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Studies on Ketene and Its Derivatives. Ⅻ.[*1] The Structure of the Self-Condensation Product of Acetoacetamide.

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Claisen and Meyer[2] reported the pyrolysis of acetoacetamide (I) to afford 2,4-dimethyl-5-oxo-1,6-dihydro-3-pyridinecarboxamide (Ⅱ-a), which, on hydrolysis, was converted to the lutidone carboxylic acid (Ⅲ-a).

We re-tested this reaction and found that 3-acetyl-4-amino-6-methyl-2-pyridone (Ⅱ-b) is the proper structure for the pyrolyzed product and that 3-acetyl-4-hydroxy-6-methyl-2-pyridone (Ⅲ-b) is the correct one for the hydrolyzed compound.

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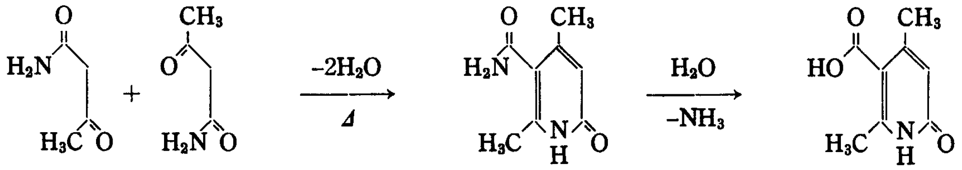
In 1882, Duisberg[1] reported the reaction of ethyl acetoacetate with ammonia to give acetoacetamide (I). Claisen and Meyer[2] investigated several reactions of I, and described that when being heated, I was hardly distilled to be transformed to a crystalline substance, $C_8H_{10}O_2N_2$ (Ⅱ). Although they did not describe the details of the experimental such as reaction conditions, yield or its physical properties, 2,4-dimethyl-5-oxo-1,6-dihydro-3-pyridinecarboxamide (Ⅱ-a) was given as the structure for this compound. Structural assignment was made on the basis of the following fact; that is, hydrolysis of Ⅱ afforded ammonia with a crystalline substance (Ⅲ), whose melting point was practically the same as that of 2,4-dimethyl-5-oxo-1,6-dihydro-3-pyridinecarboxylic acid (Ⅲ-a) which had been prepared by Nieme and Pechmann.[3] And they explained the reaction pathway as shown in Chart 1.



I Ⅱ-a Ⅲ-a

Chart 1.

When this reaction was re-investigated in our laboratory in an effort to obtain the lutidone carboxylic acid (Ⅲ-a), the results obtained were at variance with those reported by Claisen and Meyer.[2] We found that 3-acetyl-4-amino-6-methyl-2-pyridone (Ⅱ-b) is the proper structure for the compound Ⅱ and that 3-acetyl-4-hydroxy-6-methyl-2-pyridone (Ⅲ-b)[4] is the correct structure for the hydrolyzed product (Ⅲ). Moreover, the main product of this reaction is not Ⅱ but 2,6-dimethyl-4-pyrimidone (Ⅳ).[5] In this paper we will show the evidence for these conclusions.

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1) C. Duisberg : Ann., **213**, 174 (1882).

2) L. Claisen, K. Meyer : Ber., **35**, 583 (1902).

3) A. Nieme, H. Pechmann : Ann., **261**, 190 (1891).

4) S. Seto, H. Sasaki, K. Ogura : Bull. Chem. Soc. Japan, **39**, 281 (1966).

5) A. Pinner : Ber., **22**, 1616 (1889).

When dry ammonia gas was bubbled into a solution of diketene in absolute ether with ice-cooling, acetoacetamide (I) was obtained in a good yield. Heating of I afforded colorless leaves of m.p. 191~191.5°, $C_6H_8ON_2$ (IV), as a main product (52%), accompanied with pale yellowish needles of m.p. 314~317° (decomp.), $C_8H_{10}O_2N_2$ (II), as a by-product (3%). But if the pyrolysis was carried out at a reduced pressure, the yield of II increased. Table I shows the summary of this reaction.

Table I. Pyrolysis of Acetoacetamide (I) under Reduced Pressure[a)]

I (g.)	Temp. (°C)	Time (hr.)	II-b (g.)(%)	IV (g.)(%)
4	150~160	3		1.2(49)
5	160	4	1.7(45)	1.3(41)
15	165	4	3.8(31)	1.6(17)
15	175~180	4	4.3(35)	4.0(33)
10	145~160	4	2.4(30)	2.8(45)
30	140±5	4	8.0(32)	4.3(23)
58	160±10	4	15.5(32)	17.0(48)
5[b)]	135~140	3	0.14(3.4)	1.6(52)

a) *ca.* 20 mm. Hg (water jet pump). b) at normal pressure

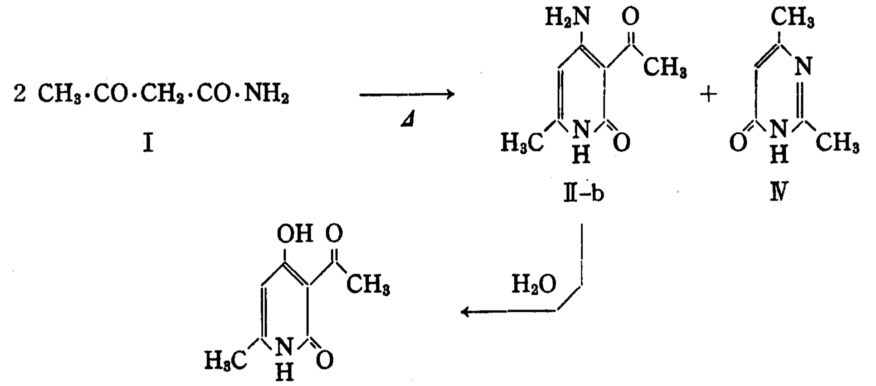

Chart 2.

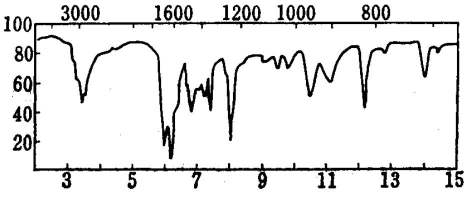

Fig. 1. Infrared spectrum of III (KBr)

As mentioned before, Claisen and Meyer[2)] described that hydrolysis of II afforded readily colorless needles of m.p. 256° (decomp.). $C_8H_9O_3N$ (III), accompanied by the evolution of ammonia. Because the melting point was approximately similar to that of 2,4-dimethyl-5-oxo-1,6-dihydro-3-pyridinecarboxylic acid (III-a) (lit. m.p. 258°[3)]), the structure II-a seemed to be likely proposed. However, as shown in Fig. 1 the infrared spectrum of III shows none of the absorption bands owing to the carboxylic acid in the region of *ca.* 1700 and 2500~3000 cm^{-1}. Moreover, attempts to obtain 4,6-dimethyl-2-pyridone from the hydrolyzed product (III) by decarboxylation reaction were unsuccessful.

Recently, Seto, *et al.*[4)] reported the reaction of diketene with acetoacetamide (I) in the presence of a catalytic amount of triethylamine giving colorless needles of m.p. 256° (decomp.), to which they assigned the structure of 3-acetyl-4-hydroxy-6-methyl-2-pyridone (III-b). Because of the similarity of the melting point, an attempt was made to compare these two compounds. Consequently, the hydrolyzed product (III) was identified unequivocally as III-b by comparison of its infrared absorption spectrum and the thin-layer chromatogram with those of an authentic specimen prepared according to the method[4] described above. In view of this fact, it seems reasonable to conclude that the structure of II is not II-a but II-b.

The main product of this reaction, colorless needles of m.p. 191°, was characterized as 2,6-dimethyl-4-pyrimidone (IV) which was synthesized from acetamidine and ethyl acetoacetate by the Pinner's method.[5]

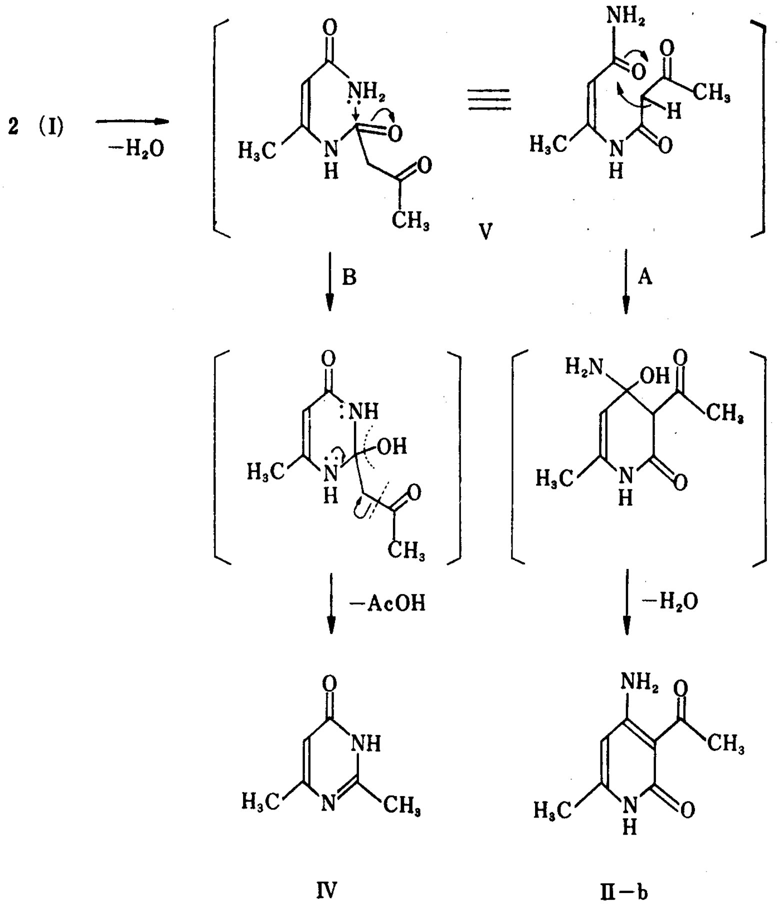

Chart 3.

Although the details of the mechanism remain obscure for the present, a probable pathway is shown in Chart 3. Though intermediates listed in the bracket were not isolated, the first stage of this reaction would be the elimination of one mole of water yielding β-acetoacetaminocrotonamide (V), and the subsequent stage might well involve the leaving of another mole of water giving II-b (pathway A) or the elimination of acetic acid to give IV (pathway B).

Experimental

Acetoacetamide (I)[1,6]

Dry NH_3 gas was passed gently into a solution of 50 ml. of diketene in 150 ml. of absolute ether with ice-cooling. After 2 hr., white crystals precipitated were collected by suction, and washed with a small amount of $CHCl_3$. Acetoacetamide (I), obtained thus, was practically pure, m.p. 53~54°, 57.5 g. (96%). Recrystallization from $CHCl_3$ gave colorless prisms of m.p. 54° (lit.[6] m.p. 54°).

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6) F. Chick, N. Wilsmore: J. Chem. Soc., **97**, 1982 (1910); M. Yamato, K. Oshima: Yakugaku Zasshi, **85**, 943 (1965).

Pyrolysis of Acetoacetamide (I)

Five grams of I was heated at 135~140°. The gas evolved during heating was identified as NH_3 by its odor, litmus test paper and Nessler reagent. After 3 hr., the residue was washed with water. The water insoluble substance was purified by crystallization from MeOH to give pale yellowish prisms of m.p. 314~317°(decomp.), 0.14 g. (3%). *Anal.* Calcd. for $C_8H_{10}O_2N_2$ (II-b): C, 57.82; H, 6.07; N, 16.86. Found: C, 57.67; H, 5.79; N, 16.33.

The water soluble fraction was condensed to dryness, and extracted with benzene. From the benzene soluble fraction 1.9 g. of crystalline solid was obtained. Recrystallization from AcOEt afforded colorless leaves of m.p. 191~191.5°, 1.6 g. (52%). *Anal.* Calcd. for $C_6H_8ON_2$ (IV): C, 58.05; H, 6.50; N, 22.57. Found: C, 57.98; H, 6.65; N, 22.29. The melting point of this compound was not depressed by admixture with an authentic sample of 2,6-dimethyl-4-pyrimidone.5)

Hydrolysis of II-b

1) A suspension of II-b (0.2 g.) in 10 ml. of 40% NaOH was heated gently. After refluxing for 2 hr., during which time NH_3 was evolved, the reaction mixture was made acidic with 10% HCl to give a white precipitate, which was collected by suction, dried, and purified by crystallization from MeOH to give colorless needles of m.p. 256°(decomp.), 0.1 g. *Anal.* Calcd. for $C_8H_9O_3N$ (III-b): C, 57.48; H, 5.43; N, 8.38. Found: C, 57.66; H, 5.61; N, 8.44. Its infrared spectrum was identical with that of an authentic specimen (III-b) prepared by the method of Seto, *et al.*4)

2) A solution of II-b (0.1 g.) in 20 ml. of 20% HCl was refluxed for 2 hr., and condensed *in vacuo*. The residue was extracted with $CHCl_3$. From the $CHCl_3$ extract 0.1 g. of crude crystals was obtained. Recrystallization from MeOH afforded 0.06 g. of III-b.

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