the reaction, stirring was continued for an additional 30 min. The reaction mixture was diluted with ice water until the formed nitrile oxide started to crystallize, kept for several hours at 0°, filtered, and the product was washed thoroughly with water. After one recrystallization from the solvent indicated in Table I, all nitrile oxides were obtained analytically pure.

Registry No.—2, 15138-43-9; **5**, 15138-44-0; **6**, 15138-31-5; **7**, 15180-26-4; **8**, 15138-32-6; **9**, 15138-33-7; **10**, 15138-34-8; **11**, 15138-35-9; **12**, 13012-32-3; **13**, 15138-37-1; **14**, 15138-38-2; 2,4,6-trimethylisophthaldialdehyde, 15138-39-3; 2,4,6-trimethylisophthaldialdoxime, 15138-40-6; 2-dimethylamino-4,6-dichloropyrimidine-5-aldehyde, 15138-41-7; 2-dimethylamino-4,6-dichloropyrimidine-5-aldoxime, 15138-42-8.

Acknowledgment.—The work reported in this publication was in part supported by the Public Health Service Research Grant IROI GM 12977-01 of the National Institutes of Health, Bethesda, Md.

Unprecedented Orientation in the Nitration of Certain 3-Hydroxypyridines

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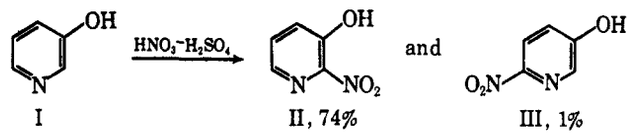
Received July 26, 1967

The chemistry of pyridines and orientation effects in substitution reactions of pyridines have been given considerable attention recently,[2,3] including review with special emphasis on methods of obtaining 4-substituted pyridines.[4] Electrophilic nitration at the 4 position of pyridines has not been observed except in the well-known cases of certain pyridine 1-oxides. However, there has appeared a singular claim to the preparation of a trinitropyridinol which was probably, but not proven to be, 3-hydroxy-2,4,6-trinitropyridine.[5] This author now wishes to present the first authentic examples of electrophilic nitration at the 4 position of pyridines.

Discussion

The general method of Wulff[6] for the preparation of 3-hydroxy-2-nitropyridine was reexamined in detail. The procedure given in the Experimental Section represented the optimal conditions with respect to time and temperature of nitration, concentration, and amount of nitrating agent, and work-up and purification procedures. This procedure gave a 74% yield of 3-hydroxy-2-nitropyridine (II) as opposed to Wulff's 50 to 57% yields.[6]



I II, 74% III, 1%

When ether was used as the final extraction solvent, fractional sublimation of the product gave a 1% yield of 5-hydroxy-2-nitropyridine (III) in addition to II. Although, III was not detected previously, it is possible that it is the same compound as that of melting point 210–211° obtained by a different method but not completely identified.[7] In this regard also, there did appear one claim to the detection of 6-substitution in the nitration of 3-ethoxypyridine.[8] This was presumably substantiated by reduction of the crude reaction mixture and paper chromatographic comparison with several, but not all, other amino-3-hydroxypyridines. Furthermore, no authentic sample of 2-amino-5-hydroxypyridine was reported in that work.[8]

We have repeated the further nitration of II according to Czuba and Plażek[5] in order to obtain 2,6-dinitro-3-hydroxypyridine. The assigned structure was reconfirmed by nmr spectroscopy (*vide infra*). This example plus the reported isolation of only 2-bromo-3-ethoxy-6-nitropyridine from the nitration of 2-bromo-3-ethoxypyridine[9] have led to the conclusion that for 3-hydroxypyridines and 3-hydroxypyridine ethers, "Nitration at C-4 is never observed, even when C-2 is blocked..."[2]

We now report that both the 4- and 6-nitro derivatives in a 4 to 1 ratio were obtained by nitration of 3-hydroxypyridine substituted in the 2 position with either methyl or chloro groups. Although, the total yield in each case was not large, the ratios should be significant. These were considered to be minimum ratios since the 6-nitro derivatives were higher melting and less soluble in both cases. On the other hand, only the 2-nitro derivatives were isolated from nitration of 3-hydroxy-4-, 5-, and 6-methylpyridines where C-2 was unsubstituted. Although minor isomers were not sought after in the latter cases, the major products were obtained in 50 to 75% of theoretical yields.

The unprecedented 4-nitration, with lesser 6-nitration, in the cases of 3-hydroxy-2-methyl- and 2-chloropyridines can be rationalized by currently accepted mechanisms (see ref 2, for discussions). Both mechanisms involving attack of nitronium ion on either the neutral hydroxypyridine or the hydroxypyridinium ion are consistent with the results and cannot be differentiated with the available information.

Nitrations rarely occur yielding single products when more than one are possible. Consequently, the formation of isomer III was not unexpected, and the formation of other mono- and dinitro derivatives was indeed anticipated. We cannot account for the absences of 4-nitro-3-pyridinols in the cases where C-2 was unsubstituted.

Structure Proofs.—The proofs of structure rest mainly on nmr and uv spectral data which are particu-

(1) Address correspondence to the author at the Eastman Kodak Co., Rochester, N. Y. 14650.

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TABLE I

NUCLEAR MAGNETIC RESONANCE (60 Mc) AND ULTRAVIOLET SPECTRA OF 3-HYDROXYPYRIDINES

3-Hydroxypyridine substituent	Chemical shift,[a] ppm					Coupling constant, Hz					Uv absorption[b]	
	2-H	4-H	5-H	6-H	Me	J_{24}	J_{25}	J_{45}	J_{46}	J_{56}	λ_{max}, mμ	ϵ_{max} (× 1000)
2-Nitro[c,d]		7.76	7.76	8.27				0	2.8	2.8	325	3.1
4-Methyl, 2-nitro[c,i]			7.57	8.08	2.47[e]					4.4	332	5.5
5-Methyl, 2-nitro[f]		7.47		7.88	2.41[e]				1.8		329	4.9
6-Methyl, 2-nitro[f,i]		7.44	7.57		2.49[e]			8.5			338	3.9
2-Methyl, 4-nitro[f]			7.67[e]	8.08	2.53[e]					5.5	363[h]	2.8
2-Chloro, 4-nitro[c]			7.95	8.16						5.5	344[h]	2.9
6-Nitro[c,g]	8.40	7.83	8.29		2.38	2.5	<1	8.8			300	8.0
2-Methyl, 6-nitro[f]		7.48	8.08		2.44[e]			8.7			305	8.8
2-Chloro, 6-nitro[f]		7.58	8.20					8.7			305	8.8
2,6-Dinitro[f]		7.95	8.51					8.6				

[a] Internal TMS = 0. [b] Methanol solvent. [c] Nmr of $CDCl_3$ solution. [d] 4-H and 5-H were equivalent-degenerate. [e] Coupled to ring protons with less than 1 Hz. [f] Nmr of solution in $CDCl_3$–DMSO-d_6 mixture. [g] Nmr of O-acetyl derivative; Uv of free OH compound. [h] Very broad peaks. [i] Reference 5.

larly pertinent to the compounds described here. These data are compiled in Table I.

The nmr parameters for pyridines have been reviewed.[10] The parameters of interest for the 2,3-disubstituted pyridines are the previously observed coupling constants $J_{4,5}$ = 7.2 to 8.2, $J_{4,6}$ = 1.4 to 2.0, and $J_{5,6}$ = 4.5 to 5.5 Hz. The magnitudes of these coupling constants are sufficiently different to allow positive assignments of structure when three substituents are present in the pyridine ring. The coupling constants for the variously substituted pyridines reported here were quite close to the established parameters and remarkably constant within themselves. Regarding the compounds of Table I, there can be no doubt that the assignments of $J_{4,5}$ = 8.5 to 8.8 and $J_{5,6}$ = 4.4 to 5.5 Hz were correct.

An exceptional spectrum was exhibited by the parent 3-hydroxy-2-nitropyridine (II). Apparently, the protons at C-4 and C-5 were so close in chemical shift that they degenerated to a single peak. This caused a zero Hz coupling for $J_{4,5}$ but yielded an equivalent coupling of 2.8 Hz for $J_{4,6}$ and $J_{5,6}$. The acetylated derivative of II did have the expected ABX pattern, although it was not submitted to detailed analysis.

5-Hydroxy-2-nitropyridine (III) was converted to its acetate ester for better solubility. A first-order analysis of the 100-Mc nmr spectrum of this derivative yielded coupling constants of $J_{4,5}$ = 8.8, $J_{2,4}$ = 2.5, and $J_{2,5}$ = <1 Hz. These values were very close to the established parameters,[10] and no other pattern of two substituents in the pyridine ring could have given them. The possibility of the two substituents being interchanged as in 2-hydroxy-5-nitropyridine was eliminated by comparison with an authentic sample.[11]

It is known that chemical shifts of the ring protons of certain pyridines are strongly dependent upon concentration and solvent.[12] Since no detailed study of these effects was attempted here, certain of the assignments in Table I must be considered to be arbitrary. For instance, in all cases where the pyridine ring had only two protons attached, the positional assignments were made so as to give the best internal consistency with regard to chemical shifts.

Further confirmation of the nmr data was given by the uv spectra tabulated in Table I. In each series, *i.e.*, 3-hydroxy-2-, 4-, and 6-nitropyridines, the λ_{max} and ϵ_{max} values fell within narrow limits. Furthermore, these series were significantly separated from each other.

It was also significant to the structural correlations that the melting points of 3-hydroxy-2-chloro- and 2-methyl-4-nitropyridines were considerably (~100°) below those of the corresponding 6-nitro isomers. This was an obvious effect of intramolecular hydrogen bonding in the 4-nitro compounds as opposed to intermolecular hydrogen bonding of hydroxyl and nitro substituents in the 6-nitro isomers.

Experimental Section

Nmr spectra were obtained on the Varian A60 and HA100 spectrometers. Uv spectra were obtained on the Beckman DK-2A spectrophotometer. Melting points were observed on a Fisher-Johns melting point apparatus and were not corrected. Microanalyses were done by or under the supervision of Mrs. L. M. Moore of these laboratories.

3-Hydroxy-2-nitropyridine (II).[6]—With ice water cooling and efficient stirring, 96 g (1.0 mole) of 3-hydroxypyridine was added gradually to 650 ml of concentrated sulfuric acid. The addition took 20 min and the internal temperature was not allowed to exceed 30°. A cold mixture of 48 ml of nitric acid (sp gr 1.50) and 92 ml of concentrated sulfuric acid was added gradually (3–5 hr) without external cooling at a rate which maintained the temperature at 40 to 45°. The mixture was allowed to stand overnight (about 16 hr), poured into 2 l. of ice and water, neutralized to $NaHSO_4$ end point (final pH 1 to 4), and extracted three times (or continuously) with ether or methylene chloride. The extract was dried over $MgSO_4$, filtered, and the solvent removed at reduced pressure leaving 105 g (75% of theoretical) of yellow crystalline product, mp 62–65° (98% purity). Sublimation at 50° (<1 mm) gave 98% recovery of yellow crystalline product, mp 67–69°.

Anal. Calcd for $C_5H_4N_2O_3$: C, 42.86; H, 2.88; N, 20.00. Found: C, 42.87; H, 3.01; N, 19.94.

3-Acetoxy-2-nitropyridine.—To a solution of 5.60 g (0.04 mole) of 3-hydroxy-2-nitropyridine and 3.16 g (0.04 mole) of pyridine in 100 ml of benzene was added dropwise 3.14 g (0.04 mole) of acetyl chloride. The mixture ws stirred an additional hour, filtered, and distilled, yielding 5.39 g (74% of theoretical) of pure product boiling at 101–107° (0.03–0.04 mm). This sample later crystallized, mp 50–51°.

Anal. Calcd for $C_7H_6N_2O_4$: N, 15.45. Found: N, 15.67.

5-Hydroxy-2-nitropyridine (III).—The nitration of 336 g of 3-hydroxypyridine as above and using ether extraction and subsequent sublimation gave 353 g of sublimed II and 6.3 g of

(10) R. F. M. White in "Physical Methods in Heterocyclic Chemistry," Vol. II, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963; J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. II, Pergamon Press Inc., New York, N. Y., 1966.

(11) This well-known pyridine derivative was available from Aldrich Chemical Co., Inc. (H-4880-8).

(12) T. Schaefer and W. G. Schneider, *J. Chem. Phys.*, **32**, 1224 (1960).

dirty looking residue. Chromatography of this residue (5 g) on 150 g of silicic acid using 1:1 benzene–ether yielded 3.8 g of crude product eluting between 1400 and 2500 ml. Sublimation at 140° (<1 mm) yielded 3.30 g (0.84% of theoretical based on starting pyridinol) of colorless crystalline product, mp 213.5–215°.

Anal. Calcd for $C_5H_4O_3$: C, 42.86; H, 2.88; N, 20.00. Found: C, 42.8; H, 2.7; N, 19.9.

5-Acetoxy-2-nitropyridine.—To a mixture of 2.00 g (0.014 mole) of III, 1.51 g (0.014 mole) of sodium carbonate and 75 ml of acetone was added 1.12 g (0.014 mole) of acetyl chloride. The mixture was heated at reflux for 11 hr and filtered and the solvent removed at reduced pressure leaving 2.8 g (100% of theoretical) of crude product, mp 100–102°. Recrystallization from a mixture of 50 ml of methanol and 50 ml of water gave the product as colorless needles, mp 111–112°.

Anal. Calcd for $C_7H_6N_2O_4$: N, 15.45. Found: N, 15.87.

3-Hydroxy-4- and -6-Nitro-2-methylpyridine (IV, V).—While maintaining a temperature of 0–5° with external ice cooling, 10.9 g (0.01 mole) of 3-hydroxy-2-methylpyridine[13] was added gradually to 70 ml of concentrated sulfuric acid; then a mixture of 7 g of nitric acid (sp gr 1.50) and 16.5 g of concentrated sulfuric acid was added over 2 hr. The resulting mixture was poured on to ice. Addition of a few milliliters of ammonium hydroxide caused precipitation of 1.55 g of crude V, mp 247–253°. Recrystallization from methanol–water gave 1.10 g (7% of theoretical) of pure V, mp 263–264°. Addition of more ammonium hydroxide to the above solution until the pH reached 3 to 4 caused precipitation of 5.00 g of crude IV, mp 183–185°. Recrystallization from methanol–water gave 3.83 g (25% of theoretical) of pure IV, mp 183–185°. Extraction of the above solution with ether gave 1.0 g of crude starting material, mp 170–173°.

Anal. Calcd for $C_6H_6N_2O_3$: C, 46.8; H, 3.9; N, 18.2. Found for V: C, 47.1; H, 4.0; N, 18.0. Found for IV: C, 46.9; H, 3.6; N, 18.1.

(13) A. P. Dunlop, U. S. Patent 2,636,882 (1953).

3-Hydroxy-4- and -6-Nitro-2-chloropyridine (VI, VII).—To 50 ml of concentrated sulfuric acid at 0° was added gradually 8.0 g (0.07 mole) of 2-chloro-3-pyridinol.[14] Then a cold mixture of 7 g of nitric acid (sp gr 1.50) and 17 g of concentrated sulfuric acid was added at a rate which maintained a temperature of 30–35°. The mixture was stirred an additional hour, poured onto ice, and treated with 50% aqueous sodium hydroxide until no more product precipitated. The product was collected by filtration and sublimed at 55° (<1 mm) yielding 2.10 g (16.5% of theoretical) of VI as the sublimate, mp 70–71°. The residue was 0.50 g (4% of theoretical) of VII, mp 197°.

Anal. Calcd for $C_5H_3ClN_2O_3$: Cl, 20.3; N, 16.1. Found for VI: Cl, 19.4; N, 15.7. Found for VII: Cl, 19.4; N, 15.6.

3-Hydroxy-5-methyl-2-nitropyridine.—In a similar manner, 3-hydroxy-5-methylpyridine[15] was nitrated and gave 76% of theoretical yield of 3-hydroxy-5-methyl-2-nitropyridine, mp 133–135°.

Anal. Calcd for $C_6H_6N_2O_3$: N, 18.2. Found: N, 18.0.

Registry No.—II, 15128-82-2; III, 15206-26-5; IV, 15128-83-3; V, 15128-84-4; VI, 15128-85-5; VII, 15206-27-6; 3-acetoxy-2-nitropyridine, 15128-86-6; 5-acetoxy-2-nitropyridine, 15128-87-7; 3-hydroxy-5-methyl-2-nitropyridine, 15128-88-8; 3-hydroxy-4-methyl-2-nitropyridine, 15128-89-9; 3-hydroxy-6-methyl-2-nitropyridine, 15128-90-2; 3-hydroxy-2,6-dinitropyridine, 15128-91-3.

Acknowledgment.—The author wishes to express his gratitude to Mrs. Tan-Wan Lin for technical assistance and to Drs. L. P. Lindeman and J. Q. Adams of Chevron Research Corporation for obtaining and discussing the nmr spectra.

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