Structure of "2-Mercaptoethyldithiocarbamic Acid"

Sir:

Recently Foye, Duvall, and Mickles (1, 2) have assigned the 2-mercaptoethyldithiocarbamic acid structure to the significantly radioprotective compound derived from reaction of equimolar amounts of 2-mercaptoethylamine (MEA) hydrochloride and carbon disulfide in ammoniacal solution. The chemical and physical properties reported for this material suggested reaction had occurred at the thiol end of the MEA molecule, rather than the amino end, producing the zwitterion of 2-aminoethyltrithiocarbonic acid.

$$HSCH_2CH_2NH_3^+Cl^- + CS_2 + NH_3 \rightarrow {}^-SC(=S)SCH_2CH_2NH_3^+ + NH_4^+Cl^-$$

Repetition of Foye's procedure (1) gave a yellow solid in about 75% yield. Like his material, it was insoluble in most common solvents and unstable in air. When isolated without washing (Foye's procedure) it melted at 80–82° dec. in a capillary. Washing with substantial quantities of water or ethanol raised the melting point without appreciably diminishing the yield or changing the infrared spectrum. In a capillary our test preparation melted at 86–88° dec., but on a block the melting point was much lower, 80–82°, and decomposition was not apparent. Foye reported a melting point of 76–78°, taken on a block. From the method of preparation, solubility behavior, and melting point data we conclude that our compound was identical with that reported by Foye. Our best washed sample (analysis below) was probably somewhat purer than his material.

Anal.—Calcd. for $C_3H_7NS_3$: C, 23.51; H, 4.61; N, 9.14; S, 62.75. Found: C, 23.15; H, 4.67; N, 9.48; S, 62.77.

To obtain physical and chemical evidence bearing on the structure problem it was necessary to find solvents for the compound. The zwitterion hypothesis suggested that highly polar solvents would be most suitable, and indeed the compound was found to be very soluble in dimethyl sulfoxide and dimethylformamide.

The proton nuclear magnetic resonance spectrum, taken in deuterated dimethyl sulfoxide with tetramethylsilane as standard, showed a broad absorption band at 7.00 p.p.m., assignable to $-NH_3^+$, and a multiplet at 3.28 p.p.m., assignable to $-CH_2-$, with relative areas almost exactly 3:4. If present, —SH should have appeared as a well defined triplet at about 1.75 p.p.m., and no such absorption was noted. The n.m.r. spectrum is thus completely consistent with the 2-aminoethyltrithiocarbonic acid zwitterion structure and totally inconsistent with the 2-mercaptoethyldithiocarbamic acid structure.

A solution of the compound in dimethylformamide reacted exothermically with benzyl chloride, and the product, obtained in low yield because of isolation difficulties, was shown by analysis to be the hydrochloride of 2-aminoethyl benzyl trithiocarbonate. This reaction and product are obviously possible only if the starting material is the zwitterion of 2-aminoethyltrithiocarbonic acid.

$${}^-SC(=S)SCH_2CH_2NH_3^+ + C_6H_5CH_2Cl \rightarrow C_6H_5CH_2SC(=S)SCH_2CH_2NH_3^+ Cl^-$$

Anal.—Calcd. for $C_{10}H_{14}NS_3Cl$: C, 42.92; H, 5.04; N, 5.01; S, 34.37; Cl, 12.67. Found: C, 42.66; H, 4.95; N, 5.12; S, 34.12; Cl, 12.61.

Finally, it was reasoned that if reaction had occurred at the thiol end of MEA, it should also be possible with mercaptoamines completely substituted on the nitrogen atom; if it had taken place at the amino end, no reaction should be possible with completely substituted mercaptoamines. To test this concept, equimolar amounts of 2-dimethylaminoethanethiol hydrochloride and carbon disulfide were reacted in the presence of excess aqueous ammonia under Foye's conditions. A yellow solid, m.p. 128–129.5° dec., was obtained in about 70% yield. The physical properties of this material were very similar to those of the MEA-CS_2 product, and its elemental analysis indicated that it resulted from combination of 1 mole of mercaptoamine with 1 mole of carbon disulfide. Since this compound can be formulated *only* as the zwitterion of 2-dimethylaminoethyltrithiocarbonic acid, its ready formation under Foye's conditions lends support to the belief that the MEA-CS_2 product is similarly constituted.

$$HSCH_2CH_2NH^+(CH_3)_2Cl^- + CS_2 + NH_3 \rightarrow {}^-SC(=S)SCH_2CH_2NH^+(CH_3)_2 + NH_4^+Cl^-$$

Anal.—Calcd. for $C_5H_{11}NS_3$: C, 33.12; H, 6.12; N, 7.73; S, 53.04. Found: C, 33.37; H, 6.14; N, 7.49; S, 52.89.

From all this evidence we conclude that the

compound reported by Foye, *et al.* (1, 2), as 2-mercaptoethyldithiocarbamic acid is actually the zwitterion of 2-aminoethyltrithiocarbonic acid. This structure is consistent also with the radioprotective activity shown by the material, since the very similar zwitterions of 2-aminoethylthiosulfuric acid and related compounds also are known to possess significant activity as radioprotectants (3, 4).

(1) Foye, W. O., Duvall, R. N., and Mickles, J., THIS JOURNAL, 51, 168(1961).
(2) Foye, W. O., and Mickles, J., *J. Med. Pharm. Chem.*, 5, 846(1962).
(3) Holmberg, B., and Sorbo, B., *Nature*, 183, 832(1959).
(4) Kaluszyner, A., Czerniak, P., and Bergmann, E. G., *Radiation Res.*, 14, 23(1961).

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Book Notices

Inorganic Chemistry. By LOUIS K. SHARP. The Williams and Wilkins Co. (exclusive U. S. agent), 428 East Preston St., Baltimore 2, Md., 1962. viii + 339 pp. 15 × 23 cm. Price $8.

The author has designed this book to meet the requirements of students of pharmacy, medicine, and allied sciences by limiting the discussions of elementary chemistry and concentrating on those subjects of particular importance to medicinal and pharmaceutical chemistry students. The author has increased the treatment of inorganic compounds handled by workers engaged in research and analytical procedures, though not actually used as medicaments, which have particular methods of preparation and purification or peculiar hazards or disposal problems associated with them. The volume is divided into two parts: Part I is concerned with fundamental material and Part II contains factual material on the elements and compounds used as medicaments or as tools in analysis and research.

Elements of General and Biological Chemistry. An Introduction to the Molecular Basis of Life. By JOHN R. HOLUM. John Wiley & Sons, Inc., 440 Park Avenue South, New York 16, N. Y., 1962. ix + 470 pp. 14.5 × 23 cm. Price $5.95.

The molecular basis of life is the general theme of this textbook designed for students who, though not intending to become chemists, will profit from an awareness of the molecular basis of life in their chosen occupations. This book is not a general introductory view of general chemistry; it singles out certain processes of life at the molecular level and treats the selected topics in some depth.

Scientific Research in British Universities and Colleges 1961–62. Department of Scientific and Industrial Research, State House, High Holborn, London, W.C. 1, 1962. U. S. agents: British Information Services, 45 Rockefeller Plaza, New York 20, N. Y. xvii + 622 pp. 13 × 21.5 cm. Price $6.50.

This paperbound volume provides an extensive listing of scientific research in progress in British universities, university colleges, and associated institutions as well as research being conducted in the colleges of advanced technology in England, Wales, Scotland, and Northern Ireland during the 1961–1962 academic year. One hundred and sixteen institutions are included. Under the listing for each institution are brief, title-like descriptions of the projects under study in the various departments along with a list of workers supervising the research. The book is well indexed—a name index, a topic index, and a subject index. In all, the indexes cover about 165 pages of the volume.

Immunoassay of Hormones. Edited by G. E. W. WOLSTENHOLME and MARGARET P. CAMERON. Little, Brown and Co., 34 Beacon St., Boston 6, Mass., 1962. xii + 419 pp. 14 × 20 cm. Price $10.75.

This book is volume 14 of the Ciba Foundation Colloquia on Endocrinology covering a symposium in which 28 scientists, representing both immunologic and endocrinologic thought, participated. The symposia dealt with the complex problem of detection and assay of hormones by immunochemical means. Major topics included in the contents of the volume are: Growth hormone, Insulin, Glucagon, Thyrotropin, Corticotropin, Gonadotropins, and Prolactin. The papers presented and the general discussion which followed the papers should represent an up-to-date review of the status of work in this area. As with previous volumes, author and subject indexes are included.

The Opium Alkaloids. By DAVID GINSBURG. John Wiley & Sons, Inc., Interscience Division, 440 Park Ave. South, New York 16, N. Y., 1962. 111 pp. 15 × 23 cm. Price $6.50.

This book covers selected topics in the field of opium alkaloids and is written to be particularly useful in teaching graduate students. It gives examples of how complex structural problems and extraordinary chemical transformations are solved. In addition, it gives pertinent data regarding structural elucidation and the chemistry of the alkaloids. The book is divided into six major groupings entitled Morphine and codeine, Thebaine, The synthesis of morphine, Sterochemical considerations, The biogenesis of morphine, and Papaverine. A subject index is appended permitting ready access to the contents.