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Studies on Ketene and Its Derivatives. XXVIII.1) Reaction of β-Aminocrotonamide with Ketene and Diketene

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The reaction of β-aminocrotonamide (V) with ketene afforded α-acetyl-β-aminocrotonamide (VII). When the reaction was carried out in the presence of triethylamine or pyridine, α-acetyl-β-acetylaminocrotonamide (VIII) was obtained. Heating of the diacetyl compound (VIII) with sodium hydroxide gave 5-acetyl-2,6-dimethyl-4(1H)-pyrimidone (IX) in good yield.

Similarly, the reaction of β-amino-N-methylcrotonamide (XII) with ketene afforded α-acetyl-β-acetylamino-N-methylcrotonamide (XV) and 5-acetyl-2,3,6-trimethyl-4(1H)-pyrimidone (XIV).

On the other hand, the treatment of β-amino-N,N-dimethylcrotonamide (XIII) with ketene resulted in the formation of a resinous product.

The reaction of V or XII with diketene yielded 3-acetyl-4-hydroxy-6-methyl-2(1H)-pyridone derivatives. The reaction of XIII with diketene gave only nitrogen free compounds.

There is a considerable literature dealing with the reaction of the enamine (I) with ketene,3–5) and the generalized reaction is the addition of the ketene to the enamine double bond giving the cyclobutanones (II). The stability of the cyclobutanones (II) obtained is widely different, for example, the non-enolizable compounds, such as the reaction product of dimethylketene and N,N-dimethylisobutenylamine, are thermally stable.4) However, if it has one or more hydrogen and can be enolizable, the cyclobutanone is usually unstable and transforms into the ring-opened compound, such as III or IV. The amino group of the enamine used in the above observations is tertiary (R_4, $R_5 \neq H$). Concerning the secondary enamine, which contains the secondary amino group (I, $R_4=H$, $R_5 \neq H$), Quadbeck6) has shown that Schiff base reacts with ketene to give C-acetyl compound if the system –N=C–CH– can rearrange to –NH–C=C–.

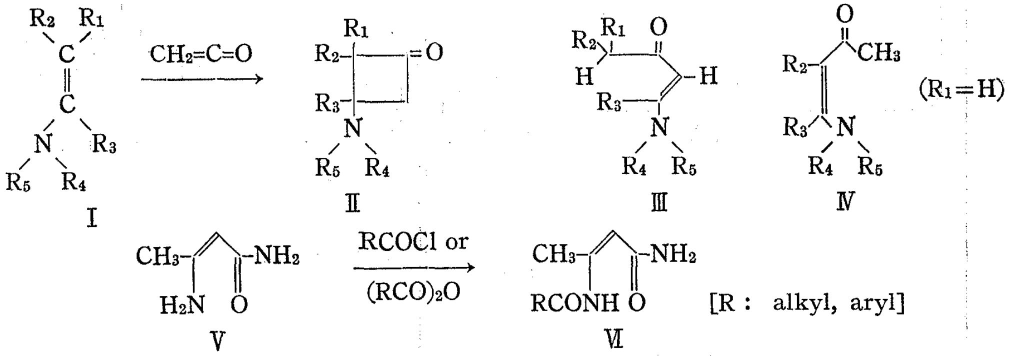

Chart 1

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1) Part XXVII: T. Kato, H. Yamanaka and J. Kawamata, *Yakugaku Zasshi*, **89**, 460 (1969).

2) Location: *Aobayama, Sendai.*

3) G.A. Berchtold, G.R. Harvey and G.E. Wilson, *J. Org. Chem.*, **26**, 4776 (1961).

4) R.H. Hasek and J.C. Martin, *J. Org. Chem.*, **26**, 4775 (1961).

5) G. Opitz, M. Kleemann and F. Zimmermann, *Angew. Chem.*, **74**, 32 (1962).

6) G. Quadbeck, *Angew. Chem.*, **68**, 361 (1956).

On the other hand, in the previous paper[7] of this series we reported that β-aminocrotonamide (V) reacted with the acylating reagent such as acid chloride or acid anhydride to give β-acylaminocrotonamide (VI) in good yield. Our interests have led us to investigate the reaction of V with ketene and diketene, because V can be considered to be a primary enamine, which is a little studied class of the enamine chemistry, and because ketene and diketene are also acylating reagents. The present paper reports that the reactions of the primary enamine such as β-aminocrotonamide (V), β-amino-N-methylcrotonamide (XII) and β-amino-N,N-dimethylcrotonamide (XIII) with ketene and diketene.

Reaction of Ketene with β-Aminocrotonamide (V), β-Amino-N-methylcrotonamide (XII) and β-Amino-N,N-dimethylcrotonamide (XIII)

When V was allowed to react with ketene in acetone, colorless prisms of mp 188° (decomp.) were obtained. The elemental analysis provided its empirical formula as the monoacetyl compound, $C_6H_{10}O_2N_2$ (VII). Its infrared (IR) spectrum is apparently different from that of the N-acetyl compound (VIa), which was prepared from V and acetic anhydride.[7]

In the nuclear magnetic resonace (NMR) spectrum of VII, a signal of the olefinic proton, which was observed in the spectra of V and VI, disappeared and a peak due to acetyl methyl protons presented at 2.69 ppm as a singlet. This fact is consistent with the structure of α-acetyl-β-aminocrotonamide (VII).

When the above reaction was carried out at room temperature in the presence of triethylamine as a catalyst, the diacetyl compound, $C_8H_{12}O_3N_2$ (VIII), was obtained in good yield. The IR spectrum of VIII shows the absorption of the acetyl carbonyl at 1717 cm^{-1} and two peaks owing to the amide carbonyl at 1670 and 1636 cm^{-1}. In the NMR spectrum, three singlet peaks due to methyl protons can be observed at 2.19, 2.31 and 2.51 ppm, and

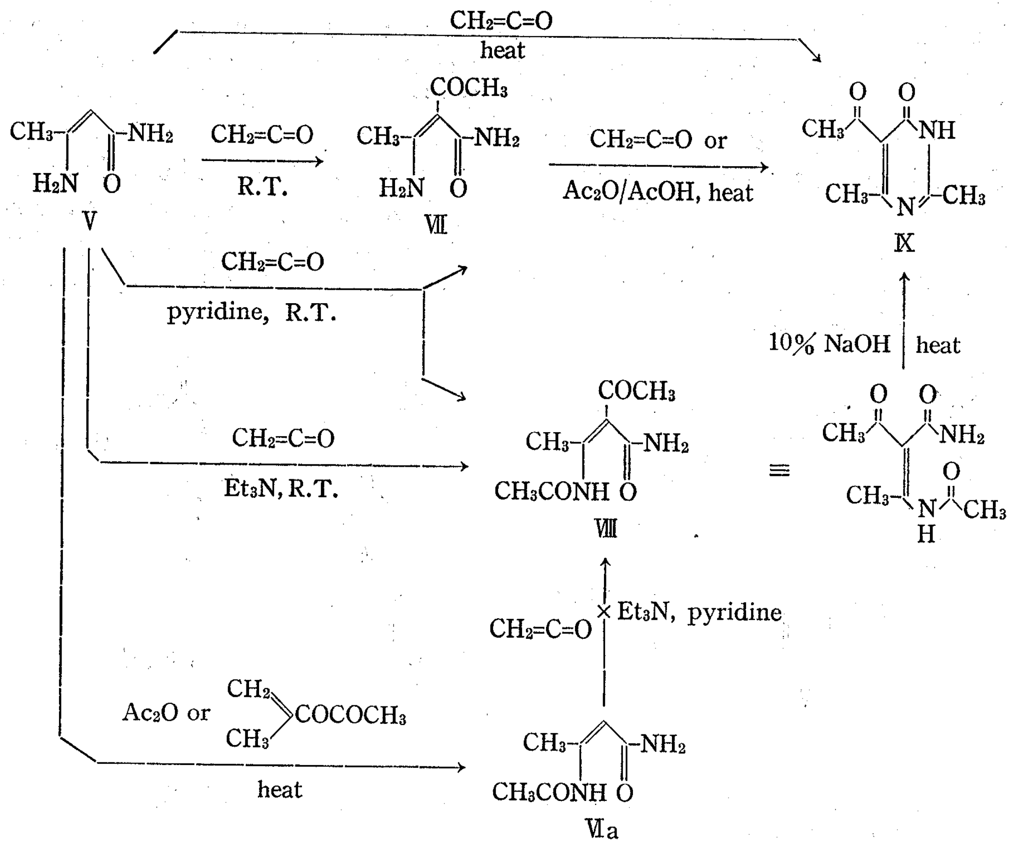

Chart 2

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[7] T. Kato, H. Yamanaka and T. Shibata, *Yakugaku Zasshi*, **87**, 955 (1967).

amide protons and a hydrogen bonding NH proton present at 5.8—6.6 ppm (2H, broad) and 12.78 ppm (1H, singlet), respectively. Based on the above fact, the structure of α-acetyl-β-acetamidocrotonamide (VIII) can be reasonably given for this product. Instead of triethylamine, the use of pyridine as a catalyst afforded the monoacetyl compound (VII) as a main product (35%) with the diacetyl derivative (VIII) as a by-product (13%).

It is of interest to note that the N-acetyl compound (VIa) can react no further with ketene even in the presence of a catalyst such as triethylamine or pyridine. Therefore, in the process of the formation of the diacetyl compound (VIII), the intermediate should be the C-acetyl compound (VII).

Heating of the diacetyl compound (VIII) with 10% sodium hydroxide afforded colorless prisms of mp 207°, $C_8H_{10}O_2N_2$ (IX), in pretty good yield. The compound IX was also obtainable by the treatment of the acetone solution of V or VII with ketene under reflux. The IR spectrum of IX indicated the presence of the amide carbonyl at 1637 cm^{-1} and acetyl carbonyl at 1695 cm^{-1}. In its NMR spectrum, three singlet peaks due to methyl groups were observed at 2.66, 2.75 and 2.94 ppm. The above data are consistent with the structure of 5-acetyl-2,6-dimethyl-4(1H)-pyrimidone (IX). IX reacted with excess phosphoryl chloride to give 5-acetyl-4-chloro-2,6-dimethylpyrimidine (X), which, on catalytic reduction with palladium catalyst, transformed into the chlorine free oil of bp 96° (15 mmHg), which was identified as 5-acetyl-2,6-dimethylpyrimidine (XI)[8,9] by the comparison of the IR spectrum and the mixed melting point of its semicarbazone with those of specimen prepared from ethoxymethylene acetylacetone and acetamidine according to the procedure reported by Claisen and Graham.

Treatment of V with isopropenyl acetate,[10] which was prepared from ketene and acetone, did not afford the C-acetyl compound (VII) but gave the N-acetyl compound (VIa).

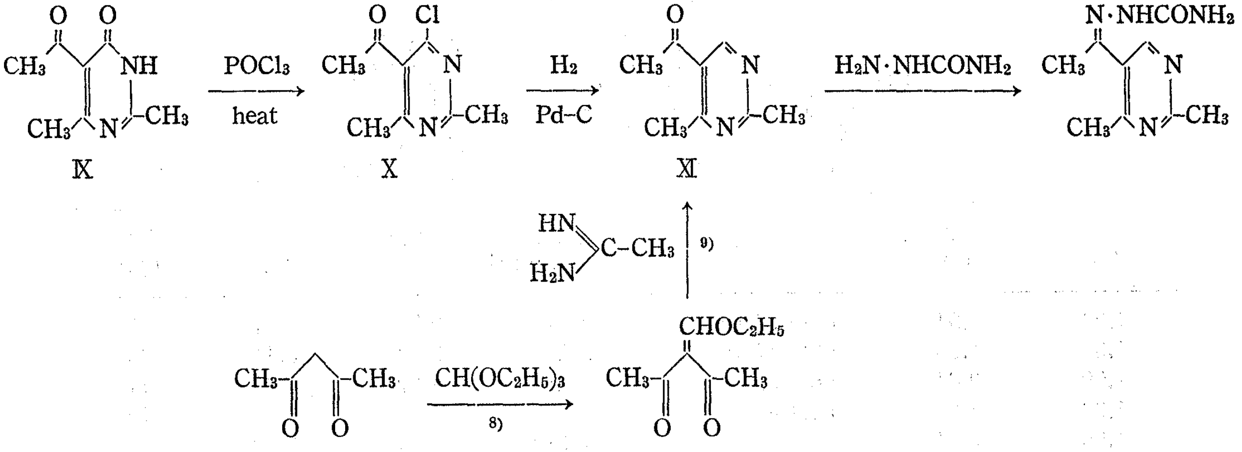

Chart 3

In this connection, attempts were made to react of ketene with the primary enamine such as β-amino-N-methylcrotonamide (XII) and β-amino-N,N-dimethylcrotonamide (XIII), which had been prepared by the reaction of ammonia with N-methylacetoacetamide[11] and N,N-dimethylacetoacetamide,[12] respectively. Thus, treatment of XII with ketene in the presence of triethylamine gave α-acetyl-β-acetylamino-N-methylcrotonamide (XV) in 33% yield with the formation of 5-acetyl-2,3,6-trimethyl-4(1H)-pyrimidone (XIV) in 18% yield. When this reaction was carried out with excess ketene, only the pyrimidone derivative (XIV) was ob-

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[8] L. Claisen, *Ann.*, **297**, 57 (1897).
[9] B. Graham, A. Griffith, C. Pease and B. Christensen., *J. Am. Chem. Soc.*, **67**, 1294 (1945).
[10] E.F. Degering and B.H. Gwynn, *J. Am. Chem. Soc.*, **64**, 2216 (1942).
[11] W. Muller, U.S. Patent 2615915 (1952).
[12] R.R. Whetstone and A.R. Stiles, U.S. Patent 2802855 (1957).

tained in 52% yield. However, the reaction of ketene with the tertiary amide (XIII) gave a resinous product, and attempts to purify were unsuccessful.

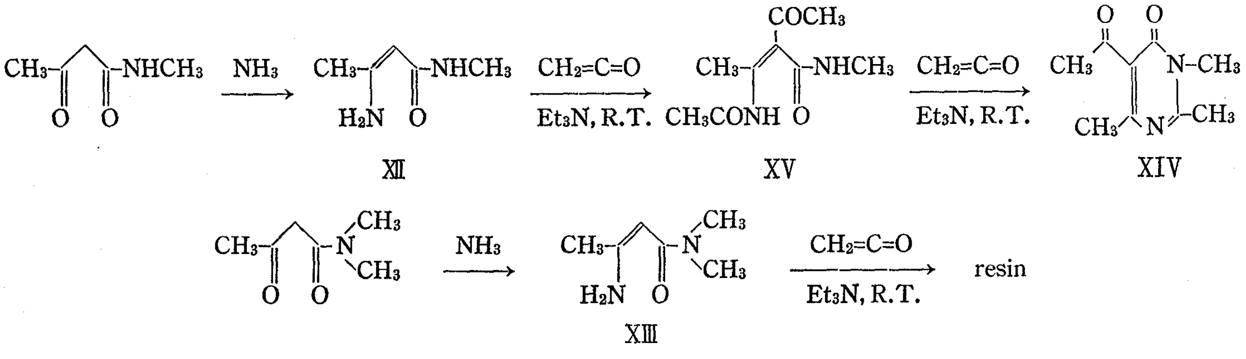
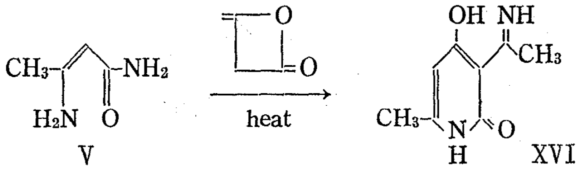


Chart 4

Reaction of Diketene with *β*-Aminocrotonamide (V), *β*-Amino-N-methylcrotonamide (XII) and *β*-Amino-N,N-dimethylcrotonamide (XIII)

It appeared of interest to investigate further the scope of this reaction with diketene in place of ketene, since little attention has been paid to the reaction of enamine with diketene. Thus, V was treated with diketene in chloroform to give colorless prisms of mp 314° (decomp.), which was identified as 3-acetimidoyl-4-hydroxy-6-methyl-2(1H)-pyridone (XVI)[13] by the comparison of its IR and NMR spectra with those of a specimen obtained in the self-condensation reaction of acetoacetamide reported in the previous paper.[14] Table I shows the summary of this reaction and the probable reaction pathway is shown in Chart 5.

TABLE I. Reaction of *β*-Aminocrotonamide with Diketene



V (g)	Diketene (g)	Solvent	Reaction temperature and time		Yield of XVI (g)	(%)
1.00	0.84	chloroform	reflux	2 hr	0.21	13
1.00	1.68	chloroform	reflux	2 hr	0.41	25
1.00	0.84	acetone	reflux	2 hr	0.28	17
1.00	1.68	acetone	reflux	2 hr	0.30	18
1.00	0.84	benzene	reflux	2 hr	0.23	14
1.00	1.68	benzene	reflux	2 hr	0.41	25
5.00	4.20	—	60°	0.5 hr	2.70	32
5.00	8.40	—	60°	0.5 hr	5.00	60

Employing the similar fashion as in the above experiment, *β*-amino-N-methylcrotonamide (XII) was treated with diketene to give colorless needles of mp 227°, $C_9H_{12}O_2N_2$ (XVII). In the NMR spectrum of XVII, three peaks due to methyl groups and a peak owing to a ring proton are present at 2.59 (3H, singlet), 2.94 (3H, singlet), 3.69 (3H, singlet) and 6.50 ppm (1H, singlet), respectively.

Based on the above data and considering the formation of XVI, 3-acetimidoyl-4-hydroxy-1,6-dimethyl-2(1H)-pyridone (XVII) will be given as the most reasonable structure for this

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[13] T. Kato, H. Yamanaka, J. Kawamata and T. Shibata, *Chem. Pharm. Bull.* (Tokyo), **16**, 1835 (1968).

[14] T. Kato, H. Yamanaka and T. Shibata, *Chem. Pharm. Bull.* (Tokyo), **15**, 921 (1967).

product. As shown in Chart 5, this compound (XVII) was prepared from ammonia and 3-acetyl-4-hydroxy-1,6-dimethyl-2(1H)-pyridone (XVIII), which was prepared from N-methylacetoacetamide and diketene.[15]

Similar treatment of β-amino-N,N-dimethylcrotonamide (XIII) with diketene resulted in the formation of resinous product with poor yields of nitrogen free compounds, such as dehydroacetic acid, 3,6-diacetyl-5-hydroxy-4,7-dimethylcoumarin, and 3,9-diacetyl-4,5,10-trimethyl-2H,8H-benzo [1,2-b:3,4-b']dipyran-2,8-dione.[16]

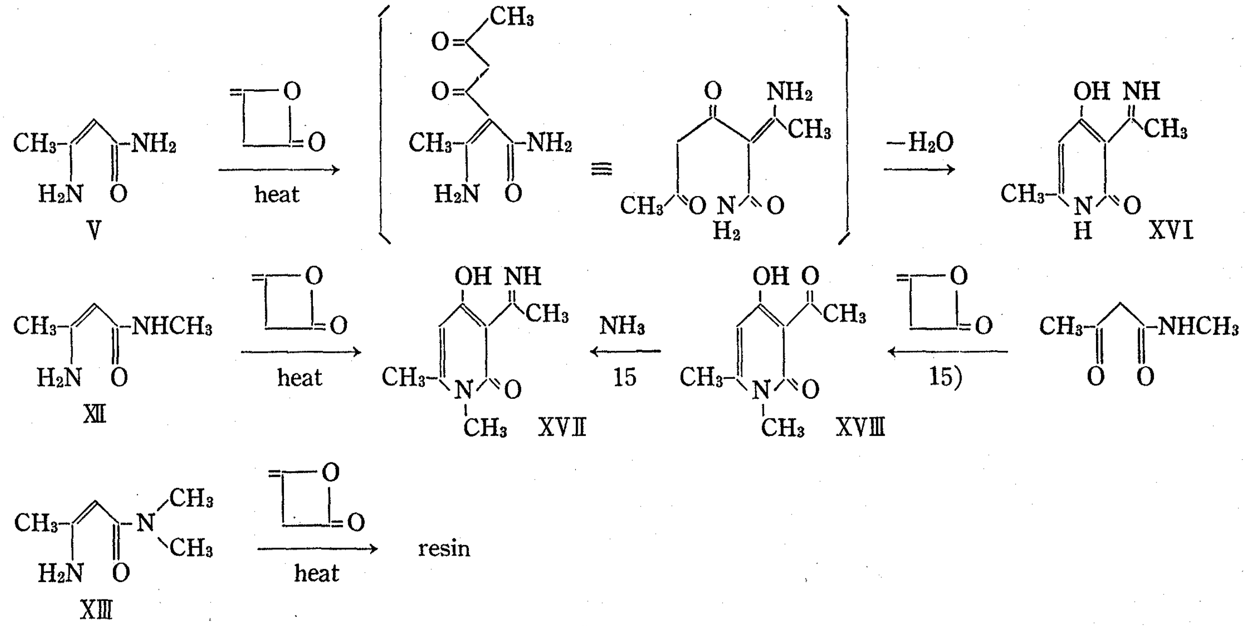

Chart 5

Experimental

α-Acetyl-β-aminocrotonamide (VII)——Ketene was prepared by pyrolysis of acetone according to the method reported by Hanford and Sauer.[17] The amount of ketene produced per hour was 0.2 mole.

Ketene gas was passed into a solution of V (1.0 g) in acetone (20 ml) at room temperature for 20 min (equivalent to 2.8 g of ketene). The solution was concentrated to precipitate crystals, which were collected and purified by recrystallization from acetone to yield 1.2 g (83%) of colorless prisms, mp 188° (decomp.). *Anal.* Calcd. for $C_6H_{10}O_2N_2$ (VII): C, 50.69; H, 7.09; N, 19.71. Found: C, 50.68; H, 6.97; N, 20.01. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3311, 3155, 1667. NMR (CF_3COOH, TMS, ppm): 2.66 (3H, s), 2.69 (3H, s).

α-Acetyl-β-acetylaminocrotonamide (VIII)——Ketene gas was passed into a solution of V (7.0 g) in acetone (80 ml) in the presence of several drops of triethylamine at room temperature for 40 min (equivalent to 5.4 g). The reaction mixture was condensed to give 10.5 g (82%) of colorless prisms (acetone), mp 147° (decomp.). *Anal.* Calcd. for $C_8H_{12}O_3N_2$ (VIII): C, 52.16; H, 6.57; N, 15.21. Found: C, 52.00; H, 6.34; N, 15.46. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3400, 3170, 1717, 1670, 1636; NMR ($CDCl_3$, TMS, ppm): 2.19 (3H, s), 2.31 (3H, s), 2.51 (3H, s), 6.21 (1H, s), 6.32 (1H, s), 12.78 (1H, s).

Reaction of β-Aminocrotonamide (V) with Ketene in the Presence of Pyridine——Into a solution of V (1.0 g) and pyridine (1 ml) in acetone (20 ml), ketene was passed at room temperature for 40 min (equivalent to 5.4 g). The reaction mixture was condensed, and the crystals precipitated were collected by filtration. Recrystallization from acetone gave 0.5 g (35%) of VII. The filtrate was concentrated to give 0.3 g (13%) of VIII. These products were identified by the comparison with authentic specimens obtained in the above run.

Reaction of β-Aminocrotonamide (V) with Isopropenyl Acetate——A mixture of V (0.5 g) and isopropenyl acetate[10] (5 ml) was refluxed on an oil bath for 4 hr. Removal of excess isopropenyl acetate by evaporation under reduced pressure afforded an oily residue, which was submitted on alumina–chromatography using

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15) T. Kato and Y. Kubota, *Yakugaku Zasshi*, submitted.

16) E. Marcus and J.K. Chan, *J. Org. Chem.*, 32, 2881 (1967).

17) W.E. Hanford and J.C. Sauer, "Org. Reactions," Vol. 3, John Wiley & Sons, Inc., New York, 1963, p. 132.

ether as a solvent to give 0.08 g (11%) of VIa, mp 177° (AcOEt), undepressed on admixture with an authentic specimen obtained by the method described in the literature.[7]

5-Acetyl-2,6-dimethyl-4(1H)-pyrimidone (IX)——1) Ketene was passed into a solution of V (1.0 g) in 80 ml of acetone under reflux for 5 hr (equivalent to 40 g). The solution was condensed *in vacuo* to yield an oily residue, which was neutralized with 10% Na_2CO_3 and the neutral solution was concentrated to dryness to provide a solid, which was washed with hot AcOEt. The AcOEt washing was dried, condensed to yield 1.0 g (57%) of colorless needles, mp 207° (acetone). *Anal.* Calcd. for $C_8H_{10}O_2N_2$ (IX): C, 57.82; H, 6.07; N, 16.86. Found: C, 58.12; H, 6.06; N, 17.10. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 2841, 1695, 1637. NMR (CF_3COOH, TMS, ppm): 2.66 (3H, s), 2.75 (3H, s), 2.94 (3H, s).

2) A mixture of VII (1.0 g), acetic acid (3 ml) and acetic anhydride (2 ml) was warmed on a water bath at 80° for 1 hr. Employing the similar fashion as the method 1) in the above run, 0.3 g (23%) of IX was obtained, undepressed on admixture with an authentic sample prepared by the method 1) in the above run.

3) A mixture of VIII (1.0 g) and 10% NaOH (4 ml) was heated on a water bath at 80° for 1 hr and neutralized with 10% HCl. The neutral solution was condensed to dryness *in vacuo* to provide a residue, which was extracted with hot AcOEt. The AcOEt extract was dried and condensed to give 0.6 g (70%) of IX, undepressed on admixture with an authentic specimen obtained in the above run.

Reaction of 5-Acetyl-2,6-dimethyl-4(1H)-pyrimidone (IX) with Phosphoryl Chloride——A mixture of IX (1.1 g) and phosphoryl chloride (3.0 g) was refluxed on an oil bath for 1 hr. Removal of excess phosphoryl chloride under reduced pressure gave an oily residue, which was poured into ice–water and neutralized with 10% Na_2CO_3. The neutral solution was extracted with ether. The ether extarct was dried, condensed, and the resulting oil was purified by distillation to give 0.9 g (72%) of 5-acetyl-4-chloro-2,6-dimethylpyrimidine (X), bp 104° (8 mmHg). Chlorine was detected by the Beilstein test. *Anal.* Calcd. for $C_8H_9ON_2Cl$ (X): C, 52.03; H, 4.88; N, 15.18. Found: C, 51.50; H, 4.47; N, 15.04. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2970, 1700. NMR ($CDCl_3$, TMS, ppm): 2.44 (3H, s), 2.60 (3H, s), 2.69 (3H, s).

Reduction of 5-Acetyl-4-chloro-2,6-dimethylpyrimidine (X)——A mixture of X (0.8 g), magnesium oxide (0.34 g) and palladium charcoal (prepared from $PdCl_2$ (0.4 g) and charcoal (2.0 g)) in 50 ml of MeOH, was shaken in H_2 until 51 ml of H_2 had been absorbed at 15°. The mixture was filtrated, and the filtrate was condensed, distilled *in vacuo* to give 0.2 g (34%) of 5-acetyl-2,6-dimethylpyrimidine (XI), bp 96° (15 mmHg) (lit. bp 62—64° (3 mmHg)), whose IR spectrum was identical in every respect with that of an authentic sample.[9] Semicarbazone, mp 197° (MeOH). *Anal.* Calcd. for $C_{10}H_{13}ON_5$ (semicarbazone of XI): C, 52.16; H, 6.32; N, 33.80. Found: C, 51.92; H, 6.21; N, 33.45.

β-Amino-N-methylcrotonamide (XII)——Dry NH_3 gas was passed into a solution of N-methylacetoacetamide (20 g) in absolute benzene (20 ml) for 2 hr (equivalent to 68 g) in an ice bath. After removal of benzene by evaporation, a crystalline solid was obtained, which was collected by filtration and recrystallized from benzene to give 1.7 g (85%) of colorless prisms, mp 115—116°. *Anal.* Calcd. for $C_5H_{10}ON_2$ (XII): C, 52.61; H, 8.83; N, 24.54. Found: C, 52.80; H, 8.79; N, 24.72. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3521, 3472, 3322, 3012, 1639. NMR ($CDCl_3$, TMS, ppm): 1.81 (3H, s), 2.75 (3H, d), 4.34 (1H, s), 5.2 (1H, broad), 6.3 (2H, broad).

β-Amino-N,N-dimethylcrotonamide (XIII)——Dry NH_3 gas was passed into a solution of N,N-dimethylacetoacetamide (1.0 g)[12] in absolute EtOH (20 ml) for 2 hr (equivalent to 68 g) under reflux. The solution was concentrated giving a solid, which was collected by filtration and purified by recrystallization from benzene to yield 0.7 g (73%) of colorless prisms, mp 117°. *Anal.* Calcd. for $C_6H_{12}ON_2$ (XIII): C, 56.22; H, 9.44; N, 21.86. Found: C, 56.38; H, 9.31; N, 22.04. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3497, 3289, 2994, 1629. NMR ($CDCl_3$, TMS, ppm): 1.83 (3H, s), 2.89 (6H, s), 4.53 (1H, s), 6.5 (2H, broad).

5-Acetyl-2,3,6-trimethyl-4(1H)-pyrimidone (XIV)——Ketene was passed into a solution of β-amino-N-methylcrotonamide (XII) (0.5 g) in acetone (20 ml) in the presence of several drops of triethylamine at room temperature for 0.5 hr (equivalent to 4 g). The reaction mixture was condensed under reduced pressure giving an oily residue, which was distilled *in vacuo* to yield 0.4 g (52%) of colorless needles, mp 89—90.5° (ether–pet. ether). *Anal.* Calcd. for $C_9H_{12}O_2N_2$ (XIV): C, 59.98; H, 6.71; N, 15.55. Found: C, 59.85; H, 6.49; N, 15.58. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1680, 1660. NMR ($CDCl_3$, TMS, ppm): 2.19 (3H, s), 2.40 (3H, s), 2.48 (3H, s), 2.42 (3H, s).

α-Acetyl-β-acetylamino-N-methylcrotonamide (XV)——Ketene was passed into a mixture of XII (3.5 g) in acetone (60 ml) in the presence of triethylamine at room temperature for 1 hr (equivalent to 8 g). Removal of acetone by evaporation gave an oily substance, which, on adding ether and pet. ether, was solidified. The solid was collected by filtration and recrystallized from ether to provide 2.0 g (33%) of XV, mp 124°. The filtrate was extracted with 10% HCl and the HCl layer was neutralized with 10% Na_2CO_3. The neutral solution was extracted with $CHCl_3$. The $CHCl_3$ extract was dried, condensed to yield 1.0 g (18%) of XIV, undepressed on admixture with an authentic sample obtained in the above run. *Anal.* Calcd. for $C_9H_{14}O_3N_2$ (XV): C, 54.53; H, 7.12; N, 14.13. Found: C, 54.40; H, 6.86; N, 14.20. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3470, 1712, 1650, 1635. NMR ($CDCl_3$, TMS, ppm); 2.15 (3H, s), 2.23 (3H, s), 2.38 (3H, s), 2.93 (3H, d), 6.5 (1H, broad), 12.7 (1H, broad).

3-Acetimidoyl-4-hydroxy-6-methyl-2(1H)-pyridone (XVI)——A mixture of V (5.0 g) and diketene (8.4 g) was warmed gently on a water bath at 60° for 0.5 hr giving a yellow solid, which was collected by filtration, washed with acetone, and recrystallized from MeOH to give 5.2 g (63%) of colorless prisms, mp 314° (decomp.), which were identified as XVI by the comparison of the IR and NMR spectra with those of an authentic sample.[14]

3-Acetimidoyl-4-hydroxy-1,6-dimethyl-2(1H)-pyridone (XVII)——1) A mixture of XII (2.2 g) and diketene (3.2 g) was warmed gently on a water bath at 60° for 1 hr giving a precipitate, which was collected by filtration, washed with ether, purified by recrystallization from acetone to provide 0.6 g (81%) of colorless needles, mp 227°. *Anal.* Calcd. for $C_9H_{12}O_2N_2$ (XVII): C, 59.98; H, 6.71; N, 15.55. Found: C, 60.18; H, 6.88; N, 15.50. IR ν_{max}^{KBr} cm^{-1}: 3077, 2882, 1656, 1642. NMR (CF_3COOH, TMS, ppm): 2.59 (3H, s), 2.94 (3H, s), 3.69 (3H, s), 6.50 (1H, s).

2) A mixture of 3-acetyl-4-hydroxy-1,6-dimethyl-2(1H)-pyridone (XVIII)[15] (0.5 g) and an NH_3–EtOH solution, prepared from dry NH_3 gas (17.3 g) and absolute alcohol (20 ml), was warmed in a sealed tube at 60° for a day. The reaction mixture was concentrated to give 0.4 g (94%) of colorless needles (XVIII) (acetone), undepressed on admixture with an authentic specimen prepared by the method 1) in the above run.

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