Synthesis of 1,4-Oxathian-2-one, 5-Methyl-1,4-oxathian-2-one, and 1,4-Oxathiepan-2-one

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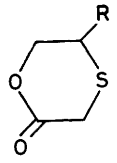
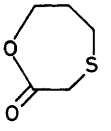
Intramolecular dehydration of 2-(2-hydroxyethylthio)acetic acid and of 2-(2-hydroxy-1-methylethylthio)acetic acid gives 1,4-oxathian-2-one and 5-methyl-1,4-oxathian-2-one, respectively. The precursor hydroxy-acids are formed by hydrolysis of the products of free radical addition of thioglycolic acid to vinyl acetate and propenyl acetate respectively. Free radical addition of thioglycolic acid to allyl chloride affords 2-(3-chloropropylthio)acetic acid, which is cyclised to 1,4-oxathiepan-2-one on treatment with potassium fluoride in glacial acetic acid. A mixture of 1,4-oxathiepan-2-one and 5-methyl-1,4-oxathian-2-one is produced on cyclodehydration of the mixture of 1 : 1 adducts formed by free radical addition of thioglycolic acid to allyl alcohol.

THE value of free radical reactions in synthetic organic chemistry [1] is most pronounced for free radical additions

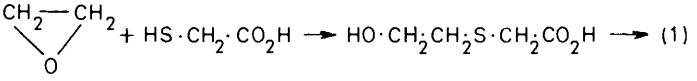


(1) R=H
(2) R=Me



(3)

to multiple bonds.[2,3] As part of a study of free radical addition reactions, the free radical addition of thiols to olefinic systems has now been utilised at essential stages in syntheses of 1,4-oxathian-2-one (1), 5-methyl-1,4-oxathian-2-one (2), and 1,4-oxathiepan-2-one (3). Of these only 1,4-oxathian-2-one had been prepared previously.[4,5] In the procedure [4,5] due to Black,[5] distillation of the product of reaction between thioglycolic acid and ethylene oxide afforded 1,4-oxathian-2-one (1) in 10% yield. The reaction is likely to have involved the *in situ* cyclisation of the intermediate hydroxy-acid (4).

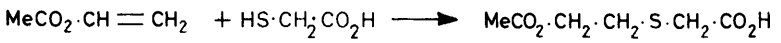


(4)

The preparations of several other derivatives of (1) have been reported; [4-9] such compounds are of interest both for their possible physiological activity [7] and for the effect of the heteroatoms on the conformation of the alicyclic system.[4]

In the improved procedure for the synthesis of (1) now reported, the acetoxy-acid (5) 63% is obtained by free radical addition of thioglycolic acid to vinyl acetate. Hydrolysis of (5) by boiling at reflux with aqueous potassium hydroxide under nitrogen gave the hydroxy-acid (4) (95%) as a viscous liquid which, within an hour of preparation, began to turn cloudy and to deposit a white polymeric solid. However, when a dilute solution of (4) in xylene was heated at reflux, in the presence of a catalytic quantity of toluene-*p*-sulphonic acid, cyclic dehydration of (4) occurred to afford 1,4-oxathian-2-one (1) (79%).

This procedure for obtaining (1) appears to be of general validity for the synthesis of substituted 1,4-oxathian-2-ones when substituted vinyl acetates are used in the first step of free radical addition. For example the free radical addition of thioglycolic acid to propenyl acetate [a 1 : 1 mixture of *cis* (6) and *trans* (7)] readily took place at 0 °C to afford the acetoxy-acid (8) (35%). Hydrolysis of (8) led to the hydroxy-acid



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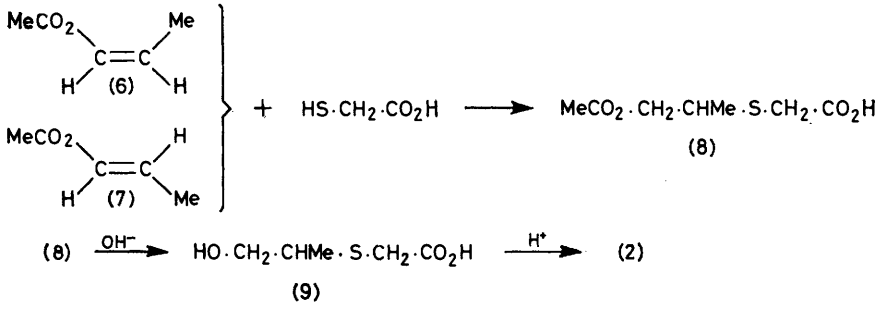
[1] D. I. Davies and M. J. Parrott, *Chem. in Britain*, 1975, **11**, 364.
[2] G. Sosnovsky, 'Free Radical Reactions in Preparative Organic Chemistry,' Macmillan, New York, 1964, particularly chs. 1—3.
[3] C. Walling and E. S. Huyser, *Org. Reactions*, 1963, **13**, 91; F. W. Stacey and J. F. Harris, jun., *ibid.*, p. 150.
[4] K. Jankowski, R. Coulombe, and C. Berse, *Bull. Acad. polon. Sci., Ser. Sci. chim.*, 1971, **19**, 661.
[5] D. K. Black, *J. Chem. Soc.* (*C*), 1966, 1708.
[6] D. Greenwood and H. A. Stevenson, *J. Chem. Soc.*, 1953, 1514.
[7] M. Schubert, *J. Amer. Chem. Soc.*, 1947, **69**, 712.
[8] L. Horner and K. Sturm, *Annalen*, 1955, **597**, 1.
[9] H. P. Kaufmann and R. Schickel, *Fette, Seifen, Anstrichm.*, 1963, **65**, 851.

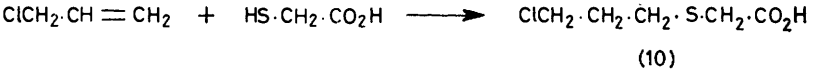
(9), which on dehydration afforded 5-methyl-1,4-oxathian-2-one (2) (82%).

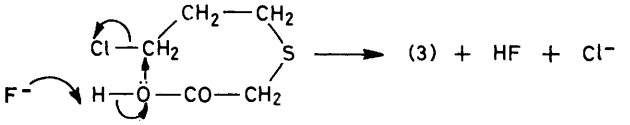
1,4-Oxathiepan-2-one (3), a hitherto unknown seven-membered ring analogue of (1), may also be prepared by



a procedure involving free radical addition. Thioglycolic acid when heated with an excess of allyl chloride [10,11] under nitrogen at 70—80 °C afforded the chloro-acid (10) 58%. A solution of this acid (10) in glacial acetic acid containing potassium fluoride, when boiled at reflux, afforded 1,4-oxathiepan-2-one (3) (94%).

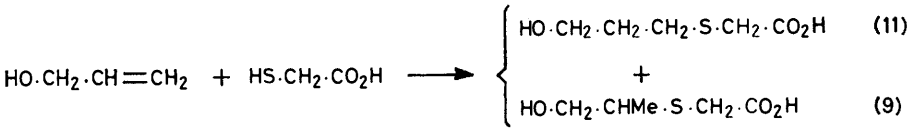
The properties of solutions of potassium fluoride in





glacial acetic acid have been investigated by Emsley,[12] and this method for cyclisation is due to Clark and Emsley.[13] The formation of (3) is suggested to proceed by an intramolecular nucleophilic displacement of chlorine, as shown.

The free radical addition of thioglycolic acid to allyl alcohol afforded a 19 : 1 mixture (85%) of the hydroxy-acids (11) and (9), which we were unable to separate



(attempts invariably led to some polymerisation and cyclisation). Dehydration of the mixture gave a 19 : 1 mixture (85%) of 1,4-oxathiepan-2-one (3) and 5-methyl-1,4-oxathian-2-one (2), which also was not separated.

[10] E. Larsson, *Acta. Univ. Lund., Sect. II, No.* 22, 1965 (*Chem. Abs.*, 1966, **64**, 12635).

[11] C. M. Buess, C. N. Yiannios, and W. T. Fitzgerald, *J. Org. Chem.*, 1957, **22**, 197.

EXPERIMENTAL

2-(2-*Methoxycarbonylethylthio*)*acetic Acid* (5).—Freshly distilled vinyl acetate (5 g, 0.058 mol) and thioglycolic acid (5 g, 0.054 mol) were mixed at room temperature and stirred. After a few minutes a vigorous exothermic reaction ensued and external cooling was necessary to keep the temperature below 50 °C. After 18 h the excess of vinyl acetate was evaporated off, and the crude product distilled to afford the *acid* (5) (6.5 g) as an oil, b.p. 119—120° at 0.02 mmHg, n_D^{20} 1.493 0 (Found: C, 40.25; H, 5.6; S, 18.25. $C_6H_{10}SO_4$ requires C, 40.5; H, 5.6; S, 17.9%), δ (60 MHz; CCl_4) 2.05 (s, Ac), 2.85 (t, $CH_2{\cdot}CH_2{\cdot}S$, *J* 6 Hz), 3.25 (s, $CH_2{\cdot}S{\cdot}CH_2CO$), 4.25 (t, $O{\cdot}CH_2{\cdot}CH_2{\cdot}S$, *J* 6 Hz), and 11.40 ($CO_2H$), $\nu_{max.}$ 3 600—3 000 (OH), 1 735 (C=O), and 1 710 cm^{-1} (C=O).

2-(2-*Hydroxyethylthio*)*acetic Acid* (4).—The acetate (5) (8.9 g, 0.05 mol) dissolved in aqueous 40% potassium hydroxide (44.8 g, 0.8 mol) was boiled at reflux under nitrogen for 5 h. The mixture was then cooled, acidified with concentrated hydrochloric acid, and extracted continuously with diethyl ether for 18 h. The extract was washed with water, dried ($MgSO_4$), and evaporated. Residual acetic acid was removed by addition of chlorobenzene and evaporation first of the acetic acid and then of chlorobenzene. The residual acid (4) (6.4 g) was a viscous liquid which polymerised rapidly but was recognisable from its spectral data: δ [60 MHz; $(CD_3)_2SO$] 2.25 (t, $O{\cdot}CH_2{\cdot}CH_2{\cdot}S$, *J* 6 Hz), 3.25 (s, $S{\cdot}CH_2{\cdot}CO$), 3.75 (t, $O{\cdot}CH_2{\cdot}CH_2{\cdot}S$,

[12] J. Emsley, *J. Chem. Soc.* (*A*), 1971, 2511.

[13] J. H. Clark and J. Emsley, *J.C.S. Dalton*, 1975, 2129.

J 6 Hz), and 7.0 (OH, CO_2H), $\nu_{max.}$ 3 600—3 000 (OH) and 1 710 cm^{-1} (C=O).

1,4-*Oxathian*-2-*one* (1).—The hydroxy-acid (4) (1 g) dissolved in diethyl ether (20 ml) was added to *p*-xylene (300 ml) containing toluene-*p*-sulphonic acid monohydrate [14] (5 mg). The mixture was then boiled at reflux in a Dean–Stark water separator; the first part of the distillate (50 ml) was removed and discarded since it contained the diethyl ether. After 5 h the mixture was cooled, washed with water (4 × 150 ml), dried ($MgSO_4$), and evaporated. Distillation of the residue afforded 1,4-oxathian-2-one (1) (0.69 g), M^+ 118, with properties as in the literature,[4,5,15] δ (60 MHz; $CDCl_3$) 3.00 (t, $CH_2{\cdot}CH_2{\cdot}S$, J 6 Hz), 3.40 (s, $S{\cdot}CH_2{\cdot}CO$), and 4.55 (t, $CH_2{\cdot}CH_2{\cdot}S$, J 6 Hz), $\nu_{max.}$ 1 740 cm^{-1} (C=O), *m/e* 118 (50%, M^+), 89 (30%, $CH_2SCH_2\overset{+}{C}{=}OH$), 88 (28%, $CH_2SCH_2\overset{+}{C}{=}O$), 74 (68%, $SCH_2\overset{+}{C}{=}O$ or $CH_2CH_2\overset{+}{S}CH_2$), 60 (84%, $CH_2\overset{+}{S}CH_2$), 59 (76%), 48 (68%), 47 (76%), 46 (100%, $CH_2\overset{+}{S}$), 45 (90%), 43 (66%, $CH_2C{=}\overset{+}{O}H$), and 42 (80%, $CH_2\overset{+}{C}{=}O$).

Propenyl Acetate [(6) + (7)].[16]—Propionaldehyde (3 g, 0.051 7 mol; freshly redistilled under nitrogen), acetic anhydride (12.65 g, 0.124 mol), and potassium acetate (1.01 g, 0.010 3 mol) were heated together for 2 h under nitrogen in a sealed tube at 150 °C. The tube was then cooled and opened and the mixture washed successively with warm water (5 × 70 ml), aqueous 0.5M-sodium hydrogen carbonate (4 × 50 ml), and warm water (2 × 70 ml) to afford a crude product which on distillation afforded a 1 : 1 mixture (0.94 g) [17] of *cis*- (6) and *trans*- (7) propenyl acetate, b.p. 104—106° at 750 mmHg (Found: C, 60.0; H, 8.0. Calc. for $C_5H_8O_2$: C, 60.0; H, 8.0%), δ (60 MHz; $CDCl_3$) 1.55—1.75 (m, $CH_3{\cdot}CH{=}$), 2.17 and 2.22 (singlets for Ac of *cis*- and *trans*-isomers), 4.65—4.7 (m, $CH_3{\cdot}CH{=}$), and 6.9—7.2 (m, $CH_3{\cdot}CO{\cdot}O{\cdot}CH{=}$), $\nu_{max.}$ 1 760 (C=O) and 1 680 cm^{-1} (C=C). A fraction collected at 178—180 °C and 750 mmHg corresponded to 1,1-diacetoxypropane (lit.,[18] 184—185° at 760 mmHg) (Found: C, 52.5; H, 7.5. Calc. for $C_7H_{12}O_4$: C, 52.5; H, 7.5), δ (60 MHz; $CDCl_3$) 0.95 (t, CH_3CH_2, J 7 Hz), 1.35—2.25 (m, $CH_3{\cdot}CH_2CH$), 2.05 (s, Ac), and 6.70 (t, $CH_2{\cdot}CH$, J 5 Hz), $\nu_{max.}$ 1 745 cm^{-1} (C=O).

2-(2-*Methoxycarbonyl*-1-*methylethylthio*)*acetic Acid* (8).—Freshly distilled propenyl acetate [(6) + (7)] (2.4 g, 0.03 mol) was stirred at 0 °C and thioglycolic acid (2.2 g, 0.03 mol) was slowly added. After 15 min the mixture was allowed to reach room temperature and left overnight with continuous stirring. Work-up as in the preparation of (4) gave the *acid* (8) (1.6 g) as an oil, b.p. 146—148° at 0.1 mmHg (Found: C, 43.8; H, 6.3; S, 16.75. $C_7H_{12}SO_4$ requires C, 43.75; H, 6.25; S, 16.65%), δ (60 MHz; $CDCl_3$) 1.3 (d, $CH_3{\cdot}CH$, J 7 Hz), 2.06 (s, OAc), 2.9—3.8 (m, $CH_3{\cdot}CH$), 3.35 (s, $S{\cdot}CH_2{\cdot}CO$), 4.15 (d, $O{\cdot}CH_2{\cdot}CH$, J 7 Hz), and 11.3 (CO_2H), $\nu_{max.}$ 3 600—3 000 (OH), 1 735 (C=O), and 1 710 cm^{-1} (C=O).

2-(2-*Hydroxy*-1-*methylethylthio*)*acetic Acid* (9).—By the procedure for the hydrolysis of (5), the ester (8) (9.6 g) afforded the hydroxy-acid (9) (7.2 g) as a viscous liquid, which rapidly became cloudy and deposited white polymeric material, but was recognisable from its spectral data: δ [60 MHz; $(CD_3)_2SO$] 1.25 (d, $CH_3{\cdot}CH$, J 7 Hz), 2.3—3.75 (m, $CH_3{\cdot}CH$), 3.25 (s, $S{\cdot}CH_2{\cdot}CO$), 4.25 (d, $O{\cdot}CH_2{\cdot}CH$, J 7 Hz), and 7.0 (OH, CO_2H), $\nu_{max.}$ 3 600—3 000 (OH) and 1 710 cm^{-1} (C=O).

5-*Methyl*-1,4-*oxathian*-2-*one* (2).—By the procedure for the cyclodehydration of (4), the hydroxy-ester (9) (1 g) afforded 5-*methyl*-1,4-*oxathian*-2-*one* (2) (0.72 g) as a viscous liquid, b.p. 75° at 0.1 mmHg, n_D^{25} 1.514 0 (Found: C, 45.4; H, 6.5. $C_5H_8SO_2$ requires C, 45.45; H, 6.05%), δ (60 MHz; $CDCl_3$) 1.30 (d, $CH_3{\cdot}CH$, J 7 Hz), 3.0—3.6 (m, $CH_3{\cdot}CH$), 3.32 (s, $S{\cdot}CH_2{\cdot}CO$), and 3.9—4.55 (m, $O{\cdot}CH_2{\cdot}CH_2$), $\nu_{max.}$ 1 740 cm^{-1} (C=O), *m/e* 132 (49%, M^+), 88 [12%, $CH_3CHSCH_2\overset{+}{C}{=}O$ or $CH_3CH(CH_2)\overset{+}{S}CH_2$], 85 (34%), 74 (34%, $CH_3CH\overset{+}{S}CH_2$ or $SCH_2\overset{+}{C}{=}O$), 73 (31%), 60 (100%), 55 (58%), 46 (100%, $CH_2\overset{+}{S}$), 43 (46%, $CH_2\overset{+}{C}{=}OH$), and 42 (49%, $CH_2\overset{+}{C}{=}O$).

2-(3-*Chloropropylthio*)*acetic Acid* (10).—A mixture of thioglycolic acid (1.8 g, 0.029 mol) and allyl chloride (2.5 g, 0.032 mol) was heated at 70—80 °C under nitrogen in a sealed tube for 6 h. After cooling, the tube was opened and the excess of allyl chloride evaporated off. Distillation of the crude product afforded the *acid* (10) (1.9 g) as an oil, b.p. 130° at 0.45 mmHg (Found: C, 35.4; H, 5.9; Cl, 20.95; S, 18.9. $C_5H_9ClO_2S$ requires C, 35.4; H, 5.9; Cl, 20.95; S, 18.8%), δ (60 MHz; $CDCl_3$) 1.8—2.3 (m, $CH_2{\cdot}CH_2{\cdot}CH_2$), 2.83 (t, $CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}S$, J 7 Hz), 3.27 (s, $S{\cdot}CH_2{\cdot}CO$), 3.65 (t, $ClCH_2{\cdot}CH_2{\cdot}CH_2$, J 7 Hz), and 11.87 (s, CO_2H), $\nu_{max.}$ 1 710 cm^{-1} (C=O).

1,4-*Oxathiepan*-2-*one* (3).—The acid (10) (1.5 g, 0.008 9 mol) was added to a hot solution of anhydrous potassium fluoride (2.1 g, 0.036 mol) in anhydrous glacial acetic acid (18 g, 0.03 mol). The mixture was boiled at reflux for 30 h, then cooled, diluted with water (50 ml), and immediately extracted with diethyl ether (3 × 50 ml). The combined extracts were concentrated to 75 ml and then quickly washed with water (5 × 75 ml) and dried (Na_2SO_4). Evaporation left 1,4-*oxathiepan*-2-*one* (3) (1.1 g) as a viscous liquid, b.p. 86° at 0.06 mmHg, n_D^{25} 1.486 0 (Found: C, 45.45; H, 6.3. $C_5H_8SO_2$ requires C, 45.45; H, 6.05%), δ (60 MHz; $CDCl_3$) 1.7—2.3 (m, $CH_2{\cdot}CH_2{\cdot}CH_2$), 2.75 (t, $CH_2{\cdot}CH_2{\cdot}S$, J 6 Hz), 3.25 (s, $S{\cdot}CH_2{\cdot}CO$), and 4.23 (t, $O{\cdot}CH_2{\cdot}CH_2$, J 6 Hz), $\nu_{max.}$ 1 725 cm^{-1} (C=O), *m/e* 132 (16%, M^+), 88 (20%, $CH_2SCH_2\overset{+}{C}{=}O$), 74 (14%, $CH_2\overset{+}{S}CH_2CH_2$ or $SCH_2\overset{+}{C}{=}O$), 73 (58%, $CH_2\overset{+}{S}CH{=}CH_2$), 61 (31%), 47 (41%, $\overset{+}{S}CH_3$), 46 (30%, $\overset{+}{S}CH_2$), 43 (100% $CH_2\overset{+}{C}{=}OH$), and 42 (18%, $CH_2\overset{+}{C}{=}O$).

19 : 1 *Mixture of* 2-(3-*Hydroxypropylthio*)- (11) *and* 2-(2-*Hydroxy*-1-*methylethylthio*)-*acetic Acid* (9).—Thioglycolic acid (4.6 g, 0.05 mol) was added dropwise, with stirring, to allyl alcohol (3 g, 0.052 mol). After several minutes an exothermic reaction ensued, and the mixture was cooled so that the temperature was kept below 50 °C. After 18 h the mixture was dissolved in ether (100 ml) and extracted with saturated aqueous sodium hydrogen carbonate (5 × 20 ml). The extract was acidified with concentrated hydrochloric acid and continuously extracted with ether overnight. The ethereal extract was dried ($MgSO_4$), filtered, and evaporated to yield a 19 : 1 mixture (6.6 g) of *hydroxy-*

[14] W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *J. Amer. Chem. Soc.*, 1961, **83**, 606.
[15] K. Jankowski and R. Coulombe, *Tetrahedron Letters*, 1971, 991.
[16] P. Z. Bedoukian, *Org. Synth.*, 1949, **29**, 14.
[17] H. O. House and V. Kramar, *J. Org. Chem.*, 1963, **28**, 3362.
[18] R. Wegscheider and E. Spath, *Monatsh.*, 1910, **30**, 846.

acids (11) and (9) as a viscous liquid, rapidly becoming cloudy and depositing polymeric white solid but recognisable from its spectral data: δ [60 MHz; $(CD_3)_2SO$] 1.25 [d, CH_3·CH in (9), *J* 7 Hz], 1.5—2.2 [m, O·CH_2·CH_2·CH_2·S of (11)], 2.75 [t, CH_2·CH_2·CH_2·S of (11), *J* 7 Hz], 3.25 (s, S·CH_2·CO), 2.65 [t, O·CH_2·CH_2·CH_2·S of (11), *J* 6 Hz], and 6.35 (OH, CO_2H) [peaks due to OCH_2·CH of (9) and CH_2CH of (9) in the regions δ 3.6 and 3.2 were masked by other peaks], $\nu_{max.}$ 3 700—2 600 (OH), 2 950 (CH), and 1 720 cm^{-1} (C=O).

19 : 1 *Mixture of* 1,4-*Oxathiepan*-2-*one* (3) *and* 5-*Methyl*-1,4-*oxathian*-2-*one* (2).—By the procedure for cyclodehydration of (4), the 19 : 1 mixture of (11) and (9) (1 g) afforded a 19 : 1 mixture of 1,4-oxathiepan-2-one (3) and 5-methyl-1,4-oxathian-2-one (2) as a viscous liquid (0.75 g), δ (60 MHz; $CDCl_3$) 1.25 [d, CH_3CH of (2), *J* 6 Hz], 1.6—2.15 [m, CH_2·CH_2·CH_2 of (3)], 2.65 [t, CH_2·CH_2·CH_2·S of (3), *J* 6 Hz], 3.15 [s, S·CH_2·CO of (2) and (3)], and 4.15 [t, O·CH_2·CH_2·CH_2 of (3), *J* 6 Hz] [other peaks of (2) were masked by those of (3)]. G.l.c.–mass spectrometry indicated M^+ for both components as 132.

We thank the S.R.C. for a CASE award (to L. H.) and financial support (to Y. D. V.). We thank Drs. P. Roffey and N. J. A. Gutteridge, Lilly Research Centre, Windlesham, for their help and interest in the work. Financial support from the Lilly Research Centre is also gratefully acknowledged.

[7/940 *Received*, 1*st June*, 1977]