AN EFFICIENT SYNTHESIS OF PYRROLO[1',2':2,3]PYRIDAZINO-[6,1-*a*]ISOINDOLES FROM 1-PHTHALIMIDOPYRROLE

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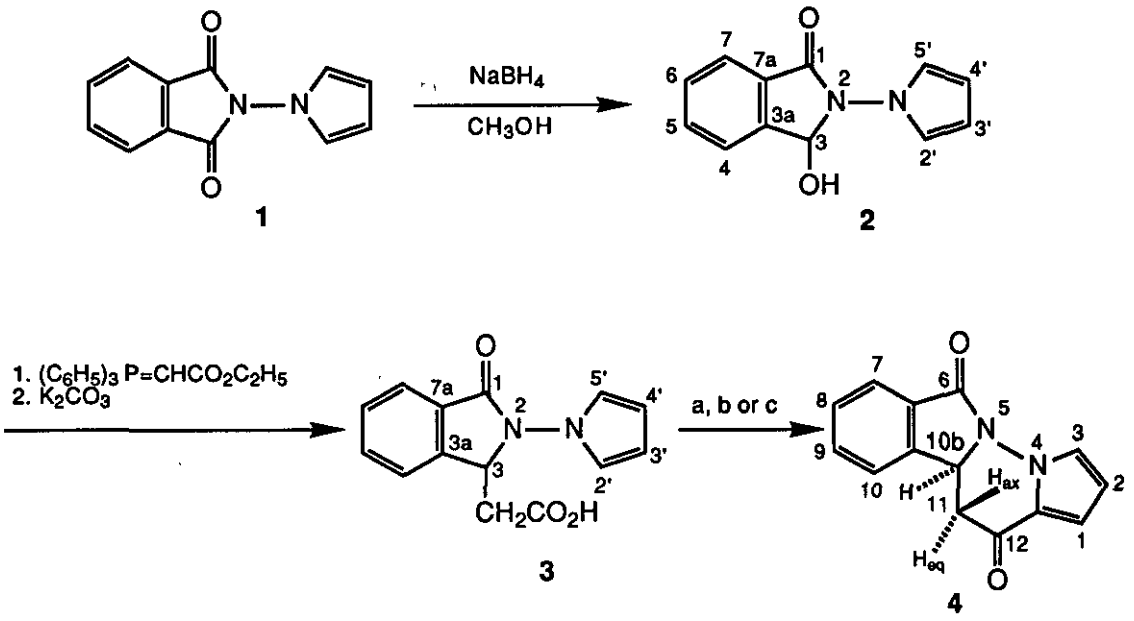
Abstract - A synthesis of pyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindole was developed. Reduction of 1-phthalimidopyrrole, followed by Wittig reaction using ethoxycarbonylmethylidenetriphenylphosphorane gave the carboxylic acid intermediate (**3**) which cyclized in the presence of boron trifluoride etherate to furnish the tricyclic ketone (**4**). Mannich reaction, Schmidt rearrangement, and reduction of the above ketone were studied.

In carrying on our exploration of the pharmacological potential of heteropolycyclic structures, we previously synthesized diazepines fused to a thiophene ring and to a pyrrole,[1] pyrrolidine[2,3] or piperidine[4] ring. On the other hand a recent work[5] showed that pyrrolotriazepine, a bicyclic system, exhibited a significant anticonvulsant activity and more recently the same group reported the synthesis of pyridopyrrolo[1,2,5]triazepines.[6] We now wish to report the synthesis of the pyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindole (**4**), a heterotricyclic skeleton leading to a triazepine system(**8**) as a potential non-diazepine anxiolytic.

As shown in Scheme 1, 1-phthalimidopyrrole (**1**),[7] prepared by acidic condensation of 1-aminophthalimide with 2,5-dimethoxytetrahydrofuran, was reduced by treatment of sodium borohydride to give the hydroxyisoindolone (**2**) in 85% yield. The Wittig reaction using ethoxycarbonylmethylidenetriphenylphosphorane and subsequent hydrolysis led to 2,3-dihydro-1-oxo-2-(pyrrol-1-yl)-1*H*-isoindole-3-acetic acid (**3**) in high yield (80 %). The cyclic product (**4**) could be obtained according to three methods. Treatment of the acid (**3**) in polyphosphoric acid at 100°C gave a poor yield (9 %) of ketone (**4**) (method a). At lower temperature the cyclization did not occur and at higher temperature the reaction gave degradation products. The second pathway (method b) consisted of heating the acid (**3**) with thionyl chloride in dichloromethane. Interestingly the acid chloride was not isolated as

described in the literature[8] and we observed a direct cyclization into the ketone (**4**) in 51 % yield. For isolating the ketone, chromatography was required. Accordingly, we tried another route suppressing this step of purification. The acid (**3**) was treated (method c) successively with *N*-ethylpiperidine, ethyl chloroformate and boron trifluoride etherate[9] to give the expected cyclic ketone (**4**) directly as a crystalline product in a better yield (67 %).

Scheme 1



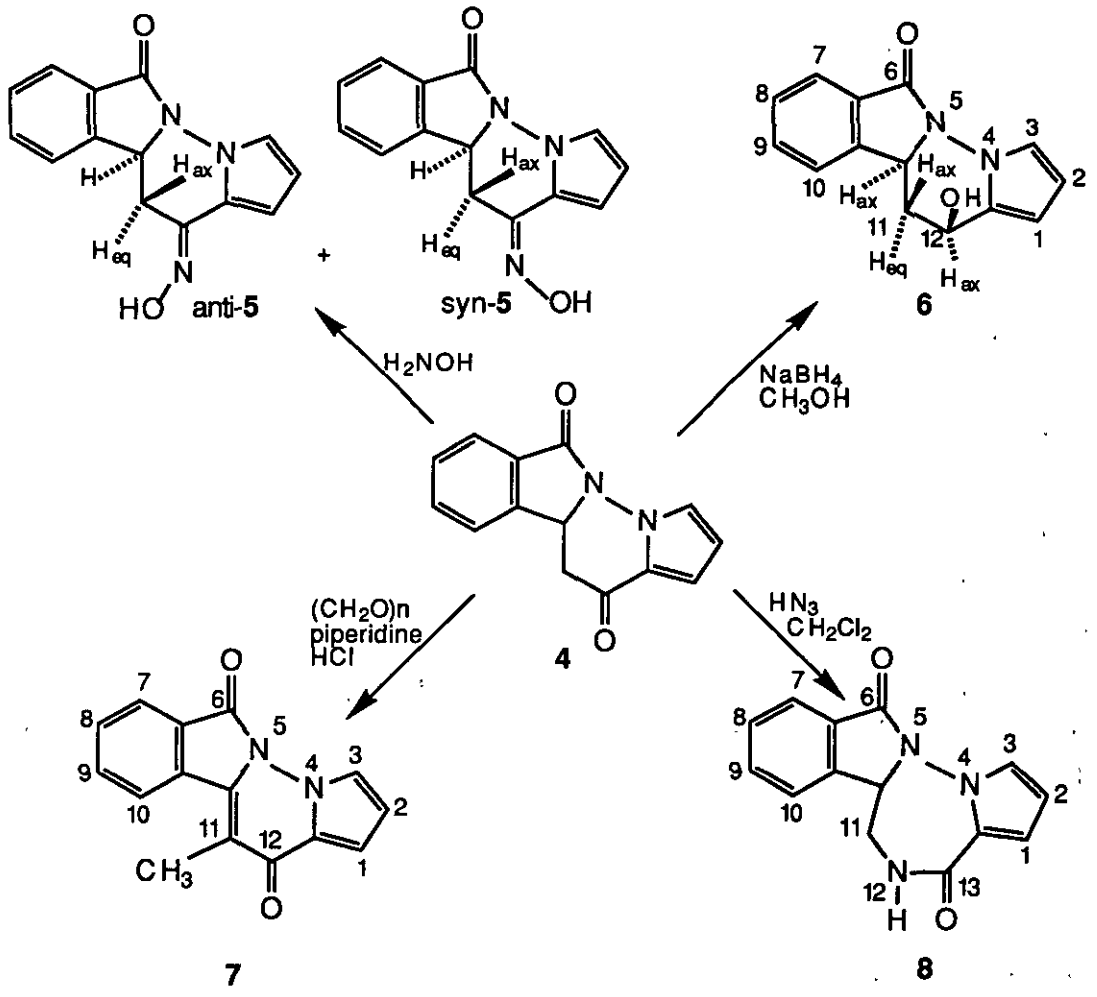
a) PPA b) $SOCl_2$, CH_2Cl_2 C) *N*-ethylpiperidine, $ClCOOC_2H_5$, BF_3, $(C_2H_5)_2O$

The structure of this new tetracyclic system was supported by the ir and nmr spectra as well as by the microanalyses. The ketone (**4**) shows characteristic signals as doublet of doublet due to the three protons of a monosubstituted pyrrole ring with usual coupling constants of J=1.6, 2.7, 4.4 Hz. Furthermore the protons at 11 position are non-equivalent and these peaks appear as a doublet of doublet at 2.73 ppm for the axial (ax) proton and at 3.23 ppm for the equatorial proton (eq) and coupling constants of J=16.6 Hz (H_{11}-ax, H_{11}-eq), J=12.4 Hz (H_{11}-ax, H_{10b}) and J=4.3 Hz (H_{11}-eq, H_{10b}). Finally, the signal of the proton H_{10b} appears as a doublet of doublet (J=4.3, 12.4 Hz) at 5.66 ppm.

To explore reactivities of the new heterocyclic skeleton, some chemical transformations were next examined. Ketone (**4**) (Scheme 2) was treated with hydroxylamine hydrochloride in the presence of sodium acetate to afford a mixture of oximes (*syn* + *anti*) in good yield (78 %). The *syn* (80 %) isomer was the major product and this result is in accordance with those obtained previously with thienoindolizidinones oximes.[2,10] For these oximes the

two protons attached to C_{11} are not equivalent in the nmr spectrum. The equatorial proton (H_{11}-eq) of the *anti* isomer is at lower magnetic field (3.95 ppm) than H_{11}-eq (3.34 ppm) of the *syn* isomer. This deshielding effect is due to the proximity of the hydroxyl group toward H_{11}-eq in the *anti* configuration. Similar effect can be observed for the proton H_1 of the pyrrole ring in the *syn* configuration. Since the mixture of oximes (**5**) could not be separated, the Beckmann rearrangement of the mixture was attempted using polyphosphoric acid. Unfortunately, we observed a completely degradation or no reaction depending on the temperature of the reaction. The Schmidt rearrangement of ketone (**4**) using sodium azide in concentrated sulfuric acid gave only one product namely 10b,11-dihydroisoindolo[2,1-*g*]pyrrolo[1,2,5]triazepin-6(6*H*),13(12*H*)-dione (**8**) in 68% yield. This [1,2,5]-triazepine corresponds to the product being expected from the Beckmann rearrangement of the major oxime. The proton nmr spectra support this assignment. The signal of C_{11} - protons shift to lower field (δ=3.60 - 3.80 ppm) and are multiplets due to the closely - NH -. Furthermore, the chemical shift of the H_1 proton of the pyrrole ring (δ=6.67 ppm), is similar to those observed in fused pyrrolopyrazinone[11] or pyrrolo[1,4]diazepinones.[1,12,13]

Scheme 2



A Mannich reaction of **4** with paraformaldehyde and piperidine gave 11-methylpyrrolo[1',2':2,3]pyridazino-[6,1-*a*]isoindole-6(6*H*),12-dione (**7**) in 76% yield. The ^{1}H nmr spectrum shows a methyl group and no piperidine ring, and the hydrogen atome of the junction is also absent. This fact suggests an elimination of piperidine from the piperidinomethyl intermediate and subsequent tautomerism of the exomethylene intermediate leading to the conjugate ketone (**7**).

Since the ketone (**4**) has two different faces, it was interesting to study the reduction. Thus, sodium borohydride reduction of **4** gave the expected alcohol (**6**). The ^{1}H nmr spectrum revealed the presence of only one isomer. The stereochemical assignment was based on the coupling constants of H_{10b}- H_{12}. The signal of H_{10b} was observed as a doublet of doublet (4.2 and 10.4 Hz). Similarly, the signal of H_{12} is a doublet of doublet with a *cis* coupling constant of 6.1 Hz and a *trans* coupling constant of 9.2 Hz. The signals of protons H_{11}-ax and H_{11}-eq are furthermore complicated with a geminal coupling constant of 12.7 Hz, H_{11}-ax is a doublet of doublet of doublet showing a geminal and two *trans* coupling constants of 9.2 and 10.4 Hz. The signal of H_{11}-eq is similar and exhibit a geminal and two *cis* coupling constants of 4.2 and 6.0 Hz. Furthermore, there is a remarkable difference of chemical shift between H_{11}-ax (1.55 ppm) and H_{11}-eq (2.74 ppm). These data strongly suggest a *cis* structure for **6**, in which the hydroxyl group has an equatorial position.

In summary, a synthesis of pyrrolo[1',2':2,3]pyridazino[6,1-*a*]isoindole was described from the ready available 1-aminophthalimide. The Schmidt rearrangement of the above ketone led to a [1,2,5]triazepine fused to a pyrrole and an isoindole rings. The stereoselective reduction of this ketone furnished a *cis* alcohol and the Mannich reaction led to an interesting α substitution with a methyl group accompagnied with an α,β-conjugation.

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 FTIR Spectrophotometer (potassium bromide). The nmr spectra were recorded on a Bruker AC-200 spectrometer (200 MHz) in DMSO-d_6 using tetramethylsilane (^{1}H) or DMSO-d_6 (^{13}C, δ=39.5 ppm) as the internal standard. 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(**2-8**) gave the expected molecular ions.

2,3-Dihydro-3-hydroxy-2-(pyrrol-1-yl)-1H-isoindole-1-one (2). Sodium borohydride (1.9 g, 0.05 mol) was

added portionwise to a suspension of 1-phthalimidopyrrole[7] (10.6 g, 0.05 mol) in methanol (100 ml) at 0-5 °C for 30 min. The mixture was stirred at 0-5 °C for 2 h. After removal of the solvent, the residue was diluted with water (50 ml) and acidified with 10% hydrochloric acid to pH 4. The resulting precipitates were collected by filtration and washed with water. Recrystallization from benzene gave 9.1 g (85%) of alcohol (**2**) as colorless crystals, mp 133-134 °C ; ir : 3314 (O-H), 1705 (C=O) cm^{-1} ; ^1H nmr : δ 6.05 (d, 1H, H-3, J=9.2 Hz), 6.13 (t, 2H, H-3' and H-4', J=2.2 Hz), 6.89 (t, 2H, H-2' and H-5', J=2.2 Hz), 7.15 (d, 1H, OH, J=9.2 Hz), 7.56-7.84 (m, 4H, H_{arom}) ; ^{13}C nmr ; δ 83.2 (d, C-3), 107.1 (d, C-3' and C-4'), 121.9 (d, C-2' and C-5'), 123.1, 124.0, 129.8 and 133.4 (d, C_{arom}), 128.9 (s, C-7a), 143.4 (s, C-3a), 164.5 (s, C=O) ; ms : m/z 214 (M^+). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28 ; H, 4.71 ; N, 13.08. Found : C, 67.41 ; H, 4.83 ; N, 13.02.

2,3-Dihydro-1-oxo-2-(pyrrol-1-yl)-1H-isoindole-3-acetic acid (3). A mixture of **2** (9.0 g, 0.042 mol) and ethoxycarbonylmethylidenetriphenylphosphorane (17.6 g, 0.05 mol) in toluene (120 ml) was refluxed for 1 h and concentrated to give a residue. A mixture of the residue and potassium carbonate (11.6 g, 0.084 mol) in water-methanol (30/120 ml) was refluxed for 2 h, concentrated, diluted with water, and washed with dichloromethane. The water layer was acidified with 10% aqueous hydrochloric acid. The precipitates were collected and washed with water. Recrystallization from ethanol afforded 8.6 g (80 %) of acid (**3**) as colorless crystals, mp 235-237 °C ; ir : 1730 and 1665 (C=O) cm^{-1} ; ^1H nmr : δ 2.71 (dd, 1H, H-CH, J=6.4 and 16.6 Hz), 2.84 (dd, 1H, H-CH, J=5.3 and 16.6 Hz), 5.31 (dd, 1H, H-3, J=5.3 and 6.4 Hz), 6.13 (t, 2H, H-3' and H-4', J=2.3 Hz), 6.95 (t, 2H, H-2' and H-5', J=2.3 Hz), 7.52-7.84 (m, 4H, H_{arom}) ; ^{13}C nmr : δ 35.6 (t, CH_2), 59.6 (d, C-3), 107.4 (d, C-3' and C-4'), 121.9 (d, C-2' and C-5'), 123.2, 123.4, 128.8 and 132.9 (d, C_{arom}), 129.1 (s, C-7a), 143.4 (s, C-3a), 165.2 (s, C=O), 171.0 (s, CO_2H) ; ms : m/z 256 (M^+). Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.61 ; H, 4.73 ; N, 10.93. Found : C, 65.44 ; H, 4.91 ; N, 11.09.

10b,11-Dihydropyrrolo[1',2':2,3]pyridazino[6,1-a]isoindole-6(6H),12-dione (4).

Procedure A : A stirred suspension of acid(**3**) (3.4 g, 13.2 mmol) in dichloromethane (100 ml) was treated with thionyl chloride (1.7 g, 14.6 mmol) and refluxed over night. The mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel eluting with chloroform to give crystals. Recrystallization from ethanol afforded 1.6 g (51%) of ketone(**4**) as colorless crystals, mp 224-225 °C ; ir : 1732 and 1663 (C=O) cm^{-1} ; ^1H nmr : δ 2.73 (dd, 1H, H_{11}-ax, J=12.4 and 16.6 Hz), 3.23 (dd, 1H, H_{11}-eq, J=4.3 and 16.6 Hz), 5.66 (dd, 1H, H_{10b}, J=4.3 and 12.4 Hz), 6.39 (dd, 1H, H_2, J=2.7 and 4.4 Hz), 6.93 (dd, 1H, H_1, J=1.6 and 4.4 Hz), 7.55-7.67 (m, 1H, H_{arom}), 7.70-7.79 (m, 3H, $2H_{arom}$ and H_3), 7.83-7.93 (m, 1H, H_{arom}) ; ^{13}C nmr : δ 41.4 (t, CH_2), 58.4 (d, C-10b), 108.3 (d, C-2), 110.8 (d, C-1), 123.1 (d, C-arom), 123.6 (d, C-3), 124.0 (d, C-arom), 121.4 (s, C-12a), 129.0 (s, C-6a), 129.1 and 133.0 (d, C-arom), 143.5 (s, C-10a), 161.9 (s, C-6), 181.7 (s, C-12) ; ms : m/z 238 (M^+). Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.57 ; H, 4.24 ; N, 11.76. Found : C, 70.43 ; H, 4.41 ; N, 11.50.

Procedure B : To a stirred solution of **3** (2.56 g, 0.01 mol) and *N*-ethylpiperidine (1.5 ml, 0.011 mol) was added dropwise ethyl chloroformate (1.1 ml, 0.011 mol) at 0 °C. The reaction mixture was stirred in an ice-bath for 2 h. Boron trifluoride etherate (48%, 5.6 ml, 0.021 mol) was added dropwise at 0 °C and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into ice-water and extracted with dichloromethane. The organic phase was washed twice with 10 % aqueous sodium hydroxide (50 ml) and then with water, dried (sodium sulfate), filtered and concentrated in vacuo. The crude product was recrystallized from ethanol to give 1.6 g (67%) of **4**.

10b,11-Dihydro-12-oximinopyrrolo[1',2':2,3]pyridazino[6,1-a]isoindole-6(6H)-one (5). A mixture of ketone (**4**) (1.2 g, 5 mmol), hydroxylamine hydrochloride (0.7 g, 10 mmol), and sodium acetate (0.8 g, 10 mmol) in aqueous 60% ethanol (50 ml) was refluxed for 5 h. Ice water cooling afforded crystalline precipitates, which were collected and washed with 50% aqueous ethanol. Recrystallization from ethanol afforded 1.0 g (78 %) of oxime (**5**) as a 4 : 1 mixture of *syn* and *anti* isomers, mp 248-50 °C ; ir : 1692 (C=O) cm^{-1}.

(*syn*)-**5** : ^1H nmr : δ 2.40 (dd, 1H, H_{11}-ax, J=12.5 and 15.0 Hz), 3.34 (dd, 1H, H_{11}-eq, J=3.7 and15.0 Hz), 5.25 (dd, 1H, H_{10b}, J=3.7 and 12.5 Hz), 6.31 (dd, 1H, H_2, J=2.9 and 4.2 Hz), 7.16 (dd, 1H, H_1, J=1.7 and 4.2 Hz), 7.60 (dd, 1H, H_3, J=1.7 and 2.9 Hz), 7.63-7.92 (m, 4H, H_{arom}), 11.30 (s, 1H, OH).

(*anti*)-**5** : ^1H nmr : δ 2.17 (dd, 1H, H_{11}-ax, J=12.2 and 16.9 Hz), 3.95 (dd, 1H, H_{11}-eq, J=4.6 and 16.9 Hz), 5.23 (dd, 1H, H_{10b}, J=4.6 and 12.2 Hz), 6.23 (dd, 1H, H_2, J=2.9 and 4.1 Hz), 6.52 (dd, 1H, H_1, J=1.6 and 4.1 Hz), 7.49 (dd, 1H, H_3, J=1.6 and 2.9 Hz), 7.55-7.90 (m, 4H, H_{arom}), 11.20 (s, 1H, OH) ; ms : m/z 253 (M^+). Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.39 ; H, 4.39 ; N, 16.59. Found : C, 66.63 ; H, 4.51 ; N, 16.48.

10b,11-Dihydro-12-hydroxy-12H-pyrrolo[1',2':2,3]pyridazino[6,1-a]isoindole-6(6H)-one(6). Sodium borohydride (0.2 g, 5 mmol) was added portionwise to a suspension of ketone (**4**) (1.2 g, 5 mmol) in methanol (20 ml) at 0-5 °C. The mixture was stirred at 0-5 °C for 2 h. After addition of water (10 ml), the mixture was neutralized with 10% aqueous hydrochloric acid , concentrated and the resulting precipitate was collected by filtration and washed successively with water and ether. Recrystallization from benzene gave 0.7 g (58%) of alcohol (**6**), mp 168-170 °C ; ir : 3403 (O-H), 1700 (C=O) cm^{-1} ; ^1H nmr : δ 1.55 (ddd, 1H, H_{11}-ax, J=9.2, 10.4 and 12.7 Hz), 2.74 (ddd, 1H, H_{11}-eq, J=4.2, 6.0 and 12.7 Hz), 5.00 (td, 1H, H_{12}, J=6.0 and 9.2 Hz), 5.21 (dd, 1H, H_{10b}, J=4.2 and 10.4 Hz), 5.48 (d, 1H, OH, J=6.3 Hz), 6.08-6.18 (m, 2H, H_1 and H_2), 7.33-7.37 (m, 1H, H_3), 7.53-7.86 (m, 4H, H_{arom}) ; ^{13}C nmr : δ 37.4 (t, C-11), 57.7 (d, C-10b), 61.5 (d, C-12), 103.1 (d, C-1), 105.3 (d, C-12), 116.6 (d, C-3), 123.0, 123.7 (d, C-arom), 127.9 (s, C-12a), 128.8, 132.8 (d, C-arom), 129.1 (s, C-6a), 144.4 (s, C-10a), 163.4 (s, 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, 69.75 ; H, 4.91 ; N, 11.57.

11-Methylpyrrolo[1',2':2,3]pyridazino[6,1-a]isoindole-6(6H),12-dione (7). A mixture of ketone (**4**) (1.5 g, 6.3 mmol), piperidine (0.7 g, 8.2 mmol), paraformaldehyde (99%, 0.4 g, 3.2 mmol) and concentrated hydrochloric acid (0.03 ml) in ethanol (10 ml) was refluxed for 2 h and cooled to room temperature. The resulting yellow solid was collected by filtration and washed with cooled ethanol. Recrystallization from ethanol afforded 1.2 g (76 %) of ketone(**7**), mp 293-294°C ; ir : 1740 and 1632 (C=O) cm^{-1} ; ^1H nmr ($CDCl_3$) : δ 2.49 (s, 3H, CH_3), 6.51 (dd, 1H, H_2, J=2.7 and 4.4 Hz), 7.02 (dd, 1H, H_1, J=1.6 and 4.4 Hz), 7.55-7,78 (m, 2H, H_{arom}), 7,91-8.00 (m, 2H, H_{arom}), 8,59 (dd, 1H, H_3, J=1.6 and 2.7 Hz) ; ms : m/z 250 (M^+). Anal. Calcd for $C_{15}H_{10}N_2O_2$: C, 71.99 ; H, 4.04 ; N, 11.20. Found : C, 72.16 ; H, 4.22 ; N, 11.01.

10b,11-Dihydroisoindolo[2,1-g]pyrrolo[1,2-b][1,2,5]triazepine-6(6H),13(12H)-dione (8). To a vigorously stirred solution of 4 (0.83 g, 3.5mmol) in dichloromethane (25 ml) was added dropwise sulfuric acid (2.4 ml) at 0 °C for 10 min. Sodium azide (0.65 g, 10 mmol) was added portionwise for 30 min at 0-5 °C and the mixture was stirred at room temperature overnight. The mixture was poured into crushed ice and neutralized with potassium carbonate. After removal of dichloromethane *in vacuo*, the resulting precipitates were collected by filtration and washed successively with water and ether. Recrystallization from ethanol afforded 0.6 g (68 %) of triazepine (**8**) as colorless crystals, mp : 333-335°C ; ir : 3300 (N-H), 1728 (C=O) cm^{-1} ; ^1H nmr: δ 3,60-3.80 (m, 2H, H_{11}), 5,40 (d, 1H, H_{10b}, J=3.4 Hz), 6.26 (dd, 1H, H_2, J=2.9 and 4.0 Hz), 6.67 (dd, 1H, H_1, J=1.7 and 4.0 Hz), 7.21 (dd, 1H, H_3, J=2.9 and 1.7 Hz), 7.47 (dd, 1H, NH, J=4.4 and 6.4 Hz), 7.56-7.68 (m, 1H, H_{arom}), 7.77-7.87 (m, 3H, H_{arom}) ; ^{13}C nmr : δ 42.8 (t, C-11), 65.3 (d, C-10b), 107.7 (d, C-2), 113.5 (d, C-1), 123.7, 124.2 (d, C-arom), 126.6 (d, C-3), 126.9 (s, C-13a), 129.4 (s, C-6a), 129.4, 134.1 (d, C-arom), 124.9 (s, C-10a), 164.1 (s, C-6), 169.7 (s, C-13) ; ms : m/z 253 (M^+). Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.39 ; H, 4.39 ; N, 16.59. Found : C, 66.16 ; H, 4.16 ; N, 16.77.

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