

Regioselective Reduction of 2-(Arylideneamino)isoindole-1,3-diones – Synthesis of Alkaloid Analogues by *N*-Acylhydrazonium Ion Aromatic π -Cyclization

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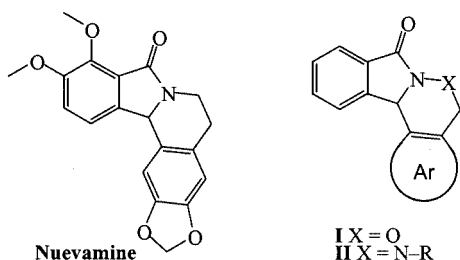
Hydroxylactams **6a–c** and **7a–c** were synthesized by successive regioselective reductions of arylideneaminophthalimides **3a–c**, which were easily available from aminophthalimide **1** and benzaldehyde (**2a**) or thiophenecarboxaldehydes **2b** and **2c**. *N*-Acylhydrazonium ions **III**, generated in the presence of Lewis acid from acetoxy derivatives **8a** and **9a** of hydroxylactams **6a** and **7a**, or in organic acid medium directly from hydroxylactams **6b** and **6c**, induced the expected

isoindolo-phthalazines **10a** and **11a** and thienopyridazino-isoindolones **12b** and **12c**. On the other hand, hydroxylactams **7b** and **7c** under acidic conditions gave the unexpected *N*-thienylmethyl-substituted thienopyridazino-isoindolones **13b** and **13c**.

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Introduction

In the course of our investigations concerning the synthesis of analogues of tetracyclic alkaloids containing an isoindole moiety, such as nuevamine, we have recently described the synthesis of fused oxazino-isoindolones **I** (Scheme 1).^[1]



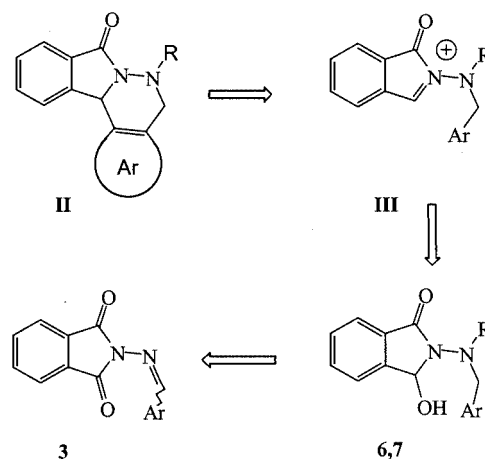
Scheme 1

The cyclization step was an intramolecular carbon–carbon bond formation involving an *N*-acyliminium ion and a π -aromatic system. Examples of this reaction have been reviewed by Speckamp,^[2] while we have previously reported the synthesis of isoindolo-dibenzazepine^[3] and various diaza heterocycles^[4] by this process. As a further development of our research, we described there the synthesis of tetracyclic systems containing a pyridazino-isoindole moiety **II**, based on an amidoalkylation step with use of an *N*-acylhydrazonium ion. Such intermediates have previously been employed to synthesize cyclic hydrazides, cyclic hydrazino acid derivatives, bridged bicyclic hydrazines aza

analogues of cocaine, and (nor-)azatropanes, by the Speckamp group,^[5] or alkaloids with the phenanthro-quinolizidine skeleton.^[6] Tetracyclic compounds depicted in the present paper have the –CO–N–N– structural feature common to several tetracyclic molecules such as diphthalazine-diones, which present analgesic and antiinflammatory activities.^[7]

Results and Discussion

As indicated in Scheme 2, our strategy involved the formation of hydroxy lactams **6** and **7** from aryliminophthalimides **3**, easily available through condensation of aminophthalimide and aromatic aldehydes. As hydroxylactams **6** and **7** could generate the *N*-acylhydrazonium ions **III** under acidic conditions,^[8] ring closure could occur through an in-

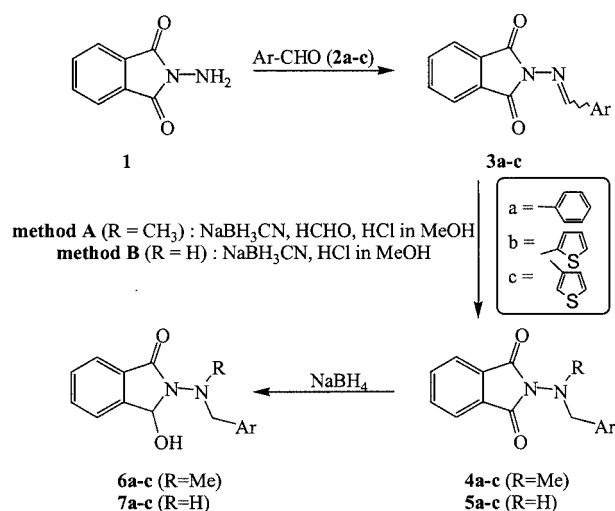


Scheme 2

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tramolecular α -heteroamido-alkylation reaction to provide **II**.

The 2-arylideneaminophthalimides **3a–c** were produced by condensations between *N*-aminophthalimide (**1**) and benzaldehyde (**2a**), thiophene-2-carboxaldehyde (**2b**), or thiophene-3-carboxaldehyde (**2c**) in good yields of up to 80% (Scheme 3). Some attempts to reduce both hydrazone and imide functions in the same time failed. Use of various hydrides such as BH_3 or DIBAH gave complex mixtures of partially reduced compounds, while that of LiAlH_4 resulted in the opening of the phthalimide ring. In addition, NaBH_4 , which reduces phthalimide derivatives to give hydroxyisoindolones^[1,4] and reduces α -nitrohydrazones,^[9] did not affect here the hydrazone function. Regioselective reduction of the hydrazone function was accomplished by use of NaBH_3CN , which had been already used in the reductive methylation of hydrazones.^[10,11] The reduction takes place in a continuously buffered (pH 3–5) solution of the hydride and formaldehyde (method A), through the addition of a methanolic solution of hydrochloric acid. Thus, *N*-methylhydrazines **4a–c** were isolated in satisfactory yields of 63 to 68%. In the absence of formaldehyde (method B) we obtained simple reduction compounds **5a–c** in good yields of 68 to 74%. As described previously, treatment of **4a–c** and **5a–c** with NaBH_4 in methanolic solution at 5 °C produced hydroxylactams **6a–c** and **7a–c**, respectively, in good yields of up to 70%.



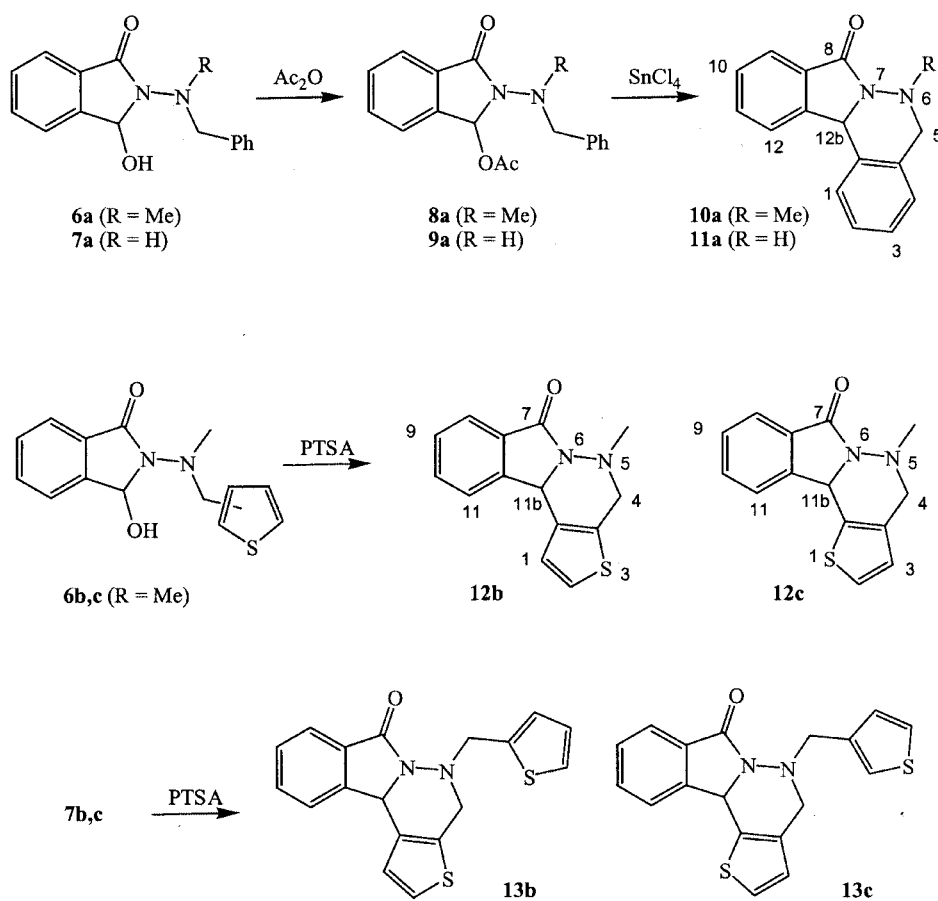
Scheme 3

Cyclization of compounds **6** and **7** in acidic medium takes place through the generation of *N*-acylhydrazonium ions, which react with the aromatic systems. Actually, previous investigations into the production of *N*-acyliminium ions in our laboratory have shown that various organic acids such as *p*-toluenesulfonic acid, formic acid, or trifluoroacetic acid (pure or diluted in CH_2Cl_2) could give satisfactory results.^[1,12] Treatment of hydroxylactams **6a** and **7a** under acidic conditions produced only complex mixtures of insoluble polymerized material. In contrast, cyclization occurred on treatment with SnCl_4 under typical Lewis acid

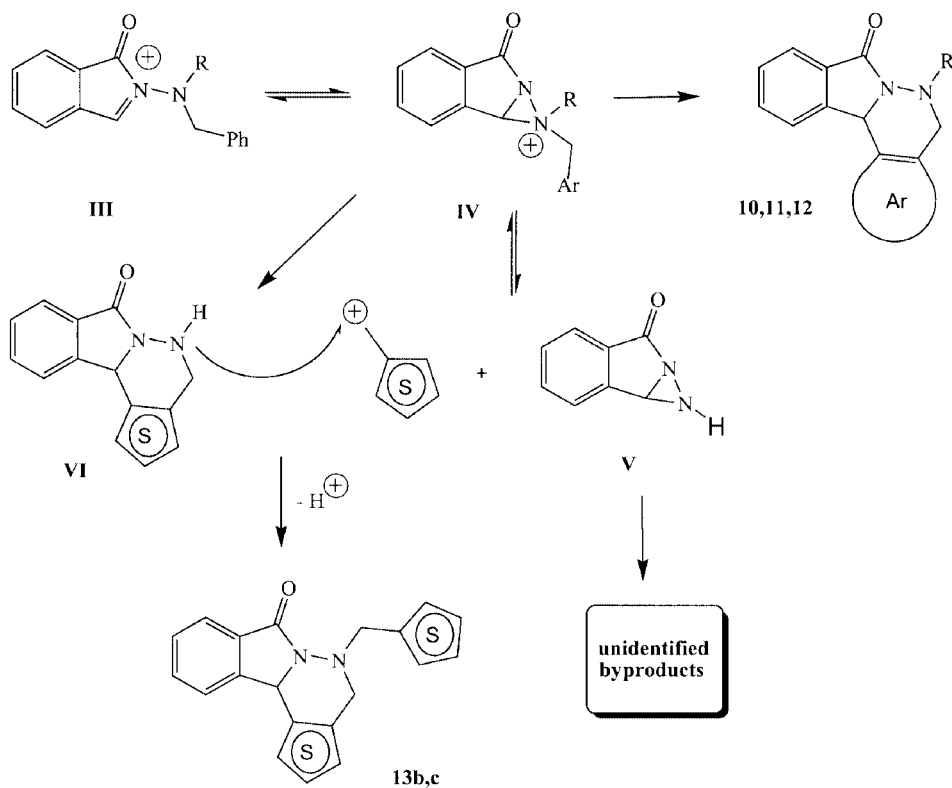
conditions starting from acetoxylactams.^[13] Accordingly, hydroxylactams **6a** and **7a** were acetylated with acetic anhydride in CH_2Cl_2 in the presence of DMAP to provide acetoxylactams **8a** and **9a**. Treatment of these with three equivalents of SnCl_4 in CH_2Cl_2 at room temperature provided the expected isoindolo-phthalazines **10a** and **11a** in moderate yields (65 and 58%, respectively, Scheme 4). Treatment of hydroxylactams **6b** and **6c** under the organic acid conditions described above afforded *N*-methyl pyridazino-isoindolones **12b** and **12c**. Since it has been demonstrated that α -chloroalkylamine can serve as an *N*-acyliminium ion source, the cyclization reaction was examined in the presence of SOCl_2 . All these distinct conditions produced only variation in the reaction yield. The best results (81 and 85% yields for **12b** and **12c**, respectively) were obtained by use of a catalytic amount of *p*-toluenesulfonic acid diluted in CH_2Cl_2 .

The structures of these compounds were confirmed by spectroscopic data and microanalysis. For instance, the ^1H NMR spectra of **12b** and **12c** each revealed the presence of a singlet at $\delta = 5.7\text{--}5.8$, corresponding to the isoindolic proton 11b, and two doublets of an AB system for the methylene group, due to the diastereotopic effect with a coupling constant $J = 15\text{--}17$ Hz characteristic of *gem* protons. In addition, the thiophene protons appeared as two doublets with a coupling constant characteristic of a 2,3-disubstituted thiophene ring. Surprisingly, cyclization of hydroxylactams **7b** and **7c** afforded not unsubstituted pyridazino-isoindolones, but *N*-thienylmethyl-substituted compounds **13b** and **13c**. The structures of **13b** and **13c** were confirmed by an array of mono- and bidimensional NMR experiments (homodecoupling, ^1H - ^{13}C heterocorrelation, DEPT). The key feature was the appearance of an additional methylene, appearing as a doublet of doublets in each ^1H NMR spectrum and as one signal in the aliphatic region and four additional peaks in the aromatic region of each ^{13}C NMR spectrum. Whatever the acidic conditions, the cyclization reaction invariably occurred to give *N*-substituted **13b** and **13c**. The best results here were obtained by use of pure trifluoroacetic acid (41 and 42% yields for **13b** and **13c**, respectively). As thioalkyl *N*-acyliminium ions could rearrange via cyclic sulfenium intermediates,^[14] the reaction sequence shown in Scheme 5 may be proposed as a mechanism for the formation of **13b** and **13c** starting from the *N*-acylhydrazonium ion intermediate **III**.

The reaction takes place through an unstable diaziridinium ion **IV** (Scheme 5), which rearranges through a π cationic cyclization in the case of all benzo derivatives and *N*-methylthieno derivatives to give the expected pyridazines **10**, **11**, and **12**. In contrast, the formation of *N*-thienylmethyl-substituted thienopyridazino-isoindolones **13b** and **13c** could be followed by transformation of **IV** into the diaziridine **V** and the formation of a thienylmethyl ion, which would be trapped by the thienopyridazino-isoindolone **VI**. It may be noted that we have previously reported the cleavage of a benzyl C–O bond of a 2-(benzyloxy)isoindolone in acidic medium.^[15] Unfortunately, those attempts to isolate **V** failed. Only insoluble, unidentified material was reco-



Scheme 4



Scheme 5

vered during the purification steps for **13b** and **13c**. The fact that the yields of the syntheses of **13b** and **13c** were good (41 and 42%; 50% theoretical) strongly suggests that the polymerized material originates from **V** rather than directly from **13b** and **13c**.

Conclusion

We have described the synthesis of aryliminophthalimides from easily available aromatic carboxaldehydes and *N*-aminophthalimide. Consecutive regioselective reduction of imine and carbonyl functions of aryliminophthalimides and generation of *N*-acylhydrazonium ions in acidic medium can easily provide isoindolobenzopyridazines and thienopyridazino-isoindolones.

Experimental Section

General Remarks: Analytical thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and column chromatography on Merck silica gel 60F (70–300 mesh). The melting points were determined on a Leitz hot plate apparatus and were uncorrected. The infrared spectra of solids (KBr) were recorded on a Perkin–Elmer FTIR paragon 1000 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 instrument in CDCl_3 as solvent, except in the cases of compounds **13b** and **13c** ($[\text{D}_6]\text{DMSO}$), and chemical shifts (δ) are expressed in ppm relative to residual CHCl_3 at $\delta = 7.27$ for ^1H and $\delta = 77.16$ for ^{13}C . The elemental analyses of final compounds were carried out by the microanalysis laboratory of INSA, Mont-Saint-Aignan, France.

2-Benzylideneaminophthalimide (3a): A stirred solution of **1** (3.2 g, 0.02 mol) and benzaldehyde (**2a**, 3.18 g, 0.03 mol) in EtOH (50 mL) was heated at reflux for 6 h and was then allowed to come slowly to 0 °C. The solid that precipitated was filtered and recrystallized from ethanol to give a pale-yellow solid (4.25 g, 86%), m.p. 162–165 °C. IR: $\tilde{\nu}_{\text{max}} = 1775\text{ cm}^{-1}$. ^1H NMR: $\delta = 7.45$ (m, 3 H), 7.76 (m, 2 H), 7.90 (m, 4 H), 9.38 (s, 1 H) ppm. ^{13}C NMR: $\delta = 123.7, 128.3, 128.7, 130.2, 131.6, 133.5, 134.6, 158.5, 165.0$ ppm. $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_2$ (250.26): calcd. C 71.99, H 4.03, N 11.19; found C 71.76, H 4.17, N 11.28.

2-(Thien-2'-ylideneamino)phthalimide (3b): A stirred solution of **1** (2 g, 0.012 mol) and thiophene-2-carboxaldehyde (**2b**, 1.2 g, 0.014 mol) and a catalytic amount of *p*-toluenesulfonic acid in toluene (40 mL) was heated at reflux for 4 h. The solvent was evaporated and the residue was recrystallized from EtOH to afford a yellow solid (2.55 g, 83%), m.p. 159–161 °C. IR: $\tilde{\nu}_{\text{max}} = 1729\text{ cm}^{-1}$. ^1H NMR: $\delta = 7.11$ (dd, $J = 3.7, 4.8$ Hz, 1 H), 7.49 (m, 2 H), 7.77 (m, 2 H), 7.87 (m, 2 H), 9.50 (s, 1 H) ppm. ^{13}C NMR: $\delta = 123.7, 127.6, 130.3, 130.6, 132.9, 134.6, 138.5, 152.7, 164.9$ ppm. $\text{C}_{13}\text{H}_8\text{N}_2\text{O}_2\text{S}$ (256.28): calcd. C 60.93, H 3.15, N 10.93; found C 60.69, H 3.33, N 11.12.

2-(Thien-3'-ylideneamino)phthalimide (3c): This compound was obtained as described above, with **5** and thiophene-3-carboxaldehyde (**2c**) as starting materials, to give a pale yellow solid (2.6 g, 84%), m.p. 166–168 °C. IR: $\tilde{\nu}_{\text{max}} = 1721\text{ cm}^{-1}$. ^1H NMR: $\delta = 7.36$ (dd, $J = 2.9, 5.1$ Hz, 1 H), 7.69 (dd, $J = 0.8, 5.1$ Hz, 1 H), 7.74 (m, 2 H), 7.78 (dd, $J = 0.8, 2.9$ Hz, 1 H), 7.88 (m, 2 H) 9.34 (s, 1 H)

ppm. ^{13}C NMR: $\delta = 123.7, 125.3, 126.8, 130.3, 130.6, 134.5, 137.1, 153.6, 165.0$ ppm. $\text{C}_{13}\text{H}_8\text{N}_2\text{O}_2\text{S}$ (256.28): calcd. C 60.93, H 3.15, N 10.93; found C 61.07, H 3.29, N 10.82.

Typical Procedure for Reductive Methylation of 3a–c (Method A): Bromocresol green (2 drops) and NaBH_3CN (10 mmol, portion-wise) were added at 10 °C to a cooled, stirred solution of **3a–c** (2 mmol) and formaldehyde (5 mmol of a 37% aqueous solution) in methanol (35 mL). During the addition, the solution was maintained at an acidic pH by addition of a methanolic HCl solution (2M). After stirring at room temperature for an additional 2 h, the mixture was quenched with saturated aqueous NaHCO_3 solution (25 mL) and the methanol was evaporated. The mixture was extracted twice with CH_2Cl_2 (50 mL), and the combined organic layers were washed with saturated NaHCO_3 solution (50 mL) and water (50 mL) and then dried with Na_2SO_4 prior to concentration and chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 95:5).

2-[Benzyl(methyl)amino]phthalimide (4a): Chromatographic purification of the crude product obtained from **3a** afforded a white solid (0.34 g, 63%), m.p. 93–95 °C. IR: $\tilde{\nu}_{\text{max}} = 1776\text{ cm}^{-1}$. ^1H NMR: $\delta = 3.04$ (s, 3 H), 4.38 (s, 2 H), 7.18 (m, 3 H), 7.35 (m, 2 H), 7.59–7.71 (m, 4 H) ppm. ^{13}C NMR: $\delta = 43.3, 60.6, 123.1, 127.7, 128.3, 129.1, 129.9, 134.1, 136.3, 167.1$ ppm. $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$ (266.30): calcd. C 72.17, H 5.30, N 10.52; found C 72.01, H 5.45, N 10.71.

2-[Methyl(thien-2'-ylmethyl)amino]phthalimide (4b): Chromatographic purification of the crude product obtained from **3b** afforded a white solid (0.36 g, 67%), m.p. 138–140 °C. IR: $\tilde{\nu}_{\text{max}} = 1722\text{ cm}^{-1}$. ^1H NMR: $\delta = 3.07$ (s, 3 H), 4.57 (s, 2 H), 6.77 (dd, $J = 3.2, 5.0$ Hz, 1 H), 6.91 (dd, $J = 1.3, 3.2$ Hz, 1 H), 7.13 (dd, $J = 1.3, 5.0$ Hz, 1 H), 7.63–7.74 (m, 4 H) ppm. ^{13}C NMR: $\delta = 43.3, 54.5, 123.1, 126.0, 126.3, 127.3, 129.9, 138.7, 166.9$ ppm. $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ (272.33): calcd. C 61.75, H 4.44, N 10.29; found C 61.96, H 4.17, N 10.05.

2-[Methyl(thien-3'-ylmethyl)amino]phthalimide (4c): Chromatographic purification of the crude product obtained from **3c** afforded a white solid (0.37 g, 68%), m.p. 111–113 °C. IR: $\tilde{\nu}_{\text{max}} = 1714\text{ cm}^{-1}$. ^1H NMR: $\delta = 3.04$ (s, 3 H), 4.39 (s, 2 H), 7.08 (m, 1 H), 7.15 (m, 2 H), 7.62 (m, 2 H), 7.70 (m, 2 H) ppm. ^{13}C NMR: $\delta = 43.3, 55.1, 123.0, 123.9, 125.7, 128.2, 129.8, 134.1, 137.1, 167.0$ ppm. $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$ (272.33): calcd. C 61.75, H 4.44, N 10.29; found C 61.66, H 4.22, N 10.38.

Typical Procedure for Reduction of 7a–c (Method B): This method was identical to method A except that formaldehyde was omitted. The crude product was recrystallized from ethanol.

2-(*N*-Benzylamino)phthalimide (5a): Recrystallization of the crude product obtained from **3a** afforded a colorless solid (0.35 g, 69%), m.p. 103–105 °C. IR: $\tilde{\nu}_{\text{max}} = 1712\text{ cm}^{-1}$. ^1H NMR: $\delta = 4.18$ (d, $J = 5.9$ Hz, 2 H), 4.78 (t, $J = 5.9$ Hz, 1 H, NH), 7.27 (m, 3 H), 7.42 (m, 2 H), 7.69 (m, 2 H), 7.80 (m, 2 H) ppm. ^{13}C NMR: $\delta = 55.2, 123.2, 128.0, 128.5, 129.2, 130.1, 134.2, 135.9, 166.3$ ppm. $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2$ (252.28): calcd. C 71.42, H 4.79, N 11.10; found C 71.59, H 4.68, N 11.23.

2-(Thien-2'-ylmethylamino)phthalimide (5b): Recrystallization of the crude product obtained from **3b** afforded a colorless solid (0.38 g, 74%), m.p. 159–161 °C. IR: $\tilde{\nu}_{\text{max}} = 1719\text{ cm}^{-1}$. ^1H NMR: $\delta = 4.45$ (s, 2 H), 6.83 (dd, $J = 3.5, 5.1$ Hz, 1 H), 7.00 (dd, $J = 1.0, 3.5$ Hz, 1 H), 7.18 (dd, $J = 1.0, 5.1$ Hz, 1 H), 7.60–7.71 (m, 4 H) ppm. ^{13}C NMR: $\delta = 52.9, 123.1, 126.0, 126.3, 127.3, 129.7, 134.0, 138.8, 166.8$ ppm. $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$ (258.30): calcd. C 60.45, H 3.90, N 10.85; found C 60.21, H 4.09, N 10.71.

2-(Thien-3'-ylmethylamino)phthalimide (5c): Purification of the crude product obtained from **3c** afforded a white solid (0.35 g, 68%), m.p. 132–134 °C. IR: $\tilde{\nu}_{\max}$ = 1718 cm⁻¹. ¹H NMR: δ = 4.47 (s, 2 H), 7.17 (m, 2 H), 7.21 (m, 1 H), 7.60 (m, 2 H), 7.65 (m, 2 H) ppm. ¹³C NMR: δ = 43.3, 55.1, 123.0, 123.9, 125.7, 128.2, 129.8, 134.1, 137.1, 167.0 ppm. C₁₃H₁₀N₂O₂S (258.30): calcd. C 60.45, H 3.90, N 10.85; found C 60.30, H 4.15, N 10.62.

Typical Procedure for the Synthesis of Hydroxylactams 6a–c and 7a–c: NaBH₄ (4 mmol in the cases of **4a** and **5a** or 10 mmol in the cases of **4b**, **4c**, **5b**, and **5c**) was added portionwise at 5 °C to a stirred solution of **4** or **5** (4 mmol) in methanol (40 mL). The mixture was stirred at 5 °C for 4 h and was then acidified to pH = 4 with dilute HCl. The solvent was evaporated and the residue was hydrolyzed with cold water (20 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL) and discarded. The organic layer was washed with brine, dried, and concentrated. The residue was purified by flash chromatography with cyclohexane/EtOAc (1:1) as eluent.

2-[Benzyl(methyl)amino]-3-hydroxy-2,3-dihydro-1H-isoindol-1-one (6a): The crude product obtained from **4a** was purified by flash chromatography to afford colorless needles (0.84 g, 78%), m.p. 100–102 °C. IR: $\tilde{\nu}_{\max}$ = 3320, 1665 cm⁻¹. ¹H NMR: δ = 2.77 (d, J = 6.4 Hz, 1 H, OH), 3.07 (s, 3 H), 4.29 (d, J = 12.4 Hz, 1 H), 4.47 (d, J = 12.4 Hz, 1 H), 5.24 (d, J = 6.4 Hz, 1 H), 7.20–7.29 (m, 3 H), 7.32–7.40 (m, 3 H), 7.44–7.55 (m, 2 H), 7.68–7.74 (m, 1 H) ppm. ¹³C NMR: δ = 43.6, 60.4, 82.0, 123.0, 123.2, 127.7, 128.4, 129.5, 129.7, 131.0, 132.3, 137.5, 141.6, 166.5 ppm. C₁₆H₁₆N₂O₂ (268.32): calcd. C 71.62, H 6.01, N 10.44; found C 71.79, H 5.82, N 10.29.

3-Hydroxy-2-[methyl(thien-2'-ylmethyl)amino]-2,3-dihydro-1H-isoindol-1-one (6b): This compound was obtained from **4b** and was purified by flash chromatography to afford a white solid (0.82 g, 75%), m.p. 147–149 °C. IR: $\tilde{\nu}_{\max}$ = 2991, 1713 cm⁻¹. ¹H NMR: δ = 3.05 (s, 3 H), 3.86 (d, J = 5.4 Hz, 1 H, OH), 4.36 (d, J = 13.4 Hz, 1 H), 4.74 (d, J = 13.4 Hz, 1 H), 5.38 (d, J = 5.4 Hz, 1 H), 6.82 (dd, J = 3.2, 4.9 Hz, 1 H), 6.91 (dd, J = 1.0, 3.2 Hz, 1 H), 7.16 (dd, J = 1.0, 4.9 Hz, 1 H), 7.39–7.50 (m, 3 H), 7.61–7.73 (m, 1 H) ppm. ¹³C NMR: δ = 43.4, 54.4, 82.2, 123.0, 123.5, 125.4, 126.5, 127.3, 129.6, 130.9, 132.3, 140.2, 141.1, 166.5 ppm. C₁₄H₁₄N₂O₂S (274.34): calcd. C 61.29, H 5.14, N 10.21; found C 61.55, H 5.01, N 10.05.

3-Hydroxy-2-[methyl(thien-3'-ylmethyl)amino]-2,3-dihydro-1H-isoindol-1-one (6c): The crude product obtained from **4c** was purified by flash chromatography to afford a white solid (0.82 g, 75%), m.p. 133–136 °C. IR: $\tilde{\nu}_{\max}$ = 3322, 1681 cm⁻¹. ¹H NMR: δ = 3.04 (s, 3 H), 3.70 (d, J = 7.2 Hz, 1 H, OH), 4.19 (d, J = 12.6 Hz, 1 H), 4.53 (d, J = 12.6 Hz, 1 H), 5.25 (d, J = 7.2 Hz, 1 H), 7.10–7.20 (m, 3 H), 7.36–7.54 (m, 3 H), 7.66–7.69 (m, 1 H) ppm. ¹³C NMR: δ = 43.6, 54.6, 82.1, 123.3, 124.2, 125.7, 126.1, 128.4, 129.6, 130.9, 132.3, 138.1, 141.8, 166.5 ppm. C₁₄H₁₄N₂O₂S (274.34): calcd. C 61.29, H 5.14, N 10.21; found C 61.20, H 5.05, N 10.14.

2-(Benzylamino)-3-hydroxy-2,3-dihydro-1H-isoindol-1-one (7a): The crude product obtained from **5a** was purified by flash chromatography to afford a white solid (0.75 g, 74%), m.p. 124–126 °C. IR: $\tilde{\nu}_{\max}$ = 3268, 1656 cm⁻¹. ¹H NMR: δ = 3.38 (d, J = 7.0 Hz, 1 H, OH), 4.15 (d, J = 12.4 Hz, 1 H), 4.24 (d, J = 12.4 Hz, 1 H), 4.90 (s, 1 H, NH), 5.50 (d, J = 7.0 Hz, 1 H), 7.28–7.40 (m, 5 H), 7.45–7.57 (m, 3 H), 7.68–7.76 (m, 1 H) ppm. ¹³C NMR: δ = 55.1, 82.2, 123.3, 123.5, 127.8, 128.6, 129.1, 129.8, 130.3, 132.5, 137.4,

141.8, 166.8 ppm. C₁₅H₁₄N₂O₂ (254.29): calcd. C 70.85, H 5.55, N 11.02; found C 70.77, H 5.29, N 10.87.

3-Hydroxy-2-(thien-2'-ylmethylamino)-2,3-dihydro-1H-isoindol-1-one (7b): This compound was obtained from **5b** and was purified by flash chromatography to afford a white solid (0.74 g, 71%), m.p. 158–160 °C. IR: $\tilde{\nu}_{\max}$ = 3352, 1672 cm⁻¹. ¹H NMR: δ = 2.63 (d, J = 5.9 Hz, 1 H, OH), 4.40–4.90 (m, 2 H), 5.04 (d, J = 5.9 Hz, 1 H), 6.87 (d, J = 4.0 Hz, 1 H), 6.95 (m, 1 H), 7.21 (d, J = 4.0 Hz, 1 H), 7.31–7.53 (m, 3 H), 7.73–7.77 (m, 1 H) ppm. ¹³C NMR: δ = 82.5, 82.9, 123.2, 125.6, 126.0, 126.7, 127.4, 129.6, 130.6, 132.5, 140.7, 141.6, 166.9 ppm. C₁₃H₁₂N₂O₂S (260.32): calcd. C 59.98, H 4.65, N 10.76; found C 60.11, H 4.45, N 10.55.

3-Hydroxy-2-(thien-3'-ylmethylamino)-2,3-dihydro-1H-isoindol-1-one (7c): The crude product obtained from **5c** was purified by flash chromatography to afford a white solid (0.76 g, 73%), m.p. 130–132 °C. IR: $\tilde{\nu}_{\max}$ = 3235, 1672 cm⁻¹. ¹H NMR: δ = 2.09 (d, J = 7.5 Hz, 1 H, OH), 4.10–4.75 (m, 2 H), 4.81 (d, J = 7.5 Hz, 1 H), 7.10–7.32 (m, 3 H), 7.42–7.49 (m, 3 H), 7.70–7.75 (m, 1 H) ppm. ¹³C NMR: δ = 82.5, 82.9, 123.2, 125.6, 126.0, 126.7, 127.4, 129.6, 130.6, 132.5, 140.7, 141.6, 166.9 ppm. C₁₃H₁₂N₂O₂S (260.32): calcd. C 59.98, H 4.65, N 10.76; found C 59.88, H 4.51, N 10.49.

3-Acetyloxy-2-[benzyl(methyl)amino]-2,3-dihydro-1H-isoindol-1-one (8a): DMAP (3.5 mmol) and acetic anhydride (2.5 mmol) were added under inert atmosphere to a solution of hydroxylactam **6a** (2.3 mmol) in CH₂Cl₂ (25 mL). The mixture was stirred at room temperature for 20 h and was then washed successively with 20 mL saturated aqueous NaHCO₃, water, 5% HCl and water. After drying, the solvent was evaporated and purification of the residue by column chromatography with a CH₂Cl₂/acetone mixture (98:2) as eluent gave a white solid (0.55 g, 77%), m.p. 86–88 °C. IR: $\tilde{\nu}_{\max}$ = 1726 cm⁻¹. ¹H NMR: δ = 2.08 (s, 3 H), 2.97 (s, 3 H), 4.24 (d, J = 12.5 Hz, 1 H), 4.50 (d, J = 12.5 Hz, 1 H), 6.60 (s, 1 H), 7.22–7.36 (m, 5 H), 7.45–7.52 (m, 3 H), 7.71–7.77 (m, 1 H) ppm. ¹³C NMR: δ = 21.1, 42.7, 60.5, 81.7, 123.1, 123.7, 127.5, 128.3, 129.1, 130.1, 131.2, 132.5, 137.3, 139.6, 167.1, 170.8 ppm. C₁₈H₁₈N₂O₃ (310.36): calcd. C 69.66, H 5.85, N 9.03; found C 69.79, H 5.69, N 9.17.

3-Acetyloxy-2-(benzylamino)-2,3-dihydro-1H-isoindol-1-one (9a): This compound was obtained from **7a** by the same procedure as described above. Purification of the residue by column chromatography with a CH₂Cl₂/acetone mixture (98:2) as eluent gave a white solid (0.48 g, 71%), m.p. 90–92 °C. IR: $\tilde{\nu}_{\max}$ = 1713 cm⁻¹. ¹H NMR: δ = 2.05 (s, 3 H), 4.13 (dd, J = 5.5, 11.7 Hz, 1 H), 4.26 (dd, J = 5.5, 11.7 Hz, 1 H), 5.83 (t, J = 5.5 Hz, 1 H), 6.82 (s, 1 H), 7.26–7.43 (m, 5 H), 7.45–7.57 (m, 3 H), 7.78–7.80 (m, 1 H) ppm. ¹³C NMR: δ = 21.0, 55.0, 81.5, 123.4, 123.9, 127.6, 128.5, 129.1, 130.5, 132.8, 137.1, 139.6, 167.1, 170.7 ppm. C₁₇H₁₆N₂O₃ (296.33): calcd. C 68.91, H 5.44, N 9.45; found C 69.17, H 5.59, N 9.58.

6-Methyl-5,12b-dihydroisoindolo[1,2-a]phthalazin-8-one (10a): SnCl₄ (5.7 mmol) was added dropwise under inert conditions to a solution of **8a** (1.9 mmol) in CH₂Cl₂ (20 mL) and the mixture was heated at reflux for 24 h. The reaction was quenched with saturated aqueous NaHCO₃ (20 mL) and the organic layer was washed twice with water (20 mL). After drying, the solvent was evaporated, and purification of the residue by flash column chromatography with a CH₂Cl₂/acetone mixture (95:5) as eluent gave a white solid (0.31 g, 65%), m.p. 94–96 °C. IR: $\tilde{\nu}_{\max}$ = 1698 cm⁻¹. ¹H NMR: δ = 2.53 (s, 3 H), 3.46 (d, J = 16.5 Hz, 1 H), 4.14 (d, J = 16.5 Hz, 1 H), 5.40 (s, 1 H), 6.72–6.78 (m, 1 H), 6.86–7.19 (m, 3 H), 7.22–7.43 (m, 2 H), 7.53–7.57 (m, 2 H) ppm. ¹³C NMR: δ = 41.5, 50.9, 55.2,

122.8, 123.3, 124.9, 126.6, 127.0, 127.1, 127.8, 128.9, 130.4, 130.9, 131.6, 142.5, 165.8 ppm. $C_{16}H_{14}N_2O$ (250.30): calcd. C 76.78, H 5.64, N 11.19; found C 76.59, H 5.69, N 11.31.

5,12b-Dihydro-6H-isoidolo[1,2-a][2,3]phthalazin-8-one (11a): This compound was obtained from **9a** by the same procedure as described above. After purification, a white solid (0.26 g, 58%) was obtained, m.p. 200–202 °C. IR: $\tilde{\nu}_{\max}$ = 1678 cm^{-1} . 1H NMR: δ = 3.96 (d, J = 15.7 Hz, 1 H), 4.34 (d, J = 15.7 Hz, 1 H), 5.73 (s, 1 H), 7.07 (m, 1 H), 7.16–7.22 (m, 1 H), 7.26–7.35 (m, 1 H), 7.41–7.50 (m, 1 H), 7.55–7.70 (m, 2 H), 7.81–7.87 (m, 2 H) ppm. ^{13}C NMR: δ = 49.8, 57.9, 123.2, 124.0, 126.0, 127.0, 127.3, 128.6, 131.2, 132.2, 132.7, 132.8, 143.5, 167.2 ppm. $C_{15}H_{12}N_2O$ (236.28): calcd. C 76.25, H 5.12, N 11.86; found C 76.37, H 5.27, N 11.72.

5-Methyl-4,11b-dihydrothieno[3',2':4,5]pyridazino[3,2-a]isoidol-7-one (12b): A solution of hydroxylactam **6b** (2 mmol) and a catalytic amount of PTSA in CH_2Cl_2 (15 mL) was heated at reflux for 8 h. After cooling, the solution was washed with diluted $NaHCO_3$ (15 mL) and water (15 mL) and then dried with Na_2SO_4 . The solvent was evaporated and the residue was recrystallized from ethanol to give a white solid (0.42 g, 82%), m.p. 181–183 °C. IR: $\tilde{\nu}_{\max}$ = 1697 cm^{-1} . 1H NMR: δ = 2.87 (s, 3 H), 3.93 (d, J = 15.3 Hz, 1 H), 4.51 (d, J = 15.3 Hz, 1 H), 5.71 (s, 1 H), 7.25 (m, 2 H), 7.42–7.49 (m, 1 H), 7.57–7.64 (m, 1 H), 7.69–7.76 (m, 1 H), 7.86–7.92 (m, 1 H) ppm. ^{13}C NMR: δ = 42.7, 52.5, 52.7, 123.1, 123.7, 124.4, 128.6, 130.4, 130.5, 130.7, 132.3, 142.5, 166.6 ppm. $C_{14}H_{12}N_2OS$ (256.33): calcd. C 65.60, H 4.72, N 10.93; found C 66.33, H 4.55, N 11.09.

5-Methyl-4,11b-dihydrothieno[2',3':4,5]pyridazino[3,2-a]isoidol-7-one (12c): The same procedure as described above, starting from **6c**, gave a white solid (0.44 g, 85%), m.p. 178–180 °C. IR: $\tilde{\nu}_{\max}$ = 1693 cm^{-1} . 1H NMR: δ = 2.97 (s, 3 H), 3.83 (d, J = 16.7 Hz, 1 H), 4.37 (d, J = 16.7 Hz, 1 H), 5.80 (s, 1 H), 6.80 (d, J = 5.4 Hz, 1 H), 7.24 (d, J = 5.4 Hz, 1 H), 7.41–7.51 (m, 1 H), 7.57–7.66 (m, 1 H), 7.68–7.74 (m, 1 H), 7.85–7.90 (m, 1 H) ppm. ^{13}C NMR: δ = 43.1, 51.6, 53.9, 122.8, 123.3, 124.2, 124.6, 125.6, 128.8, 130.4, 130.8, 132.4, 142.6, 166.3 ppm. $C_{14}H_{12}N_2OS$ (256.33): calcd. C 65.60, H 4.72, N 10.92; found C 66.45, H 4.49, N 10.69.

5-(Thien-2-ylmethyl)-4,11b-dihydrothieno[3',2':4,5]pyridazino[3,2-a]isoidol-7-one (13b): A solution of hydroxy lactam **7b** (2 mmol) in TFA (12 mL) was stirred at room temperature for 7 h. After evaporation of the acid, the residue was dissolved in CH_2Cl_2 (10 mL), washed with saturated aqueous $NaHCO_3$ (12 mL) and water (12 mL), and then dried with Na_2SO_4 . The solvent was evaporated and the residue was recrystallized from ethanol to give a white solid (0.28 g, 82%), m.p. 178–180 °C. IR: $\tilde{\nu}_{\max}$ = 1694 cm^{-1} . 1H NMR: δ = 4.01 (dd, J = 1.0, 16.1 Hz, 1 H), 4.13 (d, J = 13.7 Hz, 1 H), 4.27 (d, J = 13.7 Hz, 1 H), 4.41 (dd, J = 2.4, 16.1 Hz, 1 H), 5.66 (s, 1 H), 6.83 (d, J = 5.2 Hz, 1 H), 7.23–7.34 (m, 3 H), 7.40–7.48 (m, 1 H), 7.54–7.70 (m, 3 H), 7.78–7.86 (m, 1 H) ppm. ^{13}C NMR: δ = 50.6, 52.3, 52.7, 123.2, 124.1, 124.8,

124.9, 126.0, 126.3, 126.4, 128.5, 130.0, 130.4, 131.4, 132.4, 140.2, 142.9, 165.4 ppm. $C_{18}H_{14}N_2OS_2$ (338.45): calcd. C 63.88, H 4.17, N 8.28; found C 64.14, H 4.26, N 8.02.

5-(Thien-3-ylmethyl)-4,11b-dihydrothieno[2',3':4,5]pyridazino[3,2-a]isoidol-7-one (13c): The same procedure as described above, starting from **7c**, gave a white solid (0.29 g, 85%), m.p. 184–186 °C. IR: $\tilde{\nu}_{\max}$ = 1693 cm^{-1} . 1H NMR: δ = 4.00 (dd, J = 1.3, 16.7 Hz, 1 H), 4.17 (d, J = 13.4 Hz, 1 H), 4.27 (d, J = 13.4 Hz, 1 H), 4.40 (dd, J = 2.4, 16.7 Hz, 1 H), 5.65 (s, 1 H), 6.82 (d, J = 5.1 Hz, 1 H), 7.22–7.34 (m, 4 H), 7.38–7.48 (m, 1 H), 7.54–7.69 (m, 2 H), 7.80–7.89 (m, 1 H) ppm. ^{13}C NMR: δ = 52.0, 52.5, 54.0, 122.6, 122.9, 124.2, 124.8, 125.2, 125.7, 126.1, 127.6, 128.8, 130.7, 130.8, 132.3, 136.7, 142.6, 166.7 ppm. $C_{18}H_{14}N_2OS_2$ (338.45): calcd. C 63.88, H 4.17, N 8.28; found C 63.76, H 4.15, N 8.25.

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