Studies on Pyrrolidinones. Synthesis of 1,2,3,5,11,11a-Hexahydroindolizino[7,6-*b*]indole-3,11-dione

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Condensation of *N*-trimethylsilylindole with methyl *N*-trimethylsilyloxymethylpyroglutamate is the best method to obtain methyl *N*-indolylmethylpyroglutamate. Friedel-Crafts cyclization of the corresponding acid yields a new ketone (1,2,3,5,11,11a-hexahydroindolizino[7,6-*b*] indole-3,11-dione).

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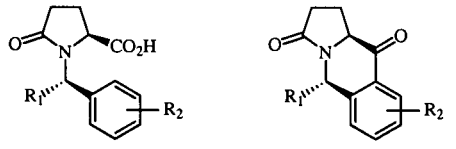
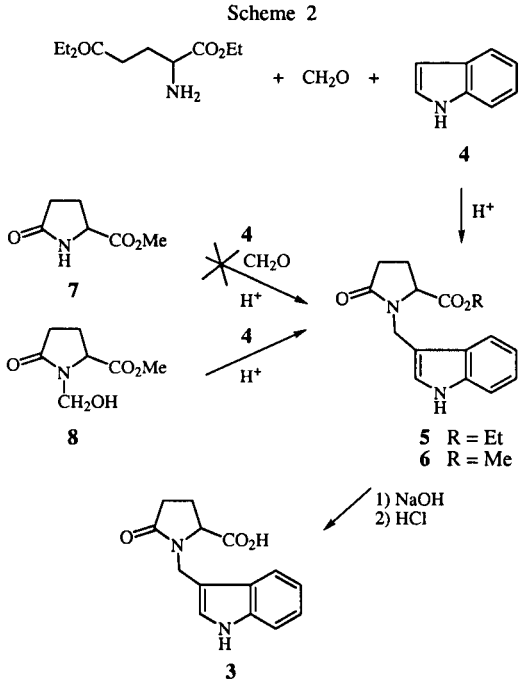
In the course of a general study on the reactivity of pyroglutamic acid derivatives [1], we have already described the synthesis of *N*-benzylpyroglutamic acids **1** [2] and their cyclization into cyclic ketones **2** [3] (Scheme 1). In this context, the indolylmethylpyroglutamic acid **3** is interesting. Indeed its synthesis was realized in the low yield of 30% by the sequences described in Scheme 2 [4] and its cyclization has not been reported.

Scheme 1



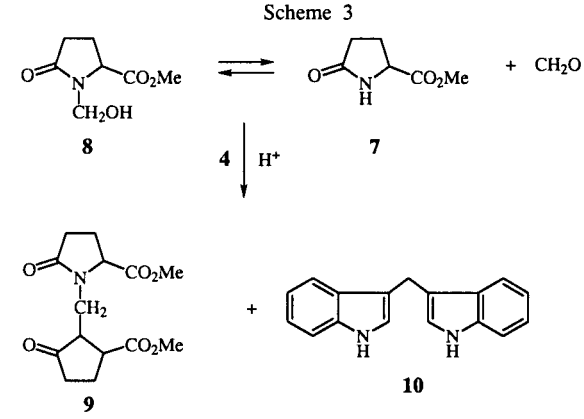
1 **2**

Scheme 2



One of the causes of the low yields in the former synthesis of acid **3** is the formation of a great amount of methylenebispyroglutamic diester **9** and methylene bis indole **10** (see Scheme 3). In a new attempt to obtain acid **3**, it was thought to start from methyl *N*-methylolpyroglutamate **8** [4] which is one of the possible reaction intermediate. Ester **6** was then obtained as a red oil, in poor yield (10%). Its saponification gives acid **3** (50% yield), also as an impure red oil. The reversibility of the formation of *N*-methylol ester **8** under acidic conditions yields formaldehyde, then the dimers of pyroglutamic esters [5] and of indole (Scheme 3).

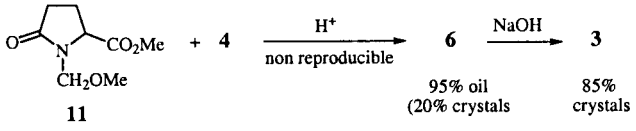
Scheme 3



Another possible starting compound was the methyl *N*-methoxymethylpyroglutamate **11** [6]. In the first reaction performed with this amide, the yield in methyl ester **6** was 95%, obtained as a red oil whose crystallization gave 20% of a pure product. The saponification of this crude reaction mixture gave 85% of pure acid **3**; but all attempts to repeat these reactions gave very bad results (Scheme 4).

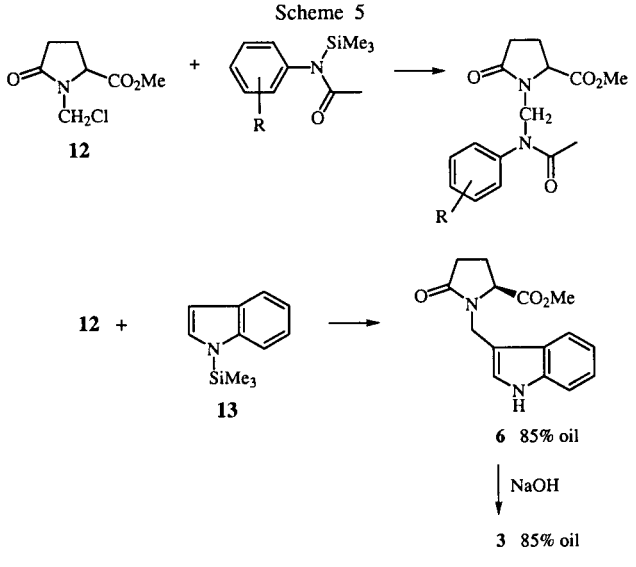
We recently described that the reaction of methyl *N*-chloromethylpyroglutamate **12** [7] with *N*-silylated amides is a very interesting way to perform Mannich reactions [7] (Scheme 5). The transposition of this sequence to *N*-trimethylsilylindole

Scheme 4



13 [8] gives an interesting result because ester **6** was obtained in 85% yield; the purity of this red oil, as checked by nmr was better than in the previous reactions, and the saponification of this oil yields 85% in acid **3**, also as an oil, but in a satisfactory state of purity (Scheme 5).

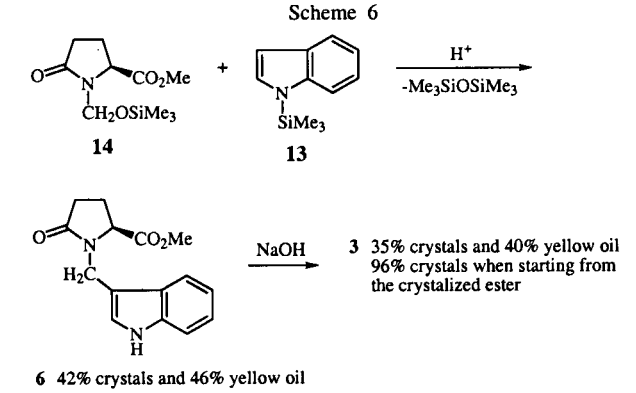
Scheme 5



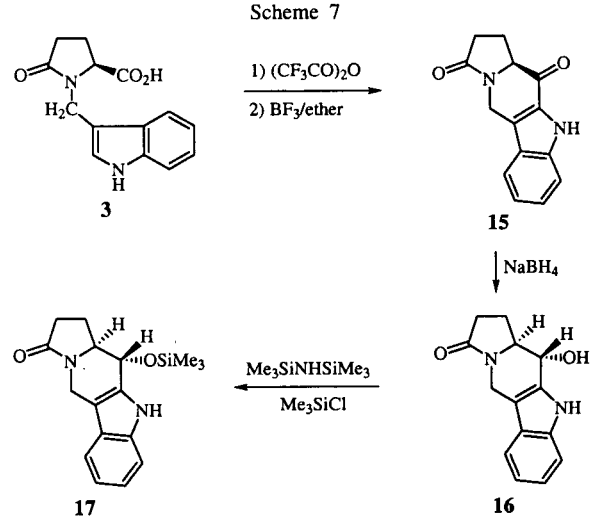
The best results were obtained when methyl *N*-trimethylsilyloxymethylpyroglutamate **14** [7] was compared with *N*-trimethylsilylindole **13** [8] (80°, H^+). Under these conditions, ester **6** was formed in 88% yield as a yellow oil which gives 42% of crystallized product. The saponification of the crude oil yields 75% of acid with good purity (yellow oil) which can be directly used in the next step; 35% of this acid crystallized. All these yields are reproducible.

The cyclization of acid **3** was accomplished, as for other electron-rich aromatic derivatives [3a], by heating the mixed anhydride (from trifluoroacetic anhydride) with boron trifluoride etherate in dichloroethane. A 98% crude yield in ketone **15** was thus obtained. In the first approach toward the reactivity of this compound, the reduction of the ketone function was accomplished with sodium borohydride, giving alcohol **16** in 55% yield, which affords a quantitative yield of trimethylsilyl ether **17** (Scheme 7).

Scheme 6



Scheme 7

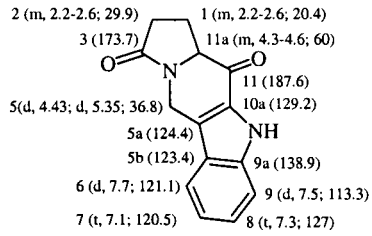


The ^1H and ^{13}C chemical shifts for ketone **15** were assigned by using different nmr experiments: the ^{13}C values of carbons 1, 2, 3, 5, 11 and 11a were determined from comparisons with other compounds in these series. The assignments of H_6 (d, 7.7 ppm) and H_9 (d, 7.5 ppm) were deduced from the NOESY correlation of H_6 with H_5 (5.35 ppm). Irradiation of H_6 shows a correlation with H_7 (7.1 ppm), and irradiation of H_9 (7.5 ppm) confirms H_8 (7.3 ppm). A proton-carbon HETCOR correlation gives the values for C_6, C_7, C_8 and C_9. Then a long range proton-carbon HETCOR correlation (two and three bond, 7 Hz) gives the ^{13}C chemical shift of C_2, C_{5a}, C_{5b} and C_{9a} and a DEPT spectrum confirms the substitutions of the different carbons (C, CH, CH_2) (Figures 1 and 2).

Compounds **3, 6, 15, 16** were tested in-vitro for their antitumor activity, according to a typical NCI protocol [9]. These compounds have no activity under the testing conditions.

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, using tetramethylsilane as an internal reference. Elemental analyses were performed by the «Service Central de Microanalyses» (CNRS, 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 chemical in bulk quantities.



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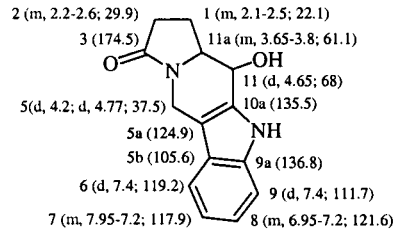

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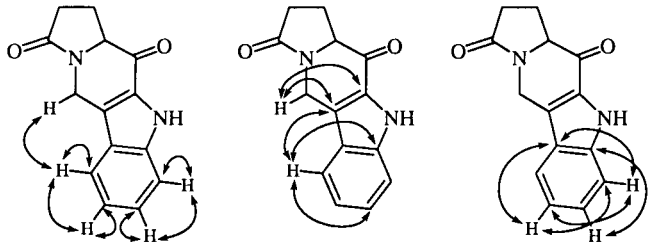
Figure 1. ^1H and ^{13}C Chemical shifts for ketone **15** and alcohol **16** in deuteriochloroform/dimethyl-d_6 sulfoxide.



15 NOESY
HETCOR (one bond)

15 HETCOR (long range)

Figure 2. Main nmr correlations for ketone **15**.

N-(3-Indolylmethyl)pyroglutamic Acid (**3**).

A stirred mixture of crude ester **6** (48.5 g, 0.178 mole) in a sodium hydroxide solution (2*N*, 200 ml) was refluxed for 1 hour. The aqueous phase was washed with dichloromethane, then the solvent traces were removed from the aqueous solution by vacuum evaporation. Concentrated hydrochloric acid was added very slowly, with good stirring, at room temperature, to the solution of the sodium salt. The viscous oil obtained was dissolved in acetone, dried (sodium sulfate), then evaporated. Starting from crystallized ester, a 96% yield of crystallized acid **3** was obtained; starting from crude ester, evaporation in part of the acetone solution gives 35% of crystallized acid **3** and evaporation of the filtrate yields 40% of oily acid **3**; mp 176° (methanol), tlc (acetonitrile/water 80/20) R_f, 0.77; $[\alpha]_D^{20}$ 70°(methanol, 10 g/l); ir (potassium bromide): ν cm^{-1} 3325 (NH, OH), 1720 (C=O), 1500 (C=C); ^1H nmr (dimethyl-d_6 sulfoxide): δ ppm 1.9-2.4 (m, 2H), 2.24-2.56 (m, 2H), 3.86 (dd, J = 5, 3.5 Hz, 1 H), 4.16 (d, J = 14.6 Hz, 1 H), 5.23 (d, J = 14.6 Hz, 1 H), 7.02 (td, J = 8, 1.3 Hz, 1 H), 7.13 (td, J = 8, 1.3 Hz, 1 H), 7.15 (s, 1 H), 7.39 (d, J = 8 Hz, 1 H), 7.54 (d, J = 8 Hz, 1 H), 10.48 (bs, 1 H, deuterium oxide exchangeable); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ ppm 22.5 (CH_2-CH), 30 (CH_2-CO), 36.4 (CH_2-N), 58 (CH-CH_2), 109.2, 111.7, 118.7, 119.3, 121.7, 125, 126.7 (Ar), 174 (CO-N), 174.8 (CO_2).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85; O, 18.58. Found: C, 65.23; H, 5.60; N, 10.61; O, 18.56.

Methyl *N*-(3-Indolylmethyl)pyroglutamate (**6**).

From Ester **11**.

A mixture of ester **11** (50 g, 0.267 mole) and indole (31.3 g, 0.267 mole) was stirred under nitrogen atmosphere. Triflic acid (0.2 ml) was added (syringe) and the mixture was heated at 90° for 33 hours (disappearance in the nmr spectrum of the characteristic peaks of compound **11**). The mixture was dissolved in dichloromethane, washed with water then dried with sodium sulfate. Evaporation of the volatile gives a red oil which can be used for the next step, or crystallized from ethyl acetate; crude yield 95% (oil), crystallized yield 20%.

From ester **14**.

A mixture of ester **14** (210 g, 0.86 mole) and *N*-trimethylsilylindole (164 g, 0.86 mole) in dichloromethane (200 ml) was stirred under nitrogen atmosphere. Triflic acid (2.5 ml, 0.0126 mole) was added *via* syringe and the mixture was refluxed for 26 hours (disappearance in the nmr spectrum of the characteristic peaks of compound **14**). The mixture of two immiscible phases was dissolved in dichloromethane, washed with water, with a potassium carbonate solution, then with water. After drying (sodium sulfate), the solution was evaporated giving an oil which crystallized in ethyl acetate; crude yield 88% (oil), crystallized yield 42%, mp 136° (ethyl acetate); tlc (ethyl acetate) R_f, 0.67; $[\alpha]_D^{20}$ (methanol, 10 g/l) 35.5°; ir (potassium bromide): ν cm^{-1} 3175 (NH), 1750 (C=O ester), 1670 (C=O lactam), 1620, 1500, 1450 (C=C); ^1H nmr (deuteriochloroform): δ ppm 2-2.68 (m, 4 H), 3.59 (s, 3H), 3.98 (dd, J = 5.1, 3.6 Hz, 1 H), 4.29 (d, J = 14.8 Hz, 1 H), 5.18 (d, J = 14.8 Hz, 1 H), 7.13 (td, J =7.7, 1.5 Hz, 1 H), 7.13 (s, 1 H), 7.22 (td, J = 7.7, 1.5 Hz, 1 H), 7.38 (d, J = 7.7 Hz, 1 H), 7.62 (d, J = 7.7 Hz, 1 H), 8.30 (bs, 1 H, deuterium oxide exchangeable); ^{13}C nmr (deuteriochloroform): δ ppm 22.7 (CH_2-CH), 30 (CH_2-C=O), 36.8 (CH_2-N), 52.3 (CH_3), 58.7 (CH-CH_2), 110.2, 111.4, 119.2, 120.1, 122.6, 124.6, 126.9, 136.6 (Ar), 172.8 (C=O-N), 175.2 (CO_2).

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29; O, 17.63. Found: C, 65.96; H, 5.97; N, 10.09; 0, 17.98.

Methyl *N*-Trimethylsilyloxymethylpyroglutamate (**14**).

A stirred mixture of methyl *N*-hydroxymethylpyroglutamate [14] (50 g, 0.289 mole), saccharin (2.6 g, 0.0145 mole) and hexamethyldisilazane (200 ml, 154 g, 0.95 mole) was refluxed for 2 hours (nitrogen). Saccharin was filtered (compound **14** is not very water sensitive), solvents were evaporated and compound **14** was distilled, bp 95° (0.1 mm Hg), yield 98%. If this synthesis is performed with less pure (oily) methyl *N*-hydroxymethylpyroglutamate, in order to avoid a too exothermic a reaction, it is necessary to add the oil slowly to the refluxing hexamethyldisilazane.

1,2,3,5,11,11a-Hexahydroindolizino[7,6-*b*]indole-3,11-dione (**15**).

Trifluoroacetic anhydride (41 ml, 0.283 mole) was added to a suspension of acid **3** (60.6 g, 0.236 mole) in dichloroethane (750 ml) under nitrogen atmosphere. The mixture was refluxed for 30 minutes then boron trifluoride etherate (140 ml, 1.14 moles) was added to the solution. The stirred mixture was stirred at room temperature for 12 hours. Part of the solvents was evaporated

giving solution **A** and a solid. The solid was filtered and washed by stirring with water, then with a potassium carbonate solution then with water until neutralization, giving 43 g of powder. Methylene dichloride was added to solution **A** which was washed with water, with a potassium carbonate solution then with water until neutralization, giving 5 g of ketone **15**, total yield 84%, mp 220° (ethyl acetate); tlc (ethyl acetate) R_f, 0.55; $[\alpha]_D^{20}$ 161° (methanol, 9 g/l); ir (potassium bromide): ν cm^{-1} 3375, 3290 (NH), 1680 (C=O ketone), 1650 (C=O lactam), 1620, 1500, 1440 (C=C); ^1H nmr (deuteriochloroform/dimethyl-d_6 sulfoxide): δ ppm 2.2-2.6 (m, 4 H), 4.3-4.6 (m, 1 H), 4.43 (d, J = 17.2 Hz, 1 H), 5.35 (d, J = 17.2 Hz, 1 H), 7.1 (t, J = 7.5 Hz, 1 H), 7.3 (t, 7.5 Hz, 1 H), 7.5 (d, J = 8.2 Hz, 1 H), 7.7 (d, J = 8.2 Hz, 1 H), 11.06 (s, 1 H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 69.99; H, 5.03; N, 11.66; O, 13.32. Found: C, 69.98; H, 4.94; N, 11.54; O, 13.21.

11-Hydroxy-1,2,3,5,11,11a-hexahydroindolizino[7,6-*b*]indol-3-one (**16**).

Sodium borohydride (1.7 g, 0.043 mole) was slowly added to a solution of ketone **15** (5.1 g, 0.021 mole) in ethanol (80 ml). The mixture was refluxed for 5 hours. After cooling, glacial acetic acid (40 ml) was added and the volatile materials were evaporated. The residue was dissolved in dichloromethane and the solution was washed with water then with aqueous hydrogenocarbonate solution. The solution was dried (sodium sulfate), then evaporated and the powder was recristallized from methanol, yield 55%; tlc (ethyl acetate) R_f, 0.3, mp 210° (methanol);$[\alpha]_D^{20}$ 140° (methanol, 10g/l); ir (potassium bromide): ν cm^{-1} 3325 (NH, OH), 1650 (C=O), 1620, 1490 (C=C); ^1H nmr (deuteriochloroform/dimethyl-d_6 sulfoxide): δ ppm 2.1-2.5 (m, 4 H), 3.65-3.8 (m, 1 H), 3.65-3.8 (m, 1 H, deuterium oxide exchangeable), 4.2 (d, J = 16.4 Hz, 1 H), 4.65 (d, J = 8.6 Hz, 1 H), 4.97 (d, J = 16.4 Hz, 1 H), 6.95-7.20 (m, 2 H), 7.4 (d, J = 8.6 Hz, 2 H), 10.48 (bs, 1 H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56; O, 13.21. Found: C, 69.11; H, 5.91; N, 11.22; O, 13.52.

11-Trimethylsilyloxy-1,2,3,5,11,11a-hexahydroindolizino[7,6-*b*]-indol-3-one (**17**).

To a stirred mixture of alcohol **16** (2 g, 0.008 mole) hexamethyldisilazane (5 ml, 0.024 mole) and imidazole (10 mg) under nitrogen atmosphere, chlorotrimethylsilane (0.1 ml) was added *via* syringe. The mixture was refluxed (ammonium chloride sublimation inside the condenser). After the end of gas evolution, the mixture was cooled. The filtration of the solid yields 100% of compound **17** as a white powder; rf 0.8 (ethyl acetate), mp 1.65-170°; ^1H nmr (acetone-d_6): δ ppm 0.25 (s, 9 H), 2-2.6 (m, 4 H), 3.75 (m, 1 H), 4.10 (d, J = 17.8 Hz, 1 H), 4.85 (d, J = 17.8 Hz, 1 H), 4.90 (m, 1 H), 6.95-7.15 (m, 2 H), 7.37 (d, J = 8 Hz, 1 H), 7.45 (d, J = 8 Hz, 1 H), 9.75 (bs, 1 H).

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