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STUDIES ON AMINO ACIDS AND PEPTIDES—I

SYNTHESIS OF N-BENZYLOXYCARBONYLENDOTHIODIPEPTIDE ESTERS

K. CLAUSEN,* M. THORSEN and S.-O. LAWESSON
Department of Organic Chemistry, University of Aarhus, DK-8000 Aarhus C, Denmark

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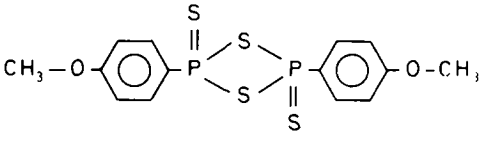
Abstract—N-Benzyloxycarbonylendothiodipeptide esters, **3**, are synthesized without racemization from the corresponding N-benzyloxycarbonyldipeptide esters, **2**, using 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide, **1**, as thionation reagent. The benzyloxycarbonyl amino-protecting group (Z) is removed from **3** by using HBr–AcOH.

To our knowledge only few thioamide containing peptides and peptide derivatives have been reported in the literature. Attempts to prepare endothiopeptides† by thionation of glycylglycine ethyl ester or tetraglycine with P_4S_{10} were quite expectedly unsuccessful.[6,7] However, a series of N-protected endothiodipeptides of the general structure XNHCHRC(S)NHCHR'COOH, where X = Tos-, Z-, or Pht‡ have been prepared by the reaction of amino acid salts with N-protected amino acid thionoesters.[2–4] Furthermore it has been stated that free endothiodipeptides can be formed by removal of the benzyloxycarbonyl group using HCl–AcOH.[2,3] du Vigneaud *et al.*[5] have reported the synthesis of [1-deamino, 9-thioglycine]oxytocin, in which the C-terminal carboxamide function of deaminooxytocin has been formally replaced by a thiocarboxamide group. The two analogs were found to possess highly different bioactivities. Recently Ressler and Banerjee[8] have reported the synthesis of thioasparagine and derivatives for use in peptide synthesis, and also Spatola[9] is working in the same field. In these cases the thioamide functions are found not in the backbone but in the side chains.

Some years ago a new thionation reagent, 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide, **1**, was introduced, which turned out to be one of the most versatile reagents known till now.[10] Thus carboxamides are easily (80°, 0.5–1 hr) transformed to the corresponding thiocarboxamides in quantitative yields.[11] As it is known that **1** reacts with nucleophiles such as amines,[12] it is obvious that in order to produce thiopeptides from peptides and **1** the amino and carboxyl groups must be protected. This paper reports an efficient and general procedure for the conversion of N-Z-protected dipeptide esters to N-Z-protected endothiodipeptide esters.



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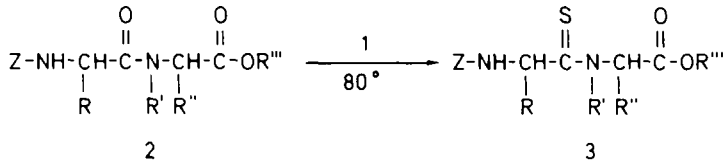
RESULTS AND DISCUSSION

N-Benzyloxycarbonyldipeptide esters, **2**, react with **1** in anhydrous benzene at 80° giving N-benzyloxycarbonylendothiodipeptide esters, **3**, in high yields (Scheme 1 and Table 1). Thionation under these conditions selectively transforms the amide function to a thioamide function, which was expected, since urethanes[13] and esters[14] do not react with **1** at 80°, but first at 110° and 140°, respectively.

All the N-protected dipeptide esters, **2a–f**, are known compounds. To our knowledge no ^{13}C NMR and UV data and only a few ^1H NMR and IR data[15,16] for this type of compounds have been reported, whereas the mass spectra have been discussed fully by Aplin *et al.*[17–19] In Table 2 ^1H and ^{13}C NMR chemical shifts and coupling constants of backbone protons and carbons are presented together with IR carbonyl absorptions (amide I and II, ester, urethane) and UV absorption maxima. The ^1H NMR spectra of these compounds show amide and urethane proton shifts in accordance with published results[15] for N-protected dipeptide esters, the reported shifts for the amide and urethane protons being found in the regions 6.5–8.5 ppm and 5.6–6.1 ppm, respectively. In all compounds the methylene protons of the Z and OBzl groups show resonances at 5.05–5.15 ppm, and the phenyl protons of the named groups are found at 7.25–7.30 ppm. For **2a** the methylene and Me protons of the OEt group show resonances at 4.15 ppm (q, 7 Hz) and 1.20 ppm (t, 7 Hz), respectively. For **2c** $\delta_{H\beta(2)} = 1.40$ (d, 7 Hz), for **2d** $\delta_{H\beta(2)} = 2.90$ (b), for **2e** $\delta_{H\beta(2)}$ and $\delta_{H\gamma(2)} =$ 1.75–2.15 (m), $\delta_{H\delta(2)} = 3.2$–3.6 (m), and for **2f** $\delta_{H\beta(1)} =$ 1.40 (d, 7 Hz). The ^{13}C NMR spectra show three (**2d** four) CO resonances assignable to urethane, amide, and ester groups. The methylene carbons of the Z and OBzl groups resonance at 66.4–67.2 ppm, and the phenyl carbons in the expected regions. For **2a** the methylene and Me carbons of the OEt group show resonances at 60.9 and 13.6 ppm, respectively. For **2c** $\delta_{C\beta(2)} = 17.5$, for **2d**

†The name endothiopeptide seems to be generally accepted for thiopeptides containing one or more –C(S)NH– function(s) in the peptide backbone.[1–5]

‡The abbreviations for the amino acids and protecting groups are those recommended by the IUPAC-IUB Commission on Biochemical Nomenclature, Pure Appl. Chem. **40**, 317 (1974). The optically active amino acids are of the L-configuration.



2 3

	R	R'	R''	R'''	N-Z-dipeptide ester 2	N-Z-endothiodipeptide ester 3 †
a	H	H	H	Et	Z-Gly-Gly-OEt	Z-Glyt-Gly-OEt
b	H	H	H	$-CH_2Ph$	Z-Gly-Gly-OBzl	Z-Glyt-Gly-OBzl
c	H	H	Me	$-CH_2Ph$	Z-Gly-Ala-OBzl	Z-Glyt-Ala-OBzl
d	H	H	$-CH_2-C(=O)-OCH_2Ph$	$-CH_2Ph$	Z-Gly-Asp(OBzl)-OBzl	Z-Glyt-Asp(OBzl)-OBzl
e	H	$-(CH_2)_3-$		$-CH_2Ph$	Z-Gly-Pro-OBzl	Z-Glyt-Pro-OBzl
f	Me	H	H	$-CH_2Ph$	Z-Ala-Gly-OBzl	Z-Alat-Gly-OBzl

Z = benzyloxycarbonyl

Scheme 1.

Table 1. Experimental and physical data for compounds 2 and 3

	N-Z-dipeptide ester 2					N-Z-endothiodipeptide ester 3		
	M.p./n_D^{22}		$[\alpha]_D$			Yield (%)	M.p./n_D^{22}	$[\alpha]_D$ [a]
	Found	Reported	Found [a]	Reported				
a	82-4	80-1[24]	-			78 [c]	82-4	-
b	110	109-10[16]	-			93	112-14 [d] 118-19	-
c	77-8	78-9[25]	-10.55	-16.5	(c=0.47, Me_2CO, 20°)[25]	97	1.5775	-11.50
d	86	86-7[26]	+5.85 [b]	+9.5	(c=2, AcOH, 22°)[26]	98	66-8	+34.75
e [e]	1.5482	oil[25]	-43.15			91	1.5389	-52.20
f	110-12	111[25]	-7.20	-24	(c=4.00, MeOH, 26°)[25]	95	1.5801	-8.20

[a] (c=2.00, AcOEt, 22°).

[b] $[\alpha]_D^{22}$ = +10.37 (c=2.43, 100% AcOH); lit.[27] $[\alpha]_D^{23}$ = +9.1 (c=2.43, 99% AcOH).

[c] This yield was obtained by crystallisation without column chromatography.

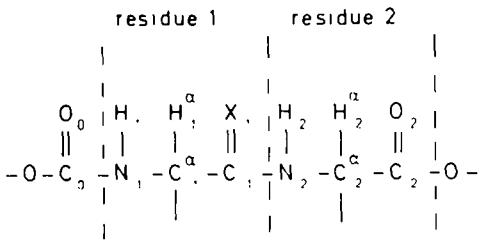
[d] This product consists of two species with different m.ps. The lower melting species can be separated by crystallisation.

[e] An equilibrium exists between to forms, which could be separated by tlc. When each of the two forms was subjected to tlc, the two original spots showed up again.

$\delta_{C\beta(2)}$ = 36.0, $\delta_{C\gamma(2)}$ = 170.1, for **2e** $\delta_{C\beta(2)}$ = 28.6, $\delta_{C\gamma(2)}$ = 24.2, $\delta_{C\delta(2)}$ = 45.5, and for **2f** $\delta_{C\beta(1)}$ = 18.5. The mass spectra of compounds **2** have features in common with those of N-Z-dipeptide alkyl esters described earlier.[17-19] Thus abundant peaks are observed for the molecular ions $[M]^+$ with the base peak in all spectra being $[C_7H_7]^+$. Also the following fragment ions are observed: $[M-PhCH_2O\cdot]^+$, $[M-R'''O\cdot]^+$ (indistinguishable from the first mentioned for **2b–f**), $[Z-NH-CHR-CO-NR'=CHR'']^+$, $[Z-NH[CHR-CO]^+$, $[Z-NH=CHR]^+$ (especially abundant for **2f**), $[Ph-CH_2-NH=CHR]^+$, $[OC-NH-CHR''-COOR''']^+$, and $[NH=CR''COOR''']^+$. Other fragment ions are $[M-R'''OH]^+$ and for the benzyl esters **2b–f** a prominent peak corresponding to loss of *m/e* 197 from the molecular ion. (Exact mass measurement on **2b** (M–197), obs. 159.045, calc for $C_5H_7N_2O_4$ 159.041).

The structural proofs of **3** are based on NMR, IR, UV, and MS. N-Protected endothiopeptide esters of type **3** have not been reported in the literature before, and no

†The symbols Glyt and Alat are used to indicate the thiocarbonyl analogs of the glycine and alanine residues, as proposed by du Vigneaud *et al.*[5]



2 : X = O

3 : X = S

Table 2. Spectroscopic data for compounds **2** and **3**

	X	^{1}H NMR (CDCl$_3$)				^{13}C NMR (CDCl$_3$)					IR (CHCl$_3$)			UV (CHCl$_3$)
		H_1	H_1^α	H_2	H_2^α	C_0	C_1^α	C_1	C_2^α	C_2	amide/ thioamide	ester	urethane	
2a	O	6.00 (t,6)	3.85 (d,6)	7.05 (t,6)	3.95 (d,6)	156.5	43.9	169.6	40.8	169.9	1650 1540	1730	1690[a]	218[b]
2b	O	5.80 (t,6)	3.85 (d,6)	6.90 (t,6)	4.00 (d,6)	156.6	44.3	169.6	41.1	169.6	1680 1520	1720-40		216[b]
2c	O	5.85 (t,6)	3.85 (d,6)	7.00 (d,7)	4.60 (m)	156.4	44.0	168.9	47.8	172.4	1660 1530	1750	1730[a]	260
2d	O	5.60 (b)	3.85 (d,6)	7.05 (b)	5.00 (m)	156.3	44.1	169.2	48.6	170.3	1640 1550	1730	1680[a]	220[b]
2e	O	5.75 (b)	3.95 (d,5)	-	4.45 (b)	156.0	43.0	166.8	58.7	171.3	1650 -	1730	1710	222
2f	O	5.75 (d,7)	4.30 (m)	6.95 (t,6)	4.00 (d,6)	156.1	50.5	173.1	41.3	169.7	1660 1480	1720	1700	260
3a	S	5.90 (t,6)	~4.2	8.60 (b)	~4.2	156.5	51.4	200.3	46.5	168.2	1525	1730	1700[a]	216[b] 258
3b	S	5.75 (t,6)	4.20 (d,6)	8.50 (b)	4.35 (d,5)	156.7	51.9	200.3	46.8	168.4	1510	1720-40		218[b] 268
3c	S	5.90 (t,6)	4.15 (d,6)	8.65 (b)	~5.0	156.6	51.6	199.4	53.3	171.6	1510	1720-40		275
3d	S	~5.5	4.15 (d,6)	8.85 (d,6)	~5.5	156.3	51.5	199.8	53.4	169.1	1515	1730-50		270
3e	S	6.20 (b)	4.05 (d,5)	-	~5.0	155.6	49.7	196.0	65.4	169.6	1190 -	1710-30		216[b] 275
3f	S	5.85 (d,7)	4.70 (m)	8.70 (b)	4.30 (d,5)	155.7	56.3	206.2	46.7	168.1	1495	1730	1700	273

[a] KBr
[b] EtOH

Table 3. Experimental, physical, and spectroscopic data for 4

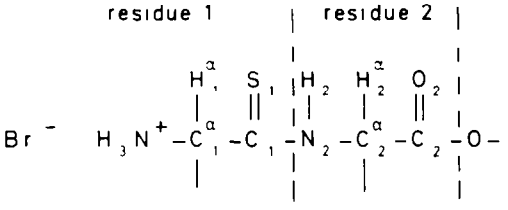
	Yield (%)	M.p.	^{1}H NMR (DMSO-d_6)				^{13}C NMR (DMSO-d_6)				IR (KBr)		UV (EtOH)
			H_3N^+	H_1^α	H_2	H_2^α	C_1^α	C_1	C_2^α	C_2	thio-amide I / II	ester	
4a[a]	95[b]	224 (d)	8.30 (b)	3.90 (m)	11.0 (b)	4.40 (d,5)	45.6	196.3	46.4	167.4	1220 1570	1745	212 266
4b	90[c] 94[d]	188–9	8.30 (b)	3.85 (m)	11.0 (b)	4.40 (d,5)	45.7	196.5	46.5	167.5	1210 1550	1730	214 264

[a] Elemental analysis: Calc.: C 28.03, H 5.09, N 10.89, S 12.47, Br 31.08. Found: C 28.01, H 5.21, N 10.65, S 12.25, Br 31.00%.

[b] 10 ml 12% HBr/AcOH, 0.5 h.

[c] 10 ml 20% HBr/AcOH, 12 h.

[d] 5 ml 36% HBr/AcOH + 1 ml anhydr. toluene, 48 h.



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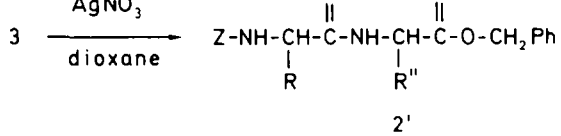
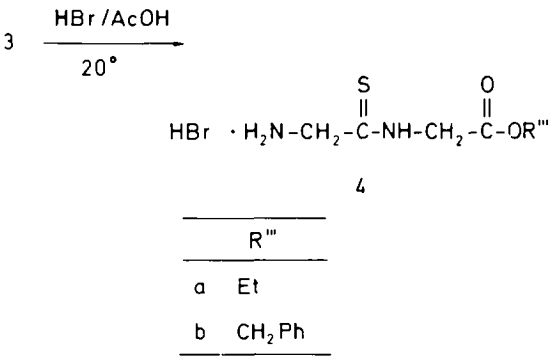
spectroscopic data are available for the closely related N-protected endothiopeptides of type XNHCHRC(S)NHR'COOH.[2-4] ^{1}H and ^{13}C NMR chemical shifts of backbone protons and carbons are presented in Table 2 as well as IR carbonyl and thiocarbonyl absorptions (thioamide II, ester, urethane) and UV absorption maxima. In ^{1}H NMR the methylene and phenyl protons of the Z and OBzl groups, and the methylene and Me protons of the OEt group of **3a** show the same shift values as described for the corresponding **2** above. Also the urethane (H_1) protons are nearly all unaffected when going from **2** to **3**. The backbone methylene and methine (H_1^α and H_2^α) protons are shifted 0.10–0.55 ppm downfield, and the amide (H_2) protons are shifted 1.55–1.75 ppm downfield. For **3c** $\delta_{H\beta(2)} = 1.40$ (d, 7 Hz), for **3d** $\delta_{H\beta(2)} = 3.1$ (d, 5 Hz), for **3e** $\delta_{H\beta(2)}$ and $\delta_{H\gamma(2)} = 1.75$–2.25 (*m*), $\delta_{H\delta(2)} = 3.5$–3.75 (m), and for **3f** $\delta_{H\beta(1)} = 1.45$ (d, 7 Hz). In ^{13}C NMR the methylene and phenyl carbons of the Z and OBzl groups, and the methylene and Me carbons of the OEt group of **3a** are unaffected when going from **2** to **3**. The same holds for the urethane CO (C_0) carbons, whereas the ester CO (C_2) carbons are shifted 0.8–1.7 ppm upfield. The backbone methylene and methine (C_1^α and C_2^α) carbons are shifted 5.8–7.6 ppm and 4.8–6.7 ppm downfield, respectively. The most remarkable difference in shift values is observed for the amide carbonyl (C_1) carbon which is shifted 29.2–33.1 ppm downfield. By a least square analysis of the chemical shifts of the carbonyl carbons of **2a–c,e,f** and the corresponding **3a–c,e,f** the following equation was found: $\delta_{C=S} = 1.62 \cdot \delta_{C=O} - 74.15$. Earlier a slightly different equation has been found for amides ~ thioamides.[11b] By using the equation in case of **2d** where three carbonyl signals are found in the same area, it was possible to make an assignment for the amide CO (C_1) carbon. For **3c** $\delta_{C\beta(2)} = 16.6$, for **3d** $\delta_{C\beta(2)} = 34.5$, $\delta_{C\gamma(2)} = 170.0$, for **3e** $\delta_{C\beta(2)} = 28.3$, $\delta_{C\gamma(2)} = 24.3$, $\delta_{C\delta(2)} = 48.6$, and for **3f** $\delta_{C\beta(1)} = 15.1$. In IR the thioamide I band falls in the fingerprint region which makes the assignment of this band difficult. For all the thiopeptides strong absorptions are observed in UV at 258–275 nm, which is in accordance with reported data for thioamide $\pi \rightarrow \pi^*$ transitions.[20] The mass spectra show abundant peaks for the molecular ions $[M]^+$ (except for **3d** which gives $[M-H^\cdot]^+$) with $[C_7H_7]^+$ as base peak in all spectra. Besides, fragment ions corresponding to $[M-SH^\cdot]^+$, $[M-PhCH_2^\cdot]^+$, $[M-PhCH_2O^\cdot]^+$, $[M-R'''O^\cdot]^+$ (indistinguishable from the former ion for **3b–f**), $[M-R'''OH]^+$, and peaks corresponding to loss of *m/e* 135 from **3a** and *m/e* 197 from **3b–f** (though not as prominent as for **2b–f**) (Exact mass measurement on **3b** (M–197), obs. 175.0175, calc. for $C_5H_7N_2O_3S$ 175.0177).

Two experiments were performed in order to find out if any racemization happened during the thionation. The N-protected endothiodipeptide esters **3c** and **3f** were allowed to react with $AgNO_3$ in dioxane[2,3] which led to formation of the starting compounds **2'c** and **2'f**. By comparison of the optical rotations of the original compounds **2** and the reproduced compounds **2'** (Table 1 and Experimental), it is noticed that no racemization happens during the thionation neither in amino acid residue 1 nor in amino acid residue 2.



	R	R''
c	H	Me
f	Me	H

The benzyloxycarbonyl group could be removed from the N-protected endothiodipeptide esters, **3**, using HBr in acetic acid under anhydrous conditions,[21] to give HBr-salts of endothiodipeptide esters, **4**. The Z-group was removed within 0.5 hr using 12% (*w/w*) HBr/AcOH at 20°. Longer reaction time and more concentrated HBr/AcOH did not affect the ester or thioamide groups (Table 3).



The structural proofs of compounds **4a** and **4b** are based on ^{1}H NMR and ^{13}C NMR as well as IR, UV, and elemental analysis (Table 3). In ^{1}H NMR the methylene, Me, and phenyl protons of the OEt and OBzl, and the methylene (H_2^a) protons show the same shift values as described for the corresponding **3** above. The methylene (H_1^a) protons are shifted 0.30–0.35 ppm upfield, and the thioamide (H_2) protons are shifted ~2.5 ppm downfield (due to the polar solvent DMSO) when going from **3** to **4**. In ^{13}C NMR the methylene, Me, and phenyl carbons of the OEt and OBzl groups, the methylene (C_2^a) and the ester CO (C_2) carbons are unaffected when comparing **3** and **4**. The methylene (C_1^a) and thioamide CO (C_1) carbons are shifted 5.8 ppm and 3.8–4.0 ppm upfield, respectively.

As a conclusion it can be stated that a new route to N-benzyloxycarbonylendothiodipeptide esters and endothiodipeptide ester HBr salts of potential value for peptide manipulations has been worked out.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 60 MHz on a Varian EM-360 spectrometer. ^{13}C NMR spectra were recorded at 20 MHz on a Varian CFT-20 spectrometer. TMS was used as internal standard and chemical shifts are expressed in δ-values. $CDCl_3$ or DMSO-d_6 were used as solvents. IR spectra were recorded on a Beckman IR-18 spectrophotometer. UV spectra were recorded on a Perkin–Elmer 402 spectrophotometer. Mass spectra were recorded on a Micromass 7070 F spectrometer operating at 70 eV using direct inlet. Elemental analyses are carried out by Løvens Kemiske Fabrik, DK-2750 Ballerup (Microanalytical Laboratory). Optical rotations were measured in a 1 dm cell in a Perkin–Elmer 241 polarimeter. Silica gel 60 (Merck) was used for chromatography. M.ps are uncorrected.

Compound **1** (now available from Fluka AG, CH-9470 Buchs SG) was prepared as described earlier.[22]

Compounds **2** were prepared by the *p*-nitrophenyl ester method.[23] The physical and spectroscopic data are presented in Tables 1 and 2.

Preparation of N-Z-endothiodipeptide esters, **3**. A typical example illustrating the preparation of these compounds is shown below.

N-[N-[(phenylmethoxy)carbonyl]thioglycyl]glycine phenylmethyl ester, **3b**. 3.56 g (0.01 mole) of **2b** and 2.02 g (0.005 mole) of **1** were heated in 10 ml anhydr benzene at 80° until the starting material was consumed (as monitored by tlc in 10% AcOEt/CH_2Cl_2). After evaporation of the solvent the residue was chromatographed on a silica gel column (CH_2Cl_2), which yielded 2,4,6-tris(4-methoxyphenyl)-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trisulfide,[22] a product formed from **1** during the reaction. Eluation was continued with 10% AcOEt/CH_2Cl_2, which after evaporation of the solvents yielded the product **3b** as a colourless solid. It was recrystallised from MeOH/Et_2O; yield 3.39 g (91%). The experimental and spectroscopic data are summarized in Tables 1 and 2.

Transformation of Z-Glyt-Ala-OBzl, **3c**, *and Z-Alat-Gly-OBzl,* **3f**, *into the corresponding* **2c** *and* **2f**. 0.0025 mole of **3** and 0.0075 mole $AgNO_3$ were refluxed in dioxane for 0.5 hr. The mixture was filtered and the products purified by column chromatography (10% AcOEt/CH_2Cl_2). **2c'**; m.p. 75–7°, $[\alpha]_D^{22}$ = −10.70 (*c* = 2.00, AcOEt). **2f'**; m.p. 110–12°, $[\alpha]_D^{22}$ = −7.30 (*c* = 2.00, AcOEt).

Removal of the Z-group from **3**. 0.005 mole of **3** was stirred with HBr/AcOH in a flask with silica gel drying tube at 20° for 0.5–48 hr. Then 100 ml of anhydr Et_2O were added and the mixture was cooled to 0°, filtered, washed with portions of anhydr Et_2O and finally dried in a vacuum desiccator. Experimental and spectroscopic data are summarized in Table 3.

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