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Studies on Ketene and Its Derivatives. LXXVI.[1] Reactions of Acetoacetamide and β-Aminocrotonamide with β-Diketone, β-Ketoaldehyde and Related Compounds

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Reactions of acetoacetamide (I) and β-aminocrotonamide (II) with 1,3-dioxo and related compounds were investigated. Namely, the reaction of I with 2,4-pentanedione (III), 4-methoxy-3-pentene-2-one (VIII), 2-formylcyclohexanone (IV), 4-hydroxy-3-butene-2-one (Va), ethyl 2-ethoxymethyleneacetoacetate (Vb), and 3-ethoxymethylene-2,4-pentanedione (Vc) afforded 3-acetyl-4,6-dimethyl-2(1H)-pyridone (IX), 3-acetyl-5,6,7,-8-tetrahydro-2-quinolone (X), 3-acetyl-6-methyl-2(1H)-pyridone (XIa), ethyl 5-acetyl-6-methyl-2(1H)-pyridone-3-carboxylate (XIb), and 3,5-diacetyl-6-methyl-2(1H)-pyridone (XIc), respectively.

On the other hand, the reaction of II with III, 4-amino-3-penten-2-one (VI), 4,4-dimethoxy-2-butanone (VII), and IV resulted in the formation of 2,4,6-trimethyl-3-pyridinecarboxamide (XII), 2,6-dimethyl-3-pyridinecarboxamide (XV), and 2-methyl-5,6,7,8-tetrahydro-3-quinolinecarboxamide (XIV), respectively.

In the case of the reaction of II with Vb, ethyl 5-carbamoyl-2,6-dimethyl-3-pyridinecarboxylate (XVIIa), ethyl 2-[(2-carbamoyl-1-methylvinylamino)methylene]acetoacetate (XVIIIa) were obtained. Similarly, II reacted with Vc to give 5-acetyl-2,6-dimethyl-3-pyridinecarboxamide (XVIIb) and 3-[(2-carbamoyl-1-methylvinylamino)methylene]-2,4-pentanedione (XVIIIb).

It is reported that cyanoacetamide reacts with β-diketone such as 2,4-pentanedione (III) to give 3-cyano-4,6-dimethyl-2(1H)-pyridone.[3] While investigating on some potential uses of acetoacetamide (I) and β-aminocrotonamide (II), which are most easily prepared from the reaction of diketene with ammonia,[4] we studied their reactions with β-dicarbonyl and related compounds, and found the novel method for the preparation of pyridine derivatives. β-Dicarbonyl compounds used in the present investigation are 2,4-pentanedione (III), 2-formylcyclohexanone (IV), 4-hydroxy-3-butene-2-one sodium salt (Va′: R=H, R′=Na), ethyl 2-ethoxymethyleneacetoacetate (Vb: R=CO_2Et, R′=Et), 3-ethoxymethylene-2,4-pentanedione (Vc:R=$COCH_3$, R′=Et), 4-amino-3-penten-2-one (VI), and 4,4-dimethoxy-2-butanone (VII).

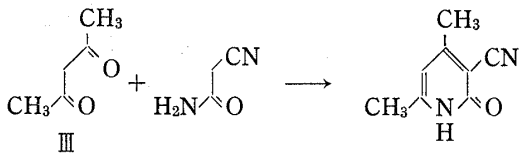


Chart 1

I. Reaction of Acetoacetamide (I)

When acetoacetamide (I) was allowed to react with 2,4-pentanedione in the presence of sodium ethoxide, colorless needles of mp 215—216°, $C_9H_{11}O_2N$ (IX), were obtained in 30% yield. The nuclear magnetic resonance (NMR) spectrum indicated the presences of three methyl groups, an aromatic proton, and an active proton presumably due to the NH group.

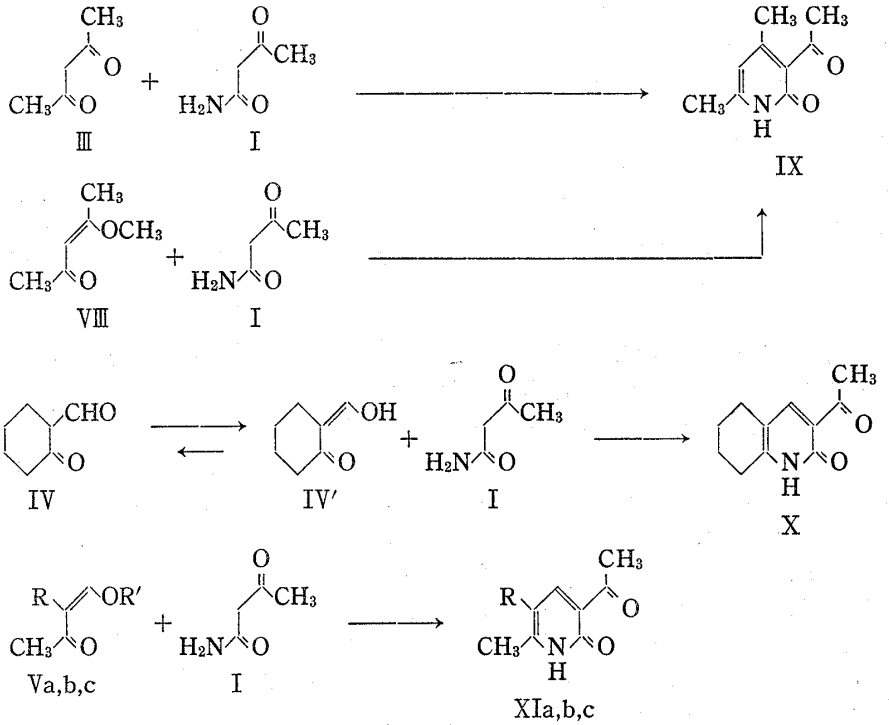
Compound IX was also obtained by the reaction of I with 4-methoxy-3-penten-2-one (VIII). These observations shows that the structure of IX is 3-acetyl-4,6-dimethyl-2(1H)-pyridone.

1) LXXV: T. Kato and T. Sakamoto, *Chem. Pharm. Bull.* (Tokyo), **23**, 168 (1975).
2) Location: *Aobayama, Sendai, 980, Japan.*
3) *a*) U. Basu, *J. Indian. Chem. Soc.*, **7**, 481 (1930); *b*) *Idem, ibid.*, **7**, 815 (1930).
4) *a*) F. Chick and N.T.M. Wilsmore, *J. Chem. Soc.*, **93**, 946 (1908); *b*) T. Kato, H. Yamanaka, and T. Shibata, *Chem. Pharm. Bull.* (Tokyo), **15**, 921 (1967).

Reaction of 2-formylcyclohexanone (IV) with I in the presence of triethylamine gave rise to 3-acetyl-5,6,7,8-tetrahydro-2(1H)-quinolone (X) in 71% yield. It is known that the enol form, 2-hydroxymethylenecyclohexanone (IV') is more stable than its tautomeric form of 2-formylcyclohexanone (IV).

Taking these facts in consideration, the reactions of I with Va, b, c, which have the similar partial structure of –CO–C=C–O–, were carried out. Namely, the reaction of 4-hydroxy-3-butene-2-one sodium salt (Va', R=H, R'=Na) with I in the presence of piperidine acetate gave pale yellow needles, $C_8H_9O_2N$ (XIa, R=H). Its structure was characterized as 3-acetyl-6-methyl-2(1H)-pyridone on the basis of spectral data, which are explained in the experimental section.

Similarly, ethyl 2-ethoxymethyleneacetoacetate (Vb, R=CO_2Et, R'=Et) reacted with I in the presence of sodium ethoxide giving ethyl 3-acetyl-6-methyl-2(1H)-pyridone-5-carboxylate (XIb, R=CO_2Et), in 90% yield. Reaction of 3-ethoxymethylene-2,4-pentanedione (Vc, R=$COCH_3$, R'=Et) with I gave 3,5-diacetyl-6-methyl-2(1H)-pyridone (XIc, R=$COCH_3$) in 83% yield.



a : R=H, R'=H (Va': R=H R'=Na)
b : R=COOEt, R'=Et
c : R=$COCH_3$, R'=Et

Chart 2

II. Reaction of β-Aminocrotonamide (II)

If the reaction of β-aminocrotonamide (II) with 2,4-pentanedione (III) proceeds in a similar manner as above, 3-acetimidoyl-4,6-dimethy-2(1H)-pyridonel (XII') would be expected to form, but the reaction of II with III in the presence of a basic catalyst did not afford any product corresponding to the pyridone derivative. However, heating of a solution of II and III in acetic acid gave rise to $C_9H_{12}ON_2$ (XII) in 27% yield. On the basis of its spectral data, XII was characterized as 2,4,6-trimethyl-3-pyridinecarboxamide. Heating of XII with phosphorus oxychloride afforded 2,4,6-trimethyl-3-pyridinecarbonitrile (XIII).

Compound XII was also obtained in 49% yield by the reaction of 4-amino-3-penten-2-one (VI) with II in acetic acid.

Similarly, reaction of II with IV in ethanol gave rise to 2-methyl-5,6,7,8-tetrahydro-3-quinolinecarboxamide (XIV) in 40% yield.

Similar reaction of II with 4,4-dimethoxy-2-butanone (VII) in acetic acid afforded a 38% yield of 2,6-dimethyl-3-pyridinecarboxamide (XV), which was hydrolyzed with dil. hydrochloric acid to give 2,6-dimethyl-3-pyridinecarboxylic acid (XVI).[5]

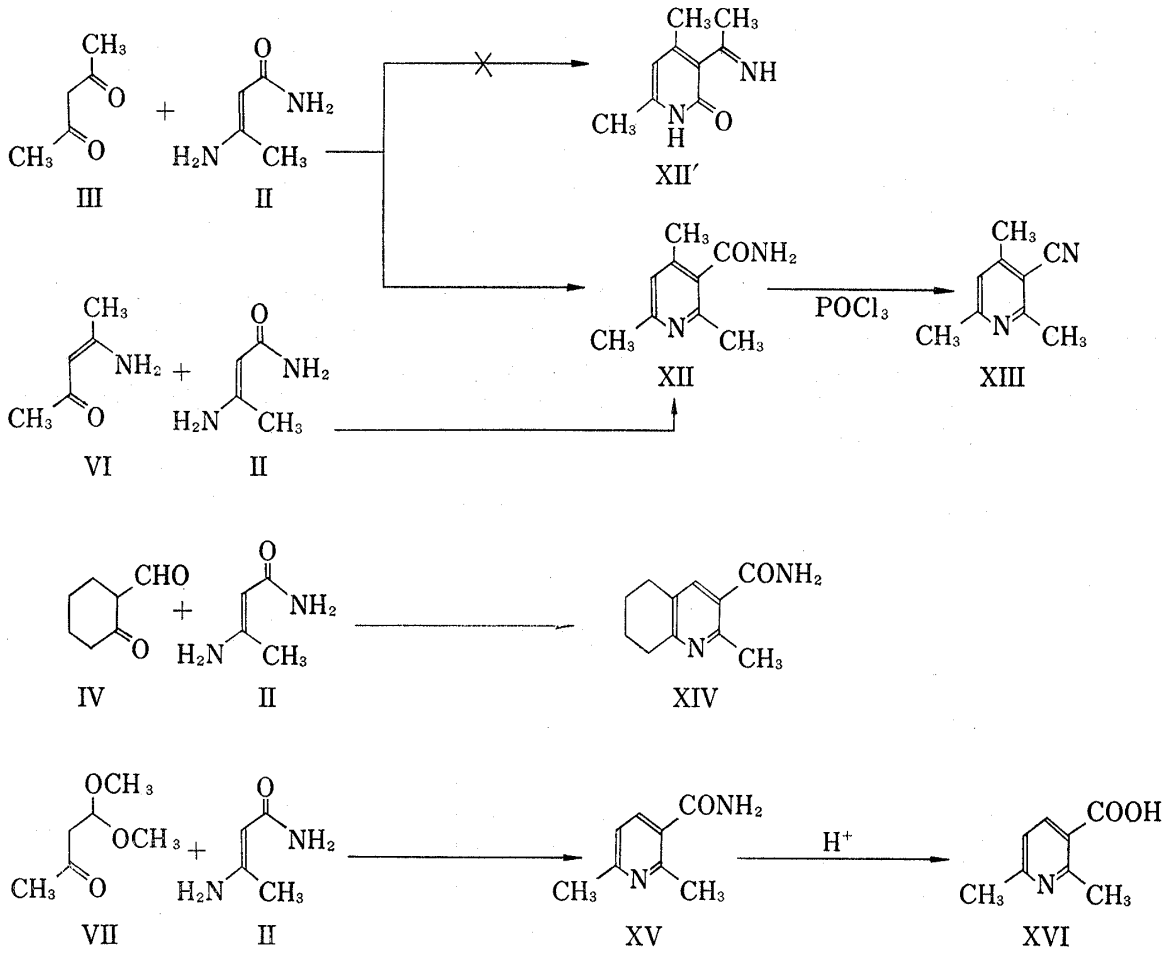


Chart 3

Reaction of II with ethyl 2-ethoxymethyleneacetoacetate (Vb, R=CO_2Et, R′=Et) in the presence of triethylamine gave rise to colorless needles, $C_{11}H_{14}O_3N_2$ (XVIIa, R=CO_2Et), and pale yellow prisms, $C_{11}H_{16}O_4N_2$ (XVIIIa, R=CO_2Et), in 25% and 21% yield, respectively.

Bottoroff, *et al.*[6] reported that ethyl 3-aminocrotonate (XIX) reacted with Vb to give diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate (XX) and ethyl 2-[(2-ethoxycarbonyl-1-methyl vinylamino)methylene]acetoacetate (XXI). In consideration of this fact, XVIIa and XVIIIa were characterized as ethyl 5-carbamoyl-2,6-dimethyl-3-pyridinecarboxylate, and ethyl 2-[(2-carbamoyl-1-methylvinylamino)methylene]acetoacetate, respectively.

Hydrolysis of XVIIa with dil. hydrochloric acid gave the known compound, 2,6-dimethyl-3,5-pyridinedicarboxylic acid (XXIIa).[7]

Heating of XVIIIa in AcOH gave 6-methyl-4(3H)-pyrimidone (XXIII),[8] which was also obtainable on treatment of XVIIIa with NaOEt.

5) L. Weiss, *Chem. Ber.*, **19**, 1308 (1886).
6) E.M. Bottoroff, R.G. Jones, E.C. Kornfeld, and M.J. Mann, *J. Am. Chem. Soc.*, **73**, 4380 (1951).
7) F. Engelmann, *Ann.*, **231**, 51 (1885).
8) S. Gabriel and J. Colman, *Chem. Ber.*, **32**, 2931 (1899).

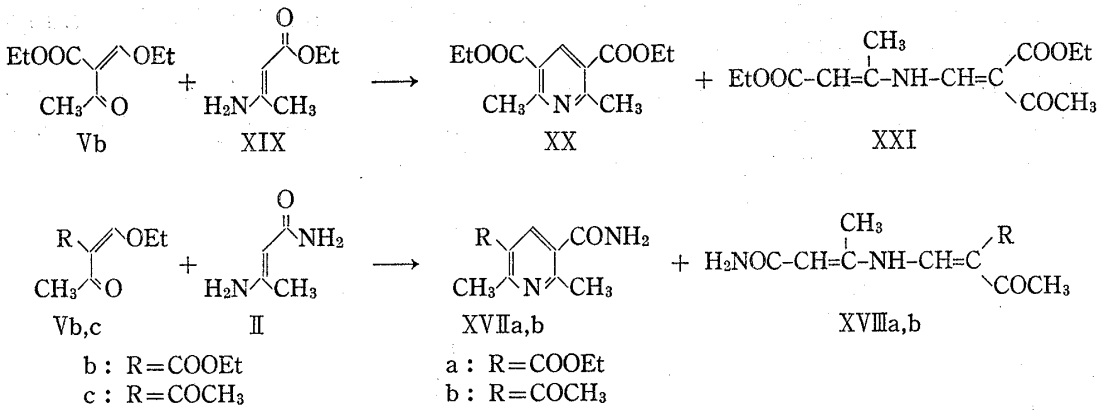


Chart 4

Similarly, reaction of II with 3-ethoxymethylene-2,4-pentanedione (Vc, R=$COCH_3$) afforded 5-acetyl-2,6-dimethyl-3-pyridinecarboxamide (XVIIb, R=$COCH_3$) and 3-([2-carbamoyl-1-methylvinylamino)methylene]-2,4-pentanedione (XVIIIb, R=$COCH_3$) in 55% and 13% yield, respectively. Hydrolysis of XVIIb gave 5-acetyl-2,6-dimethyl-3-pyridinecarboxylic acid (XXIIb) in 48% yield.

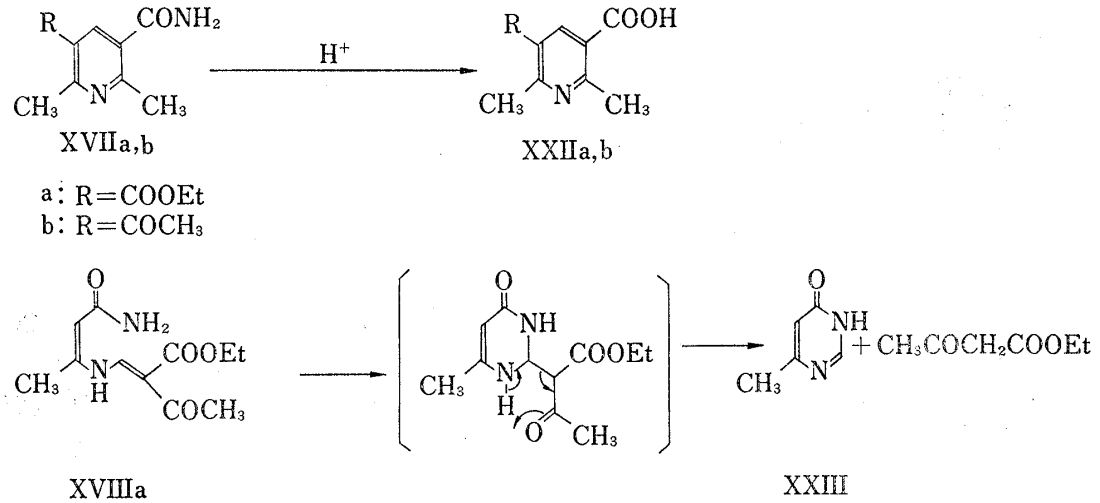


Chart 5

Experimental

All melting points are uncorrected. NMR spectra were taken with Hitachi-Perkin Elmer R-20 spectrometer, using tetramethylsilane as an internal standard. Abbreviation used: s=singlet, d=doublet, q=quartet, m=multiplet, and br=broad. IR spectra were using a JASCO IR-S spectrophotometer.

3-Acetyl-4,6-dimethyl-2(1H)-pyridone (IX)——1) To a solution of NaOEt-EtOH, prepared from Na (0.1 g) and abs. EtOH (50 ml), were added acetoacetamide (I) (3.5 g) and 2,4-pentanedione (III) (3 g) with stirring. After refluxing for 20 hr, the reaction mixture was neutralized with 10% HCl. The organic solvent was distilled under reduced pressure, and crystals separated were collected by suction. Recrystallization from MeOH gave colorless needles (IX), mp 215—216°. Yield, 1.4 g (30%). *Anal.* Calcd. for $C_9H_{11}O_2N$ (IX): C, 65.44; H, 6.71; N, 8.48. Found: C, 65.14; H, 6.63; N, 8.42. IR ν_{max}^{KBr} cm^{-1}: 3425, 3245, 3065, 1680, 1650, 1630. NMR ($CDCl_3$) ppm: 2.26 (3H, s), 2.31 (3H, s), 2.69 (3H, s), 5.96 (1H, s), 13.15—13.55 (1H, br).

The filtrate was condensed to dryness *in vacuo*, and the residue was extracted with AcOEt. The AcOEt fraction was submitted to silica gel column chromatography to give 1.1 g (37%) of the starting material (I).

2) The mixture of I (2.3 g) and 4-methoxy-3-penten-2-one (VIII) (2.3 g) in NaOEt–EtOH, prepared from Na (0.2 g) and abs. EtOH (50 ml), was refluxed for 20 hr. After being neutralized with 10% HCl, the reaction mixture was condensed *in vacuo*. The residue was extracted with AcOEt. The AcOEt solution was condensed to give a crystalline substance, which was recrystallized from AcOEt to colorless needles, mp 215—216°, undepressed on admixture with a specimene (IX) obtained in the above run. Yield 0.55 g (11%).

3-Acetyl-5,6,7,8-tetrahydro-2(1H)-quinolone (X)——A solution of I (3.5 g), 2-formylcyclohexanone (IV)[9] (3.8 g), and triethylamine (3 g) in abs. EtOH (50 ml) was refluxed for 4 hr. The reaction mixture was condensed *in vacuo*, and the residue was purified by recrystallization from EtOH–H_2O to colorless needles, mp 217—218° (decomp.). Yield, 4.0 g (71%). *Anal.* Calcd. for $C_{11}H_{13}O_2N$ (X): C, 69.09; H, 6.85; N, 7.33. Found: C, 68.93; H, 6.96; N, 7.05. IR ν_{max}^{KBr} cm^{-1}: 3380 (br), 1660, 1640, 1605. NMR (CF_3CO_2H) ppm: 1.9—2.2 (4H, m), 2.8—3.3 (4H, m), 2.81 (3H, s), 8.65 (1H, s).

3-Acetyl-6-methyl-2(1H)-pyridone (XIa)——According to the literature,[10] acetone (1.7 g) was allowed to react with ethyl formate (2.2 g) in the presence of sodium methoxide (1.62 g) to give 4-hydroxy-3-buten-2-one sodium salt (Va′, R=H, R′=Na), which was dissolved in H_2O (50 ml). To the resulting solution were added I (3.5 g) and piperidine acetate, prepared from glacial AcOH (0.5 ml) and piperidine. After refluxing for 5 hr, the reaction mixture was acidified with AcOH and condensed *in vacuo*. The residue was purified by recrystallization from AcOEt–EtOH to pale yellow needles, mp 206—207°. Yield, 1 g (22%). *Anal.* Calcd. for $C_8H_9O_2N$ (XIa): C, 63.56; H, 6.00; N, 9.27. Found: C, 63.60; H, 6.08; N, 8.90. IR ν_{max}^{KBr} cm^{-1}: 3440 (br), 3300, 3120, 1660 (br), 1610. NMR ($CDCl_3$) ppm: 2.44 (3H, s), 2.69 (3H, s), 6.21 (1H, d, J=6 Hz), 8.18 (1H, d, J=6 Hz), 13.1—13.9 (1H, br).

Ethyl 3-Acetyl-6-methyl-2(1H)-pyridone-5-carboxylate (XIb)——To a solution of EtONa–EtOH, prepared from Na (0.2 g) and abs. EtOH (100 ml), was added dropwise a solution of ethyl 2-ethoxymethyleneacetoacetate (Vb, R=CO_2Et, R′=Et) (5.6 g) in EtOH (10 ml). After stirring at room temperature for 24 hr, the reaction mixture was neutralized with 10% HCl. The solvent was removed by vacuum distillation. The residue was purified by recrystallization from EtOH–H_2O to colorless needles, mp 214—215°. Yield, 6.0 g (90%). *Anal.* Calcd. for $C_{11}H_{13}O_4N$ (XIa): C, 59.18; H, 5.87; N, 6.28. Found: C, 59.06; H, 6.03; N, 5.90. IR ν_{max}^{KBr} cm^{-1}: 3400 (br), 3160, 1715, 1685, 1660. NMR (CF_3CO_2H) ppm: 1.52 (3H, t, J=7.5 Hz), 2.88 (3H, s), 3.10 (3H, s), 4.60 (2H, q, J=7.5 Hz), 9.38 (1H, s).

3,5-Diacetyl-6-methyl-2(1H)-pyridone (XIc)——To a solution of I (3.5 g) in EtONa–EtOH, prepared from Na (0.2 g) abs. EtOH (100 ml), was added dropwise a solution of 3-ethoxymethylene-2,4-pentanedione (Vc, R=$COCH_3$, R′=Et) (4.7 g) in EtOH (10 ml). The reaction mixture was stirred at room temperature for 24 hr. After being neutralized with 10% HCl, the mixture was condensed by vacuum distillation. The residue was purified by recrystallization from EtOH–H_2O to colorless needles, mp 260° (decomp.). Yield, 4.8 g (83%). *Anal.* Calcd. for $C_{10}H_{11}O_3N_2$: C, 62.16; H, 5.74; N, 7.25. Found: C, 61.68; H, 5.77; N, 7.71. IR ν_{max}^{KBr} cm^{-1}: 3460 (br), 1700, 1680, 1655. NMR (CF_3CO_2H) ppm: 2.85 (3H, s), 2.91 (3H, s), 3.02 (3H, s), 9.22 (1H, s).

2,4,6-Trimethyl-3-pyridinecarboxamide (XII)——1) A solution of β-aminocrotonamide (II) (3 g) and 2,4-pentanedione (III) (3 g) in AcOH (10 ml) was refluxed for 1 hr. The reaction mixture was condensed *in vacuo* to give an oily residue, which was purified by silica gel column chromatography using petroleum ether, $CHCl_3$ and AcOEt as eluants. From the AcOEt elution colorless prisms (AcOEt), mp 169—170°, were obtained. Yield, 1.3 g (27%). *Anal.* Calcd. for $C_9H_{12}ON_2$ (XII): C, 65.83; H, 7.37; N, 17.06. Found: C, 65.62, H, 7.68; N, 17.27. IR ν_{max}^{KBr} cm^{-1}: 3480, 3360, 1670. NMR ($CDCl_3$) ppm: 2.31 (3H, s), 2.46 (3H, s), 2.53 (3H, s), 5.5—6.5 (2H, br), 6.80 (1H, s).

2) A solution of II (1.5 g) and 4-amino-3-penten-2-one (VI) (1.5 g) in AcOH (5 ml) was refluxed for 20 min. After removal of AcOH *in vacuo*, the resulting residue was diluted with H_2O and washed with AcOEt. The AcOEt solution was condensed to dryness. The residue was purified by recrystallization from AcOEt to colorless prisms, mp 167—170°, undepressed on admixture with a sample of XII obtained in the above run. Yield, 1.2 g (49%).

2,4,6-Trimethyl-3-pyridinecarbonitrile (XIII)——A mixture of XII (0.5 g) and $POCl_3$ (10 ml) was refluxed for 1 hr. After evaporation of $POCl_3$ *in vacuo*, the resulting residue was poured into H_2O and neutralized with $NaHCO_3$. The mixture was extracted with ether. The ether solution was condensed to dryness. The residue was distillated under reduced pressure, bp=65° (1 mm Hg). Yield, 0.24 g (58%). *Anal.* Calcd. for $C_9H_{10}N_2$ (XIII): C, 73.94; H, 6 .90; N, 19.16. Found: C, 73.85; H, 6.88; N, 19.07. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2240,1595. NMR (CCl_4) ppm: 2.46 (3H, s), 2.48 (3H, s), 2.65 (3H, s), 6.99 (1H, s).

2-Methyl-5,6,7,8-tetrahydro-3-quinolinecarboxamide (XIV)——A solution of II (3.5 g) and 2-formylcyclohexanone (IV) in EtOH (50 ml) was refluxed for 5 hr. After evaporation of the solvent *in vacuo*, the resulting residue was purified by recrystallization from AcOEt to colorless needles, mp 202—203°. Yield, 2.25 g (40%). *Anal.* Calcd. for $C_{11}H_{14}ON_2$ (XIV): C, 69.44; H, 7.42; N, 14.73. Found: C, 69.34; H, 7.42; N, 14.82. IR ν_{max}^{KBr} cm^{-1}: 3440, 3230, 1655, 1625. NMR ($CDCl_3$) ppm: 1.7—2.0 (4H, m), 2.64 (3H, s), 2.6—3.05 (4H, m), 5.8—6.7 (2H, br), 7.43 (1H, s).

2,6-Dimethyl-3-pyridinecarboxamide (XV)——A solution of II (2.5 g) and 4,4-dimethoxy-2-butanone[11]

9) C. Arinsworth, "Org. Synthesis," Coll., Vol. IV, ed. by N. Rabjohn, Jone Willey and Sons, Inc., New York, N. Y., 1963, p. 536.
10) R.P. Malliella, "Org. Synthesis," Coll., Vol. IV, ed. by N. Rabjohn, Jone Willey and Sons, Inc., New York. N. Y., 1963, p. 210.
11) E.E. Rval and L.C. Brannock, *J. Am. Chem. Soc.*, **75**, 2050 (1963).

(VII) (2.6 g) in AcOH (6 ml) was refluxed for 30 min. The mixture was condensed *in vacuo*. The residue was washed with ether. The ether insoluble residue was recrystallized from AcOEt to give 0.75 g of colorless needles (XIV), mp 179—180°. The ether washing was purified by silica gel column chromatography using $CHCl_3$ and AcOEt as eluants. The AcOEt elution afforded 0.38 g of XV. Total yield, 1.13 g (38%). *Anal.* Calcd. for $C_8H_{10}ON_2$ (XV): C, 63.98; H, 6.71; N, 18.65. Found: C, 64.23; H, 6.94; N, 18.91. IR ν_{max}^{KBr} cm^{-1}: 3360, 1670, 1610. NMR (CF_3CO_2H) ppm: 2.91 (3H, s), 3.03 (3H, s), 7.85 (1H, d, J=8.5 Hz), 8.65 (1H, d, J=8.5 Hz), 7.6—8.1 (2H, br).

2,6-Dimethyl-3-pyridinecarboxylic Acid (XVI)——A solution of XV (0.5 g) in conc. HCl (6 ml) was refluxed for 1 hr. The mixture was condensed *in vacuo*. The residue was diluted with H_2O, and neutralized with 10% NaOH. The mixture was evaporated to dryness *in vacuo*. The residual solid was extracted with AcOEt. The AcOEt solution was condensed to give a crystalline substance. Recrystallization from AcOEt gave colorless needles, mp 168—169°. (lit.[5] mp 160°). Yield, 0.35 g (70%). *Anal.* Calcd. for $C_8H_9O_2N$ XVI): C, 63.56; H, 6.00; N, 9.27. Found: C, 63.23; H, 6.25; N, 9.41.

Reaction of β-Aminocrotonamide (II) with Ethyl 2-Ethoxymethyleneacetoacetate (Vb) to give Ethyl 5-Carbamoyl-2,6-dimethyl-3-pyridinecarboxylate (XVIIa) and Ethyl 2-[(2-Carbamoyl-1-methylvinylamino)-methylene]acetoacetate (XVIIIa)——To a solution of II (3.5 g) and triethylamine (3 g) in EtOH (50 ml), was added Vb (5.6 g) dropwise. After refluxing for 1.5 hr, the reaction mixture was condensed *in vacuo*. The resulting residue was extracted with AcOEt. The AcOEt insoluble crystalline substance was recrystallized from EtOH to pale yellow prisms (XVIIIa), mp 180—181° (decomp.). Yield, 1.5 g (21%). *Anal.* Calcd. for $C_{11}H_{16}O_4N_2$ (XVIIIa): C, 54.99; H, 6.71; N, 11.66. Found: C, 55.07; H, 6.71; N, 11.61. IR ν_{max}^{KBr} cm^{-1}: 3560, 3430, 1700, 1675, 1645, 1630. NMR ($CDCl_3$) ppm: 1.31 and 1.35 (3H, t, J=7.5 Hz), 2.08 (3H, br, s), 2.46 (3H, br, s), 4.18 and 4.28 (2H, q, J=7.5 Hz), 5.12 (1H, br, s), 5.4—6.0 (2H, br), 7.95 and 8.05 (1H, d, J=14 Hz), 13.7—14.4 (1H, br). The AcOEt fraction was condensed, and the residue was purified by recrystallization from ether–acetone to colorless needles, mp 154—155°. Yield, 1.83 g (25%). *Anal.* Calcd. for $C_{11}H_{14}O_3N_2$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.18; H, 6.35; N, 12.79. IR ν_{max}^{KBr} cm^{-1}: 3490, 3350, 3300, 3130, 1715, 1675. NMR ($CDCl_3$) ppm: 1.36 (3H, t, J=7.5 Hz), 2.68 (3H, s), 2.77 (3H, s), 4.30 (2H, q, J=7.5 Hz), 5.9—6.5 (2H, br), 8.12 (1H, s).

Reaction of β-Aminocrotonamide (II) with 3-(Ethoxymethylene)-2,4-pentanedione (Vc) to give 5-Acetyl-2,6-dimethyl-3-pyridinecarboxamide (XVIIb) and 3-[(2-Carbamoyl-1-methylvinylamino)methylene]-2,4-pentanedione (XVIIIb)——To a solution of II (3.5 g) and triethylamine (3 g) in EtOH (50 ml), was added dropwise Vc (4.7 g) with swirling. The exothermic reaction was regulated by cooling in a water bath, after which time the reaction mixture was refluxed for 2 hr, and then cooled to give a crystalline substance, which was collected by suction. Recrystallization from EtOH gave pale yellow prisms (XVIIIb), mp 221—222° (decomp.). Yield, 3.2 g (55%). *Anal.* Calcd. for $C_{10}H_{14}O_3N_2$ (XVIIIb): C, 57.13; H, 6.71; N, 13.33. Found: C, 56.98; H, 6.78; N, 13.49. IR ν_{max}^{KBr} cm^{-1}: 3370, 3210, 1658, 1643, 1618. NMR (DMSO-d_6) ppm: 2.20 (3H, s), 2.35 (6H, s), 5.25 (1H, s), 6.82 (1H, br, s), 7.32 (1H, br, s), 7.83 (1H, d, J=14 Hz), 13.75 (1H, d, J=14 Hz).[12] The EtOH layer was condensed *in vacuo*, and the resulting oily residue was chromatographed on a silica gel column using $CHCl_3$ as an eluant to give colorless needles (acetone), mp 151—152°. Yield, 0.71 g (13%). *Anal.* Calcd. for $C_{10}H_{12}O_2N_2$ (XVIIIb): C, 62.28; H, 6.29; N, 14.58. Found: C, 62.46; H, 6.46; N, 14.74. IR ν_{max}^{KBr} cm^{-1}: 3410, 3210, 1690, 1655, 1615. NMR ($CDCl_3$) ppm: 2.57 (3H, s), 2.73 (6H, s), 6.0—6.5 (2H, br), 8.04 (1H, s).

2,6-Dimethyl-3,5-pyridinedicarboxylic Acid (XXIIa)——A solution of XVIIa (1 g) in 10% HCl (10 ml) was refluxed for 2 hr. After cooling, crystals separated were collected. Recrystallization from H_2O afforded colorless needles, mp 320° (decomp.) (lit.[7] mp 316°). Yield, 0.25 g (28%). *Anal.* Calcd. for $C_9H_9O_4N$ (XXIIa). C, 55.38; H, 4.65; N, 7.18. Found: C, 55.48; H, 4.51; N, 7.24.

5-Acetyl-2,6-dimethyl-3-pyridinecarboxylic Acid (XXIIb)——1) A solution of XVIIb (1 g) in 10% HCl (10 ml) was refluxed for 3 hr. After being neutralized with 10% NaOH, the reaction mixture was condensed to dryness *in vacuo*. The residue was extracted with AcOEt. The AcOEt solution was condensed, and the residue was purified by recrystallization from benzene to colorless needles, mp 166—167°. Yield, 0.5 g (48%). *Anal.* Calcd. for $C_{10}H_{11}O_3N$ (XXIIb): C, 62.16; H, 5.74; N, 7.25. Found: C, 62.40; H, 5.81; N, 7.32. IR ν_{max}^{KBr} cm^{-1}: 3400 (br), 1710, 1680. NMR ($CDCl_3$) ppm: 2.61 (3H, s), 2.79 (3H, br, s), 2.90 (3H, br, s), 8.53 (1H, s), 12.28 (1H, s).

6-Methyl-4(3H)-pyrimidone (XXIII)——1) A solution of XVIIIa (0.5 g) in AcOH (5 ml) was refluxed for 1 hr. The reaction mixture was distilled under reduced pressure, and the resulting residue was purified by recrystallization from acetone to pale yellow needles, (XXIII), mp 147—148° (lit.[8] mp 149—150°). Yield, 0.14 g (61%). *Anal.* Calcd. for $C_5H_6ON_2$ (XXIII). C, 54.54; H, 5.49, N, 25.44. Found: C, 54.26, H, 5.59, N, 25.41. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360, 1665, 1610. NMR ($CDCl_3$) ppm: 2.31 (3H, s), 2.63 (1H, s), 8.01 (1H, s), 12.08 (1H, br, s).

12) This NMR spectrum was taken with JEOL model JNM-PS-100 at 100MC using DSS as an internal standard.

From the distillate, ethyl acetoacetate was detected by gas chromatography.[13]

2) A suspension of XVIIIa (1.2 g) in 10% NaOEt–EtOH (20 ml) was stirred at room temperature for 2 days. The reaction mixture was neutralized with 10% HCl, and evaporated *in vacuo*. The residue was extracted with $CHCl_3$. The $CHCl_3$ extract gave pale yellow needles, mp 147—148°, undepressed on admixture with a sample of XXIII obtained in the above run. Yield, 0.33 g (60%).

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13) Gas chromatograph was carried out on 10% SE-30 column at 50° on Japan Electron Optics Model JGC-20KFP.