A NEW ENTRY TO PYRANO[3,2-*f*]INDOLIZINES *VIA* THE REGIOSELECTIVE FORMATION OF AN INDOLIZIDIN-7-ONE ENAMINE[1]

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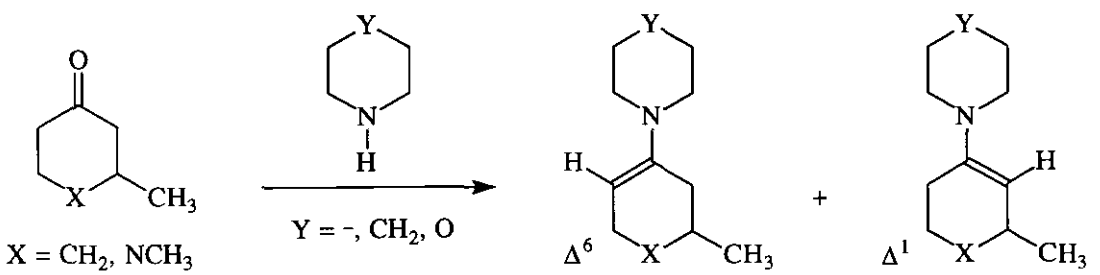
Abstract - From indolizidin-7-one (**1**), the preparation of several (pyrrolidine, piperidine and morpholine) enamines was described. The isolation of one of them (morpholine) as a pure regioisomer allowed the synthesis of pyrano[3,2-*f*]-indolizines for which only a few examples were known.

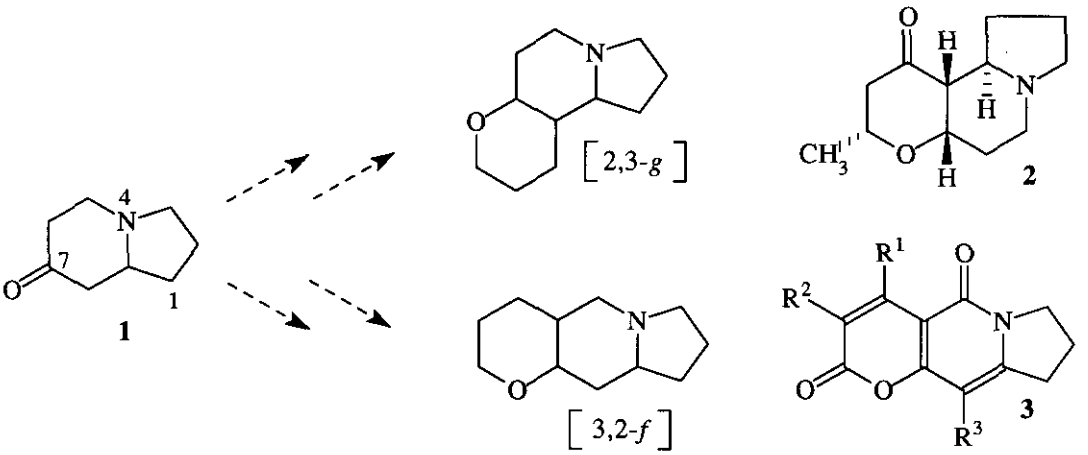
Enamines, which often lead to a regioselective substitution of ketones, are versatile compounds particularly useful in organic synthesis owing to their reactivity towards various electrophilic reagents.[2] Nevertheless this potentiality is sometimes limited by the low regioselectivity of enamines formation from nonsymmetric cyclic ketones, such as 3-methylcyclohexanone[3] or 1,2-dimethylpiperidin-4-one.[4]



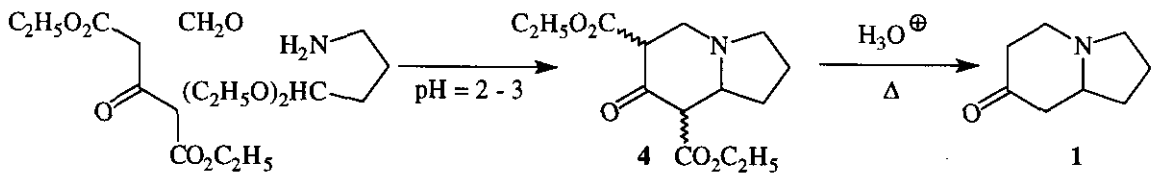
The preponderance of the Δ^6 isomer, as a result of an $A^{(1,2)}$ strain destabilizing the Δ^1 isomer, remains limited to 70 % in the most favorable case.[3] These two isomeric cyclic enamines, which are in equilibrium

in acidic medium but which are stable in neutral or basic medium,[2] have never been isolated and their study has always been performed on the mixture of the two isomers.

In the course of our studies in the field of the synthesis of condensed C_5O-C_5N heterocycles,[5] we took an interest towards the synthetic utility of enamines of indolizidin-7-one (**1**). According to the position (Δ^6 or Δ^7) of the enaminic double bond, these enamines could lead to two different modes of annulation, giving access either to the [2,3-*g*] mode in relation with the Elaeocarpus alkaloid skeleton (e.g. eleokanine E **2**)[6] or to the [3,2-*f*] mode found in some pyrano[3,2-*f*]indolizine derivatives (**3**).[7]



Among the methods reported in the literature[8] for the preparation of the required heterocyclic ketone (**1**), we chose the strategy first developed by Lions and then modified by Beckett, involving condensation of commercially available 4-aminobutanal diethyl acetal, formaldehyde and diethyl 3-oxopentanedioate in acidic medium followed by hydrolysis and the following decarboxylation of the resulting intermediate (**4**).



The preparation of **1** was so achieved in a 44% overall yield. The structure of indolizidin-7-one (**1**) was determined by ^1H and ^{13}C nmr spectroscopy. The pertinent ^1H (400 MHz) and ^{13}C (100 MHz) chemical shift values are reported in the experimental section. Furthermore the ir spectrum exhibited a strong absorption at 2790 cm^{-1} (Bolhmann bands) indicative of a trans ring junction.[9]

We have prepared the pyrrolidine, piperidine and morpholine enamines of indolizidin-7-one (**1**) according to the general method of Stork[10] The mixture of the ketone (**1**) (1 equivalent) and amine (5 equivalents) was heated under reflux in toluene with azeotropic elimination of water. By distillation, the expected enamines were isolated as viscous oils which progressively crystallized. The required reaction times and yields are indicated in the following table (Table 1).

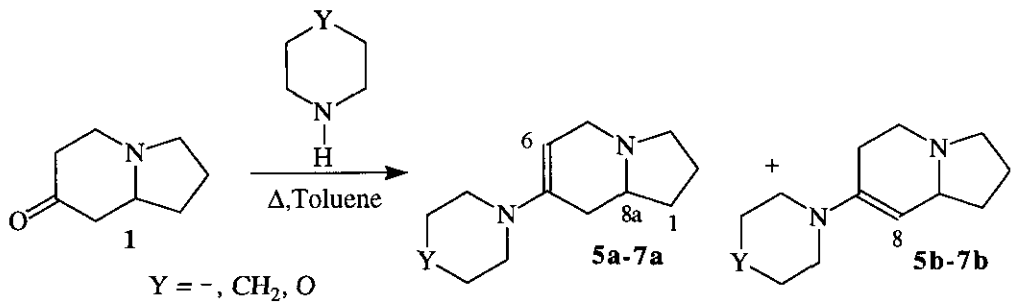


Table 1

Amine used	Enamine obtained	Reaction time (h)	Observed yield (%)	Ethylenic carbons (ppm) major	Ethylenic carbons (ppm) minor	Relative preponderance
Pyrrolidine	**5**	17	75.5	142.1 91.2	141.4 94.8	88 : 12
Piperidine	**6**	47	77	144.7 97.5	144.0 101.3	89 : 11
Morpholine	**7**	40	85	144.3 98.1	143.6 101.9	90 : 10

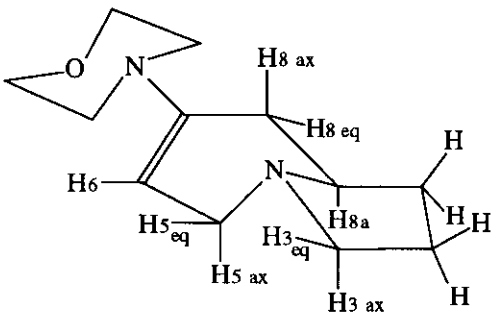
In each case the ^{13}C (75 MHz) nmr spectrum showed that the distilled product was a mixture of the two possible regioisomers (e.g. **5a** and **5b**), one of which being highly predominant. To determinate the ratio of the two regioisomers found in the mixture, a quantitative ^{13}C experiment was achieved using a long time interval between two successive pulses. For this purpose we took an interest to the characteristic 90-150 ppm range of the ethylenic carbons. A preliminary study showed that a 15 s relaxation time (T1) was a maximum for the most deshielded 143 ± 2 ppm ethylenic carbon of each of these unsaturated compounds; so we recorded the spectra of the enamines (**5-7**) using a 30 s (2 x T1) time interval between two

successive pulses during the accumulation. In these conditions, we were able to integrate the corresponding ethylenic peaks and determinate the relative preponderance of the major regioisomer. These results were also indicated in Table 1, they clearly demonstrated that the same preponderance (89 ± 1%) was observed whatever amine was used.

Fortunately we succeeded to isolate in a 70 % yield based on the starting indolizidinone, by a single recrystallization from petroleum ether, the predominant isomer in the case of the morpholine enamine (**7**). Heteronuclear (^{13}C-^{1}H) and homonuclear (^{1}H-^{1}H) shift correlations were used in a two dimensional nmr study (400 MHz , ^{1}H and 100 MHz , ^{13}C) to assign unambiguously the chemical shifts and coupling constants reported in Table 2.

Table 2

Position	Carbon atom δ, ppm	Proton (multiplicity) δ, ppm	Coupling constants (J, Hz)
1	30.7	1.46 (m) 2.00 (m)	
2	21.3	1.75 (m) 1.87 (m)	
3	53.7	ax : 2.14 (m) eq : 3.17 (ddd)	3eq-3ax : 8.7 3eq-2cis : 8.7 3eq-2trans : 2.3
5	51.3	ax : 2.78 (br d) eq : 3.53 (ddd)	5eq-5ax : 14.8 5eq-6 : 5.0 5eq-8ax : 2.0
6	97.7	4.64 (ddd)	6-5eq : 5.0 6-5ax : 2.0 6-8ax : 2.0
7	144.0		
8	33.8	ax : 2.12 (m) eq : 2.22 (m)	
8a	59.9	2.18 (m)	

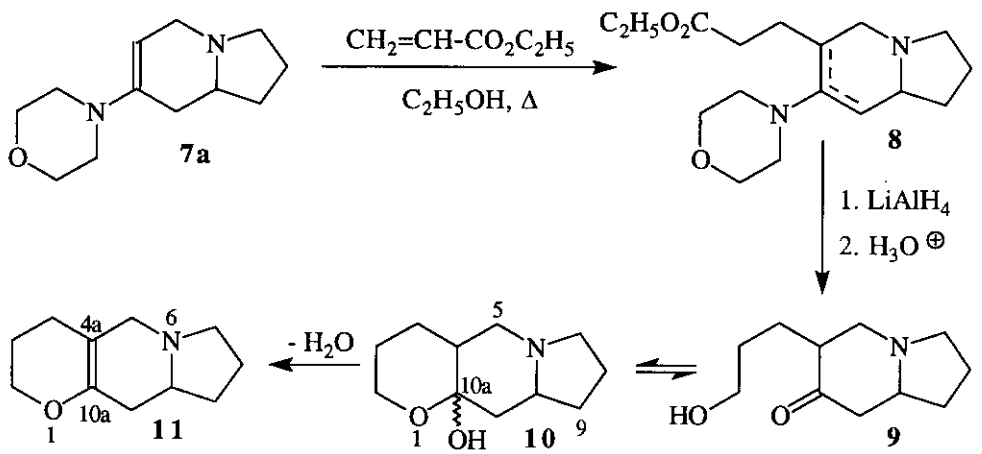


7a

The obtained results clearly demonstrated that the isolated regioisomer had its enaminic double bond at the Δ^6 position (**7a**) as shown by the absence of coupling between the ethylenic hydrogen atom and the tertiary hydrogen located at the ring junction. Furthermore the individualization of the signals of each hydrogen atom belonging to the methylene groups was indicative of a fixed conformation with a trans ring junction as corroborated by a Bohlmann band in the ir spectrum at 2805 cm^{-1}.

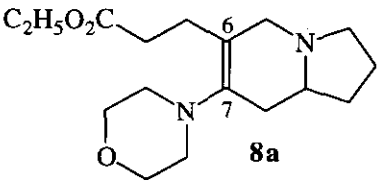
Elemental analysis as well as mass spectrometry study were in accordance with the above structure. The same structure (**5a**) or (**6a**) could also be assigned for the predominant enamine obtained when the amine used was pyrrolidine or piperidine.

In order to open a new route to linear pyrano[3,2-*f*]indolizines, we have extended to the enamine (**7a**) the strategy we have previously devised for the synthesis of 2*H*-pyrano[3,2-*c*]pyridine derivatives from the morpholine enamine of 1-benzylpiperidin-4-one.[11]

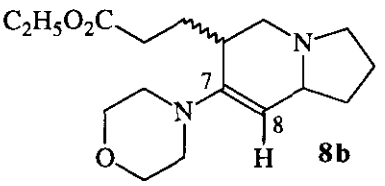


The alkylation of the enamine (**7a**) with ethyl acrylate in refluxing ethanol afforded the alkylated product (**8**) isolated by distillation in a nearly quantitative yield (taking in account the recovered enamine (**7a**)). This compound has been characterized by a ^1H nmr study : an ethylenic signal at 4.80 ppm for which integration

was 0.33H showed that **8** was a mixture of two isomeric structures (**8a**) and (**8b**) in a ratio of 2:1.



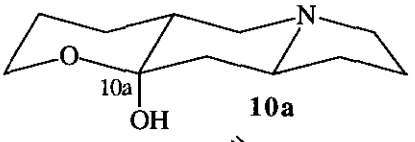
8a



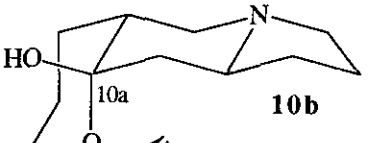
8b

This analysis was corroborated by the ^{13}C nmr study : two different C=O ester (173.5 and 173.7 ppm), three quaternary (126.0, 141.0, 147.8) and one tertiary ethylenic carbon atoms (104.8) were observed. These results showed the difficulty to introduce regioselectively a C-7/C-8 double bond in an indolizidine ring system.

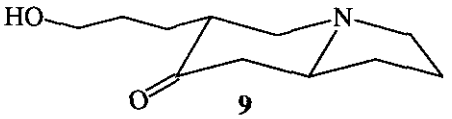
Lithium aluminium hydride reduction of the ester function of **8** followed by acid hydrolysis of the enamine group afforded the keto-alcohol (**9**) which cyclized to the bicyclic hemiketal (**10**) crystallizing in a 63.5% yield. The ir spectrum exhibited no carbonyl absorption in the solid state. On the other hand ir study in $CHCl_3$ solution showed the presence of a weak carbonyl absorption at 1710 cm^{-1} and the ^{13}C spectrum showed a weak C=O peak at 210.6 ppm. Furthermore the ^{13}C nmr spectral observation of two signals at 95.6 and 95.3 ppm easily assigned to two hemiketal carbon atoms (C-10a) involved the presence of two diastereoisomeric hemiketals. At least it may be postulated that in solution the compound (**10**) is a mixture of **10a** and **10b** in equilibrium with a small amount of the open keto-alcohol (**9**).



10a



10b



9

Finally, the azeotropic dehydration of the hemiketal (**10**) furnished in a 71.5% yield 3,4,5,7,8,9,9a,10-octahydro 2*H*-pyrano[3,2-*f*]indolizine (**11**) which represents the simplest compound ever reported in this series. This last step was performed by heating **10** in toluene with *p*-toluenesulfonic acid and separating the water formed. The structure of **11** was determinated by ^1H and ^{13}C nmr spectroscopy (the chemical shift values are reported in the experimental section) and corroborated by ir and mass spectra. The elemental analysis was in accordance with the above structure.

EXPERIMENTAL

General : Melting points were determined in capillary tubes on a Büchi *SMP 20* apparatus and are uncorrected. Proton nmr spectra at 300 or 400 MHz and carbon nmr spectra at 75 or 100 MHz were recorded on a Bruker AC 300 spectrometer or a Bruker AM 400WB spectrometer. The chemical shift data are reported in ppm and referenced to tetramethylsilane in anhydrous $CDCl_3$. The coupling constants, J, are given in Hz and the following abbreviations are used : s = singlet, d = doublet, dd = doublet of doublets, ddd = double doublet of doublets, dt = doublet of triplets, t = triplet, td = doublet of triplets, q = quadruplet, m = multiplet, br = broad, ax = axial, eq = equatorial. Ir spectra were determined on a Perkin-Elmer 1420 spectrophotometer; the absorption bands are expressed in cm^{-1}. Mass spectra were measured either on a Riber 10-10 apparatus operating with an activation energy of 70 eV or on a Kratos Concept II NH (FAB-MS Xe 8 kV) instrument. Elemental analyses were performed by Service Central de Microanalyse du CNRS.

6,8-Dicarbethoxyindolizidin-7-one (**4**) : A total of 33.0 g (0.205 mol) of commercial 4-aminobutanal diethyl acetal, 250 ml of alcohol and 0.05 g (0.15 mmol) of helianthin (methyl orange) were placed in a Erlenmeyer flask. To the stirred mixture, diluted hydrochloric acid (2.74 M) was slowly added until neutralization of the amine was complete; 75 ml of aqueous acid were necessary involving the presence of 0.205 mol of amine in the commercial reagent. At this time 15.6 ml (0.205 mol) of commercial formaldehyde solution, 41.6 g (0.205 mol) of freshly distilled diethyl 3-oxopentanedioate and 50 ml of alcohol were added. The resulting mixture was kept at room temperature for one week then concentrated in vacuo to *ca.* 250 ml. The mixture was cooled in an ice bath before the addition of 1N aqueous sodium hydroxide (205.5 ml) which caused the separation of an oily solid. The aqueous phase was separated and the residue was triturated in ether (50 ml). After 30 min the precipitate liberated was collected by filtration, twice washed by 20 ml of ether, dried in vacuo to give the title compound as a white powder (32.5 g, 55.5%); mp 94°C (lit., 92.5°C)[8]; ir (KBr) ν 2820, 1735, 1708, 1155, 1205; ir (CCl_4) ν 2805, 1745, 1665, 1620; ^{1}H nmr[12] δ 1.28 (m, 6H, CO_2-CH_2-C<u>H</u>$_3$), 1.58 and 1.70-2.15 (complex m, 4H, H-1 and H-2), 2.28 (q, J = 8.5), 2.55 (m) and 2,92 (dd, J = 14 and J = 2, 3H, H-3 ax, H-5 ax and H-8a), 3.18 (t, J = 9), 3.30 (d, J = 10) and 3.72 (dd, J = 14 and J = 1, 3H, H-3 eq, H-5 eq and H-8), 4.23 (m, 4H, CO_2-C<u>H</u>$_2$-CH_3), 12.12 (s, 1H, enol OH); ^{13}C nmr[12] δ 14.2 and 14.3 (2 CO_2CH_2<u>C</u>H_3), 21.8 and 29.6 (C-1 and

C-2), 48.7 (C-8), 53.5 and 53.6 (C-3 and C-5), 60.6, 61.1 and 62.7 (2 $CO_2\underline{C}H_2CH_3$ and C-8a), 98.5 (C-6), 166.6, 169.7 and 171.0 (2 $\underline{C}O_2CH_2CH_3$ and C-7 enol); ms (m/z, relative intensity) 238 (M^+ 9), 236 (29), 210 (46), 164 (39), 140 (20), 136 (20), 112 (21), 110 (26), 108 (25), 97 (57), 96 (43), 82 (28), 70 (100), 69 (28), 68 (23), 55 (48).

Indolizidin-7-one (**1**) : A solution of 50.0 g (0.177 mol) of 6,8-dicarbethoxyindolizidin-7-one (**4**) in 500 ml of 6M hydrochloric acid solution was refluxed in an oil bath with *ca.* 0.3 g (4.6 mmol) of zinc dust for 3.5 h. The stirred solution was cooled in a ice bath, neutralized by slow addition of aqueous 20% ammonia then exhaustively extracted with chloroform (6 x 50 ml). The organic layer was dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. Distillation of the residue afforded the title compound as a colorless liquid (19.7 g, 80%); bp 93°C / 15 torr (lit., 60-63°C / 1 torr)[8]; ir (neat) ν 2790, 1720; ir ($CHCl_3$) ν 2802, 1715 ; ^{1}H nmr δ 1.52 (m, 1H), 1.82 (m, 1H) and 1.95 (m, 2H) (H-1 and H-2), 2.24 (m, 4H) and 2.35 (m, 1H) (H-3 ax, H-5 ax, H-6 ax, H-8 ax and H-8a), 2.47 (dd, $\underline{J}$ = 11 and $\underline{J}$ = 2, 1H) and 2.58 (m, 1H, H-6 eq and H-8 eq), 3.14 (td, J = 8.7 and J = 2.3, 1H) and 3.30 (m, 1H, H-3 eq and H-5 eq); ^{13}C nmr δ 22.4 (C-2), 31.4 (C-1), 40.4 (C-6), 47.1 (C-8), 50.0 and 53.0 (C-3 and C-5), 63.9 (C-8a), 207.8 (C-7); ms (m/z, relative intensity) 139 (M^+ 100), 138 (38), 124 (10), 111 (10), 97 (47), 96 (81), 83 (15), 82 (17), 69 (42), 68 (15), 55 (20).

Pyrrolidine enamine of indolizidin-7-one (**5**) : A solution of indolizidin-7-one (9.8 g, 70.5 mmol) and pyrrolidine (29.5 ml, 25.0 g, 0.352 mol) in dry toluene (300 ml) was refluxed in a flask equipped with a water separator until no further separation of water was observed. After removal of the toluene and excess pyrrolidine under reduced pressure, the residue was distilled, giving the expected enamine (**5**) (10.2 g, 75.5%); bp 106-108°C / 0.3 torr; ir ($CHCl_3$) ν 1655; ^{1}H nmr[14] δ 1.45 (m, 1H) and 1.65-2.05 (m, 7H) (H-1, H-2 and N-CH_2-$C\underline{H}_2$-$C\underline{H}_2$-CH_2-N), 2.05-2.3 (m, 4H, H-3 ax, H-8 and H-8a), 2.81 (br d, $\underline{J}$ = 14.1, 1H, H-5 ax), 3.0 (m, 4H, N-$C\underline{H}_2$-CH_2-CH_2-$C\underline{H}_2$-N), 3.15 (td, $\underline{J}$ = 5.1 and $\underline{J}$ = 2.4, 1H, H-3 eq), 3.52 (br dd, $\underline{J}$ = 14.1 and $\underline{J}$ = 5.1, 1H, H-5 eq), 4.25 (br d, $\underline{J}$ = 5.1, 1H, H-6); ^{13}C nmr[14] δ 21.7 (C-2), 24.6 (N-CH_2-$\underline{C}H_2$-$\underline{C}H_2$-CH_2-N), 31.1 (C-1), 34.9 (C-8), 47.5 (N-$\underline{C}H_2$-CH_2-CH_2-$\underline{C}H_2$-N), 51.9 (C-5), 54.2 (C-3), 60.5 (C-8a), 91.2 (C-6), 142.1 (C-7); ms (m/z, relative intensity) 192 (M^+ 40), 191 (100), 122 (40), 120 (15), 96 (22), 71 (66), 70 (89), 68 (18).

Piperidine enamine of indolizidin-7-one (**6**) : The same procedure was applied to the preparation of **6**. Indolizidin-7-one (9.2 g, 66.2 mmol) and piperidine (32.7 ml, 28.2 g, 0.331 mol) in toluene (300 ml) furnished the title compound (**6**) (10.5 g, 77%); bp 112-114°C / 0.1 torr; ir ($CHCl_3$) ν 1650; ^{1}H nmr[14] δ 1.50, 1.57 and 1.65-2.05 (m, 10H, H-1, H-2 and N-CH_2-C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$-CH_2-N), 2.15 (m, 4H, H-3 ax, H-8 and H-8a), 2.70 and 2.80 (m, 5H, H-5 ax and N-C$\underline{H}_2$-CH_2-CH_2-CH_2-C$\underline{H}_2$-N), 3.17 (td, $\underline{J}$ = 8.6 and $\underline{J}$ = 2.2, 1H, H-3 eq), 3.52 (br dd, $\underline{J}$ = 14.7 and $\underline{J}$ = 4.0, 1H, H-5 eq), 4.62 (br d, $\underline{J}$ = 4.9, 1H, H-6); ^{13}C nmr[14] δ 21.5 (C-2), 24.3 (N-CH_2-CH_2-$\underline{C}H_2$-CH_2-CH_2-N), 25.5 (N-CH_2-$\underline{C}H_2$-CH_2-$\underline{C}H_2$-CH_2-N), 30.9 (C-1), 34.8 (C-8), 48.6 (N-$\underline{C}H_2$-CH_2-CH_2-CH_2-$\underline{C}H_2$-N), 51.7 (C-5), 54.0 (C-3), 60.3 (C-8a), 97.5 (C-6), 144.7 (C-7); ms (m/z, relative intensity) 206 ($M^{+\cdot}$ 41), 205 (100), 122 (48), 97 (24), 96 (46), 85 (32), 84 (72), 83 (21), 82 (20), 69 (25), 56 (21), 55 (27).

Morpholine enamine of indolizidin-7-one (**7**) : The same procedure was applied to the preparation of **7**. Indolizidin-7-one (9.6 g, 69 mmol) and morpholine (30.1 ml, 29.9 g, 0.343 mol) in toluene (300 ml) furnished the title compound (**7**) (12.2 g, 85%); bp 108-110°C / 0.05 torr; ir ($CHCl_3$) ν 1650. Recrystallization from petroleum ether afforded the regioisomer (**7a**) (7-morpholino-1,2,3,5,8,8a-hexahydroindolizine) as colorless crystals (10.0 g, 70%); mp 74°C; ir (KBr) 2805, 1650; ms (m/z, relative intensity) 208 ($M^{+\cdot}$ 41), 207 (100), 122 (55), 108 (18), 96 (30), 57 (22), 78 (15); Anal. Calcd for $C_{12}H_{20}N_2O$: C, 69.20; H, 9.67; N, 13.45. Found : C, 69.42; H, 9.57, N, 13.67.

6-Carbethoxyethyl-7-morpholino-1,2,3,5,8,8a-hexahydroindolizine (**8a**) and 6-Carbethoxyethyl-7-morpholino-1,2,3,5,6,8a-hexahydroindolizine (**8b**): A mixture of the precedent morpholine enamine (regioisomer (**7a**), 24.3 g, 0.117 mol) and ethyl acrylate (14 g, 0.14 mol) in absolute ethanol (200 ml), protected from moisture by a drying tube, was heated under reflux for 20 h. After removal of solvent, the residue was distilled to give after a forerun of enamine (**7a**) (16.8 g) the title compounds (**8**) as a viscous oil (11.0 g, 0.036 mol, quantitative yield taking in account the recovered enamine (**7a**));bp 148-156°C / 0.2 torr; ir (neat) ν 1735, 1635, 1650; ^{1}H nmr[15] δ 1.26 (t, $\underline{J}$ = 6.7, 3H, CO_2-CH_2-C$\underline{H}_3$), 1.54-3.56 (complex m, 18.66H, others protons), 3.72 (br t, $\underline{J}$ = 4.35, 4H, C$\underline{H}_2$-O-C$\underline{H}_2$), 4.14 (q, 2H, $\underline{J}$ = 6.7, CO_2-C$\underline{H}_2$-CH_3), 4.80 (t, J = 2.7 Hz, 0.33H, ethylenic proton); ^{13}C nmr[15] δ 14.3 (CO_2-CH_2-$\underline{C}H_3$), 21.8 (C-2), 25.2, 28.7, 31.1 and 33.4 ($\underline{C}H_2$-$\underline{C}H_2$-CO_2, C-1, C-6 (**8b**) and C-8 (**8a**)), 49.2 (N-$\underline{C}H_2$-CH_2-O, **8b**), 50.7 (N-$\underline{C}H_2$-CH_2-O, **8a**), 54.3, 54.9, 60.2 and 60.9 (C-3, C-5, C-8a and CO_2-$\underline{C}H_2$-CH_3), 67.0 (N-CH_2-

-$\underline{C}H_2$-O, **8b**), 67.4 (N-CH_2-$\underline{C}H_2$-O, **8a**), 104.8 (C-8 **8b**), 126.0 (C-6 **8a**), 141.0 (C-7 **8a**), 147.8 (C-7 **8b**), 173.5 ($\underline{C}O_2$-C_2H_5 **8a**), 173.7 ($\underline{C}O_2$-C_2H_5 **8b**); ms (m/z, relative intensity) 308 (M^+ 10), 307 (20), 222 (18), 208 (27), 207 (100), 152 (39), 122 (59), 120 (26), 108 (22), 96 (19), 82 (18), 55 (22); Anal. Calcd for $C_{17}H_{28}N_2O_3$: C, 66.21; H, 9.15; N, 9.09. Found : C, 66.41; H, 9.24, N, 9.33.

3,4,4a,5,7,8,9,9a,10,10a-Decahydro-2*H*-pyrano[3,2-*f*]indolizin-10a-ol (**10**) : A solution of the enamine ester (**8**) (11.90 g, 38.6 mmol) in dry ether (40 ml) was added dropwise at 0°C to a well stirred suspension of lithium aluminium hydride (1.47 g, 38.6 mmol) in dry ether (40 ml). The stirring was carried out and the mixture heated to boiling for 2.5 h. To the cooled solution was slowly added ethanol (5 ml) in ether (20 ml) and then dilute sulfuric acid (20%, 60 ml). The aqueous layer was heated to 60°C for 4 h then set aside overnight at room temperature. The cooled solution was basified with aqueous sodium hydroxide (10%, 70 ml) and thoroughly extracted with chloroform (4 x 30 ml). The dried solution was condensed to leave a crude solid (7.7 g) of which recrystallization from benzene gave the title compound (**10**) (4.82 g, 63.5%); mp 136°C; ir (KBr) ν 3060 (br); ir ($CHCl_3$) ν 3580, 2810, 1710 (weak); ^{1}H nmr δ 1.40, 1.5-1.95 and 2.0-2.2 (m, 2, 9 and 2H), 2.30 (m, 1H), 2.56 (s, 1H, OH exchangeable with D_2O), 2.75 (dd, J = 10.5 and J = 3.7, 1H, H-7 eq), 3.02 (td, J = 8.7 and J = 2.2, 1H, H-5 eq), 3.65 and 4.04 (m, 2H, H-2); ^{13}C nmr[16] δ 21.6, 22.0, 26.1 and 29.9 (C-3, C-4, C-8 and C-9), 43.0 and 43.8 (C-4a and C-10), 52.8 and 54.0 (C-5 and C-7), 60.9 and 61.0 (C-2 and C-9a), 95.6 (C-10a); ms (m/z, relative intensity) 197 (M^+ 49), 196 (47), 140 (21), 138 (32), 136 (37), 110 (39), 98 (20), 97 (20), 96 (46), 84 (22), 83 (75), 82 (20), 70 (100), 69 (26), 55 (39); Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found : C, 67.19; H, 9.74, N, 7.24.

3,4,5,7,8,9,9a,10-Octahydro-2*H*-pyrano[3,2-*f*]indolizine (**11**) : Compound (**10**) (4.85 g, 24.6 mmol) was dissolved in dry toluene (150 ml), *p*-toluenesulfonic acid monohydrate (*ca.* 0.2 g, 1 mmol) was added and the solution was refluxed for 15 h; the water produced was collected in a water separator. The cooled solution was treated with solid potassium carbonate, filtered, evaporated in vacuo then distilled to give the title compound (**11**) (3.15 g, 71.5%) as a colorless oil; bp 70°C / 0.4 torr, ir (neat) ν 2780, 1690, 1145; ^{1}H nmr δ 1.46, 1.65-2.10 and 2.10-2.35 (m, 1, 8 and 3H, others protons), 2.67 (br d, J = 13.9, 1H, H-5 ax), 3.16 (td, J = 8.6 and J = 2.1, 1H, H-7 eq), 3.27 (d, J = 13.9, 1H, H-5 eq), 3.83 and 4.04 (m, 2H, H-2); ^{13}C nmr δ 21.9, 22.8 and 23.0 (C-3, C-4 and C-8), 30.9 and 34.5 (C-9 and C-10), 53.9 and

54.8 (C-5 and C-7), 60.7 (C-9a), 65.7 (C-2), 102.9 (C-4a), 145.9 (C-10a); ms (m/z, relative intensity) 179 ($M^{+\cdot}$ 63), 178 (50), 150 (43), 110 (100), 95 (26), 70 (20), 67 (21), 55 (23); Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found : C, 73.81; H, 9.67, N, 7.53.

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12. Nmr assignments are related to the predominant enolic form (**12**).[13]

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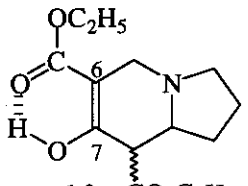
14. Nmr assignments are related to the predominant regioisomer (**5a**) or (**6a**).

15. Nmr assignments are related to the mixture (**8a**) + (**8b**).

16. Nmr assignments are related to the predominant anomer which is observed alone in the initial freshly prepared sample solution.



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