

Notes

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On the Ethanolic Hydrogen Chloride Catalyzed Decarbobenzoylation of *N*-Carbobenzoxy-DL-methionylglycine Ethyl Ester¹

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In this communication the results of experimental work on decarbobenzoylation of *N*-cbo-DL-methionylglycine ethyl ester^{3,4} with ethanolic hydrogen chloride are presented. In keeping with the reaction intermediates and mechanism previously proposed^{5,6} for acid-catalyzed decarbobenzoylations, both *S*-benzyl-DL-homocysteinylglycine ethyl ester and DL-methionylglycine ethyl ester benzyl sulfonium chloride were found as products.

Decarbobenzoylations were carried out by either refluxing the methionine derivative with ethanolic hydrogen chloride⁷ or by heating the derivative with ethanolic hydrogen chloride in a sealed tube. In both cases, it was necessary to find conditions under which decarbobenzoylation proceeded but which precluded ethanolysis of the peptide bond. Limitation of the reflux period to 30 minutes prevented appreciable peptide bond breaking while a variety of conditions (Table I and Experimental text) under which the peptide bond was stable were found for the sealed tube reactions. In general, at a given temperature, the use of high concentrations of hydrogen chloride resulted in both decarbobenzoylation and peptide bond breaking while lower concentrations resulted only in decarbobenzoylation. Our results with *N*-cbo-methionylglycine ethyl ester indicate that the peptide bond of this compound is less stable to refluxing ethanolic hydrogen chloride than that of *N*-cbo-*S*-benzyl-L-cysteinylglycine ethyl

ester, the peptide bond of the latter compound being stable to a two-hour reflux period during which time decarbobenzoylation is effected.⁸

TABLE I

EFFECTS OF ACIDITY ON DECARBOBENZOXYLATION OF *N*-CBO-DL-METHIONYLGLYCINE ETHYL ESTER

11.3 <i>N</i> HCl, 45°		8.00 <i>N</i> HCl, 45°		2.17 <i>N</i> HCl, 77°	
Time, min.	%NH ₂ -N ^a	Time, min.	%NH ₂ -N	Time, min.	%NH ₂ -N
15	1.98	15	1.20	60	1.83
30	2.56	60	1.43	120	2.55
60	4.94	120	2.23	180	3.56
120	5.56	240	3.58	360	3.51
240	5.79			540	3.48

^a Calculated for DL-methionylglycine ethyl ester benzyl sulfonium chloride, 3.53%.

From decarbobenzoylations carried out under reflux, *S*-benzyl-DL-homocysteinylglycine ethyl ester was isolated in relatively low yields⁹ and from sealed tubes experiments, both *S*-benzyl-DL-homocysteinylglycine and DL-methionylglycine ethyl ester benzyl sulfonium chloride^{10,11} were isolated by suitable treatment of the reaction mixture. In one particular experiment, *S*-benzyl-DL-homocysteinylglycine ethyl ester was not isolated following the usual reflux period and isolation procedure. In its place a compound, as yet unidentified, was found.

The replacement of *S*-methyl by *S*-benzyl observed by us also occurs⁶ on decarbobenzoylation of *N*-cbo-DL-methionylglycine with hydrogen bromide in nitromethane. However, decarbobenzoylation with ethanolic hydrogen chloride also gives rise to a sulfonium derivative while a benzyl sulfonium salt apparently does not form⁶ on decarbobenzoylation of *N*-cbo-DL-methionylglycine with hydrogen bromide in nitromethane. If a benzyl sulfonium derivative is intermediate, in both instances, in the replacement of *S*-methyl by *S*-benzyl, it would seem that the above observed difference is due to differences in stability of the benzyl sulfonium salts in the two reaction media. It might be mentioned here that in aqueous solu-

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(3) Cbc- will be used to designate the carbobenzoyloxy group.

(4) Prepared from *N*-cbo-DL-methionine and ethyl glycinate by the mixed anhydride procedure of J. R. Vaughn, Jr., and R. L. Osato, *J. Am. Chem. Soc.*, **73**, 5553 (1951).

(5) D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

(6) N. F. Albertson and F. C. McKay, *J. Am. Chem. Soc.*, **75**, 5323 (1953).

(7) Absolute ethanol saturated at room temperature with anhydrous hydrogen chloride. During the reflux period hydrogen chloride is evolved.

(8) S. Goldschmidt and C. Jutz, *Ber.*, **86**, 1116 (1953).

(9) The isolation of DL-methionylglycine ethyl ester benzyl sulfonium chloride was not attempted, albeit chloride to amino nitrogen ratios on the reaction mixture were high, indicating sulfonium salt formation.

(10) As the chloroplatinate.

(11) Under similar conditions, *N*-cbo-DL-methionine ethyl ester yielded mainly DL-methionine ethyl ester benzyl sulfonium chloride.

tion the stability of methionine methyl sulfonium salts depends upon the acid present¹² and that replacement of *S*-methyl with *S*-benzyl has been noted¹³ on refluxing methionine with benzyl chloride and hydrochloric acid.

EXPERIMENTAL

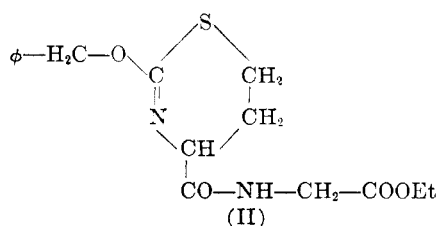
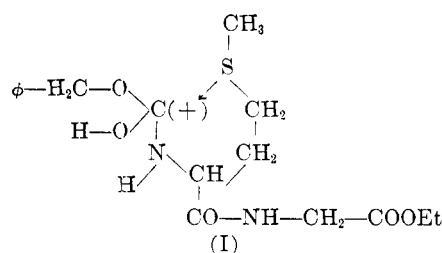
Decarboxylation by refluxing with ethanolic hydrogen chloride. Kinetic runs. One gram of *N*-cbo-DL-methionylglycine ethyl ester was refluxed for the appropriate period with 20 ml. of anhydrous ethyl alcohol which previously had been saturated at room temperature with anhydrous hydrogen chloride. After refluxing, solvent was removed *in vacuo* at 40° and the residual oil after washing with anhydrous ether was dried *in vacuo* over sodium hydroxide. Amino nitrogen¹⁴ and chloride analyses were performed on the resulting thick oils.

Anal. Calcd. for *S*-benzylhomocysteinylglycine ethyl ester hydrochloride: amino N, 4.05; Cl, 10.23. Found: after 30 min., amino N, 4.07; Cl, 12.9; After 60 min., amino N, 4.64; Cl, 15.0; After 120 min., amino N, 7.35; Cl, 16.7.

Isolation runs. After refluxing *N*-cbo-DL-methionylglycine ethyl ester with ethanolic hydrogen chloride for 30 min., solvent was removed by distillation *in vacuo* at 40°. The residual oil was dissolved in water and after cooling in an ice bath, sufficient anhydrous potassium carbonate to form a thin paste was slowly added. The oil which came out of solution was extracted with several portions of ether. After washing the combined extracts with water and drying over anhydrous sodium sulfate, the ether extract was concentrated at 40°. From one representative run, 33% of *S*-benzyl-DL-homocysteinylglycine ethyl ester was obtained as an oil.

Anal. Calcd. for C₁₅H₂₂N₂O₃S: amino N, 4.52; N, 9.04. Found: amino N, 4.43; N, 8.91.

In one particular run, 12.0 g. of *N*-cbo-DL-methionylglycine ethyl ester yielded 7.1 g. of a thick oil which rapidly solidified and after recrystallization from alcohol-water melted at 81–83°. This compound did not possess a free amino group and after hydrolysis with *N* hydrochloric acid in a sealed tube at 100° for 8 hr., only glycine and *S*-benzylhomocysteine could be demonstrated by chromatography. While further work is necessary for ascertaining the structure of this compound, it is interesting to note that it can be formulated as a dihydrothiazine (II) and formation can be



accounted for from intermediate^{5,6} (I) by a transacylation mechanism with expulsion of a methyl carbonium ion and loss of water.

Anal. Calcd. for C₁₆H₂₀N₂O₄S·H₂O/2 (II): C, 55.7; H, 6.09; N, 8.11; S, 9.28; Sap. equiv., 345. Found:¹⁵ C, 55.7; H, 6.11; N, 7.80; S, 9.13; Sap. equiv., 354.

Sealed tube experiments. Kinetic runs. At room temperature 1 g. of *N*-cbo-DL-methionylglycine ethyl ester was dissolved in 10 ml. of ethanolic hydrogen chloride and 1-ml. aliquots were pipetted into a number of tubes. The tubes were then sealed and placed in a water bath. At appropriate time intervals tubes were removed, immediately cooled in an ice bath and then opened. After removal of solvent *in vacuo*, the residual oil was dissolved in water and analyzed for amino nitrogen. The data obtained are presented in Table I.

Chloroplatinate derivative of DL-methionylglycine ethyl ester hydrochloride benzyl sulfonium chloride. One gram of *N*-cbo-DL-methionylglycine ethyl ester was dissolved in 10 ml. of 8.0*N* ethanolic hydrogen chloride and heated in a sealed tube at 45° for 5 hr. After cooling, the tube was opened and 2.5 g. of a 37% solution of platinum chloride in hydrochloric acid was slowly added. The yellow chloroplatinate was filtered off, washed with a small amount of cold, dilute hydrochloric acid and dried *in vacuo*. One gram (50%) of material, decomposing 141–143°, was obtained.

Anal. Calcd. for C₁₈H₂₈Cl₆N₂O₃PtS: C, 26.2; H, 3.54; N, 3.82; Pt, 26.6. Found: C, 26.1; H, 3.71; N, 4.10; Pt, 26.9.

S-Benzyl-DL-homocysteinylglycine. *N*-cbo-DL-methionylglycine ethyl ester (4.0 g., 0.011 mole) was heated with ethanolic hydrogen chloride (40 ml., 8.36*N*) at 77° for 1 hr.¹⁶ After cooling, the tube was opened and solvent was removed *in vacuo* at 40°. The residue was dissolved in 50 ml. of methanol and 23 ml. of 1*N* sodium hydroxide was added. After 4 hr., dilute hydrochloric acid was added to neutrality and the solution was then vacuum concentrated to dryness. The residue was extracted with a small amount of cold water to remove soluble salts and then recrystallized from water-ethanol to give *S*-benzyl-DL-homocysteinylglycine (1.0 g., 32%) m.p. 203–205°, lit.,¹³ 204°. Neutral equivalent calculated for C₁₃H₁₈N₂O₃S: 282. Found: 284.

DL-Methionine ethyl ester hydrochloride benzyl sulfonium chloride. *N*-cbo-DL-methionine ethyl ester (1.0 g., 0.0035 mole) was heated with ethanolic hydrogen chloride (10 ml., 9.6*N*) in a sealed tube at 77° for 7 hr. After cooling, the tube was opened and the contents were concentrated *in vacuo* to an oil. The oil thus obtained was washed with anhydrous ether and after drying *in vacuo* over sodium hydroxide weighed 1.1 g., a 93% yield calculated as the benzyl sulfonium salt.

Anal. Calcd. for C₁₄H₂₃Cl₂NO₂S: Cl, 20.9; N, 4.11. Found: Cl, 21.3; N, 4.07.

Since the above sulfonium salt could not be induced to crystallize, it was converted to the dibromide by passage (in ethanolic solution) through a column of IRA-410 (Br). After concentration, a residual oil was obtained which could not be induced to crystallize.

Anal. Calcd. for C₁₄H₂₃Br₂NO₂S: Br, 37.3; N, 3.26. Found: Br, 37.9, N, 3.54. A solid phosphotungstate could be obtained in 86% yield by the procedure of Lavine *et al.*¹² from the decarboxylated product.

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(14) D. D. Van Slyke, *J. Biol. Chem.*, **83**, 425 (1929).

(15) Analyses by Drs. Weiler and Strauss, Oxford.

(16) Amino nitrogen analysis indicated the liberation of one amino group.

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