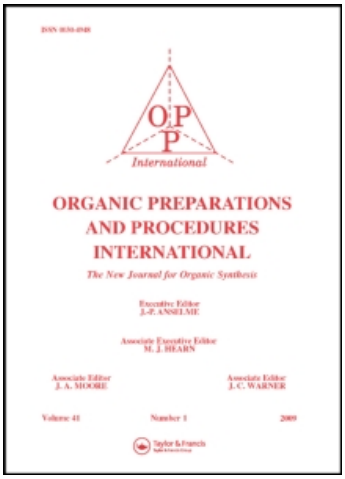

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SYNTHESES OF N-CARBOXYMETHYL DIPEPTIDES *via* N-CARBOXY α-AMINO ACID ANHYDRIDES (NCA) INTERMEDIATES

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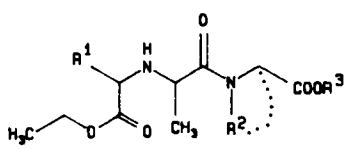
As part of our continuing effort to synthesize angiotensin-converting enzyme (ACE) inhibitors, we were interested in preparing a series of N-carboxy-methyl dipeptides 1. Recently a series of substituted N-carboxy-methyl dipeptides 1 have been obtained[1] by several groups and have been demonstrated to be potent and specific inhibitors of ACE. The importance of these compounds as a possible regulation of the renin-angiotensin system and the possibility that analogs of 1 may also function as inhibitors of other enzymes,[2] make the synthetic routes of 1 of extreme importance.



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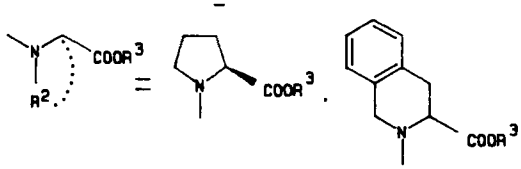
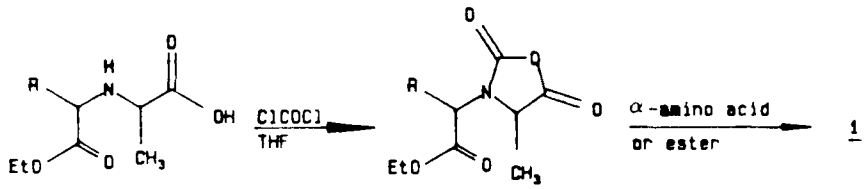
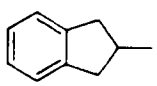


N-Carboxymethyl dipeptides have been prepared by alkylation of the parent dipeptide with α-haloesters,[1a] reductive alkylation with α-ketoesters in the presence of $NaCNBH_3$ [1a-b] or H_2 (Pd/C),[1c] and by a Strecker reaction with aldehydes.[1d] The target molecules 1 were prepared by us by coupling of the N-alkylated amino acid 2 with the appropriate α-amino acid esters in the presence of DCC, CDI, HOBT, and

EEDQ; however, the most desirable and facile route to 1 proved to be through coupling of the appropriate N-carboxy α-amino acid anhydride 3 (NCA) with α-amino acids or esters.



a) R=Me b) Me_2CHCH_2 c) $PhCH_2$ d) $PhCH_2CH_2$ e) 

The NCA method of peptide synthesis[3] has the great advantage of rapid acylation of an α-amino acid by the NCA; in our case, the reaction was complete in a matter of minutes to an hour and gave the desired amides in high yield (85-95%). Another advantage of the NCA method of amino acid coupling is that, in most cases the tedious protection and deprotection of functional groups is not necessary and therefore the NCA method gives the dipeptide directly and with minimal amounts of racemization.

The series of compounds of structures 1 of particular interest were those in which R^1= methyl, sec-butyl, benzyl, phenethyl, and 2-indanyl. The required N-alkylated alanine amino acids 2a-e were conveniently obtained by treatment of the ethyl esters of L-alanine, L-valine, L-phenylalanine, L-homophenyl-alanine,[4] and (dℓ)-N-(2-indanyl) glycine[5] respectively with either tert-butyl 2-bromopropionate or benzyl 2-bromopropionate in refluxing CH_3CN in the presence of 1.2 equivalents of Et_3N by means similar to that in the literature.[1f,6] The corresponding N-alkylated amino acid tert-butyl or benzyl esters were deesterified with either HCl/p-dioxane or by catalytic hydrogenolysis in EtOH over 10% Pd/C to give 2a-2e. The NCA intermediates 3a-e were easily prepared by simply suspending the appropriate acid 2a-e in dry THF followed by the addition of 12.5%

phosgene in toluene[7] at room temperature and then allowing the resulting solution to stir for approximately 1.5 h. The solvent was evaporated and the crude stable NCA's 3a-e were used without further purification.

The NCAs 3a-e were treated with a variety of N-(alkylated) glycine esters or acids to give the diesters or monoacids 1a-o in high isolated yields (85-95%), Table I. When the (SS)-diastereomer[1h,8] 2d is employed no signs of racemization in the acylation reaction are observed. For example, treatment of 3d of (SS)-configuration with L-proline tert-butyl ester gave 1m in 86% yield which upon treatment with HCl/p-dioxane gave the known ACE inhibitor[1a,1b] enalapril (1n) in near quantitative yield. Alternatively enalapril (1n) could be obtained in 77% yield directly from 3d-(SS) by treatment with L-proline in a mixture of THF-H_2O and 1.2 equivalents of $NaHCO_3$. The product was converted to the maleate salt which exhibited an optical rotation and melting point virtually identical to that reported.[1b]

The compound of structure 1-(SS) in which R_1 = phenethyl; R_2 = 2-indanyl and R^3 - H (1d) has also been reported as a potent and specific ACE inhibitor.[1f,9 10] The synthesis of this compound has been reported by a different route[2f] by the Takeda group and has been given the registry number CV-3317. By the NCA method of synthesis followed by deprotection with HCl/p-dioxane this 2-indanyl analog 1 is obtained in 90% overall yield and is identical in all respects, i.e. optical rotation and melting point, to that reported previously[2f] and corresponds to our registry number REV 6000-A(SS). The accepted USAN name for REV 6000-A(SS) is delapril.

EXPERIMENTAL SECTION

N-(2,3-Dihydro-1H-inden-2-yl)-N-[N-[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]glycine Hydrochloride (delapril). Representative Procedure. - N-[1-(S)-Ethoxycarbonyl-3-phenylpropyl]-(S)-alanine[1h] (2d) (5.0g, 17.9 mmol) was suspended in dry THF (25 mL) and then placed under nitrogen. An excess

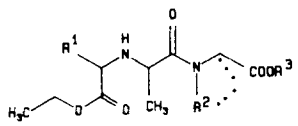


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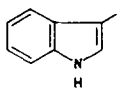
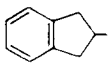
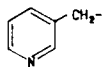
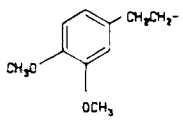
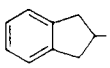
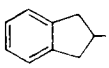
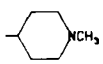
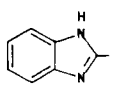
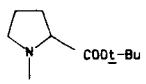
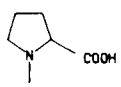
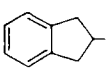
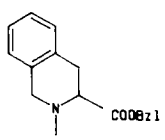
TABLE

entry[a]	R^1	R^2	R^3	Yield (%)[b]	Anal.[c]	MP (°C)
1a	CH_3		t-Bu	94	C, H, N	140 (HCl)
1b	$(CH_3)_2CHCH_2$-	〃	t-Bu	93	C, H, N	95 (HCl)
1c	$PhCH_2$-	〃	H	86	C, H, N	70
1d-(SS)	$PhCH_2CH_2$-	〃	H	94	C, H, N	80
1e		〃	H	83	C, H, N	90
1f-(SS)	$PhCH_2CH_2$-		t-Bu	90	C, H, N	76 (2HCl)
1g-(SS)	$PhCH_2CH_2$-		t-Bu	91	C, H, N	oil
1h-(SS)	$PhCH_2CH_2$-	$PhCH_2CH_2$-	H	97	C, H, N	72 (HCl)
1i-(SS)	$PhCH_2CH_2$-		t-Bu	87	C, H, N	66 (HCl)
1j		〃	H	83	C, H, N	142 (HCl)
1k-(SS)	$PhCH_2CH_2$-		t-Bu	83	C, H, N	oil
1l-(SS)	$PhCH_2CH_2$-		t-Bu	80	C, H, N	oil
1m-(SS)	$PhCH_2CH_2$-			86	C, H, N	oil
1n-(SS)	$PhCH_2CH_2$-			77	C, H, N	148-149[d]
1o-(RSS)[e]				82	C, H, N	205-206 (HCl)

(a) Mixture of diastereomers unless indicated.

(b) In the case of R^3 = H yield refers to acylation followed by deprotection with HCl/dioxane.

(c) All compounds had satisfactory C, H, and N microanalyses and were within 0.4 % of theoretical values.

(d) Maleate salt.

(e) The (RS)-diastereomer of 2e was employed. The corresponding (SSS)-diastereomer of 1o was also prepared (84%).

of phosgene (20 mL of a 12.5% solution in toluene)[7] was added dropwise with stirring. The resulting solution was stirred for 1.5 hr at room temperature. The solvent was concentrated in vacuo and the residue was placed under high vacuum (oil pump) for 1 hr. The resultant NCA 3d was used directly without further purification.

The NCA 3d was dissolved in CH_2Cl_2 (100 mL) and then tert-butyl N-(2-indanyl)glycinate[11] (5.5 g, 22.3 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 5 min. The reaction mixture was stirred at room temperature for 2 hr and then washed consecutively with H_2O, 10% aqueous $NaHCO_3$, and again with H_2O. The organic phase was dried over $MgSO_4$, filtered and concentrated to afford 1i as a pale yellow oil (7.9 g, 87%). The product was characterized as its hydrochloride salt, mp. 60°; $[\alpha]^{20}D$ = + 30.48° (c=1.0, $CHCl_3$); mass spectra (CI):509 (m + 1, 100%). Anal. Calcd for $C_{30}H_{40}N_2O_5 \cdot HCl \cdot 0.5H_2O$: C, 65.03; H, 7.64; N, 5.06; Found: C, 65.30; H, 7.69; N, 5.26.

The tert-butyl ester 1i was easily deprotected in the following manner. To 1i (1.4g, 2.75 mmol) was added 35 mL of p-dioxane which had previously been saturated with dry hydrogen chloride. The resulting solution was stirred for 2.5 h at room temperature under nitrogen and then the solvent was evaporated in vacuo to afford a colorless solid. Anhydrous Et_2O was added to the residue and the solid was collected and washed with a small amount of Et_2O to give 1d (1.3 g, 97%) as a colorless solid mp. 181°, lit.[1f] 180-183°(HBr salt); $[\alpha]^{20}D$ = + 16.44° (c = 1.0, EtOH), lit.[1f] (HBr salt) $[\alpha]^{20}D$ = + 15.6°, solvent not given). Anal. Calcd. for $C_{26}H_{32}N_2O_5 \cdot HCl \cdot 0.5 H_2O$: C 62.71; H, 6.88; N, 5.62 Found: C, 62.81; H, 6.68; N, 5.32.

Preparation of Enalapril (1n).[1b]- The following procedure is representative for those cases in which free amino acids were employed in the acylation of the NCA's 3a-e to give the target ACE inhibitors 1, R=H,

directly in one step.

The NCA of N-[1-(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-alanine[1h] (2d) (2.5 g, 8.19 mmol) was dissolved in THF (25 mL). To this L-Proline (1.4 g, 12.2 mmol) in H_2O (15 mL) in the presence of $NaHCO_3$ (1.23 g, 14.64 mmol) was added dropwise. After all the L-proline was added the resulting mixture was stirred at room temperature for 2 1/2 h. The THF was evaporated *in vacuo* (T < 55°C). Methylene chloride and H_2O were added to the residue and the pH was adjusted to 6.5 by the dropwise addition of concentrated HCl. The product was extracted twice more into CH_2Cl_2. The combined CH_2CL_2 extract was washed twice with H_2O, dried over $MgSO_4$, filtered and evaporated to afford 1n as a colorless foam (2.62 g, 85%). The maleate salt of enalapril (1n) was prepared by adding 1n (2.62 g, 6.97 mmol) in CH_3CN (20 mL) dropwise to a hot solution of maleic acid (0.83 g, 7.16 mmol) in CH_3CN (10 mL). The solution was brought slowly to room temperature and then chilled in an ice-H_2O bath. The colorless crystals that formed were filtered and washed with a small amount of cold CH_3CN followed by a small amount of Et_2O to pure 1n as the maleate salt (3.10 g, 77%): mp. 148-149°, lit[1b] 143-144.5°; $[\alpha]^{20}$ = - 42.47° (c = 1.0, CH_3OH), lit [1b] $[\alpha]^{25}$ = -42.20, c = 1.0, CH_3OH. Anal. Calcd. for $C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.16; H, 6.45; N, 5.39.

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