Studies related to Thiirans. Part 1. Synthesis of Chiral Thiirancarboxylates [1]

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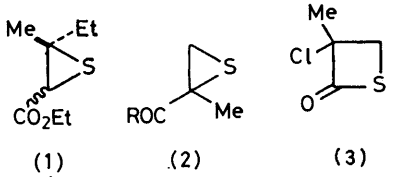
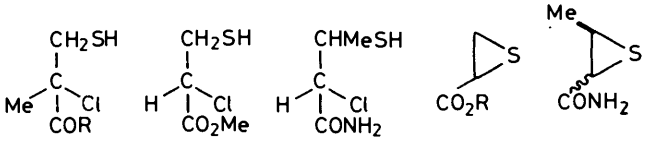
The first examples of optically active thiirancarboxylic acid derivatives are reported. Thus optically pure methyl (*S*)-thiirancarboxylate was prepared by the reaction of methyl (*R*)-cysteinate with sodium nitrite–hydrochloric acid; ethyl and n-propyl (*S*)-thiirancarboxylates were obtained in an analogous manner. (*R*)-Cysteine undergoes a corresponding deaminative cyclization to give (*R*)-thiirancarboxylic acid; the optical purity of the last-mentioned compound is 53% when dilute hydrochloric acid is employed as the reaction medium and 60% when aqueous acetic acid is used. Methyl (*S*)-thiirancarboxylate is hydrolysed by sodium hydroxide to (*S*)-thiirancarboxylic acid; the reaction occurs without any significant racemization. (*S*)-Penicillamine methyl ester reacts with sodium nitrite–hydrochloric acid to give optically pure methyl (*R*)-3,3-dimethylthiiran-2-carboxylate. (*S*)-Penicillamine undergoes an analogous reaction to give (*S*)-3,3-dimethylthiiran-2-carboxylic acid with an optical purity of 87%.

ALTHOUGH a wide variety of methods are available for the derivation of alkyl- and aryl-substituted thiirans, few of these are applicable to the synthesis of thiirancarboxylic acid derivatives.[2] In fact, in spite of numerous attempts, the preparation of the last-described class of compounds was not described until 1967.[3] A report, in 1959,[4] claiming the characterization of the compound (1) was subsequently shown [5] to be incorrect. The



(1) (2) (3)

a; R = NR_2
b; R = OMe
c; R = OH



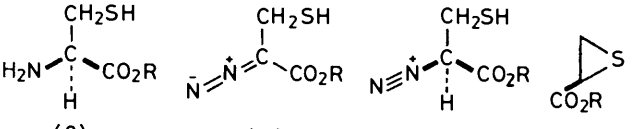
(4) (5) (6) (7) (8)

a; R = Me
b; R = H

methods investigated for the synthesis of thiirancarboxylic acid derivatives included treating glycidic esters with thiourea,[4-8] potassium thiocyanate,[4] or thioacetic acid–base;[5,8] reacting glycidamides with thiourea;[9] treating vicinal dithioacetates or vicinal halogeno-thioacetates with base;[9] subjecting thiobenzophenone and ethyl chloroacetate to the conditions of the Darzens condensation;[8] and reacting methyl α-chloroacrylate with hydrogen sulphide under basic conditions;[10] all these approaches met with failure. The first successful synthesis, leading to compounds of type (2a), was achieved by treating the thietanone (3) with ammonia or amines;[3] subsequently, the ester (2b) [11] and the acid (2c) [12] were derived. The foregoing reactions probably involve the intermediacy of chlorothiols of type (4), formed by preliminary opening of the thietanone ring. Similar compounds, *e.g.* (5) and (6), have also been prepared by the acidic hydrolysis of vicinal chloro-thioacetates; they are converted into thiirans, *e.g.* (7a) [12,13] and (8),[14] under mildly basic conditions. Other syntheses of thiirancarboxylic acid derivatives involve the cyclization of β-chloro-α-mercaptopropionates [15] and the addition of sulphur to maleates.[16]

RESULTS AND DISCUSSION

Our interest in thiirancarboxylic acid derivatives arose in connection with other work in which we required methyl 2-chloro-2-mercaptopropionate (5) in an optically active form. Since it is known that the amino-group of certain amino-acid esters, under deaminative conditions, can be replaced by halogen with an inversion of configuration,[17] we decided to investigate the reaction of methyl (*R*)-cysteinate (9a) with sodium nitrite–hydrochloric acid. When an ice-cold solution of the amine (9a) in 1M hydrochloric acid was treated with sodium nitrite (3 mol equiv.) for 5 min and the mixture was extracted with chloroform, one major product was isolated. After purification by alumina chromatography or distillation, a liquid (*ca.* 50%), $[\alpha]_D$ −24° ($CHCl_3$), was isolated which was identical (n.m.r. and mass spectroscopy) with the racemate of methyl thiirancarboxylate (7a), prepared from the chloro-thiol (5) by the action of sodium hydrogencarbonate.[12]



(9) (10) (11) (12)

(9)	(10)	(11)	(12)
a; R = Me	a; R = Me	a; R = Me	a; R = Me
b; R = Et	b; R = H	b; R = H	b; R = Et
c; R = Pr^n			c; R = Pr^n
d; R = H			d; R = H

When the deamination of the amine (9a) was performed in deuteriochloric acid, the derived thiiran

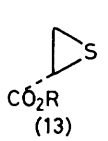
contained no deuterium (n.m.r. and mass spectroscopy); this result excluded the partial intervention of the diazo-ester (10a). It seemed likely, therefore, that the thiiran was formed from the diazonium intermediate (11a) by an S_N2-like displacement of nitrogen by the thiol group and that it was the optically pure (*S*)-enantiomer (12a).

The conversion of the cysteinate (9a) into the thiiran (12a) was of interest in two respects. First, and somewhat surprisingly, the deamination of 2-mercaptoalkylamines had not previously been investigated as a route to thiirans. Secondly, methyl thiirancarboxylate had not hitherto been available in optically active form. Accordingly, it was decided to investigate the scope of the synthesis.

This deaminative procedure could be applied to other cysteinate esters; thus ethyl (*R*)-cysteinate (9b) and n-propyl (*R*)-cysteinate (9c) afforded the thiirans (12b) and (12c) in respective yields of 42 and 22% after distillation.

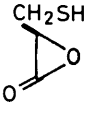
In the case of (*R*)-cysteine (9d), the deaminative procedure failed to afford the thiiran (7b). However, after some experimentation, it was found that the required material could be obtained by treating an ice-cold solution of the amino-acid hydrochloride (2 mmol) in 0.1M hydrochloric acid (10 cm^3) with sodium nitrite (6 mol) for 5 h, followed by acidification with concentrated hydrochloric acid and extraction with chloroform. This procedure afforded the thiiran (7b), as an impure syrup, in yields of 30—50%. Attempts to conduct the reaction on a larger scale resulted in a marked decrease in the yield of the chloroform-extractable material; thus yields of 15—25% of the crude acid (7b) were obtained starting with 10 mmol of the amino-acid.

To determine its optical purity, the crude acid (7b) was treated with diazomethane and the product was purified



(13)

a; R =Me
b; R =H



(14)

by alumina chromatography. The derived ester was considered to be the (*R*)-thiiran (13a) on the basis of its optical rotation {$[\alpha]_D$ +9° ($CHCl_3$)}. Circular dichroism (c.d.) measurements (EtOH) confirmed this result and indicated that the optical purity of the derivative was 53% of that of the (*S*)-thiiran (12a); thus the former compound showed a negative transition at 281 nm ($\Delta\varepsilon$ −0.71) whereas the latter displayed a positive transition at the same wavelength ($\Delta\varepsilon$ +1.34).

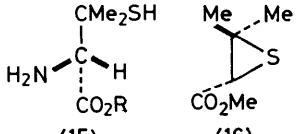
When the deamination of (*R*)-cysteine (9d) was conducted in deuteriochloric acid, the derived thiiran (after re-exchange of the carboxylic acid proton) contained no deuterium (mass and n.m.r. spectroscopy); evidently, the diazo-acid (10b) was not a reaction intermediate. It seemed likely, therefore, that the thiiran was derived from the diazonium intermediate (11b) by two competing pathways. The preferred reaction presumably involved a displacement of nitrogen by the carboxy group to give the α-lactone (14) which then isomerized to the (*R*)-thiiran (13b). The less-preferred reaction probably involved a direct displacement of nitrogen by the thiol group to give the (*S*)-thiiran (12d).

In view of the difficulty experienced in deriving the acid (13b) in adequate yield from (*R*)-cysteine (9d) and sodium nitrite–hydrochloric acid, the deamination was studied in other media. Aqueous acetic acid (50%) proved to be somewhat more effective and yields of 30—35% of the crude acid (13b) were achieved starting with 10 mmol of the amino-acid hydrochloride. Distillation of the crude product afforded a pure sample of the acid (13b), $[\alpha]_D$ +28° (Me_2CO).

To assess its optical purity, the pure acid (13b) was treated with diazomethane and the product was purified by distillation. The derived ester, $[\alpha]_D$ +15° ($CHCl_3$), was considered to be the (*R*)-thiiran (13a), possessing an optical purity of *ca.* 60%.

It has been reported that methyl thiirancarboxylate (7a) is hydrolysed by sodium hydroxide to give, after acidification, thiirancarboxylic acid (7b). When treated under corresponding conditions, the (*S*)-thiiran (12a) afforded the (*S*)-acid (12d), $[\alpha]_D$ −57° ($CHCl_3$), in 72% yield. That the hydrolysis was not accompanied by any significant racemization was confirmed by re-converting the acid into the ester using diazomethane; the optical rotation of the derived ester, $[\alpha]_D$ −21° ($CHCl_3$), was very similar to that of the optically pure (*S*)-thiiran (13a). The availability of the optically pure (*S*)-acid (12d) clearly offers the opportunity of deriving a wide range of monosubstituted thiirans of known chirality.

In order to assess the influence of alkyl substitution upon the foregoing deaminative cyclizations, the behaviour of (*S*)-penicillamine methyl ester (15a) was examined. When treated under the conditions described for the cysteinate (9a), the derivative (15a) afforded one major product which was purified by alumina chromatography to give methyl 3,3-dimethylthiiran-2-carboxylate (14%). On ths basis of its optical rotation {$[\alpha]_D$ +92° ($CHCl_3$)} and its c.d. spectrum [$\Delta\varepsilon$ −0.39 at 258 nm (EtOH)], the material was considered to be the pure (*R*)-thiiran (16). The derivative (16) was found to be significantly volatile



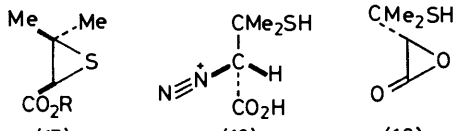
(15) (16)

a; R =Me
b; R =H

and it seemed likely that appreciable losses of the material had occurred during chromatography. In agreement

with this supposition, the yield of the (*R*)-thiiran (16) was improved to 44% when the crude product was purified by distillation.

(*S*)-Penicillamine (15b), when treated with sodium nitrite–dilute hydrochloric acid, afforded 3,3-dimethylthiiran-2-carboxylic acid. To determine its optical purity, the acid was treated with diazomethane and the product was purified by alumina chromatography. The derived ester was considered to be the (*S*)-thiiran (17a) on the basis of its optical rotation $\{[\alpha]_D -69°$ $(CHCl_3)\}$. C.d. measurements [$\Delta\varepsilon$ +0.34 at 285 nm (EtOH)] confirmed this result and indicated that the optical purity of the derivative was 87% of that of the (*R*)-thiiran (16). Clearly, the deaminative cyclization of (*S*)-penicillamine (15b) to the (*S*)-thiiran (17b) is accompanied by a greater degree of retention of configuration than the corresponding reaction of (*R*)-cysteine (9d). Presumably, this reflects an increased tendency for the diazonium species (18) to form the α-lactone intermediate (19).

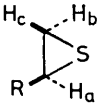


(17) (18) (19)

a; R = Me
b; R = H

The reaction of (*S*)-penicillamine (15b) with sodium nitrite–dilute hydrochloric acid was less erratic than that involving (*R*)-cysteine (9d). Thus the acid (17b), isolated as a fairly pure syrup, was obtained in 46% yield when the deamination was carried out using 10 mmol of the amino-acid.

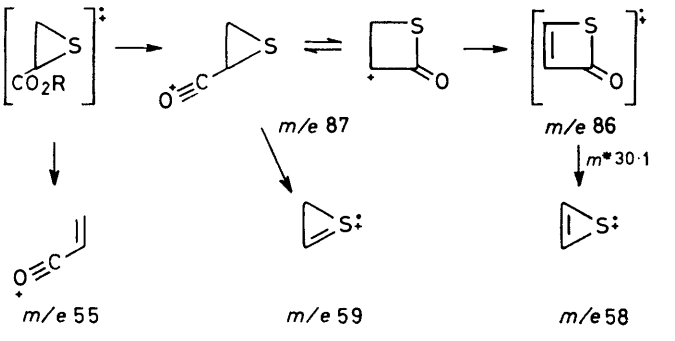
The ring protons of the thiirans (12a—d), which appeared as AMX spectra, resonated at δ 2.66 ± 0.04, 2.87 ± 0.04, and 3.40 ± 0.05 ($CDCl_3$). The protons were present as double doublets with coupling constants of 1.0 and 5.9 ± 0.1, 1.0 and 4.9 ± 0.1, and 5.9 ± 0.1



(20)

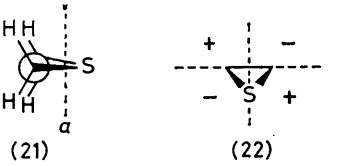
a; R = CO_2R'
b; R = Ph
c; R = Me
d; R = $CH(OH)CH_2CN$
e; R = Bu^n
f; R = Bu^t
g; R = CH_2Cl
h; R = CH_2OMe

and 4.9 ± 0.1 Hz, respectively. Since the proton of an $RCHCO_2R'$ moiety is deshielded compared with those of an RCH_2 group, the low-field double doublet was assigned to the C-2 proton [*i.e.* H_a of (20a)]; moreover, the corresponding proton of the derivatives (17a and b) appeared at δ 3.35 ± 0.02. It is well established that J_{cis} is larger than J_{trans} for vicinal protons on a three-membered ring;[18] in consequence, the double doublet at δ 2.66 ± 0.04 was assigned to the C-3 proton *trans* to the substituent [*i.e.* H_b of (20a)] and that at 2.87 ± 0.04 to the C-3 proton *cis* to the substituent [*i.e.* H_c of (20a)]. The geminal coupling constant of 1.0, the vicinal *cis* coupling constant of 5.9 ± 0.1, and the vicinal *trans* coupling



Scheme

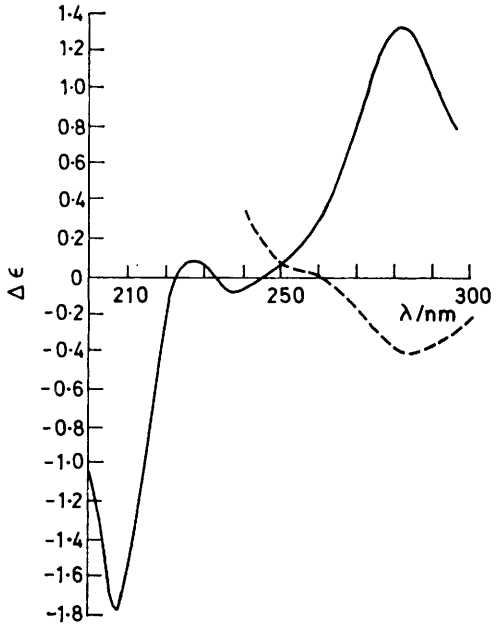
constant of 4.9 ± 0.1 Hz observed in the present study are in good agreement with the values [J_{gem} 1.1 ± 0.3, $J_{vic(cis)}$ 6.8 ± 0.8, and $J_{vic(trans)}$ 5.3 ± 0.8 Hz] previously reported[19–22] for thiirans of type (20). In the case of the thiirans (20b—h), H_c resonated at higher field than H_b indicating that the magnetic anisotropy of the R–C bond made a greater local-field contribution to the shielding of H_c than to the shielding of H_b;[19–22] clearly this effect was reversed with the thiirans (20a). Similar effects have been noted with cyclopropanes[23,24] but, interestingly, not with oxirans.[24]



(21) (22)

Prominent molecular ions were a characteristic feature of the mass spectra of the thiirans (12a—d) and (17a, b). In the case of the derivatives (12a—d) significant peaks were present at *m/e* 87, 86 (base peak), 59, 58, and 55; these were attributabed to species shown in the Scheme.

Chiral thiirans are characterized by an absorption at *ca.* 260 nm in their c.d. spectra which arises from an $n\rightarrow\sigma^*$ transition.[25] A symmetry rule has been devised which accounts for the sign of the 260 nm transition.[26] In general, substituents which are directly attached to the carbon atoms of the thiiran ring and which do not extend significantly beyond plane *a* in (21) give contributions to the optical activity having the signs depicted in (22). Thus (*S*)-methylthiiran (20c) and (*S*)-phenylthiiran (20b) show positive dichroisms; the former derivative absorbs at 264 nm ($\Delta\varepsilon$ +0.84) and the latter at 276 nm ($\Delta\varepsilon$ +2.20). The c.d. spectra of the optically pure thiirans (12a) and (16) are shown in the Figure; the signs of the $n\rightarrow\sigma^*$ transitions, which are in agreement with those predicted on the basis of the foregoing symmetry rule, provide forceful evidence for the assigned absolute stereochemistries.



C.d. spectra of methyl (*S*)-thiirancarboxylate (12a) (——) and methyl (*R*)-3,3-dimethylthiiran-2-carboxylate (16) (- - - -)

EXPERIMENTAL

Evaporations were carried out at *ca.* 40 °C using a rotary evaporator. Column chromatography was effected using B.D.H. alumina (Brockman activity III). T.l.c. was performed on silica gel either impregnated on glass fibre sheets (Gelman Instrument Company, ITLC type SA) or coated on plastic sheets (Scheicher and Schüll, F 1500 LS 254); the former sheets were developed with iodine vapour and the latter with an aqueous potassium permanganate spray. Distillations were performed by the ' Kugelrohr ' technique using a Buchi apparatus. A Bendix–Ericson automatic polarimeter was used to determine optical rotations, c.d. spectra were recorded on a Roussel–Jouan Dichrograph III, i.r. spectra were recorded on a Hilger and Watts Infrascan, and a Unicam SP 800 spectrometer was used to determine u.v. spectra. N.m.r. spectra were recorded using a Varian EM 360 spectrometer at 60 MHz with tetramethylsilane as the internal standard, and mass spectra were determined using an A.E.I. MS 9 spectrometer operating at 70 eV. Microanalyses were performed using a Hewlett–Packard 185 CHN analyser.

The amino-esters (9a—c) and (15a) were prepared as their hydrochlorides by heating (*R*)-cysteine hydrochloride or (*S*)-penicillamine in the appropriate alcohol saturated with hydrogen chloride, followed by evaporation. The hydrochloride was partitioned between dichloromethane and sodium hydrogencarbonate solution; evaporation of the organic layer afforded the pure amino-ester (n.m.r. spectroscopy) which was used immediately.

Reaction of Methyl (R)-*Cysteinate* (9a) *with Nitrous Acid.*—(*a*) Sodium nitrite (2.07 g, 30 mmol) was added in one portion to a solution of the cysteinate (9a) (1.35 g, 10 mmol) in 1M-hydrochloric acid (50 cm³) at 0 °C. The solution developed a deep red colouration which partly faded within a few minutes. After 5 min the mixture was extracted (3 ×) with chloroform and the dried ($MgSO_4$) organic layer was evaporated. Purification of the product by alumina chromatography [light petroleum (b.p. 40—60 °C) as eluant] afforded *methyl* (S)-*thiirancarboxylate* (12a) (0.555 g, 47%) as a chromatographically homogeneous liquid; $[\alpha]_D$ −25° (2.8% in $CHCl_3$); c.d. (EtOH) $\lambda_{max.}$ 281 nm (Δε +1.34); $\nu_{max.}$ (film) 1 735 cm^{-1} (ester CO); $\lambda_{max.}$ (EtOH) 211 (ε 700) and 279 nm (120); δ($CDCl_3$) 2.68 (1 H, dd, *J* 1.0 and 5.9 Hz, SC*H*HCH), 2.90 (1 H, dd, *J* 1.0 and 4.8 Hz, SCH*H*CH), 3.45 (1 H, dd, *J* 5.9 and 4.8 Hz, SC*H*CH_2), and 3.80 (3 H, s, CO_2Me); *m/e* 118 (M^+) and 86 ($C_3H_2OS^+$, base peak) (Found: M^+, 118.008 8. $C_4H_6O_2S$ requires *M*, 118.008 9).

(*b*) Experiment (*a*) was reported using deuteriochloric acid in place of hydrochloric acid. Work-up and purification of the product as before afforded the thiiran (12a) which contained no deuterium (mass and n.m.r. spectroscopy).

(*c*) Experiment (*a*) was repeated and the crude product was purified by bulb-tube distillation (oven temperature 60 °C, water-pump pressure) to give the thiiran (12a) (0.637 g, 54%); $[\alpha]_D$ −23° (1.2% in $CHCl_3$).

Reaction of Ethyl (R)-*Cysteinate* (9b) *with Nitrous Acid.*—The cysteinate (9b) (2.98 g, 20 mmol) was treated with sodium nitrite–hydrochloric acid as described for the derivative (9a). Purification of the crude product by bulb-tube distillation (oven temperature 50—60 °C, *ca.* 1 mmHg) gave *ethyl* (S)-*thiirancarboxylate* (12b) (1.10 g, 42%) as a chromatographically homogeneous liquid; $[\alpha]_D$ −32° (1.1% in $CHCl_3$); $\nu_{max.}$ (film) 1 735 cm^{-1} (ester CO); $\lambda_{max.}$ (EtOH) 215 (ε 530) and 280 nm (110); δ($CDCl_3$) 1.20 (3 H, t, *J* 7 Hz, *Me*CH_2), 2.62 (1 H, dd, *J* 1.0 and 6.0 Hz, SC*H*HCH), 2.83 (1 H, dd, *J* 1.0 and 4.9 Hz, SC*H*HCH), 3.35 (1 H, dd, *J* 6.0 and 4.9 Hz, SC*H*CH_2), and 4.18 (2 H, q, *J* 7 Hz, MeCH_2O); *m/e* 132 (M^+) and 86 ($C_3H_2OS^+$, base peak) (Found: M^+, 132.024 9. $C_5H_8O_2S$ requires *M*, 132.024 5).

Reaction of n-Propyl (R)-*Cysteinate* (9c) *with Nitrous Acid.*—The cysteinate (9c) (0.652 g, 4 mmol) was treated with sodium nitrite–hydrochloric acid as described for the derivative (9a). Purification of the crude product by bulb-tube distillation (oven temperature 50—60 °C, *ca.* 1 mmHg) gave *n-propyl* (S)-*thiirancarboxylate* (12c) (0.130 g, 22%) as a chromatographically homogeneous liquid; $[\alpha]_D$ −31° (1.5% in $CHCl_3$); $\nu_{max.}$ (film) 1 735 cm^{-1} (ester CO); $\lambda_{max.}$ (EtOH) 219 (ε 530) and 279 nm (140); δ($CDCl_3$) 0.95 (3 H, t, *J* 8 Hz, *Me*CH_2), 1.70 (2 H, sextet, *J* 8 Hz, MeC$H_2$$CH_2$), 2.62 (1 H, dd, *J* 1.0 and 6.0 Hz, SC*H*HCH), 2.83 (1 H, dd, *J* 1.0 and 5.0 Hz, SCH*H*CH), 3.38 (1 H, dd, *J* 6.0 and 5.0 Hz, SC*H*-CH_2), and 4.13 (2 H, t, *J* 8 Hz, CH_2CH_2O); *m/e* 146 (M^+) and 86 ($C_3H_2OS^+$, base peak) (Found: M^+, 146.040 1. $C_6H_{10}O_2S$ requires *M*, 146.040 1).

Reaction of (R)-*Cysteine* (9d) *with Nitrous Acid.*—(*a*) Sodium nitrite (2.07 g, 30 mmol) was added in one portion to a solution of the hydrochloride monohydrate of cysteine (9d) (1.76 g, 10 mmol) in 0.1M-hydrochloric acid (50 cm³) at 0 °C. The solution developed a deep red colouration which slowly faded. After 5 h at 0 °C the mixture was acidified to pH 1 with concentrated hydrochloric acid and extracted (3 ×) with chloroform. Evaporation of the dried ($MgSO_4$) organic layer left a syrup (0.258 g) which contained the thiiran (13b) as the major component. Treatment of the syrup with an excess of diazomethane in ether, and purification of the crude product by alumina chromatography [light petroleum (b.p. 40—60 °C) as eluant] afforded *methyl* (R)-*thiirancarboxylate* (13a) (0.088 g, 7%) as a chromatographically homogeneous liquid; $[\alpha]_D$ +9° (4.3% in $CHCl_3$); c.d. (EtOH) $\lambda_{max.}$ 281 nm (Δε −0.71). The sample was identical (n.m.r. and mass spectroscopy) with the derivative (12a).

(*b*) Experiment (*a*) was repeated using deuteriochloric acid in place of hydrochloric acid. The crude acid (13b) contained no deuterium (n.m.r. and mass spectroscopy).

(*c*) Sodium nitrite (2.07 g, 30 mmol) was added in one portion to a solution of the hydrochloride monohydrate of cysteine (9d) (1.76 g, 10 mmol) in water (25 cm^3) and glacial acetic acid (25 cm^3) at 0 °C. The solution developed a deep red colouration which gradually faded. After 1 h the pale red mixture was acidified to pH 1 with concentrated hydrochloric acid and extracted (3 ×) with chloroform. Evaporation of the dried ($MgSO_4$) organic layer with several additions of benzene (to azeotrope the acetic acid) afforded a syrup (0.338 g) which contained (n.m.r. spectroscopy) the thiiran (13b) as the major component. Purification of the crude acid (0.250 g) by bulb-tube distillation (oven temperature 50—60 °C, 0.01 mmHg) afforded (R)-*thiirancarboxylic acid* (13b) (0.062 g) as a chromatographically homogeneous waxy solid; $[\alpha]_D$ +28° (1.1% in Me_2CO); $\nu_{max.}$ (film) 1 720br cm^{-1} (acid CO); $\lambda_{max.}$ (EtOH) 212 (ε 460) and 281 nm (80); δ($CDCl_3$) 2.70 (1 H, dd, *J* 1.0 and 6.0 Hz, SC*H*HCH), 2.87 (1 H, dd, *J* 1.0 and 5.0 Hz, SCH*H*CH), and 3.37 (1 H, dd, *J* 6.0 and 5.0 Hz, SC*H*CH_2); *m/e* 104 (M^+, base peak) and 86 ($C_3H_2OS^+$, base peak) (Found: C, 34.62; H, 3.85%; M^+, 103.993 2. $C_3H_{14}O_2S$ requires C, 34.21; H, 3.53%; *M*, 103.993 2).

Treatment of the purified acid (13b) (0.124 g) with an excess of diazomethane in ether and bulb-tube distillation of the product afforded the ester (13a) (0.056 g, 38%); $[\alpha]_D$ +15° (1.6% in $CHCl_3$).

Reaction of Methyl (S)-*Thiirancarboxylate* (12a) *with Sodium Hydroxide*.—The ester (12a) (0.30 g, 2.5 mmol) was treated, dropwise during 2 h with vigorous stirring at 10 °C, with 1M-sodium hydroxide (2.3 cm^3, 2.3 mmol). After a further 0.5 h the mixture was washed with chloroform, acidified to pH 1 with concentrated hydrochloric acid, and extracted (3 ×) with chloroform. Evaporation of the dried ($MgSO_4$) chloroform extracts afforded (S)-*thiirancarboxylic acid* (12d) (0.190 g, 72%) as an essentially pure waxy solid; $[\alpha]_D$ −57° (2.7% in $CHCl_3$). The sample was identical (n.m.r. and mass spectroscopy) with the derivative (13b).

Treatment of the acid (12d) with an excess of diazomethane in ether followed by bulb-tube distillation of the product afforded the pure ester (12a) (n.m.r. spectroscopy); $[\alpha]_D$ −21° (1.0% in $CHCl_3$).

Reaction of (S)-*Penicillamine Methyl Ester* (15a) *with Nitrous Acid*.—(*a*) Sodium nitrite (0.414 g, 6 mmol) was added in one portion to a solution of the ester (15a) (0.326 g, 2 mmol) in 1M-hydrochloric acid (10 cm^3) at 0 °C. The solution developed a deep green colouration which faded within a few minutes. After 5 min the mixture was extracted with chloroform (3 ×). Evaporation of the dried ($MgSO_4$) organic layer and purification of the product by alumina chromatography [light petroleum (b.p. 40—60 °C) as eluant] afforded *methyl* (R)-3,3-*dimethylthiiran*-2-*carboxylate* (16) (0.040 g, 14%) as a chromatographically homogeneous liquid; $[\alpha]_D$ +92° (1.5% in $CHCl_3$); c.d. (EtOH) $\lambda_{max.}$ 285 (Δε −0.39); $\nu_{max.}$ (film) 1 745 and 1 725 cm^{-1} (ester CO); $\lambda_{max.}$ (EtOH) 212 (ε 850) and 259 (inflexion) nm (170); δ($CDCl_3$) 1.70 and 1.72 (each 3 H, s, CMe_2), 3.30 (1 H, s, SC*H*CMe_2), and 3.80 (3 H, s, CO_2Me); *m/e* 146 (M^+) and 87 ($C_4H_7S^+$, base peak) (Found: M^+, 146.040 9. $C_6H_{10}O_2S$ requires *M*, 146.040 1).

(*b*) The ester (15a) (0.326 g, 2 mmol) was treated with sodium nitrite–hydrochloric acid as described in the above experiment. Purification of the product by bulb-tube distillation (oven temperature 60—70 °C, water-pump pressure) afforded the pure thiiran (16) (0.128 g, 44%) as a liquid.

Reaction of (S)-*Penicillamine* (15b) *with Nitrous Acid*.—Sodium nitrite (2.07 g, 30 mmol) was added in one portion to a stirred solution of (*S*)-penicillamine (15b) (1.49 g, 10 mmol) in 0.2M-hydrochloric acid (50 cm^3) at 0 °C. The solution developed a deep green colouration which quickly faded. After 0.5 h at 0 °C the mixture was acidified (pH 4—5) with concentrated hydrochloric acid and extracted (3 ×) with chloroform. Evaporation of the dried ($MgSO_4$) organic layer left (S)-3,3-*dimethylthiiran*-2-*carboxylic acid* (17b) (0.61 g, 44%) as a chromatographically homogeneous syrup; $[\alpha]_D$ −74° (1.5% in $CHCl_3$); $\nu_{max.}$ (film) 3 200br (OH) and 1 715 cm^{-1} (acid CO); δ($CDCl_3$) 1.72 and 1.76 (each 3 H, s, CMe_2), 3.37 (1 H, s, SC*H*CMe_2), and 9.6 (1 H, br s, CO_2H, disappeared on addition of D_2O); *m/e* 132 (M^+) and 100 ($C_5H_8O_2^+$, base peak) (Found: M^+, 132.024 4. $C_5H_8O_2S$ requires *M*, 132.024 5).

Partial decomposition of the acid (17b) occurred when it was subjected to bulb-tube distillation (oven temperature 80 °C, 0.05 mmHg); the distillate was a 4 : 1 mixture of the thiiran (17b) and 2,2-dimethylacrylic acid (n.m.r. spectroscopy).

Treatment of the acid (17b) (0.40 g) with an excess of diazomethane in ether and purification of the product by bulb-tube distillation afforded *methyl* (S)-3,3-*dimethylthiiran*-2-*carboxylate* (17a) (0.25 g, 57%) as a chromatographically homogeneous liquid; $[\alpha]_D$ −69° (1.4% in $CHCl_3$); c.d. (EtOH) $\lambda_{max.}$ 285 nm (Δε +0.34). The sample was identical (n.m.r. spectroscopy) with the derivative (16).

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