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Studies on Tertiary Amine Oxides. LXVI.[1] Reactions of Quinoline 1-Oxide Derivatives with Tosyl Chloride in the Presence of Triethylamine

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Reactions of N-oxides of lepidine (**1a**) and 4-methyl- (**1b**), 4-chloro- (**1c**) and 6-methoxyquinoline (**1d**) with tosyl chloride (1 eq) and triethylamine (*ca.* 10 eq) in a mixture of chloroform and water at room temperature gave the corresponding di(2-quinolyl) ethers (**3a—d**) and N-(2-quinolyl)-2-quinolones (**4a—d**). The efficiency of this type of reaction depends upon the nature and position of the substituents.

Whereas the reaction of **1c** with carbostyril under the same conditions gave small amounts of 4-chloro-2-tosyloxyquinoline (**2c**) and N-(4-chloro-2-quinolyl)-4-chloro-2-quinolone (**4c**), that of **1d** afforded 6-methoxy-2-quinolyl 2′-quinolyl ether (**15**) and N-(6-methoxy-2-quinolyl)-2-quinolone (**16**) in 47 and 29% yields, respectively.

Keywords——nucleophilic reaction; addition-elimination course; ether cleavage; 2,2′-diquinolyl ethers; N-(2-quinolyl)-2-quinolones; 2-tosyloxyquinolines; 2-oxoquinolines

In the preceding paper, we reported that quinoline 1-oxide reacts with tosyl chloride and triethylamine in a mixture of chloroform and water to afford di(2-quinolyl) ether and N-(2-quinolyl)-2-quinolone accompanied by small amounts of 2-tosyloxyquinoline and carbostyril.[1] As a continuation of this work, similar reactions of some quinoline 1-oxide derivatives were investigated.

In the general procedure, a mixture of a quinoline 1-oxide, one equivalent of tosyl chloride and a large excess of triethylamine (*ca.* 10 eq) in a mixture of chloroform and water was stirred at room temperature for 12—13 hr. Table I summarizes the reactions of N-oxides of lepidine (**1a**) and 4-methoxy- (**1b**), 4-chloro- (**1c**) and 6-methoxyquinoline (**1d**).

Table I. Reactions of Substituted Quinoline 1-Oxides (**1a—d**) with Tosyl Chloride and Triethylamine in Chloroform-Water

	Product (%)				
1	2	3	4	5	Other
1a : 4-Me	**2a** : 10	**3a** : 6	**4a** : 11	**5a** : 30	**6** : 8
1b : 4-OMe		**3b** : 13	**4b** : 50	**5b** : 13	
1c : 4-Cl		**3c** : 55	**4c** : 35		
1d : 6-OMe		**3d** : 23	**4d** : 11	**5d** : 28	

The reaction of lepidine 1-oxide (**1a**) afforded not only 2-tosyloxylepidine (**2a**), di(4-methyl-2-quinolyl) ether (**3a**), N-(4-methyl-2-quinolyl)-4-methyl-2-quinolone (**4a**) and 4-methylcarbostyril (**5a**),[3] but also 3-tosyloxylepidine (**6**), though all in small yields. The product **6** was apparently formed through an anhydro base (**7**), and was readily converted into 3-hydroxylepidine[3] upon heating with ethanolic potassium hydroxide.

1) Part LXV: K. Shichiri, K. Funakoshi, S. Saeki, and M. Hamana, *Chem. Pharm. Bull.*, **28**, 424 (1980).
2) Location: *3-1-1, Maidashi, Higashi-ku, Fukuoka, 812, Japan.*
3) G. Kobayashi, S. Furukawa, Y. Akimoto, and T. Hoshi, *Yakugaku Zasshi*, **74**, 791 (1954).

From the reaction of 4-methoxyquinoline 1-oxide (**1b**), N-(4-methoxy-2-quinolyl)-4-methoxy-2-quinolone (**4b**) was obtained as the major product in 50% yield together with small amounts of the corresponding diquinolyl ether (**3b**) and 4-methoxycarbostyril (**5b**).

The reaction of 4-chloroquinoline 1-oxide (**1c**) gave the diquinolyl ether (**3c**) and the quinolylquinlone (**4c**) in good yields of 55 and 35%, respectively, no other products being obtained.

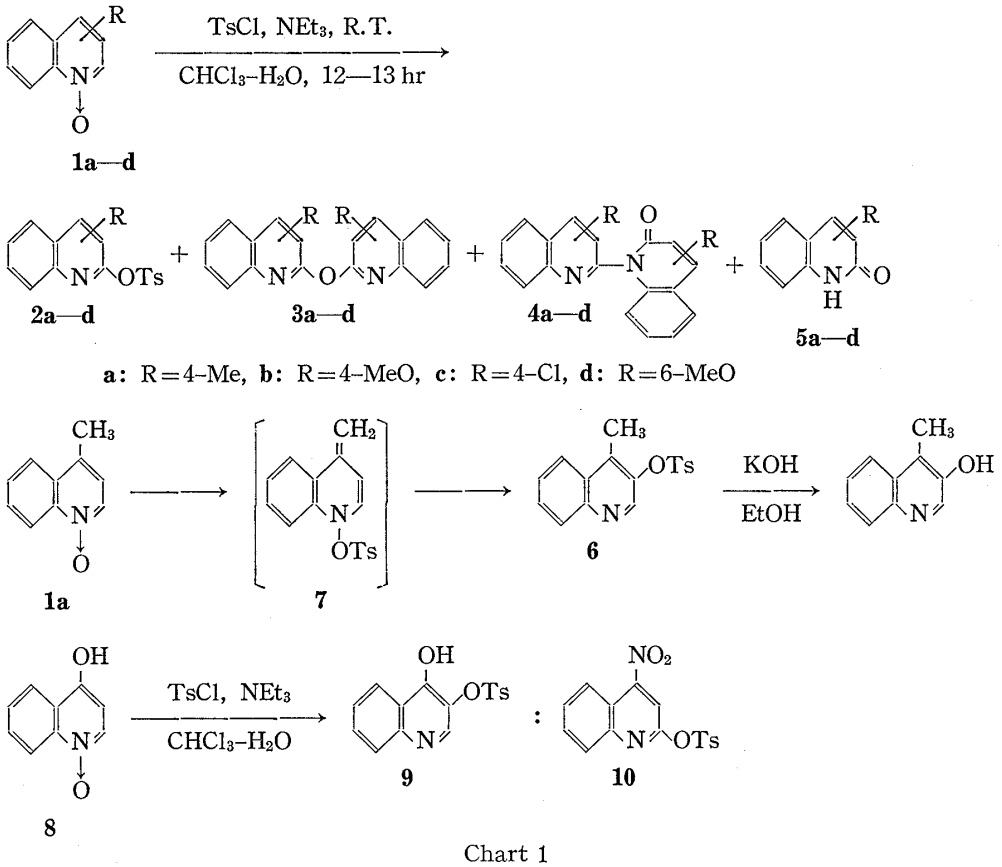

Chart 1

Table II. Some Physical Properties of **3a—d** and **4a—d**

Compd.	Appearance (Recryst. Solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{Nujol} (cm^{-1})
3a	Colorless needles ($EtOH–H_2O$)	153—155	$C_{20}H_{16}N_2O$	79.98 (80.10	5.37 5.40	9.33 9.25)	1240 (ether)
3b	Colorless needles [CH_2Cl_2–$(isoPr)_2O$]	188—188.5	$C_{20}H_{16}N_2O_3$	72.28 (72.49	4.85 4.78	8.43 8.47)	1200, 1250 (ether)
3c	Colorless pillars (CH_2Cl_2–*n*-hexane)	175—176	$C_{18}H_{10}Cl_2N_2O$	63.37 (63.48	2.95 2.65	8.21 8.30)	1235 (ether)
3d	Colorless needles ($MeOH–H_2O$)	138—139	$C_{20}H_{16}N_2O_3$	72.28 (72.32	4.85 4.83	8.43 8.39)	1220, 1250, 1260, 1280 (ether)
4a	Colorless needles ($EtOH–H_2O$)	213—215	$C_{20}H_{16}N_2O$	79.98 (79.96	5.37 5.48	9.33 9.26)	1665 (C=O)
4b	Colorless needles (EtOH)	297 (dec.)	$C_{20}H_{16}N_2O_3$	72.28 (72.15	4.85 4.84	8.43 8.53)	1240 (ether) 1655 (C=O)
4c	Colorless needles ($Me_2CO–H_2O$)	239—240	$C_{18}H_{10}Cl_2N_2O$	63.37 (63.38	2.95 2.70	8.21 8.12)	1665 (C=O)
4d	Colorless prisms (EtOH)	220—223	$C_{20}H_{16}N_2O_3$	72.28 (72.31	4.85 4.90	8.43 8.43)	1240, 1250 (ether) 1650, 1660 (C=O)

Similarly, 6-methoxyquinoline 1-oxide (**1d**) gave the diquinolyl ether (**3d**), quinolylquinolone (**4d**)[4] and 6-methoxycarbostyril (**5d**)[4] in 23, 11 and 28% yields, respectively.

The reaction of 4-quinolinol 1-oxide (**8**) followed another path, furnishing only 3-tosyloxy-4-quinolinol (**9**) in a high yield of 90%. The formation of **9** from **8** with tosyl chloride is a highly reactive process,[5] and evidently predominates over the type of reaction considered here. From the reaction of 4-nitroquinoline 1-oxide, only 4-nitro-2-tosyloxyquinoline (**10**) was isolated in a poor yield of 3%, the starting material being mostly recovered.

These results are shown in Chart 1, and some physical properties of **3a—d** and **4a—d** are listed in Table II.

Various reactions were carried out in connection with the structural elucidation of the products.

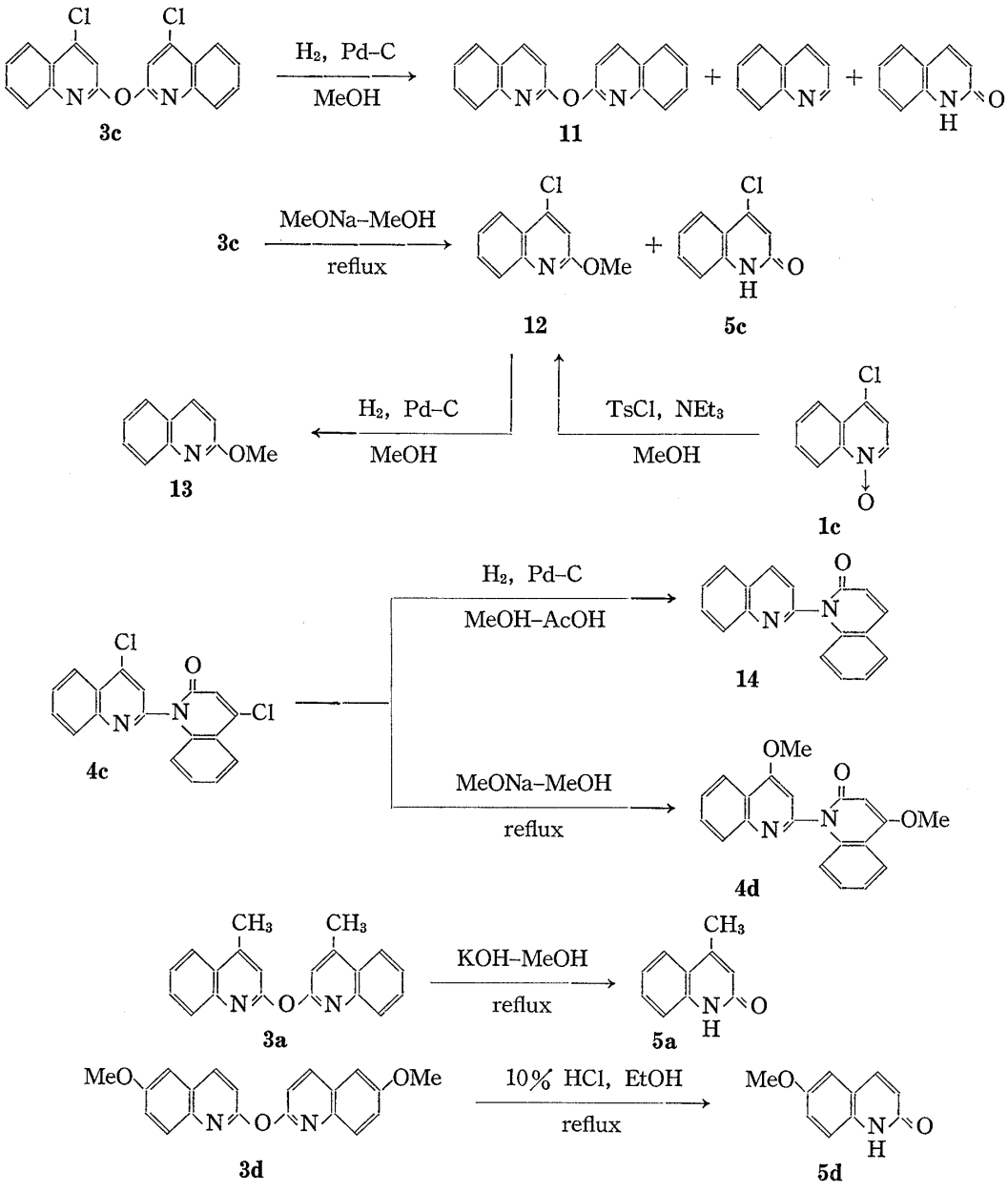

Chart 2

4) M. Hamana and I. Kumadaki, *Yakugaku Zasshi*, **86**, 1090 (1966).
5) M. Hamana and K. Funakoshi, *Yakugaku Zasshi*, **84**, 28 (1964).

Hydrogenation of di(4-chloro-2-quinolyl) ether, **3c**, in methanol over 50% palladium charcoal gave di(2-quinolyl) ether (**11**),[1] quinoline and carbostyril in 15, 21 and 38% yields, respectively. Apparently, the 4-chloro group is much more susceptible than the ether bond to catalytic reduction, as anticipated. On the other hand, treatment of **3c** with hot methanolic sodium methoxide was found to give 4-chloro-2-methoxyquinoline (**12**) and 4-chlorocarbostyril **5c**[6] in yields of 53 and 29%, respectively; no 4-methoxyquinoline derivatives were detected at all. This result indicates that, in contrast to hydrogenation, the ether linkage is much more reactive than the 4-chloro group in this case.

Reductive dechlorination of **12** to 2-methoxyquinoline (**13**) was effected in the usual way by hydrogenation in methanol over palladium charcoal, and **12** was shown to be obtainable from **1c** by treatment with tosyl chloride and triethylamine in methanol.[7]

Hydrogenation of N-(4-chloro-2-quinolyl)-4-chloro-2-quinolone **4c** in acetic acid and methanol over palladium charcoal gave the dechlorinated product (**14**),[1] and treatment with methanolic sodium methoxide under reflux afforded the corresponding 4,4′-dimethoxy compound **4b**.

Treatment of di(4-methyl-2-quinolyl) ether **3a** with ethanolic potassium hydroxide under reflux readily cleaved the ether bond, in the same way as **3c**, giving 4-methylcarbostyril **5a**[3] in 79% yield. Refluxing di(6-methoxy-2-quinolyl) ether **3d** with 10% hydrochloric acid in ethanol also brought about ready ether cleavage to afford 6-methoxy carbostyril **5d**[4] in 82% yield. These results provide additional evidence for the fact that the ether linkage of di(2-quinolyl) ethers is fairly susceptible to cleavage.

These reactions are shown in Chart 2.

In view of the mechanism proposed in the preceding paper[1] for the formation of **3** and **4**, **1c** and **1d** were treated with carbostyril in the presence of one equivalent of tosyl chloride and a large excess of triethylamine using the same solvent system in anticipation of the formation of the mixed diquinolyl ether as well as mixed quinolylquinolone. Products obtained from the reaction of **1c**, that is, 4-chloro-2-tosyloxyquinoline (**2c**, 6%) and N-(4-chloro-2-quinolyl)-4-chloro-2-quinolone (**4c**, 12%), apparently originated only from **1c** itself; however, the very low yields of products compared with the above-mentioned reaction of **1c** cannot be explained and the details of the reaction remain to be explored. On the other hand, the reaction of **1d** led to 6-methoxy-2-quinolyl 2′-quinolyl ether (**15**) and

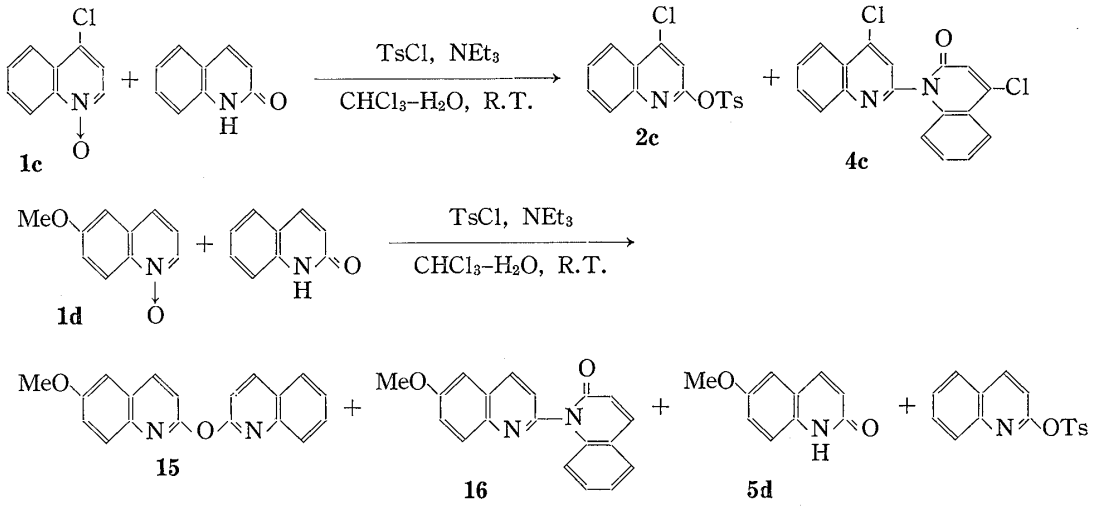

Chart 3

6) T. Itai, *Yakugaku Zasshi*, **65**(B), 4 (1945).
7) *cf*) H. Honda, Master's Thesis, Kyushu University, 1976.

N-(6-methoxy-2-quinolyl)-2-quinolone (**16**) in yields of 47 and 29%, respectively, accompanied by other products formed from **1d** or carbostyril as shown in Chart 3.

The formation of 2,2′-diquinolyl ethers as well as N-(2-quinolyl)-2-quinolones by the above-mentioned reaction seems to be fairly general and appears to depend upon the nature and position of the substituents.

Since mixed heteroaryl ethers, especially those of α,α'-, γ,γ'- and α,γ-types, are not easily synthesized, we are now investigating reactions of aromatic N-oxides with α- and γ-oxo-heteroaromatics in the presence of acylating agents and bases in the hope of providing a new route to this class of compounds, as a further extension of the above studies.

Experimental[8]

The appearance, mp, elemental analyses and the characteristic IR absorptions of **3a—d** and **4a—d** are listed in Table II.

Reaction of Lepidine 1-Oxide (1a) with TsCl and NEt_3——A solution of TsCl (2.3 g) in $CHCl_3$ (20 ml) was added dropwise to an ice-cooled and stirred solution of **1a**·1/2H_2O (1.95 g) and NEt_3 (10 ml) in $CHCl_3$ (20 ml)–H_2O (20 ml), and the reaction mixture was stirred 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 silica gel. The eluate with *n*-C_6H_{14}–CH_2Cl_2 (1: 1) gave 0.32 g (10.2%) of 2-tosyloxylepidine (**2a**), colorless needles, mp 122—124° (MeOH–H_2O). *Anal.* Calcd for $C_{17}H_{15}NO_3S$: C, 65.15; H, 4.83; N, 4.47. Found: C, 65.10; H, 4.79; N, 4.45. From the eluate with *n*-C_6H_{14}–CH_2Cl_2 (1: 3), 0.26 g (8.3%) of 3-tosyloxylepidine (**6**) was obtained as colorless pillars, mp 142—144° (MeOH). *Anal.* Calcd for $C_{17}H_{15}NO_3S$: C, 65.15; H, 4.83; N, 4.47. Found: C, 65.15; H, 4.81; N, 4.44. The CH_2Cl_2 eluate gave 0.18 g (6.0%) of di(4-methyl-2-quinolyl) ether (**3a**). NMR ($CDCl_3$) δ: 2.68 (6H, s, C_4–CH_3 and C_4'–CH_3), 7.12 (2H, s, C_3–H and C_3'–H). MS *m/e*: 300 (M^+). Elution with AcOEt gave successively 0.34 g (11.3%) of N-(4-methyl-2-quinolyl)-4-methyl-2-quinolone (**4a**) [MS *m/e*: 300 (M^+)] and 0.48 g (30.2%) of 4-methylcarbostyril (**5a**),[3] colorless needles, mp 220—222° (MeOH).

A solution of **2a** (0.3 g) in conc. HCl (20 ml) was refluxed for 3 hr to give 0.11 g (72.4%) of **5a**.

A mixture of **6** (0.3 g) and KOH (1.0 g)–EtOH (15 ml) was refluxed for 3 hr to give 0.1 g (65.8%) of 3-hydroxylepidine,[3] colorless leaflets, mp 200—202°.

Reaction of 4-Methoxyquinoline 1-Oxide (1b) with TsCl and NEt_3——A mixture of **1b** (1.75 g), NEt_3 (10 ml) and TsCl (2.3 g) in $CHCl_3$ (40 ml)–H_2O (20 ml) was allowed to react under the conditions described above. The mixture of products was chromatographed on silica gel with CH_2Cl_2 and AcOEt. The fraction eluted with CH_2Cl_2 was again chromatographed on silica gel with *n*-C_6H_{14} and AcOEt. The eluate with *n*-C_6H_{14}–AcOEt (6: 1) gave 0.21 g (12.7%) of di(4-methoxy-2-quinolyl) ether (**3b**). NMR ($CDCl_3$) δ: 4.01 (6H, s, 4-OCH_3 and 4′-OCH_3), 6.65 (2H, s, C_3–H and C_3'–H), 8.12 (2H, d, J=7.9 Hz, C_8–H and C_8'–H). MS *m/e*: 332 (M^+). The AcOEt eluate gave 0.83 g (50%) of N-(4-methoxy-2-quinolyl)-4-methoxy-2-quinolone (**4b**). MS *m/e*: 332 (M^+).

The fraction eluted with AcOEt from the first chromatography gave 0.22 g (12.6%) of 4-methoxycarbostyril (**5b**), colorless needles, mp 258—259° (MeOH). *Anal.* Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.44; H, 5.12; N, 8.01. IR ν_{max}^{Nujol} cm^{-1}: 1235 (ether), 1673 (C=O), 3140 (NH). This was identical with an authentic sample prepared from **1b** by reaction with TsCl–Na_2CO_3 in $CHCl_3$–H_2O.

Reaction of 4-Chloroquinoline 1-Oxide (1a) with TsCl and NEt_3——A mixture of **1c** (0.9 g), NEt_3 (5 ml) and TsCl (1.15 g) in $CHCl_3$ (20 ml)–H_2O (10 ml) was treated as described above, and the mixture of products was chromatographed on silica gel. Elution with CH_2Cl_2 gave 0.47 g (55.3%) of di(4-chloro-2-quinolyl) ether (**3c**). NMR ($CDCl_3$) δ: 7.46 (2H, s, C_3–H and C_3'–H). MS *m/e*: 341 (M^+). The AcOEt eluate gave 0.3 g (35.3%) of N-(4-chloro-2-quinolyl)-4-chloro-2-quinolone (**4c**). MS *m/e*: 341 (M^+).

Reaction of 6-Methoxyquinoline 1-Oxide (1d) with TsCl and NEt_3——A mixture of **1d**·2H_2O (0.88 g), NEt_3 (5 ml) and TsCl (1.15 g) in $CHCl_3$ (20 ml)–H_2O (10 ml) was treated as described above, and the mixture of products was chromatographed on silica gel. Elution with *n*-C_6H_{14}–AcOEt (7: 3) gave 0.33 g (23%) of di(6-methoxy-2-quinolyl) ether (**3d**). NMR ($CDCl_3$) δ: 3.92 (6H, s, 6-OCH_3 and 6′-OCH_3), 7.76 (2H, d, J= 8.5 Hz, C_7–H and C_7'–H), 8.80 (2H, d, C_8–H and C_8'–H). MS *m/e*: 332 (M^+). The AcOEt eluate gave 0.16 g (11.2%) of N-(6-methoxy-2-quinolyl)-6-methoxy-2-quinolone (**4d**).[4] MS *m/e*: 332 (M^+). The eluate with AcOEt–MeOH (9: 1) gave 0.21 g (28%) of 6-methoxycarbostyril (**5d**),[4] colorless prisms, mp 218—220° (EtOH-H_2O).

8) All melting points are uncorrected. IR spectra were recorded on a JASCO IR-E spectrophotometer. NMR spectra were measured with a JEOL PS-100 spectrophotometer at 100 MHz using tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL 01SG machine.

Reaction of 4-Quinolinol 1-Oxide (8) with TsCl and NEt_3——A mixture of **8** (0.80 g), NEt_3 (5 ml) and TsCl (1.15 g) in $CHCl_3$ (20 ml)–H_2O (10 ml) was stirred 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, and concentrated, and the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was passed through a silica gel column to give 1.29 g (90.2%) of 3-tosyloxy-4-quinolinol (**9**),[5] colorless needles, mp 227—228° (95% EtOH).

Reaction of 4-Nitroquinoline 1-Oxide with TsCl and NEt_3——A mixture of 4-nitroquinoline 1-oxide (0.95 g), NEt_3 (5 ml) and TsCl (1.15 g) in $CHCl_3$ (20 ml)–H_2O (10 ml) was stirred 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: 1) gave 0.11 g (3.2%) of 4-nitro-2-tosyloxyquinoline (**10**), pale yellow needles, mp 170—172° [benzene-n-C_6H_{14} (1: 3)]. *Anal.* Calcd for $C_{16}H_{12}N_2O_5S$: C, 55.82; H, 3.51; N, 8.14. Found: C, 55.93; H, 3.62; N, 7.98. MS *m/e*: 344 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1183, 1195, 1385 (SO_2), 1365, 1540 (NO_2). NMR ($CDCl_3$) δ: 2.48 (3H, s, CH_3), 7.39 (2H, d, J=8.0 Hz, two Ph–H), 8.04 (2H, d, J=8.0 Hz, two Ph–H), 7.68 (1H, s, C_3–H), 8.35 (1H, dd, C_8–H), 7.7—8.0 (3H, m, C_5–, C_6– and C_8–H). Unreacted N-oxide was recovered from the CH_2Cl_2 eluate; 0.57 g (60%).

Reaction of Di(4-chloro-2-quinolyl) Ether (3c)——1) Hydrogenation: A solution of **3c** (0.25 g) in MeOH (40 ml) was hydrogenated at normal temperature and preseure over 50% Pd-C previously prepared *in situ* from active charcoal (0.3 g) and 1% $PdCl_2$ (15 ml). After absorption of 41.2 ml of hydrogen, the solution was filtered and concentrated, then made alkaline with NH_4OH and extracted with $CHCl_3$. The residue from the $CHCl_3$ extract was chromatographed on silica gel. The CH_2Cl_2 eluate gave 0.03 g (15.0%) of di(2-quinolyl) ether (**11**),[1] colorless needles, mp 109—111° [$(isoPr)_2O$–n-C_6H_{14}]. The eluate with CH_2Cl_2–AcOEt (2: 1) gave 0.02 g (21.2%) of quinoline. The AcOEt eluate afforded 0.04 g (37.7%) of carbostyril.

2) Reaction with MeONa–MeOH: Compound **3c** (0.2 g) was added to a MeONa–MeOH solution prepared from Na (0.35 g) and anhyd. MeOH (10 ml), and the whole was refluxed for 6 hr. The reaction mixture was concentrated, treated with $NaHCO_3$ solution, and extracted with CH_2Cl_2. The residue from the CH_2Cl_2 extract was chromatographed on silica gel. The fraction eluted with n-C_6H_{14}–AcOEt (10: 1) gave 0.06 g (53%) of 4-chloro-2-methoxyquinoline (**12**), colorless needles, mp 70—71° (petr. ether). *Anal.* Calcd for $C_{10}H_8ClNO$: C, 62.03; H, 4.16; N, 7.23. Found: C, 61.95; H, 4.00; N, 7.23. The AcOEt eluate gave 0.03 g (29%) of 4-chlorocarbostyril (**5c**),[6] colorless needles, mp 345—347° (EtOH).

4-Chloro-2-methoxyquinoline (12)——An ice-cooled and stirred solution of **1c** (0.9 g) in anhyd. MeOH (30 ml) was treated with TsCl (2.1 g) in small portions, followed by NEt_3 (1.2 g), then the whole was stirred at room temperature for 5 hr. The reaction mixture was concentrated, treated with $NaHCO_3$ solution, and extracted with CH_2Cl_2. The residue from the CH_2Cl_2 extract was chromatographed on silica gel with n C_6H_{14}–CH_2Cl_2 (1: 1) to give 0.84 g (87%) of **12**.

Hydrogenation of 4-Chloro-2-methoxyquinoline (12)——A solution of **12** (0.04 g) in MeOH (40 ml) containing AcONa (0.015 g) was hydrogenated over Pd–C previously prepared *in situ* from active charcoal (0.03 g) and 1% $PdCl_2$ (2 ml). After absorption of *ca.* 1 mol eq of hydrogen, the solution was filtered and concentrated, then treated with $NaHCO_3$ solution and extracted with CH_2Cl_2. The residue from the CH_2Cl_2 extract was chromatographed on silica gel with n-C_6H_{14}–benzene (2: 1) to give two fractions. The first fraction gave 2-methoxyquinoline, which was isolated as 0.06 g (64.9%) of the picrate, mp 170—171° (EtOH). From the second fraction, 0.015 g (33%) of **12** was recovered.

Reaction of N-(4-Chloro-2-quinolyl)-4-chloro-2-quinolone (4c)——1) Hydrogenation: A solution of **4c** (0.3 g) in AcOH (20 ml)–MeOH (5 ml) containing AcONa (0.15 g) was hydrogenated at normal temperature and presuure over 50% Pd–C previously prepared *in situ* from active charcoal (0.3 g) and 1% $PdCl_2$ (15 ml). After absorption of 28.4 ml of hydrogen, the solution was filtered and concentrated, then made alkaline with $NaHCO_3$ solution and extracted with CH_2Cl_2. The residue from the CH_2Cl_2 extract was chromatographed on silica gel with CH_2Cl_2–AcOEt (1: 1). The first fraction gave 0.08 g (26.7%) of unreacted **4c**. The second one afforded 0.07 g (29.2%) of N-(2-quinolyl)-2-quinolone (**14**),[1] colorless needles, mp 172—174° (EtOH–H_2O).

2) Reaction with MeONa–MeOH: Compound **4c** (0.15 g) was added to a solution of MeONa in MeOH prepared from Na (0.3 g) and anhyd. MeOH (22 ml), and the whole was refluxed for 16 hr. After concentration, NH_4OH was added, and the resulting mixture was extracted with CH_2Cl_2. The residue from the CH_2Cl_2 extract was dissolved in CH_2Cl_2–AcOEt (1: 1) and passed through a silica gel column to give 0.13 g (98%) of **4b**.

Reaction of Di(4-methyl-2-quinolyl) Ether (3a) with KOH-MeOH——A mixture of **3a** (0.3 g) and KOH (1.0 g)–EtOH (15 ml) was refluxed for 3 hr. The reaction mixture was concentrated, made alkaline with ammonia and extracted with $CHCl_3$. The residue from the $CHCl_3$ extract was recrystallized from MeOH to give 0.25 g (78.6%) of **5a**.[3]

Reaction of Di(6-methoxy-2-quinolyl) Ether (3d) with 10% HCl-EtOH——A solution of **3d** (0.1 g) in 10% HCl (5 ml)–EtOH (8 ml) was refluxed for 3 hr. The reactants were concentrated, made alkaline with $NaHCO_3$ solution and extracted with CH_2Cl_2. The residue from the CH_2Cl_2 extract was recrystallized from EtOH–H_2O to give 0.086 g (82%) of **4d**.[4]

Reaction of 4-Chloroquinoline 1-Oxide (1c) with Carbostyril in the Presence of TsCl and NEt_3——An ice-cooled and stirred mixture of **1c** (0.45 g), carbostyril (0.36 g), NEt_3 (5 ml), $CHCl_3$ (10 ml) and H_2O (10 ml) was treated dropwise with a solution of TsCl (1.15 g) in $CHCl_3$ (10 ml), and the whole was stirred 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 first fraction, eluted with n-C_6H_{14}–CH_2Cl_2 (1: 1), afforded 0.051 g (6%) of 4-chloro-2-tosyloxyquinoline (**2c**), colorless needles, mp 135—137° [CH_2Cl_2–$(isoPr)_2O$]. *Anal.* Calcd for $C_{16}H_{12}ClNO_3S$: C, 57.57; H, 3.62; N, 4.20. Found: C, 57.52; H, 3.61; N, 4.12. The eluate with CH_2Cl_2–AcOEt (1: 1) gave 0.051 g (12%) of **4c**. IR ν_{max}^{Nujol} cm^{-1}: 1180, 1195, 1375 (SO_2). NMR ($CDCl_3$) δ: 2.47 (3H, s, CH_3), 7.28 (1H, s, C_3–H), 7.34 (2H, d, J= 8.0 Hz, two Ph–H), 8.01 (2H, d, J=8.0 Hz, two Ph–H). MS m/e: 333 (M^+). The last fraction, eluted with AcOEt, gave 0.07 g (19%) of carbostyril.

Reaction of 6-Methoxyquinoline 1-Oxide (1d) with Carbostyril in the Presence of TsCl and NEt_3——A solution of TsCl (2.3 g) in $CHCl_3$ (20 ml) was added dropwise to an ice-cooled and stirred mixture of **1d** (0.88 g), carbostyril (0.73 g), NEt_3 (5 ml), $CHCl_3$ (20 ml) and H_2O (20 ml), and the whole was stirred 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 carefully chromatographed on silica gel. The fraction eluted with n-C_6H_{14}–CH_2Cl_2 (1: 1) gave 0.16 g (10.7%) of 2-tosyloxyquinoline,[1] colorless prisms, mp 82° (n-C_6H_{14}). The CH_2Cl_2 eluate afforded 0.60 g (39.5%) of 6-methoxy-2-quinolyl-2′-quinolyl ether (**15**), colorless needles, mp 153—154° (95% EtOH). *Anal.* Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.51; H, 4.63; N, 9.25. IR ν_{max}^{Nujol} cm^{-1}: 1240, 1255 (ether). NMR ($CDCl_3$) δ: 3.92 (3H, s, OCH_3). MS m/e: 302 (M^+). The eluate with CH_2Cl_2–AcOEt (3: 1) gave 0.37 g (24.3%) of N-(6-methoxy-2-quinolyl)-2-quinolone (**16**), colorless needles, mp 197—197.5° (EtOH). *Anal.* Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.42; H, 4.76: N, 9.25. IR ν_{max}^{Nujol} cm^{-1}: 1245 (ether), 1660 (C=O). NMR ($CDCl_3$) δ: 3.97 (3H, s, OCH_3). MS m/e: 302 (M^+). In addition, 0.15 g (20.5%) of carbostyril and 0.30 g (34%) of **5d** were isolated from the fractions eluted with AcOEt and with EtOH, respectively.

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