product of the reaction is a free radical which may be isolated in the associated form (derivative of hexaphenylethane); it shows the typical behavior of these compounds. Under the influence of acids the free radical may further undergo rearrangement or reduction and oxidation to the corresponding methane and carbinol.

2. Michler's ketone dichloride and octamethyltetraminotetraphenylethylene glycol are both reduced by soluble reducing agents to octamethyltetraminotetraphenylethylene.

3. Dimethylaminodiphenylcarbinol and dimethylaminophenylisopropylcarbinol are each reduced by powerful soluble reducing agents with the formation of a pair of isomeric dimers.

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# THE REACTION OF ORGANIC HALIDES WITH PIPERIDINE. I. ALKYL BROMIDES

By JOSEPH SEMB AND S. M. McELVAIN

The reaction between a secondary amine and an organic halide is a common and useful method of preparation of tertiary amines. The reaction, as it is ordinarily carried out, is between two moles of the secondary amine and one mole of the halide with the formation of one mole of the tertiary amine and one mole of the secondary amine hydrohalide

$$2R_2NH + R'X \longrightarrow R_2NR' + R_2NH \cdot HX \tag{1}$$
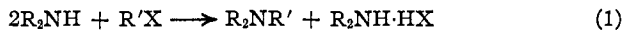
In a previous communication from this Laboratory[1] it was pointed out that certain halogen compounds did not follow the above reaction course with 3-methylpiperidine, but that the products obtained from the reaction were one mole of the secondary amine hydrohalide and one mole of unchanged secondary amine. No tertiary amine was isolated. Presumably, hydrogen halide had split out of the halogen compound with the formation of an unsaturated compound, thus

$$2R_2NH + R'X \longrightarrow R_2NH + R_2NH \cdot HX + (R''-H) \tag{2}$$

There are scattered references[2] in the literature to the loss of a molecule of halogen acid from certain halides when they are treated with various organic bases, but apparently no effort has been made to study the reaction from this point of view.

It seemed desirable, therefore, to follow the rate and course of the reaction

[1] Thayer and McElvain, THIS JOURNAL, 50, 3350 (1928).

[2] Cf. Houben–Weyl, "Die Methoden der organischen Chemie," Vol. IV, 1924, p. 243; Menschutkin, Z. physik. Chem., 5, 589 (1890); Wallach, Ann., 230, 233 (1885); Nef, ibid., 309, 164 (1899).

between different types of organic halogen compounds and a representative secondary amine. Piperidine was chosen as the amine to be used on account of its availability in the pure state, high basicity and convenient boiling point. This paper reports the results obtained from the reaction of this secondary amine with eighteen alkyl bromides.

Each reaction was carried out in sealed tubes using two moles of piperidine and one mole of the alkyl bromide in petroleum ether as a solvent. The rate of reaction was followed by opening tubes from time to time and determining the amount of the insoluble piperidine hydrobromide which had precipitated. The course of the reaction was determined at the end of a suitable reaction period by precipitating and weighing the unreacted piperidine as piperidino-formanilide with phenyl isocyanate. The amount of tertiary amine which had formed could then be calculated as the difference between the amount of piperidine which had been put into the reaction and the piperidine which was recovered as the hydrobromide and as piperidino-formanilide. From these data the course of the reaction ((1) or (2) above) was apparent. The results which were obtained are tabulated in the experimental part of the paper.

## Experimental

### Materials Used

Piperidine.—Piperidine was prepared by the hydrolysis of benzoylpiperidine[3] with 10% sodium hydroxide solution. The piperidine was removed from this alkaline solution by distillation and converted to the hydrochloride by the addition of hydrochloric acid. The solution of the hydrochloride was then evaporated to dryness and the free base liberated from its salt with a saturated potassium hydroxide solution. The piperidine layer was separated, dried with solid potassium hydroxide and finally treated with metallic sodium and distilled. It boiled at 105.4–106°.

The Alkyl Bromides.—Ethyl, n-propyl, isopropyl, sec.-butyl, tert.-butyl, diethylmethyl, tert.-amyl, benzyl and 1-methylcyclohexyl bromides were prepared from the corresponding alcohols by the Norris procedure.[4] Isobutyl and isoamyl bromides were obtained by the action of phosphorus tribromide on the corresponding alcohols.[5]   n-Butyl, n-amyl, n-hexyl, n-heptyl, cyclohexyl, phenylethyl and phenylpropyl bromides were prepared by the method of Kamm and Marvel[6] from the corresponding alcohols. 1-Methylcyclohexyl bromide apparently has not been prepared before this time. It boiled at 65–66° (19 mm.); Br calcd., 45.1; found, 44.8; $M_D$ calcd., 39.76; found, 39.86.

Phenyl isocyanate was purchased from the Eastman Kodak Company and was distilled before use.

The petroleum ether was washed with sulfuric acid and water. It was finally dried over sodium and distilled. It boiled at 50–75°.

[3] Marvel and Lazier, "Organic Syntheses," John Wiley and Sons, Inc., New York, Vol. IX, 1929, p. 16.

[4] Norris, Am. Chem. J., 38, 641 (1907).

[5] Cf. Reynolds and Adkins, THIS JOURNAL, 51, 279 (1929).

[6] Kamm and Marvel, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1921, Vol. I, p. 1.

TABLE I

RATE OF THE REACTION BETWEEN PIPERIDINE AND VARIOUS ALKYL BROMIDES AT 90°

| Alkyl group | 4 | 8 | 12 | 24 | —% Reaction in— 48 | 72 | 96 | 120 | 144 | 168 hr. |
|---|---|---|---|---|---|---|---|---|---|---|
| Ethyl | 72.2 | 80.4 | 84.3 | 93.7 | 98.4 | .. | .. | .. | .. | .. |
| n-Propyl | 45.6 | 59.5 | 66.2 | 79.3 | 89.5 | .. | .. | .. | .. | .. |
| Isopropyl | .. | .. | .. | 17.3 | 28.1 | 34.4 | .. | 44.6 | 48.5 | 51.0 |
| n-Butyl | 46.1 | 59.3 | 66.5 | 78.0 | 88.4 | .. | .. | .. | .. | .. |
| Sec.-butyl | .. | .. | .. | 6.7 | 12.0 | .. | .. | .. | 25.9 | 28.6 |
| Isobutyl | 10.0 | 16.0 | .. | 29.4 | 40.8 | .. | .. | 57.0 | .. | .. |
| Tert.-butyl | .. | .. | .. | 5.5 | 9.7 | 13.7 | .. | 16.2 | .. | 21.8 |
| n-Amyl | 48.1 | 63.6 | 69.8 | 80.7 | 90.5 | .. | .. | .. | .. | .. |
| Isoamyl | 31.1 | 44.8 | 52.8 | 65.5 | 77.4 | 82.4 | .. | .. | .. | .. |
| Diethylmethyl | .. | .. | .. | 6.2 | 9.9 | 13.1 | .. | 18.3 | .. | 23.6 |
| Tert.-amyl | .. | .. | .. | 9.1 | 15.3 | 21.3 | .. | 30.6 | .. | 38.5 |
| n-Hexyl | 49.6 | 63.7 | 70.7 | 80.7 | 88.9 | .. | .. | .. | .. | .. |
| n-Heptyl | 53.2 | 67.5 | 74.5 | 82.2 | 90.0 | .. | .. | .. | .. | .. |
| Cyclohexyl | .. | .. | .. | 1.1 | 2.4 | .. | 3.3 | .. | .. | 6.5[a] |
| 1-Methyl-cyclohexyl | .. | .. | .. | 7.2 | 12.5 | 17.4 | 21.9 | 25.7 | .. | .. |
| Benzyl | 100.5[b] | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Phenylethyl | 59.6 | 69.5 | 77.4 | 90.6 | 95.0 | .. | .. | .. | .. | .. |
| Phenylpropyl | 74.0 | 83.9 | 86.4 | 93.2 | 95.8 | .. | .. | .. | .. | .. |

[a] 11.2% in 384 hours. [b] 97.7% in 2 hours.

## General Procedure

The determination of the rate of reaction between piperidine and each alkyl bromide was made in the following manner. In a test-tube prepared for sealing was placed 0.02 mole (1.700 g. delivered by a calibrated pipet) of piperidine and a solution of 0.01 mole (1.088–1.985 g.) of the alkyl bromide in 10 cc. of petroleum ether. This latter solution was a 10-cc. aliquot taken from a solution of 0.1 mole (10.88–19.85 g.) of the bromide in 100 cc. of petroleum ether. The tube was then sealed and placed in a thermostat held at 90°. Sufficient such tubes were prepared for each bromide to allow at least two tubes to be taken for the determination of each value given in Table I. When a tube was opened for a determination the precipitated piperidine hydrobromide was filtered off, washed with petroleum ether and dried. A portion of this precipitate was analyzed for its bromine content by titration with standard silver nitrate solution. These analyses showed in every case that the precipitate was practically pure piperidine hydrobromide. The remainder of the precipitate which adhered to the sides of the reaction tube and to the filter paper was washed into the solution resulting from the above titration and further titrated with the silver nitrate solution. From these determinations the amount of piperidine hydrobromide which had precipitated could be determined.

The results of these determinations are shown in Table I. Each value in this table is the average of at least two determinations. The calculation

of the percentage reaction is based on the amount of alkyl bromide that was put into the reaction.

The determination of the course of the reaction was made after a sufficient time to allow for a reasonable amount of reaction, as shown by the above data on the rate of the reaction. The reaction tube was opened and the insoluble piperidine hydrobromide filtered off and washed with a few cc. of petroleum ether. The filtrate and washings were placed in a volumetric flask and made up to 50 cc. with petroleum ether. An aliquot, containing not more than 0.170 g.[7] of piperidine, of this solution was used for the determination of the unreacted piperidine. This aliquot was placed in a previously weighed weighing bottle (approximately 4 cm. in diameter and 6 cm. high) and made up to a volume of 30 cc. with petroleum ether. To this solution 1 cc. of phenyl isocyanate was added. A voluminous precipitate of piperidino-formanilide came down immediately. After standing for about ten minutes, the reaction mixture was filtered through a previously weighed Gooch crucible. The weighing bottle was rinsed with 10 cc. of petroleum ether and these rinsings used to wash the precipitate in the Gooch crucible. Since a small amount of the piperidino-formanilide always adhered to the side and bottom of the weighing bottle, it was dried along with the Gooch crucible in an oven at 80° and re-weighed. To the weight of piperidino-formanilide so obtained was added the weight (0.0024 g.) of the anilide which 40 cc. (the volume used in the determination) of petroleum ether was found to dissolve after several hours of shaking. By this procedure 98.5% of the piperidine was found in samples of petroleum ether containing 0.170 g. of the substance.

The results of such determinations for the eighteen alkyl bromides that were reacted with piperidine at 90° are shown in Table II. Each experimentally obtained value is the average of at least two determinations. All weights are expressed in moles $\times 10^2$ in order to allow more ready comparisons and to avoid the use of a larger number of digits. Column B represents the moles of piperidine hydrobromide precipitated from the reaction and column C the moles of unreacted piperidine determined as piperidino-formanilide. Obviously the difference between the amount of piperidine (2 moles) originally put into the reaction and the piperidine recovered as the hydrobromide and as piperidino-formanilide would represent the amount of piperidine which had reacted to form tertiary amine. This value is shown in column D. Column E shows the amount of unsaturated compound formed and represents the difference between the amount of piperidine obtained as the hydrobromide (column B) and that amount of piperidine which was converted into the tertiary amine (column D).

[7] Larger quantities of piperidine produced a too voluminous precipitate of piperidino-formanilide to be handled conveniently.

TABLE II

THE COURSE OF THE REACTION BETWEEN PIPERIDINE AND CERTAIN ALKYL BROMIDES
AT 90°

| Alkyl group | Reaction period, hours | A % reaction | B Moles × 10² piperidine hydro-bromide | C Moles × 10² unreacted piperidine[a] | D Moles × 10² tertiary amine, 2-(B + C) | E Moles × 10² unsat. cpd. B − D |
|---|---|---|---|---|---|---|
| Ethyl | 48 | 98.4 | 0.984 | 0.035 | 0.981 | +0.003 |
| n-Propyl | 48 | 89.5 | .895 | .213 | .891 | + .004 |
| Isopropyl | 168 | 51.0 | .510 | .994 | .496 | + .014 |
| n-Butyl | 48 | 88.4 | .884 | .207 | .909 | − .025 |
| Sec.-butyl | 168 | 28.6 | .286 | 1.390 | .320 | − .034 |
| Isobutyl | 120 | 57.0 | .570 | 0.826 | .604 | − .034 |
| Tert.-butyl | 168 | 21.8 | .218 | 1.781 | .022 | + .196 |
| n-Amyl | 48 | 90.5 | .905 | 0.183 | .912 | − .007 |
| Isoamyl | 72 | 82.4 | .824 | .335 | .841 | − .017 |
| Diethylmethyl | 168 | 23.6 | .236 | 1.501 | .263 | − .027 |
| Tert.-amyl | 168 | 38.5 | .385 | 1.517 | .097 | + .288 |
| n-Hexyl | 48 | 88.9 | .889 | 0.222 | .889 | .000 |
| n-Heptyl | 48 | 90.0 | .900 | .196 | .904 | − .004 |
| Cyclohexyl | 384 | 11.2 | .112 | 1.766 | .121 | − .009 |
| 1-Methylcyclohexyl | 120 | 25.7 | .257 | 1.629 | .113 | + .114 |
| Benzyl | 4 | 100.5 | 1.005 | 0.003 | .992 | + .013 |
| Phenylethyl | 48 | 95.0 | 0.950 | .047 | 1.003 | − .053 |
| Phenylpropyl | 48 | 95.8 | .958 | .044 | 0.998 | − .040 |

[a] Determined as piperidino-formanilide.

It is seen from Table II that certain secondary and tertiary bromides did not show sufficient reaction at 90° to permit the determination of the course of the reaction to have much meaning. For this reason it seemed desirable to repeat the experiments with these bromides at a higher temperature in the hope of bringing about more complete reaction. This was done by heating the reaction tubes in an oil-bath kept at 125–135° by a hot-plate. No attempt was made to control the temperature as accurately as in the experiments summarized in Table II. After the indicated reaction period the tubes were cooled, opened and the reaction product determined

TABLE III

THE COURSE OF THE REACTION BETWEEN PIPERIDINE AND CERTAIN SECONDARY AND
TERTIARY ALKYL BROMIDES AT 125–135°

| Alkyl group | Reaction period, hours | A % reaction | B Moles × 10² piperidine hydro-bromide | C Moles × 10² unreacted piperidine[a] | D Moles × 10² tertiary amine 2-(B + C) | E Moles × 10² unsat. cpd., B − D |
|---|---|---|---|---|---|---|
| Isopropyl | 48 | 73.7 | 0.737 | 0.456 | 0.807 | −0.070 |
| Sec.-butyl | 24 | 43.5 | .435 | 1.122 | .442 | − .007 |
| Tert.-butyl | 24 | 47.2 | .472 | 1.400 | .128 | + .334 |
| Tert.-amyl | 72 | 99.1 | .991 | 0.926 | .083 | + .908 |
| Cyclohexyl | 120 | 81.1 | .811 | 1.068 | .120 | + .691 |
| 1-Methylcyclohexyl | 120 | 89.5 | .895 | 0.981 | .124 | + .771 |

[a] Determined as piperidino-formanilide.

in the same manner as that described above for the experiments run at 90°. The data for these experiments are summarized in Table III. Each experimentally obtained value in this table is the average of at least two determinations.

## Discussion of Experimental Results

It is seen from Table I that there is an enormous difference in the reactivities of the three types of alkyl bromides with piperidine. As a class the primary bromides react quite completely in forty-eight hours. An exception is noted in the case of isobutyl bromide and this is due, no doubt, to the proximity of the branching in the chain to the halogen atom, for isoamyl bromide shows a distinctly greater reactivity than isobutyl bromide. Further, it may be pointed out that there appears to be a distinct alternating effect of the phenyl group on the reactivity of benzyl, phenylethyl and phenylpropyl bromides when they are compared after a four-hour period of reaction. The secondary and tertiary bromides are exceedingly unreactive when compared to the primary bromides. This fact is strikingly shown by the percentage of reaction in the forty-eight hour column of Table I. In this unreactive group cyclohexyl bromide is by far the least reactive. Conant and Hussey[8] have previously noted the extraordinary inertness of cyclohexyl chloride in their study of the rate of reaction of various alkyl chlorides with potassium iodide in acetone solution. They attributed this abnormal behavior to the cyclohexane ring. It is quite possible, however, that the reactivity which the other secondary bromides show may be due to a previous rearrangement to the more reactive primary bromide and that the unreactivity of the cyclohexyl bromide is due to the fact that it cannot rearrange to such a form.

The data summarized in Table II indicate that the primary and secondary bromides react to form tertiary amines, while the three tertiary bromides show a decided tendency to lose hydrobromic acid to form, presumably, an unsaturated compound. A relatively small positive value in column E carries no significance and, traced back to its source, probably means that the value obtained for the moles of unreacted piperidine (column C) rather than the corresponding value in column B was too high. A negative value in column E indicates that the amount of tertiary amine formed (column D) is greater than the amount of piperidine precipitated as the hydrobromide (column B). Obviously, such a ratio of reaction products is theoretically impossible, and when it is indicated it is due to a too low value in column B or C. As a group, however, the primary and secondary bromides in Table II show that there is formed practically the same number of moles of tertiary amine as of piperidine hydrobromide. The tertiary bromides, on the other hand, show a marked difference between the moles of tertiary amine and piperidine hydrobromide produced.

[8] Conant and Hussey, THIS JOURNAL, **47**, 479 (1925).

The amount of reaction which most of the secondary and tertiary bromides in Table II show is relatively small. Table III gives a better view of the behavior of these compounds. At this higher reaction temperature it is seen that isopropyl and secondary butyl bromide definitely react to form a tertiary amine, but that cyclohexyl bromide, which appeared to be showing the same type of reaction in Table II, when forced into a more complete reaction shows practically the same tendency as the tertiary bromides to lose hydrobromic acid and forms only a relatively small amount of a tertiary amine. This fact would seem to lend further support to the suggestion made above that the secondary bromides which react with piperidine to form a tertiary amine probably rearrange to primary bromides before reacting and react as such. This possibility will be tested experimentally in this Laboratory and the results reported later. The tertiary bromides in Table III follow more completely the course which they started in Table II.

## Summary

1. The rate and course of the reaction between piperidine and eighteen alkyl bromides has been determined.

2. It has been found that the primary and secondary bromides, with the exception of cyclohexyl bromide, react with piperidine to form tertiary amines. Cyclohexyl bromide and the tertiary bromides which were studied react, in the main, to lose hydrobromic acid and form, presumably, an unsaturated compound.

MADISON, WISCONSIN

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# STUDIES IN PROTEINS.
## II. CONCERNING THE UNIFORMITY OF THE PROTEIN FRACTION EXTRACTED FROM ORANGE SEED MEAL BY SALT SOLUTIONS

BY FELIX SAUNDERS

### Introduction

In a series of recent papers, Gortner and his co-workers[1] have reported the results of studies on the "peptization" of wheat flour proteins. Their figures show a great variation in the fraction of the total nitrogen extracted by various salts. From their data, the authors draw the following conclusions: (1) both anions and cations show a lyotropic series, (2) "protein 'solubility' in neutral salt solutions is, in reality, protein peptization, and

¹ Gortner, Hoffman and Sinclair, *Cereal Chemistry*, **6**, 1 (1928); "Colloid Symposium Monograph," The Chemical Catalog Co.. Inc., New York. 1928, Vol. V. p. 179.