[Chem. Pharm. Bull. 29(11)3105—3111(1981)]

Studies on Tertiary Amine Oxides. LXXIII.[1] Substitution of Aromatic N-Oxides with Radicals produced from Azo Compounds

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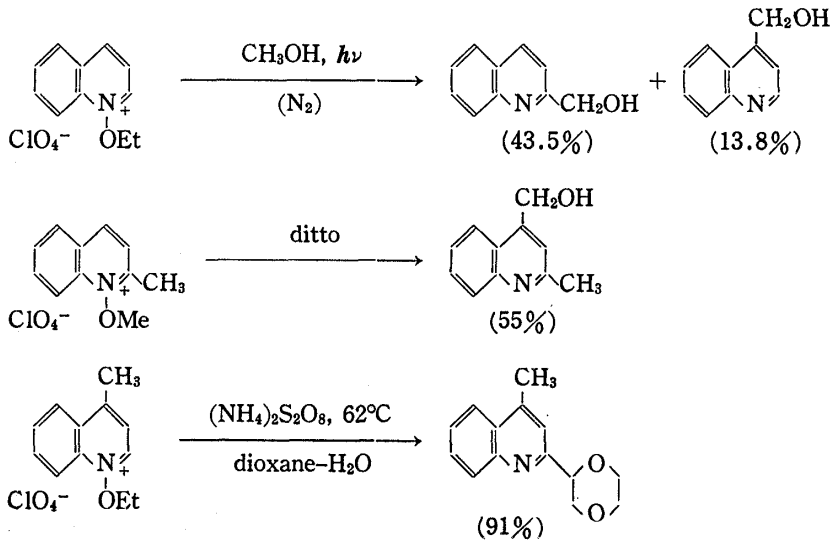
(Received April 2, 1981)

Treatment of quinoline 1-oxide (**1a**) with α,α′-azobisisobutyronitrile (AIBN) or dimethyl α,α′-azobisisobutyrate in boiling benzene for 5 h affords 2-(1-cyano-1-methylethyl)quinoline (**2a**) or 2-(1-methoxycarbonyl-1-methylethyl)quinoline (**4**) in 31.9 or 24.9% yield, respectively, accompanied with a small amount of quinoline in each case. The 1-oxides of lepidine, 3,2′-diquinolyl and 4-nitroquinoline (**1c**, **1d** and **1e**), and isoquinoline 2-oxide (**6**) similarly react with AIBN to produce the corresponding α-substituted products (**2c**, **2d**, **2e** and **7**). The reaction of pyridine 1-oxide (**8**) gives not only the 2-substituted pyridine (**9**: 1.5%) but also the 4-substituted one (**10**: 3.0%).

On the other hand, the reactions of **1a** and **6** with phenylazotriphenylmethane in boiling benzene afford the α-phenyl N-oxides (**12**: 17.2% and **14**: 34.5%) and their deoxygenated products (**13**: 3.5% and **15**: 2.9%).

Keywords——radical reaction; nucleophilic substitution; aromatic N-oxide; α,α′-azobisisobutyronitrile; dimethyl α,α′-azobisisobutyrate; phenylazotriphenylmethane; 2-phenylquinoline 1-oxide; 1-phenylisoquinoline 2-oxide

Previous papers of this series have described nucleophilic substitution of quinoline 1-oxide derivatives with α-oxyalkyl radicals generated either by photochemical[2,3] or by thermochemical means,[4] as exemplified below.



As a continuation of this work, we investigated the reaction of aromatic N-oxides with α,α′-azobisisobutyronitrile, dimethyl α,α′-azobisisobutyrate and phenylazotriphenylmethane, each of which is known to undergo thermal breakdown to free radicals with extrusion of nitrogen under rather mild conditions.[5]

In 1965, Kosuge *et al.*[6] reported that treatment of quinoline, 4-nitroquinoline and quinaldine 1-oxides with α,α′-azobisisobutyronitrile (AIBN) at 180°C in benzene for 10 h in a sealed tube gave only a very small amount of the corresponding deoxygenation products,

that is, quinoline, 4-nitroquinoline and quinaldine. However after some preliminary examinations, we found that quinoline 1-oxide (**1a**) reacts with AIBN as well as dimethyl α,α'-azobisisobutyrate (MAIB) under somewhat milder conditions to afford the 2-substituted quinolines. Thus, when **1a** was treated with AIBN for 5 h in boiling benzene, 2-(1-cyano-1-methylethyl)-quinoline (**2a**) was obtained in 31.9% yield accompanied with a small amount (2.7%) of quinoline (**3**). The reaction with MAIB under the same conditions similarly afforded 2-(1-methoxycarbonyl-1-methylethyl)quinoline (**4**) in 24.9% yield together with a trace of **3**. Both **2a** and **4** gave the same 2-isopropylquinoline (**5**) in good yields upon refluxing with 10% ethanolic potassium hydroxide (Chart 1).

While the reaction of quinaldine 1-oxide (**1b**) with AIBN gave only a trace of quinaldine with 76.4% recovery of **1b**, that of lepidine 1-oxide (**1c**) afforded the 2-substituted lepidine

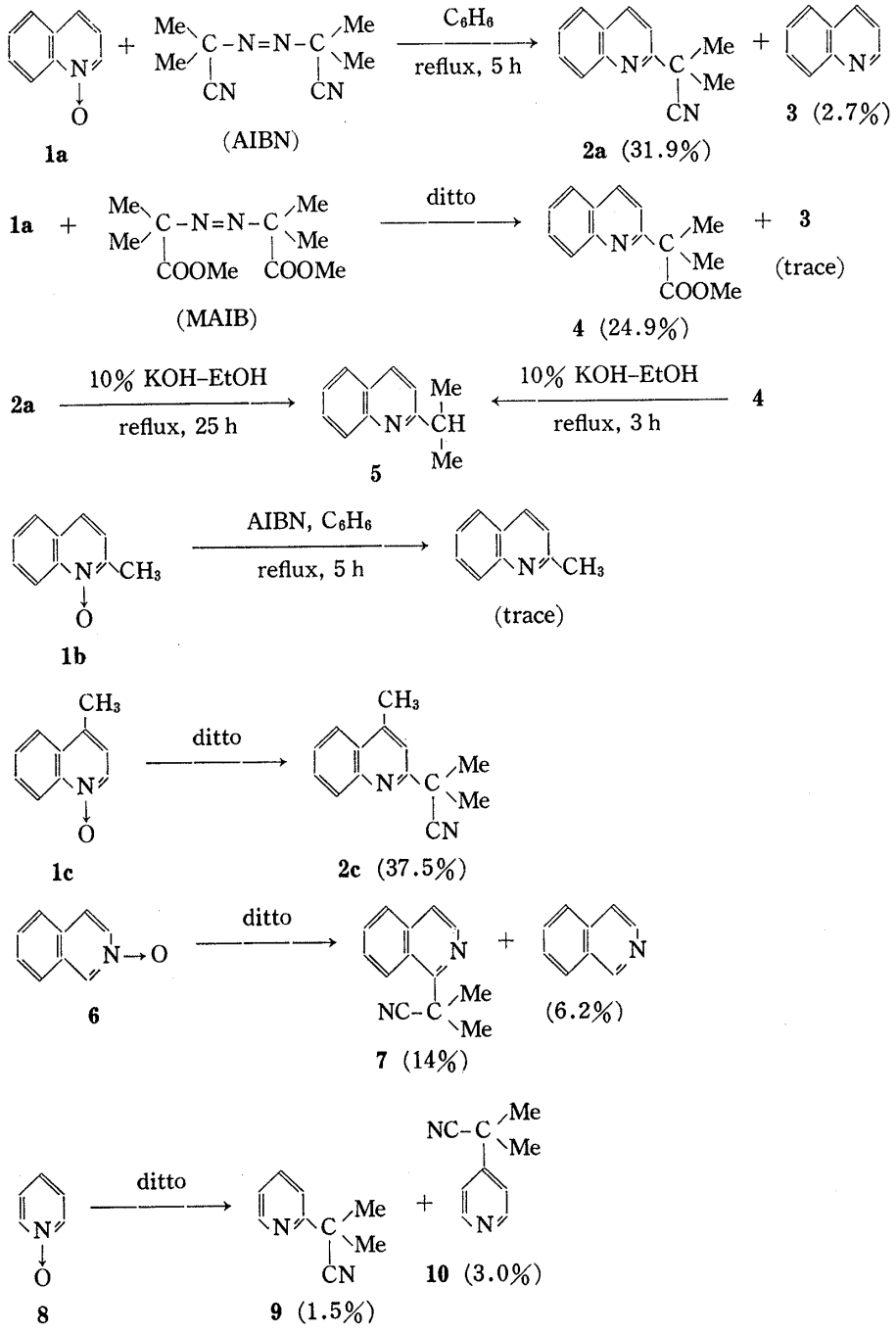


Chart 1

(**2c**) in 37.5% yield. Isoquinoline 2-oxide (**6**) also reacted with AIBN, and the 1-substituted isoquinoline (**7**) and isoquinoline were formed in 14 and 6.2% yields, respectively. In contrast to the reaction of **1a**, the 4-substituted pyridine (**10**) was also obtained besides the 2-substituted pyridine (**9**) from the reaction of pyridine 1-oxide (**8**) with AIBN. It is noticeable that the yield of **10** (3.0%) was better than that of **9** (1.5%), although the total yield was rather low as compared with those of quinoline derivatives (Chart 1).

Iwamura and Inamoto[7] have isolated addition products, such as **A** and **B** shown in Chart 2, from reactions of nitrones with AIBN in hot xylene. Taking into account these results and also the finding[8,9] that the N-oxide function of 3,2′-diquinolyl 1-oxide (**1d**) shows reactivity somewhat similar to that of nitrone in some cases, the reaction of **1d** with AIBN was carried out in anticipation of isolating an addition product. However, the reaction proceeded in the usual manner, and the 2-substituted product (**2d**) and the deoxygenated product were obtained in 21.2 and 11% yields, respectively (Chart 2).

It has been reported by Inamoto and Shimamura[10] that the decomposition of AIBN in nitrobenzene at 100°C gives a small amount of N-phenyl-O,N-bis(1-cyano-1-methylethyl)-

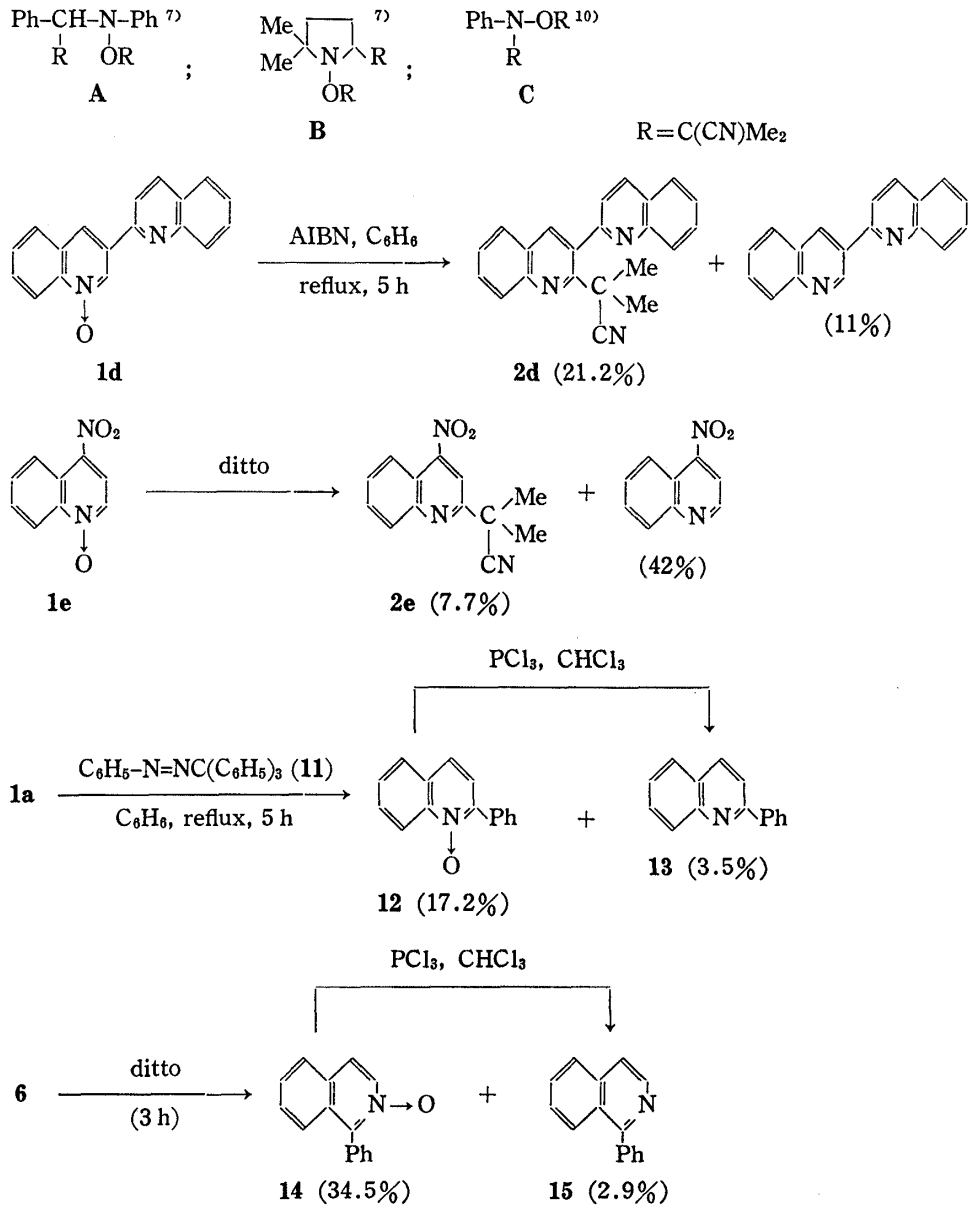


Chart 2

hydroxylamine (**C**) besides other products. In order to examine the possibility of the formation of a similar adduct of 4-nitrosoquinoline 1-oxide with AIBN, a benzene solution of 4-nitroquinoline 1-oxide (**1e**) and AIBN (2 eq) was refluxed for 5 h, but again only the 2-substituted product (**2e**) and 4-nitroquinoline[11] were produced in 7.7 and 42% yields, respectively, with no visible signs of the formation of the anticipated product (Chart 2).

Further, the reaction using phenylazotriphenylmethane (**11**)[5] as the radical source was examined with quinoline 1-oxide **1a** and isoquinoline 2-oxide **6**, and it was found that the α-phenylated N-oxides (**12** and **14**) were preferentially produced, along with smaller amounts of the deoxygenated α-phenylation products (**13** and **15**), in contrast with the above-mentioned reaction. Thus, when a benzene solution of **1a** and one equivalent amount of **11** was refluxed for 3 h, 2-phenylquinoline 1-oxide (**12**)[12] and 2-phenylquinoline (**13**)[13] were obtained in 17.2 and 3.5% yields, respectively. Similarly, the reaction of **6** with **11** afforded 1-phenylisoquinoline 2-oxide (**14**) and 1-phenylisoquinoline (**15**)[14] in 34.5 and 2.9% yields, respectively. Products **12** and **14** were smoothly converted to **13** and **15** with phosphorus trichloride (Chart 2).

The structures of the products were established principally by elementary analyses, the infrared (IR) and nuclear magnetic resonance (NMR) spectra.

As mentioned above, differences were noticed between the reaction with AIBN or MAIB and that with phenylazotriphenylmethane **11**.

The reaction mode of nitrones with AIBN[7] suggests that the formation of **2a** from **1a** and AIBN, for example, proceeds by the course involving elimination of 1-cyano-1-methylethanol from the 1,2-dihydroquinoline intermediate (**18**). As for the formation of **18** from **1a**, two stepwise courses are conceivable, that is, the one through the 2-substituted radical (**16**) and that through the O-substituted radical (**17**), although the possibility of one-step formation

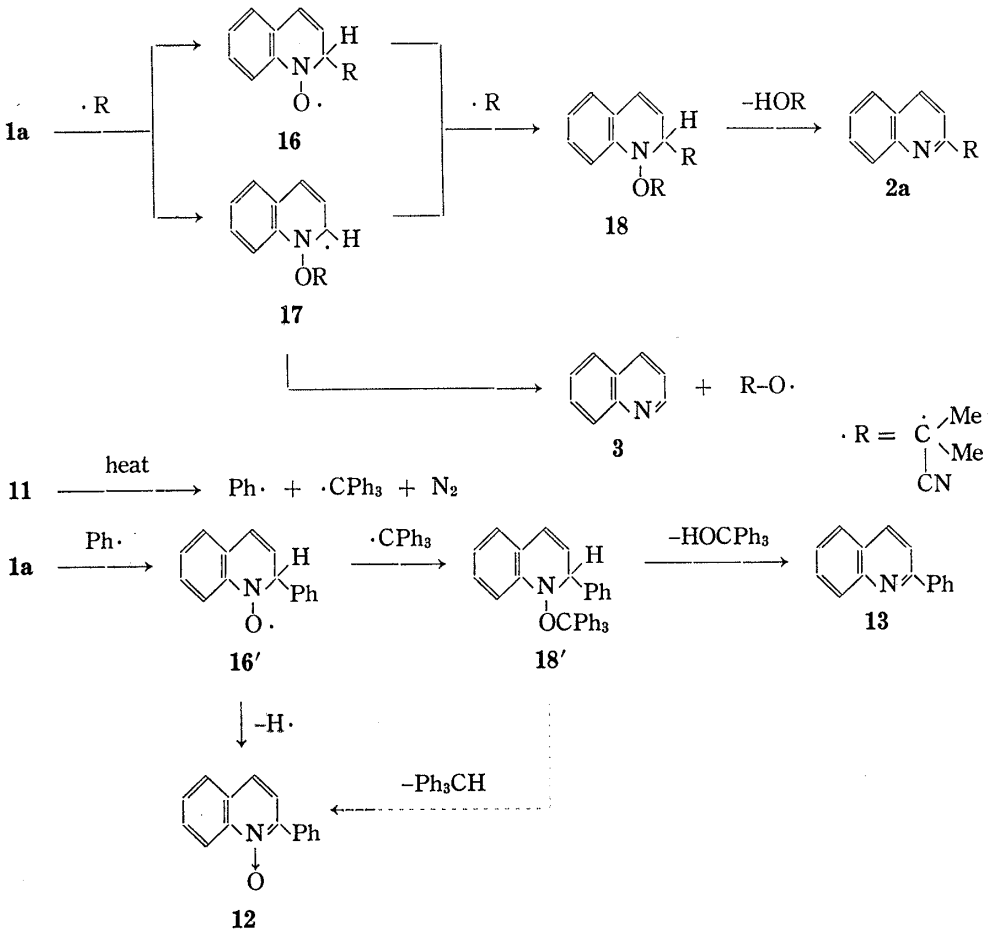


Chart 3

cannot be excluded. Homolytic cleavage of the N–O bond in **17** may account for the formation of quinoline **3**. However, this path is apparently a minor one except for the case of 4-nitroquinoline 1-oxide **1e**, and the course through **16** and **18** should be considered to be dominant in the reaction with AIBN (Chart 3).

The formation of 2-phenylquinoline **13** in the reaction of **1a** with **11** can be rationalized by liberation of triphenylcarbinol from the 1,2-dihydroquinoline intermediate (**18′**) in a similar way to that of **2a**. Although the formation of 2-phenylqionoline 1-oxide **12** may be explained by elimination of triphenylmethane, instead of triphenylcarbinol, from **18′**, an alternative course involving abstraction of hydrogen, for example by the triphenylmethyl radical, from the 2-phenylated radical (**16′**) is apparently a more probable one (Chart 3). The preferential formation of **12** may be ascribed to a steric barrier to the formation of **18′** from **16′**. Natsume *et al.*[15] have described that 2-benzylquinoline 1-oxide or 1-benzylisoquinoline 2-oxide is formed by a similar course when a toluene solution of **1a** or **6** is refluxed in the presence of di-*tert*-butyl peroxide.

Experimental

All melting and boiling points are uncorrected. IR spectra were recorded on JASCO DS-301 and JASCO IR-E spectrometers. NMR spectra were measured with JEOL JNM-PMX60 (60 MHz) and JEOL JNM-MH100 (100 MHz) spectrometers with TMS as an internal reference.

General Procedure for the Reaction of Aromatic N-Oxides with α,α′-Azobisisobutyronitrile (AIBN) or Dimethyl α,α′-Azobisisobutyrate (MAIB)——A benzene solution of an aromatic N-oxide and AIBN or MAIB was refluxed for 5 h. The cooled reaction mixture was extracted with 20% HCl, and the HCl layer was made alkaline with K_2CO_3 and extracted with ether or CH_2Cl_2. The extract was dried over anhyd. K_2CO_3, and concentrated. The residue was chromatographed on silica gel or alumina.

Reaction of Quinoline 1-Oxide (1a) with AIBN——A mixture of products obtained from the reaction of **1a** (2.9 g) with AIBN (6.56 g, 2 eq) in benzene (50 ml) was chromatographed on silica gel with n-C_6H_{14}–CH_2Cl_2 (1: 1) to give 1.25 g (31.9%) of 2-(1-cyano-1-methylethyl)quinoline (**2a**), 0.0677 g (2.7%) of quinoline, bp 150—160°C (1.1 mmHg), and 0.25 g (8.62%) of **1a**. Product **2a**: a colorless oil, bp 126—128°C (0.65 mmHg). IR ν_{max}^{neat} cm^{-1}: 2253 (CN). NMR ($CDCl_3$) τ: 8.15 (6H, s, CH_3), 1.75—2.65 (6H, m, arom-H). Picrate: yellow crystals, mp 107°C (MeOH). *Anal.* Calcd for $C_{19}H_{15}N_5O_7$: C, 53.65; H, 3.55; N, 16.47. Found: C, 53.49; H, 3.66; N, 16.11.

Reaction of 1a with MAIB——A mixture of products obtained form the reaction of **1a** (1.45 g) with MAIB (2.3 g, 1 eq) in benzene (50 ml) was chromatographed on alumina with n-C_6H_{14}–CH_2Cl_2 (1: 1) to give 0.57 g (24.9%) of 2-(1-methoxycarbonyl-1-methylethyl)quinoline (**4**) and a trace of quinoline. Product **4**: a colorless oil, bp 114—125°C (bath temp.) (0.2 mmHg). IR ν_{max}^{neat} cm^{-1}: 1735 (C=O). NMR ($CDCl_3$) τ: 8.28 (6H, s, CH_3), 6.3 (3H, s, CH_3), 1.8—2.8 (6H, m, arom-H). Picrate: yellow crystals, mp 146—148°C (EtOH). *Anal.* Calcd for $C_{20}H_{18}N_4O_9$: C, 52.40; H, 3.96; N, 12.22. Found: C, 52.08; H, 3.88; N, 12.29.

2-Isopropylquinoline (5)——1) A soltuion of **2a** (0.5 g) in 10% KOH–EtOH (10 ml) was refluxed for 25 h, and evaporated to dryness. H_2O (20 ml) was added to the residue and the solution was extracted with ether to give 0.43 g (98.5%) of **5**, a colorless oil, bp 90—100°C (bath temp.) (0.55 mmHg). NMR ($CDCl_3$) τ: 8.65 (6H, d, J=6.7 Hz, $CH(C\underline{H}_3)_2$), 6.76 (1H, heptet, J=6.7 Hz, $C\underline{H}(CH_3)_2$), 1.85—2.87 (6H, m, arom-H). Picrate: yellow crystals, mp 155°C (EtOH). *Anal.* Calcd for $C_{18}H_{16}N_4O_7$: C, 54.00; H, 3.55; N, 14.00.Found: C, 54.00; H, 4.13; N, 13.73.

2) A solution of **4** (0.23 g) in 10% KOH–EtOH (10 ml) was refluxed for 3 h to give 0.116 g (68%) of **5**.

Reaction of Quinaldine 1-Oxide (1b) with AIBN——A mixture of products obtained from the reaction of **1b** (1.61 g) with AIBN (3.3 g, 2 eq) was chromatographed on silica gel. The eluate with n-C_6H_{14}–CH_2Cl_2 (1: 1) gave 0.0423 g (2.95%) of quinaldine. From the second fraction eluted with CH_2Cl_2, 1.23 g (76.4%) of **1b** was recovered.

Reaction of Lepidine 1-Oxide (1c) with AIBN——A mixture of products obtained from the reaction of **1c** (1.59 g) with AIBN (1.64 g, 1 eq) in benzene (50 ml) was chromatographed on alumina. The first fraction eluted with CH_2Cl_2 gave 0.79 g (37.5%) of 2-(1-cyano-1-methylethyl)-4-methylquinoline (**2c**). From the second fraction eluted with AcOEt, 0.55 g (28.2%) of **1c** was recovered. Product **2c**: a colorless oil, bp 146—155°C (bath temp.) (0.3 mmHg). *Anal.* Calcd for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32. Found: C, 79.18; H, 6.13; N, 13.33. IR ν_{max}^{neat} cm^{-1}: 2260 (CN). NMR ($CDCl_3$) τ: 8.15 (6H, s, CH_3), 7.28 (3H, s, CH_3), 1.85—2.65 (5H, m, arom-H).

Reaction of 3,2′-Diquinolyl 1-Oxide (1d) with AIBN——A mixture of products obtained from the reaction of **1d** (0.55 g) with AIBN (0.1 g, 3 eq) in benzene (50 ml) was chromatographed on alumina with n-C_6H_{14} and CH_2Cl_2. The first fraction eluted with n-C_6H_{14}–CH_2Cl_2 (1: 1) gave 0.14 g (21.2%) of 2-(1-cyano-1-

methylethyl)-3,2′-diquinolyl (**2d**), colorless needles, mp 119—120°C (n-C_6H_{14}). The second fraction eluted with CH_2Cl_2 gave 0.05 g (11%) of 3,2′-diquinolyl, colorless needles, mp 175—176°C (n-C_6H_{14}–benzene).

Reaction of 4-Nitroquinoline 1-Oxide (1e) with AIBN——A mixture of products obtained from the reaction of **1e** (1.9 g) with AIBN (3.3 g, 2.3 eq) in benzene (50 ml) was chromatogrophed on silica gel with n-C_6H_{14}–AcOEt (10: 1) to give 0.186 g (7.7%) of 2-(1-cyano-1-methylethyl)-4-nitroquinoline (**2e**) and 0.727 g (42%) of 4-nitroquinoline. Product **2e**: pale yellow needles, mp 91—92°C (n-C_6H_{14}). *Anal.* Calcd for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.91; H, 4.53; N, 17.33. IR ν_{max}^{Nujol} cm^{-1}: 2225 (CN). 1520, 1360 (NO_2). NMR ($CDCl_3$) τ: 8.1 (6H, s, CH_3), 1.5—2.3 (5H, m, arom-H). 4-Nitroquinoline, pale yellow needles, mp 92—93°C (n-C_6H_{14}) was identified by direct comparison with an authentic sample.[11]

Reaction of Isoquinoline 2-Oxide (6) with AIBN——A mixture of products obtained from the reaction of **6** (10.8 g) and AIBN (19.8 g, 1.6 eq) in benzene (100 ml) was chromatographed on silica gel. The first fraction eluted with n-C_6H_{14}–CH_2Cl_2 (2: 1) gave 1.67 g (14%) of 1-(1-cyano-1-methylethyl)isoquinoline (**7**), a colorless oil, bp 142—144°C (0.3 mmHg). IR ν_{max}^{neat} cm^{-1}: 2275 (CN). NMR ($CDCl_3$) τ: 8.00 (6H, s, CH_3), 2.00—2.50 (4H, m, arom-H), 1.55 (1H, d, J=6.0 Hz, C_3–H), 1.2—1.4 (1H, m, arom-H). Picrate: yellow crystals, mp 153—154°C (MeOH). *Anal.* Calcd for $C_{19}H_{15}N_5O_7$: C, 53.65; H, 3.55; N, 16.47. Found: C, 53.59; H, 3.42; N, 16.67. The second fraction eluted with CH_2Cl_2 gave 0.48 g (6.2%) of isoquinoline.

Reaction of Pyridine 1-Oxide (8) with AIBN——A mixture of products obtained from the reaction of **8** (9.5 g) with AIBN (1.64 g, 1 eq) in benzene (100 ml) was chromatographed on alumina with n-C_6H_{14}–CH_2Cl_2 (1: 1) to give 0.215 g (1.5%) of 2-(1-cyano-1-methylethyl)pyridine (**9**) and 0.434 g (3.0%) of 4-(1-cyano-1-methylethyl)pyridine (**10**). Product **9**: a colorless oil, bp 95—97°C (0.18 mmHg). IR ν_{max}^{neat} cm^{-1}: 2290 (CN). NMR ($CDCl_3$) τ: 8.25 (6H, s, CH_3), 2.65—2.95 (1H, m, C_5–H), 2.1—2.6 (2H, m, C_3–H and C_4–H), 1.3—1.5 (1H, m, C_6–H). Picrate: yellow crystals, mp 153—154°C (EtOH). *Anal.* Calcd for $C_{15}H_{13}N_5O_7$: C, 48.00; H, 3.49; N, 18.66. Found: C, 47.76; H, 3.37; N, 18.60. Product **10**: a colorless oil, bp 125—130°C (0.18 mmHg). IR ν_{max}^{neat} cm^{-1}: 2270 (CN). NMR ($CDCl_3$) τ: 8.25 (6H, s, CH_3), 2.60 (2H, d-d, J=6.0, 1.5 Hz, C_3–H and C_5–H), 1.45 (2H, d-d, J=6.0, 1.5 Hz, C_2–H and C_6–H). Picrate: yellow crystals, mp 104—105°C (MeOH). *Anal.* Calcd for $C_{15}H_{13}N_5O_7$: C, 48.00; H, 3.49; N, 18.66. Found: C, 48.22; H, 3.57; N, 18.80.

Reaction of 1a with Phenylazotriphenylmethane (11)——A benzene solution of **1a** (1.45 g) and **11** (3.48 g, 1 eq) was refluxed for 5 h. The reaction mixture was evaporated to dryness, and the residue was taken up in CH_2Cl_2 and extracted with 20% HCl. The CH_2Cl_2 layer was dried over anhyd. Na_2SO_4, and evaporated to dryness (fraction (**A**)). The HCl solution was made alkaline with K_2CO_3, and extracted with ether and then with CH_2Cl_2. Both extracts were dried over anhyd. K_2CO_3, and evaporated to give fractions (**B**) and (**C**), respectively. Fraction (**A**) was chromatographed on alumina with CH_2Cl_2 to give 2-phenylquinoline 1-oxide (**12**).[12] Fraction (**B**) was chromatographed on alumina using n-C_6H_{14}–CH_2Cl_2 (1: 1) as an eluent to give 0.072 g (3.5%) of 2-phenylquinoline (**13**)[13] and a small amount of **12**. From fraction (**B**), 0.76 g (52.4%) of **1a** was recovered. The combined **12** (0.38 g, 17.2%) was recrystallized from benzene–n-C_6H_{14} to give pale brown needles, mp 142—143°C. *Anal.* Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.43; H, 5.29; N, 6.23. Product **13**: colorless crystals, mp 86°C, bp 160—175°C (bath temp.) (0.55 mmHg). Picrate: yellow crystals, mp 188—189°C. *Anal.* Calcd for $C_{21}H_{14}N_4O_7$: C, 58.02; H, 3.25; N, 12.90. Found: C, 58.44; H, 3.09; N, 12.90.

A solution of **12** (0.2 g) and PCl_3 (0.15 g) in $CHCl_3$ (20 ml) was heated for 15 min to give 0.116 g (62.5%) of **13**.

Reaction of 6 with 11——A solution of **6** (0.725 g) and **11** (1.75 g, 1 eq) in benzene (50 ml) was refluxed for 3 h. The reaction mixture was extracted with 10% HCl, and the extract was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The residue from the $CHCl_3$ extract was chromatographed on alumina with n-C_6H_{14}, AcOEt and MeOH. The first fraction eluted with n-C_6H_{14}–AcOEt (9: 1) gave 0.03 g (2.9%) of 1-phenylisoquinoline (**15**),[14] pale yellow crystals, mp 88—89°C (n-C_6H_{14}). *Anal.* Calcd for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.82. Found: C, 87.35; H, 5.37; N, 6.56. The second fraction eluted with MeOH gave 0.382 g (34.5%) of 1-phenylisoquinoline 2-oxide (**14**), colorless needles, mp 163—164°C (benzene).

A solution of **14** (0.111 g) and PCl_3 (0.1 g) in $CHCl_3$ (20 ml) was heated for 15 min to give 0.06 g (58.3%) of **15**.

References and Notes

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