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Studies on Ketene and Its Derivatives. LXXXI.[1] Reaction of β-Aminocrotonamide with α,β-Unsaturated Ketones

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Reaction of β-aminocrotonamide (I) with α,β-unsaturated ketones is described. Benzylideneacetophenone (IIa) reacts with β-aminocrotonamide (I) to give 2-methyl-4,6-diphenylpyridine-3-carboxamide (IIIa), 3-acetimidoyl-4,6-diphenyl-3,4-dihydro-2(1H)-pyridone (IV) and 6-carbamoyl-3,5-diphenyl-2-cyclohexenonimine (V).

Similar reaction of β-aminocrotonamide (I) with 3-buten-2-one (IIb) and 4-phenyl-3-buten-2-one (IIc) affords 2,6-dimethylpyridine-3-carboxamide (IIIb) and 2,6-dimethyl-4-phenylpyridine-3-carboxamide (IIIc), respectively.

While investigating some potential uses of diketene, we found its reaction with excess ammonia to give a quantitative yield of β-aminocrotonacetamide (I).[3] In contrast to amide and β-amino derivatives of acetoacetic acid such as acetoacetamide and ethyl β-aminocrotonate, compound I has not been extensively investigated. In the preceeding paper[4] we have reported the reaction of I with α,β-unsaturated esters to give glutarimide and pyrimidone derivatives. The present paper reports the reaction of I with α,β-unsaturated ketones to give 2-methylpyridine-3-carboxamide derivatives (III).

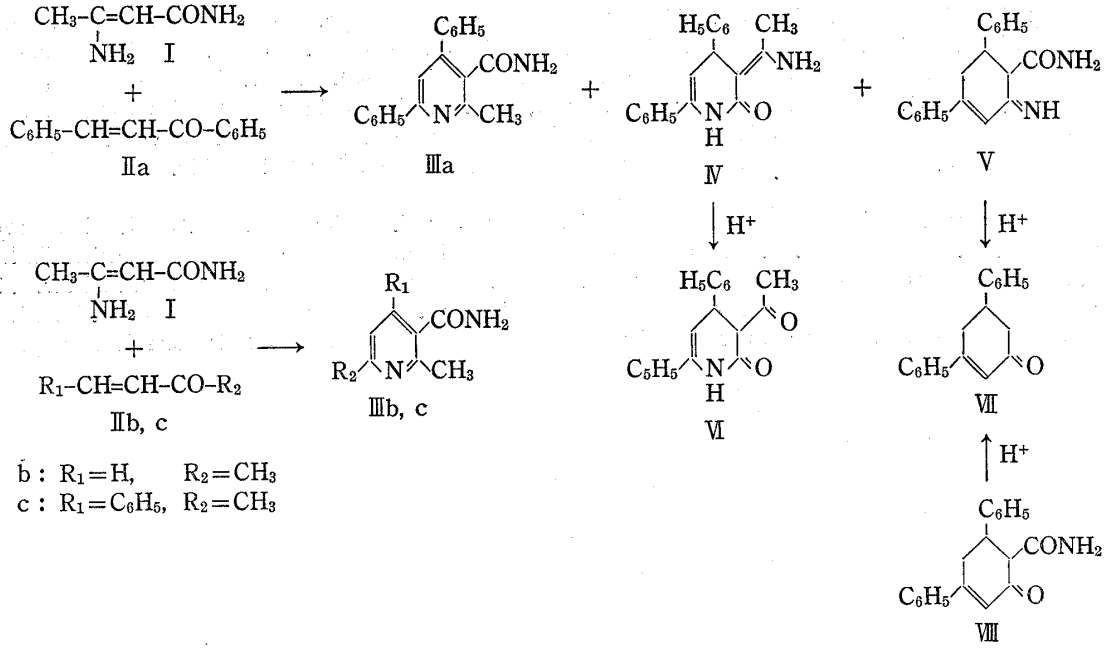

Chart 1

When β-aminocrotonamide (I) was allowed to react with benzylideneacetophenone (IIa) in ethanol under reflux, crystals of mp 216—217°, $C_{19}H_{16}ON_2$ (IIIa), and crystals of mp 235—236°, $C_{19}H_{18}ON_2$ (IV), were obtained in 36% and 4% yield, respectively.

1) Part LXXX: T. Kato, Y. Yamamoto, and M. Kondo, *Heterocycles*, 3, 927 (1975).
2) Location: *Aobayama, Sendai, 980, Japan.*
3) T. Kato, H. Yamanaka, and T. Shibata, *Tetrahedron*, 23, 2965 (1967).
4) T. Kato, H. Yamanaka, H. Fukumi, and M. Noda, *Yakugaku Zasshi*, 83, 1432 (1973).

When the reaction was carried out in the presence of triethylamine, IIIa was obtained in 34% yield besides the low yield (3%) of yellow crystals of mp 212—213° (decomp.), $C_{19}H_{18}ON_2$ (V).

Compound IIIa was identified with 2-methyl-4,6-diphenylpyridine-3-carboxamide by infrared (IR) and nuclear magnetic resonance (NMR) spectral data.

Compound IV was hydrolyzed with hydrochloric acid to give the known compound, 3-acetyl-4,6-diphenyl-3,4-dihydro-2(1H)-pyridone (VI).[5] On the basis of this fact, compound IV was identified with 3-acetimidoyl-4,6-diphenyl-3,4-dihydro-2(1H)-pyridone. Spectral data of IV are well consistent with this structure.

Hydrolysis of V with hydrochloric acid gave 3,5-diphenyl-2-cyclohexenone (VII), which was identified by the comparison with an authentic sample prepared from 6-carbamoyl-3,5-diphenyl-2-cyclohexenone (VIII).[5] From these facts, 6-carbamoyl-3,5-diphenyl-2-cyclohexenonimine (V) was given for the structure of compound V. Spectral data are consistent with its structure.

Similarly, reaction of I with 3-buten-2-one (IIb) and 4-phenyl-3-buten-2-one (IIc) gave rise to 2,6-dimethylpyridine-3-carboxamide (IIIb)[6] and 2,6-dimethyl-4-phenylpyridine-3-carboxamide (IIIc), in 12% and 8% yield, respectively. The use of triethylamine as a catalyst rather decreased the yield of IIIa and IIIb. Moreover, in these reactions products corresponding to IV and V could not be isolated.

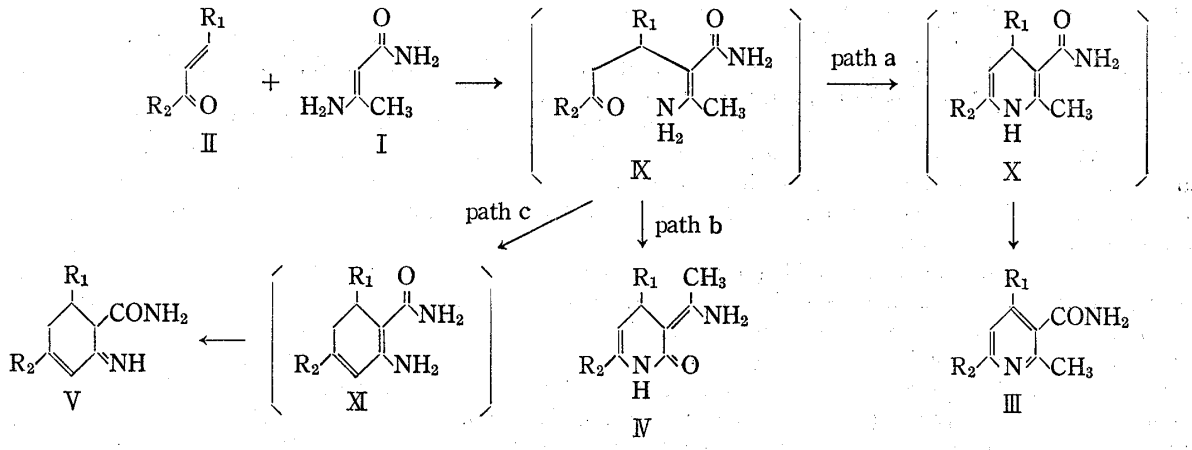

Chart 2

A likely mechanism is shown in Chart 2. The Michael addition of II to the α-carbon of β-aminocrotonamide (I) would afford the adduct IX. Cyclization of IX between the carbonyl carbon and the enamine nitrogen gives rise to the dihydropyridine intermediate (X), which is oxidized to give the product III (path a). If the cyclization occurs between the carbonyl carbon and the amide nitrogen, the compound IV can be obtained (path b). Cyclization between the carbonyl carbon and the methyl carbon would give the carbocyclic intermediate IX, which tautomerizes to the product V (path c).

Experimental[7]

Reaction of β-Aminocrotonamide (I) with Benzylideneacetophenone (IIa)——1) To a solution of I (3 g) in ethanol (50 ml) was added IIa (6.25 g) with stirring. The mixture was refluxed for 7 hr, and condensed

5) T. Kato and M. Noda, *Chem. Pharm. Bull.* (Tokyo), **23**, 2193 (1975).
6) T. Kato and M. Noda, *Chem. Pharm. Bull.* (Tokyo), **24**, 303 (1976).
7) All melting points are uncorrected. IR Spectra were measured by a JASCO DS-301 spectrometer. NMR spectra were measured on a Hitachi-Perkin Elmer R-20 spectrometer at 60 MHz using tetramethylsilane as an internal standard. Abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad.

in vacuo. The residue was extracted with AcOEt. The AcOEt solution was evaporated to dryness, and the residue was purified by silica gel column chromatography using ether as an eluant to give colorless needles (ether) of mp 216—217°. Yield, 2.3 g (36%). *Anal.* Calcd. for $C_{19}H_{16}ON_2$ (IIIa): C, 79.14; H, 5.59; N, 9.72. Found: C, 79.62; H, 5.85; N, 9.64. IR ν_{max}^{KBr} cm^{-1}: 3420, 3320, 3240, 1690, 1650. NMR (CF_3CO_2H, ppm): 8.12 (1H, s), 7.3—7.7 (2H, br), 7.5—7.6 (10H, br s). The residual solid, which was insoluble in AcOEt, was collected by suction. Recrystallization from ethanol gave colorless needles (IV) of mp 235—236°. Yield, 0.48 g (4%). *Anal.* Calcd. for $C_{19}H_{18}ON_2$ (IV): C, 78.59; H, 6.25; N, 9.25. Found: C, 78.31; H, 6.19; N, 9.41. IR ν_{max}^{KBr} cm^{-1}: 3250, 3240 (br), 1625. NMR ($CDCl_3$, ppm): 1.82 (3H, s), 4.43 (1H, d, J=6.0 Hz), 5.22 (1H, d, J=6.0 Hz), 6.5—6.58 (1H, br s), 7.22 (10H, s), 7.3—7.8 (2H, br).

2) A solution of I (3 g), IIa (6.25 g), and triethylamine (3 g) in ethanol (50 ml) was refluxed for 15 hr. The reaction mixture was condensed *in vacuo*, and the crystalline residue was purified by silica gel column chromatography using ether, $CHCl_3$, and AcOEt as eluants. The ether eluate gave 2.19 g (34%) of IIIa, mp 216—217°.

From the AcOEt eluate, a crystalline substance was obtained. Recrystallization from AcOEt gave yellow prisms (V) of mp 212—213° (decomp.). Yield, 0.35 g (3%). *Anal.* Calcd. for $C_{19}H_{18}ON_2$ (V): C, 78.59; H, 6.24; N, 9.65. Found: C, 78.50; H, 6.21; N, 9.32. IR ν_{max}^{KBr} cm^{-1}: 3500. 3360, 3280, 1600, 1590. NMR (CD_3COCD_3, ppm): 2.5—3.3 (3H, m), 4.02 (1H, d, J=8.9 Hz), 5.3—5.6 (1H, br), 6.28 (1H, d, J=1.5 Hz), 7.1—7.5 (10H, m).[8]

3-Acetyl-4,6-diphenyl-3,4-dihydro-2(1H)-pyridone (VI)——A solution of IV (0.1 g) in 10% HCl (10 ml) was heated on a steam bath for 2 hr. Crystals precipitated were collected, and recrystallized from ether to give colorless prisms, of mp 144—145° (lit[5] mp 141—142°), undepressed on admixture with a sample (VI) prepared according to the literature.[5] Yield, 0.06 g (60%).

3,5-Diphenyl-2-cyclohexenone (VII)——1) A solution of V (0.15 g) in conc. HCl (10 ml) was refluxed for 3 hr. After being neutralized with $NaHCO_3$, the mixture was extracted with ether. The solution was condensed to dryness. The residue was submitted to silica gel column chromatography using petroleum ether and ether as eluants. The ether eluate gave colorless needles of mp 83° (petroleum ether). Yield, 0.04 g (30%). *Anal.* Calcd. for $C_{18}H_{16}O$ (VII): C, 87.06; H, 6.50. Found: C, 87.07; H, 6.54. IR ν_{max}^{KBr} cm^{-1}: 1655. NMR ($CDCl_3$) ppm: 2.5—3.5 (5H, m), 6.5 (1H, s), 7.2—7.7 (10H, m).

2) A solution of 6-carboxamoyl-3,5-diphenyl-2-cyclohexenone (VIII)[5] (0.2 g) in conc. HCl (10 ml) was refluxed for 5 hr. After being neutralized with $NaHCO_3$, the mixture was extracted with ether. The ether solution was condensed, and the resulting residue was purified by silica gel column chromatography followed by recrystallization from ether to give 0.14 g (78%) of VII, mp 83°, undepressed on admixture with a sample obtained in the above run.

Reaction of β-Aminocrotonamide (I) with 3-Buten-2-one (IIb)——To a solution of I (3.5 g) in abs. ethanol (50 ml), was added dropwise a solution of IIb (2.1 g) in ethanol (10 ml) in a period of 20 min under reflux. Refluxing was continued for an additional 5 hr. The reaction mixture was condensed *in vacuo* to give an oily residue, which was submitted to silica gel column chromatography using ether as an eluant to give a crystalline substance. Recrystallization from AcOEt gave colorless needles of mp 179—180°. Yield, 0.55 g (12%). *Anal.* Calcd. for $C_8H_{10}ON_2$ (IIIb): 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. NMR ($CDCl_3$, 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).

Reaction of β-Aminocrotonamide (I) with 4-Phenyl-3-buten-2-one (IIc)——The solution of I (3 g) and IIc (4.4 g) in ethanol (50 ml) was refluxed for 30 hr. The solvent was removed by vacuum distillation and the resulting residue was purified by silica gel column chromatography using ether as an eluant to afford colorless needles (ether) of mp 191—192°. Yield, 0.55 g (8%). *Anal.* Calcd. for $C_{14}H_{14}ON_2$ (IIIc): C, 74.31; H, 6.24; N, 12.38. Found: C, 73.89; H, 6.41; N, 12.84. IR ν_{max}^{KBr} cm^{-1}: 3400, 3240, 1655, 1640 (sh). NMR (CF_3CO_2-H, ppm): 2.90 (3H, s), 2.97 (3H, s), 7.78 (1H, s), 7.3—7.8 (2H, br), 7.61 (5H, br s).

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8) This NMR spectrum was taken with JEOL model TNN-TS1000 at 100 MHz using DSS as an internal standard.