which dissolved most of the material. The filtrate was slowly treated with glacial acetic acid to precipitate the product in crystalline form, 0.10 g., 65%, m.p. 159–161°. Recrystallization from aqueous alcohol gave m.p. 165–166°. At pH 6.5, the product exhibited two maxima: at 235 mμ (ε 5700) and at 280–281 mμ (ε 13,300).

Anal. Calcd. for $C_{11}H_{12}N_4O$: C, 61.11; H, 5.59; N, 25.92. Found: C, 61.32; H, 5.46; N, 25.79.

When the above reaction was carried out with added sodium bicarbonate (one-fourth of the starting material by weight), the yield of III dropped to 38% while the yield of II rose correspondingly to 25% (isolated as the alkali-insoluble fraction, *cf.* below).

1-Benzyl-5-amino-4-imidazolecarboxamide (II).—The N-benzylamidine formate salt (I, R = C_7H_7, 0.60 g.) was refluxed for 4 hr. in methanol (50 ml.) containing sodium methylate (1.9 equiv.). The solution was neutralized with acetic acid and taken to dryness under reduced pressure. The residue was triturated with cold 1 *N* NaOH which provided the product as the crystalline insoluble portion, 0.18 g., 39%, m.p. 235–240°. On recrystallization from aqueous alcohol the amide had m.p. 249–251°. (The alkaline filtrate when brought to pH 4, yielded 6% of the isomeric product III.) At pH 6.5, a single maximum absorption in the ultraviolet was found at 266–267 mμ (ε 12,800).

Anal. Calcd. for $C_{11}H_{12}N_4O$: C, 61.11; H, 5.59; N, 25.92. Found: C, 61.51; H, 5.58; N, 25.34.

The action of heat alone (15 min. at 155–160°)[3] on the hydrochloride of I gave 15–25% yields of the ring benzyl isomer (II) in a number of runs.

9-Benzylhypoxanthine.—1-Benzyl-5-amino-4-imidazolecarboxamide (110 mg.) was heated in formamide (5 ml.) at 180° for 1.5 hr. Long needles formed on cooling which were collected, dissolved in dilute alkali, and precipitated by acidification to yield 100 mg., m.p. 295–297°.[10]

Anal. Calcd. for $C_{12}H_{10}NO$: C, 63.71; H, 4.46. Found: C, 63.40; H, 4.37.

3-Benzylhypoxanthine.—4 (5)-Benzylamino-5(4)-imidazolecarboxamide (0.40 g.) was refluxed for 30 hr. in 98% formic acid (10 ml.) followed by removal of the formic acid. The residue was stirred with water with addition of aqueous sodium bicarbonate as needed to reach neutrality. The filtered product, 0.3 g., had m.p. 282–283° which remained unaltered on recrystallization from methanol. For 3-benzylhypoxanthine, λ_{max} 255 mμ (ε 9800) was observed in 0.1 *N* HCl and λ_{max} 265 mμ (ε 9400) in 0.1 *N* NaOH.

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 25.05. Found: C, 63.70; H, 4.46; N, 24.77.

When the refluxing was carried out for only 7 hr., considerable uncyclized formyl derivative was obtainable on fractional crystallization. The intermediate obtained has been characterized below.

4(5)-N-Benzylformamido-5(4)-imidazolecarboxamide.—To the benzylamino compound (III, 0.20 g.) in 98% formic acid (1 ml.) was added acetic anhydride (5 ml.), and the solution was held at 70° for 0.5 hr. After complete removal of the reagents, the residue was crystallized from ethyl acetate to yield 0.16 g., m.p. 188–189°.

Anal. Calcd. for $C_{12}H_{12}NO_2$: C, 59.02; H, 4.95; N, 22.9. Found: C, 59.22; H, 4.09; N, 22.3.

Spectral Properties of Malonamamidine, Formamidomalonamamidine, and Carbethoxymalondiamidine.—Malonamamidine hydrochloride[3] in 0.01 *N* NaOH exhibited λ_{max} at 270 mμ (ε 7600), probably a low value due to instability at this pH. The absorption disappeared on acidification. In 0.05 *M* glycine buffer, pH 10, the peak had a low intensity, about 9% of that seen in 0.01 *N* NaOH. In acylamidomalonamamidines, absorption maxima appear at much lower pH values. Dilutions of formamidomalonamamidine hydrochloride[3] were made in a series of phosphate buffers. With increasing pH, a band at 268–270 mμ of increasing intensity was observed reaching a maximum molar extinction coefficient of 20,000 at pH 8.6 and above. It could be estimated that an acid of p*K* about 7.5 was concerned. Below pH 4.5, solutions of the amidine were transparent down to 225 mμ and the absorption observed above that pH completely disappeared on acidification. Near pH 12, the absorption gradually diminished on standing owing to hydrolysis.

Carbethoxyamidomalondiamidine dihydrochloride[11] behaved similarly with a pH-dependent band appearing at 288 mμ (ε 21,700). An estimated p*K* of 5.2 for the acid producing this species on ionization was reached from examination of the absorption at various pH values.

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[10] J. A. Montgomery and C. Temple [*J. Am. Chem. Soc.*, **83**, 630 (1961)] gave an alternate synthesis of 9-benzylhypoxanthine.

[11] E. Shaw and D. W. Woolley, *J. Biol. Chem.*, **194**, 641 (1952).

Aromatic Substitution. XXIII.[1] Nitration and Nitrosation of Pyridine with Nitronium and Nitrosonium Tetrafluoroborate. Isolation of N-Nitro- and N-Nitrosopyridinium Tetrafluoroborates

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The nitration and nitrosation of pyridine with nitronium and nitrosonium tetrafluoroborate was investigated in nitromethane, acetonitrile, tetramethylene sulfone, and sulfur dioxide solutions. Exclusive N substitution was observed, with no evidence of N → C migration, even at elevated temperatures. The stable crystalline N-nitro- and N-nitrosopyridinium tetrafluoroborates were isolated and their structure was proved through analytical and spectroscopic (infrared and n.m.r.) data. Previously reported direct N nitrations of pyridine must be considered as nitrations of pyridinium salts (formed in the acidic reaction media).

The pyridine nucleus was reported to be resistant to electrophilic nitration, which could be effected only under drastic conditions.

Friedl[3] first reported the nitration of pyridine. He obtained a 15% yield of nitropyridine with potassium nitrate and fuming sulfuric acid at 330°. Other investigators, however, using the same procedure could not obtain more than 1% yield.[4,5]

The use of nitrogen dioxide and aluminum chloride leads to an addition compound of nitrogen dioxide and pyridine.[6] 3-Nitropyridine was reported to be obtained, however, by treatment of pyridine with nitrogen dioxide and carbon dioxide at 115–120°.[7]

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[1] Part XXII: G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, *J. Am. Chem. Soc.*, **86**, 2203 (1964).

[2] Visiting Professor of Chemistry, The Ohio State University, 1963; to whom correspondence should be addressed at the Department of Chemistry, Western Reserve University, Cleveland, Ohio.

[3] F. Friedl, *Ber.*, **45**, 428 (1912); *Monatsh.*, **34**, 759 (1913).

[4] A. Kirpal and E. Reiter, *Ber.*, **58**, 699 (1925).

[5] H. J. den Hertog, Jr., and J. Overhoff, *Rec. trav. chim.*, **49**, 552 (1930).

[6] A. Schaarschmidt, H. Balzerkiewicz, and J. Gante, *Ber.*, **58**, 499 (1925).

[7] P. Schorigin and A. V. Topchiev, *ibid.*, **69**, 1874 (1936).

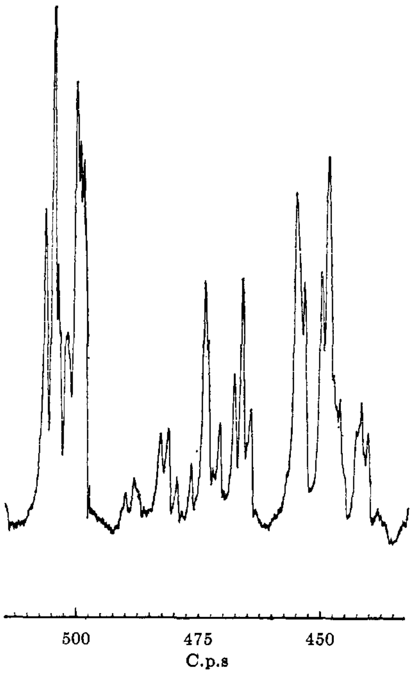


Figure 1.—N.m.r. spectrum of N-nitropyridinium tetrafluoroborate at 60 Mc. in sulfur dioxide solution at −40°.

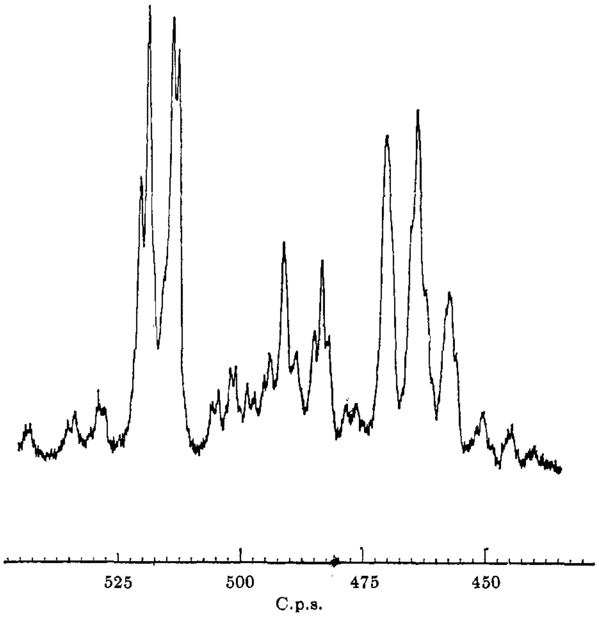


Figure 2.—N.m.r. spectrum of N-nitrosopyridinium tetrafluoroborate at 60 Mc. in sulfur dioxide solution at −40°.

The resistance of the pyridine ring toward electrophilic nitration and the formation of 3-nitropyridine as the nitration product under forceful conditions seem to indicate the formation of a positive pyridinium ion in acid nitrating media, which exerts a powerful deactivating effect by reducing the electron density throughout the ring but particularly in the 2 and 4 positions.[8]

The nitration of pyridine under "neutral" conditions has not been extensively studied. Haines and Adkins[9] found that dinitrogen pentoxide forms an addition compound with pyridine, but no nitropyridines were detected. Hetherington and Robinson[10] reported that a small amount of 3-nitro pyridine formed in the reaction of pyridine with nitryl fluoride. The hydrofluoride of 3-nitropyridine was also formed.

Foster[11] was able to show that the reaction of pyridine and dinitrogen pentoxide leads to the formation of N-nitropyridinium nitrate. Sodium hydroxide, aniline, and excess pyridine reacted with N-nitropyridinium nitrate and caused ring fission, derivatives of glutaconic dialdehyde being formed.

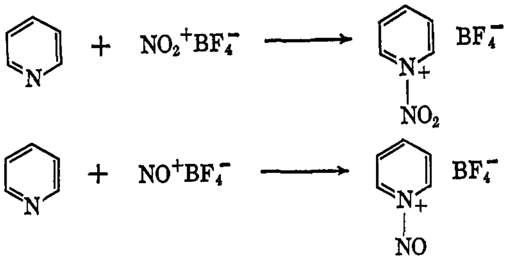
Independently, as learned after the completion of our investigations, Jones and Jones[12] studied the nitration of pyridine with nitronium tetrafluoroborate in tetramethylene sulfone solution. Based on ultraviolet, infrared, and n.m.r. spectra they concluded that the attack of the nitronium ion is on the nitrogen atom, but they have not isolated pure N-nitropyridinium tetrafluoroborate or identified secondary products (formed from cleavage reactions involving excess pyridine).

No direct electrophilic nitrosation of pyridine was reported in the literature.

Results and Discussion

To investigate the nitration and nitrosation of pyridine under "neutral" conditions we have carried out an investigation of the reaction of pyridine with nitronium and nitrosonium tetrafluoroborate.

It was found that, if pyridine were added to an *excess* of the nitronium or nitrosonium salt in tetramethylene sulfone, acetonitrile, nitromethane, or sulfur dioxide solution, a practically quantitative yield of the N-nitro- and N-nitrosopyridinium tetrafluoroborate complexes was obtained. If, however, the nitronium or nitrosonium salt was added to excess pyridine, ring cleavage only was observed (see subsequent discussion).



N-nitro and N-nitrosopyridinium tetrafluoroborate could be isolated as stable, crystalline compounds. The nitronium salt is colorless, whereas the nitrosonium salt is very slightly greenish colored. They are sensitive to moisture, but otherwise quite stable (see Experimental Section).

Spectroscopic Investigations. A. Nuclear Magnetic Resonance.—The proton magnetic resonance spectra of the isolated N-nitro- and N-nitrosopyridinium tetrafluoroborate (in sulfur dioxide solution at −40°) were obtained and show the typical characteristics of the pyridinium-type ring hydrogens (Figures 1 and 2). The chemical shifts of the ring protons, compared with those of pyridinium tetrafluoroborate in the same solvent, are summarized in Table I.

A proper analysis of the proton spectra implies an AB_2X_2 approach which was not feasible for the scope of

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[8] R. H. Mizzoni in "Pyridine and Its Derivatives," E. Klingsberg, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, Part II, p. 470.

[9] L. B. Haines and H. Adkins, *J. Am. Chem. Soc.*, **47**, 1419 (1925).

[10] G. Hetherington and P. L. Robinson, *J. Chem. Soc.*, 3512 (1954).

[11] P. W. Foster, Abstracts of Papers, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1959, and personal communication.

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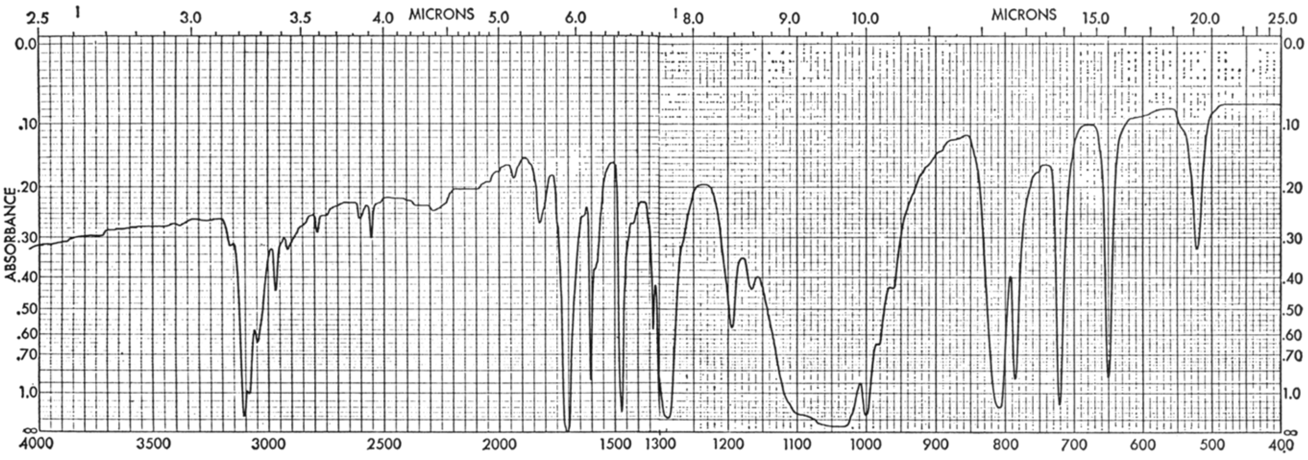


Figure 3.—Infrared spectrum of N-nitropyridinium tetrafluoroborate.

Table I

Proton Shifts[a] for Pyridinium Tetrafluoroborates in Sulfur Dioxide Solution at −40°

Compd.	Hydrogens α	Hydrogens β	Hydrogens γ
$C_5H_5N^+NO_2\ BF_4^-$	−9.15	−7.88	−8.52
$C_5H_5N^+NO\ BF_4^-$	−8.63	−7.77	−8.25
$C_5H_5N^+H\ BF_4^-$	−8.22	−7.54	−8.03

[a] δ in parts per million from external tetramethylsilane standard.

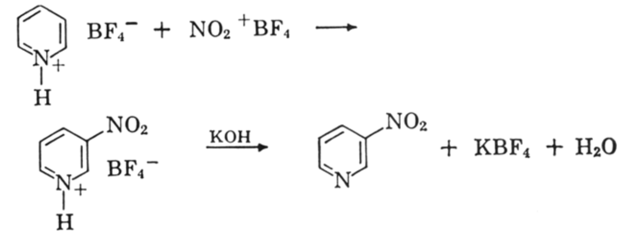
our investigation. A comparison with reported spectra of pyridinium halides[13] shows very satisfactory agreement. The *ortho* coupling constants are about 7 c.p.s., the *meta* and *para* coupling constants are considerably smaller. Chemical shifts for the different ring hydrogens atoms in substituted aromatic compounds, as the pyridinium salts are, have been ascribed to (1) charge distribution around the ring, (2) ring currents, and (3) special solvent effects.

In systems involving the same ring current and common solvent, chemical shifts among the ring hydrogens are probably directly caused by variations in the charge distribution around the rings.[14] The shifts for the α, β, and γ hydrogens relative to N^+ indicate the reduced electron density around the ring as compared with pyridine.[15] The decreasing deshielding caused by $^+NH < {}^+NNO < {}^+NNO_2$ is in accordance with the electron-withdrawing power of NO_2 and NO. The observed shifts were assumed to be unperturbed by the common anion (BF_4^-). A limited amount of work was done with increasingly bulkier anions (PF_6^-, AsF_6^-, and SbF_6^-) showing no effect of the anions on the ring protons.

Infrared Spectra.—The infrared spectra of N-nitro and N-nitrosopyridinium tetrafluoroborates were obtained as Nujol–Fluorolube mixed mulls. The spectrum of N-nitropyridinium tetrafluoroborate is shown in full in Figure 3. A comparison with the infrared spectrum of pyridinium tetrafluoroborate allows the assignment of the characteristic bonds additional to the pyridinium bands. The NO_2 asymmetric stretching is at 1705 cm.$^{-1}$, the N–N stretching at 1602 cm.$^{-1}$, and the N–N deformation at 650 cm.$^{-1}$. In N-nitrosopyridinium tetrafluoroborate the NO stretching frequency is at 1801 cm.$^{-1}$.

Chemical Behavior.—No N → C nitro (nitroso) group migration was observed on heating or even thermal decomposition of the pyridinium salts. Results indicate that direct electrophilic nitration and nitrosation of pyridine is exclusively N not C substitution.

In acid media pyridine is present as a pyridinium salt. Therefore our investigations were extended to the nitronium salt nitration of pyridinium salt. This could be effected giving preferentially the 3-nitropyridinium compound. The much weaker electrophilic nitrosonium salts did not attack pyridinium salts. N-Nitropyridinium tetrafluoroborate was found unsuitable for nitrating aromatic compounds, as toluene and benzene. It does, however, O-nitrate alcohols and water. The characteristic stability of the pyridine ring is lost when quaterization by an electron-withdrawing group has taken place.



Zincke and his co-workers observed[16] that 1-(2,4-dinitrophenyl)pyridinium chloride, readily formed from 2,4-dinitrochlorobenzene and pyridine, is quite stable in acid or neutral solution. In alkali, however, a red sodium salt is formed by rupture of the ring to a derivative of glutaconaldehyde. A crystalline dianilide may be easily obtained from the sodium salt. Similar ring openings were reported by interaction with organic amines. Konig[17] found similar lability in the adduct of pyridine with cyanogen bromide. Baumgarten[18] has shown the ease of opening the pyridine ring in the addition compounds with sulfur trioxide, chlorosulfonic acid, and ethylchlorosulfonate.

The quaternary adduct of pyridine and *p*-nitrobenzoyl chloride also promoted ring cleavage.[19]

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(13) G. Kotowycz, T. Schaeffer, and E. Bock, *Can. J. Chem.*, **42**, 2541 (1964).

(14) G. Fraenkel, *J. Chem. Phys.*, **39**, 1614 (1963).

(15) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 266–267.

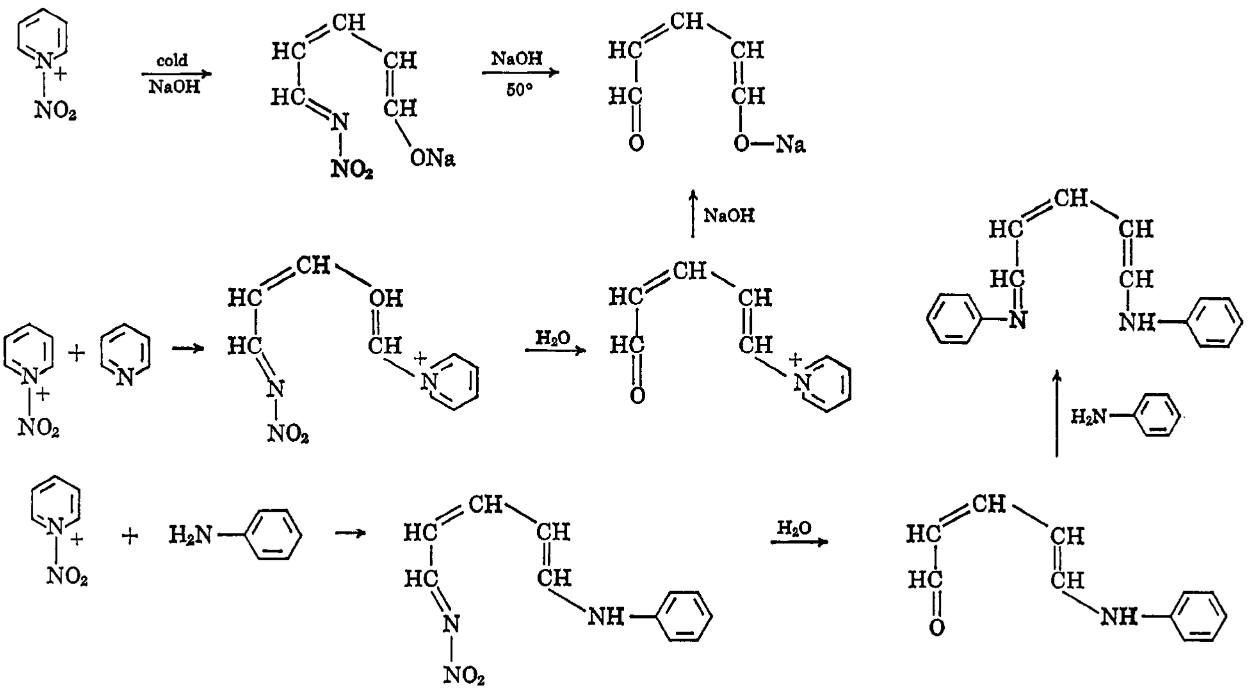
(16) T. Zincke, *Ann.*, **330**, 367 (1904); T. Zincke, *et al.*, *ibid.*, **333**, 296 (1904); T. Zincke and Winker, *ibid.*, **338**, 167 (1905); **341**, 365 (1905).

(17) W. Konig, *J. prakt. Chem.*, **69**, 105 (1904); W. Konig and R. Bayer, *ibid.*, **83**, 325 (1911).

(18) P. Baumgarten, *Ber.*, **57**, 1622 (1924); **59**, 1166 (1926).

(19) P. Pfeiffer and E. Enders, *Ber.*, **84**, 313 (1951).

SCHEME I



N-nitro- and N-nitrosopyridinium tetrafluoroborate undergo with ease opening of the pyridine ring under akaline reaction conditions. Treatment of the salts with excess pyridine, aniline or with strong aqueous sodium hydroxide results in the formation of the sodium salt of glutaconaldehyde.

Experimental Section

Nitronium tetrafluoroborate of high purity was prepared as previously described from NO_2F and BF_3.[20] Nitrosonium tetrafluoroborate was prepared from NOF and BF_3 in Freon 113 solution under similar conditions.

The organic reagent (pyridine) and solvents (nitromethane and acetonitrile) used were rigorously purified. Great care was taken to remove water. The purification of nitromethane was described previously.[21] Acetonitrile and pyridine were purified by standard methods, distilling from phosphorus pentoxide and barium oxide, respectively, in a dry nitrogen atmosphere through a Todd column. Owing to the very hygroscopic nature of both nitronium and nitrosonium salts, all operations were strictly carried out under dry nitrogen in a Kewaunee-type drybox.

Infrared spectra were obtained on a double-grating Perkin-Elmer Model 336 spectrophotometer, ultraviolet spectra on a Cary Model 14 spectrophotometer, and n.m.r. spectra on a Varian Model A-60 instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Preparation of N-Nitropyridinium Tetrafluoroborate. A. In Nitromethane.—To a cold (0°) well-stirred dispersion of 6.6 g. (0.05 mole) of nitronium tetrafluoroborate in 30 ml. of nitromethane was added an equally cold solution of 3.0 g. (0.045 mole) of pyridine in 30 ml. of nitromethane. After the addition was completed, the pale green solution was stirred for another 15 min. Benzene (2 ml.) was added in small portions to eliminate the excess unreacted nitronium salt. The major part of the solvent was then pumped off *in vacuo;* the precipitated complex was filtered, washed with cold 1,1,2-trifluorotrichloroethane, and recrystallized from nitromethane to yield 8.2 g. (95.4%) of N-nitropyridinuim tetrafluoroborate, m.p. 164–166°.

Anal. Calcd. for $C_5H_5BF_4N_2O_2$ (221.9): C, 28.34; H, 2.38; F, 35.86; N, 13.22. Found: C, 28.54; H, 2.53; F, 34.89; N, 12.98.

B. In Acetonitrile.—To a cold stirred suspension of 26.6 (0.2 mole) of nitronium tetrafluoroborate in 200 ml. of acetonitrile was added 15 g. (<0.2 mole) of pyridine dissolved in 50 ml. of acetonitrile. The reaction was carried out further as given in A.

Preparation of N-Nitrosopyridinium Tetrafluoroborate A. In Nitromethane.—A solution of 16 g. (0.2 mole) of pyridine in 120 g. of nitromethane was cooled to 0° and added dropwise into a stirred cold suspension of 23.6 g. (0.2 mole) of $NO^+BF_4^-$ in 22.50 g. of nitromethane. The reaction mixture was stirred for another 15 min. at 0° and then allowed to warm to room temperature. The solvent was pumped off *in vacuo*. The remaining slightly greenish salt was recrystallized from nitromethane, filtered, washed with cold 1,1,2-trifluorotrichloroethane, and dried *in vacuo:* m.p. 155–158°.

Anal. Calcd. for $C_5H_5BF_4N_2O$ (195.9): C, 30.65; H, 2.57; F, 38.79; N, 14.30. Found: C, 31.42; H, 2.78; F, 38.11; N, 13.97.

B. In Acetonitrile.—A solution of 16 g. of pyridine in 50 ml. of acetonitrile was added to a solution of 23.6 g. of $NO^+BF_4^-$ in 150 ml. of acetonitrile. The reaction was performed as described in A.

Ring Openings.—Both N-nitro- and N-nitrosopyridinium tetrafluoroborate gave colorless solutions in acetonitrile or tetramethylene sulfone. These solutions turned deep red upon addition of sodium hydroxide, excess pyridine, or aniline. On dilution of the alkaline solutions to a known concentration, the ultraviolet absorption spectra were identical with that given by Baumgarten[18] for the sodium salt of glutaconic dialdehyde: λ_{max} 362 mμ (log ε 4.48).

The dianil of glutaconic dialdehyde was prepared in the following way. An ice-cold suspension of either N-nitro- or N-nitrosopyridinium tetrafluoroborate in 1,1,2-trifluorotrichloroethane (Freon 113) was added slowly to 2 equiv. of aniline in the same solvent at 0°. The deep red dianil separated at once. It was purified by recrystallizations from methyl alcohol containing hydrobromic acid; the dianil hydrobromide melted at 169–171°.[22]

Anal. Calcd. for $C_{17}H_{17}BrN_2 \cdot H_2O$: C, 58.8; H, 5.5; Br, 23.0; N, 8.1. Found: C, 58.90; H, 5.43; Br, 22.95; N, 8.03.

The infrared and n.m.r. spectra were identical with those of an authentical synthetic sample. The ultraviolet spectrum was also identical with the synthetic sample and with that in the literature[23]: λ_{max} 261, 272, and 475 mμ (log ϵ_{max} 3.6, 3.75, and 4.78, respectively).

Acknowledgment.—Professor M. S. Newman is thanked for his outstanding hospitality in the use of his laboratory.

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[23] G. Schwarzenbach, K. Lutz, and E. Felder, *Helv. Chim. Acta*, **27**, 582 (1949).