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Studies on Tertiary Amine Oxides. LXXIV.[1] Reactions of Aromatic *N*-Oxides with 2-Phenyl-2-Thiazolin-4-one in the Presence of Acetic Anhydride

MOHAMMED MOHAMMED YOUSIF,[2] SEITARO SAEKI, and MASATOMO HAMANA*

Faculty of Pharmaceutical Sciences, Kyushu University, Maidashi, Higashi-ku, Fukuoka 812, Japan

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Quinoline 1-oxides (**1a**—**e**) readily react with 2-phenyl-2-thiazolin-4-one (**2**) in acetic anhydride at room temperature to afford the corresponding 5-(2-quinolyl)thiazolones (**3a**—**e**) in good yields. The reaction of 4-chloroquinoline 1-oxide (**1f**) gives 4-acetoxy-5-(4-chloro-2-quinolyl)-2-phenylthiazole (**4**). Hydrolyses of **1a**—**e** with 48% hydrobromic acid under reflux give 2-quinolinemethanethiols as the hydrobromides (**6a**—**e**). Similar results were obtained from the reaction of isoquinoline 2-oxide (**7**), but pyridine 1-oxide was unreactive.

Keywords——aromatic *N*-oxide; 2-phenyl-2-thiazolin-4-one; 2-phenyl-5-(2-quinolyl)-2-thiazolin-4-ones; 2-quinolinemethanethiols; 5-(1-isoquinolyl)-2-phenyl-2-thiazolin-4-one; 1-isoquinolinemethanethiol; nucleophilic substitution

Previous papers of this series have described reactions of aromatic *N*-oxides with 3-arylrhodanines[3] and 2-substituted 2-oxazolin-5-ones[3] in the presence of acetic anhydride. As a continuation of these studies, the reactions of aromatic *N*-oxides with 2-phenyl-2-thiazolin-4-one[5] were investigated in the presence of acetic anhydride.

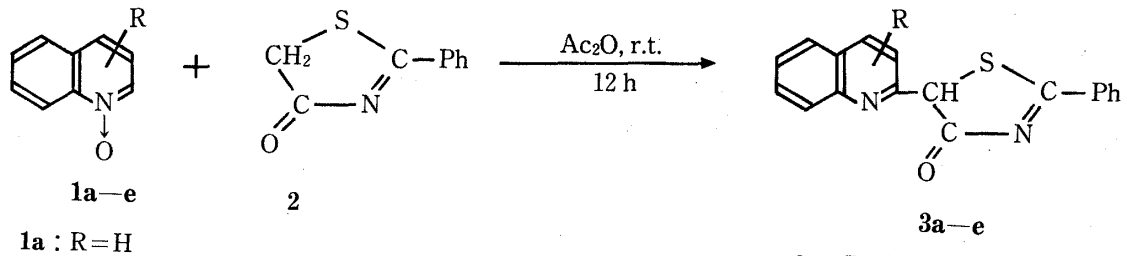
When a solution of quinoline 1-oxide (**1a**) in acetic anhydride was added dropwise to a stirred solution of 2-phenyl-2-thiazoline-4-one (**2**) in acetic anhydride, an exothermic reaction occurred and crystals separated from the reaction mixture. The reaction vessel was cooled with an external ice-bath until the addition of **1a** was completed, and then the reaction mixture was stirred at room temperature overnight. The resulting crystals were filtered and recrystallized from ethanol to give 2-phenyl-5-(2-quinolyl)-2-thiazolin-4-one (**3a**) in 67% yield.

The reactions of lepidine, 4-methoxyquinoline, 4-morpholinoquinoline and 3-bromoquinoline 1-oxides (**1b**, **1c**, **1d** and **1e**) progressed in the same way to give the corresponding thiazolone derivatives (**3b**, **3c**, **3d** and **3e**) also in good yields, but 4-acetoxy-5-(4-chloro-2-quinolyl)-2-phenylthiazole (**4**) was isolated in 87% yield from the reaction of 4-chloroquinoline-1-oxide (**1f**) (Chart 1 and Table I).

All the products gave analytical values and mass numbers (*m/e*) of the parent peaks in full agreement with the proposed structures. The infrared (IR) spectra of **3** exhibited strong bands at 1615—1635 cm^{-1}. The nuclear magnetic resonance (NMR) spectra of **3** lacked the signals due to the C_2-proton of the quinoline rings and were consistent with the expected structures. Since no NH signals could be detected for compounds **3** in spite of measurement down to low field (around δ 20), **3** seems to exist exclusively in the ketone form (3-A) in deuteriochloroform as shown in Chart 1. The methyl protons of the acetoxy group in **4** clearly appeared as a three-proton singlet at δ 2.59.

Spectral data of **3a**—**e** are given in Table II.

Oxidation of **3a** with excess 30% hydrogen peroxide in boiling acetic acid for 7 h gave quinaldic acid 1-oxide (**5**) (72%) in the usual way. Subsequently, hydrolysis of **3** to 2-quinolinemethanethiols was examined, and it was found that the corresponding 2-quinolinemethanethiols (**6a**, **6b**, **6c** **6d**, and **6e**) were easily isolable as their hydrobromides by refluxing them with 48% hydrobromic acid for 8 h. However, only resinous materials were formed upon similar treatment of **4** (Chart 2 and Table III).



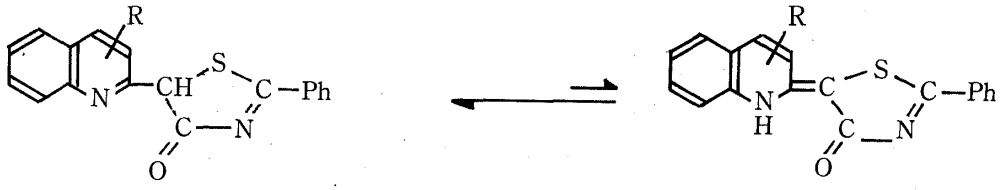
1a—e

1a : R=H
1b : R=4-Me
1c : R=4-OMe
1d : R=4-morpholino
1e : R=3-Br

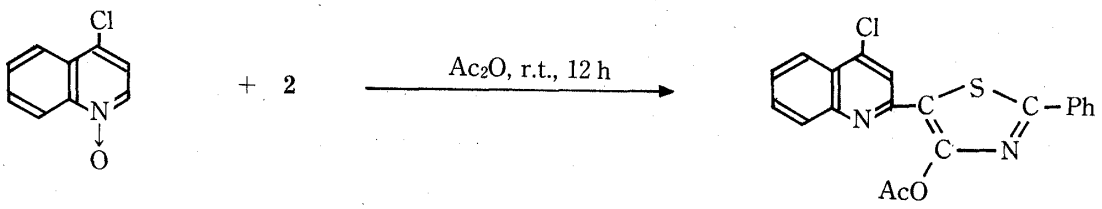
2

3a—e

3a : R=H
3b : R=4-Me
3c : R=4-OMe
3d : R=4-morpholino
3e : R=3-Br



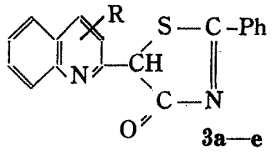
3-A **3-B**



1f **4**

Chart 1

TABLE I. 2-Phenyl-5-(2-quinolyl)-2-thiazolin-4-ones



3a—e

Compound No.	R	Yield (%)	Appearance	mp (°C)	Formula	Analyses (%) Calcd (Found) C	H	N
3a	H	67	Red needles	258—260	$C_{18}H_{12}N_2OS$	71.04 (70.81)	3.98 3.99	9.21 9.13)
3b	4-Me	78	Orange needles	188—189	$C_{19}H_{14}N_2OS$	71.69 (71.54)	4.43 4.52	8.80 8.76)
3c	4-OMe	79	Dark red needles	258—259	$C_{19}H_{14}N_2O_2S$	68.25 (68.11)	4.22 4.45	8.38 8.26)
3d	4-Morpholino	87	Yellow needles	265—266	$C_{22}H_{19}N_3O_2S$	67.85 (67.69)	4.92 4.92	10.79 10.61)
3e	3-Br	93	Orange prisms	269—270	$C_{18}H_{11}BrN_2OS$	56.39 (56.16)	2.87 2.93	7.31 7.28)

Table II. Spectral Data for **3a—e**

Compound No.	MS M^+ (*m/e*)	IR (cm^{-1}, Nujol) (C=O)	NMR (δ, $CDCl_3$) Aromatic	C_3-H	Others
3a	304	1615	7.10—8.20 (12H, m)		
3b	318	1625	7.22—8.12 (10H, m)	6.99 (1H, s)	2.63 (3H, s, Me)
3c	334	1630	7.20—8.04 (10H, m)	6.41 (1H, s)	4.11 (3H, s, OMe)
3d	389	1625	7.20—8.10 (10H, m)	6.32 (1H, s)	3.29 (4H, t, J=4.8 Hz, CH_2–N–CH_2), 3.99 (4H, t, J=4.8 Hz, CH_2–O–CH_2)
3e	382, 384	1620	7.20—8.20 (10H, m), 8.40 (1H, s, C_4–H)		

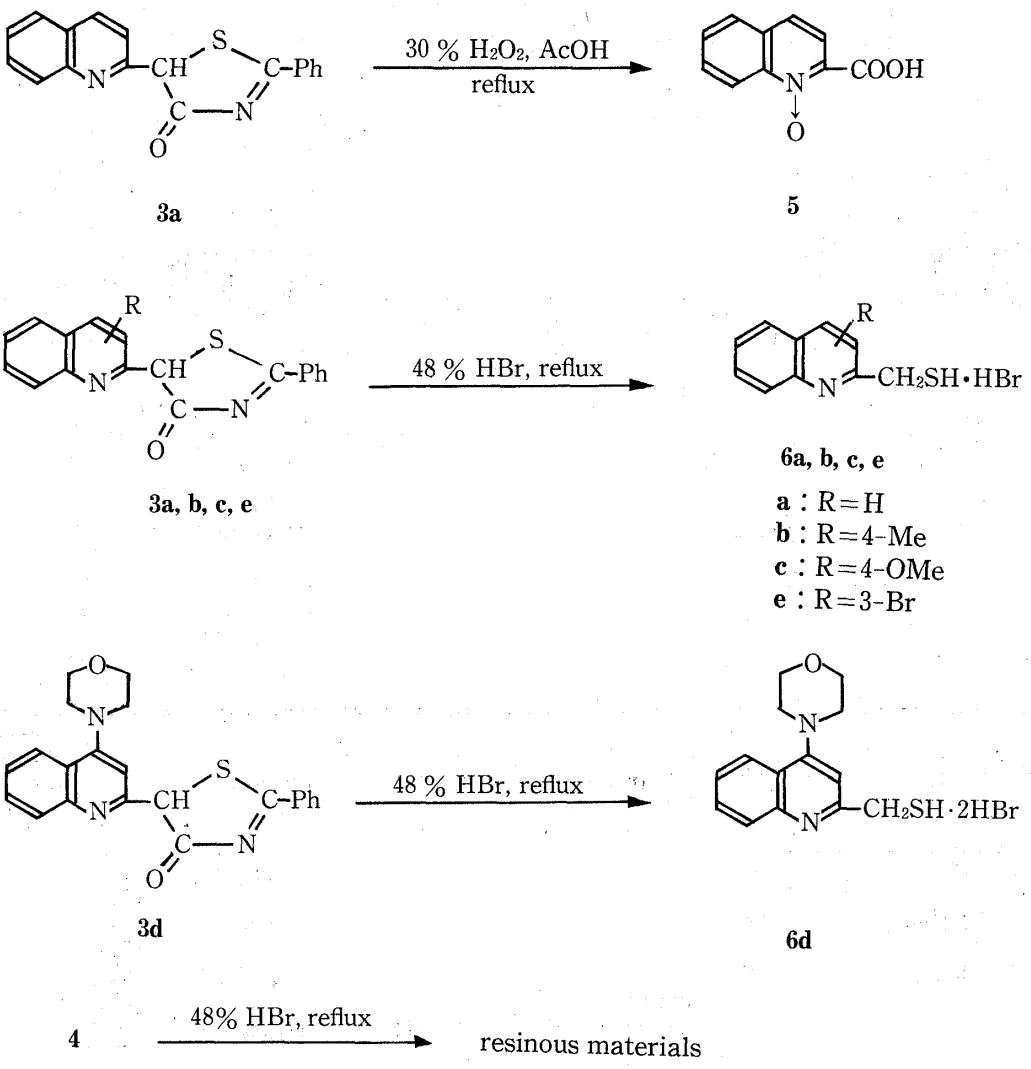
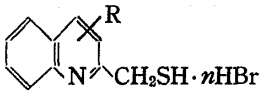


Chart 2

TABLE III. 2-Quinolinemethanethiol Hydrobromides



6a—e

Compd. No.	R	Yield (%)	Appearance	mp (°C)	MS (*m/e*) ($M^+ - n$HBr)	Formula	Analyses (%) Calcd. (Found) C	H	N
6a	H	87	Colorless prisms	150—151 (dec.)	175	$C_{10}H_{10}BrNS$	46.86 (46.71	3.91 3.92	5.46 5.32)
6b	4-Me	74	Pale yellow needles	182—184 (dec.)	189	$C_{11}H_{12}BrNS$	48.92 (48.89	4.44 4.53	5.16 5.27)
6c	4-OMe	51	White powder	199—200 (dec.)	205	$C_{11}H_{12}BrNOS$	46.14 (45.92	4.19 3.96	4.89 5.13)
6d	4-Morpholino	65	Pale brown prisms	222—223 (dec.)	232	$C_{14}H_{18}Br_2N_2OS$	39.81 (39.78	4.26 3.97	6.63 6.58)
6e	3-Br	76	Pale yellow needles	178—179 (dec.)	253, 255	$C_{10}H_8Br_2NS$	35.82 (35.93	2.98 2.74	4.18 3.95)

In the same way, isoquinoline 2-oxide (**7**) readily reacted at room temperature with **2**, and 5-(1-isoquinolyl)-2-phenyl-2-thiazolin-4-one (**8**) was obtained in 68% yield.

The structure of **8** was established by the elemental analyses, the mass spectrum (MS) (M^+: *m/e* 304) and the IR and NMR spectra. The IR spectrum of **8** exhibited a strong absorption at 1640 cm^{-1} attributed to a highly ionic carbonyl group and also an NH absorption at 3200 cm^{-1}. The NMR spectrum in deuteriochloroform showed the NH resonance signal exchangeable with deuterium oxide at δ 17.0 as a broad singlet which integrated to 0.8 proton, in addition to the aromatic multiplets, but no signal due to the C_1-proton of the isoquinoline ring was detected. These observations demonstrate that **8** exists as a tautomeric mixture of the ketone form **8**-A and the enamine form **8**-B in the ratio of 20: 80 in deuteriochloroform. Although **8**-B′ is also conceivable as an alternative enamine form of **8**, this configuration is probably negligible, because the C_8-proton signal of the isoquinoline ring appears in the normal region (δ 7.22—8.01), which indicates that the anisotropic effect of the 3-ketonic group of the thiazolone moiety does not operate, in contrast to the case of the enamine forms of 4-(1-isoquinolyl)-2-oxazolin-5-ones.[4]

Hydrolysis of **8** was readily effected by refluxing it with 48% hydrobromic acid for 8 h to give 1-isoquinolinemethanethiol hydrobromide (**9**) in 69% yield (Chart 3).

On the other hand, the reaction of pyridine 1-oxide with **2** under the same conditions resulted in the isolation of 4-acetoxy-2-phenylthiazole (**10**) as a liquid, bp 187—189 °C (15 mm Hg), no substitution product being detected.

We previously reported that 3-phenyl-5-(2-pyridyl)rhodanine undergoes hydrolysis to 2-pyridinemethanethiol upon being refluxed with 48% hydrobromic acid for 8 h, but 3-phenyl-5-(2-quinolyl)rhodanine (**11**) resists acid hydrolysis. However, it was recently found that 2-quinolinemethanethiol was also successfully obtained as the picrate in 49% yield by refluxing **11** with 48% hydrobromic acid for 12 h.

Thus, it may be concluded that the reactions of quinoline 1-oxides and isoquinoline 2-oxide with **2** proceed under much milder conditions as compared with 3-arylrhodanines,[3] and acid hydrolyses of the products are more convenient and favorable as a route to methanethiol derivatives. However, curiously, attempted substitution of pyridine 1-oxide with **2** failed; this difficulty may be overcome by more detailed examinations of the reaction conditions in the future.

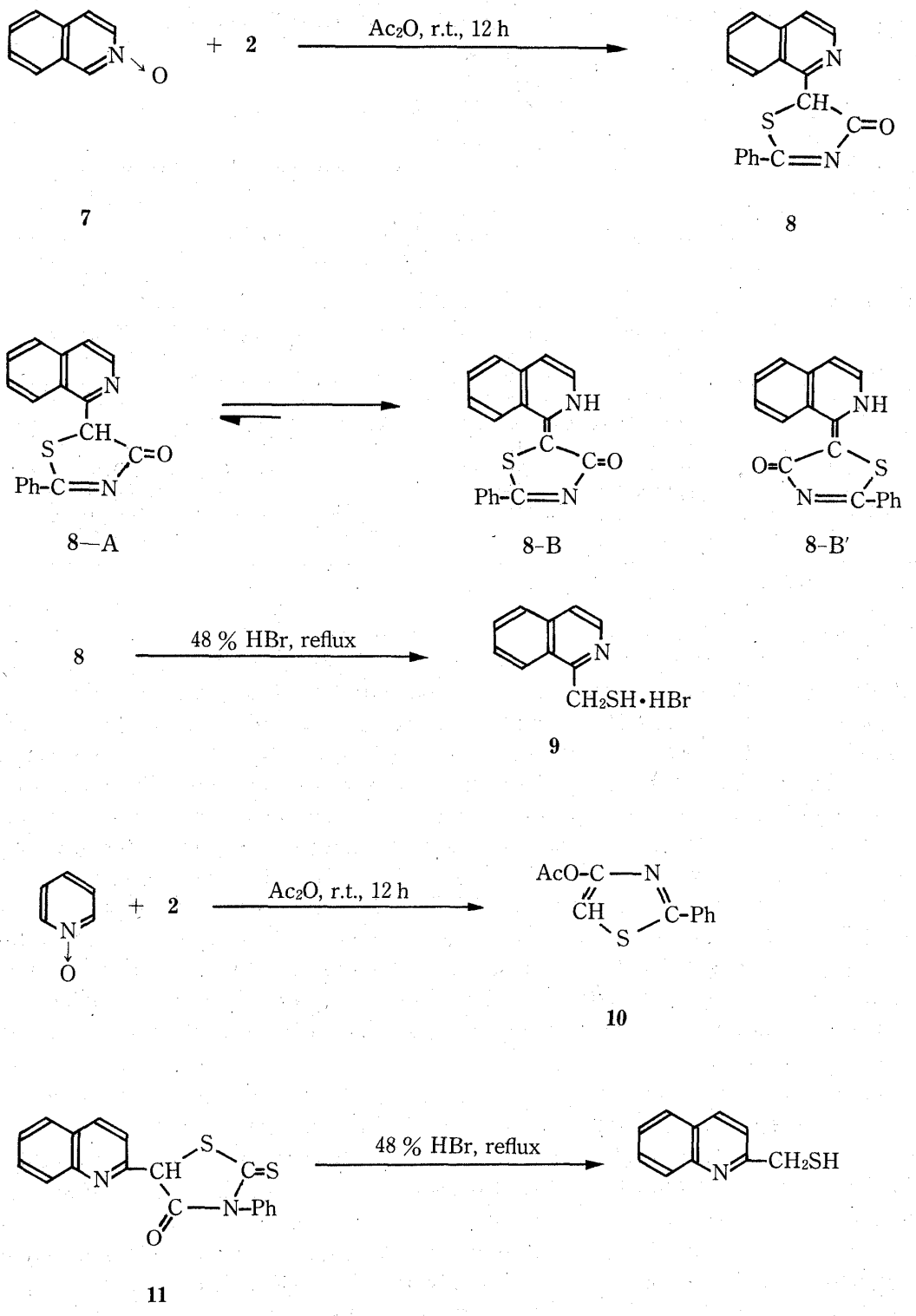


Chart 3

Experimental

All melting and boiling points are uncorrected. IR spectra were recorded on a JASCO IR-E spectrometer. NMR spectra were measured with a JEOL PS-100 spectrometer at 100 MHz using tetramethylsilane (TMS) as an internal reference. Mass spectra were obtained on a JMS 01SG spectrometer.

Reactions of Quinoline 1-Oxides (1) with 2-Phenyl-2-thiazolin-4-one (2)——A solution of **1a—f** (6 mmol) in Ac_2O (5 ml) was added dropwise to a stirred solution of **2** (5 mmol) in Ac_2O (6 ml). The reaction flask

was surrounded with an ice-bath. An exothermic reaction took place and crystals separated out from the reaction mixture. When the addition of the solution of **2** was completed, the ice-bath was removed and stirring was continued overnight at room temperature. The crystals were then filtered and recrystallized from ethanol to give 2-phenyl-5-(2-quinolyl)-2-thiazolin-4-ones (**3a**—**e**) in good yields.

The results and some physical and spectral data of **3a**—**e** are shown in Tables I and II.

Reaction of 4-Chloroquinoline 1-Oxide (1f) with 2——A solution of **1f** (1.08 g, 6 mmol) in Ac_2O (6 ml) was added dropwise to a stirred solution of **2** (0.87 g, 6 mmol) in Ac_2O (6 ml). The reaction mixture turned pink and crystals separated out. Stirring was continued at room temperature overnight, then the crystals were filtered and recrystallized from ethanol to give 2.09 g (87%) of 4-acetoxy-5-(4-chloro-2-quinolyl)-2-phenylthiazole (**4**), orange flocculents, mp 162°C. MS *m/e*: 381 (M^+), 383 ($M^+ +2$). *Anal.* Calcd for $C_{20}H_{13}ClN_2O_2S$: C, 62.89; H, 3.66; N, 7.34. Found: C, 62.99; H, 3.39; N, 7.26. IR ν_{max}^{Nujol} cm^{-1}: 1770 (C=O). NMR ($CDCl_3$) δ: 2.59 (3H, s, CH_3–CO–), 7.22—8.20 (10H, m, arom-H).

Oxidation of 3a to Quinaldic Acid 1-Oxide (5)——A mixture of **3a** (1.52 g) and 30% H_2O_2 (25 ml) was refluxed for 7 h to give an almost colorless solution. The solution was concentrated under reduced pressure and H_2O (20 ml) was added. Deposited crystals were filtered and recrystallized from methanol to give 0.67 g (72%) of **5**, pale brown needles, mp 170°C (dec.).

Hydrolyses of 3a—e to 2-Quinolinemethanethiol Hydrobromides (6a—e)——A suspension of **3a**—**e** (3 mmol) in 48% HBr (40 ml) was refluxed for 8 h to give an almost colorless solution. After cooling with an external ice-bath, the resulting crystals were filtered and recrystallized from H_2O to give benzoic acid, colorless needles, mp 121°C. The filtrate was concentrated, and the residual solid mass was recrystallized from ethanol–ether to give 2-quinolinemethanethiol monohydrobromides (**6a**—**d**) or dihydrobromide (**6e**) (Table III).

Reaction of Isoquinoline 2-Oxide (7) with 2——A solution of **7** (0.78 g, 5 mmol) in Ac_2O (5 ml) was added dropwise to a stirred solution of **2** (0.73 g, 5 mmol) in Ac_2O (6 ml). The reaction flask was surrounded with an ice-bath. When the addition of the solution of **7** was completed, the ice-bath was removed and stirring was continued at room temperature overnight. The separated crystals were filtered off and recrystallized from ethanol to give 1.03 g (68%) of 5-(1-isoquinolyl)-2-phenyl-2-thiazolin-4-one (**8**), red needles, mp 255—256°C. MS *m/e*: 304 (M^+). *Anal.* Calcd for $C_{18}H_{12}N_2OS$: C, 71.04; H, 3.98; N, 9.21. Found: C, 70.95; H, 4.05; N, 9.13. IR ν_{max}^{Nujol} cm^{-1}: 1640 (C=O), 3200 (NH). NMR ($CDCl_3$) δ: 7.22—8.01 (11.2H, m, 11 arom-H and 0.2 methine-H), 17.0 (0.8H, br s, exchangeable with D_2O, NH).

Hydrolysis of 8 to 1-Isoquinolinemethanethiol Hydrobromide (9)——A suspension of **8** (0.91 g, 3 mmol) in 48% HBr (40 ml) was refluxed for 8 h to give a colorless solution. After cooling with an ice-bath, the resulting crystals were filtered and recrystallized from H_2O to give benzoic acid. The filtrate was concentrated, and the residual solid mass was recrystallized from ethanol–ether to give 0.53 g (69%) of **9**, colorless needles, mp 187—189°C. MS *m/e*: 175 ($M^+ -$HBr). *Anal.* Calcd for $C_{10}H_{10}BrNS$: C, 46.86; H, 3.91; N, 5.46. Found: C, 46.93; H, 3.97; N, 5.53.

Attempted Reaction of Pyridine 1-Oxide with 2——A solution of pyridine 1-oxide (0.57 g, 6 mmol) in Ac_2O (6 ml) was added to a solution of **2** (0.73 g, 5 mmol) in Ac_2O (6 ml). The reaction flask was surrounded with an ice-bath. After addition of the solution of pyridine 1-oxide had been completed, the resulting solution was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the resulting oil was washed with H_2O, then distilled under reduced pressure to give 1.06 g (81%) of 4-acetoxy-2-phenylthiazole (**10**), bp 187—189°C (15 mmHg).

Hydrolysis of 3-Phenyl-5-(2-quinolyl)rhodanine (11)——A suspension of **11** (0.8 g) in 48% HBr (100 ml) was refluxed for 12 h. The resulting pale yellow solution was concentrated under reduced pressure. The residue was dissolved in H_2O (6 ml), and the solution was neutralized with K_2CO_3 then extracted with CH_2Cl_2. The oily residue from the extract was chromatographed on silica gel with *n*-C_6H_{14} and ether. The first fraction eluted with *n*-C_6H_{14} gave 0.13 g (65%) of aniline. The second fraction eluted with *n*-C_6H_{14}–ether (7: 1) yielded 2-quinolinemethanethiol as an oil, which was treated with picric acid in ether to give 0.45 g (48%) of the picrate, orange prisms, mp 164—166°C (MeOH). *Anal.* Calcd for $C_{10}H_9NS \cdot C_6H_3N_3O_7$: C, 47.52; H, 2.97; N, 13.86. Found: C, 47.55; H, 2.93; N, 13.78.

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References and Note

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