

Dithiols. Part XXV.¹ Synthesis of 2,3-Dimercaptopropionic Acid and 2,3-Dimercaptopropanol from Cysteine

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Deaminative halogenation of L-S-benzylcysteine gives L-3-benzylthio-2-chloropropionic acid, from which 2,3-bis(benzylthio)propionic acid, 2,3-bis(benzylthio)propanol, 2,3-dimercaptopropionic acid, and 2,3-dimercaptopropanol can be prepared. The reaction of the chloro-acid or its methyl ester with potassium thiobenzoate occurs with partial rearrangement (neighbouring group participation) to give mixtures of 2-benzoylthio-3-benzylthio- and 3-benzoylthio-2-benzylthio-compounds, converted by reductive processes into 2,3-dimercaptopropanol. The products are racemic or of low optical purity.

SYNTHESES of both optically active forms of 2,3-dimercaptopropanol from L-1,2-O-isopropylidenglycerol have been reported,² and we have now explored the possibility of obtaining one enantiomer of this dithiol from L-cysteine.

L-S-Benzylcysteine (1)³ was readily converted by de-

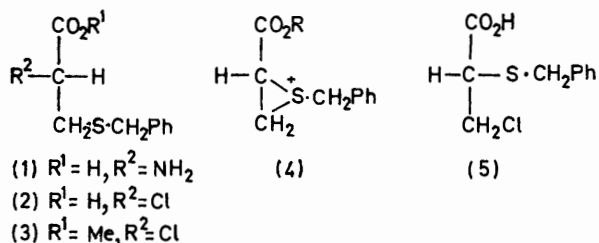
¹ Part XXIV, M. V. Jesudason and L. N. Owen, *J.C.S. Perkin I*, 1974, 1443.

aminative halogenation into a 3-benzylthio-2-chloropropionic acid, $[\alpha]_D^{25} -58.5^\circ$, to which the L-configuration (2) can be assigned on the assumption that retention of configuration occurs. Whilst this is undoubtedly true in

² A. K. M. Anisuzzaman and L. N. Owen, *J. Chem. Soc. (C)*, 1967, 1021.

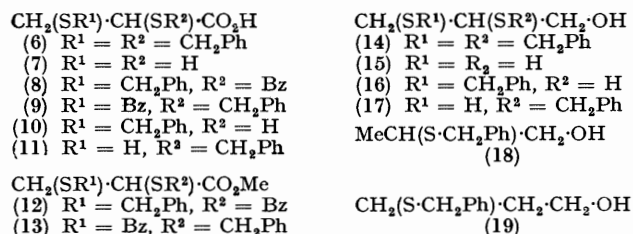
³ J. L. Wood and V. du Vigneaud, *J. Biol. Chem.*, 1939, **130**, 109.

uncomplicated examples of this type of reaction on α -amino-acids,⁴ there is the possibility in the present situation of participation by the neighbouring benzylthio-function to give the episulphonium ion (4; R = H),



which could then afford D-2-benzylthio-3-chloropropionic acid (5). An attempt to determine the constitution of the chloro-acid by desulphurisation, to give either 2- or 3-chloropropionic acid, was frustrated by concomitant dehalogenation, propionic acid being the only identifiable product. However, the c.d. curve of the chloro-ester (3) (prepared from the acid by treatment with diazomethane) showed a negative Cotton effect at λ 228 nm similar to that shown by methyl L-2-chloropropionate; furthermore, methyl D-2-benzylthiopropionate shows a strong positive Cotton effect at 229 nm,⁵ and the methyl ester of the D-acid (5) should behave likewise. We therefore conclude that the deamination was not attended by migration of the benzylthio-group.

Treatment of the chloro-acid (2) with sodium toluene- α -thiolate in methanol gave 2,3-bis(benzylthio)propionic acid (6), from which 2,3-dimercaptopropionic acid (7) was obtained by reduction with sodium in liquid ammonia, and 2,3-bis(benzylthio)propanol (14) by reduction with lithium aluminium hydride. The three products (6), (7), and (14) showed only slight optical activity, and reduction of the acid (7) with lithium aluminium hydride, and of the alcohol (14) with sodium in liquid ammonia, gave racemic 2,3-dimercaptopropanol (15). During earlier studies on the preparation of optically active 2-mercapto-propionic acid it had been found⁶ that treatment of L-2-chloropropionic acid with sodium toluene- α -thiolate gave

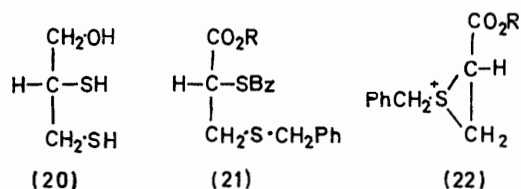


2-(benzylthio)propionic acid which was almost racemic, and the substitution reaction of the chloro-acid (2) evidently takes a similar course. However, 2-(benzylthio)propionic acid of high optical purity had been obtained⁶ by reaction of sodium L-2-chloropropionate with potassium thiobenzoate under carefully controlled

conditions, the reaction proceeding with complete inversion of configuration and with no participation of carbonylate ion; we therefore carried out a similar reaction on the salt of the chloro-acid (2). The crystalline product, which was almost optically inactive, gave the correct analytical figures for the substitution product (8), and on debenzoylation it gave an analytically pure thiol which was nevertheless a mixture of the structural isomers (10) and (11) (the n.m.r. spectrum showed two thiol resonances, one a doublet and the other a triplet). The precursor therefore must have been a mixture of the isomeric acids (8) and (9), indicating that some neighbouring group participation by the benzylthio-group had certainly occurred.

The L-methyl ester (3) on treatment with potassium thiobenzoate likewise gave a weakly optically active mixture of structural isomers (12) and (13), reduction of which with lithium aluminium hydride gave a mixture of the thiols (16) and (17), the n.m.r. spectrum again including a doublet and a triplet for the thiol protons. Furthermore, selective desulphurisation⁷ of the free thiol groups in this mixture afforded a *ca.* 2 : 1 mixture of 2- and 3-(benzylthio)propanol (18) and (19), as shown by the intensity of the C-methyl doublet in the n.m.r. spectrum. Thus the relative proportions of the original products (12) and (13) are known. Reduction, with sodium in liquid ammonia, of the mixture of thiols (16) and (17) gave 2,3-dimercaptopropanol which had an optical rotation indicating the presence of about a 10% excess of the enantiomer (20).

Although neighbouring group participation is known to occur in some substitution reactions of racemic methyl 3-benzylthio-2-chloropropionate⁸ we had nevertheless considered it worth while to undertake the study on the L-acid and L-ester because attack by a thio-nucleophile on the episulphonium ion (4) should occur at the less hindered C-3 position to give a product which, though rearranged, would have the same absolute configuration as that obtained by normal S_N2 substitution on the chloro-compound. According to this simple view, the dimercaptopropionic acid and dimercaptopropanol ultimately obtained should have been optically active irrespective



of the degree of neighbouring group participation. The loss of activity cannot be explained by substantial attack also at C-2 in the episulphonium ion (4) because this would be incompatible with the relative proportions of the thiobenzoates (12) and (13), but there is another way in which the configuration could become inverted. It

⁴ G. W. Wheland, 'Advanced Organic Chemistry,' 3rd edn., Wiley, New York, 1960, p. 386.

⁵ P. M. Scopes, R. N. Thomas, and M. B. Rahman, *J. Chem. Soc. (C)*, 1971, 1671; P. M. Scopes, personal communication.

⁶ L. N. Owen and M. B. Rahman, *J. Chem. Soc. (C)*, 1971, 2432.

⁷ L. W. C. Miles and L. N. Owen, *J. Chem. Soc.*, 1952, 817.

⁸ K.-D. Gundermann, *Annalen*, 1954, 588, 167.

has been found⁶ that an acylthio-group can be displaced by a thio-nucleophile, and this could well occur readily in the normal S_N2 product, D-2-benzoylthio-3-benzylthio-propionic acid (or the ester) (21), as a result of neighbouring group participation, to give the episulphonium ion (22), the enantiomer of the ion (4). More than one process must be involved, because the degree of rearrangement and the degree of configurational change are not equal; a combination of direct substitution and the intervention of both enantiomeric episulphonium ions could account for this.

EXPERIMENTAL

¹H N.m.r. spectra were recorded for solutions in deuteriochloroform on a Varian A-60 or HA-100 instrument, assignments to OH and SH being confirmed by deuteration; resonances for aromatic protons are omitted. I.r. spectra were measured for solutions in chloroform unless otherwise specified. Petroleum refers to the fraction of b.p. 40–60°. Organic extracts were dried over magnesium sulphate, and solvents were removed under reduced pressure below 50°.

L-3-Benzylthio-2-chloropropionic Acid (2).—Sodium nitrite (10 g) was gradually added during 6 h to a solution of L-S-benzylcysteine⁸ (14.6 g) in 6N-hydrochloric acid (1000 ml) at 0°. The mixture was stirred for a further 12 h and was then extracted with ether to give the *chloro-acid* as an oil (10.9 g), $[\alpha]_D^{28} - 58.5^\circ$ (*c* 4 in CHCl_3), ν_{max} 1710, 1600, and 1580 cm^{-1} , τ 0.50br (1H, s, CO_2H), 6.07 (2H, s, PhCH_2), 6.3 (1H, m, CH), and 6.6 (2H, m, CH_2) (Found: C, 52.1; H, 5.3; Cl, 14.6. $\text{C}_{10}\text{H}_{11}\text{ClO}_2\text{S}$ requires C, 52.1; H, 4.8; Cl, 15.4%).

A portion of the product (3.4 g) in acetic acid (10 ml) was treated with 30% hydrogen peroxide (5 ml); the mixture was heated on a steam-bath for 1 h, then concentrated, diluted with water, and extracted with chloroform to give L-3-benzylsulphonyl-2-chloropropionic acid (1.0 g), m.p. 103–104° (from chloroform-petroleum), $[\alpha]_D^{22} 0.0^\circ$ (*c* 2 in CHCl_3) and +1.6° (*c* 2 in MeOH), ν_{max} 1730, 1330, and 1130 cm^{-1} (Found: C, 45.45; H, 4.35; Cl, 13.3. $\text{C}_{10}\text{H}_{11}\text{ClO}_4\text{S}$ requires C, 45.7; H, 4.2; Cl, 13.5%).

Another portion of the benzylthio-compound (1.0 g) in ethanol (40 ml) was boiled under reflux for 2 h with freshly prepared Raney nickel (*ca.* 6 g). The cooled solution was filtered, concentrated, acidified with hydrochloric acid, and extracted with ether to give only propionic acid (60 mg), b.p. 46–48° at 10 mmHg, $n_D^{23} 1.3950$, $\tau -1.33\text{br}$ (1H, s, CO_2H), 7.68 (2H, q, CH_2), and 8.82 (3H, t, CH_3).

Methyl L-3-Benzylthio-2-chloropropionate.—Treatment of the chloro-acid (0.7 g) with ethereal diazomethane gave the *methyl ester* (0.65 g), b.p. 106–108° at 10⁻⁴ mmHg, $n_D^{25} 1.5439$, $[\alpha]_D^{28} - 44.9^\circ$ (*c* 6 in CHCl_3), ν_{max} (liquid) 1740, 1600, and 1500 cm^{-1} , τ 5.9 (1H, m, CH), 6.13 (2H, s, PhCH_2), 6.26 (3H, s, OMe), and 6.4 (2H, m, CH_2), c.d. $\Delta\epsilon_{228}(\text{MeOH}) - 1.71$ m, $\Delta\epsilon_{230}(\text{hexane}) - 2.16$ m (Found: C, 53.8; H, 5.5; Cl, 14.7. $\text{C}_{11}\text{H}_{13}\text{ClO}_2\text{S}$ requires C, 54.0; H, 5.35; Cl, 14.5%).

2,3-Bis(benzylthio)propionic Acid (6).—A solution of L-3-benzylthio-2-chloropropionic acid (15.0 g), toluene- α -thiol (24 g), and sodium hydroxide (8 g) in methanol (100 ml) and water (52 ml) was set aside, under nitrogen, for 24 h, then diluted with water and extracted with ether; the extracts were rejected. Acidification of the alkaline solution, and extraction with benzene, gave a solid (15.3 g) which on recrystallisation from benzene-petroleum gave large crystals of 2,3-bis(benzylthio)propionic acid (12.8 g), m.p. 80–81°, $[\alpha]_D^{22} - 1.4^\circ$ (*c* 8 in CHCl_3), ν_{max} 1710, 1600, and 1580 cm^{-1} ,

$\tau -0.7\text{br}$ (1H, s, CO_2H), 6.10 (2H, s, PhCH_2), 6.35 (2H, s, PhCH_2), 6.8 (1H, m, CH), and 7.3 (2H, m, CH_2) (Found: C, 64.0; H, 5.5; S, 20.0. Calc. for $\text{C}_{17}\text{H}_{18}\text{O}_2\text{S}_2$: C, 64.1; H, 5.6; S, 20.1%) (lit.,⁹ m.p. 83° for racemic compound).

2,3-Dimercaptopropionic Acid (7).—To a solution of the di-S-benzyl-compound (9.0 g) in liquid ammonia (*ca.* 100 ml) and dry ether (10 ml) small pieces of sodium were added until the blue colour persisted for 10 min. After addition of ammonium chloride to destroy the excess of sodium, the ammonia was removed in a stream of dry nitrogen, and the residue was acidified with dilute hydrochloric acid and extracted with ether to give 2,3-dimercaptopropionic acid (1.6 g), m.p. 68–69°, $[\alpha]_D^{23} - 1.1^\circ$ (*c* 4 in MeOH), ν_{max} 2580 and 1720 cm^{-1} (Found: C, 26.3; H, 4.2; S, 46.4; thiol S, 45.7. Calc. for $\text{C}_3\text{H}_6\text{O}_2\text{S}_2$: C, 26.1; H, 4.4; S, 46.4%) (lit.,¹⁰ m.p. 74–74.5°).

2,3-Bis(benzylthio)propanol (14).—2,3-Bis(benzylthio)propionic acid (4.1 g), lithium aluminium hydride (2.5 g) and dry ether (40 ml) were boiled together under reflux for 2 h. The excess of reagent was then destroyed by cautious addition of water to the cooled mixture, which was afterwards acidified with dilute hydrochloric acid. The ether layer was removed, and mixed with further ethereal extracts of the aqueous solution; it was then washed with aqueous sodium hydrogen carbonate, dried, and distilled to give the alcohol (1.9 g), b.p. 192° at 10⁻³ mmHg, $n_D^{23} 1.6080$, $[\alpha]_D^{24} + 1.5^\circ$ (*c* 4 in CHCl_3), τ 6.26 and 6.32 (s, PhCH_2) and 6.3 (m, $\text{CH}_2\cdot\text{OH}$) (total 6H), 7.3 (3H, m, CH and CH_2), and 7.95br (1H, s, OH) [lit.,¹¹ b.p. 215–230° (bath) at 10⁻⁴ mmHg, $n_D^{18} 1.6150$, for racemic compound].

Reaction of Sodium L-3-Benzylthio-2-chloropropionate with Potassium Thiobenzoate.—Sodium hydride (0.24 g) was added to a stirred solution of L-3-benzylthio-2-chloropropionic acid (2.3 g) in dry ether (50 ml). After evolution of hydrogen ceased, the sodium salt was filtered off, washed with ether, dried *in vacuo* (yield 2.4 g), and suspended in acetone (300 ml). Potassium thiobenzoate (2.1 g) was added, and the mixture was boiled under reflux for 20 h under nitrogen, then evaporated to dryness. The residue was dissolved in dilute hydrochloric acid and extracted with ether. The extract was washed with water, then dried and evaporated to give a mixture (1.3 g) of 2-benzoylthio-3-benzylthio- and 3-benzoylthio-2-benzylthio-propionic acid, m.p. 127–128° (from benzene-petroleum), $[\alpha]_D^{21} + 0.4^\circ$ (*c* 2 in CHCl_3), ν_{max} 1715, 1670, and 1600 cm^{-1} , τ 0.03br (1H, s, CO_2H), 6.02 (2H, s, PhCH_2), and 6.6br (3H, s, CH and CH_2) (Found: C, 61.7; H, 4.9; S, 19.7. Calc. for $\text{C}_{17}\text{H}_{16}\text{O}_3\text{S}_2$: C, 61.4; H, 4.85; S, 19.3%).

This mixture (0.8 g) was dissolved in *n*-ammonium hydroxide (80 ml), and, after being kept for 2 h under nitrogen, the solution was acidified (cooling) with dilute hydrochloric acid and extracted with ether. The extracts were extracted with aqueous sodium hydrogen carbonate, and these aqueous extracts were acidified and extracted with ether to give a mixture (0.5 g) of 2-benzylthio-3-mercapto- and 3-benzylthio-2-mercapto-propionic acid, as an oil, τ 1.40br (1H, s, CO_2H), 6.18 (2H, s, PhCH_2), 6.74 (1H, m, CH), 7.25 (2H, m, CH_2), 8.25 (0.6H, t, *J* 8.5 Hz, $\text{CH}_2\cdot\text{SH}$), and 8.76 (0.4H, d, *J* 7.2 Hz, CH $\cdot\text{SH}$) (Found: C, 52.6; H, 5.3. Calc. for $\text{C}_{10}\text{H}_{12}\text{O}_2\text{S}_2$: C, 52.6; H, 5.3%).

A solution of these mixed thiols (0.5 g) in chloroform (10 ml), in a stoppered flask, was covered with water (10 ml).

⁹ K.-D. Gundermann and G. Pape, *Chem. Ber.*, 1962, **95**, 2076.

¹⁰ U.S.P. 2,408,094 (*Chem. Abs.*, 1947, **41**, 775).

¹¹ N. S. Johary and L. N. Owen, *J. Chem. Soc.*, 1955, 1292.

0.1N-Iodine was added in small portions, with vigorous shaking, until a faint violet colour persisted in the chloroform layer. The latter was then separated, washed with water, and evaporated to leave a residue (0.45 g) of the mixed disulphides, m.p. 120–125° (from chloroform-petroleum), ν_{\max} 1705 and 1600 cm^{-1} , τ -1.16br (2H, s, CO_2H), 6.08 (4H, s, PhCH_2), 6.5 (2H, m, CH), and 7.1 (4H, m, CH_2) (Found: C, 53.0; H, 4.7. Calc. for $\text{C}_{20}\text{H}_{22}\text{O}_4\text{S}_2$: C, 52.8; H, 4.9%). The mixture of *p*-bromophenacyl esters, prepared from these disulphides, had m.p. 142–143° (from chloroform-petroleum) (Found: C, 51.0; H, 3.9; Br, 18.8. Calc. for $\text{C}_{26}\text{H}_{32}\text{Br}_2\text{O}_6\text{S}_4$: C, 50.9; H, 3.8; Br, 18.8%).

Reaction of Methyl L-3-Benzylthio-2-chloropropionate with Potassium Thiobenzoate.—A mixture of the chloro-ester (8.0 g), potassium thiobenzoate (7.5 g), and acetone (180 ml) was boiled under reflux for 16 h under nitrogen, and then evaporated to dryness. Extraction of the residue with ether gave a mixture (9.2 g) of methyl 2-benzoylthio-3-benzylthio- and methyl 3-benzoylthio-2-benzylthio-propionate, b.p. 180–182° at 10^{-3} mmHg, n_D^{23} 1.5985, $[\alpha]_D^{23}$ -2.3° (*c* 6 in CHCl_3), ν_{\max} (CCl_4) 1735, 1670, 1600, and 1500 cm^{-1} (Found: C, 62.2; H, 5.15; S, 18.2. Calc. for $\text{C}_{18}\text{H}_{18}\text{O}_3\text{S}_2$: C, 62.4; H, 5.2; S, 18.5%).

This mixture (4.4 g) in dry ether (140 ml) was reduced with lithium aluminium hydride (4 g) by boiling under reflux for 3 h in a nitrogen atmosphere. The product, isolated as described for the similar reduction of the bisbenzylthio-compound, was a mixture (2.2 g) of 2-benzylthio-3-mercapto- and 3-benzylthio-2-mercapto-propanol, b.p. 118–120° at 10^{-4} mmHg, n_D^{23} 1.5984, $[\alpha]_D^{23}$ +0.3° (*c* 7 in CHCl_3) and -1.2° (*c* 6 in MeOH), ν_{\max} (liquid) 3420, 2550, and 1600 cm^{-1} , τ 6.32 (s, PhCH_2) and 6.4 (m, $\text{CH}_2\cdot\text{OH}$) (total 4H), 7.35 (3H, m, CH and CH_2), 7.65br (1H, s, OH), and 8.32 (d, *J* 7.8 Hz, CH:SH) and 8.38 (t, *J* 8.6 Hz, $\text{CH}_2\cdot\text{SH}$) (total 1H) (Found: C, 55.7; H, 6.7; S, 29.7; thiol S, 15.3. Calc. for $\text{C}_{10}\text{H}_{14}\text{OS}_2$: C, 56.0; H, 6.6; S, 29.9; thiol S, 15.0%).

A solution of the mixed mercapto-alcohols (0.5 g) in ethanol (50 ml) containing Raney nickel (*ca.* 3 g) was boiled under reflux, the reaction being followed by titration of filtered samples with iodine. After 80 min, when only 15% of free thiol remained, the mixture was filtered and evaporated. The residue was taken up in ether, and the solution was washed with aqueous sodium hydroxide and with water, then dried and distilled to give a 2 : 1 mixture (0.16 g) of 2- and 3-(benzylthio)propanol, b.p. 140–150° at 10^{-4} mmHg,

n_D^{23} 1.5830, ν_{\max} (CCl_4) 3500, 1600, and 1500 cm^{-1} , τ 6.4 (4H, m, PhCH_2 and $\text{CH}_2\cdot\text{OH}$), 7.3 (2H, m, CH and CH_2), 8.0br (1H, s, OH), and 8.81 (2H, d, CH_3) (Found: S, 17.8. Calc. for $\text{C}_{10}\text{H}_{14}\text{OS}$: S, 17.6%).

Oxidation of the mixed mercapto-alcohols (0.5 g) in chloroform and water with iodine, as described above, gave the mixed disulphides as an oil (0.3 g), τ 6.24 (s, PhCH_2), 6.29 (s, PhCH_2), and 6.3 (m, $\text{CH}_2\cdot\text{OH}$) (total 4H), 7.2 (3H, m, CH and CH_2), and 7.55br (1H, s, OH) (Found: C, 56.1; H, 6.2; S, 29.9. Calc. for $\text{C}_{20}\text{H}_{26}\text{O}_2\text{S}_4$: C, 56.3; H, 6.1; S, 30.0%); this gave an α -naphthylurethane, m.p. 136–138° (decomp.) (from benzene-petroleum) (Found: C, 65.8; H, 5.4; N, 3.55; S, 16.7. Calc. for $\text{C}_{42}\text{H}_{40}\text{N}_2\text{O}_4\text{S}_4$: C, 65.9; H, 5.3; N, 3.7; S, 16.8%).

2,3-Dimercaptopropanol.—(i) Sodium, in small pieces, was added to a solution of 2,3-bis(benzylthio)propanol (1.5 g; prepared as described above) in liquid ammonia (*ca.* 30 ml) until the blue colour persisted for 20 min. The mixture was worked up, as already described, to give the dithiol (0.5 g), b.p. 64–65° at 0.1 mmHg, n_D^{22} 1.5674, $[\alpha]_D^{23}$ 0.0° (*c* 5 in MeOH) [lit.¹² n_D^{20} 1.5733; lit.² for (*R*)-compound, b.p. 65° at 10^{-4} mmHg, n_D^{18} 1.5740, $[\alpha]_D^{21}$ -9.6° in MeOH]. Reaction with cyclohexanone in the presence of hydrochloric acid gave the 2,3-*S*-cyclohexylidene derivative, m.p. 60–61° (from benzene-petroleum) [lit.² m.p. 63° for racemic compound, m.p. 50–51° for the (*R*)-form].

(ii) 2,3-Dimercaptopropionic acid (0.7 g; prepared as described above) in dry tetrahydrofuran (80 ml) was reduced with lithium aluminium hydride (1.4 g) at the b.p. for 3 h under nitrogen. Isolation in the usual way gave 2,3-dimercaptopropanol (0.3 g), b.p. 64–65° at 10^{-3} mmHg, n_D^{21} 1.5678, $[\alpha]_D^{24}$ 0.0° (*c* 5 in MeOH) (Found: thiol S, 51.5. Calc. for $\text{C}_3\text{H}_8\text{OS}_2$: thiol S, 51.6%).

(iii) The mixture of 2-benzylthio-3-mercapto- and 3-benzylthio-2-mercapto-propanol (1.8 g) in liquid ammonia (*ca.* 50 ml) was treated with sodium as described above, to give the dithiol (0.7 g), b.p. 68–70° at 10^{-4} mmHg, n_D^{22} 1.5714, $[\alpha]_D^{20}$ -0.8° (*c* 15 in MeOH) (Found: thiol S, 52.2%). The 2,3-*S*-cyclohexylidene derivative had m.p. 59–60°.

We thank the Commonwealth Scholarship Commission for an award (to M. B. R.) and Dr. P. M. Scopes for the c.d. measurements.

[4/1399 Received, 10th July, 1974]

¹² L. A. Stocken, *J. Chem. Soc.*, 1947, 592.