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Nitroimidazoles II. Synthesis and Reactions of Iodonitroimidazoles (1)

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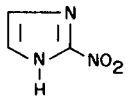
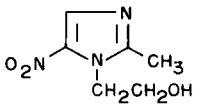
The synthesis and some chemical reactions of various iodonitroimidazoles and methods of distinguishing between the 4- and 5- nitro derivatives by UV and *p*K measurements are described.

The interesting antiprotozoal activities of the antibiotic Azamycin (I) (1,2) and the synthetic drug Flagyl® (II) (3) prompted an extension of our own work on imidazoles to include other nitroimidazoles.

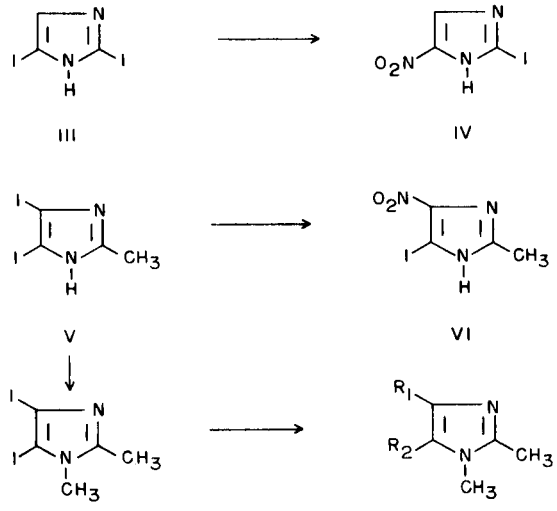


I



II

This report summarizes the synthesis and some chemical transformations of various iodonitroimidazoles. Nitration of 2,4-(or 5-)diiodoimidazole (III) (4), 2-methyl-4,5-diiodoimidazole (V) (5) and 1,2-dimethyl-4,5-diiodoimidazole (VII), obtained by methylating V, yielded 2-iodo-4-(or 5-)nitroimidazole (IV), 2-methyl-4-(or 5-) iodo-5-(or 4-)nitroimidazole (VI) and a 7:3 mixture of 1,2-dimethyl-4-nitro-5-iodoimidazole (VIII) and 1,2-dimethyl-4-iodo-5-nitroimidazole (IX) respectively.



III IV

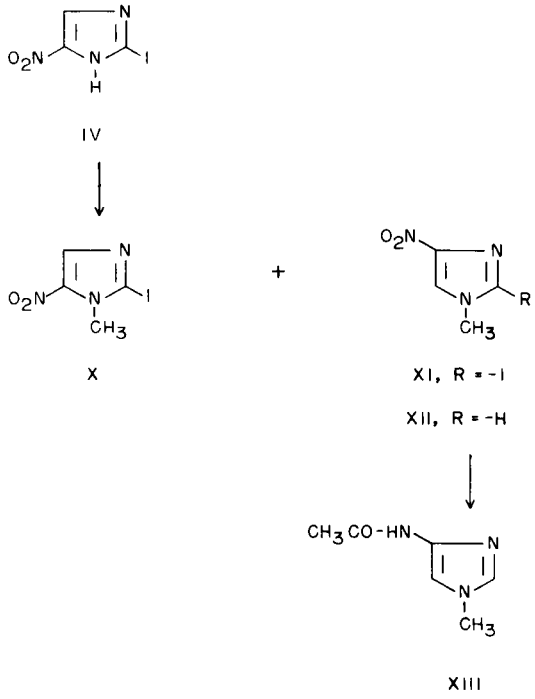
V VI

VII

VIII, R_1 = -NO_2, R_2 = -I

IX, R_1 = -I, R_2 = -NO_2

In these reactions one iodine atom is replaced by the nitro group. This is in contrast to the findings of earlier investigators who reported that the nitration of chloro- and bromoimidazoles having a hydrogen atom at either the 4 or 5 position yielded the corresponding 4 or 5-nitro-substituted analogs (6). 4,5-Dibromimidazole, which lacks a hydrogen atom at the 4 or 5 position, could not be nitrated (7).



IV

X + XI, R = -I

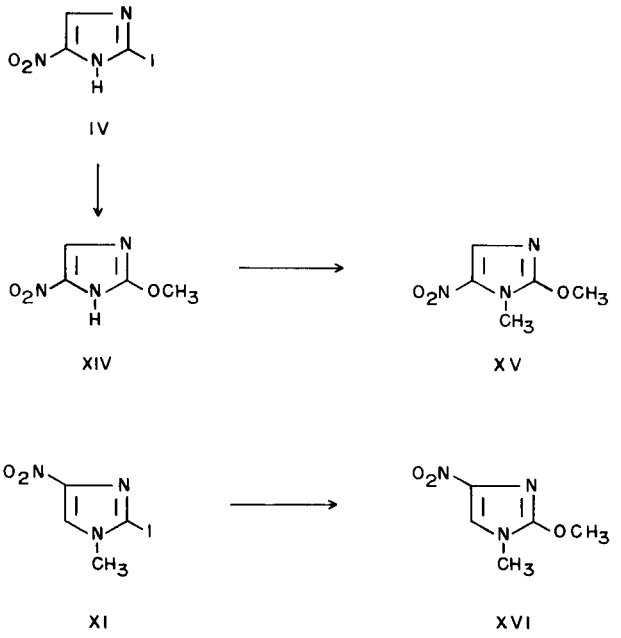
XII, R = -H

XIII

Methylation of the readily accessible 2-iodo-4 (or 5-)nitroimidazole (IV) yielded a mixture of the two *N*-methylated imidazoles X and XI which could be separated by differential solubility in acetone or due to their different basicities. The ratio of X to XI is largely dependent on the reaction conditions. The 4-nitro derivative (XI) is the main product of the reaction of IV with dimethylsulfate in the presence of alkali, whereas the 5-nitro derivative (X) is practically the sole product when the reaction is carried out in the absence of alkali.

Catalytic hydrogenation of the 4-nitroiodoimidazole derivative (XI) in the presence of acetic anhydride yielded the known 1-methyl-4-acetamidoimidazole (XIII) (8) and provided conclusive verification of structure XI. The same product (XIII) resulted when 1-methyl-4-nitroimidazole (XII) was hydrogenated under similar conditions. The isomeric 5-nitro derivative (X), on hydrogenation, yielded no reduction products which could be characterized.

The iodo group in IV is readily replaced with an alkoxy group. Thus reaction of IV with sodium methylate gives 2-methoxy-4 (or 5-)nitroimidazole (XIV). Methylation of XIV yields, in contrast to the results obtained with the corresponding iodo derivative (IV), almost exclusively 1-methyl-2-methoxy-5-nitroimidazole (XV). The isomeric 1-methyl-2-methoxy-4-nitroimidazole (XVI) is obtained from 1-methyl-2-iodo-4-nitroimidazole (XI) by reaction with sodium methylate.



The various 4- and 5-nitroimidazoles substituted with iodo and alkoxy groups discussed above are representatives of a large number of compounds prepared. The prototypes mentioned here were chosen for physico-chemical studies, in particular UV spectroscopy and *p*K measurements, which were found to be powerful tools for distinguishing between 4- and 5-nitroimidazole derivatives.

UV and *p*K-measurements with 4- and 5-nitroimidazoles:

Nitroimidazoles generally have two UV-absorption bands between 220 and 400 mμ, one with weak intensity in the 220-260 mμ region (ϵ = 3-5000) and a stronger, main band in the 300-360 mμ area (ϵ = 6-12000). However, the exact position of the maximum and the shape of the curve is characteristically altered by the position and the nature of the substituents and the *p*H of the solution. As demonstrated in Fig. 1, there is a distinct difference between the UV-absorption curves of 1-alkyl-4-nitro and 1-alkyl-5-nitroimidazole derivatives. Because the linear conjugated systems X and XV are energetically favored over the corresponding branched conjugated systems XI and XVI, the position of the main absorption maximum (in the 300-360 mμ region) of 1-alkyl-5-nitro derivatives is shifted approximately 5-20 mμ for 2-iodo derivatives and 20 mμ for 2-alkoxy derivatives) towards the longer wavelength. An even more characteristic difference appears in the 220-260 mμ region. In this area all the 5-nitro derivatives investigated by us have a distinct maximum, whereas the 4-nitro derivatives exhibit only a more or less pronounced inflection. These spectral features clearly permit the assignment of the position of the nitro group in the 1-alkyl-substituted nitroimidazoles.

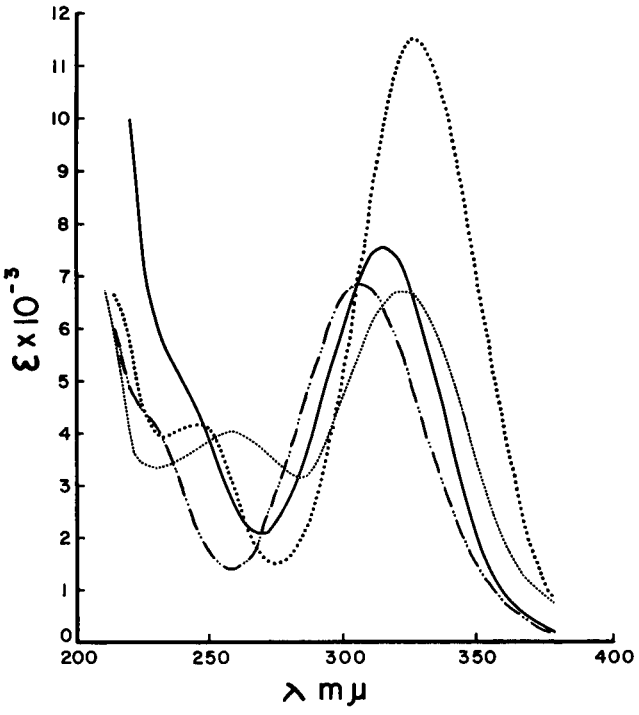


Fig. 1. UV spectra of 2-iodo-1-methyl-4-nitroimidazole XI (——), 2-iodo-1-methyl-5-nitroimidazole X (- - - -), 2-methoxy-1-methyl-4-nitroimidazole XVI (—· ·—· ·—) and 2-methoxy-1-methyl-5-nitroimidazole XV (· · · ·) in water at *p*H 6.95.

TABLE I

UV-Absorption Data and Apparent Dissociation Constants

Compound	Solvent and *p*H of the solution	Form (a)	λ max in mμ (i) = inflection	$\epsilon \cdot 10^{-3}$	pK_{a_1} (b)	pK_{a_2} (b)
IV	Methanol		235 (i); 314	4.62; 7.85	-0.85	6.82
	Buffer, *p*H 3.1	N	240 (i); 325	4.60; 6.78		
	6*M* H_2SO_4	CA	307	6.40		
	0.1*N* KOH	CB	273; 363	3.38; 9.40		
XI	Methanol		240 (i); 315	5.00; 7.60	-1.70	
	Buffer, *p*H 6.95	N	243 (i); 327	4.50; 7.82		
	6*M* H_2SO_4	CA	308	6.23		
X	Methanol		258; 323	4.08; 6.87	-0.14	
	Buffer, *p*H 6.95	N	262; 331	3.92; 6.80		
	6*M* H_2SO_4	CA	307	5.60		
XIV	Methanol		233; 330	3.78; 11.71	-0.90	6.06
	Buffer, *p*H 3.02	N	237; 330	3.68; 13.20		
	6*M* H_2SO_4	CA	225 (i); 307	3.50; 7.88		
	0.1*N* KOH	CB	237; 285; 366	3.94; 3.35; 14.16		
XVI	Methanol		235 (i); 307	3.60; 6.80	-0.44	
	Buffer, *p*H 7.10	N	240 (i); 320	3.30; 7.42		
	6*M* H_2SO_4	CA	230 (i); 294	3.30; 6.95		
XV	Methanol		247; 327	4.10; 11.50	-1.03	
	Buffer, *p*H 6.90	N	248; 339	4.25; 12.30		
	6*M* H_2SO_4	CA	225 (i); 305	3.65; 9.20		

(a) N = the neutral molecule, CA = conjugate acid and CB = conjugate base. (b) Average standard deviation = 0.06.

The main absorption band is strongly affected by the *p*H of the medium (Table I). This change permits the calculation of the apparent dissociation constants from the equation (9):

$$pK_{BH^+} = pH + \log \frac{\epsilon_B - \epsilon}{\epsilon - \epsilon_{BH^+}}$$

where ϵ_B, ϵ, ϵ_{BH^+} are the extinction coefficients, respectively, of the neutral molecule, mixture of the neutral molecule plus conjugate acid and the conjugate acid--all at the same wave length.

For the protonation of imidazoles a number of solutions of sulfuric acid were prepared in water and the corresponding Hammett acidity values H_0 were obtained from published tables (10). In the equation H_0 was substituted for *p*H, a procedure which has been used by others (11,12).

In the strong acid solutions the isosbestic points were not well defined because of the so-called "medium effect". On the assumption that the medium effect involves mainly lateral spectral shifts, the curves were shifted until they intersected at the common isosbestic point (10).

The data in Table I clearly demonstrate that 2-iodo-1-methyl-5-nitroimidazole (X) is a stronger base than the 4-nitro isomer (XI) by about 1.5 *p*K units. This differential also holds for the corresponding pair of uniodinated isomers (13). The reason for this difference is the fact that the protonation of the imidazole ring takes place predominately at the imino nitrogen (13,14). In the case of 2-iodo-1-methyl-5-nitroimidazole (X), the proton accepting hetero atom is further away from the inductive influence of the strong electron withdrawing nitro group. This presumably outweighs any differential stability of the linear conjugated system (5-nitro derivatives) over the branched conjugated system (4-nitro derivatives). This difference in the dissociation constants is, therefore, an additional factor to be considered in assigning the position of the nitro substituent.

The basicities of the 2-methoxy-4-(or 5-)nitroimidazoles are in the same order as those of the 2-iodo-4-(or 5-)nitroimidazoles. But in contrast

with the 2-iodo series, 1-methyl-2-methoxy-4-nitroimidazole was found to be a stronger base than the 5-nitro derivative ($\Delta pK = 0.6$). Because of the relatively small differences between the basicities of the isomeric 2-alkoxy-4-(and 5-)nitroimidazoles, the pK's are of little value in differentiating between the isomers. For these compounds, the assignment can easily be made on the basis of the pronounced differences in the UV spectra.

EXPERIMENTAL (15)

2-Iodo-4-(or 5-)nitroimidazole (IV).

2,4-Diiodoimidazole (III) (4), 125 g. (0.38 mole), was added in portions to a stirred nitration mixture prepared from 300 ml. of nitric acid, d = 1.5, and 300 ml. of concentrated sulfuric acid chilled to -15 to -20°. After the addition was complete, the mixture was allowed to warm to 20-25°, which temperature was maintained for 2 to 4 hours. The clear solution was poured with stirring into 1.5 volumes of ice water, and the precipitate was filtered. It was washed repeatedly with 10% sodium iodide solution in order to remove free iodine. Recrystallized from DMF or from 50% aqueous ethanol, the product weighed 80 g. (85%), m.p. 281°.

Anal. Calcd. for $C_3H_2IN_3O_2$: C, 15.07; H, 0.85; I, 53.11. Found: C, 15.25; H, 0.82; I, 53.30.

1,2-Dimethyl-4,5-diiodoimidazole (VII).

2-Methyl-4,5-diiodoimidazole (V) (5), 58 g. (0.174 mole), was dissolved in 180 ml. of 1.5*N* sodium hydroxide solution and 25 ml. of dimethylsulfate was dropped into the stirred solution at 40-50°. After chilling, the product (white prisms) was filtered and recrystallized from ethyl acetate. The yield was 54.5 g. (90%), m.p. 142°.

Anal. Calcd. for $C_5H_6I_2N_2$: C, 17.26; H, 1.74; I, 72.96. Found: C, 17.36; H, 1.75; I, 73.05.

4-(or 5-)Iodo-2-methyl-5-(or 4-)nitroimidazole (VI).

2-Methyl-4,5-diiodoimidazole (V), 70 g. (0.21 mole), was added in portions to a stirred nitration mixture prepared from 140 ml. of nitric acid, d = 1.5 and 140 ml. of concentrated sulfuric acid at -10°. After stirring at 20-25° for 2-4 hours, the reaction mixture was worked up as described for (IV). Recrystallized from DMF, the yield was 42.5 g. (83%), m.p. 271-273°.

Anal. Calcd. for $C_4H_4IN_3O_2$: C, 18.98; H, 1.59; I, 50.16. Found: C, 19.24; H, 1.53; I, 50.65.

Nitration of 1,2-Dimethyl-4,5-diiodoimidazole (VII).

1,2-Dimethyl-4,5-diiodoimidazole, 75 g. (0.216 mole), was nitrated with a mixture of 150 ml. of nitric acid, d = 1.5, and 150 ml. of concentrated sulfuric acid, first at -10° for 10 minutes and then at 0-25° for 3 hours. The mixture was stirred into 500 g. of crushed ice. The yellow nitration product contaminated with iodine was filtered. The iodine was removed by steam distillation, and the resulting product, 40 g. of a mixture of 1,2-dimethyl-5-iodo-4-nitroimidazole (VIII) and 1,2-dimethyl-4-iodo-5-nitroimidazole (IX) was separated by the following procedure.

a. 1,2-Dimethyl-5-iodo-4-nitroimidazole (VIII).

The nitration product, 40 g., was slurried with 400 ml. of 3*N* hydrochloric acid at 25-30° for 30 minutes. The undissolved material was filtered and recrystallized from acetone, yield 25 g., m.p. 204-205°.

Anal. Calcd. for $C_5H_6IN_3O_2$: C, 22.47; H, 2.26; I, 47.54. Found: C, 22.73; H, 2.30; I, 47.83.

b. 1,2-Dimethyl-4-iodo-5-nitroimidazole (IX).

The acidic filtrate from above was filtered through a column of charcoal (10 g. Norit A), the filtrate was neutralized with ammonium hydroxide and the precipitated product was recrystallized from alcohol to yield 12 g. of long, well-shaped yellow prisms, m.p. 150-151°.

Anal. Calcd. for $C_5H_6IN_3O_2$: C, 22.47; H, 2.26; I, 47.54. Found: C, 22.80; H, 2.39; I, 47.79.

2-Iodo-1-methyl-4-nitroimidazole (XI).

To a stirred solution of 75 g. of (IV) in 1*N* sodium hydroxide solution was added 33 ml. of dimethylsulfate through a dropping funnel. The temperature was maintained at 60-75°. After cooling, the product was filtered, dried and slurried with 200 ml. of acetone in order to dissolve the isomeric 5-nitro derivative. The product (XI) was filtered by suction and washed on the filter with 50 ml. acetone. Recrystallized from DMF or 50% aqueous alcohol, it formed pale yellow prisms which weighed 55 g. (69%), m.p. 240°.

Anal. Calcd. for $C_4H_4IN_3O_2$: C, 18.98; H, 1.59; I, 50.17. Found: C, 19.28; H, 1.63; I, 50.23.

2-Iodo-1-methyl-5-nitroimidazole (X).

Method A. The acetone filtrate above from the isomeric 4-nitro derivative was evaporated *in vacuo* and the residue was recrystallized from 50% aqueous alcohol. The product, m.p. 147-150°, was contaminated with the isomeric 4-nitro derivative. Method B. A stirred mixture of 23.9 g. (0.1 mole) of IV, 40 ml. of dioxan, and 11 ml. of dimethylsulfate was refluxed for 1 hour. After cooling, 100 ml. of acetone was added and the resulting slurry of the methosulfate of the product was filtered. It was dissolved in 100 ml. of water and the solution was neutralized with ammonium hydroxide with chilling. The precipitate was filtered and recrystallized from 50% aqueous alcohol. The melting point was 152° (m.m.p. with the material prepared by method A, 150°), and the yield was 12 g. (47%).

Anal. Calcd. for $C_4H_4IN_3O_2$: C, 18.98; H, 1.59; I, 50.17. Found: C, 19.25; H, 1.55; I, 50.19.

1-Methyl-4-acetaminoimidazole (XIII) (8).

Compound (XI) or (XII), 5 g., in 180 ml. of acetic acid and 10 ml. of acetic anhydride was hydrogenated at 50-100° (initial pressure, 500 psi) in the presence of 2 g. of anhydrous sodium acetate and 2 g. of 10% palladium-charcoal catalyst. After evaporation of the solvent, extraction with chloroform and crystallization from alcohol 1-methyl-4-acetaminoimidazole (8), m.p. 248-249°, was obtained. The picrate melts at 217°.

Anal. Calcd. for $C_6H_9N_3O$: C, 51.79; H, 6.52; N, 30.19. Found: C, 51.68; H, 6.54; N, 30.01.

2-Methoxy-4(or 5-)nitroimidazole (XIV).

2-Iodo-4(or 5-)nitroimidazole, 47.8 g. (0.2 mole), was added to a solution of 10 g. (0.435 mole) of sodium in 200 ml. of methanol. Toluene (600 ml.) was added, the mixture refluxed with stirring for 2 hours and then 400 ml. of methanol and toluene were distilled. The sodium salt of the product deposited as a gelatinous mass which gradually turned crystalline. It was filtered, dissolved in 100 ml. of hot water and the solution was acidified with 10 ml. of acetic acid and chilled. The crystalline product was filtered, washed with water, and recrystallized from methanol to give 18 g. (63%), m.p. 219° dec.

Anal. Calcd. for $C_4H_5N_3O_3$: C, 33.57; H, 3.52; N, 29.37; OCH_3, 21.69. Found: C, 33.88; H, 3.71; N, 29.02; OCH_3, 21.32.

2-Methoxy-1-methyl-5-nitroimidazole (XV).

Compound (XIV), 14.3 g. (0.1 mole), was dissolved in 50 ml. of 3*N* sodium carbonate solution at 60-70°, 11 ml. of dimethylsulfate was added and the mixture was stirred for 20-30 minutes. After chilling, the resulting crystals were filtered and recrystallized from ethyl acetate to give 9 g. (58%) of product, m.p. 138°.

Anal. Calcd. for $C_5H_7N_3O_3$: C, 38.22; H, 4.49; N, 26.75. Found: C, 38.46; H, 4.50; N, 27.02.

2-Methoxy-1-methyl-4-nitroimidazole (XVI).

Compound (XI), 25.3 g. (0.1 mole), was refluxed vigorously with an excess of strong methanolic sodium methylate solution (prepared from 5 g. of sodium in 50 ml. of methanol) for approximately 7 minutes. The decolorized solution was immediately poured into 200 ml. of ice-cold saturated ammonium sulfate solution, and the product was extracted with 200 ml. of ethyl acetate. The solvent was evaporated *in vacuo* and the crystalline residue was recrystallized from water or methanol to yield 7 g. (44-51%) of product, m.p. 144-144.5°.

Anal. Calcd. for $C_5H_7N_3O_3$: C, 38.22; H, 4.49; N, 26.75. Found: C, 38.13; H, 4.12; N, 26.66.

Acknowledgment.

The authors thank Dr. A. Steyermark for the microanalyses and Mr. G. Reymond for valuable technical assistance.

REFERENCES

(1) A. G. Beaman, W. Tautz, T. Gabriel and R. Duschinsky, *J. Am. Chem. Soc.*, 87, 389 (1965).

(2) G. G. Lancini and E. Lazzari, *Experientia*, 21, 83 (1965).

(3) C. Cosar, C. Crisan, R. Horclois, R. M. Jacob, J. Robert, S. Tschelitcheff and R. Vanprè, *Arzneimittel-Forsch.*, 16, 23 (1966).

(4) H. Pauly and K. Gunderman, *Ber.*, 41, 3999, 4011 (1908);

H. Pauly and E. Arauner, *J. Prakt. Chem.*, [2] **118**, 33 (1928).
(5) H. Pauly, *Ber.*, **43**, 2253 (1910).
(6) I. E. Balaban and F. L. Pyman, *J. Chem. Soc.*, **121**, 947 (1922); **125**, 1564 (1924); L. Light and F. L. Pyman, *ibid.*, **121**, 2626 (1922); F. L. Pyman and G. M. Timmis, *ibid.*, **123**, 494 (1923); J. Sarasin and E. Wagmann, *Helv. Chim. Acta*, **7**, 720 (1924); P. M. Kochergin, USSR Patent, 143401, *Chem. Abstr.*, **57**, 9859 (1962).
(7) I. E. Balaban and F. L. Pyman, *J. Chem. Soc.*, **121**, 949 (1922).
(8) F. Johnson and W. A. Nasutavicus, *J. Org. Chem.*, **29**, 153 (1964).
(9) R. J. L. Andon, J. D. Cox, and E. F. G. Herington, *Trans. Faraday Soc.*, **50**, 918 (1954).
(10) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).
(11) K. N. Bascombe and P. R. Bell, *J. Chem. Soc.*, 1096 (1959).
(12) G. G. Gallo, L. R. Pasqualucci, P. Radaelli and G. G. Lancini, *J. Org. Chem.*, **29**, 862 (1964); A. Grimison, J. H. Ridd and B. K. Smith, *J. Chem. Soc.*, 1952 (1960); M. Charton, *J. Org. Chem.*, **30**, 3346 (1965).
(13) A. Grimison, J. H. Ridd and B. V. Smith, *J. Chem. Soc.*, 1352 (1960).
(14) A. Mannschreck, W. Seitz and H. A. Staab, Berichte Bunsengesellschaft, **67**, 473 (1963).
(15) All melting points were taken with a Hoover-Thomas melting point apparatus and are not corrected. The UV-spectrophotometric measurements were carried out at room temperature on Cary spectrophotometers, Models 14M and 15 and the *p*H measurements on a Beckman Research *p*H-meter, Model 1019 using conventional electrodes. For the potentiometric titrations, a Sargent Automatic Constant Rate Burette, Model G, combined with a Sargent recorder and a Beckman Research *p*H meter were used. The buffer solutions were adjusted to the ionic strength of 0.01 between *p*H 2 and 10; therefore, no ionic-strength corrections were made.

Received October 10, 1966 Nutley, New Jersey 07110