sorbed until the insoluble sodium selenide was converted to sodium hydrogen selenide. Then 1/20 mole of I in 25 ml. of absolute alcohol was added and the flask heated to a boil. The product was hydrolyzed with hydrochloric acid in a manner similar to the preparation of III and IV. Yields of β,β'-diselenodialanine were low, never above 20%, and the products upon reprecipitation always deposited a small amount of metallic selenium.

With II the results were also discouraging. The products were never pure β,β'-diselenodialanine as the selenium content was 2 to 4% lower than the theoretical.

C. **Hydrolysis of III with Concentrated Hydriodic Acid.**—Four grams of III was refluxed seven hours with concentrated hydriodic acid. After the hydriodic acid was removed at the pump, water was added to dissolve the residue and the aqueous solution extracted with ether. Upon neutralization unchanged III, 1.7 g. was obtained. The solution was then aerated, one volume of alcohol added, and 0.6 g. of impure β,β'-diselenodialanine precipitated.

Selenium was determined by oxidation in the Parr bomb[20] using potassium chlorate, nitrogen by a micro-Kjeldahl method,[21] and halogen gravimetrically after reduction with sodium in alcohol.

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Summary

By treating the hydrochloride of methyl α-amino-β-chloropropionate with sodium benzyl selenide the amino acid β-(benzylseleno)-alanine was prepared. When reduced with sodium in liquid ammonia the benzyl group cleaved to give, after air oxidation, the selenium analog of cystine.

(20) Shaw and Reid, THIS JOURNAL, **49**, 2330 (1927).

(21) Ma and Zuazaga, *Ind. Eng. Chem., Anal. Ed.*, **14**, 280 (1942).

FARGO, NORTH DAKOTA RECEIVED AUGUST 30, 1946

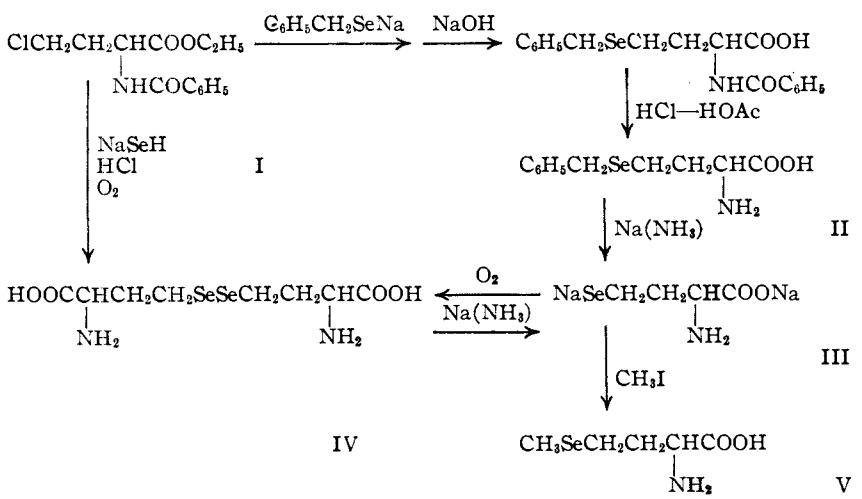
[CONTRIBUTION FROM DEPARTMENT OF AGRICULTURAL CHEMISTRY, NORTH DAKOTA AGRICULTURAL COLLEGE AND EXPERIMENT STATION]

A Synthesis of Selenium Analogs of *dl*-Methionine and *dl*-Homocystine[1,1a]

BY EDGAR PAGE PAINTER

The objective of synthesizing amino acids with selenium in place of sulfur has been stated in the accompanying paper.[2] Cystine (or cysteine) and methionine carry nearly all of the sulfur in cereal proteins but the amino acid homocystine, although it has never been identified in plants, is of interest because it can take care of animals' requirement for a sulfur containing amino acid. The selenium analog of *dl*-homocystine was therefore prepared as well as the selenium analog of *dl*-methionine.

The most direct synthesis appeared to be by alkylation of β-chloro-ethyl methyl selenide with a compound like acetamido malonic ester. This was abandoned in favor of alkylation with β-chloroethyl benzyl selenide similar to the syntheses of S-benzylhomocysteine by Patterson and du Vigneaud,[3] because benzyl selenomercaptan is far easier to prepare and handle than methyl selenomercaptan. Compounds of the type $RSeCH_2CH_2X$ were prepared, where X = OH, but all attempts to prepare the same compound where X = halogen failed.



Selenium was successfully introduced into an amino acid in the γ position by use of the compound ethyl α-benzamido-γ-chlorobutyrate (I) first prepared by Hill and Robson.[4] When I reacted with sodium hydrogen selenide and the product was hydrolyzed a poor yield of the selenium analog of homocystine (IV)

(1) Presented at the Atlantic City meeting of the American Chemical Society, April, 1946.

(1a) Published by permission of the Director, North Dakota Agricultural Experiment Station.

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

(3) Patterson and du Vigneaud, *J. Biol. Chem.*, **111**, 393 (1935).

(4) Hill and Robson, *Biochem. J.*, **30**, 248 (1936).

was obtained. The synthesis giving quite satisfactory yields was very similar to that used by Tarver and Schmidt[5] in their preparation of S-benzylhomocysteine by substituting benzyl selenomercaptan for benzylmercaptan. Reduction and methylation of the compound was carried out similar to the procedure of du Vigneaud and Patterson.[6] The reaction product of sodium benzyl selenide with I in absolute alcohol was first saponified with sodium hydroxide and α-benzamido-γ-(benzylseleno)-butyric acid isolated. The benzamido derivative was hydrolyzed with a mixture of acetic and hydrochloric acids to give II. Reduction of II with sodium in liquid ammonia goes smoothly at the boiling point of ammonia so that IV is obtained after oxidation with atmospheric oxygen. By addition of methyl iodide after reduction of II or IV with sodium in liquid ammonia the selenium analog of methionine (V) is obtained.

Experimental

α-Amino-γ-phenyl-*n*-butyric Acid.—This compound was prepared by alkylation of β-bromoethyl phenyl ether (b. p. 128° at 20 mm.)[7] with benzamidomalonic ester or with acetamidomalonic ester; one-half mole quantities of the ester were dissolved in 1000 ml. of absolute ethyl alcohol (distilled after refluxing with sodium and ethyl succinate) containing an equivalent of sodium and β-bromoethyl phenyl ether added in 10% excess. The solution was refluxed for six hours and, after cooling, the salt filtered out. When benzamidomalonic ester was alkylated, the alcohol was removed by warming on the steam-bath under a water pump vacuum, 700 ml. of 1 to 1 hydrochloric acid added, heated to boiling and glacial acetic acid added in sufficient amount to dissolve the ester at the boiling point. The solution was refluxed forty hours to hydrolyze the ester. The solution was removed by warming *in vacuo* (water pump) to a thick sirup, 500 ml. of water added and the benzoic acid extracted with ether. The aqueous solution was treated with decolorizing carbon, filtered and sodium hydroxide added to a *p*H of 5. After standing overnight in the refrigerator, the compound was filtered out and washed. By saturation of the filtrate with sodium chloride, a small amount of additional compound was obtained. The amino acid was recrystallized by dissolving in sodium hydroxide, heated to boiling with decolorizing carbon, filtered, and crystallized by addition of hydrochloric acid.

When acetamidomalonic ester was alkylated, the ester was first saponified by refluxing with 500 ml. of 10% sodium hydroxide for two hours. The solution was then concentrated *in vacuo* to remove the alcohol, 400 ml. of concentrated hydrochloric acid added and refluxed twenty hours. The product was then worked up in the same way as when the benzamido malonic ester was used. The best yields were 65%.

Anal. Calcd. for $C_{10}H_{13}O_3N$: N, 7.18. Found: N, 7.03.

α-Amino-γ-butyrolactone Hydrobromide.—One hundred grams of α-amino-γ-phenoxy-*n*-butyric acid was refluxed seven hours in 1000 ml. of 40% hydrobromic acid and the lactone hydrobromide crystallized by the method of Fischer and Blumenthal.[8] The yield was 71 g. (76%) of a compound melting at 216°.

Anal. Calcd. for $C_4H_8O_2NBr$: N, 7.70; Br, 43.90. Found: N, 7.65; Br, 43.7.

α-Benzamido-γ-butyrolactone.—Seventy-three grams (0.4 mole) of α-amino-γ-butyrolactone hydrobromide was dissolved in 600 ml. of water containing 0.8 mole of sodium hydroxide, placed in a 3-necked flask fitted with a stirrer and 800 ml. of water containing 2.4 moles of sodium hydroxide and 169 g. (1.2 moles) of benzoyl chloride slowly added. The flask was immersed in an ice-bath and the sodium hydroxide and benzoyl chloride added at a rate to keep the solution alkaline. After the last of the benzoyl chloride was added (about three hours), the ice-bath was removed and the solution stirred five hours longer. The solution was transferred to a large beaker, layered with 500 ml. of ether and concentrated hydrochloric acid added dropwise until no more benzoic acid precipitated in the aqueous layer. The benzoic acid was extracted with ether and the volume of the aqueous solution reduced *in vacuo* to about 500 ml. After standing overnight in the refrigerator, the crystals were filtered out and washed with cold water. The product was a mixture of α-benzamido-γ-butyrolactone and α-benzamido-γ-hydroxy-*n*-butyric acid. The hydroxy compound is not always converted to the lactone when heated to boiling in aqueous solution. The best method found was to dissolve in ethyl acetate, add 2–3 drops of concentrated sulfuric acid and heat to boiling on the steam-bath. Evaporate the ethyl acetate until a large crop of crystals form, treat with a little anhydrous sodium sulfate, dissolve in the minimum amount of chloroform, then crystallize by addition of 7 or 8 volumes of petroleum ether (b. p. 70–90°). A small amount of compound was recovered by extracting the aqueous solution with ethyl acetate. The yield of a compound melting at 140° was 50 g., 61%.

Anal. Calcd. for $C_{11}H_{11}O_3N$: N, 6.83. Found: N, 6.84.

Ethyl α-Benzamido-γ-chlorobutyrate I.—Fifty-five grams of α-benzamido-γ-butyrolactone was suspended in 900 ml. of absolute alcohol and saturated with dry hydrogen chloride. The alcohol was removed at reduced pressure with the air passing through the inlet tube dried by concentrated sulfuric acid. This was repeated twice using 600 ml. of alcohol. The compound (I) was dissolved in boiling ether and the ether allowed to evaporate. A small residue insoluble in ether remained. After the ether evaporated the compound was dissolved in 200 ml. of hot dioxane and precipitated by addition of 8 volumes of ice and water. Fifty-nine and five-tenths grams of a product melting at 67–68° was obtained. Upon crystallization from boiling ligroin (70–90°), 57 g., 67% melting at 71°, was obtained.

Anal. Calcd. for $C_{13}H_{16}O_3NCl$: N, 5.19; Cl, 13.15. Found: N, 5.12; Cl, 12.9.

When first prepared,[4] the melting point was reported as 45°. Later Tarver and Schmidt[5] reported 65°.

α-Amino-γ-(benzylseleno)-butyric Acid, II.—A current of nitrogen to displace the air was passed through 100 ml. of absolute alcohol, 17.1 g. (0.1 mole) of benzylselenomercaptan[2] added and 3.7 g. of potassium (or an equivalent of sodium) was added in small pieces. After the potassium dissolved, 13.5 g. (0.05 mole) of I in 100 ml. of alcohol was added and the solution refluxed for one-half hour. Forty ml. of 2 *N* sodium hydroxide was added and refluxed for one-half hour. After aeration, the alcohol was removed *in vacuo*, 300 ml. of water added and the dibenzyl diselenide extracted with benzene. The benzamido derivative of II was then precipitated by acidifying with hydrochloric acid. The compound was reprecipitated twice by dissolving in about 300 ml. of sodium hydroxide solution and addition of hydrochloric acid. Before precipitating the third time the solution was extracted with toluene, warmed with decolorizing carbon and filtered. The best yields of a compound melting at 139–140° containing 3.60% nitrogen were about 85%. The compound was dissolved in boiling toluene, filtered and crystallized by cooling to near 0°, m. p. 142–143°.

Anal. Calcd. for $C_{18}H_{19}O_3NSe$: N, 3.72; Se, 20.98. Found: N, 3.68; Se, 20.7.

Five grams of α-benzamido-γ-(benzylseleno)-butyric acid was dissolved in 30 ml. of glacial acetic acid and 50 ml. of concentrated hydrochloric acid added. The solu-

(5) Tarver and Schmidt, *J. Biol. Chem.*, **146**, 69 (1942).

(6) du Vigneaud and Patterson, *ibid.*, **109**, 97 (1935).

(7) "Organic Syntheses," **9**, 72 (1929).

(8) Fischer and Blumenthal, *Ber.*, **40**, 106 (1907).

tion was refluxed two hours, 30 ml. of water added, and the solution refluxed two more hours. After hydrolysis the solvent was removed at the vacuum of the water pump. The product was dissolved in 200 ml. of water with the aid of a few drops of hydrochloric acid, the benzoic acid extracted with benzene and the compound precipitated by addition of dilute sodium hydroxide to a *p*H of 5.5. The product was dissolved in 200 ml. of dilute sodium hydroxide, filtered, and precipitated by addition of hydrochloric acid to *p*H 5.5. Yields from the benzamido derivative were 80 to 90%. The compound crystallized as small, predominantly hexagonal plates, melting with decomposition at 250°.

Anal. Calcd. for $C_{11}H_{15}O_2NSe$: N, 5.15; Se, 29.01. Found: N, 5.13; Se, 28.8.

α,α'-Diamino-γ,γ'-diseleno-dibutyric Acid, IV. A. By Reduction with Sodium in Liquid Ammonia.—II was reduced with sodium in liquid ammonia by following the procedure used for the reduction of β-(benzylseleno)-alanine[2] to obtain the diselenide. The recovery of IV is about 90% of the theoretical. Less selenium is cleaved in the reduction and subsequent aeration than in the preparation of the selenium analog of cystine. The compound crystallized as sheets or plates mostly as parallelograms decomposing at 260°.

Anal. Calcd. for $C_8H_{16}O_4N_2Se_2$: N, 7.74; Se, 43.61. Found: N, 7.71; Se, 43.3.

B. By the Reaction of I with Sodium Hydrogen Selenide.—When I reacted with sodium hydrogen selenide by a procedure similar to that described for the preparation of the selenium analog of cystine from methyl α-amino-β-chloropropionate hydrochloride,[2] the yield of IV was less than 20%. Apparently yields are low because prolonged heating in acid solution is necessary to hydrolyze the ester and benzoyl group.

α-Amino-γ-(methylseleno)-butyric Acid, V.—To 4 g. of IV in about 150 ml. of liquid ammonia, small pieces of sodium were added until the blue color persisted for ten minutes, then 4 ml. of methyl iodide was added. The last of the ammonia was driven off by warming on the steam-bath. Ten ml. of 10% sodium hydroxide was added and the solution heated to boiling. The volume was increased to about 150 ml. and the solution neutralized (*p*H of 6) with hydriodic acid. A small amount of free iodine was present (by starch test) so the solution was extracted three times with ether. The volume was reduced to about 75 ml., and 1.5 volumes of methyl alcohol added. After cooling overnight in the refrigerator 2.6 g. of the selenium analog of methionine was obtained. The filtrate was evaporated to 20 ml. and an additional 1.1 g. (6.88% N) obtained. The amino acid can be recrystallized by dissolving in hot water and adding one volume of methyl alcohol. Yields of 80% have been obtained from IV. With II yields have been slightly less. The compound crystallizes in transparent, hexagonal sheets or plates. It is pure white and has a metallic luster. It melted with decomposition at 265°.

Anal. Calcd. for $C_5H_{11}O_2NSe$: N, 7.14; Se, 40.26. Found: N, 7.09; Se, 39.8.

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Summary

The selenium analog of S-benzylhomocysteine has been prepared and this compound has been reduced with sodium in liquid ammonia to give, after oxidation in air, the selenium analog of homocystine (α,α'-diamino-γ,γ'-diseleno-dibutyric acid). When methyl iodide is added to the reduced form in liquid ammonia, the selenium analog of methionine (α-amino-γ-(methylseleno)-butyric acid) is formed.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF FURMAN UNIVERSITY]

Photochemical Bromination of Fluorene[1]

BY JOHN R. SAMPEY AND E. EMMET REID

Introduction

The photochemical bromination of fluorene has not been studied. The similarity of the 9-bromofluorene to a side-chain bromo compound suggested that it might be prepared by the photochemical bromination of fluorene instead of *via* the fluorenol.[1a] We have found this to be the case.

Experimental

9-Bromofluorene.—To a solution of 8.3 g. of fluorene in 100 ml. of carbon tetrachloride in a 20-cm. evaporating dish under a strong mercury arc, or in direct sunlight,[2] 50 ml. of a molar solution of bromine in carbon tetrachloride was added dropwise, the rate of addition being adjusted to the disappearance of the brown color. The solvent is evaporated under an air blast, and the residue is recrystallized from hot 78% alcohol; yield 60–64% white needles of 9-bromofluorene, melting 104–105°.

Alcohol of 78% strength was found to be the best solvent for the separation of the 9-bromoisomer from the other products of bromination. The compound is soluble in hot carbon tetrachloride and hot petroleum ether, and fairly insoluble in the cold solvents, but neither solvent gives as good separation from the impurities as does alcohol. By working fast with the alcoholic solution, there was little apparent formation of the ether.

The bromination takes place with equal ease in carbon disulfide (sulfur free), care being taken to keep the inflammable vapors away from the mercury arc. There is less discoloration when the bromination is carried out in a thin-walled Erlenmeyer flask under anhydrous conditions; the flask is equipped with a dropping funnel and a calcium chloride tube; the solution is agitated a few mm. above the mercury arc, the quantity of solvent being cut to 40–50 ml. in the anhydrous bromination.

Hydrolysis of 9-Bromofluorene.—Refluxing 1.0 g. of 9-bromofluorene with 125 ml. of water for 30 minutes, and titrating for bromide ion, showed better than 90% hydrolysis.

Formation of Tetraphenylene-ethylene.—A solution of 4.5 g. of 9-bromofluorene, dissolved in 25 ml. acetone, is

(1) Presented before the Organic Division of the American Chemical Society at the 109th meeting, April 10, 1946, Atlantic City, N. J.

(1a) W. E. Bachmann and J. C. Sheehan, THIS JOURNAL, **62**, 2687–2690 (1940).

(2) The 2-bromofluorene is formed slowly even in the absence of illumination. *Cf.* C. Courtot and C. Vignati, *Bull. soc. chim.*, **41**, 58–64 (1927), and P. C. Clarkson and M. Gomberg, THIS JOURNAL, **52**, 2886 (1930).