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

THE PREPARATION OF 3-FLUOROISONICOTINIC ACID AND RELATED COMPOUNDS

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It was of interest to determine the effect of a fluorine atom adjacent to the carboxyl group on the antituberculostatic activity of isonicotinic acid hydrazide. 3-Fluoroisonicotinic acid (VII) was prepared from 3-fluoro-4-picoline (VI) and was converted to its ethyl ester (IX) and hydrazide (X). The preparation of 3-amino-4-picoline (V), a convenient starting material for this synthesis, had been described from 3-nitro-4-chloropyridine in a 4-step synthesis (1), although the yields were very poor; a better method for the synthesis of V from commercially available 2-amino-4-picoline (I) in 48.5% yield is here reported. The method of Seide (2) was used to nitrate I and the isomeric nitration products (3-nitro- and 5-nitro-2-amino-4-picoline, IIa, IIb) were, without separation, hydrolyzed (3) to the corresponding 3-nitro- and 5-nitro-2-hydroxy-4-picoline (IIIa and IIIb). [IIa and IIb could also be separated and diazotized (4) to form IIIa and IIIb.] The mixture of IIIa and IIIb then was converted with phosphorus oxychloride to the corresponding 2-chloro derivatives (IVa and IVb), which were smoothly reduced to 3-amino-4-picoline (V) with hydrogen and a Pd-charcoal catalyst in an over-all yield of 48.5% from I. After this work was completed the preparation of a mixture of IVa and IVb was reported, although neither was isolated in a pure state, and a different method of synthesis of IIIa and IIIb was used (5).

A modified Schiemann reaction (3) was employed to convert 3-amino-4-picoline (V) to 3-fluoro-4-picoline (VI); the latter was oxidized to 3-fluoroisonicotinic acid (VII) with potassium permanganate. Ethyl 3-fluorisonicotinate hydrochloride (IXa) was obtained by refluxing VII with thionyl chloride followed by addition of absolute ethanol (6). A 92% yield of 3-fluoroisonicotinic acid hydrazide (X) was obtained by refluxing IX with 85% hydrazine hydrate for 6 hours. Longer heating of IXa with hydrazine hydrate produced 3-hydroxyisonicotinic acid hydrazide, this longer heating resulting in the replacement of fluorine by a hydroxyl group.

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EXPERIMENTAL

3- and 5-Nitro-2-hydroxy-4-picoline (IIIa, IIIb). Following the method of Hawkins and Roe (3) for an isomeric compound, a 50-g. sample of 2-amino-4-picoline was converted to

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I
H2SO4, HNO3
60°, 24 hrs.
IIa
IIb
1. H2SO4–HNO3, 60°
2. HNO2, 120°
3. NaNO2
NaNO2
Dil. H2SO4
Mixture III (a + b)
IIIa
IIIb
POCl3
POCl3
PCl5
Mixture IV (a + b)
IVa
IVb
Pd—C
[H]
V
Pd—C
H
V
HBF4
EtONO
Pet. ether
60–90°
VI
KMnO4
Then H
VII
SOCl2
VIII
EtOH
IXa
NaHCO3
IX
N2H4•H2O
5.5 hrs.
X

the nitramine and allowed to rearrange to form the 3-nitro- and 5-nitro-2-amino-4-picolines (IIa and IIb); these in turn were hydrolyzed to form IIIa and IIIb. The over-all yield of mixed IIIa and IIIb from I was 80%. A sample of this mixture recrystallized from benzene had a sharp melting point of 159°; both IIIa and IIIb could be obtained by recrystallization of this mixture from water, and both IIIa and IIIb were also prepared from the corresponding aminonitropicoline as described by Lappin and Slezak (4); our melting points for these pure compounds agreed with those reported. It was found that separation of IIIa and IIIb was unnecessary, as equally good yields of (V) were obtained with the mixed compounds.

2-Chloro-5-nitro-4-picoline (IVb). A mixture of 2.5 g. of IIIb and 20 ml. of phosphorus oxychloride was warmed for 2.5 hours, the excess phosphorus oxychloride was removed under water pump pressure, and the residue was poured over cracked ice with vigorous stirring; a brown semi-solid precipitated. The oil was extracted with ether, and the ether was evaporated leaving a dark oil which distilled at 91.2° at 5 mm. but solidified on cooling giving a 60.7% yield of IVb, m.p. 38.5–39.5°.

Anal. Calc'd for $C_6H_5ClN_2O_2$: N, 16.2. Found: N, 16.4.

2-Chloro-3-nitro-4-picoline (IVa). This was made by the same procedure as employed for IVb, except that the addition of phosphorus oxychloride to IIIa was carried out cautiously, as the reaction between the two was violent. The crude product was purified by sublimation to produce a white solid melting at 52.0–52.9°; this compound was recently reported by Brown (8) as melting at 46–47°.

Anal. Calc'd for $C_6H_5ClN_2O_2$: N, 16.2. Found: N, 16.1.

It was found that equally good yields of V were possible if a mixture of isomers was used; subsequently runs were made in this same way with 35 g. of a mixture of IIIa and IIIb.

3-Amino-4-picoline (V). The mixture of IVa and IVb (25 g.), prepared as described above, 20 ml. of glacial acetic acid, 0.5 g. of sodium acetate, and a 10% palladium-charcoal catalyst (9) was hydrogenated at 65 lbs. pressure. Within 20 minutes 75% of the theoretical amount of hydrogen was absorbed, indicating the nitro group was reduced; at that time the flask was heated with an infrared lamp until 99% of the theoretical amount of hydrogen was absorbed. The reduced mixture was filtered while hot and the filtrate was evaporated to dryness. The residue was made strongly alkaline with concentrated sodium hydroxide solution, heated for 30 minutes, cooled, extracted with several portions of ether, and the ether extracts were dried over sodium hydroxide pellets. Removal of the ether left 14 g. (89.5%) of tan material that melted at 104–105°. The picrate was found to melt from 177 to 178°. [Reported (1) for 3-amino-4-picoline prepared by another method: m.p. 106°; picrate: m.p. 179–180°.]

3-Fluoro-4-picoline (VI). A modified Schiemann reaction (3) was employed starting with 24 g. of V; it was noted that 4-picoline-3-diazonium fluoborate would not decompose in boiling petroleum ether (30–60°) but in boiling 60–90° petroleum ether the salt decomposed smoothly. A yield of 17 g. of VI (68%), was obtained; VI was a colorless liquid, b.p. 135.6° (748 mm.) $n_D^{27.5}$ 1.4795.

Anal. Calc'd for C_6H_6FN: C, 64.9; H, 5.41.
Found: C, 64.7; H, 5.50.

A *picrate* was formed which crystallized from aqueous ethanol in yellow plates melting at 129–130°.

Anal. Calc'd for $C_{12}H_9FN_4O_7$: N, 16.5. Found: N, 16.3.

3-Fluoroisonicotinic acid (VII). A 3-liter, 3-necked flask fitted with a reflux condenser, mechanical stirrer, and a dropping-funnel was used for this reaction. It contained a suspension of 17 g. of 3-fluoro-4-picoline (VI) in one liter of water, which was refluxed while a saturated solution of 48 g. potassium permanganate in water was added dropwise over a 3.5-hour period. At the end of that time, the solution was steam-distilled to remove any unreacted 3-fluoro-4-picoline, and the solution was filtered while hot; the manganese dioxide filter cake was extracted twice with hot water, and the filtrates were combined and evaporated on the steam-table until solid potassium 3-fluoroisonicotinate began to

precipitate. The minimum amount of water was added to redissolve the solid, and hydrochloric acid was added until precipitation of the acid was complete; a total of 6.7 g. (45%) was produced. A sample of 3-fluoroisonicotinic acid recrystallized from water melted at 256–257°, with decomposition and sublimation.

Anal. Calc'd for $C_6H_4FNO_2$: N, 9.93. Found: N, 9.76.

Ethyl 3-fluoroisonicotinate (IX). Two g. of VII was refluxed with 20 ml. of thionyl chloride for 1.5 hours; the excess thionyl chloride was removed and absolute ethanol (19 ml.) was slowly added. The mixture was refluxed for one hour, and the excess ethanol was removed leaving a yellow liquid. This liquid, which was probably ethyl 3-fluoroisonicotinate hydrochloride (IXa), was treated with sodium carbonate, washed with water, and dried; yield 2 g. (83.4%) of ethyl 3-fluoroisonicotinate, b.p. 215° at 752 mm. (micro technique). A picrate was formed which crystallized in long yellow needles, m.p. 109–110°.

Anal. Calc'd for $C_{14}H_{11}FN_4O_9$: N, 14.0. Found: N, 13.8.

It was noted that heating this picrate in an Abderhalden drying apparatus with phosphorus pentoxide as the desiccant and methanol as the refluxing solvent caused dissociation of the picrate, leaving only picric acid, which was identified by melting point, mixture melting point with an authentic sample, and nitrogen analysis.

3-Fluoroisonicotinic acid hydrazide (X). Two g. of IX was refluxed with 1.5 ml. of 85% hydrazine hydrate and 20 ml. of 95% ethanol for 5.5 hours, the mixture was heated on a water-bath to remove the excess ethanol, and the residue was chilled to precipitate 0.7 g. of light tan crystals; an additional 1.2 g. of crude material (92% yield) was obtained by evaporating the mother liquor. Recrystallization from isopropyl alcohol, after Norit treatment, produced fine white needles, m.p. 146.8–147.8°.

Anal. Calc'd for $C_6H_6FN_3O$: C, 46.5; H, 3.90; N, 27.1.
Found: C, 46.5; H, 3.89; N, 26.7.

When hydrazine hydrate was allowed to reflux with IXa for 36 hours, the product recovered was 3-hydroxyisonicotinic acid hydrazide (10).

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