[CONTRIBUTION FROM THE BIOCHEMICAL RESEARCH FOUNDATION OF THE FRANKLIN INSTITUTE]

The Reaction between Hydrogen Selenide, Formaldehyde, and Secondary Amines

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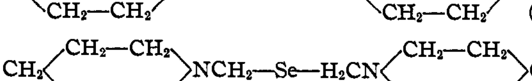
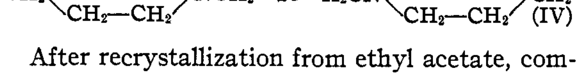
The formation of substituted *bis*-(aminomethyl) sulfides from secondary amines, formaldehyde, and hydrogen sulfide has been reported by Le Fèvre and Le Fèvre[1] and by Binz and Pence from this Laboratory.[2] The preparation of *bis*-(1-piperidylmethyl) sulfide (II) was described by the former authors; they assumed that the reaction proceeded in two stages, 1-piperidinemethanol (I) being formed in the first step

$$2C_5H_{10}NH + 2CH_2O \longrightarrow \underset{\text{(I)}}{2C_5H_{10}NCH_2OH} + H_2S \longrightarrow \underset{\text{(II)}}{C_5H_{10}NCH_2{-}S{-}H_2CNH_{10}C_5}$$

This assumption was confirmed by Binz and Pence, who prepared the same compound, as well as the morpholine analog, by treating the respective aminomethanols with hydrogen sulfide.[3]

By an extension of this reaction, analogous selenides from morpholine and piperidine have been prepared in this Laboratory. Thus 4-morpholinemethanol, or 1-piperidinemethanol, obtained by the action of formaldehyde on the corresponding amine, was found to react readily in ether solution with hydrogen selenide to yield *bis*-(4-morpholylmethyl) selenide (III), or *bis*-(1-piperidylmethyl) selenide (IV). Better yields of compound (III), however, were obtained by saturating an aqueous morpholine solution with hydrogen selenide at 0° and pouring this into cold dilute formaldehyde. Attempts to prepare similar selenides from dimethylamine and diethanolamine gave unstable oils which could not be purified.


(III)


(IV)

After recrystallization from ethyl acetate, compounds (III) and (IV) were found to be quite stable, but unlike the corresponding sulfur derivatives decomposed easily under the combined influence of solvents and air. Selenium was precipitated quantitatively when a warm dilute alcoholic solution of the morpholine selenide was aerated. Colloidal solutions of selenium, which were stable for several days, were obtained when an aqueous suspension of either selenide was treated with an equivalent amount of hydrogen peroxide.

The compounds proved to be highly toxic when injected intravenously into rats, the lethal dose being of the order of 0.012–0.017 g. per kg. of body weight.

Experimental

Hydrogen Selenide.—The hydrogen selenide used in this investigation was prepared by the action of dilute hydrochloric acid on aluminum selenide according to the procedure described by L. Moser.[4] Prior to the generation of the gas, air was removed from the generator and reaction flasks by passing a current of nitrogen through the apparatus for thirty minutes. Because of the toxicity of hydrogen selenide, all unreacted gas was absorbed in a trap containing 20% potassium hydroxide. After completion of the reaction, nitrogen was again passed through the apparatus and traces of hydrogen selenide remaining in the generator were oxidized with hydrogen peroxide.

***bis*-(4-Morpholylmethyl) Selenide (III).**—A solution of morpholine (12 cc.) in water (75 cc.) was cooled in an ice-bath and saturated with hydrogen selenide prepared from aluminum selenide (9 g.). This was poured into a cold solution of 37% formaldehyde (75 cc.) in water (150 cc.). The dense white crystalline precipitate which formed immediately was separated by filtration and recrystallized from ethyl acetate. The yield was 9.1 g. of glossy white plates, melting to a clear liquid at 136–138°. The analytical sample was dried to constant weight at 80° *in vacuo*. The selenium determination was carried out by the microprocedure of Alber and Harand.[5]

Anal. Calcd. for $C_{10}H_{20}O_2N_2Se$: N, 10.0; Se, 28.3. Found: N, 9.9; Se, 28.0.

bis-(4-Morpholylmethyl) selenide was found to be soluble in alcohol and benzene but only slightly soluble in water, decomposing rapidly in the presence of the latter, particularly when hot. When a solution of 0.7842 g. of the compound dissolved in 115 cc. of 80% ethyl alcohol at 40° was shaken in an open flask for fifteen minutes, 98.1% (0.2176 g.) of the total combined selenium precipitated as elementary selenium.

***bis*-(1-Piperidylmethyl) Selenide (IV).**—Piperidine (11.6 cc.) was added slowly with stirring to 37% formaldehyde (20 cc.) cooled in an ice-bath. Anhydrous potassium carbonate (10 g.) was then added and the mixture shaken until the solid dissolved and the solution separated into

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[1] Le Fèvre and Le Fèvre, *J. Chem. Soc.*, 1142 (1932).

[2] Binz and Pence, THIS JOURNAL, **61**, 3134 (1939).

[3] For uniformity these authors have named both sulfides as substituted 2-thiapropanes.

[4] Moser, "Reindarstellung von Gasen," Verlag Ferdinand Enke, Stuttgart, 1920, p. 75.

[5] Alber and Harand, *J. Franklin Institute*, **228**, 243–250 (1939).

two layers. The upper layer of 1-piperidinemethanol was separated and dried over anhydrous sodium sulfate.

Crude 1-piperidinemethanol (3 g.) was dissolved in dry ether (30 cc.) and treated with hydrogen selenide obtained from aluminum selenide (1 g.). A slow stream of nitrogen gas was passed through the apparatus during the reaction and continued until the ether had evaporated. The selenide remained as a white crystalline precipitate and was recrystallized by dissolving in ethyl acetate at room temperature and cooling to 0°. After drying *in vacuo* over sulfuric acid, 1.8 g. of glossy white plates, melting at 67°, were obtained.

Anal. Calcd. for $C_{12}H_{24}N_2Se$: N, 10.2; Se, 28.7. Found: N, 10.3; Se, 28.6.

bis-(1-Piperidylmethyl) selenide dissolved readily in the common organic solvents. It was only slightly soluble in water, decomposition occurring in this solvent as in the case of the morpholine analog.

Summary

1. *bis*-(4-Morpholylmethyl) and *bis*-(1-piperidylmethyl) selenides were prepared from hydrogen selenide, formaldehyde, and the corresponding secondary amines. Attempts to prepare stable selenides using dimethylamine and diethanolamine were unsuccessful.

2. Both selenides were found to be very sensitive to oxidizing agents and highly toxic when injected into rats.

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Dielectric Evidence of Molecular Rotation in the Crystals of Certain Non-aromatic Compounds*

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A molecular crystal may be considered, as a first approximation, to be a collection of rigid molecules held in a regular arrangement by rather weak intermolecular forces. In 1930 thermal evidence led Pauling to suggest that certain molecules of small moment of inertia are able to rotate in the high-temperature forms of such crystals,[1] the center of gravity of each molecule remaining at or near a point of the appropriate space lattice. He predicted that when the molecule in question is polar the dielectric constant of the high-temperature phase of the crystal should behave like that of a pure polar liquid.[2] This prediction was confirmed by measurement of hydrogen chloride, hydrogen bromide, hydrogen iodide and hydrogen sulfide, whose dielectric constants were found to drop from the high values characteristic of rotating polar molecules at transitions from one solid phase to another, instead of at the freezing points.[3,4,5] By far the greatest number of molecular crystals are organic. Dielectric, volumetric, and thermal measurements of such crystals have more recently revealed similar evidence of the rotation of organic molecules of large moment of inertia, including certain polar derivatives of camphane, cyclohexane and ethane.[6,7,8,9] Dielectric measurements have now been extended to other compounds belonging to these three classes, and show as reported below that the molecules of a surprisingly large number of organic crystals engage in rotational motion nearly or quite as freely as in the corresponding liquids.

In this communication the term "molecular rotation" will be used in the sense in which it has been generally adopted to explain the dielectric behavior of pure polar liquids. Although recent work indicates that the rotation of molecules in liquids is not free,[10] there can be no doubt that its amplitude is far greater than in most solids; *e. g.*, the dielectric constant of nitrobenzene drops from 35.8 to about 3.2 upon freezing.[11] Such a value or lower is characteristic of ordinary organic crystals, in which to a first approximation the rotational motion of the molecules is considered to be an harmonic oscillation.[12]

(*) Published with the financial assistance of an anonymous donor.

(1) Pauling, *Phys. Rev.*, **36**, 430 (1930).

(2) Debye, "Polar Molecules," Chemical Catalog Co., New York, N. Y.

(3) Cone, Denison and Kemp, THIS JOURNAL, **53**, 1278 (1931).

(4) Smyth and Hitchcock, *ibid.*, **55**, 1830 (1933).

(5) Kemp and Denison, *ibid.*, **55**, 251 (1933).

(6) Morgan, Yager and White, *ibid.* **55**, 2171 (1933).

(7) Yager and Morgan, *ibid.*, **57**, 2071 (1935).

(8) White and Morgan, *ibid.*, **57**, 2078 (1935).

(9) White and Morgan, *J. Chem. Phys.*, **5**, 655 (1937).

(10) See, *e. g.*. Debye, *Physik. Z.*, **36**, 100 (1935); *Chem. Rev.*, **19**, 171 (1936).

(11) Smyth and Hitchcock, THIS JOURNAL, **54**, 4631 (1932).

(12) For example, the lattice heat capacity calculated by Lord, Ahlberg and Andrews, *J. Chem. Phys.*, **5**, 649 (1937), for benzene approaches at room temperature the classical value of three translational and three rotational modes of harmonic motion for each molecule.