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Studies on Pyrimidine Derivatives. XL.[1] Ring Transformation of 4-Alkoxypyrimidine 1-Oxides by Reaction with Diketene

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Treatment of 4-alkoxy-6-methylpyrimidine 1-oxides with acetic anhydride followed by reaction with diketene gave 7-acetyl-4-alkoxy-2-methylisoxazolo[4,5-*c*]pyridines and 7-acetyl-4-alkoxy-3-methyloxazolo[4,5-*c*]pyridines, respectively. The structure elucidation of these compounds on the basis of spectral data and chemical reactions, and the reaction pathway of the ring transformation are described.

Keywords——pyrimidine *N*-oxide; diketene; ring transformation; oxazolo[4,5-*c*]pyridine; isoxazolo[4,5-*c*]pyridine

As reported previously, quinoline 1-oxide[2] and isoquinoline 2-oxide[3] reacted with diketene (4-methylenoxetan-2-one) in acetic acid to give 2-(2,6-dimethyl-4-oxo-3-pyranyl)-quinoline and 1-(2,6-dimethyl-4-oxo-3-pyranyl)isoquinoline, respectively. Since pyrimidine *N*-oxides are considered to have comparable reactivity to quinoline and isoquinoline *N*-oxides, our interest was focussed on the reaction of pyrimidine *N*-oxides with diketene.

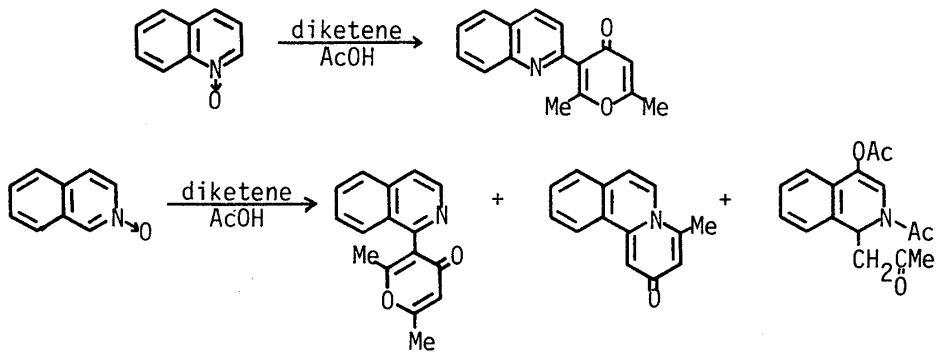


Chart 1

When 4-ethoxy-6-methylpyrimidine 1-oxide (**1b**) was treated with diketene in acetic acid, no reaction occurred, and **1b** was recovered. On the other hand, **1b** was treated with acetic anhydride in chloroform and then reacted with diketene to give two isomeric compounds, $C_{11}H_{12}N_2O_3$ (**2b** and **3b**). The structure of the major product (mp 92.5—93.5 °C, 22%) and that of the minor product (mp 91—92 °C, 8%) were determined to be 7-acetyl-4-ethoxy-2-methyloxazolo[4,5-*c*]pyridine (**2b**) and 7-acetyl-4-ethoxy-3-methylisoxazolo[4,5-*c*]pyridine (**3b**), respectively, on the basis of the following spectral data and chemical reactions.

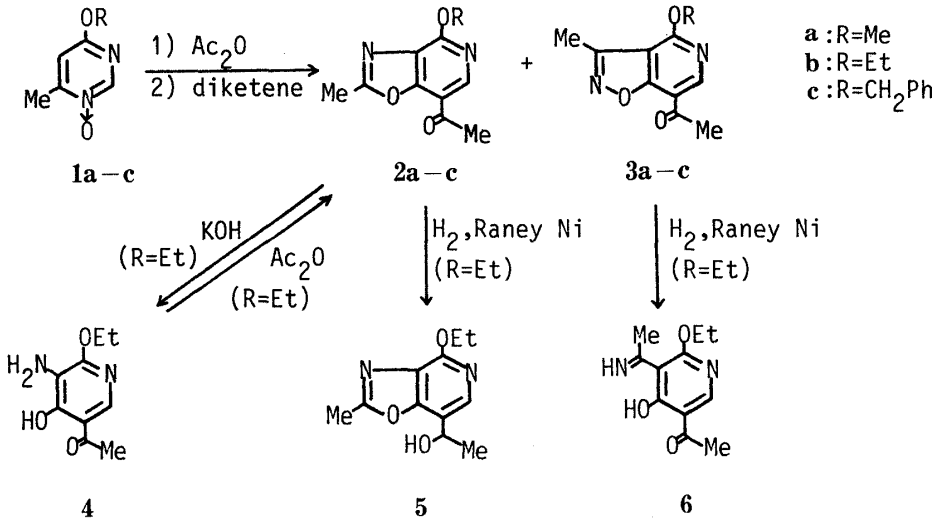
Namely, in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **2b**, signals due to an arylmethyl group and an acetyl methyl group (2.73 ppm, 6H, s) and due to an *O*-

ethyl group (1.50 ppm, 3H, t, $J=7.0$ Hz and 4.67 ppm 2H, q, $J=7.0$ Hz) were observed, together with a signal of an aromatic proton (8.67 ppm, 1H, s). The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **2b** exhibits signals due to three methyl groups as a quartet and a methylene group as a doublet together with doublet signals of aromatic carbon. The infrared (IR) spectrum of **2b** shows an absorption band corresponding to an aryl carbonyl group at 1685 cm^{-1}.

The ^{1}H-NMR spectrum of **3b** shows three singlet signals due to two methyl groups (2.67 and 2.77 ppm) and a ring proton (8.77 ppm) with signals of an *O*-ethoxyl group. The ^{13}C-NMR spectrum of **3b** is similar to that of **2b**, and the absorption band of a carbonyl group is observed at 1683 cm^{-1} in the IR spectrum of **3b**.

When **2b** was heated with potassium hydroxide in aqueous ethanol under reflux, 5-acetyl-3-amino-2-ethoxy-4-hydroxypyridine (**4**) was obtained, whereas **3b** was resistant to the above reaction conditions. Compound **4** was positive to a diazo-coupling color test and reverted to **2b** on heating with acetic anhydride.

Catalytic hydrogenation of **3b** over Raney nickel resulted in the formation of a ring-opened product, 5-acetyl-2-ethoxy-4-hydroxy-3-(1-iminoethyl)pyridine (**6**), whereas **2b** gave 4-ethoxy-7-(1-hydroxyethyl)-2-methyloxazolo[4,5-*c*]pyridine (**5**). These reactivities are consistent with the proposed structures of the two products.



1a–c 2a–c 3a–c

4 5 6

Chart 2

4-Methoxy- (**1a**) and 4-benzyloxy-6-methylpyrimidine 1-oxide (**1c**) reacted similarly with diketene to give the same type of products (**2a**, 36%; **3a**, 4%; **2c**, 20%; **3c**, 11%).

A probable pathway from **1** to **2** and **3** may be represented as follows. In connection with this pathway, Sedova *et al.*[4] reported that the bromination of 4-phenylpyrimidine 1-oxide (**7**) in acetic acid in the presence of acetic anhydride proceeds through the formation of the 1,4-diacetoxy-1,4-dihydro intermediate (**8**) to give 5-bromo-4-phenylpyrimidine 1-oxide (**9**). Furthermore, it is known that 4-alkoxypyrimidine 1-oxides, unlike **7**, have selective reactivity at the 2-position toward nucleophilic additions.[5] Therefore, the assumption of the 1,2-diacetoxy-1,2-dihydropyrimidine (**10**) as the initial intermediate is reasonable. This assumption is supported by the fact that the reaction of 4-ethoxy-2-isopropyl-6-methylpyrimidine 1-oxide with diketene under similar conditions gave no product, and the starting material was recovered. Then, diketene electrophilically attacks an enamine carbon atom of the intermediate **10** to yield the acetoacetyl intermediate (**11**). 4-Methoxy-5,6-dimethylpyrimidine 1-oxide did not undergo the ring transformation with diketene. In this case, the enamine carbon atom of the type **10** intermediate is substituted with a methyl group,

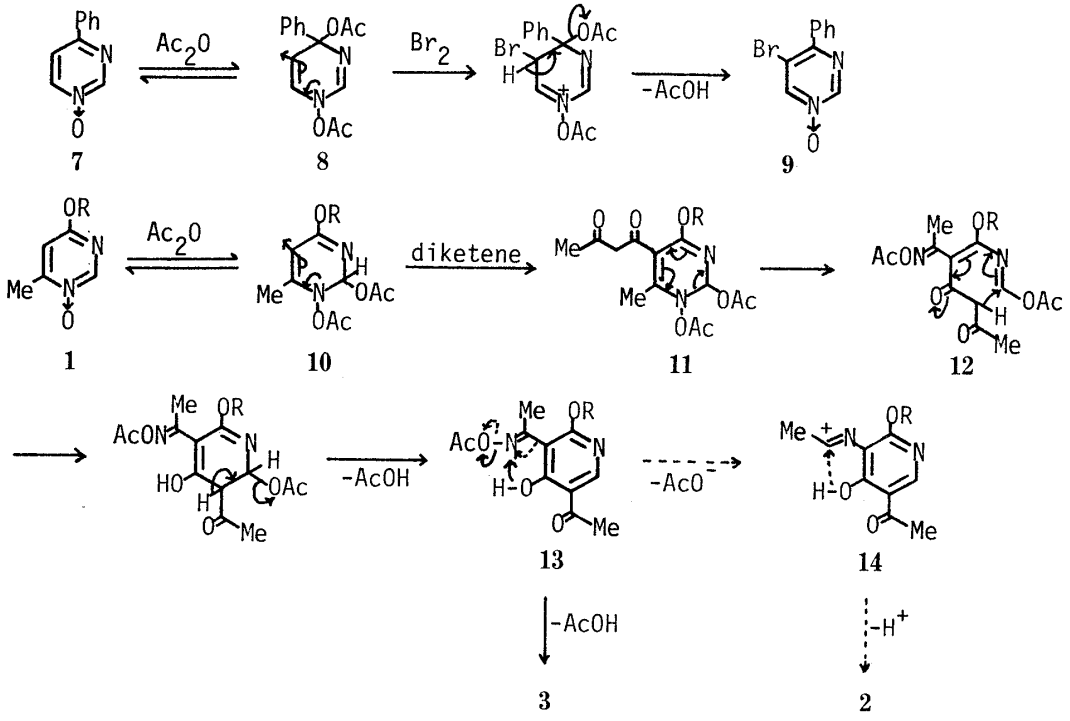


Chart 3

so that it can not react with diketene. The ring-opening and recyclization of intermediate **11** gave a pyridine intermediate (**13**) *via* **12**. The diverging point to **2** and **3** is considered to be whether Beckmann rearrangement of the intermediate **13** occurs or not. Namely, **13** cyclizes without the Beckmann rearrangement to give **3** and cyclizes accompanied with the Beckmann rearrangement to afford **2**.

Experimental

All melting points are uncorrected. IR spectra were measured with a JASCO IRA-1 spectrometer. ^{1}H-NMR spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. ^{13}C-NMR spectra were taken at 25 MHz with a JEOL JNM-FX100 spectrometer. Chemical shifts are expressed in δ (ppm) values and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, and br = broad. Mass spectra (MS) were determined with a Hitachi M-52 spectrometer.

Reaction of 4-Methoxy-6-methylpyrimidine 1-Oxide with Diketene——Acetic anhydride (5 ml) was added to a $CHCl_3$ (5 ml) solution of 4-methoxy-6-methylpyrimidine 1-oxide (**1a**) (2.80 g, 20 mmol) at 25—35 °C (inner temperature) with stirring, and then diketene (5.04 g, 60 mmol) was added at below 20 °C (inner temperature). After exothermic reaction had ceased, the mixture was stirred at room temperature for 4 h, and 30% K_2CO_3 (30 ml) was added. The mixture was stirred at room temperature overnight and extracted with $CHCl_3$. The residue obtained from the $CHCl_3$ extract, was purified by SiO_2 column chromatography using hexane–Et_3N (9 : 1, v/v) as an eluent. The first eluate gave 7-acetyl-4-methoxy-3-methylisoxazolo[4,5-*c*]pyridine (**3a**) as colorless needles, mp 145—146 °C, which were recrystallized from cyclohexane. Yield 180 mg (4%). IR ($CHCl_3$): 1687 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.65 (3H, s), 2.77 (3H, s), 4.22 (3H, s), 8.83 (1H, s). ^{13}C-NMR ($CDCl_3$): 11.272 (q), 30.478 (q), 54.776 (q), 107.379 (s), 113.602 (s), 150.120 (d), 154.639 (s), 162.567 (s), 168.438 (s), 193.153 (s). MS *m/z*: 206 (M^+), 191, 177, 150. *Anal.* Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.58. Found: C, 58.51; H, 4.98; N, 13.54.

The second eluate gave 7-acetyl-4-methoxy-2-methyloxazolo[4,5-*c*]pyridine (**2a**) as pale yellow needles, mp 136—137 °C, which were recrystallized from hexane. Yield 1.47 g (36%). IR ($CHCl_3$): 1683 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.73 (6H, s), 4.22 (3H, s), 8.67 (1H, s). ^{13}C-NMR ($CDCl_3$): 14.442 (q), 29.178 (q), 54.600 (q), 114.542 (s), 126.049 (s), 144.954 (d), 156.104 (s), 158.518 (s), 163.920 (s), 193.275 (s). MS *m/z*: 206 (M^+), 191, 177, 150. *Anal.* Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.58. Found: C, 58.04; H, 4.71; N, 13.37.

Reaction of 4-Ethoxy-6-methylpyrimidine 1-Oxide with Diketene——The residue obtained from the reaction mixture of 4-ethoxy-6-methylpyrimidine 1-oxide (**1b**) (3.08 g, 20 mmol), acetic anhydride (5 ml), and diketene (5.04 g, 60 mmol) in $CHCl_3$ (50 ml) by a procedure similar to that described above, was purified by SiO_2 column chromatography using hexane–Et_3N (9 : 1, v/v) as an eluent. The first eluate gave 7-acetyl-4-ethoxy-3-methylisoxazolo[4,5-*c*]pyridine (**3b**) as colorless needles, mp 91—92 °C, which were recrystallized from hexane. Yield

350 mg (8%). IR ($CHCl_3$): 1683 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.50 (3H, t, J=7.0), 2.67 (3H, s), 2.77 (3H, s), 4.67 (2H, q, J=7.0), 8.77 (1H, s). ^{13}C-NMR ($CDCl_3$): 11.123 (q), 14.442 (q), 30.470 (q), 63.642 (t), 107.261 (s), 113.428 (s), 150.229 (d), 154.695 (s), 162.445 (s), 168.438 (s), 193.153 (s). MS m/z: 220 (M^+), 205, 192, 177. *Anal.* Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.68; H, 5.26; N, 12.45.

The second eluate gave 7-acetyl-4-ethoxy-2-methyloxazolo[4,5-*c*]pyridine (**2b**) as colorless needles, mp 92.5—93.5 °C, which were recrystallized from hexane. Yield 970 mg (22%). IR ($CHCl_3$): 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.50 (3H, t, J=7.0), 2.73 (6H, s), 4.67 (2H, q, J=7.0), 8.67 (1H, s). ^{13}C-NMR ($CDCl_3$): 14.384 (q), 14.501 (q), 29.120 (q), 63.466 (t), 114.368 (s), 125.992 (s), 145.071 (d), 156.170 (s), 158.396 (s), 163.854 (s), 193.331 (s). MS m/z: 220 (M^+), 205, 192, 177. *Anal.* Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.15; H, 5.57; N, 12.98.

Reaction of 4-Benzyloxy-6-methylpyrimidine 1-Oxide with Diketene——The residue obtained from the reaction mixture of 4-benzyloxy-6-methylpyrimidine 1-oxide (**1c**) (2.16 g, 10 mmol), acetic anhydride (5 ml), and diketene (2.52 g, 30 mmol) in $CHCl_3$ (5 ml) by a procedure similar to that described above, was purified by SiO_2 column chromatography using hexane–Et_3N (9:1, v/v) as an eluent. The first eluate gave 7-acetyl-4-benzyloxy-3-methylisoxazolo[4,5-*c*]pyridine (**3c**) as colorless needles, mp 109—111 °C, which were recrystallized from ether. Yield 300 mg (11%). IR ($CHCl_3$): 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.65 (3H, s), 5.63 (2H, s), 7.42 (5H, s), 8.77 (1H, s). ^{13}C-NMR ($CDCl_3$): 11.330 (q), 30.529 (q), 69.043 (t), 107.496 (s), 113.720 (s), 127.989 (d), 128.341 (d), 128.632 (d), 135.738 (s), 150.120 (d), 154.639 (s), 161.975 (s), 168.551 (s), 193.097 (s). MS m/z: 282 (M^+), 267, 239, 176. *Anal.* Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.77; H, 4.89; N, 9.85.

The second eluate gave 7-acetyl-4-benzyloxy-2-methyloxazolo[4,5-*c*]pyridine (**2c**) as colorless needles, mp 127—128 °C, which were recrystallized from ether. Yield 570 mg (20%). IR ($CHCl_3$): 1682 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 2.70 (6H, s), 5.63 (2H, s), 7.2—7.7 (5H, m), 8.63 (1H, s). ^{13}C-NMR ($CDCl_3$): 14.442 (q), 29.178 (q), 68.888 (t), 114.603 (s), 126.110 (s), 128.106 (d), 128.397 (d), 136.091 (s), 144.897 (d), 156.339 (s), 157.983 (s), 163.920 (s), 193.209 (s). MS m/z: 282 (M^+), 267, 239, 176. *Anal.* Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.91; H, 4.99; N, 9.94.

Alkaline Hydrolysis of 2b——A mixture of **2b** (661 mg, 3 mmol) in EtOH (10 ml) and KOH (1.68 g, 30 mmol) in H_2O (4 ml) was refluxed for 3.5 h. After removal of the solvent *in vacuo*, the residue was diluted with H_2O and washed with ether. The aqueous solution was neutralized with 6 N HCl and extracted with $CHCl_3$. The $CHCl_3$ extract gave 5-acetyl-3-amino-2-ethoxy-4-hydroxypyridine (**4**) as yellow needles, mp 111—112 °C, which were recrystallized from MeOH. Yield 370 mg (63%). IR ($CHCl_3$): 3460, 3370, 1648 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.40 (3H, t, J=7.0), 2.58 (3H, s), 3.2—4.1 (2H, br), 4.48 (2H, q, J=7.0), 8.13 (1H, s), 12.23 (1H, s). *Anal.* Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.67; H, 6.28; N, 12.26.

Reaction of 4 with Acetic Anhydride——A mixture of **4** (588 mg, 3 mmol) and acetic anhydride (5 ml) was refluxed for 30 h. After removal of the acetic anhydride *in vacuo*, 3 N Na_2CO_3 (5 ml) was added to the residue. The mixture was stirred at room temperature for 2 h and extracted with $CHCl_3$. The residue obtained from the $CHCl_3$ extract was recrystallized from hexane to give colorless needles, mp 92—92.5 °C. This product was identical with **2b**. Yield 320 mg (49%).

Hydrogenation of 2b over Raney Nickel——A mixture of **2b** (500 mg, 2.27 mmol), Raney Ni prepared from Ni–Al alloy (0.5 g), and MeOH (10 ml) was hydrogenated under atmospheric pressure. After 6 h, absorption of H_2 (60 ml) stopped. The catalyst was filtered off, and the filtrate was evaporated. The residue was purified by Al_2O_3 column chromatography using C_6H_6 and ether as eluents. The C_6H_6 eluate gave **2b**, 40 mg (8%). The ether eluate gave 4-ethoxy-7-(1-hydroxyethyl)-2-methyloxazolo[4,5-*c*]pyridine (**5**) as colorless needles, mp 76—77 °C, which were recrystallized from ether–petr. ether. Yield 240 mg (48%). IR ($CHCl_3$): 3590, 3320 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.47 (3H, t, J=7.0), 1.67 (3H, d, J=6.0), 2.20 (1H, d, J=4.0), 2.67 (3H, s), 4.53 (2H, q, J=7.0), 4.8—5.3 (1H, m), 7.97 (1H, s). *Anal.* Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 14.28. Found: C, 59.76; H, 6.39; N, 12.95.

Hydrogenation of 3b over Raney Nickel——A mixture of **3b** (500 mg, 2.27 mmol), Raney Ni prepared from Ni–Al alloy (1.0 g), and MeOH (20 ml) was hydrogenated under atmospheric pressure. After 2 h, absorption of H_2 (60 ml) stopped. The catalyst was filtered off, and the filtrate was evaporated. The residue was extracted with $CHCl_3$, and the product obtained from the $CHCl_3$ extract was recrystallized from C_6H_6 to give 5-acetyl-2-ethoxy-4-hydroxy-3-(1-iminoethyl)pyridine as a pale yellow powder, mp 162—162.5 °C. Yield 290 mg (57.5%). IR ($CHCl_3$): 3430, 3200, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.40 (3H, t, J=7.0), 2.62 (3H, s), 2.68 (3H, s), 4.50 (2H, q, J=7.0), 8.13 (1H, s), 8.2—8.8 (1H, br), 15.0—15.8 (1H, br). *Anal.* Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 54.79; H, 6.07; N, 14.31.

References and Notes

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