[Chem. Pharm. Bull. 28(10)2892—2899(1980)]

Stable Sulfur Ylides. VIII.[1] The Reactions of 1,3-Oxazin-4-one Derivatives

Toshio Kinoshita, Yutaka Sasada, Mitsuaki Watanabe, and Sunao Furukawa

Faculty of Pharmaceutical Sciences, Nagasaki University[2]

(Received March 18, 1980)

6-Methyl-5-methylthio-2-[2(1*H*)-quinolylidene]methyl-1,3-oxazin-4-one (**1**) was treated with acid to give 4-methyl-5-methylthio-3-[2(1*H*)-quinolylidene]pyridine-2,6(1*H*,3*H*)-dione (**2**) in good yield. Similarly, 2-aminopyridine derivatives (**7a**—**e**) were obtained by the reaction of **1** with various amines. On the thermolysis of **1**, 3-methylthio-2-[2(1*H*)-quinolylidene]-3,5-dioxohexanitrile (**12**) was obtained. When **1** was treated with trifluoroacetic anhydride, a trifluoroacetyl group was introduced at the active methine moiety of **1**. No ring conversion occurred in the reaction of 6-methyl-5-methylthio-2-[2(1*H*)-quinolylidene-2-quinolyl]methyl-1,3-oxazin-4-one (**13**) with various reagents, whereas ring cleavage of the 1,3-oxazine ring of **13** was observed. Dimethylsulfonium acetyl-N-phenylcarbamoylmethylide (**18**) was treated with quinoline 1-oxide and acetyl chloride to give 4-methyl-3-methylthio-1-phenyl-5-[2(1*H*)-quinolylidene]pyridine-2,6(1*H*,5*H*)-dione (**20**) instead of the 1,3-oxazin-4-one derivative (**19**).

Keywords——stable sulfur ylides; 1,3-oxazin-4-ones; pyridine-2,6(1*H*,3*H*)-diones; quinolylpyridines; thermolysis; ring isomerization; UV; ^{1}H-NMR; high resolution MS

There are many reports on the syntheses and reactions of 1,3-oxazin-4-one derivatives.[3] In general, 1,3-oxazin-4-ones are converted to other heterocyclic ring systems upon treatment with acids, amines, bases, enamines, and so on. Therefore oxazine derivatives are potentially useful synthetic intermediates for heterocycles.

In the previous paper[1] of this series, we reported that 1,3-oxazin-4-one derivatives (**1** and **13**) were obtained by the reaction of dimethylsulfonium acetylcarbamoylmethylide with quinoline 1-oxide in the presence of acetyl chloride. In this paper we describe some reactions of these compounds.

6-Methyl-5-methylthio-2-[2(1*H*)-quinolylidene]methyl-1,3-oxazin-4-one (**1**) was dissolved in acetic acid and allowed to stand at room temperature overnight; red crystals (**2**) were obtained in nearly quantitative yield (Chart 1). The molecular formula of **2** was confirmed to be $C_{16}H_{14}N_2O_2S$ by elemental analysis and mass spectrometry (MS), and it was assumed to be a pyridine-2,6(1*H*,3*H*)-dione derivative on the basis of Kato's report.[3d] Compound **2** was desulfurized to 4-methyl-3-[2(1H)-quinolylidene]pyridine-2,6(1*H*,3*H*)-dione (**4**), and **4** was also prepared by another route *via* the 5-cyano derivate **5**. The compound **5** was obtained by the

1) Part VII: T. Kinoshita, T. Onoue, M. Watanabe, and S. Furukawa, *Chem. Pharm. Bull.*, **28**, 795 (1980).
2) Location: *1-14 Bunkyo-machi, Nagasaki 852, Japan.*
3) *a*) R.N. Lacey, *J. Chem. Soc.*, **1954**, 839, 845; *b*) R.N. Lacey and W.R. Ward, *ibid.*, **1958**, 2134; *c*) T. Kato and Y. Yamamoto, *Chem. Pharm. Bull.*, **15**, 1334 (1967); *d*) T. Kato, H. Yamanaka, Y. Yamamoto, and M. Kondo, *Yakugaku Zasshi*, **92**, 886 (1972); *e*) S. Ahmed, R. Lofthous, and G. Shaw, *J. Chem. Soc., Chem. Comm.*, **1974**, 959; *f*) T. Kato, Y. Yamamoto, and M. Kondo, *Heterocycles*, **3**, 293 (1975); *g*) *Idem, Chem. Pharm. Bull.*, **23**, 1873 (1975); *h*) I. Matsuda, S. Yamamoto, and Y. Ishii, *J. Chem. Soc., Perkin I*, **1976**, 1523; *i*) A. Maujean and J. Chuche, *Tetrahedron Lett.*, **1976**, 2905; *j*) G. Jaeger and J. Wenzelburger, *Ann. Chem.*, **1976**, 1689; *k*) T.H. Koch, R.H. Higgins, and H.F. Schuster, *Tetrahedron Lett.*, **1977**, 431; *l*) Y. Yamamoto, Y. Azuma, and T. Kato, *Heterocycles*, **6**, 1610 (1977); *m*) Y. Yamamoto and Y. Azuma, *ibid.*, **6**, 1817 (1977); *n*) *Idem, ibid.*, **9**, 185 (1978); *o*) Y. Yamamoto, Y. Azuma, and K. Miyakawa, *Chem. Pharm. Bull.*, **26**, 1825 (1978); *p*) T. Kato, Y. Yamamoto, and N. Katagiri, "The Chemistry of Heterocycles," Vol. 5, ed. by T. Kametani, T. Kato, and H. Yamanaka, Nankodo, Tokyo, 1980, p. 225.

reaction of quinoline 1-oxide and 3-cyano-4-methylpyridine-2,6(1*H*,3*H*)-dione[4] (**6**), which is an active methylene compound useful for syntheses of dyestuffs.[5] The ultraviolet (UV) spectrum of **2** was similar to that of **4** (Fig. 1), and therefore **2** was concluded to be 4-methyl-5-methylthio-3-[2(1*H*)-quinolylidene]pyridine-2,6(1*H*,3*H*)-dione. Compound **2** was also obtained by the treatment of **1** with mineral acid or sodium hydroxide, and was sufficiently acidic to form a stable salt with pyrrolidine. When **2** was treated with acetic anhydride, a remarkable color change was observed, *i.e.*, the reddish **2** was converted to a colorless compound **3**. This color change could be explained as being due to a structure change from quinolylidene-pyridone type to quinolyl-pyridine. Many tautomers of **2** can be considered, but it seems to exist predominantly as quinolylidene forms, judging from the infrared (IR) and UV spectral data (see "Experimental").

When **1** was treated with primary or secondary amines, the corresponding amino derivatives (**7a—e**) were obtained, with ring conversion (Table I). The spectral data for these amino derivatives are consistent with the proposed pyridine structure rather than pyrimidines

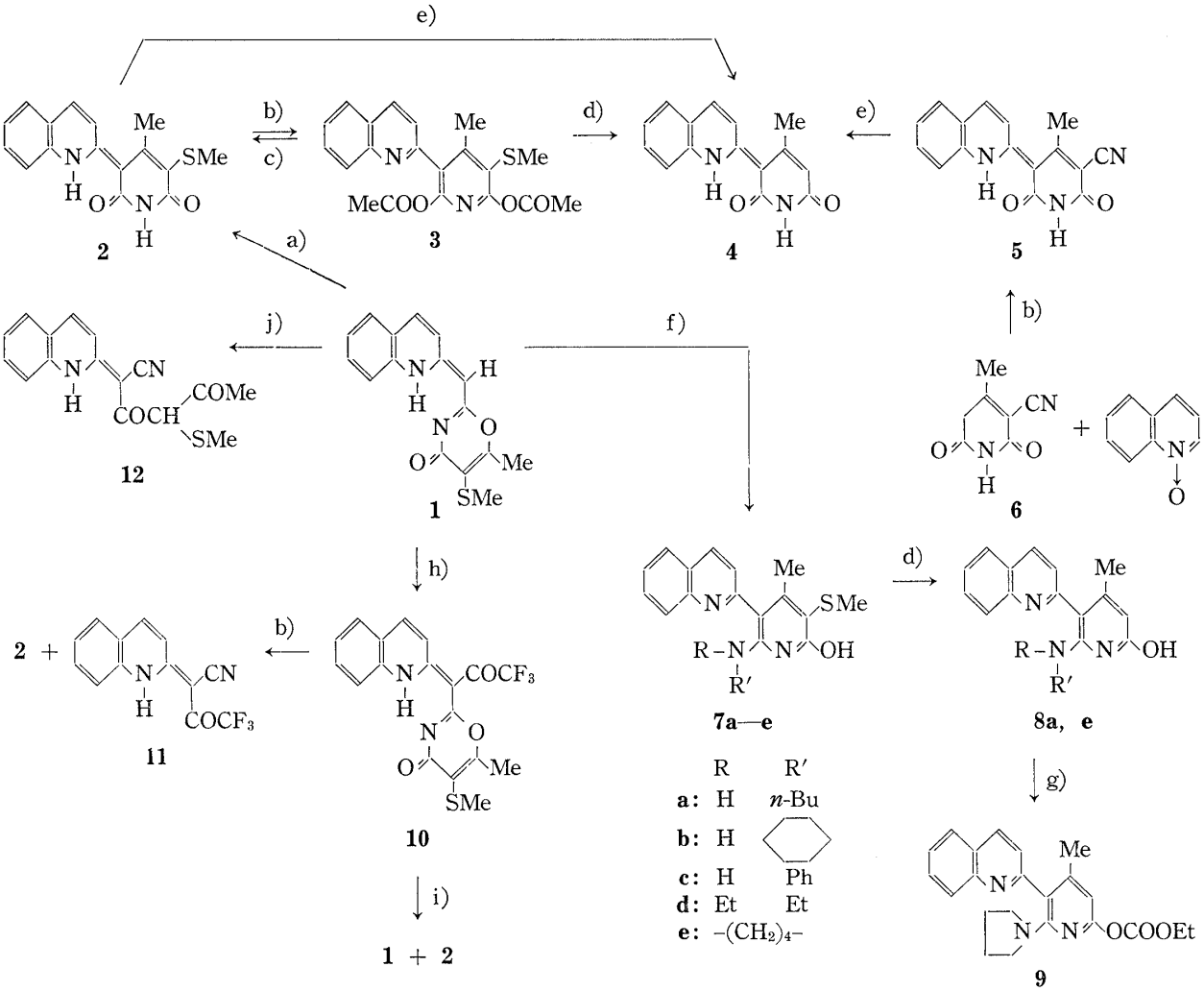

Chart 1

4) J.M. Bobbit and D.A. Scola, *J. Org. Chem.*, **25**, 560 (1960).
5) There are many patents, for example, A.M. Renfed and E. Young, Ger. Offen., 2215497; *Chem. Abst.*, **78**, 17603 (1973); J. Ribka and E. Heinrich, Ger. Offen., 2120095; *Chem. Abst.*, **78**, 45034 (1973).

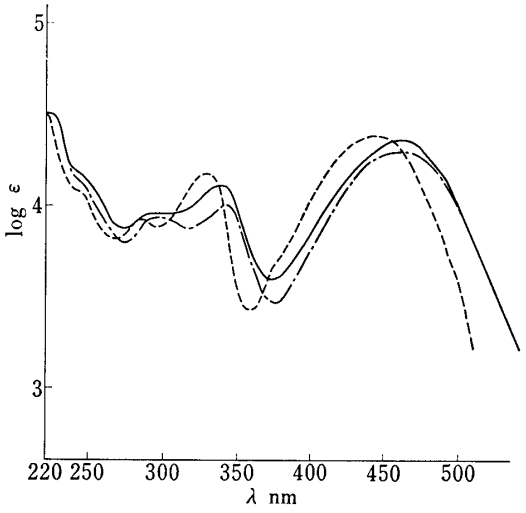

Fig. 1. UV spectra of **2** (——), **4** (------), and **20** (—·—·)

(Table III). The treatment of **1** with an enamine [1-(1-cyclohexenyl)pyrrolidine] gave **7e** insted of pyrindine derivatives.[3f] **7e** was treated with Raney nickel, followed by ethyl chloroformate to give **9**. Compound **1** appears to show characteristic reactivity towards primary amines, giving pyridine derivatives as products. Other 1,3-oxazin-4-one derivatives were converted to pyrimidines under similar conditions.[3a,c-e]

In the previous paper,[1] it was pointed out that **1** contains an active methine moiety, judging from the nuclear magnetic resonance (NMR) spectra and the result of reaction with methyl iodide or quinoline 1-oxide. Further chemical evidence is presented here. When **1** was treated with trifluoroacetic anhydride at room temperature, a yellow compound **10** was obtained in 47% yield. The molecular formula of **10** was confirmed to be $C_{18}H_{13}F_3N_2O_3S$ by high resolution mass spectrometry (HRMS), and the structure was presumed to be 6-methyl-5-methylthio-2-[2-oxo-1-[2(1*H*)-quinolylidene]-3,3,3-trifluoropropyl]-1,3-oxazin-4-one, cor-

Table I. Reactions of **1** with Various Amines and Some Properties of **7a—e**

1 (mg)	Amine (ml)	Reaction Temp. (°C) Time (hr)	Reaction Product **7**	mp (°C)	Yield mg (%)
300	*n*-Butylamine 1.0	r.t.[a] 1/12	**7a**	176—177	300(85)
300	Cyclohexylamine 2.0	r.t.[a] 19	**7b**	213—214	170(45)
300	Aniline 2.0	r.t.[a] 48	**7c**	246—247	200(54)
300	Diethylamine 2.0	Reflux 7	**7d**	234—235 (dec.)	200(57)
300	Pyrrolidine 2.0	r.t.[a] 24	**7e**	235—236	100(29)

	Appearance Recryst. Solvent	Formula	Analysis (%) Calcd (Found) C	H	N	S
7a	Yellow plates Acetone	$C_{20}H_{23}N_3OS$	67.96 (67.78	6.56 6.47	11.89 11.73	9.07 8.94)
7b	Yellow plates Acetone	$C_{22}H_{25}N_3OS$	69.43 (69.42	6.64 6.66	11.07 10.91	8.45 8.32)
7c	Pale yellow Needles Acetone–MeOH	$C_{22}H_{19}N_3OS$	70.75 (70.81	5.13 5.02	11.25 11.28	8.59 8.76)
7d	Pale yellow Needles MeOH	$C_{20}H_{23}N_3OS$	67.96 (67.85	6.56 6.59	11.89 11.77	9.07 8.90)
7e	Pale yellow Plates Acetone–MeOH	$C_{20}H_{21}N_3OS$	68.35 (68.35	6.02 6.00	11.96 11.92	9.12 8.92)

a) r.t., room temperature.

responding to substitution of a trifluoroacetyl group at the active methine site of **1**. The MS fragmentation pattern of **10** (Table II) was very similar to that of **1**.[1] The reaction of **10** with acetic anhydride at 100° gave **2** and 4,4,4-trifluoro-2-[2(1*H*)-quinolylidene]-3-oxobutanenitrile (**11**). The UV spectrum and MS fragmentation pattern (Table II) of **11** were very similar to those of 2-[2(1*H*)-quinolylidenen]-3-oxobutanenitrile.[1] The trifluoroacetyl moiety in **10** was easily removed by refluxing in ethanol to give **1** accompanied by **2**.

On the thermolysis of **1** at 200°, a rearrangement product **12** was obtained. The structure was confirmed to be 3-methylthio-2-[2(1*H*)-quinolylidene]-3,5-dioxohexanitrile by elemental analysis and spectroscopic examination; in paticular, the UV spectrum and MS (Fig. 2) were similar to those of 2-[2(1*H*)-quinolylidene]-3-oxobutanenitrile.[1]

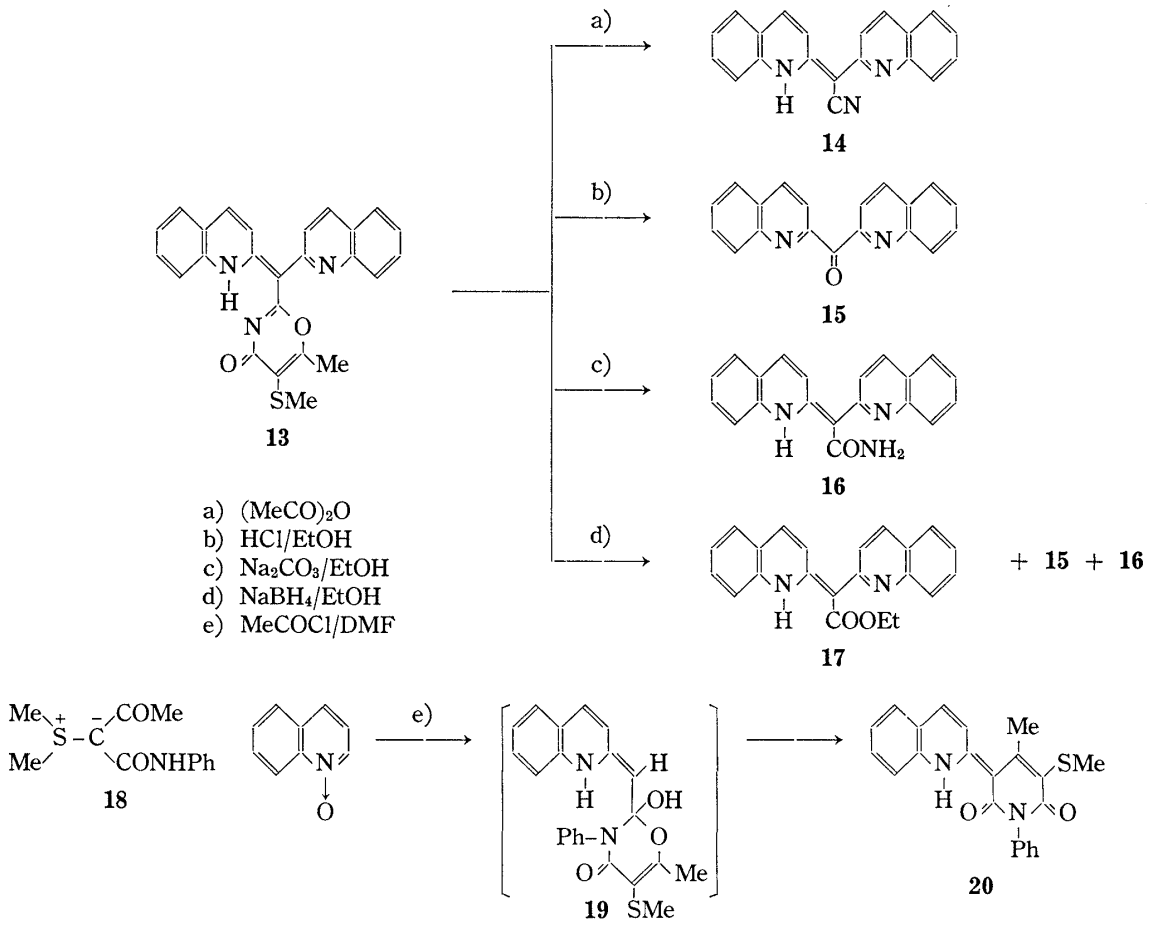

Chart 2

The reaction of 6-methyl-5-methylthio-2-[2(1*H*)-quinolylidene-2-quinolyl]methyl-1,3-oxazin-4-one (**13**) with acetic anhydride gave [2(1*H*)-quinolylidene-2-quinolyl]acetonitrile (**14**); this is analogous to the reaction of **1** with acetic anhydride.[1] However the treatment of **13** with hydrochloric acid in ethanolic solution gave a decomposition product, bis(2-quinolyl)-ketone (**15**) instead of leading to ring isomerization. It appeared that ring isomerization occurred if the compound had a mobile moiety such as hydrogen or a trifluoroacetyl group on the ylidene moiety. [2(1*H*)-Quinolylidene-2-quinolyl]acetamide (**16**) was obtained when **13** was treated with sodium carbonate. Attempted partial hydrogenation of **13** with sodium borohydride failed, giving three decomposition products (**15**, **16**, and **17**).

When dimethylsulfonium acetyl-N-phenylcarbamoylmethylide (**18**) reacted with quinoline 1-oxide in N,N-dimethylformamide (DMF) in the presence of acetyl chloride, **19** was expected, to be formed. However, 4-methyl-3-methylthio-1-phenyl-5-[2(1*H*)-quinolylidene]pyridine-

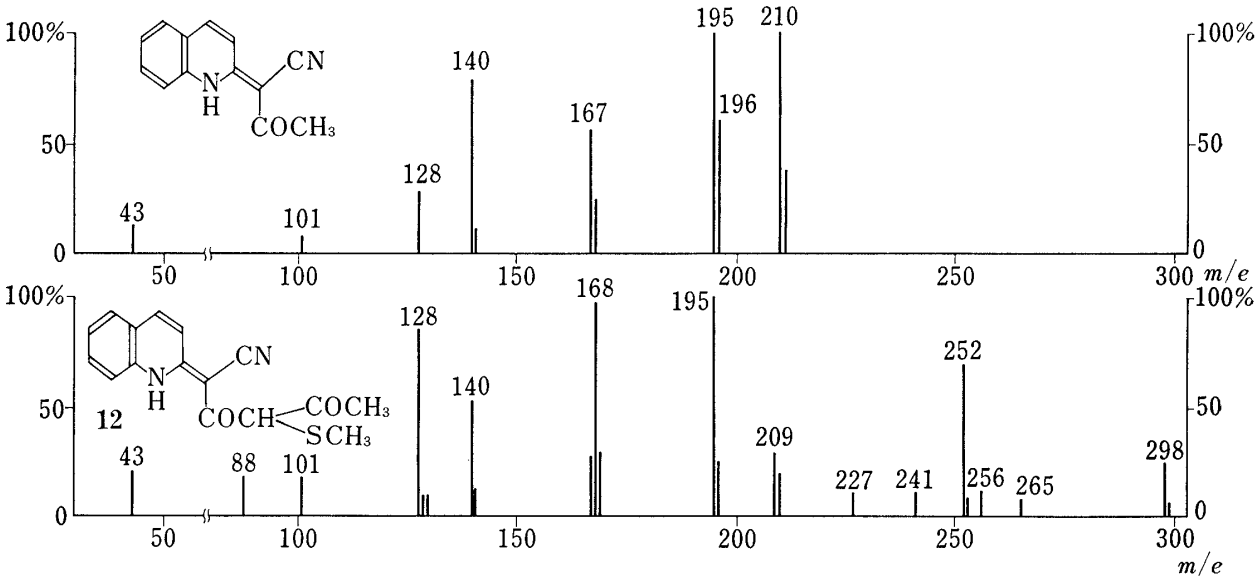

Fig. 2. Mass Spectra of 2-[2(1*H*)-Quinolylidene]-3-oxobutanenitrile and **12**

Table II. High Resolution Mass Spectral Data for **10** and **11**

Formula	Calcd	**10**		**11**	
		Found	Intensity (%)	Found	Intensity (%)
$C_{13}H_7F_3N_2O$	264.051	264.047	100	264.048	24
$C_{12}H_7N_2O$	195.056	195.059	64	195.057	100
$C_{11}H_7N_2$	167.061	167.058	62	167.060	25
$C_{10}H_6N$	140.050	140.050	31	140.047	45
$C_5H_6N_2O$	130.009	130.007	21	—	—
C_9H_6N	128.050	128.049	31	128.050	11
C_3H_4OS	87.998	88.000	77	—	—

2,6(1*H*,5*H*)-dione (**20**) was obtained directly. The structure of **20** was confirmed by elemental analysis and by the similarity of the UV spectrum to that of **2** (Fig. 1). Under the reaction conditions employed, **19** seems to be unstable.

Experimental

All melting points are uncorrected. IR spectra were taken on a JASCO IRA-2 spectrophotometer. UV spectra were taken on a Hitachi 323 spectrophotometer. NMR spectra were recorded on a JEOL JNM-PS-100 spectrometer, using tetramethylsilane as an internal standard. MS were taken on a JEOL JMS-01-SG spectrometer and HRMS were calculated with a JEOL JMD-2C microphotometer and a JEOL JEC-6 spectrum computer.

4-Methyl-5-methylthio-3-[2(1*H*)-quinolylidene]pyridine-2,6(1*H*,3*H*)-dione (**2**)——a) A solution of **1** (100 mg) in AcOH (2 ml) was allowed to stand at room temperature overnight, then excess AcOH was evaporated off *in vacuo*. The residue was diluted with H_2O, and the separated reddish-brown crystals were collected and recrystallized from MeOH to give 90 mg (90%) of **2** as red prisms, mp 249—250° (dec.). *Anal.* Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39; S, 10.75. Found: C, 64.49; H, 4.62; N, 9.14; S, 10.58. IR (KBr) cm^{-1}: 1650 (sh), 1630 (sh), 1610. UV λ_{max}^{EtOH} nm (log ε): 223 (4.52), 245 (4.18, sh), 290 (3.96, sh), 340 (4.12), 460 (4.38). MS *m/e*: 298 (M^+). NMR (trifluoroacetic acid (TFA)) δ: 2.34 (3H, s), 2.70 (3H, s), 8.0—8.5 (5H, m), 9.17 (1H, d, J=8.2 Hz).

b) A solution of **1** (600 mg, 2 mmol) in MeOH (40 ml, HCl-saturated) was refluxed for 7 hr. After removal of the solvent, H_2O was added to the residue, then this was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from MeOH to give 360 mg (60%) of **2** as red prisms, mp 249—250° (dec.).

c) A mixture of **1** (300 mg, 1 mmol), EtOH (45 ml), and 10% KOH (6 ml) was refluxed for 10 hr. After removal of the solvent, the residue was suspended in H_2O. On acidification with AcOH, the crystals become reddish-brown. This was extracted with $CHCl_3$, then the extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from MeOH to give 100 mg (33%) of **2** as red prisms, mp 249—250° (dec.).

d) A mixture of **3** (200 mg, 0.52 mmol), MeOH (15 ml), and 10% NaOH (15 ml) was heated at 95° for 2 hr. After removal of the solvent, the residue was acidified with 10% HCl, then this solution was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from MeOH to give 150 mg (96%) of **2**, mp 249—250° (dec.).

2,6-Diacetoxy-4-methyl-5-methylthio-3-(2-quinolyl)pyridine (3)——A mixture of **2** (300 mg, 1 mmol) and Ac_2O (5 ml) was heated at 130° for 6 hr. After removal of the solvent, the residue was made alkaline with 10% Na_2CO_3, then extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from ether to give 120 mg (31%) of **3** as colorless cubes, mp 135—136°. *Anal.* Calcd for $C_{20}H_{18}N_2O_4S$: C, 62.82; H, 4.75; N, 7.33; S, 8.38. Found: C, 62.56; H, 4.68; N, 7.14; S, 8.16. IR (KBr) cm^{-1}: $\nu_{C=O}$ 1770. UV λ_{max}^{EtOH} nm (log ε): 235 (4.63), 280 (3.92), 318 (3.68). MS *m/e*: 382 (M^+), 340 (M—$COCH_2$). NMR ($CDCl_3$) δ: 1.92 (3H, s), 2.32 (3H, s), 2.39 (3H, s), 2.46 (3H, s), 7.4—8.4 (6H, m).

4-Methyl-3-[2(1*H*)-quinolylidene]pyridine-2,6(1*H*,3*H*)-dione (4)——a) Preparation from **3**: A mixture of **3** (200 mg, 0.53 mmol) and Raney nickel W-2 (6 ml) in EtOH (10 ml) was refluxed for 9 hr. After filtration of the reaction mixture, the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ and chromatographed on a silica gel column. The crystals obtained from the $CHCl_3$–MeOH (3: 1) eluate were recrystallized from $CHCl_3$–MeOH (2: 1) to give 120 mg (91%) of **4** as reddish-orange flakes, mp 288—290°. *Anal.* Calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.27; H, 4.75; N, 11.04. IR (KBr) cm^{-1}: 1650 (sh), 1630 (sh), 1615. UV λ_{max}^{EtOH} nm (log ε): 244 (4.08, sh), 284 (3.93), 333 (4.20), 445 (4.40). MS *m/e*: 252 (M^+). NMR (TFA) δ: 2.48 (3H, s), 6.56 (1H, s), 7.9—8.7 (5H, m), 9.14 (1H, d, J=8 Hz).

b) Preparation from **2**: A solution of **2** (500 mg, 1.7 mmol) in 48% HBr (10 ml) was refluxed for 6 hr. The reaction mixture was concentrated *in vacuo*. The residue was diluted with H_2O and made alkaline with 10% Na_2CO_3, then this solution was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from MeOH to give 200 mg (47%) of **4**, mp 288—290°.

c) Preparation from **5**: A solution of **5** (200 mg, 0.7 mmol) in 48% HBr (2 ml) was refluxed for 10 hr. The reaction mixture was treated according to method b), providing 100 mg (55%) of **4**, mp 288—290°.

Preparation of the Pyrrolidinium Salt of 2——A mixture of **2** (300 mg, 1 mmol) and pyrrolidine (10 ml) was heated at 80° for 6 hr. After evaporating off excess pyrrolidine, the residue was recrystallized from ether to give the salt of **2** as yellowish-brown cubes, mp 228—229°. *Anal.* Calcd for $C_{16}H_{14}N_2O_2S \cdot C_4H_9N$: C, 65.01; H, 6.27; N, 11.37; S, 8.68. Found: C, 64.73; H, 6.26; N, 11.22; S, 8.68. This salt was treated with 10% HCl and the resulting crystals were shown to be identical with **2**, by IR comparison.

Table III. Spectral Data for **7a—e**

	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)	NMR (DMSO-d_6) δ	
7a	1650 (sh)	229(4.65)	0.84 (3H, t, J=7 Hz)	7.05 (1H, t, J=6 Hz)
	1617	278(4.02, sh)	1.36 (4H, m)	7.50 (1H, d, J=8 Hz)
		348(4.22)	2.18 (3H, s)	7.6—8.1 (4H, m)
		380(4.05, sh)	2.22 (3H, s)	8.39 (1H, d, J=8 Hz)
			3.24 (2H, q, J=6 Hz)	
7b	1640 (sh)	228(4.65)	1.0—1.9 (11H, m)	8.39 (1H, d, J=8 Hz)
	1620	282(4.01)	2.17 (3H, s)	12.8 (1H, b)
		349(4.20)	2.28 (3H, s)	
		380(4.10, sh)	3.9 (1H, b)	
			7.4—8.1 (5H, m)	
7c	1640 (sh)	229(4.67)	2.25 (3H, s)	8.85 (1H, s)
	1630 (sh)	320(4.12, sh)	2.29 (3H, s)	11.1 (1H, b)
	1623	360(4.30)	6.8—8.2 (10H, m)	
			8.42 (1H, d, J=8.5 Hz)	
7d	1630 (sh)	228(4.67)	0.78 (6H, t, J=7 Hz)	7.44 (1H, d, J=8 Hz)
	1610	320(4.01, sh)	2.11 (3H, s)	7.5—8.1 (4H, m)
		350(4.24)	2.25 (3H, s)	8.35 (1H, d, J=8 Hz)
			2.90 (4H, q, J=7 Hz)	11.8 (1H, b)
7e	1630 (sh)	231(4.68)	1.54 (4H, m)	7.51 (1H, d, J=8.5 Hz)
	1607	259(4.18)	2.02 (3H, s)	7.6—8.1 (4H, m)
		306(3.85, sh)	2.14 (3H, s)	8.34 (1H, d, J=8.5 Hz)
		321(3.96)	2.84 (4H, m)	10.2 (1H, b)

5-Cyano-4-methyl-3-[2(1*H*)-quinolylidene]pyridine-2,6(1*H*,3*H*)-dione (**5**)——Compound **6** (3.0 g, 20 mmol) was added to a solution of quinoline 1-oxide (2.9 g, 20 mmol) in Ac_2O (40 ml) with stirring at room temperature. The mixture was kept at room temperature for 18 hr, then the separated crystals were collected. The filtrate was concentrated *in vacuo* and the second crop was collected. The crops were combined and recrystallized from N,N-dimethylformamide to give 1.1 g (20%) of **5** as red flakes, mp *ca.* 355°. *Anal.* Calcd for $C_{16}H_{11}N_3O_2$: C, 69.30; H, 4.00; N, 15.16. Found: C, 68.90; H, 3.97; N, 14.98. IR (KBr) cm^{-1}: $\nu_{C\equiv N}$ 2190, $\nu_{C=O}$ 1650—1620 (broad).

Reaction of 1 with Various Amines (Table I)——The following reaction of **1** with *n*-butylamine illustrates the general procedure. *n*-Butylamine (1 ml) was added to **1** (300 mg, 1 mmol) at room temperature; as **1** was dissolved, the solution changed to a yellow paste. The mixture was kept at room temperature for 10 min and then was washed with ether. The insoluble crystalline mass was collected and recrystallized from acetone to give 300 mg (85%) of **7a** as yellow plates, mp 176—177° (spectral data are summarized in Table III).

Hydrochloride of 7a——A mixture of **7a** (300 mg, 0.85 mmol), EtOH (5 ml), and 10% HCl (10 ml) was refluxed for 13 hr. After cooling, the separated red crystals were collected and recrystallized from MeOH–acetone to give 200 mg (60%) of **7a**·HCl as orange prisms. *Anal.* Calcd for $C_{20}H_{23}N_3OS\cdot HCl$: C, 61.60; H, 6.20; N, 10.78; S, 8.22; Cl, 9.09. Found: C, 61.38; H, 6.23; N, 10.55; S, 8.12; Cl, 9.13. This salt was treated with 10% Na_2CO_3 and the resulting crystals were shown to be identical with **7a**, by mixed melting point determination and IR comparison.

Desulfurization of 7——a) A mixture of **7a** (300 mg, 0.85 mmol) and Raney nickel W-2 (10 ml) in EtOH (25 ml) was refluxed for 5 hr. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo*, and the residue was recrystallized from ether to give 200 mg (77%) of **8a** as yellow needles, mp 134—135°. *Anal.* Calcd for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.64. Found: C, 74.31; H, 6.88; N, 13.69. NMR ($CDCl_3$) δ: 0.92 (3H, t, $J=7$ Hz), 1.56 (4H, m), 2.22 (3H, s), 3.40 (2H, q, $J=7$ Hz), 5.78 (1H, s), 7.4—8.4 (7H, m).

b) A mixture of **7e** (300 mg, 0.85 mmol) and Raney nickel W-2 (30 ml) in EtOH (30 ml) was refluxed for 5 hr. Subsequent treatment was the same as in method a). The residue was recrystallized from AcOEt to give 180 mg (67%) of **8e** as pale yellow prisms, mp 229°. *Anal.* Calcd for $C_{19}H_{19}N_3O\cdot 1/2H_2O$: C, 72.59; H, 6.41; N, 13.37. Found: C, 72.56; H, 6.16; N, 13.35. MS *m/e*: 305 ($M^+-1/2H_2O$). NMR (DMSO-d_6) δ: 1.56 (4H, m), 1.84 (3H, s), 2.88 (4H, m), 5.80 (1H, s), 7.4—8.4 (6H, m).

6-(Ethoxycarbonyl)oxy-4-methyl-2-(1-pyrrolidinyl)-3-(2-quinolyl)pyridine Hydrochloride (**9**)——A mixture of **8e** (200 mg, 0.64 mmol) and ethyl chloroformate (4 ml) was heated at 80° for 2 hr. The separated long yellow needle crystals were collected (280 mg) and recrystallized from acetone to give 190 mg (63%) of **9** as yellow needles, mp 171—172°. *Anal.* Calcd for $C_{23}H_{25}N_3O_3S\cdot HCl\cdot 1/2H_2O$: C, 58.90; H, 5.80; N, 8.96; S, 6.84; Cl, 7.56. Found: C, 58.98; H, 5.60; N, 8.87; S, 6.95; Cl, 7.47. IR (KBr) cm^{-1}: 2250, 1988, 1760, 1630. UV λ_{max}^{EtOH} nm (log ε): 236 (4.67), 278 (4.29), 304 (4.06), 316 (3.98). MS *m/e*: 423 [M^+-(HCl and $1/2H_2O$)].

Reaction of 1 with Trifluoroacetic Anhydride (TFAA)——A solution of **1** (2.4 g, 8 mmol) and TFAA (20 ml) was allowed to stand at room temperature for 22 hr. After removing excess TFAA by evaporation, H_2O was added to the residue, and the solution was made alkaline with 5% Na_2CO_3 aq., then extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from AcOEt to give 1.5 g (47%) of **10** as yellow needles, mp 161—162°. This compound is unstable to protic solvents. *Anal.* Calcd for $C_{18}H_{13}F_3N_2O_3S$: S, 8.13. Found: S, 8.27. HRMS results are shown in Table II. IR (KBr) cm^{-1}: $\nu_{C=O}$ 1758, 1680. NMR ($CDCl_3$) δ: 2.45 (3H, s), 2.53 (3H, s), 7.5—8.5 (6H, m), 16.8 (1H, b).

Reaction of 10 with Ac_2O——A mixture of **10** (500 mg, 1.3 mmol) and Ac_2O (10 ml) was heated at 100—110° for 5 hr. After removing excess Ac_2O *in vacuo*, the residue was dissolved in MeOH and insoluble materials were filtered off. The filtrate was concentrated. The resulting crystals were recrystallized from ether to give 80 mg (24%) of **11** as yellow needles, mp 219—221° (Table II). IR (KBr) cm^{-1}: $\nu_{C\equiv N}$ 2200, $\nu_{C=O}$ 1625. UV λ_{max}^{EtOH} nm (log ε): 220 (4.63), 237 (4.23), 289 (4.26), 390 (4.28, sh), 394 (4.30). MS *m/e*: 264 (M^+). The ether-insoluble red crystals were shown to be identical with **2**, 30 mg (8%), mp 250—251° (dec.).

Ethanolysis of 10——A solution of **10** (100 mg, 0.3 mmol) in EtOH (10 ml) was refluxed for 3 hr. After removal of the EtOH, the residue was dissolved in $CHCl_3$ and the solution was chromatographed on a silica gel column. Fraction Nos. 5—14 were combined and concentrated. The residue was recrystallized from AcOEt to give **1** as the first crop, mp 190—191°, yellow needles, and **2** as the second crop, mp 250° (dec.), red prisms.

Thermolysis of 1——**1**(150 mg, 2 mmol) was heated at 200° for 5 min. The resulting material was dissolved in $CHCl_3$, and the solution was chromatographed on a silica gel column. The first fraction eluted with $CHCl_3$ was concentrated to give a red oil, which was recrystallized from acetone to give 20 mg (13%) of **12** as yellow needles, mp 135—136°. *Anal.* Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.39; H, 4.67; N, 9.37. IR (KBr) cm^{-1}: $\nu_{C=O}$ 1718, 1625. UV λ_{max}^{EtOH} nm (log ε): 222 (4.56), 241 (3.97), 293 (4.20), 400 (4.30), 415 (4.28). NMR ($CDCl_3$) δ: 2.24 (3H, s), 2.44 (3H, s), 4.80 (1H, s), 7.3—7.8 (5H, m), 8.10 (1H, d, $J=8$ Hz), 15.0 (1H, b).

Reaction of 13 with Ac_2O——A solution of **13** (100 mg, 0.24 mmol) in Ac_2O (8 ml) and AcOH (4 drops) was heated at 90—95° for 5.5 hr. After cooling, the separated crystals were collected and recrystallized from MeOH to give 30 mg (44%) of **14** as yellow needles, mp 281°. This was identical with an authentic sample[1)]

of **14** by IR comparison.

Reaction of 13 with HCl——A mixture of **13** (425 mg, 1 mmol), 10% HCl (50 ml), and EtOH (25 ml) was allowed to stand at room temperature for 26 hr. The reaction mixture was concentrated and the residue was made alkaline with 5% $NaHCO_3$ aq., then solution was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and passed through a silica gel column. After removal of the solvent, the residue was recrystallized from acetone to give 80 mg (28%) of **15** as colorless plates, mp 165—166°. This was identical with an authentic sample[6] of **15**.

Reaction of 13 with Na_2CO_3 aq.——A mixture of **13** (425 mg, 1 mmol), 3% Na_2CO_3 aq. (10 ml), and EtOH (50 ml) was stirred at room temperature for 24 hr. After removal of the solvent by evaporation *in vacuo*, the residue was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized fractionally from MeOH to give 50 mg (16%) of **16** as pale yellow needles, mp 196°. *Anal.* Calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.72; H, 4.72; N, 13.15. IR (KBr) cm^{-1}: 3360., 3170, 1685 (sh), 1660, 1653.

Reaction of 13 with $NaBH_4$——A mixture of **13** (640 mg, 1.5 mmol), $NaBH_4$ (170 mg, 4.5 mmol), and EtOH (200 ml) was stirred at room temperature for 25 hr. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was treated with 10% HCl. This solution was made alkaline with 10% Na_2CO_3, and red crystals separated. These were extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated, leaving a yellowish-brown oil. The oil was dissolved in $CHCl_3$ and chromatographed on a silica gel column. The first eluate with $CHCl_3$ was concentrated to give an oil, which was treated with 10% HCl. The resulting yellow crystals were filtered off and recrystallized from MeOH to give 120 mg (20%) of **17** (hydrochloride) as pale yellow needles, mp 216° (dec.). *Anal.* Calcd for $C_{22}H_{18}N_2O_2 \cdot 1.5HCl$: C, 66.55; H, 4.95; N, 7.06. Found: C, 67.11; H, 5.02; N, 6.82. IR (KBr) cm^{-1}: 1733, 1630 (sh), 1618. MS *m/e*: 342 ($C_{22}H_{18}N_2O_2$=M−1.5 HCl). NMR ($CDCl_3$) δ: 1.25 (3H, t, J=6.5 Hz), 3.26 (2H, q, J=6.5 Hz), 7.3—8.4 (12H, m). The fractions (Nos. 3—4) eluted with $CHCl_3$ were combined and concentrated to give a reddish-brown oil which was recrystallized from MeOH to give 30 mg (7%) of **15** as colorless needles, mp 165—166°. The 5th fraction, eluted with $CHCl_3$–MeOH (9: 1), was concentrated to give a yellow oil, which was recrystallized from MeOH to give 15 mg (3%) of **16** as pale yellow prisms, mp 195—196°.

Reaction of 18 with Quinoline 1-Oxide——A solution of AcCl (3.1 g, 40 mmol) and CCl_4 (10 ml) was added dropwise at room temperature, to a mixture of **18** (4.8 g, 20 mmol), quinoline 1-oxide (2.9 g, 20 mmol), and $CHCl_3$ (50 ml). The mixture was stirred for 4 hr. After removal of the solvent, the residue was made alkaline with 5% $NaHCO_3$ aq., then this solution was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated to about a quarter of the original volume. This solution was chromatographed on a silica gel column. The fractions eluted with $CHCl_3$–CH_3CN (10: 1) were combined and concentrated. The residue was rechromatographed on a silica gel column using $CHCl_3$–CH_3CN (10: 1). An analytical sample was recrystallized from acetone to give 700 mg (9.4%) of **20** as red prisms, mp 255°. *Anal.* Calcd for $C_{22}H_{18}N_2O_2S$: C, 70.58; H, 4.85; N, 7.58; S, 8.54. Found: C, 70.55; H, 5.11; N, 7.26; S, 8.23. IR (KBr) cm^{-1}: $\nu_{C=O}$ 1638. UV λ_{max}^{EtOH} nm (log ε): 299 (4.93), 343 (4.86), 463 (4.32). MS *m/e*: 374 (M^+). NMR ($CDCl_3$) δ: 2.36 (3H, s), 2.83 (3H, s), 7.3—8.2 (12H, m).

Acknowledgment The authors are grateful to Dr. S. Osmond deSilva of the University of Waterloo, Canada, for helpful comments and suggestions. Thank are due to Mr. K. Miyazaki for his assistance in the experimental work, to Mrs. H. Mazume for elemental analyses, and to Messrs. K. Inada, N. Yamaguchi, and M. Ohwatari for the measurements of NMR, MS, IR, and UV spectra, respectively.

6) M. Watanabe, M. Kodera, T. Kinoshita, and S. Furukawa, *Chem. Pharm. Bull.*, **23**, 2598 (1975).