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82. Chikara Kaneko and Sachiko Yamada : The Isomerization of 1a*H*-Oxazirino[2,3-*a*]quinoline 1a-carbonitrile and Its Substituted Derivatives to the Corresponding 3-Hydroxyquinoline Derivatives.*1

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The oxaziranes (Ia~d) prepared by the irradiation of the corresponding 2-cyanoquinoline 1-oxides in an aprotic solvent all rearranged to the corresponding 3-quinolinols under a variety of conditions described. The mechanism of this novel isomerization has been postulated.

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We reported previously*1,1) the photochemical isomerization of 2-cyanoquinoline 1-oxides to the corresponding oxaziranes (Ia,b,c). During the investigation of these oxaziranes, it was found that there was a radical change between the nuclear magnetic resonance spectrum of a trifluoroacetic acid solution of 3-methyl-1a*H*-oxazirino[2,3-*a*]-quinoline 1a-carbonitrile (Ia) and the spectra measured in other solvents, *i.e.*, CCl_4, $CHCl_3$, methanol, dioxane, dimethyl sulfoxide, acetic acid etc. The spectrum of Ia measured immediately after dissolution of the sample in trifluoroacetic acid showed in addition to the three sets of signals at around 2.3τ (4H, multiplet due to aromatic protons), at 2.65τ (1H, quartet due to olefinic proton, J=3 c.p.s.), and at 7.84τ (3H, doublet due to methyl group, J=3 c.p.s.), two sets of signals, one at around 1.6~1.8τ (multiplet) and the other at 6.89τ (singlet) with the relative intensity ratio of 4:3. Since in all the other solvents examined, the spectra of Ia showed only three sets of signals corresponding to the three sets of signals of Ia in trifluoroacetic acid and these signals have been assigned to the corresponding oxazirane structure (Ia),*3 it was clear that some change of Ia had taken place in trifluoroacetic acid solution.

In order to verify this assumption, we carried out preparative experiments and the investigated the rearrangement product. The phenolic compound (IIa) was obtained in quantitative yield by dissolution of Ia in trifluoroacetic acid for several hours at room temperature followed by the isolation described in the experimental part. As expected, the NMR spectrum of IIa in trifluoroacetic acid showed only two sets of signals at 1.6~1.8τ and 6.89τ and that in dimethyl sulfoxide showed similar two sets of signals (1.8~2.2τ and 7.5τ*4). The latter spectrum was completely different from that of Ia in the same solvent.

The structure of this compound was deduced to be 3-hydroxylepidine-2-carbonitrile (IIa) from its elemental analysis and spectroscopic data, and was confirmed by its conversion to 3-hydroxylepidine (Va) in the reaction sequences shown in Chart 1. The identity of Va with authentic 3-hydroxylepidine prepared by the method by Kobayashi,

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*1 This paper forms part III of "Three-membered Ring System with Two Hetero Atoms" by C. Kaneko. Part II: Rept. Res. Inst. Dental Materials, Tokyo Medico-Dental University, **2** (9), 804 (1966).

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*3 Complete assignments of NMR spectrum of Ia and other related oxaziranes in $CDCl_3$ have already been reported in the previous paper. See part II in this series.*1

*4 This signal was masked by the strong absorption of the solvent.

1) C. Kaneko, Sa. Yamada : This Bulletin, **14**, 555 (1966).

et al.[2] was established by the mixture melting point determination and their superimposable infrared (IR) and ultraviolet (UV) spectra.

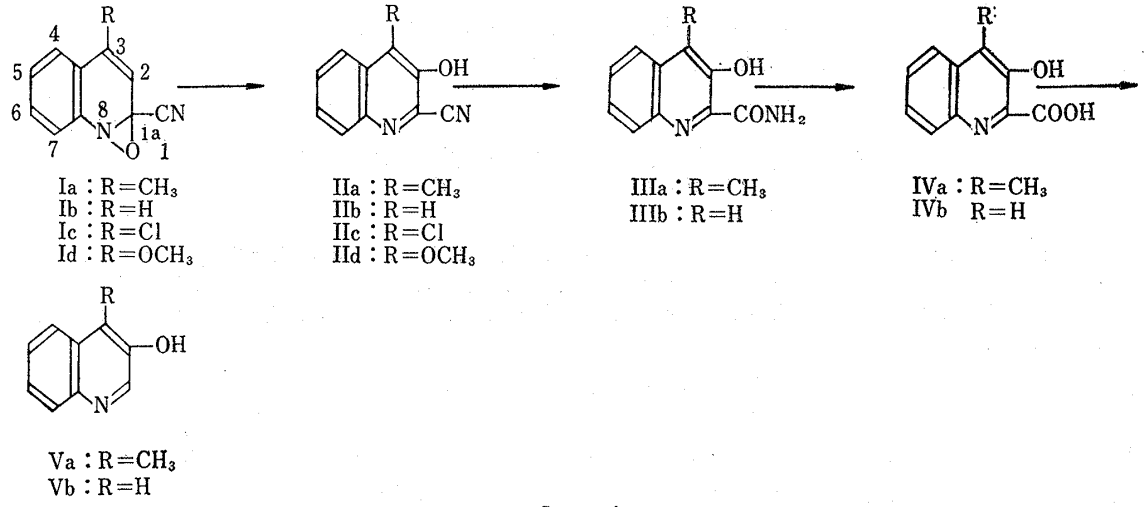

Chart 1.

Isomerization of Ia to IIa also took place at room temperature either in acetyl chloride or when a small amount of bromine was added to a dichloromethane solution of Ia. As the latter reaction proceeds under completely anhydrous conditions, it could be concluded that this rearrangement is intramolecular in nature. To effect this type of rearrangement, bond fission in the oxazirane ring in Ia must occur. The use of ionic reagents in the above reactions suggests strongly that the bond fission proceeds heterolytically. In a heterolytic bond fission of the oxazirane ring, the oxygen atom can support a developing negative charge, and either the carbon or nitrogen atoms a developing positive charge. This assumption could be supported by the facile conversion of the oxaziranes (VI) derived from aliphatic nitrones to the corresponding amides or nitrones as reported by Splitter and Calvin.[3] The reaction of VI can be formulated schematically as in Chart 2. However in our oxaziranes (I), no C-O bond cleavage products (such as the corresponding N-oxides) have been obtained, and this fact suggests the greater stabilization of the developing nitrogen cation relative to the developing carbonium ion. Based on the above consideration, the reaction mechanism shown in Chart 3, in which the formation of 2,3-epoxyquinolines (VII) as the key step is assumed, is now proposed to this novel isomerization. Since the irradiation of quinoline 1-oxides having either a hydrogen or alkyl group*5 on their 2-position in methanol gave rise directly to the corresponding carbostyrils,[4,5] probably via the initial formation of unstable oxaziranes (VIII), it seems worthy to note that no carbostyril derivatives have been obtained from a in the above reactions.

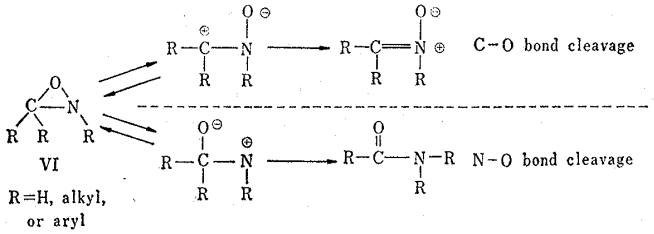

Chart 2.

*5 Irradiation of quinaldine 1-oxide in benzene under complete protection of moisture gave rise to the corresponding oxazirane,*1 which changed immediately by dissolution in protic solvents.

2) G. Kobayashi, S. Furukawa, Y. Akimoto, T. Hoshi : Yakugaku Zasshi, **74**, 791 (1954).
3) S. Splitter, M. Calvin : J. Org. Chem., **30**, 3428 (1965) and references cited therein.
4) O. Buchardt : Acta Chem. Scand., **17**, 1461 (1963); O. Buchardt, S. Becher, C. Lohse : *Ibid.*, **19**, 1120 (1965).
5) M. Ishikawa, Sa. Yamada, C. Kaneko : This Bulletin, **13**, 747 (1965); M. Ishikawa, Sa. Yamada, H. Hotta, C. Kaneko : *Ibid.*, **14**, 1102 (1966).

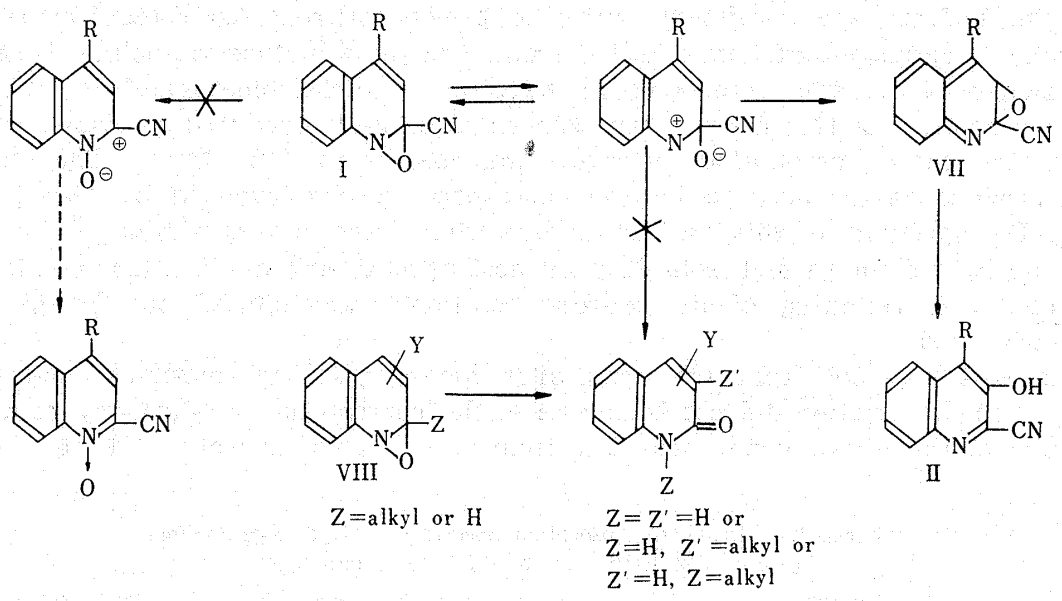

Chart 3.

This difference is due to the weaker nature of the C_{1a}-H or C_{1a}-alkyl bond in Ⅷ compared to that of C_{1a}-CN in I (the former bonds are sp_3, while the latter bond is sp in its hybridization), since the carbostyril formation from these oxaziranes requires the fission of these bonds.

Similarly, dissolution of Ib in trifluoroacetic acid gave rise to 3-hydroxyquinoline-2-carbonitrile (Ⅱb), together with a crystalline compound (Ⅸ), $C_{20}H_{12}O_2N_4$, m.p. 169~171°, in respective yields of 9% and 79%. The structure of the former compound was shown to be Ⅱb, by its direct conversion to 3-hydroxyquinoline (Vb)*[6] as shown in Chart 1. The structure of Ⅸ is still under investigation, but its dimeric nature is suspected from its molecular weight determination and the complex pattern of the proton signals in its NMR spectrum.

On the contrary, dissolution of Ib in acetyl chloride followed by removal of solvent under reduced pressure and recrystallization from methanol gave rise to Ⅱb in ca. 60% yield and in this case, no other products (*i.e.*, such as Ⅸ) have been isolated. High yield formation of the dimer (Ⅸ) from Ib in trifluoroacetic acid is probably due to the lack of a substituent at the 3-position in the latter compound. Therefore, it seems preferable to use acetyl chloride to obtain a better yield of Ⅱb from Ib. With this reagent, oxazirane (Ic) was also converted to the corresponding 3-hydroxy compound (Ⅱc).

As 2-cyanoquinoline 1-oxides were converted to the corresponding oxaziranes in high yields by irradiation in an aprotic solvent,*[1,1,6] these reactions provide a new route to the syntheses of 3-hydroxyquinaldonitriles (Ⅱ) and their related compounds (Ⅲ~Ⅴ). From the fact that these transformations of oxaziranes occur always in the presence of cationic reagents, it seems reasonable to suppose that this intramolecular rearrangement of oxygen atom is induced by a cation. Actually, the addition of boron trichloride to a benzene solution of Ia followed by the work up described in the experimental part resulted in the formation of Ⅲa. Since, under these conditions (probably in the work up process), Ⅱa was converted to Ⅲa, it seems reasonable to conclude that the initial product in this reaction was also Ⅱa.

*6 The authors are very grateful to Prof. M. Hamana, Kyushu University for supplying them an authentic sample of 3-hydroxyquinoline.

6) C. Kaneko, Sa. Yamada, M. Ishikawa : Tetrahedron Letters, No. 19, 2145 (1966).

These findings are consistent with the previously reported direct formation of 3-hydroxy-4-methoxyquinaldonitrile (IIId) from 2-cyano-4-methoxyquinoline 1-oxide by irradiation of the latter compound in benzene or dichloromethane.*[1,6] When the irradiated solution of this N-oxide was concentrated under reduced pressure at room temperature, there was obtained a crystalline mass, m.p. 205~208°.*[7] The structure of this product was deduced to be the corresponding oxazirane (Id) by the following facts : i) UV spectrum of this product in dichloromethane is very similar to the spectra of (Ia,b,c). ii) it displays high solubility in most aprotic solvents (*i.e.*, hexane, benzene, ether etc.). iii) refluxing of its benzene solution*[8] precipitated out IId in almost quantitative yield.

It is worthy to note that the oxaziranes having phenyl,[1] methyl,*[1] and styril*[9] groups at the 1a-position did not isomerize to the corresponding 3-hydroxy compounds under any of the above conditions, but isomerized in an entirely different manner,

TABLE I. Ultraviolet Absorption Spectra of 3-Hydroxyquinolines
(a; in 95% EtOH, b; in 5% K_2CO_3 solution)[a]

Compound	Solvent	mμ	log ε	mμ	log ε	mμ	log ε
IIa	a	239.5	4.89	293.5, 303	3.96, 3.92	360, 420	3.68, 3.39
	b	247.5	4.65	302, 312	3.40, 3.35	409	3.75
IIb	a	219, 225, 231.5, 244.5	4.47, 4.48, 4.49, 4.40	302(broad)	3.62	365, 410	3.52, 3.07
	b	243	4.59	304, 311	3.55, 3.56	405	3.75
IIc	a	239	4.67	297, (305)	3.68, 3.67	368, 425	3.45, 3.42
	b	248.5	4.73	307, 315	3.56, 3.57	415	3.82
IId	a	236	4.79	294.5, 304	3.95, 3.90	358, 420	3.55, 3.41
	b	246.5	4.73	303, 314	3.68, 3.68	410	3.85
IIIa	a	235	4.73	298, (305)	3.74, 3.72	362	3.71
	b	245	4.69	290, 310	3.64, 3.46	402	3.80
IIIb	a	219, 231.5	4.53, 4.62	298(broad)	3.65	359	3.63
	b	243	4.54	302(〃)	3.42	394	3.70
IVa	a	238.5	4.71	316, 327	3.59, 3.65	367	3.84
	b	247	4.63	279	3.77	361	3.89
IVb	a	216.5, 231.5	4.57, 4.61	300, 330	3.59, 3.55	362	3.73
	b	246	4.55	275	3.72	357	3.83
Va	a	224.5	4.72	(274), 281.5, (292)	3.64, 3.67, 3.60	327, 336	3.70, 3.71
	b	243	4.57	277, (284)	3.72, 3.70	358	3.75
Vb	a	233	4.46	270, 280, (292)	3.46, 3.44, 3.32	324, 336	3.64, 3.64
	b	243	4.63	271	3.82	354	3.85

a) The numbers in parentheses refer to the maxima of the shoulder peaks.

*7 The melting point of this product was same as that of IId and mixed melting point of this product with IId was not depressed. We assume that conversion of Id to IId occurred during the melting point determination.

*8 In this case, the homolytic N-O bond fission of the three-membered ring and its subsequent change to IId are also possible.

*9 So far, several stable oxaziranes having styril and 4'-substituted styril groups at the 1a-position have been prepared. Syntheses and reactions of these oxaziranes will be published soon. I. Yokoe and C. Kaneko, in preparation.

and these results will be published in the near future. From this observation, it could be concluded that the isomerization to 3-hydroxy compounds is restricted to oxaziranes having a 1a-cyano group.

The UV spectra of 3-hydroxyquinoline-2-carbonitrile derivatives so far obtained are shown in Table I. The similarity of these absorption spectra provides the evidence for the correctness of the assigned structures for IIc and IId.

Surprisingly, in contrast to the above reactions, action of diluted sulfuric acid on Ia gave rise to skatole (X) in 80% yield, and IIa was not detected in the reaction product even upon very careful examination. This reaction probably proceeds in the same way as the conversion of Ia to X in hot aqueous methanol.[1] The fact that no intermediary formation of N-cyanoformyl skatole (XI) is observed in both reactions seems to support *path a* shown in Chart 4, and exclude the alternate route, *path b*.

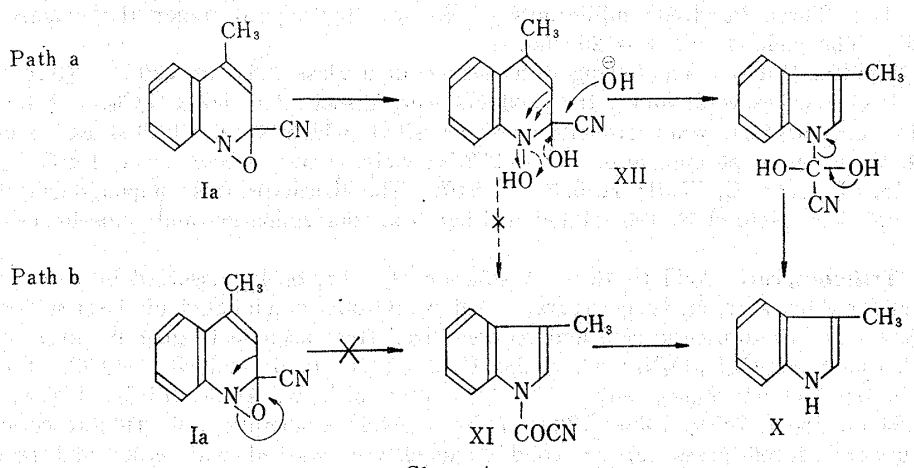

Chart 4.

The intermediary addition compound (XII) in this reaction could be derived from the initial N-O bond fission followed by addition of the solvent (cf. Chart 3).

The scope of this novel ring contraction reaction of I-type oxaziranes is now under investigation.

Experimental

All melting points were measured by capillary and are uncorrected. Infrared spectra were recorded on a Nihon Bunkō DS-301 double-beam spectrophotometer. Ultraviolet spectra were recorded on a Hitachi EPS-2 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a JNM-3H-60 (60 Mc) with tetramethylsilane as an internal reference.

Isomerization of Ia to IIa——i) A solution of 1.0 g. of Ia[1] dissolved in 10 ml. of trifluoracetic acid was stirred for 3 hr. at room temperature. The solution was concentrated *in vacuo* to leave a residue, which was solidified by addition of ether. The deposited solid was filtered, washed with ether and recrystallized from methanol to give IIa (0.89 g.), as white needles, m.p. above 300°(decomp.). *Anal.* Calcd. for $C_{11}H_8ON_2$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.43; H, 4.60; N, 15.17. IR ν_{max}^{KBr} cm^{-1}: 3410m, 2220w.

ii) To a solution of 500 mg. of Ia in 10 ml. of CH_2Cl_2, *ca.* 0.2 g. of bromine was added with stirring. Colorless needles, precipitated after standing at room temperature for several hr., were collected and recrystallized from methanol to give pure sample of IIa, m.p. above 300°(decomp.); yield, 280 mg. IR and UV spectra (cf. Table I) were superimposable with those of the sample prepared as i).

iii) The solution of 500 mg. of Ia dissolved in 10 ml. of acetyl chloride was kept at room temperature for 24 hr. The solution was concentrated *in vacuo* to leave a solid. Recrystallization from methanol gave white needles, m.p. above 300° (decomp.); yield, 390 mg., whose spectra (IR and UV) were identical with those of IIa obtained as above.

3-Hydroxylepidine-2-carboxamide (IIIa)——iva) To a solution of 1 g. of IIa[1] in a mixture of 30 ml. of methanol and 10 ml. of 5% aq. NaOH, *ca.* 2 ml. of 30% aq. H_2O_2 was added under stirring. The solution was then kept at around 50° for 1 hr. The solution was concentrated *in vacuo* to a small volume and

acidified with acetic acid to deposit a solid, m.p. 208~213°, yield, 810 mg. Recrystallization from acetone gave IIIa as pale yellow needles, m.p. 212~215°. *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.28; H, 5.09; N, 14.10. UV, cf. Table I.

ivb) To a suspension of 500 mg. of IIa in 100 ml. of benzene, 1.0 g. of BCl_3 was added under ice cooling, and the solution was kept standing at room temperature for 3 hr. The whole treatment was carried out with stirring. After addition of 5 ml. of H_2O, the reaction mixture was evaporated almost to dryness under reduced pressure, and recrystallization of the residue from methanol afforded IIIa as white needles, m.p. 212~215°, alone and on admixture with a sample of IIIa obtained by procedure iva); yield, 410 mg.

v) From Ia: Five hundred milligrams of Ia was treated under the exactly same condition described as ivb). The yield of IIIa was 340 mg.

3-Hydroxylepidine-2-carboxylic Acid (IVa)——vi) From IIa: A solution of 400 mg. of IIa in a mixture of 10 ml. of methanol and 5 ml. of 10% aq. K_2CO_3 was kept boiling for 5 hr. The solution was concentrated *in vacuo* to a small volume and acidified with 20% aq. acetic acid to deposit a solid. Recrystallization from dimethyl formamide gave IVa as yellow needles, m.p. 215~215.5°(decomp.); yield, 310 mg. *Anal.* Calcd. for $C_{11}H_9O_3N$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.91; H, 5.20; N, 7.20. IR ν_{max}^{KBr} cm^{-1}: 2920, 1696. UV, cf. Table I.

vii) From IIIa: Three hundreds milligrams of IIIa was hydrolyzed under the exactly same condition described in vi). The yield of IVa was 250 mg.

3-Hydroxylepidine (Va)——IVa (100 mg.) was heated in a glass tube at 220°. After the evolution of carbon dioxide has ceased (several min.), the products were dissolved in hot CH_2Cl_2. After filtration while hot, followed by concentration, white crystals were deposited, which were collected and recrystallized from acetone to give Va as white prisms, m.p. 201.5~202.5°; yield, 50 mg. *Anal.* Calcd. for $C_{10}H_9ON$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.21; H, 5.45; N, 8.07. The identity of this compound (Va) with an authentic 3-hydroxylepidine[2] was assured by the mixted melting point determination and superimposable IR and UV spectra.

Action of Trifluoroacetic Acid to Ib——A solution of 1.0 g. of Ib dissolved in 5 ml. of trifluoroacetic acid was stirred for 2 hr. at room temperature. Yellow needles precipitated in the reaction mixture were collected, washed with trifluoroacetic acid and recrystallized from acetone to give IX, m.p. 169~171°; yield, 530 mg. *Anal.* Calcd. for $C_{20}H_{12}O_2N_4$: C, 70.58; H, 3.55; N, 16.46; mol. wt., 340.32. Found: C, 70.35; H, 3.50; N, 16.37; mol. wt. (Rast), 351. IR ν_{max}^{KBr} cm^{-1}: 2266vw, 1765s, 1635s, 1540w, 1485w, 1460m, 1450w, 1230s, 945m, 780m, 765w, 750w, 728w, 717w. After evaporation of trifluoroacetic acid from the mother liquor under reduced pressure, the solid obtained was washed with ether and recrystallized from methanol to afford IIb as white needles, m.p. above 300°(decomp.); yield, 80 mg. *Anal.* Calcd. for $C_{10}H_6ON_2$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.19; H, 3.87; N, 16.20. IR ν_{max}^{KBr} cm^{-1}: 2230w, 1590s, 1345vs, 895m, 776w, 758m, 742m.

Action of Acetyl Chloride to Ib——Ib (500 mg.) was treated under the condition described as iii). The yield of IIb was 305 mg. White needles (from methanol), m.p. above 300°(decomp.). IR and UV spectra (cf. Table I) were superimposable with those of the sample prepared as above.

3-Hydroxyquinoline-2-carboxamide (IIIb)——IIb (500 mg.) was treated as iva). Deposited solid (m.p. 213~215°, 420 mg.) was recrystallized from acetone to give pale yellow needles, m.p. 215~216°. *Anal.* Calcd. for $C_{10}H_8O_2N_2$ (IIIb): C, 63.82; H, 4.29; N, 14.89. Found: C, 63.85; H, 4.27; N, 14.95. IR ν_{max}^{KBr} cm^{-1}: 3400m, 3180m, 1680s. UV, cf. Table I.

3-Hydroxyquinaldic Acid (IVb)——viii) From IIIb: IIIb (500 mg.) was hydrolyzed according to the procedure of vi). The deposited solid (m.p. 199°(decomp.), yield, 410 mg.) was recrystallized from acetone to give IVb as yellow needles, m.p. 200°(decomp.). *Anal.* Calcd. for $C_{10}H_7O_3N$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.27; H, 3.90; N, 7.50.

ix) From IIb: Under the exactly same condition as above, 300 mg. of IIb afforded 205 mg. of IVb, pale yellow needles, m.p. 200°(decomp.), alone and on admixture with the sample of IVb prepared in viii).

3-Hydroxyquinoline (Vb)——IVb (100 mg.) was pyrolyzed under the condition of IVa to Va, to afford Vb as pale yellow needles (from acetone), m.p. 198~199°; yield, 65 mg. *Anal.* Calcd. for C_9H_7ON: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.39; H, 5.00; N, 9.70. The identity of this compound with an authentic sample of 3-hydroxyquinoline*[6] was assured by the mixed melting point determination and their superimposable IR and UV spectra (cf. Table I).

3-Hydroxy-4-chloroquinaldonitrile (IIc)——Two hundred milligrams of Ic*[1,6] was treated under the condition of iii). The precipitates deposited in the reaction mixture was filtered and washed with ether. Recrystallization from methanol gave IIc as white needles, m.p. 230°(decomp.), yield, 50 mg. *Anal.* Calcd. for $C_{10}H_5ON_2$: C, 58.76; H, 2.47; N, 13.71. Found: C, 58.50; H, 2.48; N, 13.72. UV, cf. Table I. The mother liquor was concentrated *in vacuo* and 10 ml. of 10% aq. K_2CO_3 was added to the residue. Ether extraction followed by removal of the solvent afforded 80 mg. of 3-chloroindole[7] after recrystallization from hexane, m.p. 94~95°. *Anal.* Calcd. for C_8H_6NCl: C, 63.42; H, 4.00; N, 9.25. Found: C, 63.01; H, 4.05; N, 9.60.

7) R. Weissberger: Ber., **46**, 651 (1913).

Irradiation of 2-Cyano-4-methoxyquinoline 1-oxide in Dichloromethane——One gram of the N-oxide in 300 ml. of freshly distilled CH_2Cl_2 was irradiated as described previously*1 (Pyrex filter was used to avoid the irradiation of wavelength below 300 mμ and no precautions was taken to avoid the presence of small amounts of air in the irradiation mixture). After all of the N-oxide was consumed (checked by gas phase chromatography), the mixture was concentrated under reduced pressure at room temperature to give a pale yellow solid. The UV spectrum of this oil in CH_2Cl_2 showed two absorption maxima at 241 mμ and 312 mμ, and was quite similar to the spectra*1 of Ia~c and different from that of IId (cf. Table I). This oil was dissolved in 20 ml. of anhydrous benzene and the resultant clear solution was boiled for 2 hr., thereby, pale yellow needles precipitated out in the solution. After cooling, the precipitates (800 mg.) were collected and recrystallized from methanol to afford IId, m.p. 205~208°, alone and on admixture with an authentic sample of 3-hydroxy-4-methoxyquinaldonitrile prepared previously.*1 The portion soluble in benzene was chromatographed over silica gel. Elution with benzene afforded 90 mg. of 4-methoxyquinaldonitrile,*1 m.p. 125~126°.

Conversion of Ia to Skatole (X) in Dilute Sulfuric Acid——To 10 ml. of 10% aq. sulfuric acid solution, 1.0 g. of Ia in 50 ml. of ether was added and the solution was kept standing at room temperature. Periodical injection of the ether layer to gas phase chromatogram revealed that the peak corresponding to Ia disappeared gradually, and was replaced by the single peak corresponding to skatole (X). The whole treatment was carried out in the nitrogen atmosphere and with stirring. After 20 hr. (by this time, the complete consumption of Ia was assured by gas phase chromatography), the ether layer was separated from the aqueous layer, washed with aq. sodium bicarbonate solution and dried over Na_2SO_4. Evaporation of the solvent gave rise to a low melting point solid, which was recrystallized from hexane to afford 810 mg. of pure skatole (X), m.p. 95°, alone and on admixture with an authentic sample.

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