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Studies on Ketene and Its Derivatives. LXXVII.[1] Reaction of Diketene with Pyridineformimidates and Related Compounds to give 1,3-Oxazin-4-one Derivatives

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Reaction of diketene with ethyl pyridineformimidates (Ia—e) resulted in the formation of 6-methyl-2-pyridyl-4*H*-1,3-oxazin-4-one (IVa—c) and 2-ethoxy-6-methyl-2-pyridyl-2*H*-1,3-oxazin-4(3*H*)-one (IIIb,c).

Similar reaction with ethyl 2-quinolineformimidate (Id) and methyl 2-pyridineacetimidate (Ie) gave 6-methyl-2-(2-quinolyl)-4*H*-1,3-oxazine-4-one (IVd) and 2-methoxy-6-methyl-2-(2-pyridylmethyl)-2*H*-1,3-oxazin-4(3*H*)-one (IIIe), respectively.

The products obtained were treated with ammonia to give 6-methyl-2-substituted-4(3*H*)-pyrimidone (Va—e). Hydrolysis of IIIe gave 6-hydroxy-4-methyl-3(or 5)-(2-pyridyl)-2(1*H*)-pyridone (VIII).

Previously we have reported the reaction of diketene with aliphatic and aromatic imidates to give 2-substituted-6-methyl-1,3-oxazin-4-one derivatives.[3,4] Interest in 1,3-oxazine chemistry and the limited ways of their synthesis prompts us to report, in this note, the ready synthesis of 2-pyridyl-1,3-oxazine and 2-pyridylpyrimidine derivatives applying the above reaction.

Heating of a solution of ethyl 2-pyridineformimidate (Ia, R=2-pyridyl) and diketene (II) in chloroform in the presence of a catalytic amount of acetic acid gave colorless prisms of mp 154° (decomp.). Elemental analysis and spectral data are consistent with the structure as 6-methyl-2-(2-pyridyl)-4*H*-1,3-oxazin-4-one (IVa, R=2-pyridyl).

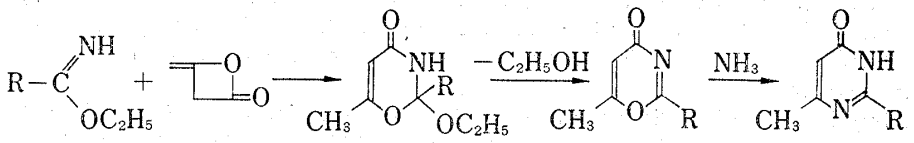
Reaction of IVa with ammonia afforded 6-methyl-2-(2-pyridyl)-4(3*H*)-pyrimidone (Va) in 67% yield. The structure of Va was identified by the comparison with an authentic sample prepared from ethyl picolinate (VIa, R=2-pyridyl) and β-aminocrotonamide (VII) applying the method reported in the previous paper.[5]

The reaction of ethyl 3-pyridineformimidate (Ib, R=3-pyridyl) with diketene (II) in chloroform at room temperature gave 2-ethoxy-6-methyl-2-(3-pyridyl)-2*H*-1,3-oxazin-4(3*H*)-one (IIIb, R=3-pyridyl) in 33% yield. When the reaction was carried out at reflux in the presence of acetic acid as a catalyst, 6-methyl-2-(3-pyridyl)-4*H*-1,3-oxazin-4-one (IVb, R=3-pyridyl) was obtained in 31% yield. Ammonolysis of IVb gave rise to 6-methyl-2-(3-pyridyl)-4(3*H*)-pyrimidone (Vb, R=3-pyridyl) in 25% yield, which was also obtained by the reaction of ethyl nicotinate (VIb, R=3-pyridyl) with β-aminocrotonamide (VII).

Similarly, reaction of ethyl 4-pyridineformimidate (Ic, R=4-pyridyl) with diketene (II) without acetic acid gave 2-ethoxy-6-methyl-2-(4-pyridyl)-2*H*-1,3-oxazin-4(3*H*)-one (IIIc, R=4-pyridyl) in 40% yield. The same reaction in the presence of acetic acid as a catalyst afforded 6-methyl-2-(4-pyridyl)-4*H*-1,3-oxazin-4-one (IVc, R=4-pyridyl) in 35% yield. Ammonolysis of IIIc gave rise to 6-methyl-2-(4-pyridyl)-4(3*H*)-pyrimidone (Vc, R=4-pyridyl), which was also obtained by the reaction of ethyl isonicotinate (VIc, R=4-pyridyl) with β-aminocrotonamide (VII).

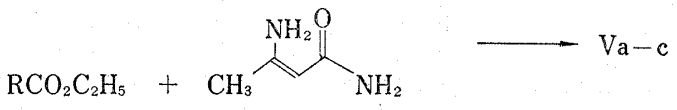
1) Part LXXVI: T. Kato and M. Noda, *Chem. Pharm. Bull.* (Tokyo), **24**, 303 (1976).
2) Location: *Aobayama, Sendai, 980, Japan.*
3) T. Kato and Y. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1334 (1967).
4) T. Kato, H. Yamanaka, Y. Yamamoto, and M. Kondo, *Yakugaku Zasshi*, **92**, 886 (1972).
5) T. Kato, H. Yamanaka, and S. Kondo, *Yakugaku Zasshi*, **90**, 509 (1970).

Similarly, reaction of ethyl 2-quinolineformimidate (Id, R=2-quinolyl) with diketene gave 6-methyl-2-(2-quinolyl)-4*H*-1,3-oxazin-4-one (IVd, R=2-quinolyl) in 30% yield, which reacted with ammonia to give 6-methyl-2-(2-quinolyl)-4(3*H*)-pyrimidone (Vd, R=2-quinolyl) in 71% yield.



Ia–d II IIIb, c IVa–d Va–d

R=a : 2-pyridyl c : 4-pyridyl
b : 3-pyridyl d : 2-quinolyl

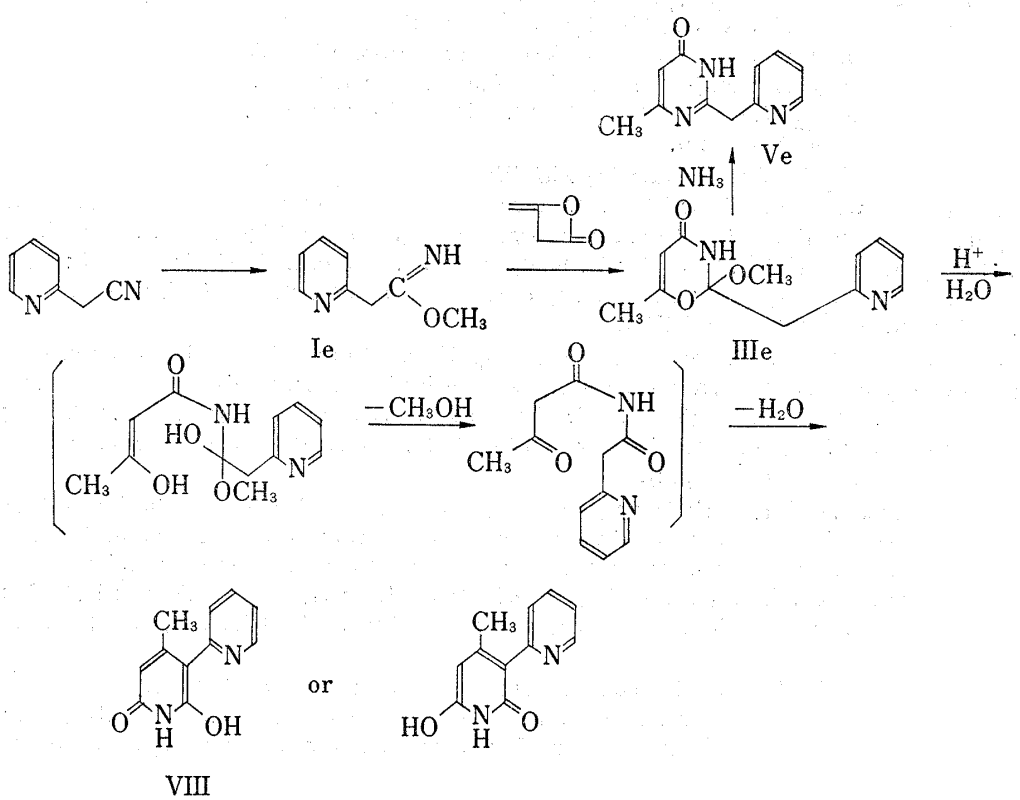


VIa–c VII

Chart 1

When methyl 2-pyridineacetimidate (Ie, R=2-pyridylmethyl) was allowed to react with diketene (II), 2-methoxy-6-methyl-2-(2-pyridylmethyl)-2*H*-1,3-oxazin-4(3*H*)-one (IIIe, R=2-pyridylmethyl) was obtained in 57% yield. Ammonolysis of IIIe gave 6-methyl-2-(2-pyridylmethyl)-4(3*H*)-pyrimidone (Ve, R=2-pyridylmethyl) in 23% yield.

Hydrolysis of IIIe with diluted hydrochloric acid gave rise to 6-hydroxy-4-methyl-3 (or 5)-(2-pyridyl)-2(1*H*)-pyridone (VIII) in 76% yield. Though details of the mechanism of the formation of VIII is not clear at present, a likely pathway is shown in Chart 2.



Ve

Ie IIIe

VIII

Chart 2

Experimental

Reaction of Ethyl 2-Pyridineformimidate (Ia) with Diketene (II)——To a solution of Ia (1.5 g) and diketene (0.9 g) in $CHCl_3$(5 ml), was added a drop of AcOH. After being refluxed for 2 hr, the reaction mixture was evaporated *in vacuo*. The resulting residue was washed with petroleum ether and ether. The residual solid was purified by recrystallization from acetone to colorless needles, mp 154° (decomp.). Yield, 0.25 g (13%). *Anal.* Calcd. for $C_{10}H_8O_2N_2$ (IVa): C, 63.83; H, 4.29; N, 14.89. Found: C, 63.75; H, 4.58; N, 14.77. Infrared (IR) $\nu_{max}^{CHCl_3}$ cm^{-1}: 1676, 1668. Nuclear magnetic resonance (NMR) ($CDCl_3$) ppm: 2.44 (3H, s), 6.16 (1H, s), 7.30—8.80 (4H, m).

6-Methyl-2-(2-pyridyl)-4(3*H*)-pyrimidone (Va)——1) To a solution of IV (1.5 g) in EtOH (5 ml), was added 28% NH_4OH (20 ml). The mixture was heated at 90—95° in a sealed tube for 2 hr, and evaporated *in vacuo*. The resulting residue was purified by recrystallization from AcOEt to colorless needles, mp 96—97°. Yield, 1 g (67%). *Anal.* Calcd. for $C_{10}H_9ON_3$ (Va): C, 64.16; H, 4.85; N, 22.45. Found: C, 63.74; H, 5.20; N, 22.23. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1667. NMR ($CDCl_3$) ppm: 2.38 (3H, s), 6.28 (1H, s), 7.25—8.75 (4H, m), 10.50—11.30 (1H, br).

2) To a solution of NaOEt–EtOH prepared from Na (1.3 g) and abs. EtOH (60 ml), were added β-aminocrotonamide (VII) (5 g) and ethyl picolinate (VIa) (7.5 g) with stirring. After refluxing for 5 hr, the mixture was neutralized with 10% HCl and condensed to dryness *in vacuo*. The residue was extracted with $CHCl_3$. The $CHCl_3$ extract was purified by recrystallization from AcOEt to colorless needles, mp 96—97°, undepressed on admixture with a sample of Va obtained in the above run. Yield, 2 g (21%).

Reaction of Ethyl 3-Pyridineformimidate (Ib) with Diketene (II)——1) To a solution of Ib (1 g) in $CHCl_3$ (5 ml), was added dropwise diketene (1 g) with stirring. The mixture was stirred at room temperature for 4 hr, and condensed *in vacuo*. After washing with petroleum ether, the resulting residue was recrystallized from ether to colorless needles, mp 98—99°. Yield, 0.84 g (33%). *Anal.* Calcd. for $C_{12}H_{14}O_3N_2$ (IIIb): C, 61.52; H, 6.02; N, 11.96. Found: C, 61.90; H, 6.24; N, 11.91. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1676. NMR ($CDCl_3$) ppm: 1.24 (3H, t, J=7 Hz), 2.05 (3H, s), 3.59 (2H, q, J=7 Hz), 5.29 (1H, s), 7.26—8.90 (5H, m, ring protons and NH).

2) A solution of Ib (1.5 g), diketene (0.9 g), and a drop of AcOH in $CHCl_3$ (5 ml) was refluxed for 30 min. The solvent was removed *in vacuo*, and the residue was purified by recrystallization from ether to yellow needles, mp 137—139° (decomp.). Yield, 0.6 g (31%). *Anal.* Calcd. for $C_{10}H_8O_2N_2$ (IVb): C, 63.82; H, 4.29; N, 14.89. Found: C, 64.01; H, 4.52; N, 14.95. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1678, 1663. NMR ($CDCl_3$) ppm: 2.39 (3H, s), 6.06 (1H, s), 7.28—9.40 (4H, m).

6-Methyl-2-(3-pyridyl)-4(3*H*)-pyrimidone (Vb)——A mixture of IVb (0.5 g) and liq. NH_3 (16 ml) was placed in a sealed tube. After allowing to stand at room temperature for a day, NH_3 was evaporated from the reaction mixture. The residue was purified by recrystallization from $CHCl_3$ to colorless needles, mp 213—214°, undepressed on admixture with a sample of Vb prepared from ethyl nicotinate (VIb) and β-aminocrotonamide according to the literature.[6] Yield, 0.12 g (25%). *Anal.* Calcd. for $C_{10}H_9ON_3$ (Vb): C, 64.16; H, 4.85; N, 22.45. Found: C, 64.03; H, 4.92; N, 22.18. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660. NMR (CF_3CO_2H) ppm: 2.86 (3H, s), 7.12 (1H, s), 8.23—9.95 (4H, m).

Reaction of Ethyl 4-Pyridineformimidate (Ic) with Diketene (II)——1) A solution of Ic (1 g) and diketene (0.6 g) in $CHCl_3$ (15 ml) was refluxed for 1.5 hr. After removal of the solvent from the reaction mixture, the residue was purified by recrystallization from ether to yellow prisms, mp 126° (decomp.). Yield, 0.6 g (40%). *Anal.* Calcd. for $C_{12}H_{14}O_3N_2$ (IIIc): C, 61.52; H, 6.02; N, 11.96. Found: C, 61.41; H, 6.15; N, 12.00. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1678. NMR ($CDCl_3$) ppm: 1.20 (3H, t, J=7 Hz), 2.03 (3H, s), 3.55 (2H, q, J=7 Hz), 5.27 (1H, s), 7.42—8.85 (5H, m, ring protons and NH).

2) A solution of Ic (1.5 g), diketene (1 g) and a drop of AcOH in $CHCl_3$ (5 ml) was refluxed for 30 min. The mixture was condensed *in vacuo*, and the residue was purified by recrystallization from ether to colorless needles, mp 150—151°. Yield, 0.66 g (35%). *Anal.* Calcd. for $C_{10}H_8O_2N_2$ (IVc): C, 63.82; H, 4.29; N, 14.89. Found: C, 63.86; H, 4.37; N, 14.98. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1682, 1665. NMR ($CDCl_3$) ppm: 2.38 (3H, s), 6.10 (1H, s), 7.90—8.10 (2H, m), 8.72—8.88 (2H, m).

6-Methyl-2-(4-pyridyl)-4(3*H*)-pyrimidone (Vc)——1) A mixture of IIIc (2.2 g) and liq. NH_3 (17 ml) was placed in a sealed tuve. After allowing to stand at room temperature for a day, NH_3 was evaporated from the reaction mixture. The residue was purified by recrystallization from acetone to colorless needles, mp 200° (decomp.). *Anal.* Calcd. for $C_{10}H_9ON_3$ (Vc): C, 64.16; H, 4.85; N, 22.45. Found: C, 64.51; H, 5.00; N, 22.59. IR ν_{max}^{KBr} cm^{-1}: 1673. NMR (CF_3CO_2H) ppm: 2.88 (3H, s), 7.19 (1H, s), 8.94 (2H, d, J=7 Hz), 9.18 (2H, d, J=7 Hz).

2) To a solution of NaOEt–EtOH prepared from Na (1.3 g) and EtOH (60 ml), were added ethyl isonicotinate (VIc) and VII (5 g). The mixture was refluxed for 5 hr, neutralized with 10% HCl, and condensed to dryness *in vacuo*. The resulting residue was washed with a small amount of H_2O, and extracted with

6) S. Konno, Dissertation (Tohoku University), **1971**, 64.

MeOH. The MeOH extract was purified by recrystallization from MeOH to colorless needles, mp 200° (decomp.), whose IR spectrum was identical in every respect with that of Vc obtained in the above run.

6-Methyl-2-(2-quinolyl)-4*H*-1,3-oxazin-4-one (IVd)——A mixture or ethyl 2-quinolineformimidate (Id) (2 g), diketene (0.9 g) and a drop of AcOH in $CHCl_3$ (5 ml) was refluxed for 6 hr. The mixture was condensed *in vacuo*, and the resulting residue was purified by recrystallization from acetone to colorless needles, mp 176—177° (decomp.). Yield, 0.7 g (30%). *Anal.* Calcd. for $C_{14}H_{10}O_2N_2$ (IVd): C, 70.58; H, 4.23; N, 11.76. Found: C, 70.22; H, 4.29; N, 11.56. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1673, 1668. NMR ($CDCl_3$) ppm: 2.49 (3H, s), 6.20 (1H, s), 7.75—8.61 (6H, m).

6-Methyl-2-(2-quinolyl)-4(3*H*)-pyrimidone (Vd)——A mixture of IVd (0.5 g) and liq. NH_3 (10 ml) was placed in a sealed tube. After allowing to stand at room temperature for a day, NH_3 was evaporated from the mixture. The residue was recrystallized from MeOH to colorless needles, mp 209° (decomp.). Yield, 0.3 g (70%). *Anal.* Calcd. for $C_{14}H_{11}ON_3$ (Vd): C, 70.87; H, 4.67; N, 17.71. Found: C, 70.68; H, 4.81; N, 17.52. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1664. NMR ($CDCl_3$) ppm: 2.42 (3H, s), 6.37 (1H, s), 7.30—8.65 (6H, m), 10.90—11.40 (1H, br).

Methyl 2-Pyridineacetimidate (Ie)——Dry HCl gas was bubbled to absolute MeOH (30 ml) under ice-cooling, to which was added dropwise a solution of 2-pyridineacetonitrile (5 g) in absolute MeOH (10 ml) with stirring. The mixture was allowed to stand at room temperature overnight. Crystals separated were collected by suction, dissolved in ice-water, and neutralized with saturated K_2CO_3. The mixture was extracted with CH_2Cl_2, and the CH_2Cl_2 solution was evaporated under reduced pressure. The resulting oily residue was purified by distillation to a colorless oil, bp 83° (2 mm Hg). Yield, 4.5 g (71%). *Anal.* Calcd. for $C_8H_{10}ON_2$ (Ie): C, 63.98; H, 6.71; N, 18.65. Found: C, 63.81; H, 6.75; N, 18.28. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650. NMR ($CDCl_3$) ppm: 3.60 (2H, s), 3.66 (3H, s), 7.00—8.60 (5H, m, ring protons and NH).

Reaction of Methyl 2-Pyridineacetimidate (Ie) with Diketene (II)——A mixture of Ie (1.5 g) and diketene (1.7 g) was kept at 30—40° on a water-bath. After 1 hr, the mixture was solidified, which was extracted with ether. The ether solution was condensed, and crystals separated were collected. Recrystallization from ether gave pale yellow prisms, mp 108° (decomp.). Yield, 1.3 g (57%). *Anal.* Calcd. for $C_{12}H_{14}O_3N_2$ (IIIe): C, 61.52; H, 6.02; N, 11.96. Found: C, 61.90; H, 6.15; N, 11.94. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1673. NMR ($CDCl_3$) ppm: 1.99 (3H, s), 3.26 (3H, s) 3.40 (2H, s), 5.17 (1H, s), 7.00—8.60 (5H, m, ring protons and NH).

6-Methyl-2-(2-pyridylmethyl)-4(3*H*)-pyrimidone (Ve)——To a solution of IIIe (1 g) in MeOH (5 ml), was added 28% NH_4OH (30 ml). The reaction mixture was placed in a sealed tube, and heated in a steam bath for 2 hr. The mixture was condensed *in vacuo*, and the residue was purified by silica-gel column chromatography using ether, $CHCl_3$, and AcOEt as eluants. The AcOEt elution gave a crystalline substance, which was recrystallized from AcOEt to yellow prisms, mp 172—173° (decomp.). Yield, 0.2 g (23%). *Anal.* Calcd. for $C_{11}H_{11}ON_3$ (Ve): C, 65.67; H, 5.51; N, 20.88. Found: C, 65.64; H, 5.44; N, 20.89. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670. NMR ($CDCl_3$) ppm: 2.30 (3H, s), 4.14 (2H, s), 6.20 (1H, s), 7.20—8.70 (4H, m), 10.90—11.70 (1H, br).

6-Hydroxy-4-methyl-3(or 5)-(2-pyridyl)-2(1*H*)-pyridone (VIII)——To a solution of IIIe (1 g) in MeOH (5 ml) and H_2O (15 ml), was added several drops of 10% HCl until the solution became acidic. The mixture was heated at 60—70° for 30 min. After cooling, crystals separated were collected. Recrystallization from MeOH gave yellow prisms mp 277—279° (decomp.). Yield, 0.65 g (76%). *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$ (VIII): C, 65.33; H, 4.98; N, 13.86. Found: C, 64.96; H, 4.87; N, 14.01. IR ν_{max}^{KBr} cm^{-1}: 1660 (sh), 1600. NMR (CF_3CO_2H) ppm: 2.42 (3H, s), 6.57 (1H, s), 7.90—9.00 (4H, m).

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