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Triazolo[4,5-*d*]pyrimidines. II.[1] On 3-Methyl- and 3-Phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines

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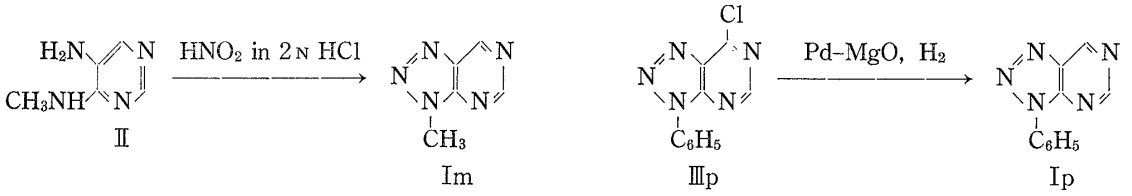
Various reactions of 3-methyl- (Im) and 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (Ip) were examined. Im was prepared by cyclization of 5-amino-4-methylaminopyrimidine (II) with nitrous acid, and Ip was prepared by the catalytic reduction of 7-chloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (IIIp) using palladium on magnesium oxide carrier as a catalyst.

In warm alkaline solution Im underwent ring fission to give 5-amino-1-methyl-1*H*-1,2,3-triazole-4-carboxaldehyde (IVm). In dilute sulfuric acid both Im and Ip underwent ring fission to yield IVm and 5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carboxaldehyde (IVp), respectively, in good yields. However, the reaction of Im with the methoxide ion resulted in the formation of 7,7′-bis[3-methyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine] (Vm) and 3-methyl-7-(5-amino-1-methyl-1*H*-1,2,3-triazol-4-yl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (VIm), although the yields were poor. Both Im and Ip dimerized in the presence of the cyanide ion to give Vm and 7,7′-bis[3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine] (Vp), respectively, in good yields. N,N-Dimethylaniline (IX) reacted with Im in dulute sulfuric acid to give 5-amino-4-[bis[4-N,N-dimethylaminophenyl]methyl]-1-methyl-1*H*-1,2,3-triazole (VIIIm) in poor yield. VIIIm was also obtained by condensation of IX and IVm in dilute sulfuric acid.

Keywords——3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines; preparation; ring fission; dimerization; mechanism

In a series of studies on the chemical properties of the 3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine ring, the present authors reported the reactions of nucleophiles with 7-chloro-3-methyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine[1] and investigated the introduction of a carbon chain into the 7-position. In the present work, the chemical properties of 3-methyl- (Im)[3] and 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (Ip) were examined.

The compound Im,[3] used as a substrate, was obtained by cyclization of 5-amino-4-methylaminopyrimidine (II) with nitrous acid. The preparation of Ip was achieved by the following method. The 7-chloro derivative of Ip (IIIp)[4] was subjected to catalytic reduction in a neutral medium at room temperature, using palladium on a magnesium oxide carrier as a catalyst, affording Ip in moderate yield. The structure of Ip thus formed was suggested by its exact mass measurement (EMM), and confirmed by its nuclear magnetic resonance (NMR)



II Im IIIp Ip

Chart 1

1) Part I: T. Higashino, T. Katori, and E. Hayashi, *Yakugaku Zasshi*, **99**, 1031 (1979).
2) Location: *a) 2-2-1 Oshika, Shizuoka-shi*; *b) 1143 Nanpeidai, Narita-shi.*
3) A. Albert, *J. Chem. Soc.* (*B*), **1966**, 427.
4) D.J. Brown and M.N. Paddon-Row, *J. Chem. Soc.* (*C*), **1967**, 1856.

spectrum, which showed singlet peaks due to the hydrogens of the 5- and 7-positions at 9.31 and 9.68 ppm, respectively.

Behavior in Acid or Alkaline Solutions

When a solution of Im in 5% sodium hydroxide was allowed to stand for 3 hr at 65°, ring fission occurred to form 5-amino-1-methyl-1*H*-1,2,3-triazole-4-carboxaldehyde (IVm).[5] This occurred even in 20% sulfuric acid at room temperature, resulting in the formation of IVm in good yield. A similar reaction was found to take place in a solution of Ip dissolved in 20% sulfuric acid at 70°, affording 5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carboxaldehyde (IVp).

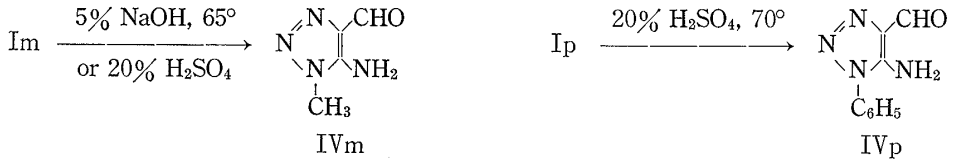


Chart 2

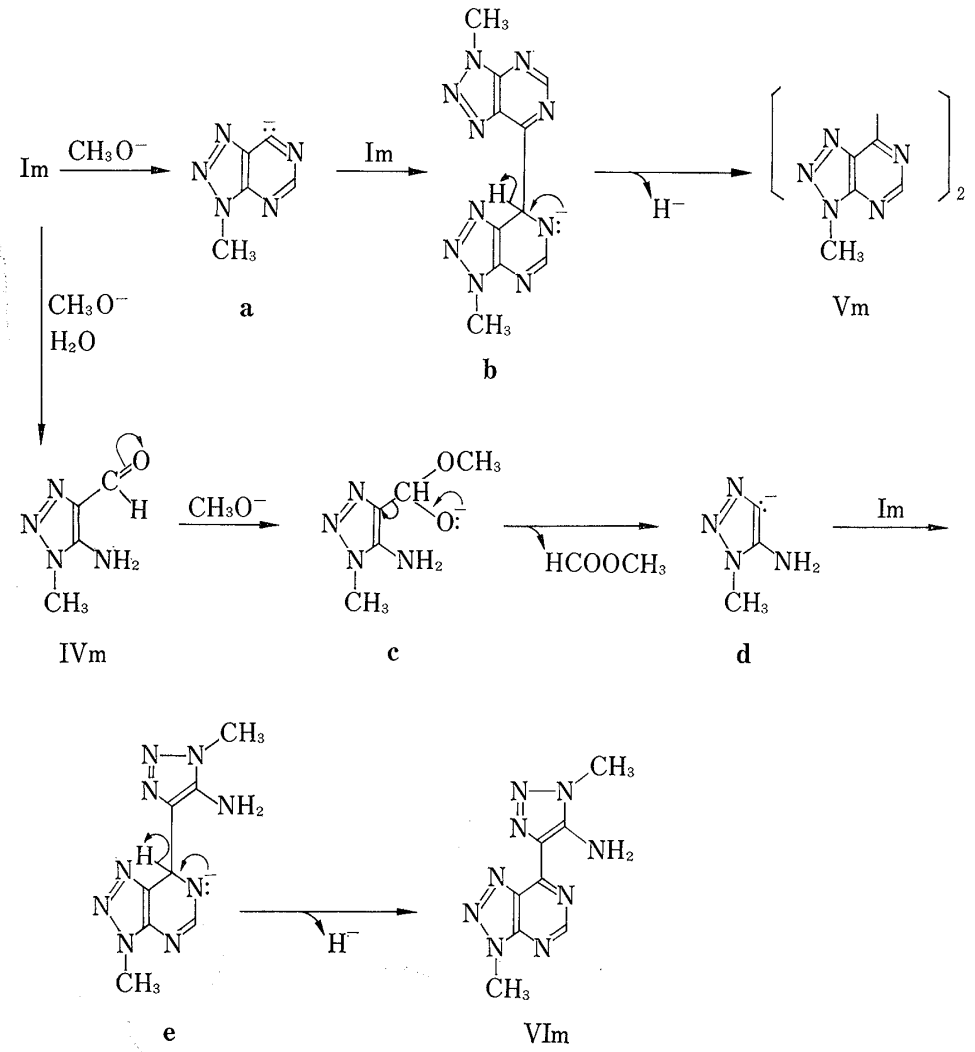


Chart 3

5) A. Albert and H. Taguchi, *J. Chem. Soc. Perkin I*, **1973**, 1629.

Compound IVm was identified by the mixed melting point test using an authentic specimen prepared by another route.[5] The structure of IVp was suggested by its EMM, and confirmed by its infrared absorption (IR) and NMR spectra, as described later.

Reaction with the Methoxide Ion

When a methanolic solution of Im and sodium methoxide was allowed to stand for 2 weeks at room temperature, 7,7′-bis[3-methyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine] (Vm) and 3-methyl-7-(5-amino-1-methyl-1*H*-1,2,3-triazol-4-yl)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (VIm) were obtained, although the yields were very poor. The structure of Vm and VIm were established on the basis of their EMM, and IR and NMR spectra as described later.

The dimerization mechanism may be written as in Chart 3. Thus, the methoxide ion removes the hydrogen of the 7-position of Im to form the carbanion (**a**). The nucleophilic addition of **a** to Im provides an intermediate N-anion (**b**) which undergoes gentle oxidation to form Vm. A possible mechanism for the formation of VIm is illustrated in Chart 3. The first step is the formation of the ring fission product (IVm) which leads to the intermediate (**c**) by the attack of a methoxide ion on the carbonyl carbon of IVm. The removal of methyl formate from **c**, by a type of Hammick reaction,[6] yields an intermediate (**d**) which adds across the N_6–C_7 bond of Im, followed by oxidation to give VIm.

Dimerization in the Presence of the Cyanide Ion

Both Im and Ip dimerized in the presence of potassium cyanide to give Vm and 7,7'-bis-[3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine] (Vp), respectively, in good yields. The structure of Vp was suggested by its EMM, and confirmed by its NMR spectrum as described later.

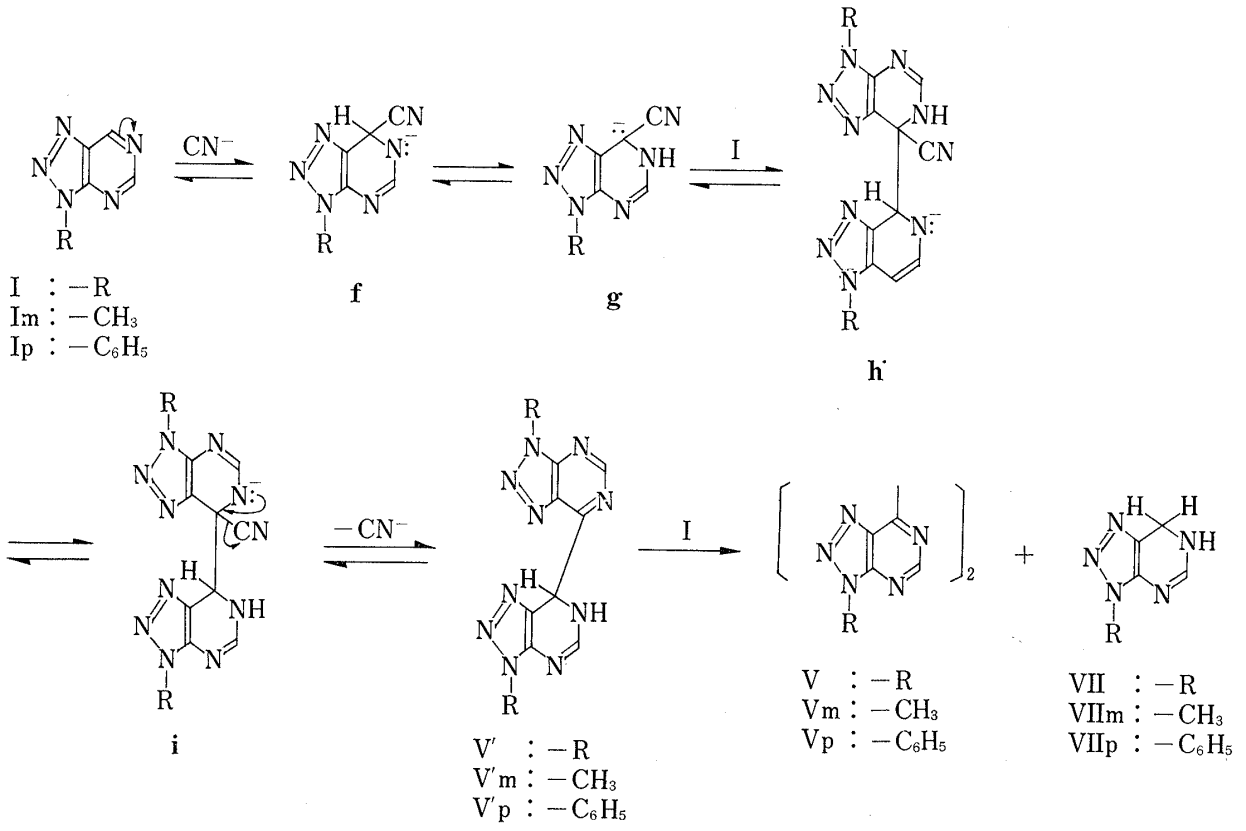


Chart 4

6) P. Dyson and D.L. Hammick, *J. Chem. Soc.*, **1937**, 1724.

Since the dimerization depends on the presence of the cyanide ion, the reaction may be a type of benzoin condensation, followed by oxidation to the fully aromatic system. In Chart 4 the intermediate (V'), corresponding to the benzoin, undergoes oxidation to give the dimerized V. In this oxidation, I probably acts as a hydride ion acceptor and is reduced to the 3-substituted 6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (VII). However, V' and VII could not be isolated.

It is well known that similar reactions occur in the case of quinazoline,[7] 4-isoquinolinecarbonitrile,[8] 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine,[9] 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine,[9] quinoxaline,[9] and pyrido[2,3-*b*]pyrazine.[9]

Reaction with N,N-Dimethylaniline (IX) in Dulute Sulfuric Acid

It has been reported that IX adds across the N_3–C_4 bond of quinazoline in dilute sulfuric acid to form 3,4-dihydro-4-(4-N,N-dimethylaminophenyl)quinazoline.[10] We found that Im reacted differently with IX in dilute sulfuric acid to give a violet dye (VIIIm), although the yield was very poor. Elemental analysis, as well as IR and NMR spectra of VIIIm (described later) suggested that it was 5-amino-4-[bis[4-N,N-dimethylaminophenyl]methyl]-1-methyl-1*H*-1,2,3-triazole.

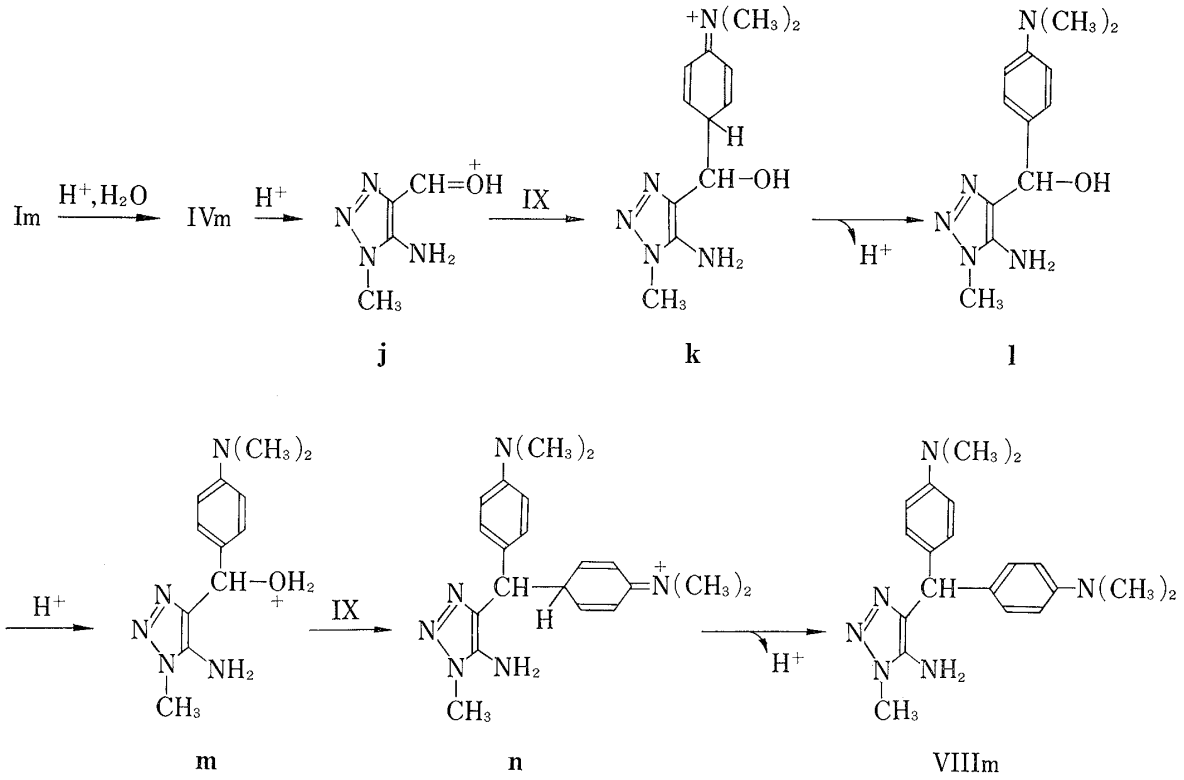


Chart 5

Since VIIIm was also obtained by condensation between IVm and IX in dilute sulfuric acid, the reaction is probably a ring fission followed by condensation between IX and the resulting IVm to give the dye (VIIIm), as shown in Chart 5.

7) W.L.F. Armarego and R.E. Willette, *J. Chem. Soc.*, **1965**, 1258.
8) E. Hayashi, H. Makino, and T. Higashino, *Yakugaku Zasshi*, **94**, 1041 (1974).
9) T. Higashino, M. Goi, and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **24**, 238 (1976).
10) T. Higashino, Y. Kawade, and E. Hayashi, *Heterocycles*, **8**, 159 (1977).

Experimental[11]

IR spectra were recorded on a Jasco IRA-1 grating infrared spectrophotometer. NMR spectra were measured at 60 Mc and 23° on a Hitachi R-24 high resolution NMR spectrometer using tetramethylsilane as an internal standard. EMM was carried out on a JEOL JMS-01SG-2 mass spectrometer combined with a JEC-6 spectrum computer. Samples were vaporized in a direct inlet system.

Preparation of Im——A solution of $NaNO_2$ (517 mg, 7.5 mmol) in H_2O (5.0 ml) was slowly added to a solution of II[12] (781 mg, 6.3 mmol) in 2 N HCl (5.0 ml) with stirring at room temperature, and the mixture was stirred at for 2.5 hr. After neutralization with K_2CO_3, the reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and passed through a column of alumina to remove impurities, eluting with $CHCl_3$. The first elution gave Im, mp 88°, as white needles from petr. ether, in 47% yield (400 mg). Im was found to be identical with 3-methyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine prepared by another route[3] by mixed mp.

Preparation of Ip——A mixture of IIIp (3.0 g, 13.0 mmol) in benzene (45 ml) and H_2O (10 ml) was added to a catalyst prepared from 1% $PdCl_2$ (10 ml) and MgO (2.7 g), and the mixture was shaken in an H_2 stream. The reaction was stopped when 13 mmol of H_2 had been absorbed. The catalyst was filtered off, and the benzene layer was separated from the filtrate and dried over Na_2SO_4. The removal of benzene gave Ip, mp 114—115°, as yellow needles from petr. ether, in 70% yield (1.8 g). EMM (*m/e*) Calcd. for $C_{10}H_7N_5$: 197.0701 (M^+). Found: 197.0701. NMR (in $CDCl_3$) ppm: 9.68 (1H, singlet, 7-H), 9.31 (1H, singlet, 5-H), 7.4—8.5 (5H, multiplet, N-C_6H_5).

Behavior of Im in 5% NaOH——A solution of Im (300 mg, 2.2 mmol) dissolved in 5% NaOH (0.5 ml) was warmed at 65° for 3 hr. The reaction mixture was allowed to stand overnight at room temperature, then the separated crystals were collected by suction and recrystallized from MeOH to give IVm, mp 193—194° as colorless prisms, in 40% yield (110 mg). IVm was identical with 5-amino-1-methyl-1*H*-1,2,3-triazole-4-carboxaldehyde prepared by another route[5] by mixed mp.

Behavior of I in 20% H_2SO_4——i) A solution of Im (300 mg, 2.2 mmol) in 20% H_2SO_4 (0.3 ml) was allowed to stand overnight at room temperature. The separated crystals were collected by suction and recrystallized from MeOH to give IVm in 51% yield (143 mg).

ii) A mixture of Ip (400 mg, 2.0 mmol), MeOH (5.0 ml), and 20% H_2SO_4 (1.0 ml) was refluxed for 2 hr. After removal of MeOH under reduced pressure, the residue was poured into H_2O (4.0 ml) and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and chromatographed on a column of alumina using $CHCl_3$ as an eluent. The first fraction gave Ip in 14% yield (56 mg), and the second gave IVp, mp 113—114° as colorless needles from benzene–petr. ether, in 39% yield (148 mg). EMM (*m/e*) Calcd. for $C_9H_8N_4O$: 188.0699 (M^+). Found: 188.0697. IR ν_{max}^{KBr} cm^{-1}: 3320, 3380 (–NH_2), 1700 (=C=O). NMR (in $CDCl_3$) ppm: 10.0 (1H, singlet, –CH=O), 7.56 (5H, singlet, N-C_6H_5), 5.75 (2H, broad singlet and exchangeable with D_2O, –NH_2).

Reaction of Im with the Methoxide Ion——Im (270 mg, 2.0 mmol) was added to a sodium methoxide solution prepared by dissolving Na (78 mg) in MeOH (1.0 ml), and the mixture was allowed to stand for 2 weeks at room temperature. The residue, obtained by the removal of MeOH under reduced pressure, was neutralized with dilute AcOH. The separated crystals were collected by suction and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and chromatographed on a column of alumina using $CHCl_3$ as an eluent. The first fraction gave Vm, mp 300° (dec.) as colorless needles from AcOH, in 13% yield (36 mg). EMM (*m/e*) Calcd. for $C_{10}H_8N_{10}$: 268.0934 (M^+). Found: 268.0916. NMR (in $CDCl_3$) ppm: 9.76 (2H, singlet, 5-H), 4.65 (6H, singlet, N-CH_3).

The crystals, which did not dissolve in $CHCl_3$, were recrystallized from MeOH to give VIm, mp above 300°, as white needles in 8% yield (18 mg). EMM (*m/e*) Calcd. for $C_8H_9N_9$: 231.0980 (M^+). Found: 231.0976. IR ν_{max}^{KBr} cm^{-1}: 3300, 3400 (–NH_2). NMR (in CF_3COOH) ppm: 9.85 (1H, singlet, 5-H), 4.52 (3H, singlet, N-CH_3), 4.17 (3H, singlet, N-CH_3).

Dimerization of I in the Presence of the Cyanide Ion——i) Potassium cyanide (100 mg) in H_2O (1.0 ml) and Im (300 mg, 2.2 mmol) in H_2O (4.0 ml) were mixed and kept at room temperature for 40 min. The separated crystalline solid was collected, washed with H_2O and dried. Recrystallization from AcOH gave Vm in 83% yield (246 mg).

ii) A mixture of Ip (197 mg, 1.0 mmol), KCN (130 mg), and dimethyl sulfoxide (2.0 ml) was stirred for 20 hr at room temperature. The reaction mixture was poured into H_2O (10 ml). The separated crystalline solid was collected by suction, washed with H_2O, and dissolved in $CHCl_3$. The $CHCl_3$ solution was dried over Na_2SO_4 and passed through a column of alumina to remove impurities, using $CHCl_3$ as an eluent, to give Vp, mp 226—270° (dec.) as slightly yellow needles, in 54% yield (106 mg). EMM (*m/e*) Calcd. for $C_{20}H_{12}N_{10}$: 392.1250 (M^+). Found: 392.1254. NMR (in $CDCl_3$) ppm: 9.70 (2H, singlet, 5-H), 7.4—8.6 (10H, multiplet, N-C_6H_5).

11) Melting points are uncorrected.
12) D.J. Brown, *J. Appl. Chem.*, **4**, 72 (1954).

Reaction of Im with N,N-Dimethylaniline (IX) in 20% H_2SO_4——A solution of Im (300 mg, 2.2 mmol), IX (532 mg, 4.4 mmol) in 20% H_2SO_4 (2.0 ml) was allowed to stand for 4 days at room temperature. The reaction mixture was neutralized with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and chromatographed on a column of alumina using $CHCl_3$ as an eluent. The first fraction gave VIIIm, mp 201—202° as violet needles from petr. ether, in 14% yield (110 mg). *Anal.* Calcd. for $C_{20}H_{26}N_6$: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.54; H, 7.48; N, 23.86. IR ν_{max}^{KBr} cm^{-1}: 3300, 3370 ($-NH_2$). NMR (in $CDCl_3$) ppm: 7.1 (2H, broad singlet and exchangeable with D_2O, $-NH_2$), 6.62, 7.02 (8H, doublet of doublets, p-C_6H_4-N, J=8.0 Hz), 5.39 (1H, singlet, $CH(Ar)_3$), 3.65 (3H, singlet, N-CH_3), 2.87 (12H, singlet, $-N(CH_3)_2$).

Reaction of IVm with IX in 20% H_2SO_4——A solution of IVm (126 mg, 1.0 mmol) and IX (242 mg, 2.0 mmol) in 20% H_2SO_4 (2.0 ml) was heated at 90° for 2 hr. The reaction mixture was neutralized with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and chromatographed on a column of alumina using $CHCl_3$ as an eluent. The first fraction gave VIIIm in 12% yield (41 mg).

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