STEREOSPECIFIC APPROACHES TO C-12 SUBSTITUTED PYRROLO[1',2':2,3]PYRIDAZINO[6,1-*a*]ISOINDOLONES

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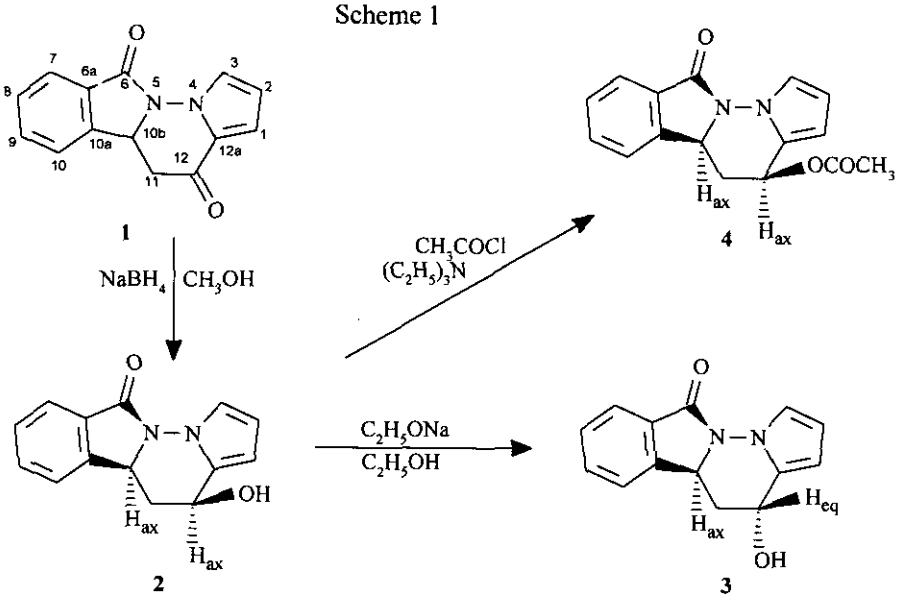
Abstract - Isomerization of the *cis*-alcohol (**2**) to the *trans*-alcohol (**3**) was achieved by treatment with sodium ethoxide in ethanol solution. Various *trans*-C_{12} substituted products (**5-10**) are prepared from alcohols (**2**), (**3**). On the other hand, *cis*-*N,N*-dimethylamino compound (**14**) was obtained in a three steps sequence from the acetic acid derivative (**11**).

Nitrogen containing tetracyclic rings as potential pharmacophoric structures for drug design in the field of central nervous system (CNS) agents led us to synthesize[1] a new heterocyclic system (**1**). Otherwise, compounds incorporating the *N*-aminopyrrole moiety have been recently reported as potential anxiolytic agents.[2,3] In our previous work[1] we described the reduction of the tetracyclic ketone (**1**) into the alcohol (**2**) (Scheme 1). The reaction was carried out using sodium borohydride in methanol and led to a single stereoisomer corresponding to a *cis* configuration between the H_{10b} and H_{12} protons in which the hydroxyl group has an equatorial position as shown in structure (**2**). A preferential hydride attack from the less hindered side furnished this product. Further support for this assignment was obtained from isomerization studies of **2** (Scheme 1). Stirring of **2** in sodium ethoxide-ethanol solution for 12 h at room temperature gave a complete conversion to isomer (**3**). Actually the ^{1}H nmr spectrum of **3** ($CDCl_3$) shows for H_{10b} a doublet of doublet exhibiting a *cis* coupling constant of 2.7 Hz (H_{10b}-H_{11}-eq) and a *trans* coupling constant of 12.4 Hz (H_{10b}-H_{11}-ax). The signal of H_{12} is a doublet of doublet with a *cis* coupling constant of 3.1 Hz (H_{12}-eq-H_{11}-ax) and a *trans* coupling constant of 2.7 Hz (H_{12}-eq-H_{11}-eq), while in the stereoisomer (**2**) the signal of H_{12}-ax exhibits a *cis* coupling constant of 4.9 Hz and a *trans* coupling constant of 9.6 Hz.

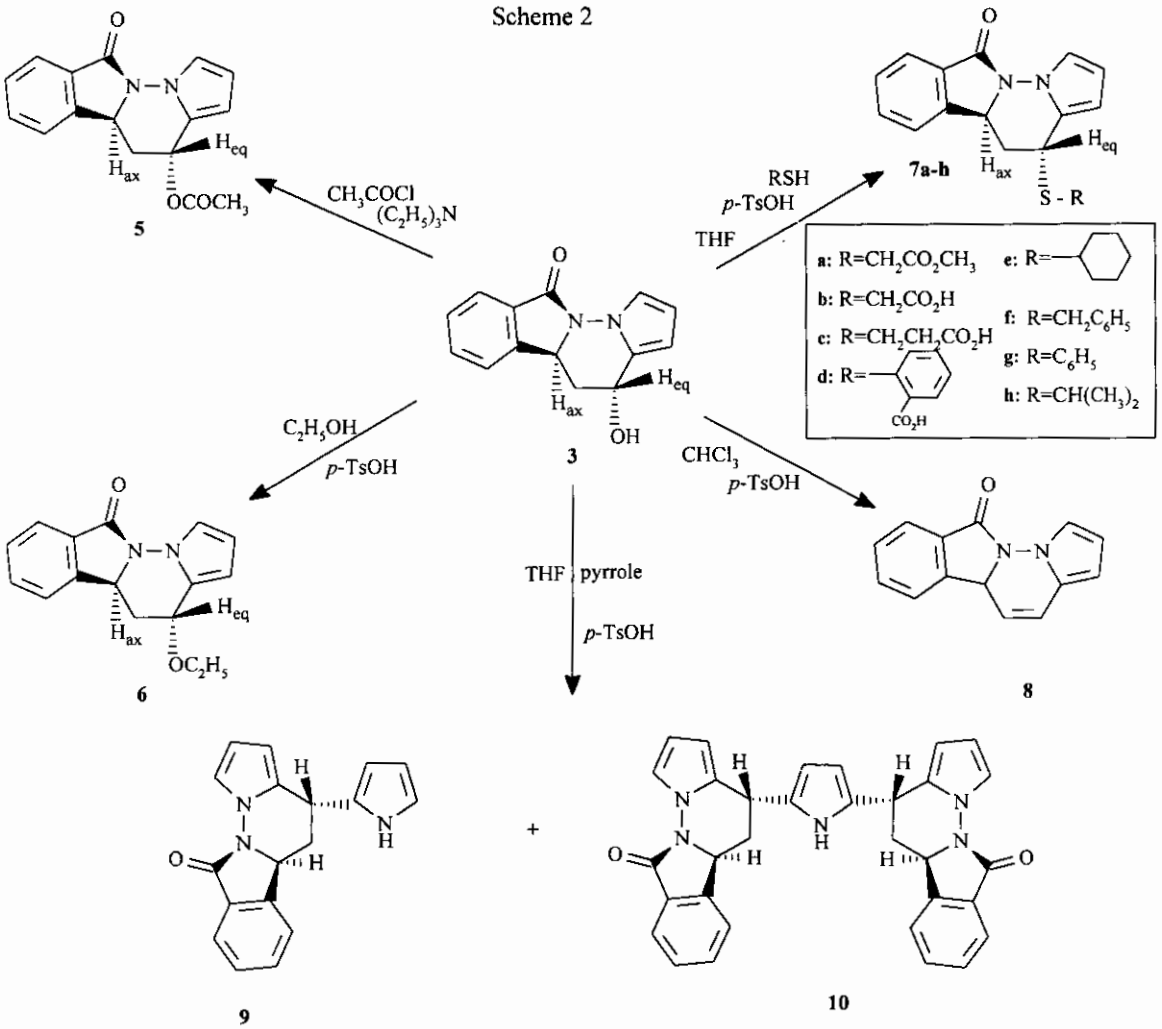
Scheme 1



The alcohol (**2**) was treated with acetylchloride in the presence of triethylamine to give the *cis*-acetate (**4**) in good yield (90 %). In the ^{1}H nmr spectrum, the signal of H_{12} is a doublet of doublet with a chemical shift of 6.09 ppm (4.95 ppm for alcohol (**2**)) and a *cis* coupling constant of 5.1 Hz (H_{12}-ax-H_{11}-eq) and a *trans* coupling constant of 6.7 Hz (H_{12}-ax-H_{11}-ax). These facts suggest a *cis* stereochemistry between the H_{10b} and H_{12} protons, which would be the expected result. In a similar manner the epimeric alcohol (**3**) led to the *trans* acetate (**5**). In the ^{1}H nmr spectrum of **5**, the signal of H_{12} appears as a triplet at 6.19 ppm (5.15 ppm for the alcohol (**3**)) with a *cis* coupling constant of 3.4 Hz (H_{12}-H_{11}-ax) and a *trans* coupling constant of 2.7 Hz (H_{12}-H_{11}-eq), which are identical with those observed for the starting alcohol (**3**). Furthermore, in the ^{13}C nmr spectra, the signals of C-10a, C-10b, C-11, C-12, and C-12a are shifted downfield for the *cis*-alcohol (**2**) and acetate (**4**) compared to the *trans* isomers (**3**) and (**5**).

On the other hand, reaction of *trans*-alcohol (**3**) with a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in ethanol at room temperature led to the *trans*-ethoxy compound (**6**) in a 67 % yield (Scheme 2). Treatment of the *cis*-alcohol (**2**) in a similar manner furnished the same *trans*-ethoxy compound (**6**). The *trans* configuration was supported by the ^{1}H nmr analysis of the product (**6**). The signal of H_{12} is a triplet at 4.63 ppm with a *cis* coupling constant of 3.2 Hz (H_{12}-H_{11}-ax) and a *trans* coupling constant of 3.0 Hz (H_{12}-H_{11}-eq). Both results suggest that the transformation occurs *via* a C_{12} carbocation (Scheme 3). Actually, this carbocation which is probably stabilized by the electron-donating effect of the pyrrole ring and the steric factors, determine the outcome of the reaction. Thus, the nucleophile approaches from the less hindered side to afford a product with a *trans* relationship between H_{10b} and H_{12}.

Scheme 2

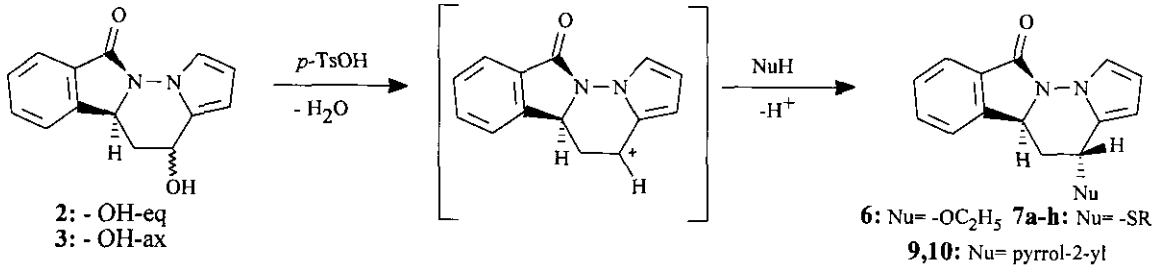


The use of different alkyl or arylthiols as nucleophiles gave the corresponding *trans* thio compounds (**7a-h**) in a moderate yields (67-82 %). On the other hand, this stable carbocation could react with a pyrrole ring to provide a mixture of 2-substituted derivative (**9**) and 2,5-disubstituted derivative (**10**) which were separated by column chromatography (silica gel-chloroform). When two equivalents of starting alcohol (**3**) were used for one equivalent of pyrrole, only the 2,5-disubstituted compound (**10**) was produced in a moderate yield of 68 %. As expected, the alcohol (**3**) (OH group at C_{12} is axial) being more reactive than the alcohol (**2**) (OH_{eq}), led to shorter reaction times during these nucleophilic substitutions.

A final point of interest is found in the facile stabilization of the carbocation when no nucleophile is present. Actually, treatment of *trans*-alcohol (**3**) with *p*-TsOH in chloroform caused dehydration to furnish the expected olefin (**8**). The conjugation with the pyrrole ring facilitate this elimination and under these conditions no [1,3] migration of the proton H_{10b} was observed. The signals of H_{10b} (m, 5.71-5.76

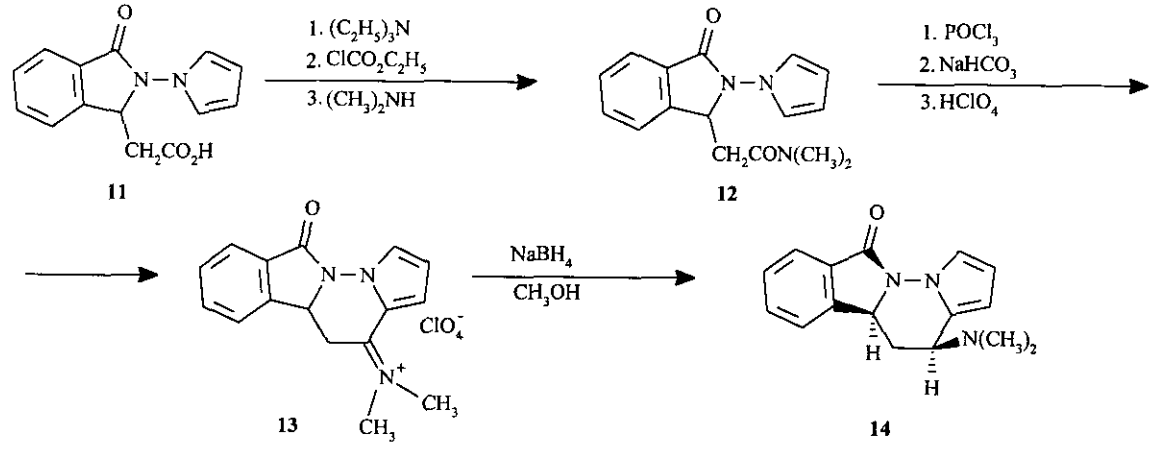
ppm), H_{12} (dd, 5.77 ppm, 1.8 and 10.6 Hz), H_{11} (dd, 6.45 ppm, 3.2 and 10.6 Hz) in the ^1H nmr spectrum of **8** support the proposed structure.

Scheme 3



Since the direct amination of an alcohol is problematic, a C-12 aminated compound with a *cis* configuration could be expected *via* the iminium intermediate (**13**). This latter was prepared from the substituted acetic acid (**11**) according to the method previously reported by us.[1]

Scheme 4



By employing the procedure[4] used for the synthesis of dimethylaminophenylpyrrolizine, the acid (**11**) was transformed into the corresponding *N,N,*-dimethylacetamide derivative (**12**) (64 %) which upon treatment successively with phosphorus oxychloride and perchloric acid led to the iminium perchlorate salt (**13**). According to the preceding results, hydride reduction using sodium borohydride (Scheme 4) occurred exclusively from the less hindered side of the iminium ion to produce the dimethylamino derivative (**14**) (75 %) with a *cis* relationship between H_{10b} and H_{12} protons. The ^1H nmr spectrum of **14** exhibits a *cis* coupling constant of 5.1 Hz (H_{12}-H_{11}-eq) and a *trans* coupling constant of 9.3 Hz (H_{12}-H_{11}-ax) similar to

those observed for both the *cis*-alcohol (**2**) and its acetate (**4**).

In conclusion, we have shown stereospecific routes to the new *cis*- and *trans*- pyrrolopyridazinoisoindole system substituted on C-12 with different functional groups such as $-OCOCH_3$, $-OC_2H_5$, $-N(CH_3)_2$, S-alkyl(or aryl) and pyrrol-2-yl.

EXPERIMENTAL

Melting points were measured on a Boetius micro hot-stage and are uncorrected. The infrared spectra were recorded on a Philips analytical PV 9 800 FT ir spectrophotometer (potassium bromide). The nmr spectra were recorded on a Bruker AC-200 spectrometer (200 MHz) in $CDCl_3$ and DMSO-d_6 (compounds **3**, **7b-d**, **9** and **13**) using tetramethylsilane (^1H) or DMSO-d_6 (^{13}C, 39.5 ppm) as internal standards. Ascending thin layer chromatography was performed on precoated of silica gel 60 F 254 (Merck) and the spots were visualized using uv 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 of Rouen, F 76130 $M^T.S^T$. Aignan. Mass spectral measurements were recorded on a AEI ms 902 S spectrometer. The compounds (**2-14**) gave the expected molecular ions.

***trans*-6,10b,11,12-Tetrahydro-12-hydroxypyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one (3).**

To a solution of sodium ethoxide (50 mg, 0.74 mmol) in absolute ethanol (10 ml) was added *cis*-alcohol (**2**)[1] (0.48 g, 2 mmol), and the mixture was stirred at room temperature for 12 h. The resulting precipitates were collected by filtration and washed with water. Recrystallization from ethanol afforded 0.40 g (84 %) of *trans*-alcohol (**3**) as colorless crystals, mp 171-172 °C ; ir : 3501 (OH), 1700 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$) : δ 1.70 (ddd, 1H, H_{11}-ax, J=3.1, 12.4 and 14.0 Hz), 1.97 (br s, 1H, OH), 2.69 (td, 1H, H_{11}-eq, J=2.7 and 14.0 Hz), 5.15 (t, 1H, H_{12}-eq, J=2.9 Hz), 5.29 (dd, 1H, H_{10b}, J=2.7 and 12.4 Hz), 6.21 (dd, 1H, H_2, J=2.7 and 4.1 Hz), 6.24 (dd, 1H, H_1, J=1.7 and 4.1 Hz), 7.47-7.68 (m, 3H, H_{arom}), 7.69 (dd, 1H, H_3, J=1.7 and 2.7 Hz), 7.88-7.96 (m, 1H, H_7) ; ^{13}C nmr (DMSO-d_6) : δ 36.7 (C-11), 54.4 (C-10b), 58.5 (C-12), 104.4 (C-1), 105.1 (C-2), 116.0 (C-3), 123.0 (C-8), 123.7 (C-7), 126.1 (C-12a), 128.8 (C-10), 129.6 (C-6a), 132.6 (C-9), 143.8 (C-10a), 162.0 (C-6) ; ms : m/z 240 (M^+). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.98 ; H, 5.04 ; N, 11.66. Found : C, 69.85 ; H, 4.97 ; N, 11.44.

***cis*-12-Acetoxy-6,10b,11,12-tetrahydropyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one (4).**

A stirred solution of *cis*-alcohol (**2**) (0.48 g, 2 mmol) in 1,2-dichlorethane (15 ml) was treated with

triethylamine (0.42 ml, 3 mmol) and acetyl chloride (0.21 ml, 3 mmol). After 6 h the mixture was quenched with cold water (5 ml). The organic phase was washed with 0.5 N hydrochloric acid (10 ml), then dried (magnesium sulfate). The solvent was evaporated *in vacuo* and the solid was recrystallized from ethyl acetate-n-hexane (2:8) to give *cis*-acetate (**4**) (0.51 g, 90 %) as a colorless solid, mp 118-120 °C; ir : 1711 and 1740 (C=O) cm^{-1}; ^1H nmr : δ 1.72 (s, 3H, CH_3), 2.24 (td, 1H, H_{11}-ax, J=7.0 and 13.7 Hz), 2.77 (ddd, 1H, H_{11}-eq, J=5.1, 6.5 and 13.7 Hz), 5.05 (t, 1H, H_{10b}, J=7.0 Hz), 6.09 (dd, 1H, H_{12}-ax, J=5.1 and 6.7 Hz), 6.12-6.25 (m, 2H, H_1 and H_2), 7.33 (t, 1H, H_3, J=2.4 Hz), 7.41-7.72 (m, 3H, H_{arom}), 7.88-7.98 (m, 1H, H_7) ; ^{13}C nmr : δ 20.7 (CH_3), 34.2 (C-11), 57.0 (C-10b), 64.0 (C-12), 105.5 (C-1), 106.3 (C-2), 119.6 (C-3), 122.4 (C-8), 122.9 (C-12a), 124.8 (C-7), 129.0 (C-10), 129.4 (C-6a), 133.1 (C-9), 144.8 (C-10a), 166.4 (C-6), 170.2 (C=O) ; ms : m/z 282 (M^+). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.06 ; H, 5.01 ; N, 9.92. Found : C, 68.07 ; H, 4.95 ; N, 9.92.

***trans*-12-Acetoxy-6,10b,11,12-tetrahydropyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one (5).** This compound was prepared from **3** (0.48 g, 2 mmol) as described for **4**, yield 0.50 g (89 %), colorless crystals, mp 159-160 °C (ethyl acetate -n-hexane) ; ir : 1707 and 1736 (C=O) cm^{-1}; ^1H nmr : δ 1.82 (ddd, 1H, H_{11}-ax, J=3.4, 12.5 and 14.4 Hz), 2.09 (s, 3H, CH_3), 2.68 (td, 1H, H_{11}-eq, J=2.7 and 14.4 Hz), 5.17 (dd, 1H, H_{10b}, J=2.7 and 12.5 Hz), 6.19 (t, 1H, H_{12}-eq, J=2.7 Hz), 6.21 (dd, 1H, H_2, J=2.8 and 4.1 Hz), 6.32 (dd, 1H, H_1, J=1.7 and 4.1 Hz), 7.43-7.68 (m, 3H, H_{arom}), 7.71 (dd, 1H, H_3, J=1.7 and 2.8 Hz), 7.86-7.98 (m, 1H, H_7) ; ^{13}C nmr : δ 21.4 (CH_3), 34.2 (C-11), 54.9 (C-10b), 62.2 (C-12), 106.1 (C-1), 107.4 (C-2), 118.0 (C-3), 120.3 (C-12a), 122.2 (C-8), 124.7 (C-7), 129.1 (C-10), 130.2 (C-6a), 132.6 (C-9), 142.5 (C-10a), 162.4 (C-6), 170.1 (C=O) ; ms : m/z 282 (M^+). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.06 ; H, 5.01 ; N, 9.92. Found : C, 67.94 ; H, 4.87 ; N, 9.67.

***trans*-12-Ethoxy-6,10b,11,12-tetrahydropyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one (6).**

A stirred suspension of the *trans*-alcohol (**3**) (0.48 g, 2 mmol) in ethanol (3 ml) was treated with a catalytic amount of *p*-toluenesulfonic acid (one crystal) at room temperature for 1 h. The mixture was poured into water (10 ml), the precipitated product was filtered and washed with water. Recrystallization from ethanol afforded **6** (0.36 g, 67 %) as colorless crystals, mp 167-169 °C ; ir : 1709 (C=O) cm^{-1}; ^1H nmr : δ 1.21 (t, 3H, CH_3, J=7.0 Hz), 1.68 (ddd, 1H, H_{11}-ax, J=3.2, 12.2 and 13.7 Hz), 2.71 (td, 1H, H_{11}-eq, J=3.0 and 13.7 Hz), 3.51 and 3.69 (qd, 2H, OCH_2, J=7.0 and 9.0 Hz), 4.63 (t, 1H, H_{12}-eq, J=3.0 Hz), 5.25 (dd, 1H, H_{10b}, J=3.0 and 12.2 Hz), 6.15-6.28 (m, 2H, H_1 and H_2), 7.46-7.68 (m, 3H, H_{arom}), 7.78 (t, 1H, H_3, J=2.3 Hz), 7.88-7.96 (m, 1H, H_7) ; ^{13}C nmr : δ 15.2 (CH_3), 35.1 (C-11), 55.1 (C-10b), 63.3 (OCH_2), 66.7 (C-12), 105.1 (C-1), 106.3 (C-2), 117.7 (C-3), 121.2 (C-12a), 122.2 (C-8), 124.4 (C-7), 128.8 (C-10),

130.4 (C-6a), 132.3 (C-9), 143.2 (C-10a), 162.4 (C-6) ; ms : m/z 268 (M^+). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.61 ; H, 6.02 ; N, 10.44. Found : C, 71.50 ; H, 6.00 ; N, 10.12.

Methyl *trans*-(6,10b,11,12-tetrahydropyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one-12-yl)thioacetate (7a). To a stirred solution of the *trans*-alcohol (**3**) (0.48 g, 2 mmol) and methyl thioglycolate (0.21 g, 2 mmol) in tetrahydrofuran (10 ml) was added catalytic amount of *p*-toluenesulfonic acid (one crystal). The reaction mixture was stirred for 3 h at room temperature. Then the mixture was diluted with water (20 ml) and extracted with dichloromethane (2x20 ml). The organic layer, washed with water (10 ml), was dried (magnesium sulfate) and concentrated to give **7a** as solid, which was recrystallized from methanol (0.44 g, 67 %), mp 147-148 °C ; ir : 1705 and 1744 (C=O) cm^{-1}; ^1H nmr : δ 1.96 (ddd, 1H, H_{11}-ax, J=4.6, 11.8 and 14.2 Hz), 2.70 (td, 1H, H_{11}-eq, J=2.6 and 14.2 Hz), 3.36 (s, 2H, SCH_2), 3.77 (s, 3H, OCH_3), 4.69 (dd, 1H, H_{12}-eq, J=2.2 and 4.6 Hz), 5.37 (dd, 1H, H_{10b}, J=2.7 and 11.8 Hz), 6.10-6.26 (m, 2H, H_2 and H_1), 7.47-7.68 (m, 3H, H_{arom}), 7.69 (dd, 1H, H_3, J=1.9 and 2.7 Hz), 7.88-7.96 (m, 1H, H_7) ; ^{13}C nmr : δ 33.3 (C-11), 33.5 (SCH_2), 36.6 (C-12), 52.6 (OCH_3), 54.8 (C-10b), 105.6 (C-1), 105.8 (C-2), 117.9 (C-3), 120.0 (C-12a), 122.2 (C-8), 124.5 (C-7), 129.0 (C-10), 130.0 (C-6a), 132.4 (C-9), 142.7 (C-10a), 162.5 (C-6), 170.8 (C=O) ; ms : m/z 328 (M^+). Anal. Calcd for $C_{17}H_{16}N_2O_3S$: C, 62.17 ; H, 4.92 ; N, 8.53. Found : C, 62.01 ; H, 4.76 ; N, 8.39.

***trans*-(6,10b,11,12-Tetrahydropyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one-12-yl)thioacetic acid (7b).** This compound was prepared from **3** (0.48 g, 2 mmol) and thioglycolic acid (0.14 ml, 2 mmol) as described for **7a**, yield 0.5 g (80 %), mp 168-170 °C (ethanol-dimethylformamide) ; ir : 1659 and 1723 (C=O) cm^{-1}; ^1H nmr : δ 1.91 (ddd, 1H, H_{11}-ax, J=4.5, 11.8 and 14.2 Hz), 2.81 (td, 1H, H_{11}-eq, J=2.4 and 14.2 Hz), 3.43 (d, 1H, SCH, J=15.4 Hz), 3.57 (d, 1H, SCH, J= 15.4 Hz), 4.68-4.72 (m, 1H, H_{12}-eq), 5.35 (dd, 1H, H_{10b}, J=2.4 and 11.8 Hz), 6.07-6.18 (m, 2H, H_2 and H_1), 7.51 (dd, 1H, H_3, J=1.9 and 3.0 Hz), 7.54-7.65 (m, 1H, H_{arom}), 7.67-7.88 (m, 3H, H_{arom}) ; ^{13}C nmr : δ 32.2 (SCH_2), 33.3 (C-11), 35.8 (C-12), 54.6 (C-10b), 105.1 (C-1), 105.3 (C-2), 117.0 (C-3), 121.3 (C-12a), 123.2 (C-8), 123.8 (C-7), 129.0 (C-10), 129.3 (C-6a), 132.8 (C-9), 143.4 (C-10a), 162.2 (C-6), 171.7 (C=O) ; ms : m/z 314 (M^+). Anal. Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.13 ; H, 4.49 ; N, 8.91. Found : C, 61.01 ; H, 4.76 ; N, 8.79.

***trans*-3-(6,10b,11,12-Tetrahydropyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one-12-yl)thiopropionic acid (7c).** This compound was prepared from **3** (0.48 g, 2 mmol) and 3-mercaptopropionic acid (0.17 ml, 2 mmol) as described for **7a**, yield 0.52 g (79 %), mp 188-190 °C (ethanol) ; ir : 1701 and 1713 (C=O) cm^{-1}; ^1H nmr : δ 1.90 (ddd, 1H, H_{11}-ax, J=4.6, 11.8 and 14.1 Hz), 2.60 (t, 2H, CH_2, J=6.5 Hz), 2.80

(td, 1H, H_{11}-eq, J=2.7 and 14.1 Hz), 2.80-3.00 (m, 2H, CH_2), 4.59-4.64 (m, 1H, H_{12}-eq), 5.30 (dd, 1H, H_{10b}, J=2.7 and 11.8 Hz), 6.08 (dd, 1H, H_1, J=1.9 and 4.0 Hz), 6.10 (dd, 1H, H_2, J=3.0 and 4.0 Hz), 7.49 (dd, 1H, H_3, J=1.9 and 3.0 Hz), 7.53-7.65 (m, 1H, H_{arom}), 7.67-7.88 (m, 3H, H_{arom}) ; ^{13}C nmr : δ 26.3 (CH_2), 33.0 (C-11), 34.4 (SCH_2), 35.1 (C-12), 54.7 (C-10b), 104.8 (C-1), 105.2 (C-2), 116.8 (C-3), 122.1 (C-12a), 123.3 (C-8), 123.7 (C-7), 129.0 (C-10), 129.3 (C-6a), 132.7 (C-9), 143.4 (C-10a), 162.3 (C-6), 173.1 (C=O) ; ms : m/z 328 (M^+). Anal. Calcd for $C_{17}H_{16}N_2O_3S$: C, 62.18 ; H, 4.91 ; N, 8.53. Found : C, 62.03 ; H, 4.70 ; N, 8.31.

***trans*-2-(6,10b,11,12-Tetrahydropyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one-12-yl)thiobenzoic acid (7d).** This compound was prepared from **3** (0.48 g, 2 mmol) and 2-mercaptobenzoic acid (0.31 g, 2 mmol) as described for **7a**, yield 0.62 g (82 %), mp 206-207 °C (ethanol-dimethylformamide) ; ir : 1672 and 1723 (C=O) cm^{-1}; ^{1}H nmr : δ 1.99 (ddd, 1H, H_{11}-ax, J=4.3, 11.6 and 14.0 Hz), 2.60 (td, 1H, H_{11}-eq, J=2.4 and 14.0 Hz), 5.19-5.24 (m, 1H, H_{12}-eq), 5.34 (dd, 1H, H_{10b}, J=2.4 and 11.6 Hz), 6.13-6.20 (m, 2H, H_2 and H_1), 7.31-7.42 (m, 1H, H_{arom}), 7.52-7.78 (m, 5H, H_{arom}), 7.80-7.91 (m, 2H, H_{arom}) ; ^{13}C nmr : δ 32.7 (C-11), 37.3 (C-12), 54.7 (C-10b), 105.7 (C-1), 105.7 (C-2), 117.1 (C-3), 120.6 (C-12a), 126.0 (CH-arom), 123.2 (C-8), 123.8 (C-7), 129.0 (C-10), 129.3 (C-6a), 129.6 (CH-arom), 130.3 (CH-arom), 132.1 (C-arom), 132.7 (C-9), 136.2 (C-arom), 143.3 (C-10a), 162.1 (C-6), 168.2 (C=O) ; ms : m/z 376 (M^+). Anal. Calcd for $C_{21}H_{16}N_2O_3S$: C, 67.01 ; H, 4.28 ; N, 7.44. Found : C, 66.95 ; H, 4.16 ; N, 7.39.

***trans*-12-Cyclohexylthio-6,10b,11,12-tetrahydropyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one (7e).** This compound was prepared from **3** (0.48 g, 2 mmol) and cyclohexanethiol (0.24 ml, 2 mmol) as described for **7a**, yield 0.51 g (75 %), mp 137-139 °C (ethanol) ; ir : 1713 (C=O) cm^{-1}; ^{1}H nmr : δ 1.20-1.55 (m, 5H, 2xCH_2 and CH), 1.57-2.20 (m, 5H, 2xCH_2 and CH), 1.95 (ddd, 1H, H_{11}-ax, J=4.6, 11.8 and 13.9 Hz), 2.57 (td, 1H, H_{11}-eq, J=2.7 and 13.9 Hz), 2.70-2.83 (m, 1H, CH), 4.54 (dd, 1H, H_{12}-eq, J=2.4 and 4.6 Hz), 5.35 (dd, 1H, H_{10b}, J=3.0 and 11.8 Hz), 6.07 (dd, 1H, H_1 , J=1.8 and 4.0 Hz), 6.18 (dd, 1H, H_2, J=3.0 and 4.0 Hz), 7.46-7.63 (m, 3H, H_{arom}), 7.65 (dd, 1H, H_3, J=1.8 and 3.0 Hz), 7.87-7.95 (m, 1H, H_{arom}) ; ^{13}C nmr : δ 25.9 (CH_2), 33.4 (C-11), 33.7 (CH_2), 33.9 (SCH), 34.8 (CH_2), 43.5 (C-12), 55.1 (C-10b), 104.6 (C-1), 105.6 (C-2), 117.2 (C-3), 122.1 (C-12a), 122.1 (C-8), 124.5 (C-7), 128.9 (C-10), 130.2 (C-6a), 132.3 (C-9), 142.9 (C-10a), 162.5 (C-6) ; ms : m/z 338 (M^+). Anal. Calcd for $C_{20}H_{22}N_2OS$: C, 70.97 ; H, 6.55 ; N, 8.28. Found : C, 70.72 ; H, 6.36 ; N, 8.01.

***trans*-12-Benzylthio-6,10b,11,12-tetrahydropyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one (7f).** This compound was prepared from **3** (0.48 g, 2 mmol) and benzyl mercaptan (0.23 ml, 2 mmol) as

described for **7a**, yield 0.5 g (72 %), mp 143-144 °C (ethanol) ; ir : 1701 (C=O) cm^{-1}; ^1H nmr : δ 1.83 (ddd, 1H, H_{11}-ax, J=4.3, 11.8 and 14.0 Hz), 2.50 (td, 1H, H_{11}-eq, J=2.7 and 14.0 Hz), 3.87 (s, 2H, SCH2), 4.39 (dd, 1H, H_{12}-eq, J=2.4 and 4.3 Hz), 5.24 (dd, 1H, H_{10b}, J=2.7 and 11.8 Hz), 6.10 (dd, 1H, H_1 , J=1.9 and 4.0 Hz), 6.19 (dd, 1H, H_2, J=2.9 and 4.0 Hz), 7.29-7.48 (m, 6H, H_{arom}), 7.49-7.61 (m, 2H, H_{arom}), 7.65 (dd, 1H, H_3, J=1.9 and 2.9 Hz), 7.80-7.91 (m, 1H, H_{arom}) ; ^{13}C nmr : δ 34.0 (C-11), 36.1 (C-12), 36.6 (SCH_2), 55.0 (C-10b), 105.1 (C-1), 105.7 (C-2), 117.4 (C-3), 121.4 (C-12a), 122.1 (C-8), 124.5 (C-7), 127.2 (CH-arom), 128.7 (CH-arom), 128.9 (CH-arom), 128.9 (C-10), 130.1 (C-6a), 132.3 (C-9), 138.1 (C-arom), 142.7 (C-10a), 162.5 (C-6) ; ms : m/z 346 (M^+). Anal. Calcd for $C_{21}H_{18}N_2OS$: C, 72.81 ; H, 5.24 ; N, 8.09. Found : C, 72.59 ; H, 5.02 ; N, 7.91.

***trans*-6,10b,11,12-Tetrahydro-12-phenylthiopyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one (7g).** This compound was prepared from **3** (0.48 g, 2 mmol) and thiophenol (0.21 ml, 2 mmol) as described for **7a**, yield 0.47 g (71 %), mp 187-188 °C (ethanol) ; ir : 1701 (C=O) cm^{-1}; ^1H nmr : δ 1.82 (ddd, 1H, H_{11}-ax, J=4.6, 11.8 and 14.1 Hz), 2.54 (ddd, 1H, H_{11}-eq, J=2.2, 3.0 and 14.1 Hz), 4.87 (dd, 1H, H_{12}-eq, J=2.2 and 4.6 Hz), 5.37 (dd, 1H, H_{10b}, J=3.0 and 11.8 Hz), 6.06 (dd, 1H, H_1 , J=1.9 and 4.0 Hz), 6.17 (dd, 1H, H_2, J=3.0 and 4.0 Hz), 7.32-7.43 (m, 4H, H_{arom}), 7.46-7.63 (m, 4H, H_{arom}), 7.65 (dd, 1H, H_3, J=1.9 and 3.0 Hz), 7.87-7.95 (m, 1H, H_{arom}) ; ^{13}C nmr : δ 33.3 (C-11), 40.1 (C-12), 54.7 (C-10b), 105.8 (C-1), 105.9 (C-2), 117.5 (C-3), 120.6 (C-12a), 122.1 (C-8), 124.5 (C-7), 128.2 (CH-arom), 128.9 (C-10), 129.3 (CH-arom), 130.2 (C-6a), 132.3 (C-9), 133.3 (CH-arom), 133.9 (C-arom), 142.7 (C-10a), 162.3 (C-6) ; ms : m/z 332 (M^+). Anal. Calcd for $C_{20}H_{16}N_2OS$: C, 72.26 ; H, 4.85 ; N, 8.43. Found : C, 72.02 ; H, 4.71 ; N, 8.30.

***trans*-6,10b,11,12-Tetrahydro-12-isopropylthiopyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one (7h).** This compound was prepared from **3** (0.48 g, 2 mmol) and 2-propanethiol (0.19 ml, 2 mmol) as described for **7a**, yield 0.41 g (69 %), mp 159-160 °C (ethanol) ; ir : 1707 (C=O) cm^{-1}; ^1H nmr : δ 1.32 (d, 3H, CH_3, J=6.7 Hz), 1.38 (d, 3H, CH_3, J=6.7 Hz), 1.97 (ddd, 1H, H_{11}-ax, J=4.7, 11.7 and 13.7 Hz), 2.59 (td, 1H, H_{11}-eq, J=2.6 and 13.7 Hz), 2.94-3.15 (m, 1H, CH), 4.51 (dd, 1H, H_{12}-eq, J=2.4 and 4.7 Hz), 5.34 (dd, 1H, H_{10b}, J=2.8 and 11.7 Hz), 6.09 (dd, 1H, H_1, J=1.9 and 4.0 Hz), 6.17 (dd, 1H, H_2 , J=3.0 and 4.0 Hz), 7.47-7.64 (m, 3H, H_{arom}), 7.65 (dd, 1H, H_3, J=1.9 and 3.0 Hz), 7.86-7.96 (m, 1H, H_7) ; ^{13}C nmr : δ 23.1 and 23.3 (CH_3), 34.5 (CH), 34.6 (C-11), 35.0 (C-12), 55.2 (C-10b), 104.7 (C-1), 105.6 (C-2), 117.4 (C-3), 122.0 (C-12a), 122.2 (C-8), 124.6 (C-7), 129.0 (C-10), 130.3 (C-6a), 132.4 (C-9), 142.9 (C-10a), 162.6 (C-6) ; ms : m/z 298 (M^+). Anal. Calcd for $C_{17}H_{18}N_2OS$: C, 68.41 ; H, 6.09 ; N, 9.39. Found : C, 68.63 ; H, 6.41 ; N, 9.29.

6*H*,10b*H*-Pyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one (8). A solution of the *trans*-alcohol (**3**) (0.48 g, 2 mmol) in dry chloroform (10 ml) was treated with a catalytic amount of *p*-toluenesulfonic acid. The mixture was then stirred at room temperature for 3 h and poured into water (10 ml). The aqueous phase was extracted with chloroform (10 ml). The organic phase, washed with water (5 ml), was dried (magnesium sulfate) and concentrated to give **8** as a colorless solid, which was recrystallized from ethanol (0.30 g, 67 %), mp 124-125 °C ; ir : 1719 (C=O) cm^{-1}; ^1H nmr : 5.71-5.76 (m, 1H, H_{10b}), 5.77 (dd, 1H, H_{12}, J=1.8 and 10.6 Hz), 6.12 (dd, 1H, H_1, J=1.7 and 3.8 Hz), 6.17 (dd, 1H, H_2 , J=2.9 and 3.8 Hz), 6.45 (dd, 1H, H_{11} , J=3.2 and 10.6 Hz), 7.27 (dd, 1H, H_3, J=1.7 and 2.9 Hz), 7.46-7.71 (m, 3H, H_{arom}), 7.82-7.98 (m, 1H, H_7) ; ^{13}C nmr : δ 59.3 (C-10b), 105.6 (C-1), 106.4 (C-2), 118.9 (C-11 and C-12), 120.3 (C-3), 122.5 (C-8), 123.8 (C-12a), 124.9 (C-7), 128.8 (C-10), 129.5 (C-6a), 133.2 (C-9), 142.0 (C-10a), 166.6 (C-6) ; ms : m/z 222 (M^+). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.65 ; H, 4.54 ; N, 12.61. Found : C, 75.51 ; H, 4.29; N, 12.31.

***trans*-6,10b,11,12-Tetrahydro-12-(pyrrol-2-yl)-pyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one (9).** A stirred suspension of the *trans*-alcohol (**3**) (0.96 g, 4 mmol) and pyrrole (0.28 ml, 4 mmol) in dry tetrahydrofuran (20 ml) was treated with a catalytic amount of *p*-toluenesulfonic acid (one crystal) at room temperature for 1 h. The mixture was poured into water (10 ml) and the aqueous phase was extracted with chloroform (2x20 ml). The organic phase, washed with water (10 ml), was dried (magnesium sulfate) and concentrated *in vacuo*. The residue (0.9 g) was subjected to chromatography (silica gel, 80 g; elution with chloroform) to give **9** (0.55 g, 48 %) and **10** (0.17 g, 17 %) as colorless solids. **9**: mp 243-245 °C (ethanol) ; ir : 1694 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$) : δ 2.04 (ddd, 1H, H_{11}-ax, J=5.0, 11.0 and 13.2 Hz), 2.76 (td, 1H, H_{11}-eq, J=3.5 and 13.2 Hz), 4.51 (t, 1H, H_{12}-eq, J=4.3 Hz), 4.86 (dd, 1H, H_{10b}, J=3.5 and 11.0 Hz), 6.05-6.16 (m, 2H, H_1 and $H_{3'}$), 6.19-6.30 (m, 2H, H_2 and $H_{4'}$), 6.62-6.69 (m, 1H, $H_{5'}$), 7.40-7.69 (m, 4H, H_3 and H_{arom}), 7.86-7.96 (m, 1H, H_7), 8.02 (br.s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 30.1 (C-12), 35.0 (C-11), 56.1 (C-10b), 103.2 (C-3'), 105.0 (C-1), 105.2 (C-2), 107.1 (C-4'), 116.7 (C-5'), 117.1 (C-3), 123.3 (C-8), 123.7 (C-7), 126.4 (C-12a), 128.9 (C-10), 129.2 (C-6a), 132.0 (C-2'), 133.0 (C-9), 144.3 (C-10a), 164.2 (C-6) ; ms : m/z 289 (M^+). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72 ; H, 5.23 ; N, 14.52. Found : C, 74.51 ; H, 5.09 ; N, 14.32. **10**: mp >260 °C; ir : 1701 (C=O) cm^{-1}; ^1H nmr : δ 2.05 (ddd, 2H, H_{11}-ax, J=5.0, 10.6 and 13.2 Hz), 2.73 (td, 2H, H_{11}-eq, J=4.0 and 13.2 Hz), 4.33 (t, 2H, H_{12}-eq, J=4.3 Hz), 4.93 (dd, 2H, H_{10b}, J=4.0 and 10.6 Hz), 5.97 (dd, 2H, H_1, J=1.7 and 3.8 Hz), 6.04 (d, 2H, $H_{3'}$ and $H_{4'}$, J=2.7 Hz), 6.25 (dd, 2H, H_2, J=3.1 and 3.8 Hz), 7.44-7.59 (m, 6H, H_{arom}), 7.62 (dd, 2H, H_3, J=1.7 and 3.1 Hz), 7.86-8.01 (m, 3H, $2H_{arom}$ and NH) ; ^{13}C nmr : δ 30.8 (C-12), 34.9 (C-11), 56.0 (C-10b), 103.8 (C-3' and C-4'), 105.3 (C-1), 105.8 (C-2), 117.5 (C-3), 122.3 (C-8), 123.6 (C-12a),

124.5 (C-7), 128.9 (C-10), 130.1 (C-6a), 131.0 (C-2' and C-5'), 132.6 (C-9), 143.4 (C-10a), 163.8 (C-6). Anal. Calcd for $C_{32}H_{25}N_5O_2$: C, 75.13 ; H, 4.93 ; N, 13.69. Found : C, 74.95 ; H, 5.02 ; N, 13.32.

2,5-Di(*trans*-6,10b,11,12-tetrahydropyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one-12-yl)pyrrole (10). This compound was prepared from **3** (0.96 g, 4 mmol) and pyrrole (0.14 ml, 2 mmol) as described for **9**, yield 0.7 g (68 %), as colorless crystals, mp >260 °C (dimethylformamide). The ir, ^{1}H nmr and ^{13}C nmr spectra of this sample were identical with those recorded for **10**.

***N,N*-Dimethyl-2,3-dihydro-3-oxo-2-(pyrrol-1-yl)-1*H*-isoindol-1-acetamide (12).** To a stirred solution of **11**[1] (2.56 g, 0.01 mol) in acetone (15 ml) at 0 °C was added dropwise triethylamine (1.4 ml, 0.01 mol). After 30 min, ethyl chloroformate (0.96 ml, 0.01 mol) was added and the reaction mixture was stirred at 0 °C for 30 min. The precipitate formed was filtered and the filtrate was concentrated to dryness. The oily residue was then dissolved in dichloromethane (20 ml) and diethylamine (2.2 ml of 40 % aqueous solution) was added. The reaction mixture was stirred at room temperature for 20 min and then poured into water (10 ml). The organic layer was washed with water (2x10 ml), dried (magnesium sulfate) and evaporated. The solid was recrystallized from toluene to give **12** (1.8 g, 64 %), mp 150-151 °C ; ir : 1636, 1715 (C=O) cm^{-1}; ^{1}H nmr : δ 2.54 (dd, 1H, H-CH, J=9.4 and 15.9 Hz), 2.88 (dd, 1H, H-CH, J=3.8 and 15.9 Hz), 2.89 (s, 3H, CH_3), 2.94 (s, 3H, CH_3), 5.48 (dd, 1H, CH, J=3.8 and 9.4 Hz), 6.25 (t, 2H, $H_{3'}$ and $H_{4'}$, J=2.3 Hz), 6.74 (t, 2H, $H_{2'}$ and $H_{5'}$, J=2.3 Hz), 7.45-7.70 (m, 3H, H_{arom}), 7.86-7.94 (m, 1H, H_7); ms : m/z 283 (M^+). Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.81 ; H, 6.06 ; N, 14.83. Found : C, 68.18 ; H, 6.08 ; N, 14.49.

***N,N*-Dimethyl-(6,10b,11,12-tetrahydropyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one-12-yl)iminium perchlorate (13).** A solution of **12** (0.9 g, 3.2 mmol) in phosphorus oxychloride (7.5 ml, 80 mmol) was refluxed for 1 h and then concentrated to dryness. The solid residue was treated with ice-water (60 ml) and stirred for 30 min. The mixture was filtered with charcoal and the filtrate was adjusted to pH=8 with sodium hydrogen carbonate. Perchloric acid was then added to the solution until pH=2. The precipitate was filtered, washed with water and dried (magnesium sulfate) to give **13** (0.9 g). Recrystallization from dimethylformamide-ethanol (7:3) afforded pale yellow crystals (0.7 g, 60 %), mp 290-292 °C ; ir : 1717 (C=O) cm^{-1}; ^{1}H nmr : δ 3.20 (dd, 1H, H_{11}-ax, J=11.2 and 17.7 Hz), 3.60 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 4.09 (dd, 1H, H_{11}-eq, J=5.1 and 17.7 Hz), 5.49 (dd, 1H, H_{10b}, J=5.1 and 11.2 Hz), 6.79 (dd, 1H, H_2 , J=2.7 and 4.9 Hz), 7.59 (dd, 1H, H_1, J=1.2 and 4.9 Hz), 7.62-7.98 (m, 4H, H_{arom}), 8.20 (dd, 1H, H_3, H=1.2 and 2.7 Hz); ^{13}C nmr : δ 34.3 (C-11), 44.9 (CH_3), 47.3 (CH_3), 55.4 (C-10b),

111.4 (C-2), 117.8 (C-12a), 122.1 (C-1), 123.8 (C-8), 124.4 (C-7), 128.6 (C-6a), 129.7 (C-10), 130.2 (C-3), 133.7 (C-9), 143.0 (C-10a), 160.9 (C-12), 162.4 (C-6). Anal. Calcd for $C_{16}H_{16}N_3O_5Cl$: C, 52.53 ; H, 4.42 ; N, 11.49. Found : C, 52.81 ; H, 4.33 ; N, 11.63.

***cis*-6,10b,11,12-Tetrahydro-12-dimethylaminopyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindol-6-one (14).** To a stirred solution of **13** (0.73 g, 2 mmol) in methanol (30 ml) was added portionwise sodium borohydride (0.23 g, 6 mmol). The reaction mixture was refluxed for 1 h and the solvent was removed under reduced pressure. The residue was taken up in dichloromethane (25 ml) and filtered. The filtrate was washed with water (2x10 ml). The organic layer was dried (magnesium sulfate) and concentrated to dryness to give a solid. Recrystallization from ether afforded **14** (0.4 g, 75 %) as colorless crystals, mp 132-134 °C; ir : 1717 (C=O) cm^{-1}; ^1H nmr : δ 1.82 (td, 1H, H_{11}-ax, J=9.4 and 13.4 Hz), 2.16 (s, 6H, 2xCH_3), 2.50 (td, 1H, H_{11}-eq, J=5.0 and 13.4 Hz), 4.09 (dd, 1H, H_{12}-ax, J=5.1 and 9.3 Hz), 4.87 (dd, 1H, H_{10b}, J=4.5 and 9.6 Hz), 6.11-6.16 (m, 1H, H_1), 6.20 (dd, 1H, H_2, J=2.7 and 4.1 Hz), 7.44 (dd, 1H, H_3, J=1.7 and 2.7 Hz), 7.45-7.66 (m, 3H, H_{arom}), 7.86-7.93 (m, 1H, H_7) ; ^{13}C nmr : δ 28.8 (C-11), 40.9 (2xCH_3), 58.1 (C-10b), 58.3 (C-12), 104.4 (C-1), 105.9 (C-2), 117.7 (C-3), 122.0 (C-8), 124.6 (C-7), 124.7 (C-12a), 128.8 (C-10), 130.1 (C-6a), 132.4 (C-9), 144.1 (C-10a), 164.4 (C-6) ; ms : m/z 267 (M^+). Anal. Calcd for $C_{16}H_{17}N_3O$: C, 71.87 ; H, 6.42 ; N, 15.72. Found : C, 71.60 ; H, 6.64 ; N, 15.86.

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