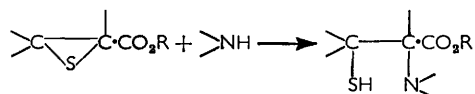


94. Small-ring Heterocyclic Compounds. Part II.¹ Reactions of Aliphatic Glycidic Esters with Thiourea and with Thioacetic Acid.

By T. C. OWEN, C. L. GLADYS, and L. FIELD.

Reactions of aliphatic glycidic esters with thiourea and with thioacetic acid gave, instead of the expected $\alpha\beta$ -epithio-esters, α -mercaptoacrylates, polymers, and diols arising by addition of water to the epoxide ring. Evidence is presented that the one known epithio-ester² is the $\beta\gamma$ -isomer, and it seems that the $\alpha\beta$ -compounds may not be easy to obtain.

IN connexion with the synthesis of compounds which afford protection against ionising radiation, the most active of which contain 2-aminoethylthio-groups,³ we wished to convert 2,3-epithio-esters into substituted cysteine derivatives by reaction with amines. The desired reaction would be analogous to that of episulphides⁴ and of glycidic esters⁵ with amines to give 2-mercaptoamines and α -amino- β -hydroxypropionates, respectively. Epithio-esters themselves may also be potential radioprotective agents since it has been suggested that a requirement for such action is ability to combine with the thiol groups of proteins.³ The episulphide ring is readily opened by thiolates, giving 2-mercapto-sulphides.⁶ However, only one epithio-ester is known.² This paper concerns some aliphatic epithio-esters, including that previously reported.



Aliphatic episulphides have been prepared from epoxides by reaction with various sulphur compounds, including thiocyanates,⁷ thiourea,^{2,6} substituted thioureas and thioamides,⁶ and thioacetic acid followed by treatment with base.^{8,9} The main criteria for success appear to be avoidance of prolonged heating or contact with alkali or thiolate ions.^{6,10} We have studied the reactions of three typical aliphatic glycidic esters, ethyl $\alpha\beta$ -epoxybutyrate (III), ethyl $\alpha\beta$ -epoxy- β -methylvalerate (X), and ethyl $\beta\gamma$ -epoxy- β -methylvalerate (XVIII), with thioacetic acid and with thiourea as potential routes to epithio-esters.

The most satisfactory recorded route to the ester (III) appears to be epoxidation of ethyl crotonate (I) with peracetic acid.¹¹ (We found neither of the recorded methods for

¹ Part I, Field and Carlile, *J. Org. Chem.*, 1961, **26**, 3170.

² Durden, Stansbury, and Catlette, *J. Amer. Chem. Soc.*, 1959, **81**, 1943.

³ Pihl and Eldjarn, *Pharmacol. Rev.*, 1958, **10**, 437 and references therein.

⁴ Jacobs, Ph.D. Thesis, Michigan State Univ., 1959; Braz, *J. Gen. Chem. (U.S.S.R.)*, 1951, **21**, 668; Schmolka and Spoerri, *J. Amer. Chem. Soc.*, 1957, **79**, 4719; Snyder, Stewart, and Ziegler, *ibid.*, 1947, **69**, 2672.

⁵ Martynov and Ol'man, *J. Gen. Chem. (U.S.S.R.)*, 1957, **27**, 1881; 1958, **28**, 592.

⁶ Culvenor, Davies, and Heath, *J.*, 1949, 282.

⁷ van Tamelen, *J. Amer. Chem. Soc.*, 1951, **73**, 3444.

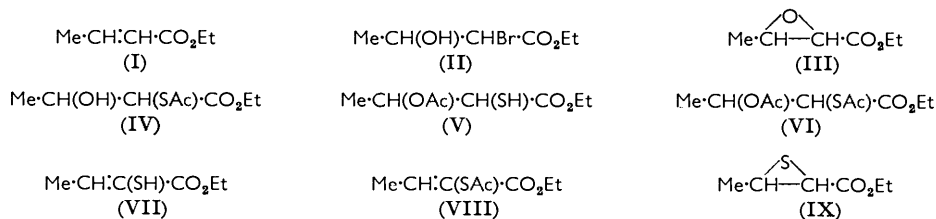
⁸ Harding, Miles, and L. N. Owen, *Chem. and Ind.*, 1951, 887; Miles and L. N. Owen, *J.*, 1952, 817; Harding and L. N. Owen, *J.*, 1954, 1528.

⁹ Goodman, Benitez, and Baker, *J. Amer. Chem. Soc.*, 1958, **80**, 1680.

¹⁰ Culvenor, Davies, and Pausacker, *J.*, 1946, 1050.

¹¹ MacPeck, Starcher, and Phillips, *J. Amer. Chem. Soc.*, 1959, **81**, 680.

the preparation of peracetic acid in inert solvents relatively free from acetic acid^{12,13} convenient for occasional laboratory use, and instead prepared such solutions from acetic anhydride and 30% hydrogen peroxide by a procedure based on that of Payne¹⁴ for monopero-phthalic acid.) The yield of glycidate (III) by this route was not good. This



ester was more conveniently obtained by reaction of ethyl crotonate with *N*-bromosuccinimide in aqueous dioxan, giving a compound considered to be ethyl α -bromo- β -hydroxybutyrate (II) (rather than the β -bromo- α -hydroxy-isomer) which gave the glycidate on treatment with aqueous base.

Ethyl glycidate (III) reacted smoothly at 45° (17 hr.) with thioacetic acid in the presence of a catalytic amount of pyridine, giving ethyl α -acetylthio- β -hydroxybutyrate (IV) with some of the isomeric ethyl β -acetoxy- α -mercaptobutyrate (V) arising by base-catalysed transfer of the acetyl group from sulphur to oxygen.⁸ A shorter reaction time or lower temperature was less satisfactory. Both products were converted into ethyl β -acetoxy- α -acetylthiobutyrate (VI) by acetic anhydride and pyridine. The formulation of these three products (IV—VI) as β -oxy- α -thio- rather than α -oxy- β -thio-compounds is based on similar additions of thiols and of thiourea to glycidic esters in acidic, basic, and neutral media.^{2,15} This was confirmed when the esters (V) and (VI) afforded ethyl 2-mercaptobut-2-enoate (VII) differing from the known ethyl 3-mercaptobut-2-enoate and from similar results in the aromatic series¹⁶ where the analogous products are well characterised.

On the basis of previous work^{8,9} reaction of the esters (IV—VI) with alkali would be expected to give ethyl $\alpha\beta$ -epithiobutyrate (IX) by rearrangement or partial hydrolysis of (IV) or (VI) to (V), followed by cyclisation with expulsion of acetate ion. However, the esters (V) and (VI) with alcoholic potassium hydroxide gave moderate yields of ethyl 2-mercaptobut-2-enoate (VII) and considerable amounts of materials which, although not investigated, are tentatively formulated as dimerised and polymerised epithio-ester. The yields of the butenoate and polymer together accounted for more than 80% of the diacetate (VI) used. When the diacetate was steam-distilled from aqueous sodium hydrogen carbonate (cf. ref. 8), it afforded ethyl 2-acetylthiobut-2-enoate (VIII) in moderate yield. No epithio-ester or ethyl crotonate was obtained in these reactions. Similar steam-distillation of the *O*-acetate (V) gave only a very small amount of organic product in the distillate and this did not liberate iodine from methyl iodide, a reaction characteristic of episulphides,¹⁷ and accordingly is not considered to have contained any epithio-ester. Compounds (V) and (VI) are therefore considered to react simultaneously in two ways with alkali: (a) Abstraction of hydrogen from the activated α -position followed by electron redistribution with expulsion of acetate ion gives the butenoates (VII) and (VIII); this reaction is unlikely in the case of the thioacetic acid addition products from simple epoxides owing to the absence there of the activating ethoxycarbonyl group. (b) The epithio-ester (IX) is formed by the route outlined above and at once

¹² Phillips, Frostick, and Starcher, *J. Amer. Chem. Soc.*, 1957, **79**, 5982.

¹³ Phillips, Starcher, and Ash, *J. Org. Chem.*, 1958, **23**, 1823.

¹⁴ Payne, *J. Org. Chem.*, 1959, **24**, 1354.

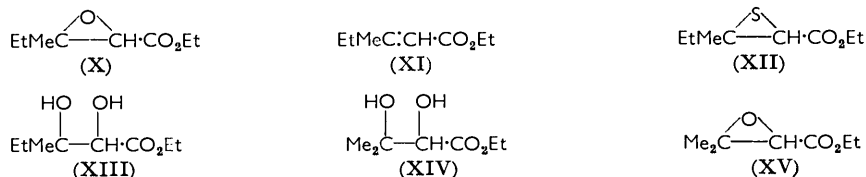
¹⁵ Culvenor, Davies, and Heath, *J.*, 1949, 278.

¹⁶ Owen, Gladys, and Field, following paper.

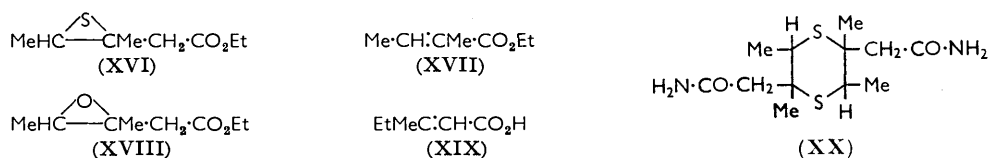
¹⁷ Helmkamp and Pettitt, *J. Org. Chem.*, 1960, **25**, 1754.

polymerises; this contrasts with the behaviour of aromatic analogues¹⁶ where decomposition occurs by desulphurisation (to give the monomeric unsaturated esters) rather than by polymerisation. The possibility that the butenoate (VII) arises by isomerisation of the episulphide (IX) seems to be precluded by the formation of the *S*-acetate (VIII) under the milder conditions of steam-distillation from bicarbonate, where the product is separated from the alkaline medium before hydrolysis of the *S*-acetyl group can occur.

Ethyl $\alpha\beta$ -epoxy- β -methylvalerate^{18,19} (X) was prepared by Darzens condensation of butanone (cf. Linstead and Mann¹⁸). With thioacetic acid and pyridine it gave very little simple addition product; instead, a compound $C_{12}H_{20}O_4S$ was obtained, sulphur and hydrogen sulphide being liberated. With potassium thioacetate in ethanol, the epoxide (X) gave ethyl 3-methylpent-2-enoate (XI) in low yield, presumably through formation



and desulphurisation of the epithio-ester (XII). Since an epithio-ester supposed to be (XII) is the only epithio-ester reported in the literature,² attempts were made to convert the epoxide (X) into it by using thiourea and sulphuric acid as in the reported procedure. The sole product, under various conditions, was the $\alpha\beta$ -dihydroxy-ester (XIII) produced by simple hydration. This ester has not been described previously although the corresponding acid is known.¹⁹ Ethyl $\alpha\beta$ -dihydroxy- β -methylbutyrate (XIV) was also the principal product from a similar reaction of ethyl $\alpha\beta$ -epoxy- β -methylbutyrate (XV).² Repetition of the reaction with thiourea and a sample of the epoxyester supposed to be (X), kindly presented by Dr. Durden, gave the reported epithio-ester [which we now consider to be (XVI)] as reported by him (slight modification of the conditions led to a higher yield). However, the refractive indices and infrared spectra of the two esters presumed both to be (X) were different: that prepared by us had b. p. $89^\circ/15$ mm., n_D^{25} 1.4238 (lit.,^{18,19} b. p. $91-95^\circ/17$ mm., $60-64^\circ/2-3$ mm., n_D^{21} 1.4255, whence $n_D^{25} \approx 1.4239$); that provided by Durden had b. p. $91^\circ/25$ mm., n_D^{25} 1.4202. The infrared spectra were



similar but differed particularly at 1740 (side peak) 1430, 1130, 1105, and 1035 cm^{-1} where our glycidic ester showed well-developed absorptions which were weak or missing in the other ester, and at 1350, 1310, 1080, 885-870, and 695 cm^{-1} where the converse was true. We first ascribed this to geometrical isomerism but, when Dr. Durden's ester (XVI) was heated with methyl iodide and acetone,¹⁷ iodine and trimethylsulphonium iodide were formed together with ethyl 3-methylpent-3-enoate (XVII) (37%) instead of the expected pent-2-enoate (XI). Since this desulphurisation is both positionally and stereochemically specific,¹⁷ at least for simple episulphides, both Dr. Durden's esters (XVI) and (XVIII) must be $\beta\gamma$ - rather than $\alpha\beta$ -derivatives. Correspondence with Dr. Durden elucidated that his glycidic ester was prepared (unpublished work) by peracetic acid

¹⁸ Linstead and Mann, *J.*, 1930, 2070.

¹⁹ Sjolander, Folkers, Adelberg, and Tatum, *J. Amer. Chem. Soc.*, 1954, **76**, 1085.

oxidation of an unsaturated ester, itself prepared by esterification of an unsaturated acid obtained by boron trifluoride-catalysed reaction of butanone with keten. It is well authenticated that 3-methylpentenoic acid is an exception to Fittig's rule of preferred conjugation in unsaturated acids and their derivatives, and Kon, Linstead, and their co-workers have shown²⁰ that the pent-2-enoic acid (XIX) is isomerised largely to the unconjugated pent-3-enoic acid on treatment with alkali, and to the unconjugated ester (XVII) during Fischer esterification with acid catalysts.

The glycidic ester (XVIII) reacted smoothly with thioacetic acid and pyridine, the crude product having the expected infrared spectrum, but as this ester is not an $\alpha\beta$ -glycidic ester, the product was not further studied. With potassium thioacetate, the ester (XVIII) gave only products tentatively formulated as episulphide polymers or products of further addition of thioacetate to the episulphide (cf. ref. 10).

Opening of the ring of the $\beta\gamma$ -episulphide (XVI) by nucleophiles did not proceed as expected. Its mixture with *o*-aminobenzenethiol, an extremely nucleophilic thiol,²¹ was unchanged in infrared spectrum on prolonged storage or on heating for several hours. Reaction with piperidine in benzene⁴ gave nitrogen-free polymers insoluble in dilute acids. With sodamide in liquid ammonia it gave no basic product, but instead a fair yield of a crystalline dimer of the amide formally derived from the ester (XVI). On the basis of infrared data and preliminary investigations, this product is probably the dithian (XX) or a positional isomer thereof. The formation of such a compound is of interest in view of the isolation of products whose properties suggest their formulation as dimers in reactions designed to give epithio-esters from glycidic esters (III), (X), and (XVIII).

Like simple aliphatic episulphides, the $\beta\gamma$ -episulphide (XVI) was stable for at least several weeks at 25° and for 22 hours in refluxing ethanol. At 115° partial desulphurisation occurred.

Certain of the compounds described are being tested for radiation-protective and general biological activity by the Department of Radiobiology, Walter Reed Army Institute of Research, Walter Reed Army Medical Centre, Washington D.C., U.S.A.

EXPERIMENTAL

Ultraviolet and infrared spectra were determined by using Cary model 14 and Perkin-Elmer model 137 Infracord spectrophotometers, respectively. Fractional distillations were carried out through Nester and Faust spinning-band columns, 18" and 36" long, with estimated efficiencies of 18 and 40 theoretical plates, referred to below as columns A and B, respectively. M. p. are corrected.

Peracetic Acid.—To anhydrous sodium carbonate (21.2 g., 0.2 mole), cooled in ice-salt, was added 30% hydrogen peroxide (28 ml., 0.23 mole). The mixture was stirred and kept at 0–5° during rapid addition of acetic anhydride (20.4 g., 0.2 mole) and for a further 45 min. Ether (80 ml.) was then added, followed by an ice-cold solution of sulphuric acid (29.4 g., 0.3 mole). The aqueous layer was saturated with ammonium sulphate and extracted six times with ether. The dried ether extracts (435 ml.) contained 0.14 mole of peracetic acid (iodometric) and very little hydrogen peroxide (permanganate) or acetic acid (titration with base).

Ethyl $\alpha\beta$ -Epoxybutyrate (III).—(a) To an ether solution of peracetic acid (0.14 mole) were added ethyl crotonate (I) (16 g., 0.14 mole) and ethyl acetate (100 ml.). Ether was removed by distillation through a 30-cm. column packed with glass beads, and the residual solution heated under reflux for 5.5 hr. and fractionated (column A) to give some unchanged ester (I) (6.3 g., 39%) followed by ester (III) (4.8 g., 26%), n_D^{25} 1.4159.

(b) A solution of potassium hydroxide (3.0 g., 0.0535 mole) in methanol (6 ml.) and water (10 ml.) was added dropwise during one hour to a stirred, ice-cooled solution of the ester (II) (see below) (10.5 g., 0.05 mole) in methanol (10 ml.) and water (12 ml.). Water was then added, the product isolated in ether, and the dried ether solution fractionated (column A) to

²⁰ Kon and Linstead, *J.*, 1925, **127**, 616; Kon, Linstead, and Wright, *J.*, 1934, 599.

²¹ Danehy and Noel, *J. Amer. Chem. Soc.*, 1960, **82**, 2511.

give the epoxide (III) (4.2 g., 65%), b. p. 94—95°/50 mm., n_D^{27} 1.4162 (lit.,¹¹ b. p. 94—95°/50 mm., n_D^{30} 1.4150). Alternatively the reaction mixture obtained from ethyl crotonate (114 g., 1 mole) and *N*-bromosuccinimide (178 g., 1 mole) was treated directly with an excess of aqueous potassium hydroxide. The product obtained on fractionation (column B) (46.6 g., ca. 35%) contained considerable amounts (ca. 20 mole % estimated by refractive index, 1.4245—1.4320, and by gas-liquid chromatography) of ethyl 2-bromobut-2-enoate identified by its infrared spectrum and by saponification to α -bromocrotonic acid, m. p. 107—108° (lit., m. p. 107—108°). This impure ester was used satisfactorily for certain further preparations.

Ethyl α -Bromo- β -hydroxybutyrate (II).—A mixture of ethyl crotonate (86.2 g., 0.76 mole), dioxan (100 ml.), and water (250 ml.) was stirred and kept at 0—5° while *N*-bromosuccinimide (135 g., 0.76 mole) was added portionwise during 40 min. After 6 hours' stirring at 0° the aqueous layer did not colour starch-iodide paper. The organic layer was isolated in ether and fractionated (column B), giving impure ethyl $\alpha\beta$ -dibromobutyrate (24.6 g., 12%), b. p. 70—71°/2—3 mm., n_D^{25} 1.4847, and *ethyl α -bromo- β -hydroxybutyrate* (50.6 g., 32%), b. p. 78°/2.3 mm., n_D^{25} 1.4661 (Found: C, 33.8; H, 5.45; Br, 38.2. $C_8H_{11}BrO_3$ requires C, 34.1; H, 5.25; Br, 37.9%), with some decomposition.

Ethyl α -Acetylthio- β -hydroxybutyrate (IV) and *β -Acetoxy- α -mercaptobutyrate* (V).—A mixture of thioacetic acid (16.7 g., 0.22 mole), pyridine (1 g., 0.013 mole), and the ester (III) (26 g., estimated as above to contain 19 g., 0.146 mole, thereof, and 7 g., 0.036 mole, of ethyl 2-bromobut-2-enoate) was kept at 45° during 17 hr. and then fractionated (column A). After a forerun of unchanged 2-bromobutenate there were obtained *ethyl β -acetoxy- α -mercaptobutyrate* (6.1 g., 20%), b. p. 75—76°/0.8 mm., n_D^{24} 1.4556 (Found: C, 46.5; H, 6.8; S, 15.4%), and *ethyl α -acetylthio- β -hydroxybutyrate* (13.7 g., 46%), b. p. 100°/0.7 mm., n_D^{24} 1.4686 (Found: C, 46.8; H, 6.8; S, 15.2. $C_8H_{14}O_4S$ requires C, 46.4; H, 6.8; S, 15.55%). Infrared spectra supported the proposed structures in that the *S*-acetate showed a strong O-H stretching frequency.

Ethyl β -Acetoxy- α -acetylthiobutyrate (VI).—A mixture of the ester (IV) (12.55 g., 0.061 mole), pyridine (10 ml.), and acetic anhydride (10 ml.) was kept at ca. 25° for 45 hr. Pyridine and some acetic anhydride were removed under reduced pressure at ca. 25°, the residue taken up in ether, washed with water, dried, and fractionated (column A), giving the *diacetate* (12.45 g., 83%), b. p. 105°/1 mm., n_D^{27} 1.4630 (Found: C, 48.6; H, 6.7; S, 12.75. $C_{10}H_{16}O_5S$ requires C, 48.4; H, 6.5; S, 12.9%). The same product (b. p., *n*, infrared spectrum) was obtained by acetylation of the ester (V) (60% yield) or a mixture (intermediate fraction from distillation) thereof with (IV).

Ethyl 2-Mercaptobut-2-enoate (VII).—2.955M-Ethanol potassium hydroxide was added dropwise to a stirred solution of the diacetate (VI) (5.8 g., 0.0234 mole) in ethanol (10 ml.) and water (6 ml.) containing thymolphthalein [13.7 ml. (0.041 mole) required]. After 1 hr the solution was poured into water. Neutral products were removed in ether, and acidic products by acidification and further extraction with ether. On distillation (column A), the former gave material (0.45 g.) of b. p. 126—128°/0.9 mm., n_D^{28} 1.4980, and a non-volatile residue (0.45 g.); the latter gave *ethyl 2-mercaptobut-2-enoate* (1.25 g., 37%), b. p. 72°/11 mm., n_D^{27} 1.5003 (Found: C, 49.5; H, 6.8; S, 22.0. $C_6H_{10}O_2S$ requires C, 49.3; H, 6.9; S, 21.9%), whose infrared spectrum shows SH and conjugated C=C and C=O stretching frequencies; there was a viscous residue (0.75 g.). Similar reaction of the ester (V) gave the same product in low yield (16%) together with considerable polymeric material.

Ethyl 2-Acetylthiobut-2-enoate (VIII).—The diacetate (VI) (5.2 g., 0.021 mole) was added dropwise during 30 min. to a solution of sodium hydrogen carbonate (10 g.) in water at 60°, the mixture being steam-distilled at ca. 150 mm. throughout the addition and for a further 30 min. The distillate was cooled to 0° as rapidly as possible. The receiver was changed and distillation continued during addition of sodium hydroxide (10 g.) in water during a further 30 min. and for 30 min. more. The steam distillates were extracted with ether and the dried ether layers fractionated (column A), giving *ethyl 2-acetylthiobut-2-enoate* (0.7 g. and 0.65 g., respectively; total 35%), b. p. 74°/7 mm., n_D^{27} 1.4915 (Found: C, 51.2; H, 6.6; S, 17.2. $C_8H_{12}O_3S$ requires C, 51.0; H, 6.4; S, 17.0%), with an infrared spectrum showing conjugated C=C and C=O stretching frequencies. Small amounts of unchanged starting material were recovered. Similar reaction of the mercapto-acetate (V) (5.2 g.) gave a very small amount of organic product (<0.1 g.).

Reactions of Ethyl $\alpha\beta$ -Epoxy- β -methylvalerate (X).—(a) *With thioacetic acid*. A mixture of the ester¹⁸ (X) (11.12 g., 0.08 mole), thioacetic acid (5.4 g., 0.071 mole), and pyridine (0.4 g.)

was kept at 45° for 95 hr. Its infrared spectrum changed considerably but showed little development of a hydroxyl group. Hydrogen sulphide was evolved and sulphur deposited. Fractionation of (column A) gave some unchanged ester (5.25 g., 47%), a small intermediate fraction (possibly the desired α -acetylthio- β -hydroxy-ester) (0.9 g.; infrared OH band), b. p. 85°/0.7 mm., n_D^{25} 1.4788, and a substance (5.4 g.), b. p. 112°/0.7 mm., n_D^{27} 1.4703 (Found: C, 55.35; H, 7.5; S, 12.2. $C_{12}H_{20}O_4S$ requires C, 55.4; H, 7.75; S, 12.3%).

(b) *With potassium thioacetate.* A solution of thioacetic acid (5 g., 0.066 mole) in methanol (20 ml.) was added slowly, with stirring, to solid potassium hydrogen carbonate (6.6 g., 0.066 mole). When gas evolution had ceased, the glycidic ester (X) (5.3 g., 0.034 mole) was added. A deep wine colour developed and crystals were deposited within 30 min. The mixture was shaken for 24 hr., then diluted with water (the precipitate dissolved) and ether, and the organic products were isolated in ether and fractionated (column A), to give *trans*-ethyl 3-methylpent-2-enoate (XI) (0.65 g., 14%), b. p. 51–52°/7.5 mm., n_D^{27} 1.4381 (infrared bands for conjugated C=C and C=O) (lit.,²⁰ b. p. 67°/24 mm., $n_D^{17.9}$ 1.4411), and an unidentified oil (1.50 g.), b. p. 82°/0.5 mm., n_D^{27} 1.5010.

(c) *With thiourea and dilute sulphuric acid.* The glycidic ester (X) (31.8 g., 0.20 mole) was treated with thiourea (23.4 g., 0.31 mole) and sulphuric acid (9.0 g., 0.19 equiv.) according to the procedure of Durden *et al.*² Fractionation (column A) of the organic product gave *ethyl α - β -dihydroxy- β -methylvalerate* (XIII) (14.4 g., 41%), b. p. 107°/7.8 mm., n_D^{25} 1.4455 (Found: C, 54.35; H, 9.1. $C_8H_{16}O_4$ requires C, 54.5; H, 9.15%).

Reactions of Ethyl β -Epoxy- β -methylvalerate (XVIII).—(a) *With thioacetic acid.* Equimolar amounts of this ester (kindly provided by Dr. J. A. Durden) and thioacetic acid with pyridine (*ca.* 10 mole %) were heated at 45° for 30 hr. Reaction was smooth; the resulting yellow oil had a strong OH stretching frequency but no band characteristic of the epoxide ring or SH group.

(b) *With potassium thioacetate.* Reaction of the ester with the thioacetic acid–potassium hydrogen carbonate mixture as above gave no epithio-ester or unsaturated ester: fractions, b. p. 86–105°/7 mm., n_D^{26} 1.5100–1.5254 (0.92 g.), and some higher-boiling material (0.96 g.) were obtained.

(c) *With thiourea and dilute sulphuric acid: ethyl β -epithio- β -methylvalerate* (XVI). Reaction of the ester (XVIII) (23.7 g., 0.15 mole) with thiourea (11.7 g., 0.154 mole) and sulphuric acid (8.5 g., 0.17 equiv.) according to the procedure of Durden *et al.*² gave results similar to those reported (17% yield). Adding chloroform (*ca.* 2 ml.) to the reaction mixture immediately before addition of the sodium carbonate increased to 58% the yield of product, b. p. 80–81°/6 mm., n_D^{25} 1.4678 (lit.,² b. p. 77–79°/7 mm., n_D^{23} 1.4683), whose infrared spectrum was identical with that recorded by Durden *et al.*² (personal communication).

Reactions of Ethyl β -Epithio- β -methylvalerate (XVI).—(a) *With sodamide–liquid ammonia.* To sodamide (from sodium, 4.2 g.) in liquid ammonia (200 ml., containing ferric nitrate, *ca.* 0.1 g.), the ester (5.2 g., 0.03 mole) in dry ether (10 ml.) was added dropwise during 20 min. and stirring was continued for a further 3 hr. Ammonium chloride (12 g.) was added, followed by ether (200 ml.), the ammonia was allowed to evaporate, and water added. Crystals (2.1 g.), m. p. 163–168°, separated and similar solid (2.5 g.) was isolated from the ether and the water layer. A portion (1.4 g.) of the solid, dissolved in ethanol, boiled with charcoal and crystallised from 2 : 3 ethanol–water, gave white crystals (0.7 g., 53%), m. p. 169–177°, recrystallised to constant m. p. 180–183° [Found: C, 49.9; H, 7.5; N, 9.7; S (turbidimetric), 21.7%; *M* (Rast), 307. $C_{12}H_{22}N_2O_2S_2$ requires C, 49.6; H, 7.6; N, 9.65; S, 22.1%; *M*, 290], insoluble in ether, water, dilute acid or base, readily soluble in ethanol. Dilute ethanol solutions rapidly reduced cold neutral permanganate but gave negative thiol tests with mercuric chloride and Fiegl's iodine–azide reagent. The product is plausibly 2,5-dicarbamoylmethyl-2,3,5,6-tetra-methyl-1,4-dithian (XX).

(b) *With methyl iodide.* (i) A mixture of the ester (XVI) (0.52 g.) with methyl iodide (12.8 g.), kept at *ca.* 25° for 3 months, became dark brown. Addition of ethanol induced crystallisation of trimethylsulphonium iodide (0.02 g., 3%), decomp. 204° (from aqueous ethanol) (lit., 203–207°). (ii) The ester (2.0 g., 0.0115 mole) was boiled in acetone (10 ml.) and methyl iodide (10 g.) for 24 hr. Volatile matter was removed at room temperature/25 mm. and collected at –80°. The residue was taken up in water–ether, and the dried ether layer combined with the volatile matter and fractionated (column A), to give ethyl 3-methylpent-3-enoate (0.614 g., 37%), b. p. 43°/5.3 mm., n_D^{27} 1.4265 (lit.,²⁰ n_D 1.4273) (Found: C, 67.7; H,

10-1. Calc. for $C_8H_{14}O_2$: C, 67.6; H, 9.9%. This product rapidly reduced cold neutral permanganate. Its ultraviolet spectrum (in 95% ethanol) demonstrated the absence of conjugated $C=C=O$, and the infrared spectrum showed the presence of $C=O$ and the absence of $C=CH_2$ and of $C=C$ conjugated to $C=O$.

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VANDERBILT UNIVERSITY, NASHVILLE, TENN., U.S.A.
[Present address (T. C. O.): COLLEGE OF TECHNOLOGY,
BYROM STREET, LIVERPOOL.]

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