The authors express their gratitude to Prof. S. Akamatsu, Professor Emeritus of Biochemistry, Chiba University Medical School, for his kind advices, and to Dr. K. Abe, Dr. T. Okuda for their encouragement throughout the studies. They are indebted to the staff of Central Analysis Room of Tokyo Research Laboratory, Tanabe Seiyaku Co., Ltd., for measurements of UV spectra and ORD and elemental analysis.

## Summary

The Sowden's synthetic procedure of D-mannosamine hydrochloride was simplified, and modified in order to prepare N-acetyl-D-mannosamine. By the action of ammonia on 1-nitro-1-deoxy-D-mannitol pentaacetate (I), I was directly transformed in a yield of 70.5% to 1-nitro-2-acetamido-1,2-dideoxy-D-mannitol (Ⅲ) without isolating the intermediate, D-*arabino*-1-nitro-tetraacetoxy-1-hexene (Ⅱ). 1-Nitro-2-acetamido-1,2-dideoxy-D-glucitol (Ⅳ) was produced as a by-product in a yield of 8.3%. The barium salt of *aci*-form of Ⅲ was decomposed with sulfuric acid in the cold in order to prevent hydrolysis of the N-acetyl group and facilitate separation of the product from the inorganic salt. The yield of N-acetyl-D-mannosamine was 66.3%. An unfractionated mixture of the two epimeric D-*arabino*-1-nitro-1-deoxy-hexitols which had been obtained from D-arabinose was acetylated and transformed to Ⅲ in a yield of 26.5% from D-arabinose.

Ⅲ and Ⅳ exhibited a negative and a positive Cotton effect respectively in their optical rotatory dispersion curves.

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## 89. **Ikuo Suzuki and Toshiaki Nakashima** : Studies on Cinnolines. I. N-Oxidation of 4-Chlorocinnoline and 4-Methoxycinnoline.

(*National Institute of Hygienic Sciences*[*1])

It has been reported[1] that cinnoline and 4-methylcinnoline gave their 1-oxide and 2-oxide on treatment with hydrogen peroxide in acetic acid, and the ratio of 1-oxide to 2-oxide was 1:2 in both cases.

The present paper deals with N-oxidation of 4-chlorocinnoline and 4-methoxycinnoline, and syntheses of 4-hydroxycinnoline N-oxides.

When 4-chlorocinnoline (I) was treated with phthalic monoperacid in ethereal solution at a room temperature for two weeks, two kinds of new N-oxide (Ⅲ, m.p. 94~94.5°, colorless needles, and Ⅳ, m.p. 150~151°, yellow needles) were isolated in 28% and 43% yields, respectively. Ⅲ and Ⅳ gave analytical values corresponding to 4-chlorocinnoline mono-N-oxide. Catalytic reduction of 4-chlorocinnoline gave mainly 4,4′-bicinnoline,[2] but catalytic hydrogenation of Ⅲ over palladium charcoal in ethanolic solution containing sodium hydroxide gave known cinnoline 1-oxide (Ⅴ),[1] m.p. 111~112°, in 62% yield,

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[*1] Tamagawa-yoga, Setagaya, Tokyo (鈴木郁生, 中島利章).

[1] M. Ogata, *et al.* : This Bulletin, **11**, 1527 (1963).

[2] J. S. Morley : J. Chem. Soc., **1951**, 1971.

and III was also synthesized from 4-nitrocinnoline 1-oxide (VI)[3] by treatment with acetylchloride at 50°. From these facts the structure of III was confirmed to be 4-chlorocinnoline 1-oxide.

The structure of IV was determined to be 4-chlorocinnoline 2-oxide, because it was transformed to the known cinnoline 2-oxide (VII),[1] m.p. 122~123°, by hydrogenation over palladium charcoal in alkaline ethanolic solution. In this reduction a small amount of colorless needles (VIII) was obtained as a by-product. VIII was proved to be identical with 4-ethoxycinnoline 2-oxide obtained by heating IV with ethanolic sodium ethoxide.

By heating with methanolic sodium methoxide, III and IV were converted to 4-methoxycinnoline 1-oxide (IX), yellow fine needles, m.p. 107~108°, and 4-methoxycinnoline 2-oxide (X), colorless needles, m.p. 176~177° in good yields, respectively. On the other hand, 4-methoxycinnoline (II) gave two kinds of 4-methoxycinnoline mono-N-oxide by N-oxidation using phthalic monoperacid in ethereal solution in 18% and 33% yields, and these both compounds were proved to be identical with the above mentioned IX and X by mixed melting point and infrared spectra. IX was also obtained by treating VI with methanolic sodium methoxide in 65% yield.

Table I.

| Starting material | Yield of | | Starting material | Yield of | |
|---|---|---|---|---|---|
| | 1-oxide (%) | 2-oxide (%) | | 1-oxide (%) | 2-oxide (%) |
| Cinnoline[1] | 19 | 40 | 4-Chlorocinnoline | 28 | 43 |
| 4-Methylcinnoline[1] | 20 | 44 | 4-Methoxycinnoline | 18 | 33 |

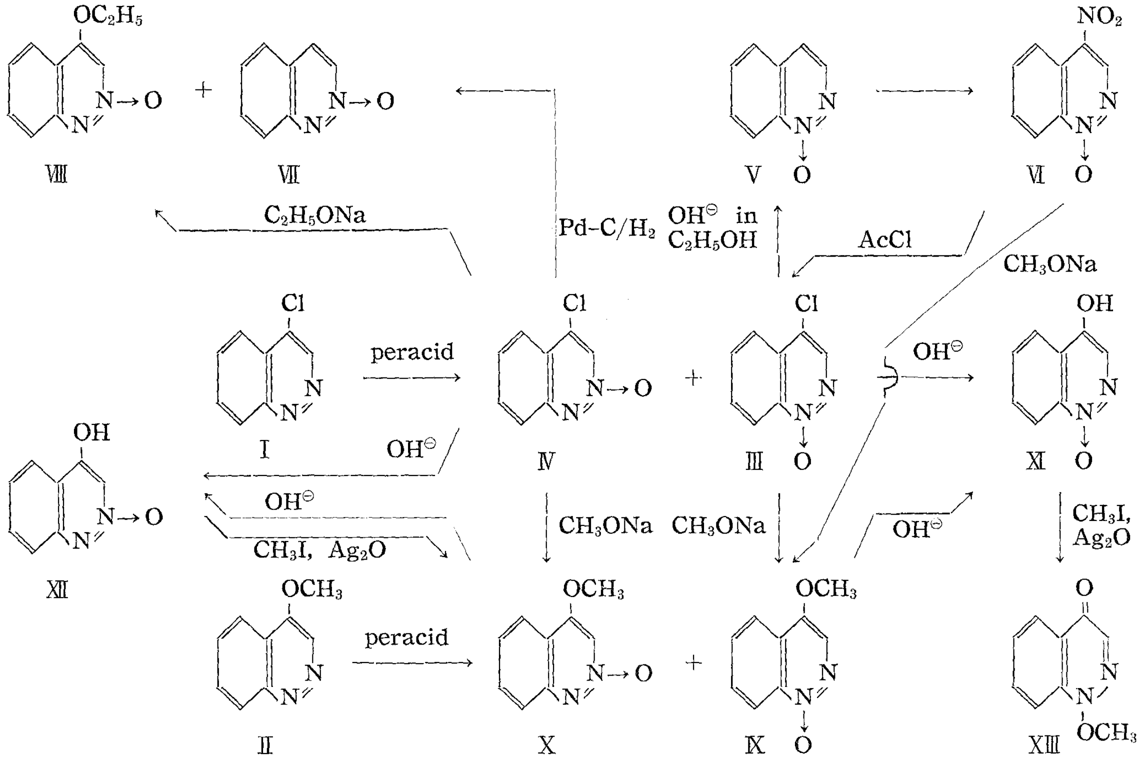

Chart 1.

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3) I. Suzuki, *et al.* : This Bulletin, **11**, 268 (1963).

Simpson and his collaborators[4,5] reported that the most basic center of cinnolines was probably N-1, and the charge distribution within the cinnoline system has been calculated.[6] Calculations indicate that N-1 has more negative charge compared with N-2. But as it can be seen from Table I, it was shown that yields of 2-oxides were much more compared with those of 1-oxides, in the N-oxidations of 4-chlorocinnoline and 4-methoxycinnoline as well as cinnoline and 4-methylcinnoline. As this fact thus obtained does not support the investigations by Simpson and other workers, further experiments will be necessary to obtain definite evidence.

The hydrolysis of III and IX with diluted sodium hydroxide solution afforded 4-hydroxycinnoline 1-oxide (XI), m.p. 153° (decomp.). By the same procedure, IV and X were hydrolyzed to 4-hydroxycinnoline 2-oxide (XII), m.p. 257° (decomp.) in good yield. By heating with methyl iodide, XII reproduced X in 50% yield accompanied with recovery of starting material in 18% and 4-hydroxycinnoline in 7% yield. On the other hand, by treating with methyl iodide, XI gave IX in 4% yield and yellow needles (XIII, m.p. 82~83°) whose analytical values agreed with a composition of $C_9H_8O_2N_2$, in 28% yield, accompanied with 4-hydroxycinnoline in 18% yield. However XIII is obviously different from IX with respect to melting point and infrared absorption spectra, and furthermore, XIII possesses a quinolone type of carbonyl band in its infrared spectrum judging from these data, this methylation product (XIII) should be 1-methoxy-4(1*H*)-cinnolinone.

## Experimental

**4-Chlorocinnoline 1-Oxide (III) and 2-Oxide (IV)**——A mixture of 7.70 g. of 4-chlorocinnoline (I) in 250 ml. of ethereal phthalic monoperacid solution (active oxygen 13.4 mg/ml.) was allowed to stand for two weeks. $Et_2O$ was evaporated and the residue was extracted with $CHCl_3$, which was washed with aq. $NaHCO_3$ solution. It was dried over anhyd. $Na_2SO_4$ and was evaporated to dryness. The residue was extracted with 100 ml. of $Et_2O$, and the $Et_2O$ insoluble substance was recrystallized from benzene to give yellow needles, m.p. 148~150°. Yield, 3.34 g. (43%). Repeated recrystallization from benzene gave yellow needles, IV, m.p. 150~151°. *Anal.* Calcd, for $C_8H_5ON_2Cl$ : C, 53.20; H, 2.70; N, 15.51. Found : C, 53.34; H, 2.90; N, 15.52.

The $Et_2O$ extracted solution was evaporated to dryness, the residue was dissolved in benzene, passed through a column of $Al_2O_3$, and eluted with benzene. The solvent was evaporated from the initial fraction of the eluate, and the residue was recrystallized from $Et_2O$ to give colorless fine needles, m.p. 91~93°. Yield, 2.14 g. (28%). Repeated recrystallization from $Et_2O$ gave colorless fine needles (III), m.p. 94~94.5°. *Anal.* Calcd. for $C_8H_5ON_2Cl$ : C, 53.20; H, 2.70; N, 15.51. Found : C, 53.41; H, 2.86; N, 15.07.

**Catalytic Hydrogenation of 4-Chlorocinnoline 1-Oxide (III)**——A mixture of 0.30 g. of III, 50 ml. of EtOH and 1 ml. of 10% NaOH was hydrogenated in the presence of Pd-C prepared from 0.1 g. of charcoal and 10 ml. of 1% $PdCl_2$ solution. After removal of the catalyst, the filtrate was neutralized with 10% HCl and distilled off under reduced pressure to dryness. The residue was extracted with benzene to remove NaCl by filtration, and the filtrate was concentrated to a small volume. The solution was passed through a column of $Al_2O_3$, and eluted with benzene. Benzene was evaporated and the residue (m.p. 107~110°, 0.15 g. 62%) was recrystallized from $Me_2CO$ to give colorless needles, m.p. 111~112°. This showed no depression of melting point on admixture with authentic cinnoline 1-oxide, and the IR spectra of the two samples were identical.

**Reaction of 4-Nitrocinnoline 1-Oxide (VI) with Acetyl Chloride**——A mixture of 0.10 g. of VI and 1 ml. of AcCl was warmed upto 50° for 30 min. After cooling, the mixture was poured in ice $H_2O$, basified with $K_2CO_3$, extracted with $CHCl_3$, and evaporated the solvent. The residue was dissolved in benzene, passed through a column of $Al_2O_3$, and eluted with benzene. Benzene was evaporated and the residue (m.p. 90~93°, 0.07 g. 74%) was recrystallized from $Et_2O$ to give colorless needles, m.p. 94~94.5°. This showed no depression of melting point on admixture with III, obtained in the above-mentioned experiment, and the IR spectra of the two samples were identical.

**4-Ethoxycinnoline 2-Oxide (VIII)**——A mixture of 0.20 g. of IV, 5 ml. of EtOH and EtONa in EtOH (1 ml. containing 29 mg. of Na) was heated on a steam bath for 30 min. EtOH was distilled off under

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4) J. C. E. Simpson : J. Chem. Soc., **1947**, 1653.
5) J. R. Keneford, *et al.* : *Ibid.*, **1950**, 1140.
6) H. C. Longuet-Higgins, C. A. Coulson : *Ibid.*, **1949**, 971.

reduced pressure to dryness. The residue was extracted with $CHCl_3$, passed through a column of $Al_2O_3$, and eluted with $CHCl_3$. $CHCl_3$ was evaporated and the residue (m.p. 188~190°, 0.18 g., 85%) was recrystallized from benzene to give colorless needles (VIII), m.p. 190~191°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_2$ : C, 63.15; H, 5.30; N, 14.73. Found : C, 63.46; H, 5.50; N, 14.63.

**Catalytic Hydrogenation of 4-Chlorocinnoline 2-Oxide (IV)**——A mixture of 1.00 g. of IV, 50 ml. of EtOH and 3 ml. of 10% NaOH was hydrogenated in the presence of Pd-C prepared from 0.3 g. of charcoal and 30 ml. of 1% $PdCl_2$ solution. After removal of the catalyst, the filtrate was neutralized with 10% HCl and distilled off under reduced pressure to dryness. The residue was extracted with benzene to remove NaCl by filtration, and the filtrate was concentrated to a small volume. The precipitates were filtered, the mother liquor was passed through a column of Florisil, and eluted with benzene. The solvent was evaporated from the initial fraction of the eluate, and the residue (m.p. 115~120°, 0.24 g., 31%) was recrystallized from $Me_2CO$ to give colorless fine needles, m.p. 122~123°. This showed no depression of melting point on admixture with authentic cinnoline 2-oxide, and the IR spectra of the two samples were identical.

The solvent was evaporated from the following fraction eluate to give a crystalline residue. Total amount 0.20 g. (19%). Recrystallization from benzene gave colorless needles, m.p. 190~191°. This showed no depression of melting point on admixture with VIII, obtained in the above-mentioned experiment, and the IR spectra of the two samples were coincident.

**4-Methoxycinnoline 1-Oxide (IX)**——1) Reaction of 4-chlorocinnoline 1-oxide (III) with MeONa : A mixture of 0.20 g. of III, 2 ml. of MeOH and MeONa in MeOH (1 ml. containing 29 mg. of Na) was heated on a steam bath for 30 min. MeOH was distilled off under reduced pressure to dryness. The residue was extracted with $CHCl_3$, passed through a column of $Al_2O_3$, and eluted with $CHCl_3$. $CHCl_3$ was evaporated and the residue (m.p. 100~105°, 0.15 g. 77%) was recrystallized from (iso-Pr)$_2$O to give light yellow fine needles (IX), m.p. 107~108°. *Anal.* Calcd. for $C_9H_8O_2N_2$ : C, 61.36; H, 4.58; N, 15.90. Found : C, 61.20; H, 4.77; N, 15.75.

2) Reaction of 4-nitrocinnoline 1-oxide (VI) with MeONa : A mixture of 0.20 g. of VI, 2 ml. of MeOH and MeONa in MeOH was heated on a steam bath for 30 min., and was preceeded as described in (1). Yield, 65%. No melting point depression was observed on admixture with IX obtained in method (1).

**4-Methoxycinnoline 2-Oxide (X)**——Reaction of 4-chlorocinnoline 2-oxide (IV) with MeONa : X was also obtained from IV using the same method described in synthesis of IX. Yield, 92%. Recrystallization from benzene gave colorless needles (X), m.p. 176~177°. *Anal.* Calcd. for $C_9H_8O_2N_2$ : C, 61.36; H, 4.58; N, 15.90. Found : C, 61.23; H, 4.66; N, 16.18.

**N-Oxidation of 4-Methoxycinnoline (II) with Phthalic Monoperacid**——A mixture of 1.00 g. of II in 70 ml. of ethereal phthalic monoperacid solution (active oxygen 13.4 mg./ml.) was allowed to stand for two weeks. $Et_2O$ was evaporated and the residue was extracted with $CHCl_3$, which was washed with aq. $NaHCO_3$ solution. It was dried over anhyd. $Na_2SO_4$ and was evaporated to dryness. The residue was recrystallized from benzene to give colorless needles, m.p. 165~170°. The mother liquor was passed through a column of $Al_2O_3$, eluted with benzene. The first eluted product was identical with the above-mentioned colorless needles. Total amount 0.36 g. (33%). Recrystallization from benzene gave colorless needles, m.p. 176~177°. This showed no depression of melting point on admixture with X, obtained by the reaction of IV with MeONa, and the IR spectra of the two samples were coincident.

The second eluted product (m.p. 90~95°, 0.20 g. 18%) was recrystallized from (iso-Pr)$_2$O to give light yellow fine needles, m.p. 107~108°. This showed no depression of melting point on admixture with IX, obtained by the reaction of III with MeONa, and the IR spectra of the two samples were coincident.

**4-Hydroxycinnoline 1-Oxide (XI)**——1) From 4-chlorocinnoline 1-oxide (III) : A mixture of 0.20 g. of III and 5 ml. of 5% NaOH was heated on a steam bath for 1.5 hr. with occasional shaking. After acidification of the solution, yellow precipitate deposited was collected, and recrystallized from MeOH to yellow fine needles (XI), m.p. 153° (decomp.), Yield, 0.12 g. (67%). *Anal.* Calcd. for $C_8H_6O_2N_2$ : C, 59.26; H, 3.73; N, 17.28. Found : C, 59.28; H, 4.24; N, 17.55.

2) From 4-methoxycinnoline 1-oxide (IX) : XI was also obtained from IX using the same method described in 1). Yield, 57%. No melting point depression was observed on admixture with XI obtained in method (1), and the IR spectra of the two samples were coincident.

**4-Hydroxycinnoline 2-Oxide (XII)**——1) From 4-chlorocinnoline 2-oxide (IV) : XII was also obtained from IV using the same method described in synthesis of XI. Yield, 89%. Recrystallization from MeOH gave colorless fine needles (XII), m.p. 257° (decomp.). *Anal.* Calcd. for $C_8H_6O_2N_2$ : C, 59.26; H, 3.73; N, 17.28. Found : C, 59.11; H, 4.08; N, 17.56.

2) From 4-methoxycinnoline 2-oxide (X) : XII was also obtained from X using the same method described in 1). Yield, 87%. No melting point depression was observed on admixture with XII obtained in method (1), and the IR spectra of the two samples were coincident.

**Methylation of 4-Hydroxycinnoline 1-Oxide (XI)**——A mixture of 0.50 g. of XI, 15 ml. of MeOH, 1.5 g. of MeI and $Ag_2O$ prepared from 1.5 g. of $AgNO_3$ was heated in a sealed tube on a steam bath for 3 hr. with occasional shaking. The precipitate was removed by filtration, and the solvent was evaporated from the filtrate. The residue was extracted with benzene, passed through a column of $Al_2O_3$, and eluted with benzene. The solvent was evaporated from the initial fraction of the eluate, and the recrystallization of the residue from (iso-Pr)$_2$O gave yellow needles (XIII), m.p. 82~83°. Yield, 0.15 g. (28%). *Anal.* Calcd. for $C_9H_8O_2N_2$ : C, 61.36; H, 4.58; N, 15.90. Found : C, 61.56; H, 4.72; N, 16.11. IR $\nu_{\max}^{\text{KBr}}$ $\text{cm}^{-1}$ : 1627, 1604.

The solvent was evaporated from the following fraction of the eluate, and gave crystals, 0.02 g. (4%). The crystals were identical with IX, obtained by the reaction of III with MeONa, by comparison of IR spectra.

The third fraction eluted with $CHCl_3$ containing 1% of MeOH. The solvent was evaporated, and gave crystals, 0.08 g. (18%). The crystals were identical with 4-hydroxycinnoline by comparison of IR spectra.

**Methylation of 4-Hydroxycinnoline 2-Oxide (XII)**——A mixture of 0.50 g. of XII, 15 ml. of MeOH, 1.5 g. of MeI and $Ag_2O$ prepared from 1.5 g. of $AgNO_3$ was heated in a sealed tube on steam bath for 3 hr. with occasional shaking. The precipitate was removed by filtration, and the solvent was evaporated from the filtrate. The residue was extracted with $CHCl_3$ and the $CHCl_3$ insoluble substance was recystallized from MeOH to give colorless fine needles, 0.09 g. (18%). Its IR spectrum coincided completely with starting material.

The extracted $CHCl_3$ solution was concentrated to small volume, passed through a column of $Al_2O_3$, and eluted with $CHCl_3$. The solvent was evaporated from the initial fraction of the eluate, and the residue (m.p. 170~174°, 0.27 g. 50%) was recrystallized from benzene to give colorless needles, m.p. 176~177°. This showed no depression of melting point on admixture with 4-methoxycinnoline 2-oxide.

The following fraction eluted with $CHCl_3$ containing 1% of MeOH. The solvent was evaporated and gave crystals 0.03 g. (7%). The crystals were identical with 4-hydroxycinnoline by comparison of IR spectra.

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## Summary

4-Chlorocinnoline 1-oxide (III), 4-chlorocinnoline 2-oxide (IV), 4-methoxycinnoline 1-oxide (IX), 4-methoxycinnoline 2-oxide (X), 4-ethoxycinnoline 2-oxide (VIII), 4-hydroxycinnoline 1-oxide (XI), and 4-hydroxycinnoline 2-oxide (XII) were synthesized. By treating with methyl iodide, 4-hydroxycinnoline 2-oxide gave X, while 4-hydroxycinnoline 1-oxide gave IX, and 1-methoxy-4(1*H*)-cinnolinone. In the N-oxidation of 4-chlorocinnoline and 4-methoxycinnoline, the yields of 2-oxides were much more compared with those of 1-oxides.

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