[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUQUESNE UNIVERSITY]

A Synthesis of S-Benzyl-*dl*-cysteine

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Wood and du Vigneaud[1] previously have synthesized S-benzyl-*dl*-cysteine from benzylthiolmethyl chloride and sodiophthalimidomalonic ester and subsequently[2] have converted it into *dl*-cystine.

In view of the use of S-benzyl-*dl*-cysteine as an intermediate in the preparation of *dl*-cystine and continued interest[3] in the synthesis of *dl*-cystine, we have synthesized S-benzyl-*dl*-cysteine from benzylmercaptoacetaldehyde by a modified Strecker synthesis.

Benzylmercaptoacetaldehyde has previously been found by Herbst[4] among the products of a reaction between S-benzyl-*l*-cysteine and pyruvic acid and was characterized by several derivatives. Fromm and Landmann[5] mention it as one of the decomposition products obtained when 1,2-dibenzylmercaptoethylene is treated with sulfuric and acetic acids. For our purpose, we have synthesized benzylmercaptoacetaldehyde by treating the sodium salt of benzylmercaptan with the dimethyl acetal of bromoacetaldehyde and hydrolyzing the obtained dimethyl acetal of benzylmercaptoacetaldehyde.

Treatment of benzylmercaptoacetaldehyde with sodium bisulfite and sodium cyanide yielded β-benzylmercapto-α-hydroxypropionitrile and this on treatment with gaseous ammonia at 100° was converted to β-benzylmercapto-α-aminopropionitrile. Hydrolysis of the latter with hydrochloric acid, followed by neutralization, yielded S-benzyl-*dl*-cysteine.

Application of the Bücherer hydantoin synthesis to benzylmercaptoacetaldehyde yielded 5-benzylmercaptomethylhydantoin. Preliminary attempts at hydrolysis of this hydantoin resulted in decomposition without yielding S-benzyl-*dl* cysteine and so no further attempts were made at obtaining S-benzyl-*dl*-cysteine by this method.

Experimental

Benzylmercaptoacetaldehyde Dimethyl Acetal.—Under reflux, 23 g. (1 gram-atom) of sodium was added slowly to 500 ml. of absolute ethanol. After solution of the sodium, 124 g. (1 mole) of benzyl mercaptan[6] was slowly added with stirring. The reaction mixture was then cooled and to it, with stirring, 169 g. (1 mole) of the dimethyl acetal of bromoacetaldehyde[7] was added over a period of ten minutes. The reaction mixture was then heated gently, the reaction proceeding vigorously at the start, and then refluxed for three hours. After cooling and filtering free of sodium bromide, 250–300 ml. of alcohol was removed by distillation. The concentrated solution was treated with 500 ml. of water and thoroughly extracted with ether. The combined ether extracts were washed once with water and dried over anhydrous sodium sulfate. After evaporation of the ether, the product was distilled at 140–141° (6 mm.); yield, 148 g. (70%) of a colorless liquid; d^{22}_4 1.0757; n^{22}_D 1.5303.

Anal. Calcd. for $C_{11}H_{16}O_2S$: C, 62.28; H, 7.55. Found: C, 62.55; H, 7.72.

Benzylmercaptoacetaldehyde.—One hundred ten grams (0.52 mole) of the dimethylacetal of benzylmercaptoacetaldehyde was heated with 350 ml. of 1 *N* sulfuric acid for one and one-half hours under reflux and with stirring. The reaction mixture was then cooled and extracted with ether. The ether extract was washed once with water and dried over anhydrous sodium sulfate. After evaporation of the ether, the product was distilled at 125.5–127° (6 mm.); yield, 65 g. (75%) of a colorless liquid; d^{22}_4 1.1105; n^{22}_D 1.5699.

Anal. Calcd. for $C_9H_{10}OS$: S, 19.28. Found: S, 19.01.

The aldehyde forms a crystalline bisulfite derivative and a crystalline yellow 2,4-dinitrophenylhydrazone, melting at 155–156°.[8] The semicarbazone, prepared in the usual fashion, consists of small white needles, melting at 105–107°.[9]

Anal. Calcd. for $C_{10}H_{13}N_3OS$: C, 53.81; H, 5.82; N, 18.82; S, 14.35. Found: C, 53.88; H, 5.47; N, 18.98; S, 14.26.

β-Benzylmercapto-α-hydroxypropionitrile.—Thirty-five grams (0.21 mole) of the aldehyde was added slowly and with shaking to a solution of 23 g. (0.22 mole) of sodium bisulfite in 75 ml. of water. After shaking for ten minutes, a pasty mass of the bisulfite derivative was obtained. To this was added, portionwise and with shaking, a solution of 11 g. (0.23 mole) of sodium cyanide in 30 ml. of water. Shaking was continued for thirty minutes after addition of the final portion of cyanide solution. The oily cyanohydrin was extracted four times with 75-ml. portions of benzene. The combined benzene extracts were washed once with a small amount of bisulfite solution, dried over anhydrous sodium sulfate and then vacuum concentrated. The crude cyanohydrin was a colorless oil which slowly turned yellow; yield 35.5 g. (86% of theory). No attempt was made at further purification, the crude cyanohydrin being used as such.

β-Benzylmercapto-α-aminopropionitrile.—Essentially the method of Pierson, *et al.*,[10] was used to prepare the aminonitrile. Thirty-five and one-half grams of crude β-benzylmercapto-α-hydroxypropionitrile was placed in a small flask arranged in a distillation setup. The flask was heated to 100° and anhydrous ammonia was bubbled through for one-half hour, the water distilling as formed. After cooling, the reaction mixture was dissolved in 100 ml. of benzene and extracted with 50-ml. portions of 10% hydrochloric acid. The combined extracts were made alkaline with concentrated ammonia and extracted three times with 75-ml. portions of benzene. The benzene extracts were combined and washed once with water, then dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude aminonitrile (23.0 g., 65%) was a yellowish oil. No attempt was made at further purification.

S-Benzyl-*dl*-cysteine.—Twenty-three grams of the crude aminonitrile was heated, under reflux, at 100° with 100 ml. of concentrated hydrochloric acid for four hours and then the reaction mixture was vacuum concentrated

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(1) Wood and du Vigneaud, *J. Biol. Chem.*, **130**, 109 (1939).

(2) Wood and du Vigneaud, *ibid.*, **131**, 267 (1939).

(3) Farlow, *ibid.*, **176**, 71 (1948).

(4) Herbst, THIS JOURNAL, **58**, 2239 (1936).

(5) Fromm and Landmann, *Ber.*, **56B**, 2290 (1923).

(6) Marker, *Ann.*, **136**, 75 (1865).

(7) Bedoukian, THIS JOURNAL, **66**, 651 (1944).

(8) Herbst[4] reports 156–157° as the melting point of this derivative.

(9) All melting points are uncorrected.

(10) Pierson, Giella and Tishler, THIS JOURNAL, **70**, 1450 (1948).

to 50 ml. To this was added 75 ml. of water and concentrated ammonia to alkalinity, followed by acetic acid to *p*H 4.5. The S-benzyl-*dl*-cysteine was filtered off and partially purified by suspending in 70 ml. of water followed by the addition of sufficient 10% sodium hydroxide to cause solution. The brown solution was filtered free of gummy material and the product was precipitated with acetic acid. Repetition of this treatment followed by a crystallization from water yielded 17 g. (67.5% of theory) of S-benzyl-*dl*-cysteine, melting at 209-211°. Another recrystallization gave material melting at 213-214°, no depression of the melting point with synthetic S-benzyl-*l*-cysteine, melting 213-214°, prepared according to du Vigneaud, *et al.*[11]

Anal. Calcd. for $C_{10}H_{13}NO_2S$: N, 6.64; S, 15.18; neut. equiv., 211. Found: N, 6.64; S, 15.26; neut. equiv.,[12] 213.

5-Benzylmercaptomethylhydantoin.—The procedure used was similar to that of Pierson, *et al.*,[10] for the preparation of 5-(β-methylmercaptoethyl)-hydantoin.

Twenty grams (0.12 mole) of benzylmercaptoacetaldehyde, 57 g. (0.59 mole) of ammonium carbonate, 12.7 g. (0.26 mole) of sodium cyanide and 340 ml. of 50% ethyl alcohol were heated under reflux, and with stirring, at 40-45° for four hours. The reaction mixture was cooled and filtered and the filter cake was washed with a small amount of 95% alcohol. The filtrate and washings were combined and concentrated *in vacuo* to one-half volume. The concentrated solution was heated under reflux to 100° and then 25 ml. of concentrated hydrochloric acid was added. The reaction mixture was allowed to remain at this temperature for ten minutes. It was then cooled and the hydantoin filtered off and recrystallized from hot water to yield 20 g. (70% of theory) of 5-benzylmercaptomethylhydantoin, white needles, m. p. 118-119°.

For purposes of comparison by mixed melting points, the *levo* 5-benzylmercaptomethylhydantoin, melting at 129-130°, was prepared from S-benzyl-*l*-cysteine and was racemized with dilute aqueous sodium hydroxide solution. The *dl*-form prepared in this fashion melted at 118-119° and showed no depression of the melting point on admixture with the hydantoin prepared from benzylmercaptoacetaldehyde.

Preliminary attempts at hydrolysis of 5-benzylmercaptomethylhydantoin with alkali or ammonium sulfide or acid resulted in decomposition without yielding S-benzyl-*dl*-cysteine.

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.90; H, 5.12; N, 11.88; S, 13.58. Found: C, 56.10; H, 4.94; N, 11.87; S, 13.32.

Summary

Benzylmercaptoacetaldehyde has been synthesized and used as a starting material for the preparation of S-benzyl-*dl*-cysteine by a modified Strecker reaction.

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[11] du Vigneaud, Audrieth and Loring, *ibid.*, **52**, 4500 (1930).

[12] The determination was carried out by a modified formol titration. The compound was dissolved in excess standard sodium hydroxide in the presence of formaldehyde and the excess sodium hydroxide was titrated with standard acid.

NOTES

Carbonyl-cyanyls of Nickel(0)

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The compound $K_4Ni(CN)_4$, discovered by Eastes and Burgess,[2] has been interpreted as an analog of nickel carbonyl, in that the cyanide ion is isoelectronic with carbon monoxide, and could replace it in complex compounds.[3] Such cyanide complexes, having the central atom in oxidation state zero, have been designated as "cyanyls" by Ormont.[4] In a search for chemical reality in this analogy, we have carried on reactions in which cyanide ion displaces carbon monoxide from nickel carbonyl, and others in which carbon monoxide displaces cyanide ion from $K_4Ni(CN)_4$. Under the conditions of the experiments, neither reaction could be brought to completion, and the products appeared to be mixtures of the intermediate compounds $KNiCN(CO)_3$, $K_2Ni(CN)_2(CO)_2$, and possibly $K_3Ni(CN)_3CO$.

Reaction of $Ni(CO)_4$ with KCN.—The first experiments showed that a yellow to orange solid (containing no dark material) is formed with the evolution of carbon monoxide when nickel carbonyl is allowed to react with solid potassium cyanide at ordinary temperatures. The solid product proved to be soluble in methyl cyanide, which then was adopted as the reaction medium. The solubility of potassium cyanide (0.03%) aided the reaction but was too low to interfere with the isolation of the product.

The apparatus employed for the reaction is shown in Fig. 1. Potassium cyanide was placed at A and dried by evacuation of the apparatus. Then methyl cyanide and nickel carbonyl were distilled in from the high-vacuum system with A at −196°, and warmed to room temperature. After three days, the carbon monoxide was removed through a trap at −196°, collected by a Töpler pump and measured. With the methyl cyanide solution at −196°, the lower part of the apparatus was sealed off *in vacuo* at D. Now the solution was melted and decanted into the weighed tubes designated as 1, 2 and 3. Next the solvent and any excess nickel carbonyl were distilled off through a vacuum tube-opener[5] operating at F, with the sample tubes 1, 2 and 3 in ice-salt to avoid decomposition of the solid product. Finally at half-hour intervals, the sample tubes were sealed off at E (leaving a tip suitable for the tube-opener) and the contents subjected to analysis. The sample-weight (usually about 0.3 g.) was determined as the gain in weight of the sealed tube and joint-socket.

The first step of the analysis was decomposition *in vacuo* at 200°, with collection and measurement of carbon

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[1] Abstracted from a thesis presented by June Chase Dayton to the Graduate School of the University of Southern California in partial fulfillment of the requirements for the degree of Master of Science.

[2] J. W. Eastes and W. M. Burgess, THIS JOURNAL, **64**, 1189 (1942).

[3] J. J. Burbage and W. C. Fernelius, *ibid.*, **65**, 1484 (1943).

[4] Ormont, *Acta Physicochim., U. R. S. S.*, **19**, 571 (1944).

[5] A. Stock, *Ber.*, **51**, 985 (1918).