Pyridineazidoximes and Furoxans[1]

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The following azidoximes and their benzoate derivatives have been synthesized: 2-pyridineazidoxime, 4-pyridineazidoxime, 2,6-pyridinediazidoxime, and terephthaldiazidoxime. Infrared spectra gave azide absorption peaks and no indication of tetrazole formation. The azidoximes did not give furoxans when treated with base. Reaction of 2,6-pyridinedihydroxamic chloride with base yielded a product identified as bis(2,2′-formaldoximino-6,6′-pyridyl)furoxan.

According to Forster[2] and Wieland,[3] attempts to prepare azidoximes led to products not having the properties usually expected of azides. It was generally concluded that these azidoximes, if formed, immediately isomerized to the corresponding N-hydroxytetrazoles. References in the literature were almost exclusively to the tetrazoles, while azidoximes were hardly mentioned.[4-6] Recently, Eloy[7] reported evidence for the existence of azidoximes.

It seemed of interest to determine whether pyridineazidoximes exist as tetrazoles or as azides. If ring formation does occur, the question arises as to whether the pyridine nitrogen or the nitrogen of the oxime is involved. On the other hand, if the azide structure is formed, can the azidoxime be an intermediate in furoxan formation?

This investigation was initiated in the early part of 1960. Pyridineazidoximes, 2,6-pyridinediazidoxime, and terephthaldiazidoxime were the compounds synthesized for structure studies. The isolation of pyridinehydroxamic chlorides as intermediates in the azidoxime preparations led us to reinvestigate the pyridinefuroxans reported by Wiley and Wakefield.[8] Our results are in full agreement with those recently reported by Poziomek and Melvin[9] indicating that chlorination of the pyridine aldoximes gives pyridine hydroxamic chloride hydrochlorides rather than the hydrochlorides of nitrile oxides as postulated by Wiley and Wakefield.

The 2- and 4-pyridineazidoximes and 2,6-pyridinediazidoxime and their benozate derivatives were prepared, together with terephthaldiazidoxime and its benzoate derivative (Table I). Infrared absorption at 2120–2160 cm.$^{-1}$, characteristic of the azide group,[10] was found in all of these azidoximes and their benzoates (Table II). Other absorption bands noted with 4-pyridineazidoxime and terephthaldiazidoxime, believed to be caused by a gradual decomposition of the azidoximes, are recorded in Table II. No tetrazole formation was observed.

TABLE I

ANALYSES OF AZIDOXIMES AND THEIR DERIVATIVES

Compound	M.p., °C.	Formula	Analyses: Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-Pyridineazidoxime	125–126°d[a]	$C_6H_5N_5O$	44.23	3.06	42.94	44.27	3.05	42.85
2-Pyridineazidoxime benzoate	114–115°d[b]	$C_{13}H_9N_5O_2$	58.42	3.37	26.21	58.48	3.31	25.91
4-Pyridineazidoxime picrate	170–171°d[b]	$C_{12}H_8N_8O_8$	36.73	2.04	28.57	37.04	2.48	28.34
4-Pyridineazidoxime	173–174°d[a]	$C_6H_5N_5O$	44.23	3.06	42.94	44.73	3.28	43.12
4-Pyridineazidoxime benzoate	122–123°d[c]	$C_{13}H_9N_5O_2$	58.42	3.37	26.21	58.44	4.06	25.75
2,6-Pyridineazidoxime	125–127°d[a]	$C_7H_5N_9O_2 \cdot 0.5H_2O$	32.81	2.34	49.21	33.19	2.53	48.57
2,6-Pyridineazidoxime benzoate	168–169°d[b]	$C_{21}H_{13}N_9O_4$	55.38	2.85	27.71	55.68	3.17	27.22
Terephthaldiazidoxime	170–171°d[b]	$C_8H_6N_8O_2$	39.02	2.48	45.52	39.42	2.80	44.92
Terephthaldiazidoxime benzoate	168–169°d[d]	$C_{22}H_{14}N_8O_4$	58.14	3.08	24.66	58.00	2.98	24.97

Recrystallization solvents were: [a] methanol–water, [b] methanol, [c] ethanol–water, [d] ethanol.

TABLE II

INFRARED SPECTRA OF AZIDOXIMES AND THEIR DERIVATIVES

Compound	Infrared absorption[a] in cm.$^{-1}$ for the azide groups
2-Pyridineazidioxime	2125
2-Pyridineazidoxime benzoate	2120
4-Pyridineazidoxime	2140, 2100,[b] and 2180[b]
4-Pyridineazidoxime benzoate	2140, 2220[b]
2,6-Pyridinediazidoxime	2140
2,6-Pyridinediazidoxime benzoate	2120
Terephthaldiazidoxime	2160, 2210,[b] and 2270[b]
Terephthaldiazidoxime benzoate	2110,[b] 2160

[a] From potassium bromide disk. [b] Indicates decomposition of the azidoxime on standing.

Since pyridineazidoximes do exist in the azide form, the possibility that they might be intermediates for furoxan formation next was explored. However, treatment of the 2-pyridineazidoxime with 5% potassium hydroxide solution gave picolinamide, while the same treatment of 4-pyridineazidoxime resulted in the formation of isonicotinic acid. This might be compared to a

(1) This work was supported by the Foundational Research Program of the Bureau of Naval Weapons.

(2) M. O. Forster, *J. Chem. Soc.*, **95**, 184 (1909).

(3) H. Wieland, *Ber.*, **42**, 4199 (1909).

(4) V. Grignard, "Traite de Chimie organique," Masson, T. XXXI, 1953, p. 1071.

(5) E. H. Rodd, "Chemistry of Carbon Compounds," Elsevier Publishing Co., New York, N. Y., 1954–1957, Vol. III-A, pp. 568, 571, and Vol. IV-A, p. 482.

(6) F. R. Benson, *Chem. Rev.*, **41**, 43, 45 (1947).

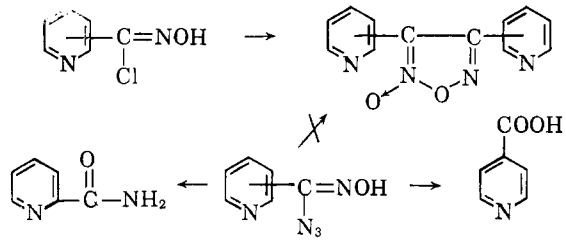
(7) F. Eloy, *J. Org. Chem.*, **26**, 953 (1961).

(8) R. H. Wiley and B. J. Wakefield, *ibid.*, **25**, 546 (1960).

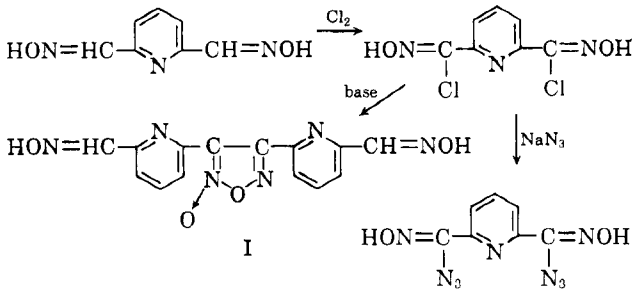
(9) E. J. Poziomek and A. R. Melvin, *ibid.*, **26**, 3769 (1961).

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 274.

comparable reaction in the benzene series in which, in either case, hydroxyphenyltetrazole was converted to benzonitrile by hot alkali.[2] Perhaps, in the presence of water, benzonitrile could be hydrolyzed to the amide or acid.



Bisbenzoylfuroxan was prepared by Ponzio[11] from benzoyl hydroxamic chloride and sodium acetate. The ease with which hydrogen chloride was lost from the hydroxamic chloride and the subsequent dimerization to furoxan was demonstrated. The hydroxamic chlorides of oximes containing basic groups also have been reported to eliminate hydrogen chloride with extreme readiness.[8] We have found 2,6-pyridinedihydroxamic chloride to be quite stable. A sample has been stored in a desiccator over potassium hydroxide pellets for a year with very little change. When 2,6-pyridinedihydroxamic chloride was treated with 10% sodium carbonate, or 5% potassium hydroxide solution, the product obtained was identified as bis(2,2′-formaldoximino-6,6′-pyridyl)furoxan (I). This identification was based on microanalysis, infrared spectra,[12] and molecular weight determination.



Experimental

All melting points are uncorrected. The 2- and 4-pyridinealdoximes, 2,6-pyridinedialdoxime, and terephthaldehyde were commercially available from the Aldrich Chemical Company. The 2- and 4-pyridinehydroxamic chloride hydrochlorides were prepared by passing chlorine into methanol solutions of the pyridinealdoximes at 5–10° for 15 min.[9] Either of these could be used directly for the azidoxime formation by adding an excess of sodium azide. Also, the pyridinehydroxamic chlorides were isolated upon careful neutralization with sodium carbonate in an ice bath and then treated with sodium azide to give the corresponding azidoximes.

General Procedure for Preparation of Pyridineazidoximes.—A solution containing 1.0 g. (0.015 mole) of sodium azide in 15 ml. of water was added slowly to 1.6 g. (0.01 mole) of 2- or 4-pyridinehydroxamic chloride dissolved in 10 ml. of methanol. The mixture was stirred at 30–40° for 30 min. and then allowed to cool. The solid obtained was recrystallized from ethanol–water. (If the pyridinehydroxamic chloride hydrochloride was used, the amount of sodium azide was increased to 3.0 g.)

The benzoate derivatives of pyridineazidoximes were prepared according to Forster.[2]

(11) G. Ponzio, *Gazz. chim. ital.*, **62**, 633 (1932).

(12) R. P. Linstead and B. C. L. Weedon, "Guide to Qualitative Organic Chemical Analysis," Butterworth's Scientific Publication, London, 1956.

2,6-Pyridinedihydroxamic Chloride.—2,6-Pyridinedialdoxime (2.0 g., 0.012 mole) was dissolved in 50 ml. of methanol, and chlorine was passed into the solution for 20 min. The temperature was kept around 40° by external cooling. When the mixture was filtered, a white solid was obtained which was recrystallized from methanol and water to give a m.p. of 164–165° dec.; yield, 2.2 g. (78%).

Anal. Calcd. for $C_7H_5N_3Cl_2O_2$: C, 35.89; H, 2.13; N, 17.94; Cl, 30.34. Found: C, 35.69; H, 2.55; N, 18.09; Cl, 30.35.

2,6-Pyridinediazidoxime.—A procedure similar to the one described for the pyridineazidoximes was followed with the exception that the amount of sodium azide was doubled and the reaction temperature was kept at 50–60°.

Terephthaldiazidoxime.—Terephthaldialdehyde was converted to terephthaldioxime with hydroxylamine hydrochloride by standard procedures; m.p. 200–201° (lit.[12] m.p. 200°).

Terephthaldihydroxamic chloride was prepared in the same manner as described for 2,6-pyridinedihydroxamic chloride; m.p. 183–185° (lit.[13] m.p. 188°).

The reaction of terephthaldihydroxamic chloride with sodium azide was carried out in methanol solution as described for the pyridineazidoximes. If the reaction mixture was kept at room temperature for an hour, the corresponding diazidoxime was obtained (Table II). When the reaction was carried out at the refluxing temperature of methanol for 1–2 hr., the corresponding dinitrile was isolated; m.p. 219–220° (lit.[14] m.p. 222°).

Anal. Calcd. for $C_8H_4N_2$: C, 74.99; H, 3.15; N, 21.87. Found: C, 74.45; H, 3.45; N, 21.89.

Reactions of 2,6-Pyridinedihydroxamic Chloride with Base. (A) With 5% Potassium Hydroxide.—To a solution of 1.0 g. (0.0042 mole) of 2,6-pyridinedihydroxamic chloride in 20 ml. of ether was added 10 ml. of 5% potassium hydroxide. Upon stirring, a solid formed which was separated, washed with water, alcohol, benzene, and ether, and finally recrystallized from dioxane–water, m.p. 222–225° dec. Infrared absorption in cm.$^{-1}$: 820 s, 995 s, 1035 w, 1150 m, 1340 m, 1400 w, 1420 w, 1490 s, and 1600 s, characteristic of furoxans.[15]

Anal. Calcd. for $C_{14}H_{10}N_6O_4$ (I): C, 51.54; H, 3.09; N, 25.76; mol. wt., 326. Found: C, 51.56; H, 2.86; N, 24.91, 25.43 (recrystallized from dioxane–methanol); mol. wt. (in dioxane), 308.

(B) With 10% Sodium Carbonate.—A suspension of 1.0 g. (0.0042 mole) of 2,6-pyridinedihydroxamic chloride in 15 ml. of 10% sodium carbonate solution was heated in a water bath for an hour. The solid was separated by filtration. Recrystallization from dioxane gave two solids: one soluble, the other insoluble. Upon drying in the air, the insoluble material became a brown powder insoluble in water and most organic solvents and with a melting point above 300°. Due to its insolubility in recrystallization solvents the crude material was subjected to analysis. The analytical results seem to fit the empirical formula for I containing a molecule of dioxane. However, analysis of this material after heating under vacuum at 110° for 4 hr. gave the second set of results for C, H, and N (given below), which were similar to the first. Hence, the attempted removal of dioxane was not successful. Infrared absorption in cm.$^{-1}$: 645 m, 700 m, 740 m, 820 s, 975 w, 995 s, 1040 w, 1050 w, 1085 w, 1125 w, 1150 m, 1175 m, 1265 m, 1350 w, 1400 w, 1425 w, 1490 s, 1600 s, 3450 s.

Anal. Calcd. for $C_{18}H_{15}N_6O_5$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.62; 52,11; H, 4.10; 2.98; N, 19.84; 20.52.

The dioxane-soluble material was recrystallized from dioxane–water, m.p. 222–225° dec., with identical infrared for I from A.

Anal. Calcd. for $C_{14}H_{10}N_6O_4$(I): C, 51.54; H, 3.09; N, 25.76. Found: C, 51.41; H, 2.79; N, 24.88, 25.30 (recrystallized from dioxane–methanol).

Reaction of Pyridineazidoximes with 5% Potassium Hydroxide.—A suspension of 0.5 g. (0.003 mole) of 2-pyridineazidoxime in 10 ml. of 5% potassium hydroxide gave immediate gas evolution. Stirring at room temperature for 24 hr. was followed by extraction with benzene. The benzene extract yielded a white

(13) H. Rheinboldt, *Ann.*, **451**, 169 (1926).

(14) I. Heilbron, "Dictionary of Organic Compounds," Vol. IV., Oxford University Press, 1953, p. 404.

(15) N. E. Boyer, F. M. Czerniak, H. S. Gutovsky, and H. R. Snyder, *J. Am. Chem. Soc.*, **77**, 4238 (1955).

solid, m.p. 106–107° (lit.[16] m.p. for picolinamide 106.5°). A melting point with 2-pyridinealdoxime was depressed.

Anal. Calcd. for $C_6H_6N_2O$: C, 59.01; H, 4.91; N, 22.95. Found: C, 59.35; H, 5.34; N, 23.07.

Following the same procedure, 4-pyridineazidoxime gave isonicotinic acid, m.p. above 300°, but starting to sublime around 270° (lit.[17] sublimes at 315°; in a sealed tube, 325–326°).

Anal. Calcd. for $C_6H_5O_2N$: C, 58.53; H, 4.06; N, 11.38. Found: C, 58.32; H, 4.04; N, 11.69.

Acknowledgment.—The authors wish to thank P. Wheeler and A. Richardson of the Analytical Branch for the microanalysis.

(16) I. Heilbron, ref. 14, p. 203.

(17) I. Heilbron, ref. 14, Vol. III, p. 97.

Nitration of Indoles. II. The Mononitration of Methylindoles[1]

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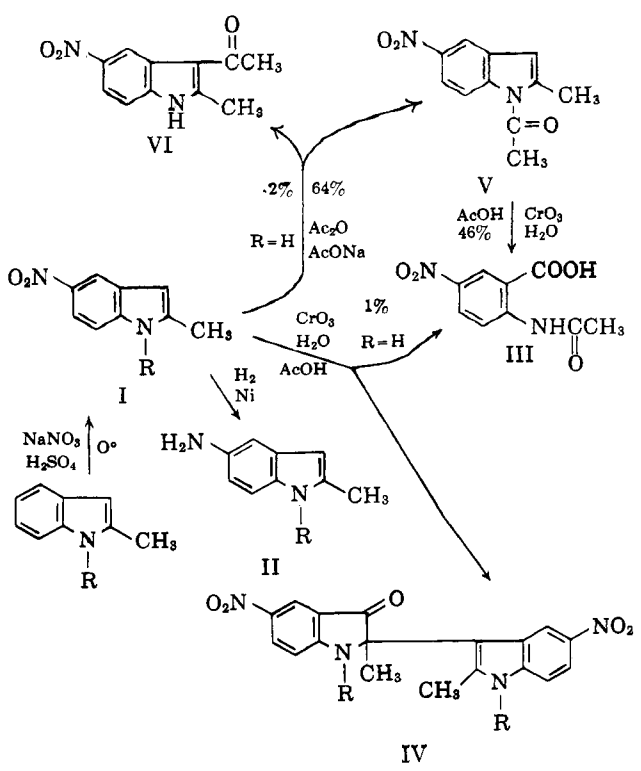
Nitration of 2-methylindole and 1,2-dimethylindole in concentrated sulfuric acid gives the corresponding 2-methyl-5-nitroindoles (Ia, 84%, and Ib, 82%). Methylation of Ia with sodamide and dimethyl sulfate in liquid ammonia gave Ib (47%). Acetylation of Ia with sodium acetate and acetic anhydride gave the 1-acetyl (V, 64%) and 3-acetyl (VI, 2%) derivatives. Chromic acid oxidation of the 1-acetyl derivative gave N-acetyl-5-nitroanthranilic acid (III, 46%), thus proving the 5-position as the position of mononitration in Ia and Ib, analogous to the corresponding nitration of 2,3-dimethylindole. Chromic acid oxidation of Ia and Ib gave the oxidative dimers IVa (19%) and IVb (31%). Catalytic hydrogenation of Ia and Ib gave the corresponding 5-amino-2-methylindoles (IIa, 61%, and IIb, 37%). Condensation of Ia with formaldehyde and benzaldehyde gave the corresponding 3,3′-methylenediindoles (XIIa, 100%, and XIIb, 58%), while the Mannich reaction of Ia with formaldehyde and dimethylamine gave 2-methyl-5-nitrogramine (XIII, 18%, and XIIa, 51%). The mechanism of formation of the various products is discussed.

In this paper, nitration of 2-methylindole and 1,2-dimethylindole in concentrated sulfuric acid clearly is shown to occur in the 5-position, and this observation is reconciled with previously known facts concerning nitration of indoles. In addition, several derivatives of the nitration products are described.

Nitration of 2-methylindole in concentrated sulfuric acid previously has been reported to give a mononitro derivative.[4] The structure has now been proved to be 2-methyl-5-nitroindole[5] (Ia, 84%) by oxidative degradation. Chromic acid oxidation gave N-acetyl-5-nitroanthranilic acid (III, 1%), a more important, insoluble product (IVa, 19%) being the result of oxidative dimerization. Acetylation of 2-methyl-5-nitroindole, however, to its 1-acetyl derivative V, 64% (formed along with 2% of the isomeric 3-acetyl derivative, VI), in the presence of sodium acetate,[6] and subsequent chromic acid oxidation, gave N-acetyl-5-nitroanthranilic acid (III) in greatly improved yield (46%). Nitration of 1,2-dimethylindole under the conditions used with 2-methylindole gave 1,2-dimethyl-5-nitroindole (Ib, 82%), the structure of which was proved by its identity with a sample prepared by methylation of 2-methyl-5-nitroindole. Chromic acid oxidation of Ib proceeded similarly to that of Ia, giving the insoluble product of oxidative dimerization IVb, 31%.



Ia, R = H (84%) IIa, R = H (61%) IVa, R = H (19%)
b, R = CH_3 (82%) b, R = CH_3 (37%) b, R = CH_3 (31%)

(1) For Paper I of this series, see W. E. Noland and R. D. Rieke, *J. Org. Chem.*, **27**, 2250 (1962).

(2) It is a pleasure to acknowledge support of the first portion of this work from the General Research Fund of the Graduate School of the University of Minnesota, used to employ Donald C. Johnson and Lowell R. Smith as research assistants during the summer of 1958. The subsequent portion of this work, not supported by the Graduate School, is contained in the Ph.D. thesis of Lowell R. Smith.[3]

(3) Taken in part from the Ph.D. thesis of Lowell R. Smith, University of Minnesota, May 1960; *Dissertation Abstr.*, **21**, 1766 (1961). It is a pleasure to acknowledge support of this portion of the work through a Frederick Gardner Cottrell grant from the Research Corporation.

(4) R. von Walther and J. Clemen, *J. prakt. Chem.*, [2] **61**, 249 (1900).

(5) Chloranil dehydrogenation of 2-methyl-5-nitroindoline also is reported to give 2-methyl-5-nitroindole, m.p. 171.5–172.5°, which was assumed to be the same as the mononitration product of 2-methylindole, m.p. 170° (ref. 4); A. P. Terent'ev, M. N. Preobrazhenskaya, A. S. Bobkov, and G. M. Sorokina, *J. Gen. Chem. USSR* (Eng. Transl.), **29**, 2504 (1959).

(6) N-Alkylation generally occurs in preference to 3-alkylation of indoles having both 1- and 3-positions open only under conditions when the anion of the indole is the reactive species (normally only under basic conditions). For a listing of several examples see, J. Szmuszkovicz, *J. Am. Chem. Soc.*, **79**, 2819 (1957). Since acylation resembles alkylation in that it too is an electrophilic reaction, it seems likely that N-acylation also occurs preferentially only under conditions when the anion of the indole (in this case, of Ia) is the reactive species. In the present case (with sodium acetate), the acidity of the indole, and hence the ease of formation of its anion, is enhanced by the fact that the indole nitrogen is also part of a *p*-nitroaniline system.