Simple Synthesis of Chiral Thiirancarboxylic Acids

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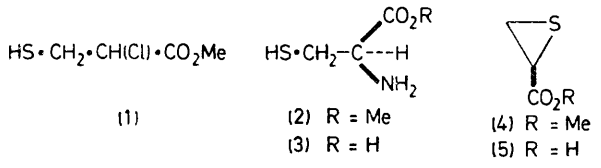
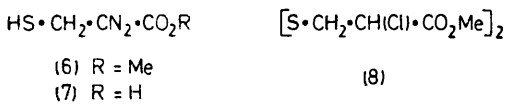
Summary Methyl (*R*)-cysteinate (**2**) is converted into methyl (*S*)-thiirancarboxylate (**4**) by sodium nitrite and hydrochloric acid; under corresponding conditions (*R*)-cysteine (**3**) affords a 3 : 1 mixture of (*R*)-thiirancarboxylic acid (**12**) and the (*S*)-enantiomer (**5**).

IN connection with other work we required methyl 2-chloro-3-mercaptopropionate (**1**). Although we were able to prepare this compound from methyl acrylate by the published four-step sequence,[1] we sought a more direct route starting from methyl (*R*)-cysteinate (**2**). Treatment of (**2**) (10 mmol) with $NaNO_2$ (30 mmol) in ice-cold M-HCl

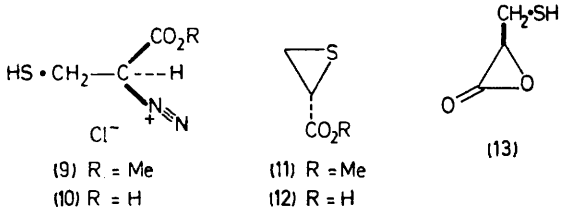
(50 cm³) for 5 min followed by chloroform extraction gave one major product which was purified by alumina chromatography. The material (47%), $[\alpha]_D$ −25° ($CHCl_3$), was identical (n.m.r. and mass spectroscopy) with the racemate of methyl thiirancarboxylate,[1] prepared from (**1**) by the action of $NaHCO_3$.



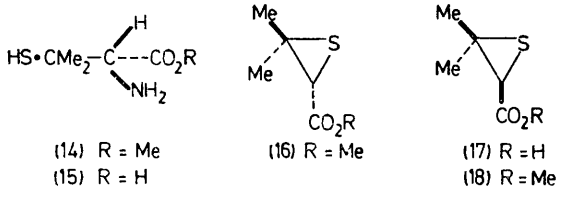
(**1**) (**2**) R = Me (**3**) R = H (**4**) R = Me (**5**) R = H



(**6**) R = Me (**7**) R = H (**8**)



(**9**) R = Me (**10**) R = H (**11**) R = Me (**12**) R = H (**13**)



(**14**) R = Me (**15**) R = H (**16**) R = Me (**17**) R = H (**18**) R = Me

When the deamination was performed in the presence of DCl, the thiiran contained no deuterium (mass spectroscopy); this result excludes the partial intervention of the diazo-ester (**6**). Moreover, when treated with $NaNO_2$ and HCl, (**1**) was converted into the dichloro-disulphide (**8**);† there was no evidence for the presence of the thiiran. It seems likely therefore that the thiiran is formed from the diazonium intermediate (**9**) by an S_N2-like displacement of nitrogen by the thiol group and that it is the (*S*)-enantiomer (**4**).

Treatment of the hydrochloride of (*R*)-cysteine (**3**) (10 mmol) with $NaNO_2$ (30 mmol) in ice-cold 0·1 M-HCl (50 cm³) for 5 h followed by acidification with conc. HCl and extraction with chloroform gave one major material (55%) which was identical (n.m.r. spectroscopy) with the racemate of thiiranearboxylic acid.[1] Esterification with diazomethane and purification of the product by alumina chromatography yielded methyl thiirancarboxylate (29%), $[\alpha]_D$ + 9° ($CHCl_3$). C.d. measurements (EtOH) confirmed that the derivative was the (*R*)-thiiran (**11**) and suggested that its optical purity was 53% of that of the (*S*)-thiiran (**4**); thus the (*R*)-thiiran (**11**) showed a negative transition at 281 nm ($\Delta\epsilon$ − 0·705) whereas the (*S*)-thiiran (**4**) displayed a positive transition at the same wavelength ($\Delta\epsilon$ + 1·34).‡

The reaction of (*R*)-cysteine with $NaNO_2$ and DCl yielded thiirancarboxylic acid which contained no deuterium at position-1 (mass spectroscopy); evidently, the diazo-acid (**7**) is not involved in the deamination. It seems likely therefore that the thiiran is derived from the diazonium intermediate (**10**) by two competitive pathways. The preferred reaction presumably involves a displacement of nitrogen by the carboxy-group to give the α-lactone (**13**),§ which then isomerises to the (*R*)-acid (**12**). The less-preferred reaction, which is *ca.* 3 times slower, probably involves a direct displacement of the nitrogen by the thiol group to give the (*S*)-acid (**5**).

Under similar conditions, (*S*)-penicillamine methyl ester (**14**) afforded (14% after alumina chromatography) methyl (*R*)-2,2-dimethylthiirancarboxylate (**16**)† ($\Delta\epsilon$ − 0·389 at 285 nm) and (*S*)-penicillamine (**15**) gave (78%) (*S*)-2,2-dimethylthiirancarboxylic acid (**17**).† The optical purity of the (*S*)-acid (**17**) was estimated to be 87% on the basis of its conversion into the (*S*)-ester (**18**) ($\Delta\epsilon$ + 0·338 at 285 nm).

The foregoing results are of interest in that they provide a simple new synthesis of thiirancarboxylates, a relatively inaccessible class of compounds.[2] Moreover, the route makes the derivatives available for the first time in optically active form.

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† The composition of new compounds was confirmed by mass spectroscopy. Structural assignments are based upon i.r., u.v., and n.m.r. spectroscopic evidence.

‡ (*S*)-Phenylthiiran is characterised by a positive transition at 277 nm ($\Delta\epsilon$ + 2·2) (I. Moretti, G. Torre, and G. Gottarelli, *Tetrahedron Letters*, 1971, 4301).

§ Persuasive evidence exists that α-lactones intervene in related displacement reactions (W. A. Cowdrey, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.* 1937,1208; E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.*, 1948, **70**, 841).

[1] L. P. Parshina, M. G. Lin'Kova, O. V. Kil'disheva, and I. L. Knunyants, *Izvest. Akad. Nauk S.S.S.R., Ser. Khim.*, 1970, 931; *Chem. Abs.*, 1970, **73**, 35130.

[2] A. V. Fokin and A. F. Kolomiets, *Russ. Chem. Rev.*, 1975, **44**, 138.