Reaction of 32 and DMAD. A solution of 561 mg (2.61 mmol) of **32** and 372 mg (2.62 mmol) of DMAD was refluxed in dioxane for 24 hr and gave 658 mg (70%) of **33** after chromatography and vacuum distillation.

Attempted Reaction of Water and Adduct 2. Heating adduct **2** in aqueous dioxane for 24 hr produced no noticeable decomposition of **2** or formation of product **33.**

Attempted Reaction in Water and Imino Ether 6b. Heating imino ether **6b** in aqueous dioxane for 0.5 hr produced no noticeable reaction as ascertained by NMR. No reaction was detected on standing at room temperature for 2 days.

Hydrolysis of Imino Ether 1b. Heating 103 mg (0.80 mmol) of **1b** and 14.5 mg (0.80 mmol) of water in 1 ml of dioxane for 3 hr at 100° in a sealed NMR tube produced 42% of *N-tert*-butylformamide and 15% of *tert*-butylamine, with 42% unreacted **1b,** by NMR. No reaction was detected by NMR upon leaving imino ether **1b** with aqueous dioxane at room temperature for 16 hr.

Acknowledgment. We acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—**1a,** 49680-36-6; **1b,** 55236-60-7; **2a,** 55236-61-8; **2b,** 55236-62-9; **6a,** 23974-38-1; **6b,** 23974-43-8; **7a,** 55236-63-0; **7b,** 55236-64-1; **8a,** 55236-65-2; **8b,** 55267-65-7; **12,** 52856-04-9; **13,** 55236-66-3; **14,** 55236-67-4; **15a,** 49680-46-8; **15b,** 23974-48-3; **16a,** 55236-68-5; **16b,** 55236-69-6; **17,** 55236-70-9; (*Z*)-**18,** 55236-71-0; (*E*)-**18,** 55236-72-1; **20a,** 5264-35-7; **20b,** 5264-35-7; **21,** 1120-64-5; **22,** 2525-16-8; **24,** 55236-73-2; **25a,** 55236-74-3; **25b,** 55236-75-4; **26,** 55236-76-5; **27,** 55236-77-6; **28,** 55236-78-7; **31,** 24427-31-4; **32,** 55236-58-3; **33,** 55236-59-4; DMAD, 762-42-5.

References and Notes

(1) O. Diels, K. Alder, T. Kashimoto, W. Friedrichson, W. Ekhardt, and H. Klare, *Justus Liebigs Ann. Chem.,* **498,** 16 (1932); O. Diels and K. Alder, *ibid.,* **510,** 87 (1934); **498,** 1 (1932).
(2) (a) R. M. Acheson, *Adv. Heterocycl. Chem.,* **15,** 1 (1973); (b) R. M. Acheson, R. T. Alpin, J. M. F. Gagan, D. R. Harrison, and G. R. Miller, *Chem. Commun.,* 451 (1966).
(3) M. Lora-Tomayo and J. L. Soto, "1,4-Cycloaddition Reactions", J. Hamer, Ed., Academic Press, New York, N.Y., 1967, Chapter 7.
(4) R. Huisgen, "Topics in Heterocyclic Chemistry", R. N. Castle, Ed., Wiley-Interscience, New York, N.Y., 1969, Chapter 8.
(5) E. Winterfeldt, *Angew. Chem., Int. Ed. Engl.,* **6,** 423 (1967).
(6) (a) R. Huisgen and K. Herbig, *Justus Liebigs Ann. Chem.,* **688,** 98 (1965); (b) R. Huisgen, M. Morikawa, K. Herbig, and E. Brunn, *Chem. Ber.,* **100,** 1094 (1967).
(7) R. Rodgers and D. G. Nielson, *Chem. Rev.,* **61,** 179 (1961).
(8) R. Glushkov and V. G. Granik, *Adv. Heterocycl. Chem.,* **12,** 185–212 (1970).
(9) (a) D. Bormann, *Justus Liebigs Ann. Chem.,* **725,** 124 (1969); (b) G. Pifferi, P. Consonni, G. Pellizza, and E. Testa, *J. Heterocycl. Chem.,* **4,** 619 (1967); (c) L. A. Paquette and T. Kakihana, *J. Am. Chem. Soc.,* **90,** 3897 (1968).
(10) See A. Hassner, J. O. Currie, Jr., A. S. Steinfeld, and R. F. Atkinson, *J. Am. Chem. Soc.,* **95,** 2982 (1973), and references cited therein, for other routes to 1-azetines.
(11) A. Hassner, M. J. Haddadin, and A. B. Levy, *Tetrahedron Lett.,* 1015 (1973).
(12) J. M. F. Gagan, *J. Chem. Soc. C,* 1121 (1966).
(13) M. Morikawa and R. Huisgen, *Chem. Ber.,* **100,** 1616 (1967).
(14) C. Szantay and L. Novak, *Chem. Ber.,* **100,** 2038 (1967).
(15) C. Szantay, L. Toke, K. Konty, and G. Kalaus, *J. Org. Chem.,* **32,** 423 (1967).
(16) F. Effenberger and R. Maier, *Angew. Chem., Int. Ed. Engl.,* **5,** 416 (1966).
(17) L. Ghosez and C. de Perez, *Angew. Chem., Int. Ed. Engl.,* **10,** 184 (1971).
(18) (a) Union Carbide Corp., Netherlands Appl. 6,507,886 (1965); *Chem. Abstr.,* **64,** 19631*a* (1966); (b) R. Fuks, R. Buijle, and H. G. Viehe, *Angew. Chem., Int. Ed. Engl.,* **5,** 585 (1966).
(19) H. G. Viehe, *Angew. Chem., Int. Ed. Engl.,* **6,** 767 (1967).
(20) H. G. Viehe, "Chemistry of Acetylenes", Marcel Dekker, New York, N.Y., 1969, p 904.
(21) (a) F. Effenberger, P. Fischer, G. Prossel, and G. Kiefer, *Chem. Ber.,* **104,** 1987 (1971), and references cited therein; (b) S. N. Balasubrahmanyam and M. Sivarajan, *Tetrahedron Lett.,* 3355 (1971), and references cited therein.
(22) Y. Hayashi, Y. Iwagami, A. Kadoi, T. Shono, and D. Swern, *Tetrahedron Lett.,* 1071 (1974).
(23) E. Winterfeldt, *Chem. Ber.,* **98,** 1581 (1965).
(24) (a) A. G. Cook, "Enamines", A. G. Cook, Ed., Marcel Dekker, New York, N.Y., 1969, pp 230–232; (b) R. Fuks and H. G. Viehe, "Chemistry of Acetylenes", H. G. Viehe, Ed., Marcel Dekker, New York, N.Y., 1969, pp 435–436 and 299–300.
(25) The Diels–Alder addition of unsaturated imines to DMAD has been shown to occur; see D. H. Aue and D. Thomas, *J. Org. Chem.,* in press.
(26) For the thermal rearrangement of 2-alkoxy-1-azetines, see ref 25.
(27) (a) F. G. Bordwell, M. L. Peterson, and C. S. Rondestvedt, *J. Am. Chem. Soc.,* **76,** 3945 (1954); (b) R. Gompper, *Angew. Chem., Int. Ed. Engl.,* **8,** 312 (1969), quoted as unpublished work of R. Gompper.
(28) R. Huisgen and G. Steiner, *J. Am. Chem. Soc.,* **95,** 5056 (1973).
(29) (a) R. Huisgen, K. Herbig, A. Siegel, and H. Huber, *Chem. Ber.,* **99,** 2526 (1966); (b) E. Winterfeldt and H. Preuss, *ibid.,* **99,** 450 (1966); (c) E. Winterfeld and H. Preuss, *Angew. Chem., Int. Ed. Engl.,* **4,** 689 (1966); (d) E. W. Truce and D. G. Brady, *J. Org. Chem.,* **31,** 3543 (1966); (e) C. H. McMullen and C. J. M. Stirling, *J. Chem. Soc. B,* 1217 (1966); (f) C. H. McMullen and C. J. M. Stirling, *ibid.,* 1221 (1966); ref 20, p 293.
(30) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Vol. 5, D. H. R. Barton and W. Doering, Ed., Pergamon Press, Oxford, 1969, p 184.
(31) A similar reaction with DMAD and benzalaniline was thought to occur by prior hydrolysis of the imine; H. R. Snyder, H. Cohen, and W. J. Tapp, *J. Am. Chem. Soc.,* **61,** 3560 (1939).
(32) Aniline adds to DMAD under the conditions of ref 31; see ref 24b, p 446.
(33) See (a) R. M. Acheson and M. W. Foxton, *J. Chem. Soc. C,* 2218 (1966); (b) R. M. Acheson, R. S. Feinberg, and J. M. F. Gagan, *ibid.,* 948 (1965); and ref 30, p 88, for deshielding by carbonyl groups.
(34) For amide additions to acetylenes, see A. W. Johnson, "The Chemistry of Acetylene Compound", Vol. II, Longmans, Green and Co., New York, N.Y., 1950, p 133; and for lactam additions to acetylenes see W. Ziegenbein and W. Franke, *Chem. Ber.,* **90,** 2291 (1957).
(35) R. H. DeWolfe, *J. Org. Chem.,* **36,** 162 (1971).
(36) Iminosulfuranes are known to hydrolyze to an amine function. See H. Kise, G. Whitfield, and D. Swern, *J. Org. Chem.,* **37,** 1121 (1972).
(37) The oxonium salts were prepared by the published procedures: H. Meerwein, *Org. Synth.,* **46,** 113, 120 (1966); T. J. Cuphrey, *Org. Synth.,* **51,** 142 (1971).
(38) See ref 29 for analogous assignments using olefinic hydrogens (ref 30).

Aromatic *N*-Oxides. IX. Reaction of *N*-Alkoxy-2- (and 4-) alkylpyridinium Salts with Base[1]

Vincent J. Traynelis* and Jon P. Kimball[2]

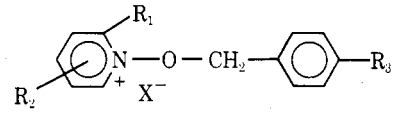
Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

Received February 27, 1975

The preparation of a number of *N*-benzyloxy- and *N*-*p*-nitrobenzyloxy-2- and 4-alkylpyridinium bromides and perchlorates are described. When these salts were treated with base, the decomposition products were primarily the corresponding alkylpyridines and benzaldehyde or *p*-nitrobenzaldehyde and in the case of the *N*-alkoxy-2-methyl- or 4-methylpyridinium salts 1-aryl-2-(2- or 4-pyridyl)ethanols **16–18** (ca. 25%) were also formed. Evidence is offered that formation of alcohols **16–18** proceeds via anhydro base **20** and **23** intermediates.

The reaction of aromatic *N*-oxides (e.g., pyridine *N*-oxide) with alkyl halides, alkyl sulfonates, or alkyl sulfates to produce *N*-alkoxy ammonium salts (e.g., *N*-methoxypyridinium methosulfate) has appeared in numerous reports in the literature.[3–14] These salts are known to undergo several types of reactions,[10] one of which is an alkaline decomposition to yield the corresponding nitrogen heterocycle and an aldehyde.[4–7,11–13] The initial report of this reaction

Table I
N-Benzyloxy-2- and -4-alkylpyridinium Salts

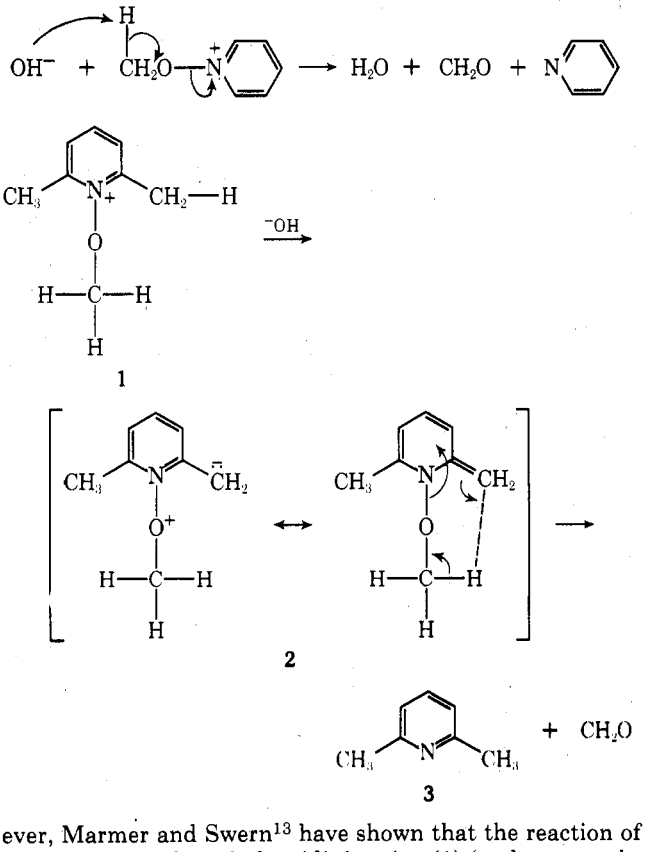


No.	Compd[a] R1	R2	R3	X	Solvent[b]	Reaction conditions Time, hr	Temp, °C	% yield
4	CH_3	H	H	Br	A	5	Reflux	96.5
5	CH_3	H	H	ClO_4				100
6	CH_3	H	NO_2	Br	B	0.5	100	53
7	C_2H_5	H	H	Br	A	1.5	*c*	83
8	C_2H_5	H	H	ClO_4				100
9	$C_6H_5CH_2$	H	H	Br	B	2.5	60–70	38
10	H	4-CH_3	H	Br	C	5	Reflux	76
11	H	4-CH_3	H	ClO_4				100
12	H	4-CH_3	NO_2	Br	B	1	70–75	75
13	H	4-$C_6H_5CH_2$	H	Br	B	1.5	60–70	85
14	CH_3	4-CH_3	H	Br	D	0.5	*c*	83
15	CH_3	6-CH_3	H	Br	A	1.5	*c*	75

[a] Analytical data (C and H) for compounds 4, 5, 6 (Br also), 8, 11, 14, and 15 (N also) were all within 0.3%. [b] A = CH_3CN; B = CH_3NO_2; C = $CHCl_3$; D = $(C_2H_5)_2O$. [c] Room temperature.

by Henze[4] described the conversion of 1-methoxyquinolinium iodide by potassium hydroxide to quinoline and formaldehyde. Subsequently, Ochiai[5] and Katritzky[6] utilized this reaction as a method for nonreductive deoxygenation of pyridine *N*-oxide derivatives; and Feely, Lehn, and Boekelheide[7] applied this reaction as a method for the synthesis of aromatic aldehydes.

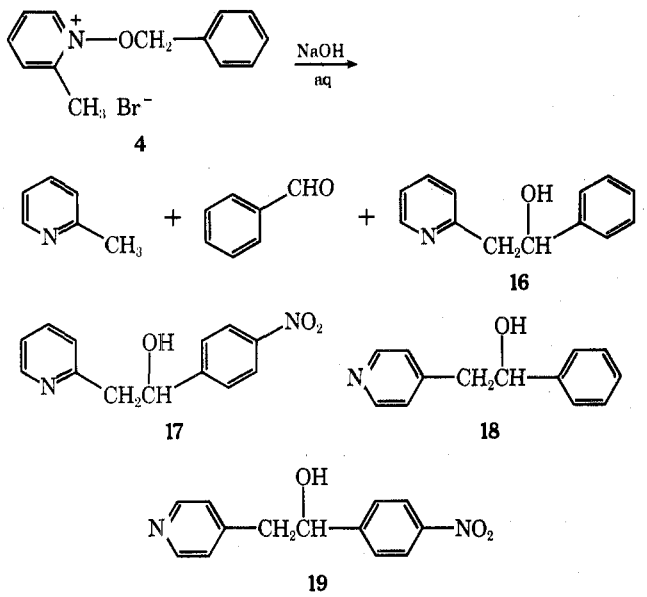
The mechanistic explanation of the alkaline decomposition of 1-methoxypyridinium methosulfate is generally viewed as a base-catalyzed E-2 type elimination.[7,10] However, Marmer and Swern[13] have shown that the reaction of 1-methoxy-2,6-dimethylpyridinium ion (**1**) (and most probably *N*-alkoxy-2-alkylpyridinium ions in general) and base proceed through the intermediate *N*-alkoxy anhydro base **2** to produce **3** and formaldehyde. We wish to report our results in this area which lend further support to Marmer and Swern's work and describe a new competing reaction.



The reaction of benzyl bromide or *p*-nitrobenzyl bromide and 2- or 4-alkylpyridine *N*-oxides was carried out in acetonitrile, nitromethane, chloroform, or ether under various conditions of temperature and time and gave *N*-benzyloxy-2- and 4-alkylpyridinium bromides in 53–96% yield (see Table I). The structures of the salts were established by their ir, NMR and mass spectra, and by elemental analysis. In the case of **4**, **7**, and **10** the bromide salts were converted to the corresponding perchlorates **5**, **8**, and **11** to facilitate elemental analyses. The mass spectra of the salts showed the molecular ion for the *N*-alkoxy cation in **4**, **9**, and **10**; however, the primary mode of fragmentation involved first reversal of the salt to the precursors benzyl bromide and the alkylpyridine *N*-oxide, then fragmentation of these latter two compounds. All of the *N*-benzyloxy salts exhibited molecular ion peaks at *m/e* 172 ($C_6H_5CH_2{}^{81}Br$) and 170 ($C_6H_5CH_2{}^{79}Br$) along with the characteristic tropylium ion at *m/e* 91 ($C_7H_7{}^+$),[15] while the fragmentation of the alkylpyridine *N*-oxide was identified by its M^+ and $(M - 16)^+$ peaks.

In general those salts with methyl or ethyl substituents on the pyridine ring were formed easily and in high yield, while considerable difficulty was encountered in the preparation of 2-benzylpyridinium salts regardless of the *N*-alkoxy group (e.g., methoxy, ethoxy, propoxy, butoxy, or benzyloxy). In the latter case inspection of models suggests that steric hindrance by the 2 substituent was probably a major inhibiting factor. In addition the 2- or 4-benzylpyridine salts **9** and **13** (an oil) reverted to starting materials on standing in solution (H_2O or D_2O); in contrast, **4** was stable in D_2O for periods up to at least 1 week.

The reaction of *N*-benzyloxy-2-methylpyridinium bromide (**4**) in aqueous sodium hydroxide gave 2-methylpyridine (68%) and benzaldehyde (70%) as previously reported by Boekelheide[7] but also produced a new product, 1-phenyl-2-(2-pyridyl)ethanol (**16**) (28% yield). 2-Methylpyridine and benzaldehyde were identified by comparison of their NMR spectra with those of an authentic sample and by preparation of known derivatives (picrate and 2,4-dinitrophenylhydrazone, respectively), while the known alcohol **16** was identified by its melting point and its ir and NMR



spectra. Inverse addition, namely salt solution added to sodium hydroxide solution, gave the same products in comparable yield, and variation of the reaction medium had little effect on the yield of alcohol **16** (23–30% yield) with the best alcohol yield obtained in dioxane–water (2:1).

Results for the alkaline decomposition of the other *N*-alkoxy salts are summarized in Table II. Condensation reactions were observed when a single methyl group was in the 2 or 4 position of the pyridine ring and gave alcohols **17**, **18**, and **19** identified by comparison of their melting points with literature values and by their ir and NMR spectra. *N*-Benzyloxy-2-ethyl-, 2,4-dimethyl-, and 2,6-dimethylpyridinium bromides produced only benzaldehyde and the corresponding alkylpyridine, while *N*-benzyloxy-2- and 4-benzylpyridinium bromides reverted to the corresponding benzylpyridine *N*-oxide.

Several reaction pathways were considered for the origin of the arylpyridylethanols **16–19**. First, the possibility of a base-catalyzed condensation of the products methylpyridine and benzaldehyde was excluded. The exposure of 2-methylpyridine and benzaldehyde or *p*-nitrobenzaldehyde to base under the same conditions as used in the alkaline decomposition of *N*-benzyloxy-2-methylpyridinium bromide did not produce alcohols **16** or **17** but gave near-quantitative yields of unreacted starting material. The preferred route in explaining the origin of alcohols **16–19** entails the formation of an intermediate anhydro base **20** which can condense with benzaldehyde, formed in a competing or subsequent reaction, to produce *N*-benzyloxy-2-(2-phenyl-2-hydroxyethyl)pyridinium salt (**21**). A base-catalyzed decomposition of **21** would form 1-phenyl-2-(2-pyridyl)ethanol (**16**) and benzaldehyde. Anhydro base **20** becomes especially attractive as an intermediate, since Marmer and Swern[13] have established that *N*-alkoxy anhydro bases are intermediates in the main reaction pathway leading to the alkylpyridine and aldehyde. Thus **20** may also undergo an intramolecular hydrogen transfer of a benzylic proton to the side chain methylene with elimination of benzaldehyde and formation of 2-methylpyridine. Therefore **20** can serve as a common intermediate, undergoing two competing reactions, which leads to the formation of all the observed reaction products.

In an attempt to increase the yield of alcohol **16** the reaction of **4** and base was performed in the presence of added excess benzaldehyde; however, only a small increase of **16** was observed. When *p*-nitrobenzaldehyde was added to the reaction of **4** and base, *p*-nitrobenzaldehyde reacted, in preference to benzaldehyde, with intermediate **20** to form the dipolar ion **21**, R = NO_2, which proceeded to alcohol **17** (10% yield) as the only alcohol product. Other products isolated from this reaction were benzaldehyde (80%), 2-methylpyridine (58%), unreacted *p*-nitrobenzaldehyde (70%), and, a real bonus, *N*-benzyloxy-2-(2-*p*-nitrophenyl-2-hydroxyethyl)pyridinium bromide (**22**, R = NO_2)

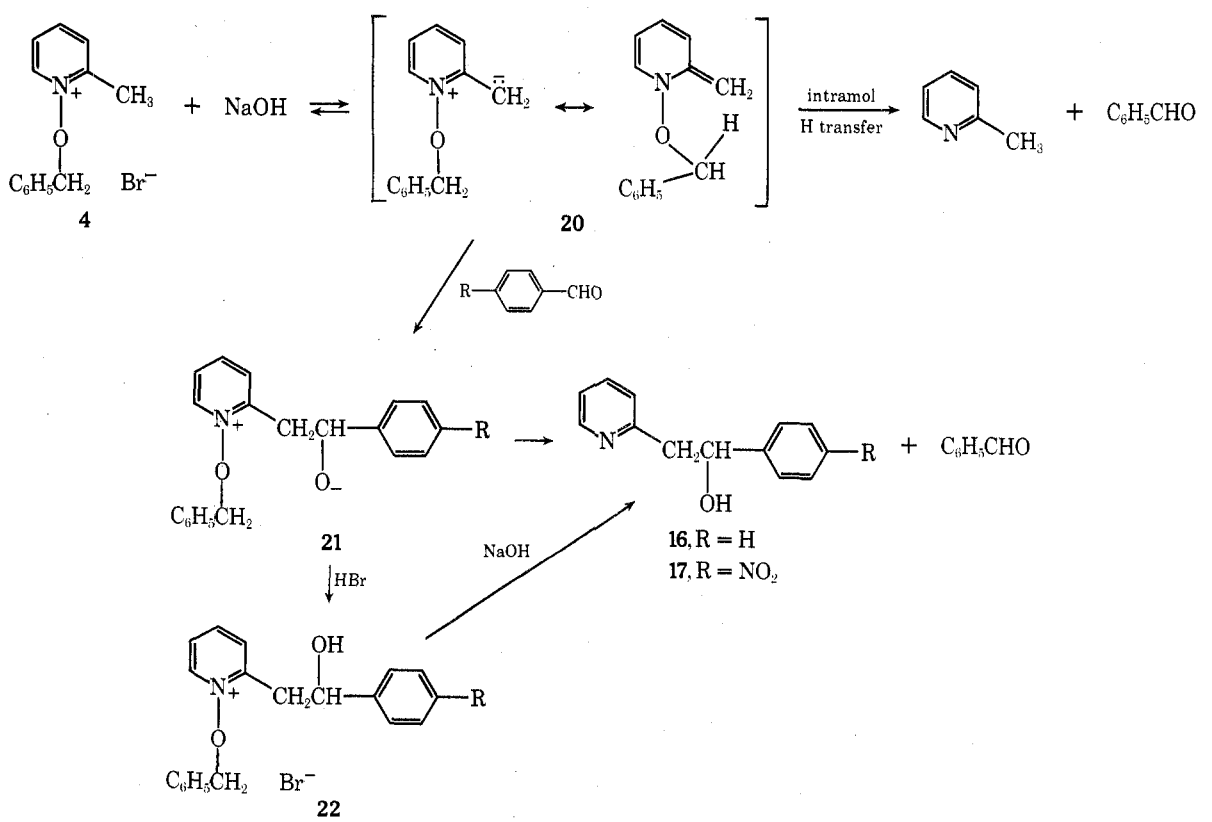
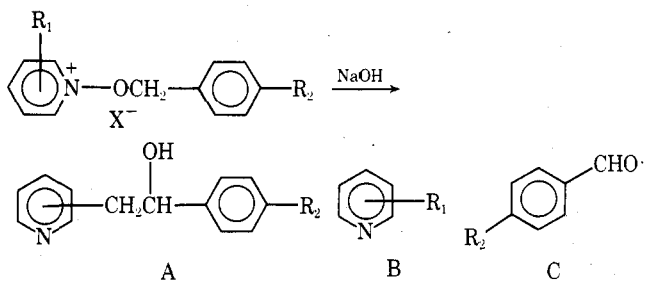


Table II
Reaction of *N*-Alkoxy-2- (and 4-) alkylpyridinium Salts with Sodium Hydroxide

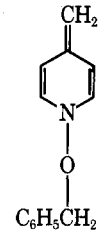


Compd	NaOH, (mmol)[a]	mmol	Solvent[b]	Time, hr	% yield A	B	C
4	(17.8)	18	A	1	29[k]	68[l]	70[m]
4	(17.8)[c]	18	A	1	26.5	67	60
4	(17.8)[d]	18	B	1	10	58	80[e,f]
4	(17.8)[d]	18	B	0.5			*g*
6	(4.6)	4.6	B	10	15[n]	62	60[o]
7	(10)	10	A	0.5		70[p]	100
9	(17.5)	19	A	1			*h*
10	(17.8)	18	A	1	18[q]	50[r]	59
12	(15.4)	16	B	1	23[s]	47	24[i]
13	(17.5)	19	A	1			*h*
14	(17.0)	18	A	1		84[t]	70
15	(6.8)	7.0	A	1		95[u]	98
22[v]	(4.5)	6.0	B	1	60		59[j]

[a] All reactions were carried out at room temperature. [b] A = H_2O; B = dioxane–H_2O (2:1). [c] This reaction was carried out by the addition of the salt 4 to NaOH. [d] The reaction was performed in the presence of *p*-nitrobenzaldehyde (17.8 mmol). [e] In addition to 80% benzaldehyde, 70% *p*-nitrobenzaldehyde, was recovered. [f] A new product, *N*-benzyloxy-2-(2-*p*-nitrophenyl-2-hydroxyethyl) pyridinium bromide (22), was formed in 13.5% yield. [g] The yield of 22 was 27.6%. Isolation of the other products was not attempted. [h] The corresponding *N*-oxide was recovered in near-quantitative yield. [i] Ca. 50% of the material was an unworkable tar. [j] Starting material, compound 22, was recovered in 36% yield. [k] Registry no., 2294-74-8.. [l] Registry no., 109-06-8. [m] Registry no., 100-52-7. [n] Registry no., 20151-01-3. [o] Registry no., 555-16-8. [p] Registry no., 100-71-0. [q] Registry no., 20151-37-5. [r] Registry no., 108-89-4. [s] Registry no., 20151-33-1. [t] Registry no., 108-47-4. [u] Registry no., 108-48-5. [v] Registry no., 55400-85-6.

(13.5%). The yield of **22**, R = NO_2, was increased to 28% when the reaction time was cut in half. Identification of **22**, R = NO_2, followed from elemental analysis, ir, and mass spectral data. The reaction of **22**, R = NO_2, in base for 1 hr at room temperature gave 59% yield of benzaldehyde, 60% yield of 1-*p*-nitrophenyl-2-(2-pyridyl)ethanol, and 36% unreacted **22**, R = NO_2. These results clearly support the above proposed sequence **20** → **21** or **22** → **16** or **17** as a reasonable pathway to these alcohols. Furthermore, the isolation of **22**, R = NO_2, can be viewed as trapping the intermediate anhydro base **20**, thus lending additional support to the Marmer–Swern mechanism of initial anhydro base formation.

The formation of 1-phenyl-2-(4-pyridyl)ethanol (**18**) and the *p*-nitro alcohol **19** from the base-catalyzed reaction of *N*-benzyloxy- and *N*-*p*-nitrobenzyloxy-4-methylpyridinium bromides can be explained as above involving an anhydro base intermediate **23**. However, the intramolecular hydrogen transfer pathway available for the fragmentation of **20** to form 2-methylpyridine and benzaldehyde is not feasible for **23** to provide 4-methylpyridine and benzaldehyde. This leaves open the possibility of a base-catalyzed E-2 elimination reaction of the *N*-benzyl-4-methylpyridinium cation or of a bimolecular fragmentation of **23** initiated by



23

either hydroxide ion or another molecule of anhydro base **23**. Deuterium-labeled experiments, similar to those used by Marmer and Swern, may shed some light on this point.

Experimental Section

***N*-Alkoxy-2- (and 4-) alkylpyridinium Salts.** An equimolar mixture of the 2- or 4-alkylpyridine *N*-oxide and benzyl bromide in the appropriate solvent (see Table I) was allowed to react for the specified time and temperature. The reaction mixture was cooled in an ice bath and the solid was filtered, washed with dry ether, and dried. In some cases the solvent of the reaction mixture was removed under reduced pressure and the residue was triturated or washed with ether, filtered, and dried.

The perchlorate salts were obtained by reaction of the *N*-benzyloxy-2- or 4-alkylpyridinium bromide in dilute hydrochloric acid with a saturated solution of sodium perchlorate. The resulting solution was filtered and dried.

Reactions of *N*-Alkoxy-2- (and 4-) alkylpyridinium Salts with Sodium Hydroxide. An appropriate volume of 1 *N* NaOH was added to a stirred solution of *N*-alkoxy-2- (or 4-) alkylpyridinium bromide (near equimolar quantities of salt and base were used, see Table II) in water or dioxane–water. The reaction mixture was stirred at room temperature for 1 hr and then acidified with 6 *N* HCl. After the acidified mixture was extracted with $CHCl_3$, the combined extracts were dried and the solvent was removed to give the aldehyde.

The acid aqueous phase was made slightly alkaline with solid $NaHCO_3$ and the precipitate was filtered and dried to give the 1-aryl-2-pyridylethanol.

The basic filtrate was extracted with $CHCl_3$, the extract was dried ($MgSO_4$) and filtered, and the solvent was removed to give the alkylpyridine.

Registry No.—**4**, 27371-06-8; **5**, 55400-75-4; **6**, 55400-76-5; **7**, 55400-77-6; **8**, 55400-78-7; **9**, 55400-79-8; **10**, 54531-19-0; **11**, 55400-81-2; **12**, 55492-94-9; **13**, 55400-82-3; **14**, 55400-83-4; **15**, 55400-84-5; 2-ethylpyidine *N*-oxide, 4833-24-3; 2-benzylpyridine *N*-oxide, 20531-86-6; 4-benzylpyridine *N*-oxide, 7259-53-2; 2,4-dimethylpyridine *N*-oxide, 1122-45-8; 2-methylpyridine *N*-oxide, 931-19-1; benzyl bromide, 100-39-0; sodium perchlorate, 7601-89-0; *p*-nitrobenzyl bromide, 100-11-8; 4-methylpyridine *N*-oxide, 1003-67-4; 2,6-dimethylpyridine *N*-oxide, 1073-23-0; 2,4-dinitrophenylhydrazone benzaldehyde, 1157-84-2.

Supplementary Material Available. The full experimental procedures for the preparation of **4–15**, their ir, NMR, and mass spectra data, and the reaction of these salts in base will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2365.

References and Notes

(1) For part VIII in this series see V. J. Traynelis, J. P. Kimball, and K. Yamauchi, *J. Org. Chem.*, **40**, 1313 (1975).
(2) Abstracted from a portion of the Ph.D. Dissertation submitted by J.P.K., West Virginia University, May 1972.
(3) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides", Organic Chemistry, Vol. 19, A. T. Blomquist, Ed., Academic Press, New York, N.Y., 1971, provides a listing of *N*-alkoxy quaternary salts of aromatic *N*-oxides.
(4) M. Henze, *Chem. Ber.*, **70**, 1270 (1937).
(5) E. Ochiai, M. Katada, and T. Naito, *J. Pharm. Soc. Jpn.*, **63**, 210 (1949); *Chem. Abstr.*, **45**, 5154 (1951).
(6) A. R. Katritzky, *J. Chem. Soc.*, 2404 (1956).

(7) W. Feely, W. L. Lehn, and V. Boekelheide, *J. Org. Chem.*, **22**, 1135 (1957).
(8) V. Boekelheide and W. Feely, *J. Am. Chem. Soc.*, **80**, 2217 (1958).
(9) N. A. Coats and A. R. Katritzky, *J. Org. Chem.*, **24**, 1836 (1959).
(10) A. R. Katritzky and E. Lunt, *Tetrahedron*, **25**, 4291 (1969).
(11) T. Kato, Y. Goto, and Y. Yamamoto, *Yakugaku Zasshi*, **84**, 287 (1964); *Chem. Abstr.*, **61**, 638*b* (1964).
(12) T. Cohen and I. H. Song, *J. Org. Chem.*, **31**, 3058 (1966).
(13) W. N. Marmer and D. Swern, *J. Am. Chem. Soc.*, **93**, 2719 (1971).
(14) T. Okamoto and H. Tani, *Chem. Pharm. Bull.*, **7**, 130, 925 (1959); H. Tani, *ibid.*, **7**, 930 (1959); W. E. Feely and E. M. Beavers, *J. Am. Chem. Soc.*, **81**, 4004 (1959); O. Cervinka, *Collect. Czech. Chem. Commun.*, **27**, 567 (1962), and subsequent papers; T. Okamoto and H. Takayama, *Chem. Pharm. Bull.*, **11**, 514 (1963); L. Bauer and L. A. Gardella, *J. Org. Chem.*, **28**, 1320 (1963), and subsequent papers; R. Eisenthal and A. R. Katritzky, *Tetrahedron*, **21**, 2205 (1965).
(15) P. N. Rylander, S. Meyerson, and H. M. Grubb, *J. Am. Chem. Soc.*, **79**, 842 (1957).

Dissociation Constants of the Amino-1,X-naphthyridines (X = 5, 6)

Ellis V. Brown,*[1] Stanley R. Mitchell,[2] and Andrew C. Plasz

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

Received March 6, 1975

The syntheses of 3-, 5-, and 8-amino-1,6-naphthyridines were accomplished. The second dissociation constants representing the transition from monocation to dication for 1,5- and 1,6-naphthyridine were determined. The first and second pK_a' values of the isomeric amino-1,5- and 1,6-naphthyridines were obtained by potentiometric and spectrophotometric methods. Only the 3-amino-1,5- and 3- and 8-amino-1,6-naphthyridines could be protonated a third time for which a third pK_a' value could be determined. The ultraviolet spectra of all the neutral molecules, mono-, di-, and, in the above-mentioned cases, trications, are presented.

The second dissociation constants of the aminoquinolines[3] and aminoisoquinolines[4] were determined previously. This was necessary in order to have a model with which the dissociation constants of the amino-1,5- and amino-1,6-naphthyridines could be correlated.

In the aminopyridines, aminoquinolines, and aminoisoquinolines, the first protonation occurs at the ring nitrogen. The pK_a' values for this process are most easily determined by potentiometric titration.[5] The second dissociation constants were obtained in highly acidic solutions. Therefore, ultraviolet spectroscopy is the method of choice[5] using the sulfuric acid–water H_0 scale[6,7] for solvent composition.

Amino-1,5-naphthyridines. Using the pK_a' values of aminopyridines and aminoquinolines as a basis, the possible position of the first protonation of the amino-1,5-naphthyridines can be advanced. The value for the first pK_a' of 1,5-naphthyridine in Table I is compared to the two values presently in the literature.[8,9] Our value (3.05 ± 0.02) was obtained by the same method that Albert and Phillips used. The pK_a' values for the amino isomers were calculated in the same manner and are also given in Table I. As in the cases of 4-aminopyridine[10] (Δ 4.02) and 4-aminoquinoline[11] (Δ 4.23), the basicity of the 4-amino-1,5-naphthyridine is enhanced (Δ 4.65) when all are compared to their parent ring systems. The 2-amino isomer (Δ 2.68) shows the same effect but to a lesser degree. The same trend is also seen with 2-aminopyridine[11] (Δ 1.63) and 2-aminoquinoline[11] (Δ 2.40). This similarity in basicity enhancement suggests that the first protonation occurs at the ring nitrogen of the substituted ring. In 3-amino-1,5-naphthyridine, the basicity is enhanced 1.85 pK units. This does not correlate with 3-aminopyridine[11] (Δ 0.75) and 3-aminoquinoline[11] (Δ 0.01), but does with 7-aminoquinoline[11] (Δ 1.71) and 3-aminoacridine[11] (Δ 2.44). This suggests that the site of the first protonation occurs at N-5—the nitrogen atom of the unsubstituted ring.

The second dissociation constants of 1,5-naphthyridine and its amino isomers appear in Table I. The antilogarithms of the individually calculated pK_a' values are averaged and converted back to a logarithm to obtain the particular pK_a' value. The maximum difference between this pK_a' value and the individually calculated values gives the "range". Albert[5] states that for a pK_a' value above 0, the range should not exceed ±0.06 units and below 0, ±0.1 units. Only in the 4-amino isomer could this satisfactory precision be obtained. Albert, Amarego, and Spinner[12] have observed similar results for the second dissociation constants of quinazoline (−5.5 ± 0.2), 4-methylquinazoline (−4.4 ± 0.2), and pyrimidine (6.3 ± 0.2). This discrepancy is probably due to the fact that the H_0 scale is based on primary aromatic amines as indicators and the function being protonated in our cases is most likely the second ring nitrogen. Arnett and Mach[13] have shown that aromatic tertiary amines do not follow the same H_0 scale as primary aromatic amines, but generate one of their own. A complete discussion of acidity functions and their abnormalities has been made by O'Conner[14] and references therein and Rochester.[15]

Only 3-amino-1,5-naphthyridine could be protonated a third time. The ultraviolet spectrum of the isolated trication at $H_0 = -10$ strongly resembles that of the dication of 1,5-naphthyridine. It has been shown with all of the aminoquinolines that the ultraviolet spectra of the isolated dications strongly resemble the quinolinium ion.[3] This would suggest that the primary amino group in 3-amino-1,5-naphthyridine is the final site of protonation. If the first protonation occurs at the 5 nitrogen as earlier suggested and the primary amino group is protonated last, then the 1 nitrogen in the substituted ring will be protonated in-between them. However, there is no evidence outside of the analogy of basicity enhancement for placing the first two protonations in this order for 3-amino-1,5-naphthyridine. In the 2- and 4-amino isomers this order should be reversed for the first two protonations.

Amino-1,6-naphthyridines. The values obtained for the first, second, and third dissociation constants for 1,6-naphthyridine and its amino isomers are given in Table II. The most basic site for protonation of 1,6-naphthyridine was shown by NMR spectroscopy to be N-6.[16] Its first pK_a' value, determined by potentiometric titration, was 3.78 ± 0.03.[17] The second dissociation constant, which was determined polarographically in aqueous perchloric acid, was found to be −0.30.[18] However, no range of values or temperature of solution was given. The second pK_a' value (−0.13 ± 0.06) was determined here with all proper specifications.