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

EXCHANGE REACTIONS OF α-HALOGENATED PYRIDINES

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During the course of a study of the chemistry of Coenzymes I and II, the need arose for a series of 3-methyl-2- and 6-halogenated pyridine methiodides. It was found that, unlike the corresponding substituted nicotinamides (1), the halogenated β-picolines reacted readily with methyl iodide.

Both 2-fluoro-3-methylpyridine and 2-fluoro-5-methylpyridine gave the rather unstable fluorine substituted methiodides in good yield. On the other hand, 2-bromo-3-methylpyridine and 2-bromo-5-methylpyridine, when treated with methyl iodide for 12 hours at 90°, yielded quantitative amounts of the corresponding iodo methiodides. Even when the reaction was carried out for a shorter period (4 hours) at a lower temperature (50°), the only products isolated, although in inferior yield, were the iodo methiodides. While this type of halogen exchange reaction is not new, having been reported in the reaction of 2-chloropyridine (2) and of 2-chloroquinoline (3) with methyl iodide, it was stated in each of these cases that prolonged treatment at 100° was required. Since the order of reactivity of the fluoro- and bromo- derivatives was the reverse of that reported in a previous paper (1) for the acid hydrolysis of 2- and 6-halogenated nicotinamides, it was decided to study the reaction further.

In our investigation, 2-fluoro, 2-chloro-, 2-bromo-, and 3-bromo-pyridine and 2-chloroquinoline were treated with excess methyl iodide at 90° for 12 hours. All but 2-fluoro- and 3-bromo-pyridine gave the corresponding iodo methiodides. When treated at lower temperatures (*circa* 50°), 2-chloro- and 2-bromo-pyridine and 2-chloroquinoline still gave the iodo methiodides, although in much poorer yield. In the case of 2-chloropyridine, some chloro methiodide was formed, but it could not be separated completely from the iodo methiodide, even by repeated fractional crystallization.

All of the above mentioned halogenated pyridines save 3-bromo- and 2-fluoropyridine and 2-fluoro-5-methylpyridine were also treated with ethyl iodide at 90° for 12 hours. Here again the iodo ethiodides were the only products isolated, except in the case of 2-fluoro-3-methylpyridine, which gave the expected, though rather unstable, fluoro ethiodide. 2-Chloroquinoline reacted to only a limited extent; prolonged treatment did not increase the yield appreciably. From a consideration of molecular models, it appears that steric factors may be critical in this case. The lack of reactivity of collidine with methyl iodide is further evidence of the importance of steric factors.

It was considered of interest to determine at what point the halogen exchange occurred. A careful fractionation of the unreacted base in the treatment of 2-chloropyridine and 2-chloroquinoline with methyl iodide at 50° indicated the

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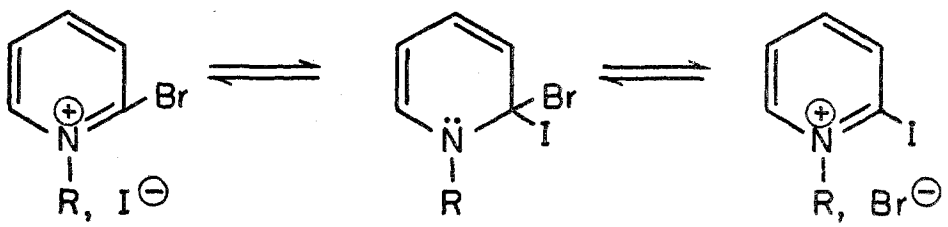
complete absence of any free iodopyridine or iodoquinoline; all of the 2-chloropyridine or 2-chloroquinoline could be accounted for as the iodo methiodide and unreacted 2-chloropyridine or 2-chloroquinoline. It seemed likely, therefore, that the exchange occurred only after methiodide formation.

To test this hypothesis, 2-bromopyridine ethobromide and 2-bromo-3-methylpyridine ethobromide, prepared by reaction of the bromopyridines with ethyl bromide, were heated with excess ethyl iodide at 100° for 12 hours. In both cases the 2-iodo compounds were isolated in good yield. It might be noted that ethobromide formation proceeds at a very much slower rate than ethiodide formation. It was further found that 2-bromopyridine ethobromide was converted to the corresponding iodo compound by refluxing with potassium iodide in methyl ethyl ketone. These results suggest the following mechanism for the halogen interchange:

$$RI + Br^- \rightleftharpoons RBr + I^-$$



Attempts to prepare the bromopyridine methiodides by methylation of the bromopyridines with methyl sulfate followed by metathesis with potassium iodide in cold aqueous solution were unsuccessful. It was found that the products had undergone appreciable bromine-iodine exchange under these conditions and were therefore unsuited as test compounds. The results are, nevertheless, additional evidence for the hypothesis that the exchange occurs after quaternary ion formation.

The reversal of the order of reactivity found for the substituted nicotinamides is believed to be due to the difference in the nature of the media in the two cases. Nucleophilic displacement of a ring fluorine atom in a pyridinium compound appears to proceed less readily than a similar displacement of a chlorine or bromine atom unless, as is the case in acid solution, conditions favor the solvation of the fluorine through hydrogen bonding. Miller and Bernstein (4) found that benzyl fluoride exhibits similar behavior, and Roe (5) has recently reported the same type of behavior for 2-fluoroquinoline.

To test the hydrolysis mechanism proposed in the first paper of this series, three of the compounds were subjected to acid hydrolysis and two to alkaline hydrolysis. Both 2-iodo-3-methylpyridine ethiodide and 2-iodo-5-methylpyridine ethiodide, when refluxed for 1 hour with 25% sodium hydroxide solution, gave good yields of the corresponding N-ethylpicolones. Acid hydrolysis of these two

compounds did not proceed so smoothly, although 1-methyl-2-pyridone was obtained in good yield from 2-iodopyridine methiodide. 2-Iodo-5-methylpyridine ethiodide gave a 47% yield of 1-ethyl-5-methyl-2-pyridone, together with complex iodinated products of uncertain nature.[2] Similar iodinated products, together with some starting material in the form of the mixed methiodide and methochloride, constituted all that could be isolated in the acid hydrolysis of 2-iodo-3-methylpyridine ethiodide.

These results substantiate the hypothesis that the quaternary nitrogen is important for hydrolysis. The rapid hydrolysis in alkaline solution, once the quaternary nitrogen is present, probably arises from the greater hydrolytic power of the hydroxide ion over that of water.

In connection with our previous work (1), 3-methylpyridine methiodide, 3-cyanopyridine methiodide, 3-carbomethoxypyridine methiodide, and 5-methylthiazole methiodide were also prepared. Very carefully purified β-picoline was used in the preparation of the methiodide, which was obtained as a yellow-orange solid melting at 79.1–80.2°. Murrill (6) had previously reported the compound as a liquid.

Unlike the α- or α′-halogenated nicotinamides (1), methyl 2-bromonicotinate and methyl 6-bromonicotinate (1) reacted readily with methyl iodide to give quantitative yields of the corresponding iodonicotinate methiodides. An investigation of this difference, for which no explanation is known, is in progress.

The spectra of all the compounds except 2-fluoro-3-methylpyridine ethiodide and methyl nicotinate methiodide, were measured in the region between 230 and 400 mμ. All of the compounds were studied at a concentration of 0.1 mg./ml. in distilled water as solvent. Substitution of halogen in the α- or α′-position of 3-methylpyridine methiodide causes a shift of about 20 mμ. in the principal absorption peak without appreciably shifting the preceding minimum. The thiazole derivative showed no such absorption peak but only a gradual decrease in intensity from an initial peak at 230 mμ. The curves are shown in Figures I–IV.

EXPERIMENTAL[3, 4]

Intermediates. The bromo-β-picolines and methyl bromonicotinates were prepared as described in a previous paper (1). The fluoro-β-picolines were obtained following the procedure of Minor, Hawkins, VanderWerf, and Roe (7). The fluoropyridine was prepared by the method of Roe and Hawkins (8). 5-Methylthiazole was prepared according to the excellent directions of McLean and Muir (9). The β-picoline was a highly purified sample prepared by Hoffman and VanderWerf (10) in this laboratory. 3-Bromo- and 3-cyano-pyridine were obtained through the kindness of the Dow Chemical Company. 2-Chloro- and 2-bromo-pyridine and 2-chloroquinoline were obtained from the Eastman Kodak Company.

All of the reactions with methyl and ethyl iodides were carried out in capped citrate bottles. Two sets of reaction conditions were employed: (A) treatment at 90° for 12 hours and

[2] Iodinated products may result from direct iodination by iodine formed as a result of oxidation during the refluxing period. Some free iodine was observed in the reflux condenser.

[3] All melting points are corrected, all boiling points are uncorrected.

[4] All analyses are by the Clark Microanalytical Laboratories, Urbana, Illinois unless starred. Starred analyses are by Microchemical Specialties Co., Berkeley 3, California.

(B) treatment at 50° for 4 hours. Since these same procedures were employed in all cases only a single example of each will be cited. The melting points and analytical data for the individual compounds are given in Table I.

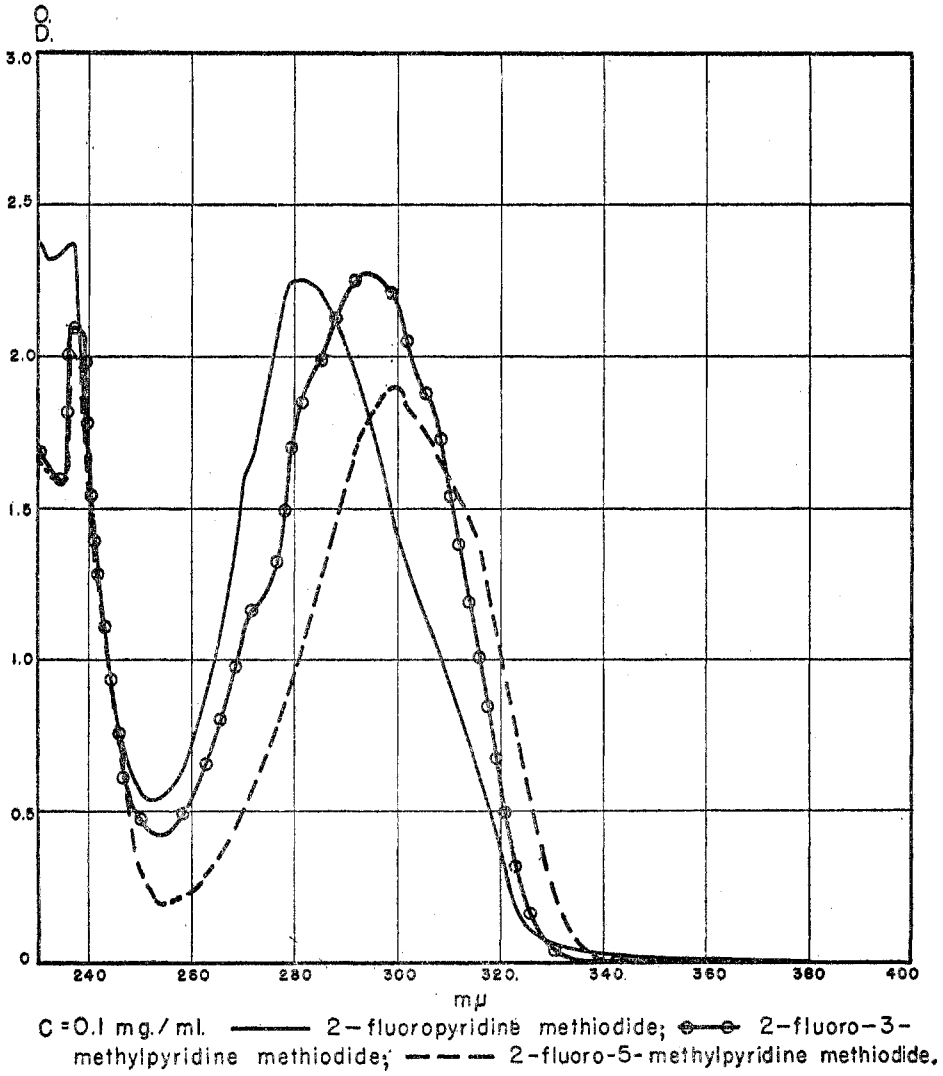


FIGURE I

Method A. A mixture of 15 g. of 2-bromo-5-methylpyridine and 50 ml. of ethyl iodide was heated for 12 hours at 90°. A crystalline precipitate started to form within an hour. The bottle was then cooled and the precipitate was washed thoroughly with dry ether. A 28 g. (98%) yield of almost pure material was obtained. Concentration of the filtrate afforded a quantitative yield. After one recrystallization from alcohol-water-ether, the 2-iodo-5-methylpyridine ethiodide had m.p. 214.5–215.1°, unchanged by repeated recrystallization. The addition of ether to the hot alcohol-water solution facilitated the recrystallization of

the more soluble members of the series. The exact excess of alkyl iodide did not appear to be critical. In all cases save that of 2-iodoquinoline ethiodide, yields of over 90% were obtained consistently.

Method B. A solution of 3 g. of 2-bromopyridine in 15 ml. of methyl iodide was heated for 4 hours at 50°. The cooled solution was then filtered and the precipitate and the mother liquor worked up separately. The 2-g. precipitate was practically pure 2-iodopyridine methiodide, m.p. 207.5–208.6°. The mother liquor was concentrated and then diluted with anhydrous ether to give an additional 0.6 g. of product having the same melting point.

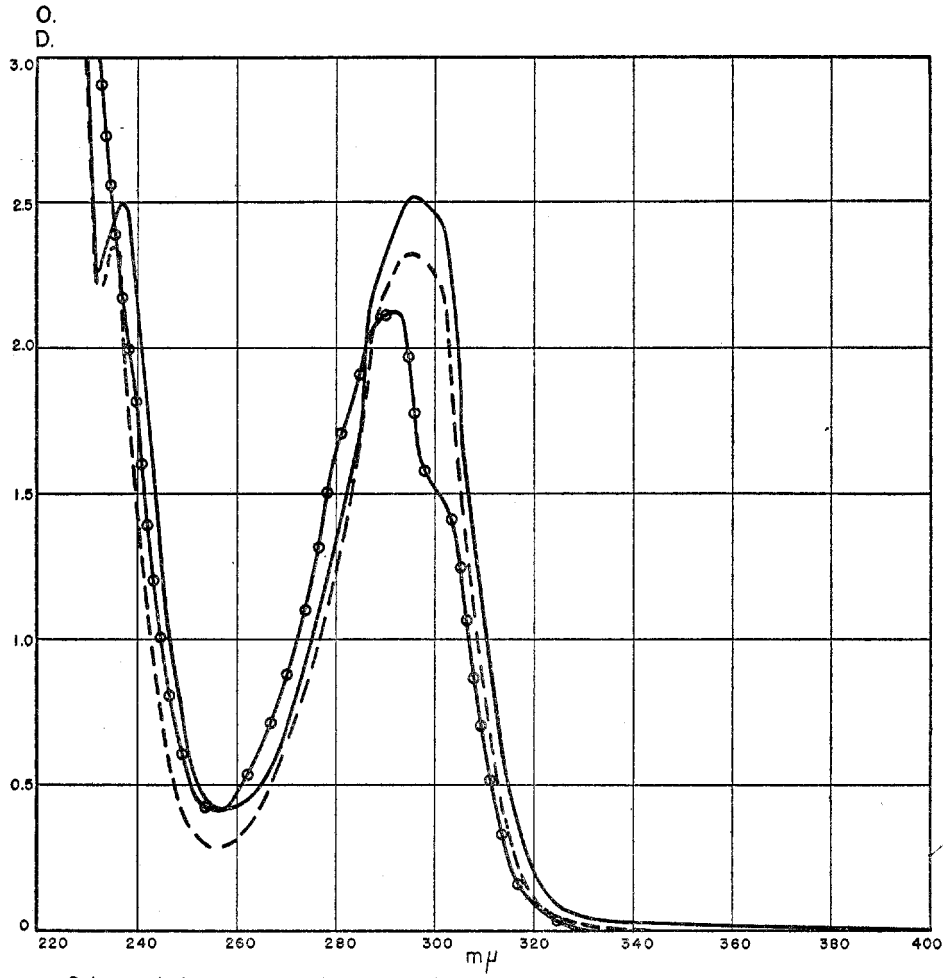


FIGURE II

In the case of 2-chloropyridine, the material isolated from the mother liquor could be resolved into pure 2-iodopyridine methiodide and a small yellow amorphous fraction, analysis of which corresponded approximately to a 75–25 mixture of 2-chloropyridine methiodide and 2-iodopyridine methiodide. The solid products were recrystallized from alcohol-water-ether as mentioned above.

Isolation of chloropyridine and chloroquinoline from reaction mixtures. Exactly 15 g. of 2-chloroquinoline was heated with methyl iodide as described in method (B). Only 1 g. of 2-iodoquinoline methiodide was obtained as yellow crystals, m.p. 210.1–211.5°. Fractional

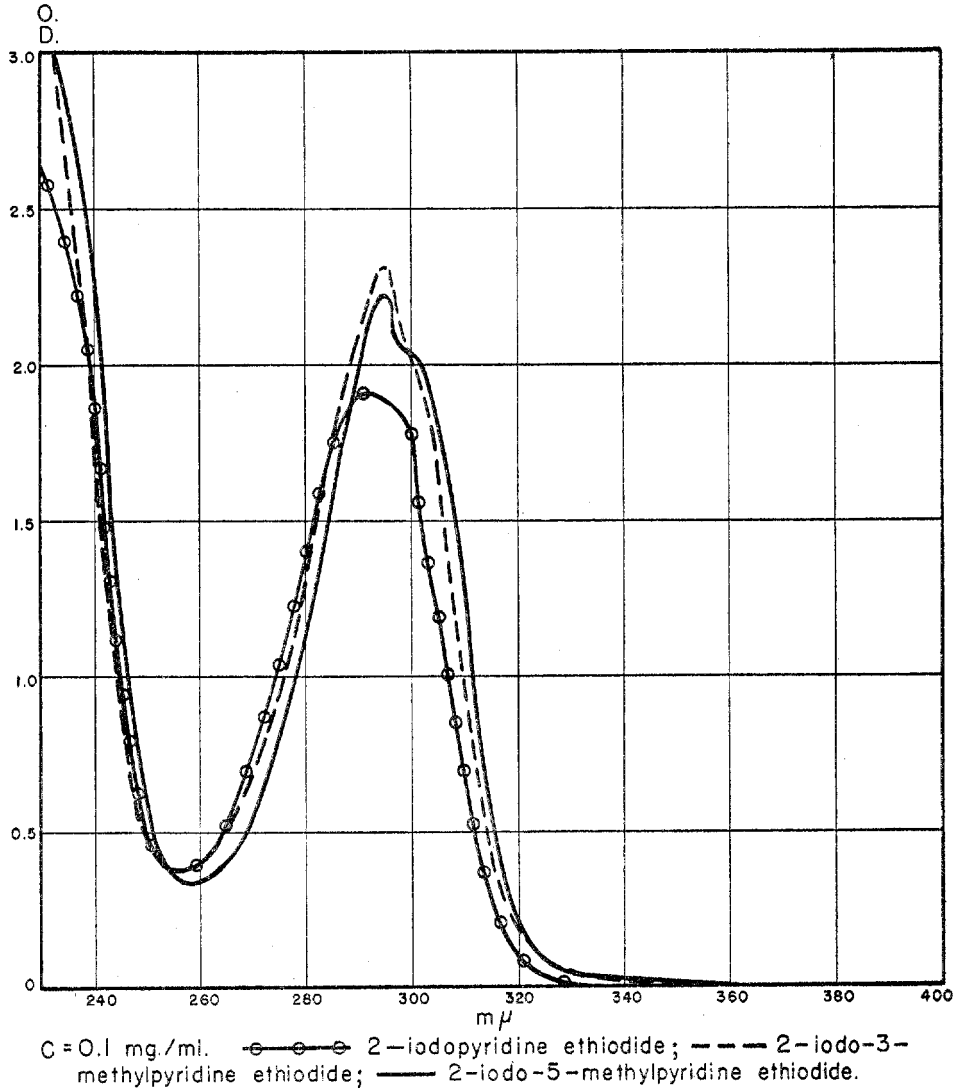


FIGURE III

distillation of the ether filtrate gave 14.5 g. of 2-chloroquinoline, b.p. 119–121°/4 mm. Similarly treated, 12 g. of 2-chloropyridine gave 5.8 g. of 2-iodopyridine methiodide and 9.1 g. of 2-chloropyridine, b.p. 163–166°/740 mm.

Attempted synthesis of bromopyridine methiodides. A mixture of 6.88 g. (0.04 mole) of 2-bromo-5-methylpyridine and 6.5 ml. of redistilled methyl sulfate was heated on a steam-bath for 12 hours. Excess methyl sulfate was then removed *in vacuo*. The residue was dissolved in 12 ml. of water and extracted with 5-ml. portions of chloroform to remove the

small amount of insoluble material. A twofold excess of potassium iodide was then added with vigorous shaking. The yellow precipitate (11 g., 90%) was recrystallized repeatedly to give colorless needles, m.p. 201.8–204.5° (decomp.). 2-Bromopyridine and 2-bromo-3-

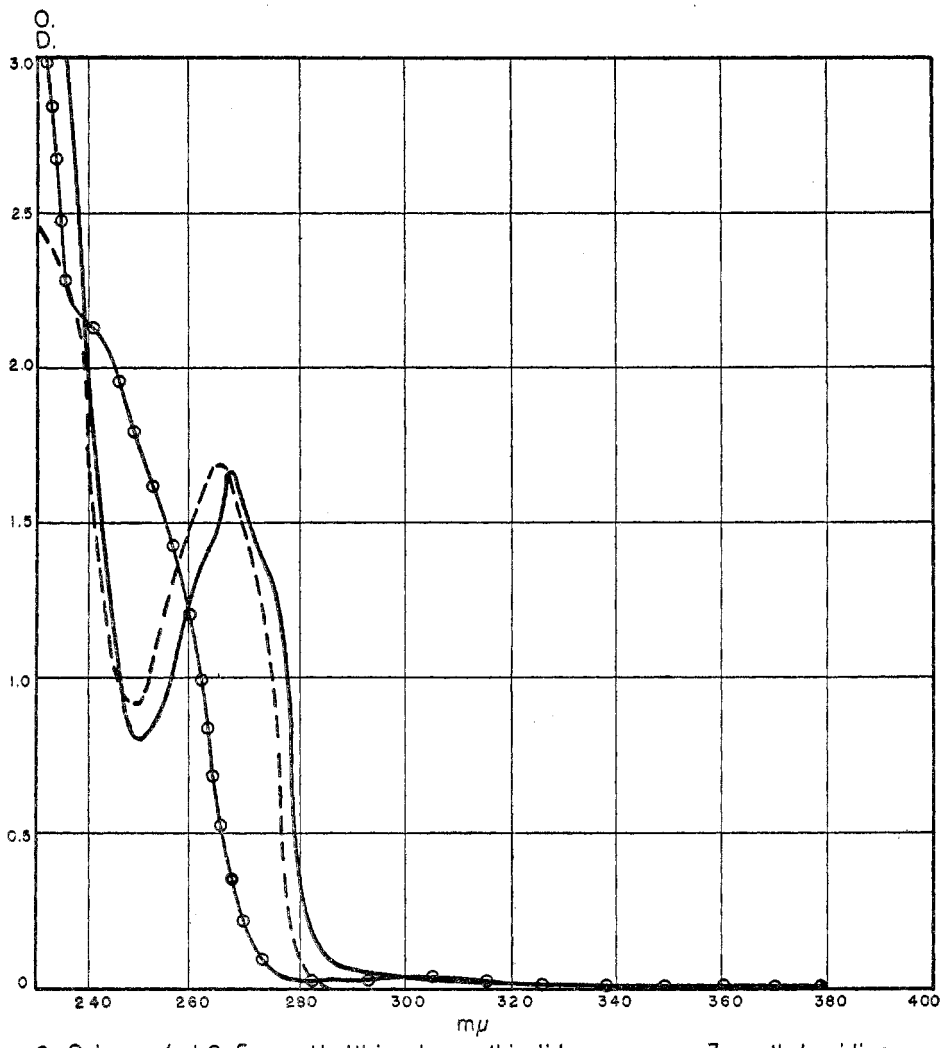


FIGURE IV

methylpyridine were treated similarly. In every case, extensive iodine-bromine interchange to form the corresponding iodo methiodides occurred, as indicated by analysis. Attempts to isolate the pure bromo methiodides were uniformly unsuccessful.

2-Bromopyridine ethobromide and 2-bromo-3-methylpyridine ethobromide. A mixture of 8.0 g. of 2-bromopyridine and 20 ml. of ethyl bromide was heated in a sealed tube at 100° for 72 hours. Dilution with ether followed by filtration gave 5.6 g. (42%) of 2-bromopyridine ethobromide, m.p. 194.0–194.9° after one recrystallization from alcohol-ether.

TABLE I

PHYSICAL AND ANALYTICAL DATA

COMPOUND	M.P., °C.[1]	FORMULA	ANALYSIS			
			N		Halogen	
			Calc'd	Found	Calc'd	Found
PYRIDINE METHIODIDES						
3-Me-	79.1– 80.2[2]	$C_7H_{10}IN$	6.0	6.0		
3-Br-	159.1–159.9[3]	C_6H_7BrIN	4.7	4.7		
3-CN-	194.5–196.1	$C_7H_7IN_2$	11.4	11.4		
3-COOMe	129.5–130.2	$C_8H_{10}INO_2$	5.0	5.0		
2-I-	209.5–210.1[4]	$C_6H_7I_2N$	4.0	4.1	73.2	73.1*
2-I-3-Me-	210.5–211.2	$C_7H_9I_2N$	3.9	4.2	70.3	70.4*
2-I-5-Me-	211.1–212.2	$C_7H_9I_2N$	3.9	4.0	70.3	69.9*
2-I-3-COOMe	187.8–188.6	$C_8H_9I_2NO_2$	3.5	3.5	62.7	62.3
2-I-5-COOMe	193.1–194.2	$C_8H_9I_2NO_2$	3.5	3.6	62.7	62.3
2-F-	71.1–72.0	$C_6H_7FI_3N$[5]	2.8	2.9		
2-F-3-Me-[6]	211.1–214.2	C_7H_9FIN	5.5	5.5		
2-F-5-Me-[7]	179.1–180.2	C_7H_9FIN	5.5	5.6		
PYRIDINE ETHIODIDES						
2-I	160.6–161.7	$C_7H_9I_2N$	3.9	4.1		
2-I-3-Me-	182.1–182.3	$C_8H_{11}I_2N$	3.7	3.9	67.7	67.5*
2-I-5-Me-	214.5–215.1	$C_8H_{11}I_2N$	3.7	3.8	67.7	67.9*
2-F-3-Me-	186.0–186.5	$C_8H_{11}FIN$	5.3	5.2		
PYRIDINE ETHOBROMIDES						
2-Br-	194.0–194.9	$C_7H_9Br_2N$	5.2	5.5*	59.9	59.6*
2-Br-3-Me-	184.2–184.9	$C_8H_{11}Br_2N$	5.0	4.8*	56.9	56.9*
2-IODOQUINOLINE ALKIODIDES						
N-Me-	210.1–211.0[8]	$C_{10}H_9I_2N$				
N-Et-	201.0–201.5[9]	$C_{11}H_{11}I_2N$	3.4	3.5		
5-METHYLTHIAZOLE METHIODIDE						
	67.1– 68.3[10]	$C_5H_8I_2NS$	2.8	2.9		

[1] All of the compounds except the 5-methylthiazole, β-picoline, and 2-fluoropyridine derivatives darkened at about 10° below their melting points. Best results were obtained when the melting point tubes were placed in a bath preheated to within 10° of the melting point. Fairly rapid heating is necessary if distinct melting points are to be obtained. [2] Murrill (6) reported this compound as an oil. [3] Decker and Kaufmann (12) reported the m.p. 146°. [4] Fischer (2) reported the m.p. 207°. [5] This compound is difficult to purify and was analyzed in the form of its periodide, steel blue crystals, m.p. 49.5–50.2°. The periodide is readily prepared by treating the methiodide in alcoholic solution with an equimolar amount of iodine as described by Murrill (6). [6] This compound, though initially white, turned yellow within a few hours, but did not seem to decompose on further standing. [7] The pure compound was completely decomposed within 2 to 3 weeks. It was even more unstable in solution. [8] Roser (3) has reported m.p. 213°. [9] Roser (3) has reported m.p. 220°. This compound could not be obtained in better than 30–35% yield despite prolonged treatment with ethyl iodide. [10] This compound could be induced to crystallize only with difficulty and was, therefore, analyzed in the form of its periodide, magnificent orange-red needles, m.p. 75.1–76.0°.

*Anal.** Calc'd for $C_7H_9Br_2N$: N, 5.2; Br, 59.9.
Found: N, 5.5; Br, 59.6.

Similarly prepared from 2-bromo-3-methylpyridine, 2-bromo-3-methylpyridine ethobromide melted at 184.2–184.9°.

*Anal.** Calc'd for $C_8H_{11}Br_2N$: N, 5.0; Br, 56.9.
Found: N, 4.8; Br, 56.9.

Reaction of 2-bromopyridine ethobromide with potassium iodide. A mixture of 2 g. of 2-bromopyridine ethobromide, 5 g. of potassium iodide, and 30 ml. of methyl ethyl ketone was refluxed for 48 hours. The mixture was cooled and the solid repeatedly recrystallized from alcohol to give a product melting at 161.2–161.9°. No melting point depression was observed on admixture with an authentic sample of 2-iodopyridine ethiodide.

*Anal.** Calc'd for $C_7H_9I_2N$: N, 3.9; I, 70.3.
Found: N, 3.8; I, 69.4.

Qualitative tests indicated the absence of detectable amounts of bromine. The nature of the impurity is unknown.

Reaction of 2-bromopyridine ethobromide and 2-bromo-3-methylpyridine ethobromide with ethyl iodide. A mixture of 1 g. of the ethobromide and 20 ml. of ethyl iodide was heated in a sealed tube at 100° for 48 hours. The product in each case was isolated, almost quantitatively, in the usual fashion. The 2-iodopyridine ethiodide melted at 159.0–160.0° and gave no depression on admixture with an authentic sample.

*Anal.** Calc'd for $C_7H_9I_2N$: N, 3.9; I, 70.3.
Found: N, 3.7; I, 69.2.

The 2-iodo-3-methylpyridine ethiodide melted at 181.9–183.1° and gave no depression on admixture with an authentic sample.

*Anal.** Calc'd for $C_8H_{11}I_2N$: N, 3.7; I, 67.7.
Found: N, 3.8; I, 67.5.

Alkaline hydrolysis experiments. A mixture of 10 g. of 2-iodo-3-methylpyridine ethiodide and 50 ml. of 25% sodium hydroxide solution was refluxed for 1 hour. A red oil began to separate within ½ hour. The oil was extractedwith chloroform, washed with saturated salt solution, dried over Drierite, and distilled *in vacuo* to give 2.4 g. (75%) of N-ethyl-3-methyl-2-pyridone, b.p. 92–95°/2 mm., n_D^{25} 1.5401.

Anal. Calc'd for $C_8H_{11}NO$: N, 10.2. Found: N, 10.4.

Similarly 10 g. of 2-iodo-5-methylpyridine ethiodide gave 2.0 g. (62%) of N-ethyl-5-methyl-2-pyridone boiling at 109–112°/1.5 mm., n_D^{25} 1.5413.

Anal. Calc'd for $C_8H_{11}NO$: N, 10.2. Found: N, 10.3.

Acid hydrolysis experiments. A mixture of 5 g. of 2-iodopyridine methiodide and 40 ml. of 6 *N* hydrochloric acid was refluxed for 24 hours. The solution was concentrated on the steam-bath, neutralized with solid sodium carbonate, and extracted with chloroform. The extract was dried and distilled to give 1.3 g. (80%) of 1-methyl-2-pyridone, b.p. 90–110°/2 mm. A solution of the oil in anhydrous ether was treated with anhydrous hydrogen chloride to give 1-methyl-2-pyridone hydrochloride, m.p. 167–168° after one recrystallization from alcohol-ether. Neundlinger (11) has reported m.p. 166°.

A mixture of 10 g. of 2-iodo-5-methylpyridine ethiodide and 50 ml. of 6 *N* hydrochloric acid was refluxed for 24 hours. The solution was concentrated and extracted with ethyl acetate to remove a highly iodinated product of uncertain composition. The solution was then extracted exhaustively with chloroform. The extract was dried and distilled to give 1.7 g. (47%) of 1-ethyl-5-methyl-2-pyridone, b.p. 111–114°/2 mm., and considerable high-boiling residue.

When treated similarly, 2-iodo-3-methylpyridine ethiodide gave only complex iodinated products. Concentration to about 10 ml. precipitated 3.7 g. of orange crystals, m.p. 103.1–104.2°. This product contained a large amount of iodine but no definite structure could be deduced for it. The same material could be isolated by neutralization of the acid solution with sodium carbonate.

Anal. Found: C, 18.2; H, 2.2; N, 3.0; I, 74.2.

Further concentration of the solution gave 5.1 g. of white crystals, m.p. 173.0–174.5°, containing chlorine as well as iodine. The analysis corresponded quite closely to that calculated for an 85–15 mixture of the methiodide and the methochloride.

Anal. Calc'd for 85% $C_8H_{11}I_2N$ and 15% $C_8H_{11}ClIN$: C, 26.9; H, 3.1; N, 3.9.
Found: C, 26.9; H, 3.1; N, 4.1.

In these latter two cases free iodine was observed in the condensers during the period of refluxing.

LAWRENCE, KANSAS

SUMMARY

1. A series of substituted pyridine methiodides has been prepared.

2. α-Substituted chlorine and α-substituted bromine in pyridine methiodide have been found to exchange readily with iodine in alkyl iodode solution. α-Substituted fluorine does not undergo this reaction under similar conditions.

3. A mechanism has been proposed to account for these results.

4. The mechanism proposed earlier for the hydrolysis of α-substituted halogen in pyridine methiodides has been further substantiated.

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