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Abstract: N-acyliminium cyclizations onto thiophene to give thieno[2’,3’;3,4]pyrrolo[2,1-a]isoindolone (2b) and benzo[a]thieno[2,3(2 or 3,4)-g]indolizinones (12a-c) were studied.

Current interest in new methods for the generation of N-acyliminium ions and their use in synthesis1 together with our interest in this area2,3 led us to investigate reactions of substituted hydroxylactams derived from N-thienylmethyl(ethyl)phthalimides.

Heterocyclization involving N-acyliminium ions (intramolecular α-amidoalkylation reaction), although known for some time1,4, have been examined in the major cases with hydroxylactams having a secondary hydroxy group. Nevertheless, it has been reported for some cyclizations with an angular alkyl group (methyl5, t-butyl6, n-butyl6).

For our part, we wished to study hydroxylactams substituted with other groups (alkyl or aryl) under acidic treatment. Thus, we report herein our results concerning two types (A and B) of precursors of polycyclic compounds analogous to the alkaloid nuevamine (C) via an intramolecular α-amidoalkylation reaction.
Precursors A and B should give a five membered ring and a six membered ring respectively. As previously mentioned, the size of this final ring seems to control the outcome of the reaction.

Actually, when hydroxylactams 1 were treated with trifluoroacetic acid only the cyclized product 2b (from 1b R=H) was obtained while in all other cases degradation occurred. For the cases R=Et, the competitive dehydration reaction leading to a non stable (polymerization in acidic medium) enamide was preferred.
To test the formation of the N-acyliminium ion intermediate we added to the trifluoroacetic mixture 1.5 equivalents of triethylsilane. In these conditions no degradation (or enamide) was observable and the expected reduced products 3a-c were isolated. Nevertheless, cyclization of the N-acyliminium ion from 1b (R=H) occurred more rapidly than reduction since the cyclic compound 2b (R=H) was obtained without compound 3b (R=H) when reaction was carried out in the presence of triethylsilane (Scheme 2). The required compounds 1a,b (R≠H) resulted from the action of the appropriate Grignard reagent onto N-thien-2(3)-ylmethylphthalimides 4a,b and we previously reported7 compounds 4a-c and 1a-c (R=H). As described in the literature8, since a strongly acidic medium seems to increase the degradation we decided to test this reaction in the presence of a Lewis acid9 with the corresponding chlorolactams 5a,b or ethoxylactam 6b. First, the action of thionyl chloride onto hydroxylactams 1a,b (R=H) led to chlorolactams 5a,b quantitatively. These chlorolactams, in the presence of tin tetrachloride, showed the same behavior (5a led to degradation and 5b led to 2b but without increasing the yield). Titanium tetrachloride in dichloromethane was recently used to generate a N-acyliminium ion10 and this methodology applied to ethoxylactam 6b gave the desired cyclic product 2b but did not increase the yield compared to that observed when trifluoroacetic acid was used with 1b (R=H).

The 1H NMR spectrum of 2b reveals an AB system for the two protons H4 (δ=3.88 ppm and δ=5.50 ppm) with a coupling constant J = 14.5 Hz. This latter proton is shifted downfield due to the proximity of the lone pair of the nitrogen atom. The H10b proton is a singlet with a chemical shift of δ=5.65 ppm, and the thiophenic protons H2 and H3 are doublets with the characteristic α,β coupling constant J = 5.1 Hz. Furthermore the 13C NMR supports this proposed structure since the C10b carbon is present with a chemical shift of δ = 55.1 ppm.

From this result and the reported work cited above4 we wished to study whether the size of the ring formed during the reaction influenced this cyclization. Actually in our conditions, it seems that a five membered ring does not occur when the junction carbon C10b is substituted with alkyl or aryl groups. Furthermore, the difference of the reactivity between the α and β position of the thiophene should not control the cyclization since six membered cyclized products from reaction of an acyliminium ion and the β position of the thiophene have been reported5,11.

So, we decided to investigate the reactivity of hydroxylactams 11a-c which were prepared from phthalimides derivatives 10a-c either by reduction of the imide function (R=H) or addition of a Grignard reagent onto the imide (R=Et, Ph) (Scheme 4). Compounds 10a-c resulted from the action of aminoethylthiophenes 9a-c onto phthalic anhydride with triethylamine in refluxing toluene. The starting 2-aminoethylthiophene 9a is commercially available, the 3-aminoethylthiophene (9b) was
prepared according to the literature\textsuperscript{12} and the 3-aminoethyl-2-chlorothiophene (9c) was synthesized from the known 2-chloro-3-formylthiophene\textsuperscript{13} (7) as shown in Scheme 3.

\[
\begin{array}{c}
\text{CHO} \\
\text{Cl} \\
\text{CHO} \\
\text{Cl} \\
\end{array}
\xrightarrow{\text{CH}_3\text{NO}_2 \text{ NaOH}}
\begin{array}{c}
\text{CH}=\text{CH-NO}_2 \\
\text{Cl} \\
\end{array}
\xrightarrow{\text{LiAlH}_4}
\begin{array}{c}
\text{CH}_2\text{CH}_2\text{NH}_2 \\
\text{Cl} \\
\end{array}
\]

\textbf{Scheme 3}

In contrast to the result observed above, the action of trifluoroacetic acid onto hydroxylactams 11a-c led to the expected indolizidinones 12a-c (Scheme 4) in good yield (68 to 92 \%). No trace of an enamide via loss of a proton and no degradation were observed. When the reaction is conducted in the presence of triethylsilane, the cyclization occurred leading to indolizidinones 12a-c and no reduced product 13 similar to 3 previously described was observed.

The three types of cyclizations with the thiophene ring (2,3 - 3,2 - 3,4) occur so the nucleophile does not control the outcome of the reaction. To confirm this result, we investigated the reactivity of hydroxylactams in the presence of thionyl chloride. Actually, if α-chloroalkyl amides are susceptible to hydrolysis and, if possible, easily eliminate hydrochloric acid to give the corresponding enamide\textsuperscript{4} they often do not require an acidic catalyst in order to serve as an $N$-acyliminium ion source. With weakly reactive nucleophiles the use of Lewis acids as catalyst is required. Hydroxylactams 11a-c treated with thionyl chloride at room temperature during two hours provided directly indolizidinones 12a-c in better yields (75 to 100 \%). The ring closure of compounds 11a-c (R=H, Et, Ph) easily occurs because a six membered ring is formed whatever the nature of the R group (H, Et, Ph).
Finally, we tested the lability of H_{11b} proton of indolizidine 12a (R=H) (Scheme 5). Actually, there are a few reports\textsuperscript{14,15} of oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) for generation of N-acyliminium ions and, this reaction offered the opportunity to substitute C_{11b} with groups other than alkyl or aryl group. Thus, treatment of 12a (R=H) with DDQ in methanol gave the expected methoxy derivative 15 in good yield probably via the N-acyliminium ion 14. In contrast to previous work\textsuperscript{15}, we did not observe oxidation of the six membered ring of the indolizidine system.
In conclusion, hydroxylactams with secondary hydroxy group gave an intramolecular $\alpha$-amidoalkylation reaction leading to five or six membered rings while hydroxylactams with a tertiary hydroxy group only gave six membered rings. Furthermore, the $N$-acyliminium ion intermediate could be trapped by reaction with triethylsilane when the cyclization process did not occur.

**Experimental**

Melting points are uncorrected. The infrared spectra of solids (potassium bromide) were recorded on a Perkin Elmer FTIR paragon 1000 spectrometer. The $^1$H and $^{13}$C NMR spectra were recorded on a Brüker AC-200 (200 MHz) instrument in deuteriochloroform solution and chemical shift ($\delta$) are expressed in ppm relative to internal TMS. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using an ultraviolet lamp or iodine vapor. E. Merck silica gel 60 F (70-300 mesh) was used for column chromatography. The elemental analyses were carried out by the microanalysis laboratory of INSA at Rouen, F 76130 M'. S'. Aignan, France. Compounds 1a,b (R=H) were prepared as previously described$^7$.

**3-Ethyl-2,3-dihydro-3-hydroxy-2-(2’ or 3’-thenyl)-1H-isoindol-1-ones (1a,b R=Et).**

General procedure: To a solution of imide 4a,b (0.243 g, 1 mmol) in dichloromethane (20 ml) was added a solution of ethylmagnesium bromide (0.5 M in ether, 6 ml, 3 mmoles). The resulting mixture was stirred for 2 hours at room temperature, then poured into 20 ml of 1 M ammonium chloride solution and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. Alkylhydroxylactams 1a (R=Et) (97% yield) and 1b (R=Et) (96% yield) were pure and sensitive to dehydration (recrystallization and mp testing) and were used in the next step without further purification.

**2,3-Dihydro-3-hydroxy-3-phenyl-2-(2’ or 3’-thenyl)-1H-isoindol-1-ones (1a,b R=Ph).**
To a solution of imide 4a,b (0.243 g, 1 mmol) in dichloromethane (20 ml) was added a solution of phenylmagnesium bromide (0.5 M in ether, 12 ml, 6 mmoles). The resulting mixture was stirred for twelve hours at room temperature, then poured into 50 ml of 1 M ammonium chloride solution and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was triturated with the minimum quantity of ether at 0°C. Recrystallization from ethanol afforded 1a (R=Ph) (73% yield; mp 166°C) and 1b (R=Ph) (78% yield; mp 174°C).


A solution of 1b (R=H) (1 mmol) in trifluoroacetic acid (3 ml) was stirred overnight. The acid was evaporated and the residue was dissolved in dichloromethane. The organic layer was washed with a solution of sodium hydrogen carbonate and dried over magnesium sulfate. Evaporation of the solvent and recrystallization from chloroform afforded pure compound 2b. Yield: 58%; mp >270°C; IR: 1682 (C=O) cm⁻¹; ¹H NMR: δ 3.88 (d, J=14.5 Hz, 1H, H₄), 5.50 (d, J=14.5 Hz, 1H, H₄), 5.65 (s, 1H, H₁₀b), 6.97 (d, J=5.1 Hz, 1H, H₃), 7.23-7.30 (m, 1H, H₁₀), 7.30 (d, J=5.1 Hz, 1H, H₂), 7.48-7.60 (m, 2H, H₈,9), 7.89-8.00 (m, 1H, H₇); ¹³C NMR: δ 35.6 (CH₂), 55.1 (CH), 123.5 (CH), 123.9 (CH), 128.1 (CH), 128.3 (CH), 129.1 (CH), 131.7 (C), 132.2 (CH), 137.2 (C), 138.7 (C), 145.3 (C), 166.8 (CO); Anal. Calcd. for C₁₃H₉NOS: C, 68.70; H, 3.99; N, 6.16. Found: C, 68.50; H, 3.71; N, 6.03.

1-Nitro-2-(2'-chlorothien-3'-yl)ethylene (8).

To a solution of 2-chloro-3-thiophenecarboxaldehyde (0.2 mol) and nitromethane (0.6 mol) in methanol (400 ml), cooled to -10°C, sodium hydroxide (200 ml, 10 M, 2 mol) was added dropwise. The resulting mixture was stirred at 0°C during 4 hours and then quenched with hydrochloric acid at 0°C (2 l, 6 N solution). Dichloromethane (400 ml) was added, the organic layer was dried over magnesium sulfate and concentrated under reduced pressure. Recrystallization from methanol afforded the nitrovinyl product 8 in 80% yield. mp 117-119°C; ¹H NMR: δ 7.09 (d, J=5.9 Hz, 1H, H₄), 7.20 (d, J=5.9 Hz, 1H, H₃), 7.49 (d, J=13.4 Hz, 1H, Hviny1), 8.03 (d, J=13.4 Hz, 1H, Hviny1); Anal. Calcd. for C₆H₄ClNOS: C, 38.01; H, 2.13; N, 7.39. Found: C, 37.88; H, 2.21; N, 7.45.

2-(2'-Chlorothien-3'-yl)ethylamine (9).

The nitrovinyl thiophene (0.06 mol) was carefully added to a slurry of lithium aluminium hydride (10 g, 0.26 mol) in anhydrous ether at 0°C. The resulting mixture was heated to reflux for six hours then cooled and water added cautiously until the lithium complex was destroyed. The salts were removed by filtration, the organic layer was dried over magnesium sulfate, and concentrated to give the amine 9 in 90% yield as a liquid. IR: 3300 (NH₂) cm⁻¹; ¹H NMR: δ 2.25 (s, 2H, NH₂), 2.27 (t, J=8.0 Hz, 2H, CH₂), 2.91 (t, J=8.0 Hz, 2H, CH₂), 6.78 (d, J=6.0 Hz, 1H, H₄), 7.02 (d, J=6.0 Hz, 1H, H₃).
**N-(2-Thienylethyl)phthalimides (10a-c).**

General procedure: A solution of phthalic anhydride (8.9 g, 60 mmol), triethylamine (2 ml) and 2-arylethylamine 10a-c (70 mmol) in toluene (60 ml) was refluxed for 12 hours. The mixture was cooled to room temperature, diluted with dichloromethane and washed with 10% hydrochloric acid. The organic layer was washed with water, dried over magnesium sulfate and evaporated under reduced pressure. Recrystallization from ethanol of the residue afforded the corresponding phthalimides.

**N-(2-(Thien-2'-yl)ethyl)phthalimide (10a).** Yield: 75%; mp 128-130°C; IR: 1708 (C=O) cm⁻¹; ¹H NMR: δ 3.20 (t, J=8.0 Hz, 2H, CH₂), 3.94 (t, J=8.0 Hz, 2H, CH₂), 7.84-7.90 (m, 2H, H₃,₄'), 7.10-7.12 (m, 1H, H₅), 7.66-7.70 (m, 2H, Hₐrom), 7.72-7.77 (m, 2H, Hₐrom); Anal. Calcd. for C₁₄H₁₁NO₂S: C, 65.35; H, 4.31; N, 5.44. Found: C, 65.54; H, 4.62; N, 5.81.

**N-(2-(Thien-3'-yl)ethyl)phthalimide (10b).** Yield: 80%; mp 115-117°C; IR: 1706 (C=O) cm⁻¹; ¹H NMR: δ 2.96 (t, J=8.0 Hz, 2H, CH₂), 3.86 (t, J=8.0 Hz, 2H, CH₂), 6.92-6.97 (m, 2H, H₃,₅'), 7.16-7.20 (m, 1H, H₂'), 7.61-7.67 (m, 2H, Hₐrom), 7.74-7.82 (m, 2H, Hₐrom); Anal. Calcd. for C₁₄H₁₁NO₂S: C, 65.35; H, 4.31; N, 5.44. Found: C, 65.12; H, 4.58; N, 5.62.

**N-(2-(2'-Chlorothien-3'-yl)ethyl)phthalimide (10c).** Yield: 70%; mp 75-77°C; IR: 1708 (C=O) cm⁻¹; ¹H NMR: δ 2.96 (t, J=8 Hz, 2H, CH₂), 3.88 (t, J=8 Hz, 2H, CH₂), 6.83 (d, J=5.4 Hz, 1H, H₄'), 7.01 (d, J=5.4 Hz, 1H, H₅'), 7.65-7.70 (m, 2H, Hₐrom), 7.72-7.76 (m, 2H, Hₐrom); Anal. Calcd. for C₁₄H₁₀ClNO₂S: C, 57.64; H, 3.45; N, 4.80. Found: C, 57.52; H, 3.42; N, 4.74.

**2,3-Dihydro-3-hydroxy-2-(thienylethyl)-1H-isouindol-1-ones (11a-c R=H).**

General procedure: To a mixture of phthalimidoethylthiophene 10a-c (4 mmol) in dry methanol (40 ml) at 0°C was added sodium borohydride (0.9 g, 24 mmol) in one portion. To this mixture were added 5 drops of ethanolic hydrochloric acid solution (prepared from 9 drops of concentrated hydrochloric acid in 15 ml of ethanol) at regular intervals (10 minutes). The reaction was controlled by TLC (dichloromethane-acetone 9/1). When starting product had disappeared (30 minutes), the excess of sodium borohydride was decomposed by careful addition of cold water (15 ml) and diluted hydrochloric acid. Sodium hydrogen carbonate was added and the solvent was evaporated. The residue was triturated with water and the hydroxylactam 11a-c was separated by filtration, washed with water, dried and recrystallized from ethanol.

**2,3-Dihydro-3-hydroxy-2-(thien-2'-ylethyl)-1H-isouindol-1-one (11a R=H).** Yield: 96%; mp 112-114°C; IR: 3220 (OH), 1658 (C=O) cm⁻¹; ¹H NMR: δ 3.09 (t, J=8.0 Hz, 2H, CH₂), 3.43-3.67 (m, 2H, CH₂), 5.50 (s, 1H, H₃), 6.74 (dd, J=1.2 and 3.6 Hz, 1H, H₅), 6.84 (dd, J=3.6 and 5.1 Hz, 1H, H₄'), 7.08 (dd, J=1.2 and 5.1 Hz, 1H, H₅'), 7.39-7.42 (m, 1H, Hₐrom), 7.51-7.55 (m, 3H, Hₐrom); Anal. Calcd. for C₁₄H₁₃NO₂S: C, 64.84; H, 5.05; N, 5.40. Found: C, 65.10; H, 5.20; N, 5.56.
2,3-Dihydro-3-hydroxy-2-(thien-3'-ylethyl)-1H-isindol-1-one (11b R=H). Yield: 98%; mp 140-142°C; IR: 3255 (OH), 1661 (C=O) cm⁻¹; ¹H NMR: δ 2.91 (t, J=8.0 Hz, 2H, CH₂), 3.40-3.71 (m, 2H, CH₂), 5.47 (s, 1H, H₃), 6.91-6.93 (m, 2H, H₄'), 7.19-7.22 (m, 1H, H₂), 7.30-7.42 (m, 1H, H₅'), 7.44-7.58 (m, 3H, H₆'), Anal. Calcd. for C₁₄H₁₃NO₂S: C, 64.84; H, 5.05; N, 5.40. Found: C, 65.05; H, 5.22; N, 5.56.

2,3-Dihydro-3-hydroxy-2-(2'-chlorothien-3'-ylethyl)-1H-isindol-1-one (11c R=H). Yield: 94%; mp 98-100°C; IR: 3250 (OH), 1660 (C=O) cm⁻¹; ¹H NMR: δ 2.85 (t, J=8.0 Hz, 2H, CH₂), 3.42-3.69 (m, 2H, CH₂), 5.54 (d, J=10.0 Hz, 1H, H₃), 6.78 (d, J=6.0 Hz, 1H, H₄'), 6.99 (d, J=6.0 Hz, 1H, H₅'), 7.36-7.44 (m, 1H, H₆'), 7.48-7.55 (m, 3H, H₇').

3-Ethyl-2,3-dihydro-3-hydroxy-2-(thienylethyl)-1H-isindol-1-ones (11a-c R=Et). In a similar manner as described for the synthesis of 1a,b (R=Et), the imides 10a-c afforded compounds 11a-c (R=Et). These products were used without further purification to avoid dehydration. On heating they are decomposed and no melting point was measured.

3-Ethyl-2,3-dihydro-3-hydroxy-2-(thien-2'-ylethyl)-1H-isindol-1-one (11a R=Et). Yield: 97%; IR: 3286 (OH), 1673 (C=O) cm⁻¹; ¹H NMR: δ 0.46 (t, J=7.4 Hz, 3H, CH₃), 2.06-2.15 (m, 2H, CH₂), 3.18-3.36 (m, 3H, CH₂-CH₂), 3.85-3.89 (m, 1H, CH₂-CH₂), 6.84-6.91 (m, 2H, H₃', H₄'), 7.11 (dd, J=1.2 and 5.1 Hz, 1H, H₅'), 7.43-7.46 (m, 3H, H₆'), 7.52 (d, J=5.4 Hz, 1H, H₇').

3-Ethyl-2,3-dihydro-3-hydroxy-2-(thien-3'-ylethyl)-1H-isindol-1-one (11b R=Et). Yield: 96%; IR: 3261 (OH), 1684 (C=O) cm⁻¹; ¹H NMR: δ 0.46 (t, J=7.4 Hz, 3H, CH₃), 1.99-2.20 (m, 2H, CH₂), 2.90-3.50 (m, 3H, CH₂-CH₂), 3.78-3.90 (m, 1H, CH₂-CH₂), 6.92-7.06 (m, 2H, H₃', H₄'), 7.20-7.25 (m, 1H, H₂'), 7.35-7.55 (m, 3H, H₆'), 7.77 (d, J=5.2 Hz, 1H, H₇').

3-Ethyl-2,3-dihydro-3-hydroxy-2-(2'-chlorothien-3'-ylethyl)-1H-isindol-1-one (11c R=Et). Yield: 90%; IR: 3229 (OH), 1682 (C=O) cm⁻¹; ¹H NMR: δ 0.47 (t, J=7.2 Hz, 3H, CH₃), 2.10-2.16 (m, 2H, CH₂), 2.95-3.27 (m, 3H, CH₂-CH₂), 3.70-3.95 (m, 1H, CH₂-CH₂), 6.85 (d, J=5.6 Hz, 1H, H₄'), 7.02 (d, J=5.6 Hz, 1H, H₅'), 7.43-7.54 (m, 3H, H₆'), 7.70 (d, J=6.8 Hz, 1H, H₇').

2,3-Dihydro-3-hydroxy-3-phenyl-2-(thienylethyl)-1H-isindol-1-ones (11a-c R=Ph). In a similar manner as described for the synthesis of 1a,b (R=Ph), the imides 10a-c afforded 11a-c (R=Ph).

2,3-Dihydro-3-hydroxy-3-phenyl-2-(thien-2'-ylethyl)-1H-isindol-1-one (11a R=Ph). Yield: 90%; mp 180-182°C; IR: 3258 (OH), 1681 (C=O) cm⁻¹; ¹H NMR: δ 2.72-2.90 (m, 1H, CH₂-CH₂), 3.09-3.24 (m, 2H, CH₂-CH₂), 3.58-3.81 (m, 1H, CH₂-CH₂), 6.71 (dd, J=1.2 and 3.6 Hz, 1H, H₃'), 6.85 (dd, J=3.6 and 5.0 Hz, 1H, H₄'), 7.06 (dd, J=1.2 and 5.0 Hz, 1H, H₅'), 7.25-7.45 (m, 8H, H₆'), 7.67 (d, J=7.0 Hz, 1H, H₇').
2,3-Dihydro-3-hydroxy-3-phenyl-2-(thien-3’-ylethyl)-1H-isoindol-1-one (11b R=Ph). Yield: 92%; mp 141-143°C; IR: 3254 (OH), 1674 (C=O) cm⁻¹; ¹H NMR: δ 2.52-2.65 (m, 1H, CH₂-CH₂), 2.85-3.20 (m, 2H, CH₂-CH₂), 3.56-3.70 (m, 1H, CH₂-CH₂), 6.78-6.85 (m, 2H, H₄-₅), 7.14-7.18 (m, 1H, H₂’), 7.21-7.50 (m, 8H, H arom), 7.68 (d, J=7.0 Hz, 1H, H arom); Anal. Calcd. for C₂₀H₁₇NO₂S: C, 71.62; H, 5.11; N, 4.18. Found: C, 71.48; H, 5.02; N, 4.11.

2,3-Dihydro-3-hydroxy-3-phenyl-2-(2’-chlorothien-3’-ylethyl)-1H-isoindol-1-one (11c R=Ph). Yield: 84%; mp 179-181°C; IR: 3312 (OH), 1684 (C=O) cm⁻¹; ¹H NMR: δ 2.54-2.68 (m, 1H, CH₂-CH₂), 2.86-3.19 (m, 2H, CH₂-CH₂), 3.55-3.69 (m, 1H, CH₂-CH₂), 6.72 (d, J=6.0 Hz, 1H, H₄), 6.96 (d, J=6 Hz, 1H, H₅), 7.28-7.47 (m, 8H, H arom), 7.74 (d, J=5.4 Hz, 1H, H arom).

Benzo[a]thieno[2,3-g]indolizinones (12a-c), general procedures:

Method a: Using conditions described above for the preparation of 2b, hydroxylactams 11a-c led to indolizinones 12a-c which were recrystallized from ethanol (68% to 92%).

Method b: To a well stirred solution of hydroxylactam 11a-c (1 mmol) in dry dichloromethane (20 ml) was added dropwise thionyl chloride (0.1 ml, 1.5 mmol). After stirring at room temperature for two hours, the solvent was evaporated. Recrystallization from ethanol afforded pure compounds 12a-c (75% to 100%).

The indicated yields below are those of method b which were always higher than those of method a.

5,11b-Dihydro-4H-benzo[a]thieno[2,3-g]indolizin-7-one (12a R=H). Yield: 100%; mp 150-152°C; IR: 1683 (C=O) cm⁻¹; ¹H NMR: δ 2.85-3.02 (m, 2H, H₄), 3.33 (ddd, J=6, 14 and 16 Hz, 1H, H₃), 4.78 (ddd, J=2, 6 and 16 Hz, 1H, H₂), 5.62 (t, J=2.0 Hz, 1H, H₁₁b), 7.18 (d, J=5.4 Hz, 1H, H₁), 7.22 (d, J=5.4 Hz, 1H, H₂), 7.45 (t, J=8.0 Hz, 1H, H₁₀), 7.51 (t, J=8.0 Hz, 1H, H₉), 7.73 (d, J=8.0 Hz, 1H, H₁₁), 7.85 (d, J=8.0 Hz, 1H, H₈); ¹³C NMR: δ 25.3 (CH₂), 37.6 (CH₂), 58.7 (CH), 122.8 (CH), 123.8 (CH), 123.9 (CH), 124.0 (CH), 128.4 (CH), 131.7 (CH), 132.2 (C), 132.3 (C), 134.2 (C), 142.2 (C), 167.9 (CO); Anal. Calcd. for C₁₄H₁₁NOS: C, 69.68; H, 4.59; N, 5.80. Found: C, 69.52; H, 4.63; N, 5.82.

5,11b-Dihydro-4H-benzo[a]thieno[3,2-g]indolizin-7-one (12b R=H). Yield: 100%; mp 114-116°C; IR: 1684 (C=O) cm⁻¹; ¹H NMR: δ 2.86-2.85 (m, 2H, H₄), 3.25 (ddd, J=6, 14 and 16 Hz, 1H, H₃), 4.72 (ddd, J=2, 6 and 16 Hz, 1H, H₂), 5.73 (t, J=2.0 Hz, 1H, H₁₁b), 6.78 (d, J=5.1 Hz, 1H, H₃), 7.19 (d, J=5.1 Hz, 1H, H₂), 7.45 (t, J=8.0 Hz, 1H, H₁₀), 7.59 (t, J=8.0 Hz, 1H, H₉), 7.75 (d, J=8.0 Hz, 1H, H₁₁), 7.83 (d, J=8.0 Hz, 1H, H₈); C NMR: δ 26.0 (CH₂), 37.3 (CH₂), 58.2 (CH), 122.8 (CH), 123.8 (CH), 123.9 (CH), 127.1 (CH), 128.5 (CH), 131.8 (CH), 132.1 (C), 132.3 (C), 134.2 (C), 144.2 (C), 167.6 (CO); Anal. Calcd. for C₁₄H₁₁NOS: C, 69.68; H, 4.59; N, 5.80. Found: C, 69.47; H, 4.52; N, 5.85.
3-Chloro-5,11b-dihydro-4H-benzo[a]thieno[3,4-g]indolizin-7-one (12c R=H). Yield: 92%; mp 166-168°C; IR: 1683 (C=O) cm\(^{-1}\); \(^1\)H NMR: \(\delta\) 2.60-2.86 (m, 2H, \(H_4\)), 3.30 (ddd, J=6, 14 and 16 Hz, 1H, \(H_3\)), 4.69 (ddd, J=2, 6 and 16 Hz, 1H, \(H_5\)), 5.62 (t, J=2.0 Hz, 1H, \(H_{10b}\)), 6.11 (s, 1H, \(H_7\)), 7.43-7.51 (m, 1H, \(H_{10b}\)), 7.59-7.62 (m, 2H, \(H_{9,11}\)), 7.83 (d, J=7.2 Hz, 1H, \(H_9\)); \(^13\)C NMR: \(\delta\) 25.7 (CH\(_2\)), 37.1 (CH\(_2\)), 57.7 (CH), 122.5 (CH), 124.0 (CH), 126.1 (CH), 128.8 (CH), 129.3 (C), 131.0 (C), 131.9 (CH), 131.9 (C), 133.7 (C), 143.6 (C), 167.6 (CO); Anal. Calcd. for C\(_{14}\)H\(_{10}\)ClNOS: C, 60.98; H, 3.66; N, 5.08. Found: C, 60.74; H, 3.62; N, 5.10.

11b-Ethyl-5,11b-dihydro-4H-benzo[a]thieno[2,3-g]indolizin-7-one (12a R=Et). Yield: 80%; mp 183-185°C; IR: 1683 (C=O) cm\(^{-1}\); \(^1\)H NMR: \(\delta\) 0.49 (t, J=7.4 Hz, 3H, \(CH_3\)), 2.01-2.34 (m, 2H, \(CH_2\)), 2.80-3.08 (m, 2H, \(H_4\)), 3.24 (ddd, J=6, 14 and 16 Hz, 1H, \(H_3\)), 4.71 (ddd, J=2, 6 and 16 Hz, 1H, \(H_5\)), 7.11 (d, J=5.4 Hz, 1H, \(H_3\)), 7.16 (d, J=5.4 Hz, 1H, \(H_2\)), 7.42 (t, J=7.4 Hz, 1H, \(H_{10}\)), 7.57 (t, J=7.4 Hz, 1H, \(H_9\)), 7.66 (d, J=7.4 Hz, 1H, \(H_{11}\)), 7.83 (d, J=7.4 Hz, 1H, \(H_9\)); \(^13\)C NMR: \(\delta\) 7.4 (CH\(_3\)), 25.1 (CH\(_2\)), 32.2 (CH\(_2\)), 34.9 (CH\(_2\)), 67.0 (C), 121.8 (CH), 123.4 (CH), 123.7 (CH), 124.1 (CH), 128.1 (CH), 131.8 (CH), 131.9 (C), 133.1 (C), 137.6 (C), 147.6 (C), 168.3 (CO); Anal. Calcd. for C\(_{16}\)H\(_{15}\)NOS: C, 71.31; H, 5.61; N, 5.20. Found: C, 71.06; H, 5.82; N, 5.32.

11b-Ethyl-5,11b-dihydro-4H-benzo[a]thieno[3,2-g]indolizin-7-one (12b R=Et). Yield: 81%; mp 141-143°C; IR: 1686 (C=O) cm\(^{-1}\); \(^1\)H NMR: \(\delta\) 0.46 (t, J=7.4 Hz, 3H, \(CH_3\)), 2.20 (q, J=7.4 Hz, 2H, \(CH_2\)), 2.60-2.82 (m, 2H, \(H_4\)), 3.16 (ddd, J=6, 14 and 16 Hz, 1H, \(H_3\)), 4.60 (ddd, J=2, 6 and 16 Hz, 1H, \(H_5\)), 6.72 (d, J=5.1 Hz, 1H, \(H_3\)), 7.14 (d, J=5.1 Hz, 1H, \(H_2\)), 7.42 (t, J=8.0 Hz, 1H, \(H_{10}\)), 7.58 (t, J=8.0 Hz, 1H, \(H_9\)), 7.66 (d, J=8.0 Hz, 1H, \(H_{11}\)), 7.82 (d, J=8.0 Hz, 1H, \(H_9\)); \(^13\)C NMR: \(\delta\) 7.7 (CH\(_3\)), 24.0 (CH\(_2\)), 34.3 (CH\(_2\)), 34.7 (CH\(_2\)), 66.9 (C), 121.8 (CH), 123.3 (CH), 123.7 (CH), 126.9 (CH), 129.3 (CH), 131.9 (CH), 133.1 (2C), 138.4 (C), 147.9 (C), 168.3 (CO); Anal. Calcd. for C\(_{16}\)H\(_{15}\)NOS: C, 71.31; H, 5.61; N, 5.20. Found: C, 71.12; H, 5.75; N, 5.26.

3-Chloro-11b-ethyl-5,11b-dihydro-4H-benzo[a]thieno[3,4-g]indolizin-7-one (12c R=Et). Yield: 75%; mp 164-166°C; IR: 1684 (C=O) cm\(^{-1}\); \(^1\)H NMR: \(\delta\) 0.50 (t, J=7.4 Hz, 3H, \(CH_3\)), 2.21 (q, J=7.4 Hz, 2H, \(CH_2\)), 2.53-2.83 (m, 2H, \(H_4\)), 3.28 (ddd, J=6, 14 and 16 Hz, 1H, \(H_5\)), 4.61 (ddd, J=2, 6 and 16 Hz, 1H, \(H_5\)), 6.53 (s, 1H, \(H_1\)), 7.40-7.48 (m, 1H, \(H_{11}\)), 7.52-7.69 (m, 2H, \(H_{9,10}\)), 7.81 (d, J=7.4 Hz, 1H, \(H_8\)); \(^13\)C NMR: \(\delta\) 7.6 (CH\(_3\)), 25.6 (CH\(_2\)), 33.9 (CH\(_2\)), 34.5 (CH\(_2\)), 66.3 (C), 121.5 (CH), 123.8 (CH), 125.8 (CH), 128.5 (CH), 128.7 (C), 131.7 (C), 132.1 (C), 132.6 (CH), 137.0 (C), 147.3 (C), 168.2 (CO); Anal. Calcd. for C\(_{16}\)H\(_{14}\)ClNOS: C, 63.26; H, 4.64; N, 4.61. Found: C, 62.97; H, 4.68; N, 4.64.

5,11b-Dihydro-11b-phenyl-4H-benzo[a]thieno[2,3-g]indolizin-7-one (12a R=Ph). Yield: 96%; mp 212-214°C; IR: 1690 (C=O) cm\(^{-1}\); \(^1\)H NMR: \(\delta\) 2.81-3.19 (m, 3H, \(H_4,4,5\)), 4.55 (ddd, J=2, 6 and 16 Hz, 1H, \(H_5\)), 6.93-6.98 (m, 2H, \(H_{arom}\)), 7.20-7.25 (m, 4H, \(H_{arom}\)), 7.40-7.58 (m, 4H, \(H_{arom}\)), 7.89 (d,
J=8.0 Hz, 1H, H₈); ¹³C NMR: δ 25.0 (CH₂), 34.5 (CH₂), 69.0 (C), 123.2 (CH), 123.4 (CH), 123.8 (CH), 126.0 (CH), 127.5 (2CH), 128.1 (CH), 128.4 (3CH), 131.4 (C), 132.2 (CH), 134.5 (C), 135.6 (C), 141.1 (C), 150.0 (C), 167.7 (CO); Anal. Calcd. for C₂₀H₁₅NOS: C, 75.68; H, 4.41; N, 4.59.

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5,1₁b-Dihydro-1₁b-phenyl-4H-benzo[a]thieno[3,2-g]indolizin-7-one (12b R=Ph). Yield: 100%; mp 204-206°C; IR: 1685 (C=O) cm⁻¹; ¹H NMR: δ 2.70-3.05 (m, 3H, H₄₄₅₅), 4.84 (ddd, J=2, 6 and 16 Hz, 1H, H₃), 6.81 (d, J=5.1 Hz, 1H, H₃), 7.03-7.08 (m, 2H, Hₐrorn), 7.22-7.27 (m, 4H, Hₐrorn), 7.40-7.60 (m, 3H, Hₐrorn), 7.80 (d, J=8.0 Hz, 1H, H₈); ¹³C NMR: δ 25.8 (CH₂), 34.0 (CH₂), 68.8 (C), 123.3 (CH), 123.7 (CH), 124.7 (CH), 126.8 (CH), 127.4 (2CH), 128.3 (CH), 128.6 (2CH), 126.8 (CH), 131.3 (C), 132.3 (CH), 135.0 (C), 135.5 (C), 141.3 (C), 150.3 (C), 167.4 (CO); Anal. Calcd. for C₂₀H₁₅NOS: C, 75.68; H, 4.41; N, 4.59. Found: C, 75.40; H, 4.57; N, 4.62.

3-Chloro-5,1₁b-dihydro-1₁b-phenyl-4H-benzo[a]thieno[3,4-g]indolizin-7-one (12c R=Ph). Yield: 90%; mp 138-142°C; IR: 1684 (C=O) cm⁻¹; ¹H NMR: δ 2.58-3.08 (m, 3H, H₄₄₅₅), 4.44 (ddd, J=2, 6 and 16 Hz, 1H, H₃), 6.65 (s, 1H, H₁), 7.06-7.11 (m, 3H, Hₐrorn), 7.22-7.30 (m, 1H, Hₐrorn), 7.37-7.57 (m, 4H, Hₐrorn), 7.88 (d, J=8.0 Hz, 1H, H₈); ¹³C NMR: δ 25.5 (CH₂), 33.9 (CH₂), 68.3 (C), 123.0 (CH), 123.9 (CH), 125.9 (CH), 127.4 (2CH), 128.4 (3CH), 128.8 (CH), 130.3 (C), 131.2 (C), 132.4 (CH), 133.8 (C), 135.1 (C), 140.6 (C), 149.8 (C), 167.4 (CO); Anal. Calcd. for C₂₀H₁₄ClNOS: C, 68.27; H, 4.01; N, 3.98. Found: C, 68.07; H, 4.03; N, 3.93.

5,1₁b-Dihydro-1₁b-methoxy-4H-benzo[a]thieno[2,3-g]indolizin-7-one (15).

To a mixture of indolizine 12a (0.241 g, 1mmol) in dry methanol (20 ml) was added dichlorodicyanobenzoquinone (DDQ) (1.6 g, 7eq). The mixture was stirred for three days at room temperature, concentrated and dissolved in dichloromethane. This solution was washed with 10% sodium hydrogen carbonate solution, dried over magnesium sulfate, concentrated under vacuum, and finally chromatographed on silica gel eluting with dichloromethane - acetone (9/1). Indolizine 15 was obtained in a 70% yield. mp 124-126°C; IR: 1654 (C=O) cm⁻¹; ¹H NMR: δ 2.91-3.04 (m, 5H, CH₃ and H₄), 3.41 (ddd, J=6, 14 and 16 Hz, 1H, H₃), 4.62 (ddd, J=2, 6 and 16 Hz, 1H, H₃), 7.17 (d, J=5.1 Hz, 1H, H₁), 7.84 (d, J=5.1 Hz, 1H, H₂), 7.52 (t, J=8.0 Hz, 1H, H₁₀), 7.65 (t, J=8.0 Hz, 1H, H₉), 7.83 (t, J=8.0 Hz, 2H, H₈,1₁); ¹³C NMR: δ 25.0 (CH₂), 34.7 (CH₂), 50.3 (CH₃), 89.2 (C), 123.0 (CH), 123.8 (2CH), 124.7 (CH), 129.8 (CH), 131.9 (C), 132.4 (CH), 134.3 (C), 137.1 (C), 143.6 (C), 167.5 (CO); Anal Calcd. for C₁₅H₁₃NO₂S: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.07; H, 4.80; N, 5.14.


