Synthesis of Isoindolo[1,3]benzoxazine Derivatives Through Intramolecular Arylation of *N*-Acyliminium Ions

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[1,3]Benzoxazines annulated to isoindole as **3** and **4** have been synthesized in three steps from *N*-chloromethylphthalimide **5** and substituted phenols **6**. The key step was the acid-catalyzed cyclization of ω-carbinol lactams **8** and **9**.

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Aromatic π-cyclization reactions initiated by several types of *N*-acyliminium ions have been proven to be a potential tool for the C-C bond construction in organic synthesis [1a,b], and the reaction leads to diverse heterocyclic systems containing a pyrrolizidine, indolizidine or a quinolizidine moiety [2a,b]. Prominent examples of these structures like the Praziquantel **1A**, the thieno-derivatives **1B,C** and the alkaloïd Nuevamine **2** exhibit respectively higher potent schistosomicide [3] and most potential CNS activity [4].

If a large variety of quinolizidine derivatives analogous to Nuevamine have been intensively investigated, the [1,3]benzodiazine annulated to pyrrolidine [5,6] or isoindole [7,8] are sparsely explored and to our knowledge no work has been done on the chemistry of [1,3]benzothiazines or [1,3]benzoxazines fused to isoindole or pyrroli-

Chart I

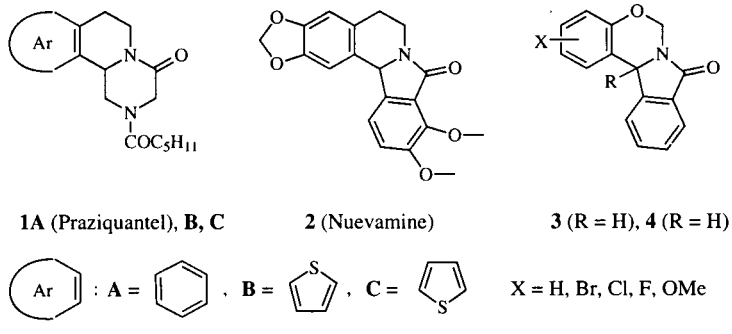
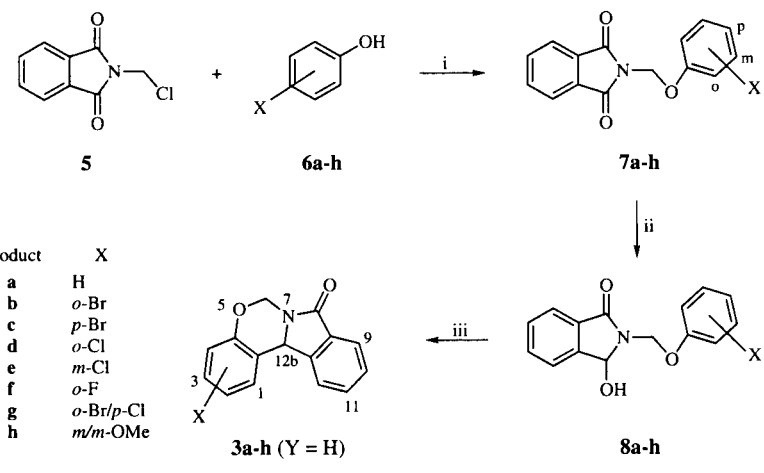


Chart II

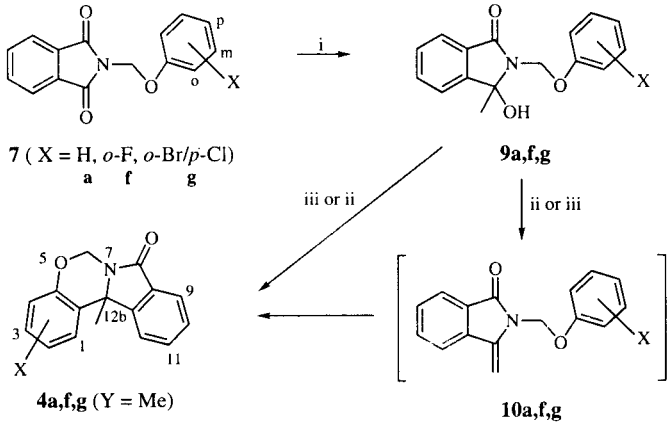


i) MeONa, Dimethylformamide or Dimethyl sulfoxide, rt, 12 hours; ii) $NaBH_4$, MeOH, 0-5°, 20 minutes to 1 hour; iii) Trifluoracetic acid, rt, 12 hours

dine rings. At the present time, only one example of an [1,3]oxazine fused to a saturated isoindole and various substituted cyclohexanes is reported in the literature [9]. Thus, in view of our interest on the synthesis of new diversely *N,O*-fused heterocyclic systems, we wish to describe herein an interesting short pathway to some substituted [1,3]benzoxazines annulated to an isoindole moiety as **3** (R = H) and **4** (R = Me).

As depicted in Chart I, the *N*-alkylated imides **7a-h** were obtained by condensation of *N*-chloromethylphthalimide (**5**) [10] with the commercially available substituted phenols **6a-h** with sodium methylate as a base in dry *N,N*-dimethylformamide or dimethyl sulfoxide at room temperature overnight (36 to 61% yields). These compounds were then submitted to reduction and addition reactions in order to study the influence of steric and electronic effects in both the reduction-addition and cyclization steps. Reduction reactions were carried out with 5 equivalents of sodium borohydride in dry methanol at 0-5° for 20 minutes to 1 hour (the reaction was monitored by tlc using silica gel and dichloromethane) and it did not need addition of acid as reported earlier for related compounds [11]; the resulting ω-carbinol lactams **8a-h** were isolated in good yields (79 to 98%). On the other hand, the addition of a Grignard reagent (methylmagnesium iodide) [12] to **7a,f,g** occurred with yields of about 95%. At this stage, the nature and the cyclization reaction occurred invariably on the two free *ortho* positions to give 1-chloro and 3-chloro-6,12b-dihydroisoindolo[2,1-*c*][1,3]benzoxazine **3e** and **3e'** in a 5.2/4.8 ratio with an overall yield of 88%. This mixture was separated by chromatography on silica gel column using dichloromethane as the eluting solvent. On the other hand, **9a,f,g** treated with trifluoroacetic acid furnished the cyclized products **4a,f,g** associated with considerable degradation in the cases of **4f** and **4g**. Furthermore, when the experimental conditions were changed using *p*-toluenesulfonic acid with toluene as the solvent in a Dean-Stark apparatus, the reaction led to the same cyclization products with a comparable yield for **4a** (70%) but lower yields for **4f** and **4g** (25%). These results indicates that only the nature of X influences the cyclization reaction (X = H or X = halogen). This reaction provides a new example of π-aromatic-*N*-acyliminium cyclizations resulting in a nitrogen-oxygen containing a 6-membered ring. It is interesting to note that in the case of **9a,f,g**, we have never isolated the methylidenephthalimidine **10** in the reaction mixture regardless of the experimental conditions used such as, pyridine-acetic anhydride under reflux or *p*-toluenesulfonic acid in dichloromethane at room temperature, in contrast to the results observed for similar structures [13,14]. This methylidenephthalimidine **10** which resulted from the dehydration reaction could be considered as an

Chart III



7 (X = H, *o*-F, *o*-Br/*p*-Cl)
a f g

9a,f,g

4a,f,g (Y = Me)

10a,f,g

i) MeMgI, diethyl ether, rt, 3 hours, H_2O; ii) Trifluoroacetic acid, rt, 12 hours;
iii) *p*-Toluenesulfonic acid, Toluene, reflux, 3 hours.

position of the substituant X attached to the benzene ring, the steric and electronic effects of the hydride ion and the carbon of methylmagnesium iodide used as the nucleophile did not affect both reactions.

Because of the small body of literaure on *N*-aryloxomethylamidals regarding the reactivity of this functionality in acidic medium, the ω-carbinol lactams **8a-h** were subjected to trifluoroacetic acid at room temperature, and led exclusively to the title substituted isoindolo[1,3]benzoxazines **3a-h**. In the case of the *m*-chloro derivative **7e**, excellent precursor to fused nitrogen-oxygen heterocyclic products containing a 7-membered ring by the Heck or by a radical cyclization reaction.

The structures of **3** and **4** were assigned on the basis of their ir and nmr (^1H and ^{13}C) spectra as well as by their microanalyses. For 1-chloroisoindolo[1,3]benzoxazine **3e** and the positional isomer 3-chloroisoindolo[1,3]benzoxazine **3e'**, a HETCOR and NOE DIFFERENCE programs were necessary to complete identification and determination of these structures. Thus, in the ^1H nmr spectra of **3a-h** and **4a,f,g** the

methylene protons (-O-CH_2-N) appear as an AB system due to the diastereotopic effect with a coupling constant of about 16 Hz characteristic of *gem* protons. Furthermore, the key feature in the ^{13}C nmr spectra of **3** and **4** was the appearance of thirteen signals for **3** and **4** in the aromatic region. Moreover, one of these resonances disappears in the corresponding DEPT program spectra, as a consequence of the intramolecular α-amidoalkylation cyclization.

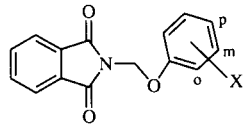
The present work reports a general methodology for the synthesis of [1,3]benzoxazines annulated to an isoindole moiety starting from *N*-chloromethylphthalimide and a substituted phenol by π-aromatic attack on the *N*-acyliminium ion as an internal electrophile, the cyclization process easily gives a 6-membered ring.

EXPERIMENTAL

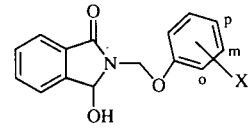
All melting points were determined using a Leitz hot plate apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer FT-IR paragon 1000 spectrometer. The nuclear magnetic resonance spectra (^1H and ^{13}C) were taken on a Bruker AC-200 (200 MHz) instrument in the solvent indicated. Chemical shifts values are reported in ppm from tetramethylsilane as an internal reference and are given in δ units and the following abbreviations are used: s for singlet, d for doublet, dd for doublet of doublets, br for broad, and finally m for multiplet. Elemental analyses were obtained in the microanalysis laboratory of the I.N.S.A at Rouen, F 76130 Mt.-St.-Aignan. Thin layer chromatography was performed on precoated plates of silica gel 60F 254 (Merck) and the spots visualized using an ultraviolet

Table 1

Yields and Physical Data of Imides **7a-h** and Hydroxylactams **8a-h**



7a-h



8a-h

Product No.	X	Position	mp°C	Yield % [a]	Formula	Analyses Calcd./Found C%	H%	N%
7a	H	–	141	36	$C_{15}H_{11}NO_3$	71.14	4.38	5.53
					(253.26)	71.34	4.17	5.63
7b	Br	*o*	192	51	$C_{15}H_{10}BrNO_3$	54.24	3.03	4.22
					(332.15)	54.17	3.29	4.32
7c	Br	*p*	143	57	$C_{15}H_{10}BrNO_3$	54.24	3.03	4.22
					(332.15)	54.31	3.09	4.06
7d	Cl	*o*	200	67	$C_{15}H_{10}ClNO_3$	62.62	3.50	4.87
					(287.70)	62.51	3.45	4.77
7e	Cl	*m*	132	52	$C_{15}H_{10}ClNO_3$	62.62	3.50	4.87
					(287.70)	62.34	3.41	4.98
7f	F	*o*	162	53	$C_{15}H_{10}FNO_3$	66.42	3.72	5.53
					(273.26)	66.16	3.66	5.45
7g	Br/Cl	*o/p*	172	61	$C_{15}H_9BrClNO_3$	49.15	2.47	3.82
					(366.60)	49.09	2.39	3.74
7h	OMe	*m/m*	167	58	$C_{17}H_{15}NO_5$	65.17	4.83	4.47
					(313.31)	65.22	4.69	4.29
8a	H	–	137	96	$C_{15}H_{13}NO_3$	70.58	5.13	5.59
					(255.27)	70.49	5.04	5.54
8b	Br	*o*	197	84	$C_{15}H_{12}BrNO_3$	53.92	3.62	4.19
					(334.17)	53.79	3.47	4.02
8c	Br	*p*	131	80	$C_{15}H_{12}BrNO_3$	53.92	3.62	4.19
					(334.17)	53.83	3.49	4.06
8d	Cl	*o*	182	92	$C_{15}H_{12}ClNO_3$	62.19	4.18	4.84
					(289.72)	62.08	4.10	4.55
8e	Cl	*m*	151	79	$C_{15}H_{12}ClNO_3$	62.19	4.17	4.83
					(289.72)	61.93	4.25	4.77
8f	F	*o*	157	98	$C_{15}H_{12}FNO_3$	65.93	4.43	5.13
					(273.26)	66.01	4.21	5.06
8g	Br/Cl	*o/p*	171	96	$C_{15}H_{11}BrClNO_3$	48.88	3.01	3.80
					(368.61)	48.69	2.89	3.58
8h	OMe	*m/m*	100	65	$C_{17}H_{17}NO_5$	64.75	5.43	4.44
					(315.32)	64.62	5.29	4.18

[a] All compounds were purified by recrystallization from anhydrous alcohol.

Table II

IR and ^1H NMR Data of Imides **7a-h** and Hydroxylactams **8a-h**

Product No.	X	IR (potassium bromide) OH	ν cm^{-1} C=O	^1H NMR Data (Deuteriochloroform/tetramethylsilane, internal) δ ppm; J = Hz
7a	H	-	1714	5.03 (s, 2H, CH_2-O), 7.26 (m, 3H, benzene), 7.28 (m, 2H, benzene), 7.74 (m, 2H, phthalimide), 7.90 (m, 2H, phthalimide)
7b	*o*-Br	-	1715	5.62 (s, 2H, CH_2-O), 6.91 (m, 1H, benzene), 7.24 (m, 2H, benzene), 7.49 (m, 1H, benzene), 7.77 (m, 2H, phthalimide), 7.88 (m, 2H, phthalimide)
7c	*p*-Br	-	1721	5.57 (s, 2H, CH_2-O), 6.92 (d, 2H, J = 9, benzene), 7.32 (d, 2H, J = 9, benzene), 7.72 (m, 2H, phthalimide), 7.84 (m, 2H, phthalimide)
7d	*o*-Cl	-	1716	5.68 (s, 2H, CH_2-O), 6.98 (m, 1H, benzene), 7.21 (m, 2H, benzene), 7.32 (m, 1H, benzene), 7.76 (m, 2H, phthalimide), 7.89 (m, 2H, phthalimide)
7e	*m*-Cl	-	1725	5.62 (s, 2H, CH_2-O), 6.98 (dd, 2H, J = 2.2, 7.8, benzene), 7.08 (t, 1H, J = 2.2, benzene), 7.18 (d, 1H, J = 7.8, benzene), 7.71 (m, 2H, phthalimide), 7.89 (m, 2H, phthalimide)
7f	*o*-F	-	1728	5.66 (s, 2H, CH_2-O), 7.02 (m, 2H, benzene), 7.15 (m, 2H, benzene), 7.75 (m, 2H, phthalimide), 7.88 (m, 2H, phthalimide)
7g	*o*-Br, *p*-Cl	-	1732	5.65 (s, 2H, CH_2-O), 7.23 (m, 2H, benzene), 7.49 (d, 1H, J = 2, benzene), 7.77 (m, 2H, phthalimide), 7.90 (m, 2H, phthalimide)
7h	*m,m*-OMe	-	1724	3.75 (s, 6H, Me), 5.62 (s, 2H, CH_2-O), 6.11 (t, 1H, J = 1, benzene), 6.28 (d, 2H, J = 1, benzene), 7.75 (m, 2H, phthalimide), 7.91 (m, 2H, phthalimide)
8a [a]	H	3302	1678	5.25 (d, 1H, J = 10.2, CH_2), 5.52 (d, 1H, J = 10.2, CH_2), 5.98 (s, 1H, CH), 6.89 (m, 3H, benzene), 7.20 (d, 1H, J = 8.2, phthalimide), 7.5 (m, 4H, phthalimide + benzene), 7.70 (d, 1H, J = 8.2, phthalimide)
8b	*o*-Br	3314	1689	5.29 (d, 1H, J = 10, CH_2), 5.86 (d, 1H, J = 10, CH_2), 6.01 (d, 1H, J = 9, CH), 6.72 (d, 1H, J = 9, OH), 6.81 (m, 1H, benzene), 7.23 (m, 2H benzene), 7.43 (m, 2H, phthalimide + benzene), 7.59 (m, 2H, phthalimide), 7.73 (m, 1H, phthalimide)
8c [a]	*p*-Br	3439	1693	5.17 (d, 1H, J = 10.4, CH_2), 5.50 (d, 1H, J = 10.4, CH_2), 5.94 (s, 1H, CH), 6.85 (d, 2H, J = 8.6, benzene), 7.30 (d, 2H, J = 8.6, phthalimide), 7.48 (m, 1H, phthalimide), 7.58 (m, 2H, phthalimide), 7.68 (d, 1H, J = 7.3, phthalimide)
8d	*o*-Cl	3309	1684	5.27 (d, 1H, J = 10, CH_2), 5.81 (d, 1H, J = 10, CH_2), 6.57 (s, 1H, CH), 6.99 (m, 1H, benzene), 7.28 (m, 1H, benzene), 7.40 (m, 2H, benzene), 7.70 (m, 3H, phthalimide), 7.91 (m, 1H, phthalimide)
8e [a]	*m*-Cl	3322	1690	5.24 (d, 1H, J = 10.2, CH_2), 5.71 (d, 1H, J = 10.2, CH_2), 5.91 (s, 1H, CH), 6.89 (m, 2H, benzene), 7.01 (m, 1H, benzene), 7.14 (m, 1H, benzene), 7.46 (m, 1H, phthalimide), 7.56 (m, 2H, phthalimide), 7.69 (m, 1H, phthalimide)
8f	*o*-F	3304	1684	3.60 (d, 1H, J = 10.5, OH), 5.30 (d, 1H, J = 10.2, CH_2), 5.61 (d, 1H, J = 10.1, CH_2), 6.05 (d, 1H, J = 10.5, CH), 6.98 (m, 3H, benzene), 7.17 (d, 1H, J = 7.9, phthalimide), 7.50 (m, 1H, benzene), 7.61 (m, 2H, phthalimide), 7.71 (d, 1H, J = 7.9, phthalimide)
8g	*o*-Br, p-Cl	3368	1692	3.36 (d, 1H, J = 10, OH), 5.51 (d, 1H, J = 11, CH_2), 5.77 (d, 1H, J = 11, CH_2), 6.07 (d, 1H, J = 10, CH), 7.37 (m, 1H, benzene), 7.47 (m, 1H, benzene), 7.52 (m, 1H, benzene), 7.64 (m, 3H, phthalimide), 7.78 (m, 1H, phthalimide)
8h	*m,m*-OMe	3349	1686	3.70 (s, 6H, Me), 5.17 (d, 1H, J = 10, CH_2), 5.49 (d, 1H, J = 10, CH_2), 5.65 (s, 1H, CH), 6.0 (t, 1H, J = 2, benzene), 6.18 (d, 2H, J = 2, benzene), 7.51 (m, 1H, phthalimide), 7.61 (m, 2H, phthalimide), 7.71 (m, 1H, phthalimide)

[a] The ^1H nmr spectra of these products were recorded in dimethyl-d_6 sulfoxide with tetramethylsilane as the internal standard.

Table III

Yields, Physical, IR and ^1H NMR Data of Isoindolo[1,3]benzoxazines **3a-h**

Product No.	X	Position	mp°C	Yield %	Formula	Analyses Calcd./Found C%	H%	N%
3a	H	-	122	86	$C_{15}H_{11}NO_2$ (237.25)	75.94 75.78	4.67 4.52	5.90 5.69
3b	Br	2	131	84	$C_{15}H_{10}BrNO_2$ (316.15)	56.99 57.05	3.19 3.05	4.43 4.36
3c	Br	4	173	82	$C_{15}H_{10}BrNO_2$ (316.15)	56.99 56.88	3.19 3.10	4.43 4.29
3d	Cl	4	160	68	$C_{15}H_{10}ClNO_2$ (271.70)	66.31 66.25	3.71 3.49	5.16 4.99

Table III (continued)

Yields, Physical, IR and ^{1}H NMR Data of Isoindolo[1,3]benzoxazines **3a-h**

Product No.	X	Position	mp°C	Yield %	Formula	Analyses Calcd./Found C%	H%	N%
3e	Cl	1	171	46	$C_{15}H_{10}ClNO_2$ (271.70)	66.31 66.21	3.71 3.60	5.16 5.10
3e'	Cl	3	164	42	$C_{15}H_{10}ClNO_2$ (271.70)	66.31 66.19	3.71 3.66	5.16 5.03
3f	F	4	89	91	$C_{15}H_{10}FNO_2$ (255.25)	70.58 70.39	3.95 3.86	5.49 5.37
3g	Br/Cl	4/2	191	78	$C_{15}H_9BrClNO_2$ (350.60)	51.39 51.18	2.59 2.42	4.00 3.89
3h	OMe	1/3	154	20	$C_{17}H_{15}NO_4$ (297.31)	68.68 68.52	5.09 5.01	4.71 4.59

Product	X	IR (Potassium bromide/ C=O) ν cm^{-1}	^{1}H-NMR Data (Deuteriochloroform/tetramethylsilane, internal) δ ppm; J = Hz
3a	H	1686	4.57 (d, 1H, J = 16.8, CH_2), 5.18 (d, 1H, J = 16.8, CH_2), 5.96 (s, 1H, CH), 7.02 (m, 2H, benzene), 7.19 (d, 2H, J = 7.3, benzene), 7.62 (m, 2H, phthalimide), 7.75 (d, 1H, J = 6.6, phthalimide), 7.88 (d, 1H, J = 6.6, phthalimide)
3b	2-Br	1709	4.45 (d, 1H, J = 17.1 ,CH_2),5.07 (d, 1H, J = 17.1, CH_2), 5.86 (s, 1H, CH), 6.79 (d, 2H, J = 9.4, Bz), 7.22 (d, 1H, J = 9.4, benzene), 7.53 (m, 3H, phthalimide), 7.8 (d, 1H, J = 7.8, phthalimide)
3c	4-Br	1701	4.56 (d, 1H, J = 17, CH_2), 5.18 (d, 1H, J = 17, CH_2), 6 (s, 1H, CH), 6.91 (t, 1H, J = 7.5, 7.8, benzene), 7.14 (d, 1H, J = 7.5, benzene), 7.45 (d, 1H, J = 7.8, benzene), 7.63 (m, 2H, phthalimide), 7.80 (m, 2H, phthalimide)
3d	4-Cl	1732	4.54 (d, 1H, J = 17, CH_2), 5.16 (d, 1H, J = 17, CH_2), 5.98 (s, 1H, CH), 7.0 (m, 2H, benzene), 7.19 (m, 1H, benzene), 7.62 (m, 2H, phthalimide), 7.82 (m, 2H, phthalimide)
3e	1-Cl	1732	4.52 (d, 1H, J = 17, CH_2), 5.15 (d, 1H, J = 17, CH_2), 5.95 (s, 1H, CH), 7.0 (m, 2H, benzene), 7.11 (m, 1H, benzene), 7.61 (m, 3H, phthalimide), 7.87 (m, 1H, phthalimide)
3e'	3-Cl	1733	4.48 (d, 1H, J = 18, CH_2), 5.19 (d, 1H, J = 18, CH_2), 5.92 (s, 1H, CH), 6.9 (m, 1H, benzene), 7.12 (m, 2H, benzene), 7.65 (m, 3H, phthalimide), 7.86 (m, 1H, phthalimide)
3f	4-F	1696	4.56 (d, 1H, J = 17.1, CH_2), 5.2 (d, 1H, J = 17.1, CH_2), 6 (s, 1H, CH), 6.97 (m, 3H, benzene), 7.59 (m, 2H, phthalimide), 7.85 (m, 2H, phthalimide)
3g	4-Br, 2-Cl	1724	4.52 (d, 1H, J = 17, CH_2), 5.18 (d, 1H, J = 17, CH_2), 5.98 (s, 1H, CH), 7.14 (m, 1H, benzene), 7.45 (m, 1H, benzene), 7.61 (m, 2H, phthalimide), 7.83 (m, 2H, phthalimide)
3h	1,3-OMe	1717	3.65 (s, 6H, Me), 5.11 (d, 1H, J = 17, CH_2), 5.44 (d, 1H, J = 17, CH_2), 5.97 (s, 1H, CH), 6.14 (s, 1H, benzene), 6.58 (m, 1H, benzene), 7.42 (m, 1H, phthalimide), 7.54 (m, 2H, phthalimide), 7.62 (m, 1H, phthalimide)

lamp or iodine vapor. E. Merck silica gel 60F (70-300 mesh) was used for column chromatography. The starting material **5** was prepared by the procedure reported in the literature [10].

General Procedure for *O*-Alkylation of Substituted Phenols **6a-h**.

To a cooled and stirred solution of substituted phenol **6** (25 mmoles) in dry *N,N*-dimethylformamide or dimethyl sulfoxide (40 ml) was added solid sodium methylate (1.62 g, 30 mmoles). After stirring for 30 minutes, *N*-chloromethylphthalimide (**5**) (4.89 g, 25 mmoles) in dry *N,N*-dimethylformamide or dimethyl sulfoxide (50 ml) was added slowly dropwise over a period of 20 minutes. The mixture was then stirred for 24 hours under a nitrogen atmosphere at room temperature and poured into ice-water. The resulting white precipitate was filtered, dried and then recrystallized from anhydrous ethanol. All the physical and chemical constants of these products are summarized in Tables I and II.

General Procedure for Reduction of Imides **7a-h** (R = H).

To a stirred solution of *N*-alkylated imide **7** (12.6 mmoles) in dry methanol (20 ml) was added slowly in portions sodium borohydride (2.38 g, 63 mmoles) at 0-5° over a period of 10 minutes. After 20 minutes to 1 hour of reaction (the reaction was monitored by tlc). The excess sodium borohydride was destroyed by adding cold water (10 ml) then diluted hydrochloric acid (10%) at 0-5° to *p*H 3. After removal of the solvent, the residue was diluted with water (45 ml) and extracted with dichloromethane. The organic layers were washed with saturated brine, dried over sodium sulfate and evaporated *in vacuo*. The oily residue after trituration with diethyl ether was recrystallized from dry ethanol to give ω-carbinol lactams **8**. All of the physical and chemical constants of these products are summarized in Tables I and II.

General Procedure for the Synthesis of ω-Methyl-ω-carbinol Lactams **9** (R = Me).

To a stirred solution of (22.2 mmoles) of methylmagnesium iodide (prepared by classical procedure from magnesium (0.54 g, 22.2 g-atoms) and methyl iodide (3.15 g, 22.2 mmoles)) in 120 ml of dry diethyl ether was added dropwise *N*-alkylated phthalimides **7a,f,g** (4.5 mmoles) in 100 ml of dry dichloromethane-diethyl ether over a period of 10 minutes. After 3 hours of reaction at room temperature, the reaction mixture was poured into a

solution of 20% ammonium chloride (100 ml) and decanted. The organic phase was washed with water, brine, dried and concentrated *in vacuo*. The resulting solid was purified by recrystallization from dry ethanol to give **9**.

2,3-Dihydro-3-hydroxy-3-methyl-2-(phenyloxomethyl)-1*H*-isoindol-1-one (**9a**).

This product was obtained from **7a** as white crystals in 98% yield, mp 122°; ir: ν 3326 (br, O-H), 1686 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.71 (s, 3H, Me), 4.29 (s, 1H, OH), 5.23 (s, 2H, N-CH_2-O), 6.91 (m, 3H, benzene), 7.20 (m, 1H, benzene), 7.41 (m, 1H, benzene), 7.55 (m, 2H, phthalimide), 7.65 (m, 1H, phthalimide), 7.77 (m, 1H, phthalimide).

Anal. Calcd. for $C_{16}H_{15}NO_3$ (269.30): C, 71.36; H, 5.61; N, 5.20. Found: C, 71.19; H, 5.35; N, 5.15.

2,3-Dihydro-3-hydroxy-3-methyl-2-(*o*-fluorophenyloxomethyl)-1*H*-isoindol-1-one (**9f**).

This compound was isolated from **7f** as colorless solid in 97% yield, mp 113°; ir: ν 3335 (br, O-H), 1691 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.77 (s, 3H, CH_3), 4.15 (s, 1H, OH), 5.27 (s, 2H, O-CH_2-N), 6.91 (m, 2H, benzene), 7.04 (m, 2H, benzene), 7.44 (m, 1H, phthalimide), 7.63 (m, 3H, phthalimide).

Anal. Calcd. for $C_{16}H_{14}FNO_3$ (287.29): C, 66.89; H, 4.91; N, 4.88. Found: C, 66.81; H, 4.78; N, 4.77.

2,3-Dihydro-3-hydroxy-3-methyl-2-(*o*-bromo-*p*-chlorophenyloxomethyl)-1*H*-isoindol-1-one (**9g**).

This compound was isolated from **7g** as colorless solid in 93% yield, mp 146°; ir: ν 3314 (br, O-H), 1671 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.77 (s, 3H, CH_3), 4.40 (s, 1H, OH), 5.26 (s, 2H, O-CH_2-N), 7.03 (m, 1H, benzene), 7.16 (m, 1H, benzene), 7.44 (m, 2H, phthalimide), 7.58 (m, 3H, benzene + phthalimide).

Anal. Calcd. for $C_{16}H_{13}BrClNO_3$ (382.64): C, 50.22; H, 3.42; N, 3.66. Found: C, 50.09; H, 3.39; N, 3.49.

General Procedure for the Synthesis of Isoindolo[1,3]benzoxazines **3a-h** (R = H).

To a stirred solution of hydroxylactam **8a-h** (6 mmoles) was added trifluoroacetic acid (10 ml). After 24 hours of reaction at room temperature, the reaction mixture was diluted with water (50 ml) and neutralized with 10% aqueous sodium hydroxide. The organic layer was separated, washed with water (50 ml), dried and concentrated *in vacuo*. The resulting crude white solid was purified (separated in case of **3e**) by chromatography on a silica gel column eluting with dichloromethane or by recrystallization from suitable solvent and gave the expected tetracyclic products **3**. All physical and spectral data of compounds **3** are summarized in Table III.

General Procedure for the Synthesis of Isoindolo[1,3]benzoxazines **4a,f,g** (R = Me).

To a stirred solution of hydoxylactam **9a**, **9f** or **9g** (10 mmoles) in dry toluene (150 ml) was added 0.2 g of *p*-toluenesulfonic acid. After 3 hours at reflux (Dean Stark apparatus), the reaction mixture was cooled and evaporated under reduced pressure. The resulting oily residue was diluted with dichloromethane (50 ml) and neutralized with 5% aqueous sodium hydroxide (50 ml). The organic layer was separated, washed with water (50 ml), dried and concentrated *in vacuo* to give after chromatography on a silica gel column eluting with dichloromethane and recrystallization from dry ethanol the expected tricyclic product **4a**, **4f** or **4g**.

6,12b-Dihydro-12b-methylisoindolo[2,1-*c*][1,3]benzoxazin-8-one (**4a**).

This product was obtained from **9a** as a white solid in 70% yield, mp 148°; ir: ν 1716 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.78 (s, 3H, CH_3), 4.44 (d, 1H, J = 17 Hz, N-CH_2-O), 5.27 (d, 1H, J = 17 Hz, N-CH_2-O), 7.04 (m, 1H, benzene), 7.18 (m, 2H, benzene), 7.61 (m, 1H, benzene), 7.70 (m, 2H, phthalimide), 7.85 (m, 2H, phthalimide); ^{13}C nmr (deuteriochloroform): δ 21 (CH_3), 40.3 (CH_2), 87.8 (C), 117.9 (CH), 122.1 (CH), 126.9 (CH), 128.4 (CH), 129.3 (C), 130.1 (CH), 130.2 (CH), 132.4 (CH), 132.6 (C), 133.2 (CH), 145.3 (C), 150.9 (C), 168.2 (CO).

Anal. Calcd. for $C_{16}H_{13}NO_2$ (251.28): C, 76.48; H, 5.21; N, 5.57. Found: C, 76.34; H, 5.09; N, 5.39.

4-Fluoro-6,12b-dihydro-12b-methylisoindolo[2,1-*c*][1,3]benzoxazin-8-one (**4f**).

This product was obtained similarly from **9f** in a yield of 20%, mp 178°; ir: ν 1689 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 1.82 (s, 3H, CH_3), 4.43 (d, 1H, J = 17 Hz, N-CH_2-O), 5.29 (d, 1H, J = 17 Hz, N-CH_2-O), 6.94 (m, 2H, benzene), 7.08 (m, 1H, benzene), 7.58 (m, 2H, phthalimide), 7.83 (m, 2H, phthalimide); ^{13}C nmr (deuteriochloroform): δ 21.1 (CH_3), 36.5 (CH_2), 88.3 (C), 114.8 (CH), 115.1 (CH), 120.1 (C), 121.8 (CH), 122.2 (CH), 124.1 (CH), 130.3 (CH), 130.8 (C), 132.7 (CH), 144.9 (C), 149.6 (C), 154.5 (C), 166.1 (CO).

Anal. Calcd. for $C_{16}H_{12}FNO_2$ (269.27): C, 71.37; H, 4.49; N, 5.20. Found: C, 71.18; H, 4.28; N, 5.22.

4-Bromo-2-chloro-6,12b-dihydro-12b-methylisoindolo[2,1-*c*]-[1,3]benzoxazin-8-one (**4g**).

This product was obtained similarly from **9g** in a yield of 25%, mp 220°; ir: ν 1724 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.79 (s, 1H, Me), 4.79 (d, 1H, J = 17 Hz, N-CH_2-O), 5.77 (d, 1H, J = 17 Hz, N-CH_2-O), 7.49 (m, 2H, benzene), 7.60 (m, 1H, phthalimide), 7.78 (m, 2H, phthalimide), 7.90 (m, 1H, phthalimide); ^{13}C nmr (deuteriochloroform): δ 26.9 (CH_3), 63.7 (C), 68.2 (CH_2), 121.4 (CH), 123.7 (CH), 124.7 (CH), 125.2 (C), 127.3 (C), 128.2 (C), 128.9 (CH), 130.7 (C), 132.4 (CH), 133.3 (CH), 138.4 (C), 149.9 (C), 167.3 (CO).

Anal. Calcd. for $C_{16}H_{11}BrClNO_2$ (364.62): C, 52.70; H, 3.04; N, 3.84. Found: C, 52.56; H, 3.00; N, 3.77.

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