A New Scaffold for Dipeptide β-Turn Mimetics: Expeditious Synthesis of an Unsaturated 6,5-Fused Bicyclic Lactam

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Reported here is an easy and short synthesis of 6-acetamido-5-oxo-1,2,3,5,6,7-hexahydro-3-indolizinecarboxylic acid, originating from β-enaminoesters derived from pyroglutamic acid. This key compound has been used as a scaffold in the synthesis of dipeptido mimetics.

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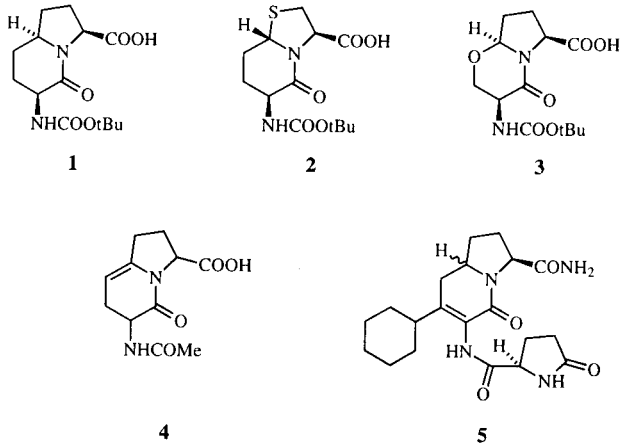
Rational design of peptidomimetics, conformationally rigid analogs of natural peptides with a restrained backbone side chain, has gained great importance in recent years; many reviews have recently been published on this subject [1]. Azabicycloalkane amino acids, used as replacements of a dipeptide motif in a natural substrate with a rigid scaffold, are an important class of such compounds [2]. In the bicyclo[4.3.0]nonane series, conformationally restricted moities for Ala-Pro dipeptides such as **1** have been described [3], with the obvious advantage over compounds such as the 1-thia [4] or 8-oxa [5] analogs (compounds **2**, **3**) of greater stability under acidic conditions (Scheme 1). In the course of our research in the field of peptidomimetics of therapeutic interest [6], we present here an easy and rapid synthesis of derivatives of indolizine **4**, designed as a rigid analog of compound **1**, with the advantage of one stereogenic center. To the best of our knowledge [1a], only one example, (**5**) of unsaturated analogs of **1** has so far been described [7].

Scheme 1

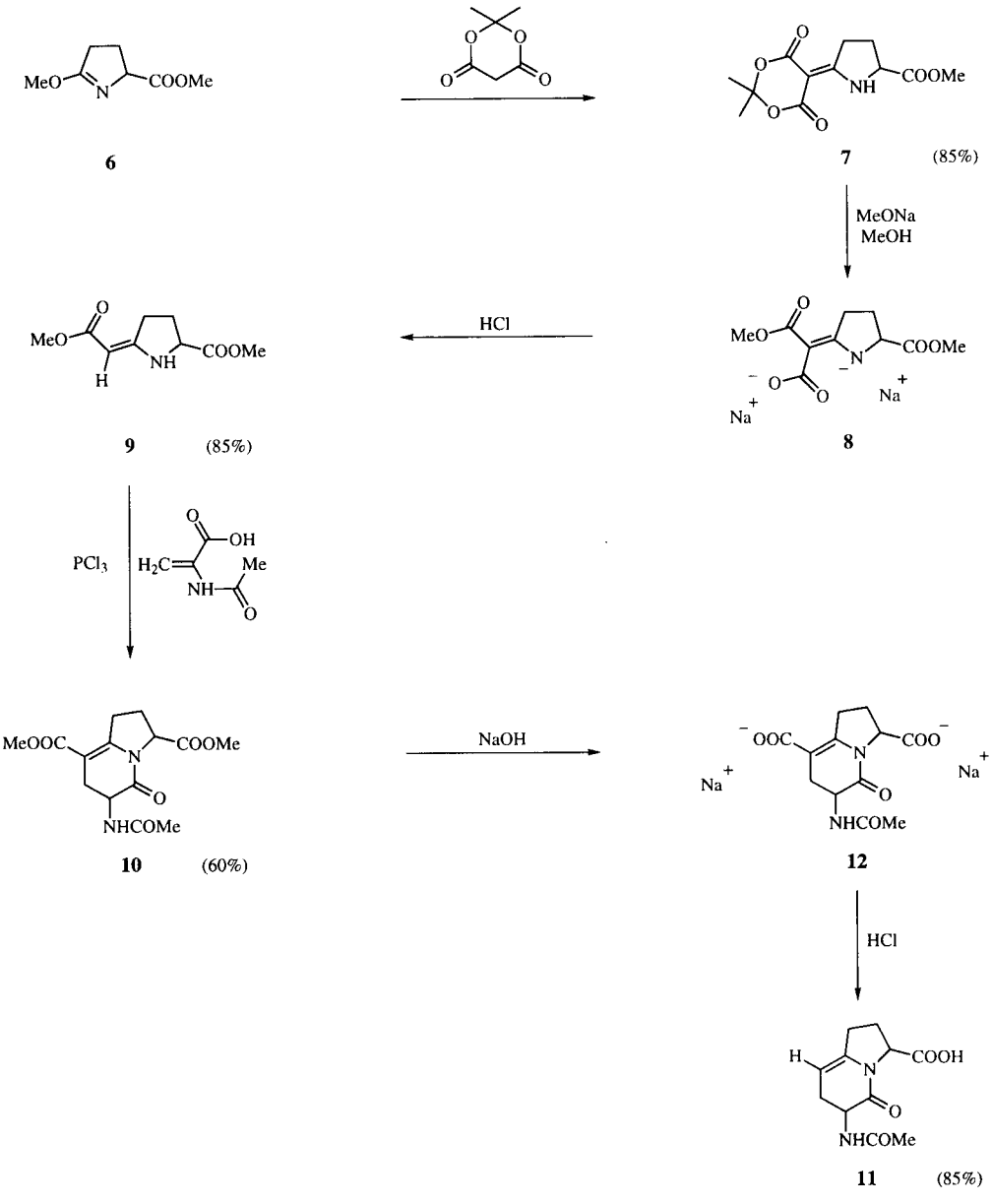


The starting point of this synthesis was the iminoether **6** derived from pyroglutamic acid [8]. Condensation with Meldrum's acid forms the enaminoester **7** [8]. The opening of Meldrum's ring was carried out with two equivalents of sodium methoxide in methanol, followed by acidification of the disodium salt **8** and spontaneous decarboxylation, giving a quantitative crude yield of the carbamate vinylogous **9** [9]. The dihydropyridinone ring was created using the method of Capps [10]: heating a solution of β-enaminoester **9** and acetamidoacrylic acid in a mixture of dioxane and toluene gives a 60% yield of diester **10** the saponification of which gives a 85% yield of hygroscopic acid **11** (Scheme 2).

A noteworthy point concerns the mechanism of the formation of diester **10**: it is known that the reaction of β-enaminoester **13** with acetyl chloride (Scheme 3) leads to the formation of either *C*-acylated **14** or *N*-acylated product **15** depending upon experimental conditions. At room temperature, the *C*-acylated kinetic compound **14** was obtained [11], whereas the *N*-acylated thermodynamic product **15** was isolated when the reaction was carried out under benzene reflux [12] or in refluxing toluene with pyridine as a catalyst [13]; we have also previously reported that the reaction of β-enaminoester **9** with acetyl chloride (90°, 20°, or 0°) yielded only a *C*-acylated compound **16** [9]. Thus the most likely mechanism for the formation of the six-membered ring starts with a Michael addition of the enamine system on acrylic acid, yielding acid **17** as an intermediate. Cyclization of acid chloride **18** formed by reaction with phosphorus trichloride gives lactam **10** (Scheme 3).

The easy saponification of the β-enaminoester function of lactam **10** is also to be considered: many reports point out the resistance of β-enaminoesters to saponification [14], and special methods such as heating with boric acid have to be used for such saponification [15]. For β-enaminoesters **9** from pyroglutamic acid, we have shown that it is very easy to saponify the 5-methoxycarbonyl group

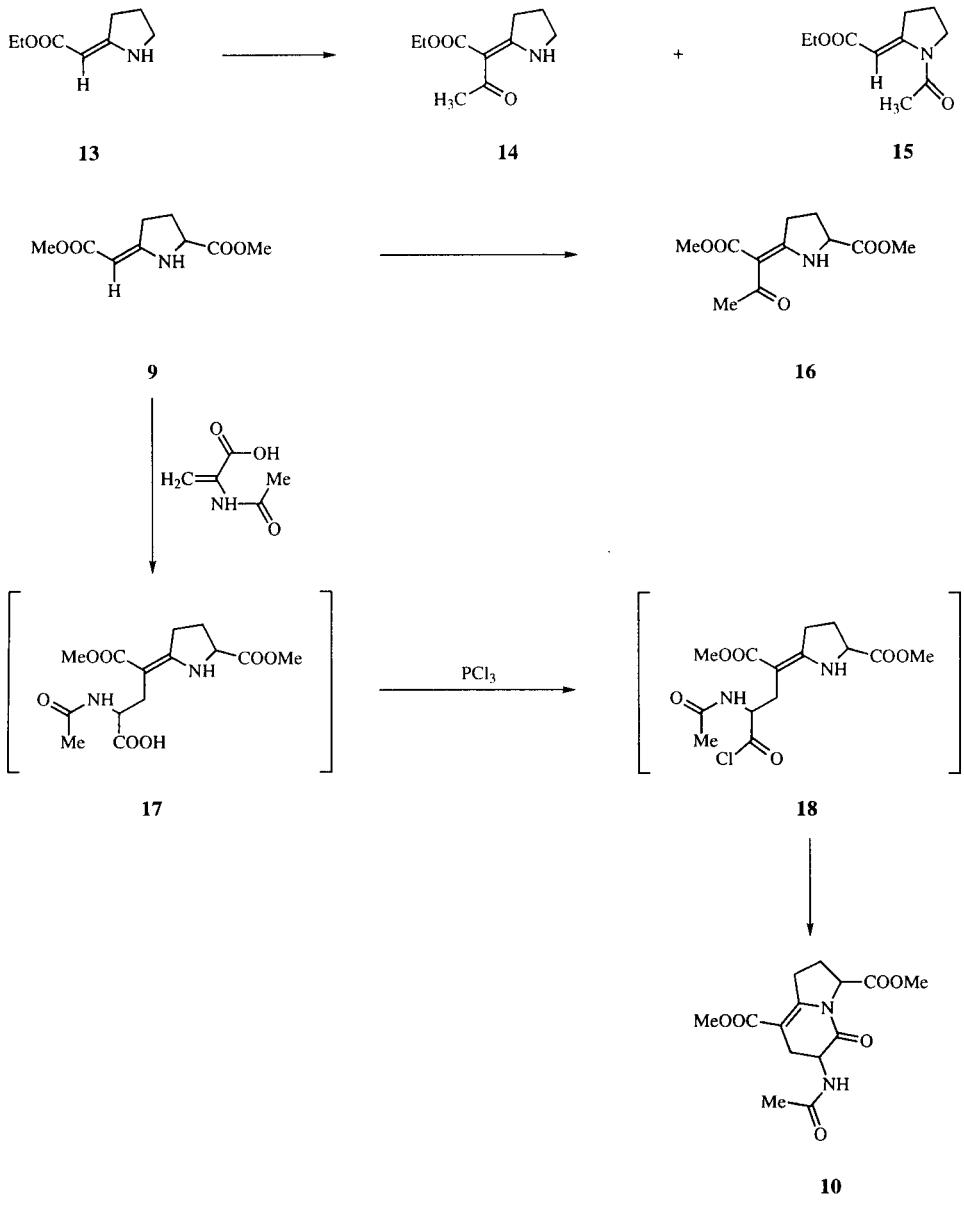
Scheme 2



[16] and that the enaminoester function can only be cleaved by using trimethylsilyl iodide [9]. Thus for compounds such as **10**, the unsaturated ester group is not to be considered as a vinylogous carbamate but as an ester group.

We took these findings into account for the synthesis of the dipeptide analog **19**: due to the hygroscopic nature of acid **11**, we did not manage to convert it into amide **19** that we had chosen as a model compound. The conversion of ester **9** into amide **20** (Scheme 4) was obtained by heating

Scheme 3



9 at 80° with benzylamine; the formation of heterocycle **21** followed by the saponification/decarboxylation of the ester group was performed without difficulty, giving a 30% yield of hygroscopic product **19**. In another reaction sequence, it is possible to use the unsaturated ester group of **10** to obtain functionalized dipeptide analogs. In that way, heating of diester **10** at 80° with benzylamine yields triamide **22** (Scheme 4).

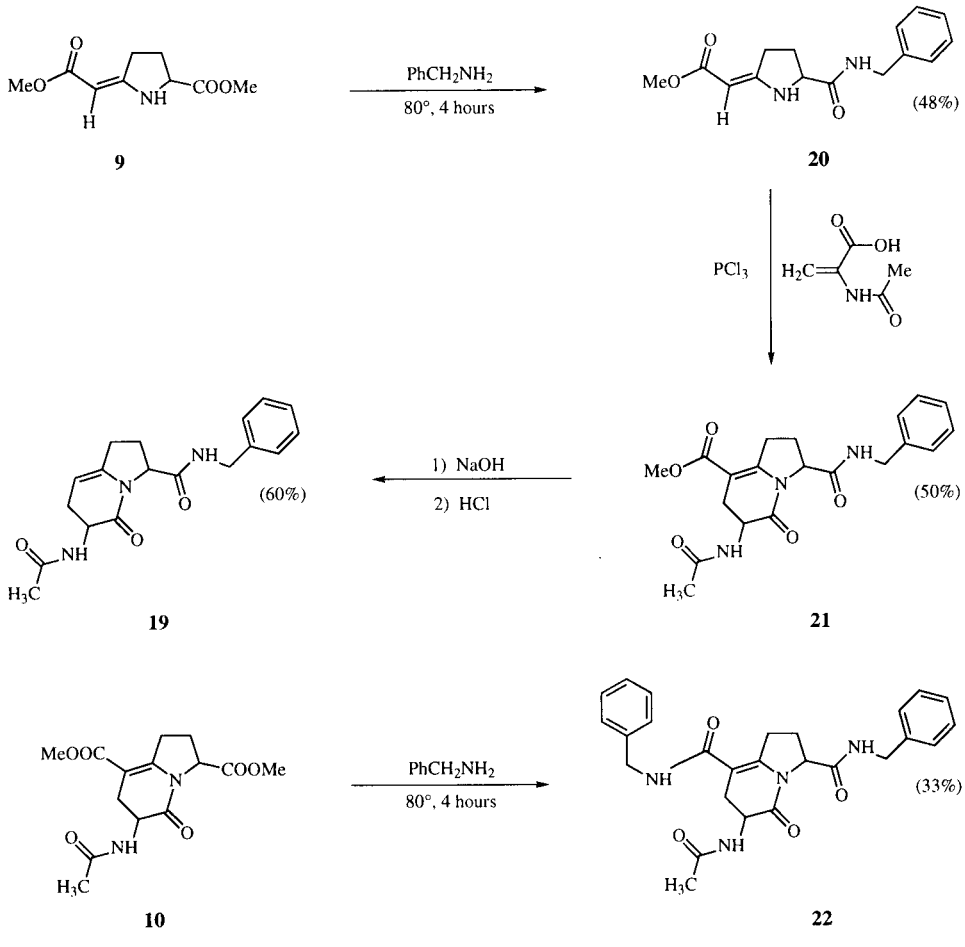
Conclusion.

We have demonstrated that, starting from pyroglutamic β-enaminoester **9**, it is possible by easy and versatile reactions to obtain dipeptide analogs such as **11** and **19** as well as functionalized compounds such as **10**, **21** and **22**.

EXPERIMENTAL

Melting points were determined on a Büchi 535 capillary melting point apparatus and are uncorrected. Column chromatography was performed on silica gel 60 230-400 Mesh purchased from Merck. The ir spectra were determined in potassium bromide with a Perkin Elmer 1310 spectrophotometer; absorbances are reported in ν (cm^{-1}). The ^1H nmr spectra were recorded on a

Scheme 4



Bruker AC 300 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are expressed in δ units (ppm) and the splitting patterns are designated as follows: s singlet, bs broad singlet, t triplet, d doublet, dd doublet of doublets, m multiplet, bm broad multiplet. The mass spectra were recorded on a quadripolar Finnigan Mat SSQ 710 instrument in the electron impact mode or chemical ionization. Elemental analyses for C, H, N, performed by the <<Service Central d'Analyses>> at the CNRS, Vernaison, France, were not carried out for moisture sensitive compounds.

Methyl (5-Methoxycarbonyl-2-pyrrolidinylidene)acetate (**9**).

A mixture of β-enaminoester **7** (5.4 g, 20 mmoles) and sodium methoxide (30% in weight in methanol, 7.2 g, 40 mmoles) in 30 ml of methanol were refluxed for 48 hours in an inert atmosphere. The sodium salt was neutralized with concentrated hydrochloric acid (3.3 ml, 40 mmoles). The inorganic salts were filtered and the methanol removed under vacuum. The residue was dissolved in 50 ml of methylene chloride, the organic layer was washed with water (3 x 50 ml), dried over magnesium sulfate, filtered and evaporated. The β-enaminoester **9** was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 5/5), 85% yield, mp 92-94°; ir (potassium bromide): ν cm^{-1} 3300 (N-H), 1745 (C=O), 1650 (C=O), 1600 (C=C), 1200 (C-O); ^1H nmr (deuteriochloroform): δ ppm 2.05-2.80 (m, 4H), 3.63 (s, 3H), 3.75 (s, 3H), 4.25-4.72 (m, 2H), 8.13 (s, 1H); ms: (electron impact) m/z 199, 168, 140, 108, 80. Physical data is identical to that of an authentic sample [9].

Methyl 6-Acetamido-8-methoxycarbonyl-5-oxo-1,2,3,5,6,7-hexahydro-3-indolizinecarboxylate (**10**).

Acetamidoacrylic acid (5.00 g, 38.7 mmoles) and phosphorus trichloride (3.33 ml, 38.7 mmoles) were added to a solution of β-enaminoester **9** (7.01 g, 35.2 mmoles) in dry dioxane (30 ml) and dry toluene (15 ml). The solution was heated at reflux in an inert atmosphere and stirred for 4 hours. The solvents were removed under reduced pressure and the residue was dissolved in chloroform and washed successively with saturated aqueous sodium hydrogen carbonate, hydrochloric acid (1*N*), water and saturated aqueous sodium chloride. The chloroform solution was dried over magnesium sulfate, filtered and the solvent was evaporated to give indolizidinone **10** which was recrystallized from ethyl acetate/acetone (1/1), yield 60%, mp 181-182°; ir (potassium bromide): ν cm^{-1} 3305 (N-H), 1740 (C=O), 1690 (C=O), 1646 (C=O); ^1H nmr (deuteriochloroform): δ ppm 2.06 (s, 3H), 2.11-2.48 (m, 2H), 2.85-3.16 (m, 2H), 3.32-3.54 (m, 2H), 3.74

(s, 3H), 3.76 (s, 3H), 4.58-4.62 (m, 1H), 4.79 (dd, 1H, J = 7.0 Hz, J' = 2.9 Hz), 6.28 (d, 1H, J = 5.4 Hz); ms: (chemical ionization) m/z 311 (MH^+), 279, 251, 192.

Anal. Calcd. For $C_{14}H_{18}N_2O_6$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.01; H, 5.84; N, 9.04.

6-Acetamido-5-oxo-1,2,3,5,6,7-hexahydro-3-indolizinecarboxylic Acid (**11**).

Indolizinone **10** (1.50 g, 4.83 mmoles) in 20 ml of sodium hydroxide (2*N*, 40 mmoles) was stirred for 2 hours at 80°. The sodium salt that formed was carefully neutralized with 20 ml of hydrochloric acid (2*N*, 40 mmoles). The solvent was removed under reduced pressure and boiling absolute ethanol was added to the mixture. Sodium chloride salt was filtered and the solvent was evaporated. The residue was crystallized from absolute ethanol/methylene chloride to yield indolizinone **11** in 85% yield, mp >100° (hygroscopic); ir (potassium bromide): ν cm^{-1} 1730 (C=O), 1670 (C=O), 1630 (C=O); ^1H nmr (dimethyl-d_6 sulfoxide): δ ppm 1.85 (s, 3H), 1.90-2.60 (m, 6H), 4.16-4.25 (m, 1H), 4.40-4.45 (m, 1H), 8.20-8.25 (s, 1H); ms: (electron impact) m/z 238, 193, 179, 134, 106, 80.

Methyl (5-Benzylaminocarbonyl-2-pyrrolidinylidene)acetate (**20**).

A solution of enaminoester **9** (1.00 g, 5.02 mmoles) in benzylamine (2.3 ml, 20.1 mmoles) was stirred at 80° for 4 hours. The solution was washed with hydrochloric acid (1*N*) and extracted using chloroform. The organic extract was dried over magnesium sulfate, filtered, and evaporated to yield an oil which was purified by chromatography on silica gel (ethyl acetate/methylene chloride 1/1). The precipitate thus obtained was recrystallized from ethyl acetate to give enaminoester **20** at 48% yield, mp 139-141°; ir (potassium bromide): ν cm^{-1} 3350 (N-H), 3300 (N-H), 1650 (C=O); ^1H nmr (dimethyl-d_6 sulfoxide): δ ppm 1.85-1.95 (m, 1H), 2.10-2.22 (m, 1H), 2.50-2.70 (m, 2H), 3.45 and 3.50 (2s, 3H), 4.27-4.46 (m, 3H), 4.42 (s, 1H), 7.22-7.36 (m, 5H), 7.86 and 8.23 (2s, 1H), 8.49-8.52 (m, 1H); ms: (electron impact) m/z 274, 140, 108, 82, 80.

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.68; H, 6.55; N, 10.01.

6-Acetamido-3-benzylaminocarbonyl-8-methoxycarbonyl-5-oxo-1,2,3,5,6,7-hexahydroindolizine (**21**).

Acetamidoacrylic acid (424 mg, 3.28 mmoles) and phosphorus trichloride (0.31 ml, 3.61 mmoles) were added to a solution of enaminoester **20** (900 mg, 3.28 mmoles) in dry dioxane (30 ml) and dry toluene (15 ml). The stirred solution was refluxed in an inert atmosphere and stirred for 4 hours. The solvents were removed under reduced pressure and the residue was dissolved in boiling acetone. Salts were filtered and acetone solution was evaporated to yield an oil which crystallized from ethyl acetate/acetone in 50% yield, mp 265-267°; ir (potassium bromide): ν cm^{-1} 3300 (N-H), 1700 (C=O), 1650 (C=O); ^1H nmr (dimethyl-d_6 sulfoxide): δ ppm 1.88 (s, 3H), 1.93-2.01 (m, 1H), 2.20-2.32 (m, 1H), 2.43-2.50 (m, 1H), 2.74-2.91 (m, 2H), 3.18-3.27 (m, 1H), 3.65 (s, 3H), 4.22-4.36 (m, 2H), 4.44-4.53 (m, 1H), 4.66-4.69 (d, 1H, J = 7.5 Hz) 7.23-7.36 (m, 5H), 8.25-8.28 (m, 1H), 8.66-8.70 (m, 1H); ms: (chemical ionization) m/z 386 (MH^+), 354, 326, 193, 106, 91.

Anal. Calcd. for $C_{20}H_{23}N_3O_5$: C, 62.33; H, 6.01; N, 10.90. Found: C, 62.41; H, 5.92; N, 10.81.

6-Acetamido-3-benzylaminocarbonyl-5-oxo-1,2,3,5,6,7-hexahydroindolizine (**19**).

Indolizinone **21** (300 mg, 0.78 mmoles) in sodium hydroxide (2*N*, 20 ml, 40 mmoles) was stirred until dissolution (about 2 hours). The sodium salt that formed was carefully neutralized with hydrochloric acid (2*N*, 20 ml, 40 mmoles) and water was removed under reduced pressure. Boiling methanol was added to the mixture. Sodium chloride salts were filtered and the solvent was evaporated. The residue crystallized from methanol/methylene chloride to yield indolizinone **19** at 60% yield, mp >100° (hygroscopic); ir (potassium bromide): ν cm^{-1} 3385 (N-H), 1650 (C=O); ^1H nmr (dimethyl-d_6 sulfoxide): δ ppm 1.83 (s, 3H), 1.84-1.90 (m, 2H), 1.92-2.15 (m, 2H), 2.20-2.40 (m, 2H), 4.05-4.15 (m, 1H), 4.20-4.30 (m, 2H), 4.40-4.50 (m, 1H), 7.23-7.30 (m, 5H), 7.70-7.80 (m, 1H), 8.30-8.40 (m, 1H); ms: (electron impact) m/z 327, 268, 239, 161, 135, 134, 106, 91, 43.

6-Acetamido-3-benzylaminocarbonyl-8-benzylaminocarbonyl-5-oxo-1,2,3,5,6,7-hexahydro-3-indolizine (**22**).

A solution of indolizinone **10** (1.0 g, 3.22 mmoles) in benzylamine (1.4 ml, 12.9 mmoles) was stirred at 80° for 4 hours. Methanol was added to the solution and the precipitate obtained was filtered and washed with methylene chloride to yield indolizinone **9** in 33% yield, mp 210°; ir (potassium bromide): ν cm^{-1} 3300 (N-H), 1660 (C=O), 1645 (C=O); ^1H nmr (dimethyl-d_6 sulfoxide): δ ppm 1.80 (bs, 3H), 2.05-2.15 (m, 1H), 2.25-2.30 (m, 1H), 2.65-2.75 (m, 2H), 3.50-3.60 (m, 2H), 4.00-4.40 (m, 6H), 7.20-7.45 (m, 10H), 7.85-7.95 (m, 1H), 8.30-8.40 (m, 1H), 8.42-8.48 (m, 1H); ms: (electron impact) m/z 460, 326, 287, 91, 43.

Anal. Calcd. For $C_{26}H_{28}N_4O_4$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.50; H, 6.31; N, 12.06.

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