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Studies on Ketene and Its Derivatives. CI.[1] Reaction of Diketene with 4-Amino-methylpyridine 1-Oxides

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The reaction of diketene with 4-amino-methylpyridine 1-oxides was examined.

4-Aminopyridine 1-oxide (**1a**) and 4-amino-3-methylpyridine 1-oxide (**1c**) reacted with diketene in the presence of triethylamine at 0——5° to give the corresponding substituted 2,6-dimethyl-4-pyrone-3-carboxamides; *i.e.*, N-(1-oxido-4-pyridyl) (**3a**) and N-(3-methyl-1-oxido-4-pyridyl) (**3c**) compounds. The reaction of diketene with 4-amino-methylpyridine 1-oxides (**1b**, **d**, and **e**) afforded 4-acetoacetamidopyridine 1-oxides (**2b**, **d**, and **e**) under the same conditions.

However, the reaction of diketene with 4-aminopyridine 1-oxides (**1f** and **g**) possessing an ethyl group at the 3-position gave N-(3-ethyl-1-oxido-4-pyridyl)-2-acetyl-3,5-dimethylphenol-4-carboxamides (**5f** and **g**), together with N-(3-ethyl-1-oxido-4-pyridyl)-2,6-dimethyl-4-pyrone-3-carboxamides (**3f** and **g**).

The mechanism of formation of compounds **5f** and **g** is discussed.

Keywords——diketene; amino-methylpyridine 1-oxides; triethylamine; acetoacetamidopyridines; N-pyridyl-2,6-dimethyl-4-pyrone-3-carboxamides; N-pyridyl-2-acetyl-3,5-dimethylphenol-4-carboxamides; catalytic reduction; hydrolysis

It has long been known that primary amines react with diketene to give acetoacetamides in good yield. However, when the reaction is carried out in the presence of a basic catalyst such as triethylamine, either 1-substituted 3-acetyl-4-hydroxy-6-methyl-2-pyridone (pyridone compound) or N-substituted 2,6-dimethyl-4-pyrone-3-carboxamide (pyrone compound) is obtained.[3] On the other hand, the reaction of diketene with aminopyridines is more complicated, affording various products. For example, 2-aminopyridines react with diketene to give 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and N-pyridylacetoacetamides.[4,5] The reaction of diketene with 3-aminopyridines gives 3-acetyl-4-hydroxy-6-methyl-1-(3-pyridyl)-2-pyridones (pyridone compounds) together with 3-acetoacetamidopyridines, whereas N-pyridyl-2,6-dimethyl-4-pyrone-3-carboxamides (pyrone compounds) are obtained exclusively from 4-aminopyridines.[6] Both pyridone and pyrone compounds are formed by the reaction of aminopyridines with two equivalent amounts of diketene. It seems likely that the difference in reactivity between 3-aminopyridine and 4-aminopyridine depends on their basicities.[6] However, the reaction of diketene with 4-amino-methylpyridine 1-oxides has not been examined in detail except for one example; that is, the reaction of diketene with 4-aminopyridine 1-oxide (**1a**) resulted in the formation of dehydroacetic acid and the recovery of the starting amine.[4]

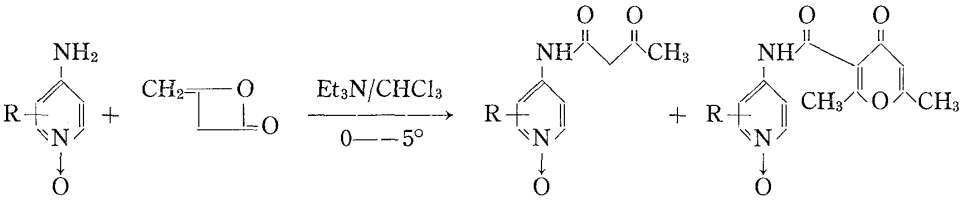
In the present paper, we describe the reaction of diketene with 4-amino-methylpyridine 1-oxides under various conditions. The 4-amino-methylpyridine 1-oxides used in this reaction

1) Part C: T. Kato, N. Katagiri, and R. Sato, *J. Org. Chem.*, **45**, (1980) in press.
2) Location: *Aobayama, Sendai 980, Japan.*
3) T. Kato, *Acc. Chem. Res.*, **7**, 265 (1974).
4) T. Kato, H. Yamanaka, T. Niitsuma, K. Wagatsuma, and M. Oizumi, *Chem. Pharm. Bull.*, **12**, 910 (1964).
5) T. Kato, H. Yamanaka, N. Katagiri, and S. Masuda, *Chem. Pharm. Bull.*, **20**, 142 (1972).
6) T. Kato, H. Yamanaka, N. Katagiri, and S. Masuda, *Chem. Pharm. Bull.*, **20**, 133 (1972).

were as follows; 4-aminopyridine 1-oxide (**1a**), 4-amino-2-methylpyridine 1-oxide (**1b**), 4-amino-3-methylpyridine 1-oxide (**1c**), 4-amino-2,6-dimethylpyridine 1-oxide (**1d**), 4-amino-3,5-dimethylpyridine 1-oxide (**1e**), 4-amino-3-ethylpyridine 1-oxide (**1f**) and 4-amino-5-ethyl-2-methylpyridine 1-oxide (**1g**).

As reported previously,[4] the reaction of diketene with the amine **1a** in chloroform at room temperature or at 0——5° resulted in the dimerization of diketene to form dehydroacetic acid, accompanied by recovery of the starting amine **1a**. However, in the presence of triethylamine as a catalyst, the reaction gave N-(1-oxido-4-pyridyl)-2,6-dimethyl-4-pyrone-3-carboxamide (**3a**) in 5% yield. The yield of pyrone **3a** was improved by the use of four equivalents of diketene. In this case, the N-acetoacetyl compound was not detected. Reactions of the amines **1b**—**g** with diketene under similar conditions gave the corresponding products, as summarized in Table I.

Table I. Reaction of Diketene with 4-Amino-methylpyridine 1-Oxides (**1a**—**g**)



1 **2** **3**

	Amine **1** g (mol)	Diketene g (mol)	Solvent $CHCl_3$ (ml)	Product yield (%) **2**	Product yield (%) **3**
1a	0.5 (0.0045)	0.5 (0.006)	13	—	5
	0.85(0.0077)	2.6 (0.031)	20	—	17
1b	3 (0.024)	3 (0.036)	30	51	Trace[e]
	3 (0.024)	6 (0.071)	35	63	Trace
1c	3 (0.024)	6 (0.071)	35	—	20[a]
	1 (0.008)	2 (0.024)	20	—	68
	1 (0.008)	2 (0.024)	20	—	23[b]
1d	1.38(0.01)	2.52(0.03)	40	18	—[a]
	1.38(0.01)	1.26(0.015)	40	18	—
	0.69(0.005)	1.26(0.015)	20	68	—
1e	1.38(0.01)	3.36(0.04)	45	13	—[e]
1f	1.38(0.01)	3.36(0.04)	45	—	6[c]
1g	3 (0.02)	5.5 (0.065)	20	—	62[a]
	3 (0.02)	6.6 (0.079)	20	—	45[d]

1a: 4-aminopyridine 1-oxide, **1b**: 4-amino-2-methylpyridine 1-oxide, **1c**: 4-amino-3-methylpyridine 1-oxide, **1d**: 4-amino-2,6-dimethylpyridine 1-oxide, **1e**: 4-amino-3,5-dimethylpyridine 1-oxide, **1f**: 4-amino-3-ethylpyridine 1-oxide, **1g**: 4-amino-5-ethyl-2-methylpyridine 1-oxide

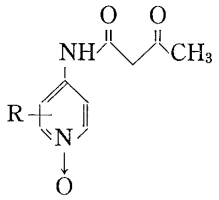
a) Without catalyst.
b) AcOH was used as a catalyst instead of Et_3N.
c) Compound **5f** was also obtained in this reaction.
d) Compound **5g** was also obtained in this reaction.
e) Compounds **2b**, **3b**, and **2e** were purified by silica gel column chromatography.

A trace of pyrone **3b** was obtained from the amine **1b** even when three equivalents of diketene were used; this reaction provided the N-acetoacetyl compound (**2b**) in 63% yield. In contrast, the reaction of the amine **1c** with diketene gave a good yield (68%) of pyrone **3c**, which was also obtained in 20% yield even in the absence of the catalyst. Furthermore, the pyrone **3c** was obtained in 23% yield when acetic acid was used as a catalyst instead of triethylamine. The reaction of diketene with the amines **1d** and **e** gave exclusively the corresponding N-acetoacetyl compounds **2d** and **e**.

When the amine **1g** was allowed to react with one equivalent of diketene, pyrone **3g** was obtained in a very poor yield. The yield of **3g** increased to 62% with the use of three equivalents of diketene, but decreased on using four equivalents of diketene in the presence of triethylamine, and instead, compound **5g** of mp 254° (dec.) was formed in 15% yield. The reaction of the amine **1f** gave pyrone **3f** and a trace of compound **5f** (mp 228—232° (dec.)).

The structural elucidation of the acetoacetamides **2** and pyrones **3** were based on the NMR and IR spectral data summarized in Tables II and III. As shown in Table III, the NMR and IR spectra of the pyrones **3a**, **b**, **c**, **f**, and **g** are similar to those of pyrone derivatives reported previously.[6] For instance, signals of the methyl groups at the 2 and 6 positions of the pyrone ring were observed at 2.8—2.9 and 2.3—2.4 ppm, respectively, and a ring proton of pyrone and an NH proton were observed near 6.3 and 12.5 ppm, respectively. The absorption bands of amide carbonyl and the carbonyl group of the pyrone ring were observed at 1690 and 1650—1660 cm^{-1}, respectively.

Table II. Physical and Analytical Data for Compound **2**



2

Compd. No.	Appearance (Recryst. solvent)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	NMR ($CDCl_3$, ppm) CH_3–	$-CH_2-$	NH	IR (KBr) cm^{-1} Amide	Ketone
2b	Prisms (Acetone)	156 (dec.)	$C_{10}H_{12}N_2O_3$	57.68 (57.71	5.81 5.68	13.46 13.32)	2.27	3.62	10.88	1686	1732
2d	Needles (Acetone)	162	$C_{11}H_{14}N_2O_3$	59.45 (59.61	6.35 6.48	12.60 12.63)	2.24	3.53	10.29	1628 1688	1660 1712[b]
2e	Needles (Acetone)	167 (dec.)	$C_{11}H_{14}N_2O_3$	59.45 (59.25	6.35 6.38	12.60 12.48)	2.47	4.09	—[a]	1641	1709

a) In CF_3COOH (DSS).
b) In $CHCl_3$.

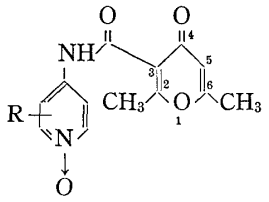
Catalytic reduction of pyrones **3c** and **g** over Raney nickel gave compounds **4c** and **g**, whose IR and NMR spectra were identical with those of authentic samples.[6]

The empirical formula of compound **5g**, $C_{19}H_{22}N_2O_4$, was determined by mass spectrometry and elemental analysis; it was formed by the reaction of three equivalents of diketene with the amine **1g**, followed by elimination of water and carbon dioxide.

Catalytic reduction of the 1-oxide **5g** over Raney nickel gave compound **6**. Though compound **5g** was stable in an alkaline solution, hydrolysis with 80% H_2SO_4 at 50° gave the amine **1g**, 3,5-dimethylphenol (**7**), 2,6-dimethyl-4-hydroxybenzoic acid (**8**) and 3-acetyl-2,6-dimethyl-4-hydroxybenzoic acid (**9**). When 10% HCl was used instead of 80% H_2SO_4, **5g** gave the amine **1g** and compound **7**. At the same time, acetic acid and carbon dioxide were detected. Based upon these chemical properties, the structure of compound **5g** was determined to be N-(5-ethyl-2-methyl-1-oxido-4-pyridyl)-2-acetyl-3,5-dimethylphenol-4-carboxamide. Spectroscopic data for compound **5g** also support the aroylamidopyridine structure.

The mechanism of formation of compound **5** can be explained as follows; amines **1f** and **g** react with diketene to give the acetoacetamidopyridines **2f** and **g**, which further react with diketene to form pyrones **3f** and **g** *via* intermediate **A**.

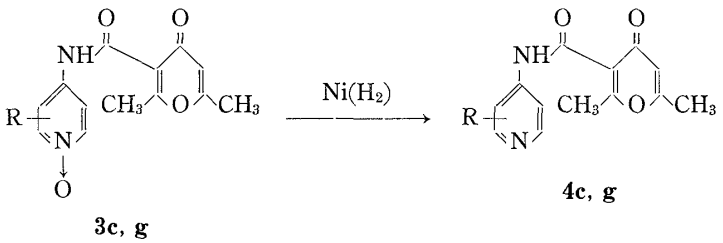
Table III. Physical and Analytical Data for Compound 3



3

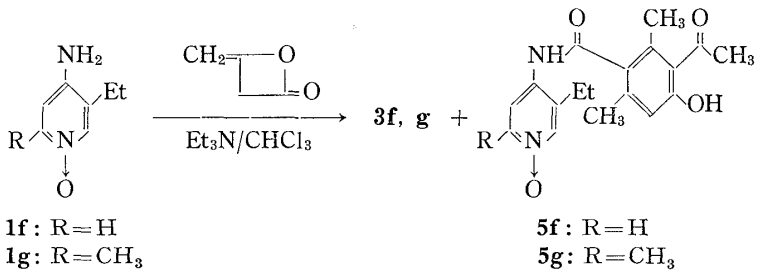
Compd. No.	Appearance (Recryst. solvent)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	NMR ($CDCl_3$, ppm) 2-CH_3	6-CH_3	5-H	NH	IR (KBr) cm^{-1} Amide	4-Pyrone
3a	Needles (MeOH)	213 (dec.)	$C_{13}H_{12}N_2O_4$	59.99 (59.26	4.65 5.04	10.77 10.44)	2.98	2.56	6.75	—[a]	1695	1650
3b	Needles (MeOH)	205 (dec.)	$C_{14}H_{14}N_2O_4$	61.31 (61.15	5.15 5.07	10.21 10.09)	2.84	2.34	6.30	12.42	1702	1658
3c	Needles (MeOH)	244—248 (dec.)	$C_{14}H_{14}N_2O_4$	61.31 (61.16	5.15 5.29	10.21 10.21)	3.05	2.58	6.83	—[a]	1685	1652
3f	Needles (EtOH–AcOEt)	240—241 (dec.)	$C_{15}H_{16}N_2O_4$	62.49 (62.23	5.59 5.45	9.72 9.56)	2.88	2.37	6.33	12.52	1688	1655
3g	Needles (MeOH–AcOEt)	193 (dec.)	$C_{16}H_{18}N_2O_4$	63.56 (63.52	6.00 6.25	9.27 9.00)	2.91	2.39	6.35	12.48	1693	1660
4c[6]							2.83	2.30	6.27	12.20	1692	1653[b]

a) In CF_3COOH.
b) In $CHCl_3$.



3c, g **4c, g**

Chart 1



1f: R=H
1g: R=CH_3

5f: R=H
5g: R=CH_3

Chart 2

On the other hand, intermediates **2f** and **g** react with intermediate **B**, which would participate in the formation of dehydroacetic acid, to afford intermediate **C**. The intermediate **C** is transformed into products **5f** and **g** *via* intermediate **D**.

This is the first reported instance of the formation of aroylamide derivatives by the reaction of diketene with primary amines.

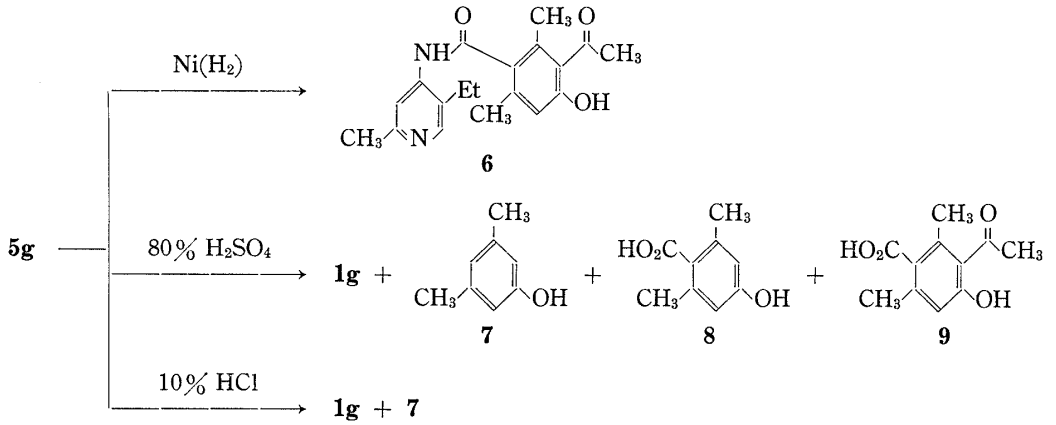


Chart 3

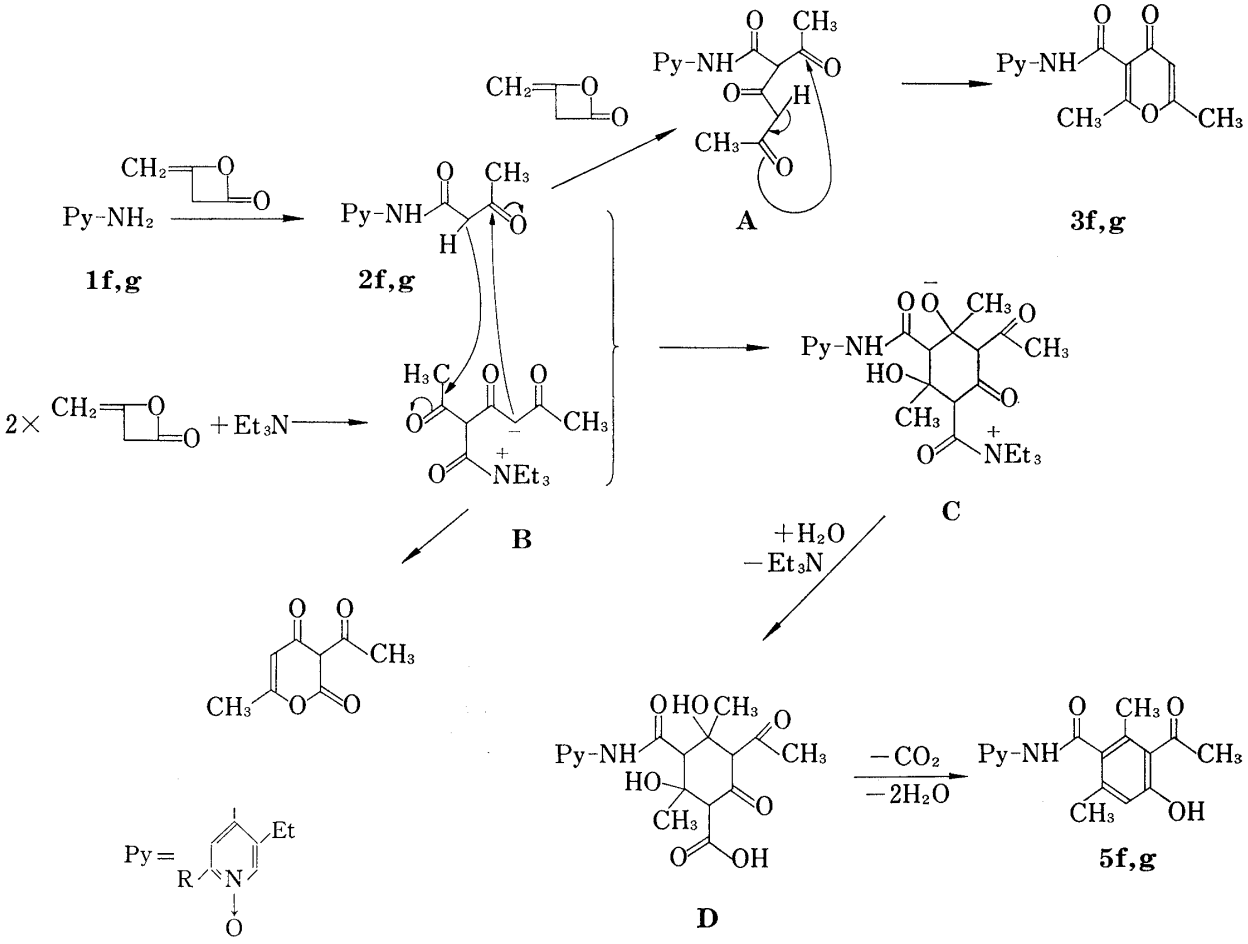


Chart 4

Experimental

IR spectra were taken on a JASCO IR-S spectrophotometer. NMR spectra were measured with a Hitachi R-20 instrument using tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi RMU-7L double focusing mass spectrometer. Melting points are uncorrected.

Reaction of Diketene with 4-Amino-methylpyridine 1-Oxides (1a—e)——General Procedure: A solution of diketene in $CHCl_3$ was added dropwise to a suspension of **1a**—**e** in $CHCl_3$ with stirring in the presence of Et_3N (3—5 drops) at 0——5°. Stirring was continued until the odor of diketene was absent. The reaction mixture was concentrated under reduced pressure and the residue was purified by recrystallization or silica gel column chromatography using a mixture of MeOH–AcOEt (1 : 9).

Reaction of Diketene with 4-Amino-methylpyridine 1-Oxides (1c, d, and g) in the Absence of Triethylamine——Following the general procedure, the reactions of the amines **1c**, **d**, and **g** with diketene in the absence of Et_3N gave compounds **3c**, **2d**, and **3g**, respectively.

Reaction of Diketene with 4-Amino-3-methylpyridine 1-Oxide (1c) in the Presence of AcOH as a Catalyst——Following the general procedure, the amine **1c** was treated with diketene in the presence of AcOH (2 ml) instead of Et_3N to give compound **3c**.

4-Amino-3-ethylpyridine 1-Oxide (1f)——A solution of 3-ethyl-4-nitropyridine 1-oxide[7] (8.4 g) in a mixture of H_2O (125 ml) and EtOH (60 ml) was shaken under hydrogen in the presence of 10% Pd-C (1.25 g) at room temperature until hydrogen uptake ceased. After removal of the catalyst and solvent, the residue was recrystallized from EtOH to give 6.9 g (quantitative yield) of the amine **1f** as colorless pillars, mp 183—185° (dec.). *Anal.* Calcd for $C_7H_{10}N_2O \cdot 1/4H_2O$: C, 58.93; H, 7.41; N, 19.63. Found: C, 58.92; H, 7.70; N, 19.59.

Reaction of Diketene with Amine 1f——A solution of diketene (3.36 g, 0.04 mol) in $CHCl_3$ (5 ml) was added dropwise to a suspension of the amine **1f** (1.38 g, 0.01 mol) in $CHCl_3$ (40 ml) with stirring in the presence of Et_3N (5 drops) at 0——5°. Stirring was continued until the odor of diketene was absent. The reaction mixture was concentrated under reduced pressure and the residue was washed with ether. The ether-insoluble material was subjected to silica gel column chromatography. Elution with MeOH–AcOEt (1 : 9) gave a trace of N-(3-ethyl-1-oxido-4-pyridyl)-3,5-dimethylphenol-4-carboxamide (**5f**) and 0.17 g (6%) of N-(3-ethyl-1-oxido-4-pyridyl)-2,6-dimethyl-4-pyrone-3-carboxamide (**3f**). Further elution gave 0.65 g (47%) of the starting amine **1f**.

5f: mp 228—232° (dec.). Colorless powder (EtOH–AcOEt). *Anal.* Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.78; H, 5.88; N, 8.63. IR (KBr) cm^{-1}: 3160, 1673, 1598. NMR (DMSO-d_6, DSS) δ: 1.17 (3H, t, $J=7.5$ Hz), 2.13 (3H, s), 2.26 (3H, s), 2.48 (3H, s), 2.56 (2H, q, $J=7.5$ Hz), 6.69 (1H, s), 7.71—8.19 (3H, m), 10.14 (1H, s), 10.16 (1H, s).

Reaction of Diketene with 4-Amino-5-ethyl-2-methylpyridine 1-Oxide (1g)——1) A solution of diketene (5.5 g, 0.065 mol) in $CHCl_3$ (5 ml) was added dropwise to a suspension of the amine **1g** (3 g, 0.02 mol) in $CHCl_3$ (15 ml) with stirring at 0——5°. Stirring was continued until the odor of diketene was absent. The reaction mixture was concentrated under reduced pressure and the residue was recrystallized from MeOH–benzene to give 3.72 g (62%) of N-(5-ethyl-2-methyl-1-oxido-4-pyridyl)-2,6-dimethyl-4-pyrone-3-carboxamide (**3g**).

2) A solution of diketene (6.6 g, 0.079 mol) in $CHCl_3$ (5 ml) was added dropwise to a suspension of **1g** (3 g, 0.02 mol) in $CHCl_3$ (15 ml) with stirring in the presence of a few drops of Et_3N at 0——5°. Stirring was continued until the odor of diketene was absent. The reaction mixture was concentrated under reduced pressure and the residue was washed with $CHCl_3$. The $CHCl_3$ solution gave 2.7 g (45%) of compound **3g**. The $CHCl_3$-insoluble residue was recrystallized from MeOH to give 1 g (15%) of N-(5-ethyl-2-methyl-1-oxido-4-pyridyl)-2-acetyl-3,5-dimethylphenol-4-carboxamide (**5g**) as a colorless powder, mp 254° (dec.). *Anal.* Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.39; H, 6.08; N, 8.16. IR (KBr) cm^{-1}: 3400, 3200, 2400 (broad), 1680, 1645. NMR (DMSO-d_6, DSS) δ: 1.13 (3H, t, $J=7.5$ Hz), 2.13 (3H, s), 2.25 (3H, s), 2.36 (3H, s), 2.45 (3H, s), 2.49 (2H, q, $J=7.5$ Hz), 6.67 (1H, s), 7.77 (1H, s), 8.16 (1H, s), 10.03 (1H, s), 10.14 (1H, s). MS *m/e*: 342 (M^+), 326 ($[M-16]^+$), 191.

3) A solution of diketene (3.36 g, 0.04 mol) in $CHCl_3$ (5 ml) was added dropwise to a suspension of the amine **1g** (1.52 g, 0.01 mol) in $CHCl_3$ (40 ml) with stirring in the presence of 1,8-diazabicyclo[5.4.0]-7-undecene (5 drops) at 0——5°. When the odor of diketene was no longer detectable, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using MeOH–AcOEt (1 : 9) as an eluant to give **5g** (0.29 g, 8%) and **3g** (0.27 g, 9%).

Catalytic Reduction of Pyrone 3c over Raney Ni——A solution of pyrone **3c** (0.5 g) in MeOH (50 ml) was shaken in hydrogen in the presence of Raney Ni (0.1 g). After the hydrogen uptake had ceased, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was extracted with hot MeOH. The MeOH extract was washed with acetone. The acetone-insoluble residue was recrystallized from EtOH to give 0.2 g (43%) of N-(3-methyl-4-pyridyl)-2,6-dimethyl-4-pyrone-3-carboxamide (**4c**) as colorless pillars, mp 213—214° (dec.) (lit.[6] mp 213—214° (dec.)).

Catalytic Reduction of Pyrone 3g over Raney Ni——A solution of pyrone **3g** (0.5 g) in EtOH (30 ml) was shaken under hydrogen in the presence of Raney Ni (0.1 g). When the hydrogen uptake was completed, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was extracted with hot MeOH and the soluble part was washed with ether. The ether-insoluble residue was recrystallized from benzene to give 0.3 g (63%) of N-(5-ethyl-2-methyl-4-pyridyl)-2,6-dimethyl-4-pyrone-3-carboxamide (**4g**) as colorless needles, mp 153—156° (lit.[6] mp 154—155°).

Catalytic Reduction of Compound 5g over Raney Ni——A suspension of compound **5g** (1 g) in MeOH (30 ml) was shaken under hydrogen in the presence of Raney Ni (0.14 g). When the hydrogen uptake ceased, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was ex-

7) J.M. Essery and K. Schofield, *J. Chem. Soc.*, **1960**, 4953.

tracted with hot MeOH, and the MeOH extract was purified by recrystallization from acetone to give 0.8 g (84%) of N-(5-ethyl-2-methyl-4-pyridyl)-2-acetyl-3,5-dimethylphenol-4-carboxamide (**6**) as colorless needles, mp 241°. *Anal.* Calcd for $C_{19}H_{22}N_2O_3$: C, 69.95; H, 7.00; N, 8.56. Found: C, 69.92; H, 6.79; N, 8.58. IR (KBr) cm^{-1}: 3240, 2940, 1661. NMR (DMSO-d_6, DSS) δ: 1.14 (3H, t, $J=7.5$ Hz), 2.13 (3H, s), 2.26 (3H, s), 2.45 (6H, s), 2.55 (2H, q, $J=7.5$ Hz), 6.68 (1H, s), 7.65 (1H, s), 8.33 (1H, s), 9.95 (1H, s), 10.10 (1H, s).

Hydrolysis of Compound 5g with 80% H_2SO_4——A solution of compound **5g** (1 g) in 80% H_2SO_4 (10 ml) was warmed at 50° for 20 min. After cooling, the solution was poured into ice-water and the mixture was extracted with ether. The ether layer was dried over Na_2SO_4 and then concentrated to give a residue, which was purified by silica gel column chromatography. Elution with *n*-hexane–ether (2: 1) gave a crystalline substance, which was recrystallized from *n*-hexane–ether to give 2,6-dimethyl-4-hydroxybenzoic acid (**8**) as colorless needles, mp 185.5—187.5° (dec.) (lit.[8] mp 185° (dec.)). Subsequent elution with *n*-hexane–ether (1: 1) gave 3-acetyl-2,6-dimethyl-4-hydroxybenzoic acid (**9**), colorless prisms (from *n*-hexane–ether), mp 201—202° (dec.). *Anal.* Calcd for $C_{11}H_{12}O_4$ (**9**): C, 63.45; H, 5.81. Found: C, 63.40; H, 5.86. IR (KBr) cm^{-1}: 3600—2400, 1690. NMR ($CDCl_3$–CD_3COCD_3) δ: 2.28 (6H, s), 2.50 (3H, s), 6.67 (1H, s), 7.5—9.0 (2H, bs). MS *m/e*: 208 (M^+).

The ether solution was subjected to thin-layer chromatography, and 3,5-dimethylphenol (**7**) was detected by comparison of its *Rf* value with that of an authentic specimen. The aqueous layer was neutralized with Na_2CO_3 and the mixture was extracted with ether. The ether solution afforded the amine **1g.**

Hydrolysis of Compound 5g with 10% HCl——A suspension of compound **5g** (1.4 g) in 10% HCl (30 ml) was refluxed for 13 hr. Acetic acid and CO_2 gas were detected during refluxing. The reaction mixture was cooled to room temperature, and was extracted with ether. The ether layer was dried and concentrated to give 0.3 g of 3,5-dimethylphenol (**7**). The aqueous layer was made alkaline with Na_2CO_3, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution gave the amine **1g**.

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