[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

THE PREPARATION OF 5-FLUORONICOTINIC ACID AND 5-FLUORONICOTINAMIDE[1]

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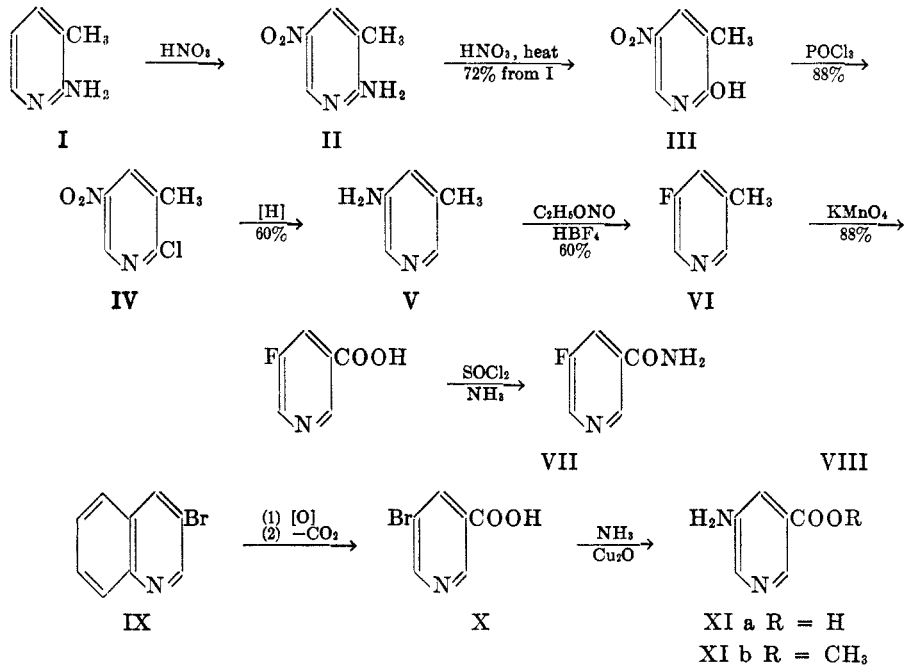
The preparation of several vitamins with fluorine replacing one or more hydrogen atoms has been undertaken as part of a study of aromatic and heterocyclic fluorine compounds being carried out in this Laboratory. Our interest in these compounds was heightened by the observation of Mitchell and Niemann (1) that 3-fluorotyrosine and 3-fluorophenylalanine act as growth inhibitors for *Neurospora crassa* 8815-3a. It was of interest to see if fluorinated vitamins would also behave as antimetabolites.

The preparation of 2- and 6-fluoronicotinic acid has already been reported (2); neither behaved as an antimetabolite. It should be noted, however, that each of these acids has a fluorine atom adjacent to the heterocyclic nitrogen; this greatly alters the basicity of that nitrogen, as shown by the fact that 2-fluoropyridine will not form a hydrochloride, whereas 3-fluoropyridine forms a stable hydrochloride. These facts indicate that 5-fluoronicotinic acid might more nearly resemble nicotinic acid in behavior than either the 2- or 6-fluoro isomer.

Two methods of synthesis of 5-fluoronicotinamide were found. The most satisfactory one started with 2-amino-3-methylpyridine, and is shown in the accompanying equations. 2-Hydroxy-3-methyl-5-nitropyridine (III) was obtained in good yield by conversion (3) of 2-amino-3-methylpyridine (I) to 2-amino-3-methyl-5-nitropyridine (II); this compound was not isolated but converted to the nitramine, which upon being heated formed 2-hydroxy-3-methyl-5-nitropyridine (III). This conversion of a nitraminopyridine to a hydroxypyridine has been observed before (4). A good yield of 2-chloro-3-methyl-5-nitropyridine (IV) was obtained by the action of phosphorus oxychloride on (III). Simultaneous reduction of the nitro group and removal of chlorine was effected by hydrogenation catalyzed by palladium-charcoal; the 3-methyl-5-aminopyridine (V) so prepared was converted to 3-methyl-5-fluoropyridine (VI) by a modification of the Schiemann reaction (5). Permanganate oxidation of (VI) produced 5-fluoronicotinic acid (VII); this was converted to 5-fluoronicotinamide using thionyl chloride and ammonia.

Several variations of the procedure outlined above were attempted. The preparation of 2-hydroxy-3-methyl-5-nitropyridine (III) by nitration of 2-hydroxy-3-methylpyridine, or by the diazotization of 2-amino-3-methyl-5-nitropyridine (II) was not very successful. Conversion of (II) to 2-chloro-3-methyl-5-nitropyridine (IV) by diazotization was accomplished in only 32% yield. Attempted deamination of 2-amino-3-methyl-5-nitropyridine (II) was completely unsuccessful; the amine would not diazotize in ethanol-sulfuric acid, and diazotization in hypophosphorus acid produced only 2-hydroxy-3-methyl-5-nitropyridine (III).

[1] The work here reported is taken from the Ph.D. Thesis of G. F. Hawkins.



A second method of preparing 5-fluoronicotinamide (VIII) starting with 3-bromoquinoline (IX) by way of 5-bromonicotinic acid (X) is outlined in the accompanying equations. Difficulty was encountered in the conversion of 5-aminonicotinic acid (XIa) to 5-fluoronicotinic acid by the Schiemann method because the diazonium fluoborate was soluble; the methyl ester (XIb) was no better in this respect. A poor yield of methyl 5-fluoronicotinate was obtained, however, using the diazonium fluosilicate (6) of (XIb); this ester was converted to 5-fluoronicotinamide (VIII). While the overall yield of this method was low, it served as a confirmation of the structure of 5-fluoronicotinic acid and its amide.

Preparation of 5-fluoronicotinic acid by oxidation of 3-fluoroquinoline (analagous to the preparation of (X) from (IX)) was attempted by several methods, all of which failed; the oxidation product contained no fluorine. Further study of this oxidation is in progress.

A study of the behavior of these compounds as antimetabolites is being made by Eli Lilly and Company, and will be reported elsewhere.

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EXPERIMENTAL

All melting points are corrected.

2-Hydroxy-3-methyl-5-nitropyridine (III). Method A. A solution of 50 g. of 2-amino-3-methylpyridine (I) (Reilly Tar and Chemical Corporation) in 240 ml. of conc'd sulfuric acid was cooled to 5° in an ice-salt bath. A mixture of 35 ml. each of conc'd sulfuric acid and conc'd nitric acid was added slowly with stirring, the temperature being kept below 10°. This mixture was then allowed to warm up to 30° overnight to convert (3) the nitramine to

2-amino-3-methyl-5-nitropyridine (II). (This product could be isolated at this point by pouring the mixture over cracked ice, neutralizing, and filtering off the yellow precipitate; it was found that better yields of (III) were obtained by carrying on the reaction without isolation of the intermediate.) The solution was stirred rapidly while 35 ml. of conc'd nitric acid was added at such a rate as to keep the temperature below 40°. Approximately 50 ml. of the solution was then poured into 100 ml. of water and heated to 120°; large quantities of gas were evolved. When gas evolution ceased the remainder of the nitrating mixture was added in 50-ml. portions with heating if necessary. When the last of the nitrating mixture had been added the solution was cooled rapidly by placing in an ice-bath and by adding ice directly to the solution; this is done to prevent darkening of the product, which proceeds rapidly at the temperature of the reaction. About 1 kg. of cracked ice was necessary to bring the temperature to 5°; the light brown precipitate weighing 46 g. was filtered off. An additional 5 g. of product was obtained by adding 10 g. of sodium nitrite to the filtrate, with stirring, and allowing to stand at room temperature. Still another 6 g. was obtained by neutralizing the filtrate from the sodium nitrite treatment; however a large amount of base and much time is required to recover this 6 g. The combined crude product was dissolved in the minimum quantity of dilute sodium hydroxide solution, stirred with charcoal, and filtered. The product was precipitated with dilute hydrochloric acid and filtered; the yield of 51 g. (71.5%) was pure enough for the next step. For analysis two further recrystallizations from hot water and decolorizing with charcoal produced a pale green-yellow solid, m.p. 228.5–229.5°. The compound was identical with that produced by the nitration of 2-hydroxy-3-methylpyridine (method B).

Anal. Calc'd for $C_6H_6N_2O_3$: N, 18.18. Found: N, 18.17, 18.37.

Method B. A solution of 20 g. of 2-hydroxy-3-methylpyridine [a by-product in the preparation (2) of 2-fluoro-3-methylpyridine] in 40 ml. of conc'd sulfuric acid was cooled to 10°. A mixture of 15 ml. of fuming nitric acid and 20 ml. of conc'd sulfuric acid was added slowly while keeping the temperature below 40°; when addition of the nitrating mixture was complete the solution was removed from the ice-bath and cooled as needed to keep the temperature below 50°. After 2.5 hours the solution was poured over cracked ice; considerable quantities of oxides of nitrogen were evolved, and a precipitate settled to the bottom. The precipitate was filtered, washed with water, and dried over phosphorus pentoxide overnight; the yield was 13.5 g. of cream colored III, m.p. 228.5–229.5°. A mixed melting point of this product and that prepared by method A was not depressed.

Preparation of 2-chloro-3-methyl-5-nitropyridine (IV). Method A. A mixture of 83 g. of 2-hydroxy-3-methyl-5-nitropyridine (III) and 400 ml. of phosphorus oxychloride was refluxed for 6 hours. The excess phosphorus oxychloride was then distilled off and the residue poured over cracked ice. The solid was filtered, and the filtrate neutralized with sodium hydroxide solution and extracted twice with 100-ml. portions of ether. The filtered solid was then dissolved in the ether, a small amount of heavy dark liquid settling out was discarded, and the ether layer dried overnight over calcium oxide. Distillation produced 81.5 g. (87.6%) of a pale yellow solid; m.p. 47–48°; b.p. 145.5° at 18 mm.

Anal. Calc'd for $C_6H_5ClN_2O_2$: N, 16.24. Found: N, 16.04.

Method B. Diazotization of 2-amino-3-methyl-5-nitropyridine (II). A solution of 25 g. of 2-amino-3-methyl-5-nitropyridine (II) in 200 ml. of conc'd hydrochloric acid was cooled to 20°, and 25 g. of calcium chloride was added with stirring. A saturated aqueous solution containing 13 g. of sodium nitrite was added slowly, the temperature being kept below 30°. The solution was stirred thirty minutes after the addition was complete, and allowed to stand three hours at room temperature. The product was then distilled with steam, the distillate eventually being cooled in an ice-bath to solidify the product which was filtered, washed, and dried. A yield of 9 g. (32%) was obtained, m.p. 47–48°; a mixed melting point with material prepared by method A showed no depression.

Anal. Calc'd for $C_6H_5ClN_2O_2$: N, 16.24. Found: N, 16.46.

The residue in the distilling flask was filtered hot, then cooled in an ice-bath. A precipitate of 7 g. of 2-hydroxy-3-methyl-5-nitropyridine (III) was obtained; this material was

identical in melting point with that described above, and a mixed melting point showed no depression.

Preparation of 3-methyl-5-aminopyridine (V). A solution of 24 g. of 2-chloro-3-methyl-5-nitropyridine (IV) in 100 ml. of glacial acetic was prepared; 14 g. of anhydrous sodium acetate and 5 g. of palladium-charcoal catalyst (7) were added. The mixture was shaken with hydrogen at 15 to 25 pounds pressure. At first the reaction was rapid and exothermic; after 70% of the theoretical amount of hydrogen had been adsorbed, however, it was necessary to heat the mixture with a lamp to force the reaction to continue; even with the addition of fresh catalyst, only 80% of the calculated hydrogen was taken up. The hot solution was filtered and evaporated to dryness. The residue was made strongly basic with conc'd sodium hydroxide and heated for 30 minutes. It was then cooled and extracted with three 75-ml. portions of ether; the solution was dried overnight with sodium hydroxide pellets. Distillation gave 9 g. (59.9%) of material whose melting point was 57–59°; b.p. 153°at 21 mm.

Anal. Calc'd for $C_6H_8N_2$: N, 25.91. Found: N, 26.09.

Preparation of 3-methyl-5-fluoropyridine (VI). A solution of 12 g. of 3-methyl-5-aminopyridine (V) in a mixture of 50 ml. of 42% fluoboric acid and 75 ml. of ethanol was cooled to −10°. Ethyl nitrite was passed in with stirring; the solution was kept below −5°. Precipitation suddenly occurred after about twenty minutes; ethyl nitrite was passed in until there was no more precipitation. The solution was poured into a mixture of 75 ml. of absolute alcohol and 100 ml. of ethyl ether which was cooled to −70° with Dry Ice; the solution was filtered and the white precipitate washed twice with cold absolute ethanol, twice with cold dry ether, and twice with petroleum ether (b.p. 30–60°) previously dried over phosphorus pentoxide. (Caution: do not allow the solid to dry; it is unstable if all solvent is removed.) The solid, dampened with petroleum ether, was transferred to a 500-ml. round-bottom flask containing 75 ml. of dried petroleum ether; a condenser was fitted to the flask. The mixture was gently warmed to initiate decomposition of the diazonium salt; the mixture was then cooled as necessary to prevent too vigorous a reaction. When the reaction seemed complete the mixture was refluxed for 30 minutes, and the solvent decanted. The petroleum ether was extracted twice with 50 ml. of dilute hydrochloric acid; these extracts were added to the flask and warmed to remove all the petroleum ether. The contents of the flask were made slightly alkaline and distilled; the 3-methyl-5-fluoropyridine was quite volatile with steam. The distillate was saturated with sodium sulfate and a few drops of sodium hydroxide were added. The organic liquid was separated, dried over sodium hydroxide pellets, and distilled. The yield of colorless 3-methyl-5-fluoropyridine was 7.4 g. (60%); b.p. 139° at 760 mm.; d^{25} 1.0837; n_D^{25} 1.4788.

Anal. Calc'd for C_6H_6FN: N, 12.61. Found: N, 12.68.

Preparation of 5-fluoronicotinic acid (VII). A mixture of 8.5 g. of 5-fluoro-3-methylpyridine and 600 ml. of water was placed in a liter flask fitted with a reflux condenser. Potassium permanganate was added to the refluxing solution, 8 g. at first, and then little by little as the solution decolorized until 26 g. had been added; the process required about three hours. The unreacted 3-methyl-5-fluoropyridine (2.8 g.) was removed by distillation, the residue in the flask filtered while hot, and the precipitate washed with hot water which was added to the filtrate. The colorless solution was evaporated to a volume of 150 ml., when hydrochloric acid was added slowly until precipitation was complete. The solid was filtered and the filtrate evaporated to 50 ml., more hydrochloric acid added, whereupon more solid precipitated. The precipitate (6.4 g., 88.4% based on amount of 3-methyl-5-fluoropyridine consumed) was recrystallized from water, yielding 5.7 g. (77.3%) of 5-fluoronicotinic acid, m.p. 195–197°.

Anal. Calc'd for $C_6H_4FNO_2$: N, 9.93. Found: N, 10.03, 10.10.

Preparation of 5-fluoronicotinamide (VIII). A solution of 3 g. of 5-fluoronicotinic acid in 50 ml. of thionyl chloride was refluxed for 12 hours; at the end of that time the excess thionyl chloride was removed by distillation at reduced pressure. Distillation of the product gave 1.5 ml. of material, b.p. 82° at 18 mm. Anhydrous ammonia was allowed to react with this acid chloride; the crude amide was twice recrystallized from water, yielding 1.1 g. of 5-fluoronicotinamide, m.p. 173–175°.

Anal. Calc'd for $C_6H_5FN_2O$: N, 20.00. Found: N, 20.03.

Preparation of methyl 5-aminonicotinate from 3-bromquinoline. The method of Graf (8) was used to convert 45 g. of 3-bromoquinoline (IX) (obtained from Eastman) to 16.5 g. of 5-bromonicotinic acid (X). Following the method of Meyer and Graf (9) 14.5 g. of 5-bromonicotinic acid was converted to 6.5 g. of 5-aminonicotinic acid (XIa). Reaction of this acid with diazomethane produced 3 g. of methyl 5-aminonicotinate (XIb), m.p. 135–137° [lit. value (9) 137°].

Preparation of 5-fluoronicotinamide (VIII). Attempts to prepare this compound from the amino acid (XIa) or its methyl ester (XIb) by the modified Schiemann reaction (5) were not successful because of the solubility of the diazonium fluoborate in both cases. Preparation was possible using the diazonium fluosilicate, however (6). A solution of 2.7 g. of methyl 5-aminonicotinate (XIb) in 50 ml. of 95% ethanol was treated with 25 ml. of 30% fluosilicic acid. The precipitated salt was filtered off and suspended in 50 ml. of glacial acetic acid; ethyl nitrite was passed into the solution until the solid had dissolved, the temperature being kept below 32° during the process. The solution was cooled in an ice-bath, and 75 ml. of dry ether was added to precipitate the diazonium fluosilicate, which was filtered and washed once with absolute ethanol and thrice with dry ether. This process was carried out in an atmosphere of carbon dioxide to prevent absorption of water by the diazonium salt. The salt weighed 4.5 g. after drying overnight in a desiccator over phosphorus pentoxide; m.p. 89° with violent decomposition. The salt was suspended in dry toluene and heated until decomposition was complete. The toluene layer was then dried over sodium sulfate and distilled; 0.4 g. of methyl 5-fluoronicotinate was obtained; b.p. 101–102° at 26 mm.; m.p. 46–50°.

Anal. Calc'd for $C_7H_6FNO_2$: N, 9.03. Found: N, 9.47.

This apparently impure ester was dissolved in 50% methanol, the solution cooled in an ice-bath, and saturated with ammonia. After standing 16 hours, the solution was evaporated to a small volume and filtered; the 5-fluoronicotinamide so formed after one recrystallization from water melted at 173–175°, and did not depress the melting point of a sample of the material prepared from 2-amino-3-methylpyridine described above.

Oxidation of 3-fluoroquinoline. A mixture of 5 g. of 3-fluoroquinoline (10) and 50 ml. of water was heated to boiling, and 32.5 g. of $KMnO_4$ dissolved in water was added through a dropping-funnel over a period of an hour. The reaction mixture was worked up exactly as described for 5-fluoronicotinic acid above. Acidification caused precipitation of a white material which did not contain fluorine. Further investigation of this product is under way. Oxidation by the method of Graf (8) and oxidation with conc'd nitric acid also failed to produce any 5-fluoronicotinic acid.

SUMMARY

Two methods of synthesis of 5-fluoronicotinamide are reported, as well as attempts to prepare it by a third method. Seven new compounds were prepared in the course of the investigation.

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