Racemization Studies in Peptide Chemistry. Re-investigation of the "β-Elimination–Readdition" Mechanism of *N*-Benzyloxycarbonyl-*S*-benzylcysteine Derivatives

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SEVERAL authors have observed that *N*-benzyloxycarbonyl-*S*-benzylcysteine esters racemize easily in the presence of base.[1] It has been proposed that this racemization proceeds either by resonance stabilization of the anion formed by α-hydrogen abstraction,[1b] or by reversible β-elimination of the benzyl thiol moiety.[1a,d] In connection with the synthesis of polyglutathione,[2] using the pentachlorophenyl active-ester method,[3] and in the light of the above observations, the racemization of *N*-benzyloxycarbonyl-*S*-benzyl-L-cysteine pentachlorophenyl ester (I) was studied in the presence of triethylamine. The possibility of the proposed "β-elimination–readdition" mechanism was investigated by allowing (I) to racemize in the presence of benzyl [^{35}S]thiol. On treatment of a 0·05 molar solution of (I) in absolute chloroform in the presence of one equivalent of benzyl [^{35}S]thiol and 3·6 or 7·2 equivalents of triethylamine for 1·5 hours, the partially racemized active ester (I) (87%) was isolated without any incorporation of radioactive sulphur. Under analogous conditions *N*-benzyloxycarbonyldehydroalanine pentachlorophenyl ester (II; m.p. 132—134°) afforded *N*-benzyloxycarbonyl-*S*-benzyl-DL-cysteine pentachlorophenyl ester (m.p. 164—165°) (79%).

It was recently stated [1d] that the racemization of *N*-benzyloxycarbonyl-*S*-benzylcysteine *p*-nitrophenyl ester (III) proceeds through β-elimination–readdition of benzyl thiol. Since this mechanism is clearly not operative in the racemization of the corresponding pentachlorophenyl ester (I), it was necessary to investigate whether the β-elimination pathway is the cause of racemization in the *p*-nitrophenyl ester (III). Racemization of (III) in the presence of benzyl [^{35}S]thiol under the conditions described for pentachlorophenyl ester (I) yielded partially racemized *N*-benzyloxycarbonyl-*S*-benzylcysteine thiobenzyl ester (IV) (82%), containing one equivalent of radioactive benzyl thiol. Compound (IV) was hydrazinolyzed† to locate the position of the radioactive sulphur and the resulting hydrazide, isolated in 98% yield, showed complete elimination of the incorporated ^{35}S. In a similar way to the corresponding pentachlorophenyl ester (II), *N*-benzyloxycarbonyldehydroalanine *p*-nitrophenyl ester on reaction with benzyl thiol in the presence of triethylamine yielded *N*-benzyloxycarbonyl-*S*-benzyl-DL-cysteine *p*-nitrophenyl ester as one of the several products.

These experiments confirm that racemization *via* β-elimination–readdition is not the mechanism for the racemization of the *p*-nitrophenyl as well as of the pentachlorophenyl esters of *N*-benzyloxycarbonyl-*S*-benzyl cysteine.

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† *N*-Benzyloxycarbonyl-*S*-benzyl-L-cysteine thiobenzyl ester, m.p. 73—75°, $[\alpha]^{22}_{D}$ − 94·8 (*c* 2 in dimethylformamide), affords the corresponding optically pure hydrazide, m.p. 134—136°, $[\alpha]^{23}_{D}$ −15·4 (*c* 1 in ethanol) (lit.[5] m.p. 133—135°, $[\alpha]_{D}$ − 14·3 (*c* 1 in ethanol).

[1] (*a*) J. A. Maclaren, W. E. Savige, and J. M. Swan, *Austral. J. Chem.*, 1958, **11**, 345; (*b*) B. Liberek, *Tetrahedron Letters*, 1963, 925, 1964, 159; (*c*) C. W. Anderson, R. M. Callahan, and J. E. Zimmerman, *Acta Chim. Acad. Sci. Hung.*, 1965, **44**, 51; (*d*) M. Bodanszky and A. Bodanszky, *Chem. Comm.*, 1967, 591.

[2] Unpublished results.

[3] (*a*) J. Kovacs, R. Giannotti, and A. Kapoor, *J. Amer. Chem. Soc.*, 1966, **88**, 2282; (*b*) J. Kovacs, L. Kisfaludy, and M. Q. Ceprini, *ibid.*, 1967, **89**, 183.

[4] B. Hegedüs, *Helv. Chim. Acta*, 1948, **31**, 737.