SYNTHESIS OF NOVEL

THIANONE ANALOGUES

OF PROSTAGLANDINS

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SUMMARY

An account of work in the synthesis of pharmacologically interesting, novel prostaglandin analogues containing heterocyclic sulphur is presented. A guide to the prostaglandin literature is included.

The route to thianone analogues involved C-alkylation of thian-3,5-dione, and attachment of an unsaturated side-chain by 1,4 addition of a lithium vinylcuprate to a conjugated enone derived from the alkylation product. The alkylation was achieved after a series of model experiments with various alkylation agents and reaction conditions, and the appropriate enone was made via hydride reduction of an enol ether of the alkylated dione, and acid-catalysed rearrangement. This process was confused by side reactions, particularly conjugate reduction of the enol ether. The enone underwent 1,4 additions without complications.

It was also proposed to make an enone appropriate for the synthesis of thiolanone analogues of prostaglandins via electrophilic chlorination of the alkylated β-diketone, then ring-contraction by elimination of hydrogen chloride and carbon monoxide. Two potential difficulties due to the presence of sulphur were anticipated: attack by the chlorinating agent at the heteroatom; and hindrance to the conjugate addition stage caused by tautomerism of the enone, whose dienol form would be a thiophene.
Model experiments to find suitable reaction conditions with carbocyclic compounds were successful, but electrophilic chlorination hampered their immediate application to the heterocyclic series.

Earlier efforts to make thiolanone analogues of prostaglandins were based on a route involving construction of a functionalised thiolanone by Dieckmann cyclisation. Attachment of one side-chain by C-alkylation was to be followed by development of a potential formyl substituent, which would be elaborated to form the unsaturated side-chain via the phosphonate modification of the Witting reaction, a less versatile method than vinylcuprate addition. However, a study of the stages leading to the alkylated thiolanone showed them to be too inefficient for practical purposes, and this route was not pursued further.
DEDICATION

To Ann
The term "prostaglandin" was coined by von Euler in 1935 to describe a then unknown active principle present in extracts of lipid-soluble acids from the human prostate gland and seminal vesicles. This factor is now known to be a mixture of several fatty acids having in common a skeleton of twenty carbon atoms. The prostaglandins are named systematically as derivatives of this hypothetical parent structure, prostananoic acid, which consists of a cyclopentane ring bearing two adjacent side-chains with a trans relationship; structure 1 shows its absolute configuration and numbering. They differ in the numbers and positions of double bonds, hydroxyl and carbonyl substituents present. It is often convenient to describe the side-chains at positions 8 and 12 as "upper" and "lower" respectively.

![Diagram of prostaglandin structures](image-url)
For purposes of semi-systematic nomenclature the prostaglandins have been divided into series differing in the arrangement of substituents in the five-membered ring, denoted by the letters A, B, C, E, F, etc. The principal naturally occurring prostaglandins are members of the E, F, A and B series; their ring substitution patterns are illustrated in partial structures 2 - 5. All series have a _trans_-13 double bond and a 15-S hydroxy group, except the G prostaglandins, in which the latter is replaced by a hydroperoxy group. The series are subdivided according to the number of double bonds present in specific locations in the side chains: _class_ 1 prostaglandins have only the _trans_-13 double bond; _class_ 2 have in addition a _cis_-5 double bond; _class_ 3 have _trans_-13, _cis_-5, and _cis_-17 double bonds. As in steroid nomenclature substituents lying below the plane of the molecule as conventionally drawn may be described by _α_, those above the molecule by _β_. The _E_ prostaglandins contain 9-keto and 11α-hydroxy groups; thus structure 6 is named prostaglandin _E_1, or PGE_1_ for greater brevity, the numerical subscript indicating the number of double bonds in the side-chains.
Chemical reduction of the 9-keto group of the E prostaglandins yields a mixture of the corresponding \( F_\alpha \) and \( F_\beta \) compounds; here the subscript describes the orientation of the newly-formed 9-hydroxy group. Of these only the \( F_\alpha \) type occur naturally, for example prostaglandin \( F_2\alpha \) (7). Dehydration of the \( \beta \)-ketol system in the E prostaglandins under mildly basic or acidic conditions leads to the A series, of which a 10,11 double bond is characteristic, for example prostaglandin \( A_3 \) (8); the conjugated enone chromophore gives rise to strong ultra-violet absorption at 217 nm. Under more strongly basic conditions the E and A prostaglandins are converted to the B type which contain a 8,12 double bond, such as prostaglandin \( B_1 \) (9); the conjugated dienone system absorbs at 278 nm. Nelson (7) has recently published an exhaustive study of prostaglandin nomenclature.

The first isolation of prostaglandins was reported in 1957 by Bergstrom and Sjovall, who obtained pure samples of prostaglandin \( E_1 \) and \( F_{1\alpha} \) from sheep seminal vesicles. The elucidation of the structures of the E, F, A and B prostaglandins has been summarised by Samuelsson, and by Bindra and Bindra. Both physical and chemical methods were used; key
information was obtained from oxidative ozonolysis of PGA₁, PGB₁ and 13,14-dihydro-PGB₁. The degradation products were separated by gas-liquid chromatography and identified by their mass spectra. X-ray crystallographic analysis of a single crystal of the tris-p-bromobenzoate of prostaglandin F₁β methyl ester provided the relative configuration at positions 8, 9, 11, 12 and 15. The absolute configuration at C-15 was determined by isolation of L-2-hydroxyheptanoic acid from ozonolysis of prostaglandin E₁ derivatives. The physical properties of several prostaglandins have been summarised by Ramwell et al. in a recent review. Crabbé lists the physical methods used in the prostaglandin field and highlights their application to some interesting structural and stereochemical problems.

OCCURRENCE AND BIOLOGICAL IMPORTANCE OF THE PROSTAGLANDINS

Early research leading to the discovery of the prostaglandins was stimulated by the observation that fresh human seminal fluid could cause contraction or relaxation of the human uterus. Prostaglandins have since been detected in almost all mammalian tissues, but generally in much lower concentration than in the human seminal vesicles, in which thirteen different prostaglandins with a total concentration of about 300 µg/ml have been found. The sea whip coral Plexaura homomalla is a rich source of 15-epi-prostaglandin A₂ (10) and its methyl ester acetate (11). Prostaglandin A₁ has recently been found in yellow onion.

Prostaglandins are highly potent, concentrations of 1 in 10⁹ being detectable by biological assay, and exhibit a wide range of striking biological effects in mammals. A large volume of literature has been published in this field, and has been frequently reviewed. The systems being studied include various types of smooth muscle,
lipid and carbohydrate metabolism, gastric secretion, and the reproductive, cardiovascular and central nervous systems. Different prostaglandins produce varying, even opposing responses in a given test system; for example, prostaglandins $E_1$ and $E_2$ cause relaxation of isolated human bronchial muscle, $E_1$ being more active, whereas prostaglandin $F_{2\alpha}$ stimulates the opposite response. Their physiological role seems to be to act as "local hormones", specificity being achieved by synthesis at the site of action and rapid metabolic deactivation.

![Chemical structure of prostaglandin](image)

Several possibilities exist for clinical uses of prostaglandins, including induction of labour, contraception, and treatment of asthma, hypertension, thrombosis, obesity, inflammation, glaucoma, gastritis, ulcers and nasal congestion. Interest in prostaglandin analogues stems from the desirability of compounds having the same order of potency, but more specific biological effects and greater resistance to metabolism.
The action of a biologically active compound can often be accounted for by the hypothesis that the key process involved is interaction at the molecular level with a "receptor" substance. In many instances, the receptor is probably a macromolecule such as an enzyme, and attachment of the small active molecule takes place at a particular active site. Such attachment may alter the properties of the macromolecule, particularly those of any other active sites it possesses and the way in which they interact with endogenous substances. This kind of effect is called an allosteric effect.

If a compound displays more than one biological action, this may be because it can interact with different receptors, each one specific for a particular effect. Chemical modification of the active substance, for instance removal or substitution of a functional group, may reduce its affinity for certain receptors and thereby produce greater specificity of biological action.

The ability of a compound to induce a biological effect depends on two independent properties: Its **affinity** for the receptors, and its **intrinsic activity**. The affinity determines the fraction of receptors occupied for a given concentration of the compound in their immediate vicinity, and the intrinsic activity determines the magnitude of the response resulting from the occupation of a given number of receptors. The molecular structure of a biologically active compound can sometimes legitimately be dissected into regions that are primarily responsible for affinity to the receptor(s), and regions on which the intrinsic activity depends. Modification
of the latter may remove the biological activity without eliminating the affinity for the receptor. The resulting compound would be a competitive antagonist of the unmodified compound (agonist), that is it would block the biological action of the agonist by competing for occupation of the receptor sites. If a modification causes partial rather than complete loss of intrinsic activity the antagonist is also a partial agonist. Antagonists can be therapeutically useful for alleviating symptoms caused by too high a concentration of an endogenous agonist.

β-Adrenergic stimulators and blockers are mentioned in order to illustrate the above points. The neurohumoral transmitter noradrenaline (12) is released by the endings of sympathetic neurones in response to nerve impulses. It is capable of interacting with two types of receptors, called α- and β-adrenergic receptors, whose existence has been demonstrated by means of specific agonists and antagonists. The usual response of a tissue in which α-receptors predominate is excitation; if β-receptors predominate it is relaxation. Important exceptions are the gut, which is always relaxed although neither receptor type has overall predominance, and the heart, which has predominantly β-receptors but is excited by noradrenaline. Substitution of one of the amino hydrogen atoms of noradrenaline for a methyl or isopropyl group, giving adrenaline (13) and isoprenaline (14) respectively, increases the potency towards β-receptors whilst diminishing the effect on α-receptors; isoprenaline is virtually a pure β-receptor stimulant, illustrating the point that molecular modification can increase biological specificity.
Specific antagonists of the β-adrenergic response, "β-blockers", can be valuable for treatment of cardiac conditions, for instance where it is desired to reduce the rate of heartbeat. The first compound found to possess this property was dichloroisoprenaline (15). It competes with isoprenaline for β-receptor sites and exhibits the same specific affinity for them, but it does not stimulate a response, so it is a competitive antagonist. Since dichloroisoprenaline was introduced, many other β-blockers have been discovered, several of them finding therapeutic applications. The structural requirements for maximum potency are very similar to those that maximise agonist activity: in addition to the effect of the N-alkyl substituent already mentioned, it is noteworthy that methylation at the carbon atom bearing the amino group decreases activity and that compounds having the R absolute configuration at the asymmetric centre (CHOH) are considerably more active than their enantiomers. The essential structural differences between β-stimulants and β-blockers are in the catechol nucleus; as a rule, the phenolic hydroxy groups of the β-stimulants are removed,
or replaced by other small substituents,\textsuperscript{31} to give β-blockers.

Other areas of research where examples of antagonist activity resulting from slight molecular modifications are found include the vitamins, metabolites and peptide hormones.\textsuperscript{32} For example, 6-aminonicotinic acid (16) is a competitive antagonist of the B-vitamin nicotinic acid (17). 2-Thiophenealanine (18) is an antimetabolite corresponding to phenylalanine (19). Antagonists of the octapeptide hormones oxytocin (20) and lysine vasopressin (21) have been made by removal of the phenolic hydroxyl group on the tyrosine link (22), or by replacing the hydroxyl with a methoxy or ethoxy group.\textsuperscript{33}
The central purpose of the work reported in this thesis was to seek a synthesis of prostaglandin analogues containing a sulphur heteroatom at position 11. The initial target compound was 11-deoxy-11-thiaprostaglandin E₁ (23).

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{H} \\
\text{S} & \quad \text{OH}
\end{align*}
\]

23

At the time when this work was started, no effects of modifications to the ring of the prostaglandin skeleton were known, and no heterocyclic analogues had been reported. Fried's group had studied a series of racemic 7-oxaprostaglandins; they found that (±)-7-oxaprostaglandin F₁α and (±)-7-oxaprostaglandin E₁ were agonists of the natural compounds. Simplification of the lower side-chain, for instance removal of the 15-hydroxy group or saturation of the 13,14 double bond, led to reduced prostaglandin agonist activity. On the other hand, agonist activity was retained on removal of the ring oxygen functions at positions 9 and 11, provided the 15-hydroxy group was present, as in compound 24.

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{H} \\
\text{12} & \quad \text{15} \\
\text{OH} \\
\end{align*}
\]

24

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{H} \\
\text{13} & \quad \\
\end{align*}
\]

25

The 7-oxaprostaglandins without ring oxygenation were found to be antagonists of prostaglandin E₁; at the low dose levels their action
was competitive. The requirements for high antagonist potency in regard to the structure of the lower side-chain were different from those for high agonist activity; antagonism was favoured by the absence of the 15-hydroxy group, by saturation or isomerisation of the 13,14 double bond, and most of all by replacement of the 13,14 double bond with an acetylenic linkage. The most potent antagonist found was 7-oxa-13-prostynoic acid (25), which had no agonist activity. Agonist and antagonist activity were both retained in homologues such as 26 containing a six-membered ring, which responded similarly to the five-membered ring compounds on modification of the lower side-chain.

![Chemical structure](image)

The introduction of sulphur in target compound 23 is justified on the basis that thia and methylene links are roughly isosteric, their valence electron structures being very similar. Compound 23 may therefore be regarded as an 11-deoxyprostaglandin analogue. Although at the time it was known that oxidation of the 15-hydroxy group of natural prostaglandins to a keto group results in loss of activity, Fried's results suggested that removal of the 11-hydroxy group need not have the same effect. Compound 23 could therefore be an agonist of the E prostaglandins, but with greater specificity of biological action. Another near isostere of a sulphur atom is the ethylenic system -CH=CH- (viz thiophene and benzene). The target compound 23 can therefore be considered an analogue of 10-homoprostaglandin A₁ (27), so its biological properties might resemble those of the A prostaglandins.
Another possibility for compound 23 is that it might be a prostaglandin antagonist. In view of the fact that agonists and their competitive antagonists sometimes have very closely related structures, it seemed that the sulphoxide derived from 23 might be a better candidate for the role of antagonist, since introduction of an oxygen function at position 11 would make it more closely resemble prostaglandin E₁.

Since the work described in this thesis was completed, reports of the syntheses of racemic 9-deoxo-9-thiaprostaglandin E₁ (28), its 11,15 epimer (29) and the optically active forms of its sulphone (30) have appeared.
SYNTHETIC STRATEGY

The extensive literature on the synthesis of prostaglandins has been covered by several review articles.°,16,17,23,39,40,41,236

Two potential approaches to the preparation of 11-thia prostaglandin analogues such as 23 are described here, each designed to utilise a particular known method of constructing the lower side-chain. The first involves a modified Wittig reaction of sodiodimethyl-2-oxoheptylphosphonate (31) with an aldehyde, as used by Corey and co-workers.42-45

\[
\begin{align*}
\text{OH} & \quad \text{CO}_2\text{H} \\
\text{CH}_3\text{O}_2\text{P} & \quad \text{O} \\
\text{Na}^- & \quad \text{O}^- \\
\text{S} & \quad \text{O} \\
\text{OH} & \quad \text{CO}_2\text{H}
\end{align*}
\]

The second features conjugate addition of a lithium alkenylcopper(I) reagent to an \(\alpha,\beta\)-unsaturated ketone. The first reports of applications of this method in prostaglandin synthesis were from Sih's group,46,47 followed closely by independent reports from Alvarez 48 and Kluge49 and their colleagues.

FIRST APPROACH

The first approach is outlined in principle in Scheme 1. The five-membered ring is constructed by Michael addition of ethyl thioglycollate to \(\alpha,\beta\)-unsaturated ester 32 (available in two steps from ethyl crotonate),50 followed by Dieckmann cyclisation of the resulting diester 33 to \(\beta\)-keto ester 34. The upper side-chain is added by \(\gamma\)-alkylation of a metal enolate of the \(\beta\)-keto ester system with ethyl 7-idoheptanoate, giving
All chiral compounds are racemic.
keto-diester 35. Thallium(I) is particularly attractive since chelated thallous salts of \(\beta\)-dicarbonyl compounds have been reported to be exclusively mono-C-alkylated by alkyl iodides.\(^{51}\) The now unwanted carbethoxy group of diester 35 is removed by hydrolysis and decarboxylation, under conditions that also cleave the acetoxy group; hydrolysis of the end-of-chain ester group is anticipated, leading to keto-acid 36. Alkaline hydrolysis conditions would be unsuitable, since \(\beta\)-keto esters are prone to cleavage \textit{via} attack by hydroxide ion on the ketone function. \(a,a\)-Disubstituted \(\beta\)-keto esters are particularly vulnerable because they are incapable of forming a resonance-stabilised enolate, which could not itself be attacked in this way. In the case of 4-carbalkoxythiolan-3-ones, cleavage is likely to be followed by a reverse Michael reaction; for instance, the 5-phenyl compound 42 gave cinnamic acid 43 on treatment with five per cent aqueous sodium hydroxide at room temperature: \(^{52}\)
It is assumed that the carboxyheptyl and hydroxymethyl side-chains of 36 preferentially adopt the thermodynamically more stable trans arrangement (isomerisation of prostaglandin $E_1$ at position 8 has been demonstrated in a mildly basic medium, potassium acetate in ethanol, at room temperature; at equilibrium the trans:cis ratio is 9:1).

Prior to elaboration of the lower side-chain, the carboxylic acid function is re-esterified, and a derivative of the carbonyl group formed to protect it from nucleophilic attack by phosphonate and hydride reducing agents; for example, thiketalisation with 1,2-dithioethane to give 1,3-dithiolane 37. The 1,3-dithiolane system is attractive because it is insensitive to dilute acids and is readily removed under near-neutral conditions, for instance with methyl iodide or "Chloramine T" (sodium $N$-chloro-$p$-toluenesulphonamide). 1,3-dioxolanes have been used in similar situations in the prostaglandin field.

The scheme proceeds by oxidation of primary alcohol 37 to aldehyde 38; suitable reagents include chromium trioxide dipyridine complex, dimethyl sulphoxide in conjunction with a dehydrating agent, or the recently described $N$-chlorosuccinimide - methyl sulphide reagent. Enone 39 is prepared from aldehyde 38 using the modified Wittig reaction with phosphonate 31, a method that has been shown to give trans olefins with a high degree of selectivity.
Reduction of the keto group and cleavage of the dithiolane protecting group of enone 39 leads to mixture of esters 40 and 41, epimeric at position 15. After chromatographic separation, the 15-S-hydroxy isomer 41 is saponified to give the desired acid 23 as a racemic mixture.

A synthesis of racemic 11-deoxy-11-oxaprostaglandin E₁ (44) and its 15-epimer by a similar route has very recently been reported. In this synthesis the ring ketone was protected by reduction to the secondary alcohol and acetylation, so that the initial product was the mixture of F prostaglandins 45. The 15-hydroxy group was then protected from the conditions used to regenerate the ring ketone as its α-ethoxyethyl ether.

During the preparation of this thesis, the application of the same sequence to the synthesis of racemic 11-deoxy-11-thiaprostaglandin E₁ mixed with its 15-epimer was described.

SECOND APPROACH

The second approach is illustrated in Scheme 2. Thian-3,5-dione (46, available in two steps from methyl thioglycollate and chloroacetone) is alkylated with ethyl 7-iodoheptanoate to give the symmetrical diketone 47. In principle, this intermediate may be converted to enone 48 by a method for cyclopentenone synthesis developed by Būchi and Egger, which has been applied to the synthesis of 11-deoxy E prostaglandins by Bagli and Bogri. In this procedure an alkylated cyclohexan-1,3-dione 54 is chlorinated at position 2 by tert-butyl hypochlorite, and the resulting
Scheme 2

\[
\begin{align*}
46 & \quad \text{Oxetane}
\rightarrow 47 & \quad \text{Thiophene}
\rightarrow 48 & \quad \text{Furan}
\rightarrow 49 & \quad \text{Thiophene}
\rightarrow 50 & \quad \text{Thiophene}
\rightarrow 51 & \quad \text{Thiophene}
\rightarrow 52 & \quad \text{Thiophene}
\rightarrow 53 & \quad \text{Thiophene}
\end{align*}
\]

\[\text{Et} = \text{C}_2\text{H}_5\]
chlorodiketone 55 converted to cyclopentenone 56 by treatment with sodium carbonate in refluxing xylene. The conversion of 55 to 56 was suggested to occur via dehydrochlorination to cyclopropanone 57, followed by loss of carbon monoxide. Similar cyclopropanone intermediates have been postulated for the Favorshkov rearrangement of \(\alpha\)-haloketones.

\[
\begin{align*}
\text{R} &= \text{C}_2\text{H}_5 \quad \text{or} \quad \text{(CH}_2\text{)}_3\text{CO}_2\text{CH}_3 \\
\end{align*}
\]

Enone 48 is converted to ester 49 via conjugate addition of a lithium alkenylcopper(I) reagent, and then to prostaglandin analogue 23 by saponification of the ester group. A suitable organocuprate may be generated from 3(S)-(\(\alpha\)-ethoxy)ethoxy-1-lithio-1-trans-octene (58), prepared from the corresponding iodoalkene 59 by treatment with lithium metal or an organolithium base. The \(\alpha\)-ethoxyethoxy group represents a potential 15-hydroxy group, protected from attack by strong base.

\[
\begin{align*}
\end{align*}
\]
Protonation of the enolate arising initially form the conjugate addition reaction is expected to lead to the thermodynamically favoured trans arrangement of the side-chains, a prediction supported by a report that no cis products were detected when reagent 58 was used to prepare prostaglandin E₁⁴⁷. High retention of double bond geometry is generally observed in conjugate addition reactions of alkenylcopper reagents.⁶⁷,⁶⁸

The products expected from the reaction of enone 48 with the cuprate derived from alkenyllithium 58 would therefore be 1,4 adduct 60 and its diastereoisomer 61. Cleavage of the α-ethoxyethyl protecting group, followed by saponification of the ester function, leads to the target compound 23 and diastereoisomer 62 respectively, in optically active form.

\[
\begin{align*}
60 & \quad R^1 = \text{C}_2\text{H}_5, \\
& \quad R^2 = \text{OCH(} \text{CH}_3\text{)OC}_2\text{H}_5 \\
61 & \quad R^1 = \text{C}_2\text{H}_5, \\
& \quad R^2 = \text{OCH(} \text{CH}_3\text{)OC}_2\text{H}_5 \\
23 & \quad R^1, R^2 = \text{H} \\
62 & \quad R^1, R^2 = \text{H}
\end{align*}
\]

A well-known method of preparing α,β-unsaturated ketones involves reduction of an enol ether of a β-diketone followed by acid-catalysed hydrolysis and rearrangement of the resulting hydroxy enol ether.⁶⁹

This procedure has been used by Sih's group to prepare cyclopent-2-enones for syntheses of prostaglandins E₁⁷⁰ and E₂⁷¹. Application to β-diketone 47 (Scheme 2), for instance via isopropyl enol ether 50, leads to enone 51, and hence via conjugate addition reactions to prostaglandin analogues such as 52 and 53 containing sulphur in a six-membered ring.
COMPARISON OF THE TWO APPROACHES

Of the two approaches to prostaglandin analogues outlined above, the second has several advantages over the first.

1. It has fewer stages; assuming that the reagents for forming the lower side-chain are available, the construction of analogue 23 involves eight steps, as opposed to eleven in the first approach.

2. Five- or six-membered rings are derived from a common intermediate.

3. A wide range of organocopper reagents can be prepared, allowing modifications to the lower side-chain to be readily made. For example, prostaglandin analogues having a 13-cis double bond can be obtained simply by starting with a cis-alkenyl iodide. This would not be possible in the first approach as outlined above, since the phosphonate modification of the Wittig reaction may be depended on to give trans olefins; it would be necessary to resort to the use of an alkylidene triphenylphosphorane as Wittig reagent. The stereochemical outcome would be less certain than with the organocopper method, and would depend on the choice of reaction conditions; the formation of a cis olefin is more probable in the absence of an alpha stabilising group (the preferential formation of cis olefins has been observed in Wittig reactions conducted in dimethylsulphoxide).

4. In the second approach, the stereochemistry at the asymmetric centre C-15 may be controlled by using an organocopper reagent derived from a resolved alkenyl halide. The Wittig-type reagent 31 used in the first approach cannot be adapted to achieve this since resonance stabilisation of the phosphonate anion by the carbonyl group is essential. This difficulty could by overcome by using an alkylidene triphenylphosphorane, but the geometry of the newly-formed double bond would be less certain (a reagent of this type, the resolved \( \beta \)-oxido ylid 63, has been employed in syntheses of prostaglandins \( F_{3\alpha} \) and \( E_3 \)).
Potential difficulties can be anticipated in both routes leading to five-membered ring compounds. In Scheme 1, it is assumed that Dieckmann cyclisation of ester 33 proceeds in the desired direction to give 34 rather than its isomer 64, in which the wrong position is activated for addition of the upper side-chain by alkylation.

In Scheme 2, the chlorination of diketone 47 might be complicated by the presence of the sulphur atom; the oxidation of thianes to their sulphoxides has been accomplished using tert-butyl hypochlorite at -78°C.78,79,80 The conjugate addition stage might be hampered by enolisation of thiolenone 48 to its thiophene form 65; studies of the tautomerism of various 3-oxothiolanes have demonstrated a substantial degree of enolisation, varying with the nature and arrangement of substituents.81-85 They are also prone to deterioration, especially via atmospheric oxidation.81
The results of experiments conducted in the context of the first synthetic approach outlined above (Scheme 1) were not very promising. Compounds 32, 33, 34 and 35 were prepared, but the yields of the last three were not good.

Most of the work on the second approach (Scheme 2) was directed towards the title compounds of this thesis, thianone analogues of prostaglandins, in order to avoid the complications anticipated in the synthesis of enone 48, the proposed precursor of five-membered ring analogues. This route was shown to be workable, the six-membered enone 51 being prepared in 9.5% overall yield from thian-3,5-dione 46 by the sequence indicated in Scheme 2. The enone was used to prepare racemic 11,15-dideoxy-11α-homo-11-thiaprostaglandin E\textsubscript{1} via its ethyl ester. Samples of the enone sent to Miles Prostaglandin Laboratories, Madison, Wisconsin, were converted to 11-deoxy-11α-homo-11-thiaprostaglandin E\textsubscript{1} (52) and its 8,12-diasterioisomer by Drs W.D. Woessner and G.P. Peruzotti, using an organocopper(I) reagent derived from vinyl lithium 58.

![Chemical Structure](image)

Useful information regarding the synthesis of five-membered cyclic enones was obtained from model experiments. In particular, it was found that the acetylenic linkage in compounds of type 54 considerably activated the molecule to electrophilic chlorination. Application of the chlorination reaction to dione 47 was hampered by attack at sulphur, as had been feared. This led to chlorination alpha to sulphur rather
than sulphotoxidation, a novel reaction; such behaviour is more typical of sulphotoxides than of sulphides. Some suggestions for modification of the approach to five-membered cyclic enones are set out at the end of the last results section.
Dieckmann condensations are base-promoted intramolecular acylations in which dicarboxylic esters are converted to cyclic $\beta$-keto esters. The employment of this condensation in organic synthesis has been reviewed by Schaefer and Bloomfield. Scheme 3 illustrates the mechanism of the process. Removal of a proton alpha to one of the carbonyl groups of the diester 66 by the action of the base gives enolate anion 67. Intramolecular nucleophilic attack by the anion on the other carbonyl group results in ring-closure to anion 68, from which the product 69 is formed by elimination of alkoxide ion. Provided it has an alpha hydrogen atom, the product is converted entirely to the resonance-stabilised enolate anion 70; it is therefore necessary to use at least one equivalent of the base to effect complete conversion. The electrically neutral cyclisation product 69 is obtained by acidification of the reaction mixture.

The formation of enolate 70 displaces all the equilibria in Scheme 3 to the right, so it is possible to achieve cyclisation using relatively weak bases such as methoxide and ethoxide. If neither ester function has an alpha methylene group this driving force is absent, and cyclisation proceeds only in the presence of a powerful base, if at all. For instance, treatment of diester 71 with triphenylmethylsodium gave only the decarboxylated product 72 in low yield; no cyclisation product was obtained from diester 73, which instead underwent a reverse Michael reaction, the thiol 74 being isolated.
In the case of an unsymmetric diester two products are possible since the initial proton abstraction may occur alpha to either ester group, unless only one of the possible products is capable of forming an enolate 70. Thus the cyclisation of sulphides of type 75 may lead to 4-carbalkoxythiolan-3-ones 76 or the 2-carbalkoxy isomers 77. Some examples of such reactions which have been reported in the literature are summarised in Table 1.

Keto-esters 76 give stable ferric enolates on treatment with ferric chloride, which are typically intense red in colour. The isomers 77 usually give a blue or green enolate; however, the colour fades because they are readily oxidised by ferric ion to dimers 78. Thus the ratio of the Dieckmann reaction products may generally be determined by titration against ferric chloride, the end-point being indicated by a permanent red colouration.

\[
\begin{align*}
R^2 & \quad \text{(R = H, CH}_3 \text{ or C}_6\text{H}_5) \\
X & = \text{CO}_2\text{R}^1 \\
78 & \\
\end{align*}
\]

The results in Table 1 are encouraging since for most of the reactions conducted in benzene or toluene at relatively high temperatures (80-120\(^{\circ}\)), ring-closure in the direction desirable for the cyclisation stage of Scheme 1 was favoured, the only exception being the example with the relatively bulky substituent \(R^2 = -(\text{CH}_2)_4\text{CO}_2\text{CH}_3\). At lower temperatures, ring-closure in the undesired direction predominated \((R^2 = \text{H, CH}_3 \text{ or C}_6\text{H}_5)\), perhaps because less activation energy is required to abstract
<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Solvent</th>
<th>Temperature</th>
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<td>$\text{CH}_3$</td>
<td>$\text{H}$</td>
<td>methanol</td>
<td>$0^\circ$</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{H}$</td>
<td>diethyl ether</td>
<td>$0^\circ$</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{H}$</td>
<td>diethyl ether</td>
<td>room temperature</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{H}$</td>
<td>diethyl ether</td>
<td>$35^\circ$</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{H}$</td>
<td>toluene</td>
<td>$80 - 120^\circ$</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{H}$</td>
<td>toluene</td>
<td>$110^\circ$</td>
</tr>
<tr>
<td>$\text{C}_2\text{H}_5$</td>
<td>$\text{H}$</td>
<td>benzene</td>
<td>$80^\circ$</td>
</tr>
<tr>
<td>$\text{C}_2\text{H}_5$</td>
<td>$\text{H}$</td>
<td>benzene</td>
<td>$80^\circ$</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>$-(\text{CH}_2)_4\text{CO}_2\text{CH}_3$</td>
<td>toluene</td>
<td>$100^\circ$</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{CH}_2\text{CO}_2\text{CH}_3$</td>
<td>toluene</td>
<td>$100^\circ$</td>
</tr>
<tr>
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<td>$\text{CO}_2\text{CH}_3$</td>
<td>benzene</td>
<td>$80^\circ$</td>
</tr>
<tr>
<td>$\text{C}_2\text{H}_5$</td>
<td>$\text{C}_6\text{H}_5$</td>
<td>diethyl ether</td>
<td>room temperature</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{C}_6\text{H}_5$</td>
<td>benzene</td>
<td>$40^\circ$</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{C}_6\text{H}_5$</td>
<td>toluene</td>
<td>$110^\circ$</td>
</tr>
<tr>
<td>$\text{CH}_3$</td>
<td>$\text{CH}_3$</td>
<td>benzene</td>
<td>$40^\circ$</td>
</tr>
<tr>
<td>$\text{C}_2\text{H}_5$</td>
<td>$\text{CH}_3$</td>
<td>diethyl ether</td>
<td>room temperature</td>
</tr>
<tr>
<td>$\text{C}_2\text{H}_5$</td>
<td>$\text{CH}_3$</td>
<td>toluene</td>
<td>$100^\circ$</td>
</tr>
</tbody>
</table>
a proton alpha to sulphur than to carbon. Another factor affecting the product ratio could be the relative solubilities of the two enolates, since the precipitation of a particular enolate would displace the overall equilibrium in its favour. This effect may have contributed to the anomalous result in the case where \( R^2 \) was \((\text{CH}_2)_4\text{CO}_2\text{CH}_3\). In this example the majority of the sodium enolate was precipitated; acidification of the solid led to a 61% yield of keto-ester which was 97% oxidisable by ferric chloride, whereas the toluene-soluble fraction of the enolate gave a 13% yield of 45% oxidisable material.

The starting materials for the Dieckmann cyclisation leading to caralkoxythiolan-3-ones may conveniently be prepared by Michael addition of thioglycollate 79 to the appropriate \( \alpha,\beta \)-unsaturated ester 80, using a catalytic quantity of base. Alternatively, the Michael and Dieckmann reactions may be performed in one process by adding first the thiol and then the alkene to a suspension of at least one equivalent of base in the reaction solvent. A modification of this method has been described 99 in which thioglycollate is added to a solution of sodium alkoxide in alcohol and the alcohol distilled out, giving sodium salt 81 free of alcohol. The salt is then dissolved in dimethysulphoxide and treated with the alkene at room temperature. The Michael reaction gives the anion leading to ring closure in the desired direction, 82.
In dimethylsulphoxide the rate of ring-closure may be competitive with that of isomerisation to the alternate anion 83, since dipolar aprotic solvents enhance the reactivity of anions. Ring-closure in the desired direction may therefore be obtainable without resort to high temperatures.

In the original report, the reaction of methyl thioglycollate and methyl acrylate was said to give keto ester 76 (R\(^1\) = CH\(_3\), R\(^2\) = H) rather than 77 (R\(^1\) = CH\(_3\), R\(^2\) = H), although no evidence was presented for this. However the method has recently been used with great success to prepare nitrile 84 from ethyl thioglycollate and ethyl
The keto-enol tautomerism of compounds of type 76 and 77 has been investigated by infra-red spectroscopy. The samples of 4-carbomethoxy-thiolan-3-one (85), an approximately 1:3 mixture of 85 and its 2-carbomethoxy isomer 86 (prepared as in reference 89) and 2-carbomethoxy-4-methylthiolan-3-one (87) were studied; comparisons were made with 2-carbomethoxycyclopentanone (88) and the corresponding ethyl ester 89.

[Chemical structures and reactions diagrams]
In the 1800-1600 cm$^{-1}$ region, the spectra of the 2-carbomethoxy compound 87 (liquid film, carbon tetrachloride or isobutanol solution) strongly resembled those of the carbocyclic compounds 88 and 89, and showed a low degree of enolisation (87: $\nu_{\text{max}}$ (CCl$_4$) 1754s (ketone CO), 1738s (ester CO), 1658w (chelated CO of enol tautomer) and 1604 cm$^{-1}$. (C=C of enol tautomer)). On the other hand, the 4-carbomethoxy compound 85 (a low-melting solid) was found to be completely enolised in a mineral oil mull, and contained only small amounts of the keto form in other media (more in isobutanol than in carbon tetrachloride or a liquid film; $\nu_{\text{max}}$ (CCl$_4$) 1755w, 1735w, 1674s and 1630s cm$^{-1}$). Acidification of the carbon tetrachloride solutions with hydrogen chloride increased the degree of enolisation of 87, but decreased it in 85. The behaviour of the mixture of 85 and 86 was intermediate between that of 85 and 87, indicating that 86 strongly resembled 87. The extent of enolisation could also be correlated with the intensity of the broad band at 3400-3080 cm$^{-1}$ (hydrogen-bonded OH).

RESULTS

As a model study for the preparation of the intermediate 34 required for the synthetic route in Scheme 1, the preparation of the known compound 90 was investigated.
The precursor of 90, diester 91, was prepared by Michael addition of methyl thioglycollate to ethyl hex-2-enoate, either as a separate stage using "Triton B" (benzyltrimethylammonium hydroxide) as base catalyst or in situ with the Dieckmann condensation.

\[
\text{CH}_3\text{O}_2\text{C} \quad \text{CO}_2\text{C}_2\text{H}_5 \quad \text{CH}_3\text{O}_2\text{C} \quad \text{CO}_2\text{C}_2\text{H}_5
\]

Cyclisations of diester 91 were carried out using sodium ethoxide in ether at room temperature (method A), and sodium methoxide in refluxing benzene (method B). The direct process was performed with sodium ethoxide in benzene as in reference 92 (method C). Finally, ethyl hex-2-enoate was treated with the S-sodio derivative of methyl thioglycollate in dimethylsulphoxide at room temperature \(^{99}\) (method D). The products were purified by distillation. The overall yields from ethyl hex-2-enoate (calculated on the molecular weight of the desired product 90) were A 48%, B 22%, C 35%, and D 56%; that is, at a given temperature the direct preparation was more efficient, and better yields were obtained at room temperature than at 80°.

Products B, C and D gave infra-red spectra (liquid film) closely resembling that of the unsubstituted compound \(^{85}\) \(^{101}\) (3100br, 1755s, 1735s, 1660 and 1620 cm\(^{-1}\)) indicating a substantial degree of enolisation. For product A the bands corresponding to the enol form were relatively weak. In their proton nuclear magnetic resonance spectra (deuteriochloroform), products C and D showed a pair of hydroxyl signals at \(\tau\) -1.2 and -0.5 of combined intensity 0.15 (C)
and 0.23H (D), whereas product A gave no detectable enol signal, in agreement with the infra-red results. The absence of enol tautomers in product A resulted in it having a relatively simple proton nuclear magnetic resonance spectrum, which was consistent with structure 90.

The four products were analysed by gas-liquid chromatography on UCW 98, using a temperature program of 120-180° at 3 deg/min. In each case two components were observed, of approximate retention times 9 and 10 min. The ratio of the areas of the peaks at 9 and 10 min was between 30:70 and 25:75 in all samples except product B, when it rose to 75:25. In the distillations of products B, C and D the distillate was arbitrarily divided into two fractions; the higher-boiling fractions had slightly more of the component of longer retention time, and slightly less enol character as judged by their infra-red spectra. The extent of enolisation did not correlate with the chromatographic results however, since these would require product B to be the least enolised, and not product A as was actually observed. Two other explanations for the presence of two components may be suggested: Dieckmann cyclisation partially in the undesired direction, and cis-trans isomerism of the carbethoxy and propyl groups with respect to the five-membered ring. The first of these is inconsistent with the proton nuclear magnetic resonance spectrum of product A, and the satisfactory elemental analysis of product C, since the alternative cyclisation product would be methyl ester 92 rather than an ethyl ester; it is also contradictory to literature reports that the desired direction of ring-closure is favoured by the use of higher reaction temperatures. 89, 90,96

Additional evidence against the presence of the unwanted keto ester 92 was obtained by treating a sample of product A with ferric chloride
until a permanent red-violet colouration was obtained. The resulting mixture was worked-up by extraction with benzene. Despite an apparently significant uptake of ferric chloride, gas-liquid chromatography of the product showed that neither component had been oxidised.

\[
\begin{align*}
\text{CH}_3\text{O}_2\text{C} & \quad \text{S} \\
& \quad \text{n-C}_3\text{H}_7
\end{align*}
\]

Ethyl 4-bromocrotonate 93 was prepared in 73% yield by allylic bromination of ethyl crotonate with N-bromosuccinimide in refluxing carbon tetrachloride, in the presence of dibenzoyl peroxide. In a literature preparation, bromoester 93 was converted to ethyl 4-acetoxy crotonate (32) in 74% yield, by refluxing 12h with potassium acetate in glacial acetic acid. An attempt to repeat this procedure gave after 15½h reflux only a 54% yield, and gas-liquid chromatography of the product indicated the presence of about 20% unchanged bromoester. This result was apparently not due to insufficient exclusion of moisture from the reaction mixture, because no further conversion of the bromo ester occurred on refluxing the product for 5h with potassium acetate in acetic acid containing 10% acetic anhydride. In another attempt to prepare acetate 32, the literature procedure was repeated using sodium acetate in place of potassium acetate. A lower yield (40%) resulted, but the product was relatively free of unchanged bromocrotonate. The apparent retardation of the metathesis by acetic anhydride prompted an experiment in which acetic acid containing 1% water was used as solvent, again with sodium acetate.
After 16h reflux a 57% yield of pure acetate 32 was achieved. The course of the reaction was investigated by gas-liquid chromatography; it was evidently accelerated by water since consumption of the bromoester was complete in 1h. Shortening the reaction period to this time raised the yield to the literature value of 74%.

The results of reactions of methyl and ethyl thioglycollate with acetate 32 under basic conditions are summarised in Table 2. The initial aim of these experiments was to prepare keto-ester 34 directly since this approach had given better yields of the model compound 90. However, complex mixtures were generally obtained, and the only product which could be isolated in useful yield was the Michael adduct 33 or 94.

In the first two runs, method D of the model experiments was used. The main product, 33, was identified by its n.m.r. spectrum. The formation of diethyl ester 33 rather than mixed ester 79 showed that alkyl exchange had occurred when methyl thioglycollate was exposed to ethanolic sodium ethoxide. In run 2, the cyclisation product 34 could
Methyl thioglycollate was treated with ethanolic sodium ethoxide, alcohol was removed, dimethylsulphoxide and alkene \(32\) added.

This product was contaminated with Michael adduct \(33\); yield corrected in accordance.

This product was not distilled.

### TABLE 2

<table>
<thead>
<tr>
<th>RUN</th>
<th>R</th>
<th>BASE</th>
<th>SOLVENT</th>
<th>TEMPERATURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_3)</td>
<td>1 equivalent sodium ethoxide(^a)</td>
<td>dimethylsulphoxide</td>
<td>room</td>
</tr>
<tr>
<td>2</td>
<td>CH(_3)</td>
<td>1 equivalent sodium ethoxide(^a)</td>
<td>dimethylsulphoxide</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CH(_3)</td>
<td>trace of &quot;Triton B&quot;</td>
<td>benzene</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CH(_3)</td>
<td>0.05 equivalents sodium ethoxide</td>
<td>1,4-dioxan</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>C(_2)H(_5)</td>
<td>1 equivalent sodium ethoxide</td>
<td>benzene</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>C(_2)H(_5)</td>
<td>1.4 equivalents sodium</td>
<td>toluene</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>C(_2)H(_5)</td>
<td>1.1 equivalents potassium tert-butoxide</td>
<td>toluene</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>C(_2)H(_5)</td>
<td>1 equivalent potassium tert-butoxide</td>
<td>benzene</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>C(_2)H(_5)</td>
<td>1 equivalent potassium tert-butoxide</td>
<td>benzene</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Methyl thioglycollate was treated with ethanolic sodium ethoxide, alcohol was removed, dimethylsulphoxide and alkene \(32\) added.
not be completely separated from the Michael adduct by distillation. Isolation of 34 from the best fraction via conversion to its copper(II) chelate was found to be inefficient, only about 10% of the amount estimated to be present by gas-liquid chromatography being recovered.

The Michael addition of methyl thioglycollate to ethyl 4-acetoxycrotonate required harsher conditions than the addition to ethyl hex-2-enoate used in the model experiments; "Triton B" (run 3) failed to promote the reaction, and even sodium ethoxide (run 4) was not a very effective catalyst.

In runs 5-9 the reaction mixtures were worked-up by pouring into water rather than acid, to separate the neutral from the acidic products, which were subsequently liberated by acidification of the aqueous phase. In titration against ferric chloride, the acidic product from run 5 gave a characteristic permanent red colour with the first drop, as expected for the desired keto-ester 34. In run 7, some of the solvent vapour was distilled out during the period of reflux, with a view to forcing the cyclisation by removing alcohols. Gas-liquid chromatographic analysis of the distillate by comparison with known mixtures indicated that approximately 0.8 equivalents of ethanol and 0.3 equivalents of tert-butanol were removed (in principle, one equivalent of each alcohol should be released by the formation of one equivalent of Dieckmann product as its enolate; some of the ethanol must therefore have been formed in side-reactions, in view of the yield of Michael adduct). Runs 8 and 9 were intended to provide Michael adduct so that its cyclisation could be studied as a separate reaction; they were essentially modifications of run 7. The results of the cyclisation study are presented in Table 3.
<table>
<thead>
<tr>
<th>RUN</th>
<th>BASE</th>
<th>SOLVENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>2 equivalents sodium ethoxide</td>
<td>xylene</td>
</tr>
<tr>
<td>11</td>
<td>1 equivalent sodium ethoxide</td>
<td>xylene</td>
</tr>
<tr>
<td>12</td>
<td>2 equivalents sodium hydride (oil dispersion)</td>
<td>toluene</td>
</tr>
<tr>
<td>13</td>
<td>2 equivalents sodium hydride (oil dispersion)</td>
<td>toluene</td>
</tr>
<tr>
<td>14</td>
<td>2 equivalents sodium hydride (oil dispersion)</td>
<td>toluene</td>
</tr>
<tr>
<td>15</td>
<td>2 equivalents sodium</td>
<td>toluene</td>
</tr>
<tr>
<td>16</td>
<td>2 equivalents sodium hydride (oil-free)</td>
<td>toluene</td>
</tr>
<tr>
<td>17</td>
<td>1 equivalent &quot;Proton Sponge&quot; (80)</td>
<td>toluene</td>
</tr>
<tr>
<td>18</td>
<td>1 equivalent &quot;Proton Sponge&quot; (80)</td>
<td>dimethylsulphoxide</td>
</tr>
</tbody>
</table>

a Reaction worked-up by pouring into water and subsequent acidification of
b Reaction worked-up by pouring into phosphate buffer (pH 6-7).
c Yield of distilled product.
In run 10 the reaction was worked-up after two equivalents of ethanol had been distilled out. The gas-liquid chromatographic analysis of the distillate indicated the presence of an unexpected component, and its infra-red spectrum had bands at 1754 and 1247 cm\(^{-1}\) in addition to those due to ethanol and xylene, suggesting that an aliphatic ester was present. The observations could be accounted for by the presence of 0.7 equivalents of ethyl acetate in the distillate, implying that the major side-reaction involved nucleophilic attack by ethoxide on the acetoxy function. In run 11 it was hoped to alleviate this problem by minimising the amount of ethoxide used, but without success. The non-nucleophilic base sodium hydride was therefore tried, so that the concentration of ethoxide ion in the reaction mixture would at least be low to start with, although its formation from ethanol liberated during the Dieckmann condensation could not be avoided. Two equivalents of hydride were used so that free ethanol would be removed from the reaction mixture without recourse to distillation, enabling a lower reaction temperature to be employed. The progress of the cyclisation was monitored by gas-liquid chromatography of acidified samples, and observation of hydrogen evolution. Hydrogen evolution did not begin immediately on mixing, and in some runs it was necessary to add a drop of ethanol to initiate the reaction. That is, the rate of condensation was negligible until a trace of ethoxide had been formed, implying that hydride itself was relatively ineffective in promoting cyclisation. Although gas-liquid chromatographs from run 12 prior to work-up were promising, the product, obtained by pouring the reaction mixture into water and subsequently acidifying the aqueous phase, was contaminated with several impurities; it therefore seemed desirable to avoid exposing the product to hydroxide ion. In later runs exposure to both alkali and strong acid was avoided by pouring the reaction mixtures into a phosphate buffer solution (pH 6-7); another possible advantage of this method of work-up was that any strongly acidic by-
products would be retained by the aqueous phase at the relatively high pH employed. The problem of separating the keto-ester from the Michael adduct 33 no longer arose, since the reactions were not worked-up until the latter has been completely consumed. However, in runs 13 and 14 separation of mineral oil (originating in the sodium hydride dispersion) from the product was troublesome. This problem was not overcome by changing the base to finely-divided sodium (run 15); in this case the consumption of 33 was relatively slow, despite the higher temperature employed, and none of the desired product 34 was obtained. The cyclisation was therefore repeated using oil-free sodium hydride (run 16). Initiation was more difficult than when the oil dispersion had been used, but the yield (17%) was as good. These conditions were the best found for the preparation of keto-ester 34 from sulphide 33.

Distillation of the products from runs 13, 14 and 16 gave, in addition to the desired keto-ester 34, a low-boiling component identified by its infra-red spectrum and gas-liquid chromatographic retention time as ethyl thioglycollate, in 5-10% yield. The occurrence of a retro-Michael reaction similar to that observed by Acheson et al 87 was therefore implied.

As an alternative to sodium hydride, "Proton Sponge" (1,8-bis-(dimethylamino)naphthalene, 95) was tried. This base is only very weakly

\[
\begin{array}{c}
\text{(CH}_3\text{)}_2\text{N} \\
\text{N(CH}_3\text{)}_2
\end{array}
\]

95
nucleophilic as a result of the steric crowding around the nitrogen atoms, but more strongly basic ($pK_a = 12.34$ in water) than ordinary aliphatic amines because the steric strain is very effectively relieved by protonation. Its base strength was evidently not sufficient to abstract a proton from sulphide however, since no reaction was observed in runs 17 and 18.

With a view to taking advantage of the weak nucleophilicity of the tert-butoxide ion, the Dieckmann ring-closure of tert-butyl ester was studied.

![Chemical structure](image)

To prepare thioglycollic acid was added to ethyl 4-acetoxycrotonate in the presence of potassium tert-butoxide to give acid, which could not be distilled owing to a strong tendency to decompose on heating. Esterification of the crude acid with excess isobutene and a catalytic amount of sulphuric acid gave ester in 40% overall yield from thioglycollic acid.

The attempts to convert tert-butyl ester to keto ester are summarised in Table 4. Sodium hydride was less effective than it had been for ring-closure of the diethyl ester; with two equivalents (run 19) a mixture of products was obtained, of which was a minor component. With one equivalent of sodium hydride (run 20) the reaction would not
<table>
<thead>
<tr>
<th>RUN</th>
<th>BASE</th>
<th>SOLVENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>2 equivalents sodium hydride</td>
<td>toluene</td>
</tr>
<tr>
<td>20</td>
<td>1 equivalent sodium hydride</td>
<td>toluene</td>
</tr>
<tr>
<td>21</td>
<td>1 equivalent sodamide</td>
<td>benzene</td>
</tr>
<tr>
<td>22</td>
<td>1.4 equivalents sodamide</td>
<td>toluene</td>
</tr>
</tbody>
</table>

\[ t-C_4H_9O_2C \xrightarrow{\text{O}_2C_2H_5} \xrightarrow{\%} \text{S} \text{O}_{\text{C}} \text{H}_3 \]

96

This product was contaminated with starting sulphide 81.

Yield after distillation.
go to completion, resulting in contamination of the product with unchanged starting material 96. When sodamide was used as the condensing base, initiation was much easier and shorter reaction times were needed. As with sodium hydride, one equivalent was found to be insufficient for complete conversion of the starting ester (run 21). In this experiment, the reaction mixture was kept at 70° for 6h after evolution of ammonia had ceased. Although gas-liquid chromatographs had indicated the formation of a significant amount of the desired product 34 during the period of ammonia evolution, most of it was evidently lost during the period of heating since the concentration in the crude reaction product was very low. In the course of the work-up a viscous, brown oil settled between the aqueous and benzene layers; it crystallised to give a light brown powder, m.p. 140° with decomposition. The infra-red spectrum (KBr) had a strong band at 1770 cm⁻¹ indicative of a 5-membered lactone ring. A possible explanation would be elimination of ethyl acetate from the desired product 34, which would lead to lactone 98.

\[ \text{\includegraphics[width=0.3\textwidth]{lactone.png}} \]

Increasing the amount of sodamide to 1.4 equivalents (run 22) resulted in complete consumption of the starting ester 96 during the period of ammonia evolution. The reaction was worked-up immediately, and the desired keto-ester 34 obtained in 18% yield. The slight improvement in comparison to the best yield obtained from diethyl ester 33 (17%) was more than outweighed by the relative inefficiency of the preparation of the tert-butyl ester 96. Moreover, ferric chloride titrations of the
products of runs 20 and 22 showed that in contrast to the cyclisation of diethyl ester \( \text{33} \), ring-closure of tert-butyl ester \( \text{96} \) occurred partly in the undesired direction, presumably giving 2-carbobutoxythiolanone \( \text{99} \). At first a violet colouration was produced, which slowly faded; at the end-point a permanent red colour was obtained. The mole ratios of desired to undesired products \( \text{34:99} \), calculated from the volumes of ferric chloride needed, were 50:50 for run 20 and 70:30 for run 22, that is a slight improvement had been obtained by increasing the reaction temperature, as expected from the literature (see page 27).
DISCUSSION

Factors Influencing the Rate and Site of Alkylation of Enolate Anions

(i) General considerations

Alkylation of carbonyl compounds under basic conditions involves bi-molecular nucleophilic displacement ($S_n$ mechanism) of a leaving group such as a halide ion from an alkylating agent, by the enolate anion of the substrate. In ambident anions such as enolates, more than one atom bears a significant proportion of the net charge as a result of resonance. In the enolates of simple ketones, the negative charge is distributed between the carbonyl oxygen and alpha carbon atoms (partial structures $\text{100}$ and $\text{101}$), and alkylation may therefore occur at either site. The majority of the charge is expected to reside on oxygen in accordance with its greater electronegativity, but for the same reason the oxygen atom is a much less reactive nucleophile than the carbon atom, and preferential C-alkylation may readily be achieved.

\[ \text{100} \quad \text{101} \]

If the equilibrium concentration of the enol tautomer of the substrate is relatively high, $\text{O}$-alkylation is more favourable. This effect is illustrated by $\beta$-keto esters (Scheme 4); alkylation can occur at the ketone oxygen and alpha carbon atoms. The correlation between propensity to $\text{O}$-alkylation and enol content is not surprising in view of the
structural similarity of the transition states (102, 103) and products (104, 105; R = alkyl) of O- and C-alkylation to the corresponding enol and keto tautomers of the substrate (104, 105; R = H). In comparison with simple ketones, the species involved in O-alkylation of β-keto esters are made more favourable by conjugation. Five- and six-membered cyclic β-keto esters are more prone to O-alkylation than the corresponding acyclic compounds. 110,111

Scheme 4

The ratio of C-:O-alkylation of enolate anions may be influenced by the reaction conditions, the nature of the counterion and solvent, and the structure and leaving group of the alkylating agent. 109,112 The paragraphs which follow describe hypotheses which rationalise the
influence of these factors and are therefore useful in choosing reaction conditions for a particular alkylation.

Considering an isolated enolate ion, for instance that of a β-keto ester, it is apparent that of the possible alkylation sites the oxygen atom is more exposed to an approaching alkylation agent than is the carbon atom. In practice the oxygen atom is shielded by association with cations (for example, by ion-pairing) and solvent molecules (solvation); the extent of C-alkylation therefore increases with the degree and strength of such association, but the overall rate of alkylation decreases since free anions are relatively reactive.

Brändström has suggested that for alkylation of metal enolates in which the cation is closely associated with the oxygen atom of the enolate, coordination of the alkylation agent to the metal could be an important factor. Such coordination would favour C-alkylation because close approach of the two carbon atoms involved would result in the formation of a six-membered ring (106), and the dipole of the alkylation agent would then be oriented so as to shift electron density onto the C-alkylation site.

Some of the effects on the C:-O-alkylation ratio are conveniently rationalised in terms of the principle of "hard" and "soft" Lewis acids.
and bases. The hardness of an acid or base depends on the nature of its acceptor or donor atom. A soft acid has an acceptor atom which is large, highly polarizable, of low positive charge, with easily excited outer electrons; the opposite characteristics result in a hard acid. Similarly, the donor atom of a soft base is usually large and highly polarisable, has low electronegativity and empty low-lying orbitals, and may easily be oxidised. According to the principle of hard and soft acids and bases, hard acids prefer to coordinate to hard bases, soft acids to soft bases; also useful is the concept of "symbiosis": a cluster of acid or base moieties of one kind around a single donor or acceptor atom is favourable compared to a combination of hard and soft moieties.

(ii) Temperature

The effect of reaction temperature on the C-:O-alkylation ratio cannot be predicted with certainty since it depends on opposing factors. For reactions subject to kinetic control, the ratio may be expected to decrease with increasing rate of dissociation of the metal enolate ion-pair, free enolate ions being particularly reactive to O-alkylation. If the enthalpy of activation of ion-pair dissociation is positive, higher temperatures favour O-alkylation; this is apparently the case when ethyl acetoacetate and cyclic 6-keto esters are alkylated in dimethylsulphoxide. In contrast, O-alkylation of ethyl acetoacetate in N-methylpyrrolidone is favoured by lower temperatures, illustrating the point that the effect of temperature cannot be predicted with certainty. For kinetically-controlled alkylations conducted in ether solvents, higher temperatures should favour C-alkylation (the dissociation of fluorenylsodium in tetrahydrofuran is exothermic).
(iii) Concentration

High concentrations of enolate should promote C-alkylation since dissociation increases with dilution. According to Brändström,\textsuperscript{114} C-alkylation should also be favoured by a high concentration of the alkylating agent, since it would then compete more effectively with the solvent for coordination sites on the metal.

(iv) Cation

The tendency of a cation to associate with the oxygen atom of an enolate increases with its hardness as a Lewis acid, \( O^- \) being a hard base. This explains why the overall rate of alkylation rises\textsuperscript{117} and the C:O-alkylation ratio usually falls\textsuperscript{109,112} in the series of cations \( Li^+, Na^+, K^+, R_4N^+ \). The order is occasionally reversed with respect to the site of alkylation, perhaps when coordination of the alkylating agent to the cation is the overriding factor;\textsuperscript{114} the alkylating agent is a soft Lewis acid since the acceptor atom is carbon. Since the hardness of a Lewis acid increases with the positive charge on the acceptor atom, multiply-charged cations such as \( Mg^{2+} \) and \( Zn^{2+} \) form enolates in which the metal and oxygen atoms are very tightly associated, and may even be regarded as covalently bound. Such cations therefore promote C-alkylation, but their usefulness is limited by the much lower reactivity of their enolates.\textsuperscript{109}

Cation-oxygen association is tightest in the solid metal enolate; in the crystal lattice, each oxygen atom may be linked to several metal atoms. Heterogeneous conditions therefore favour C-alkylation, but overall reaction rates are particularly low because interaction with the alkylating agent occurs only at the liquid-solid interface.
(v) Solvent

The nature of the solvent can have a pronounced effect on the \( \text{C-:O-alkylation ratio} \). In non-polar solvents the extent of ion-pair dissociation is low, favouring \( \text{C-alkylation} \). Polar, protic solvents (good hydrogen-bond donors) such as methanol encourage ion-pair dissociation and therefore increase the overall rate of alkylation. The solvent molecules become strongly attached to the enolate oxygen atoms by hydrogen-bonding (a hard acid - hard base interaction) \(^{115}\) so that \( \text{C-alkylation} \) is favoured. \(^{118}\)

Dipolar, aprotic solvents encourage ion-pair dissociation; they solvate cations much more strongly than anions, causing a high concentration of free enolate ions. The effect of these solvents on alkylation is therefore to increase the rate and decrease the \( \text{C-:O-alkylation ratio} \). Most of these solvents fall into two structural classes: polyethers, and those containing doubly-bound oxygen.

The polyethers, such as 1,2-dimethoxyethane and "diglyme" (diethylene glycol dimethyl ether) solvate cations by acting as polydentate ligands, \(^{119}\) their effectiveness generally increasing with the number of ether linkages. Macrocyclic polyethers \(^{119,120}\) ("crown ethers") are particularly effective since they can completely envelope a cation, provided the size of the macrocyclic ring and the ion are compatible; the resulting complexes are much more stable to dissociation by solvents than those of acyclic polyethers. The stoichiometric amount of a crown ether needed to complex the cations can therefore be very effective even in the presence of an ordinary solvent, so these ligands (many of which are solids at ordinary temperatures) are normally used as additives rather than as solvents themselves.
The effect of a slight excess of added crown ether on the alkylation of the sodium, potassium and caesium enolates of ethyl acetoacetate with ethyl p-toluenesulphonate in various solvents has been studied by Kurts and co-workers. The C-Oalkylation ratio was reduced in all the solvents studied, the effect being spectacular for non-polar solvents (a more than hundredfold decrease in benzene), intermediate for ethanol, and slight in powerful dipolar aprotic solvents, in which specific cation solvation has already occurred to a large extent. This paper has been misquoted in recent advertisements for commercially available crown ethers, which state that "The alkylation of acetoacetic ester enolates gives less O-alkylated product in the presence of a crown ether especially in weakly polar solvents".

Examples of the second main class of dipolar aprotic solvents include acetone, dimethylsulphoxide, N,N-dimethylformamide, N-methylpyrololidone and hexamethylphosphoramide. These are strong Lewis bases because the oxygen atom, at the negative end of the dipole, is sterically unhindered and highly charged, resulting in strong solvation of cations. The positive end of the dipole is sterically hindered and as a Lewis acid is soft, especially in comparison with the hydroxyl hydrogen of methanol for instance. Solvent - enolate oxygen interactions analogous to hydrogen-bonding are therefore insignificant, so the anions are left relatively free. The extent of O-alkylation of enolates has been correlated with the Lewis basicity of dipolar aprotic solvents; it increases in the series tetrahydrofuran < acetone < 1,2-dimethoxyethane < dimethylformamide < dimethylsulphoxide < dimethylacetamide < N-methylpyrololidone < hexamethylphosphoramide.

Hexamethylphosphoramide \textsuperscript{123} (107) is a particularly good example. The existence of four ionic, mesomeric forms gives rise to a very high
negative charge on the oxygen atom, and the steric crowding and diffusion of positive charge around the N-P system results in a particularly low affinity for anions. The effect of the nature of the cation on alkylations of enolates conducted in this solvent is negligible, suggesting that ion-pair dissociation is virtually complete,\textsuperscript{113} whereas in similar solvents of lower Lewis base strength, such as dimethylsulphoxide, the usual cation effect is observed.

\[
\begin{align*}
\ce{\text{N-P=O}} & \quad \text{\leftrightarrow} \quad \ce{\text{N-P-O^-}} & \quad \text{\leftrightarrow} \quad \ce{\text{N^+P-O^-}} \\
\text{etc}
\end{align*}
\]

If it is assumed that for alkylations conducted in powerful dipolar, aprotic solvents the only significant mechanistic pathway is alkylation of completely free enolate anions, it follows that the presence of a crown ether in such systems would cause the C-O-alkylation ratio to be virtually independent of which solvent was used. In fact small but significant differences are observed, and the ability of dipolar, aprotic solvents to promote C-alkylation correlates with their ability to solvate "hard" anions (chloride, acetate) rather than their ability to promote C-alkylation in the absence of a crown ether. These results led to the cautious suggestion \textsuperscript{121} that the more electrophilic of the solvents indulge in weak, specific solvation of the "hard" oxygen centres of enolate anions analogous to the strong solvation by hydrogen-bonding encountered in alcohols.
(vi) Pressure

Increasing the pressure under which an alkylation is conducted should result in a greater extent of solvation, since this process is normally accompanied by an overall decrease in volume. Pressure may therefore influence the \( C:O \)-alkylation ratio of enolates when it is strongly dependent on the degree of association of the anion with the solvent, as when a protic solvent is used. This accounts for the increased yields of \( C \)-alkylation products obtained from reactions of sodium phenoxide with allyl chloride in water or methanol\(^{124}\), and with benzyl chloride in phenol\(^{125}\), when conducted under pressures of thousands of atmospheres. In contrast, the \( C:O \)-alkylation ratios for alkylation of phenoxide in 1,2-dimethoxyethane\(^{124}\), and ethylation of ethyl acetoacetate or pentan-1,3-dione sodium salts in dimethylsulphoxide\(^{125}\) are unaffected by increased pressure, in accordance with the view that solvation of enolate oxygen is weak in dipolar aprotic solvents.

(vii) Alkylating Agent

The course of alkylation of ambident anions is often influenced by the nature of the alkyl and leaving groups of the alkylating agent. Increasing the chain length or degree of branching of the alkyl group decreases the \( C:O \)-alkylation ratio; for example, the ratio observed in alkylation of sodium ethyl acetoacetate falls along the series methyl \( \lt \) ethyl \( \lt \) n-propyl \( \lt \) \( N \)-butyl \( \lt \) i-butyl \( \lt \) cyclopentyl \( \lt \) s-butyl \( \lt \) i-propyl\(^{126}\). This effect is generally attributed to the greater steric requirement of \( C \)-alkylation; it has also been pointed out that the hardness of a carbonium ion as a Lewis acid increases in the same way\(^{115}\), so the steric effect is reinforced by increased preference for the harder alkylation site (oxygen). Carbonium ion hardness is reduced by the presence of \( \alpha,\beta \) unsaturation, which permits diffusion of the positive
charge by resonance. Alkyl groups with α,β multiple bonds (for instance allyl, benzyl and propargyl) favour C-alkylation more than the corresponding saturated species,\textsuperscript{113} as would be expected.

The C-:O-alkylation ratio usually falls in the order of leaving groups I\textsuperscript{-} > Br\textsuperscript{-} > Cl\textsuperscript{-} > SO\textsubscript{2}OR \textsuperscript{2} > SO\textsubscript{2}Ar > ClO\textsubscript{4} > R\textsubscript{2}O.BF\textsubscript{4} \textsuperscript{-},\textsuperscript{109,112} that is with increasing Lewis base hardness. This effect is consistent with the concept of symbiosis; attachment of a soft base to the site of displacement encourages attack by the softer nucleophile, and so on.\textsuperscript{115,127}

The effect of the alkylating agent is conveniently summarised by the statement that the C-:O-alkylation ratio increases with its S\textsubscript{N2} reactivity.\textsuperscript{113,128}

Side reactions

A complication which sometimes arises when the compound to be alkylated has two relatively acidic protons is the occurrence of dialkylation; for instance, both C\textsubscript{5},C\textsubscript{5} and C\textsubscript{5},O-dialkylation of ethyl acetoacetate in hexamethylphosphoramide have been observed.\textsuperscript{113} Dialkylation is made possible by proton transfer from the mono-C-alkylated product to the starting enolate anion, so that for each mole of dialkylated product formed a mole of neutral substrate is released. The rate of proton transfer increases with the reactivity of the starting enolate and may thus be influenced by the choice of cation, solvent and reaction conditions; the process is reversible, so if conditions are such that equilibrium is attained it may be suppressed by using an excess of the neutral substrate.\textsuperscript{112}

A possibility to be considered in alkylation of α-substituted β-keto esters in hydroxylic solvents is base-catalysed cleavage analogous to
the attack by hydroxide ion mentioned in the Introduction (page 15) in the case of cyclic β-keto esters this amounts to a reverse Dieckmann reaction; in the presence of a small excess of base it becomes the predominant reaction pathway. Thus high yields of substituted adipic esters 108 have been obtained by the process shown in Scheme 5.129

**Scheme 5**

\[
\begin{align*}
&\text{RO}_2\text{C} - \text{CO}_2\text{R} \quad 1-2\text{Na} \\
&\text{toluene, 110°}
\end{align*}
\]

\[
\begin{align*}
&\text{R'Hal} \\
&\text{excess ROH}
\end{align*}
\]

\[
\begin{align*}
&\text{RO}_2\text{C} - \text{CO}_2\text{R} \\
&\text{overall yield: R'Hal = CH}_2\text{I, 89%;} \\
&\text{R'Hal = CH}_2\text{=CH-CH}_2\text{Br, 80%}.
\end{align*}
\]
In the Results section following this discussion, alkylations of the sodium enolate of the 4-carbethoxythiolan-3-one 34 with ethyl 7-bromoheptanoate will be described. As the reactivity of long-chain alkyl halides is not particularly high it was desirable to use a polar solvent. The desired product 35 would result from C-alkylation, which should be favoured by the use of a protic solvent such as methanol. However, the risk of loss of the desired product 35, if not 34 itself, by the cleavage process mentioned above was considered to be high, in view of the difficulties experienced in the preparation of 34 by Dieckmann cyclisation. It was therefore decided to use a dipolar aprotic solvent; 1,2-dimethoxyethane was chosen initially since it lies early in the series of decreasing C:-O-alkylation ratio.

\[
\begin{align*}
\text{34} & \quad \text{CO}_2\text{C}_2\text{H}_5 \\
\text{O} & \quad \text{COCH}_3 \\
\text{S} & \quad \text{CO}_2\text{C}_2\text{H}_5 \\
\text{O} & \quad \text{COCH}_3
\end{align*}
\]

A report describing a study of the ethylation of ethyl acetoacetate enolate in the same solvent subsequently appeared.\textsuperscript{130} Several different cations and leaving groups were tried. For the most part the C:-O-alkylation ratio followed the usual trends, decreasing in the series L\textsuperscript{+} > N\textsuperscript{+} > K\textsuperscript{+} > Cs\textsuperscript{+} > (n-C\textsubscript{4}H\textsubscript{9})\textsubscript{4}N\textsuperscript{+} and I\textsuperscript{-} > Br\textsuperscript{-} > S\textsubscript{O}_4\textsuperscript{2-} > p-O\textsubscript{2}C\textsubscript{6}H\textsubscript{4}SO\textsubscript{2}O\textsuperscript{-}. The exceptions were alkylations of the lithium enolate with ethyl p-toluenesulphonate and diethyl sulphate, when the ratio came between those of the potassium and caesium enolates; it was suggested that the departure of the leaving group in these cases was subject to electrophilic assistance by the lithium cation. With ethyl bromide or iodide, the lithium, sodium and potassium enolates were predominantly C-alkylated, the C:O ratios ranging from 41:1 to values greater than 100:1.
More recently, reactions of alkyl halides with 2-carbethoxycyclopentanone (89) and potassium carbonate in refluxing acetone have been shown to give good yields of C-alkylated products. In the prostaglandin field, the method has been applied to the preparation of diester by alkylation of 2-carbomethoxycyclopentanone (88) with methyl 7-bromo-heptanoate.

Alkylation of Thallium(I) Enolates

A report that the reactions of thallium(I) enolates of β-dicarbonyl compounds with alkyl iodides give mono-C-alkylated products quantitatively prompted a study of such reactions, with a view to applying the method to the alkylation stage in Scheme 1. Of particular relevance were the results reported for 2-carbethoxycyclopentanone (89) from which the 2-alkylated products were obtained with methyl, ethyl and isopropyl iodides in 100, 100 and 96% yields respectively. The reactions were conducted by refluxing the thallium enolates with an excess of the alkyl iodide, without added solvent, thus maximising the degree of heterogeneity and the concentration of the alkylation agent. Heterogeneous conditions were said to be essential for specificity. The structure of a representative thallium(I) enolate, that of pentan-1,3-dione, was determined by X-ray crystallography; it is a polymeric chain in which chelate units are joined by thallium-oxygen linkages,
the metal atoms being tetracoordinate. The units are arranged with the carbon backbones on the surface of the crystal, and it was suggested that the enolate oxygen atoms might therefore be completely shielded from the approach of an alkylating agent.

\[
\begin{align*}
&\text{R} = \text{CH}_3, \text{C}_2\text{H}_5 \text{ or } \\
&\qquad (\text{CH}_3)_2\text{CH}
\end{align*}
\]

Since the original report, some doubts as to the generality of the method have arisen. Hooz and Smith observed substantial O-alkylation of a β-keto sulphoxide (which would be expected to mimic the behaviour of β-diketones), even though its thallium salt was crystalline, leading them to repeat some of the original alkylations of acetylacetone and ethyl acetoacetate. In contrast to the earlier results, they obtained O-alkylation side-products using ethyl and isopropyl iodides (particularly the latter), and C,C-dialkylation with methyl and ethyl iodides.

In the field of sulphur heterocycles, the methylations of 3-thiolene-2-one (112)\textsuperscript{134}, whose anion 115 is tridentate, and of the 3- and 5-methyl derivatives (113\textsuperscript{134} and 114\textsuperscript{134,135} respectively) have been investigated; all form crystalline thallium(I) enolates. With methyl iodide, the predominant reaction was C-alkylation at position 3, accompanied by O-alkylation and 3,5-dialkylation. Mono-C-alkylation at position 5 was only significant for the 3-methyl compound 113. In the case of 112 3,3-dialkylation and 3,3,5-trialkylation occurred to a
small extent (each 1% of total products).

\[
\begin{align*}
R^1, R^2 &= H \\
R^1 &= CH_3, R^2 = H \\
R^1 &= H, R^2 = CH_3
\end{align*}
\]

In contrast to the results obtained with methyl iodide, alkylation of the thallium(I) enolate of 5-methyl-3-thiolene-2-one (113) with dimethyl sulphate gave the O-alkylated product 116 almost exclusively. The same effect was observed in methylations of the tetrabutylammonium enolate by the ion-pair extraction method in chloroform - water, and the sodium enolate in diethyl ether - ethanol, indicating that the preferred position of alkylation depended more on the nature of the alkylating agent than the cation.
In heterogeneous alkylations of crystalline thallium(I) enolates of five- and six-membered cyclic β-diketones, O-alkylation generally predominates, often to the exclusion of C-alkylation. These results are compatible with the hypothesis that exclusive C-alkylation of the thallium salts of acyclic β-dicarbonyl compounds is a consequence of their crystal structure; this must be different in the cyclic cases since chelate formation is ruled out geometrically. In addition, the potential C-alkylation site is shielded by the ring methylene groups, rather than exposed on the crystal surface. Significant levels of mono-C-alkylation of thallium(I) enolates of five- and six-membered cyclic β-diketones have only been obtained using alkylating agents whose nature favours C-alkylation, such as methyl iodide, allyl and benzyl bromides, 3-chloro-3,3-dimethylpropyne, and methyl 7-iodohept-5-ynoate.

RESULTS

Alkylations of the thallium(I) enolate derived from 2-carbethoxycyclopentanone (89) with benzyl bromide and ethyl 7-iodoheptanoate were performed to gain experience of the method and for comparison with alkylations of carbalkoxythiolanones. The enolate, a white solid m.p. 136°, was rapidly precipitated on addition of thallium(I) ethoxide to a solution of 2-carbethoxycyclopentanone in petroleum ether. After gentle heating overnight with an excess of benzyl bromide, removal of thallium(I) bromide by filtration and distillation of the filtrate, the C-benzylation product 117 was obtained in 92% yield. Its infra-red spectrum had bands at 1753 and 1728 cm\(^{-1}\) due to the carbonyl groups of the β-keto ester system, and none in the 1720 - 1600 cm\(^{-1}\) region, as would be expected for an O-alkylation product.
The alkylation with ethyl 7-iodoheptanoate was conducted in the same way; it also resulted in exclusive C-alkylation, the product 118 being obtained in 41% yield. The low yield value was largely due to loss on distillation.

Model alkylations of carbalkoxythiolanones 85, 99, 119, 95 and 90 with benzyl bromide were performed to assess the suitability of the method for the alkylation stage of Scheme 1.

No precipitate was formed on addition of thallium(I) ethoxide to a benzene solution of 85, but a grey solid was obtained on removal of the solvent. The solid was heated with benzyl bromide; gas-liquid chromatography of the reaction mixture indicated the formation of a single product, which was precipitated on addition of diethyl ether. It was isolated in 23% yield by recrystallisation, as a white solid.
m.p. 168-169°. Elemental analysis was correct for a monobenzylation product; the infra-red spectrum showed it to be an O-alkylation product, the only bands in the 1800 - 1600 cm$^{-1}$ region being at 1637 cm$^{-1}$ (chelated, $\alpha,\beta$-unsaturated C=O) and 1605 cm$^{-1}$ (C=C). This view was supported by the proton nuclear magnetic resonance spectrum: the benzyl methylene singlet appeared at $\tau$ 5.88 showing that it was attached to oxygen. However, the expected structure 120 was ruled out by the signals for the ring methylene groups, which were complex multiplets centred approximately at $\tau$ 6.9 and 7.85, characteristic of adjacent methylenes in a rigid system. These signals were accounted for by assigning structure 121 to the product, implying that the starting $\beta$-keto ester 85 had been substantially contaminated with its 2-carbomethoxy isomer 86. Titration of a sample of the starting material against ferric chloride revealed that the 2-carbomethoxy isomer was in fact the major component (73%). Considering the failure of the thallium(I) enolate to precipitate in this instance, it was possible that the O-alkylation had been facilitated by incomplete heterogeneity.
The thallium(I) enolate of 4,5-dicarbethoxythiolan-3-one was prepared by addition of saturated ethanolic thallium(I) ethoxide to an ethanol solution of 4,5-dicarbethoxythiolan-3-one (119; a sample gave a permanent red colouration with a drop of ferric chloride), conditions reported to be effective for the preparation of thallium(I) salts of purines. Despite the high dilution involved, the enolate so obtained was a dark, viscous oil. The enolate was treated with benzyl bromide at room temperature, ether was added, thallium(I) bromide was filtered off, and the filtrate was distilled giving an oily product in 40% yield. Its infra-red spectrum had a band for a five-membered ring ketone at 1768 cm\textsuperscript{-1}, and poorly resolved ester carbonyl bands at 1740 and 1722 cm\textsuperscript{-1}; there was no indication of the presence of an \textit{O}-alkylation product in the 1700 - 1600 cm\textsuperscript{-1} region. Gas-liquid chromatography showed the presence of three components in the product, in approximate ratio 10:40:50 (relative peak areas). The main components had similar retention times; the minor component was eluted much earlier. The retention time of the latter was slightly greater than that of authentic diethyl 2-(carbomethoxymethylthio)succinate 122, so it was probably the corresponding triethyl ester 123, formed by ring-opening of the starting \beta-keto ester 119 on attack by ethanolic thallium(I) ethoxide.

![Chemical Structure](Image)

- \(122 \quad R = \text{CH}_3\)
- \(123 \quad R = \text{C}_2\text{H}_5\)

Treatment of a benzene solution of 4-carbethoxy-5-propylthiolan-3-one (90, prepared by method D described in the section on Dieckmann cyclisations)
with thallium(I) ethoxide gave the enolate as a dark green precipitate m.p. 150-160°, in 70% yield. The solid was refluxed with benzyl bromide in tetrahydrofuran. Filtration and distillation of the filtrate gave an oily product, shown by gas-liquid chromatography to contain approximately equal amounts of two components, in 10% overall yield.

The disappointing results obtained from the benzylations of model thallium(I) enolates indicated that the advantages of thallium(I) as cation in alkylations of 2-carbalkoxycyclopentanone enolates did not extend to those of carbalkoxythiolanones. It was therefore decided to employ an alkali metal cation for the alkylation stage of Scheme 1, that is the conversion of thiolanone 34 to the C-alkylated derivative 35.

![Chemical Structures](image)

For the first attempt to prepare 35, the sodium enolate of 34 was treated with one equivalent of ethyl 7-bromoheptanoate in 1,2-dimethoxyethane (the reasons for this choice of solvent are mentioned on page 57). The enolate was generated by treating 34 (prepared by Dieckmann cyclisation of diethyl ester 33 with sodium hydride: Table 3, run 14) with sodium hydride. The progress of the alkylation was followed by monitoring the consumption of the bromoheptanoate by gas-liquid chromatography. Heating was found to be necessary, and the reaction was slow even at reflux temperature. After 90h at 70-80° consumption of the bromide
had virtually ceased; the reaction was worked-up by treatment with water and diethyl ether. Unchanged β-keto ester 34 (identified by its infra-red spectrum and gas-liquid chromatographic behaviour) was recovered in 25% yield by acidifying the aqueous phase to pH 6 with phosphate buffer. Distillation of the ether extract gave unchanged ethyl 7-bromoheptanoate (30% recovery) and alkylation product in 24% yield (calculated on the molecular weight of 35). The infra-red spectrum of the product included a strong, broad band at 1735 cm\(^{-1}\), and weak bands at 1662 and 1620 cm\(^{-1}\). Although the weak bands were in the region diagnostic of an O-alkylation product, it was more likely that they were due to the presence of a trace of the enol tautomer of 34. In any event, it was apparent from the absence of strong bands in this region that O-alkylation was not a major reaction path. Gas-liquid chromatographic analysis of the alkylation product indicated the presence of a small amount of ethyl 7-bromoheptanoate and two less volatile components in approximate ratio 80:20 (relative peak areas) in favour of the first to elute.

In a second attempt to prepare 35 the solvent was changed to diglyme (diethylene glycol dimethyl ether). Compared to 1,2-dimethoxyethane, diglyme should provide stronger specific cation solvation, since it has three ether linkages instead of two; this would enhance the reactivity of the enolate anion. Diglyme is also higher-boiling than 1,2-dimethoxyethane, permitting the use of higher reaction temperatures. It was hoped that these properties would enable the reaction to be taken to completion. The sodium enolate for this run was prepared in the same manner as the previous experiment, using 34 from run 16 of Table 3. After 24 hours reaction with ethyl 7-bromoheptanoate at 45-65°, gas-liquid chromatographic analysis of the alkylation mixture indicated the formation of products similar to those obtained in 1,2-dimethoxyethane. Consumption of the bromide was incomplete, so the temperature was
raised to 70-80° for 24 hours; two additional products of longer retention time were detected. Another 24 hours at 80-90° increased the amount of the products slightly without altering their ratio. Some ethyl 7-bromohexanoate still remained; it was not affected by heating the mixture to 100-120° for 160 hours. The reaction was worked-up by pouring into water, extraction with ether, and distillation of the ether extract. The product fraction (26% yield) was arbitrarily subdivided into three portions of different boiling range. These gave similar infra-red spectra, each having a strong, broad band at 1735 cm⁻¹ and no indication of O-alkylation. Gas-liquid chromatography showed that the four components detected in the course of the reaction were present in approximate overall ratio 60:15:10:15 in order of retention time, the proportion of the more strongly adsorbed components being greatest in the portion of highest boiling range. The lowest-boiling portion was apparently a fairly good sample of the main component; it contained small amounts (5-10%) of the second component and ethyl 7-bromohexanoate, and only traces of the two least volatile components. The proton nuclear magnetic resonance spectrum of this portion provided some evidence that the main component was the desired product 35. It had five signals assigned to the carbethoxyhexyl side-chain: a quadruplet at τ 5.93 (CO₂CH₂CH₃), a broad singlet at τ 8.6 ((CH₂)₄), and triplets at τ 8.80 (CO₂CH₂CH₃), 7.75 (CH₂CO₂C₂H₅) and 7.41 (CH₂(CH₂)₅CO₂C₂H₅). The chemical shift of this last signal confirmed that alkylation had not occurred at oxygen, for if it had, this triplet would have been at about τ 6.6, and the triplet splitting confirmed the attachment of this end-of-chain methylene to a fully substituted carbon atom, there being a methylene group on its other side. The signals due to the carbethoxy group directly attached to the ring (a triplet at τ 8.76 and a quadruplet at τ 5.86) were less intense (by about 30%) than those of the side-chain carbethoxy group. The methylene group of the thiolanone ring gave a singlet at τ 6.86,
and there was a smaller singlet nearby (τ 6.72) due to an impurity. The combined integrated intensity over these two signals was equal to that over either of the methylene signals at τ 7.75 and 7.41, and the ratio between them was about 7:4.

The triplet due to the ring methine proton, at τ 6.38, had half the combined intensity of the $\text{SCH}_2$ signals. It was therefore apparent that the impurity had the ring and long side-chain of 35, but lacked the carbethoxy group directly attached to the ring. The intensity of the acetate methyl signal (τ 8) was low by about 30%, being roughly equal to the combined intensities of the two $\text{SCH}_2$ signals.

A possible structure for the impurity would be lactone 124, since its presence in about 30% concentration would account for the above data. This explanation requires that the methylene protons of the thiolanone ring of 124 be accidentally equivalent, since this group would have little rotational freedom and would therefore be expected to give rise to an AB quartet. It should be noted that the acetate methyl signal comprised two singlets (τ 7.98 and 8.01), in approximate ratio 3:2.
This effect could have been due to the presence of two geometric isomers of 35, differing in the dispositions of the ring substituents; alternatively, the smaller singlet could have been due to the approximately 30% impurity, if it were decarboxylation product 125 instead of lactone 124. The latter explanation cannot account for the overall intensity of the acetate methyl signal and the multiplicity of the end-of-chain methylene signal at $\tau$ 7.41 however. The methylene signal for the acetoxyethyl substituent was completely hidden by the ester methylene quartets.

Support for the presence of lactone 124 was supplied by the infra-red spectrum, which had a weak band at 1780 cm$^{-1}$. 
In comparison with known carbalkoxythiolanones, including model compound 90, intermediate 34 was neither easily nor efficiently prepared via Michael addition of thioglycollate to an α,β-unsaturated ester and Dieckmann cyclisation of the resulting diester. Both steps required forcing conditions, especially the Michael addition. Attempts to perform the two steps in one preparative stage led to mixtures containing Michael adduct and cyclisation product, from which the latter could not be satisfactorily separated. Distillation was ineffective, isolation of 34 via its copper(II) chelate led to a poor recovery rate, and separation by virtue of its acidity was hampered by its sensitivity to aqueous alkali. The Michael addition therefore had to be performed as a separate stage; its yield was limited, probably because the forcing conditions that were required (one equivalent of a powerful base) encouraged side-reactions. The Dieckmann cyclisation was also complicated by side-reactions, including retro-Michael reaction of the precursor and attack by ethoxide on the acetoxyethyl group, which were demonstrated by the identification of their products ethyl thioglycollate and ethyl acetate. The attack of ethoxide on 34 could be followed by formation of lactone 98:

\[
\begin{align*}
\text{CH}_2\text{C}_2\text{H}_5 & \quad \text{O} \\
\text{C}_2\text{H}_5\text{O} & \quad \text{O} \\
\text{C}_2\text{H}_5\text{O} & \quad \text{O} \\
\text{C}_2\text{H}_5 & \quad \text{O} \\
\text{CH}_3 & \quad \text{O} \\
\end{align*}
\]
The problem of nucleophilic attack by ethoxide during the Dieckmann cyclisation was partially alleviated by the use of sodium hydride as the condensing base. In addition to its low nucleophilicity, this base offered the advantage of removal of ethanol without recourse to distillation, so the ring-closure could be forced to completion at lower temperatures. No further improvement resulted from changing the Dieckmann precursor to mixed ester 96, whose cyclisation to 34 would release tert-butoxide as opposed to ethoxide. The reasons for this failure were apparently that more vigorous conditions were necessary, encouraging side-reactions, and that cyclisation occurred partly in the wrong direction, so that some ethoxide was still formed.

The ability of the thallium(I) cation to promote exclusive C-alkylation
of 2-carbethoxycyclopentanone did not extend to the carbalkoxythiolanones studied. Their thallium(I) enolates were not formed as well-defined crystalline materials, and indeed were not always solids. Attempted alkylations of 4-carbalkoxythiolan-3-ones led to mixtures of products. 2-Carbomethoxythiolan-3-one was O-alkylated, despite the use of benzyl bromide, an alkylating agent known to promote C-alkylation.

The alkylation of the sodium enolate of β-keto ester 34 with ethyl 7-bromoheptanoate in polyether solvents gave mixtures of products, in which the desired C-alkylated compound 35 predominated. There were indications that O-alkylation was negligible; however, nucleophilic attack on the acetoxy methyl group analogous to that observed in the Dieckmann reaction was suspected to have occurred under the basic conditions employed, resulting in the formation of lactone 124. The alkylation reaction was slow, and did not give a good yield of 35, so there was a need to find better reaction conditions, particularly in respect of the solvent; also, the use of ethyl 7-iodoheptanoate as alkylating agent would be expected to improve the reaction rate. The low yields of the previous stages leading to β-keto ester 34 posed the problem of the supply of this material for a study of its alkylation. Further work on model compounds would be of limited value in view of the sensitivity of the acetoxy methyl group.

In summary, there seemed little hope of making routine use of the synthetic route proposed in Scheme 1 because of the low efficiency of three early stages: the Michael addition of ethyl thioglycollate to ethyl 4-acetoxy crotonate (32 + 33), the Dieckmann cyclisation of the Michael adduct (33 + 34), and the alkylation of the Dieckmann cyclisation product (34 + 35). A contributing reason for this inefficiency seemed to be the sensitivity of the heterocyclic system to the reaction conditions, a problem that seemed likely to apply
to later stages in the synthesis.

During the period in which the work on the first approach was conducted, reports appeared in the literature of the utility of 1,4-conjugate addition reactions of lithium alkenylcopper(I) reagents and their application to prostaglandin synthesis. The second approach described here was then devised and investigated.
Fehnel and Paul \(^{144}\) prepared thian-3,5-dione (46) by the intramolecular Claisen reaction of sulphide \(^{126}\). The Claisen reaction, a general method for the preparation of \(\beta\)-diketones, involves the acylation of a ketone by an ester under basic conditions. The processes involved in the ring-closure of \(^{126}\) are shown in Scheme 6.

**Scheme 6**

\[
\begin{align*}
\text{CH}_3\text{O}_2\text{C} & \quad \text{base} \\
\text{CH}_3\text{C} & \quad \text{CH}_3\text{O} \quad \text{CH}_3\text{O} \\
\text{S} & \quad \text{S}
\end{align*}
\]

\[126\]

\[
\begin{align*}
\text{CH}_3\text{O}_2\text{C} & \quad \text{CH}_3\text{C} \\
\text{CH}_3\text{O} & \quad \text{CH}_3\text{O} \\
\text{S} & \quad \text{S}
\end{align*}
\]

\[127\]
As in the Dieckmann condensation, the driving force of the Claisen reaction is the formation of the enolate anion of the product (127 in the case of thian-3,5-dione). In principle, the enolate can be separated from neutral materials such as unconverted keto ester if the reaction mixture is worked-up by treatment with water; the β-diketone is subsequently liberated by acidification of the aqueous phase. Cyclohexan-1,3-diones can be cleaved by aqueous alkali, the products being δ-keto acids, but prolonged heating is usually necessary, so cleavage should not be significant during work-up of Claisen products by the method outlined above.

Fehnel and Paul conducted the Claisen reaction of 126 in benzene at 60°, using sodium methoxide as base. Other applications of the Claisen reaction to the preparation of six-membered cyclic β-diketones reported in the literature include the ring-closures 128 → 129, 130 → 131, and 132 → 133. In the latter example, the reaction was worked-up by pouring into water and subsequent acidification of the aqueous phase.
The enol tautomers of cyclic β-diketones (for example 134) are intrinsically less stable than the keto forms (135), in contrast to acyclic β-diketones, whose enols are stabilised by intramolecular hydrogen-bonding. Nevertheless, in the presence of hydrogen-bond acceptors the enol content of cyclic β-diketones can be very high, since in comparison with the acyclic compounds they lose little rotational freedom on enolisation. In a study of cyclohexan-1,3-dione and its 5,5-dimethyl derivative (dimedone), Yogev and Mazur showed that in dilute chloroform and cyclohexane solutions the extent of enolisation is low, but rises with increasing concentration as hydrogen-bonding between enol molecules comes more into play, dimeric forms predominating.

For solutions in "nucleophilic" solvents (good hydrogen-bond acceptors) such as diethyl ether, acetone, N,N-dimethylformamide and dimethyl-sulphoxide, the extent of enolisation is very high and virtually independent of concentration. The ultra-violet spectra of such solutions are very similar to those of the corresponding alkyl enol ethers (136), having an intense π-π* absorption at about 245nm, log ε ca 4. This similarity also extends to ethanol solutions.150
Cyclic β-diketones possessing alpha hydrogen atoms are acidic, with acid dissociation constants approaching that of acetic acid; the enol forms are vinylogues of carboxylic acids. In basic media,\textsuperscript{150,151} and at high dilutions,\textsuperscript{151} the π→π* absorption maxima of cyclohexan-1,3-diones are shifted to higher wavelength (typically 280nm). Spectra run at a variety of pH values \textsuperscript{150} show a well-defined isosbestic point between the two extremes; the high-wavelength absorption is attributed to the enolate anion (137).

Fehnel and Paul \textsuperscript{144} reported that the ultra-violet spectroscopic behaviour of thian-3,5-dione is very similar to that of cyclohexan-1,3-diones. In ethanolic hydrogen chloride thian-3,5-dione gives a spectrum similar to that of its methyl enol ether (λ\textsubscript{max} 251nm, logε 4.06); in ethanolic sodium ethoxide the absorption maximum is shifted to 280nm. Thian-3,5-dione (pK\textsubscript{a} 4.34) is a slightly stronger acid than acetic acid (pK\textsubscript{a} 4.76).

The infra-red spectra of cyclic β-diketones may include bands due to both keto and enol tautomers. For instance, the bicyclic compound \textsuperscript{131,147} gives a split carbonyl band at 1700 cm\textsuperscript{-1} characteristic of a β-diketone, and a broad band at 1630 cm\textsuperscript{-1} due to the enol forms.
The precursor of thian-3,5-dione, the sulphide 126, was prepared using the method of Eehnel and Paul. Its infra-red and proton nuclear magnetic resonance spectra were compatible with the desired structure.

Attempts to induce ring-closure of 126 using sodium methoxide or commercially obtained potassium tert-butoxide at low temperatures (-1 - -5 °) gave unsatisfactory results. Yields of thian-3,5-dione were low, ranging from 10 - 30%. Reaction mixtures worked-up by treatment with aqueous acid gave products shown by gas-liquid chromatography to be contaminated with unchanged 126. The alternative method of work-up, treatment of the reaction mixture with water and subsequent acidification of the aqueous phase, was therefore adopted. Although they were free of 126, the products so obtained were still of low purity. For instance, a run employing sodium methoxide at -1° resulted in a 28% yield of yellow solid; the yield after recrystallisation of the crude product from benzene was 4%, the recrystallised material melting at 68-79 ° (lit. 80-81 °)

The use of sodium hydride as the condensing agent was tried; sufficient hydride was used to allow for removal of the methanol formed during the ring-closure, with a view to forcing the reaction to completion. Prolonged heating was found to be necessary for complete consumption of 126 however, and the products were plainly inferior, being dark and only partly crystalline.

When freshly prepared potassium tert-butoxide was used as base, consumption of 126 as monitored by gas-liquid chromatography was rapid and complete. The yield of the crude product was high, but thian-
3,5-dione was evidently a minor component (the product was an oil, and although its ultra-violet spectrum contained an absorption maximum at the correct wavelength, the molar extinction coefficient was only 22% of the literature value for thian-3,5-dione). Distillation of the crude product led to the isolation in 51% yield of keto acid 138 as a low-melting solid, identified by its infra-red, ultra-violet and proton nuclear magnetic resonance spectra, and elemental analysis. The melting point \(^{152,153}\) and ultra-violet \(^{152}\) and nuclear magnetic resonance \(^{154}\) data were in agreement with literature values. The nuclear magnetic resonance spectrum was similar to that of methyl ester \(^{126}\), with the expected difference that no \(\text{OCH}_3\) signal was present. The formation of acid 138 was interpreted as being the result of attack by potassium hydroxide on thian-3,5-dione on treatment of the reaction mixture with water (Scheme 7), indicating that thian-3,5-dione is much more sensitive to alkali than are cyclohexan-1,3-diones.

Scheme 7

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{HO} & \quad \text{O} \\
\text{S} & \quad \text{S} \\
\text{HO} & \quad \text{HO} \\
\end{align*}
\]

138
seemed that the sensitivity of thian-3,5-dione to potassium hydroxide was greater than to sodium hydroxide, so avoidance of potassium-containing bases was desirable. Experience with the Dieckmann ring-closure of tert-butyl ester \( \text{96} \) (page 42) suggested that sodamide might be superior to sodium hydride by permitting the use of shorter reaction times. This was found to be the case for the ring-closure of keto ester \( \text{126} \); reasonable yields (about 40\%) of thian-3,5-dione sufficiently pure for further synthetic processes were obtained routinely, using 2.4 equivalents of sodamide in benzene at \( 40^\circ \). The melting point and ultra-violet spectral data of the product were in agreement with the literature values.\(^\text{144}\) Its infra-red spectrum varied with the medium employed; in dilute carbon tetrachloride solution enolisation was negligible, the carbonyl groups giving rise to a strong, split band with maxima at 1741 and 1713 cm\(^{-1}\). A dilute chloroform solution gave a similar spectrum, with additional bands of low intensity at 3300 and 1600 cm\(^{-1}\) suggesting some enolisation. In potassium bromide the enol form was predominant (strong bands at 1590 and 1545 cm\(^{-1}\)). The proton nuclear magnetic resonance spectrum of thian-3,5-dione in deuteriochloroform indicated negligible enolisation in this solvent; it consisted of two singlets at \( \tau 6.45 \) (COCH\(_2\)CO) and 6.61 (CH\(_2\)SCH\(_2\)). In contrast, Yogev and Mazur\(^\text{149}\) found that cyclohexan-1,3-dione and (to a lesser extent) dimedone are substantially enolised in deuteriochloroform solution; the keto tautomer of dimedone gives singlets at \( \tau 6.67 \) (COCH\(_2\)CO) and 7.49 (CH\(_2\)C(CH\(_3\))\(_2\)CH\(_2\)).

Cyclohexan-1,3-diones are prone to decomposition on exposure to the atmosphere, particularly in the presence of moisture.\(^\text{145}\) Similar behaviour was noticed for thian-3,5-dione, which gradually darkened and became oily. For this reason it was stored in an evacuated dessicator containing silica gel, and used as soon as possible after preparation.

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DISCUSSION

The factors influencing the alkylation of enolic compounds under basic conditions have been discussed in the context of carbalkoxythiolanones (page 46). In the absence of literature reports of C-alkylation of thian-3,5-dione, guidance was sought from studies of cyclohexan-1,3-diones. In accordance with the high degree of enolisation of cyclic 1,3-diones, O-alkylation is a major side-reaction.

The C:O-alkylation ratio of cyclohexan-1,3-dione enolate rises in the series of cations Li$^+$ < Na$^+$ < K$^+$,\(^{145,155}\) that is the opposite of the order usually observed in alkylations of enolates; this trend has been interpreted by Brändström \(^{114}\) as resulting from an increased tendency for coordination of the alkylation agent to a larger metal atom. Literature reports on the use of thallium(I) as cation in alkylations of cyclic 1,3-diketones (page 61) indicate that it offers no advantages over the alkali metals.

The effects of variations in the alkylating agent on the C:O-alkylation ratio of cyclohexan-1,3-dione follow the usual trends. C-alkylation of the potassium enolate in methanol is readily achieved with methyl iodide, but suffers from competition with O-alkylation when longer-chain alkyl groups are used. With ethyl, propyl, butyl and cetyl iodides C:O-alkylation ratios between 1:1.25 and 1:1.9 have been obtained; in each case the yield of C-alkylated product was about the same (26-28\%).\(^{155}\) Better ratios are obtained when alkylating agents with α,β-unsaturation are used.\(^{145}\) C-alkenylation products have been obtained from the potassium enolate of cyclohexan-1,3-dione in water with allyl, crotyl and 2-penten-1-yl bromides in 64, 63
and 72.5% yields respectively; in these instances di-C-alkylation rather than O-alkylation was a noticeable side-reaction. The C:O-alkylation ratio increases in the usual order of leaving groups, sulphate \( \sim \) p-toluensulphonate \( < \) bromide \( < \) iodide. \(^{155}\)

Protonic solvents, especially methanol and water, have been used extensively for alkylations of cyclohexan-1,3-dione enolates. Water is better than methanol in promoting C-alkylation, but is unsuitable when saturated alkyl groups apart from methyl are to be introduced, because the products are too susceptible to cleavage and atmospheric oxidation in the presence of aqueous alkali. \(^{145}\) This problem is less likely to arise when the alkylating agent has \( \alpha, \beta \)-unsaturation; for instance, Büchi and Egger \(^{65}\) obtained an 82.5% yield of C-alkylation product on treating cyclohexan-1,3-dione with excess aqueous potassium hydroxide and 1-bromo-2-pentyne for 15 hours at room temperature.

Dipolar aprotic solvents would be expected to promote O-alkylation. Nevertheless, in the course of a synthesis of 11-deoxy prostaglandins, Bagli and Bogri \(^{57}\) have achieved C-alkylation of cyclohexan-1,3-dione sodium enolate in dimethylformamide with methyl 7-bromohept-5-ynoate, showing that the effect of the solvent may be overcome by the use of an \( \alpha, \beta \)-unsaturated alkyl group.

Mono-C-alkylated cyclic 1,3-diones, like the unsubstituted compounds, are acidic and may therefore be separated from O- and di-alkylation products by extraction with aqueous alkali, then recovered by acidification of the aqueous phase. Since di-alkylation involves proton transfer from the mono-C-alkylated product to the starting enolate, it causes contamination of the mono-C-alkylated product with the starting diketone. Thus from the point of view of product isolation, O-alkylation may be regarded as a lesser evil than di-alkylation.
The spectroscopic properties of the mono-C-alkylated products are similar to those of the parent diones, discussed in the previous section. The wavelength of the absorption maximum in the ultra-violet spectrum is increased by about ten nanometers on introduction of the 2-alkyl group, as expected from Woodward's rules: for instance, 2-methylcyclohexan-1,3-dione has $\lambda_{\text{max}}$ 261 nm, whereas cyclohexan-1,3-dione itself absorbs at 253 nm. As with the unsubstituted diones, the absorption maximum of the mono-C-alkylation products is shifted to higher wavelength at high pH as a result of ionic dissociation. The O-alkylation products absorb at similar wavelengths to the starting diketones, but the wavelength of the absorption maximum is unaffected by pH.

Whereas C-alkylation is not expected to have much effect on the infrared spectra of cyclic $\beta$-diketones, O-alkylation is. Bands due to the conjugated carbonyl group (below 1700 cm$^{-1}$) and double bond (nearer 1600 cm$^{-1}$) are characteristic of enol ethers of cyclic $\beta$-diketones.

RESULTS

In view of the known behaviour of cyclohexan-1,3-diones, it was probable that alkylation of thian-3,5-dione with ethyl 7-iodoheptanoate as proposed in Scheme 2 would lead to a low C:O-alkylation ratio. It therefore seemed desirable to take advantage of the superiority of alkylation agents containing $\alpha,\beta$-unsaturation. This could be done by Bagli and Bogri's approach, that is by using ethyl 7-bromohept-5-ynoate as alkylating agent, so that the C-alkylation product would be compound 140. The triple bond could be removed by reduction at a later stage in the synthesis. An additional benefit accruing from the use of the acetylene would be the opportunity of preparing prostaglandin analogues containing a 5,6-cis double bond, as present in the naturally-occuring class 2 prostaglandins, via hydrogenation in the
The preparation of ethyl 7-bromohept-5-ynoate would have involved a tedious multi-stage synthesis, so model experiments with the aim of preparing compound were performed, using commercially available propargyl bromide as alkylating agent. Methanol rather than water was chosen as solvent for the initial experiments, in order to avoid the risk of attack by hydroxide on the product, since it was known from experience in the preparation of thian-3,5-dione that this risk was greater than for cyclohexan-1,3-diones.

In the first model experiment, the sodium enolate of thian-3,5-dione was generated by adding the dione to methanolic sodium methoxide. Gas-liquid chromatography of the resulting solution showed that conversion to the enolate was complete, no peak corresponding to the free dione being seen. Propargyl bromide was then added to the enolate solution, but after 21 hours at room temperature, no products were detected, and an acidified sample of the reaction mixture gave only a peak corresponding to thian-3,5-dione. It was concluded that the reaction was very slow at room temperature.

In another experiment, a reaction temperature of 35-45° was employed, and the progress of the alkylation was followed by testing droplets
of the reaction mixture with moist universal indicator paper; the reaction was considered complete after 2½ hours, by which time the pH readings had fallen to a steady value of 2.5. For work-up the reaction mixture was filtered, concentrated and treated with water, and the product was extracted with ethyl acetate. The ethyl acetate and any excess propargyl bromide were removed by evaporation, leaving a dark brown, viscous oil, obtained in 42% yield. Thin-layer chromatographic analysis of this crude product indicated that thian-3,5-dione was absent, but showed it to be a multi-component mixture. A pure product was not isolated, but the infra-red spectrum of the crude material had bands characteristic of a terminal acetylene (3120 cm⁻¹ (strong, =C-H); 2120 cm⁻¹ (C=C)), and bands reminiscent of the keto and enol forms of thian-3,5-dione (3300br, 1730s - stronger than in thian-3,5-dione itself, 1700s and 1600s,br), in agreement with the structure of the desired product 141.

An attempt was made to alkylate thian-3,5-dione with propargyl bromide, using liquid ammonia as solvent and base, with tetrahydrofuran as co-solvent, at -33°. (Liquid ammonia is an excellent base for alkylations of 2-acylcyclohexan-1,3,5-triones with 2-propenyl bromides 158). Work-up, conducted by allowing the ammonia to evaporate, acidification, and extraction with diethyl ether, led only to recovery of thian-3,5-dione (85%), identified by its infra-red spectrum. This result may have been due to the low reaction temperature rather than the absence of a powerful base, since similar results were obtained when the sodium enolate of thian-3,5-dione, generated in situ using sodamide (also prepared in situ), was subjected to the same conditions.

An investigation of the preparation of another model compound, 142, proved more fruitful. In a first attempt to prepare 142, the sodium enolate of thian-3,5-dione was alkylated with methyl 4-bromocrotonate, in methanol at room temperature. The reaction was monitored by testing
samples with moist universal indicator paper; the pH readings fell from 10 to 2 during one hour. For work-up, the reaction mixture was concentrated, and the crude product extracted from the concentrate with chloroform. The infra-red spectrum of the product had a broad hydroxyl band at $3280 \text{ cm}^{-1}$, indicating the presence of an enol, and a profusion of bands in the C=O and C=C stretching region (1720s, br, 1680, 1651, 1630 and 1600 br cm$^{-1}$), suggesting that C- and O-alkylation products 142 and 143 were both present. (The following tentative assignments were made: 1720: ester carbonyl, ring carbonyls of 142; 1680: ring carbonyl of 143; 1651: double bond in five-carbon side-chain; 1630: double bond in the ring of 143; 1600: enol tautomer of 142).

With the aim of separating these two components, the crude product was dissolved in benzene, and extraction of the C-alkylation product 142 was attempted by shaking the solution with dilute aqueous sodium hydroxide. The resulting lower layer was run immediately into dilute hydrochloric acid, in order to minimise the exposure of 142 to alkali; despite this precaution, a characterisable product was not obtained. The benzene layer was washed thoroughly with sodium hydroxide, with the aim of removing any trace of 142. Removal of solvent left an orange oil whose weight corresponded to a 32% yield of mono-alkylation product. Its infra-red spectrum was similar to that of the crude product, except
that the intensities of the bands assigned to the enol form of 142 (3280 and 1600 cm\(^{-1}\)) were considerably reduced. However, gas-liquid chromatographic analysis of the oil strongly suggested that 142 was still present, as the main component in fact. Chromatography of a methanol solution of the oil on a silicone OV1 column at 200\(^{0}\) indicated the presence of two major components eluting at 11 and 14 minutes, in approximate ratio 1:3 (relative peak areas). The larger peak disappeared when the sample was made alkaline with sodium hydroxide, behaviour expected for the C-alkylation product 142. This assignment was later confirmed when a pure sample of 142 was isolated; the component eluting at 11 minutes was presumably 143. The oily product was distilled, but no separation of the two components was achieved as judged by gas-liquid chromatography and infra-red spectroscopy.

The problem of O-alkylation in the preparation of 142 was alleviated by changing the leaving group of the alkylating agent from bromide to iodide, as expected from literature precedents, particularly for alkylations in the cyclohexan-1,3-dione series. The appropriate iodide, methyl 4-iodocrotonate, was readily prepared from methyl 4-bromo-crotonate by metathesis with sodium iodide.

For the second attempt to prepare 142, the sodium enolate of thian-3,5-dione was treated with 1.1 equivalents of methyl 4-iodocrotonate, in methanol at 0\(^{0}\). The lower reaction temperature was chosen on the basis that use of the more reactive halide should permit milder conditions to be employed. The progress of the reaction was monitored by pH testing, as before. The reading fell from pH 11 to pH 2.5 in 30 minutes, and remained at this value an hour later. For work-up, the methanol was replaced by chloroform and the resulting mixture filtered to remove a water-soluble, white precipitate, which was presumed to be sodium iodide. The infra-red spectrum of a potassium bromide
mull of the solid showed that this presumption was not entirely correct, however. Strong bands reminiscent of a carboxylate anion were observed at 1570 and 1520 cm\(^{-1}\), suggesting that the solid contained a substantial amount of the sodium enolate of thian-3,5-dione. This interpretation was confirmed by the ultra-violet spectrum of an ethanol solution, which exhibited an intense absorption at 278 nm; on acidification of the sample, the absorption maximum was shifted to 257 nm. Thus the pH test used to monitor the reaction had been misleading; the reason for this may have been that the enolate was insufficently soluble in methanol at 0°. Concentration of the chloroform solution gave an orange paste. The detection of unchanged thian-3,5-dione sodium enolate implies that a considerable amount of unchanged methyl 4-iodocrotonate would be present, so it seemed desirable to find a way of extracting the C-alkylation product with alkali. This was achieved by shaking the paste with aqueous sodium bicarbonate and chloroform. The chloroform layer was further extracted with bicarbonate, then kept aside. The combined alkaline extracts were acidified to release the crude C-alkylation product, an orange oil obtained in 33% yield via extraction with chloroform. Gas-liquid chromatographic analysis of this product, under the conditions used in the experiment with methyl 4-bromocrotonate, indicated that the C-alkylation product 142, eluting at 14 minutes, was predominant. The infra-red spectrum was similar to that of the crude product of the previous experiment, except that the bands believed to be due to the O-alkylation product 143 were considerably weaker, appearing only as shoulders. Additional evidence that 142 had been obtained was provided by the ultra-violet spectrum, which had intense absorption maxima at wavelengths characteristic of the \(\pi\rightarrow\pi^*\) transitions of an \(\alpha,\beta\)-unsaturated ester (208 nm) and the enol of a six-membered cyclic \(\beta\)-diketone (262 nm). Unchanged methyl 4-iodocrotonate, identified by its infra-red spectrum, was recovered from the chloroform layer kept aside earlier in the work-up. From the
amount obtained it was estimated that the extent of the reaction had been not more than 70%.

The reaction of the sodium enolate of thian-3,5-dione with methyl 4-iodocrotonate in methanol was repeated, using a reaction temperature of 15-18°. The progress of the reaction was again monitored by pH testing; the test was more reliable at the higher reaction temperature, since 90% of the theoretical amount of the alkylating agent was consumed. A reading of pH 2.5 was attained after 3 h reaction, compared with 30 min when the reaction was conducted at 0°. The C-alkylation product was again extracted with aqueous sodium bicarbonate and released as an oil on acidification of the alkaline extract. Initial extraction of the resulting mixture with benzene led to recovery of the crude C-alkylation product as a red oil in 32% yield; its infra-red and gas-liquid chromatographic behaviour were similar to the product obtained at 0°, but gave no indications of the presence of 143. The oil released on acidification was not completely dissolved by benzene; further extraction was performed with ether, which was found more effective. In this way a second quantity of red oil was obtained, equal in weight to the first; however, its infra-red spectrum and gas-liquid chromatographic analysis showed that it was badly contaminated with thian-3,5-dione. The first crop was combined with the product obtained at reaction temperature 0° and chromatographed on alumina to provide a small sample of the C-alkylation product 142 in relatively pure, crystalline form (melting point 135-136°).

The chromatographed material had infra-red, ultra-violet, and gas-liquid chromatographic properties similar to those of the crude products. In the ultra-violet spectrum, the absorption band assigned to the enol system was shifted to longer wavelength on increasing pH, becoming a doublet with maxima at 285 and 310 nm, thereby lending weight
to this assignment. Additional evidence that the product had the desired structure 142 was provided by a mass spectrum. The molecular ion appeared at the correct m/e value of 228 a.m.u., and the fragmentation pattern showed that the compound was a methyl ester. Fragment ions corresponding to loss of $\text{CH}_3\text{O}$ and $\text{CH}_3\text{OH}$ from the molecular ion were observed, at 197 and 196 a.m.u. respectively, and further loss of CO from these fragments gave rise to peaks at 169 and 168 a.m.u. The transitions $228 \rightarrow 196$ and $196 \rightarrow 168$ were supported by metastable peaks. The mass spectrum also suggested the presence of a dialkylation product, since a molecular ion was present at 326 a.m.u. Fragment ions corresponding to loss from this species of $\text{CH}_3\text{O}$, $\text{CH}_3\text{OH}$, $\text{CH}_2\text{O}$ and $\text{CH}_2\text{OH}$, and further loss of CO from each of these were seen, indicating the presence of two methyl ester groups. Sufficiently intense second isotope peaks were present for all the peaks discussed to allow for the natural abundance of $^{34}\text{S}$.

Comparison of the results of attempted alkylations of the sodium enolate of thian-3,5-dione in methanol with propargyl bromide and with methyl 4-iodocrotonate suggested that the iodoalkene was a more reactive alkylating agent, since higher temperatures were required to promote the reaction with the bromoalkyne. The possibility of liquid ammonia being a suitable solvent for the preparation of compound 142 was therefore not ruled out by the failure of propargyl bromide to react in this solvent. Accordingly, an experiment was performed in which thian-3,5-dione sodium enolate in liquid ammonia was treated with methyl 4-iodocrotonate under the conditions employed for the attempted alkylation with propargyl bromide. The result was little better than when propargyl bromide had been employed; gas-liquid chromatographic analysis of the crude product showed that it consisted almost entirely of thian-3,5-dione, with only a trace of 142 present.

The best solvent found for the preparation of alkenyl dione 142 from the sodium enolate of thian-3,5-dione and methyl 4-iodocrotonate was
dimethylformamide, as used by Bagli and Bogri for the alkylation of cyclohexan-1,3-dione with methyl 7-bromohex-5-ynoate. The enolate was generated in situ using sodium hydride. Useful information about three aspects of the reaction was provided by gas-liquid chromatography of samples of the alkylation mixture: (1) the rate of reaction was high, product formation being virtually complete on mixing at 40°; (2) proton transfer from 142 to the starting enolate was implied by the detection of a significant amount of free thian-3,5-dione; and (3) the level of O-alkylation, judged by the size of the peak believed to be due to compound 143, was low; methanol had therefore offered no significant advantage in this respect.

The reaction mixture was worked-up by dilution with water and extraction with ether, to give a partly solid product. The solid component was collected by filtration and washed with diethyl ether, giving the desired product 142 in 19% yield. This material had a satisfactory infra-red spectrum and gas-liquid chromatographic analysis, and melted at 132-134°. A pure sample, melting point 145°, was obtained by recrystallisation; its infra-red and ultra-violet spectra agreed with those of products from previous runs. Confirmation that the structure 142 was correct was provided by elemental analysis and a proton nuclear magnetic resonance spectrum. The latter contained a singlet at \( \tau 6.55 \) (\( \text{CH}_2\text{SCH}_2 \)) similar to the corresponding signal observed for thian-3,5-dione (\( \tau 6.61 \)), and a triplet at \( \tau 6.23 \) (\( \text{COCH(CH}_2\text{-})\text{CO} \)) corresponding to the singlet at \( \tau 6.45 \) observed for thian-3,5-dione (\( \text{COCH}_2\text{CO} \)). The remaining signals were those appropriate for the five-carbon side-chain; as with thian-3,5-dione the degree of enolisation was negligible in deuteriochloroform.

The importance of \( \alpha,\beta \)-unsaturation in the alkylating agent as a prerequisite of predominant C-alkylation of thian-3,5-dione was demonstrated
by alkylation with ethyl 7-iodoheptanoate in dimethylformamide. Gas-
liquid chromatography of reaction mixture samples enabled comparisons
with the alkylation with methyl 4-iodocrotonate to be made: (1) the
saturated iodide reacted more slowly, product formation being complete
after four hours at 35-45°; (2) proton transfer from the C-alkylation
product 47 to the starting enolate was much less prevalent; (3) as
anticipated, O-alkylation was favoured over C-alkylation. The C- and
O-alkylation products were eluted at 6 and 8 minutes respectively from
a silicone OV1 column operated at 250°. Tentative assignments were
made on the following grounds: the first peak disappeared on treating
a sample with aqueous sodium bicarbonate, and reappeared on subsequent
neutralisation; the second peak was gradually lost following treatment of
a sample with dilute hydrochloric acid (cleavage of the ether linkage
to give thian-3,5-dione was expected), and did not reappear on neutral-
isation. The assignments were later confirmed by comparison with the
isolated products.

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{R} \\
\text{S} & \quad \text{CO}_2\text{R} \\
47 \quad \text{R} &= \text{C}_2\text{H}_5 \\
145 \quad \text{R} &= \text{CH}_3 \\
144 \quad \text{R} &= \text{C}_2\text{H}_5 \\
146 \quad \text{R} &= \text{CH}_3
\end{align*}
\]

The C-:O-alkylation ratio rose during the course of the reaction; a
measure of its final value, the ratio of the areas of the gas-liquid
chromatographic peaks for 47 and 144, was 1:2.3. This ratio is com-
parable to literature values for product ratios from alkylations of
cyclohexan-1,3-dione with long-chain aliphatic iodides in methanol.\cite{155}
The low C-:O-alkylation ratio meant that a means of separating the products had to be found. The method chosen was based on the effect of sodium bicarbonate mentioned above, and its superiority over sodium hydroxide for the analogous separation of model compound 142. The reaction mixture was treated with aqueous sodium bicarbonate, and the O-alkylation product 144 together with excess ethyl 7-iodoheptanoate, extracted with diethyl ether (some 144 was precipitated at this stage). The C-alkylation product 47 was recovered via acidification of the bicarbonate solution. The efficiency of the separation, checked by gas-liquid chromatography, was very high. The C-alkylation product was virtually uncontaminated by thian-3,5-dione, confirming that the extent of proton transfer from 47 was low, and the crude yields of 47 (24%) and 144 (41%) confirmed the predominance of O-alkylation. Pure samples of the products were obtained by recrystallisation, following chromatography of the C-alkylation product on florisil. Satisfactory elemental analyses, and infra-red, ultra-violet and proton nuclear magnetic resonance spectra were obtained for each compound.

The infra-red and ultra-violet spectra of 47 were similar to those of 142, with the expected absence of absorptions due to the side-chain double bond and the α,β-unsaturated ester chromophore in 142. In contrast to 142, the ester and ring carbonyl bands (1730 and 1700 cm⁻¹) in the infra-red spectrum of 47 were resolved; the ester carbonyl of 47 is not conjugated with a double bond and therefore appears at a slightly higher frequency. The proton nuclear magnetic resonance spectrum of 47 was similar to that of 142 in having a singlet at τ 6.58 (CH₂SCH₂), a triplet at τ 6.44 (OCH(CH₂₋)CO), and signals appropriate to the nine-carbon side-chain, with no sign of enolisation in deuteriochloroform.

The spectra of 144 were as expected for an enol ether of a six-membered
cyclic β-diketone. The ultra-violet spectrum had a single strong absorption band at lower wavelength than that of 47, due to the absence of a 4-alkyl substituent; the band was not shifted on increasing pH. The infra-red spectrum had bands due to the ring carbonyl group (1640 cm\(^{-1}\)) and double bond (1607 cm\(^{-1}\)), similar to those that had been tentatively assigned to O-alkylation product 143. The proton nuclear magnetic resonance spectrum of 144 confirmed that the two methylenes adjacent to sulphur were in slightly different environments (singlets at \(\tau 6.67\) and 6.73). The vinylic proton gave rise to a singlet at \(\tau 4.62\), and the first methylene group of the side-chain a triplet at \(\tau 6.15\), showing that it was attached to oxygen.

The alkylation of the sodium enolate of thian-3,5-dione with ethyl 7-iodoheptanoate was repeated several times to provide 47 for further experiments. The reaction was conducted at room temperature for convenience, and was usually complete after running overnight; the C-O-alkylation ratio was not significantly affected by the reduction in temperature. For the first repeat run, the yield of crude 47 was increased to 32% by minor alterations in the work-up; the product was a dark brown oil, which solidified slowly on deep-freeze storage. A solvent system for recrystallisation was found which enabled pure 47 to be obtained in 14% overall yield, without recourse to chromatography.

The main difficulty in recrystallising crude 47 was its tendency to precipitate as a dark oil, which was probably due to its low melting point (the highest value recorded in the course of this work was \(48.5-49.5^\circ\)). In the hope of reducing this problem, the corresponding methyl ester 145 was prepared, by using methyl instead of ethyl 7-iodoheptanoate. The crude yield of 145 was similar to that of 47, but so was its melting point (48-49\(^\circ\)). The O-alkylation product 146
was also isolated; its melting point (42.5-43.5°) was in fact lower than that of the corresponding ethyl ester 144 (63.5-64.5°). The methyl esters 145 and 146 were identified by their infra-red, ultraviolet and proton nuclear magnetic resonance spectra, all of which were very similar to those of the ethyl esters 47 and 144.

In later repeat preparations of 47, the crude product was decolourised with charcoal. After deep-freeze storage, orange or light brown solids having a melting range of about three degrees in the region of 40° were typically obtained, in 26-27% yield. Fortunately, these materials were found to be as good as recrystallised material for subsequent conversion to six-membered enone 51.

![Chemical structure](image)

The observation that the C-O-alkylation ratio 47:144 increased during the course of the alkylation of thian-3,5-dione sodium enolate with ethyl 7-iodoheptanoate was confirmed by gas-liquid chromatographic results from the repeat runs. O-Alkylation seemed to be retarded by the presence of its product 144, the rate of formation of which fell with time, the concentration becoming virtually steady while that of the C-alkylation product 47 was still rising. This observation, coupled with the knowledge that 47 and 144 could be efficiently separated, inspired the notion that the yield of 47 might be improved if 144 were added to the alkylation mixture before the ethyl 7-iodoheptanoate, since O-alkylation should be somewhat retarded from the start. If so, a profitable use would be found for
the by-product 144. When this procedure was tried, using one equivalent of added 144, the improvement achieved was small and of doubtful significance, a 29.5% yield of charcoal-decolourised 47 being obtained. The slight increase in yield hardly justified the effort involved in purifying the added 144.

The probability of obtaining a more substantial improvement by increasing the amount of 144 added at the outset would be offset by greater difficulty in separating the desired product efficiently, and inconvenience resulting from the increased bulk of the reaction mixture, especially as more solvent would be needed. Indeed, decreasing the concentration of the reactants could well reduce the C-O-alkylation ratio, considering the results reported for cyclohexan-1,3-dione. Even if a significant improvement could be obtained in this way, it would be of limited use since a large pool of 144 would have to be accumulated.

Alkylations of the potassium and thallium(I) enolates of thian-3,5-dione with ethyl 7-iodoheptanoate were performed for comparison with that of the sodium derivative; lower levels of C-alkylation were observed. Alkylation of the potassium enolate in dimethylformamide was slightly faster than alkylation of the sodium enolate, requiring three hours at 40° as opposed to four hours. The C-O-alkylation ratio, measured by gas-liquid chromatography, was 1:3.0. The ratios observed with sodium and potassium as cation followed the usual trend found in alkylations of enolates, not the opposite as is the case with cyclohexan-1,3-dione.

Under heterogeneous conditions (in tetrahydrofuran), the thallium(I) enolate of thian-3,5-dione did not react with ethyl 7-iodoheptanoate at 40° to an extent detectable by gas-liquid chromatography. Even
on addition of the highly (Lewis) basic, dipolar aprotic solvent hexamethylphosphoramide (described on page 52), the reaction was slow, requiring 28 hours at 40°. The final C-O-alkylation ratio, estimated in the usual way, was 1:4. This result is compatible with the known behaviour of thallium(I) enolates of other cyclic β-diketones, already mentioned.

Although the yield of 47 was limited by the poor C-O-alkylation ratio, the results obtained from the investigation of the model compounds 141 and 142 gave little promise of improvement by introduction of α,β-unsaturation in the alkylating agent. Further stages in the synthesis of prostaglandin analogues were therefore carried out on 47, as proposed in Scheme 2.
CONVERSION OF 2-ALKYLTHIAN-3,5-DIONES TO SIX-MEMBERED CYCLIC ENONES

DISCUSSION

Enol Ethers of Cyclic β-Diketones

Two general methods are available for the preparation of enol ethers of cyclic β-diketones. One method, which takes advantage of the fact that the enols of β-diketones are vinylogues of carboxylic acids, is to subject the β-diketone to acid-catalysed "esterification" conditions. This principle was first employed by Frank and Hall, who prepared the ethyl enol ethers of dimedone and 5-isopropylcyclohexan-1,3-dione (147 and 148) by refluxing the diones with ethanol and benzene in the presence of p-toluenesulphonic acid, with azeotropic removal of water. These conditions failed for 2-methyl-5-isopropylcyclohexan-1,3-dione (149), which was recovered nearly quantitatively.

\[ \text{Enol Ether of Cyclic β-Diketones}\]

Frank and Hall's procedure has been widely used, often with isobutyl alcohol in place of ethanol. Examples of products include the isobutyl enol ether of 2-methylcyclohexan-1,3-dione (150) and the ethyl enol ether of cyclohexan-1,3-dione. The latter has also been prepared by the reaction of the silver "salt" of cyclohexan-1,3-dione with ethyl iodide.
The second general method for the preparation of enol ethers of cyclic β-diketones depends on their high tendency to be O-alkylated under basic conditions. Conditions which promote low C-:O-alkylation ratios are chosen, for instance use of alkylating agents having a sterically hindered alkyl group such as isopropyl, or a "hard" leaving group such as  p-toluenesulphonate. Similarly, enol esters of cyclic β-diketones may be prepared using a tertiary amine as base, and an acyl or sulphonyl chloride.

Diazomethane has been used to prepare methyl enol ethers of cyclic β-diketones, including that of thian-3,5-dione.

The spectroscopic properties of enol ethers of cyclic β-diketones have been mentioned in connection with the alkylation of thian-3,5-dione (page 83). The corresponding enol esters have similar characteristics, with some differences in the positions of absorption bands. In the ultra-violet, the wavelength of the π→π* band is shorter than that of an enol ether, and in the infra-red the stretching frequency of the double bond within the ring is higher. The frequency of the carbonyl stretching band of the ester function is higher than that of a saturated alkyl ester.
Preparation of Enones from β-Diketone Enol Ethers

Two stages are involved in the conversion of β-diketone enol ethers to enones: reduction of the carbonyl function to a secondary alcohol; and acid-catalysed hydrolysis of the reduction product. The second stage can be conveniently incorporated into the work-up of the reduction product, so the conversion may be performed in one preparative step. Alternatively, the intermediate β-alkoxyallylic alcohol can be isolated by careful alkaline work-up of the reduction product. Considerable use has been made of this enone synthesis, including variations in which the β-alkoxyallylic alcohol is derived differently, for instance from reactions of Grignard reagents or lithium acetylide with β-diketone enol ethers; the latter procedures give β-substituted enones. γ-Substituted enones may be obtained by alkylation of the enol ether prior to reduction.

A particularly good example is the preparation of 2-cyclohexenone (156) from the ethyl enol ether of cyclohexan-1,3-dione (151). The mechanism of the acid hydrolysis step in this instance has been elucidated by Stiles and Longroy.

In principle, at least two routes may be envisaged for the conversion of β-alkoxyallylic alcohol 152 to enone 156 (Scheme 8, paths A and B). Stiles and Longroy have shown conclusively that only path A - allylic rearrangement of 152 to hemiacetal 155 followed by rapid elimination of ethanol - is important. Path B involves regeneration of the carbonyl function of 152, masked as its ethyl enol ether, leading to β-ketol 158. Stiles and Longroy proposed the mechanism shown in Path A on discovering that ketol 158 (which they prepared by lithium aluminium hydride reduction of the mono-hemithioketal of cyclohexan-1,3-dione followed by removal of the protecting group with Raney
Scheme 8

Path A

\[
\text{Et} = \text{C}_2\text{H}_5
\]
nickel) is converted to $\text{156}$ at a rate slower than the formation of $\text{156}$ from $\text{152}$ by a factor of $10^8$. Indeed, $\text{152}$ is converted quantitatively to $\text{156}$ by $10^{-3}$ M hydrochloric acid at $0^\circ$, conditions which have no measurable effect on $\text{158}$. In more concentrated acid (0.1 to 5M) $\text{156}$ and $\text{158}$ are both converted to an equilibrium mixture in which the ratio $\text{156}:\text{158}$ is $2.39\pm0.09:1$. Evidence for Path A was obtained (a) from a kinetic study, which showed that the transformation of $\text{152}$ to $\text{156}$ follows a first-order rate law, the rate constant being directly proportional to the hydrogen ion concentration, and (b) by performing the reaction in $^{18}$O-enriched water. The results of the latter experiment showed that the oxygen of $\text{156}$ is derived from the solvent, but the oxygen of the eliminated ethanol is not. It was concluded that the lifetime of the alkoxyallylic cation $\text{154}$ is sufficient to allow equilibration between water molecules solvating the cation and those of the bulk of the solvent. Alternative mechanisms in which the ketone oxygen would be derived from the ethoxy group were ruled out.

Wenkert and Strike encountered an example in which the mechanisms of paths A and B were in competition. The acid-catalysed hydrolysis
of β-alkoxyallylic alcohol 159, in which the hydroxyl group is quasi-equatorial, is somewhat slow, and leads to both enone 160 and ketol 161. In ethanolic 1N-sulphuric acid conversion was complete in 5 minutes, approximately equal amounts of enone and ketol being formed; in 0.01N-acid conversion was incomplete after 36 hours and the ketol was the predominant product. In contrast, the isomeric β-alkoxyallylic alcohol 162 was readily converted to enone 163 by 0.01N-acid.

![Chemical structures](image)

The isolated ketol 161 was unaffected by either conditions, but was converted quantitatively to enone 160 on being refluxed for 2 hours in ethanolic 2N-sulphuric acid. Thus 161 could not have been formed via the mechanism of path A and equilibration of enone 160, nor could 160 have been formed via the mechanism of path B. The anomalous results obtained with 159 were therefore due to the path A process being unusually slow, and the greater preference for enone formation in the more concentrated acid showed that the rate of this process was more dependent on the hydrogen ion concentration than was the rate of formation of ketol 161.

The authors pointed out that the transition state for formation of cation 154 from 153 in path A is stabilised by overlap between the p-orbitals of the departing oxygen atom and the adjacent double bond. The rigid geometry at position 9 of 159 is unfavourable to such overlap, whereas in situations where the hydroxyl group is axial, and in acyclic
or flexible cyclic systems, a suitable conformation can be readily attained. The flexibility at position 7 of 162 is apparently sufficient to allow partial \(\pi\)-orbital overlap in the isomer having a quasi-equatorial hydroxyl group.

An early application to prostaglandin synthesis of the method described above was the preparation of enone 165 from enol ether 164. Selective reduction of the ketone carbonyl groups of 164 was accomplished with sodium borohydride in isopropyl alcohol.

![Structures](image)

More recent applications to prostaglandin synthesis have been reported by Sih's group. The preparation of enone 168 from diketone 166 was performed in two ways, via enol benzoate 169, and via isopropyl enol ether 170. Conversion of 166 to 169 by triethylamine and benzoyl chloride was accompanied by benzoylation of the alcohol function, giving 167. The efficiency of the preparation of 170 using potassium carbonate and isopropyl iodide in refluxing acetone was limited by the formation of the isomeric enol ether 171. The intermediates 169 and 170 were each reduced with sodium bis(2-methoxyethoxy)aluminium hydride in tetrahydrofuran at \(-78^\circ\); the properties of this reducing agent include selectivity at low temperatures and high solubility in hydrocarbon solvents. Hydrolysis of the reduction product from benzoate 169 to enone 168 was accomplished in 26 hours using acetic acid - water, 3:1, at 37\(^\circ\). The reduction product from isopropyl ether
170 was hydrolysed in two hours by aqueous hydrochloric acid, pH 2.5 at 25°.

The closely-related preparation of enone 173 from diketone 172 was accomplished via mesitylenesulphonate 174. Although preparation of 174 from 172 using triethylamine and 2-mesitylenesulphonyl chloride was accompanied by formation of isomer 175, the extent of this side-reaction was relatively small, and separation of the isomers was not necessary. Reduction with sodium bis(2-methoxyethoxy)aluminium hydride in toluene at -70° was followed by hydrolysis under mild conditions (oxalic acid - sodium oxalate - chloroform, two hours at room temperature).
The ultra-violet spectra of six-membered cyclic conjugated enones show a strong, pH-independent $\pi\rightarrow\pi^*$ absorption band at wavelengths approximately 30 nm shorter than those of the enols of the diketones from which they are derived. Their infra-red spectra typically have a single band in the $\mathrm{C}=\mathrm{O}$ and $\mathrm{C}=\mathrm{C}$ stretching region due to the enone system, at about 1675 cm$^{-1}$.

RESULTS

Before proceeding with the enone synthesis proposed in Scheme 2 (47 + 51), model experiments to find suitable procedures were performed on the conversion of diketone 142 to enone 176.
The first experiment in this series was an attempt to prepare isobutyl enol ether 177 by refluxing 142 in isobutyl alcohol - benzene with a catalytic quantity of p-toluenesulphonyl chloride. Water was removed from the azeotropic distillate by means of a Dean-Stark separator. The progress of the reaction, monitored by gas-liquid chromatography on a silicone OV1 column at 240°C, was very slow; after 21 hours reflux the diketone peak (4 minutes) was not noticeably reduced in size, although a small product peak (8 minutes, area less than 5% of diketone peak) did appear. The reaction mixture had darkened considerably during this time.

The conversion of diketone 142 to its isopropyl enol ether 178 by treatment with a slight excess of potassium carbonate and isopropyl iodide in refluxing acetone proceeded at a more useful rate. The mixture was refluxed for a few minutes before the isopropyl iodide was added, to allow formation of the potassium enolate of 142. Gas-liquid chromatography of reaction mixture samples showed the disappearance of most of the free diketone. Excess isopropyl iodide was added, and its consumption monitored by gas-liquid chromatography on a silicone OV1 column at 50°C, at which temperature the halide eluted after 3 minutes. The rate of alkylation apparently fell with time, the extent of the reaction being approximately 60% after 16 hours.
reflux and 80% after 86 hours. The sample taken at 86 hours was also chromatographed at a column temperature of 240°; products eluting at 5 and 6 minutes were detected, in peak area ratio 1:25, in addition to a peak corresponding to free 142 (about 20% of the total peak areas). On acidification of the sample, the major product peak virtually disappeared, and the area of the diketone peak was quadrupled; the minor product was unaffected. The facile hydrolysis of the main product to starting diketone 142 strongly suggested that it was the desired enol ether 178, and the acid-resistant minor product was probably 180, resulting from C-alkylation of 142.

![Chemical structure](image)

The reaction was complete, as judged by the size of the isopropyl iodide peak, after 135 hours reflux. Refluxing was continued to a total of 168 hours, and the reaction mixture worked-up by dilution with water, making slightly alkaline by addition of sodium hydroxide, and extraction with diethyl ether. The crude product, an oil, was obtained in 75% yield. Its gas-liquid chromatographic behaviour was similar to that of the sample described above, except that the peak for starting diketone 142 was a little smaller (about 15% of the total peak areas), and isopropyl iodide was absent (as expected from its volatility). The proposed structure of the principal product, 178, was supported by infra-red and ultra-violet spectra. The infra-red spectrum contained strong bands at 1640 and 1600 cm⁻¹ assigned to the ring carbonyl group and double bond, and a doublet with
maxima at 1386 and 1373 cm\(^{-1}\), characteristic of the symmetric deformation of geminal dimethyl groups (for isopropyl iodide this doublet appeared at 1381 and 1369 cm\(^{-1}\)). The ultra-violet spectrum was similar to that of 142 in having strong absorptions at 210 and 271 nm, as expected for 178, but was not affected by increasing the pH of the sample.

Comparison of gas-liquid chromatographic results obtained before the isopropyl iodide was added, during the course of the reaction, and from the crude product showed that the amount of free diketone 142 had been much the same throughout. The failure of the reaction to proceed to completion was therefore probably due to the initial incomplete conversion of the diketone to its potassium enolate. A brief experiment with a small sample of 142 showed that this conversion could be made complete by increasing the excess of potassium carbonate.

The crude isopropyl enol ether 178 was converted to enone 176 via reduction with eight equivalents of sodium bis(2-methoxyethoxy)aluminium hydride in tetrahydrofuran at -78\(^0\). The excess reducing agent was quenched after one hour, by addition of a tetrahydrofuran solution of acetic acid. For work-up, the reduction mixture was warmed to room temperature, poured into water and extracted with ether. The infra-red spectrum of the crude product suggested that it was a mixture of \(\beta\)-alkoxyallylic alcohol 181 (there was a hydroxyl band at 3450 cm\(^{-1}\), broad, but less diffuse than those of enols) and starting enol ether (1640 and 1600 cm\(^{-1}\)). The band near 1675 cm\(^{-1}\) anticipated for enone 176 was absent, so it seemed that negligible hydrolysis of the reduction product had occurred during its brief exposure to aqueous acetic acid. This contention was supported by the weight of the crude product, which was greater than the theoretical yield of enone 176. An ultra-violet spectrum merely indicated the presence of unchanged enol ether 178.
The crude reduction product was hydrolysed with $1.5 \times 10^{-2}$ M-hydrochloric acid in aqueous tetrahydrofuran. The hydrolysis product was obtained as an oil in 72% crude yield (from 178) by extraction with ether after 22 hours. Its infra-red spectrum had a broad band at 1665 cm$^{-1}$ characteristic of a conjugated enone, and the hydroxyl band at 3450 cm$^{-1}$ was absent. Gas-liquid chromatography on a silicone OV1 column at 240° showed a product (presumably 176) at 2 minutes, and unchanged 178, in approximate ratio 3:2; several smaller peaks were present.

A small sample of enone 176 free of enol ether 178 was obtained by chromatography of the crude hydrolysis product on florisil (the final yield from 178 was 8%). Evidence for its structure was obtained from its infra-red spectrum, which showed a strong enone band at 1670 cm$^{-1}$, and its ultra-violet spectrum, which had an intense absorption maximum at 240 nm. In the infra-red spectrum, the stretching band for the double bond in the side-chain was apparently obscured by the band at 1670 cm$^{-1}$. However, the position of the ester carbonyl band (1720 cm$^{-1}$) was typical of a crotonate, and a band characteristic of the C-H deformation of a trans-1,2-disubstituted ethylene was present (987 cm$^{-1}$). The absence of 178 was demonstrated by gas-liquid chromatography, which did however show some unidentified impurities. Further characterisation was therefore not attempted; nevertheless, the experiment was valuable as a model study since useful information about the procedures employed had been gained, and there were strong indications that a satisfactory experimental procedure could be developed.
from them.

A third model experiment, directed to the preparation of enone 176 via enol benzoate 179, was performed for comparison with the route via isopropyl enol ether 178. The O-acylation of diketone 142, with two equivalents each of triethylamine and benzoyl chloride in tetrahydrofuran at room temperature, was fast compared to the alkylation with potassium carbonate and isopropyl iodide in refluxing acetone. The extent of the acylation was greater than that of the alkylation, as could be expected from the greater excess of reagents used. The acylation mixture was filtered from 1.5 equivalents of triethylammonium chloride and the filtrate was concentrated. The infra-red spectrum of the crude product contained a band at 1787 cm⁻¹, characteristic of benzoyl chloride, and indeed the product was overweight by an amount corresponding to 0.5 equivalents of this reagent. Thus the conversion of diketone 142 to benzoate 179 had been very efficient, but was dependent on the excess of reagents, since 1.5 equivalents of benzoyl chloride had been consumed; this effect was presumably due to accidental ingress of water. Pure enol benzoate 179 was obtained in 81% yield (from 142) after chromatography of the crude product on florisil. Its purity was established by thin layer and gas-liquid chromatography (nothing eluted from a silicone OV1 column at 240° during 30 minutes). The infra-red spectrum of 179 had a strong ester carbonyl band at 1738 cm⁻¹ (vinyl benzoate) with a shoulder in its low frequency side (methyl ester). The stretching band for the side-chain double bond was just resolved (1656 cm⁻¹); it had a low-frequency shoulder, assigned to the ring double bond. The ring carbonyl band appeared at 1675 cm⁻¹, and typical bands for the aromatic ring of a benzoate were present. The ultra-violet spectrum of 179 had a strong absorption at 236 nm, midway between values predicted for the aromatic and enone chromophores. On increasing the pH of the sample the spectrum resembled
that of diketone 142 at high pH, indicating that the benzoate was readily saponified.

The reduction of enol benzoate 179 was conducted in the same way as that of isopropyl enol ether 178, except that the amount of sodium bis(2-methoxyethoxy)aluminium hydride was more than trebled (28 equivalents were used), and the reaction time was doubled. These modifications led to a crude reduction product free of starting material, whose weight corresponded to a 97% yield of β-benzoyloxyallylic alcohol 182. The absence of 179, and of 176, was apparent from the infra-red spectrum, which had no band near 1670 cm⁻¹. There were strong bands at 1738, 1711 and 1690 cm⁻¹ (the last not well resolved) assignable to the benzoate and crotonate carbonyl groups and ring double bond of 182, and bands due to the aromatic ring.

Attempts to bring about the acid hydrolysis of 182 met with failure. In the first, the reduction product was treated with acetic acid-water 3:1 at 37°, conditions reported to be successful for a similar case (page 104). Samples were taken at intervals for gas-liquid chromatography, but none of the desired product, enone 176, was detected. Work-up after 120 hours resulted in 80% recovery of 182, whose infra-red spectrum differed from that of the crude reduction product only in that the band for the ring double bond (1687 cm⁻¹) was better resolved. Its ultra-violet spectrum showed a strong band at 242 nm, which was lost with increasing pH, presumably because the benzoate function was saponified. For the second hydrolysis attempt, the recovered 182 was treated with hydrochloric acid in aqueous tetrahydrofuran (pH 2.5) at 25°. Once again no 176 was formed as judged by gas-liquid chromatography. On work-up after 240 hours it was found that most of the 182 had been converted to tarry material which was insoluble in diethyl ether. A small quantity of a yellow oil was
recovered; its infra-red spectrum showed that it was a benzoate, but it differed from that of \textsuperscript{182} in the C=O/C=C stretching region.

The key intermediate in the route to thianone analogues of prostaglandins outlined in Scheme 2, enone \textsuperscript{51}, was prepared from diketone \textsuperscript{47} via isopropyl enol ether \textsuperscript{50}. This choice of route followed from the results of the model experiments described above.

The preparation of isopropyl enol ether \textsuperscript{50} was conducted under the conditions used to prepare model compound \textsuperscript{178}, except that a large excess of potassium carbonate was used, resulting in complete consumption of the starting dione. The reaction was relatively fast, and could conveniently be performed by refluxing overnight (16 hours). Its progress was monitored by gas-liquid chromatography, using a silicone OV1 column at 250\degree. Products eluting at 7 and 8 minutes with relative peak areas 10:90 were detected. On acidification
of a sample of the reaction mixture with dilute hydrochloric acid, the major product was gradually converted to starting dione 47 (retention time 6 minutes) as expected for the desired product 50, the hydrolysis being 99% complete in thirty minutes. The minor product was unaffected, and may therefore have been the C-propyl isomer 184.

\[
\begin{align*}
\text{O} & \quad \text{CH}(\text{CH}_3)_2 \\
\text{S} & \quad \text{CO}_2\text{C}_2\text{H}_5
\end{align*}
\]

184

The ratio of the two products was independent of whether the starting material 47 had been recrystallised. In either case the crude product was a brown oil. The yield from recrystallised 47 was 97%; from non-recrystallised material it was 89% after charcoal decolourisation, a less intensely coloured product being obtained. Since recrystallisation of 47 was not very efficient, the overall yield of 50 from thian-3,5-dione was better when it was omitted (24%) than if not (13%).

Supporting evidence that the principle component was 50 was provided by spectroscopic measurements of the crude product obtained from non-recrystallised 47. The infra-red spectrum showed strong ring carbonyl and double bond stretching bands at 1640 and 1602 cm\(^{-1}\), and a geminal dimethyl doublet at 1384 and 1371 cm\(^{-1}\). The ultra-violet spectrum had an intense, pH-independent absorption maximum at 272.5 nm, a wavelength similar to that for the enol of 47, as expected. In the proton nuclear magnetic resonance spectrum, the \text{O}-isopropyl group gave rise to a doublet at \(\tau 8.68\) (CH(CH\(_3\))\(_2\)) coupled to a heptet at
The outermost lines were not visible, but the five lines that were seen had the correct relative intensities for a heptet. The first methylene group of the side-chain appeared as a triplet at \( \tau 7.70 \), showing that it was attached to a fully-substituted carbon atom bearing a double bond. As in O-alkylated dione 144, the \( \text{CH}_2\text{SCH}_2 \) system gave rise to two singlets at \( \tau 6.50 \) and 6.74. Evidence that the impurity associated with 50 was 184 was provided by a weak singlet at \( \tau 6.66 \), assigned to its ring methylene groups. The intensity of this signal (0.4H) confirmed that the concentration of the impurity was 10%.

The reduction of isopropyl enol ether 50 was attempted with sodium borohydride in methanol at 0°, conditions known to be suitable for the selective reduction of ketones in the presence of carboxylic ester groups. Four equivalents of the reducing agent were used. The progress of the reaction was followed by gas-liquid chromatography, using the conditions employed during the preparation of 50. When samples of the reduction mixture were applied directly to the column, peaks were observed at 4, 5, 6, 7 and 8 minutes. None of these were particularly large, implying that the principle components of the reaction mixture were bound to metal. More useful results were obtained from samples acidified with dilute hydrochloric acid, which gave large peaks at 4, 6 and 8 minutes and a small one at 7 minutes. On standing, the component eluting at 8 minutes (50) was gradually lost, the time required for 99% consumption being thirty minutes. At the same time, the peak at 6 minutes gradually grew; it disappeared on subsequent addition of sodium hydroxide, so it was assigned to dione 47. The peaks at 4 and 7 minutes were unaffected by these conditions. The component eluting at 5 minutes, absent in acidified samples, was suspected to be \( \beta \)-alkoxyallylic alcohol 185, for which rapid hydrolysis by hydrochloric acid was anticipated. The component
eluting at 4 minutes was assumed to be enone 51, the product of the hydrolysis of 185; this assignment was later confirmed.

\[
\begin{align*}
\text{OCH}(\text{CH}_3)_2 \\
\text{S} \\
\text{CO}_2\text{C}_2\text{H}_5 \\
\text{OH}
\end{align*}
\]

185

The ratio of the areas of the peaks due to 51 and 50 given by acidified samples was 40:60 after 80 minutes reaction time and 50:50 after 2 hours. The earlier sample effervesced on the addition of acid, showing that sodium borohydride was still present, but the later sample did not, indicating that most of the hydride had been consumed by solvolysis. The ratio of 51 to 50 was unchanged when the whole reaction mixture was acidified 90 minutes later. The mixture was then stirred at room temperature for 60 hours, to ensure complete conversion of the unchanged 50 to acidic dione 47, which was subsequently removed by replacing the solvent with diethyl ether and prolonged shaking with aqueous sodium bicarbonate.

Gas-liquid chromatography of the hydrolysis mixture showed that two new components were produced during the long exposure to acidified methanol, eluting just before enone 51 and dione 47. The second of these had the same retention time as methyl ester 145, and was removed by the sodium bicarbonate treatment as expected for this compound. Thus it was apparent that alkyl exchange with the solvent had taken place, and the other new component was probably methyl ester 185 derived from enone 51.
The yield of crude 51 obtained from the reduction-hydrolysis sequence in methanol was 49%. Gas-liquid chromatography showed that it contained the components believed to be 183 and 51, and the impurity eluting at 7 minutes, in approximate ratio of peak areas 20:65:15. Material free of the latter impurity was obtained in 23% overall yield via column chromatography on florisil; its infra-red and ultra-violet spectra were compatible with structure 51.

The problems of solvolysis of the reducing agent and alkyl exchange were alleviated in later runs by changing the reaction solvent from methanol to ethanol. As an additional precaution against solvolysis, the quantity of sodium borohydride was increased to six equivalents. The reduction of 50 was slower in ethanol than in methanol, requiring about 20 hours at room temperature, but the much slower solvolysis of the reducing agent permitted complete reduction. (In one run vigorous effervescence was observed on acidification of the reaction mixture after 30 hours at room temperature). Hydrolyses were conducted by cooling the reaction mixture to below -100, adding sufficient chilled dilute hydrochloric acid to give a final concentration of about 0.03M, and stirring at room temperature for 1 hour.

Unfortunately, the crude products obtained when ethanol was used as solvent contained a greater proportion of the component of gas-liquid chromatographic retention time 7 minutes than when methanol was used, the ratio of desired to undesired product now being about 65:35. Crude yields of 101-104% were typical, suggesting that the by-product had a higher molecular weight than enone 51. Efficient separation of the two by chromatography was difficult because the by-product eluted very soon after the desired enone. The results of chromatography on various adsorbents are summarised in Table 5. With the best of these, silica gel - celite 545, 5:1, the overall yield of enone 117
51 from thian-3,5-dione was 9.5%.

TABLE 5

Chromatographic Purification of Enone 51

<table>
<thead>
<tr>
<th>ADSORBENT</th>
<th>LOADING RATIO (adsorbent:crude 51, w/w)</th>
<th>RECOVERY OF PURE 51 (% crude 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral alumina</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Florisil</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>Silica gel</td>
<td>60</td>
<td>28&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Silica gel-- celite 545, 5:1</td>
<td>50-60</td>
<td>38-39</td>
</tr>
</tbody>
</table>

<sup>a</sup> plus a fraction 90% pure by gas-liquid chromatography (10% recovery)

The ultra-violet spectrum of enone 51 had an intense pH-independent absorption maximum at a shorter wavelength (242 nm) than dione 47 and enol ether 50, as expected, and its infra-red spectrum showed a strong band at 1671 cm<sup>-1</sup> due to the enone system. In the proton nuclear magnetic resonance spectrum, the ring methylene groups appeared as a doublet at τ 6.63 (SCH<sub>2</sub>CH) and a singlet at τ 6.68 (SCH<sub>2</sub>CO). The olefinic proton gave rise to a triplet at τ 3.24 having fine splitting due to coupling to the first methylene group of the side-chain, which appeared as a triplet at τ 7.76 similar to that observed for isopropyl ether 50. Further evidence for structure 51 was later obtained from the mass spectrum of the corresponding carboxylic acid 186.
Spectroscopic measurements of the by-product of gas-liquid chromatographic retention time 7 minutes, isolated as an oil by chromatography on florisil (30% recovery) showed that it was diol 187. There was no intense ultra-violet absorption above 210 nm, and the infra-red spectrum showed a strong hydroxyl band at 3480 cm\(^{-1}\); the sole carbonyl stretching band (1732 cm\(^{-1}\)) was assigned to the aliphatic ester function. In the mass spectrum, the molecular ion (290 a.m.u.) was not visible, but there was an intense peak at 254 a.m.u. corresponding to loss of 2H\(_2\)O. Other fragment ions observed included those corresponding to loss of C\(_2\)H\(_5\)O, H\(_2\)O + C\(_2\)H\(_5\)O, 2H\(_2\)O + C\(_2\)H\(_5\)O, H\(_2\)O + C\(_2\)H\(_5\).C(OH)=CH\(_2\) + H and 2H\(_2\)O + C\(_2\)H\(_5\).C(OH)=CH\(_2\) + H from the molecular ion.

The presence of a high molecular weight impurity, possibly isopropyl ether 188, was indicated by a molecular ion peak of very low intensity at 332 a.m.u., and relatively intense fragment ion peaks corresponding to loss of H\(_2\)O, C\(_2\)H\(_5\)O, and H\(_2\)O + C\(_3\)H\(_7\). The impurity could alternatively have been diol 189, formed by reduction of dione 184 believed to be associated with enol ether 50, but this assignment was less likely since there was no peak corresponding to loss of 2H\(_2\)O.

\[
\begin{align*}
\text{OR} & \quad \text{R'} \quad \text{CO}_2\text{C}_2\text{H}_5 \\
\text{S} & \quad \text{OH}
\end{align*}
\]

\begin{align*}
\text{187} & \quad \text{R} = \text{R}' = \text{H} \\
\text{188} & \quad \text{R} = \text{CH(CH}_3\text{)}_2, \text{R}' = \text{H} \\
\text{189} & \quad \text{R} = \text{H, R}' = \text{CH(CH}_3\text{)}_2
\end{align*}

The proton nuclear magnetic resonance spectrum of the by-product provided little positive information, although it was not incompatible with structure 187. There was no sharp singlet near \(\tau\) 6.7, suggesting
the absence of an $\text{SO}_2\text{CO}$ fragment. Instead, there was a complex six-proton pattern of signals between $\tau$ 6.0 and 7.6, assigned to the ring methylene and carbinol methine protons of 187. The complexity could have been partly due to two or three geometric isomers being present. No definite signals were seen for the remaining methine and the hydroxyl protons, but the integrated relative intensity between $\tau$ 7.9 and 9.1 was sufficient to include them.

Another by-product of the sodium borohydride reduction of enol ether 50 was obtained by further elution of the florisil column (12% recovery). This component (m.p. 47-48$^\circ$ after recrystallisation) was assigned structure 190. As in the case of diol 187, the ultra-violet spectrum showed no strong absorption above 210 nm. The infra-red spectrum indicated the presence of hydroxyl and ester groups (3450 and 1728 cm$^{-1}$), and also a ketone carbonyl group (1707 cm$^{-1}$). The mass spectrum showed the expected molecular ion at 288 a.m.u., which fragmented with initial loss of $\text{H}_2\text{O}$, $\text{C}_2\text{H}_5\text{O}$, $\text{C}_2\text{H}_5\text{O} + \text{H}$, or $\text{C}_2\text{H}_5\text{O}.\text{C(OH)}=\text{CH}_2 + \text{H}$; metastable peaks were present for all but the last of these transitions. Loss of 2$\text{H}_2\text{O}$ was not observed, indicating that only one alcoholic hydroxyl group was present.

![Chemical structures](image)

In contrast to 187, the proton nuclear magnetic resonance spectrum of ketol 190 was very informative. The hydroxyl proton appeared as a sharp doublet at $\tau$ 7.57 coupled to the signal for the carbinol methine
proton, an approximate doublet at $\tau$ 5.44. On shaking with deuterium
oxide, the latter signal collapsed to a broad singlet and the hydroxyl
signal vanished, revealing a multiplet at $\tau$ 7.5 due to the methine
proton adjacent to the ring carbonyl group. The ring methylene groups
produced a complex pattern between $\tau$ 6.5 and 7.3, fourteen lines being
discernible. This pattern was analysed with the aid of digital frequency
and relative intensity measurements. Each methylene group gave rise
to an AB quartet, and most of the quartet lines were subject to fine
splitting; some overlapped. The doublets for the methylene group
adjacent to the carbonyl function appeared at $\tau$ 6.63 and 7.07 with
coupling constant 12 Hz, an assignment supported by literature data for the 2-methylene group of (6S)-6-methylthian-3-one (191)
($\tau$ 6.56 and 7.00, 12 Hz). The chemical shifts of the other ring
methylene group were $\tau$ 6.78 and 7.19, with doublet splitting 14 Hz.
Each of these signals was coupled to the carbinol methine proton with
doublet splittings of 1.75 and 4.1 Hz respectively. The signals at
$\tau$ 7.07 and 7.19 were apparently subject to across-sulphur coupling,
since both showed doublet splitting of 2.05 Hz.

When subjected to gas-liquid chromatography, ketol 190 gave a peak
at the same retention time as enone 51, but with severe tailing,
suggesting that it was converted to 51 thermally.

The formation of by-products 187, 188 and 190 may have been due to
conjugate reduction of isopropyl enol ether 50 (Scheme 9).

Ketol 190 could also have been formed by acid-catalysed hydrolysis of
the normal reduction product 185 without allylic rearrangement, analogous
to path B of Scheme 8. The ability of this process to compete with
the rearrangement to the desired enone (path A mechanism) could be
due to conformational rigidity in the ring system, as proposed by
Wenkert and Strike to account for the formation of ketol 161 in the hydrolysis of β-alkoxyallylic alcohol 159. Such rigidity is feasible considering the non-equivalence of the geminal ring protons of ketol 190 indicated by its nuclear magnetic resonance spectrum.

A third possibility, formation of ketol 190 from enone 51, was unlikely to have occurred under the mild hydrolysis conditions that were employed.

\[
R = CH(CH_3)_2 \\
R' = -(CH_2)_6CO_2C_2H_5
\]
Carboxylic acid 186 (required for biological tests) was prepared by hydrolysis of enone 51. Suitable reaction conditions were first found by investigating the conversion of the more abundant alkoxyenone 144 (the unwanted by-product of the alkylation of thian-3,5-dione with ethyl 7-iodoheptanoate) to the corresponding acid 192.

\[
\text{O} \\
\text{S} \\
\text{O} \\
\text{CO}_2R
\]

\[144 \quad R = \text{C}_2\text{H}_5 \]

\[192 \quad R = \text{H} \]

Ethanolic potassium hydroxide was found to be unsuitable for the saponification of ester 144. Consumption of the ester, as monitored by gas-liquid chromatography, was very slow unless a trace of water was present. These conditions were evidently too harsh, since the products obtained were dark, uncharacterisable oils.

Kluge, Untch and Fried 49 have employed an enzymatic method for the hydrolysis of minute quantities of prostaglandin methyl esters. Prostaglandin E₁ was obtained in 78\% crude yield from 3.2 mg of its methyl ester, using an aqueous extract of crude hog pancreas lipase (Sigma) at pH 7. This procedure, modified for larger quantities, proved to be suitable for the hydrolysis of 144. Acid 192 was obtained in 62\% yield as a pale yellow solid, melting point 71-74°. A pure sample, melting point 74-74.5° was isolated by recrystallisation. Its spectral properties were very similar to those of ester 144, except that the carboxyl function gave rise to bands at 3020 and 1690 cm⁻¹ in the infra-red spectrum, and a broad singlet at τ -0.7 in the proton
nuclear resonance spectrum, whilst bands due to a carbethoxy group were absent.

Enzymatic hydrolysis of enone 51 gave carboxylic acid 186 as a pale yellow solid, melting point 62-64°, in 67.5% yield. A pure sample, melting point 65-65.5°, was obtained by recrystallisation. Like 192 its spectroscopic properties were closely related to those of its ester precursor, the carboxyl function giving rise to bands at 3000 and 1698 cm\(^{-1}\) in the infra-red, and a diffuse singlet at about \(\tau\) -0.6 in the nuclear magnetic resonance spectrum. The mass spectrum of acid 186 showed the molecular ion at the expected value 242 a.m.u., and characteristic fragmentations of a carboxylic acid. Fragment ions corresponding to loss of CO were present, and each of these fragmented further with loss of another H\(_2\)O, the second oxygen presumably originating in the ketone function; all these transitions were supported by metastable peaks. Fragment ions corresponding to loss of CH\(_2\)=C(OH)\(_2\) + H, CH\(_2\)=C(OH)\(_2\) + H + H\(_2\)O, and (CH\(_2\))\(_6\)CO\(_2\)H from the molecular ion were also observed.
DISCUSSION

The reactions of \( \alpha,\beta \) unsaturated carbonyl compounds with organometallic reagents derived from unstabilised cations (for example methyl or phenyl) may lead to 1,2 or 1,4 addition products. Organoalkali metal reagents normally react in the 1,2 mode, adding to the carbonyl group. Grignard reagents may react in either mode, depending on the nature of the reactants, and often give mixtures of carbonyl and conjugate (1,4) addition products. Before 1966, a favoured procedure for selective 1,4 addition was the use of copper-catalysed Grignard reactions. In that year it was demonstrated that organocopper(I) species are responsible for conjugate addition by this procedure, stimulating interest in the use of preformed organocopper(I) reagents.

The use of organocopper(I) reagents in conjugate addition reactions has been the subject of two recent review articles. The results obtained with the preformed reagents are generally superior to those obtained from copper-catalysed Grignard reactions, particularly in terms of yield and stereoselectivity. The yields of the copper-catalysed reactions tend to be sensitive to steric factors such as the bulk of the organic group of the reagent, and crowding in the unsaturated carbonyl substrate. For instance, 2-propen-2-yl magnesium bromide gives good yields (50-76%) of conjugate adducts with 2-cyclohexenones unsubstituted at position 3, but the maximum yield of 3,3-disubstituted cyclohexanone that could be obtained from isophorone and vinylmagnesium chloride...
was only 8%. In comparison, 193 was obtained in 85% yield when a preformed vinylcopper(I) reagent was used.179

\[\text{CH}_3\]
\[\text{CH}_3\]
\[\text{CH}_3\]
\[\text{CH} = \text{CH}_2\]

The organocopper(I) reagents in general use may be classified into two types having the stoichiometric formulae CUR and LiCuR₂. The degree of aggregation and solvation of these species is uncertain, as is the nature of the bonding within them. The second type are thought of as anionic 'ate-complexes Li⁺(CuR₂)⁻, and are called lithium diorganocuprates. They are probably dimeric, arranged so that the four metal atoms form a tetrahedral cluster with the organic ligands attached to the faces or edges of the tetrahedron.180

Organocopper(I) reagents of stoichiometry RCu are conveniently prepared by metathesis of a copper(I) halide with one equivalent of an organo derivative of a metal higher than copper in the electromotive series, such as lithium:

\[
\text{CuHal} + \text{LiR} \rightarrow \text{CuR} + \text{LiHal}. 
\]
They are usually solids, often unstable and not isolable, and are insoluble in solvents suitable for conjugate addition reactions such as diethyl ether. Lithium diorganocuprates are most conveniently prepared by treating a copper(I) halide with two equivalents of an organolithium reagent:

\[ \text{CuHal} + 2\text{LiR} \rightarrow \text{LiCuR}_2 + \text{LiHal} \]

They are very rarely isolable, but usually have a great advantage over CuR species in their ready solubility in ether solvents. Salt-free cuprates may be obtained from equivalent quantities of CuR-type organocopper(I) compounds and organolithium reagents:

\[ \text{CuR}^1 + \text{LiR}^2 \rightarrow \text{LiCuR}^1\text{R}^2 \]

This method offers no advantage over the previous method when \( R^1 = R^2 \) because lithium halides do not interfere in conjugate addition reactions of cuprates, and the required CuR organocopper(I) compounds are often difficult to prepare. The above reaction is more useful when "mixed" cuprates (\( R^1 \neq R^2 \)) are required; neither starting material need be salt-free.

The preparation of organocopper(I) reagents is often improved if the copper source is made soluble by means of electron-donating ligands, such as amines, phosphines, phosphites or sulphides. These ligands also form ether-soluble complexes with RCu organocopper(I) reagents, and stabilise both types, especially the lithium diorganocuprates.

A disadvantage in practice is the difficulty of removing the ligands from the conjugate addition product, although this can be alleviated to some extent by choosing volatile, or better, water-soluble ligands such as trimethyl phosphite \( (\text{CH}_3\text{O})_3\text{P} \) or hexamethylphosphorous.
The exact details of the mechanism of organocopper conjugate addition are uncertain. Free carbon radicals R are not intermediates, the fact that alkyl\(^{183}\) and alkenyl\(^{67,68}\) groups are transferred with retention of configuration being particularly strong evidence against them. It is believed that 'ate-complexes are the reactive entities involved, salt-free CuR-type reagents being ineffective for conjugate addition.\(^{181,184,185}\) Lithium organohalocuprates such as\(^{194}\) are presumably present in mixtures or CuR-type reagents and lithium salts:

\[
\text{CuR} + \text{LiI} \rightleftharpoons \text{Li}^+ (\text{ICuR})^{-}
\]

Attack of a cuprate on an \(\alpha,\beta\) unsaturated carbonyl compound such as an enone could proceed by direct nucleophilic addition to the beta carbon atom, followed by transfer of the organic group R:

The reactivity and preference for 1,4 addition shown by organocopper(1) reagents has been explained by invoking electron transfer from the cuprate to the enone \(\pi\) system as an initial step.\(^{181}\) This process would lead to a charge-transfer complex, or in the extreme of a true one-electron transfer, an organocopper(II) species and a radical anion similar to those formed during dissolving metal, electrochemical
and other one-electron transfer reductions of \(\alpha,\beta\) unsaturated ketones, \(^{186}\) the unpaired electron residing mainly on the beta carbon atom:

\[
\begin{align*}
\text{RCu(I)X} & \rightarrow \text{RCu(II)X} \\
\end{align*}
\]

The reaction could then proceed either by direct transfer of an alkyl radical \(R'\) to the beta carbon atom of \(^{197}\), \(^{181}\) or via recombination to intermediate \(^{195}\).

An interesting refinement of the one-electron transfer hypothesis has recently been proposed. \(^{180}\) It is suggested that the substrate, in the role of an oxidising agent, removes a single electron from the cuprate in dimeric form, giving a cationic species \(^{198}\) formally containing copper in both \(\text{Cu(I)}\) and \(\text{Cu(II)}\) oxidation states. This process would be followed by recombination of \(^{198}\) with radical anion \(^{197}\) to give an intermediate analogous to \(^{195}\). (More powerful oxidising agents such as oxygen might act by removing two electrons from the dimeric cuprate, which would explain the retention of stereochemistry of the \(R\) groups in the resulting dimers \(^{199}\)):

\[
\begin{align*}
\text{Li}_2\text{Cu}_2\text{R}_4 & \rightarrow (\text{Li}_2\text{Cu}_2\text{R}_4)^+ \rightarrow 2\text{Li}^+ + \frac{2}{x} \text{(CuR)}_x + \text{R-R} \\
\end{align*}
\]
This proposal followed the observation that $\alpha,\beta$ unsaturated carbonyl compounds with reduction potentials above an upper threshold value do not react with cuprate reagents, presumably because they are incapable of abstracting an electron. On the other hand, substrates with reduction potentials below a lower limit undergo reduction rather than conjugate addition, probably by abstraction of two electrons from the cuprate dimer.

In a recent paper, Hannah and Smith describe evidence that conjugate additions to $\alpha,\beta$ unsaturated ketones may proceed by transfer of two electrons from the cuprate, giving a dianion (probably complexed) and an organocopper(III) species such as $201$. Electrophilic attack would then take place at the beta carbon atom, leading to the usual products:

$$\text{C} = \text{C} \quad \text{LiCuR}_2 \quad \rightarrow \quad \text{C}^- \quad \text{O}^- \quad \text{Li}^+$$

$$\rightarrow \quad \text{C} \quad \text{C} = \text{C} \quad + \quad \text{RCu(I)}$$
The enolate \textbf{196} may take the form shown, with the oxygen atom closely associated with a lithium cation. This is certainly the case in instances where CuX is precipitated from the reaction mixture, as when lithium dimethyl cuprate is used in the absence of added ligands (methylcopper is precipitated).\textsuperscript{180} Alternatively, the enolate \textbf{196} may interact with CuX to form an 'ate-complex \textbf{202}; this would explain the general observation that only one organic group R of lithium diorganocuprates LiCuR\textsubscript{2} can be transferred to the \(\alpha,\beta\) unsaturated carbonyl substrate. Protonation of \textbf{196} or \textbf{202} during work-up leads to the final product, ketone \textbf{203}.

\[
\begin{align*}
\text{Li}^+ & \quad \text{O} \quad \text{CuX} \\
\text{R} & \quad \text{C} \quad \text{= C} \quad \text{= C} \\
\end{align*}
\]

\textbf{202} \hspace{1cm} \textbf{203}

Although CuR-type reagents are in principle more economical than cuprates LiCuR\textsubscript{2} since they permit full utilisation of the organic groups R, the cuprates are generally preferred for practical purposes since they are ether-soluble in the absence of added ligands and often give better, more reproducible yields and greater stereoselectivity. The advantage of ether-solubility is lost with organic groups such as vinyl\textsuperscript{180} whose organocopper(I)
compounds are relatively unstable, since it is then usually necessary to work at lower temperatures (preferably below \(-40^\circ\)) and a solubilised source of copper is therefore required. Nevertheless, cuprates have been used almost exclusively in applications to prostaglandin synthesis, despite the fact that preparation of the appropriately substituted vinyllithium precursors involves complex syntheses, sometimes including resolution of enantiomers. In a model prostaglandin synthesis, the CuR-type reagent 204, derived from vinyllithium 205 and copper(I) iodide, gave very low yields of conjugate adducts (about 2\%). The corresponding lithium divinylcuprate gave much better results, although it should be noted that the presence of an added ligand was necessary for really good yields.

![Chemical Structures]

- **204**  \(M = Cu\)
- **205**  \(M = Li\)
- **206**  \(M = LiCu(CN)\)
The inefficiency of lithium diorganocuprates has stimulated considerable interest in mixed cuprates LiCuRY, in which the group Y is not transferred during conjugate addition reactions. The usual approach to the design of such reagents is to choose a retained group Y whose copper(I) compound CuY can conveniently be prepared and isolated under ordinary laboratory conditions, and is itself incapable of conjugate addition. Examples include nitrile, \textit{tert}-butoxy, and some alkynyl groups, notably 1-pentynyl and 3,3-dimethyl-1-butynyl. Copper(I) \textit{tert}-butoxide and 3,3-dimethyl-1-butynylcopper(I) have the advantage of ether-solubility, but the first of these is unsuitable for addition of vinyl groups, and the second is not readily available. 1-pentynylcopper(I) is conveniently prepared from commercially available 1-pentyne, and readily ether-solubilised by the water-soluble ligand hexamethylphosphorous triamide. A mixed cuprate containing the nitrile ligand has been used for 1,4 additions of the vinyl group, but the substituted vinyl cuprate prepared from vinyl lithium and bis(triethylphosphite)copper(I) cyanide in diethyl ether or tetrahydrofuran at -78\degree, was found to be too thermally unstable.

Attention has also been given to mixed cuprates in which the retained group Y is an alkyl group capable of conjugate addition, but less reactive than the group which it is desired to transfer. These reagents are prepared by adding separately one equivalent each of the organolithium compounds containing the R and Y groups to the copper(I) source, for example:
LiCH=CH₂ + CuI → LiI + CuCH=CH₂ → LiI + LiCu(CH₃)CH=CH₂

Lithium methylvinylcuprate \(193,238\) selectively transfers the vinyl group to 2-cyclopentenone when used in tetrahydrofuran, but both groups are transferred in diethyl ether. Its advantages are that its precursors are readily available, and it can be prepared in the absence of added ligands.

Synthetic intermediates which have been used in published applications of cuprate 1,4-additions in the prostaglandin field include cyclopentenones \(207 - 211\) and vinyllithium reagents \(212 - 214\). All the products isolated (generalised structure \(215\)) have the "natural" 8,12-trans stereochemistry (prostaglandin numbering), as anticipated for protonation of their enolate precursors to give products of maximum thermodynamic stability. In one case, \(47\) it was shown conclusively that no 8,12-cis compounds were formed.

Enones of type \(207\) and \(208\) have been used in conjunction with cuprates derived from vinyllithium \(48\) and trans-vinyllithium reagents \(212,46\) and of type \(213,47,49,70,237,239\) and from the racemic and separate enantiomeric forms of the cis-vinyllithium reagent \(214\) \(194\) in order to prepare intermediates in syntheses of \(E\) prostaglandins (the use of octenylithium \(212\) leads to 15-deoxy-prostaglandins). In general, cuprates preferentially attack cyclic enones from the least hindered side of the ring, the degree of stereoselectivity increasing with the bulk of the ring substituent(s) and of the incoming group. \(174\) This preference is very great in conjugate additions leading to \(E\) prostaglandins, particularly when bulky groups such as tert-butylidimethylsilyl \(70,237\) are used to protect
$R = \text{THP}^{46,47,48,239}$

or $\text{C(CH}_3\text{)}_2\text{OCH}_3$, $^{49,194}$

$R' = \text{C}_2\text{H}_5^{46,47}$ or $\text{CH}_3^{48,49,194}$

$X = \text{H}$ or $\text{RO}^{46,195,196}$

$\text{THP} = \text{tetrahydropyran-2-yl}$
the potential 11- and 15-hydroxy groups, with the result that the substituents at positions 11 and 12 in the adducts 215 (Z ≠ H) have the "natural" trans relationship. The combinations of optically active starting materials 208 with 213 70,237 and 209 with 213 164,237 therefore provide completely stereospecific syntheses of prostaglandins E₁ and E₂. Enone 210 has been used with 212, and with a racemic version of 213 (R = α-ethoxyethoxy) to prepare 11,15-dideoxyprostaglandin E₂, and 11-deoxyprostaglandin E₂ and its 15β-diastereoisomer. 195 Another racemic version of 213 (R = tert-butyldimethylsilyl) has also been described. 182 Finally, 11-deoxy E₁ prostaglandins have been prepared from enone 211 using vinyllithium 48 and substituted vinyllithium reagents 214 194 (in racemic and in both enantiomeric forms), 213 196 and an optically inactive version of 213. 49

Good yields of adducts 215 were generally obtained from enones 207 - 211 using equivalent or slightly excessive quantities of the cuprates, notable exceptions arising when the α-methoxy-α-methyl ethyl group was used to protect the potential 15-hydroxyl function, especially in a synthesis of prostaglandin E₁ where the potential 11-hydroxyl function was similarly protected. 49

The enolates resulting from organocopper(I) conjugate additions have high positional stability, and in principle their C-alkylation represents a convenient method of introducing an alpha substituent regiospecifically. This is readily achieved when the enolate anion is a highly stabilised species such as a malonate ion. 197
However, the effectiveness of the method as a synthesis of α,β-disubstituted ketones from conjugated enones depends on the rate of alkylation being much greater than that of enolate ⇄ ketone equilibration (via proton transfer reactions), and the enolates arising from 1,4-additions to such enones tend to be rather unreactive towards organohalide alkylation agents. This low reactivity could be due to the metal-oxygen bond of copper(I) enolates 202 having a highly covalent nature, although in one case comparison with a pure lithium enolate showed little difference in alkylation reactivity.198 Some encouraging results have been obtained using dipolar aprotic solvents such as 1,2-dimethoxyethane, hexamethylphosphoramide, or tetrahydrofuran as solvents for the alkylation stage, but side reactions tend to persist if alkylation is retarded by steric hindrance, for instance when the organic group of the halide is bulky 198 or the starting enone has two beta substituents.199

When the starting enone is cyclic, the alpha and beta substituents of its conjugate addition - alkylation products are preferentially arranged for highest thermodynamic stability. For example treatment of 2-cyclohexenone with lithium dimethylcuprate in diethyl ether followed by methyl iodide in dimethoxyethane gave a 4:1 mixture of trans- and cis-2,3-dimethylcyclohexanone.198 Similarly, prostaglandin model 217 has been prepared in 69% overall yield by allyl bromide alkylation of enolate 216, generated from 2-cyclopentenone and lithium methylvinylcuprate in tetrahydrofuran.193,238

![Chemical structures](image)
In an independent prostaglandin synthesis \(^{200}\) (Scheme 10), Patterson and Fried were unable to alkylate enolate 218 directly with methyl \textit{cis}-7-bromohept-5-enoate. They overcame this problem by trapping the enolate as its trimethylsilyl ether 219, which was converted to a mixture of prostaglandin intermediate 220 and its 8,12-stereoisomer by regeneration of the lithium enolate with lithium amide, then alkylation in liquid ammonia.

**Scheme 10**

\[
\begin{align*}
\text{O} & \quad + \quad \text{LiCu} \left( \begin{array}{c}
\text{OC(CH}_3\text{)}_2\text{OCH}_3 \\
\text{M} = \text{Li or CuRLi}
\end{array} \right) \\
\rightarrow \quad \text{MO} & \quad \begin{array}{c}
\text{OC(CH}_3\text{)}_2\text{OCH}_3 \\
\text{M} = \text{Si(CH}_3\text{)}_3
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{M} & = \text{Li or CuRLi} \\
\text{M} & = \text{Si(CH}_3\text{)}_3
\end{align*}
\]
The methods of preparing organolithium reagents have recently been reviewed by Wakefield. The most general procedure involves the reaction of organic halides with lithium metal:

\[ \text{RHal} + 2\text{Li} \rightarrow \text{LiR} + \text{LiHal}. \]

A catalytic quantity of sodium must usually be present in the lithium, normally 1-2%. The rate of the reaction increases in the order of halogens Cl < Br < I, but so does the risk of Wurtz coupling.

Another favoured procedure utilises metal-halogen exchange:

\[ \text{RHal} + \text{LiR}_1 \rightarrow \text{LiR} + \text{R}_1\text{Hal}. \]

This reaction is applicable to the preparation of vinyl lithium reagents since the equilibrium lies well to the right when \( R = \text{vinyl} \) and \( R_1 = \text{alkyl} \), vinyl groups being better stabilisers of negative charge. The vinyl lithium reagents used in prostaglandin syntheses have mostly been generated from the corresponding iodides. Lithium metal is often used, but is unsuccessful in at least one instance. Metal-halogen exchange has the intrinsic disadvantage that alkyl halides are produced as by-products, and can undergo coupling reactions with organocopper(I) reagents. A neat solution to this problem is to use two equivalents of tert-butyllithium:

\[ 2t\text{-C}_4\text{H}_9\text{Li} + \text{I} \rightarrow \text{Li} + \text{C}_4\text{H}_{10} + \text{CH}_2=\text{C(C(H)}_3\text{)I} \cdot \]

The conversion of 1-alkenyl halides to 1-alkenyllithium reagents and their subsequent transformation to organocopper(I) reagents both proceed with high retention of double bond geometry.
Before proceeding with the preparation of an alkenyl halide appropriate for the construction of the lower side-chain of a prostaglandin analogue, the suitability of enone 51 as a substrate for vinylcopper conjugate addition was tested using lithium di-1-propenylcopper(I), generated from commercially available 1-bromopropene.

![Chemical Structure of 51]

1-Propenyllithium was made from 1-bromopropene (a mixture of cis and trans isomers) and lithium metal in diethyl ether at -10°C, following the procedure of Näf and Degen; it was found necessary to initiate the reaction by warming briefly to 0°C. The reason for this sluggishness may have been the relatively low concentration of sodium in the lithium employed for this experiment, which was rated 99.9% pure, compared to Näf and Degen's, which contained 1.5% sodium. Lithium di-1-propenylcuprate was prepared by adding
the 1-propenyllithium solution to 0.5 equivalents of copper(I) iodide in diethyl ether at -35°. 67

The reaction of enone 51 with three equivalents of lithium di-1-propenylcuprate gave racemic 221 in 78% yield after chromatographic purification on florisil. The stereochemistry shown for 221 was predicted on the basis that protonation of the enolate resulting from the conjugate addition should give the thermodynamically favoured trans arrangement of the side chains. Gas-liquid chromatographic analysis of the crude product (94% yield) on a column of silicone OV1 at 250° revealed the presence of a small quantity of unreacted enone 51 (retention time 4 minutes) and adduct 221 (6 minutes), the ratio of their peak areas being 8 : 92. Partial separation was achieved by florisil chromatography, so that the overall ratio for the best fractions was 5 : 95. The structure of the product 221 was confirmed by spectroscopic measurements of the best of these (ratio 3 : 97). In the ultra-violet there was no strong absorption above 215 nm, and in the infra-red spectrum there was a strong band due to the ring carbonyl group at 1711 cm⁻¹, while the presence of cis and trans alkenes was indicated by bands at 721 and 968 cm⁻¹.

In the proton nuclear magnetic resonance spectrum of 221, the ring methylene groups gave rise to AB quartets at τ 6.59/6.86 and τ 7.23/7.26. The first of these was assigned to the 11α-methylene group (numbering for 221 as an 11α-homo-11-thiaprostaglandin) on the basis that the doublet splitting of the τ 6.59 lines (J 5 Hz) was due to coupling with the 12-methine group. The high-field pair of each quartet showed fine doublet splitting (J 1.5 Hz) which could have been due either to coupling across sulphur, or across the
carbonyl group between positions 8 and 10 and between positions 11a and 12. The complex multiplets expected for the ring methine groups at positions 8 and 12, at about τ 7 and 7.8, were hidden by the AB quartets mentioned above and the triplet for the 2-methylene group at τ 7.71, but their presence was apparent from the integrated intensities in these regions.

The vinylic methyl groups (position 15) of the isomers of 221 differing in the geometry of the lower side-chain gave rise to doublets at τ 8.31 (J 4.3 Hz) and 8.37 (J 5.6 Hz). These signals overlapped to form an approximately 1:2:1 unsymmetrical triplet, indicating that roughly equal amounts of the two isomers were present.

cis - trans Isomerisation of 1-bromopropene is known to take place at room temperature, the equilibrium composition being 60-70% cis. The infra-red spectra of the pure isomers have strong alkene in-plane deformation bands of approximately equal intensity at 1285 (cis) and 1200 cm$^{-1}$ (trans). On this basis, the concentration of the cis isomer in the commercial olefin was found to be about 60%. The proton nuclear magnetic spectra of 1-halopropenes have considerable second-order character, so the proportions of the cis and trans isomers of the commercial 1-bromopropene could not be verified by inspection of its nuclear magnetic resonance spectrum.
Since the preparation and conjugate addition of lithium di-1-alkenylcuprates proceed with high retention of double bond geometry, any change in cis : trans ratio is due to different reaction rates. The rate of addition of the cis-1-propenyl moiety to enone 51 was therefore slightly less than or equal to that of its trans counterpart, in contrast to literature reports of cis isomers of lithium di-1-alkenylcuprates being more reactive than their trans isomers in conjugate additions to 2-cycloalkenones.

Having demonstrated the suitability of enone 51 as a substrate for conjugate addition of vinylcopper reagents, the synthesis of a prostaglandin analogue was undertaken. Racemic 11,15-dideoxy-11a-homo-11-thia-prostaglandin E₁ (228) was chosen as the target compound. The appropriate alkene for construction of the lower side-chain, trans-1-octenyl iodide (226) was prepared from 1-octyne in 42% yield by a method recently developed by Brown and co-workers (Scheme 11).
Scheme 11

```
H_2O  
\[ \text{Et}_2\text{O, 0°} \]

NaOH - \( \text{H}_2\text{O} \)

\[ \text{Et}_2\text{O, 0°} \]

\[ \text{I}_2 \rightarrow \text{Et}_2\text{O, 0°} \]

\[ \text{THF} = \text{tetrahydrofuran} \]
\[ \text{Et} = \text{C}_2\text{H}_5 \]
```
Catecholborane \((222, 1,3,2\text{-benzodioxaborole})\), prepared from borane-tetrahydrofuran and catechol, undergoes rapid, selective, stereospecific cis hydroboration of alkynes to yield trans-2-alkenyl-1,3,2-benzodioxaboroles in which boron is attached to the least hindered end of the acetylenic group; it therefore gives \(223\) from 1-octyne.\(^{207}\) The hydroboration products are readily hydrolysed to trans-alkenylboronic acids such as \(224\) by the action of water.\(^{209}\) Successive treatment in diethyl ether of the isolated boronic acids derived from terminal alkynes with aqueous sodium hydroxide and iodine leads to trans-1-alkenyl iodides such as \(226\) of at least 99% stereochemical purity.\(^{207}\) The reaction of iodine with alkenylborate anions such as \(225\) involves more than one mechanistic step, since the uptake of iodine is more rapid than the formation of the final product.

The reaction of trans-1-octenyl iodide with lithium metal in diethyl ether was slow, even at room temperature. Gas-liquid chromatographic analysis of the reaction mixture after 20 hours showed that about 80% of the iodide had been consumed, and dissolution of the lithium was incomplete. The presence of an organolithium reagent could be demonstrated by a Gilman colour test with Michler's ketone (4,4'-bis-dimethylaminobenzophenone):\(^{210}\) addition of the organolithium solution to the ketone in benzene, hydrolysis of the resulting lithium alkoxide with water, and addition of iodine in acetic acid led to the formation of an intense blue carbonium iodide in the organic layer. However, a white precipitate was present in the organolithium mixture, suggesting that substantial loss of the reagent had occurred by thermal decomposition, or by reaction with diethyl ether to
In subsequent experiments trans-1-octenyllithium was conveniently prepared from trans-1-octenyl iodide and two equivalents of commercially available tert-butyllithium in diethyl ether at \(-78^\circ\). An alternative method of overcoming the problems encountered with lithium metal might be the use of lithium containing 1-2% sodium, but tert-butyllithium was more readily available and offered the advantage of lower reaction temperature.

![Chemical structure](image)

\[ R = \text{C}_2\text{H}_5 \]
\[ R = \text{H} \]

Thianone ester 227 was prepared by conjugate addition of a mixed cuprate reagent, lithium trans-1-octenyl-(1-pentynyl)cuprate, to enone 51. The cuprate was generated by adding trans-1-octenyllithium solution to a small excess of 1-pentynlcopper(I) - hexamethylphosphorous triamide 1:2 complex dissolved in diethyl ether, at \(-78^\circ\).

(1-pentynlcopper(I) was prepared by reduction of copper(II) sulphate with hydroxylamine and treatment with 1-pentyne \(^{212}\)). The conjugate addition was performed by adding enone 51 to 1.2 equivalents of the mixed cuprate reagent in diethyl ether at \(-78^\circ\), gradual warming to
room temperature, and protonation of the resulting enolate with aqueous ammonium sulphate.

Flask fitted with silicone rubber septa were used for operations involving tert-butyllithium and 1-octenyllithium, and liquids were transferred by means of hypodermic syringes. In the first run the crude product (52% yield) was shown by gas-liquid chromatographic analysis on silicone OV1 at 250° to be a mixture of thianone ester 227 (retention time 20 minutes) and starting enone 51, in ratio of peak areas 60:40. Octenyl iodide (about 8% of the starting weight) was also shown to be present, using a column temperature of 170°. The poor result was attributed to loss of octenyllithium in transfer, and side reactions involving octenyl iodide, rather than inherent inefficiency of the conjugate addition. These faults were corrected by the use of hypodermic syringes mounted in spring-loaded syringe pipette holders and fitted with taps, and by increasing the amount of tert-butyllithium to a slight excess over octenyl iodide, following a precedent in the prostaglandin literature.

In the next run the crude product (105% of theoretical yield) was found to contain only 2% enone 51, but two new components were detected by gas-liquid chromatography. These components, which eluted at 8 minutes and were not completely resolved, accounted for 8% of the total peak area. No trans-1-octenyl iodide could be detected. Chromatographic purification of the crude product on silica gel led to thianone ester 227 in 50% yield free of enone 51 and homogeneous to thin layer chromatography on silica gel, but only partial removal of the new components was achieved,
their proportion falling to 5% judged as above.

The infra-red spectrum of the chromatographed product, an oil at room temperature, contained a strong band at 1705 cm\(^{-1}\) assigned to the ring carbonyl group of 227, and a band at 962 cm\(^{-1}\) as expected for a trans alkene. The proton nuclear magnetic resonance spectrum had much in common with that of model compound 221, particularly in that the ring methylene groups (positions 10 and 11a) gave rise to similar AB quartets, and the methine signals (positions 8 and 12) were obscured. The AB quartet at lower field (\(\tau\) 6.70/6.96) was assigned to the 11a-methylene group by analogy with model compound 221, and later, with acid 228. As in the model compound, fine doublet splitting of 1.5 Hz was observed for the high-field pair of lines of that AB quartet assigned to the 10-methylene group (\(\tau\) 7.26/7.34). This splitting was presumably due to coupling across the carbonyl group to the 8-methine proton. The apparent absence of coupling between the 11a-protons and that at the 12-position cannot mean that both dihedral angles are near 90° for that would be impossible. Possibly the expected coupling between one of the protons at the 11a-position and that at the 12-position is too small to have been resolved, having been reduced by a trans-coplanar arrangement of the electronegative sulphur atom and 12-methine proton.\(^{214}\)

The signals due to the olefinic protons at positions 13 and 14 (\(\tau 4.71\) and 4.44) were coupled with doublet splitting 15.5 Hz, in accordance with the trans geometry of the 13,14 double bond. The intensity of these signals was lower than theory by 5%, suggesting that the unidentified impurities in the product lacked the olefinic system. The integrated intensity for the
region (τ 7.9 - 9.0) containing the five methylene groups of the lower side-chain, five methylene groups of the upper side-chain (positions 3-7), and the ethyl ester methyl group, was low by 0.6 H, while the triplets for the other methylene groups of the upper side-chain (position two and ethyl ester, τ 7.72 and 5.85) had proper intensities. The impurities therefore seemed to lack the whole of the lower side-chain whilst retaining the upper side-chain intact. On the other hand, the intensity of the end-of-chain methyl signal (position 20, triplet at τ 9.11) was higher than theory (3.3 H), and a sharp singlet of unknown origin was present at τ 9.08. Taking into account the loss of 5% of the lower side-chain, the contribution of the impurities to the integrated intensity at τ 9.1 was 0.45 H. A reasonable explanation for these observations would be that the two impurities in the product were thianone \textsuperscript{229} and an isomeric compound; the singlet at τ 9.08 could be assigned to the \textit{tert}-butyl group, the surplus intensity in this region of the spectrum being 5% of 9H.

\[ \begin{align*}
\text{O} & \quad \text{CO}_2\text{C}_2\text{H}_5 \\
\text{S} & \quad \text{t-C}_4\text{H}_9
\end{align*} \textsuperscript{229} \]
This explanation also accounts for the difficulty encountered in separating the impurities from the desired thianone 227 by preparative liquid chromatography on silica gel, since 227 and 229 would have similar "polarity". The gas-liquid chromatographic retention times of the impurities (slightly longer than that of model thianone 221 and much shorter than that of 227) were compatible with structure 229, since retention times of structurally similar compounds on "non-polar" absorbents increase steadily with molecular weight.

The formation of compound 229 would have resulted from conjugate addition to enone 51 of lithium tert-butyl-(1-pentynyl)cuprate, implying contamination of the trans-1-octenyllithium with unreacted tert-butyllithium. Comparison of the results of the two runs led to the conclusion that the formation of impurity 229 would be prevented if a small excess of octenyl iodide over tert-butyllithium were used; loss of cuprate reagent by coupling with the excess iodide would not matter provided the excess of cuprate over enone was greater. This remedy was applied to a small-scale experiment and proved to be effective.

The mass spectrum of 227 had an intense molecular ion peak at 382 a.m.u. as expected. The principle fragment ions corresponded to loss of C_2H_5O and C_2H_5OH from the molecular ion, the latter transition being supported by a metastable peak, and a peak corresponding to loss of the entire upper side-chain by cleavage of the 8,9 bond, with and without transfer of a hydrogen atom to the remaining fragment. There were also peaks of low intensity indicating loss of water, and of the lower side-chain by a typical n-alkane fragmentation pattern (loss of CH_3, C_2H_5... C_6H_13, ...
(M-C$_3$H$_7$)$^+$ and (M-C$_6$H$_{13}$)$^+$ being relatively intense).

An experiment with model thianone 221 indicated that the enzymatic hydrolysis procedure employed for the hydrolysis of enone 51 was suitable for the hydrolysis of thianone esters in general. The carboxylic acid corresponding to 221 was thus obtained in 70% yield as a yellow oil. Its ultra-violet and infra-red spectra were similar to those of the starting ester, except that the infra-red spectrum had an extra broad band at 3000 cm$^{-1}$ due to the hydroxyl group, and the carbonyl bands were not separately resolved (1709 cm$^{-1}$).

The enzymatic procedure was much less successful when applied to the preparation of prostaglandin analogue 228 from thianone ester 227. The crude product, obtained in only 11% yield, was contaminated with starting ester, even though work-up was not attempted until no further addition of sodium hydroxide was necessary to maintain a steady pH. Droplets of oil were noticed in the reaction mixture prior to denaturation of the enzyme, so it seemed likely that the increased hydrophobic character of the substrate (due to the lengthening of the lower side-chain) had caused it to coagulate, thus preventing intimate contact between ester and enzyme.

Homogeneous, mildly alkaline hydrolysis conditions (0.05M-potassium carbonate in 3:1 methanol-water) were more successful.
The hydrolysis was complete in 66 hours at room temperature, as judged by gas-liquid chromatography, and gave the crude acid 228 as a waxy solid (melting point about 30°) in 69% yield. The product was homogeneous to thin layer chromatography on silica gel, but separation of 228 from the acids derived from the impurities in the starting ester (believed to be 229 and an isomeric compound) was not anticipated, considering experience with the ester. The crude acid resisted many attempts at recrystallisation, showing a high tendency to precipitate as an oil, but eventually a small recrystallised sample (melting point 43-49°) identical with the crude product by infra-red spectroscopy and thin layer chromatography, was obtained. Its proton nuclear magnetic spectrum showed no sign of a tert-butyl group, and was very similar to that of ester 227 apart from the expected absence of ethyl ester signals. The coupling constant relating the low-field doublet of the 11-methylene AB quartet to the 12-methine group was 2.6 Hz; no other splittings of the AB quartets assigned to the ring methylene groups were apparent.

The infra-red spectrum of acid 228 resembled that of the model acid derived from ester 221 in that it had a broad hydroxyl band at 3100 cm⁻¹ and a single carbonyl band at 1705 cm⁻¹. Its mass spectrum had a molecular ion peak at 354 a.m.u., as expected. The principle fragment ion peaks corresponded to loss from the molecular ion of H₂O (supported by a metastable peak), of CH₂=C(OH)₂ + H (McLafferty rearrangement), of the entire upper side-chain by cleavage of the 8,9 bond (with and without hydrogen transfer) and stepwise fragmentation of the lower side-chain, (M-C₃H₇)⁺ and (M-C₆H₁₃)⁺ providing the most prominent of the relevant peaks.
DISCUSSION

Electrophilic Chlorination of Sulphides and Sulphoxides

In contrast to the alpha chlorination of ketones by tert-butyl hypochlorite, which depends on the acidity of the alpha hydrogen atom(s), the reactions of electrophilic chlorinating agents with sulphides and sulphoxides commence by chlorination at sulphur. The final products may be formally the result of oxidation at sulphur or alpha chlorination, depending on the nature of the substrate, and on the reaction conditions.

Electrophilic chlorination of sulphides and sulphoxides leads initially to chlorosulphonium ions and chlorosulphoxonium ions respectively. Chlorosulphonium ions generated with tert-butyl hypochlorite are converted rapidly to tert-butoxysulphonium ions, or other alkoxysulphonium ions if an alcohol (other than tert-butanol) is employed as solvent. Alkoxysulphonium ions may be decomposed cleanly to sulphoxides by the action of sodium bicarbonate, sodium carbonate or water, or less efficiently by heat, some being unstable at room temperature. Sulphoxide was therefore a possible unwanted product of the chlorination of β-diketone intended in the synthetic route shown in Scheme 2, the desired product being the 4-chlorosulphide. The generally preferred solvent for tert-butyl hypochlorite oxidation of sulphides is methanol. In the absence of sodium carbonate or water, the rate of sulphoxide formation increases considerably on changing from a non-polar to a polar solvent.
This effect is presumably due to acceleration of the decomposition step, since the sulphonium ions are known to be formed rapidly at -78°C. Formation of α-chloro sulphides via electrophilic chlorination of sulphides has not been reported.

\[
\begin{align*}
&\text{Formation of sulphones by analogous transformations of chloro-sulphoxonium ions can occur,}\quad 215-217,219 \\
&\text{but in the absence of alcohol and of water the usual products are α-chloro sulphoxides. Exceptions arise when the substrate contains a neighbouring nucleophilic substituent, such as a hydroxy or amino group, capable of participating in the formation of a cyclic alkoxy- or alkylamino-sulphoxonium ion.}\quad 215,219-221 \\
&\text{Similar neighbouring group participation has recently been demonstrated in the tert-butyl hypochlorite oxidation of thianes containing 4-hydroxy and 4-carbonyl groups; participation of the carbonyl group is thought to involve prior formation of the ketone hydrate.}
\end{align*}
\]
The formation of α-chlorosulphoxides from chlorosulphoxonium ions may proceed by either (1) elimination of hydrogen chloride followed by nucleophilic attack by chloride ion at the alpha carbon atom (path A)\(^{215,220,222-225}\) or (2) base-promoted abstraction of an alpha proton and rapid or concerted migration of chlorine from sulphur to the alpha carbon atom (path B).\(^{226-228}\)

The stereochemistry of the chlorination of conformationally-biased thian-1-oxides has recently been studied by two groups of workers with the aim of distinguishing between the two paths, one favouring path A,\(^{222}\) the other path B.\(^{226}\) The two proposed mechanisms are incorporated in Scheme 12, which shows how their stereochemical outcomes may differ. Chlorination of trans and cis sulphoxides \(^{232}\) and \(^{233}\) leads to chlorosulphoxonium ions \(^{234}\) and \(^{235}\) respectively, which are interconvertible via nucleophilic displacement by chloride ions present in the reaction medium. Elimination of hydrogen chloride (promoted by the counter anion) requires a trans-coplanar arrangement of the departing atoms, and can therefore only occur from the cation having axial chlorine (\(^{234}\)), leading to ylid \(^{236}\). The major product of path A is therefore \(^{239}\), resulting from axial attack on \(^{236}\) by chloride ion or by hydrogen chloride.\(^{222}\) Path B, on the other hand, can account for instances in which the major product is of either type (\(^{240}\) or \(^{239}\)), since proton abstraction can occur from either chlorosulphoxonium ion (\(^{234}\) or \(^{235}\)). The resulting ylids \(^{237}\) and \(^{238}\) may be interconvertible via ion-pair formation; chlorine migration leads to the final products \(^{240}\) and \(^{239}\). If the equilibration steps are relatively slow (kinetic control) the product ratio is determined by the stereochemistry of the starting material, that is, chlorination of \(^{232}\) leads to \(^{240}\) rather than \(^{239}\) as in path A, and so on. If the chlorine migration
Scheme 12

Path A - HCI

\[ \text{Path } A \rightarrow \text{Path } B \]

R = a bulky substituent
steps are slow, the product ratio is determined by thermodynamic control.

Particularly strong evidence for path A comes from the observation that the only products formed from thian-1-oxides 232 and 233 (R = phenyl, p-chlorophenyl or tert-butyl) and excess chlorine are 2,5-dichloro compounds in which the sulphoxide oxygen and chlorine atoms are all \textit{cis} to one another and \textit{trans} to the substituent R, strongly suggesting that \textit{trans}-dixial elimination of hydrogen chloride is a vital step.\textsuperscript{222} These products would not result from path B under kinetic control, yet are certainly not the most thermodynamically stable isomers. In addition, path B would allow geminal dichlorination. Conflicting evidence is provided by the observation that the product ratio can sometimes be influenced by the presence of silver nitrate catalyst. Chlorination of 232 and 233 (R = \textit{p}-chlorophenyl) with (dichloroiodo)-benzene, normally leads mainly to 239. In the presence of silver nitrate 233 is still converted to 239, but 232 is mostly converted to 240, evidently an instance of kinetic control.\textsuperscript{226} This does not prove that path B is important in the absence of silver nitrate, but at least demonstrates that the relative importance of the two mechanisms depends on the reaction conditions.
RESULTS

In view of the risk of attack at sulphur during the chlorination of dione 47, the synthesis of model enone 241 was undertaken. The starting material for this synthesis, 2-heptylcyclohexan-1,3-dione (242), was prepared by the alkylation of cyclohexan-1,3-dione enolate with iodoheptane.

The conditions which had been employed routinely for the preparation of 47 (sodium hydride, dimethylformamide) proved unsuitable for that of 242. Gas-liquid chromatographic analysis of samples of the reaction mixture prior to work-up, on a silicone OVI column at 220°C, indicated the presence of four product components, eluting at 3, 4, 12 and 19 minutes. Only the first of these was removed on treatment of the samples with alkali, suggesting that it was the desired C-alkylation product 242, and that the others were the results of O- and di-alkylation. The ratios of the four products were about 10 : 80 : 5 : 5, that is the C : O-alkylation ratio was much lower than that for thian-3,5-dione under similar conditions, in accordance with the lower tendency of the heterocyclic diketone to enolise (see page 80).

The C-alkylation product was separated from the reaction mixture by
partitioning between diethyl ether and aqueous sodium bicarbonate, and then recovered by acidification of the aqueous extracts and extraction with diethyl ether. The crude product, obtained in only 5% yield, melted at 52-60° and was shown by gas-liquid chromatography to be contaminated with cyclohexan-1,3-dione and the major by-product eluting at 4 minutes. (The melting point of pure 242 was later found to be 90-91°.) More useful results were obtained using the conditions recommended by Stetter and Dierichs for the C-alkylation of cyclohexan-1,3-dione with saturated alkyl halides, that is with methanol as solvent and potassium as counter-ion. Work-up was conducted by removing the solvent and replacing it with diethyl ether, extraction with aqueous sodium hydroxide (more efficient than the bicarbonate) and acidification of the aqueous extract. The C-alkylation product 242 was precipitated immediately in 12% yield, and was sufficiently pure for further synthetic experiments. Gas-liquid chromatographic analysis of the mother liquor showed only a trace of cyclohexan-1,3-dione. The ultraviolet spectrum of 242 showed a strong $\pi \rightarrow \pi^*$ absorption at 263 nm (comparable to 2-methylcyclohexan-1,3-dione, 261 nm) which, as expected, was shifted to longer wavelength (294 nm) on addition of alkali. Its infra-red spectrum had typical $\beta$-diketone carbonyl bands at 1736 and 1701 cm$^{-1}$, and bands due to the enol form at 3140 and 1590 cm$^{-1}$.

No reaction was observed between dione 242 and tert-butyl hypochlorite in chloroform, even at room temperature overnight. This failure was attributed to the deactivating effect of the 2-heptyl substituent; the introduction of a 2-methyl substituent "notably decreases" the acidity of cyclohexan-1,3-diones.
This problem was solved by changing to a more polar solvent, tert-butanol, which has been found useful for chlorinations of monoketones. The tert-butyl hypochlorite was consumed within a few minutes at 25°, and chloro dione 243 was formed in quantitative yield. The product was lower-melting (47-49°) than dione 242, and had a longer gas-liquid chromatographic retention time (7 minutes on silicone OV1 at 220°). A noteworthy feature of its gas-liquid chromatographic behaviour was partial thermal decomposition to give a substance of short retention time (2 minutes), thought to be cyclopentenone 241. The infra-red spectrum of 243 showed typical β-diketone bands at 1737 and 1711 cm⁻¹, and no indication of enolic material.

\[
\begin{align*}
\text{O} & \\
\text{Cl} & \\
\end{align*}
\]

The ring-contraction of chloro dione 243 was readily achieved using Buchi and Eggar's conditions, refluxing in xylene with anhydrous sodium carbonate. Cyclopentenone 241 was obtained in 35% yield after distillation. Its gas-liquid chromatographic retention time on silicone OV1 at 220° was 2 minutes, supporting the earlier assignment of the peak due to thermal decomposition of 243. The infra-red spectrum of 241 contained bands due to the enone system at 1703 (strong) and 1630 (weak) cm⁻¹. Its
As had been feared (page 153) the first stage of the conversion of dione 47 to thiolenone 48 by the chlorination-ring-contraction sequence was hampered by the presence of the sulphur heteroatom. This was clearly demonstrated by an experiment in which 47 was treated with 0.9 equivalents of tert-butyl hypochlorite in dichloromethane at -78°C - room temperature. Formation of the desired chloro dione 231 was not expected to occur under these conditions, considering the result of the model experiment with 2-heptylcyclohexan-1,3-dione in chloroform. Nevertheless, about half of the dione was consumed as judged by gas-liquid chromatography of reaction mixture samples, and potassium iodide-starch tests were negative after one hour at room temperature. The major product, a water-soluble, white solid melting at 150-155°C with decomposition, and not eluting from silicone OV1 at 250°C within 60 minutes, was precipitated in 25% yield. These physical properties were in strong contrast to those of model chloro dione 243, suggesting that a different type of product had been formed. Thin layer chromatographic analyses showed that the liquid phase of the reaction mixture contained unchanged 47 and more of the substance which had been precipitated. An analytically pure sample of the product was obtained by recrystallisation of the precipitate; it was identified as 2-chloro compound 244 (not sulphoxide 230 as had been anticipated) by elemental analysis, and infra-red, ultra-violet, proton nuclear magnetic resonance and mass spectral data.
The infra-red and ultra-violet spectra of 244 showed it to be very enolic, and indicated that there were two enol forms, showing that the introduction of chlorine had been accompanied by loss of symmetry. In the infra-red, there were strong absorptions at 3018 (broad), 1520 and 1404 cm\(^{-1}\), and no strong band near 1050 cm\(^{-1}\) as would have been expected for a sulphoxide. The ultra-violet spectrum, measured at low pH, showed strong \(\pi \rightarrow \pi^*\) absorptions for the two enol forms at 224 and 324 nm; at high pH these shifted to 248 and 366 nm. Four bands were observed under approximately neutral conditions. Even in deuteriochloroform (in which it was sparingly soluble) 244 was substantially enolic; in the proton nuclear magnetic resonance spectrum there was no signal at about \(\tau 6.4\) as expected for the methine proton at the 4-position. The ring methylene group gave rise to a broad singlet at \(\tau 7.07\), and there was a singlet at \(\tau 0.93\) assigned jointly to the 2-proton and to the exchanging protons of the hydroxyl groups of the two epol forms.
In order to obtain a mass spectrum of 244 it was necessary to use an inlet temperature of 200°, that is 50 degrees above its decomposition temperature. The molecular ion (320/322 a.m.u.) was not observed, nor were any other chlorine-containing species apart from HCl. The heaviest ion detected (568 a.m.u.) was presumably the result of condensation of two molecules of 244 with elimination of 2HCl. Fragment ions corresponding to loss from this species of C\textsubscript{2}H\textsubscript{5}O, C\textsubscript{2}H\textsubscript{5}OH, C\textsubscript{2}H\textsubscript{5}O + C\textsubscript{2}H\textsubscript{5}OH and C\textsubscript{2}H\textsubscript{5}O + C\textsubscript{2}H\textsubscript{5}OH + CO were observed. The other principle peaks in the spectrum corresponded to the fragment ions M-Cl, -(Cl + EtOH), -OC1 and -(OC1 + EtOH). The occurrence of the condensation reaction would explain the failure of 244 to elute from the gas-liquid chromatography column.

The formation of 2-chloro compound 244 could not have occurred via initial proton abstraction at position 2 of dione 47, since this position is even less activated than position 4. A possible explanation is that the initial attack was the expected side-reaction - electrophilic chlorination at sulphur. That this did not lead to sulphoxide formation was presumably due to the influence of the carbonyl groups. The mechanism could be analogous to path B of Scheme 12, since the carbonyl groups would encourage abstraction of an alpha proton. Scheme 13 shows the postulated mechanism for the formation of 244 alongside the predicted course of the reaction leading to sulphoxide 230.

It is known that the formation of tert-butoxysulphonium ions such as 249 from chlorosulphonium ions such as 248 proceeds "quickly even at -78°" and that their equilibrium lies well in favour of the former. The conversion of alkoxy sulphonium ions to
Scheme 13

\[ \text{t-BuCl} + \text{47} \rightarrow \text{t-BuO}^- + \text{245} \]

\[ \text{Cl} \quad \text{Cl} \]

\[ \text{t-BuOH} + \text{47} \quad \text{t-BuOH} + \text{247} \]

\[ \text{via} \]

\[ \text{Cl} \quad \text{Cl} \]

\[ \text{t-BuOH} + \text{244} \]

\[ \text{t-Bu} = (\text{CH}_3)_3\text{C} \]

\[ \text{R} = (\text{CH}_2)_6\text{CO}_2\text{C}_2\text{H}_5 \]
sulphoxides is relatively slow (at least in the absence of sodium carbonate or water); for example, ethoxysulphonium ion may be kept in ethanol solution for 30 minutes at room temperature.

\[
\begin{align*}
\text{X} & = \text{Cl} \\
\text{X} & = (\text{CH}_3)_3\text{CO} \\
\text{X} & = \text{C}_2\text{H}_5\text{O}
\end{align*}
\]

The justification for proposing the route to $\alpha$-chloro sulphide shown in Scheme 13 is that ylid 247 has extra resonance stabilisation due to the beta carbonyl group, so that the overall equilibrium $247 \rightleftharpoons 245 \rightleftharpoons 246$ lies more in favour of 247 than it otherwise would. The sulphoxide oxygen atom of the corresponding ylids formed from chlorosulphoxonium ions (for example 236, 237 and 238) presumably plays a similar role, by sharing the positive charge formally located on the sulphur atom. It may be supposed that the rearrangement of ylid 247 to $\alpha$-chlorosulphide 244 would be a faster process than the formation of sulphoxide 230 from alkoxy sulphonium ion 246; the comparable chlorination of thian-1-oxides is "very fast even at low temperatures".
Neighbouring group participation of the kind observed by Klein and Stollar in thian-4-ones was evidently not operating to a significant degree in the reaction of 47 with tert-butyl hypochlorite, since this would lead to sulphoxide; such participation would require considerable distortion of the thian-3,5-dione ring.

In view of the model chlorinations, it was of interest to determine the effect of using an alcoholic solvent with dione 47. Methanol was used in preference to tert-butanol, so that a lower temperature could be employed. (2-Allyl-5-carbomethoxy-cyclohexan-1,3-dione is 2-chlorinated in 95% yield by tert-butyl hypochlorite in methanol at $0^\circ$. Any electrophilic chlorination at sulphur was expected to lead to sulphoxide rather than $\alpha$-chlorosulphide, by analogy with the reactions of sulphoxides. In terms of Scheme 13, the high concentration of methanol was expected to shift the chlorosulphonium = alkoxy sulphonium equilibrium in favour of the methoxysulphonium ion corresponding to 246, and the higher solvent polarity would accelerate the decomposition of the alkoxy sulphonium ion.

A small excess of tert-butyl hypochlorite was added to dione 47 in methanol at $-78^\circ$, followed by gradual warming to room temperature. Consumption of the dione, monitored by gas-liquid chromatography, was complete by the time the temperature had reached $0^\circ$; once again no products could be detected by gas-liquid chromatography. Evaporation of the solvent gave initially a light brown oil, which partly solidified and developed an intense purple colouration as the last traces of solvent were removed. Thin layer chromatographic analysis of the concentrate showed that it contained 2-chloro dione 244, one other major product, and one minor product, in addition to the
coloured material. An infra-red spectrum showed a strong band at 1024 cm\(^{-1}\), suggesting that the major unknown product was sulphone oxide \(^{230}\). Unfortunately, a pure sample of this component could not be isolated by preparative thin layer chromatography. However, it seemed that the principal effect of the change of solvent had been to partially divert the reaction from 2-chlorination to sulphone formation, and not to the desired 4-chlorination.

Chlorination of dione 47 at the desired position might be facilitated by the introduction of an acetylenic linkage between positions 5 and 6 of the side-chain, since 2-alkynylcyclohexan-1,3-diones are readily \(\alpha\)-chlorinated by tert-butyl hypochlorite in chloroform.\(^{57,65}\) Some improvement might also be obtained by using a more polar solvent, but choice would be limited by the condition of inertness to the chlorinating agent. Acetic acid, acetonitrile or acetone might prove suitable.\(^{218}\) An alternative approach could be to use a large excess of tert-butyl hypochlorite in a hydroxylic solvent, with the aim of obtaining a 4-chloro sulphone of type 251. The sulphone function could then be reduced at a later stage in the synthesis. Mild reagents capable of deoxygenating sulphoxides include tin(II) chloride,\(^{231}\) titanium(III) chloride,\(^{232}\) and dichloroborane.\(^{233}\)
CONCLUDING REMARKS

The accomplishment of the synthesis of enone 51 and its readiness to participate in conjugate addition reactions with lithium diorganocuprates demonstrate the usefulness of the synthetic approach of Scheme 2 for the preparation of thianone analogues of prostaglandins.

Compared to cyclohexan-1,3-dione, thian-3,5-dione, the starting material of the second approach, is more sensitive to alkali and to atmospheric degradation, less enolic, and less difficult to C-alkylate. Amongst the alkylating agents tried, the most successful was a saturated alkyl halide, ethyl 7-iodoheptanoate, halides containing α,β unsaturation giving poor results, whilst the most suitable reaction solvent found was dimethylformamide. Saturated alkyl halides and dipolar aprotic solvents do not favour C-alkylation over O-alkylation, but their use in this instance led to greater freedom from other side-reactions and to relatively good yields.

The best route found for the conversion of 2-alkylated thian-3,5-diones to six-membered enones such as 51 proceeds via isopropyl enol ethers such as 50, which are readily prepared by alkylation with isopropyl iodide, using potassium carbonate in refluxing acetone. Satisfactory conditions for acid-catalysed generation of enol ethers were not found. Sodium borohydride is a convenient reducing agent for enol ether 50, and does not attack the ester function of the side-chain; however, some 1,4 reduction, leading to diol 187, was observed.
The application of the second approach to the synthesis of prostaglandin analogues containing sulphur in a five-membered ring was hampered by the readiness of sulphur to undergo electrophilic chlorination, as had been feared. This problem may not be an insurmountable one, but the question of whether five-membered enones of type 252 would be suitable substrates for organocuprate conjugate additions remains unanswered.
EXPERIMENTAL DETAILS

Dry Solvents

Diethyl ether, petroleum ether, benzene, toluene, and xylene were stored over freshly pressed sodium wire (ca 1 g per 1 of solvent). Carbon tetrachloride was stored over phosphorous pentoxide, filtered, and distilled. Diglyme (diethylene glycol dimethyl ether) was stored over calcium hydride and distilled from lithium aluminium hydride. Tetrahydrofuran was refluxed with freshly pressed sodium wire until hydrogen evolution ceased, then distilled immediately; this procedure removed traces of peroxides as well as water. Dimethylsulphoxide, N,N-dimethylformamide and acetone were stored over Molecular Sieve 4A. Chloroform was stored over calcium chloride and distilled. tert-Butyl alcohol was refluxed with small pieces of sodium (ca 3 g per 100 ml) until the metal was about two-thirds dissolved, then distilled from the remainder.

Gases

In the following text, "nitrogen" refers to the oxygen-free gas. Nitrogen and argon were dried by passage through a wash-bottle of concentrated sulphuric acid and a U-tube of potassium hydroxide pellets, unless the gas was being used in conjunction with an aqueous system.
Reagents and Starting Materials

Solutions of inorganic reagents were aqueous unless another solvent is specified. pH Readings were made with narrow-range universal indicator papers (BDH) and are accurate to within ca 0.3 units. Alcohol-free sodium methoxide and sodium ethoxide were prepared by dissolving small portions of sodium metal in the appropriate alcohol and removing the excess solvent in vacuo (ca 1 mmHg) at about 200°. "Potassium tert-butoxide" refers to material obtained from Fluka unless specified as "freshly prepared". Cyclohexan-1,3-dione stabilised with 3% sodium chloride was obtained from Ralph N. Emanuel Ltd. It was purified prior to use by dissolution in chloroform, washing (water), drying (sodium sulphate) and concentration of the chloroform solution, recrystallisation of the residue from ethyl acetate, washing (diethyl ether), and drying in vacuo (silica gel). The purified dione, m.p. 103-105°, could be stored for long periods at -24° without deterioration.

Instrumentation and Analytical Methods

Melting points were determined on an Electrothermal IA 6301 or a Gallenkamp MF-370 apparatus, and are uncorrected.

Gas-liquid chromatographic (g.l.c.) analyses were made with a Perkin-Elmer F 11 Chromatograph fitted with a flame ionisation detector. The carrier gas was nitrogen flowing at ca 20 ml/min, and the injection temperature was 300° or 80° above the oven temperature, whichever was higher. Two types of pre-packed
columns (Perkin-Elmer) were used routinely. In each the stationary liquid phase was a silicone grease classed as "non-polar" (having no polar or polarisable functional groups) useful for general purpose separations based on volatility, and retaining "non-polar" compounds longer than "polar" compounds of similar boiling point. Diatomaceous silica, purified by washing with hydrochloric acid, and treated with dimethyldichlorosilane to convert surface silanol groups to silyl ethers (to reduce surface activity and peak tailing) was used as the support medium for both types of liquid phase. In the following text, "UCW 98" denotes a column packed with 1% UCW 98 (methyl vinyl siloxane) on Chromosorb W, and "OVL" denotes a column packed with 2½% silicone OVL (methyl siloxane) on Chromosorb G. The columns were 6 ft coils of 0.25 in o.d. glass tubing. Retention times (tR) were measured from the point of injection to the tip of the peak. Relative peak areas (expressed as a percentage in parentheses) were estimated from the products of height and half-height width.

Analytical thin layer chromatography was performed on plastic sheets pre-coated with silica gel 60 F254, layer thickness 0.25 mm (Merck). Preparative thin layer chromatography was performed on glass plates pre-coated with silica gel F254, layer thickness 2 mm (Merck). The plates were viewed under ultra-violet light; data are expressed as Rf values, the ratio of the distance travelled by the solute to the distance travelled by the solvent.
Ultra-violet spectra were measured in ethanol using a Unicam SP 800 spectrophotometer. The concentration of each sample was chosen so that the maximum absorbance in a 1 cm silica cell was ca 1. pH Effects were determined by adding a drop of either 2M-hydrochloric acid (denoted "acid") or 2M-sodium hydroxide (denoted "alkaline") to the sample cell.

Infra-red spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer. The physical state of the sample is indicated in parentheses as follows: thin liquid film (film), carbon tetrachloride solution (CCl₄), chloroform solution (CHCl₃), potassium bromide mull (KBr).

Proton nuclear magnetic resonance spectra were recorded for deuteriochloroform solutions on a Perkin-Elmer R 10 spectrometer (60MHz) or a Bruker WH90 pulse Fourier transform spectrometer (90MHz), with tetramethylsilane as internal standard. The τ scale, where tetramethylsilane is assigned a chemical shift of 10 p.p.m., is used. Intensities are expressed as numbers of protons per molecule (H).

Mass spectra were measured in an AEI MS 12 single-focusing spectrometer with electron-impact ionisation at 70 eV. Direct sample insertion was employed, at the temperature given in parentheses. Metastable peaks are denoted by an asterisk.
Microanalyses were performed by Dr. F.B. Strauss at the 
Microanalytical Laboratory, 10 Carlton Road, Oxford.

Additional abbreviations used in the following text include:
\( e \), molar extinction coefficient; \( \lambda_{\text{max}} \), wavelength of an 
absorption maximum; \( \gamma_{\text{max}} \), frequency of an absorption maximum;
b.p., boiling point; \( B \), base peak; br, broad; d, doublet;
J, coupling constant; m, multiplet; \( m/e \), mass:charge ratio;
m.p., melting point; \( M^+ \), molecular ion; q, quartet; s, strong 
(describing an infra-red absorption band) or singlet (describing
a nuclear magnetic resonance signal); t, triplet; w, weak.

**Ethyl 3-(carbomethoxymethylthio)hexanoate (91)**

A mixture of methyl thioglycollate (22 ml, 0.22 mol), ethyl
hex-2-enoate (28.4 g, 0.2 mol), 'Triton B' (40% aqueous
benzyltrimethylammonium hydroxide) (4 ml) and benzene (35 ml) was
refluxed for 15 h, cooled, washed (dilute sodium hydroxide and
water) and dried (sodium sulphate). Filtration and evaporation
gave ethyl 3-(carbomethoxymethylthio)hexanoate (91) as a colourless
oil (41.1 g, 83%), \( t_R \) (UCW 98, 120-180° at 3 deg/min) 13.4 min,
\( \gamma_{\text{max}} \) (film) 1740s,br cm\(^{-1}\). A sample was distilled (b.p. 100° at
0.15 mm Hg, recovery 70%).

**4-Carbethoxy-5-propylthiolan-3-one (90)**

**Method A**

Ethyl 3-(carbomethoxymethylthio)hexanoate (91) (25 g, 0.1 mol)
was added gradually to a chilled, stirred suspension of sodium
ethoxide (prepared from 3.5 g sodium, 0.15 mol) in dry diethyl
ether (40 ml), under nitrogen. More diethyl ether (60 ml) was
added to aid stirring of the resultant paste. The mixture was
stirred at room temperature for a few minutes, then chilled. A solution of acetic acid (9.1 ml, 0.16 mol) in ice-water (50 ml) was added, and the organic layer was separated. The ether layer was washed (water), dried (sodium sulphate) and concentrated. The residue was distilled giving 4-carbethoxy-5-propylthiolan-3-one (90) as a pale yellow oil (12.5 g, 48% from ethyl hex-2-enoate), b.p. 98-100° at 0.6 mmHg, \( t_R \) (UCW 98, 120-180° at 3 deg/min) 9.1 (35%) and 10.3 min (65%), \( \gamma_{\text{max}} \) (film) 1730s, br (ring and ester CO), 1650w (enol, chelated CO) and 1605w cm\(^{-1}\) (enol, C=C), \( \tau \) (60MHz) 5.8 (2H, q, J 7 Hz, OCH\(_2\)CH\(_3\)), 6.25 (2H, s, SCH\(_2\)CO), 6.4-8 (m, 2H, SCHCH\(_2\)CO), 8.4 (4H, br s, CH\(_2\)CH\(_2\)CH\(_3\)), 8.7 (3H, t, J 7 Hz, OCH\(_2\)CH\(_3\)) and 9.05 (3H, t, J 4 Hz, CH\(_2\)CH\(_2\)CH\(_3\)). A permanent red-violet colouration was obtained from a methanol solution of the product (90) (175 mg, 0.81 mmol) and 0.117M ferric chloride (5.95 ml, 0.70 mmol). The resulting mixture was concentrated and extracted with benzene, and the extract was washed (water) and dried (sodium sulphate) to give a purple oil (180 mg), similar in g.l.c. behaviour and infra-red absorption to 90.

Method B

The procedure of Method A was repeated, except that benzene was used in place of diethyl ether, and the reaction mixture was refluxed for 2h. For work-up, the cooled mixture was treated with ice-cold water, and the crude product was obtained by neutralising the aqueous phase with 1M-sulphuric acid, and benzene extraction. The benzene extract was dried (sodium sulphate) and concentrated, and the residue distilled to give 4-carbethoxy-5-propylthiolan-3-one (90) as a yellow oil (22% from ethyl hex-2-enoate), b.p. 80-110° at 0.5 mmHg, \( t_R \) (UCW 98,
120-180° at 3 deg/min) 9.1 (75%) and 10.3 min (25%), \( \gamma_{\text{max}} \) (film)
3100br (enol, OH) 1755s and 1735s (poorly resolved, ring and ester CO respectively), 1658, 1610 cm\(^{-1}\).

Method C \(^{92}\)

A solution of methyl thioglycollate (20 ml, 0.2 mol) in dry benzene (15 ml) was added to a stirred suspension of sodium ethoxide (prepared from 4.6 g sodium, 0.2 mol) in dry benzene (25 ml), under nitrogen, below 10°. A solution of ethyl hex-2-enoate (26.4 g, 0.186 mol) in dry benzene (20 ml) was added below 10°, and the mixture was then refluxed for 2h. Work-up as in method B above gave 4-carbethoxy-5-propylthiolan-3-one (90) as a pale yellow oil (14.0 g, 35%) b.p. 78-99° at 0.5 mmHg. (Found: C, 55.47; H, 7.39; S, 14.75. \( \text{C}_{10}\text{H}_{16}\text{SO}_3 \) requires C, 55.54; H, 7.46; S, 14.80%), \( \tau_{\text{R}} \) (UCW 98, 120-180° at 3 deg/min) 9.1 (70%) and 10.3 min (30%), \( \gamma_{\text{max}} \) (film)
3100br, 1758s, 1735s, 1662s, 1620 cm\(^{-1}\); permanent red colour with ferric chloride.

Method D \(^{99}\)

Methyl thioglycollate (20 ml, 0.2 mol) was added to a chilled, stirred solution of sodium ethoxide, prepared from sodium (4.6 g, 0.2 mol) and ethanol (100 ml). The solvent and excess thiol were removed by distillation under reduced pressure, leaving a white solid which was suspended in dry dimethylsulphoxide (10 ml). The suspension was chilled and treated with ethyl hex-2-enoate (28.4 g, 0.2 mol). The resulting mixture was stirred at room temperature for 30 min, chilled, poured into ice-cold 3M-sulphuric acid (33.5 ml), and extracted with diethyl ether.
The extract was washed (saturated sodium chloride), dried (sodium sulphate) and concentrated, and the residue was distilled to give 4-carbethoxy-5-propythiolan-3-one (90) as a pale yellow oil (23.9 g, 56%), b.p. 92-99° at 0.5 mmHg, $t_R$ (UCW 98, 120-180° at 3 deg/min) 9.1 (60%) and 10.3 min (40%), $\gamma_{\text{max}}$ (film) 3100br, 1755s, 1730s, 1660s and 1618 cm$^{-1}$.

**Ethyl 4-bromocrotonate (93) and methyl 4-bromocrotonate**

$N$-Bromosuccinimide (360 g, 2 mol) was added to a stirred solution of ethyl crotonate (250 g, 2.2 mol) in dry carbon tetrachloride (1.2 l). Dibenzoyl peroxide (10 g, 40 mmol) was added, and the mixture was heated to 75°. After an initial period of exothermicity, the mixture was heated to reflux for 3 h, cooled, filtered to remove succinimide, washed (water) and dried (sodium sulphate). Distillation gave ethyl 4-bromocrotonate (93) as a yellow oil (280 g, 72.5%), b.p. 98-110° at ca 20 mmHg, $t_R$ (OV1, 160°) 2.2 min, $\gamma_{\text{max}}$ (film) 1720s, 1654, 978 cm$^{-1}$ (trans CH=CH).

Methyl 4-bromocrotonate was prepared by the same procedure (73% yield), b.p. 94-106° at ca 20 mmHg, $\gamma_{\text{max}}$ (film) 1721s, 1657, 977 cm$^{-1}$.

**Ethyl 4-acetoxy crotonate (32)**

A mixture of ethyl 4-bromocrotonate (93) (193 g, 1 mol), sodium acetate (100 g, 1.2 mol), acetic acid (210 ml) and water (1 ml) was refluxed 1.5 h, cooled, and poured into ice-cold water (2 l).
The product was extracted with diethyl ether, and the extract was washed repeatedly (water, and sodium bicarbonate solution) to remove acetic acid, dried (sodium sulphate) and distilled to give ethyl 4-acetoxycrotonate (32) as a colourless oil (127.5 g. 74%), b.p. 120-140° at ca 20 mmHg, \( t_R \) (OV1, 160°) 2.6 min, \( \gamma_{\text{max}} \) (film) 1749 s (ethyl ester), 1668 (C=C), 1230 s (acetate), 970 cm\(^{-1}\) (trans \( CH=CH \)).

Reactions of methyl and ethyl thioglycollates with ethyl 4-acetoxycrotonate

Run 1 (Table 2)

Ethyl 4-acetoxycrotonate (111.9 g, 0.65 mol) was added to a chilled, dry dimethylsulphoxide (325 ml) suspension of the \( S \)-sodiothioglycollate obtained from sodium (15.0 g, 0.65 mol), ethanol, and methyl thioglycollate as in method D for 4-carbomethoxy-5-propylthiolan-3-one (90) (page 176). The mixture was stirred for 30 min at room temperature, chilled, poured into ice-cold 3M sulphuric acid (108 ml), and extracted with diethyl ether. The extract was washed (water, and saturated sodium chloride solution), dried (magnesium sulphate), and concentrated, and the residue was distilled to give impure 33 as a red oil (66.6 g, 35%), b.p. 140° at 1.1 mmHg. A purer sample of ethyl 4-acetoxy-3-(carbethoxymethylthio)butanoate (33) was obtained by redistillation as a pale yellow oil, b.p. 144-146° at 0.45 mmHg, \( t_R \) (UCW 98, 180°) 4.0 min, \( \gamma_{\text{max}} \) (film) 1733 s, br, \( \tau \) (60MHz) 5.6 (6H, m, two OCH\(_2\)CH\(_3\) and CH\(_2\)OOC\(_2\)CH\(_3\)), 6.4 (1H, m, SCH), 6.67 (2H, s, SCH\(_2\)), 7.36 (2H, d, \( J \) 7 Hz, high-field line had d splitting, \( J \) 2 Hz, CH\(_2\)CO\(_2\)C\(_2\)H\(_5\)), 7.94 (3H, s, COCH\(_3\)) and 8.72 (6H, t, \( J \) 7 Hz, two OCH\(_2\)CH\(_3\)).
Run 2 (Table 2)

The procedure of run 1 was repeated (0.2 mol scale), except that the ethyl 4-acetoxycrotonate (32) was added during 2.5 h at 50°, and the reaction mixture was kept at this temperature for 16 h. Distillation of the crude product at 1 mmHg gave two fractions, b.p. 126-136° (6.8 g) and 140-174° (16.8 g). G.l.c. analyses (UCW 98, 180°) showed that the higher-boiling fraction consisted mainly of ethyl 4-acetoxy-3-(carbethoxymethylthio)butanoate (33), whereas the lower-boiling fraction contained ca 50% 33 and 50% of a component of t_R 1.2 min. The latter fraction was dissolved in diethyl ether and the solution shaken with saturated copper(II) acetate solution, to give a brown, powdery copper(II) salt (1.5 g), m.p. ca 130°. The powder was shaken with 3M-sulphuric acid (1.5 ml) and diethyl ether (25 ml); it did not completely dissolve. The ether extract was filtered, washed (sodium bicarbonate solution and water), dried (magnesium sulphate) and concentrated to give 5-acetoxymethyl-4-carbethoxythiolan-3-one (34) as a brown oil (300 mg), t_R (UCW 98, 180°) 1.2 min, ν_max (film) 1740 s, 1660 (enol, chelated C=O), 1618 cm⁻¹ (enol, C=C).

Run 5 (Table 2)

Solutions of ethyl thioglycollate (21.4 ml, 0.195 mol) in dry benzene (30 ml) and ethyl 4-acetoxycrotonate (32) (31.0 g, 0.18 mol) in dry benzene (200 ml) were added consecutively to a stirred suspension of sodium ethoxide (from 4.15 g sodium, 0.18 mol) in dry benzene (60 ml), below 12°. The mixture was refluxed for 2 h, cooled, and poured into water (150 ml). The resulting organic layer was extracted further with water, dried (magnesium sulphate) and concentrated to give ethyl 4-acetoxy-3-(carbethoxymethylthio)butanoate (33) as an orange oil (20.0 g, 30%). The combined aqueous layers
were acidified to pH 3 with 3M-sulphuric acid (20 ml) and extracted with benzene. The benzene extract was dried (magnesium sulphate) and concentrated, and the residue distilled to give 5-acetoxymethyl-4-carbethoxythiolan-3-one (34) as a yellow oil (1.9 g, 4%), b.p. 128-192° at 1 mmHg, $t_R$ (UCW 98, 180°) 1.2 min, $\gamma_{\text{max}}$ (film) 1740s, 1660 and 1618 cm$^{-1}$. A sample of the latter product (34) (21.4 mg, 87 μmol) gave a permanent red colouration with 0.0117M-ferric chloride (0.09 ml, 1 μmol).

Run 9 (Table 2)

Ethyl thioglycollate (86.4 ml, 0.785 mol), in dry benzene (250 ml) was added to a stirred suspension of potassium tert-butoxide (77.0 g, 0.685 mol) in dry benzene (500 ml) under nitrogen, below 10°. Ethyl 4-acetoxycrotonate (32) (118.0 g, 0.685 mol) in dry benzene (200 ml) was added gradually, below 6°. During the next 1.5 h, the reaction temperature was allowed to rise only to 7°. The mixture was then treated with water (450 ml) the aqueous phase was extracted with benzene, and the benzene extract washed (2M potassium hydroxide and water), dried (sodium sulphate) and concentrated. The residue was distilled to give ethyl 4-acetoxy-3-(carbethoxymethylthio)butanoate (33) as a yellow oil (97.75 g, 49%), b.p. 136-139° at 0.15 mmHg, $t_R$ (UCW 98, 180°) 4.0 min, $t_R$ (OVI, 200°) 7.4 min.

5-Acetoxymethyl-4-carbethoxythiolan-3-one (34) from ethyl 4-acetoxy-3-(carbethoxymethylthio)butanoate (33) (Run 16, Table 3)

A solution of ethyl 4-acetoxy-3-(carbethoxymethylthio)butanoate (33) (48.4 g, 0.166 mol) in dry toluene (200 ml) was added to a suspension of sodium hydride (Koch-Light) (7.95 g, 0.332 mol) in dry toluene
(200 ml), stirred under nitrogen at 21-22°. The progress of the reaction was followed by observation of hydrogen evolution, and by g.l.c. of samples of the mixture. The reaction was initiated by heating to 50° and addition of a drop of ethanol. It was judged complete after 24 h at 50° and 16 h at room temperature. The mixture was cooled to 5° and poured into a vigorously stirred buffer solution consisting of sodium dihydrogen orthophosphate dihydrate (155 g) and sodium hydroxide (12 g) dissolved in water (total volume 850 ml). The mixture was extracted with toluene, the extract washed (water), dried (sodium sulphate) and concentrated, and the residue distilled to give ethyl thioglycollate as a colourless oil (1.5 g, 7.5%), b.p. 22-58° at 10 mmHg, t_R (OVI, 200°) 0.55 min, infra-red spectrum identical to that of authentic material, and 5-acetoxyethyl-4-carbethoxythiolan-3-one (34) as a pale yellow oil (7.0 g, 17%) b.p. 126-130° at 0.2 mmHg, t_R (OVI, 200°) 1.65 min, γ_max (film) 1740s, br, 1662, 1620, 1237s cm^{-1} (acetate).

**Ethyl 4-acetoxy-3-(carboxymethylthio)butanoate (97)**

A solution of thioglycollic acid (52.5 ml, 0.76 mol) in dry benzene (400 ml) was added to a stirred suspension of potassium tert-butoxide (85.1 g, 0.76 mol) in dry benzene (950 ml) under nitrogen, below 10°. A solution of ethyl 4-acetoxycrotonate (32) (133.8 g, 0.78 mol) in dry benzene (400 ml) was added, and the mixture was refluxed for 20 h, cooled, poured into mechanically-stirred ice-water (400 ml), and acidified with 1M-sulphuric acid (380 ml). The aqueous layer was extracted with benzene, and the combined benzene solutions were washed (water), dried (sodium sulphate) and concentrated to give ethyl 4-acetoxy-3-(carboxymethylthio)butanoate (97) as a red oil (159.7 g, 80%), γ_max (film) 3200s, br, 1730s, br,
Ethyl 4-acetoxy-3-(tert-butoxycarbonylmethylthio)butanoate (96)

A mixture of ethyl 4-acetoxy-3-(carboxymethylthio)butanoate (97) (59.8 g, 0.266 mol), isobutene (80 ml, collected in a receiver cooled in dry-ice - acetone) and sulphuric acid (2.4 ml) was shaken for 65 h at room temperature in a narrow-necked pressure bottle, chilled, and poured into a stirred solution of sodium hydroxide (25 g) in ice-water (330 ml). Extraction with diethyl ether, washing (potassium carbonate solution), drying (potassium carbonate) and concentration of the ether extract, followed by distillation of the residue under nitrogen using alkali-washed, thoroughly dried apparatus, gave ethyl 4-acetoxy-3-(tert-butoxycarbonylmethylthio)butanoate (96) as a pale yellow oil (28.7 g, 40% from thioglycollic acid), b.p. 136-142° at 0.3 mmHg. (Found: C, 52.70; H, 7.49; S, 10.26; C_{14}H_{24}SO requires C, 52.48; H, 7.55; S, 10.01%), \( t_{R} \) (OV1, 200°) 2.7 min, \( \gamma_{\text{max}} \) (film) 1730s, 1240 cm\(^{-1}\), \( \tau \) (60MHz) 5.71 and 5.87 (2H, AB octet part of ABX system, \( J_{\text{AB}} \) 11, \( J_{\text{AX}} \) and \( J_{\text{BX}} \) 6 Hz, SCHCH\(_2\)O), 5.85 (2H, q, \( J \) 7 Hz, collapsed to s on irradiation of t at \( \tau 8.75, \text{OCH}_2\text{CH}_3 \)), 6.53 (1H, ca quintet, \( J \) 6-7 Hz, SCH), 6.79 (2H, s, SCH\(_2\)), 7.39 (2H, d, \( J \) 7 Hz, high-field line had d splitting \( J \) 2 Hz, SCHCH\(_2\)CO), 7.97 (3H, s, COCH\(_3\)), 8.53 (9H, s, OC(CH\(_3\))\(_3\)), 8.75 (3H, t, \( J \) 7 Hz, OCH\(_2\)CH\(_3\)). In this run only 58% of the crude product was recovered in the distillate; in a previous smaller-scale preparation the recovery was 80%, so a yield of 55% should be possible.
5-Acetoxyethyl-4-carbethoxythiolan-3-one (34) from ethyl 4-acetoxy-3-(tert-butoxycarbonyl)butanoate (96)

A solution of ethyl 4-acetoxy-3-(tert-butoxycarbonyl)butanoate (96) (22.9 g, 71.5 mmol) in dry toluene (80 ml) was added to a stirred suspension of sodamide (3.9 g, 100 mmol) in dry toluene (80 ml). The progress of the reaction was followed by g.l.c. of samples of the mixture, and by observing the evolution of ammonia. The reaction temperature was raised gradually; ammonia evolution began at 50°, but did not reach a useful rate until the temperature approached 75°. The reaction was judged complete after 1 h at 75°. The cooled mixture was poured into a stirred solution of sodium dihydrogen orthophosphate dihydrate (48.5 g) and sodium hydroxide (3.75 g) in water (total volume 250 ml). The aqueous phase was extracted with more toluene, and the combined toluene solutions were washed (water), dried (sodium sulphate) and concentrated. Distillation of the residue gave 5-acetoxyethyl-4-carbethoxythiolan-3-one (34) as a yellow oil (3 g, 18%), b.p. 122-148° at 0.3 mmHg, t_R (OV1, 200°) 1.65 min. A sample of the product (78.2 mg) gave a permanent red colouration with 0.117 M ferric chloride (0.77 ml, 90 µmol); it was therefore estimated to contain 24.6 mg of 5-acetoxyethyl-2-tert-butoxycarbonylthiolan-3-one (99) (90 µmol at M. wt. 274), and hence 53.6 mg of the desired product 34 (218 µmol); the mol:mol ratio of 34:99 in the sample was therefore ca 70:30.
2-Benzyl-2-carbethoxycyclopentanone (117)

Thallium(I) ethoxide (5.1 g, 20.6 mmol) was added to a stirred solution of 2-carbethoxycyclopentanone (3.3 g, 21.2 mmol) in petroleum ether (b.p. 40-60°, dried over calcium chloride) (17 ml). A white solid, m.p. 136° was immediately formed; it was treated with benzyl bromide (20 ml) and the mixture was heated to just below reflux temperature for 16 h. The cooled mixture was filtered, the filtrate concentrated, and the residue distilled giving 2-benzyl-2-carbethoxycyclopentanone (117) as a pale yellow oil (4.7 g, 92%), b.p. 128-140° at 0.8 mmHg, £R (UCW 98, 120-200° at 5 deg/min) 19.4 min, γmax (film) 1753s, 1728s, 1605, 1494, 748, 702 cm⁻¹.

Ethyl 7-(2-carbethoxycyclopentanon-2-yl)heptanoate (118)

A mixture of the thallium(I) salt of 2-carbethoxycyclopentanone (3.9 g, 11 mmol) and ethyl 7-iodoheptanoate (9.3 g, 33 mmol) was heated to 50° for 9 h, after which g.l.c. of an acidified sample indicated complete conversion of the salt to a single product. Petroleum ether (b.p. 40-60°) (25 ml) was added, the bright yellow precipitate of thallium(I) iodide was removed by filtration, and the filtrate was concentrated, giving a brown oil (9.3 g, theory 9.6 g) which on distillation yielded ethyl 7-(2-carbethoxycyclopentanon-2-yl)heptanoate (118) as a pale yellow oil (1.4 g, 41%), b.p. 150-220° at 0.4 mmHg, £R (UCW 98, 200°) 3.2 min, γmax (film) 1730s,br cm⁻¹.
4-Benzyloxy-5-carbomethoxy-2,3-dihydrothiole (121)

Thallium(I) ethoxide (5.3 g, 21 mmol) was added to 4-carbomethoxythiolan-3-one\(^99\) (85) (3.8 g, 24 mmol) in dry benzene (10 ml), under nitrogen, and the solvent was removed under reduced pressure, leaving a grey solid which was treated with benzyl bromide (15 ml). The mixture was warmed gently for 3 h, cooled, stirred with dry diethyl ether, and filtered; g.l.c. of the filtrate showed that the only solute present was benzyl bromide. The precipitate was extracted with methanol, and the extract was concentrated, giving a pale yellow solid (6.3 g, theory 5.3 g); g.l.c. analysis indicated the presence of a single product. A sample of the solid (4.8 g) was washed with diethyl ether to remove benzyl bromide, and recrystallised from methanol - tert-butanol to give 4-benzyloxy-5-carbomethoxy-2,3-dihydrothiole (121) as white needles (0.8 g, 23%) m.p. 168-169°, \( t_\text{R} \) (UCW 98, 200-250° at 3 deg/min) 3.6 min, \( R_\text{F} \) (chloroform - methanol 4:1) 0.71, \( \gamma \text{ max} \) (nujol) 1637s (H-bonded C=O), 1605s (C=C): 1580, 1492, 797 cm\(^{-1}\), \( \tau \) (60MHz) 2.63 (5H, ca s, \( C_6H_5 \)), 5.88 (2H, s, \( CH_2O \)), 6.23 (3H, s, \( OCH_3 \)), 6.5-8.2 (4H, m, \( CH_2-CH_2 \)) (Found: C, 63.36; H, 5.80, S, 12.37. \( C_{13}H_{14}S_3O_3 \) requires C, 62.37; H, 5.64; S, 12.81%). A sample of the starting material, supposed to be 4-carbomethoxythiolan-3-one (85) (202.6 mg, 1.27 mmol), gave a permanent violet colouration with 0.117M ferric chloride (7.86 ml, 0.92 mmol), showing that it in fact contained 73% 2-carbomethoxythiolan-3-one (86).

Benzylation of 4,5-dicarbethoxythiolan-3-one (119)

A saturated ethanol solution of thallium(I) ethoxide (5.64 g, 23 mmol) was added gradually to 4,5-dicarbethoxythiolan-3-one\(^95\) (119, \( t_\text{R} \) (UCW 98, 200°) 0.9 min) (5.64 g, 23 mmol) in ethanol (25 ml), under nitrogen, at 0°. After the mixture had stood overnight at room
temperature, the solvent was removed in vacuo, leaving a black, viscous oil (10.4 g), which was extracted with dry diethyl ether (50 ml). Concentration of the ether extract gave a viscous brown oil (7.14 g) which was stirred for 16 h at room temperature with benzyl bromide (7.5 ml). Diethyl ether (20 ml) was added and a precipitate filtered off and washed (diethyl ether), giving thallium(I) bromide (5.2 g, 18 mmol). The combined diethyl ether solutions were concentrated, and the residue distilled to give the benzyla
tion product as a viscous yellow oil (3.7 g, 40%), b.p. 160-198° at 0.3-1.0 mmHg, t_R (UCW 98, 200°) 2.1 (10%), 6.5 (40%), 7.3 min (50%), γ_max (film) 1768s, 1734s, 1722s, 1601, 1492, 753, 700s, cm⁻¹.

Benzylation of 4-carbethoxy-5-propylthiolan-3-one (90)

Thallium(I) ethoxide (2.5 g, 10 mmol) was added to 4-carbethoxy-5-propylthiolan-3-one (90, prepared by method D, page 176, t_R (UCW 98, 150-200° at 5 deg/min) 3.8 and 4.2 min) (2.16 g, 10 mmol) in dry benzene (20 ml). After a few minutes stirring at room temperature, a grey precipitate (3 g), m.p. 150-160°, was filtered off. Attempts to recrystallise small samples of this material from methanol, ethanol, acetone, diethyl ether, ethyl acetate, and water were thwarted by its low solubility. The remaining solid was suspended in dry tetrahydrofuran (20 ml); benzyl bromide (3 ml) was added, and the mixture was refluxed for 16 h, cooled, and filtered to remove thallium(I) bromide. The filtrate was concentrated, and the residue was distilled to give the benzyla
tion product as a pale yellow oil (327 mg, 10%), b.p. 132-154° at 1 mmHg, t_R (UCW 98, 150-200° at 5 deg/min) 1.1 (benzyl bromide, 22%), 5.4 (6%), 8.4 (36%), 12.6 min (26%).
Ethyl 7-(5-acetoxymethyl-4-carbethoxy-3-oxothiolan-4-yl)heptanoate (35)

A solution of 5-acetoxymethyl-4-carbethoxythiolan-3-one (34, from run 16, page 180, \( t_R \) (UCW 98, 180-250° at 5 deg/min) 0.8 min) (6.54 g, 27 mmol) in dry diglyme (diethylene glycol dimethyl ether) (30 ml) was added to a stirred suspension of sodium hydride (Koch-Light) (0.64 g, 27 mmol) in dry diglyme (40 ml) under nitrogen, at 4-10°. Evolution of hydrogen began immediately. The mixture was stirred overnight at room temperature, then a solution of ethyl 7-bromoheptanoate (6.25 g, 27 mmol) in dry diglyme (20 ml) was added. The mixture was heated to 45-65° for 24 h, to 70-80° for 24 h, to 80-90° for 24 h, and finally to 100-120° for 160 h, cooled, and poured into water (100 ml). Extraction with diethyl ether, washing (water), drying (sodium sulphate), and concentration of the ether extract, followed by distillation of the residue, gave the alkylation product as an oil (2.9 g, 27%), which was divided into four fractions boiling in the range 90-200° at 0.1 mmHg, \( t_R \) (UCW 98, 180-250° at 5 deg/min) 3.25 (60%), 7.1 (15%), 9.5 (10%), 13.9 (15%) (the proportions of the four components varied from fraction to fraction, approximate mean percentages are given here).

The second fraction (0.68 g) was the best sample of ethyl 7-(5-acetoxymethyl-4-carbethoxy-3-oxothiolan-4-yl)heptanoate (35), \( t_R \) 3.25 min (80%), \( \gamma_{\text{max}} \) (film) 1780\( \nu \), 1736\( \nu \), br cm\(^{-1}\), \( \tau \) (60MHz) 5.8 (hidden m, CH\(_2\)OCOCH\(_3\)), 5.86 (q, \( J \) 7 Hz, CO\(_2\)CH\(_2\)CH\(_3\) directly attached to ring) and 5.93 (q, \( J \) 7 Hz, CH\(_2\)CO\(_2\)CH\(_2\)CH\(_3\)) (5.3 H), 6.38 (1H, ca t, \( J \) 5 Hz, SCH), 6.72 (0.35H, s, SCH\(_2\) of impurity), 6.86 (0.65H, s, SCH\(_2\)), 7.41 (2H, t, \( J \) 6.5 Hz, CO,CHCH\(_3\)), 7.75 (2H, t, \( J \) 7 Hz, CH\(_2\)CO\(_2\)-CH\(_3\)), 7.98 (1.3H, s, COCH\(_3\)), 8.01 (0.7H, s, COCH\(_3\)), 8.6 (broad s, (CH\(_2\))\(_4\)), 8.76 (t, \( J \) 7 Hz, CO\(_2\)CH\(_2\)CH\(_3\) directly attached to ring) and 8.80 (t, \( J \) 7 Hz, CH\(_2\)CO\(_2\)CH\(_2\)CH\(_3\)) (13H). A discussion of the latter spectrum appears on page 67.
Methyl thioglycollate (100 ml, 1 mol) was added under nitrogen to a stirred solution of sodium methoxide, prepared from sodium (23 g, 1 mol) and methanol (400 ml). Chloroacetone (92.5 g, 1 mol) was then added gradually. The mixture was stirred at room temperature for 15 min, refluxed for 15 min and cooled. The precipitated sodium chloride was filtered off, and the filtrate was concentrated. The residue was treated with water (500 ml), the layers were separated, and the aqueous layer was extracted with diethyl ether. The combined organic phases were washed (sodium bicarbonate solution), dried (sodium sulphate) and concentrated to give the crude product as an oil (143.5 g). The crude material (132.5 g, the capacity of a 100 ml Vigreux flask) was distilled, the remainder being combined with the crude product of a subsequent run. The distillation yielded carbomethoxymethylthiopropan-2-one (126) as a colourless oil (123.5 g, 82.5%), b.p. 78-80° at 0.075 mmHg, tR (OVI, 200°) 1.1 min, γmax (film) 1720s, br, 1432 (CH₂CO), 1358 cm⁻¹ (CH₃CO), τ (60 MHz) 6.30 (3H, s, OCH₃), 6.58 (2H, s, SCH₂COCH₃), 6.75 (2H, s, SCH₂CO₂CH₃), 7.73 (3H, s, COCH₃).

Carboxymethylthiopropan-2-one (138)

A solution of carbomethoxymethyliotioopropan-2-one (126) in dry benzene (80 ml), and one of potassium tert-butoxide (freshly prepared from potassium (8.2 g, 0.21 mol) and dry tert-butyl alcohol (180 ml)234) were added simultaneously to dry benzene (160 ml) during 1h, with stirring under nitrogen at 5°. G.l.c. analysis of the mixture indicated complete consumption of keto ester 126. After 20 min the mixture was poured into ice-cold water.
(70 ml), the upper layer was extracted with water, and the combined aqueous solutions were acidified with a cold solution of hydrochloric acid (18.6 ml, 0.21 mol) in water (30 ml). Extraction with chloroform, followed by drying (sodium sulphate) and concentration of the chloroform extract under nitrogen at room temperature gave the crude product as a yellow oil (11.75 g), \( \lambda_{\text{max}} \) 257 nm (log e 3.35) (lit \( \lambda_{\text{max}} \) 250-280 nm depending on pH (log e 4.0)). Distillation of the oil gave carboxymethylthiopropan-2-one (138) as a yellow oil which slowly crystallised (7.5 g, 51%), b.p. 130-132° at 0.03 mm Hg.

A sample was recrystallised twice from dry benzene to give white spangles, m.p. 52-53° (lit 54-55°, 152 43-45° 153), \( \lambda_{\text{max}} \) 290 nm (log e 2.22) (lit 152 290 nm (log e 2.2), \( \gamma_{\text{max}} \) (KBr) 3140 br, 1700 s, br, 1357 cm\(^{-1}\), \( \tau \) (60 MHz) 6.54 (2H, s, \( \text{SCH}_2\text{COCH}_3 \)), 6.70 (2H, s, \( \text{SCH}_2\text{CO}_2\text{H} \)), 7.70 (3H, s, \text{COCH}_3) (lit 154 \( \tau \) 6.50, 6.67, 7.67) (Found: C, 40.48; H, 5.37; S, 21.37. \( \text{C}_5\text{H}_8\text{SO}_3 \) requires C, 40.53; H, 5.44; S, 21.64%).

**Thian-3,5-dione (46)**

A suspension of sodamide (May and Baker) (69.4 g, 1.8 mol) in dry benzene (630 ml) was stirred under nitrogen at 40°, in a 5 l round-bottomed flask fitted with a thermometer, a reflux condenser, and a pressure-equalised dropping funnel. The stirrer shaft was sealed to the flask with a glycerol filled gland, and the outlet of the condenser was connected to a Dreschel bottle containing liquid paraffin. The dropping funnel was filled with a solution of carbomethoxymethylthiopropan-2-one (126) (120 g, 0.74 mol) in dry benzene (600 ml). A few drops of this solution, followed by a drop of methanol, were added to the sodamide suspension. After 10 min, the mixture developed a green colouration,
the temperature rose by a few degrees, and ammonia evolution began. The remainder of the solution of keto ester 126 was then added at a rate sufficient to maintain a reaction temperature of 42-43\(^\circ\) without external heating; about 2 h were required. The mixture, which became yellow in colour, was then stirred at 40\(^\circ\) until ammonia evolution ceased (3 h), cooled to below 10\(^\circ\), and poured cautiously, but as quickly as possible, into a vigorously-stirred mixture of a solution of concentrated hydrochloric acid (220 ml, 2.5 mol) in water (600 ml) chilled to its freezing point (about -20\(^\circ\)) and crushed ice (120 g). The final temperature of the resulting mixture was about 30\(^\circ\). The benzene layer was run immediately into a flask containing sodium sulphate, and the aqueous layer was extracted with twenty portions of benzene (120 ml each), each portion being combined immediately with the original benzene layer. The combined benzene extracts were filtered, redried (sodium sulphate) and incompletely concentrated under reduced pressure of nitrogen at 25\(^\circ\) to give a yellow paste, which was collected on a sintered-glass filter and sucked dry. The crystals remaining on the filter were washed with three portions of dry diethyl ether (50 ml each) to give thian-3,5-dione (46) as a pale yellow powder (38.0 g, 39.5\%) m.p. 78-80\(^\circ\) (lit 144 m.p. 80-81\(^\circ\)), \(\tau_{\text{R}}\) (OV1, 150\(^\circ\)) 4.5 min, \(\tau_{\text{R}}\) (OV1, 200\(^\circ\)) 1.4 min, \(R_F\) (chloroform – acetone – acetic acid 19:30:1) 0.47, \(\lambda_{\text{max}}\) 257 nm (log\(e\) 3.95) (lit 144 \(\lambda_{\text{max}}\) 250-280 nm depending on pH, log\(e\) 4.0), \(\gamma_{\text{max}}\) (CCl\(_4\)) 1741s,1713s cm\(^{-1}\), \(\gamma_{\text{max}}\) (CHCl\(_3\)) 3300br, 1730, 1711s, 1600 cm\(^{-1}\), \(\gamma_{\text{max}}\) (KBr) 3000br, 1725, 1698, 1590s, 1545s cm\(^{-1}\), \(\tau\) (60MHz) 6.45 (2H, s, COCH\(_2\)CO), 6.61 (4H, s, CH\(_2\)SCH\(_2\)). Thian-3,5-dione was stored in an evacuated dessicator containing silica gel, at -8\(^\circ\), and used as soon as possible after preparation.
Methyl 4-iodocrotonate

A solution of methyl 4-bromocrotonate (35.8 g, 0.2 mol) in methyl ethyl ketone (140 ml) was added to a stirred mixture of sodium iodide (30.8 g, 0.205 mol) and methyl ethyl ketone (160 ml) at room temperature. G.l.c. of a sample taken a few minutes later indicated complete conversion. After stirring for 1 h, the mixture was filtered to remove sodium bromide, and the methyl ethyl ketone was replaced by diethyl ether (200 ml). The ether solution was washed (sodium thiosulphate solution and water), dried (sodium sulphate) and concentrated. The residue was distilled to give methyl 4-iodocrotonate as an oil (39.9 g, 88.5%), b.p. 50-70° at 0.04 mmHg, $t_R$ (OV1, 150°) 3.2 min, $t_R$ (OV1, 200°) 1.2 min, $\gamma_{\text{max}}$ (film) 1722 s, 1651, 976 cm⁻¹. Methyl 4-iodocrotonate became discoloured with iodine on standing.

Methyl 4-(3,5-dioxothian-4-yl)but-2-enoate (142)
from methyl 4-iodocrotonate in methanol

Thian-3,5-dione (46) (4.2 g, 32 mmol) in methanol (10 ml) was added to a stirred solution of sodium methoxide (freshly prepared from sodium (745 mg, 32 mmol) and methanol (10 ml), followed by methyl 4-iodocrotonate (8.9 g, 39 mmol), under nitrogen, at 15°. The mixture was stirred for 3 h at 15-18°, after which a sample gave a reading of pH 2.5 with moist indicator paper. The methanol was removed in vacuo and the residue was treated with diethyl ether (20 ml) and ice-cold water (10 ml). The ether layer was extracted with five portions of saturated sodium bicarbonate solution (10 ml each), then kept aside. The combined aqueous layers were washed (diethyl ether), acidified to pH 1 with cold 2M-hydrochloric acid (30 ml) and extracted, initially with benzene, and afterwards with diethyl ether. Each extract was dried (sodium sulphate) and
concentrated. The ether extract gave an oil (2.3 g), \( t_R \) (OV1, 200°) 1.4 (major component, thian-3,5-dione), 13.9 min; both peaks disappeared on shaking with dilute sodium hydroxide. The benzene extract gave a red oil (2.3 g), \( t_R \) (OV1, 200°) 1.4 (minor component), 13.9 min, which was combined with similar material (2.9 g, obtained from an earlier run in which the reaction was conducted at 0°) and chromatographed on acidic alumina, Brockmann grade 1. Methyl 4-(3,5-dioxothian-4-yl)but-2-enoate (142) (2.1 g) was eluted with diethyl ether - methanol 50:1 - 4:1 as a yellow paste. The two best fractions (470 mg) as judged by g.l.c. were combined and washed with diethyl ether to give a relatively pure sample of the product 142 as a white powder (100 mg), m.p. 135-136°, \( t_R \) (OV1, 200°) 13.9 min, \( \lambda_{\text{max}} \) 211, 267 nm (log\( e \) 4.17, 4.05), \( \lambda_{\text{max}} \) (alkaline) 285, 310 nm (log\( e \) 4.05, 4.0), \( \gamma_{\text{max}} \) (KBr) 3000br (enol, OH), 1710s, 1654, 1570 (enol, C=C), 990, 973 cm\(^{-1}\), \( m/e \) (170°) 328/326 (2.26, \( M^+ \), dialkylation product), 295 (7), 294 (11), 267 (9), 266 (3), 263 (7), 262 (13), 235 (9), 234 (19), 230/228 (21, 91, \( M^+ \), monoalkylation product 142), 197 (75), 196 (96), 169 (82), 168 (92), 141 (82), 140 (86), 67 (B), 144.5*, 117.6*.

The diethyl ether solution of bicarbonate-insoluble material which had been kept aside early in the work-up was washed (2M sodium hydroxide and water), dried (sodium sulphate), and concentrated to give unreacted methyl 4-iodocrotonate as an oil (2.2 g, 9.6 mmol), \( t_R \) (OV1, 200°) 1.2 min, \( \gamma_{\text{max}} \) (film) 1722s, 1651, 976 cm\(^{-1}\).

Methyl 4-(3,5-dioxothian-4-yl)but-2-enoate (142) from methyl 4-iodocrotonate in N,N-dimethylformamide

A solution of thian-3,5-dione (46) (5.4 g, 41.5 mmol) in dry N,N-dimethylformamide was added under dry nitrogen to a stirred suspension of sodium hydride (Koch-Light) (1.0 g, 41.5 mmol) in
the same solvent (20 ml) at 0°; hydrogen evolution began immediately. The mixture was stirred for 16 h at room temperature, during which time a precipitate of the sodium enolate of 46 was formed. This solid apparently obscured the surface of the sodium hydride particles, since hydrogen evolution had stopped, even though unchanged 46 was detectable by g.l.c. The mixture was warmed to 50°, whereupon it soon became completely homogeneous. The enolate tended to crystallise out below 40°, so the methyl 4-iodocrotonate (10.3 g, 45.5 mmol) was added at this temperature. The mixture darkened towards the end of the addition, and its temperature rose to 65°; g.l.c. analysis (OV1, 200°) suggested almost complete conversion of the starting materials to a component of $t_R$ 13.9 min, and a sample gave a reading of pH 2 with moist indicator paper. After 1.3 h the reaction temperature had fallen to 28°. The mixture was chilled, and filtered to remove some white solid that dissolved easily in water and contained negligible organic material. The filtrate was treated with water (60 ml) and extracted with diethyl ether, and the extract ($t_R$ (OV1, 200°) 1.4 (46), 13.9 min) was washed (sodium thiosulphate and water), dried (sodium sulphate) and partially concentrated. The resulting paste was sucked dry onto a sintered glass filter and washed with dry diethyl ether to give the product (142) as a white powder (1.8 g, 19%) m.p. 132-134°. A purer product was obtained by recrystallisation from methanol - water 25:1 as white plates (1.1 g, 12%) m.p. 143.5-145.5°. Repeated recrystallisation from acetone gave pure methyl 4-(3,5-dioxothian-4-yl)but-2-enoate, m.p. 144.8-145.2° (Found: C, 52.62; H, 5.29; S, 13.78; $C_{10}H_{12}SO_4$ requires C, 52.61; H, 5.30; S, 14.05%), $t_R$ (OV1, 200°) 13.9 min, $t_R$ (OV1, 240°) 4.2 min, $R_F$ (chloroform - acetone - acetic acid 19:30:1) 0.57, $R_F$ (chloroform - acetone 4:1)
0.28, $\lambda_{max}$ 210, 269 nm (loge 4.06, 3.95) $\lambda_{max}$ (alkaline) 212, 285, 310 nm (loge 4.29, 4.10, 4.03), $\gamma_{max}$ (KBr) 3000 br, 1710 s, 1658, 1570, 991, 975 cm$^{-1}$, $\tau$ (90 MHz) 3.12 (1H, dt, $J$ 16, 7 Hz, trans CH$_2$CH=CH), 4.09 (1H, dt, $J$ 16, 2 Hz, trans CH$_2$CH=CH), 6.23 (1H, t, $J$ 6 Hz, CH$_2$CH(CO)$_2$), 6.30 (3H, s, OCH$_3$), 6.55 (4H, s, CH$_2$SCH$_2$), 7.19 (2H, ddd, $J$ 7, 6, 2 Hz, CHCH$_2$CH=CH).

**Ethyl 7-(3,5-dioxothian-4-yl)heptanoate (47) and ethyl 7-(5,6-dihydro-5-oxo-2H-thiin-3-yloxy)heptanoate (144)**

A solution of thian-3,5-dione (46) (48 g, 0.37 mol) in dry N,N-dimethylformamide (280 ml) was added to a suspension of sodium hydride (Koch-Light) (9.1 g, 0.38 mol) in the same solvent (120 ml) with stirring, under nitrogen, and the mixture was stirred at room temperature until it became homogeneous (the enolate did not precipitate at this dilution). Ethyl 7-iodoheptanoate ($t_R$ (OVI, 200$^0$) 3.2 min) (116 g, 0.41 mol) was added, and the mixture was stirred for 19 h at room temperature, after which time g.l.c. analysis (OVI, 250$^0$) indicated complete conversion of the starting materials to products of $t_R$ 6.2 and 8.0 min in ratio ca 1:2:1. For work-up the mixture was poured into stirred 0.5M-sodium bicarbonate (480 ml), and diethyl ether (450 ml) was added. The ether layer was extracted with three portions of 0.5M-sodium bicarbonate (30 ml each) which were combined with the main aqueous layer. The aqueous solution was then back-extracted with four portions of diethyl ether (120 ml each), which were combined with the main ether layer and kept aside. The bicarbonate extract was poured into a stirred mixture of 2M-hydrochloric acid (285 ml) and diethyl ether (300 ml). The resulting aqueous layer was extracted with seven portions of diethyl ether (one of 200 ml and six of 85 ml) which were combined with the ether layer, washed (water and saturated
sodium sulphate solution), dried and decolourised (sodium sulphate and charcoal), and concentrated to give the product (47) as a viscous, orange oil that solidified after several days in deep-freeze storage (27.5 g, 26%), m.p. 39-42°. Recrystallisation of the product of an earlier run (not decolourised) from 3:2-petroleum ether (b.p. 60-80°) - di-isopropyl ether gave three crops of white needles (total recovery 42%, 14% overall yield), m.p. 48.5 - 49.5°, 46-47.5°, and 45-47.5°. A pure sample of ethyl 7-(3,5-dioxothian-4-yl)heptanoate (47) had already been obtained from the product of the first experiment in the series by chromatography on florisil (elution with benzene - diethyl ether 19:1 and 9:1) and recrystallisation from petroleum ether (b.p. 60-80°) as white needles, m.p. 45.5-46.5° (Found: C, 58.53; H, 7.69; S, 10.78. C_{14}H_{22}SO_{4} requires C, 58.71; H, 7.74; S, 11.20%), t_{R} (OV1, 250°) 6.2 min, R_{F} (chloroform - acetone - acetic acid 19:30:1) 0.68, R_{F} (chloroform - acetone 4:1) 0.61, \lambda_{\text{max}} 275.5 nm (log \varepsilon 3.75), \lambda_{\text{max}} (alkaline) 289.5, 316 nm (log \varepsilon 3.75, 3.91), \gamma_{\text{max}} (KBr) 3200br, 1730s (ester), 1700s (ring C=O), 1610s,br (enol, C=C), \tau (90MHz) 5.87 (2H, q, J 7 Hz, OCH_{2}CH_{3}), 6.44 (1H, t, J 7 Hz, CH_{2}CH(CH_{2})_{2}, 6.58 (4H, s, CH_{2}SCH_{2}), 7.71 (2H, t, J 7 Hz, CH_{2}CO_{2}C_{2}H_{5}), 8.35 (4H, m, CH_{2}CH(CO)_{2} and CH_{2}CH_{2}CO_{2}C_{2}H_{5}), 8.67 (6H; br s, (CH_{2})_{3}), 8.75 (3H, t, J 7 Hz, CO_{2}CH_{2}CH_{3}).

The diethyl ether solution of bicarbonate-insoluble material derived from the experiment described in full above was washed (water), dried (sodium sulphate) and decolourised (charcoal), poured into an evaporating basin, and allowed to stand in the draught of a fume cupboard. The resulting sticky crystals were sucked dry on a sintered glass filter and dried in vacuo (silica gel) to give the product (144) as a pale yellow powder (39.6 g, 37.5%), m.p. 55-58°.
Recrystallisation (of 37.6 g) from petroleum ether (b.p. 60-80°) gave a crop of white needles (19.6 g) m.p. 62.5-64°, and a crop of pale yellow needles (4.9 g) m.p. 55-58°. Pure ethyl 7-(5,6-dihydro-5-oxo-2H-thiin-3-yloxy)heptanoate (144) was obtained by repeated recrystallisation from petroleum ether (b.p. 60-80°), as white needles, m.p. 63.5-64.5°, (Found: C, 58.79; H, 7.70; S, 10.94. C_{14}H_{22}S_{4} requires C, 58.71; H, 7.74; S, 11.20%), t_{R} (OVI, 250°) 8.0 min, R_{F} (chloroform - acetone - acetic acid 19:30:1) 0.70, R_{F} (chloroform - acetone 4:1) 0.55, \lambda_{max} 253.5, 326 nm (log\epsilon 4.10, 2.30, pH-independent), \gamma_{max} (KBr) 1730s (ester), 1640s (ring C=O), 1607s cm^{-1} (C=C), \tau (90MHz) 4.62 (1H, s, CO-CH=), 5.86 (2H, q, J 7 Hz, OCH_{2}CH_{3}), 6.15 (2H, t, J 6 Hz, OCH_{2}(CH_{2})_{5}), 6.67 (2H, s, SCH_{2}), 6.73 (2H, s, SCH_{2}), 7.69 (2H, t, J 7 Hz, CH_{2}CO_{2}C_{2}H_{5}), 8.35 (4H, m, OCH_{2}CH_{2} and CH_{2}CH_{2}CO_{2}C_{2}H_{5}), 8.60 (4H, br s, CH_{2}CH_{2}), 8.74 (3H, t, J 7 Hz, OCH_{2}CH_{3}).

Methyl 7-(3,5-dioxothian-4-yl)heptanoate (145) and methyl 7-(5,6-dihydro-5-oxo-2H-thiin-3-yloxy)heptanoate (146)

The alkylation of thian-3,5-dione (46) with methyl 7-iodoheptanoate (t_{R} (OVI, 200°) 2.3 min) was performed using the method described above for the ethyl ester. The C-alkylation product, methyl 7-(3,5-dioxothian-4-yl)heptanoate (145) was a viscous brown oil that crystallised slowly after two weeks deep-freeze storage (30%) as white needles m.p. 48-49° (from petroleum ether (b.p.60-80°)), t_{R} (OVI, 250°) 5.2 min, \lambda_{max} 275 nm (log\epsilon 4.28), \gamma_{max} (alkaline) 290, 316 nm (log\epsilon 4.39, 4.42), \gamma_{max} (KBr) 1730s, 1700s, 1620s, br cm^{-1}, \tau (90MHz) 6.31 (3H, s, OCH_{3}), 6.40 (1H, t, J 7 Hz, CH_{2}CH(CO)_{2}), 6.56 (4H, s, CH_{2}SCH_{2}), 7.66 (2H, t, J 7 Hz, CH_{2}CO_{2}CH_{3}), 8.30 (4H, m, CH_{2}CH(CO)_{2} and CH_{2}CH_{2}CO_{2}CH_{3}), 8.67 (6H, br s, (CH_{2})_{3}).
The 0-alkylation product, methyl 7-(5,6-dihydro-5-oxo-2H-thiin-3-yloxy)heptanoate (146) was obtained as white needles, m.p. 42.5-43.5, from petroleum ether (b.p. 60-80°); $\lambda_{\text{max}}$ 253.5, 323 nm (logɛ 4.15, 2.40, pH-independent), $\gamma_{\text{max}}$ (KBr) 1735s, 1655s, 1604s cm$^{-1}$, $\tau$ (90MHz) 4.59 (1H, s, CO-CH=), 6.15 (2H, t, $J$ 7 Hz, OCH$_2$(CH$_2$)$_5$), 6.31 (3H s, OCH$_3$), 6.64 (2H, s, SCH$_2$), 6.73 (2H, s, SCH$_2$), 7.65 (2H, t, $J$ 7 Hz, CH$_2$CO$_2$CH$_3$), 8.30 (4H, m, OCH$_2$CH$_2$ and CH$_2$CH$_2$CO$_2$CH$_3$), 8.60 (4H, br s, CH$_2$CH$_2$).

Alkylation of thian-3,5-dione potassium enolate with ethyl 7-idoheptanoate

A solution of thian-3,5-dione (46) (280 mg, 2.2 mmol) in dry tert-butanol (1.4 ml) was added gradually to a swirled mixture of potassium tert-butoxide (232 mg, 2.1 mmol) and dry diethyl ether (10 ml) at room temperature. The potassium enolate was filtered off as a pale yellow powder, which was washed with dry diethyl ether, m.p. 300° (decomp.). The enolate (130 mg, 0.8 mmol) was treated with ethyl 7-idoheptanoate (250 mg, 0.9 mmol) in dry N,N-dimethylformamide (2 ml) at 40°. The progress of the reaction was followed by g.l.c. analyses; after 3 h, no further reaction occurred, the final C:O-alkylation product ratio (47:144) being 1:3.0 as judged by peak areas.

Alkylation of thian-3,5-dione thallium(I) enolate with ethyl 7-idoheptanoate

Thian-3,5-dione (285 mg, 2.2 mmol) was dissolved in a mixture of dry benzene (4 ml) and ethanol (the minimum for homogeneity). The solution was added to thallium(I) ethoxide (500 mg, 2 mmol) in dry benzene (3 ml) at room temperature; a white precipitate of the
thallium(I) enolate was formed immediately. After 30 min it was collected as a white powder, and washed with dry benzene, ethanol, and diethyl ether; m.p. 193° (decomp.). The enolate (630 mg, 1.9 mmol) was treated with a solution of ethyl 7-iodoheptanoate (600 mg, 2.1 mmol) in dry tetrahydrofuran. Products could neither be detected by g.l.c. analysis after 16 h at room temperature, nor after 2.5 h at 40°. Hexamethylphosphoramide (Emanuel) (1 ml) was added, and the mixture kept at 40°. The alkylation then proceeded to completion in 28 h, the final C:O-alkylation product ratio (47:218) being 1:4 as judged by peak areas.

**Methyl 4-(5,6-dihydro-5-oxo-3-(2-propoxy)-2H-thiin-4-yl)but-2-enoate (178)**

A solution of methyl 4-(3,5-dioxothian-4-yl)but-2-enoate (142) (m.p. 133-143°) (459 mg, 2 mmol) in acetone (10 ml) was refluxed for a few minutes with anhydrous potassium carbonate (150 mg, 1.1 mmol), after which g.l.c. analysis indicated nearly complete consumption of 142. Isopropyl iodide (0.30 ml, 3 mmol) was added at room temperature, and the mixture was reheated to gentle reflux. The progress of the reaction was followed by g.l.c. analysis, the peak for isopropyl iodide (t_R (OVI, 50°) 3.1 min) being very slowly diminished. After 168 h reflux, the mixture was cooled and treated with water (4 ml), and the pH was adjusted to 9.5 by addition of a few drops of 2M-sodium hydroxide. Extraction with diethyl ether, followed by washing (water), drying (sodium sulphate) and concentration of the extract, gave methyl 4-(5,6-dihydro-5-oxo-3-(2-propoxy)-2H-thiin-4-yl)but-2-enoate (178) as a viscous brown oil (406 mg, 75%), t_R (OVI, 240°) 6.1 min, R_F (chloroform - acetone - acetic acid 19:30:1) 0.67, R_F (chloroform - acetone 4:1) 0.56, λ_max 210, 271 nm (logε 3.78, 3.81, pH-independent), γ_max (film) 1712s (ester), 1655 (side-chain C=C), 1640s (ring C=O), 1600s (ring C=C),
Methyl 4-((5,6-dihydro-5-oxo-2H-thiin-4-yl)but-2-enoate (176)

Methyl 4-((5,6-dihydro-5-oxo-3-(2-propoxy)-2H-thiin-4-yl)but-2-enoate (178) (400 mg, 1.5 mmol) in dry tetrahydrofuran (11 ml) was added during 40 min to a 70% solution in benzene of sodium bis(2-methoxyethoxy)aluminium hydride ("Red-Al", Emanuel) (1.75 ml, 5 mmol) in dry tetrahydrofuran (8.6 ml), stirred under nitrogen at -78°. After 1 h, a solution of acetic acid (4 ml) in dry tetrahydrofuran (4 ml) was added during 15 min. The mixture was warmed to room temperature, poured into water, and extracted with diethyl ether. The extract was washed (sodium bicarbonate solution, water, and sodium chloride solution), dried (sodium sulphate) and concentrated to give the reduction product as a viscous brown oil (332 mg), $\lambda_{\text{max}}$ 260 nm (log $\varepsilon$ 3.5, due to 178), $\gamma_{\text{max}}$ (film) 3450s,br (OH), 1720s, 1655, 1640 and 1600 (due to 178), 980 cm$^{-1}$. The reduction product was stirred for 16 h with water (20 ml), tetrahydrofuran (10 ml) and 2M-hydrochloric acid (0.8 ml) at 30°, cooled and extracted with diethyl ether. The extract was washed (water), dried (sodium sulphate) and concentrated to a viscous brown oil (228 mg), $t_R$ (OV1, 240°) 2.3 (60%), 6.1 (178, 40%), $R_F$ (chloroform - acetone 4:1) 0.58, $\gamma_{\text{max}}$ (film) 3400br, 1720s, 1665 cm$^{-1}$, which was chromatographed on florisil. Elution with benzene - diethyl ether 9:1 - 4:1 gave methyl 4-((5,6-dihydro-5-oxo-2H-thiin-4-yl)but-2-enoate (176) as a pale yellow oil (25 mg, 8%), $t_R$ (OV1, 240°) 6.1 min (80%), $R_F$ (chloroform - acetone 4:1) 0.58, $\lambda_{\text{max}}$ 240 nm (log $\varepsilon$ 3.75, pH-independent), $\gamma_{\text{max}}$ (film) 1720s, 1670s, (comparable to 2-cyclohexenone), 987 cm$^{-1}$.
Methyl 4-(3-benzoyloxy-5,6-dihydro-5-oxo-2H-thiin-4-yl)but-2-enoate (179)

Methyl 4-(3,5-dioxothian-4-yl)but-2-enoate (142) (456 mg, 2.0 mmol) in dry tetrahydrofuran (16 ml) was stirred under nitrogen at -10°. Triethylamine (0.58 ml, 4.1 mmol) was added during 1 min, followed by benzoyl chloride (0.46 ml, 4.0 mmol) in dry tetrahydrofuran (8 ml) during 20 min. The mixture was stirred 30 min at -10° and 6 h at room temperature, filtered to remove triethylammonium chloride as a white powder (424 mg, 150% of theoretical weight), m.p. 262-267° (decomp.) (lit m.p. 253-254°), poured into water, and extracted with diethyl ether. The extract was washed (sodium bicarbonate solution and water), dried (sodium sulphate) and concentrated to a viscous brown oil (814 mg, 86% of theoretical weight allowing for excess benzoyl chloride), $\gamma_{\text{max}}$ (film) 1787 cm$^{-1}$ (benzoyl chloride), which was chromatographed on florisil. Elution with benzene-diethyl ether 100:1 - 4:1 gave methyl 4-(3-benzoyloxy-5,6-dihydro-5-oxo-2H-thiin-4-yl)but-2-enoate (179) as a viscous pale yellow oil (535 mg, 81%), $R_F$ (chloroform-acetone 4:1) 0.61, $\lambda_{\text{max}}$ 236 nm (log$\varepsilon$ 4.0), $\lambda_{\text{max}}$ (alkaline) 277 and 310 nm (each log$\varepsilon$ ca 4.0), $\gamma_{\text{max}}$ (film) 3055w (aromatic CH), 1738s with low-frequency shoulder (ester carbonyl groups), 1675 (ring C=O), 1656 with low-frequency shoulder (side-chain and ring C=C), 1599, 1581w, 1450, 707 cm$^{-1}$.

Methyl 4-(3-benzoyloxy-5,6-dihydro-5-hydroxy-2H-thiin-4-yl)but-2-enoate (182)

Methyl 4-(3-benzoyloxy-5,6-dihydro-5-oxo-2H-thiin-4-yl)but-2-enoate (179) (470 mg, 1.4 mmol) in dry tetrahydrofuran (12 ml) was added during 50 min to a 70% benzene solution of sodium bis(2-methoxyethoxy)aluminium hydride (5.5 ml, 19 mmol) in dry tetrahydrofuran (24 ml)
stirred under nitrogen at -78°. After 2 h a solution of acetic acid (12.5 ml) in dry tetrahydrofuran (12.5 ml) was added during 10 min. The mixture was warmed to room temperature, poured into water, and extracted with diethyl ether. The extract was washed (sodium bicarbonate solution and water), dried (sodium sulphate) and concentrated to give methyl 4-(3-benzoyloxy-5,6-dihydro-5-hydroxy-2H-thiin-4-yl)but-2-enoate (182) as a viscous yellow oil (458 mg, 97%), \( \gamma_{\text{max}} \) (film) 3420 s, br (OH), 3055 w, 1738 s (benzoate), 1711 s (crotonate), 1690 s (ring C=C), 1594, 1447, 798 cm\(^{-1}\).

Ethyl 7-(5,6-dihydro-5-oxo-3-(2-propoxy)-2H-thiin-4-yl)heptanoate (50)

Ethyl 7-(3,5-dioxothian-4-yl)heptanoate (47, m.p. 46-49°) (6.3 g, 22 mmol) in dry acetone (45 ml) was added to a suspension of anhydrous potassium carbonate (3.6 g, 26 mmol) in dry acetone (45 ml) stirred under nitrogen, and the mixture was refluxed for 20 min. Consumption of 47 was incomplete as judged by g.l.c., so more potassium carbonate (0.6 g, 8 mmol) was added, and the mixture was refluxed for a further 15 min. Isopropyl iodide (3.3 ml, 33 mmol) in dry acetone (20 ml) was added during 3 min at 30°, and the mixture was refluxed for 16 h, cooled, poured into water (60 ml) and extracted with diethyl ether. The extract was washed (sodium thiosulphate solution, sodium bicarbonate solution, water, and saturated potassium carbonate solution), dried (potassium carbonate), and concentrated to give ethyl 7-(5,6-dihydro-5-oxo-3-(2-propoxy)-2H-thiin-4-yl)heptanoate (50) as a brown oil (7.0 g, 97%) \( t_R \) (OV1, 250°) 7.5 min (90%), 6.5 min (10%, impurity, probably the \( C \)-propylation product 183), \( \lambda_{\text{max}} \) 272.5 nm (logε 4.14, pH-independent), \( \gamma_{\text{max}} \) (film) 1730 s (ester), 1640 s (ring C=O, 1602 s (C=C), 1384 and 1371 cm\(^{-1}\) \( \text{CH(CH}_3)_2 \)). In subsequent preparations of this compound, starting dione 47 of m.p. ca 40° was employed. The product 183
was typically obtained as an orange oil in ca 89% yield after charcoal decolourisation, indistinguishable from the product of the first run by g.l.c., and by infra-red and ultra-violet spectroscopy, \( \tau \) (90 MHz) 5.48 (1H, septet, \( J \) 6 Hz, \( \text{OCH(CH}_3 \text{)}_2 \)), 5.86 (2H, q, \( J \) 7 Hz, \( \text{OCH}_2 \text{CH}_3 \)), 6.50 (2H, s, \( \text{SCH}_2 \)), 6.74 (2H, s, \( \text{SCH}_2 \)), 6.66 (0.4H, s, probably \( \text{CH}_2 \text{SCH}_2 \) signal of C-alkylation product 183), 7.70 (4H, ca t, \( J \) 7 Hz, \( \text{CH}_2 \text{(CH}_2 \text{)}_4 \text{CH}_2 \text{CO}_2 \text{C}_2 \text{H}_5 \)), 8.40 (4H, m, \( \text{CH}_2 \text{CH}_2 \text{(CH}_2 \text{)}_2 \text{CH}_2 \text{CH}_2 \text{CO}_2 \text{C}_2 \text{H}_5 \)), 8.68 (6H, d, \( J \) 6 Hz, \( \text{CH(CH}_3 \text{)}_2 \)), 8.68 (4H, br s, \( \text{CH}_2 \text{CH}_2 \)), 8.74 (3H, t, \( J \) 7 Hz, \( \text{OCH}_2 \text{CH}_3 \)).

**Ethyl 7-(5,6-dihydro-5-oxo-2H-thiin-4-yl)heptanoate (51), ethyl 7-(3,5-dihydroxythian-4-yl)heptanoate (187), and ethyl 7-(5-hydroxy-3-oxothian-4-yl)heptanoate (190)**

Solid sodium borohydride (5.7 g, 150 mmol) was added to ethyl 7-(5,6-dihydro-5-oxo-3-(2-propoxy)-2H-thiin-4-yl)heptanoate (50) (32.7 g, 100 mmol) in ethanol (600 ml), stirred under nitrogen at 0°. The mixture was stirred for 20 h at room temperature, after which none of the enol ether 50 could be detected by g.l.c. of samples acidified with 2M-hydrochloric acid. 2M-Hydrochloric acid (90 ml), chilled to its freezing point, was added to the reaction mixture as quickly as possible at -18° (there was considerable foaming as hydrogen was evolved); the temperature was not allowed to rise above -5° during the addition. The mixture was stirred 1 h at room temperature, then neutralised with 0.6 M-sodium bicarbonate (65 ml). The ethanol was removed in vacuo, and the residue was diluted with water (to ca 100 ml) and extracted with diethyl ether. The extract was washed (sodium bicarbonate solution, water, and saturated sodium sulphate solution), dried and decolourised (sodium sulphate and charcoal), and concentrated
to an orange oil (28.1 g, 104% of theoretical weight), $t_R$ (OV1, 250°) 4.0 (65%) and 7.0 min (35%). Portions of this oil were chromatographed on various adsorbents (Table 5, page 118).

Ethyl 7-(5,6-dihydro-5-oxo-2H-thiin-4-yl)heptanoate (51) was obtained most efficiently from columns packed with silica gel - celite 545 5:1 (elution with petroleum ether (b.p. 40-60°) - benzene 1:3 - 1:9 and with benzene) as a colourless oil (40%) m.p. 15-16°, $t_R$ (OV1, 250°) 4.0 min, $R_F$ (chloroform - acetone - acetic acid 17:2:1) 0.72, $\lambda_{max}$ 242 nm (log ε 3.82, pH-independent), $\gamma_{max}$ (film) 1732s, 1671s cm⁻¹, $\tau$ (90MHz) 3.24 (1H, tt, J 4, 1.5 Hz, =CH₂), 5.84 (2H, q, J 7 Hz, OCH₂CH₃), 6.63 (2H, ca d, J 4 Hz, SCH₂CH), 6.68 (2H, s, SCH₂CO), 7.68 (2H, t, J 7 Hz, CH₂CO₂C₂H₅), 7.76 (2H, t, J 7 Hz, =OCH₂CH₂), 8.37 (2H, m, CH₂CH₂(CH₂)₄CO₂C₂H₅), 8.67 (6H, br s, (CH₂)₃), 8.73 (3H, t, J 7 Hz, OCH₂CH₃).

Chromatography on florisil gave, after elution of 51, ethyl 7-(3,5-dihydroxythian-4-yl)heptanoate (187) (elution with benzene - diethyl ether 9:1 - 3:2) as a pale yellow oil (31%) $t_R$ (OV1, 250°) 7.0 min, $R_F$ (chloroform - acetone - acetic acid 17:2:1) 0.52, $\lambda_{max}$ (film) 3480, 1732s cm⁻¹, $\tau$ (90MHz) 5.85 (2H, q, J 7 Hz, OCH₂CH₃), 6-7.6 (6H, m, CH₂SCH₂ and two CHOH), 7.69 (2H, t, J 7 Hz, CH₂CO₂C₂H₅), 8.1-9.0 (13H, m, two CHOH and >CH(CH₂)₅), 8.74 (t, J 7 Hz, OCH₂CH₃), m/e (70°) 332 (0.1, M⁺, probably 188), 316/314 (0.2, 1.3), 287 (2.5), 271 (7.5), 256/254 (7, 15, M⁺, 261 - 2H₂O), 245 (1.3), 227 (10), 209 (3), 183 (47), 165 (8), 41 (B), 210.3* and 192.4*.

Further elution of the florisil column with benzene - diethyl ether 2:3 - 1:4 and with diethyl ether gave ethyl 7-(5-hydroxy-3-oxothian-4-yl)heptanoate (190) (12%), white crystals m.p. 47-8° from di-isopropyl ether, $t_R$ (OV1, 250°) 4.0 min (severe tailing), $R_F$
(chloroform - acetone - acetic acid 17:2:1) 0.52, \( \nu_{\text{max}} \) (KBr)
3450 br, 1728 s, 1707 s, \( \tau \) (900 MHz) 5.44 (1H, ca d, \( J \) 11 Hz, collapsed to br s on shaking sample with \( D_2O \), \( \text{CH}_3 \)OH), 5.88 (2H, ABq, \( J \) 12 Hz; high-field lines had d splitting \( J \) 2.05 Hz, \( \text{SCH}_2\text{CO} \)), 6.78 and 7.19 (2H, ABq, \( J \) 14 Hz, low-field lines had d splitting \( J \) 1.75 Hz, high-field lines had dd splitting, \( J \) 4.1, 2.05 Hz, \( \text{SCH}_2\text{CH} \)), 7.5 (1H, m (partly hidden), \( \text{COCH} \)), 7.57 (1H, d, \( J \) 11 Hz, disappeared on shaking sample with \( D_2O \), \( \text{OH} \)), 7.72 (2H, t, \( J \) 7 Hz, \( \text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 \)), 8.38 (4H, m, \( \text{CHCH}_2(\text{CH}_2)_3\text{CH}_2\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 \)), 8.68 (6H, br s, \( \text{CH}_2\text{CH} \)), 8.75 (3H, t, \( \text{OCH}_2\text{CH} \)), \( m/e \) (80°) 290/288 (4, 69, \( M^+ \)), 270 (2), 243 (24), 242 (B), 225 (31), 224 (19), 199 (13), 253.1*, 209.2*, 208.3*, 207.3*, 205.0*, 203.4*, 185.8*.

7-(5,6-dihydro-5-oxo-2H-thiin-3-yloxy)heptanoic acid (192)
Crude hog pancreas lipase (Sigma) (7.0 g) was stirred with a salt solution (0.1M sodium chloride, 0.05M calcium chloride, 70 ml) at 0° for 1 h. The mixture was centrifuged at 10,000 g and 0° for 30 min, and the supernatant fluid was treated with sufficient 0.5M sodium hydroxide to raise its pH to 6.5.
Finely-powdered ethyl 7-(5,6-dihydro-5-oxo-2H-thiin-3-yloxy)heptanoate (144) (1.33 g, 4.6 mmol) was stirred with 0.1% aqueous "Cutscum" (Kodak) surfactant solution (2 ml) at 0°, and the enzyme extract was added. The mixture was sonicated for 2 min with ice-salt cooling (to disperse the organic substrate), then stirred at 35°. The pH of the mixture was maintained at 6.5-7.0 by addition of 0.5M-sodium hydroxide as necessary. When alkali uptake had ceased (2.5 h) the reaction mixture was poured into acetone (100 ml), stirred for 15 min, and filtered through celite. The acetone was removed in vacuo from the filtrate, the pH was adjusted to 8, and
unchanged ester 144 removed by washing with diethyl ether. The aqueous phase was then acidified to pH 3.5 with 2M hydrochloric acid, and extracted with diethyl ether. The extract was washed (water), dried (sodium sulphate) and concentrated to give 7-(5,6-dihydro-5-oxo-thiin-3-yloxy)heptanoic acid (192) as a pale yellow solid (744 mg, 62%) m.p. 71-74°. Trace impurities were removed by two recrystallisations from acetone and one from di-isopropyl ether, which gave fine white needles (129 mg), m.p. 74-74.5°, \( \lambda_{\text{max}} \) 254 nm (log\( e \) 4.22), \( \gamma_{\text{max}} \) (KBr) 3000br, 1690s, 1660s, 1602s cm\(^{-1}\), \( \tau \) (90MHz) -0.7 (1H, br s, CO\(_2\)H), 4.58 (1H, s, =CH) 6.12 (2H, t, J 6 Hz, OCH\(_2\)H), 6.65 (2H, s, SCH\(_2\)H), 6.72 (2H, s, SCH\(_2\)H), 7.60 (2H, t, J 7 Hz, CH\(_2\)CO\(_2\)H), 8.30 (4H, m, CH\(_2\)CH\(_2\)(CH\(_2\))\(_2\)CH\(_2\)CH\(_2\)CO\(_2\)H), 8.56 (4H, br s, (CH\(_2\))\(_2\)).

7-(5,6-dihydro-5-oxo-2H-thiin-4-y1)heptanoic acid (186)

Ethyl 7-(5,6-dihydro-5-oxo-2H-thiin-4-y1)heptanoate (51) (180 mg, 0.67 mmol) was hydrolysed by the procedure described above for ester 218. The same quantity of enzyme extract was used, and the hydrolysis required 2 h. 7-(5,6-Dihydro-5-oxo-2H-thiin-4-y1)heptanoic acid (186) was obtained as a pale yellow solid (109 mg, 67.5%), m.p. 62-64°, and as white, flaky needles from petroleum ether (b.p. 60-80°), m.p. 65-65.5°, \( \lambda_{\text{max}} \) 242 nm (log\( e \) 3.82), \( \gamma_{\text{max}} \) (KBr) 3000br, 1698s, 1668s cm\(^{-1}\), \( \tau \) (90MHz) -0.6 (1H, br s, CO\(_2\)H), 3.26 (1H, tt, J 4, 1 Hz, =CH), 6.64 (2H, d, J 4 Hz, SCH\(_2\)CH=), 6.69 (2H, s, SCH\(_2\)CO), 7.62 (2H, t, J 7 Hz, CH\(_2\)CO\(_2\)H), 7.76 (2H, t, J 6.5 Hz, =CCH\(_2\)CH\(_2\)H), 8.38 (2H, m, CH\(_2\)CH\(_2\)(CH\(_2\))\(_4\)CO\(_2\)H), 8.65 (6H, br s, (CH\(_2\))\(_3\)), m/e (220°) 244/242 (0.5, 7, M\(^+\)), 224 (30), 206 (3.5), 196 (20), 181 (1), 178 (8), 163 (3), 113 (24), 53 (B), 207.3*, 189.4*, 171.5*, 161.7*. 

205
Ethyl 7-(3-oxo-5-(1-propenyl)thian-4-yl)heptanoate (221)

A solution of 1-bromopropene ($t_R$ (OV1, 60°) 1.55 and 1.65 min, overlapping) (0.45 ml, 5.2 mmol) in dry diethyl ether (5 ml) was added gradually to a stirred mixture of small pieces of lithium (BDH 99.9%) (70 mg, 10 mmol) and dry diethyl ether (10 ml) under argon, at -30°. The temperature was raised briefly to 0° to initiate the reaction, then kept at -10° for 1 h. Consumption of the 1-bromopropene was judged to be complete by g.l.c., but some solid lithium remained, so more of the olefin (0.05 ml, 0.5 mmol) was added; dissolution of the metal was complete after a further 30 min at -10°. The cold solution was added during 20 min to a suspension of anhydrous copper(I) iodide (480 mg, 2.5 mmol) in dry diethyl ether (10 ml) stirred under argon at -35°, and the resulting mixture was stirred for 1 h at -78°. A solution of ethyl 7-(5,6-dihydro-5-oxo-2H-thiin-4-yl)heptanoate (51) (408 mg, 1.5 mmol) in dry diethyl ether (8 ml) was added during 20 min below -50° and the mixture was stirred for 1.5 h at -70°, warmed slowly to 0°, poured into stirred 0.75M-hydrochloric acid (16 ml), and extracted with diethyl ether. The extract was washed (water and saturated sodium sulphate solution), dried (sodium sulphate) and concentrated to an orange oil (441 mg), $t_R$ (OV1, 250°) 5.9 (92%), 4.0 min (51, 8%), which was chromatographed on Florisil. Elution with petroleum ether (b.p. 40-60°) - benzene 1:100 - 1:3 gave ethyl 7-(3-oxo-5-(1-propenyl)thian-4-yl)heptanoate (221) as an orange oil (365 mg, 78%), $t_R$ (OV1, 250°) 5.9 and 4.0 min (the proportion of the latter component increased from the first to the last fraction of the series; it was 5% overall; spectra were measured for a fraction in which it was 3%): $\lambda_{max}$ 247.5 nm (sulphide
\( n \rightarrow \sigma^* \), 172 nm (carbonyl \( n \rightarrow \pi^* \)) \((\text{log } e 2.88, 2.39)\),
\( \gamma_{\text{max}} \) (film) 1738s, 1711s, 968 (trans \( \text{CH}=\text{CH} \)) and 721w (cis \( \text{CH}=\text{CH} \)),
\( \tau \) (90 MHz) 4.5 (2H, m, \( \text{CH}=\text{CH} \)), 5.87 (2H, q, \( \downarrow \text{J} 7 \) Hz, \( \text{OCH}_2\text{CH}_3 \)),
6.59 and 6.86 (2H, ABq, \( \downarrow \text{J} 12 \) Hz, low-field lines had d splitting
\( \downarrow \text{J} 5 \) Hz, high-field lines had d splitting \( \downarrow \text{J} 1.5 \) Hz, \( \text{SCH}_2\text{CH} \)), 7.0
(1H, partly hidden m, \( \text{CH}=\text{CH}=\text{CH} \)), 7.23 and 7.26 (2H, ABq, high-field lines had d splitting \( \downarrow \text{J} 1.5 \) Hz, \( \text{SCH}_2\text{CO} \)), 7.71 (2H, t, \( \downarrow \text{J} 7 \) Hz),
7.8 (1H, partly hidden m, \( \text{COCH} \)), 8.31 (1.5H, d, \( \downarrow \text{J} 4.3 \) Hz, \( \text{CH}=\text{CHCH}_3 \)),
8.37 (1.5H, d, \( \downarrow \text{J} 5.6 \) Hz, \( \text{CH}=\text{CHCH}_3 \)), 8.4 (4H, partly hidden m,
\( \text{CHCH}_2\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 \)), 8.7 (6H, s, \( \text{(CH}_2\text{)}_3 \)), 8.75 (3H, t, \( \downarrow \text{J} 7 \) Hz, \( \text{OCH}_2\text{CH}_3 \)).

**Borane-tetrahydrofuran complex**

A solution of freshly-distilled boron trifluoride - diethyl ether complex (47.9 g, 338 mmol) in dry diglyme (35 ml) was stirred under nitrogen at 20-22°. A 0.8 M-solution of sodium borohydride in dry diglyme (220 ml) was added from a pressure-equalised dropping funnel during 1 h. The outgoing gases were bubbled through sodium borohydride - diglyme, then dry tetrahydrofuran (90 ml) in a tared receiver cooled in ice-water, then finally through two traps containing mercury and acetone to prevent entry of air and to remove diborane from the escaping gases. On completion of the addition the generating flask was heated to 70-80° for 1 h, then cooled.

Further manipulations were performed under nitrogen. The traps were disconnected, a sample of the product (ca 1 ml) was withdrawn from the receiver by syringe, and the receiver was stoppered. Acetone (ca 100 ml) was added to the generator, the outlet was connected to the safety traps, and the apparatus was flushed with nitrogen for 30 min.
The syringe containing the product sample was weighed, discharged into acetone (10 ml) and reweighed. Water was added to the acetone solution, and the amount of boric acid that was formed was determined by titration versus 0.1M-sodium hydroxide (standardised versus boric acid) with phenolphthalein as indicator, in the presence of mannitol (1 g). From the titration result, the weight of the sample transferred from the syringe, and the weight of the product it was calculated that 185 mmol borane-tetrahydrofuran complex remained in the receiver, and that the yield of the complex had been 80%.

1,3,2-Benzodioxaborole

Borane-tetrahydrofuran complex (185 mmol) was stirred under nitrogen at 0°; outgoing gases were passed through a mercury-acetone trap. A solution of catechol (Emanuel, recrystallised from toluene and dried over silica gel in vacuo, m.p. 103-105°) (20.4 g, 185 mmol) in dry tetrahydrofuran (45 ml) was added from a pressure-equalised dropping funnel during 45 min. The tetrahydrofuran was removed by evaporation under nitrogen at ca 100 mmHg, leaving a pale yellow oil which was distilled under nitrogen from a 25 ml Vigreux flask to give 1,3,2-benzodioxaborole as a colourless oil (11.0 g, 50%), b.p. 62-72° at 65 mmHg.

trans-1-Octenyl iodide

1,3,2-Benzodioxaborole (11.0 g, 91.5 mmol) was added to freshly-distilled 1-octyne (10.2 g, 92.5 mmol) stirred under nitrogen at room temperature. The mixture was heated slowly to 70°, kept at this temperature for 2 h, then cooled to 20°. Water (100 ml) was added during 1 min, and the mixture was stirred 2 h at 25°, cooled to 0°, and filtered. The precipitate of trans-1-octenylboronic acid
which was collected on the filter was washed (water), sucked dry, dissolved in diethyl ether (90 ml) and stirred at 0°. 3M-Sodium hydroxide (91 ml) and a 0.4M-solution of iodine in diethyl ether (280 ml) were added below 10°, and the mixture was stirred at 0° for 30 min. 1M-Sodium thiosulphate (20 ml) was added, and the aqueous layer extracted with diethyl ether. The combined ether layers were filtered, washed (water), dried (sodium sulphate) and concentrated to an oil which was distilled to give trans-1-octenyl iodide as a pale yellow oil (soon discoloured by iodine) (11.6 g, 53.5%), b.p. 38-44° at 0.2 mmHg, tR (OV1, 170°) 2.4 min, γmax (film) 3038w (=CH), 1455br (=C-CH2), 939s cm⁻¹ (trans CH=CH).

1-Pentynylcopper(I) 212
A solution of copper(II) sulphate pentahydrate (2.8 g, 11 mmol) in aqueous ammonia (10.5 ml, d 0.880) was stirred under nitrogen with cold water cooling. It was treated with water (44 ml) and solid hydroxylammonium chloride (1.56 g, 22 mmol), and after 5 min, with 1-pentyne (763 mg, 11 mmol) in ethanol (50 ml). The mixture was stirred 1 h, and the yellow precipitate filtered off, washed (water, ethanol and dry diethyl ether), and dried (rotary evaporator, 50°, 20 mmHg, 2.5 h) to give 1-pentynylcopper(I) as a bright yellow powder (791 mg, 54%).

Ethyl 7-(5-(trans-1-octenyl)-3-oxothian-4-yl)heptanoate (227)
An approximately 2M-solution of tert-butyllithium in pentane (Fluka) (3.7 ml) was added dropwise, via a hypodermic syringe mounted in a syringe pipette holder, 213 to trans-1-octenyl iodide (953 mg, 4 mmol) in dry diethyl ether (5 ml) stirred under argon at -78°. The mixture was stirred for 2 h at -78°, then added
dropwise, via syringe, to a solution of 1-pentynylcopper(I) (480 mg, 3.6 mmol) in dry diethyl ether (12 ml) and hexamethyldiphosphorous triamide (1.4 ml, 7.2 mmol) at -78°C, under argon. The resulting slightly orange mixture was stirred 30 min at -78°C, treated with ethyl 7-(5,6-dihydro-5-oxo-2H-thiin-4-yl)heptanoate (51) in dry diethyl ether (6 ml), warmed to 23°C during 3.5 h, poured with stirring into 1.5M-ammonium sulphate (15 ml), filtered (celite) and extracted with diethyl ether. The extract was washed (water and 0.4M sulphuric acid), filtered (celite), washed (sodium bicarbonate solution, water, and saturated sodium sulphate solution), dried and decolourised (sodium sulphate and charcoal) and concentrated to an orange oil (1.205 g, 105% of theoretical yield), t_R (OV1, 250°C) 4.0 (51, 2%), 7.5 and 8.4 (overlapping, 8%), 20.4 min (90%) t_R (OV1, 170°C) 2.4 min (trans-1-octenyl iodide, not observed - <0.1%). A finely-divided white precipitate was liberated by the acid washings, making separation of the layers difficult; it was insoluble in 1.5M ammonium sulphate, potassium iodide solution, 2M-hydrochloric acid, and acetone, but could be dissolved in a mixture of concentrated nitric and hydrochloric acids. The resulting solution was lime-green in colour, and was shown by means of a flame test to contain copper.

For preliminary purification the orange oil was applied to a column of silica gel (12 g). Most of the material (883 mg) was eluted with benzene, as a slightly cloudy, light brown oil. Further elution with benzene - diethyl ether 1:1 gave an orange oil (165 mg) inferior to the main fraction as judged by g.l.c.
The bulk of the main fraction (860 mg) was treated with petroleum ether (b.p. 40-60°) (800 ml), whereupon a finely-divided white precipitate was formed. The mixture was centrifuged, and the supernatant fluid was chromatographed on silica gel (90 g).

Elution with petroleum ether (b.p. 40-60°) - benzene 1:1 - 1:100 and with benzene gave ethyl 7-(5-(trans-1-octenyl)-3-oxothian-4-yl)heptanoate (227) as a colourless oil (566 mg, 50%), m.p. 10-12°, $t_R$ (OV1, 250°) 7.5 and 8.4 (5%), 20.4 min (95%), $\gamma_{\text{max}}$ (film) 1730s, 1705s, 962 cm$^{-1}$ (trans CH=CH), $\tau$ (90MHz) 4.44 (dt, $J$ 15.5, 5.5 Hz, trans CH-CH=CH) and 4.71 (dd, $J$ 15.5, 7 Hz, trans CH-CH=CH) (1.9H), 5.85 (2H, q, $J$ 7.3 Hz, OCH$_2$CH$_3$), 6.70 and 6.96 (2H, ABq, $J$ 12 Hz, SCH$_2$CH), 7.26 and 7.34 (2H, ABq, $J$ 13 Hz, high-field lines had d splitting $J$ 1.5 Hz, SCH$_2$CO), 7.0 (1H, hidden m, CHCO), 7.72 (2H, t, $J$ 7.5 Hz, CH$_2$CO$_2$C$_2$H$_5$), 7.7 (1H, hidden m, CH-CH=CH), 7.98 (ca d, $J$ 5.5 Hz, CH=CH=CH$_2$), 8.40 (m, CHCH$_2$(CH$_2$)$_3$CH$_2$CH$_2$CO$_2$C$_2$H$_5$), 8.74 (br s, (CH$_2$)$_3$ and (CH$_2$)$_4$) and 8.76 (t, $J$ 7 Hz, OCH$_2$CH$_3$) (22.4H), 9.08 (s, C(CH$_3$)$_3$) and 9.11 (t, $J$ 6 Hz (CH$_2$)$_5$(CH$_3$) (3.3H) (the latter spectrum is discussed on page 148), m/e (30°) 384/382 (7, 90, M$^+$), 367 (1), 364 (1), 353 (1), 339 (7), 337 (50), 336 (27), 325 (1), 311 (1), 297 (4), 226 (20), 225 (24), 55 (B), 295.6*.

11,15-dideoxy-11a-homo-11-thiaprostaglandin E$_1$ (228)

A mixture of 0.2M potassium carbonate (11 ml) and methanol (19 ml) was added to ethyl 7-(5-(trans-1-octenyl)-3-oxothian-4-yl)heptanoate (227, $t_R$ (OV1, 250°) 7.5 and 8.4 (5%), 20.4 min (95%)) (350 mg, 0.88 mmol) in methanol (16 ml), stirred under nitrogen at room temperature. Consumption of the ester, which was monitored by g.l.c., was complete after 66 h (>99% consumption of all three eluted components). The mixture was concentrated to small volume,
diluted with water, and washed with diethyl ether; centrifugation was necessary to separate the layers. The aqueous layer was acidified to pH 2.5 with 2M-hydrochloric acid, and extracted with diethyl ether - ethyl acetate 1:1. The extract was washed (saturated sodium sulphate solution), dried and decolourised (sodium sulphate and charcoal), and concentrated to give the **crude prostaglandin analogue** (228) as a colourless oil which solidified on being "scratched" with a glass rod and stored in a glass vessel at -24° (176 mg 56%); m.p. ca 30°. Some more of the analogue (40 mg, 13%) was recovered from the diethyl ether washings; this fraction contained minor impurities detectable by g.l.c., but was indistinguishable from the main product, and from a recrystallised sample (described later), by thin layer chromatography and infra-red spectroscopy. A small portion of the main crop (7 mg) was recrystallised by dissolving it in sufficient petroleum ether (bp 40-60°) to give a saturated solution at room temperature, seeding, and keeping at 8° for 60 h. In this way a relatively pure sample of 11,15-dideoxy-11α-homo-11-thiaprostaglandin E₁ (228) was obtained as white crystals (2.5 mg), m.p. 43-9°, Rᵢ (ethyl acetate - acetic acid - iso-octane 11:2:5, saturated with water) 0.57, λ_max 251 nm (sulphide n → σ*), 310.5 nm (carbonyl n → π*) (logε 2.64, 2.38), γ_max (KBr) 3100br, 1705s, 961 cm⁻¹, τ (90MHz) 4.43 (1H, dt, j 15, 6 Hz, trans CH=CH-CH₂), 4.71 (1H, dd, j 15, 7 Hz, trans CH-CH=CH), 6.67 and 6.94 (2H, ABq, j 12 Hz, low-field lines had d splitting j 2.6 Hz, SCH₂CH), 7.0 (1H, partly hidden m, CHCO), 7.24 and 7.32 (2H, ABq, j 12 Hz, SCH₂CO), 7.64 (2H, t, j 7 Hz, CH₂CO₂H), 7.7 (1H, hidden m, CH-CH=CH), 7.98 (2H, ca d, j 6 Hz, CH=CH-CH₂), 8.38 (4H, m, CHCH₂(CH₂)₃CH₂CH₂), 8.73 (14H, br s, (CH₂)₃ and (CH₂)₄), 9.11 (3H, t, j 5.6 Hz, (CH₂)₅CH₃), m/e (150°) 356/354 (2.5, 36, M⁺), 339 (1), 336 (8),
325 (1), 311 (9), 297 (2), 293 (5), 283 (1), 269 (3), 226 (21), 225 (13), 67 (B), 318.9*, 273.2*.

2-Heptylcyclohexan-1,3-dione (242)

Methanol (100 ml) was added gradually to potassium tert-butoxide (43 g, 0.38 mol) with stirring and cooling, under nitrogen. Cyclohexan-1,3-dione (43 g, 0.38 mol) was added to the resulting solution, the temperature of the mixture was adjusted to 50°, and heptyl iodide (95 g, 0.42 mol) was added during 8 min. The mixture was refluxed for 16 h, the methanol was removed in vacuo, and diethyl ether (400 ml) was added. The precipitate of potassium iodide was removed by filtration, and the filtrate was extracted with four portions of 0.75M-sodium hydroxide (100 ml each). The alkaline extract was washed (diethyl ether), then acidified to pH 2 with concentrated hydrochloric acid (35 ml). The precipitate of 2-heptylcyclohexan-1,3-dione (242) was collected by filtration, washed (water), and dried to a white powder (9.65 g, 12%), m.p. 89-89.5°, $t_R$ (OV1, 220°) 3.8 min, $\lambda_{\text{max}}$ 263 nm (log $\varepsilon$ 4.13), $\lambda_{\text{max}}$ (alkaline) 294 nm (log $\varepsilon$ 4.29), $\gamma_{\text{max}}$ (CHCl$_3$) 3140s,br, 1736w, 1701, 1590s,br cm$^{-1}$, $\gamma_{\text{max}}$ (KBr) 1733, 1704s cm$^{-1}$. A sample of the product was recrystallised three times from di-isopropyl ether. No increase in melting point was obtained after the first recrystallisation, which raised it to 90-91°. The recrystallised material was indistinguishable from the original product by g.l.c. and spectroscopic behaviour.
A mixture of tert-butanol (37 ml, 0.39 mol) and acetic acid (24.5 ml, 0.43 mol) was added gradually to 0.8M-sodium hypochlorite* (500 ml, 0.40 mol) stirred at 0° in dim, indirect light. The mixture was stirred for 3 min, the layers were separated, and the yellow organic layer was washed (1M sodium carbonate and water) and dried (calcium chloride) to give tert-butyl hypochlorite (24.8 g, 59%). This product was stored over calcium chloride in an amber glass bottle, in darkness, at -24°. Assay (all operations were conducted in minimum light): samples of tert-butyl hypochlorite (ca 100 mg) were weighed accurately into a titration flask, treated with a solution of potassium iodide (0.6 g) in water (2 ml) and acetic acid (4 ml), and were titrated against 0.1M-sodium thiosulphate, starch indicator being added near the end-point. Assay results were of the order of 94% and were independent of the age of the tert-butyl hypochlorite.

* Commercially available sodium hypochlorite solution (Koch-Light, "pure, approximately 15% available chlorine") was found to have an oxidant concentration of 1.79M (as OCl⁻) by iodometric titration versus standard sodium thiosulphate. The 0.8M-solution used for this experiment was prepared by diluting the commercial product (224 ml) with water (to a total volume of 500 ml).
2-Chloro-2-heptylcylohexan-1,3-dione (243)


tert-Butyl hypochlorite (1.5 ml, 10 mmol) was added to 2-heptylcyclohexan-1,3-dione (242) (2.1 g, 10 mmol) in dry tert-butyl alcohol (15 ml) stirred under nitrogen at 25°; the reaction temperature was kept below 45° by means of a cold water bath. After 3 min, g.l.c. of the mixture indicated 90% consumption of 242, and an ultra-violet spectrum showed complete loss of the chromophore at 263 nm; similar results were obtained after 16 h.

The solvent was removed in vacuo to give 2-chloro-2-heptylcylohexan-1,3-dione (243) as a yellow powder (2.46 g, 100%), m.p. 46-49°, t_R (OV1, 220°) 1.8 (probably cyclopentenone (241) formed on injection; severe tailing) and 7.3 min (major component, proportion variable), 

λ_max 297 nm (log ε 2.23), γ_max (KBr) 1737, 1711s cm⁻¹. No increase in melting point could be achieved by recrystallisation.

2-Heptylcyclopent-2-enone (241)

2-Chloro-2-heptylcyclohexane-1,3-dione (243) (4.55 g, 18.5 mmol) in xylene (90 ml) was added to anhydrous sodium carbonate (dried in air at 110°) (2 g, 18.9 mmol) and the mixture was refluxed for 20 h under nitrogen, cooled, and filtered. The filtrate was washed (water), dried (sodium sulphate) and concentrated. The residue was distilled to give 2-heptylcyclopent-2-enone (241) as a colourless oil (1.67 g, 35%), b.p. 70-74° at 0.2 mmHg, 

t_R (OV1, 220°) 1.8 min, λ_max 228 nm (log ε 4.11), γ_max (film) 3040w, 1703s, 1630w cm⁻¹, τ (90MHz) 2.7 (1H, dt, J 5, 1 Hz, (CO)-C=CH), 7.5 (4H, m, (CO)-CH₂CH₂C=C), 7.81 (2H, t, J 6.5 Hz, C=C-CH₂(CH₂)₅CH₃), 8.71 (10H, br s, (CH₂)₅), 9.12 (3H, t, J 5.5 Hz, CH₃), m/e (170°) 180 (25, M⁺), 165 (1.5), 162 (1), 151 (6), 137 (20, 123 (24), 109 (26), 95 (23), 81 (18), 28 (B), 145.9°.
tert-Butyl hypochlorite (230 mg, 2.1 mmol) was added gradually to ethyl 7-(3,5-dioxothian-4-yl)heptanoate (47, \( R_F \) (chloroform - methanol 4:1) 0.70) (690 mg, 2.4 mmol) in dichloromethane (10 ml), stirred under nitrogen at \(-78^\circ\). The temperature was raised to \(20^\circ\) during 2 h, after which g.l.c. indicated ca 50\% consumption of 47, and samples of the reaction mixture failed to liberate iodine from potassium iodide solution. The mixture was filtered, and the solid phase was washed (dichloromethane) and sucked dry to give ethyl 7-(2-chloro-3,5-dioxothian-4-yl)heptanoate (244) as a white powder (166 mg, 25\%), m.p. 150-155\° (decomp) unchanged by recrystallisation from acetone - methanol 8:1 (Found: C, 52.22; H, 6.42; S, 9.73; Cl, 11.02. \( C_{14}H_{21}SClO_4 \) requires C, 52.41; H, 6.60; S, 9.99; Cl, 11.05\%), \( R_F \) (chloroform - methanol 4:1) 0.35

\( \lambda_{\max} \) 218, 250, 324, 382 nm (\( \log e \) 3.93, 4.12, 3.36, 3.31), \( \lambda_{\max} \) (acid) 224, 324 nm (\( \log e \) 4.28, 3.75), \( \lambda_{\max} \) (alkaline) 248, 366 nm (\( \log e \) 4.37, 3.76), \( \nu_{\max} \) (KBr) 3018s,br, 1730s, 1520s, 1404s, 828 cm\(^{-1}\), \( \tau \) (90MHz) 0.93 (2H, br s, S(CHCl)CO and OH of enolic tautomers), 5.87 \( (2H, q, J 7\ Hz, OCH_2CH_3) \), 7.07 \( (2H, br s, SCH_2CO) \), 7.70 \( (2H, t, J 7\ Hz, CH_2CO_2C_2H_5) \), 8.57 \( (10H, br s, (CH_2)_5) \), 8.74 \( (3H, t, J 7\ Hz, OCH_2CH_3) \), m/e (200\°) 570/568 (5, 30), 523 (40), 522 (60), 477 (30), 449 (35), 285 (45), 269 (95), 239 (50), 223 (B).

The liquid phase of the reaction mixture was concentrated to a black paste (576 mg), \( R_F \) (chloroform - methanol 4:1) 0.35 (244), 0.70 (47).
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