N-Hydroxy Amides. Part 6.[1] Synthesis and Spectroscopic Properties of 1-Hydroxypiperazine-2,5-diones

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1-Hydroxypiperazine-2,5-diones (**3a**—**f**) are prepared in good yields, starting with Boc-L-amino acids and *N*-benzyloxyglycine methyl ester. The rate of cyclisation for *N*-hydroxy and *N*-benzyloxydipeptide methyl esters are 38—77 times as large as that of phenylalanylglycine methyl ester. The c.d., ^{1}H n.m.r., i.r., and u.v. spectral data of 1-hydroxypiperazine-2,5-diones are similar to those of the corresponding piperazinediones. A difference is noted in the i.r. carbonyl frequencies in the solid state.

The synthesis of peptide analogues having *N*-hydroxy amide bonds in the chain is of interest in relation to naturally occurring peptide hydroxamic acids.[2-5] We have prepared a number of *N*-hydroxypeptides and elucidated some of their properties including iron(III) binding.[1,6] In the design or characterization of *N*-hydroxypeptides it is essential to have detailed knowledge[7] of *N*-hydroxy amide bonds. Simple, structurally rigid and chiral peptides such as 1-hydroxypiperazine-2,5-diones could be used as models, since cyclic dipeptides are known to have restricted conformational freedom.[8] Among various cyclic dipeptides,[8-11] those containing a glycine residue (*c*-Gly-X) have been studied by means of *X*-ray crystallography,[12] and i.r.,[13] u.v.,[14], c.d.,[15,16] and n.m.r.[11,15-19] spectroscopy. 1-Hydroxy- or 1,4-dihydroxypiperazine-2,5-diones have been prepared by a number of procedures,[20-22] but these were not suitable for the present synthesis of chiral piperazinediones.

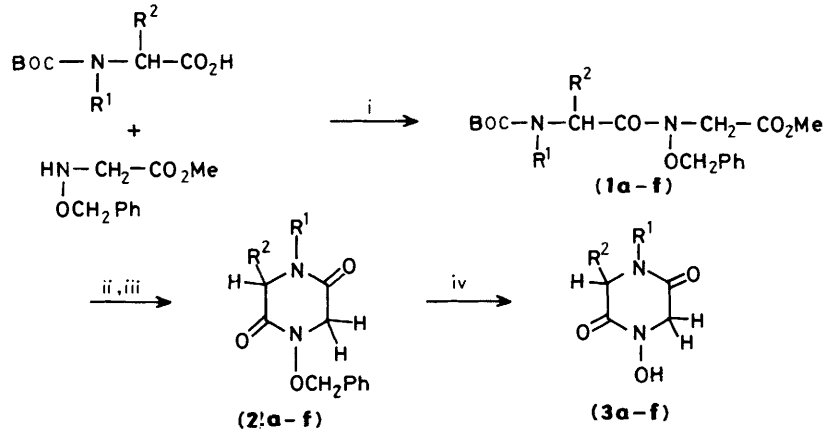
In this paper, we describe the synthesis of several piperazine-2,5-diones with an *N*-hydroxyglycine residue and compare their spectroscopic properties with those of the corresponding usual piperazinediones.

Results and Discussion

Synthesis.—The outline of the synthesis is shown in Scheme 1. *N*-Benzyloxyglycine methyl ester was acylated with Boc-L-amino acids by the mixed anhydride method,[6] to give the corresponding Boc-aminoacyl-*N*-benzyloxyglycine methyl esters (**1a**—**f**). Deprotection of the Boc group of (**1a**—**f**), followed by treatment with aqueous 5% $NaHCO_3$ at room temperature produced 1-benzyloxypiperazine-2,5-diones (**2a**—**f**). The compounds (**2a**—**f**) gave the desired 1-hydroxypiperazinediones when hydrogenated with palladium catalyst.

Cyclisation Rate.—Cyclisation rates were determined by monitoring the reaction with h.p.l.c. (Table 1). There is a notable difference in rates between usual dipeptide esters (runs 1 and 2) and *N*-hydroxy- (runs 3 and 4) or *N*-benzyloxydipeptide esters (runs 5—8). In cyclisation, a dipeptide ester must adopt a folded (*cis*) conformation at the central amide bond at least transiently. The cyclisation of H-Gly-Sar-OMe, which was shown to exist in equilibrium between *cis* and *trans* rotational isomers,[23] was much faster than that of H-Gly-Gly-OMe.[24] The *N*-hydroxy amide group was reported to adopt a *cis* conformation both in the solid state and in solution.[25,26] It is difficult, however, to obtain evidence for the present case. The rapid cyclisation of *N*-hydroxy- or *N*-benzyloxy-dipeptide esters may be explained in terms of the lower rotational barrier[27] which is needed to enter into the transition state.

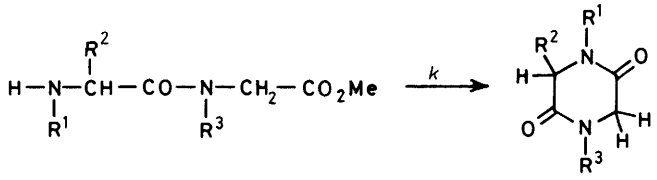
C.d. Spectra.—Some features of the c.d. curves for compounds (**3a**—**f**) are summarized in Table 2. Compared with



a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = Me$
c; $R^1 = H$, $R^2 = Pr^i$
d; R^1, $R^2 = -(CH_2)_3-$
e; $R^1 = H$, $R^2 = CH_2Ph$
f; $R^1 = H$, $R^2 = CH_2CO_2CH_2Ph$ [for (**3f**): $R^1 = H$, $R^2 = CH_2CO_2H$]

Scheme 1. *Reagents and solvents:* i, Boc^iCl/Et_3N in $THF-CH_2Cl_2$ (1:1); ii, CF_3CO_2H in CH_2Cl_2; iii, 5% $NaHCO_3$; iv, H_2/10% Pd–C [for (**2a**) ⟶ (**3a**) $H_2/Pd(OAc)_2$]

Table 1. First-order rate constants for cyclisation of dipeptide methyl esters



Run	R^1	R^2	R^3	k/min^{-1}	Relative rate
1	H	CH_2Ph	H	3.5×10^{-3}	1
2	H	Me	H	3.0×10^{-3}	0.8
3	H	CH_2Ph	OH	1.3×10^{-1}	37
4	H	Me	OH	1.8×10^{-1}	51
5	H	CH_2Ph	OCH_2Ph	1.4×10^{-1}	40
6	H	Pr^i	OCH_2Ph	2.7×10^{-1}	77
7	$-(CH_2)_3-$		OCH_2Ph	2.4×10^{-1}	69
8	H	$CH_2CO_2CH_2Ph$	OCH_2Ph	$>2.7 \times 10^{-1}$	>77

Table 2. C.d. data of piperazine-2,5-diones determined in H_2O

	c-(HO)Gly-X		*c*-Gly-X	
X	$\lambda_{max.}$ (nm)	[θ] °cm^2 dmol^{-1}	$\lambda_{max.}$ nm	[θ] °cm^2 dmol^{-1}
L-Ala	198	−10 000	197	−8 900[a]
L-Val	208	−22 800	207	−30 000[a]
L-Pro	213	+21 000	213	+18 000[b]
				+19 800
L-Phe	213	−14 400	213	−20 000
	218sh	−12 500		
L-Asp	215	−8 600		

[a] Taken from ref. 16. [b] Solvent is not specified in ref. 15.

those reported[16] in the literature, differences are apparently small and probably insignificant, indicating that the conformation taken by these two series of piperazinediones are very alike.

^{1}H *N.m.r. Study.*—A piperazinedione ring has been shown to exist mainly in three different conformations depending upon the folding angle β; a flat ring conformation with β = 0 (Type A), a 3,6-disubstituted-pseudo-axial conformation with β < 0 (Type B), and a 3,6-disubstituted-psuedo-equatorial conformation with β > 0 (Type C) (Figure).

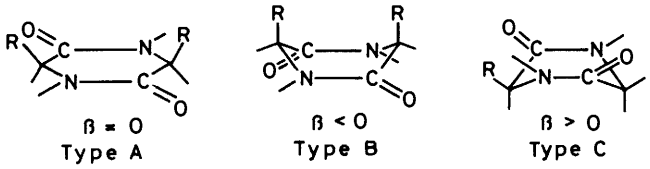


Figure. Typical conformations of a cyclic dipeptide for three different folding angles (β)

^{1}H N.m.r. spectra were obtained in [$^2H_6$]DMSO and also in D_2O for a few derivatives. The data are collected in Table 3. N–OH Proton signals were not observed. Proton signals of 1-hydroxypiperazine-2,5-diones generally appear downfield relative to the corresponding NH derivatives due to the presence of the N–OH group.

Magnetic equivalence or nonequivalence for Gly CH_2 protons has been used to predict a piperazinedione ring conformation. The equivalent chemical shifts of *N*-hydroxyglycine CH_2 for *c*-(HO)Gly-Gly (**3a**), *c*-(HO)Gly-L-Ala (**3b**), and *c*-(HO)Gly-L-Asp (**3f**) indicate that these compounds have

Table 3. Proton chemical shifts and coupling constants for 1-hydroxypiperazine-2,5-diones, *c*-(HO)Gly-X, and chemical shift differences from piperazine-2,5-diones, *c*-Gly-X[a]

	In [$^2H_6$]DMSO solution											
	(HO)Gly residue			Other residue								
	δ(p.p.m.)			δ(p.p.m.)					J(Hz)			
c-(HO)Gly-X X	α-L	α-D	$^2J_{\alpha\alpha}$ (Hz)	α	β	γ[β]	δ[γ]	NH	αβ	ββ[βγ]	αα[b]
Gly	4.07	4.07		3.81				8.16			
	(+0.22)			(−0.04)							
L-Ala	4.10	4.10		3.97	1.32			8.33	6.84		
	(+0.37)			(+0.12)	(+0.06)			(+0.28)			
L-Val	4.01	4.16	16.84	3.72	2.16	0.83	[0.92]	8.26	2.93	[6.84]	
	(+0.40)	(+0.35)		(+0.20)	(+0.06)	(+0.01)	(0)	(+0.05)			
L-Pro	4.44*	3.88	15.87	4.18*	1.7—2.3	3.46		*c*	*c*	1.22*	
	(+0.37)	(+0.29)		(0)		(−0.04)					
L-Phe	3.05*	3.72	16.36	4.22*	2.88	[3.15]	7.2[d]	8.22	4.39	13.67	0.85*
	(+0.27)	(+0.36)		(+0.14)	(−0.04)	(+0.04)		(+0.34)			
L-Asp	4.05	4.05		4.15	2.63	[2.82]		8.15	4.15	17.09	
	In D_2O solution										
L-Ala	4.34*	4.44*	17.33	4.24*	1.46				6.84		1.47*
	(+0.35)	(+0.36)		(+0.10)	(+0.03)						
L-Val	4.31	4.47	17.57	4.25	2.28	0.87	[0.92]		*e*	(6.59]	*e*
	(+0.09)	(+0.08)		(+0.13)	(+0.08)	(−0.03)	(−0.07)				
L-Pro	4.57*	4.22†	16.60	4.37*·†	1.8—2.4	3.55		*c*	*c*	2.68*	
	(+0.27)	(+0.33)		(+0.03)		(−0.07)				1.58†	

[a] Chemical shift differences are expressed as $\delta_{c\text{-(HO)Gly-X}} - \delta_{c\text{-Gly-X}}$, and are given in parentheses. Chemical shift data for piperazine-2,5-diones are those in ref. 16 and 17. [b] Coupling protons are shown by asterisk or dagger. [c] Indeterminable due to signal overlap. [d] Phenyl group. [e] Indeterminable due to broad singlet.

Table 4. Folding angles (β) for 1-hydroxypiperazine-2,5-diones, *c*-(HO)Gly-X, estimated from Δδ[a] and $^3J_{NH-C_\alpha H}$

Compound	*c*-(HO)Gly-X X	Δδ	DMSO Solution β (°)	$^3J_{NH-C_\alpha H}$ (Hz)	DMSO Solution β (°)	Type	D_2O Solution Δδ	D_2O Solution β (°)	Type
(**3a**)	Gly	0	0	1.46	+1	A			
(**3b**)	L-Ala	0	0	1.32	+2	A	−0.10	−8	B
(**3c**)	L-Val	−0.15	−12	2.68	−12	B	−0.16	−12	B
(**3d**)	L-Pro	+0.56	+43			C	+0.35	+27	C
(**3e**)	L-Phe	−0.64	−49	2.44	−9	B			
(**3f**)	L-Asp	0	0	1.22	+3	A			

[a] $\Delta\delta = \delta_L - \delta_D$.

Table 5. The carbonyl absorption frequencies of 1-benzyloxy- and 1-hydroxy-piperazine-2,5-diones[a]

Compound	KBr Disc CONH	KBr Disc $CON(OCH_2Ph)$	DMSO Solution CONH	DMSO Solution $CON(OCH_2Ph)$	Compound	KBr Disc CONH	KBr Disc CON(OH)	DMSO Solution CONH	DMSO Solution CON(OH)
(**2a**)	1 640	1 675	1 686		(**3a**)	1 695	1 637	1 689	
(**2b**)	1 660	1 690	1 681		(**3b**)	1 687	1 633	1 682	
(**2c**)	1 670	1 690	1 682		(**3c**)	1 673		1 680	
(**2d**)	1 665	1 675	1 670		(**3d**)	1 682	1 667	1 668	
(**2e**)	1 655	1 690	1 685		(**3e**)	1 669	1 649	1 680	
(**2f**)	1 640	1 660	1 685		(**3f**)	1 668	1 637	1 675	

[a] $\nu_{max.}$(cm^{-1}); concentrations in DMSO solution are in the range of 1.0×10^{-2} mol dm^{-3}.

Table 6. U.v. spectral data of piperazine-2,5-diones in water

X	*c*-(HO)Gly-X $\lambda_{max.}$ nm	*c*-(HO)Gly-X $\varepsilon \times 10^{-4}$ $dm^3\ mol^{-1}\ cm^{-1}$	*c*-Gly-X $\lambda_{max.}$ nm	*c*-Gly-X $\varepsilon \times 10^{-4}$ $dm^3\ mol^{-1}\ cm^{-1}$
Gly	187	1.42	189	1.38
			189[a]	1.35[a]
L-Ala	187	1.44	188	1.59
L-Val	189	1.50	188	1.47
L-Pro	189	1.57	188	1.44
L-Phe	187	4.93	186	4.78
L-Asp	186	1.56		

[a] From ref. 14.

a planar conformation with β = 0 (Type A). Nonequivalent *N*-hydroxyglycine CH_2 chemical shifts were observed for the three compounds (**3c**—**e**). For compound (**3c**), a Val $C_\alpha H$ signal which appears at slightly higher field (δ 3.72) is assigned the pseudo-equatorial position.[19] For compound (**3d**), we assigned the Pro $C_\alpha H$ proton at δ 4.18 to the pseudo-axial position, based on literature data.[15,17,19] These assignments indicate that proline extends its side chain in a pseudo-equatorial direction (β > 0, Type C). Considerable upfield chemical shifts of the *N*-hydroxyglycine $C_\alpha H$ protons for compound (**3e**) suggest that the phenyl ring hangs over the piperazinedione ring,[11] that is, the side chain occupies the pseudo-axial position (β < 0).

Proton chemical shift signals in D_2O generally appear downfield relative to those in [$^2H_6$]DMSO. Assignment of proton signals for compounds (**3b**), (**3c**), and (**3d**) in D_2O can be made similarly as above (Table 3).

We calculated β values according to the equations of Davies and Khaled[16] and the data presented in Table 4. Values of β = +1, +2, and +3 obtained for (**3a**), (**3b**), and (**3f**), respectively, are thought to lie within the limit of errors of β = 0 in view of the accuracy of a Karplus type equation. However, a value of β = −9 for (**3e**) is more reliable than a value derived from δ_L–δ_D. N.m.r. spectroscopy shows that the conformation of 1-hydroxypiperazinediones is very similar to that of the N–H piperazinediones.

I.r. Spectra.—In the determination of an amide bond conformation the carbonyl absorption frequency can sometimes give useful information.[8,13] I.r. spectra of several *N*-benzyloxy and *N*-hydroxy cyclic peptides were determined in the solid state (KBr disc) and in DMSO solution (Table 5).

1-Benzyloxypiperazine-2,5-diones in the solid state reveal two absorptions in the range 1 690—1 640 cm^{-1}. The higher frequency absorption is ascribed to the *N*-benzyloxy amide carbonyl group because of the strain of the benzyloxy substituent. In DMSO solution these two types of amide group appear as a broad band at 1 685—1 670 cm^{-1}.

For 1-hydroxypiperazine-2,5-diones in the solid state two absorption bands also appear in the region 1 695—1 633 cm^{-1} except for compound (**3c**). The *N*-hydroxy amide bonds are assigned to the lower frequency absorptions, which are considered to be typical of a *cis* oriented hydroxamic acid group. Here the usual *cis* amide groups absorb at higher frequencies than those observed for 1-benzyloxypiperazine-2,5-diones. In DMSO solution, one broad band appeared in the range 1 689—1 668 cm^{-1} as observed for 1-benzyloxy derivatives. These similar absorption frequencies in DMSO solution may be due to the amide carbonyl groups being exposed to the solvent, free from hydrogen bond formation.

U.v. Spectra.—Table 6 compares u.v., $\lambda_{max.}$, and ε in water for 1-hydroxypiperazine-2,5-diones and the known piperazinediones. When both series are compared, $\lambda_{max.}$ coincides within an error of ±1 nm and the molar absorption coefficient within a difference of 2—10%. In view of the fact that the c.d. spectra, which are composed of the rotational strengths,[28,29] are also in good agreement, it is concluded that the *N*-hydroxy amide bond and the N–H amide bond behave similarly in terms of u.v. absorption spectroscopy.

Experimental

All the m.p.s are uncorrected. I.r. spectra were recorded on JASCO model A302 and FT/IR-5M i.r. spectrometers. U.v. spectra were measured with a Hitachi 320A spectrophotometer under a nitrogen atmosphere. ^{1}H N.m.r. spectra were obtained with a JEOL JNM-FX 200 spectrometer with $SiMe_4$ both in $CDCl_3$ and [$^2H_6$]DMSO and sodium 3-trimethylsilylpropanesulphonate (DSS) in D_2O solution as internal standards. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter and c.d. spectra were taken with a JASCO J40AS recording spectropolarimeter with a DP-600 data processor. H.p.l.c. was carried out with a JASCO model Twincle apparatus using a column packed with Finepak SIL C_{18}. Column chromatography was performed on silica gel (Wako gel C-300). *N*-Benzyloxyglycine methyl ester hydrochloride, H-(PhCH$_2$O)Gly-OMe·HCl, was obtained according to the literature method; m.p. 125—125.5 °C (lit.,[30] 125—126 °C).

General Procedure for N-*Benzyloxy Dipeptide Methyl Esters* (**1a**—**f**): *a Typical Example*, Boc-Gly-(PhCH$_2$O)Gly-OMe (**1a**).—A solution of Boc-Gly-OH (2.14 g, 12 mmol) and triethylamine (1.22 g, 12 mmol) in THF (15 ml) was cooled to −15 °C and treated with isobutyl chloroformate (1.57 g, 11.5 mmol) in THF (10 ml). After 15 min a mixture of H-(PhCH$_2$O)Gly-OMe·HCl (2.32 g, 10 mmol) and triethylamine (1.1 g, 10 mmol) in CH_2Cl_2 (20 ml) was added to the solution. The reaction mixture was then stirred for 3 h at −15 °C, and kept for 45 h in a refrigerator. The resulting triethylammonium chloride was removed and the filtrate was evaporated to give a residue which was dissolved in AcOEt (150 ml). The resulting solution was washed with 5% aqueous $NaHCO_3$. Since unchanged H-(PhCH$_2$O)Gly-OMe was detected by t.l.c. in the extract, it was further acylated by the above procedure. The ethyl acetate solution was washed successively with 5% aqueous $NaHCO_3$, 5% aqueous citric acid, and water, dried (Na_2SO_4), and evaporated to provide a crude product which was purified by flash chromatography on silica gel with AcOEt–hexane (2:3) as eluant to afford (**1a**) (2.43 g, 69%) as an oil (Found: C, 57.1; H, 6.9; N, 7.7. $C_{17}H_{24}N_2O_6$·0.33H_2O requires C, 57.0; H, 6.95; N, 7.8%); $\nu_{max.}$(neat) 3 400 (NH), 1 740 (ester C=O), 1 720 (urethane C=O), and 1 690 cm^{-1} (amide C=O); δ($CDCl_3$) 1.45 (9 H, s, CMe_3), 3.73 (3 H, s, OMe), 4.27 (2 H, s, $C_\alpha H_2$), 4.49 (2 H, s, $C_\alpha H_2$), 4.90 (2 H, s, OCH$_2$Ph), 5.25 (1 H, br s, NH), and 7.3—7.5 (5 H, m, Ph).

Boc-L-Ala-(PhCH$_2$O)Gly-OMe (**1b**).—The double acylation product was purified by column chromatography with AcOEt–hexane (1:2) to give (**1b**) (90%) as an oil (Found: C, 59.1; H, 7.1; N, 7.55. $C_{18}H_{26}N_2O_6$ requires C, 59.0; H, 7.15; N, 7.65%; [α]$_D$ −14.8° (*c* 0.44 in MeOH); $\nu_{max.}$(neat) 3 340 (NH), 1 750 (ester C=O), 1 710 (urethane C=O), and 1 690 cm^{-1} (amide C=O); δ($CDCl_3$) 1.40 (3 H, d, *J* 6.9 Hz, Me), 1.45 (9 H, s, CMe_3), 3.70 (3 H, s, OMe), 3.85 and 4.60 (2 H, ABq, *J* 16.6 Hz, $C_\alpha H_2$), 4.80 (1 H, m, $C_\alpha H$), 4.93 and 5.02 (2 H, ABq, *J* 11.5 Hz, OCH$_2$Ph), 5.25 (1 H, br s, NH), and 7.2—7.4 (5 H, m, Ph).

Boc-L-Val-(PhCH$_2$O)Gly-OMe (**1c**).—The double acylation product was purified by column chromatography with AcOEt–hexane (1 : 2) to give (**1c**) (40%) as an oil (Found: C, 60.9; H, 7.75; N, 6.8. $C_{20}H_{30}N_2O_6$ requires C, 60.9; H, 7.7; N, 7.1%); [α]$_D$ +3° (*c* 0.68 in MeOH); $\nu_{max.}$(neat) 3 350 (NH), 1 760 (ester C=O), 1 710 (urethane C=O), and 1 670 cm^{-1} (amide C=O); δ($CDCl_3$) 0.9 and 1.0 (6 H, 2 × d, *J* 6.9 Hz, $CHMe_2$), 1.46 (9 H, s, CMe_3), 2.25 (1 H, m, $C_\beta H$), 3.73 (3 H, s, OMe), 3.90 and 4.65 (2 H, ABq, *J* 17.1 Hz, $C_\alpha H_2$), 4.75 (1 H, m, $C_\alpha H$), 4.97 and 5.08 (2 H, ABq, *J* 10.3 Hz, OCH$_2$Ph), 5.20 (1 H, br s, NH), and 7.3—7.5 (5 H, m, Ph).

Boc-L-Pro-(PhCH$_2$O)Gly-OMe (**1d**).—The double acylation product was purified by column chromatography with AcOEt–benzene (1:4) to give (**1d**) (64%) as an oil (Found: C, 60.9; H, 7.3; N, 6.85. $C_{20}H_{28}N_2O_6$ requires C, 61.2; H, 7.2; N, 7.15%); [α]$_D$ −41.7° (*c* 0.12 in MeOH); $\nu_{max.}$(neat) 1 755 (ester C=O), 1 690 (urethane C=O), and 1 655 cm^{-1} (amide C=O); δ($CDCl_3$) 1.50 (9 H, s, CMe_3), 1.8—2.3 (4 H, m, $C_\beta H_2C_\gamma H_2$), 3.3—3.6 (2 H, m, $C_\delta H_2$), 3.90 and 4.50 (2 H, ABq, *J* 17.1 Hz, $C_\alpha H_2$), 4.30 (1 H, m, $C_\alpha H$), 4.98 and 5.07 (2 H, ABq, *J* 10.3 Hz, OCH$_2$Ph), and 7.3—7.5 (5 H, m, Ph).

Boc-L-Phe-(PhCH$_2$O)Gly-OMe (**1e**). The normal acylation product was purified by column chromatography with AcOEt–hexane (2:3) as eluant and subsequent recrystallisation from Et_2O–hexane to give (**1e**) (56%), m.p. 92—93 °C (Found: C, 65.0; H, 6.7; N, 6.3. $C_{24}H_{30}N_2O_6$ requires C, 65.15; H, 6.8; N, 6.3%); [α]$_D$ +37.5° (*c* 0.2 in MeOH); $\nu_{max.}$(KBr) 3 370 (NH), 1 760 (ester C=O), 1 700 (urethane C=O), and 1 670 cm^{-1} (amide C=O); δ($CDCl_3$) 1.40 (9 H, s, CMe_3), 2.80 and 3.30 (2 H, ABq, *J* 14.9 Hz, $C_\beta H_2$), 3.95 and 4.65 (2 H, ABq, *J* 16.0 Hz, $C_\alpha H_2$), 3.76 (3 H, s, OMe), 4.97 and 5.03 (2 H, ABq, *J* 10.9 Hz, OCH$_2$Ph), 5.05 (1 H, m, $C_\alpha H$), 5.10 (1 H, br s, NH), and 7.1—7.5 (10 H, m, 2 Ph).

Boc-L-Asp(OCH$_2$Ph)-(PhCH$_2$O)Gly-OMe (**1f**). The double acylation product was purified by column chromatography with AcOEt–hexane (2:5) as eluant to give (**1f**) (39%) as an oil (Found: C, 62.5; H, 6.5; N, 5.6. $C_{26}H_{32}N_2O_8$ requires C, 62.4; H, 6.4, N, 5.6%); [α]$_D$ +15.4° (*c* 0.13 in MeOH); $\nu_{max.}$(neat) 3 350 (NH), 1 740 (ester C=O), 1 710 (urethane C=O), and 1 690 cm^{-1} (amide C=O); δ($CDCl_3$) 1.45 (9 H, s, CMe_3), 2.6—3.1 (2 H, m, $C_\beta H_2$), 3.70 (3 H, s, OMe), 3.94 and 4.50 (2 H, ABq, *J* 16.6 Hz, $C_\alpha H_2$), 4.92 and 5.03 (2 H, ABq, *J* 9.8 Hz, OCH$_2$Ph), 5.15 (2 H, s, CO_2CH_2Ph), 5.20 (1 H, m, $C_\alpha H$), 5.42 (1 H, br s, NH), and 7.2—7.5 (10 H, m, 2 Ph).

General Procedure for 1-*Benzyloxypiperazine*-2,5-*diones* (**2a**—**f**): *a Typical Example*, c-(PhCH$_2$O)Gly-L-Phe (**2e**).—Boc-L-Phe-(PhCH$_2$O)Gly-OMe (**1e**) (2.32 g, 5.2 mmol) was treated with CF_3CO_2H (25 ml) in CH_2Cl_2 (25 ml) at 0 °C to give H-L-Phe-(PhCH$_2$O)Gly-OMe·CF_3CO_2H in quantitative yield. The CF_3CO_2H salt of the dipeptide methyl ester (2.39 g, 5.2 mmol) was dissolved in 5% aqueous $NaHCO_3$ (70 ml) and stirred for 1 h at room temperature. The reaction mixture was saturated with NaCl, extracted with CH_2Cl_2 (50 ml × 3), and the combined extracts were dried (Na_2SO_4), and evaporated to give a crude product, which was recrystallised from AcOEt–Et_2O (1.38 g, 86%), m.p. 156—157 °C (Found: C, 69.55; H, 5.6; N, 9.0. $C_{18}H_{18}N_2O_3$ requires C, 69.65; H, 5.85; N, 9.0%); [α]$_D$ −47.9° (*c* 1 in MeOH); δ($CDCl_3$) 3.05—3.15 (1 H, dd, *J* 7.4 and 14.3 Hz, $C_\beta H$), 3.15—3.25 (1 H, dd, *J* 4.6 and 14.3 Hz, $C_\beta H$), 3.38 and 3.78 (2 H, ABq, *J* 17.2 Hz, $C_\alpha H_2$), 4.29 (1 H, m, $C_\alpha H$), 4.89 and 4.99 (2 H, ABq, *J* 11.4 Hz, OCH$_2$Ph), 6.05 (1 H, br s, NH), and 7.2—7.5 (10 H, m, 2 Ph).

c-(PhCH$_2$O)Gly-Gly (**2a**). H-Gly-(PhCH$_2$O)Gly-OMe·CF_3CO_2H was treated with triethylamine in THF and the mixture stirred for 2 h at room temperature; the yield of product was 37%; m.p. 209—211 °C (decomp., from MeOH–AcOEt) (Found: C, 59.25; H, 5.8; N, 12.5. $C_{11}H_{12}N_2O_3$·0.2H_2O requires C, 59.0; H, 5.6; N, 12.5%); δ([$^2H_6$]DMSO) 3.83 (2 H, s, $C_\alpha H_2$), 4.12 (2 H, s, $C_\alpha H_2$), 4.95 (2 H, s, OCH$_2$Ph), 7.3—7.5 (5 H, m, Ph), and 8.16 (1 H, br s, NH).

c-(PhCH$_2$O)Gly-L-Ala (**2b**). Yield 82%; m.p. 149—150 °C (from AcOEt) (Found: C, 61.7; H, 6.05; N, 12.0. $C_{12}H_{14}N_2O_3$ requires C, 61.5; H, 6.0; N, 12.0%); [α]$_D$ −12.3° (*c* 1 in MeOH); δ($CDCl_3$) 1.50 (3 H, d, *J* 5.7 Hz, Me), 3.96 and 4.04 (2 H, ABq, *J* 10.6 Hz, $C_\alpha H_2$), 4.10 (1 H, m, $C_\alpha H$), 5.02 (2 H, s, OCH$_2$Ph), 7.0 (1 H, br s, NH), and 7.3—7.5 (5 H, m, Ph).

c-(PhCH$_2$O)Gly-L-Val (**2c**). Yield 79%; m.p. 137—138 °C (from AcOEt–Et_2O) (Found: C, 63.95; H, 6.9; N, 10.6.

$C_{14}H_{18}N_2O_3$ requires C, 64.1; H, 6.9; N, 10.7%); $[\alpha]_D$ −33.9° (*c* 1 in MeOH); δ($CDCl_3$) 0.9 and 1.02 (6 H, 2 × d, *J* 5.7 Hz, $CHMe_2$), 2.45 (1 H, d, hept, *J* 3.5 and 5.7 Hz, $C_\beta H$), 3.90 (1 H, dd, *J* 2.3 and 3.5 Hz, $C_\alpha H$), 4.05 (2 H, s, $C_\alpha H_2$), 5.02 (2 H, s, OCH_2Ph), 6.25 (1 H, d, *J* 2.3 Hz, NH), and 7.3—7.5 (5 H, m, Ph).

c-($PhCH_2O$)Gly-L-Pro (**2d**). Yield 54%; m.p. 133—134 °C (from AcOEt–Et_2O) (Found: C, 64.45; H, 6.25; N, 10.7. $C_{14}H_{16}N_2O_3$ requires C, 64.6; H, 6.2; N, 10.75%); $[\alpha]_D$ −67° (*c* 1 in MeOH); δ($CDCl_3$) 1.8—2.6 (4 H, m, $C_\beta H_2C_\gamma H_2$), 3.4—3.7 (2 H, m, $C_\delta H_2$), 3.98 and 4.14 (2 H, ABq, *J* 13.7 Hz, $C_\alpha H_2$), 4.10 (1 H, m, $C_\alpha H$), 4.98 and 5.09 (2 H, ABq, *J* 11.1 Hz, OCH_2Ph), and 7.3—7.5 (5 H, m, Ph).

c-($PhCH_2O$)Gly-L-Asp(OCH_2Ph) (**2f**). Yield 71%; m.p. 150—151 °C (from AcOEt) (Found: C, 65.05; H, 5.5; N, 7.5. $C_{20}H_{20}N_2O_5$ requires C, 65.2; H, 5.5; N, 7.6%); $[\alpha]_D$ −2.1° (*c* 1 in AcOEt); δ($CDCl_3$) 2.8—3.0 (1 H, dd, *J* 8.1 and 17.8 Hz, $C_\beta H$), 3.0—3.2 (1 H, dd, *J* 3.4 and 17.8 Hz, $C_\beta H$), 3.99 and 4.13 (2 H, ABq, *J* 17.1 Hz, $C_\alpha H_2$), 4.35 (1 H, m, $C_\alpha H$), 5.0 (2 H, s, OCH_2Ph), 5.14 (2 H, s, CO_2CH_2Ph), 6.65 (1 H, br s, NH), and 7.3—7.5 (10 H, m, 2 Ph).

General Procedure for 1-*Hydroxypiperazine*-2,5-*diones* (**3a**—**f**): *a Typical Example*, c-(HO)Gly-L-Phe (**3e**).—A mixture containing *c*-($PhCH_2O$)Gly-L-Phe (**2e**) (500 mg, 1.6 mmol) and 10% Pd–C (50 mg) in EtOH was subjected to hydrogenation with H_2 at room temperature for 3 h. The catalyst was filtered off and the filtrate was evaporated to afford the product (**3e**) (306 mg, 85%); m.p. 233 °C (decomp., from MeOH) (Found: C, 58.95; H, 5.3; N, 12.55. $C_{11}H_{12}N_2O_3 \cdot 0.25H_2O$ requires C, 58.8; H, 5.6; N, 12.45%); $[\alpha]_D$ −18.4° (*c* 1 in DMF).

c-(HO)Gly-Gly (**3a**). Palladium acetate was used as the catalyst in place of 10% Pd–C in MeOH; yield 75%; m.p. 206 °C (decomp. from MeOH) (Found: C, 37.2; H, 4.8; N, 21.8. $C_4H_6N_2O_3$ requires C, 36.9; H, 4.65; N, 21.5%).

c-(HO)Gly-L-Ala (**3b**). Yield 87%; m.p. 223 °C (decomp. from EtOH) (Found: C, 41.45; H, 5.7; N, 19.3. $C_5H_8N_2O_3$ requires C, 41.7; H, 5.6; N, 19.45%); $[\alpha]_D$ −39.4° (*c* 0.16 in DMF).

c-(HO)Gly-L-Val (**3c**). Yield 76%; m.p. 179—180 °C (from MeOH–Et_2O (Found: C, 48.75; H, 7.05; N, 16.1. $C_7H_{12}N_2O_3$ requires C, 48.8; H, 7.0; N, 16.3%); $[\alpha]_D$ −33.4° (*c* 1 in MeOH).

c-(HO)Gly-L-Pro (**3d**). Yield 89%; m.p. 114—115 °C (from MeOH) (Found: C, 47.95; H, 6.0; N, 16.05. $C_7H_{10}N_2O_3 \cdot 0.33H_2O$ requires C, 47.7; H, 6.1; N, 15.9%); $[\alpha]_D$ −145.7° (*c* 0.3 in MeOH).

c-(HO)Gly-L-Asp (**3f**). Yield 88%; m.p. 204 °C (decomp. from MeOH) (Found: C, 38.3; H, 4.3; N, 14.8. $C_6H_8N_2O_5$ requires C, 38.3; H, 4.3; N, 14.9%); $[\alpha]_D$ +85.8° (*c* 0.12 in MeOH).

Measurement of the Cyclisation Rate of Dipeptide Methyl Esters: a Typical Example, Cyclisation of H-L-Phe-($PhCH_2O$)Gly-OMe (**1e**).—Boc-L-Phe-($PhCH_2O$)Gly-OMe (**1e**) was treated with 4 mol dm^{-3} HCl–dioxane to give H-L-Phe-($PhCH_2O$)Gly-OMe·HCl. To the mixture of HCl dipeptide ester (80 mg) and naphthalene (1.4 mg, added as an internal standard) in 50% aqueous DMF solution was added $NaHCO_3$ (400 mg) at 25 °C. The disappearance of the dipeptide ester, H-L-Phe-($PhCH_2O$)Gly-OMe, with time was monitored by subjecting aliquots to h.p.l.c. (conditions: wavelength 254 nm; flow rate 2 ml/min; solvent MeCN–H_2O 75:25 containing 0.1% H_3PO_4) at 5 min intervals. The appearance of piperazinedione derivatives was followed where possible. The semilogarithmic time conversion curves showed good linear plots, giving the first-order rate constants within a limit of ± 5% error. These data are collected in Table 1.

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