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Oxidative Cleavage of the 1,2-Linkage of 2,3-Disubstituted-4(3*H*)-quinazolinone with Hydrogen Peroxide[1]

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In oxidation of 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (I) with hydrogen peroxide, five products in addition to unreacted I were obtained from reaction mixture and identified as N-(*o*-tolyl)-2-nitrobenzamide(II), 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone 1-N-oxide (III), N-acetyl-*o*-toluidide(IV), (2-carboxyphenyl)(2-methylphenyl)diazene(V), and N-(acetyl)(*o*-tolyl)-2-nitrobenzimide (VI), respectively, and a reaction mechanism of I to II was proposed.

Keywords——oxidative cleavage reaction; hydrogen peroxide; heterocycliccompound; quinazolinone; isolation of products; reaction mechanism; drug metabolism

In the previous paper,[3] Murata and Yamamoto reported the oxidation of 2,3-disubstituted 4(3*H*)-quinazolinone with hydrogen peroxide in relationship between chemical oxidation and biological oxidation. A crystal (mp 175°) was obtained in 32% yield and its structure was identified as N-(*o*-tolyl)-2-nitrobenzamide (II) which was the same product as a metabolite of 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (I) in human.[3,4]

Furthermore, they assumed that the oxidation of I to II will proceed through its N-oxide (III). After that, Toyoshima, *et al.*[5] isolated the N-oxide from the reaction mixture under almost the same condition.

The authors are particularly interested in the oxidative reaction of I because of the similarity to biological oxidation.[4] In the connection of this study, Gorrod[6] has reviewed the biological oxidation of heterocyclic amine in detail. Very recently Beckett and Belanger[7,8] proposed an interesting mechanism for the metabolic N-oxidation of amines to their hydroxyamino and nitroso compounds after *in vitro* studies using liver homogenates and *in vivo* studies in animals and man.

On the other hand, a few heterocyclic compounds such as quinoline, carbostyril and 2-methylaminoquinoline have been known to undergo the oxidative cleavage with hydrogen peroxide and to give the corresponding nitrobenzoic acids.[9,10] Ito[10] described in detail a reaction mechanism of the oxidation of quinolines to *o*-nitrobenzoic acids with hydrogen peroxide.

However, no reports deals with 2,3-disubstituted heterocyclic compounds having two nitrogen atoms such as 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (I) as previously reported.[3]

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Table I. Reaction Products of 2-Methyl-3-*o*-tolyl-4(3*H*)-quinazolinone with Hydrogen Peroxide

Compd. No.	mp[a] (°C)	Recryst. solvent	Yield[b] (%)	Appearance	Formula	*Anal.* (%) Calcd. (Found)		
						C	H	N
I	114—116							
II	175[c]	EtOH	32.0	pale yellow needles	$C_{14}H_{12}O_3N_2$	65.62 (65.68)	4.72 (4.92)	10.93 (11.02)
III	187—189[d] (decomp.)	acetone	16.9	yellow needles	$C_{16}H_{14}O_2N_2$	72.16 (71.68)	5.31 (5.51)	10.53 (10.42)
IV	107—108[e]	H_2O	3.1	colorless needles	$C_9H_{11}ON$	72.46 (72.47)	7.43 (7.35)	9.39 (9.45)
V	138—139[f]	EtOH	2.3	orange needles	$C_{14}H_{12}O_2N_2$	70.06 (69.76)	5.04 (5.05)	11.67 (11.72)
VI	118—119	70% EtOH	2.7	yellow prisms	$C_{16}H_{14}O_4N_2$	64.42 (64.34)	4.73 (4.65)	9.39 (9.53)

a) All melting points are uncorrected.
b) Calcd. on the basis of I
c) reported [11]mp 174°
d) reported [5]mp 188—190° (decomp.)
e) reported [12]mp 104.5—106°
f) reported [13]mp 138°

In order to elucidate the mechanism for this oxidative reaction of quinazolinone, attempts were made to isolate another intermediate.

As shown in Table I, the reaction of I with hydrogen peroxide in acetic acid gave N-(*o*-tolyl)-2-nitrobenzamide (II), 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone 1-N-oxide (III), N-acetyl-*o*-toluidide (IV), (2-carboxyphenyl)(2-methylphenyl)diazene (V), and N-(acetyl)(*o*-tolyl)-2-nitrobenzimide (VI) along with considerable amounts of the starting material.

Molecular formula $C_{16}H_{14}O_4N_2$ (VI) for a new cleavage product as an intermediate was confirmed by its mass spectrum and the elementary analysis. The IR bands at 1522 and 1350 cm^{-1} indicate that VI has a nitro group. The nuclear magnetic resonance (NMR) spectrum is similar to I and III, but it has no quinazolinone ring from the data of IR of quinazolinone compounds.[14] From these analytical and spectral data, the structure of VI could be assigned as N-(acetyl)(*o*-tolyl)-2-nitrobenzimide.

In the above reaction the TLC of the reaction products was investigated, and it showed 5 to 6 spots, one of which could not be obtained in a pure state and seemed to be an unstable material besides. Further, we could not isolate any cleavage products of the 2,3-linkage from the reaction mixture. Thus, the formation mechanism of the compound (II) in the present reaction would be presumed two routes as follows.

In the oxidation of I, it confirmed that the first step was its N-oxide (III) which was an intermediate of the oxidation of I to II, since III was easily oxidized with hydrogen peroxide to give II in good yield.[5] Ito[10] reported that in oxidation of 2-methylaminoquinoline with hydrogen peroxide, *cis*-2-nitrocinnamonitrile and a small amount of carbostyril were obtained, and the formation mechanism was proposed without isolating any intermediates, based on the mechanism of the series of the hydrogen peroxide oxidation.

From our results, it would be reasonable that III is transformed *via* route A or route B into the intermediates described above by further oxidation and hydrolysis, followed by oxida-

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12) D.E. Pearson and W.E. Cole, *J. Org. Chem.*, **20**, 488 (1955).
13) W. Meer, *Chem. Zentr.*, **1903**, II, 973.
14) H. Culbertson, J.C. Decius, and B.E. Christensen, *J. Am. Chem. Soc.*, 74, 4834 (1952).

tion of N-(acetyl)(*o*-tolyl)-2-nitrosobenzimide to afford VI. Fission *via* route A affords nitroso compound, whereas the fission *via* route B occurs to give hydroxylamino compound. On the other hand, we obtained IV, and V which were regarded to be artifical products in this reaction. Under this condition, it gave no azoxy compound which was obtained by Ito.[10] Therefore, the artificial formation mechanism of azo compound (V) might be proceeded as shown in Chart 1. N-(Acetyl)(*o*-tolyl)-2-hydroxylaminobenzimide or N-(acetyl)(*o*-tolyl)-2-nitrosobenzimide is hydrolized to the intermediates such as *o*-hydroxylaminobenzoic acid or *o*-nitrosoben-

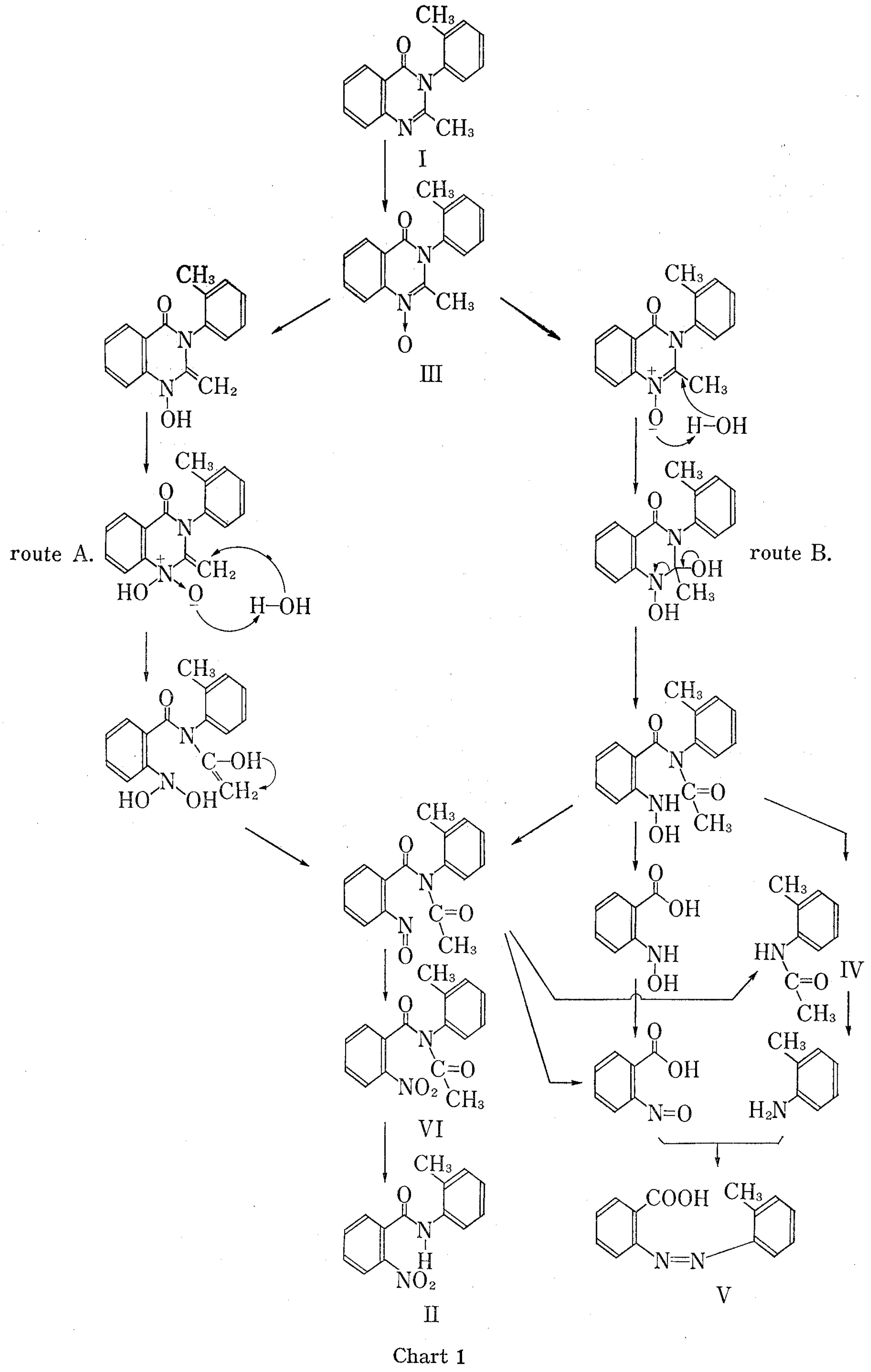

Chart 1

zoic acid and IV or *o*-toluidine by N-C bond fission at 3,4 position, followed by condensation to give V.

Finally, hydrolysis of VI would occur to give our final product(II). The formation of a new compound (VI) strongly suggests that the cleavage of quinazolinone ring occurs at the 1,2-linkage and the oxidation of I to II will proceed through III and then VI as key intermediates. On the basis of these facts and referred to the oxidation of I to II with hydrogen peroxide can be well rationalized by the mechanism shown in Chart 1.

Experimental[15]

General Method of Oxidation of 2-Methyl-3-o-tolyl-4(3*H*)-quinazolinone——To a solution of 25.0 g (0.1 mole) of I dissolved in 280 ml of AcOH, 20 ml of 30% H_2O_2 were added and was stirred at (a) 50°, (b) 70°, and (c) 90°. After 5 hr, 16 ml of 30% H_2O_2 were added again for total reaction time was (a) 50 hr, (b) 10 hr, and (c) 10 hr, respectively. After the reaction was over, the solvent was distilled off under reduced pressure.

Isolation of N-(*o*-Tolyl)-2-nitrobenzamide(II), 2-Methyl-3-*o*-tolyl-4(3*H*)-quinazolinone 1-N-Oxide(III), N-Acetyl-*o*-toluidide (IV), and N-(Acetyl)(*o*-tolyl)-2-nitrobenzimide(VI)——The dark red residue thus obtained was applied on a column of alumina treated with 10% AcOH. The column was eluted with benzene, benzene-acetone (9: 1) and benzene-acetone (3: 1), successively. Each fraction was submitted to the thin-layer chromatography (TLC) with $CHCl_3$-acetone (9: 1), and TLC showed the presence of I, II, III, and VI. On the thin layer chromatogram, four or five spots of products were found other than the spot of unreacted I. Two spots of products (*Rf* 0.22 and 0.00) exhibited yellow color fluorescence with UV light. Unreacted I was obtained from elution with benzene. This substance was recrystallized from 80% EtOH to colorless prisms, mp 114—116°, and no melting point depression was observed by mixed melting point with 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone. Pale yellow needles (II) was identified as N-(*o*-tolyl)2-nitrobenzamide with authentic sample as previously reported.[3] A yellow crystal(III) was obtained from a part of benzene-acetone (9: 1). This substance was recrystallized to yellow needles, mp 188—190° (decomp.) from acetone, which showed orange staining with Dragendorff reagent and exhibited fluorescence as yellow color with UV light. Yield, 4.51 g (16.9%). *Anal.* Calcd. for $C_{16}H_{14}O_2N_2$: C, 72.16; H, 5.31; N, 10.53. Found: C, 71.68; H, 5.51; N, 10.42. IR ν_{max}^{KBr} cm^{-1}: 1092 (for N-oxide). UV λ_{max}^{EtOH} nm (log ε): 315 (4.13). Colorless needles (IV) obtained from a part of benzene-acetone (3: 1) had 107—108°. Yield, 0.47 (3.1%). The product proved to be entirely identical as N-acetyl-*o*-toluidide with the synthetic sample by mixed melting point determination. Yellow prisms(VI) was obtained from the same fraction eluted with benzene: acetone (9: 1) after obtaining III. It showed a positive (orange color) with Dragendorff reagent, but negative reaction of Ehrlich reagent, mp 118—119° (from 70% EtOH), and the mp depressed with I (mp 114—116°). Yield, 0.81 g (2.7%). *Anal.* Calcd. for $C_{16}H_{14}O_4N_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.34; H, 4.65; N, 9.53. IR ν_{max}^{KBr} cm^{-1}: 1715, 1705 (C=O), 1522, 1360 ($-NO_2$), 1432 (aromatic-CH_3), 1375, 1460 (acetyl-CH_3). NMR (CD_3OD) δ (ppm): 1.95 (3H, s, 2-CH_3), 2.35 (3H, s, aromatic-CH_3), 6.45 (6H, multiplet, aromatic-H). Mass Spectrum *m/e*: 298 (M^+).

Isolation of (2-Carboxyphenyl)(2-methylphenyl)diazene (V)——The product V was obtained as follows: After the reaction was over at 70° or 90° for 10 hr, the excess acetic acid was evaporated under reduced pressure. The residue was poured into 15% K_2CO_3 solution. The aquous layer which showed orange red color was adjusted to pH 1.0 with 20% HCl. It was extracted with two fold volume of $CHCl_3$ and the organic phase was washed with H_2O. Evaporation of solvent afforded the orange crystal(V), mp 138—139°. Yield, 0.56 g (2.3%). The product (V) proved to be entirely identical as (2-carboxyphenyl)(2-methylphenyl)diazene with the synthetic sample reported by Meer[15] and Nomura,[16] by mixed melting point determination.

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15) Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a Nihon-bunko DS-21, and UV spectra on a Shimazu MPS-50L spectrophotometer. NMR spectra were taken on a Hitachi Model R-20A apparatus. Mass spectral measurements were run by direct insertion technique on a Nihondenshi JMS-OISG-2 spectrometer. TLC on silica gel G (E. Merck AG) was carried out by the following solvent system, $CHCl_3$: acetone (9: 1), I_2 vapor, Dragendorff and Ehrlich reagents were used as staining reagents.

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