Stepwise Oxidation of Z-Threonyl- and Z-Seryl-glycine Esters and Related Compounds†

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Z-Thr-Gly-OR and Z-Ser-Gly-OR are oxidized by different oxidizing agents, yielding the corresponding β-carbonyl derivative and/or an α-hydroxy derivative, an oxamide, and a dimeric ester of aminomalonic acid. Interconversions among oxidation products by different reagents have been observed.

The chemical oxidation of serine and threonine in oligopeptides or related derivatives has attracted much interest. For example, (i) *N*-acylserine derivatives react with $Pb(OAc)_4$, undergoing C(2)–C(3) bond fission, to yield 2-acylaminoglycolic acid derivatives [*cf.* Scheme, compound (**8**)];[1] (ii) serine derivatives react with Br_2 or HCO_3H to undergo β-elimination, followed by selective fragmentation;[2] (iii) Z-serine or Z-threonine methyl ester are converted by excess of CrO_3 in pyridine into an oxamate derivative.[3] The last report emphasises the oxidative C–C bond fission, and points out that 'the aminoacid literature contains remarkably little information on the oxidation of serine and threonine side-chains to the ketonic level.' In contrast, we previously reported[4] that protected seryl and threonyl peptides are oxidized by DMSO–DCC–H_3PO_4 to β-carbonyl derivatives which allow chemical, stereochemical, and isotopic modifications. Further studies on the stepwise oxidation of serine and threonine may allow some comparison with the oxidation occurring *in vivo*, and afford 'anomalous peptides' suitable for structure–activity and conformational studies.

Further Studies with DMSO–DCC–H_3PO_4.[5]—A model threonyl peptide (**1**) affords a β-carbonyl derivative (**3**) in almost quantitative yield, whereas a seryl peptide (**2**) affords a formyl derivative (**4**) only in 50% yield.[4] In competitive experiments, mixtures of Z-Thr-Gly-OEt (**1b**) and Z-Ser-Gly-OEt (**2b**) were treated with increasing concentrations of the oxidizing system. At low concentrations, serine is oxidized faster than threonine, in line with the behaviour of primary alcohols, which are oxidized faster than secondary ones.[5] However, sufficient amounts of the oxidant lead to the above reported yields of each β-carbonyl derivative, since the serine substrate is involved in a hemiacetalization reaction which yields a compound of structure (**5**). In order to increase the oxidation of serine, different alcohols were added to the reaction mixtures in the expectation that they would afford the corresponding hemiacetals. However, primary alcohols competed for the oxidizing system to give aldehydes, without improving the yields of the formyl derivative (**4**), and t-butyl alcohol, rather unexpectedly, inhibited the oxidation of seryl peptides at all concentrations studied (1—10M). (Experimental details are omitted for brevity.)

The bulk of our results indicates that a hemiacetal (**5**) is the most representative species of an equilibrium mixture of a formyl derivative (**4**), its enol tautomer, and unoxidized substrate (see also below).

Oxidation with Cr^{VI}.—The use of Cr^{VI} in two-[6] or one-phase systems,[7] under different conditions, leads to a complex oxidation pattern (Scheme).

A threonyl substrate (**1**) is oxidized to a β-carbonyl derivative (**3**) or an oxamide (**6**): product distribution favours the former (2:1) in pyridine at short reaction times (15 min), whereas long reaction times (15 h) or the presence of acid led to extensive formation of the oxamide (**6**). Compound (**3**) and the analogous *N*-acetamidoacetoacetyl derivative (**3'**) were demonstrated to behave as possible intermediates to the oxamide derivative.

Oxidation of a seryl substrate by Cr^{VI} under various conditions affords the oxamide (**6**) and/or the dimeric ester derivative (**7**). However, when the crude product from the DMSO–DCC–H_3PO_4 oxidation was treated with CrO_3 in pyridine, the dimeric ester derivative (**7**) was obtained in relevant yield.

Besides earlier reports on the formation of a dimeric ester upon oxidation by CrO_3–pyridine of a primary alcohol,[7c] methyl esters are obtained upon hypochlorite oxidation of aldehydes in an excess of methanol.[8] In the present case, the acidic moiety of the dimeric ester (**7**) corresponds to the 'non-natural,' or 'special' (*R,S*)-aminomalonic acid derivative,[9a] whereas its alcoholic moiety belongs to the parent seryl dipeptide (**2**). The ester derivative (**7**) may arise through the hemiacetal (**5**) and appears to be the first example of a dimeric peptide ester arising upon oxidation of serine compounds. The importance of the solvent on the formation of the ester derivative (**7**) may refer to the equilibrium concentration of hemiacetal (**5**), which may reflect, in turn, favourable non-covalent interactions between the serine substrate and its formyl derivative.

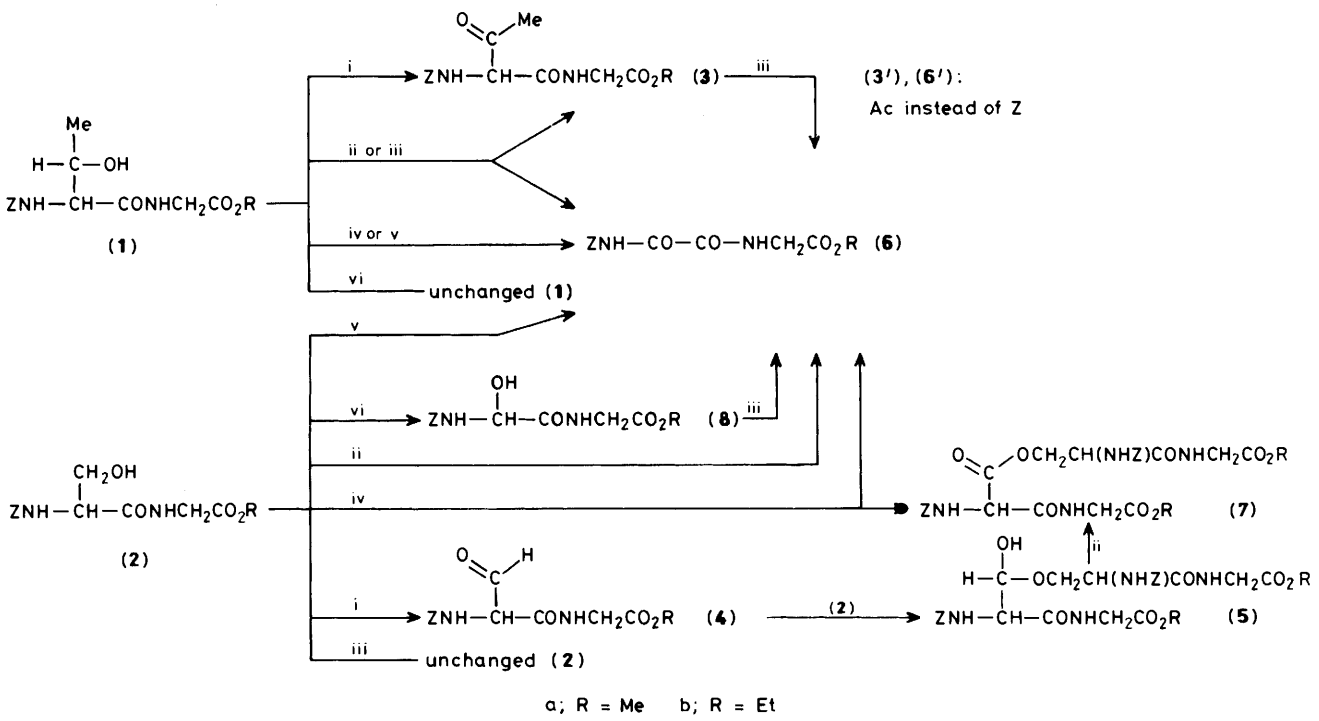
Each ester (**7a** and **b**) occurs as a pair of diastereoisomers, owing to the chiralities of the seryl moiety and the racemic aminomalonyl fragment.

Acid hydrolysis of ester (**7**) yields glycine and serine in a molar ratio of 3:1, indicating that decarboxylation of aminomalonic acid to glycine has occurred.[9b]

Since oxalic or α-hydroxy acids are known to undergo co-oxidation with an alcoholic substrate, through a mechanism that allows C–H , but not C–C bond fission,[6] we tried the co-oxidation of threonine substrates and oxalic acid by Cr^{VI}. The β-carbonyl derivative (**3**) could be satisfactorily obtained within short reaction times; in contrast, the co-oxidation of seryl peptide (**2**) by the Cr^{VI}–oxalic acid system does not stop at the β-carbonyl level; either the non-oxidized substrate (**2**) or the oxamide derivative (**6**) is isolated, according to the reaction time. No straightforward explanation of the different behaviour can be offered: enolization or hydration of the carbonyl group are known, in fact, to be involved in the chromium oxidation of aldehydes or ketones.[6b]

Oxidation with Pb^{IV}.—Lead tetra-acetate oxidizes a protected seryl peptide (**2**) to a glycolamide derivative (**8**),[1] but it

† Amino acids have the L-configuration, unless otherwise stated. Abbreviations used: DCC = dicyclohexylcarbodi-imide; DCU = dicyclohexylurea; DMSO = dimethyl sulphoxide; OEt = ethyl ester; OMe = methyl ester; Z = *N*-benzyloxycarbonyl.



Scheme. *Reagents:* i, DCC–DMSO–H_3PO_4; ii, Cr^{VI}, pyridine–CH_2Cl_2; iii, Cr^{VI}, chloroform, in the presence of oxalic acid; iv, Cr^{VI}, chloroform; v, Mn^{VII}; vi, $Pb(OAc)_4$

leaves an analogous threonyl peptide (**1**) unchanged. On the other hand, both seryl and threonyl esters are oxidized by Pb^{IV}.[1] The glycolamide derivative (**8**) is, in turn, oxidized by Cr^{VI} to the oxamide derivative (**6**).

We thought it would be interesting to compare the behaviour of different threonyl and seryl derivatives towards the Moffat system (DMSO–DCC–H_3PO_4). Accordingly, we studied (a) Z-Thr-OMe and Z-Thr-NHR, (b) Z-Ser-OMe, Z-Ser-OEt, and Z-Ser-NH_2. Threonine esters and amides and serine amides underwent 'normal' oxidation to β-carbonyl derivatives; however, the serine esters remained completely unchanged. The trend observed under the different mechanisms operating with Pb^{IV} or the Moffat system allow us to conclude that the selectivity is due both to the nature of the alcoholic moiety and to the mode of functionalization of the adjacent carbonyl group. In the electrophilic oxidation of alcohols, an adverse effect of adjacent electron-withdrawing groups has been observed.[10]

Oxidation with Mn^{VII}.—Oxidation of model threonyl or seryl peptides by potassium permanganate in chloroform or acetone[11] gave 35% of the oxamide derivative (**6**). In the former case, the balance was mainly unchanged threonyl substrate, whereas complex mixtures were obtained from the protected seryl peptides.

In conclusion, the behaviour of seryl and threonyl model compounds towards different oxidizing agents revealed some selectivities and specificities, due both to the amino acid and the functionalization pattern at the adjacent carboxy group. Further experiments, using oxidizing agents under milder conditions than those described here, are needed to shed light on the possibility of selective alteration of the oxidation level of serine and threonine in oligopeptides of biological interest.

Experimental

^1H N.m.r. spectra were determined with a Perkin-Elmer spectrometer R32 at 90 MHz; for compound (**7a**), a Bruker spectrometer operating at 200 MHz was used. Only relevant n.m.r. signals are reported. Molecular weights were determined using a Vapour Pressure Osmometer (VPO 302B) and chloroform, with biphenyl as a standard. Light petroleum had b.p. 40—60 °C.

The following compounds were prepared by known methods. Z-Thr-Gly-OEt (**1b**); Z-Ser-Gly-OMe (**2a**); *N*-[2-(benzyloxycarbonylamino)acetoacetyl]-Gly-OEt (**3b**);[4b] (*N*-benzyloxycarbonyl-α-hydroxy)-Gly-Gly-OEt (**8b**)[1] [δ($CDCl_3$) 4.0 (2 H, s, CH_2N), 4.73 (1 H, d, CH), 5.4 (1 H, t, CH_2NH), and 6.25 (1 H, d, OCONH)].

Compounds (**8**) could not be obtained by heating (**1**) with $Pb(OAc)_4$ at reflux for 1 h, conditions which *are* effective to convert compounds (**2**) into (**8**);[1] more than 80% of compound (**1**) was recovered unchanged even after 24 h heating.

N-(2-*Hydroxyiminoacetoacetyl*)*glycine Ethyl Ester*.—Sodium nitrite (6.2 g, 0.087 mol) and *N*-acetoacetylglycine ethyl ester (13.7 g, 0.073 mol)[12] in stirred water (40 ml) were treated at 0 °C with 1M HCl (100 ml) during 80 min. After 2 h at room temperature, the solution was neutralized with sodium hydrogen carbonate, and concentrated under reduced pressure. The residue was extracted with anhydrous ether (50 ml × 12), and the extract was dried (sodium sulphate) and concentrated to dryness (10.8 g, 70%) to give prisms from ether–light petroleum, m.p. 73—74 °C (Found: C, 44.5; H, 5.4; N, 12.7. $C_8H_{12}N_2O_5$ requires C, 44.4; H, 5.5; N, 12.9%).

N-[(2-*Acetamido*)*acetoacetyl*]*glycine Ethyl Ester* (**3'**; R = Et).—A sample of the above compound (11.9 g, 0.055 mol) was dissolved in glacial acetic acid (38.5 ml) and acetic anhydride (14 ml, 0.15 mol) and the solution was treated with zinc dust (14.9 g, 0.23 mol) at a rate that kept the mixture at 40 °C. After the mixture had been kept for 2 h at room temperature, ice was added (40 g) and the mixture was kept for a further 30 min and then filtered. The filtrate was extracted with chloroform until the reactivity to Fe^{3+} disappeared. The combined extracts were

washed with water, dried (Na_2SO_4), and concentrated to dryness. The resulting oil was carefully dried and triturated with light petroleum to yield a solid; recrystallization from ethyl acetate–light petroleum gave prisms, m.p. 112—113 °C (Found: C, 48.6; H, 6.8; N, 11.2. $C_{10}H_{16}N_2O_5$ requires C, 49.2; H, 6.6; N, 11.5%).

Reactions of Z-Thr-Gly-OR (**1**) *with* Cr^{VI}.—(a) N-*Benzyloxycarbonyl*-N′-*ethoxycarbonylmethyloxamide* (**6b**). A solution of Z-Thr-Gly-OEt (**1b**) (2.9 g, 8.6 mmol) in chloroform (30 ml) was added in one go to a solution of potassium dichromate (5.14 g, 17.2 mmol) in conc. sulphuric acid (10 ml)–glacial acetic acid (4 ml)–water (30 ml), cooled at 0 °C. The two-layer system was stirred for 30 min at 0 °C, then overnight allowing the temperature to increase. The organic layer and the washings of the inorganic layer (chloroform; 10 ml × 4) were combined, washed to neutrality with (in turn) 1M HCl, water, saturated sodium hydrogen carbonate, and water, dried (Na_2SO_4), and concentrated under reduced pressure. The crude solid was recrystallized from ethyl acetate–light petroleum to yield *prisms* of (**6b**) (1.46 g, 52%), slightly soluble in chloroform, acetone, acetic acid, and methanol; m.p. 120 °C; [δ($CDCl_3$) 3.92 (2 H, d, $NHCH_2$), 5.2 (2 H, s, CH_2O), 9.3 (1 H, t, *J* 6 Hz, $NHCH_2$), and 11.0 (1 H, s, CONHCO)] [Found: C, 54.7; H, 5.4; N, 8.9%; M.W., (acetone) 330. $C_{14}H_{16}N_2O_6$ requires, C, 54.54; H, 5.23; N, 9.09%; M.W. 308]; amino acid analysis: glycine 1.0; threonine 0,0 m.*

(b) *In the presence of oxalic acid; formation of* (**3b**) *and* (**6b**). A solution of Z-Thr-Gly-OEt (**1b**) (0.34 g, 1 mmol) in chloroform (5 ml) was added to a solution of potassium dichromate (0.6 g, 2 mmol) in conc. sulphuric acid (1.8 ml)–oxalic acid dihydrate (0.25 g, 2 mmol)–water (2.5 ml). The two layers were stirred for 15 min, then they were separated and worked up as under (a) above. The crude oil was recrystallized from ethyl acetate–light petroleum to yield (i) *N*-[2-(benzyloxycarbonylamino)acetoacetyl]glycine ethyl ester (**3b**), m.p. 115 °C (0.16 g, 50%); 2,4-dinitrophenylhydrazone m.p. 202—203 °C;[4b] (ii) the oxamide derivative (**6b**) (0.07 g, 20%), identical with the sample described above; (iii) some starting material was present in the mother liquor. In another experiment, the oxidation was allowed to proceed for 15 h: quantitative conversion into the oxamide (**6**) was observed.

(c) *With* CrO_3–*pyridine*. Chromium trioxide (0.6 g, 12 mmol) was dissolved in anhydrous pyridine (1.9 g, 24 mmol), diluted with anhydrous methylene dichloride (30 ml).[7b] After 15 min, a solution of Z-Thr-Gly-OEt (**1b**) (0.34 g, 1 mmol) in methylene dichloride (5 ml) was added, and the mixture was stirred for 15 min. The supernatant was separated from a dark amorphous precipitate and the latter was thoroughly washed with methylene dichloride. The filtrate and washings were combined and concentrated to dryness; the resulting oil was taken up with ethyl acetate (50 ml), washed in turn with saturated aqueous sodium hydrogen carbonate and water to neutrality, dried (Na_2SO_4), and concentrated to give a solid. Fractional recrystallization from ethyl acetate–light petroleum gave the following: (i) *N*-[2-(benzyloxycarbonylamino)acetoacetyl]glycine ethyl ester (**3b**).[4b] (0.15 g, 47%); (ii) the oxamide derivative (**6b**) (84 mg, 26%); and (iii) the balance was unchanged starting material (**1b**).

Reaction of Z-Ser-Gly-OR (**2**) *with* DMSO–DCC–H_3PO_4, *followed by* CrO_3–*Pyridine*.—A solution of Z-Ser-Gly-OMe (**2a**) (0.62 g, 2 mmol) in DMSO (3.5 ml) was added at 20 °C to a stirred solution of DCC (0.82 g, 4 mmol) in DMSO (4 ml), followed by a 3M solution of H_3PO_4 in the same solvent (0.67 ml, 2 mmol). After 2 h, the mixture was stirred and quenched with glacial acetic acid (1 ml) during 30 min and then kept at 0 °C overnight. DCU was filtered off and the solution was lyophilized to yield an oil which was dissolved in ethyl acetate (15 ml); the solution was washed with water until neutral, dried (Na_2SO_4), and concentrated to dryness. The resulting oil (0.42 g, 70%) gave an amino acid ratio serine/glycine 0.4; i.r. and ^1H n.m.r. spectra were very complex; physical and chemical properties indicated that it probably consisted of a mixture of unchanged (**2a**) and (*N*-benzyloxycarbonyl-α-formylglycyl)-glycine methyl ester (**4a**) and/or the hemiacetal (**5a**).[4] A sample of this oil, treated with CrO_3–pyridine according to the procedure followed for Z-Thr-Gly-OEt (method c), gave the diester derivative (**7a**) described below.

Reaction of Z-Ser-Gly-OR (**2**) *with Chromic Acid*.—Z-Ser-Gly-OMe (**2a**). A sample of Z-Ser-Gly-OMe (**2a**) (6.2 g, 0.02 mol) was oxidized as described for Z-Thr-Gly-OEt (**1b**) (method a). After identical work-up, the crude solid, consisting of three products, was fractionated by chromatography on a column of silica gel with ethyl acetate–cyclohexane (1:1) as eluant. The following products were obtained: (i) N-*benzyloxycarbonyl*-N′-*methoxycarbonylmethyloxamide* (**6a**) (1.49 g, 24%); m.p. 145 °C (Found: C, 53.15; H, 5.39; N, 9.45. $C_{13}H_{14}N_2O_6$ requires C, 53.06; H, 4.80; N, 9.52%); (ii) benzylcarbamate, m.p. 86 °C, identical with an authentic sample (0.76 g, 25%); (iii) *N*-benzyloxycarbonyl-*O*-[2-benzyloxycarbonylamino-*N*-(methoxycarbonylmethyl)malonamoyl]serylglycine methyl ester (**7a**) *diastereoisomers* A and B, prisms from ethyl acetate–light petroleum (0.49 g, 8%); m.p. 150—152 °C; the ^1H n.m.r. spectrum showed the two populations in different concentrations: δ($CDCl_3$) (A) 3.73 (6 H, s, 2 MeO), 3.9—4.4 (4 H, 2 m, 2 CH_2NH), 4.16 (2 H, m, $NHCHCH_2$, 4.57 (1 H, m, $NHCHCH_2$), 5.04 [m, $CH(CO)_2$], 5.82 (1 H, d, NHCH), 5.12 and 7.35 (2 s, 2 $CH_2C_6H_5$), 6.13 (1 H, d, NHCH) and 7.57 (2 H, br, 2 $NHCH_2$); (B) 3.76 (6 H, s, 2 MeO), 3.9—4.4 (4 H, 2 m, 2 CH_2NH), 4.7 (1 H, br, $NHCHCH_2$), 6.02 (1 H, d, NHCH), 6.45 (1 H, d, NHCH), 7.75 (2 H, br, 2 $NHCH_2$)]; other signals have the same δ value as those for A.

Z-Ser-Gly-OEt (**2b**). A sample of compound (**2b**) (2.78 g, 8.6 mmol), oxidized as described for Z-Thr-Gly-OEt (**1b**) (method a), gave the following products: (i) compound (**6b**) m.p. 120 °C. not depressed on admixture with a sample of the oxamide derivative obtained from (**1b**) (0.39 g, 14%); (ii) benzylcarbamate (0.28 g, 20%); (iii) N-*benzyloxycarbonyl*-O-[2-*benzyloxycarbonylamino*-N-(*ethoxycarbonylmethyl*)*malonamoyl*]*serylglycine ethyl ester* (**7b**), *two diastereoisomers*, prisms, m.p. 155 °C (from ethyl acetate–light petroleum), insoluble in water and acids, soluble in chloroform, slightly soluble in acetone and ethyl acetate (0.34 g, 12%). Spectroscopic data correspond to those of the ester derivative (**7a**) [Found: C, 55.4; H, 5.3; N, 8.4%; M.W. ($CHCl_3$) 660. $C_{30}H_{36}N_4O_{12}$ requires C, 55.89; H, 5.63; N, 8.69%; M.W. 645]. Amino acid analysis: glycine:serine (3:1).

Reactions of Z-Ser-Gly-OR (**2**) *with Chromic Acid in the Presence of Oxalic Acid*.—A sample of Z-Ser-Gly-OEt (**2b**) (0.32 g, 1 mmol) in chloroform was treated with stoicheiometric amounts of the dichromate–oxalic acid–sulphuric acid mixture, following the procedure used for the protected peptide (**1b**) (method b). The starting material was recovered unchanged (0.22 g, 70%); t.l.c. revealed the presence of traces of derivatives (**4**), (**5**), and (**6b**).

Reactions of Z-Ser-Gly-OR (**2**) *with* CrO_3–*Pyridine*.—A sample of compound (**2b**) (0.32 g, 1.1 mmol) was kept with the reagent[7b] under the conditions described for (**1b**). After identical work-up the oxamide (**6b**) (0.14 g, 46%) was obtained. The mother liquor contained only some unchanged (**2b**).

* A related α-oxamide derivative has been recently reported as an s-*cis* + s-*trans* mixture: H. Aoyama, T. Hasegawa, and Y. Omote, *J. Am. Chem. Soc.*, 1979, **101**, 5343; K. Takahashi, K. Shibasaki, K. Ogura, and H. Jida, *Chem. Lett.*, 1983, 859.

Reaction of β-Carbonyl Derivatives (**3**) *with Chromic Acid.*—A sample of *N*-[2-(benzyloxycarbonylamino)acetoacetyl]glycine ethyl ester (**3b**)[4b] (0.34 g, 1 mmol) was treated with potassium dichromate and worked up as described above under (a); a single product was obtained, identical with the oxamide (**6b**), m.p. 120 °C (0.21 g, 70%).

A sample of *N*-(2-acetamidoacetoacetyl)glycine ethyl ester (**3'b**) (0.23 g, 1 mmol) was treated with potassium dichromate and worked up as above to give N-*acetyl*-N'-*ethoxycarbonylmethyloxamide* (**6'b**) as prisms (0.14 g, 66%); m.p. 111 °C; δ($CDCl_3$) 2.5 (3 H, s, CH_3CO), 4.16 (2 H, d, $NHCH_2$), 7.9 (1 H, br, $NHCH_2$), and 9.6 (1 H, br, CONHCO) (Found: C, 44.5; H, 5.5; N, 12.7. $C_8H_{15}N_2O_6$ requires C, 44.44; H, 5.60; N, 12.96%).

Oxidation of (N-*Benzyloxycarbonyl-α-hydroxy)glycyl*-Gly-OEt (**8b**).—A sample of compound (**8b**) (0.21 g, 0.66 mmol), treated with potassium dichromate (method a), gave the oxamide (**6b**) (0.17 g, 80%).

Oxidation of Hemiacetal (**5b**) *with* Cr^{VI}.—A sample (0.4 g, 0.67 mmol) of the crude product obtained upon reaction of Z-Ser-Gly-OEt (**2b**) with DMSO–DCC–H_3PO_4 was added to the CrO_3–pyridine complex as described above (method c[7b]). Identical work-up gave the dimeric ester (**7b**), m.p. 150—152 °C (0.3 g, 75%). T.l.c. indicated the presence of traces of compound (**6b**).

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