
Communications to the Editor

UDC 547.852.7.07

Synthesis of Cinnoline N-Oxides

In the field of benzodiazine N-oxides, syntheses of quinoxaline N-oxide,[1] quinazoline N-oxide,[2] and, phthalazine N-oxide[3] have been already reported, but the synthesis of cinnoline N-oxide remained to be uninvestigated. The authors have now succeeded in the syntheses of cinnoline 1-oxide (II), 2-oxide (III), 4-methylcinnoline 1-oxide (V), and 2-oxide (VI). Heating of cinnoline (I) with hydrogen peroxide in glacial acetic acid gave cinnoline N-oxide. The product was chromatographed on alumina, and gave two isomeric cinnoline mono-N-oxides, (II), m.p. 110.5~111.5°, UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 219 (4.41), 229.5 (4.40), 303 (3.71), 315 (3.71), 351.5 (3.90), 367 (3.88), (*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) and (III), m.p. 125~126°, UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 218 (4.48), 262 (4.44), 308 (3.76), 351 (3.70), 360 (3.70), (*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). The apparent productive ratio of (II) and (III) isolated was about 1:2, but the precise ratio was observed to 1:1.4 by nuclear magnetic resonance spectral analysis.*1

N-Oxidation of 4-methylcinnoline (IV) was carried out under similar conditions to cinnoline N-oxides, and the product was separated by alumina chromatography to (V), m.p. 94~95°, UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 219 (4.42), 229.5 (4.37), 253 (3.93), 308 (3.70), 318 (3.72), 357 (3.94), 369 (3.90), (*Anal.* Calcd. for $C_9H_8ON_2$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.66; H, 5.20; N, 17.21) and (VI), m.p. 151~152°, UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 222 (4.33), 261 (4.37), 307 (3.80), 348.5 (3.70), 357 (3.68), (*Anal.* Calcd. for $C_9H_8ON_2$: C, 67.48; 5.03; N, 17.49. Found : C, 67.58; H, 5.12; N, 17.25). The ratio of isolated (V) to (VI) was about 1:2, which was almost identical with the ratio observed by nuclear magnetic resonance spectra.

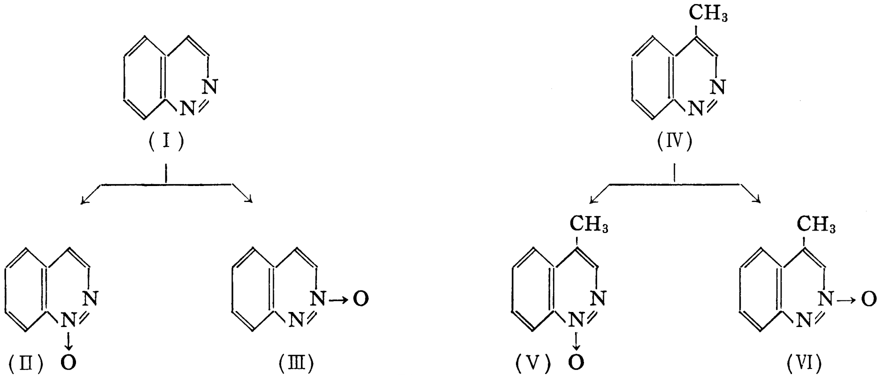

Chart 1.

In order to determine the structure of these N-oxides (II), (III), (V), and (VI), cinnoline 1-oxide (II) was synthesized from 5,6,7,8-tetrahydrocinnoline (VIII) by the following method.

N-Oxidation of 5,6,7,8-tetrahydrocinnoline (VIII) gave two isomers of 5,6,7,8-tetrahydrocinnoline N-oxides; (IX), m.p. 100~100.5°, (*Anal.* Calcd. for $C_8H_{10}ON_2$: C, 63.98; H, 6.71;

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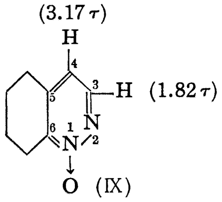
[1] H. McIlwain : J. Chem. Soc., **1943**, 322; J.K. Landquist : J. Chem. Soc., **1953**, 2816.

[2] K. Adachi : Yakugaku Zasshi, **77**, 507 (1957).

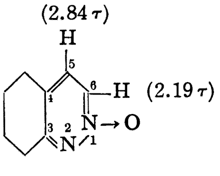
[3] E. Hayashi, T. Higashino, C. Iijima, Y. Kōno, T. Doihara : Yakugaku Zasshi, **82**, 584 (1962).

*1 Studies of nuclear magnetic resonance spectra will be reported in the near future.

N, 18.65. Found : C, 63.94; H, 6.72; N, 18.48) and (X), m.p. 127~128°, (*Anal.* Calcd. for $C_8H_{10}ON_2$: C, 63.98; H, 6.71; N, 18.65. Found : C, 63.40; H, 6.61; N, 18.19), which were separated by alumina chromatography. On the other hand, N-oxidation of 3-chloro-5,6,7,8-tetrahydrocinnoline (VII) gave 3-chloro-5,6,7,8-tetrahydrocinnoline N-oxide (XI), 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). Catalytic reduction of (XI) on palladium-carbon gave 5,6,7,8-tetrahydrocinnoline N-oxide, m.p. 100~100.5°, which was confirmed to be identical with (IX) by a comparison of their infrared absorption spectra. As shown in the previous paper of this series, N-oxidation of 3-chloro-5-methylpyridazine,[4,5] and 3-chloro-6-methylpyridazine[5,6] gave the corresponding 1-oxides respectively. Therefore N-oxide (XI) obtained from (VII) should be also 1-oxide. Further evidence for the structure of (IX) and (X) were obtained by nuclear magnetic resonance spectroscopy. It has been found by our investigation[7] on the nuclear magnetic resonace spectra of pyridazine N-oxide and its derivatives that the peaks of the ring protons appeared in the following order $\tau_{H_3}<\tau_{H_6}<\tau_{H_5}<\tau_{H_4}$ on the spectra of methyl substituted pyridazine N-oxides. This order should be retained in other alkyl substituted pyridazine N-oxides. These signal peaks of aromatic ring protons of (IX) and (X) centered at 1.82 τ, 3.17 τ and 2.19 τ, 2.84 τ respectively, and the peaks at 1.82 τ, 3.17 τ can be assigned to the protons H_3 and H_4 in (IX), and those at 2.19 τ, 2.81 τ to the protons H_6 and H_5 in (X), respectively.



(IX)



(X)

Treating with sodium methoxide, (XI) gave 3-methoxy-5,6,7,8-tetrahydrocinnoline 1-oxide (XII).

Bromination of (IX) and (XI) with N-bromosuccinimide in CCl_4 gave monobromo compounds (XIII), m.p. 145~146°, (*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), and (XIV), m.p. 93~94°, (*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) respectively, but (XII) gave a dibromo compound (XVII), 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). Further bromination of (XIII) and (XIV) with N-bromosuccinimide in CCl_4 gave dibromo compounds (XV), m.p. 149~150°, (*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) and (XVI), m.p. 137~138°, (*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). The structure of these compounds (XIII) will be reported in the near future.

Treating with sodium methoxide, (XV) afforded cinnoline 1-oxide, (II), m.p. 110.5~111.5°, which was proved to be identical with (II) obtained by N-oxidation of cinnoline (I) by a comparison of their infrared absorption spectra. Accordingly, the structure of (III) is deduced to be cinnoline 2-oxide. By the same treatment of (XVI) and (XVII), 3-chlorocinnoline 1-oxide (XVIII), m.p. 168~169°, (*Anal.* Calcd. for $C_8H_5ON_2Cl$: C, 53.18; H, 2.77; N, 15.51. Found : C, 52.85; H, 2.53; N, 15.11) and 3-methoxycinnoline 1-oxide

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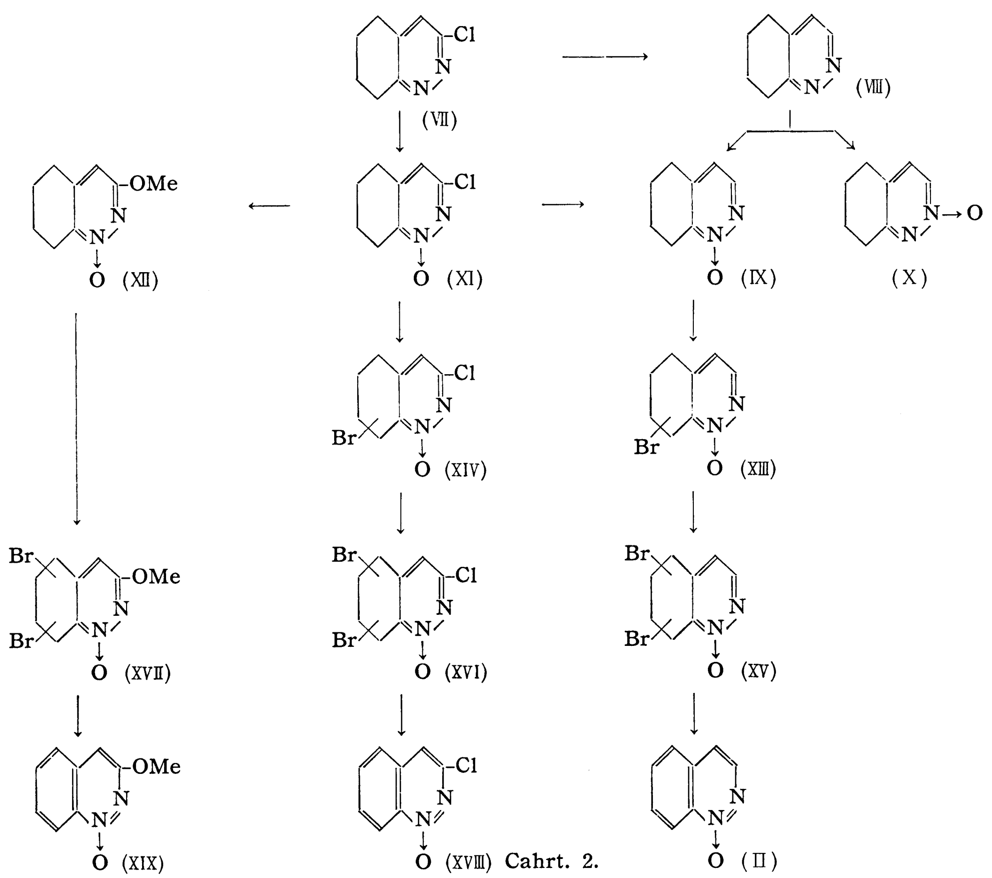
4) M. Ogata, H. Kano : This Bulletin in press.
5) H. Watanabe, M. Ogata, H. Kano : *Ibid.* in press.
6) T. Nakagome : Yakugaku Zasshi, **81**, 1048 (1961).
7) K. Tori, M. Ogata, H. Kano : This Bulletin in press.



Cahrt. 2.

(XIX), m.p. 94~95°(*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) were obtained. The structure of 4-methylcinnoline N-oxide (V and VI) were elucidated by nuclear magnetic resonance spectral analysis.

In nuclear magnetic resonance spectrum* of cinnoline 1-oxide (II), signal peaks at 1.33 τ, 1.67 τ and 2.50 τ were assigned to that of H_8, H_3 and H_4, respectively. On the other hand, in the spectrum of 2-oxide (III), signal peaks at 1.79 τ and 1.94 τ were assigned to that of H_3 and H_4 respectively. The nuclear magnetic resonance spectrum of 4-methylcinnoline N-oxide (V) shows characteristic peaks at 1.35 τ and 1.87 τ, while that of (VI) shows at 1.90 τ. From these results, (V) was considered to be 4-methylcinnoline 1-oxide (V) and (VI) was 2-oxide (VI).

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