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Stable Sulfur Ylides. VII.[1] The Reaction of Dimethylsulfonium Acetylcarbamoylmethylide with Quinoline 1-Oxide

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The reaction of dimethylsulfonium acetylcarbamoylmethylide (Ia) with quinoline 1-oxide in the presence of acetyl chloride in N,N-dimethylformamide gave 6-methyl-5-methylthio-2-[2(1*H*)-quinolylidene]methyl-1,3-oxazin-4-one (IIIa) and 6-methyl-5-methylthio-2-[2(1*H*))quinolylidene-2-quinolyl]methyl-1,3-oxazin-4-one (IVa). The structures of IIIa and IVa were established by chemical and spectral analysis. This is a new type of reaction of stable sulfur ylides.

Keywords——stable sulfur ylides; dimethylsulfonium acetylcarbamoylmethylide; dimethylsulfonium acetyl-N-acylcarbamoylmethylides; quinoline 1-oxide; 1,3-oxazin-4-one derivatives; ^{1}H and ^{13}C NMR; high resolution mass spectra

We have previously investigated the feasibility of reacting sulfur ylides which are stabilized by one or two electron-withdrawing substituents on the ylide carbon with aromatic amine oxides in the presence of acylating reagents, and the following results were obtained. Dimethyl(oxo)sulfonium benzoylmethylide underwent reaction with quinoline 1-oxide and isoquinoline

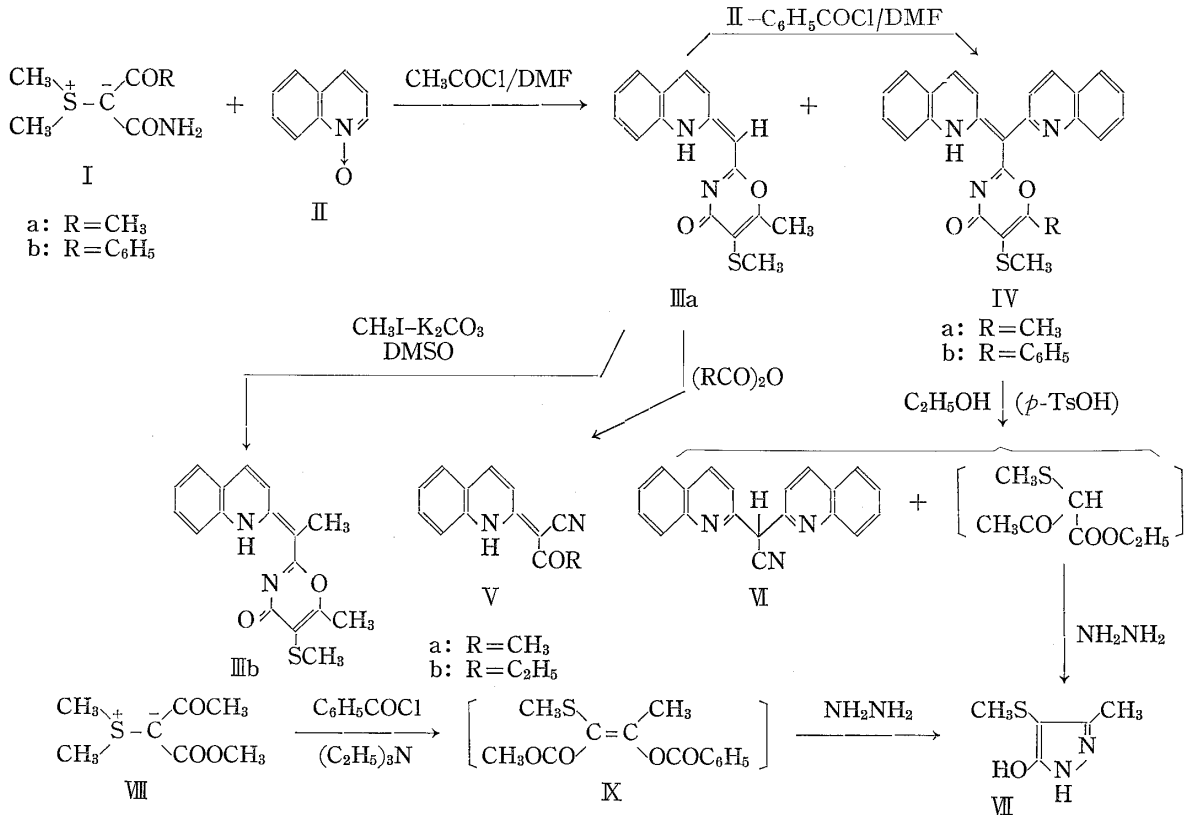


Chart 1

1) Part VI: M. Watanabe, M. Aono, T. Kinoshita, and S. Furukawa, *Yakugaku Zasshi*, **98**, 198 (1978).
2) Location: *1-14 Bunkyo-machi, Nagasaki 852, Japan.*

2-oxide in the presence of *p*-toluenesulfonyl chloride to give dimethyl(oxo)sulfonium 2-quinolylbenzoylmethylide and dimethyl(oxo)sulfonium 1-isoquinolylbenzoylmethylide, respectively.[3] The treatment of dimethylsulfonium diacetylmethylide with quinoline 1-oxide or isoquinoline 2-oxide in the presence of benzoyl chloride produced pyridoquinoline[4] or pyridoisoquinoline[1] derivatives, respectively. In analogous reactions, dimethylsulfonium acetylethoxycarbonylmethylide produced pyrroloquinoline[4] and pyrroloisoquinoline[1] derivatives when reacted with quinoline 1-oxide and isoquinoline 2-oxide, respectively.

In this paper, we report a novel reaction of dimethylsulfonium acetylcarbamoylmethylide (Ia) with quinoline 1-oxide in the presence of acetyl chloride to give 1,3-oxazin-4-ones. During this reaction acetyl chloride is involved in the 1,3-oxazin-4-one ring formation. This transformation results in the formation of a new carbon-carbon bond between the 2-position of quinoline and the terminal methyl carbon of the N-acetyl group of dimethylsulfonium acetyl-N-acetylcarbamoylmethylide, which is considered to be a key intermediate in the reaction of acetyl chloride with Ia. This is a new type of reaction of stable sulfur ylides.

The reaction of the sulfonium ylide (Ia) with quinoline 1-oxide (II) in the presence of acetyl chloride in N,N-dimethylformamide (DMF) gave two compounds, IIIa (mp 192°) and IVa (mp 292°), whose structures were established by chemical and spectral analysis.

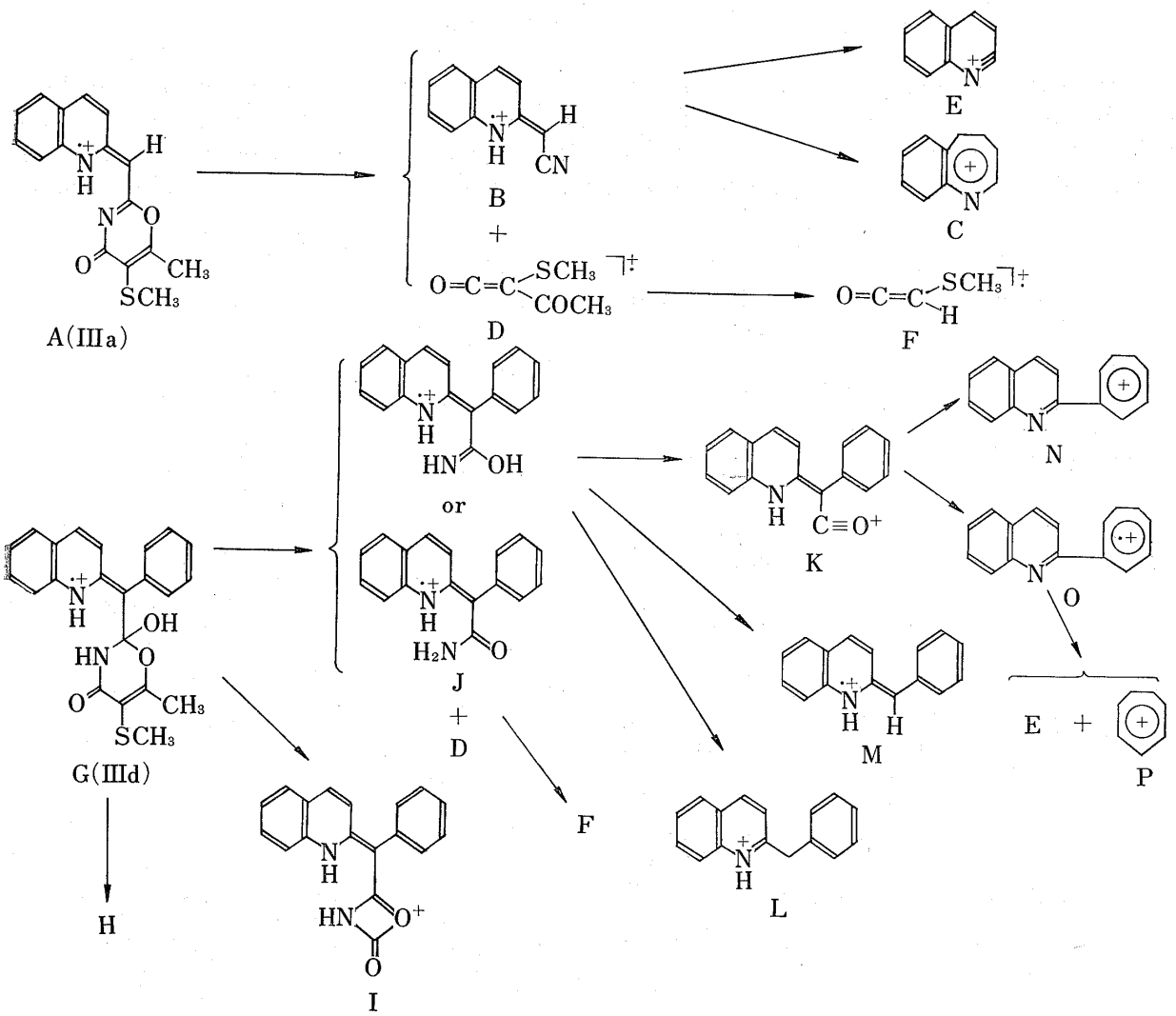


Chart 2

3) S. Furukawa, T. Kinoshita, and M. Watanabe, *Yakugaku Zasshi*, **93**, 1064 (1973).
4) M. Watanabe, M. Kodera, T. Kinoshita, and S. Furukawa, *Chem. Pharm. Bull.*, **23**, 2598 (1975).

The molecular formula of IIIa was confirmed to be $C_{16}H_{14}N_2O_2S$ by elemental analysis and high-resolution mass spectrometry (HRMS). The nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) of IIIa showed peaks at δ 2.34 (3H, singlet (s), C-CH_3), δ 2.42 (3H, s, S-CH_3), δ δ 6.81 (1H, doublet (d), J=12 Hz, quinoline C_3-H), δ 7.28—7.66 (5H, multiplet (m), aromatic protons), δ 4.94 (1H, s, disappeared on addition of D_2O), and δ 13.1 (1H, broad, disappeared on addition of D_2O). Treatment of IIIa with acetic anhydride gave Va (mp 213°).[5] Similarly, the reaction of IIIa with propionic anhydride gave Vb. The above results confirmed that the acyl groups of Va and Vb arose from the acid anhydride and that III included a skeletal 2-quinolyl-C-C-N fragment. On the other hand, MS of IIIa showed peaks at *m/e* 298 (M^+, A in Table I and Chart 2), 168 (M^+–130, B), 140 (168–28, C), 130 (M^+–168, D), 128 (quinolyl, E), and 88 (130–42), F). Of these peaks, *m/e* 168 (B) and 130 (D) were found to correspond to $C_{11}H_8N_2$ and $C_5H_6O_2S$, respectively, by HRMS (Table I). It was considered that the molecular ion underwent cleavage to the *m/e* 168 (B) and 130 (D) fragments initially. This fragmentation pattern is similar to that of 6-methyl-2-phenyl-1,3-oxazin-4-one.[6] Moreover, the fragment of *m/e* 168 (B) was further cleaved to *m/e* 140 (C) or 128 (E), and this fragment (B) was presumed to be 2-quinolylacetonitrile (or its isomer) in view of the similarity of its fragmentation pattern to that of V (see "Experimental"). The fragment of *m/e* 130 (D) was cleaved to *m/e* 88 (F) by loss of C_2H_2O. Therefore the structure of D was assumed to be ketene type (Chart 2).

Table I. High Resolution Mass Spectra of IIIa and IIId

		Formula	Relative intensity	*m/e* Calcd	*m/e* Found		Formula	Relative intensity	*m/e* Calcd	*m/e* Found
A	M^+	$C_{16}H_{14}N_2O_2S$	13	298.078	298.078	G	$C_{22}H_{20}N_2O_3S$	11	392.119	392.119
						H	$C_{21}H_{17}N_2O_3$	6	345.124	345.128
						I	$C_{18}H_{13}N_2O_2$	33	289.098	289.101
B	M^+–130	$C_{11}H_8N$	100	168.069	168.067	J	$C_{17}H_{14}N_2O$	18	262.111	262.115
						K	$C_{17}H_{12}NO$	90	246.092	246.094
						L	$C_{16}H_{14}N$	38	220.113	220.111
C		$C_{10}H_6N$	12	140.050	140.050	M	$C_{16}H_{13}N$	100	219.105	219.106
						N	$C_{16}H_{12}N$	100	218.097	218.095
						O	$C_{16}H_{11}N$	100	217.089	217.089
D	130	$C_5H_6O_2S$	26	130.009	130.007	D	$C_5H_6O_2S$	38	130.009	130.007
E		C_9H_6N	37	128.050	128.048	E	C_9H_6N	5	128.050	128.053
						P	C_7H_5	5	89.039	89.042
F		C_3H_4OS	34	87.998	88.000	F	C_3H_4OS	40	87.998	88.000

The NMR spectrum showed considerable changes when trifluoroacetic acid (TFA) was added to a solution of IIIa in chloroform-*d*. Several new peaks appeared, and the relative intensities of these new peaks increased with further addition of TFA, as shown in Fig. 1 (c and d). In particular, the signal at δ 4.85 in chloroform-*d* solution was shifted to about δ 5.6 (3) and a new signal was observed at about δ 5.0 (3′) on addition of TFA. The new signal increased in intensity, and the sum of the integral intensities of δ 5.6 and δ 5.0 increased by more than one proton unit on further addition of TFA. These phenomena can be explained in terms of the protonation of IIIa in acidic media[7] (Chart 3). The proton signals were assigned as shown in Fig. 1 (a, c, and d) and Chart 3, where the signal sources are indicated by Arabic numerals. This explanation was supported by the strong hypsochromic shift observed in the ultraviolet (UV) spectrum[8] of acidified IIIa, as shown in Fig. 2. This hypsochromic shift is clearly due to the interception of conjugation by protonation.

5) F.S. Babichev and Yu. M. Volovenko, *Khim. Geterotsikl. Soedin.*, **1975**, 1005; *Chem. Abst.*, **83**, 19301*n* (1975).
6) T.H. Koch, R.H. Higgins, and H.F. Schuster, *Tetrahedron Lett.*, **1977**, 431.
7) R. Mondelli and L. Merlini, *Tetrahedron*, **22**, 3253 (1966).
8) M. Hamana and H. Noda, *Chem. Pharm. Bull.*, **13**, 912 (1965).

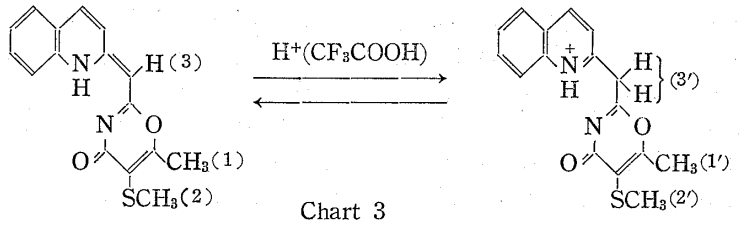


Chart 3

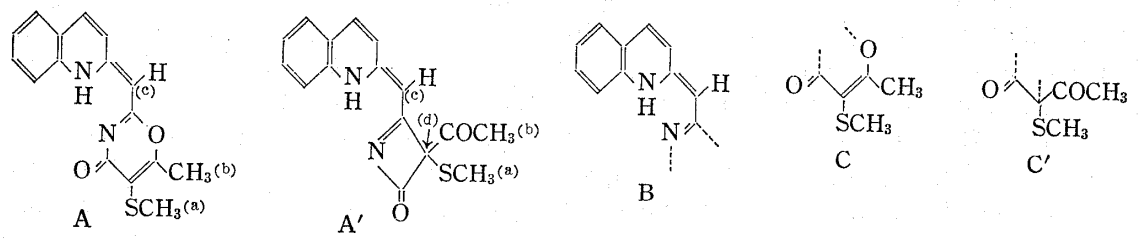


Chart 4

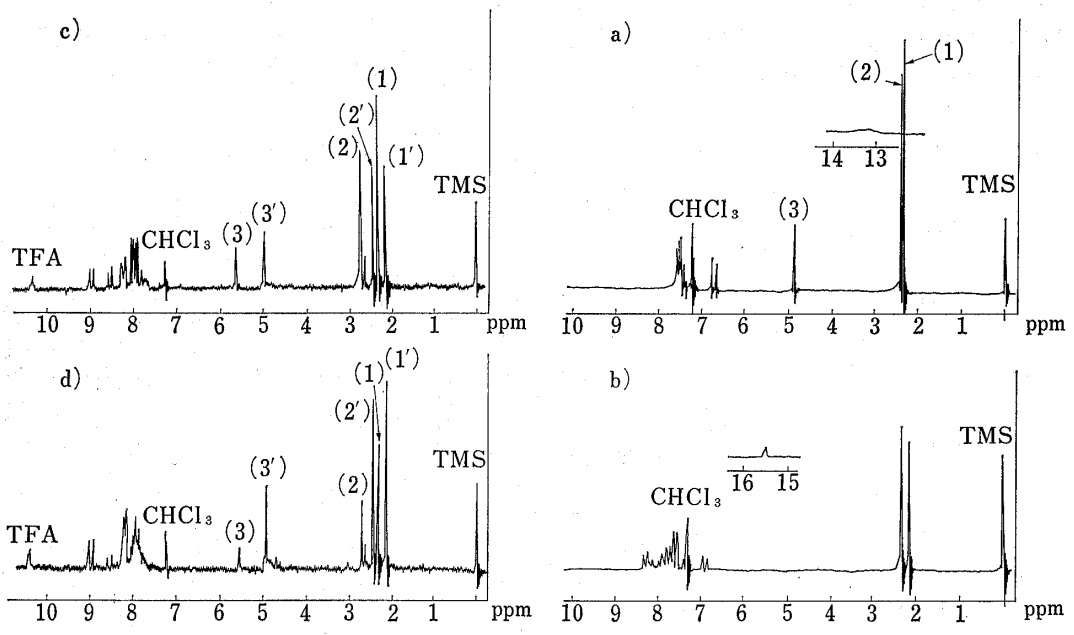


Fig. 1. NMR Spectra of IIIa and IVa

a) IIIa ($CDCl_3$). b) IVa ($CDCl_3$). c) IIIa ($CDCl_3$+TFA 6 drops). d) IIIa ($CDCl_3$+TFA 15 drops).

Based on the above results, the structure of IIIa was considered to be A or A′, composed of fragments B and C, or B and C′ (Chart 4).

The carbon-13 NMR spectrum of IIIa showed peaks at δ 165.9 (singlet), δ 163.8 (s), δ 163.5 (s), δ 112.3 (s), δ 79.4 (doublet, assigned to (c) in Chart 4), δ 18.7 (quartet, (a) or (b)), and δ 17.3 (q, (b) or (a)) in addition to the quinoline signals.[9] However, there is no signal corresponding to sp^3 carbon, shown as (d) in structure A′ (Chart 4). Therefore the structure of IIIa was confirmed to be A, 6-methyl-5-methylthio-2-[2(1*H*)-quinolylidene]methyl-1,3-oxazin-4-one.

Elemental analysis of IVa indicated the composition $C_{25}H_{19}N_3O_2S$, which corresponds to a structure in which a second molecule of quinoline is introduced into the skeleton of IIIa. The UV spectrum of IVa was very similar to that of IIIa (Fig. 2). MS of IVa gave no parent ion peak, but gave *m/e* 295 (M^+—130) as the largest ion peak produced by the electron impact ion-

9) Le. F. Johnson and W.C. Jankowski, "Carbon-13 NMR Spectra," John Wiley and Sons, Inc., New York, 1972, Spectrum Number 335.

ization method. The fragmentation pattern was similar to that of IIIa. In the MS of IVa, two main fragments (*m/e* 295 and *m/e* 130) corresponded to $C_{20}H_{13}N_3$ and $C_5H_6O_2S$, respectively, as determined by HRMS and these fragments are characteristic of 1,3-oxazin-4-one derivatives. On the other hand, the field desorption ionization method gave *m/e* 426 (M^+1, 100%) and *m/e* 295 (M–130, 45%) as the main peaks. Therefore, the initial fragmentation was considered to be as follows.

$$\underset{m/e\ 425}{C_{25}H_{19}N_3O_2S} \longrightarrow \underset{m/e\ 295}{C_{20}H_{13}N_3}^{+} + \underset{m/e\ 130}{C_5H_6O_2S}^{+}$$

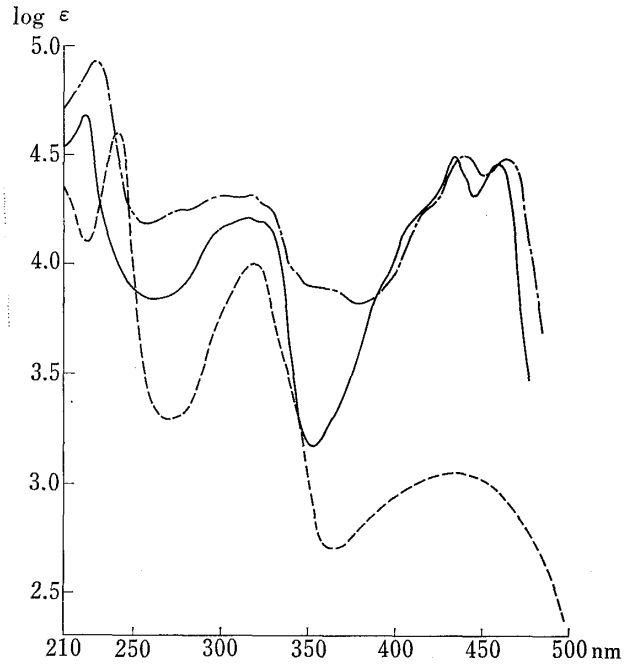


Fig. 2. Ultraviolet Spectra of IIIa (—— in EtOH, —— in pH 1.30 buffer solution) and IVa – – – – in EtOH)

When IVa was refluxed in ethanolic solution with *p*-toluenesulfonic acid as a catalyst, diquinolylacetonitrile (VI) was obtained as yellow crystals. After separation of the crystals, hydrazine hydrate was added to the mother liquor and the mixture was refluxed for a few hours. A colorless crystalline compound (mp 265° (dec.)) was obtained, which was identified as 5-hydroxy-3-methyl-4-methylthiopyrazole (VII). The identity of VII was established by its synthesis by another route. The NMR spectrum of IVa showed no peak around δ 5 corresponding to the mobile methine proton in IIIa. Therefore, the extra quinoline group should be attached to the carbon carrying this proton in IIIa. On treatment with methyl iodide and potassium carbonate or quinoline 1-oxide and benzoyl chloride, IIIb or IVb was obtained in low yield, respectively. On the bases of these results, compound IVa was presumed to be 6-methyl-5-methylthio-2-[2(1*H*)quinolylidene-2-quinolyl]methyl-1,3-oxazin-4-one.

Table II. The Reaction of Dimethylsulfonium Acetylcarbamoylmethylide(I) with Quinoline 1-Oxide

Run No.	Ylide Ia g (mmol)	Oxide II g (mmol)	Acetyl chloride g (mmol)	React. Cond.[a]	Yield of products			Molar ratio IIIa/IVa
					Total g	IIIa g (%)	IVa g (%)	
1	1.6(10)	1.45(10)	2.4(30)	1	0.96	0.90(30.2)	0.06(1.4)	17.5
2	1.6(10)	1.45(10)	1.6(20)	2	0.33	0.28(9.4)	0.05(1.2)	7.2
3	1.6(10)	1.45(10)	2.4(30)	2	0.88	0.80(26.9)	0.08(1.9)	15.0
4	1.6(10)	2.9 (20)	2.4(30)	2	0.75	0.34(11.4)	0.41(9.6)	1.2
5	1.6(10)	2.9 (20)	3.1(40)	2	0.92	0.50(16.8)	0.42(9.9)	1.7
6	1.6(10)	1.45(10)	1.6(20)	3	0.32	0.15(5.0)	0.17(4.0)	1.3
7	1.6(10)	1.45(10)	2.4(30)	3	0.34	0.12(4.0)	0.22(5.2)	0.81
8	1.6(10)	2.9 (20)	2.4(30)	3	0.53	0.02(0.7)	0.51(12.0)	0.04
9	1.6(10)	2.9 (20)	3.1(40)	3	0.62	0.01(0.4)	0.61(14.3)	0.013

a) Reaction conditions
1: Acetyl chloride was added with ice cooling, then the mixture was allowed to stand at room temperature overnight.
2: Acetyl chloride was added at room temperature (exothermic), then the mixture was allowed to stand at room temperature overnight.
3: Acetyl chloride was added at room temperature (exothermic), then the mixture was warmed at 80—90° for 15 min and allowed to stand at room temperature overnight.

In order to find optimum conditions for the reaction, various conditions were tested as shown in Table II. In general, the total yield of IIIa and IVa increased with increasing molar ratio of acetyl chloride. Compound IIIa was obtained almost exclusively at low reaction temperature (run No. 1). However the product ratio (IIIa/IVa) decreased with increasing amount of II. The yield of compound IVa rose with increasing reaction temperature and molar ratio of II (run No. 9).

When this reaction was carried out with benzoyl chloride instead of acetyl chloride as an acylating reagent, the product obtained was not a 1,3-oxazin-4-one derivative, but dimethylsulfonium acetyl-N-(2-quinolyl)carbamoylmethylide (XI), which could be hydrolyzed to 2-aminoquinoline (XII) with 10% hydrochloric acid. On the other hand, a propionyl or phenylacetyl group was introduced at the carbamoyl group, in spite of the presence of quinoline 1-oxide, by the reaction of Ia with propionyl or phenylacetyl chloride and quinoline 1-oxide. Similar reaction products (X) were obtained by the treatment of Ia with acetyl, propionyl, phenylacetyl, and *p*-nitrophenylacetyl chloride in the presence of triethylamine (Chart 5).

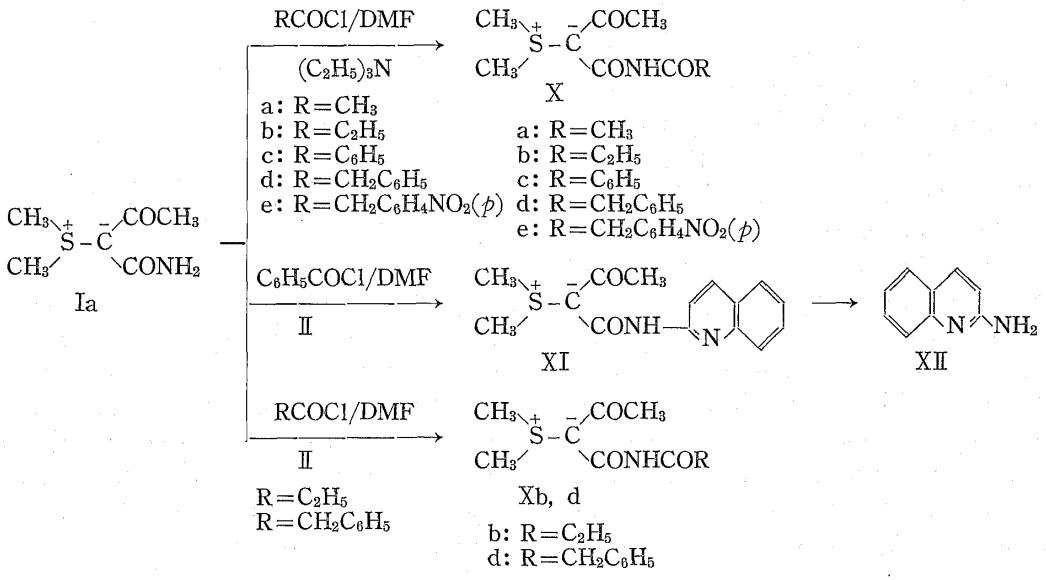


Chart 5

In order to confirm the reaction mechanism, the above N-acylylides (X) were allowed to react with quinoline 1-oxide (II) in the presence of acylating agents. Compounds Xa, Xb, Xd, and Xe gave the corresponding 1,3-oxazin-4-one derivatives. In the case of Xd, a covalent hydration product (IIId) was obtained under these reaction conditions. This compound had a melting point of 145°, and elemental analysis and HRMS indicated it to be $C_{22}H_{20}N_2O_3S$. The NMR spectrum showed three active hydrogens at δ 9.52 (1H, s, OH), δ 14.38 (1H, b, NH), and δ 15.03 (1H, s, NH). HRMS showed a characteristic 1,3-oxazin-4-one fragmentation pattern, where the molecular ion (*m/e* 392, G in Chart 2 and Table I) was cleaved to *m/e* 262 (J) and 130 (D). The fragment *m/e* 262 ($C_{17}H_{14}N_2O$, J) contained the covalent hydration region as *m/e* 130 ($C_5H_6O_2S$, D), and was the same as in the case of IIIa (Chart 2 and Table I). The structure of IIId was presumed to be 2-hydroxy-6-methyl-5-methylthio-2-[2(1*H*)-quinolylidene]benzyl-2,3-dihydro-1,3-oxazin-4-one. When Xc was treated with II in the same manner, N-benzoyl-2-methylthio-3-oxo-butylamide (XIII) was obtained. The yield of reaction products was considerably higher with acetyl and propionyl derivatives (Xa and Xb). The phenylacetyl and *p*-nitrophenylacetyl derivatives (Xd and Xe) gave decreased yields. These findings showed that at least a methyl or methylene moiety is necessary in the N-acyl group for the formation of 1,3-oxazin-4-one derivatives. However, the reaction mechanism for the formation of IIIa is not clear at this time.

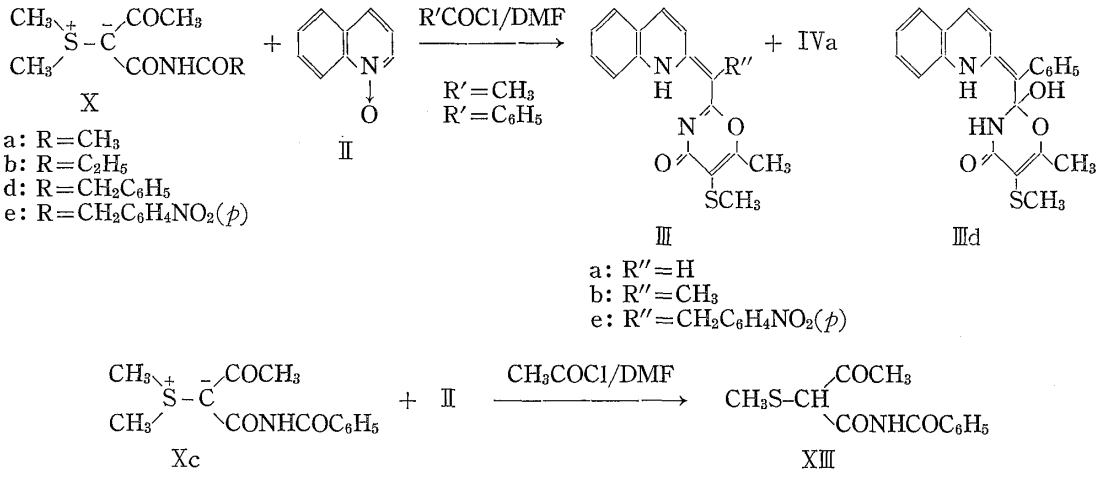


Chart 6

The present series of reactions of stable sulfur ylides with aromatic amine N-oxides shows unusual reactivity of the acetyl group, and provides a convenient means of entry into some interesting heterocyclic systems.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were taken on a JASCO IRA-2 spectrophotometer. UV spectra were taken on a Hitachi 323 spectrophotometer. NMR (proton) spectra were recorded on a JEOL JNM-PS-100, machine and NMR (C-13) spectra on a JEOL JNM-FX-60 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.

Dimethylsulfonium Acetylcarbamoylmethylide (Ia)——A solution of 50 g (0.5 mol) of acetoacetamide, 100 ml of dimethylsulfoxide, and 50 ml of acetic anhydride was allowed to stand at room temperature for 3 days. The separated crystals were collected and recrystallized from MeOH to give 56.4 g (70%) of colorless prisms, mp 207—208°. *Anal.* Calcd for $C_6H_{11}NO_2S$: C, 44.71; H, 6.88; N, 8.69. Found: C, 44.58; H, 6.74; N, 8.57. IR (KBr) cm^{-1}: $\nu_{C=O}$ 1590, 1530. UV λ_{max}^{EtOH} nm (log ε): 250 (4.20). NMR ($CDCl_3$) δ: 2.20 (3H, s), 3.02 (6H, s), 5.2 (1H, b, disappeared on addition of D_2O), 9.3 (1H, b, disappeared on addition of D_2O).

Dimethylsulfonium Benzoylcarbamoylmethylide (Ib)——A solution of benzoylacetamide (3.3 g, 20 mmol), acetic anhydride (10 ml), and dimethylsulfoxide (15 ml) was allowed to stand at room temperature for one week with stirring. The reaction mixture was concentrated to about half the original volume. The separated crystalline mass was filtered and washed with ether, then recrystallized from benzene–MeOH (or AcOEt) to give 2.6 g (58%) of colorless needles, mp 184° (dec.). *Anal.* Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27; S, 14.36. Found: C, 58.97; H, 5.88; N, 6.29; S, 14.14. IR (KBr) cm^{-1}: ν_{NH} 3300, 3140; $\nu_{C=O}$ 1620, 1595. UV λ_{max}^{EtOH} nm (log ε): 259 (4.09). NMR ($CDCl_3$) δ: 2.97 (6H, s), 5.36 (1H, b, disappeared on addition of D_2O), 7.3—7.5 (5H, m), 9.44 (1H, b, disappeared on addition of D_2O).

Reaction of Dimethylsulfonium Acetylcarbamoylmethylide (Ia) with Quinoline 1-Oxide (II)——a) Preparation of IIIa: A suspended mixture of 3.2 g (20 mmol) of Ia and 2.9 g (20 mmol) of II in 30 ml of dimethylformamide (DMF) was treated dropwise with 3.1 g (40 mmol) of acetyl chloride with stirring under ice cooling (the reaction conditions are listed in Table II). Ia gradually dissolved exothermically during the addition of acetyl chloride. About 30 min after yellowish-orange crystals began to separate, the mixture was stirred at room temperature, and this was continued overnight. The crystals were filtered off and stirred with 5% Na_2CO_3 aq. for 1 hr. This mixture was extracted with $CHCl_3$ and the extract was dried over Na_2SO_4. After removal of $CHCl_3$, the residue was recrystallized from AcOEt to give 1.8 g (30.2%) of yellowish-orange needles (IIIa), mp 191—192°. *Anal.* Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.42; H, 4.73; N, 9.39; S, 10.75. Found: C, 64.31; H, 4.65; N, 9.08; S, 10.58. IR (KBr) cm^{-1}: $\nu_{C=O}$ 1650. UV λ_{max}^{EtOH} nm (log ε): 219 (4.77), 299 (sh., 4.21), 312 (4.26), 322 (4.25), 4.15 (4.32), 432 (4.60), 461 (4.57).

b) Preparation of IVa: A suspended mixture of 1.6 g (10 mmol) of Ia and 2.9 g (20 mmol) of II in 15 ml of DMF was treated dropwise with 3.1 g (40 mmol) of acetyl chloride with stirring at room temperature, then the reaction mixture was warmed at 80—90° for 15 min on a water bath and allowed to stand at room temperature overnight. The separated crystals were filtered off and stirred with 5% Na_2CO_3 aq. for 1 hr. This mixture was extracted with $CHCl_3$ and the extract was dried over Na_2SO_4. After removal of $CHCl_3$, the residue was recrystallized from MeOH to give 0.65 g (14.3%) of yellow needles of IVa, mp 290—292°. *Anal.* Calcd for $C_{25}H_{19}N_3O_2S$: C, 70.58; H, 4.50; N, 9.88; S, 7.53. Found: C, 70.65; H, 4.39; N, 9.80; S,

7.48. UV λ_{max}^{EtOH} nm (log ε): 229 (4.94), 303 (4.32), 317 (4.31), 360 (sh), 439 (4.50), 464 (4.48). IR: (KBr) cm^{-1}: $\nu_{C=O}$ 1660. NMR ($CDCl_3$) δ: 2.16 (3H, s), 2.33 (3H, s), 6.88 (1H, d, J=9 Hz), 7.3—8.3 (12H, m), 15.6 (1H, b, disappeared on addition of D_2O).

Reaction of IIIa with Acetic Anhydride——A mixture of IIIa (0.5 g, 1.7 mmol) and acetic anhydride (10 ml) was heated at 150° for 3 hr. After removal of excess acetic anhydride by evaporation *in vacuo*, water was added to the residue and the mixture was made alkaline with 10% Na_2CO_3 aq.. This mixture was extracted with $CHCl_3$ and the extract was dried over Na_2SO_4 then passed through a silica gel column. The chloroform elute was concentrated and the residue was recrystallized from AcOEt to give 0.13 g (36%) of yellow needles (Va), mp 212—213°.[5] *Anal.* Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.20; H, 4.63; N, 13.05. UV λ_{max}^{EtOH} nm (log ε): 200 (4.74), 238 (4.04), 289 (4.31), 398 (4.27), 412 (sh., 4.21). MS *m/e* (%): 210 (M^+, 94), 195 (M–CH_3, 100), 167 (M–CH_3CO, 56), 140 (167-HCN, 81), 128 (quinolyl, 27), 43 (CH_3CO, 13).

Reaction of IIIa with Propionic Anhydride——A mixture of IIIa (0.5 g, 1.7 mmol) and propionic anhydride (20 mmol) was heated at 150° for 5 hr. The reaction mixture was treated as described above. Ten mg (2.6%) of yellow needles was obtained, mp 164—165°. *Anal.* Calcd for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38, N, 12.49. Found: C, 74.79; H, 5.39; N, 12.25. UV λ_{max}^{EtOH} nm (log ε): 220 (4.74), 238 (4.16), 290 (4.37), 398 (4.30), 412 (sh., 4.24). MS *m/e* (%): 224 (M^+, 94), 196 (M–C_2H_2, 88), 195 (M–C_2H_3, 100), 167 (M–C_2H_5CO, 92), 140 (167-HCN, 94), 128 (quinolyl, 47), 57 (C_2H_5CO, 5).

Preparation of IVa by the Reaction of IIIa with II——A solution of acetyl chloride (0.3 g, 2.3 mmol) and $CHCl_3$ (1 ml) was added to a solution of IIIa (0.5 g, 1.7 mmol), II (0.3 g, 2.1 mmol), and $CHCl_3$ (10 ml) at room temperature. The mixture gradually turned red. After a while, yellow crystals separated out. The mixture was allowed to stand at room temperature overnight. The yellow crystals were filtered off and washed with ether–AcOEt mixture (1: 1). The insoluble crystals were recrystallized from MeOH–AcOEt (1: 1) mixture to give 0.20 g (28%) of IVa, mp 290—292°. This compound was identical with an authentic sample of IVa (by IR comparison). The washing was evaporated to dryness (0.47 g), and the residue was recrystallized from AcOEt to give 0.24 g (48%) of the starting material (IIIa).

Reaction of IIIa with Methyl Iodide——A mixture of IIIa (0.5 g, 1.7 mmol), pulverized K_2CO_3 (0.2 g, 1.5 mmol), H_2O (a small amount), and dimethylsulfoxide (20 ml) was treated with CH_3I (0.4 g, 2.8 mmol). The mixture was allowed to stand at room temperature for 3.5 hr, and the color of the reaction mixture change from yellow to light green. The resulting crystals were filtered off and recrystallized from AcOEt to give orange needles of IIIb (0.05 g, 9.4%), mp 201—202°. This compound was identical with an authentic sample of IIIb prepared by another route (mixed melting point and IR comparison).

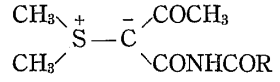
Reaction of IVa with Ethanol——A mixture of IVa (0.1 g, 0.24 mmol), *p*-toluenesulfonic acid (as a catalyst), and EtOH (30 ml) was refluxed for 39 hr. The separated long yellow needle crystals were filtered off (45 mg, 70% as VI) and recrystallized from MeOH to give yellow needles of VI, mp 283—284°. *Anal.* Calcd for $C_{20}H_{13}N_3$: C, 81.33; H, 4.44; N, 14.23. Found: C, 81.42; H, 4.27; N, 14.32. IR (KBr) cm^{-1}: $\nu_{C\equiv N}$ 2197, $\nu_{C=O}$ 1630. MS *m/e*: 295 (M^+). Hydrazine hydrate (1 drop) and AcOH (1 drop) were added to the ethanolic filtrate and the mixture was refluxed for 4 hr. The reaction mixture was evaporated to dryness *in vacuo*, and $CHCl_3$ was added to the residue with ice cooling. The separated crystals were filtered off and recrystallized from MeOH to give VII as a colorless powder, mp 263—265° (dec.). This compound was identical with an authentic specimen of 5-hydroxy-3-methyl-4-methylthiopyrazole by IR comparison.

Preparation of VII——A mixture of dimethylsulfonium acetylmethoxycarbonylmethylide (5.4 g, 31 mmol), benzoyl chloride (4.2 g, 30 mmol), triethylamine (2 drops), and acetonitrile (100 ml) was warmed at 50° for 5 hr, then allowed to stand at room temperature overnight. After removal of the solvent *in vacuo*, the residue (7.9 g) was dissolved in ether. This ether solution was washed with water and 5% $NaHCO_3$ aq., and dried over Na_2SO_4. The ether was evaporated off and the residue was fractionally distilled to give a pale yellow oil, 3.4 g (IX, 41.2%), bp_2 160°. *Anal.* Calcd for $C_{13}H_{14}O_4S$: C, 58.64; H, 5.30. Found: C, 58.84; H, 5.29. IR (KBr) cm^{-1}: $\nu_{C=O}$ 1725, 1615 (sh.). MS *m/e*: 266 (M^+). Hydrazine hydrate (0.65 ml) was added to a solution of IX (1.0 g) in EtOH (10 ml), and the mixture was refluxed for 30 min. The separated crystals were filtered off (0.6 g), and recrystallized from EtOH to give 0.5 g of colorless needles (VII), mp 264—265° (dec.). *Anal.* Calcd for $C_5H_8N_2OS$: C, 41.65; H, 5.59; N, 19.43. Found: C, 41.29; H, 5.57; N, 19.58. IR (KBr) cm^{-1}: 2600—2800 (broad), 1608, 1584, 1555. MS *m/e*: 144 (M^+).

General Procedure for Dimethylsulfonium Acetyl-N-acylcarbamoylmethylide (X)——Benzoyl chloride (20 mmol) was added to a mixture of Ia (10 mmol) and DMF (10 ml), and then triethylamine (2 ml) was added with stirring at room temperature. The mixture was allowed to stand at room temperature overnight. Excess solvent was evaporated off *in vacuo*, and the residue was made alkaline with aq. 10% Na_2CO_3. This mixture was extracted with $CHCl_3$, then the extract was dried over Na_2SO_4 and the solvent was evaporated to dryness. Ether was added to the residue, and the separated crystals were filtered and recrystallized from MeOH to give colorless crystals of X (Table III).

Dimethylsulfonium Acetyl-N-(2-quinolyl)carbamoylmethylide (XI)——Benzoyl chloride (5.6 g, 40 mmol) was added dropwise to a suspension of Ia (3.2 g, 20 mmol), II (2.9 g, 20 mmol), and DMF (30 ml) at room temperature with stirring. The resulting yellow solution became scarlet. After 15 min, pale yellow crystals separated. The mixture was left overnight at room temperature. The crystals were then filtered off and

Table III. Some Properties of Dimethylsulfonium Acetyl-N-acylcarbamoylmethylides (Xa—e)



Compound No.	R	mp (°C)	Yield (%)		Analyses (%) Calcd	Found	IR (KBr) cm^{-1} $\nu_{C=O}$	UV λ_{max}^{EtOH} nm (log ε)
Xa	CH_3	217	40	C	47.29	47.05	1665	271(4.16)
				H	6.45	6.54	1635	
				N	6.89	6.74	1615	
				S	15.75	15.82		
Xb	C_2H_5	170—172	50	C	49.76	49.90	1685	271(4.17)
				H	6.96	7.15	1675	
				N	6.45	6.33	1660	
				S	14.76	14.59		
Xc	C_6H_5	194—196	40	C	58.86	58.86	1692	236(4.47)
				H	5.70	5.94	1635	279(4.11)
				N	5.28	5.15		
				S	12.06	12.04		
Xd	$CH_2C_6H_5$	195	40	C	60.20	59.94	1665	273(4.18)
				H	6.14	6.15	1625	
				N	5.02	4.83		
				S	11.47	11.17		
Xe	$CH_2C_6H_4NO_2(p)$	187—188	43	C	51.85	51.57	1724	217(4.33)
				H	4.87	4.83	1668	274(4.38)
				N	8.64	8.60	1636	
				S	9.87	9.98		

Table IV. Reactions of X (or Ib) with II

Starting material No.	g (mmol)	II g (mmol)	RCOCl R	g (mmol)	DMF (ml)	Reaction Temp.	Time (hr)	Products			
Ib	2.2 (10)	1.45 (10)	CH_3	2.4 (30)	15	RT[a]	24	—		IVb	1.1 (22.0)
Xa	2.03 (10)	1.45 (10)	CH_3	1.5 (20)	20	RT	21	IIIa	1.37 (46.0)	IVa	0.69 (16.2)
Xa	2.03 (10)	1.45 (10)	C_6H_5	2.8 (20)	20	RT	18	—		IVa	1.3 (30.6)
Xb	2.17 (10)	1.45 (10)	CH_3	1.5 (20)	20	RT	19	IIIb	1.23 (39.4)		—
Xb	2.17 (10)	1.45 (10)	C_6H_5	2.8 (20)	20	RT	19	IIIb	0.50 (16.0)		—
Xd	1.3 (4.7)	0.8 (5.5)	CH_3	0.8 (10.2)	30	RT	24	IIId	0.14 (7.7)[b]		—
Xe	2.3 (7)	1.0 (5)	CH_3	1.1 (14)	20	RT	24	IIIe	0.02 (0.7)[b]	Xe	0.6 (26.1)[c]

a) Acetyl chloride was added under ice cooling. RT: room temperature.
b) Separated by silica gel chromatography.
c) Recovery of starting material.

suspended in aq. 10% Na_2CO_3, and this was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The residue was recrystallized from MeOH to give XI as a colorless powder (1.85 g, 30%), mp 215° (dec.). *Anal.* Calcd for $C_{15}H_{16}N_2O_2S$: C, 62.49; H, 5.59; N, 9.72; S, 11.10. Found: C, 62.43; H, 5.65; N, 9.56; S, 10.89. UV λ_{max}^{EtOH} nm (log ε): 243 (4.62), 276 (4.44), 326 (4.12), 338 (4.09). IR (KBr) cm^{-1}: $\nu_{C=O}$ 1595, 1550. NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.11 (6H, s), 7.36—8.36 (6H, m), 12.54 (1H, b, disappeared on addition of D_2O). MS *m/e*: 288 (M^+).

Hydrolysis of XI with Hydrochloric Acid——A solution of XI (0.5 g, 1.7 mmol) and 10% HCl (10 ml) was heated on a boiling water bath for 2 hr. The reaction mixture was made alkaline with aq. 10% Na_2CO_3 and this mixture was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and the solvent was evaporated off. The residue was recrystallized from ether to give 0.23 g (100%) of colorless leaflets (XII), mp 130°. *Anal.* Calcd for $C_9H_8N_2$: C, 74.97; H, 5.59; N, 19.43. Found: C, 74.59; H, 5.62; N, 19.36.

General Reaction of X with II——The case of Xa is described as an example. Acetyl chloride (1.5 g,

Table V. Some Properties of IIIb, IIId, IIIe, and IVb

Compd. No.	mp (°C) Appearance (Recryst. solvent)	Formula Analysis (%)	Calcd	Found	IR (KBr) cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)[a]	NMR ($CDCl_3$) δ[b]	MS m/e (%)	
IIIb	201—202 Orange needles (MeOH)	$C_{17}H_{16}N_2O_2S$			$\nu_{C=O}$ 1650	222(4.70)	2.04(3H, s)	312(M^+, 31)	140(32)
		C	65.34	65.45		290(4.02, sh)	2.33(3H, s)	298(9)	130(98)
		H	5.16	5.14		302(4.09, sh)	2.44(3H, s)	182(100)	129(100)
		N	8.97	9.05		339(4.17)	7.4—8.3(6H, m)	181(100)	128(95)
						440(4.20, sh)	15.7(1H, b, D_2O)	168(95)	101(73)
						464(4.40)		157(48)	88(96)
						490(4.31)		155(50)	77(95)
									43(93)
IIId	144—145 Yellow powder (AcOEt)	$C_{22}H_{20}N_2O_3S$			ν_{NH} 3400	280(4.10)	1.66(3H, s)	Table I	
		C	67.33	67.49		293(4.08)	2.24(3H, s)		
		H	5.14	5.07	ν_{OH} 3270	307(4.10)	6.40		
		N	7.14	7.01		310(4.10)	(1H, d, J=9 Hz)		
		S	8.17	8.18	$\nu_{C=O}$ 1650	319(4.12)	7.0—7.6(10H, m)		
						328(4.05)	9.52(1H, s, D_2O)		
						418(4.02)	14.38(1H, b, D_2O)		
						437(4.25)	15.03(1H, s, D_2O)		
						462(4.04)			
IIIe	235—238 Red cubes (AcOEt)	$C_{22}H_{17}N_3O_4S$			$\nu_{C=O}$ 1650	266(4.11)		419(M^+, 40)	215(19)
		C	63.00	62.70		303(4.01)		289(69)	130(39)
		H	4.08	3.96		317(4.00)		288(100)	128(20)
		N	10.02	9.96		330(3.99)		287(67)	88(30)
		S	7.64	7.69		424(4.07, sh)		259(14)	43(40)
						446(4.28)		243(47)	
						472(4.25)		242(66)	
IVb	280 Yellowish-orange needles (MeOH–$CHCl_3$)	$C_{30}H_{21}N_3O_2S \cdot H_2O$			$\nu_{C=O}$ {1655, 1642	230(4.91)	2.31(3H, s)	487(M^+, —)	128(11)
		C	71.27	71.48		266(4.34, sh)	6.8—8.5	295(100)	105(79)
		H	4.59	4.39		320(4.37)	(17H, m)	294(93)	77(44)
		N	8.31	8.23		422(4.26, sh)	15.7(1H, b, D_2O)	269(16)	
		S	6.34	6.24		444(4.53)		192(11)	
						470(4.53)		147(21)	

a) sh: shoulder.
b) D_2O: disappeared on addition of D_2O, s: singlet, d: doublet, m: multiplet, b: broad.

20 mmol) was added portionwise to a mixture of Xa (2.03 g, 10 mmol), II (1.45 g, 20 mmol), and DMF (20 ml) at room temperature with stirring. The reaction was exothermic, and the mixture became orange; it was kept at room temperature for 21 hr with stirring. The separated crystalline mass was filtered off and suspended in aq. 5% Na_2CO_3, then extracted with $CHCl_3$. The extract was dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from AcOEt to give orange-yellow needles of IIIa (1.37 g, 46.0 %), mp 192—193°. If necessary, the residue was chromatographed on a silica gel column. Compound IVa was obtained from the mother liquor (0.69 g, 16.2%, mp 290—292°). These compounds were identical with authentic samples of IIIa and IVa, respectively (mixed melting point and IR comparison).

Reaction of Xc with II——Acetyl chloride was added dropwise to a solution of Xc (0.6 g, 2.3 mmol), II (0.4 g, 2.8 mmol), and DMF (15 ml) at room temperature. The mixture was allowed to stand at room temperature for 5 days, then the solvent was evaporated off *in vacuo*. The residue was made alkaline with aq. 5% $NaHCO_3$, and this mixture was extracted with $CHCl_3$. After drying the extract, it was passed through a silica gel column. The resulting crystals were recrystallized from benzene to give 0.3 g (48.0%) of a colorless powder (XIII), mp 127—129°. *Anal.* Calcd for $C_{12}H_{13}NO_3S$: C, 57.37; H, 5.22; N, 5.58; S, 12.74. Found: C, 57.36; H, 5.26; N, 5.52; S, 12.71. IR (KBr) cm^{-1}: $\nu_{C=O}$ 1707, 1700, 1670.

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