Studies on Pyrrolidinones. Synthesis of Some Bioisosteres of 3,3,5-Trimethylcyclohexyl Pyroglutamate

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The synthesis of new *N*-(4-chlorobenzyl) and *N*-(4-chlorobenzoyl)pyroglutamic esters and amids whose the structure conserves the main structural features of the cholesterol lowering agent crilvastatin is described.

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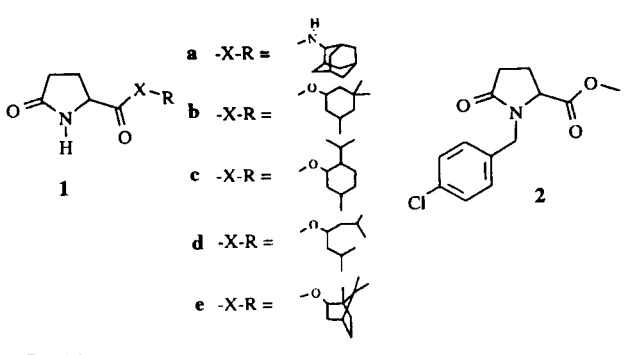
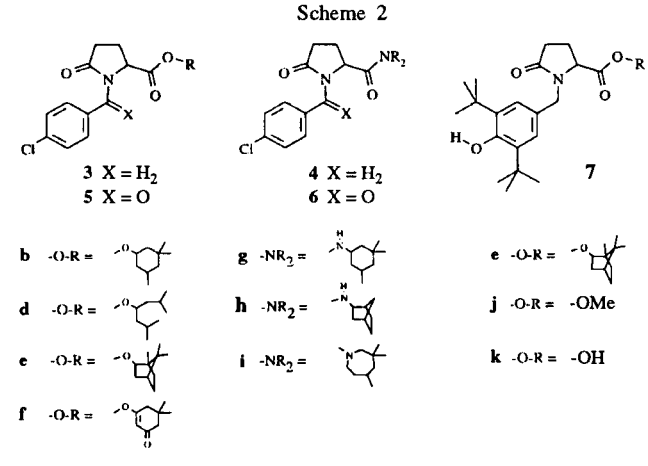
In 1986, while working on antiviral compounds, Panmedica found that adamantyl pyroglutamide **1a** possess also hypocholesterolemic properties [1], and a study carried out around this structure showed that a number of cycloaliphatic esters of pyroglutamic acid, such as 3,3,5-trimethylcyclohexyl pyroglutamate (crilvastatin) **1b** are more powerful lipid-lowering agents than **1a** [2]. In previous studies, Unilever patented several pyroglutamic esters of terpenic alcohols, for example menthyl pyroglutamate (**1c**), that have the property of lowering the skin amount of lipids [3], and Ferlux described that several *N*-substitued pyroglutamic esters are normolipidemic compounds, the more active being methyl *N*-(4-chlorobenzyl)pyroglutamate **2** [4] (Scheme 1).

Scheme 1

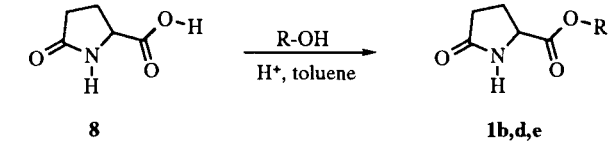


In this paper, we describe the synthesis of new products designed by mixing the main structural features of compounds **1b** and **2**. In products **3** and **4**, the *N*-(4-chlorobenzyl) substituent of **2** was conserved. In derivatives **5** and **6**, this chain was changed to a *N*-(4-chlorobenzoyl) group because a carbonyl is more polar than a methylene, while keeping approximatively the same bond orientations, and because **5** and **6** could act as prodrugs of the corresponding *N*-unsubstitued pyroglutamic derivatives **1**. In esters **1**, **3**, **5** and amides **4**, **6**, as well, the trimethylcyclohexyl group was either kept untouched (**b**, **g**) or it was opened (**d**) or even condensed (**e**, **h**), or the ring size was increased (**i**). As for **5f**, the new carbonyl group was introduced in order to produce a new potential binding site. Compounds **7** were also studied because many hypolipidemic agents possess such an antioxydant group [5] (Scheme 2).

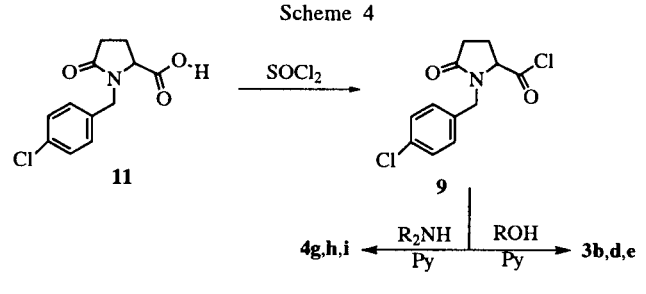
Scheme 2



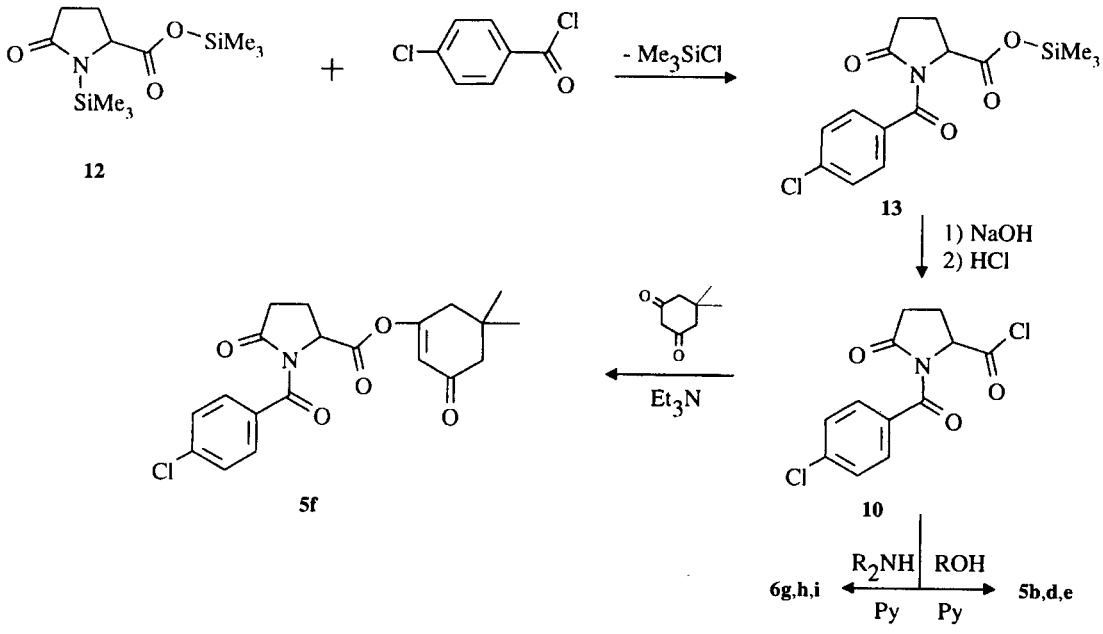
Scheme 3



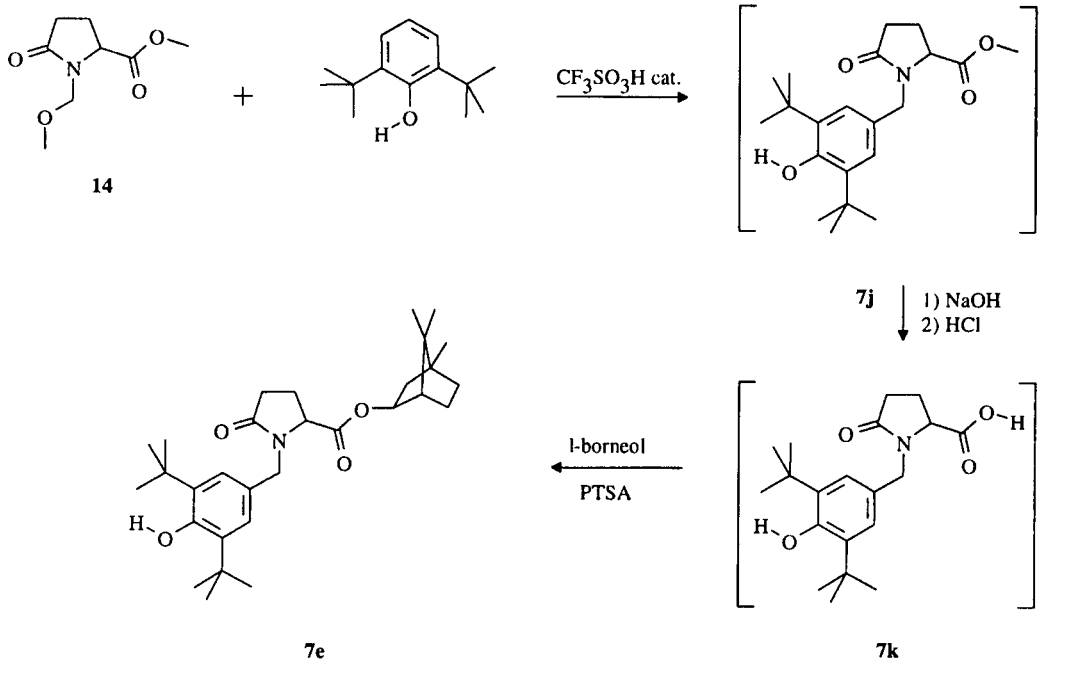
Scheme 4



Scheme 5



Scheme 6



Esters **1** were obtained from the direct esterification [6] of pyroglutamic acid **8** with alcohols in toluene (Scheme 3); esters **3**, **5** and amides **4**, **6** were synthesized by reacting acid chlorides **9**, **10** with amines or alcohols in the presence of pyridine (Schemes 4, 5); as for ester enol **5f**, it was obtained from the reaction of chloride **10** with dimedone in the presence of triethylamine (Scheme 5); the acid chloride **9** was formed by the reaction of acid **11** [7] with thionyl chloride [8]. The reaction of bis trimethylsilyl pyroglutamic acid **12** with 4-chlorobenzoyl chloride yields silyl ester **13**, whose reaction with thionyl chloride gives chloride **10** [9] (Schemes 4, 5).

A Mannich reaction of *N*-methoxymethylpyroglutamate ester **14** [10] with 2,6-ditertiobutylphenol yields ester **7j**. Saponification of this crude product gives the acid **7k**

Physical Properties of Compounds Synthesized

No.	Yield %	Mp °C or Bp °C	IR (Nujol) cm^{-1}	^1H NMR ($CDCl_3$) ppm	Analysis (%) Calcd./Found			
					C	H	N	O
1b	82	175 (0.4)	3200-3500 (N-H), 1730, 1695 (C=O), 1200 (C-O)	0.5-2.2 (m, 7H), 0.94 (bs, 9H), 2.2-2.6 (m, 4H), 4-4.3 (m, 1H), 4.5-5.2 (m, 1H), 6.7 (bs, 1H) [a]	66.37 66.07	9.15 9.08	5.53 5.49	18.95 19.24
1d	87	152 (0.07)	3100-3500 (NH), 1730, 1700 (C=O), 1200 (C-O)	0.92 (d, J = 6 Hz, 12H), 1-2 (m, 6H), 2-2.8 (m, 4H), 4-4.4 (m, 1H), 4.8-5.3 (m, 1H), 7 (bs, 1H) [a]	65.85 65.48	9.87 9.88	5.49 5.42	18.80 19.19
1e	60	110	3200, 3080 (NH), 1750, 1730, 1710, 1685 (C=O), 1260 (C-O)	0.4-2.1 (m, 7H), 0.83 (s, 3H), 0.88 (s, 6H), 2.1-2.6 (m, 4H), 4-4.3 (m, 1H), 4.7-5.1 (m, 1H), 6.5 (bs, 1H) [a]	67.90 67.77	8.74 8.87	5.28 5.24	18.09 18.14
3b	92	70	1720, 1675 (C=O), 1240 (C-O)	0.5-1.8 (m, 7H), 0.94 (bs, 9H), 1.8-2.7 (m, 4H), 3.7-4.2 (m, 1H), 3.92 (d, J = 15 Hz, 1H), 4.6-5.2 (m, 1H), 4.83 (d, J = 15 Hz, 1H), 7.15 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 2H)	66.74 66.38	7.47 7.31	3.71 3.71	12.70 12.55
3d	93	63	1730, 1710, 1660 (C=O), 1200 (C-O)	0.9 (d, J = 6 Hz, 12H), 1-1.8 (m, 6H), 1.8-2.7 (m, 4H), 3.7-4 (m, 1H), 3.82 (d, J = 15 Hz, 1H), 4.8-5.2 (m, 1H), 5.85 (d, J = 15 Hz, 1H), 7.03 (d, J = 7.5 Hz, 2H), 7.25 (d, J = 7.5 Hz, 2H)	66.39 66.25	7.96 7.89	3.69 3.90	12.63 12.70
3e	85	56	1720, 1675 (C=O), 1200 (C-O)	0.4-2.1 (m, 7H), 0.82 (bs, 3H), 0.88 (s, 6H), 2.1-2.8 (m, 4H), 3.6-4 (m, 1H), 3.85 (d, J = 14.2 Hz, 1H), 4.7-5.2 (m, 1H), 4.92 (d, J = 14.2 Hz, 1H), 7.18 (d, J = 9 Hz, 2H), 7.22 (d, J = 9 Hz, 2H)	67.77 67.79	7.24 7.31	3.59 3.55	12.31 12.12
4g	97	130	3260 (N-H), 1680, 1640 (C=O)	0.4-2.2 (m, 7H), 0.92 (bs, 9H), 2.1-2.8 (m, 4H), 3.5-4 (m, 1H), 3.9 (d, J = 14 Hz, 1H), 4.8 (d, J = 14 Hz, 1H), 5.5-5.8 (bd, 1H) [a], 7.08 (d, J = 8 Hz, 2H), 7.18 (d, J = 8 Hz, 2H)	66.92 66.79	7.76 7.96	7.43 7.36	8.49 8.76
4h	100	160	3280 (N-H), 1680, 1640 (C=O)	0.9-2.1 (m, 8H), 2.1-2.7 (m, 6H), 3.4-4 (m, 2H), 3.85 (d, J = 14 Hz, 1H), 4.72 (d, J = 14 Hz, 1H), 6.1-6.4 (bd, 1H) [a], 7.08 (d, J = 8 Hz, 2H), 7.18 (d, J = 8 Hz, 2H)	65.79 65.61	6.68 6.66	8.08 7.93	9.23 9.32
4i	100	115	1670, 1635 (C=O)	0.86 (bs, 6H), 0.9 (d, J = 12 Hz, 3H), 1-2.1 (m, 5H), 2.1-2.8 (m, 4H), 2.8-3.5 (m, 2H), 3.8 (d, J = 14 Hz, 1H), 3.9-4.3 (m, 1H), 5.05 (d, J = 14 Hz, 1H), 7.05 (d, J = 8 Hz, 2H), 7.2 (d, J = 8 Hz, 2H)	66.92 66.82	7.76 7.72	7.43 7.41	8.49 8.49
5b	60	112	1750, 1730, 1670 (C=O), 1590 (C=C), 1200 (C-O)	0.5-2.1 (m, 7H), 0.95 (bs, 9H), 2.1-2.8 (m, 4H), 4.6-5.2 (m, 2H), 7.28 (d, J = 7.5 Hz, 2H), 7.5 (d, J = 7.5 Hz, 2H)	64.36 64.20	6.69 6.67	3.57 3.61	16.33 16.04
5d	63	93	1740, 1730, 1690 (C=O), 1590, 1480 (C=C), 1200 (C-O)	0.9 (d, J = 6 Hz, 12H), 1-2 (m, 6H), 2-2.9 (m, 4H), 4.7-5.5 (m, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.5 (d, J = 8.5 Hz, 2H)	64.03 64.24	7.16 7.36	3.56 3.60	16.25 15.96
5e	56	98	1750, 1730, 1660 (C=O), 1580 (C=C)	0.4-2.1 (m, 7H), 0.83 (s, 3H), 0.89 (s, 6H), 2.1-2.9 (m, 4H), 4.6-5.2 (m, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H)	65.42 65.61	5.49 5.54	3.47 3.53	15.84 15.49
5f	73	157	1760, 1740, 1655 (C=O), 1580, 1490 (C=C)	1.11 (s, 6H), 2-2.8 (m, 4H), 2.26 (s, 2H), 2.45 (s, 2H), 4.6-51 (m, 1H), 5.93 (s, 1H), 7.4 (d, J = 8.4 Hz, 2H), 7.6 (d, J = 8.4 Hz, 2H)	61.62 61.73	5.17 5.14	3.59 3.49	20.52 20.13
6g	64	221	3330 (N-H), 1730, 1720, 1665 (C=O), 1590 (C=C)	0.4-2.1 (m, 7H), 0.88 (bs, 9H), 2.1-2.8 (m, 4H), 3.5-4.3 (m, 1H), 4.4-4.8 (m, 1H), 5.5-5.9 (bd, 1H) [a], 7.38 (d, J = 9 Hz, 2H), 7.57 (d, J = 9 Hz, 2H)	64.52 64.23	6.96 6.92	7.17 7.15	12.28 12.22
6h	69	177	3360, 3310 (N-H), 1745, 1720, 1700, 1670 (C=O), 1585 (C=C)	0.9-2.1 (m, 8H), 2.1-2.9 (m, 6H), 3.4-3.9 (m, 1H), 4.4-4.8 (m, 1H), 6.1-6.4 (bd, 1H) [a], 7.38 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H)	63.24 63.44	5.87 6.20	7.76 7.45	13.30 13.65
6i	84	62	1745, 1670, 1630 (C=O), 1590 (C=C)	0.95 (bs, 9H), 1.1-2 (m, 5H), 2-3 (m, 4H), 3-4 (m, 4H), 4.9-5.3 (m, 1H), 7.35 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H)	64.52 64.17	6.96 6.95	7.17 6.90	12.28 12.57
7a	ND	ND	ND	1.41 (s, 18H), 1.9-2.7 (m, 4H), 3.65 (s, 3H), 3.7-4.1 (m, 1H), 4 (d, J = 14 Hz, 1H), 4.75 (d, J = 14 Hz, 1H), 5.2 (s, 1H) [a], 6.98 (s, 2H)	ND			
7e	19 from **14**	161	3200-3600 (OH), 1720, 1680 (C=O), 1210 (C-O)	0.4-2.1 (m, 7H), 0.83 (s, 3H), 0.89 (s, 6H), 1.41 (s, 18H), 2.1-2.8 (m, 4H), 3.6-4 (m, 1H), 3.85 (d, J = 14 Hz, 1H), 4.8-5.3 (m, 1H), 4.95 (d, J = 14 Hz, 1H), 6.9 (s, 2H)	74.50 74.44	9.38 9.41	2.90 2.99	13.23 12.84
7j	ND	ND	ND	1.39 (s, 18H), 1.9-2.7 (m, 4H), 2.17 (s, 2H) [a], 3.85 (d, J = 15.5 Hz, 1H), 4.9 (d, J = 15.5 Hz, 1H), 6.88 (s, 2H)	ND			
9	100	ND	ND	2.1-2.7 (m, 4H), 3.9 (d, J = 14.5 Hz, 1H), 4-4.3 (m, 1H), 5 (d, J = 14.5 Hz, 1H), 7.08 (d, J = 7 Hz, 2H), 7.12 (d, J = 7 Hz, 2H)	ND			
13	100	ND	ND	0.31 (s, 9H), 2-2.8 (m, 4H), 4.6-4.9 (m, 1H), 7.35 (d, J = 9 Hz, 2H), 7.55 (d, J = 9 Hz, 2H)	ND			
14	58	ND	ND	2.1-2.9 (m, 4H), 5-5.4 (m, 1H), 7.3 (d, J = 8.7 Hz, 2H), 7.5 (d, J = 8.7 Hz, 2H)	ND			

[a] Deuterium oxide exchangeable.

which was not purified but was esterified with 1-borneol in toluene, giving a 19% overall yield in ester **7e** (Scheme 6).

Lipid lowering activity of esters and amides **1-7** was evaluated. A significant reduction in the HPL/cholesterol ratio [12] was obtained for esters **3b** and **5b**, showing the importance in this series of the trimethylcyclohexyl ester moiety for the activity, and confirming the initial hypothesis of Panmedica [2].

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a Perkin Elmer 700 spectrometer and the nmr spectra on a Hitachi Perkin Elmer R-600 at 60 MHz, using tetramethylsilane as an internal reference. Elemental analyses were performed by the <<Service Central de Microanalyses>> of CNRS in Vernaison, France. Melting points, ir spectra and elemental analyses were not determined for moisture sensitive compounds. Pyroglutamic acid was a gift of UCIB, Ivry-la-Bataille, France, which can provide this acid in bulk quantities.

3,3,5-Trimethylcyclohexyl Pyroglutamate (**1b**).

This compound was obtained from 3,3,5-trimethylcyclohexanol in the same way as ester **1d** (28 hours reflux), yield 82%, bp 175° (0.4 mm Hg).

4-(2,6-Dimethylheptyl) Pyroglutamate (**1d**).

A stirred mixture of pyroglutamic acid (50 g, 0.388 mole), 2,4-dimethyl-4-heptanol (55 g, 0.381 mole), methanesulfonic acid (2.6 g) and toluene (150 ml) was refluxed for 90 hours, while removing the water formed by using a Dean-Stark apparatus. After cooling, methylene dichoride was added and the solution was washed with a sodium carbonate solution, then with water. The organic phase was dried, evaporated then distilled, yield 87%, bp 152° (0.07 mm Hg).

L-Borneyl Pyroglutamate (**1e**).

This compound was obtained from 1-borneol in the same way as for the ester **1d**, (40 hours reflux), yield 60%, mp 110° (heptane).

3,3,5-Trimethylcyclohexyl *N*-(4-Chlorobenzyl)pyroglutamate (**3b**).

This compound was obtained from 3,3,5-trimethylcyclohexanol in the same way as for the ester **3d** (stirring at room temperature for 90 minutes), giving a 92% crude yield of ester, mp 70% (methanol/water 80/20).

2,6-Dimethyl-4-heptyl *N*-(4-Chlorobenzyl)pyroglutamate (**3d**).

A solution of acid chloride **9** (8 g, 0.030 mole) in 1,1,1-trichloroethane (10 ml) was added (30 minutes) to a cooled (-20°) mixture of 2,6-dimethyl-4-heptanol (4.1 g, 0.028 mole) and pyridine (2.5 ml). The cooling bath was removed and the stirring was continued for 45 minutes. Methylene dichloride (40 ml) was added, and the solution was washed with hydrochloric acid (140 ml, 0.06 *M*), potassium carbonate (90 ml, 0.05 *M*) then water. The organic phases were dried then evaporated, giving a 93% crude yield of ester, mp 63° (heptane).

L-Borneyl *N*-(4-Chlorobenzyl)pyroglutamate (**3e**).

This compound was obtained from 1-borneol in the same way as for the ester **3d** (stirring at room temperature for 90 minutes), giving 85% crude yield of ester (oil), mp 56° (heptane).

N-(3,3,5-Trimethylcyclohexyl)-1-(4-chlorobenzyl)pyroglutamide (**4g**).

A mixture of 3,3,5-trimethylcyclohexyl amine (3.1 g, 0.022 mole) and pyridine (3 ml) was cooled (-8°) then a solution of acid chloride **9** (6.5 g, 0.024 mole) in 1,1,1-trichloroethane (6 ml) was added (20 minutes). The cooling bath was removed and the mixture was stirred for 90 minutes. Methylene dichloride (30 ml) was added and the solution was washed with hydrochloric acid (0.06 *M*), a sodium carbonate solution (0.05 *M*) then water. The organic phase was dried and evaporated, giving a 97% crude yield of amide. The solid was refluxed in ether then filtered (twice), recrystallized in ether/dichloromethane 90/10, then refluxed in ether and filtered, mp 130°.

N-(Bicyclo[2,2,1]hept-2-yl)-1-(4-chlorobenzyl)pyroglutamide (**4h**).

This compound was obtained from norbornylamine in the same way as for the amide **4g**, giving a quantitative crude yield of product, mp 160° (diethylether/dichloromethane 50/50).

N-(3,3,5-Trimethylperhydroazepine-1-carbonyl)-1-(4-chlorobenzyl)pyrrolidin-2-one (**4i**).

This compound was obtained from 3,3,5-trimethylhexahydroazepine in the same way as for the amide **4g**, giving a quantitative crude yield of product, mp 115° (diethyl ether).

3,3,5-Trimethylcyclohexyl *N*-(4-Chlorobenzoyl)pyroglutamate (**5b**).

This compound was obtained from 3,3,5-trimethylcylohexanol in the same way as for the ester **5e**, giving a 86% crude yield of ester which was purified by recrystallization from methanol, total yield 60%, mp 112° (methanol).

4-(2,6-Dimethylheptyl) *N*-(4-Chlorobenzoyl)pyroglutamate (**5d**).

This compound was obtained from 4-(2,6-dimethyl)heptanol in the same was as for the ester **5e**, giving a 86% crude yield of ester which was purified by preparative liquid chromatography, total yield 63%, mp 93° (methanol).

L-Borneyl *N*-(4-Chlorobenzoyl)pyroglutamate (**5e**).

Acid chloride **14** (7 g, 0.025 mole) was dissolved in toluene, 1-borneol (3.6 g, 0.023 mole) was added then a solution of pyridine (2.5 ml) in toluene (15 ml) was added. The mixture was heated at 70° for 24 hours then evaporated. Methylene dichloride was added and the solution was washed with a citric acid solution (0.1 *M*), water, potassium carbonate solution water then dried and evaporated, giving a 79% yield of crude ester which was purified by preparative liquid chromatography (C_{18}, methanol/water, from 70/30 to 95/5), yield 56%; the product was dissolved in the minimum amount of refluxing hexane and cooled at room temperature. A few amount of diethyl ether was added and the mixture was refluxed. After cooling, the ester was a solid, mp 98°.

5,5-Dimethyl-3-oxocyclohexenyl *N*-(4-Chlorobenzoyl)pyroglutamate (**5f**).

A solution of dimedone (6.2 g, 0.045 mole) and triethylamine (4.5 g 0.045 mole) in methylene dichloride (100 ml) was added (90 minutes) to a solution of acid chloride **14** (12.7 g, 0.045 mole) in methylene dichloride (500 ml). After stirring at room temperature for 20 hours, the solution was washed with a sodium carbonate solution, a citric acid (0.1 *M*) solution then dried and evaporated, giving a 73% crude yield, mp 157° (acetone).

N-(3,3,5-Trimethylcyclohexyl)-1-(4-Chlorobenzoyl)pyroglutamide (**6g**).

3,3,5-Trimethylcyclohexylamine (5 g, 0.035 mole) in pyridine (3 ml) and toluene (3 ml) was added (15 minutes) to a cooled (-20°) solution of acid chloride **14** (10 g, 0.035 mole) in toluene (155 ml). After stirring for 20 minutes, the cooling bath was removed and the stirring was continued for 80 minutes then the mixture was evaporated, methylene dichloride was added and the solution was washed with a citric acid (0.25 *M*) solution then with a potassium carbonate solution, dried and evaporated, giving a 64% crude yield of amide, mp 221° (dichloromethane/-hexane).

N-(Bicyclo[2,2,1]hept-2-yl)-1-(4-chlorobenzoyl)pyroglutamide (**6h**).

This compound was obtained from norbornylamine in the same way as for the amide **6g**, giving a 69% yield of crude amide, mp 177° (hexane, -40°).

N-(3,3,5-Trimethylperhydroazepine-1-carbonyl)-1-(4-chlorobenzoyl)pyrrolidin-2-one (**6i**).

This compound was obtained from 3,3,5-trimethylhexahydroazepine in the same way as for the amide **6g** (stirring at room temperature for 66 hours), giving a 84% crude yield of amide which was purified by preparative liquid chromatography (C_{18}, methanol/water from 62/38 to 80/20), mp 62° (carbon tetrachloride/hexane, -40°).

L-Borneyl *N*-(3,5-Ditertiobutyl-4-hydroxybenzyl)pyroglutamate (**7e**).

A stirred mixture of methyl *N*-methoxymethylpyroglutamate (**14**) (46.7 g, 0.25 mole), 2,6-ditertiobutylphenol (51.6 g, 0.25 mole) and triflic acid (1 ml) was heated at 90° for 16 hours. After cooling, a solution of sodium hydroxide (30 g, 0.75 mole) in water (300 ml) was added and the mixture was refluxed for 2.5 hours. The solution was extracted with methylene dichloride and the aqueous phase was acidified with concentrated hydrochloric acid then extracted with methylene dichloride. The organic phase was dried then evaporated, giving 63.5 g of crude acid. *L*-Borneol (24.7 g, 0.161 mole), methanesulfonic acid (16.5 g) and toluene (300 ml) were added to the crude acid, and the solution was refluxed for 3.5 hours while removing water with a Dean-Stark apparatus. Ether was added and the solution was washed with a potassium carbonate solution then water, dried and evaporated, giving 30 g of crude ester which was purified by preparative liquid chromatography (C_{18}, methanol/water 80/20), giving 23.1 g of pure ester, yield 19%, mp 161°.

N-(4-Chlorobenzyl)pyroglutamoyl Chloride (**9**).

Thionyl chloride (18 ml, 29.5 g, 0.25 mole) was added (20 minutes) to a mixture of *N*-(4-chlorobenzyl)pyroglutamic acid (50 g, 0.197 mole) and dimethylformamide (0.5 ml) in methylene dichloride (75 ml). The mixture was refluxed for 3 hours, then evaporated, giving a quantitative yield of crude chloride which was not purified.

N-(4-Chlorobenzoyl)pyroglutamoyl Chloride (**10**).

Chlorobenzoyl chloride (100 g, 0.573 mole) was slowly added dropwise (70 minutes) into a refluxing solution of *N,O*-bistrimethylsilylpyroglutamic acid (**12**) (149.7 g, 0.547 mole) in tetrahydrofuran (120 ml). Reflux was continued for 2 hours more, then the solution was cooled at -10°, and thionyl chloride (42 ml, 68.5 g, 0.575 mole) was added (20 minutes). The cooling bath was removed, 175 ml of tetrahydrofuran were added and the mixture was stirred for 80 minutes then evaporated. The solid was washed with ether (400 ml), dissolved in hot (80°) toluene (20 ml/g) and filtered. The solution was evaporated, giving a 58% yield of the acid chloride.

REFERENCES AND NOTES

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