Studies on Tertiary Amine Oxides. LXVIII. (1). Reactions of Aromatic *N*-Oxides with 2-Substituted 2-Oxazolin-5-ones in the Presence of Acetic Anhydride

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Quinoline 1-oxides **1a-f** readily react with 2-phenyl- and 2-methyl-2-oxazolin-5-ones, **2a** and **2b**, in the presence of acetic anhydride to afford 2-substituted 4-(2-quinolyl)-2-oxazolin-5-ones **3a-h** in good yields. Hydrolysis of **3a-f** with 10% hydrochloric acid under refluxing conditions gives the corresponding 2-aminomethylquinoline dihydrochlorides **5a-e** or monohydrochloride **5f** also in good yields. Similar results are obtained from reactions of isoquinoline 2-oxide **9** with **2a,b** under the same conditions.

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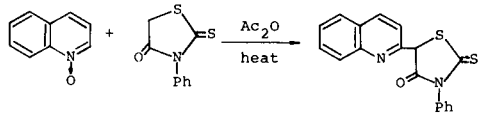
The preceding paper of this series has shown that aromatic *N*-oxides readily react with 3-arylrhodanines in the presence of acetic anhydride to give the corresponding α-substituted products in high yields as exemplified below (1).



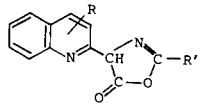
As a continuation of this work the reaction of quinoline and isoquinoline *N*-oxides with 2-phenyl- and 2-methyl-2-oxazolin-5-ones was investigated.

A mixture of hippuric acid and 3 equivalents of acetic anhydride containing a catalytic amount of anhydrous sodium acetate was heated at 90° for 30 minutes in order to form 2-phenyl-2-oxazolin-5-one **2a** (3). Without isolation of **2a**, to this solution was added at once a solution of quinoline 1-oxides **1a-f** in acetic anhydride. The solution immediately turned red, and after 1-15 minutes red crystals began to precipitate. Heating at 90° was continued further 1-2 hours until precipitation ceased, and precipitates were filtered, washed successively with ethanol and water, and recrystallized from ethanol to afford 2-phenyl-4-(2-quinolyl)-2-oxazolin-5-ones **3a-f** in generally high yield (Scheme 1 and Table I).

Subsequently, quinoline 1-oxide **1a** and 4-methoxyquinoline 1-oxide **1d** were allowed to react under the same conditions with 2-methyl-2-oxazolin-5-one **2b** preliminarily prepared from *N*-acetylglycine in the same manner. In the

Table I

4-(2-Quinolyl)-2-oxazolin-5-one



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Compound No.	R	R′	Yield %	Appearance	M.p. °C	Formula	Analysis Calcd./Found C	H	N
3a	H	Ph	86	red needles	239	$C_{18}H_{14}N_2O_2$	74.99	4.20	9.72
							74.92	4.32	9.85
3b	4-CH_3	Ph	49	reddish brown needles	219-220	$C_{19}H_{14}N_2O_2$	75.48	4.67	9.27
							75.21	4.77	9.24
3c	4-Cl	Ph	78	dark red needles	284-285	$C_{18}H_{11}ClN_2O_2$	66.91	3.41	8.36
							66.69	3.33	8.63
3d	4-OMe	Ph	83	orange prisms	275-276	$C_{19}H_{14}N_2O_3$	71.69	4.43	8.80
							71.73	4.39	8.84
3e	4-morpholino	Ph	91	red needles	245-246	$C_{22}H_{19}N_3O_3$	70.76	5.13	11.25
							70.71	5.10	11.08
3f	3-Br	Ph	93	dark red needles	277	$C_{18}H_{11}BrN_2O_2$	58.75	3.20	7.67
							58.83	3.01	7.68
3g	H	CH_3	49	reddish brown needles	174-175	$C_{13}H_{10}N_2O_2$	69.01	4.46	12.38
							69.21	4.57	12.12
3h	4-OMe	CH_3	52	yellow needles	231-233	$C_{14}H_{12}N_2O_3$	65.62	4.72	10.93
							65.70	4.59	10.82

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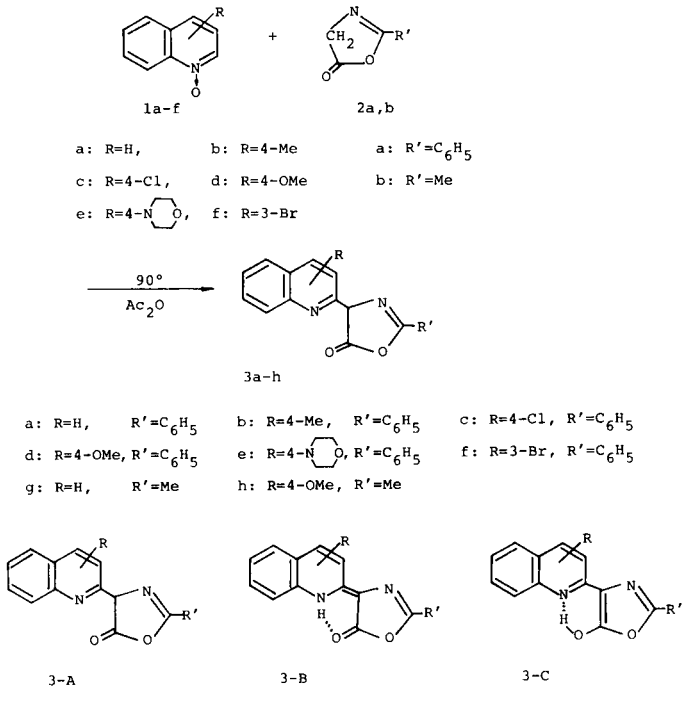
reaction of **1a**, the reactants immediately turned orange to red, and reddish brown crystals separated slowly. After heating at 90° for 3 hours, 2-methyl-4-(2-quinolyl)-2-oxazolin-5-one **3g** was obtained in a somewhat lower yield of 49%. On the other hand, no crystalline precipitates were formed in the reaction of **1d**, though reddish coloration was observed. However, 2-methyl-4-(4-methoxy-2-quinolyl)-2-oxazolin-5-one **3h** could be isolated in 52% yield upon evaporation of the reaction mixture under reduced pressure followed by chromatography on silica gel (Scheme 1 and Table I).



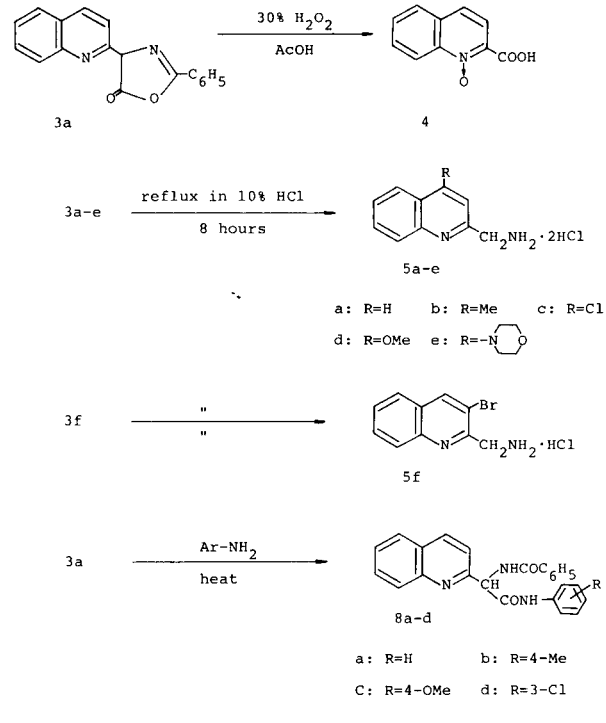
Scheme 1

All the products **3a-h** gave the analytical values and the mass numbers (m/e) of parent peaks in full agreement with the proposed structures. Their ir spectra exhibited two strong bands at 1625-1660 and 1675-1710 cm^{-1} regions, which were attributable to the azomethine and the highly ionic lactone-carbonyl groups, respectively, of the oxazolone ring. Moreover, the NH absorptions were observed at 3180-3200 cm^{-1} region for all the compounds, indicating the presence of enamine form (Table II).

The ^1H nmr spectra in deuteriochloroform showed the N-H resonance signals as broad singlets exchangeable with deuterium oxide at δ 11.4-12.0 except in the cases of **3c** and **3f**, in addition to the respective aromatic multiplets, no signals due to the C_2-proton of the quinoline ring being observed (Table II).

These observations demonstrate that most of the products **3** exist as the tautomeric mixture of the ketone form **3-A** and the enamine form **3-B**; the contribution of the enol form **3-C** seems negligible (4). From the integrated areas of the respective N-H signals, the ratios of **3-A** to **3-B** in deuteriochloroform are approximately as follows: 50:50 in **3a**, 30:70 in **3b**, 60:40 in **3d**, 20:80 in **3e**, 60:40 in **3g** and 50:50 in **3h**. On the other hand, the N-H signal could not be detected in the ^1H nmr spectra of **3c** and **3f** although the measurement was done to the low field around δ 20. Accordingly **3c** and **3f** seem to exist exclusively in the ketone form **3-A** in deuteriochloroform, however the presence of the enamine form is detectable by the ir spectra in Nujol (Table II).

When **3a** was refluxed with excess 30% hydrogen peroxide in acetic acid for 8 hours, quinaldic acid 1-oxide **4** (1) was formed in 61% yield. Then, hydrolysis of **3a-f** was examined in order to obtain 2-aminomethylquinoline derivatives. It is well known that 2-oxazolin-5-ones undergo hydrolysis with hot caustic alkaline solution (5), but attempted hydrolysis of **3a** with 10% ethanolic sodium hydroxide under refluxing conditions for 5 hours was unsuccessful, **3a** being recovered almost quantitatively. On the contrary, hydrolysis of **3a-f** was smoothly effected by refluxing in 10% hydrochloric acid for 8 hours, and the corresponding 2-aminomethylquinolines were isolated as the dihydrochlorides **5a-e** from **3a-e** and the monohydrochloride **5f** from **3f** in high yields (Scheme 2 and Table III).



Scheme 2

Griffin and Dean (6) reported that 2-phenyl-4-(4-quinolylmethylidene)-5-oxazolone **6** is convertible to 2-phenyl-4-(4-quinolylmethylidene)-5-imidazolone **7** upon successive

Table II

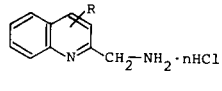
Spectral Data of **3a-h**

Compound No.	R	R'	MS M^+(m/e)	Ir (cm^{-1}, Nujol) N-H	Ir (cm^{-1}, Nujol) C=N C=O	Aromatic Protons Containing the Methine Proton	Nmr (deuteriochloroform) (δ) CH_3 or OCH_3	N-H (a)	Others
3a	H	Ph	288		1635	7.23-8.10		12.0	
				3200	1675	(11.5H, m)		(0.5H, bs)	
3b	4-CH_3	Ph	302		1645	7.22-7.90	2.60	11.5	
				3180	1705	(10.3H, m)	(3H, s)	(0.7H, bs)	
3c	4-Cl	Ph	322		1600	7.21-8.31 (m)		none	
			324	3180	1710				
3d	4-OCH_3	Ph	318		1645	6.95 (1H, s, C_5-H)	4.15	11.5	
				3185	1675	7.23-8.10	(3H, s)	(0.4H, bs)	
						(9.6H, m)			
									3.52 (4H, t, J = 4.8 Hz, CH_2-N-CH_2
3e	4-Morphorino	Ph	373		1645	7.06 (1H, s, C_3-H)		11.5	
				3180	1705	7.22-8.04		(0.8H, bs)	3.96 (4H, t, J = 4.8 Hz, CH_2-O-CH_2)
						(9.2H, m)			
3f	3-Br	Ph	366		1635	7.24-8.16 (10H, m)		none	
			368	3185	1710	8.40 (1H, s, C_4-H)			
3g	H	CH_3	226		1625	7.30-7.95	2.26	11.4	
				3180	1705	(6.6H, m)	(3H, s)	(0.4H, bs)	
3h	4-OCH_3	CH_3	256		1640	6.71 (1H, s, C_3-H)	2.13	11.35	
				3180	1695	7.15-7.63 (3.5H, m)	(3H, s, CH_3)	(0.5H, bs)	
						7.90 (1H, d.d, J = 8.0 Hz, 2.0 Hz, C_8-H)	4.08 (3H, s, OCH_3)		

(a) Each proton was exchangeable with deuterium oxide.

Table III

2-Aminomethylquinoline Hydrochloride



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Compound No.	R	Yield %	Appearance	M.p. °C	MS (m/e) (M^+-nHCl)	Formula	Analysis Calcd./Found C	H	N
5a	H	68	colorless needles	199-201 dec	158	$C_{10}H_{10}N_2$·2HCl	52.13	5.21	12.12
							51.96	5.22	12.11
5b	4-CH_3	63	white powder	218-220 dec	172	$C_{11}H_{12}N_2$·2HCl	54.08	5.82	11.43
							53.92	5.54	11.21
5c	4-Cl	72	greenish white powder	245 dec	193 195	$C_{10}H_9ClN_2$·2HCl	45.17	5.15	10.54
							44.89	5.29	10.33
5d	4-OMe	61	white needles	> 300	188	$C_{11}H_{12}N_2O$·2HCl	50.15	5.32	10.65
							49.95	5.47	10.61
5e	4- 	82	white plates	289 dec	243	$C_{14}H_{17}N_3O$·2HCl	53.32	6.01	13.33
							53.18	6.10	13.21
5f	3-Br	88	white needles	249-250	236 238	$C_{10}H_9BrN_2$·HCl	43.73	3.63	10.23
							43.65	3.74	10.04

treatment with ammonia and sodium carbonate solution in refluxing 95% ethanol as shown below. In exploring the possibility of the transformation of **3a** into the

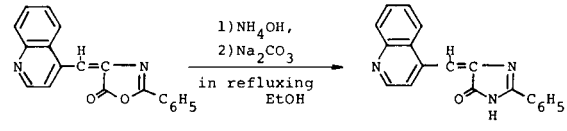

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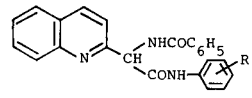
Table IV

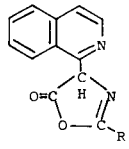


8a-d

Compound No.	R	Yield %	Appearance	M.p. °C	MS M⁺ (m/e)	Formula	Analysis Calcd./Found C	H	N
8a	H	74	white powder	197-198	381	$C_{24}H_{19}N_3O_2$	75.57	5.02	11.02
							75.26	5.05	11.03
8b	4-CH_3	81	colorless needles	188-189	395	$C_{25}H_{21}N_3O_2$	75.93	5.35	10.63
							75.73	5.24	10.40
8c	4-OCH_3	73	colorless needles	185-186	411	$C_{25}H_{21}N_3O_3$	72.98	5.14	10.21
							72.85	5.09	10.25
8d	3-Cl	68	colorless flocculent	209-210	415	$C_{24}H_{18}ClN_3O_2$	69.31	4.33	10.10
					417		69.17	4.25	10.19

Table V

4-(1-Isoquinolyl)-2-oxazolin-5-one



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Compound No.	R	Yield %	Appearance	M.p. °C	Formula	Analysis Calcd./Found C	H	N
10a	Ph	77	orange needles	245-246	$C_{18}H_{12}N_2O_2$	74.99	4.20	9.72
						74.97	4.27	9.77
10b	CH_3	64	yellow prisms	231	$C_{13}H_{10}N_2O_2$	69.01	4.46	12.38
						69.10	4.60	12.10

Table VI

Spectral Data of **10a** and **10b**

Compound No	R	MS M⁺ (m/e)	Ir (cm^{-1}, Nujol) N-H	C=N C=O	Nmr (deuteriochloroform, δ) Aromatic Protons Containing the Methine Proton	N-H (a)	Others
				1620	6.80 (1H, d, J = 7.8 Hz, C_4-H)		
10a	Ph	288	3180		7.03-8.04 (9H, m)	12.56	
				1665	9.95 (1H, dd, J = 6.0 Hz, 1.9 Hz, C_8-H)	(1H, bs)	
				1625	6.75 (1H, d, J = 7.0 Hz, C_4-H)		
10b	CH}	226	3160		7.25-7.76 (4.4H, m)	12.40	2.37
				1690	9.74 (1H, dd, J = 8.0 Hz, 1.5 Hz, C_8-H)	(0.6H, bs)	(3H, s, -CH_3)

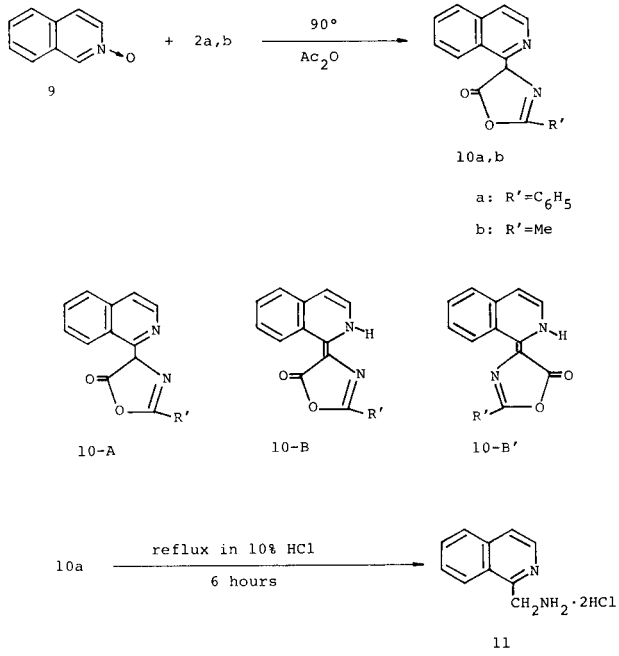
(a) Each proton was exchangeable with deuterium oxide.

imidazolone analog, **3a** was subjected to the above reaction according to the procedure of Griffin and Dean. However, no reaction occurred and **3a** was recovered quantitatively.

In connection with this study, a mixture of **3a** and a slight excess of aniline was directly heated at 150° in an

oil bath for 6 hours, when the red color of **3a** disappeared, and the anilinolysis product **8a** was obtained in 74% yield, no imidazolone derivatives being formed. Reactions with *p*-toluidine, *p*-anisidine and *m*-chloroaniline afforded the corresponding products **8b-d** also in good yields (Scheme 2). Their structures were established by the elemental analyses, the mass and the ir spectra, which exhibited two carbonyl bands and a NH band around 1650, 1690 and 3200 cm^{-1}, respectively (Table IV).

In the same way, isoquinoline 2-oxide **9** readily reacted with 2-oxazolin-5-ones, **2a** and **2b**, and the corresponding 4-(1-isoquinolyl)-2-oxazolin-5-ones, **10a** and **10b**, were obtained in 77 and 64% yields, respectively (Scheme 3 and Table V).



Scheme 3

Their analytical values and the spectral data were in full agreement with the assigned structures (Tables V and VI). As for their detailed configurations the ^1H nmr spectra in deuteriochloroform were particularly informative. The C_8-protons of the isoquinoline rings of **10a** and **10b** appeared in the fairly low field, that is, at δ 9.95 and 9.74, respectively. Such downfield shifts are probably attributed to the anisotropic effect of the carbonyl function of the oxazolone moiety, suggesting that the configurations in which the carbonyl group presents near to the C_8-proton, such as **10-A** and **10-B**, are more preferable to those such as **10-B'**. A one-proton broad singlet at δ 12.56 in the ^1H nmr spectrum of **10a** as well as a NH absorption band at 3180 cm^{-1} in its ir evidently indicate that **10a** exists principally in the enamine form **10-B**. In the spectrum of **10b**, a broad singlet at δ 12.40 due to a N-H resonance signal integrated to 0.6 proton. Accordingly, **10b** exists as a tautomeric mixture approximately composed of 60% of the enamine form **10-B** and 40% of the ketonic form **10-A**. These conclusions are supported also by other spectral data shown in Table VI.

Hydrolysis of **10a** to 1-aminomethylisoquinoline dihydrochloride **11** was effected also in good yield of 77% by refluxing in 10% hydrochloric acid (Scheme 3).

Although no satisfactory results were obtained yet with pyridine 1-oxide itself, the condensation of aromatic *N*-oxides with appropriate 2-substituted 2-oxazolin-5-ones by means of acetic anhydride followed by acid hydrolysis of the resulting products is apparently a new and promising route to the preparation of α-aminomethyl derivatives of *N*-heteroaromatics. The studies along this line 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 O1SG spectrometer.

Reaction of Quinoline 1-Oxides **1a-f** with 2-Phenyl-2-oxazolin-5-one **2a**.

A mixture of hippuric acid (5 mmoles) and anhydrous sodium acetate (0.2 g.) in acetic anhydride (5 ml.) was heated at 90° for 30 minutes in order to form **2a**. To this hot solution was added all at once a solution of **1a-f** (6 mmoles) in acetic anhydride (5 ml.). The reactants immediately turned dark red, and fine crystals began to precipitate after 1-15 minutes. Heating at 90° was continued further 1-2 hours until precipitation ceased. After cooling, precipitated crystals were filtered, washed successively with ethanol and water, and recrystallized from ethanol to give 2-phenyl-4-(2-quinolyl)-2-oxazolin-5-ones **3a-f** in good yields of 49-93%. The results and some physical data of **3a-f** are shown in Tables I and II.

Reactions of Quinoline 1-Oxide **1a** and 4-Methoxyquinoline 1-Oxide **1d** with 2-Methyl-2-oxazolin-5-one (**2b**).

A mixture of *N*-acetylglycine (5 mmoles) and anhydrous sodium acetate (0.2 g.) in acetic anhydride (5 ml.) was heated at 90° for 1 hour in order to form **2b**. To this hot solution was added all at once a solution of **1a,d** (6 mmoles) in acetic anhydride (5 ml.). The reactants immediately turned orange to red.

Reddish brown crystals slowly separated from the reaction mixture of **1a** and **2b**. After heating for 3 hours, 2-methyl-4-(2-quinolyl)-2-oxazolin-5-one **3g** was isolated by a similar processing as the above cases (Tables I and II).

No crystals separated out from the reaction mixture of **1d** and **2b**. After heating for 4 hours, the solvent was evaporated under reduced pressure, and the residue was purified by chromatography on a silica gel column with chloroform. The effluent was recrystallized from ethanol to give 2-methyl-4-(4-methoxy-2-quinolyl)-2-oxazolin-5-one **3h** (Tables I and II).

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

A mixture of **3a** (1.44 g.), 30% hydrogen peroxide (20 ml.) and acetic acid (50 ml.) was refluxed for 8 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 0.577 g. (61%) of **4**, colorless needles, m.p. 171-172° dec. (1).

Hydrolysis of **3a-f** to 2-Aminomethylquinoline Hydrochlorides **5a-f**.

A suspension of **3a-f** (2 mmoles) in 10% hydrochloric acid (50 ml.) was refluxed for 8 hours to give a colorless solution. After cooling, deposited crystals were filtered and recrystallized from water to give benzoic acid, colorless needles, m.p. 120°. The filtrate was evaporated, and the residual solid was recrystallized from ethanol to give 2-aminomethylquinoline dihydrochlorides **5a-e** or monohydrochloride **5f** (Table III).

Reactions of **3a** with Anilines.

A mixture of **3a** (3 mmoles) and aniline (5 mmoles) was heated at 150° in an oil bath for 6 hours. After cooling, ethanol (15 ml.) was added and the whole was gently heated to give a solution which was kept at room temperature overnight. The separated crystals were filtered and recrystallized from ethanol to give the anilinolysis product **8a**. From similar reactions with *p*-toluidine, *p*-anisidine and *m*-chloraniline, the corresponding products, **8b**, **8c** and **8d**, were obtained (Scheme 2 and Table IV).

Reaction of Isoquinoline 2-Oxide **9** with **2a**.

A mixture of hippuric acid (0.03 moles) and anhydrous sodium acetate (0.1 g.) in acetic anhydride (8 ml.) was heated at 90° for 30 minutes. To this hot solution was added all at once a solution of **9** (0.031 moles) in acetic anhydride (3 ml.). The reactants immediately turned red, and orange crystals began to precipitate after a few minutes. Heating at 90° was continued for 3 hours, and the reaction mixture was processed as in the reaction of **1** with **2a** to give 4-(1-isoquinolyl)-2-phenyl-2-oxazolin-5-one **10a** (Table V and VI).

Reaction of **9** with **2b**.

A mixture of *N*-acetylglycine (0.01 moles), anhydrous sodium acetate (0.1 g.) in acetic anhydride (10 ml.) was heated at 90° for 1 hour. To this hot solution was added all at once a solution of **9** (0.01 moles) in acetic anhydride (3 ml.). The reactants immediately turned orange, and yellow crystals began to separate after 15 minutes. The whole was heated at 90° for 4 hours, and similarly processed to give 4-(1-isoquinolyl)-2-methyl-2-oxazolin-5-one **10b** (Table V and VI).

Hydrolysis of **10a** to 1-Aminomethylisoquinoline **11**.

A suspension of **10a** (2.88 g.) in 10% hydrochloric acid (50 ml.) was refluxed for 6 hours. The crystals of **10a** gradually dissolved and an almost colorless solution was obtained. The solution was evaporated under reduced pressure, and the residue was recrystallized from ethanol-ether to give 0.96 g. (73%) of **11**, colorless prisms, m.p. 211-212° dec; ms: m/e 158 (M^+-2HCl).

Anal. Calcd. for $C_{10}H_{12}Cl_2N_2$: C, 52.13; H, 5.21; N, 12.12. Found: C, 52.01; H, 5.23; N, 12.11.

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