Mechanistic Studies in the Chemistry of Thiourea. Part 1. Reaction with Benzil Under Alkaline Conditions

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Benzil reacts under alkaline conditions with 1,3-dimethylthiourea to form 4,5-dihydroxy-1,3-dimethyl-4,5-diphenyltetrahydroimidazole-2-thione (**1**); with 1-methylthiourea to form 3-methyl-5,5-diphenyl-2-thiohydantoin (**9**); and with thiourea to form both the corresponding hydantoin and 3a,7a-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dithione (**19**). The use of high field n.m.r. spectroscopy and benzil labelled with carbon-13 in the carbonyl group has permitted delineation of the reaction mechanisms and detection of a number of transient intermediates.

In a previous series of papers[1] an extensive investigation into some condensation reactions of urea and *N*-alkylureas with diketo compounds was reported. It is known that there are often interesting and significant differences between the reactions of sulphur compounds and their oxygen analogues so we decided to conduct a parallel investigation into the reactions of thiourea and *N*-alkylthioureas. In this report we describe the reactions of 1,3-dimethylthiourea, 1-methylthiourea, 1,1-dimethylthiourea, and thiourea with benzil (1,2-diphenylethane-1,2-dione) in the presence of base. Using high field ^{13}C n.m.r. spectroscopy we were able to detect and identify a number of transient intermediates; these were useful in delineating mechanistic details.

Results and Discussion

1,3-*Dimethylthiourea*.—The only product isolated after reaction with benzil in the presence of base in refluxing ethanol was 4,5-dihydroxy-1,3-dimethyl-4,5-diphenyltetrahydroimidazole-2-thione (**1**), confirming the early report of Blitz.[2] This parallels the reaction of benzil with 1,3-dimethylurea.[3]

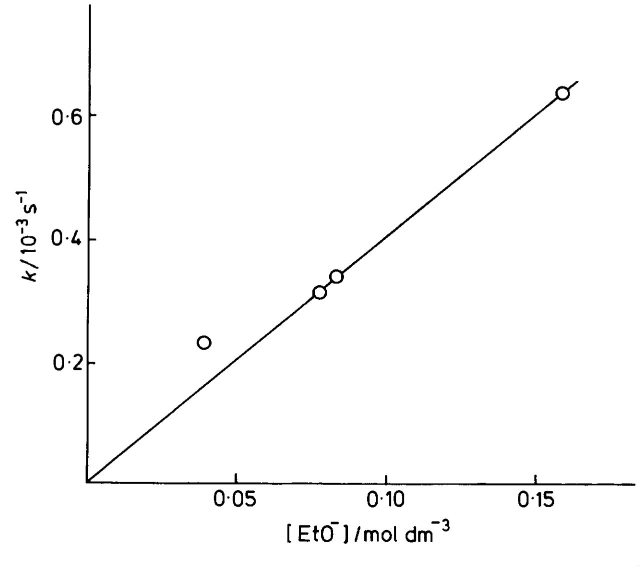
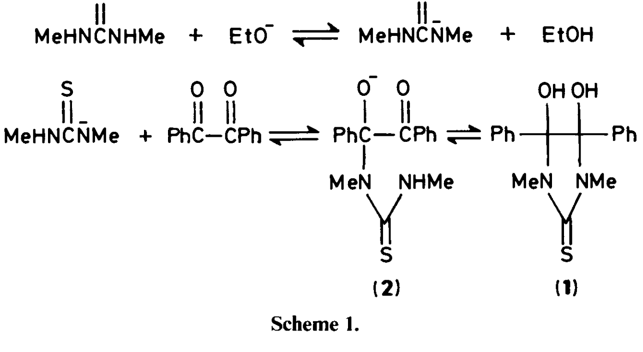


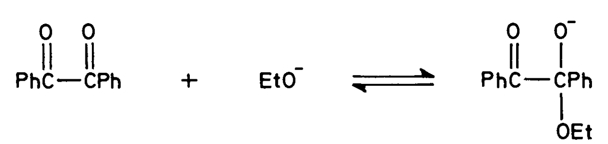
Figure 1. Reaction of benzil with 1,3-dimethylthiourea in the presence of ethoxide at 25 °C. [Dimethylthiourea] = 0.10 mol dm^{-3}; [benzil] = 10^{-2} mol dm^{-3}.

The reaction kinetics were measured by monitoring the disappearance of the benzil u.v. absorption. Each run was first order in benzil and there is a rectilinear relationship between $k_{obs.}$ and $[EtO^-]$ (Figure 1), suggesting that the reactive species in the rate-determining step is the dimethylthiourea anion. The proposed mechanism for this reaction is shown in Scheme 1. The pK_a of thiourea is not known but it is certainly a very weak acid and the anion must be present in the kinetic runs at a low, but constant, concentration. The slow step is the attack of the dimethylthiourea anion on a benzil carbonyl group to give (**2**); the subsequent ring closure is fast. This slow-step-assignment is in accord with the work of Dietz and Meyer[4] and is confirmed by the effect of substituents upon the rate of reaction and the position of equilibrium. There was no detectable reaction with 4,4′-dimethoxybenzil; for 4,4′-dimethylbenzil and benzil itself the values of the 'rate constants' ($k_{obs.}$/[dimethylthiourea]$[EtO^-]$) are 0.37 and 4.4 mol^{-2} dm^6 s^{-1}. Clearly an electron-donating substituent (methyl and methoxy) makes the benzil carbonyl less susceptible to attack by the nucleophilic thiourea anion. The equilibrium constants for diol formation were measured from the absorption of the reaction mixture at 383 nm, where the diol has only a very small absorption. For benzil the equilibrium favours the diol (K = [diol]/[dimethylthiourea][benzil] = 25), while K for 4,4′-dimethylbenzil is only 0.54. Studies on 4,4′-dichlorobenzil were impossible because of its very low solubility, and with 4,4′-dinitrobenzil the spectrum was dominated by the absorption of the nitro groups.



Scheme 1.

N.m.r. spectroscopic evidence indicates that (**2**) (Scheme 1) does not exist in measurable concentrations and so formation of (**2**) must be the slow step and cyclisation to (**1**) rapid. Another

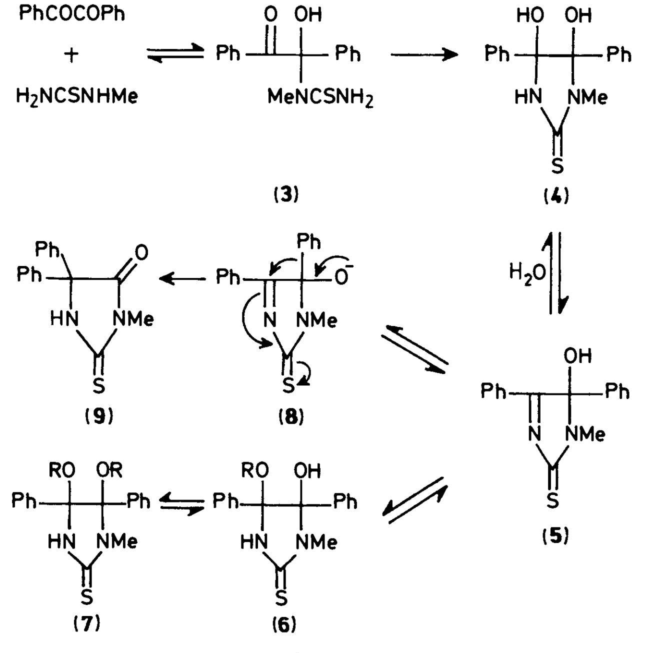


Scheme 2.

equilibrium which must occur is shown in Scheme 2. However, the work of Dietz and Meyer[4] shows that it occurs to such a small extent that the kinetics for the disappearance of benzil are not seriously affected. Also, in the calculation of K values it has been assumed that ionisation of the hydroxy groups of (**1**) is unimportant and so the position of equilibrium is independent of the base concentration.

Compound (**1**) can exist in two diastereoisomeric forms. N.m.r. spectroscopy (^1H and ^{13}C) in the presence of chemical shift reagents showed that the ratio of the concentrations of *E*-isomer to the more crowded *Z*-isomer is *ca.* 2:1; this is expected in view of the steric constraints which occur in the cyclisation of (**2**) to (**1**). The stereochemistry will be discussed in more detail later.

1-*Methylthiourea*.—Prolonged reaction with benzil in the presence of base in refluxing ethanol gave as the only isolable product 3-methyl-5,5-diphenyl-2-thiohydantoin (**9**) in high yield; this is in agreement with the work of Blitz.[2] The position of the methyl group, with respect to the two phenyl groups, was assigned by comparison with published i.r. spectra.[5] Evidence for the mechanism comes from various sources and the agreement can be best explained by first giving the proposed scheme (Scheme 3).



Scheme 3.

No reaction occurs in the absence of base and so, as with 1,3-dimethylthiourea, the first step is attack by the 1-methylthiourea anion on a benzil carbonyl to give, on protonation, (**3**). A similar process at the other end of the thiourea moiety permits cyclisation to (**4**), which is where the reaction of 1,3-dimethylthiourea ceases. However, in the case of the diol from 1-methylthiourea, dehydration can occur to give (**5**). It is possible to isolate (**5**) if 4,4′-dinitrobenzil is used in place of benzil. Compound (**5**) undergoes reversible addition of alcohol to give (**6**). When the reaction between 1-methylthiourea and benzil at 30 °C in ethanol was halted after 15 min and the solution cooled, a precipitate consisting of (**6**; R = Et) was obtained in high yield. It was identified by elemental analysis, i.r. spectroscopy and, more significantly, by ^1H n.m.r. spectroscopy. The latter contains a double doublet of quartets characteristic of the methylene of an ethoxy group attached to an asymmetric centre. Only one diastereoisomer could be detected; using a chemical shift reagent this was shown to be the less sterically crowded *E*-diastereoisomer. The fact that only compounds (**5**) and (**6**) could be isolated suggests that, if nucleophilic attack to give (**3**) is slow, cyclisation must be fast.

Reaction of (**6**) with base in refluxing ethanol gave quantitative conversion into (**9**). This reaction was accompanied by the transient formation of a species with a fairly strong u.v. absorbance, consistent with the intermediacy of (**5**). Conversion of (**6**) into (**9**) also occurred at 40 °C but there was no evidence for the formation of (**9**) at 25 °C. The significance of these observations will be apparent later.

We were able to observe the formation of (**6**) and (**7**; R = Me) directly by ^{13}C n.m.r. spectroscopy. Benzil, labelled with 20% ^{13}C in the carbonyl groups, was synthesised. The reaction with 1-methylthiourea in [$^2H_4$]methanol at 25 °C was monitored over 16 h and spectra, each with an accumulation time of 15 min, were taken at hourly intervals. All the signals corresponding to the labelled centres are displayed in Figure 2. At this temperature the reaction was very slow and no thiohydantoin formed over 16 h.

The signal at 194.4 ppm, known to be that of the benzil carbonyl, fell fairly rapidly during the first 9 h but then remained essentially constant at approximately half its original value. The other four signals, in the range 90–98 ppm, can be assigned to the four quaternary centres in (**3**), (**6**), and (**7**). The signal at 90.5 ppm appeared very rapidly after mixing and is, therefore, probably an early intermediate, *i.e.* (**3**). No signal corresponding to the carbonyl of (**3**) was detected but, as the 90.5 ppm signal is only just above the limits of detection, this is not surprising.

Using (**1**) as a model compound it was found that, for compounds of this type, the quaternary carbon shifts are in the range 90–100 ppm and replacement of OH by OMe caused a 4 ppm shift to higher frequency. We therefore assigned the signal at 94.2 ppm to the hydroxy-bearing quaternary centre in (**6**). A plot of the intensity of this signal against time is parallel with the same plot for the signal at 97.6 ppm and we conclude, therefore, that they are in the same molecule (*i.e.* the carbon at the methoxy-bearing centre). The signal at 96.7 ppm is assigned to one of the quaternary carbons of (**7**). The fact that the intensities of all five signals reached a constant value over the last 5 h indicates that (**3**), (**6**, and (**7**) are in equilibrium, requiring the intermediacy of (**4**) and (**5**). The latter must, however, be present at very low concentrations.

The same ^{13}C n.m.r. study was carried out at 40 °C, when rearrangement to the thiohydantoin (**9**) occurred (Figure 3). The signal at 194.4 ppm (benzil CO) fell to zero over 4 h but those assigned to (**9**) (174.8 and 72.5 ppm) rose only slowly over 16 h suggesting that firstly: phenyl migration [(**5**) $\longrightarrow$ (**9**)] is slower than attack on benzil and secondly, reaction intermediates are still present in the reaction mixture, even when substantial amounts of thiohydantoin have formed. Time-intensity plots for these two signals (174.8 and 72.5 ppm) are parallel, which is consistent with their being in the same molecule. The signal at 90.5 ppm, assigned to (**3**) from the run at 25 °C, rose rapidly to its maximum value over the first 10 min and fell to below the limit of detection in 1 h. The different behaviour seen at 40 °C can be explained in terms of a perturbation of the equilibria shown in Scheme 3 caused by an irreversible phenyl migration to give (**9**), an effect not observed at 25 °C. No signal corresponding to the carbonyl centre of (**3**),

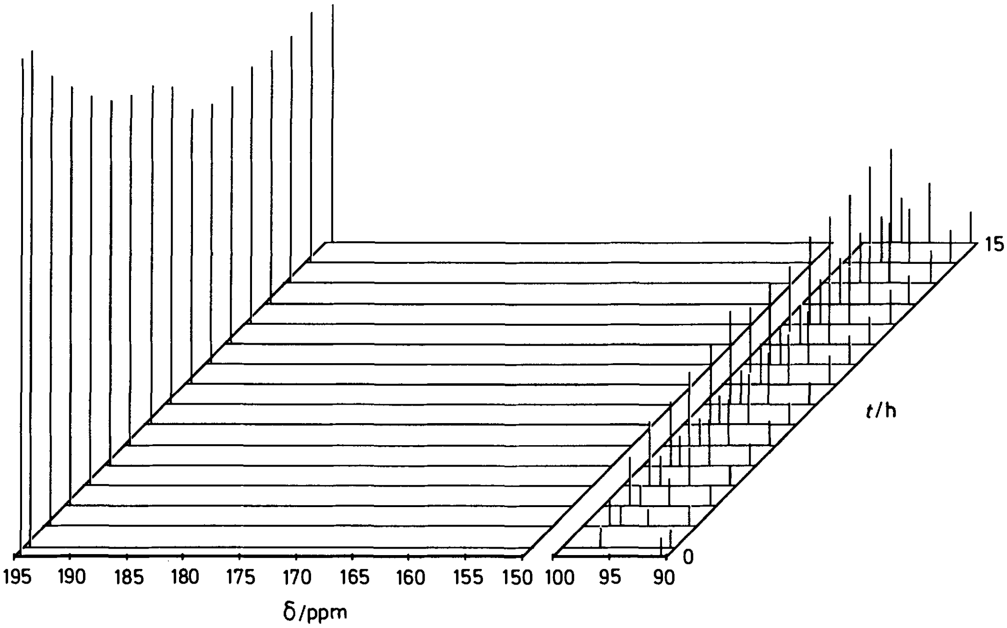


Figure 2. ^{13}C N.m.r. spectra taken at hourly intervals during the reaction of benzil with 1-methylthiourea in [$^{2}H_4$]methanol at 25 °C.

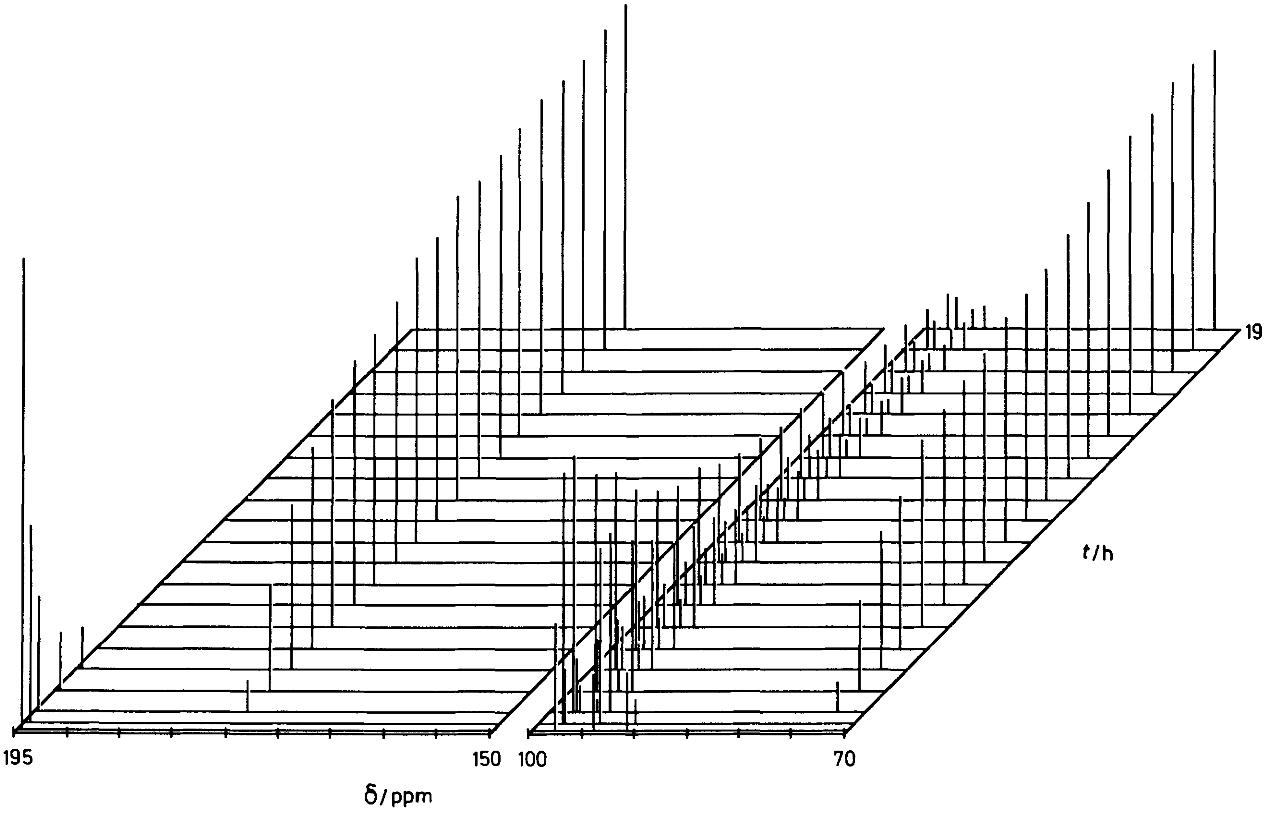


Figure 3. ^{13}C N.m.r. spectra taken at hourly intervals during the reaction of benzil with 1-methylthiourea in [$^{2}H_4$]methanol at 40 °C.

parallel to that at 90.5 ppm, was detected. This can be rationalised in terms of an n.O.e. enhancement of the quaternary carbon signal by the nearby hydrogens of the methylamine and hydroxy groups which raises it above the noise level.

The signal at 97.4 ppm was observed at 40 °C but not at 25 °C. It reached a maximum value after 10 min and then fell to below the limit of detection; no other signal paralleling that at 97.4 ppm was observed. This shift can be assigned to a quaternary centre bearing an *N*-methyl group and a hydroxy or an alkoxy group. The appropriate carbon in (**4**) is a strong possibility. The rapid reaction of benzil and the somewhat slower formation of (**9**) could give rise to a detectable amount of (**4**) in the reaction mixture. The detection of (**4**) at 40 °C but not at 25 °C can be rationalised by proposing that nucleophilic attack on a carbonyl group by an NHMe group has a larger

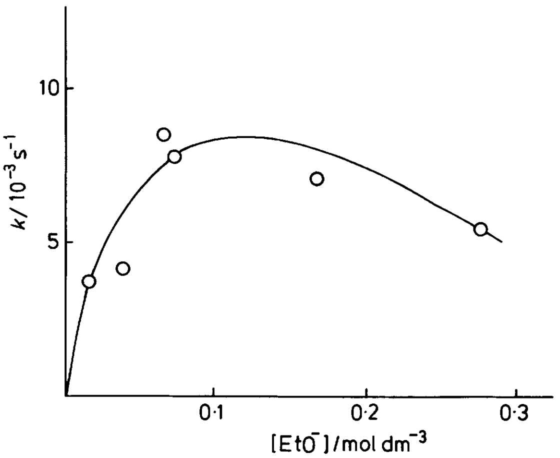


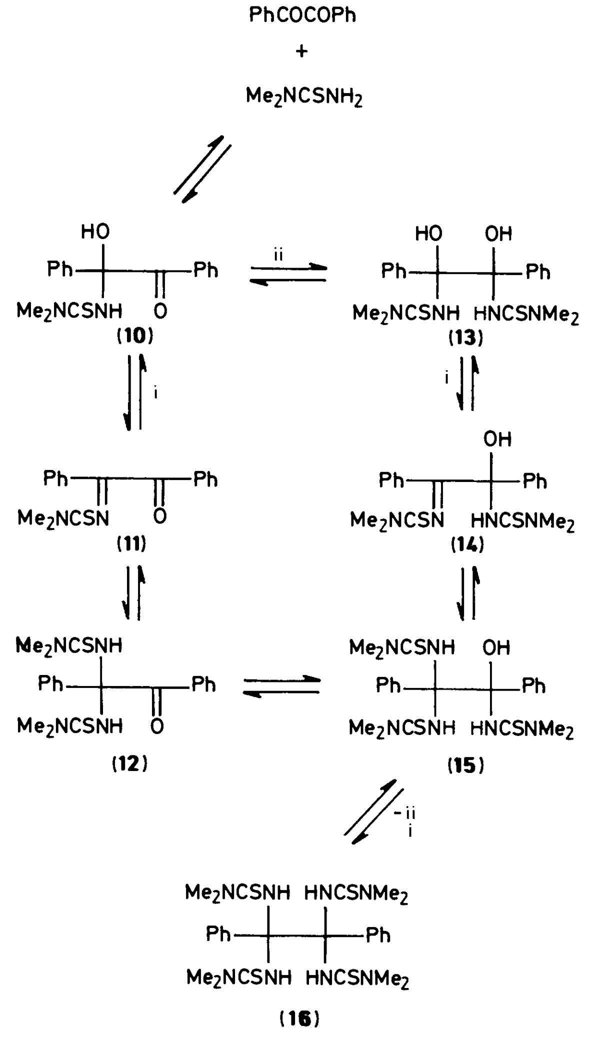
Figure 4. Effect of ethoxide concentration on the rate of conversion of (**5**) into (**9**).

activation energy than base-catalysed dehydration to give (**5**). As at 25 °C, there are signals at 97.6 and 94.2 ppm which we again assigned to structure (**6**). After 2 h the intensity of these signals decreased from a maximum in an exponential manner with a first-order rate constant of approximately $4.3 \times 10^{-4}\,s^{-1}$. The signals for thiohydantoin at 174.8 and 72.5 ppm (assigned by independent observation) increased by a first-order process with a similar rate constant. We conclude, therefore, that the signals at 97.6 and 94.2 ppm correspond to an intermediate which (i) exists in rapid equilibrium (compared with the interval between spectra) with the dehydrated intermediate (**5**), (ii) is present at a low steady state, and (iii) rearranges by a first-order process to (**9**). No signal corresponding to (**5**) was observed, consistent with its formation at a low steady state.

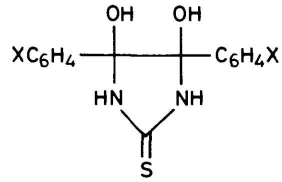
There are two remaining signals at 95.4 and 96.7 ppm, only one of which was observed at 25 °C. These are parallel, suggesting that they are in the same molecule, and they grew at a rate slower than those due to (**6**). The diol (**4**) can form only faster or at the same rate as (**6**) and so the signals cannot be assigned to (**4**). However, they can, by the same consideration, be assigned to (**7**). Compound (**7**) must be in equilibrium with (**6**) and (**5**) as no product other than (**9**) was isolated. As the reaction proceeds the water content of the medium increases and so (**6**) and (**7**) will be disfavoured and (**4**) favoured. The diol (**2**), prepared from benzil and 1,3-dimethylthiourea on refluxing in basic ethanol, showed a 5% replacement of hydroxy by ethoxy groups after 2 h reaction time.

Kinetic data for the effect of ethoxide concentration on the conversion of (**5**) into (**9**) are shown in Figure 4. In view of the complexities of the reaction pathway and the fact that increased ethoxide concentration will effect ionisation of methylthiourea as well as (**3**)–(**7**), it is difficult to make an unambiguous mechanistic deduction from this curve. The levelling off at high base concentration is consistent with complete ionisation of (**8**), since its conversion into (**9**) is slow in comparison with all other steps in the reaction. We have no explanation for the decrease at very high base concentration; it is known not to be a salt effect.

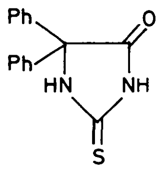
1,1-*Dimethylthiourea*.—The only products isolable from the reaction between benzil and 1,1-dimethylthiourea in refluxing basic ethanol after 2 h were unchanged starting material and eventually the products of the reaction between benzil and ethoxide[6] (benzilic acid, ethyl benzilate, benzoin, benzaldehyde, and *O,O′*-ethylenedibenzoin). We had hoped to isolate material analogous to (**3**) because the second methyl group blocks cyclisation. We could, however, detect by ^{13}C n.m.r. spectroscopy a number of compounds in equilibrium with benzil and 1,1-dimethylthiourea in basic methanol. Benzil labelled with 20% ^{13}C at the carbonyl position was used. In addition to a strong signal for benzil, there were weak, but definite, signals at 96.1, 95.3, 95.0, 87.8, 87.6, and 86.9 p.p.m. which did not change significantly with time. Because of their low intensities, unambiguous assignment is difficult; what is beyond doubt is that reaction between 1,1-dimethylthiourea and benzil does occur, although isolation of products was not possible. The three signals at lower frequency we attribute to a tertiary centre bearing one phenyl, one thiourea and one methoxy (or hydroxy) group as in (**10**), (**13**), and (**15**) (Scheme 4). These assignments were given on comparison of these data with those collected for the products from 1-methylthiourea. It is possible that the hydroxy groups shown in Scheme 4 are methoxy groups. The signals in the range 96.1–95.0 cannot be due to the same carbon bearing, in one case, a hydroxy group, and in another, a methoxy group as we know this produces a change in chemical shift of 2 ppm. It has to be assumed that signals for the carbonyl centres of (**10**) [and (**12**)] are not observed because they lack the n.O.e. of the quaternary centre due to the protons on the adjacent nitrogen and oxygen atoms. The signals at higher frequency we assign to the centres in (**12**), (**15**), and (**16**) which bear two pendant thiourea moieties. It is assumed that species (**11**) and (**14**) are present at undetectably low concentrations. All of the above assignments are tentative but do provide a rationalisation of the experimental data. Evidence for the equilibria in Scheme 4



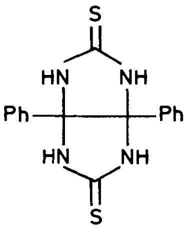
Scheme 4. *Reagents:* i, Me_2NCSNH_2; ii, H_2O.



(17) **a**; X = H
b; X = 4-Me
c; X = 4-OMe
d; X = 4-Cl
e; X = 4-NO2



(18)



(19)

Table. The yield of (**18**) and (**19**) in the reaction of thiourea with substituted benzils.

4,4′-Substituents	% Yield (**18**)	% Yield (**19**)
H	(**a**) 63	(**a**) 35
Me	(**b**) 34	(**b**) 27
OMe	(**c**) 6	(**c**) 0
Cl	(**d**) 51	(**d**) 32
NO_2	(**e**) 0	(**e**) 0

is of value in delineating the pathway for the reaction of benzil with thiourea.

Thiourea.—Under basic conditions in refluxing methanol, benzil reacts with thiourea to give a mixture of two products: 5,5-diphenyl-2-thiohydantoin (**18**) and 3*a*,7*a*-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dithione (**19**), as reported by Blitz.[2] As with methylthiourea we were able to isolate an intermediate (**17a**) by warming the reaction mixture for 5 min and then cooling it. Unlike methylthiourea the compound isolated was a diol rather than the methylated compounds (**21**) or (**22**). Reaction of (**17a**) with base in refluxing ethanol gave only the thiohydantoin (**19**). The proposed mechanism for this transformation is shown in Scheme 5; the intermediacy of the unsaturated compound (**20**) is crucial. We were able to measure the kinetics of this reaction by monitoring changes in the u.v. absorbance due to (**20**) [with which (**17a**) is in rapid equilibrium]. The results are displayed in Figure 5. The reaction is first order in ethoxide up to a limiting value of $3.65 \times 10^{-3}\ s^{-1}$ at $[EtO^-] = 0.10\ mol\ dm^{-3}$. At this ethoxide concentration all substrate must be present as the anion of (**20**) and the rate-determining process is the rearrangement of the anion to (**18a**). In methanol–methoxide the limiting value is much lower ($4.3 \times 10^{-4}\ s^{-1}$) presumably because with a sterically less demanding alcohol there is enhanced formation of (**21**) and (**22**). Substituted benzils did not yield (**17c**–**e**) although (**17b**) was obtained in moderate yield. Its rate of reaction to give a thiohydantoin was less than that of (**17a**); it is difficult to make any certain mechanistic deductions from this observation.

Reaction of (**17a**) with thiourea in basic ethanol did not result in formation of (**19**), although the latter was obtained upon reaction of thiourea with benzil. The extremely low solubility of (**19**) makes detection very easy. Compound (**17a**) cannot, therefore, be a common intermediate in the formation of (**16**) and (**19**). This fact is incorporated into the proposed mechanism (Scheme 5). The relative amount of (**19**) formed increased with an increased amount of thiourea present, even when the stoicheiometric amount had been exceeded. The amount was reduced by the presence of water and increased by the use of a sterically more hindered alcohol such as butan-1-ol and t-butyl alcohol. All of these observations are consistent with competition between thiourea and the solvent (or water) to attack an electrophilic centre to form intermediates leading to either (**18**) or (**19**). The ratio of (**18**) to (**19**) depends upon the substituent (Table).

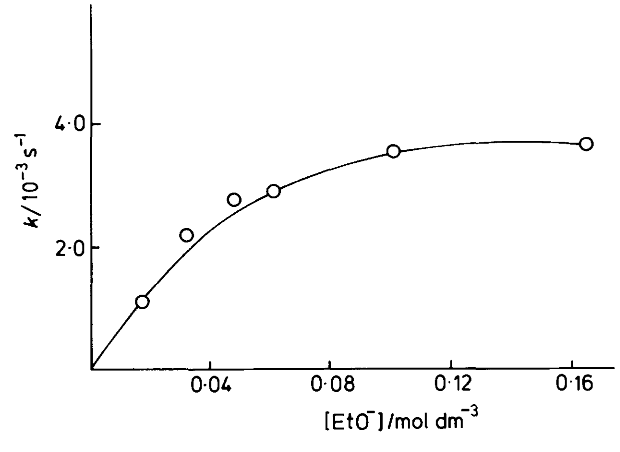


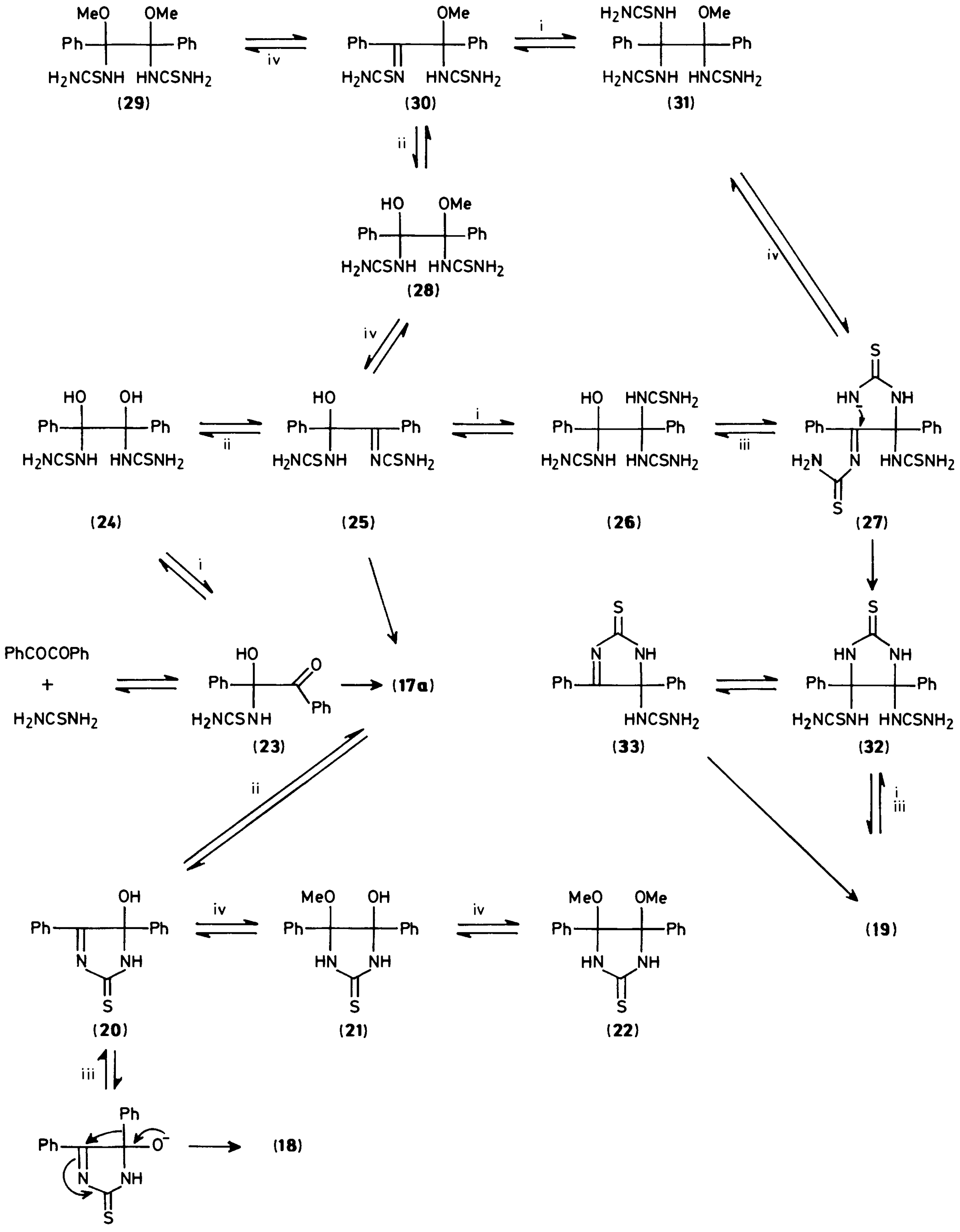
Figure 5. Effect of ethoxide concentration on the rate of conversion of (**17a**) into (**18**).

Similar results were obtained in a parallel study of the reaction of substituted benzils with urea. As the 4-methoxy group obviously decreases the susceptibility of the carbonyl to nucleophilic attack it was hoped that by using 2-methoxybenzil it might be possible to isolate an intermediate analogous to (**23**) where attack had occurred at only the carbonyl proximate to the unsubstituted phenyl group. However, only compounds analogous to (**18**) and (**19**) and unchanged starting materials were obtained.

Further insight into the mechanism was obtained by using ^{13}C labelled benzil and taking n.m.r. spectra periodically during the reaction. In the first experiment the reaction was maintained at 30 °C for 16 h and spectra were recorded at hourly intervals. The results are displayed in Figure 6.

The signal at 194.5 p.p.m. is due to benzil; it fell to half its initial value within 5 min (see later) and then decreased steadily by a first-order process over the following 16 h. This suggests the accumulation of substantial amounts of one or more intermediates. The rapid fall was accompanied by a rapid increase in signals at 93.3, 93.8, and 94.1 ppm, all of which lay in the region corresponding to carbons bearing one hydroxy group, one thiourea moiety, and one phenyl group, *i.e.* (**23**), (**17a**), and (**24**). However, there cannot be rapid equilibrium between benzil, (**17a**), and (**24**) *via* (**23**), as (**17a**) does not react with thiourea to give (**19**) and the signal for (**17a**) does not parallel that of (**24**) or of benzil. The observations instead imply formation of (**17a**) in an irreversible step. The rapid fall in the benzil signal is not due to the reaction of benzil with ethoxide, as no products from this reaction were detected. Rather, the behaviour of the benzil signal is consistent with rapid establishment of equilibria involving fairly high concentrations of intermediates [shown later to be (**23**)–(**32**)], followed by slow reaction at a rate controlled by the formation of (**17a**) and the slowest step in the production of (**19**). The fact that benzil reacts with the thiourea anion was established by Dietz and Meyer.[4]

Assignment of the other signals is based largely upon



Scheme 5. *Reagents:* i, H_2NCSNH_2; ii, H_2O; iii, H^+; iv, MeOH.

analogies with shifts from isolable and previously characterised compounds in other series. Compounds (**1**) and (**6**) have signals in the range 94.6–98.4 ppm and so it is reasonable to assign the 14 signals in Figure 6 (93.7–101.0 ppm) to compounds of these types. All the signals reached maxima fairly early in the reaction which suggests they are from intermediates formed by attack on benzil without extensive rearrangement. The number of plausible intermediates with the required structure is limited and we believe that assignment of all 14 signals necessitates the evocation of (**17a**) and (**20**)–(**32**) as detectable intermediates.

A weak signal at 93.3 ppm, which did not parallel any of the signals assigned to (**17a**) or (**20**)–(**22**), is assigned to the quaternary carbon in (**23**). It has already been shown that

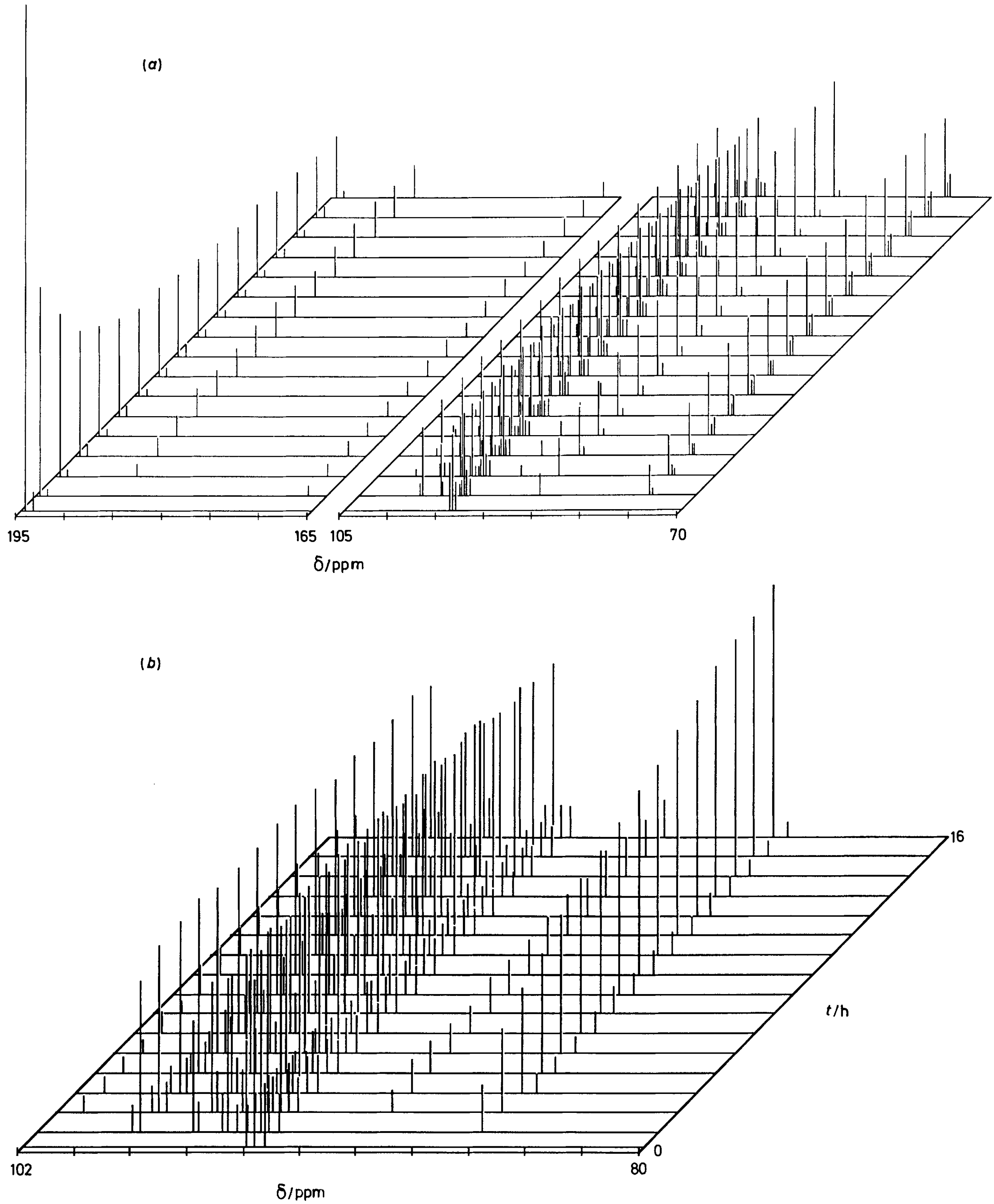


Figure 6. ^{13}C N.m.r. spectra taken at hourly intervals during the reaction of benzil with thiourea in [$^2H_4$]methanol at 30 °C: (*a*) whole spectrum; (*b*) expansion of the region 80–100 ppm.

analogous compounds in the 1-methyl- and 1,1-dimethylthiourea series [(**3**) and (**10**)] are formed. The concentration of (**23**) rose rapidly, attaining a maximum within 15 min and then fell more slowly to a level from which decline was even slower. This is consistent with a species formed rapidly but then equilibrating slowly with other intermediates on the reaction pathways [(**24**) to (**27**)], as well as undergoing irreversible conversion into (**17a**). The signals for (**17a**) and (**24**) reached maximum values at similar rates which is consistent with concurrent rather than sequential formation. The signals also

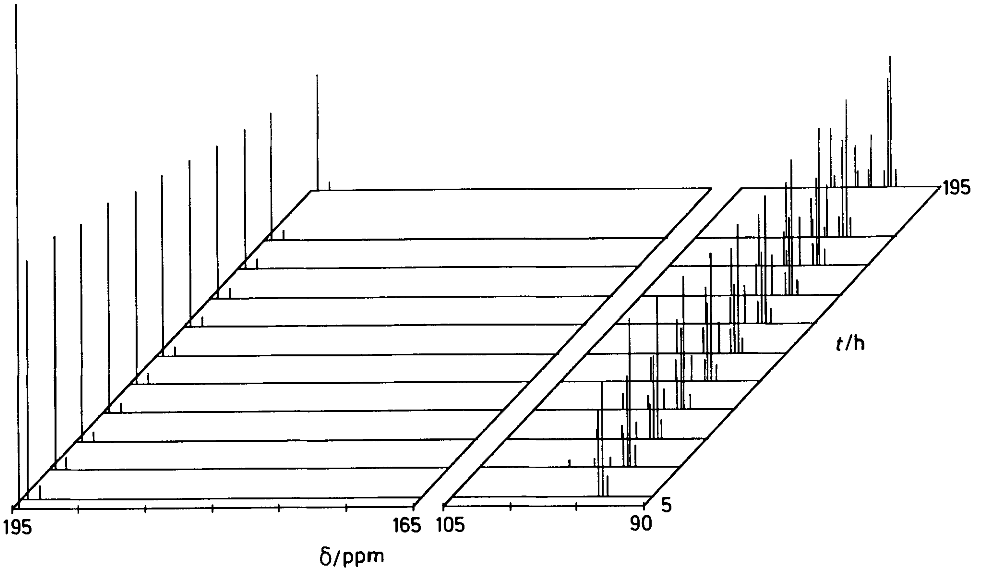


Figure 7. ^{13}C N.m.r. spectra taken at 15 min intervals during the first 2 h of the reaction of benzil with [$^2H_4$]methanol at 30 °C.

showed no parallel variation during the course of the reaction, indicating that (**17a**) and (**24**) are not in equilibrium.

The diol (**4**) is known to undergo rapid dehydration to form a carbon–nitrogen double bond. A similar reaction is expected of (**17a**) to give (**20**) which, in methanolic solution, is certain to add methanol to give (**21**) and (**22**). The four signals at 94.1, 95.2, 96.5, and 98.3 ppm we assign to the quaternary C atoms of (**20**)–(**22**). After the first 2 h all the signals showed parallel variation, consistent with the equilibria shown.

The signal at 93.8 ppm, corresponding to the quaternary carbons of (**17a**), reached its final maximum after 20 min, fell slightly over the next hour and then rose to a second maximum after 3 h. These results are consistent with the formation of (**17a**) from (**23**); the latter is formed rapidly from the reactants but the concentration falls as the slow equilibria (**23**) $\rightleftharpoons$ (**24**) $\rightleftharpoons$ (**25**) $\rightleftharpoons$ (**26**) are established. The second maximum we tentatively suggest may be due to the formation of (**17a**) from (**25**). After 4 h, signals from (**17a**), (**21**), and (**22**) show a slow steady fall with a high degree of correlation, corresponding to the formation of (**18**) by a benzilic acid type of rearrangement. To confirm the observations during the first part of the reaction, the n.m.r. experiment was repeated with the acquisition time reduced to 5 min (Figure 7) and the interval to 15 min. The signals assigned to (**21**) and (**22**) showed a smooth increase over the first 2 h, the formation of (**21**) being faster than (**22**). Two small peaks at 96.3 and 95.4 were observed in the study with long acquisition times. Their intensities over 16 h showed an excellent correlation with those of (**21**). It seems reasonable to assign these peaks to the *Z*-stereoisomer of (**21**), assuming that the predominant stereoisomer is *E* as was found for methylthiourea. An authentic sample of 5,5-diphenyl-2-thiohydantoin (**18**) had signals at 186.9 and 75.0 ppm in ethanolic solution. Thus the signals at 186.9 and 74.2 ppm, observed in the present experiments, are assigned to the carbonyl and quaternary carbons of (**18**) respectively. The two signals showed a slow increase over the 16 h and a high degree of correlation. There are five signals in the range 93.7–101.0 ppm which probably correspond to carbons bearing one phenyl, one alkoxy or hydroxy, and one thiourea moiety. None of these signals showed good correlation with those assigned to (**17a**), (**21**), or (**22**). Therefore they were credited to intermediates *en route* to the bicyclic intermediate (**19**). The signal at 93.8 reached its maximum value rapidly, fell slowly during the subsequent hour and then very slowly over the complete 16 h period. This suggests that it is an intermediate near the beginning of the reaction which slowly equilibrates with subsequent intermediates. We assign it to the acyclic diol (**24**), formed by reaction of thiourea with (**23**). The signal at 94.3 ppm rose more slowly than that corresponding to (**23**), reaching its maximum value in 20 min. It remained constant for a while but, after 1 h, fell rapidly to half its maximum value. Over the remainder of the experiment its value declined very slowly. There were no other signals which paralleled this variation and it was sufficiently intense that no other signal from the same molecule could be below the limit of detection and must, therefore, be in a symmetrical molecule. A reasonable assignment is (**29**), formed by two dehydrations and solvolyses of (**24**). No signals corresponding to the partially solvolysed material (**28**) could be detected. The chemical shift is similar to that proposed for the analogous material obtained by reaction of benzil with 1,1-dimethylthiourea. The signal at 166.9 ppm is consistent with a phenyl-substituted imine centre. The time–intensity plot does not parallel any other detected signal. The signal intensity rose more slowly than (**26**) or (**31**) and so must be due to material further along the reaction pathway leading to (**19**). As the signal does not parallel those from (**17**), (**21**), or (**22**) it cannot be due to (**20**) as these intermediates are all in equilibrium. The signal could, therefore, be due to either (**27**) or (**33**). However, there is no good correlation with the signals at 74.5 and 74.8 ppm assigned to the *Z* and *E* isomers of (**32**), with which (**33**) is in equilibrium. Thus by a process of elimination we assign it to (**27**). Presumably the other signal in (**27**), corresponding to the quaternary centre, is too weak to be detected. The concentration of (**27**) rose to a maximum more slowly than that of (**17a**), (**24**), or (**30**), which is consistent with the fact that (**27**) is formed later in the reaction. The signal at 85.7 ppm corresponds closely in chemical shift to the centre bearing two thiourea moieties in (**19**). It paralleled the signal at 98.1 ppm, which is likely to be an alcoholic centre. Thus, these two signals are assigned to (**26**). Similar signals were observed in the reaction of benzil with 1,1-dimethylthiourea. The signals assigned to (**26**) reached maximum values more slowly than those assigned to (**24**) and (**29**). Only the signal at 98.1 ppm was observed in the short acquisition time n.m.r. experiment and only became detectable after 2 h. After 4 h the signal declined gradually. Two further signals at 90.1 and 101.0 ppm are tentatively assigned to (**31**) by comparison with those assigned to (**26**), allowing for the change in chemical shift on replacement of OH by OMe. The rate of formation of (**31**) is consistent with this assignment. Assignment of the signal at 74.8 ppm follows the reasoning used for (**27**). The intensity of the signal rose more slowly than that of (**27**) but more rapidly than that of (**19**), which suggests that it could be an intermediate between them. It is a fairly intense signal and must correspond to an intermediate likely to accumulate, *i.e.* (**32**). The signal at 74.8 ppm is not parallel to any other signal of similar intensity but it is parallel to the signal at 74.5 ppm which is of approximately one tenth the intensity. This difference in intensity is far too large to be explained by an n.O.e. effect and so the signals must come from not one molecule, but two symmetrical molecules in equilibrium. Reasonable assignments are the *E* and *Z* isomers of (**32**) which can interconvert *via* (**33**). In the *Z* form of (**32**) it is impossible for the thiourea anion to be in a suitable position for S_N2 attack and expulsion of thiourea. As no (**32**) was obtained from the reaction mixture the *Z* form of (**32**) must exist in equilibrium with the **E** isomer. It is known,[6] from an *X*-ray crystallographic study, that the *Z* form of 3*a*,7*a*-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione is obtained from the reaction of urea with benzil under alkaline conditions and it is reasonable to presume that thiourea reacts in a similar way. The n.m.r. study indicates that only one isomer of (**19**) is produced and this must be the *Z* form.

An authentic sample of (**19**) has a chemical shift of 90.0 ppm in dimethyl sulphoxide (DMSO) for the tertiary carbons. This is in reasonably close agreement with a signal at 86.2 ppm (with a different solvent) observed during the n.m.r. experiment. The signal increased smoothly throughout the course of the study.

The assignment of all the signals observed in the n.m.r. studies has involved much complex argument, mainly from analogies. Few of the assignments are beyond question. However, the more important consequence of this investigation is a presentation of the complexity of a relatively simple organic reaction. In the reaction of thiourea with benzil there are only two reactants and only two products but, if our assignments are even approximately correct, there are many more intermediates; 16 according to our scheme, some on the reaction pathway and others off it. The products are decided by irreversible processes amongst the plethora of equilibria *e.g.* a phenyl migration to give the thiohydantoin and irreversible cyclisation.

Stereochemistry of Dihydroxytetrahydroimidazoles and Related Compounds.—It is possible to distinguish between the *Z* and *E* isomers of the cyclic glycols by use of a chemical-shift reagent such as Eu(fod)$_3$. The *Z* isomer can act as a bidentate chelating ligand on the europium centre in a manner analogous to that known for 1,2-dimethoxy aromatic systems. In the case of the *E* isomer the bulky phenyl substituents prevent this and so the sensitivity of the n.m.r. signals to the pressure of Eu(fod)$_3$ is much reduced.

As mentioned earlier the glycol (**1**), as isolated from the reaction mixture, contains the *E* and *Z* isomers in the ratio 2:1. This is best explained as kinetic control. With (**6**) only the *E* isomer was obtained. However, when this isomer was allowed to stand as a chloroform solution for two weeks, a little of the *Z* isomer formed. This is probably due to acid-catalysed isomerisation *via* the same imine intermediate (**5**) proposed in Scheme 3. Under alkaline conditions a similar isomeric interconversion could occur and so the isomeric composition of the product is thermodynamically controlled. Similar interconversion for (**1**) is not possible as no imine can form.

Experimental

Materials.—Thiourea and the substituted thioureas were commercial materials and used without further purification. Light petroleum refers to the fraction boiling at 40–60 °C.

M.p.s. were determined in a capillary and are uncorrected. ^1H N.m.r. spectra were recorded on a Bruker WH-360 spectrometer and ^{13}C n.m.r. spectra on a Bruker CFT-20 spectrometer with Me_4Si as the standard. I.r. spectra were recorded on a Perkin-Elmer 1420 spectrometer.

Synthetic Methods.—1,3-Dimethylthiourea (1.1 g) and benzil (2.1 g) were dissolved in ethanol (10 cm^3; 10% water) containing NaOH (0.2 g) and refluxed for 2 h. Water was added to the cooled reaction mixture, with stirring, and the precipitated 4,5-dihydroxy-1,3-dimethyl-4,5-diphenyltetrahydroimidazole-2-thione (**1**) was filtered off and washed with dichloromethane (yield 82%), m.p. 150 °C (lit.,[2] 158 °C), *m/z* 296 ($M^+ - H_2O$), δ_H([$^2H_6$]acetone) 3.30 (6 H, s) and 7.45 (10 H, m); δ_C([$^2H_6$]acetone) 30.0, 97.7, 126.7, 127.4, 127.9, 142.6, and 182.8.

1-Methylthiourea (0.9 g) and benzil (1.2 g) were dissolved in ethanol (10 cm^3; 10% water) containing NaOH (0.2 g) and the solution was refluxed for 3 h. Water (10 cm^3) was added and, after the solution had been allowed to stand for 30 min, 3-methyl-5,5-diphenyl-2-thiohydantoin (**9**) was filtered off and recrystallised from ethanol (yield 70%), m.p. 182 °C (lit.,[2] 185 °C), *m/z* 282 (M^+); $\nu_{max.}$(mull)[5] 1 725 (C=O) and 3 260 cm^{-1} (NH); δ_H($CDCl_3$) 3.30 (3 H, s), and 7.45 (10 H, m); δ_C([$^2H_6$]DMSO) 27.3, 71.3, 126.6, 128.4, 128.6, 138.1, 173.5, and 181.5.

The above procedure was repeated but instead of being refluxed, the mixture was warmed to 30 °C and kept at that temperature for 20 min. 4-Ethoxy-5-hydroxy-3-methyl-4,5-diphenyltetrahydroimidazole-2-thione (**6**; R = Et) was filtered off and washed with dichloromethane (yield 60%), m.p. 141 °C, *m/z* 282 (M^+ − EtOH), δ_H([$^2H_6$]acetone) 1.27 (3 H, t), 2.99 (3 H, s), 3.30 (1 H, d q), 3.60 (1 H, d q), and 5.13 (1 H, s) (Found: C, 65.3; H, 5.9; N, 8.4. $C_{18}H_{20}N_2O_2S$ requires C, 65.83; H, 5.90: N, 8.53%).

When the above procedure was repeated using methanol as the solvent, 5-hydroxy-4-methoxy-3-methyl-4,5-diphenyltetrahydroimidazole-2-thione was obtained (yield 70%), m.p. 136 °C, *m/z* 282 (M^+ − MeOH); δ_H($CDCl_3$) 3.00 (3 H, s), 3.30 (3 H, s), 6.93–7.40 (10 H), and 8.20 (1 H, s); δ_C($CDCl_3$) 28.9, 51.2, 94.6, 98.4, 126.7–135.4, and 182.1 (Found: C, 64.9; H, 5.7; N, 8.8. $C_{16}H_{16}N_2O_2S$ requires C, 64.96; H, 5.80; N, 8.91%). Replacement of benzil by 4,4′-dimethylbenzil in the above method for thiohydantoin synthesis gave 3-methyl-5,5-bis(4-methylphenyl)-2-thiohydantoin, (yield 65%), m.p. 152 °C, *m/z* 310 (M^+), $\nu_{max.}$(mull) 1 735 (CO) and 3 150 cm^{-1} (NH) (Found: C, 69.4; H, 5.8; N, 9.0. $C_{18}H_{18}N_2OS$ requires C, 69.6; H, 5.8; N, 9.0%). With 4,4′-dichlorobenzil was obtained 5,5-*bis*(4-*chlorophenyl*)-3-*methyl*-2-*thiohydantoin* (yield 35%), m.p. 185 °C, $\nu_{max.}$(mull) 1 738 (CO) and 3 300 cm^{-1} (NH) (Found: C, 54.7; H, 3.4; N, 8.0. $C_{16}H_{12}Cl_2N_2OS$ requires C, 54.7; H, 3.4; N, 8.0%). When 1-methylthiourea was replaced by 1-phenylthiourea, 3,5,5-*triphenyl*-2-*thiohydantoin* was obtained (yield 60%), m.p. 244 °C, $\nu_{max.}$(mull) 1 738 (CO) and 3 300 cm^{-1} (NH) (Found: C, 72.9; H, 4.71; N, 8.1. $C_{21}H_{16}N_2OS$ requires C, 73.23; H, 4.68; N, 8.13%).

Thiourea (1.5 g) and benzil (2.1 g) were dissolved in butanol (10 cm^3) containing NaOH (0.2 g) and refluxed for 2.5 h. The white precipitate of 3a,7a-*diphenyltetrahydroimidazo*[4,5-d]*imidazole*-2,5-*dithione* (**19**) was filtered off and washed with water and then ether (yield 70%), m.p. 304 °C (lit.,[2] 307 °C), *m/z* 326 (M^+), $\nu_{max.}$(mull) 3 150 cm^{-1} (NH); δ_H([$^2H_6$]DMSO) 7.45 (10 H, m); δ_C([$^2H_6$]DMSO) 90.0, 127.0, 128.1, 128.7, 135.5, and 182.7. With ethanol as solvent the yield was reduced to 30%. The other product of reaction in this solvent was 5,5-diphenyl-2-thiohydantoin, identified by comparison with a commercial sample.

Reaction of thiourea (4.20 g) and benzil (11.6 g) in ethanol (50 cm^3 water, 10%) containing NaOH (1.1 g) at room temperature for 20 min resulted in the precipitition of 4,5-*dihydroxy*-4,5-*diphenyltetrahydroimidazole*-2-*thione* (**17a**). After water had been added (10 cm^3) the solid was filtered off and washed liberally with light petroleum (yield 30%), m.p. 96 °C, *m/z* 268 ($M^+ - H_2O$); δ_H([$^2H_6$]DMSO) 7.10–7.40 (10 H, m) and 8.15 (2 H, s), δ_C([$^2H_6$]DMSO) 73.9, 127.3, 127.7, 128.2, 142.1, and 188.8. Reaction of (**1**) with methyl iodide and silver oxide gave 4,5-*dimethoxy*-1,3-*dimethyl*-4,5-*diphenyltetrahydroimidazole*-2-*thione* (yield 62%), m.p. 201 °C *m/z* 296 (M^+ − 2MeOH); δ_H(CDCl$_3$) 2.95 (3 H, s, *Z*-isomer), 3.25 (3 H, s, *E*-isomer), 3.60 (6 H, s), and 7.05 (10 H, m); δ_C(CDCl$_3$) 32.8, 51.8, 53.8, 100.4, 126.4–135.7, and 185.6 ppm.

4,4′-Dinitrobenzoin was prepared from 4-nitrobenzaldehyde by the method of Breslow,[7] using 3-ethyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium bromide. Oxidation to 4,4′-dinitrobenzil was effected by refluxing 4,4′-dinitrobenzoin in concentrated HNO$_3$ for 4 h. Water was added to the reaction mixture and the resulting yellow crystals were filtered off and recrystallised from ethanol (yield 63%), m.p. 219 °C (lit.,[8] 214 °C). 4,4′-Dichlorobenzil was prepared in a similar manner and recrystallised from toluene (yield 72%), m.p. 196 °C (lit.,[8] 198 °C).

Reaction of 1-methylthiourea (0.7 g) and 4,4′-dinitrobenzil (2.19 g) with NaOH (0.11 g) in aqueous ethanol (5.5 cm^3, 10%) under reflux for 2 h gave, on being cooled, crystals of 3,4-*dihydro*-4-*hydroxy*-3-*methyl*-4,5-*bis*-(4-*nitrophenyl*)*imidazole*-2-*thione* (**5**, with Ph replaced by $O_2NC_6H_4$–) which were washed with dichloromethane followed by ether (yield 40%), m.p. 221 °C, $\nu_{max.}$(mull) 1 635 (C=N) and 3 300 cm^{-1} (OH); δ_H(CDCl$_3$) 2.45 (3 H, s), 7.10 (1 H, s), and 7.90–8.30 (8 H, m); δ_C([$^2H_6$]DMSO), 27.3, 123–130, 148.9, and 180.5.

Benzoin containing 20% carbon-13 was prepared from [^{13}C]benzaldehyde (Merck, Sharpe, and Dohme) by the method of Breslow[7] and oxidised to benzil by reaction with nitric acid. The ^{13}C n.m.r. spectrum was identical with that of commercially available material, with the carbonyl signal intensity increased by a factor of 23. For the n.m.r. experiment labelled benzil (0.084 g) and thiourea (0.091 g) were dissolved in [$^2H_4$]methanol (1.5 cm^3) and the spectrum was recorded at 25 °C. Sodium hydroxide (0.008 g) in [$^2H_4$]methanol (0.5 cm^3) was added and the spectrum was recorded at hourly intervals for 16 h, using a 15 min acquisition time for each spectrum. For a more detailed examination of the first part of the reaction, spectra were taken at 15 min intervals for 150 min, using a 5 min acquisition time. A similar procedure was used for the reactions of 1-methylthiourea and 1,3-dimethylthiourea.

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References

1 A. R. Butler, I. Hussain, and K. M. Peet, *J. Chem. Soc., Perkin Trans. 2*, 1981, 320 and references therein.

2 H. Blitz, *Chem. Ber.*, 1908, 1792.

3 A. R. Butler and E. Leitch, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1972.

4 W. von Dietz and R. Mayer, *J. Prakt. Chem.*, 1968, **37**, 78.

5 P. Sohar, *Acta Chem. (Budapest)*, 1968, **57**, 425.

6 J. W. H. Smeets, F. G. M. Nule, W. Dreath, and R. J. M. Nolte, *J. Am. Chem. Soc.*, 1987, **109**, 928.

7 R. Breslow, *J. Am. Chem. Soc.*, 1958, **80**, 3719.

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