The chloromethyl derivatives deteriorate when heated in aqueous or aqueous acetic acid solutions.

General reduction procedure. The chloromethyl derivative (0.5 g.) in acetic acid (8 ml.) and water (2 ml.) was treated during 0.5 hr. with zinc dust (0.5 g.) and the reaction mixture heated on a steam bath for 2 hr. in all. The reaction mixture was then filtered and poured into cold water. The methyl derivative which separated was crystallized from dilute acetic acid. It was necessary to add hydrochloric acid (0.5 ml.) in the case of 7-methoxy-3,6-dichloromethyl-4-methylcoumarin to prevent the formation of the diacetoxymethyl derivative, and in the case of 7-hydroxy-3,8-dichloromethylcoumarin and 7-methoxy-3-chloromethyl-4-methylcoumarin-6-carboxylic acid to precipitate the product.

Pechmann condensations. Equimolar proportions of ethyl-α-methyl acetoacetate and the required phenol were treated with sulfuric acid (80%) and kept for 24 hr. The next day the mixture was poured into water and the product obtained crystallized from rectified spirit (see Table IV).

Acetoxy methylcoumarins were prepared by refluxing the chloromethylcoumarin in glacial acetic acid with fused sodium acetate for 2 hr. (see Table III).

Methoxymethylcoumarins were prepared by refluxing the chloromethylcoumarin with methyl alcohol in the presence of fused potassium carbonate for 6 hr. (Table III).

BARODA, INDIA

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Pyridine 1-Oxides. VII. 3-Nitropyridine 1-Oxide[1a]

EDWARD C. TAYLOR AND JOHN S. DRISCOLL[1b]

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3-Aminopyridine was converted to 3-nitropyridine 1-oxide by three different routes, the preferable one being preliminary oxidation with peroxysulfuric acid to 3-nitropyridine, followed by *N*-oxidation with 40% peracetic acid. In agreement with expectation, the nitro group of 3-nitropyridine 1-oxide could not be displaced by nucleophilic reagents such as methoxide ion and was inert toward acetyl chloride. Treatment of 3-nitropyridine 1-oxide with phosphorus oxychloride gave a mixture of 2-chloro-3-nitropyridine and 6-chloro-3-nitropyridine, and treatment with acetic anhydride gave 3-nitro-2-pyridone.

The usefulness and versatility of pyridine-1-oxides as synthetic intermediates is due both to the facility with which the *N*-oxide grouping can be introduced and selectively removed and to its unique amphoteric ability to facilitate both nucleophilic substitution and displacement reactions and electrophilic substitution reactions.[2] For example, the ready accessibility of 4-nitropyridine 1-oxides by direct nitration of the *N*-oxides,[3,4] and the ease with which such intermediates can be converted into other 4-substituted pyridine derivatives by reductive and nucleophilic displacement reactions of the 4-nitro group have been extensively exploited by organic chemists concerned with synthetic manipulations in the pyridine field.[2] The versatility of 4- (or 2-) nitropyridine-1-oxides as synthetic intermediates is due in part to conjugation of the nitro group with the *N*-oxide function, and a consequent ready displacement of the nitro group by attacking nucleophiles. With the unconjugated isomer, 3-nitropyridine 1-oxide, however, such nucleophilic displacements of the nitro group would not be expected, but facilitation of nucleophilic substitution in the 2-,4- and 6-positions should be observed. Preference for the 2-position would be anticipated by analogy, as nicotinamide-1-oxide upon treatment with phosphorus oxychloride and phosphorus pentachloride yields exclusively 2-chloronicotinonitrile,[5] and 3-halopyridine 1-oxides upon treatment with acetic anhydride give only 3-halo-2-pyridones.[6] An investigation of the chemistry of 3-nitropyridine 1-oxide thus appeared to be of both theoretical and possible synthetic interest.

3-Nitropyridine 1-oxide (III) has previously been prepared by the action of benzoyl nitrate on pyridine 1-oxide (very low yield)[7] and by direct oxidation of 3-nitropyridine with hydrogen peroxide in acetic acid (34% yield[7] and 40% yield[8]). The use of commercially available 40% peracetic acid is a convenient alternative to the above conditions and affords comparable yields (40.5%). Alternative routes were investigated but were much less satisfactory. For example, direct oxidation of 3-aminopyridine with peroxytrifluoroacetic acid gave a mixture of 3-nitropyridine (II) (21%) and 3-nitropyridine 1-oxide (III) (22%). An adaptation (I→IV→V→VI→III) of the procedure previously described by Brown[9] for the preparation of 2-nitropyridine 1-oxide from 2-

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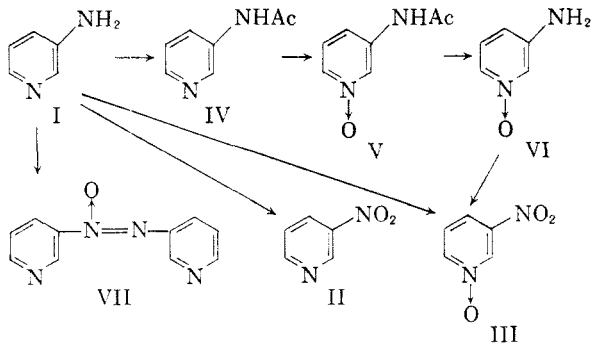
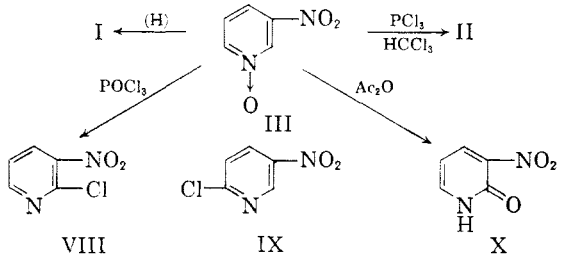


aminopyridine gave 3-nitropyridine 1-oxide (III) in only 14% overall yield.

Kimura and Takano[10] have recently reported that an attempt to prepare 3-nitropyridine (II) by oxidation of 3-aminopyridine with peroxysulfuric acid according to the method of Schickh[11] yielded only 3,3′-azoxypyridine (VII), and that further oxidation of VII was unsuccessful. Although no experimental procedure was reported, it was mentioned that Shindo[12] was able to prepare II by Schickh's method, in which the 3-aminopyridine was added to the peroxysulfuric acid. In this connection, Wiley and Hartman[13] have reported that addition of peroxysulfuric acid to a solution of 3-aminopyridine in sulfuric acid yields 3,3′-azoxypyridine and not 3-nitropyridine, and we have confirmed this result, even when 90% rather than 30% hydrogen peroxide was used. Thus, although 2- and 4-aminopyridines can be oxidized to the corresponding nitropyridines by either mode of addition,[13–15] 3-aminopyridine can be converted to 3-nitropyridine only by using the mode of addition originally specified by Schickh; namely, by addition of 3-aminopyridine to the peracid.

Treatment of 3-nitropyridine 1-oxide (III) with phosphorus trichloride resulted in smooth deoxygenation to 3-nitropyridine (II), and catalytic reduction of III gave 3-aminopyridine (I). No apparent reaction took, place when III was heated under reflux with acetyl chloride, and over 80% of the starting material was recovered unchanged. By contrast, 2- and 4-nitropyridine 1-oxides react violently with acetyl chloride at room temperature with copious evolution of nitrogen dioxide.[4,9] Refluxing III with methanolic sodium methoxide gave only a dark brown, tarry solid which rapidly absorbed water from the air and was not characterized. Analogous results were obtained when 2,6-dimethyl-3-nitropyridine 1-oxide was treated with sodium ethoxide.[16] In view of the failure of these attempts to effect nucleophilic displacement of the 3-nitro group in III, it is interesting that Katritzky, *et al.*[3] have reported the successful synthesis of 3-ethoxy- and 3-methoxypyridine 1-oxide by the action of the respective alkoxide on 3-chloropyridine 1-oxide.

A mixture of 2-chloro-3-nitropyridine (VIII) and 6-chloro-3-nitropyridine (IX) was obtained when 3-nitropyridine 1-oxide (III) was heated under reflux with phosphorus oxychloride. 3-Nitropyridine 1-oxide rearranges in 50% yield to 3-nitro-2-pyridone (X) upon heating with acetic anhydride.



Procedures have been recently described for the direct introduction of a nitrile group into the pyridine nucleus by nucleophilic attack of cyanide ion on an *O*-methyl salt of the *N*-oxide.[17,18] Although 3-nitropyridine(*p*K 0.90 ± 0.1) is reported to give a methiodide,[19] we have experienced difficulty in preparing the methiodide of 3-nitropyridine-1-oxide (*p*K − 1.2 ± 0.1).[20] Nevertheless, preliminary results indicate that cyanonitropyridines are formed in small amounts when III is subjected to this reaction. This work is still in progress.

EXPERIMENTAL[21]

3-Aminopyridine (I) was obtained from The Reilly Tar and Chemical Co. and sublimed at 60°/0.1 mm. to give clear hydroscopic plates, m.p. 63–65° (lit.,[22] m.p. 64°), which turn white upon exposure to air; *picrate*, m.p. 201–202°.

3-Acetamidopyridine (IV) was prepared as previously described[23]: m.p. 133–135° (lit. m.p. 133°).

3-Acetamidopyridine 1-oxide (V). To a solution of 14.0 g. of 3-acetamidopyridine in 15 ml. of acetic acid was slowly added 15 ml. of 40% peracetic acid, and the mixture was heated at 55° for 3 hr. and then at 65° for 4 hr. A catalytic amount of charcoal was added and the mixture heated 30

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min. at 50° to destroy residual peroxide. The acetic acid solution was then evaporated under reduced pressure and the yellow residue extracted with cold acetone to remove the last traces of acetic acid. The remaining almost colorless solid (11.7 g., 75%, m.p. 210–215°) was recrystallized from acetone to give colorless crystals, m.p. 216° (lit.,[20b] 215.5–216.5°).

3-Aminopyridine 1-oxide (VI). A mixture of 10 ml. of 10% aqueous sodium hydroxide, 50 ml. of 3% hydrogen peroxide, and 1.0 g. of 3-acetaminopyridine-1-oxide was heated under reflux for 1 hr., cooled to room temperature, an additional 25 ml. of 3% hydrogen peroxide added, and refluxing continued for an additional hour. The solution was then acidified with dilute hydrochloric acid to *p*H 6 and evaporated to dryness under reduced pressure. The residual tan solid was extracted with 100 ml. of boiling ethanol and the filtered extract evaporated to dryness. The residue was then extracted with 150 ml. of chloroform. Evaporation of the chloroform extract under reduced pressure yielded 0.51 g. (71%) of light yellow crystals, m.p. 121–124° (lit.,[24] m.p. 124–125°).

3-Nitropyridine 1-oxide (III). *Method A.* To 25 ml. of dichloromethane cooled to 2° in an ice bath was added with stirring 1.88 ml. of 90% hydrogen peroxide followed by 12.5 ml. of trifluoroacetic anhydride. The solution was stirred for 10 min. and then 1.5 g. of 3-aminopyridine dissolved in 15 ml. of dichloromethane was added dropwise over a period of 10 min. During the addition, the solution turned light green. The ice bath was removed and the solution was refluxed gently for 1 hr., during which time the color changed to light yellow. After cooling to room temperature, the solution was washed with two 100-ml. portions of water, and then with two 75-ml. portions of 10% aqueous sodium carbonate, the washings were extracted with four 200-ml. portions of chloroform, and the chloroform extracts were combined and dried over anhydrous sodium sulfate. Evaporation to dryness under reduced pressure gave 0.50 g. (22.4%) of yellow needles, m.p. 165–167°. Recrystallization from ethanol raised the melting point to 172–173° (lit.,[8] m.p. 169–169.5°).

Anal. Calcd. for $C_5H_4N_2O_3$: C, 42.9; H, 2.9; N, 20.0. Found: C, 42.9; H, 3.0; N, 20.1.

The dichloromethane solution above was dried over anhydrous sodium sulfate and evaporated to dryness to give 0.42 g. (21.2%) of 3-nitropyridine as an oil which solidified upon trituration to yellow needles, m.p. 38–39° (lit.[22] m.p. 41°).

Method B. Over a period of 90 min. 50 ml. of 40% peracetic acid was added dropwise to a stirred solution of 21.5 g. of 3-nitropyridine in 50 ml. of glacial acetic acid. The temperature of the reaction mixture rose to 100° during the addition. The dark red solution was stirred at room temperature for 4 hr. and then at 75° (oil bath temperature) for 5 hr. It was evaporated to one-half its volume under reduced pressure, 225 ml. of water added, sodium carbonate added to *p*H 8, and the resulting dark brown solution extracted with eight 250-ml. portions of chloroform. The combined extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to give 14.4 g. of a yellow solid, m.p. 135–158°. Recrystallization from ethanol then gave 9.8 g. (40.5%) of 3-nitropyridine-1-oxide, m.p. 169–171°.

Method C. To a stirred solution of 5 ml. of chloroform, 0.43 ml. of 90% hydrogen peroxide, and 3.1 ml. of trifluoroacetic anhydride prepared as described above in Method A was added slowly a solution of 0.35 g. of 3-aminopyridine-1-oxide in 25 ml. of chloroform. After addition was complete, the reaction mixture was heated under reflux for 1 hr., cooled to room temperature, and extracted with two 50-ml. portions of water followed by two 40-ml. portions of 10% aqueous sodium carbonate. The combined aqueous extracts were extracted with chloroform, and the combined chloroform solutions and extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to give 0.15 g. (34%) of 3-nitropyridine-1-oxide, m.p. 169–171°, identical in all respects with the product obtained by Methods A and B.

Reduction of 3-nitropyridine 1-oxide to 3-nitropyridine. To a stirred solution of 0.5 g. of 3-nitropyridine 1-oxide in 10 ml. of chloroform at 0° was added 0.8 ml. of phosphorus trichloride, and the mixture was stirred at 0° for 5 min. and then at 70–80° for 1 hr. It was then cooled to room temperature, added to 125 ml. of ice water, and the aqueous layer separated and made alkaline (*p*H 10) with 10% sodium hydroxide. The alkaline solution was extracted with 100 ml. of chloroform, and the chloroform solutions were combined, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give 0.19 g. (43%) of 3-nitropyridine, m.p. 38–40°, identical in all respects with an authentic sample.

Reduction of 3-nitropyridine 1-oxide to 3-aminopyridine. A solution of 1.0 g. of 3-nitropyridine-1-oxide in 150 ml. of absolute ethanol containing 0.2 g. of platinum oxide catalyst was hydrogenated at room temperature for 16 hr. at 40 p.s.i. of hydrogen. Filtration of the catalyst and evaporation of the filtrate gave 3-aminopyridine as a tan oil in quantitative yield; *picrate*, m.p. 201–202°.

Reaction of 3-nitropyridine 1-oxide with phosphorus oxychloride. A mixture of 2.0 g. of 3-nitropyridine-1-oxide and 30 ml. of phosphorus oxychloride was stirred and heated slowly to reflux over a period of 1.5 hr. The solution was then heated under reflux for 1 hr. and the excess phosphorus oxychloride removed by distillation under reduced pressure to give 1.53 g. of a brown solid, m.p. 73–92°. Continuous sublimation at 50–60°/0.1 mm. over a period of 2 weeks first yielded 0.68 g. (30%) of cubic crystals of 2-chloro-3-nitropyridine, m.p. 103–104° (lit.,[25] m.p. 101–102°), followed by 0.19 g. (8.4%) of 6-chloro-3-nitropyridine, m.p. 110° (lit.,[26] m.p. 108–110°). A mixture of 2-chloro and 6-chloro-3-nitropyridine melted at 85–94°.

Anal. Calcd. for $C_5H_3N_2O_2Cl$: C, 37.9; H, 1.9; 17.7. Found (for VIII): C, 37.9; H, 2.05; N, 17.4.

3-Nitro-2-pyridone (X). A mixture of 1.0 g. of 3-nitropyridine-1-oxide and 25 ml. of acetic anhydride was heated under reflux for 24 hr. and then evaporated under reduced pressure to near dryness. The residue was heated with 40 ml. of water for 1.5 hr. the mixture filtered to remove a small amount of an insoluble, high-melting solid, and the filtrate evaporated to dryness under reduced pressure. The residue was suspended in 10 ml. of chloroform and the mixture filtered to give 0.52 g. of crude 3-nitro-2-pyridone, m.p. 200–210°. This was refluxed in xylene for several hours, the solution filtered, and the filtrate concentrated under reduced pressure. Cooling gave 0.50 g. (50%), m.p. 220°. An additional recrystallization from boiling xylene raised the melting point to 224–225.5° (lit.,[26] m.p. 224°).

Anal. Calcd. for $C_5H_4N_2O_3$: C, 42.9; H, 2.9; N, 20.0. Found: C, 43.0; H, 3.0; N, 20.1.

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