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Studies on Pyrimidine Derivatives. XII.[1] Reaction of 4,6-Disubstituted Pyrimidine N-Oxides with Dimethyl Acetylenedicarboxylate

Hiroshi Yamanaka, Setsuko Niitsuma, Takao Sakamoto, and Michinao Mizugaki

Pharmaceutical Institute, Tohoku University[2]

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The 1,3-dipolar cycloaddition of 4-benzyloxy-6-methylpyrimidine 1-oxide (Ia) with dimethyl acetylenedicarboxylate (DMAD) gave dimethyl α-oxo-α'-(4-benzyloxy-6-methyl-2-pyrimidinyl)succinate (IIa), which was readily hydrolyzed to methyl 4-benzyloxy-6-methyl-2-pyrimidineacetate (IIIa). A similar reaction of 4-methoxy- (Ib) and 4-ethoxy-6-methylpyrimidine 1-oxide (Ic) gave corresponding methyl 2-pyrimidineacetates (IIIb, c).

On the other hand, 6-methyl-4-piperidinopyrimidine 1-oxide (Id) reacted with DMAD to give a betaine derivative, 1-(6-methyl-4-piperidino-1-pyrimidinio)-1,2-bis(methoxycarbonyl)ethenyl-2-oxide (IV).

Keywords——1,3-dipolar cycloaddition; dimethyl acetylenedicarboxylate; pyrimidine 1-oxides; methyl 2-pyrimidineacetates; dimethyl α-oxo-α'-(2-pyrimidinyl)succinates; pyrimidinyl betaines

As reported previously, in the presence of an appropriate acylating agent, 4,6-disubstituted pyrimidine N-oxides react with morpholine enamines[3] or cyanide[4] to give pyrimidines containing a carbon functional group at the 2-position. These results indicate that pyrimidine N-oxides bear a strong resemblance to quinoline 1-oxide. As part of an extensive investigation by Hamana and his co-workers, quinoline 1-oxide has been reported to give methyl α-formyl-2-quinolineacetate through 1,3-dipolar cycloaddition with methyl propiolate.[5] Thus, we investigated the cycloaddition of pyrimidine N-oxides as a carbon–carbon bond forming reaction.

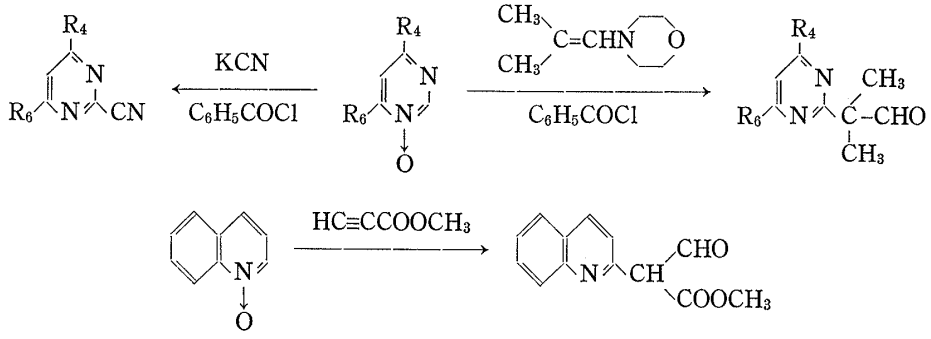

Chart 1

First, the reaction of dimethyl acetylenedicarboxylate (DMAD) with 4-benzyloxy-6-methylpyrimidine 1-oxide (Ia),[4] which is one of the most accessible pyrimidine N-oxides,

1) Part XI: H. Yamanaka, M. Komatsu, K. Tanji, S. Ogawa, S. Konno, and M. Mizugaki, *Yakugaku Zasshi*, **99**, 342 (1979).
2) Location: *Aobayama Sendai 980, Japan.*
3) H. Yamanaka, S. Niitsuma, Y. Bannai, and T. Sakamoto, *Chem. Pharm. Bull.* (Tokyo), **23**, 2591 (1975).
4) H. Yamanaka, *Chem. Pharm. Bull.* (Tokyo), **6**, 633 (1958).
5) M. Hamana, K. Funakoshi, H. Shigyo, and Y. Kuchino, *Chem. Pharm. Bull.* (Tokyo), **23**, 346 (1975).

was examined. Thus, a solution of Ia with DMAD and a catalytic amount of hydroquinone in dioxane was allowed to stand overnight to form dimethyl α-oxo-α′-(4-benzyloxy-6-methyl-2-pyrimidinyl)succinate (IIa) as pale yellow needles, mp 144° (dec.). The empirical formula of IIa, $C_{18}H_{18}N_2O_6$, showed this product to be a 1:1 adduct of Ia and DMAD. In the nuclear magnetic resonance (NMR) spectrum of IIa, signals were seen due to three methyl groups (δ 2.39, 3.78, and 3.84, 3H s each), a methylene group (δ 5.47, 2H, s), an aromatic proton on the 5-position (δ 6.20, 1H, s), and five aromatic protons on a phenyl group (δ 7.20—7.60, 5H, m), together with a broad signal (δ 15.50—16.10 1H). In the infrared (IR) spectrum (KBr) of IIa, two carbonyl bands assignable to a carbon–carbon double bond appeared at 1750, 1680, and 1620 cm^{-1}, respectively. Based on these spectral data, the predominant tautomer of this compound in chloroform solution is presumed to be IIa′ or IIa″, although there is no clear evidence for an intramolecular hydrogen bond in the IR spectrum.

On attempted purification of IIa by alumina column chromatography, the side chain was hydrolyzed and methyl 4-benzyloxy-6-methyl-2-pyrimidineacetate (IIIa) was obtained. Under identical conditions, the reaction of 4-methoxy- (Ib) and 4-ethoxy-6-methylpyrimidine 1-oxide (Ic) with DMAD resulted in the isolation of methyl 4-methoxy- (IIIb) and 4-ethoxy-6-methyl-2-pyrimidineacetate (IIIc) together with dimethyl α-oxo-α′-(4-ethoxy-6-methyl-2-pyrimidinyl)succinate (IIc). In the case of Ib with DMAD, however, pure product corresponding to IIa, c, could not be isolated by recrystallization so that the crude product was chromatographed on an alumina column to give IIIb. These results, together with a possible reaction pathway, are illustrated in Chart 2.

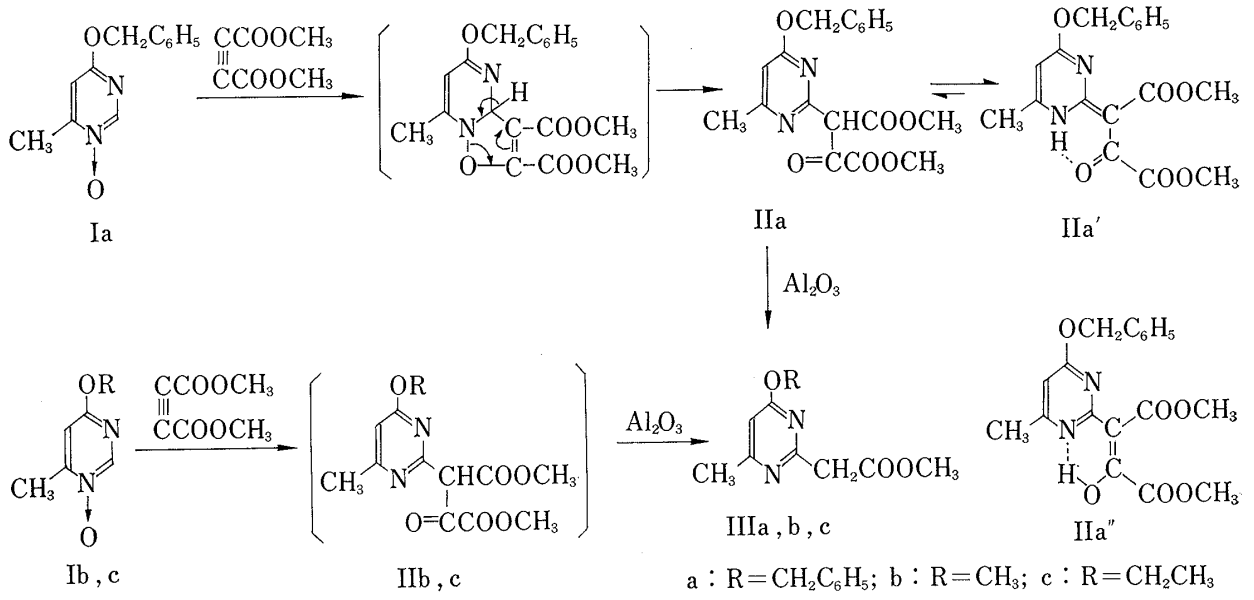

Chart 2

While the reactions of 6-methyl-4-phenylpyrimidine 1-oxide or 5-bromo-4-ethoxy-6-methylpyrimidine 1-oxide with DMAD, of Ic or 4-piperidino-6-methylpyrimidine 1-oxide (Id) with methyl tetrolate, of Ic with phenylacetylene, of Ic with ketene diphenylacetal, and of Ic with acrolein failed to give any significant product, the cycloaddition of DMAD with 4-piperidino-6-methylpyrimidine 1-oxide (Id) gave rise to another type of product, for which a betaine structure is proposed. All the spectral data are consistent with the proposed structure (IV).

6) S. Takahashi and H. Kano, *J. Org. Chem.*, **30**, 1118 (1965).

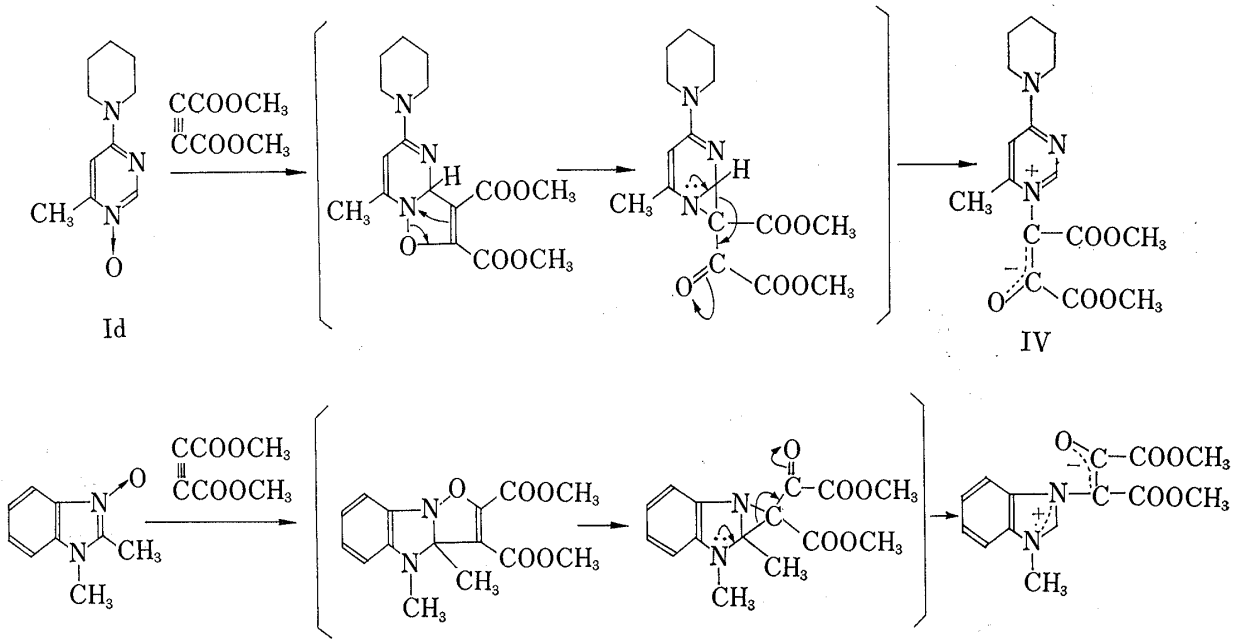

Chart 3

The proposed reaction mechanism for the conversion of Id to IV (Chart 3) is modeled on that of Kano *et al.*[6] for the reaction of benzimidazole N-oxides with DMAD, based on an aziridine intermediate.

The synthesis of pyrimidine derivatives containing a 2-acylmethyl group by the Pinner type reaction is restricted due to the reactivity of an active methylene group located in the starting amidines. In order to overcome this limitation, several devices have been reported.[7–9] Our investigation has resulted in a synthetic route to 2-pyrimidineacetic acid derivatives.

Experimental[10]

Reaction of Ia, b, c with Dimethyl Acetylenedicarboxylate——General Procedure: Dimethyl acetylenedicarboxylate was added dropwise with stirring to an ice-cooled solution of I and hydroquinone in dioxane, maintaining the temperature below 33°. After leaving the mixture to stand at room temperature for one day, removal of the dioxane gave a crystalline solid, which was purified by method 1 or method 2. Method 1: the crude product was recrystallized to give II. Method 2: the crude product was passed through a column of Al_2O_3 using ether as an eluant, followed by distillation under reduced pressure to yield III.

Reaction of Ia with Dimethyl Acetylenedicarboxylate——Compound IIa was obtained from Ia (0.50 g, 0.0023 mol), dimethyl acetylenedicarboxylate (0.57 g, 0.004 mol), hydroquinone (25 mg), and dioxane (6 ml) according to the general procedure, followed by purification according to method 1. Pale yellow needles (AcOEt) (IIa), mp 144° (dec.). Yield 341 mg (41%). *Anal.* Calcd. for $C_{18}H_{18}N_2O_6$: C, 60.33; H, 5.06; N, 7.32. Found: C, 60.23; H, 5.17; N, 7.46. IR ν_{max}^{KBr} cm^{-1}: 3600—3200, 3100—2600, 1750, 1680, 1620. NMR ($CDCl_3$) δ: 2.39 (3H, s), 3.78 (3H, s), 3.84 (3H, s), 5.47 (2H, s), 6.20 (1H, s), 7.20—7.60 (5H, m), 15.50—16.10 (1H, broad). The compound IIa (400 mg, 0.0011 mol) was converted to IIIa by passage through a column of Al_2O_3 using ether an eluant. IIIa: Colorless liquid, bp 150—160° (2 mmHg). Yield 201 mg (66% from IIa). *Anal.* Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.40; H, 6.08; N, 10.60. IR

7) S. Niitsuma, T. Sakamoto, and H. Yamanaka, *Heterocycles*, **10**, 171 (1978).
8) H. Yamanaka, T. Ono, and T. Sakamoto, Abstracts of 97th Annual Meeting of Pharmaceutical Society of Japan, part II, p. 28 (1977).
9) D.J. Brown and P. Waring, *Aust. J. Chem.*, **27**, 2551 (1974).
10) All melting points and boiling points are uncorrected. IR spectra were measured with a JASCO IRA-1 spectrometer. NMR spectra were taken at 60 MHz with a Hitachi-Perkin-Elmer R-20 spectrometer. Chemical shifts are expressed as δ (ppm) using tetramethylsilane (TMS) as an internal standard. The following abbreviations are used: s=singlet, t=triplet, q=quartet, m=multiplet.

$\nu_{max}^{CHCl_3}$ cm^{-1}: 1752. NMR ($CDCl_3$) δ: 2.41 (3H, s), 3.70 (3H, s), 3.88 (2H, s), 5.38 (2H, s), 6.49 (1H, s), 7.37 (5H, s).

Reaction of Ib with Dimethyl Acetylenedicarboxylate——Compound IIIb was obtained from Ib (0.98 g, 0.007 mol), dimethyl acetylenedicarboxylate (1.42 g, 0.01 mol), hydroquinone (50 mg), and dioxane (15 ml) according to the general procedure, followed by purification according to method 2. Colorless liquid (IIIb), bp 110—111° (4 mmHg). Yield 636 mg (46%). *Anal.* Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.47; H, 6.16; N, 14.39. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1753. NMR (C_6D_6) δ: 2.04 (3H, s), 3.34 (3H, s), 3.60 (3H, s), 3.87 (2H, s), 6.09 (1H, s).

Reaction of Ic with Dimethyl Acetylenedicarboxylate——1) Compound IIc was obtained from Ic (1.08 g, 0.007 mol), dimethyl acetylenedicarboxylate (1.42 g, 0.01 mol), hydroquinone (50 mg), and dioxane (11 ml) according to the general procedure, followed by purification according to method 1. Colorless needles (iso-PrOH) (IIc), mp 85—91° (dec.). Yield 150 mg (7%). *Anal.* Calcd. for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46. Found: C, 52.79; H, 5.69; N, 9.57. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2900—2500, 1745. NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7.5 Hz), 2.41 (3H, s), 3.76 (3H, s), 3.85 (3H, s), 4.49 (2H, q, J=7.5 Hz), 6.18 (1H, s), 15.50—16.30 (1H, broad). The mother liquor of recrystallization was purified by method 2 to give a pale yellow liquid (IIIc), bp 98—99° (2 mmHg). Yield 465 mg (32%). *Anal.* Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.38; H, 6.74; N, 13.36. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1742. NMR ($CDCl_3$) δ: 1.35 (3H, t, J=6.8 Hz), 2.40 (3H, s), 3.71 (3H, s), 3.84 (2H, s), 4.37 (2H, q, J=6.8 Hz), 6.40 (1H, s).

2) Compound IIIc was obtained from Ic (1.08 g, 0.007 mol), dimethyl acetylenedicarboxylate (1.42 g, 0.01 mol), hydroquinone (50 mg), and dioxane (11 ml) according to the general procedure, followed by purification method 2. Colorless liquid (IIIc) bp 92—95° (3 mmHg). Yield 0.62 g (42%).

3) Dimethyl acetylenedicarboxylate (1.42 g, 0.01 mol) was added dropwise with stirring to an ice-cooled solution of Ic (1.08 g, 0.007 mol) in dioxane (15 ml), maintaining the temperature below 40°. Acetic anhydride (1.02 g, 0.01 mol) was then added and the mixture was stirred at room temperature for 5 hr. After removal of the dioxane under reduced pressure, the residue was made alkaline with 3 N aq. Na_2CO_3 and the resulting oil was extracted with $CHCl_3$. Evaporation of the $CHCl_3$ gave a dark brown liquid which was purified by column chromatography (Al_2O_3, ether), followed by distillation under reduced pressure to give a pale yellow liquid (IIIc), bp *ca.* 95° (3 mmHg). Yield 200 mg (14%).

Reaction of Id with Dimethyl Acetylenedicarboxylate——Dimethyl acetylenedicarboxylate (0.71 g, 0.005 mol) was added with stirring and cooling (below 23°) to a solution of Id (540 mg, 0.0028 mol) and hydroquinone (20 mg) in $CHCl_3$ (5 ml), and the mixture was stirred at room temperature for 17 hr. After removal of the $CHCl_3$, the residue was purified by column chromatography (Al_2O_3, $CHCl_3$) to give an orange-colored solid (IV), which was recrystallized from C_6H_6–petr. benzine (70—75°) to give yellow prisms, mp 160° (dec.). Yield 130 mg (14%). *Anal.* Calcd. for $C_{16}H_{21}N_3O_5$: C, 57.30; H, 6.31; N, 12.53. Found: C, 57.28; H, 6.11; N, 12.54. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2870, 1740, 1670, 1640, 1558. NMR ($CDCl_3$) δ: 1.70 (6H, broad s), 2.49 (3H, s), 3.30—3.80 (4H, m), 3.63 (3H, s), 3.84 (3H, s), 6.78 (1H, s), 8.16 (1H, s).

5-Bromo-4-ethoxy-6-methylpyrimidine——An ethanolic solution of 5-bromo-4-chloro-6-methylpyrimidine (5.2 g, 0.025 mol in 20 ml of EtOH) was added to an ice-cooled ethanolic solution of sodium ethoxide (metallic Na 1.38 g, 0.06 g atom and abs. EtOH 30 ml), and the resulting mixture was allowed to stand at room temperature for 6.5 hr with stirring. The mixture was treated as usual to give a colorless liquid, bp 112—113° (15 mmHg), 2.96 g (55%). *Anal.* Calcd. for $C_7H_9BrN_2O$: C, 38.73; H, 4.18; Br, 36.81; N, 12.91. Found: C, 39.03; H, 4.23; Br, 36.44; N, 13.00. NMR ($CDCl_3$) δ: 1.43 (3H, t, J=6.8 Hz), 2.60 (3H, s), 4.48 (2H, q, J=6.8 Hz), 8.52 (1H, s).

5-Bromo-4-ethoxy-6-methylpyrimidine 1-Oxide——5-Bromo-4-ethoxy-6-methylpyrimidine (1.09 g, 0.005 mol) in acetic acid (3 ml) and trifluoroacetic acid (2 ml) was heated at 75—80° for 6 hr with occasional addition of 30% H_2O_2 (total 2.12 g, 0.02 mol). The reaction mixture was treated according to the usual method of direct N-oxidation of N-heteroaromatics. From the $CHCl_3$ extract, the crude N-oxide was obtained as a yellow liquid which was passed through an alumina column to give colorless needles (petr. ether), mp 96—97°, 301 mg (26%). *Anal.* Calcd. for $C_7H_9BrN_2O_2$: C, 36.07; H, 3.90; Br, 34.29; N, 11.98. Found: C, 36.31; H, 3.77; Br, 33.95; N, 12.15. IR ν_{max}^{KBr} cm^{-1}: 1260. NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7.2 Hz), 2.70 (3H, s), 4.47 (2H, q, J=7.2 Hz), 8.65 (1H, s).

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