β-DICARBONYL COMPOUNDS

COMMUNICATION 23. ACETOACETYLUREA

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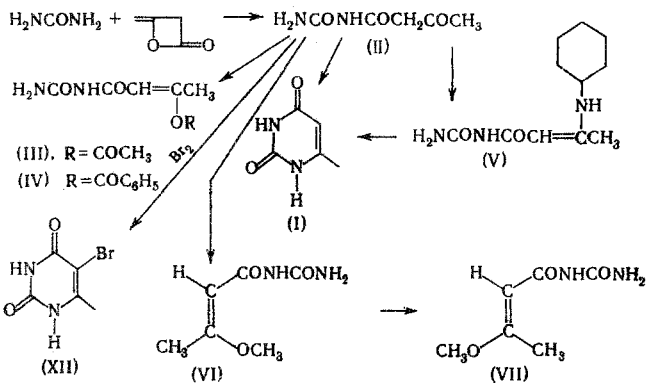
In 1939 Boese [1] took out a patent for a method of preparing 6-methyluracil (I) by the reaction of urea with ketene dimer in an inert solvent. In 1954 Iwakura and co-workers [2] gave a detailed description of the conditions for this reaction, which went in 25% yield when the reactants were boiled for 12 h in toluene. Somewhat later, Khromov-Borisov and Karlinskaya [3] reported increase in the yield of 6-methyluracil to 64-65% by the use of pyridine as catalyst and performance of the reaction in chlorobenzene at 80-125° for 1 h. In accordance with a generally accepted mechanism it was assumed [4] that the formation of 6-methyluracil from ketene dimer and urea goes through the intermediate stage of acetoacetylurea (II), which, however, had not been isolated and characterized.



We have shown that in presence of pyridine in toluene at 20-65° urea condenses with ketene dimer with formation of acetoacetylurea in 74% yield, whose structure is confirmed by its cyclization into (I) when heated for 5 h in boiling toluene. (I) can be obtained in an overall yield of 70-90% in one operation without isolation of the intermediate ureide if pyridine p-toluenesulfonate is used as cyclization agent or the reaction is conducted in acetic acid without any catalyst. In presence of free p-toluenesulfonic acid in a toluene medium, ketene dimer reacts with urea only on heating with formation of (I) in 40% yield. In presence of pyridine, however, even at an elevated temperature the formation of (I) in a toluene medium goes with very much greater difficulty, which is contrary to the data in [3]. Under the conditions stated by these authors we were only able to isolate a mixture of acetoacetylurea and (I). The condensation of butylurea with ketene dimer in toluene or chlorobenzene in presence of pyridine goes at an appreciable rate only at an elevated temperature and gives a mixture of the isomeric butylureides (VIII) and (IX), one of which (VIII) was isolated in the pure state. When this mixture was heated in boiling toluene with an addition of p-toluenesulfonic acid, the corresponding uracils (X) and (XI) were formed, and these are separated by chromatography on alumina. (XI) was identical in melting point to 3-butyl-6-methyluracil, prepared by the reaction of butyl isocyanate with 3-aminocrotonic ester [5] (see scheme on following page).

It is interesting that the condensation of butylurea with ketene dimer in pyridine solution at room temperature has a selective character and leads mainly to one of the isomeric butylureides (VIII). Acetoacetylurea gives a characteristic reaction with ferric chloride, but judging from the weak absorption in the UV region its enol content must be very small [λ_{max} 260 mμ (ε 3600 in ethanol and ε 151 in hexyl alcohol)]. The IR spectrum of the ureide (II) determined in dilute chloroform solution contains only two carbonyl frequencies at 1645 and 1635 cm^{-1}, which may be assigned to the stretching vibrations of ketonic and amide carbonyl groups which are hydrogen-bonded intramolecularly. The IR spectrum of the butyl-

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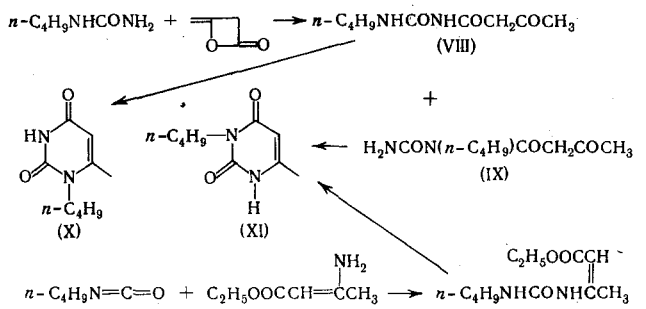

ureide (VIII) contains the usual ketonic and amide carbonyl bands at 1707 and 1655 cm^{-1}, which is evidently indicative of the lack of hydrogen-bonding in this case because of steric hindrance due to the butyl group. The absence or weakening of the hydrogen bond stabilizing the keto form may explain the higher enolizability of the butylureide (VIII) [λ_{max} 263 mμ (in alcohol), ε 9800)], as compared with the unsubstituted ureide (II). Acetoacetylurea is distinguished by the high tendency for cyclization into (I), which gives rise to difficulties in the study of its reactions with participation of keto and methylene groups. For this reason we were unable to bring about such simple reactions as C-alkylation with benzyl chloride in t-butyl alcohol and oxime formation in aqueous-alcoholic solution.

However, the ureide was able to form the following derivatives by reaction at the keto group: the 2,4-dinitrophenylhydrazone, the enol acetate (III) and benzoate (IV) by treatments with acetic anhydride and with benzoyl chloride in pyridine, the enol methyl ether (VI) by treatment with ethereal diazomethane, and the N-cyclohexyl enamine (V) by treatment with cyclohexylamine in boiling toluene. Together with these derivatives of acetoacetylurea, in almost all cases (I) was isolated. The enol esters and ethers (III), (IV), and (VI) can be converted into (I) by treatment with hot dilute hydrochloric acid for a short time, and the enamine (V) can be converted into (I) by heating it for 5 h in boiling toluene in presence of p-toluenesulfonic acid.

Neither the ureide (II) nor its enol ether (VI) forms an enamine with morpholine under fairly severe conditions (boiling toluene). In the first case, instead of the formation of the enamine the usual cyclization of the ureide into (I) occurs, and in the second case a substance is obtained of m.p. 200° and with a λ_{max} of 235 mμ (ε 21,000), but with a very similar IR spectrum and the same elemental composition as the original low-melting enol ether (VI) (m.p. 139°). Like the enol ether (VI), its high-melting isomer undergoes acid hydrolysis with simultaneous cyclization into (I). On the basis of these results it may be supposed that, in the heating of acetoacetylurea enol ether with morpholine in toluene isomerization of the cis form (VI) into the trans form (VII) occurs, in a similar way to the cis-trans isomerization of 2,4-pentanedione [6]. The bromination of acetoacetylurea is accompanied by cyclization and leads to the formation of 5-bromo-6-methyluracil (XII).

EXPERIMENTAL

Preparation of Acetoacetylurea (II). To a stirred suspension of 7.9 g of urea in 65 ml of dry toluene at about 20° first 15 ml of ketene dimer and then 2.5 ml of dry pyridine were added. During the next 30 min the temperature of the mixture attained 65°. When the mixture had cooled to 20°, the precipitate was separated and washed successively with toluene, ether, water, and methanol. We obtained 14.3 g (74%) of (II), m.p. 139-141°, raised by recrystallization from aqueous alcohol to 146-147°. R_f (here and later thin-layer chromatography was conducted on silica gel) 0.72 in 5:1 acetone—water and 0.65 in 1:5 heptane—acetone; ν 1645 and 1635 cm^{-1} (here and later $CHCl_3$); λ_{max} 260 mμ (ε 3600) (in alcohol), 260 mμ (ε 151) (in hexyl alcohol). Found %: C 41.79, 41.50; H 5.70, 5.91; N 19.65, 19.45. $C_5H_8O_3N_2$. Calculated %: C 41.67; H 5.59; N 19.43. 2,4-Dinitrophenylhydrazone, m.p. 219-220° (mixture of methanol and dioxane); λ_{max} 357 mμ (in alcohol). Found %: N 26.09, 26.02. $C_{11}H_{12}O_6N_6$. Calculated %: N 25.91.

Preparation of 6-Methyluracil (I). 1 ml of dry pyridine was added to 15.8 g of urea and 23 ml of ketene dimer in 125 ml of dry toluene at 80°, and the mixture was heated to 105°. At the end of the exothermic reaction when the mixture had cooled to 40°, 200 mg of p-toluenesulfonic acid was added, and the mixture was boiled with a water separator for about 5 h. The crystals which separated were filtered off and washed successively with ether, alcohol, water, alcohol, and ether. We obtained 24 g (72%) of (I), m.p. 306-308°, raised by crystallization from aqueous methanol to 310-312°. R_f 0.68 in 5:1 acetone—

water and 0.51 in 1 : 5 heptane—acetone. λ_{max} 259 mμ (ε 11,800) (in alcohol). Found %: C 47.66, 47.56; H 4.63, 4.75; N 21.99, 21.90. $C_5H_6O_2N$. Calculated %: C 47.50; H 4.75; N 22.20. The literature gives: m.p. of (I) 300° (decomp.) [7]; λ_{max} for uracils 260 mμ [8].

A mixture of 3 g of urea, 5.8 ml of ketene dimer, 100 mg of p-toluenesulfonic acid, and 30 ml of dry toluene was boiled with a water separator until no more water separated (about 5 h). The crystals which separated on cooling were treated as indicated above. We obtained 2.5 g (40%) of (I), m.p. 307-308°.

A suspension of 1 g of (II) in 20 ml of dry toluene was boiled for 5 h. The crystals which came down on cooling were filtered off and washed with ether. We obtained 0.85 g (98%) of (I), m.p. 305-308°.

A mixture of 1.2 g of urea, 3 ml of ketene dimer, and 15 ml of acetic acid was boiled for 6 h. The mixture was left for 12 h at room temperature, and the precipitate formed was filtered off and washed with ether and methanol. We obtained 2.3 g (91%) of (I), m.p. 308-310°.

1-Acetoacetyl-3-butylurea (VIII). 0.84 g of ketene dimer was added to 1.16 g of butylurea in 10 ml of pyridine at 15°. Exothermic reaction occurred with rise in temperature to 35°. 30 min after the mixing of the reactants the mixture was heated to 60°, and then it was left for 12 h at 20°. The precipitated (VIII) (0.4 g) melted at 140-142° and gave a color with ferric chloride. The filtrate was evaporated, the solid residue was washed with ether, and we isolated a further 0.9 g of (VIII), m.p. 143-144°; the total yield was 65%. R_f 0.35 in 2 : 1 benzene — ethyl acetate; ν 1707 and 1658 cm^{-1}; λ_{max} 263 mμ (in alcohol) (ε 9800). Found %: C 54.22, 54.12; H 8.02, 8.03; N 14.36. $C_9H_{16}O_3N_2$. Calculated %: C 54.20; H 8.0; N 14.00. 2,4-Dinitrophenylhydrazone, m.p. 155-156° (methanol). Found %: N 22.14, 22.22. $C_{15}H_{20}O_6N_6$. Calculated %: N 22.10.

Cyclization of 1-Acetoacetyl-3-butylurea into 1-Butyl-6-methyluracil (X). 0.4 g of (VIII) was heated in boiling toluene in presence of catalytic amounts of p-toluenesulfonic acid for 2 h; the mixture was then evaporated, and the precipitate was filtered off and washed with ether. We obtained 0.3 g (83%) of (X), m.p. 135-136° (from benzene). R_f 0.47 on alumina of activity II in 30 : 1 butanone—water; ν 1692 and 1618 cm^{-1}; λ_{max} 268 mμ (ε 15,200) (in alcohol). Found %: C 59.31, 59.35; H 7.32, 7.40; N 15.28, 15.46. $C_9H_{14}O_2N_2$. Calculated %: C 59.40; H 7.86; N 15.30.

The cyclization of the butylureide (VIII) can also be brought about by treatment with boiling water or with dilute hydrochloric acid at room temperature.

Preparation of 1- and 3-Butyl-6-methyluracils (X) and (XI). 0.6 ml of pyridine was added to a solution of 3.5 g of butylurea and 3 g of ketene dimer in 20 ml of chlorobenzene at 85°. Exothermic reaction occurred, and the temperature of the mixture rose to 105°. When the mixture had cooled to room temperature, it was stirred for 1 h, and the precipitate formed was filtered off and washed with boiling ether. We obtained 1.6 g of (VIII), m.p. 140-142°. From the combined filtrates we isolated a mixture of products. This mixture was heated with p-toluenesulfonic acid in boiling toluene until no more water separated. In subsequent chromatography on alumina of activity II (elution with chloroform) we obtained 0.8 g of (X), m.p. 131-132°, and 0.6 g of (XI), m.p. 179-180° (mixture of heptane and isopropyl alcohol). R_f 0.71 on alumina of activity II in 30 : 1 butanone—water; ν 1712 and 1653 cm^{-1}; λ_{max} 260 mμ (ε 8190) (in alcohol). Found %: C 59.16, 59.14; H 7.74, 7.82; N 15.82, 15.86. $C_9H_{14}O_2N_2$. Calculated %: C 59.32; H 7.74; N 15.37. For the melting point of (XI) the literature [5] gives 182-183°.

Enol Acetate of Acetoacetylurea (III). 1.8 g of acetic anhydride was added to a suspension of 1 g of (II) in 10 ml of dry pyridine. After 20-30 min the precipitated crystals were separated and washed with ether. We obtained 0.57 g of contaminated enol acetate (III), m.p. 128-129°. Crystallization from methanol gave 0.4 g (30%) of pure substance, m.p. 151-153°. R_f 0.75 (1 : 5 heptane—acetone); ν 1762, 1731, 1700, 1658 cm^{-1}; λ_{max} 227.5 mμ (ε 8110) (in alcohol). Found %: C 45.23, 45.38; H 5.58, 5.51; N 14.64, 14.75. $C_7H_{10}O_4N_2$. Calculated %: C 45.16; H 5.41; N 15.04.

In the treatment of 100 mg of the enol acetate (III) with 5 ml of boiling dilute (1 : 1) HCl for 5 min we isolated 60 mg (88%) of (I), m.p. 302-305°.

Enol Benzoate of Acetoacetylurea (IV). 2 g of benzoyl chloride was added to a suspension of 2 g of (II) in 20 ml of dry pyridine. The mixture was left for 24 h at room temperature and then evaporated to dryness; the residue was treated with 10 ml of water. The precipitate was filtered off and washed with water and alcohol. We obtained 1.2 g of contaminated enol benzoate (IV), m.p. 148-150°. Crystallization from methanol gave 0.9 g of pure substance, m.p. 174-176°. R_f 0.72 (7 : 5 heptane—acetone); ν

1727, 1705, 1693, 1658 cm^{-1}. Found %: C 58.07, 57.93; H 4.59, 4.76; N 11.52, 11.43. $C_{12}H_{12}O_4N_4$. Calculated %: C 58.06; H 4.87; N 11.28.

Enol Methyl Ether of Acetoacetylurea (VI). 0.5 g of (II) was treated with an ethereal solution of 0.5 g of diazomethane, and the mixture was left at room temperature for 72 h. We obtained 0.47 g (85%) of (VI), m.p. 136-138°. After recrystallization from ethyl acetate the melting point of the enol ether did not change. R_f 0.35 (5:1 acetone—heptane); ν 1714, 1673, 1624, 1550 cm^{-1}; λ_{max} 253 mμ (ε 16,310) (in alcohol). Found %: C 46.02, 45.90; H 6.64, 6.50; N 17.54, 17.50. $C_6H_{10}O_3N_2$. Calculated %: C 45.57; H 6.37; N 17.72.

N-Cyclohexyl Enamine of Acetoacetylurea (V). A mixture of 2 g of (II), 1.4 g of cyclohexylamine, and 25 ml of dry toluene was boiled with a water separator until no more water separated (about 5 h). The precipitate was filtered off and washed with boiling water. We obtained 1 g (32%) of (V), m.p. 194-196°. After recrystallization from methanol the melting point of the enamine did not change. R_f 0.63 (1:5 heptane—acetone); ν 1703, 1636, 1605, 1543 cm^{-1}; λ_{max} 305 mμ (ε 29,700) (in alcohol). Found %: C 58.71, 58.50; H 8.43, 8.27; N 18.73, 18.78. $C_{11}H_{19}O_2N_3$. Calculated %: C 58.68; H 8.49; N 18.65. From the aqueous mother solution we isolated (I).

Cyclization of the N-Cyclohexyl Enamine (V). A mixture of 300 mg of the enamine (V), 50 mg of p-toluenesulfonic acid, and 5 ml of dry toluene was boiled for 5 h. When the mixture was cool, the crystals were separated and washed with methanol and ether. We obtained 150 mg of (I), m.p. 305-307°.

Isomerization of the Acetoacetylurea Enol Ether (VI). A mixture of 1 g of the enol ether (VI), 0.55 g of dry morpholine, and 20 ml of toluene was boiled for 2 h. The crystals which came down on cooling were separated and washed with ether, methanol, and water. We obtained 0.48 g (48%) of the isomeric enol ether (VII), m.p. 188-190°, raised by recrystallization from aqueous methanol to 199-200°. R_f 0.55 (1:5 heptane—acetone); ν 1716, 1681, 1617, 1554 cm^{-1}; λ_{max} 246.5 mμ (ε 21,000) (in alcohol). Found %: C 45.51, 45.61; H 6.35, 6.31; N 17.80, 17.86. $C_6H_{10}O_3N_2$. Calculated %: C 45.57; H 6.37; N 17.72.

Bromination of Acetoacetylurea. 1 ml of bromine was added to a solution of 2 g of acetoacetylureide in 50 ml of glacial acetic acid at 20°. The mixture was left for 3 h, and the precipitated crystals were filtered off and recrystallized from acetic acid. We obtained 1.8 g (65%) of 5-bromo-6-methyluracil (XII), m.p. 238-240° (decomp.), undepressed by admixture of the product of the bromination of (I).

Bromination of 6-Methyluracil (I). In the bromination of 2 g of (I) in 75 ml of glacial acetic acid as described above we obtained 1.8 g (55%) of (XII), m.p. 237-240° (decomp.). The literature [9] gives m.p. 238-240°.

CONCLUSIONS

1. By the reaction of urea with ketene dimer in presence of pyridine in a toluene medium we obtained acetoacetylurea, and some of its reactions at the keto and methylene groups were studied.

2. The method of preparing 6-methyluracil was improved; it was obtained by the condensation of urea with ketene dimer in toluene in presence of pyridine and p-toluenesulfonic acid and by conducting this condensation in acetic acid in absence of any additions.

3. Conditions were found for the formation of 1-acetoacetyl-3-butylurea and also of 1- and 3-butyl-6-methyluracils by the reaction of ketene dimer with butylurea.

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