Studies on Pyrrolidinones.
Synthesis of *N*-Acylpyroglutamic Esters with Bactericide and Fungicide Properties.

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The best method to prepare *N*-acylpyroglutamic esters is to react *N*-trimethylsilylpyroglutamic esters with acid chlorides or diketene. These acylesters possess bactericide and fungicide properties against several microorganisms.

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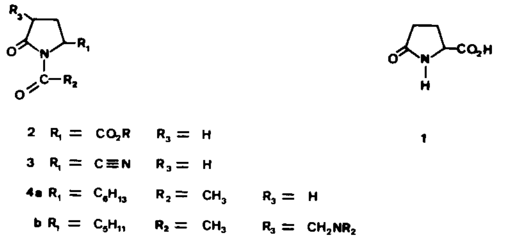
Our continuing efforts on structural modifications of 5-pyrrolidinone-2-carboxylic acid (pyroglutamic acid) (**1**) [1,2] led us to the synthesis of *N*-acylpyroglutamic derivatives **2**, **3** exhibiting fungicide and bactericide properties [3]; some related *N*-acyllactams **4** substituted by a lipophilic chain in the 5 position possess interesting microbicidal properties [4,5], and some derivatives of *N*-acylamino-esters are fungicide compounds [6,7]. A part of our program directed to *N*-acyl-5-cyano-2-pyrrolidinones **3** has already been published [8,9]. We now wish to describe our work on *N*-acylpyroglutamic esters **2**.

Scheme 1



As a matter of fact, we required a general and easy synthesis of compounds **2** and we decided not to use the ox-

Table 1

Physical Properties of Pyroglutamic Esters **5**

R	Yield %	Method	BP °C (mm Hg)	MP °C	IR (ν cm^{-1}) N-H	IR (ν cm^{-1}) C=O	NMR (δ ppm) H_5	References
CH_3	78	1	135 (0.3)	21-23	3350-3250	1735-1690	4.32	[17]
C_2H_5	89	2	143 (0.2)	52-54	3190-3080	1730-1700	4.20	[21] mp 51-53°
i-C_3H_7	75	2	112 (0.1)	60-62	3350-3250	1720-1690	4.27	
n-C_3H_7	85	2	145 (0.4)		3350-3240-3100	1735-1700	4.30	
allyl	46	2		96	3230-3130	1735-1695-1660	4.28	
n-C_4H_9	90	2	160 (0.2)	29	3340-3200-3080	1740-1695	4.41	[22] bp 157° (1.3)
t-C_4H_9	35	3		109-110	3240-3110	1730-1700-1675	4.20	[18,19,20] mp 92-99°; 106-107°
n-C_5H_{11}	92	2	151 (0.2)		3350-3250	1740-1700	4.30	
n-C_6H_{13}	82	2	162 (0.3)		3350-3240	1735-1700	4.28	
cyclo-C_6H_{11}	58	2	190 (0.2)	54-58	3210-3100	1735-1700-1660	4.22	
benzyl	59	3	185 (0.1)	50-52	3400-3170-3080	1735-1670	4.32	[19] oil bp 175° (0.06 mm)

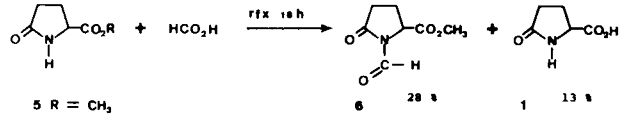
idation of *N*-acylproline esters [10,11], or the cyclization of *N*-acylglutamic derivatives [12-15]. We chose to start from pyroglutamic acid (**1**) which is an inexpensive and readily available commercial material [16].

Pyroglutamic esters were obtained by known procedures. Injection of methanol in fused (160°) pyroglutamic acid for methyl pyroglutamate (**5**) [17], reaction of pyroglutamic acid with aliphatic alcohols (azeotropic separation of water) for the other esters; the best method to obtain *t*-butyl pyroglutamate and benzyl pyroglutamate was to react the triethylammonium salt of pyroglutamic acid with benzyl or *t*-butyl chloride (*t*-butyl bromide gave a smaller yield). The reaction of pyroglutamic acid with isobutene gives good yields only when using a very great amount of solvent [18], or with an equimolar quantity of perchloric acid [19]. In other cases the yields were very low [20]. Properties and yields of the esters that we have utilized were reported in Table 1.

Reaction of Formic Acid with Methyl Pyroglutamate (Method A).

Formic acid is one of the more reactive organic acids; it is sometimes a very efficient acylating agent [23]. When compared with methyl pyroglutamate (**5**), it reacted also like a deprotective agent of the ester function [24], and a mixture of pyroglutamic acid (**1**) and methyl *N*-formylpyroglutamate (**6**) was obtained.

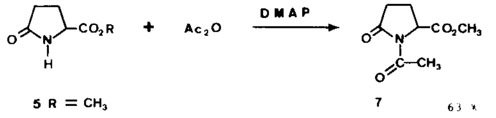
Scheme 2



Reaction of Acetic Anhydride with Methyl Pyroglutamate (Method B).

Acetic anhydride has already been used for the acylation of lactams; the yield depends mainly on the lactam structure (piperidone, 95%; pyrrolidinone, 50%) [25]. With methyl pyroglutamate, the yield was 60%. Using an acylating catalyst (dimethylaminopyridine) [26,27] increased only slightly the amount of methyl *N*-acetylpyroglutamate (**7**) (63%).

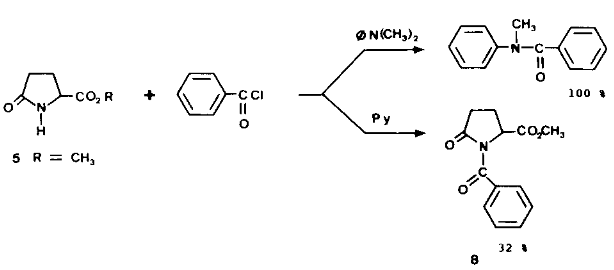
Scheme 3



Reaction of Acid Chlorides with Methyl Pyroglutamate, in the Presence of an Organic Base (Methods C and D).

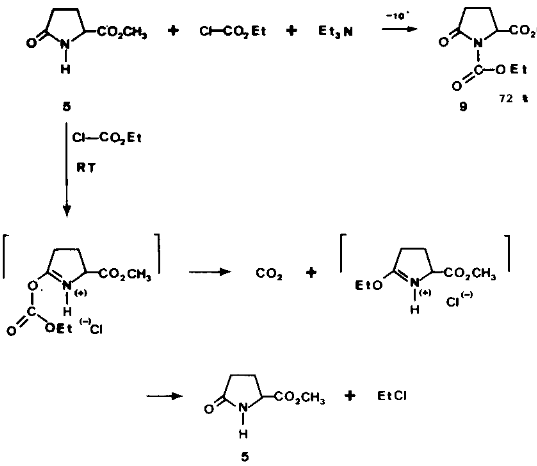
Different organic bases have been utilized in the reaction of a lactam with an acid chloride. *N,N*-Dimethylaniline was particularly recommended for benzoyl chloride [28], but using this base in the benzoylation of methyl pyroglutamate (**5**) produced only a quantitative yield of *N*-benzoylaniline. This type of reaction between an acid chloride and a tertiary amine has been known for a long time [29]. Pyridine was another suggested base for lactam acylation [30,31]. By using it, methyl *N*-benzoylpyroglutamate (**8**) was obtained in 32% yield.

Scheme 4



Triethylamine was used in the reaction between phthalimide and ethyl chloroformate [32]. With methyl pyroglutamate (**5**), the desired carbamate **9** was formed in 72% yield, at a low temperature (−10°) to avoid reaction between ethyl chloroformate and triethylamine. It is interesting to note that in the absence of triethylamine, methyl pyroglutamate decomposes the chloroformate [33].

Scheme 5



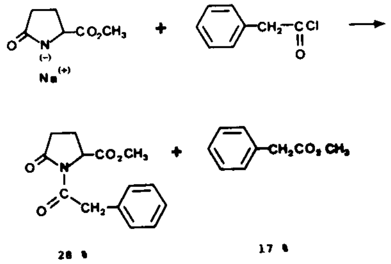
This acylation reaction, in the presence of triethylamine did not always give good results. For example, chloracetyl chloride furnished only a 35% yield of methyl *N*-chloracetylpyroglutamate (**10**) in this reaction. Under the same conditions by using acryloyl chloride, ethyl pyroglutamate and diisopropylethylamine, a yield of about 60% of an acylated product has been published [42].

Reaction of Acid Chloride with Methyl Pyroglutamate, in the Presence of a Mineral Base (Method E).

Is it possible to obtain methyl *N*-benzylpyroglutamate in 40% yield by reacting benzyl chloride with methyl pyroglutamate, in a melt with potassium carbonate and a phase transfer agent [34]. Under the same conditions, by using benzoyl chloride, methyl *N*-benzoylpyroglutamate (**8**) was formed in 35% yield.

Although the reaction between the sodium salt of a pyroglutamic ester and an acid chloride [35] or an activated ester [18,36] was described, using phenylacetyl chloride in such a reaction furnished a low yield of methyl *N*-phenylacetylpyroglutamate (**11**) (28%), with 17% of methyl phenylacetate. The formation of this last product was interesting because it can only come from an unwanted cyclization reaction of the *N*-acylester **11** (see later the reactions of *N*-acylpyroglutamic esters with bases, Scheme 11).

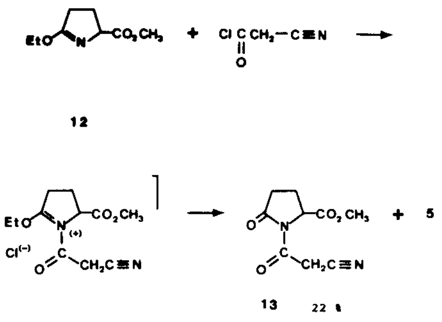
Scheme 6



Reaction of Methyl Ethoxy-2-pyrroline-5-carboxylate with Cyanoacetyl Chloride (Method F).

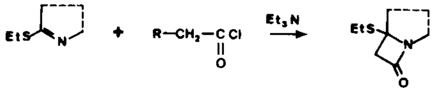
The reaction between an acid chloride and an iminoether is known to give *N*-acyllactams [37-39]. We synthesized the ethyl iminoether of methyl pyroglutamate (**12**) by using a small modification of our published procedure [34] and reacted it with cyanoacetyl chloride (Scheme 7).

Scheme 7



The low yield of this reaction was probably caused in part by traces of hydrochloric acid which were present in the acid chloride and catalyzed the decomposition of the iminoether (see the reaction of methyl pyroglutamate with ethyl chloroformate). To avoid this, an organic base was added, however, these new conditions were almost those of a known lactam synthesis [40,41] (Scheme 8), and likewise with triethylamine as well as with diisopropylethylamine, the reaction medium was very complex and we did not succeed in isolating any of the five main products which can be seen by thin layer chromatography.

Scheme 8



Reaction of *N*-Trimethylsilylpyroglutamic Esters with Acylating Agents (Method G).

None of the preceding reactions can be generalized to any acylating agent, therefore an alternative, profitable procedure was chosen: That is the reaction between an acid chloride and a *N*-trimethylsilyl lactam [43-45].

Pyroglutamic esters were silylated with a slight modification of the published lactam silylation [46,47], by substituting the less toxic toluene for benzene as a solvent. *N*-Trimethylsilylpyroglutamic esters **14** were obtained in very good yields (Table 2). Recently *t*-butyl *N*-trimethylsilylpyroglutamate was used in an acylation reaction [48], and our published synthesis of methyl *N*-trimethylsilylpyroglutamate [3,49] has already been used in an alkylation reaction [49,50].

Table 2

Physical Properties of *N*-Trimethylsilylpyroglutamic Esters **14**

R	Yield	BP °C (mm Hg)	NMR (δ ppm) H_5	NMR (δ ppm) $SiMe_3$
H [a]	95		4.3	0.27
$SiMe_3$ [a]	98	105 (0.10)	4.2	0.23-0.27
CH_3	85	88 (0.10)	4.2	0.25
C_2H_5	66	90 (0.10)	4.2	0.23
n-C_3H_7	81	94 (0.15)	4.2	0.25
i-C_3H_7	97	85 (0.10)	4.2	0.23
allyl	76	107 (0.15)	4.2	0.23
n-C_4H_9	77	115 (0.20)	4.1	0.23
t-C_4H_9	80		4.1	0.25
n-C_5H_{11}	92	151 (0.20)	4.1	0.23
n-C_6H_{13}	88	138 (0.10)	4.1	0.23
cyclo-C_6H_{11}	57	172 (0.20)	4.2	0.25
benzyl	85	137 (0.10)	4.3	0.23

[a] See the following communication.

The reaction between *N*-trimethylsilylpyroglutamic esters **14** and acid chlorides produced *N*-acylpyroglutamic esters **2** with yields often better than 85%. Acetoacetyl chloride is an unstable compound when the temperature is greater than −60° [51]. Diketene can be substituted in the acylation of trimethylsilylamides and lactams [52,53]. By using this procedure, methyl *N*-acetoacetylpyroglutamate (**15**) was obtained after hydrolysing the resulting silylenol

Table 3

Physical Properties of *N*-Acylpyroglutamic Esters **2**

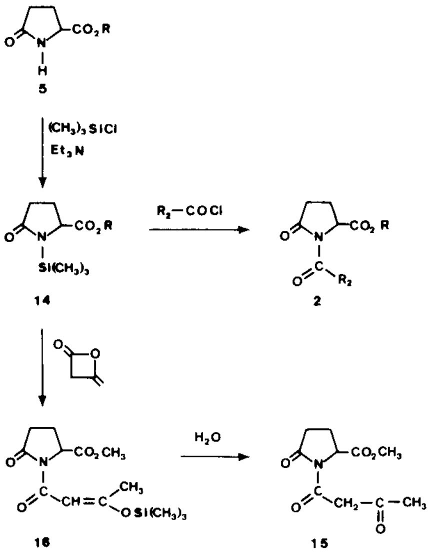
R	R_2	Method	Yield %	BP °C (mm Hg)	MP °C	IR (ν cm^{-1}) C=O	NMR (δ ppm) H_5	Elemental Analysis Calcd./Found C	H	N	O
CH_3	H	A	28	112 (0.10)	48	1760-1750-1740-1690	4.7	49.12	5.30	8.19	37.39
								48.96	4.93	8.32	37.75
CH_3	OEt	D	72	131 (0.10)	51	1760-1740-1700	4.7	50.23	6.09	6.51	37.17
								50.53	6.05	6.52	37.25
CH_3	C_6H_5	C	32	170 (0.20)	141-143	1750-1735-1660	4.9	63.15	5.30	5.67	25.89
								63.43	5.24	5.87	26.14
CH_3	CH_3	B	63		41	1750-1735-1690	4.8	51.88	5.99	7.57	34.56
								51.54	5.73	7.78	34.82
CH_3	CH_2Cl	G	95	142 (0.15)	66	1755-1695	4.8	43.80	4.59	6.38	29.17
		D	35					43.77	4.50	6.41	28.88
CH_3	CH_2-CN	F	22	170 (0.10)		1745-1705	4.7	51.43	4.80	13.33	30.45
								51.72	4.51	13.54	30.16
CH_3	CH_2-CO-CH_3	H	42	145 (0.10)	85	1740-1730-1710-1685	4.8	52.86	5.77	6.17	35.21
								52.97	5.65	5.80	35.09
CH_3	CH_2-C_4H_3S	G	42		96	1740-1685	4.7	53.92	4.90	5.24	23.94
								53.68	4.89	5.25	24.29
CH_3	CH_2-C_6H_5	G	76	185 (0.10)	45	1745-1695	4.6	64.35	5.79	5.36	24.50
		E	28					64.16	6.03	5.20	24.65
CH_3	*p*-$NO_2C_6H_4$-CH_2	G	87		107	1740-1690	4.7	54.89	4.61	9.15	31.34
								54.84	4.67	9.43	31.65
CH_3	*p*-$CH_3OC_6H_4$-CH_2	G	81	185 (0.10)	80	1740-1690	4.7	61.84	5.88	4.81	27.46
								61.60	6.04	4.84	27.65
CH_3	*p*-ClC_6H_4-CH_2	G	60		93	1745-1735-1690	4.7	56.86	4.77	4.74	21.64
								57.16	4.58	4.43	21.55
CH_3	CH_2-O-C_6H_5	G	60		112	1740-1720	4.7	60.64	5.45	5.05	28.85
								60.42	5.48	5.29	28.62
C_2H_5	CH_2Cl	G	73	138 (0.10)	45	1735-1705	4.8	46.26	5.18	5.99	27.39
								46.30	5.25	6.17	27.21
n-C_3H_7	CH_2Cl	G	72	128 (0.05)		1745-1715	4.8	48.49	5.70	5.66	25.84
								48.65	5.85	5.82	26.08

Table 3 (continued)

R	R_2	Method	Yield %	BP °C (mm Hg)	MP °C	IR (ν cm^{-1}) C=O	NMR (δ ppm) H_5	Elemental Analysis Calcd./Found C	H	N	O
n-C_3H_7	CHCl-Me	G	96	126 (0.08)		1740-1700	4.7	50.48 50.38	6.16 6.28	5.35 5.51	24.45 24.49
n-C_3H_7	CHCl-C_6H_5	G	84	191 (0.05)		1740-1705	4.8	59.35 59.37	5.60 5.58	4.33 4.49	19.77 20.12
n-C_3H_7	$CHCl_2$	G	97	148 (0.05)		1750-1715	4.8	42.57 42.30	4.64 4.68	4.97 4.99	22.69 22.92
n-C_3H_7	CH(CH_3)-O-C_6H_5	G	85	165 (0.10)		1740-1705	4.8	63.93 63.96	6.63 6.73	4.39 4.62	25.05 25.39
n-C_3H_7	p-ClC_6H_4-O-CH_2	G	82	175 (0.10)	57	1740-1710	4.8	56.56 56.38	5.34 5.39	4.12 4.09	23.55 23.50
n-C_3H_7	(2,4,5)-$Cl_3C_6H_2$-CH_2	G	71		102	1745-1725-1695	4.8	47.02 47.37	3.95 3.97	3.43 3.34	19.58 19.66
i-C_3H_7	CH_2Cl	G	96	135 (0.15)	50	1740-1730-1705	4.8	48.49 48.64	5.70 5.83	5.66 5.84	25.84 25.82
i-C_3H_7	CH(OAc)-C_6H_5	G	60		133	1750-1735-1700	4.6	62.24 62.05	6.09 6.02	4.03 4.32	27.64 28.01
allyl	CH_2Cl	G	98	137 (0.05)	76	1745-1710	4.9	48.89 49.27	4.93 5.15	5.70 6.05	26.05 26.31
n-C_4H_9	CH_2Cl	G	91	147 (0.20)		1745-1715	4.8	50.48 50.80	6.16 6.38	5.35 5.56	24.45 24.64
t-C_4H_9	CH_2Cl	G	80	132 (0.05)		1735-1710	4.7	50.48 50.31	6.16 6.42	5.35 5.13	24.45 24.76
n-C_5H_{11}	CH_2Cl	G	93	145 (0.10)		1745-1710	4.8	52.27 52.53	6.58 6.62	5.08 5.02	23.21 23.37
n-C_6H_{13}	CH_2Cl	G	93	146 (0.10)		1745-1715	4.8	53.88 54.16	6.96 7.14	4.84 5.07	22.09 22.25
cylco-C_6H_{11}	CH_2Cl	G	88	162 (0.10)		1740-1710	4.8	54.26 54.41	6.30 6.49	4.87 5.12	22.24 22.62
cyclo-C_6H_{11}	CHCl-C_6H_5	G	85	175 (0.10)		1735-1705	4.8	62.72 62.73	6.10 6.46	3.85 4.17	17.59 17.70

16 (Scheme 9). Yields and physical constants of the *N*-acylpyroglutamic esters are reported in Table 3.

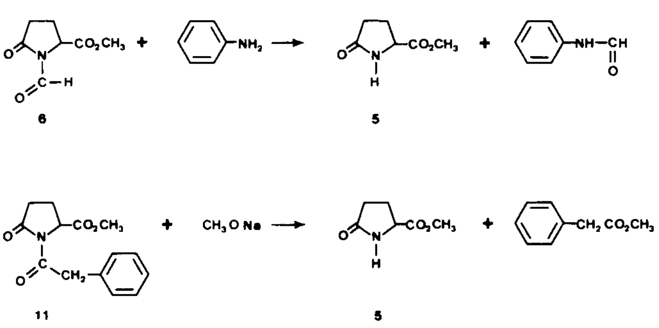
Scheme 9



Reactivity of *N*-acylpyroglutamic Esters with Nucleophiles and Bases.

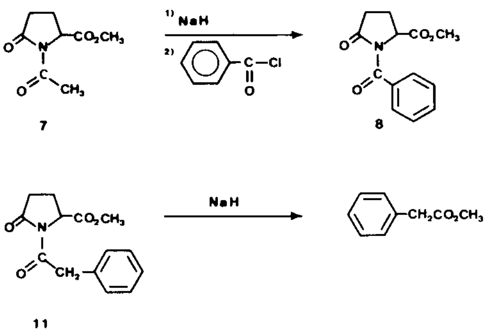
It was known that *N*-acylpyroglutamic acids reacted with nucleophiles either by opening the lactam ring, or by losing the acyl group [13,54,55]. *N*-Acylpyroglutamides reacted mainly by opening the ring [56]. Recently, loss of an acyl group in a *N*-acylpyroglutamic ester, induced by sodium borohydride was described [18]; in the same way, aniline or sodium methylate cleaved the acyl group of methyl *N*-acylpyroglutamates **6,11** (Scheme 10).

Scheme 10



The reaction of methyl *N*-acylpyroglutamates **7,11** with sodium hydride (Scheme 11), or the sodium salt of methyl pyroglutamate, acting as a base (Scheme 6), can only be understood as a cyclization reaction, producing sodium methylate. This anion cleaved the acyl group of another acyl lactam, with the formation of a new acyl ester and the production of the sodium salt of methyl pyroglutamate which can be acylated by an acyl chloride.

Scheme 11



Some nmr particularities of compounds **2** and **14** are reported in the following publication. The new acylpyroglutamic esters **2** (Table 3) were tested *in-vitro* against a variety of fungi, and both gram-negative and gram-positive bacterial strains. Most of the products tested possess activity against these organisms.

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 Central Microanalytical Department of CNRS in Vernaison, France.

Methyl Pyroglutamate (5) (Method 1).

A stirred mixture of pyroglutamic acid (**1**) [16] (6670 g, 51.7 moles) and *p*-toluenesulfonic acid (10 g) was heated at 160° and methanol (8000 ml, 198 moles) was added into the hot mixture while distilling the water and the excess methanol. The methyl pyroglutamate was distilled, yield 78%, bp 145° (0.3 mm), mp 21-23°; ir (neat): ν cm^{-1} 3350-3250 (N-H), 1735 (C=O ester), 1690 (C=O lactam), 1220 (C-O); nmr (deuteriochloroform): δ ppm 2.1-2.8 (m, 8H), 3.76 (s, 3H), 4.1-4.45 (m, 1H), 7.64 (s, 1H, deuterium oxide exchangeable).

Ethyl Pyroglutamate (Method 2).

A 300 ml soxhlet was charged alternatively with glass wool and calcium carbide and placed on a flask charged with pyroglutamic acid (**1**) [16] (221 g, 1.71 moles), *p*-toluenesulfonic acid (5 g), ethyl alcohol (500 ml) and toluene (100 ml). After 3 days at reflux, the solution was evaporated then distilled, yield 89%, bp 141-143° (0.2 mm), mp 52-54°; ir (nujol): ν cm^{-1} 3190-3080 (NH), 1730 (C=O ester), 1700 (C=O lactam), 1240 (C-O); nmr (deuteriochloroform): δ (ppm) 1.3 (t, J = 7.5 Hz, 3H), 1.95-2.7 (m, 4H), 4.18 (q, J = 7.5 Hz, 2H), 4-4.5 (m, 1H), 7.3 (s, 1H, deuterium oxide exchangeable).

t-Butyl Pyroglutamate (Method 3).

A stirred mixture of pyroglutamic acid (**1**) [16] (258 g, 2 moles), triethylamine (253 g, 2.5 moles) and tetrahydrofuran (400 ml) was heated under reflux until dissolution, then *t*-butyl chloride (231 g, 2.5 moles) was added, and reflux was continued for one week, and water (100 ml) was added, solvents were evaporated and the *t*-butyl pyroglutamate was extracted with methylene dichloride. After drying and evaporation of the solvent, the residue was washed with ether, yield 35%, mp 109-110°; ir (nujol): ν cm^{-1} 3240-3110 (NH), 1730 (C=O ester), 1700-1675 (C=O lactam); nmr (deuteriochloroform): δ ppm 1.45 (s, 9H), 2.2-2.5 (m, 4H), 4-4.3 (m, 1H), 7.2 (s, 1H, deuterium oxide exchangeable).

Benzyl Pyroglutamate (Method 3).

This method was the same as for *t*-butyl pyroglutamate, with one equivalent of benzyl chloride in acetone as the solvent. The ester was distilled with a very short path apparatus, yield 59%, bp 185° (0.1 mm), mp 50-52° (ether); ir (nujol): ν cm^{-1} 3400-3170-3080 (NH), 1735 (C = O ester), 1670 (C = O lactam), 1600, 1500 (C = C), 1185 (C-O); nmr (deuteriochloroform): δ ppm 2.1-2.7 (m, 4H), 4-4.5 (m, 1H), 5.14 (s, 2H), 6.79 (s, 5H), 7.31 (s, 1H, deuterium oxide exchangeable). It was important to perfectly dry the organic solutions of the benzyl ester before distilling, otherwise there was formation of hydrates which partly decomposed during the distillation.

Methyl 2-Ethoxypyrroline-5-carboxylate (**12**).

A stirred solution of boron trifluoride etherate (1260 ml, 10 moles) in ether (2500 ml) was heated under reflux then epichlorohydrin (595 ml, 7.75 moles) was slowly added. The solvent was removed with a water pump, ether was added to wash the residue, then removed. The solid was dissolved in methylene dichloride (1000 ml), then a solution of methyl pyroglutamate (960 g, 6.71 moles) in methylene dichloride (500 ml) was added in 10 minutes. The solution was stirred at room temperature for one hour, then refluxed for three hours. After cooling to room temperature, ether (2000 ml) was added, the flask was cooled in ice then triethylamine (1045 ml, 7.5 moles) was slowly added. Triethylammonium tetrafluoroborate was filtered, the solution was washed with water and dried, and after evaporating the solvents, the iminoether was distilled yield 65%, bp 75-80° (0.1 mm); ir (neat): ν cm^{-1} 1740 (C = O), 1640 (C = N); nmr (deuteriochloroform): δ ppm 1.33 (t, J = 7.5 Hz, 3H), 2-2.8 (m, 4H), 2.25 (s, 3H), 4.3 (q, J = 7.5 Hz, 2H), 4.4-4.7 (m, 1H).

Isopropyl *N*-Trimethylsilylpyroglutamate.

A solution of isopropyl pyroglutamate (171 g, 1 mole) in toluene (300 ml) and triethylamine (122 g, 1.2 moles) was refluxed then trimethylchlorosilane (130.4 g, 1.2 moles) in toluene (150 ml) was slowly added. The reflux was continued for four hours, and after cooling at room temperature, the precipitate of triethylamine hydrochloride was filtered and washed with toluene. The solvent was evaporated and the residue distilled, yield 97%, bp 85° (0.1 mm); nmr (deuteriochloroform): δ ppm 0.23 (s, 9H), 1.17 (s, 3H), 1.29 (s, 3H), 2-2.5 (m, 4H), 4-4.3 (m, 1H), 5.03 (m, 1H).

Methyl *N*-Formylpyroglutamate (**6**) (Method A).

A solution of methyl pyroglutamate (**5**) (50 g, 0.35 mole) in formic acid (98%, 200 ml) was refluxed for 18 hours. After evaporating the excess formic acid, the residue was dissolved in ether and the solution placed at −20° for 48 hours. By filtration, 13% of pyroglutamic acid was obtained. Methylene dichloride was added to the solution which was washed with water to remove methyl pyroglutamate. The solution was dried, then evaporated and distilled, to give 28% of acyl ester **6**, bp 112° (0.1 mm), mp 48° (ether/tetrahydrofuran); ir (nujol): ν cm^{-1} 1760-1750-1740 (C = O ester, CHO), 1690 (C = O lactam); nmr (deuteriochloroform): δ ppm 2.1-2.8 (m, 4H), 3.77 (s, 3H), 4.5-4.8 (m, 1H), 8.95 (s, 1H).

Anal. Calcd. for $C_7H_9O_4N$: C, 49.12; H, 5.30; N, 8.19; O, 37.39. Found: C, 48.96; H, 4.93; N, 8.32; O, 37.75.

Methyl *N*-Acetylpyroglutamate (**7**) (Method B).

A solution of methyl pyroglutamate (**5**) (350 g, 2.45 moles) and dimethylaminopyridine (0.5 g, 4 mmoles) in acetic anhydride (272 g, 2.67 moles) was refluxed for 3 hours. After evaporating acetic acid, ethyl ether (150 ml) and one crystal of the same compound **7** was added, and the solution was allowed to stand at 0° for one night. After filtration, a yield of 63% of acetyl compound **7** was obtained, mp 41° (ether/petroleum ether) (lit bp 138° (2 mm), oil); ir (nujol): ν cm^{-1} 1735 (C = O ester), 1690 (C = O lactam), 1220 (C-O); nmr (deuteriochloroform): δ ppm 1.9-2.9 (m, 4H), 2.55 (s, 3H), 3.79 (s, 3H), 4.6-4.9 (m, 1H).

Anal. Calcd. for $C_8H_{11}NO_4$: C, 51.88; H, 5.99; N, 7.57; O, 34.56. Found: C, 51.54; H, 5.73; N, 7.78; O, 34.82.

Methyl *N*-Benzoylpyroglutamate (**8**) (Method C).

A solution of methyl pyroglutamate (**5**) (62.9 g, 0.44 mole) and benzoyl chloride (61.6 g, 0.44 mole) in pyridine (34.7 g, 0.44 mole) was refluxed for 3 hours. After cooling, methylene dichloride was added and the solution was washed successively with water, with diluted hydrochloric acid, with a solution of potassium carbonate then with water. After evaporating the solvent, the residue was recrystallized from methanol, yield 32%, mp 141-143°; ir (nujol): ν cm^{-1} 1750, 1735, 1640 (C = O), 1600, 1575, 1490 (C = C), 1185 (C-O); nmr (deuteriochloroform): δ ppm 2-3 (m, 4H), 3.80 (s, 3H), 4.8-5.15 (m, 1H), 7.2-7.9 (m, 5H).

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67; O, 25.89. Found: C, 63.43; H, 5.24; N, 5.87; O, 26.14.

By using toluene as the solvent, potassium carbonate as a base and dibenzo-18-crown-6 as a phase transfert agent (reflux 18 hours), a 35% yield of benzoyl product **8** was obtained.

Methyl *N*-Ethoxycarbonylpyroglutamate (**9**) (Method D).

A solution of methyl pyroglutamate (**5**) (150 g, 1.05 moles) and triethylamine (295 ml, 2.12 moles) in dimethylformamide (150 ml) and ethyl ether (450 ml) was cooled (−5, −10°), then ethyl chloroformate (202 ml, 2.11 moles) was added very slowly while maintaining the same temperature (carbon dioxide evolution was not observed). The solution was allowed to warm at 0° for 8 hours and kept at this temperature for 12 hours. The solution was then allowed to warm to 10° and kept at that temperature for 8 hours. The triethylammonium chloride was filtered and the residue was dissolved in methylene dichloride, the solution was washed with water and dried. The solvent was evaporated and the product was distilled, yield 72%, bp 131° (0.1 mm), mp 51° (ether); ir (nujol): ν cm^{-1} 1740 (C = O ester), 1700 (C = O lactam), 1170 (C-O); nmr (deuteriochloroform): δ ppm 1.42 (t, J = 7.5 Hz, 3H), 2-2.9 (m, 4H), 3.78 (s, 3H), 3.81 (q, J = 7.5 Hz, 2H), 4.70 (m, 1H).

Anal. Calcd. for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51; O, 37.17. Found: C, 50.53; H, 6.05; N, 6.52; O, 37.25.

Methyl *N*-Phenylacetylpyroglutamate (**11**) (Method E).

A solution of methyl pyroglutamate (**5**) (266 g, 1.86 moles) in toluene (350 ml) was slowly added to a well stirred dispersion of sodium hydride (53.6 g, 1.86 moles, 20% in mineral oil), in toluene (200 ml). When the sodium salt formation was completed, phenylacetyl chloride (287.6 g, 1.86 moles) was added during 2 hours and the mixture was allowed to stand at room temperature for one night. Water (700 ml) was added with caution, and the organic phase was washed with sodium hydrogen carbonate, then water. After drying and evaporation of the solvent, the residue was distilled. Methyl phenylacetate (17%) was first obtained (bp 90°, 0.1 mm). The fraction with a boiling point of 170-190° (0.1 mm) was washed with petroleum ether to remove mineral oil, then it was distilled again, and compound **11** was obtained, yield 28%, bp 184° (0.1 mm). This product crystallized after several months, mp 45°; ir (neat): ν cm^{-1} 1745-1695 (C = O), 1210 (C-O); nmr (deuteriochloroform): δ ppm 1.7-2.9 (m, 4H), 3.64 (s, 3H), 4.22 (s, 2H), 4.5-4.9 (m, 1H), 7.22 (s, 5H).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.36; O, 24.50. Found: C, 64.16; H, 6.05; N, 5.20; O, 24.65.

Methyl *N*-(Cyanoacetyl)pyroglutamate (**13**) (Method F).

A solution of cyanoacetyl chloride (10.3 g, 0.1 mole) in tetrahydrofuran (15 ml) was added to a solution of iminoether **12** (17.1 g, 0.1 mole) in tetrahydrofuran (25 ml). The mixture was stirred at room temperature for one night, then the solvent was evaporated. The residue was dissolved in water and extracted with ethyl ether. The aqueous phase was extracted with methylene chloride, this organic phase was washed with water, then dried, evaporated and distilled. The nitrile **13** was obtained in 22% yield, bp 170° (0.1 mm); ir (neat): ν cm^{-1} 2260 (C ≡ N), 1745-1705 (C = O), 1220 (C-O); nmr (deuteriochloroform): δ ppm 2-3 (m, 4H), 3.76 (s, 3H), 4.13 (s, 2H), 4.7-5 (m, 1H).

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33; O, 30.45. Found: C, 51.72; H, 4.51; N, 13.54; O, 30.16.

Methyl *N*-Chloracetylpyroglutamate (Method G).

A solution of methyl *N*-trimethylsilylpyroglutamate (21.5 g, 0.1 mole) in tetrahydrofuran (80 ml) was refluxed during the addition of chloracetyl chloride (11.3 g, 0.1 mole). The reflux was continued during a night then the solvent was evaporated and the residue was distilled, yield 95%, bp 142° (0.15 mm), mp 66° (ether); ir (nujol): ν cm^{-1} 1755-1695 (C=O), 1205 (C-O); nmr (deuteriochloroform): δ ppm 2-3 (m, 4H), 3.77 (s, 3H), 4.72 (s, 2H), 4.7-5 (m, 1H).

Anal. Calcd. for $C_8H_{10}ClNO_4$: C, 43.80; H, 4.59; N, 6.38; O, 29.17. Found: C, 43.77; H, 4.50; N, 6.41; O, 28.88.

This compound, like some other *N*-chloracetylpyroglutamic esters, was slightly vesicant.

Methyl *N*-(1,3-Dioxobutyl)pyroglutamate (**15**) (Method H).

Diketene (8.5 g, 0.1 mole) was added to a solution of methyl *N*-trimethylsilylpyroglutamate (25.5 g, 0.1 mole) and triethylamine (1 ml) in tetrahydrofuran (60 ml). The mixture was stirred under reflux for 7 hours, water (2 ml) was added and the reflux was continued for 15 minutes. After evaporating the solvents, the residue was distilled. A first distillation fraction (bp < 110°, 0.1 mm) crystallized in part (dehydroacetic acid); a second fraction (bp < 140°, 0.1 mm) was eliminated (impurities); compound **15** crystallized from the third fraction (bp 145-150°), yield 42%, mp 85° (ethyl ether/methylene chloride); ir (nujol): ν cm^{-1} 1740-1730-1710-1685 (C=O), 1185 (C-O); nmr (deuteriochloroform): δ ppm 1.9-2.9 (m, 4H), 2.28 (s, 3H), 3.79 (s, 3H), 3.78 (d, J = 16.5 Hz, 1H), 4.26 (d, J = 16.5 Hz, 1H), 4.7-5 (m, 1H). A small amount of enol form was seen in the nmr spectra: 13.36 ppm (s, 0.1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.17; O, 35.21. Found: C, 52.97; H, 5.65; N, 5.80; O, 35.09.

Reaction of Methyl *N*-Formylpyroglutamate with Aniline.

A mixture of methyl *N*-formylpyroglutamate (21.6 g, 0.126 mole), aniline (9.3 g, 0.1 mole), triethylamine (10.1 g, 0.1 mole) and toluene (5 ml) was stirred under reflux for 4 hours, then ether was added and the solution was washed with water. After drying the product was distilled, yield 100% of formanilide, mp 46° (lit mp 50°) [57]. The water phase was extracted with chloroform, giving methyl pyroglutamate (**5**).

Reaction of Methyl *N*-Acetylpyroglutamate with Sodium Hydride and Benzoyl Chloride.

Methyl *N*-acetylpyroglutamate (37 g, 0.2 mole) was added to a sodium hydride (5.8 g, 0.2 mole, 20% in mineral oil) dispersion in tetrahydrofuran (200 ml). The resulting mixture was stirred under reflux for 4 hours and cooled in ice. The solid was filtered, washed with tetrahydrofuran and added to tetrahydrofuran (200 ml). A solution of phenylacetyl chloride (28.1 g, 0.2 mole) in tetrahydrofuran (50 ml) was added to the preceding dispersion cooled at 0°. After a night at room temperature, the mixture was filtered and distilled. Methyl *N*-benzoylpyroglutamate (**8**) (40%) was obtained at 170° (0.1 mm).

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