Chem. Pharm. Bull. 12 (9) 1090 ~ 1094

UDC 547.852.7.07

151. Ikuo Suzuki, Toshiaki Nakashima, Natsuko Nagasawa, and Takanobu Itai : Studies on Cinnolines. II.*1 On Nitration of Cinnoline 1-Oxide.*2

(*National Institute of Hygienic Sciences*3)

It has been reported that quinoline 1-oxide was nitrated to 4-nitroquinoline 1-oxide with mixed acid,[1] and the nitration of quinoline 1-oxide with benzoyl nitrate in chloroform occurred at β-position.[2] This paper deals with nitration of cinnoline 1-oxide (I) with mixed acid, and with benzoyl nitrate, in addition with rearrangement reaction of I with phosphoryl chloride.

The position taken by the nitro group on nitration of quinoline 1-oxide shows a striking temperature dependence, because quinoline 1-oxide gives 4-nitroquinoline 1-oxide on warming with mixture of potassium nitrate and sulfuric acid at 65~75°, and at 0~10° 5- and 8-nitro derivatives are formed. On the other hand, nitration of cinnoline 1-oxide showed some different results from nitration of quinoline 1-oxide, as shown below.

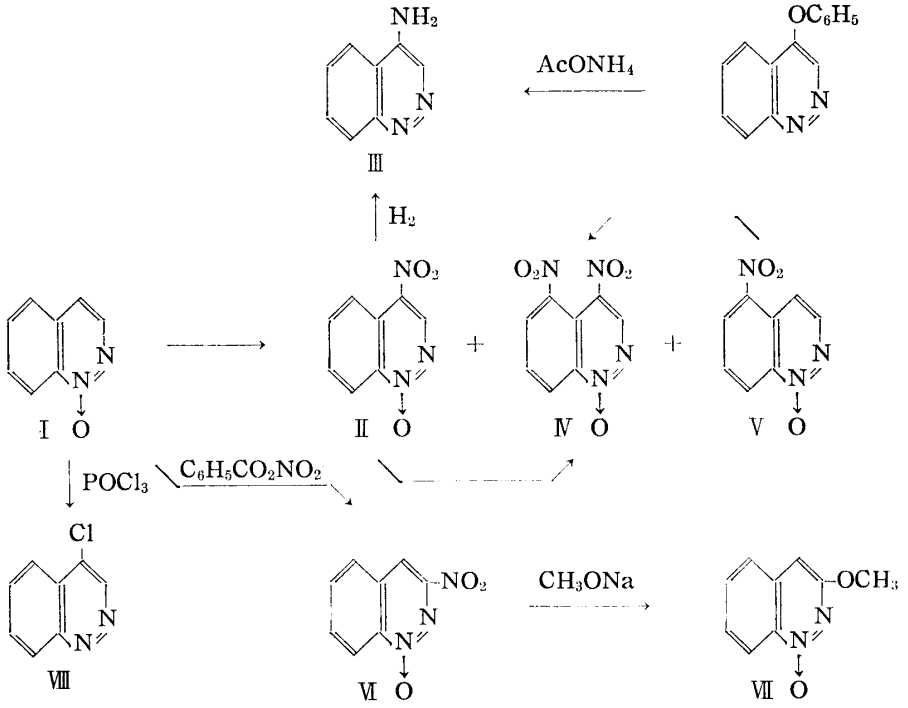

Chart 1.

When I was treated with nitric acid or potassium nitrate in sulfuric acid at 60~90°, a mononitro compound was obtained as yellow needles, m.p. 161~162°. Catalytic hydrogenation of this mononitro compound over Raney nickel gave monoamino cinnoline, m.p.

*1 Part I : This Bulletin, **12**, 619 (1964).
*2 Preliminary reports of this work were published as "Communication to the Editor" in This Bulletin, **11**, 268 (1963).
*3 Tamagawa-Yoga, Setagaya, Tokyo (鈴木郁生, 中島利章, 長沢奈都子, 板井孝信).
1) E. Ochiai, T. Okamoto : Yakugaku Zasshi, **70**, 384 (1950).
2) E. Ochiai, C. Kaneko : This Bulletin, **5**, 56 (1957); *Ibid.*, **7**, 191, 195 (1959).

NII-Electronic Library Service

208～209°, in 75% yield, which was found to be identical with 4-aminocinnoline (Ⅲ) derived from 4-phenoxycinnoline and ammonium acetate,[3] by infrared spectra and mixed melting point, hence the structure of mononitro derivative was confirmed to be 4-nitrocinnoline 1-oxide (Ⅱ).

Table I. Nitration of Cinnoline 1-Oxide (I)

No.	I (mg.)	H_2SO_4 (ml.)	HNO_3 (ml.)	Temp. (°C)	Time (hr.)	Product (%) Ⅱ	Ⅳ	Ⅴ	Recovery of I
1	500	1	0.3	90	2	26			20
2	1000	2	0.6	70	3	41			16
3	800	4	4	20+50	8+1	64		2	4
4	500	3	KNO_3, 0.2 g.	60	3	25			52
5	950	2	0.6	65	6	45			1
6	800	1.5	0.5	10～15	5	6			67
7	500	3	f. HNO_3, 3	20+50	8+1		44		
8	800	5	f. HNO_3, 5	20+50	8+1	3	50		

As it can be seen from Table I, the amount of 4-nitro compound can be increased by using excess amount of mixed acid, and by keeping at room temperature for 8 hours and warming at 50° for one hour. And differing from quinoline 1-oxide, nitration of I at 10～15° produced Ⅱ in small yield with 67% recovery of starting material and could not be obtained 5- and 8-nitrocinnoline 1-oxide.

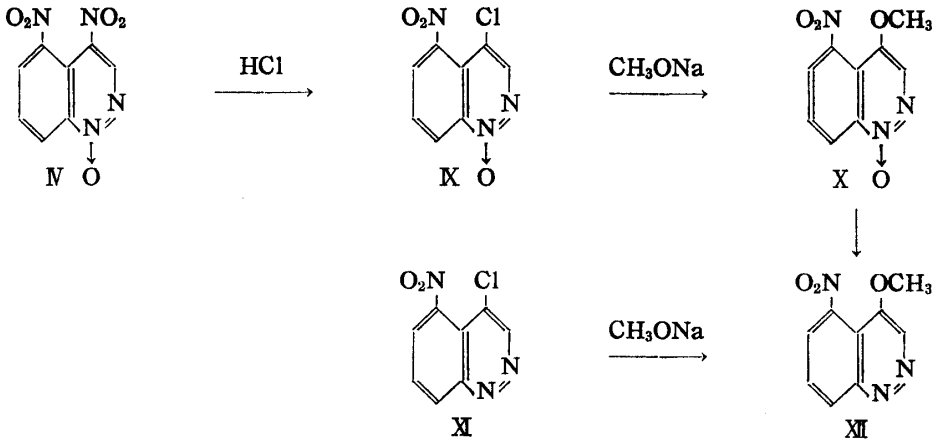

Chart 2.

I gave dinitrocinnoline 1-oxide (Ⅳ) (yellow needles, m.p. 191～192°) by warming with fuming nitric acid and sulfuric acid. As Ⅱ also afforded the dinitro compound on the same condition in good yield, one of the nitro groups of Ⅳ was located at 4-position. The reaction of Ⅳ with acetyl chloride or phosphoryl chloride resulted in the complete recovery of the starting material, but it was transformed by boiling with hydrochloric acid to pale yellow needles, m.p. 238～240°, 4-chloro-5-nitrocinnoline 1-oxide (Ⅸ). Ⅸ was converted with sodium methoxide in methanol to 4-methoxy-5-nitrocinnoline 1-oxide (X) (m.p. 222～224°) in good yield. Furthermore X was deSoxygenated with phosphorus trichloride to 4-methoxy-5-nitrocinnoline (Ⅻ) which was resulted from 4-chloro-5-nitrocinnoline[4] (Ⅺ) with sodium methoxide in methanol (Chart 2.). Moreover 5-nitrocinnoline

3) J. Keneford, K. Schofield, J. Simpson: J. Chem. Soc., **1948**, 358.
4) K. Schofield, R. S. Theobald: *Ibid.*, **1949**, 2404.

NII-Electronic Library Service

1-oxide*4 gave Ⅳ on nitration with mixed acid. From these results, it became clear that dinitro compound was 4,5-dinitrocinnoline 1-oxide (Ⅳ). The results of the nitration of I under various conditions are summerized in Table I.

Ochiai and Kaneko[2] found that quinoline 1-oxide was nitrated with benzoyl nitrate to β-positions. When I was treated with freshly prepared benzoyl nitrate in chloroform solution a mononitro derivative (Ⅵ) was obtained as yellow needles, m.p. 214~215° in 71% yield. On the other hand, Ogata, *et al.*[5] reported that 3-chloro-5,6,7,8-tetrahydrocinnoline 1-oxide gave 3-methoxycinnoline 1-oxide (Ⅶ), m.p. 94~95°, by treatment with sodium methoxide and oxidation. Ⅶ was proved identical with the above-mentioned monomethoxycinnoline 1-oxide by comparing the infrared spectra of monomethoxy compound with the authentic one which Dr. Ogata sent to us. This fact has shown that cinnoline 1-oxide was nitrated with benzoyl nitrate to 3-position as well as quinoline 1-oxide. Ⅵ gave an orange color in methanolic potassium hydroxide solution.

On the treatment with phosphoryl chloride in chloroform at room temperature for 1 hour, I was converted into 4-chlorocinnoline (Ⅷ) m.p. 76~77°, in 50% yield, as reported in pyridine and quinoline 1-oxides.[6] This compound is also obtained by reaction of 4-cinnolinol with phosphoryl chloride[7] and it was identified by infrared spectra and mixed melting point.

Experimental

4-Nitrocinnoline 1-Oxide (II) — a) With HNO_3: 800 mg. of I was added to the solution of 4 ml. each of H_2SO_4 and HNO_3 under cooling in an ice bath. The mixture was kept at room temperature for 8 hr. and warming was continued for 1 hr. at 50° on a water bath. After cooling, the mixture was poured into crashed ice. Separated yellow crystals were collected (940 mg.) and were recrystallized from Me_2CO to give 630 mg. of yellow needles (Ⅱ), m.p. 161~162°. *Anal.* Calcd. for $C_8H_5O_3N_3$: C, 50.26; H, 2.64; N, 21.99. Found: C, 50.36; H, 2.86; N, 22.45. The aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and evaporated. The crystalline residue (100 mg.) and residue obtained from mother liquor of recrystallization were dissolved in benzene and the solution was passed through Al_2O_3 column. From the first portion, eluted with benzene, 40 mg. of Ⅱ was obtained. The second fraction, eluted with benzene, was a mixture. This was divided into two fraction by passing through the other column of Al_2O_3 with benzene, 24 mg. of 5-nitrocinnoline 1-oxide (V), m.p. 182~183°, and 30 mg. of I were obtained.

b) With KNO_3: 500 mg. of I was added to 3 g. of H_2SO_4, and to the mixture was added 200 mg. of KNO_3 in small portions at 60°. The mixture was kept at 60° for 3 hr. on a water bath. After cooling the mixture was treated in the same way described above to give 160 mg. of Ⅱ with recovery of 260 mg. of I.

4,5-Dinitrocinnoline 1-Oxide (IV) — a) From cinnoline 1-oxide: To a mixture of 5 ml. each of H_2SO_4 and fuming HNO_3 was added 800 mg. of I in small portions carefully keeping at −5°. After the mixture was kept at room temperature for 6 hr., the reaction mixture was heated at 50° for 1 hr. on a water bath. After cooled, the mixture was poured into crashed ice and separated crystals were collected (900 mg.) and were recrystallized from Me_2CO to give 650 mg. of yellow needles, 4,5-dinitrocinnoline 1-oxide (Ⅳ), m.p. 191~192° (yield, 50%). *Anal.* Calcd. for $C_8H_4O_5N_4$: C, 40.69; H, 1.71; N, 23.73. Found: C, 41.06; H, 1.99; N, 23.54. The residue obtained from mother liquor of recrystallization were dissolved in benzene, and the solution was passed through Al_2O_3 column. 40 mg. of Ⅱ was obtained (Yield, 3%).

b) From 4-nitrocinnoline 1-oxide (Ⅱ): To a mixture of 0.5 ml. each of H_2SO_4 and fuming HNO_3 was added 100 mg. of Ⅱ under cooling in an ice bath. After keeping the mixture at room temperature for 7 hr., it was warmed at 50° for 1 hr. on a water bath. After cooling, the mixture was poured into crashed ice, and separated crystalline products were collected (110 mg.). The purification of the crystals over Al_2O_3 with benzene gave 84 mg. (69%), yellow needles, m.p. 189~190°. No melting point depression was observed on admixture with Ⅳ and the IR spectra of the two samples were identical.

*4 The authors will report on synthesis of 5-nitrocinnoline 1-oxide in near future.

5) M. Ogata, H. Kano, K. Tori: This Bulletin, **11**, 1527 (1963).
6) H. Gilman, S. M. Spatz: J. Am. Chem. Soc., **66**, 621 (1944); T. Kato: Yakugaku Zasshi, **75**, 1236, 1239 (1955).
7) J. R. Kenefford, J. C. E. Simpson: J. Chem. Soc., **1947**, 917.

NII-Electronic Library Service

c) From 5-nitrocinnoline 1-oxide (V) : 23 mg. of V was dissolved in 0.4 ml. of H_2SO_4 under cooling and to this solution was added 0.2 ml. of conc. HNO_3. The mixture was heated at 70~75° for 3 hr. on a water bath. After cooled, the mixture was poured into crashed ice and extracted with $CHCl_3$ extract was dried and evaporated. The purification of the residue over Florisil with $CHCl_3$ gave 3 mg. (10%) of yellow needles, IV, m.p. 186°. No melting point depression was observed on admixture with IV and the IR spectra of the two samples were identical.

Catalytic Hydrogenation of 4-Nitrocinnoline 1-Oxide (II)——A mixture of 100 mg. of II, 30 ml. of MeOH, and 0.2 g. of Raney Ni was subjected to hydrogenation. Four moles of H_2 per mole of II were absorbed. After removal of the catalyst, the filtrate was evaporated. The residue (m.p. 205~209°, 57 mg., 75%) was recrystallized from the mixture of benzene and EtOH to give colorless needles, m.p. 208~209°. This showed no depression of melting point on admixture with authentic 4-aminocinnoline, and IR spectra of the two samples were identical.

4-Chloro-5-nitrocinnoline 1-Oxide (IX)——A mixture of 100 mg. of IV and 2 ml. of conc. HCl was heated on a boiling water bath for 1 hr. To this solution, 10 ml. of H_2O was added. The mixture was evaporated under reduced pressure, and this procedure was repeated twice. The separated crystals were collected (90 mg., m.p. 234~238°, 94%), and were recrystallized from MeOH to give pale yellow needles, IX, m.p. 238~240°. *Anal.* Calcd. for $C_8H_4O_3N_3Cl$: C, 42.59; H, 1.79; N, 18.65. Found : C, 43.05; H, 2.03; N, 18.88.

4-Methoxy-5-nitrocinnoline 1-Oxide (X)——A suspension of 215 mg. of IX in 10 ml. of abs. MeOH was refluxed with 0.5 ml. of methanolic MeONa (prepared from 0.5 g. of Na and 11 ml. of MeOH) on a water bath for 1 hr. MeOH was distilled off to dryness. The residue was extracted with $CHCl_3$, and $CHCl_3$ was evaporated to dryness. The residue (180 mg. 85%) was recrystallized from the mixture of benzene and hexane to give yellow crystalline powder, X, m.p. 222~224°. *Anal.* Calcd. for $C_9H_7O_4N_3$: C, 48.87; H, 3.19; N, 19.00. Found : C, 49.34; H, 3.40; N, 18.39.

The pale yellow crystals obtained from mother liquor of recrystallization were identical with starting material (17 mg.).

4-Methoxy-5-nitrocinnoline (XII)—— a) From 4-methoxy-5-nitrocinnoline 1-oxide (X) : To a solution of 83 mg. of X dissolved in 5 ml. of $CHCl_3$, 0.3 ml. of PCl_3 was added. After standing at room temperature for 48 hr., the reaction mixture was poured onto ice, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The solvent distilled off and the residue was dissolved in the mixture of equal volumes of benzene and $CHCl_3$ and chromatographed on alumina. The initial fraction of the eluate was evaporated, and residue (10 mg., 13%) was recrystallized from benzene-hexane to give pale yellow crystalline powders, XII, m.p. 180~182°. *Anal.* Calcd. for $C_9H_7O_3N_3$: C, 52.68; H, 3.44; N, 20.48. Found : C, 52.93; H, 3.64; N, 19.86.

b) From 4-chloro-5-nitrocinnoline (XI) : A suspension of 25 mg. of XI in 2 ml. of abs. MeOH was refluxed with 0.2 ml. of methanolic MeONa (prepared from 0.5 g. of Na and 11 ml. of MeOH) on a water bath for 1 hr. MeOH was evaporated, and the residue was dissolved in $CHCl_3$ and purified by alumina chromatography. The eluted product (6 mg., m.p. 180~181°) with $CHCl_3$ was found identical with XII obtained in the above mentioned experiment on the comparison of IR spectra.

Nitration of Cinnoline 1-Oxide (I) with Benzoyl Nitrate——600 mg. of I was dissolved in 12 ml. of $CHCl_3$ and to this solution was added 0.5 ml. (1 mole) of BzCl, followed by 0.84 g. (1.2 moles) of $AgNO_3$ in small portions, below −10° to −15° with stirring. Stirring was continued for 5 hr. at the same temperature and the mixture was allowed to stand for a week at room temperature. Filtering AgCl precipitated and washing with hot $CHCl_3$, the filtrate was combined with washings and evaporated to small volume. A crystalline product (m.p. 213~215°, 556 mg., 71%) deposited was collected by filtration, and recrystallized from $CHCl_3$ to yellow needles, 3-nitrocinnoline 1-oxide (VI), m.p. 214~215°. *Anal.* Calcd. for $C_8H_5O_3N_3$: C, 50.26; H, 2.64; N, 21.99. Found : C, 50.09; H, 2.79; N, 21.60.

3-Methoxycinnoline 1-Oxide (VII)——A suspension of 100 mg. of VI in 1.5 ml. of MeOH was refluxed with 1.5 ml. of methanolic MeONa (containing 1.2 moles of Na) on a water bath for 1 hr. MeOH was distilled and evaporated to dryness. A small portion of H_2O was added to the residue, and the mixture was extracted with $CHCl_3$. The extracted $CHCl_3$ solution was dried over Na_2SO_4 and evaporated to dryness. The residue (m.p. 88~91°, 87 mg., 95%) was recrystallized from $(iso\text{-}Pr)_2O$ to give pale yellow needles, VII, m.p. 92.5~93.5°. *Anal.* Calcd. for $C_9H_8O_2N_2$: C, 61.36; H, 4.58; N, 15.90. Found : C, 61.50; H, 4.58; N, 15.81. This was identical with authentic 3-methoxycinnoline 1-oxide given by Dr. Kano on comparison of their IR spectra.

Reaction I with Phosphoryl Chloride——200 mg. of I was dissolved in 1 ml. of $POCl_3$ in small portions under cooling. After keeping the mixture at room temperature for 45 min. It was poured into crashed ice, and neutralized with K_2CO_3. It was extracted with Et_2O repeatedly and the combined extract was dried over Na_2SO_4 and evaporated. The residue was purified by alumina chromatography and eluted with $CHCl_3$. $CHCl_3$ was evaporated to dryness, the residue (112 mg., 50%) was recrystallized from Et_2O, pale yellow needles, 4-chlorocinnoline (VIII), m.p. 76~77°. No melting point depression was

NII-Electronic Library Service

observed on admixture with authentic sample prepared from 4-hydroxycinnoline with $POCl_3$, and the IR spectra of the two samples were identical.

The authors express their gratitudes to Prof. E. Ochiai, the Director of Itsuu Laboratory, for his helpful advices, and to Drs. H. Kano and M. Ogata of Shionogi Research Laboratory, who kindly sent the IR spectra of Ⅶ to us. They are also indebted to members of microanalytical center of the University of Tokyo for the analysis data and to Dr. T. Ōba for his co-operation in IR absorption measurements.

Summary

Cinnoline 1-oxide (Ⅰ) gave 4-nitrocinnoline 1-oxide (Ⅱ) and a small amount of 5-nitrocinnoline 1-oxide (Ⅴ) on warming with nitric and sulfuric acids, and gave 4,5-dinitrocinnoline 1-oxide (Ⅳ) by using fuming nitric acid in sulfuric acid. The nitration of Ⅰ with benzoyl nitrate afforded 3-nitrocinnoline 1-oxide (Ⅵ). Ⅰ was converted into 4-chlorocinnoline (Ⅷ) on the treatment with phosphoryl chloride.

(Received June 3, 1964)

[Chem. Pharm. Bull. 12 (9) 1094 ~ 1100] UDC 547.538.2.07

152. Issei Iwai and Junya Ide: Studies on Acetylenic Compounds. XXXVIII.*1 The Novel Cyclization Reaction of Diacetylenic Compounds to Naphthalene Derivatives involving Prototropic Rearrangement.

(*Research Laboratories, Sankyo Co., Ltd.**2)

Recently much attention has been drawn to the reaction of making carbon-carbon bond linkage between triple bond and carbanion[1~3] or carbene[4,5] in the field of acetylenic chemistry. Above all, it seemed to be more important to use non-activated triple bond for this reaction. Raphael and co-workers[6] reported that various diacetylenic hydrocarbons gave benzene derivatives by means of a 10% solution of potassium *tert*-butoxide in boiling bis(2-methoxyethyl) ether. Furthermore, isomerization of *cis*-4-octene-1,7-diyne with potassium *tert*-butoxide in *tert*-butyl alcohol was found to give rise to two aromatic dimers: the spiro-compound and dibenzo[*a*, *e*]cyclooctadiene by Sondheimer and Ben-Efraim.[7]

This paper deals with the cyclization reaction of 1,7-diphenyl-1,6-heptadiyne and other diyne derivatives with potassium *tert*-butoxide in *tert*-butyl alcohol to naphthalene derivatives under a remarkably mild condition. Treatment of 1,7-diphenyl-1,6-heptadiyne (1) with 14% solution of potassium *tert*-butoxide in *tert*-butyl alcohol at 62~63° for

*1 Part XXXVII: This Bulletin, **12**, 813 (1964).
*2 Nishi-shinagawa, Shinagawa-ku, Tokyo (岩井一成, 井手純也).
1) G. Stork: J. Am. Chem. Soc., **86**, 471 (1964).
2) J. E. Mulvaney, Z. G. Gardlund, *et al.*: *Ibid.*, **85**, 3897 (1963).
3) I. Iwai, T. Hiraoka: This Bulletin, **11**, 1556 (1963).
4) I. A. Dyakonov, *et al.*: O. X., **32**, 923 (1962).
5) P. Cadiot, *et al.*: Compt. rend., **255**, 950 (1962).
6) G. Eglinton, R. A. Raphael, R. G. Willis: Proc. Chem. Soc., **1961**, 247.
7) D. A. Ben-Efraim, F. Sondheimer: Tetrahedron Letters, No. 5, 313 (1963).

NII-Electronic Library Service