[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NEVADA]

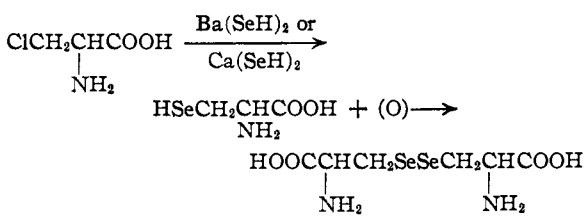
Syntheses of the Selenium Analog of *dl*-Cystine

BY LORING R. WILLIAMS AND ABRAHAM RAVVE

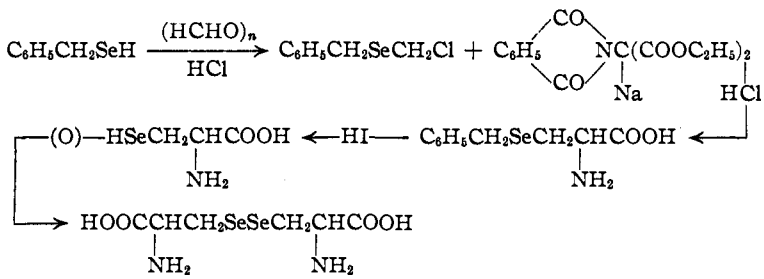
Several methods for the synthesis of the selenium analog of cystine have been previously described. Fredga[1] prepared a seleno-cystine by treating the methyl ester of α-amino-β-chloropropionic acid hydrochloride with potassium diselenide in an aqueous solution. A yellow, crystalline compound was obtained, m. p. 215° with decomposition. A 30% yield was reported. Painter[2] reported several methods for preparing the compound. Methods were sought which would avoid the prolonged use of diselenides in aqueous alkali as they are generally unstable. In these syntheses the methyl ester of α-amino-β-chloropropionic acid hydrochloride was used as the starting compound. The best yields were obtained by the use of the following method: The amino acid, β-(benzylseleno)-alanine was prepared by treating the ester with sodium benzyl selenide. The acid was reduced with sodium in liquid ammonia and the product formed by the cleavage of the benzyl group was oxidized to give the selenium analog of *dl*-cystine. Small plates (some hexagonal, some rectangular) were obtained, m. p. 222° with decomposition.

In the present investigation the selenium analog of cystine was prepared by substituting selenium analogs for the sulfur compounds used in the methods of preparation described by Abderhalden[3] and Wood and du Vigneaud[4] for the preparation of *dl*-cystine. The modifications may be summarized as follows:

(I) Abderhalden Modification.—α-Amino-β-chloropropionic acid reacted with barium hydrogen selenide or calcium hydrogen selenide and the product was oxidized.



(II) Wood and du Vigneaud Modification.—Benzyl selenol was condensed with polyoxymethylene and hydrogen chloride according to a reaction carried out by Böhme[5] in the synthesis of the ethyl homolog. Benzyl chloromethyl selenide was obtained which was condensed with sodium phthalimidomalonic ester. The resulting compound was hydrolyzed to give β-(benzylseleno)-alanine. After the benzyl group was cleaved with hydriodic acid the resulting seleno-acid was oxidized and the β,β′-diselenodialanine was separated by the procedure described by Fredga.[1]



Experimental

Method (I).—**Barium Hydrogen Selenide.**—Barium hydrogen selenide and calcium hydrogen selenide were both prepared by saturating a solution of the hydroxides with hydrogen selenide. The solutions that were formed were used as no attempts were made to isolate the compounds.

Serine.—Prepared by the method of Wood and du Vigneaud.[6]

Methyl Ester of Serine Hydrochloride.[7]—Fifteen grams of pulverized serine was suspended in 450 g. of absolute methyl alcohol and dry hydrogen chloride added until saturated. The alcohol was removed *in vacuo* and the ester remained as a white crystalline mass, m. p. 133°; yield 8.7 g., 58%.

α-Amino-β-chloropropionic Acid.—The methyl ester of α-amino-β-chloropropionic acid hydrochloride was prepared by the method of Fischer and Raske[8] and was subsequently hydrolyzed in sodium hydroxide solution. The resulting salt was carefully neutralized with hydrochloric acid to produce α-amino-β-chloropropionic acid, m. p. 160°.

β,β′-Diselenodialanine.—One gram of α-amino-β-chloropropionic acid was digested with a water solution of barium hydrogen selenide at the boiling point for two hours. The solution was filtered and just neutralized (litmus) with ammonium hydroxide. A yellow, crystalline precipitate was formed after thirty-six hours in the refrigerator, which was filtered, washed with water, alcohol and ether. The crystals were thin, yellow, hexagonal plates which turned gray upon heating to 175–180°. The crystals melted with decomposition at 213–215°; yield, 0.55 g., 20%.

The same results were obtained when calcium hydrogen selenide was used instead of barium hydrogen selenide.

Anal. Calcd. for $C_6H_{12}O_4N_2Se_2$: Se, 47.27. Found[9]: Se, 47.09.

Method (II).—**Benzyl Chloromethyl Selenide.**—Seventy-three grams of benzyl selenol[2] was placed in a flask with 25 g. of polyoxymethylene. The mixture was

(1) Fredga, *Svensk Kem. Tids.*, **48**, 160 (1936); **49**, 124 and 139 (1937).

(2) E. P. Painter, THIS JOURNAL, **69**, 229 (1947).

(3) E. Abderhalden, "Biochemisches Handlexicon," Vol. IV, 649.

(4) J. L. Wood and V. du Vigneaud, *J. Biol. Chem.*, **131**, 267 (1939).

(5) H. Böhme, *Ber.*, **69**, 1610 (1936).

(6) J. L. Wood and V. du Vigneaud, *J. Biol. Chem.*, **134**, 413 (1940).

(7) E. Fischer and W. A. Jacobs, *Ber.*, **39**, 2949 (1906).

(8) E. Fischer and K. Raske, *ibid.*, **40**, 3717 (1907).

(9) W. O. Robinson, H. C. Dudley, K. T. Williams and H. G. Byers, *Ind. Eng. Chem., Anal. Ed.*, **6**, 274 (1934).

cooled in an ice-bath and saturated with dry hydrogen chloride. To this, 30 g. of calcium chloride was added, the mixture was allowed to stand at room temperature for twenty-four hours and the solid material was removed by filtration. The liquid was a yellow oil with a very unpleasant odor. The compound was unstable at high temperatures, boiling at 158–160°, 16 mm.

β-(Benzylseleno)-alanine.—Ten grams of benzyl chloromethyl selenide was refluxed for four hours with 15 g. of sodium phthalimidomalonic ester in the presence of toluene. The toluene was removed *in vacuo*, the compound recrystallized and the white crystals were collected. The compound was unstable at high temperatures and a melting point could not be determined. Fifteen grams of the compound was suspended in 100 ml. of an ethyl alcohol and water mixture (1:1) and 10 ml. of dioxane added. Two drops of phenolphthalein solution was added and the mixture was heated to 50°. Fifteen ml. of 5 *N* sodium hydroxide solution was added dropwise with stirring at a rate to maintain a temperature of 55–60°. When all of the alkali had been added the temperature of the solution was brought up to 70°. The solution was stirred constantly while the temperature was allowed to drop to room temperature. Hydrochloric acid was added until the solution was acid to phenolphthalein and the solution was distilled to half volume *in vacuo*. Water was added to make a total volume of 150 ml. and 20 ml. of concentrated hydrochloric acid was added with the evolution of carbon dioxide. The solution was heated for one and one-half hours, more hydrochloric acid added and heating continued for two more hours. The solution was taken to dryness, the residue dissolved in water and ammonium hydroxide was added until a neutral reaction was obtained with congo red. The precipitate which consisted of β-(benzylseleno)-alanine and phthalic acid was removed by filtering, suspended in boiling ethyl alcohol and again filtered. This was repeated until all of the phthalic acid had been removed leaving the β-(benzylseleno)-alanine as a white, crystalline residue, m. p. 185°; yield, 59%.

Anal. Calcd. for $C_{10}H_{13}O_2NSe$: Se, 30.52; C, 47.0; H, 5.07; N, 5.41. Found: Se,[9] 30.03; C, 47.0; H, 5.5; N,[10] 5.42.

β,β′-Diselenodialanine.—Three and one-half grams of β-(benzylseleno)-alanine was cleaved with concentrated hydriodic acid after digesting for forty-eight hours while air was bubbled through the mixture. Yellow hexagonal plates were obtained, m. p. 215° with decomposition; yield, 0.32 g.

Anal. Calcd. for $C_6H_{12}O_4N_2Se_2$: Se, 47.27. Found: Se, 47.10.

Summary

Two syntheses of the selenium analog of cystine are described which furnish additional evidence that selenium analogs may be substituted for the sulfur compounds used in published methods for the preparation of *dl*-cystine. In the first method α-amino-β-chloropropionic acid was treated with barium hydrogen selenide or calcium hydrogen selenide and the product was oxidized to produce the selenium analog of cystine. In the second method, the Gabriel synthesis of amino acids was used to produce the selenium analog from benzyl chloromethyl selenide and sodium phthalimidomalonic ester.

(10) J. K. Parnas and R. Wagner, *Biochem. Z.*, **125**, 253 (1931).

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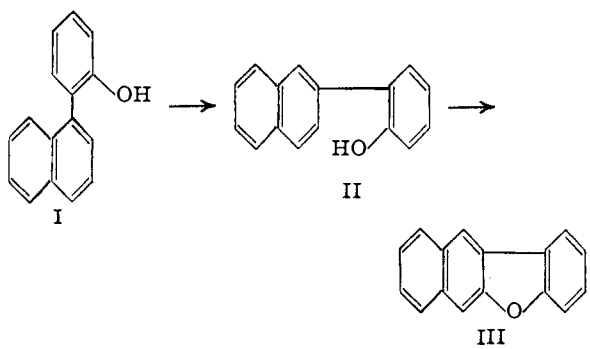
[CONTRIBUTION FROM THE U. S. BUREAU OF MINES, CENTRAL EXPERIMENT STATION]

Aromatic Cyclodehydrogenation. VII. Rearrangements in the Phenylnaphthalene Series[1]

BY MILTON ORCHIN[2] AND LESLIE REGGEL[2]

It was shown previously[3] that liquid-phase treatment of 2′-hydroxy-1-phenylnaphthalene, I, with a palladium-on-charcoal catalyst resulted in cyclodehydrogenation to 1,9-benzoxanthene. It was of interest to study the behavior of I under the vapor-phase conditions used in earlier cyclodehydrogenation studies.

Treatment of I with a chromia–alumina catalyst at 490° gave a mixture of conversion products. The first compound to be isolated from this mixture had properties and composition consistent with its formulation as the hitherto unknown 2′-hydroxy-2-phenylnaphthalene, II. It had a higher melting point than I and on treatment with diazotized *p*-nitroaniline gave a color identical with that observed for I under the same conditions. The ultraviolet absorption spectrum of II differed from that of I in the same manner as the spectrum of 2-phenylnaphthalene differed from that of 1-phenylnaphthalene.[4] Although none of this evidence fixes the position of the hydroxyl group, the isolation of compound III supports its placement in the *ortho* position, as shown in II.



I II III

A second compound isolated from the reaction mixture had properties identical with those reported[5] for benzo[b]naphtho[2,3-*d*]furan, III

(1) Published by permission of the Director, U. S. Bureau of Mines.

(2) Organic Chemist, Central Experiment Station, U. S. Bureau of Mines, Pittsburgh, Pennsylvania.

(3) Orchin, THIS JOURNAL, in press.

(4) Friedel, Orchin and Reggel, *ibid.*, **70**, 199 (1948).

(5) Robinson and Mosettig, *ibid.*, **61**, 1148 (1939).