98. The Synthesis of (*S*)-(+)-2-Amino-3-(1-adamantyl)-propionic Acid (L-(+)-Adamantylalanine, Ada) as a *'Fat'* or *'Super'* Analogue of Leucine and Phenylalanine[1])

by **Kim Quang Do, Peter Thanei, Mario Caviezel** and **Robert Schwyzer**

Institut für Molekularbiologie und Biophysik, Eidgenössische Technische Hochschule Zürich, CH-8093 Zürich

(7.III.79)

Summary

Because of its overall steric resemblance to the phenylalanine analogue, carboranylalanine, the title compound was prepared by the modified *Strecker* synthesis of *Patel & Worsley*. The use of (*S*)-(−)-α-methylbenzylamine in the synthesis, the positive trend of $[\alpha]_D$ with increasing protonation, and the thin-layer chromatographic behaviour of synthetic diastereomeric dipeptides are strong indications that the configuration at the asymmetric carbon atom is *S* (natural L). Its optical purity was ascertained by purification *via* the quinine and ephedrine salts of *t*-butoxycarbonyl-adamantylalanine. The new amino acid shall be used for studies of structure-activity relationships of phenylalanine and leucine residues in biologically active peptides. In addition, a convenient synthesis in excellent yield of the starting material, 2-(1-adamantyl)-ethanal, by *Pfitzner-Moffat* oxidation of 2-(1-adamantyl)-ethanol is described.

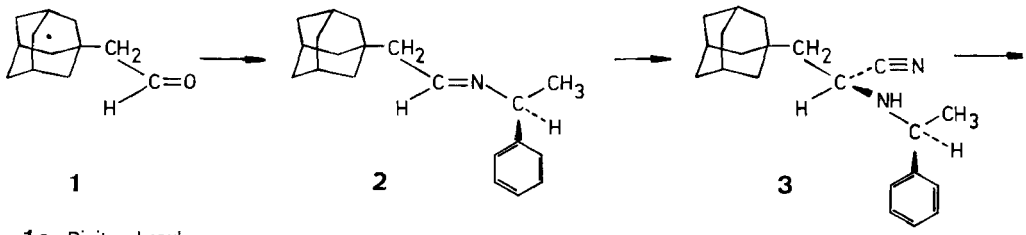
Carboranylalanine has proved to be an interesting analogue of phenylalanine for probing structure-activity and structure-binding relationships in biologically active polypeptides [1]. Its main features are pseudoaromaticity and space-filling properties. In the latter respect, it closely resembles a molecule of phenylalanine in which the phenyl ring is rotating about its 1,4-axis. We expect carboranylalanine and similar *'fat'* amino acids to be especially useful for experimentally distinguishing between the *'address'* or *'message'* quality [2] of the parent amino acid residue in a particular peptide hormone, for enhancing lipophilicity and receptor-binding properties [1], and for producing strong antagonists.

According to space-filling molecular models, (*S*)-2-amino-3-(1-adamantyl)-propionic acid (**6**, for which we propose the trivial name, L-adamantylalanine, Ada) has about the same overall size and shape as carboranylalanine, but lacks its pseudo-

[1]) Abbreviations are according to the IUPAC-IUB Commission on Biochemical Nomenclature (compiled and reprinted by the *American Society of Biological Chemists, Inc.*, Bethesda, Md. 20014, U.S.A., second edition 1975). In addition, Ada stands for L-(+)-adamantylalanine, ada for its D-enantiomer, and BOC- for *t*-butoxycarbonyl.

0018-019X/79/4/0956-09$01.00/0

aromaticity. The characteristics of its side-chain as a saturated hydrocarbon should make it a suitable analogue for probing into the structural significance of both phenylalanine and leucine for peptide conformation and biological activity. Instead of the two branches of leucine at the γ-carbon atom, it possesses three and, in addition, a cyclohexyl ring in chair conformation joining the three branches. It therefore has the properties of a large-sized *'super leucine'* besides being a non-aromatic *'fat phenylalanine'*. Two other *'fat'* analogues of valine and leucine, β-methyl-valine (or *t*-butyl-glycine), and γ-methyl-leucine (or neopentyl-glycine) are also under investigation in this laboratory [3]. It should be interesting to compare the influence of all four amino acids on peptide conformation, the *Hansch* π-values [4], and biological activities [5]. The lower homologue of adamantylalanine, α-amino-(1-adamantyl)-acetic acid, as well as its isomer, α-amino-(2-adamantyl)-acetic acid have been prepared as racemates [6]; they bear no specific resemblance to any natural amino acid.



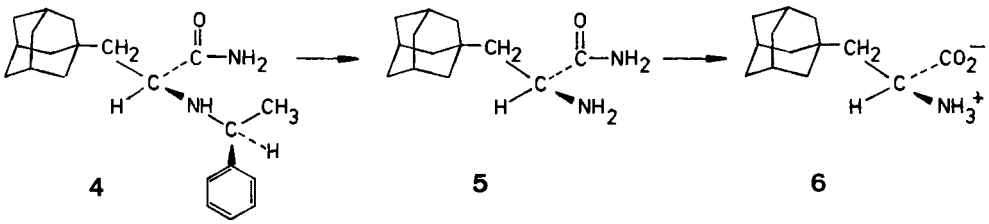
1 **2** **3**

1a Dinitrophenyl-hydrazone

1b Semicarbazone

not characterized

3a Hydrochloride



4 **5** **6**

4a Hydrochloride
4b Sulfate

5a Hydrochloride
5b Sulfate

6a Hydrochloride
6b Sulfate

The *synthesis* was carried out according to the modified *Strecker* procedure of *Patel & Worsley* [7] as shown in the *Scheme*. Physical and analytical data are displayed in *Tables 1–7*. Because of the extreme stability of the adamantyl residue, no special precautions had to be taken to avoid acid hydrolysis in the intermediate steps, as in the case of the asymmetric synthesis of γ-carboxyglutamic acid [8].

The starting point was 2-(1-adamantyl)-ethanal (**1**). This compound had been prepared by *Grignard* reaction of 1-bromomethyl-adamantane [9] and by the reaction of acetylene with 1-hydroxy-adamantane in sulfuric acid [10] [11]. Difficulties encountered with the second procedure, discrepancies in the literature with respect

Table 1. *Thin-layer chromatography of adamantylalanine and related compounds* (Rf values)[a])

Solvent	1	3	4a	4b	5a	5b	6a	6b	7	7a	7b	8a	9	9a	10	10a	11	12
BE 91[b])	0.51																	
HE 82[c])		0.42																
HE 64[c])									0.08	0.08[j])	0.08[j])							
HE 54[c])	0.64	0.71																
CM 91[d])									0.42	0.34[j])	0.35[j])							
CM 11[d])			0.31				0.28						0.76	0.77	0.52	0.23	0.69	0.37
CA 73[e])									0.22	0.22[j])	0.21[j])							
CMA 9553[f])												0.09	0.83					
BAW 1013[g])		0.74	0.58	0.61	0.38	0.40	0.38	0.41				0.55	0.81	0.80	0.58	0.43	0.78	0.61
BAW 523[g])							0.40											
BN 103[h])					0.46													
BN 104[h])		0.75	0.77	0.77		0.62	0.18	0.23										
IWP 766[i])							0.62											

[a]) Detected by I_2, ninhydrin, *Reindel-Hoppe* reagent, fluorescence quenching in UV., or other suitable means. Unless otherwise indicated, only one spot was observed on the *Merck* F254 silicagel plates. [b]) Benzene/ethanol 9:1. [c]) Hexane/ethyl acetate 8:2, 6:4 or 5:4. [d]) Chloroform/methanol 9:1 or 1:1. [e]) Chloroform/acetone 7:3. [f]) Chloroform/methanol/acetic acid 95:5:3. [g]) Butanol/acetic acid/water 10:1:3 or 5:2:3. [h]) Butanol/aqueous ammonia (25%) 10:3 or 10:4. [i]) Isopropylalcohol/water/pyridine 7:6:6. [j]) The moving spot is BOC · Ada · OH; the alcaloid remains at the origin (fluorescence quenching).

Table 2. *Physical data of adamantylalanine and related compounds.* Aspect: s = solid, c = crystalline (A); Solvent for crystallization (S); Mp. °C; [a]) Specific Rotation, $[\alpha]_D^{20}$, ($c = 1$, MeOH) unless noted

	A	S	Mp.	$[\alpha]_D^{20}$ deg.		A	S	Mp.	$[\alpha]_D^{20}$ deg.		A	S	Mp.	$[\alpha]_D^{20}$ deg.
1	oil	–	58[b])	–	**5b**	c	EtOH/H_2O	239[d])	+ 10.4[g])	**8a**	c	MeOH/H_2O	120	+ 21.2
1a	c	EtOH	170–171	–	**6**	c	MeOH/H_2O	245[d])	–[h])	**9**	c	ether	140	– 25.1
1b	c	EtOH	216	–	**6a**	c	MeOH/H_2O	> 300[d])	+ 16.2[i,j])	**9a**	c	ether/C_5H_{12}	150	+ 14.2
3	c	MeOH/H_2O	79	– 131.3[c])	**6b**	c	EtOH/H_2O	225[d])	–[i])	**10**	s	MeOH/H_2O	155	– 24.3
4a	c	acetone/H_2O	259[d])	– 25.0	**7**	c	EtOAc/C_5H_{12}	169–171	– 15.0[j,k])	**10a**	s	MeOH/H_2O	–	+ 50.7
4b	c	EtOH/H_2O	211[d])	– 17.1[e])	**7a**	c	EtOAc/C_5H_{12}	127–130	– 94.3[c])	**11**	c	ether/C_5H_{12}	160	– 36.3
5a	c	EtOH/H_2O	271–272[d])	+ 8.6[f])	**7b**	c	EtOAc/C_5H_{12}	134–137	– 26.0[c])	**11a**	s	EtOAc/C_5H_{12}	–	–

[a]) Uncorrected. [b]) Boiling point at 0.04 *Torr*. [c]) In chloroform. [d]) With decomposition. [e]) In methanol/glacial acetic acid 1:1. [f]) $c = 1.4$. [g]) In methanol/2N HCl 9:1. [h]) See **6a**, **6b**. [i]) + 5.1 in methanol/2N NH_3 1:1. [j]) Mean value of various preparations, ± 0.5°. [k]) ($c = 1$–1.3, AcOH).

to the physical properties, and the commercial availability of 2-(1-adamantyl)-ethanol [12] *(Ega Chemie)* prompted us to prepare **1** from the alcohol by *Pfitzner-Moffatt* oxidation [13]. The aldehyde **1** was easily obtained as an oil in 98% yield and characterized by its 2,4-dinitrophenylhydrazone and semicarbazone (**1a** resp. **1b**, *Table 2*). The physical data closely corresponded to those reported in [9] [10] ([11] reports m.p. 135° for **1** and m.p. 212° for **1a**). Chromatographic behaviour (TLC., *Table 1*), microanalytical data *(Table 3)*, as well as the IR. and NMR. spectra *(Table 4)* agreed with the properties expected for **1**.

Condensation of **1** with (*S*)-(−)-*α*-methylbenzylamine [14] afforded the *Schiff* base **2** in quantitative yield. Because of its instability towards moisture, **2** was not characterized, but immediately converted to the aminonitrile **3** by addition of HCN. This well-characterized, crystalline compound, obtained in about 75% yield, appeared to be somewhat unstable upon storage (elimination of HCN). Material that had to be kept for a longer period was therefore converted to the more stable, well-crystallized hydrochloride **3a**. Hydrolysis of **3** to the amide **4** was accomplished either with ethanol/conc. hydrochloric acid 2:1 (*v*/*v*) that was saturated with HCl at −10°, by reacting under pressure at 20–40°, or by dissolving the nitrile in conc. sulfuric acid at −30° and raising the temp. to 0° and 20°. The hydrochloride **4a** was obtained in over 80% yield; the sulfate **4b** was used directly in the next step and only a small sample was withdrawn for characterization. The hydrogenolytic removal of the phenylethyl group proceeded smoothly with Pd/C at atmospheric pressure (**4a** → **5a**: 86% yield; the yield of the sulfate **5b** was not determined). The amide salts **5a** and **5b** were hydrolyzed to the amino acid hydrochloride **6a** and the sulfate **6b** at 90° with conc. hydrochloric acid or 2N H_2SO_4, respectively (**6a** was obtained in 79% yield, **6b** in 59% overall yield from **3**).

Adamantylalanine (**6**), finally, was prepared as a well-crystallized compound by neutralization of solutions of **6a** and **6b** and recrystallization from dilute alcohol.

Table 3. *Analytical data of adamantylalanine and related compounds.* Elementary composition (E); calculated molecular weight (W); microanalyses: [a]) C,H,N (% calculated/% found)

	1a	**1b**	**3**	**4a**	**5b**	**6**
E	$C_{18}H_{22}N_4O_4$	$C_{13}H_{21}N_3O$	$C_{21}H_{28}N_2$	$C_{21}H_{31}ClN_2O$	$C_{13}H_{23}N_2O$, $\frac{1}{2}SO_4$	$C_{13}H_{21}NO_2$
W	358.4	235.3	308.4	362.9	271.4	223.3
C	60.31/60.24	66.35/66.38	81.77/81.67	69.49/69.40	57.54/57.04	69.92/69.69
H	6.19/ 6.22	9.00/ 9.00	9.15/ 9.14	8.61/ 8.63	8.54/ 8.67	9.48/ 9.40
N	15.63/15.50	17.86/16.88	9.08/ 8.91	7.72/ 7.71	10.32/ 9.78[b])	6.27/ 6.20[c])
	7a	**7b**	**9**	**9a**	**10**	**11**
E	$C_{38}H_{53}N_3O_6$	$C_{28}H_{44}O_5N_2$	$C_{31}H_{46}N_2O_5$	$C_{31}H_{46}N_2O_5$	$C_{22}H_{31}ClN_2O_3$	$C_{28}H_{48}N_2O_5$
W	647.8	488.7	526.7	526.7	375.0	492.7
C	70.45/70.44	68.82/69.09	70.69/70.55	70.69/70.59	64.93/64.80	68.26/68.28
H	8.24/ 8.10	9.07/ 9.20	8.80/ 8.83	8.80/ 8.85	7.68/ 7.71	9.82/ 9.79
N	6.49/ 6.31	5.73/ 5.48	5.32/ 5.29	5.32/ 5.32	6.88/ 6.74	5.69/ 5.73

[a]) Performed in the Laboratory of Organic Chemistry, ETHZ *(D. Manser)*. [b]) Sulfur analysis: 5.91/5.90. [c]) Prepared *via* the hydrochloride **6a**; **6** from the sulfate **6b** analyzed as follows (found): C 69.85, H 9.54, N 6.17%.

All the analytical data, including IR. and NMR., are consistent with the assigned structure. The mass spectrum of **6a** is dominated by the strong peak of the adamantyl residue (*m/e* 135); the molecular ion (*m/e* 223) is very weak *(Table 6)*.

The *absolute configuration* was inferred from indirect observations, because we found it impossible to degrade the extremely stable adamantyl residue with preservation of the asymmetric carbon atom and to obtain a product with recognized

Table 4. *IR. and ^{1}H-NMR. data of adamantylalanine and related compounds*[a])

	IR.		NMR.[b])				IR.		NMR.		
1	1700-1740*s*	(C=O)	1.8-2.0*m*	15	1	**7**	3440*m*	(N–H[f]))	1.45*s*	9	9
			2.2*d*	2	2		3600-2400*m*	(O–H[g]))	1.5-2.1*m*	17	8
			9.9*t*	1	3		1730/1710*s*	(C=O)	4.1-4.5*m*	1	5
							1370*s*	(CH_3)	4.5-4.9*m*	1	10
3	3270*m*	(N–H)	1.0-2.0*m*	20	4		1165*s*	(C–O)	7.6-8.0	1	11
	2200*s*	(C≡N)	3.2*t*	1	5						
			4.09*qa*	1	6	**7a**	3440*m*	(–[h]))	1.6*s*	9	9
			7.2*s*	5	7		3400-2000*w*	(NH^+)	1.6-3.9*m*	28	12
							1710*s*	(C=O)	3.9*s*	3	13
4a	3030-3150*m*	(N–H[c]))					1620*s*	(C=C)	4.0-4.7*m*	2	14
	1680*s*	(N–H[d]))					1595*s*	(COO^-)	4.9-5.6*m*	3	15
	1580*s*	(N–H[e]))					1370*s*	(CH_3)	6.3-6.5*m*	1	10
							1165*s*	(C–O)	6.9-7.3*m*	1	23
5a	3300*m*	(N–H[f]))	1.4-2.0*m*	17	8				7.25-8.3*m*	5	16
	3150*m*	(N–H[f]))	4.0*t*	1	5				8.7 ~ *d*	1	17
	1680*s*	(N–H[d]))									
	1600*s*	(N–H[e]))				**7b**	3420*m*	(N–H)	1.1*d*	3	18
							3400-2000*m*	($N-H^+$)	1.4*s*	9	9
6a	3400*m*	(O–H[g]))	1.4-2.0*m*	17	8		1690*s*	(C=O)	1.4-2.4*m*	17	8
	3100-2400*m*	(NH_3^+)	4.2*t*	1	5		1575*m*	(COO^-)	2.75*s*	3	19
	1755*s*	(C=O)					1380*s*	(CH_3)	3.1-3.5*m*	1	20
	1600*m*	(NH_3^+)					1160*s*	(C–O)	4.0-4.5*m*	1	5
	1500*m*	(NH_3^+)							4.9-5.2*m*	1	10
	1200*s*	(C–O)							5.3-5.5*m*	1	21
									7.3*s*	5	7
									8.5	3	22

[a]) The IR. spectra were determined in $CHCl_3$ with the exception of **6a** (Nujol). Wavenumbers of the absorption bands in cm^{-1}; signal intensity is: *w* = weak, *m* = medium, *s* = strong; the assignments are indicated in parentheses by partial formulae. Only characteristic IR. bands are indicated. The NMR. spectra were determined at 60 MHz with TMS as an internal standard. The solvent was $CDCl_3$ except for **6a** (CD_3OD). The data are in the order, the chemical shifts in ppm, the signal splitting (*s* = singlet, *d* = doublet, *t* = triplet, *qa* = quartet, *m* = multiplet), the number of protons found by integration and a number indicating the assignment (see footnote [b])).

[b]) The NMR. assignments are to the protons of: 1 = adamantyl; 2 = C(2) (ethane); 3 = C(1); 4 = adamantyl + C(3) + CH_3; 5 = C(2) (propionyl); 6 = benzyl; 7 = phenyl; 8 = adamantyl + C(3); 9 = CH_3 of BOC; 10 = NH of urethane; 11 = COOH (broad signal); 12 = 8 + quinine C(2-8); 13 = OCH_3 of quinine; 14 = C(2) + C(9) of quinine; 15 = vinyl of quinine; 16 = C(5′,7′,8′) of quinine + HO–C(9) + {$COO^-{}^+HN$} (the latter two protons are exchangeable with D_2O); 17 = quinine C(2′) (*J* = 5 Hz + long-range coupling); 18 = H_3C–C(1) of ephedrine (*J* = 6 Hz); 19 = H_3C–N^+ of ephedrine; 20 = C(1) of ephedrine; 21 = C(2) of ephedrine; 22 = HO–C(2) and NH_2^+ of ephedrine, broad signal, exchangeable with D_2O; 23 = C(3′) of quinine.

[c]) Amide (assoc.) + amine. [d]) Amide I. [e]) Amide II. [f]) Amide/urethane. [g]) Carboxylic acid (O–H, assoc.). [h]) N–H of urethane + O–H of quinine.

chirality, *e.g.* aspartic acid. Three lines of circumstantial evidence point to the *S*- or natural L-configuration of **6**: The first is the observation of *Patel & Worsley* [7] that the use of (*S*)-(−)-*α*-methylbenzylamine led to the production of the natural amino acids with usually more than 90% optical purity in all of their experiments. *A priori* there is no reason to expect our case to be an exception. The second observation is the increase of $[\alpha]_D$ to more positive values with increasing acidity of the solvent *(Table 2)*, an indication of the L-configuration [15]. The third supporting observation is the behaviour of diastereomeric dipeptides on TLC. According to *Wieland & Bende* [16], the diastereomer with identical chirality of the two amino acid residues generally displays the greater Rf value. This was true for the dipeptide Phe-Ada **10** (prepared from (+)-adamantylalanine, **6**) when compared with Phe-ada (*10a*, pre-

Table 5. *^{13}C-NMR. data of* N$^{\alpha}$-t-*butoxycarbonyl-adamantylalanine* (**7**)[a])

28.41	3*qa*	3 $(CH_3)_3C$
28.72	3*d*	3 C(3), C(5) and C(7) of adamantyl
32.71	*s*	1 C(1) of adamantyl
36.99	3*t*	3 C(4), C(6) and C(10) of adamantyl
42.48	3*t*	3 C(2), C(8) and C(9) of adamantyl
46.95	*t*	1 C(*β*)
50.20	*d*	1 C(*α*) (broad signal)
155.66	*s*	1 C=O of urethane (broad signal)
178.65	*s*	1 COO^-

[a]) The spectrum was determined at 100 MHz and 32° in $CDCl_3$ with TMS as an internal standard by Prof. Dr. *J.F. Oth* and *K. Hiltbrunner* in the Laboratory of Organic Chemistry, ETHZ. Heading abbreviations see *Table 4.*

[b]) The assignment of adamantyl carbon atoms was made according to 1-methyl-adamantane [20] with C(1) 29.85 (*s*), C(2,8,9) 44.65 (*t*), C(3,5,7) 31.45 (*d*) and C(4,6,10) 37.00 ppm (*t*).

Table 6. *Mass spectra of adamantylalanine hydrochloride* **6a** *and* t-*butoxycarbonyl adamantylalanine* **7**[a])

6a	223 (< 1), 178 (100), 135 (93), 107 (10), 93 (17), 79 (19), 61 (7), 55 (7), 41 (10), 28 (7)
7	278 (7), 266 (7), 249 (21), 222 (33), 205 (5), 178 (37), 135 (100), 107 (5), 93 (14), 91 (7), 79 (14), 67 (7), 57 (49), 45 (5), 43 (5), 41 (16), 29 (5)

[a]) Determined on a *Hitachi-Perkin-Elmer* RMU 6D mass spectrometer in the laboratory of PD Dr. *J. Seibl*, ETHZ. With the exception of the first signal, only those with an intensity > 5% relative to the strongest signal are recorded here. The numbers mean: *m/e* (% relative intensity).

Table 7. *Specific rotations of adamantylalanine hydrochloride* (**6a**) (in methanol) *and of* t-*butoxycarbonyl-adamantylalanine* (**7**) (in glacial acetic acid) *obtained from various experiments*

Compound and origin	$[\alpha]_D^{21}$	$[\alpha]_{546}^{21}$	(c)
7 (starting material)	− 15.1°	− 18.6°	(1.1)
7 (from **7a**, quinine salt)	− 15.2°	− 18.5°	(1.0)
7 (from **7b**, ephedrine salt)	− 14.6°	− 18.0°	(1.3)
6a (starting material)	+ 16.2°	+ 19.2°	(1.0)
6a (from **7** from **7a**)	+ 16.1°	+ 19.2°	(1.1)
6a (from **7** from **7b**)	+ 16.4°	+ 19.1°	(1.2)
6a (from **7**, starting material)	+ 16.1°	+ 19.2°	(1.3)

pared from (−)-adamantylalanine that had been obtained by the same procedure used for **6**, but with (*R*)-(+)-α-methylbenzylamine replacing its enantiomer). Further substantiation of the assignment L-(+)-Ada and D-(−)-ada using biological and other physical methods is in progress. The syntheses of dipeptides was carried out using classical peptide chemistry [17] as follows: **6** → BOC · Ada · OH (**7**) and H · Ada · O*t*Bu (**8a**); **8a** → BOC · Phe-Ada · O*t*Bu (**9**) → {H · Phe-Ada · OH, HCl} (**10**); **7** → BOC · Ada-Leu · O*t*Bu (**11**) → {H · Ada-Leu · OH, HCl} (**12**). The dipeptide **12** was prepared in order to test the suitability of BOC · Ada · OH for peptide synthesis.

The optical purity of **6** was determined by converting the acidic BOC · Ada · OH (**7**) into its quinine (**7a**) and ephedrine [(1*R*,2*S*)-(−)-methylamino-1-phenylpropan-1-ol [14]] (**7b**) salts, purifying the crystalline products, reconverting them to **7** and **6**, and comparing the specific rotations of these compounds with those of the starting materials *(Table 7)*. Judged by this procedure, the starting materials **6** and **7** were 100% optically pure. The compounds were extensively characterized as indicated in the *Tables*. All the ^{1}H-NMR. signals of **7**, **7a** and **7b** could be assigned. The ^{13}C-NMR. spectrum of **7** agrees completely with the expected structure *(Table 5)* and the mass spectrum of **7** *(Table 6)* again shows the very strong adamantyl peak (*m/e* 135), but lacks the molecular ion which is not astonishing in the case of a *t*-butoxycarbonyl derivative (a relatively strong peak at *m/e* 57 could correspond to the *t*-butyl group).

In conclusion, we feel justified to state that we have prepared L-(+)-adamantylalanine (Ada) with about 100% optical purity and in an overall yield of 40–43% starting from 2-(1-adamantyl)-ethanol.

This work was supported by research grants of the *Swiss National Science Foundation* and the *Swiss Federal Institute of Technology*. It is part of the doctoral theses of *K. Q. D.* and *P. T.*

Experimental Part

General. - Removal of solvents from dissolved products was carried out in a rotary evaporator at reduced pressure (0.1–10 *Torr*) and low temperature. Product characteristics are displayed in *Tables 1–6*. Whenever well-known procedures of peptide chemistry were applied or well-known intermediates used, reference is made to *Houben-Weyl* [17] where experimental details are given or the literature is summarized. For general remarks on instrumentation and other items, see [18].

2-(1-Adamantyl)-ethanol (**1**). A solution of 2-(1-adamantyl)-ethanol (30 g, 166.4 mmol) in dry benzene (300 ml) was treated consecutively with dimethyl sulfoxide (350 ml), pyridine (13.5 g), trifluoroacetic acid (6.6 g), and (at 0°) *N,N'*-dicyclohexylcarbodiimide (70 g, 339 mmol). All reagents were dried and redistilled before use. The mixture was left standing at 20° for 40 h. The *N,N'*-dicyclohexylurea that had formed was filtered off and washed with benzene (500 ml). The combined filtrates were washed thrice with water (300 ml each), and the aqueous phase extracted again with benzene (300 ml). The organic phases were combined, dried over sodium sulfate, and freed of solvent. The residue was dissolved in ethyl acetate (100 ml), treated with acetic acid (5 drops), and (after 15 min) filtered to remove some *N,N'*-dicyclohexylurea. The solvent was evaporated in a 250 ml flask and the slightly yellow residue distilled at 58° and 0.04 Torr under N_2. After a first fraction of 1 g, the pure, colourless product **1** (29.1 g, 98% yield) emerged as an oil.

1-[(S)-α-Methylbenzylimino]-2-(1-adamantyl)-ethane (**2**). A solution of **1** (29 g, 162.6 mmol) in diethyl ether (dry, 200 ml) was added dropwise (40 min) to an ice-cold solution of (*S*)-α-methylbenzylamine (*Fluka*, Buchs) in the same solvent (400 ml). After a further hour at 0°, the mixture was cooled to −20° (acetone/solid CO_2) and treated with small portions of pulverized, anhydrous calcium sulfate (dried for 2 h at 250°/0.03 Torr, total of 90 g). The mixture was stirred mechanically, slowly brought to

room temp., and kept overnight. It was then again cooled to 0° and treated with more anhydrous calcium sulfate (18 g). After 1 h at 20°, the calcium sulfate was removed by filtration in a dry, inert atmosphere (calcium chloride tube, *Protectan* gas). The filtration was very tedious because of the extremely fine grain of the calcium sulfate; perhaps centrifugation in an explosion-proof centrifuge would be better. The precipitate was washed with ether (100 ml) and the combined filtrates evaporated as usual: 46 g (100%) of a slightly yellowish oil. Because of its instability towards moisture, the product was not characterized, but immediately used in the preparation of the nitrile **3**.

2-[(S)-α-Methylbenzylamino]-3-(1-adamantyl)-propionitrile (**3**). A solution of **2** (45 g, about 160 mmol) in ethanol (500 ml) was placed in a flask that was connected *via* a tube with stopcocks and a lateral rubber balloon to a glass container with liquid HCN. The cooled system (0°) was evacuated and the HCN container warmed to 15–25°. After enough HCN (about 13 g, 480 mmol) had condensed in the flask containing the ethanolic solution of **2** (the process required about 30 min), the HCN container was removed, the reaction flask closed, and the reaction allowed to proceed for 50 h at room temperature. Dry N_2 was bubbled through the reaction mixture to remove excess HCN, which was absorbed in a sodium thiosulfate solution. About $\frac{1}{3}$ of the solvent was then removed by evaporation whereupon the nitrile **3** began to crystallize. The solution was warmed to 50° under an atmosphere of inert gas and carefully treated with water until turbid. Crystallization was completed at 4°, the crystals gathered by filtration and washed first with ice-cold ethanol/water 4:1, then with ice-cold ethanol/water 1:1: 23.4 g. A further crop was obtained from the mother liquor. Total yield: 34.5 g (74.7%). The *hydrochloride* of **3** crystallized as colourless rhomboeders from a chloroform/ether/HCl mixture (98% yield).

2-[(S)-α-Methylbenzylamino]-3-(1-adamantyl)-propionamide (**4**). – *Hydrochloride* (**4a**): A cold (0°) solution of the nitrile **3** (1 g, 3.2 mmol) in ethanol (50 ml) was treated with 37% hydrochloric acid (25 ml). The solution was then saturated at −10° with HCl-gas and kept in a sealed container for 15 h at 20° and 2 h at 40°. The solvents were evaporated as usual and excess HCl removed by twice adding and distilling off some water (10 ml each). The dry, colourless residue was washed well with ether to remove traces of unreacted reactand: residue 0.95 g **4a** (81%).

Sulfate (**4b**). The nitrile **3** (5 g, 16.2 mmol) was added to cold (−30°) 98% sulfuric acid (100 ml). The mixture was kept at 0° for 3 h and then at 20° for 40 h. After cooling, the solution was poured (with efficient stirring) onto chopped ice (350 g). The colourless precipitate (**4b**) was filtered off and, without drying, dissolved in methanol (100 ml). This solution was used directly in the next step (hydrogenolysis to **5**).

2-Amino-3-(1-adamantyl)-propionamide (**5**). – *Hydrochloride* **5a** *from the hydrochloride* **4a**. A solution of **4a** (220 mg, 0.6 mmol) in ethanol (20 ml) containing one equivalent of 37% hydrochloric acid (0.05 ml) was hydrogenated for 15 h at 20° and 760 Torr over 10% Pd/C (50 mg). The colourless, crystalline residue obtained after filtration and evaporation was pure **5a**: 134.6 mg (86%).

Sulfate **5b** from the sulfate **4b**. The methanolic solution obtained at the end of the preparation of **4b** (see above) was purged with nitrogen and hydrogenated for 15 h at 20° and 760 Torr over 10% Pd/C (500 mg). The solution was filtered and evaporated, and the colourless crystalline residue (pure **5b**) used for the next step (hydrolysis to **6**).

(+)-*2-Amino-3-(1-adamantyl)-propionic acid* (**6**). – *From the amide hydrochloride* **5a**. A solution of **5a** (100 mg, 0.38 mmol) in 37% hydrochloric acid (10 ml) was heated to 90° for 4 h. After 1 h, the hydrochloride **6a** began to crystallize. After cooling, the crystals were separated and washed with water. They were recrystallized from methanol/water: white needles, 80 mg (79%). This amino acid hydrochloride **6a** was dissolved in a hot mixture of methanol/5% aqueous $NaHCO_3$-solution (pH 10.5) and the solution immediately neutralized to pH 7 with dilute hydrochloric acid. The amino acid began to crystallize out already at pH 8. Most of the methanol was removed by evaporation, the crystalline phase separated and washed with water. Recrystallization from methanol/water at 90° gave colourless needles of **6**. – *From the amide sulfate* **5b**. The crude crystalline **5b** described above was suspended in 2N H_2SO_4 (100 ml) and dissolved by heating to 90°. After 4 h at this temperature and cooling to 4°, the crystals of **6b** were separated, washed with water, and dried: 2.6 g (59%). **6b** was converted to **6** in a manner similar to that described above for **6a**→**6**.

N^{α}-t-*Butoxycarbonyl-adamantylalanine (BOC·Ada·OH,* **7**). A well-stirred suspension of **6b** (4 g, 14.7 mmol) in tetrahydrofuran/water 1:1 was cooled to 0° and treated successively with triethylamine (8.2 g, 29.4 mmol) and di-*t*-butoxycarbonyl-oxide [19] (3.54 g, 16.2 mmol). After an initial reaction of 4 h, the temperature was kept at 20° for 16 h. The tetrahydrofuran was removed, the mainly aqueous residue acidified to pH 4 at 0° with 0.1N H_2SO_4. The solid precipitate was gathered by filtration, washed with water, and recrystallized from 2-propanol/water. Yield 3.9 g (82%) of pure **7**. – *Quinine salt of*

BOC · Ada · OH (**7a**). A hot solution of **7** (200 mg, 0.62 mmol) in a small volume of ethyl acetate was treated dropwise with a hot solution of quinine (220 mg, 0.68 mmol, *Fluka, puriss.*) in the same solvent. After addition of some pentane, the solution was cooled to −20°, whereupon pure **7a** (300 mg, 75%) crystallized as colourless needles. *Ephedrine salt of BOC · Ada · OH* (**7b**). This was prepared in exactly the same manner as **7a**, using (instead of quinine) (−)-ephedrine (*Fluka, purum* grade): colourless needles (240 mg, 79%). *BOC · Ada · OH*, **7**, *from* **7a** *or* **7b**. A solution of **7a** (or **7b**) in ethyl acetate was washed successively with citric acid (5%) and twice with conc. NaCl-solution, dried, and the solvent evaporated. The residue was crystallized from ethyl acetate/pentane at −20°. Yields 80–90%. *{Ada, HCl}* (**6a**, *from* **7**). A stirred solution of **7** (about 100 mg) in dioxane (5 ml) at 20° was slowly treated with conc. hydrochloric acid (5 ml). After the vigorous evolution of CO_2, the solution was kept for 30 min and evaporated. The evaporation was repeated thrice after addition of methanol in order to remove the HCl. Yield 100%. Recrystallization from methanol/ether at −20°.

{H · Ada · OtBu, HCl} (**8a**). This compound was prepared in the usual manner [17] from a suspension of **6a** (820 mg, 3.2 mmol) in dioxane (15 ml), conc. sulfuric acid (1.5 ml), and a total of 16 ml of isobutene. The ester was isolated as the free base and converted into the hydrochloride **8a** with HCl in ethyl acetate. After recrystallization from methanol/water, the yield was 650 mg or 61%. **8b** was prepared in the same manner from the (−)-enantiomer of **6**.

BOC · Phe-Ada · OtBu (**9**). This compound was prepared from BOC · Phe · OH [17] (0.5 mmol) and **8a** (0.5 mmol) in dimethylformamide (5 ml) using *N*-ethylmorpholine (0.5 mmol), 1-hydroxybenzotriazole (0.75 mmol) and dicyclohexylcarbodiimide (0.5 mmol) [17]. Yield 72%. *BOC · Phe-ada · OtBu* (**9a**) was prepared from **8b** by the same procedure.

{H · Phe-Ada · OH, HCl} (**10**) *and {H · Phe-ada · OH, HCl}* (**10a**). A solution of HCl in formic acid (0.1 N) was used to remove the *t*-butyl protecting groups according to the usual procedure [17]; yield 85%.

BOC · Ada-Leu · OtBu (**11**). The procedure was the same as for **9**; yield 70%.

{H · Ada-Leu · OH, HCl} (**12**). The preparation was similar to that of **10** and **10a**: yield 86%.

REFERENCES

[1] *W. Fischli, O. Leukart & R. Schwyzer,* Helv. *60,* 959 (1977); *A. Eberle, O. Leukart, P. Schiller, J.L. Fauchère & R. Schwyzer,* FEBS Letters *82,* 325 (1977).

[2] *R. Schwyzer,* Ann. N.Y. Acad. Sci. *297,* 3 (1977).

[3] *J.L. Fauchère & R. Schwyzer,* in preparation.

[4] *J. Iwasa, T. Fujita & C. Hansch,* J. medicin. Chemistry *8,* 150 (1964); *C. Hansch, A. Leo, S.H. Unger, K.H. Kim, D. Nikaitani & E.J. Lien,* ibid. *16,* 1207 (1973).

[5] *J.L. Fauchère,* in preparation.

[6] *B. Gaspert, S. Hromadko & B. Vranesik,* Croat. chim. Acta *48,* 169 (1976).

[7] *M.S. Patel & M. Worsley,* Canad. J. Chemistry *48,* 1881 (1970).

[8] *M. Oppliger & R. Schwyzer,* Helv. *60,* 43 (1977).

[9] *F.N. Stepanov & N.L. Dovgan,* Ž. org. Chim. *4,* 277 (1968).

[10] *K. Bott,* Tetrahedron Letters *22,* 1747 (1969); Liebigs Ann. Chem. *766,* 51 (1972).

[11] *D.R. Kell & F.J. McQuillin,* Chem. Commun. 599 (1970); J. chem. Soc. Perkin I, 2100 (1972).

[12] Review articles on adamantane and its derivatives: *H. Stetter,* Angew. Chem. *66,* 217 (1954); *74,* 361 (1962); *R.C. Fort & P. Von R. Schleyer,* Chem. Rev. *64,* 277 (1964).

[13] *K.E. Pfitzner & F.G. Moffat,* J. Amer. chem. Soc. *87,* 5661, 5670 (1965).

[14] *W. Klyne & J. Buckingham,* 'Atlas of Stereochemistry', Vol. 1, A19, Chapman and Hall, London, second edition 1978.

[15] *J.P. Greenstein & M. Winitz,* 'Chemistry of the Amino Acids', Vol. 1, p. 83, John Wiley & Sons, Inc., New York, London 1961.

[16] *T. Wieland & H. Bende,* Chem. Ber. *98,* 504 (1965).

[17] *E. Wünsch,* «Synthese von Peptiden», Bd. 15, *Houben-Weyl,* «Methoden der organischen Chemie», E. Müller, Herausgeber, Georg Thieme Verlag, Stuttgart 1974.

[18] *A. Eberle, Y.-S. Chang & R. Schwyzer,* Helv. *61,* 2360 (1978).

[19] *L. Moroder, A. Hallett, E. Wünsch, O. Keller & G. Wersin,* Hoppe-Seyler's Z. physiol. Chem. *357,* 1651 (1976).

[20] *E. Breitmaier & G. Bauer,* «^{13}C-NMR.-Spektroskopie», p. 150, Georg Thieme Verlag, Stuttgart 1977.