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Studies on Ketene and Its Derivatives. XXXII.[1] Reactions of α,β-Unsaturated Acid Anhydride with β-Aminocrotonamide and Related Compounds

Tetsuzo Kato, Hiroshi Yamanaka, and Junshi Kawamata

Pharmaceutical Institute, Tohoku University[2]

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Acylation of β-aminocrotonamide (I) with α,β-unsaturated acid anhydride (*e.g.* acrylic, crotonic and methacrylic anhydrides) afforded 2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxamide derivatives (IV), which were easily dehydrogenated by heating with Pd-black to give 2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamides. Similarly, acylation of primary enamines such as ethyl β-aminocrotonate (XIa), 4-amino-3-penten-2-on (XIb), 2-amino-1-propenyl phenyl ketone (XIc), and 2-aminocrotononitrile (XId) with acrylic anhydride afforded 5-substituted-6-methyl-3,4-dihydro-2-pyridones (XII), which were given by the reaction of the primary enamines (XI) with ethyl acrylate in the presence of sodium ethoxide.

In the previous papers of this series we have reported that diketene reacted readily with excess ammonia giving β-aminocrotonamide (I) in good yield,[3] and that I was acylated with an acylating reagent such as acid anhydride affording β-acylaminocrotonamide (II), which was transformed into 2-alkyl(or aryl)-6-methyl-3*H*-4-pyrimidone (III) in fairly good yield.[4,5]

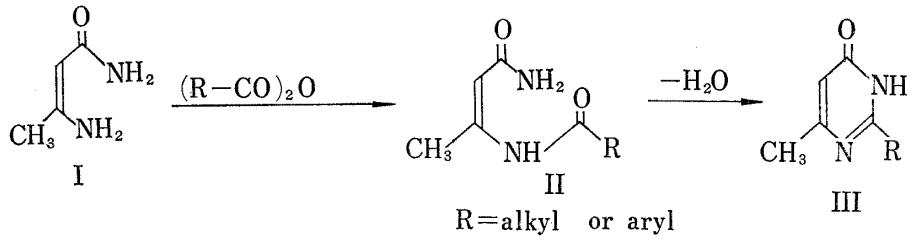


Chart 1

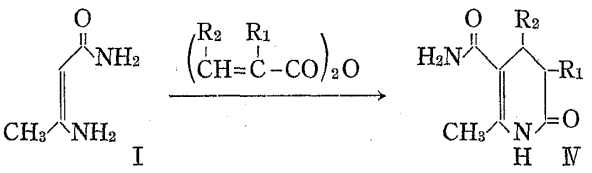
If the acylation reaction with α,β-unsaturated acid anhydride could proceed similarly, a new synthetic method of 2-alkenyl-4-pyrimidone derivatives (III, R=alkenyl) would be expected.

The present paper describes that the reaction of β-aminocrotonamide (I) with α,β-unsaturated acid anhydride did not proceed similarly as described above, but gave the 3,4-dihydro-2-pyridone compounds (IV).

When β-aminocrotonamide (I) was heated with acrylic anhydride in chloroform, colorless prisms of mp 241—242° (decomp.), $C_7H_{10}O_2N_2$ (IVa), were obtained. Similar treatment of I with crotonic anhydride and methacrylic anhydride afforded crystals of mp 199—200°, $C_8H_{12}O_2N_2$ (IVb), and mp 215—216°, $C_8H_{12}O_2N_2$ (IVc), respectively. The results are sum-

1) Part XXXI: T. Kato and M. Sato, *Chem. Pharm. Bull.* (Tokyo), **17**, 2405 (1969).
2) Location: *Aobayama, Sendai.*
3) T. Kato, H. Yamanaka, and T. Shibata, *Tetrahedron*, **23**, 2965 (1967).
4) T. Kato, H. Yamanaka, and T. Shibata, *Yakugaku Zasshi*, **87**, 955 (1967).
5) T. Kato, H. Yamanaka, and J. Kawamata, *Yakugaku Zasshi*, **89**, 460 (1969).

TABLE I.



Product	R_1	R_2	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IVa	H	H	241—242 (decomp.)	35	$C_7H_{10}O_2N_2$	54.53	6.54	18.17	54.32	6.62	18.40
IVb	H	CH_3	199—200	39	$C_8H_{12}O_2N_2$	57.13	7.19	16.66	56.84	7.39	16.53
IVc	CH_3	H	215—216	32	$C_8H_{12}O_2N_2$	57.13	7.19	16.66	57.19	7.05	16.55

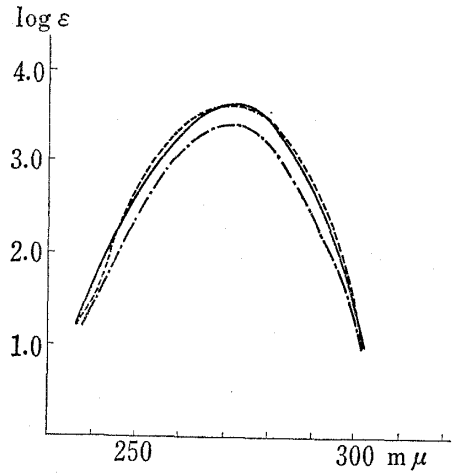


Fig. 1. UV Spectra of IVa—c (in EtOH)

----------: IVa —·—·—: IVab
———: IVc

marized in Table I. As the ultraviolet (UV) spectra of IVa—c are similar, the fundamental structure of these compounds seems to be essentially same.

Ethanolysis of IVa with dry hydrogen chloride in absolute ethanol gave ethyl δ-ketocaproate (V)[6] and diethyl α-acetylglutarate (VI),[7] which were characterized by the comparison of their infrared absorption (IR) spectra with those of the specimens prepared according to the literatures.[6,7] This fact suggested that the structure of IVa should be 2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxamide.

Heating of IVb with palladium-black afforded colorless prisms of mp 302° (decomp.), $C_8H_{10}O_2N_2$ (VII), whose IR spectrum indicated the presence of the amide carbonyls at 1669 and 1645 cm^{-1}. In its nuclear magnetic resonance (NMR) spectrum, an aromatic proton (1H, singlet) appeared at 7.10 ppm, which could not be observed in the spectrum of the IVb. Refluxing of VII with excess phosphoryl chloride afforded 4,6-dimethyl-5-cyano-2-pyridone (VIII), in almost quantitative yield. This compound was characterized by the comparison of its IR spectrum with that of the sample prepared from 2-aminocrotononitrile employing the method reported by Moir.[8,9] Chart 2 outlines the above reactions.

Based upon the data described above, the structure of 6-methyl-3,4-dihydro-2-pyridone-5-carboxamide derivative will be given as the most reasonable one of these compounds (IV). The spectral data of IV support the 3,4-dihydro-2-pyridone structure. The IR spectra of IVa—c exhibit the NH absorption at 3367—3165 cm^{-1} and two peaks due to the carbonyl groups at 1696—1645 cm^{-1}. The NMR spectra of IVa—c are also consistent with the 3,4-dihydro-2-pyridone structure; that is, 3 or 4-methyl groups give doublet peaks at 1.25—1.36 ppm and 6-methyl groups produce sharp singlets at 2.38—2.41 ppm. 3 or 4-methylene

6) A. Treibs and K. Hintermeier, *Chem. Ber.*, 87, 116 (1954).
7) H. Adkins, N. Isbell, and B.B. Wojcik, *Org. Syn.*, Coll. Vol. 2, 262 (1950).
8) J. Moir, *J. Chem. Soc.*, 81, 100 (1902).
9) Moir confirmed the structure of VIII as follows: the hydrolysis of VIII with concentrated hydrobromic acid gave 2,4-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (IX), which eliminated carbon dioxide to transit into 4,6-dimethyl-2-pyridone (X).

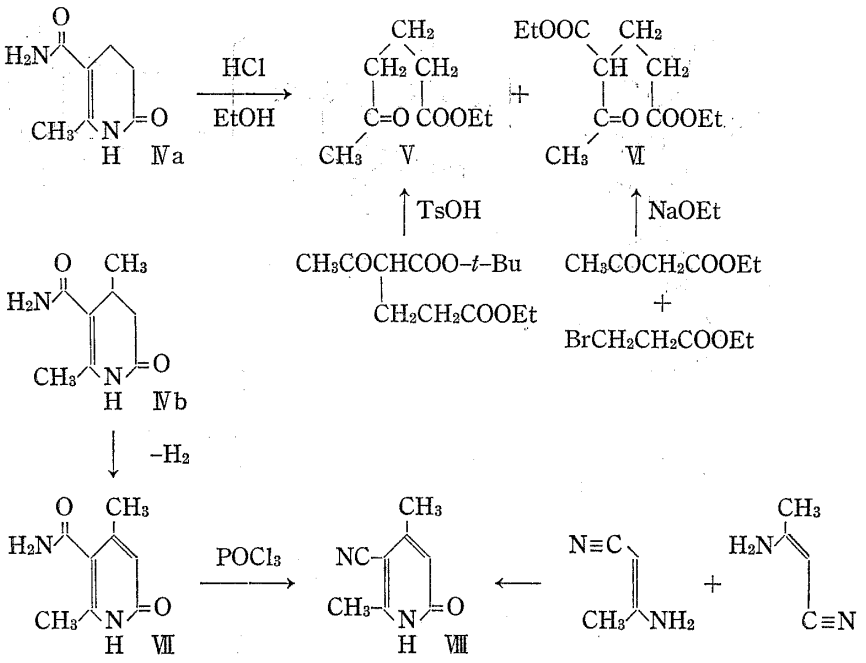
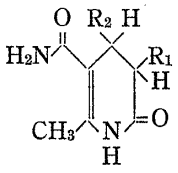


Chart 2

and methine protons appear at 2.6—3.2 ppm. None of the signals owing to olefinic protons can be observed between 5 and 8 ppm. Table II summarizes these spectral data.

Table II. Spectral Data of IVa—c



	Compound R_1	Compound R_2	IR ($\nu_{max}^{CHCl_3}$ cm^{-1}) ν_{NH}	IR ($\nu_{max}^{CHCl_3}$ cm^{-1}) $\nu_{C=O}$	NMR (CF_3COOH ppm) 6-CH_3	4-CH_3	3-CH_3	3&4-H	NH
IVa	H	H	3345 3165	1686 1645	2.40 (3H,s)	—	—	2.80 (4H,s)	9.15 (1H,s)
IVb	H	CH_3	3367 3175	1686 1664	2.38 (3H,s)	1.25 (3H, d)	—	2.6—3.2 (3H, m)	9.22 (1H,s)
IVc	CH_3	H	3356 3175	1696 1653	2.41 (3H,S)	—	1.36 (3H, d)	2.6—3.0 (3H, m)	9.06 (1H,s)

A likely pathway of this reaction is shown in Chart 3; that is, β-aminocrotonamide (I) is acylated to give β-acylaminocrotonamide (II), which, however, can not be isolated, and the next stage might well involve the intramolecular Michael addition to cyclize to IV.

In consideration of the structure of I, it appeared of interest to investigate further the scope of this reaction of the primary enamine such as XIa—d with α,β-unsaturated acid anhydride. Thus, ethyl β-aminocrotonate (XIa) was treated with acrylic anhydride to give ethyl 2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (XIIa). This compound was already prepared by the reaction of XIa with ethyl acrylate in the presence of sodium ethoxide.[10]

10) U. Schmidt, *Angew. Chem.*, **69**, 138 (1957); H.G.O. Becker, *J. Prakt. Chem.*, **12**, 294 (1961).

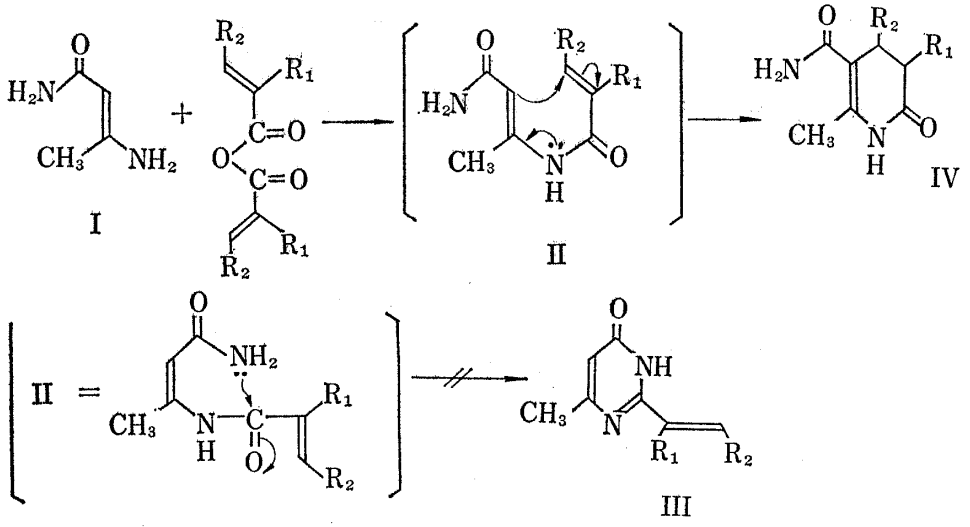
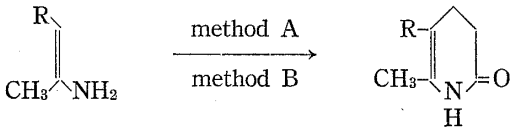


Chart 3

Table III. Melting Point and Yield of XIIa—d



Product	R	mp (°C)	Yield (%)	
			Method A	Method B
XIIa	$COOC_2H_5$	156	59	54
XIIb	$COCH_3$	141—142	75	9
XIIc	COC_6H_5	116—117	85	32
XIId	CN	213—214	42	30

method A: XI were reacted with acrylic anhydride in chloroform.
method B: XI were reacted with ethyl acrylate in the presence of sodium ethoxide.

Similarly, reactions of 4-amino-3-penten-2-on (XIb), 2-amino-1-propenyl phenyl ketone (XIc) and 2-aminocrotononitrile (XId) with acrylic anhydride (method A) afforded the dihydro-2-pyridones (XIIb—d), which were also obtained by treating with ethyl acrylate in the presence of sodium ethoxide (method B). As shown in Table III, in view of the preparation of the dihydropyridone derivatives (XII), our method (method A) seems to give more satisfactory results, and since the dehydrogenation of XII proceeds smoothly to give the pyridone compound (*e.g.* VII), this reaction will be one of the convenient methods for preparation of substituted pyridone derivatives.

Experimental

2-Methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxamide (IVa)——A solution of β-aminocrotonamide (I) (5 g) and acrylic anhydride (6.3 g) in $CHCl_3$ (70 ml) was refluxed. After 30 min the reaction mixture was condensed *in vacuo* to give an oily residue, to which water was added to give a crystalline solid. Purification by recrystallization from EtOH afforded colorless prisms, mp 241—242° (decomp.). Yield, 2.7 g (35%). Analytical and spectral data are shown in Table I, II and Fig. 1.

2,4-Dimethyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxamide (IVb)——Employing the similar fashion described above, I (6.4 g) reacted with crotonic anhydride (9.9 g) in $CHCl_3$ (100 ml) to give an oily residue, to which ether was added to afford colorless needles of mp 199—200° (EtOH). Yield, 4.3 g (39%).

2,5-Dimethyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxamide (IVc)——Following to the method given for IVa, the reaction of I (5.2 g) with methacrylic anhydride (8 g) in $CHCl_3$ (70 ml) gave 2.7 g (32%) of IVc, colorless needles of mp 215—216° (EtOH).

Ethanolysis of 2-Methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxamide (IVa)——IVa (4.0 g) was added to 20 ml of absolute EtOH, through which dry HCl had been passed in an ice bath for 20 min. After refluxing for 3.5 hr, the solution was condensed under reduced pressure and NH_4Cl precipitated was removed by filtration. The filtrate was distilled *in vacuo* to yield ethyl δ-ketocaproate[6] (V), bp 74° (1.5 mmHg), 2.1 g (51%), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2994, 1727, 1718, NMR ($CDCl_3$, TMS, ppm): 1.24 (3H, t), 2.12 (3H, s), 1.8—2.6 (6H, m) 4.11 (2H, q) and diethyl α-acetylglutarate (VI), bp 114° (1.5 mmHg), 1.5 g (25%), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2994, 1742, 1727, 1718, NMR ($CDCl_3$, TMS, ppm): 1.22 (3H, t), 1.24 (3H, t), 2.21 (3H, s), 1.7—2.7 (4H, m), 3.50 (1H, t), 4.08 (2H, q), 4.18 (2H, q). The IR spectra of these products were identical in every respect with those obtained by the literatures.[6,7]

Dehydrogenation of 2,4-Dimethyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxamide (IVb)——A mixture of IVb (1 g) and Pd-black (200 mg) was heated for 8 min at 250°. It was taken up with hot acetone (40 ml), and then with MeOH (100 ml). From the acetone fraction 0.33 g of the starting IVb was recovered, and from the MeOH soluble layer 0.42 g (42%) of 2,4-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide (VII) was obtained as colorless needles, mp 302° (decomp.). *Anal.* Calcd. for $C_8H_{10}O_2N_2$ (VII): C, 57.82; H, 6.07; N, 16.86. Found: C, 57.96; H, 5.99; N, 16.89. IR ν_{max}^{KBr} cm^{-1}: 3322, 3149, 2985, 1669, 1645. NMR (CF_3COOH, TMS, ppm): 2.60 (3H, s), 2.73 (3H, s), 7.10 (1H, s), 7.78 (2H, d).

Reaction of 2,4-Dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide (VII) with Phosphoryl Chloride——A mixture of VII (0.34 g) and $POCl_3$ (10 g) was refluxed for 30 min. After evaporation of excess $POCl_3$ under reduced pressure, the residue was poured into water to give a precipitate, which was collected by filtration and purified by recrystallization from MeOH to give colorless needles of mp 296°, undepressed on admixture with an authentic specimen prepared from 2-aminocrotononitrile according to the procedure reported by Moir.[8]

Ethyl 2-Methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (XIIa)——a) A solution of ethyl β-aminocrotonate (XIa) (1.4 g) and acrylic anhydride (1.4 g) in $CHCl_3$ (20 ml) was refluxed for 30 min. The solution was evaporated *in vacuo* and the residue was purified by recrystallization from AcOEt to give colorless prisms of mp 156°. Yield, 1.2 g (59%). IR ν_{max}^{KBr} cm^{-1}: 3226, 3125, 3003, 1695, 1625. NMR (CF_3COOH, TMS, ppm): 1.40 (3H, t), 2.35 (3H, s), 2.74 (4H, s), 4.40 (2H, q) 9.03 (1H, s).

b) According to the procedure reported by Becker,[10] 2.6 g of XIa and 2.5 g of ethyl acrylate were added to the sodium ethoxide–EtOH solution prepared from 0.56 g of Na and 30 ml of absolute EtOH. After refluxing for 8 hr, the mixture was acidified with AcOH, then was neutralized with 5% $NaHCO_3$. The solution was condensed *in vacuo* to dryness. The residue was extracted with AcOEt (or $CHCl_3$) and the AcOEt fraction was dried, condensed to give a semi-solid. Purification by recrystallization from AcOEt afforded colorless prisms of mp 156° (lit.[10] mp 156°), undepressed on admixture with a sample obtained in the above run. Yield, 2.0 g (54%).

5-Acetyl-6-methyl-3,4-dihydro-2-pyridone (XIIb)——a) Following to the procedure described in the method a) in the above run, the solution of 4-amino-3-penten-2-on (XIb) (2 g) and acrylic anhydride (2.5 g) in $CHCl_3$ (20 ml) was heated at reflux for 30 min. The solution was condensed to give a crystalline solid, which was collected by filtration, and purified by recrystallization from benzene to give colorless needles (XIIb) of mp 141—142°. Yield, 2.1 g. The filtrate was diluted with water, neutralized with 5% $NaHCO_3$, and then was condensed to dryness *in vacuo*. The residue was washed with $CHCl_3$. The $CHCl_3$ washing was dried over Na_2SO_4, filtered, condensed to give another 0.2 g of XIIb. Total yield 2.3 g (75%). *Anal.* Calcd. for $C_8H_{11}O_2N$ (XIIb): C, 62.72; H, 7.24; N, 9.14. Found: C, 62.51; H, 7.44; N, 9.14. IR ν_{max}^{KBr} cm^{-1}: 3205, 3125, 2959, 1704, 1689. NMR (CF_3COOH, TMS, ppm): 2.48 (3H, s), 2.54 (3H, s), 2.87 (4H, s), 9.27 (1H, s).

b) Employing the procedure as in the preceding experiment (b-method), XIb (2 g) reacted with ethyl acrylate (2.4 g) in the presence of sodium ethoxide in EtOH (prepared from 0.56 g of Na and 30 ml of absolute EtOH) to give 0.27 g (9%) of XIIb, mp 141—142°, undepressed on admixture with an authentic specimen obtained in the above run.

5-Benzoyl-6-methyl-3,4-dihydro-2-pyridone (XIIc)——a) According to the procedure described above, 2-amino-1-propenyl phenyl ketone (XIc) (1.56 g) reacted with acrylic anhydride (1.22 g) in $CHCl_3$ (20 ml) to give 1.77 g (85%) of XIIc, colorless prisms (benzene), mp 116—117°. *Anal.* Calcd. for $C_{12}H_{13}O_2N$ (XIIc): C, 72.54; H, 6.09; N, 6.51. Found: C, 72.67; H, 5.87; N, 6.56. IR ν_{max}^{KBr} cm^{-1}: 3205, 3115, 2959, 1701, 1681. NMR (CF_3COOH, TMS, ppm): 2.02 (3H, s), 2.90 (4H, s) 7.50 (5H, m), 9.24 (1H, s).

b) By treating XIc (0.95 g) with ethyl acrylate (0.7 g) in the presence of sodium ethoxide (prepared from 0.16 g of Na and 20 ml of absolute EtOH), 0.4 g (32%) of XIIc was obtained, mp 116—117°, undepressed on admixture with an authentic specimen obtained in the above run.

5-Cyano-6-methyl-3,4-dihydro-2-pyridone (XIId)——a) By treating 2-aminocrotononitrile (XId) (1.9 g) with acrylic anhydride (2.9 g) as described before, 1.3 g (42%) of XIId was obtained, colorless needles (acetone), mp 213—214°. *Anal.* Calcd. for $C_7H_8ON_2$ (XIId): C, 61.75; H, 5.92; N, 20.58. Found: C, 61.86;

H, 6.11; N, 20.77. IR ν_{max}^{KBr} cm^{-1}: 3195, 3125, 2929, 1686. NMR (CF_3COOH, TMS, ppm): 2.26 (3H, s), 2.74 (4H, s), 9.17 (1H, s).

b) According to the procedure described before, reaction of XId (2 g) with ethyl acrylate (2.9 g) in the presence of sodium ethoxide in EtOH (prepared from 0.67 g of Na and 30 ml of absolute EtOH) afforded 1.5 g (30%) of XIId, mp 213—214°, undepressed on admixture with an authentic specimen obtained in the above run.

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