[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, SETON HALL UNIVERSITY]

Preparation and Reactions of 2-Nitropyridine-1-oxides

BY ELLIS V. BROWN

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2-Nitropyridine-1-oxide and a number of its homologs have been prepared by the action of mixtures of fuming sulfuric acid and 27.5% hydrogen peroxide on the corresponding aminopyridine-1-oxides. Displacement of nitro by chloro has given the 2-chloropyridine-1-oxides, and these were identified where possible by means of their 4-nitro derivatives.

Because of the many reactions which it undergoes, the importance of 4-nitropyridine-1-oxide is well established,[1] and it is of interest to compare its behavior with that of the 2-isomer; however, attempts to prepare 2-nitropyridine-1-oxide by the oxidation of 2-nitropyridine have been unsuccessful.[2] We wish to report the synthesis of compounds of this class by the oxidation of 2-aminopyridine-1-oxides. Starting with the commercially available 2-aminopyridine and its homologs, we acetylated, oxidized to the corresponding N-oxides with peracetic acid (20%) and then hydrolyzed with sodium hydroxide. All of these compounds except the 4,6-dimethyl were prepared by us as the hydrochlorides and reported in another connection.[3] The aminopyridine-1-oxide and the 6-methyl-2-aminopyridine-1-oxide subsequently were reported by Adams and Miyano.[4]

The free aminopyridine-1-oxides listed in Table I were then oxidized using a mixture of 30% fuming H_2SO_4 and 27% hydrogen peroxide at 10–20°. The reaction mixture was poured onto the ice, neutralized to congo red paper with ammonium hydroxide, extracted with ether or butyl alcohol and evaporated to give the product. The yields and melting points of the 2-nitropyridine-1-oxides so prepared are listed in Table II.

TABLE I

2-AMINOPYRIDINE-1-OXIDES

Substituent	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
.....	68	164–165				
3-Methyl-	65	128–129	58.06	58.18	6.45	6.50
4-Methyl-	72	130–132	58.06	58.13	6.45	6.35
5-Methyl-	75	150–151	58.06	57.92	6.45	6.60
6-Methyl-	78	153–154				
4,6-Dimethyl-	70	149–150	60.87	60.90	7.25	7.40

TABLE II

2-NITROPYRIDINE-1-OXIDES

Substituent	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
.....	50	85–86	42.86	42.64	2.86	2.90
3-Methyl-	55	110–111	46.75	46.85	3.90	3.85
4-Methyl-	52	118–119	46.75	46.90	3.90	3.97
5-Methyl-	45	112–113	46.75	46.68	3.90	3.88
6-Methyl-	57	120–121	46.75	46.71	3.90	3.98
4,6-Dimethyl-	40	108–109	50.00	50.12	4.76	4.90

We have proved the structure of these new compounds by two reactions. The first is reduction of the N-oxide function to give the corresponding nitropyridines. All of these except the 4,6-dimethyl-2-nitropyridine have been made by Wiley and Hartman[5] by the oxidation of the aminopyridines with the fuming sulfuric acid–hydrogen peroxide mixture following the original preparation of 2-nitropyridine by Kirpal.[6] The new 4,6-dimethyl-2-nitropyridine we have prepared using the same procedure. Ochiai[1] had previously shown that 4-nitropyridine-1-oxide could be reduced to 4-nitropyridine by warming with phosphorus trichloride. By this same means we have prepared the 2-nitropyridines from the 2-nitropyridine-1-oxides and compared the compounds by melting points and mixed melting points.

A second proof was the complete reduction by catalytic hydrogenation of the 2-nitropyridine-1-oxides back to the original 2-aminopyridines. These were compared by melting points and mixed melting points and found to be identical.

When one reduces 4-nitropyridine-1-oxide with palladium at low hydrogen pressure, 4-aminopyridine-1-oxide is prepared. We have not been able to realize this reaction since complete reduction of the 2-nitro compound occurs. The 2-aminopyridine-1-oxides prepared as indicated previously are stable to air, the 4-aminopyridine-1-oxides can usually only be isolated as the hydrochlorides since they oxidize in air to the azo compound.

The nitro group in the 4-nitropyridine-1-oxides is readily replaced by chlorine using acetyl chloride, and we have displaced the nitro group in our 2-nitropyridine-1-oxides in the same manner thus preparing the corresponding 2-chloropyridine-1-oxides. For comparison it was necessary to prepare these compounds by the oxidation of the chloropyridines. Some of these chloropyridines have been prepared by previous workers. We used the method of Siede[7] in preparing all of the compounds listed in Table III. His method consists of simply diazotizing the available aminopyridines in concentrated hydrochloric acid at 0° and allowing the mixture to warm, neutralizing with ammonium

TABLE III

2-CHLOROPYRIDINE-1-OXIDE HYDROCHLORIDE

Substituent	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
.....	138–142	36.14	36.58	3.01	2.78
3-Methyl-	146–150	39.78	39.42	3.87	3.80
4-Methyl-	121–125	39.78	39.35	3.87	3.65
5-Methyl-	125–128	39.78	40.02	3.87	3.57
6-Methyl-	155–160	39.78	39.92	3.87	3.60
4,6-Dimethyl-	144–148	43.30	43.01	4.64	4.50

(1) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(2) E. Ochiai, E. Hayashi and M. Katada, *J. Pharm. Soc. Japan*, **67**, 79–81 (1947).

(3) R. W. Faessinger and E. V. Brown, Abstracts of the Buffalo meeting of the A.C.S., March, 1951.

(4) R. Adams and S. Miyano, THIS JOURNAL, **76**, 2785 (1954).

(5) R. H. Wiley and J. L. Hartman, *ibid.*, **73**, 494 (1951).

(6) A. Kirpal and W. Bohm, *Ber.*, **64**, 767 (1931).

(7) O. Siede, *ibid.*, **57**, 791 (1924).

hydroxide, extracting with ether and distilling. Although the 2-bromopyridine-1-oxides have been prepared previously, the corresponding chloro compounds have not. We oxidized all of the chloropyridine homologs with 20% peracetic acid in the usual manner and the 2-chloropyridine-1-oxide hydrochlorides were compared by melting point and mixed melting point and appear to be identical, although the rather wide melting range of these salts was somewhat unsatisfactory. We therefore nitrated them with nitric–sulfuric acid mixture to give the 4-nitro-2-chloropyridine-1-oxides, and these are listed in Table IV. After nitrating the products from the acetyl chloride reaction, comparison of melting points and mixed melting points established their identity.

TABLE IV

2-CHLORO-4-NITROPYRIDINE-1-OXIDES

Substituent	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
.....	152–153	34.38	34.51	1.72	1.88
3-Methyl-	145–146	38.19	38.23	2.65	2.50
5-Methyl-	154–155	38.19	38.31	2.65	2.69
6-Methyl-	106–107	38.19	38.14	2.65	2.81

Although no quantitative data have been obtained, there was a very obviously faster rate of reaction of acetyl chloride with 2-nitropyridine-1-oxide than with 4-nitropyridine-1-oxide in the cold, nitrogen dioxide being evolved rapidly.

Experimental

Preparation of 2-Aminopyridine-1-oxides.—All of the compounds listed in Table I were prepared from commercially available 2-aminopyridine and its homologs in the same manner. One mole of aminopyridine was refluxed 1 hr. with 100 ml. of acetic anhydride, and the acetylaminopyridine was isolated by distillation at reduced pressure or crystallization in the usual manner. The acetylaminopyridine so prepared was oxidized by a mixture of 150 ml. of glacial acetic acid and 125 ml. of 40% peracetic acid.[8] In the beginning the temperature was moderated by a cooling bath, and then the temperature was held at 70° for 3 hr. Evaporation *in vacuo* and crystallization from toluene completed the preparation of the acetylaminopyridine-1-oxides. For the hydrolysis, 72 g. of acetylaminopyridine-1-oxide was refluxed in 500 ml. of water containing 60 g. of sodium hydroxide for 3 hr. At the end of this time, the solution was acidified and evaporated under reduced pressure. The free aminopyridine-1-oxides were then isolated from the residue by crystallization from absolute ethanol (Table I).

Preparation of 2-Nitropyridine-1-oxides.—The compounds listed in Table II were prepared by oxidation of the free amino compounds listed in Table I. To a mixture of 100 ml. of fuming sulfuric acid (30%) and 50 ml. of 27.5% hydrogen peroxide[8] prepared below 20° was added a solution of 9 g. of the aminopyridine-1-oxide in 50 ml. of concd. sulfuric acid. The temperature was held at 10–15° during the addition and then maintained at 25° for 24 hr. The reaction mixture was poured onto cracked ice, neutralized with concd. ammonium hydroxide and extracted with ether, butanol or both. Evaporation of the solvent under reduced pressure and temperature not exceeding 50° gave the crude products which were recrystallized from absolute ethanol (Table II).

Reduction of the N-Oxide Function.—Following the procedure of Ochiai,[1] 1 g. of 2-nitropyridine-1-oxide was refluxed in 20 ml. of chloroform with 2 ml. of phosphorus trichloride, cooled, neutralized with sodium hydroxide and the chloroform evaporated to dryness. Crystallization from petroleum ether afforded the nitropyridines which showed no depression in melting point when mixed with the products prepared by the method of Wiley and Hartman.[5] 2-Nitro-4,6-dimethylpyridine was prepared from the commercially available 2-amino-4,6-dimethylpyridine by the method of Wiley and Hartman[5] and melted at 59–60°. The yield was 50%. *Anal.* Calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.26. Found: C, 55.32; H, 5.30. The product from reduction of the N-oxide function of 2-nitro-4,6-dimethylpyridine-1-oxide showed no depression of melting point when mixed with this nitropyridine.

Catalytic Reduction of 2-Nitropyridine-1-oxides.—One gram of the nitropyridine-1-oxide was dissolved in 50 ml. of absolute ethanol, treated with 0.5 g. of 5% palladium-on-charcoal in a Parr low pressure hydrogenator at 45 lb. per sq. inch of hydrogen pressure. When no more hydrogen was absorbed, the catalyst was filtered, the solvent evaporated and the product identified as the aminopyridine in each case.

Replacement of Nitro Group by Chloro.—Two grams of the 2-nitropyridine-1-oxide was treated with 20 ml. of acetyl chloride. A violent reaction evolving nitrogen oxides took place at once. The reaction mixture was refluxed for 0.5 hr., evaporated to dryness and the 2-chloropyridine-1-oxides isolated as the hydrochlorides by recrystallization from butanol (Table III).

Preparation of the 2-Chloropyridine-1-oxides.—All of the 2-chloropyridines were prepared by the method of Siede.[7] To a mixture of 500 ml. of concd. hydrochloric acid and 36 g. of the aminopyridine cooled to 0° was added 35 g. of sodium nitrite in the usual manner. The reaction mixture was allowed to come to room temperature overnight and was then steam distilled and fractionated *in vacuo*. Two tenths mole of the 2-chloropyridines was treated with 25 ml. of glacial acetic acid and 22 ml. of 40% peracetic acid. The temperature was moderated to 70° then held at 70° for 3 hr. A slight excess of concd. hydrochloric acid was added, and the solvent was removed at reduced pressure. The chloropyridine-1-oxide hydrochlorides were recrystallized from butanol (Table III).

Nitration of the 2-Chloropyridine-1-oxides.—To a mixture of 2.2 g. of the above hydrochloride dissolved in 3 ml. of concd. sulfuric acid was added a mixture of 2.5 ml. of fuming HNO_3 (sp. gr. 1.50) and 5 ml. of concd. sulfuric acid. The reaction mixture was heated on a steam-bath for 4 hr., neutralized with sodium carbonate and extracted with benzene. Evaporation of the benzene left practically quantitative yields of crude nitro compounds which were recrystallized from absolute ethanol (Table IV).

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(8) We are grateful to the Buffalo Electrochemical Company for a generous supply of 40% peracetic acid and 27.5% hydrogen peroxide.