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## Studies on Tertiary Amine Oxides. LXVI.<sup>1)</sup> 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 carbostyryl 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 carbostyryl.<sup>1)</sup> 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

1	Product (%)				
	2	3	4	5	Other
<b>1a</b> : 4-Me	<b>2a</b> : 10	<b>3a</b> : 6	<b>4a</b> : 11	<b>5a</b> : 30	<b>6</b> : 8
<b>1b</b> : 4-OMe		<b>3b</b> : 13	<b>4b</b> : 50	<b>5b</b> : 13	
<b>1c</b> : 4-Cl		<b>3c</b> : 55	<b>4c</b> : 35		
<b>1d</b> : 6-OMe		<b>3d</b> : 23	<b>4d</b> : 11	<b>5d</b> : 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-methyl-carbostyryl (**5a**),<sup>3)</sup> 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<sup>3)</sup> 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-methoxycarbostyryl (**5b**).

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

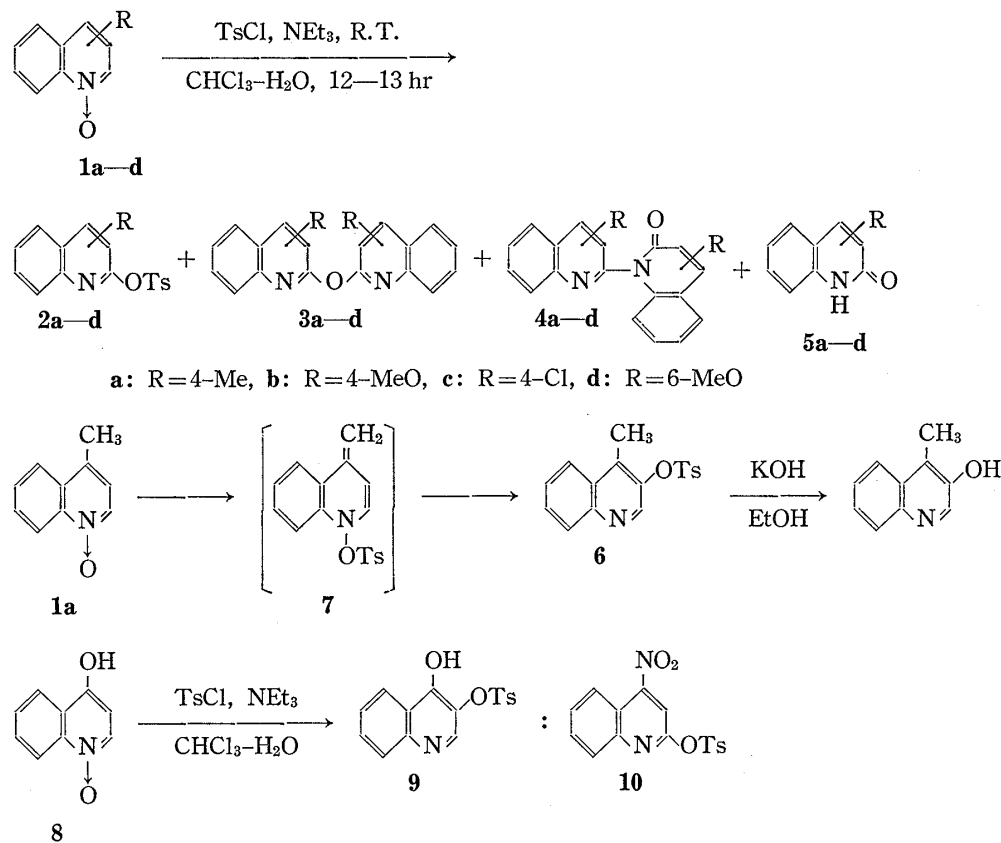


Chart 1

TABLE II. Some Physical Properties of **3a-d** and **4a-d**

Compd.	Appearance (Recryst. Solv.)	mp (°C)	Formula	Analysis (%)			IR $\nu_{\max}^{\text{Nujol}}$ (cm <sup>-1</sup> )
				Calcd (Found)			
				C	H	N	
<b>3a</b>	Colorless needles (EtOH-H <sub>2</sub> O)	153—155	C <sub>20</sub> H <sub>16</sub> N <sub>2</sub> O	79.98 (80.10)	5.37 (5.40)	9.33 (9.25)	1240 (ether)
<b>3b</b>	Colorless needles [CH <sub>2</sub> Cl <sub>2</sub> -(isoPr) <sub>2</sub> O]	188—188.5	C <sub>20</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>	72.28 (72.49)	4.85 (4.78)	8.43 (8.47)	1200, 1250 (ether)
<b>3c</b>	Colorless pillars (CH <sub>2</sub> Cl <sub>2</sub> - <i>n</i> -hexane)	175—176	C <sub>18</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O	63.37 (63.48)	2.95 (2.65)	8.21 (8.30)	1235 (ether)
<b>3d</b>	Colorless needles (MeOH-H <sub>2</sub> O)	138—139	C <sub>20</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>	72.28 (72.32)	4.85 (4.83)	8.43 (8.39)	1220, 1250, 1260, 1280 (ether)
<b>4a</b>	Colorless needles (EtOH-H <sub>2</sub> O)	213—215	C <sub>20</sub> H <sub>16</sub> N <sub>2</sub> O	79.98 (79.96)	5.37 (5.48)	9.33 (9.26)	1665 (C=O)
<b>4b</b>	Colorless needles (EtOH)	297 (dec.)	C <sub>20</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>	72.28 (72.15)	4.85 (4.84)	8.43 (8.53)	1240 (ether) 1655 (C=O)
<b>4c</b>	Colorless needles (Me <sub>2</sub> CO-H <sub>2</sub> O)	239—240	C <sub>18</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O	63.37 (63.38)	2.95 (2.70)	8.21 (8.12)	1665 (C=O)
<b>4d</b>	Colorless prisms (EtOH)	220—223	C <sub>20</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>	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**), quinolyl-quinolone (**4d**)<sup>4</sup> and 6-methoxycarbostyryl (**5d**)<sup>4</sup> in 23, 11 and 28% yields, respectively.

The reaction of 4-quinolinol 1-oxide (**8**) followed another path, furnishing only 3-tosyl-oxy-4-quinolinol (**9**) in a high yield of 90%. The formation of **9** from **8** with tosyl chloride is a highly reactive process,<sup>5</sup> 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.

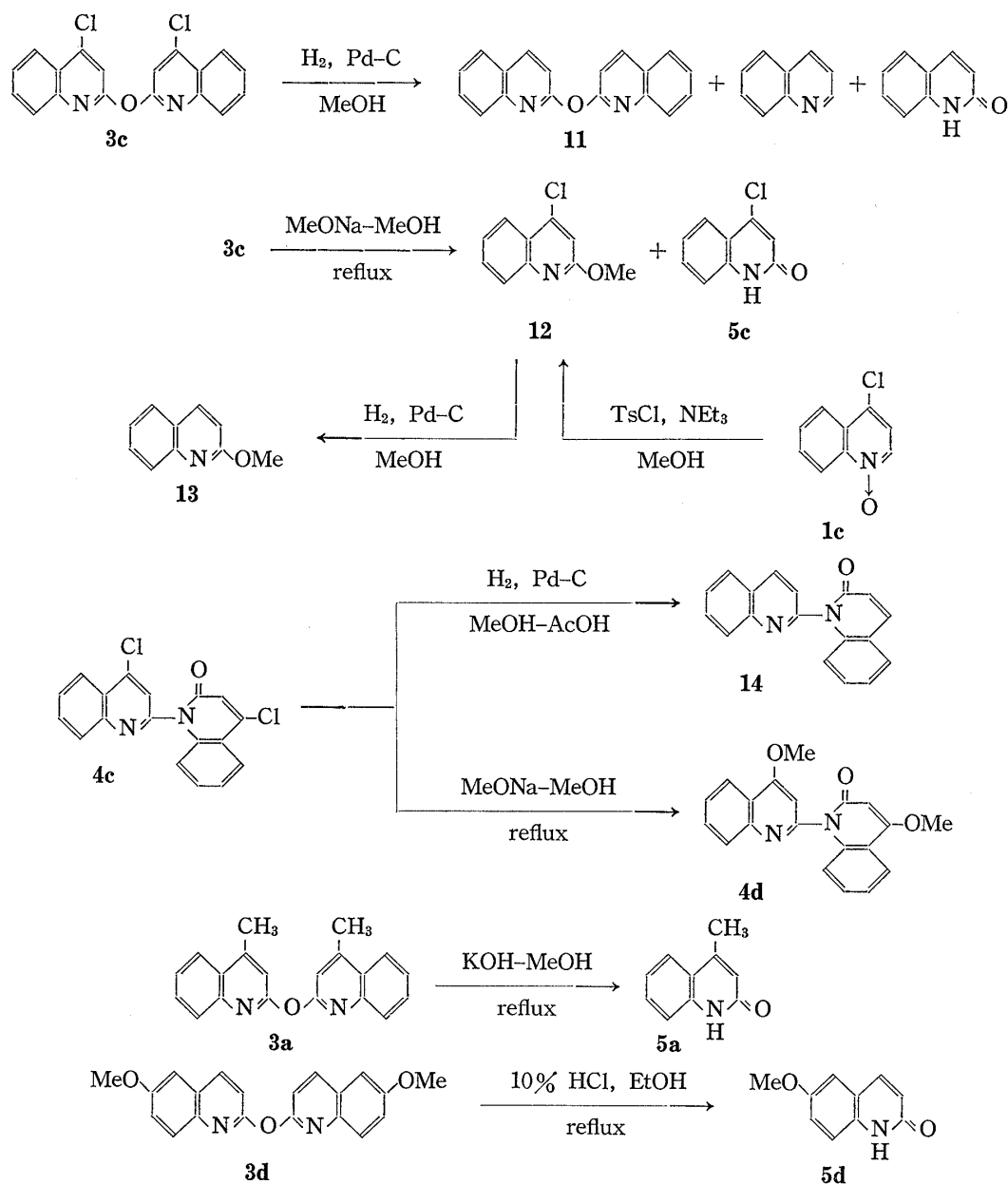


Chart 2

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**),<sup>1)</sup> quinoline and carbostyryl 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-chloro-carbostyryl **5c**<sup>6)</sup> 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.<sup>7)</sup>

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**),<sup>1)</sup> 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-methylcarbostyryl **5a**<sup>3)</sup> 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 carbostyryl **5d**<sup>4)</sup> 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<sup>1)</sup> for the formation of **3** and **4**, **1c** and **1d** were treated with carbostyryl 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

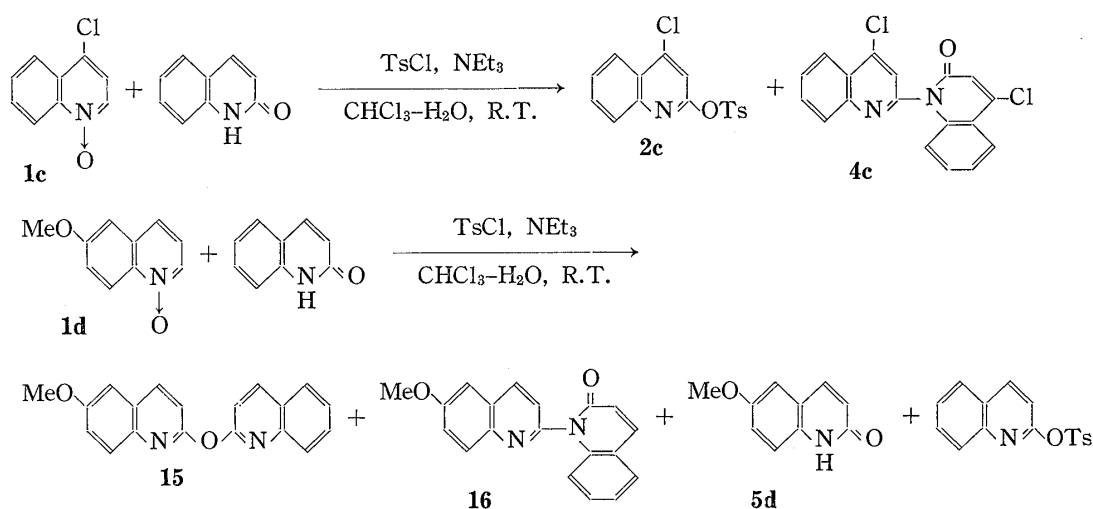


Chart 3

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 carbostyryl 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  $\alpha,\alpha'$ -,  $\gamma,\gamma'$ - and  $\alpha,\gamma$ -types, are not easily synthesized, we are now investigating reactions of aromatic N-oxides with  $\alpha$ - and  $\gamma$ -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<sup>8)</sup>

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  $\text{NEt}_3$** —A solution of TsCl (2.3 g) in  $\text{CHCl}_3$  (20 ml) was added dropwise to an ice-cooled and stirred solution of **1a**·1/2 $\text{H}_2\text{O}$  (1.95 g) and  $\text{NEt}_3$  (10 ml) in  $\text{CHCl}_3$  (20 ml)– $\text{H}_2\text{O}$  (20 ml), and the reaction mixture was stirred at room temperature for 12 hr. The  $\text{CHCl}_3$  layer was separated from the aqueous layer, which was extracted with  $\text{CHCl}_3$ . The combined  $\text{CHCl}_3$  solution was dried over  $\text{Na}_2\text{SO}_4$ , concentrated, and the residue was chromatographed on silica gel. The eluate with *n*- $\text{C}_6\text{H}_{14}$ – $\text{CH}_2\text{Cl}_2$  (1:1) gave 0.32 g (10.2%) of 2-tosyloxylepidine (**2a**), colorless needles, mp 122–124° (MeOH– $\text{H}_2\text{O}$ ). *Anal.* Calcd for  $\text{C}_{17}\text{H}_{15}\text{NO}_3\text{S}$ : C, 65.15; H, 4.83; N, 4.47. Found: C, 65.10; H, 4.79; N, 4.45. From the eluate with *n*- $\text{C}_6\text{H}_{14}$ – $\text{CH}_2\text{Cl}_2$  (1:3), 0.26 g (8.3%) of 3-tosyloxylepidine (**6**) was obtained as colorless pillars, mp 142–144° (MeOH). *Anal.* Calcd for  $\text{C}_{17}\text{H}_{15}\text{NO}_3\text{S}$ : C, 65.15; H, 4.83; N, 4.47. Found: C, 65.15; H, 4.81; N, 4.44. The  $\text{CH}_2\text{Cl}_2$  eluate gave 0.18 g (6.0%) of di(4-methyl-2-quinolyl) ether (**3a**). NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.68 (6H, s,  $\text{C}_4$ – $\text{CH}_3$  and  $\text{C}_4'$ – $\text{CH}_3$ ), 7.12 (2H, s,  $\text{C}_3$ –H and  $\text{C}_3'$ –H). MS *m/e*: 300 ( $\text{M}^+$ ). 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 ( $\text{M}^+$ )] and 0.48 g (30.2%) of 4-methylcarbostyryl (**5a**),<sup>3)</sup> 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,<sup>3)</sup> colorless leaflets, mp 200–202°.

**Reaction of 4-Methoxyquinoline 1-Oxide (1b) with TsCl and  $\text{NEt}_3$** —A mixture of **1b** (1.75 g),  $\text{NEt}_3$  (10 ml) and TsCl (2.3 g) in  $\text{CHCl}_3$  (40 ml)– $\text{H}_2\text{O}$  (20 ml) was allowed to react under the conditions described above. The mixture of products was chromatographed on silica gel with  $\text{CH}_2\text{Cl}_2$  and AcOEt. The fraction eluted with  $\text{CH}_2\text{Cl}_2$  was again chromatographed on silica gel with *n*- $\text{C}_6\text{H}_{14}$  and AcOEt. The eluate with *n*- $\text{C}_6\text{H}_{14}$ –AcOEt (6:1) gave 0.21 g (12.7%) of di(4-methoxy-2-quinolyl) ether (**3b**). NMR ( $\text{CDCl}_3$ )  $\delta$ : 4.01 (6H, s, 4-OCH<sub>3</sub> and 4'-OCH<sub>3</sub>), 6.65 (2H, s,  $\text{C}_3$ –H and  $\text{C}_3'$ –H), 8.12 (2H, d,  $J=7.9$  Hz,  $\text{C}_5$ –H and  $\text{C}_5'$ –H). MS *m/e*: 332 ( $\text{M}^+$ ). The AcOEt eluate gave 0.83 g (50%) of N-(4-methoxy-2-quinolyl)-4-methoxy-2-quinolone (**4b**). MS *m/e*: 332 ( $\text{M}^+$ ).

The fraction eluted with AcOEt from the first chromatography gave 0.22 g (12.6%) of 4-methoxycarbostyryl (**5b**), colorless needles, mp 258–259° (MeOH). *Anal.* Calcd for  $\text{C}_{16}\text{H}_9\text{NO}_2$ : C, 68.56; H, 5.18; N, 8.00. Found: C, 68.44; H, 5.12; N, 8.01. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 1235 (ether), 1673 (C=O), 3140 (NH). This was identical with an authentic sample prepared from **1b** by reaction with TsCl– $\text{Na}_2\text{CO}_3$  in  $\text{CHCl}_3$ – $\text{H}_2\text{O}$ .

**Reaction of 4-Chloroquinoline 1-Oxide (1a) with TsCl and  $\text{NEt}_3$** —A mixture of **1c** (0.9 g),  $\text{NEt}_3$  (5 ml) and TsCl (1.15 g) in  $\text{CHCl}_3$  (20 ml)– $\text{H}_2\text{O}$  (10 ml) was treated as described above, and the mixture of products was chromatographed on silica gel. Elution with  $\text{CH}_2\text{Cl}_2$  gave 0.47 g (55.3%) of di(4-chloro-2-quinolyl) ether (**3c**). NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.46 (2H, s,  $\text{C}_3$ –H and  $\text{C}_3'$ –H). MS *m/e*: 341 ( $\text{M}^+$ ). The AcOEt eluate gave 0.3 g (35.3%) of N-(4-chloro-2-quinolyl)-4-chloro-2-quinolone (**4c**). MS *m/e*: 341 ( $\text{M}^+$ ).

**Reaction of 6-Methoxyquinoline 1-Oxide (1d) with TsCl and  $\text{NEt}_3$** —A mixture of **1d**·2 $\text{H}_2\text{O}$  (0.88 g),  $\text{NEt}_3$  (5 ml) and TsCl (1.15 g) in  $\text{CHCl}_3$  (20 ml)– $\text{H}_2\text{O}$  (10 ml) was treated as described above, and the mixture of products was chromatographed on silica gel. Elution with *n*- $\text{C}_6\text{H}_{14}$ –AcOEt (7:3) gave 0.33 g (23%) of di(6-methoxy-2-quinolyl) ether (**3d**). NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.92 (6H, s, 6-OCH<sub>3</sub> and 6'-OCH<sub>3</sub>), 7.76 (2H, d,  $J=8.5$  Hz,  $\text{C}_7$ –H and  $\text{C}_7'$ –H), 8.80 (2H, d,  $\text{C}_5$ –H and  $\text{C}_5'$ –H). MS *m/e*: 332 ( $\text{M}^+$ ). The AcOEt eluate gave 0.16 g (11.2%) of N-(6-methoxy-2-quinolyl)-6-methoxy-2-quinolone (**4d**).<sup>4)</sup> MS *m/e*: 332 ( $\text{M}^+$ ). The eluate with AcOEt–MeOH (9:1) gave 0.21 g (28%) of 6-methoxycarbostyryl (**5d**),<sup>4)</sup> colorless prisms, mp 218–220° (EtOH– $\text{H}_2\text{O}$ ).

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-Quinololinol 1-Oxide (8) with TsCl and  $\text{NEt}_3$** —A mixture of **8** (0.80 g),  $\text{NEt}_3$  (5 ml) and TsCl (1.15 g) in  $\text{CHCl}_3$  (20 ml)– $\text{H}_2\text{O}$  (10 ml) was stirred at room temperature for 12 hr. The  $\text{CHCl}_3$  layer was separated from the aqueous layer, which was extracted with  $\text{CHCl}_3$ . The combined  $\text{CHCl}_3$  solution was dried over  $\text{Na}_2\text{SO}_4$  and concentrated, and the residue was dissolved in  $\text{CH}_2\text{Cl}_2$ . The  $\text{CH}_2\text{Cl}_2$  solution was passed through a silica gel column to give 1.29 g (90.2%) of 3-tosyloxy-4-quinolinol (**9**),<sup>5</sup> colorless needles, mp 227–228° (95% EtOH).

**Reaction of 4-Nitroquinoline 1-Oxide with TsCl and  $\text{NEt}_3$** —A mixture of 4-nitroquinoline 1-oxide (0.95 g),  $\text{NEt}_3$  (5 ml) and TsCl (1.15 g) in  $\text{CHCl}_3$  (20 ml)– $\text{H}_2\text{O}$  (10 ml) was stirred at room temperature for 12 hr. The  $\text{CHCl}_3$  layer was separated from the aqueous layer, which was extracted with  $\text{CHCl}_3$ . The residue from the combined  $\text{CHCl}_3$  solution was chromatographed on silica gel. The fraction eluted with  $n\text{-C}_6\text{H}_{14}$ – $\text{CH}_2\text{Cl}_2$  (1:1) gave 0.11 g (3.2%) of 4-nitro-2-tosyloxyquinoline (**10**), pale yellow needles, mp 170–172° [benzene– $n\text{-C}_6\text{H}_{14}$  (1:3)]. *Anal.* Calcd for  $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_5\text{S}$ : C, 55.82; H, 3.51; N, 8.14. Found: C, 55.93; H, 3.62; N, 7.98. MS *m/e*: 344 ( $\text{M}^+$ ). IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 1183, 1195, 1385 ( $\text{SO}_2$ ), 1365, 1540 ( $\text{NO}_2$ ). NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.48 (3H, s,  $\text{CH}_3$ ), 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,  $\text{C}_3$ –H), 8.35 (1H, dd,  $\text{C}_8$ –H), 7.7–8.0 (3H, m,  $\text{C}_5$ –,  $\text{C}_6$ – and  $\text{C}_8$ –H). Unreacted N-oxide was recovered from the  $\text{CH}_2\text{Cl}_2$  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 pressure over 50% Pd–C previously prepared *in situ* from active charcoal (0.3 g) and 1%  $\text{PdCl}_2$  (15 ml). After absorption of 41.2 ml of hydrogen, the solution was filtered and concentrated, then made alkaline with  $\text{NH}_4\text{OH}$  and extracted with  $\text{CHCl}_3$ . The residue from the  $\text{CHCl}_3$  extract was chromatographed on silica gel. The  $\text{CH}_2\text{Cl}_2$  eluate gave 0.03 g (15.0%) of di(2-quinolyl) ether (**11**),<sup>1</sup> colorless needles, mp 109–111° [(isoPr) $_2\text{O}$ – $n\text{-C}_6\text{H}_{14}$ ]. The eluate with  $\text{CH}_2\text{Cl}_2$ –AcOEt (2:1) gave 0.02 g (21.2%) of quinoline. The AcOEt eluate afforded 0.04 g (37.7%) of carbostyryl.

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  $\text{NaHCO}_3$  solution, and extracted with  $\text{CH}_2\text{Cl}_2$ . The residue from the  $\text{CH}_2\text{Cl}_2$  extract was chromatographed on silica gel. The fraction eluted with  $n\text{-C}_6\text{H}_{14}$ –AcOEt (10:1) gave 0.06 g (53%) of 4-chloro-2-methoxyquinoline (**12**), colorless needles, mp 70–71° (petr. ether). *Anal.* Calcd for  $\text{C}_{10}\text{H}_8\text{ClNO}$ : 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-chlorocarbostyryl (**5c**),<sup>6</sup> 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  $\text{NEt}_3$  (1.2 g), then the whole was stirred at room temperature for 5 hr. The reaction mixture was concentrated, treated with  $\text{NaHCO}_3$  solution, and extracted with  $\text{CH}_2\text{Cl}_2$ . The residue from the  $\text{CH}_2\text{Cl}_2$  extract was chromatographed on silica gel with  $n\text{-C}_6\text{H}_{14}$ – $\text{CH}_2\text{Cl}_2$  (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%  $\text{PdCl}_2$  (2 ml). After absorption of ca. 1 mol eq of hydrogen, the solution was filtered and concentrated, then treated with  $\text{NaHCO}_3$  solution and extracted with  $\text{CH}_2\text{Cl}_2$ . The residue from the  $\text{CH}_2\text{Cl}_2$  extract was chromatographed on silica gel with  $n\text{-C}_6\text{H}_{14}$ –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 pressure over 50% Pd–C previously prepared *in situ* from active charcoal (0.3 g) and 1%  $\text{PdCl}_2$  (15 ml). After absorption of 28.4 ml of hydrogen, the solution was filtered and concentrated, then made alkaline with  $\text{NaHCO}_3$  solution and extracted with  $\text{CH}_2\text{Cl}_2$ . The residue from the  $\text{CH}_2\text{Cl}_2$  extract was chromatographed on silica gel with  $\text{CH}_2\text{Cl}_2$ –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**),<sup>1</sup> colorless needles, mp 172–174° (EtOH– $\text{H}_2\text{O}$ ).

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,  $\text{NH}_4\text{OH}$  was added, and the resulting mixture was extracted with  $\text{CH}_2\text{Cl}_2$ . The residue from the  $\text{CH}_2\text{Cl}_2$  extract was dissolved in  $\text{CH}_2\text{Cl}_2$ –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  $\text{CHCl}_3$ . The residue from the  $\text{CHCl}_3$  extract was recrystallized from MeOH to give 0.25 g (78.6%) of **5a**.<sup>3</sup>

**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  $\text{NaHCO}_3$  solution and extracted with  $\text{CH}_2\text{Cl}_2$ . The residue from the  $\text{CH}_2\text{Cl}_2$  extract was recrystallized from EtOH– $\text{H}_2\text{O}$  to give 0.086 g (82%) of **4d**.<sup>4</sup>

**Reaction of 4-Chloroquinoline 1-Oxide (1c) with Carbstyryl in the Presence of TsCl and  $\text{NEt}_3$** —An ice-cooled and stirred mixture of 1c (0.45 g), carbstyryl (0.36 g),  $\text{NEt}_3$  (5 ml),  $\text{CHCl}_3$  (10 ml) and  $\text{H}_2\text{O}$  (10 ml) was treated dropwise with a solution of TsCl (1.15 g) in  $\text{CHCl}_3$  (10 ml), and the whole was stirred at room temperature for 12 hr. The  $\text{CHCl}_3$  layer was separated from the aqueous layer, which was extracted with  $\text{CHCl}_3$ . The residue from the combined  $\text{CHCl}_3$  solution was chromatographed on silica gel. The first fraction, eluted with  $n\text{-C}_6\text{H}_{14}\text{-CH}_2\text{Cl}_2$  (1:1), afforded 0.051 g (6%) of 4-chloro-2-tosyloxyquinoline (2c), colorless needles, mp 135–137° [ $\text{CH}_2\text{Cl}_2\text{-(isoPr)}_2\text{O}$ ]. *Anal.* Calcd for  $\text{C}_{16}\text{H}_{12}\text{ClNO}_3\text{S}$ : C, 57.57; H, 3.62; N, 4.20. Found: C, 57.52; H, 3.61; N, 4.12. The eluate with  $\text{CH}_2\text{Cl}_2\text{-AcOEt}$  (1:1) gave 0.051 g (12%) of 4c. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 1180, 1195, 1375 ( $\text{SO}_2$ ). NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.47 (3H, s,  $\text{CH}_3$ ), 7.28 (1H, s,  $\text{C}_8\text{-H}$ ), 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 ( $\text{M}^+$ ). The last fraction, eluted with AcOEt, gave 0.07 g (19%) of carbstyryl.

**Reaction of 6-Methoxyquinoline 1-Oxide (1d) with Carbstyryl in the Presence of TsCl and  $\text{NEt}_3$** —A solution of TsCl (2.3 g) in  $\text{CHCl}_3$  (20 ml) was added dropwise to an ice-cooled and stirred mixture of 1d (0.88 g), carbstyryl (0.73 g),  $\text{NEt}_3$  (5 ml),  $\text{CHCl}_3$  (20 ml) and  $\text{H}_2\text{O}$  (20 ml), and the whole was stirred at room temperature for 12 hr. The  $\text{CHCl}_3$  layer was separated from the aqueous layer, which was extracted with  $\text{CHCl}_3$ . The residue from the combined  $\text{CHCl}_3$  solution was carefully chromatographed on silica gel. The fraction eluted with  $n\text{-C}_6\text{H}_{14}\text{-CH}_2\text{Cl}_2$  (1:1) gave 0.16 g (10.7%) of 2-tosyloxyquinoline,<sup>1)</sup> colorless prisms, mp 82° ( $n\text{-C}_6\text{H}_{14}$ ). The  $\text{CH}_2\text{Cl}_2$  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  $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_2$ : C, 75.48; H, 4.67; N, 9.27. Found: C, 75.51; H, 4.63; N, 9.25. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 1240, 1255 (ether). NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.92 (3H, s,  $\text{OCH}_3$ ). MS  $m/e$ : 302 ( $\text{M}^+$ ). The eluate with  $\text{CH}_2\text{Cl}_2\text{-AcOEt}$  (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  $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_2$ : C, 75.48; H, 4.67; N, 9.27. Found: C, 75.42; H, 4.76; N, 9.25. IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 1245 (ether), 1660 ( $\text{C=O}$ ). NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.97 (3H, s,  $\text{OCH}_3$ ). MS  $m/e$ : 302 ( $\text{M}^+$ ). In addition, 0.15 g (20.5%) of carbstyryl and 0.30 g (34%) of 5d were isolated from the fractions eluted with AcOEt and with EtOH, respectively.

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