The Reaction of 2- and 4-Vinylpyridine with Hydroxylamine, Benzyloxyamine, and Phthalhydrazide

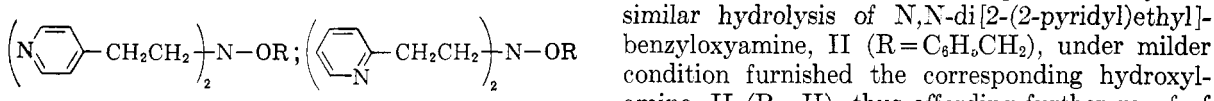
LUDWIG BAUER, ABOO SHOEB,[1] AND VINCENT C. AGWADA

Department of Chemistry, College of Pharmacy, University of Illinois, Chicago 12, Illinois

Received March 2, 1962

The addition of hydroxylamine and benzyloxyamine to 2- and 4-vinylpyridine was shown to yield the N,N-dipyridylethyl derivatives. However, phthalhydrazide reacted only with one mole of either vinylpyridine. These adducts were further characterized by their salts.

The reaction of hydroxylamine hydrochloride with 4-vinylpyridine yielded a base, $C_{14}H_{17}N_3O$, whose infrared spectrum in chloroform solution showed a band at 3600 cm.$^{-1}$, characteristic of free hydroxyl groups. The base formed a trihydrobromide and a benzoate ester which was isolated as the dihydrobromide. From this data, this base is assigned structure I (R = H).



I II

The addition of hydroxylamine (as the hydrochloride) to 2-vinylpyridine was reported[2] to afford a compound $C_7H_{10}N_2O$, m.p. 105.9–106.8°, which was formulated as N-[2-(2-pyridyl)ethyl]hydroxylamine, $2\text{-}C_5H_4NCH_2CH_2NHOH$. However, repetition of this experiment with or without modification of the procedure always gave us a solid, m.p. 105–106.5°, $C_{14}H_{17}N_3O$, and exhibited a free hydroxyl band in its infrared spectrum (in chloroform solution) and fitted the dipyridylethyl hydroxylamine structure, II (R = H). The n.m.r. spectrum also agreed with that structure. The base was further characterized by a crystalline dihydrobromide.[3] Attempts to prepare other functional derivatives of I or II (R = H) with a number of conventional reagents—(*e.g.*, acetyl chloride, arenesulfonyl chlorides, phenyl isocyanate)—gave rise to highly colored gums or amorphous solids, either as the free bases or their salts.

The reaction of benzyloxyamine with these vinylpyridines was studied. It was hoped to obtain monopyridylethyl derivatives which on catalytic hydrogenation could give rise to the monopyridylethyl hydroxylamine. However, the addition of benzyloxyamine to either 2- or 4-vinylpyridine afforded an excellent yield of the dipyridylethyl derivatives. As these compounds could not be distilled satisfactorily, they were isolated as salts. Again, the 4-pyridylethyl derivative, I ($R = C_6H_5CH_2$), crystallized as the trihydrobromide, the isomeric 2-pyridyl adduct, II ($R = C_6H_5CH_2$) as the dihydrobromide. Hydrolysis of N,N-di[2-(4-pyridyl)ethyl]benzyloxyamine I ($R = C_6H_5CH_2$), with 48% hydrobromic acid removed the benzyl group to form the hydroxy derivative I (R = H) almost quantitatively. A similar hydrolysis of N,N-di[2-(2-pyridyl)ethyl]-benzyloxyamine, II ($R = C_6H_5CH_2$), under milder condition furnished the corresponding hydroxylamine, II (R = H), thus affording further proof of structure for the 2-vinylpyridine and hydroxylamine adduct.

Benzyloxyamine was best prepared by the hydrolysis of N-benzyloxyphthalimide with concentrated hydrochloric acid in acetic acid. This procedure proved to be superior to the conventional cleavage of the phthalimido group by hydrazine as originally applied to the synthesis of O-alkylhydroxylamines.[4] The main advantage is that one avoids any separation of the hydroxylamine derivative from residual hydrazine.

The reaction of 2- and 4-vinylpyridines with amides and imides has been described. For example, the reaction with acetamide and propionamide was catalyzed by sodium metal,[5] that of phthalimide by Triton B[6a] or piperidine,[6b] and succinimide also by a basic catalyst.[7] The reaction of these vinylpyridines with 1,3-benzoxazine-2,4-dione was carried out neat and in the absence of any catalyst.[8] We have extended the acid-catalyzed addition of 2- and 4-vinylpyridine to phthalhydrazide and obtained excellent yields adducts, formulated as structure III. These pyridylethyl adducts were further characterized by their hydrobromide salts. An attempt to pyridylethylate N-hydroxyphthalimide in either acid or base gave only starting materials.

(1) Present address: Medicinal Chemistry Division, Central Drug Research Institute, Lucknow, U. P. India.

(2) H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, **77**, 5434 (1955).

(3) It is not unusual for dibasic 2-pyridylethyl substituted amines such as $2\text{-}C_5H_4NCH_2CH_2NHR$ to form either mono- or dipicrates,[2] and tribasic amines such as N-(dialkylaminoalkyl)-N-[2-(2-pyridyl)-ethyl]anilines to form dipicrates; see S. Shapiro, H. Soloway, E. Chodos, and L. Freedman, *J. Pharm. Sci.*, **50**, 1035 (1961).

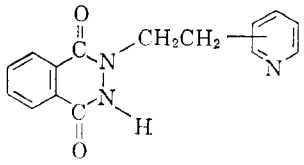
(4) A. F. McKay, D. L. Garmaise, G. Y. Paris, and S. Gelblum, *Can. J. Chem.*, **38**, 343 (1960).

(5) G. Magnus and R. Levine, *J. Am. Chem. Soc.*, **78**, 4127 (1956).

(6) (a) F. K. Kirchner, J. R. McCormick, C. J. Cavallito, and L. C. Miller, *J. Org. Chem.*, **14**, 388 (1949); (b) A. P. Gray, W. L. Archer, E. E. Spinner, and C. J. Cavallito, *J. Am. Chem. Soc.*, **79**, 3807 (1957).

(7) The method for the reaction of succinimide utilizes "basic catalysis" as described by F. K. Kirchner and C. J. Cavallito and in U. S. Patent 2,498,497, February 21, 1950, and is quoted in ref. 8, p. 2813.

(8) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **79**, 2811 (1957).



III

Experimental[9]

N,N-Di[2-(2-pyridyl)ethyl]hydroxylamine.—Redistilled 2-vinylpyridine (21.0 g.; 0.2 mole) was added to a solution of hydroxylamine hydrochloride (7 g.; 0.1 mole) in 50% aqueous acetic acid (50 ml.) and the mixture heated at 100° for 0.25 hr. The solution was cooled to 0° and sodium carbonate (32 g.; 0.3 mole) was added. The solid was filtered, dried, and freed from admixed inorganic salts by several extractions with acetone. Concentration of the acetone solution afforded the **base**, 19.9 g. (82% based on 2-vinylpyridine), m.p. 102–105°. Recrystallization from a mixture (5:3) of benzene and petroleum ether (b.p. 30–60°) gave light brown needles, m.p. 105–106.5°.

The n.m.r. spectrum (60 Mc.) in deuterochloroform[10] (using tetramethylsilane as internal standard) showed five groups of signals: A sharp signal at $\delta = 3.13$ p.p.m. which is attributed to two equivalent C_2H_4 moieties; a broad signal at $\delta = 7.88$ p.p.m. which is assigned to NOH and signals which are assigned to the α, β, and γ protons of the pyridine ring. Integral information revealed two α protons, two γ protons, four β-protons, one NOH, and eight CH_2 protons.

Anal. Calcd. for $C_{14}H_{17}N_3O$ (243.3): C, 69.13; H, 7.06; N, 17.27. Found: C, 69.23; H, 6.97; N, 17.27.

The **dihydrobromide** was isolated in almost quantitative yield by passing a stream of hydrogen bromide gas through an ice-cold ethanol solution of the **hydroxylamine**. The **salt** was recrystallized from ethanol–ether (8:5), m.p. 160–161°.

Anal. Calcd. for $C_{14}H_{19}N_3OBr_2$ (405.2); C, 41.50; H, 4.74; N, 10.37; Br, 39.44. Found: C, 41.70; H, 4.67; N 10.12; Br, 39.65.

N,N-Di[2-(4-pyridyl)ethyl]hydroxylamine.—This **hydroxylamine** was prepared in 70% yield from 4-vinylpyridine by the procedure outlined for 2-vinylpyridine. It crystallized from acetone in colorless needles, m.p. 143–144°.

Anal. Calcd. for $C_{14}H_{17}N_3O$ (243.3): C, 69.13; H, 7.06; N, 17.27. Found: C, 69.22; H, 6.93; N, 17.39.

The **trihydrobromide**, was crystallized from ethanol–ether and melted at 200–202°.

Anal. Calcd. for $C_{14}H_{20}N_3OBr_3$ (486.1): C, 34.59; H, 4.16; N, 8.65. Found: C, 34.71; H, 4.20; N, 8.57.

A solution of the above **hydroxylamine** (1.2 g.; 0.005 mole) in chloroform (25 ml.) was added in small portions (over a period of 10 min.) to a chloroform solution of benzoyl chloride (3.0 g.; 0.02 mole in 25 ml.). After standing at 25° for 2 hr., the solvents were removed *in vacuo* and the residue dissolved in 10 ml. of ice water. Addition of 20% sodium carbonate solution liberated an oil which was taken up in ether (60 ml. in all). The ethereal solution was dried (sodium sulfate) and saturated with hydrogen bromide gas at 0°. The gum which separated was dissolved in ethanol. Careful addition of anhydrous ether yielded the **benzoate dihydrobromide** (1.5 g.; 60%); which crystallized from ethanol–ether (2:1), m.p. 158–159°.

Anal. Calcd. for $C_{21}H_{23}N_3O_2Br_2$ (509.3): C, 49.52; H, 4.57; N,8.26; Br, 31.38. Found: C, 49.37; H, 4.66; N, 8.25; Br, 31.29.

The infrared spectrum of this compound (in Nujol) showed the C=O stretching frequency of the ester to be at 1740 cm.$^{-1}$.

Benzyloxyamine Hydrochloride.—A mixture of N-benzyloxyphthalimide, made by the method of McKay,[4] (77 g.; 0.3 mole), concentrated hydrochloric acid (77 ml.) and acetic acid (250 ml.) was heated under reflux for 0.25 hr., and then evaporated almost to dryness *in vacuo*. Sodium hydroxide solution was added until the solution was strongly basic and the base extracted with ether. The ether solution was dried (sodium sulfate) and then a stream of hydrogen chloride was led through it. The salt (33.8 g.; 71%) was obtained in colorless shining flakes, m.p. 232°. Lit. m.p. 230–235°[11]; 230–232°.[12]

N,N-Di[2-(2-pyridyl)ethyl]benzyloxyamine Dihydrobromide.—Redistilled 2-vinylpyridine (5.3 g.; 0.05 mole) and benzyloxyamine hydrochloride (4.0 g.; 0.025 mole) were heated in 50% aqueous acetic acid (12.5 ml.) at 100° for 0.25 hr. The solution was cooled to 0°, treated with sodium carbonate (9.6 g.; 0.91 mole), and the viscous oil which separated was extracted by ether (150 ml.). The ethereal solution was dried (sodium sulfate) and an ice-cold saturated ethanolic hydrogen bromide solution (50 ml.) was added. The salt, which separated as a gum, solidified upon standing (11.12 g.; 90%) m.p. 145–150° and was crystallized from methanol–ether (2:3) in colorless cubes m.p. 157–158°.

Anal. Calcd. for $C_{21}H_{25}N_3OBr_2$ (495.3): C, 50.80; H, 5.08; N, 8.49; Br, 32.30. Found: C, 50.83; H, 5.01; N, 8.52; Br, 32.33.

The hydrochloride or *p*-toluenesulfonate could not be obtained crystalline.

N,N-Di[2-(4-pyridyl)ethyl]benzyloxyamine Trihydrobromide.—This was prepared (83%), m.p. 169–172°, in a similar fashion from 4-vinylpyridine. It crystallized from methanol–ether (1:1) m.p. 180–180.5°.

Anal. Calcd. for $C_{21}H_{26}N_3OBr_3$ (576.3): C, 43.80; H, 4.56; N, 7.50; Br, 41.60. Found: C, 44.16; H, 4.73; N, 7.49; Br, 41.72.

The **tri-*p*-toluenesulfonate** could be prepared in 66% yield by the above procedure when the gum was treated with *p*-toluenesulfonic acid instead of hydrogen bromide. It crystallized from ethanol–ether (4:3), m.p. 149°.

Anal. Calcd. for $C_{42}H_{47}N_3S_3O_{10}$ (850.1): C, 59.33; H, 5.58; N, 4.94; S, 11.32. Found: C, 59.05; H, 5.85; N, 4.94; S, 11.14.

Hydrolysis of N,N-Di[2-(4-pyridyl)ethyl]benzyloxyamine Trihydrobromide.—A solution of the salt (1.0 g.; 0.0017 mole) in concentrated hydrobromic acid (10 ml. of 48%) and acetic acid (10 ml.) were heated under reflux for 40 min. Solvents were then removed *in vacuo* at 50°, and the residual yellow gum crystallized from ethanol (10 ml.), and anhydrous ether (5 ml.). The salt (0.82 g.; 98%) had m.p. 190–195°, undepressed when mixed with a sample of N,N-di[2-(4-pyridyl)ethyl]hydroxylamine trihydrobromide. Their infrared spectra (Nujol) were also identical. Addition of 20% sodium carbonate solution to this salt afforded the free base (m.p. 142–143°) which was identical to I (R = H).

Hydrolysis of N,N-[2-(2-Pyridyl)ethyl]benzyloxyamine Dihydrobromide.—A solution of the salt (4.0 g.; 0.0081 mole) in 48% hydrobromic acid (50 ml.) was boiled for 5 min. *only*. The solution was chilled, immediately to 0°, made alkaline with 10% sodium hydroxide solution, saturated with sodium sulfate, and the mixture extracted with ether (400 ml.). The ethereal solution was dried (sodium sulfate), the solvent removed, and the residual black gum triturated with acetone (2 ml.). The crystals (0.7 g.; 36%), which separated on standing overnight at 5°, had m.p. 104.5°. Recrystallization from acetone raised the m.p. to 105–107°,

(9) All melting points are uncorrected. Analyses were performed by Dr. Kurt Eder, Geneva, Switzerland, and Micro-Tech Laboratories, Skokie, Illinois.

(10) The spectrum was kindly determined by Dr. L. F. Johnson, Varian Associates, Palo Alto, California.

(11) R. Behrend and K. Leuchs, *Ann.*, **257**, 203 (1890).

(12) P. Mamalis, J. Green, and D. McHale, *J. Chem. Soc.*, 229 (1960), obtained this salt in 90% yield from the hydrolysis of benzyl benzohydroxamate with 6% ethanolic hydrogen chloride.

undepressed on admixture of a sample of N,N-di[2(2-pyridyl)ethyl]hydroxylamine.

N-[2-(2-Pyridyl)ethyl]phthalhydrazide.—A solution of 2-vinylpyridine (7.8 g.; 0.074 mole) and phthalhydrazide (6.0 g.; 0.037 mole) in 75% aqueous acetic acid (12 ml.) was heated at 100° for 0.5 hr. Dilution of the cold reaction mixture with 150 ml. of water afforded the product (7.75 g.; 78% based on phthalhydrazide) which crystallized from acetone as colorless needles, m.p. 156–157°.

Anal. Calcd. for $C_{15}H_{13}N_3O_2$ (267.3): C, 67.41; H, 4.87; N, 15.73. Found: C, 67.64; H, 5.06; N, 15.69.

When equimolar proportions of reactants were used, the product was isolated in 31% yield only.

The **hydrobromide** (prepared with hydrogen bromide gas in ethanol) crystallized from methanol–ether (3:5), m.p. 223–224°.

Anal. Calcd. for $C_{15}H_{14}N_3O_2Br$ (347.7): N, 12.09. Found: N, 12.06.

N-[2-(4-Pyridyl)ethyl]phthalhydrazide was prepared in 93% yield from 4-vinylpyridine (0.05 mole) and phthalhydrazide (0.025 mole). It crystallized from ethanol in colorless needles, m.p. 216–217°.

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.87; N, 15.73; Found: C, 67.56; H, 5.08; N, 15.73.

The **hydrobromide** crystallized from methanol–ether (5:2), m.p. 250°.

Anal. Calcd. for $C_{15}H_{14}N_3O_2Br$: N, 12.09. Found: N, 12.01.

Acknowledgment.—We would like to acknowledge the generous support for this work by a Grant (CY-4661) from the National Cancer Institute of the National Institute of Health, United States Public Health Service.

Photoisomerization of 2-(2,4-Dinitrobenzyl)pyridine and 2-(2-Nitro-4-cyanobenzyl)pyridine

JOHN A. SOUSA AND JULIUS WEINSTEIN

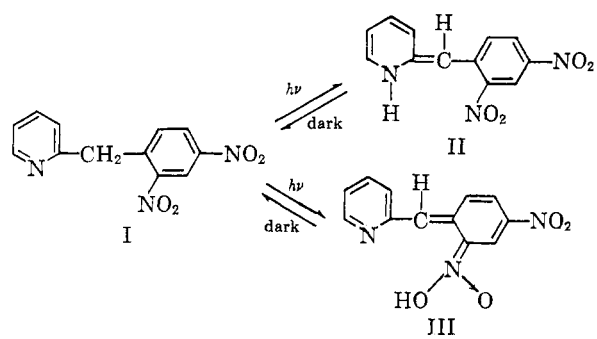
Pioneering Research Division, Quartermaster Research and Engineering Center, U.S. Army, Natick, Massachusetts

Received April 4, 1962

Kinetic data at several temperatures are reported for the dark fading reactions of the colored isomers formed by ultraviolet irradiation of solutions of 2-(2,4-dinitrobenzyl)pyridine and 2-(2-nitro-4-cyanobenzyl)pyridine. First-order reactions are observed in a variety of solvents. In these reactions, the rate of fading is considerably faster in nonpolar solvents. Activation energies and entropies of activation are reported for the dinitro compound in ethanol and ether and for the cyano compound in ethanol. The effect of solvent on the position and molar absorptivity of the ultraviolet absorption band of unirradiated dinitro compound is investigated. It is found that 2-(2-nitro-4-aminobenzyl)pyridine and 2,4-dinitrobenzyl alcohol in ethanol solution are photochromic. The relationship of structure and photochromism of compounds of the type studied is discussed.

The photochromic change from a pale yellow to a deep blue color observed when crystals of 2-(2,4-dinitrobenzyl)pyridine are exposed to light was first reported by Tschitschibabin and co-workers.[1] They also observed that the crystals faded slowly to yellow when they were stored in the dark. Recently, Hardwick, Mosher, and Passailaigue[2] reported the reversible photochromism of cooled solutions of the compound in a variety of solvents. They also reported rate measurements at several temperatures of the dark fading reaction in isopropyl alcohol solution and calculated an activation energy. The authors, however, stated that even though their measurements were crude, they found an unexplainably large spread in the data.

The mechanism of the color change has not been established unequivocally. Earlier workers[1,3] ascribed the change to the tautomeric shift I $\rightleftharpoons$ II. Although Hardwick and co-workers[2] interpreted data on the basis of this shift, they suggested the structural change I $\rightleftharpoons$ III as an alternative possibility. Support for the latter was provided recently by the observations of Mosher and co-workers[4] that 4-(2,4-dinitrobenzyl)pyridine in solution is photochromic.



Our study was undertaken in order to help elucidate the mechanism of the color change by investigating the relationship of structure to photochromism and to the kinetic and thermodynamic properties of the dark reaction.

(1) A. E. Tschitschibabin, B. M. Kuindshsi, and S. W. Benewolenskaja, *Ber.*, **58**, 1580 (1925).

(2) R. Hardwick, H. S. Mosher, and P. Passailaigue, *Trans. Faraday Soc.*, **56**, 44 (1960).

(3) W. C. Clark and G. F. Lothian, *ibid.*, **54**, 1790 (1958).

(4) H. S. Mosher, C. Souers, and R. Hardwick, *J. Chem. Phys.*, **32**, 1888 (1960).