cake obtained above, and 1.25 l. of 1 *N* sodium hydroxide were shaken in a separatory funnel and the methylene chloride layer was shaken again with 250 ml of 1 *N* sodium hydroxide and 250 ml of water. The combined aqueous phases were backwashed with 250 ml of methylene chloride and then acidified with 130 ml of concentrated hydrochloric acid. The mixture was cooled with an ice bath, filtered, washed with two 200-ml portions of water, and dried under vacuum at 50° to give 132.6 g (64%) of IIIb, mp 149–151°. Recrystallized from a mixture of 600 ml of ethanol and 1330 ml of water the product was analytically pure, mp 150.5–152.5°, and weighed 127.0 g (61.2%, 91.5% based on IIb consumed).

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; N, 6.07. Found: C, 64.84; H, 6.18.

The combined methylene chloride extracts, after alkali treatment, were dried over magnesium sulfate and evaporated under vacuum to give 74.0 g of IIb, mp 74–76.

The melting point of the 6-methylisovanillin (IIIb) obtained above, on admixture with 6-methylvanillin (Ib),[3] was depressed to 137–140°. Methylation of our IIIb and Ib[3] with methyl sulfate gave the same product, authentic 6-methylveratraldehyde (IIb), as shown by mixture melting point and infrared spectra.

Isovanillin (IIIa).—By the same procedure described above for the preparation of IIIb, 5.6 g (61%) of isovanillin (IIIa), mp 110–113°,[6] was obtained from 10 g of veratraldehyde (IIa). Part of the veratraldehyde (4.2 g) was recovered unchanged.

Acetoisovanillone (IIIc).—When 119 g (0.66 mole) of 3,4-dimethoxyacetophenone (IIc)[7] was subjected to the hydrolysis conditions described for the preparation of IIIb above, 64.2 g (58.4%, 67.2% based on IIc consumed) of acetoisovanillone (IIIc), mp 92–93°,[8] and 18.6 g of recovered 3,4-dimethoxyacetophenone were isolated.

Registry No.—IIb, 7721-62-2; IIIb, 7721-61-1.

Acknowledgment.—We wish to thank David Malarek and Thomas Fraher for capable technical assistance.

(6) This material was identified by comparison (mixture melting point) with authentic material obtained from Monsanto Chemical Co.

(7) Prepared from acetovanillone and dimethyl sulfate by the method of F. F. Blicke and W. K. Johnson, *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 441 (1956).

(8) Identical (mixture melting point, tlc) with material prepared according to the method of R. Schwarz and K. Capek, *Monatsh. Chem.*, **83**, 889 (1952).

Preparation of Aldehyde Derivatives from Picoline N-Oxides

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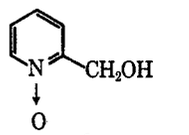
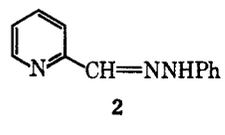
A number of methods are available for conversion of picolines to pyridine carboxaldehyde derivatives. Synthetically useful methods include selenium oxide oxidation,[1] oximation with butyl nitrite,[2] and double acylative rearrangement of picoline N-oxides.[3] A recent note on preparation of oximes of substituted pyridine-2-carboxaldehydes *via* a presumed NO heterolysis route[4] leads us to report preparation of pyridine-2- and -4-carboxaldehyde derivatives in good yields by a route involving a different type of NO heterolysis.

Hydroxymethylpyridine was prepared by the acylative rearrangement of picoline N-oxide[3,5] and oxidized to hydroxymethylpyridine N-oxide (1). When treated with phenylhydrazine in dilute sodium hydroxide, 2-hydroxymethylpyridine N-oxide is converted to pyridine-2-carboxaldehyde phenylhydrazone (2) in 79% yield.



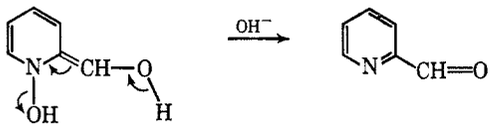
1



2

Although hydrazines may serve as oxidants in some reactions (osazone formation, amination of tropones[8]), phenylhydrazine is not the oxidant in this reaction since a 72% yield of the hydrazone is obtained based on the amount of phenylhydrazine used. No phenylhydrazone is obtained by heating phenylhydrazine and 2-hydroxymethylpyridine N-oxide in the absence of sodium hydroxide, nor by heating phenylhydrazine and 2-hydroxymethylpyridine in dilute sodium hydroxide. Reaction of 2-hydroxymethylpyridine N-oxide, phenylhydrazine, and alkali in the presence of a 20-fold excess of 2-ethylpyridine N-oxide gave only the phenylhydrazone of pyridine-2-carboxaldehyde (61%) and no evidence of the possible intermolecular oxidation product, pyridine-2-carboxaldehyde N-oxide phenylhydrazone. Oxidation of the alcohol must therefore occur at the expense of the N-oxide in a base-catalyzed intramolecular reaction.

The oxidation of the alcohol and attendant reduction of the N-oxide may proceed *via* an elimination reaction involving enolization to enolamine **3**, followed by removal of a proton from the hydroxyl group and subsequent NO fission in a step bearing some resemblance to the oxidative step of the osazone reaction (NN fission).[9] As predicted by this mechanism no phenylhydrazone was obtained on treatment of the corresponding methyl ether, 2-methoxymethylpyridine N-oxide, with phenylhydrazine and dilute sodium hydroxide. The related oxidation of alkylhydroxylamines to imines by base-catalyzed elimination of the elements of water has been observed in several other instances.[4,10]



3

(1) W. Borsche and H. Hartmann, *Ber.*, **73**, 839 (1940).

(2) S. Forman, *J. Org. Chem.*, **29**, 3323 (1964).

(3) V. Boekelheide and W. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

(4) F. A. Daniher, B. E. Hackley, Jr., and A. B. Ash, *J. Org. Chem.*, **31**, 2709 (1966).

(5) Distilled hydroxymethylpyridine, prepared by the acylative rearrangement of picoline N-oxide and subsequent hydrolysis of the acetate,[3] was found to contain 2% pyridine-2-carboxaldehyde. Although extensive investigations of the acylative rearrangement point to an ionic or radical-cage mechanism,[6] free radicals appear to be present in the reaction medium[7] and account for low yields of ethylpyridine, picoline, methane, carbon dioxide, and methyl acetate. Pyridine-2-carboxaldehyde may similarly result from abstraction of hydrogen from the major product, 2-acetoxymethylpyridine.

(6) S. Oae, T. Kitao, and Y. Kitaoka, *J. Am. Chem. Soc.*, **84**, 3359 (1962); V. J. Traynelis and P. L. Pacini, *ibid.*, **86**, 4917 (1964); T. Cohen and J. H. Fager, *ibid.*, **87**, 5701 (1965); V. J. Traynelis and A. I. Gallagher, *ibid.*, **87**, 5710 (1965); T. Koenig, *ibid.*, **88**, 4045 (1966).

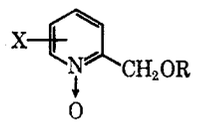
(7) V. J. Traynelis and R. F. Martello, *ibid.*, **80**, 6590 (1958); V. J. Traynelis and R. F. Martello, *ibid.*, **82**, 2744 (1960).

(8) T. Mukai, H. Tsuruta, and T. Nozoe, *Tetrahedron Letters*, 1063 (1966).

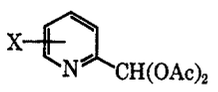
(9) F. Weygand, *Ber.*, **73**, 1284 (1940); H. S. Isbell, *Ann. Rev. Biochem.*, **12**, 207 (1943).

(10) H. Feuer, B. F. Vincent, Jr., and R. S. Bartlett, *J. Org. Chem.*, **30**, 2877 (1965).

Boekelheide and Linn[3] have shown that acylative rearrangement of acetates of substituted 2-hydroxymethylpyridine N-oxide (**4a**) is in many instances a useful route to the aldehyde derivative (**5**). We find that



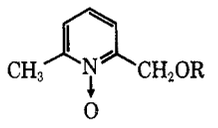
4a, R = Ac
b, R = H



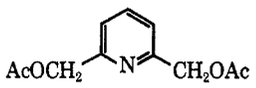
5

base-catalyzed NO fragmentation of hydroxymethylpyridine N-oxide (**4b**) offers an alternative preparative route to such compounds, in some cases yielding carbonyl derivatives not obtainable *via* the acylative rearrangement.

For example acylative rearrangement of 6-methyl-2-acetoxymethylpyridine N-oxide (**6a**) was found[3] to give 2,6-bisacetoxymethylpyridine (**7**) rather than the diacetate of 6-methylpyridine-2-carboxaldehyde. Base-catalyzed fission of the N-oxide (**6b**) in the presence of phenylhydrazine, however, gives the aldehyde product, 6-methylpyridine-2-carboxaldehyde phenylhydrazone (**8**).



6a, R = Ac
b, R = H



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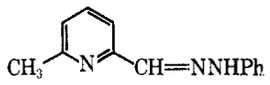

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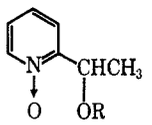
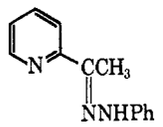


9a, R = Ac
b, R = H



10

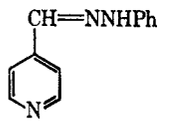
An attempt[3] to prepare a ketone derivative by acylative rearrangement of 2-(α-acetoxyethyl)pyridine N-oxide (**9a**) gave only recovered starting material. The ketone derivative (**10**) is obtained, however, by base-catalyzed N-oxide fission of the corresponding alcohol (**9b**). Formation of the ketone as judged from the rate of precipitation of the phenylhydrazone is quite slow (Table I); thus it is not surprising that Boekelheide and Linn were able to prepare alcohol **9b** in 79% yield by saponification of acetate **9a** without noting N-oxide fission to give the ketone.

Structurally related hydroxymethyl heterocyclic N-oxides also undergo oxidation *via* N-oxide cleavage; 4-hydroxymethylpyridine N-oxide gives pyridine-4-carboxaldehyde phenylhydrazone (**11**) on treatment with phenylhydrazine and sodium hydroxide, while the 3 isomer fails to undergo N-oxide fission. Pyridine-4-carboxaldehyde was also detected as the oxime by substituting hydroxylamine for phenylhydrazine. Pyrazine-2-carboxaldehyde 4-oxide phenylhydrazone (**12**) is prepared directly from 2-acetoxymethylpyrazine di-N-oxide (**13**) by treatment with base and phenylhydrazine. Hydroxymethylquinoline N-oxide forms an immediate precipitate with phenylhydrazine in dilute sodium hydroxide and gives an 87% yield of quinoline-2-carboxaldehyde phenylhydrazone (**14**) after 2 hr at 80°. Under comparable conditions the yield of pyridine-2-carboxaldehyde phenylhydrazone from 2-hydroxymethylpyridine N-oxide was only 18% after 3 hr, reaching 80% only after 20 hr. Quinoline and quinolinium compounds have often been observed to be more reactive than pyridine and pyridinium congeners in reactions involving the imine character of the heterocyclic nitrogen.[11] This is probably ascribable to the reduced aromaticity of the heteroring in the benzo analogs of pyridine.

TABLE I
CONVERSION OF HETEROCYCLIC HYDROXYALKYL N-OXIDES INTO PHENYLHYDRAZONES

	Hydrazone isolated	Reacn time, hr	Yield, %	Mp, °C
Pyridine N-oxides				
2-Hydroxymethyl	**2**	3	18	174–176[a,b]
		20	79	
2-Methoxymethyl	None	72	0	
3-Hydroxymethyl	None	20	0	
4-Hydroxymethyl	**11**	4	70	175–176[c]
6-Methyl-2-hydroxymethyl	**8**	7	5	199[d]
2-(α-Hydroxyethyl)	**10**	69	19	147–151[e]
Other heterocycles				
2-Hydroxymethyl-quinoline N-oxide	**14**	0.3	77	205–206[a,b]
		2	87	
2-Acetoxymethylpyrazine di-N-oxide	**12**	46	26	239

[a] A. Kaufmann and L. G. Vallette, *Ber.*, **46**, 49 (1913). [b] Melting point undepressed by admixture of phenylhydrazone prepared from authentic carboxaldehyde. [c] R. Graf, G. Perathoner, and M. Tatzel, *J. Prakt. Chem.*, **146**, 88 (1936). [d] S. Furukawa and Y. Kuroiwa, *Pharm. Bull. (Tokyo)*, **3**, 332 (1955). [e] R. Kuhn and W. Munzing, *Ann.*, **585**, 29 (1952).



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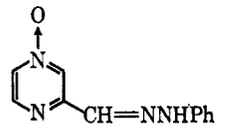
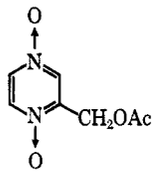


12



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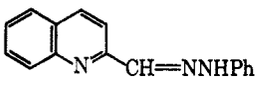

14

Experimental Section

Materials.—2-Hydroxymethylpyridine N-oxide,[3] 6-methyl-2-hydroxymethylpyridine N-oxide,[12] 2-hydroxymethylquinoline N-oxide,[13] 2-(α-hydroxyethyl)pyridine N-oxide,[3] and 2-acetoxymethylpyrazine di-N-oxide[14] were prepared by previously described methods. 2-Methoxymethylpyridine and 3- and 4-hydroxymethylpyridine N-oxides were obtained from the Aldrich Chemical Co.

Preparation of Phenylhydrazones.—Phenylhydrazones were prepared from heterocyclic α-hydroxyalkyl N-oxides by heating 1 equiv of the hydroxymethyl N-oxide compound with 1 equiv of phenylhydrazine and 1 equiv of sodium hydroxide in water at 80°. All phenylhydrazones were very insoluble in water and crystallized as formed in the hot solution. Reaction times and yields are shown in Table I.

(11) N. B. Chapman and D. Q. Russel-Hill, *J. Chem. Soc.*, 1563 (1956); R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," Interscience Publishers, Inc., New York, N. Y., 1960, p 213.
(12) S. Furukawa, *Yakugaku Zasshi*, **78**, 957 (1958).
(13) E. Ochiai, S. Suzuki, Y. Utsunomiya, T. Ohmoto, K. Nagamoto, and M. Itoh, *ibid.*, **80**, 339 (1960).
(14) M. Asai, *ibid.*, **79**, 1273 (1959).

2-Methoxymethylpyridine N-Oxide.—Twenty milliliters (27.9 g, 0.227 mole) of 2-methoxymethylpyridine in 130 ml of acetic acid and 20 ml of 30% hydrogen peroxide (0.175 mole) was heated at 80° for 18 hr. Another 15 ml (0.14 mole) of 30% hydrogen peroxide was added and heating was continued for 8 more hr. The solvent was removed at reduced pressure and the residual oil was distilled under vacuum. The fraction distilling between 116 and 121° (3.2 mm) was collected and redistilled giving 6.84 g (31%) of pale yellow 2-methoxymethylpyridine N-oxide: bp 127–129° (3 mm), n^{22}D 1.5690. Nmr in deuterium oxide showed aromatic hydrogens at τ 1.84–3.02 (complex); methylene, 5.52 (singlet); and methoxyl, 6.66 (singlet). Ultraviolet showed λ_{max}^{EtOH} 261 mμ (ε 10,600). Physical constants and nmr spectrum were unchanged following redistillation.[15] *Anal.* Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.59; H, 6.63; N, 10.51.

Pyridine-4-carboxaldehyde Oxime.[17]—A solution of 121 mg (1.75 mmoles) of hydroxylamine hydrochloride and 283 mg (2.26 mmoles) of 4-hydroxymethylpyridine N-oxide in 10 ml of 1 *N* sodium hydroxide was heated on a steam bath. A few needles formed after a few hours. When no increase in precipitate was observed after 16 hr, an additional 100 mg (1.45 mmoles) of hydroxylamine hydrochloride was added. No increase in precipitate resulted. After 24 hr the solution was cooled; no further precipitate separated. However on neutralizing with acetic acid a copious precipitate of fine needles separated immediately. Crude pyridine-4-carboxaldehyde oxime, (123 mg, 45% yield) was collected and recrystallized from water, mp 131°.

Pyrazine-2-carboxaldehyde 4-Oxide Phenylhydrazone.—A solution of 154 mg (0.83 mmole) of 2-acetoxymethylpyrazine di-N-oxide[14] and 0.083 ml (0.83 mmole) of phenylhydrazine in 20 ml of water plus 0.32 ml (0.32 mmole) of 1 *N* sodium hydroxide was heated under a nitrogen atmosphere on a steam bath. A total of 1.02 ml of 1 *N* sodium hydroxide was added in portions over a 76-hr period. The yellow, crystalline phenylhydrazone (47 mg, 26% yield) which had precipitated during the first 46 hr was collected. No more precipitate formed on further heating. An analytical sample of pyrazine-2-carboxaldehyde-4 oxide phenylhydrazone (mp 239–341° dec) was prepared by two recrystallizations from ethanol: λ_{max}^{EtOH} 234 mμ (ε 16,200), 254 (17,200), 387 (24,500). *Anal.* Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15; Found: C, 61.45; H, 4.69; N, 26.03.

2-Hydroxymethylpyridine.—Twenty-five milliliters of acetoxymethylpyridine prepared by the method of Boekelheide and Linn[3] was added to 50 ml of concentrated hydrochloric acid, and the mixture was heated at reflux for 3 hr. Solvent was then removed by evaporation. The residue was extracted with 90 ml of chloroform. The chloroform solution was shaken vigorously with potassium carbonate paste and filtered. Solvent was removed, and the residue was distilled. A 5-ml fraction of hydroxymethylpyridine was collected between 105 and 111° (25 mm) [lit.[18] bp 112–113° (16 mm)].

Detection of Aldehyde.[5]—The nmr spectrum of neat 2-hydroxymethylpyridine showed in addition to the expected signals (aromatic hydrogen, τ 1.45–2.76; methylene, 5.14) a signal at τ 0.7 attributed to the aldehydic hydrogen of pyridine-2-carboxaldehyde, estimated to be present in concentration of 1–2%. The infrared spectrum had a very weak carbonyl absorption at 1713 cm^{-1}. Heating 109 mg (1.0 mmole) of this preparation of hydroxymethylpyridine with 0.10 ml (0.98 mmole) of phenylhydrazine briefly in 5 ml of water gave 3.2 mg, 1.6% yield, of pyridine-2-carboxaldehyde phenylhydrazone identified by mixture melting point. No further phenylhydrazone was detected when reaction times were extended up to 5 days.

Registry No.—2-Methoxymethylpyridine N-oxide, 7727-04-0; pyridine-4-carboxaldehyde oxime, 696-54-8; pyrazine-2-carboxaldehyde 4-oxide phenylhydrazone, 7727-06-2; **2**, 7727-07-3; **11**, 7757-39-3; **6**, 7727-08-4; **10**, 7734-05-6; **14**, 7727-09-5; **12**, 7727-06-2.

(15) The 2-methoxymethylpyridine was characterized by the following physical constants: bp 76–78° (18 mm),[16] n^{22}D 1.4978. Nmr in deuterium oxide showed aromatic hydrogens at τ 1.68–3.20 (complex), methylene 5.62 (singlet), and methoxyl 6.75 (singlet).

(16) T. Naito and K. Veno, *Yakugaku Zasshi*, **79**, 1277 (1959).

(17) S. Veibel and I. G. K. Andersen, *Anal. Chim. Acta*, **14**, 320 (1956).

(18) C. Harries and G. H. Lenart, *Ann.*, **410**, 107 (1915).

Acknowledgment.—We wish to thank Mrs. Jeanette Teague for preparing 2-methoxymethylpyridine N-oxide. This work was supported by Public Health Service Grant GM-11966.

Obedience to the Brown Selectivity Relationship in a Heterogeneous System. Competitive Ethylations over a Zeolite Catalyst

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Received August 24, 1966

While zeolites (molecular sieves) have long been utilized as adsorbents and ion exchangers,[1] it is only recently that their catalytic application has come into prominence.[2,3] Notably, the faujasite family of zeolites, with their highly accessible, intracrystalline volume, has presented unusual opportunities for catalysis, when appropriate base exchange to substantially eliminate their alkali metal content was practiced. Thus, we have found that rare earth exchanged X- and Y-type faujasites are versatile catalysts for organic reactions such as alkylation and related reactions,[4,5] the condensation of carbonyl compounds with aromatics to form bisarylalkanes,[6] and the aldol condensation.[6]

Generally, the patterns of substrate reactivity and product distribution in the zeolite-catalyzed alkylations were similar to the corresponding features reported for alkylations with strong protonic acids such as sulfuric and hydrofluoric acids, and promoted Lewis acids.[4] For alkylation of simple aromatics with olefins, transfer of a catalyst proton to olefin was proposed, with the generation of an *adsorbed* carbonium ion-like species, which was then attacked in a Rideal-like mechanism by aromatic to form alkylaromatic product.[5] Recently, we have studied the competitive alkylation of toluene and benzene with ethylene using a rare earth exchanged X-type zeolite and found that not only were *ortho–para* orientation and substrate selectivity observed, but also quantitative correlation of these data with Brown's selectivity relationship.[7]

Experimental Section

Gas chromatographic analyses of alkylbenzenes were carried out with a Perkin-Elmer 154-DG chromatograph with flame-ionization detector, using a 300-ft stainless steel capillary column containing a 3:2 mixture of 1,2,3-tris(2′cyanoethoxy)-propane and oxybis(2-ethylbenzoate). The column temperature was 80° and the hydrogen flow rate was 3 cc/min. Retention times (in minutes) relative to injection were benzene (5.52), toluene (7.53), ethylbenzene (10.62), *p*-ethyltoluene (16.9),

(1) R. M. Barrer, *Endeavour*, **23**, 122 (1964).

(2) P. B. Weisz, V. J. Frilette, R. W. Maatman, and E. B. Mower, *J. Catalysis*, **1**, 307 (1962).

(3) V. J. Frilette, P. B. Weisz, and R. L. Golden, *ibid.*, **1**, 301 (1962).

(4) P. B. Venuto, L. A. Hamilton, P. S. Landis, and J. J. Wise, *ibid.*, **5**, 81 (1966).

(5) P. B. Venuto, L. A. Hamilton, and P. S. Landis, *ibid.*, **5**, 484 (1966).

(6) P. B. Venuto and P. S. Landis, *ibid.*, **6**, 237 (1966).

(7) L. M. Stock and H. C. Brown, *J. Am. Chem. Soc.*, **81**, 3323 (1959), and references therein.