579. *The Preparation, via Thiuronium Salts, of Optically Active Thiols.*

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Fractional crystallisation of (±)-*S*-1-methylheptylthiuronium (+)-camphor-10-sulphonate did not effect resolution into the diastereoisomeric salts.

(+)-2-Bromo-octane has been converted, by reaction with thiourea, into the thiuronium bromide, and thence into (−)-octane-2-thiol. (+)-α-Methylphenethyl toluene-*p*-sulphonate similarly gave the corresponding thiuronium toluene-*p*-sulphonate, which yielded (−)-1-phenylpropane-2-thiol. The (−)-sulphonic ester has similarly been converted into the (+)-thiol.

A mechanism is proposed in which thiourea and the alkyl bromide or sulphonate undergo a bimolecular reaction with inversion of the configuration of the asymmetric carbon atom.

The stereochemistry of several olefin addition reactions, in which either the olefin or the reagent is asymmetric, has been investigated.[1] For a further study, a quantity of an optically active thiol was required, a compound having a single asymmetric centre directly attached to the thiol group being preferable.

Levene and Mikeska [2] prepared (+)-butane-, (+)- and (−)-pentane-, and (−)-octane-2-thiol by the reaction of the optically active halides with potassium hydrogen sulphide. Kenyon, Phillips, and their co-workers [3] obtained the last thiol by the analogous reaction with (+)-1-methylheptyl toluene-*p*-sulphonate; they also prepared (−)-butane-2-thiol and (−)-1-phenylpropane-2-thiol by the following method: reaction of the optically active 1-methylalkyl toluene-*p*-sulphonate with potassium thiocyanate gave the alkyl thiocyanate; alkaline hydrolysis of the latter, during which oxidation occurred, yielded the dialkyl disulphide, which on reduction gave the thiol.

The preparation of thiols *via* the thiuronium salts, of which there are many examples, appears to be the most satisfactory general method. The only instances of the use of optically active reactants relate to the preparation of sugar and terpene derivatives. *S*-(Tetra-*O*-acetyl-β-D-glucosyl)thiuronium bromide has been prepared; [4,5] with methanolic ammonia in the presence of ammoniacal silver nitrate it gave the silver salt of 1-thio-D-glucose.[4] Subluskey and King,[6] by heating camphene and related terpenes with thiourea and toluene-*p*-sulphonic acid, obtained *S-iso*bornylthiuronium toluene-*p*-sulphonate. They also prepared this salt by heating bornyl toluene-*p*-sulphonate with thiourea; the bornyl ester was about 8% optically pure: it yielded a salt which had a small rotation, but became optically inactive on recrystallisation. Salt of higher rotation was isolated as a crop from the camphene reaction. From both active and inactive salts specimens of *iso*bornanethiol (a solid) were prepared, but all were optically inactive. It is not clear how far, if at all, this loss of activity is due to racemisation, and to what extent it results from the separation of (±)-material from mixtures of low optical purity. Fractional crystallisation of *S-iso*bornylthiuronium (+)-camphor-10-sulphonate, prepared from camphene of about 9% optical purity, led to the separation of the diastereoisomeric salts, one of which was obtained optically pure; however, these salts were not converted into the thiols.

The literature then points to two methods whereby optically active thiols may be prepared *via* thiuronium salts: (1) The preparation of the (±)-*S*-alkylthiuronium salt of an optically active acid, followed by its resolution by fractional crystallisation into the diastereoisomeric salts; these are then converted into the enantiomeric thiols.

[1] Abbott and Arcus, *J.*, 1952, 1515; Arcus and Strauss, *ibid.*, p. 2669; Arcus and Smyth, *J.*, 1955, 34.
[2] Levene and Mikeska, *J. Biol. Chem.*, 1924, **59**, 475; 1925, **63**, 89; 1927, **75**, 593.
[3] Kenyon, Phillips, and Pittman, with (in part) Shackleton, Kahn, Yorston, and Cochinaras, *J.* 1935, 1072.
[4] Schneider and Eisfeld, *Ber.*, 1928, **61**, 1260.
[5] Bonner and Kahn, *J. Amer. Chem. Soc.*, 1951, **73**, 2241.
[6] Subluskey and King, *ibid.*, p. 2647.

(2) Conversion of an optically active alkyl halide, or reactive ester, into the corresponding thiuronium salt and thence into the active thiol.

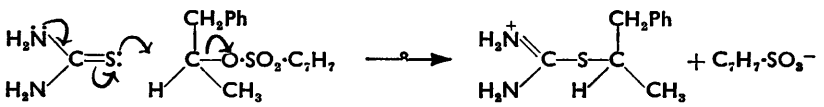
(±)-2-Bromo-octane was converted into *S*-1-methylheptylthiuronium bromide, which with sodium (+)-camphor-10-sulphonate gave (±)-*S*-1-methylheptylthiuronium (+)-camphor-10-sulphonate; this salt crystallised well from ethyl acetate and from heptan-4-one, but fractional crystallisation did not result in a separation of isomers. The recrystallised salt was converted into the thiuronium benzoate, into the thiol, and, by treatment with alkali and chloro-2 : 4-dinitrobenzene without isolation of the thiol, into 2 : 4-dinitrophenyl 1-methylheptyl sulphide; all these compounds were optically inactive.

(−)-Octan-2-ol, on reaction with phosphorus tribromide under conditions described by Gerrard,[7] gave (+)-2-bromo-octane; this compound was converted into the thiuronium bromide, an oil, which with sodium benzoate gave the solid thiuronium benzoate; the latter on treatment with sodium hydroxide yielded (−)-octane-2-thiol.

Of the methods for the conversion of octanol into bromo-octane developed by Gerrard, the procedure was used which appears to give the most useful combination of optical and chemical yields. Alcohol and bromide of the same sign of rotation have the same configuration,[3] whence this method of preparation involves inversion; however, some degree of racemisation also occurs, the extent being unknown since the rotatory power of optically pure 2-bromo-octane is unknown. By analogy with other replacement reactions of 2-bromo-octane,[8] the reaction of this compound with thiourea in ethanol very probably proceeds with inversion, and substitution may be completely bimolecular; further, the data on rotatory powers and configurations tabulated by Kenyon *et al.*[3] indicate the (−)-thiol and the (+)-bromide to be of opposite configurations.

(+)-α-Methylphenethyl toluene-*p*-sulphonate, on reaction with thiourea in ethanol, gave (+)-*S*-α-methylphenethylthiuronium toluene-*p*-sulphonate, which on treatment with sodium hydroxide yielded (−)-1-phenylpropane-2-thiol. The (−)-sulphonic ester similarly gave the (+)-thiol.

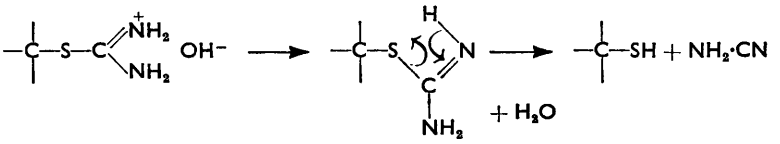
The (+)- and the (−)-sulphonic ester were prepared from (+)- and (−)-1-phenylpropan-2-ol by reaction with toluene-*p*-sulphonyl chloride and pyridine (Phillips [9]), a process in which the bonds of the asymmetric carbon atom are not disturbed. The reaction of the sulphonic ester with thiourea is considered, from the following data, to proceed with inversion, and probably by the bimolecular mechanism: (*a*) The kinetics of the reaction between tetra-*O*-acetyl-α-D-glucosyl bromide and thiourea have been studied polarimetrically by Bonner and Kahn,[5] who found the reaction to be of the second order; the thiuronium salt so formed showed no mutarotation, whence it is concluded that the reaction is not reversible. These authors put forward a mechanism similar to that given below. (*b*) Kenyon *et al.*,[3] from a comparison of rotatory powers, conclude that 1-phenylpropan-2-ol and 1-phenylpropane-2-thiol of opposite signs of rotation are of opposite configurations. (*c*) α-Methylphenethyl toluene-*p*-sulphonate reacts with inversion with numerous reagents,[3] and with ethanolic potassium acetate and valerate (the two instances in which the alcohol was regenerated by hydrolysis of the product) the inversion is respectively 97 and 96%.[9] The following mechanism is proposed for the reaction of the sulphonic ester with thiourea:

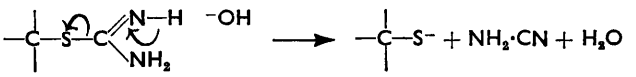


The nitrogenous product of the decomposition of thiuronium salts is dicyandiamide.[10] The monomeric cyanamide can be formed from the thiuronium cation by either of two slightly different mechanisms: (1) the removal of a proton by hydroxyl ion (or, in the decomposition of *S*-alkylthiuronium hydrogen carbonates studied by Horák.[11] by the

[7] Gerrard, *J.*, 1945, 850, expt. no. 2.
[8] Hughes, Ingold, and Masterman, *J.*, 1937, 1196.
[9] Phillips, *J.*, 1923, **123**, 44.
[10] Bernthsen and Klinger, *Ber.*, 1879, **12**, 574.
[11] Horák, *Chem. Listy*, 1954, **48**, 414.

HCO_3^- ion), followed by rearrangement as shown. (2) Formation of the free base followed by its reaction with a second hydroxyl ion, yielding the thiol anion. In neither mechanism are the bonds of the asymmetric carbon atom disturbed, whence it retains the configuration which it had in the thiuronium salt.

(1) 

(2) 

Experimental

M. p.s are corrected.

(±)-2-Bromo-octane (25·5 g.) and thiourea (10·1 g.), in solution in ethanol (100 ml.), were heated under reflux for 5 hr.; the ethanol was distilled under reduced pressure, and (±)-*S*-1-methylheptylthiuronium bromide (35·0 g.) was obtained as an oil. To a suspension of this compound (35 g.) in water (100 ml.) was added a solution of sodium (+)-camphor-10-sulphonate (33 g.) in water (150 ml.); the oily product, on being cooled to −80°, gave a solid (29 g.), m. p. 106—112°, $[\alpha]_{5893}^{20}$ +24·5° (*l* 1·0; *c* 4·988 in EtOH). This material was recrystallised from ethyl acetate and from heptan-4-one, to constant specific rotatory power in both instances, and yielded (±)-S-1-*methylheptylthiuronium* (+)-*camphor*-10-*sulphonate*, m. p. 119°, $[\alpha]_{5893}^{20}$ +26·3° (*l* 1·0; *c* 4·991 in EtOH) (Found: N, 6·75; S, 15·45. $C_{19}H_{36}O_4N_2S_2$ requires N, 6·65; S, 15·3%).

This sulphonate (12·6 g.) was stirred with 1·5N-sodium carbonate (40 ml.) for 2 hr. at 50°; the chilled solution was then acidified to Congo-red with 3N-hydrochloric acid, and thrice extracted with ether. The extract was washed with water and dried (Na_2SO_4), and the ether evaporated under reduced pressure. The product was distilled, and yielded (±)-octane-2-thiol (2·5 g.), b. p. 83—84°/26 mm., n_D^{20} 1·4500, optically inactive to sodium light. Decomposition, drying, evaporation, and distillation were conducted in nitrogen.

This thiol (1·15 g.) and chloro-2 : 4-dinitrobenzene (1·6 g.), in ethanol (26 ml.), together with sodium hydroxide (0·36 g.) in aqueous ethanol (1 : 1, 3 ml.), were heated under reflux for 10 min. The hot solution was filtered, and from the cold filtrate there separated a product (1·2 g.) which after two recrystallisations from ethanol yielded (±)-2 : 4-*dinitrophenyl* 1-*methylheptyl sulphide*, yellow needles, m. p. 50° (Found: N, 8·75; S, 10·05. $C_{14}H_{20}O_4N_2S$ requires N, 8·95; S, 10·25%).

The sulphonate, above, was similarly treated, and gave (±)-2 : 4-dinitrophenyl 1-methylheptyl sulphide, m. p. and mixed m. p. 50°, optically inactive in solution in methanol.

On the addition of sodium benzoate (0·8 g.) in water (10 ml.) to (±)-*S*-1-methylheptylthiuronium bromide (1·0 g.) suspended in water (10 ml.), there was precipitated (±)-*S*-1-methylheptylthiuronium benzoate (0·9 g.) having, after recrystallisation from ethanol, m. p. 140—141°. Similar treatment of the above sulphonate [2·1 g. in 10 ml. of aqueous methanol (9 : 1)] yielded the benzoate, which after recrystallisation had m. p. and mixed m. p. 140—141°; it was optically inactive in solution in ethanol.

(±)-Octan-2-ol was resolved by Kenyon's method.[12] Reaction of (−)-octan-2-ol (12·4 g.; α_{5893}^{21} −4·09°, *l* 0·5) at −10° with phosphorus tribromide (17·1 g.), according to Gerrard,[7] yielded (+)-2-bromo-octane (6·3 g.), b. p. 81—82°/20 mm., n_D^{20} 1·4500, α_{5893}^{18} +20·20° (*l* 0·5). This bromo-octane (2·0 g.) and thiourea (0·8 g.) in solution in ethanol (8 ml.) were heated under reflux for 5 hr. The ethanol was evaporated under reduced pressure and to the remaining oil was added a solution of sodium benzoate (1·5 g.) in water (15 ml.); there separated the thiuronium benzoate (2·2 g.), which was filtered off and washed with ether. The benzoate (3·1 g.) was heated under reflux for 2 hr. in nitrogen with sodium hydroxide (0·8 g.) in water (20 ml.). The organic layer was separated from the cooled reaction mixture; the aqueous layer was acidified with hydrochloric acid, and the benzoic acid was filtered off; the organic layer was combined with the ether extract of the aqueous layer, and the whole treated as

[12] Kenyon, *Org. Synth.*, Coll. Vol. I, 2nd Edn., 1941, p. 418

described for the sulphonate decomposition. There was obtained (−)-octane-2-thiol (1·1 g.), b. p. 80—82°/25 mm., n_D^{20} 1·4520, α_{5893}^{22} −9·29° (*l* 0·5) (Found: S, 21·95. Calc. for $C_8H_{18}S$: S, 21·9%). This thiol (0·50 g.) was allowed to react with chloro-2 : 4-dinitrobenzene (0·71 g.), as for the (±)-compound; from the filtrate there separated (+)-2 : 4-dinitrophenyl 1-methylheptyl sulphide (0·61 g.), m. p. 40—45°, $[\alpha]_{5893}^{22}$ +54° (*l* 0·5; *c* 0·890 in EtOH). It was not recrystallised, because, like the bromo-octane from which it was derived, it is considered to be partially racemic.

1-Phenylpropan-2-one (42 g.) was heated with a solution of aluminium *iso*propoxide (prepared from propan-2-ol, 280 ml., and aluminium, 27 g.), and the acetone formed was slowly distilled off; the solution was evaporated under reduced pressure, and the chilled product was slowly added with stirring to 50% sulphuric acid (600 ml.) and ice. The whole was extracted with ether; the extract was dried (K_2CO_3), and yielded (±)-1-phenylpropan-2-ol (30 g.), b. p. 108—112°/18 mm., n_D^{18} 1·5205.

Powdered toluene-*p*-sulphonyl chloride (25·8 g.) was added to a solution of (±)-1-phenylpropan-2-ol (18·4 g.) in dry pyridine (13 ml.); the whole was kept at room temperature for 2 days, then stirred with water. The solid product, after being washed with dilute hydrochloric acid and water, yielded (±)-α-methylphenethyl toluene-*p*-sulphonate (35·3 g.), m. p. 86—89°. It (14·5 g.) was heated under reflux with thiourea (3·8 g.) in ethanol (10 ml.) for 2 hr. The hot solution was chilled in ice–salt; the solid which separated was filtered off, washed with ether to remove any unchanged sulphonic ester, and twice recrystallised from ethanol; it yielded (±)-S-α-*methylphenethylthiuronium toluene*-p-*sulphonate* (13·9 g.), m. p. 180—181° (Found: C, 55·8; H, 6·25; S, 17·6. $C_{17}H_{22}O_3N_2S_2$ requires C, 55·7; H, 6·05; S, 17·5%).

This sulphonate (12·2 g.) and quinol (0·1 g.) were stirred with 6N-sodium hydroxide (25 ml.) for 45 min. at 60—65°. The chilled mixture was acidified to Congo-red with 3N-hydrochloric acid and thrice extracted with ether. The extract was washed with water, and dried (Na_2SO_4), quinol (0·3 g.) having been added. The ether was evaporated, and the product distilled; decomposition, drying, evaporation, and distillation were conducted in nitrogen. There was obtained (±)-1-*phenylpropane*-2-*thiol* (4·1 g.), b. p. 106—108°/18 mm., n_D^{18} 1·5448, $[R]_D$ 48·08 (Calc., 48·04) (Found: S, 20·7, 20·9. $C_9H_{12}S$ requires S, 21·0%).

(±)-1-Phenylpropane-2-thiol (0·42 g.) in ethanol (2 ml.) was added to mercuric cyanide (0·8 g.) in water (40 ml.). A solid separated on chilling of the solution; it was twice recrystallised from chloroform–ethanol (1 : 1), and yielded *mercury* (±)-α-*methylphenethyl mercaptide*, m. p. 88—89° (Found: C, 43·2; H, 4·4. $C_{18}H_{22}S_2Hg$ requires C, 42·95; H, 4·6%).

(±)-1-Phenylpropan-2-ol was resolved by the method briefly described by Kenyon *et al.*[13, 3] This alcohol (115 g.) was added to a solution of phthalic anhydride (125 g.) in dry pyridine (130 ml.), and the whole was heated for 4½ hr. on a steam-bath; it was then cooled and poured into 6N-hydrochloric acid (500 ml.) and ice. The product was washed with dilute hydrochloric acid, and water; (±)-α-methylphenethyl hydrogen phthalate so prepared (150 g.) had m. p. 112—115°. Brucine (206·5 g.) was cautiously added to a hot solution of this phthalate (149 g.) in acetone (1500 ml.). The alkaloidal salt which separated on cooling was recrystallised four times from acetone and yielded brucine (+)-α-methylphenethyl phthalate (70·5 g.), m. p. 151—153°. This salt (2·5 g.), 3N-hydrochloric acid (1·5 ml.), ether (10 ml.), and water (10 ml.) were shaken together; the aqueous layer was separated and further thrice extracted with ether; the combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. (+)-α-Methylphenethyl hydrogen phthalate so obtained was dried to constant weight (0·86 g.) *in vacuo* over phosphoric oxide; it had $[\alpha]_{5893}^{20}$ +48·0°, $[\alpha]_{5461}^{20}$ +57·8° (*l* 2·0; *c* 4·225 in $CHCl_3$). When a portion of the brucine salt was recrystallised a further four times, it yielded hydrogen phthalate of the same rotatory power. The hydrogen phthalate obtained by the decomposition, as above, of 44·5 g. of brucine (+)-α-methylphenethyl phthalate was dissolved in 5N-sodium hydroxide (40 ml.), and steam was passed through the solution. The distillate was saturated with potassium carbonate and four times extracted with ether; the extract was dried (K_2CO_3) and evaporated under reduced pressure. Distillation of the product yielded (+)-1-phenylpropan-2-ol (6·8 g.), b. p. 104°/15 mm., α_{5893}^{19} +13·61°, α_{5461}^{19} +16·48° (*l* 0·5), n_D^{20} 1·5210, n_D^{25} 1·5190. The filtrate from which the brucine (+)-alkyl phthalate had separated yielded, on evaporation, a crop (165 g.) which, after three recrystallisations from acetone, gave brucine (−)-α-methylphenethyl phthalate (135·5 g.), m. p. 85—87°. (−)-α-Methylphenethyl hydrogen phthalate, isolated as above, had $[\alpha]_{5893}^{20}$ −47·3°, $[\alpha]_{5461}^{20}$ −57·3° (*l* 2·0; *c* 4·262 in $CHCl_3$), and yielded (−)-1-phenylpropan-2-ol (20·0 g.), b. p. 116—117°/23 mm., α_{5893}^{23} −26·24°, α_{5461}^{23} −31·6° (*l* 1·0), n_D^{20} 1·5204, n_D^{25} 1·5182.

[13] Pickard and Kenyon, *J.*, 1914, **105**, 1124.

(+)-1-Phenylpropan-2-ol (16·2 g.; α_{5893}^{19} +13·59°, *l* 0·5) was converted, by the method used for the (±)-alcohol, into (+)-α-methylphenethyl toluene-*p*-sulphonate (30 g.), m. p. 67·5—68°, $[\alpha]_{5893}^{20}$ +25·2° (*l* 2·0; *c* 4·999 in $CHCl_3$). It (29 g.) was converted, as for the (±)-ester, into (+)-*S*-α-methylphenethylthiuronium toluene-*p*-sulphonate (31 g.; it was washed with ether but not recrystallised), $[\alpha]_{5893}^{20}$ +4·3° (*l* 2·0; *c* 4·976 in EtOH). This compound (50 g.) was converted, by the method described for the (±)-thiuronium salt, into (−)-1-phenylpropane-2-thiol (13·2 g.), b. p. 111°/23 mm., n_D^{24} 1·5425, α_{5893}^{23} −13·46°, α_{5780}^{24} −14·50°, α_{5461}^{24} −16·54°, α_{4358}^{24} −34·0° (*l* 1·0) (Found: C, 70·9; H, 8·3; S, 20·8, 21·0. Calc. for $C_9H_{12}S$: C, 71·0; H, 7·9; S, 21·0%). It yielded, as for the (±)-thiol, *mercury (+)-α-methylphenethyl mercaptide*, m. p. 124°, $[\alpha]_{5893}^{22}$ +100° (*l* 1·0; *c* 5·00 in $CHCl_3$) (Found: C, 43·2; H, 4·85%).

(−)-1-Phenylpropan-2-ol (19·7 g.; α_{5893}^{23} −13·12°, *l* 0·5) was similarly converted into (−)-α-methylphenethyl toluene-*p*-sulphonate (37·4 g.), m. p. 62·5—64·5°, $[\alpha]_{5893}^{24}$ −22·9° (*l* 2·0; *c* 5·173 in $CHCl_3$), thence into (−)-*S*-α-methylphenethylthiuronium toluene-*p*-sulphonate (24 g.), $[\alpha]_{5893}^{21}$ −4·5° (*l* 2·0; *c* 5·001 in EtOH), of which 22·4 g. were converted into (+)-1-phenylpropane-2-thiol (4 g.), b. p. 104°/17 mm., n_D^{20} 1·5450, α_{5893}^{17} +6·08°, α_{5780}^{19} +6·26°, α_{5461}^{19} +7·31°, α_{4358}^{19} +14·6° (*l* 0·5); it gave mercury (−)-α-methylphenethyl mercaptide, m. p. 123·5—124·5°, $[\alpha]_{5893}^{23}$ −100° (*l* 1·0; *c* 2·054 in $CHCl_3$).

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