Studies on Tertiary Amine Oxides. LXVII (1). Reactions of Aromatic *N*-Oxides with 3-Arylrhodanines in the Presence of Acetic Anhydride

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Quinoline 1-oxides **1** readily react with 3-arylrhodanines **2** in the presence of acetic anhydride to afford 3-aryl-5-(2-quinolyl)rhodanines **3** in high yields. These products resist hydrolysis under both alkaline and acidic conditions, but is oxidized to quinaldinic acid 1-oxide **4** with 30% hydrogen peroxide in hot acetic acid. Besides isoquinoline 2-oxide **5**, pyridine 1-oxide **7a** also reacts in the same way to give 3-aryl-5-(2-pyridyl)rhodanines **8**, although the reactivity of γ-picoline 1-oxide **7b** is considerably lower. Contrary to **3**, 3-phenyl-5-(2-pyridyl)rhodanine **8a** is successfully hydrolyzed with boiling 48% hydrobromic acid to 2-pyridinemethanethiol **10** in 57% yield.

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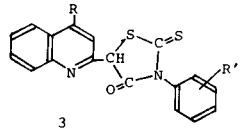
As a further extension of studies on the reaction of aromatic *N*-oxides with active methylene compounds in the presence of acylating agents (3), reactions with those of heterocyclic series were investigated and many interesting results were obtained. This paper deals with our observations on reactions using 3-arylrhodanines as active methylene compounds (4).

Taking into account the usual procedure for the condensation reaction of rhodanines, quinoline 1-oxide **1a** was allowed to react with 3-arylrhodanines **2a-h** in hot acetic anhydride containing sodium acetate. When **1a** in acetic anhydride was added at once to a solution of **2** in acetic anhydride, containing a catalytic amount of anhydrous sodium acetate, heated at 90°, the solution immediately turned orange to red, and after a few minutes fine crystals began to precipitate. After heating was continued further 1-2 hours until precipitation ceased, precipitates were recrystallized from acetic acid to give 3-aryl-5-(2-quinolyl)rhodanines **3a-h** in good to high yields (69-94%) (Table I and Scheme 1).

Table I

3-Aryl-5-(2-quinolyl)rhodanine



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Compound No.	R	R'	Yield %	Appearance	M.p. °C	Ir (cm⁻¹) (Nujol) C=O	Formula	Analysis Calcd./Found C	H	N
3a	H	H	89	Red needles	>300	1635	$C_{18}H_{12}N_2OS_2$	64.58	3.57	8.33
								64.03	3.57	8.40
3b	H	*p*-Me	93	Orange flocculent	>300	1640	$C_{19}H_{14}N_2OS_2$	65.14	4.03	8.00
								64.81	4.08	8.01
3c	H	*m*-Me	96	Red prisms	>300	1640	$C_{19}H_{14}N_2OS_2$	65.14	4.03	8.00
								65.10	4.00	8.07
3d	H	*o*-Me	69	Reddish orange needles	>300	1635	$C_{19}H_{14}N_2OS_2$	65.14	4.03	8.00
								65.03	3.92	8.05
3e	H	*p*-OMe	94	Red needles	>300	1630	$C_{19}H_{14}N_2O_2S_2$	62.29	3.85	7.65
								62.15	3.88	7.60
3f	H	*o*-OMe	91	Red plates	270-271	1635	$C_{19}H_{14}N_2O_2S_2$	62.29	3.85	7.65
								62.41	3.85	7.73
3g	H	*m*-NO_2	84	Orange granules	>300	1645	$C_{18}H_{11}N_3O_3S_2$	56.69	2.88	10.49
								56.91	3.01	10.31
3h	H	*m*-Cl	92	Red plates	292-293	1635	$C_{18}H_{11}ClN_2OS_2$	58.33	2.97	7.55
								57.97	3.17	7.35
3i	Cl	H	86	Red prisms	>300	1640	$C_{18}H_{11}ClN_2OS_2$	58.33	2.97	7.55
								57.64	3.09	7.30
3j	Me	H	86	Red needles	>300	1635	$C_{19}H_{14}N_2OS_2$	65.14	4.03	8.00
								64.67	4.11	8.05
3k	OAc	H	73	Brown needles	275-276	1630 1770	$C_{20}H_{14}N_2O_3S_2$	60.91	3.58	7.10
								60.17	3.64	6.95

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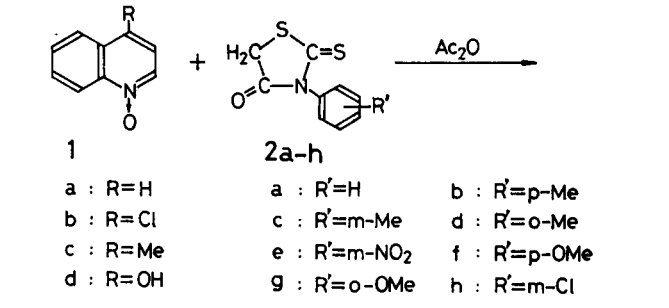
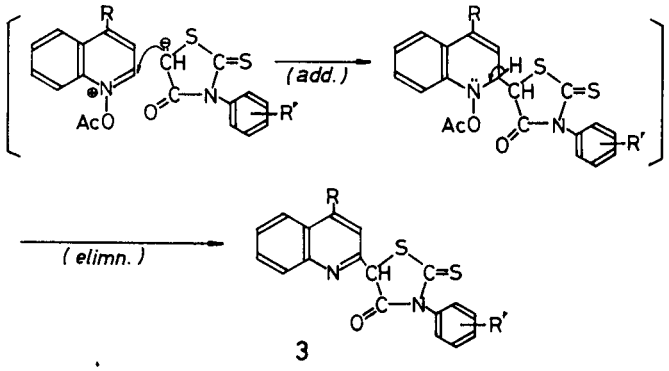
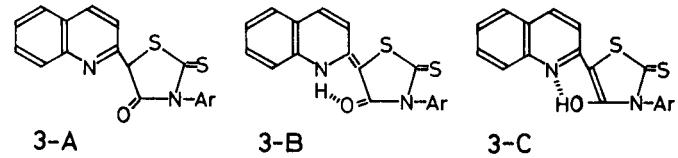
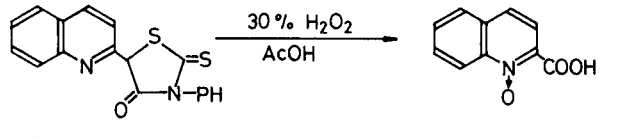
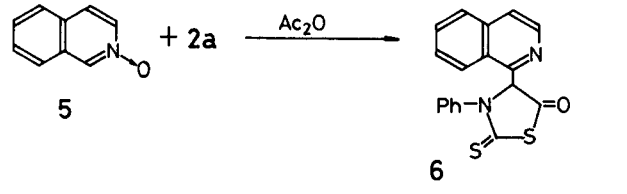




a : R=H, R'=H
b : R=H, R'=p-Me
c : R=H, R'=m-Me
d : R=H, R'=o-Me
e : R=H, R'=m-NO2
f : R=H, R'=p-OMe
g : R=H, R'=o-OMe
h : R=H, R'=m-Cl
i : R=Cl, R'=H
j : R=Me, R'=H
k : R=OAc, R'=H







Scheme 1

Some reaction conditions were next examined with the reaction of **1a** and 3-phenylrhodanine **2a**. The reaction in acetic anhydride at 90° without sodium acetate proceeded in essentially the same way; in view of the usual examples of this type of reaction (3,5), sodium acetate is likely not necessary for the initiation of the reaction. Treatment of **1a** with **2a** and 1.2 equivalents of acetic anhydride in hot dimethylformamide (DMF) afforded only the 2-substituted quinoline **3a** in the same yield of 89%, no *N*-ylide formation being noticed contrary to our expectation (3f). The reaction using benzoyl chloride and triethylamine in chloroform proceeded at room temperature to give also **3a** though in a lower yield of 42%. However, the use of tosyl chloride and triethylamine in chloroform was not effective, **2a** being recovered almost quantitatively.

All the products **3a-h** gave the analytical values and the mass numbers (m/e) of the parent peaks in full agreement with the postulated structures. Their ir spectra did not show any absorptions in the 1720-1730 cm^{-1} region characteristic of the carbonyl group in 3-arylrhodanines (6), but instead displayed absorptions around 1640 cm^{-1} indicative of highly ionic carbonyl groups (7).

Because of their highly sparing solubilities in the usual organic solvents, the ^1H nmr spectra of the products could not be determined except the product **3h**. The ^1H nmr spectrum of **3h** in deuteriochloroform showed two one-proton doublets at δ 6.70 and 7.80 (J = 10.0 Hz), which could be assigned to the β- and γ-protons of the quinoline ring, respectively (8), but not signal due to the α-proton was observed. There was also noticed a broad singlet exchangeable with deuterium oxide at δ 13.3 which integrated to 0.75 proton and could be reasonably assigned to a N-H group, besides an aromatic multiplet due to eight protons at δ 7.22-7.83.

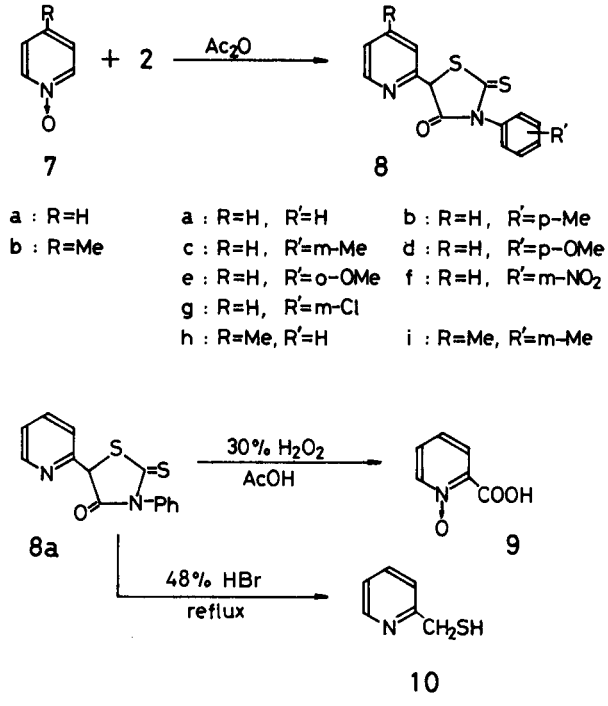
Thus, it was revealed that, at least in **3h**, the enamine form **3-B** was the most predominant species among three tautomeric structures (**3-A**, **3-B**, **3-C**). It may well be considered that the structures of the other **3** also have substantially the same features.

When **3a** was refluxed with excess 30% hydrogen peroxide in acetic acid for 10 hours, quinaldinic acid 1-oxide **4** (9) was formed in 43% yield. In order to obtain 2-quinolinemethanethiol or its related compound, alkaline hydrolysis of **3a** was examined under various conditions, but all attempts were unsuccessful and **3a** was mostly recovered, contrary to the cases of 5-arylidenerhodanines which undergo alkaline hydrolysis to give α-mercaptoacrylic acids (10). For instance, when **3a** was refluxed in ethanolic sodium hydroxide for 8 hours followed by acidification of the resulting solution, **3a** was recovered almost quantitatively. It was further found that **3a** stoutly resisted acid hydrolysis, and treatment with Raney nickel (W-4) (11) in acetic acid at refluxing temperature gave rise to only resinification.

Subsequently, reactions of 2-chloroquinoline and quinaldine 1-oxides with **2a** were attempted in hot acetic anhydride or in hot DMF in the presence of acetic anhydride, but only **2a** was recovered almost quantitatively in each case. On the other hand, 4-chloroquinoline and lepidine 1-oxides, **1b** and **1c**, readily reacted with **2a** when heated in acetic anhydride containing a catalytic amount of sodium acetate to afford the corresponding 2-substituted quinolines, **3i** and **3j**, in good yields. From the reaction of 4-quinolinol 1-oxide **1d** with **2a** under the same conditions, 5-(4-acetoxy-2-quinolyl)-3-phenylrhodanine **3k** was obtained in 73% yield. The ir spectrum of **3k** exhibited two carbonyl bands at 1770 and 1630 cm^{-1}, and its ^1H nmr spectrum in deuteriochloroform showed a one-proton singlet at δ 6.70 assignable to the β-proton of the quinoline ring, a three-proton singlet at δ 2.49 due to a methyl group, a broad singlet at δ 13.3 which integrated to 0.35 proton and an aromatic multiplet due to nine protons at δ 7.2-7.8.

Further, isoquinoline 2-oxide **5** was found to react with **2a** in the same way, giving 5-(1-isoquinolyl)-3-phenylrhodanine **6** in 85% yield.

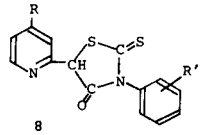
These reactions should be assumed to proceed by the addition-elimination mechanism in the usual way as shown



Scheme 2

Table II

3-Aryl-5-(2-pyridyl)rhodanine



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Compound No.	R	R'	Yield %	Appearance	M.p. °C	Ir (cm^{-1}) (Nujol) C=O	Formula	Analysis Calcd./Found C	H	N
8a	H	H	78	Orange needles	272 dec.	1630	$C_{14}H_{10}N_2OS_2$	58.74	3.52	9.79
								58.78	3.61	9.29
8b	H	*p*-Me	84	Orange needles	>300	1625	$C_{15}H_{12}N_2OS_2$	60.00	4.03	9.33
								59.60	4.08	9.26
8c	H	*m*-Me	61	Orange needles	262-263	1625	$C_{15}H_{12}N_2OS_2$	60.00	4.03	9.33
								59.73	4.10	9.34
8d	H	*p*-OMe	81	Reddish orange needles	>300	1630	$C_{15}H_{12}N_2O_2S_2$	56.96	3.82	8.86
								56.64	3.86	8.77
8e	H	*o*-OMe	76	Orange needles	250 dec.	1625	$C_{15}H_{12}N_2O_2S_2$	56.96	3.82	8.86
								56.64	3.87	8.71
8f	H	*m*-NO_2	56	Brown cubes	273 dec.	1630	$C_{14}H_9N_3O_3S_2$	50.76	2.74	12.69
								50.94	2.81	12.72
8g	H	*m*-Cl	79	Yellow needles	275-277	1630	$C_{14}H_9ClN_2OS_2$	52.41	2.81	8.73
								52.34	2.81	8.73
8h	Me	H	32	Brown needles	>300	1625	$C_{15}H_{12}N_2OS_2$	60.00	4.03	9.33
								59.69	3.60	9.70
8i	Me	*m*-Me	23	Yellow needles	225-226	1630	$C_{16}H_{14}N_2OS_2$	61.14	4.49	8.91
								59.90	5.04	8.93

in Scheme 1 (3b, 3c), and the enhanced reactivity of 3-arylrhodanine as active methylene compound is very noticeable, which fact is supported by reactions of pyridine 1-oxide **7a**.

The reaction of **7a** with 3-arylrhodanines **2** in hot acetic anhydride containing a catalytic amount of sodium acetate took place in practically the same manner as that of **1**, giving 3-aryl-5-(2-pyridyl)rhodanines **8a-g** in generally good yields after 5 hour's heating. Treatment of **7a** with **2a** and 1.3 equivalent acetic anhydride in hot DMF afforded **8a** also in a good yield of 72%. Nevertheless, the reaction of γ-picoline 1-oxide **7b** with 3-phenyl- and 3-(*m*-tolyl)-rhodanine, **2a** and **2c**, under the same conditions gave the corresponding 2-substituted pyridines, **8h** and **8i**, in considerably lower yields of 32 and 23%, respectively. Accordingly, the pyridine nucleus of the benzenoid structure is potentially less reactive as compared with naphthoidal quinoline nucleus in these cases too, in spite of the high reactivity of pyridine 1-oxide itself (Table II, Scheme 2).

Products thus obtained were again sparingly soluble in the usual organic solvents and the ^1H nmr spectra could not be measured. However, their analytical values, the mass numbers (m/e) of the parent peaks and the carbonyl bands at 1625-1630 cm^{-1} region in the ir spectra were in good agreement with the assigned structures.

Oxidation of 3-phenyl-5-(2-pyridyl)rhodanine **8a** with an excess of 30% hydrogen peroxide in boiling acetic acid for 6 hours gave picolinic acid 1-oxide **9** in 52% yield.

Further, acid hydrolysis of **8a** was successfully effected contrary to the case of **3a**. When **8a** was refluxed with 48% hydrobromic acid for 8 hours, 2-pyridinemethanethiol **10** (12) was obtained in 57% yield. This result is very interesting for its synthetic implication of such a heteroaromatic methanethiol. In order to widen the scope of this type of reaction, further studies using various *S*-heterocycles are in progress in our laboratory.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded on a JASCO IR-E spectrophotometer. Nmr spectra were measured with a JEOL PS-100 spectrometer at 100 MHz using tetramethylsilane as the internal reference. Mass spectra were obtained on a JMS 01SG spectrometer.

Reaction of Quinoline 1-Oxides **1a-d** with 3-Arylrhodanines **2a-h**. Method A.

A solution of **1a-d** (6 mmoles) in acetic anhydride (5 ml.) was added all at once to a solution of **2a-h** (5 mmoles) and anhydrous sodium acetate (0.1 g.) in acetic anhydride (5 ml.) heated at 90°. The reactants immediately turned orange to red, and fine crystals began to precipitate after 1-5 minutes. Heating was continued further 1-2 hours until precipitation ceased. After cooling, precipitated crystals were filtered and recrystallized from acetic acid to give 3-aryl-5-(2-quinolyl)rhodanines **3a-k** in high yields of 69-96%.

The results and some physical data of **3a-k** are shown in Table I. The mass numbers (m/e) of the parent peaks of products perfectly agreed with the respective structures.

Reaction of Quinoline 1-Oxide **1a** with 3-Phenylrhodanine **2a**.

a) Method B.

Quinoline 1-oxide **1a** (0.87 g., 6 mmoles) was treated with **2a** (1.05 g., 5 mmoles) in acetic anhydride heated at 90° in a similar manner with Method A, but without sodium acetate, to give 1.50 g. (89%) of 3-phenyl-5-(2-quinolyl)rhodanine **3a**.

b) Method C.

A solution of **1a** (0.87 g., 6 mmoles) and acetic anhydride (0.71 g., 7 mmoles) in DMF (4 ml.) was added all at once to a solution of **2a** (1.05 g., 5 mmoles) in DMF (4 ml.) heated at 90°. The reactants immediately turned red, and red crystals precipitated. After heating was continued for 1 hour, similar processing gave 1.50 g. (89%) of **3a**.

c) Method D.

A solution of **1a** (0.73 g., 5 mmoles) and benzoyl chloride (0.9 g., 7 mmoles) in chloroform (8 ml.) was added to a solution of **2a** (1.0 g., 4.9 mmoles) and triethylamine (0.71 g., 7 mmoles) in chloroform (50 ml.), and the reactants were stirred overnight at room temperature. The red colored reaction mixture was evaporated, and the residue was washed with hot ethanol and then recrystallized from acetic acid to give 0.67 g. (42%) of **3a**. From the ethanolic washings, 0.55 g. (55%) of **2a** was recovered.

Oxidation of **3a** to Quinaldinic Acid 1-Oxide **4**.

A mixture of **3a** (1.68 g.), 30% hydrogen peroxide (20 ml.) and acetic acid (50 ml.) was refluxed for 10 hours to give an almost colorless solution. The solution was evaporated under reduced pressure, and water (20 ml.) was added. Deposited crystals were recrystallized from methanol to give 0.41 g. (43%) of **4**, pale brown needles, m.p. 169-170° dec. (9).

Reaction of Isoquinoline 1-Oxide **5** with **2a**.

A solution of **5** (0.78 g., 5 mmoles) in acetic anhydride was added to a solution of **2a** (1.1 g., 5 mmoles) and sodium acetate (0.1 g.) in acetic anhydride (8 ml.) heated at 90°. The reactants were heated for 2 hours, red-brown crystals precipitated were filtered and recrystallized from acetic acid to give 1.4 g. (84%) of 5-(1-isoquinolyl)-3-phenylrhodanine **6**, red prisms, m.p. 300°; ir (nujol): 1625 cm^{-1} (C=O); ms: m/e 336 (M^+).

Anal. Calcd. for $C_{18}H_{11}ON_2S_2$: C, 64.28; H, 3.60; N, 8.33. Found: C, 63.97; H, 3.64; N, 8.36.

Reaction of Pyridine 1-Oxides **7** with **2**. Method A.

A solution of **7** (3.5 mmoles) in acetic anhydride (5 ml.) was added at once to a solution of **2** (3 mmoles) and sodium acetate (0.1 g.) in acetic anhydride (7 ml.) heated at 90°. The reactants were heated for 5 hours, orange precipitates were filtered and recrystallized from acetic acid to give 3-aryl-5-(2-pyridyl)rhodanines **8a-i**.

The results and some physical data of **8a-i** are shown in Table II. The mass numbers (m/e) of the parent peaks of products perfectly agreed with the respective structures.

Reaction of Pyridine 1-Oxide **7a** with **2a**. Method C.

A solution of **7a** (0.33 g., 3.5 mmoles) and acetic anhydride (0.4 g., 4 mmoles) in DMF (5 ml.) was added to a solution of **2a** (0.63 g., 3 mmoles) in DMF (6 ml.) heated at 90°. The reactants were heated for 5 hours, orange precipitates were filtered and recrystallized from acetic acid to give 0.62 g. (72%) of 3-phenyl-5-(2-pyridyl)rhodanine **8a**.

Oxidation of **8a** to Picolinic Acid 1-Oxide, **9**.

A mixture of **8a** (0.57 g.), 30% hydrogen peroxide (25 ml.) and acetic acid (30 ml.) was refluxed for 5 hours to give an almost colorless solution. The solution was evaporated under reduced pressure, and the residue was recrystallized from water to give 0.13 g. (52%) of picolinic acid 1-oxide **9**, colorless needles, m.p. 166-167° dec. It was identified by direct comparison with an authentic sample.

Hydrolysis of **8a** to 2-Pyridinemethanethiol **10**.

A suspension of **8a** (0.4 g.) in 48% hydrobromic acid (40 ml.) was refluxed for 8 hours. The resulting pale yellow solution was evaporated

under reduced pressure. The residue was dissolved in water (3 ml.), neutralized with potassium carbonate and extracted with dichloromethane. The oily residue from the extract was chromatographed on silica gel column with *n*-hexane and ether. The first fraction eluted with *n*-hexane gave 0.065 g. (51%) of aniline. The second one eluted with *n*-hexane-ether (9:1) yielded **10** (12) as an oil, which was treated in ether with picric acid to give 0.283 g. (57%) of picrate, yellow prisms, m.p. 171-172° (from methanol).

Anal. Calcd. for $C_6H_7NS \cdot C_6H_3O_7N_3$: C, 40.68; H, 2.85; N, 15.82. Found: C, 40.78; H, 2.72; N, 15.66.

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