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

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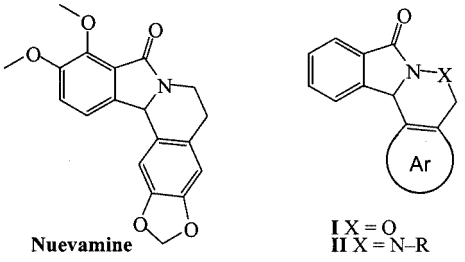
Hydroxylactams **6a**–**c** and **7a**–**c** were synthesized by successive regioselective reductions of arylideneaminophthalimides **3a**–**c**, which were easily available from aminophthalimide **1** and benzaldehyde (**2a**) or thiophenecarboxaldehydes **2b** and **2c**. *N*-Acylhydrazonium ions **III**, 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**.

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]

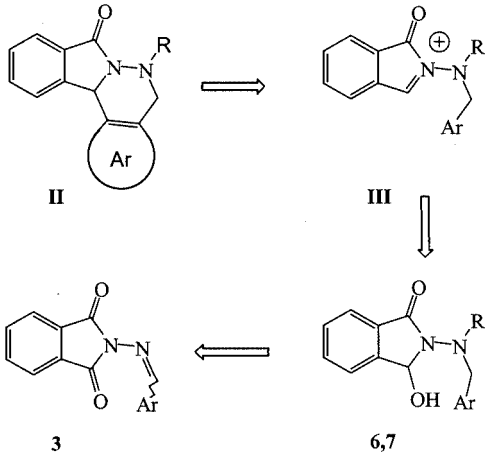


Scheme 1

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 diphthalazinediones, 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*-acylhydrazoniums ions **III** under acidic conditions,[8] ring closure could occur through an in-



Scheme 2

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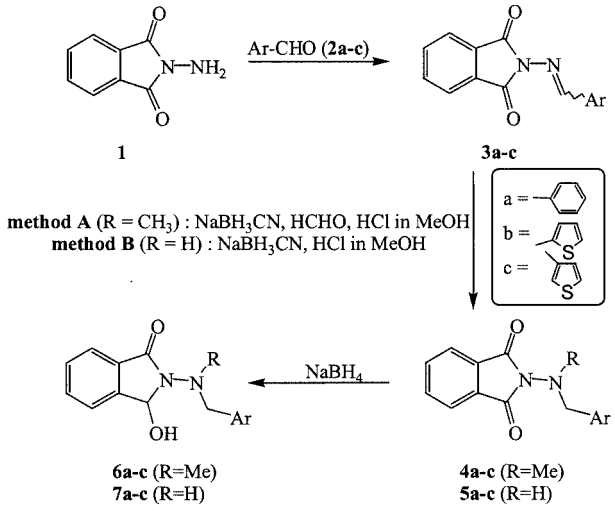
tramolecular α-heteroamido-alkylation reaction to provide **II**.

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%.

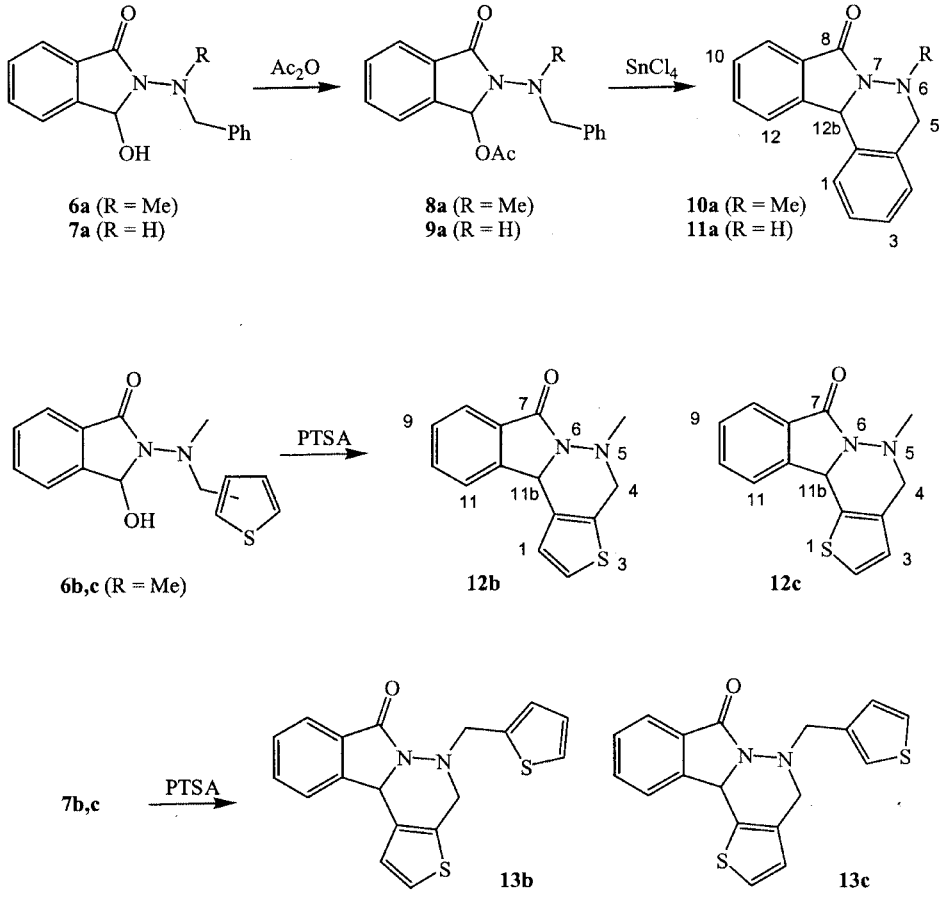


Scheme 3

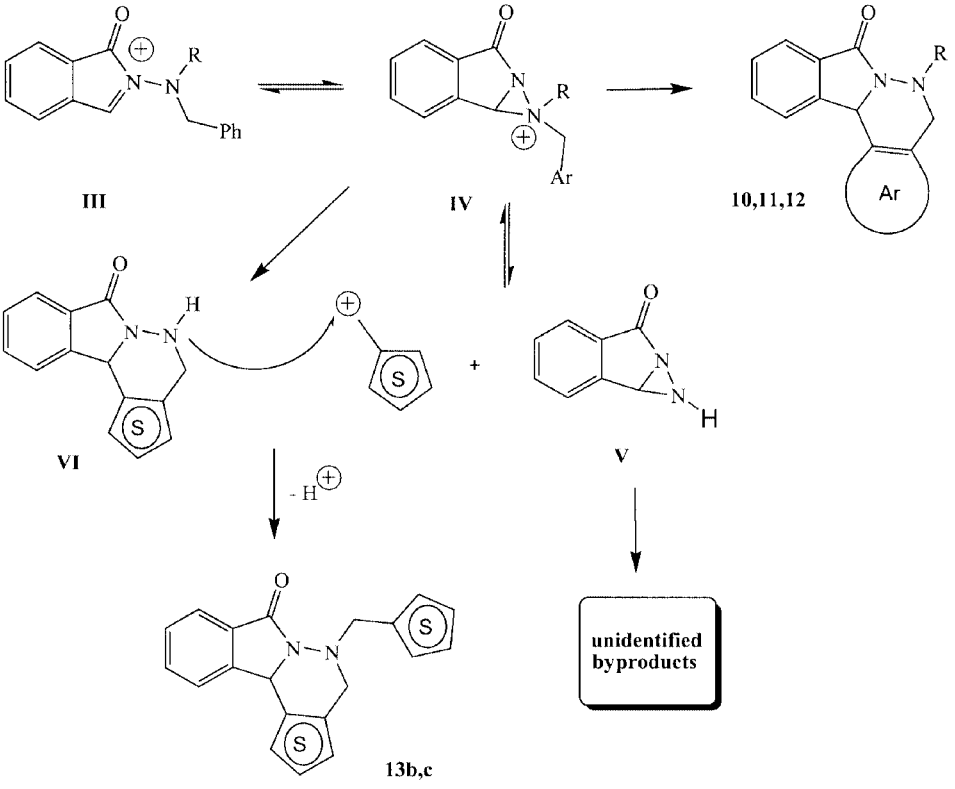
Cyclization of compounds **6** and **7** in acidic medium takes place through the generation of *N*-acylhydrazonium ions, which react with the aromatic systems. Actually, previous investigations into the production of *N*-acyliminium ions in our laboratory have shown that various organic acids such as *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 $\delta = 5.7-5.8$, 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 $J = 15-17$ 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 ^{1}H 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** ([D_6]DMSO), and chemical shifts (δ) are expressed in ppm relative to residual $CHCl_3$ at δ = 7.27 for ^{1}H and δ = 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: $\tilde{\nu}_{max}$ = 1775 cm^{-1}. ^{1}H NMR: δ = 7.45 (m, 3 H), 7.76 (m, 2 H), 7.90 (m, 4 H), 9.38 (s, 1 H) ppm. ^{13}C NMR: δ = 123.7, 128.3, 128.7, 130.2, 131.6, 133.5, 134.6, 158.5, 165.0 ppm. $C_{15}H_{10}N_2O_2$ (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: $\tilde{\nu}_{max}$ = 1729 cm^{-1}. ^{1}H NMR: δ = 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: δ = 123.7, 127.6, 130.3, 130.6, 132.9, 134.6, 138.5, 152.7, 164.9 ppm. $C_{13}H_8N_2O_2S$ (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: $\tilde{\nu}_{max}$ = 1721 cm^{-1}. ^{1}H NMR: δ = 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: δ = 123.7, 125.3, 126.8, 130.3, 130.6, 134.5, 137.1, 153.6, 165.0 ppm. $C_{13}H_8N_2O_2S$ (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, portionwise) 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 (CH_2Cl_2/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: $\tilde{\nu}_{max}$ = 1776 cm^{-1}. ^{1}H NMR: δ = 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: δ = 43.3, 60.6, 123.1, 127.7, 128.3, 129.1, 129.9, 134.1, 136.3, 167.1 ppm. $C_{16}H_{14}N_2O_2$ (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: $\tilde{\nu}_{max}$ = 1722 cm^{-1}. ^{1}H NMR: δ = 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: δ = 43.3, 54.5, 123.1, 126.0, 126.3, 127.3, 129.9, 138.7, 166.9 ppm. $C_{14}H_{12}N_2O_2S$ (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: $\tilde{\nu}_{max}$ = 1714 cm^{-1}. ^{1}H NMR: δ = 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: δ = 43.3, 55.1, 123.0, 123.9, 125.7, 128.2, 129.8, 134.1, 137.1, 167.0 ppm. $C_{14}H_{12}N_2O_2S$ (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: $\tilde{\nu}_{max}$ = 1712 cm^{-1}. ^{1}H NMR: δ = 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: δ = 55.2, 123.2, 128.0, 128.5, 129.2, 130.1, 134.2, 135.9, 166.3 ppm. $C_{15}H_{12}N_2O_2$ (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: $\tilde{\nu}_{max}$ = 1719 cm^{-1}. ^{1}H NMR: δ = 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: δ = 52.9, 123.1, 126.0, 126.3, 127.3, 129.7, 134.0, 138.8, 166.8 ppm. $C_{13}H_{10}N_2O_2S$ (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. ^{13}C NMR: δ = 43.3, 55.1, 123.0, 123.9, 125.7, 128.2, 129.8, 134.1, 137.1, 167.0 ppm. $C_{13}H_{10}N_2O_2S$ (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: $NaBH_4$ (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 CH_2Cl_2 (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-1*H*-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. ^{13}C 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. $C_{16}H_{16}N_2O_2$ (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-1*H*-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. ^{13}C 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. $C_{14}H_{14}N_2O_2S$ (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-1*H*-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. ^{13}C 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. $C_{14}H_{14}N_2O_2S$ (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-1*H*-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. ^{13}C 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. $C_{15}H_{14}N_2O_2$ (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-1*H*-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. ^{13}C 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. $C_{13}H_{12}N_2O_2S$ (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-1*H*-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. ^{13}C 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. $C_{13}H_{12}N_2O_2S$ (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-1*H*-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 CH_2Cl_2 (25 mL). The mixture was stirred at room temperature for 20 h and was then washed successively with 20 mL saturated aqueous $NaHCO_3$, water, 5% HCl and water. After drying, the solvent was evaporated and purification of the residue by column chromatography with a CH_2Cl_2/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. ^{13}C 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. $C_{18}H_{18}N_2O_3$ (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-1*H*-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 CH_2Cl_2/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. ^{13}C 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. $C_{17}H_{16}N_2O_3$ (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): $SnCl_4$ (5.7 mmol) was added dropwise under inert conditions to a solution of **8a** (1.9 mmol) in CH_2Cl_2 (20 mL) and the mixture was heated at reflux for 24 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (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 CH_2Cl_2/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. ^{13}C 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-6*H*-isoindolo[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*]isoindol-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*]isoindol-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*]isoindol-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*]isoindol-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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