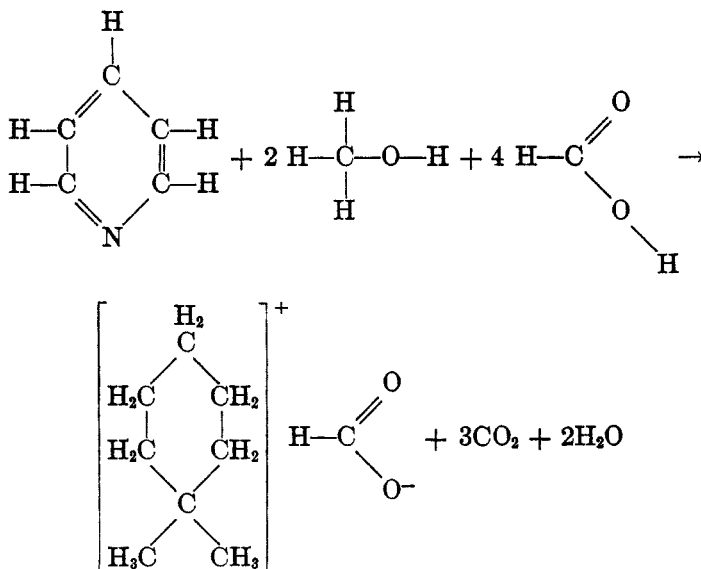


THE REDUCTION OF THE PYRIDINE RING BY
FORMIC ACID

FRANK R. MAYO*

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During an investigation of quaternary pyridinium salts, the appearance of a paper by Clarke, Gillespie, and Weisshaus¹ on the methylation of primary and secondary amines with formaldehyde and formic acid led to the application of this process to pyridine. For conversion of a secondary to a tertiary amine, they recommend refluxing the amine for 8 to 12 hours with 1.1 moles of 35 per cent. aqueous formaldehyde and 2.5 moles of 90 per cent. formic acid. When pyridine was thus treated for 64 hours, only a negligible reaction resulted. Heating a similar mixture under pressure for two hours at 175° or 200° yielded a small proportion of quaternary salt. Subsequent work showed that under these conditions, formaldehyde could be replaced by an equivalent quantity of methanol with no decrease in yield. Investigation of the quaternary salt thus formed revealed that it was not the expected *N*-methylpyridinium formate but *N,N*-dimethylpiperidinium formate, in which the pyridine ring had been completely reduced. The overall reaction was therefore

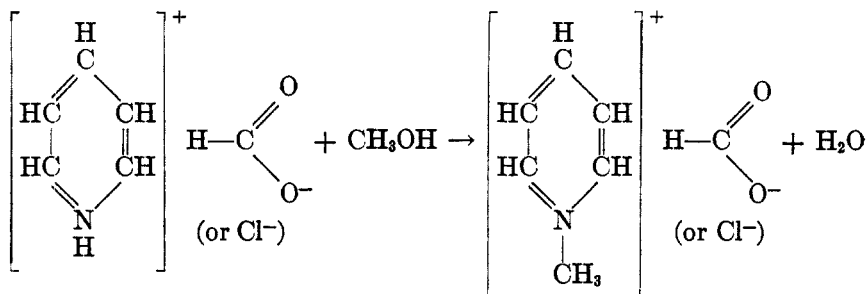


* Present address, Department of Chemistry, The University of Chicago.

¹ CLARKE, GILLESPIE, AND WEISSHAUS, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

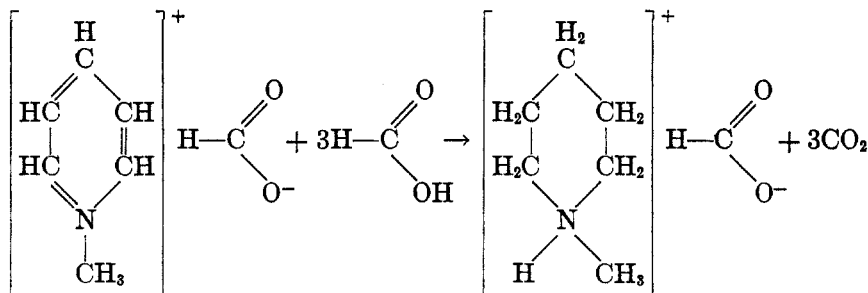
At the time, the large-scale preparation of this salt seemed desirable. Attempts to improve the yields led to the elucidation of the mechanism by which this reaction takes place. The details are given in the experimental part. From them the following conclusions are drawn concerning the mechanism of the high-temperature reaction between pyridine, methanol, and formic acid.

(1) The first step in the reaction is the formation of *N*-methylpyridinium formate, although none of this salt has been sought or found in the final product. Under similar conditions, the analogous reaction with hydrochloric acid takes place to the extent of 80 or 90 per cent.



It is concluded that the nitrogen atom is methylated before the ring is reduced because, under the same conditions, pyridine was not reduced by formic acid alone, and because piperidine was not readily alkylated by formic acid and methanol.

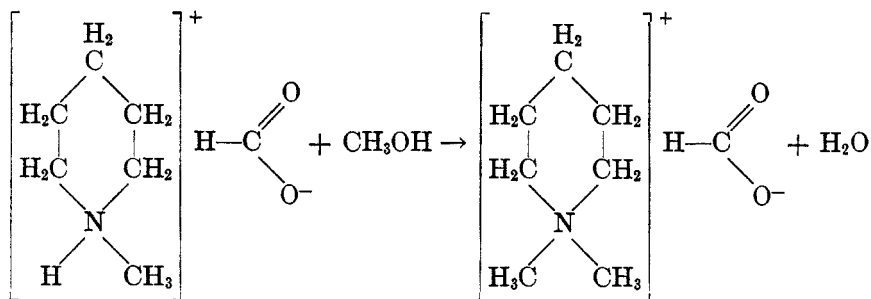
(2) The second step in the reaction is the reduction of methylpyridinium formate to *N*-methylpiperidinium formate by formic acid.



Methylpyridinium formate is readily reduced by formic acid, while methylpyridinium chloride is not reduced at all, except in the presence of alkali metal formate which can produce a greater concentration of formate than can formic acid. Since formate ion rather than free formic acid takes part in the reduction, it is concluded that methylpyridinium formate

is reduced by rearrangement to *N*-methyl-dihydropyridine and carbon dioxide. Reduction is completed by repeated salt formation with formic acid and rearrangement. No intermediate unsaturated bases have been isolated, but indications of their presence have been found. Small quantities of high-boiling bases which have been obtained are thought to be dimers of intermediate products. The data show that reduction of the pyridinium salt is practically complete when sufficient formic acid is present. The complete reduction of the formate in the absence of methanol shows that methylation is not a necessary part of the reduction mechanism. Why methylpyridinium chloride with 10 to 20 per cent. of potassium formate is largely reduced by formic acid in the presence of methanol but only slightly in its absence is not clear.

(3) The final step in the reaction is the methylation of *N*-methylpiperidinium formate by methanol to give *N,N*-dimethylpiperidinium formate.



Data show that this reaction proceeds easily with a yield of better than 50 per cent. under the usual experimental conditions.

EXPERIMENTAL

Low-temperature reaction.—One-half mole of c.p. pyridine was mixed with 1.25 moles of 88–90% c.p. formic acid and 0.55 mole of c.p. 37% formaldehyde. The mixture was heated on a steam bath under a reflux condenser for 64 hours. Evaporation of the product showed that no more than traces of quaternary salt had been formed.

Conditions of high-temperature reaction.—All subsequent preparations and experiments were carried out in thin-walled, unstoppered, Pyrex bottles of about 130 cc. capacity. The bottles fitted rather snugly in securely sealed steel bombs of about 230 cc. capacity. The bombs were heated in an oil bath. On cooling and opening, large quantities of carbon monoxide (from thermal decomposition of formic acid) and carbon dioxide were evolved. Slow release of this gas was necessary to prevent its violent liberation from the liquid in the bottle. In all normal experiments, the reaction mixtures were liquid, homogenous, and almost colorless, before and after heating. The quantities of reagents used depended on the capacity of the bottle and usually included one-fourth mole of pyridine.

Isolation and identification of reaction products.—The reaction product was trans-

ferred from the bottle to a distilling flask and heated to a liquid temperature of approximately 160° at 20 mm. pressure to remove pyridine, formic acid and methanol. (Pyridine formate,² C₅H₅N·3HCO₂H, boils at 66° at 20 mm. and 148-50° at atmospheric pressure.) The residue, designated hereafter as crude dimethylpiperidinium formate, contained small proportions of formic acid and reduced and unreduced non-quaternary bases in addition to the dimethylpiperidinium salt. The crude product was usually a colorless, low-melting, deliquescent solid. It was purified, for purposes of identification, by treating it with enough aqueous sodium hydroxide to liberate all the non-quaternary bases. The latter were then distilled out at about 50 mm. pressure until the liquid temperature reached 80-100°. The residue was acidified with formic acid and concentrated nearly to dryness. Sodium formate was separated from the organic formate by means of alcohol in which the sodium salt is only slightly soluble. The alcohol was then removed by distillation. The residue could be heated to 190° at 35 mm. for a short period (2 to 5 minutes) without much decomposition, in order to remove solvents. At room temperature the product was a pale yellow, deliquescent solid, melting at 140-80°. The yield on purification was 70-75% of the weight of the crude salt. Judging from its color and melting range, the *N,N*-dimethylpiperidinium formate was still not very pure, but it was too soluble in water and alcohols to be recrystallized conveniently. It was completely soluble in fairly concentrated sodium hydroxide solution, as is characteristic of quaternary salts.

This salt was identified positively by converting it to the chloride by repeated concentration *in vacuo* of concentrated hydrochloric acid solutions of the salt. The *N,N*-dimethylpiperidinium chloride thus obtained could be recrystallized from hot methyl or ethyl alcohols or from the cold absolute alcohols by addition of anhydrous ether. The recrystallized, colorless product was dried over phosphorus pentoxide *in vacuo* and analyzed.

Anal. Calc'd for C₇H₁₄ClN: C, 56.15; H, 10.78; N, 9.37; Cl, 23.70; mol. wt. in water, 149.59/2.

Found: C, 55.02; H, 10.55; N, 9.64; Cl, 23.6; mol. wt. in water, 71.0.

Because of the hygroscopic nature of the salt, the agreement is considered adequate in the above analyses, for which indebtedness to Mr. G. F. Palfrey is acknowledged.

N,N-Dimethylpiperidinium chloride was also prepared directly from piperidine. Technical piperidine, methyl chloride, and methanol in the molar proportions of 1:1.16:1.1 were heated as in previous experiments for 1 hour at 200°. Non-quaternary bases were removed as in the case of the formate, and the chloride was recrystallized and dried. The yield, based on the piperidine, was 60%. This salt and the one prepared from pyridine through the formate decomposed at approximately 340° and 330° respectively. The latter showed more reaction with bromine water and alkaline permanganate than the former, indicating that the salt from pyridine was not entirely free from incompletely reduced salts, which is not surprising in view of its method of preparation.

Reaction of pyridine, formaldehyde, and formic acid.—Table I summarizes bomb experiments with pyridine, formaldehyde, and formic acid. It is evident that the reaction proceeds nearly as well at 175° as at 200° and it is therefore assumed that the reaction goes to completion (or equilibrium) at the higher temperature. Attempts to replace formic acid as reducing agent by formaldehyde failed because of the formation of tars. Such experiments were based on the erroneous assumption that the end product was *N*-methylpyridinium formate.

² GARDNER, *Ber.*, **23**, 1591 (1890).

Reaction of pyridine, methanol, and formic acid.—Table II shows that 11–15% yield of crude *N,N*-dimethylpiperidinium formate can be obtained from an equimolecular mixture of pyridine, methanol, and formic acid. Increasing the proportion of either methanol or formic acid improves the yield slightly but increasing the proportions of both to the theoretical increases the yield to nearly 60%. Pyridine does not react with either formic acid or methanol alone. The non-quaternary bases in one experiment were isolated by partial distillation of the reaction mixture

TABLE I
REACTION OF PYRIDINE, FORMALDEHYDE, AND FORMIC ACID

MOLES ^a 37% AQ. FORMALDEHYDE	MOLES ^a 88–90% FORMIC ACID	REACTION		YIELD ^a CRUDE <i>N,N</i> -DIMETHYLPYRIDINIUM FORMATE (%)	REMARKS
		Time, hours	Temp., °C.		
1.1	2.5	2	175	12	3 experiments
1.1	2.5	2	200	15–20	
2.5	0.1	2	200	0 ^b	2 experiments
1.65	1.1	1	200	0 ^b	

^a Based on pyridine used.

^b Product a black, water-insoluble tar.

TABLE II
REACTION OF PYRIDINE, METHANOL, AND FORMIC ACID

MOLES ^a METHANOL	MOLES ^a 88–90% FORMIC ACID	REACTION TIME AT 200°, HOURS	YIELD ^a CRUDE <i>N,N</i> -DIMETHYLPYRIDINIUM FORMATE (%)	REMARKS
1.0	1.0	1	11–15	3 experiments
1.25	1.5	1	17	
1.0	1.5	1	19	2 moles ^a H ₂ O added
1.0	3.0	1	12	
2.0	1.0	1	16	
3.0	1.0	1	19	
2.0	4.0	1	59	Considerable <i>N</i> -methylpiperidine found
0.0	4.0	1	0	
3.0	0.0	1	0	

^a Based on pyridine used.

after it had been made alkaline with sodium hydroxide. That the base had the odor and approximate boiling point of piperidine and yet was a tertiary amine (gave no reaction with carbon disulfide, while piperidine reacts vigorously) was considered sufficient evidence that it was *N*-methylpiperidine.

Reduction of *N*-methylpyridinium salts with formic acid.—When methylpyridinium chloride and formic acid in the proportion of 1 mole to 4 were heated for 1 hour at 200°, the salt was recovered practically unchanged. A similar result was obtained when 1.33 moles of methanol were added to the same mixture. It was then found that the

addition of sodium or potassium formate caused reaction to take place. Since sodium formate was not very soluble in the reaction mixture, potassium formate was used in subsequent experiments.

Two procedures were used in the experiments with potassium formate. In the first, methylpyridinium chloride was dissolved in 88–90% formic acid, with or without methanol, and the required proportion of 50% aqueous potassium formate was then added. In the other, methylpyridinium chloride was dissolved in an equivalent quantity of 50% aqueous potassium formate. Most of the water was then removed at reduced pressure, and potassium chloride crystallized out, leaving a very concentrated solution of methylpyridinium formate. The mixture was extracted with methanol whereby all of the methylpyridinium formate and 7–12% of the potassium chloride were dissolved, leaving 88–93% of the latter to be removed by filtration. The solvents were then largely removed from the filtered solution by heating at reduced pressure. The residue consisted of 0.07 to 0.12 mole of potassium chloride and 15–40 g. of water per mole of methylpyridinium formate. It was then treated as shown in Table III.

TABLE III
REDUCTION OF METHYLPIRIDINIUM SALTS WITH FORMIC ACID

INITIAL REACTION MIXTURE, MOLES ^a				REACTION PRODUCTS, MOLES ^a			
Potassium Formate added	Potassium chloride removed	88–90% Formic acid	Methanol	Pyridine	<i>N</i> -Methylpiperidine	Quaternary salts	Unaccounted for
1.0	0.93	3.25	2.00	none	0.18	0.17 piperidinium	0.65
1.0	0.90	3.30	1.20	0.03	0.29	0.37 piperidinium	0.31
1.0	0.88	3.30	none	0.04	0.52	0.04 mixture	0.40
0.055	none	3.36	1.55	0.03	0.28	0.39 mixture	0.30
0.060	none	3.50	none	0.03	0.02	Balance mostly unchanged methylpyridinium chloride	
0.105	none	3.53	none	0.03	0.04		

^a Based on *N*-methylpyridinium chloride used.

In all cases the reaction mixtures were heated for one hour at 200°. The product was completely converted to chloride by repeated concentration with hydrochloric acid and a final heating *in vacuo*. Aqueous sodium hydroxide was added and the mixture was distilled until the liquid temperature reached about 80° at 120 mm. In the first experiment in Table III, the bases in the distillate were separated from water by the addition of solid sodium hydroxide. They were shown to be substantially free from pyridine (no color on treatment with 1-chloro-2,4-dinitrobenzene and sodium hydroxide) and piperidine (no heat evolved on treatment with carbon disulfide). Since they boiled below 110° and had the odor of piperidine, it was assumed that they consisted almost entirely of *N*-methylpiperidine (b.p. 107°). In the other experiments, the distillate was titrated with standard hydrochloric acid, using phenolphthalein and bromophenol blue as indicators, thus giving the amount of strong base (*N*-methylpiperidine) and weak base (pyridine) in the distillate. The residue from the distillation was acidified, separated from alkali chlorides as previously described, dried, and weighed. The quaternary chlorides were identified qualitatively by their melting points as *N*-methylpyridinium chloride (m.p. 137°), *N,N*-dimethylpiperidinium chloride (dec. near 330°), or a mixture of the two.

The recorded yields of the products in Table III correspond to products actually isolated or determined by titration. The part of the original salt which is not accounted for should probably be distributed proportionately among the three types of products listed. In the analysis, some pyridine distilled with the formic acid and excess hydrochloric acid and was thus lost. During the alkaline concentration of the quaternary salt, a small part was decomposed and a small proportion of non-quaternary bases did not distill out completely. In all experiments in Table III in which considerable reduction took place, except the first, one-third to one-half of the total bomb contents were found in the bomb outside of the Pyrex bottle. Presumably they blew out of the bottle when the pressure was released, for they had the same physical characteristics as the bottle contents and did not contain much iron. In these experiments, the bomb contents outside are assumed to be the same as those inside the bottle and are so included in Table III, although they were not included in the analyses. Leakage of gases and vapors from the bomb may also account for some of the deficiency in material. The reversible dissociation of methylpyridinium chloride into pyridine and methyl chloride accounts for the pyridine and dimethylpiperidinium chloride formed in the experiments without added methanol.

Table III shows that methylpyridinium formate is almost completely reduced by formic acid; the presence of methanol has no great influence on the extent of reduction although it does determine whether the reduced salt will be tertiary or quaternary. In the presence of sufficient methanol a large part of the reduction product is further alkylated to quaternary salt. However, the presence of methanol makes a great difference in the extent of reduction by formic acid of a methylpyridinium salt mixture which contains about ten times as much chloride as formate. In the presence of methanol, most of the pyridinium salt is reduced; in its absence, reduction is negligible.

Methylation of piperidine and N-methylpiperidine with methanol and formic acid.—Piperidine is not readily alkylated by methanol and formic acid. When these three substances were mixed in the molecular proportion of 1:2.1:1.1 and heated for one hour at 200°, no more than a trace of quaternary salt was formed, demonstrated by the fact that the product was almost completely volatile. However, *N*-methylpiperidine is readily alkylated by methanol and formic acid under the same conditions. When heated for 1 hour at 200° in the proportion of 1:1.25:1.15, the mixture yielded 59% of crude, colorless, crystalline *N,N*-dimethylpiperidinium formate, indicating that this step may determine the yield in the reaction starting with pyridine.

Preparation of N-methylpyridinium chloride.—*N*-Methylpyridinium chloride was conveniently prepared³ by passing methyl chloride for a few hours into pure pyridine at 70°. The quaternary salt crystallized out of the pyridine. The salt was a pure-white, crystalline, deliquescent solid, becoming orange on heating, and melting at 137° (uncorrected).

N-Methylpyridinium chloride was also prepared by heating pyridine hydrochloride with 2 moles of absolute methanol,⁴ or 2.5 moles of 37% formaldehyde, for 2 hours at 200° in the apparatus described. Yields were 80–90%. Pyridine hydrochloride was separated from the product with sodium hydroxide by methods already indicated.

³ ERNST AND BERNDT, *U. S. Patent* 1,960,334; *Chem. Abstr.*, **28**, 4434 (1934).

⁴ HAACK, *German Patent* 593,670; *Chem. Abstr.*, **28**, 3421 (1934). OSTERMAYER, *Ber.* **18**, 591 (1885).

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SUMMARY

Pyridine reacts with formic acid and methanol (or formaldehyde) at 175° to 200° to give up to 60 per cent. yield of *N,N*-dimethylpiperidinium formate. *N*-Methylpyridinium formate and *N*-methylpiperidine are shown to be intermediate products.