Mechanistic Studies in the Chemistry of Urea. Part 6.[1] Reaction of Urea, 1-Methylurea, and 1,3-Dimethylurea with Acetophenone in Acid Solution

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In acid solution acetophenone undergoes self-condensation to give dypnone, with elimination of water. If urea or 1-methylurea is present further reaction may occur to give dihydropyrimidin-2-one.

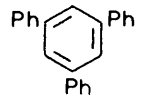
In Part 5 [1] we showed that, in the reaction of a diketone with urea or an *N*-alkylated urea, the presence of one alkyl, rather than an aryl, group α to the carbonyl function can have a profound effect on the course of the reaction. Before considering the reactions of diacetyl (butane-2,3-dione) we thought it would be of interest to examine the reactions of urea and *N*-alkylated ureas with mono-ketones. In this report we describe some reactions of acetophenone.

RESULTS AND DISCUSSION

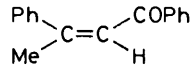
(a) *Urea.*—Equimolar amounts of urea and acetophenone react with elimination of water, which was removed by azeotropic distillation. Three substances were isolated from the products. Two were the expected self-condensation products of acetophenone, *viz.* 1,3,5-triphenylbenzene (1) and 1,3-diphenylbut-2-en-1-one (dypnone) (2). The latter is generally prepared by the reaction of acetophenone with aluminium t-butoxide.[2] We have shown, by ^1H and ^{13}C n.m.r. spectroscopy, that the dypnone we obtained is a mixture of the two isomeric forms (2a and b). The two high field singlets in the ^1H n.m.r. spectrum (δ 2.42 and 2.54) show that there are two methyl groups in slightly different environments. There is some evidence of splitting in each of these singlets, due to allylic coupling, but the coupling constants are too small to determine. The total peak area of these two singlets was taken as equivalent to six protons. There is a doublet (δ 7.10), probably due to the methine proton in (2a), and the peak area indicates one proton. There is another methine proton doublet at lower field (δ 7.89) but it is too close to the aromatic protons to allow separate determination of the peak area. The complete peak area for the region δ 7.20—7.98, which includes the methine proton of (2b), corresponds to 21 protons. This is correct for the two phenyl groups of (2a and b) and the methine proton of (2b). The peak areas here, and those for the methyl protons, show that the two isomers are present in equal amounts.

Further evidence for two isomers of dypnone comes from an examination of the ^{13}C n.m.r. spectrum. There again, two shifts corresponding to the two methyl groups (δ 17.80 and 25.41 p.p.m.), both of which become quartets in the off-resonance spectrum, and there are two shifts corresponding to two carbonyl groups (δ 189.68 and 190.24 p.p.m.).

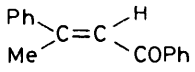
The third product of reaction is the one of greatest interest to us. This one does contain nitrogen and all the spectroscopic data prove that it is 1,6-dihydro-2-hydroxy-6-methyl-4,6-diphenylpyrimidine (3). This compound was first prepared by the reaction of urea and acetophenone by Scholtz,[3] who proposed an open-chain structure. This was questioned by Folkers and Johnson,[4] who suggested that the product was a reduced pyrimidine. Our evidence supports this assignation.



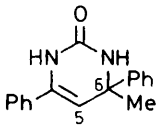
(1)



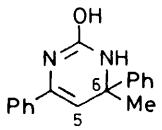
(2a)



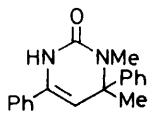
(2b)



(3)



(4)



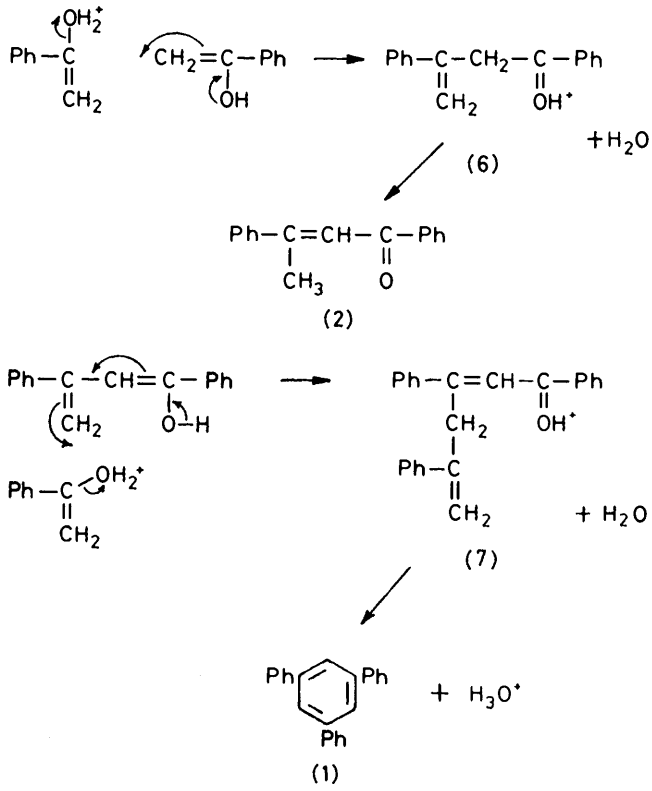
(5)

The nomenclature of reduced pyrimidines has been discussed by Brown.[5]

Details of the n.m.r. spectra are given in the Experimental section and only points of special interest will be discussed here. In the ^1H n.m.r. spectrum only one NH signal is seen (δ 8.66) suggesting that (3) exists as the hydroxy-compound (4) rather than in the oxo-form. The doublet at δ 5.35 is of some interest. It is the proton at position 5 split by the NH proton. The splitting disappears on spin tickling. In the ^{13}C n.m.r. spectrum the shifts at δ 104.49 and 57.04 p.p.m. are due to C-5 and -6; the former becomes a doublet in the off-resonance spectrum, while the latter remains as a singlet.

A satisfactory reaction mechanism is one which rationalises formation of all three products. Such a mechanism is shown in Schemes 1 and 2. Protonation of the enolic form of acetophenone makes it a good leaving group (water). The unprotonated enolic form of acetophenone can act as a nucleophile and reaction between the two results in the formation of (6) with the elimination of water. Deprotonation and a prototropic

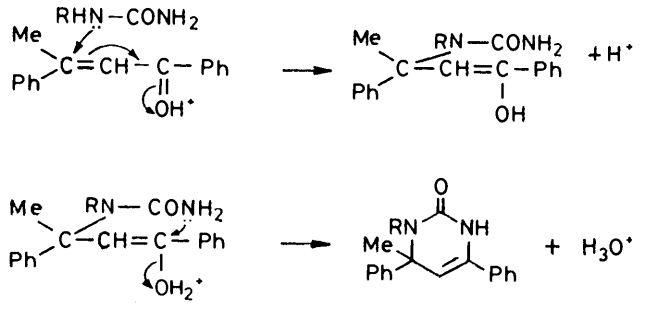
shift yields dypnone (2). However, reaction of the enolic form of dypnone with another molecule of protonated acetophenone results in the formation of (7), with elimination of water. Cyclisation of (7) can occur, with



SCHEME 1

elimination of more water and deprotonation, to give triphenylbenzene (1). When urea was omitted from the mixture dypnone was the main product.

However, in the presence of urea dypnone undergoes a reaction other than formation of triphenylbenzene.



R = H or Me

SCHEME 2

As shown in Scheme 2, urea may act as a nucleophile and undergo a Michael condensation with dypnone, which is an unsaturated ketone. Protonation of the initial adduct provides a good leaving group (water) for cyclisation to occur.

(b) 1-*Methylurea*.—The main product here was (5). All the spectroscopic data are consistent with this structure. The only question is the position of the NMe group relative to the ring double bond. In the ^{1}H n.m.r. spectrum the methine hydrogen was split into a doublet and the splitting disappeared on addition of D_2O and on spin tickling. These observations are consistent with structure (4). The structure is right for the mechanism shown in Scheme 2 assuming that the NHMe group is the more nucleophilic end of the 1-methylurea molecule.

(c) 1,3-*Dimethylurea*.—The only product obtained, even after refluxing for 51 h, was dypnone. The reason for this must be steric. The presence of a methyl group must prevent the cyclisation step shown in Scheme 2 and so there is nothing to drive the reaction towards the stable, cyclic dihydropyrimidine.

Similar reactions to those described above were tried with benzophonone but, in all cases, unchanged starting materials were recovered.

EXPERIMENTAL

The removal of water by azeotropic distillation has been described previously.[1]

(a) *Urea*.—Urea (0.1 mol), acetophenone (0.1 mol), benzene (50 ml), and trifluoroacetic acid (5 ml) were refluxed for 11 h. The benzene was decanted to leave a red gum. Most of the gum dissolved in methanol but there remained some crystals of triphenylbenzene (1) which was recrystallised from acetone, m.p. 172° (lit.,[4] 174°), *m/e* 306 (M^+), $\delta_H(CDCl_3)$ 7.10—7.75 (m), $\delta_C(CDCl_3)$ 125.19, 127.39, 127.54, 128.86, 141.23, and 142.40 p.p.m.

The methanol was removed and the residue was put onto an alumina column. The column was eluted with ether and then with methanol. Removal of the ether gave a yellow liquid, which was 2-*benzoyl*-1-*methyl*-1-*phenylethylene* (12), *m/e* 222 (M^+), $\nu_{max.}$ 1 690 and 1 660 (C=O) and 1 600 cm^{-1} (C=C), $\delta_H(CDCl_3)$ 2.42 (3 H, s), 2.54 (3 H, s), 7.10 (1 H, d, *J* 2 Hz), and 7.20—7.98 (21 H, m), δ_C 17.80, 25.41, 121.06, 125.69, 126.51, 127.43, 127.73, 128.06, 128.33, 131.60, 132.05, 136.36, 138.64, 141.77, 153.75, 189.68, and 190.24 p.p.m.

Solvent was removed from the methanol eluant to give a solid, 4-*methyl*-4,6-*diphenyldihydropyrimidin*-2-*one* (3), m.p. 170°, *m/e* 264 (M^+), $\nu_{max.}$ (mull) 3 240 (NH), 1 690 (C=O), and 1 650 cm^{-1} (C=C), δ([$^2H_6$]DMSO) 1.62 (3 H, s), 5.35 (1 H, d, *J* 2 Hz), 7.18—7.55 (10 H, m), and 8.66 (1 H, s), δ_C([$^2H_6$]-DMSO) 30.80, 57.04, 104.49, 124.79, 125.38, 126.35, 128.11, 128.29, 134.04, 148.78, and 153.86 p.p.m. (Found: C, 77.1; H, 6.1; N, 10.6. $C_{17}H_{16}N_2O$ requires C, 77.25; H, 6.1; N, 10.6%).

(b) 1-*Methylurea*.—The above procedure was repeated using 1-methylurea and refluxing for 20 h. After removal of the benzene a yellow oil remained which solidified on standing. Crystals of 3,4-*dimethyl*-4,6-*diphenylpyrimidin*-2-*one* were recrystallised from ethanol, m.p. 193°, *m/e* 278 (M^+), $\nu_{max.}$ (mull) 3 200 (NH), 1 680 (C=O), and 1 665 cm^{-1} (C=C), $\delta_C(CDCl_3)$ 1.68 (3 H, s), 2.86 (3 H, s), 5.00 (1 H, d, *J* 2 Hz), 5.90 (1 H, s), and 7.20—7.50 (10 H, m), $\delta_C(CDCl_3)$ 30.93, 32.26, 56.68, 109.91, 124.84—129.29, 135.53, 139.30, 147.80, and 155.54 p.p.m. (Found: C, 77.75; H, 6.65; N, 10.2. $C_{18}H_{18}N_2O$ requires C, 77.65; H, 6.5; N, 10.05%). No other products of reaction were isolated.

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REFERENCES

[1] Part 5, A. R. Butler, I. Hussain, and E. Leitch, *J.C.S. Perkin II*, 1980, 106.
[2] J. Wislicenus, *Annalen*, 1895, **302**, 236.
[3] A. Scholtz, *Arch. Pharm.*, 1915, **253**, 111.
[4] K. Folkers and T. B. Johnson, *J. Amer. Chem. Soc.*, 1933, **55**, 3361.
[5] D. J. Brown, 'The Pyrimidines,' Interscience, New York, 1962, ch. 12.
[6] A. F. Odell and C. W. Hines, *J. Amer. Chem. Soc.*, 1913, **35**, 82.