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INTRAMOLECULAR ADDITION OF A HYDROXYL TO A *N*-ACYL-IMINIUM SYSTEM. APPLICATION TO THE SYNTHESIS OF ISOINDOLO-[2,1-*a*][3,1]BENZOXAZINE AND ISOINDOLO[1,2-*c*][2,4] BENZOXAZEPINE DERIVATIVES

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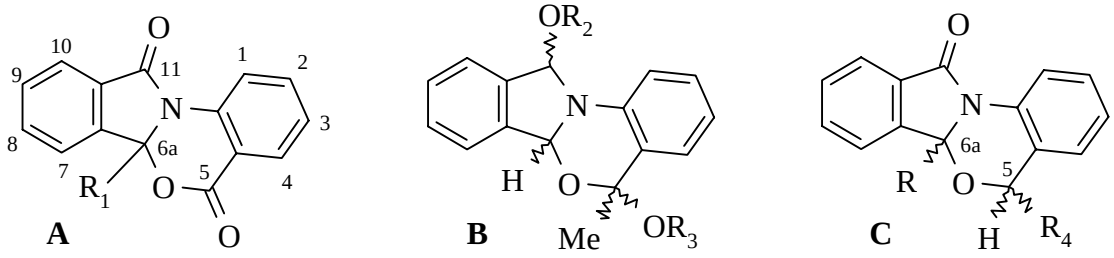
Abstract - The titled compounds were prepared by the reaction of hydroxylated lactam (**3a-c)** or (**10)** with *p*-toluenesulfonic acid in dichloromethane. The ratio of diastereomeric mixtures (**4b**/**5b** (2/1) or **4c**/**5c** (2/1) or **11**/**12** (5/1)) is discussed.

The isoindolo[2,1-*a*][3,1]benzoxazines and their derivatives are known heterocycles. The most of them have been synthesized from anthranilic acid or the corresponding ester. Condensation of these starting materials with 2-acyl(or formyl)benzoic acids[1-5] or phthalic anhydride[6] gave isoindolo[2,1-*a*][3,1]-benzoxazine-5,11-diones (**A)** diversely substituted (R_1 = H, OH, Me, C_6H_5, *p*-$MeOC_6H_4$, …). More recently,[7] the Baeyer-Villiger oxidation of the 1*H*-isoindolo[2,1-*a*]indole-11-carboxaldehyde led to a mixture of **A** (R = H, 34%) accompanied by the 10b-hydroxy-10b*H*-isoindolo[2,1-*a*]indole-5,11-dione.

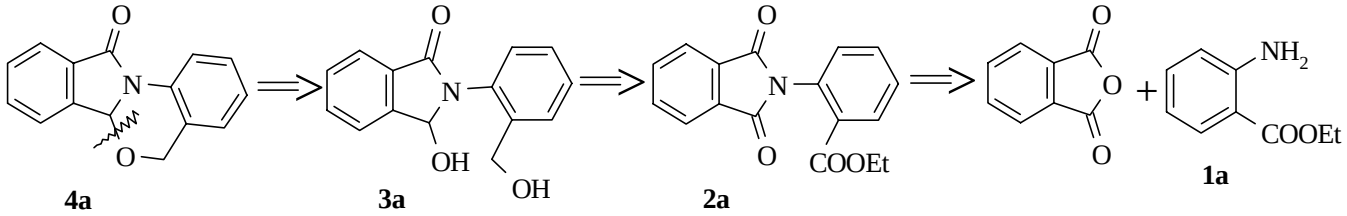


All of these derivatives are 5,11-diones and to our knowledge only one report[8] described the preparation (from phthalaldehyde and substituted acetophenones) of isoindolo[2,1-*a*][3,1]benzoxazines (**B)** substituted at C_5 and/or C_{11}. Furthermore, they were obtained in a relatively poor yield (25 to 35%) and accompanied with two other products and without stereocontrol of the reaction. From these results we wish to report that the reaction of an appropriated hydroxylated lactam with an acid offers a convenient

synthetic route for obtaining a variety of isoindolo[2,1-*a*][3,1]benzoxazines **C** with two chiral carbons C_5 and C_{6a}. A generalization of that cyclization is illustrated by the synthesize of isoindolo[1,2-*c*][2,4]-benzoxazepine derivatives **11** and **12**.

This tetracyclic system (**C)**, after retrosynthetic analysis, could be the result of the formation of carbon-oxygen bond using *N*-acyliminium ion-nucleophilic heteroatom. It is well known that hydroxylactam can give a substitution product[9] under an acid catalyst in the presence of a nucleophile *via* a *N*-acyliminium ion. We recently reported the use of sulfur or nitrogen atom as a nucleophile.[10-12] Althought glycolic acid or its ester did not react[10] under these conditions the oxygen atom has already been used as nucleophile.[13-15] Thus it was reasonable to investigate the reaction depicted in Scheme 1.

Scheme 1

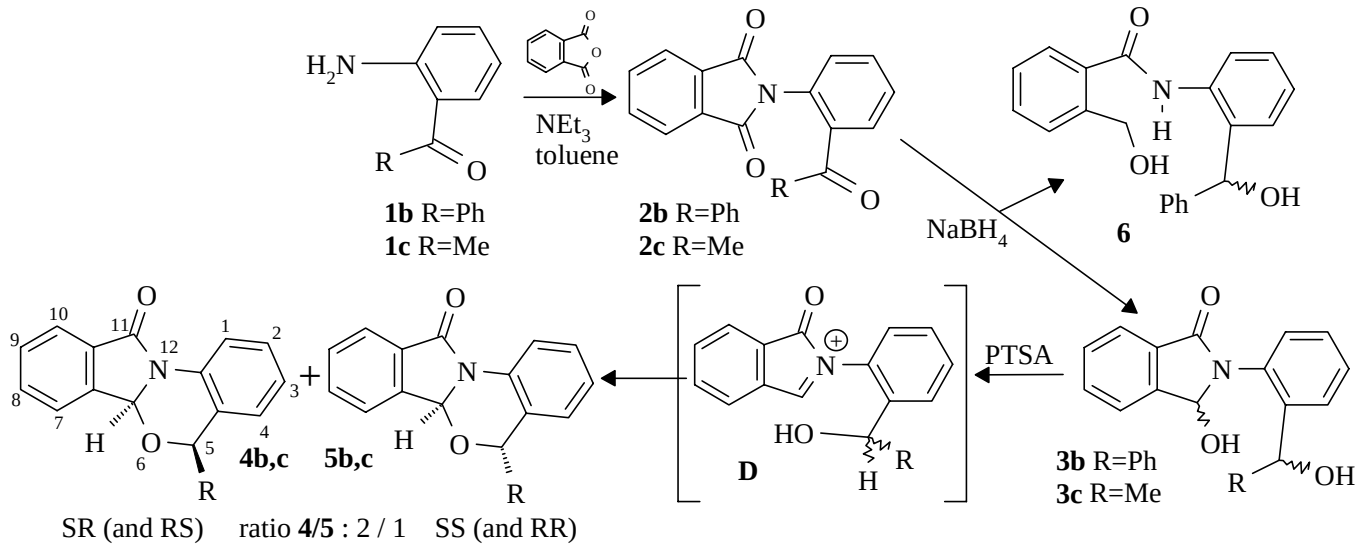


When ethyl anthranilate (**1a)** was allowed to react with phthalic anhydride in refluxing toluene, known compound (**2a)**[16] was obtained. This imide-ester (**2a)** was reduced with sodium borohydride into hydroxylactam-alcohol (**3a)** accompanied with the opened compound. Interestingly the reduction occurred on both the imide function and the ester function. The direct reduction with sodium borohydride of the ester function was rather unexpected. Actually, under the same conditions the ester function of the 2-(2-methoxycarbonylbenzyl)phthalimide did not react.[11] The proximity of the hydroxyl group obtained after reduction of the imide (**2a)** seems to favor the attack of the ester function by the sodium borohydride. The opened compound (similar to **6**) was easily separated from the mixture by solubilisation in cold dichloromethane. Consequently the insoluble hydroxylactam-alcohol (**3a)** was treated with a catalytic amount of *p*-toluenesulfonic acid in dichloromethane. The isoindolo[2,1-*a*][3,1]benzoxazine (**4a)** was obtained as a racemic mixture in a quantitative yield.

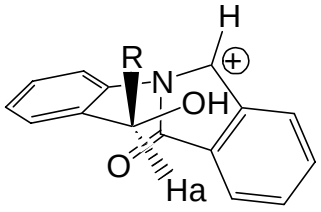
Since the reaction of a *N*-acyliminium ion with a π-nucleophile is stereocontrolled[9] we considered a similar reaction with chiral alcohol (**3b)** (R = Ph) and (**3c)** (R = Me) as nucleophiles (Scheme 2). Condensation of 2-aminobenzophenone (**1b)** with phthalic anhydride in boiling toluene in the presence of triethylamine furnished the known phthalimide (**2b)**.[17] Sodium borohydride reduction of **2b** gave the expected hydroxylactam-alcohol (**3b)** as a 2/1 diastereomeric mixture (racemic form) accompanied by the opened compound (**6)**. The latter was the single product when the reaction time was extended. A further acid treatment (*p*-toluenesulfonic acid in dichloromethane at room temperature) of the mixture afforded the isoindolo[2,1-*a*][3,1]benzoxazinones (**4b)** and (**5b)** *via* the *N*-acyliminium ion (**D)** (R = Ph) as a 2/1

diastereomeric mixture (racemic). The ratio was determined by analysis of the crude product mixture by ^{1}H NMR (200 MHz) spectroscopy. They were separated by single recrystallization from ethanol.

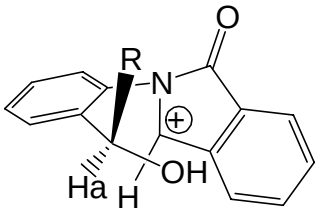
Scheme 2



Spectral analysis (NOE difference experiments) showed that the relative stereochemistry of the major diastereomer (**4b)** exhibits a *cis* relationship between H_5 and H_{6a}. Furthermore, the proton H_{6a} was shifted to lower field in **4b** (δ H_{6a} = 6.18 ppm) than in **5b** (δH_{6a} = 5.79 ppm) due to the anisotropic effect of the phenyl group. A similar shift has been observed with oxazolopiperidones.[15] This stereoselectivity was rationalized in terms of a chair like transition state. In the intermediate **E** the phenyl group prefers a pseudo-equatorial orientation and the oxygen atom reacts with the carbocation. This conformation minimizes the interaction between the axial hydrogen Ha and the five membered ring in constast to the **F** conformation. Furthermore, it is interesting to note that the *N*-acyliminium ion-aromatic cyclization did not occur since the possible isoindolo[2,1-*a*] dibenzo[*c*,*f*]azepine was not observed.



F



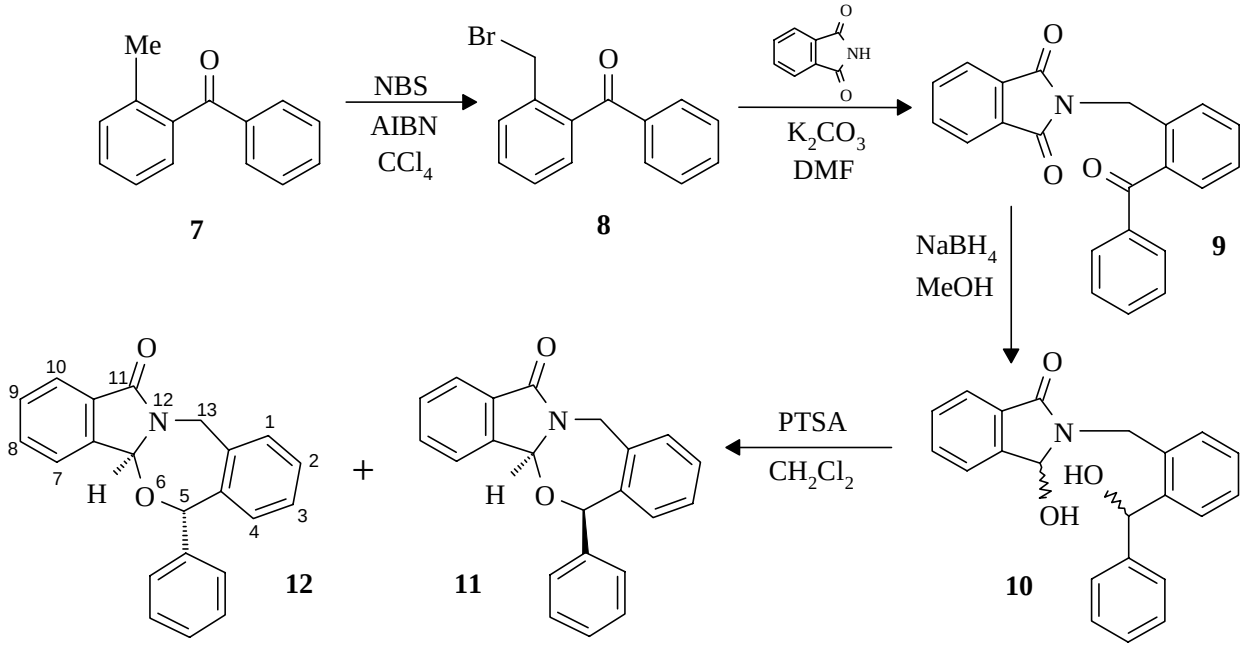
E

An identical approach was tested for the preparation of **4c** and **5c**. Actually, it has been reported[18] that the condensation of *o*-aminoacetophenone (**1c)** with phthalic anhydride gave a mixture of the phthalimide (**2c)** and an isoindoloquinolinedione. That mixture was dependent on the conditions of the reaction.

In a similar manner as above, the hydroxylactam (**3c)** *via* the *N*-acyliminium ion (**D)** (R =Me) led to a 2/1 diastereomeric mixture of **4c** and **5c**. The major diastereomer was found to be **4c** after analysis of the

NMR spectral data. For both **4c** and **5c** the proton H_5 is now a quadruplet due to the presence of the methyl group. In contrast to the phenyl derivatives (**4b)** and (**5b)**, the chemical shifts of protons H_{6a} are very close, 5.24 and 5.34 ppm for **4c** and **5c** respectively. The diastereoselectivity of the reaction can be explained by the same way than for **4b**/**5b**. As above, only the hydroxyl group acted as a nucleophile. Actually, the possible dehydration of the alcohol (**3c)** into the styrene derivative acting as a π-nucleophile leading to an isoindolo[2,1-*a*]quinoline has not been observed.

Scheme 3



A generalization of that reaction is illustrated in Scheme 3. 2-Bromomethylbenzophenone (**8)** was prepared from the 2-methylbenzophenone (**7)** by a standard method – treatment with *N*-bromo-succinimide in the presence of catalytic amount of azobisisobutyronitrile. In the following step, reaction with phthalimide gave 2-(*N*-phthalimidomethyl)benzophenone (**9)** in 77% yield calculated from **7**. Ketone (**9)** was first synthetized by Veber[19] by acylation of the phenyl group of *N*-methylphenylphthalimide. Diastereoselective reduction of ketone (**9)** with sodium borohydride in methanol gave the expected mixture of diols (**10)**. Analysis of the crude reaction mixture of diastereomers (**10)** by ^{1}H NMR spectroscopy established their ratio to be 5/1. Upon standing 20 min the solution (DMSO-d_6) of diastereomers underwent isomerisation to equilibrium ratio 1/1.

It is remarkable that the cyclization of this mixture in mild catalytic medium of *p*-toluenesulfonic acid, led to the formation of isoindolo[1,2-*c*][2,4]benzoxazepine (**11**/**12)** in the same unchanged ratio 5/1 (*cis/trans*). This mixture was separated by flash column chromatography and the separated *trans* diastereomer was underwent the NMR experiment. After standing in solution of $CDCl_3$ and PTSA (catalytic), the equilibrium *cis/trans* ratio 2/1 was determined. The relative configuration of *trans* and *cis*

isomers was established by ^{1}H NMR spectrum, two dimensional NMR spectroscopy spectra and NOE experiments. Based on the large NOE enhancement between H_5 (6.16 ppm) and H_{6a} (6.31 ppm) protons, the relative configuration of the chiral centers at positions C_5 and C_{6a} of **11** has been determined as *cis*. Similarly to **4b** and **5b**, the NMR signal of proton H_{6a} of *trans* isomer (**12)** (6.13 ppm) was shifted to higher field when compared with the corresponding proton in the *cis* isomer (**11)** (6.31 ppm).

In conclusion, this paper reports an efficient entry into stereoselectively 5-substituted isoindolo-[2,1-*a*][3,1]benzoxazinones and 5-substituted isoindolo[1,2-*c*][2,4]benzoxazepinones.

EXPERIMENTAL

Melting points are uncorrected. The IR spectra of solids (potassium bromide) were recorded on a Perkin Elmer FTIR paragon 1000 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz) instrument in deuterochloroform solution unless otherwise noted and chemical shifts (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. MS spectral measurements were recorded on a MS 902 S spectrometer. Phthalimides (**2b)**[17] and **(2c)**[18] were prepared as indicated in literature.

2-(2-Ethoxycarbonylphenyl)phthalimide (2a).

A solution of phthalic anhydride (8.9 g, 60 mmol), triethylamine (200 mmol) and ethyl *o*-aminobenzoate (**1a)** (9.9 g, 60 mmol) in toluene (60 mL) was refluxed for 24 h in a flask fitted with a Dean-Stark apparatus. The mixture was cooled to rt and was concentrated under reduced pressure. Recrystallization of the residue from ethanol afforded the corresponding phthalimide (**2a)** (17.3 g, 98%) and mp: 105-106 °C. This compound has been described from a suitable anilide derivative[16] mp:106° C (80%).

2,3-Dihydro-3-hydroxy-2-[2-hydroxymethylphenyl]-1*H*-isoindol-1-one (3a).

To a mixture of phthalimide (**2a)** (1.18 g, 4 mmol) in dry methanol (40 mL) at 10 °C was added sodium borohydride (0.9 g, 24 mmol) by portions. To this mixture were added 5 drops of ethanolic hydrochloric acid solution [prepared from 9 drops of concentrated hydrochloric acid in ethanol (15 mL)] at regular intervals (10 min). The reaction was monitored by TLC. The excess of sodium borohydride was decomposed by careful addition of cold water (15 mL) and 10 % hydrochloric acid. Sodium hydrogen carbonate was added and the solvent was evaporated. The residue was triturated with water and the solid was separated by filtration, washed with water, dried and triturated with dichloromethane. The residue was separated by filtration and was recrystallized from acetone to furnish pure **3a** (0.61 g, 60%), mp 158

°C; IR: 3265 (OH), 1679 (C=O) cm^{-1}; ^1H NMR: δ 3.17 (br s, 1 H, OH), 4.12 (br s, 1 H, OH), 4.45 (d, *J* = 12 Hz, 1 H, CH_2), 4.54 (d, *J* = 12 Hz, 1 H, CH_2), 6.19 (s, 1 H, CH), 7.22-7.68 (m, 7 H, H_{arom}), 7.85 (d, *J* = 7 Hz, 1 H, H_{arom}); ^{13}C NMR: δ 59.4 (CH_2), 83.8 (CH), 122.9 (2CH), 123.8 (CH), 127.2 (2CH), 127.8 (CH), 129.6 (CH), 131.1 (C), 132.5 (CH), 133.8 (C), 141.2 (C), 145.4 (C), 165.5 (CO); MS (EI, 70 ev) *m/z*: 255 ($M^{+\cdot}$ 20%), 237 ($M^{+\cdot}$- H_2O 100%), 219 (53%), 209 (95%), 180 (47%), 133 (48%), 122 (89%), 105 (91%). Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.36; H, 5.04; N, 5.55.

2,3-Dihydro-3-hydroxy-2-[2-hydroxyphenylmethylphenyl]-1*H*-isoindol-1-one (3b).

This compound was prepared in a yield of 74% as a 2/1 ratio of diastereomers, from phthalimide (**2b)** as described for reduction of **2a** into **3a**. The crude product was chromatographed (silica gel – chloroforme/acetone 10/2) to furnish pure **3b** as a 2/1 ratio of isomers. IR: 3323 (OH), 1663 (C=O) cm^{-1}.

Major isomer: ^1H NMR (DMSO-d_6): δ 5.93 (s, 1 H, OH), 6.43 (s, 1 H, CH), 6.50 (s, 1 H, CH), 6.75 (s, 1 H, OH), 6.74 (d, *J* = 8 Hz, 1 H, H_{arom}), 7.05-7.93 (m, 11 H, $H_{arom.}$), 8.39 (d, *J* = 8 Hz, 1 H, H_{arom}); ^{13}C NMR: δ 69.0 (CH), 84.0 (CH), 123.0 (CH), 123.9 (CH), 126.1 (2CH), 126.5 (CH), 127.0 (CH), 127.8 (2CH), 127.9 (CH), 128.3 (CH), 128.9 (CH), 129.6 (CH), 131.0 (C), 132.6 (CH), 134.4 (C), 143.9 (C), 144.4 (C), 145.4 (C), 166.8 (CO).

Minor isomer: ^1H NMR (DMSO-d_6): δ 5.93 (s, 1 H, OH), 6.42 (s, 1 H, CH), 6.50 (s, 1 H, CH), 6.75 (s, 1 H, OH), 6.74 (d, *J* = 8 Hz, 1 H, H_{arom}), 7.05-7.93 (m, 11 H, $H_{arom.}$), 8.39 (d, *J* = 8 Hz, 1 H, H_{arom}); ^{13}C NMR: δ 68.9 (CH), 83.9 (CH), 123.9 (CH), 124.4 (CH), 127.1 (2CH), 127.8 (CH), 127.8 (CH), 128.5 (2CH), 128.7 (CH), 129.3 (CH), 129.3 (CH), 129.5 (CH), 132.1 (C), 133.3 (CH), 135.7 (C), 144.7 (C), 144.8 (C), 145.0 (C), 166.8 (CO).

2,3-Dihydro-3-hydroxy-2-[2-(1-hydroxyethyl)phenyl]-1*H*-isoindol-1-one (3c).

This compound was prepared in a yield of 80% as a 2/1 ratio of diastereomers, from phthalimide (**2c)** as described for reduction of **2a** into **3a**. IR: 1711 (C=O), 3403 (OH) cm^{-1}; MS (EI, 70 ev) *m/z*: 251 ($M^{+\cdot}$- H_2O) (85%), 236 (55%), 208 (38%), 180 (18%), 136 (49%), 133 (41%), 116 (28%), 118 (34%), 105 (100%).

Major isomer: ^1H NMR (DMSO-d_6): δ 1.32 (d, *J* = 6 Hz, 3 H, CH_3), 4.63 (br s, 1 H, OH), 4.88 (q, *J* = 7 Hz, 1 H, CH), 6.13 (d, *J* = 9 Hz, 1 H, CH), 6.72 (d, *J* = 9 Hz, 1 H, OH), 7.31-7.35 (m, 3 H, $H_{arom.}$), 7.69-7.78 (m, 5 H, $H_{arom.}$); ^{13}C NMR: δ 24.2 (CH_3), 63.4 (CH), 83.5 (CH), 122.4 (CH), 123.3 (CH), 126.0 (CH), 126.8 (CH), 127.7 (CH), 129.0 (2CH), 130.8 (C), 132.0 (CH), 133.3 (C), 145.1 (C), 145.4 (C), 165.9 (CO).

Minor isomer: ^1H NMR (DMSO-d_6): δ 1.35 (d, *J* = 6 Hz, 3 H, CH_3), 4.74 (q, *J* = 6 Hz, 1 H, CH), 4.75 (br s, 1 H, OH), 6.21 (d, *J* = 9 Hz, 1 H, CH), 6.66 (d, *J* = 9 Hz, 1 H, OH), 7.38-7.46 (m, 3 H, $H_{arom.}$), 7.58-7.66 (m, 5 H, $H_{arom.}$); ^{13}C NMR: δ 24.4 (CH_3), 63.6 (CH), 84.1 (CH), 122.4 (CH), 123.3 (CH), 126.1 (CH), 126.8 (CH), 127.7 (CH), 129.1 (2CH), 130.9 (C), 132.0 (CH), 133.4 (C), 145.0 (C), 145.9 (C), 166.0 (CO).

5,6a-Dihydro-isoindolo[2,1-*a*][3,1]benzoxazin-11-one (4a).

A solution of diol (**3a)** (2.55 g, 10 mmol), *p*-toluenesulfonic acid (catalytic amount) in dichloromethane (100 mL) was stirred for 30 min (the reaction was monitored by TLC). The solution was washed successively with a saturated sodium hydrogen carbonate solution, then with water and was dried (magnesium sulfate) and filtered. The solution was concentrated under reduced pressure and the residue recrystallized from ethanol to furnish pure oxazine (**4a)** (2.37 g, 100%); mp 188 °C; IR: 1710 (C=O) cm^{-1}; ^{1}H NMR: δ 5.02 (d, *J* = 15 Hz, 1 H, H_{12}), 5.23 (d, *J* = 15 Hz, 1 H, H_{12}), 5.87 (s, 1 H, H_{10b}), 7.00-7.17 (m, 2 H, H_{arom}), 7.29-7.36 (m, 1 H, H_{arom}), 7.48-7.70 (m, 3 H, H_{arom}), 7.88 (d, *J* = 8 Hz, 1 H, H_{arom}), 8.37 (d, *J* = 8 Hz, 1 H, H_{arom}); ^{13}C NMR: δ 68.4 (CH_2), 85.0 (CH), 119.4 (CH), 122.8 (C), 123.4 (CH), 123.9 (CH), 123.9 (CH), 124.3 (CH), 127.8 (CH), 130.4 (CH), 132.6 (CH), 132.7 (C), 134.0 (C), 140.0 (C), 165.1 (CO); MS (EI, 70 ev) *m/z*: 237 ($M^{+\cdot}$ 100%), 236 (65%), 209 (29%), 208 (35%), 180 (22%), 105 (27%). Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.42; H, 4.98; N, 5.86.

5,6a-Dihydro-5-phenylisoindolo[2,1-*a*][3,1]benzoxazin-11-one (4b and 5b).

Compounds (**4b)** and (**5b)** were synthesized from **3b** with a yield of 100% using the same procedure than for **4a**. Recrystallization from ethanol of the 2/1 ratio of **4b**/**5b** permitted to separate the two isomers as pure products. Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.82; N, 4.47. Found: C, 80.36; H, 4.71; N, 4.48.

Isomer (**4b)** : mp 254 °C; IR: 1695 (C=O) cm^{-1}; ^{1}H NMR: δ 6.18 (s, 1 H, CH), 6.20 (s, 1 H, CH), 6.71 (d, *J* = 8 Hz, 1 H, H_{arom}), 7.00 (t, *J* = 8 Hz, 1 H, H_{arom}), 7.20-7.44 (m, 6 H, H_{arom}), 7.52-7.72 (m, 3 H, H_{arom}), 7.86-7.99 (m, 1 H, H_{arom}), 8.42 (d, *J* = 8 Hz, 1 H, H_{arom}); ^{13}C NMR: δ 81.7 (CH), 85.2 (CH), 119.4 (CH), 123.8 (CH), 123.9 (CH), 124.0 (CH), 126.7 (C), 127.0 (CH), 128.2 (CH), 128.7 (2CH), 128.9 (CH), 129.0 (2CH), 130.5 (CH), 132.6 (CH), 132.9 (C), 134.3 (C), 140.0 (C), 140.1 (C), 165.2 (CO).

Isomer (**5b)** : mp 159 °C; IR: 1709 (C=O) cm^{-1}; ^{1}H NMR: δ 5.79 (s, 1 H, CH), 6.19 (s, 1 H, CH), 7.05-7.63 (m, 11 H, H_{arom}), 7.82-7.94 (m, 1 H, H_{arom}), 8.52 (d, *J* = 8 Hz, 1 H, H_{arom}); ^{13}C NMR: δ 77.8 (CH), 79.0 (CH), 119.4 (CH), 122.7 (C), 123.2 (CH), 123.4 (CH), 123.8 (CH), 127.1 (CH), 128.3 (CH), 128.5 (2CH), 128.6 (CH), 129.2 (2CH), 130.1 (CH), 132.4 (CH), 132.8 (C), 134.6 (C), 140.0 (C), 140.4 (C), 165.3 (CO).

5,6a-Dihydro-5-methylisoindolo[2,1-*a*][3,1]benzoxazin-11-one (4c and 5c).

Compounds (**4c)** and (**5c)** were synthesized from **3c** with a yield of 90% using the same procedure than for **4a**. Recrystallization from ethanol of the 2/1 ratio of **4c**/**5c** permitted to separate the two isomers as pure products. IR: 1711 (C=O) cm^{-1}; MS (EI, 70 ev) *m/z*: 251 ($M^{+\cdot}$) (13%), 321 (10%), 273 (27%), 265 (29%), 250 (60%), 240 (24%), 149 (100%), 148 (100%). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.45; H, 5.21; N, 5.53.

Isomer **(4c)** : mp: 150 °C; ^{1}H NMR: δ 1.65 (d, *J* = 6 Hz, 3 H, CH_3), 5.31 (q, *J* = 6 Hz, 1 H, CH), 5.97 (s, 1 H, CH), 7.17-8.41 (m, 8 H, $H_{arom.}$); ^{13}C NMR: δ 21.1 (CH_3), 74.3 (CH), 84.7 (CH), 119.5 (CH), 123.6

(CH), 124.0 (CH), 124.1 (CH), 124.6 (CH), 125.5 (C), 127.9 (CH), 130.4 (CH), 132.6 (CH), 132.0 (C), 133.8 (C), 140.3 (C), 165.1 (CO).

Isomer **(5c)** : mp: 110 °C; ^{1}H NMR: δ 1.76 (d, *J* = 7 Hz, 3 H, CH_3), 5.27 (q, *J*= 7 Hz, 1 H, CH), 6.02 (s, 1 H, CH), 7.12-8.35 (m, 8 H, $H_{arom.}$); ^{13}C NMR: δ 22.1 (CH_3), 72.4 (CH), 78.7 (CH), 119.7 (CH), 123.3 (CH), 124.0 (CH), 124.1 (CH), 124.6 (CH), 125.5 (C), 127.8 (CH), 130.3 (CH), 132.9 (CH), 133.3 (C), 133.8 (C), 140.6 (C), 165.1 (CO).

2-(*N*-Phthalimidomethyl)benzophenone (9).

To a solution of 2-methylbenzophenone (**7)** (1.96 g, 10 mnol) in carbon tetrachloride (25 mL) was added portionwise *N*-bromosuccinimide (1.76 g, 10 mmol) and AIBN (0.02 g). The mixture was stirred at 50°C for 48 h. After elimination of succinimide by filtration, the filtrate was concentrated under reduced pressure. To the crude bromomethylbenzophenone **(8)** (2.7 g) was added phthalimide (1.5 g, 10 mmol), potassium carbonate (1.1 g, 8 mmol) and *N*,*N*-dimethylformamide (25 mL). This mixture was stirred overnight, diluted with water, extracted with ether (3 x 20 mL), and dried (magnesium sulfate). The solvent was evaporated under reduced pressure and the solid was recrystallized from ethanol to give the 2-(*N*-phthalimidomethyl)benzophenone **(9)** (2.62 g, 77%) (from **7**) as a colorless solid, mp: 115 °C (lit.,[19] 107-108 °C). IR: 1717 (C=O), 1655 (C=O) cm^{-1}; ^{1}H NMR: δ 5.06 (s, 2 H, NCH_2), 7.27-7.86 (m, 13 H, $H_{arom.}$); ^{13}C NMR : δ 38.9 (CH_2), 123.3 (2CH), 126.8 (CH), 128.4 (2CH), 128.6 (CH), 129.4 (CH), 130.4 (2CH), 130.9 (CH), 131.9 (2C), 133.2 (CH), 134.0 (2CH), 136.0 (C), 137.6 (C), 137.9 (C), 167.9 (2CO), 197.7 (CO); MS (EI, 70 ev) *m/z* : 341 (M^+).

2,3-Dihydro-3-hydroxy-2-[2-hydroxyphenylmethylphenylmethyl]-1*H*-isoindol-1-one (10).

To a mixture of **9** (0.5 g, 15 mmol) in dry methanol (20 mL) at 0-10°C was added sodium borohydride (0.69 g, 30 mmol) by portions. This mixture was stirred for 2 h and monitored by TLC (dichloromethane-acetone 5:1). After 2 h, starting material has disappeared and the excess of sodium borohydride was decomposed by addition of cold water and 10% hydrochloric acid to the neutral pH.

The precipitate was separated by filtration, washed with water, dried, and recrystallized from ethanol to give a 5/1 ratio of diastereomers **10** (0.41 g, 79%); IR: 3299 (OH), 3061 (OH), 1672 (C=O) cm^{-1}; MS (EI, 70 ev) *m/z* : 343 $(M - H_2)^{+\cdot}$, 327 $(M - H_2O)^{+\cdot}$, 249, 195, 194.

Major isomer: ^{1}H NMR (DMSO-d_6): δ 4.41 (d, *J* = 16 Hz, 1 H, NCH_2), 4.99 (d, *J* = 16 Hz, 1 H, NCH_2), 5.63 (s, 1 H, CH), 5.85 (d, *J* = 4 Hz, 1 H, OH), 6.08 (d, *J* = 4 Hz, 1 H, CH), 6.66 (s, 1 H, OH), 7.22-7.75 (m, 13 H, $H_{arom.}$); ^{13}C NMR: δ 39.4 (CH_2), 70.6 (CH), 80.4 (CH), 122.6 (CH), 123.8 (CH), 126.6 (CH), 127.0 (2CH), 127.1 (CH), 128.0 (CH), 128.1 (2CH), 128.2 (CH), 129.2 (CH), 129.5 (CH), 131.4 (C), 132.1 (CH), 134.1 (C), 142.9 (C), 144.4 (C), 145.1 (C), 166.2 (CO).

Minor isomer: ^{1}H NMR (DMSO-d_6): δ 4.50 (d, *J* = 16 Hz, 1 H, NCH_2), 4.82 (d, *J* = 16 Hz, 1 H, NCH_2), 5.56 (s, 1 H, CH), 5.86 (d, *J* = 4 Hz, 1 H, OH), 6.11 (d, *J* = 4 Hz, 1 H, CH), 6.58 (s, 1 H, OH), 7.22-7.75

(m, 13 H, $H_{arom.}$); ^{13}C NMR: δ 39.4 (CH_2), 70.5 (CH), 80.3 (CH), 122.5 (CH), 123.7 (CH), 126.9 (2CH), 128.1 (2CH), 127.2 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 129.4 (CH), 129.2(CH), 131.3 (C), 132.1 (CH), 134.1 (C), 142.7 (C), 144.2 (C), 144.9 (C), 166.1 (CO).

5,6a-Dihydro-5-phenylisoindolo[1,2-*c*][2,4]benzoxazepin-11-one (11 and 12)

The diols (**10)** (0.5 g, 1.5 mmol) was stirred in dry dichloromethane (20 mL) with a catalytic amount of *p*-toluenesulfonic acid for 30 min at rt. The solution was washed with saturated sodium hydrogen carbonate, with water, dried over magnesium sulfate and concentrated under reduced pressure. Recrystallization from ethanol gave the corresponding oxazepines (**11)** and (**12)** with a ratio of 5/1 and with a yield of 70%, IR: 1694 (C=O), 1059 (C-O-C) cm^{-1}; MS (EI, 70 ev) *m/z* : 327 ($M^{+\cdot}$), 250, 249, 220, 195, 194. Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.97; H, 5.23; N, 4.22.

Isomer **(11)** : mp: 223 °C; ^1H NMR: δ 4.82 (d, *J* = 15 Hz, 1 H, H_{13}), 5.31 (d, *J* = 15 Hz, 1 H, H_{13}), 6.16 (s, 1 H, H_5), 6.31 (s, 1 H, H_{6a}), 6.57 (d, *J* = 7 Hz, 1 H, H_{arom}), 7.06-7.56 (m, 11 H, H_{arom}), 7.79 (d, *J* = 7 Hz, 1 H, H_{arom}); ^{13}C NMR: δ 45.1 (CH_2), 81.7 (CH), 90.9 (CH), 123.4 (CH), 123.5 (CH), 127.1 (2CH), 127.7 (CH), 127.9 (CH), 128.3 (CH), 128.4 (3CH), 129.2 (CH), 129.9 (CH), 132.0 (CH), 132.4 (C), 136.6 (C), 139.1 (C), 141.2 (C), 141.7 (C), 166.0 (CO).

Isomer **(12)** : mp: 209 °C ; ^1H NMR: δ 4.73 (d, *J* = 16 Hz, 1 H, H_{13}) , 5.30 (d, *J* = 16 Hz, 1 H, H_{13}), 5.54 (s, 1 H, H_5), 6.13 (s, 1 H, H_{6a}), 6.64 (d, *J* = 8 Hz, 1 H, H_{arom}), 7.06-7.58 (m, 11 H, H_{arom}), 7.81-7.84 (d, *J* = 7 Hz, 1 H, H_{arom}); ^{13}C NMR: δ 45.2 (CH_2), 78.3 (CH), 86.4 (CH), 123.4 (CH), 123.4 (CH), 128.4 (2CH), 127.0 (CH), 127.9 (CH), 128.2 (CH), 128.7 (CH), 128.7 (2CH), 129.5 (CH), 130.1 (CH), 132.3 (CH), 132.9 (C), 136.5 (C), 139.1 (C), 141.5 (C), 141.2 (C), 167.1 (CO).

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