, ethyl n-propyl, and di-n-propyl disulphide were 179, 284, 450, 432, 675, and 1032 c.c., respectively. A linear relation was observed on plotting log retention volume against molecular weight, as expected for a homologous series.[16]

TABLE 2.

Physical properties of unsymmetrical disulphides, $RS{\cdot}SR'$.

R	R′	B. p.	n_D^{20}	Purity (%)	Recorded	Ref.
Me	Et	131—133°	1·5130	97	B. p. 135°, n_D^{20} 1·5146	17, 2
Me	Pr	69—71°/43 mm.	1·5070	98	n_D^{20} 1·4917	1
Et	Pr	85—86°/44 mm.	1·5008	99·4	B. p. 173°, n_D^{20} 1·5019	1
Et	Allyl *	75°/26 mm.	1·5251	99·5	—	—

* Twice distilled (Found: S, 47·1. $C_5H_{10}S_2$ requires S, 47·8%).

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[13] Milligan, Saville, and Swan, *J.*, 1963, 3608.

[14] Levi, *Gazzetta*, 1932, **62**, 776.

[15] Schubert, *J. Biol. Chem.*, 1936, **114**, 341.

[16] James and Martin, *Biochem. J.*, 1952, **50**, 679; Keulemans, " Gas Chromatography," Reinhold Publ. Corp., New York, 1961, p. 75.

[17] Britzinger and Langheck, *Chem. Ber.*, 1953, **86**, 557.

Synthesis of Unsymmetrical Disulphides.—General method. The alkanethiol (50 mmoles) was added rapidly to a stirred solution of the Bunte salt (50 mmoles) in 0·5M-phosphate buffer (pH 8; 100 ml.) at 0—5°, and the temperature then allowed to rise spontaneously. After the desired reaction time the product was extracted with ether (3 × 15 ml.) and distilled. Yields and purity of the products are shown in Table 1, and the physical properties of four unsymmetrical disulphides in Table 2.

The following modifications to the general method were also applied.

(1) Incorporation of (*a*) barium or (*b*) strontium ions. Barium or strontium chloride (60 mmoles) was added to the reaction mixture, 0·2M-trishydroxymethylaminomethane buffer (pH 8; 100 ml.) being used in place of phosphate buffer. Barium or strontium sulphite was subsequently removed by filtration under pressure with a filter-aid (Celite), and the product isolated from the filtrate by ether-extraction.

(2) Reaction at pH 5. Citrate buffer (0·5M; pH 5; 100 ml.) was used in place of phosphate buffer.

(3) Incorporation of formaldehyde. Formaldehyde (35% w/v; 60 mmoles) was added before addition of the thiol. The ethereal extracts were washed several times with water in this case.

(4) Incorporation of sodium *m*-formylbenzenesulphonate. Sodium *m*-formylbenzenesulphonate [18] (60 mmoles) was used instead of formaldehyde as in experiment (3). The results obtained by these various modifications in the synthesis of ethyl methyl disulphide are shown in Table 3.

TABLE 3.

Products of reaction of thiols (RSH) and Bunte salts ($R'S\cdot SO_3Na$) by modifications of the general method.

R	R′	Reaction time (hr.)	Method	Yield (%) *	Molar ratio of disulphides RS·SR	RS·SR′	R′S·SR′	Molar ratio of total disulphides to other products
Et	Me	2	1a	20 †	2	98	0	
Et	Me	1	1b	8 †	5	92	3	
Et	Me	3	2	5 †	10	89	1	
Et	Me	3	3	46	5	93	2	2 : 1
Me	Et	3	3	30	0	100	0	4 : 1
Et	Me	3	4	59	4	95	1	
Me	Et	3	4	59	3	94	3	

* Distilled product. † Insufficient for distillation.

Disproportionation of Ethyl Methyl Disulphide.—(1) A solution of methanethiol (1 mmole) in 0·5M-phosphate buffer (pH 8; 20 ml.) containing ethyl methyl disulphide (1 mmole) was shaken for 3 hr. and then extracted with ether (3 × 5 ml.). The ethereal extracts were analysed by g.l.c. without prior evaporation.

(1a) As for (1), but formaldehyde (35% w/v; 1 ml.) was included in the reaction mixture.

(2) As for (1), but sodium sulphite (1 mmole) was used in place of methanethiol.

(2a) As for (2), but including formaldehyde (35% w/v; 1 ml.).

The molar ratios of dimethyl, ethyl methyl and diethyl disulphide formed by each of these reactions are shown in Table 4.

TABLE 4.

Effect of formaldehyde on the disproportionation of ethyl methyl disulphide induced by (1) methanethiol and (2) sodium sulphite.

Expt.	Reagent	Molar ratio of products Me_2S_2	MeS_2Et	Et_2S_2	Expt.	Reagent	Molar ratio of products Me_2S_2	MeS_2Et	Et_2S_2
1	MeSH	32	55	13	2	Na_2SO_3	26	46	28
1a	$MeSH-CH_2O$	<1	100	<1	2a	$Na_2SO_3-CH_2O$	10	83	7

(*Ethylthio*)*methanol*.—Ethanethiol (6·2 g.) and formaldehyde (35%; 15 ml. w/v) were shaken at room temperature with 0·5M-phosphate buffer (pH 8; 100 ml.) for 2 hr. The product was

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[18] Wallach and Wüsten, *Ber.*, 1883, **16**, 150; Moore and Thomas, *J. Amer. Chem. Soc.*, 1922, **44**, 367.

then isolated by extraction with ether (3 × 25 ml.) and distilled. The main fraction (4·6 g., 50%) had b. p. 73°/32 mm., n_D^{20} 1·4850 (Found: C, 39·4; H, 8·9; S, 34·4. C_3H_8OS requires C, 39·1; H, 8·7; S, 34·8%). However, it was decomposed by g.l.c. giving three peaks ascribed to formaldehyde, (ethylthio)methanol, and bisethylthiomethane.

Spectra.—The proton magnetic resonance spectrum, measured in carbon tetrachloride solution with a Varian A-60 instrument and tetramethylsilane as internal standard (δ 0·00 p.p.m.), showed a triplet (δ 1·31 p.p.m.) due to $CH_3{\cdot}CH_2$, a quartet (δ ~2·72 p.p.m.) due to $CH_3{\cdot}CH_2{\cdot}S$, a sharp singlet (δ 4·76 p.p.m.) due to $S{\cdot}CH_2{\cdot}OH$, and a broad singlet (δ 3·94 p.p.m.) due to the hydroxyl group. The assignments were confirmed by integration. Formaldehyde which gives a signal close to δ 10·0 p.p.m., was absent.

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