The Synthesis and Reduction of Optically Active 2-Mercaptopropionic Acid and Some Derivatives

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Nucleophilic displacement reactions, by thioacetate, thiobenzoate, methanethiolate, and toluene-α-thiolate, on methyl L-*O*-*p*-tolylsulphonyl-lactate, methyl L-2-chloropropionate, and sodium L-2-chloropropionate, have been used to prepare D-2-acylthio- and D-2-alkylthio-propionic acids and esters. Extensive racemisation occurs when an excess of thioacetate or thiobenzoate is used; this is attributed to further S_N2 displacement, with acetylthio or benzoylthio as a leaving group. Concomitant acyl exchange also occurs, with retention of configuration, by a different mechanism. Thus methyl D-2-acetylthiopropionate with potassium thiobenzoate gives methyl D-2-benzoylthiopropionate.

Reduction of L-(2-methylthio)propionic acid with diborane proceeds without racemisation, but the L-(2-methylthio)propanol obtained by reduction of the same acid with lithium aluminium hydride is of lower optical purity. Appreciable racemisation also occurs in the reduction, with lithium aluminium hydride, of methyl D-(2-methylthio)-propionate and of methyl D-(2-benzoylthio)propionate.

The formation of D-2-mercaptopropanol, of known configuration, by reduction of (+)-2-mercaptopropionic acid, its acyl derivatives, and its esters, establishes the D-configuration of the latter compounds.

ALTHOUGH reduction of a carbonyl function by lithium aluminium hydride does not normally affect a neighbouring asymmetric centre, it was found [1] that the 2,3-dimercaptopropanol obtained by such reduction of the (*R*)-aldehyde (1), unlike that obtained by a different synthesis, was optically inactive. It was suggested that racemisation was facilitated by the additional stabilisation which would be afforded to the enolate anion by resonance involving a 3*d* orbital of the sulphur atom [see formulae (2)]. To study the possible operation of this effect when a carboxy-, rather than an aldehydic function, is involved, optically active 2-mercaptopropionic acid (9) and various derivatives have now been prepared and subjected to reduction.

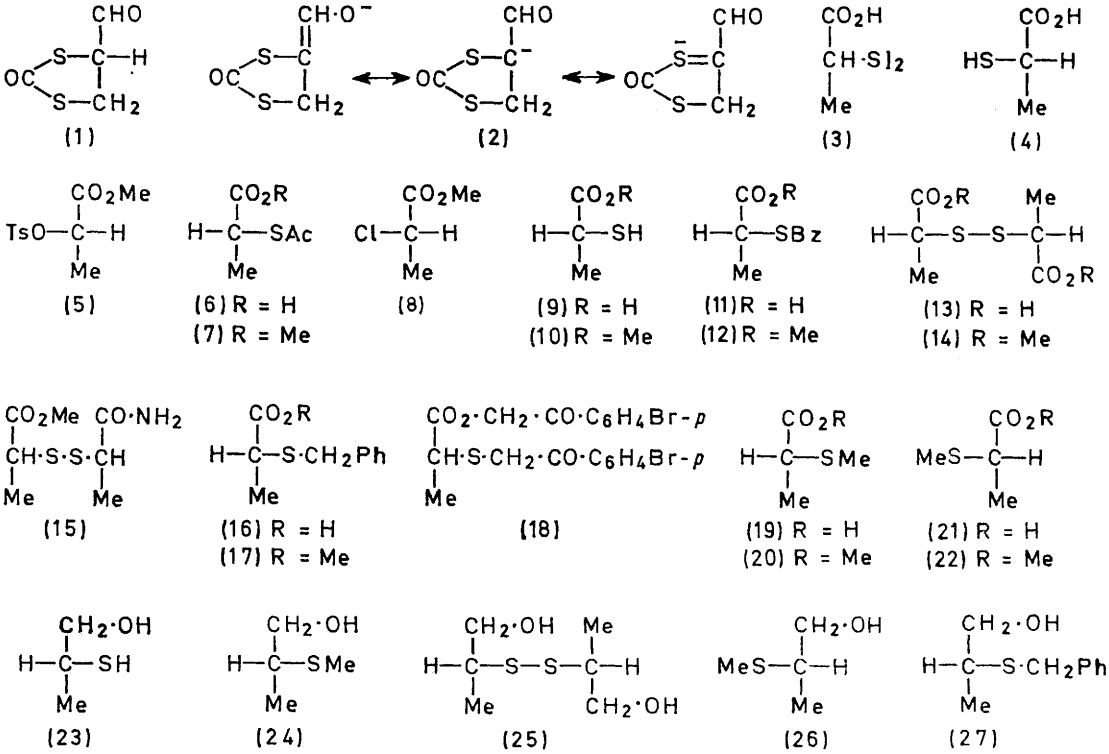
Resolution (with 1-phenylethylamine) of the racemic form of 2,2′-dithiodipropionic acid (3) was first effected by Lovén; [2] reductive fission then afforded optically

[1] A. K. M. Anisuzzaman and L. N. Owen, *J. Chem. Soc.* (*C*), 1967, 1021.
[2] J. M. Lovén, *J. prakt. Chem.*, 1908, (2), **78**, 63.

pure (—)-2 mercaptopropionic acid. A similar procedure was used by Bernton,[3] who obtained both enantiomers. Levene and Mikeska [4] converted (+)-alanine, *via* (—)-2-bromopropionic acid, into a (+)-xanthate, and cleaved this with ammonia to give (+)-2-mercaptopropionic acid (of poor optical purity) which they considered, on the basis of molecular rotation differences,[5] to have (in modern terminology) the L-configuration (4),* but Fredga [6] came to the opposite conclusion by application of the quasi-racemate method.

It is now known [7] that deaminative halogenation of an α-amino-acid with nitrosyl bromide occurs with retention of configuration, and that (—)-2-bromopropionic acid is in the L-series. Although this is contrary to Levene's belief at the time, the discrepancy with regard to the configuration of the mercapto-acid is not automatically removed by this correction, because his assignment did not involve any assumption regarding the stereochemical course of the reaction leading to the xanthate. The consequences of substitution reactions in α-halogeno-acids are in any event not safely predictable since they may occur with retention or with inversion of configuration according to whether or not there is participation by the carboxylate anion,[8] though the recent work of Bonner [9] suggests that with thio-nucleophiles the product would be formed with inversion.

In the present work, new syntheses of the mercapto-acid have been developed, based on the toluene-*p*-sulphonate of methyl L-lactate,† on methyl L-2-chloropropionate, and on L-2-chloropropionic acid, and it has been found that it is immaterial to the configuration of the product whether the introduction of the thio-function is performed on the esters or on the sodium salt. Consequently, inversion can be confidently assumed, and the results confirm Fredga's configurational assignment.



Treatment of the toluene-*p*-sulphonate (5) of methyl L-lactate with potassium thioacetate (1 mol.) in boiling acetone gave methyl D-(2-acetylthio)propionate (7), $[\alpha]_D$ +119° (for further details of specific rotations see Experimental section). The same product, but with $[\alpha]_D$ +138°, was similarly obtained from methyl L-2-chloropropionate (8), whilst from sodium L-2-chloropropionate there was obtained D-2-acetylthiopropionic

* For the compounds discussed in the present paper the DL-system is used, since this gives an immediately recognisable absolute configuration, and correlations are more clearly indicated than with the *RS*-system. Fortuitously, with the exception of the aldehyde (1), every D-compound mentioned has the *R*-configuration, and every L-compound the *S*-configuration.

† Caution is advisable in assuming the configuration of crude lactic acid from the sign of rotation. A laevorotatory commercial specimen, labelled D-(—)-lactic acid, on esterification gave methyl (—)-lactate, which is known to have the L-configuration. The acid was in fact L-(+), but the observed rotation was false because of the presence of a small amount of L-(—)-lactide, which has a very large rotation of opposite sign.

[3] A. Bernton, Dissertation, Uppsala, 1932.
[4] P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, 1924, **60**, 1.
[5] P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, 1925, **63**, 85; P. A. Levene, T. Mori, and L. A. Mikeska, *ibid.*, 1927, **75**, 337.
[6] A. Fredga, *Arkiv Kemi, Min., Geol.*, 1940, **14***B*, No. 12; *Tetrahedron*, 1960, **8**, 126.
[7] G. W. Wheland, 'Advanced Organic Chemistry,' 3rd edn., Wiley, New York, 1960, p. 386.
[8] Ref. 7, p. 385.
[9] W. A. Bonner, *J. Org. Chem.*, 1967, **32**, 2496; 1968, **33**, 1831.

acid (6), $[\alpha]_D$ +137°, which on hydrolysis with aqueous hydrochloric acid gave D-2-mercaptopropionic acid (9), $[\alpha]_D$ +47°. Acetylation of this thiol regenerated the thiolacetate (6), but with $[\alpha]_D$ +119°; clearly the acid hydrolysis had caused some racemisation. A better procedure was treatment of the thiolacetate (6) with aqueous ammonia, which gave almost optically pure mercapto-acid, $[\alpha]_D$ +53°. Esterification of the acetylthio-acid (6) with diazomethane gave the ester (7) with the enhanced rotation of $[\alpha]_D$ +143°.

Reaction of the L-toluene-*p*-sulphonate (5) with potassium thiobenzoate gave the D-thiolbenzoate (12), $[\alpha]_D$ +82°, but, as with the thiolacetate, a product of higher optical purity, $[\alpha]_D$ +99°, was obtained from methyl L-2-chloropropionate; probably the lactic acid used as a source of the toluene-*p*-sulphonate was not optically pure. From sodium L-2-chloropropionate, D-2-benzoylthiopropionic acid (11), $[\alpha]_D$ +103°, was obtained, which with diazomethane afforded the ester (12), $[\alpha]_D$ +102°; these specimens were shown to be optically pure by debenzoylation of the acid (11) with aqueous ammonia, which gave D-2-mercaptopropionic acid (9), $[\alpha]_D$ +57°, oxidation of which gave the DD-disulphide (13), $[\alpha]_D$ +421°, a slightly higher value than that reported by Bernton [3] for the resolved material.

Optically pure mercapto-acid can therefore be obtained by synthesis, but the conditions are critical. In particular, an excess of nucleophile must be avoided in the displacement reaction, otherwise the resulting thiolacetate or thiolbenzoate has a significantly diminished rotation. This effect was further demonstrated by subjecting a specimen of the thiolacetate (7), having $[\alpha]_D$ +130°, to two further treatments with potassium thioacetate in acetone, whereupon the rotation fell successively to +115° and +82°, whereas the same specimen was unchanged when heated in acetone alone. It seemed therefore that racemisation might be occurring by S_N2 displacement of the acetylthio-group itself. If this were so it would be expected that the D-thiolacetate (7) should react with potassium thiobenzoate to give the L-thiolbenzoate. Experiment showed that displacement did indeed occur, but mainly with *retention* of configuration to give the D-thiolbenzoate (12), $[\alpha]_D$ +58°.

Vaughan and Baumann [10] have shown that carboxylic esters react with thiolate ions in two ways. The alkyl group can be attacked to form carboxylate ion and a sulphide (S_N2 mechanism) [equation (1)], and ester exchange can occur by attack of thiolate on the ester carbonyl function [equation (2)]. They also showed

$$R^1S^- + R^2O{\cdot}COR^3 \longrightarrow R^1SR^2 + {}^-O{\cdot}COR^3 \qquad (1)$$

$$R^1S^- + R^2O{\cdot}COR^3 \longrightarrow R^2O^- + R^1S{\cdot}COR^3 \qquad (2)$$

that the thiolester thus produced can itself be attacked at the alkyl group (S_N2 mechanism) [equation (3)]. Clearly,

$$R^1S^- + R^1S{\cdot}COR^3 \longrightarrow R^1SR^1 + {}^-S{\cdot}COR^3 \qquad (3)$$

the thiolester produced in equation (2) could undergo further ester exchange by a reaction analogous to (2), though this would not be experimentally detectable under the conditions of ref. 10 because the alkyl function R^1 in the thiolester is identical with that of the attacking thiolate. In the present situation, however, the thiolate is the benzoylthio-anion, so that ester exchange with the thiolacetate (7) would proceed as in equation (4) (R = 1-methoxycarbonylethyl). The liberated thiol

$$BzS^- + RSAc \longrightarrow RS^- + BzSAc \qquad (4)$$

would then be acylated by the mixed thioanhydride, with retention of configuration, to give the thiolbenzoate (12); any thiolacetate (7) formed by the alternative mode of acylation would of course re-enter the reaction sequence. Attack by thiobenzoate anion on the 'alkyl' group of the thiolacetate (7), *i.e.* the originally expected S_N2 displacement with inversion [analogous to reaction (3)], must presumably also be occurring, to account for the partial racemisation observed. Attack by thiolate ion on the methyl ester function, which would lead to the free carboxylic acid [reaction (1)], may also occur in these reactions, but evidently not to any large extent since the yield of ester was usually high.

Displacement reactions on the ester (5) or (8) with thioacetate or thiobenzoate in methanol, rather than in acetone, resulted in partial or complete solvolysis to give methyl D-2-mercaptopropionate (10), also obtained by controlled treatment of the acetylthio-compound (7) with aqueous ammonia, and by brief treatment of D-2-mercaptopropionic acid with diazomethane. Oxidation of the methyl ester (10) with iodine gave dimethyl DD-2,2′-dithiodipropionate (14), the optically pure form of which was made by esterification of the disulphide (13). When the acetylthio-compound (7) was treated with methanolic rather than with aqueous ammonia, and for a longer time, the product was a mixture of mercapto-ester (10) and mercapto-amide. On oxidation this gave a mixture of disulphides from which the amide-ester (15) was separated by chromatography.

Treatment of the toluene-*p*-sulphonate (5) with sodium benzyl sulphide in methanol gave methyl (2-benzylthio)propionate, which had a very low rotation and on acid hydrolysis furnished crystalline racemic (2-benzylthio)propionic acid, identical with that prepared by benzylation of racemic 2-mercaptopropionic acid. However, sodium L-2-chloropropionate under similar conditions gave D-(2-benzylthio)propionic acid (16) as an oil, $[\alpha]_D$ +261°, from which almost optically pure D-2-mercaptopropionic acid, $[\alpha]_D$ +56°, was obtained by debenzylation with sodium and liquid ammonia. Esterification of the benzyl compound (16) with diazomethane gave the methyl ester (17), but an attempt to characterise the acid (16) as a *p*-bromophenacyl ester gave a product in which the bromine–sulphur ratio was 2 : 1; it was identified as *p*-bromophenacyl 2-(*p*-bromophenacylthio)propionate (18), evidently formed through the intermediate sulphonium bromide by loss of benzyl bromide.

[10] W. R. Vaughan and J. B. Baumann, *J. Org. Chem.*, 1962, **27**, 739.

With sodium methyl sulphide in ethanol the toluene-*p*-sulphonate (5) gave a mixture of 2-(methylthio)propionic acid and 2-ethoxypropionic acid. This attack on the ester methyl group [*cf.* equation (1)] occurred also when the reaction was performed in acetone, though the product then was only D-(2-methylthio)propionic acid (19), $[\alpha]_D$ +30° (extensively racemised). Prolonged treatment of a specimen of D-2-mercaptopropionic acid (72% optically pure) with diazomethane gave methyl D-(2-methylthio)propionate (20), $[\alpha]_D$ +69°, from which the acid (19), $[\alpha]_D$ +59°, was obtained by acidic hydrolysis. The optically pure enantiomer, L-(2-methylthio)-propionic acid (21), $[\alpha]_D$ −85°, was conveniently obtained by resolution of the racemic form with (−)-ephedrine; esterification of the resolved acid gave the pure L-ester (22), $[\alpha]_D$ −96°.

Methyl sulphides are cleaved by sodium in liquid ammonia,[11] but 2-mercaptopropionic acid could not be prepared in this way from the methylthio-compound (21) because fission of the other carbon–sulphur bond occurred preferentially, to yield only propionic acid.

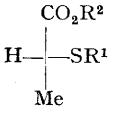
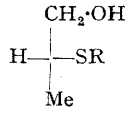
Reduction of the optically pure disulphide (13) with lithium aluminium hydride gave D-2-mercaptopropanol (23), $[\alpha]_D$ −26·1°. The L-enantiomer of this alcohol, previously prepared [1] from D-mannitol by a route which established its configuration, had $[\alpha]_D$ +24·5°; in the present calculations the higher figure has been taken to represent optically pure material. The formation of the D-alcohol by the reductive process clearly confirms the configuration of the mercapto-acid (9) and of all the related compounds. Selective methylation of the D-alcohol with sodium hydride and methyl iodide gave D-(2-methylthio)propanol (24).

When the disulphide (13) was reduced with diborane it gave DD-2,2′-dithiodipropanol (25), which was also obtained by oxidation of D-2-mercaptopropanol (23) with iodine.

To determine the extent of racemisation in a reaction it is not necessary to use an optically pure specimen, provided that the rotations of optically pure starting material and product are known. The acetyl compound (6) and its methyl ester (7) had not been obtained optically pure, but the theoretical values were calculated by simple proportion on the basis of the known purity of the specimen of mercapto-acid which had been acetylated to give a particular sample of the derivative (6).

Reduction, with lithium aluminium hydride in ether, of the mercapto-acid (9), its methyl ester (10), the acetylthio-acid (6), its methyl ester (7), and the benzoylthio-ester (12) gave, in each case, D-2-mercaptopropanol (23). Comparison of the optical purity of the product with that of the starting material showed that racemisation occurred to a significant extent only with the benzoyl compound (see Table). Similar reduction of L-(2-methylthio)propionic acid (21) to L-(2-methylthio)propanol (26) and of the D-methyl ester (20) to the D-alcohol (24) also led to some loss of activity. However, when the L-acid (21) was reduced with diborane the resulting alcohol (26) was optically pure, and this result was confirmed by a similar reduction of the D-acid (19). This freedom from racemisation can be attributed to the non-basic character of diborane compared with lithium aluminium hydride.

Hydride reductions of 2-mercaptopropionic acid and its derivatives

Compound reduced			Reagent	Product	
					
R^1	R^2	Optical purity (%)		R	Optical purity (%)
H	H	73	$LiAlH_4$	H	72
H	Me	73	$LiAlH_4$	H	74
Ac	H	93	$LiAlH_4$	H	94
Ac	Me	92	$LiAlH_4$	H	93
Bz	Me	78	$LiAlH_4$	H	70
Me	H	36	B_2H_6	Me	37
Me *	H	100	$LiAlH_4$	Me	90
Me *	H	100	B_2H_6	Me	100
Me	Me	70	$LiAlH_4$	Me	60
$PhCH_2$	H	98	B_2H_6	$PhCH_2$	98 †
$PhCH_2$	H	98	$LiAlH_4$	$PhCH_2$	96
$PhCH_2$	Me	98	$LiAlH_4$	$PhCH_2$	97

* Enantiomer. † Reaction assumed to be free from racemisation.

On the basis of the quality of the 2-mercaptopropionic acid obtained from it on debenzylation, the D-(2-benzylthio)propionic acid (16) was at least 98% optically pure. When this was reduced with diborane it gave D-(2-benzylthio)propanol (27), which, it can now be assumed, has the same optical purity. Reduction of the same acid with lithium aluminium hydride gave a product with only a slightly smaller rotation, and similar reduction of the methyl ester (17) also resulted in negligible racemisation. Debenzylation, with sodium and liquid ammonia, of the (benzylthio)propanol provided yet another source of D-2-mercaptopropanol.

Thus the reduction of a carboxy-function with lithium aluminium hydride may in certain cases cause some degree of racemisation at a neighbouring optically active centre attached to sulphur, though to a relatively small extent under the conditions used in the present work. The effect of the thio-function may also be encountered in other types of reaction; this was illustrated in attempts to prepare D-(2-benzylthio)propionic acid (16) by benzylation, with benzyl chloride and sodium hydroxide, of D-2-mercaptopropionic acid (9). Extensive racemisation occurred, and the product showed only low optical activity.

The racemisation of L-(2-methylthio)propionic acid (21) and of D-(2-benzylthio)propionic acid (16) in an excess of aqueous sodium hydroxide at 40°, followed polarimetrically, showed first-order kinetics; the respective rate constants were $19{\cdot}1 \times 10^{-6}$ and $6{\cdot}3 \times 10^{-6}$ s^{-1}. D-2-Mercaptopropionic acid (9) was unchanged

[11] E. D. Brown, S. M. Iqbal, and L. N. Owen, *J. Chem. Soc.* (*C*), 1966, 415.

under these conditions, racemisation presumably being inhibited by the negative charge on the thiolate ion; Bernton [3] also noted this stability, but he records a negative rotation for a solution of the (+)-acid in an excess of alkali, which is incorrect.

Under facilities provided by the University of London Intercollegiate Research Service, measurements of the c.d. of many of the above compounds were made at Westfield College (Professor W. Klyne and Dr. P. M. Scopes).[12]

EXPERIMENTAL

Unless stated otherwise, i.r. spectra were measured for solutions in chloroform (Unicam SP 200), u.v. spectra for solutions in ethanol (Unicam SP 800), ^{1}H n.m.r. spectra for solutions in deuteriochloroform (by Mrs. A. I. Boston or Mr. P. N. Jenkins; Varian A60 or HA100 instruments), and optical rotations for solutions in chloroform.

Organic extracts were dried over magnesium sulphate and concentrated under reduced pressure at a bath temperature not exceeding 50°.

Methyl L-*Lactate*.—Crude L-lactic acid (Koch–Light or Fluka) was concentrated at 60° *in vacuo* to remove most of the water and was then esterified azeotropically with methanol in the presence of benzene and toluene-*p*-sulphonic acid (1% of the amount of lactic acid). The methyl ester had b.p. 61—62° at 23 mmHg, n_D^{26} 1·4102, α_D^{22} −8·32° (1 dm) (lit.,[13] α_D^{20} −9·01°).

Methyl L-O-p-*Tolylsulphonyl-lactate*.—Treatment of the foregoing ester (1·3 g) in pyridine (1·5 g) with toluene-*p*-sulphonyl chloride (2·4 g) for 12 h at 0° gave the *toluene*-p-*sulphonate* (5) (0·7 g), b.p. 120—122° at 10^{-3} mmHg, n_D^{20} 1·5048, $[\alpha]_D^{23}$ −32·6° (*c* 2·9), $\nu_{max.}$ (CCl_4) 1760, 1600, 1390, and 1200 cm.$^{-1}$, τ 5·06 (1H, q, CH), 6·32 (3H, s, OMe), 7·55 (3H, s, tolyl-Me), and 8·48 (3H, d, Me) (Found: C, 51·2; H, 5·4; S, 12·3. $C_{11}H_{14}O_5S$ requires C, 51·1; H, 5·5; S, 12·4%).

In some large-scale preparations, when the time of reaction was 20—30 h, a small amount of lower-boiling material was isolated. This was free from sulphur, but contained chlorine, and was methyl D-2-chloropropionate, α_D^{22} +17·4° (1 dm); $\nu_{max.}$ (CCl_4) 1750 cm^{-1}, τ 5·60 (1H, q, CH), 6·23 (3H, s, OMe), and 8·30 (3H, d, Me).

L-2-*Chloropropionic Acid*.—Treatment of L-alanine, $[\alpha]_D^{22}$ +14·8° (*c* 12 in 5N-HCl) in 6N-hydrochloric acid, with sodium nitrite,[14] gave the chloro-acid, which after distillation through a spinning-band column had b.p. 76—77° at 6 mmHg, n_D^{24} 1·4326, α_D^{22} −17·7° (1 dm) (lit.,[14] b.p. 77° at 10 mmHg, n_D^{25} 1·4322, α_D^{25} −18·2°).

Methyl L-2-*Chloropropionate*.—The acid (12·5 g) was treated with a slight excess of ethereal diazomethane to give the ester (8) (11·3 g), b.p. 46° at 30 mmHg, n_D^{20} 1·4178, α_D^{23} −30·3° (1 dm) (lit.,[15] b.p. 80—82° at 110 mmHg, α_D −27·8°).

Methyl D-(2-*Acetylthio*)*propionate* (7).—(i) Methyl L-*O*-*p*-tolylsulphonyl-lactate (1·0 g), potassium thioacetate (1·0 g), and dry acetone (40 ml) were stirred and boiled together under reflux for 18 h in a nitrogen atmosphere. The mixture was then cooled and filtered, and the salts were thoroughly washed with acetone. The combined filtrate and washings were concentrated, then diluted with water and extracted with ether. The extract was washed with water and worked up to provide the *thiolacetate* (0·5 g), b.p. 42—44° at 0·3 mmHg, n_D^{20} 1·4692, $[\alpha]_D^{20}$ +81·8 (*c* 2·2), $\lambda_{max.}$ 230 nm (ε 3500), $\nu_{max.}$ 1735 and 1695 cm.$^{-1}$, τ 5·76 (1H, q, CH), 6·28 (3H, s, OMe), 7·68 (3H, s, SAc), and 8·50 (3H, d, Me) (Found: C, 44·5; H, 6·0; S, 19·85. $C_6H_{10}O_3S$ requires C, 44·4; H, 6·2; S, 19·8%).

When the quantity of potassium thioacetate was halved, the product had $[\alpha]_D^{28}$ +119° (*c* 1·5) but was otherwise the same.

(ii) Methyl L-2-chloropropionate (14·2 g) and potassium thioacetate (13·8 g) in acetone (300 ml) under the same conditions gave the thiolacetate (17·4 g), b.p. 42—46° at 10^{-3} mmHg, n_D^{23} 1·4678, $[\alpha]_D^{24}$ +137·7° (*c* 9·6).

(iii) Methyl L-2-chloropropionate (1·6 g) and potassium thioacetate (3·2 g) in methanol (40 ml) were stirred together for 1 h at ambient temperature and then boiled for 1 h under reflux. The product, isolated as already described, contained some free thiol, and it was treated with acetic anhydride (1·4 g) in pyridine (8 ml) for 14 h to afford the same thiolacetate (n.m.r. spectrum) (1·1 g), b.p. 52—54° at 10^{-3} mmHg, n_D^{22} 1·4684, $[\alpha]_D^{23}$ +121·3° (*c* 8·4).

(iv) D-(2-Acetylthio)propionic acid, $[\alpha]_D$ +137·3° (see later) (0·6 g) was treated with a slight excess of ethereal diazomethane to give the same ester (0·6 g), b.p. 34° at 10^{-4} mmHg, n_D^{20} 1·4704, $[\alpha]_D^{25}$ +143·4° (*c* 6·3).

D-(2-*Acetylthio*)*propionic Acid* (6).—A solution of L-2-chloropropionic acid (24 g) in dry ether (50 ml) was slowly added to a stirred suspension of sodium hydride (5·8 g) in dry ether (100 ml). A further small amount of the acid was then added to make the solution distinctly acidic, and the precipitated salt was collected, washed with ether, and dried *in vacuo*. It had m.p. 168—169° (decomp.), $[\alpha]_D^{19}$ +3·1° (*c* 2·2 in water).

The sodium salt (26·1 g), potassium thioacetate (24 g), and acetone (800 ml) were stirred together for 12 h at ambient temperature and then boiled under reflux for 12 h, all under nitrogen. The solvent was then removed, and the residue was dissolved in water, acidified at 0° with hydrochloric acid, and extracted with ether to give an oil (18·3 g), which contained a trace of free thiol. It was therefore dissolved in benzene and washed with water. The recovered material on distillation gave the *acetylthio-compound*, b.p. 88° at 10^{-3} mmHg, n_D^{25} 1·4895, $[\alpha]_D^{28}$ +137·3° (*c* 3·9), $\lambda_{max.}$ 231 nm (ε 3600), $\nu_{max.}$ 1720 and 1690 cm.$^{-1}$, τ −0·90 (1H, s, CO_2H), 5·72 (1H, q, CH), 7·60 (3H, s, SAc), and 8·44 (3H, d, Me) (Found: C, 40·2; H, 5·5; S, 21·4. $C_5H_8O_3S$ requires C, 40·5; H, 5·4; S, 21·6%).

Methyl D-(2-*Benzoylthio*)*propionate* (12).—(i) Methyl L-*O*-*p*-tolylsulphonyl-lactate (38·7 g), potassium thiobenzoate (53 g), and acetone (550 ml) were stirred and boiled together for 16 h under nitrogen. The product, isolated as described for the thiolacetate, was distilled to give the *thiolbenzoate* (29·4 g), b.p. 108—110° at 10^{-4} mmHg, n_D^{23} 1·5545, $[\alpha]_D^{25}$ +82·3° (*c* 5·2), $\lambda_{max.}$ 208 (ε 9700), 238 (11,100), and 265 nm (8900), $\nu_{max.}$ (CCl_4) 1740, 1680, and 1600 cm^{-1}, τ 5·65 (1H, q, CH), 6·36 (3H, s, OMe), and 8·48 (3H, d, Me) (Found: C, 59·1; H, 5·4; S, 14·35. $C_{11}H_{12}O_3S$ requires C, 58·9; H, 5·4; S, 14·3%).

When the reaction was carried out under the same condi-

[12] P. M. Scopes, R. N. Thomas, and M. B. Rahman, *J. Chem. Soc.* (*C*), 1971, 1671.
[13] T. Purdie and J. C. Irvine, *J. Chem. Soc.*, 1899, **75**, 483.
[14] S.-C. J. Fu, S. M. Birnbaum, and J. P. Greenstein, *J. Amer. Chem. Soc.*, 1954, **76**, 6054.
[15] K. Freudenberg, W. Kuhn, and I. Bumann, *Ber.*, 1930, **63**, 2380.

tions, but in methanol, most of the product distilled at 70—90° and 18 mmHg, and was a mixture of methyl 2-mercaptopropionate and methyl benzoate; it showed $\nu_{max.}$ 2590, 1730, and 1600 cm^{-1}.

(ii) Methyl L-2-chloropropionate (2·5 g), potassium thiobenzoate (3·7 g), and acetone (200 ml), refluxed for 21 h, similarly gave the thiolbenzoate (4·4 g), b.p. 118—120° at 10^{-2} mmHg, n_D^{23} 1·5542, $[\alpha]_D^{25}$ +99·3° (*c* 11·4).

(iii) D-(2-Benzoylthio)propionic acid, $[\alpha]_D^{25}$ +102·8° (see later) (0·5 g), with a slight excess of diazomethane in ether, gave the same ester (0·5 g), b.p. 90—92° at 10^{-4} mmHg, n_D^{26} 1·5522, $[\alpha]_D^{25}$ +102·4° (*c* 5·9).

D-(2-*Benzoylthio*)*propionic Acid* (11).—Sodium L-2-chloropropionate (4·8 g), freshly prepared as already described, was stirred with potassium thiobenzoate (6·8 g) and acetone (400 ml) for 12 h at ambient temperature and then boiled under reflux for 24 h. The mixture was worked up in the same way as for the similar reaction with thiolacetate, and gave the *acid* (6·1 g) as fine needles, from petroleum (b.p. 40—60°), m.p. 62—63°, $[\alpha]_D^{25}$ +102·8° (*c* 3·4), $\lambda_{max.}$ 208 (ε 9000), 238 (10,700), and 265 nm (8500), $\nu_{max.}$ 1720, 1670, 1600, and 1585 cm^{-1} (Found: C, 57·0; H, 4·9; S, 15·1. $C_{10}H_{10}O_3S$ requires C, 57·1; H, 4·8; S, 15·25%).

Racemisation by Excess of Nucleophile.—Methyl D-(2-acetylthio)propionate, $[\alpha]_D^{24}$ +130·2° (13·3 g) was treated with potassium thioacetate (15 g) in boiling acetone (250 ml) for 19 h. The recovered ester had $[\alpha]_D^{24}$ +115·5° (*c* 5·8), and a portion was treated again in the same way for 53 h. The distilled product had b.p. 42—44° at 10^{-2} mmHg, n_D^{20} 1·4700, $[\alpha]_D^{24}$ +82·2° (*c* 9·5).

A sample of the material, $[\alpha]_D^{24}$ +115·5°, was heated in boiling acetone for 28 h. The recovered product had b.p. 40—42° at 10^{-2} mmHg, n_D^{21} 1·4690, $[\alpha]_D^{27}$ +114·8° (*c* 6·4).

Reaction of Methyl D-(2-*Acetylthio*)*propionate with Potassium Thiobenzoate.*—The preceding acetylthio-compound, $[\alpha]_D^{24}$ +115·5°, (1·8 g) and potassium thiobenzoate (9·2 g) were boiled under reflux in acetone (200 ml) for 3 days. The filtered solution, worked up in the usual way, gave an oil which was fractionally distilled to give (i) mainly methyl D-(2-acetylthio)propionate (1·1 g), b.p. 54—56° at 0·1 mmHg, n_D^{22} 1·5025, $[\alpha]_D^{23}$ +64·0 (*c* 7·5), identified by the n.m.r. spectrum; and (ii) methyl D-(2-benzoylthio)propionate (0·8 g), b.p. 106—108° at 0·1 mmHg, n_D^{22} 1·5535, $[\alpha]_D^{23}$ +57·8° (*c* 7·9), identified by i.r. and n.m.r. spectra.

Methyl D-(2-*Benzylthio*)*propionate* (17).—(i) Methyl L-*O*-*p*-tolylsulphonyl-lactate (25·8 g) in methanol (30 ml) was added to a solution prepared from sodium (4·6 g), methanol (200 ml), and toluene-α-thiol (26·8 g). The mixture was stirred and boiled under reflux for 16 h under nitrogen. The filtered solution was then worked up as described for other displacements, and the resulting ethereal extract was washed with aqueous sodium hydroxide and then with water before being dried. The *benzylthio-compound* (18·1 g), which was almost completely racemic, had b.p. 150—152° at 8 mmHg, n_D^{22} 1·5376, $[\alpha]_D^{24}$ +0·3° (*c* 9), τ 6·22 (2H, s, S·CH_2), 6·37 (3H, s, OMe), 6·72 (1H, q, CH), and 8·64 (3H, d, Me) (Found: C, 62·6; H, 7·0; S, 15·2. $C_{11}H_{14}O_2S$ requires C, 62·8; H, 6·7; S, 15·2%).

A portion of the ester (4·1 g) was boiled under reflux with 0·5N-hydrochloric acid (100 ml) for 20 h. The solid which crystallised from the cooled solution was collected and recrystallised from petroleum (b.p. 60—80°) to give (2-benzylthio)propionic acid, m.p. 77—78°, $[\alpha]_D^{24}$ +0·5° (*c* 2), τ 0·84 (1H, s, CO_2H), 6·12 (2H, s, S·CH_2), 6·72 (1H, q, CH), and 8·60 (3H, d, Me) (Found: C, 61·3; H, 6·3; S, 16·1. Calc. for $C_{10}H_{12}O_2S$: C, 61·2; H, 6·2; S, 16·3%) (lit.,[16] m.p. 78—79°). The m.p. was not depressed when the acid was mixed with a sample prepared by treatment of racemic 2-mercaptopropionic acid with benzyl chloride and sodium hydroxide.

(ii) A slight excess of ethereal diazomethane was added to a solution of D-(2-benzylthio)propionic acid, $[\alpha]_D^{26}$ +261·5°, (see later) (1·0 g) in ether (20 ml). Distillation then afforded the D-*ester* (1·0 g), b.p. 92—93° at 10^{-3} mmHg, n_D^{27} 1·5346, $[\alpha]_D^{28}$ +236·8° (*c* 8·9), $\lambda_{max.}$ 208 nm (ε 11,300) (Found: C, 63·0; H, 6·6; S, 15·0%).

D-(2-*Benzylthio*)*propionic Acid* (16).—(i) L-2-Chloropropionic acid (10·8 g) in methanol (25 ml) was added to a solution of toluene-α-thiol (25 g) and sodium hydroxide (8 g) in methanol (60 ml) and water (40 ml). The mixture was stirred for 24 h under nitrogen and then diluted with water and extracted with ether. The extracts were rejected and the aqueous solution was acidified with hydrochloric acid and extracted with ether. This ethereal solution was extracted with aqueous potassium carbonate, the organic layer again being rejected. The carbonate solution was washed thrice with ether before being acidified and finally extracted with ether to give an oil (11·2 g), $[\alpha]_D^{25}$ +256·3° (*c* 3·6 in EtOH) which was dissolved in cyclohexane–petroleum (b.p. 60—80°) and stored at *ca.* 0°. After several weeks a small amount of crystalline material, m.p. 73—75°, $[\alpha]_D$ +39·4°, was removed, and the remaining solution was evaporated to give the D-acid as an oil, $[\alpha]_D^{26}$ +261·5° (*c* 2·1 in EtOH), $\lambda_{max.}$ 209 (ε 9850) and 230infl nm (950), $\nu_{max.}$ (CCl_4) 1705, 1590, and 1500 $cm.^{-1}$. Claeson and Pedersen [17] also obtained this acid as an oil, $[\alpha]_D$ +251°, but reported that after chromatography it had m.p. 72—82°, $[\alpha]_D$ +250°. In our experience it is only the racemic or largely racemic acid which can be obtained as a solid.

When a sample of this acid (0·5 g) was treated with *p*-bromophenacyl bromide (0·7 g) in aqueous ethanolic sodium hydroxide in the usual way the product was p-*bromophenacyl* (2-p-*bromophenacylthio*)*propionate* (18), m.p. 152—153° (from aqueous ethanol) (Found: C, 45·6; H, 3·3; S, 6·4. $C_{19}H_{16}Br_2O_4S$ requires C, 45·6; H, 3·2; S, 6·4%).

(ii) A solution of sodium hydroxide (2·4 g) in water (30 ml) was added to a vigorously stirred mixture of D-2-mercaptopropionic acid, $[\alpha]_D^{28}$ +46·5° (*c* 8·2 in EtOAc) (2 g) and benzyl chloride (2·8 g) in water (10 ml), under nitrogen. After 1 h, extraction with ether removed the excess of benzyl chloride, and the alkaline solution was then acidified and extracted with ether to give an oil, which crystallised from petroleum (b.p. 60—80°) as the mainly racemised acid, m.p. 71—75°, $[\alpha]_D^{25}$ +21·8° (*c* 2·5 in EtOH).

L-(2-*Methylthio*)*propionic Acid* (21).—Prepared by treatment of 2-mercaptopropionic acid (21·2 g) in aqueous 40% sodium hydroxide (60 ml) with dimethyl sulphate (25 g), added dropwise, with stirring, at 100° under nitrogen, the racemic *S*-methyl acid (17·4 g) had b.p. 110° at 10 mmHg, n_D^{18} 1·4842 (lit.,[18] b.p. 105—106° at 8 mmHg, n_D^{25} 1·4815).

(−)-Ephedrine hydrochloride (3·3 g) was treated with an excess of aqueous sodium hydroxide and the base was extracted into chloroform. To the dried extract the racemic

[16] L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.*, 1949, 3109.

[17] G. Claeson and J. Pedersen, *Acta Chem. Scand.*, 1968, **22**, 3155.

[18] A. Mooradian, C. J. Cavallito, A. J. Bergman, E. J. Lawson, and C. M. Suter, *J. Amer. Chem. Soc.*, 1949, **71**, 3372.

S-methyl acid (1·8 g) was added, and the solvent was removed. The solid residue was dissolved in hot ethyl acetate and the filtered solution was set aside to crystallise. The first crop was removed, and two further crops were obtained by successive concentration of the filtrate. The first crop was recrystallised from fresh ethyl acetate and the mother liquors were used to recrystallise the second crop, the process being extended in the usual way. The progress of the fractional crystallisation was followed by observations of m.p. and rotation of each crop. The pure salt ultimately obtained (0·6 g), m.p. 140—141°, $[\alpha]_D^{22}$ −41·8° (*c* 2), was then treated with a slight excess of dilute hydrochloric acid, and the solution was saturated with salt and extracted with ether to give the L-acid (0·2 g), b.p. 118—120° at 13 mmHg, n_D^{22} 1·4815, $[\alpha]_D^{22}$ −84·6° (*c* 1·9 in H_2O), $\lambda_{max.}$ 206 (ε 1050) and 247infl nm (300) (lit.,[19] $[\alpha]_D^{25}$ −81·6°). Similar results were obtained on ten times this scale.

Methyl L-(2-*Methylthio*)*propionate* (22).—The L-acid (0·5 g) was esterified with a slight excess of ethereal diazomethane to give the *methyl ester* (0·4 g), b.p. 58—60° at 12 mmHg, n_D^{21} 1·4591, $[\alpha]_D^{25}$ −96·3° (*c* 4·9), $\lambda_{max.}$ 206 (ε 1150) and 247infl nm (400) (Found: C, 45·05; H, 7·5; S, 24·1. $C_5H_{10}O_2S$ requires C, 44·8; H, 7·5; S, 23·9%).

Sodium–Ammonia Reduction of L-(2-*Methylthio*)*propionic Acid*.—Sodium was added to a solution of the acid (2·0 g) in liquid ammonia (*ca.* 80 ml) until a persistent blue colour was obtained. The excess was then destroyed with ammonium chloride and the ammonia was allowed to evaporate off in a stream of nitrogen. The residue was covered with ether and then shaken with ice-cold dilute hydrochloric acid. The organic layer was removed, and the aqueous portion was extracted twice more with ether. Evaporation of the dried extracts gave propionic acid (0·8 g), b.p. 64° at 20 mmHg, n_D^{22} 1·3868, τ −1·17 (1H, s, CO_2H), 7·62 (2H, q, CH_2), and 8·84 (3H, t, Me), characterised as the *p*-bromophenacyl ester, m.p. 60°.

D-(2-*Methylthio*)*propionic Acid* (19).—Methanethiol, prepared from *S*-methylisothiouronium sulphate (80 g), was passed into a solution prepared from sodium (9·2 g) in dry methanol (500 ml). Evaporation gave the sodium thiolate, which was twice suspended in dry acetone and recovered by evaporation. It was then suspended in dry acetone (200 ml), containing methyl L-*O*-*p*-tolylsulphonyl-lactate (25·8 g), and the mixture was boiled under reflux for 16 h in a nitrogen atmosphere, and worked up as usual to give only a trace of oil. The aqueous portion was therefore acidified and extracted with ether. This furnished the partly racemised D-acid (1·3 g), b.p. 108° at 8 mmHg, n_D^{23} 1·4815, $[\alpha]_D^{23}$ +30·1° (*c* 4·2 in H_2O).

Methyl D-(2-*Methylthio*)*propionate* (20).—D-2-Mercaptopropionic acid, $[\alpha]_D^{23}$ +42·3°, (see later) (2·3 g) was treated with a large excess of ethereal diazomethane. After 24 h, the solution was washed with aqueous sodium hydroxide and with water, and evaporated to give the S-*methyl ester* (2·1 g), b.p. 58—60° at 12 mmHg, n_D^{18} 1·4622, $[\alpha]_D^{24}$ +68·9° (*c* 3·6), $\nu_{max.}$ (liquid) 1735 cm^{-1}, τ (CCl_4) 6·31 (3H, s, OMe), 6·79 (1H, q, CH), 7·90 (3H, s, SMe), and 8·59 (3H, d, Me) (Found: C, 44·6; H, 7·3; S, 23·35. $C_5H_{10}O_2S$ requires C, 44·8; H, 7·5; S, 23·9%).

Hydrolysis of this partly racemic ester (0·7 g) with aqueous 1·6% hydrochloric acid (60 ml) at 100° for 16 h gave D-(2-methylthio)propionic acid (0·4 g), b.p. 112—113° at 12 mmHg, n_D^{21} 1·4835, $[\alpha]_D^{24}$ +58·6° (*c* 6·3 in H_2O).

[19] A. Mellander, *Arkiv Kemi, Min., Geol.*, 1937, 12*B*, No. 27.

D-2-*Mercaptopropionic Acid* (9).—(i) A mixture of D-(2-acetylthio)propionic acid, $[\alpha]_D^{28}$ +137·3°, (see before) (9·5 g) and 1·6% hydrochloric acid (100 ml) was boiled under reflux in a nitrogen atmosphere. When the hydrolysis was complete (6 h; judged by disappearance of the absorption band at 231 nm), the solution was extracted with ether to yield the mercapto-acid (4·9 g), b.p. 99—100° at 8 mmHg, n_D^{24} 1·4742, $[\alpha]_D^{28}$ +46·5° (*c* 8 in EtOAc).

A portion of this specimen (2 g) in acetic anhydride (3 ml) and sulphuric acid (0·1 g) was set aside for 15 h, then diluted with water and extracted with ether to give the regenerated acetylthio-acid (1·3 g), b.p. 98—100° at 10^{-5} mmHg, n_D^{22} 1·4906, $[\alpha]_D^{27}$ +118·6° (*c* 6·1).

(ii) A solution of the same acetylthio-acid, $[\alpha]_D^{28}$ +137·3° (0·6 g) in N-ammonium hydroxide (16 ml) was observed polarimetrically until a constant value, α_D 0°, was attained (1·5 h). The solution was then cautiously acidified (cooling) with hydrochloric acid and extracted with ether to give the mercapto-acid (0·3 g), b.p. 98—100° at 10 mmHg, n_D^{22} 1·4785, $[\alpha]_D^{27}$ +53° (*c* 7·8 in EtOAc).

(iii) A solution of D-(2-benzoylthio)propionic acid, $[\alpha]_D^{25}$ +102·8° (see before) (3·6 g) in N-ammonium hydroxide (80 ml), worked up in the same way after 1·5 h, gave optically pure D-2-mercaptopropionic acid (1·2 g), b.p. 60° at 0·15 mmHg, n_D^{22} 1·4790, $[\alpha]_D^{25}$ +57·1° (*c* 6·9 in EtOAc), $\lambda_{max.}$ 206 (ε 700) and 235infl nm (210). Bernton [3] recorded b.p. 101—102° at 12 mmHg; $[\alpha]_D$ +59·2° (at 15°), +58·8° (at 18°), +58·3° (at 20°) (in EtOAc).

Oxidation, with N-iodine, of an aqueous solution of the mercapto-acid, followed by extraction with ether, afforded DD-2,2′-dithiodipropionic acid (13), which after recrystallisation from benzene had m.p. 114—115°, $[\alpha]_D^{25}$ +421·2° (*c* 2·1 in H_2O), $\lambda_{max.}$ 210 (ε 2550) and 251infl nm (750). Bernton [3] reported $[\alpha]_D^{25}$ +417·1° (in H_2O).

(iv) Sodium, in small pieces, was added to a solution of (2-benzylthio)propionic acid, $[\alpha]_D^{26}$ +261·5° (see before), in liquid ammonia (*ca.* 80 ml) until a blue colour persisted for 15 min. The solution was worked up as described for a similar reduction of the *S*-methyl analogue, and gave the mercapto-acid (1·2 g), b.p. 70—72° at 0·1 mmHg, n_D^{24} 1·4805, $[\alpha]_D^{25}$ +56·2° (*c* 6·4 in EtOAc).

Methyl D-2-*Mercaptopropionate* (10).—(i) A solution of methyl D-(2-acetylthio)propionate, $[\alpha]_D^{24}$ +137·7° (see before) (1·6 g) in N-ammonium hydroxide (40 ml) showed a slight change, α_D +3·29 ⟶ +3·15°, in 2 h; after a further 2 h the rotation was the same, and the solution was therefore worked up as previously described to give the *mercapto-ester* (1·1 g), b.p. 42° at 11 mmHg, n_D^{23} 1·4540, $[\alpha]_D^{25}$ +55·4° (*c* 4·4), $\nu_{max.}$ (liquid) 2590 and 1740 cm^{-1}, τ (CCl_4) 6·30 (3H, s, OMe), 6·63 (1H, q, CH), 7·98 (1H, d, SH), and 8·59 (3H, d, Me) (Found: thiol-S, 26·9. $C_4H_8O_2S$ requires S, 26·7%).

Reaction of a portion of this ester with 3,5-dinitrobenzoyl chloride in pyridine gave *methyl* D-2-(3,5-*dinitrobenzoylthio*)-*propionate*, m.p. 69—70° (from aqueous ethanol), $[\alpha]_D^{22}$ +62° (*c* 1·1), $\nu_{max.}$ 1730, 1670, 1625, and 1555 cm^{-1} (Found: C, 42·2; H, 3·4; N, 8·9; S, 10·4. $C_{11}H_{10}N_2O_7S$ requires C, 42·0; H, 3·2; N, 8·9; S, 10·2%).

(ii) A specimen of D-2-mercaptopropionic acid, $[\alpha]_D^{23}$ +42·3° (*c* 2·1 in EtOAc) (2·4 g) was treated with ethereal diazomethane until a slight excess was present. The solution was immediately evaporated to give the mercapto-ester (2·2 g), b.p. 44—46° at 12 mmHg, n_D^{18} 1·4570, $[\alpha]_D^{22}$ +47·5° (*c* 3·0).

Dimethyl DD-2,2′-*Dithiodipropionate* (14).—(i) Methyl D-

(2-acetylthio)propionate, $[\alpha]_D^{24}$ +137·7° (3·3 g), on ammonolysis as already described, gave the mercapto-ester (2·5 g) which, without distillation, was oxidised with N-iodine (as described for the oxidation of 2-mercaptopropionic acid) to give the *disulphide* (2·1 g), b.p. 80—82° at 10^{-4} mmHg, n_D^{23} 1·5014, $[\alpha]_D^{26}$ +341·1° (*c* 3·8), $\lambda_{max.}$ 210 (ε 3050) and 230infl nm (2000), $\nu_{max.}$ 1730 cm^{-1} (Found: C, 40·1; H, 5·8; S, 26·3. $C_8H_{14}O_4S_2$ requires C, 40·3; H, 5·9; S, 26·9%).

(ii) DD-2,2′-Dithiodipropionic acid (see before) (0·3 g), on treatment with ethereal diazomethane, gave the same disulphide (0·2 g), b.p. 70—72° at 10^{-5} mmHg, n_D^{22} 1·5019, $[\alpha]_D^{26}$ +357·8° (*c* 6·8).

1-*Carbamoylethyl* 1-*Methoxycarbonylethyl Disulphide* (15).—A solution of methyl D-(2-acetylthio)propionate, $[\alpha]_D^{23}$ +137·7° (1 g) in dry methanol (50 ml), saturated at 0° with ammonia, was set aside for 21 h, then evaporated. The residue was taken up in dilute hydrochloric acid and extracted with chloroform to give a mixture of mercapto-ester and mercapto-amide (i.r. spectrum) which was oxidised with iodine. Chromatography of the product on silica and elution with chloroform gave a solid, which on repeated crystallisation from chloroform–petroleum (b.p. 40—60°) furnished the *ester-amide* (60 mg), m.p. 92—95°, $[\alpha]_D^{22}$ 0° (*c* 0·5), $\nu_{max.}$ 3400, 1725, 1685, and 1590 cm^{-1} (Found: C, 37·5; H, 5·7; N, 6·4. $C_7H_{13}NO_3S_2$ requires C, 37·6; H, 5·8; N, 6·3%).

DD-2,2′-*Dithiodipropanol* (25).—Diborane, generated in a period of 2 h by the addition of boron trifluoride–ether complex (45% w/w; 12 g) in dry bis(2-methoxyethyl) ether (8 ml) to a stirred suspension of sodium borohydride (1·2 g) in the same solvent (10 ml),[20] was continuously transferred in stream of nitrogen to a solution of DD-2,2′-dithiodipropionic acid (0·4 g) in tetrahydrofuran (10 ml). The solvent was then evaporated off and the residue was shaken with cold aqueous sodium hydrogen carbonate and extracted with ether to give the *diol* (0·2 g), b.p. 150—160° at 10^{-5} mmHg, n_D^{21} 1·5380, $[\alpha]_D^{27}$ +193·7° (*c* 2·3), $\lambda_{max.}$ 205 (ε 1500) and 253infl nm (600), τ 6·28 (4H, dd, 2 × CH_2·O), 7·07 (2H, q, 2 × CH), 7·19br (2H, s, 2 × OH), and 8·70 (6H, d, 2 × Me) (Found: C, 39·4; H, 7·8; S, 34·9. $C_6H_{14}O_2S_2$ requires C, 39·5; H, 7·7; S, 35·2%). The n.m.r. spectrum was identical with that of a specimen prepared by oxidation of D-2-mercaptopropanol with N-iodine.

D-2-*Mercaptopropanol* (23).—(i) A slurry of lithium aluminium hydride (0·5 g) in dry ether (30 ml) was slowly added to a stirred solution of D-2,2′-dithiodipropionic acid (0·4 g) in dry ether (30 ml), under nitrogen. Afterwards the mixture was boiled under reflux for 2 h, then cooled, and cautiously treated with water. Acidification with dilute hydrochloric acid (cooling), saturation with salt, and extraction with ether then gave D-2-*mercaptopropanol* (0·25 g), b.p. 54—55° at 10 mmHg, n_D^{25} 1·4823, $[\alpha]_D^{25}$ −26·1° (*c* 5·3), $\lambda_{max.}$ 206 (ε 500) and 230infl nm (100) (Found: thiol-S, 35·0. C_3H_8OS requires S, 34·8%) (for the enantiomer, lit.,[1] b.p. 50—51° at 20 mmHg, n_D^{12} 1·4870, $[\alpha]_D^{22}$ +24·5°).

(ii) D-2-Mercaptopropionic acid, $[\alpha]_D^{23}$ +42·3° (EtOAc) (1·1 g), similarly reduced, gave the alcohol (0·6 g), b.p. 61—62° at 27 mmHg, n_D^{18} 1·4825, $[\alpha]_D^{25}$ −18·8° (*c* 4·1) (Found: thiol-S, 35·2%).

(iii) Methyl D-2-mercaptopropionate, $[\alpha]_D^{22}$ +47·5, (1·7 g) similarly gave the alcohol (0·75 g), b.p. 54° at 14 mmHg, n_D^{22} 1·4825, $[\alpha]_D^{24}$ −19·3° (*c* 3·8).

(iv) D-(2-Acetylthio)propionic acid, $[\alpha]_D^{27}$ +133·9°, (2·2 g) gave the alcohol (0·5 g), b.p. 51° at 16 mmHg, n_D^{21} 1·4820, $[\alpha]_D^{24}$ −24·6° (*c* 4·6).

(v) Methyl D-(2-acetylthio)propionate, $[\alpha]_D^{24}$ +137·7°, (1·6 g) gave the alcohol (0·4 g), b.p. 52—54° at 15 mmHg, n_D^{21} 1·4827, $[\alpha]_D^{25}$ −24·3° (*c* 6·4).

(vi) Methyl D-(2-benzoylthio)propionate, $[\alpha]_D^{25}$ +80·2°, (4·5 g) gave the alcohol (1·5 g), b.p. 54° at 17 mmHg, n_D^{20} 1·4825, $[\alpha]_D^{24}$ −18·2° (*c* 5·2), $\nu_{max.}$ 3500 and 2590 cm^{-1}.

(vii) D-(2-Benzylthio)propanol, $[\alpha]_D^{27}$ +33·5°, (see later) (0·50 g) in liquid ammonia (30 ml) was reduced with sodium by the general method previously described, and gave the alcohol (0·15 g), b.p. 56—58° at 15 mmHg, n_D^{24} 1·4809, $[\alpha]_D^{27}$ −24·7° (*c* 3·7).

D-(2-*Methylthio*)*propanol* (24).—(i) Methyl D-(2-methylthio)propionate, $[\alpha]_D^{24}$ +67·7° (1·0 g) in dry ether (40 ml) was reduced with lithium aluminium hydride (0·8 g) in ether (40 ml) under the conditions already described above to give D-(2-*methylthio*)*propanol* (0·3 g), b.p. 70—72° at 12 mmHg, n_D^{22} 1·4844, $[\alpha]_D^{24}$ −8·7° (*c* 7·2), $\nu_{max.}$ (liquid) 3440 cm^{-1}, τ 6·42 (2H, d, CH_2·O), 7·22 (1H, q, CH), 7·3br (1H, s, OH), 7·92 (3H, s, SMe), and 8·72 (3H, d, Me) (Found: C, 45·5; H, 9·4; S, 29·9. $C_4H_{10}OS$ requires C, 45·2; H, 9·5; S, 30·2%).

(ii) D-(2-Methylthio)propionic acid, $[\alpha]_D^{23}$ +30·1° (0·5 g) was dissolved in tetrahydrofuran and reduced with diborane, prepared from sodium borohydride (0·8 g) as already described. The D-(2-methylthio)propanol so obtained (0·3 g) had b.p. 67—68° at 15 mmHg, n_D^{22} 1·4842, $[\alpha]_D^{28}$ −5·3° (*c* 5·1).

(iii) D-2-Mercaptopropanol, $[\alpha]_D^{24}$ −24·6°, (0·39 g) in dry ether (20 ml) was stirred under nitrogen with sodium hydride (0·22 g) for 24 h. Methyl iodide (0·6 g) was added, and the stirring was continued for 15 h. The mixture was then washed with water and with N-sodium hydroxide, and again with water. The dried ethereal solution on evaporation gave D-(2-methylthio)propanol (50 mg), b.p. *ca.* 66° at 12 mmHg, n_D^{25} 1·4815, $[\alpha]_D^{27}$ −13·6° (*c* 2·2). The n.m.r. spectrum was similar to that of the alcohol prepared by method (i).

L-(2-*Methylthio*)*propanol* (26).—(i) Optically pure L-(2-methylthio)propionic acid $[\alpha]_D^{22}$ −84·6°, (0·5 g), reduced with diborane as described in (ii) for the D-isomer, gave the L-alcohol (0·3 g), b.p. 64—65° at 10 mmHg, n_D^{25} 1·4830, $[\alpha]_D^{26}$ +14·6° (*c* 5·8), $\lambda_{max.}$ 206 nm (ε 1400).

(ii) The same L-acid (0·6 g) was reduced with lithium aluminium hydride (0·8 g), under the conditions previously described, to give the L-alcohol (0·3 g), b.p. 65—66° at 10 mmHg, n_D^{22} 1·4833, $[\alpha]_D^{24}$ +13·1° (*c* 8·1).

D-(2-*Benzylthio*)*propanol* (27).—(i) D-(2-Benzylthio)-propionic acid, $[\alpha]_D^{26}$ +261·5°, (0·5 g) was reduced with diborane, from sodium borohydride (0·8 g), as already described, to give the D-alcohol (0·4 g), b.p. 82—84° at 10^{-4} mmHg, n_D^{23} 1·5610, $[\alpha]_D^{27}$ +33·5° (*c* 4·0), $\lambda_{max.}$ 208 nm (ε 10,000) (Found: C, 65·7; H, 7·7; S, 17·5. $C_{10}H_{14}OS$ requires C, 65·9; H, 7·7; S, 17·6%).

(ii) The same acid (0·6 g), reduced with lithium aluminium hydride (0·8 g), gave the alcohol (0·45 g), b.p. 78—80° at 10^{-4} mmHg, n_D^{22} 1·5616, $[\alpha]_D^{26}$ +32·7° (*c* 7·7).

(iii) Methyl D-(2-benzylthio)propionate, $[\alpha]_D^{28}$ +236·8°, (0·6 g), similarly reduced with lithium aluminium hydride (0·8 g) gave the alcohol (0·4 g), b.p. 82—84° at 10^{-4} mmHg, n_D^{23} 1·5612, $[\alpha]_D^{27}$ +33·3° (*c* 8).

Racemisation of L-2-*Methylthio*- and D-2-*Benzylthio-propionic Acid*.—Each acid (0·003 mol) was made up to

[20] H. C. Brown, ' Hydroboration,' Benjamin, New York, 1962.

5·00 ml in 4·98N-sodium hydroxide. The stoppered solutions were kept at 40°, and the rotations (1 dm) were observed periodically:

	t/h:	0	0·5	1·5
Methylthio-		−2·05	−1·87	−1·64
Benzylthio-		+11·30	+10·96	+10·79
	t/h:	3·5	18·5	44
Methylthio-		−1·40	−0·55	−0·10°
Benzylthio-		+10·37	+7·35	+4·12°

Obtained from the slopes of the straight-line plots of log α_D against *t*, the first-order rate constants were $19{\cdot}1 \times 10^{-6}$ and $6{\cdot}3 \times 10^{-6}$ s^{-1}.

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