Experimental

Pyrazinium Salts (IIa, b, and c, Table I).—A solution of 0.2 mole of the pyrazine I and 0.2 mole of benzyl bromide in 125 ml. of acetone was heated under reflux for 2 hr. The pyrazinium salt which precipitated was removed by filtration. The filtrate was heated under reflux to cause precipitation of additional pyrazinium salt II. The process was repeated to give three crops of salt. The combined yield of II (a, b, or c) was stirred with acetone, and the suspension was separated by filtration. The solid was dried to give the salt II, in analytical purity.

Reduction of the Pyrazinium Salts (II) with Sodium Borohydride.—A solution of 0.06 mole of the pyrazinium salt (II) in 100 ml. of water was added slowly to a solution of 2.4 moles (9.1 g.) of sodium borohydride in 50 ml. of water. The mixture was stirred for 10 min. after the addition was complete, and then 10% hydrochloric acid was added until effervescence ceased. The solution was heated under reflux for 2 hr. to hydrolyze the amine boranes, and, with cooling, the solution was neutralized with sodium hydroxide. Sodium chloride was added to decrease the solubility of the amine, and the mixture was extracted with ether. After drying, the ether extracts were concentrated and the residue was distilled. The products are listed in Table II.

The Stereochemistry of the Product of the Sodium Borohydride Reduction of 1-Benzyl-2,5-dimethylpyrazinium Bromide (IIc).—A solution of 5.1 g. of isomeric 1-benzyl-2,5-dimethylpiperazines (IIIc) from the reduction of IIc dissolved in 60 ml. of ethanol was treated with hydrogen for 11 hr. at atmospheric pressure over 3 g. of 5% palladium on charcoal. The catalyst was removed by filtration, and the filtrate was divided into two portions of 30 ml.

Evaporation of the solvent from one portion gave a solid residue which was purified by sublimation to give 0.2 g. of solid, m.p. 113.5–115.5°. The melting point was not depressed on mixing with authentic *trans*-2,5-dimethylpiperazine,[8] m.p. 114–116°, and the infrared spectra of the solids were identical. The second portion of the hydrogenation product was converted to the picrate by treatment with a saturated alcoholic solution of picric acid. Recrystallization of the solid from ethanol–water gave 1.3 g. of picrate, m.p. 306–307° dec. The picrates of authentic samples of *cis*- and *trans*-2,5-dimethylpiperazine decompose at 272–273° and 307–308°, respectively.

Acknowledgment.—The authors wish to express appreciation to the National Cancer Institute of the National Institutes of Health for partial support of this research by Grant CA-04143 and continuation grants. The n.m.r. spectra were determined using a Varian A-60 spectrometer made available by Grant G 22718 from the National Science Foundation.

Aromatic N-Oxides. II.[1] N-Acetoxypyridinium Perchlorates

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A convenient method for preparing N-acetoxypyridinium perchlorates is reported. Reactions of these salts with water, ethanol, sodium acetate, triethylamine, and potassium cyanide have been studied. The reaction of 2-methylquinoline 1-oxide with acetic anhydride to yield 1-acetoxy-2-methylquinolinium acetate has been found to be reversible.

Many workers have postulated N-acyloxypyridinium ions, for example the cation of I, as intermediates in reactions. A partial list includes three groups[3–5] who have studied the mechanism of the formation of 2-pyridylmethyl acetate from 2-methylpyridine 1-oxide and acetic anhydride. Other workers have obtained products which may be postulated to occur by reaction of an N-acyloxypyridinium ion with cyanide ion,[6] chloride ion,[7] hydrogen and platinum,[8] enolate of ethyl cyanoacetate,[9] enamines,[10] tertiary amines,[11] and carboxylate salts.[12]

While our work was in progress the first report of the isolation of an N-acetoxypyridinium salt, 1-acetoxy-2-methylpyridinium picrate,[13] was made. We have obtained several N-acetoxypyridinium perchlorates as a result of titrating aromatic N-oxides dissolved in acetic anhydride–acetic acid solutions with perchloric acid in acetic acid.[1] By using the foregoing procedure two additional N-acetoxypyridinium perchlorates have been prepared.[14]

A more convenient method for preparing N-acetoxypyridinium perchlorates is the reaction of perchloric acid in acetic anhydride with a pyridine N-oxide dissolved in acetic anhydride and acetic acid. The products are obtained in high yield and generally do not require purification for further use. In this preparation the acylating agent is probably CH_3CO^+ or $(CH_3CO)_2OH^+$ or both.[15,16] The N-acetoxypyridinium perchlorates prepared in this manner are listed in Table I.

The structure assignments of the N-acetoxypyridinium perchlorates were based on their elemental analyses, infrared absorptions about 1830 cm.$^{-1}$,[13] and their hydrolysis to parent N-oxides.

Since pyridine is an excellent leaving group in the reaction of N-acylpyridinium ions[17] with nucleophiles and since aromatic N-oxides are less basic than pyridine,[18] one may expect N-acyloxypyridinium ions, for example the cation of I, to react with nucleophiles at the carbonyl carbon (attack a). The formation of anhydrides[12] from the reaction of the product of

(1) (a) Paper I: C. W. Muth, *et al.*, *Anal. Chem.*, **34**, 1163(1962); (b) from the M.S. Thesis, 1961, and Ph.D. Dissertation, 1964, of R. S. Darlak; (c) presented in part before the Organic Division of the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1962.

(2) This author wishes to express his appreciation for a fellowship given by the U. S. Office of Education, Department of Health, Education, and Welfare, during 1960–1963.

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

(4) V. J. Traynelis and R. F. Martello, *ibid.*, **80**, 6590 (1958).

(5) S. Oae, T. Kitao, and Y. Kitaoka, *ibid.*, **84**, 3359 (1962).

(6) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 243.

(7) I. J. Pachter, *J. Am. Chem. Soc.*, **75**, 3026 (1953).

(8) M. Hamana and K. Funagoshi, *Yakugaku Zasshi*, **80**, 1027 (1960).

(9) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 415 (1963).

(10) M. Hamana and M. Yamazaki, *ibid.*, **11**, 1331 (1963).

(11) M. Hamana and O. Hishino, *Yakugaku Zasshi*, **84**, 35 (1964).

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(13) V. J. Traynelis, A. I. Gallagher, and R. F. Martello, *J. Org. Chem.*, **26**, 4365 (1961).

(14) V. J. Traynelis and P. L. Pacini, *J. Am. Chem. Soc.*, **86**, 4917 (1964).

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(16) H. Burton and D. Paraill, *J. Chem. Soc.*, 1203 (1950).

(17) Q. E. Thompson, *J. Am. Chem. Soc.*, **73**, 5841 (1951).

(18) H. H. Jaffé and G. O. Doak, *ibid.*, **77**, 4441 (1955).

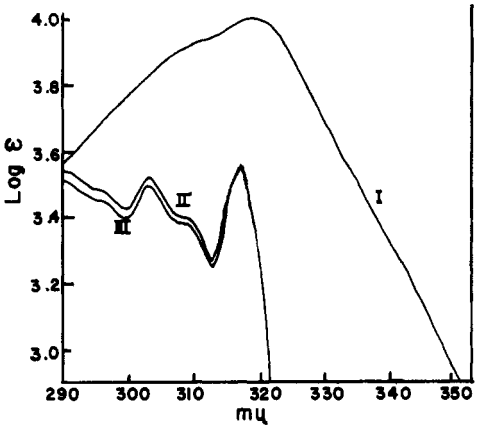
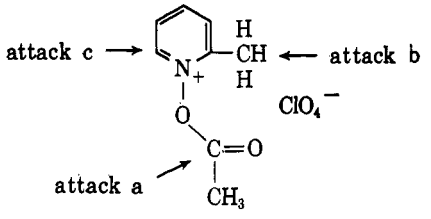


Figure 1.—Ultraviolet absorption spectra in acetic anhydride: I, 1-acetoxy-2-methylquinolinium perchlorate, λ_{max} 320 mμ (log ε 4.00); II, 1-acetoxy-2-methylquinolinium perchlorate and sodium acetate, λ_{max} 317 mμ (log ε 3.51); and III, 2-quinolylmethyl acetate, λ_{max} 317 mμ (log ε 3.55).



I

pyridine 1-oxide and acid chlorides with carboxylate ions probably involves attack a. Secondly, if N-acyloxypyridinium ions are intermediates in the reaction of 2- and 4-alkylpyridine N-oxides with acid anhydrides to form 2- and 4-pyridylmethyl esters,[3-5] respectively, then bases should remove a proton from the alkyl group (attack b) of the cation of I to initiate the formation of product. Thirdly, N-acyloxypyridinium ions may be expected to react with nucleophiles at the 2- and (or) 4-positions (attack c), since N-alkylpyridinium ions,[19] N-alkoxypyridinium ions,[20] N-acylpyridinium ions,[21] and pyridine undergo reactions with nucleophiles at these positions. All three types of reactions have been found.

TABLE I

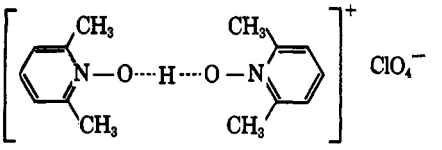
N-ACETOXYPYRIDINIUM PERCHLORATES

N-Acetoxy perchlorate of	% yield using 70% $HClO_4$	M.p.,[a] °C.	Calcd. mol. wt.	—Neut. equiv.— Method A	Method B
2-Methylpyridine, I	80	153–154.5	252	126	250
Pyridine, II	79	125–127.5	238	119	237
3-Methylpyridine, III	85	143.5–144.5	252	127	251
4-Methylpyridine, IV	79	84.5–86	252	127	253
2,6-Dimethylpyridine, V	96	145–147.5	266	133	267
Quinoline, VI	45	154.5–155.5	288	144	288
2-Methylquinoline, VII	87	152–153	302	152	301
Isoquinoline, VIII		Oil[b]			

[a] With decomposition. [b] The infrared spectrum of this oil indicated the N-acetoxy derivative.

When each of the N-acetoxypyridinium perchlorates listed in Table I was dissolved in water and the resulting solutions were titrated with aqueous base, neutralization equivalents were obtained which are approximately one-half the molecular weight of the N-acetoxypyridinium perchlorate. The observed neutralization equivalents are listed under method A in Table I. These data may be explained by assuming that water attacks the carbonyl carbon (attack a) of the N-acetoxypyridinium ion to produce the parent aromatic N-oxide and $CH_3CO_2H_2^+$. In contrast, the neutralization equivalents obtained by dissolving the N-acetoxypyridinium perchlorates in hot ethanol followed by titration with aqueous base (Table I, method B) are approximately the same as the molecular weights of the N-acetoxypyridinium perchlorates. These data may be explained by assuming that ethanol also attacks the carbonyl carbon. The expected products are the parent aromatic N-oxide and protonated ethyl acetate. Additional evidence for nucleophilic attack at the carbonyl carbon will be cited later.

1-Acetoxy-2,6-dimethylpyridinium perchlorate and the corresponding derivatives of quinoline, isoquinoline, and 2-methylquinoline when treated with small amounts of water or ethanol yielded di(aromatic N-oxide) hydrogen perchlorates, for example, di(2,6-dimethylpyridine 1-oxide) hydrogen perchlorate (IX). A description of some properties of these compounds may be found in the Experimental section in Table II.



IX

The structure assignment for di(2,6-dimethylpyridine 1-oxide) hydrogen perchlorate (IX) was made by Szafran[22] who prepared this compound by treating 2 moles of 2,6-dimethylpyridine 1-oxide with 1 mole of 70% perchloric acid in methanol. Vozza[23] has prepared and has studied some properties of similar compounds.

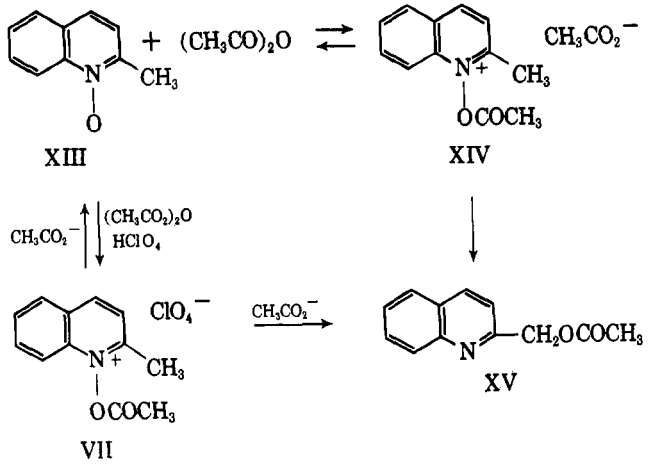
Compound IX must dissociate when dissolved in water because aqueous solutions of both IX and 2,6-dimethylpyridine 1-oxide have very similar ultraviolet spectra (λ_{max} 250 mμ). Compound IX when allowed to react with excess diazomethane yielded 1-methoxy-2,6-dimethylpyridinium perchlorate (89%).

The ultraviolet spectrum of 1-acetoxy-2-methylquinolinium perchlorate (VII) (Figure 1) in acetic anhydride is almost identical with the initial ultraviolet spectrum of a solution made from 2-methylquinoline 1-oxide dihydrate and acetic anhydride. This substantiates Furukawa's[24] hypothesis that 2-methylquinoline 1-oxide dihydrate reacts very rapidly with acetic anhydride to form 1-acetoxy-2-methylquinolinium acetate (XIV). This can be inferred because, at the concentrations involved, the ultraviolet absorbances of acetate and perchlorate ions are negligible.

The addition of sodium acetate in acetic acid to a solution of 1-acetoxy-2-methylquinolinium perchlorate

(19) K. Hafner, *Angew. Chem.*, **67**, 302 (1955).
(20) T. Okamoto and H. Tani, *Chem. Pharm. Bull.* (Tokyo), **7**, 925 (1959); *Chem. Abstr.*, **54**, 22644 (1960).
(21) W. E. Doering and W. E. McEwen, *J. Am. Chem. Soc.*, **73**, 2104 (1951).
(22) M. Szafran, *Bull. Acad. Polon. Sci., Ser. sci. chim.*, **11**, 111 (1963).
(23) J. F. Vozza, *J. Org. Chem.*, **27**, 3856 (1962).
(24) S. Furukawa, *Yakugaku Zasshi*, **79**, 492 (1959).

SCHEME I



(VII) in acetic anhydride produced a solution, the ultraviolet spectrum of which became the same as the spectrum of authentic 2-quinolylmethyl acetate (Figure 1). Also, the reaction of compound VII and sodium acetate in acetic anhydride during 1 hr. at 18° afforded 2-quinolylmethyl acetate (XV) in 71% yield. Therefore, 1-acetoxy-2-methylquinolinium ion when allowed to react with acetate ion in acetic anhydride produces a rearranged product, 2-quinolylmethyl acetate (XV). This type of reaction is believed to be initiated by removal of a proton from the methyl group by acetate ion (attack b).[3-5] (See Scheme I.)

The introduction of an acetoxy group to XV in the reaction of VII with sodium acetate is believed to be an intramolecular reaction because VII when treated with either triethylamine or potassium cyanide in acetonitrile afforded high yields of 2-quinolylmethyl acetate (XV). If the former reaction were intermolecular, one would expect the added bases to be incorporated in the product in the latter reactions. Similarly, Oae[25] has observed that all of the O^{18} of $C_6H_5CO^{18}Cl$ when the latter was treated with XIII was incorporated in the product, 2-quinolylmethyl benzoate.

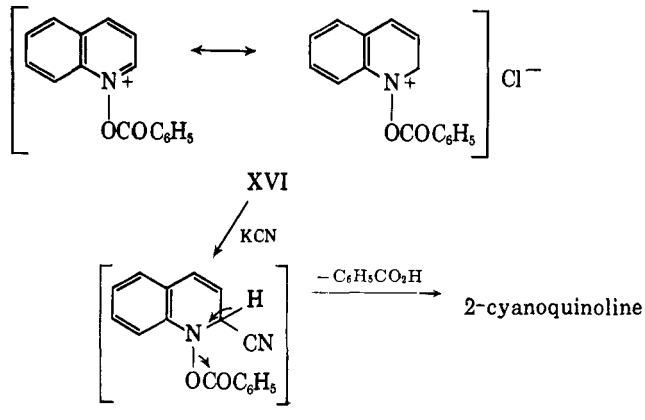
Reports on the mechanism of the reaction of pyridine N-oxides and acylating agents, including the most recent,[14,25,26] have not been explicit about the formation of N-acetoxypyridinium ions. We have made observations which lead us to conclude that this initial reaction is reversible; that is, acetate ion makes attack a. 1-Acetoxy-2-methylquinolinium perchlorate (VII) tagged with C^{14} at the carbonyl carbon was treated with sodium acetate in acetic anhydride and the reaction was interrupted by adding excess perchloric acid. The 1-acetoxy-2-methylquinolinium perchlorate (VII), recovered after 8.5 min. of reaction at about 18°, based on equal weights of initial and recovered VII, had only about 10% of the original radioactivity. This loss in activity can be explained by assuming that the added acetate ion displaced the acetyl group containing labeled carbon and that the generated N-oxide molecule then attacked unlabeled acetic anhydride which was in large excess to form unlabeled 1-acetoxy-2-methylquinolinium perchlorate (VII). Since the initial reactants for the foregoing equilibrium, 1-acetoxy-2-methylquinolinium and acetate ions, have been detected by ultraviolet studies (see earlier) during the reaction of 2-methylquinoline 1-oxide and acetic anhydride, one can conclude that the later reaction is also reversible.

The reaction of the cation of 1-acetoxy-2-methylquinolinium perchlorate (VII) with acetate ion is faster at the carbonyl carbon (attack a) than it is to form rearranged product (involving attack b) XV. This conclusion is based on the observation that the reaction of 1-acetoxy(carbonyl-C^{14})-2-methylquinolinium perchlorate with sodium acetate in acetic anhydride for 1 hr. at 18° afforded 2-quinolylmethyl acetate (XV) in 71% yield with retention of only one-fourth of the original radioactivity (on an equal molar basis).

The type of equilibra shown in Scheme I can be used to explain why 1-acetoxy-2-methylquinolinium perchlorate (VII) when treated with sodium butyrate in butyric anhydride yielded 2-quinolylmethyl butyrate rather than 2-quinolylmethyl acetate (XV) and also why acetic butyric anhydride was a product. One can theorize that reaction of the cation of VII with butyrate ion produces N-oxide XIII, which reacts with butyric anhydride to yield 1-butyroxy-2-methylquinolinium cation, which is induced in the presence of carboxylate ion to rearrange to 2-quinolylmethyl butyrate. Under the conditions of the experiment 2-quinolylmethyl acetate does not react to yield 2-quinolylmethyl butyrate.

The reaction of 1-acetoxy-2-methylpyridinium picrate with sodium acetate in acetic acid, conducted under reflux for 2 hr., has been reported[13] to yield no rearranged product, 2-pyridylmethyl acetate. Possibly this result is due to (1) the reaction of 1-acetoxy-2-methylpyridinium cation with acetate ion to form 2-methylpyridine 1-oxide which is complexed by picric acid and/or (2) the short reaction time. When 1-acetoxy-2-methylpyridinium perchlorate, sodium acetate, and acetic acid were heated under reflux for 33 hr., the rearranged product, 2-pyridylmethyl acetate, was obtained in 58% yield; however, when the reflux time was 16 hr., the yield of 2-pyridylmethyl acetate was about 30%.

1-Benzoyloxyquinolinium chloride (XVI) has been postulated[6] as an intermediate in the reaction of quinoline 1-oxide, benzoyl chloride, and potassium cyanide (modified Reissert synthesis) for the preparation of 2-cyanoquinoline.



In preliminary experiments to test this hypothesis 2-acetoxyisoquinolinium perchlorate (VIII) was prepared *in situ* and was allowed to react with potassium cyanide. The yield of 1-cyanoisoquinoline was 29%.

(25) S. Oae and S. Kozuka, *Tetrahedron*, **20**, 2671 (1964).

(26) S. Oae, Y. Kitaoka, and T. Kitao, *ibid.*, **20**, 267, 2685 (1964); S. Oae and S. Kozuka, **20**, *ibid.*, 2691 (1964).

In a similar experiment 1-acetoxyquinolinium perchlorate (VI) was converted to 2-cyanoquinoline in 15% yield. These are examples of attack c by the nucleophile on a N-acetoxypyridinium ion. Additional experiments of this type are planned.

In contrast to the foregoing, both 1-acetoxy-2,6-dimethylpyridinium perchlorate (V) and 1-acetoxy-2-methylquinolinium perchlorate (VII) when allowed to react with potassium cyanide in either acetic anhydride or dioxane afforded high yields of acetates which resulted from rearrangement reactions (attack b).

Experimental[27]

Preparation of N-Acetoxypyridinium Perchlorates.—An ice-cold solution of 1.3 g. (0.013 mole) of 70% perchloric acid in 5 ml. of acetic anhydride was added dropwise during 20 min. to a stirred, ice-cold solution of 1.0 g. (0.010 mole) of freshly distilled 2-methylpyridine 1-oxide in 10 ml. of acetic acid and 20 ml. of acetic anhydride. After continued cooling for about 20 min., white crystals were separated by filtration in a dry nitrogen atmosphere. The white crystals of 1-acetoxy-2-methylpyridinium perchlorate (I), m.p. 153.5–154.5° dec., after being washed with anhydrous ether weighed 1.85 g. (80%). The other N-acetoxy perchlorates listed in Table I were prepared in the same way except for 1-acetoxypyridinium perchlorate (II) and 1-acetoxy-2,6-dimethylpyridinium perchlorate (V). 1-Acetoxy-2-methylquinolinium perchlorate (VII) was also prepared by inverse addition.

1-Acetoxy-2,6-dimethylpyridinium perchlorate (V) was prepared by adding with stirring an ice-cold solution of 5.8 g. of 70% perchloric acid (0.041 mole) in 9.8 g. of acetic anhydride to 5.0 g. (0.041 mole) of 2,6-dimethylpyridine 1-oxide with ice cooling. The yield of white crystals, m.p. 145–148° dec., after washing with anhydrous ether was 10.45 g. (96%). 1-Acetoxypyridinium perchlorate (II) was prepared in a similar manner.

Generally, the N-acetoxy perchlorates were not recrystallized, but 1-acetoxy-2-methylquinolinium perchlorate (VII) can be recrystallized from 4:1 acetic acid–acetic anhydride or from acetone. The N-acetoxypyridinium perchlorates readily reacted with moisture but were not so hygroscopic as their parent N-oxides.

The perchlorates studied were stable as solids at room temperature and even in boiling acetic acid or acetic anhydride; however, we recommend that the perchlorates be handled in small quantities and behind shields.

Titration of Water Solutions and of Ethanolic Solutions of N-Acetoxypyridinium Perchlorates with Aqueous Sodium Hydroxide. Method A.—The perchlorates listed in Table I were dissolved in 50 ml. of warm distilled water; the solutions were cooled to room temperature and were titrated with aqueous sodium hydroxide using phenolphthalein as the indicator.

Method B.—The perchlorates were dissolved in 25 ml. of hot absolute ethanol (solution had odor of ethyl acetate); the solutions were immediately diluted with 25 ml. of distilled water and titrated with aqueous sodium hydroxide using phenolphthalein as the indicator.

Conversion of N-Acetoxypyridinium Perchlorates to Parent Aromatic N-Oxides.—A solution of 5.0 g. (0.019 mole) of 1-acetoxy-4-methylpyridinium perchlorate (IV) in 10 ml. of water was made alkaline with 20% sodium carbonate solution. The mixture was cooled in an ice bath and then filtered to remove white crystals which were recrystallized from ethyl acetate to yield 0.7 g. (32%) of 4-methylpyridine 1-oxide, m.p. 181–183°, m.m.p. 181–183° with authentic 4-methylpyridine 1-oxide.

Likewise, 1-acetoxy-2,6-dimethylpyridinium perchlorate (V) and 1-acetoxy-2-methylquinoline perchlorate (VII) were converted to their respective parent N-oxides, 2,6-dimethylpyridine 1-oxide and 2-methylquinoline 1-oxide.

(27) All melting points are uncorrected. All elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. All infrared measurements were made with a Perkin-Elmer Model 21 spectrophotometer. The samples were in potassium bromide unless otherwise indicated. Ultraviolet measurements for Figure 1 were made with a Beckman DU spectrophotometer; other ultraviolet measurements were made with a Bausch and Lomb 505 recording spectrophotometer.

Hydrogen Perchlorates of Dimers of Aromatic N-Oxides.—1-Acetoxy-2-methylquinolinium perchlorate (VII, 4.0 g., 0.013 mole) was dissolved in either 25 ml. of water or in 25 ml. of ethanol and the solution was cooled in an ice bath; white crystals separated which were collected by filtration. After the product was recrystallized three times from water, 2.9 g. (53%) of di(2-methylquinoline 1-oxide) hydrogen perchlorate (XI), m.p. 220–221°, was obtained. The other compounds listed in Table II were prepared by the same procedure.

The hydrogen perchlorates of the dimers of the N-oxides were dissolved in water and titrated with aqueous sodium hydroxide using phenolphthalein as the indicator. The results from the titrations are listed in Table II.

TABLE II

HYDROGEN PERCHLORATES OF DIMERS OF AROMATIC AMINE N-OXIDES

Hydrogen perchlorate of dimer of N-oxide of	% yield	M.p., °C.	Calcd. mol. wt.	Neut. equiv.
2,6-Dimethylpyridine	54	185.5–187[a]	347	346
Quinoline	40	188–189	391	388
2-Methylquinoline	53	220–221[b]	419	418
Isoquinoline	50	156.5–157.5	391	392

[a] Lit.[22] m.p. 185.5–186° dec. [b] Lit.[22] m.p. 215° dec.

1-Methoxy-2,6-dimethylpyridinium Perchlorate.—An excess of ethereal diazomethane was added dropwise to 75 ml. of anhydrous ether containing 1.7 g. (0.0049 mole) of di(2,6-dimethylpyridine 1-oxide) hydrogen perchlorate (IX). During the addition of diazomethane the mixture was stirred vigorously. The mixture was allowed to stand overnight and was filtered to remove white solid which was recrystallized from ethanol to yield 1.03 g. (89%) of 1-methoxy-2,6-dimethylpyridinium perchlorate as white crystals, m.p. 163–164°. The n.m.r. spectrum of the product[28] taken in deuteriochloroform showed a chemical shift for the methoxy hydrogens of 4.22 p.p.m. respective to tetramethylsilane.

Anal. Calcd. for $C_8H_{12}ClNO_5$: C, 40.43; H, 5.09; N, 5.89. Found: C, 40.20; H, 4.98; N, 6.02.

The analytical results for compounds I–VI and VIII–XII are given in Table III.

TABLE III

ELEMENTAL ANALYSES

	Calcd., %			Found, %		
Compd.	C	H	N	C	H	N
I	35.38	3.39	5.90	35.36	3.21	5.89
II	38.18	4.01	5.57	37.89	4.14	5.56
III	38.18	4.01	5.57	37.94	4.11	5.47
IV	38.18	4.01	5.57	38.08	4.16	5.51
V			5.27			5.20
VI	45.93	3.50	4.87	45.98	3.53	4.68
VIII	47.77	4.01	4.64	47.76	4.23	4.52
IX	48.62	5.24	8.10	48.75	5.44	7.92
X			7.17			7.03
XI	57.35	4.57	6.69	57.61	4.52	6.62
XII	55.32	3.87	7.17	55.36	3.78	7.19

2-Pyridylmethyl Acetate from 1-Acetoxy-2-methylpyridinium Perchlorate (I) and Sodium Acetate in Acetic Acid.—A mixture of 5.64 g. (0.0255 mole) of I in 30 ml. of anhydrous acetic acid[29] and 4.0 g. (0.0488 mole) of sodium acetate in 30 ml. of anhydrous acetic acid was heated under reflux for 33 hr. and was allowed to stand at room temperature for 16 hr. The mixture was made alkaline with 10% sodium hydroxide and was extracted with chloroform. The chloroform solution was dried over calcium chloride and concentrated by distillation, and the residue was distilled to yield 1.98 g. (58%) of 2-pyridylmethyl acetate as a pale yellow oil, b.p. 64–66° (0–1 mm.), $n^{18}D$ 1.5070 (lit.[3] $n^{20}D$ 1.4969). The picrate of the product melted at 164–166° (lit.[3] m.p. 168–168.5°).

(28) *We wish to thank Varian Associates, Palo Alto, Calif., for these measurements.*

(29) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1957, p. 281.

In a similar experiment in which the reflux time was 16 hr. the yield of 2-pyridylmethyl acetate was 31%. The infrared spectra of the products were nearly the same.

Reactions of 1-Acetoxy-2-methylquinolinium Perchlorate (VII). A. With Sodium Butyrate in Butyric Anhydride to Form 2-Quinolylmethyl Butyrate.—A mixture of 3.4 g. (0.011 mole) of VII, 1.23 g. (0.011 mole) of anhydrous sodium butyrate, and 30 ml. of butyric anhydride was stirred for 2 hr. at room temperature. The mixture was diluted with 200 ml. of ethyl ether and the insoluble material was removed by filtration. The ethereal solution was concentrated and the residue was distilled through a 4-in. Vigreux column. The fraction with boiling point at 100° (2 mm.) (fraction A) consisted of butyric acid and acetic butyric anhydride. A later fraction, 1.6 g. (58%), b.p. 153–154° (2 mm.), was a light yellow liquid whose infrared spectrum was identical with the infrared spectrum of 2-quinolylmethyl butyrate. Also, the mixture melting point of the picrate of the product with authentic picrate gave no depression. In other experiments the yield of 2-quinolylmethyl butyrate varied from 55 to 79%.

2-Quinolylmethyl butyrate was prepared in 69% yield from 2-methylquinoline 1-oxide and butyric anhydride.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.33; H, 6.59. Found: C, 73.51; H, 6.64.

Fraction A was analyzed by means of a Perkin-Elmer vapor fractometer Model 154, using a 0.25 in. × 6 ft. column packed with polypropylene glycol, UCON Oil LB-550-X, on Chromosorb W. This fraction contained butyric acid and acetic butyric anhydride. These components were identified by their retention times and by peak enhancement. Butyric acid and acetic butyric anhydride had retention times of 2.7 and 3.4 min., respectively. The column temperature was 200°; helium pressure was 20 p.s.i. with rotameter at 3.4.

The higher boiling fraction was heated under reflux with 10 ml. of 10% hydrochloric acid for 2 hr. The solution was cooled and extracted five times (5 ml. each) with ether. The combined ether extracts were dried over magnesium sulfate and the ether was removed by distillation through a 6-in. Heli-Pak column. The residue was identified as butyric acid by vapor phase chromatography.

B. With Triethylamine in Acetonitrile.—A mixture of 2.00 g. (0.007 mole) of VII, 1.34 g. (0.013 mole) of triethylamine, and 50 ml. of acetonitrile was stirred at room temperature for 9 hr. The reddish brown solution was concentrated using reduced pressure and the residue was twice chromatographed on alumina. Ethanol was both the solvent and the eluent for the chromatograms. The yield of light orange liquid, whose infrared spectrum was practically the same as that of 2-quinolylmethyl acetate, was 1.00 g. (75%). A picrate of the oil melted at 155–156°; mixture melting point with the picrate of authentic 2-quinolylmethyl acetate showed no depression.

C. With Potassium Cyanide in Acetonitrile.—This was carried out as was reaction B except that potassium cyanide was used instead of triethylamine. The yield of 2-quinolylmethyl acetate as a light orange oil was 90%.

Isotopic Studies with 1-Acetoxy(carbonyl-C^{14})-2-methylquinolinium Perchlorate (VII). A. Preparation of VII.—Solution A was prepared by adding 1.4 g. (0.0098 mole) of 70% perchloric acid to 3 ml. of acetic anhydride which was cooled in an ice bath. Solution B was prepared by consecutively adding 0.95 g. (0.006 mole) of anhydrous 2-methylquinoline 1-oxide, b.p. 164–166° (0–1 mm.), and 2 ml. of acetic anhydride which contained 185 mg. of acetic anhydride-1-C^{14}, 0.05 mc. (New England Nuclear Corp., Boston 18, Massachusetts), to 5 ml. of acetic acid which was cooled in an ice bath. Solution B was added to solution A with constant stirring and with cooling in an ice bath. White crystals were removed by filtration and were washed with anhydrous ether while under a dry nitrogen atmosphere. The yield of labeled VII was 1.46 g. (81%), m.p. 149–153° dec., and activity 877 c.p.m./mg.

B. Interruption of Reaction of 1-Acetoxy(carbonyl-C^{14})-2-methylquinolinium Perchlorate (VII) with Sodium Acetate.—To 18 ml. of freshly distilled acetic anhydride was added 0.45 g. (0.0015 mole) of labeled VII (727 c.p.m./mg.) with stirring. Anhydrous sodium acetate (0.122 g., 0.0015 mole) was added and the mixture was allowed to react at 17–19° with stirring. To a 5-ml. portion after 2.5 min. was added 0.5 ml. of 1 *N* perchloric acid and after 8.5 min. a 10-ml. portion was treated with 1 ml. of 1 *N* perchloric acid. Both portions were treated in the following manner. Anhydrous ether was added and the resulting solid material was separated by filtration and washed with anhydrous ether. A portion was retained for counting and the remainder was leached with acetone. The acetone solution when cooled in a Dry Ice bath yielded 1-acetoxy-2-methylquinolinium perchlorate (VII). The counting results are listed in Table IV.

TABLE IV

ACTIVITY OF 1-ACETOXY-2-METHYLQUINOLINIUM PERCHLORATE (VII) AFTER REACTION WITH SODIUM ACETATE

Time, min.	Recrystallized from acetone	M.p., °C.	C.p.m./mg.
0	No	149–153 dec.	727
2.5	No	132–135 dec.	404
2.5	Yes		369
2.5[a]	Yes		790
8.5	No	96–103 dec.	50
8.5	Yes	140–143 dec.	64

[a] Control run; no sodium acetate was added. Infrared spectra indicated that unaltered starting material was recovered.

When acetic acid, acetic acid–acetic anhydride (4:1), or acetic acid plus fuming sulfuric acid was used to recrystallize labeled VII, a loss in radioactivity was observed.

C. 2-Quinolylmethyl Acetate(carbonyl-C^{14}) (XV).—A solution of 0.285 g. (0.00096 mole) of labeled VII (877 c.p.m./mg.) in 11.4 ml. of acetic anhydride was effected by stirring. To this solution was added 0.083 g. (0.001 mole) of sodium acetate; the temperature was 17–19° for 1 hr., and then 1 ml. of 1 *N* perchloric acid was added. Anhydrous ether was added and the resulting ethereal solution was decanted from a precipitate. Sodium bicarbonate solution (3%) was added to the precipitate until the solution was basic to litmus. This mixture was extracted with ethyl ether and the ethereal solution was washed with water, dried, and concentrated to yield 0.135 g. (71%) of 2-quinolylmethyl acetate (XV). An infrared spectrum of the product matched that of pure material. The product had 349 c.p.m./mg. which on an equal molar basis is about one-fourth of the activity of the starting material.

D. Preparation of Samples for Counting Radioactivity.—A solution of approximately 15 mg. of sample/ml. of acetonitrile was made for each sample to be counted. A 0.1-ml. sample of solution was deposited on a piece of filter paper from which the solvent was allowed to evaporate. The filter paper was placed in a glass vial, and a solution of toluene and a scintillator were added. The activity was counted by a Model 314 EX-2 Tri-Carb liquid scintillation counting system during 10 min. Duplicate runs were made, and the average was reported.

1-Cyanoisoquinoline from 2-Acetoxyisoquinolinium Perchlorate (VIII).—Isoquinoline 2-oxide (5 g., 0.0345 mole) was dissolved in an ice-cold solution of 25 ml. of acetic acid and 20 ml. of acetic anhydride. To this solution with external ice cooling was slowly added a nearly ice-cold solution of 4.93 g. (0.345 mole) of 70% perchloric acid in 10 ml. of acetic anhydride. After the foregoing solution was cooled with ice, 2.2 g. (0.034 mole) of potassium cyanide in 90 ml. of acetic acid and 10 ml. of acetic anhydride were added slowly. The solution which immediately became cloudy was allowed to stand in an ice bath overnight after which white solid was removed by filtration. As ether was added to the filtrate, more white solid separated which was removed by filtration. The filtrate was concentrated, the residue was leached with ether, and the ethereal solution was concentrated to a deep brown residue. This residue was crystallized four times from water to yield 1.56 g. (29%) of 1-cyanoisoquinoline, m.p. 85–86° (lit.[30] m.p. 88–89°). The infrared spectrum showed a band at 2240 cm.$^{-1}$ assignable to the cyano group.

1-Cyanoisoquinoline (0.18 g.) was hydrolyzed[31] to yield 0.05 g. (17%) of 1-carboxyisoquinoline (from water), m.p. 159–160° (lit.[30] m.p. 161°).

2-Cyanoquinoline from 1-Acetoxyquinolinium Perchlorate (VI).—To a solution of 5.0 g. (0.0345 mole) of quinoline 1-oxide in 50 ml. of acetic acid and 50 ml. of acetic anhydride surrounded by an ice bath was added a nearly ice-cold solution of 4.9 g.

(30) J. J. Padbury and H. G. Tindwall, *J. Am. Chem. Soc.*, **67**, 1269 (1945).

(31) N. Cheronis and J. Entrikin, "Semimicro Qualitative Organic Analysis," Interscience Publishers, Inc., New York, N. Y., 1957, p. 501.

(0.0345 mole) of 70% perchloric acid in 10 ml. of acetic anhydride and 150 ml. of acetic acid. The solution was cooled to 0° and 4.5 g. (0.069 mole) of potassium cyanide in 100 ml. of acetic acid and 20 ml. of acetic anhydride was added. After the mixture had stood in an ice bath for 0.5 hr., white solid was removed by filtration. The filtrate on a steam bath was concentrated *in vacuo*. The red residue was leached with ether and the ethereal solution was washed three times with water and dried over Drierite. The solution was concentrated and the red residue was distilled (145–150° at 5 mm.) to yield after crystallization from water 0.8 g. (15%) of 2-cyanoquinoline, m.p. 91–92° (lit.[32] m.p. 94°). The infrared spectrum showed a band at 2240 cm.$^{-1}$ assignable to the cyano groups.

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(32) A. Kaufman, P. Dondliker, and H. Burkhardt, *Chem. Ber.*, **46**, 2929 (1913).

The Hantzsch Reaction. I. Oxidative Dealkylation of Certain Dihydropyridines

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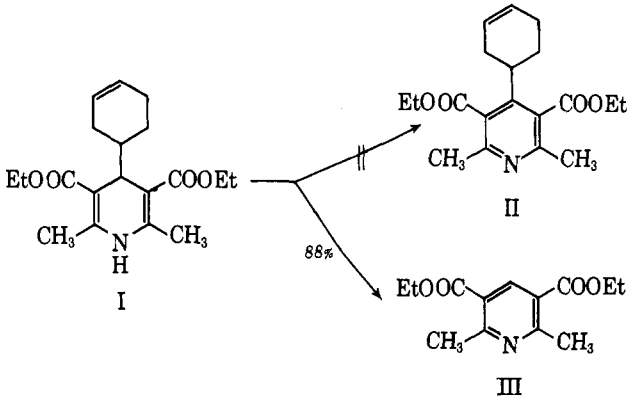
Oxidation of certain Hantzsch dihydropyridines (4-alkyl-3,5-dicarbethoxy- and 3,5-dicyano-1,4-dihydrolutidines) caused unexpected loss of the 4-substituent in addition to aromatization. A mechanism for the reaction is proposed.

One of the most widely used syntheses of pyridines is that developed by Hantzsch in 1882.[1,2] In a typical Hantzsch procedure, an aldehyde, ammonia, and a β-keto ester are condensed to give a dihydropyridine, which is subsequently oxidized to the pyridine.

In the course of attempting to synthesize a 4-cyclohexenylpyridine (II) by oxidation of the corresponding dihydropyridine (I) we found that the sole product was the *dealkylated* material III. This anomalous result led us to study the mechanism of the oxidation of the Hantzsch dihydropyridines.



The voluminous literature relating to the Hantzsch reaction reveals two pertinent references. In 1885, Engelmann[3] observed that, on oxidation of 2,6-dimethyl-3,5-dicarbethoxy-4-isopropyl-1,4-dihydropyridine (Table II, IVa, R = isopropyl) with "nitrous fumes," the isopropyl group was lost and III was obtained. In 1888, Jeanrenaud[4] noted the loss of the benzyl group when IVa (R = benzyl) was oxidized with nitrogen trioxide. Ayling[5] in 1938 reported that, when these same dihydropyridines were dehydrogenated with sulfur, the normal 4-substituted pyridines (A, Table II) were obtained.

A series of 4-substituted 3,5-dicarbethoxy- (IVa) and 3,5-dicyanodihydrolutidines (IVb) were prepared (Table I) and oxidized with nitrous acid in order to provide information necessary to postulate a mechanism for the reaction. The results of the oxidation experiments are tabulated in Table II.

Inspection of the table reveals that in the diester series (IVa), whenever R is a group having a moderate to strong electron-releasing ability (*e.g.*, secondary alkyl or benzyl[6]), it will be lost during the oxidation. In the cyano series (IVb), however, only when the R group is a strong electron releasor (*i.e.*, benzyl or *t*-butyl, but not secondary alkyl) does dealkylation occur.

These results are consistent with a mechanism involving elimination of a carbonium ion during the course of the oxidation; they also serve to emphasize the important influence of steric factors.

The unlikely possibility that the reaction involves a carbanionic displacement was eliminated since IVa (R = isopropyl) was recovered unchanged after stirring with sodium hydride in benzene while oxygen was bubbled through the solution. The most likely mechanism involves attack at the 1-position, as shown in eq. 1.[7]

(1) A. Hantzsch, *Ann.*, **215**, 1 (1882).

(2) R. A. Barnes, F. Brody, and P. R. Ruby, "Pyridine and Its Derivatives. Part I," in "The Chemistry of Heterocyclic Compounds," E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp. 80 and 500.

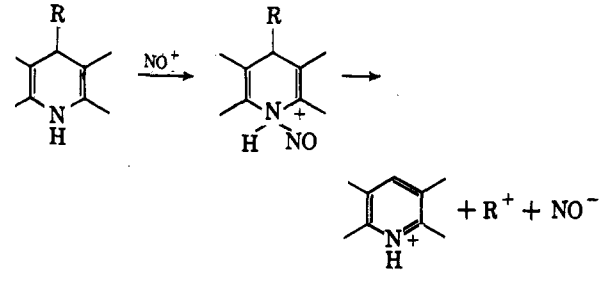
(3) F. Engelmann, *Ann.*, **231**, 37 (1885).

(4) A. Jeaurenaud, *Ber.*, **21**, 1783 (1888).

(5) E. E. Ayling, *J. Chem. Soc.*, 1014 (1938).

(6) The 4-*t*-butyl compound (IVa) could not be prepared, presumably because of steric hindrance.

(7) In this and subsequent discussions of mechanism, the result would be the same whether one postulates the first step to be hydride extraction, as in eq. 1, or nitrosation, as follows.



(1a)