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Studies on Ketene and Its Derivatives. LXVIII.[1] Reaction of Diketene with N-Imino-pyridinium, -quinolinium, and -isoquinolium Ylides

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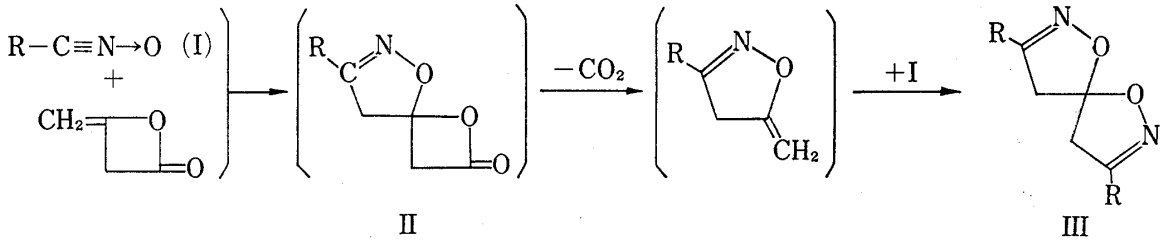
1-Iminopyridinium ylide reacted with diketene to give 1-(N-acetoacetylimino)-pyridinium ylide (VI), which, on treatment with sodium ethoxide, was transformed to 3-acetyl-2-hydroxypyrazolo[1,5-*a*]pyridine (XI). On the other hand, reaction of diketene with 1-(N-methylimino)pyridinium ylide afforded directly 3-acetyl-1-methyl-pyrazolo[1,5-*a*]pyridin-2-one (VIII).

Reaction of diketene with 1-iminoquinolinium ylide (XIII) and 2-iminoisoquinolinium ylide (XVI) gave rise to 3-acetyl-2-hydroxypyrazolo[1,5-*a*]quinoline (XV) and 3-acetyl-2-hydroxypyrazolo[1,5-*a*]isoquinoline (XVII), respectively.

d'Alcontres, *et al.*[3] reported that diketene reacts with nitrile oxide (I) to yield bi-isoxazolinic spiro compounds (III) with loss of carbon dioxide, according to Chart 1. This reaction involves 1,3-dipolar cycloaddition of nitrile oxide to the olefinic moiety of diketene giving a spiro intermediate (II), which keeps the β-lactone ring intact. Sasaki[4] reported the reaction of 5-nitrofuran-2-carbohydroxamoyl chloride with diketene to give 3-(5-nitro-2-furyl)-5-methyl-isoxazole, in which 1,3-dipolar cycloaddition of nitrile oxide involves. A similar example was observed in the 1,3-dipolar cycloaddition of azomethine oxide to diketene.[5]



II III

Chart 1

Since few literatures are available concerning such reaction of diketene involving only the olefinic double bond of diketene,[6] we were interested in the reaction of 1,3-dipolar compounds with diketene. The present paper reports the reaction of diketene with azomethine imines, such as 1-iminopyridinium ylide (V), 1-(N-methylimino)pyridinium ylide (X), 1-iminoquinolinium ylide (XIV), and 2-iminoisoquinolinium ylide (XVI), which are known as 1,3-dipolar compounds.[7]

When 1-iminopyridinium ylide (V), prepared from 1-aminopyridinium iodide (IV), was allowed to react with diketene, an oily product (VI) was obtained after purification by silica

1) Part LXVII: T. Kato, M. Sato, and Y. Kitagawa, *Chem. Pharm. Bull.* (Tokyo), **23**, 365 (1975).
2) Location: *Aobayama, Sendai, 980, Japan.*
3) G.S. d'Alcontres, G. Cum, and M. Gattuso, *Recerca Sci.*, **37**, 750 (1967).
4) T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Japan*, **42**, 258 (1969).
5) M.C. Aversa, G. Cum, G.S. d'Alcontres, and N. Uccella, *J. Chem. Soc. Perkin I*, **1972**, 222.
6) *e.g.*, T. Kato, *Accounts of Chemical Research*, **7**, 265 (1974).
7) *e.g.*, R. Huisgen, R. Grashey, and R. Krischke, *Tetrahedron Letters*, **1962**, 387; T. Okamoto, M. Hirobe, Y. Tamai, and E. Yabe, *Chem. Pharm. Bull.* (Tokyo), **14**, 506, 523 (1966); V. Boekelheide and N.A. Fedoruk, *J. Org. Chem.*, 33, 2062 (1968).

gel column chromatography. VI was difficultly purified by distillation, but spectral data and elemental analysis of its picrate (mp 134°) suggested the structure being 1-(N-acetoacetyl imino)pyridinium ylide (VI).

Reaction of the oil (VI) with excess methyl iodide gave rise to crystals of mp 155°, $C_{10}H_{13}O_2N_2I$ (VII). Infrared (IR) and nuclear magnetic resonance (NMR) spectra suggested the structure being 1-(N-methyl-N-acetoacetylamino)pyridinium iodide (VII). Treatment of VII with sodium ethoxide afforded 3-acetyl-1-methylpyrazolo[1,5-*a*]pyridin-2-one (VIII). Spectral data were well consistent with this structure. This compound (VIII) was also obtained from the reaction of 1-(N-methylamino)pyridinium iodide (IX) with diketene in the presence of potassium carbonate.

Treatment of VI with sodium ethoxide in abs. ethanol gave rise to 3-acetyl-2-hydroxypyrazolo[1,5-*a*]pyridine (XI) in 60% yield.

Methylation of XI with methyl iodide gave N-methyl (VIII) and O-methyl derivative (XII), in 26% and 36% yield, respectively.

Similarly, 1-aminoquinolinium iodide (XIII) was allowed to react with diketene in the presence of potassium carbonate to give the cyclic product (XV) in 31% yield. In this case, 1-(N-acetoacetylimino) derivative corresponding to VI could not be isolated.

Lastly, 2-iminoisoquinolinium ylide (XVI) was allowed to react with diketene giving 3-acetyl-2-hydroxypyrazolo[5,1-*a*]isoquinoline (XVII) in 11% yield.

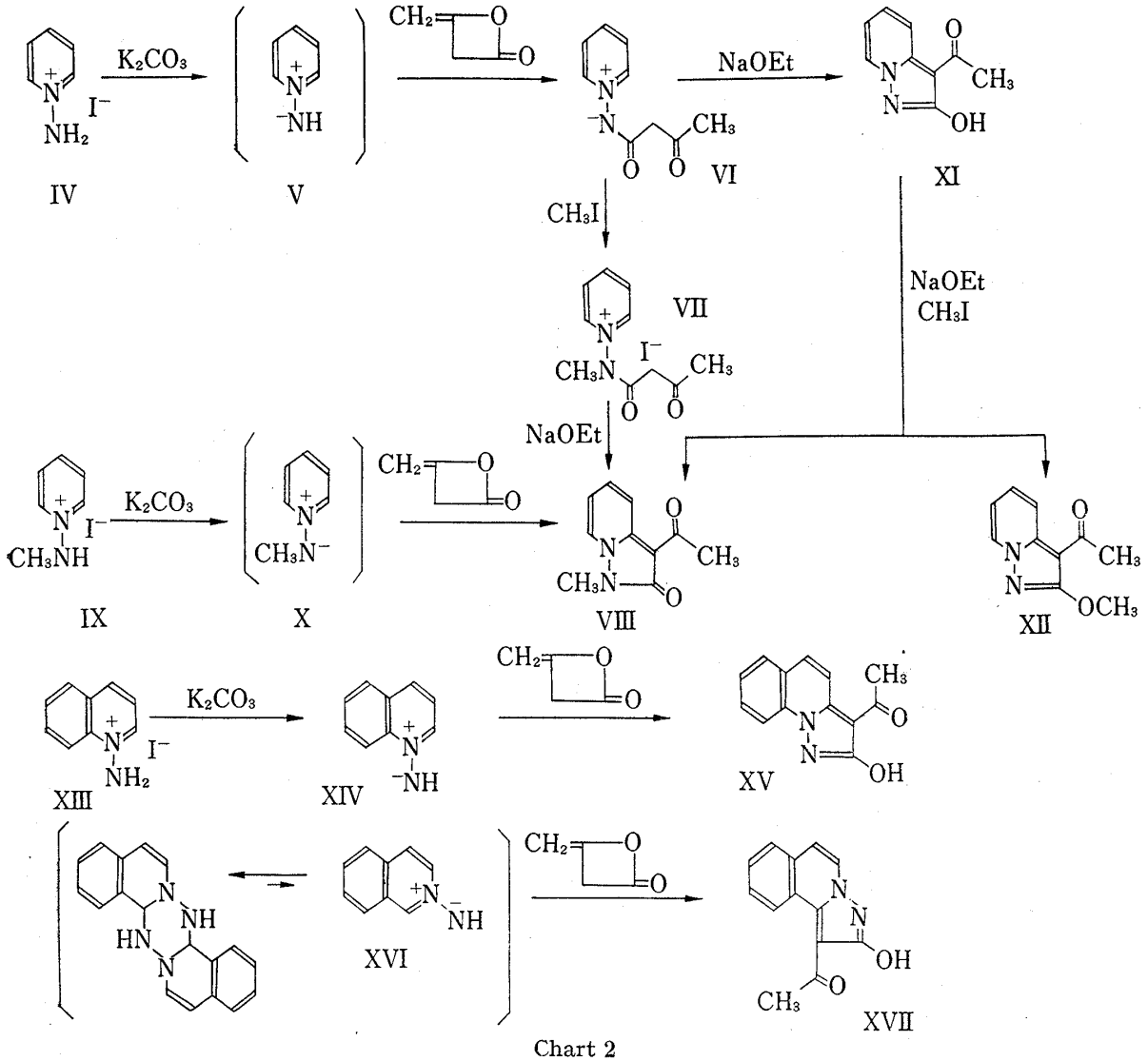


Chart 2

Although the reaction gives a [3+2→5]cycloadduct intermediate such as D, strictly speaking, the category of the reaction does not fall into the so-called 1,3-dipolar cycloaddition reaction[8] which is observed in the above mentioned instances.[3-5] Reaction mechanism is ambigous at present, a likely interpretation is shown in Chart 3. N-Imines produced from 1-amino quaternary ammonium iodide react with diketene as nucleophiles to give N-acylated dipolar intermediates such as A, another canonical form (B) of which is transformed to the tautomeric structure (C). Cyclization of C, along path-a, affords 3,9-dihydropyrazolo[1,5-a]-pyridine derivative (D) as an intermediate, which is oxidized to give the pyrazolo[1,5-*a*]pyridine type derivatives (VIII). In the case of 1-iminopyridinium ylide (V), tautomerization of the intermediate C proceeds along path b to give the stable N-imine (VI), which, on treatment with sodium ethoxide, is transformed to the cyclic compound (XI).

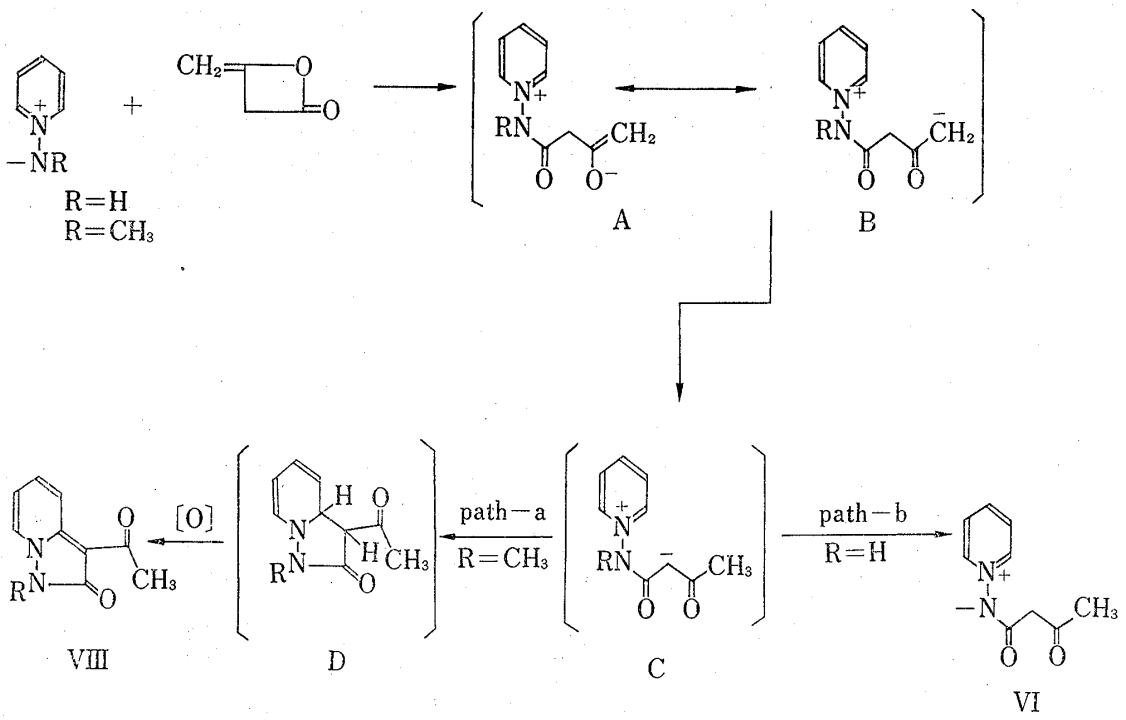


Chart 3

Experimental

All melting points were determined by a calibrated Yanagimoto melting point apparatus. IR spectra were measured by a JASCO DS-301 spectrometer. NMR spectra were measured on a Hitachi-Perkin Elmer R-20 spectrometer and reported as δ value (ppm) relative to trimethylsilane as an internal standard. Mass spectra were obtained on a Hitachi Double Focusing Mass Spectrometer RMU-7L.

1-(N-Acetoacetylimino)pyridinium Ylide (VI)——To a solution of 1-aminopyridinium iodide (IV) (2.2 g) in dimethylformamide (DMF) (20 ml), was added K_2CO_3 (1.4 g) at room temperature with stirring. After 30 min, diketene (1.6 g) was added dropwise at 20—25°, and stirring was continued for an additional 30 min. The solvent was removed by vacuum distillation, and the resulting residue was submitted to silica gel column chromatography using ether, acetone and then MeOH as eluants. The ether and acetone eluted fraction afforded N-free crystalline substance (diketene polymer). The MeOH elution gave a brown oil (VI). Yield, 1.6 g (89.2%). IR ν_{max}^{Nujol} cm^{-1}: 1700. NMR (CF_3CO_2H) ppm: 2.48 (3H, s), 4.08 (2H, s), 8.05—8.95 (5H, m). Mass Spectrum: 178 (M^+). Picrate; mp 137°, yellow needles (EtOH). *Anal.* Calcd. for $C_9H_{10}O_2N_2 \cdot C_6H_3O_7N_3$ (VI-picrate): C, 44.23; H, 3.22; N, 17.20. Found: C, 44.25; H, 3.33; N, 16.99.

1-(N-Acetoacetyl-N-methylamino)pyridinium Iodide (VII)——A solution of VI (3.5 g) in CH_3I (10 g) was allowed to stand at room temperature (20—23°) overnight. Crystals precipitated were collected, and recrystallized from EtOH to give yellow needles of mp 155°. Yield, 5 g (85%). *Anal.* Calcd. for $C_{10}H_{13}$-

8) R. Hüisgen, R. Grashey, and J. Sauer, "The Chemistry of Alkenes," ed. by, S. Patai, Interscience Publishers, Inc., New York, 1964, pp. 741—929.

O_2N_2I (VII): C, 37.73; H, 4.08; N, 8.80. Found: C, 37.62; H, 4.29; N, 8.60. IR ν_{max}^{KBr} cm^{-1}: 1710, 1680. NMR (CF_3CO_2H) ppm: 2.52 (3H, s), 3.93 (3H, s), 4.33 (2H, s), 8.10—9.20 (5H, m).

3-Acetyl-2-hydroxypyrazolo[1,5-*a*]pyridine (XI)——To a solution of VI (1.7 g) in abs. EtOH (20 ml), was added an NaOEt–EtOH solution prepared from Na (0.25 g) and abs. EtOH (10 ml). After stirring for 1 hr at room temperature, the solvent was distilled off under reduced pressure. The residue was diluted with H_2O and neutralized with 10% HCl. The crystalline substance separated was collected by suction, and recrystallized from MeOH–AcOEt to give colorless needles, of mp 211°. Yield, 1.0 g (60%). *Anal.* Calcd. for $C_9H_8O_2N_2$ (XI): C, 61.36; H, 4.58; N, 15.90. Found: C, 61.12; H, 4.96; N, 15.64. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1638. NMR (CF_3CO_2H) ppm: 2.98 (3H, s), 7.48—8.90 (4H, m).

3-Acetyl-1-methylpyrazolo[1,5-*a*]pyridin-2-one (VIII)——1) To a suspension of VII (4.4 g) in abs. EtOH (40 ml), was added dropwise a solution of NaOEt–EtOH prepared from Na (0.7 g) and abs. EtOH (10 ml) under ice-cooling. After stirring for 30 min, the solvent was removed by vacuum distillation. The resulting residue was diluted with H_2O, neutralized with 10% HCl, and extracted with $CHCl_3$. The $CHCl_3$ soluble fraction was submitted to silica gel column chromatography using ether, acetone and then MeOH as eluants. The MeOH eluted fraction gave colorless needles (MeOH–AcOEt) of mp 228°. Yield, 1.2 g (43%). *Anal.* Calcd. for $C_{10}H_{10}O_2N_2$ (VIII): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.28; H, 5.39; N, 14.67. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660, 1640. NMR (CF_3CO_2H–$CDCl_3$) ppm: 2.68 (3H, s), 3.75 (3H, s), 7.10—8.50 (4H, m).

2) To a solution of 1-(N-methylamino) pyridinium iodide (IX, 2.9 g) in DMF (20 ml), was added K_2CO_3 (1.4 g) under ice-cooling. After stirring for 30 min, diketene (3.4 g) was added and the stirring was continued for an additional 30 min. The solvent was distilled off under reduced pressure, and the residue was neutralized with 10% HCl. The crystalline substance separated was purified by recrystallization from MeOH–AcOEt to colorless needles of mp 228°, undepressed on admixture with a sample (VIII) obtained in the above run. Yield, 0.7 g (19%).

Methylation of 3-Acetyl-2-hydroxypyrazolo[1,5-*a*]pyridine (XI) with CH_3I——To an NaOEt–EtOH solution prepared from Na (0.07 g) and abs. EtOH (30 ml), was added XI (0.53 g). The mixture was refluxed for 1 hr, and the solvent was evaporated. The resulting residue was dissolved in DMF, and CH_3I (0.4 g) was added dropwise. The reaction mixture was heated on a steam bath for 1 hr, and then condensed *in vacuo*. The residue was extracted with $CHCl_3$. The $CHCl_3$ layer was condensed to give a crystalline substance, which was purified by recrystallization from MeOH to colorless needles of mp 138° (XII). Yield, 0.2 g (35%). *Anal.* Calcd. for $C_{10}H_{10}O_2N_2$ (XII): C, 63.15; H, 5.30; N, 14.63. Found: C, 63.26; H, 5.27; N, 14.57. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. NMR ($CDCl_3$) ppm: 2.48 (3H, s), 4.10 (3H, s), 6.68—8.35 (4H, m).

The mother liquor was condensed, and purified by silica gel column chromatography using ether, acetone and MeOH as eluants. The MeOH eluted fraction gave colorless needles (MeOH–AcOEt) of mp 228°, undepressed on admixture with a sample of VIII. Yield, 0.15 g (26%).

3-Acetyl-2-hydroxypyrazolo[1,5-*a*]quinoline (XV)——A mixture of 1-aminoquinolinium iodide (2.7 g) and K_2CO_3 (1.5 g) in DMF (20 ml) was stirred for 30 min at room temperature, and diketene (1.7 g) was added under ice-cooling. After stirring for an additional 1 hr, the mixture was condensed *in vacuo*, and the residue was extracted with EtOH. The EtOH fraction was condensed, and the residue was purified by silica gel column chromatography using ether and acetone as eluants. The acetone elution afforded a crystalline substance. Recrystallization from AcOEt gave colorless needles of mp 246°. Yield, 0.7 g (31%). *Anal.* Calcd. for $C_{13}H_{10}O_2N_2$ (XV): C, 69.01; H, 4.46; N, 12.38. Found: C, 69.20; H, 4.58; N, 12.20. IR ν_{max}^{KBr} cm^{-1}: 1630. NMR (pyridine–DMSO) ppm: 2.68 (3H, s), 7.30—8.40 (6H, m), 11.90 (1H, b).

3-Acetyl-2-hydroxypyrazolo[5,1-*a*]isoquinoline (XVIII)——2-Iminoisoquinolinium ylide dimer (2.8 g), prepared from 2-aminoisoquinolinium iodide according to the literature,[9] was dissolved in benzene (30 ml), and diketene (2.5 g) was added to this solution. After refluxing for 3 hr, the reaction mixture was cooled. The crystalls precipitated were collected by suction, and recrystallized from EtOH to give pale yellow needles of mp 295°. Yield, 0.4 g (11%). *Anal.* Calcd. for $C_{13}H_{10}O_2N_2$ (XVII): C, 69.01; H, 4.46; N, 12.38. Found: C, 69.15; H, 4.58; N, 11.93. IR ν_{max}^{KBr} cm^{-1}: 1640. NMR (CF_3CO_2H) ppm: 3.00 (3H, s), 7.69—8.40 (5H, m), 9.45 (1H, m).

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9) B. Ágai and K. Lempert, *Tetrahedron*, **28**, 2069 (1972).