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Synthesis of Indoles: Tetrahydropyrazino[1,2-*a*]indole-1,4-dione and Pyrazino[1,2-*a*]indole-6,13-diones from Piperazine-2,5-diones

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ABSTRACT

The readily available piperazine-2,5-dione has been used to prepare both 1:1 (1–3**), with stereotopic methylene protons; and 2:1 (**4–6**) arylmethylenepiperazine-2,5-diones in above average yields. The halo-derivatives,** 1, 4 **and** 5 **were cyclized to pyrazino[1,2-*a*]indoles,** 7–9**, using copper bronze. Indole compounds** 7 **and** 9 **were further treated, separately, with lithium aluminium hydride, sodium borohydride, lithium hydroxide monohydrate and butyl lithium to yield 2-substituted indoles** 10–13**.**

KEYWORDS

Indoles, piperazine-2,5-diones, arylaldehydes, 1:1 adducts, 2:1 adducts.

1. Introduction

Piperazine-2,5-dione derivatives have been isolated as terrestial plant alkaloids. They exhibit valuable biological properties, such as antifungal,[1] antitumor,[2] and antibiotic[3] activities. Most are simple monofunctional derivatives while others contain two substituents at the methylene positions of the piperazine-2,5-dione. Examples include the cytotoxic antitumor C-3 and C-6 disubstituted unsymmetrical piperazine-2-5-dione derivatives, neihumicin and albonoursin.[3,4,5] Generally, the unsymmetrical C-3 and C-6 disubstituted piperazine-2,5-diones are more cytotoxic than the corresponding symmetrical piperazine-2,5-diones.[3] X-ray crystallographic studies have shown that the presence of *N* and/or α-C substituents play an important role in determining the conformations of the piperazine-2,5-diones.[6] This property has been exploited to study conformational directing effects and stereoselectivity. For example, chiral induction in carbon–carbon bond formation reactions can be obtained with methylene piperazine-2,5-diones.[7] This chiral induction has found application in the synthesis of optically active amino acids *via* bis-lactam ethers of piperazine-2,5-dione.[8]

Here we report the ability to generate indoles from arylmethylenepiperazine-2,5-diones, and bis(arylmethylene) piperazine-2,5-diones. No such reactions of piperazine-2,5-diones have been reported in the literature. Hydrolysis of the piperazine-2,5-dione rings in the products of cyclization could produce 2-substituted indoles. This is particularly important because indoles are most reactive at the 3-position, and will react at this position before substituents can be added, as electrophiles, to the 2-position

2. Results and Discussion

The condensation of piperazine-2,5-dione with aldehydes to generate 1:1 3-([arylmethylidene]piperazine-2,5-diones) or 2:1, (3,6-bis(arylmethylidene)piperazine-2,5-diones) adducts has been reported.[5,9] In the present study, an attempt was made to avoid the use of acetyl protection and piperazine-2,5-dione was condensed with a range of aldehydes using potassium acetate as base in the presence of one mole equivalent of acetic anhydride, to yield adducts **1–3** (Table 1).

The *Z*-configuration of the double bond was established through 2D NMR experiments. The non-equivalence of the 6-H protons suggested that the adducts were not planar, but existed in a stable skewed conformation. Chem3D[10] molecular model rendition of the molecules revealed that one proton resided in a more axial orientation than the other. The preference observed for the skewed conformation indicates that the nitrogen at position 1 must be sp^3 hybridized and the lone-pair of electrons is aligned *cis* or *trans* to the neighboring 6-H methylene protons. By contrast, the nitrogen at position 4 must be more amide-like and sp^2 hybridized. The rate of inversion at the nitrogen must be slow on the NMR time scale so that the neighboring protons appear non-equivalent and couple to each other and to the NH proton. Variable temperature experiments revealed that at 366 K, the 1-NH and 6-H protons resonated as broad triplets, and not as distinct doublets of doublets as in the spectrum obtained at room temperature. However, when the temperature was further increased to 380 K, all the triplets collapsed to broad singlets, indicating that with increase in temperature, the rate of inversion was also increased. By contrast, the nitrogen at position 4 must retain its amide character as the proton attached to it continued to resonate at δ 10.53 ppm at higher temperature. The unexpected but consistent nature of the 6-H proton signals in these molecules was surprising in view of the reported synthesis of other arylmethylidenepiperazine-2,5-diones without mention of these spectroscopic features.

When piperazine-2,5-dione was condensed with two mole equivalents of aldehydes, 3,6-bis-arylmethylidenepiperazine-2,5-diones, **4–6**, were obtained (Table 2). The ^{1}H NMR spectra of these adducts indicated that they were all symmetrical (3-*Z*, 6-*Z*-configuration). Olefin geometry was confirmed by

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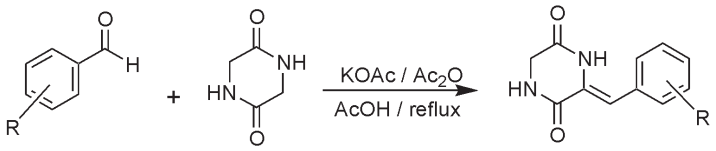
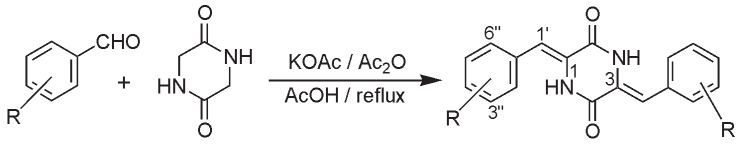
Table 1 Yield and isomer ratio of 3-[arylmethylidene]piperazine-2,5-diones **1–3**.



1-3

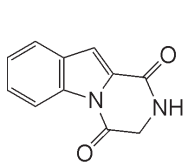
Adduct	Time /h	2″-R	5″-R	% Yield	m.p. /°C	(Z):(E)
1	3	Cl	H	75	298–300	100:0
2	5	Cl	NO_2	55	365–367	100:0
3	16	OMe	OMe	41	305–306	100:0

Table 2 Yield and isomer ratio of 3, 6-bis(arylmethylene)piperazine-2,5-diones **4–6**.



4-6

Adduct	Time /h	2″-R	5″-R	% Yield	m. p. /°C	(Z):(E)
4	3	Cl	H	50	355–357	100:0
5	5	Cl	NO_2	48	320–322	100:0
6	16	OMe	OMe	38	285–286	100:0



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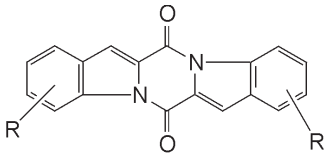
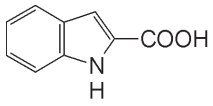


8: $R^2 = R^9 = NO_2$; **9**: R = H



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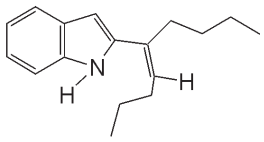

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NOESY NMR experiments. Electron-donating methoxy groups slowed the rate of condensation and gave lower yields.

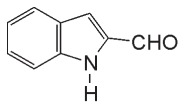
Ullmann reactions generally utilize finely divided copper, a copper (I) salt or an isolable organocopper compound as catalyst, during halogen displacement.[11,12] Treatment of **1, 4** and **5** with copper gave, after work-up and recrystallization, fluorescent products **7–9**. All the products showed a change in chemical shift of what was the olefinic proton signal. The extra ring current of electrons generated as a result of cyclization, makes the protons in question aromatic and therefore more deshielded. Solubility was very poor at room temperature, even in very polar solvents like trifluoracetic acid. The marked insolubility of the products was found difficult to explain. Cyclization of the 2:1 adducts, **4** and **5**, was achieved at a higher temperature and with longer reaction times than for the 1:1 adduct.

Compounds **7** and **9** reacted with lithium aluminium hydride and sodium borohydride to afford carboxaldehyde **10** and alcohol **11**.

The yields were found to vary with the molar ratio of the lithium aluminium hydride used and the reaction temperature (Table 3).

The results indicate that more selective reduction to the aldehyde can be achieved at the lower temperature and with higher molar equivalents of the reductant. The yield of the alcohol was somewhat higher at 25°C. Reduction of **9** proceeds with perfect atom economy, since no loss of an equivalent mole of glycine occurs, unlike that of **7**.

Base hydrolysis ($LiOH.H_2O$) of **9** afforded the 2-carboxylic acid **12** that could have been obtained by attack of the hydroxy nucleophile on either of the carbonyl groups of the piperazine-2,5-dione portion of the molecule. BuLi addition to **7** afforded butylpent-1-enylindole **13** (Z-configuration). **13** could only have been formed through nucleophilic attack by the reagent at the conjugated amide carbonyl group; it is therefore likely that the reduction and hydrolytic reactions proceeded in the same way. The addition indicated that the conjugated carbonyl group of the indolepiperazine-2,5-diones was the most electrophilic. This approach can be used to prepare a range of 2-substituted indoles which can be used in further transformations.



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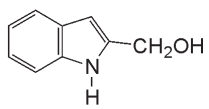

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3. Experimental

3.1. General

Melting points were measured on a Reichert microscope and are uncorrected. Ultraviolet spectra were measured on a Hitachi U-3200 spectrophotometer and refer to solutions in absolute

Table 3 Reductive cleavage of **7** and **9** (R = indol-2-yl).

Compound	Reductant	Mol. equiv	Temp. /°C	(**10**) RCHO /%	(**11**) RCH_2OH (%)
7	$LiAlH_4$	0.25	0	97	1
7	$LiAlH_4$	0.5	25	83	5
7	$NaBH_4$	0.25	0	85	1
7	$NaBH_4$	0.5	0	90	2
9	$LiAlH_4$	0.25	0	90	2
9	$LiAlH_4$	0.5	25	89	3

MeOH. Infrared spectra were recorded on a Perkin-Elmer 298 IR spectrometer. The samples were either prepared as neat films or Nujol mulls. ^{1}H NMR spectra were recorded in designated solvents on a Bruker DMX 500 (500 mHz) Avance instrument. Data are reported as follows: chemical shift (δ) in ppm downfield from tetramethylsilane (TMS), number of protons, multiplicity, observed coupling constant(s) (J in Hz) and proton assignment. Multiplicities are reported as singlet (s), broad singlet (br s), doublet (d), broad doublet (br d), doublet of doublets (dd), triplet (t), multiplet (m). The ^{13}C NMR spectra were also recorded on a Bruker DMX 500 spectrometer at 75.06 mHz and are reported in ppm downfield from TMS. The electron impact (EI) mass spectra were recorded on a VG Quattro mass spectrometer with an ionizing potential of 70 eV and an ion source temperature of 220°C. The principal ion peaks m/z are reported together with their percentage intensities relative to the base peak. HRMS were recorded on a Bruker Daltonics (Bellerica, MA), BiopAPEX II 7T FT/ICR mass spectrometer.

3.2. General Procedure for Preparation of Adducts 1–6[13]

Molar equivalents of piperazine-2,5-dione and the aldehydes (1:1 adducts) or 2 mole equivalents of aldehydes (2:1 adducts), anhydrous KOAc, glacial AcOH (3 drops) were dissolved together at r.t. and the mixture warmed to reflux temperature. Reactions were monitored by thin layer chromatography analysis until all the aldehyde had reacted. Upon cooling, the mixture gave a precipitate which was collected and recrystallized from EtOH.

3-[(Z)-1-(2-Chlorophenyl)methylidene]piperazine-2,5-dione (**1**)

2-Chlorobenzaldehyde (1.60 g, 11.5 mmol), reacted to give **1** as white needles, (0.90 g, 75%), m.p. 298–300°C; δ_H (500 MHz, DMSO-d_6 at 278 K) 3.40 (1H, dd, J 10.0, 5.3 Hz, 6-H_a), 3.46 (1H, dd, J 10.0, 5.6 Hz, 6-H_b), 4.54 (1H, dd J 5.5, 5.3 Hz; 1-NH), 6.78 (1H, s, 1′-H), 7.33 (2H, dd, J 7.5, 2.0 Hz, 4″-H and 5″-H), 7.49 (1H, dd, J 7.5, 2.0 Hz, 3″-H), 7.61 (1H, dd, J 2.0, 7.2 Hz, 6″-H), 10.53 (1H, br s, 4-NH); δ_C (500 MHz, DMSO-d_6 at 360 K) 45.2 (C-6), 110.2 (C-1′), 127.7 (C-4″), 129.1 (C-3), 129.7 (C-3″), 129.8 (C-5″), 130.8 (C-6″), 132.3 (C-1″), 133.4 (C-2″), 159.6 (C-2), 164.8 (C-5); λ_{max}/nm (MeOH) 208 (ε 2.4 × 10^4), 231 (1.5 × 10^4), 260 (1.1 × 10^4); ν_{max}/cm^{-1} (Nujol): 3015, 2590, 1650, 1450, 1350,780, 700, 690; m/z 236 (M^+, 4%), 208 (6), 180 (12), 170 (8), 141 (15), 140 (100), 127 (14), 125 (5), 109 (17), 100 (40), 99 (22), 91 (7), 82 (12), 81 (16), 70 (17), 69 (81), 68 (52), 56 (13), 54 (44), 52 (18), 44 (35), 43 (52), 42 (63), 41 (79); (Found: C, 55.63; H, 3.83; N, 11.84; Calc. for $C_{11}H_9ClN_2O_2$ (236.65): C, 55.83; H, 3.86; N, 11.61%).

3-[(Z)-1-(2-Chloro-5-nitrophenyl)methylidene]piperazine-2,5-dione (**2**)

2-Chloro-5-nitrobenzaldehyde, (1.00 g, 5.5 mmol), reacted to give **2** as yellow needles, (0.82 g, 55%), m.p. 365–367°C; δ_H (500 MHz, DMSO-d_6) 3.41 (1H, dd, J 10.0, 5.4 Hz, 6-H_a), 3.45 (1H, dd, J 10.0, 5.2 Hz, 6-H_b), 4.60 (1H, dd, J 5.4, 5.2 Hz, 1-NH), 6.73 (1H, s, 1′-H), 7.80 (1H, d, J 8.7 Hz, 3″-H), 8.16 (1H, dd, J 9.0, 2.5 Hz, 4″-H), 8.37 (1H, d, J 2.5 Hz, 6″-H), 11.00 (1H, br s, 4-NH); δ_C (500 MHz, DMSO-d_6) 72.6 (C-6), 109.2 (C-1′), 124.4 (C-3), 126.5 (C-3″), 130.6 (C-1″), 131.0 (C-3″), 133.5 (C-4″), 140.2 (C-2″), 146.8 (C-5″), 157.8 (C-2), 172.4 (C-5); ν_{max}/cm^{-1} (Nujol) 2300, 1700, 1650, 1500, 1380, 1350, 1250, 1150, 1050, 850, 750; m/z 281 (M^+, 0.5%), 246 (100), 218 (3), 216 (8), 200 (39), 179 (7), 172 (3), 150 (8), 125 (7), 123 (22), 114 (17), 97 (4), 87 (5), 73 (6), 60 (8), 57 (6), 45 (11), 43 (17); (Found: C, 46.58; H, 2.93; N, 14.55; Calc. for $C_{11}H_8ClN_3O_4$ (281.64): C, 46.91; H, 2.86; N, 14.92%).

3-[(Z)-1-(2,5-Dimethoxyphenyl)methylidene]piperazine-2,5-dione (**3**)

2,5-Dimethoxybenzaldehyde (2.00 g, 12.00 mmol) reacted to give **3** as yellow needles, (1.30 g, 41%), m.p. 305–306°C; δ_H (500 MHz, DMSO-d_6) 3.40 (1H, dd, J 10.0, 5.6 Hz, 6-H_a), 3.46 (1H, dd, J 10.0, 5.3 Hz, 6-H_b), 3.73 (3H, s, 5″-OCH_3), 3.78 (3H, s, 2″-OCH_3), 4.52 (1H, dd, J 5.6, 5.3 Hz, 4-NH); 6.78 (1H, s, 1′-H), 6.91 (1H, dd, J 9.8, 3.0 Hz, 4″-H), 6.92 (1H, s, 6″-H), 7.01 (1H, d, J 9.8 Hz, 3″-H), 10.04, (1H, br s, 4-NH); δ_C (500 MHz, DMSO-d_6) 45.1 (C-6), 55.8 (2″-OCH_3), 56.4 (5″-OCH_3), 110.0 (C-1′), 112.7 (C-3″), 114.7 (C-4″), 115.7 (C-6″), 123.0 (C-1″), 127.2 (C-3), 151.4 (C-2″), 15.2 (C-5″), 160.0 (C-2), 164.5 (C-5); λ_{max}/nm (MeOH) 204 (ε 3.1 × 10^5), 271 (4.7 × 10^5). 371 (5.4 × 10^5); ν_{max}/cm^{-1} (Nujol) 2500, 1690, 1600, 1450, 1360, 1290, 1000; m/z 263 (M+1, 4%), 262 (M^+, 34), 232 (10), 231 (100), 216 (3), 190 (4), 176 (8), 163 (8), 162 (21), 136 (15), 119 (13), 97 (9), 81 (13), 69 (18), 60 (25), 55 (17), 45 (43), 43 (63); (Found: C, 59.30; H, 5.37; N, 10.47; Calc. for $C_{13}H_{14}N_2O_4$ (262.25): C, 59.53; H, 5.38; N, 10.68%)

3,6-Bis-[(Z)-1-(2-chlorophenyl)methylidene]piperazine-2,5-dione (**4**)

2-Chlorobenzaldehyde (3.20 g, 22.9 mmol) and piperazine-2,5-dione (1.30 g, 11.45 mmol), reacted after 3 h to afford **4** as yellow prisms, (3.94 g, 48%), m.p. 320–322°C; δ_H (500 MHz, DMSO-d_6 at 366 K) 6.79 (2H, s, 1′-H), 7.34-7.39 (4H, m, 4″-H and 5″-H), 7.51 (2H, dd, J 7.2, 2.0 Hz, 6″-H), 7.60 (2H, dd, J 7.2, 2.0 Hz, 3″-H), 10.48 (2H, br s NH); δ_C (500 MHz, DMSO-d_6 at 366 K) 111.9 (C-1′), 127.8 (C-4″ and C-5″), 128.7 (C-3), 130.1 (C-3″ and C-6″), 132.2 (C-1″), 133.7 (C-2″), 157.6 (C-2); ν_{max}/cm^{-1} (Nujol) 3020, 1850, 1680, 1650, 1450, 1380, 710; m/z 358 (M^+, absent), 326 (6%), 325 (36), 323 (100), 288 (6), 287 (27), 259 (3), 246 (5), 172 (5), 171 (28), 153 (5), 151 (11), 144 (21), 116 (11), 115 (17), 114 (7), 89 (18), 55 (9), 45 (18), 43 (27); (Found: C, 60.31; H, 3.16; N, 8.01; Calc. for $C_{18}H_{12}Cl_2N_2O_2$ (358.27): C, 60.34; H, 3.35; N, 7.82%).

3,6-Bis-[(Z)-1-(2-chloro-5-nitrophenyl)methylidene]piperazine-2,5-dione (**5**)

2-Chloro-5-nitrobenzaldehyde (2.00 g, 11.0 mmol) and piperazine-2,5-dione (0.63 g, 5.5 mmol), reacted after 5 h to give **5** as yellow needles, (2.49 g, 50%), m.p. 355–357°C; δ_H (500 MHz,

DMSO-d_6) 6.74 (2H, s, 1′-H), 7.80 (2H, d, *J* 8.8 Hz, 3″-H), 8.16 (2H, dd, *J* 8.8, 3.0 Hz, 4″-H), 8.34 (2H, d, *J* 3.0, 6″-H), 10.93 (2H, br s, NH); δ_C (500 MHz, DMSO-d_6) 109.3 (C-1′), 124.4 (C-4″), 126.5 (C-6″), 130.6 (C-3), 131.0 (C-1″), 133.5 (C-3″), 140.2 (C-2″), 146.8 (C-5″), 157.7 (C-2); λ_{max}/nm (MeOH) 210 (ε 1.2 × 10^5), 214 (1.3 × 10^5), 276 (3.2 × 10^5), 326 (2.1 × 10^5); ν_{max}/cm^{-1} (Nujol) 2300, 1680, 1650, 1410, 1450, 1350, 1300, 810, 710; *m*/*z* 448 (M^+, absent), 335 (M-113, 2%), 334 (13), 333 (44), 303 (3), 302 (21), 310 (33), 299 (12), 285 (8), 257 (24), 256 (49), 255 (7), 254 (6), 241 (20), 233 (22), 228 (21), 227 (100), 201 (100), 189 (43), 173 (94), 156 (27), 149 (80), 131 (74), 129 (30), 128 (22), 115 (20), 103 (19), 91 (9), 85 (7), 57 (9), 43 (13), 41 (16) (Found: C, 47.80; H, 2.07; N, 12.18; Calc. for $C_{18}H_{10}Cl_2N_4O_6$ (449.18) C, 48.13; H, 2.24; N, 12.47%)

3,6-Bis-[(Z)-1-(2,5-dimethoxyphenyl)methylidene]piperazine-2,5-dione (**6**)[14]

2,5-Dimethoxybenzaldehyde (2.00 g, 12.00 mmol), piperazine-2,5-dione (0.68 g, 6.00 mmol), anhyd. NaOAc (5.00 g), Ac_2O (3 drops) and AcOH (10 mL) were refluxed together for 16 h. Upon cooling the mixture gave a yellow solid that was recrystallized from EtOH to afford **6** as yellow needles, (1.87 g, 38% yield), m.p. 285–286°C (lit.[14] m.p. 282–283°C); δ_H (500 MHz, DMSO-d_6) 3.73 (6H, s, 5″-OCH_3), 3.78 (6H, s, 2″-OCH_3), 6.78 (2H, s, 1′-H), 6.92 (2H, dd, *J* 7.2, 3.0 Hz, 3″-H), 6.95 (2H, d, *J* 3.0 Hz, 6″-H), 7.00 (2H, dd, *J* 7.2, 2.0 Hz, 4″-H), 10.10, (2H, br s, NH).

3.3. Cyclization of Selected Adducts

General procedure for cyclization

The arylmethylinepiperazine-2,5-dione, copper bronze (0.005 g), and quinoline were refluxed together. The solution was cooled and filtered through filter aid to remove excess copper. The filtrate was washed with 10% aq. HCl (3 times) and the solid obtained was recrystallized from AcOH to afford the indole-piperazine-2,5-diones.

1,2,3,4-Tetrahydropyrazino[1,2-a]indole-1,4-dione (**7**)[14]

Arylmethylenepiperizine-2,4-dione **1** (0.40 g, 1.70 mmol), reacted in a Wood's metal bath at 180°C for 2 h to afford **7** as yellow platelets (0.32 g, 94% yield) m.p. 245-246°C (lit.[14] m.p. 242–245°C); δ_H (500 MHz, DMSO-d_6 at 366K) 3.45 (1H, dd, *J* 10.0, 6.0 Hz, 3-H_a), 3.52 (1H, dd, *J* 10.0, 6.0 Hz, 3-H_b), 4.07 (1H, dd, *J* 10.0, 6.0 Hz, 2-NH), 7.43 (1H, dd, *J* 7.1, 2.0 Hz, 7-H), 7.60 (1H, dd, *J* 7.1, 2.0 Hz, 8-H), 7.79 (1H, s, 10-H), 7.86 (1H, dd, *J* 7.1, 2.0 Hz, 6-H), 8.47 (1H, d, *J* 7.1, 2.0 Hz, 9-H); δ_C (500 MHz, DMSO-d_6 at 366 K) 72.7 (C-3), 116.4 (C-6), 117.2 (C-9), 123.9 (C-5a), 125.5 (C-8), 129.1 (C-6a), 129.2 (C-7), 130.1 (C-10a), 136.4 (C-9), 153.6 (C-2), 163.8 (C-5); λ_{max}/nm (MeOH) 239 (ε 1.7 × 10^5), 269 (2.0 × 10^5), 271 (2.0 × 10^5), 273 (2.0 × 10^5); ν_{max}/cm^{-1} (Nujol) 2500, 1700, 1350, 1360, 1100, 1000; *m*/*z* 201 (M+1, 3%), 200 (M^+, 36), 144 (7), 143 (96), 116 (5), 115 (100), 100 (3), 89 (3), 88 (20), 63 (7), 62 (12), 56 (8), 50 (5), 43 (4).

2,9-Dinitro-6H,13H-indolo[1′,2′:4,5]pyrazino[1,2-a]indole-6,13-dione (**8**)

Bis(arylmethylene)piperazine-2-5-dione **5** in dry DMF (5 mL) reacted for 3 h to afford **8** as yellow powder (0.35 g, 80%) m.p. 300–302°C; δ_H (500 MHz, DMSO-d_6 at 366K) 8.08 (1H, s, 7-H and 14-H), 8.49 (2H, dd, *J* 8.9, 2.0 Hz, 4-H and 11-H), 8.65 (2H, d, *J* 8.9 Hz; 3-H and 10-H), 8.85 (2H, d, *J* 2.0 Hz, 1-H and 8-H); δ_C (500 MHz, DMSO-d_6 at 366 K) 119.3 (C-7 and C-14), 125.4 (C-3 and C-10), 126.8 (C-1 and C-8), 131.6 (C-6a and C-13a), 132.0 (C-7a and C-14a), 134.5 (C-4 and C-11), 141.2 (C-4a and C11a), 147.0 (C-2 and C-9), 156.7 (C-6 and C-13); *m*/*z* 376 (M^+, absent), 368 (8%), 306 (3), 290 (2), 287 (2), 236 (5), 213 (2), 201 (6), 183 (10), 157 (3), 152 (5), 137 (8), 123 (8), 107 (9), 95 (18), 81 (29), 69 (66), 57 (98), 55 (100), 43 (99) (Found: *m*/*z* 399.0657; Calc. for $C_{18}H_8N_4O_6Na$: 399.1406 [M+Na]).

6H, 13H-Indolo[1′,2′:4,5]pyrazino[1,2-a]indole-6,13-dione (**9**)[15]

Bis(arylmethylene)piperazine-2-5-dione **4** reacted in a Wood's metal bath at 200°C for 3 h to afford **9** as yellow platelets (0.13 g, 52%), m.p. 320–322°C, (lit.[15] m.p. 326–328°C); δ_H (500 MHz, DMSO-d_6 at 366K) 7.40 (2H, , *J* 7.2, 7.2, 2.0 Hz, 1-H and 8-H), 7.60 (2H, , *J* 7.2, 7.2, 2.0 Hz, 2-H and 9-H), 7.78 (2H, s, 7-H and 14-H), 7.85 (2H, dd, *J* 8.2, 2.0 Hz, 4-H and 11-H), 8.46 (2H, dd, *J* 7.2, 2.0 Hz, 3-H and 10-H);δ_C (500 MHz, DMSO-d_6 at 366 K) 116.5 (C-7 and C-14), 117.3 (C-1, C-4, C-8 and C-11), 124.0 (C-2, C-3, C-9 and C-10), 125.6 (C-7a and C-13a), 131.6 (C-6a and C-14a), 136.6 (C-4a and C-11a), 153.7 (C-6 and C-13); λ_{max}/nm (MeOH) 223 (ε 5.5 × 10^5), 274 (6.0 × 10^5), 305 (3.1 × 10^5), 360, (3.8 × 10^5); ν_{max}/cm^{-1} (Nujol) 3500, 2200, 1500, 1450, 1350, 1050; *m*/*z* 288 (M+2, 23%), 287 (M+1, 27), 286 (M^+, 72), 258 (8), 229 (5), 144 (16), 143 (47), 129 (5), 117 (15), 116 (25), 115 (100), 114 (52), 91 (5), 90 (18), 88 (38), 87 (11), 69 (17), 63 (36), 55 (43), 43 (69)) (Found: C, 75.46; H, 3.43; N, 9.72; Calc. for $C_{18}H_{10}N_2O_2$ (286.27) C, 75.52; H, 3.52; N, 9.78%).

3.4. Reduction of 7 and 8 with $LiAlH_4$

General procedure for reduction

The compounds were each dissolved in dry THF and the solution slowly added to a solution of $LiAlH_4$ in dry THF. The mixture was stirred at the specified temperature for 2 h. EtOAc (10 mL) was added to the mixture and the resulting solution poured into H_2O (50 mL). The inorganic layer was extracted with EtOAc (3 × 20 mL). The combined extracts were dried over $MgSO_4$ and the solvent evaporated off in *vacuo* to give a residue that was subjected to column chromatography and the major fractions eluted with EtOAc-light petroleum (1:1).

1H-Indol-2-ylcarboxaldehyde **10** *and 1H-indole-2-ylmethanol* **11**[16]

$LiAlH_4$ (0.05 g, 1.30 mmol) reacted with indolopiperazine-2,5-dione **7** (0.25 g, 1.25 mmol) at r.t. to give a white solid that was subjected to column chromatography using EtOAc-light petroleum (1:1) to afford two fractions. The first fraction was identified as indole-2-aldehyde **10**, as white platelets (0.15 g, 83%), m.p 139–141°C (lit.[16] m.p. 141–142°C); δ_H (500 MHz, $CDCl_3$) 7.20 (1H, dd, *J* 1.1, 7.9 Hz, 4-H), 7.29 (1H, dd, *J* 1.5 Hz, 3-H), 7.40-7.46 (2H, m, 5-H and 6-H), 7.75 (1H, d, *J* 7.91 Hz, 7-H), 9.32 (1H, br s, NH), 9.86 (1H, s, CHO);δ_C (500 MHz, $CDCl_3$) 112.4 (C-3), 114.8 (C-5), 121.2 (C-6), 123.4 (C-4), 127.2 (C-7), 127.3 (C-3′), 135.8 (C-7′), 137.9 (C-2), 182.1 (CHO); *m*/*z* 149 (M+3, 6%), 146 (M+1, 10), 145 (M^+, 100), 144 (72), 117 (7), 116 (19), 114 (2), 95 (2), 90 (16), 89 (50), 88 (5), 81 (5), 76 (2), 73 (8), 69 (9), 63 (19), 57 (100, 50 (7), 43 (17).

The second fraction was identified as 1H-indol-2-ylmethanol **11**, as white needles (0.01 g, 5%), m.p. 70–72°C (lit.[16] m.p. 76–77°C); δ_H (500 MHz, $CDCl_3$) 2.05 (1H, br s, OH), 4.80 (2H, s, CH_2), 6.39 (1H, d, *J* 1.1 Hz, 3-H), 7.11-7.21 (2H, m, 5-H and 6-H), 7.29 (1H, dd, *J* 0.8, 7.9 Hz, 4-H), 7.58 (1H, d, *J* 7.9 Hz, 7-H), 8.41 (1H, br s, NH); δ_C (500 MHz, $CDCl_3$) 58.5 (CH_2OH), 100.5 (C-3), 110.5 (C-6), 119.8 (C-5), 120.5 (C-4), 122.1 (C-7), 128.0 (C-2), 136.3 (C-3′), 137.5 (C-7′); *m*/*z* 149 (M+3, 5%), 148 (M+1, 10), 147 (M^+, 100), 146 (12), 144 (5), 131 (7), 130 (78), 129 (100), 128 (20), 119 (4), 118 (28), 117 (19), 116 (5), 104 (3), 103 (13), 102 (19), 101 (5), 95 (5), 91 (23), 89 (29), 85 (6), 83 (7), 81 (11), 77 (17), 73 (16), 69 (22), 65 (10), 63 (25), 60 (9), 57 (16), 55 (17), 51 (13), 50 (7), 45 (5), 43 (17).

$LiAlH_4$ also (0.10 g, 2.6 mmol) reacted with **8** (0.37 g, 1.3 mmol) at 0°C to give a white solid that was subjected to column chromatography using EtOAc-light petroleum (1:1) to afford **10** (0.17 g, 89%) and **11** (0.01g, 3%).

3.5. Reductive Cleavage of 9 with $NaBH_4$

$NaBH_4$ (11.34 g, 0.3 mmol.) was added slowly to the solution of **9** (0.12 g, 0.60 mmol) in EtOH. The mixture was stirred at 0°C for 2 h. EtOAc (10 mL) was added to the mixture and the resulting solution poured into H_2O (50 mL). The inorganic layer was extracted with EtOAc (3 × 20 mL). The combined extracts were dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give a residue that was subjected to column chromatography and the major fractions eluted with EtOAc-light petroleum (1:1) and were characterized as **10** (0.13 g, 90%) and **11** (0.06 g, 2%).

3.6. Base Hydrolysis of 9

$LiOH.H_2O$ (0.25 g, 2.86 mmol) was added to a solution of **9** (0.12 g, 0.60 mmol) in THF (5 mL) and the mixture stirred at r.t. for 2 h. The mixture was poured into H_2O (20 mL), and the aqu. layer was extracted with $CHCl_3$ (3 × 20 mL). The organic extracts were combined and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford a residue that was subjected to column chromatography using EtOAc-light petroleum (1:1) to afford 1H-indole-2-carboxylic acid **12**[16] as brown platelets (0.55 g, 57%) m.p. 200–202°C (lit.[16] m.p. 206–207°C); δ_H (500 MHz, DMSO-d_6) 6.78 (1H, dd, *J* 1.1 Hz, 3-H), 6.94 (1H, dd, *J* 1.1, 7.9 Hz, 5-H), 7.08 (1H, dd, *J* 1.1, 7.9 Hz, 6-H), 7.42 (1H, dd, *J* 0.8, 7.5 Hz, 4-H), 7.51 (1H, d, *J* 7.9 Hz, 7-H), 11.13 (1H, br s, NH), 12.81 (br s, OH); δ_C (500 MHz, DMSO-d_6), 103.9 (C-3), 112.6 (C-5), 119.3 (C-6), 121.4 (C-4), 122.5 (C-7), 127.9 (C-3′), 129.3 (C-7′), 136.4 (C-2), 167.4 (COOH).

3.7. BuLi Addition to 7

BuLi (1.0 mL of 1.2 M, 2.5 mmol) was added to a solution of indolepiperazine-2,5-dione **7** (0.20 g, 1.00 mmol) in THF (5 mL) at 0°C and the mixture was stirred for 2 h, diluted with aqu. HCl (50%, 20 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford a brown oil that was subjected to column chromatography using EtOAc-light petroleum (1:1) and the major fraction identified as 2-[(Z)-1-butylpent-1-enyl]-1H-indole **13** as a brown oil (0.15 g, 62%). δ_H (500 MHz, $CDCl_3$) 0.92-0.94 (6H, m, 1′- and 9′-CH_3), 1.39-1.55 (4H, m, 2-′ and 8′-CH_2), 2.24 (2H, q, 6′-CH_2), 2.31 (2H, q, 3′-CH_2), 2.49 (2H, t, *J* 7.9 Hz, 6′-CH_2), 5.81 (1H, t, *J* 7.3 Hz; 4′-CH), 6.46 (1H, s, 3-H), 7.13 (1H, dd, *J* 8.0, 2.0 Hz, 5-H), 7.23 (1H, dd, *J* 8.0, 2.0 Hz, 6-H), 7.29 (1H, dd, *J* 8.0, 2.0 Hz, 7-H), 7.55 (1H, dd, *J* 8.0, 2.0 Hz; 4-H), 8.08 (1H, br s, NH); δ_C (500 MHz, $CDCl_3$) 13.9 (C-9′), 14.0 (C-1′), 22.9 (C-8′), 23.0 (C-2′), 29.0 (C-7′), 30.3 (C-6′), 31.9 (C-3′), 99.7 (C-3), 110.3 (C-7), 119.8 (C-5), 120.6 (C-4), 121.9 (C-6), 126.2 (C-4′), 129.1 (C-3a), 132.1 (C-5′), 136.3 (C-7a), 139.7 (C-2);); λ_{max}/nm (MeOH) 210 (ε 4 × 10^5), 205 (4.8 × 105), 291 (5.2 x10^5); ν_{max}/cm^{-1} (Nujol) 2300, 1600, 1450, 1350; *m/z* 242 (M+1, 13%), 241 (M+1, 67), 241 (M^+, 67), 226 (6), 212 (35), 199 (21), 198 (100), 185 (6), 184 (35), 170 (22), 168 (35), 159 (54), 157 (35), 156 (34), 144 (73), 142 (14), 130 (34), 117 (35), 115 (290, 106 (14), 95 (8), 89 (43), 81 (22), 77 (17), 70 (10), 57 (26), 55 (37), 43 (60; (Found: *m/z* 240.1757; Calc. for $C_{17}H_{23}N$: 240.1758).

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