CARBOBENZOXY DERIVATIVES OF *S*-AMINOALKYL-L-CYSTEINES*

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In connection with certain studies of modifications of lysine and *S*-aminoalkylcysteine side-chains in proteins, it was necessary to prepare derivatives of *S*-aminoalkylcysteines with the α-amino group blocked. Bezas and Zervas[1] have developed a practical procedure for the synthesis of N^{α}-carbobenzoxylysine from the N^{ϵ}-benzylidene derivative, and it seemed possible to prepare similar derivatives of the aminoalkylcysteines by routine application of their method. They carried out the carbobenzoxylation reaction at −5 to −10°, and noted the appearance of N^{ϵ}-carbobenzoxylysine as a by-product if the temperature were allowed to rise.

In the present study, the reaction was deliberately carried out at 10°, and simultaneous yields of 20% of N^{ϵ}- and 60% of N^{α}-carbobenzoxylysine were obtained. This reaction temperature was therefore used in the carbobenzoxylation of N^{ω}-benzylidene-*S*-aminoalkylcysteines with the intention of simultaneously obtaining samples of both the N^{α}- and N^{ω}-carbobenzoxy derivatives. At 10° both the N^{α}- and N^{ω}-derivatives were obtained from N^{ω}-benzylidene-*S*-aminopropylcysteine (SAPC), but only the N^{α}-derivative from N^{ω}-benzylidene-*S*-aminoethylcysteine (SAEC). The relative order of yields of the N^{ω}-carbobenzoxy compounds at 10° (lysine > SAPC ⩾ SAEC) seems to coincide with that of decreasing stability of the N^{ω}-benzylidene compounds to hydrolysis. Benzylidenelysine is not recrystallizable from water, benzylidene-SAPC decomposes considerably to benzaldehyde in the process, and benzylidene-SAEC may be recrystallized nearly quantitatively.

Experimental

All melting points are uncorrected; microanalyses were by the Australian Microanalytical Service, Melbourne.

The benzylidenation reactions were carried out according to Bezas and Zervas.[1]

Products Obtained from L-*Lysine*

(i) *Benzylidenation reaction.*—N^{ϵ}-Benzylidene-L-lysine was obtained in 77% yield.

(ii) *Carbobenzoxylation reaction.*—The products were N^{α}-carbobenzoxy-L-lysine (yield 61%) {m.p. 227–228° (from H_2O), $[\alpha]_D^{20}$ −7·3° (*c*, 5 in 0·5N HCl)‡} and N^{ϵ}-carbobenzoxy-L-lysine (20%) {m.p. 262° (from AcOH), $[\alpha]_D^{20}$ +14·0 (*c*, 5 in 0·5N HCl)}.

Products Obtained from S-*Aminoethyl-*L-*cysteine* (L-*SAEC*)

(i) *Benzylidenation reaction.*—There was no immediate crystallization of the benzylidene compound; 48 hr at −10° was necessary. L-*2-Amino-3-(2-benzalaminoethylthio)propionic acid*

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‡ Neither datum agrees with the literature.[1] Melting points of amino acids vary markedly with the conditions of determination, but the discrepancy in optical rotations cannot be explained.

[1] Bezas, B., and Zervas, L., *J. Am. chem. Soc.*, 1961, **83**, 719.

(N^{ω}-benzylidene-L-SAEC) was obtained in 58% yield, m.p. 161° (fine needles from H_2O), $[\alpha]_D^{20}$ −50·5° (*c*, 10 in 1N KOH) (Found: C, 57·3; H, 6·3; N, 11·4; S, 12·7. $C_{12}H_{16}N_2O_2S$ requires C, 57·1; H, 6·4; N, 11·1; S, 12·7%).

(ii) *Carbobenzoxylation reaction.*—L-*2-Benzyloxycarbonylamino-3-(2-aminoethylthio)propionic acid* (N^{α}-carbobenzoxy-L-SAEC) (85% yield), m.p. 227–228° (from H_2O), $[\alpha]_D^{20}$ −23·1° (*c*, 5 in 0·5N HCl) (Found: C, 52·2; H, 6·4; N, 9·4; S, 10·7. $C_{13}H_{18}N_2O_4S$ requires C, 52·3; H, 6·1; N, 9·4; S, 10·8%).

Products Obtained from S-*Aminopropyl-*L-*cysteine* (L-*SAPC*)

(i) *Benzylidenation reaction.*—L-*2-Amino-3-(3-benzalamino-1-propylthio)propionic acid* (N^{ω}-benzylidene-SAPC) was obtained in 91% yield, m.p. 164° (coarse prisms from H_2O; decomposition was obvious if there was overheating), $[\alpha]_D^{20}$ −3·4 (*c*, 10 in 1N KOH) (Found: C, 58·2; H, 6·7; N, 10·5; S, 12·1. $C_{13}H_{18}N_2O_2S$ requires C, 58·6; H, 6·8; N, 10·5; S, 12·0%).

(ii) *Carbobenzoxylation reaction.*—L-*2-Benzyloxycarbonylamino-3-(3-amino-1-propylthio)propionic acid* (N^{α}-carbobenzoxy-L-SAPC) was obtained in 47% yield, m.p. 216° (from H_2O), $[\alpha]_D^{20}$ −5·1° (*c*, 5 in 0·5N HCl) (Found: C, 53·8; H, 6·4; N, 8·7; S, 10·0. $C_{14}H_{20}N_2O_4S$ requires C, 53·8; H, 6·4; N, 9·0; S, 10·3%); and L-*2-amino-3-(3-benzyloxycarbonylamino-1-propylthio)propionic acid* (N^{ω}-carbobenzoxy-L-SAPC) was obtained in 7% yield, m.p. 197° (recrystallized by Lindley's[2] procedure), $[\alpha]_D^{20}$ ±0·3° (*c*, 5 in 0·5N HCl) (Found: C, 53·7; H, 6·7; N, 8·9; S, 10·3. $C_{14}H_{20}N_2O_4S$ requires C, 53·8; H, 6·4; N, 9·0; S, 10·3%).

Notes on Benzylidenation Reactions

A number of attempts were made to condense *S*-aminoethylhomocysteine with benzaldehyde, but no product, crystalline or otherwise, separated from the reaction mixture. No decision was made between the alternative hypotheses that the benzylidene derivative was too unstable to form under the reaction conditions or that it was formed but would not crystallize from solution (compare the tardy crystallization of benzylidene-SAEC).

Notes on Carbobenzoxylation Reactions

N^{ω}-Carbobenzoxy-SAPC was extremely insoluble in cold water and crystallized quantitatively on the final neutralization of the reaction mixture; the N^{α} compound was then isolated as described[1] for the lysine derivative. On neutralization of the reaction mixture from N^{ω}-benzylidene-SAEC, a carbobenzoxy-SAEC crystallized out to a final high yield on chilling the solution, and only a little more of the same product was obtained on working up the mother liquors. Since it was not identical with the extremely water-insoluble N^{ω}-carbobenzoxy compound, m.p. 204–206°, already described as an intermediate in Lindley's[2] synthesis of SAEC, it could be identified as the N^{α}-derivative. This point was checked by mixed melting point determinations with an authentic sample of the N^{ω}-derivative, in case the product were a second crystalline form of the latter.

[2] Lindley, H., *Aust. J. Chem.*, 1959, **17**, 296.