

Mechanistic Studies in the Chemistry of Urea. Part 5.¹ Reaction of Urea, 1-Methylurea, and 1,3-Dimethylurea with 1-Phenylpropane-1,2-dione in Acid Solution

By Anthony R. Butler,* Ishtiaq Hussain, and Elizabeth Leitch, Department of Chemistry, The University, St. Andrews, Fife KY16 9ST

In acid solution 1-phenylpropane-1,2-dione reacts with urea to give a bicyclic compound (2), with 1,3-dimethyl- and 1,3-diethyl-urea to give the spiro-compounds (4) and (10), and with 1-methylurea to give a bicyclic compound of possible structure (11), (12), or (13). Mechanisms for formation of the first three compounds are suggested and the tendency of the diol intermediates to eliminate water is discussed. The methyl group of the dione is one site of reaction.

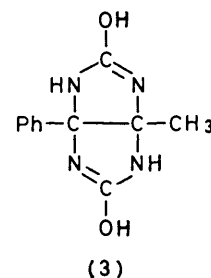
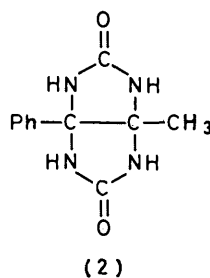
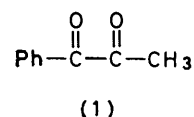
In Part 4¹ we described products obtained by the reaction of benzil with urea, 1-methylurea, and 1,3-dimethylurea in acidic conditions. With the first two there is reaction between two moles of urea and one mole of benzil to give a bicyclic compound, analogous to (2) below, with the elimination of two moles of water. Reaction with 1,3-dimethylurea led to formation of a hydantoin. One reason for the present series of studies is to examine the reaction between urea and diacetyl, which is a reaction used extensively in the clinical assay of urea.² However, in spite of the importance of this reaction, the chemistry involved is unknown. Once the investigation had started we quickly found the reaction to be one of surprising obscurity and decided that this was due to the presence of two reactive methyl groups in diacetyl, both of which are adjacent to carbonyl groups. To simplify matters we turned to benzil, which has no methyl groups, with the results described in Part 4 and summarised above. Our next step was to examine the reactions of 1-phenylpropane-1,2-dione (1) which has only one methyl group adjacent to a carbonyl group, and has been suggested³ as a reagent for the assay of urea. The results of this study are contained in this report.

RESULTS AND DISCUSSION

The acid used throughout was trifluoroacetic acid (TFA) and water formed during the reaction was removed by azeotropic distillation with benzene in a Dean and Stark apparatus.

(a) *Urea*.—Reaction was complete in *ca.* 1 h and a crystalline product was obtained. Molecular weight determination and elemental analysis gave a molecular formula of C₁₁H₁₂N₄O₂, which corresponds to reaction of one mole of the dione with two moles of urea and elimination of two moles of water. This immediately suggested 3a-methyl-7a-phenyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (2) as the structure of the product. The i.r. spectrum is consistent with the presence of amide carbonyl groups, NH groups, and the absence of C=N. Determination of the n.m.r. spectra was difficult as the compound was insoluble in all the usual solvents. However, it was soluble enough in [2H₆]dimethyl sulphoxide at 110° to allow measurement of the ¹H n.m.r. spectrum. This had four singlets with relative peak areas 3 : 1 : 1 : 5. The first and the last are clearly due to the methyl and

the phenyl group, while the others, at δ 6.61 and 6.93, are due to two of the remaining protons. The fact that only two out of the four remaining are observable suggests that exchange is occurring. The compound may, of course, exist in the tautomeric form (3). The only suitable solvent for measurement of the ¹³C n.m.r. spectrum was TFA. Such a strongly acidic substance is obviously not the solvent of choice but, when the solvent was removed after the spectrum had been obtained, the material was recovered unchanged. We



have, therefore, confidence that the results obtained do correspond to the carbon skeleton of the product. There were five shifts as well as a group at δ 127.79—135.31 p.p.m. corresponding to the carbons of the phenyl group. The two at lowest field, δ 164.93 and 164.64 p.p.m., indicate that the two carbonyl groups are in slightly different magnetic environments. Of the others, two (δ 82.37 and 85.07 p.p.m.) remained as singlets in an off-resonance spectrum, which is right for the two tertiary carbons common to both rings. The shift at highest field (δ 23.96 p.p.m.) became a quartet in the off-resonance spectrum, which is right for a methyl group. The ¹³C n.m.r. spectrum is, therefore, entirely consistent with structure (2).

(b) *1,3-Dimethylurea*.—The nature of the reaction with this compound was easier to elucidate than that with 1-methylurea and so we shall consider it next. The reaction time was *ca.* 4 h and the product was a beautiful but intractable purple tar. The intractable

tar is well known, but the colour may make this one unique. However, neutralisation and extensive treatment by column chromatography led, eventually, to the isolation of crystals. The purple colour will be discussed later. Molecular weight determination and elemental analysis gave a molecular formula for this product of $C_{15}H_{20}N_4O_2$. This corresponds to reaction of two moles of 1,3-dimethylurea and one mole of dione, with elimination of two moles of water. This immediately suggested a structure analogous to (2) with four NMe groups, but this was shown not to be the case.

The only distinctive and diagnostic feature of the i.r. spectrum was a strong absorption at 1710 cm^{-1} corresponding to an amide carbonyl.

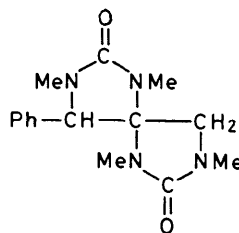
Methylation of the nitrogens appears to be responsible for increased solubility of the product and the ^1H and ^{13}C n.m.r. were obtained by using $[\text{}^2\text{H}_3]\text{chloroform}$ as solvent. The ^1H n.m.r. spectrum at 100 MHz had four overlapping singlets at high field (δ 2.65–2.79), a singlet at δ 4.53, and a multiplet corresponding to the aromatic protons. The relative peak areas were 14 : 1 : 5, which gives the correct number of protons corresponding to the molecular formula, but indicates that the methyl group of the dione has not remained intact. Addition of a lanthanide shift reagent (fod) $_3\text{Eu}$ improved slightly the resolution of the high field peaks, giving relative peak areas of 3 : 3 : 8. This suggests that there is a methylene group with a chemical shift identical to that of two of the NMe groups. More successful resolution of this part of the spectrum came from a spectrum run at 220 MHz. The four singlets are better resolved and, more significantly, a doublet appears slightly downfield. The relative peak areas of the doublet and the overlapping singlets are 1 : 13. The doublet suggests geminal coupling of a methylene group with the other half of the doublet buried in the overlapping singlets of the NMe groups. We suggest, therefore, that the structure of the product of reaction is 1,3-dimethyl-2-oxo-5-phenyltetrahydroimidazole-4-spiro-4'-(1',3'-dimethyltetrahydroimidazole-2'-one) (4). A model of the compound does indicate that there should be geminal coupling of the methylene group. The shift of the methine proton is at low field, but this is due to deshielding by the phenyl group.

This structure was confirmed by a study of the ^{13}C n.m.r. spectrum. There are four peaks in the region δ 24.58–29.90 p.p.m. corresponding to the NMe groups, four in the region δ 127.13–134.35 p.p.m. corresponding to the phenyl ring, and one at δ 158.51 p.p.m. due to the two carbonyl groups. There are three others, at δ 50.54, 66.49, and 77.89 p.p.m., and the shifts are consistent with structure (4). In the off-resonance spectrum these became a triplet, a doublet, and the low-field one remained as a singlet. This is exactly what is required for a methylene, a methine, and a tertiary carbon.

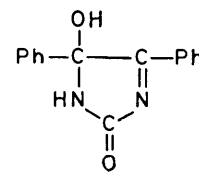
Compound (4) has a centre of chirality at the spiro-carbon atom and must exist in two enantiomeric forms. However, an examination of a chloroform solution of (4) in a polarimeter showed that the product was racemic.

The compound gave an intense blue fluorescence with a broad emission band originating at 350 nm.

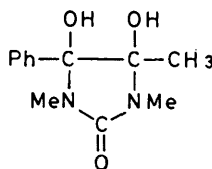
For the formation of (4) we see that the methyl group of the dione has become a centre of reaction, an effect which was not observed in the reaction with urea. In our discussion¹ of the reaction of urea and benzil we suggested that one driving force was the tendency to eliminate water, leading to (5) as an intermediate. This intermediate can then react with another molecule of urea. This mechanism will also explain the formation of (2). However, with 1,3-dimethylurea an intermediate analogous to (5) is not possible and we must consider what else can happen to (6). The analogous intermediate



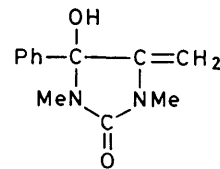
(4)



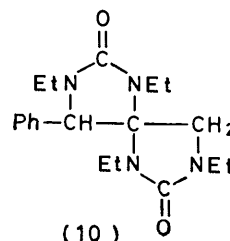
(5)



(6)



(7)



(10)

from benzil, described in Part 4, undergoes a pinacol rearrangement. However, the presence of the methyl group permits elimination of water in another way to give (7). The protonated form of (7) can then add dimethylurea in the manner shown in the Scheme.

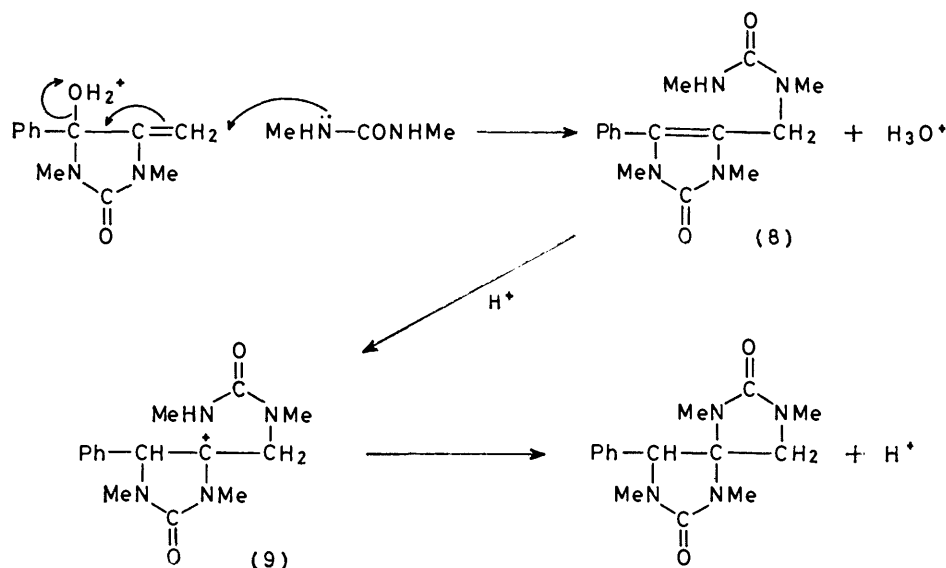
Protonation of (7) at the hydroxy group provides the molecule with a good leaving group (water) and 1,3-dimethylurea can attack in a manner analogous to a Michael addition. This, on loss of a proton, gives the intermediate (8). Cyclisation of this compound can occur if the double bond is protonated. Admittedly the most favourable site for protonation is on the carbon remote from the phenyl group but this is a non-productive process. Protonation of the carbon adjacent to the phenyl group to give (9), even if a minor process, provides a cationic centre which can be attacked by the

favourable disposed NHMe group and this, on loss of a proton, gives the desired product (4).

(c) 1,3-Diethylurea.—Structure (4) is sufficiently unexpected that we wanted to be certain that the *N*-methyl groups remained intact, and so we examined the reaction of 1,3-diethylurea with the dione. The reaction is sluggish but crystals were isolated. The expected product is (10). The mass spectrum and elemental analysis of the product were in agreement with this structure, and the i.r. spectrum indicated amide carbonyl groups. The ^1H n.m.r. spectrum had five sets of peaks. There were three sets of multiplets, with relative peak

water and *one carbon atom*. During the azeotropic distillation evolution of carbon dioxide was detected by passing the vapours through baryta water. The same experiment was performed with 1,3-dimethylurea in place of 1-methylurea but, in this case, the result was negative. The i.r. spectrum suggested the presence of NH, C=O, and C=C groupings. A methanolic solution of the material decolorised neutral potassium permanganate, which also suggests a carbon-carbon double bond. Neither the dione (1), nor 1-methylurea react in the same way.

It was interesting to find that a similar product was



SCHEME

areas 12 : 8 : 5. These clearly correspond to the methyl groups, the *N*-methylene groups, and the aromatic protons. There is a singlet at δ 4.56 due to the single methine proton and a double doublet at δ 3.71 (J 8 Hz). In this compound there is no overlapping of the *N*-ethyl groups and the methylene protons, and so the double doublet is observed in its entirety. The essential features of the ^{13}C n.m.r. spectrum are the same as those of (4). The off-resonance spectrum produces a doublet, a singlet, and a triplet for the skeletal carbon atoms. This work has confirmed that the *N*-alkyl groups do, indeed, remain intact and provides additional proof of the structure of (4).

(d) 1-Methylurea.—The product obtained from the reactions of 1-phenylpropane-1,2-dione and 1-methylurea is so unexpected, and its method of formation so mysterious, that we report our finding with some hesitation. During the azeotropic distillation about two moles of water were formed for every mole of dione present. After removal of the benzene and chromatography of the residue, crystals were obtained. Elemental analysis indicated a formula of $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}_2$ and this was confirmed by the mass spectrum. This formula corresponds to reaction of two moles of dione and two moles of methylurea, with loss of four moles of

obtained by Kuono and Ueda⁴ on reaction of 1-butylurea with (1) and glucoronolactone in aqueous phosphoric acid. The molecular formula of their product was $\text{C}_{27}\text{H}_{32}\text{O}_2\text{N}_4$ which is condensation of two molecules of (1) with two molecules of 1-butylurea and loss of four moles of water and one carbon. We shall return to their proposed structure shortly.

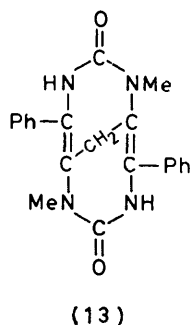
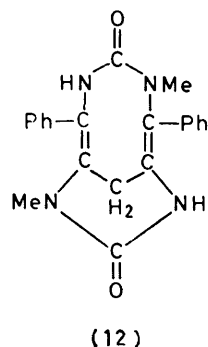
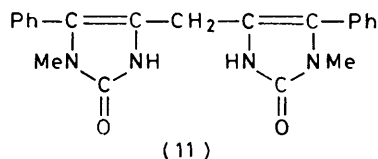
The ^1H n.m.r. spectrum of our compound in $[\text{}^2\text{H}_6]$ -dimethyl sulphoxide was very simple: three singlets with relative peak areas 6 : 2 : 12 at δ 2.82, 4.04, and 7.30, respectively. We assign these to two *N*-methyl groups, a methylene in a carbon skeleton, two phenyl groups overlapping with two broad peaks due to NH.

The ^{13}C n.m.r. spectrum was equally simple: peaks corresponding to the carbonyl groups, the phenyl carbons, and the *N*-methyl groups and three others at δ 20.31, 115.46, and 118.77 p.p.m. In the off-resonance spectrum the first became a triplet, while the other two remained as singlets. The second and third shifts are right for an unsymmetrical C=C group, while the first must be due to a methylene group.

The simplicity of the spectrum, in spite of the high molecular weight, suggests a molecule with a plane of symmetry. Structures (11)–(13) are consistent with the data. Kouno and Ueda⁴ propose a structure analo-

gous to (11) but their evidence is inconclusive and they do not speculate on the difficult mechanistic problem posed. A similar compound was obtained by reaction of diacetyl and 1,3-dimethylurea⁵ and we will delay further discussion on this problem until the data for that compound are published. The evidence for one structure is then more compelling.

Colour Reactions.—Formation of (4) was accompanied by a dramatic colour change and this matter was investigated further. If a solution of (4) in water was acidified a purple colour developed at once and intensified over several hours. Similar observations were reported by Kouno and Ueda.⁴ The colour was



destroyed on addition of alkali. Extraction of this product yielded a yellow oil, which by t.l.c. was shown to be a mixture. We were unsuccessful in elucidating the nature of the reaction. Protonation of (4) does not obviously give a species with an extended chromophoric system.

Products from the reaction of urea and 1-methylurea also gave coloured products in acid solution, but these reactions were not investigated. The latter appears to be a simple protonation.

EXPERIMENTAL

The method of azeotropic distillation has been described previously.¹

The reaction time for urea was 1 h. An excess of methanol was added to the contents of the flask and the precipitate filtered off. The material was dissolved in hot dimethyl sulphoxide (DMSO) and brought out of solution by addition of methanol. After filtration the material was washed with acetone to give 3a-methyl-4a-phenyl-tetrahydroimidazo[4,5-d]imidazole-2,5-dione (2), m.p. 348°, M^+ 232; ν_{\max} (mull) 3 220—3 100 (NH), 1 730, and 1 680 cm^{-1} (C=O), δ_{H} ($[\text{}^2\text{H}_6]$ DMSO; 110°) 0.8 (3 H, s), 6.61 (1 H, s), 6.93 (1 H, s), and 7.36 (5 H, s), δ_{C} (TFA) 23.96, 82.37, 85.07, 127.79, 131.04, 132.41, 135.31, 164.64, and 164.93 p.p.m. (Found: C, 57.0; H, 5.2; N, 24.15. $\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}_2$ requires C, 56.95; H, 5.2; N, 24.15%).

The reaction time with 1,3-dimethylurea was 4 h. Benzene was removed by evaporation to leave a purple syrup. This was put on to an alumina column and eluted with chloroform. Removal of the solvent left an orange liquid which, on standing, deposited crystals. The crystals were washed with ethyl acetate and recrystallised from acetone to give 1,3-dimethyl-2-oxo-5-phenyltetrahydroimidazole-4-spiro-4'-(1',3'-dimethyltetrahydroimidazole-2'-one) (4), m.p. 148°, M^+ 288, ν_{\max} (mull) 1 710 cm^{-1} (C=O), δ_{H} (CDCl_3) 2.65—2.79 (14 H, unresolved singlets), 4.53 (1 H, s), and 7.16—7.46 (5 H, m), δ_{C} (CDCl_3) 24.58, 24.70, 28.27, 29.90, 50.54, 66.49, 77.89, 127.13, 128.71, 134.35, and 158.51 p.p.m. The shift at δ 77.89 p.p.m. was observed when $[\text{}^2\text{H}_6]$ acetone was used as the solvent. In this solvent the other shifts show very slight changes from those quoted (Found: C, 62.4; H, 7.05; N, 19.4. $\text{C}_{15}\text{H}_{20}\text{N}_4\text{O}_2$ requires C, 62.5; H, 7.0; N, 19.45%).

The reaction time for 1,3-diethylurea was 1.5 h. The benzene was removed and the residue put on an alumina column (type H) and eluted with ethyl acetate. Removal of the solvent left a yellow liquid and addition of ether produced a solid. The solid was filtered off and washed with ether to give crystals of 1,3-diethyl-2-oxo-5-phenyltetrahydroimidazole-4-spiro-4'-(1',3'-diethyltetrahydroimidazole-2'-one) (10), m.p. 114°, M^+ 344, ν_{\max} (mull) 1 710 cm^{-1} (C=O), δ_{H} (CDCl_3) 0.86—1.34 (12 H, m), 2.5—3.5 (8 H, m), 3.71 (2 H, dd, J 8 Hz), 4.56 (1 H, s), and 7.14—7.44 (5 H, m), δ_{C} (CDCl_3) 12.56, 12.80, 15.35, 34.71, 35.99, 37.96, 49.61, 65.86, 78.90, 135.44, 127.75, 129.15, and 158.74 p.p.m. (Found: C, 66.2; H, 8.5; N, 16.0. $\text{C}_{15}\text{H}_{28}\text{N}_4\text{O}_2$ requires C, 66.25; H, 8.2; N, 16.25%).

The reaction time for 1-methylurea was 4 h. Unchanged 1-methylurea was filtered off and the benzene removed by evaporation. The residue was put onto an alumina column and eluted with chloroform. After removal of the solvent an orange liquid remained which deposited crystals by addition of acetone on standing. The material was recrystallised from methanol, m.p. 290° (decomp.), M^+ 360, ν_{\max} (mull) 3 155—3 110 (NH), 1 600 (C=C), and 1 680 cm^{-1} (C=O), δ_{H} ($[\text{}^2\text{H}_6]$ DMSO) 2.82 (6 H, s), 4.04 (2 H, s), and 7.30 (12 H, s), δ_{C} ($[\text{}^2\text{H}_6]$ DMSO) 19.66, 26.63, 114.80, 118.10, 126.79, 128.24, 129.74, and 153.13 p.p.m.

The vapours from the reaction mixture were passed through a cold trap and then through baryta water, which turned milky.

The above preparation was repeated with the reactants at room temperature and allowed to stand overnight to see if we could isolate an intermediate before the loss of CO_2 . The product was worked up in the same way as before and an identical product was obtained.

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