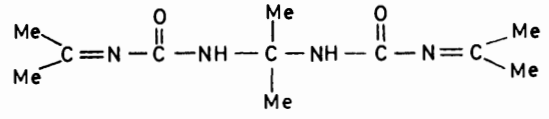
Mechanistic Studies in the Chemistry of Urea. Part 7.[1] Reaction with Acetone and Mesityl Oxide

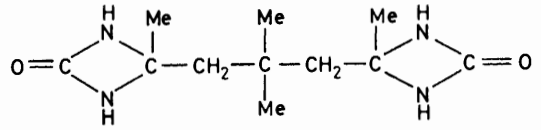
By **Anthony R. Butler** * and **Ishtiaq Hussain**, Department of Chemistry, The University, St. Andrews, Fife KY16 9ST

By application of spectral methods it has been confirmed that the structure of the product of reaction between urea and acetone under acid conditions is (3). A mechanism for this reaction has been proposed. If acetone is replaced by mesityl oxide then the product is (7), rather than (6). A similar mechanism operates in this reaction. Analogous products are obtained with 1-methylurea, but 1,3-dimethylurea does not react under these conditions.

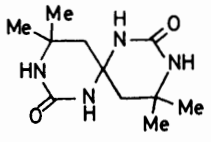
In our study of the reactions of ketones and urea we come now to the special case of acetone. It is special in that it has been examined several times previously and different structures have been proposed for the reaction product. The first report appears to be that of Weinschenk [2] who suggested (1) on the grounds that an alkaline hydrolysis gave acetone, ammonia, and CO_2. Harvey [3] proposed (2) in a patent. On the basis of spectral evidence Hatt and Triffett [4] and Zigeuner *et al.*[5] proposed a hydropyrimidine (3). This is supported by the observation that (3) can be obtained by reaction of phorone (4) and urea. According to Hatt and Triffett there is a doublet in the 60 MHz ^{1}H n.m.r. spectrum in D_2O solvent (80°), δ 1.30 (12 H), and this splitting is difficult to understand. More recently Inoi *et al.* proposed (5). In their ^{1}H n.m.r.



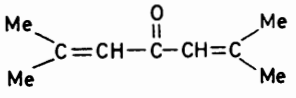
(1)



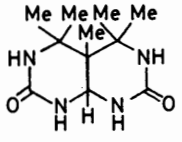
(2)



(3)



(4)

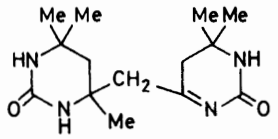


(5)

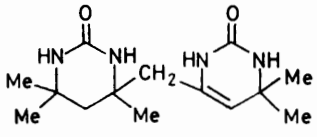
spectrum the two pairs of geminal methyl protons appear as a singlet, δ 1.56, but for the second singlet, δ 2.40, it had to be assumed that the chemical shifts of the other methyl protons and the proton at the bridgehead were identical, which is unlikely.

We prepared the product of reaction of urea and acetone and confirmed its molecular formula. The ^{1}H n.m.r. spectrum in trifluoroacetic acid was, in general, consistent with (3), but a molecular model indicated that the methyl groups of each geminal pair were not in the same environment (which should lead to two singlets, of equal intensity, not a doublet as noted by Hatt and Triffett [4]) and there should also be geminal splitting of the two methylene protons. When the ^{1}H n.m.r. in [$^2H_6$]DMSO at 120° was recorded these features were observed. There were two equal singlets at δ 1.15 and 1.18 and a distorted double doublet centred at δ 1.89 (J_{gem} 14 Hz). The ^{13}C n.m.r. spectrum supported (3) rather than any other proposed structure. Apart from the methyl groups and carbonyl groups there are only three different carbon atoms in (3) and the noise-decoupled spectrum had peaks at δ 48.01, 52.98, and 68.32 p.p.m. In the off-resonance spectrum the first became a triplet and the other two remained as singlets. We conclude, therefore, that (3) is the correct structure.

Acid hydrolysis of the acetone–urea adduct gives a compound of molecular formula $C_{14}H_{24}N_4O_2$ for which Hatt and Triffett [4] proposed structure (6), without any knowledge of the n.m.r. spectrum. The same compound is obtained by the reaction of mesityl oxide and urea and we prepared a sample in this manner. The ^{1}H n.m.r. spectrum in trifluoroacetic acid has three very close low-field singlets (15 H), two distorted double doublets (4 H) suggesting two methylene groups in different environments, and one singlet olefinic proton. These data are

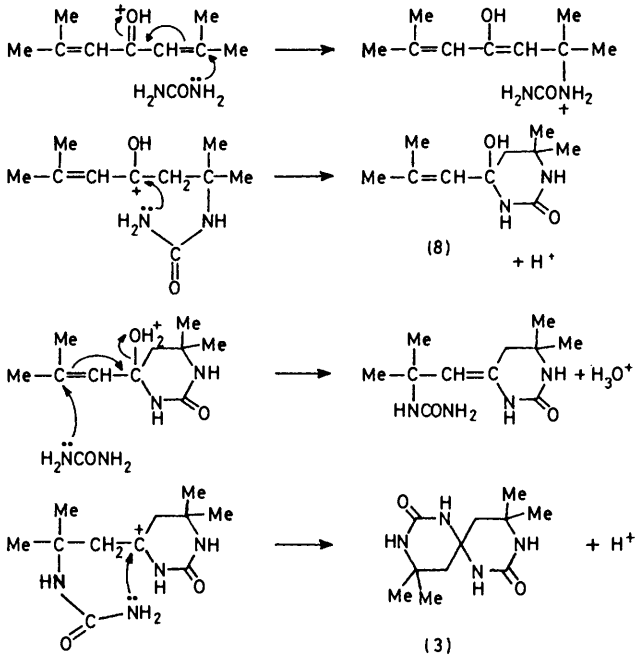


(6)



(7)

not in agreement with (6) but suggest, instead, structure (7). This structure was confirmed by the noise-decoupled ^{13}C n.m.r. spectrum. Aside from the methyl groups, the spectrum indicated at least nine different carbon atoms and the shifts were consistent with structure (7). In the off-resonance spectrum the two peaks assigned to the methylene groups (δ 45.80 and 45.96 p.p.m.) became triplets, one olefinic carbon (δ 114.04



(8)

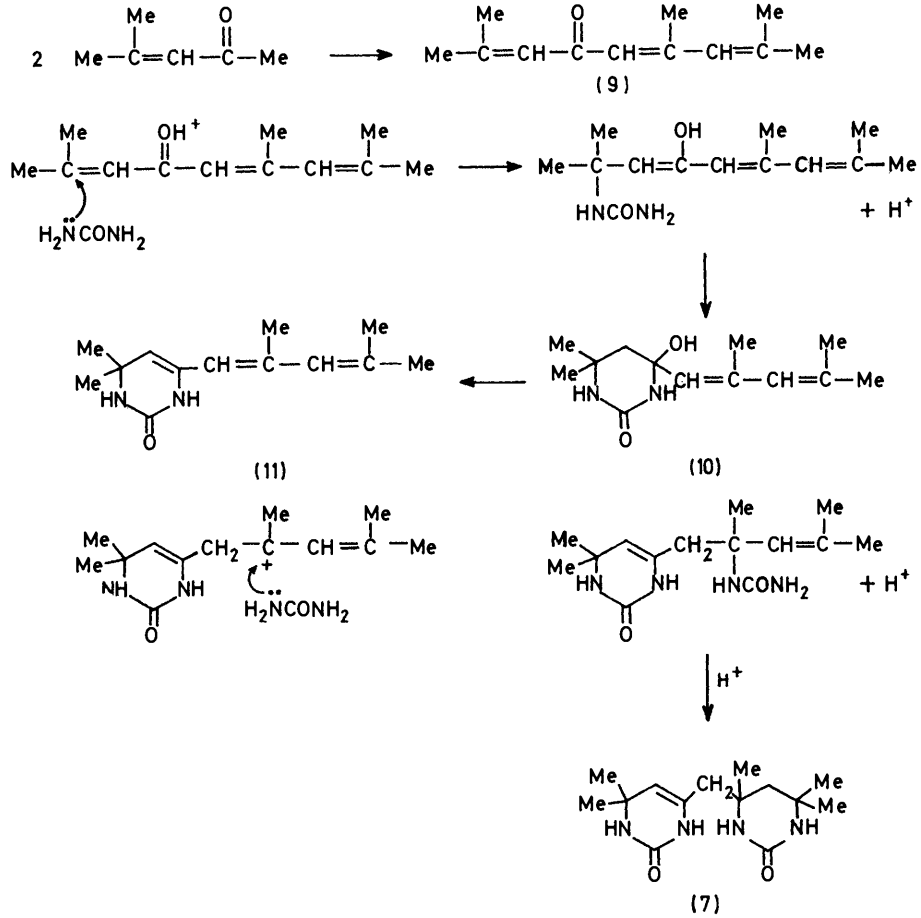
(3)

SCHEME 1

p.p.m.) became a doublet and all the others remained as singlets. The results agree with structure (7).

Compound (3) is formed from phorone (4) and urea and this suggests that part of the reaction is the condensation of three molecules of acetone to give (4). Mesityl oxide is probably the first product but this appears to react faster with a third molecule of acetone than with urea, as (7) is not formed in the reaction between urea and acetone. The formation of (4) could have a mechanism similar to that described previously for the formation of dypnone.[1] The mechanism could then follow the course shown in Scheme 1. Protonation of (4) then makes it susceptible to a Michael condensation reaction with urea. If the resulting double bond is protonated then cyclisation can be effected to give (8). Protonation of the hydroxy-group facilitates a second Michael condensation by urea, this time with elimination of water. Protonation of the remaining double bond effects a second cyclisation and formation of the spiro-compound (3).

The reaction with mesityl oxide must follow a different course, although two similar cyclisations occur. The first step appears to be condensation of two molecules of mesityl oxide to form (9). A Michael condensation followed by cyclisation gives (10), which can eliminate water with creation of a double bond in the ring (11).



(9)

(10)

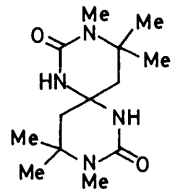
(11)

(7)

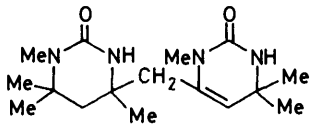
SCHEME 2

Protonation of the two remaining double bonds in succession permits nucleophilic attack by urea and cyclisation to (7). The strange course of the reactions may be due to the low basicity of urea linked with a fair degree of nucleophilicity and the readiness of the intermediates to eliminate the elements of water, the diuretic effect.

Reaction of 1-methylurea with acetone under similar experimental conditions gave an analogous product (12).



(12)



(13)

The structure was elucidated from the ^1H and ^{13}C n.m.r. spectra. The most diagnostic features of the ^1H n.m.r. spectrum were three singlets (each of 6 H) at δ 1.27, 1.36, and 2.72, generated by the methyl groups, and a distorted double doublet (4 H) at δ 2.22 corresponding to the two methylene groups. There are two variations of (12) with the methyl groups in different relative positions, and we were unable to distinguish between them and thus establish the structure unambiguously. However, if we assume that the mechanism is that shown in Scheme 1, and that the NMe group is the more nucleophilic part of the molecule, then (12) is the resulting product. A side product in this reaction was dimethylcyanuric acid.

The reaction of 1-methylurea with mesityl oxide follows the same course as that of urea and the product is (13). All the spectral data are consistent with this structure. Again there are two other possibilities but this one was selected because of the absence of an allylic coupling of the olefinic proton, as had been noted previously.[1] Unfortunately, the mechanism in Scheme 2 leads to the NMe groups in different relative positions. At present we have no way of fixing the structure unambiguously.

The only product obtained on the reaction of acetone and 1,3-dimethylurea was 1,3,5-trimethylcyanuric acid.

EXPERIMENTAL

The general preparative procedure has been described previously.[1] The physical properties of the products are as follows.

(a) 4,4′-*Spirobi*-6,6-*dimethyl*-3,4,5,6-*tetrahydropyrimidin*-2(1H)-*one* (3).—This was recrystallised from water, m.p. 265° (lit.,[2] 265°), $\nu_{max.}$ 3 510, 3 340, and 3 215 (NH) and 1 660 cm^{-1} (C=O); δ_H ([$^2H_6$]DMSO; 120°) 1.15, 1.18 (12 H, 2s), 1.89 (4 H, dd, *J* 14 Hz), and 5.88, 5.99 (4 H, 2s); δ_C 30.22, 48.01, 52.98, 68.32, and 158.63 p.p.m. (Found: C, 51.15; H, 8.4; N, 22.4. $C_{11}H_{22}N_4O_3$ requires C, 51.15; H, 8.6; N, 21.7%).

(b) 6,6-*Dimethyl*-4-(4,6,6-*trimethyl*-2-*oxoperhydropyrimidin*-4-*ylmethyl*)-3,6-*dihydropyrimidin*-2(1H)-*one* (7).—After chromatography the product was recrystallised from methanol, m.p. 302° (lit.,[4] 295°); $\nu_{max.}$ 3 428 and 3 220 (NH), 1 695 (C=O), and 1 670 cm^{-1} (C=C); $\delta_H(CF_3CO_2H)$ 1.45, 1.49, 1.59 (15 H, 3s), 2.04 (2 H, dd, *J* 14 Hz), 2.56 (2 H, dd, *J* 14 Hz), 4.86 (1 H, s), 7.07 (1 H, s), and 8.26 (1 H, s); $\delta_C(CF_3CO_2H)$ 28.44, 30.62, 31.08, 31.57, 45.80, 45.96, 53.65, 55.70, 56.48, 114.04, 128.73, 158.20, and 158.47 p.p.m. (Found: C, 59.45, H, 8.65, N, 19.85. $C_{14}H_{24}N_4O_2$ requires C, 59.75; H, 8.6; N, 19.9%).

(c) *Spiro-compound* (12).—After removal of benzene the residue was purified by column chromatography (Al_2O_3). The material was eluted with $CHCl_3$ and recrystallised from $CHCl_3$, m.p. 328°; *m/e* 268 (M^+), $\nu_{max.}$ 3 290 (NH), 1 670, and 1 655 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 1.27 (6 H, s), 1.36 (6 H, s), 2.22 (4 H, dd, *J* 14 Hz), 2.72 (6 H, s), and 5.14 (2 H, s); δ_C 18.44, 27.74, 28.81, 31.72, 44.23, 48.37, 58.24, and 156.86 p.p.m. (Found: C, 57.85; H, 8.85; N, 20.9. $C_{13}H_{24}N_4O_2$ requires C, 58.2; H, 9.0; N, 20.85%).

(d) *Pyrimidinylmethylpyrimidone* (13).—After removal of the benzene the residue was purified by column chromatography (Al_2O_3). The product was eluted with $CHCl_3$ and recrystallised from acetone, m.p. 202°; *m/e* 308 (M^+); $\nu_{max.}$ 3 210 (NH), 1 680, 1 660 (C=O) and 1 630 cm^{-1} (C=C); $\delta_H(CDCl_3)$ 1.23 (9 H, s), 1.31 (3 H, s), 1.53 (3 H, s), 2.02 (2 H, dd, *J* 14 Hz), 2.47 (2 H, dd, *J* 14 Hz), 2.85 (3 H, s), 3.13 (3 H, s), 4.77 (1 H, s), 5.82 (1 H, s), and 6.66 (1 H, s); δ_C 28.27, 28.51, 28.81, 29.62, 30.28, 30.43, 31.69, 35.99, 48.05, 48.79, 56.69, 112.22, 137.36, 153.56, and 156.21 p.p.m. (Found: C, 61.55; H, 9.45; N, 18.6. $C_{16}H_{28}N_4O_2$ requires C, 62.3; H, 9.15; N, 18.15%).

[9/598 *Received*, 18*th April*, 1979]

REFERENCES

[1] Part 6, A. R. Butler and I. Hussain, preceding paper.
[2] A. Weinschenk, *Ber.*, 1901, **34**, 2185.
[3] M. T. Harvey, U.S.P. 2592565.
[4] H. H. Hatt and A. C. K. Triffett, *Chem. Comm.*, 1965, 439
[5] G. Zigeuner, E. Fuchs, H. Brunnetti, and H. Sterk, *Monatsh.*, 1966, **97**, 36.