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NEW SYNTHESIS OF L-SELENOCYSTEINE DERIVATIVES AND PEPTIDES*

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Increased attention has been given in this laboratory (1) and elsewhere (2,3) to the effects on chemical and biological properties of replacing sulfur by selenium in peptides and proteins. For the advancement of research in this area it became essential to develop convenient methods for the preparation of selenium-containing amino acids and peptides bearing selectively removable protecting groups. We found such a method by converting derivatives of L-serine and L-serine-containing peptides to the corresponding derivatives of L-selenocysteine and L-selenocysteine-containing peptides.

The nucleophilic displacement of the O-p-toluenesulfonate group of L-serine derivatives by an alkyl selenide anion afforded a convenient procedure for preparing the corresponding L-selenocysteine derivatives in analogy with a meth-

*Abbreviations: Z = benzyloxycarbonyl-; BOC = tert.-butyloxycarbonyl-; Tos = p-toluenesulfonate; BZL = benzyl-; BZLN = p-nitrobenzyl-; SeCys = selenocysteine residue.

od previously described for the synthesis of L-cysteine compounds (4). Thus the reaction of Z-O-Tos-L-Ser-OBZL* (m.p. 75-77°, $[\alpha]_D^{24}$ -7.4° (c=2, DMF)) with sodium benzyl selenolate in dimethylformamide-acetone resulted in Z-Se-BZL-L-SeCys-OBZL (I, Table I), which was readily converted to the hydrazide (II). The azide of II was coupled with L-Pro-L-Leu-Gly-NH_2 (5) to provide the protected tetrapeptide amide (III), Z-Se-BZL-L-SeCys-L-Pro-L-Leu-Gly-NH_2 (1,2,6), in good yields and with high optical purity. Similarly, BOC-O-Tos-L-Ser-OBZLN (m.p. 115-116°, $[\alpha]_D^{23}$ +13.8° (c=2, $CHCl_3$)) (7) was smoothly converted with sodium benzyl selenolate to BOC-Se-BZL-L-SeCys-OBZLN (IV).

Encouraged by these favorable results, we applied this nucleophilic displacement reaction to O-Tos-serine peptides. Accordingly, Z-O-Tos-L-Ser-Gly-OBZL (m.p. 87-90°, $[\alpha]_D^{23}$ +15.6° (c=2, $CHCl_3$)) and BOC-O-Tos-L-Ser-Gly-OBZL (m.p. 100-101°, $[\alpha]_D^{23}$ +15.1° (c=2, $CHCl_3$)) were converted to Z-Se-BZL-L-SeCys-Gly-OBZL (V) and BOC-Se-BZL-L-SeCys-Gly-OBZL (VI), respectively, in excellent yields. Following partial deprotection of VI, the dipeptide Se-BZL-L-SeCys-Gly-OBZL was allowed to react with Z-L-Glu(α-OBZL)-OH in the presence of N,N'-dicyclohexylcarbodiimide (8) to yield the protected selenoglutathione (VII).

The transformation of serine moieties to selenocysteine moieties in a broad spectrum of biologically active peptides is under investigation.

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* The crystalline O-Tos-L-serine derivatives gave correct elemental analyses.

TABLE I

Selenocysteine Derivatives and Peptides

	Compound	Yield, % M.P., °C	O.R.	Formula M. Wt.	Calculated/Found % C	% H	% N
I	Z-Se-BZL-L-SeCys-OBZL	89	$[\alpha]_D^{28}$ -39.2°	$C_{25}H_{25}NO_4Se$	62.4	5.3	3.1
		84-85	(c=2, DMF)	482.5	62.2	5.2	2.9
II	Z-Se-BZL-L-SeCys-NH-NH_2	88	$[\alpha]_D^{22}$ -20.2°	$C_{18}H_{21}N_3O_3Se$	53.8	5.3	10.3
		137-139	(c=2, DMF)	406.4	53.4	5.3	10.3
III	Z-Se-BZL-L-SeCys-L-Pro-L-Leu-Gly-NH_2 [a]	60	$[\alpha]_D^{24}$ -54.1°	--	--	--	--
		163-164	(c=2, DMF)	--	--	--	--
IV	BOC-Se-BZL-L-SeCys-OBZLN	88	$[\alpha]_D^{23}$ -18.3°	$C_{22}H_{26}N_2O_6Se$	54.8	5.6	5.6
		99-102	(c=2, DMF)	493.4	55.3	5.4	5.8
V	Z-Se-BZL-L-SeCys-Gly-OBZL	70	$[\alpha]_D^{25}$ -28.9°	$C_{27}H_{28}N_2O_5Se$	60.0	5.1	5.3
		91-93	(c=2, 95% EtOH)	539.5	60.1	5.2	5.1
VI	BOC-Se-BZL-L-SeCys-Gly-OBZL	79	$[\alpha]_D^{24}$ -27.5°	$C_{24}H_{30}N_2O_5Se$	56.1	5.8	5.6
		90-92	(c=2, MeOH)	505.5	56.5	5.9	5.9
VII	Z-L-Glu(α-OBZL)-Se-BZL-L-SeCys-Gly-OBZL	62	$[\alpha]_D^{24}$ -26.1°	$C_{39}H_{41}N_3O_8Se$	61.7	5.4	5.5
		148-150	(c=1, DMF)	758.7	61.5	5.6	5.7

[a] Previously the following constants were reported for III: m.p. 154-156°, $[\alpha]_D^{25}$ -48.1° (c=0.7, DMF), ref. 6; m.p. 162-163°, $[\alpha]_D^{18}$ -52.3° (c=2, DMF), ref. 1,2.

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