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Studies on Ketene and Its Derivatives. XLVI.[1] Mass Spectrometric Studies of 3-Acetyl-4-hydroxy-6-methyl-1-pyridyl-2-pyridones and N-Pyridyl-2,6-dimethyl-4-pyrone-3-carboxamides

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The reaction of diketene with amino-methylpyridines (Ia—i) was investigated, and the products were identified by the mass spectroscopic study. The reaction of 2- (Ia) and 3-amino-methylpyridines (Ib,d,f,h) with diketene gave the pyridone derivatives (IIIa, b,d,f,h), but 4-amino-methylpyridines (Ic,e,g,i) afforded the pyrone derivatives (IVc, e,g,i). The mass spectrum of III showed the characteristic peaks at *m/e* 243, 215, 187 and 175, and in the case of IV the strong peaks were observed at *m/e* 151, 108, 67 and 43. Each fragmentation pathways were discussed.

Previous works in this series[3,4] have shown the reaction of diketene with the aromatic primary amine to give acetoacetanilide (II, Py=aryl), 3-acetyl-1-aryl-4-hydroxy-6-methyl-2-pyridone (III, Py=aryl), and 2,6-dimethyl-4-pyrone-3-carboxanilide (IV, Py=aryl). For example, the reaction of aniline with an equivalent amount of diketene gave acetoacetanilide, but the reaction with excess diketene in the presence of a basic catalyst such as triethylamine afforded 3-acetyl-4-hydroxy-6-methyl-1-phenyl-2-pyridone (III, Py=phenyl). In the case of aminopyridines results obtained were more complicated; that is, the reaction of 2-aminopyridine with diketene in organic solvent gave 2-methyl-4*H*-pyrido(1,2-*a*)pyrimidin-4-one, but 3- and 4-aminopyridine afforded 3-acetoacetamidopyridine (II, Py=3-pyridyl) and N-(4′-pyridyl)-2,6-dimethyl-4-pyrone-3-carboxamide (IV, Py=4-pyridyl),[5] respectively.

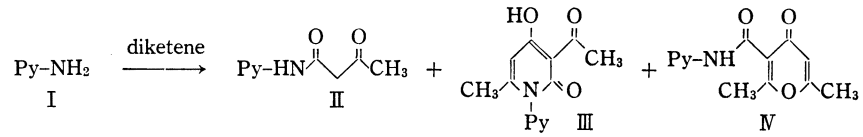
The present paper deals with the reaction of diketene with aminomethylpyridine and the identification of the products by the mass spectroscopic study.

When 2-amino-6-methylpyridine (Ia) was allowed to react with diketene in chloroform, 2-acetoacetamido-6-methylpyridine (IIa) was obtained in good yield (89%) and none of other products were detected. When this reaction was carried out in benzene instead of chloroform, the yield of IIa decreased to 68% and the pyridone derivative (IIIa) was obtained in 15% yield. In addition, the reaction in acetic acid afforded IIIa (12%) and the pyrone derivative (IVa) in 38.8% yield. Similarly, 3-amino-6-methylpyridine (Ib) reacted with diketene in chloroform giving the acetoacetate (IIb) and the pyridone derivative (IIIb). Thus, nine kinds of amino-methylpyridines (Ia—i) were allowed to react with diketene. The results are summarized in Table I.

As shown in Table I, 3-aminopyridines (Ib,d,f,h) transformed to the pyridone derivatives (IIIb,d,f,h) and 4-aminopyridines (Ic,e,g,i) gave mainly the pyrone derivative (IVc,e,g,i). Furthermore, the pK_a value of I seems to play some role in the formation of the product; that is, the pyrone derivative (IV) can be obtained from more basic amine (over pK_a 9) and the pyridone derivative (III) is obtainable from acidic one (less than pK_a 8).

1) Part XLV: T. Kato and T. Sakamoto, *Yakugaku Zasshi*, **91**, 1174 (1971).
2) Location: *Aobayama, Sendai.*
3) T. Kato and Y. Kubota, *Yakugaku Zasshi*, **87**, 1212 (1967).
4) T. Kato, H. Yamanaka, T. Niitsuma, K. Wagatsuma and M. Oizumi, *Chem. Pharm. Bull.* (Tokyo), **12**, 910 (1964).
5) The structure of this product was misproposed as the pyridone derivative (III, Py=4-pyridyl).[4]

TABLE I. Reaction of Diketene with Amino-methylpyridines



Compound I (g)	pK_a Value	Diketene (g)	Solvent (ml)	Reaction time (hr)	Product (%) II	III	IV
a 1.08		2.52	$CHCl_3$ (15)	3.0	88.5	—	—
a 1.08	7.4	2.52	C_6H_6 (20)	1.0	67.7	15.5	—
a 1.08		2.52	CH_3COOH (15)	1.0	—	11.6	38.8
b 0.54	6.7	1.26	$CHCl_3$ (15)	0.5	18.8	5.0	—
c 1.08	9.7	2.52	$CHCl_3$ (20)	0.5	—	—	50.4
d 3.24	6.8	7.60	$CHCl_3$ (50)	0.5	43.4	15.5	9.0
e 0.54	9.4	1.26	$CHCl_3$ (15)	0.5	—	—	19.4
f 0.61		1.26	$CHCl_3$ (15)	0.5	—	72.1	—
f 1.22	7.5	2.52	CH_3COOH (15)	1.0	—	41.9	2.0
g 2.44	10.1	5.04	$CHCl_3$ (50)	0.5	—	—	60.7
h 0.70	8.0	1.25	$CHCl_3$ (15)	0.5	54.5	28.0	—
i 0.60	9.9	1.26	$CHCl_3$ (15)	1.0	—	—	13.9

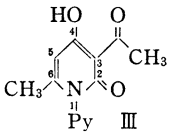
I: a: 2-amino-6-methylpyridine, b: 3-amino-6-methylpryidine, c: 4-amino-2-methylpyridine, d: 3-amino-2-methylpyridine, e: 4-amino-3-methylpyridine, f: 3-amino-2,6-dimethylpyridine, g: 4-amino-2,6-dimethylpyridine, h: 3-amino-2,4,6-trimethylpryidine, i: 4-amino-3-ethyl-6-methylpyridine

The infrared (IR) and nuclear magnetic resonance (NMR) spectral data of these products are summarized in Table II and III. These spectral data are essentially identical with those of the pyridone and pyrone derivatives derived from aniline, respectively. The characteristic found in NMR data is the chemical shift of the enolic proton of the pyridone compound (III) and the NH proton of the pyrone derivative (IV); that is, as shown in Table II and III, the OH proton appears at near 15.8 ppm as a singlet, but the NH proton is presented at near 12 ppm as a broad signal.

Mass Spectra of the Pyridone Derivatives (III)

Djerassi and his co-worker[6] reported that the mass spectrum of 4-hydroxy-6-methyl-2-pyridone (IIIm) shows strong peaks at *m/e* 125 (M^+), 97, 84 (base peak), 69, 57, 55, and 42.

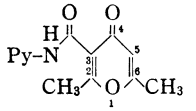
TABLE II. Nuclear Magnetic Resonance and Infrared Spectral Data of III



III	Py	NMR ($CDCl_3$ ppm,) 6-Methyl	Acetyl methyl	5-Proton	Enol-proton	IR$\nu_{C=O}$ ($CHCl_3$)
a	2-methyl-6-pyridyl	1.92	2.60	5.88	15.76	1664
b	6-methyl-3-pyridyl	1.95	2.60	5.94	15.83	1658
d	2-methyl-3-pyridyl	1.87	2.60	5.96	15.82	1658
f	2,6-dimethyl-3-pyridyl	1.88	2.61	5.93	15.73	1664
h	2,4,6-trimethyl-3-pyridyl	1.88	2.65	6.00	15.81	1661
p	phenyl[3]	1.95	2.65	5.90	15.76	1647

6) A.M. Duffield and C. Djerassi, *Acta Chem. Scand.*, **20**, 361 (1966).

TABLE III. Nuclear Magnetic Resonance and Infrared Spectral Data of IV



IV

IV	Py	NMR ($CDCl_3$, ppm)				IR $\nu_{max}^{CHCl_3}$ cm^{-1}	
		2-CH_3	6-CH_3	5-H	NH	Amide	4-Pyrone
a	2-methyl-6-pyridyl	2.80	2.27	6.27	12.00	1684	1656
c	2-methyl-4-pyridyl	2.83	2.30	6.26	12.20	1695	1654
d	2-methyl-3-pyridyl	2.86	2.32	6.30	12.08	1701	1658
e	3-methyl-4-pyridyl	2.83	2.30	6.27	12.20	1692	1653
f	2,6-dimethyl-3-pyridyl	2.83	2.30	6.29	12.00	1692	1656
g	2,6-dimethyl-4-pyridyl	2.80	2.27	6.26	12.17	1695	1653
i	3-ethyl-6-methyl-4-pyridyl	2.85	2.31	6.28	12.17	1692	1656
j	4-pyridyl[4]	2.82	2.30	6.22	12.20	1704	1658
k	*p*-nitro-phenyl[3]	2.85	2.30	6.30	11.67	1686	1650

The mass spectrum of IIIn,[7] which has an acetyl group at 3 position of IIIm, is essentially identical with that of IIIm. As shown in Chart 1, two possible fragmentation pathways are considered as plausible; the one is the genesis of ion IIIm by loss of ketene from the molecular ion of IIIn, and the other is the formation of ion a by the initial loss of methyl radical from IIIn. That is to say, the spectrum of IIIn displays a strong molecular ion peak (*m/e* 167), while the loss 15 mass units affords the ion a (*m/e* 152) as the base peak. The peaks at *m/e* 124, 96, and 68 can be explained by step-wise loss of three moles of carbon monoxide from the ion a to give the ion b,c, and d, successively.

Elimination of ketene from the molecular ion (IIIn) would lead to the ion IIIm (*m/e* 125). The peak at *m/e* 55 (ion f) could be visualized as an initial loss of carbon monoxide from the ion IIIm followed by the expulsion of ketene. Elimination of hydrogen radical from ion e gives ion c' (*m/e* 96), which subsequently loses carbon monoxide to form ion d (*m/e* 68). The peak at *m/e* 84 may come from IIIm by the elimination of CH≡CO·, and this postulate is in agreement with the composition of ion g (C_4H_6ON) determined for this fragment by high resolution mass spectrometry.

Portion of the ion g yielded at *m/e* 84 could also arise from the molecular ion IIIn. The ion at *m/e* 69 can be assigned as the structure h, which is converted from ion III'n *via* III'm.

The spectrum of the N-ethyl derivative (IIIo)[7] is quite similar to that of IIIn, because the elimination of ethylene from the molecular ion IIIo (*m/e* 195) affords the ion IIIn (*m/e* 167), which arises the same fragmentation as described above. The ion i at *m/e* 112 corresponds to the ion g (*m/e* 84) observed in the fragmentation of IIIn, and arises from the molecular ion IIIo or ion j (*m/e* 153), which is presumably transformed from IIIo by the loss of ketene. Therefore, it is reasonably concluded that ion g (*m/e* 84) and ions corresponding to it are characteristic for the fragmentation of 4-hydroxy-6-methyl-2-pyridone compound (III).

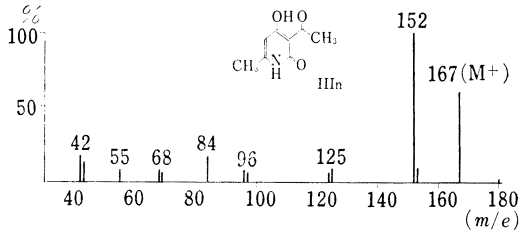


Fig. 1. Mass Spectrum of IIIn

7) T. Kato and Y. Kubota, *Yakugaku Zasshi*, **89**, 1477 (1969).

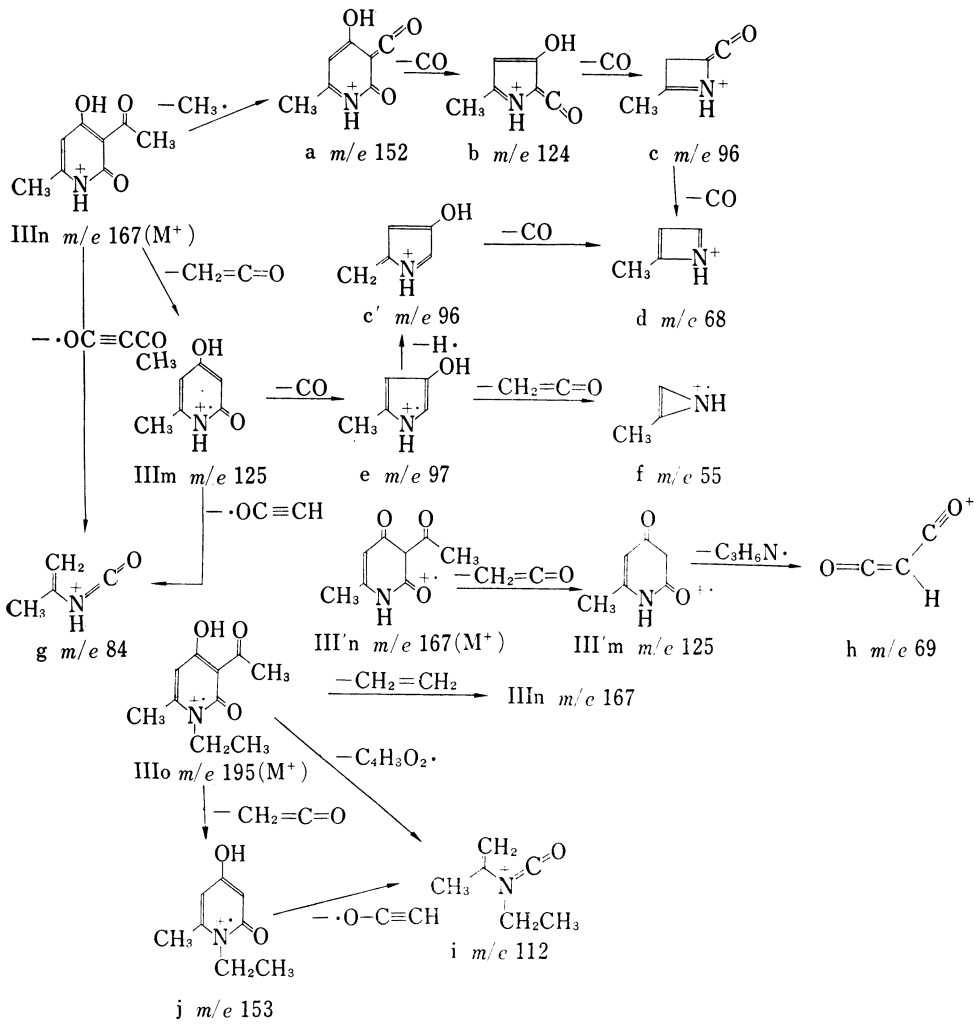
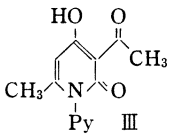


Chart 1

On the other hand, the spectra of IIIa, IIIb and IIId display same peaks corresponding to *m/e* 258 (M^+), 243, 215, 187 and 159. As discussed before, these peaks correspond to the fragmentation ions (ion IIIn, ion a, ion b, ion c and ion d) appeared in the case of IIIn or IIIo. But the ion k at *m/e* 216, which might arise from the molecular ion (*m/e* 258) by loss of ketene, can not be detected in the spectra of these three (IIIa, IIIb and IIId). The peak at *m/e* 147 (ion m) could be formed from the characteristic ion l (*m/e* 175) by expulsion of carbon monoxide. The ion at *m/e* 146 can be assigned structure n on the basis of its composition ($C_9H_{10}N_2$), which was determined by the high resolution mass spectrometry. The peak at *m/e* 133 (ion p) arises presumably from ion o, which is formed by the ring cleavage of the molecular ion by the retro-Diels Alder reaction.

On the other hand, as shown in Table IV large differences in the relative intensity of the peak at *m/e* 251 (M^+-1) can be observed among the spectra of IIIa, IIIb and IIId. The reason for this could be explained as following; *i.e.*, this peak can be formed by the elimination of hydrogen radical from pyridine ring. Therefore, compound IIIa, which has hydrogen at β-position of pyridine ring, should show the strongest peak at *m/e* 257 (ion q) among

TABLE IV. Relative Intensity of M^+-1 and M^+-CH_3-H_2O of III



III	Py	M^+-1		M^+-CH_3-H_2O	
		m/e	%	*m/e*	%
a	2-methyl-6-Pyridyl	257	88.0	225	0
b	2-methyl-5-Pyridyl	257	39.0	225	0
d	2-methyl-3-Pyridyl	257	0	225	9.2
f	2,6-dimethyl-3-pyridyl	271	0	239	13.0
h	2,4,6-trimethyl-3-pyridyl	285	0	253	9.8

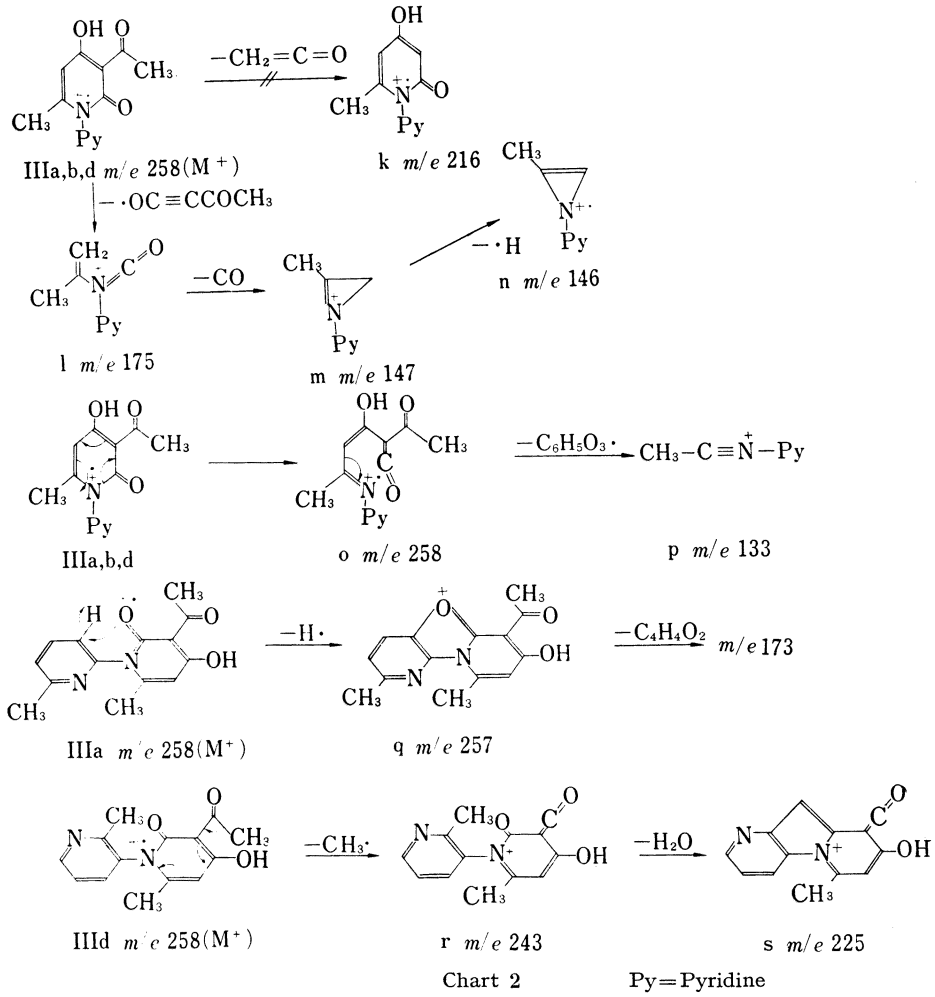


Chart 2 Py=Pyridine

three compounds. The peak at *m/e* 173 is observed in the spectra of IIIa and IIIb, but cannot be observed in the spectrum of IIId. The peak at *m/e* 225 (ion s) can be observed only in the spectrum of IIId. This peak may be due to loss of water from ion r (M^+-CH_3), in which

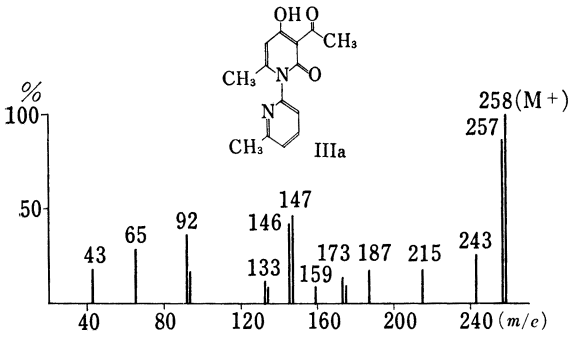


Fig. 2. Mass Spectrum of IIIa

the methyl group of pyridine is adjacent to the carbonyl oxygen of pyridone. The relative intensity of M^+-1 and M^+-CH_3-H_2O are shown in Table IV.

Mass Spectra of 4-Pyrone-3-carboxamide Derivatives (IV)

The behaviours of 2,6-dimethyl-4-pyrone (IVm) upon electron impact was investigated by Tatematsu, *et al.*,[8] and its fragmentation was classified to two pathways. The one is; i) the elimination of carbon monoxide from the molecular ion, and the other is; ii) the retro-Diels Alder cleavage of the 4-pyrone ring. Though a similar fragmentation to that of IVm would be expected, the pattern of 4-pyrone-3-carboxamide derivatives (IVa, IVc, and IVd) showed some different behaviours from that of IVm on account of the large effect of the amide group at 3-position. The characteristic feature of the fragmentation pattern is; i) the same fragmentation as that of the first one of IVm, and ii) the cleavage of 4-pyrone ring through the effect of the amide group at 3-position, and iii) the simple fragmentation of the amide group and the formation of amino-methylpyridine radical cation. i) The first one is elimination of carbon monoxide from the molecular ion (IVa, IVc, and IVd) to give ion t (*m/e* 230). The ion at *m/e* 230 affords ion u (*m/e* 215) by loss of methyl radical, and loss of another mole of carbon monoxide from ion u produces ion v (*m/e* 187). ii) The second process is an important fragmentation; that is, the ion at *m/e* 124 arises from the molecular ion *via* synchronous mechanism with the formation of picolyl isocyanate and the cleavage of 4-pyrone ring. The ion at *m/e* 124 may be formed by removal of a non-bonding electron from either the carbonyl oxygen or the ring oxygen of the pyrone, and can be assigned structure w (*m/e* 124) or y (*m/e* 124), respectively. The ion w produces the ion x (*m/e* 85) by loss of methylacetylene radical. On the other hand, the ion y generates an ion z (*m/e* 109) and an ion aa (*m/e* 42) by loss of methyl radical and C_5H_5O, respectively. Further loss of carbon monoxide from ion z produces ion bb (*m/e* 81). iii) The last fragmentation is the formation of an ion cc (*m/e* 151), which is observed as a base peak or a very strong peak. The ion cc (*m/e* 151) produces an ion ee (*m/e* 67) by elimination of $C_4H_4O_2$ due to the retro-Diels Alder reaction. McLafferty rearrangement of IVa, c, d (*m/e* 258) results in the loss of $C_8H_6O_3$ to give the ion at *m/e* 108 (Ia, c, d).

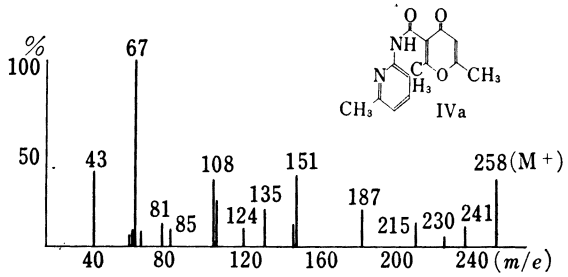


Fig. 3. Mass Spectrum of IVa

Experimental

Reaction of Diketene with 2-Amino-6-methylpyridine (Ia)——1) Diketene (2.52 g, 0.03 mole) was added to a solution of Ia (1.08 g, 0.01 mole) in $CHCl_3$ (15 ml). After refluxing for 3 hr, the reaction mixture was condensed to give a crystalline solid, which was purified by recrystallization from benzene to give 2-acetoacetamido-6-methylpyridine (IIa) as colorless prisms, mp 101—102°. Yield, 1.7 g (88.5%). *Anal.* Calcd. for $C_{10}H_{12}O_2N_2$ (IIa): C, 62.48; H, 6.29; N, 14.58. Found: C, 62.73; H, 6.39; N, 14.25. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1709,

8) H. Nakata and A. Tatematsu, *Shitsuryo Bunseki*, **15**, 5 (1967).

i) IVa,c,d m/e 258(M^+) $\xrightarrow{-CO}$ t m/e 230 $\xrightarrow{-CH_3\cdot}$ u m/e 215 $\xrightarrow{-CO}$ v m/e 187

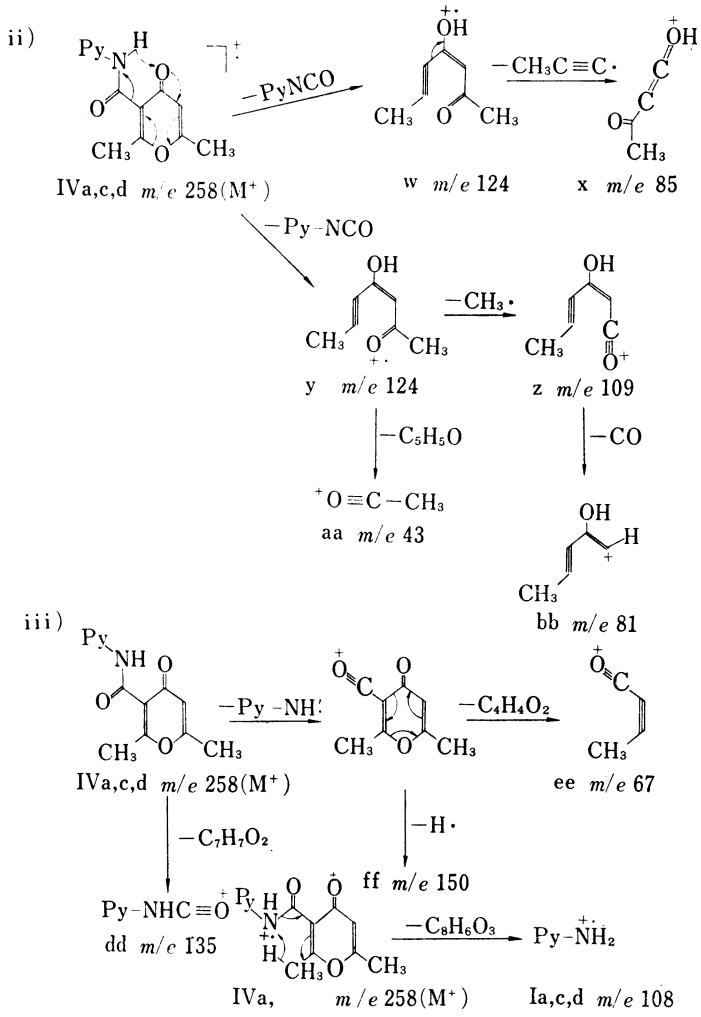


Chart 3 Py=Pyridine

1684. NMR ($CDCl_3$, ppm): 2.29 (3H, singlet), 2.41 (3H, singlet), 3.57 (2H, singlet), 6.8—8.0 (3H, ring protons), 9.12 (NH).

2) Diketene (2.52 g) was added to a solution of Ia (1.08 g) in abs. benzene (20 ml), and the mixture was refluxed for 1 hr. After cooling, crystals separated were collected by suction. Recrystallization from benzene gave 1.3 g (67.7%) of IIa, mp 101—102°, undepressed on admixture with a sample obtained in the above run. The mother liquor was condensed to give 3-acetyl-4-hydroxy-6-metyl-1-(6-metyl-2-pyridyl)-2-pyridone (IIIa) as colorless needles, mp 195—197°. Yield, 0.4 g (15.5%). *Anal.* Calcd. for $C_{14}H_{14}O_3N_2$ (IIIa): C, 65.10; H, 5.47; N, 10.85. Found: C, 65.40; H, 5.50; N, 11.17.

3) Diketene (2.52 g) was added to a solution of Ia (1.08 g) in AcOH (15 ml). After refluxing for 1 hr, the reaction mixture was condensed *in vacuo* giving a crystalline solid. Recrystallization from benzene gave 0.3 g (11.6%) of IIIa, mp 195—197°, undepressed on admixture with a sample obtained in the above run. The mother liquor was condensed to give N-(6-methyl-2-pyridyl)-2,6-dimethyl-4-pyrone-3-carboxamide (IVa) as colorless plates, mp 174—175°. Yield, 1.0 g (38.8%). *Anal.* Calcd. for $C_{14}H_{14}O_3N_2$ (IVa): C, 65.10; H, 5.47; N, 10.85. Found: C, 64.99; H, 5.48; N, 10.82.

Reaction of Diketene with 3-Amino-6-methylpyridine (Ib)——A suspension of Ib (0.54 g, 0.005 mole) and diketene (1.26 g, 0.015 mole) in $CHCl_3$ (15 ml) was refluxed for 0.5 hr, and the reaction mixture was condensed. The residue was purified by chromatography on alumina using benzene as eluent to give 3-acetoacetamido-6-methylpyridine (IIb) as colorless needles (from benzene), mp 111—113°. Yield, 0.36 g (18.8%). *Anal.* Calcd. for $C_{10}H_{12}O_2N_2$ (IIb): 62.48; H, 6.29; N, 14.58. Found: C, 62.63; H, 6.30; N, 14.67. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1718, 1695. NMR ($CDCl_3$, ppm): 2.27 (3H, singlet), 2.47 (3H, singlet), 3.56 (2H, singlet), 7.0—8.6 (3H, ring protons), 9.53 (NH). The mother liquor was condensed to give 3-acetyl-4-hydroxy-6-methyl-1-(6-methyl-3-pyridyl)-2-pyridone (IIIb) as pale yellow needles, mp 195—196°. Yield, 0.13 g (5.0%). *Anal.* Calcd. for $C_{14}H_{14}O_3N_2$ (IIIb): C, 65.10; H, 5.46; N, 10.85. Found: C, 65.41; H, 5.71; N, 10.85.

Reaction of Diketene with 4-Amino-2-methylpyridine (Ic)——A suspension of Ic (1.08 g) and diketene (2.52 g) in $CHCl_3$ (20 ml) was heated under reflux for 0.5 hr, and the solvent was removed. The resulting residue was purified by alumina chromatography using $CHCl_3$ as a solvent to give N-(2-methyl-4-pyridyl)-2,6-dimethyl-4-pyrone-3-carboxamide (IVc) as colorless needles (from AcOEt), mp 164—165°. Yield, 1.3 g (50.4%). *Anal.* Calcd. for $C_{14}H_{14}O_3N_2$ (IVc): C, 65.10; H, 5.46; N, 10.85. Found: C, 64.91; H, 5.39; N, 10.80.

Reaction of Diketene with 3-Amino-2-methylpyridine (Id)——A suspension of Id (3.24 g, 0.03 mole) and diketene (7.69 g, 0.09 mole) in $CHCl_3$ (50 ml) was heated under reflux for 0.5 hr. The reaction mixture was condensed, the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was passed into an alumina column. The eluate was evaporated and purified by recrystallization from benzene to give 0.7 g (9.0%) of N-(2-methyl-3-pyridyl)-2,6-dimethyl-4-pyrone-3-carboxamide (IVd) as colorless needles, mp 205—206°, and 2.5 g (43.4%) of 3-acetoacetamido-2-methylpyridine (IId) as pale green needles, mp 99—100°. The mother liquor was condensed, and the residue was purified by column chromatography on silica gel using petroleum ether–ether (2:1) to give 3-acetyl-4-hydroxy-6-methyl-1-(2-methyl-3-pyridyl)-2-pyridone (IIId) as colorless prisms (benzene–cyclohexane), mp 183—184°. Yield, 1.2 g (15.5%). *Anal.* Calcd. for $C_{14}H_{14}O_3N_2$ (IVd): C, 65.10; H, 5.46; N, 10.85. Found: C, 65.27; H, 5.50; N, 10.79. *Anal.* Calcd. for $C_{10}H_{12}O_2N_2$ (IId): C, 62.48; H, 6.29; N, 16.65. Found: C, 62.73; H, 6.39; N, 16.57. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1709, 1681. NMR ($CDCl_3$, ppm): 2,30 (3H, singlet), 2.53 (3H, singlet), 3.60 (2H, singlet), 7.0—8.4 (3H, ring protons), 9.45 (NH). *Anal.* Calcd. for $C_{14}H_{14}O_3N_2$ (IIId): C, 65.10; H, 5.46; N, 10.85. Found: C, 65.44; H, 5.66; N, 10.78.

Reaction of Diketene with 4-Amino-3-methylpyridine (Ie)——A suspension of Ie (0.54 g) and diketene (1.26 g) in $CHCl_3$ (15 ml) and refluxed for 0.5 hr, and the reaction mixture was condensed. The residue was purified by column chromatography on alumina using ether as eluent to give N-(3-methyl-4-pyridyl)-2,6-dimethyl-4-pyrone-3-carboxamide (IVe) as pale yellow plates (benzene), mp 213—214° (decomp.). Yield, 0.29 g (19.4%). *Anal.* Calcd. for $C_{14}H_{14}O_3N_2$ (IVe): C, 65.10; H, 5.46; N, 10.85. Found: C, 65.31; H, 5.69; N, 10.46.

Reaction of Diketene with 3-Amino-2,6-dimethylpyridine (If)——1) Diketene (1.26 g, 0.015 mole) was added to a solution of If (0.61 g, 0.005 mole) in $CHCl_3$ (15 ml). After refluxing for 0.5 hr, the reaction mixture was condensed to give a crystalline substance. Recrystallization from $CHCl_3$–cyclohexane gave 3-acetyl-1-(2,6-dimethyl-3-pyridyl)-4-hydroxy-6-methyl-2-pyridone (IIIf) as colorless needles, mp 223—225°. Yield, 0.98 g (72.1%). *Anal.* Calcd. for $C_{15}H_{16}O_3N_2$ (IIIf): C, 66.16; H, 5.92; N, 10.29. Found: C, 66.36; H, 5.99; N, 10.41.

2) A mixture of If (1.22 g) and diketene (2.52 g) in AcOH (15 ml) was heated under reflux for 1 hr. The reaction mixture was condensed *in vacuo* to give a crystalline substance, which was purified by recrystallization from benzene to give 1.14 g (41.9%) of IIIf, mp 223—225°, undepressed on admixture with a sample obtained in the above run. The mother liquor was condensed, and the residue was purified by column chromatography on silica gel using $CHCl_3$ as eluent to give N-(2,6-dimethyl-3-pyridyl)-2,6-dimethyl-pyrone-3-carboxamide (IVf) as colorless needles (benzene), mp 196—197°. Yield, 55 mg (2.0%). *Anal.* Calcd. for $C_{15}H_{16}O_3N_2$ (IVf): C, 66.16; H, 5.92; N, 10.29. Found: C, 65.94; H, 5.99; N, 10.31.

Reaction of Diketene with 4-Amino-2,6-dimethylpyridine (Ig)——Following the procedure given for the first run of IIIf, Ig (2.44 g) was treated with diketene (5.04 g) in $CHCl_3$ (15 ml) to give N-(2,6-dimethyl-4-pyridyl)-2,6-dimethyl-4-pyrone-3-carboxamide (IVg) as coloress needles (MeOH). mp 188—189°. Yield, 3.3 g (60.7%). *Anal.* Calcd. for $C_{15}H_{16}O_3N_2$ (IVg): C, 66.16; H, 5.92; N, 10.29. Found: C, 66.57; H, 6.08; N, 10.43.

Reaction of Diketene with 3-Amino-2,4,6-trimethylpyridine (Ih)——Diketene (1.25 g) was added to a suspension of Ih (0.7 g) in $CHCl_3$ (15 ml). After refluxing for 0.5 hr, the solvent was removed to give crystalline substance. Recrystallization from benzene gave 3-acetoacetamido-2,4,6-trimethylpyridine (IIh) as pale yellow leaves, mp 137—138°. Yield, 0.6 g (54.5%). The mother liquor was condensed to give 3-acetyl-4-hydroxy-6-methyl-1-(2,4,6-trimethyl-3-pyridyl)-2-pyridone (IIIh) as colorless prisms, mp 168—170°. Yield, 0.35 g (28.0%). *Anal.* Calcd. for $C_{12}H_{16}O_2N_2$ (IIh): C, 65.43; H, 7.32; N, 12.72. Found: C, 65.51; H, 7.20; N, 13.14. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1712, 1675. NMR ($CDCl_3$, ppm): 2.11 (3H, singlet), 2.30 (3H, singlet), 2.35 (3H, singlet), 3.56 (2H, singlet), 6.83 (1H, singlet), 8.62 (NH). *Anal.* Calcd. for $C_{16}H_{18}O_3N_2$ (IIIh): C, 67.11; H, 6.34; N, 9.78. Found: C, 67.38; H, 6.61; N, 9.79.

Reaction of Diketene with 4-Amino-3-ethyl-6-methylpyridine (Ii)——Following the procedure given for IVg, Ii (0.6 g) was treated with diketene (1.26 g) in $CHCl_3$ (15 ml) to give N-(3-ethyl-6-methyl-4-pyridyl)-

2,6-dimethyl-4-pyrone-3-carboxamide (IVi) as colorless needles (benzene–cyclohexane), mp 154—155°. Yield, 0.2 g (13.9%). *Anal.* Calcd. for $C_{16}H_{18}O_3N_2$ (IVi): C, 67.11; H, 6.34; N, 9.78. Found: C, 66.93; H, 6.40; N, 9.83.

Determination of pK_a——The pK_a values of amines (Ia—i) were determined from pH titration curves in aqueous solution. A solution of amine (0.005 M) was prepared by dilution with CO_2–free H_2O. Titration was carried out on the Tōa model HM-5A pH meter equipped with the external electrode assembly. Each of the above solutions (30 ml) was titrated with 0.1 N HCl in a 50 ml beaker at 20°.

Measurement of Mass Spectra——The mass spectra were obtained with JEOL JMS-01SG double focussing mass spectrometer using an ionizing energy of 75 eV and a direct inlet.

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