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Studies on Ketene and Its Derivatives. XLVII.[1] Reaction of 2-Aminopyridine with Diketene

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Reaction of diketene with 2-aminopyridine (Ia), 2-amino-4-methylpyridine (Ib), and 2-amino-3-methylpyridine (Ic) gave 2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one (IIIa), 2,8-dimethyl-4H-pyrido[1,2-*a*]pyrimidin-4-one (IIIb), and 2,9-dimethyl-4H-pyrido[1,2-*a*]-pyrimidin-4-one (IIIc), respectively. Isomeric 2-one derivatives, such as 4-methyl-2H-pyrido[1,2-*a*]pyrimidin-2-one (IVa) and 4,8-dimethyl-2H-pyrido[1,2-*a*]pyrimidin-2-one (IVb), were prepared by reaction of α-bromocrotonic acid with Ia and Ib, respectively. The differences were sufficiently great to permit mass, nuclear magnetic resonance, infrared and ultraviolet spectral data in a distinction of the structures between the 4-one (III) and 2-one derivatives (IV).

Ealier experiments[3–5] had indicated that 2-aminopyridine (Ia) reacted with ethyl acetoacetate to give 4-methyl-2H-pyrido[1,2-*a*]pyrimidin-2-one (IVa). At the same time, Khitrik[4] reported that 2-acetoacetamidopyridine (IIa), which may be obtained by warming Ia with ethyl acetoacetate,[6,7] cyclized to give the same compound when treated with cold sulphuric acid. He also considered this to have structure IVa. On the other hand, Antaki and Petrow[8] discovered that when ethyl β-aminocrotonate was heated with 2-bromopyridine, a cyclized compound was obtained in unspecified yield which was identical with that synthesized by previous workers,[3–5] however, Antaki formulated their product as 2-methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one (IIIa).

From the experimental evidence reported, no difinite conclusion could be adduced as to the structure of the product since it was not certain in which of these reactions rearrangements occurred. In 1952, Adams and Pachter[9] studied ultraviolet (UV) absorption spectra and structures of pyrido[1,2-*a*]pyrimidone derivatives (III and IV), and they concluded that the above compound must have the structure IIIa because of the similarity of its spectrum not to those of pyrido[1,2-*a*]pyrimidin-2-ones (IV) but to those of 4-ones (III).

In the preceeding paper of this series,[10] we have reported the reaction of Ia with diketene to give 2-acetoacetamidopyridine (IIa) and the same cyclized product reported by previous authors, to which we formulated the structure as IIIa on the basis of the conclusion reported by Adams and Pachter.[9] Nevertheless, Stöckelmann, *et al.*[11] reported recently that diketene reacted with 2-amino-4-methylpyridine (Ib) and 2-amino-3-methylpyridine (Ic) to give 4,-8-dimethyl-2H-pyrido[1,2-*a*]pyrimidin-2-one (IVb) and 4,9-dimethyl-2H-pyrido(1,2-*a*)pyrimi-

1) Part XLVI: T. Kato, H. Yamanaka, N. Katagiri and S. Masuda, *Chem. Pharm. Bull.* (Tokyo), **20**, 133 (1972).
2) Location: *Aobayama, Sendai.*
3) G.B. Crippa and E. Scevola, *Gazz. Chim. Ital.*, **67**, 327 (1937).
4) S.N. Khitrik, *J. Gen. Chem.* (*USSR*), **9**, 1109 (1939).
5) C.R. Hauser and M.J. Weiss, *J. Org. Chem.*, **14**, 453 (1949).
6) F.C. Palazzo and A. Tamburini, *Alli acad. Lincei*, **20**, 37 (1911); *Chem. Abstr.*, **5**, 1586 (1911).
7) C.F.H. Allen, J. Van Allan and C.V. Wilson, *J. Am. Chem. Soc.*, **66**, 1805 (1944).
8) H. Antaki and V. Petrow, *J. Chem. Soc.*, **1951**, 551.
9) R. Adams and I.J. Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952).
10) T. Kato, H. Yamanaka, T. Niitsuma, K. Wagatsuma and M. Oizumi, *Chem. Pharm. Bull.* (Tokyo), **12**, 910 (1964).
11) G. Stöckelmann, H. Specker and W. Riepe, *Chem. Ber.*, **102**, 455 (1969).

din-2-one (IVc), respectively. Structural assignment was made on the basis of mass spectral data; that is, the ion at *m/e* 119, which can be observed in 5% intensity of molecular peak, should have the formula of C_8H_9N formed by elimination of CO and HCN from M^+ ion. Because the elimination of CH_3CN from M^+-CO ion, which may support the structure IIIb, could not be observed, these products must have the 2-one structures such as IVb and IVc.

Therefore, we reinvestigated the structures of pyrido[1,2-*a*]-pyrimidone derivatives obtainable from diketene and 2-aminopyridines, and we have found that spectral data are consistent with the 4-one structure (III), but not with the 2-one structure (IV) which was proposed by Stöckelmann, *et al.*[11]

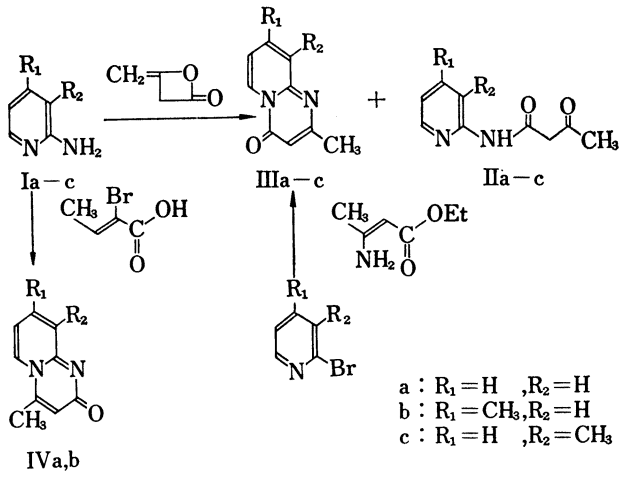


Chart 1

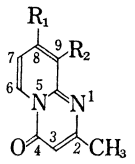
When 2-aminopyridine (Ia) was heated with diketene in organic solvent such as benzene or chloroform, colorless needles of mp 120—121° (IIIa) and colorless prisms of mp 109—110° (IIa) were obtained.[10] When this reaction was carried out in water, IIIa was obtained in 11% yield with the recovery (59%) of the starting material (Ia). Reaction of 2-amino-4-methylpyridine (Ib) with diketene in benzene afforded colorless leaves of mp 122—123° (IIb) in 17% yield and colorless needles of mp 135—137° (IIIb) in 50% yield. Similar treatment of Ib in water gave IIIb in 12% yield, but none of other products corresponding to the pyridopyrimidone derivative were detected.[12] Though melting point and yield are different from those reported by Stöckelmann, *et al*,[11] nuclear magnetic resonance (NMR) and infrared (IR) spectral data of IIIb are identical with those reported in the litrature. Similarly, reaction of 2-amino-3-methylpyridine (Ic) with diketene in both benzene and water gave the same pyridopyrimidone derivative of mp 129—131° (IIIc), but the product of mp 73° reported in the litrature[11] could not be detected.

In order to compare the spectral data, attempts to prepare authentic samples of 4-one (III) and 2-one (IV) derivatives were made. Thus, employing the procedure given for the 4-one derivative (III) reported by Antaki and Petrow,[8] 2-bromopyridine and 2-bromo-4-methylpyridine were treated with ethyl β-aminocrotonate giving IIIa and IIIb, respectively. Modifying the method given for the 2-one derivative (IV) reported by Adams and Pachter,[9] 2-aminopyridine (Ia) and 2-amino-4-methylpyridine (Ib) were allowed to react with α-bromocrotonic acid to give IVa and IVb, respectively.

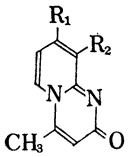
As shown in Table I, it may be possible to establish a distinction between III and IV. The UV spectral patterns of group III are closely resemble with one another, and exhibit marked differences from those of group IV. The IR spectra show the carbonyl stretching of III over 1675 cm^{-1} and those of IV below 1657 cm^{-1}. In the NMR spectra of either III and IV, C-3 proton shows almost the same chemical shift at 6.24—6.45 ppm, however, C-6 proton of III shifts at lower field (*ca.* 9 ppm) than that of IV (*ca.* 8 ppm). The lower shift of C-6 proton of III is apparently due to the anisotropy of the carbonyl oxygen at 4-position. Acturely, C-6 proton of 1-ethoxycarbamoyl-4H-quinolizin-4-one (V)[13] is appeared at

12) Stöckelmann, *et al.* obtained VIb (mp 120°) in 95% yield in this reaction.
13) T. Kato and T. Chiba, *Yakugaku Zasshi*, **89**, 1464 (1969).

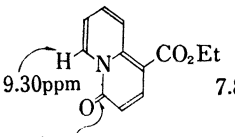
TABLE I



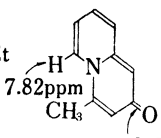
IIIa–c



IVa,b



V



VI 1645cm⁻¹

No.	R_1	R_2	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	NMR ($CDCl_3$, ppm) C_6-H	NMR ($CDCl_3$, ppm) C_3-H	UV λ_{max}^{EtOH} mμ (log ε)
IIIa	H	H	1675	9.05	6.42	230 (4.0) 338 (3.9)
IIIb	CH_3	H	1680	8.92	6.45	227 (4.0) 339 (4.1)
IIIc	H	CH_3	1675	8.92	6.35	227 (3.9) 338 (4.0)
IVa	H	H	1657	7.95	6.24	228 (4.4) 278 (3.8) 326 (3.5)
IVb	CH_3	H	1650	7.88	6.24	228 (4.4) 278 (3.9) 322 (3.4)

9.3 ppm, and that of 4-methyl-2H-quinolizin-2-one (VI) at 7.82 ppm.[14] Also, IR spectrum of the former (V) shows the carbonyl stretching at 1660 cm^{-1}, and that of the latter (VI) at 1645 cm^{-1}.

Mass spectra of IIIa and IVa are shown in Fig. 1 and 2. The striking difference between the two is the presence of ion at *m/e* 120 ($C_6H_4ON_2$) and *m/e* 92 ($C_5H_4N_2$) which can be observed only in the spectrum of IVa in 81% and 68% intensity, respectively. The formation of these ions can be explained by the retro-Diels Alder reaction; that is, elimination of $CH{\equiv}C\text{-}CH_3$ (40 mass units) from M^+ ion (*m/e* 160) affords an ion at *m/e* 120, which transforms into *m/e* 92 ion by loss of CO. Because the retro-Diels Alder reaction seems to occur difficultly in IIIa structure, they are important fragment ions in distinguishing between these two structures.

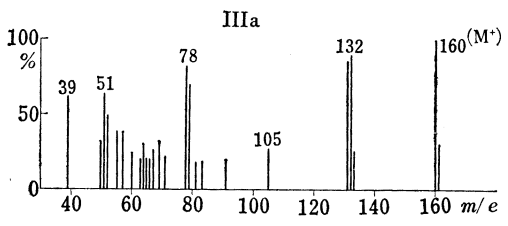


Fig. 1

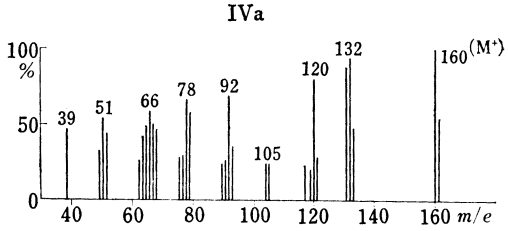


Fig. 2

A likely fragmentation pathway is shown in Chart 2. The ion at *m/e* 105 is observed in either two spectra. High resolution mass spectrum shows that *m/e* 105 ion appeared in the spectrum of IIIa has only one formula of $C_6H_5N_2$ ($M^+-C_3H_3O$), but that of IVa has the formula of C_7H_7N(M^+—CO-HCN)besides $C_6H_5N_2$. This ion is corresponding to the ion

14) T. Kato and T. Atsumi, *Yakugaku Zasshi*, **87**, 961 (1967).

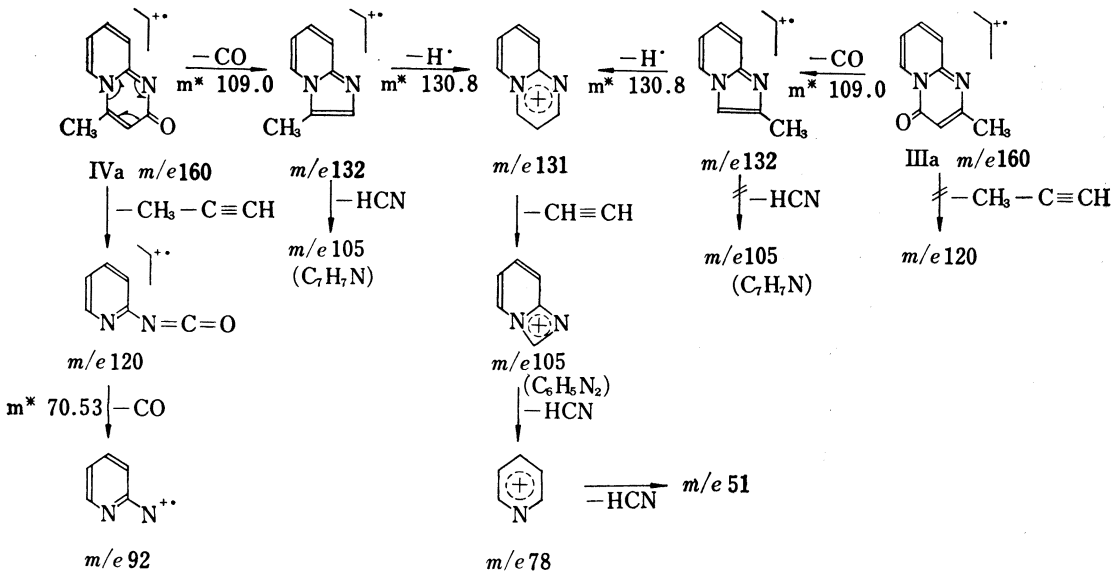


Chart 2

at *m/e* 119 of the picoline derivatives, to which Stöckelmann, *et al.*[11] gave the formula of C_8H_9N (M^+-CO-HCN) and they thought that this could be observed only in the spectrum of 2-one derivatives (IV). However, as shown in Table II, *m/e* 119 ion can be observed in both spectra of IIIb and IVb, and *m/e* 119 ion of IVb represents two formulae. Because the intensity of *m/e* 119 ion is not so strong, this ion seems to be unsuitable to distinguish IIIb from IVb. In order to make distinction between IIIb and IVb, ions at *m/e* 134 and *m/e* 106 are important fragments, which can be observed merely in IVb by the retro-Diels Alder reaction. In the spectrum listed in the litrature,[11] none of these two peaks can be observed.

It is reasonably concluded, therefore, that the product obtained by the reaction of 2-aminopyridine (I) and diketene is not the 2-one derivative (IV) but the 4-one derivative (III).

TABLE II

Compound No.	Mass *m/e*								
	M^+	M^+-CO	M^+-CHO	$M^+-C_3H_4$	$M^+-C_2H_3O$	$M^+-C_3H_3O$ M^+-C_2HON	$M^+-C_4H_4O$	$M^+-C_3H_3ON$	$M^+-C_4H_3ON$
IIIa	$C_9H_8ON_2$[a] 160(100)[b]	$C_8H_8N_2$ 132(95.6)	$C_8H_7N_2$ 131(86.7)	—	—	$C_6H_5N_2$ 105(24.4)	—	C_6H_5N 91(19.0)	C_5H_5N 79(69.0)
IIIb	$C_{10}H_{10}ON_2$ 174(100)	$C_9H_{10}N_2$ 146(86.2)	$C_9H_9N_2$ 145(67.1)	—	$C_8H_7N_2$ 131(10.0)	$C_7H_7N_2$ 119(8.2)	—	C_7H_7N 105(5.9)	C_6H_7N 93(16.0)
IIIc	$C_{10}H_{10}ON_2$ 174(100)	$C_9H_{10}N_2$ 146(98.3)	$C_9H_9N_2$ 145(69.1)	—	$C_8H_7N_2$ 131(8.0)	$C_7H_7N_2$ 119(10.3)	—	C_7H_7N 105(9.3)	C_6H_7N 93(20.0)
IVa	$C_9H_8ON_2$ 160(100)	$C_8H_8N_2$ 146(93.3)	$C_8H_7N_2$ 131(88.6)	$C_6H_4ON_2$ 120(81.0)	—	$C_6H_5N_2$ C_7H_7N 105(23.3)	$C_5H_4N_2$ 92(67.6)	C_6H_5N 91(24.8)	C_5H_5N 79(57.1)
IVb	$C_{10}H_{10}ON_2$ 174(100)	$C_9H_{10}N_2$ 146(86.3)	$C_9H_9N_2$ 145(84.0)	$C_7H_6ON_2$ 134(51.0)	$C_8H_7N_2$ 131 (24.2)	$C_7H_7N_2$ C_8H_9N 119 (8.5)	$C_6H_6N_2$ 106 (10.2)	C_7H_7N 105 (10.2)	C_6H_7N 93 (13.1)

a) component *b*) mass unit (intensity)
The component was determined by JMS-01SG double focussing mass spectrometer (Chamber. Temp. 250°, Ionizing Energy 75eV)

Experimental

2-Methyl-4H-pyrido[1,2-*a*]pyrimidin-4-one (IIIa)——1) According to the procedure reported in the previous paper,[10] 2-aminopyridine (Ia, 1.6 g) was treated with diketene (2 g) in benzene (10 ml) to give 1.5 g (50 %) of IIa as colorless prisms, mp 109—110° (lit. mp 111°),[3] and 0.7 g (26 %) of IIIa as colorless needles, mp 120—121° (lit. mp 121°).[10]

2) This procedure was carried out employing the method reported by Stöckelmann, *et al.*[11] To a solution of 2-aminopyridine (Ia, 2.4 g) in H_2O (25 ml) was added diketene (2.1 g) dropwise at room temperature with stirring at such rate that the temperature did not rise above 40°. Stirring was continued untill stimulative odor of diketene died away. The solvent was removed by vacuum distillation to give a crystalline residue, which was purified by alumina column chromatography. From the ether eluent 0.5 g (11 %) of IIIa, mp 120—121°, was obtained. From the $CHCl_3$ eluent 1.4 g (59 %) of 2-aminopyridine (Ia) was recovered.

3) This procedure was carried out employing the manner reported by Antaki and Petrow.[8] A mixture of 2-bromopyridine (3.2 g), ethyl β-aminocrotonate (2.8 g), K_2CO_3 (3 g), and copper bronz (0.1 g) was heated at 180—200° for 2 hr. After being cooled, the mixture was extracted with benzene. The benzene fraction was condensed to give a crystalline solid, which was recrystallized from ether to give colorless needles (IIIa), mp 120—121°. Yield, 1.4 g (48 %).

4-Methyl-2H-pyrido[1,2-*a*]pyrimidin-2-one (IVa)——This was prepared modifying the procedure given for 2H-pyrido (1,2-a)pyrimidin-2-one reported by Adams and Pachter.[9] A mixture of 2-aminopyridine (Ia, 4.7 g), α-bromocrotonic acid (8.2 g), and *tert*-butylcatechol (0.3 g) was heated at 140—160° for 6 hr. The mixture was extracted with MeOH, and the MeOH layer was condensed and was allowed to stand in a refrigerator overnight. Crystalline precipitated was collected by suction, and dissolved in H_2O. After neutralizing with 10% KOH, the solution was condensed in vacuo to dryness. The residue was purified by recrystallization from benzene–$CHCl_3$ to colorless needles (IVa), mp 208—211° (decomp.). Yield, 0.4 g (5%). *Anal.* Calcd. for $C_9H_8ON_2$ (IVa): C, 67.48; H, 5.03; N, 17.49. Found: C, 67.30; H, 5.23; N, 17.47.

2,8-Dimethyl-2H-pyrido[1,2-*a*]pyrimidin-4-one (IIIb)——1) Employing the similar fashion as described in the first run of IIIa, a solution of 2-amino-4-methylpyridine (Ib, 2.7 g) and diketene (3.1 g) in benzene (50ml) was refluxed for 1 hr. The solution was condensed *in vacuo*, and cooled. The crystals precipitated were collected. Recrystallization from ether gave colorless leaves (IIb), mp 122—123°. Yield, 0.8 g (17%). *Anal.* Calcd. for $C_{10}H_{12}O_2N_2$ (IIb): C, 61.93; H, 6.28; N, 14.74. Found: C, 62.48; H, 6.29; N, 14.58.

The mother liquor was condensed, and the residue was dissolved in ether. The ether solution was passed into an alumina column. The ether eluent was condensed, and crystals separated was collected and recrystallized from ether to give colorless needles (IIIb), mp 135—137°. Yield, 2.1 g (50 %). *Anal.* Calcd. for $C_{10}H_{10}ON_2$ (IIIb): C, 68.95; H, 5.79; N, 16.08. Found: C, 69.22; H, 5.91; N, 15.97.

2) According to the procedure reported by Stöckelmann, *et al.*,[11] 2-amino-4-methylpyridine (Ib, 2.7 g) was allowed to react with diketene (2.1 g) in H_2O (25 ml). Similar treatment described in the second run of IIIa afforded colorless needles of mp 135—137°, undepressed on admixture with a sample of IIIb obtained in the above run. Yield, 0.5 g (12 %).

3) Employing the similar procedure described in the third run of IIIa, reaction of 2-bromo-4-methylpyridine (3.44 g) with ethyl β-aminocrotonate (2.78 g) afforded 2.7 g (82 %) of IIIa as colorless needles, mp 135—136°.

4,8-Dimethyl-2H-pyrido[1,2-*a*]pyrimidin-2-one (IVb)——According to the procedure given for IVa, reaction of 2-amino-4-methylpyridine (Ib, 5.4 g) with α-bromocrotonic acid (8.2 g) in xylene (100 ml) in the presence of *tert*-butylcatechol (0.3 g) afforded colorless needles of mp 223—225° (decomp.). Yield, 0.9 g (10 %). *Anal.* Calcd. for $C_{10}H_{10}ON_2$ (IVb): C, 68.95; H, 5.79; N, 16.08. Found: C, 68.79; H, 5.98; N, 15.92.

2,9-Dimethyl-4H-pyrido[1,2-*a*]pyrimidin-4-one (IIIc)——1) According to the procedure descrived in the first run of IIIa, reaction of 2-amino-3-methylpyridine (Ic, 2.7 g) with diketene (3.1 g) in benzene (50 ml) afforded colorless needles (ether) of mp 129—131°. Yield, 1.3 g (29 %). *Anal.* Calcd. for $C_{10}H_{10}ON_2$ (IIIc): C, 68.95; H, 5.79; N, 16.08. Found: C, 68.82; H, 5.82; N, 15.90.

2) Employing the similar fashion described in the second run of IIIa, reaction of 2-amino-3-methylpyridine (Ic, 5.4 g) with diketene (4.2 g) in H_2O (50 ml) afforded 1.2 g (14 %) of IIIc with the recovery of the starting Ic (2.9 g, 54%).

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