Mechanism Study of Base-Catalyzed Cyclization of 2-Nitrophenylhydrazine in Aqueous Solution

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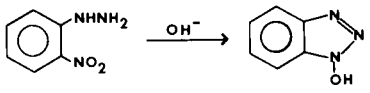
Received January 25, 1978

The mechanism of cyclization of 2-nitrophenylhydrazine to 1-hydroxybenztriazole in alkaline aqueous solutions is studied. Kinetic parameters, product distribution and activation parameters are determined. A mechanism involving direct attack of the β-hydrazino nitrogen on the nitrogen of the nitro group with elimination of water is postulated. Substituted 2-nitrophenylhydrazines are synthesized and studied under the same conditions.

J. Heterocyclic Chem., 15, 545 (1978)

Introduction.

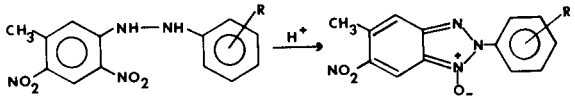
The facile condensation of 2-nitrophenylhydrazine (**1**) to 1-hydroxybenztriazole (**2**) in alkaline media was first discovered and studied in the late 19th century (1). Since



1 2

that time, considerable work has been done using this reaction as a synthetic pathway for 2- and 3-substituted 1-hydroxybenztriazole derivatives.

Derivatives of **2**, where the substituents are in the phenyl ring, have also been prepared *via* this reaction (2). 2,4-Dinitrophenylhydrazine reacts under basic conditions to form a mixture of 1-hydroxy-6-nitrobenztriazole, 3,3-dinitroazoxybenzene and *m*-dinitrobenzene (3). Acid catalyzed reactions of 2-nitrohydrazobenzene derivatives (**3**) yield *N*-arylbenztriazole *N*-oxides (**4**) which are tautomeric with the hydroxybenztriazole (4).



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While base-catalyzed conversion of 2-nitrophenylhydrazines to 1-hydroxybenztriazoles has been extensively studied with respect to the synthetic applications, very little has been reported on the mechanism of these reactions. This paper explores this reaction in terms of the mechanism involved.

Results and Discussion.

Rate Equation.

The rate of cyclization of **1** was studied at *p*H 9.0 (tris-hydroxymethylaminomethane (TRIS) buffer) at 25.0° using several different initial concentrations of **1**. The pseudo first-order rate constants were identical (within the experimental error) for each concentration studied. These data suggest that the reaction is first-order with respect to **1**. The effect of hydroxide concentration was studied by measuring the pseudo first-order rate constants for the reaction of **1** as a function of *p*H. The results of this study are presented in Figure 1 and Table I. The slope of the line drawn (m = 1) indicates that the rate equation contains a term that is first-order with respect to hydroxide ion concentration. Each *p*H value was studied at differing buffer concentrations. None of the data suggest catalysis by the buffer species.

Based on these observations, the rate equation for the cyclization of **1** can be written as Equation 1.

$$V = k_1 [2\text{-NPH}] [OH^-] \quad (1)$$

In this case, 2-NPH represents the free base form of **1**. This rate equation, however, is kinetically equivalent to

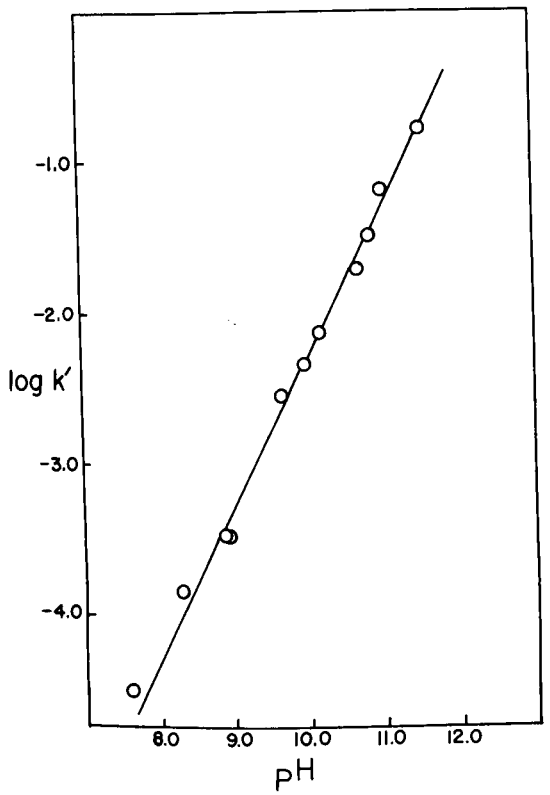


Figure 1. Partial *p*H-rate profile for the decomposition of 2-nitrophenylhydrazine in aqueous solution. The rate constant, k′, is a pseudo-first order constant with units of sec^{-1}. Ionic strength = 0.15*M*; acetonitrile = 0.83 per cent (v/v).

Table I

Rate Constants for Cyclization of 2-Nitrophenylhydrazine in Water at 25°

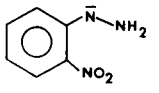
*p*H	No. of Trials	10^4 (2-NPH) (*M*)	(Buffer) (*M*)	10^3 k_{obs} (sec^{-1})	k_{OH} (M^{-1} sec^{-1})
11.55	3	1.64		163	45.9
11.03	3	1.64		66.2	61.9
10.85	5	1.64	0.025 (a)	31.0	43.8
10.85	4	1.64	0.015 (a)	33.3	47.0
10.65	4	1.64	0.025 (a)	19.3	43.0
10.65	8	1.64	0.0125 (a)	19.8	44.2
10.20	3	1.64	0.025 (a)	7.41	46.6
10.20	4	1.64	0.0125 (a)	7.40	46.6
10.00	3	2.46	0.025 (a)	4.50	45.0
9.00	2	4.01	0.05 (b)	0.354	35.4
9.00	4	3.08	0.05 (b)	0.335	33.5
9.00	2	2.47	0.05 (b)	0.407	40.7
9.00	2	1.85	0.05 (b)	0.313	31.3
9.00	2	2.47	0.07 (b)	0.353	35.3
9.00	2	2.47	0.025 (b)	0.378	37.8
8.95	3	1.64	0.05 (b)	0.33	37.0
8.95	3	1.64	0.025 (b)	0.36	40.6
8.33	2	1.64	0.05 (b)	0.144	67.6
7.60	2	1.64	0.05 (b)	0.0291	73.1

(a) Bicarbonate Buffer. (b) TRIS Buffer.

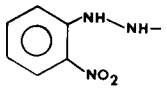
Equation 2.

$$V = k_2 [2\text{-}NP^-] \quad (2)$$

In this equation, 2-NP^- represents the mono-anion of **1** either **1a** or **1b**) and k_2 is equal to k_1 Kw/Ka where Kw is the autoprotolysis constant for water and Ka is the acid dissociation constant for the formation of the mono-anion.



1a



1b

While these rate equations are kinetically indistinquishable, other data may be used to differentiate between them. Furthermore, the position of the charge on the anion is of importance in mechanistic considerations.

If anion formation is occurring a significant spectral shift should be observed. Since the substrate decomposes rapidly at high *p*H, it is not possible to obtain a complete spectrum at *p*H greater than 8 before appreciable reaction occurs. Complete scans were obtained, however, in the *p*H region of 1.5 to 8.0. Above this *p*H range, measurement of absorbance were made at the wavelength maximum of 435 nm. To minimize the effect of reaction on the absorbance readings, the substrate was added to the buffer solution in the spectrophotometer and the absorbance was measured as rapidly as possible. By placing the substrate (0.025 ml.) in an empty cuvette and adding three milliliters of buffer to the sample *via* a syringe fitted through a specially modified sample compartment on the Cary 15, initial absorbance values were obtained within five seconds of the start of the reaction. The results of this study are shown in Figure 2. The initial increase in absorbance at 435 nm (*p*H 1.4-4.0) is due to the conversion of the cation to the free base form (p*K*a-3.45 (11)). Above *p*H 4 the absorbance was essentially constant throughout the *p*H range up to 11.5. At the highest *p*H studied, the absorbance obtained was slightly lower (0.830). However, it was not possible to determine if this lower absorbance was due to spectral shift or the inability to measure the absorbance at the start of the reaction. Although there does not appear to be a spectral shift indicative of the formation of a mono-anion, the p*K*a for this process need only be about 13-13.5 in order for this experiment to fail in its detection. Furthermore, even

Table II

Spectral Data for 1-Hydroxybenztriazole

Authentic Sample			Cyclization of 2-Nitrophenylhydrazine		
*p*H	max	log e	*p*H	max	log e
9.0	303 nm	3.73	9.0	303 nm	3.66
	280	3.65		280	3.68
10.0	303	3.73	10.0	303	3.73
	280	3.65		280	3.66
11.0	303	3.74	11.0	303	3.73
	280	3.66		280	3.65

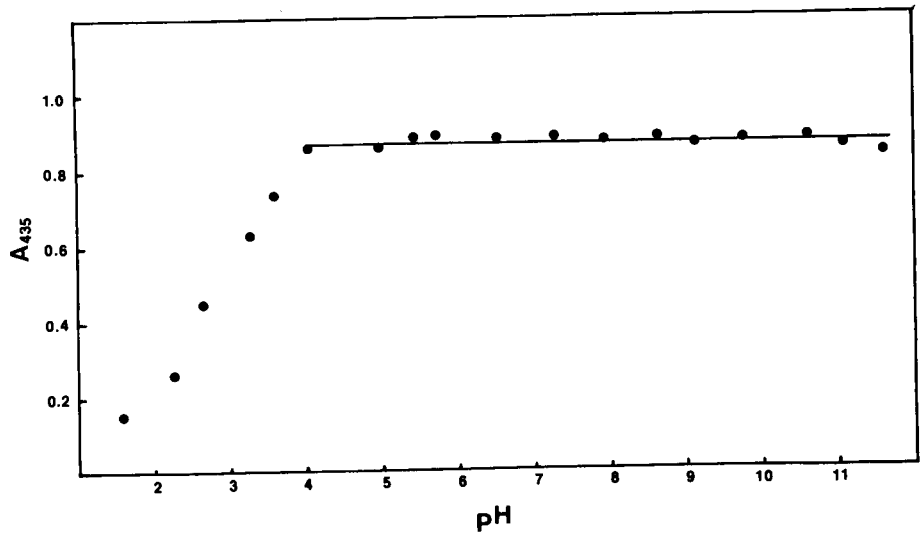


Figure 2. Plot of A_{435} for 2-nitrophenylhydrazine as a function of *p*H.

though such a p*K*a is quite high, the resulting small concentration of a highly reactive mono-anion would have a significant effect on the rate of reaction. If indeed a mono-anion is formed, **1a** is more likely than **1b** since the anion on the nitrogen adjacent to the ring would be stabilized by resonance. Further evidence for **1a** being the preferred anion is obtained from the nmr spectrum of **1** in deuteriochloroform. The protons on the β-nitrogen appear as a singlet at δ 3.65 ppm while the proton on the α-nitrogen appears as a singlet at δ 8.7 ppm with TMS as the reference standard. These values are assigned on the basis of the nmr spectrum of 1-methyl-1-(2-nitrophenyl)-hydrazine (**9**) in which case only the β-protons are present. These protons appear at 3.70 ppm. The large shift value for the proton on the α-nitrogen is consistent with extensive deshielding which indicates decreased electron density. Hence, the proton on the α-nitrogen is more acidic than the proton on the β-nitrogen.

Product Distribution.

Only one product, 1-hydroxybenztriazole (**2**) was isolated from the alkaline reaction mixture. By exhaustive ether extraction of the reaction mixture (after being made acidic) 98 percent of total **1** was recovered as **2**. Ultraviolet spectra of the reaction mixtures were essentially identical to the spectra of equivalent concentrations of authentic 1-hydroxybenztriazole at *p*H 9,10,11 (Table II). Based on these observations, **2** is the only product formed in significant amounts in the alkaline reaction of **1**. These findings are considerably different from those previously reported for the base-catalyzed reaction of 2,4-dinitrophenylhydrazine (3).

Activation Parameters.

The dependence of rate on temperature is shown in

Table III
Data for Arrhenius Plot

Temperature (K)	10^3 k_{obs} (sec^{-1})	log k_{OH} (a)
298	4.50	1.65
303	8.18	1.75
308	13.7	1.82
313	28.1	1.98
318	47.3	2.07

(a) $k_{OH} = k_{obs}$ divided by (OH^-).

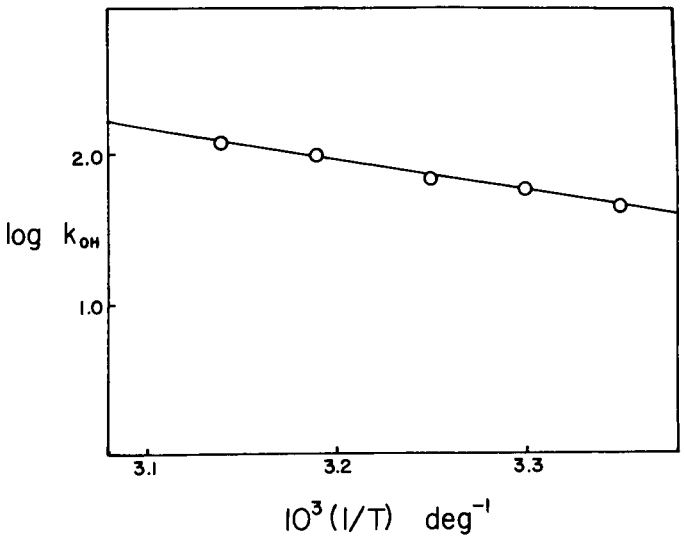
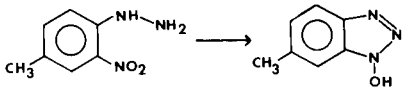


Figure 3. Arrhenius plot for the decomposition of 2-nitrophenylhydrazine in aqueous solutions. The rate constant $k_{OH} = k/(OH^-)$. *p*H = 10.00 (± 0.04); ionic strength = 0.15*M*; acetonitrile = 0.83 per cent (v/v).

Figure 3. The second-order rate constants plotted were calculated by dividing the pseudo first-order rate constants by the hydroxide-ion concentrations as determined by *p*H measurement (Table III). Since the hydroxide ion concentrations were determined from *p*H, the appropriate autoprotolysis constant for water (Kw) was used at each temperature to calculate $[OH^-]$ ($[OH^-] = Kw/[H^+]$). The line in Figure 3 was obtained by linear regression analysis and found to have a slope of -2024 deg^{-1}. The correlation coefficient of this line was 0.996 with a standard error of the estimate of 0.0134 (Sy.x). Evaluation of these data gave the following results: energy of activation, (Ea) = 9.26 kcal $mole^{-1}$, enthalpy of activation ($\Delta H^{\ddagger}$) = 8.65 kcal $mole^{-1}$, and entropy of activation ($\Delta S^{\ddagger}$) = -22.2 e.u.

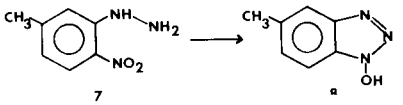
Mechanism.

The possibility of monoanion formation leads to the postulation of the following mechanism. If this mechanism is operative the substitution of either the 4 or 5 position of the 2-nitrophenylhydrazine should lead to two products because of the symmetrical intermediate (**1c**) formed in this pathway. By synthesizing both the 4- and 5-methyl-2-nitrophenylhydrazines and subjecting them both to alkaline conditions, we have been able to rule out this mechanism. In the case of 4-methyl derivative (**5**) only 6-methyl-1-hydroxybenztriazole (**6**) was formed.



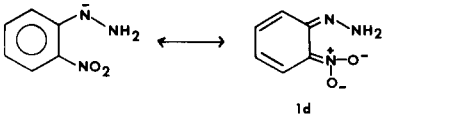
5 6

In the case of the 5-methyl derivative (**7**) only the 5-methyl-1-hydroxybenztriazole (**8**) was formed (see Experimental for data). In neither case was more than one product formed.



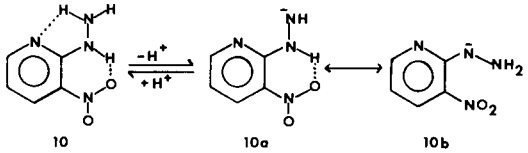
7 8

An alternative mechanism also involves the formation of a monoanion. In this mechanism, the mono-anion undergoes a tautomeric shift to form a nitronic acid. This is followed by rapid attack of the nitrogen anion on the positively charged nitrogen of the nitronic acid with the elimination of water. Since the formation of the nitronic acid is not favored at high *p*H, a similar mechanism can also be postulated. Once this specie (**1d**) is formed, the amino group could attack the positively charged nitrogen of the nitro group with the elimination of a water molecule. This mechanism is more logical in that it does not require the formation of the nitronic acid.



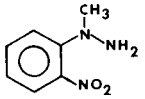
1d

The cyclization reaction of 2-hydrazino-3-nitropyridine (**10**) at *p*H 9.0 was considerably slower than that of 2-nitrophenylhydrazine. At *p*H 9.0 and 25° the average value (n = 5) for the observed first-order rate constant for **10** is seven times slower than for **1**. This decrease in rate may be explained in terms of intramolecular hydrogen bonding which tends to increase the p*K*a for proton loss. In this case intramolecular hydrogen bonding stabilizes the protons on the hydrazino nitrogens and would hence increase the p*K*a. The sevenfold rate decrease would require only a small change in p*K*a.



10 10a 10b

1-Methyl-1-(2-nitrophenyl)hydrazine (**9**) reacted much slower (half-life greater than 24 hours) than **1** under the same conditions. This is not unexpected since the mono-anion could not form on the α-hydrazino nitrogen. Furthermore, the benztriazole ring cannot be formed without loss of the methyl group.



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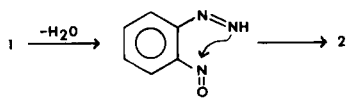
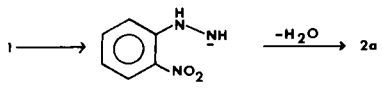
Another possibility in this system is the simultaneous reduction of the nitro group to a nitroso group and oxidation of the hydrazino group followed by ring closure.



However, the addition of sodium bisulfite, ascorbic acid or extensive purging with nitrogen had no effect on the rate of cyclization of **1a**.

Finally, it has not been shown that the formation of



a monoanion with the charge residing on the β-hydrazino nitrogen is not involved. However, formation of the anion on the α-hydrazino nitrogen would be stabilized by ring resonance; whereas, this anion would not.

EXPERIMENTAL

Materials and Apparatus.

Unless otherwise stated, chemicals were analytical reagent grade and were used directly. All water was double distilled in glass.

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected; boiling points are uncorrected. Spectral measurements were made with a Cary Model 15 spectrophotometer equipped with thermostated cell compartment. The temperature of the cell compartment was maintained to ± 0.1° by a circulating water bath. Thermometers used carried an ASTM certificate. The *p*H measurements were made with either a Radiometer *p*H meter model 52 equipped with a Radiometer combination electrode (GK 2321C) or a Beckman Research *p*H meter equipped with a Corning combination electrode (476050). Elemental analyses were performed by Baron Consulting Co., Orange, Ct. or Microanalysis, Inc., Wilmington, Delaware. Mass spectral analyses were performed on a Hitachi RMU-7 spectrometer. Standard *p*H buffer solutions were prepared according to Bates (5). Acetonitrile was redistilled from phosphorus pentoxide; the fraction boiling at 81.5° was collected. 2-Ntirophenylhydrazine, m.p. 90° (lit. (6) m.p. 90°) was recrystallized from a water-methanol mixture. 2-Nitrophenylhydrazine hydrochloride was recrystallized from methanol, m.p. 195-199° dec.

Anal. Calcd. for $C_6H_7N_3O_2$·HCl: C, 38.00; H, 4.26; N, 22.16. Found: C, 38.26; H, 4.37; N, 21.97.

Kinetics of 2-Nitrophenylhydrazine Cyclization.

The decomposition of 2-ntirophenylhydrazine in aqueous solutions was followed by measuring the decrease in absorbance at 435 nm as a function of time. Pseudo first-order rate constants were calculated from plots of log (A_t-A_∞) versus time, where A_∞ is the absorbance at infinite time and A_t is the absorbance at the time interval taken. Reactions were run at various buffer concentrations in order to evaluate buffer catalysis. All solutions were adjusted to an ionic strength of 0.15*M* with sodium perchlorate. Similar procedures were used to measure the rates of reaction for 1-methyl-1-(2-nitrophenyl)hydrazine and 2-hydrazino-3-nitropyridine.

Investigation of the Cyclization Products of 2-Nitrophenylhydrazine.

Two hundred milligrams of 2-nitrophenylhydrazine hydrochloride were dissolved in 50 ml. distilled water. A saturated solution of sodium hydroxide was added dropwise with stirring until the solution decolorized (*p*H 11.5). The solution was adjusted to *p*H 7 and extracted with three 25-ml. portions of ether. The ether fractions were combined, dried with anhydrous sodium sulfate, and evaporated to dryness. The aqueous fraction was made basic (*p*H 11) and extraction procedure was repeated. The aqueous fraction was then made acidic (*p*H 1-2) and extracted as before. Only the acidic fraction yielded a significant residue. This residue was recrystallized from hot water, yielding white needles melting at 155° and having the following elemental composition: C, 53.55; H, 3.69; and N, 30.08.

Another sample of 2-nitrophenylhydrazine hydrochloride was treated in the same manner with extraction from the acidic phase being repeated in a quantitative fashion in order to determine the yield of the product.

Effect of *p*H on Initial Absorbance at 435 nm.

Buffer solutions were prepared and adjusted to the appropriate *p*H values by the addition of 0.1*N* hydrochloric acid or sodium hydroxide. Buffers used were: a) glycine (7.505 g. glycine and 5.85 g. sodium chloride per liter), *p*H 1.5-3.6; b) succinic acid (4.90 g. per liter) and sodium borate (19.06 g. per liter) mixed in varying proportions, *p*H 4.0-6.0; c) potassium dihydrogen phosphate (13.6 g. per liter) and sodium borate (19.06 g. per liter), mixed in varying proportions, *p*H 6.5-9.2; and d) sodium borate (19.06 g. per liter), *p*H 10.7-11.7. Exactly 3.0 ml. of the buffer was placed in a 1 cm cell in the Cary 15 spectrophotometer and allowed to equilibrate to 25.0°. Exactly 0.025 ml. of 2-nitrophenylhydrazine solution (0.0227*M* in acetonitrile) was added to the buffer and the absorbance at 435 nm was measured as quickly as possible. *p*H values of the solutions were again measured after addition of the 2-nitrophenylhydrazine. In all cases the *p*H did not change by more than 0.05 units.

Synthesis of 4-Methyl-2-nitrophenylhydrazine Hydrochloride (**5**).

4-Methyl-2-nitroaniline (11 g.) was mixed with 30 ml. of concentrated hydrochloric acid and stirred. The resulting pale-yellow slurry (chilled to 0°) was treated by the dropwise addition of a solution of sodium nitrite (6 g. in 10 ml. water); the temperature being maintained at 0° during this addition. The resulting solution was filtered while cold. The filtrate was adjusted to *p*H 3 by dropwise addition of a saturated solution of sodium hydroxide. The resulting solution was filtered and added to a solution of 20.5 g. of sodium sulfite in 100 ml. of 1*N* sodium hydroxide. During this addition the temperature was also maintained at 0°. After two hours the solution was acidified with concentrated hydrochloric acid and allowed to stand at room temperature overnight. A dark foam on the top of an orange slurry was aspirated off and the slurry was filtered with the precipitate being dried at 50° (*in vacuo*) for two hours. The precipitate was then recrystallized from hot water. A second crop of crystals was obtained by chilling (in refrigerator) the filtrate overnight. The precipitates were heated in a sufficient quantity of hydrochloric acid to effect solution. Yellow leaflets precipitated from this solution upon standing at room temperature, m.p. 200-203° dec. The mass spectrum (e.i.) of this compound showed a parent peak at m/e 167.

Anal. Calcd. for $C_7H_{10}ClN_3O_2$: C, 41.29; H, 4.95; N, 20.64. Found: C, 41.22; H, 4.89; N, 20.45.

Base Degradation of 4-Methyl-2-nitrophenylhydrazine.

The hydrochloride salt (0.203 g.) was suspended in 50 ml. of water containing 2 percent acetonitrile. Fifty ml. of 0.4*M* sodium hydroxide was added to the solution. The solution was stirred for 24 hours at room temperature. The solution was then adjusted to *p*H 7.2 and extracted with three 100 ml. portions of ether. The aqueous layer was acidified with hydrochloric acid (*p*H 2.2) and extracted with ether as before. The aqueous phase was made basic (*p*H 12) and extracted again. The ether fractions were dried over anhydrous sodium sulfate and evaporated to dryness. Only the acidic extract yielded a significant residue. The residue was

recrystallized from methyl ethyl ketone giving a m.p. 181-182° (literature melting point, (7) 178-179°). The mass spectrum displayed a parent peak at m/e 149. These data are consistent with 6-methyl-1-hydroxybenztriazole (**6**).

Anal. Calcd. for $C_7H_7N_3O$: C, 56.38; H, 4.70; N, 28.19. Found: C, 56.13; H, 4.71; N, 28.18.

Based on a molecular weight of 167 for the monohydrate, a recovery of 85 percent of theoretical was obtained.

A portion of the alkaline reaction mixture was chromatographed on silica gel plates (0.25 mm, fluorescent background) in a variety of solvents. Only one spot was observed in acetone, chloroform, ethyl acetate, benzene, methanol, chloroform:ethyl acetate 1:1, one percent acetic acid in methanol, and one percent ammonium hydroxide in methanol.

Synthesis of 5-Methyl-2-nitrophenylhydrazine (**7**).

This compound was synthesized according to the method of Mangini and Colonna (8). The observed melting point was 128-129° (lit. (8) m.p. 131-132°). The free base was converted to the hydrochloride salt by dissolving 0.28 g. in 10 ml. of hot methanol and adding 10 ml. of concentrated hydrochloric acid. The mixture was then evaporated to dryness. The residue was recrystallized from concentrated hydrochloric acid giving a product melting at 192-195° dec. The mass spectrum of this compound gave a parent peak at m/e 167. This corresponds to the molecule after the loss of HCl.

5-Methyl-1-hydroxybenztriazole (**8**).

5-Methyl-2-nitrophenylhydrazine (0.167 g.) was dissolved in a mixture of acetonitrile (1 ml.), 0.1*N* hydrochloric acid (15 ml.) and water (34 ml.). Twenty-five ml. of 0.4*N* sodium hydroxide was added to this solution and the resulting mixture was stirred for two hours at room temperature. The *p*H was adjusted to 7.0 with 1*N* hydrochloric acid and extracted with three 100 ml. portions of ether. The ether fractions were then discarded. The aqueous fraction was adjusted to *p*H 1.3 with 1*N* hydrochloric acid and extracted with four 100 ml. portions of ether. The combined ether fractions were dried for 16 hours over anhydrous sodium sulfate. Removal of the ether *in vacuo* gave 0.141 g. of a residue melting at 183-184° dec. Recrystallization from methyl ethyl ketone gave a product melting at 187-188° (lit. (9); 188-189°; lit. (8), 184° dec.).

Product Study of Based-Catalyzed Cyclization of 4-Methyl-2-nitrophenylhydrazine (**5**) and 5-Methyl-2-nitrophenylhydrazine (**7**).

4-Methyl-2-nitrophenylhydrazine (0.051 g.) was dissolved in a mixture of water and acetonitrile (99:1). The resulting solution was made basic (*p*H 10-11) by the dropwise addition of 1*N* sodium hydroxide. 5-Methyl-2-nitrophenylhydrazine (0.051 g.) was treated in the same fashion. Samples from each solution were spotted on a silica gel thin-layer plate (0.25 mm). Authentic samples of 6-methyl-1-hydroxybenztriazole (**6**) and 5-methyl-1-hydroxybenztriazole (**8**) (in aqueous alkaline solutions) were also spotted on the same plate. The plate was then developed twice with tetrahydrofuran as the mobile phase. Each sample yielded only one spot when examined under visible or ultraviolet light. The R_f values were: **5** (after cyclization) (0.65), **6** (0.66), **7** (after cyclization) (0.56) and **8** (0.53).

Synthesis of 1-Methyl-1-(2-nitrophenyl)hydrazine Hydrochloride (**9**).

Methylhydrazine (3.5 g.) was dissolved in 10 ml. of ethanol (95%) and added to a solution of *o*-chloronitrobenzene (5 g.) in 25 ml. ethanol (95%). The process was repeated until 5 samples had been prepared. Each sample was placed in large screw-cap tubes (50 ml.) with Teflon-lined screw caps. The samples were then immersed in boiling water for 14 hours. The contents of the tubes were combined and the solvent removed *in vacuo*. The residual dark red oil was taken up in chloroform and extracted with two 50 ml. portions of 0.1*N* hydrochloric acid. The aqueous fraction was adjusted to *p*H 6 and extracted with two 50 ml. portions of dichloromethane. After drying over anhydrous sodium sulfate, the dichloromethane was removed by evaporation under a gentle nitrogen flow. The residue was recrystallized in a minimum amount of hot concentrated hydrochloric acid to yield large yellow prisms melting at 180-184° dec. Mass spectral analysis gave a parent ion peak of m/e 167 which corresponds to the free base. Infrared and nmr spectra were consistent with the expected product. A phenylhydrazone derivative of 1-methyl-1-(2-nitrophenyl)-hydrazine was prepared by reacting this compound with 3-nitrobenzaldehyde. After purification the derivative melted at 155° (lit. m.p. 156° (10)).

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