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94. Ikuo Suzuki, Toshiaki Nakashima, and Natsuko Nagasawa : Studies on Cinnolines. III.*1 Oxidation of 5- and 8-Nitrocinnoline.

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It has been reported that cinnoline and its derivatives, such as 4-methylcinnoline,[1] 4-chlorocinnoline, and 4-methoxycinnoline,[2] gave their 1- and 2-oxides on treatment with hydrogen peroxide or phthalic monoperacid. Ochiai and Okamoto[3] obtained 5-nitroquinoline N-oxide by N-oxidation of 5-nitroquinoline using hydrogen peroxide in acetic acid in good yield.

In the present paper, we wish to report that oxidation of 5- and 8-nitrocinnoline by hydrogen peroxide in acetic acid gave nitroindazole derivatives accompanied with the usual products, such as nitrocinnoline N-oxides.

Heating of 5-nitrocinnoline (I) with hydrogen peroxide in glacial acetic acid at 60~70° for 8 hours, gave two kinds of monoxide (II : m.p. 182~183°, yellow needles in 18% yield, and III : m.p. 213~215°, yellow needles in 43%) whose analytical values corresponded to $C_8H_5O_3N_3$, and pale yellow needles (IV : m.p. 201~203°, yield 16%). III was identical with 5-nitrocinnoline 2-oxide synthesized by nitration of cinnoline 2-oxide using nitric and sulfuric acids.[4] Nitration of II afforded 4,5-dinitrocinnoline 1-oxide,[5] which was obtained by nitration of 4-nitrocinnoline 1-oxide with sulfuric and fuming nitric acids. Therefore II was confirmed to be 5-nitrocinnoline 1-oxide. IV was proved to be identical with 4-nitroindazole, synthesized independently by a known method,[6] by mixed melting point determination and by comparison of infrared spectra of both compounds.

A similar N-oxidation of 8-nitrocinnoline (V) using hydrogen peroxide in acetic acid at 70° for 8 hours afforded 8-nitrocinnoline 2-oxide (VI) in 20% yield, and pale yellow needles in 45% yield, m.p. 181~183°, whose analytical values corresponded to composition of $C_7H_5O_2N_3$. The latter product was found to be identical with 7-nitroindazole (VII) obtained by a known method,[6] by comparing its infrared spectra and determination of the mixed melting point. Furthermore, N-oxidation V afforded a small amount of yellow needles, $C_8H_5O_3N_3$, m.p. 182~184°. This compound was proved to be identical with authentic sample of 8-nitro-4-cinnolinol (VIII) prepared according to the method of Alford.[7] Ochiai and his co-workers[8] reported that quinoline derivatives having bulky groups at 8-position such as 8-quinolinecarboxylic acid did not produce their N-oxides by N-oxidation using hydrogen peroxide, but gave 3-hydroxy compounds such as 3-hydroxy-8-quinolinecarboxylic acid. Similary, it was found that V did not afford 8-nitrocinnoline 1-oxide, but it gave 4-cinnolinol (VIII) different from 8-quinolinecaboxylic acid.

In order to investigate the mechanism of the ring contraction of cinnoline, the experiments changing the oxidizing agent were carried out. The results obtained are shown in Table I and II.

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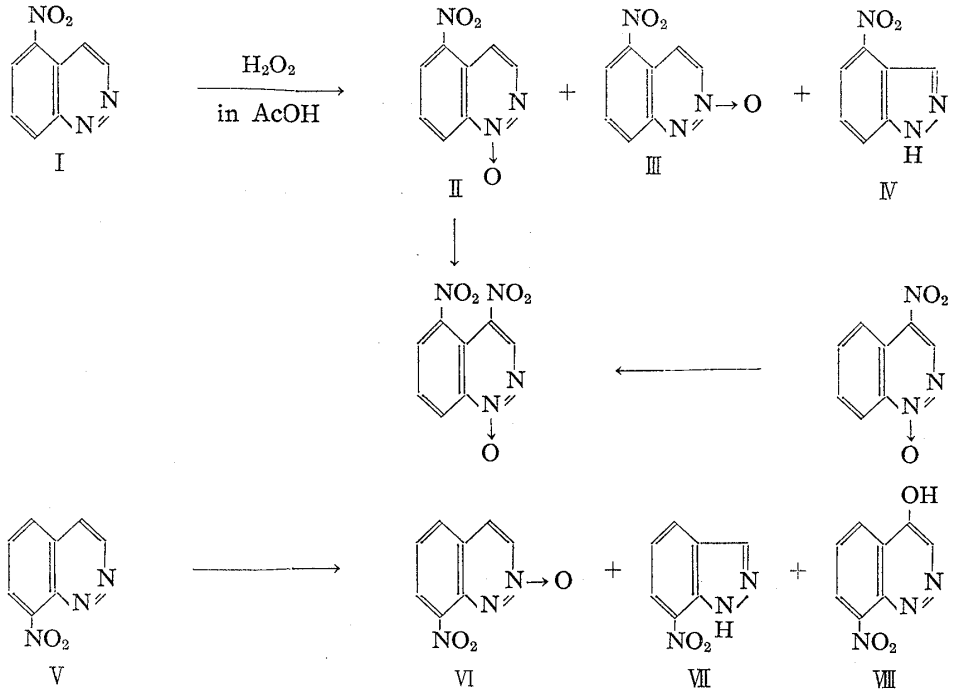

Table I. Oxidation of 5-Nitrocinnoline (I)

I (mg.)	Oxidizing agent	Temp. (°C)	Time (hr.)	Products (%) II	III	IV	Recovery
450	3 ml. 30% H_2O_2 in 5 ml. AcOH	60~70	8	18	43	16	—
100	3.2 mol. $K_2S_2O_8$ in H_2SO_4	40	4	20	46	18	5

Table II. Oxidation of 8-Nitrocinnoline (V)

II (mg.)	Oxidizing agent	Temp. (°C)	Time (hr.)	Products (%) VI	VII	VIII	Recovery
600	3 ml. 30% H_2O_2 in 6 ml. AcOH	60~70	8	20	45	3	—
100	4 ml. 30% H_2O_2	75	8	26	31	6	—
100	phthalic monoperacid	5	7 days	6	16	45	—
100	1 ml. 30% H_2O_2 in 3 ml. H_2SO_4	65	3	18	7	trace	42
100	1.2 mol. $K_2S_2O_8$ in H_2SO_4	40	3	11	35	2	20
100	2.2 mol. $K_2S_2O_8$ in H_2SO_4	40	3.5	12	28	trace	29
100	3.2 mol. $K_2S_2O_8$ in H_2SO_4	40	3.5	18	47	trace	—
100	CrO_3 (0.1 g.) in AcOH	20	2	—	—	15	59

As shown in Table II, when V was treated with hydrogen peroxide, phthalic monoperacid, persulfuric acid, and hydrogen peroxide in sulfuric acid, VII is isolated. On the contrary, oxidation of V using chromic acid in acetic acid gave VIII, and could not find VII. We expected this ring contraction and hydroxydation of V were carried out through some intermediates followed by rearrangement. However, in the oxidation of nitrocinnoline derivatives no intermediate and no carboxylic compound could be isolated from the reaction mixture. Moreover, on oxidation of III and VIII with hydrogen peroxide in acetic acid unchanged III and VIII were recovered. In addition, V was unchanged by heating in acetic acid, and reaction of 8-nitrocinnoline with hydrogen peroxide in alkali

solution gave mainly a resinous compound with 32% recovery of the starting material. On the other hand, oxidation of I using persulfuric acid gave II, III, and IV, but no hydroxy compound could be isolated.

Further work is in progress on mechanism of the contraction reaction of cinnoline and of the formation of 4-hydroxy compound and will be reported at a later date.

Experimental

Oxidation of 5-Nitrocinnoline (I)——a) With H_2O_2 in AcOH : A mixture of 450 mg. of I, 5 ml. of AcOH and 3 ml. of 30% H_2O_2 was heated at 60~70° for 8 hr. on a water bath. To the reaction mixture, 5 ml. of H_2O was added. The mixture was evaporated under reduced pressure, and this procedure was repeated twice. The separated crystals were collected and dissolved in $CHCl_3$. The solution was passed through Al_2O_3 column. From the first fraction eluted with $CHCl_3$, 68 mg. of 5-nitrocinnoline 1-oxide (II), m.p. 182~183°, yellow needles (from acetone), was obtained. *Anal.* Calcd. for $C_8H_5O_3N_3$: C, 50.26; H, 2.64; N, 21.99. Found : C, 50.58; H, 3.17; N, 22.50. II gave 4,5-dinitrocinnoline 1-oxide by nitration using mixed acid as described in preceding report.[5] Evaporation of the second fraction of the eluates gave 210 mg. of crystals. The recrystallization of the crystals from EtOH gave yellow needles, m.p. 215~217°. No melting point depression was observed on admixture with 5-nitrocinnoline 2-oxide (III) which was obtained from nitration of cinnoline 2-oxide, and the IR spectra of the two samples were identical. The third fraction eluted with $CHCl_3$ containing 5% MeOH gave 60 mg. of pale yellow crystals. The recrystallization from H_2O gave IV, pale yellow needles, m.p. 201~203°, undepressed by admixture with 4-nitroindazole prepared by a known method, and the IR spectra of the two samples were identical. *Anal.* Calcd. for $C_7H_5O_2N_3$: C, 51.54; H, 3.09; N, 25.76. Found : C, 51.38; H, 3.00; N, 26.26. The aqueous layer was neutralized with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4 and evaporated. The residue was dissolved in $CHCl_3$. The solution was passed through Al_2O_3 column. By treating the eluate as described above, 23 mg. of II (total yield 72 mg.) and 14 mg. of IV (total yield 74 mg.) were obtained.

b) With $K_2S_2O_8$ in H_2SO_4 : To a well stirred suspension of 495 mg. of $K_2S_2O_8$ in 0.25 ml. of ice-cold conc. H_2SO_4, 2 g. of crashed ice was added and this mixture was added to a solution of 100 mg. of I in 0.5 ml. of conc. H_2SO_4. The mixture was warmed at 40° for 3.5 hr. with occasional stirring. After cooling, the mixture was poured onto crashed ice, and neutralized with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhyd. Na_2SO_4, concentrated to a small volume, passed through a column of Al_2O_3, and eluted with $CHCl_3$. The solvent was evaporated from initial fraction of the eluates, and the residue was dissolved with benzene. The following eluate with $CHCl_3$ containing 5% MeOH, afforded 17 mg. of IV. The benzene solution was passed through the other column of Al_2O_3, and eluted with benzene. The first eluate gave 5 mg. of starting material, the second eluate afforded 21 mg. of II and the third one gave 48 mg. of III.

Oxidation of 8-Nitrocinnoline (V)——a) With H_2O_2 in AcOH : A mixture of 600 mg. of V, 6 ml. of AcOH, and 3 ml. of 30% H_2O_2 was treated in the same way described in oxidation of I. Separated crystals were collected by filtration and were extracted with benzene. Benzene-insoluble crystals (130 mg.) were collected by filtration and recrystallization from EtOH afforded pale yellow needles, m.p. 228° (decomp.). No melting point depression was observed on admixture with 8-nitrocinnoline 2-oxide (VI) which was obtained from nitration of cinnoline 2-oxide, and the IR spectra of the two samples were identical. The filtrate was evaporated and the recrystallization of the residue (250 mg.) from benzene gave VII, pale yellow needles, m.p. 181~183°, undepressed by admixture with 7-nitroindazole prepared by a known method, and the IR spectra of the two samples were identical. *Anal.* Calcd. for $C_7H_5O_3N_2$: C, 51.54; H, 3.09; N, 25.76. Found : C, 51.65; H, 2.96; N, 25.68. The aqueous layer was neutralized with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over anhyd. Na_2SO_4 and evaporated. The residue was dissolved in benzene. The solution was passed through Al_2O_3 column. The first eluate gave 23 mg. of VII (total yield 273 mg.), and the third one with $CHCl_3$ gave 20 mg. of 8-nitro-4-cinnolinol (VIII), m.p, 182~184°, undepressed by admixture with an authentic sample, and the IR spectra of the two samples were idetical.

b) With H_2O_2 : A mixture of 100 mg. of V in 4 ml. of 30% H_2O_2 was warmed at 75° for 8 hr. To this solution, H_2O was added, and it was evaporated under reduced pressure. The residue was dried in a desiccator and extracted with $CHCl_3$. The $CHCl_3$ solution was concentrated to a small volume, and passed through a column of Florisil, and eluted with $CHCl_3$. The first eluate gave 29 mg. of VII, the second eluate afforded 7 mg. of VIII and the third one gave 28 mg. of VI.

c) With phthalic monoperacid : A mixture of 100 mg. of V in 15 ml. of ethereal phthalic monoperacid solution (active oxygen 13 mg./ml.) was allowed to stand for a week at 5°. The ether solution was evaporated, and the residue was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with aq. $NaHCO_3$ solution, and dried over anhyd. Na_2SO_4, and passed through Florisil column. By treating the eluates as described in (b), 15 mg. of VII, 49 mg. of VIII and 6 mg. of VI were obtained respectively.

d) With H_2O_2 in 10% H_2SO_4 : A mixture of 100 mg. of V, 3 ml. of 10% H_2SO_4, and 1 ml. of 30% H_2O_2 was warmed at 65° for 3 hr. After cooling the mixture was neutralized with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhyd. Na_2SO_4, concentrated to a small volume, passed through a column of Florisil, and eluted with $CHCl_3$. The solvent was evaporated from the initial fraction of the eluates, and the residue was dissolved with benzene. From the following fraction, 19 mg. of VI was obtained. The benzene solution was passed through a column of Al_2O_3, and eluted with benzene. The first eluate gave 7 mg. of VII, the second eluate afforded 42 mg. of starting material, and the third one gave trace of VIII.

e) With $K_2S_2O_8$ in H_2SO_4 : The reaction V (100 mg.) with $K_2S_2O_8$ was carried out in a manner similar to the experiment described in (b) under oxidation of I, and treatment of the dried $CHCl_3$ solution by the same method as described in (d) afforded 44 mg. of VII, trace of VIII, and 19 mg. of VI.

f) With CrO_3 in AcOH : To a solution of 100 mg. of V in 1 ml. of AcOH, a solution of 0.1 g. of anhyd. CrO_3 in 0.1 ml. of H_2O was added. The mixture was allowed to stand at room temperature for 2 hr., and poured into crashed ice, and neutralized with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhyd. Na_2SO_4, and evaporated. The residue was dried in a desiccator and extracted with benzene, and passed through a column of Al_2O_3, and eluted with benzene. The first eluate gave 59 mg. of starting material, the second eluate gave 15 mg. of VIII.

g) With H_2O_2 in 5% NaOH : A mixture of 100 mg. of V, 5 ml. of 5% NaOH, and 1 ml. of 30% H_2O_2 was allowed to stand for 3 hr. at room temperature. The reaction mixture was neutralized with 5% HCl, and evaporated under reduced pressure. The resinous substance was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhyd. Na_2SO_4, concentrated to a small volume, passed through of Al_2O_3 column. Elution with benzene gave 32 mg. of starting material.

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Summary

The oxidation of 5-nitrocinnoline (I) with hydrogen peroxide in acetic acid, and with persulfuric acid in sulfuric acid afforded 5-nitrocinnoline 1-oxide (II), 5-nitrocinnoline 2-oxide (III), and 4-nitroindazole (IV). The oxidation of 8-nitrocinnoline (V) with hydrogen peroxide in acetic acid, with hydrogen peroxide, with phthalic monoperacid, with hydrogen peroxide in 10% sulfuric acid, and with persulfuric acid in sulfuric acid afforded 8-nitrocinnoline 2-oxide (VI), 7-nitroindazole (VII), and 8-nitro-4-cinnolinol (VIII). On the other hand, the oxidation of V with chromic acid in acetic acid gave only VIII with recovery of V.

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