Catalytic Reduction of 3-Phenyl-6-chloropyridazine 2-Oxide (XX) : Formation of 3-phenylpyridazine 2-Oxide (XVIII)——A mixture of 70 mg. of XX, 2 ml. of MeOH, 0.5 ml. of 28% NH_4OH and 50 mg. of 10% Pd-C was subjected to hydrogenation. When the reaction mixture was treated in the same way as described above, 15 mg. of XVIII as colorless scales, m.p. 131~132° was obtained. This was identified with XVIII derived from XVII by comparison of their IR spectra.

3-Phenyl-6-chloropyridazine (XVI)——To a solution of 0.5 g. of XIII dissolved in 10 ml. of $CHCl_3$, 1.0 g. of $POCl_3$ was added, the mixture refluxed for 2 hr. The solvent was removed *in vacuo*. The residue was neutralized with Na_2CO_3, and extracted with $CHCl_3$. $CHCl_3$ was distilled and the residue was recrystallized from EtOH to colorless scales, m.p. 158~160°. Yield, 10 mg. This was identified with XVI by comparison of their IR spectra.

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Summary

3-Chloro, 3-methyl, 3-methoxy, 3-benzyloxy, and 3-phenyl-6-cyanopyridazine (III, VI, X, XII, XIV) was synthesized from 3-chloro, 3-methyl, 3-methoxy, 3-benzyloxy, and 3-phenylpyridazine 1-oxide (II, V, IX, XI, XIII).

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237. Masaru Ogata, Hideo Kano, and Kazuo Tori : Pyridazines. VIII.*1 Syntheses and Nuclear Magnetic Resonance Spectra of Cinnoline N-Oxides.*2

(*Shionogi Research Laboratory, Shionogi & Co., Ltd.**3)

Several investigations have been made on the syntheses of benzodiazine N-oxides such as quinoxaline N-oxides,[1] quinazoline N-oxides,[2] and phthalazine N-oxides.[3] Study of cinnoline N-oxides, however, has been limited to synthesis of 4-arylcinnoline N-oxides,[4] and the position of their N-O groups has not been determined.

This paper describes synthetic and structural studies of cinnoline N-oxides, including nitration of 3-methoxycinnoline 1-oxide. Furthermore, nuclear magnetic resonance (NMR) spectra of cinnoline N-oxides are investigated.

Cinnoline (I) was readily converted into its isomeric N-oxides on treatment with hydrogen peroxide in acetic acid. The product was chromatographed on alumina to separate

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1* Part VII This Bulletin, **11**, 1522 (1963).

*2 Preliminary reports of this work were published as "Communication to the Editor" in this Bulletin, **10**, 1123 (1962); **11**, 681 (1963).

*3 Fukushima-ku, Osaka (尾形 秀, 加納日出夫, 通 和夫).

1) H. McIlwain : J. Chem. Soc,. **1943**, 322; J.K. Landquist : *Ibid.*, **1953**, 2816.
2) A. Adachi : Yakugaku Zasshi, **77**, 507 (1957).
3) E. Hayashi, T. Higashino, C, Iijima, Y. Kono, T. Doihara : Yakugaku Zasshi, **82**, 584 (1962).
4) C.M. Atkinson, J.C.E. Simpson : J. Chem. Soc., **1947**, 1649.

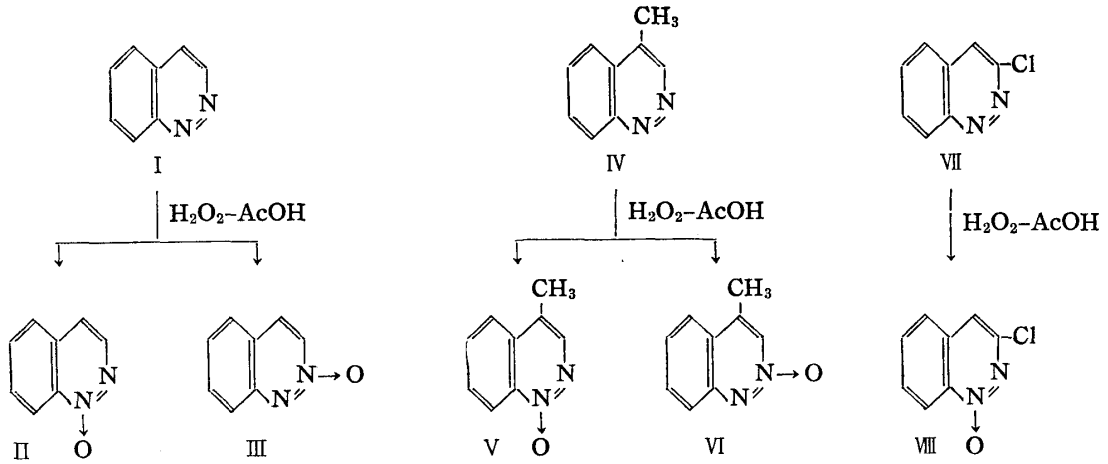


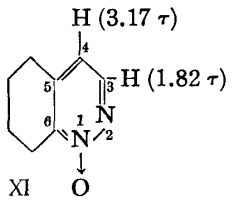
Chart 1.

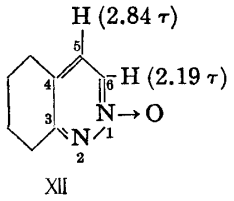
the isomers (II and III), the apparent ratio of which was about 1:2. The precise ratio was found to be 1:1.4 by NMR spectroscopy, as quoted later.

By the same procedure, 4-methylcinnoline (IV) was oxidized to its N-oxides, which were separated into two isomers (V and VI). The ratio of V to VI was 1:2, which agrees with the ratio determined by NMR spectroscopy. N-Oxidation of 3-chlorocinnoline (VII) gave the sole product, 3-chlorocinnoline N-oxide (VIII).

For determination of the structures of these N-oxides, cinnoline 1-oxides (II and VIII) were synthesized from 3-chloro-5,6,7,8-tetrahydrocinnoline (IX)[5] and 5,6,7,8-tetrahydrocinnoline (X)[5] by the following methods. N-Oxidation of X with hydrogen peroxide in acetic acid gave two isomeric 5,6,7,8-tetrahydrocinnoline N-oxides (XI and XII). The XI to XII ratio obtained by NMR spectroscopy was 4:3. On the other hand, IX was oxidized with hydrogen peroxide in acetic acid to afford 3-chloro-5,6,7,8-tetrahydrocinnoline N-oxide (XIII) as a sole product. Catalytic hydrogenation of XIII over palladium-carbon afforded 5,6,7,8-tetrahydrocinnoline N-oxide, which was proved to be identical with XI by comparison of their infrared spectra. Reaction of XIII with sodium methoxide and with sodium methylmercaptide gave 3-methoxy-5,6,7,8-tetrahydrocinnoline N-oxide (XIV) and 3-methylthio-5,6,7,8-tetrahydrocinnoline N-oxide (XV), respectively.

As shown in previous papers of this series, N-oxidation of 3-chloro-5-methylpyridazine[6] and 3-chloro-6-methylpyridazine[7,8] gave the corresponding 1-oxides. Therefore, XIII derived from IX is to be also the 1-oxide. Further evidence for the structures of XI and XII was obtained from their NMR spectra. Recent NMR studies of pyridazine N-oxides[9] have shown that the signal of the ring protons of methylpyridazine N-oxides appears in the order, $\tau_{H_3}<\tau_{H_6}<\tau_{H_5}<\tau_{H_4}$. This order is believed to be retained in the other alkyl derivatives. Therefore, the signal peaks at 1.82 τ and 3.17 τ in XI can be





5) R.H. Horning, E.D. Amstutz : J. Org. Chem., **20**, 707 (1955).
6) M. Ogata, H. Kano : This Bulletin, **11**, 35 (1963).
7) T. Nakagome : Yakugaku Zasshi, **81**, 1048 (1961).
8) M. Ogata, H. Kano : This Bulletin, **11**, 29 (1963).
9) K. Tori, M. Ogata, H. Kano : This Bulletin, **11**, 235 (1963).

assigned to the proton H_3 and H_4, respectively. Similary, the signal of the proton H_6 and H_5 in XII appears at 2.19 τ and 2.84 τ, respectively. From these facts, XI and XV are considered as the 1-oxide and XII is as the 2-oxide.

Bromination of XI and XIII with N-bromosuccimide in carbon tetrachloride gave only their monobromo derivatives (XVI and XVII), respectively, even though an excess of N-bromosuccimide was used. Further, XVI and XVII were brominated with N-bromosuccimide in carbon tetrachloride to their dibromo derivatives (XIX and XX). Bromination of XIV with N-bromosuccimide in carbon tetrachloride gave its dibromo derivative (XVIII), even though equimolar amount of N-bromosuccimide was used.

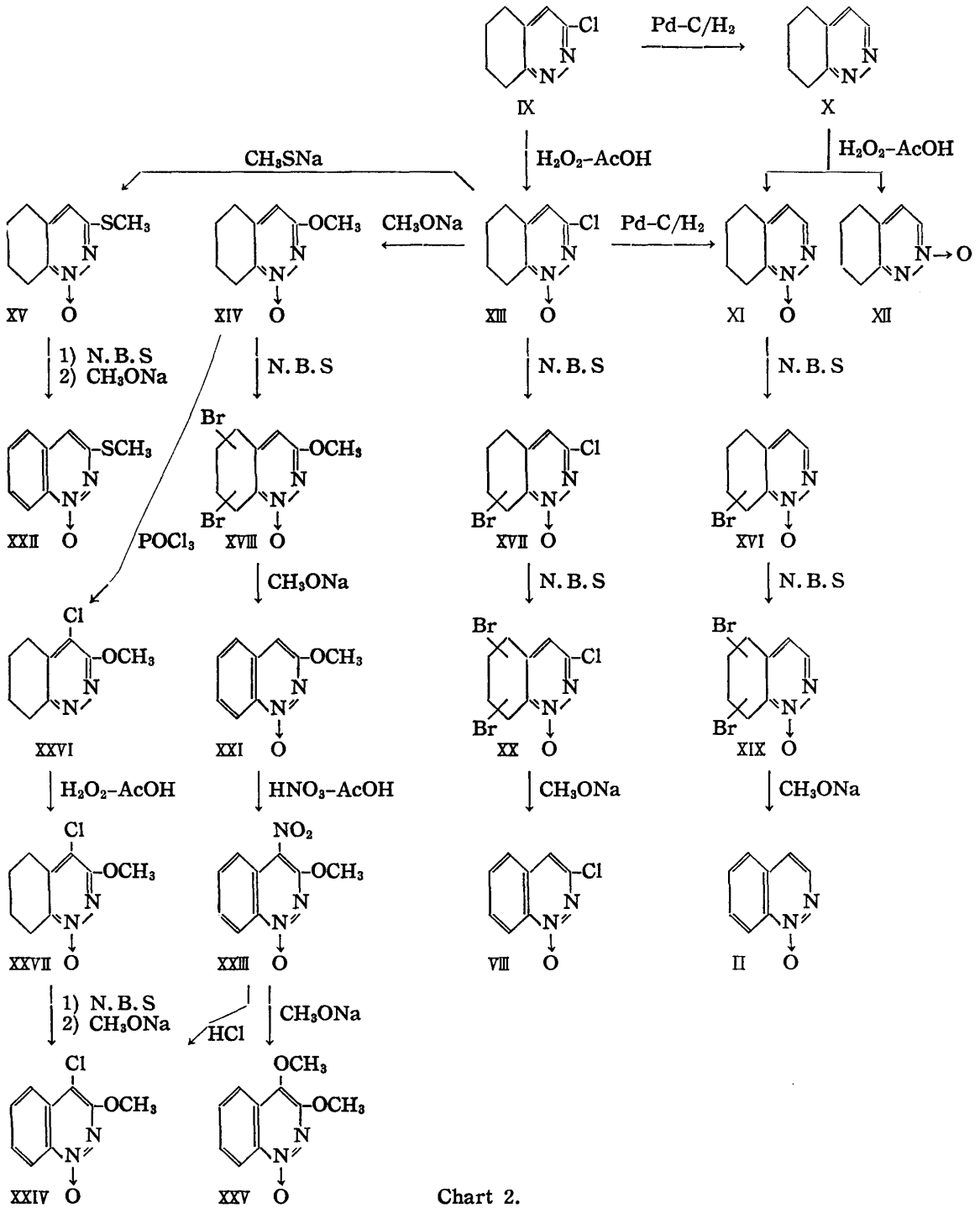


Chart 2.

On treatment with sodium methoxide in methanol, XIX and XX afforded cinnoline 1-oxide and 3-chlorocinnoline 1-oxide in poor yield, which are proved to be identical with II and VIII, respectively, by comparison of their infrared spectra. Accordingly, the structure of XIII can be decided to be cinnoline 2-oxide. By the same treatment used for XVIII, 3-methoxycinnoline 1-oxide (XXI) was prepared in good yield. Bromination of XV with N-bromosuccimide in carbon tetrachloride gave an oily product, which was converted into 3-methylthiocinnoline 1-oxide (XXII) on treatment with sodium methoxide.

Positions of substituted bromine atoms in XVI, XVII, XVIII, XIX, and XX were determined by their NMR spectra. The NMR spectra of XI, XVI, XVII, XVIII, XIX, and XX are shown in Fig. 1 together with the spectrum of monobromo-6-methyl-5,6,7,8-tetrahydrocinnoline 1-oxide (XXXVII) for the purpose of comparison.

Synthesis of XXXVI was made as shown in Chart 3. Heating a mixture of 4-methylcyclohexanone (XXVIII) and diethyl oxomalonate afforded an addition product (XXIX). Treating of XXIX with hydrazine hydrate in ethanol gave ethyl 3-hydroxy-6-methyl-5,6,7,8-tetrahydro-4-cinnolinecarboxylate (XXX). Hydrolysis of XXX with dil. sodium hydroxide afforded 3-hydroxy-6-methyl-5,6,7,8-tetrahydro-4-cinnoline carboxylic acid (XXXI), which was decarboxylated to 6-methyl-5,6,7,8-tetrahydro-3-cinnolinol (XXXII). Chlorination of XXXII with phosphoryl chloride gave 3-chloro-6-methyl-5,6,7,8-tetrahydrocinnoline (XXXIII). N-Oxidation of XXXIII gave 3-chloro-6-methyl-5,6,7,8-tetrahydrocinnoline 1-oxide (XXXIV), which was hydrogenated over palladium-carbon to 6-methyl-5,6,7,8-tetrahydrocinnoline 1-oxide (XXXV). Bromination of XXXV gave monobromo derivatives (XXXVI). On the other hand, bromination of 3-methoxy-6-methyl-5,6,7,8-tetrahydrocinnoline 1-oxide (XXXVII) derived from XXXIV gave only a resinous oily product.

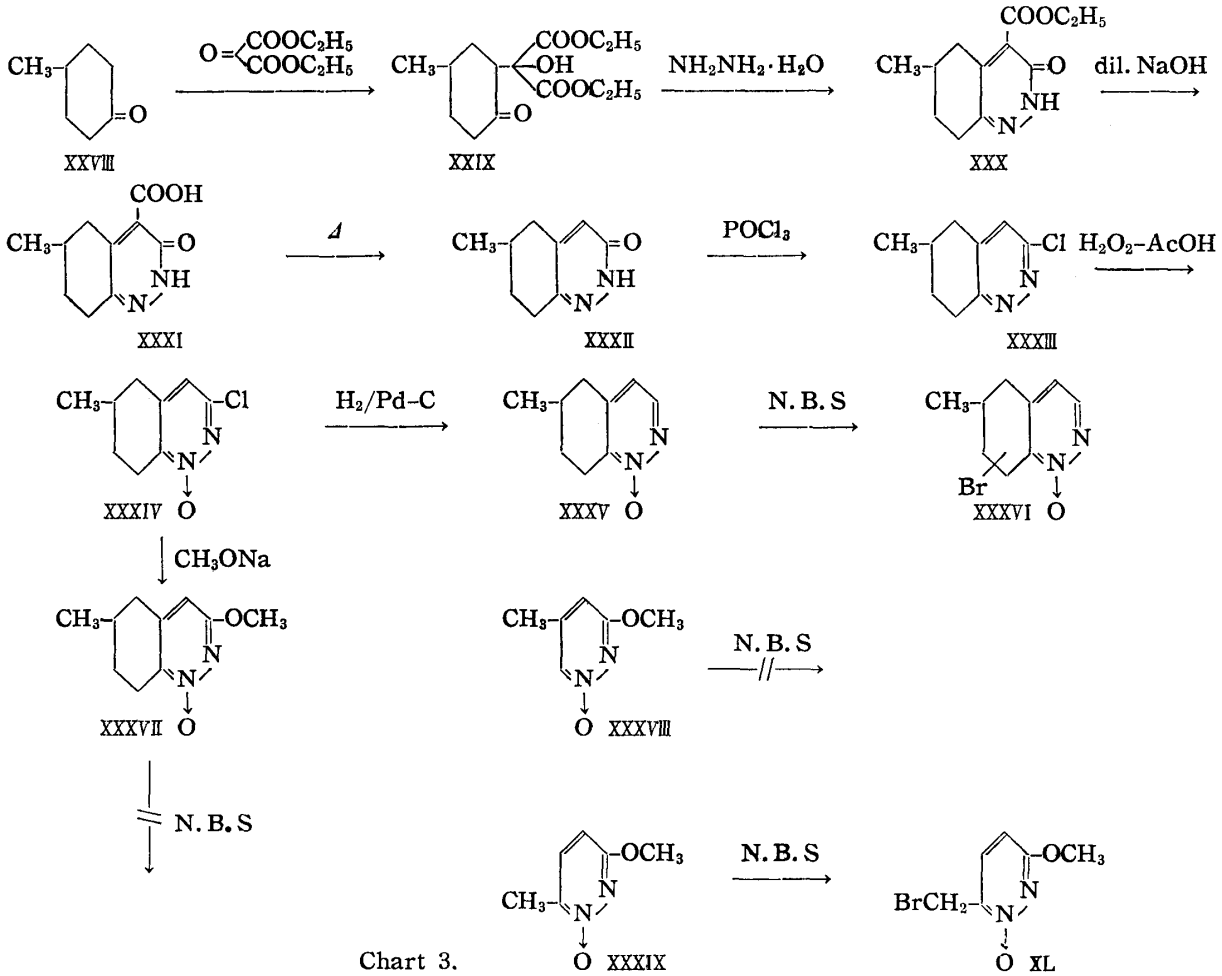


Chart 3.

As shown in Fig. 1 (a), the NMR spectrum of XI exhibits that the signals of the C_6- and C_7-methylene protons appear at higher fields than those of the C_5- and C_8-methylene protons and that the relative integral areas of their signals is in a ratio of 4:4. As to the spectra of XVI or XVII [Fig. 1 (b) or (c)], the integral area ratio of these signals is 4:2. Further, the signal of the proton attached to the bromine-bearing carbon atom appears at 4.57 τ (in XVI) or 4.55 τ (in XVII) as a triplet-like pattern, the X part of an ABX system. Therefore, the bromine atom in XVI or XVII is substituted at the C_5- or C_8-position. On the other hand, in the spectrum of XXXVI [Fig. 1 (d)], the signal of the

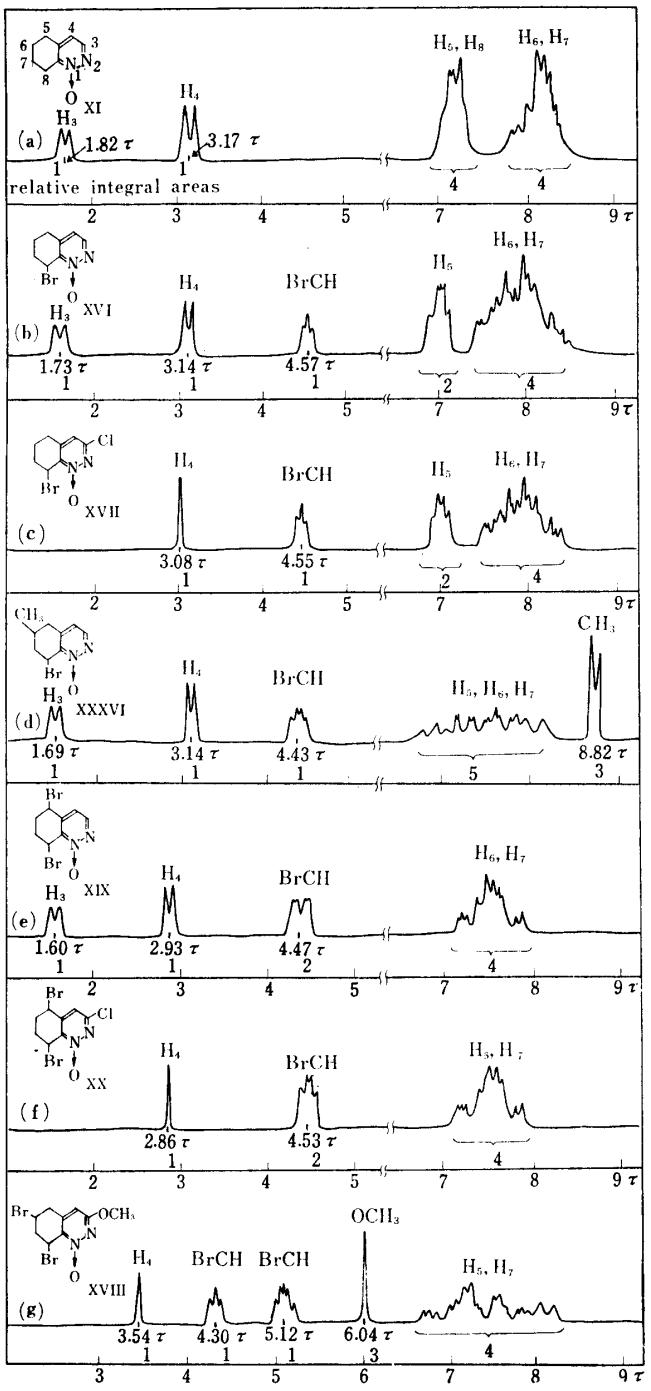
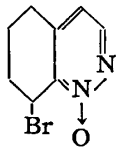
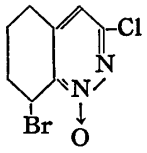


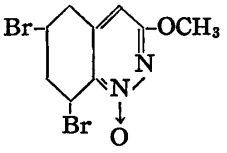
Fig. 1. Nuclear Magnetic Resonance Spectra of 5,6, 7,8-Tetrahydrocinnoline N-Oxides, at 60 Mc.p.s., in deuterochloroform

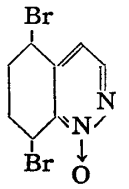
proton on the bromine-bearing carbon atom appears at 4.43 τ as a quartet. If this proton was attached to the C_5-position, the signal pattern would be a doublet. Therefore, the bromine atom in XXXVI should be attached to the C_8-position, Accordingly, the bromine atom in XVI or XVII can be assumed to be located at the C_8-position. The spectrum of XIX or XX [Fig. 1 (e) or (f)] indicates that the relative integral areas of the signals of the C_6- and C_7-protons, those of the C_5- and C_8-protons, and those of the protons on the bromine-bearing carbon atoms (4.53 τ in XIX or 4.47 τ in XX) are in a ratio of 4:0:2. Therefore, the bromine atoms in XIX and XX are attached to the C_5- and C_8-position. In contrast to these cases, the signals of the protons on the bromine-bearing carbon atoms in XVIII are found at 4.30 τ as a triplet and at 5.12 τ as a quintet, as shown in Fig. 1 (g). Accordingly, the bromine atoms in XVIII are attached to either C_5- and C_7-positions or C_6- and C_8-positions. For clarifying this point bromination of 3-methoxy-5-methylpyridazine 1-oxide (XXXVIII) and 3-methoxy-6-methylpyridazine 1-oxide (XXXIX) was carried out in the same method as that for XVIII. The reaction of XXVIII resulted in recovery, whereas treatment of XXXIX gave 3-methoxy-6-bromomethylpyridazine 1-oxide (XL). From these results, the bromine atoms in XVIII may be attached to C_6- and C_8-positions.

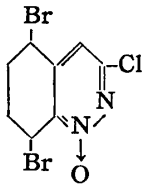
Consequently, the bromo compounds (XVI, XVII, XVIII, XIX, XX, and XXVI) can be assigned the following structures, although the determination of configuration of bromine atoms in these compounds is not possible at the present time.

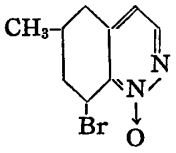

XVI


XVII


XVIII


XIX


XX


XXVI

Nitration of XXI with nitric acid in acetic acid at 45° gave 3-methoxy-mononitrocinnoline 1-oxide (XXIII). The position of nitro group was determined by the following method. On treatment with conc. hydrochloric acid XXIII gave 3-methoxymonochlorocinnoline 1-oxide (XXIV). XIV was converted into 3-methoxy-4-chloro-5,6,7,8-tetrahydrocinnoline 1-oxide (XXVI) by treating with phosphoryl chloride in chloroform. Oxidation of XXVI with perbenzoic acid in chloroform solution gave 3-methoxy-4-chloro-5,6,7,8-tetrahydrocinnoline 1-oxide (XXVII). Bromination of XXVII gave an oily product, which was converted into XXIV in poor yield by treating with sodium methoxide under a condition similar to that case of XXI. Therefore, the nitro group in XXIII is attached to the 4-position. The reaction of XXIII with sodium methoxide in methanol afforded 3,4-dimethoxycinnoline 1-oxide (XXV).

As already mentioned, 4-methylcinnoline (VI) was oxidized to its N-oxides (V) and (VI). Their ultraviolet absorption spectra can serve to determine their structures. As shown in Fig. 2 (a and b) the spectra of V and VI are closely similar to those of II and III, respectively. Therefore, V may be 1-oxide, and VI may be 2-oxide. Further evidence for the determination of the structures of these N-oxides was obtained by their nuclearmagnetic resonance spectra, as discussed later.

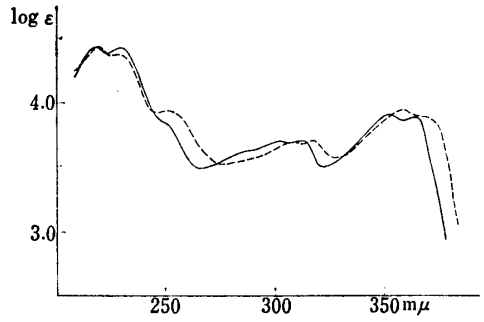


Fig. 2(a). Ultraviolet Absorption Spectra (in EtOH)

—— II ------ V

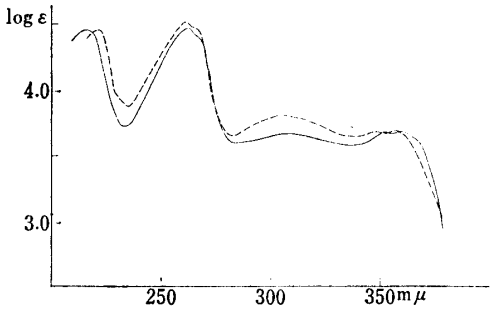


Fig. 2(b). Ultraviolet Absorption Spectra (in EtOH)

—— III ------ VI

Solvent effect on the ultraviolet spectra of II, III, and XXI was also examined by using heptane, 95% ethanol, and water as the solvent. The spectra examined are shown in Fig. 3 (a~c), showing that characteristic blue shift for these N-oxides increases with increasing polarity of solvent. These results are strictly consistent with those obtained from the studies of the other heteroaromatic N-oxides by Kubota, *et al.*[10,11]

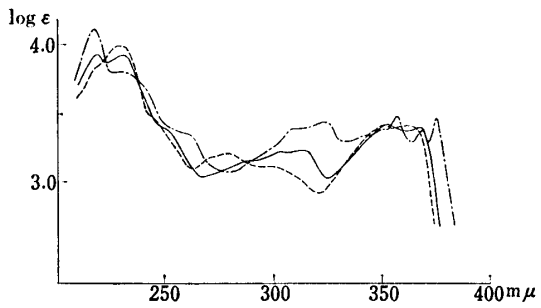


Fig. 3(a). Ultraviolet Absorption Spectra of Cinnoline 1-Oxide (II)

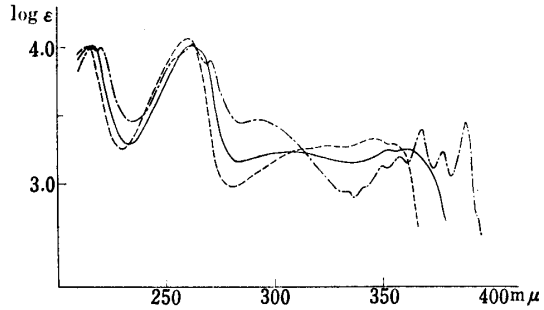
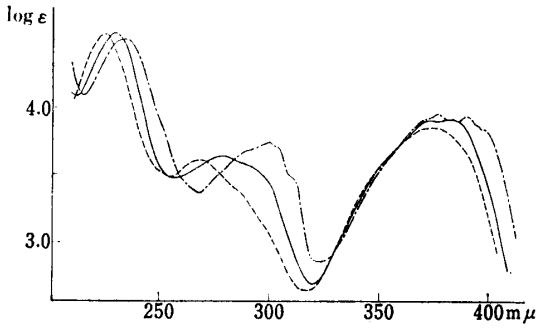


Fig. 3(b). Ultraviolet Absorption Spectra of Cinnoline 2-Oxide (III)



------ Heptane
——— EtOH
---------- H_2O

Fig. 3(c). Ultraviolet Absorption Spectra of 3-Methoxycinnoline 1-Oxide (XXI)

Nuclear Magnetic Resonance Spectra of Cinnoline N-Oxides

In a previous paper of this series,[9] we have reported that the ring proton signals in NMR spectra of pyridazine N-oxides appear in the order, $\tau_{H_3}<\tau_{H_6}<\tau_{H_5}<\tau_{H_4}$, as already quoted. It can be expected from a Hückel MO calculation[12] that the signal of the proton H_6 attached to the carbon atom adjacent to the N-O group (*ortho*-position) appear

10) H. Hirayama, T. Kubota : Yakugaku Zasshi, **72**, 1025 (1952).
11) T. Kubota, H. Miyazaki : This Bulletin, **9**, 948 (1961).
12) T. Kubota, H. Watanabe, : Bull. Chem. Soc. Japan, **36**, 1093 (1963).

at a higher field than do those of the other protons, because there is a quantitative relationship between the chemical shift and local pi-electron distributions in aromatic molecules, as has frequently been reported.[13] Contrary to this expectation, the signal of the proton H_6 appears at a considerably lower field. To explain this fact, we have conjectured the presence of the magnetic anisotropy of the N-O group. The effect of this anisotropy probably includes effects of the electric field produced by the N-O group and of the lone-pair electrons on the oxygen atoms. We consider that this anisotropy effect is similar to that observed for a carbonyl group[14] or for an nitro group.[15] This consideration has also been suggested by Baldeschwieler and Randall[16] in connection with the NMR study of pyridine N-oxides by Katritzky and Lagowski.[17] Therefore, it is reasonable to assume that the proton at a *peri*-position to the N-O group of cinnoline N-oxides also shows its signal peak at a lower field than other signals, owing to this anisotropy of the N-O group. In fact, the proton H_8 at the *peri*-position to the N-O group in quinoline 1-oxide derivatives shows its signal at a considerably lower field than the expected position.[18]

Table I. Nuclear Magnetic Resonance Parameters of Cinnoline N-Oxides

Compound	τ_{H_3}	τ_{H_4}	τ_{H_8}	τ_{OCH_3}	τ_{CH_3}	$J_{3,4}$	$J_{4,8}$
Cinnoline 1-oxide (II)	1.67	2.50	1.33	—	—	6.2	0.9
4-Methylcinnoline 1-oxide (V)	1.87	—	1.35	—	7.42	1.0	—
3-Chlorocinnoline 1-oxide (VIII)	—	2.48	1.48	—	—	—	0.9
3-Methoxycinnoline 1-oxide (XXI)	—	3.08	1.52	5.93	—	—	1.0
3-Methoxy-4-chlorocinnoline 1-oxide (XXIV)	—	—	1.52	5.82	—	—	—
Cinnoline 2-oxide (III)	1.79	1.94	—	—	—	7.0	—
4-Methylcinnoline 2-oxide (VI)	1.90	—	—	—	7.37	1.0	—

Fig. 4 shows the spectra of the cinnoline N-oxides examined. As shown in Fig. 4 (a and c), the spectra of II exhibits three characteristic signal peaks at about 1.33 τ as a multiplet, at 1.67 τ as a doublet and at 2.50 τ as a slightly doubling doublet, whereas the spectra of VIII shows two characteristic signal peaks at 1.48 τ as a multiplet and at 2.48 τ at a slightly doubling singlet. Since substitution of a chlorine or methyl group in an aromatic system produces a little effect on the position of ring proton signals,[9,19] the doublet signal at 1.67 τ (disappears in the spectrum of VIII) can be assigned to the proton H_3. In the spectrum of XXI, two characteristic signals are found at about 1.52 τ as a multiplet and at 3.08 τ as a slightly doubling singlet [see, Fig. 4 (d)], whereas in the spectrum of XXIV, only one characteristic signal peak appears at about 1.52 τ as a multiplet. Therefore, the signal at 3.08 τ can be assigned to the proton H_4 in XXI, and accordingly, the signals at 2.48 τ in VIII and at 2.50 τ in II are due to the protons H_4. Introduction of a methoxyl group into an aromatic ring results in large up-field shifts of the signals of ring protons, as has already been noted.[9,19] The remaining characteristic multiplet signal at a lower field in these compounds is believed to be due to the proton H_8, because the proton H_8 in quinoline 1-oxide series shows its signal around 1.2~1.4 τ owing to the anisotropic effect of the N-O group, as explained above.

13) For example, see, H. Spiesecke, W.G. Schneider: Tetrahedron Letters, No. 14, 468 (1961); T. Schaefer, W.G. Schneider: Can. J. Chem., **41**, 966 (1963).
14) L.M. Jackman: "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 121 (1959), Pergamon Press, New York, N.Y.
15) A.C. Huitric, W.F. Trager: J. Org. Chem., **27**, 1926 (1962); I. Yamaguchi, Mol. Phys., **6**, 105 (1963).
16) J.D. Baldeschwieler, E.W. Randall: Proc. Chem. Soc., **1961**, 303.
17) A.R. Katritzky, J.M. Lagowski: J. Chem. Soc., **1961**, 43.
18) K. Tori, M. Ogata, H. Kano: to be published; refer to K. Tori, M. Ogata, H. Kano: This Bulletin, **11**, 681 (1963).
19) For example, see, J.A. Pople, W.G. Schneider, H.J. Bernstein: "High-resolution Nuclear Magnetic Resonance," 259 (1959), McGraw-Hill Book Co., Inc., New York, N.Y.

On the other hand, in the spectrum of III [Fig. 4 (f)], an AB type quartet appears at a lower field, which can be assigned to the protons H_3 and H_4. The high field part of this quartet is slightly coupled to another proton. This signal at 1.94 τ is due to the proton H_4, as quoted later, and accordingly, another signal at 1.79 τ is the proton H_3.

The structure determination of V and VI can be made by investigating their nuclear magnetic resonance spectra. As shown in Fig. 4 (b), in the spectrum of V, a signal characteristic of the proton H_8 appears at about 1.35 τ. The proton H_3 in V and VI shows its signal as a clear quartet due to the coupling with the methyl group at 1.87 τ and at 1.90 τ, respectively. Therefore, V is cinnoline 1-oxide, and hence, VI is 2-oxide. This result is quite consistent with that obtained from the ultraviolet absorption spectra.

Nuclear magnetic resonance spectral parameters obtained are listed in Table I.

The magnitude of the magnetic anisotropy effect of the N-O group on the proton at a *peri*-position is discussed in our another paper.[18]

Long-range spin coupling between protons of different ring in an aromatic compound has been found in the case of the coupling between H_4 and H_8 of quinoline derivatives,[20] and between H_3 and H_7 of indene and benzofuran derivatives.[21] As can be seen from Fig. 4 (a, c, d, and e), the signal due to the proton H_4 is split to a slightly doubling doublet by an additional coupling. This doubling is probably due to the coupling between the protons H_4 and H_3. All the $J_{4,3}$ values obtained are about 1.0 c.p.s. and are similar to that of the quinoline derivatives.[20]

Analysis of the N-oxidation products from I and from IV was carried out by using NMR spectroscopy. The measurement of the signal integral areas due to the proton H_8 in II and due to the proton H_4 in III leads to the conclusion that the product

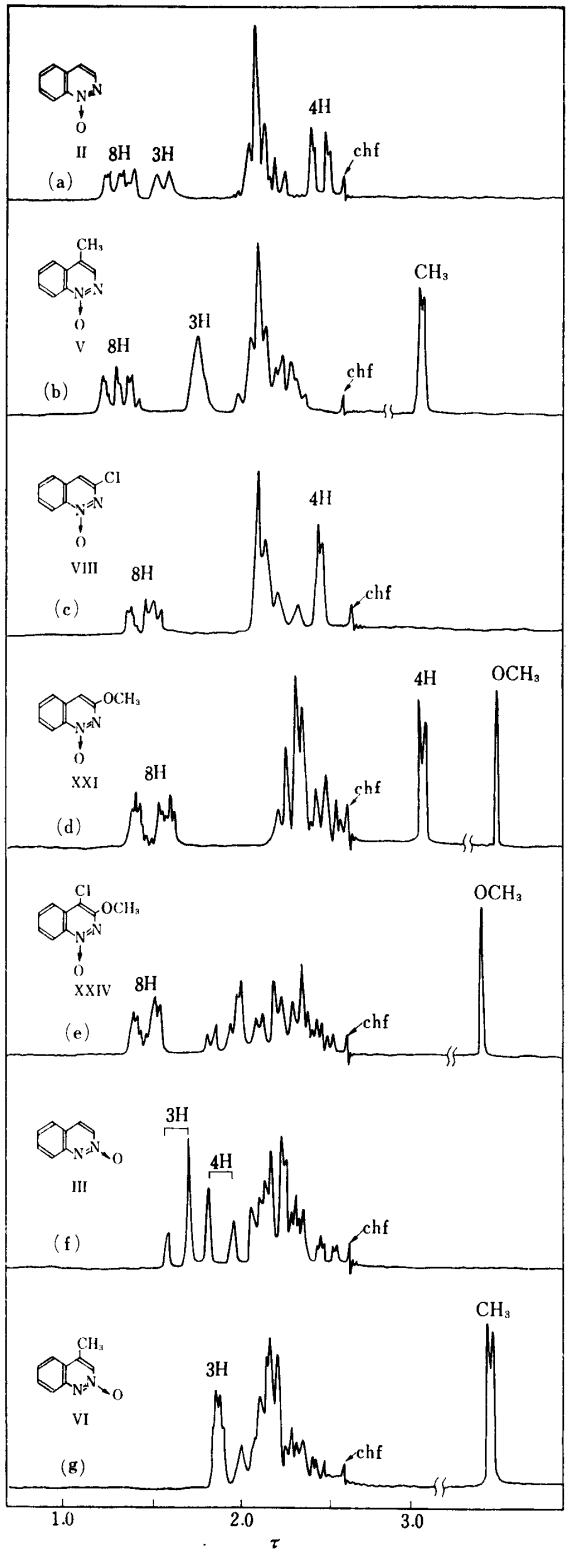


Fig. 4. Nuclear Magnetic Resonance Spectra of Cinnoline N-Oxides, at 60 Mc.p.s., in 10% Solution in Deuterochloroform

20) F. A. L. Anet : J. Chem. Phys., **32**, 1274 (1960).
21) J. A. Elvidge, R. G. Foster : J. Chem. Soc., **1963**, 590.

ratio of II to III is 1:1.4. Similarly, the product ratio of V to VI on N-oxidation of IV is determined to be 1:1.9 by comparing the intensity areas of their methyl signals.

Experimental*4

Cinnoline 1-Oxide (II) and 2-Oxide (III)——A mixture of 2.0 g. of I, 10 ml. of AcOH, and 5 ml. of 30% H_2O_2 was heated at 70° for 3 hr., additional 5 ml. of 30% H_2O_2 was added, and the mixture again heated at the same temperature for 3 hr. To this solution, 10 ml. of H_2O was added and AcOH was evaporated under reduced pressure. This procedure was repeated twice. After neutralization with Na_2CO_3, the solution was extracted with $CHCl_3$ and the $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and evaporated. The residue was dissolved in benzene and chromatographed on alumina, and the column was eluted with benzene. The residue from the fraction eluted with benzene was recrystallized from benzene-petr. benzin to give pale yellow plates (II), m.p. 100~111°. Yield, 430 mg. Repeated recrystallization from benzene-petr. benzin gave nearly colorless plates, m.p. 110.5~111.5°. *Anal.* Calcd. for $C_8H_6ON_2$: C, 65.75; H, 4.14; N, 19.17. Found : C, 66.13; H, 4.23; N, 19.01. The residue from the fractions eluted with $CHCl_3$ was recrystallized from benzene to afford pale yellow plates (III), m.p. 123~126°. Yield, 900 mg. Repeated recrystallization from benzene gave colorless plates, m.p. 125~126°. *Anal.* Calcd. for $C_8H_6ON_2$: C, 65.75; H, 4.14; N, 19.17. Found : C, 65.65; H, 4.14; N, 18.84

4-Methylcinnoline 1-Oxide (V) and 2-Oxide (VI)——A mixture of 2.0 g. of IV, 10 ml. of AcOH, and 5ml. of 30% H_2O_2 was treated in the same way as described above. The residue from the fractions eluted with benzene was recrystallized from benzene-petr. benzin to give pale yellow needles (V), m.p. 93~95°. Yield, 440 mg. Repeated recrystallization from benzene-petr. benzin gave pale yellow needles, m.p. 94~95°. *Anal.* Calcd. for $C_9H_8ON_2$: C, 67.48; H, 5.03; N, 17.49. Found : C, 67.48; H, 5.03; N, 17.21. The residue from the fractions eluted with $CHCl_3$ was recrystallized from benzene to afford pale yellow needles (VI), m.p. 151~152°. Yield, 970 mg. *Anal.* Calcd. for $C_9H_8ON_2$: C, 67.48; H, 5.03; N, 17.49. Found : C, 67.58; H, 5.12; N, 17.25.

3-Chlorocinnoline 1-Oxide (VIII)——i) From VII : A mixture of 140 mg. of VII, 5 ml. of AcOH, and 2 ml. of 30% H_2O_2 was treated in the same way as described above. The residue obtained from $CHCl_3$ extract was recrystallized from benzene to give pale yellow needles, m.p. 158~163°. Yield, 75mg. Repeated recrystallization from benzene gave pale yellow needles, m.p. 168~169°. *Anal.* Calcd. for $C_8H_5ON_2Cl$: C, 53.18; H, 2.77; N, 15.51. Found : C, 52.79; H, 2,83; N, 15.07.

ii) From XX : To a solution of $NaOCH_3$, prepared from 50 mg. of Na and 5 ml. of MeOH, 380 mg. of XX was added and the mixture was refluxed for 1 min. After evaporation of MeOH, the residue was dissolved in H_2O and extracted with $CHCl_3$. The product was chromatographed on alumina. The residue from the fractions eluted with benzene was recrystallized from benzene-cyclohexane to give pale yellow needles, m.p. 168~169°. Yield, 10 mg. This was identified with VIII derived from VII, by comparison of their IR spectra.

5,6,7,8-Tetrahydrocinnoline 1-Oxide (XI) and 2-Oxide (XII)——A mixture of 2.7g. of X, 30 ml. of AcOH, and 15 ml. of 30% H_2O_2 was treated in the same way as described above. The residue obtained from the $CHCl_3$ extract was chromatographed on alumina. The residue from the fractions eluted with benzene was recrystallized from benzene to give colorless needles (XI), m.p. 100~100.5°. Yield, 510 mg. *Anal.* Calcd. for $C_8H_{10}ON_2$: C, 63.98; H, 6.91; N, 18.65. Found : C, 63.94; H, 6.72; N, 18.48. The residue from the fractions eluted with $CHCl_3$ was recrystallized from benzene to give colorless needles (XII), m.p, 127~128°. Yield, 290 mg. *Anal.* Calcd. for $C_8H_{10}ON_2$: C, 63.98; H, 6.91; N, 18.65. Found: C, 63.40; H, 6.61; N, 18.19.

3-Chloro-5,6,7,8-tetrahydrocinnoline 1-Oxide (XIII)——A mixture of 10 g. of IX, 70 ml. of AcOH, and 30 ml. of 30% H_2O_2 was treated in the same way as described above. The residue was recrystallized from benzene-cyclohexane to afford colorless needles, m.p. 125~126°. Yield, 7.07 g. Repeated recrystallization from benzene-cyclohexane gave colorless needles, m.p. 133~134°. *Anal.* Calcd. for $C_8H_9ON_2Cl$: C, 52.33; H, 4.88; N, 15.18. Found : C, 52.28; H, 5.15; N, 15.32.

3-Methoxy-5,6,7,8-tetrahydrocinnoline 1-Oxide (XIV)——To a solution of $NaOCH_3$, prepared from 100 mg. of Na and 10 ml. of MeOH, 500 mg. of XIII was added, and the mixture was refluxed for 1 hr. After evaporation of MeOH, the residue was dissolved in H_2O and extracted with $CHCl_3$. Removal of the solvent left crude crystals, which were recrystallized from benzene-cyclohexane to give colorless needles, m.p. 101~102°. Yield,400 mg. *Anal.* Calcd. for $C_9H_{12}O_2N_2$: C, 59.98; H, 6.71; N, 15.55. Found : C, 60.27; H, 6.74; N, 15.32.

Catalytic Reduction of 3-Chloro-5,6,7,8-tetrahydrocinnoline 1-Oxide (XIII) : Formation of 5,6,7,8-Tetrahydrocinnoline 1-Oxide (XI)——A mixture of 3.5 g. of XIII, 30 ml. of MeOH, 10 ml. of 28% NH_4OH, and 0.5g. of 10% Pd-C was subjected to hydrogenation. After one molar equivalent of H_2 was

*4 Melting points were determined on a Kofler-Block "Monoscope IV" and are uncorrected.

absorbed, the catalyst was filtered and MeOH was evaporated. The residue was dissolved in H_2O, extracted with $CHCl_3$, and $CHCl_3$ was evaporated. The residue was recrystallized from benzene-cyclohexane to afford colorless needles, m.p. 95~97°. Yield, 2.5 g. Repeated recrystallization from benzene gave colorless prisms, m.p. 100~100.5°. This was identified with XI, derived from XIII, by comparison of their IR spectra.

3-Methylthio-5,6,7,8-tetrahydrocinnoline 1-Oxide (XV)——A mixture of 1.65 g. of XV, 5 ml. of abs. MeOH, and 5 ml. of 20% MeSNa-MeOH was refluxed for 30 min. After evaporation of MeOH, the residue was dissolved in H_2O and extracted with $CHCl_3$. Removal of the solvent left crude crystals, which were recrystallized from benzene-cyclohexane to give colorless needles, m.p. 124~125.5°. Yield, 1.2 g. *Anal.* Calcd. for $C_9H_{12}ON_2S$: C, 55.09; H, 6.17; N, 14.28. Found : C, 55.20; H, 6.25; N, 14.18.

5,6,7,8-Tetrahydro-monobromocinnoline 1-Oxide (XVI)——A mixture of 1.2 g. of XI, 2.25 g. of N-bromosuccimide, 200 mg. of Bz_2O_2, and 40 ml. of CCl_4 was refluxed for 15 min. After evaporation of CCl_4, the residue was dissolved in $CHCl_3$ and washed with 10% NaOH. After evaporation of $CHCl_3$, the residue was recrystallized from MeOH to give colorless prisms, m.p. 146~147°. Yield, 650 mg. *Anal.* Calcd. for $C_8H_9ON_2Br$: C, 41.94; H, 3.93; N, 12.24. Found : C, 41.89; H, 4.04; N, 12.44.

3-Chloro-5,6,7,8-tetrahydro-monobromocinnoline 1-Oxide (XVIII)——A mixture of 1.0 g. of XIII, 1.16 g. of N-bromosuccimide, 100mg. of Bz_2O_2, and 15 ml. of CCl_4 was refluxed for 30 min. The reaction mixture was treated in the same way as described above. The residue obtained from the $CHCl_3$ extract was recrystallized from EtOH to give colorless needles, m.p. 93~94°. Yield, 500 mg. *Anal.* Calcd. for $C_8H_8ON_2ClBr$: C, 36.36; H, 3.03; N, 10.60. Found : C, 36.55; H, 3.14; N, 10.09.

5,6,7,8-Tetrahydro-dibromocinnoline 1-Oxide (XIX)——A mixture of 900 mg. of XVI, 900 mg. of N-bromosuccimide, 50 mg. of Bz_2O_2, and 20 ml. of CCl_4 was refluxed for 30 min. The reaction mixture was treated in the same way as described above. The residue obtained from the $CHCl_3$ extract was dissolved in benzene and chromatographed on alumina, the column was eluted with benzene. The residue from the fraction eluted with benzene was recrystallized from EtOH to give colorless needles, m.p. 149~150°. Yield, 400 mg. *Anal.* Calcd. for $C_8H_8ON_2Br_2$: C, 31.36; H, 2.60; N, 9.09. Found : C, 31.54; H, 2.87; N, 9.18.

3-Chloro-5,6,7,8-tetrahydro-dibromocinnoline 1-Oxide (XX)——A mixture of 1.05 g. of XVII, 910 mg. of N-bromosuccimide, 100 mg. of Bz_2O_2, and 20 ml. of CCl_4 was refluxed for 30 min. The reaction mixture was treated in the same way as described above. The residue from the fractions eluted with benzene was recrystallized from EtOH to give colorless prisms, m.p. 137~138°. Yield, 390 mg. *Anal.* Calcd. for $C_8H_7ON_2Br_2Cl$: C, 28.02; H, 2.04; N, 8.17. Found : C, 28.34; H, 2.31, N, 8.41.

3-Methoxy-5,6,7,8-tetrahydro-dibromocinnoline 1-Oxide (XVIII)——A mixture of 750 mg. of XIV, 2.5 g. of N-bromosuccimide, 100 mg. of Bz_2O_2, and 10 ml. of CCl_4 was refluxed for 15 min. The reaction mixture was treated in the same way as described above. The residue from the fraction eluted with benzene was recrystallized from EtOH to give colorless needles, m.p. 146~147°. Yield, 640 mg. Repeated recrystallization from EtOH gave colorless needles, m.p. 151~152°. *Anal.* Calcd. for $C_9H_{10}O_2N_2Br_2$: C, 31.95; H, 2.96; N, 8.28. Found : C, 31.84; H, 3.15; N, 8.06.

Cinnoline 1-Oxide (II)——To a solution of $NaOCH_3$, prepared from 100 mg. of Na and 10 ml. of MeOH, 1.9 g. of XIX was added and the mixture was refluxed for 2 min. The reaction mixture was treated in the same way used for VIII-ii). The residue from the fractions eluted with benzene was recrystallized from benzene-cyclohexane to afford pale yellow plates, m.p. 109~110°. Yield, 45 mg. Repeated recrystallization from benzene-cyclohexane gave nearly colorless plates, m.p. 110.5~111.5°. This was identified with II, derived from I, by comparison of their IR spectra.

3-Methoxycinnoline 1-Oxide (XXI)——To a solution of $NaOCH_3$, prepared from 50 mg. of Na and 2 ml. of MeOH, 150 mg. of XVIII was added, and the mixture was refluxed for 10 min. on a water bath. After evaporation of MeOH, the residue was dissolved in H_2O, and extracted with $CHCl_3$. After evaporation of $CHCl_3$, the residue was recrystallized from benzene-petr. benzin to give yellow needles, m.p. 94~95°. Yield, 50 mg. *Anal.* Calcd. for $C_9H_8O_2N_2$: C, 61.36; H, 4.58; N, 15.90. Found : C, 61.01; H, 4.57; N, 15.52.

3-Methylthiocinnoline 1-Oxide (XXII)——A mixture of 500 mg. of XV, 1.0 g. of N-bromosuccimide, 50 mg. of Bz_2O_2, and 10 ml. of CCl_4 was refluxed for 10 min. The reaction mixture was treated in the same way as that for XIX. The residue from the fractions eluted with benzene was treated with $NaOCH_3$ solution (Na, 50 mg.; MeOH, 5 ml.) as described for VIII-ii). The residue from the fractions eluted with benzene was recrystallized from benzene-petr. benzin to give yellow needles, m.p. 119~120°. Yield, 45 mg. *Anal.* Calcd. for $C_9H_8ON_2S$: C, 56.25; H, 4.20; N, 14.58. Found : C, 56.10; H, 4.37; N, 14.18.

Ethyl 3-Hydroxy-6-methyl-5,6,7,8-tetrahydro-4-cinnolinecarboxylate (XXX)——A solution of 26.2 g. of XXVIII and 40.7 g. of diethyl oxomalonate was heated at 170° for 2.5 hr. After being cooled, the solution was mixed with 100 ml. of EtOH and 15 g. of hydrazine hydrate and the mixture was refluxed for 2.5 hr. After evaporation of EtOH, the residue was added to H_2O and acidified with dil. HCl and the resulting crystals were collected. Recrystallization from H_2O gave colorless needles, m.p. 155~156°. Yield, 10.7 g. *Anal.* Calcd. for $C_{12}H_{16}O_3N_2$: C, 61.00; H, 6.83; N, 11.86. Found : C, 61.13; H, 6.91; N, 12.13.

3-Hydroxy-6-methyl-5,6,7,8-tetrahydro-4-cinnolinecarboxylic Acid (XXXI)——A mixture of 9.5 g. of XXX and 10 ml. of 10% NaOH was heated on a water bath for 30 min. After being cooled, the solution was acidified with dil. HCl. The deposited crystals were collected, and recrystallized from H_2O to give colorless needles, m.p. 174° (decomp.). Yield, 6.74 g. *Anal.* Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.68; H, 5.81; N, 13.46. Found : C, 57.36; H, 5.90; N, 13.24.

6-Methyl-5,6,7,8-tetrahydro-3-cinnolinol (XXXII)——XXXI (6.75 g.) was heated at 180° until the evolution of gas ceased. The product was recrystallized from benzene to give colorless prisms, m.p. 196°. Yield, 4.0 g. *Anal.* Calcd. for $C_9H_{12}ON_2$: C. 65.83; H, 7.37; N, 17.06. Found : C, 65.41; H, 7.11; N, 17.56.

3-Chloro-6-methyl-5,6,7,8-tetrahydrocinnoline (XXXIII)——A mixture of 300 mg. of XXXII and 3 ml. of $POCl_3$ was heated on a water bath for 10 min. $POCl_3$ was evaporated under reduced pressure, and the residual oil was poured onto ice. The solution was neutralized with Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated and the residue was recrystallized from petr. ether to give colorless needles, m.p. 66~67°. Yield, 180 mg. *Anal.* Calcd. for $C_9H_{11}N_2Cl$: C, 59.17; H, 6.03; N, 15.34. Found : C, 58.84; H, 6.10; N, 15.51.

3-Chloro-6-methyl-5,6,7,8-tetrahydrocinnoline 1-Oxide (XXXIV)——A mixture of 2.0 g. of XXXIII, 15 ml. of AcOH, and 7 ml. of 30% H_2O_2 was treated in the same way as that for XIII. The residue obtained from the $CHCl_3$ extract was recrystallized from benzene-cyclohexane to afford colorless needles, m.p. 122~128°. Yield, 1.7 g. Repeated recrystallization from benzene-cyclohexane gave colorless needles, m.p. 133~135.5°. *Anal.* Calcd. for $C_9H_{11}ON_2Cl$: C, 54.41; H, 5.54; N, 14.10. Found : C, 54.72; H, 5.70; N, 14.57.

6-Methyl-5,6,7,8-tetrahydrocinnoline 1-Oxide (XXXV)——A mixture of 1.45 g. of XXXIV, 20 ml. of MeOH, 28% NH_4OH, and 0.5 g. of 10% Pd-C was subjected to hydrogenation. When the reaction mixture was treated as described for XI, 700 mg. of XXXV as colorless needles, m.p. 120~122° was obtained. *Anal.* Calcd. for $C_9H_{12}ON_2$: C, 65.83; H, 7.37; N, 17.06. Fonnd : C, 66.12; H, 7.42; N, 17.25.

6-Methyl-5,6,7,8-tetrahydro-monobromocinnoline 1-Oxide (XXXVI)——A mixture of 500 mg. of XXXV, 700 mg. of N-bromosuccimide, 50 mg. of Bz_2O_2, and 5 ml. of CCl_4 was treated in the same way used for XVI. 50 mg, of XXXVI was obtained as colorless prisms, m.p. 144~145°. *Anal.* Calcd. for $C_9H_{11}ON_2Br$: C, 44.44; H, 4.52; N, 11.52. Found : C, 44.56; H, 4.72; N, 11.60.

3-Methoxy-6-methyl-5,6,7,8-tetrahydrocinnoline 1-Oxide (XXXVII)——To a solution of $NaOCH_3$, prepared from 500 mg. of Na, and 20 ml. of MeOH, 1.7 g. of XXXIV was added and the mixture was treated in the same way used for XIV. 1.1 g. of XXXVII was obtained as colorless plates, m.p. 168~169°. *Anal.* Calcd. for $C_{10}H_{14}O_2N_2$: C, 61.83; H, 7.27; N, 14.42. Found : C, 61.84; H, 7.37; N, 14.34.

3-Methoxy-6-bromomethylpyridazine 1-Oxide (XL)——A mixture of 500 mg. of XXXIX, 780 mg. of N-bromosuccimide, 50 mg. of Bz_2O_2, and 6 ml. of CCl_4 was refluxed for 30 min. The reaction mixture was treated in the same way as that for XVI. The residue obtained from the $CHCl_3$ extract was recrystallized from benzene to give colorless scales, m.p. 133~134°. Yield, 110 mg. *Anal.* Calcd. for $C_6H_7O_2N_2Br$: C, 32.87; H, 3.20; N, 12.79. Found : C, 33.54; H, 3.43; N, 12.72.

3-Methoxy-4-nitrocinnoline 1-Oxide (XXIII)——To a solution of 200 mg. of XXI dissolved in 8 ml. of AcOH, 2 ml. of conc. HNO_3 was added with stirring at room temperature and the mixture was poured into ice water, extracted with $CHCl_3$, and $CHCl_3$ was evaporated. The residue was recrystallized from EtOH to give yellow needles, m.p. 154~155°. Yield, 145 mg. *Anal.* Calcd. for $C_9H_7O_4N_3$: C, 48.87; H, 3.19; N, 19.00. Found : C, 48.47; H, 3.27; N, 18.71.

3-Methoxy-4-chlorocinnoline 1-Oxide (XXIV)——i) From XXIII : XXIII (70 mg.) was added to 1 ml. of conc. HCl, and the mixture was heated on a boiling water bath for 1 hr. The reaction mixture was poured into ice water, extracted with $CHCl_3$, and $CHCl_3$ was distilled off. The residue was recrystallized from EtOH to give pale yellow needles, m.p. 170°. Yield, 55 mg. *Anal.* Calcd. for $C_9H_7O_2N_2Cl$: C, 51.18; H, 3.33; N, 13.31. Found : C, 51.22; H, 3.39; N, 13.01.

ii) From XXVII : A mixture of 0.3 g. of XXVII, 0.55 g. of N-bromosuccimide, 50 mg. of Bz_2O_2, and 5 ml. of CCl_4 was refluxed for 15 min. The reaction mixture was treated in the same way used for XIX. The residue from the fraction eluted with benzene was treated with $NaOCH_3$ solution (Na, 30 mg.; MeOH, 3 ml.) in the same way as that for VIII-ii). The residue from the fraction eluted with benzene was recrystallized from benzene-cyclohexane to give yellow needles, m.p. 165~169°. Repeated recrystallization from EtOH gave yellow needles, m.p. 169~170°. Yield, 5 mg. This was shown to be identical with XXIV derived from XXIII, by comparison of their IR spectra.

3-Methoxy-4-chloro-5,6,7,8-tetrahydrocinnoline (XXVI)——To a cold solution of 1.2 g. of XIV dissolved in 15 ml. of $CHCl_3$, 2.5 g. of $POCl_3$ was added and the mixture refluxed for 20 min. The solvent was removed under reduced pressure. The residue was neutralized with Na_2CO_3 while cooling, and extracted with $CHCl_3$. $CHCl_3$ was evaporated and the residue was recrystallized from petr. ether to yield 840 mg. of colorless needles, m.p. 105~107°. Repeated recrystallization from petr. ether gave colorless needles, m.p. 108~109°. *Anal.* Calcd. for $C_9H_{11}ON_2Cl$: C, 54.41; H, 5.54; N, 14.11. Found: C, 54.52; H, 5.64; N, 13.70.

3-Methoxy-4-chloro-5,6,7,8-tetrahydrocinnoline 1-Oxide (XXVII)——A mixture of 950 mg. of XXVI,

2 ml. of 30% H_2O_2, and 4 ml. of AcOH was treated in the same way as that for XIII. The residue obtained from the $CHCl_3$ extract was recrystallized from benzene-cyclohexane to colorless needles, m.p. 117~122°. Yield, 490 mg. Repeated recrysallization from cyclohexane gave colorless needles, m.p. 132~133°. *Anal.* Calcd. for $C_9H_{11}O_2N_2Cl$: C, 50.35; H, 5.13; N, 13.05. Found : C, 50.08; H, 5.31; N, 12.89.

3,4-Dimethoxycinnoline 1-Oxide (XXV)——To a solution of $NaOCH_3$, prepared from 20 mg. of Na and 1 ml. of MeOH, 70 mg. of XXIII was added and the mixture was refluxed for 30 min. After evaporation of MeOH, the residue was dissolved in H_2O, extracted with $CHCl_3$, and $CHCl_3$ was evaporated. The residue was recrystallized from benzene-cyclohexane to give yellow prisms, m.p. 116~117°. Yield, 35 mg. *Anal.* Calcd. for $C_{10}H_{10}O_3N_2$: C, 58.25; H, 4.89; N, 13.58. Found : C, 58.10; H, 4.94; N, 13.46.

All the NMR spectra were taken with a Varian A-60 analytical NMR spectrometer system on 10% (w/v) solution in deuterochloroform containing about 1% tetramethylsilane as an internal reference. The chemical shifts are expressed on τ-units and coupling constants are in c.p.s. Accuracy limits are about $\pm 0.02\tau$ in chemical shift and about ± 0.3 c.p.s. in coupling constant.

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Summary

Cinnoline 1-oxide (II), cinnoline 2-oxide (III), 4-methylcinnoline 1-oxide (V), 4-methylcinnoline 2-oxide (VI), 3-chlorocinnoline 1-oxide (VIII), and 3-methoxycinnoline 1-oxide (XXI) were synthesized. For confirmation of the structure of these compounds, cinnoline 1-oxide (II) and 3-chlorocinnoline 1-oxide (VIII) were prepared from their corresponding 5,6,7,8-tetrahydro derivatives (XI and XIII) by bromination with N-bromosuccimide followed by dehydrobromination with sodium methoxide. The structures of isomeric 4-methylcinnoline N-oxides were determined by the application of ultraviolet and nuclear magnetic resonance spectroscopies.

The nuclear magnetic resonance spectra of the cinnoline N-oxides synthesized were examined. The interpretation of the spectra was made in connection with those of pyridazine N-oxides and of quinoline N-oxides. The proton H_8 shows its signal peak at a lower field than do the other protons, owing to the magnetic anisotropy effect of the N-O group.

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