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Nitration of Mononitroquinolines

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Seven mononitroquinolines were nitrated to yield dinitroquinolines. It was found that the nitration occurred in the benzene portion of the mononitroquinolines, and at a carbon with comparatively large values of q_r, $f_r^{(E)}$, and $S_r^{(E)}$, except in the case of 5-nitroquinoline (IV).

Keywords——mononitroquinoline nitration; 3-acetamidoquinoline nitration; Hückel method; mononitroquinoline reaction indices; dinitroquinolines; 3-acetamido-mononitroquinolines

It is widely known that some nitroquinolines, such as 2-[2] and 4-nitroquinolines,[3] and derivatives of 4-nitroquinoline 1-oxide,[4] possess strong carcinogenic activity.[5a–c] In this connection, we have already reported[6] that the approximate superdelocalizabilities of the carbons carrying the nitro group in some carcinogenic mononitroquinolines are comparatively large; the π-electron densities of all carbons in seven mononitroquinolines were simultaneously calculated by the simple Hückel method. We next studied the nitration of the seven mononitroquinolines to determine whether the second nitro group will be placed on the most π-electron-rich carbon or the carbon having the largest value of $f_r^{(E)}$ or $S_r^{(E)}$. The results of these studies are described here.

Although the nitration of 5- (IV), 6- (V), 7- (VI), and 8-nitroquinolines (VII) has already been carried out,[7] our experiments started with a re-examination of the reported data. These mononitroquinolines were treated with potassium nitrate or fuming nitric acid in concentrated sulfuric acid, with heating on a water bath, to yield dinitroquinolines in all cases. The results of the reactions of IV, V, and VII, shown in Chart 1, were essentially in accord with the reported ones. In the case of VI, three dinitro compounds were obtained, contrary to the reported results.[7] The products were purified by preparative thin-layer chromatography (TLC) on silica gel, yielding 6,7-dinitroquinoline (XI) in addition to the known compounds, 5,7-dinitroquinoline (VIII) and 7,8-dinitroquinoline (X). The structure of XI was elucidated from its proton magnetic resonance (PMR) spectrum. This showed a singlet (two protons) at 8.40 ppm, suggesting the presence of *p*-standing protons and therefore the occurrence of substitution at C-6.

The results of nitration of mononitroquinolines which carry a nitro group on the pyridine ring will be described next. 2-Nitroquinoline[2] (I) was nitrated with potassium nitrate

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2) E. Hayashi and T. Saito, *Yakugaku Zasshi*, **89**, 108 (1969).
3) I. Nakayama, *Yakugaku Zasshi*, **71**, 1088 (1951).
4) E. Ochiai, M. Ishikawa, and Z. Sai, *Yakugaku Zasshi*, **63**, 280 (1943).
5) *a)* K. Mori, M. Kondo, M. Tamura, H. Ichimura, and A. Ohta, *Gann*, **60**, 609 (1969); *b)* K. Mori, M. Kondo, M. Tamura, H. Ichimura, and A. Ohta, *Gann*, **60**, 663 (1969); *c)* W. Nakahara, F. Fukuoka, and T. Sugimura, *Gann*, **48**, 129 (1957).
6) T. Kurihara, H. Ichimura, T. Igaki, and A. Ohta, *Chem. Pharm. Bull.* (Tokyo), **19**, 37 (1971).
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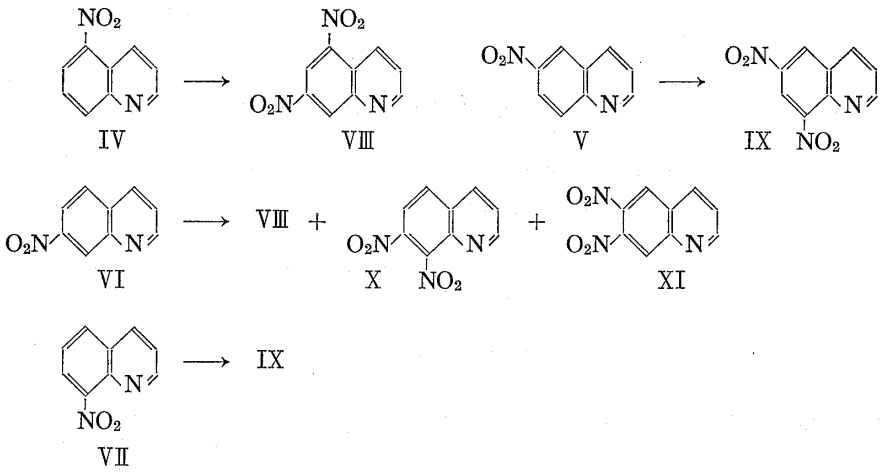

Chart 1

in concentrated sulfuric acid to give two dinitroquinolines, which were separated by preparative TLC to give 2,5-dinitroquinoline (XII) and 2,8-dinitroquinoline (XIII). The PMR spectra of both products showed an ABC-type pattern, with signals at 7.75 (1H, t, $J_{AB}=J_{BC}=4.5$ Hz), 8.49 (1H, dd, $J_{AB}=4.5$ Hz, $J_{AC}=0.8$ Hz), and 8.86 ppm (1H, q, $J_{BC}=4.5$ Hz, $J_{AC}=0.8$ Hz) in the spectrum of XII, and at 7.96 (1H, t, $J_{AB}=J_{BC}=4.5$ Hz), 8.07 (1H, dd, $J_{AB}=4.5$ Hz, $J_{AC}=1.5$ Hz), and 8.36 ppm (1H, dd, $J_{BC}=4.5$ Hz, $J_{AC}=1.5$ Hz) in that of XIII. It can be concluded that the second nitro group was introduced at C-5 or C-8 on the nitration of I.

In order to determine the structures of XII and XIII, several reactions were carried out. First, each product was hydrolyzed by treatment with hydrochloric acid in methanol to afford carbostyril derivatives. On the other hand, 2-chloro-5-nitroquinoline (XVIII) and 2-chloro-8-nitroquinoline (XIX), prepared from 5-nitroquinoline 1-oxide (XVI) and 8-nitroquinoline 1-oxide (XVII), respectively, by treatment with sulfuryl chloride,[4] were converted to the corresponding carbostyrils[8,9] (XIV and XV) by hydrolysis in hydrochloric acid. The carbostyril derived from the dinitroquinoline (XII), was found to be identical with the specimen (mp 292°) prepared from XVI[8] (infrared (IR) spectra and melting point on admixture of the two compounds). XV was also identical with a specimen (mp 158—160°) derived

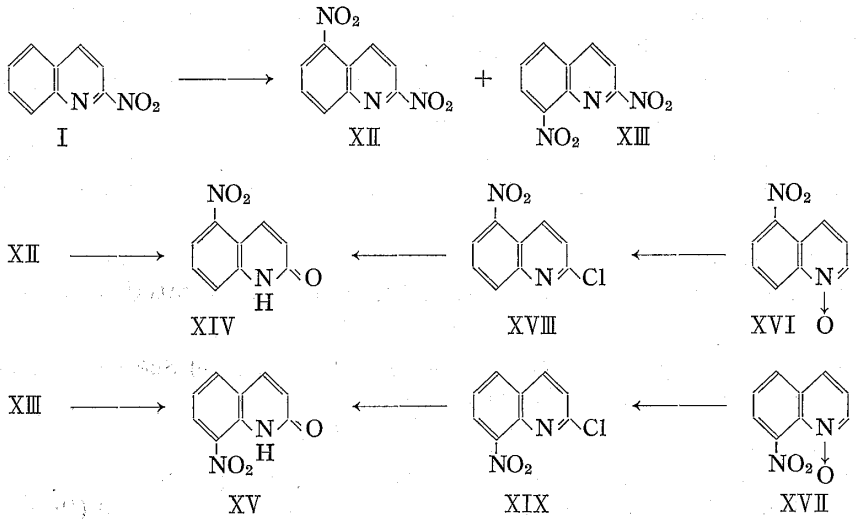

Chart 2

8) A. Claus and A. Schedler, *J. Prakt. Chem.*, [2], **53**, 392 (1884).

from XVII by the reported method.[9] These findings suggest that the second nitro group was introduced into the 5- and 8-positions, respectively, on the nitration of I.

Nitration of 3-nitroquinoline[10] (II) was also carried out to give two dinitro compounds, 3,5-dinitroquinoline (XX) and 3,8-dinitroquinoline (XXI), which were separated by preparative TLC. Both products showed an ABC-type pattern in their PMR spectra, as in the spectra of XII and XIII. Namely, substitution may occur at C-5 or C-8. In order to clarify the structures of these products, XX and XXI were converted to the diacetamidoquinolines (XXII and XXIII) derived from the nitration products of 3-acetamidoquinoline[11] (XXIV), as described below.

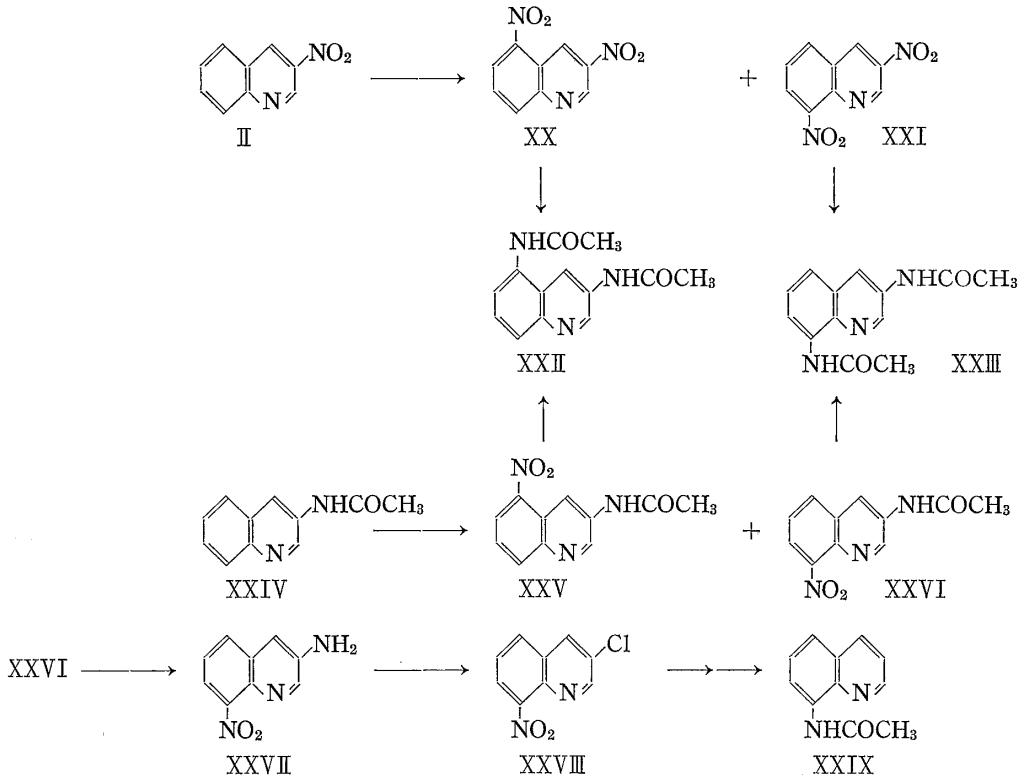

Chart 3

The products were subjected to catalytic hydrogenation to give the corresponding diaminoquinolines, which were converted immediately to the diacetates, without purification. On the other hand, the nitration of XXIV was re-examined.[12] XXIV was treated with fuming nitric acid in concentrated sulfuric acid with cooling to yield a pale yellow mononitro compound (XXVI), in addition to the known 3-acetamido-5-nitroquinoline (XXV). XXVI was converted to 8-acetamidoquinoline[13] (XXIX) through several steps, as shown in Chart 3. This suggests that the nitration products of XXIV were the 5- and 8-nitro compounds. The diacetamidoquinoline (XXII) derived from one of the nitration products of II was identical with 3,5-diacetamidoquinoline prepared from 3-acetamido-5-nitroquinoline (XXV) by reduction and subsequent acetylation, while XXIII was identical with 3,8-diacetamidoquinoline (XXIII) derived from XXVI in the same way. It was therefore concluded that the nitration of II occurred at two positions, C-5 and C-8, to give two dinitro compounds.

9) A. Claus an G. Pollitz, *J. Prakt. Chem.*, [2], **41**, 44 (1880).
10) F.C. Uhle and W.A. Jacobs, *J. Org. Chem.*, **10**, 76 (1945).
11) R.R. Renshaw and H.L. Friedman, *J. Am. Chem. Soc.*, **61**, 3320 (1939).
12) T. Naito, *Yakugaku Zasshi*, **67**, 104 (1947).
13) A. Claus and A. Schedler, *J. Prakt. Chem.*, [2], **53**, 404 (1884).

4-Nitroquinoline[3] (III) was heated with potassium nitrate in concentrated sulfuric acid on a water bath. The products were shown to be two dinitro compounds, which were separated by preparative TLC. In the PMR spectra of the products, an ABC-type pattern was observed. Accordingly it may be presumed that the second nitro group was located at C-5 or C-8.

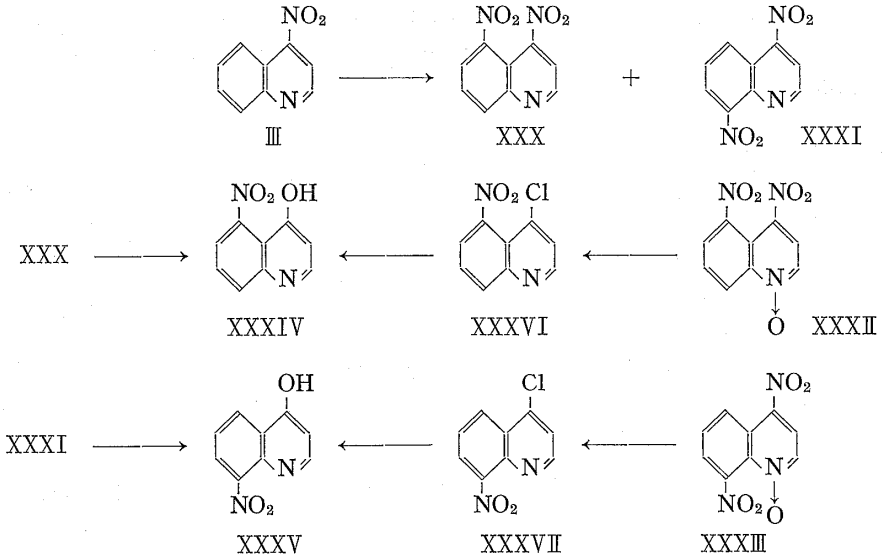

Chart 4

In order to establish the structures of 4,5-dinitroquinoline (XXX) and 4,8-dinitroquinoline (XXXI), these products were related to 4,5-dinitroquinoline 1-oxide[14] (XXXII) and 4,8-dinitroquinoline 1-oxide[14] (XXXIII), respectively, as described below. Namely, XXX and XXXI were each hydrolyzed in an acidic medium to furnish the hydroxyl compounds, XXXIV and XXXV, respectively. On the other hand, XXXII and XXXIII were treated with phosphorus trichloride in ethyl acetate with heating to afford 4-chloro-5-nitroquinoline[15] (XXXVI) and 4-chloro-8-nitroquinoline[15] (XXXVII), respectively, which were converted to the corresponding 4-hydroxyquinolines by acidic hydrolysis in the reported manner.[15] XXXIV (mp 325°), derived from XXX, was found to be identical with 4-hydroxy-5-nitroquinoline[15] (mp 325°), prepared from XXXVI, by comparison of the IR spectra, while XXXV (mp 200—202°) was identical with 4-hydroxy-8-nitroquinoline (mp 198.5—199.5°), derived from XXXVII, by the same criterion. These data show that III gave 4,5- (XXX) and 4,8-dinitroquinoline (XXXI) on nitration.

Discussion

Table I lists the π-electron density (q_r), frontier electron density ($f_r^{(E)}$), and superdelocalizability ($S_r^{(E)}$), calculated by the simple Hückel method,[6] for each carbon of the seven mononitroquinolines. The nitrated positions in each mononitroquinoline upon nitration, and the yields of the dinitroquinolines are given in Table II.

As shown in these tables, the second nitro group is introduced only into the benzene portion of the quinoline ring in all cases and, moreover, at a carbon having comparatively large values of q_r, $f_r^{(E)}$, and $S_r^{(E)}$. There is a particularly good correlation between the $S_r^{(E)}$ value and the nitration position, except in the case of IV. Although III, IV, and VII have

14) E. Ochiai and T. Okamoto, *Yakugaku Zasshi*, **70**, 22 (1950).
15) R.W. Gouley, G.W. Moersch, and H.S. Mosher, *J. Am. Chem. Soc.*, **69**, 303 (1947).

a nitro group at the α-position of the quinoline ring in common, the substitution position on IV was not that expected from the results of calculation.

The shapes of the highest occupied molecular orbital (HOMO) of C-5, C-6, C-7, and C-8 in the seven mononitroquinolines are shown in Fig. 1; all the mononitroquinolines show the same pattern. Because the mononitroquinolines may be protonated in an acidic medium,

Table I. The π-Electron Densities and Reaction Indices of the Mononitroquinolines[a)]

Compound and position	q_r		$f_r^{(E)}$		$S_r^{(E)}$	
	Neat	+N	Neat	+N	Neat	+N
2-Nitroquinoline						
5	0.98861	0.96059	0.44560	0.55964	0.93809	0.85728
6	0.98902	1.00003	0.17688	0.26111	0.84545	0.85011
7	0.97982	0.94165	0.13257	0.09629	0.81573	0.74106
8	1.10438	1.03257	0.46684	0.60347	0.97109	0.95196
3-Nitroquinoline						
5	0.97094	0.94932	0.42667	0.54247	0.90568	0.83803
6	1.00362	1.00799	0.20604	0.27543	0.87120	0.86111
7	0.96598	0.93886	0.10380	0.08098	0.78816	0.73446
8	1.01535	1.03208	0.47480	0.59270	0.98137	0.94569
4-Nitroquinoline						
5	0.99278	0.96906	0.44151	0.55634	0.93012	0.86212
6	0.98933	0.99934	0.17563	0.25031	0.84484	0.84944
7	0.98386	0.95120	0.12706	0.09977	0.81948	0.75640
8	1.00399	1.02959	0.46384	0.59566	0.96067	0.94497
5-Nitroquinoline						
6	0.93371	0.94228	0.14441	0.21212	0.78604	0.79128
7	0.98429	0.95450	0.11785	0.09034	0.81048	0.75251
8	0.95118	0.97714	0.40528	0.52332	0.86973	0.86115
6-Nitroquinoline						
5	0.91459	0.89528	0.39546	0.51351	0.84703	0.78687
7	0.95692	0.92091	0.15677	0.12518	0.81576	0.74091
8	1.01618	1.03266	0.46693	0.57971	0.97399	0.93806
7-Nitroquinoline						
5	0.98957	0.96589	0.43854	0.55289	0.92957	0.85695
6	0.97909	0.97818	0.22359	0.28492	0.86942	0.84788
8	0.94641	0.97654	0.43446	0.57508	0.90805	0.89979
8-Nitroquinoline						
5	0.92349	0.90719	0.37399	0.48248	0.81996	0.77033
6	1.00458	1.00767	0.18095	0.23463	0.85719	0.84834
7	0.91628	0.89667	0.08576	0.07317	0.74443	0.70647

a) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, 1961, p. 117.

Table II. The Yields of Dinitroquinolines (%)

Compound No.	Nitrated position						
	2	3	4	5	6	7	8
I	—			40			33
II		—		22			41
III			—	46			18
IV				—		35	
V					—		31
VI				14	10	—	8
VII					38		—

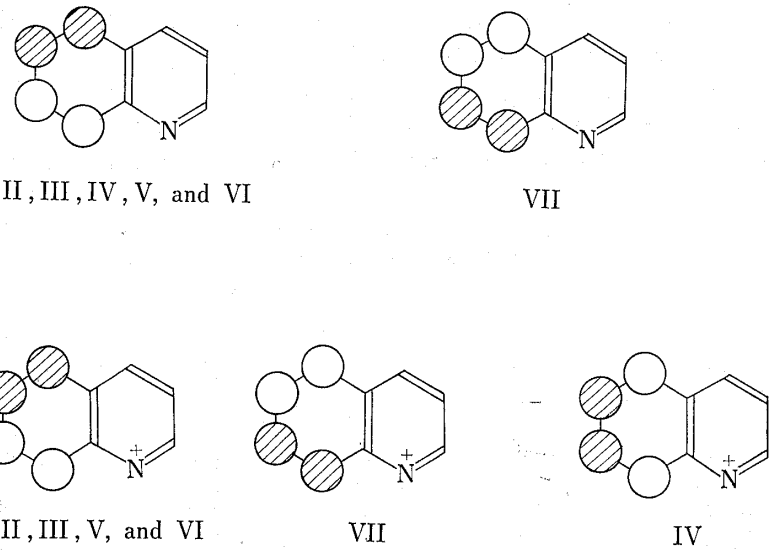

Fig. 1. The Nodal Properties of HOMOs of the Mononitroquinolines

The shaded and unshaded areas correspond to the negative and positive regions of the wave function, respectively.

the HOMOs of the mononitroquinolinium salts were also calculated, as shown in Fig. 1. The shape of the HOMO of the IV salt differs from those of other quinolinium salts. This suggests that the substitution position in IV cannot be predicted simply from the values of q_r, $f_r^{(E)}$, and $S_r^{(E)}$. In order to explain the reaction of IV, other factors must be taken into consideration.

Overall, it seems reasonable to conclude that there is a good correlation between the nitration position of mononitroquinolines and various reaction indices.

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. UV spectra were measured with a Hitachi EPS-II spectrophotometer, PMR spectra were recorded with a JEOL-PS-100 instrument using tetramethylsilane as an internal standard, and mass spectra (MS) were measured with a Hitachi RMU-7L spectrometer.

Nitration of 7-Nitroquinoline (VI)——A mixture of 400 mg (2.3 mmol) of VI, 12 ml of conc. H_2SO_4, and 8 ml of fuming nitric acid (d=1.52) was heated under reflux for 6 hr. After cooling, the reaction mixture was poured into ice-water and 40 mg (8%) of X was collected (crystalline precipitate) by suction. The crystals were purified by sublimation at 190°/5 torr and recrystallization from benzene to give colorless crystals, mp 220—221°. *Anal.* Calcd. for $C_9H_5N_3O_4$: C, 49.32; H, 2.30; N, 19.18. Found: C, 49.34; H, 2.22; N, 19.48. PMR (CF_3COOD) δ: 8.42 (1H, d, $J_{5,6}$=10 Hz, H_5), 8.52 (1H, q, $J_{2,3}$=6 Hz, $J_{3,4}$=9 Hz, H_3), 8.92 (1H, d, $J_{5,6}$=10 Hz, H_6), 9.50 (1H, dd, $J_{3,4}$=9 Hz, $J_{2,4}$=1.8 Hz, H_4), and 9.63 (1H, dd, $J_{2,3}$=6 Hz, $J_{2,4}$=1.8 Hz, H_2). MS m/e: 219 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 251 (3.86).

The filtrate was made alkaline with powdered K_2CO_3 and extracted with $CHCl_3$. The usual work-up of the extract gave 129.5 mg of yellow crystals, which showed two spots on a silica gel TLC plate. Each component was separated by preparative TLC on silica gel (thickness: 1.5 mm, developed three times with $CHCl_3$). The CH_2Cl_2 extract of the upper part of the chromatogram gave 71 mg (14%) of VIII as yellow crystals, which were recrystallized from EtOH to furnish pale yellow needles, mp 176—177.5°. *Anal.* Calcd. for $C_9H_5N_3O_4$: C, 49.32; H, 2.30; N, 19.18. Found: C, 49.50; H, 2.03; N, 19.32. PMR (CF_3COOD) δ: 8.58 (1H, q, $J_{2,3}$=9 Hz, $J_{3,4}$=6 Hz, H_3), 9.52 (1H, d, $J_{6,8}$=2 Hz, H_8), 9.61 (1H, d, $J_{3,4}$=6 Hz, H_4), 9.69 (1H, d, $J_{6,8}$=2 Hz, H_6), 10.09 (1H, d, $J_{2,3}$=9 Hz, H_2). MS m/e: 219 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 241 (3.93), 295 (3.64).

The lower part of the chromatogram was also extracted with CH_2Cl_2 and worked up as before to give 50 mg (10%) of XI as pale yellow crystals, which were recrystallized from EtOH to afford colorless prisms, mp 163—164°. *Anal.* Calcd. for $C_9H_5N_3O_4$: C, 49.32; H, 2.30; N, 19.18. Found: C, 49.52; H, 2.12; N, 19.20. PMR (CF_3COOD) δ: 8.48 (1H, q, $J_{2,3}$=6 Hz, $J_{3,4}$=9 Hz, H_3), 9.04 (2H, s, H_5 and H_8), 9.41 (1H, d, $J_{3,4}$=9 Hz, H_4), 9.59 (1H, d, $J_{2,3}$=6 Hz, H_2). MS m/e: 219 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 249 (3.84), 257 (3.81, shoulder), 293 (3.43).

Nitration of 2-Nitroquinoline (I)——KNO_3 (707 mg, 7.0 mmol) was added portionwise to a mixture of 400 mg (2.3 mmol) of I and 14 ml of conc. H_2SO_4 at 70° with stirring. After heating at this temperature for a further 2 hr, the reaction mixture was poured into ice-water. The pale yellowish crystals (522 mg), collected by suction, showed two spots on a silica gel TLC plate. The two substances were separated from each other by preparative TLC on silica gel (thickness 1.5 mm) using a mixture of $CHCl_3$ and benzene (9: 1) as a developer. Extraction of the upper band on the chromatogram with acetone gave 150 mg (33%) of pale yellow crystals, which were recrystallized from EtOH to furnish colorless needles of XII, mp 179—180°. *Anal.* Calcd. for $C_9H_5N_3O_4$: C, 49.32; H, 2.30; N, 19.18. Found: C, 49.61; H, 2.29; N, 19.26. PMR (CF_3COOD) δ: 7.34 (1H, d, $J_{3,4}=6$ Hz, H_4), 7.75 (1H, t, $J_{6,7}=J_{7,8}=4.5$ Hz, H_7), 8.32 (1H, dd, $J_{7,8}=4.5$ Hz, $J_{6,8}=1.5$ Hz, H_8), 8.49 (1H, d, $J_{3,4}=6$ Hz, H_3), 8.86 (1H, dd, $J_{6,7}=4.5$ Hz, $J_{6,8}=1.5$ Hz, H_6). MS *m/e*: 219 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 231 (3.87).

The lower band on the chromatogram was also extracted with acetone to give 186.4 mg (40%) of XIII, as yellowish crystals, which were recrystallized from benzene to furnish colorless prisms, mp 180—181.5°. *Anal.* Calcd. for $C_9H_5N_3O_4$: C, 49.32; H, 2.30; N, 19.18. Found: C, 49.55; H, 2.17; N, 19.41. PMR (CF_3COOD) δ: 7.38 (1H, d, $J_{3,4}=6$ Hz, H_3), 7.96 (1H, t, $J_{5,6}=J_{6,7}=4.5$ Hz, H_6), 7.98 (1H, d, $J_{3,4}=6$ Hz, H_3), 8.07 (1H, dd, $J_{5,6}=4.5$ Hz, $J_{5,7}=1.5$ Hz, H_5), 8.36 (1H, dd, $J_{6,7}=4.5$ Hz, $J_{5,7}=1.5$ Hz, H_7). MS *m/e*: 219 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 236 (3.91).

5-Nitrocarbostyril (XIV) from 2,5-Dinitroquinoline (XII)——A mixture of 15 mg (0.07 mmol) of XII, 3 ml of MeOH, 0.3 ml of conc. HCl, and 0.2 ml of H_2O was refluxed for 4 hr. The reaction mixture was diluted with H_2O and 8.1 mg (64%) of XIV, as a yellow precipitate, was collected by suction. Recrystallization of these crystals from EtOH gave pale yellow needles, mp 302—303° (dec.) (lit.[8] mp 304°).

8-Nitrocarbostyril (XV) from 2,8-Dinitroquinoline (XIII)——A mixture of 15 mg (0.07 mmol) of XIII, 3 ml of MeOH, 0.3 ml of conc. HCl, and 0.2 ml of H_2O was heated under reflux for 4 hr. After cooling, the reaction mixture was diluted with a small amount of water, made alkaline with powdered $KHCO_3$, and extracted with $CHCl_3$. The usual work-up of the extract gave 12.7 mg (98%) of XV, as yellow crystals, which were recrystallized from benzene to furnish yellow prisms, mp 162—162.5° (lit.[9] mp 168°).

Nitration of 3-Nitroquinoline (II)——A mixture of 87 mg (0.5 mmol) of II and 3 ml of conc. H_2SO_4 was treated slowly with 151 mg (1.5 mmol) of KNO_3 at 70° with stirring. After heating for 2 hr, the reaction mixture was poured into ice-water. The yellow precipitate (60 mg), collected by suction, showed two spots on a silica gel TLC plate. Each component was separated by preparative TLC on silica gel (thickness 1.5 mm) using a mixture of benzene and $CHCl_3$ (9: 1, developed three times). The uppper band on the chromatogram was extracted with acetone and worked up as usual to give 45 mg (41%) of XXI as yellowish crystals, which were recrystallized from benzene to yield colorless needles, mp 171—173°. *Anal.* Calcd. for $C_9H_5N_3O_4$: C, 49.32; H, 2.30; N, 19.18. Found: C, 49.38; H, 2.29; N, 19.23. PMR (CF_3COOD) δ: 8.00 (1H, t, $J_{5,6}=J_{6,7}=7.5$ Hz, H_6), 8.55 and 8.98 (each 1H, dd, $J=7.5$ Hz, $J=1.5$ Hz, H_5 and H_7), 9.74 (2H, s). MS *m/e*: 291 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 229 (4.03), 285 (3.67), 384 (3.61), 430 (3.91).

Extraction of the lower band on the chromatogram with acetone gave 24.2 mg (22%) of XX, which was recrystallized from EtOH to furnish colorless needles, mp 132—134°. *Anal.* Calcd. for $C_9H_5N_3O_4$: C, 49.32; H, 2.30; N, 19.18. Found: C, 49.57; H, 2.26; N, 19.27. PMR (CF_3COOD) δ: 8.40 (1H, t, $J_{6,7}=J_{7,8}=7.5$ Hz, H_7), 8.90 (2H, dd, $J_{6,7}=J_{7,8}=7.5$ Hz, $J_{6,8}=1.5$ Hz, H_6 and H_8), 10.10 (1H, d, $J_{2,4}=2.5$ Hz, H_4), 10.45 (1H, d, $J_{2,4}=2.5$ Hz, H_2). MS *m/e*: 291 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 248 (4.13), 305 (3.64).

Nitration of 3-Acetamidoquinoline (XXIV)——Fuming nitric acid ($d=1.52$, 3.5 ml) was added gradually to a mixture of 6.50 g (35 mmol) of XXIV and 21 ml of conc. H_2SO_4 under ice cooling with stirring over a period of 15 min. After standing for 1 hr, the reaction mixture was poured into ice-water and made alkaline with powdered K_2CO_3. The yellow powder (7.15 g) was collected by suction and purified by column chromatography on silica gel (Wakogel C-200, 210 g), using $CHCl_3$ and AcOEt as eluants. The $CHCl_3$/AcOEt (1: 1) fraction gave 600 mg (3%) of XXVI and the $CHCl_3$/AcOEt (3: 7) fraction yielded 4.50 g (60%) of XXV. XXVI: pale yellow needles (recrystallized from H_2O), mp 181—182°. *Anal.* Calcd. for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.18. Found: C, 57.36; H, 4.05; N, 18.36. MS *m/e*: 231 (M^+). PMR ($CDCl_3$) δ: 2.30 (3H, s), 7.56 (1H, t, $J=_{5,6}=J_{6,7}=8$ Hz, H_6), 7.92 (1H, dd, $J_{5,6}$ or $J_{6,7}=8$ Hz, $J_{5,7}=2$ Hz, H_5 or H_7), 7.99 (1H, dd, $J_{6,7}=J_{5,6}=8$ Hz, $J_{5,7}=2$ Hz, H_7 or H_5), 8.76 (1H, d, $J_{2,4}=3$ Hz, H_4), 8.95 (1H, d, $J_{2,4}=3$ Hz, H_2). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 254 (4.25), 285 (3.62), 330 (3.40). IR (KBr) cm^{-1}: 1670 (C=O), 1360 and 1530 (NO_2).

3,5-Diacetamidoquinoline (XXII) from 3,5-Dinitroquinoline (XX)——XX (30 mg, 0.14 mmol) was catalytically hydrogenated in the presence of 10% Pd–C (30 mg) in EtOH solution. The product (22 mg) was immediately acetylated with Ac_2O (5 ml) and a few drops of conc. H_2SO_4. The reaction mixture was poured into ice-water, made alkaline with solid K_2CO_3, and extracted with $CHCl_3$. The usual work-up of the extract gave 28.2 mg (84%) of XXII, which was recrystallized from water to furnish colorless needles, mp 235°. *Anal.* Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.27. Found: C, 64.09; H, 5.40; N, 17.18. PMR ($CDCl_3$) δ: 2.31 (6H, s). MS *m/e*: 243 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 231 (3.74), 255 (4.26), 325 (3.41).

3,5-Diacetamidoquinoline (XXII) from 3-Acetamido-5-nitroquinoline (XXV)——XXV (217 mg, 0.9 mmol) dissolved in EtOH (40 ml) was catalytically hydrogenated in the presence of 10% Pd–C (200 mg). Without purification, the product was acetylated with 10 ml of Ac_2O and a few drops of conc. H_2SO_4. The

usual work-up gave colorless crystals (98 mg, 45%), which were recrystallized from water to furnish colorless needles, mp 235—236°.

3,8-Diacetamidoquinoline (XXIII) from 3,8-Dinitroquinoline (XXI)——XXI (105 mg, 0.48 mmol) was catalytically reduced in the presence of 10% Pd–C (100 mg) in 30 ml of EtOH. The crude product (64.2 mg) was acetylated with Ac_2O (10 ml) and a few drops of conc. H_2SO_4. After work-up as before, the crude crystals (89.5 mg) were purified by preparative TLC on silica gel (thickness 1.5 mm), using a mixture of $CHCl_3$/EtOH (9: 1) as a developer, to give colorless crystals (58 mg, 48%), which were recrystallized from water to furnish colorless needles, mp 217—218°. *Anal.* Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.27. Found: C, 64.33; H, 5.43; N, 17.53. PMR ($CDCl_3$) δ: 2.30 (6H, d, J=7 Hz, $COCH_3$). MS *m/e*: 243 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 235 (3.87), 263 (4.17). IR (KBr) cm^{-1}: 1660 (C=O).

3,8-Diacetamidoquinoline (XXIII) from 3-Acetamido-8-nitroquinoline (XXVI)——XXVI (100 mg, 0.43 mmol) was catalytically reduced and the product was acetylated as described for the reaction of XXV. The crude acetate (72.2 mg, 83%) was purified by preparative TLC on silica gel (thickness 1.5 mm), using a mixture of $CHCl_3$ and EtOH (9: 1) as a developer, to afford 44 mg (50%) of colorless crystals, which were recrystallized from water to furnish colorless needles, mp 215—216°, undepressed on admixture with XXIII derived from XXI. The IR spectra of the samples were identical.

3-Amino-8-nitroquinoline (XXVII)——A mixture of 300 mg (1.2 mmol) of XXVI and 1.2 ml of conc. HCl was heated at 80° for 15 min, poured into ice-water, and made alkaline with solid K_2CO_3. The yellow powder (237 mg, 100%) was collected by suction and recrystallized from EtOH to afford yellow needles, mp 187—188.5°. *Anal.* Calcd. for $C_9H_7N_3O_2$: C, 57.14; H, 3.92; N, 22.21. Found: C, 57.25; H, 3.66; N, 22.43. MS *m/e*: 205 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 211 (4.26), 223 (4.19, shoulder), 345 (4.01), 404 (3.66, shoulder).

3-Chloro-8-nitroquinoline (XXVIII)——A solution of $NaNO_2$ (33.2 mg, 0.48 mmol) in water (2.6 ml) was added dropwise to a solution of XXVII (85 mg, 0.48 mmol) in 15% HCl (1.7 ml) under ice cooling with stirring for 20 min. A solution of Cu_2Cl_2 (454.4 mg, 2.29 mmol) dissolved in conc. HCl (2 ml) was then added dropwise with ice cooling and the mixture was allowed to stand at room temperature for a while. The reaction mixture was then made alkaline with solid K_2CO_3 and extracted with $CHCl_3$. The extract was worked up as usual to give 57.2 mg (64%) of XXVIII as a yellow powder, which was recrystallized from MeOH to furnish pale brown leaflets, mp 144.5—145° (lit.[16] mp 139—140°).

8-Acetamidoquinoline (XXIX)——A mixture of XXVIII (38 mg, 0.18 mmol), AcONa (40 mg, 0.49 mmol), and 10% Pd–C (40 mg) in AcOH (4 ml) was shaken under a stream of H_2. After removal of the catalyst by suction, the filtrate was made alkaline with solid K_2CO_3 and extracted with $CHCl_3$. An oily mass (16 mg), obtained from the extract by the usual work-up, was dissolved in Ac_2O (2 ml) and allowed to stand for 1 hr at room temperature. The reaction mixture was then poured into ice-water, made alkaline with solid K_2CO_3 and extracted with $CHCl_3$. The usual work-up of the extract gave 14.3 mg of a crystalline mass, which was purified by preparative TLC on silica gel (thickness 1.5 mm) to give 7 mg (39%) of XXIX as colorless crystals, which were recrystallized from water to furnish colorless needles, mp 103° (lit.[13] mp 103°). The melting point of this product was not depressed by admixture with 8-acetamidoquinoline (mp 103°), prepared from 8-aminoquinoline. The IR spectra of both compounds were the same.

Nitration of 4-Nitroquinoline (III)——KNO_3 (302 mg, 3 mmol) was added gradually to a mixture of III (174 mg, 1 mmol) and conc. H_2SO_4 (6 ml) at 70° with stirring, and the mixture was heated for a further 2 hr.

Treatment of the reaction mixture with ice-water afforded 160 mg of a precipitate, which was collected by suction. The crude products, which showed two spots on a silica gel TLC plate, were separated from each other by preparative TLC on silica gel (thickness 1.5 mm) using a mixture of benzene and $CHCl_3$ (2: 1, developed three times). Extraction of the upper band on the chromatogram with acetone gave 40 mg (18%) of XXXI, which was recrystallized from EtOH to furnish colorless needles, mp 189.5—191°. *Anal.* Calcd. for $C_9H_5N_3O_4$: C, 49.32; H, 2.30; N, 19.18. Found: C, 49.37; H, 2.03; N, 19.18. PMR (CF_3COOD) δ: 8.25 (1H, q, $J_{5,6}$=7.5 Hz, $J_{6,7}$=8 Hz, H_6), 8.55 (1H, d, $J_{2,3}$=5 Hz, H_2 or H_3), 8.82 (1H, dd, $J_{5,6}$=7.5 Hz, $J_{5,7}$=1.25 Hz, H_5), 9.20 (1H, dd, $J_{6,7}$=8 Hz, $J_{5,7}$=1.25 Hz, H_7), 9.67 (1H, d, $J_{2,3}$=5 Hz, H_2 or H_3). MS *m/e*: 219 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 250 (3.77), 320 (3.64).

The acetone extract of the lower band on the chromatogram gave 100 mg (46%) of XXX, which was recrystallized from EtOH to afford colorless prisms, mp 192—193°. *Anal.* Calcd. for $C_9H_5N_3O_4$: C, 49.32; H, 2.30; N, 19.18. Found: C, 49.37; H, 2.03; N, 19.28. PMR (CF_3COOD) δ: 7.95 (1H, dd, $J_{7,8}$=6 Hz, $J_{6,8}$=1.25 Hz, H_8), 8.21 (1H, t, $J_{7,8}$=6 Hz, $J_{6,7}$=7 Hz, H_7), 8.30 (1H, d, $J_{2,3}$=5 Hz, H_2 or H_3), 8.45 (1H, dd, $J_{6,7}$=7 Hz, $J_{6,8}$=1.25 Hz, H_6), 9.23 (1H, d, $J_{2,3}$=5 Hz, H_2 or H_3). MS *m/e*: 219 (M^+). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 249 (3.78), 382 (3.68).

4-Hydroxy-5-nitroquinoline (XXXIV) from 4,5-Dinitroquinoline (XXX)——A mixture of 13 mg (0.06 mmol) of XXX, 0.5 ml of conc. H_2SO_4 and 0.5 ml of H_2O was heated on a water bath for 2 hr. The reaction mixture was poured into ice-water and made alkaline with $KHCO_3$. The yellow precipitate was collected by suuction (4 mg, 24%) and recrystallized from water to give yellow needles of mp 325° (darkening) (lit.[15] mp 340° (dec.)). IR (KBr) cm^{-1}: 1640, 1608, 1575, 1498, 1330, 1200, 1120, 1048, 790, 740.

4-Chloro-5-nitroquinoline (XXXVI)——A suspension of 50 mg (0.2 mmol) of XXXII and 120 mg of PCl_3 in 5 ml of AcOEt was refluxed for 1 hr, poured into ice-water and extracted with AcOEt. The usual

work-up of the extract gave 31.1 mg (70%) of yellow crystals, which were recrystallized from MeOH to furnish pale yellow needles of XXXVI, mp 142—144.5° (lit.[15] mp 144—148°).

4-Hydroxy-8-nitroquinoline (XXXV) from 4,8-Dinitroquinoline (XXXI)——A mixture of 20 mg (0.09 mmol) of XXXI, 4 ml of MeOH, 0.45 ml of conc. HCl, and 0.3 ml of H_2O was refluxed for 2 hr. The reaction mixture was then poured into ice-water and made alkaline with solid $KHCO_3$. A small amount of the colorless precipitate was collected by suction and recrystallized from MeOH to afford colorless needles of mp 181°, which appeared to be 4-methoxy-8-nitroquinoline. MS *m/e*: 204 (M^+). PMR ($CDCl_3$) δ: 4.00 (3H, s, OCH_3).

The filtrate was extracted with $CHCl_3$ to yield yellow crystals (10 mg, 60%) of XXXV, which were recrystallized from benzene to furnish yellow prisms, mp 200—202° (lit.[15] mp 201—202°). IR (KBr) cm^{-1}: 1645, 1600, 1570, 1530, 1500, 1365, 1308, 1180, 1020, 815, 760.

4-Chloro-8-nitroquinoline (XXXVII)——A solution of 50 mg (0.2 mmol) of XXXIII and 120 mg of PCl_3 in 5 ml of AcOEt was refluxed for 1 hr and worked up as described for the reaction of XXXII. The product (62.5 mg) was purified by column chromatography on Florisil (10 g) using benzene and a mixture of benzene/$CHCl_3$ (1 : 1). The yellow crystals (40 mg, 96%) thus obtained were recrystallized from EtOH to furnish pale yellow needles, mp 126.5—127° (lit.[15] mp 126.5—128°).

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