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Studies on 1,3-Benzoxazines. III.[1] Reaction of Imidoyl Chlorides of 1,3-Benzoxazines with 2-Hydroxy- or 2-Mercaptopyridine N-Oxides: A Novel S-N Bond Formation *via* Electrocyclic Rearrangement

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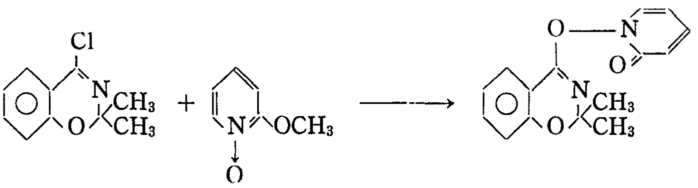
A novel S–N bond formation through 3,3-sigmatropic rearrangement in the reaction of imidoyl chlorides of 1,3-benzoxazines (**1**) with 2-mercaptopyridine N-oxide (**8**) is described. Treatment of the imidoyl chlorides (**1a**—**f**) with 2-hydroxypyridine N-oxide (**2**) afforded the corresponding pyridone derivatives (**3a**—**f**). When 2-mercaptopyridine N-oxide (**8**) was used instead of **2**, the thiopyridones (**7**) or N-oxides (**9**) were obtained and both compounds were transformed to 3-(2-pyridylthio)-4-oxo-2,3-dihydro-1,3-benzoxazines (**13**) through electrocyclic rearrangement on heating in a suitable solvent.

Keywords——imidoyl chloride; 1,3-benzoxazine; 2-hydroxypyridine N-oxide; 2-mercaptopyridine N-oxide; electrocyclic rearrangement; X-ray analysis

In earlier reports,[1,2] we have described the reaction of imidoyl chlorides of 1,3-benzoxazine derivatives with various pyridine N-oxides, involving intramolecular rearrangement to the α-position of the pyridine ring or the side chain of an alkyl substituted pyridine ring. As an exception, we found that the reaction of 2-methoxypyridine N-oxide (**2**) with 2,2-dimethyl-4-chloro-2H-1,3-benzoxazine (**1a**) gave 2,2-dimethyl-4-(2-oxo-1H-pyrid-1-yl)oxy-2H-1,3-benzoxazine (**3a**) without the intramolecular rearrangement as outlined in Chart 1. The pyridone derivative (**3a**) showed some pharmacological activities.



1a **2** **3a**

Chart 1

As a continuation of our studies of 1,3-benzoxazines, we investigated the independent synthesis of **3** using 2-hydroxypyridine N-oxide (**4**) and the reaction of imidoyl chlorides (**1**) with 2-mercaptopyridine N-oxide (**8**) instead of **4**, and found a novel S–N bond formation through electrocyclic rearrangement. This S–N bond formation *via* electrocyclic rearrangement is the first example of its type as far as we know.

Generally, 2-hydroxypyridine N-oxide gave O-alkylation or O-acylation products of the N-oxide group by the reaction with alkyl or acyl halides.[3] On the other hand, the reaction of 2-mercaptopyridine N-oxide with alkyl or acyl halides afforded the corresponding products of S-alkylation or S-acylation.[3] Thus, pyridone derivatives (**3**) should be obtained by the reaction of **4** with imidoyl chlorides of 1,3-benzoxazines (**1**).

The reaction of imidoyl chloride (**1a**) with **4** in chloroform in the presence of triethylamine (Et_3N) under reflux for 3 h afforded the pyridone derivative (**3a**), in 85% yield. It was identical in all respects with a sample obtained by the reaction of **1a** with **2** reported previously.[2]

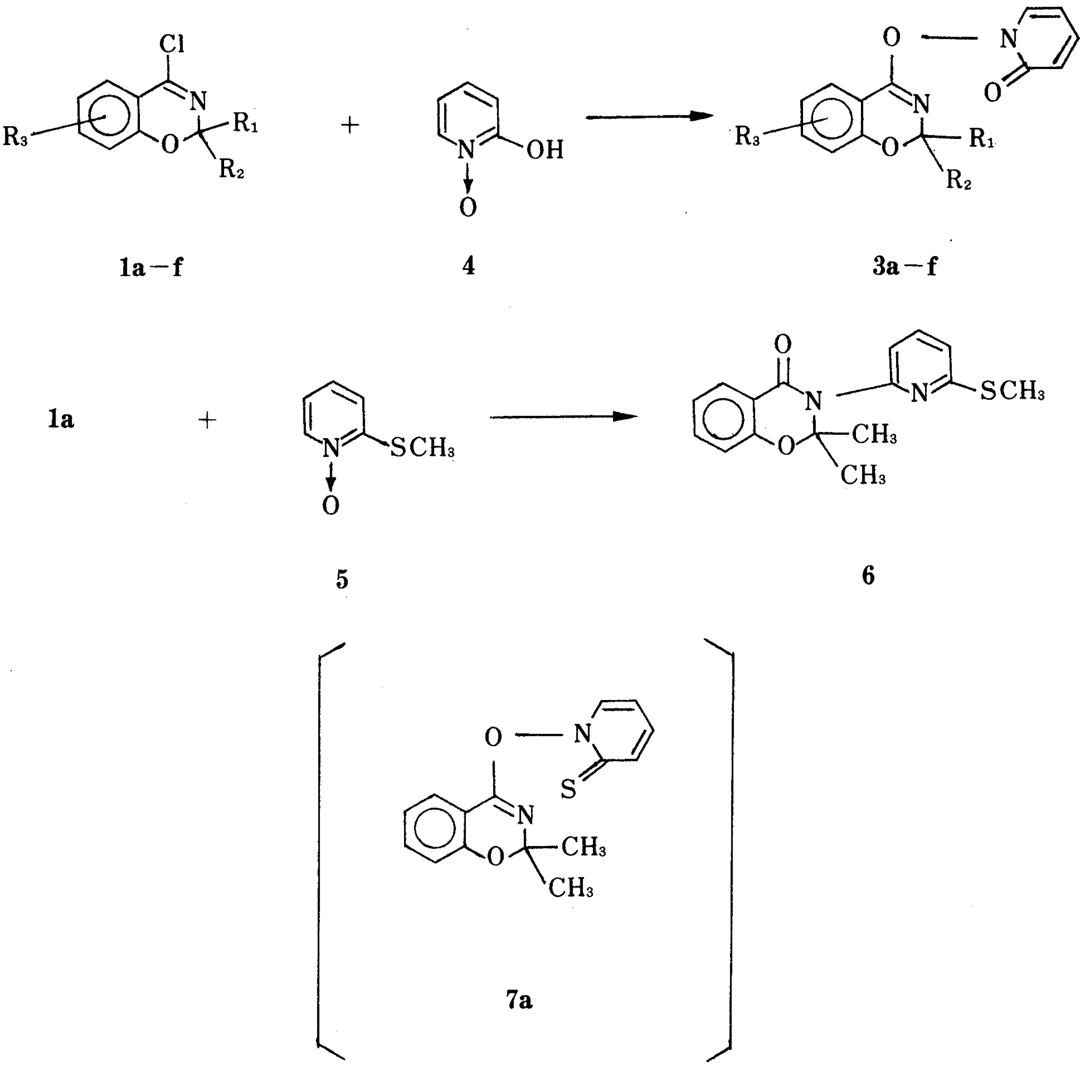
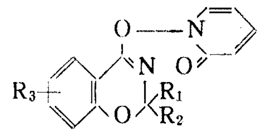


Chart 2

TABLE I. Pyridone Derivatives (3)



Compd. No.	R_1	R_2	R_3	mp °C	Yield (%)	Formula	Analysis (%) Calcd (Found) O	H	N
3a	CH_3	CH_3	H	77— 78	85	$C_{15}H_{14}N_2O_3$	66.65 (66.78	5.22 5.28	10.37 10.33)
b	C_2H_5	C_2H_5	H	128—129	88	$C_{17}H_{18}N_2O_3$	68.44 (68.37	6.08 6.20	9.39 9.31)
c	H		H	109—110	81	$C_{18}H_{18}N_2O_3$	69.66 (69.62	5.85 5.78	9.03 9.12)
d	CH_3	CH_3	6-Cl	112—114	80	$C_{15}H_{13}ClN_2O_3$	59.12 (59.28	4.30 4.34	9.19 9.17)
e	CH_3	CH_3	6-OCH_3	103—104	85	$C_{16}H_{16}N_2O_4$	63.99 (63.83	5.37 5.29	9.33 9.12)
f	CH_3	CH_3	7-Cl	129—130	89	$C_{15}H_{13}ClN_2O_3$	59.12 (59.26	4.30 4.29	9.19 9.26)

Similar reactions were undertaken with some derivatives of **1** with **2** and the results are summarized in Chart 2 and Table I. Then, we carried out the reaction of 2-methylthiopyridine N-oxide (**5**) with **1a** under similar reaction conditions in order to get the corresponding thiopyridone derivative (**7a**). Contrary to our expectation, **5** did not give a thiopyridone compound by the reaction with **1a**, but afforded the product of rearrangement to the α-position on the pyridine ring, 2,2-dimethyl-3-(6-methylthiopyrid-2-yl)-4-oxo-2,3-dihydro-1,3-benzoxazine (**6**), in 92% yield. The structure of **6** was assigned on the basis of elemental analysis ($C_{16}H_{16}N_2O_2S$), mass (MS) (M^+: *m/e* 300), infrared (IR) and nuclear magnetic resonance (NMR) spectra. The formation of this product may be explained by the mechanism proposed in the previous paper.2)

We next investigated the reaction of imidoyl chlorides with 2-mercaptopyridine N-oxide (**8**) and obtained very interesting results.

Treatment of **1a** with **8** in chloroform in the presence of excess Et_3N under reflux for 3 h gave yellow prisms of mp 135—138°C in 84% yield, whose elemental analysis and mass spectrum (M^+: *m/e* 286) were consistent with the empirical formula $C_{15}H_{14}N_2O_2S$. The IR spectrum showed a new absorption band at 1680 cm^{-1} due to a C=N bond. The NMR spectrum in deuteriochloroform ($CDCl_3$) at 35°C showed very complicated signals. Therefore, NMR measurement was carried out in $CDCl_3$ at −35°C. It seems that the spectral pattern and the integrations of the protones at lower field (aromatic protons) and at higher field (dimethyl acetal groups) are quite similar to those of the pyridone derivative (**3a**). These results lead to 7a as a possible structure of this reaction product. According to the literature,3) however, S-alkylation should occur predominantly rather than O-alkylation in the reaction of 2-mercaptopyridine N-oxide with alkylating agents. The IR spectrum, however, showed no pyridine

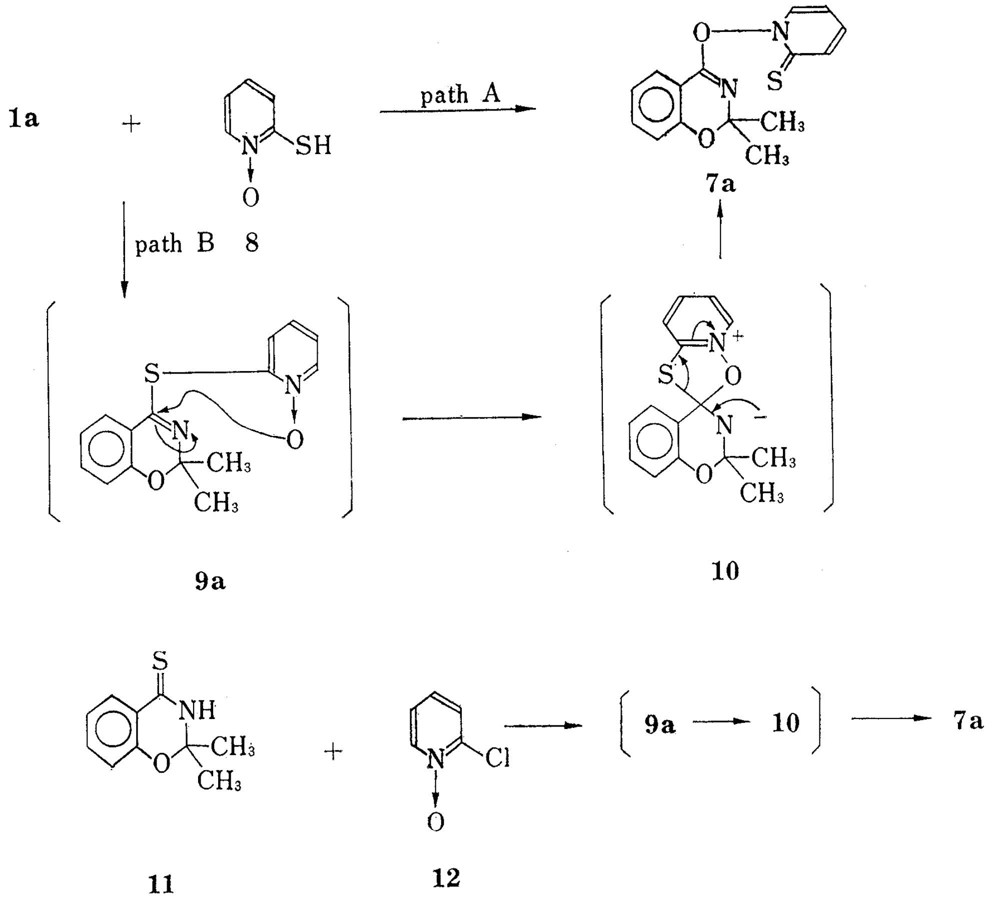


Chart 3

N-oxide absorption band in the 1300—1200 cm^{-1} region and the NMR spectrum showed no typical signals at lower field (around 8.5 ppm) due to the α-proton of the pyridine N-oxide. To confirm the structure of this reaction product, an X-ray study was carried out and its structure was unambigously determined to be 2,2-dimethyl-4-(2-thioxo-1H-pyrid-1-yl)oxy-2H-1,3-benzoxazine (**7a**). The NMR spectrum, which showed very complicated signals at 35°C as described above, was ascribed to the formation of another new compound such as **13a**, as will be described later, in solution in the NMR probe.

Two possible routes can be considered for the formation of **7a**: path A is a direct O-alkylation reaction and path B is a migration reaction in which S-alkylation occurs first, followed by S→O migration *via* **10** to give the product (**7a**). In order to determine which mechanism actually operates, the reaction of 2,2-dimethyl-4-thioxo-2,3-dihydro-1,3-benzoxazine (**11**) with 2-chloropyridine N-oxide (**12**) in dimethylformamide in the presence of sodium hydride was carried out, and only **7a** was obtained in 64% yield (Chart 3). Compound **7a** would be produced through S→O migration of the initially formed N-oxide derivative (**9a**) in this reaction. This result supported path B as the route for the formation of **7a**. Several attempts to obtain the N-oxide compound (**9a**) under mild reaction conditions were unsucceessful.

When a $CDCl_3$ solution of **7a** was set aside for 24 h at room temperature, the NMR spectrum showed quite different signals as compared with that initially recorded, which suggested that **7a** was transformed to some new compound. To isolate the new compound, a solution of **7a** in an aprotic solvent such as CH_3CN, C_6H_6, $CHCl_3$ or dioxane was heated under reflux for a while under neutral reaction conditions to afford colorless prisms (**13a**) of mp 129—131°C in 96% yield (using $CHCl_3$ as a solvent). When a base (Et_3N) was added to this reaction medium, the new compound could not be obtained and only the starting thiopyridone (**7a**) was recovered. At present, we have no explanation for the failure of this reaction in the presence of the base. The structure of the new compound, 2,2-dimethyl-3-(2-pyridylthio)-4-oxo-2,3-dihydro-1,3-benzoxazine (**13a**), was assigned on the basis of spectroscopic and elemental analysis data ($C_{15}H_{14}N_2O_2S$). The MS exhibited a molecular ion at *m/e* 286, which was the same as that of the thiopyridone derivative (**7a**). The IR spectrum showed a new absorption band at 1670 cm^{-1} which was a typical amide band of 3-substituted 4-oxo-2,3-dihydro-1,3-benzoxazine derivatives.[2] The NMR spectrum of **13a** showed a singlet at 1.77 ppm (6H) due to the dimethyl acetal groups, a doublet of doublets at 8.03 ppm (1H, J=2 and 8 Hz) assigned to the proton at the 5-position on the benzoxazine ring and another doublet of doublets at 8.55 ppm (1H, J=2 and 5 Hz) due to the α-proton on the pyridine ring. The structure was determined from the physical data and by comparison of the spectral data with those of the sample prepared independently by the reaction of 2,2-dimethyl-4-oxo-2,3-dihydro-1,3-benzoxazine (**15**) with 2-pyridylsulfenyl bromide (**16**), and by X-ray analysis (Fig. 1).

A plausible mechanism for the formation of **13a** involving 3,3-sigmatropic rearrangement is depicted (*via* **14**) in Chart 4.

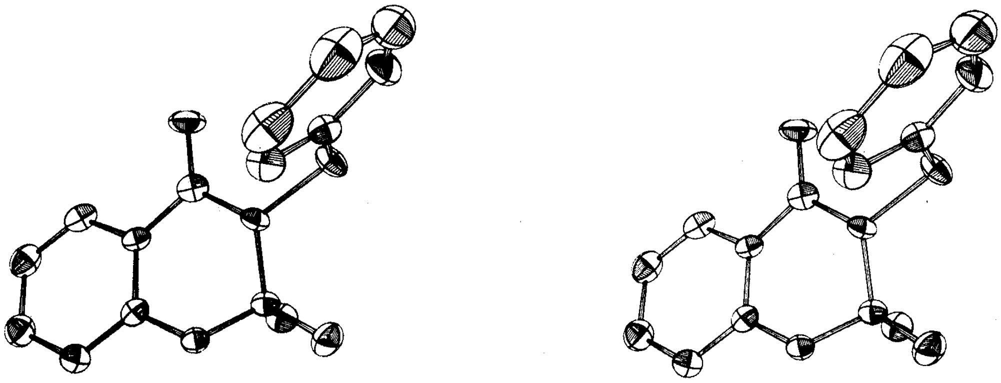


Fig. 1. Perspective Views of the Molecular Structure of **13a**

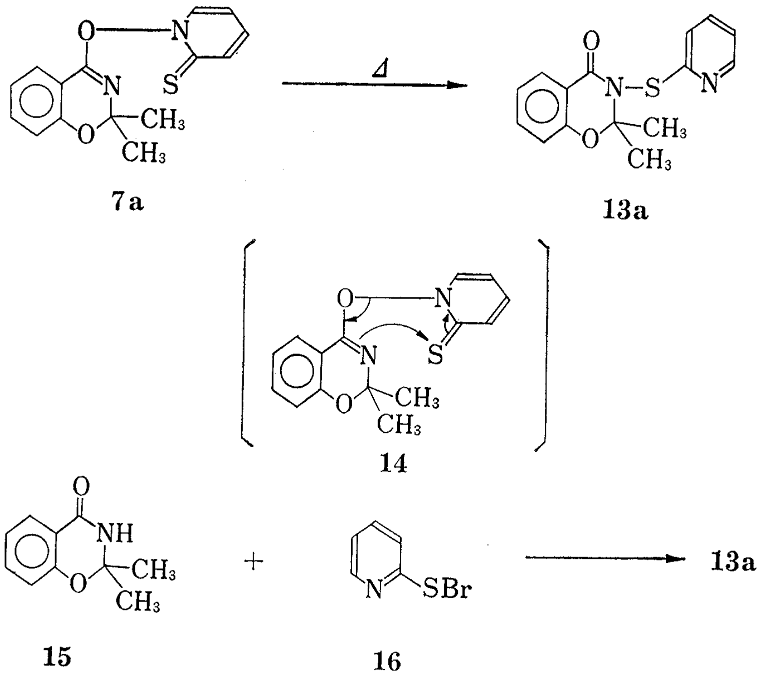


Chart 4

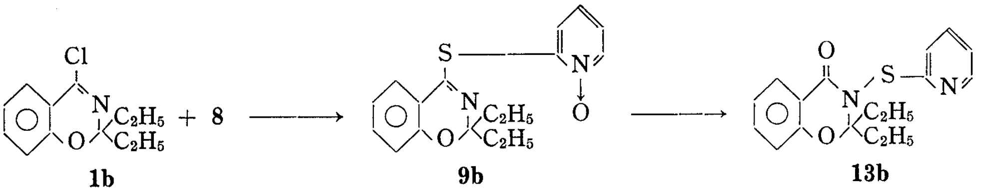


Chart 5

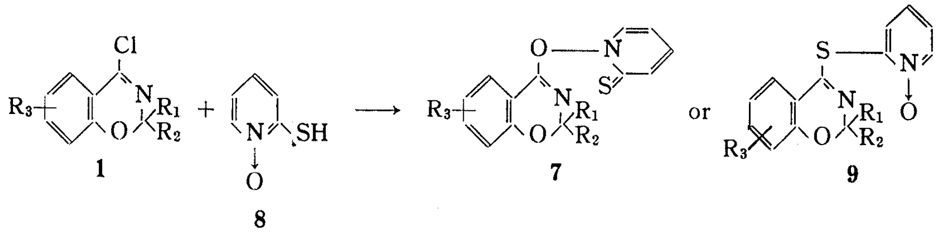
When 2,2-diethyl-4-chloro-2H-1,3-benzoxazine (**1b**) was treated with **8** under similar reaction conditions, a new reaction product, 2,2-diethyl-4-(1-oxido-2-pyridyl)thio-2H-1,3-benzoxazine (**9b**), was obtained in 63% yield, and the thiopyridone derivative was not isolated (Chart 5). The structure of **9b** was deduced from its spectral data and was confirmed by X-ray analysis. The elemental analysis and the MS (M^+: *m/e* 314) indicated that the molecular formula is $C_{17}H_{18}N_2O_2S$. In the NMR spectrum of **9b**, a triplet and quartet due to the diethyl acetal groups appeared at 0.95 (6H) and 1.85 ppm (4H), respectively, and a doublet of doublets (1H, $J=3$ and 5 Hz) due to the α-proton on the pyridine ring appeared at 8.25 ppm. The product (**9b**) was not transformed into the thiopyridone derivative on boiling with $CHCl_3$ without a base (Et_3N). However, **9b** was readily converted into 2,2-diethyl-3-(2-pyridylthio)-4-oxo-2,3-dihydro-1,3-benzoxazine (**13b**) in 92% yield on refluxing with ethyl acetate instead of $CHCl_3$. The formation of **13b** from **9b** could occur *via* an electrocyclic rearrangement of the initial S→O migrated thiopyridone compound.

In order to study the scope of these reactions, several derivatives of imidoyl chlorides (**1**) were treated with **8**. As summarized in Table II, thiopyridone compounds such as 7 were obtained in the case of **1a**, **f** and **g**, and N-oxide compounds such as **9** were obtained from **1b**, **d** and **e**.

We have no explanation for the differences in the formation of thiopyridones and N-oxide compounds according to substituents. As mentioned above, both types of compound could yield 3-(2-pyridylthio)-4-oxo-2,3-dihydro-1,3-benzoxazine derivatives (**13**) through an electrocyclic rearrangement on heating in a suitable solvent; the results are summarized in Table III.

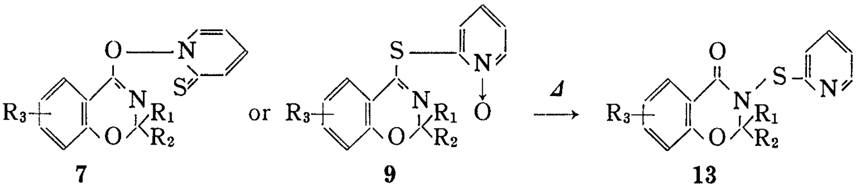
The results of pharmacological experiments will be reported and discussed elsewhere.

TABLE II. Reaction of Imidoyl Chlorides of 1,3-Benzoxazine Derivatives with Pyridine N-Oxide (**8**)



	Starting material (1) R₁	R₂	R₃	Compd. No.	Product (7 or 9) mp °C	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	S
1a	CH_3	CH_3	H	**7a**	135—138	84	$C_{15}H_{14}N_2O_2S$	62.91	4.92	9.78	11.19
								(62.86	4.95	9.81	11.25)
b	C_2H_5	C_2H_5	H	**9b**	78— 80	63	$C_{17}H_{18}N_2O_2S$	64.94	5.77	8.91	10.19
								(64.84	5.92	8.83	10.23)
d	CH_3	CH_3	6-Cl	**9d**	99—100	66	$C_{15}H_{13}ClN_2O_2S$	56.16	4.08	8.73	9.99
								(56.03	4.22	8.65	10.08)
e	CH_3	CH_3	6-OCH_3	**9e**	132—134	71	$C_{16}H_{16}N_2O_3S$	60.74	5.09	8.85	10.13
								(60.89	5.25	8.94	10.01)
f	CH_3	CH_3	7-Cl	**7f**	122—124	81	$C_{15}H_{13}ClN_2O_2S$	56.16	4.08	8.73	9.99
								(55.91	4.17	8.87	9.91)
g	CH_3	CH_3	7-CH_3	**7g**	117—118	78	$C_{16}H_{16}N_2O_2S$	63.97	5.36	9.32	10.67
								(63.88	5.48	9.32	10.85)

TABLE III. 3-(2-Pyridylthio)-4-oxo-4H-1,3-benzoxazine Derivatives (**13**)



Starting material	Compd. No.	R₁	R₂	R₃	Product (13) mp °C	Solvent	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	S
7a	**13a**	CH_3	CH_3	H	129—131	$CHCl_3$	96	$C_{15}H_{14}N_2O_2S$	62.91	4.92	9.78	11.19
									(63.06	4.94	9.82	11.26)
9b	**b**	C_2H_5	C_2H_5	H	88— 89	CH_3CO_2-C_2H_5	92	$C_{17}H_{18}N_2O_2S$	64.94	5.77	8.91	10.19
									(65.00	5.88	8.90	10.07)
9d	**d**	CH_3	CH_3	6-Cl	112—113	$CHCl_3$	96	$C_{15}H_{13}ClN_2O_2S$	56.16	4.08	8.73	9.99
									(56.33	4.22	8.76	10.08)
9e	**e**	CH_3	CH_3	6-OCH_3	132—134	Xylene	88	$C_{16}H_{16}N_2O_3S$	60.74	5.09	8.85	10.13
									(60.92	5.15	8.82	10.01)
7f	**f**	CH_3	CH_3	7-Cl	116—118	$CHCl_3$	94	$C_{15}H_{13}ClN_2O_2S$	56.16	4.08	8.73	9.99
									(55.97	4.12	8.73	10.25)
7g	**g**	CH_3	CH_3	7-CH_3	95— 96	$CHCl_3$	97	$C_{16}H_{16}N_2O_2S$	63.97	5.36	9.32	10.67
									(63.81	5.46	9.27	10.77)

Experimental

All melting points are uncorrected. IR spectra were recorded on a Jasco IRA-2 spectrophotometer. NMR spectra were determined on a Varian A-60 or HA-100 instrument using tetramethylsilane as an internal standard; coupling constants are given in Hz. MS were taken on a JEOL JMS-01SG instrument.

Reaction of the Imidoyl Chlorides of 1,3-Benzoxazines (1a—f) with 2-Hydroxypyridine N-Oxide (4)——General Procedure: A solution of imidoyl chloride (0.01 mol) and pyridine N-oxide (0.012 mol) in chloroform (30 ml) was boiled under reflux for 3—5 h in the presence of triethylamine (0.02 mol). After cooling, the solution was washed with water and the solvent was evaporated off. The residue was chromatographed on silica gel eluting with benzene–ethyl acetate (3: 1) to give **3**. Melting points and analytical data are summarized in Table I.

Reaction of 2-Methylthiopyridine N-Oxide (5) with 1a——A solution of 2-methylthiopyridine N-oxide[4] (0.8 g) and **1a** (1.0 g) in 1,2-dichloroethane (30 ml) was refluxed for 8 h in the presence of triethylamine (0.75 g). After cooling to room temperature, the solution was washed with water and the solvent was evaporated off. The residue was chromatographed on silica gel eluting with benzene–ethyl acetate (1: 1) to give **6** (1.38 g), mp 136—137°C ($CHCl_3$–hexane). *Anal.* Calcd for $C_{16}H_{16}N_2O_2S$: C, 63.97; H, 5.36; N, 9.32; S, 10.67. Found: C, 64.16; H, 5.41; N, 9.41; S, 10.70. IR $\nu_{\max}^{\text{Nujol}}$ 1670 (C=O). NMR ($CDCl_3$) δ: 1.80 (6H, s, $<^{CH_3}_{CH_3}$), 2.53 (3H, s, SCH_3), 6.90—8.10 (7H, m, aromatic H).

Reaction of 2-Mercaptopyridine N-Oxide (8) with Imidoyl Chlorides of 1,3-Benzoxazines (1a—g)——General Procedure: A solution of imidoyl chloride (0.01 mol) and pyridine N-oxide (0.01 mol) in chloroform (25 ml) was boiled under reflux for 3—5 h in the presence of triethylamine (0.02 mol). After cooling, the organic layer was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* at low temperature. The residual solid was recrystallized from $CHCl_3$–hexane (containing a small amounts of triethylamine) to give **7** or **9**. Melting points, yields and analytical data are listed in Table II.

Reaction of 2,2-Dimethyl-4-thioxo-2,3-dihydro-1,3-benzoxazine (11) with 2-Chloropyridine N-Oxide (12)——A solution of 2,2-dimethyl-4-thioxo-2,3-dihydro-1,3-benzoxazine[5] (1.9 g) in DMF (5 ml) was added to a stirred suspension of sodium hydride (50% oil, 0.53 g) in DMF (30 ml) under ice-cooling. A solution of 2-chloropyridine N-oxide in DMF (5 ml)–triethylamine (1 ml) was added dropwise with stirring to the above mixture under ice-cooling. After being stirred for 8 h at 80°C, the mixture was poured into water (100 ml), and extracted with ether. The ether solution was washed with 2.8% NH_4OH and concentrated *in vacuo* at low temperature. The residue was recrystallized from $CHCl_3$–hexane (containing a small amounts of triethylamine) to give **7a** (1.85 g), mp 135—138°C.

Preparation of 3-(2-Pyridylthio)-4-oxo-2,3-dihydro-1,3-benzoxazines (13) from 7 or 9——General Procedure: A solution of thiopyridone (**7**, 0.01 mol) or N-oxide (**9**, 0.01 mol) in chloroform (5 ml) was boiled under reflux for 1—5 h. After removal of the solvent, the residue was recrystallized from ethyl acetate–hexane to give **13**. Melting points, yields and analytical data are summarized in Table III.

Reaction of 2,2-Dimethyl-4-oxo-2,3-dihydro-1,3-benzoxazine (15) with 2-Pyridylsulfenyl Bromide (16)——A solution of 2,2-dimethyl-4-oxo-2,3-dihydro-1,3-benzoxazine (3.6 g) in THF (10 ml) was added to a stirred suspension of sodium hydride (50% oil, 1.0 g) in THF (50 ml) under ice-cooling. A solution of 2-pyridylsulfenyl bromide (3.0 g) in DMF (30 ml) was added dropwise with stirring to the above mixture at −20°C. After being stirred for 1 h at room temperature, the mixture was poured into water (150 ml), and extracted with ether. The ether solution was washed with water and concentrated. The residue was chromatographed on silica gel eluting with benzene–ethyl acetate (3: 1) to give 1.8 g of **13a**, mp 129—131°C.

Structure Determination of 7a, 9b and 13a by X-Ray Analysis——The crystal structures of **7a**, **9b** and **13a** were determined by the single crystal X-ray diffraction technique. The compound **7a** is monoclinic, space group $P2_1/c$, with $a=13.646(5)$, $b=9.233(3)$, $c=13.260(5)$ Å, $\beta=107.44(5)°$ and $Z=4$. The compound **9b** is orthorhombic space group $P2_12_12_1$, with $a=9.111(2)$, $b=8.976(2)$, $c=17.185(3)$ Å and $Z=4$. The compound **13a** is triclinic, space group $P\bar{1}$, with $a=11.043(5)$, $b=9.496(4)$, $c=7.726(3)$ Å, $\alpha=106.60(5)$, $\beta=68.80(4)$, $\gamma=113.02(5)°$ and $Z=2$. Intensity data for the three compounds were collected with a Rigaku four-circle diffractometer (graphite-monochromated CuKα). The measurement, every 51 reflections, of three standard reflections for compound **9b** indicated a linear intensity loss ($<15\%$) over the period of data collection, and corrections for this decay were made. The structures of the three compounds were solved and refined by use of the MULTAN program[6] and least-squares refinements. The R values obtained in the final least-squares cycles were 0.052 (1796 reflections), 0.093 (856 reflections) and 0.074 (2060 reflections) for the compounds **7a**, **9b** and **13a**, respectively.

References and Notes

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