Synthetic Approaches to the Thiathromboxanes. Part 1. Preparation of Functionalised Dihydrothiopyrans

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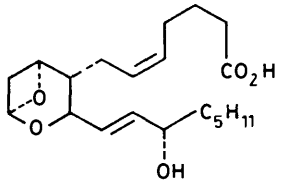
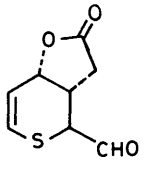
A hetero-Diels–Alder reaction between diethyl thioxomalonate and derivatives of hexa-3,5-dienoic acid yields 5,6,6-trisubstituted 5,6-dihydro-2*H*-thiopyrans. The hydrolysis and decarboxylation of these compounds has been investigated. The iodo-lactonisation of these compounds has given a variety of products. Efficient routes have been developed to 4-formyl-3a,7a-dihydro-4*H*-thiopyrano[4,3-*b*]furan-2(3*H*)-one dimethyl acetal and the related malonic ester.

The prostacyclins and complementary thromboxanes (**1**) have generated much interest both as models for the preparation of drugs and because of their important biological properties. Carba- and thia-analogues of thromboxane A_2 have attracted attention[1] because of their greater stability to hydrolysis compared with the bicyclo[3.1.1] system of thromboxane. We set out to develop a route to the thia- and dithia-thromboxane A_2 analogues. The broad strategy of the approach is similar to that Corey developed for the prostaglandins[2] and required a functionalised intermediate to which the two side chains could be attached and which allowed the four-membered ring to be introduced at a late stage. A compound which might fulfill these requirements was the lactone (**2**) which became the initial target.

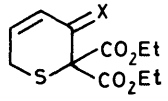
At the inception of this work it was known that oxomalonate could act as a dienophile in Diels–Alder reactions.[3] In addition



(**1**)



(**2**)

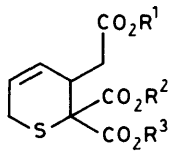


(**3**) X = H,OAc
(**4**) X = H,OH
(**5**) X = O

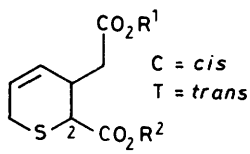
the original demonstration by Middleton[4] that hexafluorothioacetone is a reactive dienophile was followed by the use of thiobenzophenone,[5] methyl cyanodithioformate,[6] dithioesters,[7] and α-acyl dithioesters[8] in such a role. Vyas and Hay[6] showed that the regiochemistry of thioxo addition to unsymmetrical dienes was the reverse of that with the oxo group. In the light of these results we investigated the generation of thioxomalonate *in situ* from oxomalonate and P_4S_{10} and its trapping by dienes.† In the first experiment 1-acetoxybutadiene reacted to give the adduct (**3**) which could be hydrolysed to the alcohol (**4**) and then oxidized to the ketone (**5**). Spectroscopic data were in accord with these structures but to put the matter beyond doubt the structure of the acetate was determined by *X*-ray crystallography. The dihydrothiopyran ring of (**3**) adopts a half-chair conformation with the acetoxy group pseudo-axial; presumably the 1,3-interaction of this group with the sulphur lone pair is energetically less than that with the syn-clinal ethoxycarbonyl ethyl group (Figure 1).

No directly comparable structure seems to have been reported so Table 1 lists selected geometric features for the dihydrothiopyran ring. Recently the structure of a dihydrothiopyranoxide has appeared;[9] in comparison the ring in the oxide, which also adopts the half-chair conformation, is less planar and the bond corresponding to S–C(1) seems to be lengthened.

With the regiochemistry of addition firmly established the reaction was carried out with a number of relevant dienes. Ethyl and methyl hexa-3,5-dienoates were treated with P_4S_{10} and diethyl oxomalonate in boiling THF to give the adducts (**6**) and (**7**) in 60—70% yield. The ethyl ester (**6**) showed $\lambda_{max.}$ 219 nm (ε 1 800) and δ_H 5.83 (1 H, ddt, *J* 10.5, 4.5, and 2 Hz), 5.72 (1 H, dm, *J* 10.5 Hz), 3.41 (1 H, m), 3.13 (1 H, dq, *J* 18 and 2 Hz), 2.95 (1 H, ddt, *J* 18, 4.5, and 1 Hz), 2.49 (1 H, dd, *J* 16 and 8.5 Hz), and 2.38 (1 H, dd, *J* 16 and 5.5 Hz) in addition to the ester signals. Hexa-3,5-dienoic acid gave an unsatisfactory yield (24%) of the

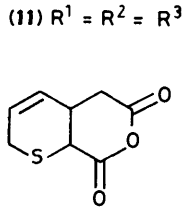


(**6**) $R^1 = R^2 = R^3 = Et$
(**6A**) (*S*-oxide)
(**7**) $R^1 = Me$, $R^2 = R^3 = Et$
(**8**) $R^1 = H$, $R^2 = R^3 = Et$
(**9**) $R^1 = CH_2CCl_3$, $R^2 = R^3 = Et$
(**10**) $R^1 = R^2 = H$, $R^3 = Et$
(**11**) $R^1 = R^2 = R^3 = H$

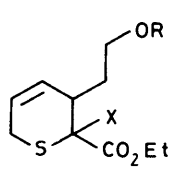


C = *cis*
T = *trans*

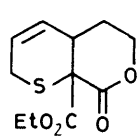
(**12**) $R^1 = Et$, $R^2 = Bu$
(**13**) $R^1 = R^2 = H$
(**14**) $R^1 = H$, $R^2 = Et$
(**15**) $R^1 = R^2 = Et$
(**15A**) (*S*-oxide)



(**16**)



(**17**) R = Ac, X = CO_2Et
(**18**) R = H, X = CO_2Et
(**19**) R = X = H



(**20**)

† Thioxomalonate has also been generated by the reaction of dibromomalonate with KS(CS)OEt (J. L. Herrman, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 1973, 2433).

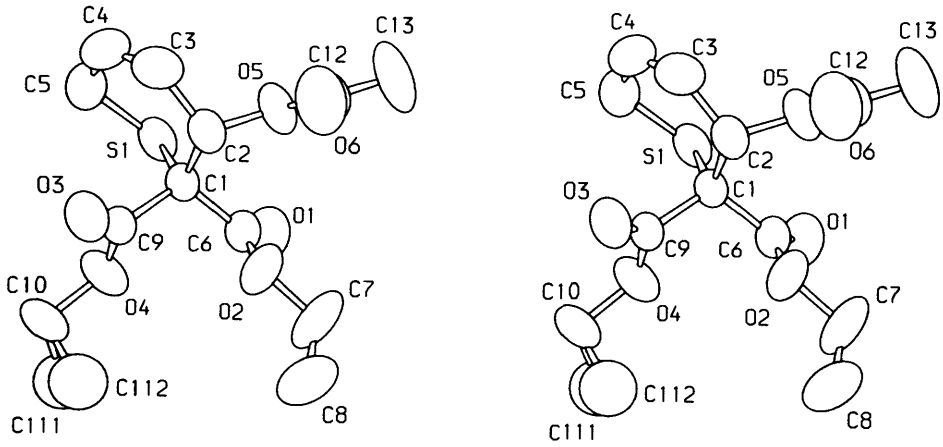


Figure 1. Compound (3)

Table 1.

Atoms				Bond lengths			Bond angles		Torsion angles
A	B	C	D	A–B	B–C	C–D	ABC	BCD	ABCD
S	C(1)	C(2)	C(3)	1.810(3)	1.519(5)	1.486(6)	111.8(2)	114.8(3)	47
C(1)	C(2)	C(3)	C(4)			1.309(7)		125.4(4)	−13
C(2)	C(3)	C(4)	C(5)			1.478(8)		126.9(4)	1
C(3)	C(4)	C(5)	S			1.802(5)		113.1(3)	−23
C(4)	C(5)	S	C(1)					96.7(2)	47
C(5)	S	C(1)	C(2)						−60
C(5)	S	C(1)	C(6)			1.531(5)		106.7(2)	180
C(5)	S	C(1)	C(9)			1.536(4)		110.3(2)	63
S	C(1)	C(2)	C(5)			1.459(4)		105.1(3)	−74

The atoms C(1), C(6), O(1), O(2), C(7) are co-planar within 0.001 Å, C(1), C(9), O(3), O(4), C(10) within 0.009 Å, and C(2), O(5), O(6), C(12), C(13) within 0.015 Å

adduct (**8**) and since we were unable to hydrolyse selectively the triesters (**6**) or (**7**) to this acid in good yield other routes were developed. The acetate of hexa-3,5-dien-1-ol gave the adduct (**17**) in good yield. In an attempt to remove the acetoxy group with NaOEt–EtOH the monoesters (**19**) were obtained as a *cis*/*trans* mixture. Since the triester (**6**) is inert to these conditions the intermediacy of the lactone (**20**) is likely, followed by cleavage to the mixed carbonate and thence to (**18**) and diethyl carbonate. Acid-catalysed transesterification gave the alcohol (**18**) which was oxidized to the acid (**8**). The alcohol (**18**) could be converted into the corresponding aldehyde by Swern oxidation.[10] The most satisfactory route to the monoacid (**8**) utilised 2,2,2-trichloroethyl hexa-3,5-dienoate which gave the adduct (**9**) in good yield; reduction with Zn–AcOH then generated the acid (**8**).

When oxomalonate was replaced by butyl glyoxalate* addition to ethyl hexa-3,5-dienoate occurred in poor yield to give a 4:1 mixture of *trans*- and *cis*-isomers (**12**). In the major isomer 2-H resonated at δ 3.46 (*J* 3.8 Hz) and in the minor at 3.82 (*J* 4.5 Hz). On alkaline hydrolysis a 4:1 mixture of the dicarboxylic acids (**13**) was obtained with 2-H in the major isomer at δ 3.54 (*J* 3.5 Hz) and in the minor at δ 3.88 (*J* 4.5 Hz). On treatment with Ac_2O the acids were converted into the anhydrides (**16**) which, on hydrolysis, gave the original mixture of acids. The major anhydride isomer showed 2-H as a doublet at δ 4.08 (*J* 11 Hz) suggesting a *trans*-ring junction. On this basis, both acids and esters with 2-H at δ *ca.* 3.8 were assigned *cis* stereochemistry. In conjunction with the *E*-stereochemistry† of ethyl hexa-3,5-dienoate these results suggest that the *exo* transition state is favoured for these hetero Diels–Alder reactions.

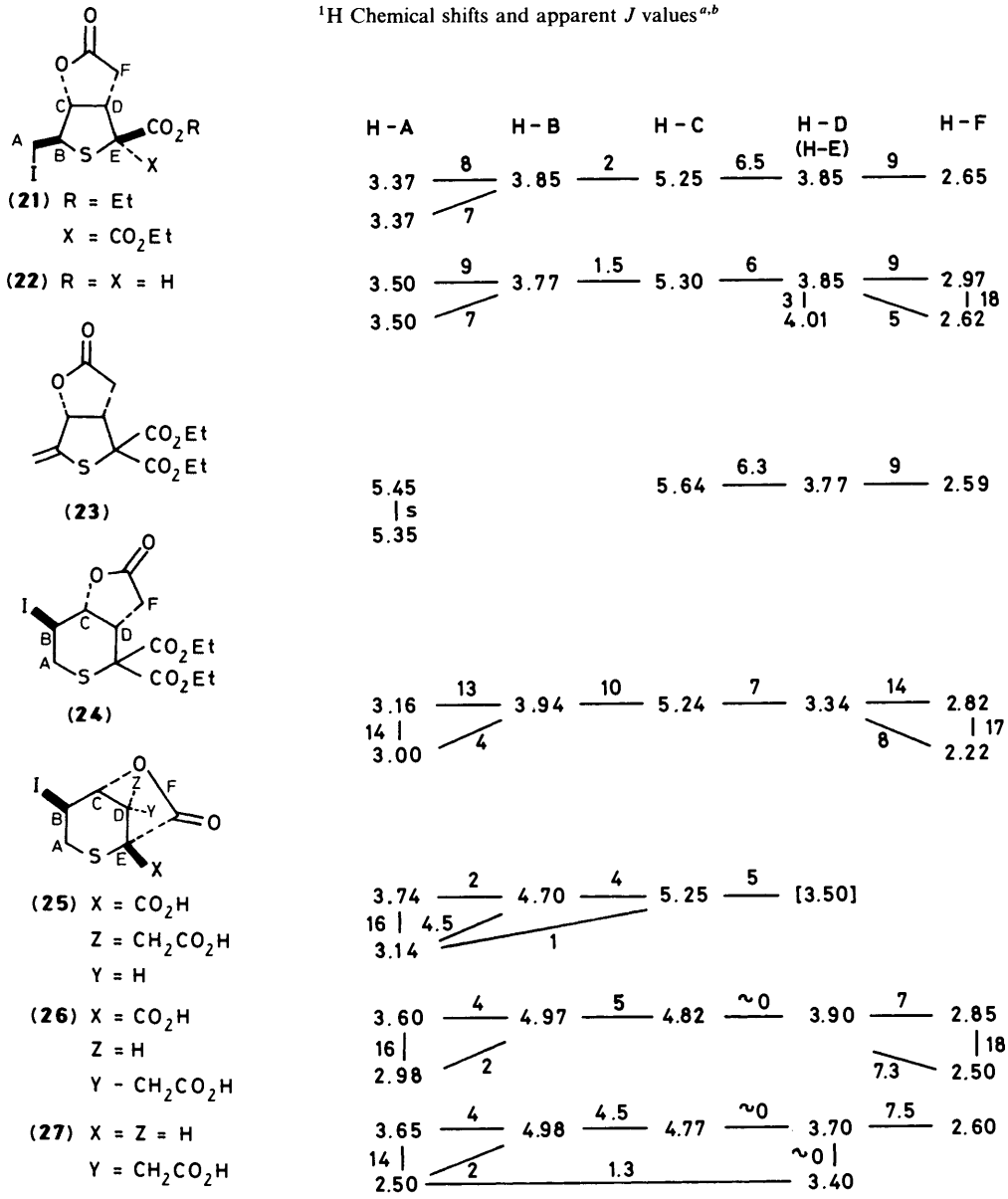
Hydrolysis of the triesters (**6**) and (**7**) with an excess of base gave the tricarboxylic acid (**11**) which on decarboxylation gave a 3:1 mixture of *trans* and *cis*-acids (**13**). Hydrolysis of the triesters (**6**) and (**7**) with 2 equivalents of base gave the dicarboxylic acid (**10**) in good yield. Decarboxylation of (**10**) yielded a 4:1 mixture of the *trans*- and *cis*-half esters (**14**). The stereochemical assignments were confirmed by n.O.e. difference spectroscopy. A 2D-COSY spectrum established that the δ 3.51 signal was coupled to one of two hydrogens at δ 2.97 and gave a 20% n.O.e., while the δ 3.83 signal coupled to one at δ 3.10, gave an 8% enhancement.

Our initial efforts to prepare the unsaturated γ-lactone (**33**) concentrated on the preparation of the iodo lactone (**24**). Reaction of the triester (**6**) with I_2–MeCN[11] gave a mixture of products from which the tetrahydrothiophene (**21**) was isolated in *ca.* 25% yield. Its ^{1}H n.m.r. spectrum was in accord with this structure, which was confirmed by reaction with diazabicyclo[5.4.0]undec-5-ene (DBU) in PhMe to give the unsaturated lactone (**23**) and with K_2CO_3–MeOH giving the hydroxy acid

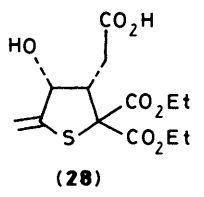
* Since then a number of methods for the generation of thioaldehydes have been developed but we have not applied them. (See G. W. Kirby and A. W. Lochhead, *J. Chem. Soc., Chem. Commun.*, 1983, 423; J. E. Baldwin and R. C. G. Lopez, *Tetrahedron*, 1983, **39**, 1487).

† This was established by ^{1}H n.m.r. and contrasts with α,β-unsaturated esters and acids where the *Z*-isomer predominates (K. Beelitz, G. Hohne, and K. Praefcke, *Z. Naturforsch.*, 1978, **33**, 417). This may be due to the very low concentration of *cisoid*-diene likely to be present.

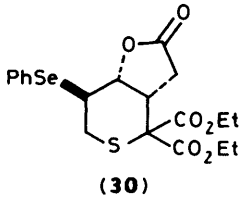
^{1}H Chemical shifts and apparent J values[a,b]



[a] Resonances for alkyl groups of esters are not indicated. [b] Assignments were made using extensive decoupling experiments



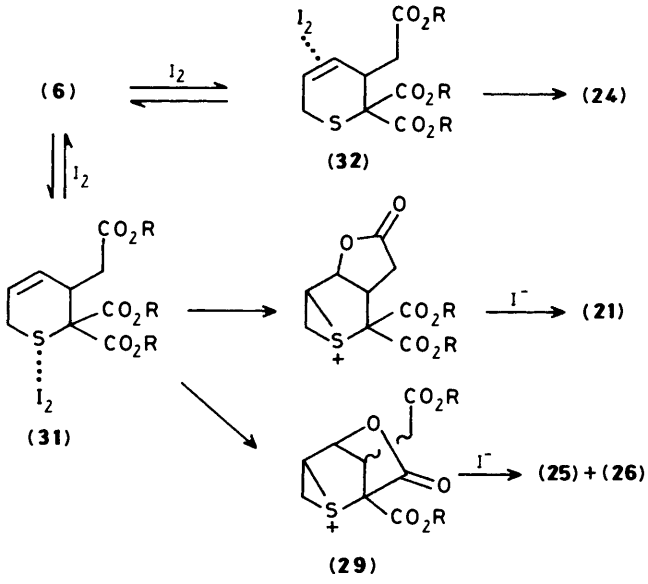
(28)



(30)

(28). On warming under vacuum the acid (28) was converted into the lactone (23). Reaction of the monoacid (8) with KI_3–$NaHCO_3$–H_2O[12] also gave the lactone (21) in an improved 67% yield. These iodolactonisations were slow, requiring many hours before starting material had all reacted. When the monoacid (8) in a stirred mixture of Triton B-MeOH–H_2O–CH_2Cl_2 was treated with I_2 a rapid (*ca.* 15 min) conversion into the iodothiopyran (24) occurred in high yield. The ^{1}H n.m.r. spectrum of (24) is in accord with the structure. When the thiopyran (24) was exposed to the reaction conditions for the conversion of (6) into the tetrahydrothiophene (21) it was unchanged, suggesting that the lactone (24) is not an intermediate in the formation of (21). The dramatic difference in the rates and products of these two iodolactonisations must be intimately connected with solvent effects. If, as seems likely, reaction in the two-phase system occurs in the CH_2Cl_2 phase, then the carboxylate ion would be more nucleophilic than the hydrated ion in the aqueous phase and could effect the reaction as shown in the Scheme. Two types of charge-transfer complexes between I_2 and the thiopyrans are likely involving the alkene and sulphur centres,[13] the latter being present at higher concentration.* The nucleophilic carboxylate ion could react in (32) to give the lactone (24) in a concerted process; reaction of the carboxylate in (31) would give the

* The acyl hypoiodite is a possible intermediate but it is sterically unlikely that it could form the required (*trans*-) iodonium ion in an intramolecular reaction.



Scheme.

episulphonium ion (**29**) in a process of higher energy in CH_2Cl solution.

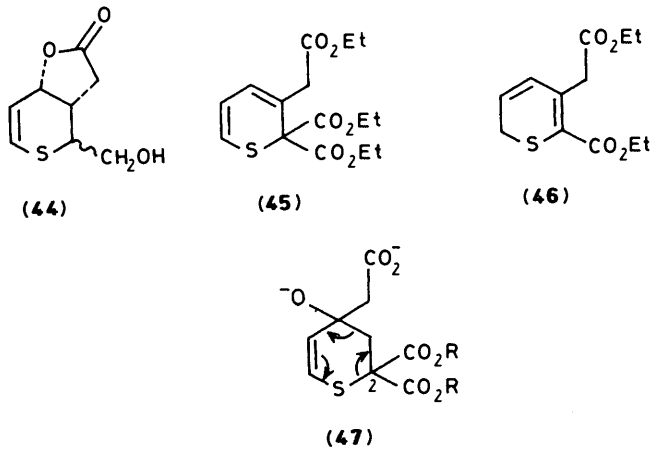
In aqueous solution the energetics of the competing processes are reversed and reaction occurs *via* the sulphur or perhaps the related sulphonium iodide complex. In acetonitrile, where the participating group is the weakly nucleophilic carboxy or carboxyethyl, again (**31**) is the dominant intermediate.

We next investigated the dehydroiodination of the iodide (**24**) with disappointing results. Use of DBN in nonpolar solvents failed to give any reaction while DBN in CCl_4–Me_2SO and $LiCO_3$–LiCl–HCO·NMe_2 gave the ring-contracted chloro compound (**21**; I = Cl). Li_2CO_3–HCO·NMe_2 gave the known unsaturated lactone (**23**). Stronger bases led to destruction of the molecule; with $LiNPr^i_2$, a high yield of diethyl malonate was obtained. These results brought us to the view that the molecule could not readily attain the conformation with the axial I necessary for E_2 reaction and that in polar solvents ionisation in the equatorial I conformation formed episulphonium ion and thence ring-contracted products. They also suggested that a *syn*-elimination could form the alkene. To this end, the monoacid (**8**) was treated[14] with PhSeCl to give the lactone (**30**) which, on oxidation with H_2O_2, gave the unsaturated lactone (**33**) in 29% overall yield. No efforts were made to improve this process since a more satisfactory procedure was discovered concurrently.

We also briefly investigated the iodolactonisation of the tri- and di-carboxylic acids (**11**) and (**13**). Reaction of (**11**) with KI_3–H_2O in the presence of 1 mol equiv. of $NaHCO_3$ gave a mixture from which the two iodolactones (**25**) and (**26**) were isolated in 21 and 16% yields respectively. The structures were assigned on the basis of their ^1H n.m.r. spectra. It is apparent from the pattern of coupling constants in both isomers that the iodine and oxygen substituents are both axial in contrast to their diequatorial disposition in the lactone (**24**). This suggests that both (**25**) and (**26**) are bridged lactones differing only in the stereochemistry of the acetic acid side-chain. From molecular models of bicyclo[3.2.1]ring systems it is apparent that the two-atom bridge distorts the six-membered ring such that the torsion angles to the bridging methylene hydrogens are eq.-eq. *ca.* 35° and eq.-ax. *ca.* 85°. On this basis the isomer with J(3-H, 2-H) ~ 0 Hz is assigned structure (**26**) and that with J 5.3 Hz structure (**25**). The formation of bridged lactones probably follows from the predominant species present in solution being the mono-anions of the malonic acid group of (**11**). Iodolactonisation of the *cis-trans*-mixture (1:3) of the dicarboxylic acid (**13**) gave a mixture from which the bridged lactone (**27**) was isolated in 15% yield, together with 8% of the ring-contracted compound (**22**). Structural assignments were based on the similarity of their ^1H n.m.r. spectra to compounds (**26**) and (**21**). It is obvious that lactone (**27**) must arise from the minor *cis*-isomer of (**13**). The stereochemistry of the carboxy group in (**22**) cannot be assigned unambiguously but its n.m.r. spectrum is consistent with its formation from the *trans*-isomer (**13**). Iodolactonisation of the ester (**15**) gave only ring contracted products.

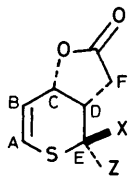
The poor yields which we obtained under conventional iodolactonisation conditions can make mechanistic speculation questionable. However, it is notable that only ring-contracted products were isolated when lactonisation of the acetic acid was involved while no ring-contracted bridged lactones were found. Our working hypothesis, shown in the Scheme, offers a possible explanation, suggesting that complex (**31**) is converted into the bridged episulphonium ion (**29**) which reacts with iodide at the secondary carbon forming a bicyclo[3.2.1.] system rather than the more strained bicyclo[2.2.1] arrangement.

We next investigated the reactions of the thiopyran sulphoxides (**6A**) and (**15A**) with $(CF_3CO)_2O$. The oxides were readily prepared by *m*-chloroperbenzoic acid oxidation of the esters (**6**) and (**15**). Pummerer[15] reaction of the triethyl ester (**6A**) gave a crude product containing trifluoroacetates and the γ-lactone (**33**) in 41% yield accompanied by the diene (**45**)



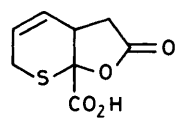
(11%). The ^1H n.m.r. spectrum of (**45**) established the presence of three vinyl protons, three ethoxy groups, and a methylene group and conjugation was indicated by $\lambda_{max.}$ 245 and 321 nm. When the reaction time was extended to 20 h the diene (**45**) became the major product isolated. Reaction of the sulphoxide (**15A**) under similar conditions gave the diene (**46**) which, apart from the ethoxy absorption, showed in its ^1H n.m.r. spectrum two vinyl protons and two methylene groups.

In an attempt to improve the yield of γ-lactone (**33**) the reaction of the triester (**6**) with *N*-chlorosuccinimide[16] was investigated; the γ-lactone (**33**) was indeed formed, but was accompanied by the diene (**45**) and other unidentified products. However the reaction of the acid (**8**) with *N*-chlorosuccinimide gave the lactone (**33**) in 75% yield. The conversion of the lactone (**33**) into the aldehyde (**2**) was attended by unexpected difficulties. The lactone (**33**) was inert to a variety of acid-catalysed and S_N2 conditions for ester cleavage whilst, in contrast, it was completely destroyed under a variety of basic conditions. Eventually it was found that LiOH–H_2O–tetrahydrofuran followed by acidification and heating gave a *cis*-



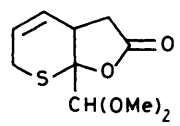
(33) X = Z = CO_2Et

	H-A		H-B		H-C		H-D (H-E)		H-F
(33) X = Z = CO_2Et	6.18	10	5.82	—	5.50	7.5	3.59	12	2.82
								8	17 / 2.40
(34) X = H, Z = CO_2H	6.56	10	5.96	4	5.19	6	3.22	7.7	2.76
							7 / 3.84		
(35) X = CO_2H, Z = H	6.48	10	5.79	2	5.31	8	3.58	12	2.84
							3 / 3.63	9	17 / 2.43
(36) X = $CH(OMe)_2$ Z = H	6.27	10.5	5.80	3	5.00	6	3.1	10	2.52
							0 / 3.1	7.5	17 / 2.93
							5.5 / 4.47		
(2) X = CHO, Z = H	6.43	10.5	5.95	3.5	5.33	8	3.49	11	2.71
							3.5 / 4.23	8.5	17.5 / 2.92
							~0 / 9.71		



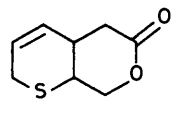
(38)

	3.26	5.2	6.22	10.5	5.91	~1.5	3.54	8.8	3.17
	17 / 3.39	~2		1.5				4	17 / 2.35



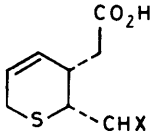
(39)

				~1					
	3.04	4	6.03	10.5	5.71	5	3.35	?	3.04
	17 / 3.28	~6			2.5			4	17 / 2.28



(40)

	3.22	~4	5.95	11	5.71	3.5	7.16	6.5	2.75
	17.5 / 3.07	~4			4.53	5	7 / 3.30	8	17.5 / 2.62
					12	4.30	6.9		



(42) X = O

	3.01	2	5.87	1.2	5.77	?	3.07	10	2.77
	19.5 / 2.77	5			9.62	~0	0 / 3.47	5	17.5 / 2.64

(43) X = $(OMe)_2$

	3.28	2	5.76	12	5.90	?	2.91	8	2.78
	18 / 2.85	5			4.47	7.5	0 / 2.87	6	16.5 / 2.63

and *trans*-mixture of the acids (**34**) and (**35**) in a reproducible yield (50%). The instability of the lactone (**33**) to basic conditions contrasts with the normal behaviour of its dihydro derivative.* This, coupled with some evidence that opening of the lactone ring leads to degradation, and some results reported in Part 2, prompts us to the view that the alkoxide (**47**) is unstable when there are *two* electron-withdrawing groups at C-2; an anion accelerated retro-Diels–Alder reaction is a possibility. The 7:5 mixture of acids (**34**) and (**35**) could be separated by t.l.c. The ^1H n.m.r. spectra confirmed the gross structures but did not allow an unambiguous assignment of stereochemistry. An *X*-ray crystallographic structure deter-

* The dihydrolactone was prepared by Bu_3SnH reduction of the iodolactone.

Table 2.

				Bond lengths			Bond angles		
A	B	C	D	A–B	B–C	C–D	ABC	BCD	τ
S–	C(1)–	C(2)–	C(3)	1.736(2)	1.311(3)	1.472(3)	127.0(2)	126.1(2)	−1
C(1)–	C(2)–	C(3)–	C(6)			1.523( )		115.7(2)	−10
C(2)–	C(3)–	C(6)–	C(7)			1.510( )		115.8(2)	+41
C(3)–	C(6)–	C(7)–	S			1.814( )		113.1(2)	−56
C(6)–	C(7)–	S–	C(1)					100.7(1)	+39
C(7)–	S–	C(1)–	C(2)						−13
C(3)–	O(1)–	C(4)–	C(5)	1.472(2)	1.324(2)	1.485(3)	110.0(2)	110.8(2)	+1
O(1)–	C(4)–	C(5)–	C(6)			1.512(3)		102.5(2)	+20
C(4)–	C(5)–	C(6)–	C(3)			1.523(3)		101.7(2)	−32
C(5)–	C(6)–	C(3)–	O(1)					102.8(2)	+33
C(6)–	C(3)–	O(1)–	C(4)						−22
C(8)–	C(7)–	C(6)–	C(5)	1.502(3)			113.7(2)	114.5(2)	−176
S–	C(7)–	C(6)–	C(5)						+62
C(2)–	C(3)–	C(6)–	C(5)						−84
C(7)–	C(6)–	C(3)–	O(1)						+158
C(1)–	C(2)–	C(3)–	O(1)					108.0(2)	−125
C(3)–	O(1)–	C(4)–	O(4)			1.209(3)		120.6(2)	−179
C(6)–	C(5)–	C(4)–	O(4)					128.6(2)	−159
S–	C(7)–	C(8)–	O(81)			1.323(3)	107.3(1)	111.0(2)	−85
S–	C(7)–	C(8)–	O(82)			1.194(3)		125.0(2)	+94

In the table, each distance and angle is recorded once only.

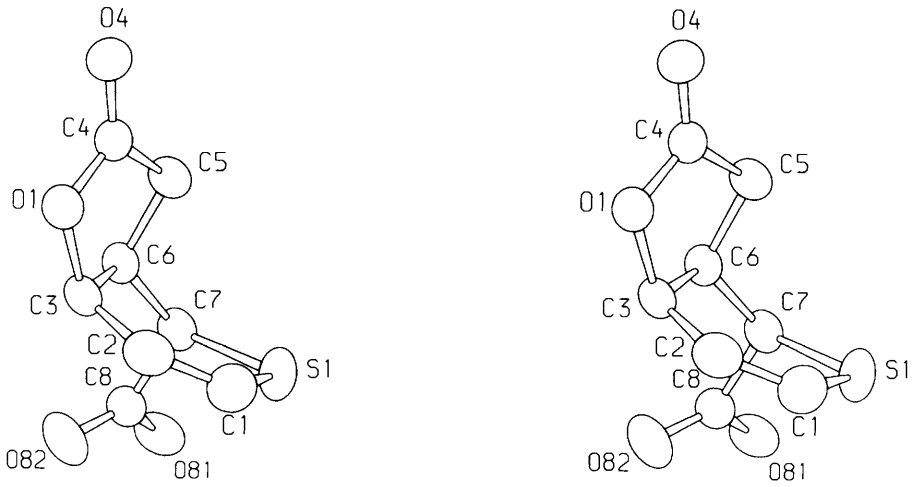


Figure 2. Compound (**35**)

mination showed that the minor isomer had a *trans*-relationship of the carboxy and acetic side chains. A search of the *X*-ray Crystallographic Data Base revealed that no structure with this ring nucleus had been reported previously, so we list in Table 2 selected bond lengths, bond angles, and torsion angles. The six-membered ring adopts (Figure 2) a flattened half-chair conformation with the carboxy group and acetic side chains antiperiplanar (176°). The lactone ring is in an envelope conformation with C-6 as the flap. The positions of the hydrogen atoms were determined allowing a constant to be derived for the Karplus equation. The expression, $J = 11 \cos^2\theta$, was found to be of general application in this series of compounds and suggests that the acid has the same conformation in solution as in the solid state.

A variety of methods were examined for the conversion of the carboxy group to aldehyde with no success. To our surprise the acids (**34**) and (**35**) were not reduced by B_2H_6 under standard conditions but reduction of the acid chlorides with $LiBH_4$ gave the mixture of alcohols (**44**). However, we were unable to oxidize the alcohols to the aldehydes in useful yields, using a number of methods. Reaction of the alcohol mixture with $(COCl)_2$–Me_2SO [10] gave a miniscule yield of aldehyde and a low yield of the α-MeS aldehyde.

Reaction of the dicarboxylic acids (**13C**) and (**13T**) with *N*-chlorosuccinimide gave the lactone (**38**) while the anhydride (**16**) was converted into the diene (**46**) by the same reagent after hydrolysis. These results are in accord with the mechanistic proposal that acidic protons are eliminated from sulphonium intermediates [17] and made it clear that lactonisation in the desired direction would be possible only if C-2 was disubstituted or if the acidity of the 2-H was reduced. To this end the anhydride (**16**) was reduced with $LiBH_4$ to the lactone (**40**). The anhydride was prepared from a 2:1 mixture of the acids (**13C**) and (**13T**) which, together with *J* 7 Hz for the ring junction protons, indicates that the lactone is the *cis*-isomer. When the difficulties of oxidising the alcohols (**44**) became apparent, this approach was abandoned and we investigated preparation of the acetal (**36**). Reduction of the half ester (**14**) with 2.2 mol of

Bu^i_2AlH at −78 °C gave the aldehyde (**42**) (94%) which was converted into the dimethyl acetal (**43**) (96%) by reaction with $SmCl_3 \cdot 8H_2O$–MeOH–$HC(OMe)_3$;[18] extended reaction times or use of other catalysts led to esterification of the carboxy group. All our evidence (t.l.c., capillary g.l.c., ^1H n.m.r. spectra) supports the view that compounds (**42**) and (**43**) and, indeed, subsequent compounds, are single isomers despite (**42**) having been prepared from a *cis*, *trans* mixture of esters (**14**). Oxidation of the aldehyde (**2**) to the *cis*-acid (**35**) establishes the *cis*-stereochemistry in this series. It is possible that, due to acidity of 2-H, the Al co-ordinated aldehyde forms an enol aluminate which is stereoselectively protonated on the least hindered face of the complex on work-up.

The reaction of the acetal (**43**) with *N*-chlorosuccinimide–CH_2Cl_2 gave the lactone (**36**). Its structure followed from its ^1H n.m.r. spectrum and chemical correlation with the *cis*-acid (**35**). However, the best yield obtained was *ca.* 40% and the reaction proved capricious especially on scaling up. T.l.c. of the reaction mixture indicated that the lactone (**36**) was the only mobile product present and, indeed, isolated. Since HCl is a by-product, the reaction in the presence of 8% (v/v) 1,2-epoxypropane was examined. The lactone (**36**) was obtained in 44% yield but a new lactone was also isolated in 30% yield. This compound was assigned structure (**39**) on the basis of its ^1H n.m.r. spectrum. In order to try and get a better understanding of this reaction and to develop a reliable method for the preparation of the lactone (**36**), the reaction was studied using capillary g.l.c. with an internal standard. The results are summarised in Table 3 and allow the following conclusions to be drawn. (*a*) Starting material has reacted in *ca.* 5 min.; (*b*) in the absence of epoxypropane the lactone (**36**) was partially destroyed, but the yield of the lactone (**39**) was small and did not increase with time; (*c*) when epoxypropane was present *before* addition of the chlorinating agent the initial yield of the lactone (**36**) was reduced almost by one half, but was not degraded and the initial yield of the lactone (**39**) increased slowly with time. The addition of the epoxypropane 2 min after the *N*-chlorosuccinimide allowed a compromise and gave reproducible (*ca.* 75%) yields of the lactone (**36**) when the concentration of starting material is 5 g l^{-1}. We do not have a complete explanation for these observations but it is possible that either different sulphonium intermediates and/or different bases for the decomposition of these intermediates are involved in the absence and presence of epoxypropane. In the first case, chloride ion could react with the *N*-chlorosuccinimide to give Cl_2, which is the chlorinating agent for the bulk of the material by a chain reaction. In the second, Cl^- would act as base, giving thioxonium ion intermediates. When the concentration of Cl^- is reduced then a different sulphonium ion (*S*-succinimido or *S*-chloro?) base pair is formed and reacts more slowly and with different selectivity. Attempts to test these ideas gave inconclusive results.

Hydrolysis of the acetal (**36**) to the aldehyde (**2**) gave poor yields in aqueous systems but reaction with anhydrous formic acid[19] gave the aldehyde in acceptable yield.

Experimental

N.m.r. spectra were recorded at 300 MHz in $CDCl_3$, unless otherwise reported. I.r. spectra were measured in $CHCl_3$, and u.v. spectra in EtOH.

Ethyl 6,6-Bisethoxycarbonyl-5,6-dihydro-2H-thiopyran-5-yl-acetate (**6**).—Diethyl oxomalonate (14.41 g), P_4S_{10} (7.73 g), and ethyl hexa-3,5-dienoate (8.62 g) in dry THF (70 ml) were boiled under reflux in a N_2 atmosphere for 20 h. After evaporation of THF under reduced pressure the dark residue was repeatedly extracted with Et_2O and the extracts concentrated to give a brown oil. Flash chromatography on silica gel 60 eluting with hexane–Et_2O (2:1) gave the *triester* (**6**) (13.43 g) as a yellow oil (Found: C, 54.1; H, 6.9; S, 9.9%. M^+, 330.1137. $C_{15}H_{22}O_6S$ requires C, 54.5; H, 6.7; S, 9.9%; *M*, 330.1132).

Table 3. G.c. peak height ratios to internal standard[a]

	Time			Ratio
	0 1	36	39	(36:39)
(a) NCS–CH_2Cl_2	10 min	1.12	0.05	22.4
	19 h	0.69	0.04	17.3
	0 1			
(b) NCS–CH_2Cl_2–C_3H_6O	5 min	0.55	0.22	2.5
	20 min	0.58	0.39	1.5
	3 h	0.50	0.56	0.9
	0 1			
(c) NCS–CH_2Cl_2–C_3H_6O after	20 min	1.26	0.14	9.0
2 min.	19 h	1.07	0.25	4.3

[a] n-$C_{16}H_{34}$ as internal standard.

The following thiopyrans were prepared in a similar way using diethyloxomalonate. (*a*) Compound (**7**) from methyl hexa-3,5-dienoate (69%), m.p. 59—60 °C (pentane–Et_2O) (Found: C, 52.9; H, 6.5; S, 10.6. $C_{14}H_{20}O_6S$ requires C, 53.1; H, 6.4; S, 10.1%); δ_H(CCl_4, 60 MHz) 5.76 (2 H, br s), 4.18 (4 H q, *J* 7 Hz), 3.62 (3 H, s), 3.37 (1 H, m), 3.05 (2 H, br s), 2.44 (2 H, d, *J* 7 Hz), and 1.28 (6 H, t, *J* 7 Hz);

(*b*) Compound (**8**) from hexa-3,5-dienoic acid (24%), m.p. 82—84 °C [EtOAc–light petroleum (b.p. 40—60 °C)] (Found: C, 52.1; H, 6.2; S, 11.0. $C_{13}H_{18}O_6S$ requires C, 51.6; H, 6.0; S, 10.6%); δ_H($CDCl_3$, 300 MHz), 5.95 (1 H, dd, *J* 11 and 5 Hz), 5.79 (1 H, m), 4.29 (4 H, m), 3.48 (1 H, m), 3.21 (1 H, dd, *J* 18 and 2 Hz), 3.03 (1 H, dd, *J* 18 and 5 Hz), 2.62 (1 H, dd, *J* 16 and 9 Hz), 2.55 (1 H, dd, *J* 16 and 6 Hz), and 1.25 (6 H, m);

(*c*) Compound (**9**) from 1,1,1-trichloroethylhexa-3,5-dienoate (90%), m.p. 65—66 °C (hexane) (Found: C, 41.5; H, 4.4; S, 7.2. $C_{15}H_{19}Cl_3O_6S$ requires C, 41.4; H, 4.4; S, 7.4%); δ_H($CDCl_3$, 60 MHz), 5.91 (2 H, m), 5.77 (2 H, s), 4.26 (4 H, q, *J* 7 Hz), 3.56 (1 H, m), 3.16 (2 H, m), 2.72 (2 H, d, *J* 7 Hz), and 1.28 (6 H, t, *J* 7 Hz). Zn–AcOH Reduction gave the acid obtained in (*b*) (78%);

(*d*) Compound (**17**) from hexa-3,5-dienyl acetate, yellow oil (75%) (Found: M^+, 330.1132. $C_{15}H_{22}O_6S$ requires *M*, 330.1137); δ_H($CDCl_3$, 60 MHz) 5.89 (2 H, m), 4.26 (2 H, m), 4.28 (2 H, q, *J* 7 Hz), 4.25 (2 H, q, *J* 7 Hz), 3.14 (2 H, br s), 2.65 (1 H, m), 2.05 (3 H, s), 1.78 (2 H, m), 1.30 (3 H, t, *J* 7 Hz), and 1.27 (3 H, t, *J* 7 Hz);

(*e*) Compound (**3**) from 1-acetoxybuta-1,3-diene, m.p. 89—90 °C (EtOH) (Found: C, 51.6; H, 6.1; S, 10.3. $C_{13}H_{18}O_6S$ requires C, 51.6; H, 6.0; S, 10.6%); δ_H($CDCl_3$, 90 MHz), 6.05 (2 H, m), 5.85 (1 H, m), 4.24 (4 H, q, *J* 7 Hz), 3.18 (2 H, m), 2.05 (3 H, s), and 1.27 (3 H, t, *J* 7 Hz).

(*f*) Compound (**12**) (using butyl glyoxylate) from ethyl hexa-3,5-dienoate, yellow oil (15%) (Found: M^+, 286.1236. $C_{14}H_{22}O_4S$ requires *M*, 286.1239); δ_H($CDCl_3$, 90 MHz) 5.80 (2 H, m), 4.12 (4 H, m), 3.82 (0.5 H, d *J* 4 Hz), (0.8 H, d, *J* 4 Hz), 3.17 (3 H, m), and 2.98 (2 H, m).

Hexa-3,5-dienoic Acid and its Esters.—The acid and the methyl and ethyl esters were prepared by deconjugation of the corresponding sorbates* (LDA–HMPA or LDA–TMU). The trichloroethyl ester was prepared from the acid, trichloroethanol, and dicyclohexycarbodi-imide in CH_2Cl_2–pyridine as a liquid, b.p. (bath) 60 °C/0.005 Torr (84%) (Found: C, 39.6; H, 3.9. $C_8H_9Cl_3O_2$ requires C, 39.5; H, 3.8%).

* See footnote on p. 663.

6,6-*Dicarboxy*-5,6-*dihydro*-2H-*thiopyran*-5-*ylacetic Acid* (**11**).—The triester (**6**) (235 mg) in EtOH (5 ml) and water (5 ml) containing NaOH (2 g) was stirred at 20 °C for 14 h. The solution was brought to pH 1 with 2M HCl and then saturated with NaCl and extracted with EtOAc (3 × 50 ml). Work-up of the extracts gave the *tricarboxylic acid* (**11**) (158 mg), m.p. *ca.* 125 °C (decomp); $\delta_H(CD_3COCD_3$, 60 MHz) 10.05 (3 H, s), 5.82 (2 H, m), 3.45 (1 H, m), 3.12 (2 H, m), and 2.54 (2 H, d, *J* 7 Hz).

6-*Carboxy*-5,6-*dihydro*-2H-*thiopyran*-5-*ylacetic Acid* (**13**).—(*a*) 20% Aqueous NaOH (12 ml) was added to a solution of the diester (**12**) (1.1 g) in EtOH (3 ml) and the mixture boiled under reflux (N_2 atmosphere) for 4 h. The solution was acidified to pH 1 with 2M HCl and extracted with Et_2O (3 × 60 ml). Concentration of the dried extract gave the cis- and trans-*acids* (**13**) (650 mg), m.p. 177—179 °C (MeCN–Et_2O) (Found: C, 47.8; H, 5.1. $C_8H_{10}O_4S$ requires C, 47.5; H, 4.9%); $\delta_H(CD_3COCD_3$, 80 MHz), 5.85 (2 H, m), 3.85 (0.25 H, d, *J* 43 Hz), 3.54 (0.75 H, d, *J* 3.5 Hz), 3.20 (1 H, m), 3.19 (2 H, m), and 2.56 (2 H, d, *J* 7.5 Hz). The acid (**13**) was dissolved in Ac_2O and after 4 h the mixture was evaporated to give the anhydride (**16**), m.p. 127—130 °C (Found: M^+, 184.0193. $C_8H_8O_3S$ requires *M*, 184.0194); $\delta_H(CD_3COCD_3$, 90 MHz), 5.97 (1 H, m), 5.68 (1 H, d, *J* 11 Hz), 4.08 (1 H, d, *J* 11 Hz), 3.56 (1 H, br d, *J* 16 Hz), 3.15 (2 H, m), 2.89 (1 H, d, *J* 14 Hz), 2.54 (1 H, dd, *J* 14 and 4 Hz); $\nu_{max.}(CHCl_3)$ 1 820 and 1 770 cm^{-1}. Hydrolysis gave the starting acid (**13**).

(*b*) If the acidified solution from hydrolysis of the triester (**6**) (323 mg) (previous experiment) was boiled under reflux for 20 min and then worked up as described, a mixture of the *cis*- and *trans*-dicarboxylic acids (**13**) (176 mg) was obtained as a yellow oil which solidified with time, $\delta_H(CDCl_3$, 60 MHz) 5.92 (2 H, m), 3.87 and 3.54 (d, *J* 4.3 and 3.5 Hz respectively), 3.14 (3 H, m), and 2.58 (2 H, m). The same mixture was obtained when the acid (**11**) was heated at 130 °C. Dissolution of the mixture in Ac_2O gave a *cis*- and *trans*-anhydride mixture.

6-*Ethoxycarbonyl*-5,6-*dihydro*-2H-*thiopyran*-5-*ylacetic Acid* (**14**).—The triester (**7**) (3.3 g) was dissolved in EtOH (35 ml) and water (35 ml) containing NaOH (1 g). After 12 h the solution was acidified with 5M HCl, saturated with NaCl, and extracted with EtOAc (2 × 50 ml). Concentration of the dried extract gave the *dicarboxylic acid* (**10**), m.p. 125—130 °C (decomp.) ($CHCl_3$) (Found: C, 48.4; H, 5.1; S, 11.7. $C_{11}H_{14}O_6S$ requires C, 48.2; H, 5.1; S, 11.7%); $\delta_H(CD_3COCD_3$, 90 MHz), 5.85 (2 H, m), 4.17 (2 H, q, *J* 7 Hz), 3.45 (1 H, m), 3.12 (2 H, m), 2.55 (2 H, d, *J* 7 Hz), and 1.23 (3 H, t, *J* 7 Hz). The acid was heated at 130 °C under a N_2 atmosphere for 0.75 h to give a dark oil which was purified by flash chromatography on silica gel 60 eluting with $CHCl_3$–MeOH (19:1) to afford the acid (**14**) (1.85 g) as an oil (Found: C, 52.3; H, 6.3; S. 14.0. $C_{10}H_{14}O_4S$ requires C, 52.2; H, 6.1; S, 13.9%); $\delta_H(CD_3COCD_3$, 220 MHz), 5.90 (1 H, br d, *J* 11 Hz), 5.77 (1 H, br d, *J* 11 Hz), 4.17 (2 H, m), 3.83 (0.2 H, d, *J* 4.5 Hz), 3.51 (0.7 H, d, *J* 3.5 Hz), 3.22 (1 H, m), 3.10 (0.2 H, m), 2.97 (2 H, m), 2.55 (2 H, m), and 1.22 (3 H, t, *J* 7 Hz).

6-*Ethoxycarbonyl*-5-(2-*hydroxyethyl*)-5,6-*dihydro*-2H-*thiopyran* (**18**).—The acetate (**17**) (109 mg) was dissolved in EtOH containing NaOEt (*ex.* 10 mg Na). After 4 h, 2M HCl (40 ml) was added and the mixture extracted with EtOAc (4 × 20 ml). The dried extracts were concentrated to give a mixture of starting material and product. Preparative t.l.c. eluting with hexane–Et_2O (1:2) gave the *alcohol* (**19**) (37 mg) (Found: M^+, 216.0818. $C_{10}H_{16}O_3S$ requires *M*, 216.0820); $\delta_H(CDCl_3$, 60 MHz), 5.83 (2 H, br s), 4.19 (2 H, q, *J* 7 Hz), 3.74 (2 H, t, *J* 6 Hz), 3.40 (1 H, d, *J* 4 Hz), 3.12 (2 H, m), 2.79 (1 H, m), 1.82 (2 H, q, *J* 6 Hz), and 1.27 (3 H, t, *J* 7 Hz).

6,6-*Bisethoxycarbonyl*-5-(2-*hydroxyethyl*)-5,6-*dihydro*-2H-*thiopyran* (**18**).—Acetyl chloride (4 ml) was added to EtOH (40 ml) and, after 5 min, the acetate (**17**) (1.14 g) was dissolved in the solution. After 6 h saturated aqueous $NaHCO_3$ (120 ml) was added and the mixture extracted with EtOAc (3 × 60 ml); the dried extracts were concentrated to give an oil which was chromatographed on silica gel 60 eluting with hexane–Et_2O to afford the alcohol (**18**) (603 mg) as a colourless oil (Found: M^+, 288.1022. $C_{13}H_{20}O_5S$ requires *M*, 288.1031); $\delta_H(CDCl_3$, 60 MHz), 5.90 (2 H, m), 4.25 (2 H, q, *J* 7 Hz), 4.21 (2 H, q, *J* 7 Hz), 3.77 (2 H, *J* 6 Hz), 3.27 (1 H, m), 3.15 (2 H, br s), 1.26 (2 H, m), 1.28 (3 H, t, *J* 7 Hz), and 1.25 (3 H, t, *J* 7 Hz). On oxidation with Jones' reagent the alcohol (**18**) gave the acid (**8**) identical with material prepared previously.

6,6-*Bisethoxycarbonyl*-5-*formylmethyl*-5,6-*dihydro*-2H-*thiopyran*.—Me_2SO (340 μl) in CH_2Cl_2 (1 ml) was added to $(COCl)_2$ (200 μl) at −78 °C. After 5 min the alcohol (288 mg) in CH_2Cl_2 (1 ml) was added to the solution now at −15 °C. After 15 min Et_3N (1.4 ml) was added followed by water (20 ml) the mixture was then extracted with CH_2Cl_2 (2 × 15 ml). Concentration of the dried extracts and chromatography of the product on silica gel 60 eluting with hexane–Et_2O gave the *aldehyde* as an oil (181 mg) (Found: M^+, 286.0867. $C_{13}H_{18}O_5S$ requires *M*, 286.0871); $\delta_H(CDCl_3$, 60 MHz) 9.84 (1 H, t, *J* 1.5 Hz)]. It gave a 2,4-dinitrophenylhydrazone, m.p. 120—122 °C (EtOAc) (Found: C, 49.3; H, 4.7; N, 12.0. $C_{19}H_{22}N_4O_8S$ requires C, 48.9; H, 4.8; N, 12.0%).

Iodolactonisation of the Tricarboxylic Acid (**11**).—A solution of I_2 (103 mg) and KI (200 mg) in water (6 ml) was added dropwise to a solution of the acid (**11**). The pH of the solution was maintained at its original value by addition of aqueous $NaHCO_3$ over 5 h. After a further 12 h, aqueous $Na_2S_2O_5$ was added to destroy the excess of I_2 and, after addition of 2M HCl, the solution was extracted with EtOAc (3 × 60 ml). Evaporation of the dried extract gave a mixture which was chromatographed on a silica HF_{254} plate using double elution with PhMe–Et_2O–HCO_2H (17.5:5:3). Elution of the two major bands gave the *lactone* (**25**) (32 mg), m.p. 166—167 °C (decomp.) ($CHCl_3$–Me_2CO), $\nu_{max.}$ 1 790 and 1 735 cm^{-1} (Found: C, 29.0; H, 2.5; I, 33.5. $C_9H_9IO_6S$ requires C, 29.0; H, 2.7; I, 34.0%) and the *lactone* (**26**) (25 mg), m.p. 156—95 °C (decomp.), *m/z* 328 ($M - CO_2$). Reaction of (**26**) with CH_2N_2–Et_2O gave a dimethyl ester *m/z* 273.0437. ($M - 1$ requires 273.0433).

Iodolactonisation of the Triethyl Ester (**6**).—I_2 (4 g) was added to the ester (**6**) (1.4 g) in MeCN (30 ml). After 8 days, Et_2O (100 ml) was added and the solution shaken with aqueous $Na_2S_2O_5$. The ethereal extract, after drying, was concentrated to give crude iodolactone (1.63 g) containing *ca.* 20% starting material. A portion (150 mg) was purified by double elution with PhMe–Et_2O–HCO_2H (17.5:5:3) on a silica HF_{254} plate. Removal of the lower 1/3 of the main band gave the *lactone* (**21**) (39 mg), m.p. 71—72 °C (Et_2O), $\nu_{max.}$ 1 790, and 1 735 cm^{-1} (Found: C, 36.5; H, 3.7%; M^+, 427.9798, $C_{13}H_{17}IO_6S$ requires C, 36.5; H, 4.0%; *M*, 427.9793).

Dehydroiodination of Lactone (**21**).—A solution of the lactone (**21**) (83 mg) in PhMe (1 ml) containing DBU (50 mg) was heated under a N_2 atmosphere for 1 h at 75 °C. After removal of the PhMe the residue was chromatographed on silica HF_{254} eluting with PhMe–Et_2O–HCO_2H (17.5:5:3). The least polar fraction gave the *alkene* (**23**) (15 mg) as an oil, $\nu_{max.}$ 1 785, 1 735, and 1 620 cm^{-1} (Found: M^+, 300.0667. $C_{13}H_{16}O_6S$ requires *M*, 300.0667). The more polar component was the *hydroxy acid* (**28**)

(12 mg), $\nu_{max.}$ 1 735 cm^{-1} which, after 2 h *in vacuo* (0.2 Torr) was converted into the lactone (**23**).

Iodolactonisation of the Monocarboxylic Acid (**8**).—(*a*) The acid (**8**) (150 mg) dissolved in saturated aqueous $NaHCO_3$ (40 ml) was treated dropwise with I_2 (508 mg) and KI (1.004 g) in water (10 ml). After 8 h, work-up as before gave the *lactone* (**21**) (142 mg) identical with the compound prepared previously.

(*b*) I_2 (1.37 g) was added to a vigorously stirred mixture of the acid (**8**) (540 mg), Triton B in MeOH [0.76 ml of a 40% (w/v) solution], CH_2Cl_2 (18 ml), and water (4 ml). After 15 min, aqueous $Na_2S_2O_5$ was added and the mixture extracted with Et_2O (3 × 30 ml). The combined extracts were successively shaken with 2M HCl, saturated aqueous $NaHCO_3$, and brine and then dried and concentrated to give the *lactone* (**24**) (727 mg), m.p. 109—112 °C ($CHCl_3$–hexane), $\nu_{max.}$ 1 790 and 1 730 cm^{-1} (Found: C, 36.8; H, 4.1; I, 29.4; S, 7.9. $C_{13}H_{17}IO_6S$ requires C, 36.5; H, 4.0; I, 29.6; S, 7.5%). The lactone (**24**) was unchanged on exposure to the conditions for reaction (*a*).

Rearrangement of the Lactone (**24**).—(*a*) A solution of the lactone (**24**) (43 mg) in $HCONMe_2$ (2 ml) containing Li_2CO_3 (10 mg) and LiCl (6 mg) was heated at 100 °C. After 2.5 h, the cooled mixture was poured into 2M HCl and extracted with Et_2O. The extract was washed with 2M HCl and saturated aqueous $NaHCO_3$, dried, and concentrated to yield the *chloro lactone* (28 mg) as an oil, $\nu_{max.}$ 1 790 and 1 730 cm^{-1} (Found: M^+, 336.0438. $C_{13}H_{17}ClO_6S$ requires M, 336.0436). The same compound was obtained on boiling under reflux in CCl_4–Me_2SO (8:1) containing DBU (100 mg).

(*b*) The iodo lactone (**24**) (35 mg) in $HCONMe_2$ (1 ml) containing Li_2CO_3 (10 mg) was heated at 100 °C for 20 h. Work-up as before gave the unsaturated lactone (**23**) (5 mg) identical with the material prepared previously.

2,2-*Bisethoxycarbonyl*-5-*phenylseleno*-3,4-*tetrahydrothiopyrancarbolactone* (**30**).—Et_3N (55 mg) was added to the acid (**8**) (150 mg) in CH_2Cl_2 (3 ml) and the solution stirred under a N_2 atmosphere whilst it was cooled to −78 °C. PhSeCl (106 mg) was added to the mixture which was then kept at −78 °C for 30 min. The residue obtained on evaporation of the solvent was purified by thick layer chromatography (silica HF_{254}, CH_2Cl_2 elution) to give the *selenide* (**30**) (115 mg), m.p. 112—113 °C ($CHCl_3$–light petroleum), $\nu_{max.}$ 1 780 and 1 725 cm^{-1}; δ_H 7.63 (2 H, m), 7.34 (3 H, m), 4.95 (1 H, dd, *J* 9.5 and 7 Hz), 4.35 (4 H, m), 3.38 (1 H, dd, *J* 13, 7, and 7 Hz), 3.04 (1 H, dt, m *J* 9 and 9.5 Hz), 2.80 (1 H, dd, *J* 17 and 13 Hz), 2.70 (2 H, d, *J* 9 Hz), 2.13 (1 H, dd *J* 17 and 7 Hz), 1.25 (3 H, t, *J* 7 Hz), 1.21 (3 H, t, *J* 7 Hz) (Found: C, 49.6; H, 4.6; H, 4.6. $C_{19}H_{22}O_6SSe$ requires C, 49.9; H, 4.9%).

2,2-*Bisethoxycarbonyl*-3,5-*dihydro*-2H-*thiopyran*-3,4-*carbolactone* (**33**).—A 3% solution of H_2O_2 in aqueous tetrahydrofuran (0.113 ml) was added to the selenide (**30**) (30 mg) in tetrahydrofuran (0.5 ml) at −20 °C. The solution was warmed to 0 °C and kept for 15 h. After addition of aqueous $Na_2S_2O_5$ the solution was extracted with Et_2O. The dried extracts were concentrated to give an oil which was purified by thick layer chromatography [silica HF_{254}, Et_2O–hexane (2:1)] to give the unsaturated lactone (**33**) (11 mg) identical with an authentic sample.

Iodolactonisation of the Dicarboxylic Acids (**13**).—A solution of I_2 (85 mg) and KI (157 mg) in water (4 ml) was added to the acid (**13**) (68 mg) in a mixture of $NaHCO_3$ (30 mg), water (3 ml), and MeOH (3 ml). After 14 h the reaction mixture was worked up as before and the product chromatographed on a silica HF_{254} plate eluting with PhMe–Et_2O–HCO_2H (17.5:5:3). The least polar fraction gave the *lactone* (**27**) (9 mg), m.p. 159—162 °C, $\nu_{max.}$ 1 785, and 1 720 cm^{-1} (Found: M^+, 327.9275. $C_8H_9IO_4S$ requires M, 327.9268). A mixed fraction was also obtained.

Oxidation and Rearrangement of the Triethyl Ester (**6**).—The ester (**6**) (400 mg) in CH_2Cl_2 (4 ml) was treated with 85% *m*-chloroperbenzoic acid (250 mg). After 1 h Et_2O (60 ml) was added and the solution shaken successively with aqueous $Na_2S_2O_5$ and aqueous $NaHCO_3$. Concentration of the dried solution gave an oil (397 mg) which was chromatographed on silica gel eluting with pentane–EtOAc (1:1) to give the *sulphoxides* (**6A**) (350 mg), δ_H 6.50 (2 H, m), 4.25 (6 H, m), 3.67 (1 H, m), 3.39 (2 H, m), 2.78 (2 H, m), and 1.25 (9 H, m); *m/z* 346. $(CF_3CO)_2O$ (4 ml) was added to the sulphoxides (**6A**) (72 mg) at 0 °C. After 10 min the ice-bath was removed. After a further 1 h evaporation under reduced pressure gave an oil (79 mg) which was chromatographed on silica gel eluting with pentane–Et_2O (1:1) to give the lactone (**33**) (19 mg), m.p. 80—82 °C (CCl_4). (Found: C, 51.8; H, 5.5; *S*, 10.4%; M^+, 300.0658. $C_{13}H_{16}O_6S$ requires C, 52.0; H, 5.4; S, 10.7%; M, 300.0667); $\nu_{max.}$ 1 795, and 1 740 cm^{-1}; $\lambda_{max.}$ 235 nm.

If the product from the Pummerer rearrangement was hydrolysed with $NaHCO_3$–H_2O–MeOH and the product purified by thick layer chromatography on silica HF_{254}, an improved yield (41%) of the lactone (**33**) was obtained. In addition, the *diene ester* (**45**) (11%) was isolated as an oil, $\nu_{max.}$ 1 740 cm^{-1}; δ_H 6.22 (3 H, m), 4.20 (6 H, m), 3.39 (2 H, m s), and 1.27 (9 H, t, *J* 7 Hz); $\lambda_{max.}$ 245, and 321 nm; *m/z* 328. The latter was the major product when the reaction with $(CF_3CO)_2O$ was extended to 20 h.

Oxidation and Rearrangement of the Diethyl Ester (**15**).—The diester (**15**) (207 mg) was processed as in the previous experiment. Chromatography on silica gel gave the *diene* (**46**) (27 mg) as an oil, $\nu_{max.}$ 1 740 cm^{-1}; δ_H 5.92 (2 H, m), 4.22 (4 H, m), 3.71 (2 H, s), 3.22 (2 H, m), and 1.28 (6 H, m); $\lambda_{max.}$ 345 nm (Found: M^+, 256.0774. $C_{12}H_{16}O_4S$ requires M, 256.0769).

Reaction of the Acid (**8**) *with* N-*Chlorosuccinimide*.—*N*-Chlorosuccinimide (1.04 g) was added to a stirred solution of the acid (**8**) (2.33 g) in PhH (70 ml). After 4 h, the mixture was diluted with Et_2O (100 ml) and filtered. The filtrate was shaken with aqueous $NaHCO_2$ and brine. The dried Et_2O solution was concentrated to give the lactone (**33**) (1.71 g), identical with the material prepared previously.

Reaction of the Dicarboxylic Acid (**13**) *with* N-*Chlorosuccinimide*.—*N*-Chlorosuccinimide (60 mg) was added to the acid (90 mg) in $CHCl_3$ (5 ml). After 10 min, the filtered mixture was extracted with aqueous $NaHCO_3$. The extract was acidified with 2M HCl, washed with saturated brine, and extracted with Et_2O (2 × 10 ml). The dried extract was concentrated to yield an oil which was purified by t.l.c. on silica HF_{254} eluting with PhMe–Et_2O–HCO_2H (17.5:5:3) to give the *lactone acid* (**38**) (50 mg); $\nu_{max.}$ 1 795, and 1 725 cm^{-1}; δ_H[$(CD_3)_2CO$] 6.22 (1 H, m) 5.91 (1 H, d, *J* 10.5 Hz), 3.54 (1 H, m), 3.39 (1 H, br d, *J* 17 Hz), 3.26 (1 H, dd, *J* 17 and 5.2 Hz), 3.17 (1 H, dd, *J* 17.2 and 8.8 Hz), and 2.35 (1 H, dd, *J* 17.2 and 4 Hz) (Found: M^+, 200.0139. $C_8H_8O_4S$ requires M, 200.0144).

Reaction of Anhydride (**16**) *with* N-*Chlorosuccinimide*.—The anhydride (**16**) (39 mg) in CH_2Cl_2 was treated with *N*-chlorosuccinimide (28 mg) overnight after which the solvent was removed and the residue digested with aqueous $NaHCO_3$ (10 ml). The solution was then processed as in the previous experiment to give the *diene acid* (**46**) (27 mg), $\nu_{max.}$ 1 710 cm^{-1}; δ_H[$(CD_3)_2CO$] 6.15 (1 H, d, *J* 9.5 Hz), 5.82 (1 H, dt, *J* 9.5 and 5.5 Hz), 3.75 (2 H, s) 3.22 (2 H, d, *J* 5.5 Hz) (Found: M^+, 200.0147. $C_8H_8O_4S$ requires M, 200.0144).

Table 4. Atom co-ordinates for compound (3)

Atom	x/a	y/b	z/c
S(1)	0.902 7(1)	0.125 5(1)	0.446 2(1)
C(1)	0.767 1(3)	0.233 2(3)	0.383 1(2)
C(2)	0.656 6(4)	0.305 2(3)	0.420 7(2)
C(3)	0.728 4(6)	0.374 3(4)	0.491 4(2)
C(4)	0.868 8(7)	0.355 7(5)	0.528 6(2)
C(5)	0.984 4(5)	0.264 5(5)	0.508 3(3)
C(6)	0.681 0(5)	0.135 6(4)	0.322 5(2)
C(7)	0.494 6(11)	0.137 7(9)	0.210 0(4)
C(8)	0.484 3(10)	0.198 5(8)	0.147 9(3)
C(9)	0.850 0(4)	0.343 6(4)	0.347 4(2)
C(10)	1.017 2(7)	0.374 9(6)	0.268 6(3)
C(111)	1.022 8(17)	0.312 3(16)	0.204 3(8)
C(112)	0.924 4(18)	0.391 0(15)	0.196 3(8)
C(12)	0.409 1(4)	0.227 2(5)	0.426 7(3)
C(13)	0.322 4(6)	0.103 1(7)	0.439 1(4)
O(1)	0.697 9(4)	0.012 1(3)	0.321 5(2)
O(2)	0.587 7(4)	0.210 4(4)	0.272 7(2)
O(3)	0.839 1(3)	0.466 5(3)	0.354 5(2)
O(4)	0.933 0(4)	0.283 1(3)	0.307 7(2)
O(5)	0.554 5(3)	0.194 3(3)	0.433 2(2)
O(6)	0.360 3(4)	0.342 9(4)	0.413 2(3)
H(2)	0.598	0.375	0.387
H(3)	0.665	0.439	0.512
H(4)	0.901	0.407	0.575
H(51)	1.047	0.223	0.553
H(52)	1.049	0.322	0.485
H(71)	0.392	0.128	0.218
H(72)	0.536	0.044	0.208
H(81)	0.556	0.159	0.125
H(82)	0.504	0.296	0.155
H(83)	0.385	0.185	0.118
H(131)	0.232	0.096	0.401
H(132)	0.298	0.110	0.485
H(133)	0.383	0.021	0.439

Reduction of the Anhydride (**16**) *with* $LiBH_4$.—The anhydride (**16**) (88 mg) in tetrahydrofuran (5 ml) was added to $LiBH_4$ (25 mg) and tetrahydrofuran (5 ml) under a N_2 atmosphere. After 45 min, water (2 ml) was added and, when effervescence ceased, this was followed by 2M HCl. After 1 h the solution was saturated with NaCl and extracted with EtOAc (2 × 25 ml). Concentration of the dried extract gave an oil which was purified by t.l.c. on silica HF_{254} eluting with pentane–EtOAc (1:1) to give the *lactone* (**40**) (36 mg); $\nu_{max.}$ 1 735 cm^{-1} (Found: M^+, 170.0402. $C_8H_{10}O_2S$ requires M, 170.0401).

Hydrolysis and Decarboxylation of the Lactone Ester (**33**).—$LiOH{\cdot}H_2O$ (200 mg) was added to the lactone (**33**) (300 mg) in tetrahydrofuran (5 ml) and water (5 ml) under a N_2 atmosphere. After 20 h, the dark mixture was acidified with 6M HCl and boiled under reflux for 2 h. The cooled mixture was extracted with Et_2O (2 × 20 ml) and CH_2Cl_2 (20 ml). The dried extracts were concentrated to give an oil (229 mg) which was chromatographed on silica gel eluting with CH_2Cl_2–AcOH (9:1) to give a mixture of *cis*- and *trans*-acids (**34**) and (**35**) (147 mg). The epimers were separated by t.l.c. on silica HF_{254} eluting with CH_2Cl_2–AcOH (4:1): *cis*-acid (**34**), m.p. 128—130 °C (Found: M^+, 200.0148. $C_8H_8O_4S$ requires M, 200.0143).

To characterize the acids, they were converted into their acid chlorides [$(COCl)_2$] and these were then treated with Me_2CHCN_2 to give an *amide*, m.p. 185—187 °C (hexane–$CHCl_3$), $\nu_{max.}$ 1 780, and 1 670 cm^{-1} (Found: C, 54.6; H, 6.2; N, 5.7. $C_{11}H_{15}NO_3S$ requires C, 54.8; H, 6.3; N, 5.8%).

Reduction of the Acids (**34**) *and* (**35**).—$(COCl)_2$ (54 μl) was added to a solution of the acids (2 + 3) (100 mg) and $HCONMe_2$ (10 μl) in $MeOCH_2CH_2OMe$ (1 ml) under a N_2 atmosphere. After 15 min the solution was cooled to −46 °C and $LiBH_4$ (14 mg) in Et_2O (80 μl) added. After 15 min, the cooling bath was removed and 2M HCl added. The mixture was extracted with EtOAc (3 × 10 ml) and the organic extract shaken with aqueous $NaHCO_3$, dried, and concentrated to give the *alcohols* (**44**) (61 mg) as a 7:3 mixture of isomers, δ_H [$(CD_3)_2CO$] 6.52 (d, J 10 Hz), 6.47 (d, J 9.5 Hz), 5.86 (dd, J 10 and 4 Hz), 5.74 (dd, J 9.5 and 3 Hz), 5.22 (dd, J 8 and 3 Hz), 5.06 (bdd, J 6 and 4 Hz), 3.87 (d, J 5 Hz), 3.71 (m), 2.75 (m), and 2.43 (dd, J 17 and 8 Hz) (Found: M^+, 186.0355. $C_8H_{10}O_3S$ requires M, 186.0351).

Table 5. Atomic co-ordinates for compound (35)

Atom	x/a	y/b	z/c
S(1)	0.955 4(1)	0.842 6(1)	0.120 7(0)
O(1)	0.698 2(2)	0.305 1(2)	0.171 6(1)
O(4)	0.658 9(2)	0.327 5(2)	0.306 6(1)
O(81)	0.682 1(2)	0.041 7(2)	−0.030 3(1)
O(82)	0.666 9(2)	0.709 7(2)	−0.055 6(1)
C(1)	1.004 5(2)	0.589 2(3)	0.111 0(1)
C(2)	0.906 0(2)	0.433 7(3)	0.103 4(1)
C(3)	0.731 8(2)	0.441 7(3)	0.102 7(1)
C(4)	0.684 1(2)	0.411 4(3)	0.241 7(1)
C(5)	0.702 5(2)	0.631 6(3)	0.226 4(1)
C(6)	0.668 1(2)	0.644 9(3)	0.127 7(1)
C(7)	0.737 0(2)	0.830 4(3)	0.091 7(1)
C(8)	0.690 9(2)	0.849 1(3)	−0.005 9(1)
H(1)	1.116 7(27)	0.568 8(34)	0.114 6(14)
H(2)	0.949 5(25)	0.310 4(31)	0.097 8(13)
H(3)	0.668 6(21)	0.389 9(26)	0.049 9(11)
H(51)	0.633 5(26)	0.709 5(34)	0.254 1(14)
H(52)	0.815 0(25)	0.667 3(31)	0.249 0(14)
H(6)	0.552 6(23)	0.646 5(28)	0.107 5(12)
H(7)	0.701 5(22)	0.945 6(29)	0.116 1(12)
H(81)	0.668 6(28)	1.054 1(37)	−0.083 2(15)

Reduction of the Half Esters (**14**).—A 1.2M solution of Bu^i_2AlH in hexane (21.1 ml) was added to the esters (**14**) (2.65 g) in PhMe (100 ml) cooled to −78 °C under a N_2 atmosphere, the solution temperature being kept below −55 °C. After 2 h at −70 °C, EtOH (20 ml) was added and the mixture allowed to reach ambient temperature. 2M HCl (100 ml) was added and the mixture extracted with EtOAc (100 ml and then 3 × 50 ml). The combined EtOAc extracts were shaken with saturated aqueous $NaHCO_3$ (3 × 75 ml) and then acidified to pH 1 with 2M HCl. After saturation with NaCl the solution was extracted with EtOAc (3 × 75 ml), and the extract shaken with brine, dried, and concentrated to give the *aldehyde* (**42**) (2.02 g), m.p. 82—84 °C (pentane–Et_2O), $\nu_{max.}$ 1 710 cm^- (Found: C, 51.5; H, 5.4; S, 17.1%; M^+, 186.0349. $C_8H_{10}O_3S$ requires C, 51.6; H, 5.4; S, 17.2%; M, 186.0351).

Acetalisation of the Aldehyde (**42**).—$SmCl_3{\cdot}8H_2O$ (211 mg) in MeOH (4 ml) was added to a solution of the aldehyde (**42**) (982 mg) in $HC(OMe)_3$ (5.6 g). After 20 min, EtOAc (50 ml) was added and the solution shaken with water (3 × 20 ml), dried, and concentrated to give the *acetal* (**43**) (1.17 g), m.p. 84—86 °C (pentane–Et_2O), $\nu_{max.}$ 1 710 cm^{-1} (Found: C, 51.9; H, 7.3; S, 13.8%; M^+, 232.0761. $C_{10}H_{16}O_4S$ requires C, 51.7; H, 7.0; S, 13.8%; M, 237.0769).

Lactonisation of the Acetal Acid (**43**).—(*a*) *N*-Chlorosuccinimide (658 mg) in CH_2Cl_2 (10 ml) was added to the acetal (**43**) (1.04 g) in CH_2Cl_2 (200 ml). After 2 min, 1,2-epoxypropane (20 ml) was added and 5 min later the solution was concentrated

under induced pressure to *ca.* 20 ml. This solution was applied to a silica gel column and flash chromatographed eluting with Et_2O–pentane to give the *lactone* (**36**) (760 mg), m.p. 43 °C (Et_2O–pentane); $\nu_{max.}$ 243 nm (ε 5 800) (Found: C, 52.1; H, 6.3%; M^+, 230.0617. $C_{10}H_{14}O_4S$ requires C, 52.2; H, 6.1%; *M*, 230.0613).

(*b*) *N*-Chlorosuccinimide (55 mg) was added to the acetal (**43**) (87 mg) in CH_2Cl_2 (25 ml) and 1,2-epoxypropane (3 ml). After 40 min, the solution was concentrated to *ca.* 1.5 ml and purified by flash chromatography as described. The lactone (**36**) (39 mg) was obtained and also a second *lactone* (**39**) (26 mg) as an oil, $\nu_{max.}$ 1 785 cm^{-1} (Found: M^+, 230.0617. $C_{10}H_{14}O_4S$ requires *M*, 230.0613).

Preparation of the Aldehyde Lactone (**2**).—Freshly distilled HCO_2H (2 ml) was added to the acetal (**36**) (157 mg) in CH_2Cl_2 (5 ml). After 14 h, CH_2Cl_2 (50 ml) was added and the solution shaken with saturated aqueous $NaHCO_3$ (3 × 20 ml). Concentration of the dried extracts gave the *aldehyde* (**2**) (103 mg), m.p. 94 °C (Et_2O); $\nu_{max.}$ 1 790 and 1 720 cm^{-1}; $\lambda_{max.}$ 243 nm (ε 4 500) (Found: C, 54.2; H, 4.4%; M^+, 184.0198. $C_8H_8O_3S$ requires C, 52.2; H, 4.4%; *M*, 184.0194).

The acetal (**36**) was reformed by reaction of the aldehyde (**2**) with BF_3–MeOH–$HC(OMe)_3$ in 70% yield.

Oxidation of the aldehyde with Jones' reagent gave a 47% yield of the *cis*-acid (**34**) identical with that prepared previously.

Crystal Data.—For compound (**3**). $C_{13}H_{18}O_6S$ (3), M = 302, monoclinic, a = 9.059(4), b = 9.527(3), c = 18.772(5) Å, β = 103.77(3)°, U = 1574 $Å^3$, Z = 4, D_c = 1.27 g cm^{-1}, μ(Mo-K_α, λ = 0.710 69) = 2.4 cm^{-1}, space group $P2_1/c$ (No. 14), 2168 reflexions with $F > 3\sigma(F)$, R = 6.9%.

From a sample of transparent, colourless, irregular-shaped crystals, a specimen of dimensions 0.52 × 0.42 × 0.40 mm was mounted on an Enraf-Nonius CAD-4 computer-controlled single-crystal diffractometer and intensity data collected to a value of 25° using Mo-K_α radiation. Standard reflexion monitoring suggested no crystal deterioration during data collection and no absorption correction was applied ($\mu R < 0.13$). An earlier analysis, in 1978, in which 198 E values >1.8 collected on a Hilger and Watts diffractometer system together with the MULTAN direct methods program had yielded a solution, was used as the starting point. Difference Fourier series and least-squares refinement of positional and isotropic thermal parameters confirmed the structure which exhibited high B values in the ethyl groups. Disorder at one methyl position prevented five of the hydrogen atoms being directly located. Anisotropic refinement of all non-hydrogen atoms, C(11) excluded, converged satisfactorily. Alternate site-occupancy and B-value refinement at the site of the disorder suggested two sites of equal occupancy, C(111) and C(112). Hydrogen atom positions were recalculated to maintain C–H distances of 0.98A (methyls 0.95 Å). During the final cycles the weighting scheme $w^{-1} = (0.45 - 0.07F + 0.0117F^2)$ was employed to give uniform $w \cdot \Delta F^2$ distribution over the range of F values. The final R was 6.90%. The final atomic co-ordinates are listed in Table 4.

For compound (**35**).$C_8H_8SO_4$, M = 200, monoclinic, a = 8.456(3), b 6.593(2), c = 15.603(4) Å, β = 101.34°, U = 852.9 $Å^3$, D_c = 1.56 g cm^{-1}, μ(Mo-K_α) = 3.74 cm^{-1}, space group $P2_1/c_1$ (No. 14), 1174 unique reflexions with $F > 3\sigma(F)$, R = 2.89%.

The crystals were transparent, colourless plates with well-formed faces. One, of dimensions 0.32 × 0.21 × 0.11 mm, was mounted on an Enraf-Nonius CAD-4, computer-controlled, single-crystal diffractometer and used for collection of intensity data up to θ = 23°. The scan range was given by (0.8 + 0.35 tan) and the aperture dimension was 4 mm^2. Standard reflexion monitoring suggested no crystal deterioration during data collection. No absorption correction was applied. The structure was solved by direct methods using the program MULTAN-76. The most likely E-map showed all the non-hydrogen atoms. The positions of the stereochemically constrained hydrogen atoms were calculated and that of the hydroxy hydrogen, H(81), found from a difference map after initial isotropic thermal refinement. After full-matrix anisotropic refinement of the non-hydrogen atoms the final R was 2.89%. The final weighting scheme used was $w = (0.23—0.019F + 0.001F^2)$. The final atomic parameters are given in Table 5 and selected bond lengths and angles in Table 2.

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