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50. Haruyuki Ito : Synthesis of Nitro Compounds by Means of Oxidation of Acylamino Compounds. XII.*1 About the Reaction Mechanism of Oxidation of Quinoline.

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A new reaction which affords *o*-nitrobenzoic acid by hydrogen peroxide oxidation of quinoline has been reported in the previous paper by Kosuge[1] and a reaction mechanism was proposed as follows. The first step of this reaction was oxidation of quinoline to its 1-oxide, followed by rearrangement to carbostyril, which was oxidized to *o*-nitrobenzoic acid as shown in Chart 1.

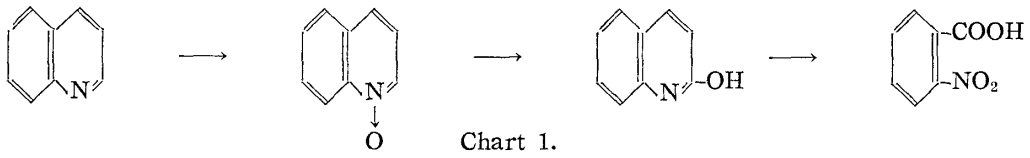

Chart 1.

Further investigation about the assumed mechanism was carried out, and a reasonable mechanism of this reaction was proposed in the present paper.

Route of Formation of Carbostyril 1-Oxide by Oxidation of Quinoline with Hydrogen Peroxide

The first step of Chart 1 may be entirely doubtless, since it is the well-known fact that quinoline 1-oxide is formed by oxidation of quinoline with hydrogen peroxide in acetic acid in an excellent yield. The formation of carbostyril from quinoline 1-oxide reported by Ochiai, *et al.*[2,3] and Katada[4] was the reaction *via* Reissert's compounds which were formed by addition of acetic anhydride or tosyl chloride to quinoline 1-oxide. But, in the condition of the present oxidation, the rearrangement of quinoline 1-oxide to carbostyril did not occur. Quinoline 1-oxide was heated in acetic acid or in acetic acid containing sulfuric acid, which was used as stabilizer of hydrogen peroxide, but carbostyril could not be detected in the reaction mixture, and therefore, it was not an intermediate of the oxidation to *o*-nitrobenzoic acid.

It was found that carbostyril 1-oxide and carbostyril were obtained in yields of 4.7 and 0.5% respectively on a weak oxidation of quinoline 1-oxide. Carbostyril 1-oxide was considered to be one of intermediates of the reaction steps, since this compound was oxidized to *o*-nitrobenzoic acid in satisfactory yield of 62%. The reaction which affords carbostyril 1-oxide by oxidation of quinoline 1-oxide was the method of Hamana,[5] which was the oxidation with potassium ferricyanide in alkaline medium and the mechanism was explained to be the oxidation of a pseudo-base as well as the oxidation of ordinary quinolinium salts. In the present oxidation, however, it was unreasonable to assume the mechanism as oxidation of a pseudo-base, since the reaction proceeded in acidic medium.

It would be reasonable that the route of the formation of carbostyril was considered to be an oxidative deoxidation of carbostyril 1-oxide, since some of analogous reaction

*1 Part XI : This Bulletin, **12**, 337 (1964).
*2 Oshika, Shizuoka (伊藤晴之).
1) T. Kosuge : This Bulletin, **2**, 397 (1954).
2) E. Ochiai, T. Okamoto : Yakugaku Zasshi, **68**, 88 (1948).
3) E. Ochiai, I. Yokokawa : *Ibid.*, **75**, 213 (1955).
4) M. Katada : *Ibid.*, **67**, 51 (1947).
5) M. Hamana : Private communication. cf. M. Hamana, M. Yamazaki : This Bulletin, **10**, 51 (1962).

have been known, *e.g.* the formation of 2-nitropyridine by nitration of pyridine 1-oxide with a mixture of potassium nitrate and sulfuric acid,[6] and the formation of 4-imidazolepropionic acid by oxidation of 2-mercapto-4-imidazolepropionic acid with ferric chloride.[7] Actually, carbostyril was obtained by weak oxidation of its N-oxide, and this was done with three moles of 30% hydrogen peroxide in acetic acid for one hour in yields of 4.5 and 10%. In order to confirm the oxidative deoxidation of N-oxide with hydrogen peroxide, the similar oxidation was carried out using carefully purified quinoline 1-oxide and quinoline was taken up as its picrate in yield of 1.5%. Carbostyril was oxidized to carbostyril 1-oxide in 3.2% yield by the analogous oxidation.

From these empirical facts, it was confirmed that there was a mutual conversion between carbostyril and carbostyril 1-oxide in oxidative medium of hydrogen peroxide as well as the relation between quinoline and quinoline 1-oxide (Chart 2).

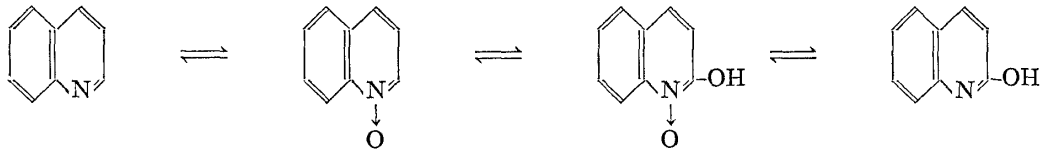

Chart 2.

Route to *o*-Nitrobenzoic Acid from Carbostyril 1-Oxide by the Oxidation with Hydrogen Peroxide

In spite of efforts, any intermediate of oxidation of carbostyril 1-oxide to *o*-nitrobenzoic acid was not obtained. However, in the oxidation of 2-methylaminoquinoline, *cis-o*-nitrocinnamonitrile was obtained,[*3] which pointed out the oxidative cleavage of 1~2 bond of quinoline ring. This would suggest a possibility of oxidative cleavage of 1~2 bond of carbostyril 1-oxide to 2-nitrocinnamic acid.

In the oxidation of quinoline with hydrogen peroxide, 2,2′-dicarboxyazoxybenzene was obtained, which was regarded to be a by-product of this reaction. Considering the formation of the azoxy compound, it was presumed that a nitroso compound was formed by oxidative cleavage of carbostyril 1-oxide before the formation of the nitro compound, and a hydroxylamino or amino compound was formed by hydrolytic cleavage of carbostyril 1-oxide or carbostyril. Based on these facts and referred to the mechanism of the oxidation of acylamino compounds presented in Part IX[8] of this series, a reasonable mechanism of the oxidation of carbostyril 1-oxide to *o*-nitrobenzoic acid was proposed as shown in Chart 3.

Carbostyril 1-oxide would be transformed to 2-nitrosocinnamic acid through the processes of N-oxidation, hydrolytic cleavage of 1~2 bond and dehydration at the nitrogen position. 2-Nitrosocinnamic acid would be oxidized to *o*-nitrobenzoic acid *via* 2-nitrocinnamic acid. On the other hand, carbostyril 1-oxide would be hydrolized to 2-hydroxylaminocinnamic acid or oxidatively deoxidized to carbostyril, which would be hydrolized to 2-aminocinnamic acid and further oxidized to 2-hydroxylaminocinnamic acid. *o*-Nitrosocinnamic acid would be condensed with 2-hydroxylamino or 2-aminocinnamic acid to form azoxy or azo compound, either being oxidized to 2,2′-dicarboxylazobenzene. This reaction mechanism would be regarded as the reverse reaction forming carbostyril 1-oxide by reductive cyclization of ethyl 2-nitrocinnamoate.[9]

*3 Details will be discussed in Part XIII, This Bulletin, **12**, 350 (1964).

6) M. Katada : Yakugaku Zasshi, **67**, 56 (1947).
7) S. Akabori : Ber., **66**, 151 (1933).
8) H. Ito : This Bulletin., **12**, 326 (1964).
9) F. Friedrender, H. Ostermaier : Ber., **14**, 1916 (1881); *Ibid.*, **15**, 332 (1882).

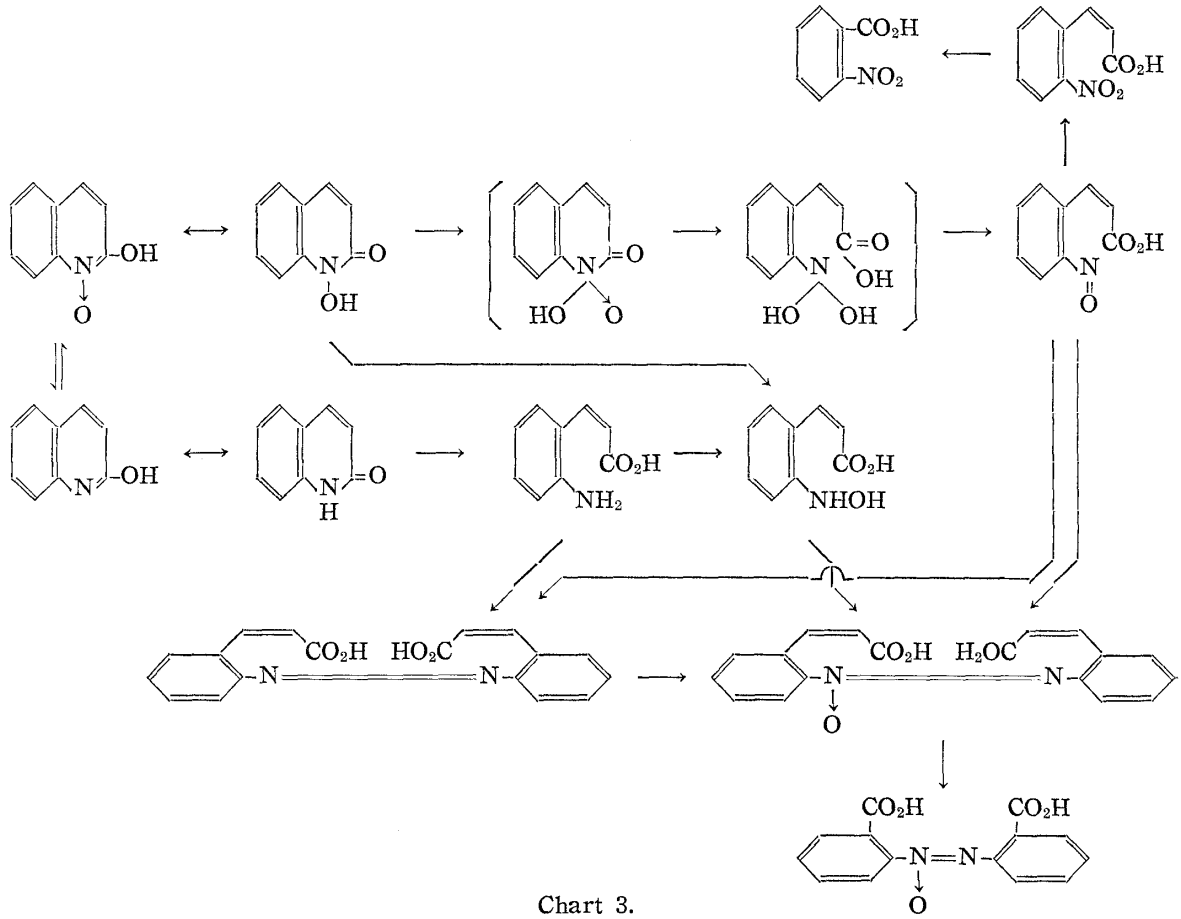

Chart 3.

A Mild Oxidation of Quinoline with Hydrogen Peroxide

Quinoline 1-oxide was oxidized to carbostyril 1-oxide as shown above. In order to ascertain that N-oxide was necessary to achieve the oxidation at 2-position, a mild oxidation of quinoline with hydrogen peroxide was investigated and this was done in a water medium using a small amount of acetic acid, just to dissolved quinoline. Thus the formation of acetic peracid was restricted. The hydrogen peroxide oxidation of quinoline in this medium afforded colorless needles, m.p. 195~196°, in yield of 3%. Recrystallization of this substance afforded colorless needles, C_9H_7ON, m.p. 198~198.5°. It formed picrate, m.p. 239~242°(decomp.), oxalate, m.p. 205~206°(decomp.) and tosylate, m.p. 90~92° and was confirmed to be 3-quinolinol by mixed melting point determination and comparison of their infrared absorption spectra.

Ochiai, *et al.*[10] have reported the oxidation at 3-position of quinoline derivatives. 3-Quinolinol were obtained in good yields in the cases of 8-substituted quinolines, where the N-oxidation was restricted by the steric hindrance of the substituents at 8-position. In the present reaction, restriction of the N-oxidation was performed by change of the oxidation medium.

The oxidation of a quinolinium salt was next tried. A stoichiometric amount of sulfuric acid was added to a mixture of quinoline in water and the mixture was submitted to the hydrogen peroxide oxidation. Light brown crystals, m.p. 216~218°, were obtained and recrystallization of this product gave colorless needles, C_9H_7ON, m.p. 223°(decomp.), which formed picrate, m.p. 193~194°, oxalate, m.p. 191°(decomp.) and tosylate, m.p. 85~87°. By comparison of infrared spectra and admixture, it was identified as 5-quinolinol.

10) E. Ochiai, C. Kaneko, T. Kosuge, *et al.* : This Bulletin, 8, 126 (1960).

Experimental*4

Formation of Carbostyril 1-Oxide and Carbostyril by Oxidation of Quinoline 1-Oxide——A mixture of 4 g. of quinoline 1-oxide and 8.4 ml. of 30% H_2O_2 in 40 ml. of AcOH was heated on a steam bath for 2 hr. The mixture was evaporated under reduced pressure, 20 ml. of H_2O was added to the residue and it was evaporated to dryness again. To the orange brown residue was added H_2O and it was extracted twice with 30 ml. of Et_2O. The combined Et_2O solution was shaken with 10% Na_2CO_3 and then with 10% NaOH. The Na_2CO_3 layer was neutralized with dil. HCl and extracted with $CHCl_3$, the $CHCl_3$ solution was submitted to Al_2O_3 chromatography after drying over Na_2SO_4 and 0.21 g. of light brown crystals, m.p. 179~182°, was obtained from a part of $CHCl_3$ eluate, which exhibited red color with $FeCl_3$. This substance was recrystallized from benzene to colorless prisms, m.p. 185~186°, and no melting point depression was observed by mixed melting point with carbostyril 1-oxide. *Anal.* Calcd. for $C_9H_7O_2N$: C, 67.07; H, 4.36; N, 8.89. Found : C, 66.77; H, 4.38; N, 8.69. The NaOH layer was submitted to silicagel chromatography, and 0.02 g. of yellowish crystals was obtained. Recrystallization of this substance gave colorless prisms, m.p. 192~194°, which was identified as carbostyril by admixture.

Treatment of Quinoline 1-Oxide with Acetic Acid containing Sulfuric Acid——A mixture of 4 g. quinoline 1-oxide, 40 ml. of AcOH and 8 ml. of 1% H_2SO_4 was heated on a steam bath for 8 hr. The mixture was evaporated under reduced pressure, and the residue was extracted with Et_2O, the Et_2O solution was extracted with 10% NaOH after washing with 10% Na_2CO_3. The NaOH extract was neutralized and extracted with Et_2O, 0.2 g. of yellowish brown oil was obtained from Et_2O solution. Its $CHCl_3$ solution was chromatographed over a silica-gel column using $CHCl_3$, but a substance proved to be carbostyril was not obtained.

Formation of *o*-Nitrobenzoic Acid by Oxidation of Carbostyril 1-Oxide——A mixture of 1 g. of carbostyril 1-oxide and 13.5 ml. of 30% H_2O_2 in 9 ml. of AcOH was heated on a steam bath for 20 hr. The mixture was evaporated under reduced pressure, the residue was dissolved in 200 ml. of $CHCl_3$, and it was extracted with 5% Na_2CO_3. The extract was neutralized with dil. HCl and 0.55 g. of yellowish crystals, m.p. 138~142° was obtained. Recrystallization from H_2O gave colorless needles, m.p. 147~148°, which was shown to be *o*-nitrobenzoic acid by admixture. Yield 62%.

Formation of Carbostyril by Oxidation of Carbostyril 1-Oxide——a) A mixture of 1 g. of carbostyril 1-oxide and 2 ml. of 30% H_2O_2 in 9 ml. of AcOH was heated on a steam bath for 1 hr. The mixture was evaporated under reduced pressure, the residue was extracted with Et_2O and the Et_2O solution was extracted with 10% Na_2CO_3. The Na_2CO_3 extract was neutralized with 10% HCl and 0.1 g. of the light brown solid was obtained, which exhibited red color with $FeCl_3$. Recrystallization from benzene gave colorless prisms, m.p. 185~186°(the recovery of carbostyril 1-oxide). The residual Et_2O solution of Na_2CO_3 extraction was extracted with 10% NaOH, the extract was neutralized with 10% HCl, deposit was taken up with $CHCl_3$, the $CHCl_3$ extract was dried over Na_2SO_4 and it was separated by chromatography over silica-gel column using $CHCl_3$. 0.05 g. of yellowish crystals, m.p. 190~193°, was obtained from a part of $CHCl_3$ eluate. This substance was recrystallized from benzene to colorless prisms melted at 195~196°, whose identity with carbostyril was confirmed by the mixed melting point determination. *Anal.* Calcd. for C_9H_7ON : C, 74.74; H, 4.86; N, 9.65. Found : C, 74.35; H, 4.71; N, 9.72.

b) A mixture of 0.71 g. of carbostyril 1-oxide and 1.4 ml. of 30% H_2O_2 in 18 ml. of AcOH was heated on a steam bath. After 3 hrs' heating 1 ml. of 30% H_2O_2 was added to the mixture and the reaction was continued for 3 hr. After cooling, insoluble material was filtered off and the filtrate was evaporated *in vacuo*, the residue was washed with 10% Na_2CO_3 and then extracted with 10% NaOH. The NaOH solution was neutralized with 10% HCl and 0.11 g. of brown crystals, m.p. 189~192°, was obtained as precipitate. Recrystallization of this substance gave prisms melted at 194.5~196°, which was identified as carbostyril by admixture.

Formation of Quinoline by Oxidation of Quinoline 1-Oxide with Hydrogen Peroxide——The purification of quinoline 1-oxide was carried out as follows. Quinoline 1-oxide was vacuum-distilled and a fraction of $b.p_5$ 165~166° was collected, the distilled N-oxide was dissolved in H_2O and the solution was steam-distilled to remove a trace of quinoline. The residual solution was evaporated under reduced pressure and to the residue were added Et_2O and theoretical amount of H_2O to dihydrate.

To a solution of 2 g. of quinoline 1-oxide dihydrate in 20 ml. of AcOH was added 4 ml. of 30% H_2O_2. The mixture was heated on a steam bath for 5 hr. and neutralized with conc. NH_4OH under H_2O-cooling and steam-distilled. The distillate was extracted with benzene, and the benzene solution was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was converted to its picrate, and 0.06 g. of yellow needles, m.p. 195~202°, was obtained. This was recrystallized from MeOH to yellow needles melted at 202~203°, which was identified as quinoline picrate by admixture.

Formation of Carbostyril 1-Oxide by Oxidation of Carbostyril with Hydrogen Peroxide——A mixture of 2 g. of carbostyril and 40 ml. of 30% H_2O_2 in 20 ml. of AcOH was heated on a steam bath for

*4 All melting points were uncorrected.

5 hr. The mixture was evaporated to dryness under reduced pressure, 15 ml. of H_2O was added to the residue and the mixture was evaporated in the same manner. The residue was extracted with 10% Na_2CO_3, and the alkaline solution was neutralized with 10% HCl and shaken with $CHCl_3$. The extract was dried over Na_2SO_4, separated by chromatography over silica-gel column and 0.07 g. of yellowish crystals, m.p. 180~183°, was obtained. Recrystallization from benzene gave colorless prisms, m.p. 185~186°, which was proved to be carbostyril 1-oxide by admixture. 0.7 g. of crude carbostyril, m.p. 185~192°, was recovered from residual mass of Na_2CO_3 extract by extraction with 10% NaOH, followed by neutrallization.

Formation of 2,2′-Dicarboxyazoxybenzene by Oxidation of Quinoline with Hydrogen Peroxide——A mixture of 4.3 g. of quinoline and 14 ml. of 30% H_2O_2 in 40ml. of AcOH was heated on a steam bath for 20 hr. To the mixture was added $KMnO_4$, and deposit of MnO_2 was filtered off and the filtrate was evaporated under reduced pressure. The reddish residue was extractd with 10% Na_2CO_3, the extract was neutralized with 10% HCl, shaken with Et_2O, the Et_2O solution was dried over Na_2SO_4 and evaporated to dryness. The residue was washed with benzene and 0.1 g. of brownish material was obtained. This substance was recrystallized to yellowish needles, m.p. 239~240.5° (decomp.), which undepressed with 2,2′-dicarboxyazoxybenzene. *Anal.* Calcd. for $C_{14}H_{10}O_5N_2$: C, 58.74.; H, 3.52; N, 9.76. Found : C, 58.51; H, 3.55; N, 9.98. From the benzene washing, 0.01 g. of *o*-nitrobenzoic acid and quinoline 1-oxide were obtained through a silica-gel column.

Oxidation of Quinoline to 3-Quinolinol——12.9 g. of quinoline was dissolved in 12 ml. of AcOH, 15 ml. of 30% H_2O_2 and 120 ml. of H_2O were added to the solution, and the mixture was heated on a steam bath for 5 hr. 5 ml. of 85% HCOOH was added to the reaction mixture and it was heated for further 3 hr. It was cooled and neutralized with $NaHCO_3$ and extracted with Et_2O. The Et_2O layer was shaken with 10% NaOH, the NaOH layer was acidified with conc. HCl and the precipitate was removed by filtration. The acidic aq. solution was neutralized with $NaHCO_3$ and extracted with Et_2O. The Et_2O solution was evaporated to dryness, the residue was dissolved in $CHCl_3$ and purified by chromatography through an Al_2O_3 column. From a part of Me_2CO eluate, 0.5 g. of needles, m.p. 195~196° was obtained. This was recrystallized from benzene to colorless needles, m.p. 198~198.5°. *Anal.* Calcd. for C_9H_7ON: C, 74.74; H, 4.86; N, 9.65. Found : C, 74.28; H, 4.85; N, 9.73. When admixed with 3-quinolinol, no melting point depression was observed. IR spectrum of this substance was superimposable with that of 3-quinolinol. Picrate (from EtOH), yellow needles, m.p. 239~242° (decomp.). *Anal.* Calcd. for $C_{15}H_{10}O_8N_4$: C, 48.13; H, 2.69; N, 14.97. Found : C, 48.09; H, 2.70; N, 14.82. Oxalate (from EtOH), colorless needles, m.p. 205~206° (decomp.). Tosylate (from Et_2O-petr. ether), m.p. 90~92°.

Oxidation of Quinolinium Sulfate to 5-Quinolinol——A mixture of 12.9 g. of quinoline, 9.8 g. conc. H_2SO_4 and 20ml. of 30% H_2O_2 in 120 ml. of H_2O, was heated on a steam bath for 5 hr. and 5 ml. of 85% HCOOH was added and heating was continued for further 3 hr. After cool, the mixture was treated and purified with the same manner as above. 0.4 g. of light brown crystals, m.p. 216~218° (decomp.) was obtained from a part of Me_2CO eluate of chromatography. Recrystallization gave colorless needles, m.p. 223° (decomp.). *Anal.* Calcd. for C_9H_7ON : C, 74.74; H, 4.86; N, 9.65. Found : C, 74.44; H, 4.86; N, 9.68. This substance was identified as 5-quinolinol by admixture and comparison of IR spectra. Picrate (from EtOH-Et_2O), yellow needles, m.p. 193~194°. Oxalate (from EtOH-benzene), colorless needles, m.p. 191° (decomp.). Tosylate (from EtOH), colorless needles, m.p. 85~87°.

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Summary

A reaction mechanism of the oxidation of quinoline to *o*-nitrobenzoic acid with hydrogen peroxide was suggested. In the mechanism, the main intermediates were quinoline 1-oxide, carbostyril 1-oxide, 2-nitrosocinnamic acid and 2-nitrocinnamic acid. It was experimentally confirmed that the oxidation of 2-position of quinoline 1-oxide in acidic medium and oxidative deoxidation of quinoline 1-oxide and carbostyril 1-oxide took place during the hydrogen peroxide treatment. In a restricted oxidation with hydrogen peroxide, quinoline was oxidized to 3-quinolinol and quinolinium sulfate afforded 5-quinolinol.

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