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Studies on Ketene and Its Derivatives. LXII.[1] Reaction of Ketene and Diketene with 2-Pyridyl Isocyanate and Isothiocyanate

Tetsuzo Kato and Shinichi Masuda

Pharmaceutical Institute, Tohoku University[2]

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2-Pyridylisocyanate (IIa) reacted with diketene to give 3-acetyl-2-hydroxy-4H-pyrido[1,2-*a*]pyrimidin-4-one (IIIa), 3-acetyl-4-hydroxy-6-methyl-1-(2-pyridyl)-2-pyridone (IVa), and 2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one (Va). On the other hand, reaction of diketene with 2-pyridylisothiocyanate (IIb) afforded only 3-acetyl-2-mercapto-4H-pyrido-[1,2-*a*]pyrimidin-4-one (IIIb).

Reaction of ketene with IIa and IIb gave rise to 2-acetoxy-4H-pyrido[1,2-*a*]pyrimidin-4-one (VIa) and 2-acetylthio-4H-pyrido[1,2-*a*]pyrimidin-4-one (VIb), respectively.

It has been reported that[3,4] 2-pyridyl isocyanate (IIa) and 2-pyridyl isothiocyanate (IIb) undergo readily dimerization reaction to give 3-(2-pyridyl)pyrido[1,2-*a*][1,3,5]triazine-2,4-dione (Ia) and its dithione derivative (Ib), respectively. The reaction involves 1,4-dipolar addition toward the N=C double bond of another mole of isocyanate.

Our interest is focussed on the reaction of ketene and diketene with these isocyanate derivatives (IIa, IIb), because ketene and diketene are known as active agents toward both of the 1,4-dipolar compound[5] and the C=N double bond.[6] The present paper reports the reaction of ketene and diketene with 2-pyridyl isocyanate (IIa) and 2-pyridyl isothiocyanate (IIb).

Though heating of Ib resulted in decomposition readily to IIb *in situ*, Ia did not decompose to IIa. Therefore, 2-picolinoyl azide was used as a starting material for the preparation of 2-pyridyl isocyanate (IIa).[7]

Heating of picolinoyl azide in diketene followed by column chromatography and recrystallization afforded brown leaves of mp 210°, $C_{10}H_8O_3N_2$ (IIIa), colorless prisms of mp 169°, $C_{13}H_{12}O_3N_2$ (IVa), and colorless needles of mp 119°, $C_9H_8ON_2$ (Va).

Compound (Va) was identified as 2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one by the comparison with an authentic sample prepared from 2-aminopyridine and diketene according to the literature.[8]

Infrared (IR) spectrum of IIIa showed the exsistence of carbonyl at 1720, 1690, and 1634 cm^{-1} ($CHCl_3$). The unclear magnetic resonance (NMR) spectrum showed a singlet at 2.78 ppm ($CDCl_3$) presumably due to methyl protons, multiplet signals at 7.00—8.05 ppm (3H) and 9.05 ppm (1H) and a broad signal at 15.60 ppm (1H), which disappeared by adding D_2O. The reaction of 2-hydroxy-4H-pyrido[1,2-*a*]pyrimidin-4-one (VIIa)[9] with acetyl chloride in the presence of sodium ethoxide, gave rise to IIIa besides the O-acetyl derivative (VIa).

1) Part LXI: T. Kato, Y. Yamamoto, and S. Takeda, *Yakugaku Zasshi*, **94**, 627 (1974).
2) Location: *Aobayama, Sendai, 980, Japan.*
3) U. Gizycki and G. Oertel, *Angew. Chem.*, **80**, 362 (1968).
4) H.M. Blatter and H. Lukaszewski, *Tetrahedron Letters*, **1965**, 1087.
5) T. Kato and T. Chiba, *Yakugaku Zasshi*, **89**, 1464 (1969).
6) *e.g.*, T. Kato and Y. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 959 (1965).
7) Y. Otsuji, Y. Koda, M. Kubo, M. Fukukawa, and E. Imoto, *Nippon Kagaku Zasshi*, **80**, 1307 (1959).
8) T. Kato, H. Yamanaka, N. Katagiri, and S. Masuda, *Chem. Pharm. Bull.* (Tokyo), **20**, 142 (1972).
9) A.E. Tschitschibabin, *Chem. Ber.*, **57**, 1169 (1924).

These results are consistent with the structure 3-acetyl-2-hydroxy-4H-pyrido[1,2-*a*]pyrimidin-4-one (IIIa).

Compound (IVa) was identified as 3-acetyl-4-hydroxy-6-methyl-1-(2-pyridyl)-2-pyridone by the comparison of its spectral data with those of 1-substituted pyridone derivatives reported in the previous papers.[10,11] Namely, the IR spectrum ($CHCl_3$) of IVa showed the carbonyl absorption at 1654 cm^{-1}, and the NMR spectrum ($CDCl_3$) showed singlet signals at 1.98 ppm (3H, 6-methyl), 2.60 ppm (3H, acetyl methyl), 5.89 ppm (1H, 5-H), and at 15.89 ppm (1H, enol proton), besides a complex multiplet signals at 7.20—8.75 ppm (4H) due to pyridine ring protons. These spectral data were unequivocally similar with those of the 3-acetyl-4-hydroxy-6-methyl-1-substituted 2-pyridone derivatives obtained from the reactions of diketene with aniline or aminopicolines.[11]

When ketene gas was bubbled into a solution of picolinoyl azide in dry benzene under refluxing, pale brown leaves of mp 143°, $C_{10}H_8O_3N_2$ (VIa) were obtained in good yield. Elemental analysis and spectral data of VIa are consistent with the structure 2-acetoxy-4H-pyrido[1,2-*a*]pyrimidin-4-one. Hydrolysis of VIa with 10% sodium bicarbonate gave rise to a known compound (VIIa).[9] As described previously, acetylation of VIIa with acetyl chloride in the presence of sodium ethoxide gave rise to the 2-acetoxy derivative (VIa) and the 3-acetyl derivative (IIIa).

Next, the reaction of 2-pyridyl isothiocyanate (IIb) was carried out. As described previously, IIb undergoes the dimerization to give Ib at room temperature, which, on heating, generates IIb *in situ*.[3] Therefore, Ib was used as a starting material.

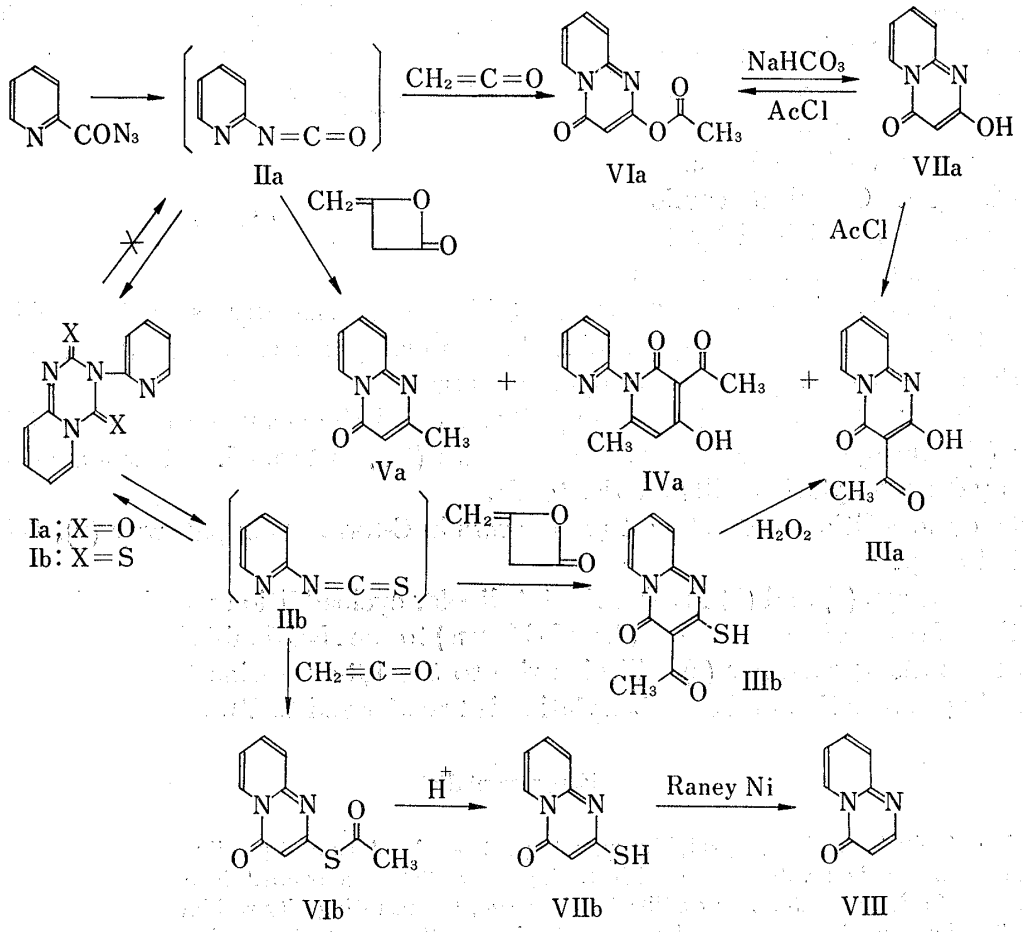

Chart 1

10) T. Kato and Y. Kubota, *Yakugaku Zasshi*, **87**, 1212 (1969).
11) T. Kato, H. Yamanaka, N. Katagiri, and S. Masuda, *Chem. Pharm. Bull.* (Tokyo), **20**, 133 (1972).

Thus, heating of a solution of Ib and diketene in dry benzene afforded yellow needles of mp 222° (decomp.), $C_{10}H_8O_2N_2S$ (IIIb), which, on treatment with hydrogen peroxide, was converted to IIIa. Therefore, 3-acetyl-2-mercapto-4H-pyrido[1,2-*a*]pyrimidin-4-one was reasonably given for the structure of IIIb. The IR and NMR spectral data were well consistent with the structure.

Similarly, refluxing of a solution of Ib in acetone under bubbling of ketene gas gave pale brown needles of mp 185°, $C_{10}H_8O_2N_2S$ (VIb), assignable to 2-acetylmercapto-4H-pyrido-[1,2-*a*]pyrimidin-4-one. Hydrolysis of VIb gave rise to the deacetylated product (VIIb), which on catalytic reduction with Raney Nickel, was transformed to 4H-pyrido[1,2-*a*]pyrimidin-4-one.[12]

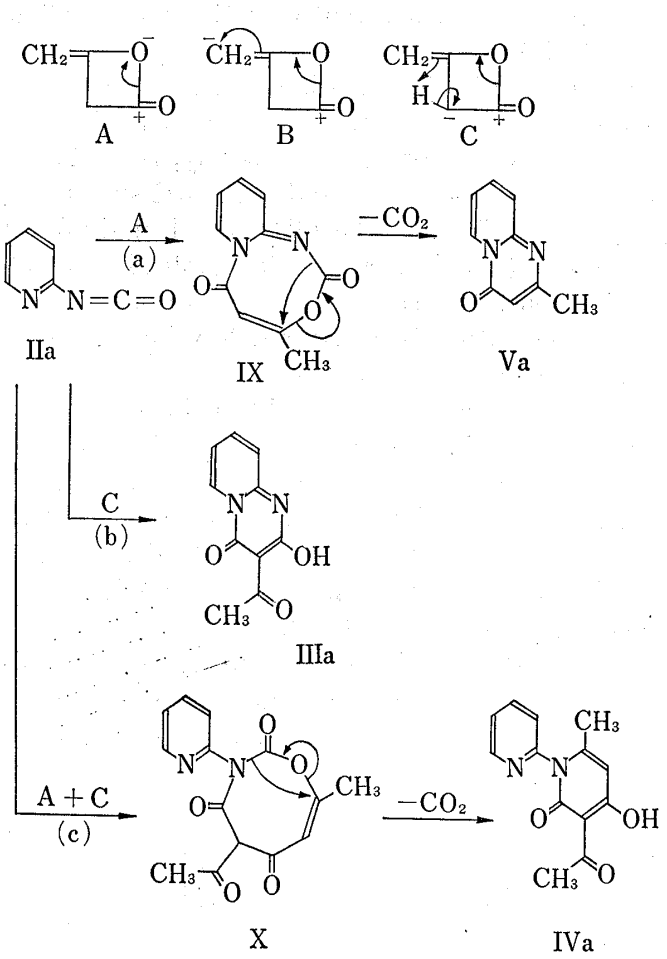

Chart 2

Although the details of the mechanism remain obscure at present, a plausible pathway for the formations of IIIa, IVa, and Va from IIa is depicted in Chart 2. Chemical reaction of diketene can be explained by the activities residing in several forms such as A, B, and C. The carbonyl carbon of diketene acts usually as an electrophile, on the other hand, the oxetane ring oxygen (A), the exo methylene carbon (B), and the oxetane ring methylene carbon (C) have nucleophilic characters.

If diketene (A-form) adds to the ring nitrogen and the isocyanato carbon of IIa along pathway (a), the pyrido-oxadiazocine intermediate (IX) is formed. Rearrangement of IX followed by decarboxylation will give rise to Va.

If the cycloaddition of diketene to IIa occurs in C-form along pathway (b), IIIa can be obtained directly.

Both pathways (a) and (b) involve the 1,4-dipolar cycloaddition reaction of IIa, however, the addition of two moles of diketene (A and C forms) to the N=C double bond of the isocyanato moiety of IIb along pathway (c) will give rise to the 1,3-oxazocine type intermediate (X), which on ring contraction and decarboxylation is transformed to VIa.

Experimental[13]

Reaction of Diketene with 2-Pyridyl Isocyanate (IIa)——A solution of picolinoyl azide (3.7 g, 0.02 mole) in diketene was warmed on a steam bath with stirring at 80—85° for 5 hr until the evolution of N_2 had ceased. After removal of excess diketene by distillation *in vacuo*, the resulting oily residue was washed with 100 ml of ether. To the ether insoluble fraction was added a small amount of MeOH, and scrubbed with a glass rod to give a crystalline solid, which was collected and purified by recrystallization from MeOH to afford

12) R. Adams and I.J. Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952).
13) All melting points were uncorrected.

3-acetyl-2-hydroxy-4H-pyrido[1,2-*a*]pyrimidin-4-one (IIIa) as brown leaves of mp 210°. Yield, 3.9 g (74.5%). *Anal.* Calcd. for $C_{10}H_8O_3N_2$ (IIIa): C, 58.82; H, 3.95; N, 13.72. Found: C, 59.10; H, 4.12; N, 13.63. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2300—2900, 1720, 1690, 1634. NMR (in $CDCl_3$) ppm: 2.78 (3H, s), 7.00—8.05 (3H, m), 9.05 (1H, m), 15.60 (1H, b). The ether soluble fraction was condensed and the residue was purified by column chromatography on silica gel. The petroleum ether (42—48°)–ether mixture (1: 1) and ether were used as eluting solvents. From the petroleum ether–ether eluted fraction a crystalline substance was obtained. Recrystallization from ether gave 3-acetyl-4-hydroxy-6-methyl-1-(2-pyridyl)-2-pyridone (IVa) as colorless prisms of mp 169°. Yield, 0.5 g (8.2%). *Anal.* Calcd. for $C_{13}H_{12}O_3N_2$ (IVa): C, 63.92; H, 4.95; N, 11.47. Found: C, 63.74; H, 4.88; N, 11.61.

The ether eluted fraction was purified by recrystallization from ether to give 2-methyl-4H-pyrido[1,2-*a*]-pyrimidin-4-one (Va) as colorless needles of mp 119°, undepressed on admixture with an authentic sample obtained according to the literature.[8] Yield, 0.2 g (5.0%).

Reaction of Ketene with 2-Pyridyl Isocyanate (IIa)——Ketene was prepared by pyrolysis of acetone according to the literature.[14] The amount of ketene produced per hour was 0.3 mole. Ketene gas was bubbled into a suspension of IIa (3.7 g, 0.02 mole) in dry benzene (30 ml), under reflux for 20 min. The reaction mixture was condensed to dryness *in vacuo*, and the oily residue was scrubbed with a glass rod after addition of a small amount of MeOH. The resulting crystalline solid was recrystallized from MeOH to give 2-acetoxy-4H-pyrido[1,2-*a*]pyrimidin-4-one (VIa) as pale brown leaves of mp 143°. Yield, 4.1 g (80.4%). *Anal.* Calcd. for $C_{10}H_8O_3N_2$ (VIa): C, 58.82; H, 3.95; N, 13.72. Found: C, 59.22; H, 4.35; N, 14.07. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1778, 1700. NMR (in $CDCl_3$) ppm: 2.34 (3H, s), 6.21 (1H, s), 7.05—8.00 (3H, m), 9.06 (1H, m).

Hydrolysis of VIa with 10% $NaHCO_3$——To a solution of VIa (0.2 g) in $CHCl_3$ (10 ml) was added 10 ml of 10% $NaHCO_3$. After stirring at room temperature for 0.5 hr, a crystalline substance separated was collected. Recrystallization from H_2O gave 2-hydroxy-4H-pyrido[1,2-*a*]pyrimidin-4-one (VIIa) as pale brown needles of mp 296° (decomp.). Yield, 0.1 g (62.9%).

The IR spectrum was identical in every respect with that of VIIa obtained according to the literature.[9]

Acylation of VIIa with Acetyl Chloride——To a suspension of VIIa (6.5 g, 0.04 mole) and NaOEt (2.7 g, 0.04 mole) in dry benzene (50 ml) was added 3.2 g of AcCl and the mixture was heated under reflux for 15 hr. After cooling, crystals separated were filtered off and the filtrate was condensed *in vacuo*. The residue was purified by column chromatography on silica gel using ether as an eluant. From the first part of the ether eluted fraction, colorless leaves of mp 143° were obtained, undepressed on admixture with a sample of VIa obtained in the above run. Yield, 2.4 g (29.2%).

The second part of the ether fraction was condensed and the residue was purified again by column chromatography on silica gel using ether as an eluant. A crystalline substance obtained was recrystallized from MeOH to give IIIa as colorless leaves of mp 210°. Yield, 0.5 g (6.0%). The IR spectrum was identical in every respect with that of IIIa obtained in the above run.

Reaction of Diketene with 2-Pyridyl Isothiocyanate (IIb)——Diketene (2.5 g, 0.03 mole) was added to a solution of 3-(2-pyridyl)pyrido[1,2-*a*][1, 3, 5]triazin-2,4-dithione (Ib, 2.7 g, 0.01 mole) in dry benzene (50 ml) and the mixture was refluxed for 5 hr.

After removal of the solvent by vacuum distillation, the residue was recrystallized from MeOH to give 3-acetyl-2-mercapto-4H-pyrido[1,2-*a*]pyrimidin-4-one (IIIb) as yellow needles of mp 222°. Yield, 3.4 g (77.2 %). *Anal.* Calcd. for $C_{10}H_8O_2N_2S$ (IIIb); C, 54.55; H, 3.66; N, 12.72. Found: C, 54.32; H, 3.75; N, 12.68. IR ν_{max}^{KBr} cm^{-1}: 3200—2800, 1700, 1645. NMR (in CF_3COOH) ppm: 3.02 (3H, s), 7.62—8.75 (3H, m), 9.30 (1H, m).

Reaction of IIIb with Hydrogen Peroxide——To a solution of IIIb in 1N KOH (50 ml) was added 10 ml of 3% H_2O_2 in H_2O (50 ml) under ice cooling with stirring. After stirring at room temperature for 1 hr, a small portion of MnO_2 was added to the reaction mixture to decompose excess H_2O_2 and filtered. The filtrate was neutralized with 10% HCl and extracted with $CHCl_3$. The $CHCl_3$ fraction was condensed to dryness *in vacuo*, and the residue was recrystallized from MeOH to give IIIa as colorless leaves of mp 210°. Yield 0.1 g (50.0%). The IR spectrum was identical in every respect with that of IIIa obtained in the above run.

Reaction of Ketene with IIb——Ketene was bubbled into a solution of Ib (2.7 g, 0.01 mole) under reflux for 20 min. The reaction mixture was condensed to dryness *in vacuo* and the residue was recrystallized from benzene to give 2-acetylthio-4H-pyrido[1,2-*a*]pyrimidin-4-one (VIb) as pale brown needles of mp 185°. Yield 3.6 g (81.8%). *Anal.* Calcd. for $C_{10}H_8O_2N_2S$ (VIb): C, 54.55; H, 3.66; N, 12.72. Found: C, 55.04; H, 3.78; N, 12.73. IR ν_{max}^{KBr} cm^{-1}: 1705, 1685. NMR (in $CDCl_3$) ppm: 2.50 (3H, s), 6.89 (1H, s), 7.00—7.35 (3H, m), 9.00 (1H, m).

Hydrolysis of VIb——A suspension of VIb (1.1 g) in 90% MeOH (20 ml) was refluxed for 0.5 hr. After cooling, the crystals separated were collected by filtration and recrystallized from MeOH to give 2-mercapto-4H-pyrido[1,2-*a*]pyrimidin-4-one (VIIb) as yellow needles of mp 218° (decomp.). Yield 0.7 g (81.0%).

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

Anal. Calcd. for $C_8H_6ON_2S$ (VIIb): C, 53.93; H, 3.40; N, 15.73. Found: C, 54.09; H, 3.42; N, 15.86. IR ν_{max}^{KBr} cm^{-1}: 1670. NMR (in CF_3COOH) ppm: 6.78 (1H, s), 7.75—8.80 (3H, m), 9.40 (1H, m).

Reaction of VIIb with Raney Nikel To a solution of VIIb (0.5 g) in 3% NH_4OH (20 ml) was added 3.0 g of Raney Ni, and the reaction mixture was refluxed for 2 hr. After cooling Raney Ni was filtered off and the filtrate was condensed to dryness *in vacuo*. The residue was recrystallized from petroleum ether to give 4H-pyrido[1,2-*a*]pyrimidin-4-one (VIII) as colorless needles of mp 128° (lit.[12] mp 127°). Yield, 0.35 g (70.0%).

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