Mechanistic Studies in the Chemistry of Urea. Part 10.[1] Reaction of Urea and 1,3-Dimethylurea with Cyclohexane-1,2-dione and of Imidazolidin-2-one (Ethyleneurea) with Several α-Diketones

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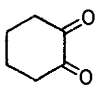
Products formed by the reaction of cyclohexane-1,2-dione (1) with urea and with 1,3-dimethylurea in an acid medium have been examined. Compounds with ten-membered rings, (3a and b), are formed in both reactions. In strongly acid solution both (3a and b) form highly coloured products by protonation of the hydroxy-groups and loss of water. This identifies the chromophore in a colorimetric procedure using the oxime of cyclohexane-1,2-dione (nioxime), for the determination of urea concentrations. The cyclic urea imidazolidin-2-one (2) does not give isolable products on reaction with benzil and 1-phenylpropane-1,2-dione. With diacetyl polymeric material forms. However, a compound containing a ten-numbered ring (8) does form, in good yield, on reaction with cyclohexane-1,2-dione.

IN our studies of the reactions of urea and *N*-alkylureas with α-diketones in the presence of acid we have found that, in many instances, cyclic compounds are formed. We thought it might be of interest to see if, on starting with either a cyclic urea or a cyclic diketone, polycyclic products are formed. The cyclic compounds chosen were cyclohexane-1,2-dione (1) and imidazolidin-2-one (2).

RESULTS AND DISCUSSION

Reactions of Cyclohexane-1,2-*dione* (1).—The most readily characterised product was obtained on treatment with 1,3-dimethylurea. Reaction was effected in the manner described previously and a solid was recovered from the reaction mixture. On heating, this material lost water before melting. In the mass spectrum there was a peak at *m/e* 328 but clearly this may be the molecular ion after loss of one or more molecules of water. The material was soluble in both chloroform and water. Elemental analysis gave an empirical formula of $C_9H_{16}N_2O_3$. The i.r. spectrum indicated the presence of carbonyl and hydroxy-groups. From the evidence so far we propose structure (3a) and the peak at *m/e* 328 in the mass spectrum is ($M^+ - 4H_2O$).



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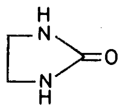

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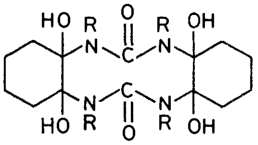
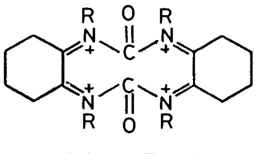
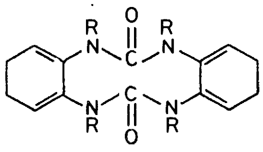


(3) a; R = Me
b; R = H

The n.m.r. spectra of the product gave confirmation of this structure. In the ^1H n.m.r. spectrum at 100 MHz there were two singlets at δ 1.82 and 2.30 and a collection of unresolved singlets in the range 2.76—3.77. The pair of singlets we assign to the ring methylene groups and the others to *N*-methyl groups. Compound (3a) may exist in a number of stereoisomeric forms and so the *N*-methyl groups are in different magnetic environments. The spectrum at 360 MHz was not more informative; it improved on the one at lower field only in that the *N*-methyl peaks were better resolved. The ^{13}C n.m.r. spectrum was more diagnostic and indicated, as well as *N*-methyl and carbonyl groups, three carbon atoms of different shifts in the molecule. These are the carbon atoms of the cyclohexane ring and one, with a shift of δ 58.0 p.p.m. is right for a carbon atom bearing hydroxy-group.



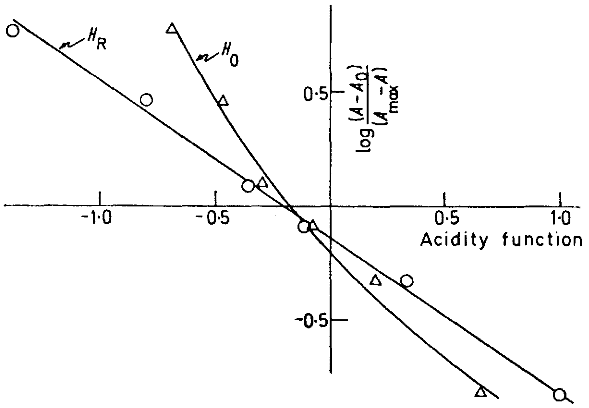
(4) a; R = Me
b; R = H



(5) a; R = Me
b; R = H

Addition of (3a) to 5M-HCl produced a purple solution which changed to yellow on standing. This reaction could be due to protonation of the hydroxy-groups followed by loss of water to give a conjugated cation. If all four hydroxy-groups were protonated then the product would be (4a), a conjugated tetracation. The conjugation explains the colour. The ^{13}C n.m.r. spectrum of (3a) dissolved in 5M-HCl has no peak at δ 58.0 p.p.m. indicating loss of all the hydroxy-groups. There is also a peak at δ 151.2 p.p.m. which we can ascribe to the $-C=N=$ group of (4a). The formation of a tetracation is surprising but it is not without precedent. All four nitrogens of hexamethylenetetramine are protonated on solution in sulphuric acid.[2] The coloured species is not stable and it could react further by slow deprotonation and formation of olefinic double bonds to give a molecule (5a) which is no longer conjugated. An aged solution of (3a) in 5M-HCl does have peaks in the range δ 120.3—128.4 p.p.m. in the ^{13}C n.m.r. spectrum.

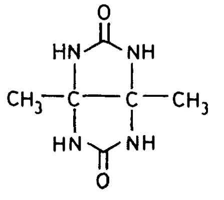
The purple solution is just stable enough to permit determination of the concentration of the coloured species as a function of acidity. The isosbestic points and the absorbance maximum remained fixed as the acidity was increased. This is not what is expected if stepwise protonation occurs, *i.e.* complete conversion to the monocation before a second protonation commences. The spectral evidence accords better with partial conversion to the final product, *viz.* the tetracation (4a). The extensive conjugation in (4a) may be the driving force in this reaction. The only species present in acid solution are therefore, (3a) and (4a), excluding any products of proton loss from (4a). Therefore, we were able to measure spectrophotometrically the ratio [(4a)] : [(3a)] as a function of acid concentration. The term log [(4a)] : [(3a)] was plotted against two acidity functions H_0 and H_R (Figure). With the latter the curve is rectilinear and has a slope of —0.7. A correlation with H_R, rather than H_0, is right for a process involving protonation of a hydroxy-group and loss of water and supports the proposed chemical changes. However, we are unable to give meaning to the magnitude of the slope.



Variation in the absorbance of (3a) at 580 nm with acidity

Reaction of urea and cyclohexane-1,2-dione under the same conditions gave a solid which also produced an intense colour when dissolved in acid. This product was more difficult to characterise, partly because of its low solubility. The i.r. spectrum suggested the presence of NH and OH groups and carbonyl groups and, from elemental analysis, the empirical formula is $C_7H_{12}N_2O_3$. Extensive fragmentation occurred in the mass spectrometer and so it was not possible to determine the molecular weight by this method. However, the evidence so far is consistent with a structure which is the analogue of (3a) without the *N*-methyl groups, *i.e* (3b). Unlike (3a), this compound is not soluble in the solvents regularly used for n.m.r. spectroscopy, but does dissolve in trifluoroacetic acid (TFA). Intense colours develop rapidly if the solution is warmed, but at ambient temperatures the reaction is slow enough to allow recording of the ^1H and ^{13}C n.m.r. spectra. Provided the TFA solution was not allowed to stand for too long, it was possible to recover the material from solution unchanged. In the ^1H n.m.r. spectrum there are two broad singlets at high field, which we assign to the hydrogens of the cyclohexane ring, and a broad singlet at much lower field (NH and/or OH). The ^{13}C n.m.r. spectrum is more informative; resonances occur at δ 17.6, 31.8, 79.4, and 165.5 p.p.m. The first two we assign to the cyclohexane methylene groups, the third to the carbon bearing a hydroxy-group, and the last to the carbonyl groups.

As mentioned previously, a solution of (3b) becomes intensely coloured on warming. This is of relevance to analytical biochemistry. Reaction between urea and the dioxime of cyclohexane-1,2-dione (nioxime) has been proposed [3] as a colorimetric method for the determination of urea concentrations in biological fluids. From the work described above we conclude that the analytical reaction involves hydrolysis of the dioxime to cyclohexane-1,2-dione and reaction with urea to form (3b). Protonation and loss of water gives the coloured tetracation (4b) and this is the chromophore. The colour developed depends upon the acidity, the temperature, and the time of heating. In the words of the original report:[3] 'La coloration est mauve au départ, puis violette. Elle évolue ensuite lentement, passant par le bleu, puis le vert'. The lack of colour stability has probably been responsible for the infrequent use made of the procedure. Otherwise it does have a number of advantages over the use of diacetyl mono-oxime, which is one of the most widely used reagents for the determination of urea concentrations. Its reactions with urea have been described previously.[4] We suggest that the changing colours described by Siest [3] are due to deprotonation of (4b) to give molecules containing one, two, three, and four double bonds. The final product is (5b). Elucidation of the chemistry involved in these colour changes does not immediately suggest a way of improving the reaction as an analytical procedure.



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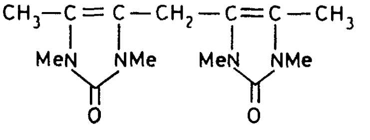
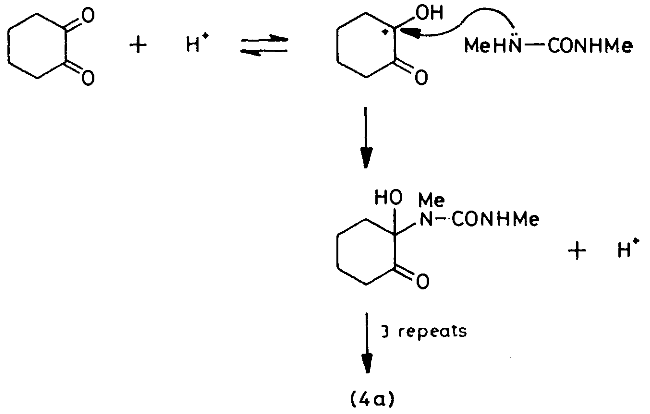


(7)

We can now compare the reactions of cyclohexane-1,2-dione with a non-cyclic analogue, diacetyl. The latter reacts with urea to give, initially, the bicyclic compound (6).[4] Models indicate that the equivalent compound from cyclohexane-1,2-dione is so crowded as to resist formation. The reaction, therefore, takes a different course and the much less crowded compound (4a) is formed. The mechanism for the formation of (4a) is quite straight forward, involving protonation of the ketogroup and attack of the cationic centre thus created by the nucleophile urea (Scheme).



SCHEME

Diacetyl and 1,3-dimethylurea react to give the unexpected product (7) and reaction involves loss of a methyl group.[4] A parallel reaction with a cyclic diketone is not possible and so the product is analogous to that obtained on reaction with urea.

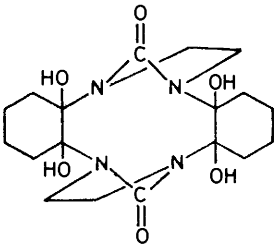
Reactions of Imidazolidin-2-one (2).—This compound is so closely related to 1,3-dimethylurea that we hoped it might react in a similar manner to give a number of unusual polycyclic compounds. In this we were disappointed. There was no evidence of reaction with benzil and only an intractable tar was obtained on reaction with 1-phenylpropane-1,2-dione. The product obtained from diacetyl and (2) appears to be polymeric. The mass spectrum was typical for that of a polymer with the peak of highest *m/e* value at 264. At low ionisation a peak at *m/e* 348 was observed. In the i.r. spectrum there was no sign of a hydroxy-group. The ^1H n.m.r. spectrum indicated the persistence of methyl and *N*-methylene groups in the product but the ratio of integrations is 1 : 2, rather than 3 : 2 as would be expected for material formed from equal numbers of molecules of diacetyl and (2). We are unable to deduce a structure for this polymer.

The final experiment in this series was the reaction of a cyclic urea with a cyclic α-diketone, *i.e.* imidazolidin-2-one (2) and cyclohexane-1,2-dione (1). No tar formed and a crystalline product was obtained. On heating the product water was evolved before the material melted The peak at highest *m/e* in the mass spectrum was at 274, which is not easy to accommodate. The i.r. spectrum indicated the presence of hydroxy and carbonyl groups. The ^1H n.m.r. spectrum suggested the presence of hydroxy, NCH_2, and cyclohexane protons in the ratio 1 : 2 : 4 and, on the basis of this spectrum, we propose structure (8). The number of possible stereoisomers of (8) makes the ^{13}C n.m.r. spectrum complex. However, in the spectrum there is evidence for four different types of carbon atoms in the molecule, ring methylene groups, *N*-methylene groups, carbons bearing a hydroxy-group, and carbonyl groups. Although the spectrum is too complex to confirm the proposed structure there is nothing in it which is inconsistent.

Compound (8) does not give intense colours in acid solution. The nitrogen-to-nitrogen bridge enforces a stereochemistry about nitrogen that makes formation of positively charged nitrogen, as in (4), impossible.

The difference in the reactivity of (2) and 1,3-dimethylurea is quite strange. Steric crowding should be slight for (2) and we expected it to react with benzil in the same way as 1,3-dimethylurea to give the diol (9), which should then rearrange to give a hydantoin.[5] The fact that this does not occur is difficult to explain. The diol (9) is not particularly strained and so formation is not unfavourable. It is equally difficult to explain why reaction of (2) with 1-phenylpropane-1,2-dione and with diacetyl does not parallel the reactions of 1,3-dimethylurea.[5,6] However, we did find in a previous study [1] that imidazolidin-2-one readily forms polymeric materials. The large ring in (8) may make its formation occur with an ease not possible in the reactions discussed above.

This is the final paper in this series.



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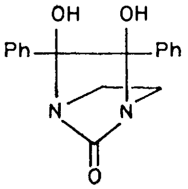

(9)

EXPERIMENTAL

General Method.—A mixture of urea, diketone, and TFA were refluxed in benzene and the water formed during reaction removed by means of a Dean and Stark apparatus. The method has been described previously.[5]

Reaction of 1,3-*Dimethylurea with* (1).—After refluxing equimolar quantities for 3 h benzene was removed to leave a viscous liquid. This was purified by column chromatography (basic alumina) and eluted with acetonitrile and ethanol. The first eluent contained unchanged (1), while the second, after removal of the solvent, yielded a yellow liquid. A solution of this in ethanol was poured into light petroleum with vigourous stirring and a precipitate formed. After filtration 1,5,10,14-*tetrahydroxy*-2,4,11,13-*tetramethyl*-2,4,11,13-*tetra-azatricyclo*[12.4.0.$0^{5,10}$]*octadecane*-3,12-*dione* (3a) (yield 70%) was washed with ether and dried. Decomposition (*i.e.* loss of water) commenced at *ca.* 164°, *m/e* 328 ($M^+ - 4H_2O$), $\nu_{max.}$ 3 500—3 100 (OH) and 1 700—1 640 cm^{-1} (C=O), δ_H ($CDCl_3$) 1.82br (8 H, s), 2.30br (8 H, s), and 2.76—3.77 (12 H, unresolved), δ_C ($CHCl_3$) 18.3, 19.7, 27.3—30.9, 58.0, 153.7, and 153.9 p.p.m. (Found: C, 55.9; H, 6.4; N, 14.6. $C_{18}H_{32}N_4O_6$ requires C, 54.0; H, 8.05; N, 14.0%). The material is damp and requires drying before analysis. During the drying it is difficult to avoid some elimination of water. This explains the poor analysis and, particularly, the low hydrogen content. However, the C : N ratio of 9 : 2 is correct for (3a).

For the spectral study of acid solutions of (3a) equal volumes of a 0.1M aqueous solution of (3a) and aqueous HCl were mixed and the spectrum recorded immediately on a Unicam SP 800 spectrophotometer. The concentration of the coloured species was measured by the absorbance of the solution of 580 nm in a cell of 1 mm path length. Acidity function data were those of Paul and Long [7] (H_0) and Arnett and Mach [8] (H_R).

Reaction of Urea with (1).—The above procedure was repeated using urea in place of 1,3-dimethylurea. After refluxing for 2 h, the reaction mixture was cooled and a large volume of acetone added. The precipitate was filtered off, washed with water, acetone, and ether to give the *demethylated compound* (3b) (yield 60%) as a powder, m.p. (decomp.) 326°, $\nu_{max.}$ 3 340 (NH and OH), 1 710, and 1 615 cm^{-1} (C=O), δ_H (TFA) 1.74 (s) and 7.2vbr (s), δ_C (TFA) 17.6, 31.8, 79.4, and 165.5 p.p.m. (Found: C, 48.9; H, 6.45; N, 16.75. $C_{14}H_{24}N_4O_6$ requires C, 48.85; H, 7.0; N, 16.25%).

The filtrate was deep purple and addition of ether produced a violet solid. This appears to be a mixture (see Discussion section) and we were unable to characterise it with certainty. In the ^{13}C n.m.r. spectrum there were peaks at δ 132.7, 137.5, and 149.2 p.p.m. This is consistent with formation of olefinic double bonds as in (5b).

Reaction of Imazolidin-2-one (2) *with* (1).—After refluxing equimolar quantities of the reactants in benzene with TFA for 3 h the contents of the flask were cooled and light petroleum added with stirring. The solid which separated was filtered off and recrystallised from chloroform to give crystals of 1,5,10,14-*tetrahydroxy*-2,4,11,13-*bisethylene*-2,4,11,13-*tetra-azatricyclo*[12.4.0.0^{5,10}]*octadecane*-3,12-*dione* (8) (yield 80%), m.p. (decomp.) 180°, *m/e* 274 [$M^+ - 2H_2O - (CH_2NH)_2CO$], $\nu_{max.}$ 3 140—3 400 (OH) and 1 650—1 710 cm^{-1} (C=O), δ_H ($CDCl_3$) 2.0—2.4 (16 H, 2s), 3.45 (8 H, s), and 4.2—4.5 (4 H, s), δ_C ($CHCl_3$) 21.7—29.3, 37.7—40.6, 52.5, 62.3, 158.9, 159.7, and 160.1 p.p.m. (Found: C, 53.1; H, 6.05; N, 13.3. $C_{18}H_{28}N_4O_6$ requires C, 54.5; H, 7.1; N, 14.1%). The problems associated with elemental analysis, described previously, apply here. The C : N ratio is 9 : 2.

[0/961 *Received*, 23*rd June*, 1980]

REFERENCES

[1] Part 9, A. R. Butler and I. Hussain, preceding paper.

[2] R. J. Gillespie and S. Wasif, *J. Chem. Soc.*, 1953, **221**.

[3] G. Siest, *Clin. Chim. Acta*, 1967, **18**, 155.

[4] A. R. Butler and I. Hussain, *J.C.S. Perkin II*, 1981, 302.

[5] A. R. Butler, and E. Leitch, *J.C.S. Perkin II*, 1980, 103.

[6] A. R. Butler, I. Hussain, and E. Leitch, *J.C.S. Perkin II*, 1980, 106.

[7] M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1.

[8] E. M. Arnett and G. W. Mach, *J. Amer. Chem. Soc.*, 1966, **88**, 1177.