Polycyclic Systems: Synthesis of Isoindolo[2,1-*b*]-pyrrolo[1,2-*d*][2,4]benzodiazocine and Isoindolo-[1,2-*d*]pyrrolo[1,2-*a*][1,5]benzodiazocine

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The synthesis of isoindolo[2,1-*b*]pyrrolo[1,2-*d*][2,4]benzodiazocine **7** and isoindolo[1,2-*d*]pyrrolo[1,2-*a*]-[1,5]benzodiazocine **13** are described starting from 2-(2-methoxycarbonyl)benzylphthalimide **1a** and ethyl α-bromohomophthalate **9** respectively.

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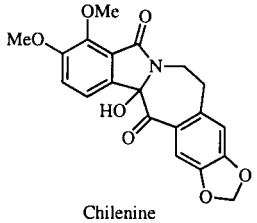
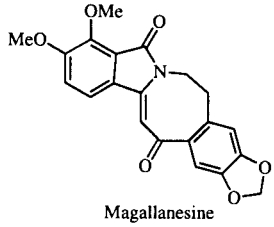
Over the last ten years many synthetic efforts have been directed toward synthesis of polycyclic compounds containing an isoindole, pyrrole, benzazepine, benzazocine, or benzodiazepine systems because a number of natural products as chilenine [1,2] or magallanesine [2,4] have these moieties and present potential biological activities. Recently we described [5] some thienothiazocinoisoindolediones from mercaptothiophenes and chloromethylphthalimide. With our interest in the synthesis of diversely substituted polycyclic systems [5-9] we wish to report herein an interesting approach to [1,3] or [1,5] diazocines annelated to isoindole and pyrrole moieties and either a benzene ring or a thiophene ring.



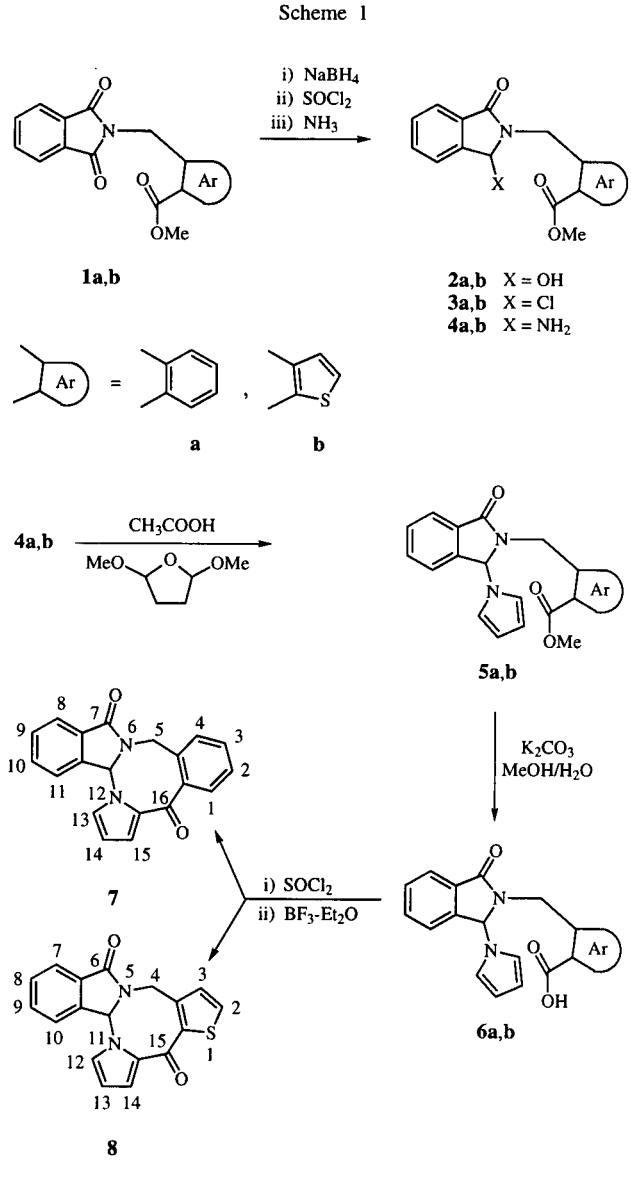
Chilenine



Magallanesine

The [1,3]diazocines were prepared as indicated in Scheme 1. Reduction of imide **1a** by sodium borohydride in the presence of acid [10] gave the hydroxylactam **2a** (X = OH). The latter was treated with thionyl chloride in dichloromethane and the resulting chlorolactam **3** (X = Cl) submitted to the action of ammonia in dichloromethane [11] led to the 3-amino derivative **4a** (X = NH_2) [12] in an overall yield of 74%. Reaction of the amino group with 2,5-dimethoxytetrahydrofuran in acetic acid, according to the Clauson-Kaas procedure [13], provided the pyrrole derivative **5** (58%). Saponification of **5** with potassium carbonate furnished the corresponding acid **6a** (99%). Treated with thionyl chloride in dichloromethane **6a** gave the acid chloride which under Friedel-Crafts cyclization conditions using boron trifluoride as a catalyst afforded the expected ketone **7** in 48% yield. The ketone **7** exhibits a N-CH_2 methylene ^1H nmr signal as two doublets with chemical shifts of 4.12 and 5.21 ppm with a coupling constant of J = 14 Hz. The N-CH-N proton appears as a singlet with a chemical shift of 6.35 ppm and the pyrrole presents a AMX system characteristic of a 1,2 disubstituted pyrrole.

Scheme 1



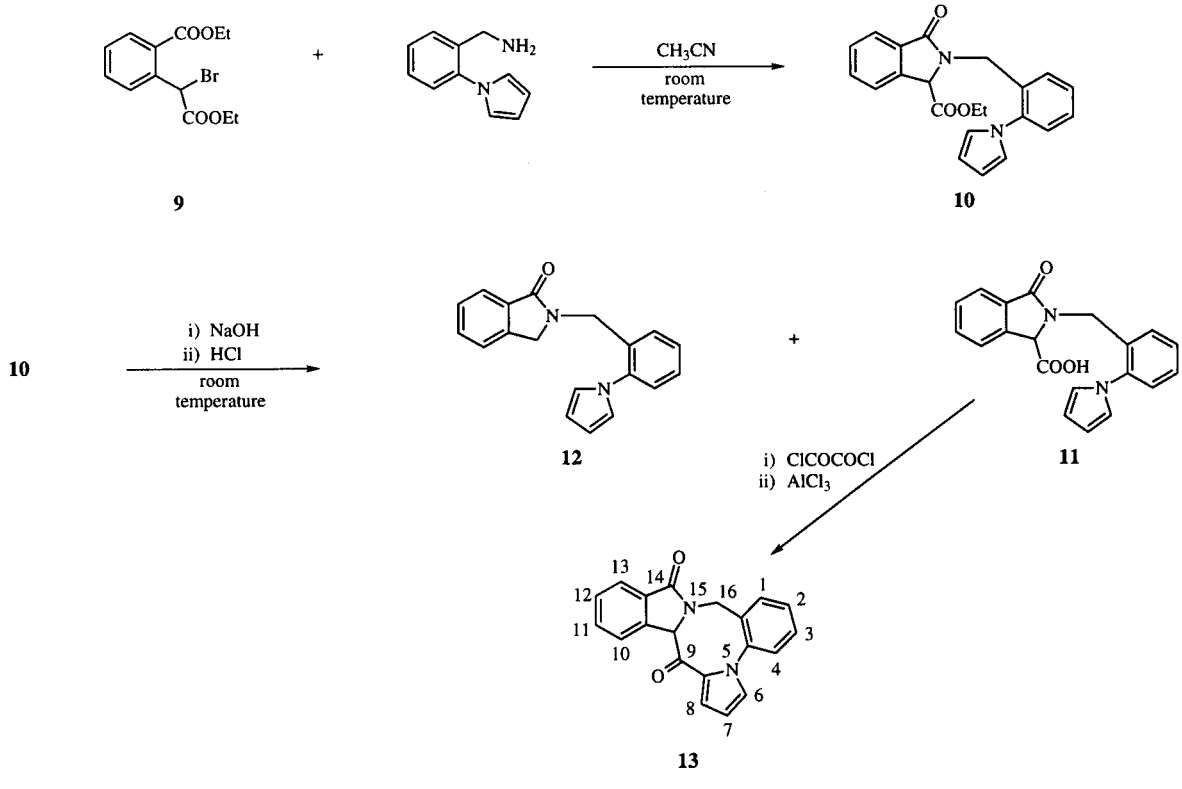
A generalization of this procedure could be given starting from the known methyl 3-phthalimidomethylthiophene-2-carboxylate **1b** [14]. According to Scheme 1 in five steps the ester **1b** gave the expected thieno[2',3':6,7]-[1,3]diazocino[2,1-*a*]isoindoledione **8** in an overall yield of 26%.

The isoindolo[1,2-*d*]pyrrolo[1,2-*a*][1,5]benzodiazocine **13** isomer of **7** has been synthesized as shown in Scheme 2. Reaction of *o*-(pyrrol-1-yl)benzylamine [15] with diethyl bromohomophthalate **9** [9] in acetonitrile at room temperature led to the phthalimidine **10** (72%). This reaction was similar to that used in our previous work [9] describing a new access to ethyl phthalimidine-3-carboxylate. Saponification of the ester **10** by sodium hydroxide at room temperature furnished the acid **11** accompanied with a small amount of **12**. Actually, as previously mentioned [16] we have observed that *N*-substituted phthamidine-3-carboxylic acids were very sensitive to decarboxylation. A light heating or even on standing at room temperature decarboxylation occurred. These acids might be conserved in a cold storage (-18°). Compounds **11** and **12** were separated by chromatography (silica gel, dichloromethane-acetone) to get analytical samples. Nevertheless, the mixture **11** + **12** was sufficiently pure to react in the next step. Submitted to oxalyl chloride at 0°, **11** gave the acid chloride which was cyclized in a Friedel-Crafts procedure using aluminium trichloride (99.99%) as a catalyst. The unreactive compound **12** was separated from **13** by chromatography (silica gel, dichloromethane). The benzodiazocine **13** was obtained in a 80% yield.

A similar reaction conducted with thionyl chloride, followed by the action of aluminiun trichloride gave poor yield. The structure of **13** was supported by spectroscopic measurements as well as by microanalysis. Details are reported in the Experimental. In view of the ^{1}H nmr spectra the distinguish between **7** and **13** was particularly evident with respect to the chemical shift of N-CH-CO proton in **13** (δ = 4.83 ppm), compared to the corresponding N-CH-N proton in **7** (δ = 6.35 ppm). The chemical shifts of the other protons are similar.

In summary, we have described the synthesis of isoindolopyrrolo[2,4] or [1,5]benzodiazocine from ready available *N*-substituted 3-(pyrrol-1-yl)phthalimide or phthalimidine-3-carboxylic acid derivatives. Further studies of these polycyclic systems and biological screening are under investigations and will be published soon.

Scheme 2



EXPERIMENTAL

Melting points are uncorrected. The infrared spectra of solids (potassium bromide) were recorded on a Perkin Elmer FTIR paragon 1000 spectrometer. The ^1H and ^{13}C nmr spectra were recorded on a Bruker AC-200 (200 MHz) instrument in deuteriochloroform solution and the chemical shifts (δ) are expressed in ppm relative to internal tetramethylsilane. 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. The amines **4a,b** were synthesized as previously described [12].

2,3-Dihydro-3-(pyrrol-1-yl)-2-(2-methoxycarbonylarylmethyl)-1*H*-isoindol-1-ones **5a,b**.

General Procedure.

A solution of aminolactams **4a,b** (10 mmoles), dimethoxytetrahydrofuran (0.65 ml) in acetic acid was refluxed for 4 hours. The solution was concentrated under reduced pressure then the residue was dissolved in dichloromethane. The organic layer was washed with a solution of sodium hydrogen carbonate, dried and concentrated under reduced pressure. The residue was chromatographed (silica gel, dichloromethane). Recrystallization from ethanol afforded pure compounds **5a,b**.

2,3-Dihydro-3-(pyrrol-1-yl)-2-(2-methoxycarbonylbenzyl)-1*H*-isoindol-1-one (**5a**).

This compound was obtained in a yield of 58%, mp 110°; ir: 1714 (C=O), 1694 (C=O) cm^{-1}; ^1H nmr: δ 3.77 (s, 3H, CH_3), 4.40 (d, J = 14 Hz, 1H, NCH_2), 5.31 (d, J = 14 Hz, 1H, NCH_2), 6.07 (t, J = 2 Hz, 2H, $H_{pyrrole}$), 6.13 (s, 1H, CH), 6.40 (t, J = 2 Hz, 2H, $H_{pyrrole}$), 7.12-7.41 (m, 4H, H_{arom}), 7.44-7.55 (m, 2H, H_{arom}), 7.79-7.92 (m, 2H, H_{arom}).

Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.60; H, 5.29; N, 8.05.

2,3-Dihydro-3-(pyrrol-1-yl)-2-(2-methoxycarbonylthien-3-ylmethyl)-1*H*-isoindol-1-one (**5b**).

This compound was obtained in a yield of 62%, mp 125°; ir: 1715 (C=O), 1702 (C=O) cm^{-1}; ^1H nmr: δ 3.80 (s, 3H, CH_3), 4.72 (d, J = 16 Hz, 1H, NCH_2), 5.12 (d, J = 16 Hz, 1H, NCH_2), 6.08 (t, J = 2 Hz, 2H, $H_{pyrrole}$), 6.26 (s, 1H, CH), 6.49 (t, J = 2 Hz, 2H, $H_{pyrrole}$), 6.99 (d, J = 5 Hz, 1H, $H_{thiophene}$), 7.20-7.30 (m, 1H, H_{arom}), 7.33 (d, J = 5 Hz, 1H, $H_{thiophene}$), 7.45-7.55 (m, 2H, H_{arom}), 7.85-7.95 (m, 1H, H_{arom}).

Anal. Calcd. for $C_{19}H_{16}N_2O_3S$: C, 64.76; H, 4.58; N, 7.95. Found: C, 64.67; H, 4.51; N, 7.92.

2,3-Dihydro-3-(pyrrol-1-yl)-2-(2-carboxyarylmethyl)-1*H*-isoindol-1-one **6a,b**.

General Procedure.

A mixture of esters **5a,b** (3 mmoles), potassium carbonate (0.8 g), water (2 ml) and methanol (8 ml) was stirred under reflux for 2 hours. After cooling, the solution was concentrated under reduced pressure. Water and dichloromethane were added and the organic layer was discarded. The aqueous layer was washed with dichloromethane and acidified with hydrochloric acid (10%) to *p*H = 2. Compounds **6a,b** were extracted with dichloromethane several times. After removal of the solvent, the residue was recrystallized from acetone to give pure **6a,b**.

2,3-Dihydro-3-(pyrrol-1-yl)-2-(2-carboxybenzyl)-1*H*-isoindol-1-one (**6a**).

This compound was obtained in a yield of 99%, mp 191°; ir: 3023 (OH), 1706 (C=O), 1691 (C=O) cm^{-1}; ^1H nmr: δ 4.60 (d, J = 16 Hz, 1H, NCH_2), 5.35 (d, J = 16 Hz, 1H, NCH_2), 6.01 (t, J = 2 Hz, 2H, $H_{pyrrole}$), 6.23 (s, 1H, CH), 6.47 (t, J = 2 Hz, 2H, $H_{pyrrole}$), 7.14-7.18 (m, 1H, H_{arom}), 7.26-7.45 (m, 3H, H_{arom}), 7.49-7.60 (m, 2H, H_{arom}), 7.91-8.02 (m, 2H, H_{arom}).

Anal. Calcd. for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 71.95; H, 4.84; N, 8.44.

2,3-Dihydro-3-(pyrrol-1-yl)-2-(2-carboxythien-3-ylmethyl)-1*H*-isoindol-1-one (**6b**).

This compound was obtained in a yield of 97%, mp 240°; ir: 2942 (OH), 1698 (C=O), 1664 (C=O) cm^{-1}; ^1H nmr: δ 4.57 (d, J = 17 Hz, 1H, NCH_2), 4.97 (d, J = 17 Hz, 1H, NCH_2), 6.01 (t, J = 2 Hz, 2H, $H_{pyrrole}$), 6.65 (t, J = 2 Hz, 2H, $H_{pyrrole}$), 6.74 (s, 1H, CH), 6.80 (d, J = 5 Hz, 1H, $H_{thiophene}$), 7.29-7.42 (m, 1H, H_{arom}), 7.57-7.71 (m, 3H, H_{arom} + $H_{thiophene}$), 7.76-7.88 (m, 1H, H_{arom}).

Anal. Calcd. for $C_{18}H_{14}N_2O_3S$: C, 63.89; H, 4.17; N, 8.28. Found: C, 63.98; H, 3.93; N, 8.25.

Cyclization of Acids **6a,b** into Diazocines **7** and **8**.

General Procedure.

A mixture of acid **6a,b** (3.5 mmoles), dry dichloromethane (20 ml) and thionyl chloride (0.3 ml) was stirred under reflux until all solid has disappeared. Reflux was continued for 30 minutes. After cooling, the solution was evaporated. The residue was dissolved in dry dichloromethane (50 ml). To this solution of acid chloride was added a solution of borontrifluoride-etherate complex (1.4 ml, 48% in ether). Stirring was continued for 3 days, then the solution was poured in cold water and the mixture was decanted. The aqueous layer was extracted with dichloromethane (20 ml). The combination of organic layers was washed with water, dried and evaporated. The solid was recrystallized from chloroform to give **7** or **8**.

5,11b-Dihydroisoindolo[2,1-*b*]pyrrolo[1,2-*d*][2,4]benzodiazocine-7,16-dione (**7**).

This compound was obtained in a yield of 48%, mp >270°; ir: 1699 (2C=O) cm^{-1}; ^1H nmr: δ 4.12 (d, J = 14 Hz, 1H, H_5), 5.21 (d, J = 14 Hz, 1H, H_5), 6.23-6.27 (m, 1H, H_{14}), 6.35 (s, 1H, H_{11b}), 6.48-6.50 (m, 1H, $H_{pyrrole}$), 7.32-7.66 (m, 8H, 7H_{arom} + 1$H_{pyrrole}$), 7.86-7.97 (m, 1H, H_8); ^{13}C nmr: δ 41.7 (CH_2), 67.6 (CH), 110.9 (CH), 122.1 (CH), 124.2 (CH), 124.3 (CH), 124.7 (CH), 129.3 (CH), 130.4 (CH), 130.8 (CH), 131.2 (CH), 132.2 (C), 132.3 (CH), 133.1 (CH), 133.4 (C), 136.1 (C), 138.0 (C), 140.2 (C), 164.0 (CO), 182.5 (CO).

Anal. Calcd. for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 75.98; H, 4.36; N, 8.82.

4,10b-Dihydropyrrolo[1',2':3,4]thieno[2',3':6,7][1,3]diazocino[1,2-*a*]isoindole-6,15-dione (**8**).

This compound was obtained in a yield of 56%, mp >270°; ir: 1704 (C=O), 1696 (C=O) cm^{-1}; ^1H nmr: δ 3.91 (d, J = 14 Hz, 1H, H_4), 5.33 (d, J = 14 Hz, 1H, H_4), 6.26 (t, J = 3 Hz, 1H, H_{13}), 6.38-6.43 (m, 1H, $H_{pyrrole}$), 6.64 (s, 1H, H_{10b}), 7.10 (d, J = 5 Hz,

1H, H_3), 7.15-7.25 (m, 1H, H_{arom}), 7.45-7.55 (m, 1H, $H_{pyrrole}$), 7.58-7.65 (m, 2H, H_{arom}), 7.66 (d, J = 5 Hz, 1H, H_2), 7.85-7.95 (m, 1H, H_7); ^{13}C nmr: δ 36.3 (CH_2), 68.2 (CH), 111.1 (CH), 120.4 (CH), 123.5 (CH), 124.2 (CH), 124.5 (CH), 130.8 (CH), 130.9 (CH), 132.6 (CH), 133.4 (C), 134.3 (CH), 134.7 (C), 136.4 (C), 138.5 (C), 144.5 (C), 164.4 (CO), 175.4 (CO).

Anal. Calcd. for $C_{18}H_{12}N_2O_2S$: C, 67.48; H, 3.78; N, 8.74. Found: C, 67.10; H, 3.78; N, 8.68.

2,3-Dihydro-3-ethoxycarbonyl-2-[2-(pyrrol-1-yl)benzyl]-1*H*-isoindol-1-one (**10**).

To a solution of diethyl α-bromohomophthalate **9** (3.15 g, 10 mmoles) in dry acetonitrile was added under an atmosphere of argon the *o*-(pyrrol-1-yl)benzylamine (3.5 g, 20 mmoles), and the resulting mixture was stirred at room temperature for 8 hours. The salt that formed was removed by filtration, and the filtrate was concentrated. The oily residue was purified by column chromatography (silica gel-dichloromethane) to give the ester **10** (2.6 g, 72%); ir: 1746 (C=O), 1702 (C=O) cm^{-1}; ^1H nmr: δ 1.16 (t, J = 7 Hz, 3H, CH_3), 3.98-4.09 (m, 2H, CH_2), 4.26 (d, J = 15 Hz, 1H, CH_2-N), 4.66 (s, 1H, CH), 5.23 (d, J = 15 Hz, 1H, CH_2-N), 6.29 (t, J = 2 Hz, 2H, $H_{pyrrole}$), 6.75 (t, J = 2 Hz, 2H, $H_{pyrrole}$), 7.27-7.33 (m, 4H, H_{arom}), 7.47-7.50 (m, 3H, H_{arom}), 7.81-7.90 (m, 1H, H_{arom}).

Anal. Calcd. for $C_{22}H_{20}N_2O_3$: C, 73.31; H, 5.59; N, 7.77. Found: C, 73.02; H, 5.52; N, 7.79.

Saponification of Ester **10** to Acid **11**.

To the ester **10** (3.6 g, 10 mmoles) in 20 ml of ethanol was added sodium hydroxide (0.8 g, 20 mmoles) in 5 ml of water. The reaction mixture was stirred at room temperature for 12 hours, concentrated *in vacuo,* diluted with water and washed with dichloromethane and decanted.

2,3-Dihydro-2-[2-(pyrrol-1-yl)-benzyl]-1*H*-isoindol-1-one (**12**).

The above organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a solid which was recrystallized from ethanol to furnish pure **12** (0.6 g, 10%), mp 109°; ir: 1683 (C=O) cm^{-1}; ^1H nmr: δ 4.08 (s, 2H, CH_2-N), 4.67 (s, 2H, CH_2-N), 6.34 (t, J = 2 Hz, 2H, pyrrole), 6.83 (t, J = 2 Hz, 2H, pyrrole), 7.31-7.36 (m, 5H, H_{arom}), 7.43-7.49 (m, 2H, H_{arom}), 7.86 (d, J = 7 Hz, 1H, H_{arom}).

Anal. Calcd. for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 78.86; H, 5.54; N, 9.73.

2,3-Dihydro-3-carboxy-2-[2-(pyrrol-1-yl)benzyl]-1*H*-isoindol-1-one (**11**).

The previous aqueous layer was acidified with (10%) hydrochloric acid solution to *p*H = 2 and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and concentrated to give acid **1** (2 g, 62%). An analytical sample was obtained from a chromatography (silica gel-dichloromethane/acetone 9/1), mp 80° dec; ir: 2885 (OH), 1742 (C=O), 1700 (C=O) cm^{-1}; ^1H nmr: δ 4.36 (d, J = 15 Hz, 1H, CH_2N), 4.72 (s, 1H, CH), 5.27 (d, J = 15 Hz, 1H, CH_2N,), 6.19 (t, J = 2 Hz, 2H, $H_{pyrrole}$), 6.73 (t, J = 2 Hz, 2H, $H_{pyrrole}$), 7.26-7.60 (m, 7H, H_{arom}), 7.81 (d, J = 7 Hz, 1H, H_{arom}).

10b,16-Dihydroisoindolo[1,2-*d*]pyrrolo[1,2-*a*][1,5]benzodiazocine-9,14-dione (**13**).

A mixture of acid **11** (1 g, 3 mmoles) in dry dichloromethane (20 ml), oxalyl chloride (0.3 ml) and 3 drops of *N,N*-dimethylformamide was stirred for 4 hours. The solution was evaporated under reduced pressure and the residue was dissolved into dry dichloromethane (20 ml) to furnish a solution of the corresponding acyl chloride. This solution was added dropwise to a stirred mixture of aluminium trichloride (99.99%, 1.5 g, 11 mmoles) and dry dichloromethane (40 ml). Stirring was continued for 1 hour. The solution was poured into cold water and decanted. The aqueous layer was extracted once with dichloromethane (20 ml). The combination of organic layers was dried over magnesium sulfate and concentrated. Recrystallization from ethanol gave pure **13** (0.7 g, 80%), mp 261°; ir: 1702 (C=O), 1645 (C=O) cm^{-1}; ^1H nmr: δ 4.17 (d, J = 13 Hz, 1H, H_{16}), 4.83 (s, 1H, H_{9a}), 5.40 (d, J = 13 Hz, 1H, H_{16}), 6.46-6.49 (m, 1H, $H_{pyrrole}$), 7.05 (t, J = 2 Hz, 1H, $H_{pyrrole}$), 7.37-7.57 (m, 8H, $1H_{pyrrole}$ + $7H_{arom}$), 7.82 (d, J = 7 Hz, 1H, H_{13}); ^{13}C nmr: δ 42.0 (CH_2), 62.8 (CH), 111.7 (CH), 121.6 (CH), 123.8 (CH), 125.5 (CH), 126.3 (CH), 128.7 (CH), 129.7 (CH), 130.3 (CH), 130.9 (CH), 131.0 (C), 131.4 (CH), 131.6 (CH), 132.1 (CH), 135.3 (C), 139.7 (C), 140.2 (C), 166.8 (CO), 180.2 (CO).

Anal. Calcd. for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.35; H, 4.41; N, 8.93.

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