of 2,10-dichlorophenoxaphosphine (bp 135° at about 5 mμ), which melted at 120–122°.

Anal. Calcd for $C_{12}H_7Cl_2OP$: Cl, 26.35; P, 11.51. Found: Cl, 26.15; P, 11.54.

2-Chlorophenoxaphosphinic Acid.—2,10-Dichlorophenoxaphosphine was hydrolyzed and oxidized in an alkaline solution of hydrogen peroxide to give (after acidification) 2-chlorophenoxaphosphinic acid in 95% yield. After recrystallization the product melted at 240–242°.

Anal. Calcd for $C_{12}H_8ClO_3P$: Cl, 13.30; P, 11.62; neut equiv, 266.6. Found: Cl, 13.14; P, 11.49; neut equiv, 267.7.

2-Chloro-10-phenylphenoxaphosphine.—2-Phenoxy-5-chlorobenzenediazonium tetrafluoroborate (31.0 g, 0.10 mole), 100 ml of anhydrous ethyl acetate, 17.9 g (0.10 mole) of phenylphosphonous dichloride (Eastman P6544), and 2.0 g of copper(I) bromide were allowed to react according to the procedure described for the preparation of 2,10-dichlorophenoxaphosphine. After the evolution of nitrogen was complete, the mixture was allowed to stir for 1 hr. Powdered aluminum (1.8 g) was then added to the flask. The mixture was refluxed for 1 hr and was stirred overnight. The usual isolation procedure gave 9.6 g (31%) of 2-chloro-10-phenylphenoxaphosphine (bp 160° at about 5 mμ). The product, which was recrystallized from aqueous alcohol with the aid of a seed crystal of 10-phenylphenoxaphosphine, had a melting point of 41.5–42.0°.

Anal. Calcd for $C_{18}H_{12}ClIOP$: Cl, 11.41; P, 9.97. Found: Cl, 11.54; P, 9.84.

2-Chloro-10-phenylphenoxaphosphine 10-Oxide.—2-Chloro-10-phenylphenoxaphosphine was oxidized in an alkaline solution of aqueous ethanol with hydrogen peroxide to give a 98% yield of 2-chloro-10-phenylphenoxaphosphine 10-oxide. The melting point was 150–151° after recrystallization from a mixture of ethanol and 6 *N* hydrochloric acid. A crystal of 10-phenylphenoxaphosphine 10-oxide was used for seeding.

Anal. Calcd for $C_{18}H_{12}ClO_2P$: Cl, 10.85; P, 9.48. Found: Cl, 10.87; P, 9.48.

2-Chloro-10-methyl-10-phenylphenoxaphosphonium Iodide.—2-Chloro-10-phenylphenoxaphosphine and a slight excess of methyl iodide were heated in a sealed tube at 100° for 4 hr. The product was recrystallized from a mixture of ethanol and petroleum ether (bp 30–60°); mp 238.0–240.5°, yield 72%. The nmr spectrum of the compound dissolved in deuteriochloroform displayed absorption at τ 6.61 (doublet, J_{PCH} = 14.5 cps) owing to the methyl group.

Anal. Calcd for $C_{19}H_{15}ClIOP$: C, 50.42; H, 3.34. Found: C, 50.57; H, 3.47.

2-Chloro-10-benzyl-10-phenylphenoxaphosphonium Chloride.—2-Chloro-10-phenylphenoxaphosphine and a slight excess of benzyl chloride were heated at 100° for 4 hr. The product, which was recrystallized from a mixture of ethanol and petroleum ether, did not melt below 300°. The yield of 2-chloro-10-benzyl-10-phenylphenoxaphosphonium chloride was 41%. The nmr spectrum of the compound in trifluoroacetic acid displayed absorption at τ 5.60 (doublet, J_{PCH} = 13.6 cps) owing to the methylene protons.

Anal. Calcd for $C_{25}H_{29}Cl_2OP$: Cl, 15.85; P, 6.92. Found: Cl, 15.98; P, 7.11.

10-Methyl-10-phenylphenoxaphosphonium Iodide.—10-Phenylphenoxaphosphine was dissolved in an excess of methyl iodide, and the resulting solution was allowed to stand overnight in a stoppered flask. The precipitated product (85%) melted at 244–245° (lit.[10] mp 236–237°). The nmr spectrum in deuteriochloroform displayed absorption owing to the methyl group at τ 6.65 (doublet, J_{PCH} = 13.7 cps).

Anal. Calcd for $C_{19}H_{16}IOP$: C, 54.57; H, 3.86. Found: C, 54.41; H, 3.78.

10-Ethyl-10-phenylphenoxaphosphonium Iodide.—10-Phenylphenoxaphosphine and a slight excess of ethyl iodide were heated in a sealed tube at 100° for 2 hr. After recrystallization from ethanol–petroleum ether, the product melted at 255–257°; yield, 55%. The nmr spectrum in deuteriochloroform displayed absorption at τ 6.11 (two quartets, J_{PCH} = 12.3 cps and J_{HCCH} = 7.3 cps) owing to the methylene group and absorption at τ 8.87 (two triplets, J_{PCCH} = 22.2 cps) owing to the methyl group.

Anal. Calcd for $C_{20}H_{18}IOP$: P, 7.17. Found: P, 7.20.

10-Benzyl-10-phenylphenoxaphosphonium Chloride.—10-Phenylphenoxaphosphine was dissolved in a large excess of benzyl chloride, and the resulting solution was allowed to stand in a stoppered flask for 4 days. The precipitated product (50%) was removed by filtration and washed with carbon tetrachloride; mp >300°. The nmr spectrum in trifluoroacetic acid displayed absorption at τ 5.60 (doublet, J_{PCH} = 13.7 cps).

Anal. Calcd for $C_{25}H_{19}Cl_2OP$: C, 74.54; H, 5.00; Cl, 8.80; P, 7.69. Found: C, 74.45; H, 5.09; Cl, 8.92; P, 7.45.

Registry No.—IV, 15042-79-2; V, 15042-80-5; VI, 15042-81-6; VII, 15040-61-6; VIV, 15040-62-7; IX, 15040-63-8; X, 15040-64-9; 10-methyl-10-phenylphenoxaphosphonium iodide, 15040-65-0; 10-ethyl-10-phenylphenoxaphosphonium iodide, 15040-66-1; 10-benzyl-10-phenylphenoxaphosphonium iodide, 15040-67-2.

(10) F. G. Mann and I. T. Millar, *J. Chem. Soc.*, 3746 (1953).

Nitrile Oxides. X. An Improved Method for the Preparation of Nitrile Oxides from Aldoximes[1]

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It was recently reported that nitrile oxides could be prepared by dehydrogenation of the corresponding aldoximes with alkali hypohalogenites, preferably sodium hypobromite, in alkaline aqueous solution.[2] Yields were generally very satisfactory with aromatic monoaldoximes bearing no functional substituents on the aromatic ring, but they decrease sharply when the method was extended to dialdoximes or heterocyclic aldoximes particularly if the molecule contained an additional tertiary amino group.[1]

We have now found that N-bromosuccinimide (NBS) in N-dimethylformamide (DMF) solution is a superior dehydrogenating agent for the conversion of aldoximes into nitrile oxides. Other N-halogenated compounds, such as N-bromophthalimide or N-chloro-*p*-toluenesulfonamide, gave less favorable results. Base (1 mole) is also necessary to complete the reaction. If the oxime and the nitrile oxide were both relatively stable species, it made no difference whether the base was added first and then the NBS or *vice versa*. In the latter case, the reaction apparently proceeded first to the hydroximic acid bromide which was subsequently dehydrobrominated by the base to the nitrile oxide. If the aldoxime, however, contained other groups sensitive to attack by NBS the former procedure might lead to undesirable products resulting from additional bromination.[3] As bases, sodium methylate or triethylamine were used in most cases with equal success. Since, however, triethylamine is attacked by NBS, it is preferable to add the NBS to the oxime prior to the introduction of the amine. At temperatures between 5 and 15°, the reaction was always complete within 1 hr. Dilution of the reaction mixture with water precipitated the nitrile oxide, often almost analytically pure, while the formed succinimide stayed in solution.

Our results (in comparison with the other method where data were available) are compiled in Table I.

(1) Previous communication by C. Grundmann and R. Richter, *J. Org. Chem.*, **32**, 2308 (1967).

(2) C. Grundmann and J. M. Dean, *ibid.*, **30**, 2809 (1965).

(3) For example, Table I, **7** and **9**, and footnotes *g* and *j*.

TABLE I

PREPARATION OF NITRILE OXIDES FROM ALDOXIMES

No.	Compound	Yield, % NaOBr–NaOH, H_2O	Yield, % NBS–$NaOCH_3$, DMF[a]	Yield, % NBS–Et_3N, DMF
1	2,4,6-Trimethylbenzonitrile oxide[b]	82	81	90
2	2,4,6-Trimethylisophthalobisnitrile oxide[c]	25–30	60	81
3	4-Dimethylamino-2,6-dimethylbenzonitrile oxide[d]	12–15	54	...
4	4-Dimethylamino-2,6-dimethylisophthalobisnitrile oxide[d]	15	52	...
5	2-Methoxy-1-naphthonitrile oxide[e]	...	...	86
6	2,6-Dimethoxy-1-naphthonitrile oxide[f]	...	70	...
7	2,6-Dimethoxy-5-bromo-1-naphthonitrile oxide[g,h]	...	48	...
8	2,7-Dimethoxy-1-naphthonitrile oxide[i]	...	69	...
9	2,7-Dimethoxy-8-bromo-1-naphthonitrile oxide[j,k]	...	...	68
10	9-Methylanthracene-9-nitrile oxide[l]	40, 65[o]	57	52
11	2-Dimethylamino-4,6-dichloropyrimidine-5-nitrile oxide[m]	0[p]	...	73
12	2,4,6-Trimethoxypyrimidine-5-nitrile oxide[d,n]	19	...	80

[a] If not otherwise indicated, the base was always added prior to the NBS to the DMF solution of the aldoxime. [b] See ref 2. [c] A melting point value of 138–139° dec, (from ethyl acetate). *Anal.* Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.99; N, 13.86; mol wt, 202. Found: C, 65.17; H, 5.08; N, 13.70; mol wt, 200 (acetone). [d] See ref 3. [e] A melting point value of 101–103° (from methanol–H_2O). *Anal.* Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03; mol wt, 199. Found: C, 72.53; H, 4.70; N, 7.22; mol wt, 201 (acetone). [f] A melting point value of 120–122° [from benzene–petroleum ether (bp 35–45°)]. *Anal.* Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11; mol wt, 229. Found: C, 67.92; H, 4.80; N, 6.21; mol wt, 232 (acetone). [g] 6-Dimethoxy-1-naphthaldoxime in DMF consumed 1 mole of NBS without addition of base forming exclusively 2,6-dimethoxy-5-bromo-1-naphthaldoxime (**14**), see Experimental Section. Addition of a 2nd mole of NBS and of 1 mole of $NaOCH_3$ at this stage yielded **7**. [h] A melting point value of 192–194° dec (from DMF–methanol). *Anal.* Calcd for $C_{13}H_{10}BrNO_3$: C, 50.67; H, 3.27; Br, 25.94; N, 4.55; mol wt, 308. Found: C, 50.90; H, 3.49; Br, 26.05; N, 4.49; mol wt, 297 (DMF). [i] A melting point value of 123–124° (from methanol). *Anal.* Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11; mol wt, 229. Found: C, 68.21; H, 4.95; N, 6.20; mol wt, 233 (acetone). [j] Compound **9** was obtained by adding first 2 moles of NBS to the aldoxime solution in DMF, followed by the addition of 1 mole of Et_3N. If this aldoxime was reacted only with 1 mole of NBS, no uniform brominated aldoxime, as **14**, could be isolated, but a mixture of starting material, brominated oximes, and nitrile oxides was formed. The position of the bromine in **14**, **7**, and **9** has not been proven, but deduced from analogous reactions, *cf.*, R. Adams, M. M. Miller, C. F. McGrew, and A. N. Anderson, *J. Am. Chem. Soc.*, **64**, 1795 (1942). [k] A melting point value of 172–174° (from DMF–methanol). *Anal.* Calcd for $C_{13}H_{10}BrNO_3$: C, 50.67; H, 3.27; Br, 25.94; N, 4.55; mol wt, 308. Found: C, 50.52; H, 3.30; Br, 26.01; N, 4.65; mol wt, 292 (DMF). [l] A melting point value of 165° (yellow needles, from toluene). *Anal.* Calcd for $C_{16}H_{13}NO$: C, 82.38; H, 4.75; N, 6.01; mol wt, 233. Found: C, 82.50; H, 4.81; N, 5.85; mol wt, 240 (benzene). [m] A melting point value of 159–162° dec (from DMF–methanol). *Anal.* Calcd for $C_7H_6Cl_2N_4O$: C, 36.07; H, 2.60; Cl, 30.43; N, 24.05; mol wt, 233. Found: C, 35.89; H, 2.71; Cl, 30.18; N, 23.83; mol wt, 229 (DMF). [n] A melting point value of 145–147° dec; (from 95% ethanol). [o] With NaOBr in DMF–H_2O. [p] Preparation of **11** by this method was not possible as the aldoxime lost chlorine quickly by hydrolysis.

Experimental Section[4]

Starting Materials.—The intermediates in the synthesis of the nitrile oxides **1–12** were prepared by procedures described in the literature except for the following new compounds.

2,6-Dimethoxynaphthalene-1-aldoxime (**13**) was obtained from the aldehyde and an aqueous ethanolic solution of equivalent amounts of hydroxylamine hydrochloride and sodium carbonate (85%). The oxime was recrystallized from ethanol–H_2O, mp 160–163°. *Anal.* Calcd for $C_{13}H_{13}NO_3$: N, 6.06. Found: N, 6.14.

5-Bromo-2,6-dimethoxynaphthalene-1-aldoxime[5] (**14**) was obtained when 1.16 g of **13** was dissolved in 10 ml of DMF and a solution of 0.89 g of NBS in 5 ml of DMF was added within 5 min at 0°. After an additional 7 min, the reaction mixture was diluted with H_2O (50 ml), whereby **14** (1.13 g) was obtained as a slightly yellow crystalline precipitate which was recrystallized from DMF–ethanol and H_2O, mp 217–220° dec. *Anal.* Calcd for $C_{13}H_{12}BrNO_3$: Br, 25.77; N, 4.52. Found: Br, 25.56; N, 4.64.

2,4,6-Trimethylisophthaldialdehyde could not be obtained from bismethylolmesitylene by any of the recommended methods for the oxidation of benzylic alcohols to aldehydes, except by the procedure of Partch.[6] Lead tetraacetate (160 g) was added to a solution of bismethylolmesitylene (32 g) in pyridine (1450 ml) and the deep brown solution was stirred at 25° for 24 hr when it had turned pale yellow, indicating the completion of the reaction. The solvent was completely removed by vacuum distillation from a 50–60° warm water bath, and the residue was dissolved in H_2O (500 ml) and extracted twice with 300 ml of ether each. After repeated washing with 2 *N* sulfuric acid, 2 *N* sodium hydroxide, and finally H_2O, the ether was distilled leaving the crude dialdehyde as a yellowish crystalline mass (26 g, 83%). Recrystallization of a probe from ligroin (bp 60–65°) yielded colorless needles, mp 79°. *Anal.* Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.87. Found: C, 74.83; H, 7.10.

The dioxime (27 g, 91%) was obtained from the crude dialdehyde (25 g) in aqueous methanol with equivalent amounts of hydroxylamine hydrochloride and potassium hydroxide. One recrystallization from 2 l. of benzene yielded pure 2,4,6-trimethylisophthaldialdoxime (68%), mp 148–149°. *Anal.* Calcd for $C_{11}H_{14}N_2O_2$: N, 13.59. Found: N, 13.45.

2-Dimethylamino-4,6-dichloropyrimidine-5-aldehyde was prepared from 2-dimethylamino-4,6-dichloropyrimidine b the recently described procedure.[1] Essential for a good yield was the exact maintenance of a reaction temperature of 90° over a period of 18 hr. After recrystallization from aqueous methanol, the aldehyde was obtained in yellowish needles (51%), mp 142°. *Anal.* Calcd for $C_7H_7Cl_2N_3O$: C, 38.21; H, 3.21; Cl, 32.33; N, 19.10. Found: C, 38.29; H, 3.27; Cl, 32.07; N, 19.24.

The aldehyde (2.2 g) was dissolved in boiling ethanol (50 ml) and a solution of hydroxylamine hydrochloride (0.7 g) and sodium carbonate (0.55 g) in H_2O (5 ml) was added. After refluxing for 5 min, the reaction mixture was chilled in ice and water was added to complete precipitation of the formed 2-dimethylamino-4,6-dichloropyrimidine-5-aldoxime (2.1 g, 89%). Recrystallization from aqueous methanol yielded almost colorless needles, mp 165°. *Anal.* Calcd for $C_7H_8Cl_2N_4O$: Cl, 30.17; N, 23.83. Found: Cl, 30.35; N, 23.82.

Dehydrogenation of Aldoximes to Nitrile Oxides.—To the aldoxime (5 mmoles), dissolved or suspended in 8–15 ml DMF, was added 5 mmoles of sodium methylate for each oxime group. After the reaction mixture was cooled to 10–15°, a solution of NBS in DMF (5 mmoles for each oxime group in 5 ml of solvent) was added with efficient stirring within 10–15 min.

In the case of triethylamine as base, the NBS solution was added first to the aldoxime solution or suspension followed by the addition of a solution of triethylamine in DMF (5 mmoles for each oxime group in 5 ml of solvent) within 5 min. To complete

(4) Melting points were determined with the Fisher-Johns melting point apparatus and are uncorrected. Microanalyses were by Galbraith Laboratories, Knoxville, Tenn. Molecular weights were determined by the osmometric method, the applied solvent is indicated in parentheses in the footnotes to Table I.

(5) See Table I, footnote *j*.

(6) R. E. Partch, *Tetrahedron Letters*, 3071 (1964).

the reaction, stirring was continued for an additional 30 min. The reaction mixture was diluted with ice water until the formed nitrile oxide started to crystallize, kept for several hours at 0°, filtered, and the product was washed thoroughly with water. After one recrystallization from the solvent indicated in Table I, all nitrile oxides were obtained analytically pure.

Registry No.—2, 15138-43-9; **5**, 15138-44-0; **6**, 15138-31-5; **7**, 15180-26-4; **8**, 15138-32-6; **9**, 15138-33-7; **10**, 15138-34-8; **11**, 15138-35-9; **12**, 13012-32-3; **13**, 15138-37-1; **14**, 15138-38-2; 2,4,6-trimethylisophthaldialdehyde, 15138-39-3; 2,4,6-trimethylisophthaldialdoxime, 15138-40-6; 2-dimethylamino-4,6-dichloropyrimidine-5-aldehyde, 15138-41-7; 2-dimethylamino-4,6-dichloropyrimidine-5-aldoxime, 15138-42-8.

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Unprecedented Orientation in the Nitration of Certain 3-Hydroxypyridines

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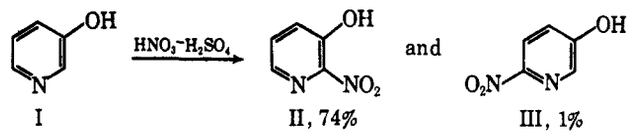
The chemistry of pyridines and orientation effects in substitution reactions of pyridines have been given considerable attention recently,[2,3] including review with special emphasis on methods of obtaining 4-substituted pyridines.[4] Electrophilic nitration at the 4 position of pyridines has not been observed except in the well-known cases of certain pyridine 1-oxides. However, there has appeared a singular claim to the preparation of a trinitropyridinol which was probably, but not proven to be, 3-hydroxy-2,4,6-trinitropyridine.[5] This author now wishes to present the first authentic examples of electrophilic nitration at the 4 position of pyridines.

Discussion

The general method of Wulff[6] for the preparation of 3-hydroxy-2-nitropyridine was reexamined in detail. The procedure given in the Experimental Section represented the optimal conditions with respect to time and temperature of nitration, concentration, and amount of nitrating agent, and work-up and purification procedures. This procedure gave a 74% yield of 3-hydroxy-2-nitropyridine (II) as opposed to Wulff's 50 to 57% yields.[6]



I II, 74% III, 1%

When ether was used as the final extraction solvent, fractional sublimation of the product gave a 1% yield of 5-hydroxy-2-nitropyridine (III) in addition to II. Although, III was not detected previously, it is possible that it is the same compound as that of melting point 210–211° obtained by a different method but not completely identified.[7] In this regard also, there did appear one claim to the detection of 6-substitution in the nitration of 3-ethoxypyridine.[8] This was presumably substantiated by reduction of the crude reaction mixture and paper chromatographic comparison with several, but not all, other amino-3-hydroxypyridines. Furthermore, no authentic sample of 2-amino-5-hydroxypyridine was reported in that work.[8]

We have repeated the further nitration of II according to Czuba and Plażek[5] in order to obtain 2,6-dinitro-3-hydroxypyridine. The assigned structure was reconfirmed by nmr spectroscopy (*vide infra*). This example plus the reported isolation of only 2-bromo-3-ethoxy-6-nitropyridine from the nitration of 2-bromo-3-ethoxypyridine[9] have led to the conclusion that for 3-hydroxypyridines and 3-hydroxypyridine ethers, "Nitration at C-4 is never observed, even when C-2 is blocked..."[2]

We now report that both the 4- and 6-nitro derivatives in a 4 to 1 ratio were obtained by nitration of 3-hydroxypyridine substituted in the 2 position with either methyl or chloro groups. Although, the total yield in each case was not large, the ratios should be significant. These were considered to be minimum ratios since the 6-nitro derivatives were higher melting and less soluble in both cases. On the other hand, only the 2-nitro derivatives were isolated from nitration of 3-hydroxy-4-, 5-, and 6-methylpyridines where C-2 was unsubstituted. Although minor isomers were not sought after in the latter cases, the major products were obtained in 50 to 75% of theoretical yields.

The unprecedented 4-nitration, with lesser 6-nitration, in the cases of 3-hydroxy-2-methyl- and 2-chloropyridines can be rationalized by currently accepted mechanisms (see ref 2, for discussions). Both mechanisms involving attack of nitronium ion on either the neutral hydroxypyridine or the hydroxypyridinium ion are consistent with the results and cannot be differentiated with the available information.

Nitrations rarely occur yielding single products when more than one are possible. Consequently, the formation of isomer III was not unexpected, and the formation of other mono- and dinitro derivatives was indeed anticipated. We cannot account for the absences of 4-nitro-3-pyridinols in the cases where C-2 was unsubstituted.

Structure Proofs.—The proofs of structure rest mainly on nmr and uv spectral data which are particu-

(1) Address correspondence to the author at the Eastman Kodak Co., Rochester, N. Y. 14650.

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(3) E. Klingsberg, Ed., "Pyridine and Its Derivatives," Vol. I–IV, Interscience Publishers, Inc., New York, N. Y., 1960–1964.

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