Synthesis of Chiral Piperazin-2-ones as Model Peptidomimetics

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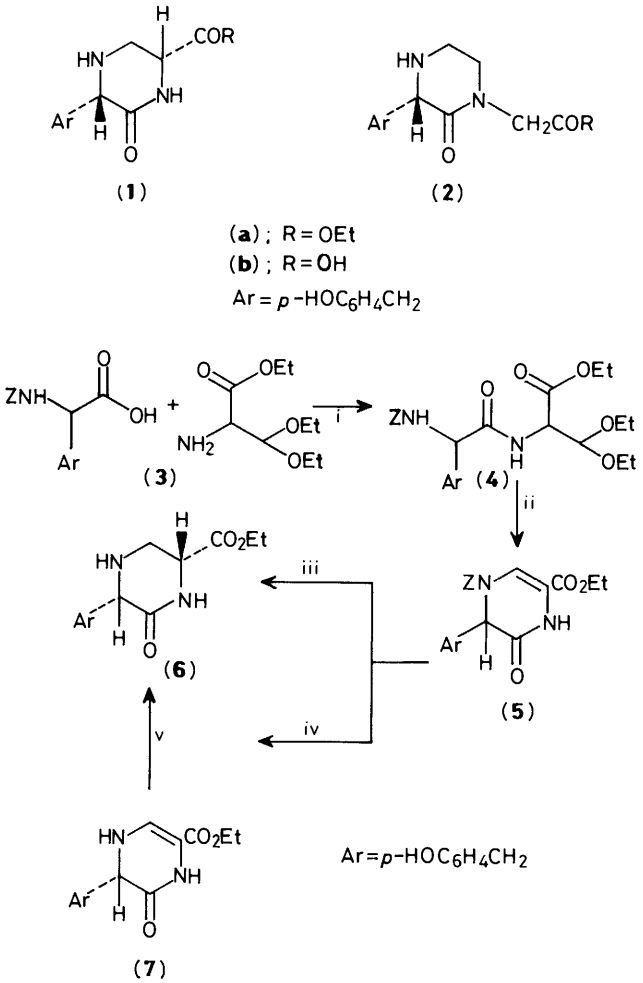
The enantiospecific synthesis of (3*S*,6*R*)-6-ethoxycarbonyl-3-(*p*-hydroxybenzyl)piperazin-2-one (**1**) and (3*S*)-1-(ethoxycarbonylmethyl)-3-(*p*-hydroxybenzyl)piperazin-2-one (**2**) and their enantiomers is described. The chiral C-6 centre of (**1**) is generated by a regiospecific protonation of the enamide precursor.

The elucidation of the bioactive conformation of small polypeptide modulators remains a challenging target. Central to this goal is that the determination of local structural features (β-I, β-II, or γ-turn) of a particular polypeptide backbone provides access to conformational mimicry[1] by synthetic surrogates capable of stabilizing the secondary structure.[2–4] We have reported previously[5] on the effects conferred upon the neurotransmitter Leu-enkephalin through conformational constraints imposed by piperazinones (**1**) and (**2**) which are peptidomimetics for the first and second residue. Since the original report, the inclusion of lactams into biologically active peptides has gained wide acceptance. Here, we describe a general procedure for the synthesis of the lactams (**1**) and (**2**) and their enantiomers, peptidomimetics which on incorporation into the backbone of important peptide neurotransmitters generate analogues with interesting biological activity.[6,7]

Results and Discussion

The synthon (**1**) was prepared as shown in Scheme 1. Coupling of ethyl 2-amino-3,3-diethoxypropionate[8] with Z-L-tyrosine gave the corresponding diastereoisomeric dipeptide (**4**) which after acid hydrolysis afforded directly the vinylogous amide (**5**) in 70% yield. 70% Trifluoroacetic acid (TFA) proved to be the best medium for reaction while aqueous AcOH or HCl afforded only partial hydrolysis of the acetal and no cyclization. Catalytic reduction of (**5**) with $Pd(OH)_2$ in the presence of a slight excess of HCl afforded the amine hydrochloride which was neutralized to the crystalline free base (**6**). Unexpectedly only a single diastereoisomeric component was detected in the product mixture. In addition, when HCl was omitted from the reaction medium only the enamide (**7**) could be isolated, no trace of reduced material being produced. Thus the reduction of (**5**) must involve hydrogenolysis of the Z group followed by enantiospecific electrophilic attack by $H^+\alpha$ to the ethoxycarbonyl group and catalytic reduction of the iminium ion.[9] This mechanism was confirmed by performing the reaction in EtOD–DCl which resulted in the complete and stereospecific incorporation of deuterium α to the ethoxycarbonyl group. The amine (**6**) could also be obtained by reduction of the enamide (**7**) by the method of Borch *et al.*[10] Thus reaction of (**7**) with $NaCNBH_3$ in THF–MeOH in the presence of HCl (pH 3—4) again afforded a single diastereoisomer corresponding to that obtained by catalytic reduction. Single crystal *X*-ray crystallography of (**6**) showed that the new chiral centre has the *R* configuration and the 3*S*-hydroxybenzyl and 6,*R*-ethoxycarbonyl substituents are in the pseudoaxial position.[11] Using D-tyrosine as starting material gives the (3*R*,6*S*)-piperazin-2-one. We infer that the conformation of the 3-hydroxybenzyl substituent of the enamide (**7**) must be such that in the transition state (**8**) (Figure 1) it effectively shields the α-face from electrophilic attack.



Scheme 1. *Reagents and Conditions:* i, DCC, HOBT, CH_2Cl_2; ii, 70% TFA–H_2O; iii, $Pd(OH)_2$, H_2, HCl then neutralize; iv, $Pd(OH)_2$, H_2, EtOH; v, $NaCNBH_3$, HCl, MeOH

The synthon (**2**) was prepared in enantiomerically pure form using a strategy similar to the one described above. Thus, reaction of a suitably protected tyrosine with ethyl N-(2,2-dimethoxyethyl)glycinate using EEDQ‡ (Scheme 2) in MeOH gave the corresponding dipeptide (**11**) in 80% yield con-

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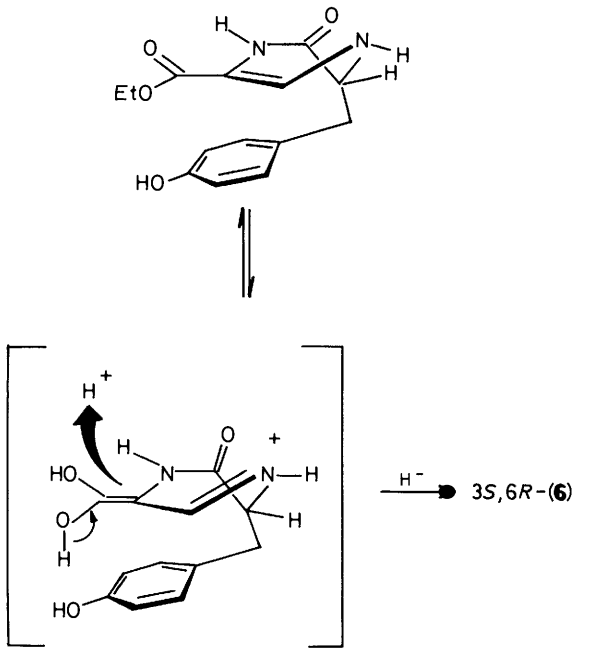
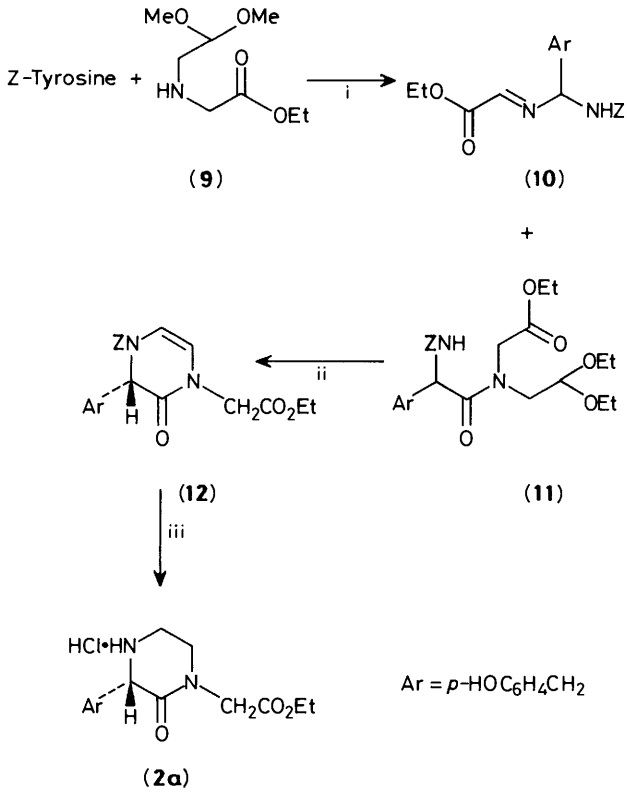
‡ 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline.



(8)

Figure 1.



Scheme 2. *Reagents and Conditions:* i, EEDQ/MeOH; ii, 70% aq. TFA, 2 h; iii, $Pd(OH)_2$, H_2, HCl, EtOH

taminated with some elimination product (**10**). Treatment of the acetal as above with 70% TFA solution gave the enamine (**12**). Hydrogenolysis was uneventful affording the amine hydrochloride (**2a**) in 80% yield.

Our own investigations revealed that (**2a**) is an atypical antidepressant in several animal models and this will be the subject of a future publication.

Variations in the above general pathway provide entry into interesting peptidomimetics with modified substituents and stereochemical control. Incorporation of these synthons into biologically active peptides could offer better insight into local backbone geometry.

Experimental

^1H N.m.r. spectra were recorded at 60 or 90 MHz using Varian T60 and EM-390 spectrometers. Chemical shifts are reported as δ values downfield from tetramethylsilane or sodium 3-trimethylsilylpropionate 2,2,3,3-d_4. I.r. spectra were recorded on a Perkin-Elmer 257 spectrophotometer and optical rotations were measured on a Perkin-Elmer 141 polarimeter in the solvent and concentration specified. M.p.s were determined on a Buchi SMP-20 apparatus and are uncorrected. Mass spectra were recorded on an AEI-MS-902 spectrometer.

Ethyl 2-Amino-3,3-diethoxypropionate (**3**).—A solution of *N*-formylglycinate (36 g) in ethyl formate (100 ml) was added dropwise over a period of 3 h to a mixture of potassium t-butoxide (40 g) in benzene (400 ml) at 5—15 °C. (**CAUTION**: foaming). Stirring was continued for an additional 2 h after which the yellow mixture was allowed to stand at 4 °C for 18 h. The supernatant was discarded and the gelatinous deposit dissolved in ethanol (200 ml). This solution was then diluted with methylene dichloride (300 ml) and cooled to −20 °C and treated with dry HCl gas for 4 h: it was then stirred at room temperature for an additional 24 h. (Note: failure to maintain low temperature results only in decomposition products.) The solution was concentrated under reduced pressure and the resulting syrup was suspended in ether (500 ml). The mixture was treated with saturated aqueous K_2CO_3 until strongly basic when the phases were separated and the organic phase was washed further with water, dried (Na_2SO_4), and evaporated under reduced pressure to afford an oil (50 g). Vacuum distillation of this afforded (**3**) (36 g, 70%), b.p. 68—70 °C, 0.2 mmHg; $\delta_H(CDCl_3)$ (1 H, d, 2-CH), 4.2 (2 H, q), 3.9—3.3 (5 H, m), 1.7 (2 H, s, NH_2), and 1.3 (9 H, m).

Ethyl N-(2,2-*Dimethoxyethyl*)*glycinate* (**9**).—To a stirred ice-cold mixture of Na_2CO_3 (1.6 g) and aminoacetaldehyde dimethyl acetal (1.05 g) in absolute ethanol (20 ml) was added ethyl iodoacetate (2.2 g) dropwise over 0.5 h. The mixture was stirred vigorously for 2 h at 0 °C and overnight at ambient temperature. The solids were filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in ether (50 ml) and washed thoroughly with water (100 ml). The ethereal phase was dried (Na_2SO_4) and evaporated under reduced pressure to afford the ester (**9**) as an oil (1.2 g, 60%), b.p. 58—60 °C, 0.1 mmHg; $\delta_H(CDCl_3)$ 4.5 (1 H, t, CH), 4.3 (2 H, q), 3.5 (2 H, s), 3.4 (6 H, s), 2.8 (2 H, d), 1.8 (1 H, s, NH), and 1.3 (3 H, t).

General Procedure for the Coupling Reaction.—Dipeptide (**4**). To an ice-cold solution of (**3**) (650 mg) in ethyl acetate (30 ml) was added Z-L-tyrosine (1 g) and EEDQ (810 mg; recrystallized from ether). The ice-bath was removed after 2 h and the solution was extracted sequentially with 1M HCl (×3) and 5% aqueous $NaHCO_3$ (×3) and washed with water. It was then dried (Na_2SO_4) and evaporated to afford the dipeptide (**4**) (1.6 g, 100%) as a viscous oil R_F 0.5, benzene–ethyl acetate (2:1); $\delta_H(CDCl_3)$ 7.4 (5 H, s, carbamate aromatic), 6.9 (5 H, q, ArH and NH), 5.6 (1 H, d, NH), 5.2 (2 H, s, CH_2O), 5.0—4.3 (3 H, m), 4.3 (2 H, q), 3.9—3.3 (4 H, m), and 1.3 (9 H, m).

General Procedure for Cyclization.—Vinylogous amide (**5**). The dipeptide (**4**) (1.5 g) in a 25 ml flask equipped with a mechanical stirrer was treated with 70% aqueous trifluoroacetic acid (10 ml) and the mixture was stirred vigorously for 2 h at ambient temperature. It was then evaporated under high vacuum to afford a viscous gum which was dissolved in ether (50 ml). The solution was then extracted with 2M NaOH (3 × 20 ml), dried (Na_2SO_4), and evaporated to give a red gum. This was chromatographed on silica gel (Mallinkrodt) with benzene–ethyl acetate (3:1) as eluant. The product was crystallized from benzene–light petroleum (b.p. 35—60 °C) to afford the amide (**5**) as crystals (1 g, 70%), m.p. 133—136 °C; $\delta_H(CDCl_3)$ 8.0 (1 H, s, C=CH), 7.5 (1 H, s, NH), 7.2 (5 H, s), 6.6 (4 H, q, ArH), 5.0 (3 H, m), 4.2 (2 H, q), 2.9 (2 H, d, CH_2Ph), and 1.3 (3 H, t); *m/z* 410 (40% M^+); $[\alpha]_D^{20}$ = +244.7 (*c* 0.81 in MeOH). The D-isomer had m.p. 130—134 °C and $[\alpha]_D^{20}$ = −245.5 (*c* 1.05 in MeOH).

Enamine (**12**). The same procedure with (**11**) as starting material yielded the enamine (**12**). The L-isomer had m.p. 138—141 °C, $[\alpha]_D^{20}$ = +134.2 (*c* 2.05 in MeOH); *m/z* 424 (30% M^+); $\delta_H(CDCl_3)$ 7.3 (5 H, s, carbamate Ph), 7.2—6.2 (6 H, m, Ph, OH, CH=CH), 6.6 (1 H, q, CH=CH), 5.4 (3 H, m, α-CH), 4.2 (4 H, m), 2.9 (2 H, d, β-CH_2 tyr), and 1.3 (3 H, t). The D-isomer had m.p. 137—139 °C, $[\alpha]_D^{20}$ = −137.0 (*c* 1.35 in MeOH).

The Hydrochloride Salt of 1-(*Ethoxycarbonylmethyl*)-3-(*p-hydroxybenzyl*)*piperazin*-2-*one* (**2a**).—A solution of (**12**) (900 mg) in absolute ethanol (30 ml) was treated with $Pd(OH)_2$ (150 mg) and concentrated HCl (0.5 ml). The mixture was hydrogenated at 40 p.s.i. H_2 for 4 h. The mixture was filtered through Celite to remove the catalyst and the filtrate was evaporated under reduced pressure; addition of ether to the residue gave a precipitate. This was recrystallized from ethanol–ether to afford the title compound (**2a**) (540 mg, 78%) (a white powder). The L-isomer had m.p. 216—217 °C and $[\alpha]_D^{20}$ = −93° (*c* 0.68 in H_2O); $\nu_{max.}$(KBr) 3 000 cm^{-1} (NH_2), 1 740 cm^{-1} (CO_2Et), and 1 640 cm^{-1} (CONH); $\delta_H(D_2O)$ 7.2 (4 H, q), 4.5 (1 H, t, H-3), 4.3 (2 H, d, N-CH_2O), 4.3 (2 H, q), 3.8—3.4 (4 H, m, NCH_2CH_2N), 3.2 (2 H, m, CH_2Ph), and 1.3 (3 H, t) (Found: C, 54.6; H, 6.35; N, 8.5. $C_{14}H_{21}ClN_2O_4$ requires C, 54.76; H, 6.45; N, 8.52%). The D-isomer had m.p. 213—215 °C, $[\alpha]_D^{20}$ = +91.6 (*c* 0.60 in H_2O).

Hydrogenation of the Vinylogous Amide (**5**).—The enamide (**5**) (6 g) was dissolved in absolute ethanol (100 ml) and treated with concentrated HCl (2.4 ml) and $Pd(OH)_2$ (600 mg). The mixture was hydrogenated at 40 p.s.i. H_2 for 4 h. The mixture was filtered through Celite to remove the catalyst and the filtrate was evaporated under reduced pressure to afford a brown foam (4.2 g). This was dissolved in water and treated with solid K_2CO_3. The solid mass was extracted with methylene dichloride, and the extract dried (Na_2SO_4) and evaporated under reduced pressure. The residual solid was recrystallized from methanol to give white crystals (3.2 g, 70%). The 3*S*,6*R*-isomer had m.p. 204—206 °C, $[\alpha]_D^{20}$ = −140.1 (*c* 0.61 in 0.1M HCl); *m/z* 278 (40% M^+); $\nu_{max.}$(KBr) 3 000 cm^{-1} (NH), 1 740 cm^{-1} (CO_2Et), and 1 650 cm^{-1} (CONH); $\delta_H(D_2O$–DCl) 7.1 (4 H, q, Ph), 5.4 (1 H, t, $CHCO_2$), 4.3 (1 H, t, C_3H), 4.2 (2 H, q), 3.7 (2 H, d, CH_2N), 3.3 (2 H, m, CH_2Ph), and 1.3 (3 H, t) (Found: C, 60.2; H, 6.8; N, 10.0. $C_{14}H_{18}N_2O_4$ requires C, 60.42; H, 6.88; N, 10.06%). The 3*R*,6*S*-isomer had m.p. 204—206 °C and $[\alpha]_D^{20}$ = +140.6 (*c* 0.57 in 0.1M HCl).

Deuteriated (**1a**). Hydrogenation of (**5**) was repeated with deuterioethanol and deuterium chloride; the product had m.p. 205—207 °C; $\delta_H(D_2O$/DCl) 7.1 (4 H, q, ArH), 4.3 (1 H, t, C_3H), 4.2 (2 H, q, CO_2Et), 3.7 (2 H, d, $CDCH_2N$), 3.3 (2 H, m, CH_2Ph), and 1.3 (3 H, t).

Reduction with $NaCNBH_3$.—The enamide (**7**) (1 g) was suspended in a mixture of THF–MeOH 10:1, v:v; 30 ml) and treated with methanolic HCl until the solution reached pH 3 (moist pH paper). $NaCNBH_3$ (260 mg) in MeOH (5 ml) was added dropwise with vigorous stirring. The pH was monitored and adjusted so that the solution remained acidic. After complete addition, the mixture was stirred for an additional 10 h. It was then evaporated under reduced pressure, and the residual solid dissolved in saturated aqueous Na_2CO_3. The mixture was extracted with methylene dichloride and the combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residual solid was recrystallized from methanol to afford crystals (690 mg) (70%), m.p. 204—206 °C, $[\alpha]_D^{20}$ = −140.2 (*c* 0.60 in 0.1M HCl). No trace of any other diastereoisomer was detected in the mother liquor.

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