[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

STUDIES ON THE ACID HYDROLYSIS OF α-HALOGENATED PYRIDINE COMPOUNDS[1]

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During a recent investigation of the chemistry of Coenzyme I and II the methiodides of 2- and 6-fluoronicotinamides were required. Reaction of the corresponding fluoronicotinamides with excess methyl iodide under pressure, followed by recrystallization from water, was found to give only the hydroxynicotinamides. When ethyl iodide was substituted for methyl iodide no reaction whatever occurred. The corresponding bromonicotinamides were unreactive toward either halide.

It was further observed that the successful preparation of the fluoronicotinamides appeared to be dependent upon the presence of a small amount of thionyl chloride. Frequently, when all traces of thionyl chloride were removed from the acid chloride, hydrolysis occurred during the initial recrystallization from water. When this was not done, hydrolysis did not occur. Hydroxynicotinamides were also isolated as by-products of the successful preparation of the amides. No such difficulty was observed in the preparation of 2-bromo- or 6-chloro-nicotinamides.

Because of these observations, a study of the relative ease of acid hydrolysis of various halogens when substituted in the α-position in pyridine was undertaken. Although it has been known for some time that α- and γ-halogen on pyridine is more reactive than aromatic halogen, relatively little systematic work has been done on the subject. Skraup (1) found that α-chloroquinoline was hydrolyzed to carbostyril by dilute acid at 120°. Later Decker (2) found that ten minutes at the boiling point sufficed for the acid hydrolysis of 8-nitro-2-chloroquinoline. He suggested that the formation of the strongly positive quaternary nitrogen was in part responsible for the ease of hydrolysis. The results of Wibaut (3), who found that N-4-pyridyl-4-chloropyridinium chloride and its bromine analog are hydrolyzed to the corresponding pyridones by dilute acid at room temperature, support this hypothesis. Räth (4) has reported that 2-chloropyridine, 5-nitro-, 5-chloro-, and 3-chloro-5-nitro- 2-chloropyridine are all hydrolyzed to the corresponding pyridones by hydrochloric acid at 150°. Bobranski (5) found that 4-chloroquinoline was converted to 4(1)-quinolone on acid treatment at 150°, and Wibaut (3) reported that 2,6-dibromopyridine could be cleaved by acid at 150° but not at 100°.

These facts suggest that while α- and γ-halogen on the pyridine nucleus is somewhat activated, the activation is not so great as some authors have supposed in the past. The electronic similarity of pyridine and nitrobenzene proposed by

[1] We are indebted to the United States Public Health Service for a fellowship granted to one of us (H. L. B.).

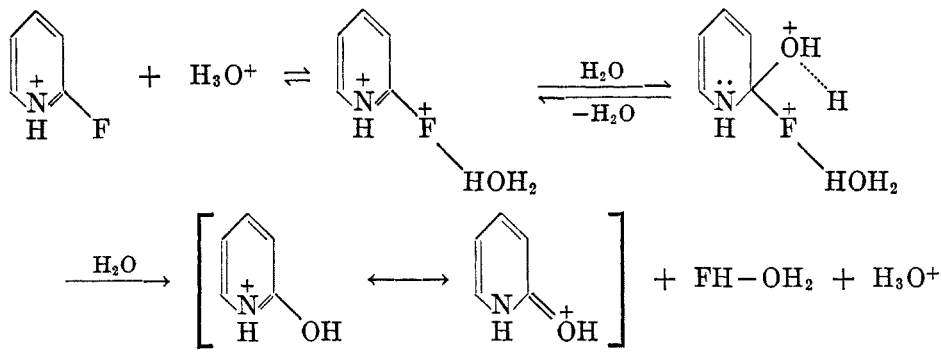
Erlenmeyer[2] (6) on biochemical grounds provides a frame of reference from which to interpret the reactivity of α- and γ-halogen. On this basis the variation in lability becomes more intelligible. Just as the chlorine of *o*- or *p*-nitrochlorobenzene is more reactive than that of chlorobenzene, so is that of α- or γ-chloropyridine. Just as the halogen of 2,4-dinitrochlorobenzene is more reactive than that of nitrochlorobenzene, so is the halogen of 8-nitro-2-chloroquinoline more reactive than that of 2-chloroquinoline.

Although Wibaut (3) has reported the hydrolysis of 2,6-dibromopyridine to 2-bromo-6-hydroxypyridine by means of alcoholic sodium hydroxide, on the whole alkaline hydrolysis is much less readily effected, as the experimental results reported below will show. None of the fluoro- or bromo-nicotinic acids or picolines showed appreciable alkaline hydrolysis. This is to be expected since the activating quaternary nitrogen is present in acid but not in basic solution. In confirmation it was found that 2-iodo-3-methyl- and 2-iodo-5-

TABLE I

RESULTS OF HYDROLYTIC EXPERIMENTS

HYDROLYSIS	NO HYDROLYSIS
2-Fluoropyridine	2-Chloropyridine
2-Fluoro-3-methylpyridine	2-Bromopyridine
2-Fluoro-5-methylpyridine	2-Bromo-3-methylpyridine
2-Fluoronicotinic acid	2-Bromo-5-methylpyridine
6-Fluoronicotinic acid	
2-Bromonicotinic acid	
6-Bromonicotinic acid	
2-Chloroquinoline	



methyl-pyridine ethiodides were readily hydrolyzed to the corresponding N-ethylpicolones in good yield by means of warm sodium hydroxide solution[3].

Hydrolysis with 6 *N* hydrochloric acid for twenty-four hours was selected as the standard treatment. Increasing the time to forty-eight or seventy-two hours

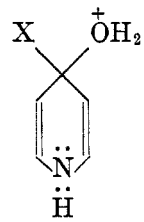
[2] N-diethyl *m*-nitrobenzamide was found to possess the same analeptic action as the corresponding pyridine derivative. Also *o*-sulfanilamidonitrobenzene was found to possess antibacterial activity comparable to that of sulfapyridine.

[3] The experimental details will be found in a paper now in press.

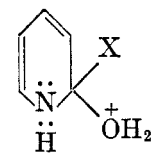
did not change the results summarized in Table I. In all cases the corresponding hydroxy compounds were isolated. While all of the fluoro derivatives were hydrolyzed, the only bromo compounds which were hydrolyzed were those which contained an additional activating group. The results are consistent with the following electronic mechanism:

The lesser tendency of chlorine and bromine to form hydrogen bonds as well as their lower electronegativity both operate to decrease the lability of these halogens as compared with fluorine[4]. When, however, another labilizing group is present, as in the bromonicotinic acids or in 2-chloroquinoline, hydrolysis does occur.

The same considerations do not seem to apply to γ-halogen, which is in general much more reactive. Thus moist γ-chloropyridine (7) is converted on distillation to γ-pyridone hydrochloride. Also γ-fluoropyridine (8) cannot be isolated because of its rapid conversion to N-γ-pyridyl-γ-pyridone. Presumably this is due to the greater resonance stabilization of the *p*-quinoidal type intermediate structure (I) as compared with the *o*-quinoidal type structure (II).[5]



(I)



(II)

The formation of the hydroxynicotinamides in the reaction of the fluoronicotinamides with methyl iodide can easily be correlated with the above results. A considerable decomposition of methyl iodide occurs at 80° and the initial aqueous solutions are sufficiently acidic (pH < 1) to effect the observed hydrolysis.

As indicated in the experimental results, an acidic by-product was present during the first recrystallization from water. Unless precautions were taken to limit the period of heating and the amount of water to a minimum the fluoroamides would not precipitate from the acidic solution. Concentration of the solution did not give the original fluoroamides but the hydroxyamides. The acidity increases on concentration, suggesting an autocatalytic hydrolysis which proceeds readily once the solution is even mildly acidic. Once freed of this acidic by-product the fluoroamides are stable toward water. The hydroxyamides must be considered to be artifacts.

Surprisingly, attempts to convert 6-bromonicotinic acid to the acid chloride

[4] Added in press. Such an acid catalysis has recently been reported for the benzyl fluorides by Miller and Bernstein, *J. Am. Chem. Soc.*, **70**, 3600 (1948).

[5] See Waters (9) for a discussion of the significance of the transition state in substitution reactions.

with either thionyl chloride or oxalyl chloride under a variety of conditions resulted in halogen exchange. Ammonolysis of the crude acid chloride so formed gave only 6-chloronicotinamide. Attempted ammonolysis of methyl 6-bromonicotinate with alcoholic ammonia led to recovery of the original ester.

EXPERIMENTAL[6, 7]

Preparation of intermediates. The 2- and 6-fluoro-3-methylpyridines, nicotinic acids, and nicotinamides were prepared by the method of Minor, Hawkins, *et al.* (10). 2-Bromo-3-methylpyridine and 2-bromo-5-methylpyridine were prepared in 87% and 80% yields, respectively, by the methods of Allen (11) for the preparation of 2-bromopyridine.

Best results were obtained when a stiff, tantalum Hershberg stirrer was used, as the mixtures become quite thick during the course of the reaction. Less concentrated hydrobromic acid (40%) may be used in place of the 48% acid, but the results are not so satisfactory (*ca.* 75–80% yields). The *2-bromo-3-methylpyridine* boiled at 82–86° at 9 mm. Mariella (12) has reported the boiling point as 76–77° at 7 mm.

* *Anal.* Calc'd for C_6H_6BrN: N, 8.2. Found: N, 8.3, 8.5.

The *2-bromo-5-methylpyridine* boiled at 73–77° at 8 mm.

* *Anal.* Calc'd for C_6H_6BrN: N, 8.2. Found: N, 8.3, 8.5.

Preparation of 6-bromonicotinic acid. Exactly 122.3 g. of 2-bromo-5-methylpyridine was added to a solution of 278 g. of potassium permanganate in 3 l. of water. The mixture was stirred under reflux for five hours. Then 15 g. of potassium permanganate was added and refluxing was continued for an additional hour. The mixture was distilled until all of the unreacted 2-bromo-5-methylpyridine (about 45 g.) was recovered. The hot solution was then filtered and the precipitated manganese dioxide was twice stirred with boiling water and re-filtered. The combined filtrate and washings were concentrated to 600 ml.,[8] filtered, and acidified with concentrated hydrochloric acid. About 90–100 g. of crude acid was obtained. After recrystallization from water it melted at 193.0–193.9°.

* *Anal.* Calc'd for $C_6H_4BrNO_2$: N, 6.9. Found: N, 7.0, 7.1.

The crude acid may be directly converted to the amide. The acid was characterized as the methyl ester. Esterification by means of diazomethane gave much better results than the use of methanol with either dry hydrogen chloride or sulfuric acid as catalyst. To an ether solution of 0.1 mole of diazomethane a slight excess of the acid as a slurry in ether was added gradually with shaking until the yellow color vanished. The ether solution was washed with 10% sodium carbonate solution, then with saturated brine, and distilled to give 18.1 g. (84%) of the *methyl ester* boiling at 107–110° at 4 mm. An analytical sample, m.p. 108.5–110.0°, was obtained by vacuum sublimation.

Anal. Calc'd for $C_7H_6BrNO_2$: N, 6.5. Found: N, 6.4, 6.3.

The *2-bromonicotinic acid* was prepared in exactly the same way in the same yield. After recrystallization from water it melted at 249.1–250.4°.

* *Anal.* Calc'd for $C_6H_4BrNO_2$: N, 6.9. Found: N, 7.0, 7.1.

The acid was characterized as the *methyl ester* prepared in the same way as its isomer. A 92% yield of ester boiling at 95–97° at 1.4 mm. was obtained. After recrystallization from dilute alcohol it melted at 107.2–108.3°.

Anal. Calc'd for $C_7H_6BrNO_2$: N, 6.5. Found: N, 6.3

Attempted preparation of 6-bromonicotinamide. A mixture of 30 g. of 6-bromonicotinic acid and 300 ml. of thionyl chloride was refluxed for twenty hours. Excess thionyl chloride

[6] All melting points corrected, all boiling points uncorrected.

[7] All analyses by Clark Microanalytical Laboratories, Urbana, Illinois, unless starred. Starred analyses are by Arlington Laboratories, Fairfax, Virginia.

[8] The fact that neither the fluoro- nor the bromo-nicotinic acids hydrolyzed during the concentration of these alkaline solutions is evidence for the absence of any rapid alkaline hydrolysis reaction.

was removed *in vacuo*. The residue was added as a slurry in dioxane or benzene to 75 ml. of cold, stirred concentrated ammonium hydroxide. The mixture was stored overnight and then filtered to give 26.2 g. of crude *6-chloronicotinamide*. After recrystallization from water it melted at 213.5–214.2°. Kushner (13) reported the m.p. as 212–213°.

Anal. Calc'd for $C_6H_5ClN_2O$: C, 45.9; H, 3.2; Cl, 22.6; N, 17.9.
Found: C, 45.7; H, 3.4; Cl, 22.7; N, 17.7.

The use of smaller amounts of thionyl chloride and shorter reflux periods, as well as dilution with benzene, served only to decrease the yield of 6-chloronicotinamide. Treatment of the acid with oxalyl chloride in benzene gave a quantitative yield of the chloroamide, even when the reflux period was shortened to four hours.

In an attempted ammonolysis of methyl 6-bromonicotinate, a mixture of 1 g. of the ester, 10 ml. of concentrated ammonium hydroxide, and 10 ml. of methanol was refluxed for eighteen hours. The solution was concentrated and cooled. The starting ester, m.p. 108.3–110.2°, crystallized from the solution. Extension of the reflux period had no appreciable effect on the results. In view of the results of Kushner (13) with the corresponding methyl 6-chloronicotinate, use of more drastic conditions is precluded.

2-Bromonicotinamide. This product was prepared in 80% yield by treatment of 2-bromonicotinic acid with thionyl chloride according to the procedure described for the attempted preparation of 6-bromonicotinamide. It exhibited an unusual melting point behavior. It softened appreciably at 140°, resolidified at 147°, melted at 171–172°, resolidified at 175–176° and finally decomposed at about 260°.

Anal. Calc'd for $C_6H_5BrN_2O$: C, 35.8; H, 2.5.
Found: C, 35.5; H, 2.6.

2-Fluoropyridine. This product was prepared in good yield according to the method of Roe and Hawkins (8). 2-Fluoropyrimidine could not be successfully prepared in this manner. 2-Chloropyridine, 2-bromopyridine, and 2-chloroquinoline were Eastman products.

Reaction of substituted amides with ethyl iodide. In each case a 2-g. sample of amide was heated with 25 ml. of ethyl iodide for twelve hours at 110° in a sealed tube. The ethyl iodide was then removed by evaporation and the residue recrystallized from water. In all cases the original amide was recovered in good yield.

Reaction of the amides with methyl iodide. These reactions were carried out in a sealed tube at 80°. The chloro- and bromonicotinamides were recovered unchanged. The behavior of the fluoroamides was quite different. The 2-fluoroamide dissolved in the methyl iodide on heating but later separated out again as a red oil. Immediate evaporation after solution had occurred gave only the original amide. After twelve hours of heating the methyl iodide was removed by distillation, the residue was taken up in water (very soluble) and extracted with ether to remove free iodine. The solution was concentrated somewhat, cooled and the crystalline product filtered off. The compound was recrystallized from water. The solubility was much lower at this stage. The behavior of 6-fluoronicotinamide was similar except that it did not dissolve in the methyl iodide. The *2-hydroxyamide* sintered at 265° and melted at 270.1–272.0°.

Anal. Calc'd for $C_6H_6N_2O_2$: C, 52.1; H, 4.3; N, 20.3.
Found: C, 51.9; H, 4.1; N, 20.9.

Acid hydrolysis gave the known *2-hydroxynicotinic acid* melting at 260.0–261.2°, with gas evolution, after recrystallization from water. Philips (14) reported 256°.

Anal. Calc'd for $C_6H_5NO_3$: C, 51.7; H, 3.6; N, 10.1.
Found: C, 51.4; H, 3.3; N, 10.1.

It was further identified as the *methyl ester*, m.p. 152.1–153.3°, prepared by the method of Kirpal (15) who reported m.p. 153°. The *6-hydroxyamide* melted at 313.0–314.4°.

Anal. Calc'd for $C_6H_6N_2O_2$: C, 51.9; H, 4.3.
Found: C, 52.0; H, 4.5.

Acid hydrolysis gave the known *6-hydroxynicotinic acid*, which sintered at 305–308° and melted at 309°. Von Pechmann (16) reported the m.p. 303°.

Anal. Calc'd for $C_6H_6N_2O_2$: C, 51.7; H, 3.6; N, 10.1.
Found: C, 51.7; H, 3.1; N, 10.0.

The acid was further identified as the *methyl ester*, m.p. 166.1–167.5°, prepared by the method described by Meyer (17), who reported the m.p. 164°.

Preparation of 2- and 6-fluoronicotinamides. When the preparation was carried out exactly as described by Minor, Hawkins, *et al.* (10) the fluoroamides were easily obtained. Working up the mother liquors gave a small amount of the corresponding hydroxyamides. Frequently, however, when the last traces of thionyl chloride were removed by the repeated addition and vacuum distillation of dry benzene the hydroxyamides were the sole products. Judging from the solubility behavior, the actual hydrolysis seemed to occur during the first recrystallization from water. The *p*H of the freshly prepared solution was 6.4. If the solution was concentrated, the *p*H dropped to 3.9 within a short time. Although on smaller scale runs (*ca.* 2 g.) the fluoroamides did not hydrolyze during the brief period required to concentrate the solution, nevertheless hydrolysis did occur during the much longer period required for large runs (*ca.* 70 g.) when carried out on the steam-bath. If solution was effected with a minimum of water and prompt cooling employed, pure fluoroamides were obtained in good yield.

Acid hydrolysis of the compounds in Table I. One-gram samples of each compound were refluxed for twenty-four hours with 10 ml. of 6 *N* hydrochloric acid. Results were as follows:

Bromo- and fluoro-nicotinic acids. On cooling, the hydroxynicotinic acids crystallized. The acids, after recrystallization from water, were identified by melting point and mixed melting point.

2-Chloroquinoline. The product was *2-hydroxyquinoline*, m.p. after recrystallization from alcohol 199.0–200.1°, which separated in quantitative yield from the acid solution. Morgan (18) reported the m.p. as 199–200°.

2-Fluoro-, 2-chloro-, 2-bromo-, 2-fluoro-3-methyl-, 2-fluoro-5-methyl-, 2-bromo-3-methyl-, and 2-bromo-5-methyl-pyridines. The acid solutions were made alkaline with sodium carbonate. In all cases except that of the fluoro derivatives the solutions were repeatedly extracted with ether. Chloroform was used for the fluoro derivatives. The extracts were washed, dried over sodium sulfate, and concentrated. The chloro and bromo derivatives were recovered unchanged in almost quantitative yield. From 2-fluoropyridine, *2(1)-pyridone*, b.p. 290–295° (730 mm.), m.p. 106–107°, was obtained in 60% yield. From the fluoropicolines, the corresponding picolones were obtained in 66% yield. 3-Methyl-2-(1)-pyridone,[9] after sublimation *in vacuo*, melted at 138.0–139.5°. Seide (19) reported the m.p. 140°.

Anal. Calc'd for C_6H_7NO: N, 12.8. Found: N, 12.7, 12.8.

5-Methyl-2(1)-pyridone, after recrystallization from benzene, melted at 183.0–184.1°.

Anal. Calc'd for C_6H_7NO: N, 12.8. Found: N, 12.8.

Alkaline hydrolysis studies. Two gram samples of 2-fluoro-3-methylpyridine and 2-bromo-3-methylpyridine were refluxed with 10 ml. of 25% sodium hydroxide solution in water or 50% alcohol for four days. No appreciable reaction occurred in any case, the starting material being recovered in each instance.

SUMMARY

1. A study has been made of the reactions of methyl and ethyl iodides with 2-bromo, 6-chloro- and 2- and 6-fluoro-nicotinamides. N-alkylation could not be effected in any instance; however, after treatment with methyl iodide, the fluoronicotinamides underwent hydrolysis to the corresponding hydroxynicotinamides during the course of the subsequent isolation procedure. This hydrolysis

[9] This compound has also been isolated as a by-product of the preparation of 2-fluoro-3-methylpyridine by the procedure of ref. 10.

was catalysed by acidic products formed during the attempted methylation reaction.

2. Comparative studies have shown that fluorine substituted in the α-position on the pyridine nucleus is more labile toward acid-catalysed hydrolysis than either chlorine or bromine.

3. A mechanism which accounts for the comparative ease of acid-catalysed hydrolysis of α-fluoropyridines is proposed.

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