Studies on the Synthesis of the Cofactor, Methoxatin
and on Simple Thioaldehydes

by

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Abstract

The first part of this thesis describes how the protected phenylalanines 16, 22 and 60 were synthesised and their oxidations investigated as sources of indolines 41, 53 and 81, which would be further elaborated to the pyrroloquinoline system of the cofactor, methoxatin 2. Oxidative
cyclisation procedures effective for phenylalanine were found to be unsatisfactory, giving no recognisable products. However, evidence presented shows that treatment of aminophenols 16, 22 and 60 with lead dioxide in dichloromethane gave the quinoneimines 39, 49 and 63, but no cyclised derivatives of such quinoneimines could be isolated.

In the second part, thioaldehydes are shown to be preparatively useful intermediates in organic synthesis. Thiobenzaldehyde 83 and thioacetaldehyde were generated by the thermolysis of thiosulphinates 102 and 100 respectively, and trapped with aromatic and aliphatic 1,3-dienes by inter-

\[
\begin{align*}
\text{R} & \quad \text{S}^+ \quad \text{S} \quad \text{S} \quad \text{R} \\
\text{102} & \quad R = \text{Ph} \\
\text{100} & \quad R = \text{Me}
\end{align*}
\]

molecular Diels-Alder reactions. The adducts of thiobenzaldehyde and thioacetaldehyde with anthracenes are themselves sources of the thioaldehydes when heated, and sources of 9-substituted dihydroanthracenes when reduced with sodium in liquid ammonia. An example of intramolecular Diels-Alder reaction between an aliphatic thioaldehyde and an aliphatic 1,3-diene is presented, as is an example of an 'ene' reaction of thiobenzaldehyde 83.
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PART I

The Synthesis of the Cofactor, Methoxatin
INTRODUCTION

The work described in the first part of this thesis is directed towards the synthesis of a novel cofactor, which may be involved in the oxidative processes of some bacteria.

Discovery and Characterisation of the Cofactor

Certain *Pseudomonas* species of bacteria termed methylotrophs use methanol as their only source of carbon, both for building cellular compounds and for providing energy by its combustion.\(^1\) The alcohol dehydrogenase is therefore a central enzyme to these bacteria and it was found to be unusual\(^2\) in that it contained no appreciable quantities of metals, notably iron, had no reaction with molecular oxygen and was not a flavoprotein. Its activity was independent of nicotinamide nucleotides and only phenazine methosulphate could act as hydrogen acceptor. This combination of properties led to its being classified apart from all other enzymes. Several other methylotrophic bacteria, which could subsist on other C\(_1\) compounds, such as methane and methylamine,\(^1,3\) were later found to have alcohol dehydrogenases with similar characteristics.\(^4,5,6\)

At the time that the novel properties of these enzymes were discovered, it was noticed that they contained a unique prosthetic group. Preliminary spectroscopic studies of the prosthetic group suggested that it might be a pteridine derivative, figure 1,\(^7\) a neopterin cyclic phosphate,\(^8\) a lumazine derivative,\(^4\) or a quinone.\(^9,10\)
Recently, an X-ray crystallographic study of a material isolated from a *Pseudomonas* strain revealed pyrroloquinoline structure 1.\textsuperscript{11,12} The isolated compound was found to be racemic at C-5, and since acetone had been used in the isolation procedure,\textsuperscript{11,13} it was suggested that 1 was an aldol adduct.
between acetone and the active cofactor \textit{in vivo} \textsuperscript{2}. Quinone \textsuperscript{2} was given the trivial name methoxatin,\textsuperscript{11,12,13} and has also been referred to as pyrrolo quinoline quinone.\textsuperscript{14} The structure of methoxatin \textsuperscript{2} is in full agreement with the electron spin resonance\textsuperscript{9,14} and external nuclear double resonance\textsuperscript{10} experiments which have been carried out on the whole enzyme and on cofactor preparations.

Methoxatin has also been found in alcohol dehydrogenases from non-methylotrophic bacteria, such as ethanol-grown \textit{Acinetobacter calcoaceticus} which cannot subsist on methanol,\textsuperscript{15} and in glucose dehydrogenases.\textsuperscript{6,16} It is not known how widespread methoxatin will turn out to be, but current commercial interest centres around its presence in bacteria which convert methanol into nutritive single-cell protein.\textsuperscript{17}

Since the discovery of a new cofactor is a rare occurrence, and since the chemical structure of methoxatin has only been known for a short time, there is active interest in its general chemistry and the possible mechanism of oxidation.\textsuperscript{18} Studies are therefore in progress directed towards establishing its properties \textit{in vivo}\textsuperscript{19} and \textit{in vitro}.\textsuperscript{20}

An important, and as yet unresolved problem is that methanol dehydrogenases have not been reconstituted from the cofactor and the cofactor-free enzyme, the apoenzyme.\textsuperscript{4} The reconstitution is necessary in order to prove that the presumed cofactor is indeed the critical component which restores activity to the apoenzyme, and not simply an artefact of the isolation procedure.

These further experiments which are to be carried out require a greater quantity of methoxatin than that available by isolation from natural sources. It was to this end that we
embarked on its synthesis. When the work was begun, there was no published synthesis of methoxatin.

**Known Syntheses of Methoxatin**

The tricyclic structure of methoxatin 2 suggests that an immediate synthetic precursor will have two rings and will require elaboration of the third. Candidates for the bicyclic precursor are likely to fall into four categories: quinolines, indoles, pyrrylpyridines and large-ring pyridines or pyrroles, depending on which bond in the methoxatin skeleton is the last to be made, figure 2. This list of synthetic approaches is by no means exhaustive, since one can also imagine ring contractions

![Diagram of molecular structures](image)
and expansions, for example, which are not covered by the above classification, but it covers the most direct schemes.

The large-ring compounds are likely to be difficult precursors to achieve, while on the other hand, many syntheses of quinolines, indoles, pyridines and pyrroles already exist. In fact, of the three published syntheses of methoxatin, one goes \textit{via} a quinoline, another \textit{via} an indole, and the third \textit{via} a pyrrylpyridine.

Any of these heterocycles chosen as a precursor would have to be highly substituted in a specific manner in order that transformation of its functional groups to those of methoxatin might be straightforward. Preparation of such a heterocycle would be very involved, and this is amply demonstrated in Weinreb's synthesis.\textsuperscript{21} The crucial intermediate is quinoline 3, which was prepared in twelve steps from dimethoxytoluene 4 in an overall yield of 4.5%. The substitution pattern of quinoline 3 allowed its conversion into methoxatin in only three steps in an
overall yield of 33%.

The alternative to making a highly and specifically functionalised precursor to the pyrroloquinoline system of methoxatin was tried by Hendrickson. In his synthesis, the low-yielding cyclisation to tricycle 5, figure 3, came in the early stages, and was followed by an arduous nine-step sequence, producing methoxatin in 52% yield from 5.

An elegant solution to the apparent paradox of requiring a highly functionalised precursor to the tricyclic system without that precursor necessitating a laborious synthesis was provided by Corey. Intermediate indole 6 was prepared in six steps from commercially available aniline 7 in an overall yield of 40%, and
could be transformed into methoxatin in another six steps in an overall yield of 49%. The key reaction which introduced the third ring was the combination of indole 6 with enone 8 via a 1,4-addition followed by nucleophilic attack at the ketone

Figure 4
carbonyl group by the carbon atom at the 7-position on the indole which is activated to electrophilic attack by both the pyrrole and amine nitrogen atoms, figure 4. Treatment with dry hydrogen chloride aromatised the pyridine ring.

An Alternative Synthetic Strategy

The synthetic approach described in this thesis offers a radically different alternative to the three syntheses outlined above. This is because, in addition to being directed at the production of methoxatin, it tries to explore the inherent reactivity of some types of molecules thought to be reasonable intermediates in the biosynthesis of this cofactor. It must be stressed that the biosynthesis of methoxatin has not been defined, and the suggestions that follow are only based on chemically reasonable intermediates and reactions, and a knowledge of the compounds available in vivo.

It is readily discerned that the entire carbon and nitrogen atom skeleton of methoxatin 2 is available in the two naturally-occurring amino acids, phenylalanine and glutamic acid, figure 5. Therefore, formally, methoxatin represents an adduct of these amino acids at a suitable oxidation level. Three bonds must be formed to convert the two amino acids into the necessary tricyclic structure. That which closes the pyrrole ring has ample precedent in both biosynthetic 24 and in vitro 25 reactions, when one considers that methoxatin has hetero atoms at the 5 and 6 positions of the so-formed dihydroindole, figure 6. The second carbon-nitrogen bond could be formed by condensation of the glutamic acid amine with a quinone carbonyl group, and the carbon-carbon bond remaining
Figure 5

may rely on the susceptibility of the indole C-7 to electrophilic attack which has been demonstrated.\textsuperscript{23}

Figure 6

An attractive route to methoxatin, therefore, would involve a series of oxidations on a mixture or adduct of phenylalanine and glutamic acid.
Dihydroxyphenylalanine, dopa, 9, is oxidised to dopachrome 10 in the biosynthesis of the pigment, melanin. dopachrome 10 then decarboxylates, quinone 11 undergoes an internal oxidation-reduction, and indole 12 oxidises and

Figure 7
polymerises to the pigment, figure 7. Dopachrome is sufficiently long-lived for its solution to be handled chemically, though crystallisation has so far proved elusive. It has been trapped with hydroxylamine and hydrazines which condense at the 5-keto group, giving crystalline derivatives.

The 6-keto function is deactivated with respect to the 5-keto group, because it is part of a vinylogous amide and so condensation of the ammonia derivatives does not occur at this position.

The substitution pattern for methoxatin synthesis, however, requires oxygen at the indole 5-position and nitrogen at the 6-position. It is clear that treating a dopachrome solution with glutamic acid, or a synthetic equivalent, will not provide a compound which can be oxidised to methoxatin.

This problem may be overcome by incorporating the nitrogen atom on the phenylalanine at the desired position before the oxidation. The work which follows describes the reactions of aminohydroxyphenylalanine derivatives aimed
at mimicking the oxidative cyclisation of dopa 9.
RESULTS AND DISCUSSION

Preparation of Aminophenols

All aminophenols used were made from nitrophenol 15. A synthesis of nitrophenol 15 which allowed its preparation in quantities of at least up to 20g had been developed as part of an undergraduate project, figure 8.

\[
\begin{align*}
\text{CH}_3\text{OH} \quad \text{(i) } \text{Ac}_2\text{O} / \text{C}_{5}\text{H}_5\text{N} \quad \text{(ii) NBS} \\
\text{NO}_2
\end{align*}
\]

Aminophenol 16 was prepared by acidic formamide hydrolysis of nitrophenol 15, followed by hydrogenation of
the nitrophenol salt 17 and neutralisation of hydrochloride salt 18 in the absence of oxygen, figure 9. Aminophenol 16 could be crystallised under argon and obtained in 94% yield from nitrophenol 15. Since aminophenol 16 was oxygen-sensitive and had five protons exchangeable with water, determining its purity by n.m.r. spectroscopy was difficult. Instead, a sample was treated with acetic anhydride and pyridine and the solution evaporated under high vacuum, driving off the
excess acetic anhydride, the acetic acid formed and pyridine. The n.m.r. spectrum of this crude solid showed only the signals due to triacetyl derivative 19, and its melting point agreed with that of analytically pure product, showing that the aminophenol 16 could not have contained impurities such as formylated or unreduced materials.

This procedure of determining the purity of air-sensitive compounds by acetylation was used frequently, in each case the physical properties of the crude material being compared against those of an analytically pure sample.

Treating aminophenol 16 with one equivalent of oxoglutarate 20 in refluxing benzene gave benzoxazine 21 in 31-63% yield, figure 10. The infrared absorption at 1625 cm\(^{-1}\) was indicative of C=N stretch. Formation of the imine with the aromatic amino group of aminophenol 16 may be less favoured than the reaction with the aliphatic amine, but cyclisation giving the stable benzoxazine nucleus precludes imine dissociation in the case of the aromatic amine alone. Benzoxazine 21 was purified by chromatography, but was an unstable red oil which was taken on to the next stage before serious decomposition set in. Reduction of the imine bond of
benzoxazine 21 and lactone opening was performed with sodium cyanoborohydride in a methanol and acetic acid mixture. Destruction of excess reductant with acid, followed by neutralisation and extraction under argon gave alkylaminophenol 22 in excellent yield. Acetylation gave diacetyl derivative 23, which was still slightly air-sensitive, but could be chromatographed. Diacetyl derivative 23 was a mixture of diastereoisomers and careful inspection of the aromatic region of the 300 MHz proton n.m.r. spectrum showed some signals, which were well separated from the rest, coming from two compounds. This
The phenomenon was clearer in the chlorinated derivative discussed below.

Similarly, formylaminobenzoxazine $\text{24}^{30}$ could be reduced to aminophenol $\text{25}$ and acetylated, giving mixture of diastereomers $\text{26}$. Both derivatives $\text{23}$ and $\text{26}$ have a secondary aromatic amine which is too sterically crowded to allow its acetylation under the usual conditions employed. The alternative structures where the aromatic amine is acetylated
and the phenol is not could be ruled out by the chemical shift of the α-proton of the glutamic acid part of the molecules. In both derivatives 23 and 26, its chemical shift was between 4.02 and 4.27 δ, while had the aromatic amine been acetylated, the expected chemical shift would be 4.5 δ or even further downfield.

Another route to alkylaminophenol 22 tried was formamide hydrolysis of benzoxazine 24 followed by imine reduction. The benzoxazine nucleus was sensitive to aqueous acid, so the amide hydrolysis was carried out in anhydrous acidic ethanol, and acetylation of the product gave acetamidobenzoxazine 27. However, when the hydrolysis product was hydrogenated and then acetylated, only triacetyl derivative 19 was isolated, showing that imine hydrolysis had occurred. Attempts to isomerise the imine in benzoxazine 24 to an N-acetylenamine in 28 prior to amide hydrolysis, thus eliminating the functionality which is sensitive to aqueous acid, were unsuccessful. Only imide 29 could be isolated under a variety of conditions, which were sufficiently vigorous to cause substantial decomposition, demonstrating the stability of the benzoxazine nucleus.

Alkylaminophenol 22 contained the whole carbon and nitrogen skeleton of methoxatin, and its oxidation was the next stage in the synthesis.
Aminophenol Oxidations

Many reagents have been used to cyclise oxidatively aminoethylcatechols to the aminochrome, e.g. figure 7, and those which were successful with dopa were tried first.

Especially relevant was a report that the methyl ester of dopa was oxidatively cyclised to methyl dopachrome, which could be reduced and acetylated, giving triacetyl indoline. We prepared ethyl dopa hydrochloride salt by Fischer-Speier esterification of dopa and carried out the analogous oxidation with potassium ferricyanide. Reduction with sodium dithionite and acetylation gave triacetyl indoline, figure 11, which was already known.
but which had only been isolated in an impure state. In our hands, it was purified easily by chromatography and showed
geometric isomerism about the amide system. In deuterochloroform, the ratio of isomers, as determined by 300 MHz proton n.m.r. spectroscopy was 72:28, while in deuteracetone, it was 90:10.

Repeating the oxidation, reduction and acetylation on aminophenol hydrochloride salt 18 gave nothing of comparable polarity to that of indoline 32 which could be the desired product, despite analogous colour changes. The material must have polymerised under the reaction conditions, but carrying out the procedure at 30 times greater dilution, which was the practical limit, failed to give better results.

The potassium ferricyanide oxidation was performed in an aqueous buffer at pH 8, in which alkylaminophenol 22 could not be dissolved. When the oxidising agent was added to a mixture of alkylaminophenol 22 in buffer, no colour change was observed as had been evident with ethyl dopa 31 and aminophenol 18.

An oxidising system known to take dopa to dopachrome is sodium periodate in aqueous solution. When ethyl dopa 33, prepared by neutralising hydrochloride salt 31, was treated with two equivalents of sodium periodate in a u.v. cell, the characteristic absorption of dopachrome was observed, which could be quenched by sodium borohydride, giving rise to an absorption due to ethyl leucodopachrome 34, figure 12. The analogous treatment of aminophenol 16 gave similar colour changes, but the u.v.-visible spectra showed that the maxima were broad as well as of different intensity and wavelength when compared to those of the ethyl dopa 33 reactions.
Following the oxidations by u.v.-visible spectroscopy
offered three major advantages over performing them on a
preparative scale each time. The time employed was much less
than that required to carry out the oxidation, quench the
products and separate and characterise the derivatives. Often
a procedure for quenching the reaction was not established.
Secondly, the quantities used in experiments were approximately
two orders of magnitude less which was important when the
aminophenols were the products of moderately long, linear
syntheses. Finally, unstable intermediates could be detected,
especially using low-temperature techniques, giving additional
information about the course of the reaction.

Further attempts with sodium periodate led to new
conditions being found which took ethyl dopa 33 to ethyl dopa-
chrome 35, figure 12. Using methanol as the solvent produced
the same spectroscopic changes on an ethyl dopa 33 solution as
had been observed in water, and to determine that the products were the same, the reaction was performed preparatively. Quenching with sodium borohydride, followed by acid and acetylation gave four products, figure 13. Indoles 36 and 37 resulted from over-oxidation, but were only present in small amounts, and halogenated derivatives such as 36 and 38 are produced whenever a halogen-containing oxidant is used.  

![Figure 13](image-url)

Overall, the yield of oxidatively cyclised derivatives was an encouraging 58%.

Strikingly similar spectra were observed when aminophenol 16 was treated with sodium periodate in methanol. The absorption had the same shape and intensity as that from ethyl dopa 33
oxidation, but was shifted 35 nm to longer wavelength. On reduction with sodium borohyride, the change was the same as that with ethyl dopachrome 35. Repeating the reaction on a preparative scale, as had been successful with ethyl dopa 33, failed to give any analogous products with an indoline skeleton.

Sodium periodate in dimethylformamide and silver(I) oxide in methanol did not produce the characteristic absorption of ethyl dopachrome from ethyl dopa solutions, so were not tried on aminophenols 16 and 22.

The spectral changes observed upon oxidising aminophenol 16 in water and methanol demonstrated that no starting material remained. Since no products of the desired polarity were found, it can be assumed that the oxidations were followed by polymerisation. It is interesting to ask why the catechol derivative 33 oxidises and cyclises to products stable enough to be quenched, derivatised and isolated, while the aminophenol 16 polymerises.

Aminophenol 16 is in all likelihood first oxidised to α-quinoneimine 39. Simple hydrolysis of the imine, if it occurred to quinoneimine 39 would give rise to quinone 40, which is the likely intermediate in ethyl dopachrome 35 formation. Since no products from ethyl dopachrome are isolated after the work-up, one must assume either that imine hydrolysis is not an important reaction, or that quinone 40 is not an intermediate in the cyclisation. The second of these possibilities goes against several electrochemical investigations. 35
Once quinoneimine 39 is formed, two possibilities are open to it: cyclisation to indoline 41 and polymerisation by routes such as intermolecular condensations or Diels-Alder additions. The polymerisation has precedent, and it is reasonable to suggest that while quinone 40 has a sufficiently electrophilic ring to close the carbon-nitrogen bond, quinoneimine 39 has a less electrophilic ring which does not allow cyclisation. This difference in electrophilicities may be the reason why competing polymerisation predominates in the case of the aminophenol.

On the other hand, indoline 41 may be formed by cyclisation, in which case it will be oxidised to quinoneimine 42 because of the relative potentials of systems $16 \rightleftharpoons 39$ and $41 \rightleftharpoons 42$. It may then be quinoneimine 42 which undergoes polymerisation.
Oxidative conditions were discovered which converted aminophenol 16 to quinoneimine 39 without cyclisation.

Stirring a solution of aminophenol 16 in dichloromethane with lead dioxide and sodium sulphate at \(-78^\circ C\) in a u.v. cell, followed by centrifugation, gave an absorption with a maximum at 390 nm. This absorption is at a similar wavelength to that of quinoneimine 43, obtained by oxidising aminophenol 44, but substantially different to that of quinoneimines 45\textsubscript{a} and 45\textsubscript{b} obtained from diaminophenol 46. Therefore, the product from oxidising aminophenol 16 was assigned uncyclised quinoneimine structure 39.
Air-sensitive diaminophenol 46 was prepared from dinitrophenol 47 by catalytic hydrogenation, and its purity
confirmed by acetylation to derivative 48.

A solution of quinoneimine 39 in dichloromethane was stable at -80°C for two hours, but decomposed rapidly at room temperature, decomposition being monitored by its u.v. spectrum. This precluded the separation of the solution from the excess lead dioxide without the extensive loss involved in filtration through a filter aid at close to room temperature.

Similarly, alkylaminophenol 22 was oxidised to a solution absorbing with a maximum at 400 nm, which was assigned quinoneimine structure 49. The absorption decayed slowly at -80°C, and rapidly at room temperature. However, while quinoneimine 39 solution decomposed giving negligible absorption
at wavelengths longer than 270 nm, quinoneimine 49 gave a maximum at 295 nm as that at 400 nm disappeared. Comparison with the u.v. spectrum of an authentic sample suggested benzoxazine formation, figure 14, which probably arises by 1,5 hydrogen migration in quinoneimine 49, giving imine 50 which has regained aromaticity. Lactonisation then gives benzoxazine 21. The structure of benzoxazine was confirmed by repeating the oxidation on a preparative scale. Acetylation gave benzoxazine 27 in an overall yield of 23% based on aminophenol 22, which must be the minimum yield for oxidation to quinoneimine 49.

Equally, benzoxazine 21 was formed when the oxidation was followed at temperatures between -13 and 40°C. In these cases, the chromophore of intermediate quinoneimine 49 was not observed.

The oxidising systems lead tetraacetate in dichloromethane at room temperature and silver(I) oxide in refluxing dichloromethane also gave benzoxazine 21 with alkylaminophenol 22, but silver(II) oxide in dichloromethane at -10°C produced unknown, drastic changes in the u.v. spectrum. A benzoxazine was again produced when alkylaminophenol 25 was treated with lead dioxide in dichloromethane at -10°C.

t-Butyl hypochlorite39 on alkylaminophenol 22 gave no benzoxazines, but instead an aromatic chlorination product. This suggested either direct chlorination of the aromatic ring or that an initially formed $N$-chloramine 51 transferred chlorine to the aromatic ring more readily than it eliminated the elements of hydrogen chloride under these conditions, figure 15. The product was characterised as the diacetyl derivative 52, which showed a coupling constant of 2 Hz between the two
aromatic protons in the 300 MHz proton n.m.r. spectrum, implying a 1,2,3,5-tetrasubstituted ring.

Like its unchlorinated analogues 23 and 26, diacetyl derivative 52 has two chiral centres and was a diastereomeric mixture, which gave rise to two sets of signals in the n.m.r. spectrum. In this case, each aromatic proton gave two doublets.
When the t-butyl hypochlorite oxidation was followed by u.v. spectroscopy, the absorbance of alkylaminophenols 22 and 25 increased, the maximum not changing its wavelength. This is characteristic of nuclear halogenation of these species.

In the oxidations of alkylaminophenol 22, the production of benzoxazines points directly to the intermediacy of quinoneimine 49. This is the quinoneimine which we originally wanted to prepare, in order to cyclise it to an indoline derivative 53, figure 16. However, the conditions
tried led consistently to hydrogen migration which restored aromaticity to the quinone ring, figure 14, rather than amine attack on the quinone, which, after hydrogen transfer, would also restore aromaticity, figure 16.

It is possible that the charge separation in an intermediate such as \( 54 \) is a major factor which disfavours this route. This could be overcome by positioning a Lewis acid, \( A^+ \), at the nitrogen atom of the quinoneimine \( 49 \), figure 17. Copper(II) was chosen as the most hopeful Lewis acid,

![Chemical structure](image)

Since it is known to coordinate with both oxygen and nitrogen in 5-membered rings, and oxidise phenols and catechols in the presence of oxygen.\(^{40}\) The palmitate (hexadecanoate) salt\(^ {41}\) was used since it is soluble in organic solvents, contains no water of crystallisation, and the palmitate ion is not strongly
nucleophilic.

Adding copper(II) palmitate to an oxidised solution of alkylaminophenol 22 in tetrahydrofuran at -78°C followed by acetylation gave only benzoxazine 27, acetylated aminophenol 23 and polymeric material. Therefore, 1,5 hydrogen migration was still occurring in quinoneimine 49, and it is possible that the copper(II) was not effectively localised at the quinoneimine oxygen and nitrogen atoms, or that it was aiding the hydrogen shift.
Amidophenol Preparations and Oxidations

A certain way of decreasing the electron density at the aromatic nitrogen atom is to convert it from an amine to an amide nitrogen. Attaching the acyl group requires that the glutaric acid moiety no longer be included, in order to have a hydrogen atom on the nitrogen for ease of oxidation, figure 18. Quinoneimide 55 should undergo cyclisation more easily than imines 39 and 49 since the negative charge previously located on the aromatic nitrogen atom upon cyclisation is now spread on to the oxygen atom of an amide too: intermediate 56.

\[
\text{Et}_2\text{O}_2\text{C-} \begin{array}{c}
\text{H}_2\text{N} \\
\text{OH}
\end{array} \begin{array}{c}
\text{NH} \\
\text{O} \quad \text{R}
\end{array} \rightarrow \text{Et}_2\text{O}_2\text{C-} \begin{array}{c}
\text{H}_2\text{N} \\
\text{N} \quad \text{R}
\end{array} \begin{array}{c}
\text{O} \\
\text{R}
\end{array} - 2\text{H}
\]

55

\[
\text{Et}_2\text{O}_2\text{C-} \begin{array}{c}
\text{H}_2\text{N} \\
\text{O} \quad \text{R}
\end{array} \begin{array}{c}
\text{N} \\
\text{H} \quad \text{R}
\end{array} \rightarrow \text{Et}_2\text{O}_2\text{C-} \begin{array}{c}
\text{H}_2\text{N} \\
\text{OH}
\end{array} \begin{array}{c}
\text{NH} \\
\text{O} \quad \text{R}
\end{array}
\]

56

etc.

Figure 18
The acyl group chosen was benzoyl because in a study of the oxidations of amidophenols 57, it was shown that only imide 58b was sufficiently stable to isolate and crystallise, figure 19. It was hoped to prepare a sample of imide 58b,

\[
\text{CH}_3\text{OH} \quad \text{Pb(OAc)}_4 \rightarrow \quad \text{CH}_3\text{O} \\
\text{57} \quad \text{58} \\
\text{a} \ R = \text{COMe} ; \quad \text{b} \ R = \text{COPh} ; \quad \text{c} \ R = \text{SO}_2\text{Ph} .
\]

Figure 19

measure its absorption maximum and extinction coefficient, so estimates of the amount of quinoneimide in other solutions could be made, using the same extinction coefficient as an approximation.

Benzamidophenol 57b\(^{43}\) was prepared from aminophenol 59\(^{30}\) by monobenzoylation.\(^{44}\) It crystallised as both needles and plates, but on heating slowly, the plates were converted into needles just before the melting point. Spectroscopic data were the same for the two allotropes.

After several unsuccessful attempts at oxidising benzamidophenol 57b by the literature procedure,\(^{42}\) a low yield of crystalline quinoneimide 58b was obtained, which allowed
n.m.r., u.v.-visible and infrared spectra to be obtained. The u.v.-visible spectrum showed an absorption with a maximum at 390 nm and an extinction coefficient of 1250 in dichloromethane.

Knowing the absorption maximum of quinoneimide $58b$ allowed the efficiency of benzamidophenol $57b$ oxidation to be maximised. Lead dioxide in dichloromethane at $0^\circ\text{C}$ was found to be cleaner than lead tetraacetate under the same conditions, though the yield of quinoneimide $58b$ appeared to be 25% in both cases. At $-78^\circ\text{C}$, there was no oxidation.

Lead dioxide in acetonitrile also gave a maximum at 390 nm of the same intensity as in dichloromethane, but the yield could not be estimated since the extinction coefficient of quinoneimide $58b$ in this solvent was not known. Lead dioxide and sodium periodate in methanol gave no quinoneimide $58b$, though benzamidophenol $57b$ was slowly consumed.

Preparation of the benzamidophenol derivative of alanine $60$ required for cyclisation began with nitrophenol $15$, figure 20. Catalytic hydrogenation gave an air-sensitive aminophenol which was immediately dibenzoylated under argon, giving stable benzamidophenyl benzoate $61$. Acid hydrolysis of the formamide
of benzoate 61 gave hydrochloride salt 62 quantitatively as an amorphous solid, which was treated with dried potassium carbonate in anhydrous ethanol. The solution was acidified, the ethyl benzoate extracted, and after neutralisation of its ammonium salt, benzamidophenol 60 was isolated by extraction. Infrared spectroscopy showed both ester and amide carbonyl group stretching frequencies at 1730 and 1660 cm\(^{-1}\). The chemical shifts of the three aromatic protons from the phenylalanine part of the molecule showed that the aromatic amine was acylated and that the phenol was not. The chemical shift of the amino acid \(\alpha\)-proton of 3.76 \(\delta\) is strongly indicative of
an unacylated amino acid.

Oxidation of benzamidophenol 60 by lead dioxide in dichloromethane at 0°C gave u.v. absorption similar to that of quinoneimide 58b, suggesting the formation of uncyclised quinoneimide 63. However, the model for cyclised quinones, 64a and 64b gave quite unsatisfactory results, so the comparison of the chromophore of oxidised benzamidophenol 60 could only be made against the model for uncyclised quinoneimide. Since it was not known where quinones 64a and 64b might absorb, because no model was available, their presence could not be ruled out. In the investigations into other systems, vide supra, comparison of the chromophore could always be made against both models, thus eliminating one possibility with greater certainty than was possible in this case.

The model for cyclised quinones 64a and 64b was oxidised benzamidophenol 65, prepared from aminonitrophenol 66 by
monobenzoylation\textsuperscript{45} followed by catalytic hydrogenation of benzamidophenol 67. Benzamidophenol 65 was insoluble in dichloromethane and so the oxidation was performed in acetonitrile. However, oxidised solutions of both amidophenols 60 and 65 in acetonitrile showed no change in their u.v.-visible spectrum after 17 hours at 0°C. This apparent stability aroused suspicion that the solutions had polymerised before the first spectrum was recorded, since no other quinones or quinoneimines encountered survived for longer than 30 minutes at this temperature. Additionally, the solution of oxidised benzamidophenol 65 had its maximum at 357 nm, while oxidised benzamidophenol 60 absorbed strongly at all wavelengths shorter than 370 nm, masking the crucial region.

The problems faced in following the oxidation of benzamidophenol 60 by u.v.-visible spectroscopy forced these reactions to be run under preparative conditions. Fortunately, the quenching of $o$-quinonemobenzimides was already known to be possible. Passing hydrogen chloride through a solution of quinoneimide 58b in ether is reported to give a chlorinated derivative.\textsuperscript{42} The authors claim that the major product is
either 68 or 69, and evidence presented later will show that it is 68 and 70 which are formed, figure 21.

Chromatography on silica gel of benzamidophenols such as 57b and 60 was not possible, perhaps because reversible formation of orthoamide occurred on the silica, figure 22.
In order to stabilise the benzamidophenols to silica gel, they were acylated. It is known that treatment of an \( o \)-acylaminophenol with an acylating agent supplying a different acyl group to that already present causes an equilibrium mixture to be formed, figure 23.\(^4^4\) This suggested benzoylation of the material to be chromatographed, in order that mixtures such as in figure 23 be avoided. However, benzoylation of benzamidophenol 57b introduced a second phenyl group with a complex pattern in the proton n.m.r. spectrum, and would introduce a third phenyl group too, in the case of benzamidophenol 60. Since the aromatic region of the proton n.m.r. spectrum was crucial in deciding whether cyclisation had occurred by analysing the splitting pattern of the signals, complicating this area of the spectrum by benzoylation was out of the question.

\[
\begin{align*}
\text{OH} & \quad \xrightarrow{\text{(PhCO)}_2\text{O}/\text{C}_6\text{H}_5\text{N}} \\
\text{NHCOMe} & \\
\end{align*}
\]

Figure 23
Instead, benzamidophenols were acetylated, giving rise to a mixture which will be represented as 71.

\[
\text{CH}_3\text{NCHOPh} \overset{\text{Ac}_2\text{O}/\text{C}_5\text{H}_5\text{N}}{\longrightarrow} \text{CH}_3\text{NCO}_2\text{Ph}
\]

Mixtures such as 71 were not separable by chromatography, and the 300 MHz proton n.m.r. spectra gave no signs of their being mixtures. Thus, 71 only gave two singlets in the methyl region. However, the infrared spectrum showed a double ester C=O stretch band at 1750 and 1775 cm\(^{-1}\), and reduction with lithium aluminium hydride in tetrahydrofuran followed by \(p\)-nitrobenzoylation gave derivatives 72 and 73, figure 24, showing that 71 was indeed a mixture.

Oxidation of benzamidophenol 60 by lead dioxide in dichloromethane at 0°C followed by quenching with hydrogen chloride and acetylation of the product gave chlorinated mixtures 74 and 75 in very low yields and a great deal of polymer. Mixture 75 was readily identified as the 1,2,3,4-tetrasubstituted aromatic by the coupling constant of 8 Hz between the two protons on that ring, while mixture 74 was identified as the 1,2,4,5-tetrasubstituted aromatic by comparison with products from the oxidation and hydrogen chloride quench of benzamidophenol 57b.
CH$_3$OCOMe + CH$_3$OCOPh

71

\[ \text{LiAlH}_4 \]

CH$_3$OH + CH$_3$OH

\[ \text{p-NO}_2\text{NC}_6\text{H}_4\text{COCl} / \text{C}_5\text{H}_5\text{N} \]

CH$_3$OCOC$_6$H$_4$NO$_2$ + CH$_3$OCOC$_6$H$_4$NO$_2$

72

73

Figure 24
When 57b was subjected to these conditions and acetylated, two mixtures 76 and 77 were isolated. Mixture 77 showed the 8 Hz coupling seen in mixture 75, but mixture 76 showed two singlets in the aromatic region of the n.m.r. spectrum. In order to eliminate the possibility of structures 78, which might also show two singlets in the aromatic region, the methyl protons' frequency was irradiated. Only the upfield aromatic singlet was affected by this, its line width collapsing to that of the reference chloroform signal, showing that the two aromatic protons appearing as singlets were not equally coupled to the benzylic methyl group. These observations are
only consistent with structure 76.

Diluting the dichloromethane solution of oxidised benzamidophenol 60 with methanol, which might have the necessary polarity to help a cyclisation as in figure 18 (R=Ph), gave no improvement in yields on quenching the quinones and acetyllating. The only products isolated were uncyclised mixture 74 and polymeric materials. Acetic acid, magnesium methoxide and trimethyl borate were added to the solutions, hoping to catalyse the ring closure by increasing the positive charge at the quinoneimide nitrogen and oxygen atoms, but were uniformly unsuccessful. Raising the temperature of the methanol to reflux only succeeded in transesterifying the alanine ester, giving mixture 79 after quenching along with polymer.

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{AcNH} \\
\text{Cl} & \quad \text{Me} \\
\text{H} & \quad \text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{AcNH} \\
\text{Cl} & \quad \text{Me} \\
\text{H} & \quad \text{Ph}
\end{align*}
\]

As with alkylaminophenol 22, treatment of benzamidophenol 60 with t-butyl hypochlorite gave products chlorinated on the aromatic ring as well as unreacted material, which were isolated as their acetyl derivatives, 74, 75 and 80. The intermediacy of a quinoneimide such as 63 was ruled out since the solution did not attain the orange-red colour associated with them. Chlorination was therefore directed by the
electron-releasing hydroxyl group of benzamidophenol 60, since the aromatic nitrogen atom, being acylated, did not facilitate aromatic electrophilic substitution as it had done in alkylaminophenol 22, where it was not acylated, *vide supra*.

**Conclusion**

Despite the varied oxidative conditions tried on unsubstituted aminophenol 16, alkylaminophenol 22 and benzamidophenol 60, no product was isolated with the desired indoline ring system. At best, low yields were obtained of compounds which can be rationalised as being formed from uncyclised quinones: benzoxazines from quinoneimine 49 and chlorinated benzamidophenols from quinoneimide 63. This contrasts sharply with the relative ease with which ethyl
dopa 33 could be oxidatively cyclised, giving indolines 32 and 38 in good yields after reductive work-up and acetylation.

This difference in products cannot be ascribed to the quinone rings of imines 39 and 49 and imide 63 not being sufficiently electrophilic to attack the aliphatic amine. In the case of p-quinonemonoimides at least, it has been shown that sulphur\(^{46}\) and chlorine\(^{47}\) nucleophiles prefer to add 1,4 to the unsaturated imide system rather than 1,4 to the unsaturated ketone system in intermolecular reactions,
e.g. figure 25. Also, it has been shown here that chloride prefers to add 1,4 or 1,6 to the unsaturated imide system of an o-quinonemonoimide than to the unsaturated ketone, vide supra.

\[
\begin{align*}
\text{R} & = \text{CH}_2\text{CHNHCOCH}_2\text{CH}(\text{NH}_2)\text{CO}_2\text{H} \\
& \quad \text{CONHCH}_2\text{CO}_2\text{H} \\
& \quad \text{and} \\
\text{CH}_2\text{CH}(\text{CO}_2\text{H})\text{NHCOCH}_3
\end{align*}
\]

Figure 25

If this preference translates to nitrogen nucleophiles, ring closure to an indoline should be more favoured for quinoneimide 63 than for quinone 40.

Should ring closure have taken place in the case of quinoneimide 63, producing indoline 81, then this would have been further oxidised to quinones 64a and 64b, either by lead dioxide, if the cyclisation had occurred in dichloromethane, or by uncyclised quinoneimide 63, if it occurred only upon dilution with methanol. The lack of any materials derived from quinones 64a and 64b in the products isolated implies that if any such quinones were formed, they reacted further
before they could be quenched, or that the quenching techniques were not suitable.
EXPERIMENTAL

General Procedures

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected.

Infrared spectra were measured on either a Perkin-Elmer 297 or a Perkin-Elmer 681 infrared spectrophotometer. The following abbreviation is used: br - broad.

Ultra-violet and visible spectra were recorded on a Unicam SP. 800A or a Perkin-Elmer 555 spectrophotometer. Extinction coefficients are given in units of dm$^3$mol$^{-1}$cm$^{-1}$.

Proton nuclear magnetic resonance spectra were obtained on Perkin-Elmer R24 (60 MHz), Perkin-Elmer R32 (90 MHz) or Bruker WH 300 (300 MHz) spectrometers. Chemical shifts are reported in parts per million downfield from tetramethylsilane, $\delta$.

Tetramethylsilane or protonated solvent was used as internal standard. The following abbreviations are used: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet, br - broad.

Mass spectra were obtained on a VG Micromass 16F spectrometer under electron impact (E.I.) or chemical ionisation (C.I.) conditions, or on a VG Micromass ZAB-1F spectrometer under in beam electron impact (I.B.E.I.) or desorption chemical ionisation (D.C.I.) conditions. The chemical ionisation techniques used ammonia as the reagent gas.

Microanalysis was carried out under the supervision of Dr. Strauss of the Dyson Perrins Laboratory.

Qualitative thin layer chromatography was carried out on commercially prepared plates coated with Merck silica gel 60 F$_{254}$. Preparative layer chromatography was carried out on plates coated with Merck silica gel PF$_{254+366}$.200x200x2 mm.
Column chromatography refers to the use of Hopkin and Williams silica gel M.F.C. without binder for thin layer chromatography, or Merck thin layer chromatography silica H type 60 unless neutral aluminium oxide is specified for which Fluka type 507C, 100-125 mesh alumina was used.

Flash chromatography was performed with Merck silica gel 60 for column chromatography 230-400 mesh.

Solvents were distilled prior to use. Where stated, solvents and reagents were dried by the following procedures:

- Acetic acid: distilled from phosphorus pentoxide and stored over molecular sieves.
- Acetic anhydride: distilled from phosphorus pentoxide and stored over molecular sieves.
- Acetone: distilled from anhydrous potassium carbonate and stored over molecular sieves.
- Acetonitrile: distilled from calcium hydride.
- Benzene: distilled from sodium wire.
- Dichloromethane: distilled from calcium hydride.
- Diethyl ether: distilled from sodium wire.
- Dimethylformamide: distilled from calcium hydride under reduced pressure and stored over molecular sieves.
- Dimethylsulphoxide: distilled from calcium hydride under reduced pressure.
- Ethanol: distilled from magnesium ethoxide and stored over molecular sieves.
- Methanol: distilled from magnesium methoxide.
- Pyridine: distilled from calcium hydride and stored over molecular sieves.
- Tetrahydrofuran: distilled from sodium wire and benzophenone.
- Toluene: distilled from sodium wire.
Abbreviations:  
DMF - dimethylformamide  
DMSO - dimethylsulphoxide  
LDA - lithium diisopropylamide  
THF - tetrahydrofuran  
\( \text{M} \) - molar = mol dm\(^{-3}\)  
\( \text{mM} \) - 10\(^{-3}\) molar = mol m\(^{-3}\)

Petroleum ether refers to the fraction b.p. 40–60°C, and ether refers to diethyl ether.
Preparation of Ethyl (2RS)-3-(4-Amino-3-hydroxyphenyl)alanine

16. - Ethyl (2RS)-N-formyl-3-(3-hydroxy-4-nitrophenyl)alanine 15 (1.00 g; 3.55 mmol) in dry ethanol (20 ml) was stirred with 1.1 M hydrogen chloride in dry ethanol (20 ml; 22 mmol HCl) at 20°C for 21 h and evaporated to give a yellow solid. The solid and 10% palladium on charcoal (40 mg) in methanol (20 ml) were deoxygenated and shaken under hydrogen at 18°C for 1 h, filtered through Celite under argon and evaporated, giving an off-white foam. The foam was dissolved in deoxygenated water (10 ml), deoxygenated saturated sodium hydrogen carbonate solution (5 ml) added, and the solution extracted into deoxygenated ethyl acetate (5 x 20 ml). The combined extracts were dried (Na₂SO₄) under argon, filtered and evaporated, giving a pink foam and colourless oil. Recrystallisation from deoxygenated ethyl acetate gave ethyl (2RS)-3-(4-amino-3-hydroxyphenyl)alanine 16 (747 mg; 94%) as a white solid, which was used without further purification.

Acetylation of Ethyl (2RS)-3-(4-Amino-3-hydroxyphenyl)alanine

16. - A sample of ethyl (2RS)-3-(4-amino-3-hydroxyphenyl)alanine 16 was stirred in acetic anhydride (0.5 ml) and pyridine (1.0 ml) at room temperature for 30 min. Evaporation in vacuo and recrystallisation from ethanol gave ethyl (2RS)-3-(4-acetamido-3-acetoxyphenyl)-N-acetylalanine 19 as white needles, m.p. 183-187°C (decomp.), (Found: C, 58.50; H, 6.43; N, 7.98. C₁₇H₂₂N₂O₆ requires C, 58.28; H, 6.33; N, 8.00%), ν max (Nujol) 3 330, 1 735, 1 720, 1 690, 1 680, 1 640, 1 520 and 1 220 cm⁻¹, δ(CD₃SOCD₃; 300 MHz) 1.13 (3H, t, J 7 Hz, CH₃CH₂), 1.81, 2.06 and 2.30 (3 x 3H, 3 x s, 3 x CH₃CO), 2.81-2.99 (2H, m, ArCH₂), 4.04 (2H, q, J 7 Hz, CH₃CH₂O), 4.40 (1H, m, O₂CCHN), 6.98 (1H, d, J 2 Hz, C-2 ArH), 7.06 (1H, dd, J 8, 2 Hz, C-6 ArH), 7.77
(1H, d, J 8 Hz, C-5 ArH), 8.33 (1H, d, J 7 Hz, CONHCH) and 9.39 (1H, s, CONHAr), and m/e (E.I.) 350 (1, M⁺), 308 (6), 291 (20), 249 (57), 231 (40), 207 (100), 193 (23), 164 (54) and 123 (49).

Preparation of 7-[(2RS)-2-Amino-2-ethoxycarbonylethyl]-3-(2-ethoxycarbonylethyl)-2H-1,4-benzoxazin-2-one 21.- Ethyl (2RS)-3-(4-amino-3-hydroxyphenyl)alanine 16 (96 mg; 0.429 mmol) and diethyl 2-oxoglutarate 20 (86 mg; 0.426 mmol) in dry, deoxygenated benzene (20 ml) were refluxed under dry nitrogen with a Dean-Stark trap for 5 h. The solution was cooled and evaporated, and the yellow oil separated by column chromatography (95% CH₂Cl₂, 5% CH₃OH) giving 7-[(2RS)-2-amino-2-ethoxycarbonyl-ethyl]-3-(2-ethoxycarbonylethyl)-2H-1,4-benzoxazin-2-one 21 (98 mg; 63%) as a red-brown oil, ν_max (CHCl₃) 1 735 and 1 625 cm⁻¹, which was used without further purification.

Preparation of Ethyl (2RS)-3-{4-[(1RS)-3-Ethoxycarbonyl-1-methoxycarbonylpropylamino]-3-hydroxyphenyl}alanine 22.- 7-[(2RS)-2-Amino-2-ethoxycarbonylethyl]-3-(2-ethoxycarbonylethyl)-2H-1,4-benzoxazin-2-one 21 (95 mg; 0.262 mmol) in dry methanol (1 ml) was added to 90-95% sodium cyanoborohydride (26 mg; 0.37-0.39 mmol) in dry methanol (3 ml) with molecular sieves 3 Å under dry nitrogen. Dry acetic acid (0.5 ml) was added and the mixture stirred at room temperature under dry nitrogen for 1 h. Deoxygenated concentrated hydrochloric acid was added, lowering the pH to 1, and the solution stirred under argon at room temperature for 15 min. The solution was evaporated and the solid residue dissolved in deoxygenated saturated sodium hydrogen carbonate solution (3 ml) and extracted into deoxygenated ethyl acetate (3 x 10 ml). The combined extracts were washed with deoxygenated saturated sodium hydrogen carbonate solution
(4 x 5 ml), deoxygenated water (4 x 5 ml) and deoxygenated saturated brine (5 ml). Drying (Na₂SO₄) under argon and evaporation of the solution gave ethyl (2RS)-3-{4-[(1RS)-3-ethoxycarbonyl-1-methoxycarbonylpropylamino]-3-hydroxyphenyl}alanine 22 (86 mg; 83%) as a pale pink oil which was used without further purification.

**Acetylation of Ethyl (2RS)-3-{4-[(1RS)-3-Ethoxycarbonyl-1-methoxycarbonylpropylamino]-3-hydroxyphenyl}alanine 22.** - A sample of the product from the above reaction (10 mg) was stirred with acetic anhydride (0.5 ml) and pyridine (1 ml) at room temperature for 30 min and evaporated in vacuo. Column chromatography (95% CH₂Cl₂, 5% CH₃OH) gave ethyl (2RS)-3-{3-acetoxy-4-[(1RS)-3-ethoxycarbonyl-1-methoxycarbonylpropylamino]phenyl}-N-acetylanaline 23 as a very pale orange oil, (M⁺ 480.2106. C₂₃H₃₂N₂O₉ requires 480.2108), ν_max (CHCl₃) 3 420 br, 1 730 br, 1 675, 1 520 br, 1 375 and 1 190 cm⁻¹, δ(CDCl₃; 300 MHz) 1.22-1.29 (6H, m, 2 x CH₃CH₂), 2.00 (3H, s, CH₃CONH), 2.10-2.23 (2H, m, CH₂CH₂CO₂Et), 2.37-2.56 (5H, m, CH₃CO₂ + CH₂CH₂CO₂Et), 3.02 (2H, m, ArCH₂), 3.73 (3H, s, CO₂CH₃), 4.03-4.27 (6H, m, 2 x CH₃CH₂O + O₂CCNHR), 4.53 (1H, m, ArNH), 4.80 (1H, m, O₂CCNHO), 5.98 (1H, br d, J 8 Hz, CONH), 6.56 (1H, 2 x d, J 8 Hz, C-5 ArH) and 6.77-6.82 (2H, m, C-2 and C-6 ArH), and m/e (E.I.) 480 (13, M⁺), 422 (19), 379 (18), 347 (21), 337 (28), 336 (100), 294 (81), 263 (30), 260 (53), 216 (25) and 43 (29).

**Preparation of Ethyl (2RS)-3-{4-[(1RS)-3-Ethoxycarbonyl-1-methoxycarbonylpropylamino]-3-hydroxyphenyl}-N-formylalanine 25.** - 3-(2-Ethoxycarbonylethyl)-7-[(2RS)-2-ethoxycarbonyl-2-formamidoethyl]-2H-1,4-benzoxazin-2-one 24 (99 mg; 0.25 mmol) was reduced and the product extracted as above, giving ethyl
(2RS)-3-{4-[(1RS)-3-ethoxycarbonyl-1-methoxycarbonylpropylamino]-3-hydroxyphenyl}-N-formylalanine 25 (85 mg; 80%) as a pale pink oil, which was used without further purification.

Acetylation of Ethyl (2RS)-3-{4-[(1RS)-3-ethoxycarbonyl-1-methoxycarbonylpropylamino]-3-hydroxyphenyl}-N-formylalanine 25.- A sample of the product from the above reaction was acetylated as before. Column chromatography (95% CH₂Cl₂, 5% CH₃OH) gave ethyl (2RS)-3-{3-acetoxy-4-[(1RS)-3-ethoxycarbonyl-1-methoxycarbonylpropylamino]phenyl}-N-formylalanine 26 as a colourless oil, (M⁺ 466.1951. C₂₂N₃0N₂ requires 466.1951), νmax (CHCl₃) 3 420 br, 1 735 br, 1 690 and 1 190 cm⁻¹, δ (CDCl₃; 300 MHz) 1.22-1.29 (6H, m, 2 x CH₃CH₂), 2.08-2.20 (2H, m, CH₂CH₂CO₂Et), 2.36 (3H, s, CH₃CO₂), 2.40-2.53 (2H, m, CH₂CH₂CO₂Et), 3.04 (2H, m, ArCH₂), 3.71 (3H, s, CO₂CH₃), 4.02-4.22 (5H, m, 2 x CH₃CH₂O + O₂CCNHar), 4.52 (1H, d, J 8 Hz, ArNH), 4.86 (1H, m, O₂CCNHCOCO), 6.21 (1H, br d, J 5 Hz, CONH), 6.54 (1H, m, ArH), 6.78-6.84 (2H, m, 2 x ArH) and 8.15 (1H, s, HCO), and m/e(E.I.) 466 (10, M⁺), 391 (25), 346 (35), 336 (61), 294 (79), 262 (100), 216 (40) and 43 (43).

Hydrolysis of Benzoxazin-2-one 24.- 0.92 M Hydrogen chloride in dry ethanol (1.3 ml; 1.2 mmol HCl) was added to 3-(2-ethoxycarbonylethyl)-7-[(2RS)-2-ethoxycarbonyl-2-formamidomethyl]-2H-1,4-benzoxazin-2-one 24 (100 mg; 0.26 mmol) in dry ethanol (3 ml), and the solution stirred at room temperature for 11.5 h. Evaporation gave a white solid which was dissolved in dry pyridine (2 ml) and acetic anhydride (2 ml), stirred at room temperature for 1.2 h and evaporated in vacuo giving a pasty residue. Recrystallisation from ethanol-ether gave
7-[(2RS)-2-acetamido-2-ethoxycarbonylethyl]-3-(2-ethoxycarbonyl-ethyl)-2H-1,4-benzoxazin-2-one **27** (23 mg; 22%) as white crystals, m.p. 147-148°C, (Found: C, 60.03; H, 6.20; N, 6.78. C\(_{20}\)H\(_{24}\)N\(_2\)O\(_7\) requires C, 59.40; H, 5.98; N, 6.93%), \(\nu\)\(_{\text{max}}\) (CHCl\(_3\)) 3 430, 1 740, 1 680, 1 625, 1 500 and 1 380 cm\(^{-1}\), \(\delta\) (CDCl\(_3\); 300 MHz) 1.27 and 1.29 (6H, 2 x t, J 7, 7 Hz, 2 x CH\(_3\)CH\(_2\)), 2.02 (3H, s, CH\(_3\)CO), 2.85 (2H, t, J 7 Hz, CH\(_2\)CH\(_2\)CO\(_2\)Et), 3.14-3.32 (4H, m, CH\(_2\)CH\(_2\)CO\(_2\)Et + ArCH\(_2\)), 4.13-4.25 (4H, m, 2 x CH\(_3\)CH\(_2\)O), 4.90 (1H, m, O\(_2\)CCHNH), 6.01 (1H, br d, J 7 Hz, CONH), 7.03 (1H, d, J 1.7 Hz, C-8 Ar\(\text{H}\)), 7.11 (1H, dd, J 8, 1.7 Hz, C-6 Ar\(\text{H}\)) and 7.61 (1H, d, J 8 Hz, C-5 Ar\(\text{H}\)), and \(m/e\) (E.I.) 404 (8, \(M^+\)), 359 (25), 345 (100), 299 (30), 244 (38), 215 (42), 158 (37), 102 (60) and 43 (85).

**Hydrolysis and Hydrogenation of Benzoxazin-2-one** **24.**

1.3 M Hydrogen chloride in dry ethanol (3 ml; 3.9 mmol HCl) was added to 3-(2-ethoxycarbonylethyl)-7-[(2RS)-2-ethoxycarbonyl-2-formamidoethyl]-2H-1,4-benzoxazin-2-one **24** (200 mg; 0.51 mmol) in dry ethanol (6 ml), and the solution stirred at room temperature for 42 h. Evaporation gave a foam which was dissolved in dry ethanol (6 ml) and added to the solid remaining from hydrogenating platinum oxide (210 mg) and evaporating to dryness. Dry triethylamine (5 drops) was added, the mixture deoxygenated and stirred under hydrogen at room temperature for 23 h. The solution was filtered through Celite under argon and evaporated, giving a white foam which was dissolved in deoxygenated pyridine (2 ml), deoxygenated acetic anhydride (0.5 ml) added, and the solution stirred at room temperature under argon for 2.5 h. Evaporation *in vacuo* gave a white-green oil which was separated by column chromatography (neutral aluminium oxide; 95% CHCl\(_3\), 5% CH\(_3\)OH).
giving ethyl (2RS)-3-(4-acetamido-3-acetoxyphenyl)-N-acetylaniline 19 (40 mg; 22%) as white needles.

Acetylation of 3-(2-Ethoxycarbonylthethyl)-7-[(2RS)-2-ethoxycarbonyl-2-formamidoethyl]-2H-1,4-benzoazin-2-one 24.

a. Dimethylaminopyridine and acetic anhydride. 3-(2-Ethoxycarbonylthethyl)-7-[(2RS)-2-ethoxycarbonyl-2-formamidoethyl]-2H-1,4-benzoazin-2-one 24 (100 mg; 0.26 mmol) in pyridine (2 ml) was stirred with acetic anhydride (1 ml) and 4-dimethylaminopyridine (10 mg; 0.08 mmol) at room temperature for 26 h. Evaporation in vacuo and preparative layer chromatography (EtOAc) gave 7-[(2RS')-2-(N-acetyl-N-formylamino)-2-ethoxycarbonylthethyl]-3-(2-ethoxycarbonylthethyl)-2H-1,4-benzoazin-2-one 29 (43 mg; 38%) as a pale yellow oil, \( \text{M}^+ 432.1533 \). \( \text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_8 \) requires 432.15327, \( \nu_{\max} (\text{CHCl}_3) 1735, 1685, 1625 \text{ and } 1370 \text{ cm}^{-1}, \delta(\text{CDCl}_3; 300 \text{ MHz}) 1.24 \text{ and } 1.25 \text{ (6H, } 2 \text{ x } t, \ J 7.2, 7.2 \text{ Hz, } 2 \text{ x CH}_3\text{CH}_2), 2.32 \text{ (3H, s, CH}_3\text{CO), 2.82 (2H, t, } \ J 7 \text{ Hz, } \text{CH}_2\text{CH}_2\text{CO}_2\text{Et}), 3.19 (2H, t, } \ J 7 \text{ Hz, CH}_2\text{CH}_2\text{CO}_2\text{Et}), 3.27-3.35 (1H, dd, } \ J 14.3, 10.2 \text{ Hz, one of ArCH}_2), 3.55-3.61 (1H, dd, } \ J 14.3, 5.7 \text{ Hz, one of ArCH}_2), 4.11-4.24 (4H, m, 2 x CH}_3\text{CH}_2\text{O), 5.42 (1H, dd, } \ J 10.1, 5.7 \text{ Hz, O}_2\text{CCHN), 7.04 (1H, d, } \ J 1.7 \text{ Hz, C-8 ArH), 7.12 (1H, dd, } \ J 8.1, 1.8 \text{ Hz, C-6 ArH), 7.57 (1H, d, } \ J 8.1 \text{ Hz, C-5 ArH) and 8.95 (1H, s, CHO), and } m/e(\text{EI}) 432 (4, M^+), 387 (10), 345 (45), 299 (13), 271 (11), 244 (22), 158 (13), 141 (31), 127 (22), 84 (23) \text{ and } 43 (100).

b. Sodium acetate and acetic anhydride. 3-(2-Ethoxycarbonylthethyl)-7-[(2RS)-2-ethoxycarbonyl-2-formamidoethyl]-2H-1,4-benzoazin-2-one 24 (100 mg; 0.26 mmol) and sodium acetate (20 mg; 0.24 mmol) were refluxed in acetic anhydride for 2.5 h and cooled. The solution was filtered and evaporated in vacuo giving
a brown oil purified by preparative layer chromatography (EtOAc) giving 7-[(2RS)-2-(N-acetyl-N-formylamino)-2-ethoxycarbonyylethyl]-3-(2-ethoxycarbonyylethyl)-2H-1,4-benzoxazin-2-one \(29\) (45 mg; 38%).

c. Lithium diisopropylamide and acetic anhydride. 0.25 M Lithium diisopropylamide solution (4:1 THF:hexane) (2.5 ml; 0.68 mmol LDA) was added to 3-(2-ethoxycarbonyylethyl)-7-[(2RS)-2-ethoxycarbonyl-2-formamidoethyl]-2H-1,4-benzoxazin-2-one \(2n\) (109 mg; 0.28 mmol) in dry THF (2 ml) at room temperature, giving a black suspension not dissolved by adding further dry THF (3 ml). After 20 min, acetic anhydride (0.12 ml) was added, clearing the suspension, and the solution evaporated. The solid residue was triturated with chloroform (5 ml), the solution filtered and evaporated and the new residue separated by preparative layer chromatography (90% CHC\(_3\), 10% CH\(_3\)OH) giving 7-[(2RS)-2-(N-acetyl-N-formylamino)-2-ethoxycarbonyylethyl]-3-(2-ethoxycarbonyylethyl)-2H-1,4-benzoxazin-2-one \(29\) (28 mg; 23%).

Preparation of Ethyl 3-(3,4-Dihydroxyphenyl)alanine Hydrochloride Salt 31. 3-(3,4-Dihydroxyphenyl)alanine \(9\) (999 mg; 5.07 mmol) was suspended in dry ethanol (8 ml) and hydrogen chloride passed through for 1.5 h without cooling. Hydrogen chloride flow was stopped and the solution refluxed for 1 h. Evaporation gave ethyl 3-(3,4-dihydroxyphenyl)alanine hydrochloride salt \(31\) (1.24 g; 93%) as a white foam which was used without further purification.

Potassium Ferricyanide Oxidation of Ethyl 3-(3,4-Dihydroxyphenyl)alanine Hydrochloride Salt 31.- Ethyl 3-(3,4-dihydroxyphenyl)alanine hydrochloride salt \(31\) (256 mg; 0.98 mmol) in buffer (75 ml; buffer made from 22.6 g \(\text{Na}_2\text{HPO}_4.12\text{H}_2\text{O}\) + 0.5 g \(\text{KH}_2\text{PO}_4\) in 1000 ml water; pH 8.1) was
stirred vigorously and potassium ferricyanide (2.037 g; 6.19 mmol) in buffer (50 ml) added. The solution turned red and after 6 sec, freshly dissolved sodium dithionite (1.369 g; 7.87 mmol) in buffer (25 ml) was added. The solution decolourised, and after 1 sec, concentrated hydrochloric acid (2.5 ml) was added. The solution was evaporated to dryness and the residue stirred with pyridine (25 ml) and acetic anhydride (25 ml) at room temperature for 19 h. Filtration through Celite, washing the solid with dichloromethane, and evaporation gave a residue which was dissolved in 2 M hydrochloric acid (25 ml) and extracted into dichloromethane (3 x 25 ml). The combined extracts were diluted with dichloromethane (60 ml), washed with saturated sodium hydrogen carbonate solution (2 x 25 ml) and water (4 x 50 ml), dried (Na₂SO₄) and evaporated, giving a pale yellow foam. Flash chromatography (95% CH₂Cl₂, 5% CH₃OH) gave ethyl N-acetyl-5,6-diactoxy-2,3-dihydroindo-2-carboxylate (210 mg; 61%) as white needles (EtOAc - petroleum ether), m.p. 84.5-88.5°C, (Found: C, 58.54; H, 5.36; N, 4.22). C₁₇H₁₉NO₇ requires C, 58.45; H, 5.48; N, 4.01%). ν_max(CHCl₃) 1 765br, 1 670, 1 490, 1 400, 1 370 and 1 200 cm⁻¹, δ(CDCl₃; 300 MHz) 1.30 (3H, br t, J 7.1 Hz, CH₃CH₂), 2.01 (0.9H, s, CH₃CON), 2.17 (2.1H, s, CH₃CON), 2.27 and 2.29 (6H, 2 x s, 2 x CH₃CO₂), 3.10 (0.3H, m, part of ArCH₂), 3.25-3.31 (0.7H, dd, J 16.8, 2.2 Hz, part of ArCH₂), 3.48 (0.3H, dd, J 15, 12 Hz, part of ArCH₂), 3.62 (0.7H, dd, J 16.8, 11.1 Hz, part of ArCH₂), 4.18-4.37 (2H, m, CH₃CH₂O), 4.93 (0.7H, dd, J 10.8, 2.9 Hz, part of O₂CCHN), 5.18 (0.3H, m, part of O₂CCHN), 7.00-7.07 (1.3H, m, C-4 ArH + part of C-7 ArH) and 8.08 (0.7H, s, part of C-7 ArH), and m/e(E.I.) 349 (21, M⁺), 307 (37), 265 (100), 223 (92), 150 (83) and 43 (82).
Preparation of Ethyl 3-(3,4-Dihydroxyphenyl)alanine 33.-
Ethyl 3-(3,4-dihydroxyphenyl)alanine hydrochloride salt 31 (564 mg; 2.16 mmol) in water (15 ml) was deoxygenated and deoxygenated
0.5 M potassium carbonate solution (4.4 ml; 2.2 mmol K₂CO₃) added. The solution was extracted into deoxygenated ethyl acetate (6 x 20 ml) and the combined extracts dried (Na₂SO₄) under argon and evaporated, giving ethyl 3-(3,4-dihydroxyphenyl)alanine 33 (460 mg; 94%) as a white foam, which was used without further purification.

Acetylation of Ethyl 3-(3,4-Dihydroxyphenyl)alanine 33.-
A sample of ethyl 3-(3,4-dihydroxyphenyl)alanine 33 was stirred in deoxygenated pyridine (2 ml) and deoxygenated acetic anhydride (1 ml) at room temperature under argon for 45 min and evaporated, giving ethyl N-acetyl-3-(3,4-diacetoxyphenyl)alanine, νmax (CHCl₃) 3 430, 1 770, 1 735, 1 675, 1 500, 1 370, 1 260, 1 180, 1 110, 1 010 and 910 cm⁻¹, δ(CDCl₃; 90 MHz) 1.21 (3H, t, J 7 Hz, CH₃CH₂O), 1.98 (3H, s, CH₃CON), 2.25 (6H, s, 2 x CH₃CO₂), 3.09 (2H, m, ArCH₀), 4.15 (2H, q, J 7 Hz, CH₃CH₂O), 4.83 (1H, m, O₂CCHN), 6.19 (1H, br d, J 7 Hz, CONH) and 6.93-7.16 (3H, m, 3 x ArH).

Oxidation of Ethyl 3-(3,4-Dihydroxyphenyl)alanine 33 in Water.- 2.0 mM Ethyl 3-(3,4-dihydroxyphenyl)alanine 33 in water (0.5 ml; 0.0010 mmol) was added to water (2.0 ml) in a 10mm u.v. cuvette at room temperature. To this, 4.0 mM sodium periodate in water (0.5 ml; 0.0020 mmol) was added. The solution immediately turned red, and after 1 min, the u.v.-visible spectrum showed λmax 470 nm (Abs 0.96) which had decayed after 30 min at 18°C.
Oxidation and Reduction of Ethyl 3-(3,4-Dihydroxyphenyl)-alanine 33 in Water.- 2.0 mM Ethyl 3-(3,4-dihydroxyphenyl)alanine 33 in water (0.5 ml; 0.0010 mmol) was added to water (1.5 ml) in a 10mm u.v. cuvette at 14°C. To this was added 40 mM sodium periodate in water (0.5 ml; 0.0020 mmol) turning the solution red, and after 15 sec stirring, 8.0 mM sodium borohydride in water (0.5 ml; 0.0040 mmol), turning the solution orange-yellow. After 1 min, the solution was colourless and the u.v.-visible spectrum showed $\lambda_{\text{max}}$ 310 nm (Abs 1.68).

Oxidation and Reduction of Ethyl 3-(3,4-Dihydroxyphenyl)-alanine 33 in Methanol.- Ethyl 3-(3,4-dihydroxyphenyl)alanine 33 (50 mg; 0.22 mmol) in dry methanol (10 ml) was added to sodium periodate (97 mg; 0.46 mmol) in dry methanol (40 ml) at 0°C, turning the solution red. Stirring at 0°C for 2 min and adding freshly prepared sodium borohydride (85 mg; 2.2 mmol) in dry methanol (10 ml) gave a pale orange solution. After a further 3 min, 2.0 M hydrochloric acid (11 ml; 22 mmol HCl) was added and the solution evaporated to dryness. The resulting yellow solid was stirred with pyridine (10 ml) and acetic anhydride (10 ml) at 9°C for 1 h and evaporated, giving another yellow solid, which was triturated with dichloromethane (2 ml) and the solution filtered and evaporated. Column chromatography (90% CH$_2$Cl$_2$, 10% CH$_3$CN) gave ethyl 5,6-diacetoxy-7-iodoindole-2-carboxylate 36 (2 mg; 2%) as a colourless oil which solidified to a white solid, m.p. 180-184°C, ($M^+$ 430.9870. C$_{15}$H$_{14}$INO$_6$ requires 430.9868), $\nu_{\text{max}}$(CHCl$_3$) 3 440, 1 780, 1 710, 1 530, 1 425, 1 370, 1 270, 1 200 and 1 015 cm$^{-1}$, $\lambda_{\text{max}}$(EtOH) 206 (23 800), 237 (23 600) and 293 (19 200), $\delta$(CDCl$_3$; 300 MHz) 1.45 (3H, t, $J$ 7 Hz, CH$_3$CH$_2$), 2.33 (3H, s, CH$_3$CO), 2.42 (3H, s, CH$_3$CO), 4.44 (2H,
q, \( J = 7 \) Hz, \( CH_3CH_2O \), 7.35 (1H, d, \( J = 2 \) Hz, ArH), 7.48 (1H, s, ArH) and 8.88 (1H, br s, NH), and \( m/e \) (E.I.) 431 (10, \( M^+ \)), 389 (28), 347 (100), 301 (43) and 43 (38), ethyl 5,6-diacetoxy-2,3-dihydro-7-iodoindole-2-carboxylate 38 (14 mg; 14%) as a colourless oil, \( (M^+ 433.0019. C_{15}H_{16}INO_6 \) requires 433.0024), \( \nu_{\text{max}}(CHCl_3) 3380 \) br, 1770, 1735, 1460, 1370 and 1200 cm\(^{-1}\), \( \lambda_{\text{max}}(EtOH) 216 \) (25 900) and 307 (4 100), \( \delta(CDC_3; 300 \text{ MHz}) 1.33 (3H, t, \( J = 7 \) Hz, \( CH_3CH_2 \)), 2.26 (3H, s, \( CH_3CO \)), 2.38 (3H, s, \( CH_3CO \)), 3.53 (2H, m, ArCH2), 4.25 (2H, m, \( CH_3CH_2O \)), 4.48 (1H, m, O2CCHN), 4.58 (1H, br s, NH) and 6.88 (1H, s, ArH), and \( m/e \) (E.I.) 433 (20, \( M^+ \)), 391 (35), 349 (100), 276 (83), 149 (42) and 43 (38), ethyl 5,6-diacetoxyindole-2-carboxylate 37 (2 mg; 3%) as a colourless oil which solidified to a white solid, m.p. 127-132°C, \( (M^+ 305.0899. C_7H_5NO_6 \) requires 305.0899), \( \nu_{\text{max}}(CHCl_3) 3460, \) 1770, 1705, 1370, 1200 and 905 cm\(^{-1}\), \( \lambda_{\text{max}}(EtOH) 202 (14 200), \) 220 (17 200) and 296 (13 600), \( \delta(CDC_3; 300 \text{ MHz}) 1.42 (3H, t, \( J = 7 \) Hz, \( CH_3CH_2 \)), 2.33 (6H, 2 x s, 2 x \( CH_3CO \)), 4.41 (2H, q, \( J = 7.1 \) Hz, \( CH_3CH_2O \)), 7.19 (1H, m, ArH), 7.26 (ArH under \( CHCl_3 \), 7.47 (1H, s, ArH) and 8.96 (1H, br s, NH), \( \delta(CH_3COCD_3; 300 \text{ MHz}) 1.37 (3H, t, \( J = 7 \) Hz, \( CH_3CH_2 \)), 2.29 (6H, 2 x s, 2 x \( CH_3CO \)), 4.38 (2H, q, \( J = 7 \) Hz, \( CH_3CH_2O \)), 7.21 (1H, s, ArH), 7.39 (1H, s, ArH) and 7.53 (1H, s, ArH), and \( m/e \) (E.I.) 305 (11, \( M^+ \)), 263 (21), 221 (100), 175 (57) and 43 (57), and ethyl \( N \)-acetyl-5,6-diacetoxy-2,3-dihydroindole-2-carboxylate 32 (30 mg; 39%) as a colourless oil.

**Oxidation of Ethyl (2RS)-3-(4-Amino-3-hydroxyphenyl)-alanine 16 in Methanol.** - \( 2.0 \text{ mM} \) Ethyl (2RS)-3-(4-amino-3-hydroxyphenyl)alanine 16 in methanol (0.5 ml; 0.0010 mmol) was added to 0.8 \text{ mM} \) sodium periodate in dry methanol (2.5 ml;
0.0020 mmol) in a 10mm u.v. cuvette at 0°C. The solution turned violet and after 1 min, the u.v.-visible spectrum showed $\lambda_{\text{max}}$ 500 nm (Abs 0.82) which decayed after 10 min at room temperature.

**Oxidation and Reduction of Ethyl (2RS)-3-(4-Amino-3-hydroxyphenyl)alanine 16 in Methanol.**- 2.0 mM Ethyl (2RS)-3-(4-amino-3-hydroxyphenyl)alanine 16 in methanol (0.5 ml; 0.0010 mmol) was added to 1.0 mM sodium periodate in dry methanol (2.0 ml; 0.0020 mmol) in a 10mm u.v. cuvette at 0°C. The solution turned violet and after 1 min stirring, 8.0 mM sodium borohydride in methanol (0.5 ml; 0.0040 mmol) was added. After 5 min, the u.v.-visible spectrum showed $\lambda_{\text{max}}$ 296 nm (Abs 1.6).

**Oxidation of Ethyl (2RS)-3-(4-Amino-3-hydroxyphenyl)alanine 16 in Dichloromethane.**- Lead dioxide (23 mg) and freshly baked sodium sulphate (12 mg) in a dry 10mm u.v. cuvette sealed with a sceptum cap were purged with dry nitrogen and deoxygenated dry dichloromethane (1 ml) added. The mixture was cooled to -78°C and 0.72 mM ethyl (2RS)-3-(4-amino-3-hydroxyphenyl)alanine 16 in deoxygenated dry dichloromethane (0.5 ml; 0.00036 mmol) was added over 1 min, while stirring. The mixture was stirred for a further 4 min at -78°C, centrifuged at -78°C and the u.v.-visible spectrum at -80°C showed $\lambda_{\text{max}}$ 390 nm.

**Oxidation of o-Aminophenol 44 in Dichloromethane.**- o-Aminophenol 44 (2.0 mg; 0.018 mmol) in dry dichloromethane (25 ml) was stirred with lead dioxide (350 mg) and freshly baked sodium sulphate (100 mg) at between -14 and -10°C for 5 min, filtered, and the u.v.-visible spectrum at -14°C showed $\lambda_{\text{max}}$ 374 nm.
Preparation of 2,4-Diaminophenol 46.- 80% 2,4-Dinitrophenol 47 (1.00 g; 4.3 mmol) and 10% palladium on charcoal (50 mg) in methanol (30 ml) were shaken under hydrogen at room temperature for 1.75 h, the solution filtered through Celite under nitrogen and its volume reduced (to 10 ml). Deoxygenated ether was added and the solution cooled to -15°C separating a cream solid. Recrystallisation from methanol-ether under argon gave 2,4-diaminophenol 46 (290 mg; 53%) as off-white plates.

Acetylation of 2,4-Diaminophenol 46.- 2,4-Diaminophenol 46 (10 mg) was dissolved in deoxygenated pyridine (1 ml) and deoxygenated acetic anhydride (0.5 ml) and the solution stirred at room temperature under argon for 4 h. Evaporation in vacuo gave 2,4-diacetamidophenyl acetate 48, δ(CD$_3$SOCD$_3$; 90 MHz) 1.97 and 2.00 (6H, 2 x s, 2 x CH$_3$CO), 2.20 (3H, s, CH$_3$CO), 6.94 (1H, d, $J$ 9 Hz, C-6 ArH), 7.40 (1H, dd, $J$ 9, 2.7 Hz, C-5 ArH), 7.98 (1H, d, $J$ 2.7 Hz, C-3 ArH), 9.23 (1H, br s, NH) and 9.87 (1H, br s, NH).

Oxidation of 2,4-Diaminophenol 46 in Acetonitrile.- Lead dioxide (23 mg) and freshly baked sodium sulphate (19 mg) in a dry 10mm u.v. cuvette sealed with a sceptum cap were purged with dry nitrogen and deoxygenated, dry acetonitrile (1 ml) added. The mixture was cooled to -15°C and 0.72 mM 2,4-diaminophenol 46 in deoxygenated, dry acetonitrile (0.5 ml; 0.00036 mmol) was added over 0.5 min while stirring. The mixture was stirred for 5 min at -10°C, centrifuged at -5°C and the u.v.-visible spectrum at -40°C showed $\lambda_{max}$ 272 nm (Abs 2.9) and 426 nm (Abs 0.67).
Oxidation of Ethyl (2RS)-3-{4-[(1RS)-3-Ethoxycarbonyl-1-methoxycarbonylpropylamino]-3-hydroxyphenyl}alanine 22 in Dichloromethane.— Lead dioxide (24 mg) and freshly baked sodium sulphate (20 mg) in a dry 10mm u.v. cuvette sealed with a sceptum cap were purged with dry nitrogen and deoxygenated, dry dichloromethane (1 ml) added. The mixture was cooled to -78°C and 0.72 mM ethyl (2RS)-3-{4-[(1RS)-3-ethoxycarbonyl-1-methoxycarbonylpropylamino]-3-hydroxyphenyl}alanine 22 in deoxygenated, dry dichloromethane (0.5 ml; 0.00036 mmol) was added over 1.5 min while stirring. The mixture was stirred for a further 4 min at -78°C, centrifuged at -78°C, and the u.v.-visible spectrum at -80°C showed $\lambda_{\text{max}}$ 400 nm. The maximum decayed a little after 3 h at -80°C. The solution was then warmed to 19°C, stirred for 5 min and centrifuged. The u.v.-visible spectrum at 19°C showed $\lambda_{\text{max}}$ 295 nm and no maximum at 400 nm.

Oxidation and Acetylation of Ethyl (2RS)-3-{4-[(1RS)-3-Ethoxycarbonyl-1-methoxycarbonylpropylamino]-3-hydroxyphenyl}alanine 22.— Ethyl (2RS)-3-{4-[(1RS)-3-ethoxycarbonyl-1-methoxycarbonylpropylamino]-3-hydroxyphenyl}alanine 22 (50 mg; 0.13 mmol) in dry dichloromethane (100 ml) was stirred with lead dioxide (2.5 g) and freshly baked sodium sulphate (700 mg) under dry nitrogen at 14°C for 10 min, and the solution filtered through tightly-packed Celite and evaporated, giving a viscous brown oil. Pyridine (7 ml) and acetic anhydride (3 ml) were added and the mixture stirred at room temperature for 2 h and evaporated in vacuo. The residue was separated by preparative layer chromatography (95% CH$_2$Cl$_2$, 5% CH$_3$OH), giving 7-[(2RS)-2-acetamido-2-ethoxycarbonylethyl]-3-(2-ethoxycarbonylethyl)-2H-1,4-benzoxazin-2-one 27 (12 mg; 23%) as an oil, and two unidenti-
fied materials (6 mg and 3 mg) which showed the two triplets in the 300 MHz n.m.r. spectrum characteristic of 3-(CH₂CH₂CO₂)-benzoxazin-2-one and the benzoxazin-2-one u.v. spectrum \( \lambda_{\text{max}} \) 295 nm.

**Chlorination of Ethyl (2RS)-3-{4-{[(1RS)-3-Ethoxycarbonyl-1-methoxycarbonylpropylamino]-3-hydroxyphenyl}alanine 22.**

Ethyl (2RS)-3-{4-[(1RS)-3-ethoxycarbonyl-1-methoxycarbonylpropylamino]-3-hydroxyphenyl}alanine 22 (45 mg; 0.11 mmol) in deoxygenated dichloromethane (20 ml) at -74°C was stirred under argon and 98.6% t-butyl hypochlorite (16 \( \mu l \); 0.14 mmol) added. After stirring 15 min, the solution was warmed to room temperature and evaporated. The red-brown residue was dissolved in deoxygenated pyridine (3 ml) and deoxygenated acetic anhydride (2 ml), and the solution stirred at room temperature under argon for 1 h. Evaporation in vacuo gave a red-brown oil which was separated by preparative layer chromatography (94% CH₂Cl₂, 6% CH₃OH), giving ethyl (2RS)-3-{3-acetoxy-5-chloro-4-[(1RS)-3-ethoxycarbonyl-1-methoxycarbonylpropylamino]phenyl}-N-acetyl-alanine 52 (22 mg; 39%) as a colourless oil, (M⁺ 514.1718). C₂₃H₃₁ClN₂O₉ requires 514.1718), \( \nu_{\text{max}}(\text{CHCl}_3) \) 3 420 br, 1 740 br, 1 675, 1 500, 1 375 and 1 190 cm⁻¹, \( \delta(\text{CDCl}_3; 300 \text{ MHz}) \) 1.23-1.28 (6H, m, 2 x CH₃CH₂), 2.00-2.25 (5H, m, CH₃CON + CH₂CH₂CO₂Et), 2.35 (3H, 2 x s, CH₃CO₂), 2.44-2.53 (2H, m, CH₂CH₂CO₂Et), 2.99-3.05 (2H, m, ArCH₂), 3.68 (3H, s, CO₂CH₃), 4.09-4.23 (5H, m, 2 x CH₃CH₂O + O₂CCHNHR), 4.33 (1H, m, ArNH), 4.78 (1H, m, O₂CCHNHCO), 6.05 (1H, d, \( j \) 7.5 Hz, CONH), 6.68 (1H, 2 x d, \( j \) 1.7, 1.7 Hz, ArH) and 6.93 (1H, 2 x d, \( j \) 1.7, 1.7 Hz, ArH), and \( m/e(\text{E.I.}) \) 514 (4, M⁺), 413 (13), 370 (18), 328 (25) and 43 (100).
Oxidation of Ethyl (2RS)-3-{4-[(1RS)-3-ethoxycarbonyl-1-methoxycarbonylpropylamino]-3-hydroxyphenyl}alanine 22 in the Presence of Copper(II) Palmitate. Ethyl (2RS)-3-{4-[(1RS)-3-ethoxycarbonyl-1-methoxycarbonylpropylamino]-3-hydroxyphenyl}alanine 22 (50 mg; 0.13 mmol) in dry THF (5 ml) was added to lead dioxide (2.5 g) and freshly baked sodium sulphate (700 mg) in dry THF (95 ml) at -78°C under dry nitrogen over 1 min while stirring. The stirring was continued at -78°C for 5 min and then copper(II) palmitate (84 mg; 0.16 mmol) in dry THF (20 ml) was added over 2.5 min. Stirring continued at -78°C for 10 min, then while warming the solution to room temperature over 20 min, and at room temperature 10 min. The solution was filtered through Celite and evaporated. The green solid residue was dissolved in pyridine (6 ml) and acetic anhydride (3 ml) and the solution stirred at room temperature for 2 h. Evaporation in vacuo gave a green solid which was passed down a short column of silica (95% CH₂Cl₂, 5% CH₃OH) and then purified by preparative layer chromatography (95% CH₂Cl₂, 5% CH₃OH), giving 7-[(2RS)-2-acetamido-2-ethoxycarboxylethyl]-3-(2-ethoxycarboxylethyl)-2H-1,4-benzoxazin-2-one 27 (15 mg; 29%) and ethyl (2RS)-3-{3-acetoxy-4-[(1RS)-3-ethoxycarbonyl-1-methoxycarbonylpropylamino]phenyl}-N-acetylalanine 23 (6 mg; 10%).

Preparation of 2-Benzamido-5-methylphenol 57b. - 2-Amino-5-methylphenol 59 (2.25 g; 18.3 mmol) and benzoic anhydride (4.55 g; 20.1 mmol) in pyridine (30 ml) were heated at 97-98°C for 30 min, cooled and poured into ice-water (150 ml). The solid formed was filtered, washed with water and dried. Recrystallisation from hot benzene in portions gave 2-benzamido-5-methylphenol 57b (2.95 g; 71%) as needles and plates, m.p. 166-173°C, (lit. 43 169°C).
Preparation of 4-Methyl-\(\text{o-benzoquinone-1-benzimide 58b.}-\)

2-Benzamido-5-methylphenol \(57b\) (192 mg; 0.85 mmol) in dry dichloromethane (15 ml) was cooled to 0\(^\circ\)C under dry nitrogen, precipitating some solid. Lead tetraacetate (376 mg; 0.85 mmol) was added over 5 min while stirring rapidly, and stirring continued for a further 5 min. The solution was filtered under suction and evaporated rapidly on an oil pump until barely mobile. Ether (1-2 ml) was added to the residue and the solution discarded. More ether (1 ml) was added, and this solution filtered and cooled to -78\(^\circ\)C, giving 4-methyl-\(\text{o-benzoquinone-1-benzimide 58b (4 mg; 2\%) as orange crystals, m.p. 60-62\(^\circ\)C (decomp.) (lit.}\)\(^{38}\) 65.6-66\(^\circ\)C), \(\nu_{\text{max}}\) (KBr) 1675, 1610, 1235, 1050, 1020, 790 and 700 cm\(^{-1}\), \(\lambda_{\text{max}}\) (CH\(_2\)Cl\(_2\)) 234 (20000) and 390 (1250), and \(\delta\) (CDCl\(_3\); 300 MHz) 2.17 (3H, d, \(\text{J} 1.5\) Hz, CH\(_3\)Ar), 6.16 (1H, d, \(\text{J} 2\) Hz, C-5 =CH), 6.73 (1H, dd, \(\text{J} 9.7, 2.05\) Hz, C-3 =CH), 6.79 (1H, d, \(\text{J} 9.7\) Hz, C-2 =CH), 7.41-7.46 (2H, m, \(\text{m benzoyl ArH}\)), 7.53-7.57 (1H, m, \(\text{p benzoyl ArH}\)) and 7.81-7.84 (2H, m, \(\text{o benzoyl ArH}\)).

Lead Tetraacetate Oxidation of 2-Benzamido-5-methylphenol 57b.- 2-Benzamido-5-methylphenol 57b (38 mg; 0.17 mmol) in dry dichloromethane (3 ml) was cooled to 0\(^\circ\)C under dry nitrogen, precipitating some solid. Lead tetraacetate (37 mg; 0.084 mmol) was added in one portion and the mixture stirred rapidly at 0\(^\circ\)C. After 5 min, a portion of solution (0.03 ml) was withdrawn, diluted (to 3 ml) and the u.v.-visible spectrum taken.
Lead Dioxide Oxidation of 2-Benzamido-5-methylphenol 57b.

2-Benzamido-5-methylphenol 57b (0.6 mg; 0.003 mmol) in dry dichloromethane (1 ml) was added to lead dioxide (28 mg) in dry dichloromethane (2 ml) in a u.v. cuvette at 0°C. The mixture was stirred rapidly at 0°C for 5 min, centrifuged and the u.v.-visible spectrum showed $\lambda_{\text{max}}$ 392 nm (Abs 0.38).

Preparation of Ethyl (2RS)-3-(4-Benzamido-3-benzyloxyphenyl)-N-formylalanine 61.

Ethyl (2RS)-N-formyl-3-(3-hydroxy-4-nitrophenyl)alanine 15 (933 mg; 3.31 mmol) and 10% palladium on charcoal (25 mg) in methanol (40 ml) were deoxygenated and shaken under hydrogen without cooling. After 30 min, the solution was filtered through Celite under argon and evaporated, giving a grey foam with colourless oil. This was dissolved in deoxygenated pyridine (5 ml) and benzoyl chloride (0.90 ml; 7.8 mmol) added over 2 min, while swirling the solution. Heat was evolved and a solid precipitated out. The mixture was swirled at 15°C for 30 min and evaporated in vacuo, giving a yellow-orange solid and oil. The mixture was dissolved in ethyl acetate (100 ml) and water (10 ml) and the organic phase separated and washed with water (10 ml) and saturated brine (10 ml). Drying (Na$_2$SO$_4$) and evaporation gave a pink foam which was purified by column chromatography (75% CH$_2$Cl$_2$, 25% CH$_3$CN), giving ethyl (2RS)-3-(4-benzamido-3-benzyloxyphenyl)-N-formylalanine 61 (1.10 g; 72%) as a pale orange foam, (Found: C, 67.72; H, 5.38; N, 6.12. C$_{26}$H$_{24}$N$_2$O$_6$ requires C, 67.82; H, 5.25; N, 6.08%), $\nu_{\text{max}}$(CHCl$_3$) 3 420 br, 3 020, 1 740, 1 685, 1 520, 1 240, 1 125, 1 095, 1 055, 1 025, 910 and 705 cm$^{-1}$, $\delta$(CDCl$_3$; 300 MHz) 1.29 (3H, t, $J$ 7.2 Hz, CH$_3$CH$_2$), 3.21 (2H, m, ArCH$_2$), 4.24 (2H, q, $J$ 7.2 Hz, CH$_3$CH$_2$O), 4.97 (1H, m, O$_2$CCHNH), 6.28
(1H, br d, J 7.7 Hz, CONH\textsubscript{CH}), 7.09-7.11 (2H, m, C-2 and C-6 Ar\textsubscript{H}), 7.38-7.43 (2H, m, m benzoyl Ar\textsubscript{H}), 7.48-7.58 (3H, m, p + m benzoyl Ar\textsubscript{H}), 7.68-7.77 (3H, m, p + o benzoyl Ar\textsubscript{H}), 8.08 (1H, br s, CONH\textsubscript{Ar}) and 8.21-8.29 (4H, m, HCO + C-5 Ar\textsubscript{H} + o benzoyl Ar\textsubscript{H}), and m/e(C.I.) 461 (3, M+1\textsuperscript{+}), 339 (15), 293 (23), 208 (22), 122 (93) and 105 (100).

Preparation of Ethyl (2RS)-3-(4-Benzamido-3-hydroxyphenyl)-alanine 60.- Ethyl (2RS)-3-(4-benzamido-3-benzoyloxoyphenyl)-\textit{N}-formylalanine 61 (1.08 g; 2.35 mmol) in ethanol (20 ml) was stirred with 1.1 M hydrogen chloride in ethanol (10 ml; 11 mmol HCl) at 11-18°C for 21 h. The mixture was then evaporated, giving hydrochloride salt 62 (1.10 g) as a white solid. Freshly baked potassium carbonate (0.75 g; 5.4 mmol) and dry ethanol (80 ml) were added and the mixture stirred at 17-24°C for 24 h. The green-yellow solution was neutralised with saturated aqueous ammonium chloride solution, filtered and evaporated. The residue was dissolved in ethyl acetate (200 ml) and water (200 ml), the aqueous phase separated, taken to pH 7.7 with saturated sodium hydrogen carbonate solution (32 ml) and extracted into ethyl acetate (3 x 600 ml). Drying (\textsubscript{Na\textsubscript{2}}SO\textsubscript{4}) and evaporation gave ethyl (2RS)-3-(4-benzamido-3-hydroxyphenyl)alanine 60 (503 mg; 65%) as pale brown plates, m.p. 131.5-135°C, \(\nu_{\text{max}}(\text{CHCl}_3)\) 3 420, 3 360, 3 300, 3 020, 1 730, 1 660 br, 1 605, 1 525, 1 425, 1 215, 1 205, 1 030, 780 br, 730 br and 665 cm\textsuperscript{-1}, \(\delta(\text{CDCl}_3; 300 \text{ MHz})\) 1.30 (3H, t, J 7.1 Hz, CH\textsubscript{3}CH\textsubscript{2}), 2.81-2.88 (1H, dd, J 13.7, 8.0 Hz, one of ArCH\textsubscript{2}), 3.05-3.11 (1H, dd, J 13.7, 4.9 Hz, one of ArCH\textsubscript{2}), 3.76 (1H, dd, J 8.0, 5.3 Hz, O\textsubscript{2}CCHN), 4.22 (2H, q, J 7.1 Hz, CH\textsubscript{3}CH\textsubscript{2}O), 6.73 (1H, dd, J 8.2, 2.0 Hz, C-6 Ar\textsubscript{H}), 6.82 (1H, d, J 1.8 Hz, C-2 Ar\textsubscript{H}), 7.49-7.63 (4H, m, C-5 Ar\textsubscript{H} + m + p benzoyl Ar\textsubscript{H}), 7.92 (2H, m, o benzoyl Ar\textsubscript{H}) and 8.34 (1H, br s,
CONH\_), and m/e(E.I.) 328 (3, \(M^+\)), 255 (10), 227 (44), 122 (20), 105 (100) and 77 (42).

Preparation of 2-Benzamido-4-nitrophenol 67.- 96% 2-Amino-4-nitrophenol 66 (3.0 g; 18.7 mmol) and benzoyl chloride (2.2 ml; 19.0 mmol) were mixed well at 20°C. After an induction period of 2 min, a rapid, exothermic reaction took place, turning the powder pink. The solid was heated at 100°C for 1 h and recrystallised from boiling aniline, washing the crystals with a little ethanol, to give 2-benzamido-4-nitrophenol 67 (3.05 g; 63%) as pale yellow pins, (decomp. >200°C), \(\delta\)(CD\(_3\)SOCD\(_3\); 90 MHz) 6.99 (1H, d, \(J\) 9 Hz, C-6 ArH\_), 7.37-7.42 (3H, m, \(m + p\) benzoyl ArH\_), 7.78-7.94 (3H, m, C-5 ArH\_ + o benzoyl ArH\_), 8.66 (1H, d, \(J\) 2.7 Hz, C-3 ArH\_) and 9.46 (1H, br s, CONH\_).

Preparation of 4-Amino-2-benzamidophenol 65.- 2-Benzamido-4-nitrophenol 67 (300 mg; 1.16 mmol) and 10% palladium on charcoal (50 mg) in THF (30 ml) was deoxygenated and shaken under hydrogen at room temperature for 3 h. The solution was filtered through Celite under argon and the volume reduced (to 2 ml) by evaporation. Deoxygenated ether was added and the solution cooled, giving 4-amino-2-benzamidophenol 65 (185 mg; 72%) as golden plates, (decomp. >165°C), (M\(^+\) 228.0897. C\(_{13}\)H\(_{12}\)N\(_2\)O\(_2\) requires 228.0899), \(\nu\)\(_{\text{max}}\) (Nujol) 3 450, 3 390, 3 360, 3 140 br, 1 640, 1 600, 1 545, 1 270, 1 200, 855, 800 and 700 cm\(^{-1}\), \(\delta\)(CD\(_3\)SOCD\(_3\); 300 MHz) 4.60 (2H, br s, NH\(_2\)), 6.31 (1H, dd, \(J\) 8.5, 2.6 Hz, C-5 ArH\_), 6.64 (1H, d, \(J\) 8.5 Hz, C-6 ArH\_), 7.05 (1H, d, \(J\) 2.2 Hz, C-3 ArH\_), 7.50-7.62 (3H, m, \(m + p\) benzoyl ArH\_), 7.95 (2H, d, \(J\) 7.0 Hz, o benzoyl ArH\_), 8.64 (1H, br s, OH or CONH\_) and 9.45 (1H, br s, OH or CONH\_), and m/e(E.I.) 228 (36, \(M^+\)), 210 (27), 123 (100), 105 (94) and 77 (69).
Oxidation of 4-Amino-2-benzamidophenol 65 in Acetonitrile.- 1.4 mM 4-Amino-2-benzamidophenol 65 in dry acetonitrile (1 ml; 0.0014 mmol) was added to lead dioxide (31 mg) and freshly baked sodium sulphate (23 mg) in dry acetonitrile (2 ml) in a 10 mm u.v. cuvette at 0°C. The mixture was stirred at 0°C for 3 min, centrifuged and the u.v.-visible spectrum at room temperature showed \( \lambda_{\text{max}} \) 357 nm (Abs 1.44), which remained unchanged after standing the solution at 0°C for 21 h.

Oxidation of Ethyl (2RS)-3-(4-Benzamido-3-hydroxyphenyl)-alanine 60 in Acetonitrile.- 1.45 mM Ethyl (2RS)-3-(4-benzamido-3-hydroxyphenyl)alanine 60 in dry acetonitrile (1 ml; 0.00145 mmol) was treated as above and the u.v.-visible spectrum at room temperature showed \( \lambda_{\text{max}} \) 471 nm (Abs 0.55), which decayed to \( \lambda_{\text{max}} \) 471 nm (Abs 0.45) after 17 h at 0°C.

Benzoylation of 2-Benzamido-5-methylphenol 57b.- 2-Benzamido-5-methylphenol 57b (1.00 g; 4.41 mmol) and benzoyl chloride (0.56 ml; 4.83 mmol) in pyridine (10 ml) were swirled at room temperature for 5 min, and then heated at 75-80°C for 30 min. Cooling and pouring into ice-water (100 ml) gave a solid which was filtered off and recrystallised from hot ethanol, giving 2-benzamido-5-methylphenyl benzoate (944 mg; 65%) as white rods, m.p. 142-147°C (lit.50 162-163°C), \( \nu_{\text{max}} \) (CHCl₃) 3 450, 1 740 br, 1 680, 1 520, 1 240 and 710 cm⁻¹, \( \delta \) (CDCl₃; 300 MHz) 2.40 (3H, s, CH₃Ar), 7.13-7.18 (2H, m, C-4 + C-6 ArH), 7.37-7.43 (2H, m, \( m \) benzoyl ArH), 7.46-7.57 (3H, m, \( p + m \) benzoyl ArH), 7.65-7.78 (3H, m, \( p + o \) benzoyl ArH), 7.97 (1H, br s, CONH), 8.17 (1H, d, J 8 Hz, C-3 ArH) and 8.22-8.26 (2H, m, o benzoyl ArH).
Acetylation of 2-Benzamido-5-methylphenol 57b. - 2-Benzamido-5-methylphenol 57b (22 mg; 0.097 mmol) was stirred in pyridine (0.5 ml) and acetic anhydride (0.5 ml) at 17°C for 1.5 h. The solution was evaporated in vacuo, giving mixture 71 as a white solid, $\nu_{\text{max}}$(CHC1$_3$) 3 440 br, 1 775, 1 750, 1 680, 1 520 and 1 195 cm$^{-1}$, $\delta$(CDCl$_3$; 300 MHz) 2.37 (6H, 2 x s, 2 x CH$_3$), 7.02 (1H, br s, C-6 ArH), 7.12 (1H, br d, $J$ 8 Hz, C-4 ArH), 7.48-7.61 (3H, m, m + p benzoyl ArH), 7.83-7.87 (3H, m, CONH + o benzoyl ArH) and 8.08 (1H, d, $J$ 8 Hz, C-3 ArH), and $m/e$(E.I.) 269 (2, $M^+$), 227 (8), 209 (11), 147 (10), 105 (100), 77 (39) and 43 (11).

Reduction of Mixture 71. - Mixture 71 (50 mg; 0.186 mmol) in dry THF (5 ml) was added to 90-95% lithium aluminium hydride (49 mg; 1.2 mmol) in deoxygenated, dry THF (5 ml) at 19°C under dry nitrogen over 2 min, and the mixture then stirred at 19°C for 10 min and refluxed for 2 h. The mixture was cooled, water (0.05 ml) added, then 2.0 M sodium hydroxide solution (0.10 ml) and more water (0.15 ml). The solution was filtered through a glass sinter under argon and evaporated, giving a yellow oil, to which was added 97% p-nitrobenzoyl chloride (159 mg; 0.83 mmol) in deoxygenated dichloromethane (5 ml) and pyridine (3 ml). The solution was stirred at 19-22°C under argon for 15 h and evaporated, giving a yellow solid. Trituration with dichloromethane (2 ml) and separation of the solution by column chromatography (CH$_2$Cl$_2$) gave 2-[N-benzyl-N-(4-nitrobenzoyl)amino]-5-methylphenyl 4-nitrobenzoate 72 (39 mg; 41%) as a white foam, $R_f$ 0.23, (Found: C, 65.91; H, 3.89; N, 7.90. C$_{28}$H$_{21}$N$_3$O$_7$ requires C, 65.75; H, 4.14; N, 8.22%), $\nu_{\text{max}}$(CHC1$_3$) 1 750, 1 650, 1 605, 1 530, 1 510, 1 350, 1 260, 1 130, 1 070,
1 015, 910, 860 and 715 cm$^{-1}$, $\delta$(CDCl$_3$; 300 MHz) 2.35 (3H, s, ArCH$_3$), 5.02 (2H, ABq, $J$ 14.2 Hz, NCH$_2$Ph), 6.98-7.03 (3H, m, C-3 + C-4 + C-6 ArH), 7.23-7.32 (5H, m, NCH$_2$C$_6$H$_5$), 7.44-7.48 (2H, m, p-nitrobenzoyl ArH), 8.00-8.04 (4H, m, p-nitrobenzoyl ArH) and 8.33-8.37 (2H, m, p-nitrobenzoyl ArH), and m/e(I.B.E.I.) 511 (3, $M^+$), 361 (18), 345 (33), 150 (40), 104 (23) and 91 (100), and 2-[N-ethyl-N-(4-nitrobenzoyl)amino]-5-methylphenyl 4-nitrobenzoate 73 (13 mg; 16%) as a white solid, $R_f$ 0.13, ($M^+$ 449.1215. C$_{23}$H$_{19}$N$_3$O$_7$ requires 449.1222), $\nu_{\max}$ (CHCl$_3$) 3 020, 1 750, 1 650, 1 605, 1 530, 1 510, 1 350, 1 315, 1 260, 1 220, 1 210, 1 100, 1 070, 1 015, 780 br, 735 br and 665 cm$^{-1}$, $\delta$(CDCl$_3$; 300 MHz) 1.25 (3H, t, $J$ 7 Hz, CH$_3$CH$_2$), 2.38 (3H, s, ArCH$_3$), 3.73-3.85 (1H, m, one of NCH$_2$CH$_2$), 3.99-4.11 (1H, m, one of NCH$_2$CH$_2$), 7.05-7.13 (3H, m, C-3 + C-4 + C-6 ArH), 7.76 (4H, m, p-nitrobenzoyl ArH) and 8.35 (4H, m, p-nitrobenzoyl ArH), and m/e(I.B.E.I.) 449 (8, $M^+$), 283 (100), 150 (91), 104 (44) and 76 (23).

Oxidation of Ethyl (2RS)-3-(4-Benzamido-3-hydroxyphenyl)-alanine 60 in Dichloromethane.- Ethyl (2RS)-3-(4-benzamido-3-hydroxyphenyl)alanine 60 (49 mg; 0.149 mmol) in dry dichloromethane (40 ml) was cooled to 0°C under dry nitrogen and lead dioxide (3.0 g) and freshly baked sodium sulphate (1.0 g) added. The mixture was stirred at 0°C for 7 min, centrifuged and the orange solution decanted from the solid. Hydrogen chloride was passed through the solution for 5 min, which was then evaporated and the solid residue stirred with pyridine (10 ml) and acetic anhydride (10 ml) at 18°C for 1 h. Evaporation in vacuo gave a residue which was dissolved in dichloromethane (60 ml) and water (15 ml). The organic solution was washed with saturated
brine (10 ml), dried (Na$_2$SO$_4$) and evaporated, leaving an oil which was separated by column chromatography (75% CH$_2$Cl$_2$, 25% CH$_3$CN) giving mixture 74 (1.5 mg; 2%) as a colourless oil, $\nu$$_{\text{max}}$(CHCl$_3$) 3 420, 1 770 br, 1 740, 1 680, 1 510, 1 370 and 710 cm$^{-1}$, $\delta$(CDCl$_3$; 300 MHz) 1.26 (3H, t, $J$ 7.1 Hz, CH$_3$CH$_2$), 2.00 (3H, s, CH$_3$CONHCH), 2.37 (3H, s, CH$_3$CO), 3.16-3.23 (1H, dd, $J$ 13, 6.9 Hz, one of ArCH$_2$), 3.26-3.34 (1H, dd, $J$ 13, 6.2 Hz, one of ArCH$_2$), 4.20 (2H, m, CH$_3$CH$_2$O), 4.87 (1H, q, $J$ 7 Hz, O$_2$CCHN), 6.11 (1H, br d, $J$ 8 Hz, CONHCH), 7.11 (1H, s, C-6 ArH), 7.44-7.63 (m, $m+p$ benzoyl ArH), 7.81-7.85 (m, o benzoyl ArH), 7.97 (1H, br s, CONHAr) and 8.46 (1H, s, C-3 ArH), and $m$/e(D.C.I.) 466 (36, M+NH$_3$+1$^+$), 464 (100, M+NH$_3$+1$^+$), 404 (33), 402 (93), 362 (25), 360 (73), 139 (42) and 77 (27), and mixture 75 (2.5 mg; 4%) as a colourless oil, $\nu$$_{\text{max}}$(CHCl$_3$) 3 440, 1 785, 1 740, 1 680, 1 515, 1 375 and 710 cm$^{-1}$, $\delta$(CDCl$_3$; 300 MHz) 1.27 (3H, t, $J$ 7 Hz, CH$_3$CH$_2$), 2.01 (3H, s, CH$_3$CONHCH), 2.45 (3H, s, CH$_3$CO), 3.19-3.27 (1H, dd, $J$ 13, 7 Hz, one of ArCH$_2$), 3.32-3.39 (1H, dd, $J$ 13, 7 Hz, one of ArCH$_2$), 4.20 (2H, m, CH$_3$CH$_2$O), 4.93 (1H, q, $J$ 7 Hz, O$_2$CCHN), 6.06 (1H, br d, $J$ 8 Hz, CONHCH), 7.18 (1H, d, $J$ 8 Hz, C-6 ArH), 7.44-7.64 (m, $m+p$ benzoyl ArH), 7.81-7.88 (m, o benzoyl ArH + CONHAr) and 8.25 (1H, d, $J$ 8 Hz, C-5 ArH), and $m$/e(D.C.I.) 466 (35, M+NH$_3$+1$^+$), 464 (100, M+NH$_3$+1$^+$), 404 (25), 402 (68), 362 (8) and 360 (23).

Oxidation of 2-Benzamido-5-methylphenol 57b in Dichloromethane. - 2-Benzamido-5-methylphenol 57b (50 mg; 0.22 mmol) in dry dichloromethane (40 ml) was cooled to 0°C under dry nitrogen, and lead dioxide (3.0 g) and freshly baked sodium sulphate (0.82 g) added. The mixture was stirred rapidly at 0°C for 7 min, centrifuged and the orange solution decanted from the solid.
Hydrogen chloride was passed through the solution for 1 min, instantly turning it orange-pink, the solution was then evaporated, and the residue dissolved in pyridine (5 ml) and acetic anhydride (2 ml). Stirring at 19°C for 1 h and evaporation in vacuo gave a pink oil which was separated by column chromatography (CH$_2$Cl$_2$) giving mixture 76 (5 mg; 7%) as a white solid, R$_f$ 0.33 (M$^+$ 303.0666. C$_{16}$H$_{14}$ClNO$_3$ requires 303.0662), $\nu_{\text{max}}$(CHCl$_3$) 3 440 br, 1 770, 1 680, 1 510, 1 370, 1 190, 1 140 and 710 cm$^{-1}$, $\delta$(CDCl$_3$; 300 MHz) 2.37 (3H, s, CH$_3$), 2.38 (3H, s, CH$_3$), 7.08 (1H, s, C-6 ArH), 7.48-7.63 (3H, m, m + p benzoyl ArH), 7.82-7.88 (3H, m, CONH + o benzoyl ArH) and 8.36 (1H, s, C-3 ArH), and m/e(I.B.E.I.) 303 (1, M$^+$), 263 (3), 261 (9), 201 (4), 199 (13), 183 (10), 181 (26), 159 (29), 157 (98), 105 (100), 77 (30) and 43 (49), and mixture 77 (9 mg; 14%) as a white solid with colourless oil, R$_f$ 0.25, (M$^+$ 303.0663. C$_{16}$H$_{14}$ClNO$_3$ requires 303.0662), $\nu_{\text{max}}$(CHCl$_3$) 3 440, 1 780 br, 1 680, 1 610, 1 585, 1 510, 1 450, 1 405, 1 370, 1 310, 1 250, 1 190, 1 170, 1 040, 820 and 710 cm$^{-1}$, $\delta$(CDCl$_3$; 300 MHz) 2.41 (3H, s, CH$_3$), 2.44 (3H, s, CH$_3$), 7.20 (1H, d, J 8 Hz, C-4 ArH), 7.48-7.62 (3H, m, m + p benzoyl ArH), 7.80-7.85 (3H, m, CONH + o benzoyl ArH) and 8.11 (1H, d, J 8 Hz, C-3 ArH), and m/e(I.B.E.I.) 305 (1, M$^+$), 303 (2, M$^+$), 263 (3), 261 (10), 183 (4), 181 (12), 105 (100) and 77 (27).

**Oxidation of Ethyl (2RS)-3-(4-Benzamido-3-hydroxyphenyl)-alanine 60 Diluted with Methanol.** Ethyl (2RS)-3-(4-benzamido-3-hydroxyphenyl)alanine 60 (50 mg; 0.152 mmol) in dry dichloromethane (40 ml) was cooled to 0°C under dry nitrogen and lead dioxide (3.0 g) and freshly baked sodium sulphate (1.0 g) added. The mixture was stirred at 0°C for 6 min, centrifuged, and
the orange solution decanted from the solid into dry methanol (250 ml) at 0°C. The solution was stirred at 0°C for 2 min and then hydrogen chloride passed through for 5 min, warming the solution to room temperature. Evaporation gave an oil which was stirred with pyridine (10 ml) and acetic anhydride (10 ml) at 15°C for 1 h. Evaporation in vacuo gave a brown oil which was dissolved in dichloromethane (60 ml) and water (15 ml). The organic solution was washed with saturated brine (10 ml), dried (Na₂SO₄) and evaporated leaving an oil which was separated by column chromatography (75% CH₂Cl₂, 25% CH₃CN) giving mixture 74 (5 mg; 7%) as a pale yellow oil.

Oxidation of Ethyl (2RS)-3-(4-Benzamido-3-hydroxyphenyl)-alanine 60 Diluted with Acetic Acid in Methanol.- Ethyl (2RS)-3-(4-benzamido-3-hydroxyphenyl)alanine 60 (50 mg; 0.152 mmol) was oxidised and centrifuged as above, giving a turbid orange-red solution which was decanted from the solid into dry acetic acid (15 ml) in dry methanol (250 ml) at 0°C. Treatment of the mixture as above, including acetylation and work-up gave an orange-brown oil which was separated by column chromatography (65% CH₂Cl₂, 35% CH₃CN) giving mixture 74 (5.5 mg; 8%) as a yellow oil, benzamide (3 mg; 16%) and mixture 80 (2 mg; 3%) as a yellow oil, δ(CDCl₃; 300 MHz) 1.28 (3H, t, J 7 Hz, CH₃CH₂), 2.02 (3H, s, CH₃CONHCH), 2.36 (3H, s, CH₃CO), 3.14 (2H, m, ArCH₂), 4.21 (2H, q, J 7.2 Hz, CH₃CH₂O), 4.87 (1H, m, O₂CCHN), 6.03 (1H, br d, J 7.7 Hz, CONHCH), 7.00-7.04 (2H, m, C-2 + C-6 ArH), 7.48-7.60 (3H, m, m + p benzoyl ArH), 7.84 (2H, m, o benzoyl ArH), 7.95 (1H, br s, CONHAr) and 8.23 (1H, d, J 8.2 Hz, C-5 ArH).
Oxidation of Ethyl (2RS)-3-(4-Benzamido-3-hydroxyphenyl)-alanine 60 Diluted with Magnesium Methoxide in Methanol.- Ethyl (2RS)-3-(4-benzamido-3-hydroxyphenyl)alanine 60 (50 mg; 0.152 mmol) was oxidised and centrifuged as above, giving a turbid orange-red solution which was decanted from the solid into magnesium methoxide (3.8 g; 20.9-24.4 mmol) in dry methanol (250 ml) at 0°C. Treatment of the mixture as above including acetylation in pyridine (20 ml) and acetic anhydride (10 ml) followed by the work-up gave a red-brown oil which was separated by column chromatography (70% CH₂Cl₂, 30% CH₃CN) giving small amounts of unidentified materials.

Oxidation of Ethyl (2RS)-3-(4-Benzamido-3-hydroxyphenyl)-alanine 60 Diluted with Trimethyl Borate in Methanol.- Ethyl (2RS)-3-(4-benzamido-3-hydroxyphenyl)alanine 60 (50 mg; 0.152 mmol) was oxidised and centrifuged as above, giving a turbid orange-red solution which was decanted from the solid into dry trimethyl borate (20 ml) in dry methanol (250 ml) at 0°C. Treatment of the mixture as above, including acetylation and work-up gave a red-brown oil which was separated by column chromatography (70% CH₂Cl₂, 30% CH₃CN), giving mixture 74 (6 mg; 9%) as a colourless oil, and mixture 75 (1 mg; 2%) as a colourless oil.

Oxidation of Ethyl (2RS)-3-(4-Benzamido-3-hydroxyphenyl)-alanine 60 Diluted with Refluxing Methanol.- Ethyl (2RS)-3-(4-benzamido-3-hydroxyphenyl)alanine 60 (49 mg; 0.149 mmol) was oxidised and centrifuged as above, giving a turbid orange-red solution which was decanted from the solid into dry methanol (250 ml) at reflux. Treatment of the mixture as above, including acetylation and work-up gave a red-brown oil which was separated
by column chromatography (70% CH$_2$Cl$_2$, 30% CH$_3$CN), giving mixture 79 (1.5 mg; 2%) as a yellow oil δ(CDCl$_3$; 300 MHz) 2.02 (3H, s, CH$_3$CONHCH), 2.39 (3H, s, CH$_3$CO), 3.17–3.25 (1H, dd, $J$ 13, 7 Hz, one of ArCH$_2$), 3.28–3.36 (1H, dd, $J$ 13, 7 Hz, one of ArCH$_2$), 3.76 (3H, s, CH$_3$O), 4.90 (1H, m, O$_2$CCHN), 6.09 (1H, br d, $J$ 7 Hz, CONHCH), 7.09 (1H, s, C-6 ArH), 7.43–7.61 (m, m + p benzoyl ArH), 7.79–7.85 (m, o benzoyl ArH), 7.96 (1H, br s, CONHAr) and 8.48 (1H, s, C-3 ArH), and m/e (D.C.I.) 452 (2, M+NH$_3$+1$^+$), 450 (5, M+NH$_3$+1$^+$), 390 (3), 388 (8), 331 (3), 329 (9), 139 (47), 122 (100) and 35 (48).

**Chlorination of Ethyl (2RS)-3-(4-Benzamido-3-hydroxyphenyl)-alanine 60.** Ethyl (2RS)-3-(4-benzamido-3-hydroxyphenyl)-alanine 60 (51 mg; 0.155 mmol) in dry methanol (40 ml) was cooled to –78°C under dry nitrogen and 0.83 M tert-butyl hypochlorite in dry methanol (0.19 ml; 0.158 mmol) added. After 1 min stirring, the solution was warmed to 20°C over 2 min, and stirred at 20°C for a further 2 min. Hydrogen chloride was passed through the solution for 5 min, raising the temperature to 37°C, and it was then evaporated. The residue was stirred in pyridine (10 ml) and acetic anhydride (10 ml) for 1 h at 18°C and worked-up as above, giving a residue which was separated by column chromatography (70% CH$_2$Cl$_2$, 30% CH$_3$CN), giving mixture 74 (20 mg; 29%) as a colourless oil, mixture 75 (6 mg; 8%) as a colourless oil, and mixture 80 (19 mg; 30%) as a colourless oil.
PART II

Studies on Simple Thioaldehydes
INTRODUCTION

Instability of Simple Thioaldehydes

Little work has been done on thioaldehydes in comparison to their oxygen analogues, and as a consequence, they are poorly understood. Early attempts to prepare them invariably led to the isolation of oligomeric and polymeric species, often with the desired empirical formula,\(^{51}\) strongly suggesting that the elusive monomeric thioaldehydes were indeed being formed, but were not stable under the reaction and isolation conditions.

This difficulty in preparing compounds with a double bond between carbon and a second row element is similarly encountered in forming methylenesilanes\(^{52}\) and methylene phosphoranes,\(^{53}\) figure 26, and contrasts with the ease of formation of olefins, imines and carbonyl compounds. In the case of thioaldehydes, it may be explained by the poor overlap of the large sulphur 3p

\[
\begin{align*}
\text{\textbackslash C\textbackslash =\textbackslash C\textbackslash} & \quad \text{\textbackslash C\textbackslash =\textbackslash N\textbackslash} & \quad \text{\textbackslash C\textbackslash =\textbackslash O\textbackslash} \\
\text{olefins} & \quad \text{imines} & \quad \text{carbonyl compounds} \\
\text{\textbackslash C\textbackslash =\textbackslash S\textbackslash i\textbackslash} & \quad \text{\textbackslash C\textbackslash =\textbackslash P\textbackslash} & \quad \text{\textbackslash C\textbackslash =\textbackslash S\textbackslash} \\
\text{methylenesilanes} & \quad \text{methylene phosphines} & \quad \text{thiocarbonyl compounds}
\end{align*}
\]

Figure 26
orbital and the smaller carbon 2p orbital, giving a weak π bond which is thermodynamically disfavoured with respect to the alternative σ bonds formed upon polymerisation. This mismatching of orbital size is overcome when the oxidation state of the sulphur is increased, and so thioaldehyde-S-oxides are found to be stable, isolable compounds, figure 27. Furthermore, thioaldehydes have a greater susceptibility to polymerisation than thioketones since they offer less steric hindrance to attack at the sp² hybridised carbon atom.

\[
\text{H} \quad \text{C=S+} \quad \text{R} = \text{Me, Et, } n-C_5H_{11}.
\]

Figure 27

Electronically Stabilised Thioaldehydes

It was not until 1960 that the first stable, monomeric compound containing the thioaldehyde group was reported. The electronic factors which conferred stability on thioaldehyde...
were soon reproduced in other systems, and so now several classes of stabilised thioaldehydes are known, e.g. figure 28. The significant feature which links these thioaldehydes is the conjugation of the carbon-sulphur double bond with an electron-rich centre; for example, a nitrogen atom with a lone pair of electrons, a sulphur atom with an available lone pair, or a phosphonium ylid. These lone pairs provide delocalisation, including canonical forms where the carbon-sulphur bond is no longer a double bond, e.g. figure 29. The analogous aldehydes in the oxygen series would be vinylogous formamides, thioformates,
etc., which while exhibiting some of the properties of aldehydes, are clearly not representative of this class of compounds. We can therefore expect that these stabilised thioaldehydes are equally unrepresentative of all thioaldehydes.

**Transient Thioaldehydes**

The only instance of a thioaldehyde being isolated in a condensed phase where electron-rich substituents as described above are not present is in the preparation of thio-benzaldehyde 83 and thioacrolein 84 at liquid nitrogen temperatures. These thioaldehydes were generated by flash

\[
\begin{align*}
\text{R} & \quad \text{ca. 630 °C} \\
\text{H} & \quad \text{ca. 1 millisecond}
\end{align*}
\]

\[
\begin{align*}
83 & \quad R = \text{Ph} \\
84 & \quad R = \text{CH=CH}_2
\end{align*}
\]
vacuum pyrolysis of the corresponding allyl sulphide, figure 30. The authors found that decomposition, which was followed by monitoring the infrared spectrum, set in above 110K in the case of thiobenzaldehyde, while thioacrolein decomposed slowly at 77K. This indicates that the isolation under the usual laboratory conditions of monomeric thioaldehydes without electronic stabilisation is doomed to failure. An isolated report\textsuperscript{59} of the characterisation at room temperature of two unstabilised thioaldehydes, 85 and 86, is seriously in question, especially

\begin{align*}
\text{CHS} & \quad \text{Me} \\
\text{Me} & \quad \text{CHS} \\
85 & \quad 86
\end{align*}

since the quoted n.m.r. data do not match the proposed structures. Simple thioaldehydes such as thioformaldehyde 87\textsuperscript{60} and

\begin{align*}
\text{CH}_3\text{S}\text{Cl} & \quad \xrightarrow{860\text{K}} \quad \text{CH}_2\text{=S} + \text{HCl} \\
87 & \\
\text{S} & \quad \xrightarrow{660\text{K}} \quad \text{CH}_2\text{=S} + \text{HCl} \\
84 & \quad \mid \mid \\
\text{Figure 31}
\end{align*}
thioacrolein $^{84,61}$ have been produced in the gas phase at high temperatures, figure 31, and spectral measurements have been carried out. However, chemical properties other than polymerisation have not been stated.

Recently, Vedejs has demonstrated that thioaldehydes with strongly electron-withdrawing substituents on the thio-carbonyl carbon atom can be trapped with electron-rich dienes. $^{62,63}$ In all but one case, $^{62}$ the thioaldehydes were generated by photochemical Norrish Cleavage of acetophenone derivatives 88, figure 32. $^{64}$ The yields of dihydrothians 89 were generally good (38-76% based on acetophenones 88), but from a preparative angle, the reaction has the inherent drawback that the products often have chromophores of similar wavelength to those of the starting materials, so some product is inevitably destroyed photochemically as the reaction is driven to completion.

![Diagram of reaction](image)
Our interest in the generation and reactivity of thioaldehydes derives from their recurrence in the literature as possible intermediates in the biosynthesis of penicillin. The \textit{in vivo} intermediates between the Arnstein tripeptide 90 and iso-penicillin N 91 are not known, but thioaldehydes 92\textsuperscript{65} and

\begin{align*}
\text{90} & \\
\text{91} & \\
\text{92} & \\
\text{93} & \\
\text{94} &
\end{align*}
have been suggested as candidates for consideration, and as an intermediate in cephalosporin biosynthesis. While some work has been done in vitro on model systems, our understanding of thioaldehydes such as 92, 93 and 94, which are neither stabilised by conjugation with electron-rich centres nor strongly electron-deficient, is based on isolated reports of transient thioaldehydes.

The work described here explores thiobenzaldehyde and thioacetaldehyde as simple aromatic and aliphatic examples of thioaldehydes without electronic bias.
RESULTS AND DISCUSSION

Generation and Trapping of Thiobenzaldehyde and Thiacetaldehyde

The method of forming thioaldehydes chosen was the thermolysis of alkyl thiosulphinates 95, figure 33, which has been studied as a way of generating sulphenic acids 96.

![Figure 33](image)

path a. The alternative cleavage, path b, is less favoured, since a stronger C-S bond is broken instead of the weak S-S bond, and is only observed when path a is unavailable, such as with t-butyl thiosulphinates 97. In the absence of a trap, sulphenic acids undergo a dehydration reaction which generates alkyl thiosulphinate, equation [1]. Therefore, the overall reaction in the thermolysis of a symmetrical alkyl thiosulphinate
98 can be expressed by equation [2], showing that, apart from the desired thioaldehyde, the only product is water.

Symmetrical alkyl thiosulphinates 98 are readily prepared by oxidation of the corresponding disulphide 99, and the oxidation can be carried out selectively in the presence of olefinic bonds. Ethyl thiosulphinate 100 was prepared in this way from diethyl disulphide 101 which was in turn made from ethanethiol.
However, it was found convenient to prepare benzyl thiosulphinate 102 by the oxidation of benzyl mercaptan 103 with sodium nitrite in aqueous acetic acid. This procedure uses readily available materials and the product crystallises out of the reaction mixture, requiring a single recrystallisation to achieve the literature melting point. The modest yields obtained (29-46% based on thiol 103) were therefore felt to be justified.

Benzyl thiosulphinate 102 was a solid which kept well if refrigerated. On the other hand, ethyl thiosulphinate 100 was an obnoxiously smelling oil which disproportionated completely within five days at 0°C to the disulphide 101 and thiosulphonate 104. Disproportionation was slower but noticeable over a period of days at -78°C, so the reagent was used as soon as possible after preparation and always stored at -78°C. The analogous, rapid disproportionation of methyl methanethiosulphinate has been noted.
The boiling point of ethyl thiosulphinate 100 given by Small et al.74 (67°C at 0.5 mmHg) is above that obtained in our preparation (47°C at 0.5 mmHg). However, later authors78 question Small's boiling point of methyl methanethiosulphinate, having obtained 65°C at 1.1 mmHg rather than the quoted 64°C at 0.5 mmHg. They suggest that Small et al. had decomposed their thiosulphinate and were recording the boiling point of the corresponding thiosulphonate. It seems probable that a similar decomposition gave rise to their anomalously high boiling point of 67°C at 0.5 mmHg in the case of ethyl thiosulphinate 100, especially since Small et al. later report79 the equivalent boiling point of 56°C at 0.2 mmHg for ethyl thiosulphonate 104.

Benzyl thiosulphinate 102 was heated in the presence of anthracene under a variety of conditions, and adduct 105 was obtained in a maximum yield of 97% based on thiosulphinate 102.

\[
\begin{align*}
\text{Benzyl thiosulphinate} & + \text{anthracene} \\
\rightarrow & \text{adduct}
\end{align*}
\]

It was found that the thermolysis was complete after one hour at 100°C and longer reaction times simply reduced the yield, table. An excess of anthracene was essential to trap the thiobenzaldehyde 83 efficiently, since using only one equivalent, based on thioaldehyde, gave a poor yield.
The preferred solvent was toluene, because anthracene has a higher solubility in toluene at 100°C than in refluxing benzene. It is convenient to use the minimum volume of solvent, so that when the reaction is complete, as much excess anthracene as possible crystallises out on cooling, and chromatographic separation of adduct $105$ from anthracene remaining in solution is simplified. The solubility of adduct $105$ in both toluene and benzene was always sufficient that only pure anthracene crystallised on cooling the reaction mixtures.

Similarly, adduct $106$ was obtained when 9,10-dimethylanthracene was employed as the trapping agent, and dihydrothian $107$ when 2,3-dimethylbutadiene was used. 9,10-Dimethylanthracene was prepared from anthracene by bis(chloromethylation)$^{80}$ followed by reduction with lithium aluminium hydride,$^{81}$ figure 34. Reactions involving 2,3-dimethylbutadiene, which has a boiling point of 69°C at 760 mmHg, were carried out in toluene at 100°C in sealed flasks.

That products $105$, $106$ and $107$ were 1:1 adducts of thiobenzaldehyde and the relevant diene was confirmed by

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Reaction time (h)</th>
<th>Equivalents of anthracene (based on thiosulphinate 102)</th>
<th>Yield of adduct $105$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>toluene</td>
<td>98-100</td>
<td>1</td>
<td>10</td>
<td>97</td>
</tr>
<tr>
<td>toluene</td>
<td>96-97</td>
<td>6</td>
<td>10</td>
<td>93</td>
</tr>
<tr>
<td>toluene</td>
<td>100-103</td>
<td>20</td>
<td>10</td>
<td>79</td>
</tr>
<tr>
<td>benzene</td>
<td>80</td>
<td>20</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>toluene</td>
<td>99-103</td>
<td>20</td>
<td>2</td>
<td>19</td>
</tr>
</tbody>
</table>

Table
elemental analysis of carbon, hydrogen and sulphur.

Adduct 106 showed a very broad signal in the aromatic region of the 300 MHz proton n.m.r. spectrum, integrating to two protons and shifted upfield with respect to the other eleven aromatic protons. This was assigned to the protons $H_a$ and $H_b$, figure 35. At 60 MHz, the n.m.r. spectrum showed
H<sub>a</sub> and H<sub>b</sub> equivalent, while cooling the sample at 300 MHz resolved the broad singlet into two separate signals, one even further upfield, and the second merging with the other aromatic protons' signals, showing rotation around bond c being frozen out. The upfield shift of proton H<sub>b</sub> is caused by its position over the aromatic ring formerly of anthracene.

The trapping of thiobenzaldehyde was unsuccessful when 9,10-diacetoxyanthracene was used. This compound was insoluble in refluxing toluene, and when the solvent was changed to dimethylformamide, in which it was soluble, no adduct was detected, and diacetoxyanthracene was almost totally recovered. This failure suggests either that the 1,3-diene system in 9,10-diacetoxyanthracene is too sterically hindered to allow thiobenzaldehyde to add to it, which seems unlikely after the successful use of 9,10-dimethylanthracene, or that dimethylformamide is not a suitable solvent for clean thiosulphinate thermolysis to thioaldehydes.

Omitting any trapping agent during thermolysis in toluene gave rise to a blue colour, which turned pink after approximately fifteen minutes. The visible spectrum of the blue solution showed a maximum at 580-590 nm and a shoulder at 610 nm, which was in complete agreement with the electronic spectrum at 77K of thiobenzaldehyde obtained by a different route. This lends further evidence to the idea that our reaction generates thiobenzaldehyde which is consequently trapped by the diene.

In a similar manner, thioacetaldehyde was generated by subjecting ethyl thiosulphinate 100 to thermolysis in toluene. In the presence of anthracene, 9,10-dimethylanthracene and 2,3-dimethylbutadiene, the products 108, 109 and 110 were
isolated. In the cases of adduct 108 and dihydrothian 110, the coupling constants in the proton n.m.r. spectra showed the connection of the segment previously the thioaldehyde with that previously part of the diene.

All ethyl thiosulphinate 100 reactions were performed in sealed flasks.

**Anthracene Adducts as Sources of Thioaldehydes**

The anthracene adduct of thiobenzaldehyde, 105, proved to be an efficient and clean source of thiobenzaldehyde itself. Heating adduct 105 in toluene at 100°C in the presence of 2,3-dimethylbutadiene cleanly gave anthracene and dihydrothian 107 after one hour, equation [3].
However, the anthracene adduct of thioacetaldehyde, 108, was far more resistant to thermolysis, and heating at 100°C for 24 hours gave 71% unreacted starting material. Adduct 109 was expected to be more labile to heat, since the retro Diels-Alder reaction would eliminate the steric interaction between the thioacetaldehyde methyl group and the anthracene methyl group, which is not present in adduct 108. Indeed, heating adduct 109 at 103°C for 24 hours gave only 28% unreacted starting material, and heating at 130°C for 24 hours in the presence of 2,3-dimethylbutadiene gave 9,10-dimethylanthracene, dihydrothian 110, and no trace of adduct 109, equation [4].

A similar strategy of dienophile protection by 9,10-dimethylanthracene has been employed in the case of nitrosocarbonyl compounds, figure 36.82
Adducts between thioaldehydes and anthracenes, such as 105, 106, 108 and 109 have a carbon-sulphur bond which is doubly benzylic. Reductive cleavage of such a bond after adduct formation provides a novel entry into 9-substituted 9,10-dihydroanthracenes from the parent anthracene, figure 37.
The reduction was found to proceed smoothly and in high yield with sodium in refluxing ammonia in the case of thioacetaldehyde adduct 108, though neither the free thiol 111 formed nor its acetyl derivative 112 gave a sufficiently strong molecular ion in the mass spectrum for an accurate mass analysis to be possible. However, thiobenzaldehyde adduct 105 gave only
9,10-dihydroanthracene under the same conditions, a triply benzylic carbon-carbon bond being cleaved too. The required reduction to thiol 113 was accomplished by lowering the reaction temperature to -78°C, and thiol 113 was characterised as its acetyl derivative 114.

**Carbocyclic Ring Formation**

It was considered important to determine whether thioaldehydes would react with 1,3-diene systems intramolecularly, as well as intermolecularly, since this would give a useful entry into carbocyclic systems. Five-membered carbon rings are currently receiving much attention due to their widespread occurrence in new biologically active compounds. The proposed ring closure is shown in figure 38, and the necessary thio-

![figure 38](image-url)

**Figure 38**

116
Aldehyde 115 was generated from thiosulphinate 116.

Bromodiene 117 was made by the method of Descoins and Henrick. Crotonaldehyde was added to cyclopropyl magnesium bromide and alcohol 118 treated with hydrobromic acid86 to give bromodiene 117. The 300 MHz proton n.m.r. spectrum of diene 117 showed approximately 15% of (3Z,5E) isomer and 85% of the desired (£,£) isomer. The bromodiene 117 was converted into the Grignard reagent, and treated with ethylene oxide,87
giving a 17% yield of alcohol 119. The low yield was probably due to loss of ethylene oxide through evaporation before it reacted (boiling point 13.5°C at 760 mmHg). Treatment of alcohol 119 with sodium hydride in tetrahydrofuran followed by toluene-4-sulphonyl chloride gave tosylate 120. This procedure was found to be superior to treatment of the alcohol 119 with excess toluene-4-sulphonyl chloride in pyridine.

Displacement of tosylate by thiourea in dimethylsulphoxide was found to be very slow. After 20 hours at room temperature and work-up, only 19% of desired thiol 121 was obtained, figure 39, and 66% of starting tosylate 120 remained, so potassium thioacetate was tried as the sulphur nucleophile instead. This reagent was prepared freshly under anhydrous conditions from potassium hydride and thioacetic acid, rather

\[
\text{OSO}_2\text{C}_6\text{H}_4\text{CH}_3 \quad \text{S}=\text{C(NH}_2\text{)}_2
\]

\[
\text{NH}_2 \quad \text{NaOH} \quad \text{H}_2\text{O}
\]

Figure 39
than by the aqueous literature procedure, and used in dimethylformamide at room temperature instead of in refluxing acetone or ethanol. Thioacetate was obtained in excellent yield and hydrolysed to thiol. Oxidation with iodine gave disulphide, which did not give a sufficiently strong molecular ion in the mass spectrum for accurate mass analysis. Since thiol contained 15% of the \((5Z,7E)\) isomer, disulphide was produced as a mixture of the three compounds \(123a, 123b\) and \(123c\). However, the 300 MHz proton n.m.r. spectrum could only distinguish between the \((5Z,7E)\) and \((5E,7E)\) fragments, regardless of whether a \((5Z,7E)\) or \((5E,7E)\) fragment made up the other half of the disulphide molecule. As expected, the ratio of \((5Z,7E)\) to \((5E,7E)\) fragments was 15:85, as had been the case in all molecules from bromodiene.

Disulphide mixture was oxidised with one equivalent of meta-chloroperbenzoic acid to thiosulphinic acid, which was not purified, but showed an absorption band in the
infrared spectrum at 1075 cm\(^{-1}\) indicative of thiosulphinate S=O stretch. Presumably, thiosulphinate mixture 116 contained four different compounds, without counting the separate enantiomers possible caused by the thiosulphinate linkage's chirality, since symmetrical disulphides 123\(a\) and 123\(c\) would each give one thiosulphinate, while unsymmetrical disulphide 123\(b\) would give another two.

The crude thiosulphinate mixture 116 was heated in toluene, giving a 40% yield of thiabicyclononene 124 over the peracid oxidation and thermolyses steps. The yield is based on starting disulphide 123 containing 15% of \((5Z,7Z)\) isomer.

Bicyclononene 124 could not be separated into the two racemic diastereomers, though gas liquid chromatography and high pressure liquid chromatography were tried. The 300 MHz
n.m.r. spectrum showed the two diastereomers, figure 40, and integration of the methyl groups' doublets showed that they
were present in a ratio of 1:1. This was confirmed by capillary gas liquid chromatography. Studies on Diels-Alder reactions of triene esters 125 and 126 have shown that

\[ \text{CO}_2\text{Me} \]

125

\[ \text{CO}_2\text{Me} \]

126

there is a slight favouring of the trans-fused over the cis-fused product in the bicyclo[4.3.0]nonene systems generated, though no comparable selectivity was observed in our case.

There was also a third component present in thiabicyclo-nonene 124 separable only by capillary gas liquid chromatography, which could not be used preparatively. It accounted for 5% of the whole, and the peak with the largest \text{m/e} ratio in its mass spectrum was at 152 mass units. Since bicyclononenes 124 had a mass of 154, then it is possible that this third component of the mixture either had a further degree of unsaturation than bicyclononenes 124, or was a bicyclononene 127 formed from the cis,trans-thioaldehyde 128, which did not give a molecular ion, but immediately lost two hydrogen atoms in the mass spectrometer. Extraneous peaks at 1.26 (doublet, \(j = 7\) Hz), 2.28-2.38 (multiplet) and 5.83-5.93 (multiplet) \(\delta\) in the 300 MHz proton n.m.r. spectrum of bicyclononenes 124 were in
all likelihood due to this third component, and are indicative of a similar bicyclononene structure such as 127.

The successful intramolecular trapping of a thioaldehyde shows that this is a feasible ring-forming reaction.

An 'Ene' Reaction

The final investigation into thioaldehyde reactivity looks into the 'ene' reaction. This has been observed to occur

\[
\text{CF}_3 \quad \text{CF}_3 \\ + \quad \text{S} \\ \rightarrow \quad \text{CF}_3 \quad \text{CF}_3
\]

with electron-deficient thioketones, e.g. equation [5].

Benzyl thiosulphinate 102 was heated with \( \beta \)-pinene in toluene and the isolated products were thiols 129 and sulphide 130 in a ratio of 2:1. The two products arise from different orientations of thiobenzaldehyde addition with respect to
110

Diastereomeric mixture of thiols 129 gave an acetyl derivative mixture 131 upon acetylation, while sulphide 130 was recovered unchanged after the same treatment.

An attempted 'ene' reaction with cyclododecene only gave back the olefin in quantitative yield.

Conclusion

The success encountered in trapping thiobenzaldehyde and thioacetaldehyde from the thermolyses of thiosulphinates 102 and 100 with both aromatic and aliphatic dienes in high yields suggests that these reactions could be exploited with a variety of structural and electronic elements in the diene and dienophile not used previously.

Notably, thiobenzaldehyde generated in this way has useful reactivity with dienes which are only moderately electron-rich at the temperature employed, in contrast to Vedejs's findings at room temperature. He reported\textsuperscript{63} that the photochemical generation of thiobenzaldehyde at or below 28°C in the presence of 2-ethoxybutadiene failed to give any low molecular weight sulphur-containing products, figure 41.
The reversible trapping of thioaldehydes on aromatic dienes represents a valuable synthetic supplement to the straightforward thermolysis of thiosulphinates. The trapping and liberation of the thioaldehydes is clean and high yielding. The regeneration of the thioaldehyde takes place with the formation of the relatively inert anthracene or 9,10-dimethylanthracene as the only other product. This freeing of the thioaldehyde, therefore, takes place in the absence of water and sulphenic acids, unlike the generation from thiosulphinates, and in the absence of potentially destructive irradiation, unlike the photochemical methods described earlier.\(^{63,64}\) An area is opened, wherein thioaldehydes can be masked temporarily, permitting chemical elaboration of a remote site on the molecule, and deprotected under neutral, anhydrous conditions, for use in carbon-carbon bond forming reactions.

These results, in conjunction with the successful intramolecular trapping of a thioaldehyde with a 1,3-diene
system and the preliminary investigation into the 'ene' reaction, contribute towards establishing simple thioaldehydes as potentially useful synthetic intermediates in carbon-carbon bond forming reactions.
General procedures are described in Part I, page 51.

_Preparation of Diethyl Disulphide_ **101.**— 96% Sodium hydroxide (81.3 g; 1.95 mol) and potassium iodide (5 g) in water (500 ml) were cooled to 6°C and ethanethiol (121 g; 1.95 mol) added over 5 min with stirring and external cooling. The solution temperature rose to 19°C and was allowed to fall to 6°C. Iodine (250 g; 0.98 mol) was added over 30 min, keeping the solution temperature below 25°C, and then enough ethanethiol to discolour the solution. The mixture was extracted into ether (2 x 1000 ml) and the combined extracts dried (Na₂SO₄) and evaporated, giving a red oil. Distillation under reduced pressure gave diethyl disulphide **101** (105 g; 88%) as a red oil, b.p. 94-95°C at 90 mmHg (lit. 23 154°C at 760 mmHg), δ(CDCl₃; 60 MHz) 1.3 (6H, t, J 7 Hz, CH₃CH₂) and 2.7 (4H, q, J 7 Hz, CH₃CH₂S).

_Preparation of S-Ethyl Ethanethiosulphinate_ **100.**— Diethyl disulphide **101** (12.1 g; 99 mmol) in dichloromethane (1000 ml) was cooled to 2°C. While stirring vigorously and cooling in an ice-water bath, 80-90% meta-chloroperbenzoic acid (20.1 g; 93-105 mmol) in dichloromethane (300 ml) was added over 25 min, the reaction temperature staying below 5°C. The solution was warmed to 20°C and stood for 1 h. 5% Sodium hydrogen carbonate solution (200 ml; 120 mmol NaHCO₃) was added and the mixture stirred vigorously for 10 min. The aqueous layer was separated, and extracted with dichloromethane (200 ml) which was added to the main solution. 2% Sodium hydrogen carbonate solution (150 ml; 89 mmol NaHCO₃) was added,
the mixture shaken for 10 min and the aqueous phase separated, extracted with dichloromethane (150 ml) which was added to the main solution. Drying (Na$_2$SO$_4$) and evaporation gave an oil which was distilled under reduced pressure, giving $S$-ethyl ethanethiosulphinate 100 (9.56 g; 70%) as a colourless oil, b.p. 43-47°C at 0.5 mmHg, $\nu_{max}$ (liquid film) 2980, 2930, 2880, 1455, 1380, 1265, 1080 and 970 cm$^{-1}$ and $\delta$(CDCl$_3$; 300 MHz) 1.39 and 1.44 (6H, 2 x t, $J$ 7 Hz, 2 x CH$_3$CH$_2$) and 3.13 (4H, m, 2 x CH$_3$CH$_2$).

Preparation of $S$-Benzyl Phenylmethanethiosulphinate 102.- Benzyl mercaptan 103 (5.0 ml; 5.29 g; 42.7 mmol) in acetic acid (24 ml) was stirred as sodium nitrite (11.8 g; 171 mmol) in water (16 ml) was added over 25 min, keeping the solution at 22-25°C with intermittent cooling. First the solution turned red, then a red oil separated, and this solidified at the end of the addition. The solid was filtered off, washed with water and then a little ethanol. Drying gave a white solid which was recrystallised (benzene - petroleum ether) giving $S$-benzyl phenylmethanethiosulphinate 102 (1.61 g; 29%) as white flakes, m.p. 81-83°C (lit. 76-82°C), $\delta$(CDCl$_3$; 60 MHz) 4.22 and 4.26 (4H, 2 x s, 2 x ArCH$_2$) and 7.23 and 7.28 (10H, 2 x s, ArH).

Preparation of 9,10-Dihydro-9,10-(2-phenyl-1-thiaethano)-anthracene 105.- $S$-Benzyl phenylmethanethiosulphinate 102 (262 mg; 1.00 mmol) and anthracene (1.78 g; 10.0 mmol) in dry toluene (15 ml) were stirred and heated at 98-100°C under dry nitrogen for 1 h. Cooling the solution to room temperature precipitated out anthracene (1.16 g; 65%) as white flakes, which was filtered off. The solution was evaporated and the
solid obtained separated by flash chromatography (70% petroleum ether, 30% C₆H₆), giving anthracene (268 mg; 15%) as white flakes and adduct 105 (580 mg; 97%) as a white solid. Recrystallisation of the adduct 105 (toluene - hexane) gave white prisms, m.p. 160-163°C (decomp.), (Found: C, 84.20; H, 5.40; S, 10.90. C₂₁H₁₆S requires C, 83.96; H, 5.37; S, 10.67), λmax(CH₃CN) 212 (36 000) and 279 (3 000) nm, νmax(KBr) 3 025 and 1 450 cm⁻¹, δ(CD₂SOCD₂; 300 MHz) 4.57 and 4.69 (2 x 1H, 2 x d, j 2.5 Hz, Ar₂CHCH + Ar₂CHCH(Ph)S), 5.59 (1H, s, Ar₂CHS), 6.77-6.88 (3H, m, ArH), 7.05 (1H, m, ArH), 7.10-7.29 (6H, m, ArH), 7.42 (1H, m, ArH) and 7.48-7.55 (2H, m, ArH), and m/e(E.I.) 178 (100) and 121 (29).

Preparation of 9,10-Bis(chloromethyl)anthracene.- Dioxan (1200 ml) and concentrated hydrochloric acid (200 ml) were saturated with hydrogen chloride, 90% anthracene (150 g; 0.76 mol) and paraformaldehyde (130 g; 4.3 mol CH₂O) added, and the mixture stirred and heated to 85°C over 20 min and at 85-87°C for 2 h, while hydrogen chloride was passed through. Refluxing, b.p. 88°C, for 3 h without hydrogen chloride stream followed by standing at room temperature for 18 h gave a yellow solid which was filtered off, twice suspended in dioxan (270 ml) and filtered. It was washed with more dioxan (270 ml) and dried, giving 9,10-bis(chloromethyl)anthracene (93.0 g; 45%) as a yellow solid, m.p. 248-255°C (decomp.) (lit. 258-260°C (decomp.)) which was used without further purification.

Preparation of 9,10-Dimethylanthracene.- 90-95% Lithium aluminium hydride (50 g; 1.18-1.25 mol) in dry THF (1000 ml) was stirred as 9,10-bis(chloromethyl)anthracene (90.8 g; 0.33
mol) was added over 35 min, keeping the solution at just below reflux. Further dry THF (500 ml) was added and the mixture refluxed under dry nitrogen for 20 h and cooled. While stirring, water (50 ml) was added dropwise over 1 h, then 2.0 M sodium hydroxide solution (100 ml) over 5 min, and then more water (150 ml). The solution was filtered through a glass sinter, washing the solid with THF, and the solution volume reduced by evaporation (to 350 ml), giving 9,10-dimethylanthracene (56.2 g; 82%). A single recrystallisation (hot toluene) gave yellow crystals (31.0 g; 45%), m.p. 180–183.5°C (lit.96 183.6–184.2°C).

Preparation of 9,10-Dihydro-9,10-dimethyl-9,10-(2-phenyl-1-thiaethano)anthracene 106. – S-Benzyl phenylmethanethiosulphinate 102 (257 mg; 0.98 mmol) and 9,10-dimethylanthracene (2.02 g; 9.8 mmol) in dry toluene (15 ml) were stirred and heated at 96–99°C under dry nitrogen for 20 h. Cooling the solution to room temperature precipitated 9,10-dimethylanthracene (1.11 g; 55%) as yellow crystals, which was filtered off. The solution was evaporated and the solid obtained separated by flash chromatography (70% petroleum ether, 30% C₆H₆), giving 9,10-dimethylanthracene (509 mg; 25%) and adduct 106 (557 mg; 87%). Recrystallisation of the adduct 106 (toluene – hexane) gave pale green needles, m.p. 140–150°C (decomp.), (Found: C, 84.11; H, 6.42; S, 9.56. C_{23}H_{20}S requires C, 84.10; H, 6.14; S, 9.76%), λ_max(CH₃CN) 280 (2 900) nm, ν_max(KBr) 3 065–2 900 and 1 450 cm⁻¹, δ(CD₂Cl₂; 300 MHz) 1.74 and 2.33 (2 x 3H, 2 x s, 2 x CH₃), 4.24 (1H, s, PhCHS), 6.55 (2H, br s, ArH) and 7.02–7.50 (11H, m, ArH), and m/e(E.I.) 206 (100), 191 (32) and 121 (29).
Preparation of 3,6-Dihydro-4,5-dimethyl-2-phenyl-2H-thian 107.- S-Benzyl phenylmethanethiosulphinate 102 (262 mg; 1.00 mmol) and 2,3-dimethylbutadiene (1.64 g; 20.0 mmol) in dry toluene (15 ml) were sealed in a tube and stirred and heated at 96-99°C for 20 h. Evaporation and flash chromatography (70% petroleum ether, 30% C₆H₆) gave thian 107 (385 mg; 95%) as a colourless oil, b.p. 130-135°C at 0.4 mmHg (Kugelrohr), (Found: C, 76.45; H, 7.80; S, 15.54. C₁₃H₁₆S requires C, 76.41; H, 7.89; S, 15.69%), νmax (liquid film) 3 100 - 2 820, 1 500 and 1 450 cm⁻¹, δ(CDCl₃; 300 MHz) 1.73 and 1.78 (2 x 3H, 2 x br s, CH₃C=CCH₃), 2.40-2.49 and 2.53-2.65 (2 x 1H, 2 x m, PhCHCH₂), 2.93 and 3.48 (2 x 1H, 2 x m, SCH₂C=), 3.98 (1H, dd, J 6, 9 Hz, PhCHS) and 7.25-7.38 (5H, m, ArH), and m/e (E.I.) 204 (60, M⁺) and 122 (100).

Preparation of 9,10-Diacetoxyanthracene.- Anthraquinone (20.0 g; 96 mmol) and 90% zinc powder (20.0 g; 275 mmol) in acetic anhydride (50 ml) and DMF (50 ml) were refluxed for 6 h. The mixture was poured into water (1000 ml), precipitating a solid which was filtered off, washed with water and dried. Recrystallisation (acetic acid) gave 9,10-diacetoxyanthracene (15.9 g; 56%) as pale yellow pins, decomp. >260°C, δ(CF₃CO₂H; 90 MHz) 2.7 (6H, s, 2 x CH₃CO) and 7.7 (8H, m, ArH).

Attempted Trapping with 9,10-Diacetoxyanthracene.- S-Benzyl phenylmethanethiosulphinate 102 (262 mg; 1.00 mmol) and 9,10-diacetoxyanthracene (2.94 g; 10.0 mmol) in dry DMF (20 ml) were heated at 102-104°C under dry nitrogen for 1 h. The solution was cooled and poured into toluene (250 ml) precipitating 9,10-diacetoxyanthracene (2.39 g; 81%) which was filtered
off. The filtrate was washed with water (3 x 50 ml) and saturated brine (50 ml) and evaporated, giving a solid. Flash chromatography (C₆H₆ followed by 50% C₆H₆, 50% CH₂Cl₂ followed by CH₂Cl₂) gave 9,10-diacetoxyanthracene (381 mg; 13%) as a pale brown solid.

Thermolysis of S-Benzyl Phenylmethanethiosulphinate without a Trap.- S-Benzyl phenylmethanethiosulphinate (262 mg; 1.00 mmol) in dry toluene (15 ml) was heated at 98-100°C under dry nitrogen. After 5 min, a portion of the solution (1.0 ml) was withdrawn, diluted three-fold with toluene and the u.v.-visible spectrum showed λ_max 580-590 and 610 (shoulder) nm.

Preparation of 9,10-Dihydro-9,10-(2-methyl-1-thiaethano)-anthracene.- 77% S-Ethyl ethanethiosulphinate (695 mg; 3.9 mmol) and anthracene (8.9 g; 50 mmol) in dry toluene (75 ml) were sealed in a tube and stirred and heated at 97°C for 14 h. Cooling precipitated anthracene (6.37 g; 71%) as white flakes, which was filtered off. Evaporation of the filtrate and flash chromatography (70% petroleum ether, 30% C₆H₆) gave anthracene (1.36 g; 15%) and adduct (1.53 g; 82%) as a pale yellow solid. Recrystallisation of adduct (toluene - hexane) gave white crystals, m.p. 169-171°C, (Found: C, 79.96; H, 5.75; S, 13.20. C₁₆H₁₄S requires C, 80.63; H, 5.92; S, 13.45%), λ_max(CH₃CN) 225 (ε 200) and 278 (ε 700) nm, ν_max(KBr) 3 070 - 2 860, 1 470 and 1 455 cm⁻¹, δ(CD₃COCD₃; 300 MHz) 1.11 (3H, d, J 6 Hz, CH₃CH), 3.44 (1H, qd, J 6, 3 Hz, CH₃CHS), 4.54 (1H, d, J 3 Hz, Ar₂CHCH), 5.25 (1H, s, Ar₂CHS), 7.10-7.23 (4H, m, ArH) and 7.32-7.43 (4H, m, ArH), and m/e(E.I.) 238 (5, M⁺) and 178 (100).
Preparation of 9,10-Dihydro-9,10-dimethyl-9,10-(2-methyl-1-thiaethano)anthracene 109.- 94% S-Ethyl ethanethiosulphinate 100 (231 mg; 1.57 mmol) and 9,10-dimethylanthracene (3.09 g; 15.0 mmol) in dry toluene (25 ml) were sealed in a tube and stirred and heated at 99-101°C for 1 h. Cooling precipitated 9,10-dimethylanthracene (1.11 g; 36%) as yellow prisms, which was filtered off. The filtrate was evaporated and the solid residue separated by flash chromatography (70% petroleum ether, 30% C₆H₆), giving 9,10-dimethylanthracene (1.24 g; 40%) as a yellow solid and adduct 109 (632 mg; 76%) as a pale yellow solid, m.p. 128-133°C (decomp.), (Found: C, 81.40; H, 7.05. G 18 H 18 S requires C > 81.15; H, 6.81; S, 12.04%), λ max(CH₃CN) 278 (2 300) nm, νmax(KBr) 3 075 - 2 895, 1 455, 790, 765, 740, 710, 655 and 625 cm⁻¹, δ(CD₂Cl₂; 300 MHz) 0.98 (3H, d, J 6.6 Hz, CH₃CH), 2.04 and 2.21 (2 x 3H, 2 x s, 2 x Ar₂CCH₃), 3.24 (1H, q, J 6.6 Hz, CH₃CHS) and 7.16-7.43 (8H, m, ArH), and m/e(D.C.I.) 267 (15, M+1⁺), 207 (100), 206 (44) and 193 (24). All attempts at recrystallisation gave crystals of lower melting point.

Preparation of 3,6-Dihydro-2,4,5-trimethyl-2H-thian 110.- 77% S-Ethyl ethanethiosulphinate 100 (181 mg; 1.0 mmol) and 2,3-dimethylbutadiene (1.64 g; 20.0 mmol) in dry toluene (10 ml) was sealed in a tube and stirred and heated at 95-97°C for 20 h. Evaporation and flash chromatography (90% petroleum ether, 10% C₆H₆) gave thian 110 (235 mg; 83%) as a mobile, colourless oil, b.p. 70-87°C at 17 mmHg (Kugelrohr), (Found: C, 67.74; H, 9.91; S, 22.64. C₈H₁₄S requires C, 67.54; H, 9.92; S, 22.54%), ν max (liquid film) 2 960 - 2 820 and 1 450 cm⁻¹, δ(CDCCl₃; 300 MHz) 1.27 (3H, d, J 7 Hz, CH₃CH), 1.63 and 1.69 (2 x 3H, 2 x br s, CH₃C=CCH₃), 1.93-2.06 and 2.17-2.26 (2 x 1H,
2 x m, CH₃CH₂), 2.78-2.95 (2H, m, one of =CCH₂S + CH₃CHS) and 3.33 (1H, m, one of =CCH₂S), and m/e(E.I.) 142 (100, M⁺).

**Heating 9,10-Dihydro-9,10-(2-phenyl-1-thiaethano)-anthracene 105.** Adduct 105 (300 mg; 1.00 mmol) and 2,3-dimethylbutadiene (840 mg; 10.2 mmol) in dry toluene (10 ml) were sealed in a tube and stirred and heated at 98-99°C for 1 h. The solution was evaporated and the residue separated by flash chromatography (80% petroleum ether, 20% C₆H₆), giving anthracene (165 mg; 92%) and thian 107 (188 mg; 92%).

**Heating 9,10-Dihydro-9,10-(2-methyl-1-thiaethano)-anthracene 108.** Adduct 108 (238 mg; 1.00 mmol) and 2,3-dimethylbutadiene (820 mg; 10.0 mmol) in dry toluene (10 ml) were sealed in a tube and stirred and heated at 100-102°C for 24 h. The solution was evaporated and the residue separated by flash chromatography (70% petroleum ether, 30% C₆H₆), giving anthracene (45 mg; 25%) as a white solid and adduct 108 (170 mg; 71%) as a white solid.

**Heating 9,10-Dihydro-9,10-dimethyl-9,10-(2-methyl-1-thiaethano)anthracene 109.** Adduct 109 (266 mg; 1.00 mmol) and 2,3-dimethylbutadiene (830 mg; 10.1 mmol) in dry toluene (10 ml) were sealed in a tube and stirred and heated at 129-131°C for 24 h. The solution was evaporated and the residue separated by flash chromatography (90% petroleum ether, 10% C₆H₆), giving 9,10-dimethylanthracene (142 mg; 69%) as a green-yellow solid and thian 110 (69 mg; 49%) as a colourless oil.
Reduction of 9,10-Dihydro-9,10-(2-methyl-1-thiaethano)-anthracene 108. - Adduct 108 (119 mg; 0.50 mmol) was stirred in liquid ammonia (25 ml) at -33°C under argon and sodium added portionwise until the solution remained blue. Methanol (3.0 ml) was added, decolourising the solution which was then evaporated. The residue was dissolved in water (20 ml) and ether (40 ml), the aqueous phase extracted into ether (2 x 40 ml) and the combined ethereal solutions dried (Na₂SO₄) and evaporated, giving a pale yellow oil. Column chromatography (70% petroleum ether, 30% C₆H₆) gave 1-(9,10-dihydro-9-anthryl)-ethanethiol 111 (99 mg; 84%) as a colourless oil, \( \nu_{\text{max}} \) (liquid film) 3 070 - 2 820, 2 570, 1 480 and 1 450 cm\(^{-1}\), \( \delta(\text{CD}_2\text{Cl}_2; \ 300 \text{ MHz}) 1.27 \) (3H, d, \( J = 7 \) Hz, \( \text{CH}_3\text{CH} \)), 1.43 (1H, d, \( J = 6 \) Hz, \( \text{SH} \)), 3.27 (1H, m, \( \text{SCH} \)), 3.85 (1H, d, \( J = 18 \) Hz, one of \( \text{Ar}_2\text{CH}_2 \)), 3.93 (1H, d, \( J = 7 \) Hz, \( \text{Ar}_2\text{CHCH} \)), 4.25 (1H, d, \( J = 18 \) Hz, one of \( \text{Ar}_2\text{CH}_2 \)) and 7.23-7.42 (7H, m, \( \text{ArH} \)), and m/e (E.I.) 179 (100).

Acetylation of 1-(9,10-Dihydro-9-anthryl)ethanethiol 111. - Thiol 111 (80 mg; 0.33 mmol) in dichloromethane (6 ml) was stirred at 27°C with acetyl chloride (0.2 ml; 2.8 mmol) and pyridine (1.0 ml) added. After 20 min, water (5.0 ml) was added, the aqueous phase acidified to pH 1 with 2.0 M hydrochloric acid, and the organic layer separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic solutions dried (Na₂SO₄) and evaporated. Flash chromatography (20% petroleum ether, 80% C₆H₆) gave S-[1-(9,10-dihydro-9-anthryl)ethyl] thioacetate 112 (52 mg; 55%) as a colourless oil, \( \nu_{\text{max}}(\text{CHCl}_3) 3 020, 1 690 \) (C=O) and 1 455 cm\(^{-1}\), \( \delta(\text{CD}_2\text{Cl}_2; \ 300 \text{ MHz}) 1.13 \) (3H, d, \( J = 7 \) Hz,
CH₂CH), 2.21 (3H, s, CH₃CO), 3.81-3.93 (2H, m, one of Ar₂CH₂ + CH₃CHS), 4.13 (1H, d, J 6 Hz, Ar₂CHCH), 4.25 (1H, d, J 18 Hz, one of Ar₂CH₂) and 7.19-7.42 (8H, m, ArH), and m/e(C.I.) 283 (11, M+1⁺), 207 (17) and 179 (100).

Reduction of 9,10-Dihydro-9,10-(2-phenyl-1-thiaethano)-anthracene 105.

At -33°C. Adduct 105 (150 mg; 0.50 mmol) was stirred in liquid ammonia (35 ml) at -33°C under argon, and sodium added portionwise until the solution remained blue. Methanol (2.0 ml) was added, decolourising the solution which was then evaporated. The residue was dissolved in water (20 ml) and ether (40 ml), the aqueous phase separated and extracted into ether (2 x 40 ml) and the combined ethereal solutions dried (Na₂SO₄) and evaporated, giving an off-white solid (105 mg). Recrystallisation (ethanol) gave 9,10-dihydroanthracene (65 mg; 72%) as white crystals, m.p. 107-110°C (lit. 97-109-110°C).

At -78°C. Adduct 105 (151 mg; 0.50 mmol) in liquid ammonia (20 ml) was cooled to -78°C under argon, and while stirring, sodium was added portionwise until the solution remained blue. The solution was then stirred for 3 h at -78°C, methanol (2.0 ml) added discharging the blue colour, and the mixture evaporated. The residue was dissolved in water (150 ml) and ether (150 ml), the aqueous phase separated and extracted with ether (2 x 100 ml) and the combined ethereal solutions dried (Na₂SO₄) and evaporated. Flash chromatography (75% petroleum ether, 25% C₆H₆) gave (9,10-dihydro-9-anthryl)(phenyl)-methanethiol 113 (101 mg; 67%) as a colourless oil, v max(CHCl₃) 3020, 1485 and 1455 cm⁻¹, δ(CD₂Cl₂; 300 MHz) 1.98 (1H, d,
$J$ 5 Hz, SH), 3.60 and 3.70 (2 x 1H, 2 x d, $J$ 18 Hz, Ar$_2$CH$_2$), 4.28 (1H, dd, $J$ 7, 5 Hz, CHCHSH), 4.35 (1H, d, $J$ 7 Hz, Ar$_2$CHCH) and 6.90-7.47 (13H, m, ArH), and m/e(E.I.) 268 (3) and 178 (100).

Acetylation of (9,10-Dihydro-9-anthryl)(phenyl)methanethiol 113. - Thiol 113 (76 mg; 0.25 mmol) in dry dichloromethane (10 ml) was stirred at 22°C with acetyl chloride (0.2 ml; 2.8 mmol) and pyridine (0.3 ml) added. After 15 min, water (5 ml) was added, the aqueous phase acidified to pH 1 with 2.0 M hydrochloric acid, and the organic layer separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic solutions washed with saturated brine (5 ml), dried (Na$_2$SO$_4$) and evaporated. Flash chromatography (40% petroleum ether, 60% C$_6$H$_6$) gave S-a-(9,10-dihydro-9-anthryl)benzyl thioacetate 114 (80 mg; 92%) as a white solid. Recrystallisation (toluene - hexane) gave white crystals, m.p. 105-108°C, (Found: C, 79.98; H, 5.89; S, 9.44. C$_{23}$H$_{20}$OS requires C, 80.19; H, 5.85; S, 9.31%), $\nu$$_{max}$(CHCl$_3$) 3 020, 1 690 (C=O) and 1 455 cm$^{-1}$; $\delta$(CD$_2$Cl$_2$; 300 MHz) 2.37 (3H, s, CH$_3$CO), 2.96 and 3.49 (2 x 1H, 2 x d, $J$ 19 Hz, Ar$_2$CH$_2$), 4.43 and 4.87 (2 x 1H, 2 x d, $J$ 6 Hz, PhCHS + Ar$_2$CHCH), 6.55 (2H, m, ArH), 6.99-7.30 (10H, m, ArH) and 7.50 (1H, m, ArH), and m/e(E.I.) 179 (100).

Preparation of 1-Cyclopropyl-2-buten-1-ol 118. – Bromocyclopropane (16.5 ml; 24.1 g; 199 mmol) in dry THF (35 ml) was added under dry nitrogen to magnesium turnings (4.86 g; 200 mmol) in dry THF (150 ml) over 20 min, maintaining gentle refluxing. The solvent volume was increased (to 400 ml) and the mixture refluxed for 30 min. Freshly distilled croton-
aldehyde (16.5 ml; 14.0 g; 200 mmol) in dry THF (50 ml) was added over 10 min, keeping the solution just below refluxing temperature, the solution refluxed for 10 min, and stirred as it cooled for 30 min. Water (3 ml) was added and then ammonium chloride (16 g; 300 mmol) in water (100 ml). Water (400 ml) and ether (200 ml) were added, the aqueous phase extracted into ether (2 x 300 ml) and the combined ethereal solutions dried (Na₂SO₄) and evaporated. Distillation under reduced pressure gave 1-cyclopropyl-2-buten-1-ol 118 (9.86 g; 44%) as a colourless oil, b.p. 43°C at 4.0 mmHg - 40°C at 2.0 mmHg (lit. 85 57°C at 7 mmHg).

Preparation of 1-Bromo-3,5-heptadiene 117. - 1-Cyclopropyl-2-buten-1-ol 118 (9.76 g; 87.1 mmol) at 0°C was stirred vigorously in an ice-water bath and 48% hydrobromic acid (40 ml) added over 2 min. Vigorous stirring was continued for 15 min at 0°C, the aqueous layer separated, extracted into petroleum ether (2 x 50 ml) and the combined organic phases washed with saturated brine (100 ml), saturated sodium hydrogen carbonate solution (100 ml) and more saturated brine (100 ml). Drying (Na₂SO₄) and evaporation gave a pale yellow oil which was distilled under reduced pressure, giving 1-bromo-3,5-heptadiene 117 (10.7 g; 70%) as a colourless oil, b.p. 54°C at 7 mmHg - 59°C at 5 mmHg (lit. 85 63°C at 6 mmHg). (E,E)-1-Bromo-3,5-heptadiene, δ(CDCl₃; 300 MHz) 1.74 (3H, br d, J 6 Hz, CH₃CH=), 2.64 (2H, m, =CHCH₂CH₂), 3.40 (2H, t, J 7 Hz, CH₂CH₂Br), 5.53 (1H, m, =CHCH₂CH₂), 5.69 (1H, m, CH₃CH=) and 6.00-6.17 (2H, m, =CH-CH=).

Preparation of 5,7-Nonadien-1-ol 119. - Freshly distilled 1-bromo-5,7-heptadiene 117 (9.71 g; 55.5 mmol) in dry ether
(50 ml) was added under dry nitrogen to magnesium turnings (1.35 g; 55.6 mmol) in dry ether (50 ml) over 15 min, maintaining gentle refluxing. The mixture was refluxed for 1 h, cooled to 0°C, and ethylene oxide (11 ml; 9.9 g; 225 mmol) in dry ether (20 ml) at 0°C added over 10 min. The solution was heated, and solvent distilled off reducing the volume of the solution (to 80 ml) over 20 min. Dry benzene (100 ml) was added and the mixture refluxed gently. After 45 min, the solution had set to a clear gel, so it was allowed to stand at room temperature under dry nitrogen for 14 h. Adding water (3 ml) turned the gel fluid and ammonium chloride (10 g; 187 mmol) in water (50 ml) was added too, followed by 2.0 M hydrochloric acid to dissolve the precipitate. The aqueous phase was separated, extracted into ether (2 x 100 ml) and the combined organic solutions dried (Na$_2$SO$_4$) and evaporated, giving a pale yellow oil. Distillation under reduced pressure gave a colourless oil, b.p. 48-60°C at 0.008 mmHg, which was purified by flash chromatography (CH$_2$Cl$_2$ followed by 90% CH$_2$Cl$_2$, 10% EtOAc), giving 5,7-nonadien-1-ol 119 (1.33 g; 17%) as a colourless oil, $\nu$)$_{\text{max}}$ (liquid film) 3 340 br (O-H), 3 020, 2 930, 2 860, 1 455, 1 440, 1 060 and 985 cm$^{-1}$ and $m/\epsilon$(E.I.) 140 (7, M$^+$), 139 (21), 123 (24), 111 (33), 99 (44), 85 (56), 83 (71), 81 (74), 71 (59), 67 (46), 55 (84), 43 (100) and 41 (68). ($E,E$)-5,7-Nonadien-1-ol $\delta$(CDCl$_3$; 300 MHz) 1.42-1.64 (5H, m, $=\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 1.75 (3H, d, $J$ 6 Hz, CH$_3$CH=), 2.11 (2H, q, $J$ 6 Hz, $=\text{CHCH}_2\text{CH}_2$), 3.66 (2H, t, $J$ 6 Hz, CH$_2$CH$_2$OH), 5.58 (2H, m, CH=C=C=CH) and 5.93-6.09 (2H, m, $=\text{CH}-\text{CH}=)$.
Preparation of 5,7-Nonadien-1-yl Toluene-4-sulphonate

**a. Sodium hydride.** 50% Sodium hydride dispersion in oil (530 mg; 11.04 mmol NaH) was washed under dry nitrogen with petroleum ether (2 x 4 ml) and dry THF (20 ml) added. 5,7-Nonadien-1-ol 119 (1.27 g; 9.07 mmol) in dry THF (20 ml) was added over 5 min, and the mixture stirred under dry nitrogen at 60°C for 16 h. The suspension was cooled in a bath at -5°C and toluene-4-sulphonyl chloride (1.90 g; 9.97 mmol) in dry THF (20 ml) added over 10 min. The mixture was stirred at 7-12°C for 6 h, ether (50 ml) added, and the solution washed with ice-water (3 x 30 ml), dried (Na₂SO₄) and evaporated. The pale orange oil was separated by flash chromatography (50% petroleum ether, 50% CH₂Cl₂ followed by 90% CH₂Cl₂, 10% EtOAc), giving toluene-4-sulphonyl chloride (92 mg; 5%) as white needles, m.p. 60-65°C, 5,7-nonadien-1-yl toluene-4-sulphonate 120 (1.74 g; 65%) as a colourless oil, (M⁺ 294.1290. C₁₆H₂₂O₃S requires 294.1290), νmax (liquid film) 3020, 2940, 2860, 1600, 1450, 1360, 1190, 1175, 1050, 980, 955 br, 930, 810, 730 and 660 cm⁻¹, and m/e (I.B.E.I.) 294 (3, M⁺), 122 (51), 107 (24), 94 (100), 93 (64), 91 (59), 79 (91), 67 (12), 65 (19), 55 (16) and 41 (21); (E,E)-5,7-nonadien-1-yl toluene-4-sulphonate, δ(CDCl₃; 300 MHz) 1.42 and 1.65 (2 x 2H, 2 x m, =CCH₂CH₂CH₂CH₂O), 1.74 (3H, d, J 6 Hz, CH₃CH=), 2.03 (2H, q, J 6 Hz, =CHCH₂CH₂), 2.48 (3H, s, CH₃Ar), 4.04 (2H, t, J 6 Hz, CH₂CH₂O), 5.45 (1H, m, =CHCH₂CH₂), 5.59 (1H, m, CH₃CH=), 5.91-6.05 (2H, m, =CH-CH=) and 7.58 (4H, 'ABq', ArH), and 5,7-nonadien-1-ol 119 (224 mg; 18%) as a colourless oil.

**b. Pyridine.** Toluene-4-sulphonyl chloride (615 mg; 3.23 mmol) was added to 5,7-nonadien-1-ol 119 (225 mg; 1.61 mmol)
in pyridine (5 ml) at 0°C. The solution turned orange and was left at 0°C for 22 h. Pouring into ice-water (40 ml) gave a turbid pink solution which was extracted with ether (3 x 50 ml) and the combined extracts dried (Na₂SO₄) and evaporated. The pale orange oil was purified by flash chromatography (50% petroleum ether, 50% CH₂Cl₂), giving 5,7-nonadien-1-yl toluene-4-sulphonate 120 (85 mg; 18%) as a colourless oil.

Reaction of 5,7-Nonadien-1-yl Toluene-4-sulphonate 120 with Thiourea.

5,7-Nonadien-1-yl toluene-4-sulphonate 120 (310 mg; 1.05 mmol) and thiourea (88 mg; 1.16 mmol) in dry DMSO (2 ml) were stirred at 20-22°C under dry nitrogen for 20 h. 2 M Sodium hydroxide solution (8 ml) was added and stirring continued for 40 min. The solution was acidified to pH 3 with 2 M hydrochloric acid (7 ml) and extracted into dichloromethane (3 x 20 ml). The combined extracts were dried (Na₂SO₄) and evaporated. Flash chromatography (85% petroleum ether, 15% C₆H₆ followed by 50% petroleum ether, 50% CH₂Cl₂) gave 5,7-nonadiene-1-thiol 121 (31 mg; 19%) as a volatile, colourless oil, (M⁺ 156.0973. C₉H₁₆S requires 156.0973), v_{max}(liquid film) 3020, 2930, 2860, 1445 br and 985 cm⁻¹, and m/e(E.I.) 156 (26, M⁺), 155 (100), 127 (26), 113 (11), 101 (44), 95 (27), 93 (24), 87 (41), 81 (58), 79 (44), 67 (36), 55 (39) and 41 (18); (E, E)-5,7-nonadiene-1-thiol δ(CDCl₃; 300 MHz) 1.32-1.70 (5H, m, =CHCH₂CH₂CH₂CH₂SH), 1.74 (3H, d, J 6 Hz, CH₃CH=), 2.08 (2H, q, J 6 Hz, =CHCH₂CH₂), 2.55 (2H, q, J 6 Hz, CH₂CH₂SH), 5.58 (2H, m, CH=C-C=CH) and 6.02 (2H, m, =CH=CH=), and 5,7-nonadien-1-yl toluene-4-sulphonate 120 (203 mg; 66%) as a colourless oil.
Preparation of Potassium Thioacetate. - 20-25% Potassium hydride in oil (5.9 g; 29.4-36.8 mmol KH) was washed under dry nitrogen with petroleum ether (3 x 10 ml) and dry THF (20 ml) added. Freshly distilled thioacetic acid (3.2 ml; 3.4 g; 44.7 mmol) in dry THF (10 ml) was added dropwise over 15 min, and the mixture stirred under dry nitrogen at 18-22°C for 20 h. The solution was filtered off and the solid washed under dry nitrogen with dry THF (2 x 15 ml). Drying in vacuo gave potassium thioacetate (3.72 g) as a hygroscopic white powder which was stored under dry argon.

Preparation of S-(5,7-Nonadien-1-yl) Thioacetate. - 5,7-Nonadien-1-yl toluene-4-sulphonate (1.3 g; 4.4 mmol) and potassium thioacetate (1.0 g; 8.8 mmol) in dry DMF (15 ml) were stirred under dry nitrogen at 20-21°C. After 19.5 h, water (100 ml) was added and the turbid white solution extracted into ether (3 x 100 ml). The combined organic solutions were washed with water (2 x 100 ml), dried (Na$_2$SO$_4$) and evaporated. The pale yellow oil was purified by flash chromatography (70% petroleum ether, 30% CH$_2$Cl$_2$), giving S-(5,7-nonadien-1-yl) thioacetate (840 mg; 95%) as a mobile, colourless oil, (M$^+$ 198.1075. C$_{11}$H$_{18}$OS requires 198.1078), $\nu_{\text{max}}$ (liquid film) 3 020, 2 930, 2 860, 1 695 (C=O), 1 355, 1 135, 985, 730 and 625 cm$^{-1}$, and m/e (E.I.) 198 (12, M$^+$), 155 (42), 121 (17), 101 (44), 87 (54), 79 (35), 55 (24) and 43 (100); S-[(E,E)-5,7-nonadien-1-yl] thioacetate (CDC$_3$; 300 MHz) 1.40-1.62 (4H, m, =CCH$_2$CH$_2$CH$_2$S), 1.73 (3H, d, J 6 Hz, CH$_3$CH=), 2.08 (2H, q, J 6 Hz, =CHCH$_2$CH$_2$), 2.33 (3H, s, CH$_3$CO), 2.88 (2H, t, J 6 Hz, CH$_2$CH$_2$S), 5.56 (2H, m, =CH=CH=) and 6.00 (2H, m, =CH=CH=).
Hydrolysis of S-(5,7-Nonadien-1-yl) Thioacetate 122. -

2.0 M Potassium hydroxide in methanol (5.5 ml; 11 mmol KOH) was added to S-(5,7-nonadien-1-yl) thioacetate 122 (1.01 g; 5.10 mmol) in methanol (5 ml) and the solution stirred under nitrogen at 19-21°C for 16 h, cooled and 2.0 M hydrochloric acid (5.5 ml; 11 mmol HCl) added slowly, taking the pH to 1. Water (30 ml) was added and the mixture extracted into ether (3 x 40 ml), the combined extracts dried (Na₂SO₄) and evaporated. Flash chromatography (90% petroleum ether, 10% C₆H₆) gave 5,7-nonadiene-1-thiol 121 (559 mg; 70%) as a colourless oil.

Preparation of Di-5,7-nonadien-1-yl Disulphide 123. -

5,7-Nonadiene-1-thiol 121 (559 mg; 3.58 mmol) was added over 3 min to 96% sodium hydroxide (146 mg; 3.50 mmol) and potassium iodide (21 mg) in water (2 ml) cooled in an ice-water bath. A white precipitate fell out. Dioxan (1 ml) was added, the mixture warmed to 18°C, and iodine (450 mg; 1.77 mmol) added with stirring. The precipitate dissolved, an oil separated out, and after 15 min, a little thiol 121 in dioxan (0.5 ml) was added to discharge the colour of the solution. Water (20 ml) and ether (30 ml) were added, the aqueous phase separated, extracted with ether (2 x 30 ml) and the combined organic solutions dried (Na₂SO₄) and evaporated. Flash chromatography (90% petroleum ether, 10% CH₂Cl₂) gave di-5,7-nonadien-1-yl disulphide 123 (285 mg; 51%) as a colourless oil, νₒ (liquid film) 3 020, 2 930, 2 860, 1 445 br and 985 cm⁻¹, and m/e (C.I.) 328 (6, M+NH₃+1⁺), 310 (1, M⁺) and 155 (100); (E,E)-5,7-nonadien-1-yl disulphides 123a and 123b δ(CDCl₃; 300 MHz) 1.51 (2H, m, two of =CCH₂CH₂CH₂CH₂S), 1.65-1.81 (5H,
Preparation and Thermolysis of S-(5,7-Nonadien-1-yl)
5,7-Nonadiene-1-thiosulphinate 116.- Di-5,7-nonadien-1-yl
disulphide 123 (112 mg; 0.36 mmol) in dichloromethane (5 ml)
was cooled to -20°C under dry nitrogen and while stirring,
80-90% meta-chloroperbenzoic acid (73 mg; 0.34-0.38 mmol)
in dichloromethane (2 ml) was added over 15 min, causing a
white solid to precipitate out. The mixture was stirred at
-20°C for a further 15 min, at -10°C for 20 min, and at 19°C
for 30 min, the solid dissolving. 2% Sodium hydrogen carbonate
solution (2 ml; 0.48 mmol NaHCO₃) was added and the mixture
stirred vigorously for 10 min. The aqueous layer was separated,
extracted into dichloromethane (2 ml) and the combined organic
solutions stirred vigorously with 0.5% sodium hydrogen
carbonate solution (2 ml; 0.12 mmol NaHCO₃) for 10 min. The
aqueous layer was again separated and extracted into dichloro-
methane (2 ml). The combined organic solutions were dried
(Na₂SO₄) and evaporated, giving a colourless oil (124 mg),
ν max (CH₂Cl₂) 1 075 and 990 cm⁻¹, which was dissolved in dry
toluene (6 ml) and sealed in a flask. Stirring and heating
at 96-97°C for 45 min, cooling and evaporation gave a yellow
liquid. Column chromatography (90% petroleum ether, 10%
CH₂Cl₂) gave 3-methyl-2-thiabicyclo[4.3.0]non-4-ene 124 (38
mg; 40%) as a colourless oil, ν max (CH₂Cl₂) 3 020, 2 970,
2 880 and 1 450 cm⁻¹, and δ(CDCl₃; 300 MHz) 1.35 and 1.43
(3H, 2 x d, J 7, 7 Hz, CH₃CH), 1.55-1.70 (2H, m, two of
CH₂CH₂CH₂), 1.73-2.17 (4H, m, four of CH₂CH₂CH₂), 2.45-2.59
m, CH₃CH= + two of =CH₂CH₂CH₂CH₂S), 2.10 (2H, q, J 6 Hz,
=CH₂), 2.69 (2H, m, CH₂S), 5.48-5.74 (2H, m, CH=C-C=CH)
and 5.95-6.08 (2H, m, =CH=CH=).
(1H, m, =CCHCHS), 3.22-3.32 (1H, m, =CCHCHS), 3.38-3.56 (1H, m, =CCHS) and 5.62-5.83 (2H, m, CH=CH). Capillary gas liquid chromatography (S.G.E. Superox 0.1 vitreous silica capillary column: 0.33mm internal diameter, 25m length; 130-170°C) showed three peaks, in order of elution, one diastereoisomer of bicyclononene $124$ m/e(E.I.) 154 (57, $M^+$), 139 (13), 125 (12), 121 (42), 118 (18), 105 (11), 97 (10), 94 (57), 79 (100) and 39 (36), other diastereoisomer of bicyclononene $124$ m/e(E.I.) 154 (100, $M^+$), 139 (45), 125 (93), 111 (42), 105 (23), 97 (49), 79 (76) and 39 (41), and impurity m/e(E.I.) 152 (100), 137 (19), 123 (66), 121 (37), 110 (34), 97 (27), 91 (73), 45 (45) and 39 (45).

$\beta$-Pinene 'Ene' Reaction. - S-Benzyl phenylmethane-thiosulphinate $102$ (263 mg; 1.00 mmol) and (1)$-\beta$-pinene (1.36 g; 10 mmol) in dry toluene (15 ml) was heated at 95-99°C for 20 h under dry nitrogen, cooled and the solution evaporated. Flash chromatography (95% petroleum ether, 5% C$_6$H$_6$) gave (2-pinen-10-yl)(phenyl)methanethiol $129$ (193 mg; 37%) as a colourless oil, ($M^+$ 258.1443. C$_{17}$H$_{22}$S requires 258.1442), $\nu_{max}$(CHCl$_3$) 3 000 - 2 840, 1 495 and 1 455 cm$^{-1}$, $\delta$(CD$_2$Cl$_2$; 300 MHz) 0.77 and 0.85 (3H, 2 x s, CH$_3$C), 0.98 and 1.18 (1H, 2 x d, $J$ 8 Hz, SH), 1.28 (3H, 2 x s, CH$_3$C), 2.03-2.43 (7H, m, aliphatic CH), 2.51-2.72 (2H, m, aliphatic CH), 4.05-4.18 (1H, m, PhCHSH), 5.23 and 5.38 (1H, 2 x m, =CH) and 7.20-7.38 (5H, m, ArH), and m/e(E.I.) 258 (100, $M^+$), 189 (90) and 91 (78), and benzyl (2-pinen-10-yl) sulphide $130$ (99 mg; 19%) as a colourless oil which turned pink on standing, ($M^+$ 258.1443. C$_{17}$H$_{22}$S requires 258.1442), $\nu_{max}$(CHCl$_3$) 3 000 - 2 840, 1 495 and 1 455 cm$^{-1}$, $\delta$(CD$_2$Cl$_2$; 300 MHz) 0.88
(3H, s, CH₃), 1.18 (1H, d, J 8 Hz aliphatic CH), 1.32 (3H, s, CH₃), 2.13 and 2.22 (2 x 1H, 2 x m, aliphatic CH), 2.28-2.33 (2H, m, aliphatic CH), 2.40-2.47 (1H, m, aliphatic CH), 2.98 (2H, m, =CCH₂S), 3.62 (2H, s, PhCH₂S), 5.38 (1H, m, =CH) and 7.20-7.33 (5H, m, ArH), and m/e (E.I.) 258 (5, M⁺), 134 (40), 119 (50) and 91 (100).

Acetylation of (2-Pinen-10-yl)(phenyl)methanethiol 129.-

Thiol 129 (118 mg; 0.46 mmol) in pyridine (2 ml) was stirred and acetyl chloride (0.2 ml; 2.8 mmol) added, the mixture turning solid. Dichloromethane (6 ml) was added and the mixture stirred at 27°C for 15 min. Water (5 ml) was added, the aqueous phase acidified to pH 1 with 2.0 M hydrochloric acid and the organic layer separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic solutions dried (Na₂SO₄) and evaporated. Flash chromatography (70% petroleum ether, 30% C₆H₆) gave S-α-(2-pinen-10-yl)benzyl thioacetate 131 (80 mg; 59%) as a colourless oil, νmax(CHCl₃) 3 040 - 2 840 and 1 690 (C=O) cm⁻¹, δ(CDCl₃; 300 MHz) 0.67 and 0.76 (3H, 2 x s, CH₃CCH₃), 0.90 and 1.04 (1H, 2 x d, J 8 Hz, aliphatic CH), 1.24 (3H, s, CH₃CCH₃), 1.95-2.35 (9H, m, CH₃CO + aliphatic CH), 2.58-2.64 (2H, m, aliphatic CH), 4.64-4.74 (1H, m, PhCHS), 5.13 and 5.26 (1H, 2 x br s, =CH) and 7.18-7.33 (5H, m, ArH), and m/e (E.I.) 300 (1, M⁺), 224 (69), 181 (65) and 123 (100).
Some of the work described in this part of the thesis has been published in a Communication.\textsuperscript{98}
References


   
   
   
   
   

   


   
   
   
   

   
   
   
   
   


