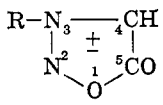
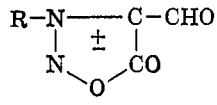
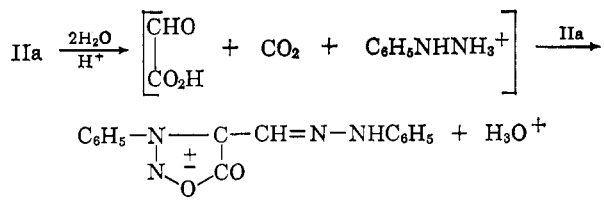


Ia, R = C_6H_5
Ib, R = $C_6H_5CH_2$



IIa, R = C_6H_5
IIb, R = $C_6H_5CH_2$

The ultraviolet and infrared spectra of the sydnonecarboxaldehydes were consistent with the structure (II) proposed. Furthermore, oxidation of IIa with potassium permanganate in acetone produced a small quantity of 3-phenyl-4-sydnonecarboxylic acid, which proved to be identical with an authentic sample.[4] On standing, the acidic filtrate from IIa deposited red crystals of the phenylhydrazone (III) of IIa, which presumably formed by reaction of unhydrolyzed IIa with the phenylhydrazine generated *in situ* by acid hydrolysis of IIa. Attempts to isolate the phenylhydrazone of glyoxylic acid were unsuccessful.



III

Both III and the 6-purinylhydrazone of IIa were prepared by conventional methods. They have been submitted to the Cancer Chemotherapy National Service Center (CCNSC) for screening for anticancer activity.

Experimental[5]

3-Phenyl-4-sydnonecarboxaldehyde (IIa).—N-Methylformanilide (28.4 g., 0.210 mole) and phosphoryl chloride (31.7 g., 0.205 mole) were mixed, and, after 0.5 hr., 30.0 g. (0.186 mole) of Ia was added portionwise with swirling and cooling as needed to keep the temperature below 45°. Hydrogen chloride was evolved vigorously. After standing overnight, the viscous, dark-brown mixture was dissolved in 150 ml. of acetone and poured (stirring) into 750 ml. of ice water. The yellow-orange precipitate was filtered, washed (cold water), and dried to yield 18.4 g. (52.1%) of 3-phenyl-4-sydnonecarboxaldehyde (IIa), m.p. 143–146°. Three recrystallizations from the minimum amount of boiling absolute ethanol afforded irregular, pale yellow plates, m.p. 147–150° dec. (with sublimation from 125°), λ_{max}^{EtOH} 240 and 321 mμ (ε 11,500 and 9780), λ_{max}^{KBr} 5.64 (sydnone C=O) and 6.10 μ (aldehyde C=O).

Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.84; H, 3.18; N, 14.73. Found: C, 57.05; H, 3.35; N, 14.55.

After several days at room temperature, the aqueous filtrate from the crude IIa deposited clusters of red needles, shown to be identical (mixture melting point and infrared spectra) with authentic III (see below). The yield was 1.7 g. (equivalent to 2.5 g. of IIa).

3-Phenyl-4-sydnonecarboxaldehyde Phenylhydrazone (III).—Addition of aqueous phenylhydrazine hydrochloride to IIa in ethanol produced III, red needles, m.p. 173–174° (ethyl acetate–hexane); λ_{max}^{EtOH} 245, 297, and 424 mμ (ε 8790, 12,800, and 12,100); λ_{max}^{KBr} 5.78 (sydnone C=O), 6.28, 6.40, and 6.52 μ (probably C=N).

Anal. Calcd. for $C_{15}H_{12}N_4O_2$: N, 19.99. Found: N, 19.43.

3-Phenyl-4-sydnonecarboxaldehyde 6-Purinylhydrazone.—6-Hydrazinopurine[6] (0.16 g., 1.1 mmoles) in 9 ml. of boiling water containing 1 drop of acetic acid was added to IIa (0.20 g., 1.1 mmoles) in 15 ml. of hot ethanol and the mixture was heated 15 sec. over steam and cooled 4 hr. in ice; the yellow solid was washed and dried to yield 0.27 g. (80%) of purinylhydrazone. This highly insoluble material was recrystallized three times from the minimum amount of hot (100°) dimethyl sulfoxide (to which water was added up to turbidity) to yield the analytical sample, m.p. 290–293° dec. (softening at 281°); $\lambda_{max}^{dioxane}$ 274 and 385 mμ (ε 44,800 and 13,000); λ_{max}^{KBr} 5.85 (sydnone C=O), 6.20, and 6.32 μ (probably C=N).

Anal. Calcd. for $C_{14}H_{10}N_8O_2$: C, 52.17; H, 3.13; N, 34.77. Found: C, 52.12; H, 2.98; N, 34.80.

3-Phenyl-4-sydnonecarboxylic Acid.—To a solution of IIa (*ca.* 0.1 g.) in 7 ml. of acetone was added solid potassium permanganate (*ca.* 0.2 g.) in small portions with stirring. After 5 min., excess permanganate was removed by addition of solid sodium sulfite. The filtered solution was poured into 14 ml. of cold water and the unchanged aldehyde was removed by filtration. The acidified filtrate was extracted with four 15-ml. portions of ether, and the combined extracts were dried and evaporated to yield 20 mg. of white solid, m.p. 190–193° dec., λ_{max}^{EtOH} 220 and 309 mμ (ε 14,500 and 8960), λ_{max}^{KBr} 5.52 (sydnone C=O) and 5.97 μ (acid C=O) This sample was identical (mixture melting point and infrared spectrum) with an authentic sample.[4]

3-Benzyl-4-sydnonecarboxaldehyde (IIb).—N-Methylformanilide (5.0 g., 0.037 mole) and 5.6 g. (0.036 mole) of phosphoryl chloride were allowed to stand 0.5 hr., cooled in an ice bath, and treated (stirring) with 5.6 g. (0.032 mole) of Ib. Next day the brown gum was dissolved in 15 ml. of dioxane and poured into ice, giving IIb as a waxy orange solid (1.0 g., 15%). Chromatography from benzene on a silica column (elution with 10% chloroform or ethyl acetate in benzene) yielded orange prisms, m.p. 79–80°; λ_{max}^{MeOH} 240.5 and 318.5 mμ (ε 9060 and 8560); λ_{max}^{KBr} 3.24, 3.41, 5.64 (sydnone C=O), and 6.09 μ (aldehyde C=O).

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.81; H, 3.95; N, 13.72; mol. wt., 204.2. Found: C, 58.89; H, 3.82; N, 13.91; mol. wt. (Rast), 204.

(4) Kindly supplied by Dr. Hiroshi Kato; H. Kato and M. Ohta, *Bull. Chem. Soc. Japan*, **32**, 282 (1959).

(5) All melting points are uncorrected. The ultraviolet spectra were obtained with a Cary recording spectrophotometer, and the infrared spectra with a Beckman IR-5 double-beam instrument by use of the potassium bromide pellet procedure. Combustion analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by Galbraith Laboratories, Inc., Knoxville, Tenn.

(6) A liberal sample was kindly supplied to us through the courtesy of Ronald B. Ross of CCNSC.

A Convenient Preparation of Chloroform-*d*[1]

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Chloroform-*d* of purity sufficient for most n.m.r. spectroscopy can be prepared conveniently and economically by a modification of the original synthesis of this compound by Breuer.[2] Breuer prepared chloroform-*d* by the following reactions.

$$2Na + 2D_2O \longrightarrow 2NaOD + 2D_2\uparrow$$

$$NaOD + Cl_3CCHO \longrightarrow CDCl_3 + NaCHO_2$$

The first reaction involves the loss of deuterium from the reaction and the danger of explosion of the liberated deuterium. To avoid these difficulties, an alternative preparation of sodium deuterioxide by the reaction of sodium peroxide and deuterium oxide was used. Sodium peroxide is a common chemical which is obtainable in the anhydrous state. It reacts with deuterium oxide.

(1) Other preparations of chloroform-*d* are listed in A. Murray and D. Williams, "Organic Syntheses with Isotopes," Interscience Publishers, Inc., New York, N. Y., 1958, p. 1477. See also M. T. Forel, *et al.*, *Bull. soc. chim. France*, 1922 (1959); P. J. Paulsen and W. D. Cooke, *Anal. Chem.*, **35**, 1560 (1963).

(2) F. W. Breuer, *J. Am. Chem. Soc.*, **57**, 2236 (1935).

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

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]

(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 = 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.

(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.