the methoxyamine II, the known product in similar systems in the presence of potassium carbonate,[6] was being produced.

$$ArCHO + R_2NH + CH_3OH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\underset{OCH_3}{|}}{ArCHNR_2} + H_2O$$
II

$$K_1 = \frac{k_1}{k_{-1}} = \frac{[II][H_2O]}{[ArCHO][R_2NH]} \quad (1)$$

Equilibrium Constant.—The equilibrium constant K_1 was calculated from both ultraviolet and infrared spectrophotometric determination of piperonal. The values obtained at 25.0° were $K_1 = 2.4 \pm 0.1$ for eight runs over a range of 0.045–0.45 M piperidine and 0.50–1.21 M water (ultraviolet); $K_1 = 1.9 \pm 0.5$ for seventeen runs, 0.12–1.2 M piperidine, 0.14–0.36 M piperonal, and no added water (infrared). The data are consistent with the net reaction (1). Increasing the already high pH by adding sodium methoxide did not change the equilibrium constant. This seems to eliminate the concentration of the conjugate base of Ia as an important variable. Typical results are shown in Table I.

TABLE I

EQUILIBRIUM CONCENTRATIONS[a] IN METHANOL AT 25°

[ArCHO][b]	[R₂NH]	[H₂O]	[II][c]	K
9.2×10^{-5}	0.0232	0.05	9.2×10^{-5}	2.2
10.0×10^{-5}	0.091	0.50	4.4×10^{-5}	2.4
12.3×10^{-5}	0.091	1.21	2.1×10^{-5}	2.3
4.9×10^{-5}	0.453	0.51	9.5×10^{-5}	2.2
0.0132	1.067[c]	0.139[c]	0.139	1.4
0.0336	0.134[c]	0.104[c]	0.104	2.4
0.0280	0.276[c]	0.124[c]	0.124	2.0
0.0689	0.468[c]	0.276[c]	0.276	2.4

[a] Moles per liter. [b] Measured by ultraviolet (first four runs) or infrared (last four runs). [c] Calculated assuming reaction as in eq. 1.

Rate Constants.—From four kinetic runs at room temperature and 0.03–0.8 M piperidine, $k_1 = 0.049 \pm 0.006$ l. mole^{-1} min.$^{-1}$. The piperonal concentration was 10^{-4} M so that the forward reaction was pseudo first order. Equilibrium was established in these experiments due to a small but significant amount of water in the methanol; the first-order rate constants were calculated from the initial rates and divided by the piperonal concentrations to give the second-order constant k_1. Since the twenty-sevenfold variation in piperidine concentration would lead to a change of 0.7 pH unit, it appears that the rate is insensitive to pH in the alkaline solutions studied.

The calculated value of k_{-1} referred to below, is then 0.049/2.2 or 0.022 l. mole^{-1} min.$^{-1}$ for the hydrolysis of II by dilute solutions of water in methanol.

We prepared the diamine (III) from piperonal and piperidine in benzene, according to Stewart and Hauser.[6] The rate of hydrolysis of III to piperonal was proportional to the water concentration. The second-order rate constant is 0.025 ± 0.02 l. mole^{-1} min.$^{-1}$ (nine runs, 0.025–0.25 M water). This value is so close to the calculated k_{-1} (eq. 1) as to suggest that the reaction of III with methanol to form II is rapid, followed by rate-controlling hydrolysis of II. We confirmed this by treating III with methanol. The n.m.r. spectrum of the solution showed piperonal to be absent at this stage. After one minute, methanol and piperidine were removed by evaporation. Hydrolysis and titration of the residue showed that III had lost 1 equiv. of piperidine as in eq. 2.

$$\underset{III}{ArCH(NR_2)_2} + CH_3OH \xrightarrow{fast} \underset{\underset{OCH_3}{|}}{ArCHNR_2} + R_2NH \quad (2)$$
II

Thus methanolysis appears to be the first step in the mechanism of hydrolysis of the diamine III when the water concentration is low.

Experimental

Rate and Equilibrium Studies.—Solutions of piperonal and piperidine (freshly treated to remove pyridine[7]) were prepared in reagent-grade methanol. The water content of each component was determined by Karl Fisher titration. Ultraviolet spectra were determined on a Perkin-Elmer Spectracord. Infrared measurements of the 5.9- and 6.2-μ carbonyl peaks were made on a Perkin-Elmer Model 21, using silver chloride cells.

N,N′-(3,4-Methylenedioxybenzylidene)bispiperidine (III).—This compound, prepared by the method of Stewart and Hauser,[6] was recrystallized from isooctane, to yield white crystals, m.p. 74–78°. Hydrolysis gave 97–100% of the theoretical quantity of piperonal (ultraviolet spectrum) and of piperidine (titration). Neither the infrared nor the n.m.r. spectrum showed characteristic aldehyde absorption.

Anal. Calcd. for $C_{19}H_{26}N_2O_2$: N, 9.27. Found: N, 9.08.

Acknowledgment.—We are grateful to the National Science Foundation for a research grant and to Mrs. Winnie Faye Coyne and Mr. Robert A. Pages for n.m.r. spectra.

(6) A. T. Stewart and C. R. Hauser, *J. Am. Chem. Soc.*, **77**, 1099 (1955). See also E. P. Burrows, R. F. Hutton, and W. D. Burrows, *J. Org. Chem.*, **27**, 316 (1962).

(7) T. E. Young and E. D. Amstutz, *J. Am. Chem. Soc.*, **73**, 4773 (1951)

Direct Formylation of Sydnones[1a,b]

CHARLES J. THOMAN, S. J., DENYS J. VOADEN, AND I. MOYER HUNSBERGER[1c]

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts

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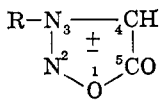
The ease with which the sydnone ring undergoes a variety of electrophilic substitution reactions led us to suggest that its reactivity was comparable to that of thiophene.[1a] We now wish to report that the direct formylation of 3-phenylsydnone (Ia) and of 3-benzylsydnone (Ib) by the Vilsmeier procedure[2] introduces the aldehyde group into the 4-position under conditions remarkably similar to those used in formylating thiophene.[3]

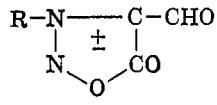
(1) (a) Sydnones. IV. Part III: J. M. Tien and I. M. Hunsberger, *J. Am. Chem. Soc.*, **83**, 178 (1961). (b) Part of this work was performed at Fordham University. Supported, in part, by grants (CY-2962 and CA, 5478) from the National Cancer Institute of the Public Health Service. (c) To whom all inquiries should be sent.

(2) A. Vilsmeier and A. Haack, *Ber.*, **60B**, 119 (1927); A. W. Weston and R. J. Michaels, *Org. Syn.*, **31**, 108 (1951).

(3) W. J. King and F. F. Nord, *J. Org. Chem.*, **13**, 635 (1948).

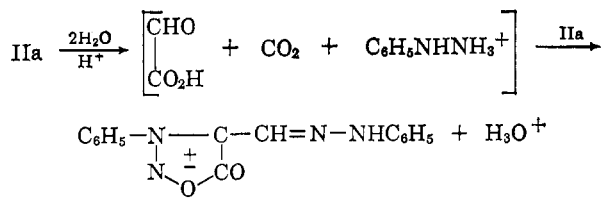


Ia, R = C_6H_5
Ib, R = $C_6H_5CH_2$



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]

RONALD KLUGER

The Chandler Laboratories, Columbia University, New York 27, New York

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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).