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Quinoline Derivatives. XVI.[1,2] Nitration of 2-Anilino-4-methylquinoline with the Mixed Acid of Nitric and Sulfuric Acid

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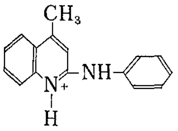
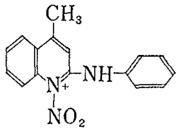
Nitration of 2-anilino-4-methylquinoline (I) with mixed acids gives different products according to the concentration of sulfuric acid used. In 50% sulfuric acid solution, 2-(*o*-nitroanilino)-4-methylquinoline (II) and 2-(*p*-nitroanilino)-4-methylquinoline (IV) are formed in approximately equal quantity, while in 85% sulfuric acid solution, IV and 2-(*p*-nitroanilino)-4-methyl-6-nitroquinoline (V) are mainly formed. In 95% sulfuric acid, V and a small amount of 2-(2′,4′-dinitroanilino)-4-methyl-6-nitroquinoline (VI) are formed.

On the other hand, nitration of I with acetyl nitrate results in the characteristic formation of II and 2-(2′,4′-dinitroanilino)-4-methylquinoline (III). It is certain, therefore, that nitration of I with nitric acid in 95% sulfuric acid and that with acetyl nitrate have a different reaction mechanism; the former reaction proceeding in  type and the latter in  type.

The previous report of this series[2] described the properties of 2-anilino-4-methylquinoline (I) to nitration reagents. Reaction of I with acetyl nitrate gave 2-(*o*-nitroanilino)-4-methylquinoline (II) in a high yield, while the same reaction carried out in dichloromethane chararcteristically gave 2-(2′,4′-dinitroanilino)-4-methylquinoline (III). III was not formed by the reaction of I with nitric acid or of the mononitrate of I and sulfuric acid. The mononitrate of I, when dissolved in conc. sulfuric acid, forms II, 2-(*p*-nitroanilino)-4-methylquinoline (IV), and 2-(*p*-nitroanilino)-4-methyl-6-nitroquinoline (V), and though their yield differes according to the reaction temperature, their yield is generally poor (Chart 1).

In the present series of work, nitration of I with nitric acid after dissolving it in conc. sulfuric acid was examined since V is not obtained by the reaction of I with acetyl nitrate or nitric acid, and in order to obtain V in a good yield.

The same method of nitration was also applied to some nitroanilino-4-methylquinolines and comparative examinations were made on the products from compounds already possessing a nitro substituent. Further, mass spectra of I and its nitro derivatives were measured and comparative examinations were made on their fragmentation.

In order to elucidate the reason for marked difference in the yield of V (Chart 1) according to the reaction temperature, the following experiments were carried out in order to examine whether this was due to the polar effect of the quinoline ring nitrogen and α-anilino nitrogen (–N= and –NH–) or to the effect of preliminarily introduced substituent, 4′-NO_2 or 6-NO_2 group.

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[1] Part XV: Y. Hamada, I. Takeuchi, and H. Matuoka, *Chem. Pharm. Bull.* (Tokyo), **18**, 1026 (1970).

[2] A preliminary communication of this work appeared in *Chem. Pharm. Bull.* (Tokyo), **17**, 2250 (1969).

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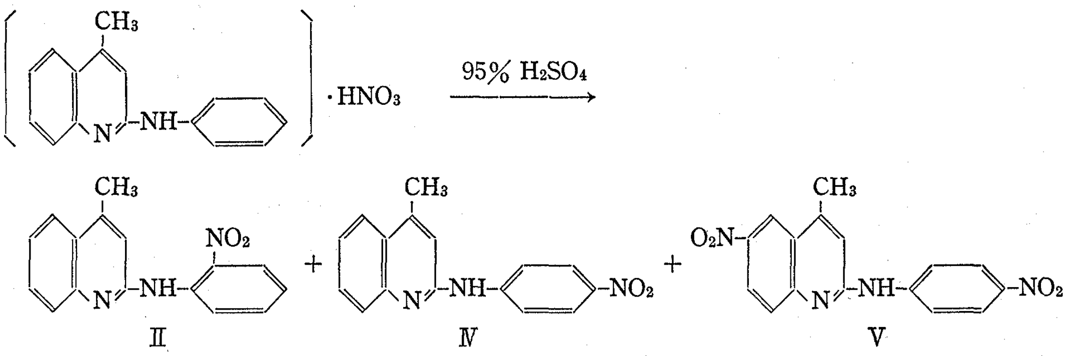

reaction temperature (°C)	Yield (%) II	IV	V
0	30	35	6
60	20	25	30

Chart 1

Ochiai and Okamoto[4] stated that, in the nitration of quinoline and its N-oxide, the polar effect of the N-oxide function was highly dependent on the reaction temperature. Hamana and Nagayoshi[5] said, in relation to the nitration of the N-oxides of 6-substituted quinoline derivatives, that their orienting effect is dependent on the concentration of sulfuric acid rather than on the reaction temperature. Suzuki and others[6] made a detailed report on the formation of nitrated compounds relative to the concentration of sulfuric acid an reaction temperature in the nitration of cinnoline 2-oxide.

Based on these past literature, nitration of I in sulfuric acid solution was carried out in various concentrations of sulfuric acid and at varied temperatures, and results thereby obtained are listed in Table I.

Table I. Nitration of 2-Anilino-4-methylquinoline (I) with 1.5 Moles HNO_3 (d. 1.38) in Various Concentration of H_2SO_4

I(g)	Concn. (%) of H_2SO_4	Temp (°C)	Time (hr)	Yield (%) of II	IV	V	VI
1.0	50	60	3	33.0	50.0	trace	—
0.5	75	0	1	8.4	58.5	3.0	—
0.5	85	0	1	1.7	42.0	21.4	—
0.5	85	60	1	—	trace	25.0	trace
0.5	95	0	1	—	—	23.0	5.0
0.5	95	60	3	—	—	68.7	8.5

Nitration of I with nitric acid in sulfuric acid gives II, IV, V, and VI. Compounds II to V were identified by mixed melting test with authentic samples[2] and comparison of their infrared (IR) spectra.

VI is obtained as yellow needles, mp 287—288°, $C_{16}H_{11}O_6N_5$, m/e 369 (M^+); IR ν_{max}^{KBr} 3280, 3080 (NH) cm^{-1}. These IR absorptions are similar to those (3285 and 3100 cm^{-1}) of 2-(2′,4′-dinitroanilino)-4-methylquinoline (III) (Fig. 1). Since the nitration of III with nitric acid in 95% sulfuric acid gives a compound (VI′) having the same melting point and exhibit-

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[4] E. Ochiai and T. Okamoto, *Yakugaku Zasshi*, **70**, 384 (1950).
[5] M. Hamana and T. Nagayoshi, *Chem. Pharm. Bull.* (Tokyo), **14**, 319 (1966).
[6] I. Suzuki, T. Nagashima, and N. Nagasawa, *Chem. Pharm. Bull.* (Tokyo), **14**, 816 (1966).

ing the same IR spectrum, these compounds were presumed to be 2-(2′,4′-dinitroanilino)-4-methyl-6-nitroquinoline.

The selective formation of III by the reaction of I and acetyl nitrate in dichloromethane or chloroform solution2) was applied to 2-anilino-4-methyl-6-nitroquinoline (VII) and 2-(2′,4′-dinitroanilino)-4-methyl-6-nitroquinoline was obtained (Chart 2a). The fact that this product was identical with VI and VI′ was established by the mixed melting point test and IR spectral comparison.

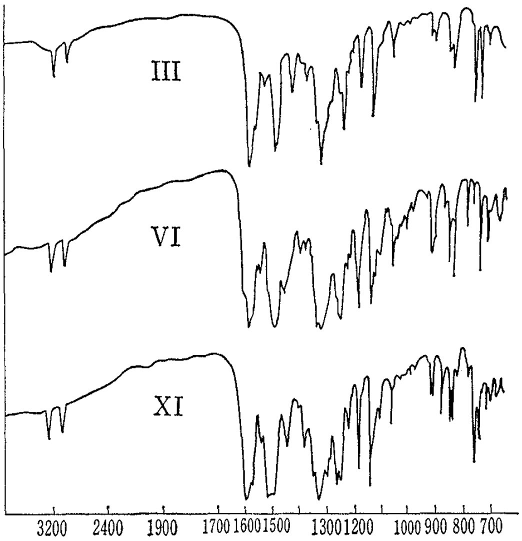

Fig. 1. Infrared Spectra of III, VI and XI in KBr Pellet

It will be seen from Table I that the formation of II decreases markedly with increasing concentration of sulfuric acid and is no longer formed in 85% sulfuric acid at 60°. IV is formed in a fair yield in 50—75% sulfuric acid but makedly decreases in 85% sulfuric acid at 60°, suggesting its transition to V. In contrast, yield of V increases gradually with increasing concentration of sulfuric acid and gradual rise in temperature, and V is obtained as its sulfate of yellow crystalline powder of mp above 300° when I is reacted with nitric acid in 85—95% sulfuric acid at 60°.

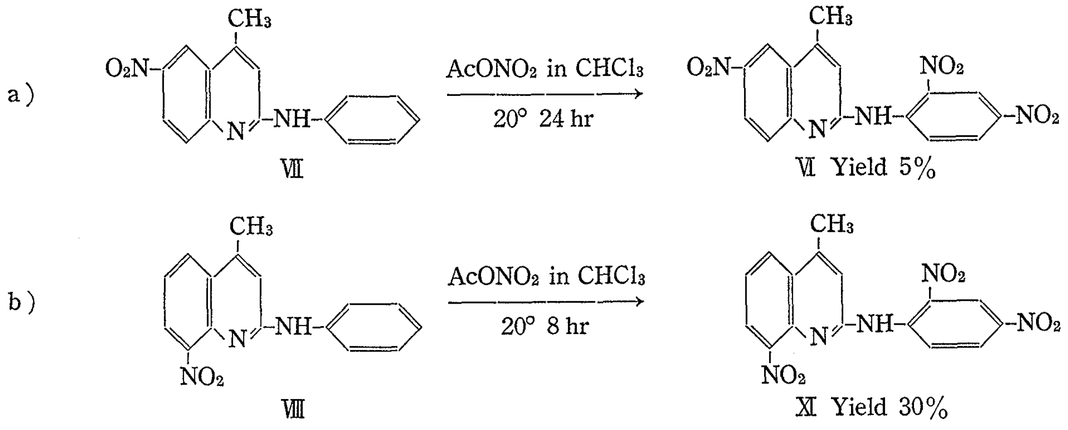

Chart 2

From these results, it is assumed that, in the nitration of I with nitric acid in 95% sulfuric acid, substitution of the nitro group is limited to the 6-position in the quinoline ring and 4′-position in the anilino group. In this reaction, 2-(2′,4′dinitroanilino)-4-methylquinoline was not obtained. These facts have clarified the differecne in the reaction products obtained by nitration of I with nitric acid and that with acetyl nitrate, and suggest that the mechanism of nitration differes in these two kinds of reaction. Such a different mechanism is illustrated in Chart 3 and further detailed examination on these points will be the subject of a separate report.7)

Results of nitration of nitroanilino-4-methylquinolines with nitric acid in sulfuric acid solution are listed in Table II.

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7) Y. Hamada, Y. Ito, H. Yanagawa, T. Mizuno, and M. Hirota, *Nippon Kagaku Zasshi*, **91**, 402 (1970).

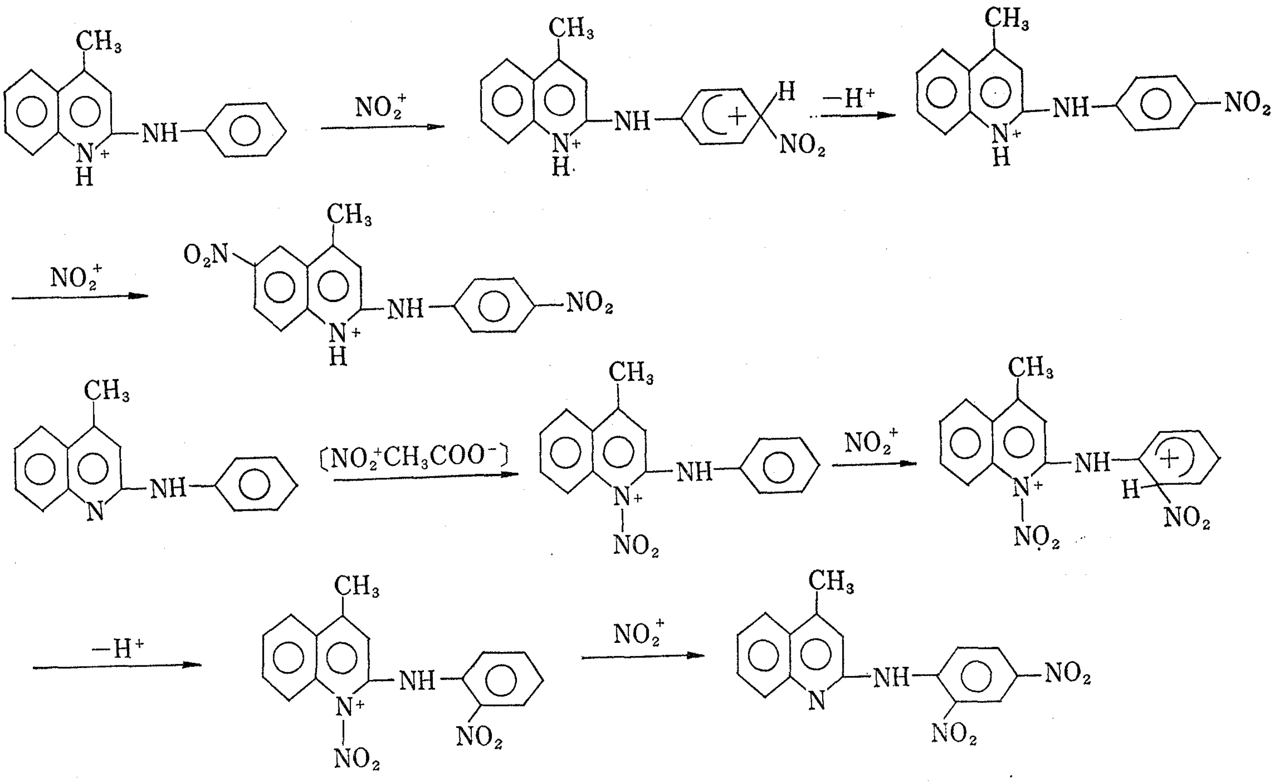
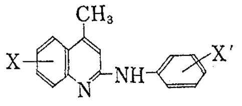
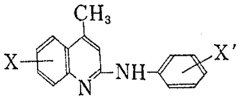


Chart 3

Table II. Nitration of Nitro Derivatives of 2-Anilino-4-methylquinoline with 1.5 Moles HNO_3 (d. 1.38) in 95% H_2SO_4

Starting material			Reaction condition		Product (yield %)	
			Temp (°C)	Time (hr)	V	VI
II	H	2'-NO_2	0	1	—	95a)
IV	H	4'-NO_2	0	1	—	— (recovery 100%)
			60	3	95a)	—
III	H	2',4'-$(NO_2)_2$	0	1	—	55a)
VII	6-NO_2	H	60	3	10a)	— (recovery 90%)
V	6-NO_2	4'-NO_2	60	3	—	75a)

Starting material			Reaction condition		Product (yield %)		
			Temp (°C)	Time (hr)	X	IX	XI
VIII	8-NO_2	H	60	3	5b)	80b)	10b)
IX	8-NO_2	4'-NO_2	60	3	—	—	95a)

a) and b) Explained in Experimental.

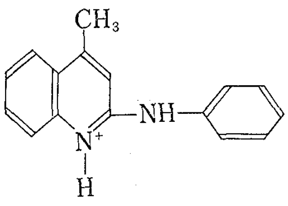
Nitration of 2-anilino-4-methyl-8-nitroquinoline (VIII) with nitric acid in sulfuric acid gave IX as the main product, and reddish yellow needles (X), mp 233°, and yellowish green needles (XI), mp 299° as by-products. IX was established as 4-methyl-2-(*p*-nitroanilino)-8-nitroquinoline by mixed melting point test with an authentic sample2) and by IR spectral comparison.

X, $C_{16}H_{12}O_4N_4$, *m/e* 324 (M^+); IR ν_{max}^{KBr} 3320 cm^{-1} (NH), was identified as 4-methyl-2-(*o*-nitroanilino)-8-nitroquinoline by mixed melting point test with an authentic speciment synthesized by fusion of 2-chloro-4-methyl-8-nitroquinoline and *o*-nitroaniline in the presense of anhydrous sodium acetate for 1 hr at 160—165°, and by their IR spectral comparison.

XI, $C_{16}H_{11}O_6N_5$, *m/e* 369 (M^+); IR ν_{max}^{KBr} 3280, 3080 (NH) cm^{-1} (Fig. 1), was identified as 2-(2',4'-dinitroanilino)-4-methyl-8-nitroquinoline by mixed melting point test with an authentic specimen prepared by nitration of VIII with acetyl nitrate in chloroform solution (Chart 2-b), and by their IR spectral comparison.

Nitration of 2-anilino-4-methylquinoline derivatives with a nitro group was carried out on mononitro compounds having a nitro group in 2'-position (II) and 4'-position (IV) in the anilino group, and those with a nitro group in 6-position (VII) and 8-position (VIII) of the quinoline ring, and products therefrom were compared. In the case of IV and VIII, the corresponding dinitro compounds (V and X) are obtained as the main product under the same reaction conditions. While VI is formed in approximately quantitative yield from IV, X and XI are formed from VIII, due to lower basicity of its ring nitrogen by the effect of electron-attracting nature of the nitro group in 8-position of VIII.

The fact that VII is practically resistant to nitration at 60° for 3 hours, with slight formation of V, and that II forms VI in a quantitative yield, in one step under a mild condition, may be explained as the lowering of the basicity of either of the nitrogen atoms due to electron-attracting nature of the nitro group adjacent to the nitrogen atoms in the quinoline ring and in α-anilino group (-N=C-NH-). The same explanation can be applied to the nitration products from dinitro compounds having substituents in the 2',4'-positions of the anilino portion (III), one in 6-position of the quinoline ring and the other in 4'-position of the anilino group (V), and in 4'- and 8-positions (IX).



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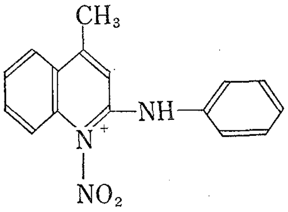

2

From these experimental results, it may be concluded that nitration of 2-anilino-4-methylquinoline (I) with nitric acid in sulfuric acid results in substitution at 2', 4', and 6 positions, in that order, and other positions are hardly substituted.

From the great basicity of the quinoline ring-nitrogen, nitration of I in acid solution is expected to proceed in two ionic forms of **1** and **2**.

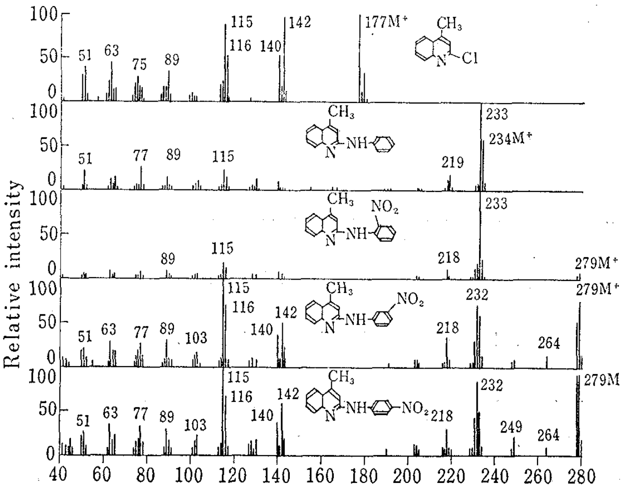

Fig. 2. Mass Spectra of 2-Chloro-4-methylquinoline and 2-Anilino-4-methylquinoline Derivatives

Mass Spectra

The mass spectra of 2-anilino-4-methylquinolines and their starting compounds were measured to compara-

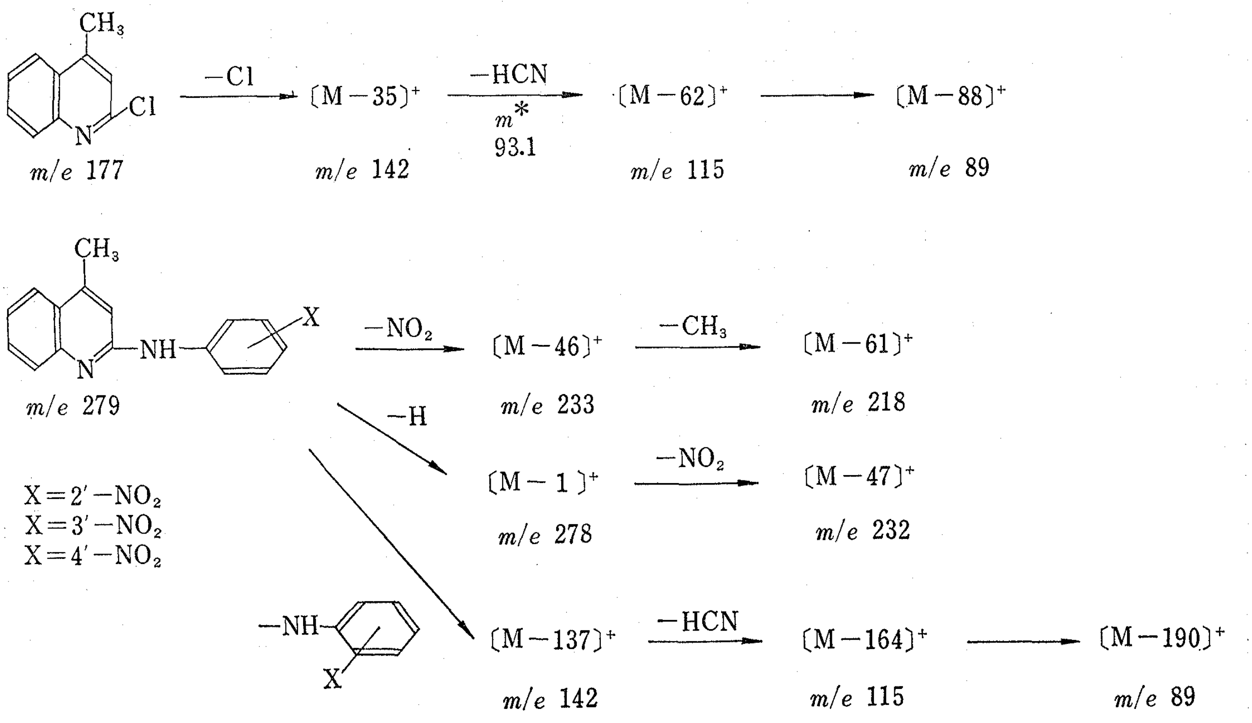

Chart 4

tively examine the difference, if any, in the fragmentation due to position isomers. The result of such measurements is given in Fig. 2. From this result, following fragmentation was considered. When there is a nitro group in 2′-position, molecular ion peak is small and a large peak of *m/e* 233, with the nitro group severed, is observed. This peak indicates that the compound has been stabilized with liberation of the nitro group. When there are a nitro group at 3′- or 4′-positions, there is a base peak at *m/e* 115, showing the severance of the anilino bonding. This fact is suggested from its similarity to the fragmentation of the starting material, 2-chloro-4-methylquinoline.

Experimental

Nitration of 2-Anilino-4-methylquinoline (I)——a) With 50% H_2SO_4 and HNO_3 at 60°: To a solution of 1 g of I dissolved in 40 ml of 50% H_2SO_4, 0.3 ml of HNO_3 (sp. gr. 1.38) was added dropwise at room temperature, the mixture was stirred at 60° for 3 hr, cooled, and poured into 200 ml of ice water. This acid solution was neutralized with NH_4OH, the reddish brown precipitate thereby formed was collected, washed with H_2O, and dried. This precipitate was dissolved in benzene, the solution was concentrated, and 0.4 g (33%) of II was obtained as orange needles, mp 168—169°. The residue was recrystallized from EtOH to 0.6 g (50%) of IV as yellow prisms, mp 252—254°.

b) With 75% H_2SO_4 and HNO_3 at 0°: To a solution of 0.5 g of I dissolved in 10 ml of 75% H_2SO_4, 0.15 ml of HNO_3 (sp. gr. 1.38) was added dropwise at 0°, the mixture was stirred for 1 hr at the same temperature, and poured into 100 ml of ice water. After standing overnight, the yellow precipitate thereby formed was collected, washed with water, and dried. The crude crystals were dissolved in pyridine–benzene mixture (1:5) and the solution was passed through an Al_2O_3 column, which was eluted with the same solvent. The initial orange effluent afforded 50 mg (8.4%) of II and the next yellow effluent gave 0.35 g (58.5%) of IV. The yellow adsorbed portion was eluted with acetone and afforded 20 mg (3%) of V as yellow needles, mp 302—304°.

c) With 85% H_2SO_4 and HNO_3 at 0°: A solution of 0.5 g of I dissolved in 10 ml of 85% H_2SO_4 was treated with 0.15 ml of HNO_3 (sp. gr. 1.38) and treated as in b), affording 10 mg (1.7%) of II, 0.25 g (42%) of IV, and 0.15 g (21.4%) of V.

d) With 85—95% H_2SO_4 and HNO_3: In a similar manner as above and as shown in Table I, the mixture was stirred at the temperature and time as indicated. The reaction mixture was poured into 100 ml of ice water, allowed to stand overnight, and the yellowish green precipitate formed was collected by filtration.

This precipitate was washed in a small volume of acetone, filtered, and the crude crystals were dried. The crystals were then washed with 3 ml of hot pyridine to be separated into yellowish brown filtrate and yellow crystalline powder. The filtrate was mixed with benzene (1:3) and passed through an Al_2O_3 column, which was developed with the same solvent. The initial yellowish green effluent afforded a trace of IV, pale reddish adsorbed band gave a trace of IV, and the pale yellow adsorbed band gave a small amount of V.

The yellow crystalline powder (1.0 g, 25%) melted at above 310°, and was fused with metallic Na. Sulfur was detected with sodium nitroprusside reagent ($Na_2Fe(CN)_5(NO)$). Neutralization with hot 10% NaOH gave V and the above was considered to be the monosulfate of V. *Anal.* Calcd. for $C_{16}H_{14}O_8N_4S$: C, 45.5; H, 3.34; N, 13.27. Found: C, 46.14; H, 3.11; N, 13.09.

Yield of products from the reaction of I with 95% H_2SO_4 and HNO_3 is shown in Table I.

Reaction of 2-Anilino-4-methyl-6-nitroquinoline (VII) and $AcONO_2$——To a solution of 0.5 g of VII dissolved in a mixture of 10 ml of $CHCl_3$ and 2.5 ml of $AcONO_2$ at room temperature, 2.5 ml of $AcONO_2$ was further added and the mixture was allowed to stand at room temperature for 24 hr. The reddish brown reaction mixture was poured into ice water, and yellow crystals that precipitated out were separated from the reddish brown solvent layer. The solvent layer was washed with water, $CHCl_3$ was evaporated, and the residue was dissolved in pyridine–benzene mixture (1:3). This solution was passed through an Al_2O_3 column and 50 mg of the starting VII was recovered from the red effluent. The yellow effluent afforded yellow needles which were recrystallized from acetone to 5 mg (5%) of 2-(2′,4′-dinitroanilino)-4-methyl-6-nitroquinoline (VI), mp 287—288°. *Anal.* Calcd. for $C_{16}H_{11}O_6N_5$: C, 52.24; H, 3.00; N, 18.97. Found: C, 52.03; H, 2.73; N, 18.79. Mass Spectrum *m/e*: 369 (M^+). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3280, 3080 (NH).

Reaction of 2-Anilino-4-methyl-8-nitroquinoline (VIII) and $AcONO_2$——A solution of 0.5 g of VIII dissolved in a mixture of 10 ml of $CHCl_3$ and 2.5 ml of $AcONO_2$ at room temperature, further added with 2.5 ml of $AcONO_2$, was allowed to stand at 20° for 8 hr, until needle crystals precipitated out into the reddish brown reaction mixture. The yellow precipitate was collected by filtration, washed with a small volume of $CHCl_3$, and recrystallized from acetone–benzene mixture to 2-(2′,4′-dinitroanilino)-4-methyl-8-nitroquinoline (XI) as yellowish green needles, mp 289—299°. Yield, 0.2 g (30%). *Anal.* Calcd. for $C_{16}H_{11}O_6N_5$: C, 52.03; H, 3.00; N, 18.97. Found: C, 52.04; H, 2.98; N, 18.77. Mass Spectrum *m/e*: 369 (M^+). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3280, 3080 (NH).

2-(*o*-Nitroanilino)-4-methyl-8-nitroquinoline (X)——A mixture of 0.5 g of 2-chloro-4-methyl-5-nitroquinoline, 0.6 g of *o*-nitroaniline, and 0.1 g of anhyd. AcONa was fused by heating in an oil bath at 100°, the orange reaction mixture was heated at 160—165° for 1 hr, and cooled. The orange solid was dissolved in hot benzene, AcONa was removed by filtration, and the filtrate was evaporated to dryness. *o*-Nitroaniline was removed by dissolving in benzene and sparingly soluble crystalline substance was recrystallized from acetone–benzene mixture to lustrous orange needles, mp 231—233°. Yield, 0.1 g (15%). *Anal.* Calcd. for $C_{16}H_{12}O_4N_4$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.15; H, 3.69; N, 16.97. Mass Spectrum *m/e*: 324 (M^+). IR $\nu_{\max}^{\text{KBr}}$: 3320 cm^{-1} (NH).

Nitration of Nitro Derivatives of 2-Anilino-4-methylquinoline (II—V and VII—IX in Table II)——A solution of 0.5 g of the starting material dissolved in 10 ml of conc. H_2SO_4 was chilled to 0°, 0.1—0.2 ml of HNO_3 (sp. gr. 1.38) was added dropwise at 0°, and the mixture was stirred for 1 hr at 0° or for 3 hr at 60°. The reaction mixture was poured into ice water, yellow precipitate thereby formed was collected by filtration, washed with H_2O, neutralized with 10% Na_2CO_3, washed with H_2O, and dried. The product was purified by either (a) recrystallization from acetone or acetone–benzene mixture or (b) dissolved in pyridine–benzene mixture (1:3) and passed through an Al_2O_3 column, effluent evaporated, and residue recrystallized from acetone or acetone–benzene mixture. Details are shown in Table II. Chromatographic absorption band: Yellowish green band gave X as orange needles, mp 213°; red band gave XI as yellowish green needles, mp 289—299°; yellowish brown band gave IX as yellow needles, mp 304—306°.

The products (V, VI, IX, X, and XI) obtained by this method were confirmed by mixed fusion test and identical IR spectra with authentic samples obtained by a different route of synthesis.

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