Catalytic Reduction of 4-Nitropyridine 1-Oxide

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We had occasion to prepare 4-aminopyridine 1-oxide. A search of the literature revealed some contradictory statements regarding the catalytic reduction of 4-nitropyridine 1-oxide. Ochiai (1) states that "upon catalytic reduction with palladium on carbon, in neutral medium, both 4-nitropyridine as well as quinoline 1-oxides are reduced to the 4-amino 1-oxides and no further." On the other hand, Katritzky and Monro (2), using 5% palladium/carbon, formed 4-aminopyridine in 90% yield. Other workers obtained 45% (3) and 64% (7) yields of 4-aminopyridine 1-oxide under similar conditions, while Berson and Cohen (4) quantitatively reduced 4-ethyl-2-methyl-4-nitropyridine 1-oxide to the corresponding 4-amino 1-oxide.

In our hands, the reduction of 4-nitropyridine 1-oxide with palladium on carbon in ethanol afforded 4-aminopyridine 1-oxide (**2**) in 48% yield along with, at least, six other compounds (see Table I). In order to simplify the isolation of these products, the reaction mixture was acetylated and the excess acetic anhydride was hydrolyzed.

Attempted crystallization of the reaction products afforded a small amount of colorless crystals (compound 3a). The remaining material was subjected to chromatography. All but two of the compounds thus obtained are known pyridine derivatives and were identified as: 4,4′-azopyridine (**4**), 4,4′-hydrazopyridine (**5**), 4,4′-azopyridine 1-oxide (**6**), 4-acetamidopyridine (**7**), and its 1-oxide (**8**).

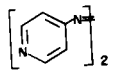
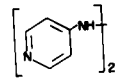
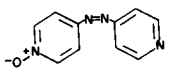
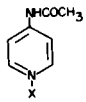
The mass spectrum of compound **3a** indicates a molecular weight of 110, while the ^{1}H nmr spectrum shows the presence of an A_2B_2 proton system. Acetylation of this compound afforded a monoacetyl derivative, $C_7H_8N_2O_2$ (**3b**), whose ^{1}H nmr spectrum still showed the presence of an A_2B_2 pattern as well as a three-proton singlet due to an acetyl methyl group. From these data, we conclude that compound **3a** is 4-hydroxylamino pyridine, and **3b** is its monoacetylated derivative.

In addition to these compounds, a material, $C_9H_{11}N_3O_3$ (**9**) was isolated in 1.4% yield. Neither the ^{1}H nmr spectrum nor the mass spectral fragmentations of this compound (see Experimental) aided in its structure identification. We can only surmise that this compound arises from an impurity in the 4-nitropyridine 1-oxide.

Compounds **2**, and **4** thru **8** have been prepared from 4-nitropyridine 1-oxide by use of a variety of chemical reducing agents (5,9). While the formation of most of these compounds (10) *via* hydrogenation in the presence of palladium has not been observed before, it is not unexpected.

Table I

Percentage Yields of Various Reduction Products of 4-Nitropyridine 1-Oxide

Compound (Number)		Percent Yield
	**2**	48
	**3a**	4.6
	**4**	13
	**5**	11
	**6**	2.2
	**7** X = nil	1.4
	8 X = O	0.7
$C_9H_{11}N_3O_3$	**9**	1.4

EXPERIMENTAL (6)

Hydrogenation of 4-Nitropyridine 1-Oxide.

A mixture of 5.0 g. (0.035 mole) of 4-nitropyridine 1-oxide, 200 ml. of ethanol and 10% palladium/carbon was shaken 20 hours with hydrogen (initial pressure, 41 psi) in a Paar apparatus. The catalyst was removed by filtration through a pad of Celite. The filtrate was stripped of solvent to give a reddish-brown thick oil which was dissolved in 20 ml. of methyl ethyl ketone and 5 ml. of acetic anhydride and warmed on the steam bath for 1 hour.

After 5 minutes a yellow solid began to deposit. The mixture was heated 10 minutes with 3 ml. of water and the resultant solution was treated with charcoal, filtered and stripped of solvents. Attempted crystallization from methyl ethyl ketone gave only a small amount (0.18 g.) of colorless crystals (**3a**) m.p. 242-250°.

The methyl ethyl ketone solution was treated with solid sodium carbonate to remove residual acetic acid, filtered and stripped of solvent to give a semi-solid red residue composed of 6 materials (tlc, alumina/ethyl acetate). These were separated *via* chromatography on 200 g. of grade 3 neutral alumina. Elution with ethyl acetate gave first an orange solid (**4**), 0.41 g., a pale yellow solid (**7**), 0.05 g., then a dark orange solid (**6**) (contaminated with **7**), 0.10 g., 10% absolute ethanol/ethyl acetate eluted a 3-component mixture, 0.04 g. not investigated; 25% absolute ethanol/ethyl acetate gave a colorless solid (**9**), 0.12 g., 50% absolute ethanol/ethyl acetate eluted an orange-red solid composed of 3 materials, (**4**, **5** and **8**) 0.4 g. followed by a colorless solid **2**, 1.9 g.

Compound **2**, 4-aminopyridine-1-oxide, was hygroscopic, had a mass spectral: mw 110, and gave a hydrochloride salt, m.p. 180° (absolute ethanol) (m.p. 181-183° (lit) (7)).

The orange-red solid mixture was triturated with ether and benzene which removed some 4,4′-azopyridine (**4**). When it was heated with 4 ml. of 50% absolute ethanol/ethyl acetate a colorless solid (35 mg.) did not dissolve, had m.p. 261-262°, and an ir spectrum that is the same as that of 4-acetamidopyridine 1-oxide (**8**) (m.p. 260-261° (lit) (8)). Extraction with ethyl acetate of the material in the mother liquor gave a light orange material (0.25 g.) that turned darker on standing. Mass spectrum: mw 186; ^{1}H nmr (deuteriochloroform): A_2B_2 pattern at δ 6.56 and 8.26 and a broad peak at 4.5 ppm, area ratio *ca.* 1:1:1 and is therefore 4,4′-hydrazopyridine (**5**).

Compound **6**, was crystallized from acetone to give a brick-red powder, m.p. 157-158° (m.p. 160-161° (lit) (9)). Mass spectrum: mw 200; ir (Nujol): very similar to that of 4,4′-azopyridine 1,1′-dioxide.

Compound **7**, 4-acetamidopyridine, after trituration with benzene had m.p. 145.5-147° which was not depressed by admixture with a sample prepared by acylation of 4-aminopyridine. The ir spectra of the two compounds were identical.

Compound **4**, 4,4′-azopyridine, crystallized from water as fine orange needles, was dried *in vacuo* at room temperature, (m.p. 105.5-107° (lit) (10)); mass spectrum: mw 184; ^{1}H nmr (deuteriochloroform): A_2B_2 pattern at δ 7.78 and 8.96 ppm, area ratio 1:1.

Compound **3**, 4-hydroxylaminopyridine, crystallized from aqueous 80% ethanol as a fine powder, m.p. 250-251° dec.; mass spectrum: mw 110; ^{1}H nmr (TFAA): A_2B_2 pattern at δ 8.15 and 6.95 ppm, area ratio 1:1. Since an adequate elemental analysis could not be obtained, the material (*ca.* 30 mg.) was treated with acetic anhydride on the steam bath for 1½ hours. Water was then added and the solution was evaporated to dryness under reduced pressure. The residue was dissolved in water, made basic to *p*H 9 and evaporated. Exhaustive extraction of the residue with chloroform gave *O*-acetyl-4-hydroxylaminopyridine (**3b**) which was twice crystallized by dissolution in a few drops of ethanol and addition of *ca.* 0.5 ml. of hot ethyl acetate to give fine colorless needles, m.p. 265-267° dec.; mass spectrum: mw 152.

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.00; H, 5.26; N, 18.21.

Solid **9** did not melt below 300°, was insoluble in chloroform, and crystallized as glistening platelets from ethanol; mass spectrum: mw 209 (210 = 20% of 209); ^{1}H nmr (TFAA): δ 9.35 (broad), 9.18 (broad), 2.53 (s) ppm, area ratio *ca.* 1:1:3, DMSO-d_6: δ 9.18 (broad), 8.72 (s), 2.13 (s) ppm, area ratio *ca.* 1:1:3; ir (Nujol): 3280 (m), 3210 (w), 1650 (m), 1635 (m), 1565 (m), 1510 (s) cm^{-1}.

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.81; H, 5.22; N, 20.30.

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(6) ^{1}H Nmr Spectra were obtained with a Hitachi Perkin-Elmer R-20B Nmr spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector. The ionizing voltage employed was 70 eV. Elemental analyses were done by the Analytical Services Laboratory, of The University of Alabama, Department of Chemistry. Melting points are uncorrected.

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(10) Catalytic reduction of 4-nitropyridine 1-oxide with "Uruchibara Ni" has been reported to form compounds **4** and **5** as well as 4,4′-azopyridine 1,1′-dioxide (11).

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