Reactions of Substituted Pyridines and Their N-oxides with Ethanolic Sodium Hydroxide and Various Alkoxides (1,2)

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2-Benzoylpyridine 1-oxide with ethanolic sodium hydroxide yielded acyl nucleophilic displacement products and a redox product, 2-(α-hydroxybenzyl)pyridine. 3-Benzoylpyridine 1-oxide under the same conditions yielded only a reduction product, 3-(α-hydroxybenzyl)pyridine 1-oxide, whereas 4-benzoylpyridine 1-oxide yielded only a redox product, 4-(α-hydroxybenzyl)pyridine. The redox reaction which is promoted by base occurs with an α-hydroxybenzylpyridine 1-oxide which results from a carbonyl reduction of the starting material. The benzoylpyridine 1-oxides reacted qualitatively the same with sodium ethoxide or isopropoxide as they did with ethanolic sodium hydroxide, but they reacted differently with potassium t-butoxide or aluminum isopropoxide. The cyano- and benzenesulfonyl-pyridine 1-oxides reacted with ethanolic sodium hydroxide to yield pyridinecarboxylic acids and 1-hydroxypyridones, respectively.

During a study of base-catalyzed cyclodehydrations of 2-nitro-2'-methylsubstituted biphenyls (1) in methanolic sodium hydroxide we observed that the cyclization products, 6-substituted phenanthridine 5-oxides (2), reacted with hydroxide ion by attack on the aromatic nucleus (path *a*) or by attack on the side chain (path *b*) (4). When R was cyano or benzenesulfonyl the product was

R = CN, C₆H₅SO₂ (path *a*)
R = C₆H₅CO (path *b*)
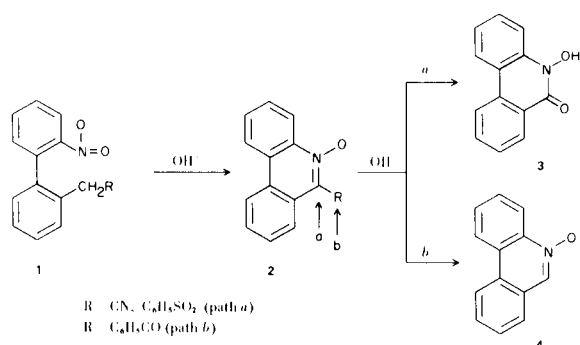
N-hydroxyphenanthridinone (3) from path *a*, whereas when R was benzoyl the product was phenanthridine 5-oxide (4) from path *b*. 6-Cyanophenanthridine under the conditions which converted 6-cyanophenanthridine 5-oxide to 3, yielded 6-carboxyphenanthridine by path *b* (4).

These results were the impetus for the present report in which qualitative comparisons are made of the reactivities

of all of the isomeric cyanopyridines and their 1-oxides with ethanolic sodium hydroxide. The same kind of study was made with all of the benzenesulfonylpyridines and their 1-oxides and with all of the benzoylpyridines and their 1-oxides. Benzoylpyridine 1-oxides, compounds with the most varied behavior with ethanolic sodium hydroxide, were also studied with various alkoxides. In Table I the results of the reactions of the 18 aforementioned compounds with 0.67 N ethanolic sodium hydroxide are tabulated.

All of the cyanopyridines and their 1-oxides yielded normal hydrolysis products as do most other cyanoazaaromatic N-oxides (5). The exceptions which react by path *a* include four N-oxides, each of which has one or two benzo groups: 6-cyanophenanthridine 5-oxide (4), 2-cyanoquinoxalinone 1-oxide (6,7), 2-cyanobenzimidazole 3-oxide (8) and 1-cyanoisoquinoline 2-oxide (9) which gave a product from path *b* (36%) as well as a product from path *a* (30%). Benzocyanoazaaromatic N-oxides probably react by path *a* because of the large π system which is present for delocalizing the negative charge of the addition product of the cyanoazaaromatic N-oxide and the nucleophile.

The benzenesulfonylpyridines and their 1-oxides reacted by path *a* except for 3-benzenesulfonylpyridine which did not react. Reaction by path *a* is in agreement with the low susceptibility of sulfur of the sulfonyl group for nucleophilic attack (10). The lower reactivity of 3-benzenesulfonylpyridine in comparison with its 1-oxide

TABLE I

Reactions of Substituted Pyridines and their 1-Oxides with 0.67 N
Ethanolic Sodium Hydroxide Under Reflux (a)

Compound	Type Reaction			Product (% Yield)
	Path a (b)	Path b (c)	Redn (d)	
2-Cyanopyridine		+		Picolinic acid (64%)
3-Cyanopyridine		+		Nicotinic acid (95%)
4-Cyanopyridine		+		Isonicotinic acid (93%)
2-Cyanopyridine 1-oxide		+		Picolinic acid 1-oxide (81%)
3-Cyanopyridine 1-oxide		+		Nicotinic acid 1-oxide (67%)
4-Cyanopyridine 1-oxide		+		Isonicotinic acid 1-oxide (95%)
2-Benzenesulfonylpyridine	+			Benzenesulfinic acid (64%)
3-Benzenesulfonylpyridine				63% recovery
4-Benzenesulfonylpyridine	+			Benzenesulfinic acid (81%)
2-Benzenesulfonylpyridine 1-oxide	+			Benzenesulfinic acid (88%)
3-Benzenesulfonylpyridine 1-oxide	+			3-Ethoxypyridine (71%)
4-Benzenesulfonylpyridine 1-oxide	+			4-Ethoxypyridine (65%)
2-Benzoylpyridine			+	2-(α-Hydroxybenzyl)pyridine (50%)
3-Benzoylpyridine			+	3-(α-Hydroxybenzyl)pyridine (95%)
4-Benzoylpyridine			+	4-(α-Hydroxybenzyl)pyridine (64%)
2-Benzoylpyridine 1-oxide	+			Benzoic acid (48%)
3-Benzoylpyridine 1-oxide				77% recovery
4-Benzoylpyridine 1-oxide			+	4-(α-Hydroxybenzyl)pyridine (51%)

(a) Reflux time usually 6-8 hours but varied from 2-31 hours. (b) Nucleophilic attack on the ring. (c) Nucleophilic attack on the side chain. (d) Reduction.

conforms to the larger electron-withdrawing effect of the N-oxide group in comparison with the ring nitrogen without oxygen.

Each of the benzoylpyridine 1-oxides reacted in one or two of three different ways with various metallic alkoxides:
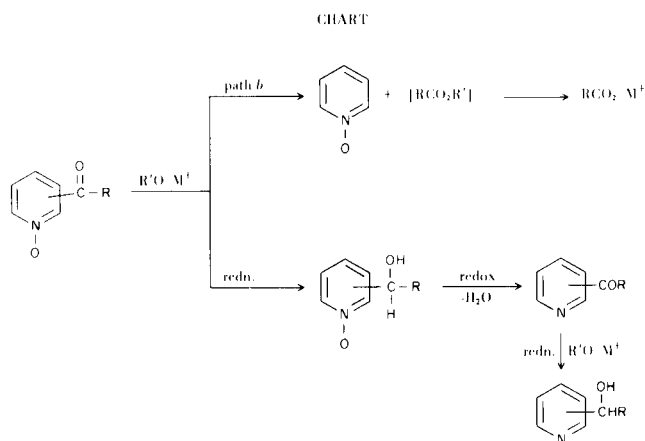
CHART

1, path b; 2, reduction of carbonyl group to an alcohol; 3, base-promoted conversion of alcohol produced by reaction 2 to a ketopyridine (redox reaction) which was reduced to a pyridyl carbinol (see Chart).

For a summary of the reactions of benzoylpyridines and their 1-oxides with ethanolic sodium hydroxide and various alkoxides see Table II. These results indicate the tendency for displacement (path b) is enhanced by (1) the presence of the N-oxide function, (2) the location of the benzoyl group in the 2 position, (3) the use of a nucleophile which cannot readily take part in a Meerwein-Ponndorf-Verley (MPV) reduction of a carbonyl group.

Only 2-benzoylpyridine 1-oxide reacted by path b with ethanolic sodium hydroxide, methanolic sodium hydroxide, sodium ethoxide or sodium isopropoxide. This is the basis for the first two generalizations. The lack of reaction by path b of the 3- and 4-benzoylpyridine 1-oxides is attributed to the smaller electron-withdrawing influence of the N-oxide on each of the 3- and 4-positions than on the 2-position.

TABLE II

Reactions of Benzoylpyridines and Benzoylpyridine 1-Oxides with Alkoxides

	Ethanolic Sodium Hydroxide	Sodium Ethoxide-Ethanol	Sodium Isopropoxide-2-Propanol	Aluminum Isopropoxide-2-Propanol	Methanolic Sodium Hydroxide	Potassium t-Butoxide-2-Methyl-2-propanol
2-Benzoylpyridine 1-oxide	Disp (48%) (a)	Disp (72%), Redox (8%) (c)	Disp (31%), Redox (44%)	Redn (74%) (b)	Disp (90%)	Disp (64%)
3-Benzoylpyridine 1-oxide	N. R. (77%) (d)	N. R., Redn (26%)	N. R. (49%), Redn (35%)	Redn (84%)		Disp (42%)
4-Benzoylpyridine 1-oxide	Redox (51%)	Redox (68%)	Redox (98%)	Redn (81%)	N. R. (92%)	Disp (39%)
2-Benzoylpyridine	Redn (50%)	Redn (89%)				Disp (36%)
3-Benzoylpyridine	Redn (95%)					Disp (45%)
4-Benzoylpyridine	Redn (64%)					Disp (45%)

(a) Disp (%) = Percent yield of displacement product (benzoic acid). (b) Redn (%) = Percent yield of carbonyl reduction product (α-hydroxybenzylpyridine 1-oxides/α-hydroxybenzylpyridines). (c) Redox (%) = Percent yield of redox product (α-hydroxybenzylpyridine). (d) N. R. (%) = Percent recovery of amine starting material.

The third generalization about displacement is based on two considerations. First, displacement did occur with all six of the benzoyl derivatives when each was treated with potassium t-butoxide, an alkoxide which cannot take part in a MPV reduction reaction. Secondly, the other nucleophiles excluding aluminum isopropoxide gave increasing amounts of displacement with 2-benzoylpyridine 1-oxide in going from sodium isopropoxide, to sodium ethoxide, to methanolic sodium hydroxide. This trend reflects the decreasing tendency of these nucleophiles to take part in the reduction of the keto group (11,12) which is a competing reaction. In these competing reactions, the carbonyl group is being attacked by oxygen of the nucleophile (path b) or by hydride transfer from the nucleophile (reduction).

Reduction of a carbonyl group to a hydroxy group without any subsequent reaction, was accomplished when each of the benzoylpyridine 1-oxides was treated with aluminum isopropoxide. The redox reaction did not occur in these cases because of the low basicity of aluminum isopropoxide (13). The redox reaction occurred with 4-benzoylpyridine 1-oxide when the alkoxide was both a MPV reagent and a strong base (sodium ethoxide or isopropoxide).

The redox reaction was discovered during a study to determine whether the N-oxide group was reduced before the carbonyl group was reduced in the reaction of 4-benzoylpyridine 1-oxide with ethanolic sodium hydroxide. 4-(α-Acetoxybenzyl)pyridine 1-oxide when treated with ethanolic sodium hydroxide yielded 4-(α-hydroxybenzyl)-pyridine. 4-(α-Acetoxybenzyl)- or 4-(α-hydroxybenzyl)-pyridine 1-oxide when treated with aqueous sodium hydroxide yielded 4-benzoylpyridine. These results are in agreement with an initial reduction of the carbonyl group of 4-benzoylpyridine 1-oxide by ethanolic sodium hydroxide to yield 4-(α-hydroxybenzyl)pyridine 1-oxide which subsequently underwent a MPV reduction to yield 4-(α-hydroxybenzyl)pyridine, the product isolated.

The base-promoted redox reactions reported here are analogous to those reported for α-hydroxyalkylazaaromatic N-oxides with aqueous sodium hydroxide (14-17). Base-promoted redox reactions of azaaromatic N-oxides will be the subject of a later report.

EXPERIMENTAL

All temperatures are uncorrected. Infrared spectra were recorded on a Beckman IR-8 or a Perkin-Elmer IR-137 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian HA-60 high resolution spectrometer with TMS as the internal standard.

Cyano- and benzoylpyridines were obtained from commercial sources and were recrystallized if necessary.

Cyanopyridine 1-Oxides.

2-Cyanopyridine (10 g.) was converted to the corresponding 1-oxide by the procedure of Ochiai (18) for the conversion of pyridine to pyridine 1-oxide. The yield after recrystallization from ethanol was 4.7 g. (41%) of colorless crystals, m.p. 119-120° (lit. (19) m.p. 117-118°, (20) m.p. 123-124°).

3-Cyanopyridine 1-oxide was prepared similarly, m.p. 173.5-174.5° (lit. (21) m.p. 175-176°).

4-Cyanopyridine 1-oxide was prepared in an analogous manner, m.p. 221-222° (lit. (18) m.p. 220-221°).

2-Benzenesulfonylpyridine 1-Oxide.

2-Phenylthiopyridine 1-oxide (5.00 g., 0.024 mole) (22), 8 ml., (0.024 mole) of 40% peracetic acid and 20 ml. of acetic acid were heated for 4 hours at 90°, cooled, and made slightly basic by adding dilute sodium hydroxide solution. The resulting solution was extracted with 3 successive 25-ml. portions of chloroform. The combined chloroform extracts were washed with saturated sodium chloride solution, dried (magnesium sulfate) and concentrated in vacuo. The residue was crystallized from benzene-ligroin yielding 4.9 g. (87%) of 2-benzenesulfonylpyridine 1-oxide as colorless crystals, m.p. 164-165°.

Anal. Calcd. for $C_{11}H_9NO_3S$: C, 56.15; H, 3.86; N, 5.96; S, 13.63. Found: C, 56.42; H, 4.01; N, 5.77; S, 13.47.

3-Phenylthiopyridine 1-Oxide.

3-Chloropyridine 1-oxide, m.p. 57-60° (lit. (23), m.p. 59-60°), was heated under reflux for 20 hours with sodium thiophenoxide by the method used to prepare 2-phenylthiopyridine 1-oxide. The title compound as a monohydrate, m.p. 62-63°, was obtained as colorless crystals in 64% yield after crystallization from ether.

Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.73; H, 4.98; N, 6.33; S, 14.48. Found: C, 59.75; H, 5.00; N, 6.36; S, 14.42.

3-Benzenesulfonylpyridine 1-Oxide.

By the method used to prepare 2-benzenesulfonylpyridine 1-oxide, 3-phenylthiopyridine 1-oxide was converted to the title compound, m.p. 160-161°, in 45-54% yields after recrystallization from benzene-ethanol.

Anal. Calcd. for $C_{11}H_9NO_3S$: C, 56.15; H, 3.86; N, 5.95; S, 13.63. Found: C, 56.34; H, 3.72; N, 6.15; S, 13.48.

4-Benzenesulfonylpyridine 1-Oxide.

By the method used to prepare 2-benzenesulfonylpyridine 1-oxide, 4-phenylthiopyridine 1-oxide, m.p. 138-139° (lit. (24), m.p. 137°), was converted to the title compound, m.p. 139.5-140.5°, in 67-78% yields after recrystallization from benzene. A mixed m.p. with starting material gave a depression.

Anal. Calcd. for $C_{11}H_9NO_3S$: C, 56.15; H, 3.86; N, 5.96; S, 13.63. Found: C, 56.32; H, 3.73; N, 5.80; S, 13.37.

2-Benzenesulfonylpyridine.

Four milliliters (0.046 mole) of phosphorus trichloride was slowly added to a solution of 3.0 g. (0.013 mole) of 2-benzenesulfonylpyridine 1-oxide and 30 ml. of chloroform at 0-5°. After the initial reaction subsided the mixture was heated at 90-100° for 1 hour. The mixture was cooled to 0-5° and made alkaline with dilute sodium hydroxide solution. The layers were separated and the aqueous layer was extracted successively with two 10-ml. portions of chloroform. The organic layers were combined, washed with saturated sodium chloride solution, dried (magnesium sulfate) and concentrated in vacuo. The solid residue was crystallized from benzene-ligroin yielding 2.27 g. (81%) of 2-benzenesulfonylpyridine as colorless crystals, m.p. 89-90°.

Anal. Calcd. for $C_{11}H_9NO_2S$: C, 60.25; H, 4.14; N, 6.39; S, 14.63. Found: C, 60.40; H, 3.96; N, 6.55; S, 14.85.

3-Benzenesulfonylpyridine.

This compound was prepared as was 2-benzenesulfonylpyridine. The title compound was obtained in 51-55% yields after recrystallization from benzene-ligroin as colorless crystals, m.p. 106-107°.

Anal. Calcd. for $C_{11}H_9NO_2S$: C, 60.25; H, 4.14; N, 6.39; S, 14.63. Found: C, 60.08; H, 4.24; N, 6.49; S, 14.58.

4-Benzenesulfonylpyridine.

This was prepared as was 2-benzenesulfonylpyridine. The title compound was obtained in 85% yield after crystallization from ligroin (90-100°), m.p. 125-126° (lit. (25), m.p. 125°). Picrate, m.p. 160-161° (ethanol).

2-Benzoylpyridine 1-Oxide.

This was prepared in experiments modeled after the synthesis of pyridine 1-oxide (26). Peracetic acid (50 ml. of 40%) was added dropwise during 1 hour to 20.2 g. (0.11 mole) of 2-benzoylpyridine in 40 ml. of acetic acid. The resulting solution was kept at 55-60° for 10 hours. Then the solution was concentrated using reduced pressure to a red oil which was dissolved in chloroform. The chloroform layer was washed successively with 5% sodium bicarbonate solution and water. The chloroform layer after drying (magnesium sulfate) was concentrated to an orange oil which after trituration with ether yielded pale yellow crystals which were recrystallized from benzene-petroleum ether. The yield of 2-benzoylpyridine 1-oxide was 12.6 g. (57%), m.p. 97.5-99°; ir (potassium bromide) 1680 (C=O), 1240 cm^{-1} (N-O).

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.56; N, 7.03. Found: C, 72.19; H, 4.73; N, 6.95.

3-Benzoylpyridine 1-Oxide.

This compound was prepared (43% and 49%) like 2-benzoylpyridine 1-oxide was prepared. 3-Benzoylpyridine 1-oxide: light yellow oil; b.p. 195-200° (0.2 mm); ir (neat) 1660 (C=O), 1270 cm^{-1} (N-O).

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.56; N, 7.03. Found: C, 72.14; H, 4.80; N, 7.11.

The picrate (ethanol) melted at 149-150° and the 2,4-dinitrophenylhydrazone melted at 235° with decomposition.

4-Benzoylpyridine 1-Oxide.

This compound was prepared (51 and 57%) as was 2-benzoylpyridine 1-oxide. 4-Benzoylpyridine 1-oxide: colorless crystals (benzene), m.p. 131-133°; ir (potassium bromide) 1655 (C=O), 1260 cm^{-1} (N-O).

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.56; N, 7.03. Found: C, 72.55; H, 4.60; N, 6.89.

The picrate (ethanol) melted at 126-127° and the 2,4-dinitrophenylhydrazone melted at 228-229° with decomposition.

4-(α-Acetoxybenzyl)pyridine.

This compound prepared from the parent alcohol and acetyl chloride in the presence of pyridine; yield, 75%; colorless oil, b.p. 138-140° (0.7 mm); ir (neat) 1700 (C=O) and 1200 cm^{-1} (C-O); nmr (deuteriochloroform) τ 1.4 (d, 2, 2,6-pyridine), 2.7 (m, 9, aromatic), 3.2 (s, 1, benzylic), and 6.5 (s, 3, CH_3).

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.86; H, 5.72; N, 6.42.

4-(α-Acetoxybenzyl)pyridine 1-Oxide.

This compound was prepared from the foregoing acetate as

2-benzoylpyridine 1-oxide was from 2-benzoylpyridine; yield, 88%; white crystals, m.p. 133.5-134°; ir (potassium bromide) 3400 (OH), and 1740 cm⁻¹ (C=O); nmr (deuteriochloroform) τ 1.8 (d, 2, 2,6-pyridine 1-oxide), 2.7 (m, 7, aromatic), 3.3 (s, 1, benzylic), 7.8 (s, 3, CH_3).

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.24; H, 5.37; N, 5.68.

Reactions of Cyano-, Benzenesulfonyl-, and Benzoylpyridines and Their 1-Oxides with 0.67 N Sodium Hydroxide.

The reaction of 2-cyanopyridine 1-oxide with ethanolic sodium hydroxide which will be described is typical of the other seventeen reaction systems.

To 75 ml. of anhydrous ethanol containing 2.00 g. (0.05 mole) of sodium hydroxide was added 1.00 g. (0.008 mole) of 2-cyanopyridine 1-oxide. The solution was heated under reflux for 8 hours, diluted with water, made slightly acidic with hydrochloric acid, and concentrated. The residue was crystallized from methanol to yield 0.94 g. (81%) of picolinic acid 1-oxide as light brown crystals, m.p. 160° dec. (lit. (27) 160° dec.).

The results of this reaction and the other seventeen reactions are summarized in Table I. The reflux periods were generally 6-8 hours but varied from 2-31 hours.

Reactions of Benzoylpyridine 1-Oxides with Alkoxides.

The reaction of 2-benzoylpyridine 1-oxide with sodium isopropoxide which is typical of the other reactions summarized in Table II will be described. Dry 2-benzoylpyridine 1-oxide (3.20 g., 0.016 mole) and 0.065 mole sodium isopropoxide in 100 ml. of 2-propanol were heated under reflux for 4.5 hours. The mixture was acidified with 6 N hydrochloric acid and the volume was reduced to *ca.* 50 ml. The residue was made basic with sodium bicarbonate solution and extracted with two 50-ml. portions of ether. The ether extract was dried (magnesium sulfate) and concentrated to give 1.30 g. (44%) of 2-(α-hydroxybenzyl)pyridine: m.p. 75-78° (lit. (28) m.p. 78°); and ir spectrum (potassium bromide) identical to that of authentic 2-(α-hydroxybenzyl)pyridine. The aqueous layer from the ether extraction was concentrated and acidified with 6 N hydrochloric acid to precipitate 0.60 g. (31%) of benzoic acid: m.p. 119-121°; mixed m.p. gave no depression; and ir spectrum (potassium bromide) identical to that of authentic benzoic acid. The filtrate from benzoic acid was evaporated to dryness and the residue was made basic with sodium bicarbonate solution. The mixture was extracted with 75 ml. of chloroform. The extract was concentrated to a dark oil which was identified as hydrated pyridine 1-oxide by examination of its ir spectrum.

The other reactions summarized in Table II were done in a similar manner with variations of ratios of base to pyridine compound in some cases. For pyridine compounds which gave both displacement and/or redox reactions, the ratio of base to pyridine compound was varied from 4:1 to 10:1.

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(1) Supported in part by U. S. Office of Education, Department of HEW (RSD) and by the West Virginia University Senate

Committee on Research Grants (JCP).

(2) Presented in part before the First Central Regional Meeting of the ACS, Akron, Ohio, May, 1968 and in part before the Second International Congress of Heterocyclic Chemistry, Montpellier, France, July, 1969.

(3) Taken from the dissertations of RSD (1964) and JCP (1972) submitted to the Department of Chemistry in partial fulfillment for the Ph.D. degrees.

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