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Reactions of 1,2-Bis(1*H*-indol-2-yl)ethane: Formation of Indolo[2,3-*c*]carbazole and Cyclohept[1,2-*b*:5,4-*b*′]bisindole Derivatives

Jan Bergman,[a,b,*] Tomasz Janosik,[a,b] Larisa Yudina,[a,†] Eric Desarbre,[a,‡] Göran Lidgren[a,§] and Lennart Venemalm[a,‡]

[a]*Unit for Organic Chemistry, CNT, Department of Biosciences at Novum, Karolinska Institute, Novum Research Park, SE-141 57 Huddinge, Sweden*

[b]*Södertörn University College, SE-141 04 Huddinge, Sweden*

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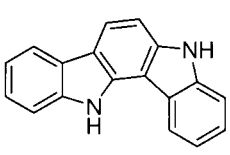
Abstract—1,2-Bis(1*H*-indol-2-yl)ethane **(9)** has been prepared and converted into indolo[2,3-*c*]carbazole **(8)** using palladium acetate in refluxing acetic acid. Reaction of **9** with CoF_3 in hot TFA led to isolation of cyclohept[1,2-*b*:5,4-*b*′]bisindole derivatives **11** and **12**, which could be elaborated into further derivatives. Treatment of **9** with orthoesters, aldehydes and ketones under acidic conditions afforded additional bisindoles containing a seven-membered ring.

Many indolocarbazoles display interesting biological activities, in particular derivatives of indolo[2,3-*a*]carbazole[1] **(1)**, such as the alkaloids K-252a[2] **(2)** and staurosporine[3] **(3)**, which both are potent PKC inhibitors. The isomeric system indolo[3,2-*b*]carbazole[4] **(4)** has been identified as an in vivo product in the gastro-intestinal tract of humans in connection with consumption of cruciferous vegetables,[5] and has also been demonstrated to possess strong affinity to the aryl hydrogen (Ah) receptor.[6] The even more powerful Ah-receptor ligands, namely the formyl derivatives[7] **5** and **6** of indolo[3,2-*b*]carbazole have recently been prepared in our laboratory (Scheme 1).[8]

Recently, the surprisingly little studied systems indolo[3,2-*a*]carbazole **(7)** and in particular indolo[2,3-*c*]carbazole **(8)** have also attracted the attention of our group. Thus, we have developed synthetic procedures aiming at indolo[3,2-*a*]-carbazole[9] **(7)**, as well as the angular isomer **8**.[10] So far, no biological activities have been reported for compounds containing the ring systems **7** or **8**, however several aza analogues of **7** have been shown to be powerful benzodiazepine receptor ligands.[11]



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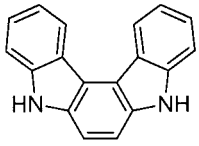

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In a preliminary communication, we have reported the formation of indolo[2,3-*c*]carbazole **(8)** from 1,2-bis(1*H*-indol-2-yl)ethane **(9)**, as well as the preparation of novel cycloheptindole derivatives on treatment of **9** with CoF_3 in refluxing TFA.[12] In the first approach towards the desired ring system **8**, the bisindole **9** was chosen as the precursor, since it is available in fair yield (32–48%) from the coupling of the metallated 2-methylindole derivative **10** with 1,2-diiodoethane.[12] The intermediate **10** was prepared according to Katritzky,[13] using 2-methylindole instead of indole. Several coupling reagents were tried, e.g. iodine; the best results were however obtained using 1,2-diiodoethane. A synthesis of compound **9** from *N*-protected *o*-toluidine in inferior yield has also been recently reported by Mahboobi,[14] who seemed to be unaware of our preliminary paper. In fact, **9** had been reported already in 1992 by Lavilla, who obtained the bisindole **9** as a by-product from the reaction of 2-methylindole *N*-carboxylic acid with *N*-methylpyridinium salts.[15] When refluxed with $Pd(OAc)_2$ in acetic acid, **9** could be transformed into indolo[2,3-*c*]carbazole, although the yields were low (25–57%) probably due to degradation of the product during the reaction. At this stage, the cyclization of **9** was also

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* Corresponding author. Tel.: +46-8-608-9204; fax: +46-8-711-6869; e-mail: jabe@cnt.ki.se

† Institute of New Antibiotics, Moscow 119867, Russia

‡ Pharmacia and Upjohn AB, SE-751 82 Uppsala, Sweden

§ Swedish Pharmaceutical Society, SE-111 81 Stockholm, Sweden

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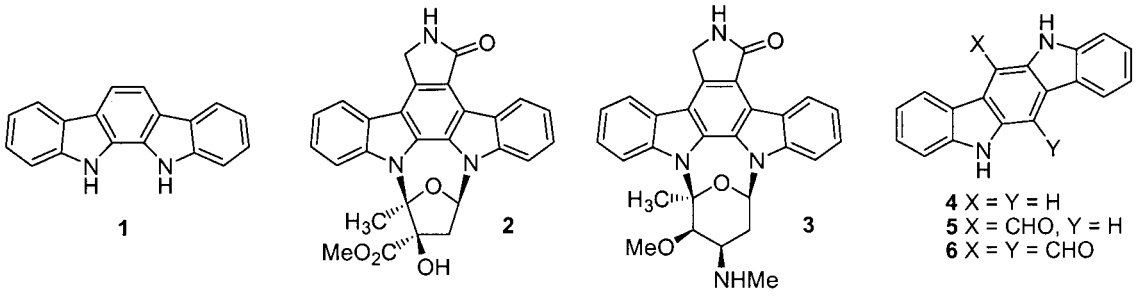


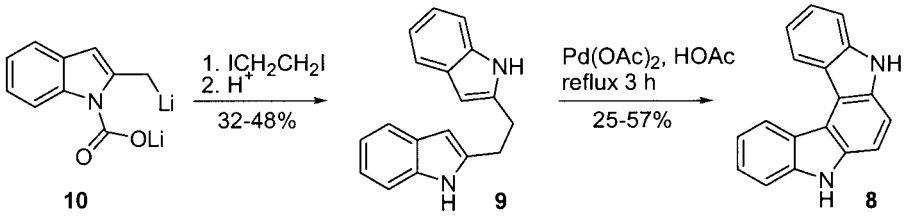
Scheme 1.

attempted using DDQ in dioxane, which also led to formation of **8** in very low yield, presumably due to incorporation of DDQ into the precursor **9**, a phenomenon that has been previously observed for simple indoles (Scheme 2).[16]

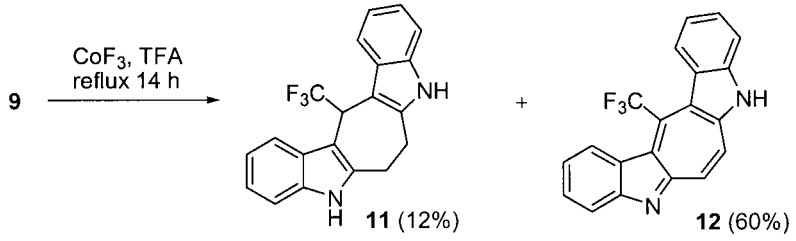
Thus, a different approach was tried, namely use of CoF_3 in refluxing trifluoroacetic acid, a reagent which has been used previously for coupling of activated aromatics.[17] However, an unexpected reaction was observed, as two products containing a seven membered ring could be isolated after chromatography and were assigned the structures **11** and **12**. As expected, the deep red compound **12** was the main product (60% yield), whereas the sensitive cycloheptindole **11** could be isolated only in low yield (Scheme 3).

Therefore, an alternative preparation of **11** was accomplished in 53% yield by treatment of **9** with trifluoroacetaldehyde ethyl hemiacetal in TFA at room temperature. Reduction of the red compound **12** with sodium borohydride in ethanol gave **13**, which could also be obtained by dehydrogenation of **11** with palladium on charcoal in refluxing diglyme, albeit in low yield. On addition of D_2O to a solution of **12** in deuterated DMSO, formation of the leuco compound **14** was observed, which is analogous to the behaviour of the rosindoles studied already by Emil Fischer.[18] Another interesting feature of compound **12** is the equivalence of the two indole units in the ^1H and ^{13}C NMR spectra, which indicates rapid prototropy (Scheme 4).

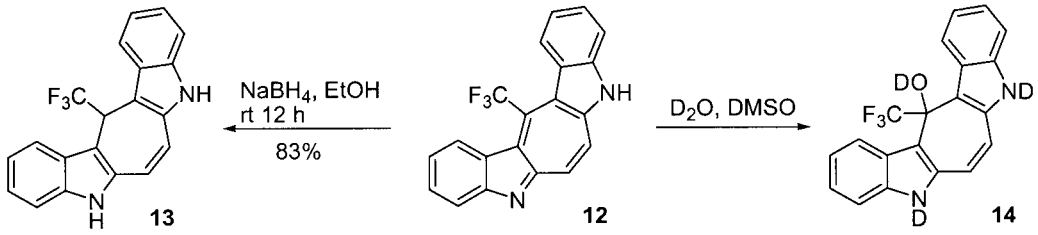
A series of seven membered ring compounds was prepared by reacting 1,2-bis(1*H*-indol-2-yl)ethane **9** with orthoesters, ketones, aldehydes or protected derivatives thereof in acidic



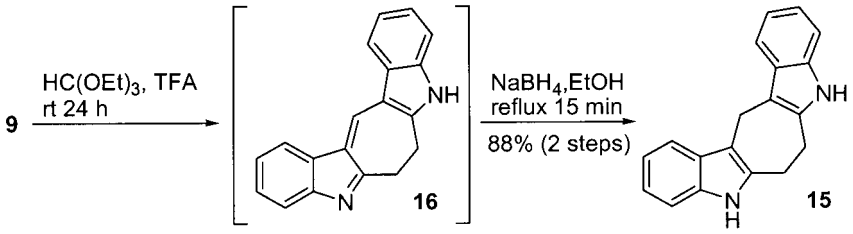
Scheme 2.



Scheme 3.



Scheme 4.



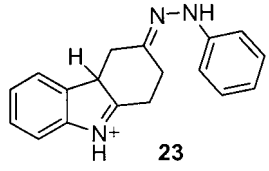
Scheme 5.

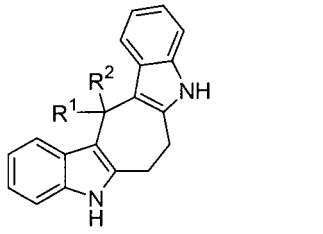
media. Thus, the parent ring system **15** could be conveniently obtained in a one-pot procedure by treatment of **9** with triethyl orthoformate in TFA, and subsequent reduction of the red intermediate **16** with sodium borohydride in ethanol. As anticipated, compound **15** is sensitive towards oxidation, but was however reasonably stable when stored in a freezer (Scheme 5).

In a similar manner, compounds **17**–**19** were obtained in good yields (65–86%) when **9** was treated with *p*-nitrobenzaldehyde, 3,4-methylenedioxybenzaldehyde or acetone, respectively, under acidic conditions (TFA or *p*-TsOH). Cycloheptindoles **17** and **18** displayed an interesting ^{1}H NMR pattern for the methylene signals of the seven membered rings, a feature which can be attributed to restricted inversion due to the bulky substituents. Similar inversion effects in a related series of substituted 9,10-dihydrophenathrenes have been reported previously.[19] In this context it might be mentioned that the interesting seven membered product **20** has been obtained some time ago from the acid induced dimerization of 2-(α-hydroxyisopropyl)indole (Scheme 6).[20]

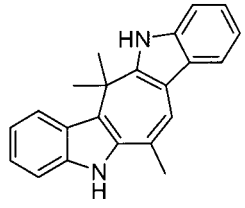
Within the context of this work, an attempt was made to prepare indolo[2,3-*c*]carbazole **(8)** by double cyclization of the bisphenylhydrazone **21** with phosphorus trichloride in toluene or xylene. Reactions of arylhydrazones with PCl_3 have previously been reported to yield indoles.[21] Thus, when **21** was treated with PCl_3 in refluxing toluene, two main products could be isolated, namely the desired indolo[2,3-*c*]carbazole **(8)** and 3-aminocarbazole **(22)** in yields of 8 and 43%, respectively. When the reaction was performed in refluxing xylene instead of toluene, the same products could be isolated in yield comparable with those above, but the reaction time was shortened from 6 h to 30 min (Scheme 7).

Interestingly, formation of the expected indolo[3,2-*b*]-carbazole **(4)** could not be detected in these experiments. In the standard procedure for **4** due to Robinson,[4] **21** is treated with sulfuric acid in acetic acid. Hereby the isomer **8** is not formed, but **22** is a major side product.[22] To account for this, we speculate that, in the medium used in the Robinson procedure, the second cyclization takes place on the protonated species **23** which will prevent formation of the particular hydrazine necessary for the formation of **8**.[23]

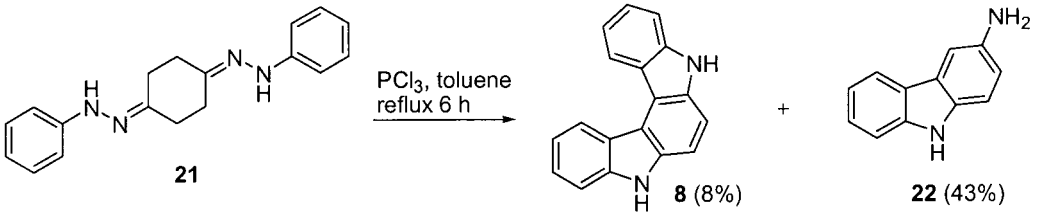




17 R^1 = H, R^2 = 4-$O_2NC_6H_4$
18 R^1 = H, R^2 = 3,4-$(OCH_2O)C_6H_3$
19 R^1 = R^2 = CH_3



Scheme 6.



Scheme 7.

Experimental

^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX 300 (300 MHz) spectrometer, ^{19}F NMR spectra were measured on a Varian Unity Plus instrument (operating at 376 MHz) with TFA as external reference. IR spectra were acquired on a Perkin–Elmer 1600 FT-IR instrument. Mass analyses were performed on a Micromass Platform II spectrometer. High resolution mass spectra were performed by Sveriges Lantbruksuniversitet (SLU), Uppsala, Sweden. Melting points were taken on a Büchi B-545 apparatus or a Reichert Kofler hot stage and are uncorrected. All solvents were purified by distillation or were HPLC grade. The trifluoroacetaldehyde ethyl hemiacetal used was a generous gift from Central Glass Co., Saitama, Japan. Chromatography was performed on Merck Silica Gel 60.

1,2-Bis(1*H*-indol-2-yl)ethane (9). A solution of 2-methylindole (6.55 g, 50 mmol) in THF (40 ml) was treated with *n*-BuLi in hexanes (32 ml, 1.6 M, 51 mmol) at −78°C under N_2, the resulting reaction mixture was kept at −78°C for 1 h, followed by introduction of CO_2 (g) during 15 min at −78°C. The solvents were removed at reduced pressure, meanwhile the temperature was allowed to reach 20°C. The residue was dissolved in THF (50 ml), thereafter *t*-BuLi in pentane (30 ml, 1.7 M, 51 mmol) was slowly added during 15 min at −78°C, followed by stirring for 30 min. 1,2-Diiodoethane (7.04 g, 25 mmol) in THF (15 ml) was added slowly at −78°C, the mixture was thereafter kept at −78°C for 3 h. The reaction was quenched by addition of sat. aq. NH_4Cl (100 ml) at −78°C, the mixture was then allowed to reach rt overnight. After separation, the aqueous phase was extracted with CH_2Cl_2 (50 ml); the combined organic extracts were washed with brine and dried over $MgSO_4$. Evaporation of the solvents gave a beige residue, which afforded 1,2-bis(1*H*-indol-2-yl)ethane **(9)** as a colourless solid (2.41 g, 37%) after trituration with Et_2O (25 ml); mp 264–266°C (dec.). IR (KBr) 3393, 3047 (w), 2909 (w), 1544, 1458, 1415, 1290, 1013, 788, 746 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ 11.00 (s, 2H), 7.40 (d, J=7.6 Hz, 2H), 7.29 (d, J=7.9 Hz, 2H), 7.00 (app. t, J=7.5 Hz, 2H), 6.92 (app. t, J=7.9 Hz, 2H), 6.19 (s, 2H), 3.16 (s, 4H); ^{13}C NMR (DMSO-d$_6$) δ 139.3 (s), 135.9 (s), 128.3 (s), 120.1 (d), 119.1 (d), 118.6 (d), 110.6 (d), 98.3 (d), 27.3 (t); MS (EI) *m*/*z* 260 (M$^+$, 11), 130 (100), 103 (11), 77 (20). HRMS (EI) *m*/*z* Calcd for $C_{18}H_{16}N_2$ 260.1313; found 260.1312.

Indolo[2,3-*c*]carbazole (8) from 1,2-bis(1*H*-indol-2-yl)-ethane (9). A mixture of 1,2-(1*H*-bisindol-2-yl)ethane **9** (130 mg, 0.5 mmol) and $Pd(OAc)_2$ (123 mg, 0.55 mmol) in acetic acid (5 ml) was heated at reflux for 3 h. Evaporation of the solvent and column chromatography (CH_2Cl_2) gave **8** (73 mg, 57%) as a white solid, spectral data identical with those published previously.[10]

Reaction of 1,2-bis(1*H*-indol-2-yl)ethane (9) with CoF_3 in TFA

A mixture of 1,2-bis(1*H*-indol-2-yl)ethane **(9)** (260 mg, 1 mmol) and CoF_3 (128 mg, 1.1 mmol) in TFA (10 ml) was heated at reflux for 18 h. After cooling, water was added, and the resulting precipitate was collected and dried. Chromatography (2–3% MeOH in CH_2Cl_2) afforded cycloheptindole **11** (40 mg, 12%) as a colourless solid; mp 296–297°C (dec.). IR (KBr) 3395, 3059 (w), 2926 (w), 1462, 1334, 1252, 1160, 1141, 1105, 1010, 855, 740 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ 11.13 (s, 2H), 7.80–7.75 (m, 2H), 7.09–7.01 (m, 4H), 5.42 (q, J_{H-F}=9.5 Hz, 1H), 3.40–3.30 (m, 2H), 3.10–3.00 (m, 2H); ^{13}C NMR (DMSO-d$_6$) δ 138.0, 134.1, 128.7, 128.0 (q, $^1J_{C-F}$= 282 Hz), 120.6, 118.7, 118.1, 110.6, 103.4, 36.2 (q, $^2J_{C-F}$=29 Hz), 24.4; ^{19}F NMR (DMSO-d$_6$) δ −66.85 (d, J_{F-H}=9.2 Hz) ppm; MS (EI) *m*/*z* 340 (M$^+$, 46), 271 (100), 256 (7), 135 (25). HRMS (EI) *m*/*z* Calcd for $C_{20}H_{15}N_2F_3$ 340.1187; found 340.1186.

Further elution with 5–10% MeOH in CH_2Cl_2 gave compound **12** (200 mg, 60%) as deep red crystals; mp 275–277°C (dec.). IR (KBr) 3440 (br), 2920 (w), 2817 (w), 2745 (w), 2690 (w), 1670, 1618, 1590, 1455, 1375, 1205, 1195, 854, 755 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ 14.89 (br s, 1H), 8.95 (s, 2H), 8.54–8.52 (m, 2H), 8.00 (d, J=8.0 Hz, 2H), 7.87 (app. t, J=7.2 Hz, 2H), 7.68 (app. t, J=7.1 Hz); MS (EI) *m*/*z* 336 (M$^+$, 100). HRMS (EI) *m*/*z* Calcd for $C_{20}H_{11}N_2F_3$ 336.0874; found 336.0887.

Independent synthesis of compound 11

To a solution of 1,2-bis(1*H*-indol-2-yl)ethane **(9)** (260 mg, 1 mmol) in TFA (10 ml) was added trifluoroacetaldehyde ethyl hemiacetal (0.16 ml, 1.38 mmol), the mixture was stirred at rt for 90 min. After evaporation of the solvent and chromatography (CH_2Cl_2), **11** (179 mg, 53%) was isolated as a colourless solid. The spectral data were identical with those of the material obtained from the reaction of **9** with CoF_3 in TFA.

Reduction of 12 with $NaBH_4$ in ethanol

The red compound **12** (34 mg, 0.1 mmol) was suspended in EtOH (5 ml), whereupon $NaBH_4$ (20 mg, 0.53 mmol) was added in one portion. The mixture was stirred for 12 h at rt. The yellow clear solution was diluted with water (10 ml) and was left standing for 4 h. The precipitate was collected by filtration, washed with water and dried to yield **13** (28 mg, 83%) as a off-white powder; mp 316–319°C (dec.). IR (KBr) 3394, 1630, 1453, 1338, 1259, 1157, 1114, 858, 746 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ 11.47 (s, 2H), 8.00 (d, J=7.8 Hz, 2H), 7.39 (d, J=7.9 Hz, 2H), 7.21–7.09 (m, 4H), 6.85 (s, 2H), 5.95 (q, J_{H-F}=9.2 Hz, 1H); ^{13}C NMR (DMSO-d$_6$) δ 136.6, 134.6, 128.1, 127.7 (q, $^1J_{C-F}$=283 Hz), 122.5, 119.5, 119.3, 118.8, 111.0, 105.1, 36.8 (q, $^2J_{C-F}$=30 Hz); ^{19}F NMR (DMSO-d$_6$) δ −70.02 (d, J_{F-H}=9.1 Hz) ppm; MS (EI) *m*/*z* 338 (M$^+$, 24), 269 (100), 134 (25). HRMS (EI) *m*/*z* Calcd for $C_{20}H_{13}N_2F_3$ 338.1031; found 338.1032.

Treatment of 12 with D_2O in DMSO-d$_6$

To a solution of **12** (5 mg) in DMSO-d$_6$ (0.5 ml) was added D_2O (0.1 ml), which quickly led to the formation of the leuco compound **14** (within one minute, the conversion was approx. 85% as measured by NMR). ^{1}H NMR (DMSO-d$_6$) δ 8.26 (d, J=8.1 Hz, 2H), 7.34 (d, J=8.1 Hz,

2H), 7.13 (app. t, *J*=7.2 Hz, 2H), 7.02 (app. t, *J*=7.2 Hz, 2H), 6.78 (s, 2H).

Cyclohept[1,2-*b*:5,4-*b*′]bisindole (15). Triethyl *ortho*-formate (190 μl, 1.14 mmol) was added to a solution of 1,2-bis(1*H*-indol-2-yl)ethane **(9)** (260 mg, 1 mmol) in TFA (8 ml); the resulting deep red mixture was stirred at rt for 24 h. The solvent was removed at reduced pressure and the residue was dissolved in ethanol (15 ml), followed by addition of sodium borohydride (228 mg, 6 mmol) in portions during 5 min. Heating at reflux for 15 min gave a clear yellow solution, which was thereafter allowed to cool and diluted with water (15 ml), whereupon a whitish precipitate formed. After filtration, washing with water and drying, **15** (240 mg, 88%) was obtained as a cream coloured solid, mp 230°C (dec.). This material is sensitive towards oxidation and slowly turns pink on standing if not stored in a evacuated desiccator. IR (KBr) 3388, 2906 (w), 2800 (w), 1461, 1450, 1420, 1324, 1179, 1006, 743 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.76 (s, 2H), 7.56 (d, *J*=7.5 Hz, 2H), 7.29 (dd, *J*=6.8, 1.7 Hz, 2H), 7.06–6.97 (m, 4H), 4.16 (s, 2H), 3.14 (s, 4H); ^{13}C NMR (DMSO-d_6) δ 135.7 (s), 134.3 (s), 128.7 (s), 120.2 (d), 118.1 (d), 117.3 (d), 110.4 (d), 107.7 (s), 25.7 (t), 19.7 (t); MS (EI) *m*/*z* 272 (M^+, 80), 271 (100), 269 (23), 256 (17), 154 (9), 130 (10). HRMS (EI) *m*/*z* Calcd for $C_{19}H_{16}N_2$ 272.1313; found 272.1295.

Reaction of 1,2-bis(1*H*-indol-2-yl)ethane (9) with 4-nitrobenzaldehyde

A mixture of 1,2-bis(1*H*-indol-2-yl)ethane **(9)** (130 mg, 0.5 mmol) and 4-nitrobenzaldehyde (81 mg, 0.54 mmol) was heated at reflux in EtOH (5 ml) containing TFA (3 drops) for 3.5 h. After cooling, the solvent was evaporated and the residue subjected to chromatography (CH_2Cl_2) to yield **17** (169 mg, 86%) as a yellowish solid; mp 272–273°C (dec.). IR (KBr) 3399, 3052 (w), 2915 (w), 1592, 1518, 1461, 1346, 744 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.96 (s, 2H), 8.02 (d, *J*=8.8 Hz, 2H), 7.69 (d, *J*=8.8 Hz, 2H), 7.63 (d, *J*=7.5 Hz, 2H), 7.27 (d, *J*=7.5 Hz, 2H), 7.01 (app. t, *J*=7.2 Hz, 2H), 6.95 (app. t, *J*=7.3 Hz, 2H), 6.00 (s, 1H), 3.40–3.30 (m, 2H), 3.16–3.06 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 155.4 (s), 145.4 (s), 136.0 (s), 134.4 (s), 128.3 (d), 128.0 (d), 123.4 (d), 120.5 (d), 118.5 (d), 117.8 (d), 111.0 (s), 110.6 (d), 37.9 (d), 25.4 (t); MS (EI) *m*/*z* 393 (M^+, 18), 272 (21), 271 (100), 269 (23), 256 (10), 154 (10), 135 (28), 130 (7). HRMS (EI) *m*/*z* Calcd for $C_{25}H_{19}N_3O_2$ 393.1477; found 393.1479.

Reaction of 1,2-bis(1*H*-indol-2-yl)ethane (9) with 3,4-methylenedioxybenzaldehyde

1,2-Bis(1*H*-indol-2-yl)ethane **(9)** (260 mg, 1 mmol) was refluxed with 3,4-methylenedioxybenzaldehyde (155 mg, 1.03 mmol) and *p*-toluenesulfonic acid (10 mg) in EtOH (15 ml) for 14 h. After cooling, the product **18** (210 mg) was collected, washed with ethanol and dried. The mother liquor was concentrated, and a second crop of **18** (45 mg) was collected after trituration with Et_2O. Total yield 255 mg (65%). Whitish solid, mp 320–322°C (dec.). IR (KBr) 3408, 3385, 2907 (w), 1498, 1482, 1459, 1436, 1243, 1037, 922, 795, 744 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.84 (s, 2H), 7.62 (d, *J*=7.5 Hz, 2H), 7.27 (d, *J*=7.6 Hz, 2H), 7.03–6.92 (m, 6H), 6.68 (d, *J*=7.8 Hz, 1H), 5.84 (s, 2H), 5.77 (s, 1H), 3.38–3.31 (m, 2H), 3.11–3.03 (m, 2H); ^{13}C NMR δ 146.8 (s), 144.8 (s), 141.8 (s), 135.4 (s), 134.4 (s), 128.3 (s), 120.2 (d), 119.9 (d), 118.3 (d), 118.0 (d), 112.4 (s), 110.5 (d), 107.8 (d), 107.6 (d), 100.5 (t), 37.7 (d), 25.5 (t).

Reaction of 1,2-bis(1*H*-indol-2-yl)ethane (9) with acetone

A mixture of 1,2-bis(1*H*-indol-2-yl)ethane **(9)** (130 mg, 0.5 mmol) and TFA (58 μl, 0.75 mmol) in acetone (5 ml) was stirred at rt for 24 h. Et_2O (20 ml) was added, followed by washing with sat. aq. $NaHCO_3$ (3×10 ml), drying over $MgSO_4$ and evaporation of the solvent. After chromatography (CH_2Cl_2), the product **19** was isolated as a pale yellowish solid (120 mg, 80%); mp 275–277°C (dec.). IR (KBr) 3403, 2932 (w), 1459, 1428, 1334, 1184, 1076, 746 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.71 (s, 2H), 7.80 (d, *J*=7.7 Hz, 2H), 7.28 (d, *J*=7.5 Hz, 2H), 7.04–6.92 (m, 4H), 3.08 (s, 4H), 2.00 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 135.2 (s), 134.0 (s), 127.5 (s), 121.0 (d), 119.7 (d), 118.6 (s), 117.8 (d), 110.8 (d), 37.5 (s), 31.0 (q), 27.1 (t); MS (EI) *m*/*z* 300 (M^+, 15), 286 (17), 285 (79), 283 (18), 269 (20), 256 (12), 170 (81), 168 (21), 155 (19), 154 (29), 130 (100), 128 (35), 115 (21), 103 (18), 77 (32). HRMS (EI) *m*/*z* Calcd for $C_{21}H_{20}N_2$ 300.1626; found 300.1635.

Reaction of bisphenylhydrazone 21 with PCl_3

To bisphenylhydrazone **21** (2.92 g, 10 mmol) suspended in toluene (40 ml), was added PCl_3 (2.75 g, 20 mmol) dropwise at rt. The mixture was thereafter heated at reflux for 6 h. After cooling, the mixture was diluted with acetone (250 ml) and filtered. The filtrate was immediately evaporated with silica gel whereupon flash chromatography (hexane–EtOAc, 2:1) took place to yield indolo[2,3-*c*]-carbazole **(8)** (210 mg, 8%). The spectral data of this material were identical with those previously reported.[10]

The insoluble material after the treatment with acetone was suspended in EtOH (40 ml) and filtered. The filtrate was diluted with water (600 ml) and the pH was adjusted to 9 by addition of NaOH. This operation gave a precipitate which was collected by filtration, washed with water and dried to yield 3-aminocarbazole[22] **(22)** (780 mg, 43%).

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