Notes

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On the Ethanolic Hydrogen Chloride Catalyzed Decarbobenzoxylation of *N*-Carbobenzoxy-DL-methionylglycine Ethyl Ester[1]

OSCAR GAWRON AND FRANK DRAUS[2]

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In this communication the results of experimental work on decarbobenzoxylation 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 decarbobenzoxylations, both *S*-benzyl-DL-homocysteinylglycine ethyl ester and DL-methionylglycine ethyl ester benzyl sulfonium chloride were found as products.

Decarbobenzoxylations were carried out by either refluxing the methionine derivative with ethanolic hydrogen chloride[7] or by heating the derivative with ethanolic hydrogen chloride in a sealed tube. In both cases, it was necessary to find conditions under which decarbobenzoxylation 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 decarbobenzoxylation and peptide bond breaking while lower concentrations resulted only in decarbobenzoxylation. 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 decarbobenzoxylation is effected.[8]

TABLE I

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

11.3*N* HCl, 45°		8.00*N* HCl, 45°		2.17*N* 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 decarbobenzoxylations carried out under reflux, *S*-benzyl-DL-homocysteinylglycine ethyl ester was isolated in relatively low yields[9] 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 occurs[6] on decarbobenzoxylation of *N*-cbo-DL-methionylglycine with hydrogen bromide in nitromethane. However, decarbobenzoxylation with ethanolic hydrogen chloride also gives rise to a sulfonium derivative while a benzyl sulfonium salt apparently does not form[6] on decarbobenzoxylation 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-

(1) Abstracted in part from the doctoral thesis of Frank Draus.

(2) Present address, Dept. of Physiology, School of Dentistry, University of Pittsburgh.

(3) Cbo- will be used to designate the carbobenzoxy 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 present[12] and that replacement of *S*-methyl with *S*-benzyl has been noted[13] on refluxing methionine with benzyl chloride and hydrochloric acid.

EXPERIMENTAL

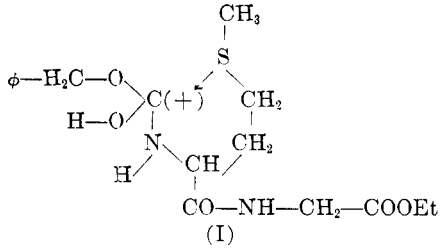
Decarbobenzoxylation by refluxing with ethanolic hydrogen chloride. Kinetic runs. One gram of *N*-cbo-DL-methionylglycine ethyl ester was refluxed for the appropriate period with 20 ml. of anhydrous ethyl alcohol which previously had been saturated at room temperature with anhydrous hydrogen chloride. 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 nitrogen[14] 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.

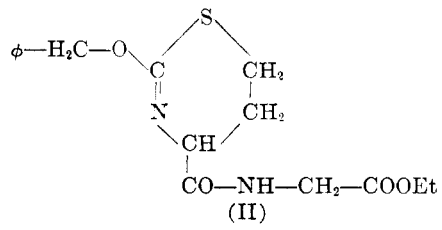
Isolation runs. After refluxing *N*-cbo-DL-methionylglycine ethyl ester with ethanolic hydrogen chloride for 30 min., solvent was removed by distillation *in vacuo* at 40°. The residual oil was dissolved in water and after cooling in an ice bath, sufficient anhydrous potassium carbonate to form a thin 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 $C_{15}H_{22}N_2O_3S$: 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



(I)



(II)

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 $C_{16}H_{20}N_2O_4S \cdot H_2O/2$ (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 platinic 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 $C_{16}H_{26}Cl_6N_2O_3PtS$: 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 $C_{13}H_{18}N_2O_3S$: 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 $C_{14}H_{23}Cl_2NO_2S$: 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 ethanol 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 $C_{14}H_{23}Br_2NO_2S$: 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 decarbobenzoxylated product.

DEPARTMENT OF CHEMISTRY
DUQUESNE UNIVERSITY
PITTSBURGH 19, PA.

(12) T. F. Lavine, N. F. Floyd, and M. S. Cammaroti, *J. Biol. Chem.*, **207**, 107 (1954).

(13) C. A. Dekker and J. S. Fruton, *J. Biol. Chem.*, **173**, 471 (1948).

(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.