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Ring Contraction of 3-Hydroxyquinolines to Oxindoles with Hydrogen Peroxide in Acetic Acid[1]

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8-Nitroquinoline (I) was contracted to 7-nitrooxindole (III) *via* 3-hydroxy-8-nitroquinoline (II) with hydrogen peroxide in acetic acid.

3-Hydroxyquinoline-8-carboxylic acid (XIV) and its ethyl ester (XV) were also contracted to oxindole-7-carboxylic acid (XVI) and its ethyl ester (XVII), respectively, in the same conditions. On the other hand, 3-hydroxyquinoline and 3-hydroxy-8-methylquinoline (XX) did not undergo contraction in the above conditions.

In a previous paper[3] it was shown 5- and 8-nitrocinnoline gave 4- and 7-nitroindazole on warming with hydrogen peroxide in acetic acid. In this connection, the oxidation of 8-substituted quinoline derivatives under the same conditions was carried out in order to investigate the mechanism of the above ring contraction.

When 8-nitroquinoline (I) was heated with hydrogen peroxide in acetic acid at 70° for 8 hours, yellow needles, mp 225° (decomp.), whose analytical values corresponded to $C_8H_6O_3N_2$ (III), were isolated in 18% yield. As shown in Chart 1, compound III was reduced catalytically over palladium-carbon to form the amino compound (IV), which was converted into chloro compound (V) by diazotization with sodium nitrite in hydrochloric acid, followed by Sandmeyer reaction. Catalytic hydrogenation of V over palladium-carbon gave oxindole (VI), which was found to be identical with authentic oxindole[4] by infrared spectra and mixed melting point determination. Therefore, compound III was considered to be 7-nitrooxindole. Further, the structure of III was confirmed by its conversion to 7-benzoylaminooxindole(IX);[5,6] the reaction of III with phosphoryl chloride gave 2-chloro-7-nitroindole (VII), and VII was reduced catalytically over palladium-carbon to give amino compound (VIII), followed by Schotten-Baumann reaction. In addition, as shown in Table II, the structure confirmed as III is consitent with its nuclear magnetic resonance (NMR) spectrum, which shows the methylene protons as a singlet at τ 6.33 (2H) and three aromatic protons. From these results, it has become evident that I was contracted to 7-nitrooxindole with hydrogen peroxide in acetic acid.[7]

Ochiai and his co-workers[8] reported that quinoline derivatives having bulky groups at 8-position such as 8-quinolinecarboxylic acid did not produced their N-oxides by oxidation using hydrogen peroxide, but gave 3-hydroxy compounds.

1) Presented in part to the 86th Annual Meeting of Pharmaceutical Society of Japan, Sendai, October 1966.
2) Location: *1–18–1 Kamiyoga, Setagaya, Tokyo.*
3) I. Suzuki, T. Nakashima, and N. Nagasawa, *Chem. Pharm. Bull.* (Tokyo), **13**, 713 (1965).
4) S. Sugasawa, I. Satoda, and J. Yanagisawa, *Yakugaku Zasshi*, **58**, 139 (1938).
5) J. Thesing, G.S. Emler, and G. Mohr, *Chem. Ber.*, **95**, 2205 (1962).
6) H.E. Johnson and D.G. Crosby, *J. Org. Chem.*, **28**, 2794 (1963).
7) Recently, a report of Palmer and Russell (*J. Chem. Soc.*, **1968**, 2626) has shown that 4-methyl-8-nitroquinoline was oxidized by hydrogen peroxide in acetic acid to produced 2-amino-3-nitroacetophenone and unknown product which exhibited infrared absorption bands at 3300 (OH), 1730 (C=O), 1633 (C=C), and 1530 (NO_2) cm^{-1}.
8) E. Ochiai, C. Kaneko, I. Shimada, Y. Murata, T. Kosuge, S. Miyashita, and C. Kawasaki, *Chem. Pharm. Bull.* (Tokyo), **8**, 126 (1960).

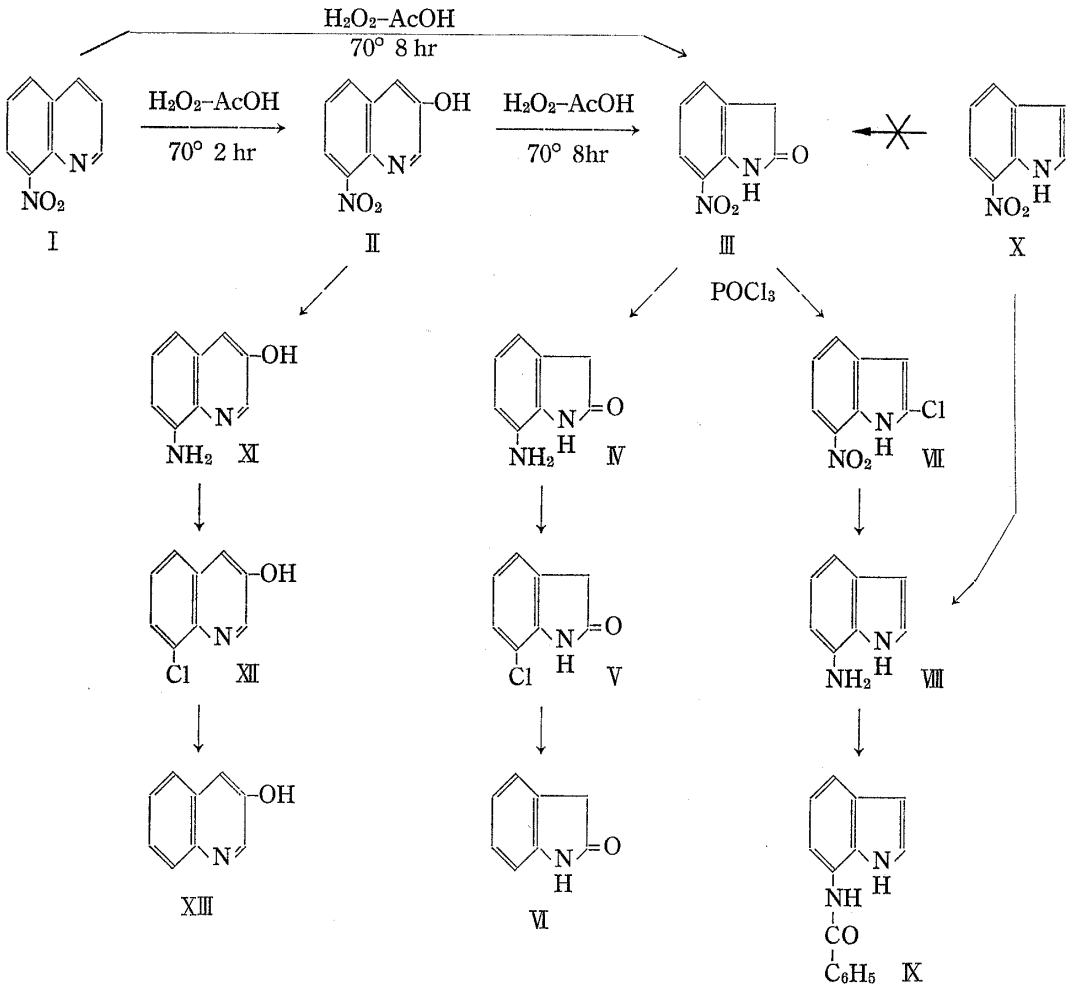

Chart 1

In view of this point, following experiments carried out; oxidation being interrupted for 2 hours under the above conditions gave 3-hydroxy-8-nitroquinoline (II) in 21% yield. The NMR spectrum of II (Table I) exhibited the adjacent three aromatic protons and two aromatic protons (J=2.6 cps) due to *meta* position. Furthermore, the structure of II was confirmed by its conversion to 3-hydroxyquinoline[9] by the steps outlined in Chart 1.

Table I. Nuclear Magnetic Resonance Spectral Data of 3-Hydroxyquinoline Derivatives

Compound	H_2	H_4	H_5	H_6	H_7	$J_{2,4}$	$J_{5,6}$	$J_{6,7}$	$J_{5,7}$
II	1.22 (d)	2.27 (d)	2.00 (q)	2.34 (q)	1.88 (q)	2.6	7.7	9.2	1.4
XIV	1.22 (d)	2.14 (d)	1.82 (q)	2.28 (q)	1.65 (q)	2.7	8.2	7.4	1.4
XV	1.30 (d)	2.39 (d)	2.31 (q)	2.46 (t)	2.04 (q)	2.6	7.8	7.8	2.3
XX	1.33 (d)	2.48 (d)	2.3—2.7 (ABC type)			2.8			

chemical shift, τ, in CD_3SOCD_3 from TMS coupling constant, in cps

Next, when II was heated with hydrogen peroxide in acetic acid at 70° for 8 hours, III was produced in 45% yield. Therefore, from the above results, II was considered to be an intermediate of this contraction, but an alternative mechanism is formation of 7-nitroindole (X) and then further oxidation to give III, because Witkop[10] reported that 3-methyloxindole was obtained by oxidation of 3-methylindole using peracetic acid.

9) W.H. Mills and W.H. Watson, *J. Chem. Soc.*, **1910**, 741.
10) V.B. Witkop, *Ann.*, **558**, 98 (1947).

Under the above oxidative conditions X was recovered only in 7% yield and thin-layer chromatography (TLC) gave no indication of III. Further, II was warmed with only acetic acid at 70° for 8 hours. In this reactions, since II was nearly quantitatively recovered and there was no evidence of III by TLC, it is concluded that this contraction is acid catalyzed oxidation *via* 3-hydroxy compound, but not *via* indole derivatives.

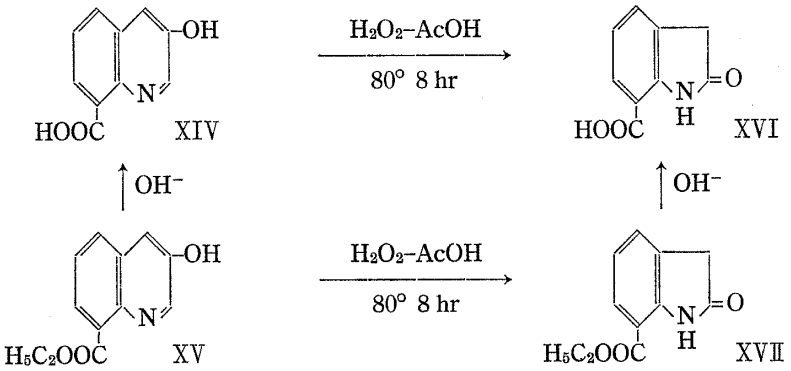

Chart 2

To extend the scope of the reaction, it was applied to 3-hydroxyquinoline-8-carboxylic acid (XIV) and its ethyl ester (XV). Oxidation of XIV and XV using hydrogen peroxide in acetic acid 80° for 8 hours afforded oxindole-7-carboxylic acid (XVI) and its ethyl ester (XVII) in 16 and 17% yields, respectively, as indicated in Chart 2. XV and XVII were converted into their carboxylic acid with diluted sodium hydroxide solution. Structures of XVI and XVII were confirmed by means of analytical data and NMR spectra, whose signals are similar to those of III, as seen in Table II.

Table II. Nuclear Magnetic Resonance Spectral Data of Oxindole Derivatives

Compound	H_4	H_5	H_6	$H_{3,3'}$	$J_{4,5}$	$J_{5,6}$
III	2.38 (d)	2.88 (t)	2.02 (d)	6.33 (s)	8	8
XVI	2.56 (d)	2.98 (t)	2.30 (d)	6.43 (s)	9	9
XVII	2.53 (d)	2.96 (t)	2.28 (d)	6.42 (s)	9	9

chemical shift, τ, in CD_3SOCD_3 from TMS coupling constant, in cps

As can be seen from above results, quinoline derivatives having bulky and electron-withdrawing groups at 8-position afforded oxindole derivatives by oxidation with hydrogen peroxide in acetic acid. On the contrary the same oxidation of 8-methylquinoline (XVIII) which has electrondonating group at 8-position, gave 8-methylquinoline N-oxide (XIX)[11] and 3-hydroxy-8-methylquinoline (XX) in 8 and 9% yields, respectively and XVIII did not yield oxindole derivatives.

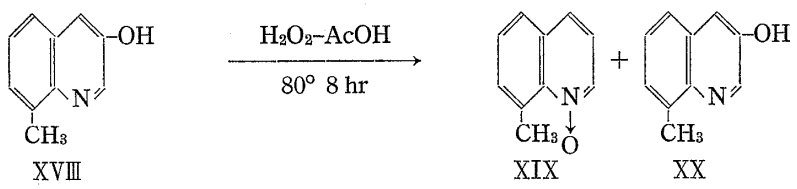

Chart 3

The structure of XX was proved to be identical with 3-hydroxy-8-methylquinoline by NMR and IR spectra.

11) O. Buchardt, J. Becher, and C. Lohse, *Acta Chem. Scand.*, **19**, 1120 (1965).

When XX was treated hydrogen peroxide in acetic acid under the same conditions, XX was recovered in 18% yield and no other reaction products could be obtained. An attempted oxidation of 3-hydroxyquinoline itself with hydrogen peroxide in acetic acid resulted in the recovery of the unchanged material, and also oxindole and indole could not be detected by TLC.

Recently it has been reported[12] that quinoline N-oxides gave indole derivatives by photochemical reaction. In connection with this experiments, oxidation of 8-nitroquinoline N-oxide[13] was carried out using hydrogen peroxide in acetic acid at 70° for 8 hours, but no spots of II and III were observed by TLC. Accordingly, it is clear that this ring contraction do not proceed *via* their N-oxides.

The further investigation of reaction mechanism is under way, but evidently the above ring contraction of 8-substituted quinolines having bulky and electron-withdrawing groups takes place *via* 3-hydroxy compounds differing from the oxidation of 8-nitrocinnoline.

Experimental[14]

7-Nitrooxindole (III)——A mixture of 2.00 g of I, 16 ml of AcOH and 4 ml of 30% H_2O_2 was heated at 70° for 4 hr on a water bath, further 4 ml of 30% H_2O_2 was added, and the mixture again heated at the same temperature for 4 hr. After cooling, the separated crystals were collected by filtration and washed with water. The filtrate and washings were combined and evaporated to a small volume under reduced pressure. The separated crystals were combined with the above crystals and recrystallization of crystals from MeOH gave 7-nitrooxindole (III) as yellow needles, mp 225° (decomp.). Yield, 0.27 g (18%). *Anal.* Calcd. $C_8H_6O_3N_2$: C, 53.93; H, 3.40; N, 15.73. Found: C, 53.96; H, 3.27; N, 15.57.

7-Aminooxindole (IV)——A mixture of 1.50 g of III and 50 ml of EtOH was hydrogenated in H_2 stream over Pd-C prepared from 0.3 g of charcoal and 15 ml of 1% $PdCl_2$ solution. The catalyst was removed by filtration. The filtrate was evaporated to a small volume and the separated crystals were recrystallized from EtOH to give 1.09 g (87%) of colorless needles, mp 247—249°. *Anal.* Calcd. for $C_8H_8ON_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.50; H, 5.34; N, 18.80.

7-Chlorooxindole (V)——To mixture of 0.36 g of IV and 10 ml of conc. HCl, saturated solution containing 165 mg of sodium nitrite was added dropwise at −25——30°. This solution was added to freshly prepared solution of copper chloride in HCl under cooling. The precipitates were collected by filtration and washed with H_2O. The filtrate and washings were combined and extracted with $CHCl_3$. The precipitates obtained above were dissolved in this extracted solution, and the solution was concentrated to about 100 ml. The solution was purified by alumina (acidic) chromatography and eluted $CHCl_3$. $CHCl_3$ was evaporated to dryness and the residue (mp 214—217°, 0.34 g, 83%) was recrystallized from MeOH to give colorless needles (V), mp 215—217°. *Anal.* Calcd. for C_8H_6ONCl: C, 57.33; H, 3.61; N, 8.36. Found: C, 56.99; H, 3.39; N, 8.22.

Oxindole (VI)——A mixture of 0.21 g of V and 30 ml of EtOH was hydrogenated in H_2 stream over Pd-C prepared from 0.1 g of charcoal and 5 ml of 1% $PdCl_2$ solution. After the removal of catalyst, the filtrate was evaporated to dryness. The residue was dissolved in benzene, passed through a column of acidic Al_2O_3, and eluted with $CHCl_3$. The eluate was evaporated and the residue (mp 116—120°, 0.14 g, 84%) was recrystallized from benzene to give pale yellow prisms, VI, mp 125—127°. This showed no depression of melting point on admixture with authentic oxindole derived from the known method and IR spectra of these two compounds were identical.

2-Chloro-7-nitroindole (VII)——A mixture of 0.28 g of III and 4 ml of $POCl_3$ was refluxed for 1 hr. After cooling the mixture was poured into ice water and extracted with benzene. The solution was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by alumina (acidic) chromatography and eluted with benzene. Benzene was evaporated to dryness and the residue (mp 125—126°, 0.24 g, 78%) was recrystallized from MeOH to give yellow needles (VII), mp 126—127°. *Anal.* Calcd. for $C_8H_5O_2N_2Cl$: C, 48.87; H, 2.56; N, 14.25. Found: C, 48.75; H, 2.62; N, 14.30.

7-Benzoylaminoindole (IX)——i) A mixture of 0.27 g of VII and 20 ml of EtOH was hydrogenated in H_2 stream over Pd-C prepared from 0.1 g of charcoal and 5 ml of 1% $PdCl_2$ solution. After the removal

12) M. Ishikawa, S. Yamada, H. Hotta, and C. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **14**, 1102 (1966); O. Buchardt, J. Becher, and C. Lohse, *Acta Chem. Scand.*, **20**, 2467 (1966).

13) E. Ochiai and T. Okamoto, *Yakugaku Zahssi*, **70**, 22 (1950).

14) All melting points were not corrected. NMR spectra were obtained at 100 Mcps on JNM 4H-100 spectrometer in CD_3SOCD_3 containing tetramethylsilane as an internal standard.

of catalyst, the filtrate was evaporated to dryness. The residue (7-aminoindole) was suspended in 10% NaOH, and to this suspension, 1 ml of PhCOCl was added and shaken for 1 hr. The separated crystals were collected by filtration and washed with H_2O. The filtrate and washings were combined and extracted with $CHCl_3$. The crystals obtained above were dissolved in this $CHCl_3$ solution and the solution was concentrated to a small volume. The $CHCl_3$ solution was passed through a column of Al_2O_3 and eluted with $CHCl_3$. The eluate gave 0.13 g of IX (mp 213—215°, 40%). The recrystallization from EtOH gave colorless needles, mp 216.5—217° (lit.,[6] mp 217—218°). *Anal.* Calcd. for $C_{15}H_{12}ON_2$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.52; H, 4.89; N, 11.86.

ii) X was treated in the same way described above to give IX. No melting point depression was observed on admixture with 7-benzoylaminoindole and the IR spectra of the two samples were identical.

3-Hydroxy-8-nitroquinoline (II)——A mixture of 3.00 g of I, 24 ml of AcOH and 6 ml of 30% H_2O_2 was heated at 70° for 2 hr. After cooling, the mixture was poured into ice water. The separated crystals were collected by filtration and was washed with H_2O. The filtrate and washings were combined and extracted with $CHCl_3$. The crystals obtained above were dissolved in the extracted solution and the solution was dried over Na_2SO_4 and passed through a column of acidic Al_2O_3 and eluted with $CHCl_3$. From the first portion eluted with $CHCl_3$, trace of III was obtained. The second fraction eluted with $CHCl_3$ containing 20% MeOH gave crude crystals of II (mp 174—177°, 0.73 g, 21%). The recrystallization from 80% MeOH gave II as yellow needles, mp 182—183°. *Anal.* Calcd. for $C_9H_6O_3N_2 \cdot 1/2H_2O$: C, 54.27; H, 3.54; N, 14.07. Found: C, 54.44; H, 3.79; N, 14.35.

3-Hydroxy-8-aminoquinoline (XI)——A mixture of 0.30 g of II and 30 ml of EtOH was hydrogenated in H_2 stream over Pd–C prepared from 0.1 g of charcoal and 5 ml of 1% $PdCl_2$ solution. After the removal of catalyst, the filtrate was evaporated to dryness. The residue was recrystallized with benzene to give 0.19 g (63%) of XI as yellow needles, mp 173° (decomp.). *Anal.* Calcd. for $C_9H_8ON_2$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.05; H, 5.33; N, 17.41.

3-Hydroxy-8-chloroquinoline (XII)——To suspension of 150 mg of XI and 5 ml of conc. HCl, saturated solution containing 65 mg of sodium nitrite was added dropwise keeping at −10°. This solution was added dropwise to a solution of CuCl in HCl prepared from 2 g of $CuSO_4$. After the mixture was allowed to stand at room temperature for 1 hr, the solution was evaporated to dryness. The residue was extracted with ether and the solution was dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from benzene to gave 40 mg (24%) of XII as colorless needles, mp 239° (decomp.). *Anal.* Calcd. for C_9H_6ONCl: C, 60.18; H, 3.37; N, 7.80. Found: C, 60.72; H, 3.37; N, 7.77.

3-Hydroxyquinoline (XIII)——A mixture of 40 mg of XII and 20 ml of EtOH was hydrogenated in H_2 stream over Pd–C prepared from 0.1 g of charcoal and 5 ml of 1% $PdCl_2$ solution. After the removal of catalyst, the filtrate was evaporated to dryness. The residue was dissolved in MeOH–H_2O (2:1), passed through a column of ion-exchange resin (Amberite 120), and eluted with NH_4OH–MeOH–H_2O (2:20:80). The solvent was evaporated from the eluate. The residue was dissolved in benzene containing 5% MeOH and again passed through a column of Al_2O_3. The solvent was evaporated to dryness and the residue was recrystallized from benzene to give 10 mg (31%) of XIII as colorless needles, mp 192—195°. This showed no depression of melting point on admixture with authentic 3-hydroxyquinoline and IR spectra of the two samples were identical.

Ethyl Oxindole-7-carboxylate (XVII)——A mixture of 2.33 g of XV, 20 ml of AcOH and 4.6 ml of 30% H_2O_2 was heated at 80° for 4 hr, further 4.6 ml of 30% H_2O_2 was added and the mixture again heated at the same temperature for 4 hr. After cooling, the solution was evaporated to dryness under reduced pressure. The residue was dissolved in $CHCl_3$ and passed through a column of Al_2O_3, and the eluate was evaporated to dryness. The purification of the residue over Florisil with benzene gave crude XVII. The recrystallization from benzene gave 0.52 g (24%) of XVII as colorless needles, mp 119—121°. *Anal.* Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.14; H, 5.39; N, 7.23.

3-Hydroxyquinoline-8-carboxylic Acid (XIV)——A mixture of 1.84 g of XV and 25 ml of 5% NaOH was heated at 50° for 1 hr. After cooling, the mixture was acidified with 10% HCl. The separated crystals were recrystallization from MeOH to give 1.51 g (94%) of 3-hydroxyquinoline-8-carboxylic acid as yellow needles, mp 284° (decomp.). This showed no depression of melting point on admixture with authentic sample and IR spectra of the two samples were identical.

Oxindole-7-carboxylic Acid (XVI)——i) A mixture of 500 mg of XIV, 30 ml of AcOH and 6 ml of 30% H_2O_2 was heated at 80° for 4 hr, further 6 ml of 30% H_2O_2 was added and the mixture again was heated at the same temperature for 4 hr. After cooling, the solution was evaporated to dryness under reduced pressure. To the residue, a small portion of H_2O was added, the solvent was evaporated under reduced pressure, and this procedure was repeated twice. To the residue, a small portion of H_2O was added and the separated crystals were collected by filtration. The recrystallization of crystals from MeOH gave oxindole-7-carboxylic acid as colorless needles, mp 243° (decomp.). Yield, 80 mg (17%). *Anal.* Calcd. for $C_9H_7O_3N$: C, 61.03; H, 3.98; N, 7.91. Found: C, 60.53; H, 3.99; N, 8.21.

ii) A mixture of 100 mg of XVII and 2 ml of 5% NaOH was heated at 50° for 1 hr. After cooling, the solution was acidified with 10% HCl. The separated crystals were recrystallized from MeOH to give

XVI, mp 243° (decomp.). Yield, 57 mg (66%). This compound was identified as oxindole-7-carboxylic acid by comparison of these IR spectra.

Oxidation of 8-methylquinoline (XVIII)——A mixture of 1.0 g of XVIII, 8 ml of AcOH and 2 ml of 30% H_2O_2 was heated at 80° for 4 hr, further 2 ml of 30% H_2O_2 was added and the mixture again was heated at the same temperature for 4 hr. After cooling, the solution was evaporated to dryness under reduced pressure. To the residue, a small portion of H_2O was added, the solvent was evaporated under reduced pressure and this procedure was repeated twice. The residue was extracted with $CHCl_3$. The solution was washed with 5% $NaHCO_3$, dried over Na_2SO_4 and passed through a column of acidic Al_2O_3. From the first fraction eluted with $CHCl_3$, XVIII was recovered in 14% (140 mg) yield. From the second fraction recrystallization from ether containing H_2O gave 8-methylquinoline N-oxide (XIX) as colorless needles, mp 57—59° (lit.,[11] mp 51—53°). Yield, 90 mg (8%). NMR (τ) 1.5—2.7 (multiplet, 6H, aromatic protons), 6.92 (singlet, 3H, CH_3 protons). Picrate, yellow needles (from MeOH). *Anal.* Calcd. for $C_{10}H_9ON \cdot C_6H_3O_7N_3$: C, 49.47; H, 3.12; N, 14.43. Found: C, 49.30; H, 3.16; N, 14.64. From the third fraction with $CHCl_3$ containing 2% MeOH, crystals were obtained. Yield, 100 mg (9%). Recrystallization from benzene gave 3-hydroxy-8-methylquinoline (XX) as colorless needles, mp 211° (decomp.). *Anal.* Calcd. for $C_{10}H_9ON$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.38; H, 5.39; N, 8.80.

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