Mechanistic Studies in the Chemistry of Thiourea. Part 3.[1] Acid-catalysed Reaction with 1-Phenylpropane-1,2-dione and Related Compounds

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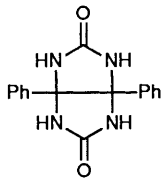
Reaction of thiourea with 1-phenylpropane-1,2-dione in the presence of acid results in formation of 4,4'-methylenebis(5-phenyl-4-imidazoline-2-thione) **11c**. A mechanism of reaction is proposed, based on intermediates isolated from this and related reactions and on the detection of intermediates by ^{13}C NMR spectroscopy using labelled reactants. With 1,3-dimethylthiourea the reaction ceases on formation of 1-(1,3-dimethyl-5-phenyl-2-thio-4-imidazolinyl)methyl-1,3-dimethylthiourea **4a** and the analogue of this derived from thiourea is proposed as an intermediate in the formation of **11c**. The two isomeric *N*-methyl analogues (**11a** and **11b**) of **11c** are obtained on reaction of 1-phenylpropane-1,2-dione with 1-methylthiourea. 1-Phenylbutane-1,2-dione and 1,3-diphenylpropane-1,2-dione react similarly, but 3-methyl-1-phenylbutane-1,2-dione does not react at all.

In part 2[1] we described the products obtained in the acid-catalysed reactions of thiourea and *N*-alkylthioureas with benzil (1,2-diphenylethane-1,2-dione). Reaction occurs at both reactive centres *i.e.* the two carbonyl groups. Replacing one phenyl group by a methyl group introduces a third reactive centre with the possibility of more complex products. This was found to be the case in the reaction of urea and *N*-alkylureas with 1-phenylpropane-1,2-dione.[2]



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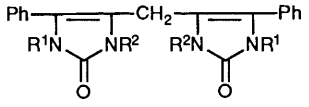
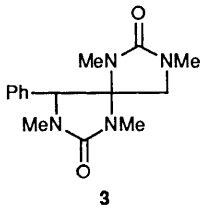


2 a; R^1 = Me, R^2 = H
b; R^1 = H, R^2 = Me
c; R^1 = R^2 = Me



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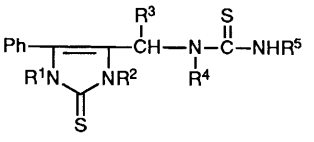
Urea itself gives **1**, reaction with 1-methylurea gives **2a** and/or **2b**, while 1,3-dimethylurea gives the spiro-compound **3**. In previous, related studies we found[1,3] that thioureas may give products which are not analogous to those obtained from ureas and we thought that this might be the case here. Also, it was hoped that the application of ^{13}C NMR spectroscopy, used successfully in our study of the mechanism of reaction of benzil with thioureas under alkaline conditions,[3] might provide insight into the mechanisms operative in acid-catalysed reactions.

Results and Discussion

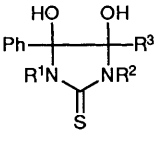
1,3-*Dimethylthiourea*.—Acid-catalysed reaction of 1-phenylpropane-1,2-dione with at least two equivalents of 1,3-dimethylthiourea gave **4a** as the only isolable product. Elemental analysis indicated a formula of $C_{15}H_{20}N_4S_2$; there was a molecular ion peak at 320 in the mass spectrum, and the IR spectrum showed an N–H stretch. There were four signals



4 a; R^1 = R^2 = R^4 = R^5 = Me, R^3 = H
b; R^1 = R^2 = R^3 = R^4 = R^5 = Me,
c; R^1 = R^2 = R^4 = R^5 = Me, R^3 = Ph
d; R^1 = R^2 = R^3 = R^4 = R^5 = H

corresponding to non-equivalent methyl groups in the ^1H NMR spectrum, as well as one corresponding to an isolated methylene group. On treatment with methyl iodide and silver oxide (Purdie's reagent) the N–H stretching frequency was lost as well as one, but only one, of the thione signals in the ^{13}C NMR spectrum. It was replaced by a new signal corresponding to a methyl thioether. It is known[3] that Purdie's reagent will not methylate 1,3-dimethyl-4,5-diphenyl-4-imidazoline-2-thione but will methylate the sulfur of thiourea. All these data are consistent with structure **4a**.

When only one equivalent of 1,3-dimethylthiourea was used the product obtained was the diol **5a**, which was obtained as



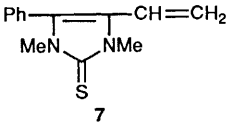
5 a; R^1 = R^2 = R^3 = Me
b; R^1 = R^2 = Me, R^3 = CH_2Ph
c; R^1 = R^2 = H, R^3 = CH_2Ph
d; R^1 = R^2 = H, R^3 = Me

a mixture of diastereomers. They were distinguished by using a europium shift reagent, the *Z*-isomer coordinating more strongly because of its ability to act as a bidentate ligand. The two aminol signals of the *Z*-isomer had molar sensitivities to the shift reagent in chloroform of 8.3 and 12.3, while those of the *E*-isomer were only 2.48 and 2.31. Compound **5a** was also formed by reaction of 1-phenylpropane-1,2-dione with 1,3-dimethylthiourea under neutral conditions with a *Z*:*E* ratio of 13:1. On addition of acid the ratio fell to 3:1. This suggests that in the neutral reaction there is kinetic control of the product but addition of acid provides a route for conversion of *Z* into *E* and the isomer ratio is then thermodynamically controlled. It is

probable that, in the formation of **5a**, initial attack occurs at the carbonyl group adjacent to the phenyl to give **6**. Models of **6** show little sign of stereoelectronic factors which might favour formation of *Z*-**5a** but it is possible to rationalise the result by considering a hydrogen bond between the hydroxy and keto groups of **6** which would hold it in a configuration where nucleophilic attack by the pendant amino group on the carbonyl centre gave the *Z* isomer exclusively.

In the presence of acid **5a** reacts with 1,3-dimethylthiourea to give **4a**, which suggests that **5a** is an intermediate in the formation of **4a** from dione and 1,3-dimethylthiourea. Although **5a** parallels the first product obtained by the reaction of benzil with 1,3-dimethylurea,[4] subsequent reaction is possible by loss of a proton from the methyl group.

The influence of the alkyl group upon the course of the reaction appears to be small. Thus, 1,3-dimethylthiourea reacts with 1-phenylbutane-1,2-dione in the presence of acid to give **4b**. This reacts thermally, in the presence of acid, by loss of 1,3-dimethylthiourea to give **7**. The alkyl group in the dione may,



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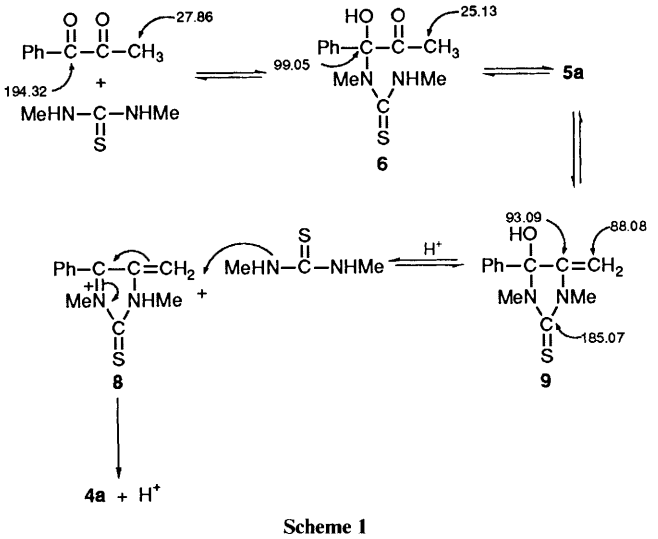
however, affect the reaction for steric reasons. Thus, the acid-catalysed reaction of an excess of 1,3-dimethylthiourea with 1,3-diphenylpropane-1,2-dione to give **5b** and then **4c** is much slower than that of 1-phenylpropane-1,2-dione. Compound **4c** does not readily eliminate 1,3-dimethylthiourea to give an olefinic side chain. A much bulkier group, as in 3-methyl-1-phenylbutane-1,2-dione, prevents reaction altogether.

The isolation of intermediates mentioned already, and the ^{13}C NMR studies to be described shortly, are best understood in terms of the mechanism shown in Scheme 1. The key steps



Scheme 1

are acid-catalysed loss of two molecules of water from **5a** to give **8**, and the subsequent addition of a second molecule of 1,3-dimethylthiourea to produce **4a**.

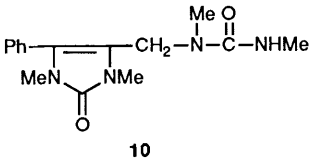
The course of the reaction was investigated by the ^{13}C NMR technique described previously,[3] with the dione labelled at the 1- or 3-positions. In all experiments the reactants were dissolved in THF in an NMR tube, the NMR spectrometer 'shimmed' to give the best possible resolution, and the reaction initiated by addition of trifluoroacetic acid (TFA). As reaction occurs even in neutral solution, some **5a** was present before acid was added. Three runs will be described but preliminary studies, some with unlabelled material, were necessary to optimise the reaction conditions to give suitable rates of reaction.

In experiment (i) material labelled with 20% carbon-13 at the 1-position ($^{13}C{=}O$) was used and in (ii) material was labelled with 25% carbon-13 at the 3-position ($^{13}CH_3$). Spectra were recorded every hour, with a 15 min acquisition time, over 16 h and in (ii) the DEPT 135 pulse sequence was used. This increased the sensitivity of the experiment and also indicated the number of hydrogens attached to the labelled centre in the reaction intermediates. In experiment (iii) a sample of **5a** with no label was allowed to react with a slight molar excess of 1,3-dimethylthiourea. The ^{13}C NMR spectra were taken every 90 min with a 30 min acquisition time. In (i) and (ii) some signals corresponding to unlabelled carbons were also observed. If plots of intensity against time for two or more signals were parallel it was assumed that the signals arose from the same molecule or from two molecules in rapid equilibrium with each other.

In (i) and (ii) the signals at 194.32 and 27.86 ppm (see Scheme 1) showed a steady decline with time. In (i) a new signal at 99.05 ppm was observed even before acid was added. This is not the chemical shift of the aminol carbons of **5a** and must be an intermediate between reactants and **5a**. In experiment (ii) a new signal at 25.13 ppm formed at a similar rate. These results (a large change in the chemical shift of the carbonyl and only a small change in that of the methyl) are consistent with formation of **6**. In (iii) we were able to look at the second half of the reaction leading to formation of **4a**. There was an immediate appearance of small signals due neither to the isomers of **5a** nor to 1,3-dimethylthiourea. The shifts suggest the presence of a thione (185.07), a phenyl group, an aminol centre (93.09), two *N*-methyl groups (32.79 and 30.70) and, most significantly, a methylene group (88.08 ppm). These signals are consistent with the formation of **9** by the dehydration of **5a**. This assignment was confirmed by looking for the same signals in the spectra obtained from the labelled reactants in (i) and (ii). In the former the label was fairly rapidly converted into the aminol (93.09) after addition of acid, reached a maximum after 1 h, and then fell steadily as the concentration of **4a** rose. In (ii) a strong methylene signal, inverted by DEPT, was observed at 88.08 ppm. All the results confirm the formation of **9**. The penultimate step, we suggest, is acid-catalysed elimination of water from **9** to give **8** and then attack by a second molecule of 1,3-dimethylthiourea as shown in Scheme 1. We could obtain no NMR signals to confirm the formation of **8** but this may mean that it is formed at concentrations below the limit of detection.

1,3-*Dimethylurea*.—One purpose of this research was to compare products obtained, under identical conditions, from ureas and thioureas. The work described above showed that the product obtained from 1,3-dimethylthiourea is different from that we obtained with 1,3-dimethylurea[2] but we felt it would be valuable to confirm that **3** is the *only* product obtained in the latter reaction.

1,3-Dimethylurea was refluxed with 1-phenylpropane-1,2-dione in acidified THF and the product analysed by preparative TLC. It was found to contain three products. As well as that found previously, *i.e.* **3**, two other products were identified: **2c** and **10**. It would seem likely that **10** is an intermediate *en route*



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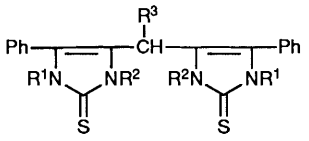
to **3** and **2c** and that, for some reason, with 1,3-dimethylthiourea

the reaction does not proceed beyond this point. We will return to the mechanism of reaction later.

1-*Methylthiourea.*—The acid-catalysed reaction of 1-phenylpropane-1,2-dione with 1-methylthiourea gave a mixture of **11a** and **11b** and parallels the reaction of 1-methylurea. Both **11a**



11a; $R^1 = Me, R^2 = R^3 = H$
b; $R^1 = R^3 = H, R^2 = Me$
c; $R^1 = R^2 = R^3 = H$
d; $R^1 = R^2 = H, R^3 = Me$
e; $R^1 = R^2 = H, R^3 = Ph$

and **11b** can undergo tautomerism to give a thiol group in each ring and, during work-up, oxidation to give disulfide linkages occurs. We think, for steric reasons, that this is an intermolecular rather than an intramolecular reaction but could not obtain mass spectral evidence for the dimer, even by FAB MS. This may be because of low solubility. Formation of the disulfide was detected because the highest peak in the MS was two units below the molecular weight of **11a** or **11b**, consistent with cleavage of the two S–S bonds during fragmentation. In the reaction of thiourea with dione in glacial acetic acid–HCl, the oligomer formed by condensation of formaldehyde and thiourea was detected by ^{13}C NMR but could not be detected when THF–TFA was used as solvent, although the sulfur-containing products were the same. Further discussion of the mechanism of formation of **11a** and/or **11b** will be delayed until the results for thiourea have been described.

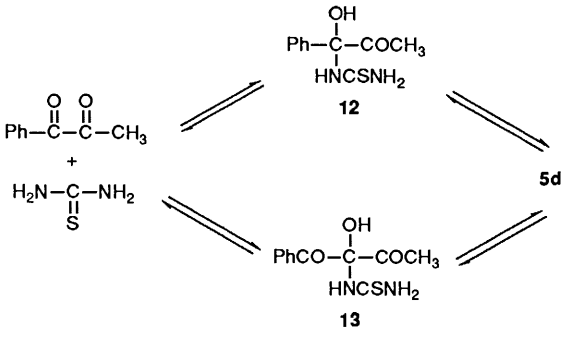
Thiourea.—The sole isolable product from the reaction of thiourea with 1-phenylpropane-1,2-dione was **11c**, formed formally by condensation of two molecules of dione with two molecules of thiourea and *loss of one carbon.* The compound was characterised fully and, in particular, the ^{13}C NMR spectrum had a simplicity consistent with a symmetrical molecule possessing an isolated methylene group, unsplit, and inverted in DEPT. Reaction of 1,3-dimethylurea with butane-2,3-dione gives a comparable product[5] and, in that case, the structure was confirmed by X-ray crystallography.[6] Also, in that case, evidence was obtained to show that the other product of reaction was formaldehyde.[5]

As with **11a** and **11b**, tautomerism of **11c** can occur to give two thioimidazole rings. For this reason, the ^{13}C NMR spectrum does not contain signals characteristic of a carbon–carbon double bond. During work-up oxidation to a disulfide occurs; the sulfur–sulfur bond may be inter- or intra-molecular.

TFA was found to be an effective catalyst in a number of solvents for the formation of **11c**. Squaric acid * is less effective. HCl in glacial acetic acid is another good system. Aqueous acids do not work and this suggests that acid-catalysed dehydration occurs. Reaction of 1-phenylbutane-1,2-dione gave, rather than a single product, a mixture from which **11e** was separated and characterised. The other components were difficult to obtain pure but examination of the crude product by IR, ^1H, and ^{13}C NMR spectroscopy suggested that **4c** and **5c** were present. We were able to detect benzaldehyde and benzoic acid by application of GC–MS to the water-soluble products of reaction. Presumably benzoic acid was formed by oxidation of benzaldehyde during work-up. Reaction of thiourea with 1-phenylbutane-1,2-dione and with 1,3-diphenylpropane-1,2-dione gave **11d** and **11e** respectively.

In neutral conditions thiourea reacts with 1-phenylpropane-1,2-dione to give **5d**. On addition of acid this is converted into **11c**, suggesting that **5d** is an intermediate in the acid-catalysed production of **11c**.

Further insight into the mechanism of formation of **11c**, a somewhat remarkable reaction, was gained using dione labelled with ^{13}C at the 1- and 3-positions and observing the progress of the reaction by ^{13}C NMR spectroscopy. After a number of preliminary runs, some using ^1H NMR spectroscopy, conditions giving a reaction of suitable rate were established. Difficulty was experienced in finding a suitable deuteriated solvent in which thiourea is soluble; aqueous THF was found to be acceptable but not ideal. Three runs will be reported in detail: (iv) with dione labelled at the 1-position (the carbonyl) and a slight excess of thiourea, the reaction was monitored by taking a spectrum every hour with an acquisition time of 15 min, (v) with dione labelled at the 3-position (the methyl group) and a slight excess of thiourea, monitoring the reaction by use of the DEPT 135 pulse sequence, and (vi) a sample of unlabelled **5d** was prepared and its reaction on addition of acid was monitored by taking an NMR spectrum every 90 min with an acquisition time of 30 min. In all experiments the reagents, apart from the acid, were placed in a tube, the instrument 'shimmed' to give optimum operating conditions, and a spectrum recorded. The results are best understood by reference to the proposed mechanisms shown in Schemes 2 and 3.

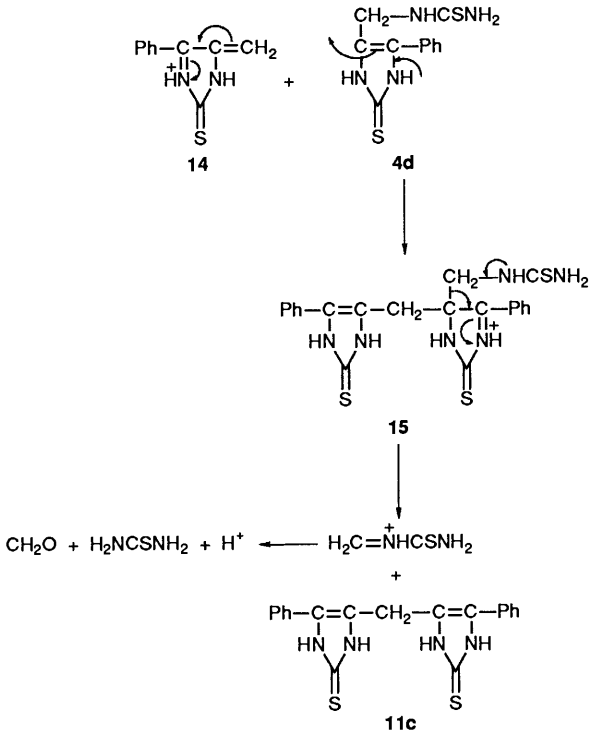


Scheme 2

The equilibria shown in Scheme 2 were established even in neutral conditions. In run (iv) the carbonyl label gave new signals at 99.05 and 201.15 ppm corresponding to **12** and **13**. In run (v) the methyl label gave new signals at 28.95 and 26.74 ppm, again consistent with formation of **12** and **13**. With time there was complete conversion in both cases into **5d** with four signals derived from the two labels at 22.17, 25.85, 94.93 and 96.69 ppm, as expected for the formation of both the *E* and *Z* forms of **5d**. Addition of acid caused no immediate change in the relative sizes of these signals, suggesting that the equilibrium mixture is thermodynamically, rather than kinetically, controlled. The most reasonable mechanism for interconversion of the two isomers is dehydration across the carbon–nitrogen bond and addition in the opposite sense. Experiment (vi) indicated that, in the absence of acid, **5d** does not decompose significantly into dione and thiourea.

On addition of acid, in both (iv) and (v), there was a dramatic fall in signals from the labels in **5d** to one tenth of their equilibrium values; they continued to decrease with time until they were below the limit of detection. The signals from **12** and **13** behaved in a similar way and those observations lead to the rather trivial conclusion that **12** and **13** are intermediates in the formation of **5d**. In both runs (iv) and (v) signals at 131.73 and 28.52 ppm from **11c**, derived from the labelled atoms in **5d**, rose rapidly during the first hour but more slowly after that. This

* 3,4-Dihydroxycyclobutane-1,2-dione.



Scheme 3

parallelled the disappearance of the labelled signals in **5d** and is consistent with **5d** being an intermediate *en route* from reactants to **11c**. No new, transient signals appeared and so, rather disappointingly, there is no substantial accumulation of any intermediates between **5d** and **11c**. Surprisingly, we noted that formation of **11c** from pre-formed **5d** was slower than from thiourea and 1-phenylpropane-1,2-dione. One inference is that **11c** is formed, not from two molecules of **5d**, but by reaction of one molecule of **5d** with another species, so that **5d** is not all that is required to generate **11c**. At the same time it was noted that **11c** did not appear until **5d** had shown significant reversion to dione and thiourea, after addition of acid. Signals corresponding to the dione were observed but not one corresponding to thiourea. These observations lead us to propose the mechanism shown in Scheme 3. Without direct evidence it is difficult to be certain, but the scheme is consistent with such evidence as is available. We suggest that reaction occurs between **14** and **4d**. Intermediate **14** is formed by the acid-catalysed elimination of water from **5d** and the methylated equivalent [*i.e.* **8**] appeared in Scheme 1. As suggested in Scheme 1, some of this reacts with thiourea to give **4d** to give the second molecule required for the formation of **11c**. Hence the need for reversion of **5d** to give thiourea in run (vi) before **11c** formed. Condensation occurs with formation of **15** which, on elimination of CH_2=NH–$CSNH_2$, gives the observed product **11c**. A small methylene signal at 31.73 ppm was detected in (v), consistent with formation of **14**. This mechanism avoids some of the difficulties in a previously proposed mechanism [3] for the analogous reaction of 1,3-dimethylurea with butane-2,3-dione.[5]

Conclusions

Initially we thought that the reactions of thioureas might be more complex than those of ureas because the former may act as sulfur as well as nitrogen nucleophiles. This has not been borne out by experiment. As far as the reactions of 1-phenylpropane-1,2-dione are concerned it is the presence of the extra reactive centre (the methyl group) which leads to complex reactions and this is the same for both ureas and thioureas. This is the last paper in this series.

Experimental

Instrumentation.—This has been described previously.[3] The number of attached hydrogens in the ^{13}C NMR spectra was determined by the DEPT 135 pulse sequence.

Materials.—All starting materials were reagent grade unless otherwise stated. Labelled materials were obtained from Merck, Sharp and Dohme. 1-Phenylpropane-1,2-dione was made by a literature preparation.[7] 1-Phenylbutane-1,2-dione was made by bubbling HCl through a solution of butyrophenone (1.34 g) in diethyl ether (75 cm^3) whilst amyl nitrite (12.3 g) was added dropwise over 1 h. The mixture was allowed to stand overnight and the oxime extracted with aqueous NaOH (1 mol dm^{-3}: 4 × 50 cm^3). The extract was cautiously acidified with H_2SO_4 until a pink precipitate formed and then further conc. H_2SO_4 (40 cm^3) was added. The mixture was steam distilled over 7 h and the distillate extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and the solvent removed to leave the dione in 65% yield. It was characterised by its ^{13}C NMR spectrum. 1,3-Diphenylpropane-1,2-dione was prepared by the method of Cromwell [8] and characterised by its ^1H and ^{13}C NMR spectra, which indicated a mixture of the keto and enol forms.

2-Phenyl-1,3-dithiane was prepared by the method of Seebach *et al.*[9] The dithiane (3.3 g) was dissolved in THF (100 cm^3) and cooled to −70 °C under dry nitrogen when *tert*-butyllithium in hexane (1.5 mol dm^{-3}, 15 cm^3) was added and the mixture allowed to warm to −30 °C. After 30 min the mixture was again cooled to −70 °C and 1-iodo-2-methylpropane (1.9 g) in THF (25 cm^3) added dropwise over 15 min. The mixture was warmed to room temperature and allowed to stand overnight under nitrogen. The dithiane moiety was oxidised with claycop [10] (see below) and the resulting ketone oxidised to the diketone by the method of Kornblum and Frazier [11] to give 3-methyl-1-phenylbutane-1,2-dione, 72%, b.p. 62 °C at 1 mmHg (lit.,[12] 58–60 °C); $\delta_H(CDCl_3)$ 0.70 (6 H, d), 2.00 (1 H, septet) and 7.50–8.00 (5 H, m); $\delta_C(CDCl_3)$ 22.81, 25.15, 128.20, 128.66, 129.01, 132.88, 188.62 and 199.47.

Preparation of Labelled Compounds.—The main problems here were finding routes with sufficiently high yields and which used commercially available labelled starting materials. Much effort was expended on the exploration of syntheses which were later abandoned.

1-[^{13}C]-1-*Phenylpropane*-1,2-*dione.* 1-[^{13}C]-1-phenylpropan-1-one (propiophenone) (0.60 g) was dissolved in a 1:1 mixture of CH_2Cl_2 and ethyl acetate and stirred under nitrogen. Copper(II) bromide (2.70 g) was added slowly and the mixture refluxed under nitrogen for 3 h. The copper(I) bromide was filtered off and washed with CH_2Cl_2. The solvent in the filtrate and washing was removed by evaporation and the residue (a bromoketone) immediately dissolved in acetonitrile (5 cm^3). Silver nitrate (1.70 g) was added and the mixture stirred for 36 h while protected from light. The solid was filtered off and the solvent removed by evaporation. The residue was dissolved in DMSO (25 cm^3) and, after addition of sodium acetate (0.49 g), the mixture was stirred for 25 min, poured into brine (250 cm^3), and extracted with 40–60 light petroleum (100 cm^3).[12] The extract was washed with brine (250 cm^3), dried with $MgSO_4$, and the solvent removed by evaporation. The diketone was firstly purified by column chromatography (silica/4:1 light petroleum–dichloromethane). The product had IR and ^{13}C NMR spectra identical with that of commercial 1-phenylpropane-1,2-dione and was shown to be pure by TLC.

3-[^{13}C]-1-*Phenylpropane*-1,2-*dione.* 2-Benzyl-1,2-dithiane

was prepared from 1,3-dithiane and benzyl bromide by the method of Corey and Erickson.[13] A sample (4.8 g) was dissolved in dry THF under nitrogen and cooled to −75 °C and after dropwise addition of butyl lithium in hexane (1.7 mol dm^{-3}, 15 cm^3), the mixture was warmed to −30 °C and kept at that temperature for 30 min. After cooling to −70 °C [^{13}C]methyl iodide (30.0 g) in THF (25 cm^3) was added dropwise. The mixture was warmed to room temperature, allowed to stand overnight, and the THF removed by evaporation. Water (100 cm^3) was added, the 2-benzyl-2-methyl-1,3-dithiane extracted with CH_2Cl_2 (3 × 50 cm^3), and the extract dried ($MgSO_4$). The dithiane was oxidised to phenylacetone by stirring with claycop[10] (28 g) for 20 h at room temperature. The spent reagent was removed by filtration. The next step was oxidation by the method of Kornblum and Frazier.[11] After addition of ethyl acetate (150 cm^3) and copper(II) bromide (10 g) to the filtrate, the mixture was refluxed under nitrogen for 4 h. The copper(I) bromide was filtered off, the filtrate dried ($MgSO_4$) and the solvent removed by evaporation to give 1-bromo-1-phenylpropan-2-one. The product was dissolved in acetonitrile (40 cm^3) and, after addition of silver nitrate (5–7 g), stirred at room temperature for 36 h. After removal of silver bromide and acetonitrile the residue was taken up in CH_2Cl_2 (50 cm^3), washed with water (100 cm^3), dried ($MgSO_4$) and the solvent removed. The residue was dissolved in DMSO (100 cm^3), sodium acetate (0.7 g) added, the whole stirred for 30 min at room temperature, and then poured into brine (250 cm^3). After extraction with 40–60 light petroleum (3 × 50 cm^3), the organic solution was washed with water (300 cm^3), dried ($MgSO_4$), and the solvent removed. Final purification was effected by distillation using a Kugelrohr system to give 3-[^{13}C]-1-phenylpropane-1,2-dione in 45% yield, showing only one spot by TLC.

Synthetic Procedures.—In some instances obtaining analytically pure samples proved impossible as the products were too insoluble to recrystallise and they were identified by spectroscopic means.

1-Phenylpropane-1,2-dione (0.74 g; 0.005 mol) and 1,3-dimethylthiourea (1.10 g; 0.012 mol) were dissolved in THF (5 cm^3), 2 drops of TFA added, and the mixture refluxed for 6 h. Aqueous $NaHCO_3$ (1 mol dm^{-3}; 10 cm^3) was added and the mixture stirred vigorously for 30 min. The white precipitate was filtered off and washed with water (25 cm^3) and diethyl ether (25 cm^3) to give 1,3-dimethyl-1-(1,3-dimethyl-2-thio-5-phenyl-4-imidazolinyl)methylthiourea (**4a**), 51%, m.p. 181 °C, *m/z* 320 (M^+); ν_{max}/cm^{-1} 3323 (NH); δ_H($CDCl_3$) 2.73 (3 H, s), 3.20 (3 H, s), 3.57 (3 H, d), 3.73 (3 H, s), 5.40 (2 H, s), 5.90 (1 H, broad) and 7.60 (5 H, m); δ_C($CHCl_3$) 33.14, 33.19, 33.34, 33.46, 45.89 (CH_2), 122.14, 127.19, 129.22, 130.37, 130.46, 163.20 and 183.25 (Found: C, 55.9; H, 6.10; N, 17.2. $C_{15}H_{20}N_4S_2$ requires C, 56.2; H, 6.29; N, 17.4%).

1-Phenylpropane-1,2-dione (1.48 g; 0.01 mol) and 1,3-dimethylthiourea (1.08 g; 0.01 mol) were dissolved in aqueous THF (7 cm^3; 5:2 v/v) and stirred for 2 days at room temperature. Water (25 cm^3) was added and the THF removed by evaporation. The residue was extracted with CH_2Cl_2 (2 × 20 cm^3) and the extract washed with water (15 cm^3), dried ($MgSO_4$), and the solvent removed by evaporation. The product was a mixture of the *Z* and *E* forms of 4,5-dihydroxy-1,3,4-trimethyl-5-phenyltetrahydroimidazole-2-thione (**5a**) as a red oil which solidified on prolonged standing, 95%, *m/z* 206 ($M^+ - H_2O$), ν_{max}/cm^{-1} 3290 and 3420 (OH); δ_H([$^2H_8$]THF) 1.00 (3 H, s), 2.95 (3 H, s), 3.10 (3 H, s), 3.30 (3 H, s), 4.56 (2 H, broad) and 7.20–7.30 (5 H, m); δ_C([$^2H_8$]THF) 2.17, 25.46, 29.12, 29.84, 30.56, 87.24, 90.87, 91.00, 93.98, 126.60, 128.59, 128.93, 136.74 and 182.07.

5a (0.50 g) and 1,3-dimethylthiourea (0.42 g) were dissolved in THF (10 cm^3). After addition of TFA (1 drop) the mixture was refluxed for 3 h. Water (25 cm^3) was added, the THF removed by evaporation, and the residue extracted with CH_2Cl_2. The extract was washed with water (10 cm^3), dried ($MgSO_4$), and the solvent removed by evaporation to give **4a**, identified by comparison of its IR spectrum with that of a previous sample.

1-Phenylbutane-1,2-dione (0.89 g) and 1,3-dimethylthiourea (1.15 g) were dissolved in THF (10 cm^3) and TFA (2 drops) added. After refluxing for 4 h and cooling, aqueous $NaHCO_3$ (1 mol dm^{-3}; 25 cm^3) was added and the mixture stirred vigorously for 30 min. The solution was extracted with CH_2Cl_2 and the extract washed with water (25 cm^3), dried ($MgSO_4$), and the solvent removed to give a deep yellow oil. The oil was dissolved in 40–60 light petroleum containing 15% acetone. On standing white crystals appeared and were filtered off and washed with light petroleum to give 4-ethylene-1,3-dimethyl-5-phenyl-4-imidazoline-2-thione (**7**), 22%, m.p. 113 °C, *m/z* 230 (M^+); no NH bonds in the IR spectrum; δ_H($CDCl_3$) 3.50 (3 H, s), 3.82 (3 H, s), 5.20 (1 H, d), 5.35 (1 H, d of d) and 7.30–7.45 (5 H, m); δ_C($CDCl_3$) 33.25, 33.47, 117.03, 122.51, 124.90, 128.07, 128.67, 129.00, 129.37, 130.39 and 162.92. Solvent was removed from the filtrate by evaporation to yield a gum which, on repeated washing with light petroleum, gave white crystals of 1-[1-(1,3-dimethyl-5-phenyl-2-thio-1,2-dihydroimidazolyl)ethyl]-3-methylthiourea (**4b**), 20%, m.p. 189 °C, *m/z* 334 (M^+), ν_{max}/cm^{-1} 3350 (NH); δ_H($CDCl_3$) 0.85 (3 H, d), 2.73 (3 H, s), 2.97 (3 H, d), 3.14 (3 H, s), 3.26 (3 H, s), 6.62 (1 H, q) and 7.60 (5 H, m); δ_C($CDCl_3$) 15.79, 30.29, 31.96, 32.22, 32.69, 51.68, 124.43, 128.99, 129.55, 130.38, 131.37, 162.14 and 181.65.

Reaction of 4-methyl-1-phenylbutane-1,2-dione (0.8 g) and 1,3-dimethylthiourea (1.20 g) in THF (10 cm^3) acidified with TFA gave, after the normal workup, only unchanged starting material as confirmed by IR spectroscopy.

1,3-Diphenylpropane-1,2-dione (0.45 g) and 1,3-dimethylthiourea (0.41 g) were dissolved in THF (10 cm^3), 1 drop TFA added, and the mixture refluxed for 90 min. Aqueous $NaHCO_3$ (1 mol dm^{-3}; 25 cm^3) was added and the mixture stirred vigorously for 30 min. The mixture was extracted with CH_2Cl_2 (10 cm^3) and the extract washed with water, dried ($MgSO_4$) and the solvent removed by evaporation to leave a red oil which proved impossible to separate into its components but was thought to be a mixture of **4c** and **5b** because of substantial *m/z* peaks at 396 [M^+ for **4c**] and 310 [$M^+ - H_2O$ for **5b**] and signals in the ^{13}C NMR spectrum at 60.86 (CH of **4c**) and 93.16 (quarternary aminol of **5b**).

Reaction of 1-phenylpropane-1,2-dione (1.48 g) and 1,3-dimethylurea (1.8 g) in the usual manner gave a yellow oil which solidified on standing. By the use of preparative TLC (silica with CH_2Cl_2 as solvent) three products were separated and identified: 1,3-dimethyl-5-phenyltetrahydroimidazole-4-spiro-4′-(1′,3′-dimethyltetrahydroimidazole)-2,2′-dione (**3**), m.p. 148 °C (lit.,[2] 148 °C), *m/z* 288 (M^+), and ^{1}H and ^{13}C NMR spectra were identical with those observed previously;[2] 4,4′-methylenebis(1,3-dimethyl-5-phenyl-4-imidazolin-2-one) (**2c**), *m/z* 388.190 08 (M^+ for $C_{23}H_{24}O_2N_4$ 388.190 12); δ_H($CDCl_3$) 2.70 (6 H, s), 3.43 (6 H, s), 3.83 (2 H, s) and 7.6 (10 H, m); δ_C($CDCl_3$) 19.48 (CH_2), 29.17, 30.47, 114.44, 121.28, 128.47, 129.55, 129.65, 130.05 and 153.39; 1,3-dimethyl-1-(1,3-dimethyl-2-oxo-5-phenyl-4-imidazolinyl)methylurea (**10**), *m/z* 288.158 75 (M^+ for $C_{15}H_{20}O_2N_4$ 288.158 80), ν_{max}/cm^{-1} 3250 (NH); δ_H($CDCl_3$) 2.55–3.33 (14 H) and 7.3 (5 H, m); δ_C($CDCl_3$) 27.69, 27.97, 28.71, 31.77, 39.99, 115.92, 123.75, 128.99, 129.55, 130.08, 130.19, 153.77 and 158.64.

1-Methylthiourea (0.96 g) and 1-phenylpropane-1,2-dione (0.74 g) were placed in THF (5 cm^3) with 1 drop TFA and the mixture refluxed for 5 h. Aqueous $NaHCO_3$ (1 mol dm^{-3}, 10 cm^3) was added and the whole mixture stirred for 30 min. THF was removed by evaporation, the solid filtered off and washed

with water (50 cm^3) and diethyl ether (25 cm^3) to give a mixture of 4,4′-methylenebis(1-methyl-5-phenyl-4-imidazoline-2-thione) (**11a**) and 4,4′-methylenebis(3-methyl-5-phenyl-4-imidazoline-2-thione) (**11b**), 50%, *m/z* 390 ($M^+ - 2H$); ^1H and ^{13}C NMR spectra showed a number of overlapping peaks consistent with a mixture of **11a** and **11b** but hardly diagnostic.

The same procedure was applied to the reaction of thiourea with 1-phenylpropane-1,2-dione to give 4,4′-methylenebis(5-phenyl-4-imidazoline-2-thione) (**11c**), 70%, m.p. 226 °C, *m/z* M^+ not observed; $\delta_H([^2H_6]DMSO)$ 4.20 (2 H, s) and 7.20–7.30 (10 H, m); $\delta_C([^2H_6]DMSO)$ 26.47 (CH_2) and 126–135 (7 signals) (Found: C, 62.6; H, 4.61; N, 15.37. $C_{19}H_{16}N_4S_2$ requires C, 62.6; H, 4.42; N, 15.37%). Thiourea (0.9 g) and 1-phenylpropane-1,2-dione (2.15 g) were placed in aqueous THF (7 cm^3, 5:2 v/v) and stirred for 3 days at room temperature. Water (10 cm^3) was added and the THF removed by evaporation. The residue was extracted with CH_2Cl_2, washed with water (15 cm^3) and dried ($MgSO_4$). The solvent was removed by evaporation and the residue titurated with 40–60 light petroleum to give a gum consisting of the *E* and *Z* isomers of 4,5-dihydroxy-4-methyl-5-phenyltetrahydroimidazole-2-thione (**5d**), 60%, *m/z* 206 ($M^+ - H_2O$); $\delta_H([^2H_8]THF)$ 0.85 and 1.40 (3 H, s) and 7.20–7.30 (5 H, m); $\delta_C([^2H_8]THF)$ 21.98, 25.85, 93.11, 94.45, 94.93, 96.68, 126.44, 126.98, 127.21, 127.37, 127.88, 128.09, 184.51 and 185.15. Reaction of thiourea with 1-phenylbutane-1,2-dione gave 4-[1-(5-phenyl-2-thio-4-imidazolinyl)ethyl]-5-phenyl-4-imidazoline-2-thione (**11d**), recrystallised from 1:1 v/v aqueous ethanol, 65%, m.p. 150 °C; $\delta_H([^2H_6]DMSO)$ 1.50 (3 H, d), 5.4 (1 H, q) and 7.20–7.30 (10 H, m); $\delta_C([^2H_6]DMSO)$ 20.35, 44.43 and 127–133 (7 signals). Reaction of thiourea with 1,3-diphenylpropane-1,2-dione gave 4-[phenyl(5-phenyl-2-thio-4-imidazolinyl)methyl]-5-phenyl-4-imidazoline-2-thione (**11e**), 48%, m.p. 168 °C (decomp.); $\delta_C([^2H_6]DMSO)$ 51.24 (CH), 127.73–135.54 (11 signals). A small amount of the crude product was subjected to GC–MS. There were substantial signals in 2 fractions corresponding to benzaldehyde (*m/z* 106, 105 and 77) and benzoic acid (*m/z* 122, 105 and 77). There is no detectable reaction between thiourea and 3-methyl-1-phenylbutane-1,2-dione.

In an effort to detect the formation of formaldehyde **5a** (2.5 g), thiourea (1.0 g), dimedone (1.5 g) and TFA (1 drop) were dissolved in THF (25 cm^3), and stirred at room temperature for 2 days. The solvent was removed and the residue was examined by TLC (silica/CH_2Cl_2). One component was found to have an R_f value identical with that of the formaldehyde–dimedone adduct. GC–MS of the residue gave one fraction with a signal at *m/z* 292 (formaldehyde–dimedone adduct) as well as peaks at 234 ($M - H_2O$ for **5a**).

NMR Experiments.—The following procedure is typical: 1-[^{13}C]-1-phenylpropane-1,2-dione (0.025 cm^3) and thiourea (0.025 g) were dissolved in a mixture of $[^2H_8]THF$ (0.5 cm^3) and H_2O (0.2 cm^3), warmed to 30 °C and a spectrum recorded. TFA (0.025 cm^3) was added and the ^{13}C NMR spectra recorded automatically at hourly intervals for 16 h, using a 15 min acquisition time for each spectrum. With the dione labelled in the methyl group the spectrum was recorded using a DEPT 135 pulse sequence.

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