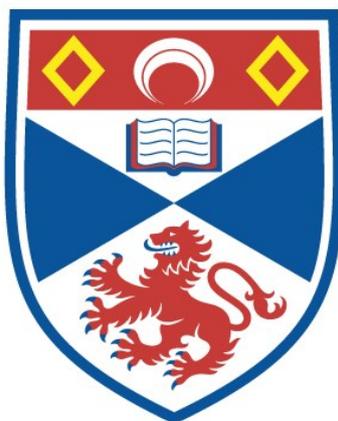


A MECHANISTIC STUDY OF THE ACID AND BASE
CATALYSED REACTIONS OF THIOUREA, 1-
SUBSTITUTED THIOUREAS AND 1, 3-
DISUBSTITUTED THIOUREAS WITH 1,2-DIKETONES

Christopher John Broan

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1989

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A mechanistic study of the acid and base
catalysed reactions of thiourea, 1-substituted
thioureas and 1,3-disubstituted thioureas with
1,2-diketones

being a thesis presented by
CHRISTOPHER JOHN BROAN BSc.

to the

UNIVERSITY OF ST. ANDREWS

in application for

THE DEGREE OF DOCTOR OF PHILOSOPHY

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Abstract

Thiourea, 1-substituted thioureas and 1,3-disubstituted thioureas react under acidic or basic catalysis with 1,2-diketones to give a wide variety of products. The nature of the product or products depends on the conditions used, the degree of substitution of the thiourea and on the nature of the aromatic or aliphatic groups attached to the dicarbonyl unit of the diketone. The mechanisms of formation of the various products have been investigated by a variety of techniques, including the determination of rate equations by ultraviolet spectroscopy, the influence of side group substituents on the rate and course of the reactions and the synthesis of putative intermediates on the reaction pathway. The single most informative technique used was, without a doubt, the detection of low concentrations of transient intermediates and side products by the application of carbon-13 nmr spectroscopy to the reaction as it progressed using carbon-13 labelled diketones to enhance the detection of low level intermediates. It has been shown convincingly that some organic reactions proceed via a small number of irreversible processes amongst a very complex set of more rapid equilibrium processes.

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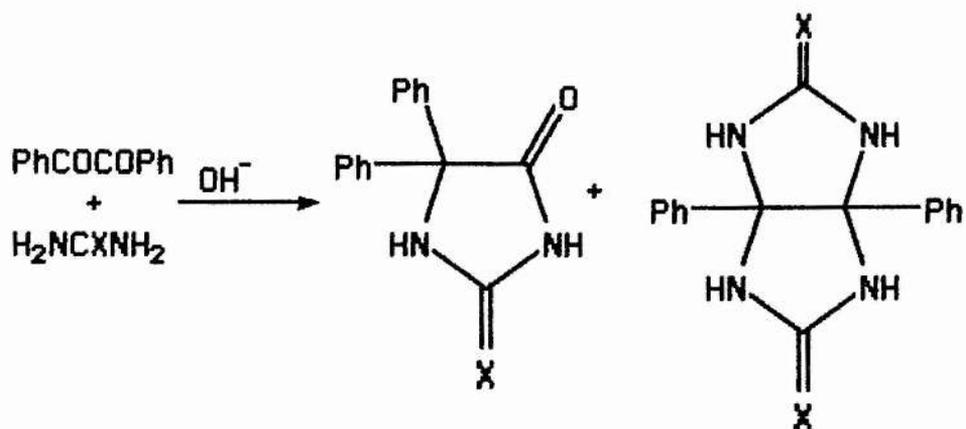
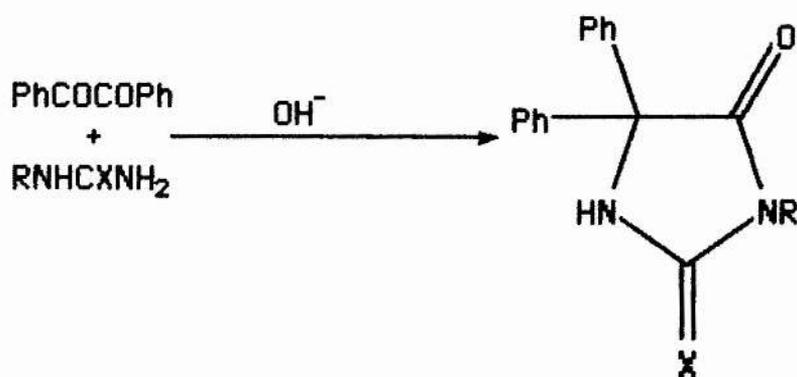
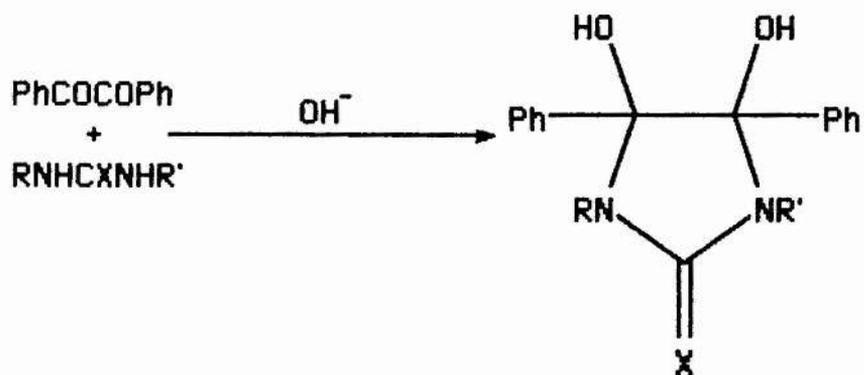
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Chapter 1

The base catalysed reactions of
thiourea, 1-substituted thioureas
and 1,3-disubstituted thioureas
with benzil and substituted benzils

Scheme 1



Introduction

An extensive investigation into the reaction of urea and N-alkylureas with 1,2 diketones has been reported¹. It is known that there are often significant differences between the reactions of ureas and thioureas and so it was decided to investigate the reactions of the latter with the diketone benzil, with the eventual aim of rationalising the effect of replacing oxygen by sulphur.

The base catalysed reaction of thiourea and N-substituted-2-thioureas with benzils gives a variety of products depending on the degree of N-substitution of the thiourea. When the thiourea has two secondary amine centres the product is a 1,3-disubstituted-4,5-diphenyl-4,5-dihydroxytetrahydroimidazole-2-thione. Ureas with two secondary amine centres yield analogous products (see scheme 1).

When the thiourea contains one primary and one secondary amino group the reaction has been employed to produce 3-substituted thiohydantoins, many of which are pharmacologically active, but the mechanism of this dramatic rearrangement has received little attention. We now report the results of a variety of mechanistic and stereochemical studies on this system, with particular reference to carbon-13 nmr spectroscopy applied to both static and dynamic systems. We propose a mechanism with features somewhat analogous to the benzilic acid rearrangement. The base catalysed reaction of 1-substituted ureas with benzil also yields analogous 3-substituted hydantoins. See scheme 1.

The reaction of benzil with thiourea itself gives 5,5-diphenyl-2-thiohydantoin but also a second product 3a,7a-diphenyltetrahydroimidazo(4,5-*d*)-imidazole-2,5-dithione. Again the base catalysed reaction between urea and benzil gives analogous products¹ as shown in scheme 1. We have studied the mechanism of the reaction of benzil with thiourea by a variety of techniques, of which the single most informative has undoubtedly been the application of carbon-13 nmr spectroscopy to the reaction as it proceeded utilising carbon-13 enriched substrate.

The key feature of the carbon-13 studies has been the direct observation of a very large number of intermediates along the reaction path or in equilibrium with species on the reaction path, in the case of thiourea some 14 intermediates, as well as two reagents and two products, have been either detected directly or inferred with a high degree of confidence from the data.

Scheme 2

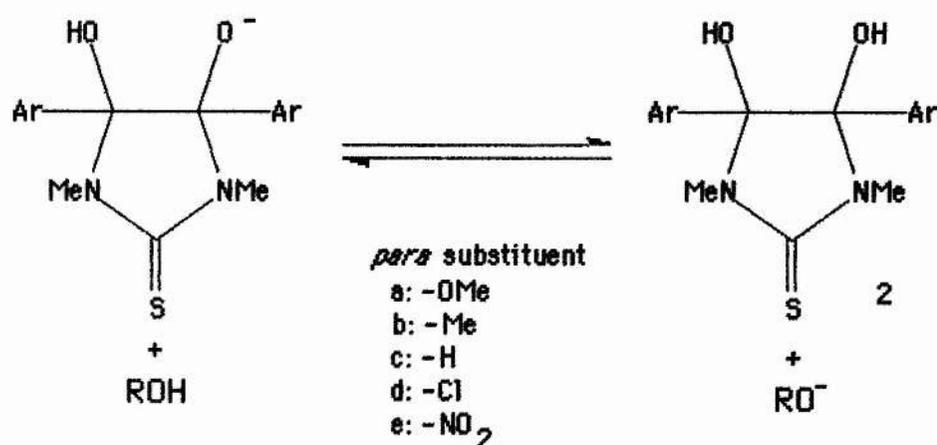
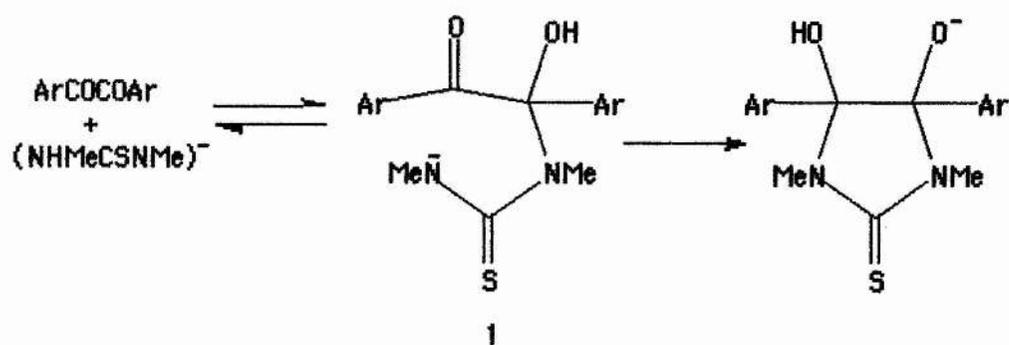
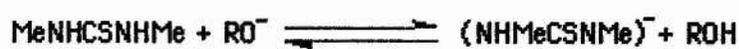
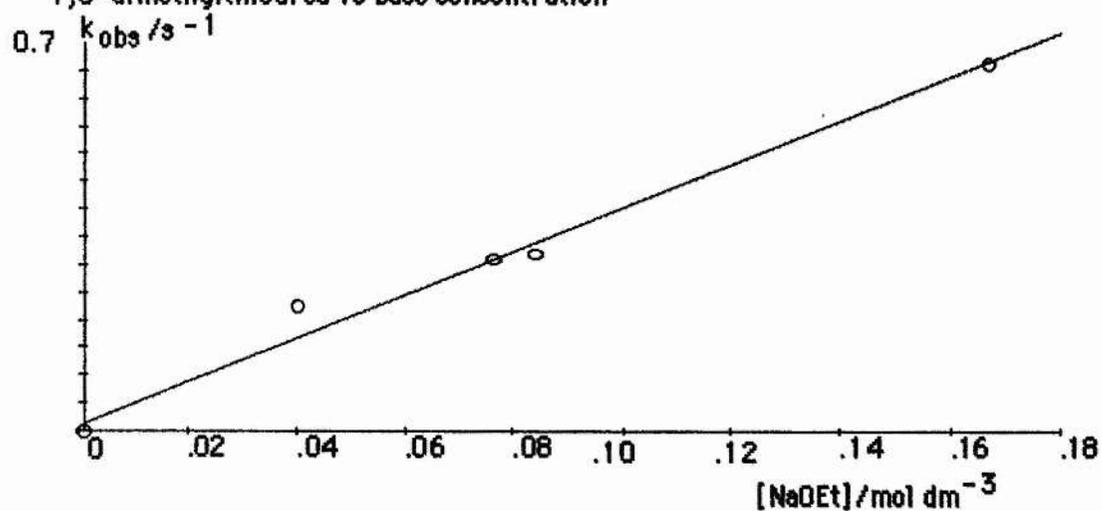


Figure 1

Variation of pseudo first order rate of reaction of benzil with 1,3-dimethylthiourea vs base concentration



Results and discussion

1,3-dimethyl-2-thiourea. - 1,3-Dimethyl-2-thiourea, benzil and base react in alcohol to give 1,3-dimethyl-4,5-diphenyl-4,5-dihydroxytetrahydroimidazole-2-thione (2) only, as Biltz² reported in 1908. The present studies confirmed that this product is formed rapidly and exclusively and that the reaction is reversible. The reaction was shown to be reversible by means of prolonged reflux of (2) in basic ethanol, which yielded a small amount of a red oil with an infra red spectrum identical to the product of refluxing benzil in basic ethanol, which is reported to be³ a mixture of benzoic acid, benzoin, benzaldehyde and ethyldibenzoin.

The equilibrium constants and the third order rate constants for the destruction of benzil for a number of 4-substituted benzils were determined by ultraviolet spectroscopy. The reaction shows a first order dependence on the concentrations of benzil, 1,3-dimethylthiourea and base, with nil reaction in neutral media, as shown in figure 1.

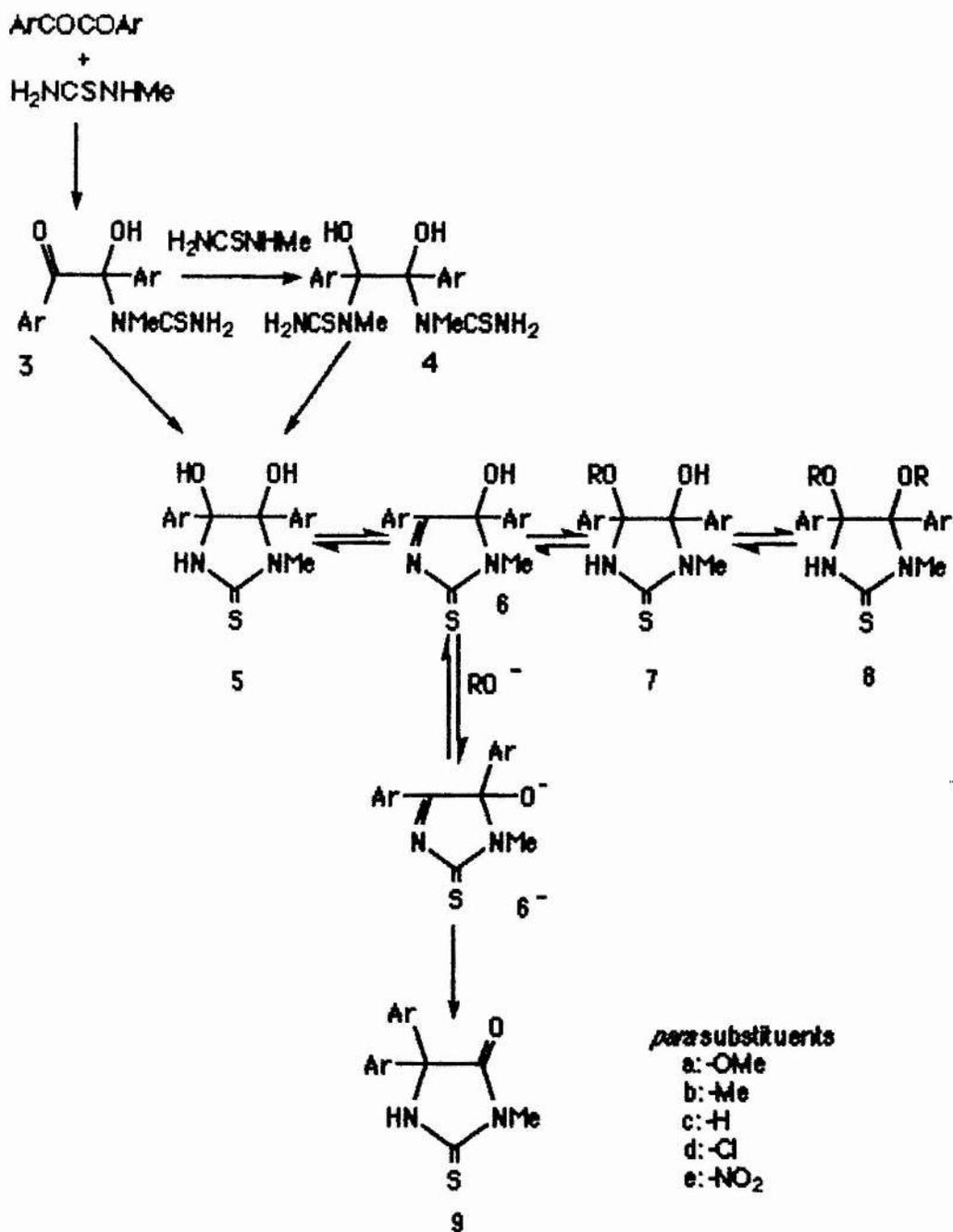
The rate of reaction and the equilibrium between (2) and the reagents are both reduced by the presence of electron donating aromatic substituents. The third order rate constant for benzil (first order in benzil, dimethylthiourea and ethoxide ion) is $4.40 \text{ s}^{-1} \text{ M}^{-2}$, for 4,4'-dimethylbenzil $0.37 \text{ s}^{-1} \text{ M}^{-2}$ and for 4,4'-dimethoxybenzil it is immeasurably small. The corresponding equilibrium constants are 25.0 M^{-1} for benzil and 0.54 M^{-1} for 4,4'-dimethylbenzil. It was not possible to detect any reduction in the absorbance of 4,4'-dimethoxybenzil at all. It was not possible to obtain rate or equilibrium constants for 4,4'-dichlorobenzil or 4,4'-dinitrobenzil spectrophotometrically. In the case of dichlorobenzil this was because (2d) was highly insoluble and precipitated out of solution and for dinitrobenzil because the absorption due to the nitroaromatic group swamped that of the carbonyl. We can however estimate

due to the nitroaromatic group swamped that of the carbonyl. We can however estimate minimum values of the equilibrium constants from the isolated yields which gives values of 3.0M^{-1} for dichlorobenzil and 4.0M^{-1} for dinitrobenzil. These results are completely consistent with the conclusions of Dietz and Mayer⁴ that the reaction occurs via nucleophilic attack by deprotonated thiourea upon the carbonyl centre of benzil followed by a rapid cyclisation.

The diol (2) can exist in two diastereoisomeric forms. It was shown by means of carbon-13 and proton nmr in the presence of a chemical shift reagent that the ratio of the E isomer to the more crowded Z isomer is approximately 2:1. The method will be discussed in detail under the stereochemistry heading at the end of this chapter.

If (2) was refluxed in basic ethanol for a prolonged period substitution of the hydroxyl groups by the solvent was observed, presumably via a nucleophilic substitution process.

Scheme 3



1-methylthiourea.—Refluxing 1-methylthiourea and benzil in basic alcohols again gives only one final product which is, as Biltz² stated, 1-methyl-5,5-diphenyl-2-thiohydantoin (9).

We propose the mechanism shown in scheme 3, based primarily on a series of carbon-13 nmr spectra taken during the course of the reaction. The first step is again nucleophilic attack by the N-methyl terminus of the thiourea anion on the carbonyl centre to give (3). The free amino group of the thiourea substituent can then be deprotonated and attack the remaining carbonyl centre of (3) to give (5). In contrast to the diol (2) produced from benzil and 1,3-dimethylthiourea, (5) can eliminate water to give (6). Utilising 4,4'-dinitrobenzil allows the isolation of (6e), possibly simply because the nitro substituents promote precipitation of the material. (6) can undergo solvent addition to give (7). If the reaction is halted after a few minutes (7) can be isolated in quite high yields, implying that none of the steps above is rate determining. The proton nmr of (7) shows a complex double doublet of quartets corresponding to the methylene centre of an ethoxy substituent attached to an asymmetric centre. Only one diastereoisomer can be detected. It was confirmed using a chemical shift reagent that, in contrast to the 1,3-dimethyl case, the product isolated was exclusively the less sterically crowded E diastereoisomer.

The rate determining step is a phenyl migration somewhat analogous to the benzilic acid rearrangement, although occurring under considerably milder conditions. Dissolution of (7) in neutral ethanol leads to the establishment, over approximately 10 minutes, of an equilibrium between (6) and (7). (6) is highly conjugated and thus absorbs strongly in the ultraviolet region. However, in the presence of a catalytic amount of base the equilibrium is established very rapidly and a base catalysed rearrangement to give (9) occurs slowly. The dependence of the rate constant upon

ethoxide ion concentration shown in figure 2 implies that the active species is the anion of (6). Whilst recognising the limits of the 'arrow' notation we feel that the mechanism shown, with the aromatic ring acting as a nucleophile and the charge displaced onto the sulphur, is a reasonably good representation of the somewhat unusual rearrangement.

The origin of the decrease in rate at higher base concentration is uncertain. The rate is independent of the concentration of an inert electrolyte, therefore ionic strength is not the determining factor. We suggest competition between nucleophilic attack by ethoxide anions on (6) and the rearrangement but are unable to substantiate the theory, although the dependence on ethoxide ion concentration of the rate of rearrangement of the diol (12), which has no ethoxy substituent, shows no such decrease.

Recent MNDO SCF-MO calculations on the benzilic acid rearrangement⁴ indicate that a single electron transfer pathway via a diradical anion is a energetically favourable process for benzil itself. However the presence of a large excess of tetrachlorobenzoquinone, which should react rapidly with any radicals present, has no effect whatsoever on the rate of the rearrangement in ethanol at a sodium ethoxide concentration of 0.10 M. This result could still be consistent with a very short lived diradical intermediate which rearranges too fast to react with the tetrachlorobenzoquinone but it will be difficult, if not impossible, to distinguish this possibility from a spin paired transition state.

The rate of reaction will show a complex dependence on the nature of the aromatic substituents since there will be two conflicting effects. An increase in the electron density on the aromatic group will increase its migratory aptitude, since the migrating group can be thought of as acting as the nucleophile "Ar⁻". On the other hand an increase in the electron density on the carbon atom to which the non-migrating aromatic substituent is attached will reduce its electrophilicity and slow the reaction.

Since the reaction shows a complex dependence on base concentration, a number of rate determinations at differing basicity would be required for each substituent. It was concluded that the information available would be of little mechanistic significance and did not justify the amount of time required. For thiourea the analogous reaction did show a limiting rate at high basicity and substituent effects were examined, although few conclusions could be drawn.

Since we are confident that the N-methylated end of the thiourea acts as the initial nucleophile, in theory it would be possible to use a series of unsymmetrically substituted benzils to prepare a number of materials of type (7) where the substituents on the migrating aromatic group (attached to the N-methyl side) are varied whilst the nature of the other aromatic is held constant. This would allow the two competing effects above to be separated. However preparation of a series of such benzils would be somewhat time consuming and the problem of the variation of the rate with base concentration would still have to be overcome.

Unfortunately, diol (12) formed from thiourea, which does show a limiting, base independent rate of rearrangement, cannot be used since it is possible for both of the aromatic groups to migrate. By labelling one of the carbons derived from the benzil carbonyl it would be possible to calculate the relative extent of migration of each of the two aromatics, but this would again be subject to both of the competing effects discussed above.

A number of other N-substituted 5,5-diphenyl-2-thiohydantoins were obtained utilising a variety of 1-substituted 2-thioureas including 1-phenyl and 1-(4-nitrophenyl)-thiourea.

The reaction was followed using carbon-13 nmr spectroscopy utilising benzil with 20% carbon-13 enrichment at the carbonyl position. The reaction was carried out in tetradeuterated methanol over a period of 16 hours, taking spectra at hourly

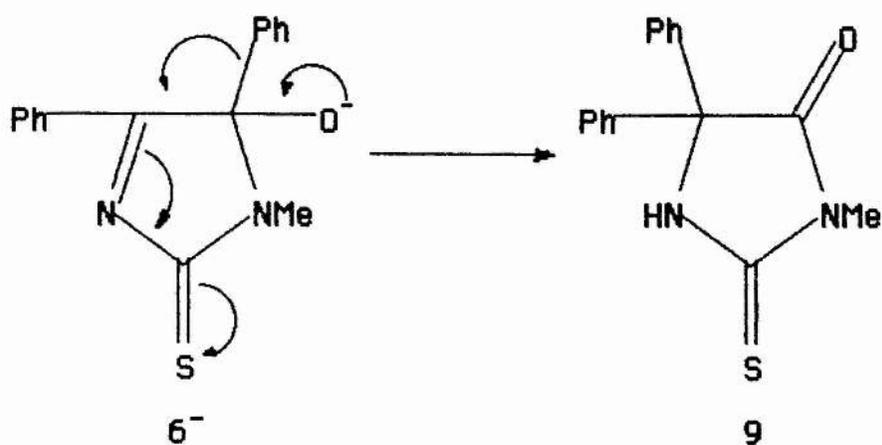
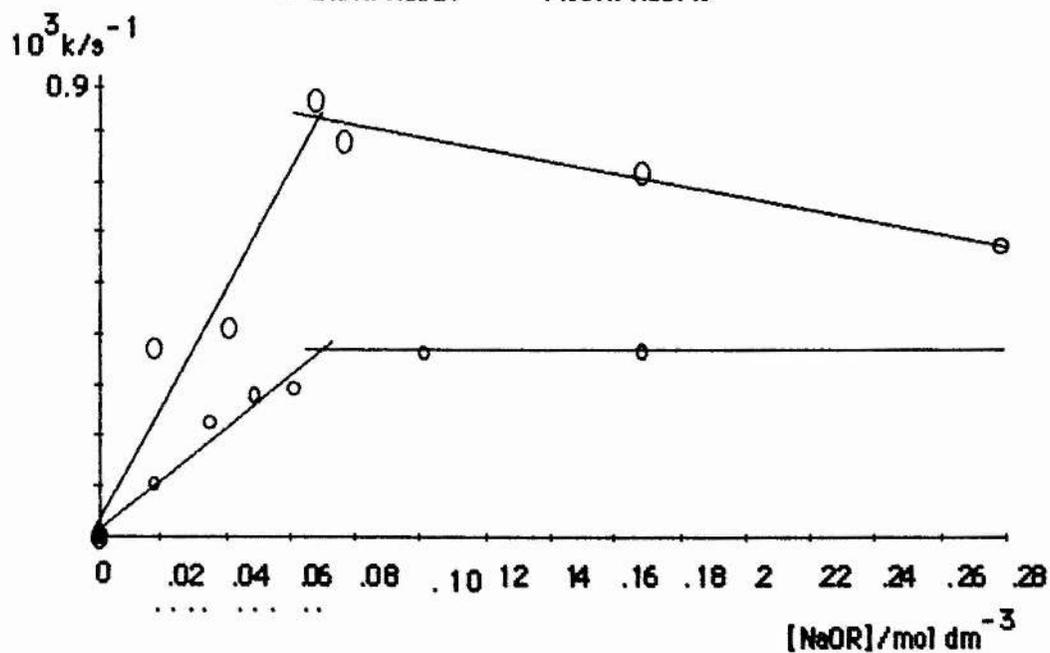


Figure 2

First order rate of rearrangement of (7) to (9) vs base concentration

○ EtOH/NaOEt ◐ MeOH/NaOMe



intervals. The results are summarised in figures 3 and 4 and are fully consistent with the mechanism shown in scheme 3.

The normalised variation with respect to time of each signal was compared to that of each of the other signals in turn. Signals which showed a high degree of correlation were presumed to correspond to either non-equivalent centres within the same substance or to different materials whose rate of equilibration was rapid in comparison to the hourly time difference between successive spectra.

Two experiments were carried out utilising identical reagent concentrations. In the first run at 25 centigrade no signals corresponding to the thiohydantoin (9) were detected after 16 hours. However at 40 centigrade the phenyl rearrangement proceeded readily so that after 16 hours (9) was the predominant component of the system. This result is consistent with the temperature dependence of the rearrangement of the diol (19) derived from thiourea and benzil to the thiohydantoin (23), which was studied over the range 30 to 50 centigrade by ultraviolet spectroscopy. The dependence followed an Arrhenius plot with an exponential term corresponding to an activation energy of approximately 105 Kilojoules per mole. This rearrangement was chosen in preference to that of (7) to (9) because it reaches a limiting rate which is independent of base concentration which must therefore correspond to complete deprotonation of (20), thus allowing us to neglect the effects of temperature on the ionisation of the unsaturated material. The two rearrangements are very closely related so it is reasonable to assume that the temperature dependence of the rate of rearrangement of (7) is similar. This result allows us to calculate that the rate of rearrangement at 40 centigrade is approximately eight times greater than at 25 centigrade. The results of the two carbon-13 studies are consistent with a temperature dependence equal to or larger than this value.

The signal at 194.46 ppm is unambiguously assigned to the carbonyl centre of benzil by means of a spectrum taken before the addition of the other reagents. At 40

Figure 3: successive carbon-13 nmr spectra during the base catalysed reaction of benzil and 1-methylthioureas at 25 centigrade

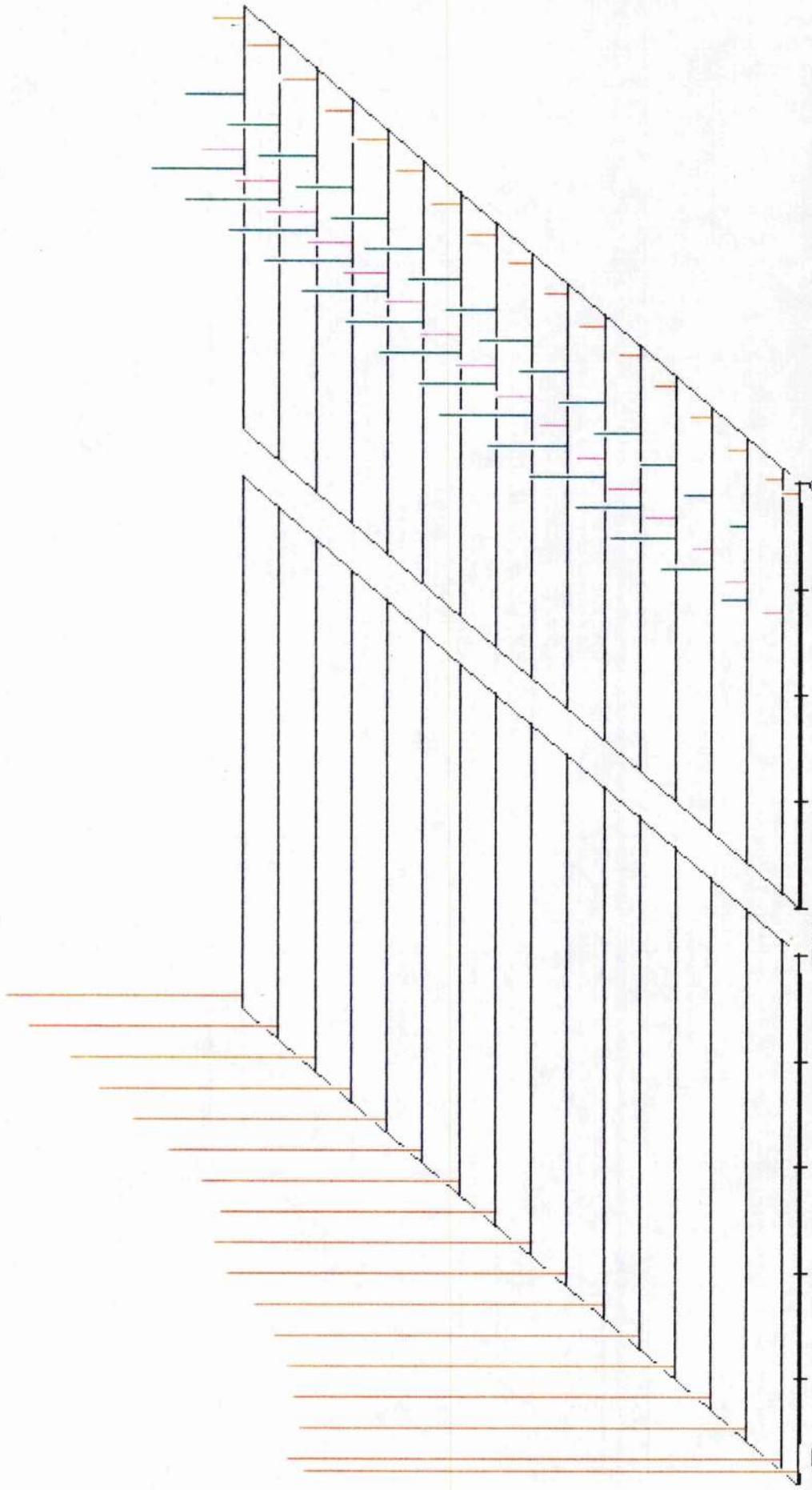


Figure 4: Successive carbon-13 nmr spectra over 18h during the reaction of benzil and 1-methylthiourea at 40 centigrade

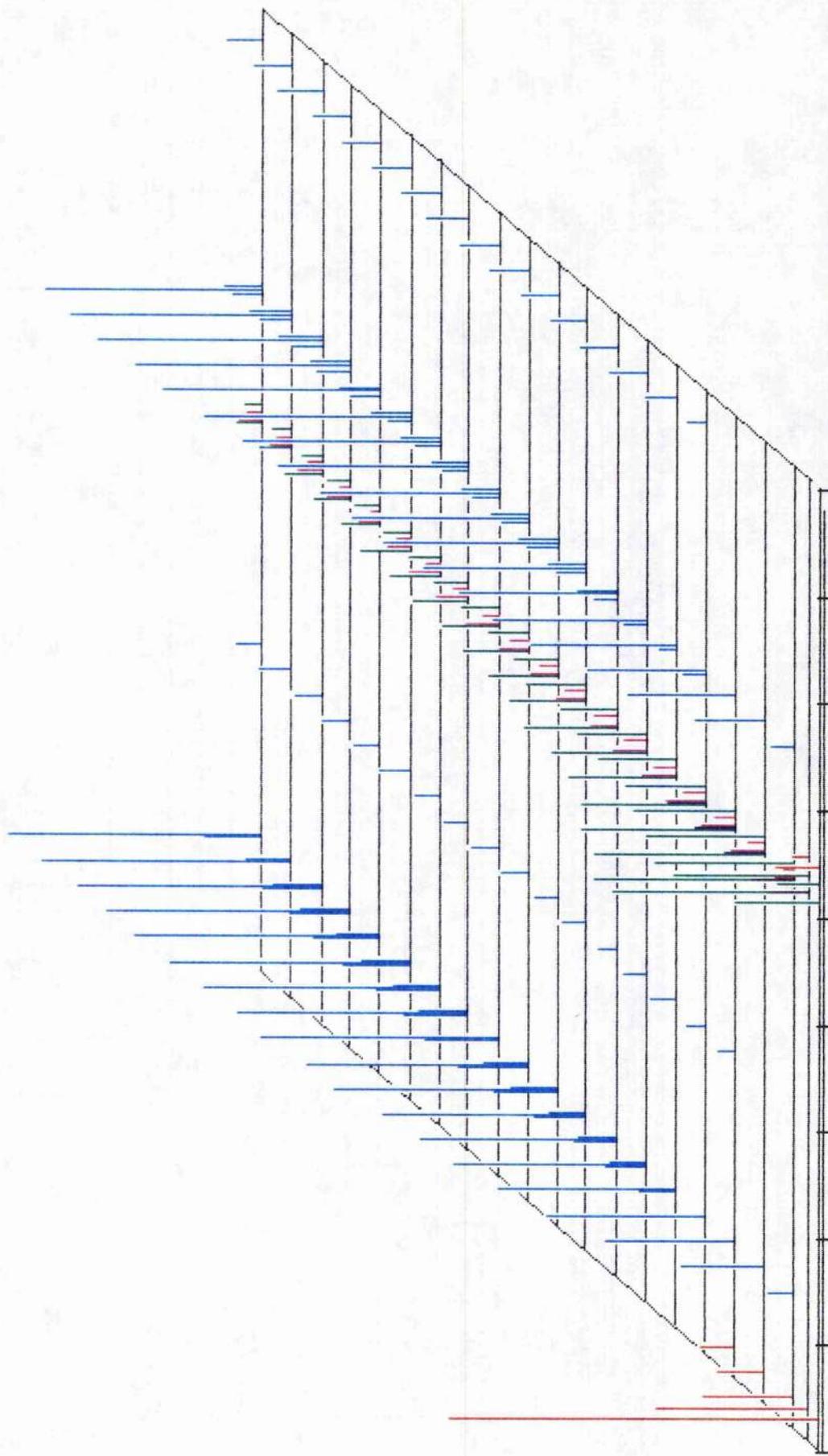
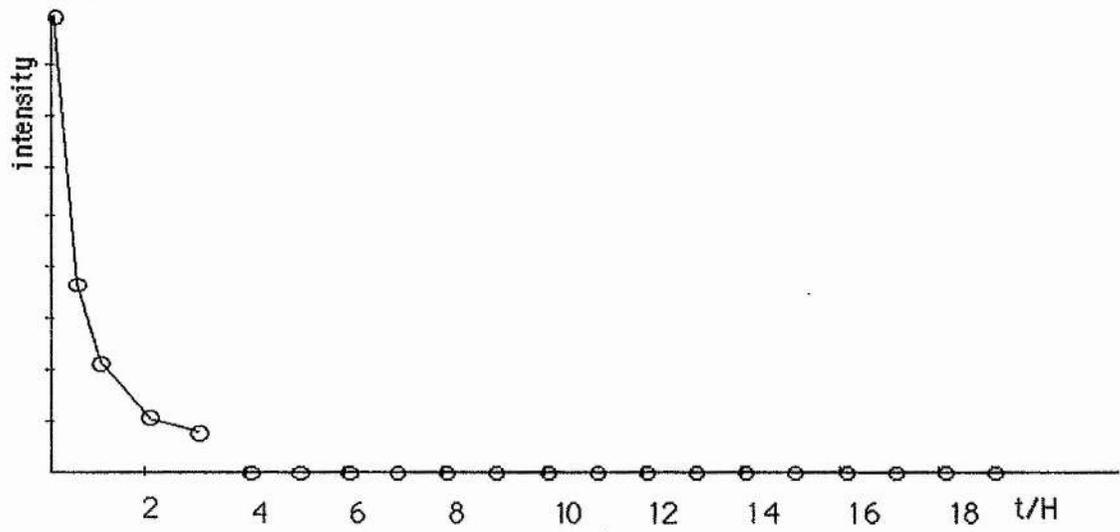
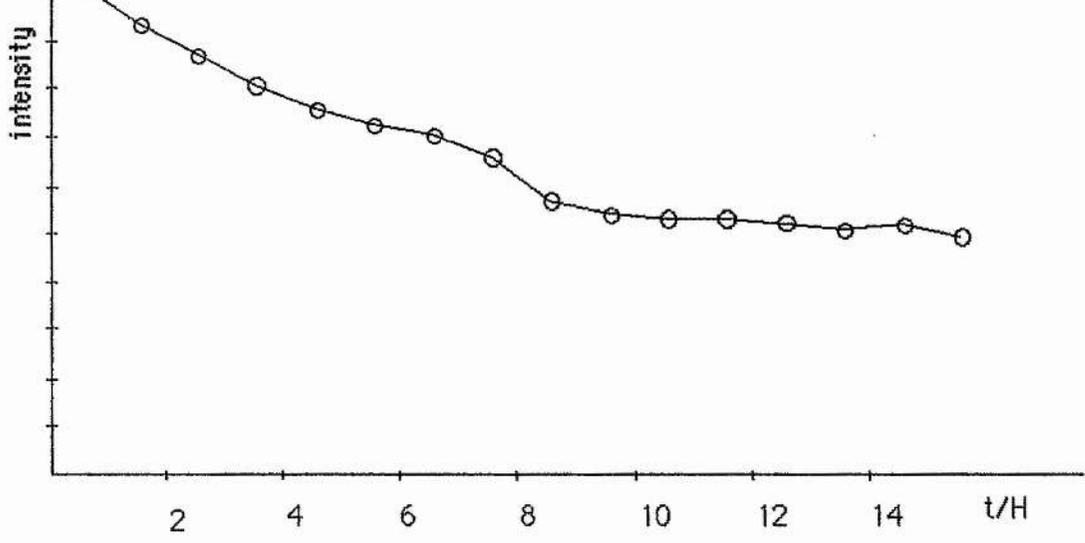


Figure 5: Variation of benzil carbonyl signal at 194.464 ppm during its base catalysed reaction with 1-methylthiourea at 40 C.



Variation of benzil signal at 194.5 ppm during its base catalysed reaction with 1-methylthiourea at 25 C

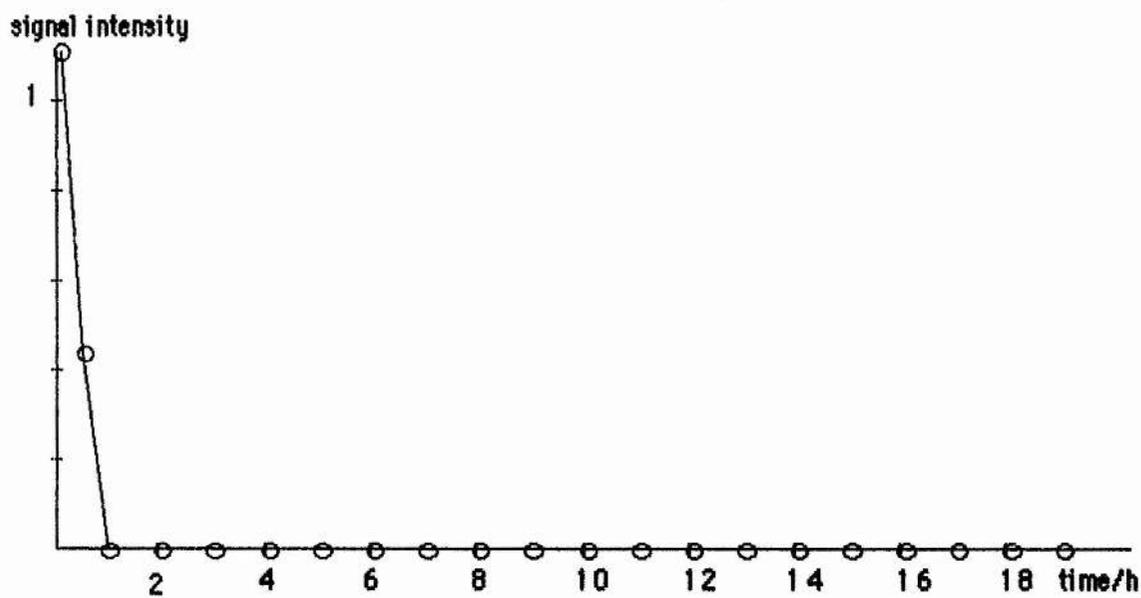


centigrade the signal intensity falls rapidly, becoming undetectable within the first 4 hours. However at 25 centigrade the intensity falls very slowly for the first 9 hours and then remains essentially constant at approximately half its original value, implying that an equilibrium condition has been attained between benzil and the intermediates (3), (4), (5) and (8). At 25 centigrade the rate of the phenyl migration step appears to be negligible. We cannot explain the curious 'hump' in the plot between 5 and 8 hours. See figure 5.

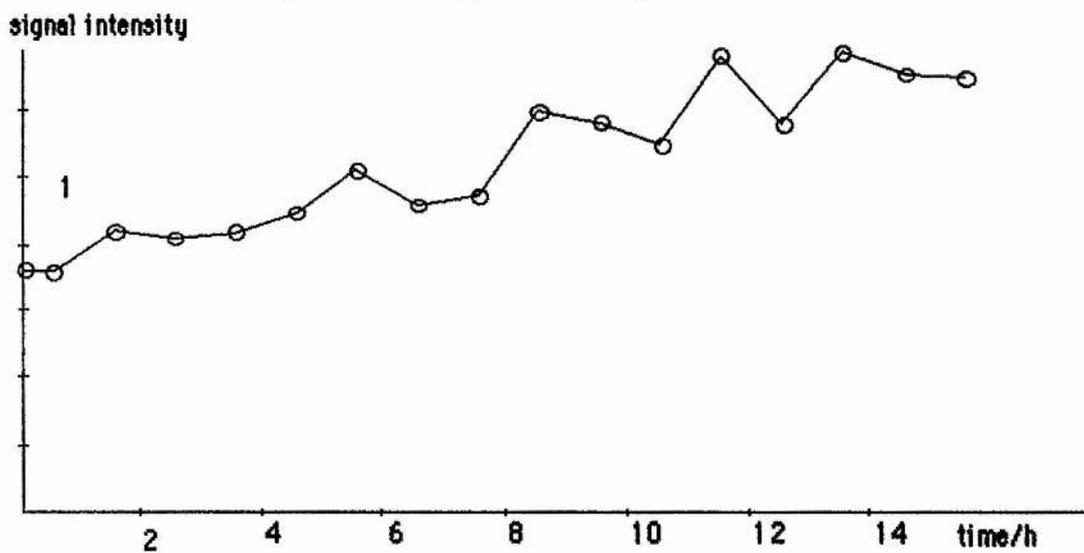
Dietz and Mayer ⁵ have shown that 2,2'-dimethoxybenzil is particularly X ref ↑ resistant to attack by the thiourea anion, presumably due to a combination of electronic and steric effects. Therefore it was predicted that 2-methoxybenzil would undergo attack readily on the phenyl substituted carbonyl but that cyclisation via attack on the methoxyphenyl substituted carbonyl would be slowed. It was thus hoped to isolate a material analogous to (3). In fact under conditions ranging from room temperature to reflux in methanol a mixture containing only reagents and product was obtained. The initial nucleophilic attack on the phenyl substituted carbonyl centre is known to be rapid at temperatures exceeding 40 centigrade from the nmr evidence below and from the rapid precipitation of (7) at higher reagent concentrations. Since no material analogous to (7) is isolated we know that the rate of cyclisation must be slowed. Hence the only explanation for our failure to obtain an analogue of (3) is that formation of (3) is a rapid but reversible process, with the equilibrium lying towards the reagents. We have spectroscopic evidence that none of the cyclic materials (2),(7) or (11) exists in equilibrium with benzil, thus the cyclisation step must be irreversible. On treating benzil with 1,1-dimethylthiourea no materials could be isolated other than the reagents, although low concentrations of a species analogous to (3) could be detected in the solution by carbon-13 nmr. This is also consistent with reversible formation of (3).

The cyclic diol (2) obtained by reaction of benzil and 1,3-dimethylthiourea, its

Figure 6
Variation of signal at 90.881 ppm at 40 centigrade



Variation of signal at 90.539 ppm at 25 centigrade

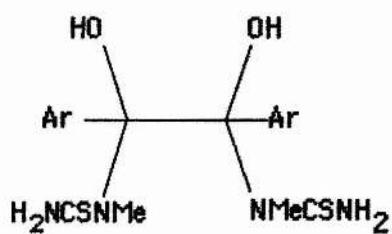
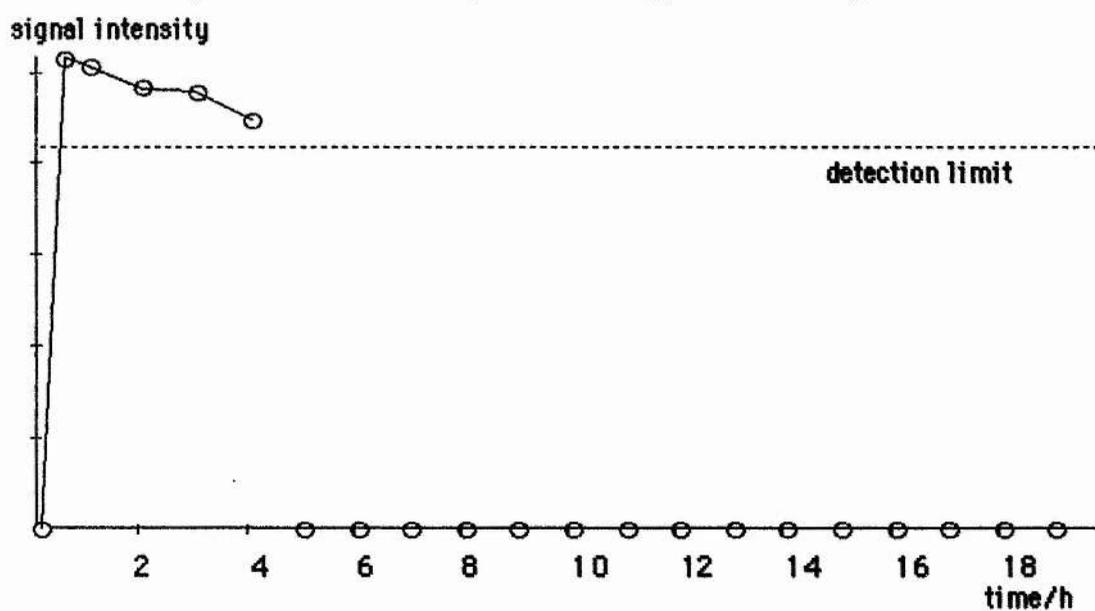


derivative obtained by methylation of the hydroxy groups and compound (7) have all been isolated and characterised. Their quaternary centres all show a carbon shift in the 90–100 ppm range. Thus it appears reasonable to assign all the shifts observed in this range during the course of the reaction to quaternary carbons of dihydroxytetrahydroimidazoles such as (2) and (5) or their methylated analogues, such as (7).

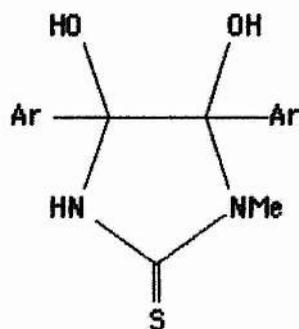
Methylation of the hydroxy groups of (2) increases the chemical shift of the quaternary carbons by 4.4 ppm from 96.0 ppm to 100.4 ppm in neutral solution. Unfortunately, the situation is complicated in basic media by the possibility of deprotonation of the alcoholic groups, leading to an increase in electron density. The equilibrium between the alcohol and the anion will thus affect the apparent shift of the alcoholic centres. Furthermore the basicity of the system changes during the course of the reaction, since 1-methylthiourea, (4), (5), (7) and (9) must all differ in the basicity of their amine centres. Thus the apparent shift of the alcoholic centres alters slightly during the course of the reaction.

The signal at 90.88 ppm at 40 centigrade and 90.54 ppm at 25 centigrade is not present before the addition of base to the mixture of 1-methylthiourea and benzil but it appears extremely rapidly when the catalyst is added. At 25 centigrade it attains approximately half its maximum intensity within the first 15 minutes and rises slowly until a constant value (allowing for the low signal to noise ratio of this low intensity peak) is attained after approximately 12 hours. However at 40 centigrade it attains its maximum value within 10 minutes and falls very rapidly thereafter, halving in intensity within 30 minutes and falling below the limit of detection within an hour. These results imply that the signal corresponds to an intermediate near the beginning of the reaction sequence. The shift corresponds to a carbon bearing hydroxyl and thiourea substituents, possibly an acyclic species. The assignment most consistent with both the chemical shift and the variation over time of the intensity and thus the concentration

Figure 7: Variation of signal at 97.42 ppm at 40 centigrade



4



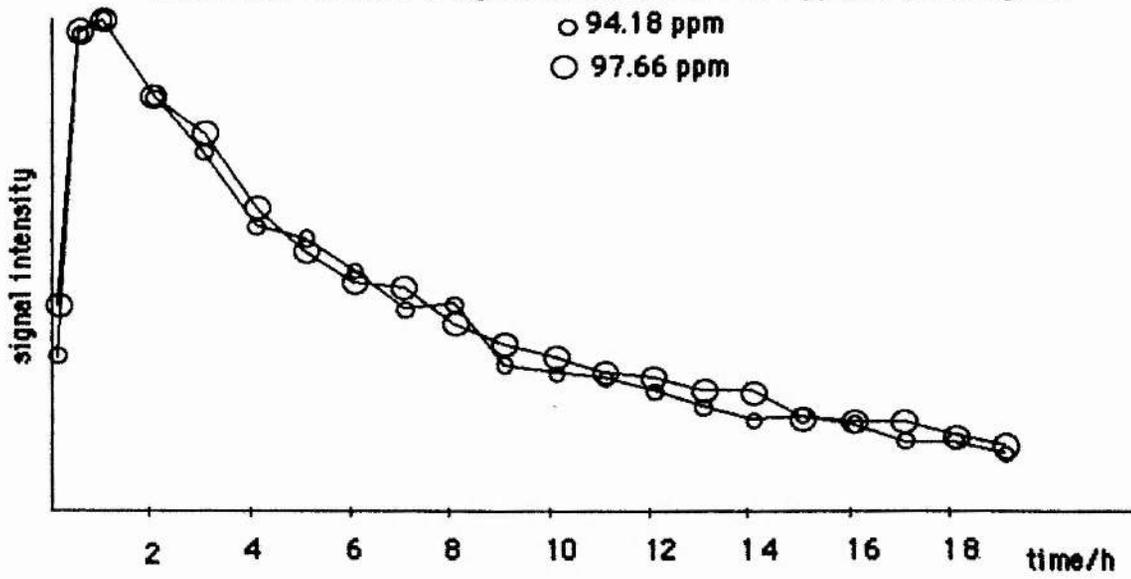
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is the quaternary centre of (3). No signal corresponding to the carbonyl centre of (3), with a parallel variation was detected. This can be rationalised in terms of NOE enhancement of the quaternary carbon's signal by the nearby protons of the methylamine and hydroxyl groups, given that this signal was itself near to the limit of detection. See figure 6.

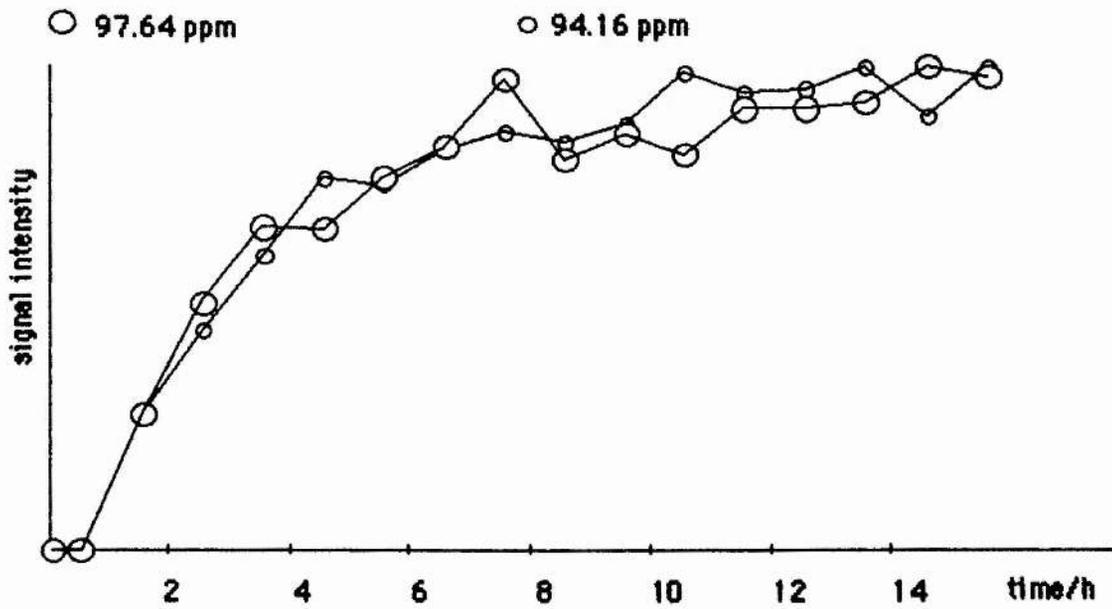
The signal at 97.42 ppm detected at 40 centigrade appears to have no analogous signal at 25 centigrade, which is somewhat surprising for an intermediate formed extremely rapidly at the higher temperature. The signal reaches its maximum value, which is again only just above the limit of detection, within the first 10 minutes and then falls slowly until it becomes undetectable. See figure 7. The chemical shift is again consistent with a carbon bearing one hydroxy or alkoxy and one thiourea substituent and again no signal showing a parallel variation could be detected. The two most plausible assignments for this signal are the quaternary carbon of (5) bearing an N-methyl substituent (assuming that the signal corresponding to the other centre is below the detection limit because the signal observed has a NOE enhancement due to the protons of the N-methyl group), or the two equivalent quaternary centres in (4).

Neither the observed shift or the variation over time allows us to distinguish between these possibilities. Both species would be predicted to be formed rapidly and to reach a fairly low maximum concentration. The cyclic diol (5) would be expected to be destroyed quite rapidly by dehydration across the carbon-secondary nitrogen bond followed by solvolysis of the imine to give (7) but a combination of rapid formation from benzil and rapid destruction could conceivably give rise to a slow fall in the overall concentration. The double adduct (4) would be expected to react much more slowly since it can only cyclise by a nucleophilic substitution reaction, which will be much slower than a base catalysed dehydration to an imine. The cyclisation reaction must take place with expulsion of the 1-methylthiourea anion because otherwise a bicyclic material analogous to (25) would be produced. No evidence for such a product

Figure 8
Normalised variation of signals at 97.66 and 94.18 ppm at 40 centigrade



Normalised variation of signals at 94.16 and 97.64 ppm at 25 centigrade



exists.

The surprising result that this signal is only detectable at the higher temperature can likewise be rationalised for both assignments. For (5) it can be assumed that its rate of formation via a nucleophilic attack on a carbonyl centre has a higher temperature dependence than the rate of the base catalysed dehydration. A higher concentration of (3) at higher temperatures can be rationalised by considering the favourable entropy of activation for an intramolecular cyclisation reaction compared to an intermolecular reaction. This is primarily a rotational term and thus at normal temperatures will be essentially invariant with temperature. Therefore as the temperature increases the intermolecular reaction will become less disfavoured with respect to the intramolecular one.

The signals at 97.65 ppm and 94.16 ppm show an excellent degree of correlation in experiments at both 25 and 40 centigrade. At 25 centigrade the signals increase more slowly than that due to (3), reaching an essentially constant level after approximately eight hours. No signals corresponding to the thiohydantoin (9) were detected in this experiment. In contrast at 40 centigrade the maximum intensity is reached within two hours and the signals then decrease smoothly. The decrease correlates well with a first order decay with a rate constant of approximately $4.3 \times 10^{-5} \text{ s}^{-1}$. This decay shows an excellent correspondence with the signals corresponding to 5,5-diphenyl-3-methyl-2-thiohydantoin (9), which increase by a first order process with a very similar rate constant. Thus we may conclude that these signals correspond to an intermediate which is in very rapid equilibrium, compared to the interval between spectra, with the dehydrated intermediate (6) which rearranges by a first order process into the thiohydantoin (9). The chemical shifts are consistent with the quaternary centres of (7), which has been shown spectroscopically to be in extremely rapid equilibration with (6) which rearranges by a first order process to give (9). Hence the signal at 97.65 ppm is assigned to the methoxy substituted carbon

Figure 9: normalised variation of signals at 174.75 and 72.50 ppm at 40 Centigrade

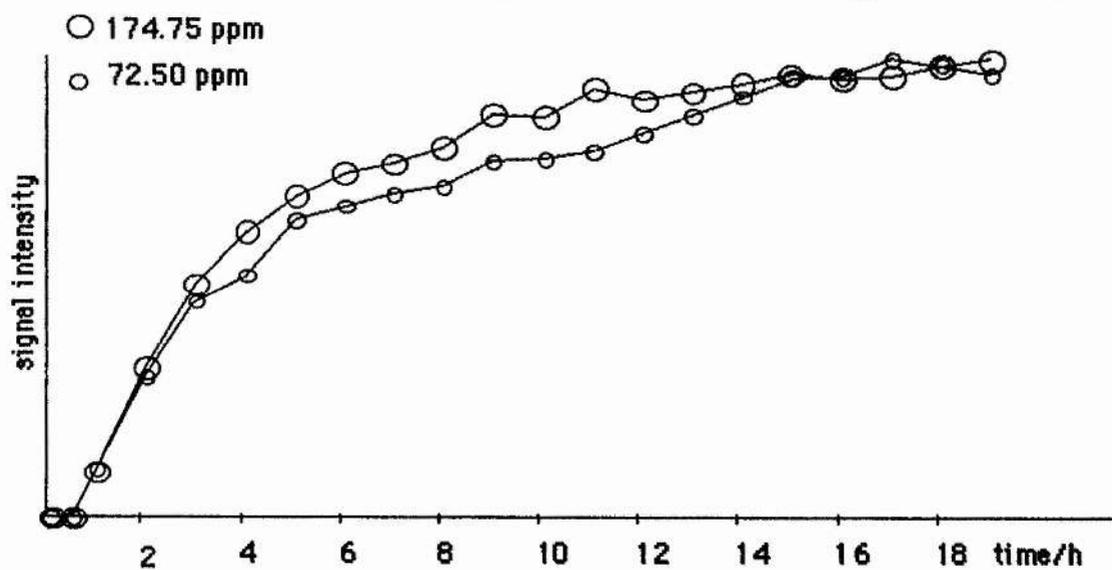
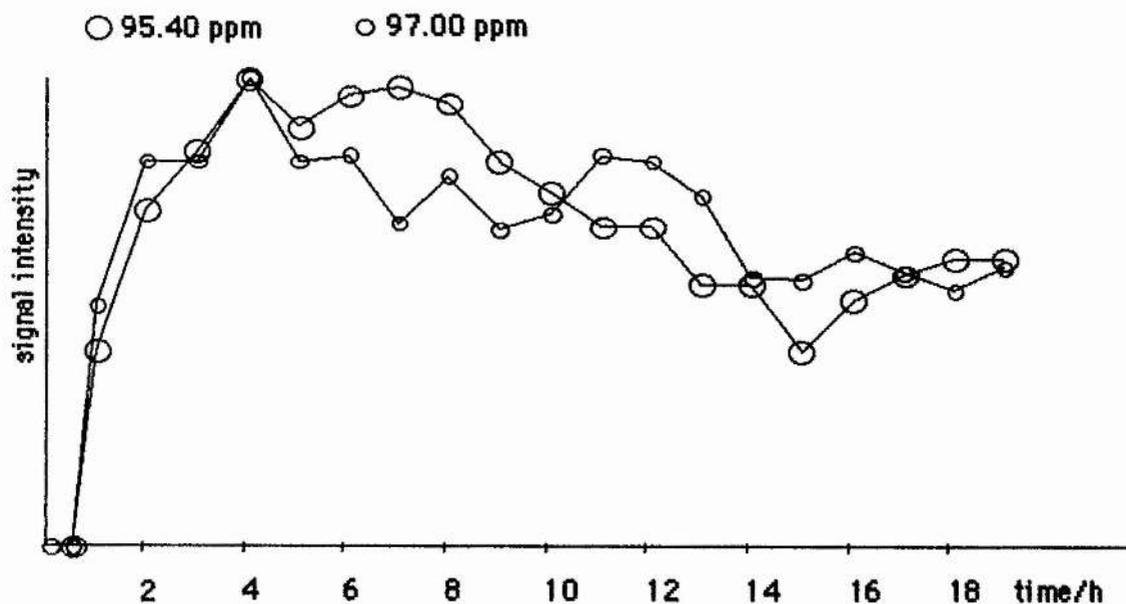


Figure 10: normalised variation of signals at 95.40 and 97.00 ppm at 40 centigrade



and the signal at 94.16 ppm to the alcoholic carbon of (7).

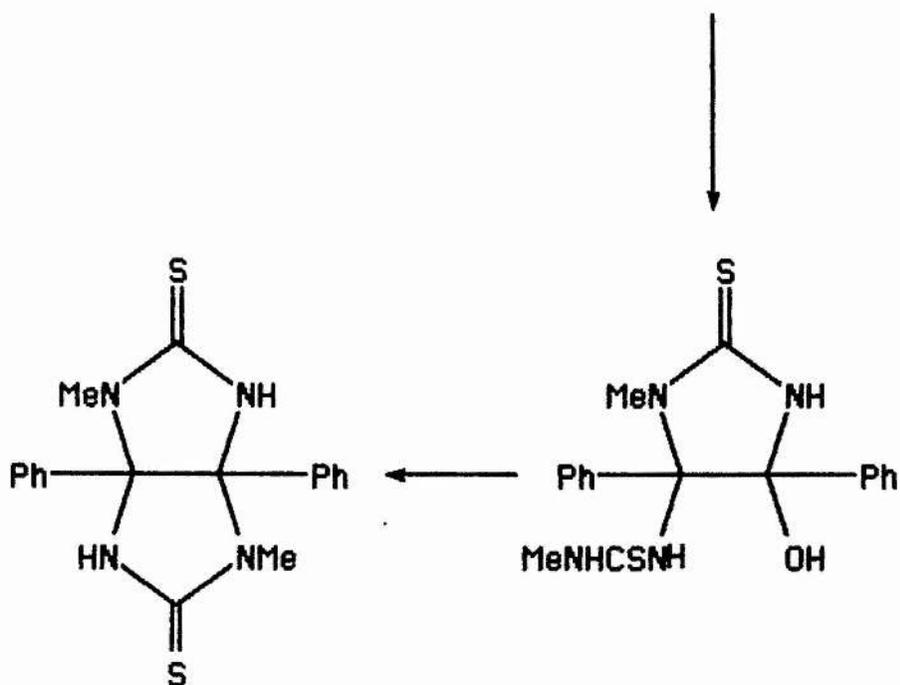
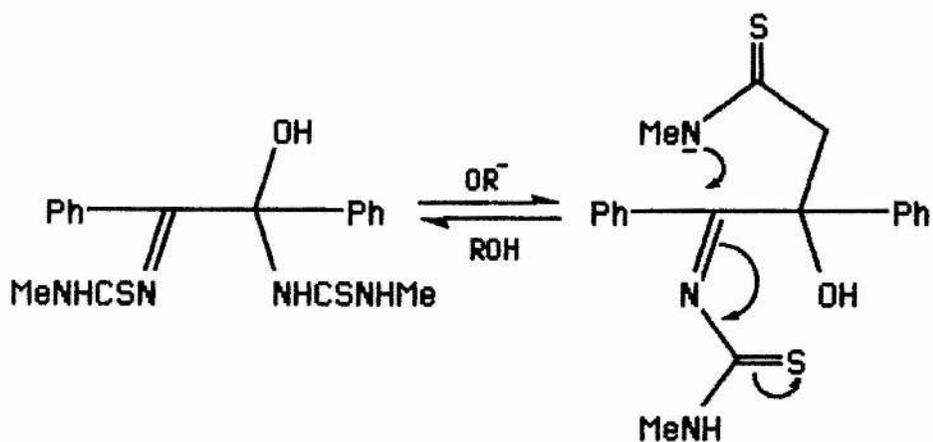
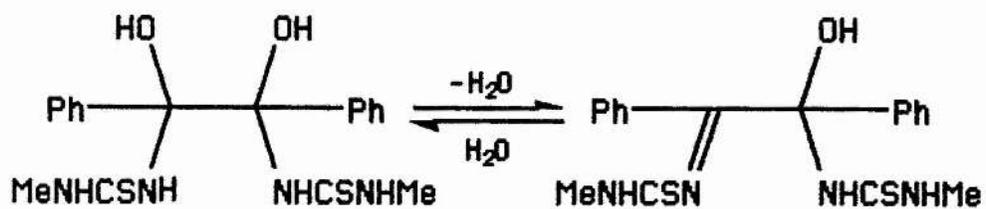
No signal in the region corresponding to an imine centre, such as that of (6), were detected. This implies that the concentration of (6) in the system is extremely low and thus that the equilibrium between (6) and (7) lies very far towards the solvated species.

Four signals at 174.75 ppm, 139.0 ppm, 73.5 ppm and 26.12 ppm all show a high degree of correlation and all appear only in the experiment run at 40 centigrade. All four signals correspond to the spectrum of 3-methyl-5,5-diphenyl-2-thiohydantoin, being assigned to the carbonyl centre, the ipso carbon of the two phenyl groups, the quaternary carbon bearing the two phenyls and the N-methyl group respectively. The thiohydantoin signals increase following a first order rate law as discussed above. The absence of thiohydantoin at 25 centigrade is consistent with spectroscopic studies which showed that at 25 centigrade the rate of the base catalysed rearrangement of (6) to (9) is negligible. See figure 9.

Two more signals are observed in the region characteristic of the quaternary carbons of the cyclic diols at 95.4 and 97.0 ppm. At 25 centigrade the intensity of the signals increases slowly throughout the period studied at a rate considerably lower than the signals due to (7). At 40 centigrade the signals again increase in intensity much more slowly than those due to (7), reaching a maximum after approximately four hours and then falling very slowly throughout the remainder of the period studied. See figure 10. The diol (5) will be formed more rapidly than (7), thus these signals definitely do not correspond to (5).

The rate of formation could imply that these signals correspond to a material formed via (7) and the slow rate of destruction at 40 centigrade implies that it is not in a rapid equilibrium with (6) compared to the interval between spectra. However no material other than the thiohydantoin has been isolated as a product, so the material must eventually rearrange either to (6) or (7) or directly to (9). The most

Scheme 4



reasonable assignment of these two signals is to the material (8) formed by a direct nucleophilic substitution of the hydroxyl group of (7) by a methoxide ion. This process will be slow in comparison to the process of dehydration followed by solvolysis which leads to the extremely rapid solvolysis of (5). The methoxy group can itself undergo nucleophilic attack by water to regenerate (7). The rearrangement of (7) to (9) releases one mole of water per mole of thiohydantoin so as the reaction proceeds the water content of the system will increase and therefore so will the likelihood of (8) being hydrolysed to (7). The diol (2) prepared from benzil and 1,3-dimethylthiourea in refluxing basic ethanol shows approximately 5% replacement of the hydroxyl group by solvent after two hours reaction.

No bicyclic product analogous to (25) is obtained using 1-methylthiourea, which is consistent with attack by the secondary amino group on the carbonyl centre first, followed by cyclisation. If the primary group attacked then it would be possible for the product to dehydrate and then undergo attack by a second thiourea to give a material analogous to (18) which could then cyclise via dehydration followed by an intramolecular Micheal reaction (see scheme 4). It was shown that the absence of a bicyclic product is not due simply to the lower nucleophilicity of the N-substituted thiourea allowing intramolecular cyclisation to compete more effectively with attack by a second thiourea to give (4) by using a ten fold excess of 1-methylthiourea with respect to benzil. No bicyclic product was observed.

1,1-Dimethylthiourea. - It was not possible to isolate any material generated by reaction between 1,1-dimethylthiourea and benzil or any substituted benzil. After two hours reflux in basic ethanol the only materials obtained were benzil, 1,1-dimethylthiourea and a red oil with properties identical to the product obtained by refluxing benzil alone in basic ethanol.

It did, however, prove possible to detect a number of materials existing in equilibrium with benzil and 1,1-dimethylthiourea in basic methanol by means of carbon-13 nmr, again utilising benzil enriched to 20% carbon-13 at the carbonyl position.

Signals of low intensity compared to that of the benzil carbonyl centre with shifts corresponding to centres with one phenyl, one thiourea and one methoxy or alcoholic substituent were detected at 96.05 ppm, 95.34 ppm and 95.04 ppm. Signals of similarly low intensity corresponding to centres with one phenyl and two thiourea substituents were also detected at 87.79 ppm, 87.63 ppm and 86.87 ppm.

These results are most consistent with the series of equilibria shown in scheme 5, assuming that the dehydrated materials (11) and (14) are present at undetectably low concentrations and also that the signals due to the carbonyl centres of (10) and (12) are not observed because they lack the nuclear Overhauser enhancement of the quaternary centres caused by the protons on the adjacent nitrogen and oxygen atoms. It should also be noted that (10), (13) and (15) can all undergo dehydration followed by solvolysis to give materials where the alcoholic group has been replaced by a methyl ether. It is known from the methylation of (2) that this replacement causes a change in chemical shift of approximately four ppm, therefore the signals observed, with no more than one ppm separation between them, cannot correspond to hydroxy and methoxy substituted forms of a single one of the species shown in scheme 5. Although the scheme shows the alcoholic forms only for simplicity, the rate at which the similar carbon centre of (7) undergoes dehydration and solvolysis implies that we are in fact observing

the methyl ether derivatives only. Furthermore, the dithiourea substituted centre of (15) has a 25% greater signal intensity than the other centre. However a thiourea substituent and a hydroxyl group both bear a single proton in very similar positions relative to the substituted centre and therefore should give rise to similar nuclear Overhauser enhancements. However if the hydroxyl group has been replaced by a trideuterated methoxy substituent no enhancement will occur because the sample is not being irradiated in the deuterium transition frequency range. Hence the signal at 96.05 ppm is assigned to the quaternary centre of (10) or its methylated analogue, that at 95.34 ppm to the two equivalent centres of (13) and the signal at 95.04 ppm to the alcoholic or methoxy substituted centre of (15). The signal at 87.79 ppm is assigned to the centre of (12) bearing two pendant thioureas, the one at 87.63 ppm to the similar centre of (15) and the signal at 86.87 ppm to the two equivalent quaternary centres of (16).

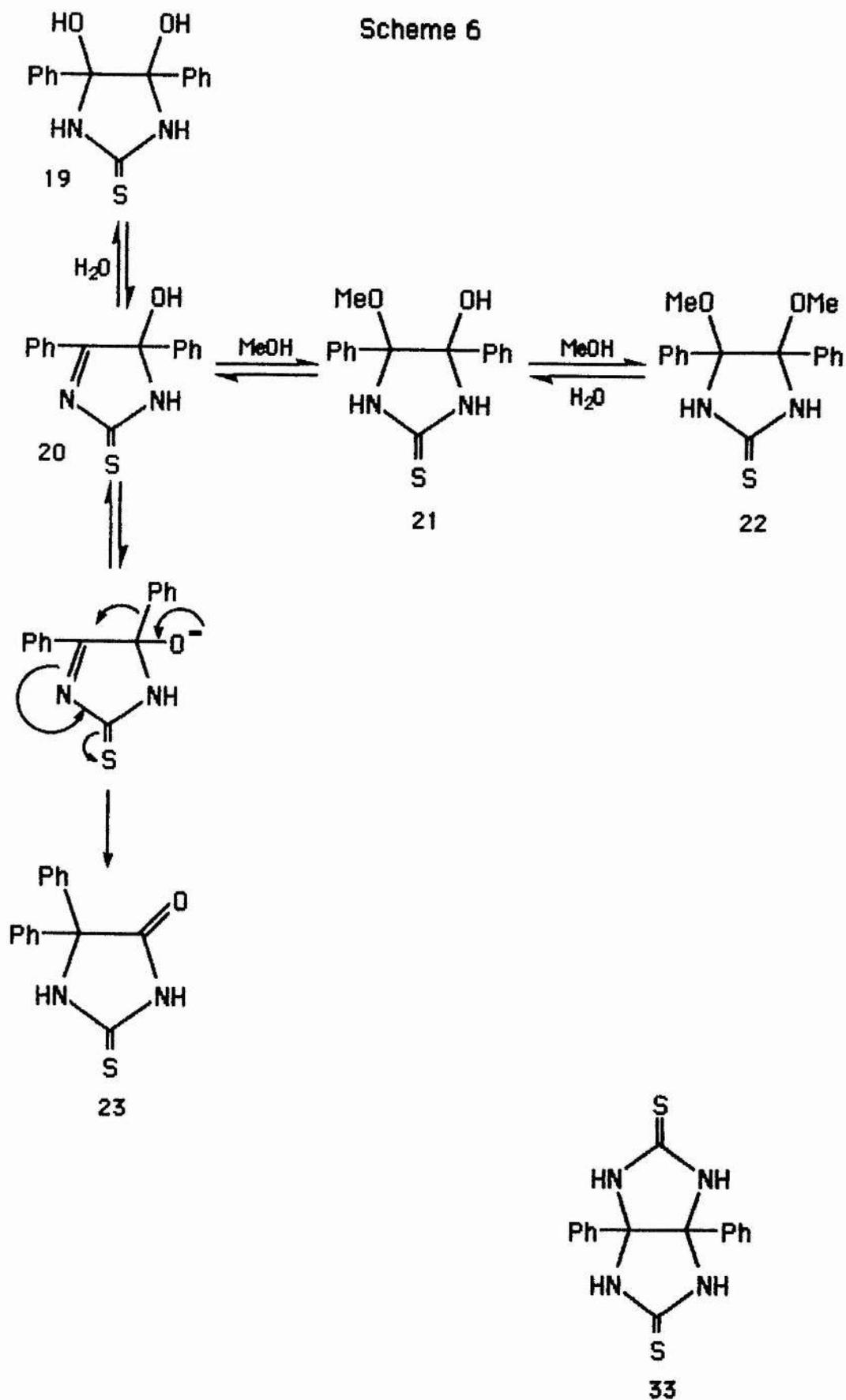
It is not possible to evaluate accurate equilibrium constants for this series of reactions from the relative intensities of these signals and that of benzil because of the differences in nuclear Overhauser effects between the different centres discussed above. However, maximum values of the species' concentrations with respect to benzil can be obtained if we assume that the enhancement is negligible, which we know to be incorrect because if this were so we would observe signals due to the carbonyl centres of (10) and (12) and also because the two quaternary centres of (15) give signals of different intensity. The observed intensities are summarised in table 1.

TABLE 1

compound	mean signal intensity (benzil=1.000)
(10)	0.010
(12)	0.015
(13)	0.020
(15)	0.017
(16)	0.015

We cannot explain why the equilibrium constant for the reaction of (10) and 1,1-dimethylthiourea to give (13) is so much larger than that for the reaction of dimethylthiourea and benzil to give (10). The rate of the reverse, thiourea elimination, reaction should be very similar in each case, thus attack by dimethylthiourea on the second carbonyl of (10) must be favoured in comparison to attack on one of the carbonyls of benzil. It is difficult to explain this since (10) will be more sterically hindered than benzil and the carbonyl centres of benzil will be, if anything, more electrophilic than that of (10) due to the inductive removal of electrons by the adjacent carbonyl group. There is little evidence to suggest that the two adjacent carbonyls have a strongly stabilising interaction and indeed some to suggest that in solution they are not coplanar and thus cannot interact mesomerically at all. The only plausible rationalisation for the higher rate of attack by dimethylthiourea on (10) than benzil is some form of anchimeric assistance by the pendant dimethylthiourea, possibly through one of the nitrogens acting as a hydrogen bond donor or acceptor.

Scheme 6



Thiourea.—Thiourea reacts with benzil under basic conditions in alcohol to give a mixture of the two products 5,5-diphenyl-2-thiohydantoin (23) and 3a,7a-diphenyltetrahydro-imidazo(4,5-*d*)imidazole-2,5-dithione (33) as Biltz² reported.

As in the case of 1-methylthiourea, it proved possible to isolate an intermediate from the reaction mixture after a few minutes gentle warming. However in this case the glycol (19) was obtained rather than the products of solvolysis (21) or (22). Carbon-13 nmr on the dynamic system later showed that the rate of (19) formation is much greater than its rate of dehydration and attack by the solvent.

The mechanism of (23) production from the glycol (19) is exactly analogous to that for (9) described in the previous section, ie dehydration to give (20) and then a benzylic acid type rearrangement. The rearrangement could again be followed by ultraviolet spectroscopy from the rate of destruction of the conjugated and highly chromophoric species (20), which exists in rapid equilibrium with (19). The rate again shows first order dependence on base up to a limiting rate of $3.65 \times 10^{-3} \text{ s}^{-1}$, approximately half that for (7). But, in contrast to (7), there is no decrease in rate at higher ethoxide concentration. This is good evidence that the rate decrease is due to a pre-equilibrium between (7) and (6) plus free ethoxide ions. See figure 11 and scheme 6.

In methanol, using sodium methoxide as base, the limiting, base independent, rate constant is $4.3 \times 10^{-4} \text{ s}^{-1}$, which is approximately an order of magnitude less than in ethanol. This may be because the less sterically hindered alcohol can attack the carbon-nitrogen double bond more readily.

Except for the case of 4,4'-dimethylbenzil, it proved impossible to isolate materials analogous to (19) when 4,4' disubstituted benzils were used. The rate of rearrangement for the 4,4' dimethyl compound (19b) reached a limiting value of

Figure 11: Rate of (23) production from (19) vs sodium ethoxide concentration

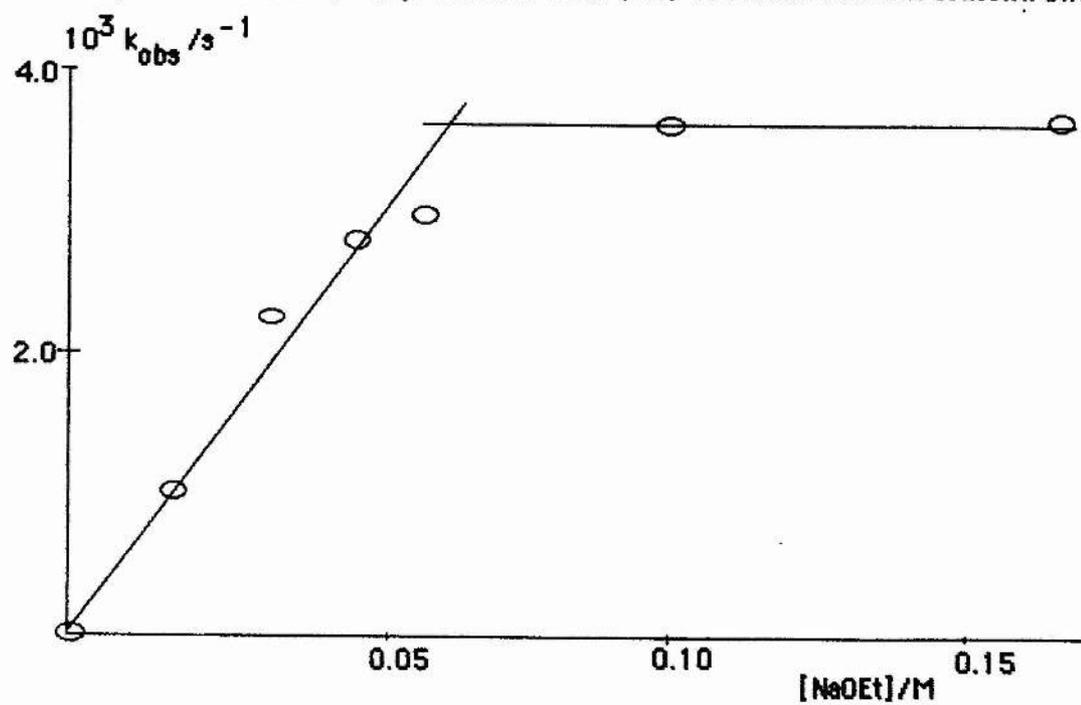
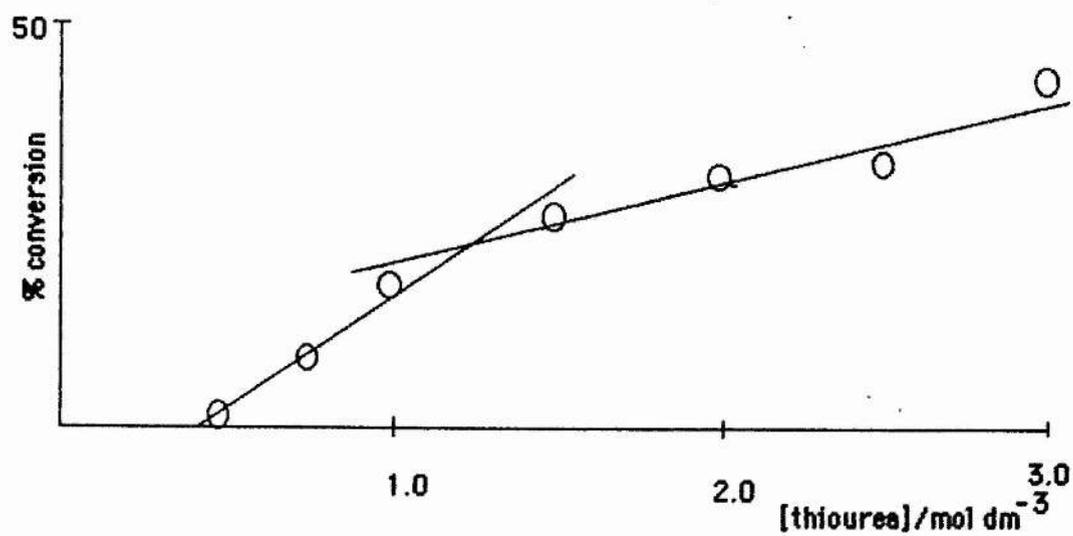


Figure 12: Percentage of benzil converted into (33) vs thiourea concentration
initial [benzil]=1.00 M, [NaOH]=0.50 M in 90% aqueous ethanol



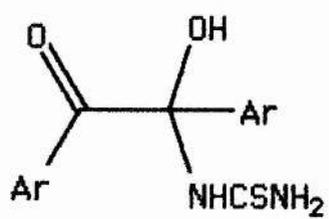
approximately one third of the rate for the unsubstituted material (19c). The limiting rate was reached at a lower basicity and again does not decrease at higher base concentrations. No mechanistic conclusions can be drawn from this result because of the competing effects discussed for 1-methylthiourea above. In contrast to 1-methylthiourea, thiourea did not react with 4,4'-dinitrobenzil at all, thus no compound (20e) analogous to (6e) could be obtained. The temperature dependence of the first order rate of rearrangement of (19c) to (23c), under conditions where the limiting, base independent, rate has been reached, is shown in table 2. The results correspond to an Arrhenius plot with an activation energy of approximately 105 KJ mol⁻¹. The rate was obtained by monitoring the rate of destruction of (20) by uv spectroscopy at 383nm at a sodium ethoxide concentration of 0.1 molar and an initial concentration of (19) of approximately 0.001 molar.

TABLE 2

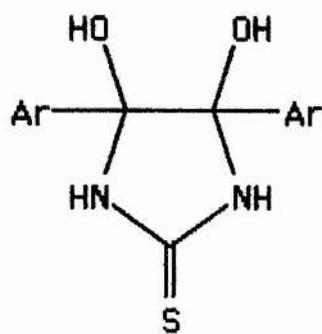
T/Kelvin	10 ⁴ k _{lim} /s ⁻¹
294.0	4.7
299.2	12.9
310.7	51.8
316.3	91.4

Somewhat surprisingly (33) is not formed via nucleophilic substitution of the hydroxyl groups of (19) by thiourea. This was proved by refluxing (19) in basic ethanol together with a five fold excess of thiourea. Only the product of the benzilic acid rearrangement, the thiohydantoin (23), was obtained and no trace of (33) was detected. The extremely low solubility of (33) in ethanol makes it highly likely that even trace amounts could be readily detected.

The yield of (33) increases with the concentration of thiourea even when the stoichiometric ratio of thiourea to benzil is greatly exceeded(see figure 12). The yield



17



19

is reduced by the presence of a nucleophile such as water and increased by using a more sterically hindered alcohol up to a limiting value of approximately 70% yield for both *n* and *t*-butanol. All these observations are consistent with competition between thiourea and the solvent (or water) to attack an electrophilic centre to give intermediates leading to (23) or (33) respectively.

The ratio of (33) to (23) produced depends on the nature of the aromatic substituents as shown in table 3. Given the complexity of the system no straightforward explanation of these results can be given. The yields are quite consistent with those obtained for the base catalysed reaction of urea and 4,4' substituted benzils in this laboratory and elsewhere^{1,4}.

TABLE 3

4,4' substituents	yield (33) /%	yield (23) /%
OMe	0	6.0
Me	26.7	34.0
H	34.6	63.4
Cl	32.0	50.5
NO ₂	0	0

Under the same conditions using 2-methoxybenzil yields of 2.8% of (33) and 12% of (23) were obtained. It has been shown⁴ that 2-methoxy aromatic substituents decrease the susceptibility of the carbonyl centres of 2,2'-dimethoxybenzil to nucleophilic attack by urea and thiourea. Therefore it was hoped that 2-methoxybenzil might undergo rapid attack at the carbonyl adjacent to the unsubstituted phenyl but much slower attack at the other carbonyl, allowing us to isolate a material of type (17).

Furthermore, had we succeeded in isolating the analogue of (19) with one phenyl and one 2-methoxyphenyl substituent the rate of the aromatic migration rearrangement of the dehydrated form (20) might have allowed us to separate the kinetic effects of phenyl substitution on the migrating group and on the electron density of the imine centre.

Figure 13: successive carbon-13 nmr spectra at hourly intervals during the reaction of thiourea with benzil under base catalysis.

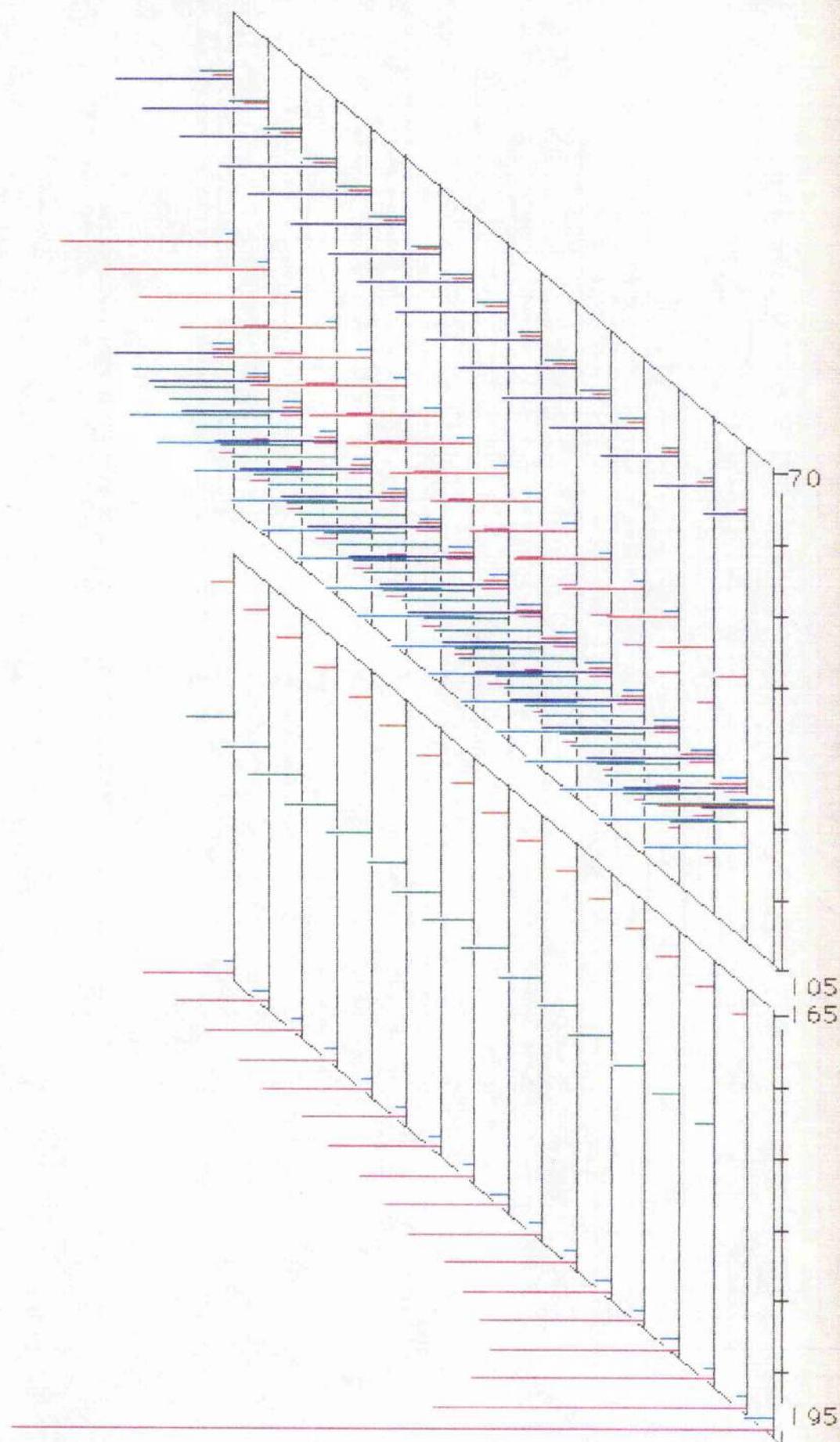


Figure 14: Expansion of alcoholic centre region of carbon-13 nmr spectra during reaction of benzil and thiourea under base catalysis

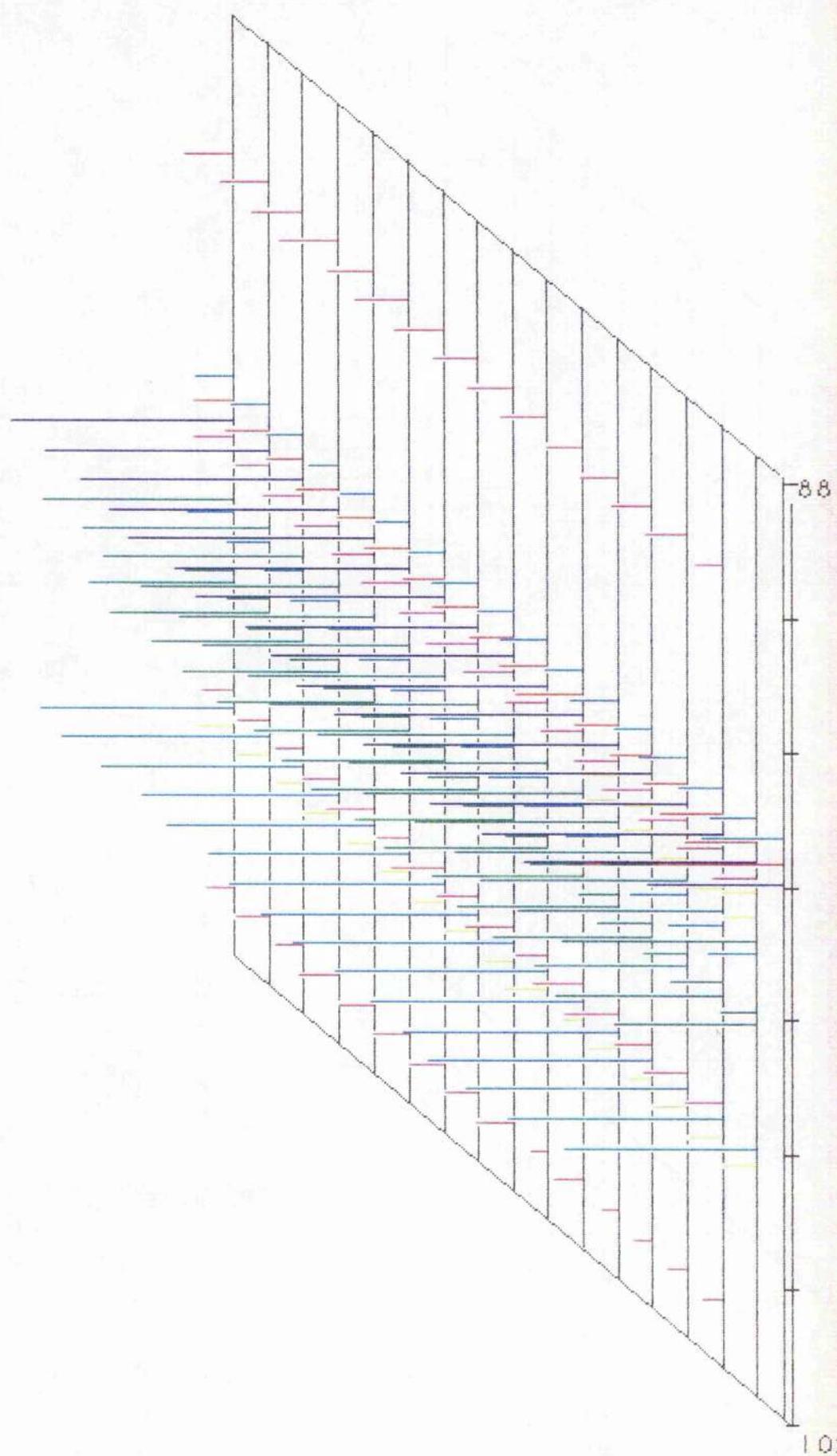
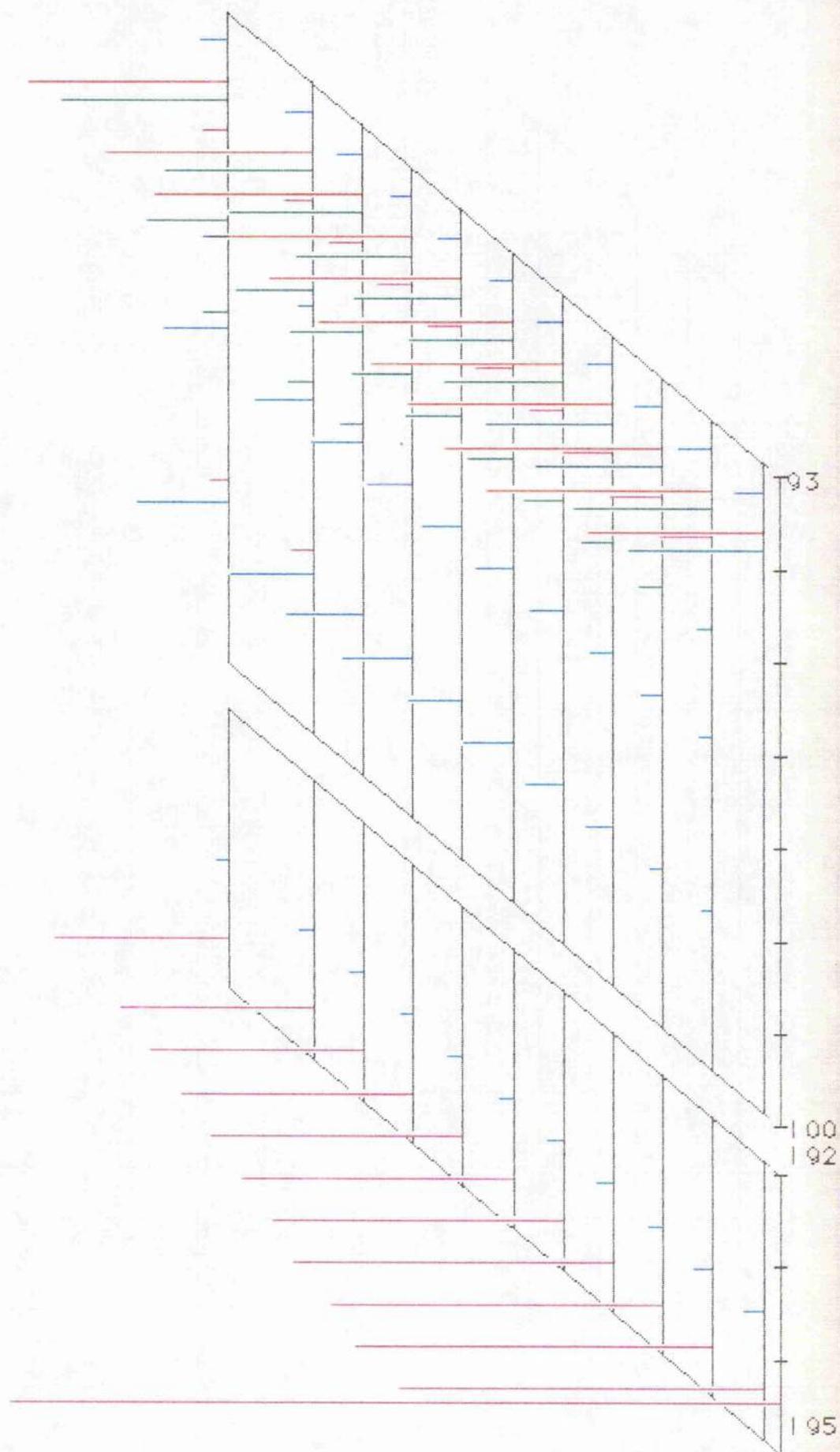


Figure 15: successive carbon-13 nmr spectra at 15 minute intervals during the first two hours of the reaction of thiourea with benzil under base catalysis



Unfortunately, it proved impossible to isolate any materials from the system except (23), (33) and the reagents themselves.

The application of carbon-13 spectroscopy to the dynamic system using benzil enriched to 20% carbon-13 at the carbonyl position gave the results summarised in figures 13, 14 and 15 from which scheme 7 was derived. The assignments are discussed in detail below.

Two experiments were carried out. In the first experiment a 0.2 mol dm^{-3} solution of benzil with a three fold excess of thiourea in basic methanol was used. The solution was held at 30 degrees centigrade for 16 hours during which spectra were taken at hourly intervals. Each spectrum had an acquisition time of approximately 15 minutes. Although each spectrum was obtained using exactly the same number of scans, the signal intensities showed quite marked deviations from a smooth variation over time, especially in the case of signals of barely detectable intensity such as those due to (31).

In the first experiment a large number of the signals reached essentially constant intensities within the first hour of the reaction, so a second experiment was carried out to study the first two hours in greater detail. Again a 0.2 mol dm^{-3} solution of benzil with a three fold excess of thiourea in basic methanol was used, but in this case spectra were taken at 15 minute intervals with an acquisition time of approximately 5 minutes.

Unfortunately, it was necessary to prepare the labelled benzil from 20% carbon-13 enriched benzaldehyde by means of the benzoin condensation reaction. This reaction couples two benzaldehyde molecules without any means of selection between labelled and unlabelled substrate, thus we obtained a statistical amount (4%) of doubly labelled benzil after oxidation and work up. This meant that we observed two small carbon-13 satellites to each peak, each one being one tenth the intensity of the signal due to the singly labelled material.

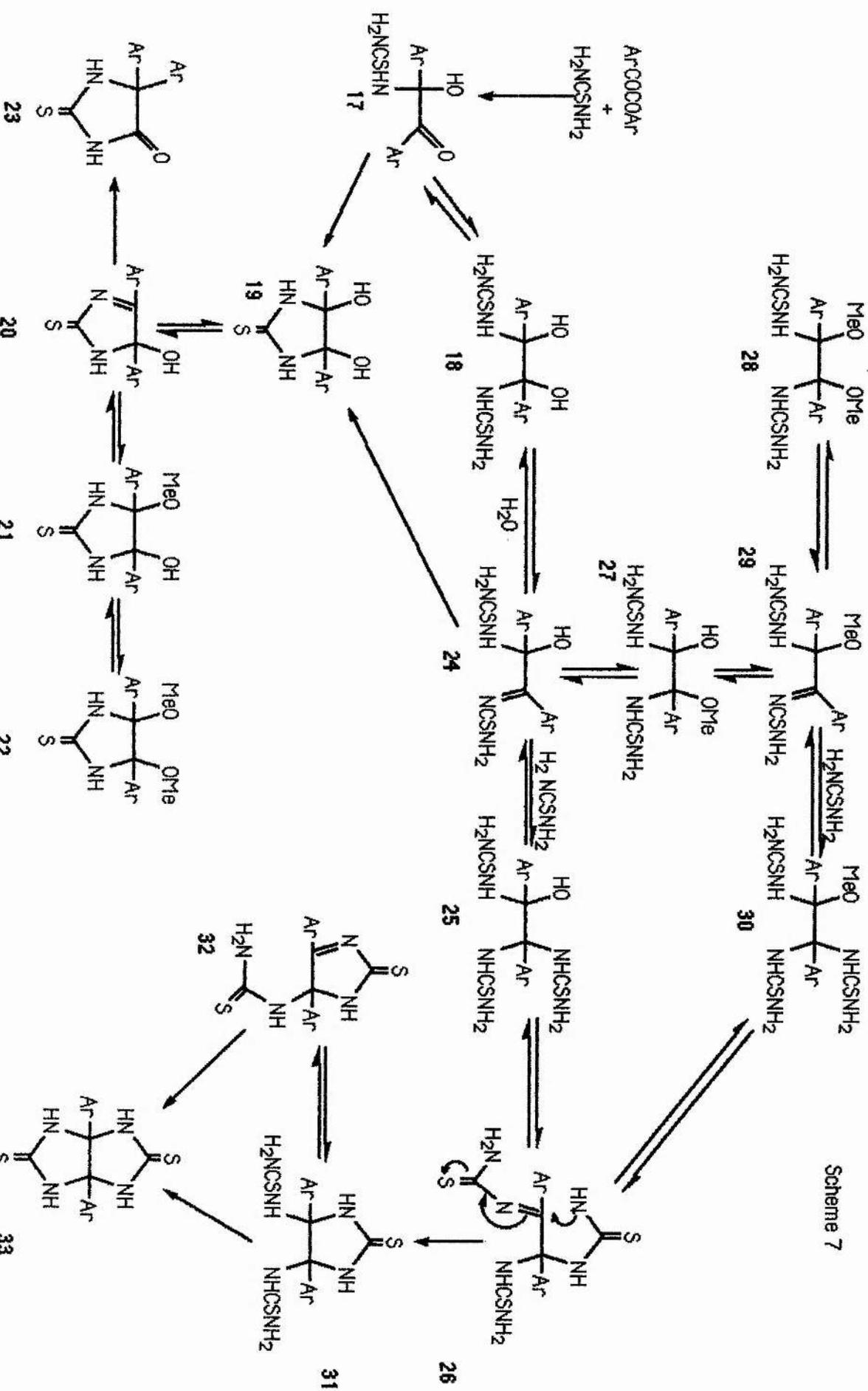
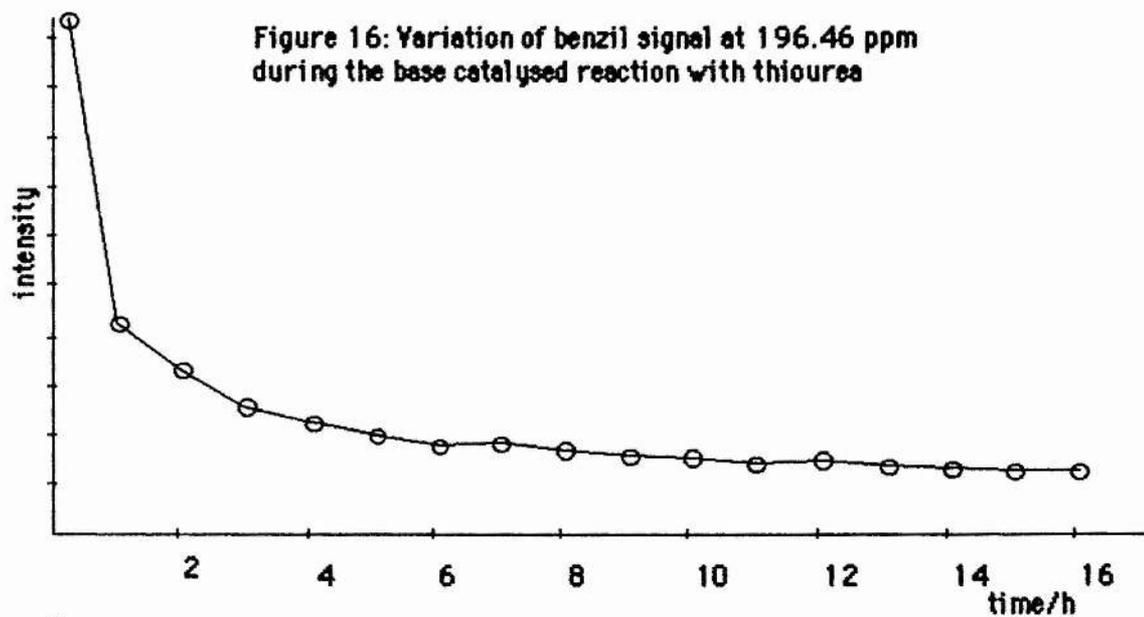


Figure 16: Variation of benzil signal at 196.46 ppm during the base catalysed reaction with thiourea



Variation of benzil signal over the first two hours of the reaction

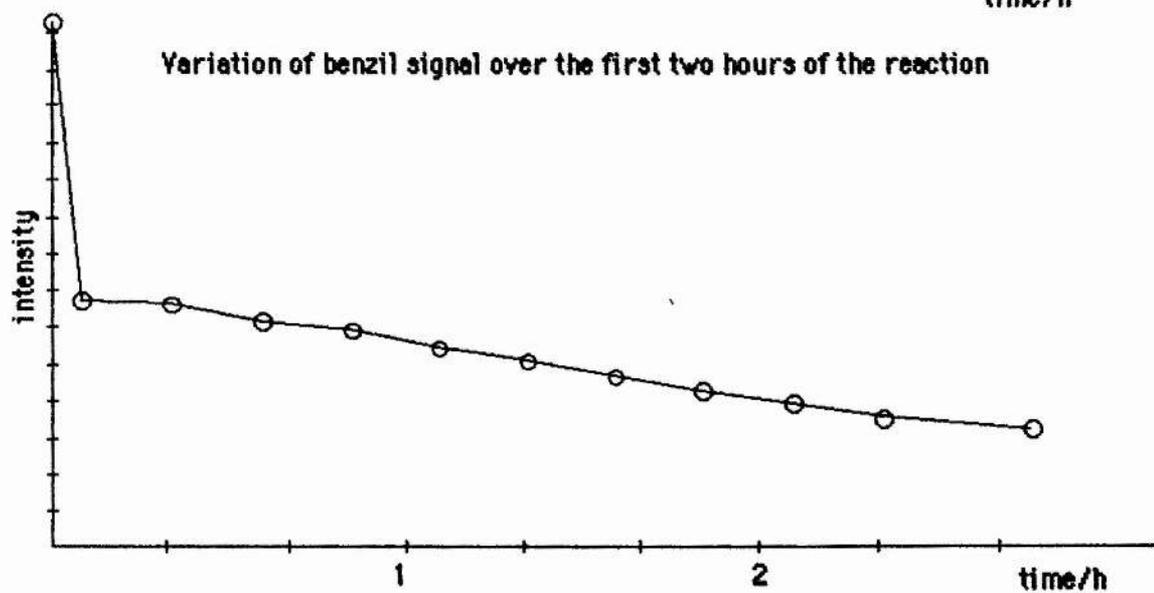
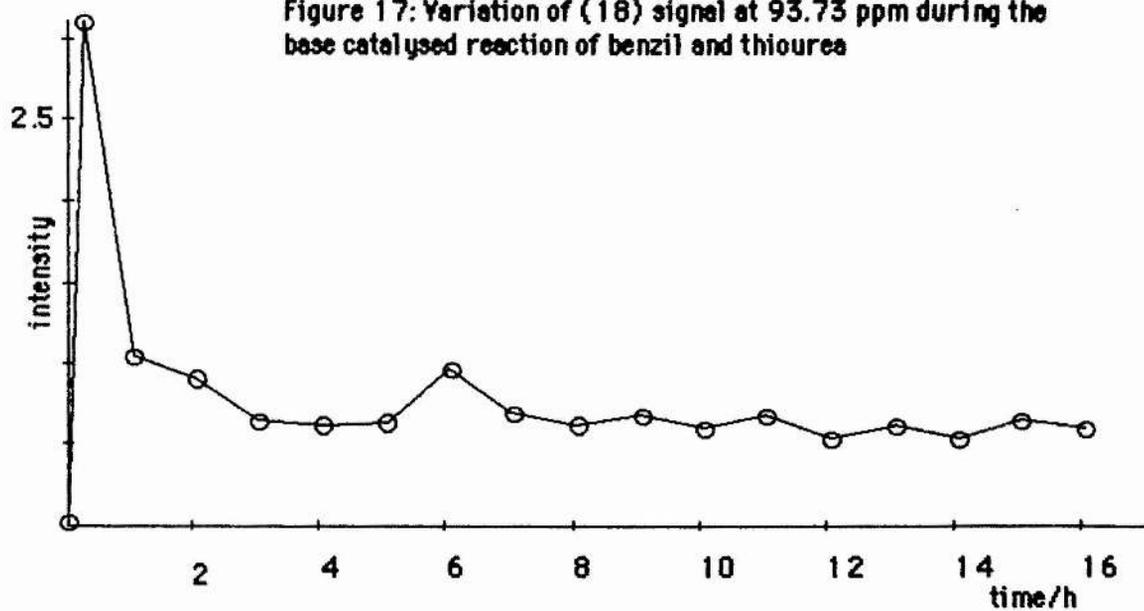
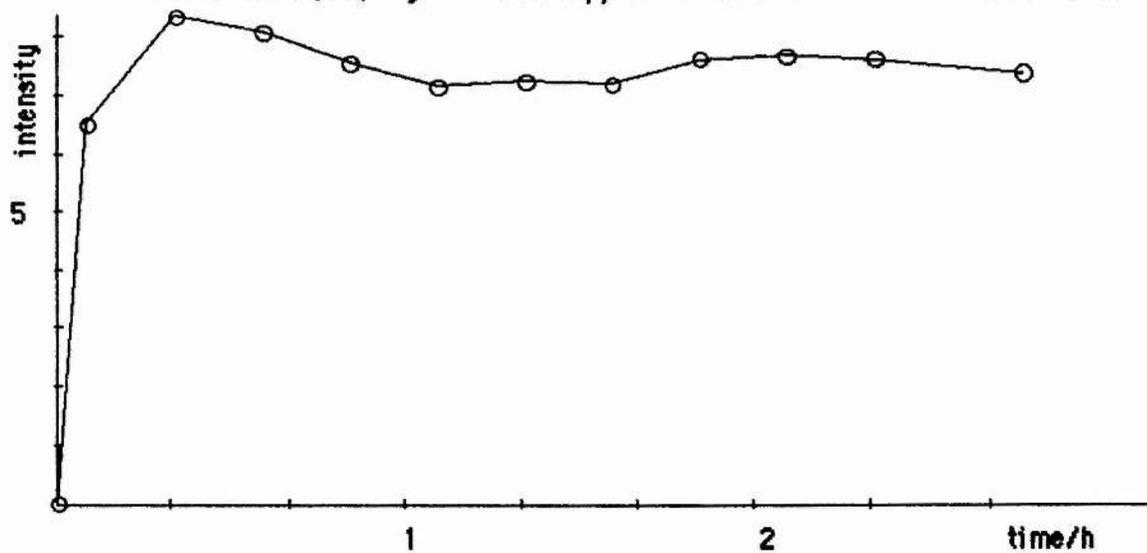


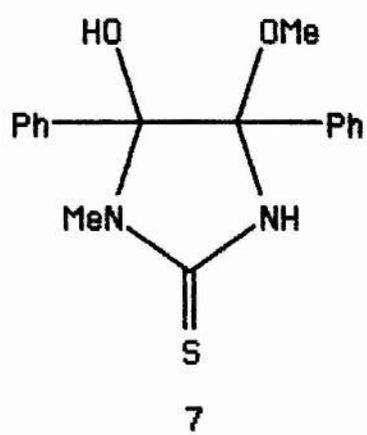
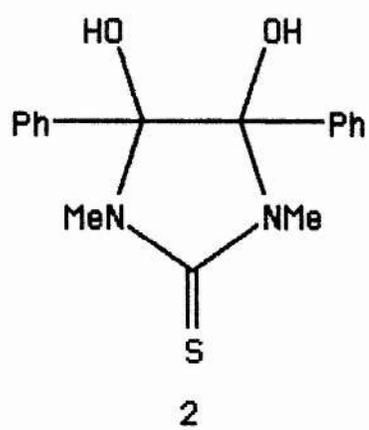
Figure 17: Variation of (18) signal at 93.73 ppm during the base catalysed reaction of benzil and thiourea



Variation of (18) signal at 93.75 ppm over the first two hours of the reaction



The signal at 194.46 ppm corresponds unambiguously to the carbonyl centre of benzil. The intensity of this signal shows an extremely rapid fall to approximately half its original value within five minutes of the addition of base, followed by a slow, steady decrease in intensity, which appears to follow a first order rate law. This extremely rapid fall is accompanied by a corresponding rapid increase in the intensity of three signals at 93.314 ppm, 93.77 ppm and 94.06 ppm, all of which lie in the region corresponding to carbons with one hydroxyl, one thiourea and one phenyl substituent. See figures 15 and 16. This behavior cannot be explained by an extremely rapid equilibrium between benzil and the two diols (18) and (19) via the mono-substituted material (17). Whilst this is consistent with the benzil concentration falling rapidly to a constant non-zero level, followed by a slow steady fall as the diols (18) and (19) rearrange to give (23) and (33) respectively displacing the equilibrium and consuming more benzil, we know that (18) and (19) are not in equilibrium, because (19) does not react with thiourea to give any (33), formed via (18). The variation over time of (19)'s intensity does not parallel that of either (18) or benzil itself (see figures 16, 17 and 18). Both of these results imply, very reasonably, that the cyclisation step giving rise to (19) is irreversible. In fact this is not quite accurate, as has been shown by prolonged reflux of the cyclic diol (2) in basic ethanol, which gives a very small amount of the products of the reaction between benzil and sodium ethoxide after approximately 4 hours. However in a case such as this when the diol reacts further this rate of ring opening is negligible. The rapid fall cannot correspond to a rapid reaction between benzil and the sodium hydroxide, which is present in approximately half the concentration of the benzil, because no products corresponding to the action upon benzil of base in the absence of thiourea have been detected. An analysis of substituent effects upon the rate of benzil's destruction carried out by Dietz and Meyer⁴ confirms that attack by thiourea anion upon the carbonyl centre of neutral, unreacted benzil is the rate determining step.

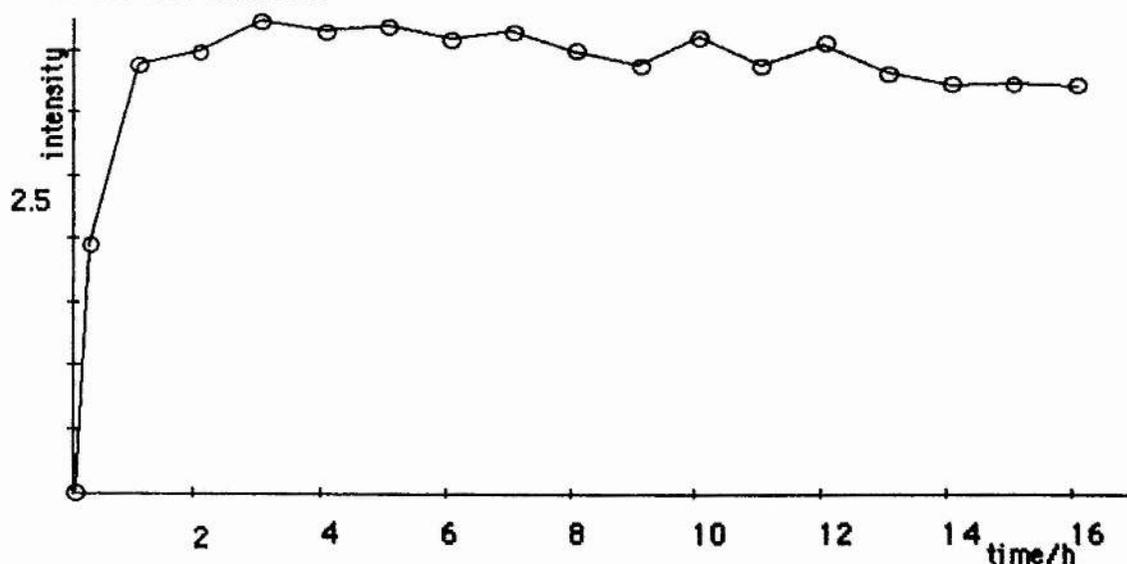


The only explanation of benzil's behavior which is consistent with all the facts depends on the following. The thiourea and sodium hydroxide will be in a very rapid proton-transfer equilibrium. From the results of Dietz and Meyer⁴, it is known that the nucleophilic species is the thiourea anion. The experimental conditions had a base concentration approximately one half of the benzil concentration. Thus, if we make the reasonable assumption that the intermediates are of similar or slightly greater acidity than thiourea, as the total intermediate concentration grows the concentration of the thiourea anion falls until an equilibrium condition is established. The slow, steady fall in benzil concentration over the sixteen hour period studied is consistent with a low, constant concentration of thiourea anion reacting with an excess of benzil, rather than the pseudo first order process which would be observed if the benzil were reacting with the three-fold excess of neutral thiourea.

The equilibria between each of the intermediates and its corresponding anion will, of course, be rapid in comparison with the nmr timescale at 25 centigrade, so we will only observe the time average signal. The differing acidities of the various intermediates thus add to the difficulties in assigning the various signals on the basis of their chemical shifts. The signals due to the alcoholic centres of these intermediates all show different small but steady upfield shifts as the reaction proceeds, which may well be due to variations in the basicity of the medium altering the degree of ionisation of each of the intermediates to a different extent.

The diol (2) produced from the reaction of 1,3-dimethylthiourea with benzil shows a signal corresponding to the hydroxy bearing carbon at 97.7 ppm in acetone. Also (7) shows signals at 94.6 and 98.4 ppm in chloroform, corresponding to the hydroxy and methoxy bearing carbons respectively. Thus it is reasonable to assign the 14 signals observed in the 93.7-101.0 ppm range to carbons in analogous chemical environments, ie bearing one phenyl, one alkoxy and one thiourea substituent. The peaks all reach their maxima comparatively early in the course of the reaction, which is

Figure 18: Variation of (19) signal at 93.946 ppm during the base catalysed reaction of thiourea and benzil



Variation of (19) signal at 93.946 ppm during the first two hours of reaction

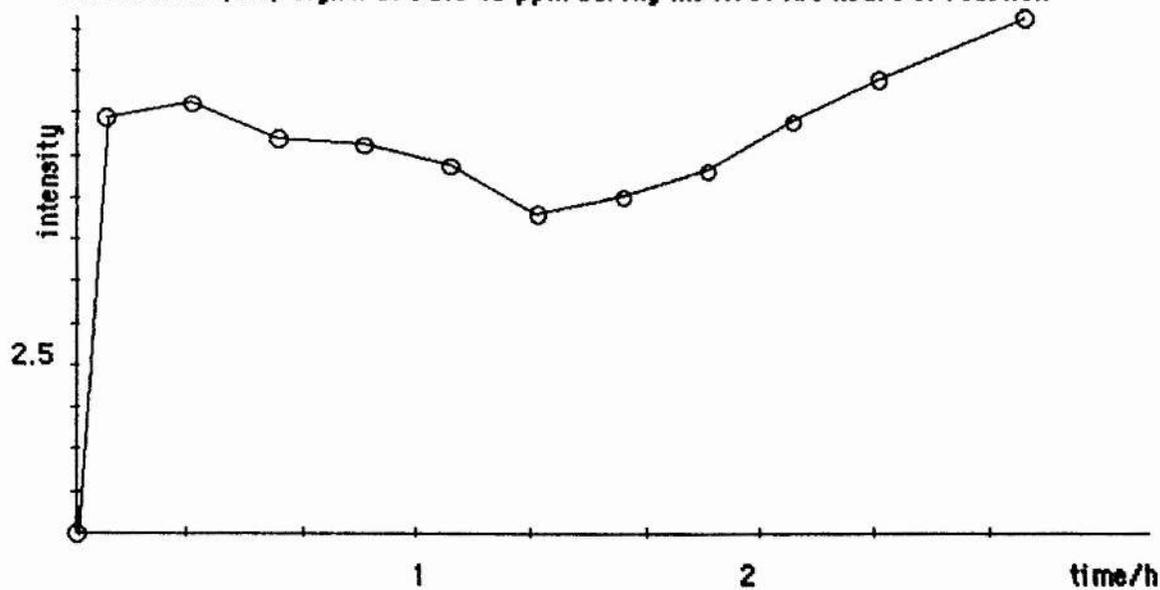
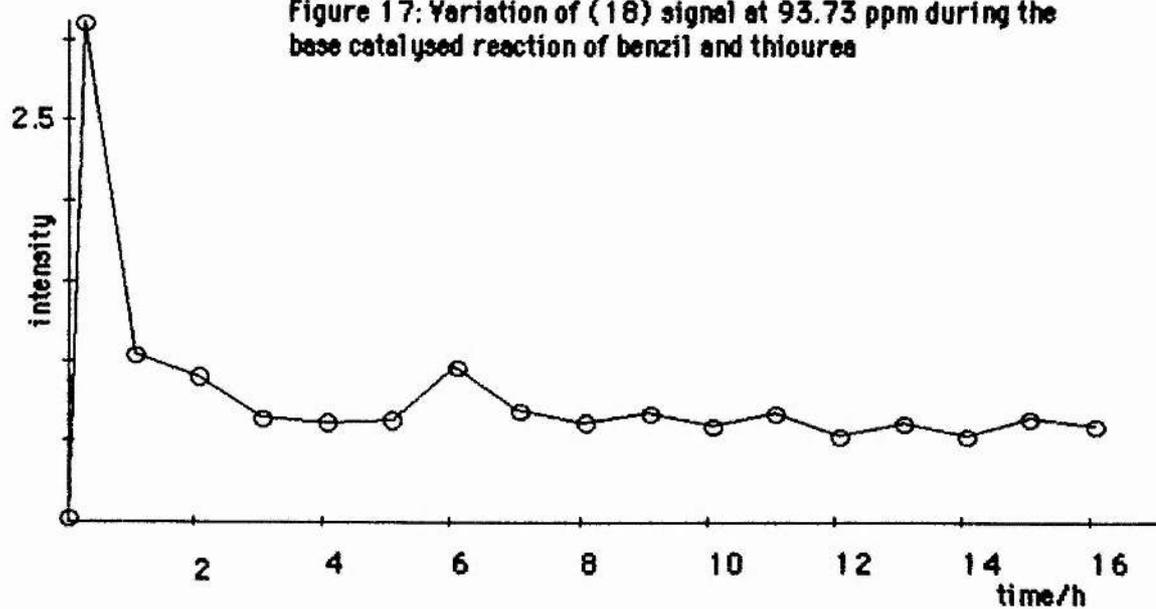


Figure 17: Variation of (18) signal at 93.73 ppm during the base catalysed reaction of benzil and thiourea



Variation of (18) signal at 93.75 ppm over the first two hours of the reaction

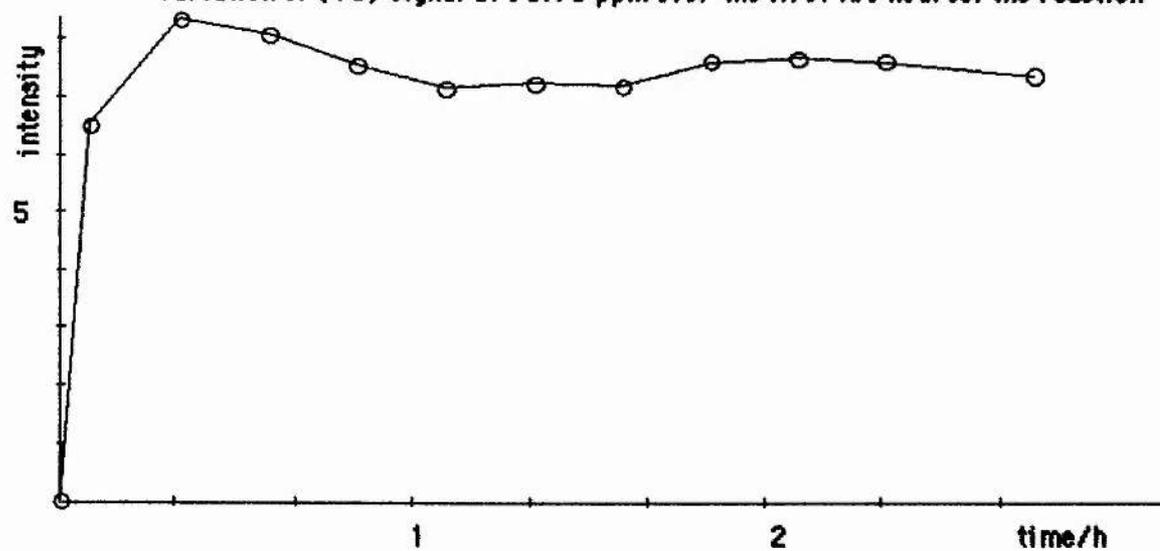
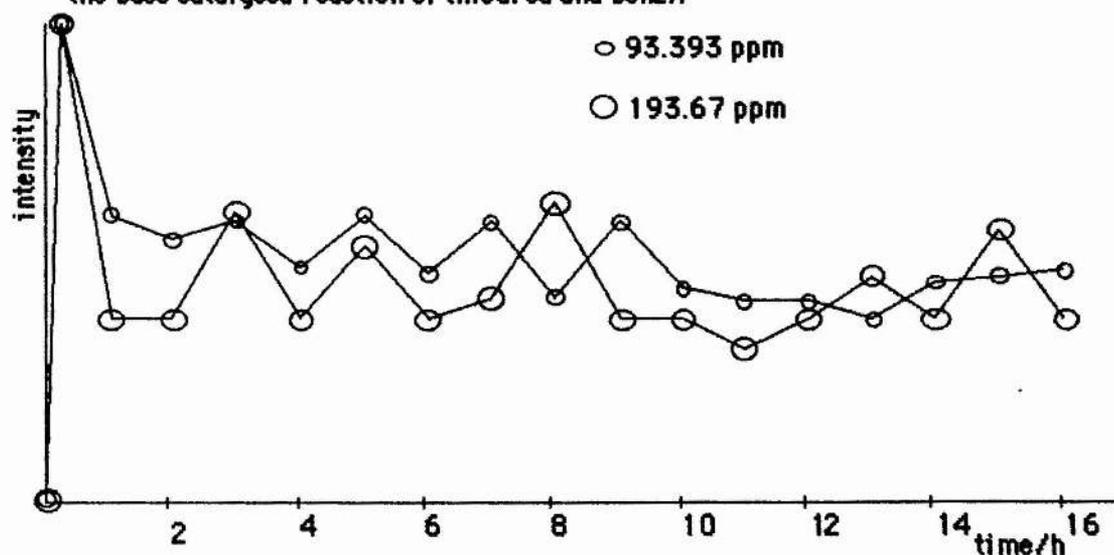
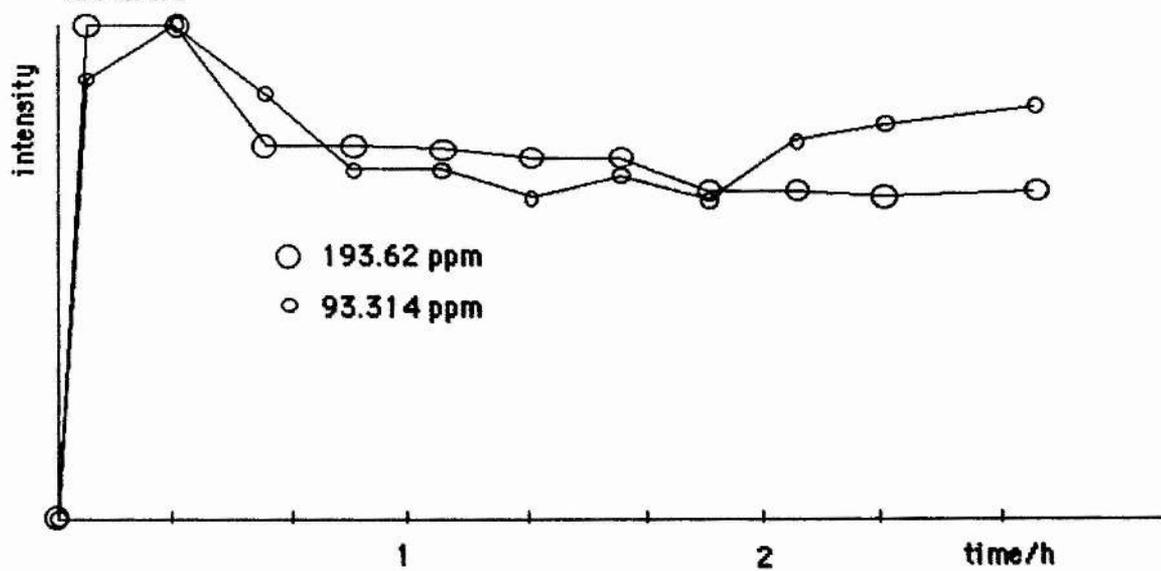


Figure 19: Normalised variation of (17) signals at 93.393 and 193.67 ppm during the base catalysed reaction of thiourea and benzil



Normalised variation of (17) signals at 93.314 and 193.62 ppm during the first two hours



consistent with centres formed by simple attack on benzil's carbonyl centre with little subsequent rearrangement. Unfortunately the diol (19) isolated from the reaction of thiourea and benzil was sufficiently soluble for carbon-13 nmr only in DMSO, which has a strong solvent effect on the alcoholic carbon's chemical shift. The value obtained was 73.9 ppm. There are a limited number of plausible structures containing this thiourea substituted alcoholic centre, of which the most reasonable are (17)-(22) and (27)-(31).

A weak signal at 93.314 ppm, corresponding to a thiourea substituted centre is observed which shows a good correlation with a signal at 193.62 ppm, corresponding to a carbonyl centre. These two signals are therefore assigned to (17). It has been shown previously that the analogous materials in the 1-methylthiourea reaction (3) and the 1,1-dimethylthiourea reaction (10) exist in equilibrium with benzil and so it seems reasonable to assume that (17) does also. The concentration of (17) rises extremely rapidly, attaining a maximum in between 5 and 20 minutes and then falls quite rapidly to an essentially constant level. This is consistent with a species formed very rapidly which then undergoes a somewhat slower equilibration with other species in the system, principally (18). See figure 19.

Compound (17) can undergo intramolecular nucleophilic cyclisation to give (19) or it can undergo attack by a second thiourea anion to give the acyclic diol (18). Both (18) and (19) reach their maximum concentrations within the first 20 minutes of the reaction at very similar rates. This implies that both processes occur simultaneously, rather than (19) being formed via (18). It is known that (18) cannot be formed via (19) because (19) gives no (33) on treatment with a large excess of thiourea. The signals corresponding to (18) and (19) do not show parallel variation in intensity over the course of the reaction, implying that they are not in equilibrium. See figures 17 and 18.

The cyclic diol (5) formed from benzil and 1-methylthiourea is known to

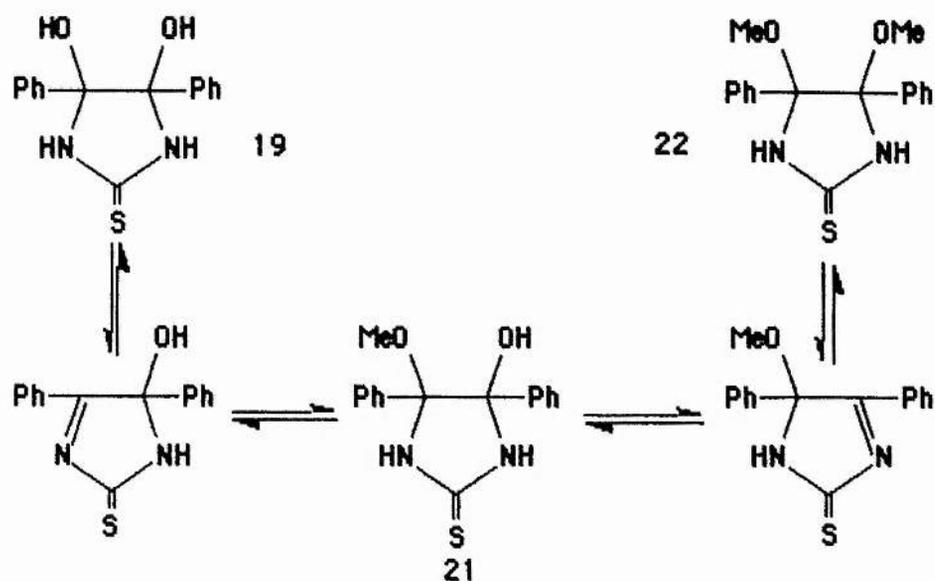
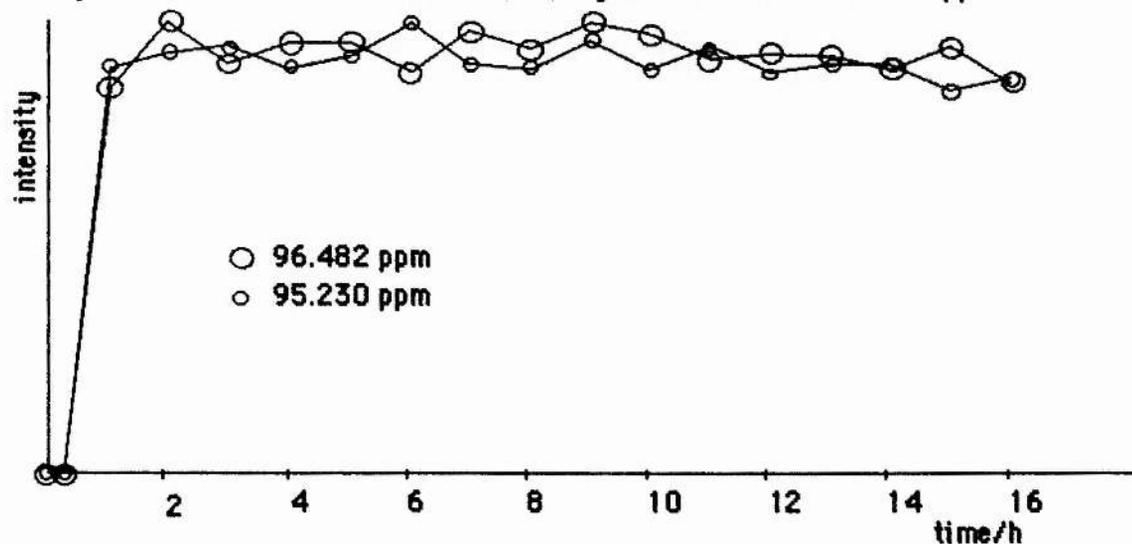


Figure 20: Normalised variation of (21) signals at 96.482 and 95.23 ppm



Normalised variation of (21) signals at 95.226 and 96.412 ppm during the first two hours of reaction

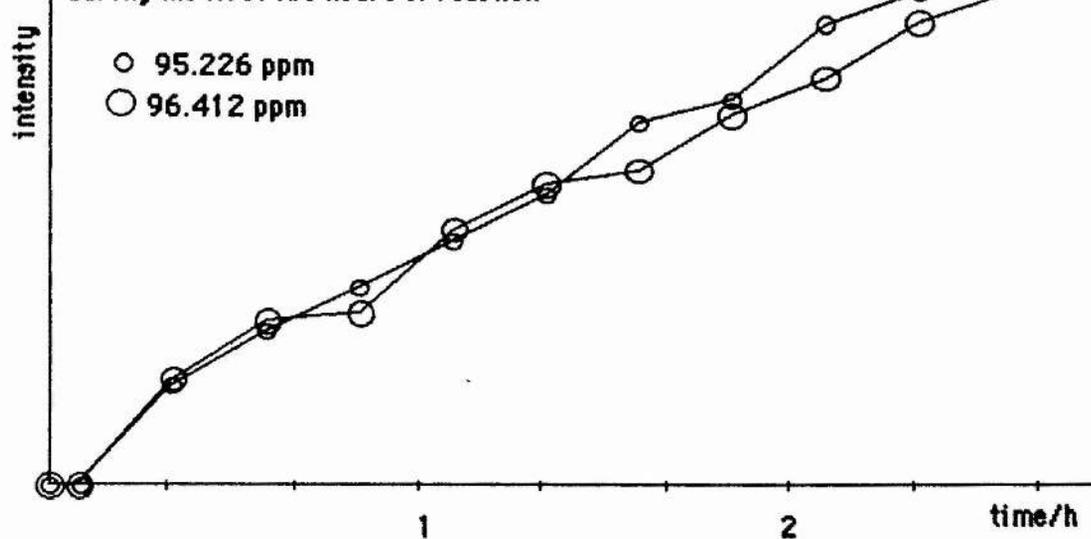
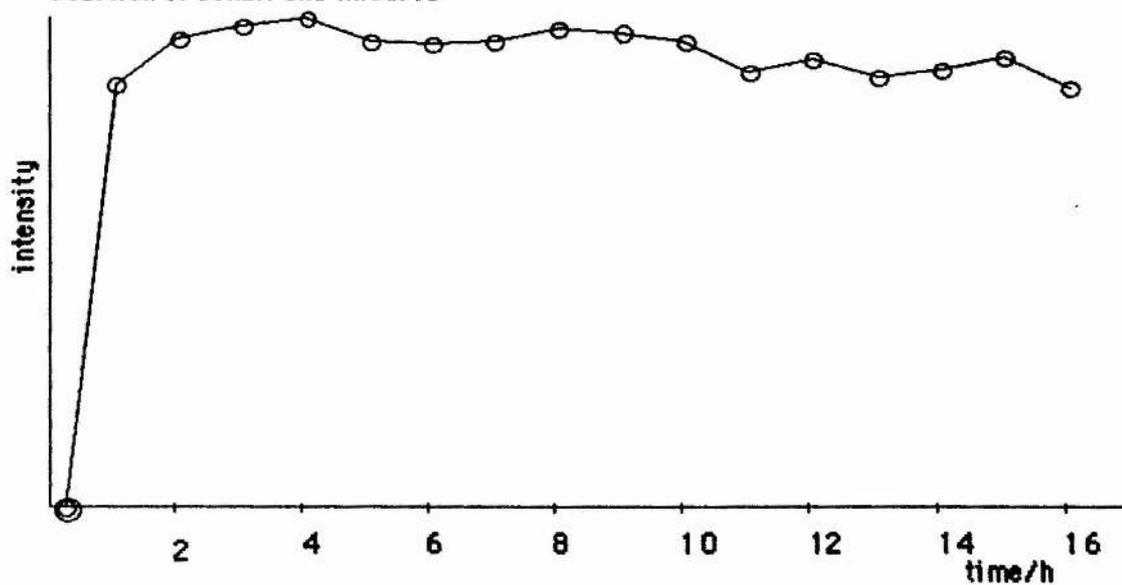
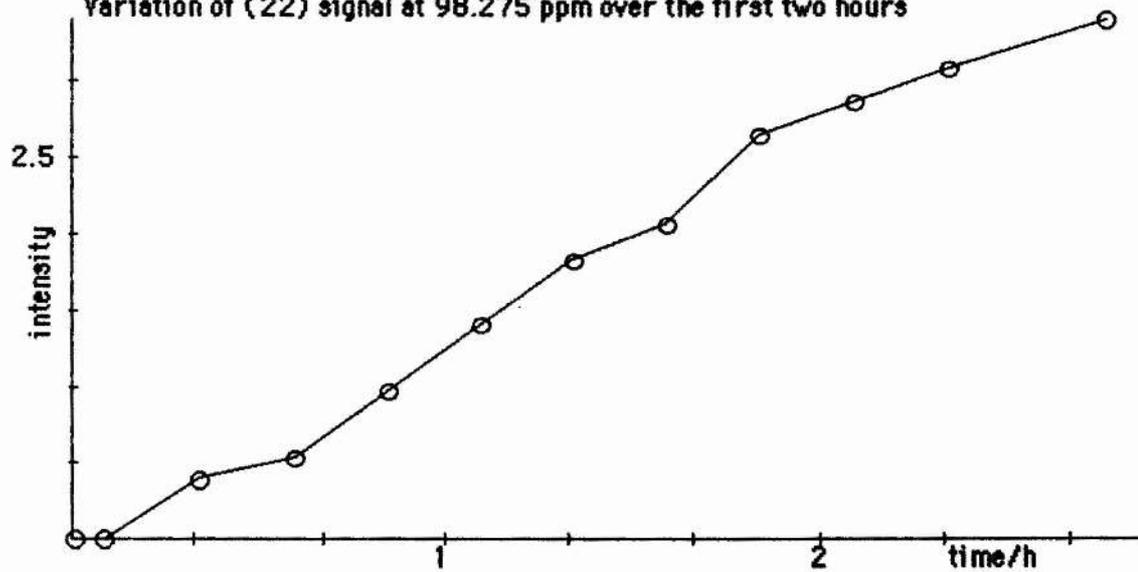


Figure 21: Variation of (22) signal at 98.336 ppm during the base catalysed reaction of benzil and thiourea



Variation of (22) signal at 98.275 ppm over the first two hours

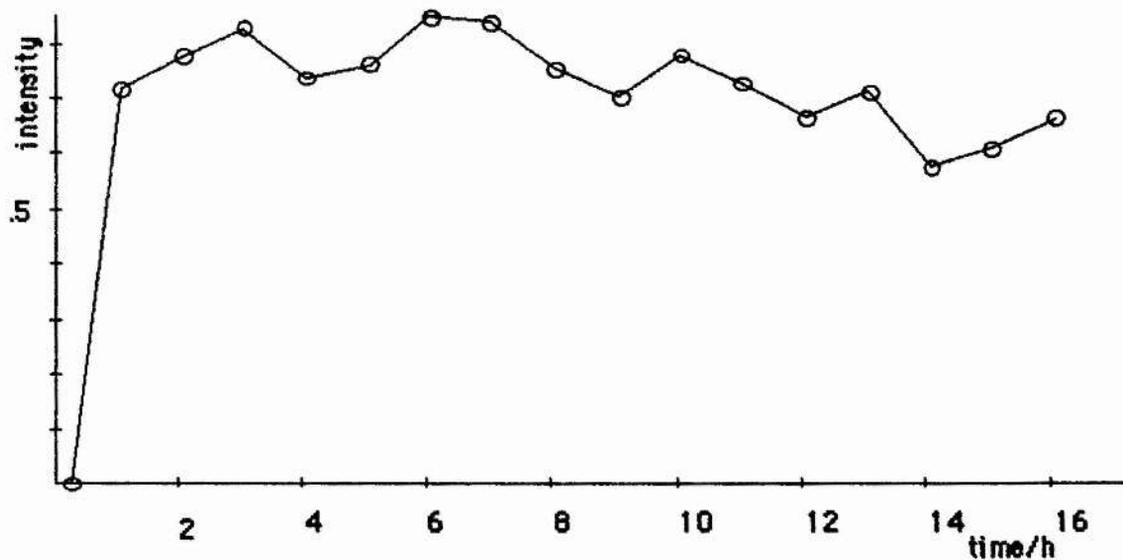


undergo rapid dehydration across the carbon-nitrogen bond followed by solvation to give (7), which has been isolated and fully characterised. Thus we would expect (19) to be capable of exchanging one or both of its hydroxyl groups via (20) to give the compounds (21) and (22). This is indeed the case and we observe four intense signals corresponding to the hydroxyl bearing carbon of (19) at 94.06 ppm, the hydroxyl and methoxyl bearing carbons of (21) at 95.23 and 96.482 ppm respectively and the methoxyl bearing carbon of (22) at 98.336 ppm. After the first two hours of the reaction all four signals show a very high degree of correlation, consistent with species in an equilibrium rapid in comparison to the interval between successive spectra. See figures 20 and 21.

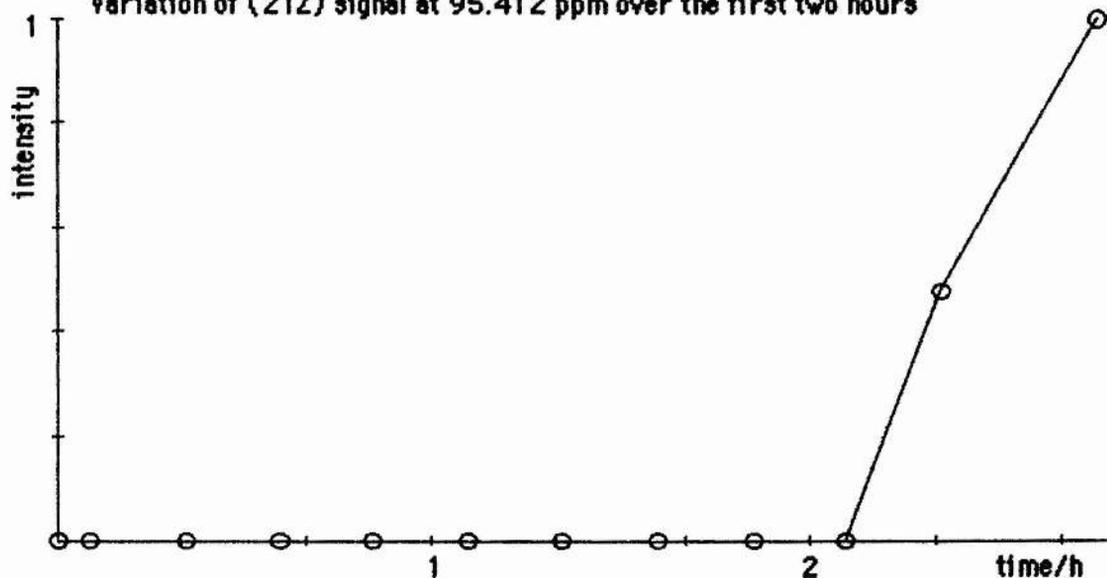
As discussed above (19) is formed extremely rapidly, reaching its first maxima within 20 minutes of the addition of base to the system. Its concentration then falls slightly over the next hour, and then rises more slowly to reach its maximum value after approximately three hours. This probably corresponds to an essentially constant rate of formation, as discussed above for the constant rate of benzil destruction, and an approach to equilibrium between (19), (21) and (22) which is probably first order in (19) with a similar overall rate to the rate of (19) formation from benzil. After four hours all three intermediates (19), (21) and (22) show a very slow, steady fall, with a high degree of correlation. This corresponds to the formation of the thiohydantoin (23) via the benzilic acid rearrangement of (20), as discussed for 1-methylthiourea above.

In the study carried out with short acquisition times over the first two hours of the reaction only, both (21) and (22) show a smooth increase over the full two hour period, with the initial rate of (22) formation being slightly less than that for (21) formation and showing less of a tendency for the intensity to level off as the equilibrium is approached. See figures 20 and 21. The intensity variation of (21) and (22) over the first few hours of the study over 16 hours, using fifteen minute acquisition times,

figure 22: Variation of (21Z) signal at 95.416 ppm during the base catalysed reaction of benzil and thiourea



Variation of (21Z) signal at 95.412 ppm over the first two hours



appears to be somewhat distorted, possibly because the concentration will change markedly during the period of the spectrum's acquisition. However this experiment does imply that (22) reaches its maximum value at around four hours whereas (21) reaches a maximum an hour earlier. This result should however be treated with caution since the differences between the maxima and the intensities taken before and after them are similar to the noise level.

Two smaller peaks at 96.283 ppm and 95.416 ppm were observed in the study with long acquisition times only. Their intensity variation over sixteen hours shows an excellent correlation with that of (21), allowing for the level of noise present, and their chemical shifts are also very similar to (21). See figure 22. Both had an intensity approximately one sixth that of the (21) peaks at 96.482 ppm and 95.23 ppm. The most reasonable assignment of these two peaks is to a diastereoisomer of (21). In the case of 1,3-dimethylthiourea the diol (2) isolated from the reaction with benzil was found to be predominantly in the E form. Thus it seems reasonable to assign the high intensity (21) peaks to the E form and the lower intensity signals to the more sterically crowded Z form of (21). The low intensity peaks do not appear in the spectra taken with five minute acquisition times until over two hours has elapsed. This may imply that the Z form of (21) is formed more slowly than the E, or it may simply be due to the extremely low intensity of the smoothly increasing signals rendering them difficult to distinguish from the noise. An alternative interpretation of these peaks is as carbon-13 coupled satellites of one of the diol peaks due to the doubly labelled benzil substrate. However both the intensity ratios with respect to the other cyclic diols and the chemical shifts are inconsistent with this interpretation.

An authentic sample of 5,5-diphenyl-2-thiohydantoin, (23), gives signals at 176.86 ppm and 74.98 ppm in neutral ethanol. These shifts are consistent with the assignment of the two signals at 176.86 ppm and 74.21 ppm to the carbonyl and quaternary carbons of (23) respectively. These two signals show a slow increase

throughout the period studied and a high degree of correlation, consistent with an assignment to two dissimilar centres in the same species. See figure 23.

A sample containing identical concentrations of benzil, thiourea and base to those used in these kinetic experiments was held at 20 degrees centigrade for five days. After three days the intensity of the signal at 88.4 ppm due to (33) reached a constant value (with respect to an internal reference), but even after five days no signals due to the thiohydantoin (23) could be detected. It was assumed that, since the concentration of (33) had reached a constant value, all the intermediates (24)-(31) en route to (33) had reacted and therefore that all the signals present were due to intermediates en route to (23). This was confirmed by warming the sample to 55 degrees centigrade for four hours, after which signals at 176.9 ppm and 75.0 ppm were detected, corresponding to the thiohydantoin. The intensities of the intermediate signals were greatly reduced, the signal corresponding to (33) remaining at an essentially constant intensity. This is consistent with the results of the dynamic carbon-13 nmr experiment using labelled benzil and 1-methylthiourea, where at 25 centigrade no detectable amount of thiohydantoin was produced after 14 hours, whereas at 40 centigrade the thiohydantoin producing reaction was virtually complete in the same period.

The signals detected were at 98.21 ppm, 96.32 ppm, 95.88 ppm, 95.58 ppm, 95.13 ppm, 94.78 ppm and 93.9 ppm. They correspond to the signals observed during the kinetic runs at 98.336 ppm, assigned to (22), 96.32 ppm, assigned to (21), 96.28 ppm and 95.42 ppm, both assigned to the Z isomer of (21), 95.23 ppm, assigned to (21) and 94.06 ppm, assigned to (19). This is a useful confirmation that all of these signals, which show an approximately parallel intensity variation after the first two hours, correspond to the set of equilibrating intermediates (19), (21) and (22) en route to (23).

There are another five signals in the 93.7-101 ppm range corresponding to

figure 23: Normalised variation of (23) signals at 74.21 and 186.50 ppm during the base catalysed reaction of thiourea and benzil

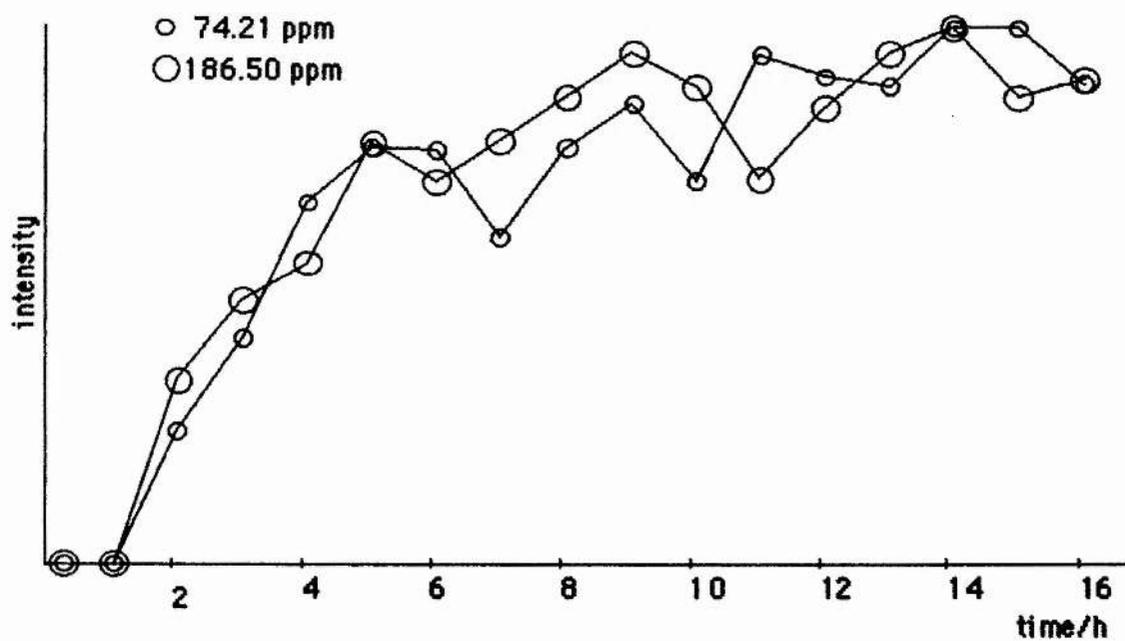
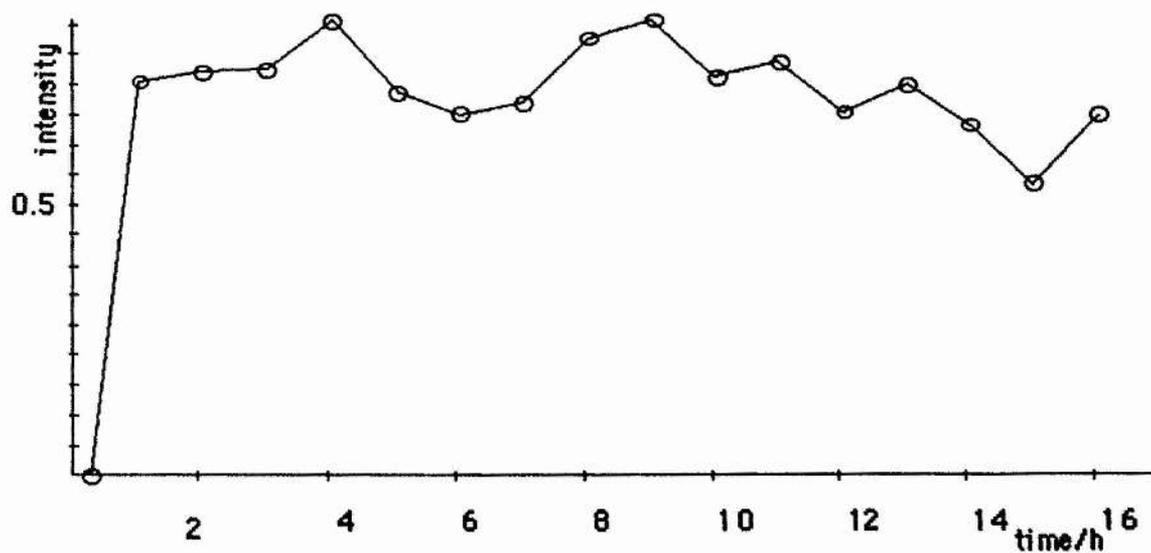
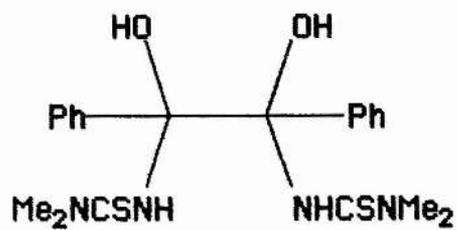
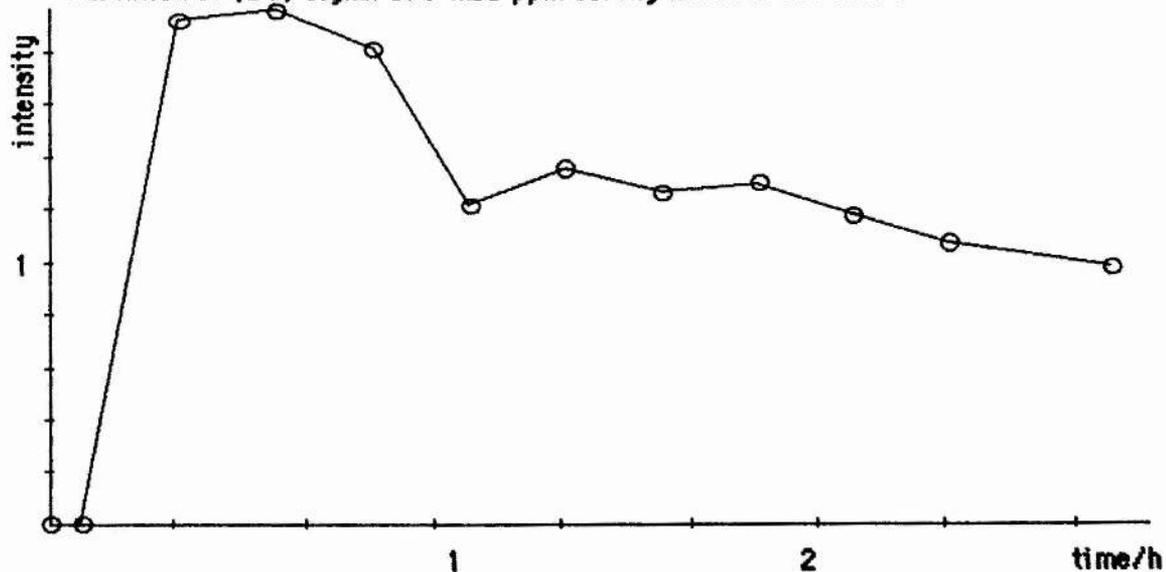


Figure 24: Variation of (28) signal at 94.30 ppm during the base catalysed reaction of thiourea and benzil



Variation of (28) signal at 94.26 ppm during the first two hours



carbons bearing one phenyl, one hydroxy or alkoxy and one thiourea substituent. None of these signals show an intensity variation parallel to any of (19), (21) or (22). Therefore these signals are assigned to intermediates en route to the bicyclic compound (33).

The signal at 93.75 ppm reaches its maximum intensity extremely rapidly, within less than 20 minutes, and then falls rather more slowly to a virtually constant level. Its intensity then falls extremely slowly throughout the sixteen hour period studied. This implies that it corresponds to an intermediate near the beginning of the reaction scheme which exists in a comparatively slowly established equilibrium with other materials in the system. Therefore it has been assigned to the acyclic diol (18), formed by the attack of a second thiourea on (17). See figure 17.

The signal at 94.25 ppm rises more slowly than that corresponding to (17), reaching its maximum intensity in approximately 20 minutes. The intensity remains approximately constant between 20 minutes and 1 hour and then falls quite sharply to just over half its maximum intensity. During the remainder of the period studied its intensity falls very slowly. There are no other signals which vary in parallel with it and its intensity is sufficient to imply that any other signal corresponding to the same species will be above the detection threshold. This implies that it corresponds to a symmetrical species with both quaternary carbons in the same chemical and magnetic environment. The most reasonable assignment consistent with the above is the compound (28) formed by two dehydrations and solvolyses of (18). See figure 24. No signal corresponding to the partially solvolysed material (27) could be detected. The chemical shift is consistent with the value of 95.34 ppm for the analogous material detected in equilibrium with benzil and 1,1-dimethylthiourea (13).

The signal at 166.85 corresponds to the chemical shift range of a phenyl substituted imine centre. The intensity plot is not parallel to any other detectable signal. The intensity of the signal is itself only just detectable, hence the large

Figure 25: Variation of (26) signal at 166.85 ppm during the base catalysed reaction of benzil and thiourea

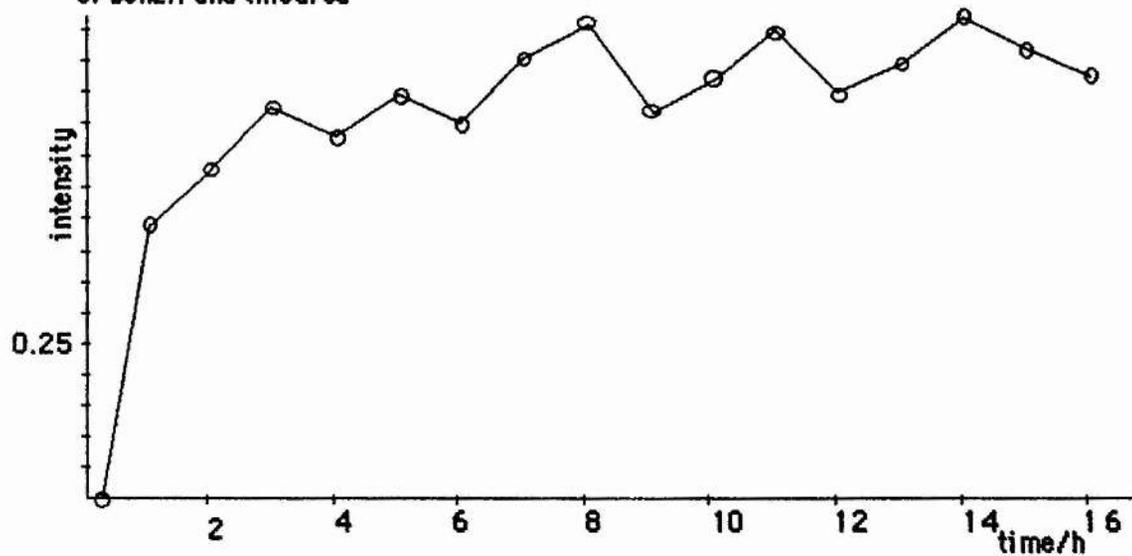
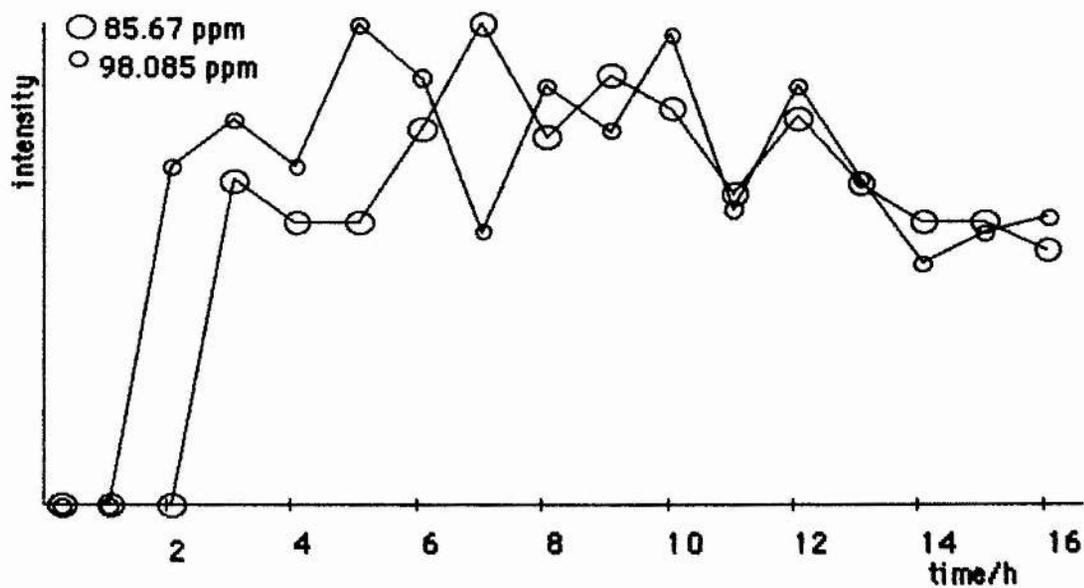


Figure 26: Normalised variation of (25) signals at 85.67 and 98.085 ppm during the base catalysed reaction of benzil and thiourea



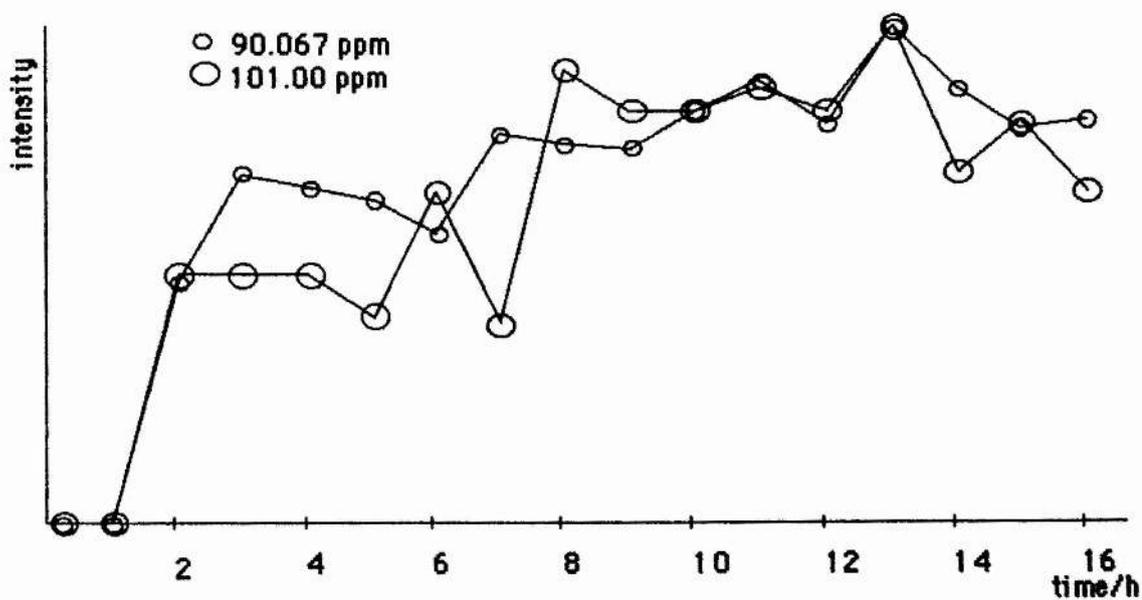
apparent deviations from a smooth curve. It cannot correspond to (20) because it is not parallel to any of the signals due to (19), (21) or (22). The intensity rises more slowly than that due to (25) or (28) and so it cannot be due to either (24) or (29) and it is not parallel to the two isomers of (31), so it cannot be due to (32). Thus by a process of elimination the signal is assigned to the imine centre of (26). The concentration of (26) rises comparatively rapidly over the first three hours, although much more slowly than that of the diol (18) or (25) or (29) which supports the idea that (26) is produced via (18), (25) and (29). From about six hours onward the concentration appears to be virtually steady throughout the remainder of the period studied. The concentration of (26) is too small for the signal to reach detectable intensity using a five-minute acquisition time so the variation over the first two hours could not be followed in detail. See figure 25.

The signal at 85.67 ppm corresponds closely in chemical shift to the centre bearing two thioureas in (33). Its variation in intensity over time shows a good correlation, allowing for the poor signal to noise ratio of these very weak peaks, with a signal at 98.085 ppm, corresponding to an alcoholic centre. Thus these two signals are assigned to (25). The analogous material (15) detected in equilibrium with benzil and 1,1-dimethylthiourea has chemical shifts of 87.63 ppm and 95.04 ppm for the centre bearing two thioureas and the alcoholic centre respectively.

The signals assigned to (25) rise to their maximum values more slowly than those due to (18) or (28) but more rapidly than those of (26), which is consistent with a substance intermediate between them in the reaction scheme. Only the signal at 98.085 ppm is observed in the short acquisition time experiment and that only reaches a detectable level after two hours. After the first three or four hours the signal intensity falls very slowly for the remainder of the period studied. See figure 26.

There are two more signals at 90.067 ppm and 101 ppm which show a similar variation to (25), although with an even lower initial rate of formation which

Figure 27: Normalised variation of (30) signals at 90.067 and 101.00 ppm during the base catalysed reaction of thiourea with benzil



is only just greater than (26)'s. Given that the replacement of the hydroxyl group by a methyl ether tends to increase the chemical shift, all other factors being equal, we assign these signals to the centres of (30) bearing two thioureas and one thiourea and one methyl ether respectively. See figure 27.

The signals at 74.81 and 74.46 ppm show an excellent correlation of their intensity plots but the ten fold difference in their intensities is far too great for them to correspond to different centres within the same molecule. They must therefore correspond to two materials in an equilibrium rapid compared with the interval between spectra. The signal intensities rise more slowly than that of (26) and more rapidly than that of (33), which implies that they correspond to materials intermediate between them in the reaction scheme. The shifts are more consistent with a carbon bearing two thiourea centres, such as that of (33) which gives a signal at 86.19 ppm, than one bearing one thiourea and one hydroxyl group, which give signals typically in the 94-100 ppm range. The most reasonable assignment consistent with all the above is the cyclic product of intramolecular attack by one of (26)'s thiourea groups on its imine group ie (31). Applying the well-known preferred geometry of attack by a nucleophile upon a carbonyl centre to the very similar case of the imine centre of (30), as proposed by Baldwin et al⁵, we can see little evidence for any preferential attack by either the thiourea on the same side of the imine plane as the phenyl substituent or that on the opposite side. Thus a mixture of two stereoisomers (31E) and (31Z) should be produced in roughly equal amounts. Models indicate that (31E) and (31Z) should have different average orientations of the phenyl ring with respect to the adjacent carbon and thus should have different anisotropic through-space effects on their magnetic environments, as for (33) where the chemical shift values of a chemically very similar centre is 12.4 ppm greater. The high degree of correlation between the signals and the dramatic difference in their intensities implies that a process must exist to allow the isomers to interconvert. The most plausible mechanism for this process is elimination

Figure 28: Normalised variation of (31E) signal at 74.81 ppm and (31Z) signal at 74.46 ppm during the base catalysed reaction of thiourea and benzil

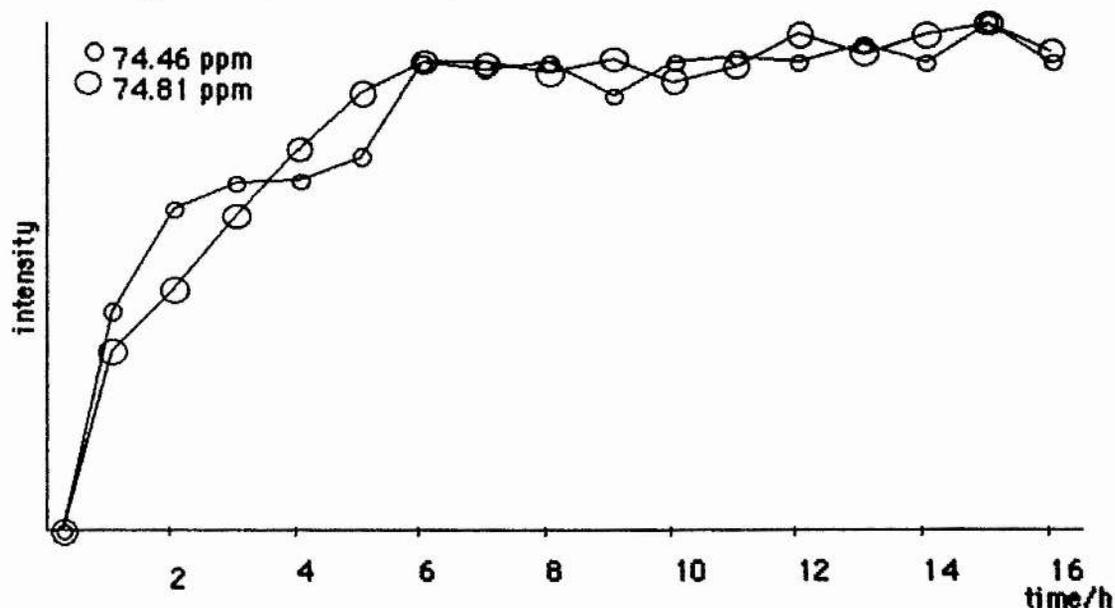
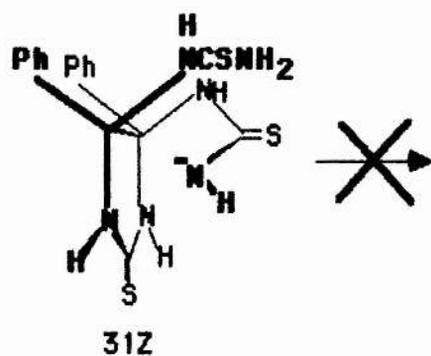
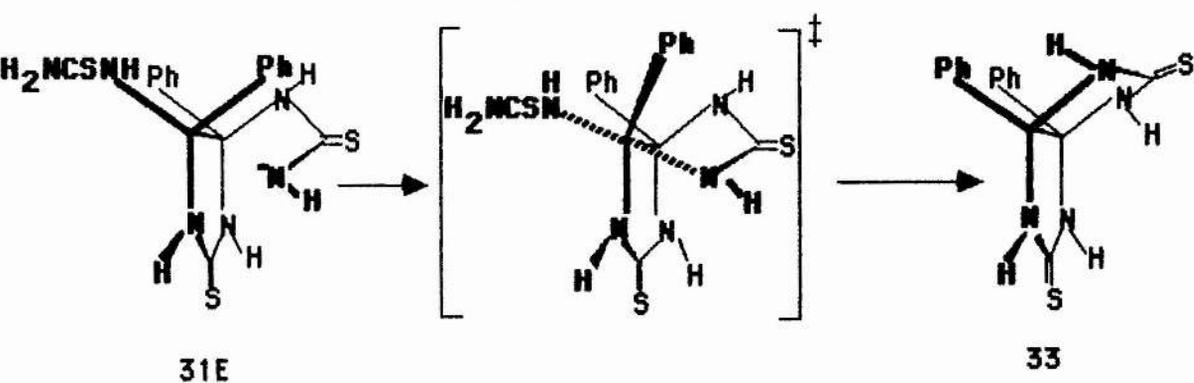


Figure 29: Concerted cyclisation of (31) to yield (33)



of thiourea across the carbon-nitrogen bond to give (32). It is highly probable that the more intense signal at 74.81 ppm corresponds to the less crowded E isomer. See figure 28.

Molecular models suggest that if the reaction of (31) to (33) occurs entirely via a concerted S_N2 like mechanism then it should be subject to stereochemical control. In the E isomer (31E) the nitrogen atom of one thiourea substituent is almost perfectly disposed to attack the adjacent carbon, expelling the other thiourea substituent as the nucleofuge. (see figure 29). Thus the cyclisation reaction should be relatively facile. In contrast to this, in the Z isomer it is impossible for one thiourea to reach the correct position for an S_N2 attack on the adjacent carbon with expulsion of the other thiourea. Thus cyclisation of (31Z) to (33) should not proceed at all via an S_N2 type process. No substance corresponding to (31) was isolated from this system, thus some process for the destruction of (31Z) must exist. The most plausible candidate for this process is elimination of thiourea to give (32).

It is of course quite possible for the imine centre of (32) to be attacked by the pendant thiourea to give (33) directly. The importance of this route in comparison to the concerted process is difficult to measure but models indicate that the pendant thiourea can attack the unsaturated centre of (32) to give both Z and E isomers of (33), whereas the concerted mechanism gives the Z isomer only. The two isomers are estimated to be of similar stability, the ring strain in the E isomer being offset by the steric interactions of the two phenyl groups in the Z form. We cannot quantify this because both structures are too complex for the available molecular mechanics programs.

The base catalysed condensation of benzil with urea gives 5,5-diphenylhydantoin and 3a,7a-diphenyltetrahydro-imidazo(4,5-d)imidazole-2,5-dione (34). It is reasonable to assume that this reaction proceeds by a very

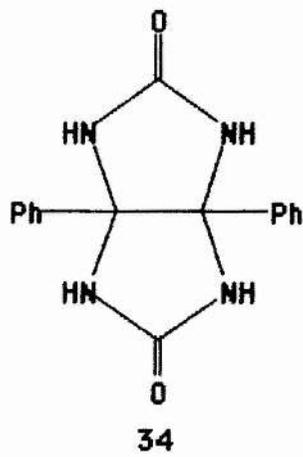
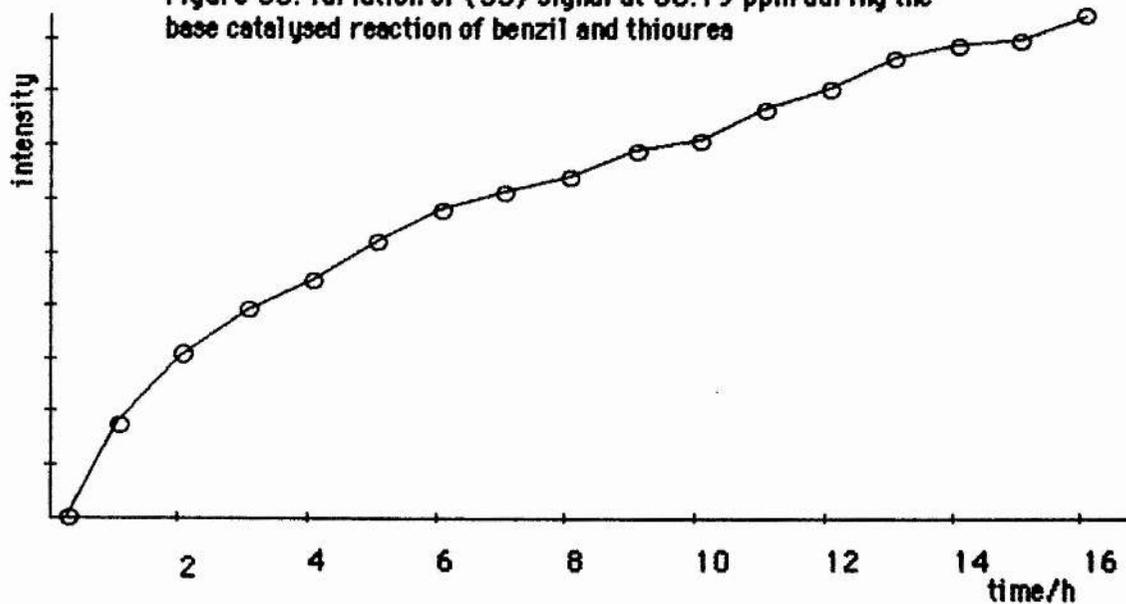


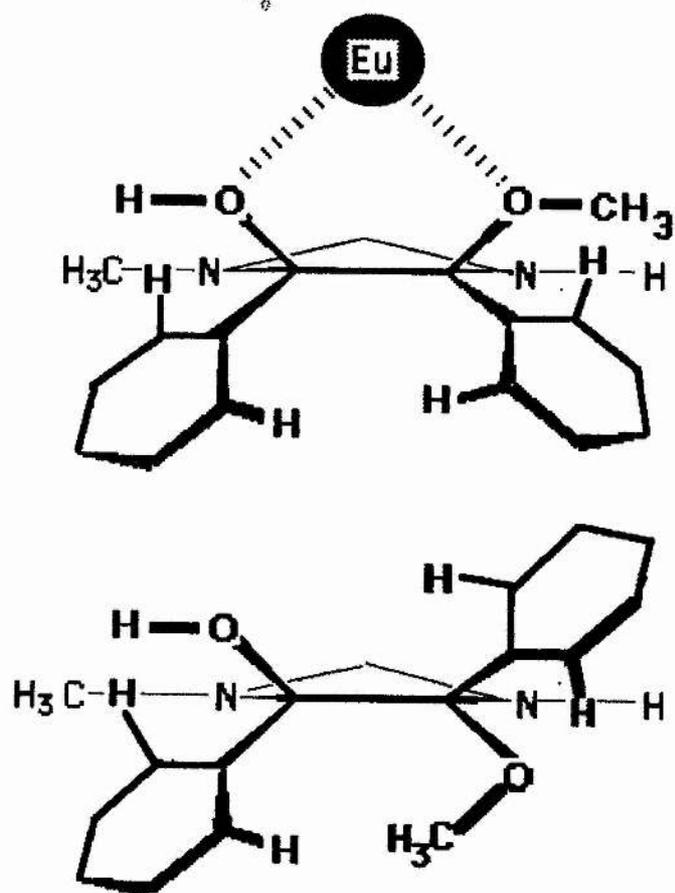
Figure 30: Variation of (33) signal at 86.19 ppm during the base catalysed reaction of benzil and thiourea



similar pathway to the reaction studied, since the reagents, products and reaction conditions used are completely analogous. Smeets et al⁶ have obtained a crystal structure for a derivative of this material which shows the two phenyl groups arranged in the Z configuration. The yield of the derivative is not 100%, so we cannot be absolutely certain that only the Z isomer is produced. However the carbon-13 nmr results for thiourea imply that only one isomer of (33) is produced and it is reasonable to assume this holds for urea also. If this result is indeed correct it implies that the primary process for the cyclisation of (31) is concerted nucleophilic substitution rather than elimination of thiourea to give (32) followed by nucleophilic addition to the unsaturated centre thus generated.

An authentic sample of the bicyclic product (33) shows a chemical shift in DMSO of 89.98 ppm. This is a reasonably close correspondence to the signal at 86.19 ppm, allowing for the difference in solvents, which increases smoothly throughout the course of the period studied. Both the shift and the intensity plot are completely consistent with the assignment of this signal to the bicyclic product (33). See figure 30.

Figure 31: Co-ordination of (7E) to the Europium centre of a chiral shift reagent



Stereochemistry of the dihydroxytetrahydroimidazoles

It is possible to distinguish between the Z and E isomers of these cyclic glycols by means of a chemical shift reagent such as $\text{Eu}(\text{fod})_3$. The Z isomer can act as a bidentate chelating ligand on the europium centre (see figure 31). In the case of the E isomer the bulky phenyl substituents prevent this so that the sensitivity of the alcoholic carbon atoms' shifts, and the proton shifts of the methoxy centres if present, to the concentration of shift reagent is much reduced. See table 4.

The sample of (7) isolated from the reaction of 1-methylthiourea and benzil is exclusively E. However, on allowing (7) to stand in chloroform for approximately two weeks some of the Z isomer is produced. It is probable that this interconversion is brought about by the traces of hydrochloric acid usually present in commercial chloroform. Studies of the acid catalysed reactions of benzil and thiourea later showed that (7) and (2) both exist in equilibrium with an epoxide when treated with acid in a non-nucleophilic solvent.

TABLE 4

substituents				change in OMe proton shift (ppm per mole c.s.r.)		change in C-OR carbon-13 shift (ppm per mole c.s.r.)	
N1	N3	O4	O5	Z	E	Z	E
H	H	H	H	-	-	309.4	2.0
H	Me	H	Me	4.98	0.17	-	-
Me	Me	Me	Me	7.77	0.33	95.95	1.75

The hydroxy groups have less steric interaction with the ligands of the shift reagent than the more bulky methoxy groups, thus the europium can approach the carbon centres of the diol (19) more closely than those of the dimethoxy material and so the change in the carbon-13 chemical shift of the quaternary carbon is even greater.

In the case of the glycol (3) formed from 1,3-dimethylthiourea it is not possible for the Z and E isomers to interconvert via a planar imine centre since the nitrogen substituents prevent dehydration across the C-N bond. Thus we may assume that the 2:1 ratio of E to Z isomer observed is entirely the result of kinetic control.

In contrast, the methoxy and ethoxy substituted compounds formed from benzil and 1-methylthiourea must, in order to have incorporated a molecule of the solvent, have undergone at least one dehydration to give a planar centre. Thus the diastereoisomer ratios of (7), (21) and (22) are both entirely under thermodynamic control. The steric energy of interaction appears to be quite considerable since no (7Z) was detected in the isolated material and the ratio of (21E) to (21Z) detected during the non-equilibrium carbon-13 nmr experiments was approximately 6:1.

EXPERIMENTAL SECTION

Infra red spectra were taken on a Perkin-Elmer 1420 ratio recording spectrophotometer, ultraviolet spectra on Pye-Unicam SP8-150 spectrophotometer, proton nmr spectra on a Bruker WH-360 spectrometer and carbon-13 nmr spectra on a Bruker CFT-20 spectrometer. Time resolved carbon-13 spectra were taken at the SERC nmr spectroscopy service at the University of Edinburgh on a Bruker W60 spectrometer. All melting points were uncorrected. First order rate constants were obtained by the method of Kezdy and Swinbourne⁷.

1,3-dimethyl-4,5-dihydroxy-4,5-diphenyltetrahydroimidazole-2-thione(2)-
 1,3-Dimethylthiourea (1.10g), benzil (2.10g) and sodium hydroxide (0.20g) were placed in aqueous ethanol (10% H₂O, 10ml) and refluxed for 2 hours. The solution was allowed to cool, water (10ml) was added and the mixture stirred for 30 min. The white precipitate was filtered off and washed with dichloromethane (25ml). Yield 82%

mp	150-1 C	(lit ¹ 158-9 C)
M/Z-H ₂ O	296	(C ₁₇ H ₁₈ N ₂ O ₂ S=314 g mol ⁻¹)
¹ H nmr (D ₆ acetone)	7.45ppm, 10H,m (Ph); 3.30ppm, 6H,s (NMe)	
¹³ C nmr (D ₆ acetone)	182.75 (C=S), 142.55, 127.94, 127.38, 126.70 (Ph); 97.71 (C-OH); 30.00 (NMe)	

5-ethoxy-4-hydroxy-3-methyl-4,5-diphenyltetrahydroimidazole-2-thione(7)-
 1-methylthiourea (1.81g), benzil (4.20g) and sodium hydroxide (0.20g) were placed in aqueous ethanol (10%, 10ml) and warmed gently to approximately 30 C over a period of 20 minutes. When the amount of solid precipitated appeared to have reached a maximum it was filtered off and washed with dichloromethane (10ml). Yield was variable, typically around 60%.

mp	140-2 C	
M/Z-EtOH	282	(C ₁₈ H ₂₀ N ₂ O ₂ S=328 g mol ⁻¹)
analysis	64.33% C (17.97), 5.96% H (19.84), 8.35% N (2.00)	
¹ H nmr (D ₆ acetone)	7.61 (1H,s NH), 7.16-6.93 (10H,m Ph), 5.13 (1H,s,OH), 3.60 (1H,d of q OCH ₂ CH ₃ attached to asymmetric C), 3.30 (1H,d of q OCH ₂ CH ₃ attached to asymmetric C), 2.99 (3H,s NCH ₃), 1.27 (3H,t, OCH ₂ CH ₃)	
¹³ C nmr (D ₆ acetone)	182.06 (C=S); 135.44-126.7 (7 signals-2 non-equivalent Ph); 98.38 (C-OMe); 94.58 (C-OH); 51.24 (OMe); 28.89 (NMe)	

Carrying out the same procedure using the same reagent concentrations but with methanol as solvent yields *5-methoxy-4-hydroxy-3-methyl-4,5-diphenyltetrahydroimidazole-2-thione*

mp	135-7 C	
M/Z-MeOH	282	(C ₁₇ H ₁₈ N ₂ O ₂ S=314 g mol ⁻¹)
¹ H nmr (CDCl ₃)	8.20, 1H,s (NH); 7.40-6.93, 10H,m (Ph); 3.30, 3H,s (OCH ₃); 3.00, 3H,s (NCH ₃)	
¹³ C nmr (CDCl ₃)	182.06 (C=S); 135.44-126.69 (7 signals-two non-equivalent Ph); 98.38 (C-OMe); 94.58 (C-OH); 51.24 (OCH ₃); 28.89 (NCH ₃)	

4,5-dihydroxy-4,5-diphenyltetrahydroimidazole-2-thione (19)- Thiourea (4.20g), benzil (11.60g) and sodium hydroxide (1.10g) were placed in aqueous ethanol (10%, 50ml) and stirred for a period of 20 minutes at room temperature (approx 20 C). When the amount of solid precipitated appeared to have reached a maximum water (10ml) was added and the precipitate was filtered off and washed with petrol until the washings remain colourless. Yield was variable, typically around 30%.

mp	95-6 C	
M/Z-H ₂ O	268	(C ₁₅ H ₁₄ N ₂ O ₂ S=286 g mol ⁻¹)
¹ H nmr (D ₆ DMSO)	8.15, 2H,s (OH); 7.40-7.10, 10H,m (Ph)	
¹³ C nmr (D ₆ DMSO)	188.82 (C=S); 142.06, 128.18, 127.67, 127.26 (Ph);	

73.91 (C-OH)

5,5-diphenyl-3-methyl-2-thiohydantoin (9)- 1-methylthiourea (0.91g), benzil (1.20g) and sodium hydroxide (0.20g) were placed in aqueous ethanol (10%, 10ml) and refluxed for 3 hours. Water (10ml) was added and the white solid filtered off after standing for 30 min. The product was recrystallised from ethanol (10ml). Yield 70%

mp	182-3 C	(lit ¹ 185 C)
M/Z	282	(C ₁₆ H ₁₄ N ₂ OS=282 g mol ⁻¹)
NH str	3260 cm ⁻¹	(lit ⁸ 3270 cm ⁻¹)
C=O str	1725 cm ⁻¹	(lit ⁸ 1730 cm ⁻¹)
¹ H nmr (CDCl ₃)	7.45ppm, 5H,m (Ph); 3.30ppm, 3H,s (NCH ₃)	
(lit ⁸ 3.25ppm)		
¹³ C nmr (DMSO/D ₂ O)	181.54 (C=S); 173.47 (C=O); 138.14, 128.64, 128.42, 126.60 (Ph); 71.35 (C(Ph) ₂); 27.33 (NCH ₃)	

5,5-di(4-methylphenyl)-3-methyl-2-thiohydantoin (9, Ar=4-methylphenyl)- was obtained by the same procedure as above replacing benzil by 4,4-dimethylbenzil (1.34g). Yield 65%

mp	151-3	
M/Z	310	(C ₁₈ H ₁₈ N ₂ OS=310 g mol ⁻¹)
NH str	3150 cm ⁻¹ , C=O str 1735 cm ⁻¹	
analysis	69.43% C, 5.77% H, 8.96% N	
theoretical	69.65% C, 5.84% H, 9.02% N	

5,5-di(4-chlorophenyl)-3-methyl-2-thiohydantoin (9, Ar=4-Chlorophenyl)- was obtained by the same procedure as above replacing benzil by 4,4-dichlorobenzil (2.73g). Yield 35%

mp	184-5
M/Z	not observed
NH str	3130 cm^{-1} , C=O str 1747 cm^{-1}
analysis	54.65% C, 3.43% H, 7.96% N
theoretical	54.70% C, 3.42% H, 7.98% N

3,5,5-triphenyl-2-thiohydantoin- was obtained by the same procedure as 5,5-diphenyl-3-methyl-2-thiohydantoin replacing 1-methylthiourea by 1-phenylthiourea. Yield 60%.

mp	244-5
M/Z	not observed
NH str	3300 cm^{-1} , C=O str 1738 cm^{-1}
analysis	72.88% C, 4.71% H, 8.09% N
theoretical	73.23% C, 4.68% H, 8.13% N

3a,6a-diphenyltetrahydro-imidazo(4,5-d)imidazole-2,5-dithione (33) -thiourea (1.52g), benzil (2.10g) and sodium hydroxide (0.20g) were dissolved in n-butanol and refluxed for 2.5 hours. The white ppt was filtered off and washed with water (10ml) and ether (10ml). Yield 70%. The use of sodium butoxide as base increases the yield by 5%. The reaction also occurred readily in ethanol but the yield was reduced to approximately 30%.

mp	303-4 C	(lit ¹ 307 C)
M/Z	326	($C_{16}H_{14}N_4S_2=326\text{ g mol}^{-1}$)
NH str	3150 cm^{-1}	
¹ H nmr (D ₆ DMSO):	7.45ppm, m (Ph)	
¹³ C nmr (D ₆ DMSO)	182.66 (C=S); 135.51, 128.66, 128.14, 126.97 (Ph);	
89.98 (C(NHR) ₂)		

5,5-diphenyl-2-thiohydantoin(23)- thiourea (1.00g), benzil (2.10g) and sodium hydroxide (0.20g) were dissolved in aqueous ethanol (10%, 10ml) and refluxed for 2.5 hours. The *3a,6a-diphenyltetrahydro-imidazo(4,5-d)imidazole-2,5-dithione* was filtered off and washed with ethanol (10ml). Water (20ml) was added to the combined filtrate and washings and the solution was distilled down to approximately 10ml. The thiohydantoin was then filtered off and washed with dichloromethane (10ml).

mp	236-8	(authentic sample 237-9)
M/Z	268	($C_{16}H_{14}N_2OS=282 \text{ g mol}^{-1}$)

Infra red spectrum was a perfect match with a commercial sample (Aldrich)

^1H nmr (DMSO/ D_2O)	7.45, m (Ph)
^{13}C nmr (DMSO/ D_2O)	196.75 (C=S); 175.09 (C=O); 142.12, 127.86, 127.05, 126.84 (Ph); 73.37 (C(Ph) $_2$)

4,5-dimethoxy-4,5-diphenyltetrahydroimidazole-2-thione-

4,5-dihydroxy-4,5-diphenyltetrahydroimidazole-2-thione (2.57g) and silver oxide (2.3g) were dissolved in methyl iodide (5ml) and warmed gently for 20 minutes. The silver iodide precipitate was filtered off and washed with acetone (10ml). The washings were combined with the filtrate and the solvents removed on the rotary evaporator to give a crystalline solid which was recrystallised from methanol.

mp	200-2	
M/Z-2MeOH	296	($C_{19}H_{22}N_2O_2S=342 \text{ g mol}^{-1}$)

IR shows no O-H str band

^1H nmr ($CDCl_3$)	7.05 (10H, m Ph), 3.60 (6H, s NCH_3), 3.25 (3.6H, s OCH_3 (E isomer)), 2.95 (2.4H, s OCH_3 (Z isomer))
^{13}C nmr ($CDCl_3$)	185.63 (C=S); 135.73-126.42 (7 signals-2 non-equivalent Ph); 100.43 (C-OMe); 53.81 (OCH_3 (E isomer)); 51.84 (OCH_3 (Z isomer)); 32.84 (NCH_3)

3,4-dihydro-4-hydroxy-4,5-di(4-nitrophenyl)-3-methylimidazole-2-thione
 (8)- 1-methylthiourea (0.70g), 4,4-dinitrobenzil (2.19g) and sodium hydroxide
 (0.11g) were placed in aqueous ethanol (10%, 5.5ml) and refluxed for 2 hours. The
 orange solid was filtered off, washed with dichloromethane and then with ether until the
 washings were colourless. Yield 40%

mp	221-3	
M/Z	not observed	(C ₁₆ H ₁₂ N ₄ O ₅ S=372 g mol ⁻¹)
OH str	3300 cm ⁻¹ (br,w);	C=N str 1635 cm ⁻¹
¹ H nmr (CDCl ₃)	8.30-7.90, 8H,m (Ar);	7.10, 1H,s (OH); 2.45, 3H,s (NCH ₃)
¹³ C nmr (DMSO/D ₂ O)	180.47 (C=S);	148.86 (C=N); 130-123 (Ar); 27.33 (NCH ₃)
analysis	51.55% C, 3.28% H, 15.00% N	
theoretical	51.66% C, 3.25% H, 15.06% N	

The substituted benzils not available commercially and the benzil enriched with
 carbon-13 at the carbonyl position were prepared via Breslow's thiazolium salt
 catalysed benzoin condensation⁹, followed by oxidation with nitric acid.

4,4-dinitrobenzil: -p-nitrobenzaldehyde (7.10g), triethylamine (1.52g) and
 3-ethyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium bromide (0.62g) were
 dissolved in ethanol (15ml), refluxed for 90 minutes under dry nitrogen and the
 solvent and triethylamine removed on the rotary evaporator. Water (20ml) was added
 and distilled off on the rotary evaporator to ensure the removal of all the ethanol (nitric
 acid reacts explosively with alcohols). The benzoin was oxidised by refluxing in
 concentrated nitric acid (15ml) for 4 hours, water (75ml) added and the crystals
 filtered off. The 4,4-dinitrobenzil was recrystallised from ethanol (50ml). Yield
 63%.

mp	219-20	(lit ¹⁰ 214)
C=O str	1688 cm ⁻¹	

4,4'-dichlorobenzil:—was prepared in the same way from 4-chlorobenzaldehyde (6.58g). It was recrystallised from toluene (30ml). Yield 72%.

mp	195-6	(lit ¹⁰ 198-9)
C=O str	1655 cm ⁻¹	

Carbon-13 enriched benzil—was prepared in the same way from benzaldehyde with 20% carbon-13 enrichment at the carbonyl centre (5.00g). It was not recrystallised but only washed repeatedly with water until the washings were colourless.

The carbon-13 spectrum was identical to a commercially available sample with the carbonyl signal intensity increased by a factor of 22.7. The spectrum revealed traces of the thiazolium catalyst but this proved to be completely stable to the experimental conditions and showed no reaction with the thioureas.

Carbon-13 enriched benzil (0.0840g) and thiourea (0.0913g) were dissolved in tetradeuteromethanol (1.5ml) thermostatted at 25 C and the initial carbon-13 spectrum recorded. Sodium hydroxide (0.008g) dissolved in tetradeuteromethanol (0.5ml) was then added and the carbon spectra recorded automatically at hourly intervals for sixteen hours using a fifteen minute acquisition time for each spectrum. This procedure was repeated using identical reagent concentrations taking spectra at fifteen minute intervals over the first 150 minutes of reaction, using a five minute acquisition time.

Carbon-13 enriched benzil (0.0420g) and 1-methylthiourea (0.0198g) were dissolved in tetradeuteromethanol (1.5ml) thermostatted at 25 C and the initial carbon-13 spectrum obtained. Sodium hydroxide (0.004g) dissolved in

tetradeuteromethanol (0.5ml) was added and the carbon spectrum taken at hourly intervals for seventeen hours using a fifteen minute acquisition time for each spectrum.

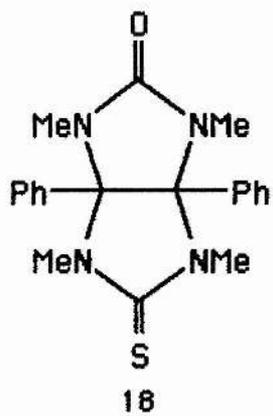
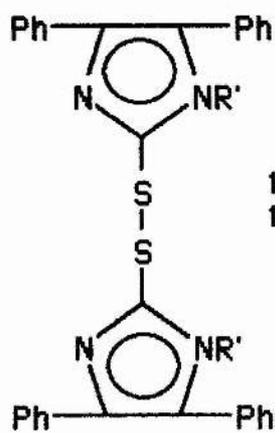
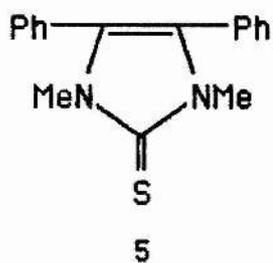
The experiment was repeated using identical reagent concentrations and the same spectral interval but thermostating the mixture at 40 C.

APPENDIX 1: LITERATURE REFERENCES

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Chapter 2

The acid catalysed reactions of
thiourea, 1-substituted thioureas
and 1,3-disubstituted thioureas
with benzil and substituted benzils



Introduction

In contrast to the base catalysed reactions described in chapter 1, where each thiourea reacted in essentially the same manner as the urea with corresponding nitrogen substituents, the replacement of ureas by thioureas with identical substituents on nitrogen has a dramatic effect upon the course of the acid catalysed reaction with benzil and completely alters the nature of the products.

Again in contrast to the base catalysed reactions, the presence of alkyl or aryl substituents upon the nitrogen atoms of the thiourea has little effect upon the course of its reaction with benzil under acidic conditions, except for the case of 1,1' disubstitution which inhibits reaction completely. All the thioureas examined reacted with benzil to give a 1,3-dihydro-4,5-diphenylimidazole-2-thione with the corresponding nitrogen substituents, such as (5), (11) and (17), together with varying proportions of the corresponding urea and a bicyclic material which can be regarded as one imidazole-2-thione fused to one imidazole-2-one, such as (18). The amount of 1,3-dihydro-4,5-diphenylimidazole-2-thione and the sum of the amounts of the urea and the bicyclic material obtained were exactly equivalent. We show below that the proposed mechanism requires precisely this result.

All of the acid catalysed processes occur readily under a wide range of conditions, ranging from ethanolic hydrochloric acid to titanium tetrachloride in dry ether.

Scheme 1

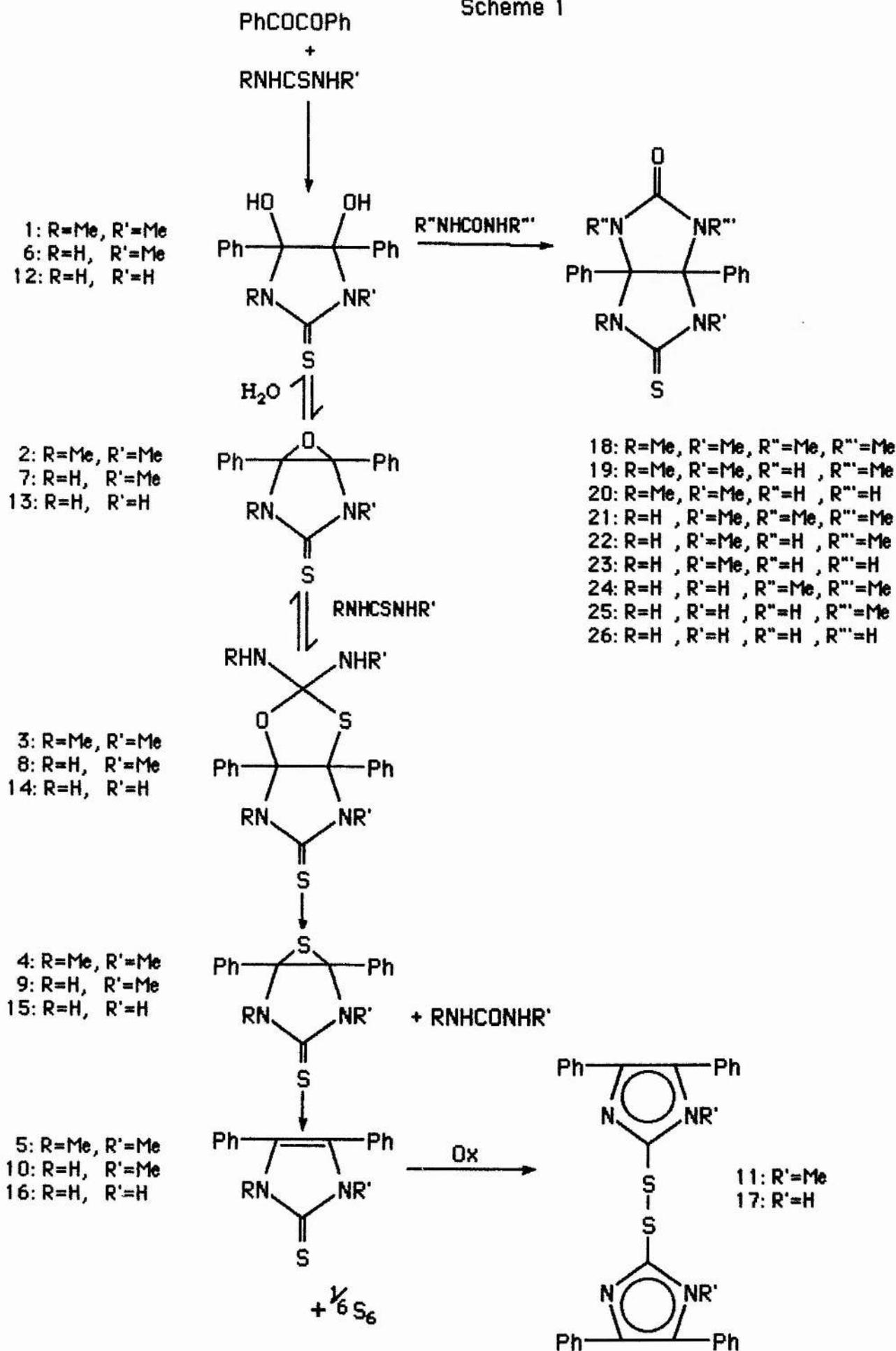
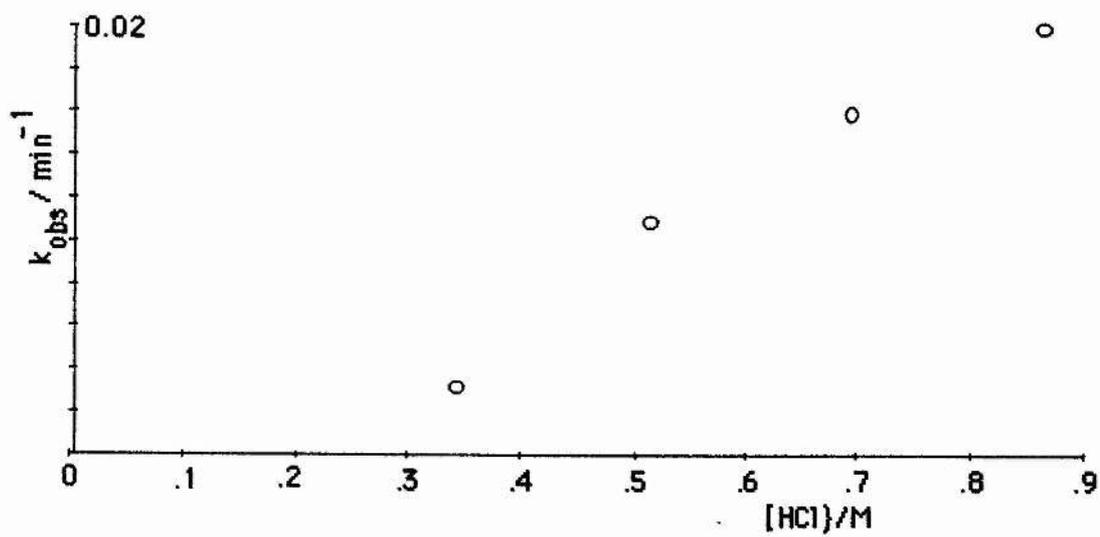


Figure 1: Pseudo first order rate constant for (5) production from (1) and excess 1,3-dimethylthiourea vs acid concentration



Results and Discussion

The primary evidence in favour of the sequence shown in scheme 1 was obtained by unambiguous preparation of the majority of the intermediates shown, together with kinetic data obtained by ultraviolet spectroscopy. The acid catalysed reactions proved much less amenable to study by means of carbon-13 nmr than the base catalysed series, although some useful information was obtained by following the course of the reaction using benzil enriched to 22% carbon-13 at the carbonyl position.

The reaction sequence will be discussed in detail for the reaction of 1,3-dimethylthiourea with benzil to give 1,3-dimethyl-4,5-diphenyl-2-thioimidazole (5), 1,3-dimethylurea and trace amounts of 3a,7a-diphenyltetrahydrotetramethylimidazo-[4,5-d]-imidazole-2-one-5-thione (18), principally because the independent preparation of the various intermediates was most successful in this particular case.

The first step in the sequence is, as might be predicted from the reaction of 1,3-dimethylurea with benzil¹, addition of the 1,3-dimethylthiourea to benzil to give the cyclic diol (1). This material can be prepared readily from the base catalysed reaction of 1,3-dimethylthiourea with benzil discussed in chapter 1 and has been completely characterised by mass spectroscopy, elemental analysis and infra-red, ultraviolet, proton and carbon-13 nmr spectroscopy. Diol (1) reacts under acidic conditions with any thiourea, irrespective of the latter's nitrogen substitution pattern, to give the unsaturated material (5) and the corresponding urea. Compound (5) absorbs strongly at 340nm, where the absorbance of (1) is negligible, and it proved possible to obtain good pseudo first order rate constants for the reaction in alcoholic hydrochloric acid spectrophotometrically. The rate increases with acid concentration as shown in figure 1, thus the acid is not required merely to catalyse the formation of the diols, which does not occur in neutral media, and hence we may conclude that

protonation of the diol's hydroxyl group is required for the reaction to proceed. The rate also shows fractional order dependence on the concentration of the thiourea when it is in at least ten-fold excess (see table 1). Since 1,3-dimethylthiourea is hygroscopic and the rate constant shows very high sensitivity to the water content at low water concentrations, the reaction was carried out in ethanol containing 2% water by volume. Unfortunately the decrease in the protonating power of the medium caused by the water made it necessary to carry out the reaction at reflux, removing samples at intervals, to obtain a reasonable rate.

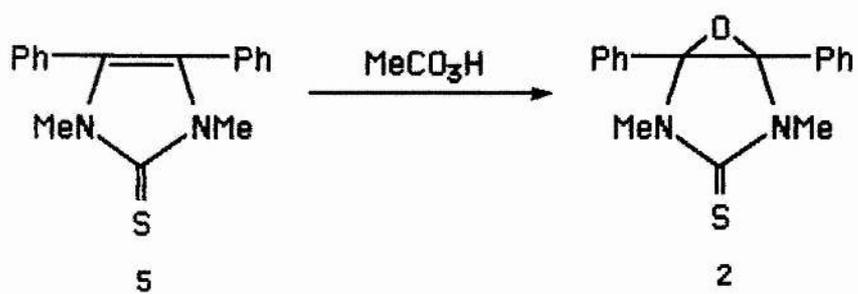
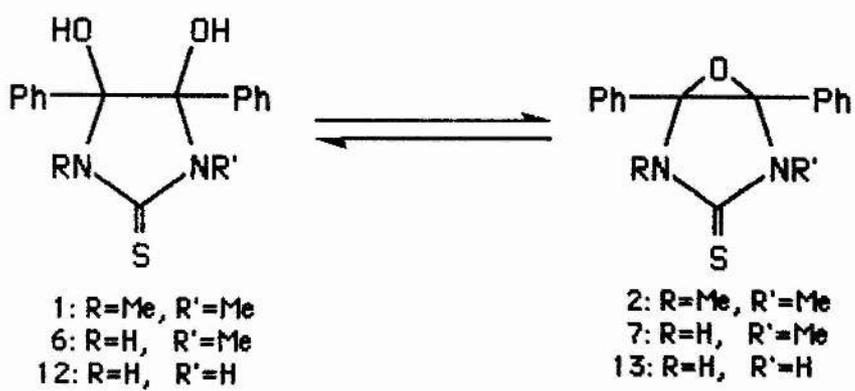
Table 1

[1,3-dimethylthiourea]/M	$10^4 k_{\text{obs}}/\text{min}^{-1}$
0.0	0.41
0.05	1.58
0.10	1.64
0.15	1.70
0.20	1.76

k_{obs} is the pseudo first order rate constant for (5) production in 98% aqueous ethanol at reflux at a hydrochloric acid concentration of 0.26 M.

The rate also depends to some extent on the degree of nitrogen substitution of the reagent thiourea, which will be discussed in more detail at a later stage.

Reaction between epoxides and thioureas to give episulphides (thiiranes) and the corresponding urea are not uncommon and a mechanism via a cyclic intermediate such as (3), (8) or (14) as shown in scheme 1 has been proposed². Thermal desulphurization of episulphides to olefins is also known to occur in many systems and it has been shown to particularly facile in the case of di-aromatic substituted episulphides³. Stilbene oxide has been shown to react with thiourea to give stilbene



presumably along with urea and elemental sulphur⁴. The reaction is also known to occur when thiourea is replaced by sodium isothiocyanate and a very similar mechanism has been proposed⁵. These reactions have been the subject of a review⁶.

When elemental sulphur is generated slowly in dilute solution by the reaction of sodium thiosulphate and hydrochloric acid it is reported⁷ that the allotrope produced is not the familiar cyclooctasulphur but cyclohexasulphur or Engel's sulphur. This allotrope is soluble in organic media such as toluene and dichloromethane. The absence of sulphur precipitate in our system suggests that this soluble allotrope is being produced. This is not unreasonable given that we are again producing elemental sulphur very slowly in a dilute medium, mimicking the conditions normally required for cyclohexasulphur production. The addition of water to the product solution leads to the formation of a colloidal suspension which was shown to contain sulphur by mass spectroscopy.

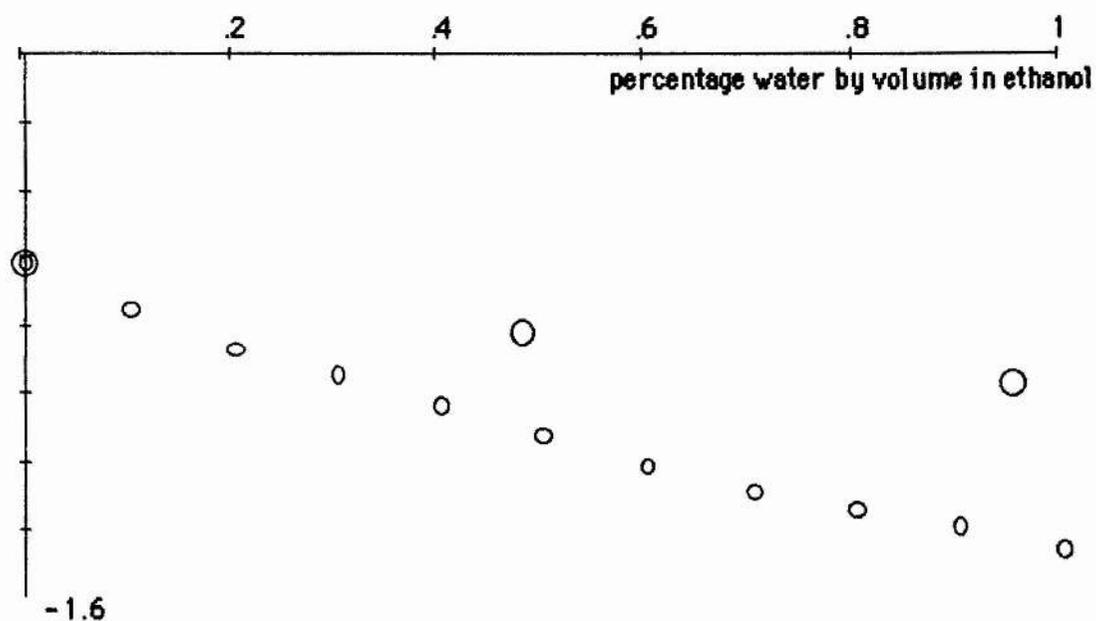
We have excellent evidence that acid catalysed dehydration of the diols (1), (6) and (12) to give epoxides (2), (7) and (13) respectively could be a step on the reaction pathways although we cannot prove that it actually is one. Olefin (5) can be treated with peracetic acid generated in situ from acetonitrile and hydrogen peroxide to yield the epoxide (2) in good yield. The thione centre of (5) remains intact and does not react with the peracid, as is shown by the retention of the carbon-13 signal at 162.73 ppm in (2). This once again demonstrates the unreactivity of the thiourea moiety compared to a thiocarbonyl group, which normally reacts with peracids by the addition of oxygen to the sulphur atom.

The epoxide (2) reacts extremely rapidly in both acidic and neutral media in the presence of excess 1,3-dimethylthiourea to give (5) in excellent yield, together with 1,3-dimethylurea. The rate of reaction between (2) and thiourea to give (5) could in theory be monitored spectrophotometrically in the same way as the reaction of (1) with thioureas. However the reaction is too fast to measure by any method other

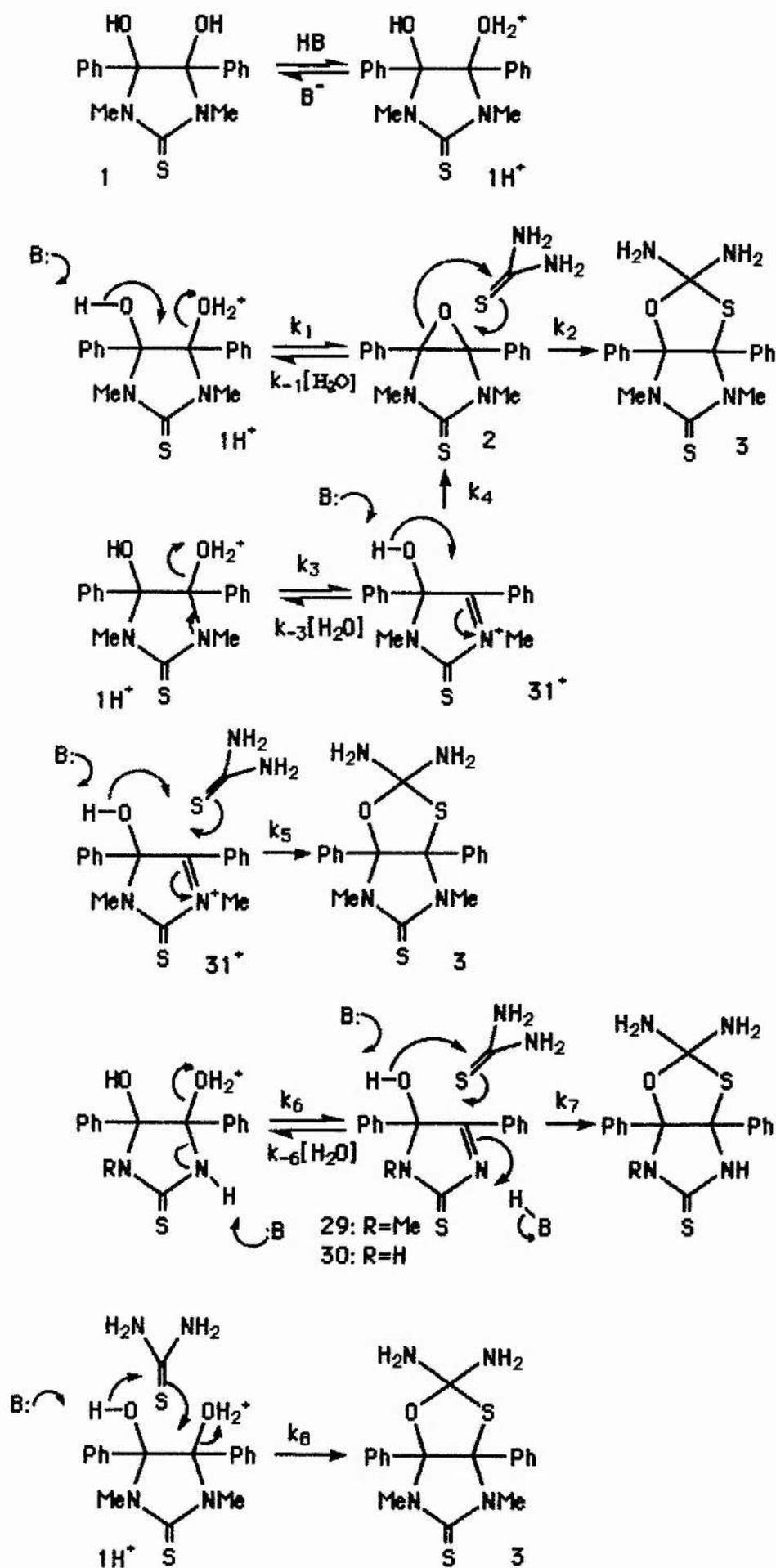
Figure 2: Acidity function and rate of (5) production versus water content of ethanol

○ Acidity function for primary anilines

○ \log (pseudo first order rate constant for (5) production) - 1.085



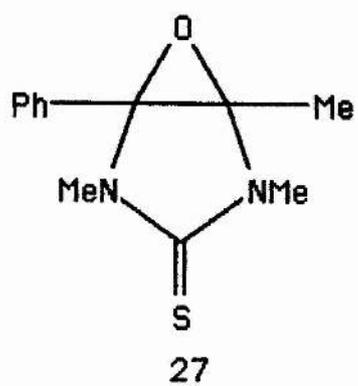
Scheme 2



than stopped flow techniques, the concentration of (5) reaching its final value within 10 seconds of the addition of the thiourea solution irrespective of the pH.

An attempt was made to show that the rate determining step in the reaction of (1) to give (5) is in fact a dehydration process from the dependence of the rate of reaction on the concentration of water at a constant acid concentration. The rate does indeed decrease very strongly at constant acid concentration in ethanol on addition of even very low concentrations of water (see figure 2). Unfortunately this strong dependence on water concentration in slightly aqueous solvents is reflected in the equally strong dependence of the acidity functions of non-aqueous solvents on small concentrations of water. This is usually ascribed to protons being solvated much more effectively by water than any other common solvent. Comparison of the dependence of the rate on water content with a relevant acidity function is difficult; not only because the diol can be protonated on either the nitrogen or the oxygen centres, with only the latter leading to reaction, but also because the only acidity function determined for ethanol/water mixtures, due to Braude and Stern⁸, refers to primary anilines. The rate shows a smaller dependence on the water concentration than this acidity function (see figure 2). The significance of this result, if any, is not readily apparent.

We can distinguish four separate acid catalysed routes from the diols (1), (6) and (12) to the oxathiolane intermediates (3), (8) and (14) respectively, which are summarised in scheme 2. We have shown conclusively that the reaction can proceed via the epoxides (2), (7) and (13) but it can also proceed via direct nucleophilic substitution of the protonated hydroxyl group by thiourea. In the case of (6) and (12) reaction can proceed via dehydration across the carbon-nitrogen bond of the neutral diol to give imines (29) and (30) respectively followed by nucleophilic attack by thiourea on the carbon. In the case of (1) reaction can occur via unimolecular dehydration of the protonated diol to give charged quaternary imine (31), the imino carbon of which can undergo nucleophilic attack either intermolecularly by thiourea to give (3) or



intramolecularly by the adjacent hydroxyl group to give the epoxide (2). The analogous charged imines formed from (6) or (12) can of course undergo both the above reactions and also lose a proton from nitrogen to give (29) and (30) respectively.

From the immeasurably fast rate of formation of (5) from (2) and any thiourea discussed above we can assume that the decomposition of (3) to (4) and the desulphurization of (4) are both extremely fast processes compared to the formation of (2) and therefore not rate determining. Hence we may approximate that the rate of formation of (3), which cannot be measured, corresponds to the rate of formation of (5), which may be conveniently followed by ultraviolet spectroscopy.

We know that epoxide (2) reacts very rapidly with thiourea and that its rate of formation from (1) is much slower. Hence we can apply the steady state approximation to its concentration to obtain equation 1 for the rate of (3) formation via epoxide (2)

$d[3]/dt_{ep}$

$$d[3]/dt_{ep} = k_1 k_2 [DMTU] [(1^+)] / (k_{-1} [water] + k_2 [DMTU]) \quad 1$$

[DMTU] is the concentration of 1,3-dimethylthiourea and [water] the concentration of water.

The reaction of (2) with 1,3-dimethylthiourea is known to be very rapid and a similar epoxide (27), which was prepared during the investigations to be described in chapter 3, proved very resistant to acid catalysed hydrolysis. Hence we can assume that the rate of hydrolysis of the epoxide is negligible in comparison to its rate of reaction with thioureas which simplifies equation 1 to equation 2

$$d[3]/dt_{ep} = k_1 [(1^+)] \quad 2$$

The protonated diol ($1H^+$) can also eliminate water in a different way to give the quaternary charged imine (31^+). This species can react with water to regenerate ($1H^+$), react with thiourea to give (3) or rearrange to the epoxide (2). The first process is non-productive although it will have a profound influence on the relative

rates of reaction of the two possible isomers of (1) as will be discussed below. If we make the reasonable assumption that the second and third processes are both much more rapid than the rate of ($1H^+$) dehydration to give (31^+), then the concentration of (31^+) will be sufficiently small for the application of the stationary state approximation to [(31)] giving an equation for the rate of (3) formation via the imidazole, $d[3]/dt_{im}$.

$$d[3]/dt_{im} = (k_5 + k_4 k_2) [31^+] [DMTU] \quad 3$$

$$\text{but } [31^+] = k_3 [1H^+] / (k_{-3} [H_2O] + k_4 + k_5 [DMTU]) \quad 4$$

$$\text{Hence } d[3]/dt_{im} = k_3 (k_5 + k_4 k_2) [1H^+] [DMTU] / (k_{-3} [H_2O] + k_4 + k_5 [DMTU]) \quad 5$$

$$\text{ie } k_{im} = k_3 (k_5 + k_4 k_2) [DMTU] / (k_{-3} [H_2O] + k_4 + k_5 [DMTU]) \quad 6$$

The rate of direct nucleophilic substitution of (1^+), $d[3]/dt_{sb}$, of course follows equation 7

$$d[3]/dt_{sb} = k_8 [(1^+)] [DMTU] \quad 7$$

It is reasonable to assume that the rate of direct nucleophilic substitution of non protonated (1) is negligible.

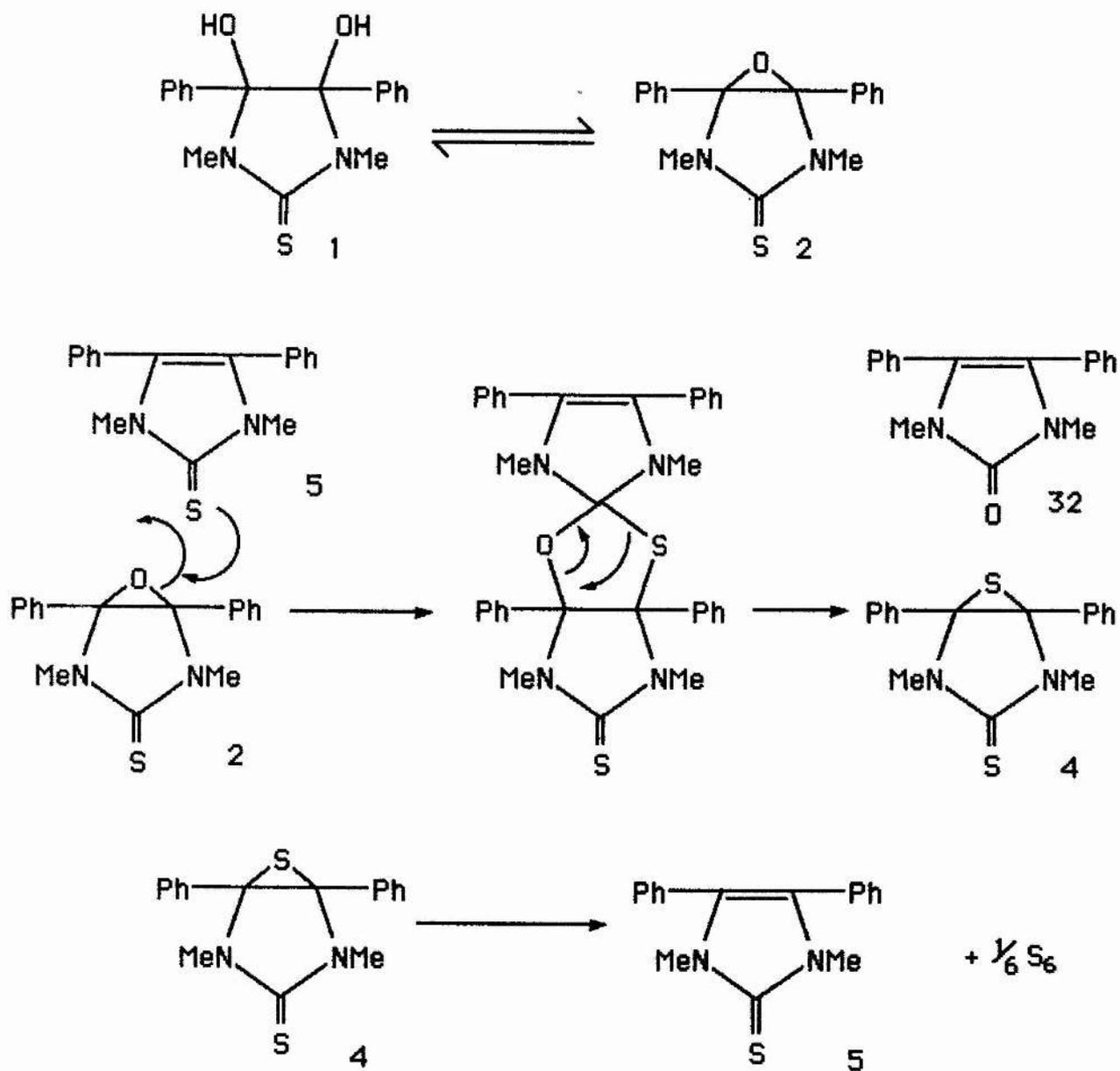
The total rate of (3) formation is given by equation 8

$$d[3]/dt = k_{obs} [(1)] = (k_1 + k_{im}) [(1^+)] + k_8 [(1^+)] [DMTU] \quad 8$$

Equation 8 contains three terms which are respectively zero, first and fractional order in 1,3-dimethylthiourea concentration, thus analysis of the dependence of the rate of (5) formation on 1,3-dimethylthiourea concentration will be difficult if not impossible. Taken with the high susceptibility of the rate of reaction to the presence of water and the hygroscopic nature of 1,3-dimethylthiourea, it was concluded that further studies of this aspect of the reaction were not worthwhile.

Because of the negligible contribution of the terms corresponding to attack by

Scheme 3



the thiourea on the epoxide and the quaternary imine to the observed rate the difference in overall rate of reaction between (1) and thiourea or 1,3-dimethylthiourea is quite small and due only to the difference in the rates of direct nucleophilic substitution *k_g*. This conceals a much higher difference in the rate of nucleophilic attack by thiourea and 1,3-dimethylthiourea on (2) and (31⁺) which has been confirmed by a competition experiment in which (2) was treated with an excess of an equimolar mixture of thiourea and 1,3-dimethylthiourea. Only trace amounts of 1,3-dimethylurea were produced. In fact, in acid in the absence of external thiourea (5) can react with (1), or to be precise with (2), to give (32) and another molecule of (5) (see scheme 3). Nevertheless in the presence of two equivalents of thiourea no trace of (32) could be detected by mass spectroscopy. When (5) is treated with an excess of a less hindered epoxide such as ethylene oxide in THF (32) is obtained rapidly in excellent yield.

It has been shown by use of a europium shift reagent that (1) is produced from 1,3-dimethylthiourea and benzil by base catalysis as a mixture of the E and Z isomers in a ratio of approximately two to one (see chapter 1). Acid catalysed epoxidation of glycols is normally a stereospecific process proceeding with complete inversion of configuration at one centre. Hence if reaction took place entirely via elimination to give the epoxide followed by addition of thiourea we would expect the Z isomer, which cannot dehydrate by the usual concerted process since this would give an impossibly strained E form of (2), to react very much more slowly. The Z isomer can only form an epoxide via a high energy barrier S_N1 type process requiring the intermediacy of a carbocation. The formation of a carbocation will be especially unfavourable in a non-aqueous solvent which will solvate charged species poorly compared to aqueous media (as demonstrated by the strong dependence of Braude and Stern's acidity function⁸ of anilines in ethanol on even trace amounts of water). Carbon-13 studies during the course of the reaction showed that the two isomers of (1) do indeed react at significantly different rates (see

Figure 3: Variation carbon-13 of signals due to E and Z isomers of (1) during reaction with 1,3-dimethylthiourea in ethanolic hydrochloric acid.

○ (1Z) 94.85 ppm ○ (1E) 95.64 ppm

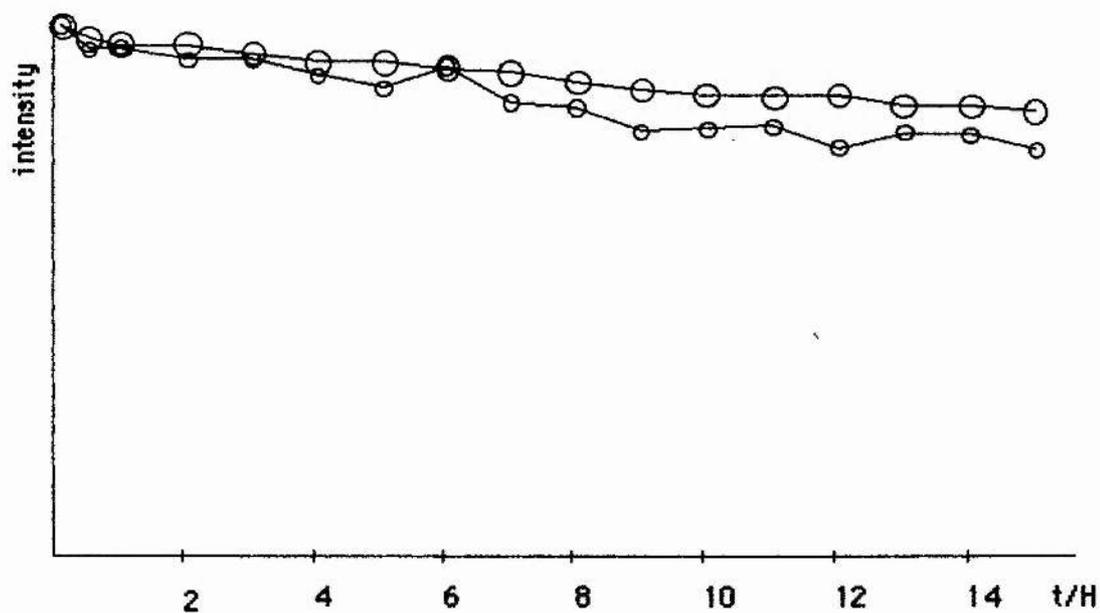
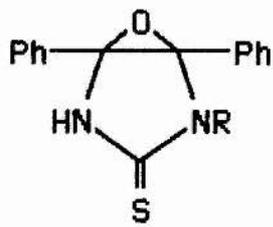


figure 3), which is consistent with the reaction pathway via the epoxide making a significant contribution to the overall rate of (3) formation. The Z isomer of the protonated diol ($1H^+$) can, however, react with thiourea by direct nucleophilic substitution of the protonated hydroxyl group or it can dehydrate in a unimolecular process to give (31^+), which can itself react with thiourea to give (3) or alternatively react with water to regenerate ($1H^+$) as either the Z or E isomer. On prolonged storage of a sample of (1) in commercial chloroform, which normally contains traces of hydrochloric acid, (1) isomerises over a period of days to give a higher proportion of the less sterically crowded E isomer via such a process.

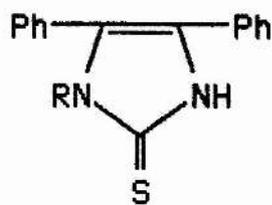
Whilst we can assume that the rate of substitution of the hydroxyl group by thiourea either directly or via (31^+) is approximately the same for both isomers, we cannot determine the rate of the isomerisation reaction. The difference in rates of reaction with thiourea between the Z and the E isomers corresponds not only to the rate of reaction of the E isomer via the epoxide but also to the rate of isomerisation of the Z form to the more reactive E isomer.

The difference in rates of destruction of the Z and E form is approximately one third the total rate of destruction of the E form. The significance of this result is uncertain, not only because of the unknown rate of isomerisation of (1) but also because we cannot determine the relative amounts of the Z and E isomers of (1) generated by the acid catalysed reaction. Thus we cannot make truly quantitative comparisons with the results obtained from obtaining the dependence of the rate of (5) formation on 1,3-dimethylthiourea concentration spectrophotometrically.

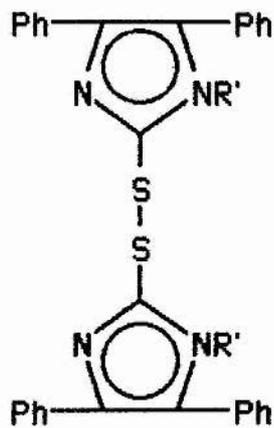
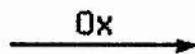
No signals due to the epoxide centres of (2) could be detected but from its rate of reaction with 1,3-dimethylthiourea we can predict that its concentration would be undetectably small even if reaction proceeded entirely via (2). The rate of reaction was unfortunately rather lower than ideal, because the sample of hydrochloric acid in hexadeuteroethanol used proved to be unstable and so the actual acidity of the reaction



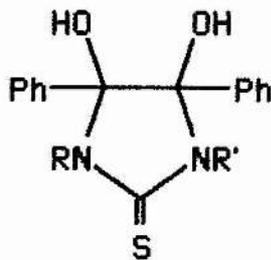
7: R=Me
13: R=H



10: R=Me
16: R=H



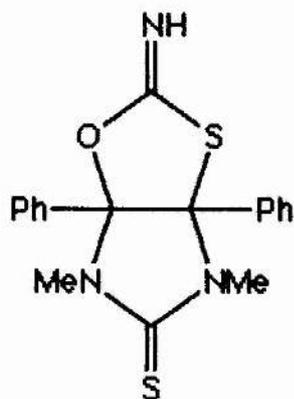
11: R'=Me
17: R'=H



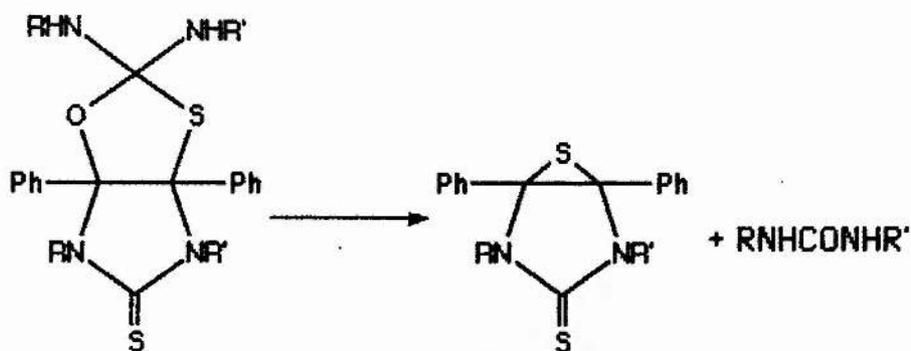
1: R=Me, R'=Me
6: R=H, R'=Me
12: R=H, R'=H

medium was rather less than that which had previously been found to be appropriate using non carbon-13 enriched material. Given that the likelihood of any of the intermediates reaching detectable concentrations at a higher acid concentration was small it was decided not to expend more of the extremely expensive labelled benzil on a repeat experiment. The unusual choice of acid and solvent was dictated by the solubility of (5) in the commonly available deuterated solvents and the strong dependence of the rate of reaction upon the concentration of water.

In the reactions of 1-methylthiourea and thiourea with benzil there is a complication which makes preparation of the epoxide intermediates (7) and (13) impossible. Compounds (10) and (16) have a secondary amine adjacent to a thioketone group and so can tautomerise to aromatic 2-thioimidazoles. Thiols are particularly prone to oxidation to bisulphides and under the mildly oxidising conditions used (10) and (16) are oxidised to the bisulphide dimers (11) and (17) respectively. Obviously it is impossible to oxidise the delocalised system with peroxy acid to give (7) or (13), unlike the isolated double bond of (5). We have however prepared the diol (12) and an analogue of (6) where one hydroxyl group is replaced by a methyl ether by base catalysed reaction of the relevant thiourea with benzil in methanol (see chapter 1). When treated with any thiourea under acid conditions (6) gives (11) and (12) gives (17) together with the relevant bicyclic compound (21-26). It is therefore very reasonable to propose that thiourea and 1-methylthiourea follow the same reaction pathway as 1,3-dimethylthiourea. Compound (12) when treated with a large excess of 1-methylthiourea gave no trace of (11), which can readily be detected from the distinctive proton chemical shift of the methyl group attached to an aromatic imidazole. This shows that under the conditions of these experiments dissociation of the diols to benzil and thiourea is negligible, since any free benzil thus produced is much more likely to react with the large excess of 1-methylthiourea than with the very small amount of thiourea present.

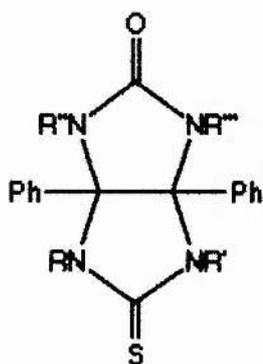


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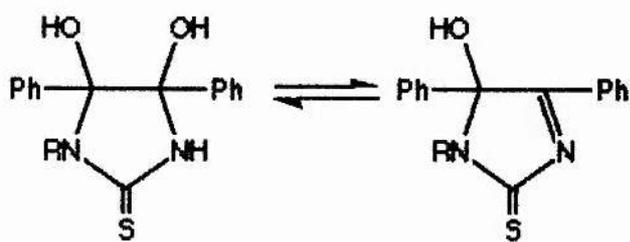


3: R=Me, R'=Me
8: R=H, R'=Me
14: R=H, R'=H

4: R=Me, R'=Me
9: R=H, R'=Me
15: R=H, R'=H



18: R=Me, R'=Me, R''=Me, R'''=Me
19: R=Me, R'=Me, R''=H, R'''=Me
20: R=Me, R'=Me, R''=H, R'''=H
21: R=H, R'=Me, R''=Me, R'''=Me
22: R=H, R'=Me, R''=H, R'''=Me
23: R=H, R'=Me, R''=H, R'''=H
24: R=H, R'=H, R''=Me, R'''=Me
25: R=H, R'=H, R''=H, R'''=Me
26: R=H, R'=H, R''=H, R'''=H



6: R=Me
12: R=H

29: R=Me
30: R=H

Epoxides are known to be converted to episulphides by a number of reagents other than thiourea, including potassium isothiocyanate. Thus (1) was refluxed for five hours with two equivalents of potassium isothiocyanate in ethanolic hydrochloric acid. Remarkably, instead of the predicted products (5) and potassium isocyanate we obtained a virtually quantitative yield of (33), which is a close analogue of the proposed intermediate (3). Intermediates of this type have been trapped with 4-nitrobenzoyl chloride during the reaction of propylene oxide with sodium isothiocyanate⁹ and the hydrochloride salt synthesised¹⁰ but this is the first case that we are aware of where the free base form is stable.

We now come to discuss the fate of the urea expelled from (3),(7) and (13) to give (4),(8) and (14) respectively and also the origin of the bicyclic compounds (18-26).

The diols (1) and (12) and an analogue of (6) with one hydroxyl group replaced by a methyl ether can be prepared independently by the base catalysed condensation of benzil and thiourea in methanol. In acid in the absence of thiourea and urea all three undergo a very slow reaction of the type shown in scheme 2. However, all three react readily with urea to give (20), (26) and (23) respectively. Diols (6) and (12) react rapidly, reaction being complete within 10 minutes at room temperature with a 0.10 M concentration of diol and 0.20 M thiourea in THF acidified with TFA whilst (1) requires two hours reflux at the same TFA and urea concentrations. No reaction occurs in the absence of acid. It is probable that (6) and (12) react via dehydration across the carbon-nitrogen bond to give (29) and (30) respectively followed by attack by urea on the imine centre thus produced whilst (1) can only react by direct nucleophilic substitution of a hydroxyl group. This is very similar to the results obtained for the reactions of benzil with various N-substituted ureas¹, where urea and 1-methylurea gave bicyclic products very readily via dehydration but only a diol analogous to (1) could be obtained from 1,3-dimethylurea and benzil. It is not possible to obtain

accurate rate constants for these reactions because no chromophoric species is produced or destroyed and there is little difference in the chemical shifts of the aromatic protons between the diol and the bicycle. Although the quaternary carbons have very different carbon-13 shifts, the acquisition time for carbon-13 nmr is too long to obtain meaningful results even for saturated solutions of the diols.

Refluxing (1) with 1,3-dimethylthiourea yielded (5) and 1,3-dimethylurea almost entirely, although traces of (18) can be detected in the crude product mixture by mass spectroscopy. Under the same conditions thiourea reacts with benzil to give approximately equimolar amounts of (6) and (26) in good yield and no urea can be detected. This is because of the greater susceptibility of (12) to attack by the urea produced.

These reactions are a good example of the dramatic difference in reactivity sometimes brought about by replacing oxygen by sulphur. In the case of urea the most nucleophilic site is the terminal amine, reacting with (1) to give (20), but for thiourea the strongest nucleophile is the sulphur atom, reacting with (1) or (2) to give (3) and hence (5).

EXPERIMENTAL SECTION

Infra red spectra were taken on a Perkin-Elmer 1420 ratio recording spectrophotometer, ultraviolet spectra on Pye-Unicam SP8-150 spectrophotometer, ^1H nmr spectra on a Bruker WH-360 spectrometer and carbon-13 nmr spectra on a Bruker CFT-20 spectrometer. Time resolved carbon-13 spectra were taken at the SERC nmr spectroscopy service at the University of Edinburgh on a Bruker W60 spectrometer. All melting points are uncorrected. First order rate constants were obtained by the method of Kezdy and Swinbourne¹¹. Chemical shifts are in ppm relative to TMS.

Di(4,5-diphenyl-2-imidazolyl)disulphide (17):- Thiourea (1.52g) and benzil (2.10g) were placed in ethanol (8ml). Aqueous hydrochloric acid (2ml, 10 molar) was added and the solution refluxed for 4 hours. On cooling and addition of water (20ml) a white precipitate was obtained, filtered off and washed with acetone (15ml) to give a mixture of (17) and 3a,7a-diphenyltetrahydro-imidazo[4,5-d]-imidazole-2-one-5-thione (26). The mixture was washed repeatedly with acetone to give pure (17) in 55% yield.

Infra-red spectrum shows perfect match with a published spectrum¹².

mp	272-4 C	lit ¹³ 280 C
M/Z	252	($\text{C}_{15}\text{H}_{12}\text{N}_2\text{S}=252 \text{ g mol}^{-1}$)
^1H nmr (D_6DMSO)	7.40-7.30 (Ph)	
^{13}C nmr (D_6DMSO)	137.69, 128.87, 128.37, 127.78, 125.06	

Di(4,5-diphenyl-3-methyl-2-imidazolyl)disulphide (11)- 1-methylthiourea (1.80g) and benzil (2.10g) were placed in ethanol (8ml). Aqueous hydrochloric acid (2ml, 10 molar) was added and the solution refluxed for 3 hours. On cooling a white precipitate was obtained which was filtered off and washed with dichloromethane until

the washings were colourless to give (11) in 63% yield.

mp	268-71 C
M/Z	266.086894 (C ₁₆ H ₁₄ N ₂ S=266.08776 g mol ⁻¹)
analysis	62.2% C (16.03), 4.21% H (12.90), 9.05% N (2.00)
¹ H nmr (D ₆ DMSO)	7.40-7.30 10H,m (Ph); 3.40 3H,s (NMe)
¹³ C nmr (D ₆ DMSO)	130.65, 129.44, 129.31, 129.17, 128.88, 128.44, 127.49, 126.37, 31.80

1,3-Dimethyl-4,5-diphenyl-2-thioimidazole(5)- 1,3-dimethylthiourea (2.08g) and benzil (2.10g) were placed in ethanol (8ml). Aqueous hydrochloric acid (2ml, 10 molar) was added and the solution refluxed for 4 hours. A white precipitate was obtained, filtered off and washed with acetone (25ml) to give (5) in 71% yield.

mp	225-8 C
M/Z	280 (C ₁₇ H ₁₆ N ₂ S=280 g mol ⁻¹)
analysis	65.96% C (17.16), 4.98% H (15.45), 8.96% N (2.00)
¹ H nmr (CDCl ₃)	7.40-7.30 10H,m (Ph); 3.60 6H,s (NMe)
¹³ C nmr (CDCl ₃)	184.05, 134.68, 130.19, 128.55, 128.09, 127.79, 33.33

4,5-diphenyl-4,5-dihydroxytetrahydroimidazole-2-thione(12)- Thiourea (4.20g), benzil (11.60g) and sodium hydroxide (1.10g) were placed in aqueous ethanol (10%, 50ml) and stirred for a period of 20 minutes at room temperature (approx 20 C). When the amount of solid precipitated appeared to have reached a maximum water (10ml) was added and the precipitate was filtered off and washed with petrol until the washings remain colourless. Yield was variable, typically around 30%.

mp	95-6 C
M/Z-H ₂ O	268 (C ₁₅ H ₁₄ N ₂ O ₂ S=286 g mol ⁻¹)
analysis	62.83% C, 4.86% H, 9.66% N
theoretical	62.92% C, 4.93% H, 9.78% N

^1H nmr (D_6DMSO) 8.15, 2H,s (OH); 7.40-7.10, 10H,m (Ph)
 ^{13}C nmr (D_6DMSO) 188.82 (C=S); 142.06,128.18,127.67,127.26 (Ph);
 73.91 (C-OH)

3a, 7a-diphenyltetrahydroimidazo[4,5-d]imidazole-2-one-5-thione (26)-

4,5-diphenyl-4,5-dihydroxytetrahydroimidazole-2-thione (0.23g) and urea (0.12g) were placed in toluene (10ml). One drop of TFA was added and the solution stirred for 10 minutes at room temperature. The white precipitate filtered off and washed with water (20ml) and acetone (10ml). Yield 90%.

mp greater than 330 C
 M/Z 310 ($\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_2\text{S}=310 \text{ g mol}^{-1}$)
 analysis 61.80% C, 4.43% H, 17.97% N
 theoretical 61.91% C, 4.54% H, 18.05% N
 infra-red 3160 s,br NHstr; 1660 s carbonyl
 solubility too low for nmr spectroscopy in all available solvents

1,3-dimethyl-4,5-diphenyl-4,5-dihydroxytetrahydroimidazole-2-thione (1)-

1,3-Dimethylthiourea (1.10g), benzil (2.10g) and sodium hydroxide (0.20g) were placed in aqueous ethanol (10% H_2O , 10ml) and refluxed for 2 hours. The solution was allowed to cool and water (10ml) was added. After stirring for 30 min the white solid was filtered off and washed with dichloromethane (25ml). Yield 82%

mp 150-1 C (lit¹ 158-9 C)
 M/Z- H_2O 296 ($\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2\text{S}=314 \text{ g mol}^{-1}$)
 ^1H nmr ($\text{D}_6\text{acetone}$) 7.45ppm, 5H,m (Ph); 3.30ppm, 3H,s (NMe)
 ^{13}C nmr ($\text{D}_6\text{acetone}$) 182.75 (C=S); 142.55, 127.94, 127.38, 126.70 (Ph);
 97.71 (C-OH); 30.00 (NMe)

6,8-Dimethyl-3a, 7a-diphenyltetrahydroimidazo[4,5-d]imidazole-2-one-5-thione-

(22)- urea (0.70g) and 1,3-dimethyl-4,5-diphenyl-4,5-dihydroxytetrahydroimidazole-2-thione (3.12g) were placed in THF (25ml). One

drop of TFA was added and the solution refluxed for 2 hours. Water (10ml) was added and the white precipitate filtered off and washed with ether (10ml). Yield 50%.

mp	>310 C	
M/Z	338	(C ₁₈ H ₁₈ N ₄ OS=338 g mol ⁻¹)
analysis	63.79%C , 5.31%H , 16.50%N	
theoretical	63.88%C , 5.36%H , 16.56%N	
¹ H nmr (CDCl ₃)	7.4, 10H,m; 3.3, 6H,s	
¹³ C nmr (CDCl ₃)	183.473, 159.559, 134.487, 128.515, 128.013, 127.237, 87.310, 31.245	

1,3-Dimethyl-4,5-diphenyl-4,5-epoxy-tetrahydroimidazole-thione(2)-

1,3-dimethyl-4,5-diphenyl-2-thioimidazole (2.80g) was dissolved in methanol (20ml). Acetonitrile (0.83g) was added and hydrogen peroxide (1.30g 30% aqueous solution) was added dropwise. The mixture was stirred overnight and the white precipitate filtered off. Yield 62%.

mp	241-5 C	
M/Z	296	(C ₁₇ H ₁₆ N ₂ OS=296 g mol ⁻¹)
analysis	68.81%C , 5.36%H , 9.38%N	
theoretical	68.89%C , 5.44%H , 9.45%N	
¹ H nmr (D ₆ acetone)	7.4-7.2 ppm 10H,m (Ph); 3.60ppm 6H,s (NMe)	
¹³ C nmr (D ₆ acetone)	162.73, 130.357, 128.835, 128.737, 128.254, 127.961, 33.537	

1,3-Dimethyl-4,5-diphenyl-2-oxoimidazole(32)-

1,3-Dimethyl-4,5-diphenyl-2-thioimidazole (0.20g) and ethylene oxide (0.50g) were dissolved in THF (10ml) and stirred at room temperature for 2 hours. The solvent and excess ethylene oxide were removed on the rotary evaporator and the solid washed with acetone (10ml). Yield 70%.

mp	>300 C	lit ¹⁴ 330-5 C
M/Z	264.124663	C ₁₇ H ₁₆ N ₂ O=264.12625 g mol ⁻¹

3-imino-6,8-dimethyl-1,5-diphenyl-2-oxa-4-thia-6,8-diazabicyclo[3.3.0]octane-7-thione (33)-

1,3-dimethyl-4,5-diphenyl-4,5-dihydroxytetrahydroimidazole-2-thione (0.20g) and potassium thiocyanate (0.10g) were dissolved in THF (5ml). TFA (0.5ml) was added and the solution refluxed for 5 hours. Water (10ml) was added and the solution extracted with dichloromethane (2 lots of 5ml), dried with magnesium sulphate and the solvent removed on the rotary evaporator to give pale pink crystals of (33) in 80% yield.

mp	188-91 C	
M/Z	355.078482	C ₁₈ H ₁₇ N ₃ O ₂ =355.08129
¹ H nmr (D ₆ acetone)	7.4-7.2 ppm	10H,m (Ph); 3.40ppm 3H,s (NMe);
		3.30ppm 3H,s (NMe)
¹³ C nmr (D ₆ acetone)	188.28, 184.46, 131.01, 130.00, 129.01, 128.56,	
	127.02, 109.66, 90.55, 32.07, 31.71	

Non-equilibrium carbon-13 studies on the reaction of (1) to give (5):- The optimum temperature and acid concentration were determined using unlabelled (1) prepared as described above by ultraviolet spectroscopic analysis of samples of the mixture taken at two hour intervals diluted by a factor of one thousand. The sample of (1) enriched to 20% carbon-13 at the quaternary carbon was prepared in situ from carbon-13 enriched benzil, prepared as described in chapter 1.

Benzil enriched to 20% carbon-13 at the carbonyl centre (0.0452g) and 1,3-dimethylthiourea (0.0894g) were dissolved in hexadeuterated ethanol (2.0ml) and sodium metal (0.005g) was added. After 1 hour when carbon-13 nmr showed that all the benzil had reacted to give (1) ethanolic hydrochloric acid was added and the solution maintained at 40 C overnight. Sixteen carbon-13 spectra were taken at hourly intervals, each with an acquisition time of 15 minutes. Unfortunately the ethanolic hydrochloric acid proved to be unstable, thus the acid concentration of the

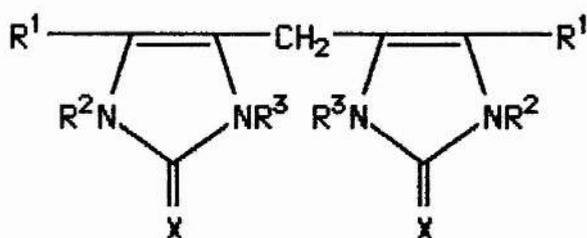
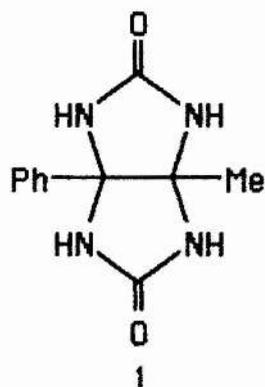
sample, measured after the experiment was complete, proved to be 0.086 M instead of the previously determined optimum of 0.60 M.

Appendix 1: Literature References

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Chapter 3

The acid catalysed reactions of
thiourea, 1-substituted thioureas
and 1,3-disubstituted thioureas
with 1-phenyl-1,2-propanedione
and related 1-phenyl-1,2-diketones



2: $R^1 = \text{Me}$, $R^2 = \text{H}$, $R^3 = \text{H}$, $X = \text{O}$

3: $R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{H}$, $X = \text{S}$

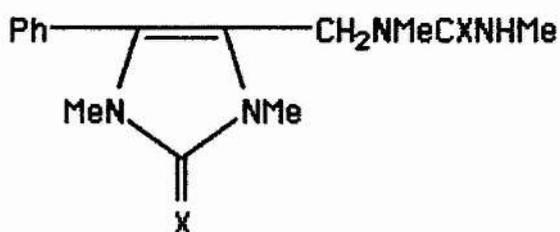
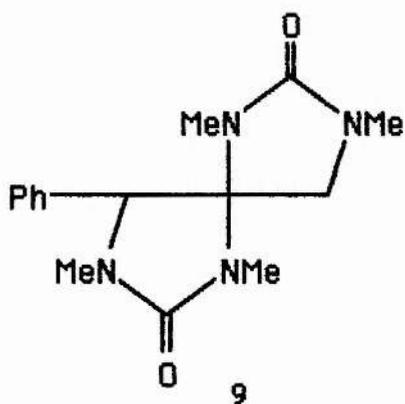
4: $R^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = \text{H}$, $X = \text{O}$

5: $R^1 = \text{Me}$, $R^2 = \text{Me}$, $R^3 = \text{H}$, $X = \text{O}$

6: $R^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = \text{H}$, $X = \text{S}$

7: $R^1 = \text{Me}$, $R^2 = \text{Me}$, $R^3 = \text{Me}$, $X = \text{O}$

8: $R^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = \text{Me}$, $X = \text{O}$



10: $X = \text{O}$

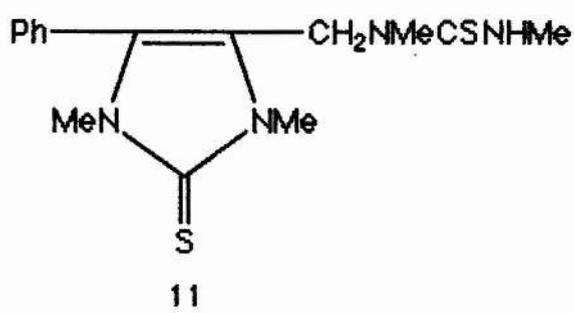
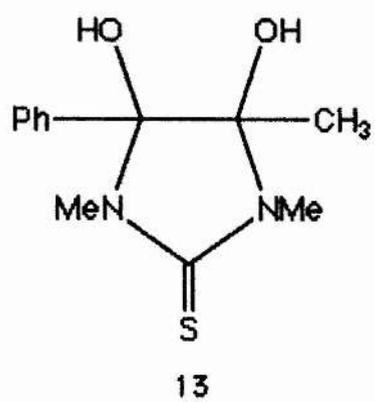
11: $X = \text{S}$

Introduction

Benzil can react with ureas or thioureas only through its two carbonyl positions, the phenyl groups remaining unchanged throughout the course of the reaction irrespective of whether acid or base catalysis is employed. In contrast to this, 1,2-diones containing one or more aliphatic groups adjacent to the diketone unit, such as 1-phenyl-1,2-propanedione or biacetyl, can react at an aliphatic centre as well as at both of the carbonyl centres.

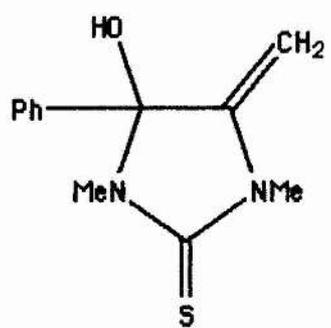
The remarkable products of the acid catalysed reactions of urea, 1-methylurea and 1,3-dimethylurea with 1-phenylpropanedione¹ and biacetyl² have been reported previously. Urea was reported to react with 1-phenyl-1,2-propanedione under acid conditions to give (1), which is not unexpected, together with a minor product which was not characterised. However, urea reacts with biacetyl under acid catalysis to give the somewhat surprising product (2) formed by the condensation of two molecules each of urea and biacetyl with the loss of 4 molecules of water and *one carbon atom*. Still more remarkably, the carbon was reported to be lost in the form of formaldehyde. We have now shown that thiourea reacts with 1-phenylpropane-1,2-dione to give the analogous product (3) under acidic conditions, again with the elimination of formaldehyde. 1-Methylurea was reported to react similarly with 1-phenylpropanedione to give (4) and with biacetyl to give (5). The latter was completely and unambiguously identified by means of X-ray crystallography. Again we have shown that 1-methylthiourea gives the analogous product (6) with 1-phenylpropane-1,2-dione. 1,3-Dimethylurea was reported to react with biacetyl to yield (7) but with 1-phenylpropanedione to give only (10). In contrast 1,3-dimethylthiourea reacts with 1-phenylpropane-1,2-dione under acid conditions to give only (11). The reaction of dimethylurea with 1-phenyl-1,2-propanedione has been reinvestigated and shown to yield a mixture of (8), (9) and (10).

We have investigated the acid catalysed reactions of thiourea and N-substituted thioureas with a variety of 1,2-diketones with one aromatic and one aliphatic group adjacent to the diketone unit. The mechanisms of the reactions with the simplest of these, 1-phenylpropane-1,2-dione, has been studied in detail by carbon-13 nmr spectroscopy applied to the system as the reaction proceeds using two samples of 1-phenylpropane-1,2-dione enriched with carbon-13 at the 1 and 3 positions respectively. Where possible putative intermediates have also been prepared, although this proved to be somewhat difficult in many cases.



1,3-Dimethylthiourea: Under acid catalysis 1-phenyl-1,2-propanedione reacts with at least two equivalents of 1,3-dimethylthiourea to give (11) as the sole significant product. The compound has been characterised by mass spectroscopy and infra-red, proton and carbon-13 nmr spectroscopy. Its elemental analysis gives a composition of $C_{15}H_{20}N_4S_2$, which also matches the molecular ion peak at 320 mass units. The proton nmr shows four non-equivalent N-methyl groups and one phenyl group with integrals corresponding to two 1,3-dimethylthioureas reacting with each diketone and a signal at 5.40 ppm with an integral corresponding to a methylene group. On methylation with Purdie's reagent the NH stretching band in the infra-red is lost, as is one of the thione signals in the carbon-13 spectrum at 162.75 ppm. This signal is replaced by a signal at 67.93 ppm and a new signal is observed at 19.72 ppm, corresponding to a methyl thioether. This is consistent with methylation of one thiourea group in the molecule only. The thione centre of 1,3-dimethyl-4,5-diphenyl-2-thioimidazole is known not to be methylated by Purdie's reagent (see chapter 1) so it is reasonable to assume that the 2-thioimidazole moiety of (11) is also stable to Purdie's reagent. Hence the thione signal at 162.75 ppm must correspond to a pendant thiourea moiety, which can be S-methylated via the thioenol tautomer.

When 1-phenyl-1,2-propanedione is treated under acid conditions with only one equivalent of 1,3-dimethylthiourea the product is mainly the cyclic glycol (13), as would be expected from the first stage of the acid catalysed reaction of benzil with 1,3-dimethylthiourea described in chapter 2. The diketone and 1,3-dimethylthiourea also react slowly in neutral solution at room temperature to give (13) even when more than one equivalent of 1,3-dimethylthiourea is used. Compound (13) has been completely characterised by mass spectroscopy, elemental analysis, infra-red spectroscopy and proton and carbon-13 nmr spectroscopy. It appears to be produced as a mixture of the two possible diastereoisomers. The two isomers can be distinguished

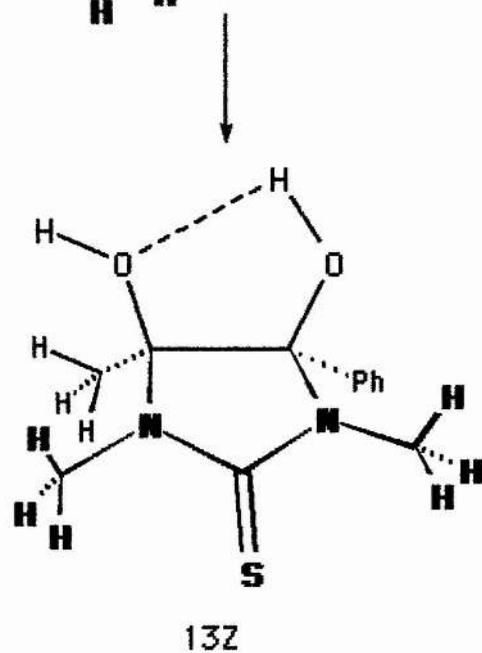
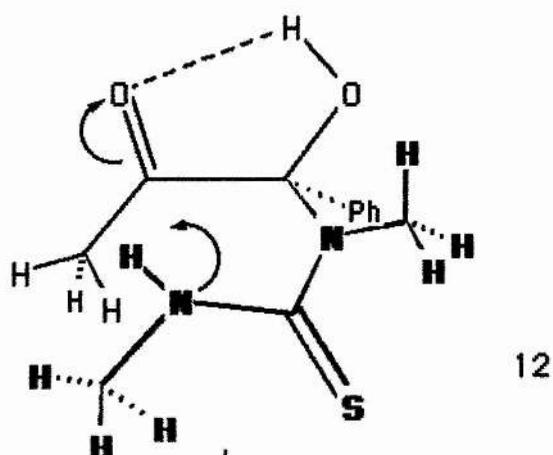
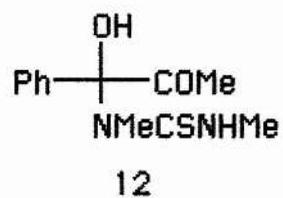


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by the use of a europium chemical shift reagent, the Z isomer co-ordinating much more strongly to the europium centre than the E because of its ability to act as a bidentate ligand. This is exactly analogous to the method of distinguishing between the Z and E isomers of 4,5-diphenyl-4,5-dihydroxytetrahydroimidazole-2-thione using $\text{Eu}(\text{fod})_3$ discussed in detail in chapter 1. The Z isomer shows four aromatic signals, two aminol signals at 96.38 and 93.04 ppm, two N-methyl signals at 31.48 and 30.70 ppm and the 4-methyl signal at 23.67 ppm in aqueous THF. The aminol signals show molar sensitivities to the shift reagent of 8.34 and 12.31 ppm respectively in chloroform. The E isomer shows four aromatic signals, aminol signals at 97.98 and 94.40 ppm, N-methyl signals at 32.14 and 30.83 ppm and the 4-methyl signal at 21.04 ppm in aqueous THF. The aminol signals show molar sensitivities to the shift reagent of 2.48 and 2.31 ppm respectively in chloroform. These are essentially no higher than the 2.22 ppm of the single aminol centre of (14), which obviously cannot act as a bidentate ligand. Traces of (14) were present in the sample of (13) to which the shift reagent was added.

Compound (13) can be prepared by the reaction of 1,3-dimethylthiourea and 1-phenyl-1,2-propanedione under neutral conditions. This is in contrast to the failure of benzil to react with 1,3-dimethylthiourea, or indeed any other thiourea, in the absence of acid or base catalysis. It was shown by the application of carbon-13 nmr to the dynamic system that the 1,3-dimethylthiourea attacks the carbonyl centre adjacent to the phenyl group first to give (12), rather than attacking the aliphatic carbonyl centre first, as would be predicted from its failure to attack the carbonyl centres adjacent to the aromatic groups of benzil under neutral conditions. It is not at all obvious why this occurs. The predominant isomer produced in both the neutral and the acid catalysed reactions is the Z form. The product of the neutral reaction has a ratio of Z to E isomer of approximately 13:1 according to the intensities of the methyl signals

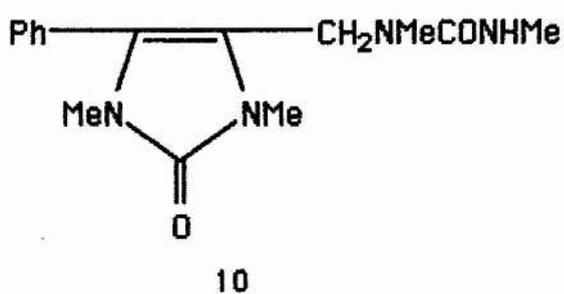
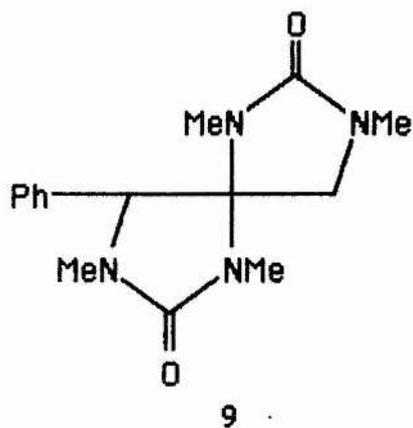
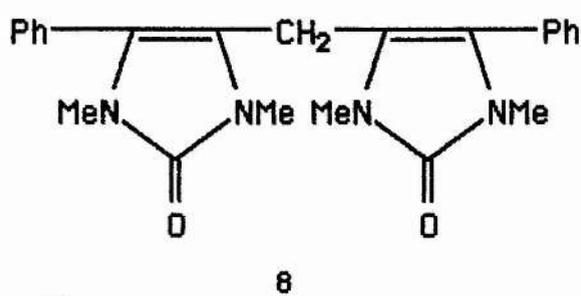
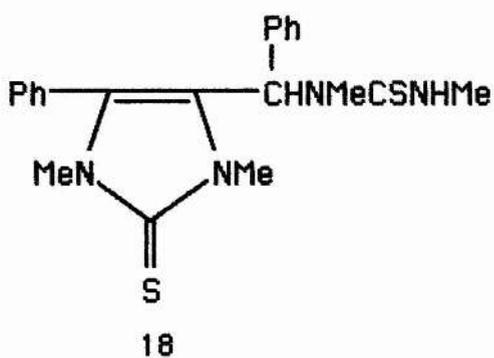
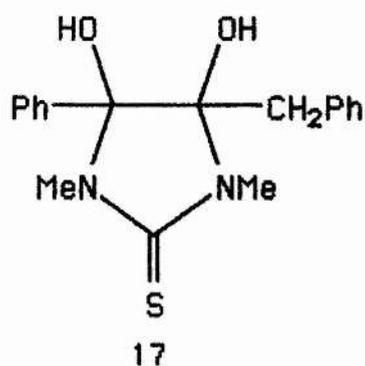
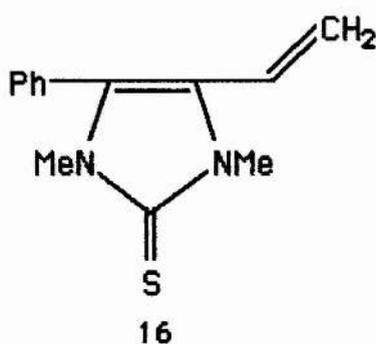
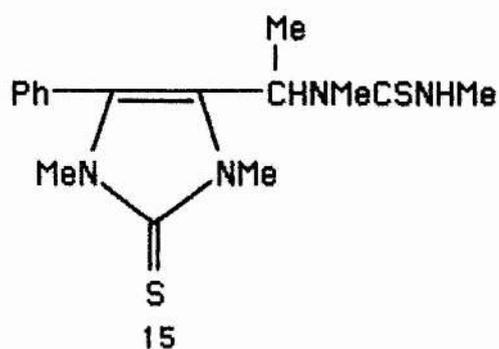
Figure 1: Possible hydrogen bonded configuration of (12)



in a carbon-13 DEPT experiment where there is no distortion due to differences in nuclear Overhauser effects between the two isomers. On the addition of acid to the mixture of isomers the ratio of Z to E decreases to approximately 3:1. This must correspond to the setting up of an equilibrium between the two isomers, probably via either ring opening to (12) or dehydration to (14). Hence the isomer ratio of the product of the neutral reaction must be under kinetic, rather than thermodynamic, control. Models of (12), show little sign of stereoelectronic factors which might favour the formation of one isomer of (13) over the other. It is, however, possible to rationalise the result by considering a hydrogen bond between the hydroxyl and ketone functions of (12), holding it in a configuration where nucleophilic attack by the pendant thiourea on the carbonyl centre gives the Z isomer exclusively (see figure 1).

Compound (13) reacts readily under acid catalysis with an excess of 1,3-dimethylthiourea to yield (11) as the sole isolable product. The reaction was shown by one of the carbon-13 nmr experiments described below to be more rapid than the reaction of 1-phenyl-1,2-propanedione with 2 equivalents of 1,3-dimethylthiourea. No 5-phenyl-1,3,4-trimethylimidazole-2-thione was detected. The acid catalysed reaction of 4,5-diphenyl-4,5-dihydroxytetrahydroimidazole-2-thione with any thiourea to give 4,5-diphenylimidazole-2-thione occurs via dehydration to the epoxide, as was discussed in chapter 2. Hence (13) must fail to dehydrate to give an epoxide under acidic conditions. The most reasonable explanation of this result is that acid catalysed dehydration of (13) leads instead to (14).

The carbon-13 nmr of the isolated sample of (13) showed a weak signal at 88.00 ppm corresponding to the exocyclic methylene of (14), formed by dehydration during work-up, this material was later shown to be a crucial intermediate in (11) production by means of carbon-13 nmr studies during the course of the reaction. An attempt to dehydrate (13) to (14) using toluene sulphonic acid in refluxing toluene



with azeotropic removal of water failed to give significant quantities of (14).

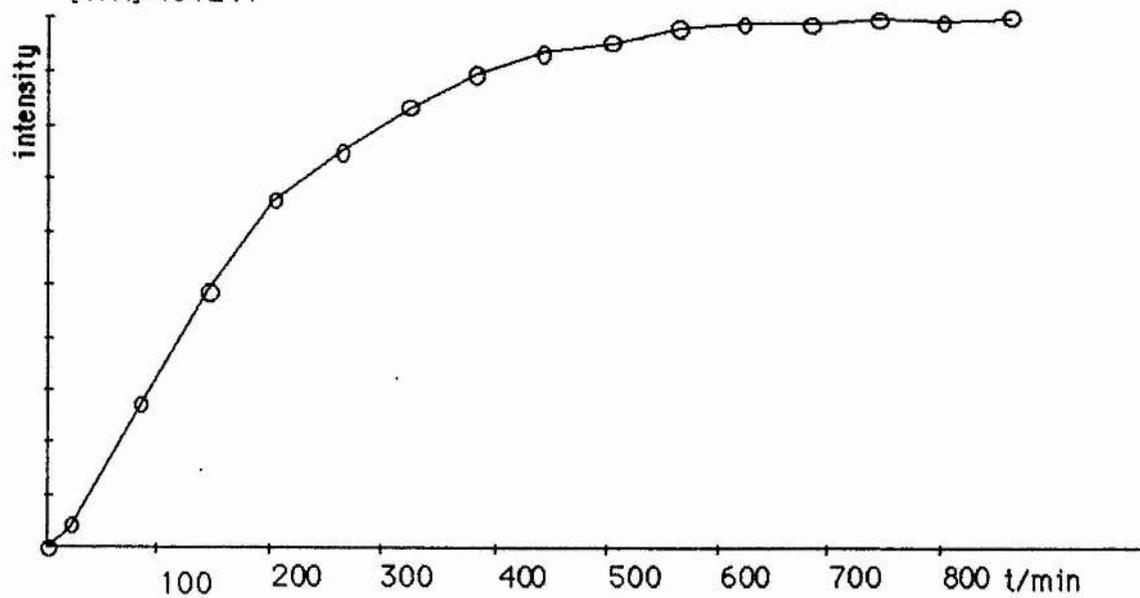
The influence of the nature the alkyl group of the diketone on the course of the reaction appears to be small. Thus 1,3-dimethylthiourea reacts with 1-phenyl-1,2-butanedione under acid catalysis to give mostly (15). However, in contrast to (11), thiourea can be eliminated from the side chain of (15) either thermally or under acid catalysis to yield (16). This shows that under acidic conditions the thiourea group of the side chain can act as a nucleofuge, which will be of relevance to the proposed mechanism of the reaction of 1-phenyl-1,2-propanedione with thiourea and 1-methylthiourea discussed below. Treatment of (15) with TFA in THF at reflux yields (16) and 1,3-dimethylthiourea slowly.

The alkyl group may have an influence on the rate of the reaction through steric interaction with the attacking dimethylthiourea. Thus excess 1,3-dimethylthiourea reacts under acid catalysis with 1,3-diphenyl-1,2-propanedione to give, after 6 hours at reflux in THF, a mixture of (17) and (18), whereas (1) production is complete after two hours under analogous conditions. Unlike (15), (18) cannot eliminate dimethylthiourea to give an olefinic side chain.

If a more sterically demanding alkyl group still is used then the dione may fail to react with 1,3-dimethylthiourea at all. Thus 3-methyl-1-phenyl-1,2-butanedione was recovered almost quantitatively after seven hours reflux with a large excess of 1,3-dimethylthiourea in THF containing TFA.

The acid catalysed reaction of 1,3-dimethylurea with 1-phenyl-1,2-propanedione is reported¹ to yield only (9) but the mechanism of its formation which was proposed invoked a material (10) analogous to the 1,3-dimethylthiourea product (11). The reaction of 1,3-dimethylurea with 1-phenyl-1,2-propanedione in THF catalysed by TFA was re-investigated and found to give a complex mixture of products. The three major products were separated by preparative tlc and characterised by

Figure 2: Variation of (11) signal at 28.839 ppm in experiment with [TFA]=.012 M



Variation of (11) signal at 28.87 ppm in experiment with [TFA]=.031 M

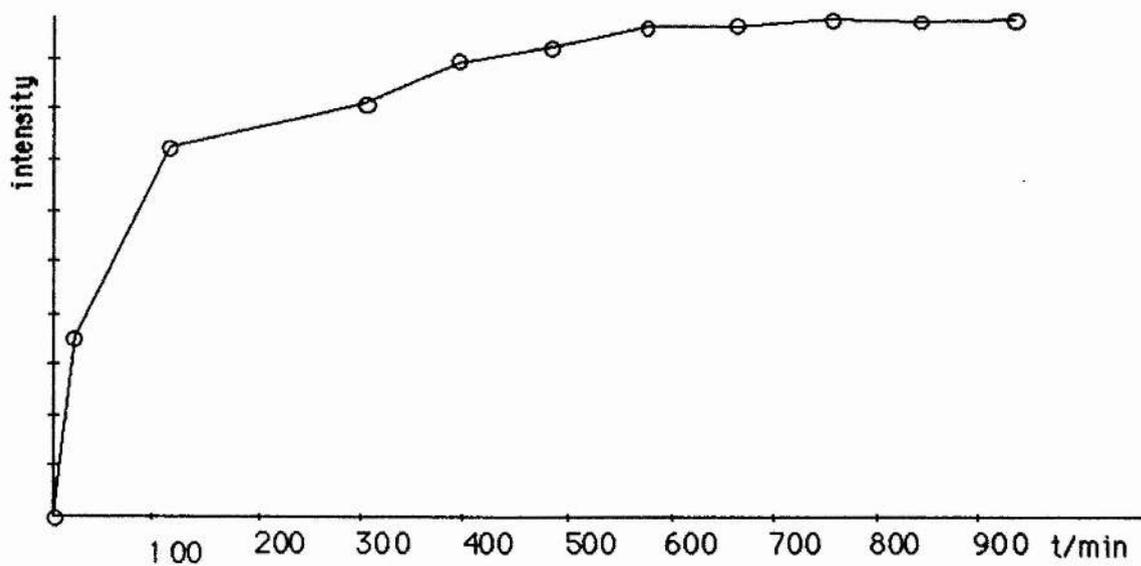
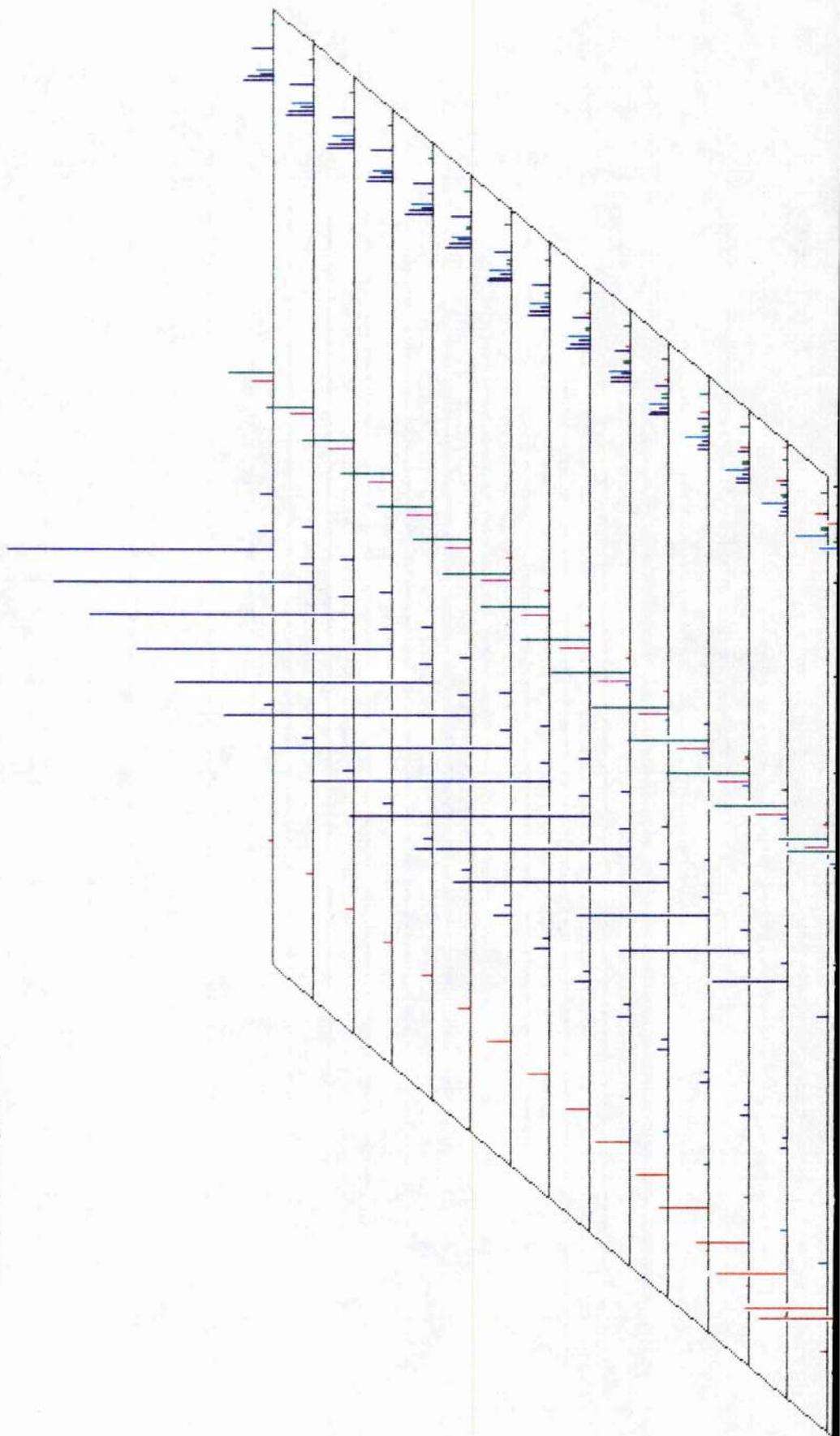


Figure 3. Successive carbon-13 nmr spectra during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 1-position and 1,3-dimethylurea



carbon-13 and proton nmr, solution state infra-red spectroscopy in deuteriochloroform and mass spectroscopy. The products proved to be (9), as reported, and also (8) and (10). The proposed mechanism of (9) production invoked (10) as an intermediate and, indeed, prolonged reflux of the crude product mixture in THF under acidic conditions yielded a mixture which was shown by tlc to contain (8) and (10) only. Interestingly, 1,3-dimethylthiourea and 1-phenylpropane-1,2-dione did not give detectable quantities of an analogue of (8), even when carbon-13 labelled substrate was used which allowed the detection of materials at 0.1% the concentration of (11). We can offer no convincing explanation for this result. Again in contrast to the 1,3-dimethylurea case, (11) did not give a spiro compound analogous to (9) on prolonged reflux in acidic THF. Again we cannot give a convincing explanation of this result. It is tempting to conclude that these two differences are related in some way but in the absence of supporting evidence this possibility should be treated with caution.

The course of the reaction was investigated by the application of carbon-13 nmr spectroscopy to the mixture as the reaction proceeded. Four reactions were carried out, all of them in aqueous THF (2:5) with an initial diketone concentration of 0.25 M and an initial 1,3-dimethylthiourea concentration of 0.60 M. In the first two runs the TFA concentration was adjusted to give an appropriate rate of reaction using non carbon-13 labelled substrate taking carbon-13 spectra every 90 minutes with a 30 minute acquisition time. The rate of the reaction proved to be moderately sensitive to the TFA concentration (see figure 2). In the next run 1-phenyl-1,2-propanedione enriched to 20% carbon-13 at the 1 position was used, with spectra being taken every 60 minutes with a 15 minute acquisition time. The results of this experiment are shown in figure 3. In the fourth run 1-phenyl-1,2-propanedione enriched to 25% carbon-13 at the 3-position was used and carbon-13 spectra were again taken at hourly intervals with a 15 minute acquisition time but this time the DEPT pulse

Figure 4: Successive DEPT 135 carbon-13 nmr spectra during the acid catalysed reaction of 1-phenyl-1,2-propenedione labelled at the 3-position and 1,3-dimethylurea

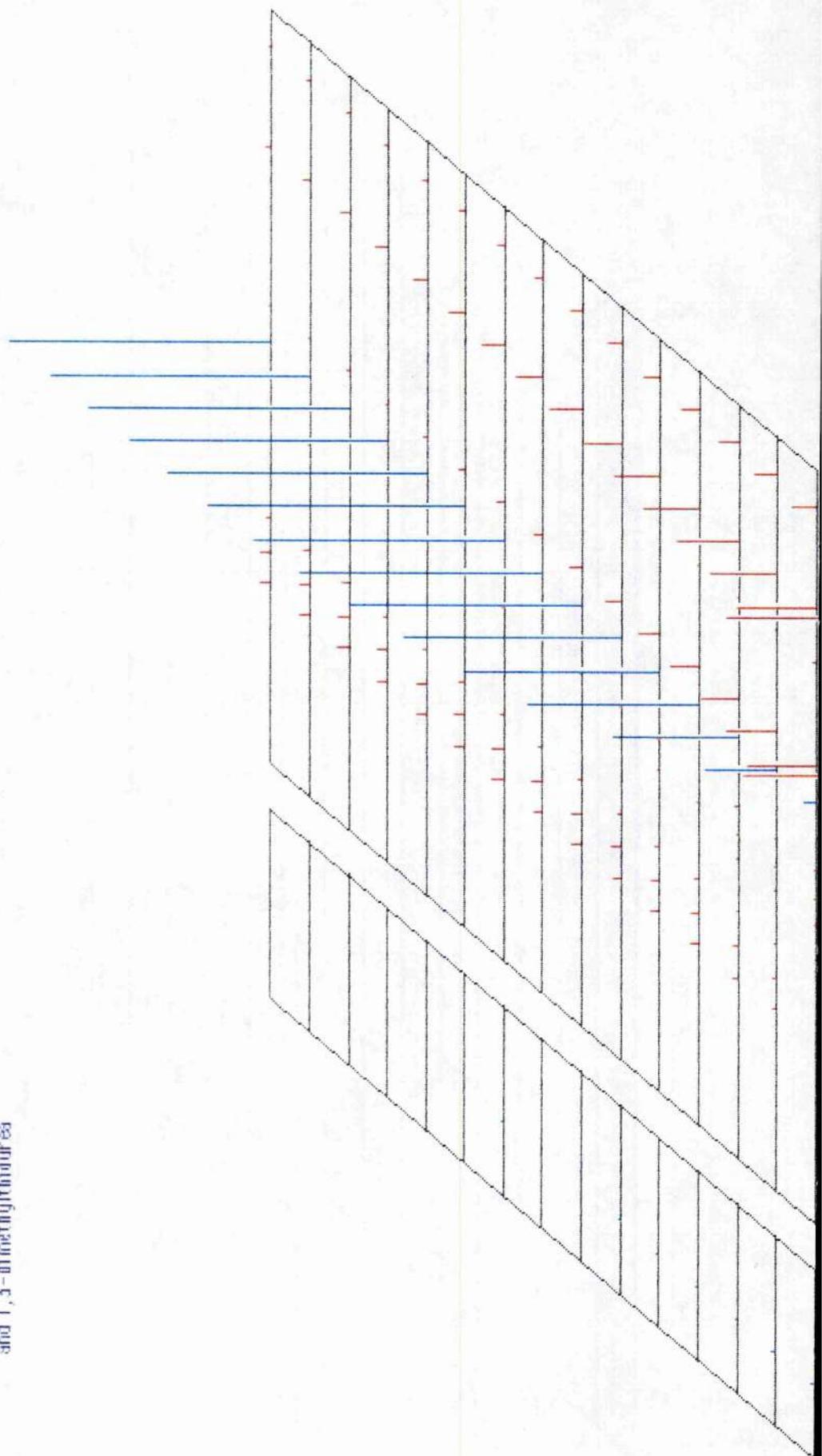
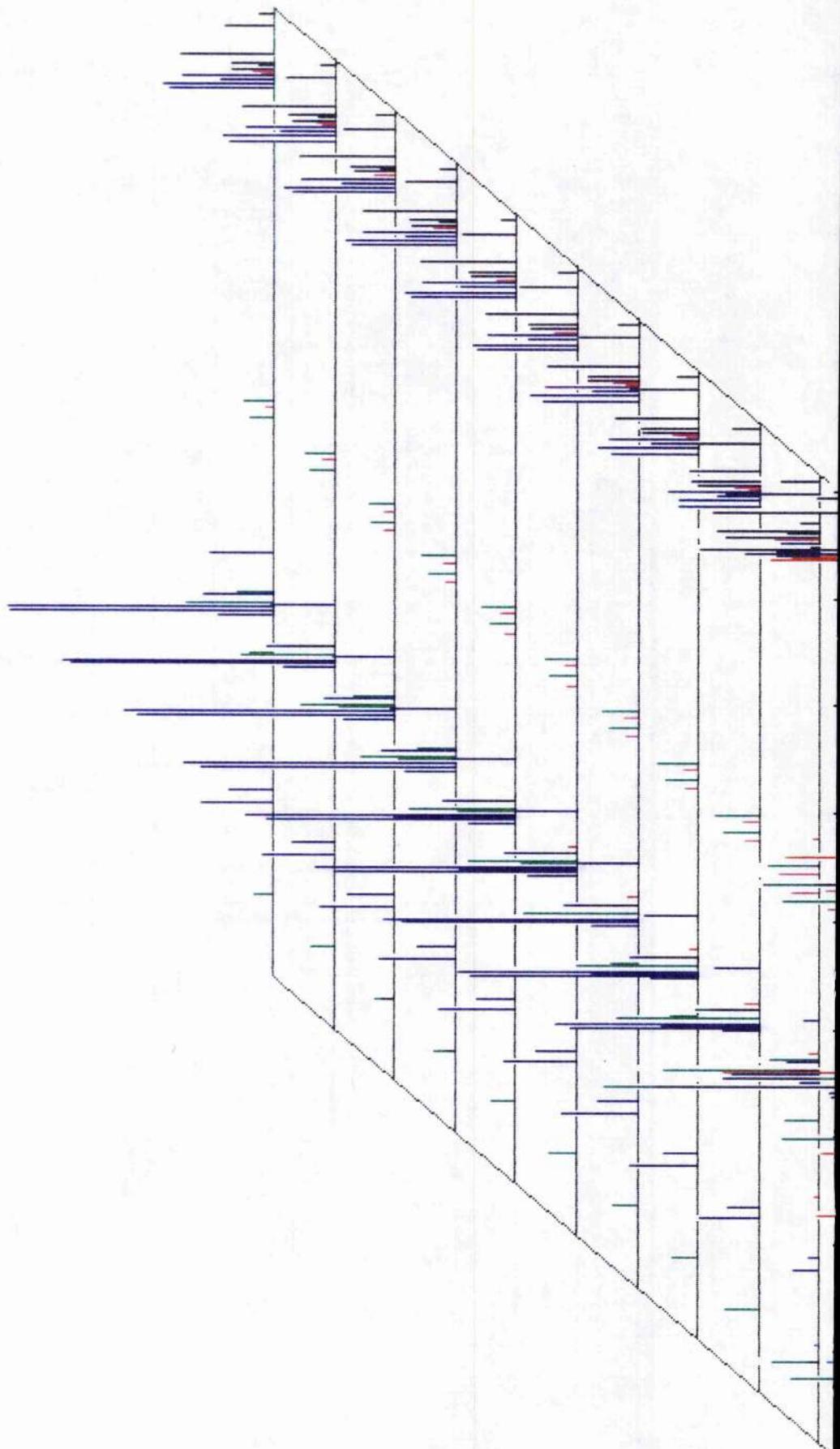
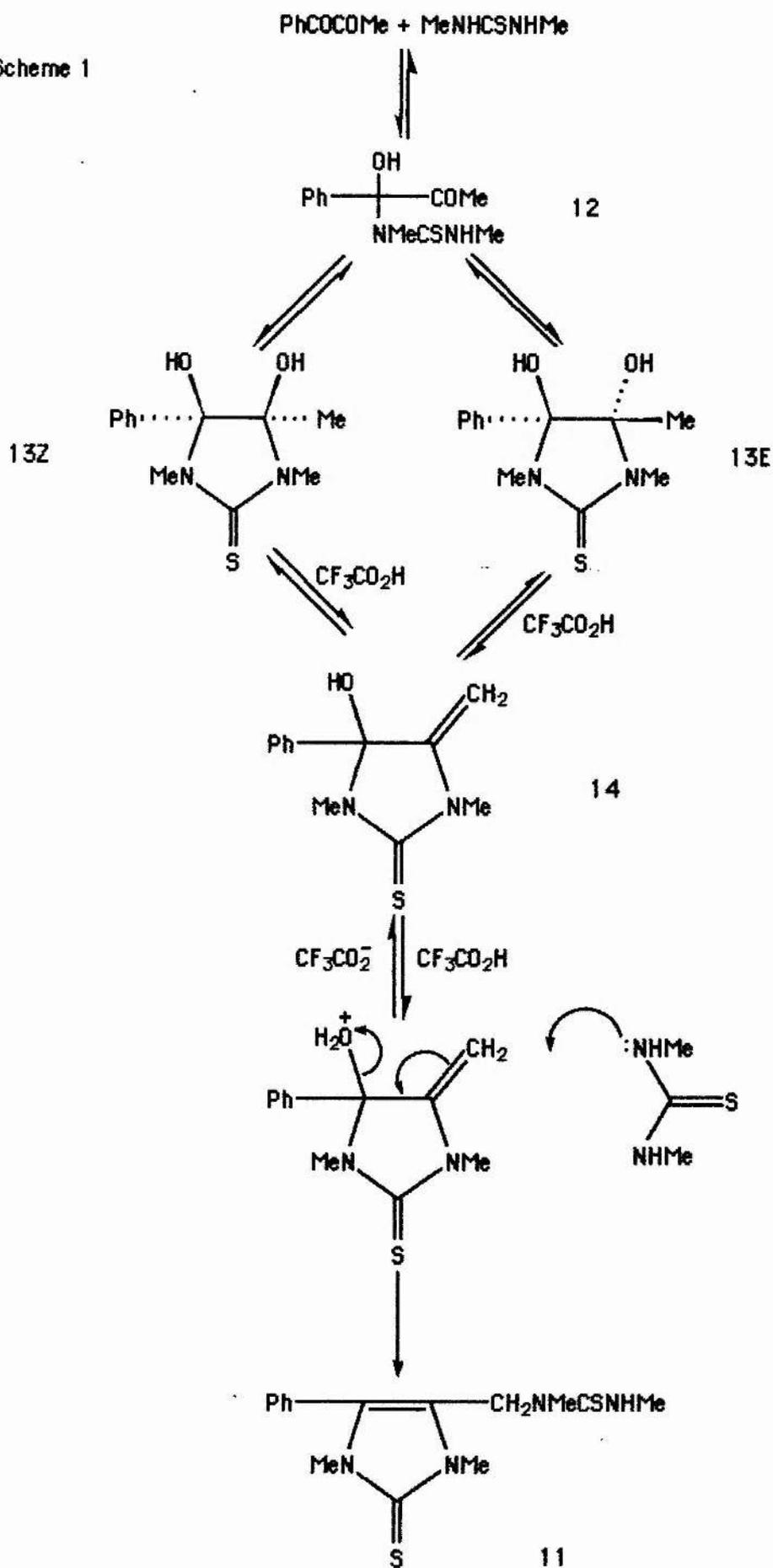


Figure 5: Successive carbon-13 nmr spectra during the acid catalyzed reaction of (13) and (14) with 1,3-dimethylthiourea



Scheme 1



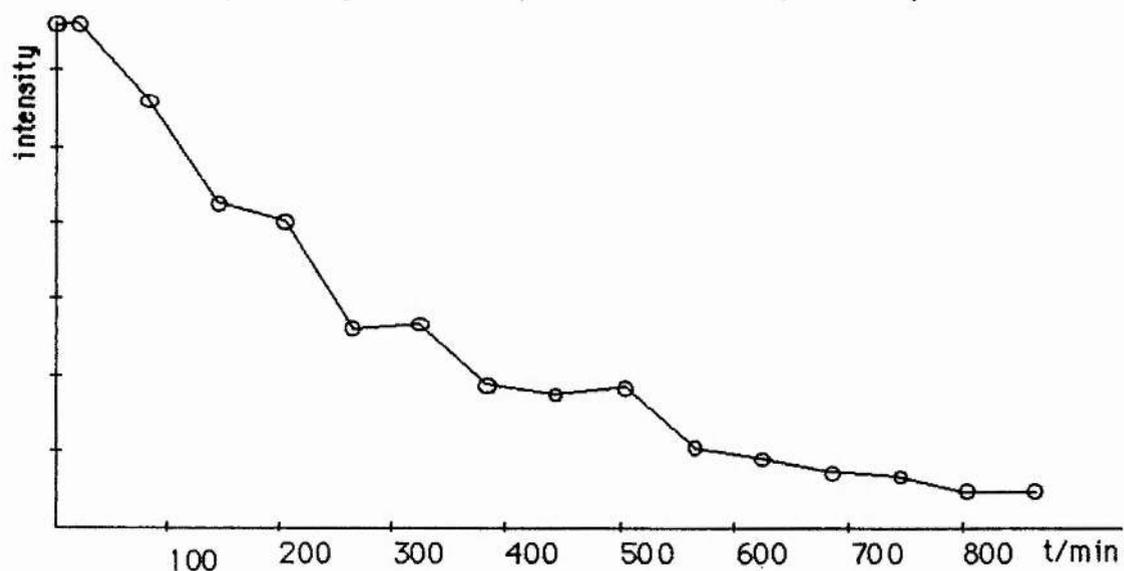
sequence was used which gave increased sensitivity as well as allowing us to determine the number of protons attached to the labelled centre in each intermediate. The results are shown in figure 4. Note that the CH₂ signals are denoted by colour rather than being inverted. In the last experiment a concentration of (13) containing no carbon-13 labels of 0.30 M was used instead of the diketone together with a slight excess of 1,3-dimethylthiourea, again in aqueous THF with a TFA concentration of 0.012 M. The carbon-13 spectra were taken every 90 minutes with a 30 minute acquisition time. The results of this experiment are shown in figure 5.

The combined results of all these experiments give the mechanism shown in scheme 1, which is in fact very similar to that proposed for the reaction of 1-phenyl-1,2-propanedione and 1,3-dimethylurea to give (9)¹.

In all the experiments the reactants were placed in the neutral solvent and the nmr spectrometer 'shimmed' to give the best possible resolution before the measured volume of TFA was added. Thus, because 1,3-dimethylthiourea and 1-phenylpropanedione react even in the absence of acid to give (12) and (13), in both the third and fourth experiment some (13) was present before the acid was added. The length of time needed to obtain the best resolution varied between the experiments so that the relative amounts of diketone, (12) and (13) in the initial solution before acid was added varied between the experiments.

An authentic sample of 1-phenyl-1,2-propanedione gave carbon-13 nmr signals at 203.49, 194.32, 134.51, 130.24, 129.41, 128.77 and 27.87 ppm in aqueous THF. Thus the signal due to labelled centres at 194.318 ppm in the third experiment and 27.85 ppm in the fourth experiment are undoubtedly due to the diketone. In the third experiment signals due to unlabelled centres at 203.49 and 27.87 ppm were observed which showed excellent correlation with the signal due to the labelled 1-position. In both these experiments and also in the experiments using

Figure 6: Variation of 1-phenyl-1,2-propanedione labelled 1-position signal at 194.32 ppm during its acid catalysed reaction with 1,3-dimethylthiourea



Variation of 1-phenyl-1,2-propanedione labelled 3-position methyl signal at 27.85 ppm during its acid catalysed reaction with 1,3-dimethylthiourea

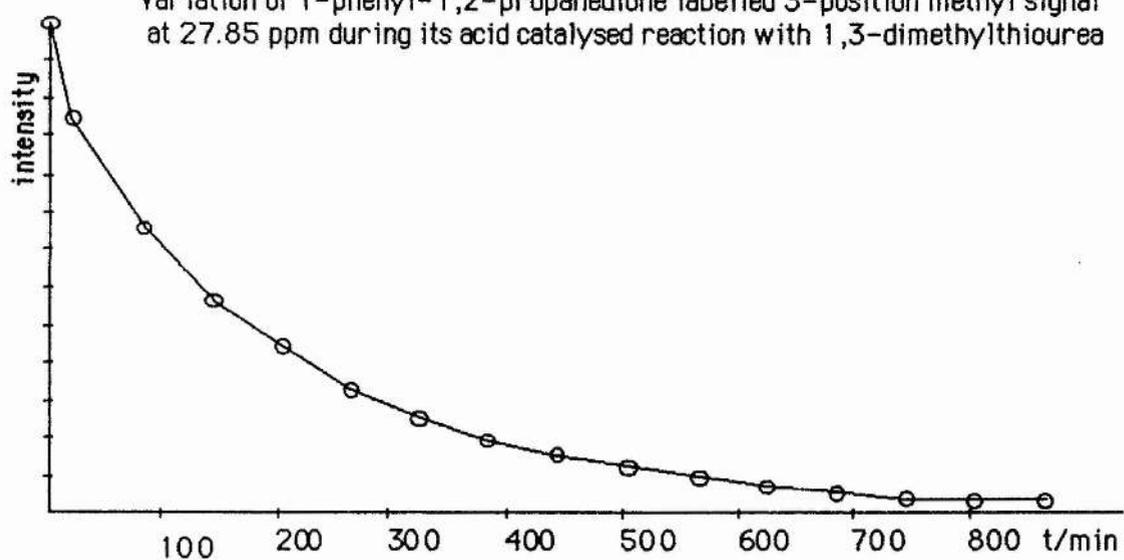
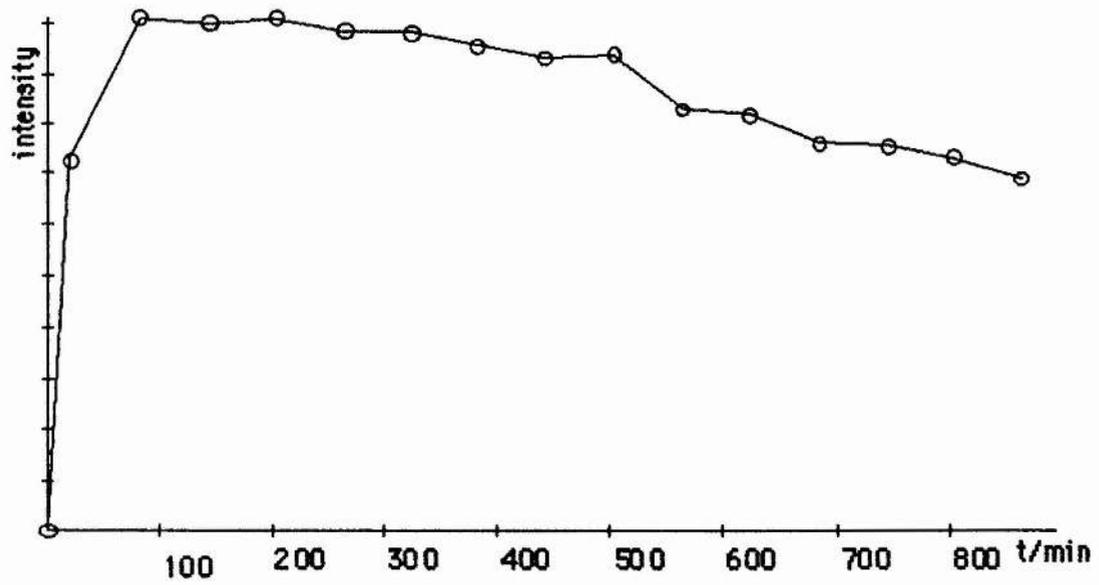
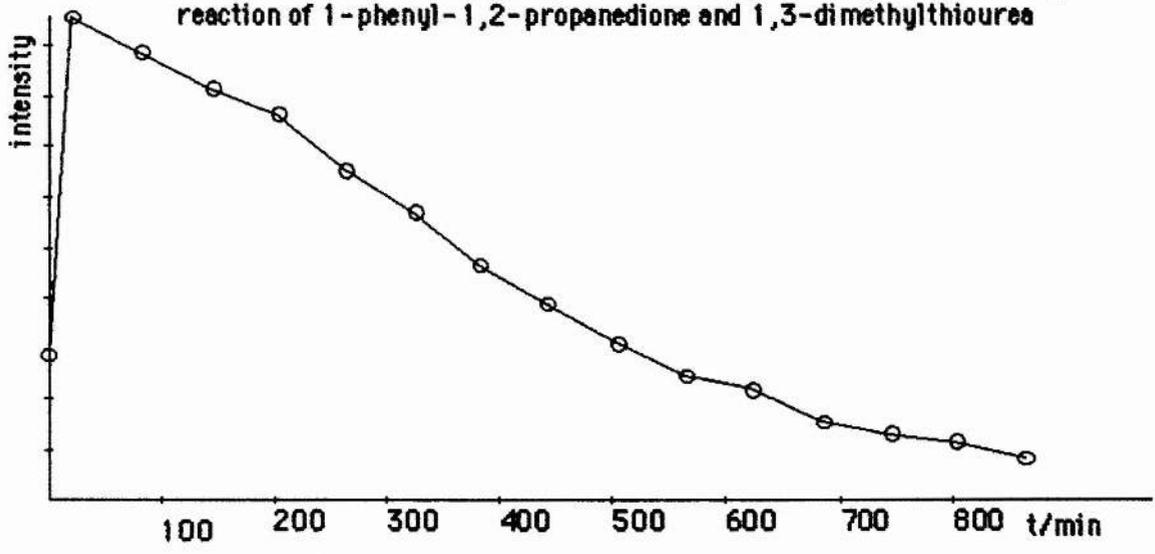


Figure 7: Variation of (¹³E) signal at 97.98 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 1-position and 1,3-dimethylthiourea



Variation of (¹³E) methyl signal at 21.00 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione and 1,3-dimethylthiourea



Variation of (¹³E) signal at 97.93 ppm during the acid catalysed reaction of (13) and 1,3-dimethylthiourea

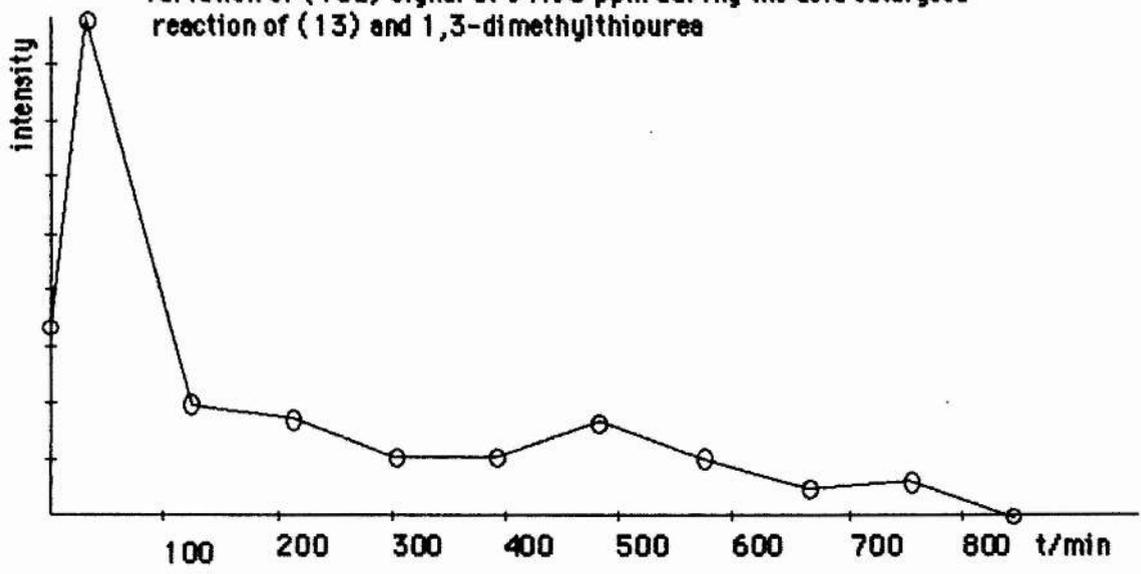
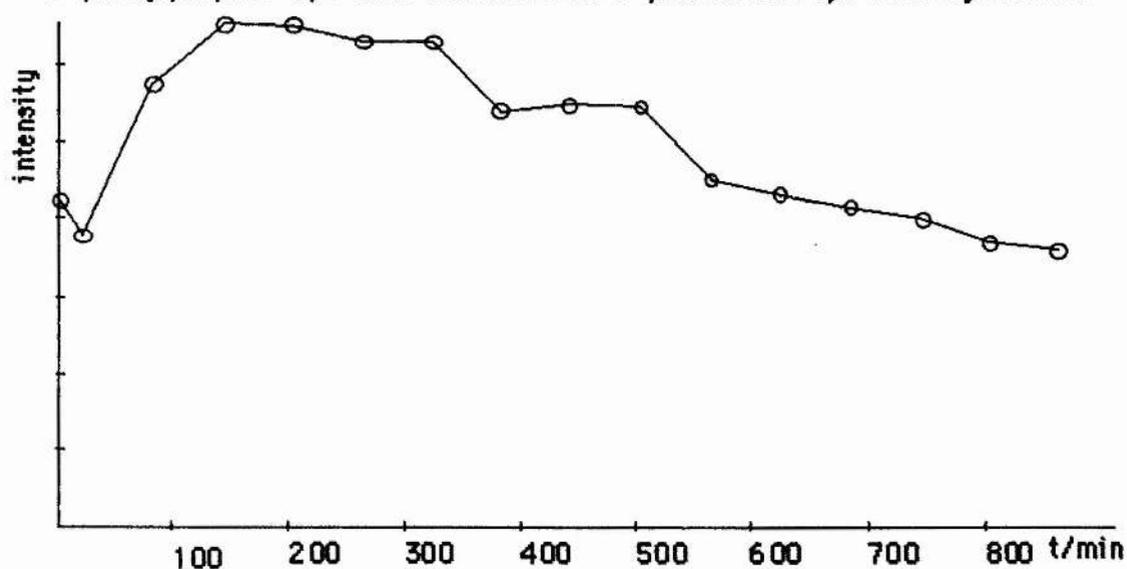
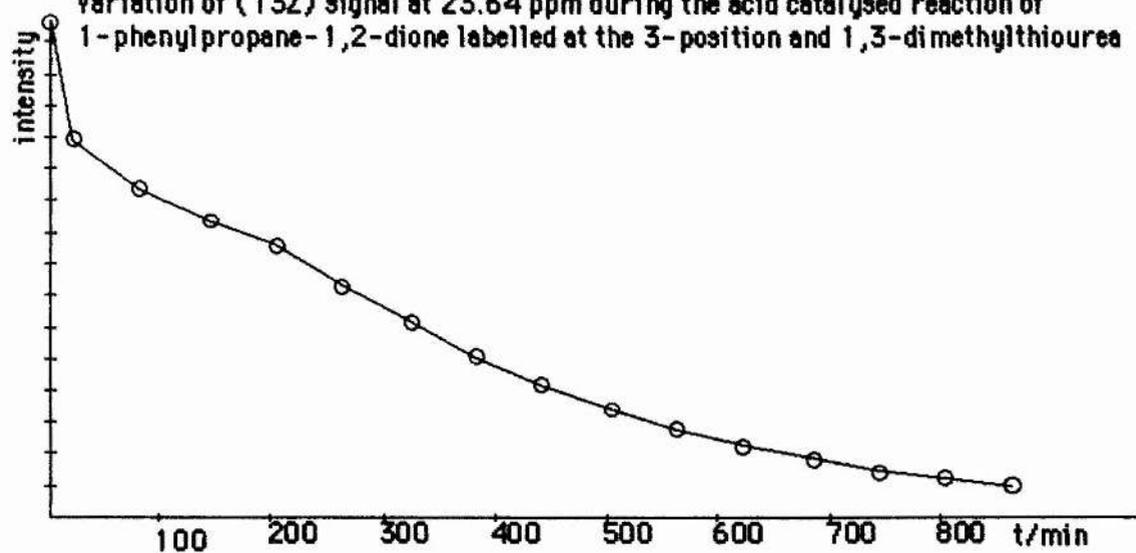


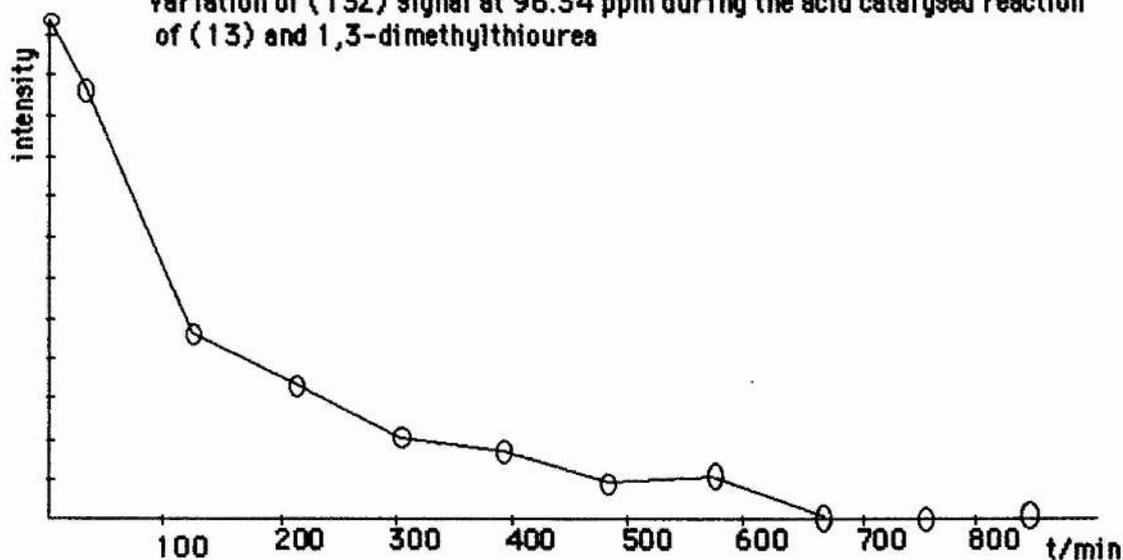
Figure 8: Variation of (^{13}C) signal at 96.38 ppm during the acid catalysed reaction of 1-phenylpropane-1,2-dione labelled at the 1-position and 1,3-dimethylthiourea



Variation of (^{13}C) signal at 23.64 ppm during the acid catalysed reaction of 1-phenylpropane-1,2-dione labelled at the 3-position and 1,3-dimethylthiourea



Variation of (^{13}C) signal at 96.34 ppm during the acid catalysed reaction of (13) and 1,3-dimethylthiourea

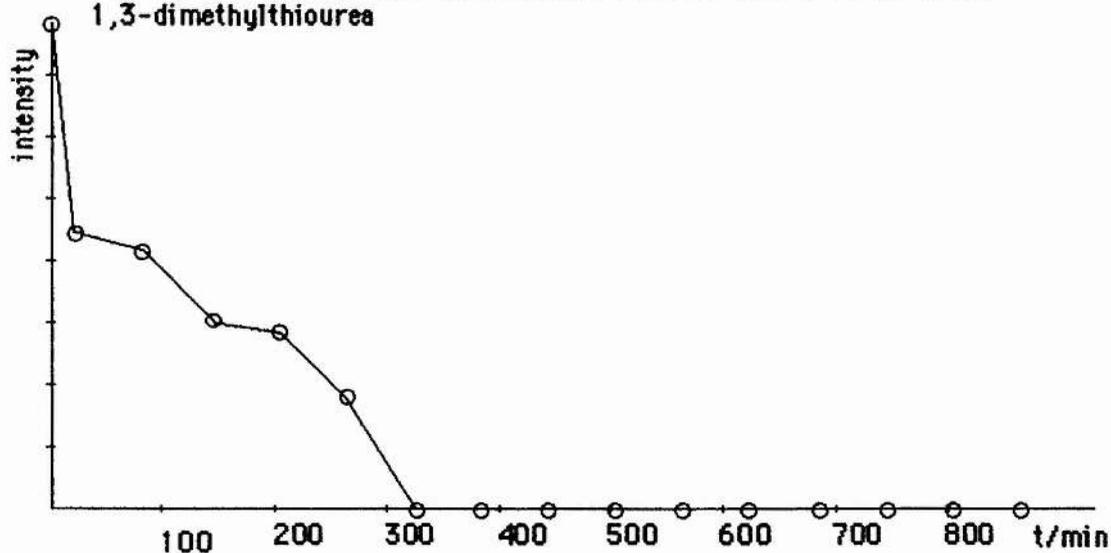


unlabelled diketone all the diketone signals show a smooth steady fall throughout the period studied. See figure 6. The signals are not, of course, observed in the fifth experiment.

The sample of (13) isolated from the neutral reaction of 1,3-dimethylthiourea and 1-phenyl-1,2-propanedione consists of a mixture of the E and Z isomers. In the absence of acid there is no plausible mechanism for the interconversion of the two isomers so the relative amounts of each must be kinetically controlled by the relative rates of cyclisation of (12) to (13E) and (13Z) under neutral conditions. On the addition of acid the intensities of the (13Z) signals fall abruptly and the intensities of the (13E) signals rise equally rapidly (see figures 7 and 8). This presumably corresponds to the introduction of a means of interconversion of the two isomers, possibly via dehydration to (14) or acid catalysed ring opening to (12), so that the relative amounts of (13E) and (13Z) are under thermodynamic, rather than kinetic, control. Once the equilibrium between the isomers is established both isomers show a smooth, steady decrease in concentration throughout the period studied, except for the third experiment where the concentration of the Z isomer first falls as the concentrations of (13E) and (13Z) approach equilibrium and then rises for the next two hours before falling for the remainder of the period studied. This is because 'shimming' the nmr spectrometer was particularly rapid for this experiment, so the (13) concentration before the acid was added was less than in the fourth experiment and the diketone concentration higher because there was less time for the neutral reaction of 1,3-dimethylthiourea and the diketone to occur.

In the third experiment a signal is observed at 99.053 ppm before the acid is added. The chemical shift is appropriate for an aminol centre but it does not match any of the shifts of either of the isomers of (13) and it also does not vary over time in parallel with the signals due to either isomer. Under neutral conditions

Figure 9: Variation of (12) methyl signal at 25.13 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 3-position and 1,3-dimethylthiourea



Variation of (12) signal at 99.05 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 1-position and 1,3-dimethylthiourea

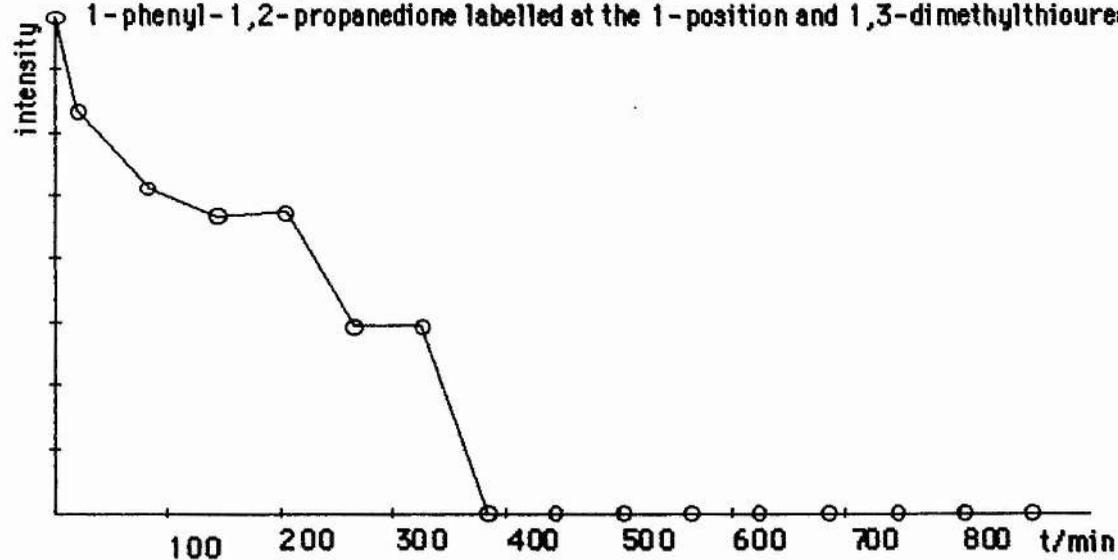
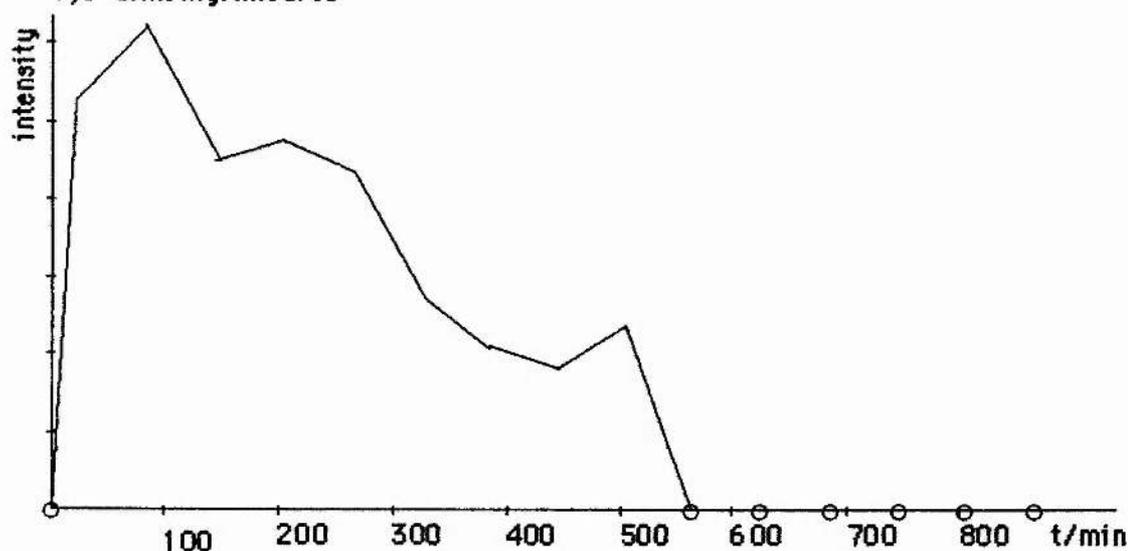
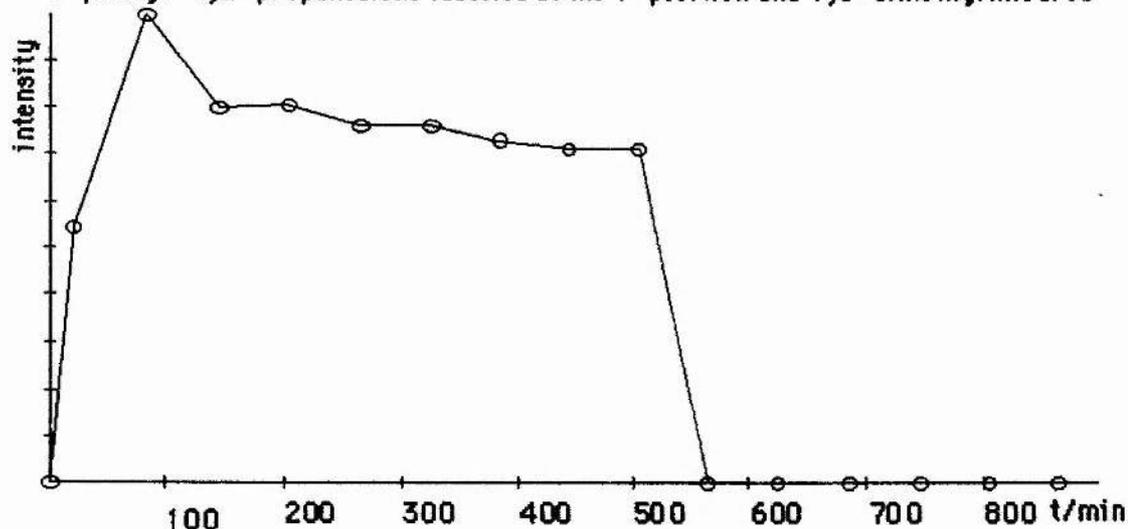


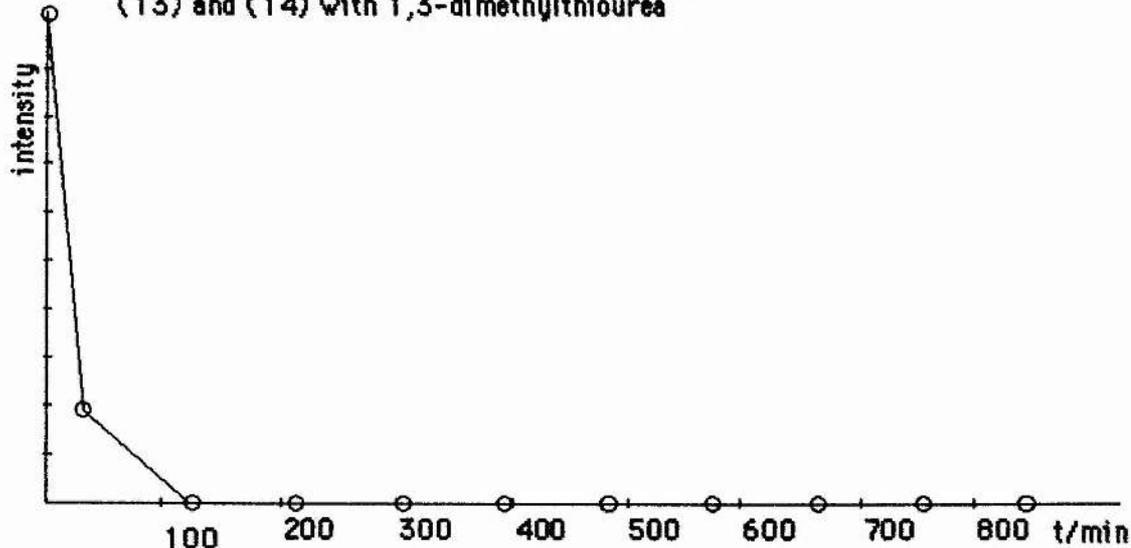
Figure 10: Variation of (14) methylene signal at 88.045 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 3-position and 1,3-dimethylthiourea



Variation of (14) signal at 93.14 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 1-position and 1,3-dimethylthiourea



Variation of (14) signal at 88.08 ppm during the acid catalysed reaction of (13) and (14) with 1,3-dimethylthiourea



1,3-dimethylthiourea and 1-phenyl-1,2-propanedione are known to react to give only (13), so it is reasonable to assign this signal to a material intermediate between the reagents and (13). The signal shows an intensity variation very similar to the diketone, which implies that it corresponds to an intermediate which exists in equilibrium with the reagents. No other strong signals are observed which correlate with the signal other than those unambiguously assigned to the diketone, although two weak signals corresponding to N-methyl groups at 27.96 and 27.78 ppm are observed which show a reasonable match. In the fourth experiment a methyl signal at 25.13 ppm is observed which shows a similar intensity variation to the diketone signal at 27.85 ppm. See figure 9. No other parallel signals were observed, so it must correspond to a carbon derived from the labelled 3-position of the diketone. The shift of the carbon derived from the labelled 1-position in the first experiment is consistent with an aminolic centre rather than a carbonyl, which implies that the signal corresponds to (12), rather than the isomeric material formed by nucleophilic attack by the 1,3-dimethylthiourea on the carbonyl adjacent to the methyl group. No signal due to the labelled carbonyl centre of such an intermediate was detected.

In the fifth experiment a third material besides 1,3-dimethylthiourea and the two isomers of (13) was present in the mixture before the acid was added. The material had carbon-13 signals corresponding to a thione group at 185.07 ppm, four phenyl signals, a signal corresponding to an aminol centre at 93.09 ppm, a methylene signal at 88.08 ppm and two N-methyl signals at 32.79 and 30.70 ppm. From the characteristic signals of the exocyclic methylene and aminol groups it was assigned as (14), formed by dehydration during work-up. On the addition of acid the concentration of (14) falls abruptly. See figure 10. The only signals to increase in concert with the rapid fall in (14)'s concentration are those positively assigned to (11), therefore (14) must be an intermediate en route to (11). In the third experiment a signal at 93.13

Figure 11: Normalised variation of (14) methylene signal at 88.045 ppm and rate of (11) production during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 3-position and 1,3-dimethylthiourea

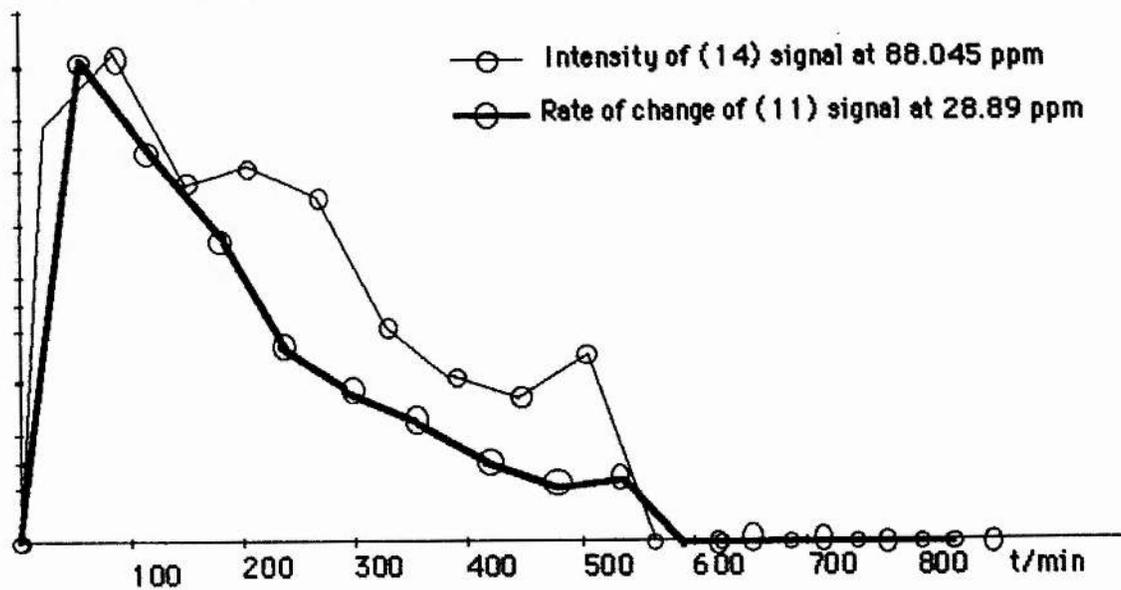
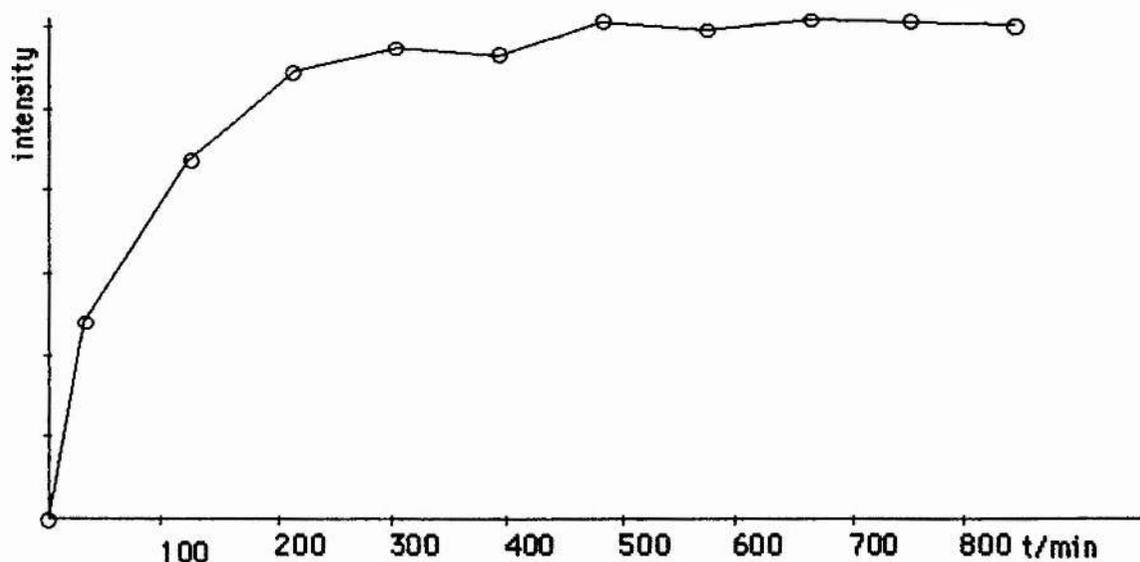
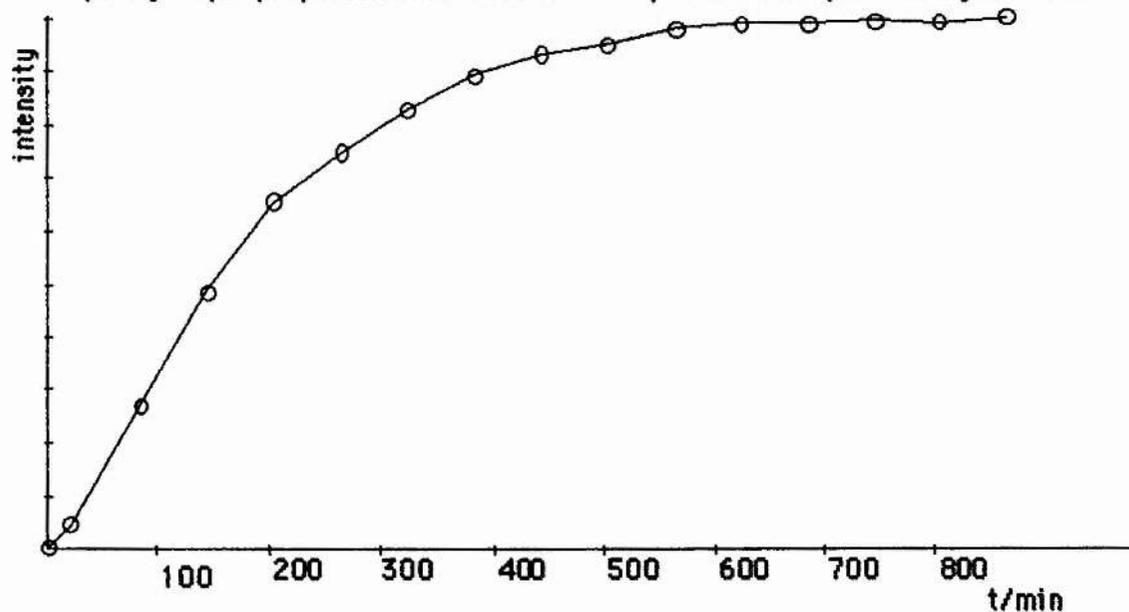


Figure 12: Variation of (11) signal at 34.458 ppm during the acid catalysed reaction (13) and (14) with 1,3-dimethylthiourea.

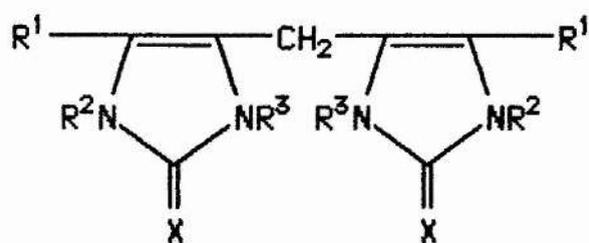


Variation of methylene signal at 28.84 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 3-position and 1,3-dimethylthiourea



ppm corresponding almost exactly to the amino centre of (14) and derived from the labelled 1-position of the diketone appears very rapidly on the addition of acid, rises to a maximum after 1 hour and then falls steadily, reaching an undetectably low concentration shortly before the final concentration of (11) is reached. In the fourth experiment a methylene signal derived from the labelled 3-position of the diketone is observed at 88.05 ppm which varies in an almost identical way over the course of the reaction and again is assigned to (14). In both cases the rate of (11) formation corresponds very well with the intensity of the signals due to (14). See figure 11.

The product of the reaction (11) shows signals at 168.01, 165.79, 133.23, 132.45, 132.32, 131.73, 129.20, 121.47, 35.27, 34.46, 33.50 and 28.89 ppm. All of these signals vary in parallel over the course of the reaction and all have been confirmed to be due to (11) by spiking the final product solutions with authentic samples of the authentic material. The signal at 121.47 ppm is derived from the 1-position of the diketone and the methylene signal at 28.89 ppm from the 3-position as can be seen from the stacked plots of the third reaction (figure 3) and the fourth reaction (figure 4) respectively. The rate of (11) production is slightly faster from 1,3-dimethylthiourea and (13) in the fifth experiment than from 1,3-dimethylthiourea and 1-phenyl-1,2-propanedione in the third and fourth experiments but in all cases the concentration rises smoothly to a constant level attained after the concentrations of all the other species in the solution have fallen below the limit of detection. See figure 12.

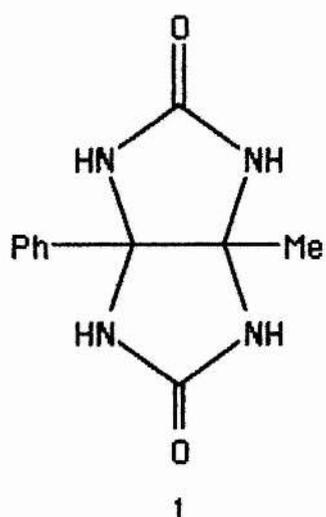


2: $R^1 = \text{Me}$, $R^2 = \text{H}$, $R^3 = \text{H}$, $X = \text{O}$

3: $R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{H}$, $X = \text{S}$

4: $R^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = \text{H}$, $X = \text{O}$

6: $R^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = \text{H}$, $X = \text{S}$

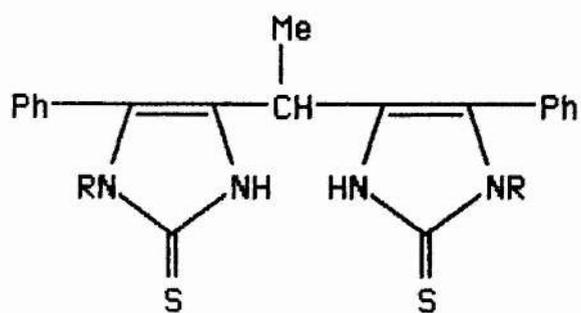


Thiourea and 1-methylthiourea: Under acid catalysis 1-phenyl-1,2-propanedione condenses with thiourea to give (3) as the sole isolable product. The material has been fully characterised by infra-red spectroscopy, proton and carbon-13 nmr spectroscopy and elemental analysis. No molecular ion is observed in the mass spectrum. The composition of (3) corresponds to the condensation of two molecules each of thiourea and diketone with the elimination of four molecules of water and *one carbon atom*. This product is closely analogous to the reported product of the acid catalysed reaction of urea and biacetyl (2)². The acid catalysed reaction of urea and 1-phenyl-1,2-propanedione is reported to yield (1) as the major product¹, together with a minor product which was assigned as the analogue of (3) without complete characterisation.

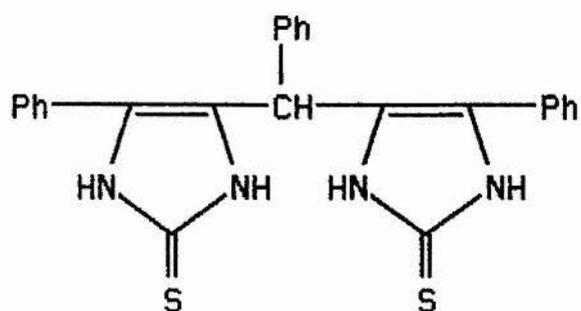
The reaction is catalysed efficiently by TFA in a variety of solvents although other acids may be used. Squaric acid catalyses the reaction slowly in THF but aqueous hydrochloric acid in THF is not effective. Concentrated aqueous hydrochloric acid is however effective when glacial acetic acid is used as the solvent. It would appear that the reaction requires acid catalysis and also a dehydration process. Concentrated sulphuric acid would also appear to fit these conditions but unfortunately it reacts rapidly with thiourea. Strangely, the reaction proceeds readily in aqueous THF when catalysed by TFA.

The acid catalysed reaction of 1-methylthiourea and 1-phenyl-1,2-propanedione yields (6) as the only isolable product. The material has been fully characterised by mass spectroscopy, elemental analysis, infra-red spectroscopy and proton and carbon-13 nmr spectroscopy. The product is exactly analogous to the reported product of the acid catalysed reaction of 1-methylurea and 1-phenyl-1,2-propanedione (4)¹, which was unambiguously characterised by X-ray crystallography.

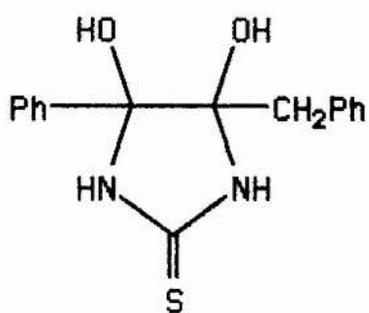
In the reaction of 1-methylurea and 1-phenyl-1,2-propanedione the carbon atom was reported to be lost in the form of formaldehyde, which was trapped using



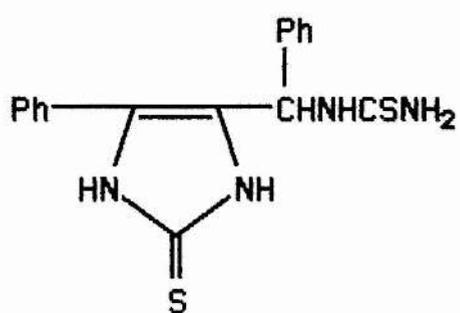
19: R=H
20: R=Me



21



22



23

dimedone². In the reaction of thiourea and 1-phenyl-1,2-propanedione in glacial acetic acid catalysed by hydrochloric acid the oligomer formed by condensation of formaldehyde and thiourea was detected by carbon-13 nmr but it could not be detected when the reaction was carried out in THF catalysed by TFA. The replacement of the methyl group of the diketone by bulkier groups did however allow the appropriate aldehyde to be detected. Formaldehyde was, however, successfully trapped using dimedone in a related reaction which will be described below.

Thiourea reacts with 1-phenyl-1,2-butanedione in THF containing TFA to yield (19) as the only isolable product. Again the product has been fully characterised by infra-red spectroscopy, elemental analysis, carbon-13 nmr spectroscopy and proton nmr spectroscopy, the latter clearly showing the loss of one aliphatic group from the molecule.

1-Methylthiourea reacts with 1-phenyl-1,2-butanedione in THF containing TFA to a yield mixture of products of which (20) is the principal component. Compound (20) has again been fully characterised by infra-red spectroscopy, elemental analysis, carbon-13 nmr spectroscopy and proton nmr spectroscopy, the latter again showing the loss of one aliphatic group from the molecule.

In both the above reactions attempts to detect acetaldehyde or its oligomers with thiourea or 1-methylthiourea respectively were unsuccessful.

Thiourea reacts with 1,3-diphenyl-1,2-propanedione under the same conditions to yield a complex mixture of products, the principal components of which are (21), (22) and (23). Compound (21) was separated from the remaining products and fully characterised by infra-red spectroscopy, elemental analysis and carbon-13 and proton nmr spectroscopy. The other components of the mixture could not be readily separated but could be identified by the application of infra-red spectroscopy, carbon-13 nmr spectroscopy and mass spectroscopy to the mixture. Application of gas chromatography-mass spectroscopy to the soluble components of the product mixture

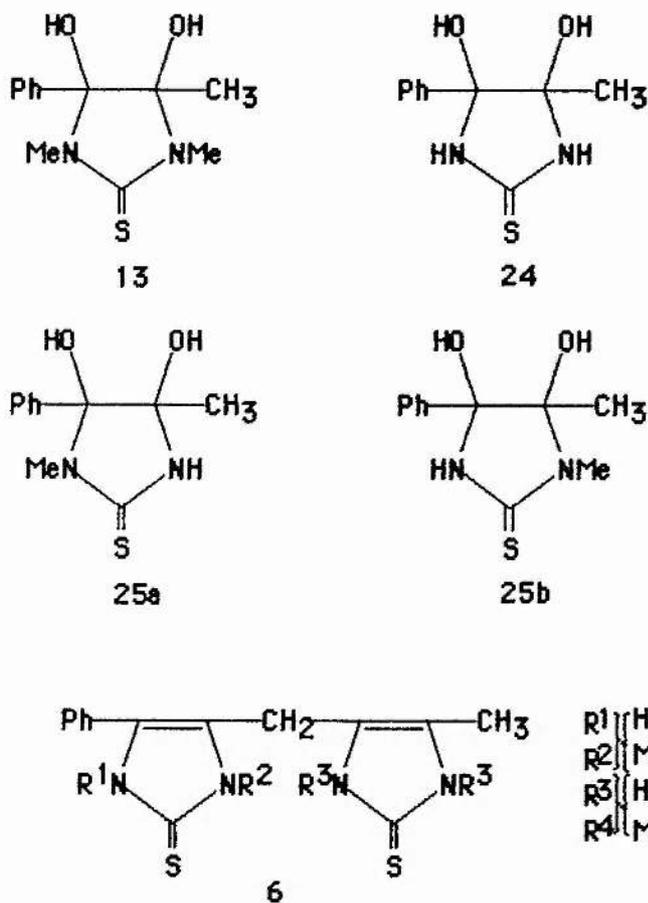
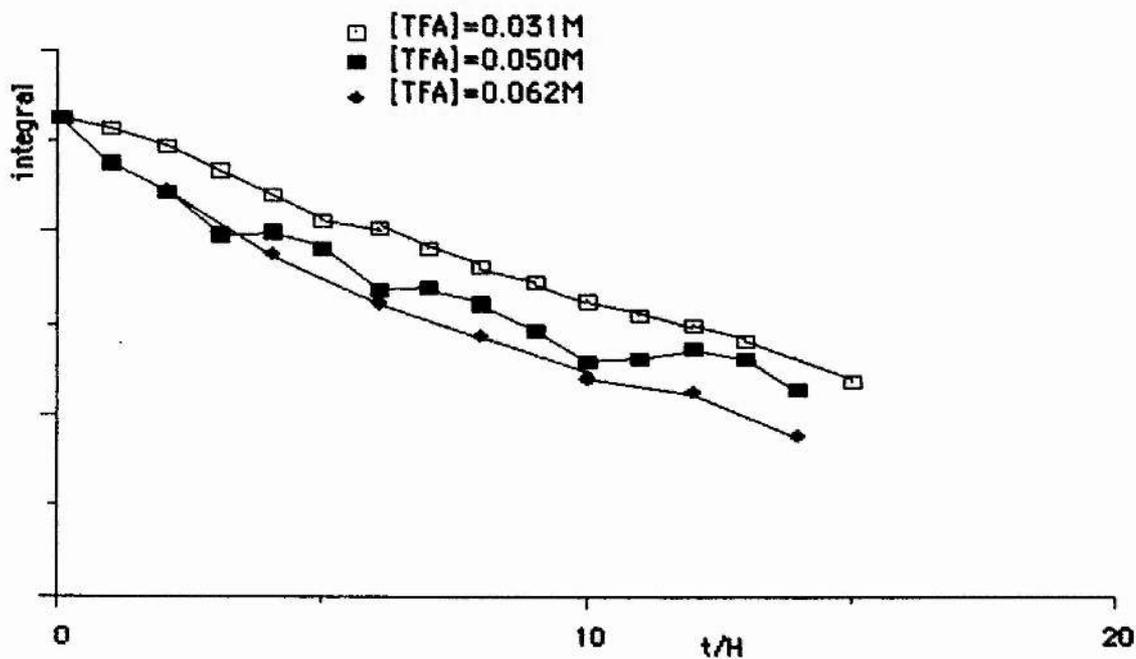


Figure 13: Normalised variations of combined reagent aliphatic proton integrals over time at various [TFA].



allowed us to detect benzaldehyde and benzoic acid, formed by oxidation of the benzaldehyde.

In the absence of acid catalysis 1,3-dimethylthiourea reacts with 1-phenyl-1,2-propanedione to yield (13). Thiourea also reacts slowly with 1-phenyl-1,2-propanedione under neutral conditions to yield the analogous diol (24), which has again been fully characterised. The diol (24) reacts in THF acidified with TFA to yield a mixture consisting principally of (3) but containing also some minor products which were not fully characterised.

The course of the reaction has again been studied by the application of carbon-13 nmr spectroscopy to the system as the reaction proceeds utilising carbon-13 enriched substrates. Only the reaction of 1-phenyl-1,2-propanedione with thiourea was studied to avoid the possibility of the production of isomers of (6) or (25) with the N-methyl groups in different positions as shown.

In contrast to the reaction of 1,3-dimethylthiourea with 1-phenyl-1,2-propanedione, the rate of the reaction could easily be monitored using proton nmr, which has the advantages of experimental simplicity and the absence of the nuclear Overhauser effect so that the signal integrals give quantitative information. The reaction temperature, solvent and acid concentration could be adjusted to give the optimum rate of reaction by monitoring the rate of loss of the diketone's aliphatic group by proton nmr. It was not possible to monitor the rate of formation of (3) directly because the aliphatic group's signal partially overlapped with the signal of the thiourea protons. The dependence of the rate upon the acid concentration is shown in figure 13. It can be seen that the rate of reaction is quite insensitive to the acid concentration, so it was decided to use a low acid concentration in the hope that this would lead to higher concentrations of any acid sensitive intermediates present. Unfortunately, even at a TFA concentration of 0.031 M the concentrations of all the intermediates were so low that they could not be reliably distinguished from the low concentrations of impurities present in the sample

Figure 14: Successive carbon-13 nmr spectra during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 1-position and thiourea

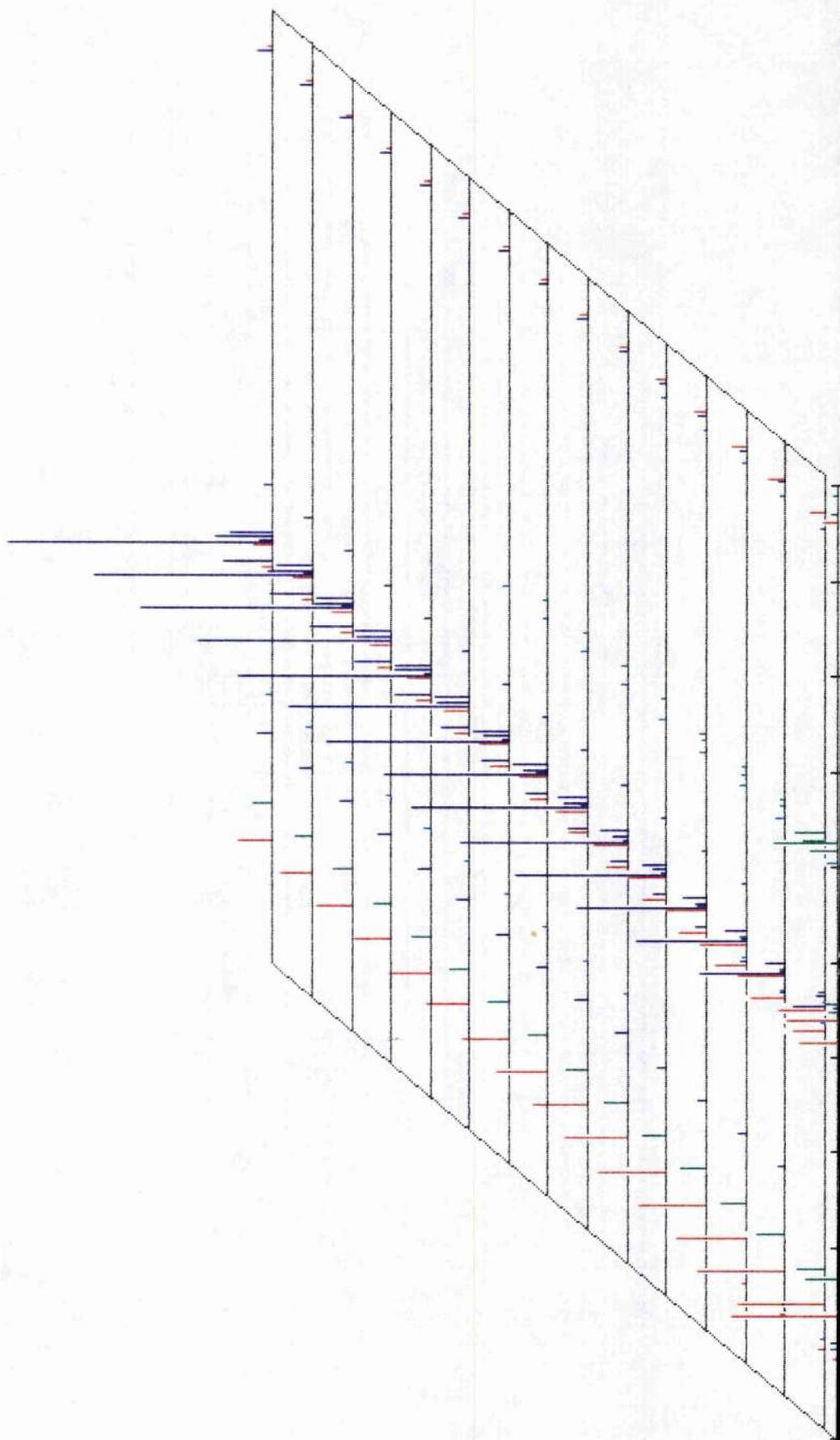


Figure 15. Successive DEPT 135 carbon-13 nmr spectra during the acid catalysed reaction of 1-phenyl-1,2-propanediol and thioarea

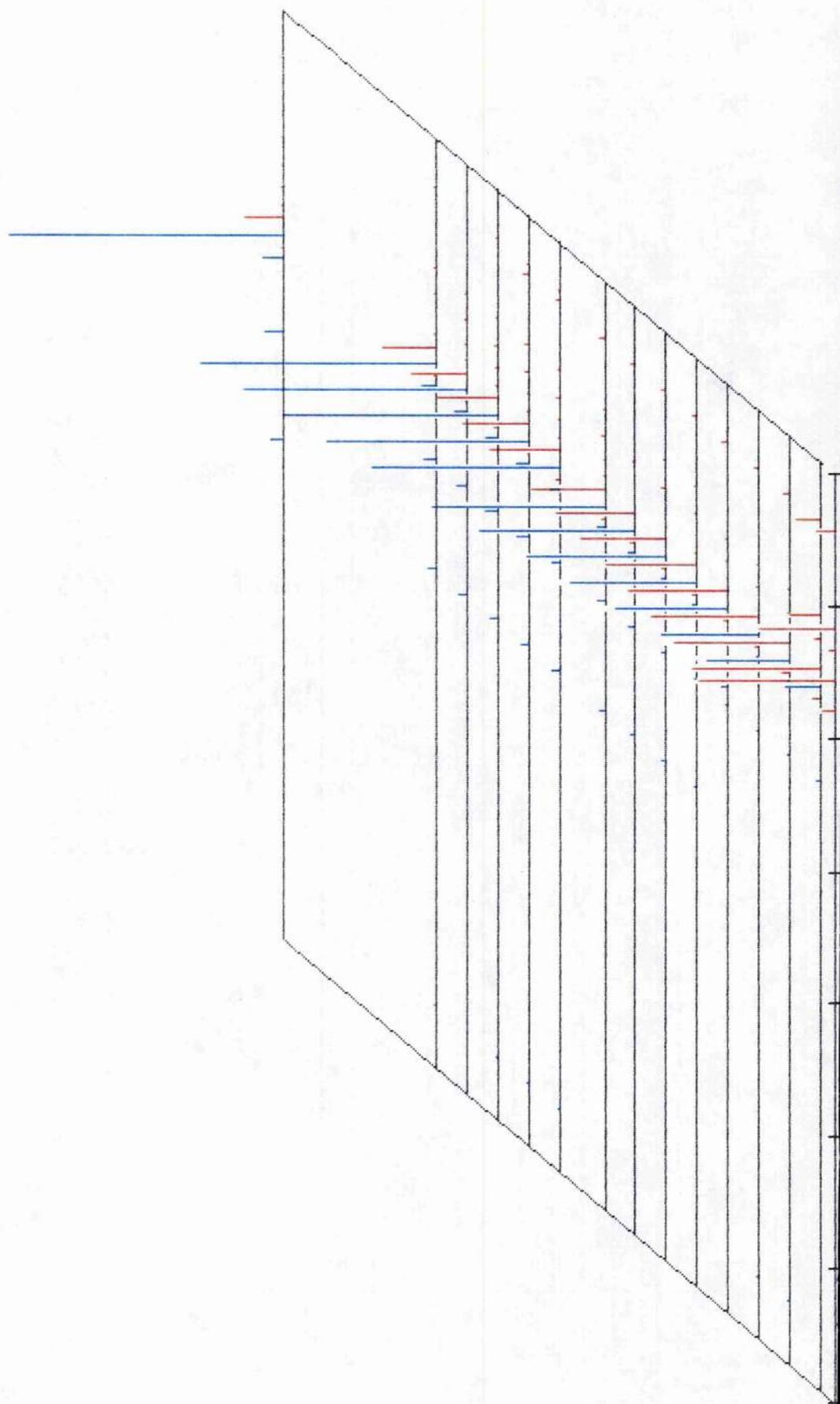
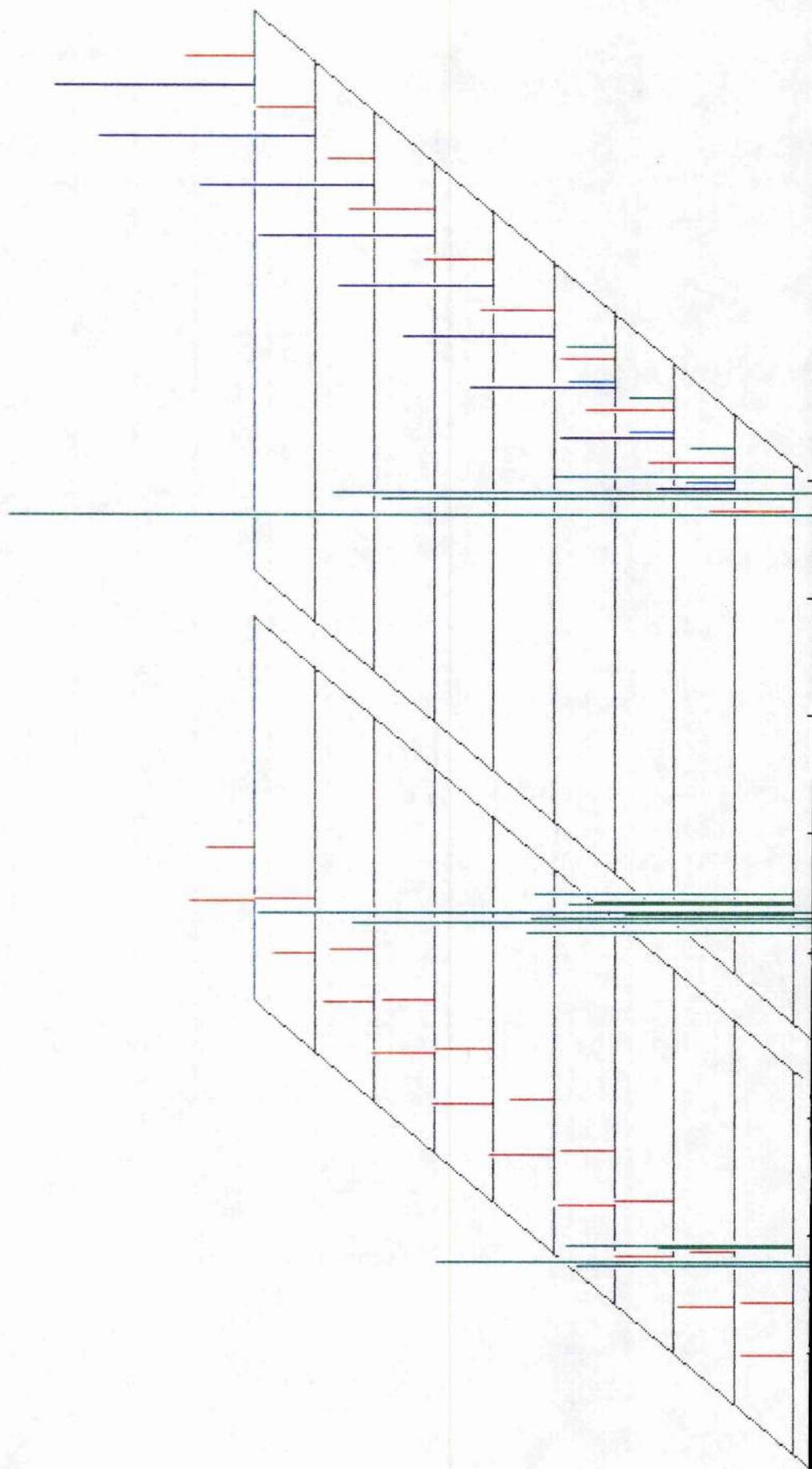


Figure 16: Successive carbon-13 nmr spectra during the acid catalyzed reaction of (2.4) to give (3)



of the labelled diketone even after purification by distillation and column chromatography. Those impurities which were stable under the experimental conditions were of course readily distinguished, but it was not possible to be certain that some of the impurities did not react with the acid, giving spurious changing signals which could be mistaken for intermediates in the reaction. Some difficulty was experienced in finding a non-nucleophilic solvent miscible with the diketone in which the saturated thiourea concentration was satisfactory. Aqueous THF was found to give acceptable results, although the saturated thiourea concentration was still less than ideal.

Three experiments were carried out studying the course of the reaction by carbon-13 nmr once the optimum conditions had been determined. In the first of these 1-phenyl-1,2-propanedione labelled at the 1-position was used together with a slight excess of thiourea, taking carbon-13 nmr spectra at hourly intervals with a fifteen minute acquisition time. The results of this experiment are summarised in figure 14. In the second experiment 1-phenyl-1,2-propanedione labelled at the 3-position was used together with a slight excess of thiourea, again taking carbon-13 nmr spectra at hourly intervals with a fifteen minute acquisition time but this time using the DEPT 135 pulse sequence so that only the carbons with attached protons corresponding to the labelled centre (and the aromatic groups) were detected. The results of this experiment are summarised in figure 15. Note that the methyl and methylene signals are distinguished by colour in this figure rather than by inversion of the methylenes. In the third experiment a sample of the diol (24) prepared separately and containing no carbon-13 label was used, taking spectra at 90 minute intervals with a 30 minute acquisition time. The results of this experiment are summarised in figure 16.

In all three experiments the reagents were placed in the neutral solvent and the nmr spectrometer 'shimmed' to give the optimum spectrum before the TFA was added. Hence, since thiourea and 1-phenyl-1,2-propanedione react in neutral solution to give

Scheme 2

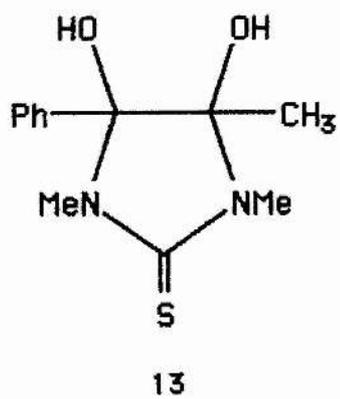
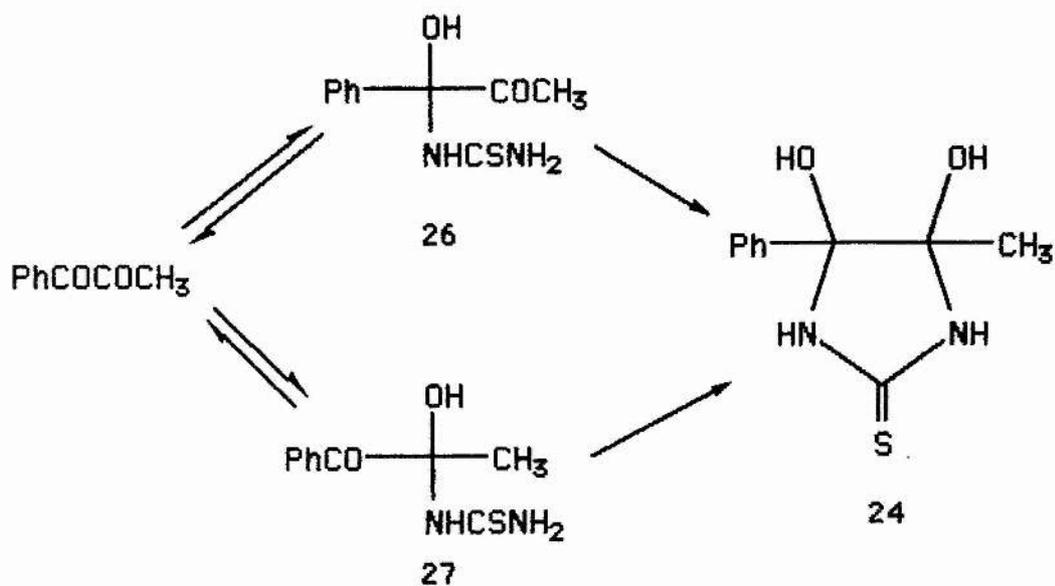
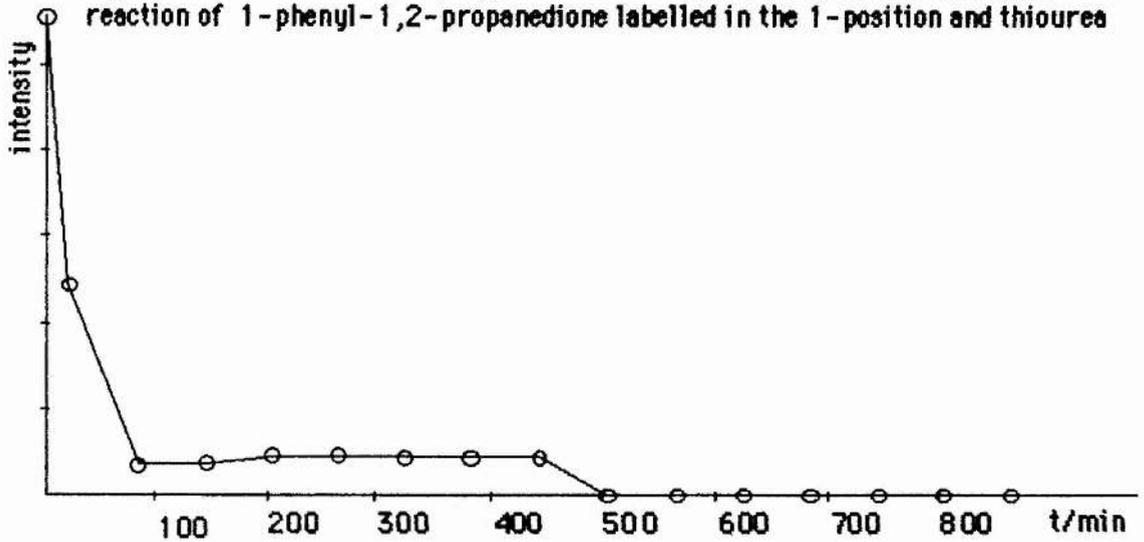
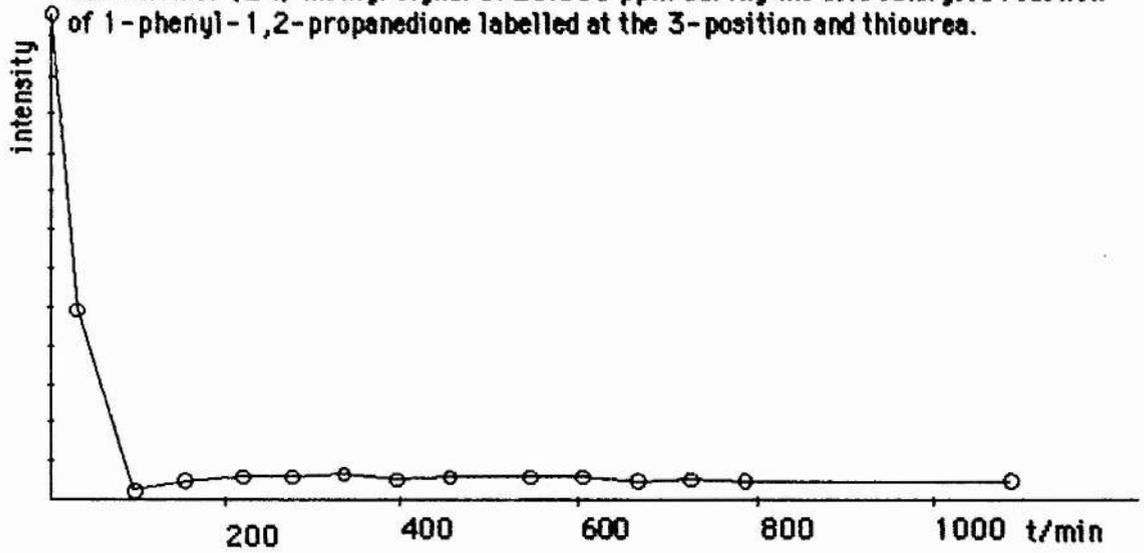


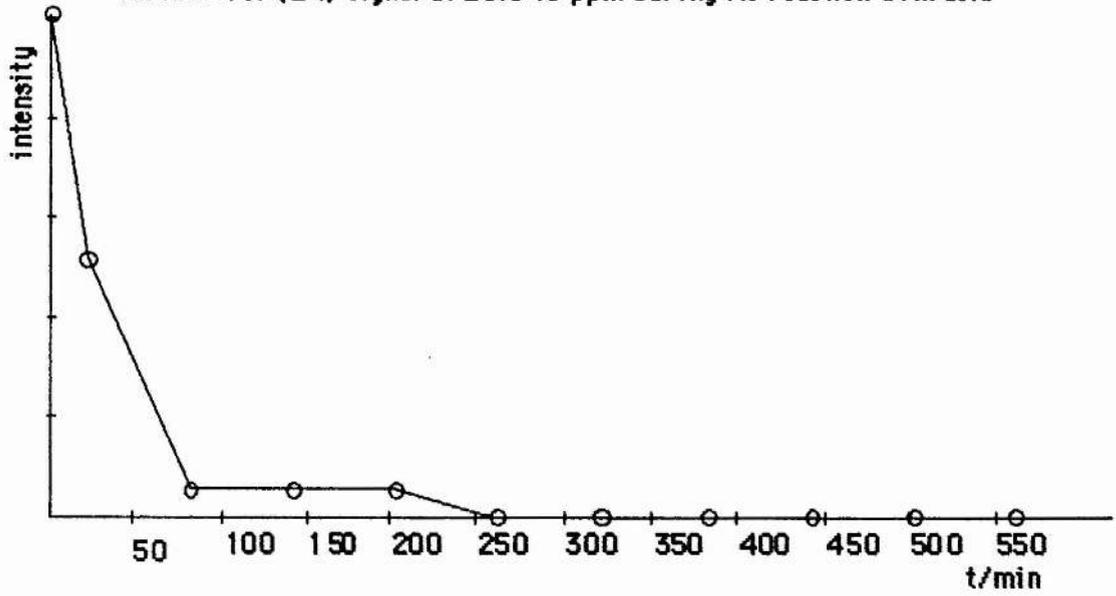
Figure 17: Variation of (24) signal at 94.933 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled in the 1-position and thiourea



Variation of (24) methyl signal at 25.850 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 3-position and thiourea.



Variation of (24) signal at 25.845 ppm during its reaction with acid



(24) the equilibria shown in scheme 2 must be set up in the system before the addition of acid at the start of the experiment. Indeed signals at 99.045 ppm in the first experiment and 28.948 ppm in the second experiment, corresponding to the aminol and methyl signals of (26) are observed before the acid is added. The analogous intermediate in the reaction of 1,3-dimethylthiourea and 1-phenyl-1,2-propanedione (12) showed corresponding signals at 99.053 and 25.129 ppm. Signals at 201.148 ppm in the first experiment and 26.737 ppm in the second experiment, corresponding to the carbonyl and methyl centres of (27) are also observed before the addition of the TFA. Signals derived from the labelled 1-position of the diketone at 96.688 and 94.933 ppm in the first experiment and methyl signals derived from the labelled 3-position at 25.850 and 22.171 ppm in the second experiment, corresponding to the Z and E isomers of the diol (24) are also present before the addition of acid. All these shifts are consistent with those of the isolated sample of (24) in aqueous THF. In contrast to (13), it appears that the two isomers can interconvert even in neutral conditions. The signals corresponding to the two isomers vary in parallel throughout the course of the reaction and there is no sign of a change in the isomer ratio on the addition of acid to the system. Thus the two isomers must exist in equilibrium in the neutral solution unless the kinetically controlled ratio of Z to E produced in the cyclisation step is coincidentally similar to the thermodynamic equilibrium value. The most reasonable mechanism for the interconversion of the two isomers is dehydration across one carbon-nitrogen bond. In the third experiment it was shown that in the absence of acid (24) does not decompose significantly to diketone and thiourea.

On the addition of acid to the equilibrium system set up in the first two experiments and summarised in scheme 2 the intensities of all the (24) signals of both isomers fall dramatically to approximately one tenth their initial value with respect to an internal reference. The intensities then decrease very, very slowly until they fall beneath the limit of detection, as shown in figure 17. The signals corresponding to the

Figure 22: Variation of thiourea signal at 186.537 ppm during its acid catalysed reaction with 1-phenyl-1,2-propanedione

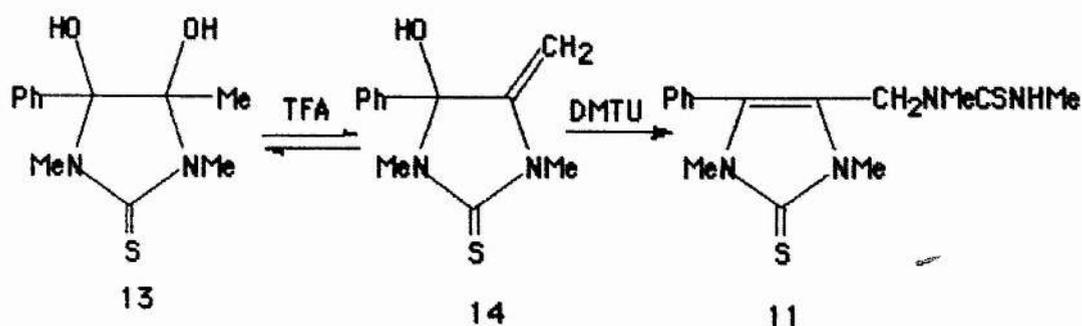
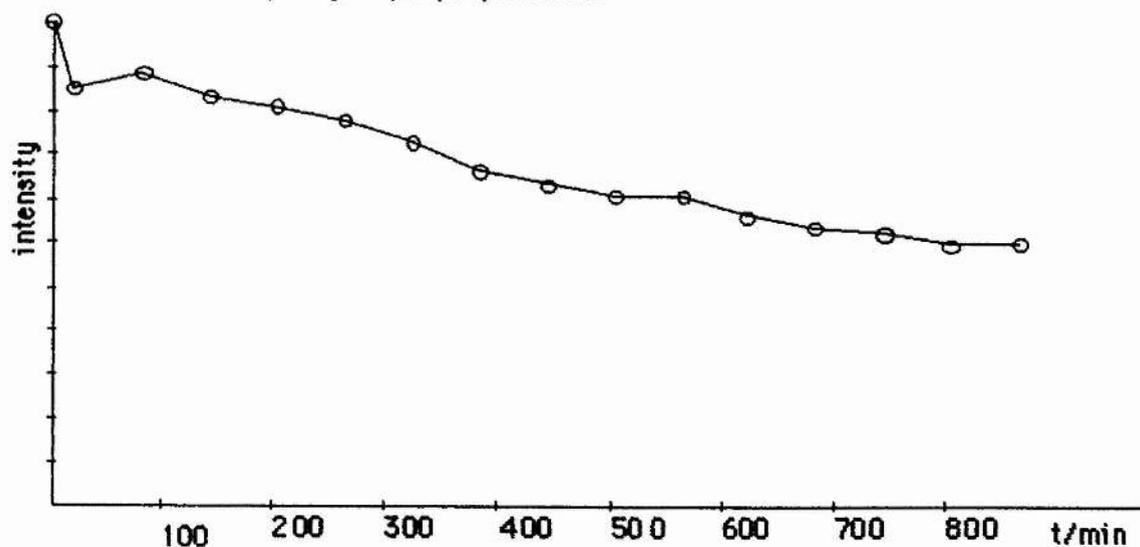
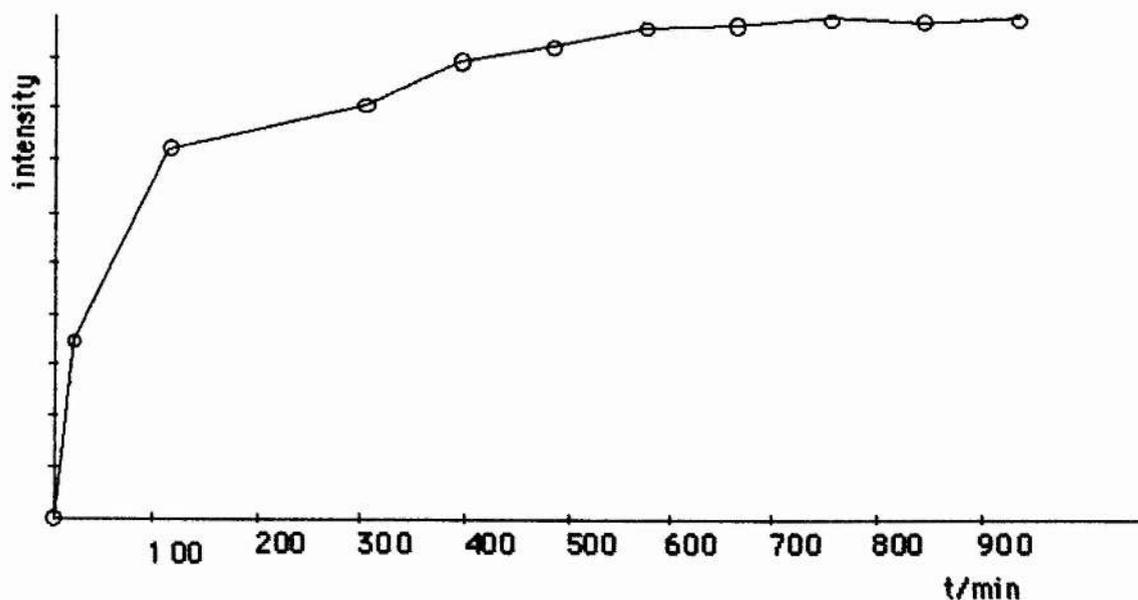
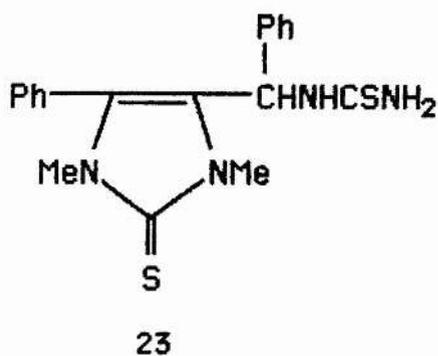
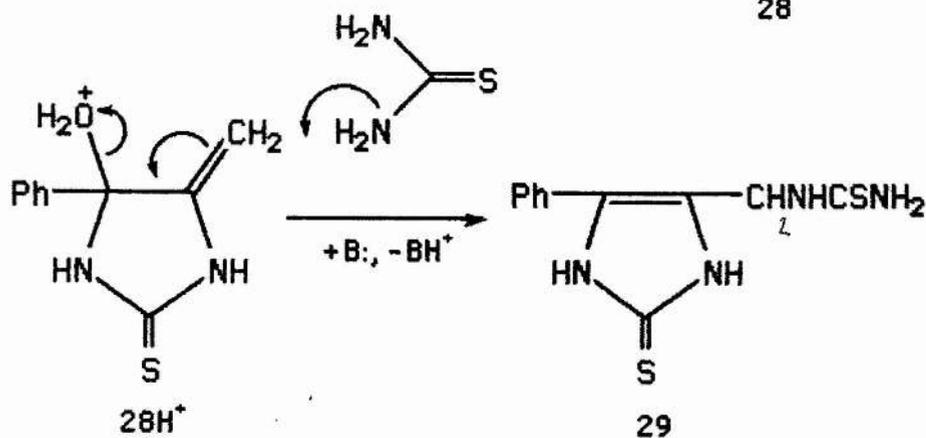
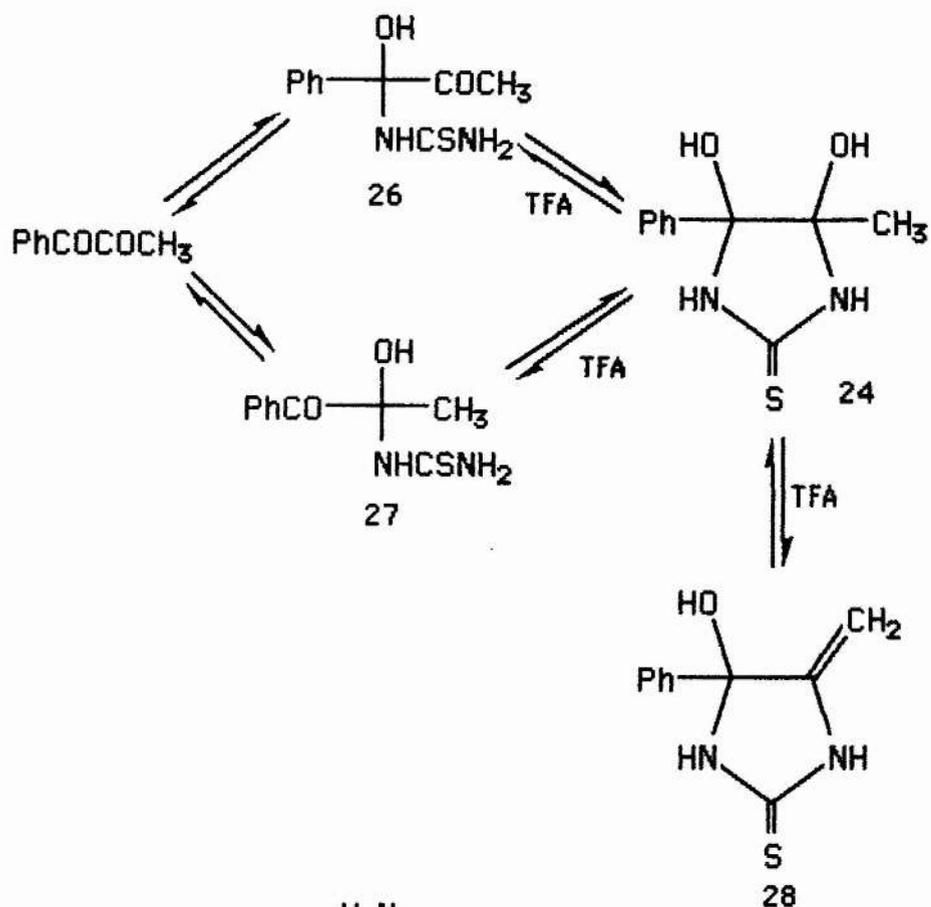


Figure 2: Variation of (11) signal at 28.87 ppm in experiment with [TFA]=.031 M



Scheme 3



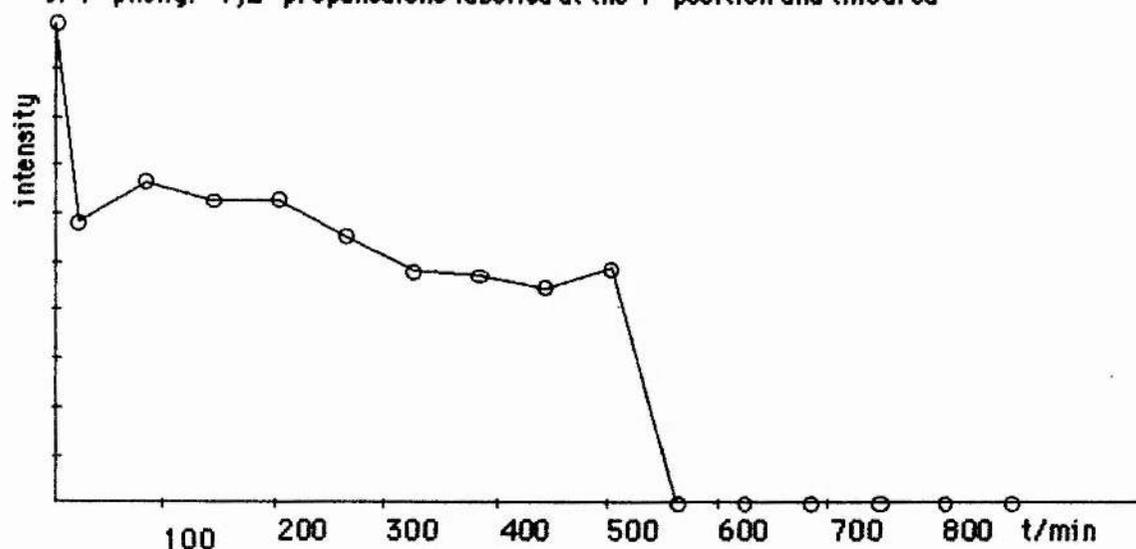
two acyclic adducts (26) and (27) all fall rapidly to approximately half their previous value on the addition of acid and then decrease very slowly and smoothly over the remainder of the period studied or until they fall below the limit of detection. This probably corresponds to acid catalysis of their cyclisation reactions to (24). See figures 18 and 19 respectively.

The concentration of (3) increases very rapidly on the addition of TFA to the equilibrium mixture of (24), (25), (26) diketone and thiourea for the first hour but increases smoothly at a more moderate rate thereafter. See figure 20. This implies that one or more of the species present in solution before the acid is added is an intermediate en route to (3). The rate of (3) production appears to correlate best with the concentration of (24). The rapid disappearance of (24) on the addition of acid is not accompanied by the appearance of any signals of similar intensity other than those of (3), thus (24) must be an intermediate en route to (3).

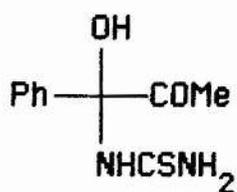
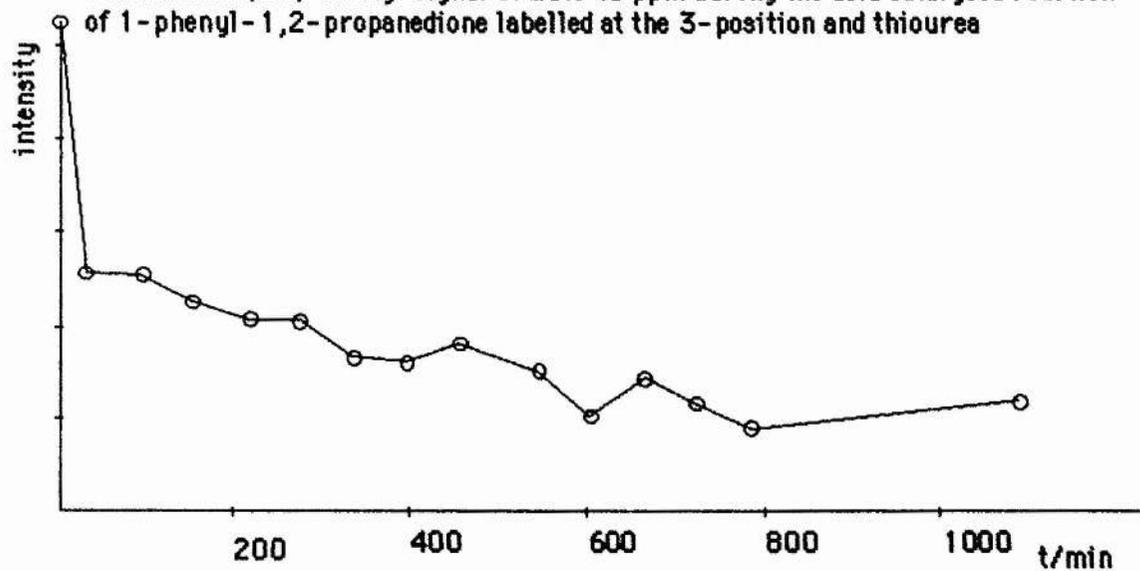
The initial rate of formation of (3) in the third experiment, using previously prepared (24) as the sole starting material, is in fact slower than in the experiments where the acid is added to a mixture containing a lower concentration of (24) together with 1-phenyl-1,2-propanedione, thiourea, ⁷(~~27~~) and (26). This implies that (24) \times must react with one of the other species in the solution en route to (3). In fact in the third experiment (3) is only detected after some (24) has undergone acid catalysed dissociation to thiourea and 1-phenyl-1,2-propanedione, the latter of which was detected from its carbonyl signals, which were just above the limit of detection. See figure 21.

In the equilibrium mixture before the addition of acid the concentration of (24) is some five times that of (25) or (26), according to the DEPT experiment where the signal intensities of carbons with the same number of attached protons correspond to their concentrations exactly. Thus if (3) was produced from the condensation of one molecule of (24) and one of either ⁷(~~25~~) or (26) the concentration of (24) would fall \times

Figure 18: Variation of (26) signal at 99.045 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 1-position and thiourea

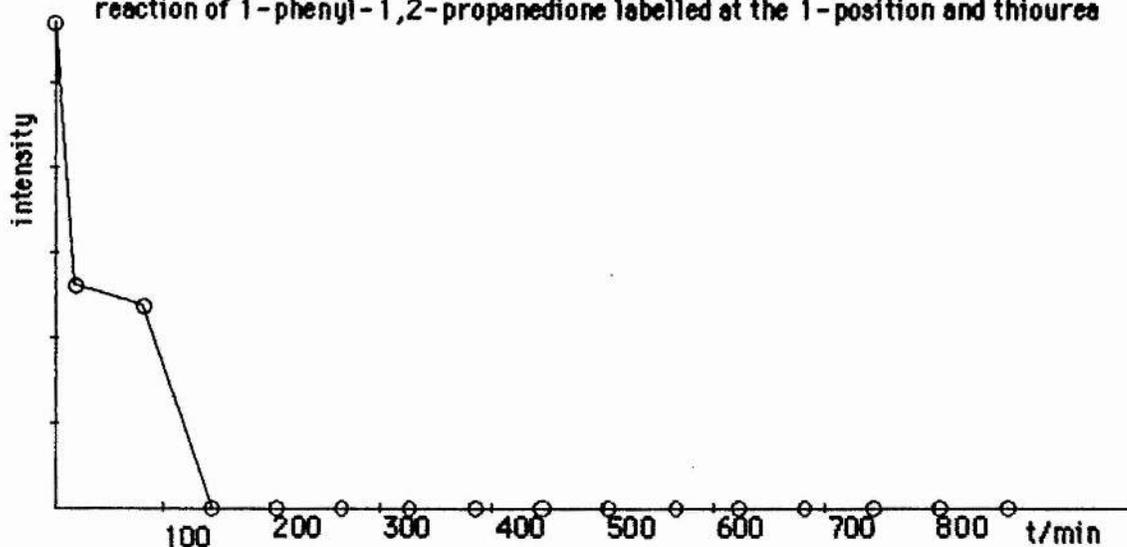


Variation of (26) methyl signal at 28.948 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 3-position and thiourea



26

Figure 19: Variation of (27) signal at 201.148 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 1-position and thiourea



Variation of (27) methyl signal at 26.737 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 3-position and thiourea.

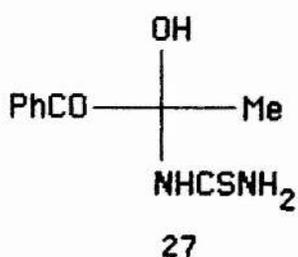
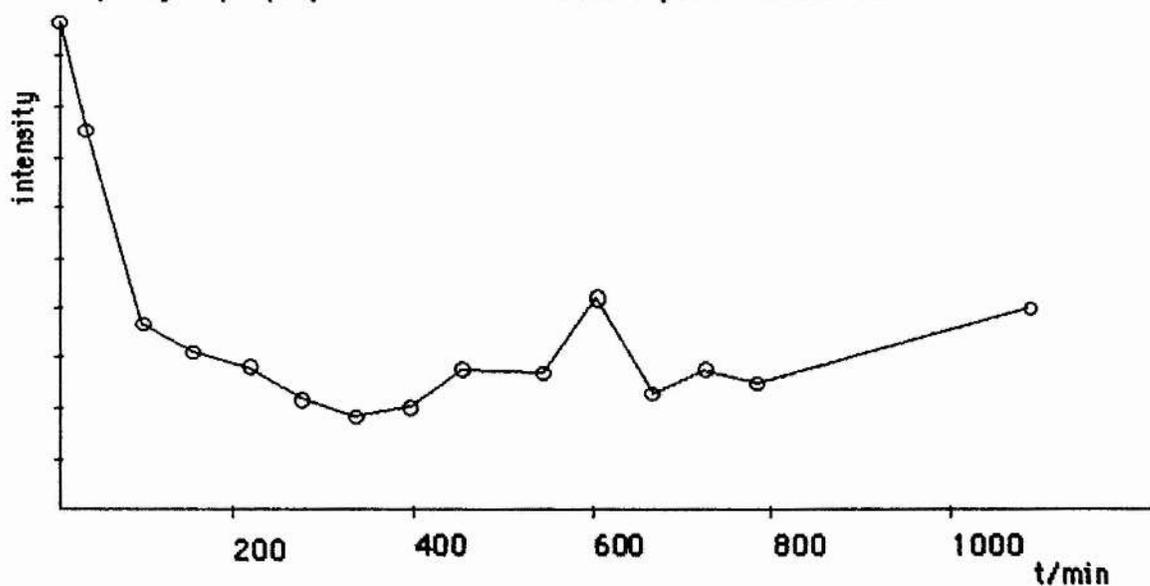
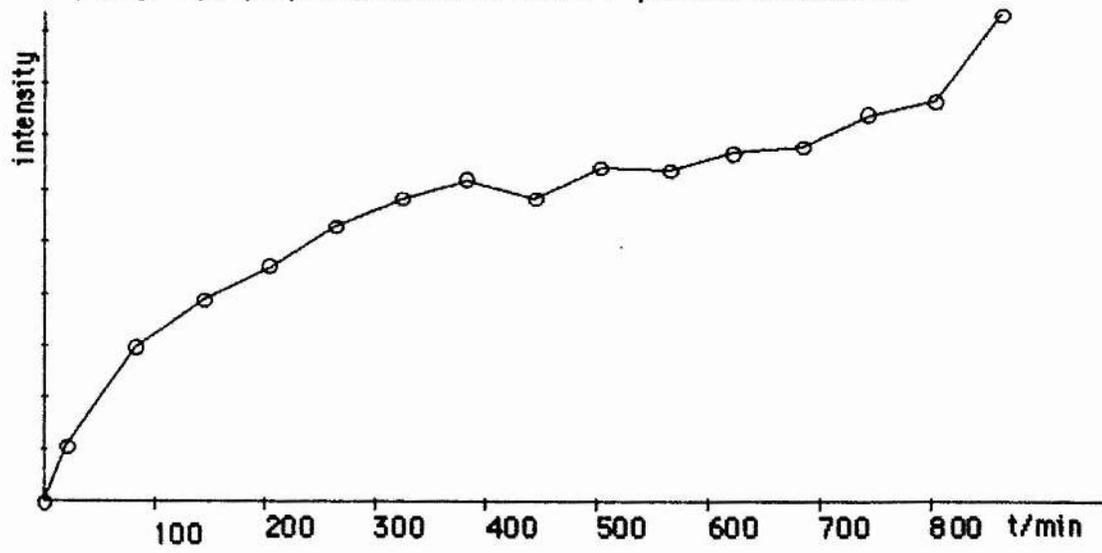
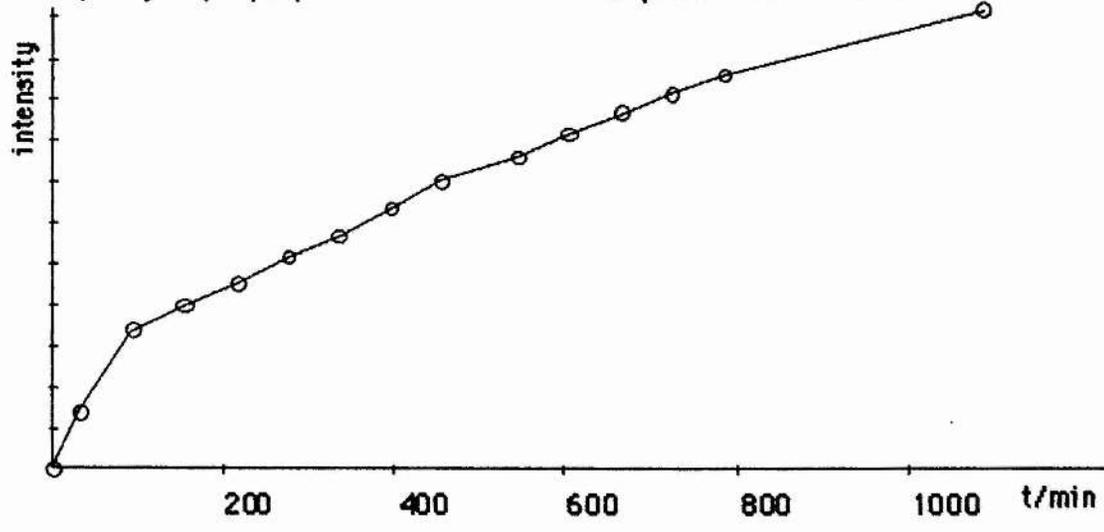


Figure 20: Variation of (3) signal at 131.74 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled in the 1-position and thiourea.



Variation of (3) methylene signal at 28.515 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 3-position and thiourea



Variation of (3) signal at 28.52 ppm during the reaction of (R10) with acid

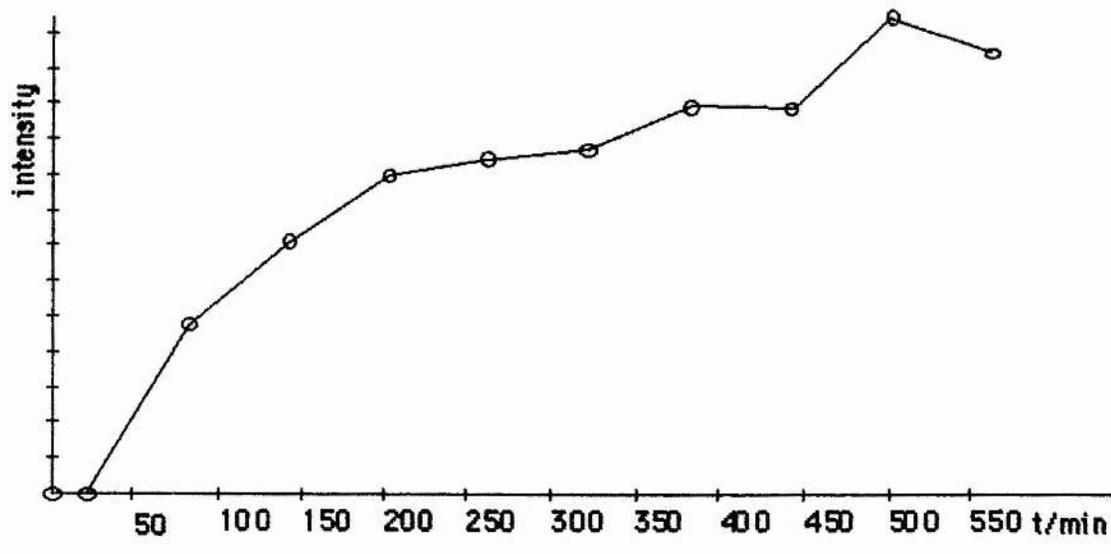
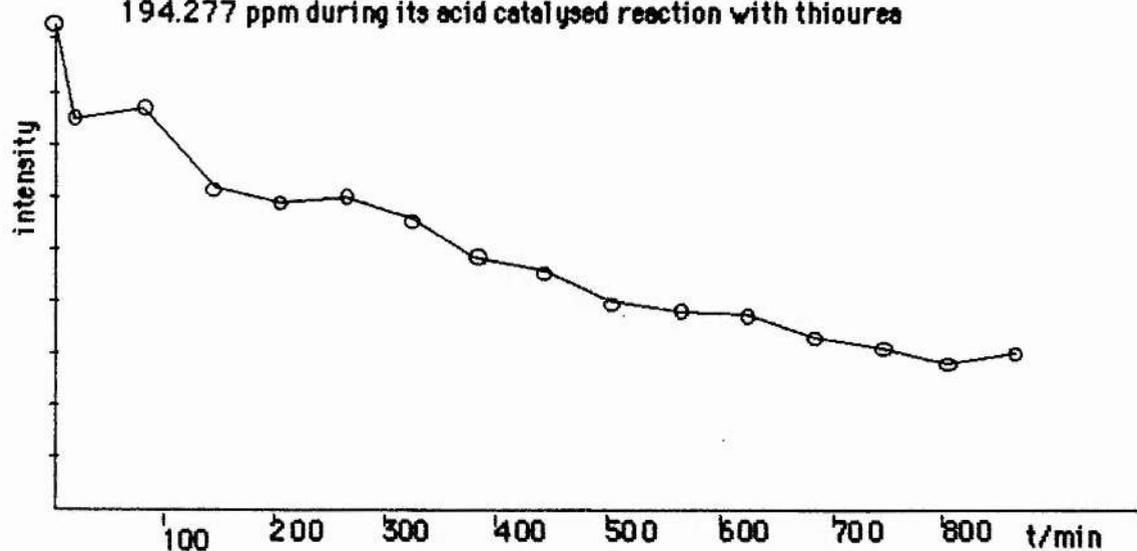


Figure 21: Variation of 1-phenyl-1,2-propanedione labelled 1-position at 194.277 ppm during its acid catalysed reaction with thiourea



Variation of 1-phenyl-1,2-propanedione labelled 3-position methyl signal at 27.841 ppm during its acid catalysed reaction with thiourea

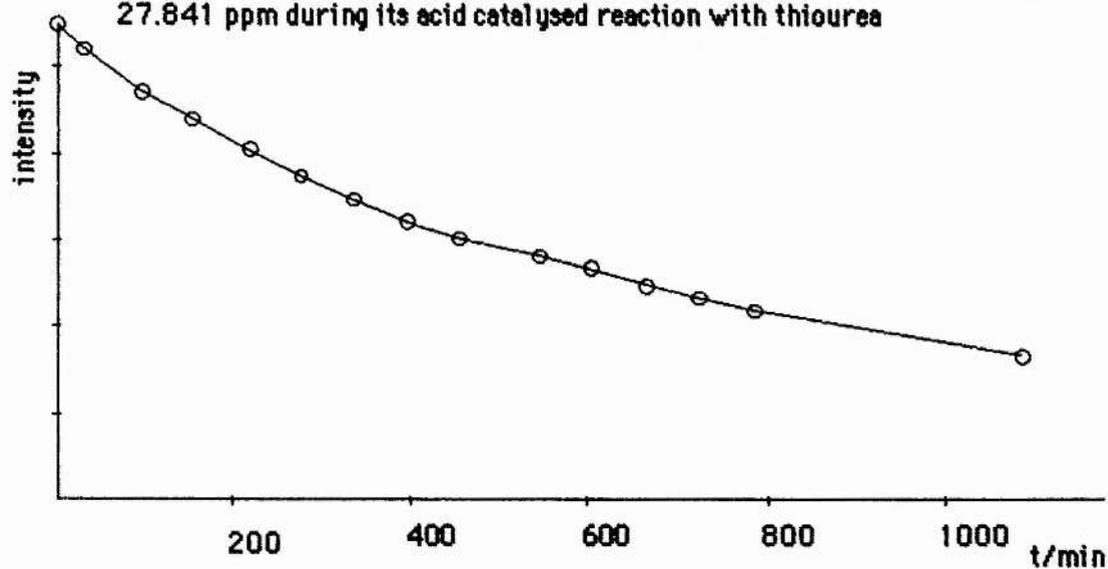
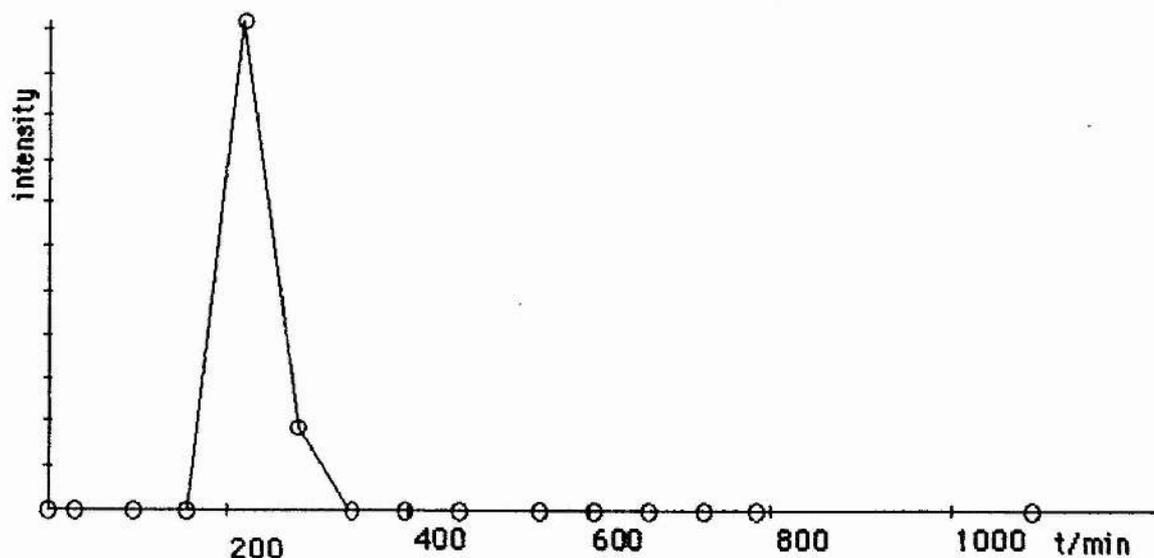


Figure 23: Variation of (29) methylene signal at 31.429 ppm during the acid-catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 3-position and thiourea.



Variation of (29) signal at 31.734 ppm during the reaction of (24) with acid

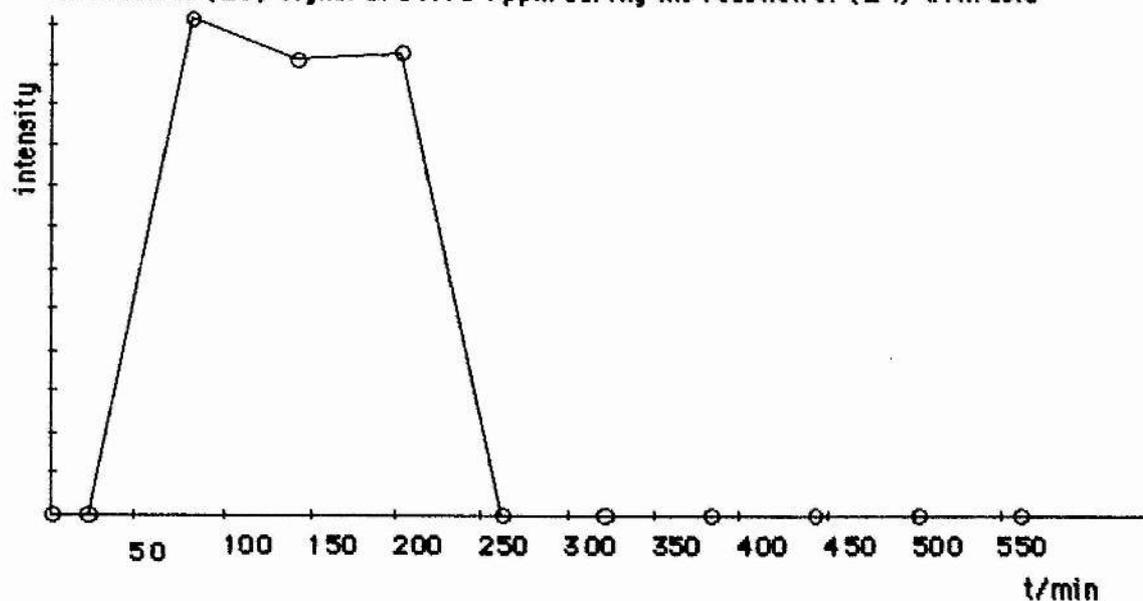


Figure 21a: Variation of 1-phenyl-1,2-propanedione signal at 28.00 ppm during the reaction of (24) with acid

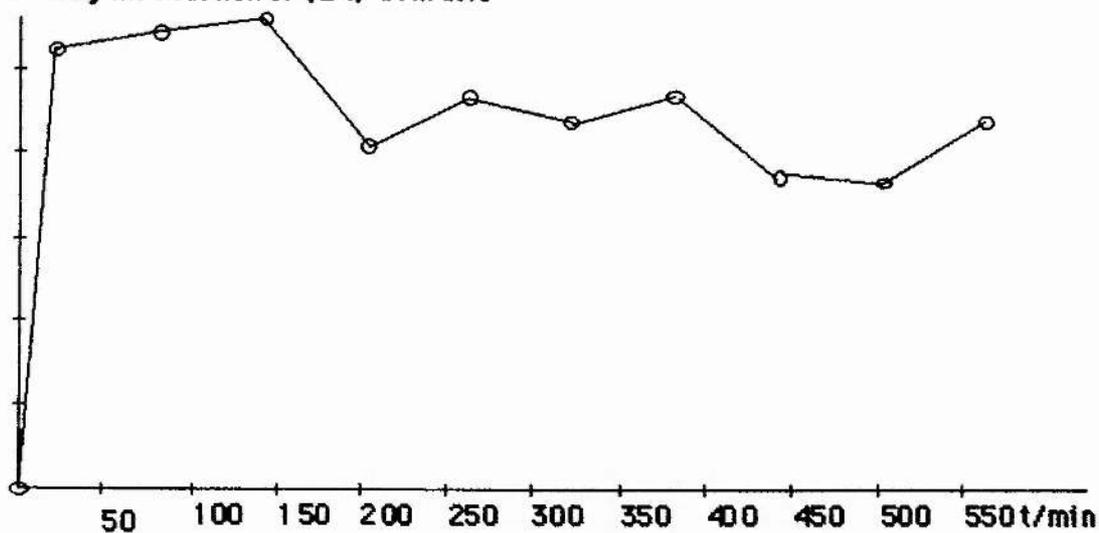
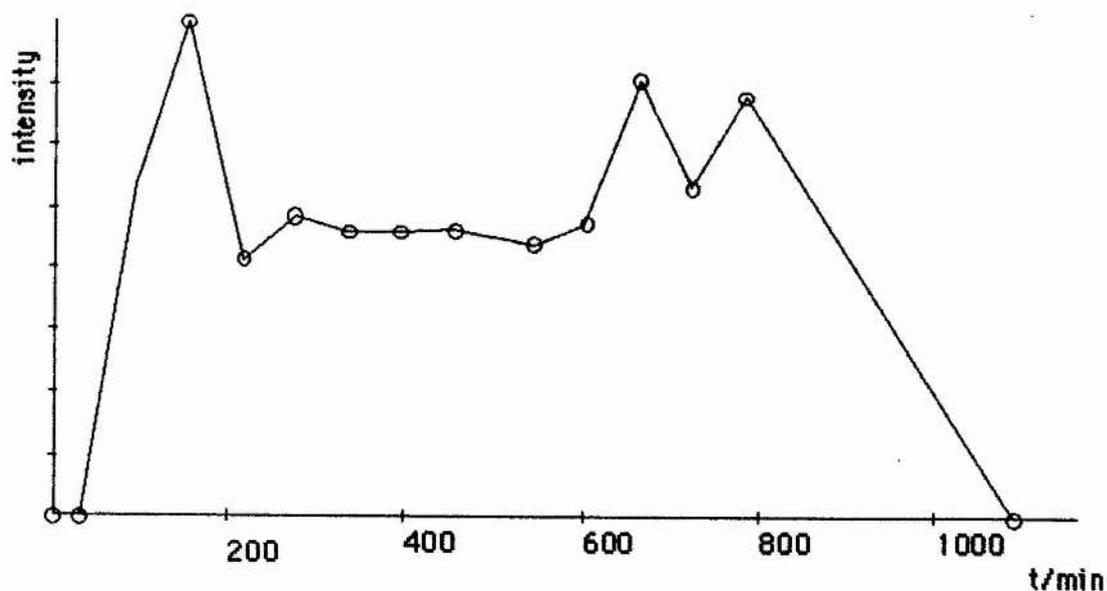


Figure 24: Variation of formaldehyde/thiourea oligomer methylene signal at 52.672 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 3-position and thiourea.



by no more than one fifth on the addition of acid, even if all the (25) or (26) present at the time were to react with it. The results cannot be explained in terms of rapid reaction of thiourea and diketone to give (25) or (26), which then reacts rapidly with (24) because there is no rapid fall in the thiourea or diketone concentrations on the addition of TFA to the system (see figures 21 and 22). The only satisfactory explanation of all the above results is that two molecules of (24) condense to yield one molecule each of (3) and formaldehyde *catalysed by another species in the system*.

In the acid catalysed reaction of 1-phenyl-1,2-propanedione with 1,3-dimethylthiourea on the addition of TFA the diol (13) is dehydrated to (14), which then adds a second 1,3-dimethylthiourea molecule to give the final product (11). The rate of (11) formation in the same solvent at the same temperature and TFA concentration as used for the thiourea experiments is extremely rapid, see figure 2. It therefore seems reasonable to assume that on the addition of TFA (24) can also be rapidly dehydrated to (28), although the distinctive methylene signal, which should be at a similar chemical shift to that of (14) at 88.08 ppm, was not detected, and that (28) can be protonated and attacked by a second thiourea molecule to yield (29) as shown in scheme 3. In the experiment using 1-phenyl-1,2-propanedione labelled at the 3-position and thiourea a very weak methylene signal at 31.429 ppm is observed briefly after the addition of TFA to the system which could be consistent with (29). See figure 23.

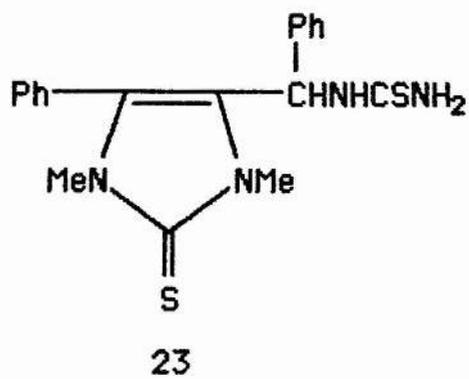
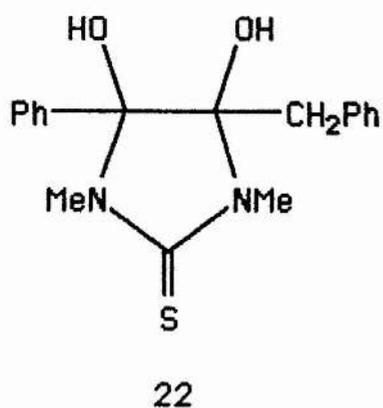
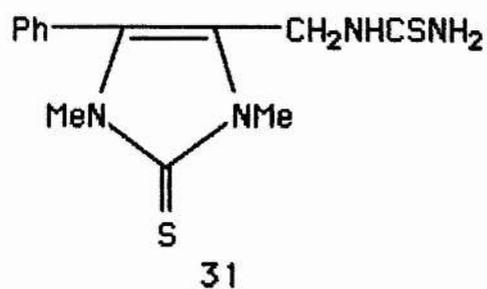
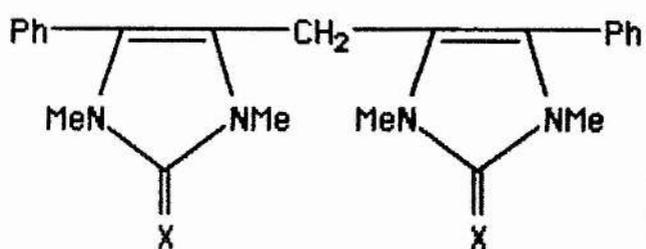
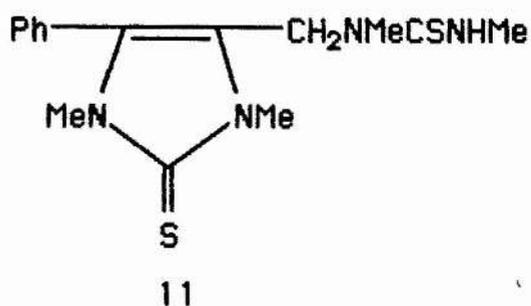
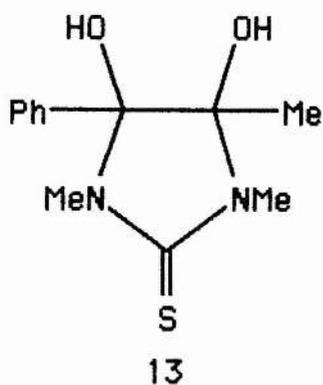
We have evidence that the presence of secondary amine groups in the imidazole ring does not prevent the addition of thiourea to the aliphatic centre from the detection of (23) in the product mixture of the reaction of thiourea and 1,3-diphenyl-1,2-propanedione.

In the experiment in which unlabelled (24) was treated with TFA to yield (3) the diol was shown to dissociate by the detection of the carbonyl signals of 1-phenyl-1,2-propanedione after the addition of acid to the solution. The aromatic

carbonyl group is not close to any protons in the diketone so its signal should not be subject to appreciable nuclear Overhauser effect enhancement. Hence if this signal is detectable then the thiocarbonyl centre of the thiourea, which is also unlikely to be subject to n.O.e. enhancement should also be detectable at the same concentration. However, no thiourea signal was detected at any point in the reaction. This is consistent with the thiourea reacting with another species in the system, the most plausible candidate being reaction with (28) to yield (29). A signal at 31.734 ppm was detected during the course of the reaction which could be consistent with (29). See figure 23.

From all of the above arguments we can be reasonably certain that (3) is formed by the condensation of (24) and (29) to regenerate thiourea and form (3) along with formaldehyde. Whether this condensation is acid catalysed or not is unclear, although it definitely takes place in the presence of acid. As was discussed earlier in respect of the conversion of (15) to (16), protonated thioureas can act as nucleofuges, which may well be of relevance to the mechanism.

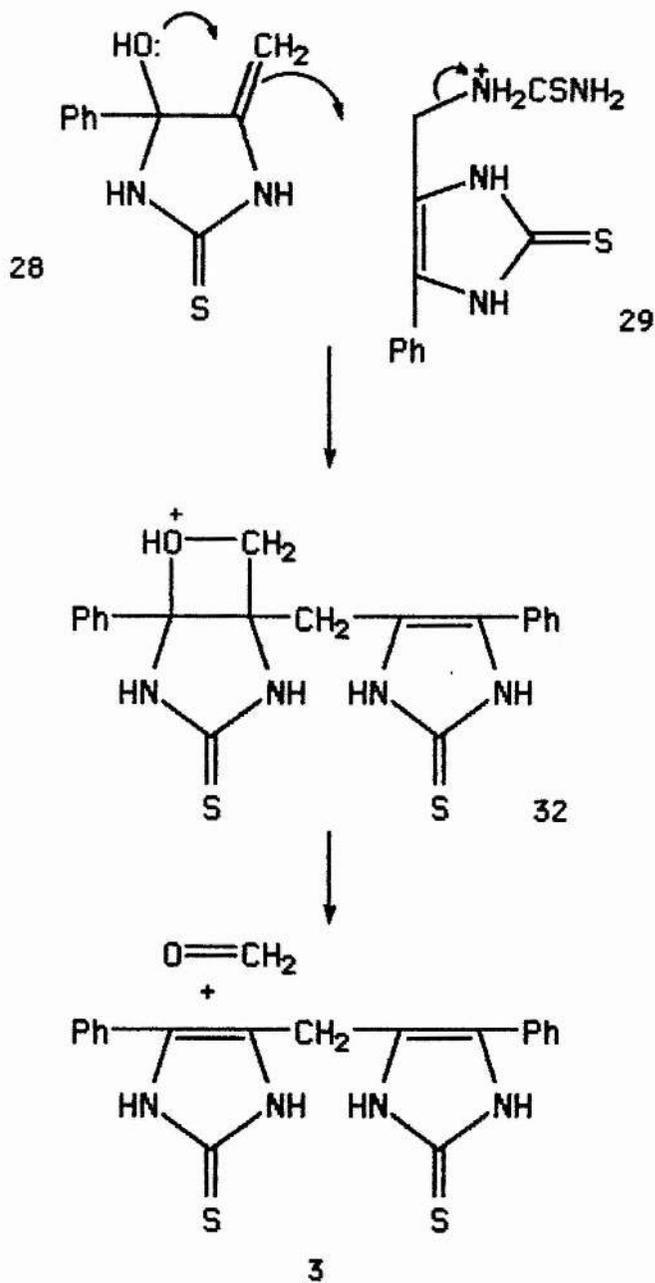
The solubility of formaldehyde in the reaction mixture was surprisingly small, no formaldehyde carbonyl signal being observed in any of the carbon-13 nmr experiments. However, in the experiment using 1-phenyl-1,2-propanedione labelled in the 3-position a weak methylene signal was detected at 52.672 ppm, consistent with one of the oligomers known to be formed from formaldehyde and thiourea under acid catalysis. In aqueous THF containing the same concentration of TFA formaldehyde reacted with a large excess of thiourea to yield an oligomer with a methylene signal at 51.289 ppm. The formaldehyde oligomer was detected only when diketone labelled in the 3-position was used, which is consistent with the formaldehyde being derived from the methyl group of the 1-phenyl-1,2-propanedione, as expected. The signal is extremely weak and does not appear to show any significant correlation with the signals assigned to (3). This could be consistent with the oligomers existing in equilibrium with free formaldehyde, which boils out of the solution. See figure 24.



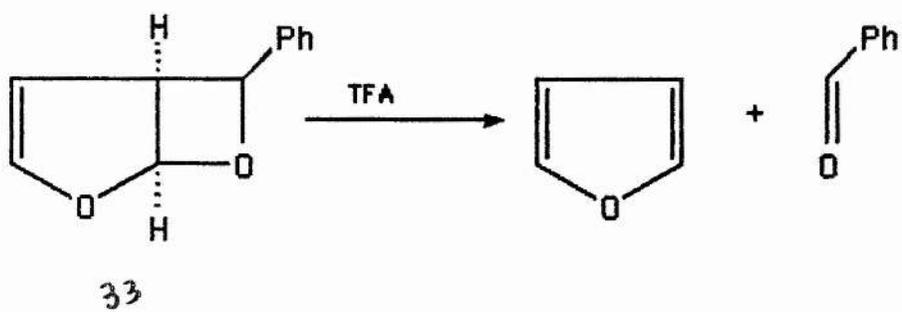
The condensation of (24) and (29) to yield (3) raises the question of why the analogous materials produced from 1-phenyl-1,2-propanedione and 1,3-dimethylthiourea, (11) and (13), both of which are present in the reaction mixture at significant concentrations, do not condense similarly to yield (30). The reaction of 1,3-dimethylurea and 1-phenyl-1,2-propanedione yields a mixture of products including (8), thus the presence of two secondary amine groups in the thiourea cannot be the determining factor. We have evidence that the determining factor is in fact the ability of the pendant thiourea to be displaced in a nucleophilic substitution reaction. Thus (13) treated with one equivalent of thiourea in refluxing THF acidified with TFA gave not the expected product (31) but the analogue of (3), (30). Since no carbonyl containing reagents were used in this experiment it was possible to place a trapping reagent for aldehydes, dimedone, in the reaction mixture without interfering with the course of the condensation. After 2 days stirring in a sealed container at room temperature a mixture of (13), (30), thiourea and the adduct of formaldehyde and dimedone was obtained. This result implies that 1-phenyl-1,2-propanedione reacts with 1,3-dimethylthiourea to yield (11) but with thiourea to yield (3) only because thiourea is a superior nucleofuge. It is possible that steric interactions between the 3-methyl groups of (11) and (13) might also inhibit their reaction. Steric factors are also likely to account for the much reduced reactivity of (22) with (23), which allowed both to be isolated from the product mixture of the reaction of 1,3-diphenyl-1,2-propanedione and thiourea.

We have good experimental evidence for the intermediacy of (29) and (24), or a species in equilibrium with (24), in the formation of (3). The exact manner of their condensation and of intermediates subsequent to this en route to (3) must, however, be somewhat more speculative since the process is so fast that no intermediates could be detected. The elimination of the aliphatic group in the form of an aldehyde is a highly unusual process for which few precedents exist. The Norrish type II reaction generates

Scheme 4



Scheme 5

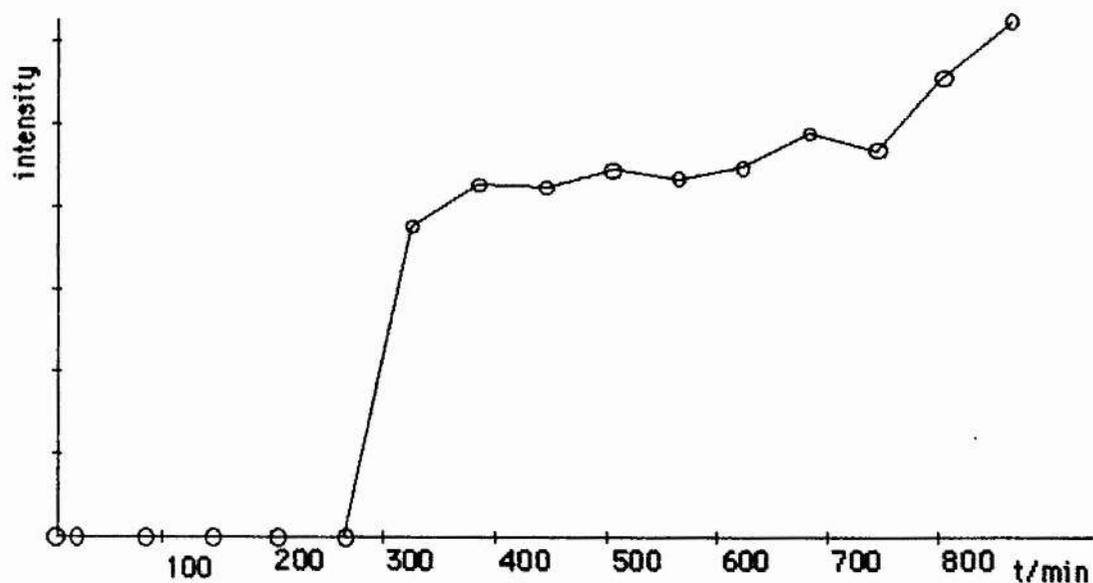


aldehydes as one product³ but it is a photochemical process and the above reaction occurs readily in the darkness of an nmr spectrometer. Formaldehyde is also reported to be eliminated during the Decker oxidation of certain pyridinium salts with potassium hexacyanoferrate but the conditions are unlikely to be relevant to our reaction⁴. Methyl ethers have also been known to react to generate formaldehyde⁵ but there is no plausible way for conversion of the methyl group of 1-phenyl-1,2-propanedione into a methyl ether.

The least improbable model for our system is the thermolysis of an oxetane ring containing material (32) formed during the condensation of (28) and (29) as proposed in scheme 4. The decomposition step has a close precedent in the decomposition of the strained oxetane fused with a five membered dihydrofuran ring in the Z conformation (33), which has been reported to proceed rapidly at moderate temperature in the presence of TFA⁶ to yield benzaldehyde and furan in good yield as shown in scheme 5. We have a small amount of evidence in favour of this proposal in the form of the detection of traces of some possible side products derived from breakdown of the oxetane ring in the other possible fashion during the carbon-13 nmr experiments using labelled substrates. The decomposition of the oxetane (32) is the last rate determining step in the formation of (3) and also in the formation of the side products so their normalised signal intensities should show a high degree of correlation with those assigned to (3).

In the experiment utilising 1-phenyl-1,2-propanedione labelled at the 1-position a very weak signal at 163.866 ppm is detected after 5 hours which rises slowly thereafter in parallel with the signals due to (3). The shift is consistent with a carboxylic acid centre and no signals other than those definitely assigned to (3) rise in parallel with it. The shift is not consistent with formaldehyde and it is not due to oxidation of formaldehyde to formic acid because no corresponding methyne signal is detected in the experiment using diketone labelled in the 3-position, which should yield carbon-13 enriched formaldehyde and hence carbon-13 enriched formic acid if

Figure 25: Variation of benzoic acid signal at 163.866 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 1-position and thiourea



Variation of (3) signal at 131.74 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled in the 1-position and thiourea.

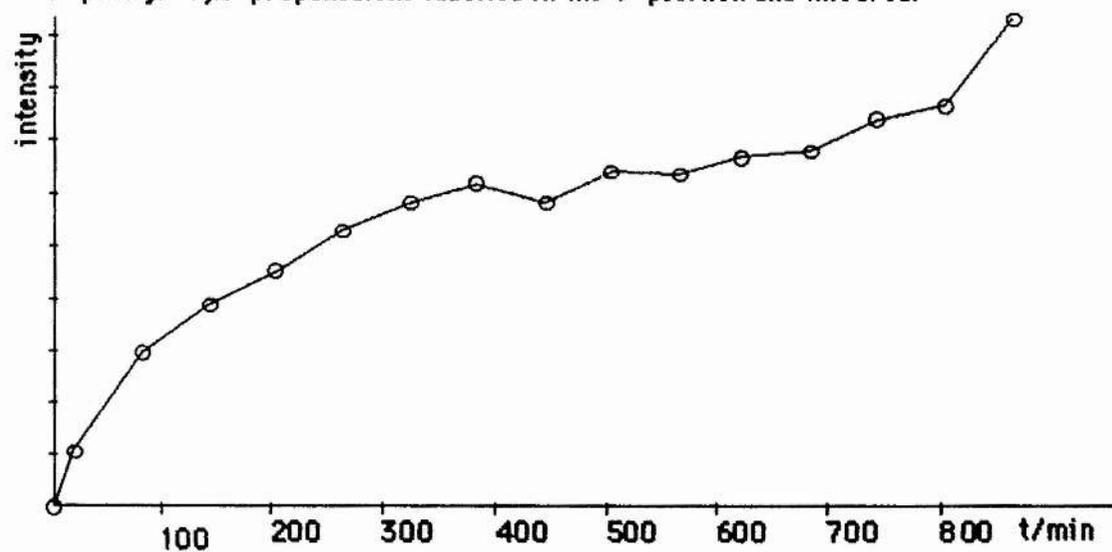
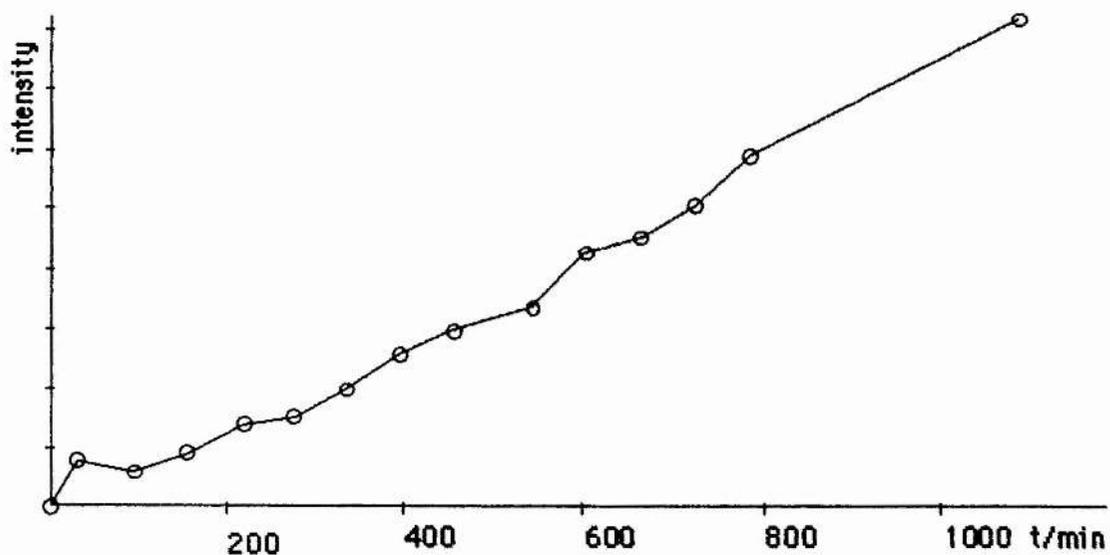
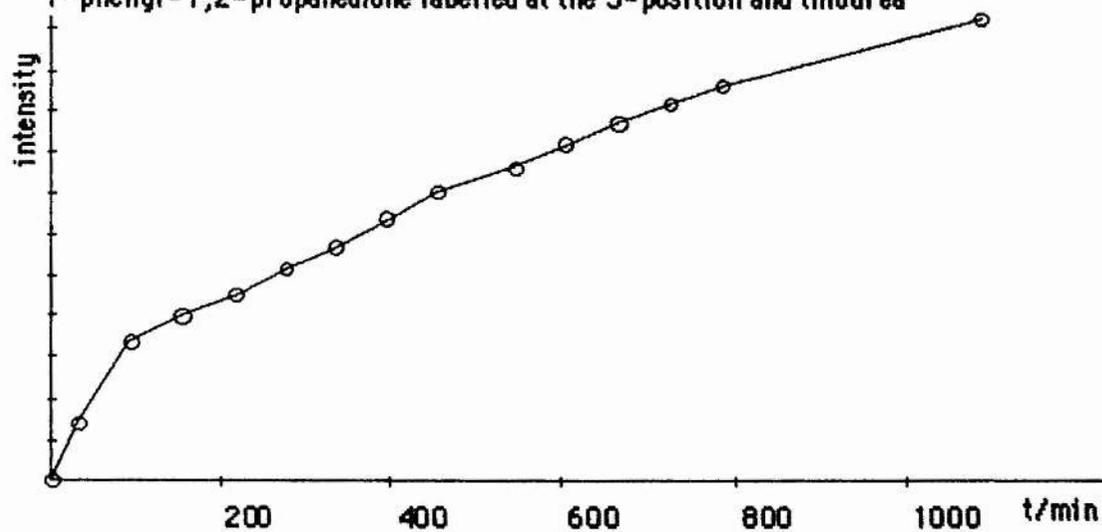


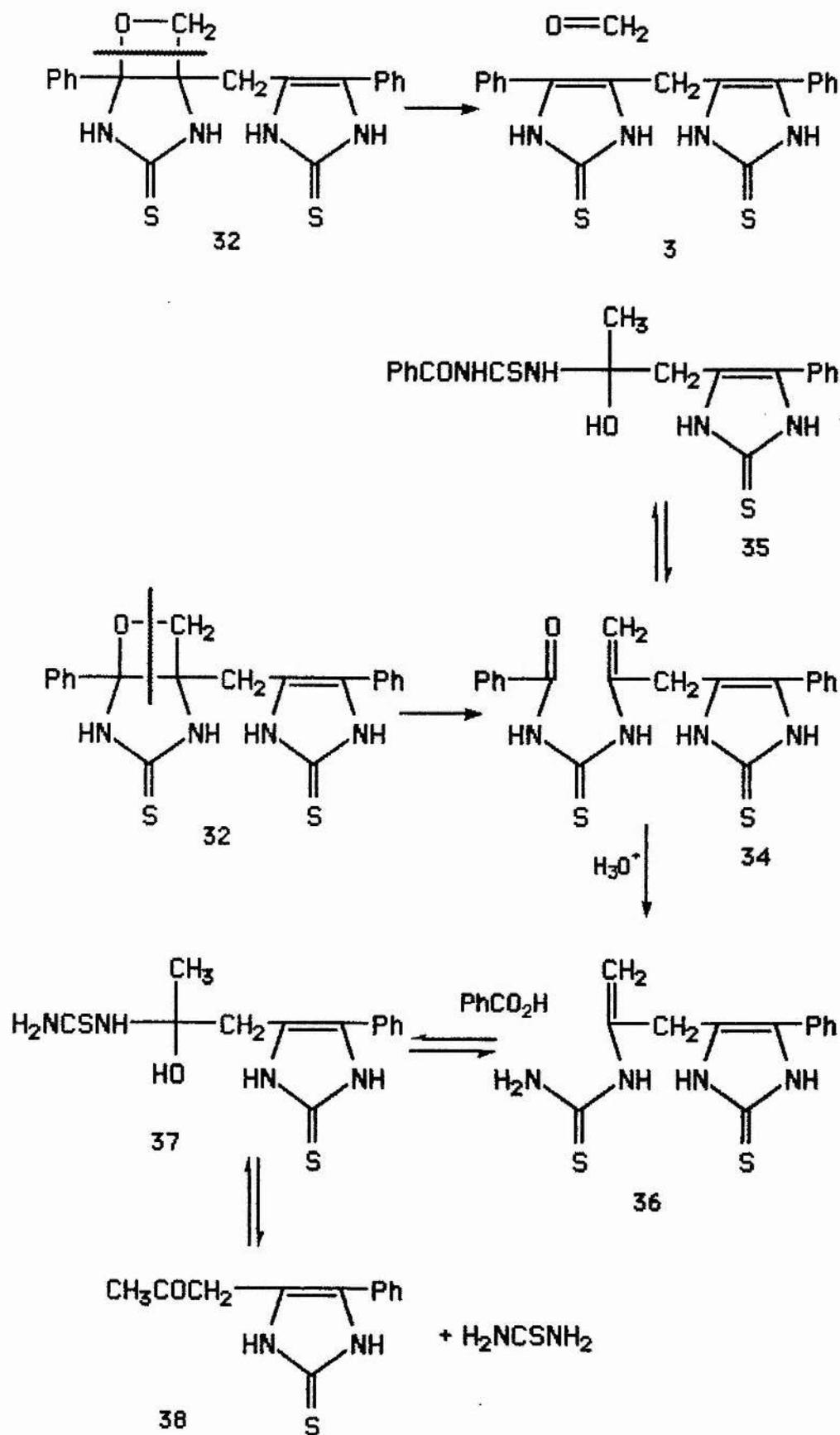
Figure 26: Variation of methylene signal at 32.093 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 3-position and thiourea



Variation of (3) methylene signal at 28.515 ppm during the acid catalysed reaction of 1-phenyl-1,2-propanedione labelled at the 3-position and thiourea

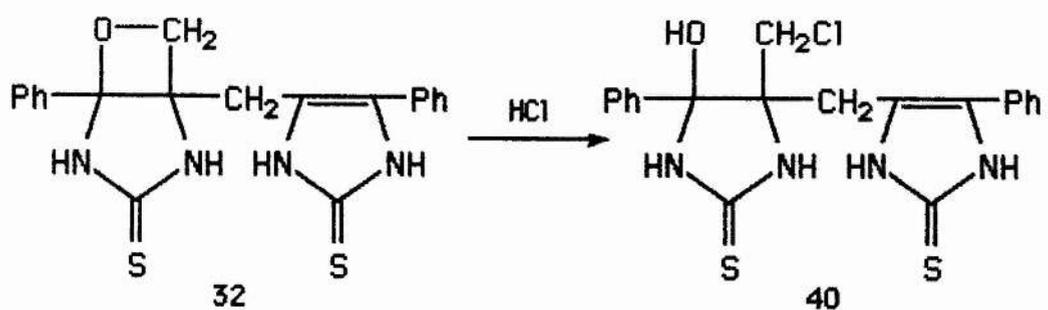
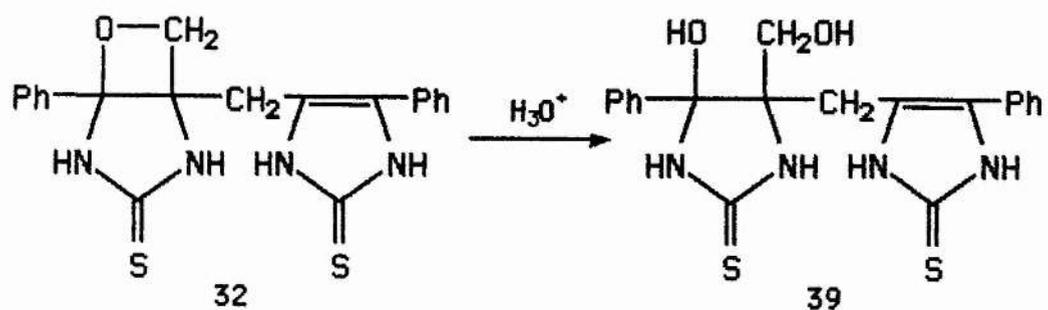


Scheme 6



oxidation occurred. The absence of any other parallel signals other than those assigned to (3) implies that the signal is probably due to a carbon centre derived from the labelled 1-position of the diketone. It is of course also possible that the signal is due to the product of the action of TFA on one of the unidentified impurities present in the 1-phenyl-1,2-propanedione but it seems a considerable coincidence that such a material would be formed at such a similar rate to (3). See figure 25.

In the experiment utilising 1-phenyl-1,2-propanedione labelled at the 3-position and the DEPT 135 pulse sequence three weak methylene signals are observed at 36.213, 32.093 and 29.300 ppm together with three weak methyl signals at 27.354, 24.813 and 21.832 ppm. All the signals show a good correlation with the methylene signal at 28.515 ppm definitely assigned to (3). See figure 26. Again it is not possible to rule out the possibility that these signals correspond to the product of the action of TFA on one of the unidentified impurities present in this sample of 1-phenyl-1,2-propanedione but it seems an even less credible coincidence that this impurity should also react at a similar rate to the formation of (3). All of these side products can be rationalised by considering cleavage of (32) in the other sense to that leading to (3) and formaldehyde as shown in scheme 6. The product of cleavage (34) can add water to give (35) or decompose to yield benzoic acid, with the carboxylic acid correctly derived from the 1-position of the diketone, and (36), which can plausibly equilibrate with (37) and (38). The imidazole centres of (35), (37) and (38) derived from the 1-position of the other diketone are likely to be in the aromatic region of the carbon-13 spectrum and therefore swamped by the signals due to the phenyl groups of the other species in the system. Both the methyl groups and methylene groups of each of (35), (37) and (38) are derived from the 3-positions of the two diketones from which (32) is derived, so that they should indeed only be observed when 1-phenyl-1,2-propanedione labelled at the 3-position is used. The strongest methylene signals of those corresponding to (35), (37) and (38) is approximately 6%



of the total of all the methylene signal intensities. Since in the DEPT experiment the relative signal intensities of carbons with the same number of attached protons correspond exactly to their relative concentrations it is not surprising that none of these side products has been isolated.

Oxetanes are known to react by nucleophilic addition as well as ring opening⁷ but attempts to detect the product (39) of hydrolysis of (32) in the products of the reaction in aqueous THF and the product (40) of attack by hydrochloric acid on (32) in the products of reaction using hydrochloric acid in acetic acid were both unsuccessful. This is not surprising given that the rate of decomposition of (32) at 30 C is such that the material cannot be detected even in the experiments using 22% carbon-13 labelled substrate.

EXPERIMENTAL SECTION

Infra red spectra were taken on a Perkin-Elmer 1420 ratio recording spectrophotometer, ultraviolet spectra on Pye-Unicam SP8-150 spectrophotometer, proton nmr on a Bruker WH-360 spectrometer and carbon-13 nmr spectra, including time resolved carbon-13 spectra were taken on a Bruker AM 300 spectrometer. All melting points were uncorrected.

4,4'-methylenebis-(5-phenyl-4-imidazolin-2-thione) (3): Thiourea (0.85g) and 1-phenyl-1,2-propanedione (0.82g) were placed in THF (10ml). One drop of TFA was added and the mixture refluxed for four hours. Saturated sodium hydrogen carbonate (10ml) was added and the mixture stirred for thirty minutes. The THF was removed on the rotary evaporator and the white solid filtered off and washed with water (50ml) and twice with acetone (25ml). The yield was 70%.

mp	225-7 C
M/Z	not observed
analysis	49.54%C (18.99), 3.65%H (16.67), 12.17%N (4.00)
¹ H nmr (D ₆ DMSO)	7.30-7.20 (10H,m); 4.2 (2H,s)
¹³ C nmr (D ₆ DMSO)	128.87(CH), 127.96(CH), 126.75(CH), 26.47(CH ₂)

4-methyl-5-phenyl-4,5-dihydroxytetrahydroimidazole-2-thione (24):-

Thiourea(0.90g) and 1-phenyl-1,2-propanedione were dissolved in aqueous THF (7ml 5:2 v/v) and stirred for three days at room temperature. Water (10ml) was added and the THF removed on the rotary evaporator. The product was extracted with dichloromethane, washed with water (15ml) and dried with magnesium sulphate. The solvent was removed on the rotary evaporator and the product titrated in petrol (25ml) to give a sticky mass. The product was a mixture of the Z and E isomers of (24). The combined yield of both isomers was 60%.

M/Z	224	(C ₁₀ H ₁₂ N ₂ O ₂ S=224 g mol ⁻¹)	-120
¹ H nmr (D ₈ THF)		7.30-7.20 (5H,m), 1.40 (s), 0.85 (s) (total 3H)	
¹³ C nmr (D ₈ THF)		185.15, 184.51, 129.09, 128.64, 128.09, 127.88, 127.37, 127.21, 126.98, 126.44, 96.68, 94.93, 94.45, 93.11, 25.85, 21.98	

The diol (24) (0.10g) was dissolved in THF (2ml) and 1 drop of TFA was added. The solution was stirred overnight at room temperature. Saturated sodium hydrogen carbonate solution (4ml) was added and the mixture stirred for 30 minutes. The white precipitate was filtered off and dried. The product had proton, carbon-13 and infra-red spectra identical to (3).

1-phenyl-1,2-butanedione: n-Butyrophenone (1.36g) was placed in ether (75ml) and hydrogen chloride was bubbled through the solution whilst amyl nitrite (12.30g) was added dropwise over one hour. Hydrochloric acid was bubbled through the mixture for a further 90 minutes and it was then allowed to stand overnight. The oxime was extracted with aqueous sodium hydroxide (4 lots of 50ml).

The solution was acidified cautiously with sulphuric acid until a pink precipitate forms and then a further 40ml of concentrated sulphuric acid was added dropwise. The mixture was steam distilled over a period of seven hours and the distillate was extracted with dichloromethane. The extract was dried with magnesium sulphate and the solvent removed on the rotary evaporator to give 1-phenyl-1,2-butanedione in 65% yield.

1,1-bis-(5-phenyl-4-imidazolyl-2-thione)-ethane (19): Thiourea (0.70g) and 1-phenyl-1,2-butanedione (0.70g) were placed in THF (5ml). One drop of TFA was added and the mixture refluxed for four hours. The excess thiourea was filtered off,

saturated sodium hydrogen carbonate (10ml) was added and the mixture stirred for thirty minutes. The THF was removed on the rotary evaporator and the solution extracted with dichloromethane, washed with water (50ml), dried with magnesium sulphate and the solvent removed on the rotary evaporator. The solid was recrystallised from aqueous ethanol (1:1).

mp	149-53 C
M/Z	not observed
¹ H nmr (D ₆ DMSO)	7.30-7.20 (10H,m), 5.4 (1H,not resolved), 1.5 (3H,d)
¹³ C nmr (D ₆ DMSO)	132.91, 129.87-127.40(6 peaks), 44.43, 30.61, 20.34

1,3-diphenyl-1,2-propanedione: Acetophenone (6.0g) was placed in ethanol (50ml) and sodium metal (0.2g) added piecewise. When hydrogen evolution ceased benzaldehyde (5.3g) was added and the mixture stirred for two hours at room temperature. The products were partitioned between dichloromethane and brine (100ml of each) and the brine extracted with more dichloromethane (50ml). The combined organic portions were treated with bromine at room temperature until the red colour did not discharge after 15 minutes. The product was filtered off and washed with water and petrol.

The 2,3-dibromo-1,3-diphenylpropanone was placed in aqueous ethanol (50ml, 95%), sodium acetate (6.80g) was added and the mixture refluxed for five hours. Saturated brine (50ml) was added, the ethanol was removed on the rotary evaporator and the product extracted with ether (2 lots of 50ml). The solution was washed with brine (50ml), dried with magnesium sulphate and the solvent removed on the rotary evaporator.

The product was dissolved in THF (20ml) and diethylamine (7.32g) was added. The mixture was stirred overnight and then refluxed for thirty minutes. Water (25ml) was added and the THF removed on the rotary evaporator. The product was extracted with dichloromethane, dried with magnesium sulphate and the solvent removed on the rotary evaporator.

The product was stirred overnight in ethanol (10ml) containing aqueous hydrochloric acid (10ml, 10M). Water (25ml) was added and the THF removed on the rotary evaporator. The product was extracted with dichloromethane, dried with magnesium sulphate and the solvent removed on the rotary evaporator. The product exists as a mixture of the keto and enol forms in slow equilibrium compared to the nmr timescale.

^1H nmr (neat)	7.70-7.20 (m), 6.30 (s), 5.10 (s)
^{13}C nmr (neat)	199.16, 193.36, 191.94, 146.82-127.14 (16 peaks), 122.04, 119.39, 45.35

bis-(5-phenyl-4-imidazolyl-2-thione)-phenylmethane (21): Thiourea (0.60g) and 1,3-diphenyl-1,2-propanedione (0.72g) were placed in THF (10ml). One drop of TFA was added and the mixture refluxed for two hours. Saturated sodium hydrogen carbonate (10ml) was added and the mixture stirred for thirty minutes. A very small sample was removed for analysis by GCMS. The THF was removed on the rotary evaporator and the solution extracted with dichloromethane (10ml), washed with water (25ml), dried with magnesium sulphate and the solvent removed on the rotary evaporator. The yield was 48%.

mp	168-80 C (decomposition)
M/Z	not observed
^1H nmr (D_6DMSO)	7.40-6.55
^{13}C nmr (D_6DMSO)	143.68(qtr), 139.21(qtr), 136.54-127.73 (12 peaks all CH or qtr), 51.24 (CH)

GCMS analysis of the crude product mixture detected the following

benzaldehyde	106(70%), 105(80%), 77(100%)
benzoic acid	122(70%), 105(100%), 77(80%)
(21)	264 (12%), 206 (10%), 91(100%), 77(40%)

4,4'-methylenebis-(1-methyl-5-phenyl-4-imidazolin-2-thione) (6a) and

4,4'-methylenebis-(3-methyl-5-phenyl-4-imidazolin-2-thione) (6b):

1-methylthiourea (0.96g) and 1-phenylpropanedione (0.74g) were placed in THF (5ml). One drop of TFA was added and the mixture refluxed for five hours. Saturated sodium hydrogen carbonate (10ml) was added and the mixture stirred for thirty minutes. The THF was removed on the rotary evaporator and the white solid filtered off and washed with water (50ml) and ether (25ml). The combined yield of the two isomers was 50%.

mp	131-8 C	
M/Z	390	(C ₂₁ H ₁₈ N ₄ S ₂ =390 gmol ⁻¹) ?
¹ H nmr (D ₆ DMSO)	8.2-7.0 (10H,m); 4.5-2.6 (8H,m)	
¹³ C nmr (D ₆ DMSO)	133.25-127.13 (13 peaks all CH or qtr), 122.93 (qtr), 65.69 (CH ₂), 32.45-29.46 (5 peaks all CH ₃)	

1-Phenyl-1,2-butanedione (0.50g) and 1-methylthiourea (0.56g) were placed in THF (5ml), one drop of TFA was added and the solution refluxed for four hours. Sodium hydrogen carbonate solution (5ml) was added, the mixture stirred for thirty minutes and the THF removed on the rotary evaporator. The product was extracted with dichloromethane, dried with magnesium sulphate and the solvent removed to give a pale orange solid. The carbon-13 and proton nmr of the product was consistent with a mixture of at least two of the three possible isomers of 1,1-bis-(N-methyl-5-phenyl-4-imidazolin-2-thione)-ethane, where the methyl group may be present on N1 or N3 of each imidazole, and also 4-ethyl-1-methyl-5-phenylimidazole-2-thione and/or 5-ethyl-1-methyl-4-phenylimidazole-2-thione. Purification of this complex mixture was not attempted.

The reaction between 1,3-diphenyl-1,2-propanedione and 2 equivalents of 1-methylthiourea in THF catalysed by TFA also gave a complex mixture of products which could not be readily separated or analysed. The mass spectrum showed peaks consistent with the presence of at least one isomer of N-methyl-4-benzyl-5-phenyl-4,5-dihydroxytetrahydroimidazole-2-thione and one isomer of N-methyl-4-benzyl-5-phenylimidazole-2-thione

1-(1,3-dimethyl-5-phenyl-2-thioxoimidazolyl)methyl-1,3-dimethylthiourea (11):-
1-phenyl-1,2-propanedione (0.74g) and 1,3-dimethylthiourea (1.10g) were placed in THF (5ml), two drops of TFA were added and the mixture refluxed for six hours. Sodium hydrogen carbonate solution (10ml) was added and the mixture stirred vigorously for 30 minutes. The white precipitate was filtered off and washed with water (25ml) and ether (25ml). Yield was 51%. (11) exists in two tautomers which interconvert slowly enough to be distinguished by proton nmr but rapidly in comparison to relaxation in carbon-13 nmr.

mp	181-2 C
M/Z	320 (C ₁₅ H ₂₀ N ₄ S ₂ =320 gmol ⁻¹)
analysis	55.85%C, 6.10%H, 17.15%N
theoretical	56.22%C, 6.29%H, 17.48%N
IR shows NHstr	3250 (s)
¹ H nmr (CDCl ₃)	7.60 (5H,m), 5.90 (1H,broad s), 5.40 (2H,d), 3.73 (3H,d), 3.57 (3H,d), 3.20 (3H,d), 2.73 (3H,s)
¹³ C nmr (CDCl ₃)	183.25 (qtr), 163.20 (qtr), 130.46 (qtr), 130.37 (CH), 129.74 (CH), 129.22 (CH), 127.19 (qtr), 122.14 (qtr), 45.89 (CH ₂), 33.46 (CH ₃), 33.34 (CH ₃), 33.19 (CH ₃), 33.14 (CH ₃)

1,3,4-trimethyl-5-phenyl-4,5-dihydroxytetrahydroimidazole-2-thione (13):

1,3-dimethylthiourea (2.08g) and 1-phenyl-1,2-propanedione (1.48g) were dissolved in aqueous THF (7ml 5:2 vv) and stirred for two days at room temperature. Water (25ml) was added and the THF removed on the rotary evaporator. The product was extracted with dichloromethane, washed with water (15ml), dried with magnesium sulphate and the solvent removed on the rotary evaporator. The product was a mixture of the Z and E isomers of (13) in the form of a red oil which solidifies on prolonged standing. The combined yield of both isomers was 95%.

M/Z	252	($C_{12}H_{16}N_2O_2S=252 \text{ g mol}^{-1}$)
infra-red shows OH str bands at 3420 and 3290 cm^{-1}		
^1H nmr (D_6 DMSO)	7.30-7.20 (5H,m); 4.56 (broad s); 3.30 (s); 3.10 (s); 2.95(3H,s); 1.0 (3H,s)	
^{13}C nmr (D_8 THF)	182.07 (qtr); 136.74 (q); 128.93 (CH); 128.59 (CH); 126.60 (CH); 93.98 (qtr); 91.00 (qtr); 90.87 (qtr); 87.24 (qtr); 30.56 (CH_3); 29.84 (CH_3); 29.12 (CH_3); 25.46 (CH_3); 21.73 (CH_3)	

1,3,4-trimethyl-5-phenyl-4,5-dihydroxytetrahydroimidazole-2-thione

(0.50g) and 1,3-dimethylthiourea (0.42g) were placed in THF (10ml), one drop of TFA was added and the mixture refluxed for three hours. Water (25ml) was added, the THF removed on the rotary evaporator and the product extracted with dichloromethane. The extract was washed with water (10ml), dried with magnesium sulphate and the solvent removed on the rotary evaporator. The product had an infra-red spectrum identical to that of (11).

4,4'-methylenebis-(1,3-dimethyl-5-phenyl-4-imidazolin-2-thione) (30)

1,3,4-trimethyl-5-phenyl-4,5-dihydroxytetrahydroimidazole-2-thione (2.52g) and thiourea (1.00g) were placed in THF (25ml), one drop of TFA was added and the mixture

refluxed for 5 hours. Water (25ml) was added, the THF removed on the rotary evaporator and the product filtered off and washed with acetone (25ml).

mp	230-2 C
M/Z	not observed- highest peak 217 mass units
analysis	65.31%C, 5.83%H, 13.52%N
theoretical	65.68%C, 5.75%H, 13.32%N
^1H nmr (CDCl_3)	7.20-7.10 (10H,m); 3.63 (s); 3.43 (s); 3.33 (s); (total of 14H)
^{13}C nmr (CDCl_3)	163.271 (qtr), 130.611 (qtr), 130.323 (CH), 129.412 (CH), 129.046 (CH), 127.395 (qtr), 120.730 (qtr), 33.369 (CH_3), 32.310 (CH_3), 30.898 (CH_2)

1,3,4-trimethyl-5-phenyl-4,5-dihydroxytetrahydroimidazole-2-thione (2.52g), thiourea (1.00g) and dimedone (1.50g) were placed in THF (25ml), one drop of TFA was added and the mixture stirred for 2 days at room temperature. The product mixture was shown by tlc (petrol/ CH_2Cl_2 10:1) to contain a component with R_f identical to an authentic sample of the adduct formed between dimedone and formaldehyde in THF containing TFA. The mass spectrum of the crude product mixture showed a peak at 292 mass units, identical to an authentic sample of the adduct of dimedone and formaldehyde, as well as peaks at 252 and 234 mass units, corresponding to (13) and (13)- H_2O respectively, and 217 mass units, identical to the highest mass peak of (30).

1-(1-(1,3-dimethyl-5-phenyl-2-thioxo-imidazol)ethyl)-1,3-dimethylthiourea (15) and *1,3-dimethyl-4-ethenyl-5-phenylimidazole-2-thione* (16):-

1-phenyl-1,2-butanedione (0.89g) and 1,3-dimethylthiourea (1.15g) were placed in THF (10ml), two drops of TFA were added and the mixture refluxed for four hours. Sodium hydrogen carbonate solution (25ml) was added and the mixture stirred vigorously

for 30 minutes. The solution was extracted with dichloromethane (10ml) and the extract was washed with water, dried with magnesium carbonate and the solvent removed on the rotary evaporator to give a deep yellow oil. The oil was taken up in petrol containing the minimum possible amount of acetone. On standing white crystals of (16) came out of solution. The solvent was removed on the rotary evaporator to yield a gummy mass which was washed in petrol to give (15)

(15)

mp	189-92 C	
M/Z	334	(C ₁₆ H ₂₂ N ₄ S ₂ =334 g mol ⁻¹)
IR shows NHstr 3350 (s)		
¹ H nmr (CDCl ₃)	7.60 (5H,m); 6.62 (1H,q); 3.46 (s); 3.26 (s); 3.14 (s); 2.97(d); 2.73 (s) [total of 12H]; 0.85 (3H,d)	
¹³ C nmr (CDCl ₃)	181.65 (qtr); 162.14 (qtr); 131.37 (CH); 130.38 (CH); 129.55 (CH); 128.99 (CH); 124.43 (qtr); 51.68 (CH); 32.69 (CH ₃); 32.22 (CH ₃); 31.96 (CH ₃); 30.29 (CH ₃); 15.79 (CH ₃)	

(16)

mp	112-4 C	
M/Z	230	C ₁₃ H ₁₄ N ₂ S=230 g mol ⁻¹
IR shows no NH bands at all		
¹ H nmr (CDCl ₃)	7.45-7.30 (5H,m); 6.35 (1H,d of d); 5.35 (1H,d); 5.20 (1H,d); 3.82 (3H,s); 3.50 (3H,s)	
¹³ C nmr (CDCl ₃)	162.92 (qtr); 130.39 (CH); 129.37 (CH); 129.00 (CH); 128.67 (qtr); 128.07 (qtr); 124.90 (qtr); 122.51 (CH); 117.03 (CH ₂); 33.47 (CH ₃); 33.25 (CH ₃)	

4-Methyl-1-phenyl-1,2-butanedione: 2-Phenyl-1,3-dithiane was prepared from benzaldehyde and 1,3-propanedithiol by the method of Seebach¹⁰.

2-Phenyl-1,3-dithiane (3.30g) was placed in dry THF (100ml) and cooled to -70 C under dry nitrogen, t-butyllithium (15ml 1.5 M) in hexane was added and the mixture allowed to warm up to -30 C. This temperature was maintained for 30 minutes, the mixture was cooled to -70 C, 1-iodo-2-methylpropane (1.90g) in dry THF (25ml)

was added dropwise over 15 minutes and the mixture allowed to warm up to room temperature under dry nitrogen overnight. The dithiane moiety was oxidised with "claycop"⁸ and the resulting ketone oxidised to a diketone by the method of Kornblum and Frazier⁷ as described in detail for the preparation of carbon-13 labelled 1-phenyl-1,2-propanedione below.

¹ H nmr (CDCl ₃)	8.00-7.50 (5H,m), 2.00 (1H,sept), 0.70 (6H,d)
¹³ C nmr (CDCl ₃)	199.47, 188.62, 132.88, 129.01, 128.66, 128.20, 25.15, 22.81

4-Methyl-1-phenyl-1,2-butanedione (0.35g) and thiourea (0.20g) were placed in THF (10ml), 1 drop of TFA was added and the mixture was refluxed for 4 hours. Sodium hydrogen carbonate solution (10ml) was added and the mixture stirred vigorously for 30 minutes. The solution was extracted with dichloromethane (10ml) and the extract was washed with water, dried with magnesium carbonate and the solvent removed on the rotary evaporator to give only unreacted 4-Methyl-1-phenyl-1,2-butanedione (0.25g) (proved by infra-red and proton nmr spectroscopy).

4-Methyl-1-phenyl-1,2-butanedione (0.85g) and 1,3-dimethylthiourea (1.20g) were placed in THF (10ml), 1 drop of TFA was added and the mixture was refluxed for 5 hours. Sodium hydrogen carbonate solution (10ml) was added and the mixture stirred vigorously for 30 minutes. The solution was extracted with dichloromethane (10ml) and the extract was washed with water, dried with magnesium carbonate and the solvent removed on the rotary evaporator to give only unreacted 4-Methyl-1-phenyl-1,2-butanedione (0.61g) (proved by infra-red and proton nmr spectroscopy).

1,3-Dimethylthiourea (0.41g) and 1,3-diphenyl-1,2-propanedione were placed in THF (10ml), one drop of TFA was added and the solution refluxed for 90 minutes.

Sodium hydrogen carbonate solution (25ml) was added and the mixture stirred vigorously for 30 minutes. The solution was extracted with dichloromethane (10ml) and the extract was washed with water, dried with magnesium carbonate and the solvent removed on the rotary evaporator to give a dark red oil. The product proved to be an intractable mixture with two of the major components being

a) *1-(1-(1,3-dimethyl-5-phenyl-2-thioxo-imidazol)benzyl)-1,3-dimethylthiourea*

(18) $C_{21}H_{24}N_4S_2=396 \text{ g mol}^{-1}$, carbon-13 shows signal at 60.86 ppm (CH)

b) *4-benzyl-1,3-dimethyl-5-phenyl-4,5-dihydroxytetrahydroimidazole-2-thione*

(17) $(C_{18}H_{20}N_2O_2S)-H_2O=310 \text{ g mol}^{-1}$, carbon-13 shows aminol signal at 93.16 ppm (qtr).

1-Phenyl-1,2-propanedione (1.48g) and 1,3-dimethylurea (1.80g) were placed in THF (10ml), five drops of TFA was added and the solution refluxed for 4 hours. Sodium hydrogen carbonate solution (25ml) was added and the mixture stirred vigorously for 30 minutes. The solution was extracted with dichloromethane (10ml) and the extract washed with water, dried with magnesium sulphate and the solvent removed on the rotary evaporator to give a yellow oil which solidified on standing to become a glass. The product proved to be a mixture of three major components which were separated by preparative thin layer chromatography.

(9)	
M/Z	not observed
IR shows no NH or OH bands	
^1H nmr (CDCl_3)	7.6-7.4 (5H,m); 4.42 (1H,s); 2.87 (s); 2.77 (s); 2.67 (s); [total of 14H]; 0.85 (3H,d)
literature ¹	7.4 (5H,m); 4.53 (1H,s); 4 singlets 2.65-2.79 (14H)
^{13}C nmr (CDCl_3)	159.11 (qtr); 134.74 (qtr) 131.37 (CH); 129.55 (CH); 128.99 (CH); 78.41 (qtr); 67.00 (CH); 50.91 (CH ₂); 30.46 (CH ₃); 28.84 (CH ₃); 25.28 (CH ₃); 25.14 (CH ₃)
literature ¹	77.89 (qtr); 66.49 (CH); 50.54 (CH ₂)

1-(1,3-dimethyl-5-phenyl-2-thioxoimidazol)methyl-1,3-dimethylurea (10)

IR shows NHstr 3490 (s)

^1H nmr (CDCl_3)	7.6-7.2 (5H,m); 3.33-2.55 (m,14H)
^{13}C nmr (CDCl_3)	158.64 (qtr); 153.77 (qtr); 130.19 (CH); 130.08 (CH); 129.55 (CH); 128.99 (qtr); 123.75 (qtr); 115.92 (qtr); 39.99 (CH_2); 31.77 (CH_3); 28.71 (CH_3); 27.97 (CH_3); 27.69 (CH_3)

4,4'-methylenebis-(1,3-dimethyl-5-phenyl-4-imidazolin-2-one) (8)

M/Z not observed

IR shows no NH or OH bands

^1H nmr (CDCl_3)	7.7-7.5 (5H,m) ¹⁰ ; 3.83 (2H,s); 3.43-2.70 (8H,m) ¹²
^{13}C nmr (CDCl_3)	153.39 (qtr); 130.05 (qtr); 129.65 (CH); 129.55 (CH); 128.47 (CH); 121.28 (qtr); 114.44 (qtr); 30.47 (CH_3); 29.17 (CH_3); 19.48 (CH_2)

1-Phenyl-1,2-propanedione labelled in the 1 position with 20% carbon-13 was prepared from carbon-13 enriched propiophenone by the method of Kornblum and Frazier⁷.

Propiophenone (0.60g) was placed in a mixture of dichloromethane and ethyl acetate (10ml, 1:1) and stirred under nitrogen whilst cupric bromide (2.70g) was added in small quantities. The mixture was then refluxed under nitrogen for three hours. The cuprous bromide was filtered off and washed with dichloromethane (10ml) and the combined filtrate and washings washed with water (25ml). The solvent was removed on the rotary evaporator to give the highly lachrymatory bromoketone which was immediately dissolved in acetonitrile (5ml). Silver nitrate (1.70g) was added and the mixture stirred in the absence of light for 36 hours. The solvent was removed on the rotary evaporator and the product taken up in dichloromethane (10ml), washed with water (25ml), dried with magnesium sulphate and the solvent was removed on the rotary evaporator.

The product was dissolved in DMSO (25ml) and sodium acetate (0.49g) was added.

The mixture was stirred at room temperature for 25 minutes and then poured into saturated brine (250ml) and extracted twice with redistilled petrol (100ml). The extract was washed with brine (250ml), dried with magnesium sulphate and the solvent removed on the rotary evaporator. The diketone was then finally purified by column chromatography on silica eluting with petrol/dichloromethane (4:1). The product had infra-red and carbon-13 nmr spectra identical to a commercial sample of 1-phenyl-1,2-propanedione and was shown to be pure by thin layer chromatography.

1-Phenyl-1,2-propanedione enriched with carbon-13 at the methyl position was prepared from carbon-13 enriched methyl iodide.

2-Benzyl-1,3-dithiane was prepared from 1,3-dithiane and benzyl bromide by the method of Corey⁹.

¹ H nmr (CDCl ₃)	7.2 (5H,s); 4.1 (1H,t); 2.9 (2H,d); 2.7 (4H,m); 1.8
(2H,m)	
lit ³	7.15 (5H,s); 4.07 (1H,t); 2.88 (2H,d); 2.63 (4H,m);
1.83 (2H,m)	

2-Benzyl-1,3-dithiane (4.83g) was dissolved in dry THF under dry nitrogen and cooled to -75 C in an acetone/dry ice bath. A solution of t-butyllithium in petrol (15ml, 1.7 M) was added dropwise and the mixture allowed to warm up to -30 C and maintained at between -35 and -30 C for 30 minutes by addition of dry ice to the bath. The mixture was then cooled to -75 C and methyl iodide (3.00g) dissolved in dry THF (25ml) was added dropwise. The mixture was allowed to warm up slowly to room temperature overnight, the THF was removed on the rotary evaporator, water (100ml) was added and the 2-methyl-2-benzyl-1,3-dithiane extracted with dichloromethane (3 lots of 50ml) and dried with magnesium sulphate. In a practice run using unlabelled methyl iodide a sample was removed and characterised at this point.

^1H nmr (CDCl_3) 7.2 (5H,s); 3.4 (2H,s); 2.9 (4H,m); 1.8 (2H,m); 1.6 (3H,s)

The dithiane solution was then stirred for 20 hours at room temperature with 28g cupric nitrite on bentonite ("claycop")⁸ and the reagent filtered off.

^1H nmr (CDCl_3) 7.1 (5H,s); 3.6 (2H,s); 2.1 (3H,s)

The phenylacetone was oxidised to 1-phenyl-1,2-propanedione by the method of Kornblum and Frazier⁷. Ethyl acetate (150ml) was added to the dichloromethane solution of phenylacetone and then cupric bromide (10g) was added gradually to the stirred solution under nitrogen. The mixture was refluxed for 4 hours under nitrogen, the cuprous bromide filtered off and washed with dichloromethane, the ethyl acetate removed on the rotary evaporator and the combined filtrate and washings dried with magnesium sulphate and the solvent removed on the rotary evaporator.

^1H nmr (CDCl_3) 7.1 (5H,m); 7.0 (1H,s); 1.9 (3H,s)

The bromoketone was dissolved in acetonitrile (40ml), silver nitrate (5.70g) added and the mixture stirred for 36 hours at room temperature. The silver bromide was filtered off and washed with dichloromethane, the acetonitrile was removed on the rotary evaporator, the combined filtrate and washings taken up in dichloromethane (50ml), washed with water (100ml), dried with magnesium sulphate and the solvent removed on the rotary evaporator.

The product was dissolved in DMSO (100ml), sodium acetate (0.70g) was added, the mixture stirred for 30 minutes at room temperature and then poured into brine (250ml) and extracted with redistilled petrol (3 lots of 50ml). The product was washed with water (300ml), dried with magnesium sulphate and the petrol removed on the rotary evaporator. Final purification was carried out by distillation using a Kugelrohr system to give 1-phenyl-1,2-propanedione completely pure by tlc in 45% yield.

Under normal circumstances this yield would not be acceptable for synthesis of a

labelled compound but because of the difficulties experienced in attempting to prepare 1-phenylpropanedione from methyl iodide by other routes and because of time constraints it was necessary to accept it in this case. The problems experienced using alternative routes are discussed in more detail in Appendix 1.

1-Phenylpropanedione enriched with carbon-13 at the 1-position (0.025ml) and thiourea (0.0274g) were dissolved in a mixture of fully deuterated THF (0.5ml) and non-deuterated water (0.2ml) thermostatted at 30 Centigrade and the initial carbon-13 spectrum recorded. TFA (0.025ml) was then added and the carbon spectra recorded automatically at hourly intervals for sixteen hours using a fifteen minute acquisition time for each spectrum. A similar experiment was carried out using 1-phenylpropane-1,2-dione with no carbon-13 label taking spectra at ninety minute intervals using a thirty minute acquisition time for each spectrum.

1-Phenylpropanedione enriched with carbon-13 at the 3-position (0.025ml) and thiourea (0.0274g) were dissolved in a mixture of fully deuterated THF (0.5ml) and non-deuterated water (0.2ml) thermostatted at 30 Centigrade and the initial carbon-13 spectrum recorded using the DEPT 135 pulse sequence. TFA (0.025ml) was then added and the DEPT carbon spectra recorded automatically at hourly intervals for sixteen hours using a fifteen minute acquisition time for each spectrum.

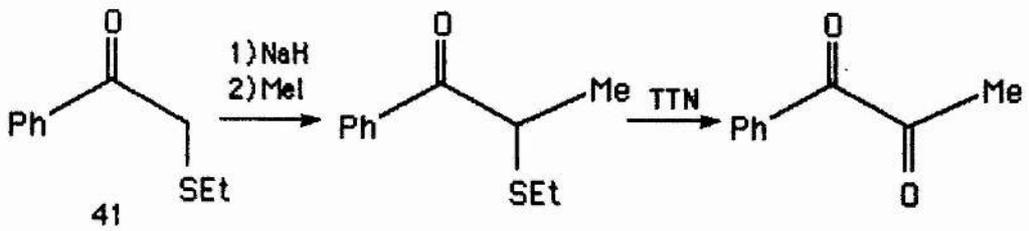
Diol (24) (0.036g) was placed in a mixture of fully deuterated THF (0.5ml) and non-deuterated water (0.2ml) thermostatted at 30 Centigrade and the initial carbon-13 spectrum recorded. TFA (0.025ml) was then added and the carbon spectra recorded automatically at ninety minute intervals for sixteen hours using a thirty minute acquisition time for each spectrum. It was confirmed that the main product of the reaction was (3) by spiking the final product mixture with an authentic sample and taking carbon-13 and DEPT spectra.

1-Phenylpropanedione enriched with carbon-13 at the 1-position (0.025ml) and 1,3-dimethylthiourea (0.0437g) were dissolved in a mixture of fully deuterated THF

(0.5ml) and non-deuterated water (0.2ml) thermostatted at 30 Centigrade and the initial carbon-13 spectrum recorded. TFA (0.010ml) was then added and the carbon spectra recorded automatically at hourly intervals for sixteen hours using a fifteen minute acquisition time for each spectrum. A similar experiment was carried out using 1-phenylpropane-1,2-dione with no carbon-13 label taking spectra at ninety minute intervals using a thirty minute acquisition time for each spectrum.

1-Phenylpropanedione enriched with carbon-13 at the 3 position (0.025ml) and thiourea (0.0437g) were dissolved in a mixture of fully deuterated THF (0.5ml) and non-deuterated water (0.2ml) thermostatted at 30 Centigrade and the initial carbon-13 spectrum recorded using the DEPT 135 pulse sequence. TFA (0.010ml) was then added and the DEPT carbon spectra recorded automatically at hourly intervals for sixteen hours using a fifteen minute acquisition time for each spectrum.

Diol (13) (0.044g) and 1,3-dimethylthiourea (0.036g) were placed in a mixture of fully deuterated THF (0.5ml) and non-deuterated water (0.2ml) thermostatted at 30 Centigrade and the initial carbon-13 spectrum recorded. TFA (0.025ml) was then added and the carbon spectra recorded automatically at ninety minute intervals for sixteen hours using a thirty minute acquisition time for each spectrum. It was confirmed that the main product of the reaction was (11) by spiking the final product mixture with an authentic sample and retaking the carbon-13 spectrum.



APPENDIX 1: How not to prepare carbon-13 labelled 1-phenyl-1,2-propanedione

(please note that the successful route is detailed in the experimental section of this chapter.)

I am certain that a vast untapped body of work exists suitable for publication only in the new proposed Journal of Negative Results.

Letter published in New Scientist

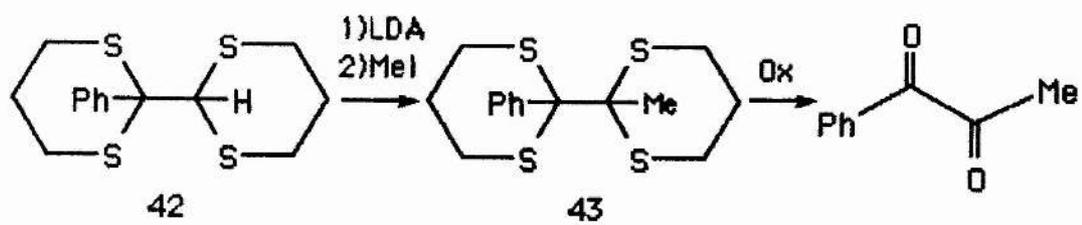
The major constraint upon the synthesis of 1-phenylpropanedione labelled with carbon-13 in the methyl position was, as is frequently the case with the preparation of labelled materials, the availability and cost of the carbon-13 enriched precursors. In the case of this particular preparation a small quantity of 67% carbon-13 methyl iodide was available as surplus from a previous project and so only syntheses using this substrate were considered.

The most obvious route to 1-phenylpropanedione using methyl iodide is to treat the anion of acetophenone with methyl iodide to give (on work up) propiophenone, followed by oxidation of the methylene group by successive treatment with cupric bromide, silver nitrate and sodium acetate in dimethylsulphoxide which had already been used with great success as detailed in the experimental section. Unfortunately this route is not practicable in a case where the alkyl iodide cannot be used in a large excess because a second acetophenone anion will attack the carbonyl centre of the propiophenone to give a tertiary alcohol. Therefore this route was discarded immediately. The same argument holds for the 2-ethylsulphide of acetophenone (41) which has been converted into phenylpropanedione in an overall yield of 50% by successive treatment with base and methyl iodide followed by oxidation with thallium

trinitrate¹¹. The high cumulative toxicity of the latter reagent is also a strong argument against this route.

The above discussion describes the two basic requirements of the reagent to be used. Firstly, of course, the product of its reaction with methyl iodide should be readily converted in a few high yield operations into phenylpropanedione. This requirement is not as trivial as it might at first appear because there appear to be remarkably few published procedures for the preparation of 1,2-diketones in adequate yields for isotopically labelled syntheses. Secondly, and a much more serious restriction, the product of reaction with methyl iodide should not itself be vulnerable to attack by a second nucleophile or rearrange in the basic conditions required to generate the nucleophile from the neutral precursor.

An initially promising proposal was to prepare 2-phenylpropyne from the reaction of lithium phenylacetylide and methyl iodide and then oxidise the acetylene directly to the dione. Methyl iodide is reported to react efficiently with a large variety of alkyl substituted terminal acetylenes to give the corresponding alkyl methyl acetylenes in yields of up to 95%¹². Furthermore, a highly efficient catalytic oxidation of a variety of acetylenes, including 1-phenyl-3-butyne, to the corresponding 1,2 diones in yields of up to 80% has recently been published¹³. Indeed using commercially available 2-phenylpropyne the oxidation procedure proved to be most satisfactory, giving phenylpropanedione of excellent purity in high yields. The condensation of methyl iodide with phenylacetylene was, however, found to proceed readily but not to give significant quantities of 2-phenylpropyne. A more extensive literature search was then carried out and it was discovered that 2-phenylpropyne rearranges rapidly under strongly basic conditions to give a complicated mixture of products including 1-phenylpropyne anion and a variety of allenes. The rapidity of the rearrangement compared to alkyl substituted 2-propynes was described as being due to

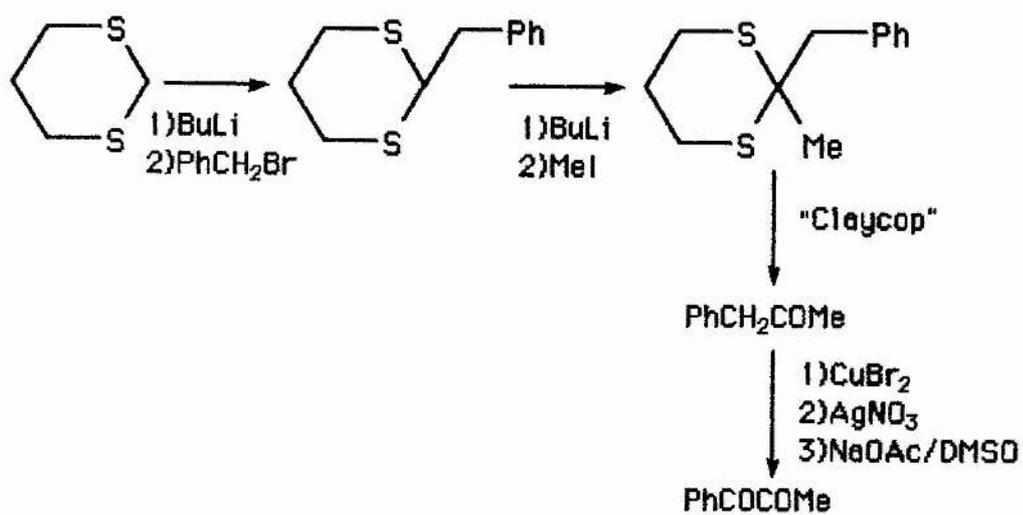


the 'resonance stabilising effects of the aromatic substituent'¹⁴.

Probably the most effective carbanion stabilising group which can readily be converted to a carbonyl centre is the 1,3-dithiane moiety. It also has the added advantage that the neutral group is highly resistant to nucleophilic attack which makes reagents based on one or more dithiane centres highly suitable for the proposed synthesis.

The first proposal was for the preparation of (42) where the second carbonyl centre was inserted as a protected thioketal before deprotonation and reaction with the methyl iodide to give (43). It was originally hoped that both thioketal groups in (43) could be removed by one reagent in a single step to give an elegant and efficient synthesis with only two steps involving the labelled material. It was found to be possible to prepare (42) quite efficiently by acid catalysed condensation of phenylacetaldehyde and 1,3-propanedithiol in dichloromethane. In many preparations utilising 1,3-dithianes the most difficult step is the oxidation of the dithiane moiety to a carbonyl function, thus it was thought appropriate to prepare (43) similarly from 1,3-propanedithiol and 1-phenylpropanedione in order to find an appropriate oxidation method.

It proved in fact not to be possible to oxidise (43) directly to 1-phenylpropanedione with any single reagent. All of the dithiane oxidation reagents described in the literature¹⁵ that we investigated proved to oxidise one of the thioketals to a carbonyl group very efficiently and rapidly giving a mixture of two isomeric 1-oxo dithianes. These species are notoriously difficult to oxidise and virtually all of the reagents investigated failed at this point. The only reagent of those we investigated which did oxidise 1-oxo dithianes efficiently was N-bromosuccinamide and silver nitrate^{15,16}. Unfortunately, if sufficient reagent was used to perform two dithiane oxidations the 1-phenylpropanedione product was itself oxidised to acetic and benzoic acids. The final oxidation regime therefore consisted of two steps, the first being



oxidation of one thioketal centre only with Laszlo's reagent "claycop"⁸. This reagent was chosen from the many suitable because of the simplicity of the isolation procedure characteristic of supported reagents. The mixture of isomeric 1-oxo dithianes was then oxidised using sufficient N-bromosuccinamide and silver nitrate to oxidise one dithiane only. This two step oxidation gave quite satisfactory yields.

The step that had been predicted to be the most difficult having been overcome, the only remaining problem was to optimise the reaction of deprotonated (42) with methyl iodide, which was not expected to present any great difficulties since 1,3-dithianes are in common use as protecting groups for ketones and for the umpolung reaction of carbonyls with alkyl iodides. To our great dismay, however, (42) proved to decompose rapidly in the presence of one equivalent of strong base even at -78 Centigrade to give a reddish material which was not identified.

The efficient reaction of dithiane anions with methyl iodide was, however, used in the successful synthesis. 2-Benzyl dithiane was treated successively with base and labelled methyl iodide to give 2-benzyl-2-methyldithiane which was oxidised to phenylacetone with "claycop"⁸. The problem with this route which led to the investigation of (43) above is that phenylacetone contains two activated alkyl centres adjacent to the carbonyl so that oxidation with the usual reagents such as selenium oxide yields a mixture of 1-phenylpropanedione and benzylacetaldehyde. Oxidation with selenium oxide, for instance, yields only 60% phenylpropanedione¹⁷. Bromination of ketones with two activated alkyl groups also tends to yield a mixture of products but in this particular case, perhaps because the phenyl group stabilises the conjugated form of the enol tautomer, bromination with cupric bromide gave almost exclusively 1-phenyl-1-bromoacetone. This was converted to the nitrite with silver nitrate and the nitrite eliminated to give the diketone with sodium acetate as detailed in the experimental section.

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