$$2Na_2O_2 + 2D_2O \longrightarrow 4NaOD + O_2\uparrow$$

The reaction utilizes all deuterium to form the sodium deuterioxide and avoids the danger of explosion since oxygen, instead of deuterium, is evolved. Deuterium oxide, used as solvent, is recoverable without significant loss of purity.

Experimental

To 60 ml. of deuterium oxide in a 500-ml. three-necked flask equipped with reflux condenser, dropping funnel, and well-sealed stirrer, under dry nitrogen, contained in an ice-salt bath, was added cautiously with stirring 40 g. of sodium peroxide, followed by 98 g. of anhydrous chloral[3] (prepared by passing vapors of redistilled chloral over Drierite kept at 100°[2]) during 40 min. The ice was allowed to melt and the two layers that formed were separated. The chloroform was washed with water at pH 6 and dried over magnesium sulfate. The product was filtered and distilled (b.p. 62°) to give chloroform-*d* in yields averaging 90%, with 95% isotopic purity (isotopic purity determined by the nuclear magnetic resonance spectrum). The product was stored under nitrogen in sealed vials.[4]

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[3] Trichloroacetophenone and hexachloroacetone are possible substitutes for chloral [W. Boyer, *et al.*, *J. Am. Chem. Soc.*, **73**, 770 (1951); P. J. Paulsen and W. D. Cooke, (ref. 1)].

[4] Deuterioethanol can be added as a stabilizer [P. J. Paulsen and W. D. Cooke, (ref. 1)].

The Reaction of Piperidine with Commercial Chloroform and Other Halomethanes

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In a recent note[1] the authors reported that from the reaction of piperidine with chloroform they isolated piperidine hydrochloride and detected the presence of N-formylpiperidine. Observations made in these laboratories, where the above reaction forms part of a wider investigation involving many bases, including alkaloids and organic halides, indicate that such a conclusion must be reassessed in terms of the purity of the chloroform.

It has been shown that commercial chloroform B.P. currently manufactured mainly by direct chlorination methods contains chlorobromomethane (0.2–0.5% v./v.) and methylene chloride (up to 0.1% v./v.) which cannot be removed by the usual fractionation methods of purification.[2,3] Such impurities were not present in chloroform obtained from earlier bleach processes.[4] Of these impurities, it is chiefly the chlorobromomethane which reacts with bases, "purified" chloroform (freed from these impurities) being almost unreactive.[2-5] The extent of reaction depends on the steric requirements of the base.[3,6] A study[3] of the rates of reaction of piperidine with chloroform B.P. and "purified" chloroform indicated that the base did not react to any appreciable extent with the latter, even at 60°.

The purpose of this communication is to show that impurities found in chloroform B.P. can react with piperidine to produce a number of products including piperidine hydrochloride, piperidine hydrobromide, and 1,1′-dipiperidylmethane. Equimolecular quantities of piperidine and chloroform B.P. interact to produce a mixture of piperidine hydrochloride and hydrobromide. The extent to which this reaction occurs after standing for 24 hr. (1% yield) is in agreement with that recorded by Pierce and Joullie[1] but the melting point found for the solid does not agree with their value. Infrared evidence is not helpful in elucidating the nature of the product as it does not distinguish between piperidine hydrochloride and hydrobromide. Its identity was established, however, by obtaining the same product from the interaction of piperidine and authentic chlorobromomethane. A second product of this reaction was shown to be 1,1′-dipiperidylmethane. The latter is also formed, together with the hydrobromide and hydrochloride, respectively, of the base, when piperidine reacts with either methylene bromide or methylene chloride.

Whereas piperidine reacts readily at room temperature with both chlorobromomethane and methylene bromide, boiling under reflux is required for the base to react with methylene chloride. This is not unexpected since the ease with which halogens are replaced by nucleophillic groups (I > Br > Cl) is related to the bond energies (C–Cl > C–Br > C–I).

The products from the reaction of piperidine with excess chlorobromomethane are obtained in yields which are almost quantitatively related to this equation.

$$4C_5H_{10}NH + CH_2X_2 \longrightarrow 2C_5H_{10}NH{\cdot}HX + C_5H_{10}N{\cdot}CH_2{\cdot}NC_5H_{10}$$
$$(X = \text{halogen})$$

When excess piperidine is used in the reaction with methylene bromide, the products again are formed in proportions approximating to the above equation.

On treating piperidine with "purified" chloroform, only a very small amount (0.025%) of piperidine hydrochloride is formed after 24 hr. Heating the reactants for several days, however, increases the yield (6%) and also facilitates the detection of a second product, N-formylpiperidine.

Experimental

Materials.—The three samples of chloroform used were I, b.p. 60–61.5°, n^{20}_D 1.4460, B.P. quality; II, b.p. 61.0–61.5°, n^{20}_D 1.4460, B.P. quality purified by successive washings with concentrated sulfuric acid and distilled water and drying overnight over calcium chloride which was removed by filtration, the filtrate being distilled through a 30-cm. Dufton column; III, b.p. 60.5–61.0°, n^{20}_D 1.4455, B.P. quality "purified" by boiling under reflux for several days with strychnine when recovery of the solvent yielded a sample of chloroform free from chlorobromomethane and methylene chloride.[3,4]

Chlorobromomethane was dried over calcium chloride and distilled through a 30-cm. Dufton column. The fraction boiling at 68–69°, n^{20}_D 1.4818, was collected.

Methylene bromide was dried over calcium chloride and distilled from a Claisen flask with a fractionating side arm, b.p. 96–97°, n^{20}_D 1.5420.

Methylene chloride was dried over calcium chloride and distilled from a Claisen flask with a fractionating side arm, b.p. 40–41°, n^{20}_D 1.4250.

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[1] A. Pierce and M. M. Joullie, *J. Org. Chem.*, **27**, 2220 (1962).

[2] A. C. Caws and G. E. Foster, *J. Pharm. Pharmacol.*, **9**, 824 (1957).

[3] H. Williams, *ibid.*, **11**, 400 (1959).

[4] D. I. Coomber and B. A. Rose, *ibid.*, **11**, 703 (1959).

[5] H. Williams, *Chem. Ind.* (London), 900 (1960).

[6] H. Williams, to be published.

Piperidine was purified by standing over potassium hydroxide pellets for 1 week. The pellets were removed by filtration and the filtrate was distilled through a 30-cm. Dufton column, b.p. 105–106°, n^{20}_{D} 1.4527.

Commercial anhydrous ether and benzene were allowed to stand over sodium for 1 week and redistilled.

Reaction of Piperidine and Chloroform.—Piperidine (8.5 g., 0.1 mole) was mixed separately with (1) chloroform I (11.9 g., 0.1 mole), (2) chloroform II (11.9 g., 0.1 mole), and (3) chloroform III (11.9 g., 0.1 mole). After 24 hr., excess anhydrous ether was added to each solution. A white solid (0.11 g.) precipitated immediately from reactions 1 and 2, whereas reaction 3 yielded only a slight precipitate (0.003 g.), m.p. 245°, corresponding to piperidine hydrochloride, after standing for a short time. The product of reactions 1 and 2 had a melting point of 236° and a mixture of both produced no depression in the melting point. (Pierce and Joullie[1] record 244° as the melting point of this product.)

The same product was produced next by interaction of piperidine (0.1 mole) with "purified" chloroform III (0.1 mole) containing authentic chlorobromomethane (0.5% v./v.), and by mixing piperidine (0.1 mole) with authentic chlorobromomethane (0.1 mole), when a vigorous exothermic reaction occurred and a white solid separated almost immediately. In Table I the melting points and mixture melting points of the products prepared by the various methods A, B, and C are listed.

Table I

Sample[a]	M.p., °C.
A	235
B	234
C	234
A + B	235
A + C	234
B + C	235

[a] A = piperidine + chloroform B.P. (I), B = piperidine + chlorobromomethane, C = piperidine + chlorobromomethane in "purified" chloroform (III).

The following considerations contribute towards the elucidation of the structure of this product. The substance gives qualitative reactions for bromide.[7] After controlled oxidation with nitric acid,[8] the aqueous solution gave a precipitate with silver nitrate. The volumes of 0.1 *N* silver nitrate required before and after treating the solid with sodium and alcohol (Stepanov method) were identical. Hence, both the chlorine and bromine are ionized and the product appears to be an equimolecular mixture of piperidine hydrochloride and piperidine hydrobromide.

Anal. Calcd. for $C_5H_{11}N \cdot HCl \cdot C_5H_{11}N \cdot HBr$: C, 41.74; H, 8.35; N, 9.74; ionic Br, 27.83, ionic Cl. 12.34. Found, for the products formed from reaction of piperidine with (a) chlorobromomethane (b) chloroform B.P. (I), (c) chloroform II, and (d) "purified" chloroform (III) containing chlorobromomethane: (a) C, 41.46; H, 8.59; N, 9.56; ionic Br, 28.06; ionic Cl, 12.51. (b) ionic Br, 25.33; ionic Cl, 15.08; (c) ionic Br, 24.42; ionic Cl, 14.50; and (d) ionic Br, 27.65; ionic Cl, 13.06.

A higher proportion of chloride in (b) and (c) may be due to reaction of the base with the methylene chloride impurity.[3] Finally, the products formed by methods A, B, and C (see Table I) did not depress the melting point of a mixture of authentic piperidine hydrochloride and hydrobromide (234°).

Reaction of Piperidine with Chlorobromomethane.—Piperidine (25.5 g., 0.3 mole) was added to chlorobromomethane (64.8 g., 0.5 mole) in dry benzene (100 ml.) contained in a flask fitted to a condenser carrying a tube containing calcium chloride and soda lime. The reaction was markedly exothermic and a turbidity formed within 3–5 min. After 24 hr., the white crystalline solid was removed by filtration, washed with dry benzene, and dried, yielding 20.96 g., m.p. 236°. It did not depress the melting point of a mixture of authentic piperidine hydrochloride and hydrobromide.

Anal. Calcd. for $C_5H_{11}N \cdot HBr \cdot C_5H_{11}N \cdot HCl$: Br, 27.83; Cl, 12.34. Found: Br, 28.53; Cl, 11.98.

The filtrate was concentrated and then fractionated under reduced pressure to give a colorless liquid (X) in 12.30-g. yield, b.p. 55–58° (0.8 mm.), 238° (760 mm.), n^{20}_{D} 1.4825.

Reaction of Piperidine with Methylene Bromide.—Piperidine (51 g., 0.6 mole) was added to methylene bromide (17.4 g., 0.1 mole) in dry benzene (50 ml.) in a flask fitted as before. The reaction was again exothermic and a white solid commenced separating within 0.25 hr. After 48 hr., the white crystalline solid was recovered and dried, yielding 29.73 g., m.p. 235°. It did not depress the melting point of authentic piperidine hydrobromide.

Anal. Calcd. for $C_5H_{11}N \cdot HBr$: Br, 48.19. Found: Br, 48.00.

The filtrate on fractionation under reduced pressure gave a colorless liquid (Y) in 15.03 g. yield, b.p. 58° (0.7 mm.), 238° (760 mm.), n^{20}_{D} 1.4820.

Reaction of Piperidine with Methylene Chloride.—Piperidine (17 g., 0.2 mole) was added to methylene chloride (25.5 g., 0.3 mole) in dry benzene (50 ml.) in a flask fitted as before. The reaction was exothermic, but no solid separated on standing for 2 hr. After boiling under reflux for 24 hr., the white crystalline solid which had formed was removed by filtration, washed with dry benzene, and dried, yielding 14.71 g., m.p. 243°. It did not depress the melting point of authentic piperidine hydrochloride.

Anal. Calcd. for $C_5H_{11}N \cdot HCl$: Cl, 29.16. Found: Cl, 28.71.

The filtrate on fractionation under reduced pressure gave a colorless liquid (Z) in 3.61-g. yield, b.p. 60° (1.0 mm.), 236° (760 mm.), n^{30}_{D} 1.4825.

Authentic 1,1′-dipiperidylmethane was prepared from piperidine and aqueous formaldehyde.[9] It was a colorless liquid, b.p. 58–60° (1.0 mm.), 238° (760 mm.), n^{20}_{D} 1.4825; lit. b.p. 235°, n^{25}_{D} 1.4810.[10]

Anal. Calcd. for $C_{11}H_{22}N_2$: C, 72.52; H, 12.09. Found: C, 72.95; H, 12.01.

Identification of Liquids X, Y, and Z.—The identity of liquids X, Y, and Z was established by the following considerations. Their boiling points and refractive indices were identical with those ofa uthentic 1,1′-dipiperidylmethane; the infrared spectra of X, Y, Z, and authentic 1,1′-dipiperidylmethane were identical.

Anal. Calcd. for $C_{11}H_{22}N_2$: C, 72.52; H, 12.09; N, 15.38. Found for X: C, 72.98; H, 12.02; N, 15.99. Found for Y: C, 71.75; H, 12.06. Found for Z: C, 71.81; H, 12.13.

In the preparation according to the directions of Erhenberg[11] of derivatives with carbon disulfide, X, Y, and Z gave products, which after recrystallization from petroleum ether (b.p. 60–80°) had identical melting points (60°). Mixtures of these derivatives, in turn, with an authentic sample of the carbon disulfide derivative of 1,1′-dipiperidylmethane showed no depression in melting point (lit.[11] m.p. 58°).

Reaction of Piperidine with "Purified" Chloroform III.—Piperidine (17 g., 0.2 mole) was added to "purified" chloroform (35.7 g., 0.3 mole) in dry benzene (50 ml.) in a flask fitted as before. After boiling under reflux for 120 hr., a small quantity of white crystals had separated. These were removed by filtration, washed with "purified" chloroform, and dried, yielding 1.53 g., m.p. 245°. It did not depress the melting point of authentic piperidine hydrochloride.

Anal. Calcd. for $C_5H_{11}N \cdot HCl$: Cl, 29.16. Found: Cl, 29.22.

The filtrate on fractionation under reduced pressure gave a colorless liquid in 0.13-g. yield, b.p. 48–50° (1.0 mm.), whose properties (infrared spectrum, mercuric chloride derivative) were identical with those of authentic N-formylpiperidine.[1]

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(7) F. Fiegel, "Spot Tests," Vol. 1, 4th Ed., Elsevier Publishing Co., London, 1954, p. 246.

(8) "British Pharmacopoeia," Pharmaceutical Press, London, 1958, p. 509.

(9) Knoevenagel, *Ber.*, **31**, 2585 (1898).

(10) T. C. Simmons and F. W. Hoffmann, *et al.*, *J. Am. Chem. Soc.*, **79**, 3429 (1957).

(11) Erhenberg, *J. prakt. Chem.*, [2]**36**, 117 (1877).

1,12-Dioxa[5.5]paracyclophane

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We wish to report the isolation and characterization of 1,12-dioxa[5.5]paracyclophane[2] (III), a by-product of the solvolysis of 4-(*p*-hydroxyphenyl)butyl brosylate