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Acyliminium Ion Cyclizations: Synthesis of Thieno[2',3':3,4]pyrrolo[2,1-*a*] isoindolone and Benzo[*a*]thieno[2,3(3,2 or 3,4)-*g*]indolizinones

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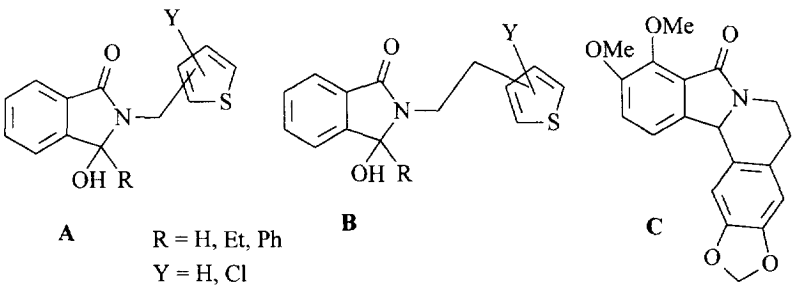
Abstract: *N*-acyliminium cyclizations onto thiophene to give thieno[2',3':3,4]pyrrolo[2,1-a]isoindolone (**2b**) and benzo[a]thieno[2,3(3,2 or 3,4)-g]indolizinones (**12a-c**) were studied.

Current interest in new methods for the generation of *N*-acyliminium ions and their use in synthesis[1] together with our interest in this area[2,3] 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 time[1,4], 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 (methyl[5], *t*-butyl[6], *n*-butyl[6]).

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.

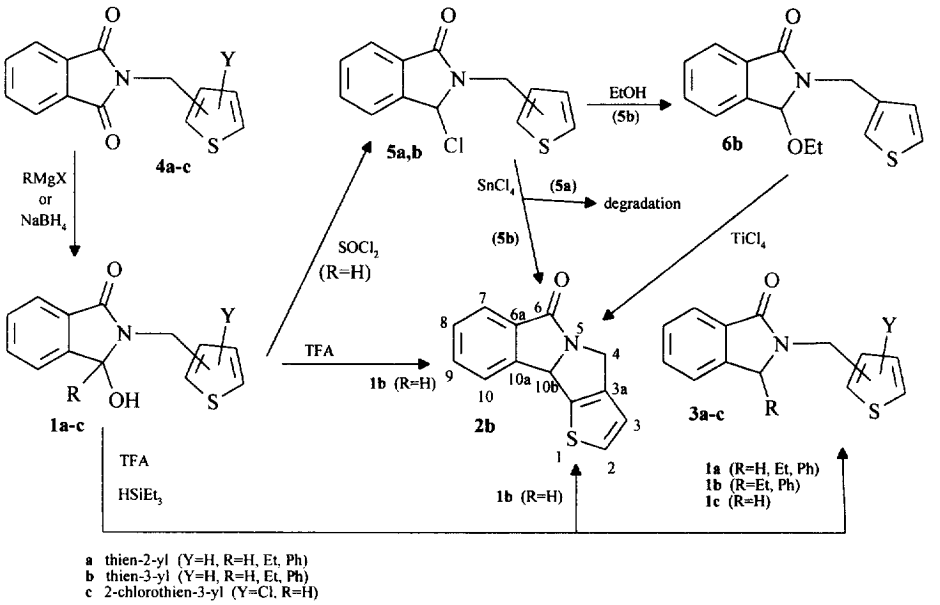


Scheme 1

* Fax: 02.35.21.22.08

Precursors **A** and **B** should give a five membered ring and a six membered ring respectively. As previously mentioned[4], the size of this final ring seems to control the outcome of the reaction.

Actually, when hydroxylactams **1** were treated with trifluoroacetic acid[4,6] 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.



Scheme 2

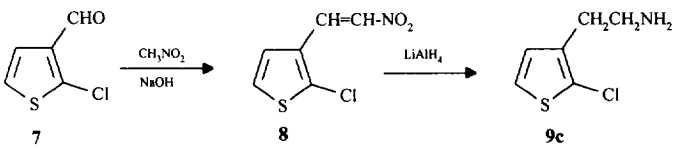
To test the formation of the *N*-acyliminium ion intermediate we added to the trifluoroacetic mixture 1.5 equivalents of triethylsilane. In these conditions no degradation (or enamide) was observable and the expected reduced products **3a-c** were isolated. Nevertheless, cyclization of the *N*-acyliminium 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 reported[7] compounds **4a-c** and **1a-c** (R=H). As described in the literature[8], since a strongly acidic medium seems to increase the degradation we decided to test this reaction in the presence of a Lewis acid[9] 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 ion[10] 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 ^{1}H NMR spectrum of **2b** reveals an AB system for the two protons H_4 (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 H_{10b} proton is a singlet with a chemical shift of δ=5.65 ppm, and the thiophenic protons H_2 and H_3 are doublets with the characteristic α,β coupling constant J = 5.1 Hz. Furthermore the ^{13}C NMR supports this proposed structure since the C_{10b} carbon is present with a chemical shift of δ = 55.1 ppm.

From this result and the reported work cited above[4] 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 C_{10b} 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 reported[5,11].

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[12] and the 3-aminoethyl-2-chlorothiophene (**9c**) was synthesized from the known 2-chloro-3-formylthiophene[13] (**7**) as shown in Scheme 3.



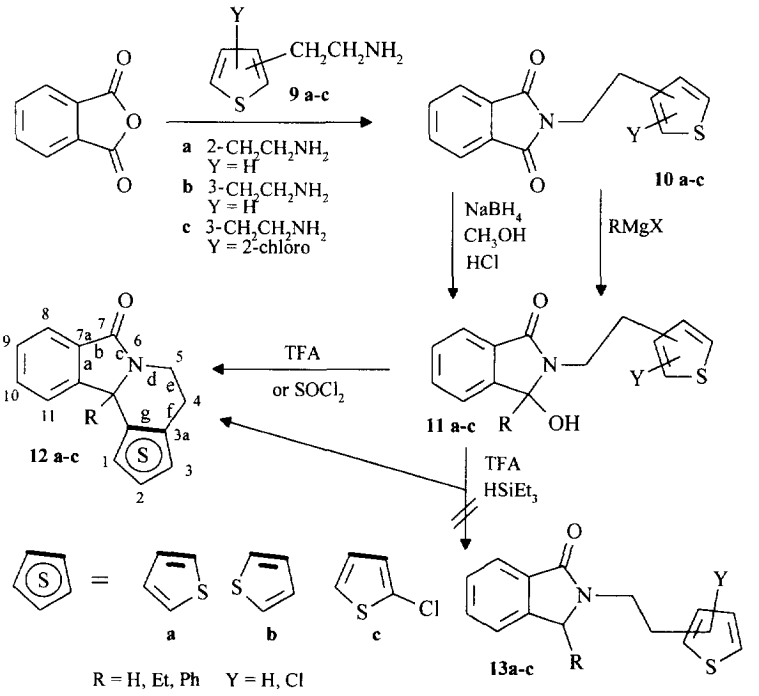
7 8 9c

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.

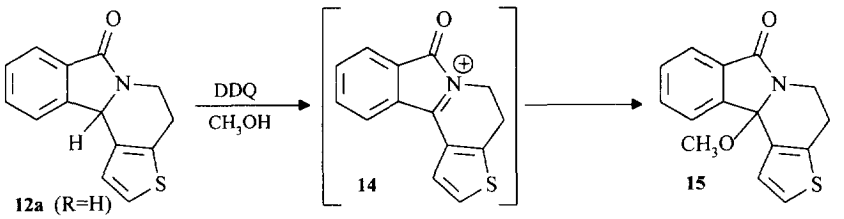
The three types of cyclizations with the thiophene ring (2,3 - 3,2 - 3,4) occur so the nucleophile does not control the outcome of the reaction. To confirm this result, we investigated the reactivity of hydroxylactams in

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[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).



Scheme 4

Finally, we tested the lability of H_{11b} proton of indolizidine **12a** (R=H) (Scheme 5). Actually, there are a few reports[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[15], we did not observe oxidation of the six membered ring of the indolizidine system.



Scheme 5

In conclusion, hydroxylactams with secondary hydroxy group gave an intramolecular α-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 (δ) 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^{t}. S^{t}. 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)-1*H*-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 1M 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)-1*H*-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 1M 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).

4,10$_b$-Dihydrothieno[2',3';3,4] pyrrolo[2,1-a] isoindol-6-one (2b).

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=0) cm^{-1};^{1}H NMR: δ 3.88 (d, J=14.5 Hz, 1H, H_4), 5.50 (d, J=14.5 Hz, 1H, H_4), 5.65 (s, 1H, H_{10b}), 6.97 (d, J=5.1 Hz, 1H, H_3), 7.23-7.30 (m, 1H, H_{10}), 7.30 (d, J=5.1 Hz, 1H, H_2), 7.48-7.60 (m, 2H, $H_{8,9}$), 7.89-8.00 (m, 1H, H_7). ^{13}C NMR: δ 35.6 (CH_2), 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 $C_{13}H_9NOS$: 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 **9** in 80% yield. mp 117-119°C; ^{1}H NMR: δ 7.09 (d, J=5.9 Hz, 1H, H_4), 7.20 (d, J=5.9 Hz, 1H, H_5), 7.49 (d, J=13.4 Hz, 1H, H_{vinyl}), 8.03 (d, J=13.4 Hz, 1H, H_{vinyl}); Anal. Calcd. for $C_6H_4ClNO_2S$: 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 **10** in 90% yield as a liquid. IR: 3300 (NH_2) cm^{-1}; ^{1}H NMR: δ 2.25 (s, 2H, NH_2), 2.27 (t, J=8.0 Hz, 2H, CH_2), 2.91 (t, J=8.0 Hz, 2H, CH_2), 6.78 (d, J=6.0 Hz, 1H, H_4), 7.02 (d, J=6.0 Hz, 1H, H_5).

***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=0) cm^{-1}; ^{1}H NMR: δ 3.20 (t, J=8.0 Hz, 2H, CH_2), 3.94 (t, J=8.0 Hz, 2H, CH_2), 7.84-7.90 (m, 2H, $H_{3',4'}$), 7.10-7.12 (m, 1H, $H_{5'}$), 7.66-7.70 (m, 2H, H_{arom}), 7.72-7.77 (m, 2H, H_{arom}); Anal. Calcd. for $C_{14}H_{11}NO_2S$: 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=0) cm^{-1}; ^{1}H NMR: δ 2.96 (t, J=8.0 Hz, 2H, CH_2), 3.86 (t, J=8.0 Hz, 2H, CH_2), 6.92-6.97 (m, 2H, $H_{4',5'}$), 7.16-7.20 (m, 1H, $H_{2'}$), 7.61-7.67 (m, 2H, H_{arom}), 7.74-7.82 (m, 2H, H_{arom}); Anal. Calcd. for $C_{14}H_{11}NO_2S$: 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=0) cm^{-1}; ^1H NMR: δ 2.96 (t, J=8 Hz, 2H, CH_2), 3.88 (t, J=8 Hz, 2H, CH_2), 6.83 (d, J=5.4 Hz, 1H, $H_{4'}$), 7.01 (d, J=5.4 Hz, 1H, $H_{5'}$), 7.65-7.70 (m, 2H, H_{arom}), 7.72-7.76 (m, 2H, H_{arom}); Anal. Calcd. for $C_{14}H_{10}ClNO_2S$: 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)-1*H*-isoindol-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)-1*H*-isoindol-1-one (11a R=H). Yield: 96%; mp 112-114°C; IR: 3220 (OH), 1658 (C=0) cm^{-1}; ^1H NMR: δ 3.09 (t, J=8.0 Hz, 2H, CH_2), 3.43-3.67 (m, 2H, CH_2), 5.50 (s, 1H, H_3), 6.74 (dd, J=1.2 and 3.6 Hz, 1H, $H_{3'}$), 6.84 (dd, J=3.6 and 5.1 Hz, 1H, $H_{4'}$), 7.08 (dd, J=1.2 and 5.1 Hz, 1H, $H_{5'}$), 7.39-7.42 (m, 1H, H_{arom}), 7.51-7.55 (m, 3H, H_{arom}); Anal. Calcd. for $C_{14}H_{13}NO_2S$: 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)-1*H*-isoindol-1-one (11b R=H). Yield: 98%; mp 140-142°C; IR: 3255 (OH), 1661 (C=0) cm^{-1}; ^1H NMR: δ 2.91 (t, J=8.0 Hz, 2H, CH_2), 3.40-3.71 (m, 2H, CH_2), 5.47 (s, 1H, H_3), 6.91-6.93 (m, 2H, $H_{4',5'}$), 7.19-7.22 (m, 1H, $H_{2'}$), 7.30-7.42 (m, 1H, H_{arom}), 7.44-7.58 (m, 3H, H_{arom}); Anal. Calcd. for $C_{14}H_{13}NO_2S$: 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)-1*H*-isoindol-1-one (11c R=H). Yield: 94%; mp 98-100°C; IR: 3250 (OH), 1660 (C=0) cm^{-1}; ^1H NMR: δ 2.85 (t, J=8.0 Hz, 2H, CH_2), 3.42-3.69 (m, 2H, CH_2), 5.54 (d, J=10.0 Hz, 1H, H_3), 6.78 (d, J=6.0 Hz, 1H, $H_{4'}$), 6.99 (d, J=6.0 Hz, 1H, $H_{5'}$), 7.36-7.44 (m, 1H, H_{arom}), 7.48-7.55 (m, 3H, H_{arom}).

3-Ethyl-2,3-dihydro-3-hydroxy-2-(thienylethyl)-1*H*-isoindol-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)-1*H*-isoindol-1-one (11a R=Et). Yield: 97%; IR: 3286 (OH), 1673 (C=0) cm^{-1}; ^1H NMR: δ 0.46 (t, J=7.4 Hz, 3H, CH_3), 2.06-2.15 (m, 2H, CH_2), 3.18-3.36 (m, 3H, CH_2-CH_2), 3.85-3.89 (m, 1H, CH_2-CH_2), 6.84-6.91 (m, 2H, $H_{3',4'}$), 7.11 (dd, J=1.2 and 5.1 Hz, 1H, $H_{5'}$), 7.43-7.46 (m, 3H, H_{arom}), 7.52 (d, J=5.4 Hz, 1H, H_{arom}).

3-Ethyl-2,3-dihydro-3-hydroxy-2-(thien-3'-ylethyl)-1*H*-isoindol-1-one (11b R=Et). Yield: 96%; IR: 3261 (OH), 1684 (C=0) cm^{-1}; ^1H NMR: δ 0.46 (t, J=7.4 Hz, 3H, CH_3), 1.99-2.20 (m, 2H, CH_2), 2.90-3.50 (m, 3H, CH_2-CH_2), 3.78-3.90 (m, 1H, CH_2-CH_2), 6.92-7.06 (m, 2H, $H_{4',5'}$), 7.20-7.25 (m, 1H, $H_{2'}$), 7.35-7.55 (m, 3H, H_{arom}), 7.77 (d, J=5.2 Hz, 1H, H_{arom}).

3-Ethyl-2,3-dihydro-3-hydroxy-2-(2'-chlorothien-3'-ylethyl)-1*H*-isoindol-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, CH_3), 2.10-2.16 (m, 2H, CH_2), 2.95-3.27 (m, 3H, CH_2-CH_2), 3.70-3.95 (m, 1H, CH_2-CH_2), 6.85 (d, J=5.6 Hz, 1H, $H_{4'}$), 7.02 (d, J=5.6 Hz, 1H, $H_{5'}$), 7.43-7.54 (m, 3H, H_{arom}), 7.70 (d, J=6.8 Hz, 1H, H_{arom}).

2,3-Dihydro-3-hydroxy-3-phenyl-2-(thienylethyl)-1*H*-isoindol-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)-1*H*-isoindol-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, CH_2-CH_2), 3.09-3.24 (m, 2H, CH_2-CH_2), 3.58-3.81 (m, 1H, CH_2-CH_2), 6.71 (dd, J=1.2 and 3.6Hz, 1H, $H_{3'}$), 6.85 (dd, J=3.6 and 5.0 Hz, 1H, $H_{4'}$), 7.06 (dd, J=1.2 and 5.0 Hz, 1H, $H_{5'}$), 7.25-7.45 (m, 8H, H_{arom}), 7.67 (d, J=7.0 Hz, 1H, H_{arom}).

2,3-Dihydro-3-hydroxy-3-phenyl-2-(thien-3'-ylethyl)-1*H*-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, CH_2-CH_2), 2.85-3.20 (m, 2H, CH_2-CH_2), 3.56-3.70 (m, 1H, CH_2-CH_2), 6.78-6.85 (m, 2H, $H_{4',5'}$), 7.14-7.18 (m, 1H, $H_{2'}$), 7.21-7.50 (m, 8H, H_{arom}), 7.68 (d, J=7.0 Hz, 1H, H_{arom}); Anal. Calcd. for $C_{20}H_{17}NO_2S$: 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)-1*H*-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, CH_2-CH_2), 2.86-3.19 (m, 2H, CH_2-CH_2), 3.55-3.69 (m, 1H, CH_2-CH_2), 6.72 (d, J=6.0 Hz, 1H, $H_{4'}$), 6.96 (d, J=6 Hz, 1H, $H_{5'}$), 7.28-7.47 (m, 8H, H_{arom}), 7.74 (d, J=5.4 Hz, 1H, H_{arom}).

Benzo[a]thieno[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.

5,11$_b$-Dihydro-4*H*-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, H_4), 3.33 (ddd, J=6, 14 and 16 Hz, 1H, H_5), 4.78 (ddd, J=2, 6 and 16 Hz, 1H, H_5), 5.62 (t, J=2.0 Hz, 1H, H_{11b}), 7.18 (d, J=5.4 Hz, 1H, H_1), 7.22 (d, J=5.4 Hz, 1H, H_2), 7.45 (t, J=8.0 Hz, 1H, H_{10}), 7.51 (t, J=8.0 Hz, 1H, H_9), 7.73 (d, J=8.0 Hz, 1H, H_{11}), 7.85 (d, J=8.0 Hz, 1H, H_8); ^{13}C NMR: δ 25.3 (CH_2), 37.6 (CH_2), 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 $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80. Found: C, 69.52; H, 4.63; N, 5.82.

5,11$_b$-Dihydro-4*H*-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, H_4), 3.25 (ddd, J=6, 14 and 16 Hz, 1H, H_5), 4.72 (ddd, J=2, 6 and 16 Hz, 1H, H_5), 5.73 (t, J=2.0 Hz, 1H, H_{11b}), 6.78 (d, J=5.1 Hz, 1H, H_3), 7.19 (d, J=5.1 Hz, 1H, H_2), 7.45 (t, J=8.0 Hz, 1H, H_{10}), 7.59 (t, J=8.0 Hz, 1H, H_9), 7.75 (d, J=8.0 Hz, 1H, H_{11}), 7.83 (d, J=8.0 Hz, 1H, H_8); ^{13}C NMR: δ 26.0 (CH_2), 37.3 (CH_2), 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 $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N,

5.80. Found: C, 69.47; H, 4.52; N, 5.85.

3-Chloro-5,11$_b$-dihydro-4*H*-benzo[a]thieno[3,4-g]indolizin-7-one (12c R=H). Yield: 92%; mp 166-168°C; IR: 1683 (C=0) cm^{-1}; ^{1}H NMR: δ 2.60-2.86 (m, 2H, H_4), 3.30 (ddd, J=6, 14 and 16 Hz, 1H, H_5), 4.69 (ddd, J=2, 6 and 16 Hz, 1H, H_5), 5.62 (t, J=2.0 Hz, 1H, H_{11b}), 6.11 (s, 1H, H_1), 7.43-7.51 (m, 1H, H_{10}), 7.59-7.62 (m, 2H, $H_{9,11}$), 7.83 (d, J=7.2 Hz, 1H, H_8); ^{13}C NMR: δ 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.

11$_b$-Ethyl-5,11$_b$-dihydro-4*H*-benzo[a]thieno[2,3-g]indolizin-7-one (12a R=Et). Yield: 80%; mp 183-185°C; IR: 1683 (C=0) cm^{-1}; ^{1}H NMR: δ 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_5), 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_8); ^{13}C NMR: δ 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.

11$_b$-Ethyl-5,11$_b$-dihydro-4*H*-benzo[a]thieno[3,2-g]indolizin-7-one (12b R=Et). Yield: 81%; mp 141-143°C; IR: 1686 (C=0) cm^{-1}; ^{1}H NMR: δ 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_5), 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_8); ^{13}C NMR: δ 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-11$_b$-ethyl-5,11$_b$-dihydro-4*H*-benzo[a]thieno[3,4-g]indolizin-7-one (12c R=Et). Yield: 75%; mp 164-166°C; IR: 1684 (C=0) cm^{-1}; ^{1}H NMR: δ 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: δ 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.

5,11$_b$-Dihydro-11$_b$-phenyl-4*H*-benzo[a]thieno[2,3-g]indolizin-7-one (12a R=Ph). Yield: 96%; mp 212-214°C; IR: 1690 (C=0) cm^{-1}; ^{1}H NMR: δ 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, H_8); ^{13}C NMR: δ 25.0 (CH_2), 34.5 (CH_2), 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 $C_{20}H_{15}NOS$: C, 75.68; H, 4.41; N, 4.59. Found: C, 75.66; H, 4.48; N, 4.69.

5,11$_b$-Dihydro-11$_b$-phenyl-4*H*-benzo[a]thieno[3,2-g]indolizin-7-one (12b R=Ph). Yield: 100%; mp 204-206°C; IR: 1685 (C=0) cm^{-1}; ^{1}H NMR: δ 2.70-3.05 (m, 3H, $H_{4,4,5}$), 4.84 (ddd, J=2, 6 and 16 Hz, 1H, H_5), 6.81 (d, J=5.1 Hz, 1H, H_3), 7.03-7.08 (m, 2H, H_{arom}), 7.22-7.27 (m, 4H, H_{arom}), 7.40-7.60 (m, 3H, H_{arom}), 7.90 (d, J=8.0 Hz, 1H, H_8); ^{13}C NMR: δ 25.8 (CH_2), 34.0 (CH_2), 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 $C_{20}H_{15}NOS$: C, 75.68; H, 4.41; N, 4.59. Found: C, 75.40; H, 4.57; N, 4.62.

3-Chloro-5,11$_b$-dihydro-11$_b$-phenyl-4*H*-benzo[a]thieno[3,4-g]indolizin-7-one (12c R=Ph). Yield: 90%; mp 138-142°C; IR: 1684 (C=0) cm^{-1}; ^{1}H NMR: δ 2.58-3.08 (m, 3H, $H_{4,4,5}$), 4.44 (ddd, J=2, 6 and 16 Hz, 1H, H_5), 6.65 (s, 1H, H_1), 7.06-7.11 (m, 3H, H_{arom}), 7.22-7.30 (m, 1H, H_{arom}), 7.37-7.57 (m, 4H, H_{arom}), 7.88 (d, J=8.0 Hz, 1H, H_8); ^{13}C NMR: δ 25.5 (CH_2), 33.9 (CH_2), 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 $C_{20}H_{14}ClNOS$: C, 68.27; H, 4.01; N, 3.98. Found: C, 68.07; H, 4.03; N, 3.93.

5,11$_b$-Dihydro-11$_b$-methoxy-4*H*-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=0) cm^{-1}; ^{1}H NMR: δ 2.91-3.04 (m, 5H, CH_3 and H_4), 3.41 (ddd, J=6, 14 and 16 Hz, 1H, H_5), 4.62 (ddd, J=2, 6 and 16 Hz, 1H, H_5), 7.17 (d, J=5.1 Hz, 1H, H_1), 7.84 (d, J=5.1 Hz, 1H, H_2), 7.52 (t, J=8.0 Hz, 1H, H_{10}) , 7.65 (t, J=8.0 Hz, 1H, H_9) , 7.83 (t, J=8.0 Hz, 2H, $H_{8,11}$); ^{13}C NMR: δ 25.0 (CH_2), 34.7 (CH_2), 50.3 (CH_3), 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 $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.07; H, 4.80; N, 5.14.

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