Studies on Pyrrolidinones. Synthesis of 1-[(*N*-Acetylaryl-amino)methyl]pyroglutamic Acid Derivatives

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Pyroglutamic acid was transformed into 1-[(*N*-Acetylarylamino)methyl]pyroglutamic acid derivatives by using trimethylsilyl variations of the Mannich reaction.

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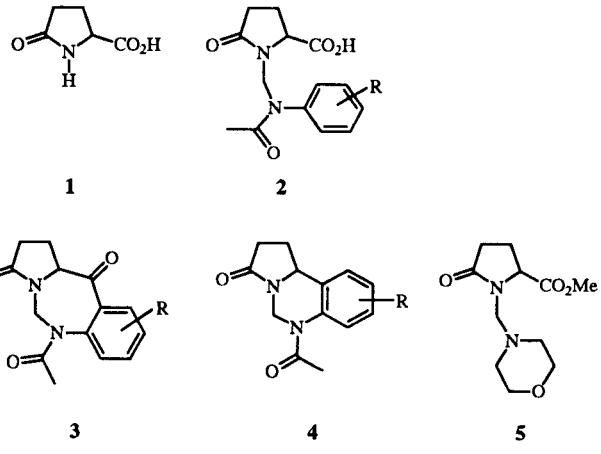
Our continuing efforts on structural modifications of 5-pyrrolidinone-2-carboxylic acid (pyroglutamic acid) (**1**) [1] have led us to the synthesis of a large number of *N*-substituted pyroglutamic acids [2]. We are now interested in acids **2** *N*-substituted by an arylaminomethyl group [3] because they could lead to the condensed heterocycles **3** and **4** [4] (Scheme 1).

Scheme 1

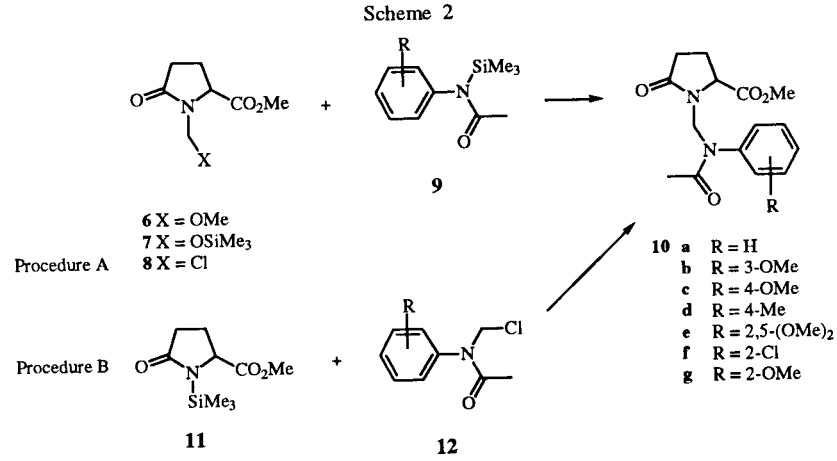


To obtain acids **2**, the classical Mannich reaction approach was used. This reaction has been studied in the aminoacid series [5] and some examples are known concerning pyroglutamic derivatives [6]. We previously used this method for the synthesis of *N*-arylmethyl pyroglutamic acid derivatives [7] and of *N*-morpholinomethyl ester **5** [2b]. Acids **2** are formally obtained from the condensation between a pyroglutamic derivative, a substituted acetanilide and formaldehyde. In order to avoid the formation of dimers [6b,c,7a] it is preferable to use a two step procedure. The literature shows that the Mannich reaction is easier, giving less impurities when performed with silyl intermediates [8], so we have studied the procedures shown in Scheme 2 .

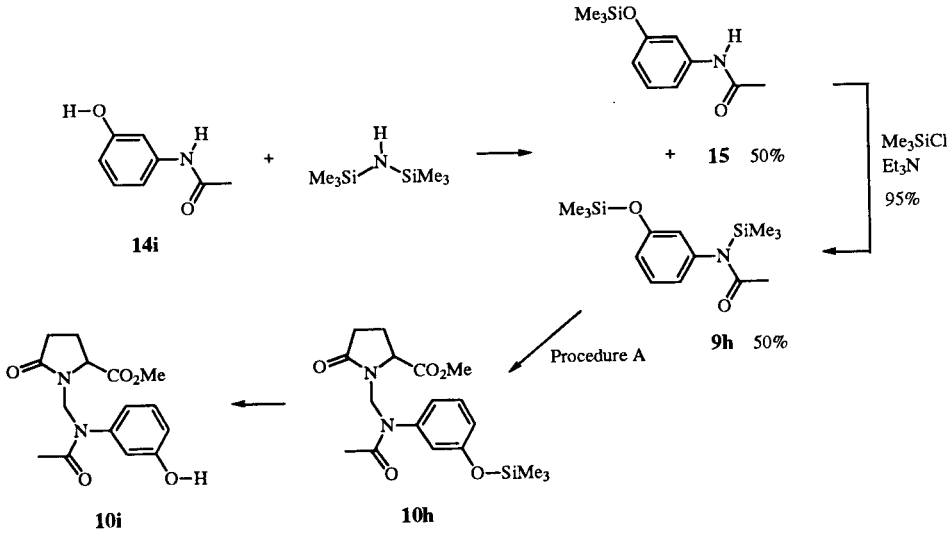
First experiments performed on esters **6** or **7** showed that the yields of compound **10a** (R = H) were low (<50%) whatever experimental conditions may be in terms of solvent (acetonitrile, dichloromethane or chloroform), catalyst (tin tetrachloride or triflic acid) or temperature. However procedure A and B gives best yields (60-70%) for compounds **10a** (R = H) (chloroform, reflux two hours); we used these procedures for the synthesis of methyl esters **10a-f.** Phenol **10i** was obtained after desilylation of ester **10h** synthesized by procedure A with the disilylated amidophenol **9h** (Scheme 3).

In these reactions (procedures A and B), it was found very important to entirely remove hydrochloric acid present in chloromethyl amides **8** and **12** (Scheme 2) because it decomposes the silyl compounds **9** or **11** (Scheme 4).

Scheme 2

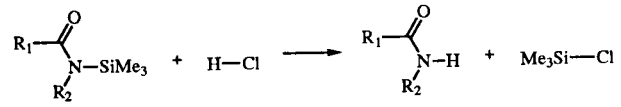


Scheme 3



The addition of solid potassium carbonate to a chloroform solution of amides **8** and **12** decomposes these compounds, giving a complex mixture of products, so the elimination of hydrochloric acid was accomplished by slightly heating the neat chloromethyl amides under vacuum (40°, 0.01 mm Hg, 24 hours).

Scheme 4



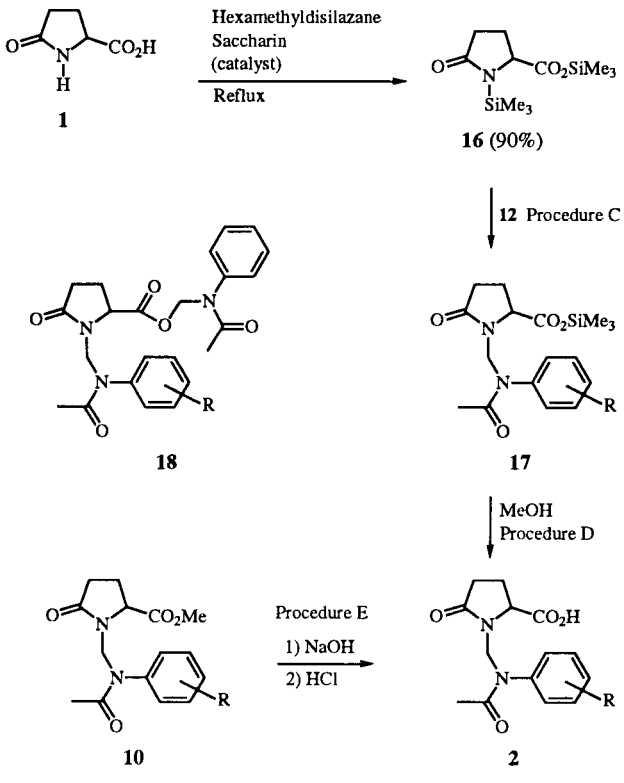
9, 11

We have previously shown that *N,O*-bistrimethylsilylpyroglutamic acid **16** [9] reacts with benzyl bromide, giving silyl *N*-benzylpyroglutamate in a very good yield [2e]. This clearly indicates that the *N*-silyl group of **16** is more reactive with electrophiles that the *O*-silyl function, so chloromethylamides **12** were reacted with compound **16** [9] (prepared in an easier manner by using hexamethyldisilazane) (procedure C, Scheme 5). Silyl esters **17** were thus obtained in 60-70% yields. A nmr observation of the crude reaction mixture showed that the formation of another product occured, probably the ester **18**. It is possible to purify the silyl products **17** by distillation, but that proves to be unnecessary because a methanol solvolysis of the crude esters directly gives the acids **2** in a 50-60% yield (procedure D) (Scheme 5). These acids also can be obtained by saponification of the methyl esters **10** (procedure E) (Scheme 5).

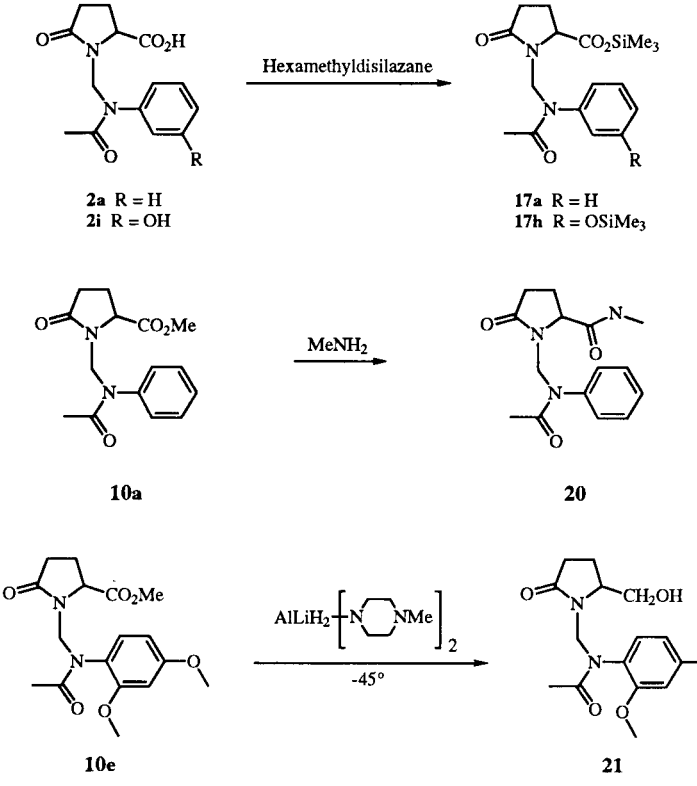
Some derivatives of acids **2** were interesting to synthesize; **19** was obtained by using general procedure A (Scheme 6); silyl esters **17** (Scheme 5, procedure C) can also be formed by silylation of acids **2** (Scheme 7) ; as for amide **20** and alcohol **21,** they were obtained as shown in Scheme 7. The formation of alcohol **21** confirms that it is very difficult to obtain aldehydes from reduction of pyroglutamic esters [12].

As shown in Scheme 3, refluxing amidophenol **14i** with hexamethyldisilazane gives a 50/50 mixture of silyl compounds **9h** and **15**. Even with ammonium bromide as the

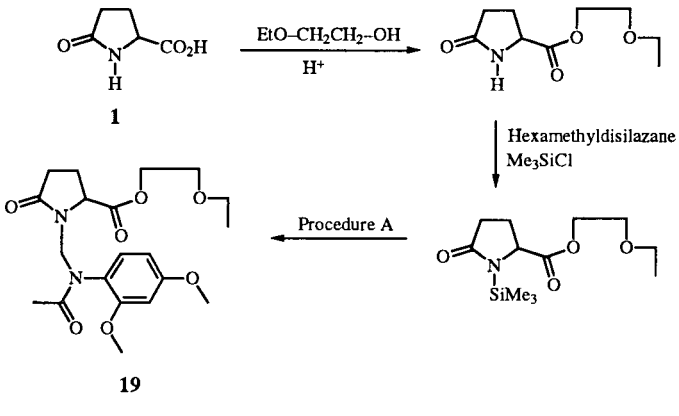
Scheme 5



Scheme 7

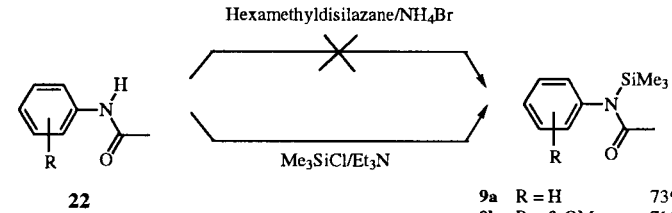


Scheme 6



Syntheses of methyl *N*-chloromethylpyroglutamate **8a** has been described already starting from methyl *N*-methylolpyroglutamate and thionyl chloride [2b], or from methyl pyroglutamate, formaldehyde and chlorotrimethylsilane [10] (Scheme 10). To obtain products **8b**, we used either this method or the reaction of chlorotrimethylsilane with compound **7** [11] (Scheme 10).

Scheme 8



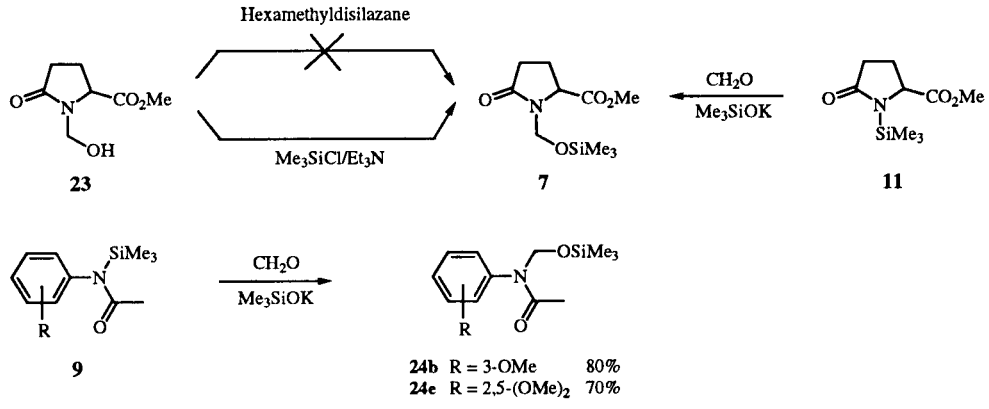
9a	R = H	73%
9b	R = 3-OMe	71%
9c	R = 4-OMe	78%
9e	R = 2,5-(OMe)$_2$	80%
9f	R = 2-Cl	96%

catalyst, the same reaction performed with amides **22** gives only a low yield of silyl amides **9.** We obtained these products by heating amides **22** with chlorotrimethyl silane in triethylamine (Scheme 8).

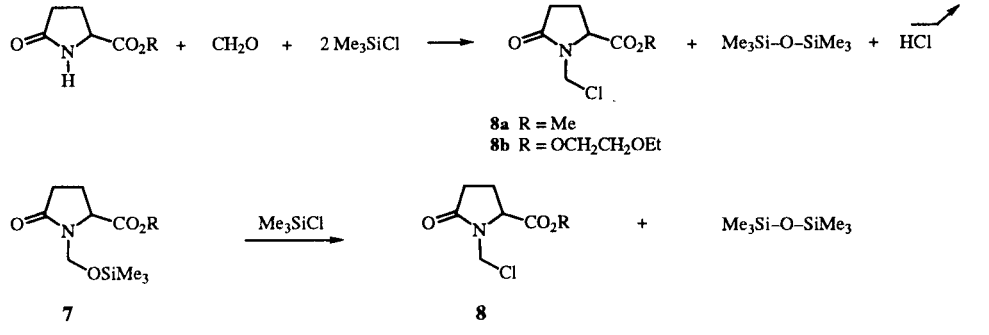
In the same way, *N*-methylol ester **23** [7a] does not react with hexamethyldisilazane without catalyst, but yields 90% of compound **7** by heating with chlorotrimethyl silane in triethylamine. This product can also be obtained in 50% yield from the reaction of *N*-silyl ester **11** with formaldehyde and a catalytic amount of potassium silanolate. In the same conditions, compounds **24b,e** are obtained in good yields from *N*-silyl amides **9b,e** (Scheme 9).

As for *N*-chloromethylacetanilides **12**, they are formed by the same general methods as *N*-chloromethylpyroglutamate **8**. The purest compounds are obtained by refluxing an excess of acetanilides **22** and chlorotrimethylsilane with formaldehyde in chloroform (procedure F). In that way, the purification of products **12** is easy because, at low temperature, acetanilides in excess are not soluble in the mixture of chloroform and

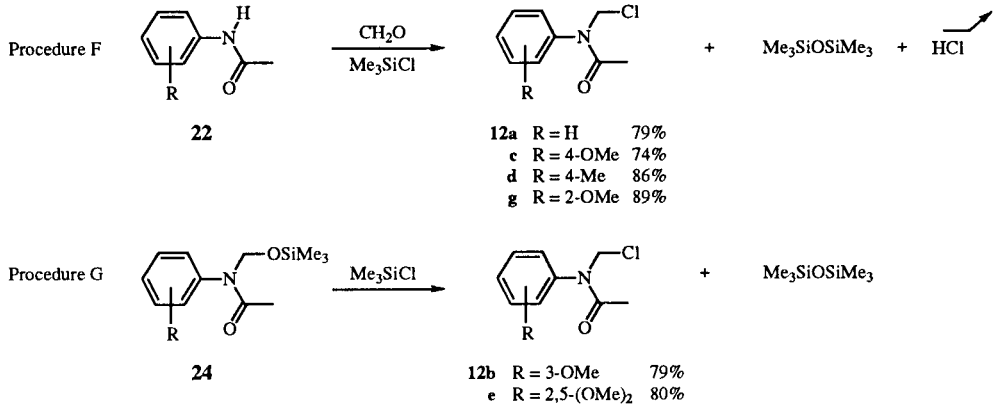
Scheme 9



Scheme 10



Scheme 11



chlorotrimethylsilane with the formed hexamethyldisiloxane formed. Some acetanilides as **22b** do not react under these conditions. In that case, it is possible to obtain the *N*-chloromethyl product starting from *N*-trimethylsilyloxymethylanilides **24** (procedure G) (Scheme 11).

It is noteworthy that acids **2** and esters **10** generally exhibit in their ^1H and ^{13}C nmr spectra a single absorption pattern (the N-CH_2-N group giving two doublets (J ~ 12 Hz) separated by 0.1 to 1 ppm. In the spectra of compounds substituted in the *ortho* position (**2e,f,g, 10e,f,g, 19, 21**) a pattern of two or more distinct rotational isomers is present, owing to the rotational barrier of a hindered amide [13,14] (see Figure 1, ^1H nmr spectra of esters **10a** and **19**).

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a Perkin Elmer 700 spectrometer and the nmr spectra on a Varian Gemini 2000 at 200 MHz for ^1H and 50 MHz for ^{13}C,

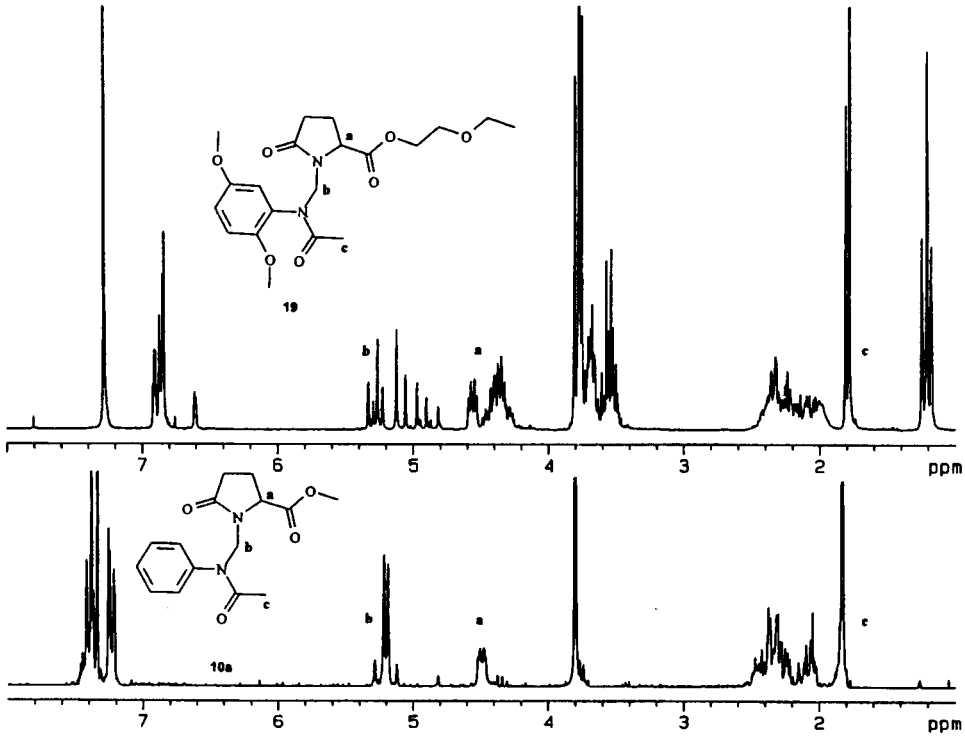


Figure 1. Top: 200 MHz ^1H spectrum of ester **19**; bottom 200 MHz ^1H nmr spectrum of ester **10a**.

Table 1

Elemental Analysis of New Compounds
Calcd./Found

No.	Formula	C	H	N	O
2a	$C_{14}H_{16}N_2O_4$	60.86	5.84	10.14	23.16
		60.47	5.80	10.16	22.98
2b	$C_{15}H_{18}N_2O_5$	58.82	5.92	9.15	26.12
		58.51	5.94	9.13	26.46
2c	$C_{15}H_{18}N_2O_5$	58.82	5.92	9.15	26.12
		58.83	5.89	9.24	25.78
2d	$C_{15}H_{18}N_2O_4$	62.06	6.25	9.65	22.04
		61.90	6.39	9.67	21.83
2e	$C_{16}H_{20}N_2O_6$, H_2O	54.23	6.26	7.91	31.60
		53.97	6.25	7.90	31.38
2f	$C_{14}H_{15}N_2O_4Cl$	54.11	4.87	9.02	20.60
		53.93	5.03	8.92	20.65
2g	$C_{15}H_{18}N_2O_5$	58.82	5.92	9.15	26.12
		58.71	6.05	8.95	26.02
2i	$C_{14}H_{16}N_2O_5$	57.53	5.52	9.58	27.37
		57.14	5.55	9.68	26.90
10a	$C_{15}H_{18}N_2O_4$	62.06	6.25	9.65	22.04
		61.97	6.17	9.58	22.29
10b	$C_{16}H_{20}N_2O_5$	59.99	6.29	8.74	24.97
		59.62	6.41	8.33	25.31
10c	$C_{16}H_{20}N_2O_5$	59.99	6.29	8.74	24.97
		60.21	6.16	8.70	24.42
10d	$C_{16}H_{20}N_2O_4$	63.14	6.62	9.20	21.03
		62.95	6.58	9.16	21.32
10e	$C_{17}H_{22}N_2C_6$	58.28	6.33	8.00	27.40
		58.15	6.35	8.13	27.20
10f	$C_{15}H_{17}N_2O_4Cl$	55.48	5.28	8.63	19.71
		55.47	5.47	8.55	19.89

Table 1 (Continued)

Elemental Analysis of New Compounds
Calcd./Found

No.	Formula	C	H	N	O
10i	$C_{15}H_{18}N_2O_5$	58.82	5.92	9.15	26.12
		58.94	5.97	9.21	25.94
19	$C_{20}H_{28}N_2O_7$, $1/2H_2O$	57.54	7.00	6.71	28.74
		57.64	7.05	7.05	28.47
20	$C_{15}H_{19}N_3O_3$	62.27	6.62	14.52	16.59
		62.08	6.61	14.58	16.30
21	$C_{16}H_{22}N_2O_5$	59.62	6.88	8.69	24.82
		59.88	7.20	8.29	24.54

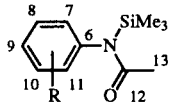
using tetramethylsilane as an internal reference. Elemental analyses were performed by the Service Central de Microanalyses of CNRS in Vernaison, France. Melting points, ir spectra and elemental analyses were not determined for moisture sensitive compounds. Pyroglutamic acid was a gift of UCIB, Ivry-la-Bataille, France, which can provide this acid in bulk quantities.

2-Ethoxyethyl Pyroglutamate.

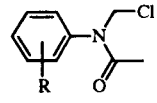
A stirred mixture of pyroglutamic acid **1** (246 g, 2 moles), 2-ethoxyethanol (270 g, 3 moles) and *para*-toluene sulfonic acid (6 g) in toluene (200 ml) was refluxed for 12 hours while removing the water formed (Dean-Stark trap). After neutralization (sodium acetate), the solvents were evaporated and the residue was distilled, bp = 162° (0.6 mm Hg), 79% yield; ^1H nmr (deuteriochloroform): δ ppm 1.21 (t, J = 6.4 Hz, 3H), 2.15-2.3 (m, 1H), 2.3-2.45 (m, 2H), 2.45-2.6 (m, 1H), 3.53 (q, J = 6.4 Hz, 2H), 3.6-3.7 (m, 2H), 4.25-4.35 (m, 3H), 7.25 (bs, 1H, deu-

Table 2

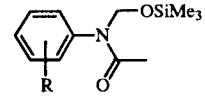
Physical Properties of Amides **9**, **12** and **24**



9



12



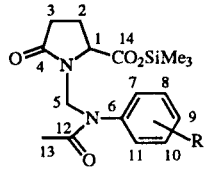
24

No.	R	Yield %	BP (mm Hg)	^{1}H NMR (deuteriochloroform) δ ppm
9a	H	73	55 (0.02)	0.22 (s, 9H), 1.75 (s, 3H), 6.4-7.5 (m, 5H)
9b	8-OMe	71		0.24 (bs, 9H), 1.80 (s, 3H), 3.76 (s, 3H), 6.1-6.9 (m, 3H), 6.9-7.4 (m, 1H)
9c	9-OMe	78		0.22 (s, 9H), 1.78 (s, 3H), 3.80 (s, 3H), 6.89 (bs, 4H)
9e [a]	7,10-$(OMe)_2$	80		0.16, 0.17 (2s, 9H), 1.74, 1.77 (2s, 3H), 3.78, 3.79 (2s, 3H), 3.82, 3.84 (2s, 3H), 6.55-7 (m, 3H)
9f [a]	7-Cl	96		0.21, 0.37 (2s, 9H), 1.77, 1.78 (2s, 3H), 6.7-7.5 (m, 4H)
9h	8-$OSiMe_3$	50 [b] 95 [c]	105 (0.05)	0.26 (s, 18H), 1.79 (s, 3H), 6.5-73 (m, 4H)
12a	H	79		1.92 (s, 3H), 5.52 (s, 2H), 7.1-7.6 (m, 5H)
12c	9-OMe	74		1.89 (s, 3H), 3.85 (s, 3H), 5.50 (s, 2H), 6.97 (d, J = 9 Hz, 2H), 7.23 (d, J = 9 Hz, 2H)
12d	9-Me	86		1.90 (s, 3H), 2.41 (s, 3H), 5.5 (s, 2H), 7.18 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H)
12e	7,10-$(OMe)_2$	80		1.90 (s, 3H), 3.85 (s, 6H), 4.65 (d, J = 10.2 Hz, 1H), 5.3 (d, J = 10.2 Hz, 1H), 6.8-7.5 (m, 3H)
12g	7-OMe	89		1.86 (s, 3H), 3.87 (s, 3H), 4.94 (d, J = 9.9 Hz, 1H), 6 (d, J = 9.9 Hz, 1H), 6.9-7.45 (m, 4H)
24b	8-OMe	80	80 (0.1)	0.09 (s, 9H), 1.9 (s, 3H), 3.7 (s, 3H), 5.1 (bs, 2H), 6.54-7.05 (m 3H), 7.05-7.3 (m, 1H)
24e	7,10-$(OMe)_2$	70	86 (0.1)	0.10 (s, 9H), 1.83 (s, 3H), 3.78 (s, 6H), 4.59 (d, J = 9.4 Hz, 1H), 5.69 (d, J = 9.4 Hz, 1H), 6.8-6.9 (m, 3H)

[a] Two conformers. [b] From **14i**. [c] From **15**.

Table 3

NMR Spectra of Silyl Esters **17**

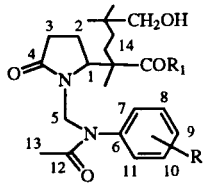


17

No.	R	^{1}H NMR (deuteriochloroform) δ ppm	^{13}C NMR (deuteriochloroform) δ ppm
17a	H	0.35 (s, 9H), 1.82 (s, 3H), 2-2.18 (m, 1H), 2.18-2.6 (m, 3H), 4.4-4.5 (m, 1H), 5.15 (d, J = 13.4 Hz, 1H), 5.25 (d, J = 13.4 Hz, 1H), 7.15-7.55 (m, 5H)	-0.3 ($SiMe_3$), 22.5 (C13), 23.6 (C2), 29.1 (C3), 54.8 (C5), 60.9 (C1), 128.1 (C7, C11), 128.5 (C9), 129.8 (C8, C10), 142.2 (C6), 172.3 (C4), 172.7 (C12), 175.8 (C14)
17c	9-OMe	0.33 (s, 9H), 1.77 (s, 3H), 1.9-2.4 (m, 4H), 3.74 (s, 3H), 4.3-4.5 (m, 1H), 5.09 (bs, 2H), 6.8 (d, J = 8 Hz, 2H), 7.08 (d, J = 8 Hz, 2H)	
17d	9-Me	0.35 (s, 9H), 1.82 (s, 3H), 2-2.6 (m, 4H), 2.35 (s, 3H), 4.35-4.45 (m, 1H), 5.12 (d, J = 13.4 Hz, 1H), 5.24 (d, J = 13.4 Hz, 1H), 7.11 (d, J = 9.1 Hz, 2H), 7.19 (d, J = 9.1 Hz, 2H)	-0.3 ($SiMe_3$), 22.5 (C13), 23.6 (C2), 29.1 (C3), 54.8 (C5), 60.9 (C1), 127.8 (C8, C10), 130.5 (C7, C11), 138.3 (C9), 139.7 (C6), 172.4 (C4), 172.7 (C12), 175.7 (C16)
17g	7-OMe	0.34 (s, 9H), 1.72 (s, 3H), 1.8-2.4 (m, 4H), 3.78 (s, 3H), 4.9-5.3 (m, 1H), 6.6-7.4 (m, 4H)	
17h	8-OSiMe	0.27 (s, 9H), 0.33 (s, 9H), 1.82 (s, 3H), 1.90-2.5 (m, 4H), 4.3-4.4 (m, 1H), 5.18 (bs, 2H), 6.7-6.95 (m, 3H), 7.05-7.3 (m, 1H)	

Table 4

Yields and Physical Properties of Compounds **2, 10, 19, 21, 21**



2, 10, 19, 20, 21

No.	R	R_1	Yield % (Procedure)	MP°C (Solvent) BP°C (mm Hg)	IR (K Br) ν cm^{-1}
2a (hydrate)	H	OH	62 (D) 68 (E)	176 (H_2O)	3450 (OH), 1735, 1670, 1650 (C=O, 1600, 1500, 1450 (C=C)
2b	8-OMe	OH	70 (E)	195 (H_2O)	3350 (OH), 1730, 1710 (C=O), 1600, 1585, 1495, 1455 (C=C)
2c	9-OMe	OH	64 (D)	192 (MeOH)	3400 (OH), 1730, 1680, 1640 (C=O), 1600, 1590, 1515, 1460 (C=C)
2d	9-Me	OH	55 (D) 38 (E)	176 (MeOH)	3350 (OH), 1725, 1680, 1640 (C=O), 1600, 1510, 1450 (C=C)
2e	7,10-$(OMe)_2$	OH	60 (E)	148 (MeOH)	3350 (OH), 1725, 1690, 1650 (C=O), 1600, 1510, 1460 (C=C)
2f	7-Cl	OH	82 (E)	198 (H_2O)	3380 (OH), 1725, 1680, 1650 (C=O), 1600, 1510, 1460 (C=C)
2g	7-OMe	OH	50 (D)	184 (H_2O)	3380 (OH), 1730, 1720, 1680, 1650 (C=O), 1620, 1600, 1510, 1460 (C=C)
2i	8-OH	OH	70 (E)	257 (MeOH)	3150 (OH), 1750, 1690, 1620 (C=O), 1590, 1510, 1470 (C=C)
10a	H	OMe	60 (A) 70 (B)	124 (tetrahydrofuran)	1750, 1715, 1700, 1660 (C=0), 1595, 1580, 1495, 1440 (C=C)
10b	8-OMe	OMe	70 (B)	95 (MeOH)	1750, 1710, 1700, 1660, (C=O), 1605, 1585, 1500, 1450 (C=C)
10c	9-OMe	OMe	66 (B)	98 (MeOH)	1750, 1710, 1695, 1655 (C=O), 1600, 1580, 1495, 1450 (C=C)
10d	9-Me	OMe	67 (B)	114 (MeOH)	1745, 1705, 1660 (C=O), 1600, 1580, 1515, 1450 (C=C)
10e	7,10-$(OMe)_2$	OMe	68 (A)	101 (MeOH)	1755, 1695, 1675, 1655 (C=O), 1605, 1585, 1515, 1450 (C=C)
10f	7-Cl	OMe	38 (A)	75 (MeOH) 165 (0.2)	1750, 1710, 1700, 1660 (C=O), 1600, 1580, 1505, 1450 (C=C)
10h	8-$OSiMe_3$	OMe	94 (A)	<200 (0.4)	
10i	8-OH	OMe	70 (from **10h**)	171 (MeOH)	3250 (OH), 1760, 1710, 1635 (C=O), 1605, 1590, 1485, 1450 (C=C)
19	7,10-$(OMe)_2$	OCH_2CH_2OEt	70 (A)	185 (0.03)	1745, 1700, 1670 (C=O), 1615, 1590, 1510 (C=C)
20	H	NHMe	93	187 (MeOH)	3300 (NH), 1700, 1660 (C=O), 1600, 1500, 1440 (C=C)
21	7,10-$(OMe)_2$		20	86 (AcOEt/Heptane)	3400 (OH), 1700, 1660 (C=O), 1600, 1495, 1445 (C=C)

terium oxide exchangeable); ir (neat): ν cm^{-1} 3240 (N-H), 1735, 1700 (C=O), 1195 (C-O).

Anal. Calcd. for $C_9H_{11}NO_4$: C, 53.72; H, 7.51; N. 6.96; O, 31.80. Found: C, 53.79; H, 7.69; N, 6.88; O, 31.54.

2-Ethoxycthyl *N*-Trimethylsilylpyroglutamate.

A stirred mixture of 2-ethoxyethyl pyroglutamate (403 g, 2 moles), hexamethyldisilazane (323 g, 2 moles) and chlorotrimethylsilane (5 ml) was refluxed for 10 hours (nitrogen). The solvents were evaporated and the residue was distilled, bp = 145° (0.2 mm Hg); ^1H nmr (deuteriochloroform): δ ppm 0.21 (s, 9H), 1.12 (t, J = 7 Hz, 3H), 1.9-2.7 (m, 4H), 3.2-4.2 (m, 4H), 4-4.4 (m, 3H).

Methyl 1-[(Acetylanilino)methyl]pyroglutamate (**10a**).

Procedure A.

A stirred mixture of *N*-chloromethyl ester **8a** (145 g, 0.73 mole) and *N*-silylamide **9a** (151.4 g, 0.73 mole) in chloroform (200 ml) was refluxed for 2 hours then kept at -40° for 48 hours. The solid was filtered, the solvents were evaporated and the residue was crystallized in methanol, yield 60%.

Procedure B.

A stirred mixture of *N*-silyl ester **11** and *N*-chloromethyl amide **12a** in chloroform was refluxed for 2 hours then treated as in procedure A, yield 70%.

Other esters **10** were obtained following the same procedures A and B (Tables 2 and 3).

Trimethylsilyl 1-[(*N*-Acetylanilino)methyl]pyroglutamate (**17a**).

A stirred mixture of ester **16** (305 g, 1.12 moles), *N*-chloromethylacetanilide (**12**) (208 g, 1.12 moles) in chloroform (200 ml) was refluxed for 2 hours, giving a 68% yield of ester **17a**.

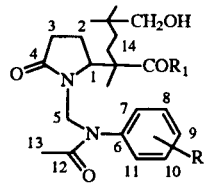
Procedure D.

1-[(*N*-Acetylanilino)methyl]pyroglutamic Acid (**2a**).

Methanol (50 ml) was added to the crude silyl ester **17a** obtained from the above procedure. The mixture was stirred for

Table 5

NMR Spectra of Compounds **2**, **10**, **19**, **20** and **21**



2, 10, 19, 20, 21

No.	R	R_1	^{1}H NMR (deuteriochloroform) δ ppm	^{13}C NMR (deuteriochloroform) δ ppm
2a (hydrate)	H	OH	1.92 (s, 3H), 2.1-2.6 (m, 4H), 4.4-4.5 (m, 1H), 5.2 (d, J = 13.6 Hz, 1H), 5.35 (d, J = 13.6 Hz, 1H), 6.3 (bs, 1H [a]), 7.2-7.5 (m, 5H)	22.2 (C13), 23.6 (C2), 29.1 (C3), 55.1 (C5), 60.1 (C1), 127.9 (C8, C10), 129.1 (C9), 130 (C7, C11), 141.6 (C6), 174 (C4), 174.5 (C12), 176.3 (C14)
2b	8-OMe	OH	1.95 (s, 3H), 2.1-2.6 (m, 4H), 3.8 (s, 3H), 4.4-4.5 (m, 1H), 5.19 (d, J = 13.8 Hz, 1H), 5.30 (d, J = 13.8 Hz, 1H), 6.8-6.95 (m, 3H), 7.31 (t, J = 8.6 Hz, 1H), 7.8 (bs, 1H [a])	22.1 (C13), 23.7 (C2), 29.2 (C3), 55 (C5), 55.5 (OMe), 60.2 (C1), 113.7 (C7), 114.3 (C9), 120.1 (C11), 130.7 (C10), 142.7 (C6), 160.7 (C8), 174.5 (C4, C12), 176.3 (C14)
2c	9-OMe	OH	1.90 (s, 3 H), 2-2.6 (m, 4H), 3.81 (s, 3H), 4.4-4.5 (m, 1H), 5.13 (d, J = 13.4 Hz, 1H), 5.28 (d, J = 13.4 Hz, 1H), 5.61 (bs, 1H [a]), 6.90 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H)	22.2 (C13), 23.6 (C2), 29.2 (C3), 55.1 (C5), 55.5 (OMe), 59.9 (C1), 115.1 (C8, C10), 129 (C7, C11), 134.3 (C6), 159.6 (C9), 174 (C4), 174.7 (C12), 176.3 (C14)
2d	9-Me	OH	1.90 (s, 3H), 2.05-2.6 (m, 4H), 2.37 (s, 3H), 4.4-4.5 (m, 1H), 5.16 (d, J = 13.6 Hz, 2H), 5.2 (bs, 1H [a]), 5.33 (d, J = 13.6 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.6 Hz, 2H)	21.2 (Me), 22.3 (C13), 23.5 (C2), 29.2 (C3), 55 (C5), 59.7 (C1), 127.6 (C8, C10), 130.7 (C7, C11), 138.9-139 (C6, C9), 174.1 (C4), 174.4 (C12), 176.3, (C14), (Dimethyl-d_6 sulfoxide) 20.6 (Me), 22.2 (C13), 22.5 (C2), 28.7 (C3), 53.2 (C5), 57.6 (C1), 128 (C8, C10), 130 (C7, C11), 137.3 (C9), 139.1 (C6), 170.7 (C4), 173.6 (C12), 174.7 (C14)
2e [b]	7.10-$(OMe)_2$	OH	(Deuteriomethanol) 1.79, 1.81 (2s, 3H), 2-2.2 (m, 1H), 2.2-2.5 (m, 3H), 3.75-3.77 (2s, 3H), 3.83-3.85 (2s, 3H), 4.45-4.55 (m, 1H), 4.95, 5.12 (2d, J = 13.7 Hz, 1H), 5.28, 5.29 (2d, J = 13.7 Hz, 1H), 6.7-6.75 (m, 0.5 H), 6.9-7.1 (m, 2.5 H)	(Deuteriomethanol) 21.6-21.8 (C13), 24-24.2 (C2), 30.2-30.3 (C3), 54.3-54.9 (C5), 56.5 $(OMe)_2$, 60.3-60.7 (C1), 113.8-114.3 (C9), 116.2-116.3-116.4-117.3 (C8, C11), 131.4-131.8 (C6), 150.9-151.1 (C10), 155.5-155.8 (C7), 175.2 (C4), 175.5 (C12), 178.5 (C14)
2f [b]	7-Cl	OH	1.86, 1.91 (2s, 3H), 2.1-2.25 (m, 1H), 2.25-2.55 (m, 3H), 4.5-4.6 (m, 1 H), 4.94-5.18 (2d, J = 14 Hz, 1H), 5.29, 5.47 (2d, J = 14 Hz, 1H), 6.9 (bs, 1H [a]), 7.05, 7.65 (m, 4H)	21.6, 22 (C13), 23, 23.6 (C2), 29, 29.2 (C3), 53.8, 54.6 (C5), 58.8, 60.3 (C1), 128.3, 128.9 (C10), 130.1, 130.3, 130.4, 130.5 (C8, C9), 130.8, 130.9 (C11), 132.9, 133.1 (C7), 139.5, 139.7 (C6), 173.4, 173.9 (C4), 174.3, 174.4 (C12), 176.3, 176.7 (C14)
2g [c]	7-OMe	OH	1.85, 1.86, 1.87 (3s, 3H), 2.1-2.6 (m, 4H), 3.85, 3.88 (2s, 3H), 4.45-4.55 (m, 1H), 4.55 (bs, 1H [a]), 4.99, 5.38, 5.40 (3d, J = 13.8 Hz, 1H), 5.14, 5.41, 5.43 (3d, J = 13.8 Hz, 1H), 6.9-7.1 (m, 2H), 7.2-7.4 (m, 2H)	(Dimethyl-d_6 sulfoxide) 21.3, 21.6 (C13), 22.3, 22.4 (C2), 28.6, 28.8 (C3), 51.4, 52.9 (C5), 55.6, 55.7 $(OMe)_2$, 57.1, 57.8 (C1), 112, 112.4 (C8), 120.7, 121.2 (C10), 129.3, 129.4 (C6), 129.7, 129.9 (C9), 130.1, 130.2 (C11), 154.5, 155.3 (C7), 171.1, 171.3 (C4), 173.6 (C12), 174.6 (C14)
2i	8-OH	OH	(Deuteriomethanol) 1.85 (s, 3H), 2.05-2.2 (m, 1H), 2.2-2.5 (m, 3H), 4.35-4.45 (m, 1H), 5.13 (d, J = 13.3 Hz, 1H), 5.28 (d, J = 13.3 Hz, 1H), 6.7-6.85 (m, 3H), 7.24 (t, J = 7.2 Hz, 1H)	(Deuteriomethanol) 22.3 (C13), 24.3 (C2), 30.2 (C3), 55.3 (C5), 60.6 (C1), 116.2 (C9), 116.8 (C7), 120.1 (C11), 131.7 (C10), 144 (C6), 160.1 (C8), 174.5 (C4), 175.4 (C12), 178.5 (C14)
10a	H	OMe	1.83 (s, 3H), 2-2.2 (m, 1H), 2.2-2.5 (m, 3H), 3.80 (s, 3H), 4.45-4.55 (m, 1H), 5.15 (d, J = 13.8 Hz, 1H), 5.24 (d, J = 13.8 Hz, 1H), 7.18-7.28 (m, 2H), 7.30-7.45 (m, 3H)	22.4 (C13), 23.5 (C2), 29.1 (C3), 52.6 (CO_2Me), 54.7 (C5), 59.7 (C1), 128 (C7, C11), 128.5 (C9), 129.9 (C8, C10), 142 (C6), 172.4 (C4), 172.9 (C12), 175.9 (C14)
10b	8-OMe	OMe	1.86 (s, 3H), 2-2.6 (m, 4H), 3.78 (s, 3H), 4.3-4.6 (m, 1H), 5.22 (bs, 2H), 6.7-7.3 (m, 4H)	
10c	9-OMe	OMe	1.82 (s, 3H), 1.95-2.2 (m, 1H), 2.2-2.6 (m, 3H), 3.81 (s, 3H), 4.45-4.55 (m, 1H), 5.10 (d, J = 13.8 Hz, 1H), 5.21 (d, J = 13.8 Hz, 1H), 6.90 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H)	22.4 (C13), 23.6 (C2), 29.1 (C3), 52.6 (CO_2Me), 54.9 (C5), 55.5 (OMe), 59.8 (C1), 115 (C8, C10), 129.1 (C7, C11), 134.9 (C6), 159.4 (C9), 172.8 (C4), 173 (C12), 175.8 (C14)
10d	9-Me	OMe	1.81 (s, 3H), 2.35 (s, 3H), 1.9-2.7 (m , 3H), 3.8 (s, 3H), 4.3-4.6 (m, 1H), 5.2 (bs, 2H), 7.18 (bs, 4H)	
10e [b]	7.10-$(OMe)_2$	OMe	(Dimethyl-d_6 sulfoxide) 1.67, 1.70 (2s, 3H), 1.8-2.05 (m, 1H), 2.05-2.6 (m, 3H), 3.69-3.71 (2s, 3H),	(Dimethyl-d_6 sulfoxide) 21.2, 21.6 (C13), 22.2 (C2), 28.5, 28.7 (C3), 51.5, 52.1 (C5), 52.1, 53 (CO_2Me),

Table 5 (continued)
NMR Spectra of Compounds **2**, **10**, **19**, **20** and **21**

			3.76, 3.79 (2s, 3H), 4.32-4.42, 4.48-4.58 (2m, 1H), 4.73-4.95 (2d, J = 13.8 Hz, 1H), 5.06, 5.13 (2d, J = 13.8 Hz, 1H), 6.8-7.1 (m, 3H)	55.4, 55.5, 55.9, 56 $(OMe)_2$, 57.1, 58 (C1), 112.6, 113 (C9), 114.2, 114.4 (C11), 115.2, 116.2 (C8), 129.9, 130.5 (C6), 148.5, 149.3 (C10), 153.1, 153.4 (C7), 171.3, 171.5 (C4), 172.5, 172.7 (C12), 174.7, 174.8 (C14)
10f [b]	7-Cl	OMe	1.81 (s, 3H), 2-2.2 (m, 1H), 2.2-2.5 (m, 3H), 3.82, 3.84 (2s, 3H), 4.55-4.65 (m, 1H), 4.88, 5.13 (2d, J = 13.9 Hz, 1H), 5.25, 5.31 (2d, J = 13.9 Hz, 1H), 7.1-7.55 (m, 4H)	21.8, 22 (C13), 23.1, 23.4 (C2), 29, 29.2 (C3), 52.6, 52.7 (CO_2Me), 54, 54.3 (C5), 59.3, 59.9 (C1), 128.2, 128.9 (C10), 130.1, 130.3, 130.4, 130.5 (C8, C9) 130.8, 130.9, (C11), 132.9, 133.1 (C7), 139.5, 139.7 (C6), 172.4, 172.7 (C4), 173.2 (C12), 175.7, 176 (C14)
10h	8-$OSiMe_3$	OMe	0.27 (s, 9H), 1.84 (s, 3H), 2-2.7 (m, 4H), 3.79 (s, 3H), 4.3-4.6 (m, 1H), 5.18 (bs, 2H), 6.7-7.3 (m, 4H)	
10i	8-OH	OMe	1.87 (s, 3H), 2-2.6 (m, 4H), 3.82 (s, 3H), 4.45-4.55 (m, 1H), 5.15 (d, J = 12.9 Hz, 1H), 5.29 (d, J = 12.9 Hz, 1H), 6.65 (bs, 2H), 6.65 (t, J = 2.4 Hz, 1H), 7.15 (t, J = 8.1 Hz, 1H), 8.26 (bs, 1H [a])	22.2 (C13), 23.4 (C2), 29.3 (C3), 52.7 (CO_2Me), 54.7 (C5), 59.9 (C1), 114.9 (C9), 116 (C7), 118.9 (C11), 130.5 (C10), 142.6 (C6), 158.2 (C8), 172.6 (C4), 172.9 (C12), 176.8 (C14)
19 [c]	7.10-$(OMe)_2$	OCH_2CH_2OEt	1.21, 1.22 (2t, J = 7 Hz, 3H), 1.79, 1.81 (2s, 3H), 1.8-2.5 (m, 4H), 3.45-3.62 (4q, J = 7 Hz, 2H), 3.6-3.75 (m, 2H), 3.76, 3.77, 3.78, 3.81 (4s, 6H), 4.2-4.5 (m, 2H), 4.5-4.6 (m, 1H), 4.57 (d, J = 14.1 Hz) and 4.63 (d, J = 13.6 Hz) and 4.79 (d, J = 13.6 Hz), (all: 1H), 4.68 (d, J = 14.1 Hz) and 4.96 (d, J = 13.6 Hz), and 5 (d, J = 13.6 Hz) (all: 1H), 6.59-6.62 (m, 0.5 H), 6.8-6.95 (m, 2.5H)	15.1 (CH_2CH_3), 21.6, 21.9 (C13), 23.1, 23.4 (C2), 29.2, 29.4 (C3), 53.9 (C5), 55.8, 56 $(OMe)_2$, 59, 59.3 (C1), 64.3, 64.4 (CO_2CH_2), 66.6 (OCH_2CH_3), 68.2, 68.3 ($CO_2CH_2CH_2$), 112.2, 112.6 (C9), 114, 114.7 (C11), 115.4, 116.4 (C8), 130.9, 131 (C6), 149.2, 149.5 (C10), 153.6, 154.2 (C7), 172.2, 172.5 (C4), 172.9, 173, (C12), 175.6, 175.7 (C14)
20	H	NHMe	1.80 (s, 3H), 2-2.4, (m, 3H), 2.4-2.8 (m, 1H), 2.79 (s, 0.5 H), 2.81 (s, 0.5 H), 4.15-4.25 (m, 1H), 5.04 (d, J = 13.6 Hz, 1H), 5.15 (d, J = 13.6 Hz, 1H), 7.01 (bs, 1H [a]), 7.10 (dd, J = 7.3, 1.8 Hz, 2H), 7.34 (d, J = 7.3 Hz, 2H), 7.27-7.41 (m, 1H)	22.6, 22.8 (C2, C13), 26.4 (NHMe), 29.7 (C3), 54.2 (C5), 60.2 (C1), 127.9 (C8, C10), 128.8 (C9), 130.1 (C7, C11), 141.6 (C6), 171.6 (C4), 172.1 (C12), 176.1 (C14)
21 [b]	7.10-$(OMe)_2$		1.7-2.6 (m, 5H), 1.85 (s, 3H), 3.77 (s, 3H), 3.79 (s, 2H), 3.84 (s, 3H), 5.14, 5.37 (2d, J = 13.4 Hz, 1H), 5.15, 5.46 (2d, J = 13.4 Hz, 1H), 6.57-6.60 (m, 0.5 H), 6.81-6.95 (m, 2.5, 1H),	21.3, 21.5 (C13), 21.8, 22 (C2), 29.9, 30.2 (C3), 52.7, 53.4 (C5), 55.7, 55.8, 56 $(OMe)_2$, 58.2, 58.9 (C1), 64.2, 65 (C14), 112.1, 112.7 (C9), 114.2, 114.8 (C11), 115.2, 116.2 (C8), 130.3, 130.5 (C6), 149.1, 149.6 (C10), 153.7, 154.2 (C7), 173.1, 173.7 (C4), 176.4, 176.6 (C12)

[a] This peak disappears upon addition of deuterium oxide. [b] Two conformers. [c] Many conformers.

90 minutes then the solvents were evaporated. Acid **2a** crystallized from water.

Procedure E.

1-[(*N*-Acetyl-3-methoxyanilino)methyl]pyroglutamic Acid (**12b**).

A stirred mixture of methyl ester **10b** (144 g, 0.45 mole) and sodium hydroxide (19.8 g, 0.5 mole) in water (300 ml) was refluxed for 6 hours. The aqueous phase was washed with methylene dichloride, acidified (hydrochloric acid) and extracted with methylene dichloride. The organic phase was dried (sodium sulfate) and evaporated, giving a 70% yield of acid **2b**.

Procedure F.

N-Chloromethylacetanilide (**12a**).

A stirred mixture of acetanilide (134 g, 1 mole), polyoxymethylene (29.4 g, 0.98 mole), chlorotrimethylsilane (226 g, 300 ml, 2.35 moles) in chloroform (400 ml) was heated at 50° for 16 hours, kept at -40° for 24 hours then filtered. The solvents were evaporated and the solution was stirred *in vacuo* for 24 hours (0.05 mm Hg, 40°), yield 79%.

Procedure G.

N-Choromethyl-*N*-(2,5-dimethoxyphenyl)acetamide (**12e**).

A stirred mixture of *N*-trimethylsilyloxymethylanilide **24e** and chlorotrimethylsilane (3 equivalents) was refluxed for 27 hours then evaporated, giving a quantitative crude yield of amide **12e**. Other chloromethylamides **12** were obtained following the same procedures F and G.

Methyl *N*-Trimethylsilyloxypyroglutamate (**7**).

From Methyl *N*-Trimethylsilylpyroglutamate (**11**).

A stirred mixture of ester **11** (10 g, 0.046 mole), polyoxymethylene (2.9 g, 0.0931 mole) and potassium trimethylsilanolate (0.05 g) in tetrahydrofuran (20 ml) was refluxed for 2 hours. The residue obtained after evaporation was distilled, yield 50%.

From Methyl *N*-Methylolpyroglutamate (**23**).

A stirred mixture of ester **23** (100 g, 0.58 mole) and chlorotrimethylsilane (125.3 g, 1.53 mole) in triethylamine (500 ml) was refluxed for 2 hours (nitrogen). Triethylamine hydrochloride was filtered (nitrogen), and the residue obtained after evaporation was distilled, yield 97%, bp 95° (0.1 mm Hg); ^{1}H nmr (deuteriochloroform): δ ppm 0.13 (s, 9H), 2-2.7 (m, 4H), 3.76 (s, 3H), 4.64 (d, J = 9.8 Hz, 1H), 5.23 (d, J = 9.8 Hz, 1H).

Methyl *N*-Chloromethylpyroglutamate (**8a**).

A stirred mixture of metyl pyroglutamate [6c] (200 g, 1.4 moles), polyoxymethylene (42.8 g, 1.42 moles) and chlorotrimethylsilane (455 g, 532 ml, 3 moles) in chloroform (300 ml) was refluxed for 2 hours then kept at -40° for 24 hours. The solid was filtered, the solvents were evaporated and the solution was stirred for 24 hours (0.05 mm Hg, 40°), yield 91%; ^{1}H nmr (deuteriochloroform): δ ppm 2.1-2.3 (m, 1H), 2.3-2.6 (m, 3H), 3.8 (s, 3H), 4.4-4.5 (m, 1H), 4.92 (d, J = 10.6 Hz, 1H), 5.71 (d, J = 10.6 Hz, 1H).

2-Ethoxyethyl *N*-Chloromethylpyroglutamate (**8b**).

This compound was obtained following the same method as for **8a**, in 94% yield, ^{1}H nmr (deuteriochloroform): δ ppm 1.19 (t, J = 7 Hz, 3H), 1.9-2.7 (m, 4H), 3.52 (q, J = 7 Hz, 2H), 3.6-3.8 (m, 2H), 4.2-4.6 (m, 3H), 4.96 (d, J = 10. 1 Hz, 1H), 5.66 (d, J = 10.1 Hz, 1H).

N-Trimethylsilylacetanilide (**9a**).

A stirred mixture of acetanilide (**22a**) (200 g, 1.48 moles) and chlorotrimethylsilane (320 g, 374 ml, 3 moles) in triethylamine (1000 ml) was refluxed for 90 minutes (nitrogen). Triethylamine hydrochloride was filtered (nitrogen) and washed with toluene. The solvents were evaporated and the residue was distilled, bp = 55° (0.02 mm Hg), yield 73%; ^{1}H nmr (deuteriochloroform): δ ppm 0.22 (s, 9H), 1.75 (s, 3H), 6.4-7.5 (m, 4H).

Other silylamides **9** were obtained following the same procedure.

3-Trimethylsilyloxyacetanilide (**15**) and *N*-Trimethylsilyl-*N*-(3-trimethylsilyloxyphenyl)acetamide (**9h**).

A stirred mixture of 3-acetamidophenol (**14i**) (50 g, 0.33 mole) and hexamethyldisilazane (107 g, 0.66 mole) was refluxed for 6 hours (nitrogen). The solvents were evaporated and the residue was distilled (It is necessary to heat all the parts of the distillation apparatus because these compounds crystallize easily), giving **9h**, 50% yield, bp = 105° (0.03 mm Hg); ^{1}H nmr (deuteriochloroform): δ ppm 0.26 (s, 18H), 1.79 (s, 3H), 6.5-7.3 (m, 4 H) and **15**, 50% yield, bp = 115° (0.02 mm Hg), ^{1}H nmr (deuteriochloroform): δ ppm 0.23 (s, 9H), 2.09 (s, 3H), 6.5-7.4 (m, 4H), 8.4 (bs, 1H).

When a mixture of **15** (42 g, 0. 188 mole), chlorotrimethylsilane (30.6 g, 0.282 mole, 36 ml) and triethylamine (150 ml) was refluxed for 5 hours, a 95% yield of **9h** was obtained after filtration of triethylamine hydrochloride, evaporation of the solvents and distillation of the residue.

Methyl 1-[(*N*-Acetyl-3-trimethylsilyloxyanilino)methyl]pyroglutamate (**10h**).

A stirred mixture of methyl *N*-chloromethylpyroglutamate (**8**) (42 g, 0.22 mole) and silylamide **9h** (55.5, g, 0.188 mole) in dichloromethane (120 ml) was refluxed for 6 hours. The solvents were evaporated and the residue was distilled (kugelrohr), giving **15** (4.6 g, bp< 140°, 0.2 mm Hg) then **10h**, 66.4 g, 94% yield (bp < 200°, 0.4 mm Hg).

Methyl 1-[(*N*-Acetyl-3-hydroxyanilino)methyl]pyroglutamate (**10i**).

Compound **10h** (66.4 g) was dissolved in dichloromethane and stirred with water. The organic phases were dried (sodium sulfate), the solvents were evaporated. The residue was crystallized in ethyl acetate, the precipitate was washed with ether and ester **10i** was recrystallized from methanol, yield 70%.

N,O-Bistrimethylsilylpyroglutamic acid (**16**).

Hexamethyldisilazane, (1650 ml, 7.8 moles) was added to a mixture of pyroglutamic acid (516 g, 4 moles) and saccharin (5 g, 27.3 mmoles), and the mixture was refluxed for two hours. The residue obtained after evaporation of the excess of hexamethyldisilazane was distilled giving a 90% yield of product **16**, identical to the known compound [9].

Trimethylsilyl 1-[(*N*-Acetylanilino)methyl]pyroglutamate (**17a**).

From Acid **2a**.

A stirred mixture of acid **2a** (3 g, 0.011 mole) and hexamethyldisilazane (1.9 g, 1.3 ml, 0.011 mole) was refluxed (nitrogen) for 2 hours then evaporated, giving a quantitative crude yield of ester **17a**.

By using the same procedure, ester **17h** was obtained in a quantitative crude yield.

N-Methyl-1-[(*N*-acetylanilino)methyl]pyroglutamide (**20**).

A stirred mixture of methyl ester **10a** (19.4 g, 0.067 mole) and methanol (40 ml) was saturated with methylamine gas (from 15 ml of 40% aqueous methylamine, and 15 g of sodium hydroxide). After 16 hours, the solid was filtered then washed with methanol, giving a 93% yield of amide **20**.

N-(2,5-Dimethoxyphenyl)-*N*-[(trimethylsilyloxy)methyl]-acetamide (**24e**).

A stirred mixture of silylamide **9e** (81 g, 0.3 mole), polyoxymethylene (9.2 g, 0.31 mole) and potassium trimethylsilanolate (0.1 g) in chloroform (90 ml) was refluxed for 5 hours, then kept at -40° for 60 hours. The residue obtained after filtration and evaporation of the solvents was distilled, yield 70%.

Amide **24b** was obtained following the same procedure (80%).

REFERENCES AND NOTES

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[1] B. Rigo, P. Cauliez, D. Fasseur and F. X. Sauvage, *Trends Heterocyclic Chem.*, **2**, 155 (1991).

[2a] N. Kolocouris and B. Rigo, *Chim. Chron., New Ser.*, **II**, 309 (1982); [b] B. Rigo, J. de Quillacq, E. Fossaert and N. Kolocouris, *J. Heterocyclic Chem.*, **21**, 1393 (1984); [c] B. Rigo, D. Couturier and N. Kolocouris, *J. Heterocyclic Chem.*, **23**, 1769 (1986); [d] B. Rigo and D. Couturier, *J. Heterocyclic Chem.*, **22**, 207 (1985); [e] B. Rigo, P. Gautret, A. Legrand, S. El Ghammarti and D. Couturier, *Synth. Commun.*, **24**, 2609 (1994); [f] B. Rigo, R. Dolaine, S. El Ghammarti and D. Couturier, *J. Heterocyclic Chem.*, **33**, 1063 (1996).

[3] We previously described the synthesis of compound **10c** [2f].

[4] A preliminary report on the synthesis of heterocycle **4** has already been published: B. Rigo, S. El Ghammarti and D. Couturier, *Tetrahedron Letters*, **37**, 485 (1996).

[5] J. H. Short and C. W. Ours, *J. Heterocyclic Chem.*, **12**, 869 (1975).

[6a] Ajinomoto Co, Inc., Japan Kokai 74 01.558 (1974); *Chem. Abstr.*, **81**, 13377a (1974); [b] C. Miquel, P. Pigache, B. Rigo and N. Kolocouris, *J. Heterocyclic Chem.*, **17**, 1447 (1980); [c] P. Cauliez, B. Rigo, D. Fasseur and D. Couturier, *J. Heterocyclic Chem.*, **28**, 1143 (1991).

[7a] B. Rigo, E. Fossaert, J. de Quillacq and N. Kolocouris, *J. Heterocyclic Chem.*, **21**, 1381 (1984); [b] B. Rigo and C. Laruelle, *J. Heterocyclic Chem.*, **34**, 279 (1997).

[8] N. A. Orlova, I. Y. Belavin, V. N. Sergeev, A. G. Shipov and Y. I. Baukov, *J. Org. Chem. USSR*, **54**, 635 (1984); N. A. Anisimova, E. P. Kramvora, I. Y. Belavin and Y. I. Baukov, *J. Gen. Chem. USSR*, 1631 (1986).

[9] B. Rigo, C. Lespagnol and M. Pauly, *J. Heterocyclic Chem.*, **25**, 59 (1988).

[10] A. G. Shipov, N. A. Orlova and Y. I. Baukov, *J. Gen. Chem. USSR*, 2362 (1984).

[11] V. P. Kozyukov, V. P. Kozyukov and V. F. Mironov, *J. Gen. Chem. USSR*, 1222 (1982).

[12] J. Deskus, M. B. Smith and T. Simandan, *Synth. Commun.*, **26**, 3137 (1996).

[13] B. M. Pinto, W. A. Szarek and T. B. Grindley, *Org. Magn. Reson.*, **22**, 676 (1984).

[14] E. Roth, J. Altman, M. Kapon and D. Ben-Ishai, *Tetrahedron.*, **51**, 801 (1995).

[15] Considerable help in the ^{13}C and ^{1}H peak assignments was obtained by using the ACD/CNMR and ACD/HNMR softwares from Advanced Chemistry Development Inc., Toronto, Canada.

[16] Systematic IUPAC names of compounds described in the Experimental were obtained by using the ACD/NAME software from Advanced Chemistry Development Inc., Toronto, Canada.