Chem. Pharm. Bull. 28(2) 424—430 (1980)

Studies of Tertiary Amine Oxides. LXV.[1] Reaction of Quinoline 1-Oxide with Tosyl Chloride in the Presence of Triethylamine

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(Received May 28, 1979)

The reaction of quinoline 1-oxide (**1**) with tosyl chloride (1 eq) and a large excess of triethylamine in a mixture of chloroform and water at room temperature gave 2-tosyloxyquinoline (**2**; trace), di(2-quinolyl) ether (**3**; 46%), N-(2-quinolyl)-2-quinolone (**4**; 35%) and carbostyril (**5**; 19%). Products **3** and **4** presumably originate from nucleophilic attack of carbostyril anions (**5'a** and **5'b**) on the tosyl chloride adduct of **1** (**11**).

"Di(2-quinolyl) ether" reported by Murakami and Matsumura[3] to be obtained by heating **1** with tosyl chloride was shown in fact to be an equimolar complex of **4** and **5**, and the nature of the reaction was clarified in detail.

Keywords——nucleophilic reaction; tosyl chloride adduct of quinoline 1-oxide; di(2-quinolyl)ether; N-(2-quinolyl)-2-quinolone; ambident ion of carbostyril; cleavage of ether linkage

In 1951 Murakami and Matsumura[3] reported that heating a tosyl chloride adduct of quinoline 1-oxide at 190—200° gave a minute amount of di(2-quinolyl) ether in addition to carbostyril, 4-chloroquinoline and N-(2-quinolyl)-2-quinolone. Ochiai *et al.* treated a chloroform solution of quinoline 1-oxide and tosyl chloride with sodium carbonate solution at room temperature to produce only carbostyril in good yield (83%),[4a] while refluxing the solution yielded not only carbostyril (14—15%) but also 4-chloroquinoline (13%) and N-(2-quinolyl)-2-quinolone (12%).[4b]

During the course of our studies on nucleophilic reactions of aromatic N-oxides in the presence of acylating agents, we found that di(2-quinolyl) ether was formed as the main product together with the usual products upon treatment of quinoline 1-oxide with tosyl chloride and triethylamine at room temperature in a mixture of chloroform and water. Since di(2-quinolyl) ether thus obtained was evidently different from that reported by Murakami and Matsumura,[3] we re-examined their work and succeeded in resolving the discrepancies.

A mixture of quinoline 1-oxide (**1**), tosyl chloride (1 eq) and a large excess of triethylamine in a mixture of chloroform and water was stirred at 0° for 1 hr and then at room temperature overnight. Chromatography of silica gel with *n*-hexane, dichloromethane and ethyl acetate gave 2-tosyloxyquinoline[5] (**2**, trace), di(2-quinolyl) ether (**3**, 46%), N-(2-quinolyl)-2-quinolone[6] (**4**, 35%) and carbostyril (**5**, 19%) (Chart 1).

Products **2**, colorless prisms, mp 82°, and **4**, colorless needles, mp 172—174°, were identified by direct comparison with authentic samples prepared by the reported methods.[5,6a]

The main product **3** was recrystallized from *n*-hexane–diisopropyl ether as colorless needles of mp 109—111°. It gave analytical values in agreement with the empirical formula $C_{18}H_{12}$-

1) Part LXIV: M. Hamana and S. Kumadaki, *Chem. Pharm. Bull.*, **26**, 3856 (1978).
2) Location: *3-1-1, Maidashi, Higashi-ku, Fukuoka, 812, Japan.*
3) M. Murakami and E. Matsumura, *Nippon Kagaku Zasshi*, **72**, 509 (1951).
4) *a*) E. Ochiai and T. Yokokawa, *Yakugaku Zasshi*, **75**, 213 (1955); *b*) E. Ochiai and T. Watanabe, and S. Suzuki, *ibid.*, **76**, 1421 (1956).
5) C.T. Cavallito and T.H. Haskel, *J. Am. Chem. Soc.*, **66**, 1927 (1944).
6) *a*) K. Takeda and K. Hamamoto, *Yakugaku Zasshi*, **73**, 1158 (1953); *b*) F. Ramirez and P.W. von Ostwalden, *J. Am. Chem. Soc.*, **81**, 156 (1959); *c*) S. Kajihara, *Nippon Kagaku Zasshi*, **86**, 1060 (1965).

N_2O, and its mass spectrum gave a molecular ion at *m/e* 272 and a fragment ion characteristic of an aromatic ether formed by extrusion of CO at *m/e* 244.[7] Its infrared (IR) spectrum showed an ether band at 1240 cm^{-1}, and the nuclear magnetic resonance (NMR) spectrum lacked the signal due to the C_2-proton of a quinoline ring and showed two 2-proton doublets at δ 7.32 (J=8.8 Hz) and 8.20 assignable to the C_3- and C_4-protons of two quinoline rings, respectively.

The ether linkage of **3** is appreciably susceptible to cleavage. Thus, hydrogenation of **3** in methanol–acetic acid at ordinary temperature and pressure over 50% palladium charcoal gave quinoline and carbostyril, and refluxing **3** with 40% hydrobromic acid for 4 hr or with ethanolic potassium hydroxide for 5 hr yielded 2-bromoquinoline (**6**) or 2-ethoxyquinoline[8] (**7**), respectively, together with carbostyril **5** in each case.

These spectral and chemical observations unambiguously established the structure of **3** shown here.

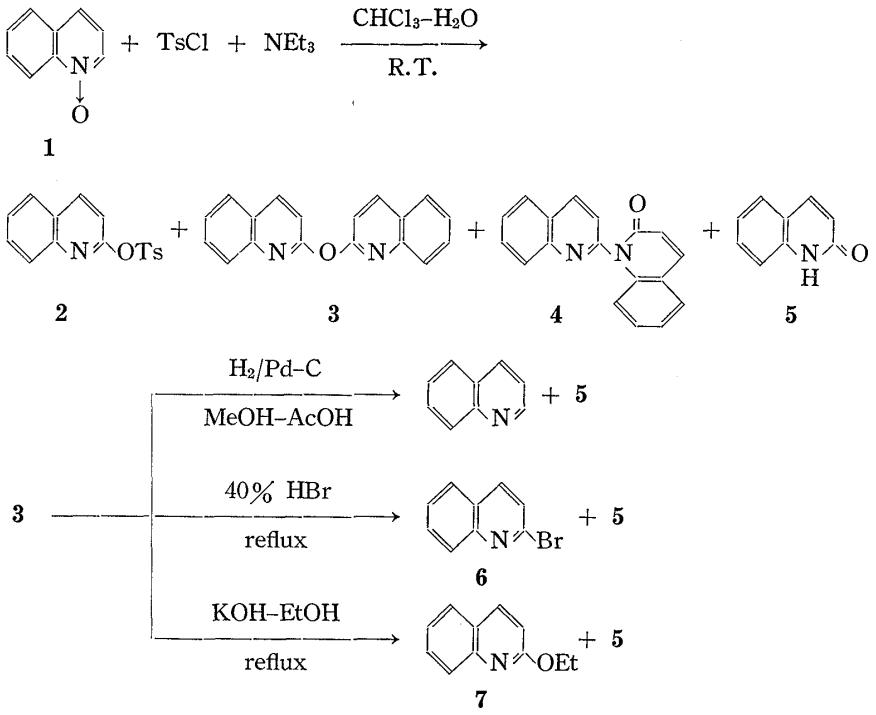

Chart 1

Subsequently in exploring the features of the reaction, various conditions were examined. Initially, the effect of the nature of the acylating agent was investigated, and it was found that tosyl chloride was the only one effective for the formation of **3**; the use of benzoyl chloride gave neither **3** nor **4** but carbostyril **5** as the predominant product (62%), together with a small amount of 2-benzoyloxyquinoline[5] (**8**, 4%). The reaction with mesyl chloride yielded no definite product; another type of reaction apparently occurs, which is now under investigation.

While the reaction using one or two equivalents of triethylamine afforded products **2**, **3**, **4**, and **5**, the main product was carbostyril **5** in each case (52 and 35%) and the yields of **3** fell to 11 and 16%, respectively. Apparently a large amount of triethylamine is required for the formation of **3** in preparatively significant yields. On the other hand, the use of N-methylpyrrolidine and benzyltrimethylammonium hydroxide curiously gave no definite products.

As for the reaction medium, a dichloromethane–water system was found to be as effective as chloroform–water, producing **3** and **4** in 46 and 22% yields, respectively. The reactions in

7) J.H. Beynon, G.R. Lester, and A.E. Williams, *J. Phys. Chem.*, **63**, 1861 (1959).
8) A. Kaufmann and V.P. de Petherd, *Ber.*, **50**, 336 (1917).

acetone–water, acetonitrile–water or water itself also yielded **3** and **4** but the results were unsatisfactory, and the use of an organic solvent, such as chloroform or dichloromethane alone was ineffective.

Table I shows the results of representative reactions thus examined.

Table I. Reaction of Quinoline 1- Oxide (**1**) with Tosyl Chloride and Triethylamine[a]

NEt_3 (eq)	Reaction medium	Product (%)			
		2	**3**	**4**	**5**
10	$CHCl_3$–H_2O	Trace	46	35	19
1	$CHCl_3$–H_2O	7	11	4	52
2	$CHCl_3$–H_2O	6	16	9	35
10	H_2O	—	27	13	9
10	CH_2Cl_2–H_2O	—	46	22	—
10	Acetone–H_2O	—	9	48	23
10[b]	$CHCl_3$–H_2O	4[c]	—	—	62

a) All reactions were carried out at 0°-room temperature for 12—13 hr (see "Experimental").
b) PhCOCl was used in place of TsCl.
c) 2-Benzoyloxyquinoline, colorless needles, mp 95° (EtOH–H_2O).[5]

In order to elucidate the structure of the product (**A**) described as di(2-quinolyl) ether by Murakami and Matsumura,[3] we re-examined the reaction of **1** with tosyl chloride according to their procedure, and obtained carbostyril **5**, 4-chloroquinoline, N-(2-quinolyl)-2-quinolone **4** and product **A** in practically the same manner.

Murakami and Matsumura deduced the structure of **4** only on the basis of the elemental analysis [$C_{18}H_{12}N_2O$],[3] and we confirmed that their view was correct. They stated that **A** had the empirical formula $C_{18}H_{12}N_2O \cdot 1/2H_2O$, and formed colorless minute plates of mp 171—172° when recrystallized from ether–benzene; depression of melting point was noted upon admixture with **4** of the same melting point, 171—172°.

We confirmed these observations, but found that the IR spectrum of **A** shows no band due to an ether linkage but instead has a carbonyl band at 1660 cm^{-1}. Chromatography on silica gel with dichloromethane and ethyl acetate caused separation into the quinolylquinolone **4** and carbostyril **5** in a mole ratio of 1:1. A mixture of equimolar **4** and **5** was recrystallized from ether–benzene to afford compound **A**, which was identical with the specimen obtained from the above re-examination. Since the IR spectrum of **A** was not completely superposable upon that of a simple mixture of **4** and **5**, as shown in Figs. 1 and 2, it was concluded that **A** is not an equimolar mixture but a molecular complex of **4** and **5**.

As described by Murakami and Matsumura, heating 2-chloroquinoline with carbostyril at 200° in a sealed tube for 4 hr gave **A**, and treatment of **A** with 40% hydrobromic acid at 130—140° for 3 hr yielded **5** and **4**, which was subsequently converted into yellow prisms (**9**) of mp 224—226° by heating with ethanolic potassium hydroxide. Treatment of **9** with ethanol in the presence of phosphorus pentoxide gave the corresponding ethyl ester (**10**), which was identical with the specimen obtained by the reaction of 2-bromoquinoline, **6** with ethyl *o*-aminocinnamate. Further, **4** was formed by heating **9** as well as **10**. Thus compound **9** was identified as *o*-(2-quinolylamino)cinnamic acid formed by hydrolysis of the amide linkage of **4**. In connection with these reactions, it was found that **4** was also obtainable by treatment of quinoline 1-oxide **1** and *o*-aminocinnamic acid with benzoyl chloride and potassium carbonate in dimethylformamide at room temperature.

These reactions are illustrated in Chart 2.

Since the presence of water and a large amount of triethylamine is required for the formation of di(2-quinolyl) ether **3** as well as N-(2-quinolyl)-2-quinolone **4**, the reaction can be consid-

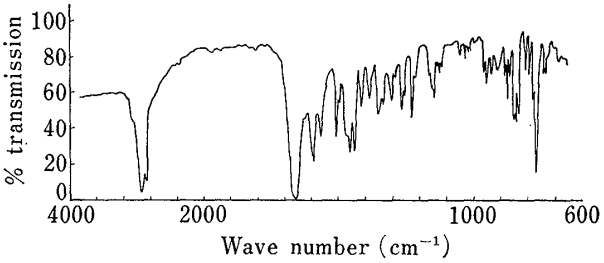

Fig. 1. IR Spectrum of **A**

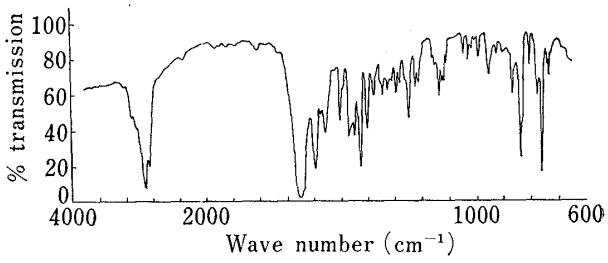

Fig. 2. IR Spectrum of a Mixture of **4** and **5**

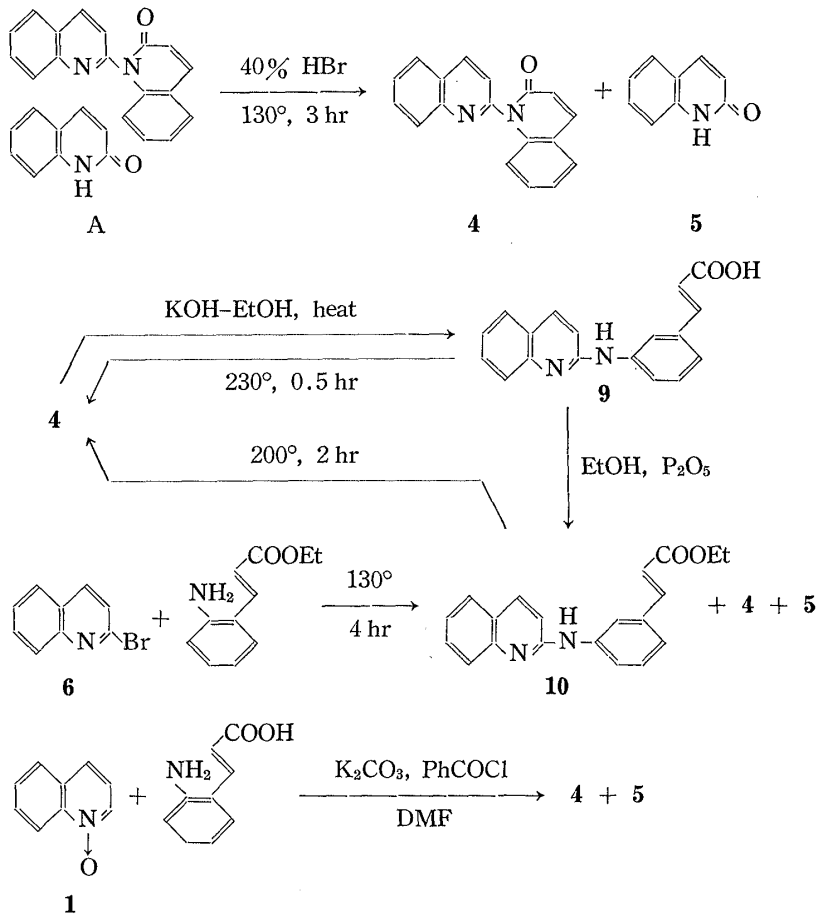

Chart 2

ered to proceed as shown in Chart 3. The first product is undoubtedly carbostyril **5**, formed *via* the tosyl chloride adduct of **1** (**11**) and the 1,2-dihydroquinoline intermediate (**12**), and the formation of other products can be rationalized in terms of further conversions of **5**. Tosylation of **5** under basic conditions affords 2-tosyloxyquinoline **2**. Because of the electronic character of the carbostyril anion **5′**, its nucleophilic attack at the electron-deficient 2-position of **11** proceeds by two courses, a and b; that is the attack by **5′a** or **5′b**, followed by elimination of *p*-toluenesulfonic acid from the 1,2-dihydroquinoline intermediate, **13** or **14**, gives the ether **3** or the quinolyquinolone **4**.

As for the formation of **4**, the interaction of **1** with **2** can be considered as an alternative course (c).[6,10] However, taking account of the reaction conditions, course b is apparently much more favorable than course c, at least in the above reaction. In exploring this aspect,

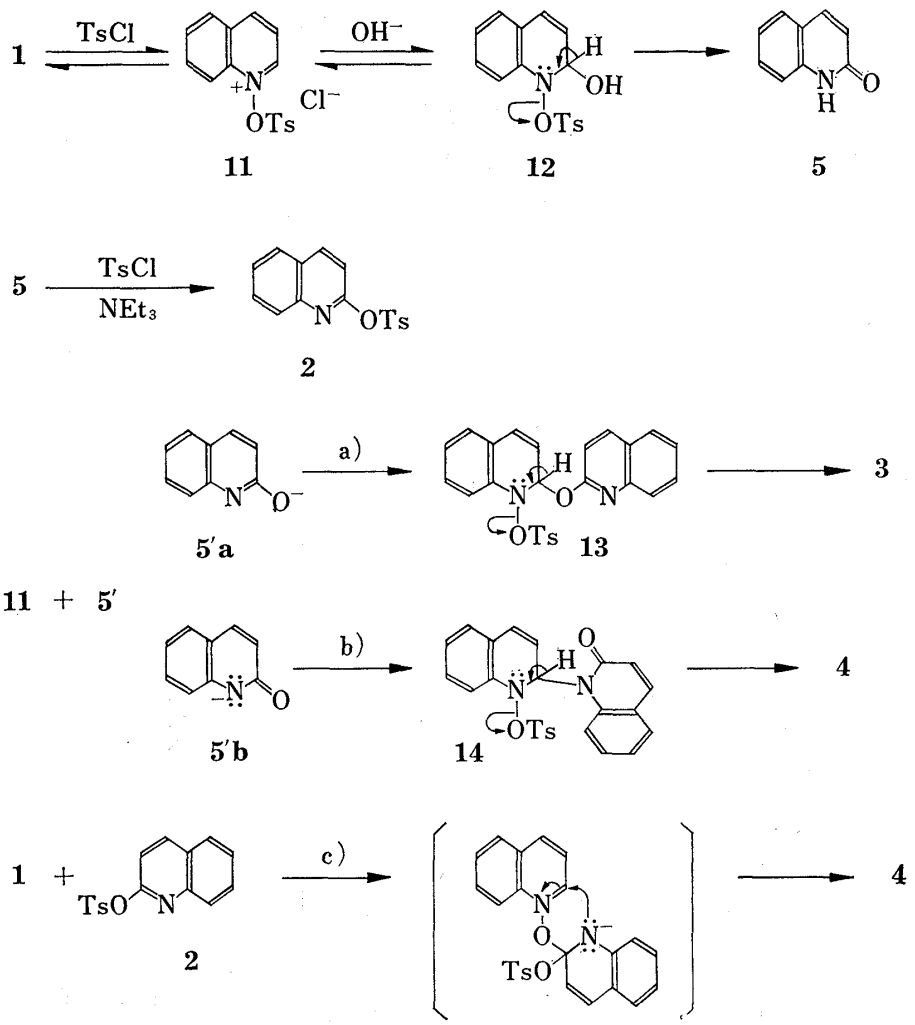

Chart 3

1 was allowed to react with **5** under the same conditions to give **3** and **4** in 28 and 16% yields, respectively, accompanied by a small amount of **2** and a large amount of **5**.

Experimental[9]

Reaction of Quinoline 1-Oxide (1) with Tosyl Chloride and Triethylamine——1) A solution of TsCl (2.3 g, 1.2 eq) in $CHCl_3$ (20 ml) was added dropwise with stirring to an ice-cooled mixture of quinoline 1-oxide dihydrate ($1 \cdot 2H_2O$, 1.81 g), NEt_3 (10 ml, *ca.* 10 eq) and $CHCl_3$ (20 ml)–H_2O (20 ml), and the reactants were stirred at the same temperature for 1 hr and then at room temperature for 12 hr. The $CHCl_3$ layer was separated from the aqueous layer, which was extracted with $CHCl_3$. The combined $CHCl_3$ solution was dried over Na_2SO_4, concentrated, and the residue was chromatographed on a silica gel column. The eluate with *n*-C_6H_{14}–CH_2Cl_2 (1: 1) gave a trace of 2-tosyloxyquinoline (**2**), colorless prisms, mp 82° (*n*-C_6H_{14}), which was identical with an authentic sample.[5] The CH_2Cl_2 effluent was recrystallized from (iso-Pr)$_2$O–*n*-C_6H_{14} to give 0.626 g (46%) of di(2-quinolyl) ether (**3**), colorless needles. *Anal.* Calcd for $C_{18}H_{12}N_2O$: C, 79.39; H, 4.44; N, 10.29. Found: C, 79.38; H, 4.42; N, 10.34. IR ν_{max}^{Nujol} cm^{-1}: 1240 (ether). NMR ($CDCl_3$) δ: 7.32 (2H, d, J=8.8 Hz, C_3–H and C_3'–H), 7.44—7.93 (8H, m, aromatic protons), 8.20 (2H, d, C_4–H and C_4'–H). MS *m/e*: 272 (M^+), 244 (M^+-CO). Monopicrate: yellow needles, mp 199—201° (EtOH). *Anal.* Calcd for $C_{18}H_{12}N_2O \cdot C_6H_3N_3O_7$: C, 57.49; H, 3.02; N, 13.97. Found: C, 57.89; H, 2.95; N, 13.90. The fraction eluted with *n*-C_6H_{14}–AcOEt (1: 1) was recrystallized from EtOH–H_2O to give 0.476 g (35%) of N-(2-quinolyl)-

9) All melting points are uncorrected. IR spectra were recorded on a JASCO IR-E spectrophotometer. NMR spectra were meaeured with a JEOL PS-100 spectrometer at 100 MHz using tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL O1SG machine.

2-quinolone (**4**), colorless needles, mp 172—174°; this material was identical with an authentic sample.[6a] The AcOEt eluate gave 0.276 g (19%) of carbostyril **5**, colorless needles, mp 200° (MeOH).

2) A similar run using **1**·$2H_2O$ (1.81 g), NEt_3 (1 ml, 1 eq), TsCl (2.1 g, 1.2 eq) and $CHCl_3$ (40 ml)–H_2O (20 ml) gave 0.21 g of **2** (7%), 0.3 g of **3** (11%), 0.1 g of **4** (7%) and 0.7 g of **5** (52%).

3) TsCl (2.1 g) was added in small portions to an ice-cooled mixture of **1**·$2H_2O$ (1.81 g), NEt_3 (10 ml) and H_2O (40 ml), with stirring, and the whole was processed in the same way as 1) to give 0.73 g of **3** (27%), 0.35 g of **4** (13%) and 0.13 g of **5** (9%).

Reactions of Di(2-quinolyl) Ether (3)——1) Hydrogenolysis: A solution of **3** (0.23 g) in AcOH (20 ml)–MeOH (6 ml) containing AcONa (0.15 g) was hydrogenated at normal temperature and pressure over 50% Pd-C previously prepared *in situ* from active charcoal (0.3 g) and 1% $PdCl_2$ (15 ml). After the absorption of *ca.* 1 mol of hydrogen (28.9 ml), the filtered and concentrated solution was acidified with 10% HCl and then made alkaline with $NaHCO_3$, and extracted with CH_2Cl_2. The residue from the CH_2Cl_2 extract was chromatographed on silica gel. The eluate with CH_2Cl_2–AcOEt (10: 1) gave quinoline, which was isolated as 0.03 g (16%) of the picrate, mp 199—200°. The eluate with CH_2Cl_2–AcOEt (1: 1) afforded 0.05 g (40.7%) of **5**, mp 200°.

2) Reaction with HBr: A solution of **3** (0.25 g) in 40% HBr (30 ml) was refluxed for 4 hr, concentrated *in vacuo*, made alkaline with K_2CO_3 solution and extracted with $CHCl_3$. The residue from the extract was chromatographed on silica gel. The CH_2Cl_2 eluate gave 0.03 g (15%) of 2-bromoquinoline **6**, colorless needles, mp 50—51° (EtOH). The AcOEt eluate afforded 0.24 g (90%) of **5**.

3) Reaction with KOH–EtOH: A solution of **3** (1.0 g) in EtOH (40 ml) was treated with KOH (3.0 g)–H_2O (5 ml), and the whole was refluxed for 5 hr. The reaction mixture was concentrated *in vacuo*, made alkaline with NH_4OH and extracted with $CHCl_3$. The residue from the extract was chromatographed on silica gel. Elution with CH_2Cl_2 gave two fractions. The first fraction gave 0.37 g (58%) of 2-ethoxyquinoline **7**,[8] identified as the picrate, yellow plates, mp 143—144° (MeOH). From the second fraction, 0.15 g (15%) of **3** was recovered. The eluate with AcOEt gave 0.42 g (79%) of **5**.

Compound A——1) A solution of **4** (0.27 g) and **5** (0.15 g) in benzene (10 ml) was treated with ether (10 ml), and the whole was shaken for a few minutes and then left to stand to deposit crystals. Recrystallization from ether–benzene gave **A** (0.35 g).

2) Chromatography of **A** (0.1 g) on silica gel afforded 0.06 g of **4** on elution with CH_2Cl_2–AcOEt (1: 1) and 0.03 g of **5** on elution with AcOEt.

Reaction of N-(2-Quinolyl)-2-quinolone (4) with KOH–EtOH——A solution of **4** (1.0 g) in EtOH (40 ml) was treated with KOH (3.0 g)–H_2O (5 ml), and the whole was refluxed for 8 hr, concentrated *in vacuo*, made alkaline with NH_4OH and extracted with $CHCl_3$ to give a trace of unreacted **4**. The mother liquor from $CHCl_3$ extraction was acidified with AcOH to give a precipitate, which was recrystallized from MeOH to yield 1.05 g (93%) of *o*-(2-quinolylamino)cinnamic acid (**9**), yellow prisms, mp 232—234° (dec.). *Anal.* Calcd for $C_{18}H_{14}N_2O_2 \cdot H_2O$: C, 70.11; H, 5.23; N, 9.09. Found: C, 69.98; H, 5.36; N, 8.73. IR ν_{max}^{Nujol} cm^{-1}: 3500 (NH), 2400—2700 (OH), 1600, 1638 (C=O). MS *m/e*: 290 (M^+).

Ethyl *o*-(2-Quinolylamino)cinnamate (10)——1) A solution of **9** (5.0 g) in anhyd. EtOH (30 ml) was treated with P_2O_5 (1.0 g), and the whole was refluxed for 5 hr, then the solvent was removed. K_2CO_3 solution was added to the residue, and the solution was extracted with $CHCl_3$. The residue from the extract was chromatographed on silica gel with AcOEt to give 0.51 g (93%) of **10** as a viscous oil. IR ν_{max}^{Nujol} cm^{-1}: 3300—3400 (NH), 1728, 1250 (ester). Picrate: yellow needles, mp 135—136° (EtOH). *Anal.* Calcd for $C_{20}H_{18}NO_2 \cdot C_6H_3N_3O_7$: C, 57.04; H, 3.87; N, 12.79. Found: C, 56.79; H, 3.81; N, 12.71.

2) A mixture of **6** (0.45 g) and ethyl *o*-aminocinnamate (0.45 g) was heated on an oil bath kept at 130° for 4 hr. The cooled reaction mixture was made alkaline with Na_2CO_3 solution and extracted with CH_2Cl_2. The residue from the extract was chromatographed on silica gel. From the first fraction, eluted with CH_2Cl_2, 0.10 g (22%) of **6** was recovered. The eluate with *n*-C_6H_{14}–AcOEt (3: 1) gave 0.13 g (22%) of **4**. The eluate with *n*-C_6H_{14}–AcOEt (3: 2) afforded 0.05 g (7%) of **10**. Further, 0.20 g (64%) of **5** was obtained from the AcOEt eluate.

N-(2-Quinolyl)-2-quinolone (4)——1) Ethyl *o*-(2-quinolylamino)cinnamate **10** (0.7 g) was heated on an oil bath kept at 200° for 2 hr. The reactants were dissolved in AcOEt, then passed through a silica gel column to afford 0.41 g (68%) of **4**, colorless scales, mp 173—174° (MeOH–H_2O).

2) *o*-(2-Quinolylamino)cinnamic acid **9** (0.3 g) was heated on an oil bath kept at 230° for 5 hr. The reaction mixture was dissolved in $CHCl_3$, and passed through a silica gel column to give 0.12 g (45.3%) of **4**.

3) PhCOCl (1.5 g) was added dropwise to an ice-cooled and stirred solution of **1** (1.45 g), **9** (1.75 g) and K_2CO_3 (5 g) in DMF (10 ml). The reactants were stirred at 0° for 3 hr and then at room temperature for 12 hr. Water was added and the resulting solution was made alkaline with K_2CO_3, then extracted with $CHCl_3$. The residue from the extract was chromatographed on silica gel. The eluate with CH_2Cl_2–AcOEt (3: 1) gave 0.52 g (36%) of **4**, and that with AcOEt afforded 0.48 g (33%) of **5**.

Reaction of Quinoline 1-Oxide (1) with Carbostyril (5) in the Presence of TsCl and NEt_3——A solution of TsCl (1.15 g) in $CHCl_3$ (20 ml) was added dropwise to an ice-cooled and stirred solution of **1**·$2H_2O$ (0.905 g), **5** (0.725 g) and NEt_3 (10 ml) in $CHCl_3$ (20 ml)–H_2O (20 ml), and the reactants were stirred at 0° for 1 hr and then at room temperature for 12 hr. The $CHCl_3$ layer was separated from the aqueous layer, which was

extracted with $CHCl_3$. The residue from the combined $CHCl_3$ solution was chromatographed on silica gel. The fraction eluted with n-C_6H_{14}–CH_2Cl_2 (1: 2) gave 0.01 g (0.7%) of **2**. The CH_2Cl_2 eluate afforded 0.381 g (29%) of **3**. The eluate with CH_2Cl_2–AcOEt (4: 1) gave 0.214 g (16%) of **4**. The last fraction, eluted with AcOEt, afforded 0.582 g of **5**.

Acknowledgement This work supported in part by the Takeda Science Foundation, and this is gratefully acknowledged. Thanks are also due to Mr. K. Ishimura for elemental analysis, to Miss M. Kawamura for the measurement of mass spectra and to Mr. A. Tanaka for the measurement of NMR spectra.