

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

THE REACTION OF ALKYL BROMIDES WITH PYRIDINE

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Although considerable work has been done on the relative ease of replacement of halogen in organic compounds by other groups, the only quantitative work concerning the relative ease of removal of hydrogen halide from organic halides is that of Brussoff,¹ who measured the rate of formation of olefin during the reaction of alkyl halides with alcoholic potassium hydroxide. It is not possible to compare the behavior of the various halides from this work, however, because no attempt was made to determine the rate of side reactions, the extent of which varied from 7 to 83% of the total reaction taking place. A more exact comparison of the rates of removal of halogen acid should be of interest, not only from the standpoint of preparing unsaturated compounds or avoiding their formation, but also as a possible means of determining whether there is any difference in the reactivity or mobility of various types of hydrogen, *i. e.*, primary, secondary or tertiary, comparable to the differences in the reactivity of various types of halogen in replacement reactions. There is also the possibility of correlating these results with the reactivity of the halogen atom and with such reactions as the dehydration of alcohols and the reducing action of the Grignard reagent.

As indicated in a previous note² an investigation of the reaction of alkyl halides with tertiary amines was undertaken with the above points in view. The use of tertiary amines for the removal of hydrogen halide from organic halides to form unsaturated compounds is quite well known³ and has for our purpose an advantage over alkalies in that alcohol would not have to be used as a solvent, and side reactions that would be difficult to follow are avoided. Menschutkin⁴ has used triethyl- and triamylamine to follow the rate of formation of quarternary ammonium salts and Clarke and a number of others⁵ have used pyridine for the same purpose. Recently Semb and McElvain⁶ reported the rate of formation of tertiary amines from piperidine and a large number of organic bromides, and have also reported the relative amounts of tertiary amine and unsaturated hydrocarbon that had been formed at the end of a certain number of hours of reaction. Preliminary investigation of the action of triamylamine, dimethylaniline, pyridine

¹ Brussoff, *Z. physik. Chem.*, **34**, 129 (1900).² Noller and Dinsmore, *THIS JOURNAL*, **53**, 1185 (1931).³ Cf. Semb and McElvain, *ibid.*, **53**, 690 (1931), Ref. 2.⁴ Menschutkin, *Z. physik. Chem.*, **5**, 589 (1890); **6**, 41 (1890).⁵ Clarke, *J. Chem. Soc.*, **97**, 416 (1910); **99**, 1927 (1911); **101**, 1788 (1912); **103**, 1689 (1913); Norris, *THIS JOURNAL*, **50**, 3042 (1928); Kerr, *J. Chem. Soc.*, 239 (1929); Mukhin, *Chem. Abstracts*, **24**, 2942 (1930); Tronov, *ibid.*, **24**, 590 (1930).

and quinoline, indicated that pyridine was most satisfactory for our purpose.⁶ By titrating the reaction mixture first with standard alkali and then determining the amount of ionized halogen in the same solution by the Volhard method, we have been able to follow the rates of formation of both hydrogen ion and total bromide ion. The difference between the two gives the rate of formation of pyridinium bromide, a reaction that appears to take place independently but simultaneously with the removal of hydrogen bromide. While the incidence of side reactions prevents exact comparisons, it is believed that the results obtained express at least semi-quantitatively the relative ease of removal of hydrogen halide, that they give values for the rates of formation of pyridinium halides in agreement with previous work on the reactivity of the halogen atom in organic compounds, and that they throw considerable light on the mechanism of the reaction as a whole.

Experimental Part

Reagents. Pyridine.—A commercial refined pyridine was dried over solid potassium hydroxide and carefully fractionated through a 1-meter column of the Vigreux type. After the vapors reached the boiling point of pyridine, a large forerun was removed and a middle cut boiling at 114.8–115.2° was used.

Alkyl Bromides.—The ethyl bromide was a commercial product, *t*-butyl bromide was prepared from the alcohol and acetyl bromide, and the remaining bromides were prepared from the alcohol and phosphorus tribromide at 0°. All bromides were thoroughly washed with cold concentrated sulfuric acid, allowed to stand over anhydrous potassium carbonate with occasional shaking until sweet and free from acid, and fractionally distilled. The boiling point ranges were as follows: ethyl, 38.8–39.3°; *n*-propyl, 70.7–70.9°; *i*-propyl, 60.4–61.1°; *n*-butyl, 100.8–101.4°; *i*-butyl,⁷ 91.3–92.9°; *s*-butyl, 91.8–92.8°; *t*-butyl, 71–73°.

General Procedure.—Bulbs of about 10 cc. capacity were blown from 13-mm. Pyrex tubing, drawn out and sealed to 5 mm. tubing. Pyridine and alkyl bromide were weighed directly into a glass-stoppered flask (mol. ratio 1:11) and well mixed. From this mixture, 5 cc. portions were pipetted into the tared bulbs, the bulbs sealed and

⁶ There is the possibility of an exchange of organic radicals if the alkyl amines are used, while quinoline gives colored products with the alkyl bromides. Thus *n*-butyl bromide gave a deep red solution when heated with quinoline and a red resinous solid was isolated from the reaction mixture. The nature of this product was not investigated.

⁷ This material was found to contain from 0.8 to 1.2% *t*-butyl bromide when analyzed according to the method of Michael, *Ann.*, 379, 287 (1911), and was used for some of the preliminary work. Subsequent results were obtained with material that boiled at 91.6–91.8° and which contained less than 0.1% of *t*-butyl bromide. This was prepared by heating eleven moles of bromide with one mole of pyridine in sealed bulbs for three hours at 148.8°, after which the bulbs were cooled and opened, the bromide decanted, washed four times with cold concentrated sulfuric acid, shaken with anhydrous potassium carbonate until free of acid and fractionated. Subsequent work indicated that simply refluxing for three hours with the pyridine should be sufficient. This treatment for the removal of tertiary bromide is much more economical than the hydrolytic procedure of Michael.

weighed again. The bulbs were fitted to corks which fit into holes in the cover of the constant temperature ($148.8 \pm 0.2^\circ$) bath. The holes in the cover were large enough to permit the passage of the bulb so that bulbs could be withdrawn without removing the cover. The bulbs were withdrawn at intervals and plunged at once into an ice-water-bath. The small part of the bulb was opened, connected to a water pump and the excess bromide completely distilled at room temperature.⁸ The bulb was then broken in a heavy-walled beaker, the contents dissolved in water and titrated with 0.1 *N* standard sodium hydroxide solution to a distinct pink color with phenolphthalein. Care was taken not to overstep the end-point. The same solution was then acidified with dilute nitric acid and the total bromide ion determined by the Volhard method.⁹ The rate of reaction of *t*-butyl bromide was too rapid to measure at 148.8° and it was run at 92.0° , together with *s*-butyl bromide at the same temperature for comparison.

Discussion of Results

Before attempting to analyze the experimental data, a few remarks should be made concerning the procedure used. The temperature chosen was that at which most of the rates could be determined within a reasonable time. A large excess of one of the reagents was used in order to increase the rate of reaction, and so that the reaction might be considered as pseudo-monomolecular. The choice of the bromide for the excess reagent seems, in the light of the results obtained, to have been unfortunate. In the first place the alkyl pyridinium bromides and pyridine hydrobromides are insoluble in the alkyl bromide and precipitate during the course of the reaction. In the second place the excess bromide appears to be the cause of an apparent reaction greater than 100%. This point will be discussed later.

When the amounts of hydrogen ion and of total bromide ion were plotted against the time, typical curves for monomolecular reactions were obtained. It was found that the amount of hydrogen bromide approached an approximately constant value which was less than that approached by the total bromide ion; that is, barring the unlikely assumption that the quaternary ammonium salt is in equilibrium with pyridine hydrobromide and unsaturated hydrocarbon,¹⁰ two independent reactions are taking place, the direct removal of hydrogen bromide and the formation of alkyl-pyridinium bromide. Therefore the formation of quaternary ammonium salt is not an intermediate step in the removal of hydrogen bromide.

⁸ In the early runs the excess bromide was not removed and in some cases interfered with the titrations.

⁹ Blanks were run in all cases to determine the extent of the reaction taking place before immersion in the bath, and at least two runs made on each bromide. Results could be readily duplicated to within less than 2%.

¹⁰ Direct evidence against this assumption is the fact that *t*-butyl bromide is completely converted into pyridine hydrobromide whereas *i*-butyl bromide gives a mixture of pyridine hydrobromide and *i*-butylpyridinium bromide. Since both bromides yield the same olefin, any equilibrium would necessitate the final reaction mixture having the same composition in both cases.

Accordingly the values for the amount of pyridine hydrobromide were subtracted from the corresponding values for the total bromide ion in order to obtain the amount of alkylpyridinium bromide formed. If now the two independent reactions are both pseudomonomolecular, the ratio of pyridine hydrobromide to alkylpyridinium bromide should be constant. This was

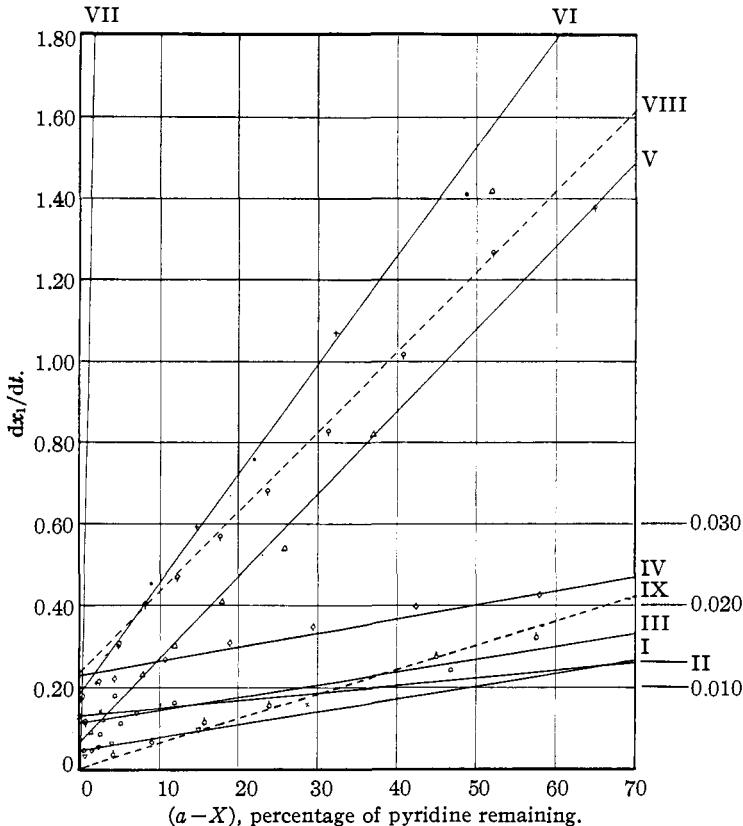


Fig. 1.—Change in rate of formation of pyridine hydrobromide, solid curves at 148.8° ; I, ethyl, ∇ ; II, *n*-butyl, \times ; III, *n*-propyl, \circ ; IV, isobutyl, \diamond ; V, isopropyl, Δ ; VI, *sec.*-butyl, $+$; VII, *tert.*-butyl, calculated from measurements at 92° . Dotted curves at 92° : VIII, *tert.*-butyl, \circ ; IX, *sec.*-butyl, \bigcirc , scale at right.

found to be approximately so especially for the earlier part of the reaction but not sufficiently constant to give the data a purely analytical treatment. We therefore plotted the data and graphically determined the change in the rates of formation at different times. These values were then plotted against the percentage of pyridine remaining, as shown in Figs. 1 and 2. Using the formula $dx/dt = K(a-X)$ where X is the total bromide ion formed, that is, $x_1 + x_2$, it follows that the slopes of these curves corre-

spond to the velocity constants K which have been summarized in Table I. The relative rates of reaction taking the rate for *n*-butyl bromide as unity have also been included in the table.

At 148.8° the rate of reaction of *t*-butyl bromide was so great that not even an approximate velocity constant could be determined. To obtain such an approximation, the rate was measured at 92° together with that of

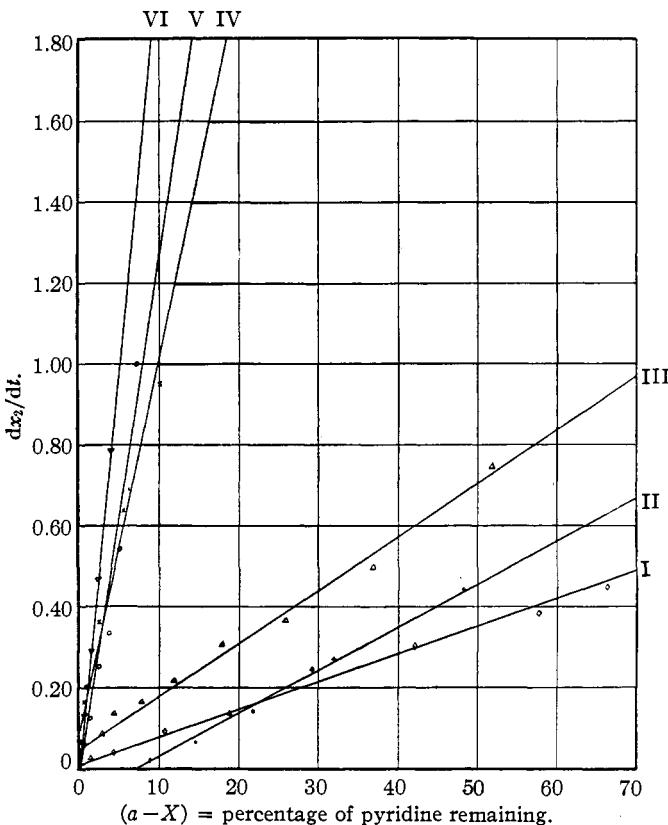


Fig. 2.—Change in rate of formation of alkylpyridinium bromide at 148.8°: I, isobutyl, \diamond ; II, *sec*.-butyl, +; III, isopropyl, Δ ; IV, *n*-butyl, \times ; V, *n*-propyl, \odot ; VI, ethyl, ∇ ; *tert*.-butyl not measurable—slope probably less than isobutyl.

s-butyl bromide at the same temperature. It was found that *t*-butyl bromide gave entirely pyridine hydrobromide and no quaternary salt within the limits of experimental error. The rate of formation of pyridine hydrobromide from *s*-butyl bromide at 92° was 1/89 of that at 148.8°, and therefore the rate of formation of pyridine hydrobromide from *t*-butyl bromide at 148.8° was estimated as 89 times that at 92°.

It is apparent that, from a practical standpoint, the method of removing

TABLE I
VELOCITY CONSTANTS AND RELATIVE RATES OF FORMATION OF PYRIDINE
HYDROBROMIDE AND OF ALKYL PYRIDINIUM BROMIDE FROM VARIOUS
ALKYL BROMIDES AT 148.8°

Alkyl bromide	Pyridine hydrobromide K_1	Rel. rate of formation	Alkylpyridinium bromide K_2	Rel. rate of formation	Conant's "Relative reactivity of alkyl chlorides"
Ethyl	0.003	1.5	0.200	2.1	1.9-2.5
<i>n</i> -Propyl	.003	1.5	.129	1.4	1.0-1.1
<i>i</i> -Propyl	.020	10.0	.013	0.14	0.015
<i>n</i> -Butyl	.002	1.0	.094	1.0	1.0
<i>i</i> -Butyl	.003	1.5	.007	0.07	...
<i>s</i> -Butyl	.027	13.5	.008	.09	0.022
<i>t</i> -Butyl (calcd.)	1.75	875.0018
<i>s</i> -Butyl (at 92°)	0.0003				
<i>t</i> -Butyl (at 92°)	.0197				

hydrogen halide from organic compounds by means of tertiary amines would not be applicable to primary halides and would be only moderately successful for secondary halides, with the possible exception of alicyclic compounds such as cyclohexyl bromide, which appears to lose hydrogen bromide quite readily.³ For tertiary halides the method should be quite satisfactory.

Comparison with Results of Other Investigators.—Comparing the relative rates of formation of alkylpyridinium bromide, taking the velocity coefficient of *n*-butyl chloride as unity, with the relative "reactivities" of the chlorine atom as determined by Conant and Hussey,¹¹ we find substantially qualitative agreement. That is, the primary halides are more reactive than the secondary. While Conant's results indicate a 100-fold difference and ours only a 10-fold difference, this might readily be accounted for by the fact that the comparison is between chlorides on the one hand and bromides on the other. As has been often noted, the ethyl compound is considerably more reactive than the higher normal halides. Unfortunately we have not been able to make accurate measurements for quaternary salt formation on *t*-butyl bromide, and Conant gives no data on *i*-butyl chloride. Our results seem to indicate that although *i*-butyl bromide is a primary halide its rate of reaction is of the same order as the secondary halides. Conant has found that the branching of the carbon chain in the case of *i*-amyl chloride causes the relative reactivity to drop from 1.26 to 0.65 and from our results it appears that when the side chain is closer to the halogen atom the rate is still more markedly decreased. This is also in agreement with the work of Semb and McElvain, who found that after forty-eight hours the percentage reaction with piperidine was *n*-amyl, 90.5, isoamyl, 77.4 and isobutyl, 40.8.

Considering what is probably the more important part of this work,

¹¹ Conant and Hussey, THIS JOURNAL, 47, 476 (1925).

because no other satisfactory quantitative work has been done along this line, namely, the relative ease of removal of hydrogen halide, we find that the order of relative rates of formation of pyridine hydrobromide is the reverse of that of the relative rates of formation of alkylpyridinium bromide; that is, the primary halides lose hydrogen bromide least readily and the rates for all of them are of the same order. The secondary halides lose hydrogen bromide seven to nine times as fast as the fastest reacting primary halide, while the only tertiary bromide studied loses hydrogen bromide about 80 times more rapidly than the secondary halides and about 800 times more rapidly than the primary halides.¹² In fact, in the case of *t*-butyl bromide hydrogen bromide is lost so readily that the rate of quaternary salt formation could not be determined.

This order is the same as that found for such reactions as the hydrolysis of alkyl bromides in neutral solution¹³ and the dehydration of alcohols.¹⁴

It has also been pointed out¹⁵ that only tertiary halides give satisfactory yields of hydrocarbons with zinc alkyls.¹⁶

¹² Because of the side reactions taking place, some of the values for the individual rate constants may be in error by as much as 100%. This, however, does not alter the general conclusions in regard to the relative reactivity of the different types of halides, as can be readily seen from Figs. 1 and 2.

¹³ Nicolet and Stevens, *THIS JOURNAL*, 50, 135 (1928); Straus, *Ann.*, 370, 366 (1909); Michael, Ref. 7.

¹⁴ Adkins and Perkins, *THIS JOURNAL*, 47, 1163 (1925); Adkins and Lazier, *ibid.*, 47, 1719 (1925); 48, 1671 (1926).

¹⁵ Noller, *ibid.*, 51, 597 (1929).

¹⁶ It is of interest to note that in those reactions where the order of reactivity is primary > secondary, namely, the reactions with inorganic iodides, thiosulfates, alkali alcoholates, enolates and phenolates, one reactant is an ion, whereas in those reactions where the order is tertiary > secondary > primary only non-polar molecules are involved. In view of the recent work of Herzfeld and Scheibe, *Z. physik. Chem.*, 7B, 390 (1930), which shows that the photochemical dissociation of methyl halides is into radicals and halogen atoms, it seems entirely possible that those reactions where the first order holds involve the removal of the halogen as an ion, whereas in those reactions where the second order holds, the halogen leaves the molecule as an atom. It is readily conceivable that both types of reaction may take place with pyridine if one assumes that when hydrogen bromide is removed, the hydrogen and bromine are removed simultaneously as atoms and that when quaternary salt formation takes place, the halogen separates as ion.

An alternative hypothesis is that the order of the true relative lability of the halogen is tertiary > secondary > primary and that in the reaction of large groups such as the ionic reactants and amines, "steric hindrance" plays an overwhelming role. This is partly supported by the behavior of *n*-amyl and *i*-amyl, and *n*-butyl, and *i*-butyl compounds. "Steric hindrance" would not be likely to play a large part in the case of small molecules such as water and alcohol, nor in reactions such as the dehydration of alcohols or the elimination of hydrogen bromide. On the other hand, one is at a loss to explain on this basis why large molecules such as zinc di-*n*-butyl react only with tertiary halides and why the hydrolysis of esters is so markedly affected by "steric hindrance." Moreover, if "steric hindrance" determines the course of the reaction

Side Reactions.—The most obvious inaccuracy of our experimental method is the fact that the total amount of reaction goes to a greater or less degree above 100%, the maximum being 108%. We have been unable to detect impurities such as phosphates, sulfates, silicon or boron compounds after typical runs when the reaction has been allowed to proceed above 100%, and the same results are obtained in quartz as in Pyrex tubes. The plotted data show that beyond the point where all the pyridine has reacted, the increase in hydrogen ion is approximately equal to the increase in total reaction. That is, the formation of quaternary ammonium salt stops as soon as all the pyridine is gone but the formation of titratable hydrogen ion continues. Moreover, the formation of this excess hydrogen bromide reaches equilibrium with some other product of the reaction, probably unsaturated hydrocarbon. The following series of experiments illustrate these points.

Six Pyrex tubes and one fused silica tube containing pyridine and excess isopropyl bromide (molar ratio 1:11) were heated at 148.8° for two and one-half hours, the time previously shown to be sufficient to reach complete reaction. All tubes were removed and cooled, and two Pyrex tubes and the quartz tube set aside for analysis. The remaining four Pyrex tubes were distilled to dryness at room temperature *in vacuo*. Two of these were

TABLE II
EXPERIMENTS ON SIDE REACTIONS

	H ⁺ , %	Total Br ⁻	Alkylpyridinium bromide
Pyrex tubes heated two and one-half hours	72.7	101.9	29.2
	73.0	101.5	28.5
Fused silica tube heated two and one-half hours	72.7	101.3	28.6
Tubes from which excess bromide was distilled after two and one-half hours and which were resealed and heated for an additional two and one-half hours	72.9	100.7	27.8
	72.6	101.3	28.7
Tubes treated as above except that fresh bromide was added before resealing	79.3	108.1	28.8
	80.6	108.1	27.5

one might expect the total rate in the reaction with pyridine to be markedly decreased with the primary halides whereas one actually finds that the total rate of reaction of the primary halides is greater than that of the secondary halides.

One of the Referees has suggested that the mechanism of the removal of hydrogen halide may consist of the incipient withdrawal of a hydrogen ion, because of the capacity of a tertiary amine to accept a proton, which would promote the liberation of halogen as anion; and that tertiary halides lose hydrogen halide more readily than secondary or primary because of the greater number of hydrogen atoms available for elimination of hydrogen halide. Such an explanation would apply also to the dehydration of the alcohols but not to the hydrolysis of the alkyl halides. Of course, there is no reason for supposing that all three reactions have a common mechanism other than the fact that they show the same order of reactivity for the different types of compounds.

then resealed and to each of the remaining two tubes was added eleven moles more of pure *i*-propyl bromide. These were then sealed and all four tubes heated at 148.8° for another two and one-half hours. The results are given in Table II.

The only way in which we have been able to account for these results is to assume that the excess bromide decomposes under the action of heat to give hydrogen bromide, which combines in some unknown way with the other products of the reaction to give a product which is sufficiently stable to prevent loss of hydrogen bromide during the distillation of the excess bromide and yet sufficiently unstable to be in equilibrium with the unsaturated hydrocarbon at the temperature of the reaction.

The fact that the amount of quaternary ammonium salt does not change on prolonged heating indicates that the Ladenburg rearrangement of alkyl-pyridinium halides to alkyl pyridine hydrohalides takes place to only a very slight extent under the conditions of our experiments and in most cases there is no indication that it takes place at all. What might be interpreted as Ladenburg rearrangement is most marked in the case of *n*-butyl bromide, where the amount of quaternary ammonium salt decreased to the extent of about 2% four hours after it had reached its maximum value.

Still another side reaction seems to take place in the case of *i*-butyl bromide. The experimental data show that the curve for the rate of formation of pyridine hydrobromide actually crosses that for quaternary salt formation. We believe that this anomalous behavior is due to the rearrangement of *i*-butyl bromide to *t*-butyl bromide, which then reacts very rapidly with the pyridine to form almost exclusively pyridine hydrobromide.

Summary

1. The total rates of reaction with pyridine, and the rates of formation of pyridine hydrobromide have been determined for the seven alkyl bromides from ethyl to butyl. The results indicate that the removal of hydrogen bromide and quaternary salt formation are two simultaneous independent reactions.

2. The order for the relative rates of quaternary salt formation is primary > secondary, which is in accordance with the results of previous investigators on metathetical reactions where the second reactant is an ion.

3. The order for the relative rates of removal of hydrogen bromide is tertiary > secondary > primary, which is the same as that known to exist for the relative rates of hydrolysis and alcoholysis of alkyl halides, and for the relative rates of dehydration of alcohols.

4. The method of removing hydrogen halide from organic compounds by means of tertiary amines appears to be applicable to tertiary halides and less successfully to secondary halides but inapplicable to primary halides.

5. Under the present experimental conditions, the Ladenburg rearrangement does not take place to an appreciable extent. A rather unsatisfactory explanation is given for the fact that the total reaction appears to proceed to an extent greater than 100%. Rearrangement of *i*-butyl to *t*-butyl bromide appears to take place during the course of the reaction and this probably accounts for the anomalous behavior of *i*-butyl bromide.

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[CONTRIBUTION NO. 15 FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

REDUCTION OF NITROGUANIDINE. I. PRELIMINARY STUDY OF THE OXIDATION POTENTIAL OF THE NITRO-NITROSOGUANIDINE SYSTEM¹

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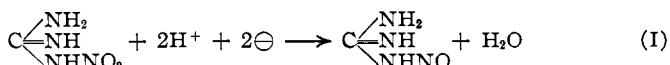
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Introduction

Nitroguanidine as an oxidizing agent has been only superficially studied and it is of peculiar interest because of the variety of reduction products which may be obtained from this substance and because of its close analogy to such important substances as nitric acid and nitrobenzene on the one hand and hydrazine and aniline on the other. Since it was thought that a knowledge of the free energy changes and the equilibrium constants for the reactions involved in the reduction of nitroguanidine would be of aid in furthering the studies on this topic, it was decided to attempt to measure the e. m. f. developed by the various nitroguanidine or derived systems.

The first system chosen for study was nitro-nitrosoguanidine, because nitrosoguanidine was the first definite reduction product of nitroguanidine known at that time and also because the preparation and properties of nitrosoguanidine were being studied in this Laboratory.

Theoretical Considerations.—It has been known from the work of Thiele in 1893² that nitroguanidine may be reduced to nitrosoguanidine in acid solution by nascent hydrogen (*i. e.*, zinc). If we assume that the reaction proceeds in accordance with the equation



¹ This paper was constructed from part of the thesis submitted by Mr. Sabetta to the faculty of the Polytechnic Institute of Brooklyn in June, 1931, in partial fulfillment of the requirements for the degree of Master of Science in Chemistry. It was presented before the Division of Physical and Inorganic Chemistry at the Eighty-second meeting of the American Chemical Society in Buffalo, N. Y., August 31 to September 4, 1931.

² Thiele, *Ann.*, 273, 133 (1893).