

## Michael reaction of glutamic acid and diethylglutamate

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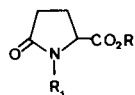
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Starting from glutamic acid or diethyl glutamate, some derivatives of *N*-(2-carboxyethyl), *N*-(3-oxobutyl) and *N*-(2-cyanoethyl)pyroglutamic acid were synthesized.

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*N*-Substituted pyroglutamic acid derivatives **1** can be obtained by a Mannich reaction starting from glutamic acid (**2**) or ester **3** and an aromatic type compound [1], or by the reaction of a halogenated product with the salt **4** [2] or the silylated lactam **5** [3]. When aromatic or halogenated compounds are not very reactive, these methods produce poor yields.

Scheme 1

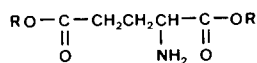


**1** R, R<sub>1</sub> = H

**5** R = H R<sub>1</sub> = Si(CH<sub>3</sub>)<sub>3</sub>

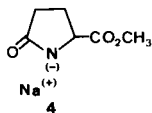
**13** R = CH<sub>3</sub> R<sub>1</sub> = H

**16** R = C<sub>2</sub>H<sub>5</sub> R<sub>1</sub> = H



**2** R = H

**3** R = C<sub>2</sub>H<sub>5</sub>



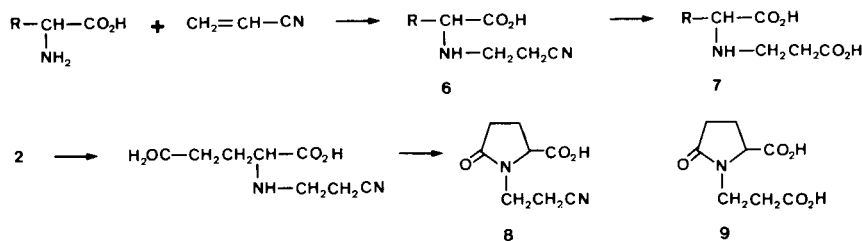
In 1950, McKinney *et al* described the addition of eleven aminoacids to acrylonitrile, and the hydrolysis of seven of the obtained cyanoethylaminoacids **6** to the diacids **7**; in this sequence, glutamic acid (**2**) yielded *N*-(cyanoethyl)pyroglutamic acid (**8**). But curiously, McKinney does not describe the diacid **9** [4,5] (Scheme 2).

In this report, we wish to describe the preparation of the diacid **9**, some aspects of the reactivity of the acid **8**, and the synthesis of *N*-(3-oxobutyl)pyroglutamic acid derivatives.

From our experiments, hydrolysis of cyanoacid **8** using the McKinney method (2*N* barium hydroxide, reflux) [5], or the Ford technique (barium hydroxide octahydrate, 95°) [6], do not yield the diacid **9**, however this compound can be obtained by the saponification of the diester **10** [7].

Even a minute amount of sodium chloride inhibit the crystallization of diacid **9**. Thus the sodium ions were removed with an ion-exchange resin. Because of this, diacid **9** precipitated after evaporation of the solvents and the product was recrystallized from acetone (59% yield) (Scheme 3).

Scheme 2



Scheme 3

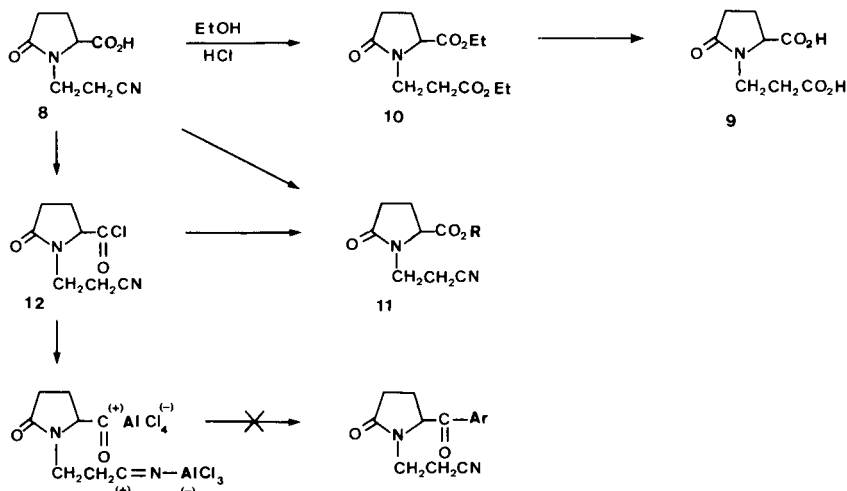


Table 1

Physical and Analytical Data for Cyanoesters **11**

R	Method	Yield (%)	MP °C (solvent)	BP °C (mm Hg)	n <sub>D</sub> <sup>20</sup>	Formula	Analysis (%)					
							Calcd.			Found		
							C	H	N	C	H	N
Me	A	84	63 (ether)	164 (0.4)		C <sub>9</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>	55.10	6.12	14.28	55.28	5.98	14.13
Et	A	75		156 (0.05)	1.4804	C <sub>10</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	57.14	6.66	13.33	57.03	6.82	13.36
<i>i</i> -Pr	A	77		151 (0.2)	1.4727	C <sub>11</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>	58.92	7.14	12.50	58.78	7.21	12.50
<i>n</i> -Bu	A	83		162 (0.2)	1.4770	C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>	60.50	7.56	11.76	60.45	7.67	11.55
CH <sub>2</sub> CH <sub>2</sub> -O-Et	A	87		179 (0.1)	1.4796	C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub>	56.69	7.08	11.02	56.85	7.12	10.93
Benzyl	A	85		205 (0.4)	1.5358	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>	66.17	5.98	10.29	65.92	5.95	10.48
Phenyl	B	76	92 (CCl <sub>4</sub> )			C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	65.11	5.42	10.85	65.30	5.45	10.65
Cholesteryl	B	88	143 (heptane)			C <sub>36</sub> H <sub>52</sub> N <sub>2</sub> O <sub>3</sub>	76.28	9.80	5.08	76.04	9.99	5.10

In this sequence, the diester **10** was obtained using hydrochloric acid as a catalyst. When the catalyst was replaced by *para*-toluenesulfonic acid, the nitrile group remained intact, and the cyanoesters **11** were obtained in good yield (Table 1, method A). The phenol and cholesterol esters were prepared by using the acid chloride **12** (Table 1, method B). This acid chloride reacted with aluminium trichloride to give an insoluble salt which does not react in Friedel-Crafts reactions (*N*-methyl and *N*-(arylmethyl)pyroglutamic acid chlorides yielded ketones in these reactions [2a,8] (Scheme 3).

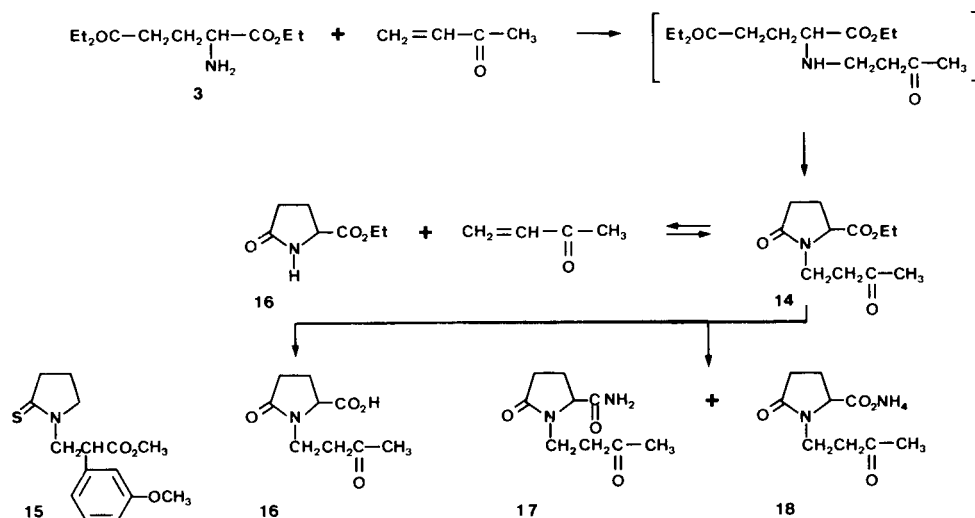
In another set of reactions, we tried to obtain other types of *N*-substituted pyroglutamic derivatives by a Michael reaction. We did not succeed in adding glutamic acid (**2**) or diethyl glutamate (**3**) to acrolein, benzylidene acetophenone or 4-vinylpyridine (acid or basic catalyst) [9]. Methyl vinyl ketone [10] and glutamic acid (**2**) do not give

pyroglutamic derivatives and with methyl pyroglutamate (**13**), these gave only a low yield of ester **14** (catalyst Na or Triton B, reflux in toluene). However, by using diethyl glutamate (**3**) in ether, ketone **14** was obtained in 87% crude yield (Scheme 4).

In comparison with thiolactame **15** [11], ketone **14** was partly decomposed by a retro-Michael reaction during its vacuum distillation and in fact, a less pure product was obtained by a slow distillation with a stilling-band column than with a rapid distillation using a short path Vigreux column. Chromatography of the distilled compound on alumina column produced the ketoester **14** with 97% purity. Even with the presence of 3% ethyl pyroglutamate in the ester **14**, pure acid **16** and amide **17** can be obtained.

The amide **17** was found to be inactive in hormonal tests and to possess only a marginal sedative activity [12].

Scheme 4



## 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 Thiais, France.

*N*-(2-Carboxyethyl)pyrrolutamic Acid (9).

A mixture of diester **10** (85.7 g, 0.33 mole), sodium hydroxide (27 g, 0.67 mole) and water (250 ml) was heated under reflux for 1 hour. After cooling, the solution was subjected to an Amberlite IR-120 ion-exchange resin, the water was evaporated, and the residue was dissolved in tetrahydrofuran, the solution dried and evaporated. The precipitate was recrystallized from acetone, yield 59%, mp 117°; ir (nujol):  $\nu$   $\text{cm}^{-1}$  3250 (OH), 1740, 1700 (C=O, acid), 1640 (C=O, amide); nmr (deuteriochloroform with DMSO- $d_6$ , 5%):  $\delta$  ppm 1.9-2.5 (m, 4H), 2.55 (t, J = 7 Hz, 2H), 2.9-4.1 (m, 2H), 4.1-4.5 (m, 1H), 10.34 (s, 2H, this peak disappears upon addition of deuterium oxide).

Anal. Calcd. for  $\text{C}_6\text{H}_{11}\text{NO}_3$ : C, 47.76; H, 5.51; N, 6.96; O, 39.77. Found: C, 47.62; H, 5.51; N, 7.25; O, 39.85.

*N*-(2-Cyanoethyl)pyrrolutamic Acid Esters **11** (Method A).

A stirred mixture of acid **9** (0.5 mole), *para*-toluenesulfonic acid (0.5 g) and alcohol (methanol, 9 moles; ethanol, 10 moles in benzene; 2-propanol, 6 moles in benzene; butanol, 4 moles; 2-ethoxyethanol, 3 moles in xylene; benzyl alcohol, 1.6 moles) was heated as water was removed by azeotropy. After the reaction, the solution was washed with a sodium acetate solution and the ester extracted with chloroform. The chloroform solution was dried, the solvent was evaporated and the residue distilled.

*N*-(2-Cyanoethyl)pyrrolutamic Acid Chloride (**12**).

A stirred mixture of acid **9** (53 g, 0.29 mole) and thionyl chloride (80 ml) was heated at 55°. After the reaction, the solution was evaporated and the chloride recrystallized from benzene, yield 77%, mp 72°.

Anal. Calcd. for  $\text{C}_6\text{H}_9\text{ClN}_2$ : C, 47.88; H, 4.48; N, 13.97. Found: C, 47.80; H, 4.52; N, 13.78.

Phenyl *N*-(2-Cyanoethyl)pyrrolutamate.

A solution of chloride **12** (13.4 g, 0.066 mole) in dioxane (10 ml) and chloroform (40 ml) was added over a period of 1 hour, to a cooling solu-

tion of phenol (6.1 g, 0.064 mole) in pyridine (10 ml). The resulting solution was heated at 65° for 3 hours. The solvents were evaporated and 30 ml of diluted hydrochloric acid was added. The precipitate was filtered, washed with water, dried and recrystallized from carbon tetrachloride, yield 76%, mp 92°; ir (nujol):  $\nu$   $\text{cm}^{-1}$  2250 (CN), 1760-1680 (C=O), 1580 (Ar).

Cholesteryl *N*-(2-Cyanoethyl)pyrrolutamate.

A solution of chloride **12** (5 g, 0.024 mole) in chloroform (20 ml) was added to cholesterol (3 g, 0.0077 mole) in pyridine (20 ml). The mixture was heated at 80° for 3 hours. The solvents were evaporated and water (50 ml) was added. The precipitate was recrystallized from heptane, yield 88%, mp 143°; ir (nujol):  $\nu$   $\text{cm}^{-1}$  2240 (CN), 1750-1700 (C=O).

Ethyl *N*-(3-Oxobutyl)pyrrolutamate (**14**).

A solution of methyl vinyl ketone (105 g, 1.5 mole) was slowly added to a solution of diethyl glutamate (296 g, 1.46 moles) in ether (650 ml), giving an exothermic reaction, then the mixture was heated under reflux. After reaction, the solvent was evaporated, benzene (300 ml) was added and the diethyl ester was cyclized by heating under reflux for 5 hours. The solvents were evaporated and the product distilled quickly under vacuum. The fourteen fractions taken between 140° and 150° (0.05 mm Hg) were analysed by gpc (column SE 30, 175°), yield 84% of ketoester **14** [15-20% impurities, mainly ethyl pyrrolutamate (**16**)].

A part of this product (25 g) was eluted on an aluminium oxide, activated, neutral column (20 x 4 cm), with a mixture of cyclohexane-ether 50/50 as eluant. The first fractions were ketoester **14** (97% pure); ir (neat):  $\nu$   $\text{cm}^{-1}$  1770-1740-1720;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  ppm 1.28 (t, J = 6.7 Hz, 3H), 2.12 (s, 3H), 2.1-2.4 (m, 4H), 2.75 (t, J = 7 Hz, 2H), 3-3.9 (m, 2H), 4.18 (q, J = 6.7 Hz, 2H), 4.2-4.4 (m, 1H).

Anal. Calcd. for  $\text{C}_{11}\text{H}_{17}\text{NO}_4$ : C, 58.13; H, 7.54; N, 6.16; O, 28.16. Found: C, 56.59; H, 7.67; N, 6.04; O, 29.74.

*N*-(3-Oxobutyl)pyrrolutamic Acid (**16**).

A stirred suspension of ester **14** (10 g, 0.044 mole) in 1*N* sodium hydroxide (45 ml) was heated at 80° for 45 minutes. Then the solution was acidified with diluted hydrochloric acid (0.045 mole). The solvent was evaporated, the residue extracted in tetrahydrofuran, the solution was filtered, dried, treated with Darco and cooled at 0°. The crystalline acid was recrystallized in acetone. It was necessary to avoid the use of ether in the recrystallization because it inhibits the acid crystallization process. The yield of pure acid **16** was 40%, mp 138°; ir (nujol):  $\nu$   $\text{cm}^{-1}$  1740-1720-1640;  $^1\text{H}$  nmr (deuteriochloroform with DMSO- $d_6$ , 5%):  $\delta$  ppm

2.11 (s, 3H), 2-2.5 (m, 4H), 2.74 (t,  $J = 6$  Hz, 2H), 3-3.9 (m, 2H), 4-4.4 (m, 1H), 10.79 (s, 1H disappears upon addition of deuterium oxide).

*Anal.* Calcd. for  $C_9H_{13}O_4N$ : C, 54.26; H, 6.58; N, 7.03; O, 32.13. Found: C, 54.18; H, 6.44; N, 7.05; O, 32.00.

*N*-(3-Oxobutyl)pyroglutamide (**17**).

A solution of ester **14** (7 g, 0.03 mole) in ammonium hydroxide (15 ml) and water (5 ml) was stirred at 0° for 24 hours. The solvents were evaporated and the residue stirred in a mixture of ether-ethanol. The crystalline product was dissolved in anhydrous ethyl alcohol (solution A). The insoluble residue was a small amount of ammonium salt **18**, mp 72°; ir (nujol):  $\nu$   $cm^{-1}$  1730-1650 (C=O);  $^1H$  nmr (deuterium oxide):  $\delta$  ppm 2-2.6 (m, 4H), 2.20 (s, 3H), 2.9 (t,  $J = 7$  Hz, 2H), 3.1-4 (m, 2H), 4.2-4.5 (m, 1H).

*Anal.* Calcd. for  $C_9H_{16}N_2O_4$ : C, 49.99; H, 7.46; N, 12.96; O, 29.60. Found: C, 49.92; H, 7.44; N, 13.02; O, 29.83.

Ether was added to the solution A and the amide **17** precipitated, yield 41%, mp 138°; ir (nujol):  $\nu$   $cm^{-1}$  3390-3210 (N-H), 1720-1680 (C=O);  $^1H$  nmr (deuterium oxide):  $\delta$  ppm 2.10 (s, 3H), 1.8-2.5 (m, 4H), 2.6-3 (m, 2H), 3.1-3.8 (m, 2H), 3.8-4.3 (m, 1H).

*Anal.* Calcd. for  $C_9H_{14}N_2O_3$ : C, 54.53; H, 7.12; N, 14.14; O, 24.22. Found: C, 54.55; H, 7.05; N, 14.35; O, 24.10.

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