residue and the resulting slurry was again evaporated to a small volume. Addition of water and filtration then gave 0.53 g. of a gray solid, m.p. 170–171°. An additional 0.30 g. of product was recovered from the filtrate to give a total yield of 0.83 g. (76%). The product was recrystallized from water without change in the melting point. Benzimidazole is reported to melt at 170°.[20]

Acetamidine Acetate.—A mixture of 32.4 g. of ethyl orthoacetate and 15.4 g. of ammonium acetate was heated under reflux for 45 minutes, while a stream of dry ammonia was bubbled through. The reaction mixture was then distilled at an oil bath temperature of 155-160° until the temperature of the condensing vapors fell below 75°. This required about 25 minutes and yielded 18.5 g. of distillate. The residue was cooled to room temperature and filtered and the collected solid washed with a small amount of ethanol and dried; yield 16.5 g., m.p. 189–191°. An additional 3.25 g. of product was obtained from the filtrate for a total yield of 19.75 g. (84%). Acetamidine acetate is reported to melt at 185–187°.[21] Furthermore, this material was identical with an authentic sample of acetamidine acetate prepared by treatment of acetamidine hydrochloride with sodium acetate.

(20) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

(21) H. G. Rule, *ibid.*, **113**, 3 (1918).

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Pyridine-1-oxides. V. 4-Substituted Nicotinic Acid-1-oxides[1]

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4-Nitronicotinic acid-1-oxide (I), prepared from 3-picoline by conversion to the 1-oxide, nitration and subsequent oxidation, was utilized as an intermediate for the synthesis of 4-chloronicotinic acid-1-oxide (II), 4-hydroxynicotinic acid-1-oxide (III), 4-benzyloxynicotinic acid-1-oxide (IV), 4-hydroxynicotinic acid (V), 4-mercaptonicotinic acid-1-oxide (VI), 4-aminonicotinic acid-1-oxide (VII), 4-aminonicotinic acid (VIII), 4-hydrazinonicotinic acid-1-oxide (IX) and 4-hydroxylaminonicotinic acid-1-oxide (X).

The utility of the N-oxide grouping as an intermediate in heterocyclic synthesis has received wide recognition,[3] and it is to be anticipated that many new synthetic applications will be found. The present paper extends our earlier work[1,4-6] dealing with the utilization of the N-oxide grouping in pyridine chemistry and is concerned with the synthesis of a number of 4-substituted nicotinic acid derivatives starting with the readily accessible 4-nitronicotinic acid-1-oxide (I).[5]

It was reported earlier[5] that the reaction of 4-nitronicotinic acid-1-oxide(I) with acetyl chloride yielded 4-chloronicotinic acid-1-oxide (II). We have now found that this reaction, when run at 100°, is accompanied by the formation of significant amounts (15–20%) of 4-hydroxynicotinic acid-1-oxide (III), whereas less than 1% of the latter contaminant is formed at 70°. An improved preparation of pure II is reported in the Experimental. Alkaline hydrolysis of II gave 4-hydroxynicotinic acid-1-oxide (III), from which 4-hydroxynicotinic acid (V) was prepared by catalytic reduction.

Alternate routes to III and V were found in the acid hydrolysis and catalytic reduction, respectively, of 4-benzyloxynicotinic acid-1-oxide (IV), which was prepared by the action of sodium benzylate on I.

The lability of the chloro substituent in 4-chloronicotinic acid-1-oxide(II) was further demonstrated by treatment with potassium hydrosulfide to give 4-mercaptonicotinic acid-1-oxide (VI) and by treatment with ammonium hydroxide to give 4-aminonicotinic acid-1-oxide (VII). Catalytic reduction of the latter compound yielded 4-aminonicotinic acid (VIII), identical with the product of reduction of 4-nitronicotinic acid-1-oxide (I). Treatment of VIII with nitrous acid provided a third synthetic route to 4-hydroxynicotinic acid (V).

Since hydrazine hydrate in the presence of a small amount of Raney nickel has been reported to be effective for the reduction of aromatic nitro groups[7] but to be ineffective for the reduction of the N-oxide grouping in 4-picoline-1-oxide,[8] it was thought that these conditions might make possible a direct conversion of I to 4-aminonicotinic acid-1-oxide (VII). However, treatment of I with hydrazine hydrate in the presence of Raney nickel yielded predominately 4-hydrazinonicotinic acid-1-oxide (IX) along with a small amount of the expected 4-aminonicotinic acid-1-oxide (VII).

A possible alternative procedure for carrying out the direct conversion of I to VII appeared to be treatment of I with boiling ammonium sulfide solution, since it has been reported[9,10] that this reagent is effective for the conversion of 4-nitropyridine-1-oxide and its methyl homologs to the corresponding 4-aminopyridine-1-oxides. The product of the reaction of I with this reagent, however, proved to be 4-hydroxylaminonicotinic acid-1-oxide (X). Catalytic reduction of X yielded 4-aminonicotinic acid (VIII), although in one instance 4-aminonicotinic acid-1-oxide (VII) was obtained, apparently as a result of poisoning of the catalyst by residual sulfur.

Experimental[11]

4-Chloronicotinic Acid-1-oxide (II).—A suspension of 4.0 g. of 4-nitronicotinic acid-1-oxide in 20 ml. of acetyl chloride

(1) For the previous paper in this series, see E. C. Taylor and N. E. Boyer, *J. Org. Chem.*, **24**, 275 (1959).

(2) Parke, Davis and Co. Fellow, 1957–1958.

(3) For a recent review of this field, see A. R. Katritzky, *Quart. Revs.*, **10**, 395 (1956).

(4) E. C. Taylor, A. J. Crovetti and N. E. Boyer, THIS JOURNAL, **79**, 3549 (1957).

(5) E. C. Taylor and A. J. Crovetti, *ibid.*, **78**, 214 (1956).

(6) E. C. Taylor and A. J. Crovetti, *J. Org. Chem.*, **19**, 1633 (1954).

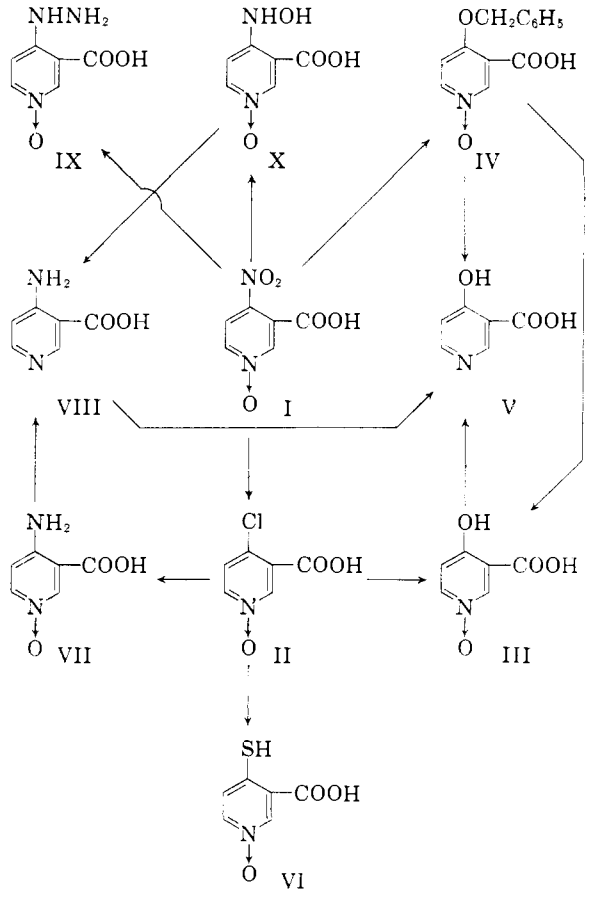
(7) D. Balcom and A. Furst, THIS JOURNAL, **75**, 4334 (1953).

(8) R. L. Bixler and C. Niemann, *J. Org. Chem.*, **23**, 575 (1958).

(9) R. W. Faessinger and E. V. Brown, Abstracts of Papers, 121st A.C.S. Meeting 1952, p. 24-K.

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

(11) All melting points are uncorrected.



in a 100-ml. round-bottom flask provided with a reflux condenser and calcium chloride drying tube was heated under reflux with magnetic stirring at 70–74° (oil-bath temperature) for 4.25 hours. Nitrogen dioxide evolution commenced after 3 minutes of heating. The mixture was allowed to cool slowly to room temperature and the precipitated solid separated by filtration and added immediately, in small portions and with stirring, to 25 g. of crushed ice. The resulting suspension was refrigerated overnight, filtered and the collected solid dried at 50° to give 2.92 g. of white crystals, m.p. 170° dec. Evaporation of the aqueous filtrates to a small volume and trituration of the residual oil with a few drops of water resulted in the separation of an additional 0.08 g. of product, m.p. 166° dec.; total yield, 3.0 g. (80%). Recrystallization from water with the use of charcoal gave white needles, m.p. 169–170° dec. The previously reported preparation of this compound yielded an impure sample, m.p. 145–146° dec.

Anal. Calcd. for $C_6H_4NO_3Cl$: C, 41.5; H, 2.3; N, 8.1. Found: C, 41.3; H, 2.3; N, 8.3.

Addition of the acetyl chloride filtrate above to 35 g. of crushed ice, followed by concentration of the resulting solution under reduced pressure and trituration of the residual oil with water, yielded 0.03 g. of 4-hydroxynicotinic acid-1-oxide, identical with an authentic sample (see below).

4-Hydroxynicotinic Acid-1-oxide (III). **Method A.**—A mixture of 1.0 g. of 4-chloronicotinic acid-1-oxide, 1.0 g. of sodium hydroxide and 25 ml. of water was heated under reflux for 3.5 hours, cooled and acidified with hydrochloric acid. The light yellow solid which separated was collected by filtration and dried at 50° *in vacuo;* yield 0.56 g. (63%), m.p. 255–256° dec. Recrystallization from water raised the decomposition point to 260°.

Anal. Calcd. for $C_6H_5NO_4$: C, 46.45; H, 3.25; N, 9.0. Found: C, 46.6; H, 3.1; N, 9.0.

Method B.—A mixture of 0.5 g. of 4-benzyloxynicotinic acid-1-oxide and 10 ml. of concentrated hydrochloric acid was heated under reflux for 45 minutes. The mixture gradually turned cloudy as benzyl alcohol was formed. The reaction mixture was cooled, extracted with two 5-ml. portions of benzene, and the aqueous layer concentrated to a small volume under reduced pressure. Chilling and trituration with a few drops of ice-water resulted in the separation of 0.22 g. of white crystals, m.p. 259–260° dec. An additional 0.03 g. was obtained by concentration of the filtrate and working up as before; total yield, 0.25 g. (79%).

Hydrolysis of 4-benzyloxynicotinic acid-1-oxide could also be carried out by refluxing with water, but the yield of 4-hydroxynicotinic acid-1-oxide was less and some unchanged starting material was recovered.

4-Benzyloxynicotinic Acid-1-oxide (IV).—To a stirred solution of 5.0 g. of 4-nitronicotinic acid-1-oxide in 150 ml. of benzyl alcohol was added dropwise, over a period of 20 minutes, a solution of sodium benzylate (prepared from 1.68 g. of sodium and 75 ml. of benzyl alcohol). The temperature of the reaction mixture was held at 50–70° by means of a hot-water-bath. Heating was continued for 7.5 hours, the precipitated buff-colored salt was collected by filtration, washed with acetone and dissolved in 25 ml. of water. The resulting orange solution was acidified with 6 *N* hydrochloric acid to *p*H 1, chilled to 0°, and the precipitated solid filtered off, washed with cold water and dried to give 5.12 g. (77%) of colorless crystals, m.p. 168°. Recrystallization from warm water with a minimum of heating (to avoid hydrolysis to 4-hydroxynicotinic acid-1-oxide) yielded the analytical sample, m.p. 172–176°.

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 63.7; H, 4.5; N, 5.7. Found: C, 63.5; H, 4.8; N, 5.7.

4-Hydroxynicotinic Acid (V). **Method A.**—To a solution of 1.0 g. of 4-benzyloxynicotinic acid-1-oxide in 100 ml. of warm glacial acetic acid was added 0.25 g. of 20% palladium hydroxide-on-carbon catalyst and the mixture was allowed to stand overnight at room temperature. It was then hydrogenated at room temperature for 22 hours under 3 atmospheres pressure. The reduction mixture was filtered to remove catalyst and 1.5 l. of ether was added. Chilling and filtering then yielded 0.29 g. (51%) of a light tan solid, m.p. 245–247° dec. Vacuum sublimation at 150° (0.05 mm.) yielded white crystals with the same melting point.

Anal. Calcd. for $C_6H_5NO_3$: C, 51.8; H, 3.6; N, 10.1. Found: C, 52.0; H, 3.6; N, 10.3.

Method B.—A solution of 0.5 g. of 4-hydroxynicotinic acid-1-oxide in 150 ml. of hot glacial acetic acid was cooled to room temperature and 1.0 g. of 10% palladium-on-carbon catalyst added. Hydrogenation at 70° for 29 hours gave 0.36 g. (80%) of 4-hydroxynicotinic acid, m.p. 249° dec., identical with the product obtained by method A.

Method C.—To a solution of 8.0 g. of 4-aminonicotinic acid in 64 ml. of 10% sulfuric acid at 60° was added 6 g. of sodium nitrite dissolved in 40 ml. of water. After addition was complete, the reaction mixture was warmed for a few minutes on a steam-bath and then heated under reflux for 1.5 hours. Concentration of the solution and chilling resulted in the separation of 6.9 g. of white needles which consisted of a mixture of 4-hydroxynicotinic acid and the sulfate salt of 4-aminonicotinic acid. The desired product was readily obtained by vacuum sublimation of the mixture at 170° (0.01 mm.) to give a white sublimate, m.p. 242° dec. Resublimation of this sublimate yielded pure 4-hydroxynicotinic acid, m.p. 245–246° dec., identical with the products obtained by methods A and B.

4-Mercaptonicotinic Acid-1-oxide (VI).—To a solution of 10 g. of solid potassium hydrosulfide[12] in 100 ml. of hot absolute methanol was added 5.0 g. of 4-chloronicotinic acid-1-oxide, and the mixture was heated under reflux for 21 hours and then evaporated to dryness under reduced pressure. The residue was dissolved in a small amount of water, filtered and the filtrate acidified with hydrochloric acid and chilled. The crude product which separated was recrystallized from boiling water to give 1.22 g. of an insoluble white solid, m.p. 201° dec., and 2.33 g. (47.5%) of yellow crystals, m.p. 204° dec. Recrystallization of the yellow crystals from water did not change the decomposition point. Sodium fusion tests for sulfur (lead acetate, sodium nitroprusside) were positive.

Anal. Calcd. for $C_6H_5NO_3S$: C, 42.1; H, 2.95; N, 8.2. Found: C, 42.4; H, 3.25; N, 8.1.

The white solid, m.p. 201° dec., obtained above was insoluble in water as well as in the usual organic solvents, in-

(12) A. Rule, *J. Chem. Soc.*, 558 (1911).

cluding boiling dimethylformamide, and could not be sublimed. It could be dissolved in base and reprecipitated with acid, but all efforts to obtain an analytical sample in this manner were fruitless. Although the decomposition point of this compound (201°) is close to that of 4-mercaptonicotinic acid-1-oxide (204°), examination of the infrared spectra of the two compounds showed them to be distinctly different. The structure of this white by-product is not known.

4-Mercaptonicotinic acid-1-oxide could also be prepared from 4-chloronicotinic acid-1-oxide by reaction with potassium hydrosulfide generated *in situ* in methanol, but the yield was lower. This reaction was also accompanied by the formation of the above-mentioned white by-product, m.p. 201° dec.

4-Aminonicotinic Acid-1-oxide (VII).—A solution of 2.0 g. of 4-chloronicotinic acid-1-oxide in 60 ml. of concentrated ammonium hydroxide was heated in a 200-ml. pressure bottle (safety shield!) at 100° for 24 hours. After cooling, the reaction mixture was evaporated under reduced pressure to about 15 ml. and acidified to *p*H 3 with hydrochloric acid. The mixture was then chilled and filtered to give 0.86 g. (48%) of a tan solid, m.p. 270.5° dec. Recrystallization from water with the use of charcoal yielded white crystals but did not change the melting point.

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.7; H, 3.9; N, 18.2. Found: C, 46.8; H, 3.9; N, 18.1.

4-Aminonicotinic Acid (VIII). **Method A.**—A suspension of 18.4 g. of 4-nitronicotinic acid-1-oxide in 300 ml. of glacial acetic acid was hydrogenated in the presence of 4 g. of 5% palladium-on-carbon catalyst in a low-pressure Parr apparatus. The hydrogenation was allowed to proceed at room temperature for 30 minutes and the reaction mixture was then warmed to 60° for an additional 30 minutes. The catalyst was removed by filtration, the filtrate concentrated under reduced pressure to about half its volume, and 1.5 l. of ether added. The collected white solid (15.8 g., m.p. 342° dec.) was recrystallized from dilute acetic acid to give colorless crystals, m.p. 357° dec.

Anal. Calcd. for $C_6H_6N_2O_2$: C, 52.2; H, 4.4; N, 20.2. Found: C, 51.9; H, 4.2; N, 20.6.

Method B.—A solution of 0.92 g. of 4-aminonicotinic acid-1-oxide in 100 ml. of glacial acetic acid was hydrogenated at 40 p.s.i. and at 45° for 20 hours in the presence of 0.25 g. of 20% palladium hydroxide-on-carbon catalyst. The product was isolated as described above; yield of crude product 0.64 g. (78%). Recrystallization from water yielded colorless crystals, m.p. 351° dec.

Method C.—Hydrogenation of a suspension of 0.97 g. of 4-hydroxylaminonicotinic acid-1-oxide in glacial acetic acid in the presence of 0.25 g. of 20% palladium hydroxide-on-carbon catalyst for 23 hours at 45–60° and 45 p.s.i. yielded 0.27 g. of unchanged starting material (filtered off with the catalyst) and 0.25 g. (44%) of crude 4-aminonicotinic acid, m.p. 316–317° dec., isolated from the filtrate as described above. The product was purified by recrystallization from water. The products obtained by methods B and C were identical in all respects with the products obtained by method A.

4-Hydrazinonicotinic Acid-1-oxide (IX).—To a solution of 5.0 g. of 4-nitronicotinic acid-1-oxide in 350 ml. of hot methanol containing 4.0 g. of 85% hydrazine hydrate was added a small amount of Raney nickel catalyst, and the foaming mixture was boiled for 2 minutes and then heated gently on a steam-bath for 18 hours. Filtration yielded 0.5 g. of unchanged starting material. Concentration of the filtrate under reduced pressure to 10 ml. and chilling resulted in the separation of a small amount of dark solid which was filtered off and discarded; further concentration of the methanol filtrate then gave 3.13 g. of a tan solid, m.p. 220° dec. Fractional crystallization from water yielded 0.26 g. (6.9%) of colorless 4-aminonicotinic acid-1-oxide, m.p. 270° dec., and 0.9 g. (22%) of yellow crystals, m.p. 231° dec.

Anal. Calcd. for $C_6H_7N_3O_3$: C, 42.6; H, 4.2; N, 24.85. Found: C, 42.6; H, 4.3; N, 24.4.

4-Hydroxylaminonicotinic Acid-1-oxide (X).—Hydrogen sulfide was bubbled into 40 ml. of 7 *N* ammonium hydroxide for 10 minutes at room temperature, the resulting solution of ammonium sulfide allowed to cool for 30 minutes, and 3.0 g. of 4-nitronicotinic acid-1-oxide added. A condenser was attached to the reaction flask and the mixture was heated under reflux for 2 minutes, 20 ml. of water added, and refluxing continued for 10 minutes. The solid which separated upon initial mixing of the reagents had now completely dissolved to give an orange-brown solution. The reaction mixture was then transferred to a 125-ml. erlenmeyer flask and hydrogen sulfide was passed through the solution (at room temperature) for 10 minutes. The mixture was then boiled for 10 minutes, cooled again to room temperature, and hydrogen sulfide bubbled through for 10 minutes. The above procedure was repeated a third time, and the reaction mixture was then cooled, filtered to remove precipitated sulfur (1.2 g.) and the filtrate acidified with hydrochloric acid. Cooling overnight resulted in the separation of a yellow solid which was collected by filtration, washed with water and dried; yield 1.74 g., m.p. 211–213° dec. Recrystallization from water yielded 1.44 g. (52%) of yellow crystals, m.p. 219° dec., which turned dark upon exposure to air and light, and which gave a negative sodium fusion test for sulfur.

Anal. Calcd. for $C_6H_6N_2O_4$: C, 42.4; H, 3.6; N, 16.5. Found: C, 42.5; H, 3.7; N, 16.9.

When the initial reaction mixture was heated under reflux for 1 hour rather than 10 minutes, and then worked up as described above, a mixture of crystals was obtained which could be hand-separated to give 4-aminonicotinic acid-1-oxide (19%) and 4-hydroxylaminonicotinic acid-1-oxide (34%).

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