Studies on Pyrrolidinones. Synthesis of Methyl *N*-(4-Nitrobenzyl)pyroglutamate

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Methyl *N*-trimethylsilylpyroglutamate is reacted with 4-nitrobenzyl chloride to yield methyl *N*-(4-nitrobenzyl)pyroglutamate.

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Our continuing efforts on structural modifications of 5-pyrrolidinone-2-carboxylic acid (pyroglutamic acid) (**1**) [1,2] have led us to the synthesis of 1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-dione derivatives (**2**). Starting materials for these compounds were the esters **3**, which were obtained by the reaction of the sodium salt **4** [3]; moreover, the esters **3** display interesting hypolipemic, cardiovascular, analgesic properties [3b].

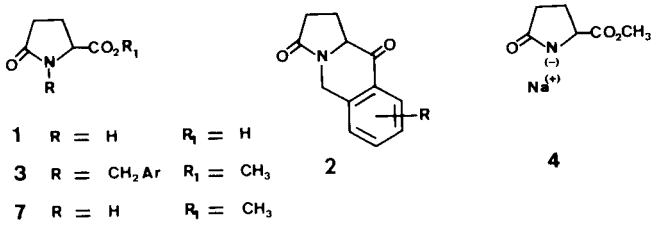
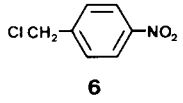


Figure 1



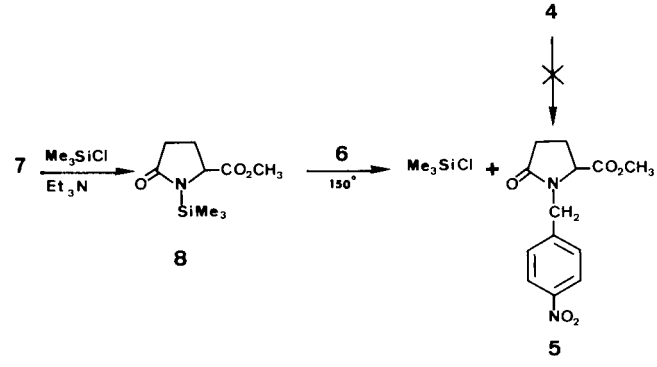


Figure 2

Although 4-nitrobenzyl chloride reacts in a normal way with some heterocyclic anions [4], methyl *N*-(4-nitrobenzyl)pyroglutamate (**5**) cannot be formed by this method because the sodium salt **4**, acting as a base, transforms it in 4,4'-dinitrotranstilbene [5,6,7], as well as in toluene as in ethanol [3]. In the same way, treatment of methyl pyroglutamate (**7**) with **6**, in the presence of alumina coated with potassium fluoride [8,9] produces only the stilbene. We found however that heating chloride **6** and methyl *N*-trimethylsilylpyroglutamate (**8**), in the absence of any base, in an oil bath at 150°, produced the ester **5** in a fairly good yield (71%) if the trimethylchlorosilane formed was removed continuously by distillation. When the mixture was heated under reflux conditions, the pot temperature was lower and the yield was only 35%.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a Perkin Elmer 700 spectrometer, 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.

Methyl *N*-Trimethylsilylpyroglutamate (**8**) [10].

A stirred solution of methyl pyroglutamate (**7**) (143 g, 1 mole) and triethylamine (101 g, 1 mole) in toluene (400 ml) was heated at 80° under nitrogen atmosphere. Trimethylchlorosilane (127 ml, 1 mole) in toluene (100 ml) was then added dropwise over 3 hours and the mixture heated to reflux for 3 hours. At this time the reaction mixture was cooled to room temperature and the precipitate of triethylamine hydrochloride was filtered, washed with toluene (500 ml). The solvent was evaporated and the residue distilled to give 85% of compound **8**, bp 88° (0.1 mm); rmn (deuteriochloroform): δ ppm 0.26 (s, 9H), 2.1-2.7 (m, 4H), 3.72 (s, 3H), 4.1-4.4 (m, 1H). This compound was used directly for the synthesis of ester **5**.

Methyl *N*-(4-Nitrobenzyl)pyroglutamate (**5**).

A stirred mixture of 4-nitrobenzyl chloride (5.1 g, 0.03 mole) and silyl compound **8** (6.4 g, 0.03 mole) was heated under nitrogen atmosphere for 40 hours at 150° in a vessel equipped with a short distillation head. During the course of the reaction trimethylchlorosilane evolved. The nmr yield was 76%. After cooling, 5 ml of ether was added and the precipitate was filtered and decolorized with activated carbon in methanol. The white product obtained after evaporation of the solvent was washed with ether, yield 71%, mp 153° (methanol); ir (nujol): ν cm^{-1} 1735, 1670 (C=O), 1600 (C=C), 1510 (NO_2); nmr (deuteriochloroform): δ ppm 2-2.7 (m, 4H), 3.66 (s, 3H), 4.06 (m, 1H), 4.21 (d, J = 15.6 Hz, 1H), 5.02 (d, J = 15.6 Hz, 1H), 7.41 (d, J = 9 Hz, 2H), 8.17 (d, J = 9 Hz, 2H).

Anal. Calcd. for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07; O, 28.75. Found: C, 56.37; H, 4.96; N, 9.90; O, 28.78.

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