Mechanistic Studies in the Chemistry of Thiourea. Part 2.[1] Reaction with Benzil in Acid Solution

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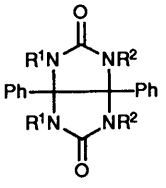
Benzil reacts with 1,3-dimethylthiourea, 1-methylthiourea, and thiourea in acid solution to give 4,5-diphenyl-4-imidazolines (**3**) which, in the cases of 1-methylthiourea and thiourea, readily form disulphides **11**. Another product of reaction is a bicyclic compound **4** in which it appears that in one thiourea moiety sulphur has been replaced by oxygen. A mechanistic pathway for the formation of **3** and **4** is proposed involving thiourea acting as a sulphur nucleophile, urea as a leaving group, and the thermal decomposition of thiiranes.

In a previous report[2] we described the products obtained by the reaction of urea and substituted ureas with benzil under acid conditions. The products obtained were found to depend upon the degree of *N*-substitution of the urea: urea itself gave **1a**, reaction with 1-methylurea produced **1b** but **2** was obtained



1 **a** $R^1 = R^2 = H$
b $R^1 = Me$, $R^2 = H$
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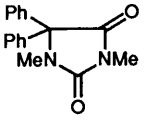

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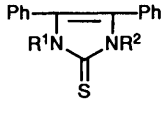
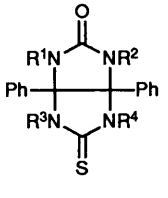
from 1,3-dimethylurea. Replacement of oxygen by sulphur in urea and related compounds often leads to significant changes in product type and reaction pathway and so we now report a parallel investigation of the reactions between benzil and a number of thioureas.

Results and Discussion

1,3-Dimethylthiourea.—Three products were isolated from the reaction of this thiourea with benzil in refluxing acidified ethanol: 1,3-dimethyl-4,5-diphenylimidazoline-2-thione (**3a**), the bicyclic compound **4a** and 1,3-dimethylurea. The formation of



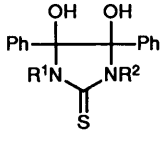
3 **a** $R^1 = R^2 = Me$
b $R^1 = H$, $R^2 = Me$



4 **a** $R^1 = R^2 = R^3 = R^4 = Me$
b $R^1 = R^2 = H$, $R^3 = R^4 = Me$
c $R^1 = R^2 = R^3 = H$, $R^4 = Me$
d $R^1 = R^2 = R^3 = R^4 = H$

4a, a bicyclic compound with a carbonyl group in one ring and a thiocarbonyl group in the other, was, at first, somewhat surprising. It could have been formed by the partial oxidative desulphurisation of the sulphur analogue of **1c** but we could obtain no evidence for the prior formation of that product, nor for the formation of **1c** itself, which should have been formed on more complete desulphurisation. Therefore, any proposed mechanism for the overall reaction must allow for the formation of **4a** as a primary product.

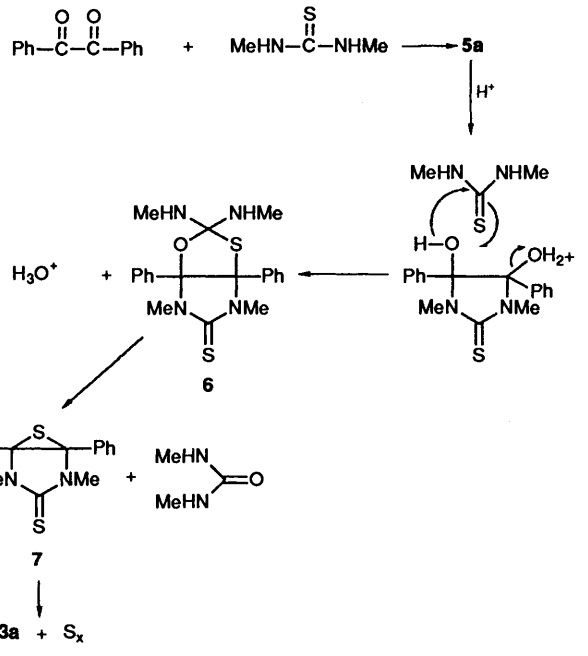
A clue to the probable mechanism for the formation of **3a** came from reports in the literature concerning the deoxygenation of epoxides by reaction with thiourea. Culvenor *et al.*[3] found that reaction of stilbene oxide with thiourea resulted in the formation of stilbene, urea and elemental sulphur. The mechanism of reactions of this type was investigated by Bordwell and Andersen[4] who proposed formation of a thiirane which then undergoes desulphurisation to give an olefinic double bond. We propose a similar mechanism for the formation of **3a** but, rather than an epoxide, the crucial intermediate is a diol (**5**). All our previous work on the reactions



5 **a** $R^1 = R^2 = Me$
b $R^1 = H$, $R^2 = Me$
c $R^1 = R^2 = H$

of urea with benzil in acid solution[2] indicate the initial formation of such a diol and so it is not unreasonable to suggest that a similar intermediate is formed in the case of 1,3-dimethylthiourea *i.e.* **5a**. Our proposed mechanism for the conversion of **5a** into **3a** is shown in Scheme 1 and is similar to that of Bordwell and Andersen.[4]

Protonation of the diol **5a** generates a good leaving group and attack by the nucleophilic sulphur of 1,3-dimethylthiourea effects elimination of water and cyclisation to give the heterocyclic bicycle **6**. Decomposition of **6**, with urea as a leaving group (a reaction for which there is considerable biological precedence) generates the thiirane **7** and 1,3-dimethylurea, one of the products isolated from the reaction mixture. The thermal instability of thiiranes is well-known and is the generally accepted explanation for the difficulties experienced in their isolation.[5] Thermal decomposition is a particularly ready reaction in the case of thiiranes with two attached aromatic groups[6] and produces elemental sulphur which normally comes out of solution spontaneously. This we never observed in spite of the low solubility of normal sulphur in organic solvents. However, when elemental sulphur is generated slowly in dilute solution, as by the reaction of sodium thiosulphate and acid, it is claimed[7] that the allotrope produced



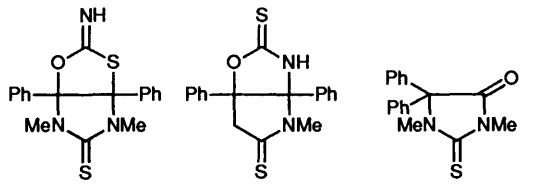
Scheme 1

is not the familiar cyclooctasulphur but cyclohexasulphur or Engel's sulphur. This allotrope is soluble in organic solvents such as toluene and dichloromethane and the formation of cyclohexasulphur may explain the absence of precipitated sulphur in our reactions. On the other hand, the apparent low solubility of the more common cyclooctasulphur in ethanol (our solvent) may be a matter of wettability,[8] which is avoided if the sulphur is produced *in situ*. Addition of water to our reaction mixtures resulted in the production of a fine precipitate of cyclooctasulphur, the identity of which was confirmed by the very characteristic mass spectrum.

Partial confirmation of this reaction scheme came from our observations on the reactivity of the isolated diol **5a**, which is proposed as an intermediate in Scheme 1. It was prepared by the base-catalysed reaction of 1,3-dimethylthiourea with benzil and, under these conditions it can readily be isolated.[1] Reaction of **5a** with 1,3-dimethylthiourea in the presence of acid gave **3a** in high yield, a result consistent with its intermediacy. The intermediacy of **6** proved more difficult to demonstrate.

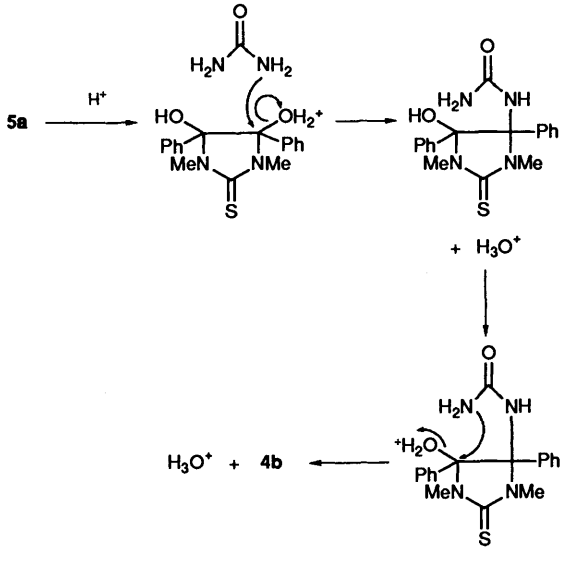
Thiourea is not the only reagent which will convert epoxide into thiiranes; potassium thiocyanate is also effective[9] and we examined its efficacy in our system. Diol **5a** was refluxed with two equivalents of potassium thiocyanate in acidified tetrahydrofuran (THF). Instead of the expected products (**3a**, potassium cyanate, and sulphur) a crystalline material of formula $C_{18}H_{17}N_3OS_2$ was obtained which we hoped would be **8a**, a close analogue of the proposed intermediate **6** in the reaction of benzil with 1,3-dimethylthiourea. An intermediate of this type was proposed by van Tamelen[9] in the reaction of potassium thiocyanate with an epoxide. However, chemical shifts in the ^{13}C NMR spectrum (Experimental) indicated a molecule with two thiocarbonyl groups and structure **8b** is probable. Intermediates of type **8a** have been trapped by reaction with 4-nitrobenzyl chloride,[10] but the free base is too unstable to isolate. The fact that our product was readily isolated does suggest that it has a different structure. Also, had it been **8a** it would have reacted further, *via* a thiirane, to give **3a**, but **8b** was resistant to further reaction. The intermediacy of **6** remains somewhat speculative but it is difficult to find a convincing alternative.

We have rationalised the formation of **3a** and of 1,3-dimethylurea, but not (so far) formation of the bicyclic product



8a **8b** **9**

4a. At the same time we have to explain why the thiohydantoin (**9**) is not formed when the corresponding hydantoin (**2**) is the only product isolated from the reaction of the oxygen analogue of **5a** with acid. The key observation is that **5a** reacts slowly with urea in the presence of acid to give an almost quantitative yield of **4b**. We conclude, therefore, that **4a** results from the reaction of diol **5a**, formed from benzil and 1,3-dimethylthiourea, with the 1,3-dimethylurea released during the formation of **3a**. The yield of the bicyclic compound is low in comparison with that obtained in reaction with urea as there is competition with the reaction of the diol with the 1,3-dimethylthiourea also present in the reaction mixture and which results in the formation of the other product of reaction **3a**. A mechanistic pathway for the reaction of urea with **5a** is shown in Scheme 2. Only a trace of

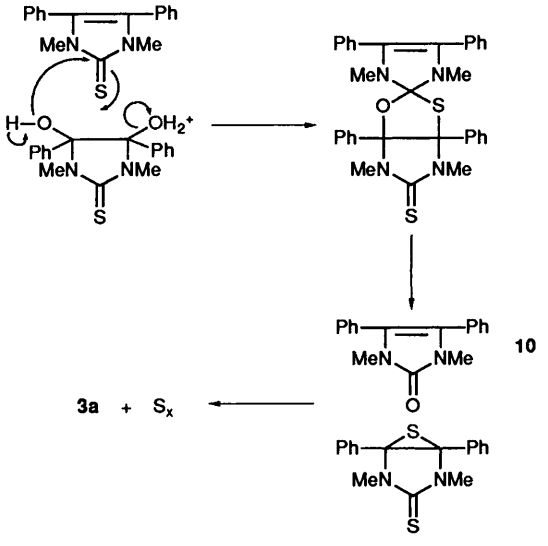


Scheme 2

bicyclic compound **4a** is obtained if 1,3-dimethylthiourea is used in place of urea in reaction with **5a**; the 1,3-dimethylurea released is a poor nitrogen nucleophile in comparison with the much stronger sulphur nucleophilicity of the unchanged 1,3-dimethylthiourea and so **3a** is the dominant product. The absence of **9** as a product, which could be produced by a mechanism parallel to that proposed previously[2] for the production of 1,3-dimethyl-5,5-diphenylhydantoin from 1,3-dimethylurea and benzil, must be a matter of competition. 1,3-Dimethylurea can act only as a nitrogen nucleophile and it is fairly weak and so rearrangement to the hydantoin, leading to formation of a stable carbonyl group, is the preferred reaction. However, 1,3-dimethylthiourea can act as a sulphur nucleophile and, as such, forms **3a** and this occurs more readily than rearrangement to a thiohydantoin. What is not clear is why **5a** reacts so readily with urea, acting as a nitrogen nucleophile to give **4a**, rather than undergoing rearrangement.

It appears that thiourea is a much stronger sulphur nucleophile than 1,3-dimethylthiourea. Reaction of **5a** in acid with equimolar amounts of thiourea and 1,3-dimethylthiourea gave only a trace of 1,3-dimethylurea, as determined by mass spectrometry; the main product was urea. The high nucleo-

philicity of sulphur in thioureas leads to an interesting product from the reaction of **3a** with **5a**, in the presence of acid, but in the absence of any added thiourea. Apparently **3a** is recovered unchanged but the other product is **10**; a possible mechanism is shown in Scheme 3. There is, in fact, an exchange of sulphur: **3a**

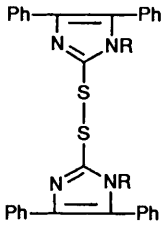


Scheme 3

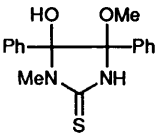
has been converted into **10** and **5a** into **3a**. In the presence of an excess of thiourea no **10** was detected. A similar mechanism explains our observation that **10** is obtained in high yield by reaction of **3a** with ethylene oxide.

During our study[1] of the reaction of 1,3-dimethylthiourea with benzil under alkaline conditions, we obtained considerable insight into the reaction mechanism by taking NMR spectra at timed intervals with a reaction mixture containing ^{13}C-enriched benzil. The success was a consequence of the accumulation of transient intermediates at reasonably high concentrations. Application of the same technique to the present reaction was far less successful as it appears that the slow step is formation of the diol **5a** and there is no accumulation of intermediates thereafter. However, it is possible to gain some insight into the stereochemistry of the reaction by this technique. The diol **5a** was prepared from ^{13}C-labelled benzil under alkaline conditions when, even in the presence of an excess of 1,3-dimethylthiourea, no further reaction occurred. The reaction mixture was then acidified and the disappearance of **5a** monitored by NMR spectroscopy. It was shown previously,[1] by use of a europium shift reagent, that **5a** produced in the base catalysed reaction is a mixture of *E* and *Z* isomers in the ratio 2:1. The signal at 95.64 ppm, corresponding to the tertiary carbon of (*E*)-**5**, disappeared more rapidly than that at 94.85 ppm due to *Z*-**5a**. For the mechanism shown in Scheme 1 it is not unreasonable that the *E* form should react more rapidly than the *Z* form. The fact that (*Z*)-**5a** does react suggests that the isomerisation of *Z* to *E* is slower than the subsequent reaction of (*E*)-(**5a**), although other explanations are possible. Disappointingly we could not detect the transient formation of **6** by NMR spectroscopy.

1-*Methylthiourea.*—Reaction with benzil follows the same route as that of 1,3-dimethylthiourea and the product is **3b** but this was not isolated. Because of the mobile hydrogen in **3b**, immediate isomerisation to the thiol occurs and this, by aerial oxidation, is converted into the disulphide **11a**. There were no signals in the ^{13}C NMR spectrum corresponding to the double bond of **3b**. No bicycle of type **4** was isolated but it seems, for reasons given later, that such a compound was formed but lost in the washing of the product. Reaction of **12**, prepared by the base catalysed reaction of 1-methylthiourea with benzil in alkaline methanol, with urea gave the bicyclic compound **4c** in high yield. This process is much faster than the analogous reaction of **5a** with urea to give **4b** by the pathway shown in Scheme 2. The reason for this is that reaction of **12** involves elimination of a molecule of methanol in place of water and the former is a better leaving group. In view of the formation of **4c** in the above reaction it seems probable that some bicyclic compound of type **4** forms on reaction of 1-methylthiourea with benzil, but we were unable to isolate it and assume that it was lost on washing. The reaction of 1-methylthiourea with benzil displays no features which are not better examplified by the reaction of 1,3-dimethylthiourea, except for the formation of a disulphide.



11 a R = Me
b R = H



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Thiourea.—Reaction is similar to that of 1-methylthiourea and **11b** was isolated after work up. The bicyclic compound **4d** was also obtained. Reaction of urea with **5c**, prepared by the base catalysed reaction of thiourea with benzil, also gave **4d**.

Conclusions

As in the acid catalysed reactions of ureas with benzil, the first product obtained from a thiourea is a diol (**5**). Subsequent reaction with more thiourea results in the formation of double bond, sulphur and a urea. The urea thus formed can react with the unchanged diol to give a bicyclic compound of type **4**. The reactions of thioureas are different from those of ureas because thioureas can act as sulphur as well as nitrogen nucleophiles.

Experimental

Materials.—All materials were reagent grade unless otherwise specified. The diols **5a–c** were prepared as described previously.[1] The preparation of ^{13}C-labelled benzil has also been reported previously.[1]

Physical Methods.—All IR spectra were taken on a Perkin Elmer 1420 spectrometer. Bruker WH-360 and CFT-20 spectrometers were used to record the NMR spectra. Time-resolved spectra were recorded on a Bruker W60 spectrometer in the SERC unit at the University of Edinburgh. All chemical shifts are relative to TMS. M.p.s were taken in a capillary and are uncorrected.

In the experiments to measure the rates of reaction of (*E*)-**5a** and (*Z*)-**5a** the main difficulty was to arrange the reaction conditions such that reaction was complete in *ca.* 20 h, in order to allow adequate time of accumulation for the NMR spectra. Rates were determined by UV spectroscopy and the appropriate conditions ascertained. Benzil enriched to 20% with ^{13}C at the carbonyl group (0.045 g) and 1,3-dimethylurea (0.089 g) were dissolved in [$^2H_6$]ethanol (2.0 cm^3) and sodium (0.005 g) was added. After 1 h it was shown by NMR spectroscopy that complete conversion into **5a** had occurred. Ethanolic HCl (0.1 cm^3) was then added and the solution maintained at 40 °C overnight. Sixteen ^{13}C NMR spectra were taken at hourly intervals with the results described above.

Synthetic Methods.—1,3-Dimethylthiourea (2 g) and benzil (2.1 g) were dissolved in ethanol. After addition of conc. HCl (2 cm^3) the mixture was refluxed for 4 h. The white precipitate was filtered off and washed with acetone to give 1,3-*dimethyl*-4,5-*diphenyl*-4-*imidazoline*-2-*thione* (**3a**), 71%, m.p. 225 °C, *m/z* 280 (M^+); $\delta_H(CDCl_3)$ 3.60 (6 H, s), and 7.30–7.40 (10 H, s); $\delta_C(CDCl_3)$ 33.3, 127.8, 128.1, 128.6, 130.2, 134.7 and 184.1 (Found: C, 72.9; H, 5.5; N, 9.9. $C_{17}H_{16}N_2S$ requires C, 72.9; H, 5.71; N, 10.0%). The filtrate was evaporated to dryness. The crude residue, when examined by MS, showed a small peak at 366 corresponding to **4a**. Recrystallisation from ethanol gave pure 1,3-dimethylurea which was identified by mixed m.p.

4,5-Dihydroxy-1,3-dimethyl-4,5-diphenyltetrahydroimidazole-2-thione (**5a**) (3.1 g) and urea (0.7 g) were suspended in THF (25 cm^3). Trifluoroacetic acid (TFA) (1 drop) was added and the mixture refluxed for 2 h. Water (10 cm^3) was added and the white solid filtered off and washed with ether to give 1,3-*dimethyl*-3a,6a-*diphenyl*-5-*thioxohexahydroimidazo*[4,5-d]*imidazol*-2(1H)-*one* (**4b**), 50%, m.p. > 310 °C; *m/z* 338 (M^+); $\delta_H(CDCl_3)$ 3.30 (6 H, s) and 7.40 (10 H, m); $\delta_C(CDCl_3)$ 31.2, 87.3, 127.2, 129.0, 128.5, 134.5, 159.6 and 183.5 (Found: C, 63.8; H, 5.3; N, 16.5. $C_{18}H_{18}N_4OS$ requires C, 63.9; H, 5.32; N, 16.5%).

Compound **5a** (0.2 g) and potassium thiocyanate (0.1 g) were dissolved in THF (5 cm^3). After addition of TFA (0.5 cm^3) the solution was refluxed for 5 h. Water (10 cm^3) was added and the whole extracted with dichloromethane (2 × 5 cm^3), dried ($MgSO_4$) and the solvent removed by evaporation to give pink crystals of 3-imino-6,8-dimethyl-1,5-diphenyl-2-oxa-4-thia-6,8-diazabicyclo[3.3.0]octane-7-thione (**8a**) 80%, m.p. 188 °C; *m/z* 355.08127 (M^+ 355.08129); $\delta_H(CD_3COCD_3)$ 3.30 (3 H, s) 3.40 (3 H, s) and 7.20–7.40 (10 H, m); $\delta_C(CD_3COCD_3)$ 31.7, 32.1, 90.6, 109.7, 127.0, 128.6, 129.0, 130.0, 131.0, 184.5 and 188.3.

1,3-Dimethyl-4,5-diphenyl-4-imidazoline-2-thione (**3a**) (0.2 g) and ethylene oxide (0.5 g) were dissolved in THF (10 cm^3) and stirred at room temperature for 2 h. The solvent and excess of ethylene oxide were removed by evaporation and the residue washed with acetone to give 1,3-*dimethyl*-4,5-*diphenyl*-4-*imidazolin*-2-*one* (**10**), 70%, m.p. > 330 °C (lit.,[11] 330–335) *m/z* 264.12566 (M^+ 264.126 25).

1-Methylthiourea (1.8 g) and benzil (2.1 g) were dissolved in ethanol (8 cm^3). After addition of conc. HCl (2 cm^3) the mixture was refluxed for 3 h, cooled, the white solid filtered off, and washed with a large volume of dichloromethane to give the *disulphide* **11a**, 63%, m.p. 286 °C; $\delta_H([^2H_6])$ 3.40 (3 H, s) and 7.30–7.40 (10 H, m); $\delta_C([^2H_6]DMSO)$ 31.8, 126.4, 127.5, 128.4, 128.9, 129.2, 129.3, 129.4 and 130.7 (Found: C, 72.5; H, 4.96; N, 10.7. $C_{32}H_{28}N_4S_2$ requires C, 72.5; H, 4.90; N, 10.6%).

Thiourea (1.52 g) and benzil (2.1 g) were dissolved in ethanol (8 cm^3). After addition of conc. HCl (2 cm^3) the mixture was refluxed for 4 h and then cooled. After addition of water a precipitate was obtained and washed with acetone. The residue was refluxed with ethanol (200 cm^3), the insoluble fraction removed and shown to be **11b**, 55%, m.p. 272 °C (lit.,[12] 280); *m/z* 251 ($M^+/2$), IR spectrum identical with that published; [13] $\delta_H([^2H_6]DMSO)$ 7.30–7.40 (10 H, m); $\delta_C([^2H_6]DMSO)$ 125.1, 127.8, 128.4, 128.9 and 137.7. The ethanol filtrate was concentrated and gave a white crystalline material which was shown to be **4d** by comparison (m.p., IR) with the material prepared below.

4,5-Dihydroxy-4,5-diphenyltetrahydroimidazole-2-thione (**5c**) (0.23 g) and urea (0.12 g) was suspended in toluene. After addition of TFA (0.1 cm^3) the mixture was stirred at room temperature for 10 min. The white solid was filtered off and washed with water (20 cm^3) and acetone (10 cm^3) to leave 3a,6a-*diphenyl*-5-*thioxohexahydro*[4,5-d]*imidazol*-2-*one* (**4d**), 90%, m.p. > 330 °C, *m/z* 310 (M^+); ν_{max}/cm^{-1} (mull) 1660 (NH) and 3160 (C=O) (Found: C, 61.8; H, 4.43; N, 18.0. $C_{16}H_{14}N_4OS$ requires C, 61.9; H, 4.54; N, 18.1%.)

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