Chem. Pharm. Bull. 17(11)2250—2255(1969)

UDC 547.831.5.04

Quinoline Derivatives. XIV.[1] Chemistry of 2-(Phenylamino)-lepidine Derivatives

Torizo Takahashi, Yoshiki Hamada, and Yoshio Ito

Faculty of Pharmacy, Meijo University[2]

(Received March 13, 1969)

Reaction of 2-anilinolepidine with 1.2 mole of nitric acid in acetic acid at room temperature afforded only a mononitrate (VIII). Dissolution of VIII into 98% sulfuric acid under ice chilling afforded 2-(*o*-nitroanilino) lepidine (I), 2-(*p*-nitroanilino)lepidine (III), and 2-(*p*-nitroanilino)-6-nitrolepidine (V).

Reaction of VII with acetyl nitrate in dichloromethane at room temperature for 3 hr afforded I in 75% yield, while prolongation reaction time to 15 hr afforded 2-(2′,4′-dinitroanilino)lepidine (IV) in 95% yield. III was obtained by reaction of VII with a large excess of nitric acid. These reaction are optimal for the selective nitration of the anilino group of VII, in order to afford *o*-nitro (I), *p*-nitro (III), and *o*,*p*-dinitro (IV) derivertives.

One of the present authors[3] earlier reported partial reduction of the nitro group in dinitrophenylaminolepidines, and showed that, in general, the nitro group in 8-position is more easily reduced than that in 6-position in the reduction of 6,8-dinitroquinoline,[4] while the reverse was true in the case of 2-anilino-6- and -8-nitrolepidines, the nitro group in 6-position being more easily reduced than that in 8-position. These experimental evidences were recently confirmed by Hamada and others[5] from molecular orbital method.

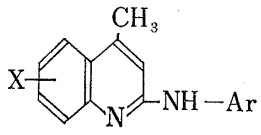
In order to elucidate the chemical nature of phenylaminolepidines, reaction of 2-anilinolepidine to nitration reagents was examined in the present series of work. For the sake of comparison, nitration was carried out with nitric acid in acetic acid or sulfuric acid, and with acetyl nitrate in various organic solvents. Acetyl nitrate is known as the reagent that selectively substitutes a nitro group into the *ortho* position.[6,7a] It has also been used for the nitration of quinoline 1-oxide derivatives.[7b] There are various methods for the preparation of acetyl nitrate and the method of Pictet[7a] was used in the present series of experiments. From the present studies, a good method was found for the syntheses of 2-(*o*-nitroanilino)-lepidine (I), 2-(*p*-nitroanilino)lepidine (III), and 2-(2′,4′-dinitroanilino)lepidine (IV) in a high yield by nitration of 2-anilinolepidine.

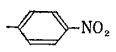
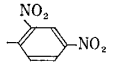
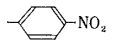
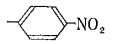
The compounds I to VI were synthesized by the following method in order to obtain authentic samples for identification of the nitrated derivatives. By the modification of the method reported in Part VIII of this series,[3] 2-chlorolepidine was reacted with *o*-, *m*-, or *p*-nitroaniline, or 2,4-dinitroaniline in pyridine to obtain I, II, III,[8] and IV, respectively. Similarly, *p*-nitroaniline was reacted with 2-chloro-6- or 2-chloro-8-nitrolepidine to obtain

1) Part XIII: Y. Hamada, *Yakugaku Zasshi*, **88**, 1097 (1968).
2) Location: *Tempaku-cho, Showa-ku, Nagoya* 468, *Japan*.
3) Y. Hamada, *Yakugaku Zasshi*, **83**, 943 (1962).
4) H. Artmann, *J. Pr. Chem.* (2), **53**, 206 (1903).
5) Y. Hirota and Y. Hamada, unpublished data.
6) F. Francis, *J. Chem. Soc.*, **89**, 1 (1906); *idem*, *Ber*, **39**, 3798 (1906); P.H. Griffiths, W.A. Walkey, and H.B. Watson, *J. Chem. Soc.*, 631 (1934); A.E. Oxford, *J. Chem. Soc.*, **2004** (1926); K. Halvarson and L. Melander, *Arkiv. Kemi*, **11**, 77 (1957); F. Arnal, *J. Soc. Chem. Ind.*, **48**, 159T (1929).
7) *a*) A. Pictet and E. Khotinsky, *Ber.*, **40**, 1163 (1907); *b*) E. Ochiai and C. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **5**, 59 (1957); *c*) M.J.S. Dewar and D.S. Urch, *J. Chem. Soc.*, **1958**, 3079 (1958).
8) Y. Hamada, *Yakugaku Zasshi*, **82**, 937 (1962).

2-(*p*-nitroanilino)-6-nitrolepidine[9] (V) and 2-(*p*-nitroanilino)-8-nitrolepidine[9] (VI). Details of these syntheses are summarized in Table I.

Table I.



Compd. No.	X	Ar	Yield (%)	Appearance (recryst. solvt.)	mp[a] (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
I	H		30	reddish yellow needles(benzene)	168—169	$C_{16}H_{13}O_2N_3$	68.80	4.69	15.05	68.75	4.55	14.97
II	H		32	yellow needles (benzene)	196—197	$C_{16}H_{13}O_2N_3$	68.80	4.69	15.05	69.19	4.59	14.89
III	H		40	yellow needles (acetone+benzene)	239—240	$C_{16}H_{13}O_2N_3$	68.80	4.69	15.05	68.97	4.50	14.75
IV	H		20	bright yellow needles (acetone+benzene)	253—254	$C_{16}H_{12}O_4N_4$	59.26	3.73	17.28	59.15	3.41	17.03
V	6-NO_2		40	yellow needles (acetone+benzene)	302—304	$C_{16}H_{12}O_4N_4$	59.26	3.73	17.28	59.58	3.70	16.57
VI	8-NO_2		40	yellow needles (acetone+benzene)	304—306	$C_{16}H_{12}O_4N_4$	59.26	3.73	17.28	59.34	3.62	16.98

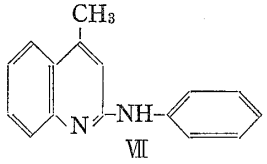
a) All melting points are uncorrected.

Result of nitration of 2-anilinolepidine (VII) by following method is illustrated in Chart 1.

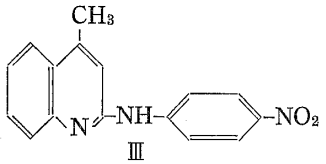
Nitration with Nitric Acid in Acetic Acid

Reaction of VII with 1.2 mole of nitric acid (d_4^{20} 1.38) in acetic acid at 20° failed to yield a nitrated derivative and only a mononitrate (VIII) was obtained, which was identified in the following way. Ultraviolet (UV) spectra of VII and III in neutral and alkaline solution showed no marked change while shift of absorption maxima to a shorter wave-length was observed in acid solution[10] (Table II). Titration of VII in glacial acetic acid with potassium perchlorate resulted in consumption of only 1 mole of perchlorate for 1 mole of VII, indicating that the nitrogen in the quinoline ring had consumed one mole of the perchlorate. Infrared (IR) spectrum of VIII in KBr pellet showed absorptions for ammonium and C=$\overset{+}{N}$H at 3050—2950 (m) (broad) and 1670—1650 (s) cm^{-1}. Elementary analytical values of VIII corresponded to those of the mononitrate of VII. VIII quite easily reverted to VII by treatment with 5% potassium carbonate.

Table II.



VII



III

UV λ_{max}^{EtOH} mμ (log ε)	270 (5.91)	350 (4.45)	220 (6.15)	390 (6.18)
UV $\lambda_{max}^{1/10N\ NaOH}$ mμ (log ε)	270 (5.91)	350 (4.45)	220 (6.15)	390 (6.18)
UV $\lambda_{max}^{1/10N\ HCl}$ mμ (log ε)	300 (5.95)	320 (4.35)	300 (6.15)	360 (6.15)

9) Y. Hamada, *Yakugaku Zasshi*, **82**, 944 (1962).
10) K. Hamamoto and T. Kubota, *Yakugaku Zasshi*, **73**, 1162 (1953).

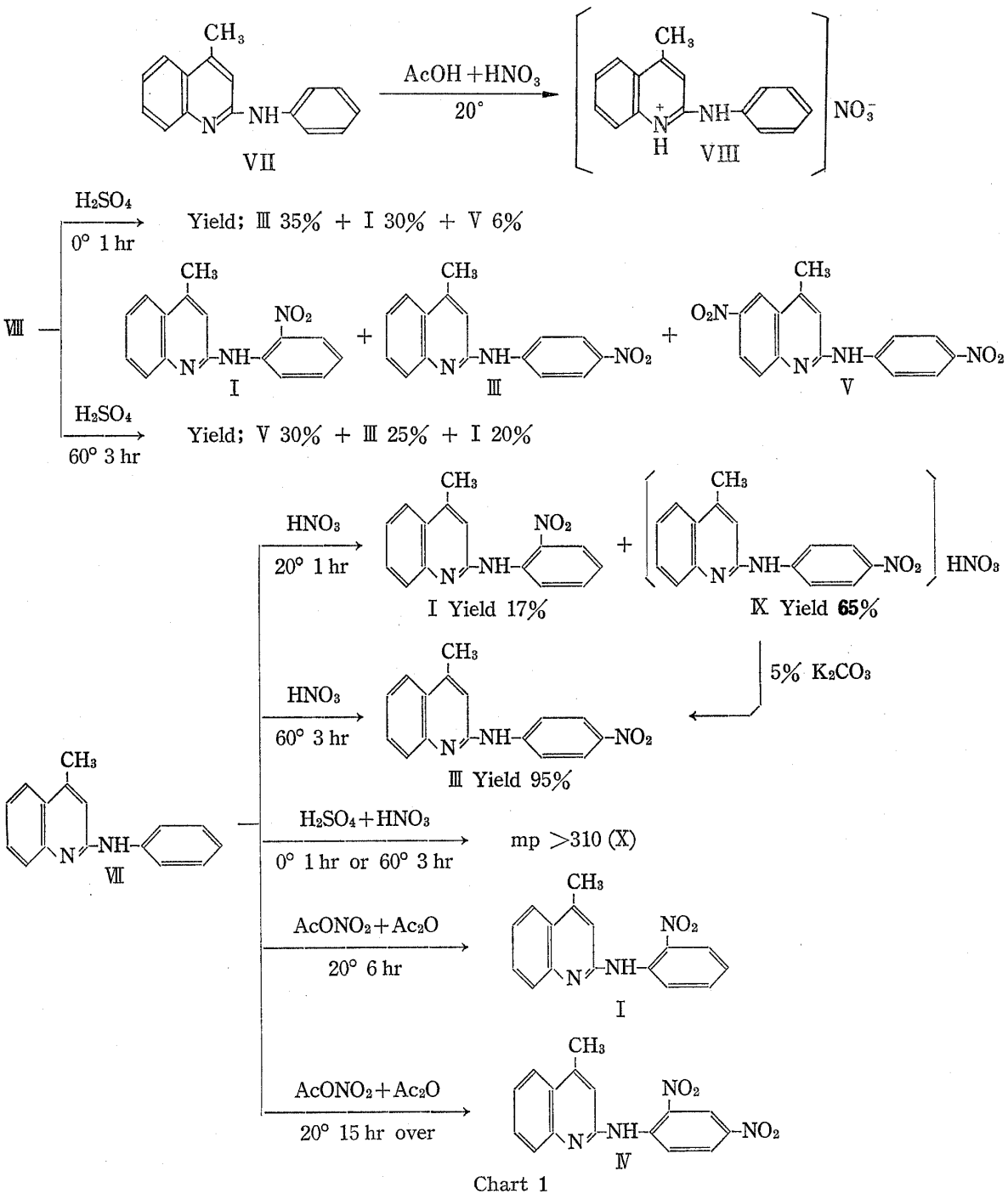


Chart 1

Reaction of VIII and Sulfuric Acid

VIII was dissolved in 98% sulfuric acid with ice chilling and I, III, and V were obtained. These compounds were identified with the corresponding authentic samples, shown in Table I, synthesized by a different route, by mixed melting point and IR spectra. Yield of V differed markedly according to reaction temperature of 0° and 60°.

Reaction of VII with Nitric Acid

VII was dissolved in a large excess of nitric acid (d_4^{20} 1.38) and, when the solution was allowed to stand at room temperature (15—20°), I and IX formed but when heated at 60°, III was produced quantitatively. I and III were identified with the corresponding authentic samples listed in Table I. This reaction is the most ideal for producing only III from VII. IX was identified as the nitrate of III by neutralization with 5% potassium carbonate.

Reaction of VII with Sulfuric Acid

VII was dissolved in 98% sulfuric acid with ice chilling and nitric acid (d_4^{20} 1.38) was added to the solution. Reaction at either 0° or 60° afforded yellow crystals (X) melting above 310°. Details on the identification of X will be reported in a subsequent paper.

Reaction of VII with Acetyl Nitrate

Acetyl nitrate was synthesized by the method of Pictet[7a] from nitrogen pentoxide[11] (d_4^{20} 1.5405) and acetic anhydride (d_4^{20} 1.083). The product obtained in the present work showed bp 34—36° (45—50 mmHg) d_4^{20} 1.2016, which differed from that of bp 22° (70 mmHg) reported in the literature.[7a]

Reaction of VII with acetyl nitrate in acetic anhydride at room temperature within 6 hr afforded only I, while the reaction for over 15 hr produced IV. These compounds were

Table III. Nitration with $AcONO_2$ Reagent in Ac_2O at Room Temperature

VII[a] (g)	Reaction condition		Yield (%)		
	$AcONO_2$ (ml)	time (hr)	I	IV	
0.5	0.1	24	—	—	(recovery)
0.5	0.2	6	10.0	—	
0.5	2.0	3	8.0	—	
0.5	2.0	15	—	7.2	
0.5	2.0	24	—	11.0	

a) Solubled in 5 ml Ac_2O.
substance nitrated: 2-(anilino)lepidine (VII)
product: 2-(*o*-nitroanilino)lepidine (I)
: 2-(2,4-dinitroanilino)lepidine (IV)

Table IV. Nitration with $AcONO_2$ Reagent in Organic Solvents at Room Temparature

VII (g)	Solvnent (ml)	Reaction conditions			Yield (%)			
		$AcONO_2$ (ml)	Time (hr)	Temp (°C)	I	III	IV	Total
0.5	CCl_4 (5)	1.0	5 min	18—20	—	—	—	(recovery)
0.5	$CHCl_3$ (3)	0.2	24	18—20	—	—	—	(recovery)
0.5	$CHCl_3$ (5)	1.0	3	25[b]	42	30	—	72
0.5	$CHCl_3$ (2)	2.0	3	18—20	67	—	14	81
0.5	$CHCl_3$ (2)	2.0	5	18—20	58	—	22	80
1.0	$CHCl_3$ (5)	4.0	20[a]	18—20	—	—	95	
0.5	CH_2Cl_2 (3)	0.2	24	18—20	—	—	—	(recovery)
0.5	CH_2Cl_2 (5)	1.0	3	25[b]	50	28	—	78
0.5	CH_2Cl_2 (2)	2.0	3	18—20	75	—	14	89
0.5	CH_2Cl_2 (2)	2.0	5	18—20	42	—	42	82
1.0	CH_2Cl_2 (5)	4.0	15[a]	18—20	—	—	95	
0.5	benzene (5)	1.0	0.5	45[b]	42	25	—	67
0.5	benzene (5)	2.0	0.5	45[b]	40	40	—	80
0.5	Nil	4.0	5	18—20	92	—	28	120

a) time until production of precipitate in the solvent
b) maximum temperature elevated by heat of reaction
substance nitrated: 2-(anilino)lepidine (VII)
product: 2-(*o*-nitroanilino)lepidine (I)
: 2-(*p*-nitroanilino)lepidine (III)
: 2-(2,4-dinitroanilino)lepidine (IV)

11) E.C. Horning, "Org.Synthese," Collected Vol. III, 1955, p. 804.

identified by mixed melting point and comparison of IR spectra with the corresponding authentic samples listed in Table I. However, the yield of these products was quite poor when reacted in acetic anhydride, as shown in Table III, and an attempt was made to increase the yield by the use of organic solvents as given in Table IV.

Reaction of VII and acetyl nitrate in dichloromethane in a ratio of 500 mg to 2 ml, at room temperature (15—20°) for 3 hr afforded I in 75% yield, while prolongation of the reaction time to 15 hr afforded IV in 95% yield. These reaction conditions are optimal for the selective nitration of the anilino group of VII, and afforded *o*-nitro and *o,p*-dinitro derivatives. The good effect of dichloromethane as a solvent in the nitration with acetyl nitrate is considered to be due to its large solubilization for organic compounds.

I can be obtained in 92% yield when VII is directly dissolved in acetyl nitrate with ice chilling, at the ratio of 500 mg to 4 ml, but this reaction has some shortcomings.

Acetyl nitrate (d_4^{20} 1.2016) undergoes slow decomposition at 20—25°, and decomposes explosively by the presence of a small amount of water or by reaction heat at 50—60°. When dry, it is a stable colorless liquid and has small reactivity with VII below 15°. Consequently, effective range of the reaction temperature between VII and acetyl nitrate is so small that, very often, acetyl nitrate undergoes instant decomposition by heat of the reaction, and there is a difficulty in the formation of IV. In order to improve these points, dichloromethane and chloroform were tried as the reaction solvent and they were found to be very effective.

Stability of acetyl nitrate in these organic solvents falls in the order of carbon tetrachloride, dichloromethane, chloroform, and benzene. Acetyl nitrate is stable or undergoes decomposition only very slowly in 30% concentration in carbon tetrachloride up to 40—50° and in dichloromethane and chloroform up to 30°, but undergoes rapid decomposition in benzene in 20% concentration at 20°.

Formation of III, as listed in Table IV, occurs only when rise in temperature resulted from the heat of reaction. Such a phenomenon is observed when a large amount of dichloromethane or chloroform is used, or when benzene is used as a solvent.

The reaction of VII and acetyl nitrate in carbon tetrachloride results in immediate precipitation of yellow substance but neutralization with 5% potassium carbonate gives the recovered starting material.

These experimental results have revealed the following points:

1) Heating of 2-(phenylamino)lepidine in nitric acid results in the introduction of a nitro group into *para*-position of its anilino portion.

2) Reaction of 2-(phenylamino)lepidine with acetyl nitrate results in the formation of *o*-nitro or *o,p*-dinitro derivatives of the anilino group, and the quinoline ring is not nitrated. Dichloromethane is suitable as a reaction solvent in using acetyl nitrate and also gives good effect on higher yield of the product.

Experimental

2-(Arylamino)lepidines (I to IV)——A mixture of 0.045 mole of 2-(arylamino)lepidine, 0.016 mole aniline (*o*-NO_2, *m*-NO_2, *p*-NO_2, 2,4-$(NO_2)_2$), and 0.5 ml of pyridine was refluxed in an oil bath at 200° for 5 hr. When cooled, the crystalline mass was washed with 3% HCl and water, neutralized with 5% K_2CO_3, and crystals were collected. After drying, the crystalline product was fractionated with benzene and the benzene-insoluble portion was recrystallized from acetone–benzene (*cf.* Table I). IR ν_{max}^{KBr} cm^{-1}: I 3320 (N-H), II 3365 (N-H), III 3350 (N-H), IV 3100 and 3280 (N-H).

2-(*p*-Nitroanilino)-6-nitrolepidine (V) and 2-(*p*-Nitroanilino)-8-nitrolepidine VI)——A mixture of 0.0045 mole of 2-chloro-6-or 2-chloro-8-nitrolepidine, 0.0058 mole of *p*-nitroaniline, and 0.5 ml of pyridine was refluxed on an oil bath at 200° for 3 hr and treated as in the foregoing (*cf.* Table I). IR ν_{max}^{KBr} cm^{-1}: V 3350 (N-H), VI 3330 (N-H).

Reaction of VII and HNO_3 in AcOH Solution——To a solution of 1 g of VII dissolved in 15 ml of AcOH, 0.2 ml of HNO_3 was added dropwise. Yellow crystals that precipitated out after 15 min were collected by filtration, washed with three 20 ml portions of water, and dried in air. Yield of VIII, mp 154° (decomp.),

was quantitative. *Anal.* Calcd. for $C_{16}H_{15}O_3N_3$: C, 64.63; H, 5.09; N, 14.14. Found: C, 64.59; H, 5.06; N, 13.99.

Titration of 2-Anilinolepidine (VII) in Nonaqueous Solution——After drying over silica gel in a desiccator for 1 hr, 25.5 mg of VII (purity, 98.5%) was dissolved in 2 ml of glacial AcOH for nonaqueous titration and titrated with 0.1N $HClO_4$ (*f* 0.998), using methyl rosanilin chloride as an indicator. Theoretical value: 0.1N $HClO_4$ 1 ml=23.4 mg $C_{16}H_{14}N_2$. Found: 0.1N $HClO_4$ 1.07 ml=25.5 mg $C_{16}H_{14}N_2$.

Reaction of VII and HNO_3——i) A solution of 1 g of VII dissolved in 50 ml of HNO_3 at room temperature was allowed to stand for *ca.* 1 hr and the reddish brown reaction mixture was poured into 500 ml of ice water. The yellowish brown crystalline pricipitate was collected by filtration, dried, and recrystallized from benzene. I was obtained from the solution and IX from the residue.

ii) A solution of 1 g of VII dissolved in 20 ml of HNO_3 with stirring under ice chilling was maintained for *ca.* 10 min, heated to 60°, and stirred for 3 hr at that temperature. The pale yellow reaction mixture was poured into 200 ml of ice water, the yellow crystals were neutralized with 10% NaOH, and collected by filtration. The crystals were washed with water dried, and recrystallized from acetone–benzene. A small amout of III was further obtained from the solution (*cf.* Table I).

Preparation of Acetyl Nitrate[7a]——To 300 g of Ac_2O chilled to below −10°, 160 g of N_2O_5[11] was added dropwise during about 2 hr, the mixture was maintained at this temperature for 2 hr, and allowed to stand at room temperature(15—20°) overnight. About 100 ml of pale brownish liquid of bp 34—36° (45—50 mmHg) was obtained from the reaction mixture. This liquid became colorless and clear at below 15°. This substance turned wet KI-starch paper blue.

Reaction of VII and $AcONO_2$ in Ac_2O——A solution of 500 mg of VII dissolved in 15 ml of Ac_2O was maintained at room temperature under reaction conditions listed in Table III. The reaction mixture was poured into ice water, neutralized with 10% K_2CO_3, and a yellow oily substance was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. K_2CO_3, the solvent was evaporated, and the residue was recrystallized from benzene. I was obtained from the solution and IV from the benzene–insoluble portion, recrystallized from acetone–benzene (*cf.* Tables I and III).

Reaction of VII and $AcONO_2$ in CH_2Cl_2 and $CHCl_3$——A solution of 500 mg of VII in CH_2Cl_2 or $CHCl_3$ was maintained under reaction conditions listed in Table IV, poured into ice water, and the organic solvent layer was washed three times with cold water, 5% K_2CO_3, and water. Evaporation of the solvent left yellowish brown to reddish brown substance which was dried and recrystallized from benzene. I was obtained by concentration of the solution, and the insoluble portion was recrystallized from acetone–benzene. III or IV was obtained from the solution (*cf.* Tables I and IV).

When the reaction was carried out for 15 or 20 hr (*cf.* Table IV), the reaction was stopped when yellow needle crystals had precipitated out thoroughly, the crystals were collected by filtration, and washed with cold water until the washing was no longer acidic. The crystals were dried and recystallized from acetone-benzene to afford IV (*cf.* Tables I and IV).

Reaction of VII and $AcONO_2$ in Benzene——A solution of 500 mg of VII in benzene was maintained under the reaction conditons listed in Table IV, with initial temperature of 20° which rose to a maximum of 45° by the heat of reaction and again fell to 20° with precipitation of yellowish brown crystals. The reaction mixture became yellowish brown crystalline mass in about 30 min from the start of the reaction. This crystalline mass was collected by filtration and recrystallized from benzene to afford I and III (*cf.* Tables I and IV).

Reaction of VII and $AcONO_2$ in CCl_4——VII did not dissolve in $AcONO_2$ under the reaction conditions listed in Table IV but precipitated pale yellow crystals. The crystals were collected by filtration, washed with water, and neutralized with 10% K_2CO_3. Recrystallization from benzene afforded the recovered starting material (100%).

Reaction of VII and $AcONO_2$——A solution of 500 mg of VII dissolved in 4 ml of $AcONO_2$ with ice chilling was maintained at below 0° for 15 min and then allowed to stand at room temperature by which the insoluble matter dissolved to give a yellowish brown solution. This solution was maintained under reaction conditions listed in Table IV, poured into ice water, and the solid was collected by filtration. The solid was washed with cold water, dried in air, and heated in 10% K_2CO_3 solution on a boiling water bath for 15 min. The yellowish brown crystals so obtained were recrystallized from benzene as above and 0.55 g of I and 0.2 g of IV (from acetone–benzene) were obtained (*cf.* Tables I and IV).

Acknowledgement The authors are indebted to the members of the Analysis Center of this University for elemental analyses.