Tetrahedron Vol. 41, No. 3, pp. 511 to 518, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

OXIDATIVE DEGRADATION OF 8-NITROQUINOLINE WITH HYDROGEN PEROXIDE IN ACETIC ACID A POSSIBLE MECHANISM THROUGH 3,4-EPOXIDE OF QUINOLINE RING[1]

Toyo Kaiya and Yutaka Kawazoe*
Faculty of Pharmaceutical Sciences, Nagoya City University
Tanabedori, Mizuho-ku, Nagoya 467, Japan

(*Received in Japan* 27 *October* 1984)

Abstract —— The treatment of 8-nitroquinoline with hydrogen peroxide and acetic acid at 60°C afforded 7-nitroindole, 7-nitro-2-oxindole, 2-amino-3-nitrobenzoic acid, 2-amino-3-nitrobenzaldehyde, 3,4-dihydro-3,4-trans-dihydroxy-8-nitrocarbostyril, 3,4-trans-dihydro-3-hydroxy-4-acetoxy-8-nitrocarbostyril, and 1-(2-amino-3-nitrophenyl)-2-hydroxy-ethanone. The reaction mechanism acceptable in elucidating the formation of these products involves, at the initial step of reaction, an epoxidation of the 3,4-double bond of the 1,2-dihydro adduct of quinoline ring.

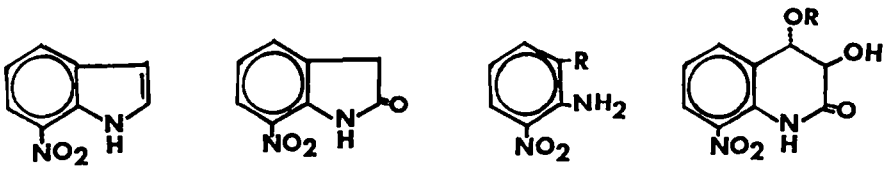
Quinoline derivatives are, in general, N-oxygenated with hydrogen peroxide in acetic acid to give their N-oxides in excellent yields.[2] The by-products thereby often produced are 3-hydroxyquinolines, the yield depending on the substituent and the position at which it is located.[3] Nakashima and Suzuki[4] reported that quinolines substituted with an electron-deficient bulky group at the 8-position, such as 8-nitroquinoline and quinoline-8-carboxylic acid, gave 7-substituted oxindoles under the usual N-oxygenation conditions. Palmer and Russell reported that 4-methyl-8-nitroquinoline gave 2-amino-3-nitroacetophenone as the only identifiable product under similar conditions as above.[5] In connection with our study on the biological oxidation of quinoline derivatives,[6] the present study concerns the reaction mechanism of the oxidative degradation of 8-nitroquinoline (8NQ) in the presence of hydrogen peroxide and acetic acid.

The product analysis enabled us to speculate a possible mechanism that the oxidative degradation of 8NQ is initiated by the epoxidation of the 3,4-double bond of the 1,2-adduct(II in Chart 1). This is followed by various types of subsequent reactions to give products **1** to **7**, as shown on next page. The mechanism proposed in this study seems to require a revision of the reaction mechanism previously reported on the formation of 3-hydroxyquinoline derivatives as by-products in the N-oxygenation reaction. The latter reaction mechanism involved electrophilic hydroxylation of an enamine once formed by the addition of a nucleophile to the C-4 of the quinoline ring (Chart 2).[3]

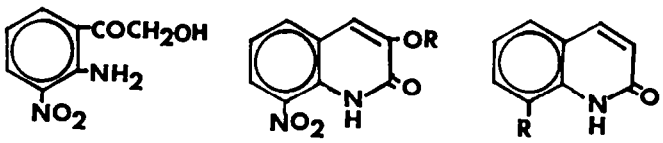
RESULTS

The reaction was carried out by treating of 8NQ with 30% hydrogen peroxide in acetic acid at 60°C for 8 hours. The reaction mixture was poured into water and extracted with chloroform. Both the chloroform and water layers were thoroughly examined by preparative thin-layer chromatography (PTLC). Seven products were isolated (compounds **1** to **7**). The reaction yields of these products seems to depend sensitively on the reaction temperature and duration. In most cases we

examined, about 0.5 molar equivalent of the starting material were converted to products **1** to **7**. Yields: **1**, 0.2%; **2**, 25%; **3**, 2.0%; **4**, 9.9%; **5**, 5.6%; **6**, 0.2%; and **7**, 7.4%. The others were unidentified and they may be further degraded oxidation products. The starting material itself was not recovered under this reaction condition. Neither 3-hydroxy-8-nitroquinoline, 8-nitrocarbostyril (**10**), nor 8-nitroquinoline N-oxide was detected in the reaction mixture. Since 3-hydroxy-8-nitroquinoline was isolated under milder reaction conditions, the 3-hydroxy derivative must be one of the reaction intermediates. In contrast, 8-nitrocarbostyril (**10**) and 8-nitroquinoline N-oxide are not possible intermediates because they are quite stable under the reaction condition employed.



1 **2** **3** R:COOH, **6** R:CHO **4** R:H, **5** R:$COCH_3$



7 **8** R:H, **8a** R:$COCH_3$ **9** R:H, **10** R:NO_2

1 to 7 are the reaction products.

Compounds **1**, **2** and **3** are known compounds which were identified by comparison of their melting points and spectroscopic data with those in literature: 7-nitroindole (**1**),[7,8] 7-nitro-2-oxindole (**2**),[4] and 2-amino-3-nitrobenzoic acid (**3**),[9] respectively.

Compound **4**, mp 247-250°C, was revealed to have the molecular formula of $C_9H_8N_2O_5$ from the elemental analysis and high resolution mass spectrum (HRMS). Its ^1H NMR and ^{13}C NMR spectra showed the presence of a vic-trisubstituted benzene ring, δ_H 7.28(t, J=8 Hz), 7.87(dd, J=2 and 8 Hz), and 8.11(dd, J=8 and 2 Hz), two adjacent secondary hydroxyl groups, δ_H 4.14(d) and 4.72(d), and a carbonyl group, δ_C 170.1, whose infrared (IR) absorption appeared at 1698 cm^{-1}. From these data, the structure of **4** was deduced to be 3,4-dihydro-3,4-dihydroxy-8-nitrocarbostyril.

The two hydroxyl groups must be trans-oriented, since the coupling constant between H-3 and H-4 was 8 Hz. The ^1H and ^{13}C NMR spectra of **5**, $C_{11}H_{10}N_2O_6$, were very similar to those of **4** (Tables 1 and 2) and showed the presence of an acetyl group, δ 2.12(3H, s), indicating that **5** should be the monoacetate of **4**. The position to which the acetyl group was attached was determined by the ^{13}C NMR spectrum: C-10 of **4** (δ 129.8) moved upfield to δ 124.3 in the spectrum of **5**, while the carbonyl carbon(C-2, δ 170.1) scarcely shifted(δ 169.6). Thus, the acetoxyl group must be located at the C-4 position of **4**. Treatment of **5** with acetic anhydride and pyridine gave **8a**, $C_{11}H_8N_2O_5$, and reaction of **4** with the same reagents afforded **8a** and **8**, $C_9H_6N_2O_4$. Compound **8** was also obtained by alkaline hydrolysis of **8a**. The ^1H NMR spectrum of **8a** revealed the presence of an acetoxyl group (δ 2.40(3H, s)), and an isolated aromatic proton(δ 7.67(s)), indicating that

8a was a dehydration product of **5**. The position of the acetoxyl group was deduced by the inspection of the ^{13}C NMR spectra of the related compounds; 2-hydroxyquinoline(**9**)[10,11] and 8-nitrocarbostyril(**10**)[12] (Table 2). Comparison of the spectra of **10** and **8a** showed that both the carbonyl(C-2) and the aromatic carbons of **10** shifted upfield in the spectrum of **8a** (δ 160.8 → 156.1 and 140.6 → 128.7, respectively). Consequently the structure of **8a** was determined as 3-acetoxy-8-nitrocarbostyril. Treament of **5** with thionyl chloride in pyridine resulted in **8a**, while in the case of **4** no reaction occurred.

As for compound **6**, $C_7H_6N_2O_3$, the presence of a vic-trisubstituted benzene ring(δ_H 6.78(dd,J=9 and 7 Hz), 7.79(d,J=7 and 1 Hz), and 8.40(dd, J=9 and 1 Hz)) and an aldehyde group(δ_H 9.91, δ_C 192.9) was deduced from its ^1H and ^{13}C NMR spectra, the structure of which was determined as 2-amino-3-nitrobenzaldehyde.

Compound **7**, $C_8H_8N_2O_4$, was found to have a primary hydroxyl group(δ_H 4.78(2H, broad s), δ_C 65.5(t)) and a carbonyl group(δ_C 200.9(s)) in addition to a vic-trisubstituted benzene ring. Acetylation of **7** gave its monoacetate, $C_{10}H_{10}N_2O_5$. Its ^1H NMR spectrum reveals that the primary hydroxyl group was acetylated-(δ 5.33(2H,s)). Consequently the structure of **7** was deduced to be 1-(2-amino-3-nitrophenyl)-2-hydroxyethanone.

DISCUSSION

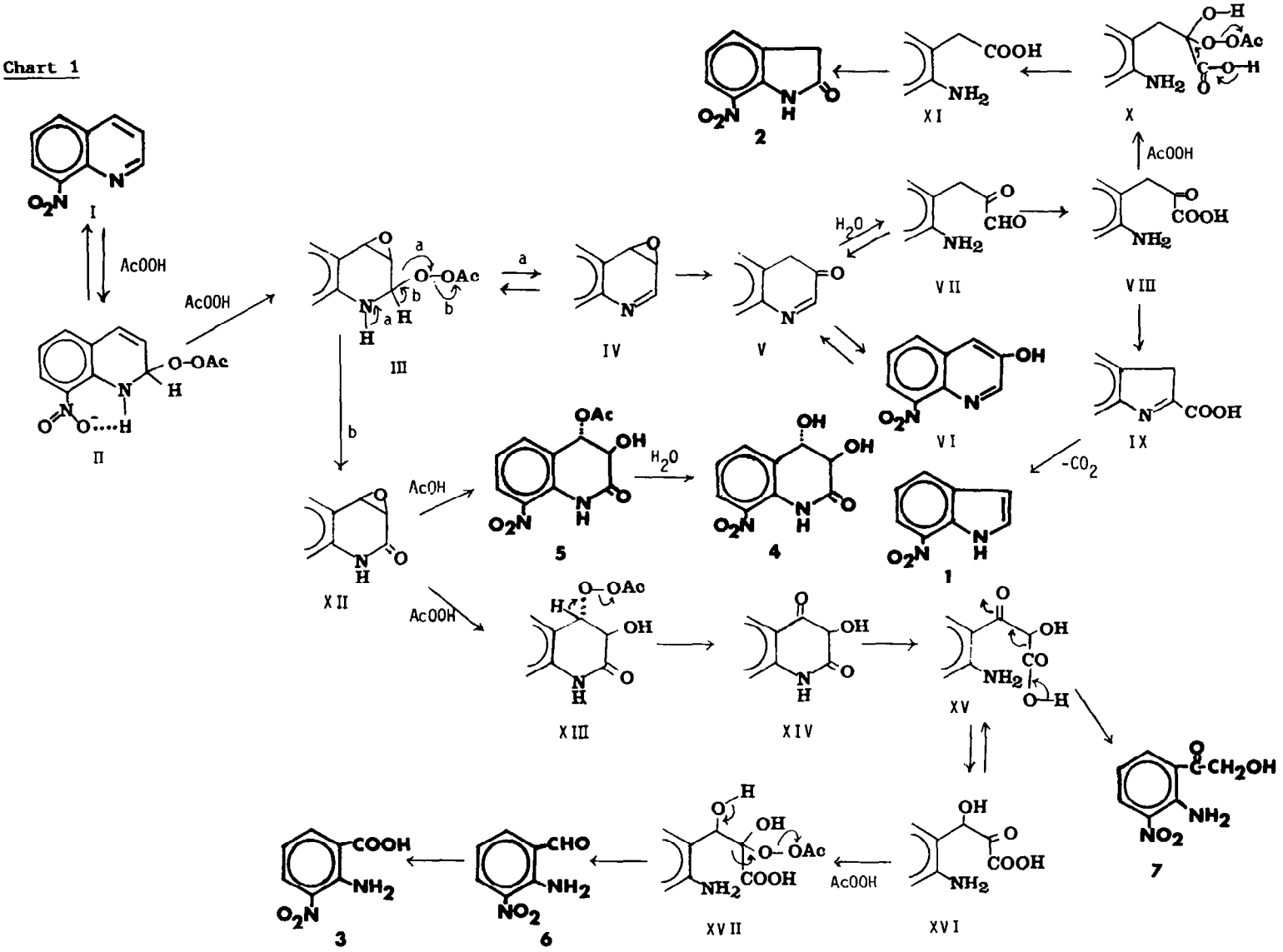
One might realize a possible reaction mechanism which elucidates the formation of all the products isolated in the present study, as shown in Chart 1. Thus, the stereoelectronic effect of the 8-nitro group must not only retard the N-oxygenation rate of the ring nitrogen but also stabilize the N-protonated 1,2-adduct(II) via hydrogen bonding between the nitro and imino functions. It may, therefore, be expected that 8NQ is more likely, than other quinoline derivatives, to undergo epoxidation reaction with peracid through the non-aromatic alkenic structure(II) to give a 3,4-epoxy derivative(III). The 1,2-adduct(II) is formulated as the acetoperoxy adduct at the 2-position. An acetoxy or hydroxy ion might be substituted for the acetoperoxy ion. It is worth noting that the addition of sodium acetate to the reaction mixture did not change the rate of reaction and the ratio of products to any appreciable extent.

When the epoxide(III) is dehydrated to the arene oxide(IV), it must readily be rearranged to the ketone(V) which is enolized to 3-hydroxyquinoline(VI). It is well known that the hydroxylation process via arene oxides is involved in the enzymic hydroxylation of aromatic nuclei.[13] Here, it is reasonable that the epoxide ring is cleaved exclusively at the C-4 carbonium ion rather than the C-3 position.

When V is hydrated, the amino-aldehyde(VII) produced might be oxidized to an amino-acid(VIII) which might be converted to two types of indole derivatives, **1** and **2**, as illustrated in Chart 1. One might say that 3-hydroxyquinoline(VI) is the reaction intermediate for the formation of the indoles which is consistent with the previous arguement made by Nakashima et al.[4]

In the case where the acetoxy ion is removed from the adduct epoxide(III), an amide-epoxide(XII) may be produced. When the epoxide ring of XII is opened by an attack of an acetoxy ion, **5** is produced. The product **5** may be partially hyrolyzed to **4** under the reaction conditions employed. Alternatively, when the epoxide ring of XII is cleaved by the attack of an acetoperoxy ion, a ketol-amide(XIV) may be produced, which may then be hydrolyzed to a ß-keto-acid(XV). The latter may be expected to undergo a ß-elimination of the carboxyl group to give **7**. In the case where XV is equilibrated to the α-keto-acid(XVI)

Chart 1


I
II
III
IV
V
VI
VII
VIII
IX
X
XI
2
XII
5
4
1
XIII
XIV
XV
7
XVI
XVII
6
3
AcOOH
AcOH
H2O
-CO2

prior to the ß-elimination, the keto group in XVI may be oxidized to XVII which may readily be converted to an amino-aldehyde(**6**). The oxidation of **6** may give **3**.

The mechanism described here seems to be acceptable in elucidating the formation of the identified products. According to the proposed mechanism, although the details may be alterable, the formation of 3-hydroxyquinoline derivatives is well illustrated by the epoxidation of the alkenic 3,4-double bond of the 1,2-adduct, followed by its conversion to the arene oxide and then by aromatization through the so-called NIH shift.[13] (Route 1 in Chart 2). This mechanism seems to be preferable to the previous argument which involves the electrophilic hydroxylation of an enamine formed by the addition of a nucleophile to the C-4 position of the quinoline ring (Route 2 in Chart 2).[3]

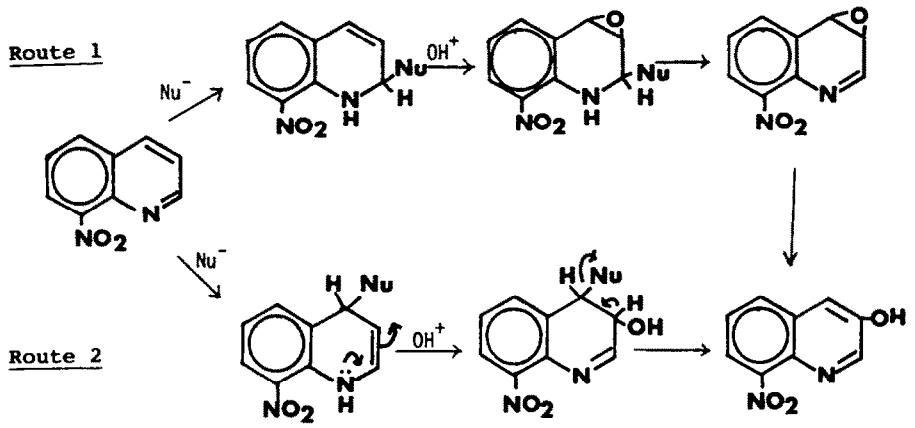


Chart 2 Two possible mechanisms for formation of 3-hydroxyquinolines

EXPERIMENTAL

Melting points were obtained on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi EPI-G3 spectrometer. NMR spectra were obtained on a JEOL JNM-MH-100 and a JEOL JNM-FX-100 spectrometers. Chemical shifts are reported in ppm downfield from the internal TMS and apparent splittings are given in Hz. Mass spectral data were obtained on a JEOL JMS-DX-300 mass spectrometer. The ^{1}H and ^{13}C NMR data are summarized in Tables 1 and 2. The ^{13}C NMR assignments were confirmed by selective proton decoupling techniques.

Reaction of 8NQ with 30%H_2O_2 in AcOH, and separation of the products.

To a solution of 8NQ(1.00 g) in AcOH(8 ml), 2.0 ml of 30%H_2O_2 was added and heated at 60°C for 4 hours, an additional 2.0 ml of 30%H_2O_2 were added, and the mixture was kept at the same temperature for 4 hours. To the mixture, H_2O was added and extracted with $CHCl_3$. The precipitates separated during the concentration of the $CHCl_3$ layer in vacuo(**2**, 125 mg) were filtered off. The filtrate was applied to PTLC(12%MeOH in $CHCl_3$) and separated into fractions 1, 2 and 3. Fraction 1 was re-chromatographed(PTLC, $CHCl_3$) and separated into **1**(2 mg) and **6**(1 mg). In the same way, **5**(36 mg) and **7**(83 mg) were obtained from fraction 2(solvent of PTLC: 7%MeOH in $CHCl_3$). Fraction 3 was re-chromatographed to give **5** (20 mg) and fraction 4. Fraction 4 was repeatedly chromatographed (10%MeOH in $CHCl_3$) to give compounds **5**(7 mg) and **3**(21 mg). The cloudy water-soluble fraction was filtered and the filtrate was concentrated in vacuo. The crystals(**2**, 117 mg) obtained by adding MeOH to the residue were filtered off. The filtrate was applied

to PTLC(12%MeOH in $CHCl_3$) and separated into fractions 5, 6, 7 and 8. Fractions 5 and 6 were purified by PTLC($CHCl_3$) to give **1**(trace) and **2**(9 mg), respectively. From fraction 7, **5**(12 mg) was obtained. Concentration of fraction 8 in vacuo yielded crystals(**4**, 53 mg). After the removal of **4** the filtrate was purified by PTLC(10%MeOH in $CHCl_3$) to afford **4**(75 mg) and **5**(10 mg).

When the reaction was carried out at 70°C (the same condition as Nakashima's[4]) and the $CHCl_3$-soluble fraction was examined, compounds **1**, **2**, **5**, **6** and **7** were obtained.

7-Nitroindole(**1**) Recrystallization from 40%MeOH gave yellow needles, mp 101°C(lit.[7] 95-97°C). (Found: C,59.32; H,3.70; N,17.33. Calc for $C_8H_6N_2O_2$: C,59.26; H,3.73; N,17.28%). HRMS(Found: 162.0419. Calc for $C_8H_6N_2O_2$: 162.0429). MS: m/z 162(M^+), 116(M^+-NO_2).IR(KBr) 3375, 1480, 1320 cm^{-1}. The IR spectrum was identified with that of 7-nitroindole.[7]

7-Nitro-2-oxindole(**2**) Recrystalliization from MeOH afforded light-yellow needles, mp 226°C(decomp) (lit.[4] 225°C(decomp)). (Found: C,53.64; H,3.29; N,15.78. Calc for $C_8H_6N_2O_3$: C,53.93; H,3.40; N,15.73%). HRMS(Found: 178.0365. Calc for $C_8H_6N_2O_3$: 178.0378). MS: m/z 178(M^+), 160(M^+-H_2O), 131(M^+-NO_2-H). IR(KBr)1720, 1620, 1590, 1512, 1320 cm^{-1}.

2-Amino-3-nitro-benzoic acid(**3**) Recrystallization from diluted MeOH gave yellow needles, mp 201°C(lit.[9] 208-209°C). (Found: C,46.65; H,3.39; N,15.45. Calc for $C_7H_6N_2O_4$: C,46.16; H,3.32; N,15.38%). HRMS(Found: 182.0321. Calc for $C_7H_6N_2O_4$: 182.0327). MS: m/z 182(M^+), 164(M^+-H_2O). IR(KBr): 3438, 3325, 3100-2800, 1670, 1615, 1560, 1510, 1445, 1250cm^{-1}.

3,4-Dihydro-3,4-dihydroxy-8-nitrocarbostyril(**4**) Recrystallization from MeOH afforded light-yellow needles, mp 247-250°C. (Found: C,48.10; H,3.44; N,12.56. Calc for $C_9H_8N_2O_5$: C,48.22; H,3.60; N,12.50%. HRMS (Found: 224.0459. Calc for $C_9H_8N_2O_5$: 224.0433). IR(KBr): 3280, 1698, 1610, 1530, 1475 cm^{-1}

4-Acetoxy-3,4-dihydro-3-hydroxy-8-nitrocarbostyril(**5**) Recrystallization from MeOH gave yellow needles, mp 167°C(decomp). (Found: C,49.56; H,3.63; N,10.65. Calc for $C_{11}H_{10}N_2O_6$: C,49.63; H,3.79; N,10.52%). HRMS(Found: 266.0550. Calc for $C_{11}H_{10}N_2O_6$: 266.0538). MS: m/z 266(M^+), 206(M^+-AcOH). IR(KBr): 3400-3300, 1750, 1705, 1610, 1525, 1465, 1225 cm^{-1}.

2-Amino-3-nitrobenzaldehyde(**6**) Recrystallization from MeOH afforded yellow needles, mp 137-138°C. (Found: C,50.91; H,3.57: N,17.13. Calc for $C_7H_6N_2O_3$: C,50.60; H,3.64; N,16.86%). HRMS (Found: 166.0379. Calc for $C_7H_6N_2O_3$: 166.0378). MS: m/z 166(M^+), 149(M^+-OH), 138(M^+-CO). IR(KBr): 3430, 3300, 1670, 1615, 1555, 1510, 1430, 1255 cm^{-1}.

1-(2-Amino-3-nitrophenyl)-2-hydroxyethanone(**7**) Recrystallization from MeOH gave brown needles, mp 172-173°C. (Found: C,48.97; H,3.94; N,13.93. Calc for $C_8H_8N_2O_4$: C,48.98; H,4.11; N,14.28%). HRMS(Found: 196.0477. Calc for $C_8H_8N_2O_4$: 196.0483). MS: m/z 196(M^+), 178(M^+-H_2O), 165(M^+-CH_2OH). IR(KBr): 3475, 3390, 3280, 1720, 1655, 1610, 1510, 1350, 1315, 1245 cm^{-1}.

Acetate of **7** Compound **7** was acetylated with Ac_2O/C_5H_5N at room temperature and purified by PTLC($CHCl_3$). Recrystallized from MeOH, yellow needles, mp 143.5-145.5°C. (Found: C,50.67; H,4.16; N,11.88. Calc for $C_{10}H_{10}N_2O_5$: C,50.42; H,4.23; N,11.76%). HRMS(Found: 238.0592. Calc for $C_{10}H_{10}N_2O_5$: 238.0589). MS: m/z 238(M^+), 165(M^+-CH_2OAc). IR(KBr): 3450, 3310, 1740, 1665, 1615, 1552, 1250 cm^{-1}.

3-Acetoxy-8-nitrocarbostyril(**8a**) Compound **5** was treated with Ac_2O/C_5H_5N at room temperature and purified by PTLC(5%MeOH in $CHCl_3$). Recrystallization from MeOH gave fine crystals, 166°C (decomp). (Found: C,53.00; H,2.78; N,11.14. Calc for $C_{11}H_8N_2O_5$: C,53.23; H,3.25; N,11.29%). HRMS(Found: 248.0441. Calc for $C_{11}H_8N_2O_5$:

Table 1 ^{1}H NMR chemical shifts (ppm) (Coupling constants (Hz) are given in parentheses)

Compound (Solvent)	H-1	H-2	H-3	H-4	H-5	H-6	H-7	others
1 (chl.[a])	9.94(br)	7.42(t,3)	6.73(t,3)	8.00(d,8)	7.21(t,8)	8.18(d,8)		
2 (dim.[b])			3.66(2H,s)	7.61(dd,7&1)	7.14(dd,7&9)	7.97(dd,9&1)		
4 (dim.)	9.90(br-s)		4.14(d,8)	4.72(d,8)	7.87(dd,8&2)	7.28(t,8)	8.11(dd,8&2)	6.06(1H,br)[c]
								6.14(1H,br)[c]
5 (dim.)	10.00(br)		4.33(d,8)	5.95(d,8)	7.71(dd,8&2)	7.24(t,8)	8.11(dd,8&2)	2.12(3H,s)
								6.24(1H,d,6)[c]
8 (dim.)				7.27(s)	7.96(dd,8&1)	7.34(t,8)	8.21(dd,8&1)	
8a (chl.)	11.26(br)			7.67(s)	7.90(dd,9&2)	7.38(t,9)	8.51(dd,9&2)	2.40(3H,s)
9 (chl.)	12.81		6.72(d,9.5)	7.80(d,9.5)				
10 (dim.)	10.96		6.74(d,10)	8.12(d,10)	8.15(dd,8&2)	7.41(t,8)	8.46(dd,8&2)	

	H-4	H-5	H-6	others
3 (dim.)	8.29(dd,8&2)	6.73(t,8)	8.24(dd,8&2)	8.56(1H,br)[c]
6 (chl.)	7.79(dd,7&1)	6.78(dd,9&7)	8.40(dd,9&1)	8.65(2H,br), 9.91(1H,s)
7 (dim.)	8.20(dd,8&2)	6.75(t,8)	8.33(dd,8&2)	4.78(2H,br-s), 8.80(1H,br-s)[c]
Ac-**7** (chl.)	7.94(dd,8&2)	6.72(t,8)	8.45(dd,8&2)	2.26(3H,s), 5.33(2H,s), 8.85(2H,br)

[a]Measured in $CDCl_3$. [b]Measured in DMSO-d_6. [c]Disappeared by adding D_2O.

Table 2 ^{13}C NMR chemical shifts (ppm)

Compound[a]	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	others
2	176.2	34.8	130.3	121.2	122.2	140.0	130.8	129.5		
4	170.1	70.8	69.4	133.6	122.2	124.7	134.2	131.4	129.8	
5	169.6	67.9	70.9	134.6	122.5	125.9	134.7	132.1	124.3	168.4(s), 20.7(q)
8	157.8	146.8	112.8	133.3	121.7	123.5	133.3	127.5	123.5	
8a	156.1	140.9	128.7	135.4	122.2	127.0	133.9	130.7	121.0	168.0(s), 20.2(q)
9[b]	162.0	121.7[d]	140.1	127.8	121.9[d]	130.2	115.2	139.0	119.1	
10	160.8	122.6	140.6	135.9	121.5	127.5	133.3[e]	132.9[e]	121.5	

	C-1	C-2	C-3	C-4	C-5	C-6	others
3	115.5	146.8	132.4	131.3	113.9	139.6	
6[c]	122.1	146.3	132.9	133.0	114.6	144.3	192.9(d)
7	118.6	146.0	132.6	132.0	113.9	139.1	200.9(s), 65.5(t)
Ac-**7**[c]	118.6	147.1	133.6	133.2	113.8	137.5	193.1(s), 170.4(s), 65.8(t), 20.5(q)

[a]Measured in d_6-DMSO solution unless otherwise stated. [b]Measured in 10%$CDCl_3$ in d_6-DMSO solution. [c]Measured in $CDCl_3$ solution. [d,e]Assignments may be reversed.

248.0433). MS: m/z 248(M^+), 206(M^+-CH_2CO), 160(206-NO_2). IR(KBr): 3290, 1753, 1680, 1525, 1315 cm^{-1}.

Hydrolysis of **8a**(**8**) To an MeOH solution(2 ml) of **8a**(36 mg) were added a few drops of 10%KOH. After 15 minutes, the mixture was neutralized with 5%HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was recrystallized from $CHCl_3$-MeOH to give yellow powder(**8**, 12 mg), mp 235°C(decomp). (Found: C,52.34; H,2.80; N,13.75. Calc for $C_9H_6N_2O_4$: C,52.43; H,2.93; N,13.59%). HRMS(Found: 206.0336. Calc for $C_9H_6N_2O_4$: 206.0326). MS: m/z 206(M^+), 160(M^+-NO_2), 132(M^+-NO_2-CO). IR(KBr): 3325, 1630, 1600 cm^{-1}.

Reaction of **4** with Ac_2O and C_5H_5N Acetic anhydride(1 ml) and C_5H_5N(1 ml) were added to 30 mg of **4** and the mixture was kept overnight at room temperature. Water was added to the mixture and extracted with ether. The ether layer was evaporated. Adding $CHCl_3$-MeOH mixture to the residue, crystals(**8**, 1 mg) were separated and filtered off. The filtrate was purified by PTLC(5%MeOH in $CHCl_3$) to afford **8a**(16 mg).

Reaction of **5** with $SOCl_2$ in C_5H_5N Pyridine(1 ml) and a few drops of $SOCl_2$ were added to 50 mg of **5** and kept at room temperature for 15 minutes. To the mixture was added H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was separated by PTLC(6%MeOH in $CHCl_3$) to afford **8a**(6 mg) and the starting material(**5**, 15 mg).

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