Studies on Tertiary Amine Oxides. XLVII.¹⁾ Reaction of Quinoline 1-Oxide Derivatives with Cyanogen Bromide

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Reactions of various substituted quinoline 1-oxides with cyanogen bromide in ethanol were investigated. The corresponding ethyl N-(8-quinolyl)carbamates were formed in most cases, but their yields were rather low except reactions of N-oxides of 4-quinolinol (If), 4-aminoquinoline (Ig), 2-quinolinol (IXf), 5-nitroquinoline (XXVI) and 6-chloroquinoline (XXX). In addition to 8-quinolylcarbamates, 2-quinolylcarbamates (VIc and VIe) were obtained from reactions of 4-ethoxyquinoline 1-oxide (Ic) and lepidine 1-oxide (Ie), and further the 6-quinolylcarbamate (VII) was also isolated in the latter case. The reaction of 4-quinolinol 1-oxide (If) gave the 3-quinolylcarbamate (VIII) as the main product besides 8-quinolyl derivatives, IIIf and IIIi. 2-Imino-1,2,4-oxadiazolo[2,3-*a*]quinoline hydrobromide (XVI) was produced without the participation of ethanol in a good yield of 65% from the reaction of 2-aminoquinoline 1-oxide (IXg). From 8-ethoxycarbonylaminoquinoline 1-oxide (XX), a small amount of 2,8-bis(ethoxycarbonylamino)-quinoline (XXI) was obtained. The features and mechanisms of some reactions were also discussed.

A previous paper of this series has described that quinoline 1-oxide reacts with cyanogen bromide in alcohols to afford alkyl N-(2-, 6- and 8-quinolyl)carbamates.³⁾ As a continuation of this work, various derivatives of quinoline 1-oxide were treated with cyanogen bromide in ethanol.

At first, reactions of 4-substituted quinoline 1-oxides (Ia—Ig) were examined. For the general procedure, an ethanol solution of an N-oxide and 1.5 equivalents of cyanogen bromide was refluxed on a water-bath. Table I summarizes the reaction conditions and the results thus obtained.

Reactions of 4-chloro- (Ia) and 4-bromoquinoline 1-oxides (Ib) afforded only 8-substituted quinolines as ethyl N-quinolylcarbamate; however, not only ethyl N-(4-halogeno-8-quinolyl)-carbamates (IIa and IIb) but also the 4-ethoxy-8-quinolyl derivative (IIc) were formed in each case. Similarly to the reaction of quinoline 1-oxide,³⁾ the corresponding quinolylcarbostyrils (IIIa and IIIb) and carbostyrils (IVa and IVb) were also isolated.

From the reaction of 4-ethoxyquinoline 1-oxide (Ic), 2-quinolylcarbamate (VIc) (11.2%) was obtained besides 8-quinolylcarbamate (IIc) (17.2%) and the quinolylcarbostyril (IIIc) (5%), while 4-ethoxycarbostyril was not detected in this case.

A similar reaction of 4-nitroquinoline 1-oxide (Id) gave small amounts of 4-bromo- (IIb) and 4-ethoxy-8-quinolylcarbamates (IIc) accompanied by 80% recovery of Id. The reaction carried out at 90—100° in a sealed tube for 12 hours led only to slight increase of products, Id being also recovered in 42% yield.

Since 4-halogeno and 4-nitro groups of quinoline 1-oxide ring are highly susceptible to nucleophilic displacement reaction, the formation of IIC from Ia, Ib and Id as well as that of IIb from Id are understandable. However, it is not necessarily clear at which step the displacement occurred. Because of no formation of 4-ethoxy-2-quinolylcarbamate VIc in reactions of Ia and Ib, it seems improbable that IIC originates only from Ic first formed.

1) Part XLVI: M. Hamana and M. Yatabe, *Yakugaku Zasshi*, **94**, 566 (1974).

2) Location: *Katakasu, Higashi-ku, Fukuoka*.

3) M. Hamana and S. Kumadaki, *Chem. Pharm. Bull.* (Tokyo), **21**, 800 (1973).

TABLE I. Reactions of 4-Substituted Quinoline 1-Oxides with Cyanogen Bromide in Ethanol

I	Reaction condition		Quinolyl-carbamate	Products (%)			Recovered I (%)
	Temp.	Time (hr)		III	IV	V	
Ia	reflux	3	IIa 10.9 IIc 15.8	IIIa 3.5	IVa 26.7	Va 10.9	5.6
Ib	reflux	3	IIb 4.1 IIc 4.6	IIIb 3.7	IVb 69.6	—	—
Ic	reflux	3	IIc 17.2 VIc 11.2	IIIc 5.0	—	Vc 10.5	—
Id	reflux	5	IIb 2.1 IIc 2.3	—	—	—	80.0
	90—100° (sealed tube)	12	IIb 8.8 IIc 3.1	—	—	—	42.1
			IIe 9.1 VIe 7.4				
			IIh 1.5 VII 3.0				
Ie	reflux	1	IIh 21.6 III 3.2 VIII 47.4	IIIe 37.0	IVe 1.3	Ve 13.3	6.0
If	reflux	1	IIg 36.0	—	—	—	—
Ig	reflux	1	IIg 36.0	—	—	—	—

a: R=Cl, b: R=Br, c: R=OEt, d: R=NO₂, e: R=CH₃, f: R=OH, g: R=NH₂,
h: R=CHBr₂, j: R=H

Refluxing an ethanol solution of IIa and cyanogen bromide for 5 hours did afford IIc, but its yield was only 17%; accordingly the alternative path from IIa or IIb to IIc cannot be regarded as the main route in reactions of Ia and Ib. These results may suggest that there is a possibility that the exchange of 4-halogeno group with ethoxyl group would occur at some intermediary step of the reaction of N-oxides with cyanogen bromide and ethanol.

It is well known that, when Id is treated with an acylating agent, the 4-nitro group first reacts and then the N-oxide function is attacked by the reagent in most cases.⁴⁾ Therefore, it may be presumed that a small part of Id might be initially attacked by cyanogen bromide to give 4-bromo compound Ib, which in turn would give rise to the products IIb and IIc, while the N-oxide group of Id itself resists the reaction with cyanogen bromide.

The reaction of lepidine 1-oxide (Ie) resulted in the formation of practically all the type of products hitherto obtained; there were produced the 2-, 6- and 8-quinolylcarbamates (VIe, VII and IIe) together with 4-dibromomethyl-8-quinolyl compound (IIh) as quinolylcarbamates in respective small yields, and the quinolylcarbostyryl (IIIe) and carbostyryl (IVe) were also isolated. The formation of IIh is not strange from the fact that cyanogen bromide may act as a brominating agent.⁵⁾

The formation of these quinolylcarbamates may be explained by similar mechanisms proposed in the previous paper.³⁾ As for the formation of IIe and VII from Ie, an anhydro-

4) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967, pp. 367—371.

5) a) W. Steinkopf, *Ann.*, **431**, 78 (1923); b) A.H. Klopp and G.F. Wright, *J. Org. Chem.*, **4**, 142 (1939).

base (**B**) may be also conceivable as an intermediate besides the usual 1,2-dihydroquinoline (**A**); however, the formation of the quinolylcarbostyryl (**IIIe**) in comparatively large amount apparently shows that the 1,2-dihydro-type intermediate **A** is more probable.

From the results of reactions of **Ic** and **Ie**, an electron-donating group on the 4-position of quinoline ring is apparently prone to facilitate 2-quinolylcarbamate formation to some extent.

The reaction of 4-quinolinol 1-oxide (**If**) proceeded readily even at room temperature, and gave 4-hydroxy-3-quinolyl- (**VIII**), 4-hydroxy-8-quinolylcarbamates (**IIIf**) and 3-bromo derivative of **IIIf** (**IIIi**) in 47.4, 21.6 and 3.2% yields, respectively, no other product being isolated.

This is the first example of formation of a 3-quinolylcarbamate from the reaction of quinoline 1-oxide derivative with cyanogen bromide, and the predominant formation of **VIII** is in accordance with the fact that 1-acyloxy-4-quinolinol betaine readily undergoes cleavage of N-acyloxy bond concerted with attack by a nucleophile at the 3-position.⁶⁾ On the other hand, the appreciable formation of 8-quinolylcarbamate (**IIIf**) agrees with a characteristic of the reaction of cyanogen bromide with quinoline 1-oxides. Thus, it is interesting that both characteristic features are noticed in this case.

The reaction course can be reasonably rationalized by the initial formation of 1-cyanato betaine (**C**) followed by the extrusion of the cyanate anion from the quinolone form (**D**) derived from **C** and by attack of the anion at the electron-deficient 3- and 8-positions of the quinoline ring as shown in Chart 1.

Chart 1

From 4-aminoquinoline 1-oxide (**Ig**), 4-amino-8-quinolylcarbamate (**IIIg**) was obtained in 36% yield as a sole product.

It is very significant that the N-oxide function of **If** or **Ig** was overwhelmingly attacked by cyanogen bromide in spite of the presence of hydroxyl or amino group capable of reacting with the reagent, which fact apparently indicates that the reactivity of N-oxide function toward cyanogen bromide is very high.

6) a) M. Hamana and K. Funakoshi, *Yakugaku Zasshi*, **84**, 28 (1964); b) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **15**, 474 (1967).

The structures of products thus obtained were confirmed by elemental analysis, the infrared (IR) and nuclear magnetic resonance (NMR) spectra and also by the reaction sequences shown in Chart 2.

Chart 2

Subsequently, the reaction of some 2-substituted quinoline 1-oxides was similarly investigated.

From 2-chloroquinoline 1-oxide (IXa), carbostyryl was obtained in 52.2% yield together with very small amounts of two other products conceivable to be quinolylcarbamates from their IR spectra.

The reaction of quinaldine 1-oxide (IXe) afforded 8-quinolylcarbamate (Xe), its ω,ω -dibromo derivative (Xh), quinaldine (XI) and ω,ω -dibromoquinaldine⁷⁾ (XII) in 3.5, 3.9, 12.6 and 9.6% yields, respectively. Compound Xe was proved identical with an authentic sample prepared from 8-aminoquinaldine⁸⁾ and ethyl chloroformate.

The reaction of 2-quinolinol 1-oxide (IXf) occurred with comparative ease to give 8-ethoxycarbonylaminocarbostyryl (Xf) in 39% yield. It was proved identical with an authentic

7) D.L. Hammick, *J. Chem. Soc.*, 1926, 1302.

8) K. Madeja, *J. Prakt. Chem.*, 17, 97 (1862).

sample prepared from 8-ethoxycarbonylaminoquinoline 1-oxide (XX) by treatment with tosyl chloride and potassium carbonate solution. Heating of Xf at 190° resulted in cyclization to 1,2-dihydro-4*H*-imidazolo[5,4,3-*i,j*]quinolin-2,4-dione (XIII) concerted with the elimination of an ethanol molecule. On the other hand, hydrolysis of Xf with concentrated hydrochloric acid or 20% sodium hydroxide gave the corresponding amino compound (XIV), which was in turn converted to 1,2,3-triazolo[4,5,1-*i,j*]quinolin-2-one (XV) by diazotization.

These results are shown in Chart 3.

Chart 3

Although 2-aminoquinoline 1-oxide (IXg) reacted with cyanogen bromide even at room temperature, an ethanol solution was refluxed for 1 hour in order to complete the reaction, and colorless needles (XVI) of the empirical formula $\text{C}_{18}\text{H}_8\text{ON}_3 \cdot \text{H}_2\text{O}$ was obtained in a good yield of 65%. An aqueous solution of XVI deposited silver bromide on treatment with silver nitrate solution, and IXg was regenerated by heating XVI with concentrated hydrochloric acid. Upon treatment with sodium nitrite, XVI was converted into 1,2,4-oxadiazolo[2,3-*a*]-quinolin-2-one (XVII) which was identical with the sample prepared from 2-ethoxycarbonylaminoquinoline 1-oxide⁹⁾ (XVIII). Thus, XVI was determined to be 2-imino[1,2,4]oxadiazolo[2,3-*a*]-quinoline hydrobromide. Attempts to isolate the free base of XVI by treatment with sodium hydrogen carbonate or silver nitrate failed to give an untractable mixture of several products. Treatment of IXg with cyanogen bromide and sodium acetate in ethanol¹⁰⁾ also gave not the free base of XVI but instead 2-acetoaminoquinoline 1-oxide (XIX).

9) H. Tanida, *Yakugaku Zasshi*, **79**, 1063 (1959).

10) G.I. Poos, J.D. Rosenan, and J.T. Shu, *J. Org. Chem.*, **29**, 1809 (1964).

Apparently, ethanol did not participate in the formation of XVI differently from before-mentioned reactions. Then, the reaction of IXg with cyanogen bromide was carried out using acetic acid instead of ethanol as a solvent to give XIX as a sole product in 44% yield, no formation of XVI being noticed; cyanogen bromide may be assumed to facilitate acetylation of IXg similarly to the reaction of sodium salicylate with cyanogen bromide in acetic acid reported by Thyagarajan and Rajagopalan.¹¹⁾

Further attempted reaction of XIX with cyanogen bromide in hot ethanol gave no product and XIX was quantitatively recovered (Chart 4).

In regard to the reaction mechanism, two courses are conceivable as illustrated in Chart 4; the first, course a, is initiated by the attack of cyanogen bromide at the 2-amino group to give a cyanamide intermediate, and the alternative course b involves conversely the formation of 1-cyanato intermediate at the first step. Although the fact that XVII is obtainable by heating XVIII seems to suggest course a, the reaction is more likely to follow course b in view of the fact that cyanogen bromide reacts not with the 4-amino group but the N-oxide function in the reaction of Ig.

Chart 4

The results obtained from reactions of IXa, IXb and XIX indicate that a reaction proceeding through an 1,4-dihydroquinoline intermediate, such as 1-cyanato-2-chloro-4-bromo-1,4-

11) B.S. Thyagarajan and K. Rajagopalan, *Tetrahedron Letters*, 1965, 729.

dihydroquinoline, hardly takes place in these cases, differently from the reaction of 2-substituted quinoline 1-oxides with enamines in the presence of an acylating agent.^{6b,12)} On the contrary, the reaction of IXf is apparently promoted by easy formation of an 1,2-dihydroquinoline intermediate (**E**), to give Xf. It is also interesting that the reaction of IXg followed another path which did not involve the participation of ethanol.

Finally, reactions of some other substituted quinoline 1-oxides will be described.

TABLE II. Reactions of 8-Ethoxycarbonylaminoquinoline 1-Oxide (XX) with Cyanogen Bromide in Ethanol

Reaction condition			Products (%)	Recovered XX (%)
Temp.	Time (hr)	Additive		
Reflux	5	—	XXI 8	58
90—100° (sealed tube)	10	—	XXII 11, XXIII 32, XXIV 19	—
Reflux	5	AcONa	XXI 11	78

Chart 5

12) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), 14, 762 (1966).

8-Ethoxycarbonylaminoquinoline 1-oxide (XX) was not so reactive, and 2,8-bis(ethoxycarbonylamino)quinoline (XXI) was produced in a small yield of 8%. The reaction under the stronger condition only caused bromination and gave 5-bromo derivatives of XXI, IIj and XX (XXII, XXIII and XXIV); the expected increase of XXI formation was not only effected but conversely its formation itself was not detected. The amount of XXI was slightly increased in the reaction in the presence of sodium acetate. Table II shows these results.

Hydrolysis of XXI with hot concentrated hydrochloric acid afforded 2,8-diaminoquinoline (XXV), which was further diazotized to give before-mentioned XV.

From the reaction of 5-nitroquinoline 1-oxide (XXVI), ethyl N-(5-nitro-8-quinolyl)carbamate (XXVII), 2-ethoxy-5-nitroquinoline (XXVIII) and 5-nitrocarbostyryl (XXIX) were obtained in 39.5, 10 and 18.4% yields, respectively. The structures of XXVII and XXVIII are apparent from reactions formulated in Chart 5.

A similar reaction of 6-chloroquinoline 1-oxide (XXX) gave ethyl N-(6-chloro-8-quinolyl)carbamate (XXXI) as a major product (37%), accompanied with the corresponding quinolylcarbostyryl (XXXII) and carbostyryl (XXXIII).

These results are illustrated in Chart 5.

Experimental¹³⁾

Reaction of 4-Chloroquinoline 1-Oxide (Ia) with BrCN—A mixture of Ia (1.8 g) and BrCN (1.59 g) in EtOH (20 ml) was refluxed for 3 hr. After EtOH was evaporated *in vacuo*, the residue was treated with H₂O and extracted with CHCl₃. The extracted substances were chromatographed on alumina using petr. ether, ether, CHCl₃ and MeOH as eluents. The petr. ether–ether (3:1) eluate gave 0.28 g of ethyl N-(4-chloro-8-quinolyl)carbamate (IIa) and 0.41 g of ethyl N-(4-ethoxy-8-quinolyl)carbamate (IIc). IIa: colorless needles, mp 99° (ether). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3330 (NH), 1734 (C=O), 1227 (C–O). NMR τ (CDCl₃): 1.42 (1H, d, *J*=4.8 Hz, C₂–H), 1.54 (1H, dd, *J*_{7,6}=7.2 and *J*_{7,5}=2.4 Hz, C₇–H), 5.73 (2H, q, *J*=7.2 Hz, –CH₂–CH₃), 8.67 (3H, t, *J*=7.2 Hz, –CH₂CH₃). Anal. Calcd. for C₁₂H₁₁O₂N₂Cl: C, 57.49; H, 4.39; N, 11.18. Found: C, 56.33; H, 4.45; N, 10.99. Picrate: yellow prisms, mp 143–144° (MeOH). Anal. Calcd. for C₁₂H₁₁O₂N₂·Cl·C₆H₃O₇N₃: C, 45.05; H, 2.92; N, 14.60. Found: C, 45.21; H, 2.89; N, 14.27. IIc: colorless pillars, mp 119.5° (ether). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3310 (NH), 1720 (C=O), 1224 (C–O). Anal. Calcd. for C₁₄H₁₆O₃N₂: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.57; H, 6.07; N, 10.36. Picrate: yellow pillars, mp 189.5–190.5° (MeOH). Anal. Calcd. for C₁₄H₁₆O₃N₂·C₆H₃O₇N₃: C, 49.08; H, 3.91; N, 14.31. Found: C, 48.78; H, 3.92; N, 14.22. The fraction eluted with ether was recrystallized from acetone to give 0.06 g of 4-chloro-N-(4-chloro-2-quinolyl)carbostyryl (IIIa), colorless needles, mp 234–236°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1669 (C=O). Anal. Calcd. for C₁₈H₁₀ON₂Cl₂: C, 63.34; H, 2.93; N, 8.21. Found: C, 63.77; H, 3.19; N, 8.02. The CHCl₃–MeOH (30:1) eluate afforded 0.1 g of Ia. The fraction eluted with MeOH was recrystallized from MeOH to give 0.48 g of 4-chlorocarbostyryl (IVa), colorless needles, mp 249–250°. Anal. Calcd. for C₉H₆ONCl: C, 60.17; H, 3.34; N, 7.80. Found: C, 59.17; H, 3.37; N, 7.64. It was proved identical with an authentic sample by admixture and IR spectral examination. Further, the mother liquor from CHCl₃–extraction was made alkaline with K₂CO₃ and extracted with CHCl₃ to give 0.18 g of 4-chloroquinoline (Va), bp 130–135° (2-mmHg) (bath temp.). Picrate: yellow needles, mp 215° (MeOH).

Reactions of Ethyl N-(4-Chloro-8-quinolyl)carbamate (IIa)—1) Catalytic reduction of IIa (0.1 g) with hydrogen over 5% Pd-C (0.05 g) was carried out in the presence of AcONa (0.05 g) in EtOH (10 ml) to give 0.07 g (83.3%) of ethyl N-(8-quinolyl)carbamate³⁾ (IIj).

2) Reaction with EtONa: A mixture of IIa (0.1 g) and EtONa–EtOH (prepared from 0.01 g of Na and 10 ml of EtOH) was refluxed for 4.5 hr. The products were chromatographed on alumina with petr. ether–ether (2:1) to give 0.08 g of IIa (80%) and 0.02 g of IIc (19%).

3) Reaction with BrCN in EtOH: A solution of IIa (55 mg) and BrCN (32 mg) in EtOH (10 ml) was refluxed for 5 hr, and the reaction mixture was concentrated *in vacuo*, treated with NaHCO₃ solution and extracted with ether. The extract residue was chromatographed over alumina with petr. ether–ether (2:1) to give 40.8 mg (74.3%) of IIa and 9.8 mg (17.2%) of IIc.

Reaction of 4-Bromoquinoline 1-Oxide (Ib) with BrCN—1) A mixture of Ib (1.12 g) and BrCN (0.8 g) in EtOH (10 ml) was refluxed for 3 hr, evaporated *in vacuo*, treated with NaHCO₃ solution and extracted with CHCl₃. The extract was evaporated and treated with ether to give precipitates, which were recrystallized from MeOH to afford 0.78 g of 4-bromocarbostyryl (IVb), colorless needles, mp 268°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1653

13) All melting and boiling points are uncorrected. NMR spectra were measured with JNM-3H-60 spectrometers at 60 MC using TMS as internal reference.

(C=O). *Anal.* Calcd. for C_9H_6ONBr : C, 48.21; H, 2.68; N, 6.25. Found: C, 48.33; H, 2.69; N, 6.55. The fraction soluble in ether was chromatographed on alumina with petr. ether, ether and $CHCl_3$. The petr. ether-ether (2:1) eluate gave successively 0.06 g of ethyl N-(4-bromo-8-quinolyl)carbamate (IIb) and 0.06 g of IIc. IIb: colorless needles, mp 107.5–108° (petr. ether). IR ν_{max}^{Nujol} cm^{-1} : 3330 (NH), 1733 (C=O), 1222 (C–O). NMR $\tau(CDCl_3)$: 1.44–1.57 (2H, m, C_2 -H and C_7 -H), 2.23–2.59 (3H, m, C_3 -H, C_5 -H and C_6 -H), 5.76 (2H, q, $J=6.9$ Hz, $-CH_2CH_3$), 8.64 (3H, t, $J=6.9$ Hz, $-CH_2CH_3$). *Anal.* Calcd. for $C_{12}H_{11}O_2N_2Br$: C, 48.81; H, 3.73; N, 9.49. Found: C, 49.16; H, 3.73; N, 9.63. Picrate: yellow prisms, mp 143–144° (MeOH). *Anal.* Calcd. for $C_{12}H_{11}O_2N_2Br \cdot C_6H_3O_7N_3$: C, 41.22; H, 2.67; N, 13.36. Found: C, 40.98; H, 2.53; N, 13.67. The $CHCl_3$ eluate afforded 0.04 g of the quinolylcarbostyryl IIIb, colorless needles, mp 250–252° (MeOH). IR ν_{max}^{Nujol} cm^{-1} : 1663 (C=O). *Anal.* Calcd. for $C_{18}H_{10}ON_2Br_2$: C, 50.23; H, 2.33; N, 6.51. Found: C, 50.73; H, 2.46; N, 6.41.

2) Catalytic reduction of IIb (0.021 g) under the similar condition to that of IIa gave 0.021 g (95.5%) of IIj.³⁾

Reaction of 4-Ethoxyquinoline 1-Oxide (Ic) with BrCN—A mixture of Ic (1.0 g) and BrCN (0.7 g) in EtOH (10 ml) was refluxed for 3 hr, evaporated *in vacuo*, treated with $NaHCO_3$ solution and extracted with $CHCl_3$. The extracted substances were chromatographed on alumina with petr. ether, ether and MeOH. The petr. ether-ether (1:1) eluate gave 0.2 g of IIc. The ether eluate afforded 0.13 g of ethyl N-(4-ethoxy-2-quinolyl)carbamate (VIe), colorless needles, mp 124° (ether). IR ν_{max}^{Nujol} cm^{-1} : 3180–3120 (NH), 1733 (C=O), 1234–1224 (C–O). NMR $\tau(CDCl_3)$: 0.43 (1H, broad, NH), 1.50–2.80 (5H, m, aromatic protons), 5.67 (2H, q, $J=7$ Hz, $-CH_2CH_3$), 5.82 (2H, q, $J=7$ Hz, $-CH_2CH_3$), 8.46 (3H, t, $J=7$ Hz, $-CH_2CH_3$), 8.85 (3H, t, $J=7$ Hz, $-CH_2CH_3$). *Anal.* Calcd. for $C_{14}H_{18}O_3N_2$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.57; H, 6.06; N, 10.36. The MeOH eluate yielded 0.04 g of the quinolylcarbostyryl IIIc, colorless needles, mp 276–277° (MeOH). IR ν_{max}^{Nujol} cm^{-1} : 1638, 1650 (C=O). *Anal.* Calcd. for $C_{22}H_{20}O_3N_2$: C, 73.31; H, 5.59; N, 7.77. Found: C, 73.33; H, 5.72; N, 7.18. The mother liquor from $CHCl_3$ -extraction gave 0.08 g of 4-ethoxyquinoline (Ve), bp 150–160° (2 mmHg) (bath temp.).

Reactions of 4-Nitroquinoline 1-Oxide (Id) with BrCN—1) A mixture of Id (0.95 g) and BrCN (0.8 g) in EtOH (20 ml) was refluxed for 5 hr. The reaction mixture was cooled to deposit 0.65 g of Id, which was filtered, and the filtrate was evaporated *in vacuo*, treated with H_2O and extracted with $CHCl_3$. The extracted substances were chromatographed on alumina with petr. ether, ether and $CHCl_3$. The first fraction eluted with petr. ether-ether (3:1) gave 0.03 g of IIb and the second one eluted with petr. ether-ether (1:1) afforded 0.03 g of IIc. From the $CHCl_3$ eluate, an additional 0.11 g of Id was recovered. The total amount of recovered Id was 0.76 g.

2) A mixture of Id (0.95 g) and BrCN (0.80 g) in EtOH (6 ml) was heated at 90–95° in a sealed tube for 12 hr to give 0.13 g of IIb, 0.04 g of IIc and 0.40 g of recovered Id.

Reaction of Lepidine 1-Oxide (Ie) with BrCN—A mixture of Ie (1.68 g) and BrCN (1.59 g) in EtOH (20 ml) was refluxed for 1 hr, evaporated *in vacuo*, treated with H_2O and extracted with $CHCl_3$. The extracted substances were chromatographed on alumina with petr. ether, ether, $CHCl_3$ and MeOH. The first fraction eluted with petr. ether-ether (4:1) was recrystallized from petr. ether to give 0.21 g of ethyl N-(4-methyl-8-quinolyl)carbamate (IIe), colorless prisms, mp 59.5–60°. IR ν_{max}^{Nujol} cm^{-1} : 3340 (NH), 1724 (C=O), 1220 (C–O). *Anal.* Calcd. for $C_{13}H_{14}O_2N_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.73; H, 6.17; N, 12.42. It was proved identical with an authentic sample prepared from 8-aminolepidine.¹⁴⁾ Picrate: yellow prisms, mp 184–187° (decomp.) (MeOH). *Anal.* Calcd. for $C_{13}H_{14}O_2N_2 \cdot C_6H_3O_7N_3$: C, 49.67; H, 3.73; N, 15.25. Found: C, 49.89; H, 4.00; N, 15.11. The petr. ether-ether (3:2) eluate gave 0.05 g of ω,ω -dibromo derivative of IIe (IIh), light yellow needles, mp 126–128° (ether). *Anal.* Calcd. for $C_{13}H_{12}O_2N_2Br_2$: C, 40.21; H, 3.09; N, 7.22. Found: C, 40.67; H, 3.58; N, 7.58. From the ether eluate, 0.17 g of ethyl N-(4-methyl-2-quinolyl)carbamate (VIe) was obtained. VIe: colorless prisms, mp 132–133° (ether). IR ν_{max}^{Nujol} cm^{-1} : 3140, 3100 (NH), 1726 (C=O), 1221 (C–O). NMR $\tau(CDCl_3)$: 1.75–2.74 (5H, m, aromatic protons), 5.69 (2H, q, $J=7.8$ Hz, $-CH_2CH_3$), 7.72 (3H, s, CH_3), 8.71 (3H, t, $J=7.8$ Hz, $-CH_2CH_3$). *Anal.* Calcd. for $C_{13}H_{14}O_2N_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.83; H, 6.11; N, 12.05. It was proved identical with an authentic sample prepared from 2-aminolepidine.¹⁵⁾ The $CHCl_3$ eluate yielded 0.56 g of the quinolylcarbostyryl IIIe, colorless needles, mp 213–214°. IR ν_{max}^{Nujol} cm^{-1} : 1665 (C=O). *Anal.* Calcd. for $C_{20}H_{16}ON_2$: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.65; H, 5.39; N, 9.78. From the $CHCl_3$ -MeOH (40:1) eluate, 0.1 g of Ie was recovered. The MeOH eluate gave 0.02 g of 4-methylcarbostyryl¹⁶⁾ (IVe), colorless needles, mp 221° (MeOH). The mother liquor from $CHCl_3$ -extraction was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The extracted substances were chromatographed on alumina. The fraction eluted with ether gave 0.19 g of lepidine (Ve), bp 140–150° (18 mmHg) (bath temp.), picrate: mp 213–215°. The $CHCl_3$ eluate afforded 0.07 g of ethyl N-(4-methyl-6-quinolyl)carbamate (VII), light yellow needles, mp 213–214° (acetone). IR ν_{max}^{Nujol}

14) M. Ishikawa and I. Kikkawa, *Yakugaku Zasshi*, **75**, 33 (1955).

15) E. Diepolder, *J. Prakt. Chem.*, [2], **106**, 58 (1923).

16) H. Tanida, *Yakugaku Zasshi*, **78**, 611 (1958).

cm^{-1} : 3180 (NH), 1730 (C=O), 1253 (C-O). *Anal.* Calcd. for $\text{C}_{13}\text{H}_{14}\text{O}_2\text{N}_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.05; H, 6.06; N, 12.17.

Syntheses of 8- (IIe) and 2-Ethoxycarbonylaminolepindines (VIe)—1) To an ice-cooled solution of 8-aminolepidine¹⁴⁾ (0.06 g) in pyridine (0.5 g) was added ethyl chloroformate (0.07 g) with stirring, and the whole was kept at room temperature for 24 hr. The reaction mixture was concentrated *in vacuo*, treated with NaHCO_3 solution and extracted with ether to give 0.08 g (92%) of IIe, mp 59.5–60.0° (petr. ether).

2) VIe: To an ice-cooled solution of 2-aminolepidine¹⁵⁾ (0.07 g) in pyridine (2 ml) was added ethyl chloroformate (0.15 g) with stirring, and the whole was heated at 90° for 4.5 hr to give 0.01 g (9.8%) of VIe, mp 132–133°, accompanied by recovery of 0.055 g of 2-aminolepidine.

Hydrolysis of Ethyl N-(4-Methyl-6-quinolyl)carbamate (VII)—A mixture of VII (0.015 g) and conc. HCl (1 ml) was refluxed for 7 hr. The reaction mixture was evaporated *in vacuo*, made alkaline with K_2CO_3 solution and extracted with CHCl_3 to give 0.005 g of 6-aminolepidine, light yellow needles, mp 169–170° (ether). It was proved identical with an authentic sample¹⁷⁾ by admixture and IR spectral examination.

Reaction of 4-Quinolinol 1-Oxide (If) with BrCN—A mixture of If (1.61 g) and BrCN (1.59 g) in EtOH (10 ml) was refluxed for 1 hr. After EtOH was evaporated, the residue was dissolved in CHCl_3 , which was successively washed with NaHCO_3 solution and a saturated solution of NaCl and evaporated. The residue was chromatographed on alumina with CHCl_3 and MeOH. The CHCl_3 effluent was recrystallized from MeOH to give 1.10 g of ethyl N-(4-hydroxy-3-quinolyl)carbamate (VIII), colorless needles, mp 203° (decomp.). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3350 (NH), 1720 (C=O), 1209 (C-O). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_3\text{N}_2$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.76; H, 4.74; N, 12.04. The CHCl_3 -MeOH (20: 1) eluate afforded 0.50 g of ethyl N-(4-hydroxy-8-quinolyl)carbamate (IIIf), colorless needles, mp 315° (decomp.) (MeOH). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3140 (NH), 1720 (C=O), 1232 (C-O). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_3\text{N}_2$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.14; H, 5.12; N, 12.37. From the MeOH eluate, 0.10 g of 3-bromo-4-hydroxy-8-ethoxycarbonylaminoquinoline (IIi), colorless needles, mp 240–300° (decomp.) (MeOH), was obtained. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3260 (NH), 1703 (C=O), 1253 (C-O). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{11}\text{O}_3\text{N}_2\text{Br}$: C, 46.31; H, 3.57; N, 9.00. Found: C, 46.61; H, 3.53; N, 9.14.

4-Hydroxy-8-aminoquinoline—1) Hydrolysis of IIIf: A mixture of IIIf (70 mg) and conc. HCl (2 ml) was refluxed for 7 hr. The reaction mixture was evaporated *in vacuo* and treated with NaHCO_3 solution to precipitate crystals which were filtered and recrystallized from MeOH to give 20 mg (41.4%) of 4-hydroxy-8-aminoquinoline, colorless scales, mp 254–256° (decomp.). It was proved identical with a sample prepared in 2).

2) Hydrolysis of IIc: A mixture of IIc (70 mg) and conc. HCl (2 ml) was refluxed for 7 hr and processed as described above to give 30 mg of colorless needles, mp 90° (MeOH). It was shown to be 4-ethoxy-8-aminoquinoline from the IR spectrum. A mixture of this product (20 mg) and HI (1.5 ml) was refluxed for 7 hr. The reaction mixture was concentrated *in vacuo* and the residue was treated successively with Na_2SO_3 and H_2O , and made alkaline with NaHCO_3 to precipitate 6 mg of 4-hydroxy-8-aminoquinoline, colorless needles, mp 254–256° (decomp.) (MeOH). *Anal.* Calcd. for $\text{C}_9\text{H}_8\text{ON}_2$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.91; H, 5.12; N, 17.82.

Conversion of Ethyl N-(4-Hydroxy-3-quinolyl)carbamate (VIII) to Ethyl N-(3-Quinolyl)carbamate—

1) A mixture of VIII (0.2 g) and POCl_3 was heated on a water-bath for 3 hr, concentrated *in vacuo*, treated with H_2O and made alkaline with NaHCO_3 . The product was extracted with CHCl_3 and purified by chromatography on alumina in ether to give 0.21 g (97.2%) of ethyl N-(4-chloro-3-quinolyl)carbamate, colorless needles, mp 97–97.5° (ether). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3265 (NH), 1648 (C=O), 1260 (C-O). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{11}\text{O}_2\text{N}_2\text{Cl}$: C, 57.49; H, 4.39; N, 11.18. Found: C, 57.40; H, 4.27; N, 11.33.

2) Catalytic reduction of 4-chloro-3-quinolylcarbamate (0.2 g) with hydrogen over 10% Pd-C (0.05 g) was carried out in the presence of AcONa (0.08 g) in MeOH (3 ml) to give 0.17 g (99%) of ethyl N-(3-quinolyl)carbamate, light yellow needles, mp 144–144.5° (ether or acetone). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3170 (NH), 1723 (C=O), 1215 (C-O). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_2\text{N}_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.22; H, 5.55; N, 12.98. It was proved identical with an authentic sample prepared from 3-aminoquinoline.¹⁸⁾

Catalytic Reduction of 3-Bromo-4-hydroxy-8-ethoxycarbonylaminoquinoline (IIi)—Catalytic reduction of IIi (70 mg) with hydrogen over 10% Pd-C (50 mg) was carried out in the presence of AcONa (25 mg) in MeOH (30 ml) to afford 50 mg (95.8%) of IIIf, colorless needles, mp 315° (MeOH).

Reaction of 4-Aminoquinoline 1-Oxide (Ig) with BrCN—A mixture of Ig (0.5 g) and BrCN (0.5 g) in EtOH (50 ml) was refluxed for 1 hr, evaporated *in vacuo*, treated with H_2O and NaHCO_3 , and extracted with CHCl_3 . The extract was passed through an alumina column to give 0.26 g of ethyl N-(4-amino-8-quinolyl)carbamate (IIg), light yellow needles, mp 128° (MeOH). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3476, 3330, 3286, 3206 (NH and NH_2), 1714 (C=O), 1240 (C-O). NMR τ (CDCl_3): 1.58–1.75 (2H, m, C_2 -H and C_7 -H), 2.67 (2H, m, C_5 -H and C_6 -H), 3.45 (1H, d, $J=4.8$ Hz, C_8 -H), 5.72 (2H, q, $J=7.5$ Hz, $-\text{CH}_2\text{CH}_3$), 8.68 (3H, t, $J=7.5$ Hz, $-\text{CH}_2\text{CH}_3$). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{13}\text{O}_2\text{N}_3$: C, 62.31; H, 5.68; N, 18.13. Found: C, 61.99; H, 5.39; N, 18.43.

17) R. Huisgen, *Ann.*, **559**, 174 (1948).

18) E. Ochiai, Ch. Kaneko, and J. Inomata, *Yakugaku Zasshi*, **78**, 584 (1958).

4,8-Diaminoquinoline—1) Hydrolysis of IIg: A mixture of IIg (0.1 g) and conc. HCl (3 ml) was refluxed for 8 hr to give 0.06 g (87%) of 4,8-diaminoquinoline,¹⁹ colorless pillars, mp 184° (MeOH). *Anal.* Calcd. for C₉H₈N₂: C, 67.89; H, 5.71; N, 26.40. Found: C, 67.92; H, 5.67; N, 26.65.

2) From IIa: A mixture of IIa (0.1 g) and CuSO₄·5H₂O (0.03 g) in conc. NH₄OH (1.6 ml) was heated at 170° in a sealed tube for 16 hr. The reaction mixture was treated with K₂CO₃ and extracted with CHCl₃ to give 0.05 g (77.2%) of 4,8-diaminoquinoline,¹⁹ colorless pillars, mp 184° (MeOH).

Reaction of 2-Chloroquinoline 1-Oxide (IXa) with BrCN—A mixture of IXa (1.0 g) and BrCN (0.88 g) in EtOH (10 ml) was refluxed for 5 hr, evaporated *in vacuo*, treated with NaHCO₃ solution and extracted with CHCl₃. The extracted substances were chromatographed on alumina with ether, CHCl₃ and MeOH. The ether effluent was composed of several products, among which two kinds of quinolylcarbamate were detected by IR spectrum; however, their structures were not confirmed because of their minute amounts. The CHCl₃-MeOH (20: 1) eluate gave 0.42 g of carbostyryl.

Reaction of Quinaldine 1-Oxide (IXe) with BrCN—1) A mixture of IXe (1.68 g) and BrCN (1.5 g) in EtOH (20 ml) was refluxed for 5 hr, evaporated *in vacuo*, treated with H₂O and extracted with CHCl₃. The extracted substances were chromatographed on alumina with petr. ether, ether and CHCl₃. The petr. ether-ether (3: 1) eluate afforded two fractions. The first one gave 0.29 g of ω,ω -dibromoquinaldine⁷⁾ (XII), colorless needles, mp 118—119° (ether). The second fraction contained two components inseparable by column chromatography; it was converted into a mixture of picrates. On fractional recrystallization from MeOH, there were isolated the picrate of ethyl N-(2-dibromomethyl-8-quinolyl)carbamate (Xh) and that of ethyl N-(2-methyl-8-quinolyl)carbamate (Xe). Picrate of Xh: yellow needles, mp 141—142°, 0.24 g. *Anal.* Calcd. for C₁₃H₁₂O₂N₂Br₂·C₆H₅O₇N₃: C, 36.95; H, 2.43; N, 11.35. Found: C, 37.31; H, 2.59; N, 11.62. Picrate of Xe: yellow prisms, mp 185—190° (decomp.), 0.16 g. The free Xe obtained from its picrate formed colorless prisms, mp 47—48° (petr. ether). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3340 (NH), 1720 (C=O), 1203 (C-O). It was proved identical with an authentic sample prepared by another route described in 2). The CHCl₃ eluate gave 0.46 g of IXe. The mother liquor from CHCl₃-extraction was made alkaline with K₂CO₃ and extracted with CHCl₃. The extract residue was chromatographed on alumina with ether, CHCl₃ and MeOH. The ether eluate afforded 0.18 g of quinaldine (XI), bp 130—150° (2 mmHg) (bath temp.). An additional 0.1 g of IXe was obtained from the CHCl₃ (40: 1) eluate. The total amount of IXe was 0.56 g.

2) Synthesis of Xe: A solution of 8-aminoquinaldine⁹⁾ (0.3 g), ethyl chloroformate (0.3 g) in pyridine (3 ml) was kept at room temperature for 24 hr to give 0.35 g of Xe, colorless prisms, mp 47—48° (petr. ether). *Anal.* Calcd. for C₁₃H₁₄O₂N₂: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.72; H, 6.27; N, 11.85. Picrate: yellow prisms, mp 185—190° (decomp.) (MeOH). *Anal.* Calcd. for C₁₃H₁₄O₂N₂·C₆H₅O₇N₃: C, 49.67; H, 3.73; N, 15.25. Found: C, 49.65; H, 3.53; N, 15.05.

Reaction of 2-Quinololinol 1-Oxide (IXf) with BrCN—A mixture of IXf (0.81 g) and BrCN (0.8 g) in EtOH (25 ml) was refluxed for 5 hr. The reaction mixture was concentrated under reduced pressure to a third volume and cooled to deposit crystals, which were filtered and recrystallized from EtOH to yield 0.34 g of 8-ethoxycarbonylamino carbostyryl (Xf), colorless needles. The filtrate was evaporated *in vacuo*, treated with H₂O and extracted with CHCl₃. The extracted substances were chromatographed on alumina to afford an additional 0.11 g of Xf from the CHCl₃-MeOH (25: 1) eluate. The total amount of Xf was 0.45 g. It decomposed at 190° accompanied by gas evolution and solidified, and again decomposed at 275—315°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3300, 3160 (NH and OH), 1720 (C=O), 1234 (C-O). *Anal.* Calcd. for C₁₂H₁₂O₃N₂: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.62; H, 5.15; N, 12.15. It was proved identical with an authentic sample prepared by the reaction described below.

Synthesis and Reactions of 8-Ethoxycarbonylamino carbostyryl (Xf)—1) Synthesis: i) A solution of IIj (1.08 g) and 30% H₂O₂ (0.5 g) in AcOH (3.5 ml) was heated at 60—70°. After 3 hr, another 30% H₂O₂ (0.4 g) was added to the reaction mixture, and heating at the same temperature was continued further 6 hr. The reaction mixture was concentrated *in vacuo*, treated with H₂O and extracted with CHCl₃. The extract residue was recrystallized from ether to give 0.77 g (66.4%) of 8-ethoxycarbonylaminoquinoline 1-oxide (XX), pale yellow needles, mp 128—129°. *Anal.* Calcd. for C₁₂H₁₂O₃N₂: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.97; H, 5.02; N, 11.71.

ii) To an ice-cooled solution of fine powder of maleic anhydride (2.38 g) in CHCl₃ (10 ml) was added with stirring 60% H₂O₂ (0.5 g), and stirring was continued for 2 hr under ice-cooling. A solution of IIj (0.7 g) in CHCl₃ (5 ml) was added dropwise to the above solution, and the whole was kept in a refrigerator for 5 days, and the resulting precipitates were filtered and washed with CHCl₃. The combined filtrate and washings was successively washed with a saturated solution of NaHCO₃ and that of NaCl, dried over Na₂SO₄ and evaporated to give 0.4 g (53.3%) of XX.

iii) A solution of XX (0.18 g) and TsCl (0.25 g) in CHCl₃ (5 ml) was shaken for 4 hr with K₂CO₃ (0.2 g)-H₂O (5 ml). After standing overnight, the CHCl₃ layer was separated, washed with 10% K₂CO₃ and H₂O, and CHCl₃ was removed. The residue was purified by chromatography over alumina in ether, CHCl₃ and

19) R.W. Gouley, G.W. Moers, and H.S. Mosher, *J. Am. Chem. Soc.*, **69**, 303 (1947).

MeOH. The CHCl_3 -MeOH (20:1) eluate afforded 0.005 g (2.8%) of Xf. The major fraction eluted with ether and CHCl_3 was not explored.

2) Thermolysis of Xf: Thermolysis of Xf (80 mg) in an oil bath maintained at 190° resulted in decomposition accompanied by gas evolution. After cooling, the solidified residue was recrystallized from MeOH to yield 60 mg (93%) of 1,2-dihydro-4*H*-imidazo[5,4,3-*i,j*]quinolin-2,4-dione (XIII), colorless needles, mp 280 — 315° (decomp.). *Anal.* Calcd. for $\text{C}_{10}\text{H}_6\text{O}_2\text{N}_2$: C, 64.51; H, 3.25; N, 15.05. Found: C, 64.54; H, 3.12; N, 14.72.

3) Hydrolysis: i) A mixture of Xf (0.3 g) and 20% NaOH (4 ml) was heated for 8 hr on a water-bath, cooled and bubbled with CO_2 gas to deposit crystals of 8-aminocarbostyryl (XIV) which on recrystallization from MeOH formed pale yellow needles, mp 280 — 300° (decomp.), 0.18 g (87%). *Anal.* Calcd. for $\text{C}_9\text{H}_8\text{ON}_2$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.45; H, 5.08; N, 17.50. Refluxing a mixture of Xf and conc. HCl for 7 hr gave XIV in about the same yield.

ii) To an ice-cooled mixture of XIV (20 mg), H_2O (2 drops) and H_2SO_4 (4 drops) was added dropwise a saturated solution of NaNO_2 , and the whole was ice-cooled for 2.5 hr. Adding H_2O (5 ml) to the reaction mixture deposited crystals which were filtered and recrystallized from MeOH to give 20 mg (93.5%) of 1,2,3-triazolo[4,5,1-*i,j*]quinolin-2-one (XV), colorless needles, mp 208° (decomp.). *Anal.* Calcd. for $\text{C}_9\text{H}_5\text{ON}_3$: C, 63.16; H, 2.94; N, 24.55. Found: C, 63.33; H, 3.12; N, 24.41.

Reaction of 2-Aminoquinoline 1-Oxide (IXg) with BrCN—1) A solution of IXg (1.6 g) and BrCN (1.6 g) in EtOH (20 ml) was refluxed for 1 hr, and evaporated *in vacuo*. The residue was recrystallized from MeOH to give 1.5 g of 2-imino[1,2,4]oxadiazolo[2,3-*a*]quinoline hydrobromide (XVI), colorless prisms, mp 230 — 231° (decomp.). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3390 (H_2O), 1700 ($\text{C}=\text{NH}$). *Anal.* Calcd. for $\text{C}_{10}\text{H}_7\text{ON}_3 \cdot \text{HBr} \cdot \text{H}_2\text{O}$: C, 42.27; H, 3.55; N, 14.79. Found: C, 42.13; H, 3.46; N, 14.77.

2) To an ice-cooled mixture of IXg (1.6 g) and AcONa (0.9 g) in EtOH (15 ml) was added BrCN (1.17 g) EtOH (10 ml), and the whole was stirred with ice-cooling. The reaction mixture was concentrated *in vacuo*, treated with H_2O and extracted with CHCl_3 . The extract was passed through an alumina column to give 0.4 g (19.8%) of 2-acetoaminoquinoline 1-oxide (XIX), colorless needles, mp 196 — 197° (acetone). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3190 (NH), 1697 ($\text{C}=\text{O}$). It was proved identical with an authentic sample.²⁰

3) A mixture of IXg (0.8 g), AcONa (0.45 g) and BrCN (0.59 g) in AcOH (15 ml) was refluxed for 1.5 hr evaporated *in vacuo*, treated with H_2O , made alkaline with K_2CO_3 and shaken with CHCl_3 . The deposited crystals were filtered and recrystallized from MeOH- H_2O to give 0.31 g (38.8%) of IXg. The CHCl_3 layer was separated and evaporated to give 0.41 g of XIX.

Reactions of 2-Imino[1,2,4]oxadiazolo[2,3-*a*]quinoline Hydrobromide (XVI)—1) Hydrolysis: A mixture of XVI (0.4 g) and conc. HCl (4 ml) was refluxed for 10 hr to give 0.23 g (83.3%) of IXg.

2) Reaction with NaNO_2 : XVI (0.45 g) was dissolved in H_2O (10 ml) by warming for a few minutes and then cooled. To this mixture was added NaNO_2 (0.12 g), and the whole was kept at room temperature for 10 min and then heated at 60 — 70° for 1 hr. After cooling, the deposited crystals were filtered and recrystallized from MeOH to give [1,2,4]oxadiazolo[2,3-*a*]quinolin-2-one (XVII) which was proved identical with an authentic sample⁹ prepared from XVIII.

Reactions of 8-Ethoxycarbonylaminoquinoline 1-Oxide (XX) with BrCN—1) A mixture of XX (0.5 g) and BrCN (0.5 g) in EtOH (10 ml) was refluxed for 5 hr, evaporated *in vacuo*, treated with H_2O and extracted with CHCl_3 . The extract residue was chromatographed on alumina. The first fraction eluted with petr. ether-ether (1:1) gave 0.05 g of 2,8-bis(ethoxycarbonylamino)quinoline (XXI), colorless prisms, mp 161 — 162° (acetone). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3110 (NH), 1741 ($\text{C}=\text{O}$), 1233 ($\text{C}-\text{O}$). *Anal.* Calcd. for $\text{C}_{13}\text{H}_{17}\text{O}_4\text{N}_3$: C, 59.39; H, 5.65; N, 13.86. Found: C, 59.40; H, 5.49; N, 13.82. From the second fraction, 0.29 g of XV was recovered.

2) A mixture of XX (1.2 g), BrCN (1.2 g) and EtOH (6 ml) was heated in a sealed tube on a boiling water-bath for 20 hr. The mixture of products obtained by the similar treatment was chromatographed on alumina with petr. ether and ether. The petr. ether-ether (4:1) effluent was recrystallized from EtOH gave 0.48 g of ethyl N-(5-bromo-8-quinolyl)carbamate (XXIII), colorless needles, mp 89 — 90° . IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3375 (NH), 1738 ($\text{C}=\text{O}$), 1200 ($\text{C}-\text{O}$). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{11}\text{O}_2\text{N}_2\text{Br}$: C, 48.81; H, 3.73; N, 9.49. Found: C, 49.11; H, 3.63; N, 9.66. From the petr. ether-ether (3:2) eluate, 0.07 g of colorless pillars, mp 95.5° , was obtained. Its structure was not elucidated. The petr. ether-ether (1:1) effluent was recrystallized from acetone to afford 0.22 g of 5-bromo-2,8-bis(ethoxycarbonylamino)quinoline (XXII), colorless needles, mp 171 — 172° . IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3365 (NH), 1747, 1735 ($\text{C}=\text{O}$), 1218 ($\text{C}-\text{O}$). NMR τ (CDCl_3): 1.77 (1H, d, $J=8.4$ Hz, $\text{C}_4\text{-H}$), 2.41 (1H, d, $J=8.4$ Hz, $\text{C}_8\text{-H}$), 5.68 (4H, q, $J=7.25$ Hz, $-\text{CH}_2\text{CH}_3$), 8.63 (6H, t, $J=7.25$ Hz, $-\text{CH}_2\text{CH}_3$). The fraction eluted with ether was recrystallized from acetone to give 0.3 g of 5-bromo-8-ethoxycarbonylaminoquinoline 1-oxide (XXIV), pale yellow prisms, mp 162° . IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3055 (NH), 1730 ($\text{C}=\text{O}$), 1230 ($\text{C}-\text{O}$). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{11}\text{O}_3\text{N}_2\text{Br}$: C, 46.30; H, 3.54; N, 9.00. Found: C, 46.29; H, 3.67; N, 9.32.

20) E.V. Brown, R.M. Novack, and A.A. Hamdan, *J. Org. Chem.*, **26**, 2831 (1961).

3) A similar reaction to that described in 1) was carried out in the presence of 1.5 equivalents of AcONa to give XXI in 11% yield accompanied by 78% recovery of XX.

Reactions of 2,8-Bis(ethoxycarbonylamino)quinoline (XXI) and 5-Bromo-2,8-bis(ethoxycarbonylamino)-quinoline (XXII)—1) Reduction of XXII to XXI: A solution of XXII (30 mg) in MeOH (10 ml) was hydrogenated over 10% Pd-C (50 mg) to give 15 mg (62.5%) of XXI.

2) Hydrolysis of XXI: A mixture of XXI (0.5 g) and conc. HCl (5 ml) was refluxed for 7 hr to give 0.25 g (95%) of 2,8-diaminoquinoline (XXV), colorless needles, mp 116.5–117° (ether). *Anal.* Calcd. for C₉H₉N₃: C, 67.90; H, 5.70; N, 26.40. Found: C, 68.12; H, 5.42; N, 26.49.

3) Reaction of XXV with NaNO₂: A solution of XXV (20 mg) in 50% H₂SO₄ (1 ml) was treated with NaNO₂ in the usual way, and the whole was kept at room temperature for 1 hr. To the reaction mixture was added the same amount of H₂O, and the mixture was warmed at 40° for 10 min to afford 20 mg (93%) of XV.

Conversion of 5-Bromo-8-ethoxycarbonylaminoquinoline 1-Oxide (XXIV) through XXIII to 5-Bromo-8-aminoquinoline—1) A solution of XXIV (0.12 g) in MeOH (25 ml) was hydrogenated over Raney Ni (0.06 g) to give 0.1 g (87.7%) of XXIII.

2) A mixture of XXIII (0.12 g) and conc. HCl (15 ml) was refluxed for 10 hr to afford 0.08 g (88%) of 5-bromo-8-aminoquinoline, pale yellow needles, mp 109–110° (MeOH). It was proved identical with an authentic sample obtained from another route.²¹⁾

Reaction of 5-Nitroquinoline 1-Oxide (XXVI) with BrCN—A solution of XXVI (1.9 g) and BrCN (1.59 g) in EtOH (30 ml) was refluxed for 5 hr, evaporated *in vacuo*, treated with H₂O and NaHCO₃, and shaken with CHCl₃. The deposited crystals were filtered and recrystallized from MeOH to give 0.16 g of 5-nitrocarbostyryl (XXIX), colorless needles, mp 300–301°. The fraction dissolved in CHCl₃ was chromatographed on alumina. The petr. ether effluent was recrystallized from acetone to afford 0.22 g of 2-ethoxy-5-nitroquinoline (XXVIII), pale yellow pillars, mp 133–134°. NMR τ (CDCl₃): 1.23 (1H, d, J =9.0 Hz, C₄-H), 1.7–2.0 (2H, m, C₆-H and C₈-H), 2.34 (1H, dd, $J_{7,8}$ =8.25 and $J_{7,6}$ =6.75 Hz, C₇-H), 2.93 (1H, d, J =9.0 Hz, C₃-H), 5.46 (2H, q, J =7.5 Hz, –CH₂CH₃), 8.53 (3H, t, J =7.5 Hz, –CH₂CH₃). *Anal.* Calcd. for C₁₁H₁₀O₃N₂: C, 60.54; H, 4.63; N, 12.84. Found: C, 60.40; H, 4.36; N, 12.78. Refluxing XXVIII (0.1 g) with conc. HCl (2 ml) for 1 hr afforded 0.08 g (92%) of XXIX. The fraction eluted with petr. ether–ether (4:1) was recrystallized from MeOH to give 1.03 g of ethyl N-(5-nitro-8-quinolyl)carbamate (XXVII), pale yellow needles, mp 122–123°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3346 (NH), 1753 (C=O), 1250 (C–O). NMR τ (CDCl₃): 0.78 (1H, dd, $J_{4,3}$ =8.4 and $J_{4,2}$ =1.5 Hz, C₄-H), 1.14 (1H, dd, $J_{2,3}$ =4.5 and $J_{2,4}$ =1.5 Hz, C₂-H), 1.53 (2H, s, C₆-H and C₇-H), 2.43 (1H, dd, $J_{3,2}$ =4.5 and $J_{3,4}$ =8.4 Hz, C₃-H), 5.68 (2H, q, J =7.5 Hz, –CH₂CH₃), 8.62 (3H, t, J =7.5 Hz, –CH₂CH₃). *Anal.* Calcd. for C₁₂H₁₁O₄N₃: C, 55.13; H, 4.25; N, 16.09. Found: C, 55.07; H, 4.34; N, 16.27. From the CHCl₃ eluate, 0.35 g (18.4%) of XXVI was recovered. The MeOH eluate gave an additional 0.1 g of XXIX. The total amount of XXIX was 0.26 g.

Synthesis and Hydrolysis of Ethyl N-(5-Nitro-8-quinolyl)carbamate (XXVII)—1) To an ice-cooled solution of IIj (0.54 g) in conc. H₂SO₄ (3 ml) was added KNO₃ (0.28 g), and the whole was kept overnight in a refrigerator. Adding ice-water to the reaction mixture deposited crystals, which were filtered, washed with 10% K₂CO₃ and H₂O, and chromatographed on alumina. The ether eluate gave 0.57 g (87.7%) of XXVII. The CHCl₃ effluent was recrystallized from MeOH to afford 0.06 g (9.2%) of pale yellow needles, mp 113°. This is assumed to be 7-nitro derivative from its IR spectrum.

2) A mixture of XXVII (0.3 g) and conc. HCl (3 ml) was refluxed for 7 hr to give 0.2 g (91%) of 5-nitro-8-aminoquinoline, orange needles, mp 300–301° (MeOH).

Reaction of 6-Chloroquinoline 1-Oxide (XXX) with BrCN—1) A mixture of XXX (1.8 g) and BrCN (1.59 g) in EtOH (20 ml) was refluxed for 3 hr. After the usual processing, the mixture of products was chromatographed on alumina with petr. ether, ether, CHCl₃ and MeOH. The petr. ether–ether (3:1) effluent was recrystallized from MeOH to give 0.93 g of ethyl N-(6-chloro-8-quinolyl)carbamate (XXXI), colorless needles, mp 110°. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3330 (NH), 1738 (C=O), 1249 (C–O). NMR τ (CDCl₃): 1.29 (1H, dd, $J_{2,3}$ =3.9 and $J_{2,4}$ =1.5 Hz, C₂-H), 1.62 (1H, d, J =2.25 Hz, C₇-H), 2.02 (1H, dd, $J_{4,3}$ =8.25 and $J_{4,2}$ =1.5 Hz, C₄-H), 5.68 (2H, q, J =6.9 Hz, –CH₂CH₃), 8.62 (3H, t, J =6.9 Hz, –CH₂CH₃). *Anal.* Calcd. for C₁₂H₁₁O₂N₂Cl: C, 57.49; H, 4.39; N, 11.18. Found: C, 57.86; H, 4.12; N, 11.37. The CHCl₃ eluate gave 0.3 g of 6-chloro-N-(6-chloro-2-quinolyl)carbostyryl (XXXII), colorless fine needles, mp 231–232° (MeOH). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1660 (C=O). *Anal.* Calcd. for C₁₃H₁₀ON₂Cl₂: C, 63.34; H, 2.93; N, 8.21. Found: C, 63.53; H, 3.19; N, 8.28. The MeOH eluate afforded 0.21 g of 6-chlorocarbostyryl (XXXIII), colorless needles, mp 263°.

2) Catalytic reduction of XXXI (0.1 g) with hydrogen over 10% Pd-C (0.1 g) was carried out in the presence of AcONa (0.05 g) in MeOH (20 ml) to give 0.06 g of IIj.

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21) A. Claus and Setzer, *J. Prakt. Chem.*, **53**, 390 (1896).