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% NH₄OH 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 needles, 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 XII dissolved in 10 ml. of CHCl₃, 1.0 g. of POCl₃ was added, the mixture refluxed for 2 hr. The solvent was removed in vacuo. The residue was neutralized with Na₂CO₃, and extracted with CHCl₃. CHCl₃ 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.

The author expresses his gratitude to Prof. Emeritus E. Ochiai of the University of Tokyo, Dr. K. Takeda, Director of this laboratory, and to Dr. H. Kano of this laboratory, for their helpful guidances and encouragements. He also thanks Dr. T. Itai of National Institute of Hygienic Sciences for providing the valuable suggestion. Thanks are also to Dr. H. Watanabe, Dr. T. Yoshizaki, Dr. Y. Matsui, and Mr. M. Takanaka for dipole moment and infrared spectral measurements, and to the members of the Analysis Room of this laboratory for elemental analysis.

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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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.6 Study of cinnolnine N-oxides, however, has been limited to synthesis of 4-arylcinolnine N-oxides,9 and the position of their N-O groups has not been determined.

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

Cinnolnine (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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*2 Preliminary reports of this work were published as "Communication to the Editor" in this Bulletin, 10, 1123 (1962); 11, 681 (1963).
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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)\(^9\) and 5,6,7,8-tetrahydrocinnoline (X)\(^9\) 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 (XII) as a sole product. Catalytic hydrogenation of XII 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 XII 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\(^7\) gave the corresponding 1-oxides. Therefore, XII 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\(^8\) have shown that the signal of the ring protons of methylpyridazine N-oxides appears in the order, \(\tau_{\text{HIg}} < \tau_{\text{HIg}} < \tau_{\text{Hg}} < \tau_{\text{Hg}}\). This order is believed to be retained in the other alkyl derivatives. Therefore, the signal peaks at 1.82 \(\tau\) and 3.17 \(\tau\) in XI can be

\[H(3.17 \tau)\]

\[H(1.82 \tau)\]

\[H(2.84 \tau)\]

\[H(2.19 \tau)\]

---

assigned to the proton H₂ and H₄, respectively. Similarly, the signal of the proton H₄ and H₆ in III appears at 2.19 τ and 2.84 τ, respectively. From these facts, XI and XIV are considered as the 1-oxide and XIII is as the 2-oxide.

Bromination of XI and XIII with N-bromosuccinimide in carbon tetrachloride gave only their monobromo derivatives (XVI and XVII), respectively, even though an excess of N-bromosuccinimide was used. Further, XVI and XVII were brominated with N-bromosuccinimide in carbon tetrachloride to their dibromo derivatives (XIX and XX). Bromination of XIV with N-bromosuccinimide in carbon tetrachloride gave its dibromo derivative (XVIII), even though equimolar amount of N-bromosuccinimide 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 XIX can be decided to be cinnoline 2-oxide. By the same treatment used for XVII, 3-methoxyxocinnoline 1-oxide (XXI) was prepared in good yield. Bromination of XV with N-bromosuccinimide in carbon tetrachloride gave an oily product, which was converted into 3-methylthiocinnoline 1-oxide (XXXII) 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 (XVIII) and diethyl oxomalonate afforded an addition product (XXX). Treating of XXX with hydrazine hydrate in ethanol gave ethyl 3-hydroxy-6-methyl-5,6,7,8-tetrahydro-4-cinnoline carboxylate (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 XXXII 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.

![Chemical Diagram](image-url)
As shown in Fig. 1 (a), the NMR spectrum of XI exhibits that the signals of the C₆- and C₇-methylene protons appear at higher fields than those of the C₅- and C₄-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 C₄- or C₅-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-Tetrahydrocinnamine N-Oxides, at 60 Mc.p.s., in deuterochloroform
proton on the bromine-bearing carbon atom appears at 4.43 ppm as a quartet. If this proton was attached to the C3-position, the signal pattern would be a doublet. Therefore, the bromine atom in XXXVI should be attached to the C4-position. Accordingly, the bromine atom in XVI or XVII can be assumed to be located at the C4-position. The spectrum of XIX or XV [Fig. 1 (e) or (f)] indicates that the relative integral areas of the signals of the C4- and C7-protons, those of the C2- and C4-protons, and those of the protons on the bromine-bearing carbon atoms (4.53 ppm in XIX or 4.47 ppm in XV) are in a ratio of 4:0:2. Therefore, the bromine atoms in XIX and XV are attached to the C4- and C6-positions. In contrast to these cases, the signals of the protons on the bromine-bearing carbon atoms in XVII are found at 4.30 ppm as a triplet and at 5.12 ppm as a quintet, as shown in Fig. 1 (g). Accordingly, the bromine atoms in XVII are attached to either C6- and C7-positions or C6- and C4-positions. For clarifying this point bromination of 3-methoxy-5-methylpyridazine 1-oxide (XVIII) and 3-methoxy-6-methylpyridazine 1-oxide (XXIX) was carried out in the same method as that for XV. The reaction of XVIII resulted in recovery, whereas treatment of XXIX gave 3-methoxy-6-bromomethylpyridazine 1-oxide (XL). From these results, the bromine atoms in XVII may be attached to C6- and C4-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.

\[ \text{XXVI} \]
\[ \text{XVII} \]
\[ \text{XVIII} \]
\[ \text{XIX} \]
\[ \text{XX} \]

Nitration of XXI with nitric acid in acetic acid at 45° gave 3-methoxy–mononitrocinnoline 1-oxide (XXII). The position of nitro group was determined by the following method. On treatment with conc. hydrochloric acid XXI 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 (XXVIII). Bromination of XXVII gave an oily product, which was converted into XXVII in poor yield by treating with sodium methoxide under a condition similar to that case of XXI. Therefore, the nitro group in XXII is attached to the 4-position. The reaction of XXII with sodium methoxide in methanol afforded 3,4-dimethoxycinnoline 1-oxide (XXIV).

As already mentioned, 4-methylcinnoline (VI) was oxidized to its N-oxides (V) and (VII). 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 nuclear magnetic resonance spectra, as discussed later.
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)

**Nuclear Magnetic Resonance Spectra of Cinnoline N-Oxides**

In a previous paper of this series,10 we have reported that the ring proton signals in NMR spectra of pyridazine N-oxides appear in the order, $\tau_{H_3} < \tau_{H_4} < \tau_{H_5} < \tau_{H_6}$ as already quoted. It can be expected from a Hückel MO calculation12 that the signal of the proton $H_6$ attached to the carbon atom adjacent to the N-O group (ortho-position) appear

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.\textsuperscript{13} Contrary to this expectation, the signal of the proton $H_4$ 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\textsuperscript{14} or for a nitro group.\textsuperscript{15} This consideration has also been suggested by Baldeschwieler and Randall\textsuperscript{16} in connection with the NMR study of pyridine N-oxides by Katritzky and Lagowski.\textsuperscript{17} Therefore, it is reasonable to assume that the proton at a periphery-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 $H_4$ at the periphery-position to the N-O group in quinoline 1-oxide derivatives shows its signal at a considerably lower field than the expected position.\textsuperscript{18}

**Table I. Nuclear Magnetic Resonance Parameters of Cinnoline N-oxides**

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\tau_{H_2}$</th>
<th>$\tau_{H_4}$</th>
<th>$\tau_{H_6}$</th>
<th>$\tau_{OCH_3}$</th>
<th>$\tau_{CH_2}$</th>
<th>$J_{H_4}$</th>
<th>$J_{H_5}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinnoline 1-oxide (II)</td>
<td>1.67</td>
<td>2.50</td>
<td>1.33</td>
<td>—</td>
<td>6.2</td>
<td>6.2</td>
<td>0.9</td>
</tr>
<tr>
<td>4-Methylcinnoline 1-oxide (V)</td>
<td>1.87</td>
<td>—</td>
<td>1.35</td>
<td>—</td>
<td>7.42</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>3-Chlorocinnoline 1-oxide (VI)</td>
<td>—</td>
<td>2.48</td>
<td>1.48</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3-Methoxycinnoline 1-oxide (XXI)</td>
<td>—</td>
<td>3.08</td>
<td>1.52</td>
<td>5.93</td>
<td>—</td>
<td>—</td>
<td>0.9</td>
</tr>
<tr>
<td>3-Methoxy-4-chlorocinnoline 1-oxide (XXIV)</td>
<td>—</td>
<td>—</td>
<td>1.52</td>
<td>5.82</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
</tr>
<tr>
<td>Cinnoline 2-oxide (III)</td>
<td>1.79</td>
<td>1.94</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>7.0</td>
<td>—</td>
</tr>
<tr>
<td>4-Methylcinnoline 2-oxide (VI)</td>
<td>1.90</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>7.37</td>
<td>1.0</td>
<td>—</td>
</tr>
</tbody>
</table>

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 $\tau$ as a multiplet, at 1.67 $\tau$ as a doublet and at 2.50 $\tau$ as a slightly doubling doublet, whereas the spectra of III shows two characteristic signal peaks at 1.48 $\tau$ as a multiplet and at 2.48 $\tau$ 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,\textsuperscript{8,19} the doublet signal at 1.67 $\tau$ (disappears in the spectrum of II) can be assigned to the proton $H_4$. In the spectrum of XXII, two characteristic signals are found at about 1.52 $\tau$ as a multiplet and at 3.08 $\tau$ 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 $\tau$ as a multiplet. Therefore, the signal at 3.08 $\tau$ can be assigned to the proton $H_4$ in XXI, and accordingly, the signals at 2.48 $\tau$ in II and at 2.50 $\tau$ in III 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.\textsuperscript{8,19} The remaining characteristic multiplet signal at a lower field in these compounds is believed to be due to the proton $H_4$ because the proton $H_4$ in quinoline 1-oxide series shows its signal around 1.2~1.4 $\tau$ owing to the anisotropic effect of the N-O group, as explained above.


\textsuperscript{18} K. Tori, M. Ogata, H. Kano: to be published; refer to K. Tori, M. Ogata, H. Kano: This Bulletin, 11, 681 (1963).

\textsuperscript{19} For example, see, J.A. Pople, W.G. Schneider, H.J. Bernstein: "High-resolution Nuclear Magnetic Resonance," 239 (1960), 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 H₄ and H₅. The high field part of this quartet is slightly coupled to another proton. This signal at 1.94 τ is due to the proton H₅, as quoted later, and accordingly, another signal at 1.79 τ is the proton H₄.

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 H₃ appears at about 1.35 τ. The proton H₃ 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. ²⁰

Long-range spin coupling between protons of different ring in an aromatic compound has been found in the case of the coupling between H₄ and H₅ of quinoline derivatives, ²¹ and between H₁ and H₇ of indene and benzofuran derivatives. ²¹ As can be seen from Fig. 4 (a, c, d, and e), the signal due to the proton H₄ is split to a slightly doubling doublet by an additional coupling. This doubling is probably due to the coupling between the protons H₄ and H₅. All the J₄₅ 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 H₄ in II and due to the proton H₄ in III leads to the conclusion that the product

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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**

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% H₂O₂ was heated at 70° for 3 hr., additional 5 ml. of 30% H₂O₂ was added, and the mixture again heated at the same temperature for 3 hr. To this solution, 10 ml. of H₂O was added and AcOH was evaporated under reduced pressure. This procedure was repeated twice. After neutralization with Na₂CO₃, the solution was extracted with CHCl₃ and the CHCl₃ layer was dried over anhyd. Na₂SO₄, 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. benz in to give pale yellow plates (II), m.p. 100~111°. Yield, 430 mg. Repeated recrystallization from benzene-petr. benz in gave nearly colorless plates, m.p. 110.5~111.5°. **Anal.** Calcd. for C₁₅H₁₅N₃O₂: 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 CHCl₃ was recrystallized from benzene to afford pale yellow plates (III), m.p. 123~125°. Yield, 900 mg. Repeated recrystallization from benzene gave colorless plates, m.p. 125~126°. **Anal.** Calcd. for C₁₇H₁₇N₃O₂: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.65; H, 4.14; N, 18.84

4-Methyleniminone 1-Oxide (V) and 2-Oxide (VI)—A mixture of 2.0 g. of IV, 10 ml. of AcOH, and 5 ml. of 30% H₂O₂ was treated in the same way as described above. The residue from the fractions eluted with benzene was recrystallized from benzene-petr. benz in to give pale yellow needles (V), m.p. 93~95°. Yield, 440 mg. Repeated recrystallization from benzene-petr. benz in gave pale yellow needles, m.p. 94~95°. **Anal.** Calcd. for C₁₅H₁₅N₃O₂: 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 CHCl₃ was recrystallized from benzene to afford pale yellow needles (VI), m.p. 151~152°. Yield, 970 mg. **Anal.** Calcd. for C₁₇H₁₇N₃O₂: 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 VIII, 5 ml. of AcOH, and 2 ml. of 30% H₂O₂ was treated in the same way as described above. The residue obtained from CHCl₃ 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 C₁₅H₁₃N₃O₂Cl: 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 NaOCH₃, 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 H₂O and extracted with CHCl₃. 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 VIII, by comparison of their IR spectra.

5,6,7,8-Tetrahydrocinnoline 1-Oxide (XI) and 2-Oxide (XII)—A mixture of 2.7 g. of X, 30 ml. of AcOH, and 15 ml. of 30% H₂O₂ was treated in the same way as described above. The residue obtained from the CHCl₃ 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 C₁₅H₁₅N₃O₂: 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 CHCl₃ was recrystallized from benzene to give colorless needles (XII), m.p. 127~128°. Yield, 290 mg. **Anal.** Calcd. for C₁₅H₁₅N₃O₂: 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% H₂O₂ 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 C₁₆H₁₇N₃O₂Cl: 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 NaOCH₃, 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 H₂O and extracted with CHCl₃. 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 C₁₅H₁₆N₃O₂: 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% NH₄OH, and 0.5g. of 10% Pd-C was subjected to hydrogenation. After one molar equivalent of H₂ was

**Melting points were determined on a Kofer-Block "Monoscope IV" and are uncorrected.**
absorbed, the catalyst was filtered and MeOH was evaporated. The residue was dissolved in H₂O, extracted with CHCl₃, and CHCl₃ 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 X₄ derived from X₁, by comparison of their IR spectra.

3-Methylthio-5,6,7,8-tetrahydrocinoline 1-Oxide (XV) — A mixture of 1.65 g. of X₁, 5 ml. of abs. MeOH, and 5 ml. of 20% MeSnMe—MeOH was refluxed for 30 min. After evaporation of MeOH, the residue was dissolved in H₂O and extracted with CHCl₃. 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 C₅H₇ON₄S: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.20; H, 6.25; N, 14.18.

5,6,7,8-Tetrahydro-monobromocinoline 1-Oxide (XVI) — A mixture of 1.2 g. of X₁, 2.25 g. of N-bromosuccinimide, 200 mg. of Bz₂O₂, and 40 ml. of CC₁₄ was refluxed for 15 min. After evaporation of CC₁₄, the residue was dissolved in MeOH to give colorless prisms, m.p. 146°–147°. Yield, 650 mg. Anal. Calcd. for C₄H₇ON₃Br: 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-monobromocinoline 1-Oxide (XVIII) — A mixture of 1.0 g. of X₁, 1.16 g. of N-bromosuccinimide, 100 mg. of Bz₂O₂, and 15 ml. of CC₁₄ was refluxed for 30 min. The reaction mixture was treated in the same way as described above. The residue obtained from the CHCl₃ extract was recrystallized from EtOH to give colorless needles, m.p. 93°–94°. Yield, 500 mg. Anal. Calcd. for C₅H₇ON₃ClBr: C, 36.36; H, 3.05; N, 10.60. Found: C, 36.55; H, 3.14; N, 10.09.

5,6,7,8-Tetrahydro-dibromocinoline 1-Oxide (XIX) — A mixture of 900 mg. of X₁, 200 mg. of N-bromosuccinimide, 50 mg. of Bz₂O₂, and 20 ml. of CC₁₄ was refluxed for 30 min. The reaction mixture was treated in the same way as described above. The residue obtained from the CHCl₃ 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 C₄H₇ON₃Br₂: 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-dibromocinoline 1-Oxide (XX) — A mixture of 1.05 g. of X₁, 910 mg. of N-bromosuccinimide, 100 mg. of Bz₂O₂, and 20 ml. of CC₁₄ 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 C₅H₇ON₃Br₂Cl: 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-dibromocinoline 1-Oxide (XVIII) — A mixture of 750 mg. of X₁, 2.5 g. of N-bromosuccinimide, 100 mg. of Bz₂O₂, and 10 ml. of CC₁₄ 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 C₅H₇O₃NBr₂: 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 NaOCH₃ prepared from 100 mg. of Na and 10 ml. of MeOH, 1.9 g. of X₁ was added and the mixture was refluxed for 2 min. The reaction mixture was treated in the same way used for X–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 NaOCH₃ prepared from 50 mg. of Na and 2 ml. of MeOH, 150 mg. of X₇₈ was added, and the mixture was refluxed for 10 min. on a water bath. After evaporation of MeOH, the residue was dissolved in H₂O, and extracted with CHCl₃. After evaporation of CHCl₃, the residue was recrystallized from benzene-petr. benzoin to give yellow needles, m.p. 94°–95°. Yield, 50 mg. Anal. Calcd. for C₅H₇O₃N₂: 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 X₁, 1.0 g. of N-bromosuccinimide, 50 mg. of Bz₂O₂, and 10 ml. of CC₁₄ 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 NaOCH₃ solution (Na, 50 mg.; MeOH, 5 ml.) as described for VII–II. The residue from the fractions eluted with benzene was recrystallized from benzene-petr. benzoin to give yellow needles, m.p. 119°–120°. Yield, 45 mg. Anal. Calcd. for C₅H₇O₃N₂: 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 X₇₈ and 40.7 g. of diethyl oxalomalonate 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 H₂O and acidified with dil. HCl and the resulting crystals were collected. Recrystallization from H₂O gave colorless needles, m.p. 155°–156°. Yield, 10.7 g. Anal. Calcd. for C₁₃H₁₈O₃N₂: 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-cinnolinocarboxylic 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 H2O to give colorless needles, m.p. 174°(decomp.). Yield, 6.74 g. \( \text{Anal. Calcd. for C}_{13}\text{H}_{18}\text{O}_{4}\text{N}: 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)—(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. \( \text{Anal. Calcd. for C}_{13}\text{H}_{18}\text{O}_{4}\text{N}: 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 POCl3 was heated on a water bath for 10 min. POCl3 was evaporated under reduced pressure, and the residual oil was poured onto ice. The solution was neutralized with Na2CO3 and extracted with CHCl3. The CHCl3 layer was evaporated and the residue was recrystallized from petr. ether to give colorless needles, m.p. 66°—67°. Yield, 180 mg. \( \text{Anal. Calcd. for C}_{13}\text{H}_{18}\text{ClO}: 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 XXXII, 15 ml. of AcOH, and 7 ml. of 30% H2O2 was treated in the same way as that for XII. The residue obtained from the CHCl3 extract was recrystallized from benzene-cyclohexane to afford colorless needles, m.p. 122°—128°. Yield, 1.7 g. Recrystallized from benzene-cyclohexane gave colorless needles, m.p. 133°—135.5°. \( \text{Anal. Calcd. for C}_{13}\text{H}_{18}\text{ClO}: 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% NH4OH, 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. \( \text{Anal. Calcd. for C}_{13}\text{H}_{18}\text{O}_{4}\text{N}: C, 65.83; H, 7.37; N, 17.06. Found: C, 66.12; H, 7.42; N, 17.23.} 

6-Methyl-5,6,7,8-tetrahydro-1-monoheptamonomonocinnoline 1-Oxide (XXXVI)—A mixture of 500 mg. of XXXV, 700 mg. of N-bromosuccinamide, 50 mg. of BzCl, and 5 ml. of CCl4 was treated in the same way used for XXXIV. 50 mg. of XXXVI was obtained as colorless prisms, m.p. 144°—145°. \( \text{Anal. Calcd. for C}_{13}\text{H}_{18}\text{O}_{4}\text{N}: 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 NaOCH3, prepared from 500 mg. of Na, and 20 ml. of MeOH, 1.7 g. of XXXVII was added and the mixture treated in the same way used for XIV. 1.1 g. of XXXVII was obtained as colorless plates, m.p. 168°—169°. \( \text{Anal. Calcd. for C}_{13}\text{H}_{18}\text{O}_{4}\text{Cl}: 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-bromosuccinamide, 50 mg. of BzCl, and 6 ml. of CCl4 was refluxed for 30 min. The reaction mixture was treated in the same way as that for XVI. The residue obtained from the CHCl3 extract was recrystallized from benzene to give colorless scales, m.p. 133°—134°. Yield, 110 mg. \( \text{Anal. Calcd. for C}_{13}\text{H}_{18}\text{O}_{4}\text{N}: 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 (XXXIII)—To a solution of 200 mg. of XXI dissolved in 8 ml. of AcOH, 2 ml. of conc. HNO3 was added with stirring at room temperature and the mixture was poured into ice water, extracted with CHCl3, and CHCl3 was evaporated. The residue was recrystallized from EtOH to give yellow needles, m.p. 154°—155°. Yield, 145 mg. \( \text{Anal. Calcd. for C}_{13}\text{H}_{18}\text{O}_{4}\text{N}: 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 (XXXIV)—i) From XXXII (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 CHCl3, and CHCl3 was distilled off. The residue was recrystallized from EtOH to give pale yellow needles, m.p. 170°. Yield, 55 mg. \( \text{Anal. Calcd. for C}_{13}\text{H}_{18}\text{O}_{4}\text{Cl}: C, 51.18; H, 3.33; N, 13.31. Found: C, 51.22; H, 3.39; N, 13.01.} 

ii) From XXXVII: A mixture of 0.3 g. of XXXVII, 0.55 g. of N-bromosuccinimide, 50 mg. of BzCl, and 5 ml. of CCl4 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 NaOCH3 solution (Na, 30 mg.; MeOH, 3 ml.) in the same way as that for VIIi). 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 XXII derived from X, 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 CHCl3, 2.5 g. of POCl3 was added and the mixture refluxed for 20 min. The solvent was removed under reduced pressure, and the residue was neutralized with Na2CO3 while cooling, and extracted with CHCl3. CHCl3 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°. \( \text{Anal. Calcd. for C}_{13}\text{H}_{18}\text{O}_{4}\text{Cl}: 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% H₂O₂, and 4 ml. of AcOH was treated in the same way as that for XIII. The residue obtained from the CHCl₃ extract was recrystallized from benzene-cyclohexane to colorless needles, m.p. 117~122°. Yield, 490 mg. Repeated recrystallization from cyclohexane gave colorless needles, m.p. 132~133°. Anal. Calcd. for C₁₈H₁₁O₂N₂Cl : C, 50.35; H, 5.13; N, 13.05. Found : C, 50.08; H, 5.31; N, 12.89.

3,4-Dimethoxychinonoline 1-Oxide (XXV) — To a solution of NaOCH₃, prepared from 20 mg. of Na and 1 ml. of MeOH, 70 mg. of XXV was added and the mixture was refluxed for 30 min. After evaporation of MeOH, the residue was dissolved in H₂O, extracted with CHCl₃, and CHCl₃ was evaporated. The residue was recrystallized from benzene-cyclohexane to give yellow prisms, m.p. 116~117°. Yield, 35 mg. Anal. Calcd. for C₁₃H₁₅O₂N₂ : 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 ±0.02 τ 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-methoxychinonoline 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 H₈ 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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