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# 2,2'-Biindolyl Revisited. Synthesis and Reactions.

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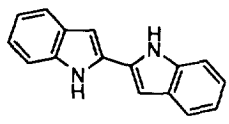
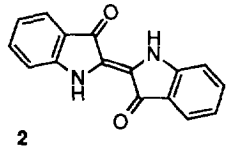
**Abstract:** An improved synthesis of 2,2'-biindolyl (**1**) is described. Derivatives of **1** with a variety of substituents in the 3,3'-positions, such as the 3,3'-diformyl derivative **19** have been synthesized. Potential syntheses of indolocarbazole alkaloids from such derivatives are outlined.

2,2'-Biindolyl (**1**) as a structural element is present in the dyes indigo (**2**) and Tyrian purple (6,6´-dibromoindigo, **3**) known from ancient times.



**1**



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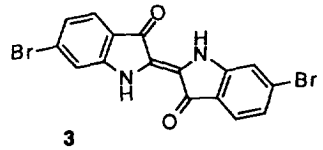
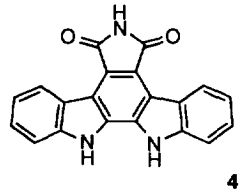


**3**

More recently, a number of natural products containing the 2,2'-biindolyl unit have been isolated, and have attracted considerable attention, not only because of their novel chemical architecture, but also due to their diverse pharmacological profiles.[1-3] Our efforts in this area include the synthesis of the slime mould pigment arcyriaflavin A (**4**) and the aglycon of the antitumor antibiotic rebeccamycin (**5**).[4,5] One member of the group has also contributed to the synthesis of a number of sponge pigments, *e.g.* fascaplycin (**6**).[6] 5,6,5',6'-Tetrahydroxy-2,2'-biindolyl (**7**) has been obtained by degradation of melanochrome, a biosynthetic intermediate of the animal pigment eumelanine.[7] The juxtaposition of the two nitrogens in 2,2'-biindolyls has also been exploited in the construction of various ligand systems, *e.g.* **8**.[8]

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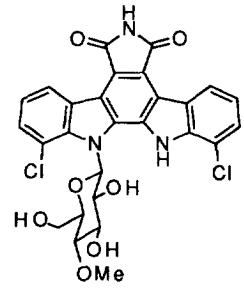


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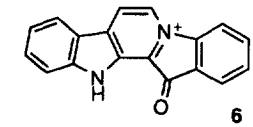


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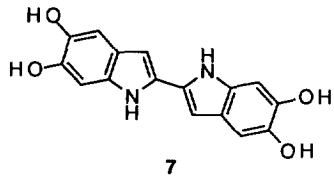


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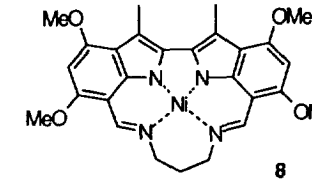
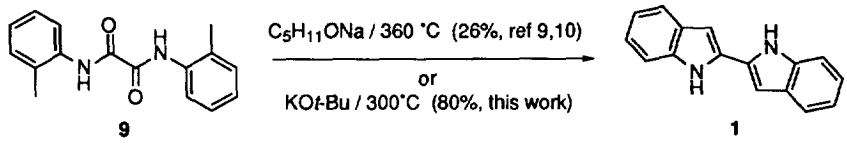


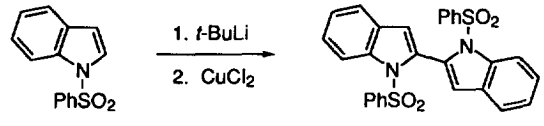

8

In this paper we will disclose a convenient synthesis, as well as some chemical transformations, of 2,2'-biindolyl (**1**).

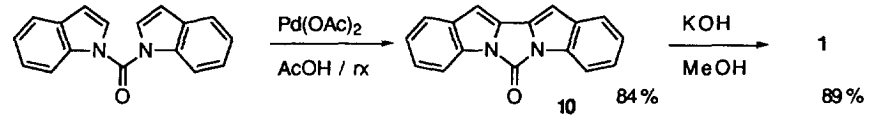
2,2'-Biindolyl (**1**) was first synthesized by Madelung from the *o*-toluidide **9**, using the reaction which now bears his name (Eq. 1).[9,10] The yield is modest and the reaction conditions (sodium *n*-amylate /360 °C) are harsh, precluding the synthesis of 2,2'-biindolyls with sensitive substituents in the benzene portion of the molecule. A number of modifications have been reported,[11-13] but the original Madelung procedure was still prefered by our group. Other methods to synthesize the parent 2,2'-biindolyl molecule involving inter- or intra-molecular coupling (Eq. 2 & 3)[14] have been developed in our lab. Although the milder conditions in these two-step sequences permit substituents in the benzene rings, the mediocre yield in combination with low reaction temperature (Eq. 2) or the necessity of equimolar amounts of palladium acetate (Eq. 3), makes large scale synthesis by these procedures less amenable. A coupling similar to the one depicted in Eq. 2 employing 1-methoxyindoles has also been described.[15] 2,2'-Biindolyls were also encountered as by-products in the palladium promoted coupling of indol-2-yl tributylstannanes[16,17] or 1-(benzenesulphonyl)-2-indolyl zinc chloride[18] with various electrophiles. By using 2-bromo- or 2-iodo-substituted indoles as an electrophilic component in coupling reactions, unsymmetrical 2,2'-biindolyls have been obtained in excellent yields (Eq. 4).[17] Homocoupling of 1-(benzenesulphonyl)-2-indolyl tributylstannane employing equimolar amounts of $Cu(NO_3)_2$ gave the corresponding N,N'-disubstituted 2,2'-biindolyl in modest yield.[19] A less convergent multistep synthesis of unsymmetrically substituted 2,2'-biindolyls has likewise been reported.[20]



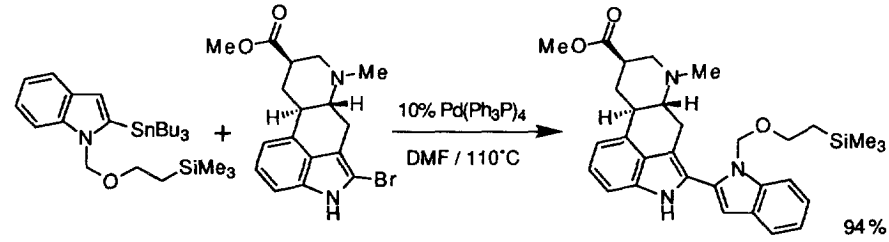

9 1 (Eq. 1)




(Eq. 2)

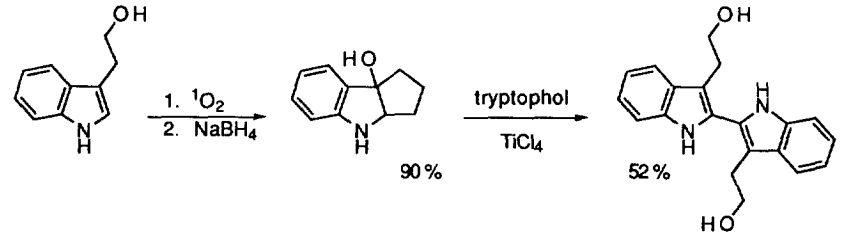



(Eq. 3)

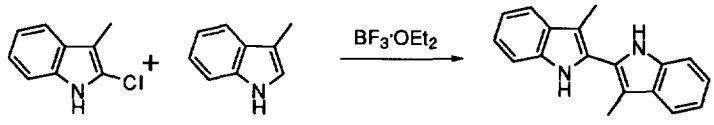



(Eq. 4)

A variety of methods limited to the syntheses of 2,2'-biindolyls with 3,3'-substituents are also known. These include the acid induced dimerization of 3-substituted indoles[21,22] (we will report on these reactions elsewhere[23]), oxidative transformations (Eq. 5)[24] and dimerizations utilising 2-chloroindoles (Eq. 6).[25] 2,2-Biindolyls were also formed in low yields during the synthesis of chloroindoles from the corresponding oxindoles by treatment with $POCl_3$.[25]



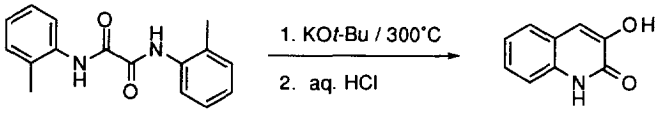

(Eq. 5)




(Eq.6)

Returning to the original Madelung protocol,[9,10] we again investigated the influence of different bases on the outcome of the reaction. By using butyllithium, indoles with phenyl or bulky alkyl groups in the 2-position have been prepared in high yields at room temperature.[26] However, treatment of **9** with *tert*- butyllithium, or lithium diisopropylamide under various reaction conditions invariably led to mixtures of the starting material and the desired 2,2'-biindolyl (**1**). In our hands it was impossible to develop a convenient separation procedure of these compounds based on either chromatography, crystallisation or sublimation. Finally, a substantial improvement of the yield (80%) was obtained when potassium *tert*-butoxide was used (Eq.1). In addition, the reaction temperature could be decreased from 360 °C to 300 °C. Although this decrease was insufficient to allow synthesis of 2,2'-biindolyls substituted in the benzene rings, it was now much more convenient to prepare **1** on a multigram scale. As difficulties in the synthesis of **1** by the Madelung synthesis have been noted in the literature[27] it must be stressed that careful control of the reaction temperature is an essential component in the success of this synthesis.

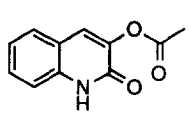
By acidification of the alkaline filtrate obtained after isolation of the crude 2,2'-biindolyl (**1**), small amounts (5-10%) of 3-hydroxy-2-quinolone (**11** ) could be isolated. This side reaction (Eq. 7), with the anion of 2-methylaniline as a leaving group, was observed already by Madelung.[28] Acetylation of **11** (no experimental details given) gave a compound which Madelung believed to be a diacetyl derivative, and which was later synthesized by 1h reflux of **11** in $Ac_2O$ (no yield reported) and correctly characterised as the 3-acetoxy derivative **12**.[29] The compound has recently also been obtained in 65% yield by a prolonged (27h) reaction of **11** with $Ac_2O$ in pyridine at room temperature.[30] We found that **12** was efficiently obtained after 10 min reflux in $Ac_2O$ from which it crystallized in 81% yield upon cooling.




**9** **11**

(Eq. 7)

Reduction of readily available indigo (**2**) should constitute an attractive straightforward route to **1**. We have however so far been unable to reduce **2** beyond the 3-hydroxy-2,2'-biindolyl (**13**) stage in acceptable yields.[31] All our attempts to induce a double Fischer cyclization of **14** have failed.[4] However, a low yield of the 1,1'-dimethyl derivative of **1** from the corresponding bis-methyl-phenylhydrazone has been reported by this route.[32]



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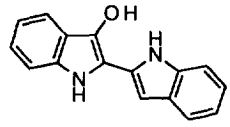

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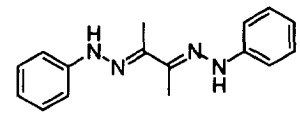
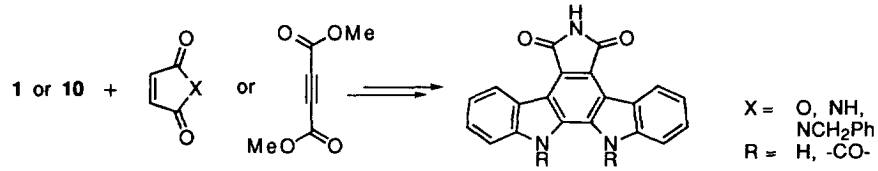


14

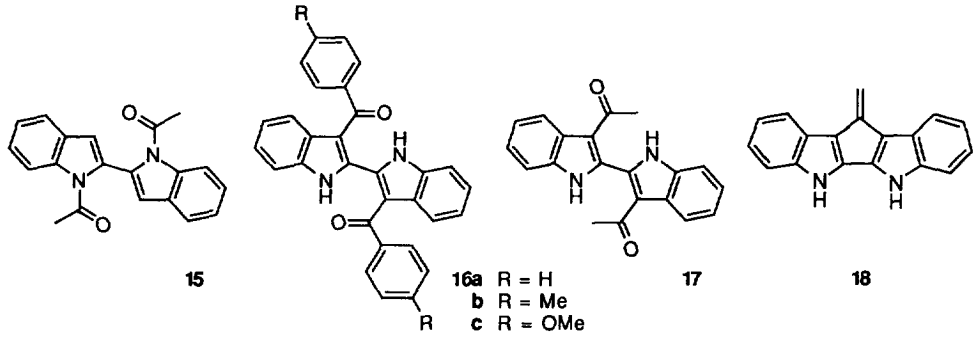
Having large amounts of 2,2'-biindolyl (**1**) available we now investigated its reaction with different dienophiles (dimethyl acetylenedicarboxylate, maleimides and maleic anhydride) under various conditions. Our hope was that a cycloaddition reaction (Eq. 8) should lead to indolo[2,3-*a*]-carbazoles, the structural mainframe of arcyriaflavin A (**4**) and rebeccamycin (**5**). The reactions were sluggish, but when they did occur, TLC analysis of the reaction mixtures revealed a large number of products. Connection of the two nitrogen atoms in **1** with a suitable link, as in *e.g.* **10**, will convert the non-planar 2,2'-biindolyl into a cisoid derivative which should be more prone to undergo cycloaddition reactions, but disappointingly no improvement was observed. Compound **10** which we previously prepared according to (Eq. 3)[14] was found to be more conveniently prepared by reaction of **1** and 1,1'-carbonyldiimidazole in refluxing DMF. On cooling crystalline **10** precipitated in 81% yield.




(Eq. 8.)

As more convenient routes to indolocarbazoles emerged at this time during the investigation,[4,5] the cycloaddition approach was gradually abandoned. However, this route has been investigated by others,[15,33-36] but the reported modest yields, harsh reaction conditions and/or tedious work up procedures, illustrates the difficulties associated with this scheme.

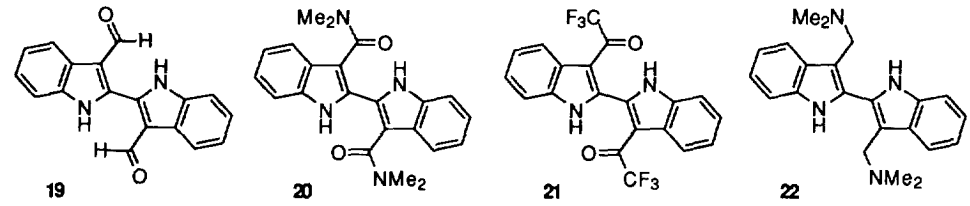
The nucleophilic 3-positions in **1** opens the possibility to introduce groups which subsequently could be used for construction of an indolocarbazole skeleton. Several reactions of **1** with electrophiles were investigated by Madelung.[10,37] However, as the nitrogens in **1** are also susceptible to electrophilic substitution, mixtures of products were often encountered. Thus, treatment of **1** with acetic anhydride gave mixtures of 1-acetyl- and 1,1'-diacetyl-2,2'-biindolyl (**15**) and C-acylated products. In contrast, **1** reacted cleanly at both its 3-positions with hot benzoyl chloride to give **16a**. A similar reaction with acetyl chloride did not give the corresponding 3,3'-diacetyl substituted compound **17**. Instead, **18** was claimed to be formed. The reaction of magnesium-salts of indoles is known to give C-alkylation on reaction with electrophiles, and this was found to be true also for the magnesium-salt of **1**.[10,37] In this way **16a** and **17** was obtained from benzoyl chloride and acetyl chloride, respectively, although the yield of the latter was low.




**15** **16a** R = H **b** R = Me **c** R = OMe **17** **18**

On reinvestigation of these reactions we found that a high yield of the 1,1'-diacetylated product **15** was obtained cleanly on reaction of **1** in a 1:1 mixture of $Ac_2O/Et_3N$. Heating (220°C, 5 min) of **1** with aroyl chlorides gave the expected 3,3'-diacylated derivatives **16a**, **16b** and **16c**, in excellent yields. The NMR-spectra were indicative of restricted rotation in these compounds. As stated before, **1** reacted with 1,1'-dicarbonyldiimidazole to give the N,N'-carbonyl compound **10** in high yield.

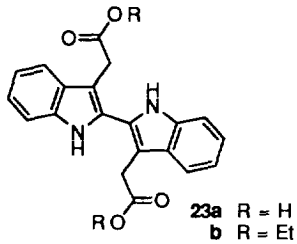
As a consequence of the difficulties to cleanly obtain **17** from **1**, or its magnesium-salt, with acetyl chloride or acetic anhydride, a number of reliable reactions that are known to introduce carbonyl substituents in the 3-position of an indole were investigated. Thus, the Vilsmeier reaction with dimethyl formamide/$POCl_3$ cleanly afforded **19** and the reaction of **1** with Viehe's reagent (phosgene iminium chloride, $Me_2N{=}CCl_2^+\ Cl^-$)[38] gave the amide **20** after aqueous work-up. In sharp contrast to the reaction of **1** with $Ac_2O$, the bright yellow compound **21** was obtained[31] in high yield when **1** was dissolved in trifluoroacetic anhydride/dioxane at 35°C. The Mannich reaction (HCHO /$Me_2NH$/AcOH) with **1** gave **22**.



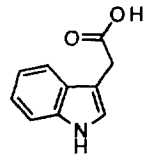

**19** **20** **21** **22**

However, our attempts to convert compounds **19-22** to **23** were fraught with difficulties. A more direct route would be to insert an acetic acid group through the reaction with ethyl diazoacetate.[39] Thus, the copper promoted reaction of **1** with three equivalents of ethyl diazoacetate in refluxing xylene cleanly inserted two acetic acid ester groups to give **23b**. Similar experiments with rhodium catalysts gave inferior results. Of interest in this context is a report that **23a** might be the active metabolite of the plant hormone indoleacetic acid (**24**).[40] When a lower diazoacetate/**1** ratio in hot toluene was employed, the mono-substituted compound **25** could be isolated. At a lower reaction

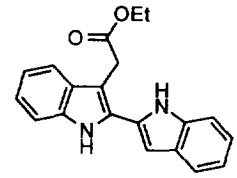
temperature (refluxing ethyl acetate) **1** did not react at all, but instead the carbethoxy carbene generated from ethyl diazoacetate dimerized to give diethyl fumarate which formed a 1:1 complex with **1**. This complex was readily isolated and could be purified by recrystallization without loss of the diethyl fumarate. A similar complexation phenomenon was observed during our attempts to synthesize the 3,3'-bis-acetyl compound **17** from **1** and acetic anhydride. On refluxing **1** in $Ac_2O$/dioxane a very stable complex of **1** and dioxane was obtained. This complex lost dioxane only after heating at 140°C in vacuum to give analytically pure **1**.




**23a** R = H
**b** R = Et




**24**




**25**

To shed some light on the relative reactivity of the 3-positions of indole, **1** and 2,3'-biindolyl, a few competitive experiments were performed. Thus, by reacting a mixture of indole, **1** and the Mannich reagent (1:1:1) it was found that indole is more reactive that **1**. In contrast, a 1:1:1 mixture of **1**, 2,3'-biindolyl and the Vilsmeier reagent gave almost exclusively the known 3-formyl-2,3'-biindolyl.[41]

**Acknowledgements:** This work was supported by the Swedish Natural Science Research Council and by Stiftelsen Lars Hiertas Minne. Mass spectra were kindly recorded by Jan-Erik Lindgren, Astra Arcus, Sweden.

**Experimental**

Melting points were determined on a Reichert WME Kofler hot stage or on a Leitz 1008 melting point microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR instrument. NMR spectra were obtained on a Varian UNITYplus (400 MHz) or on a Bruker VP-200 (200 MHz) instrument. Mass spectra were obtained on a Finnigan MAT SSQ710 instrument with direct inlet at 70 eV. Elemental analyses were performed by NOVO Microanalytical Laboratory, Bagsvaerd, Denmark.

**2,2'-Biindolyl (1) and 3-hydroxy-2-quinolone (11).**

KO*t*-Bu (224 g, 2 mol) was added at rt to a slurry of oxalyl-*o*toluidide (**7**), (107 g, 0.4 mol) in *t*-BuOH (600 ml) in a 4l 3-neck round bottom flask equipped with a distillation head, thermometer and a stopcock. The mixture was slowly heated[42] to 225°C under a slow stream of nitrogen until all the solvent was distilled off. (Also large amounts of white voluminous solid sublimes off during this time.) The temperature was then carefully increased with concomitant gas evolution until the

solid cake completely melted at 270°C to give a brown viscous liquid. The temperature was kept at 270°C for 15 min and then carefully raised to 300°C with vigorous gas evolution. When the effervescence ceased the mixture was cooled to rt. (It is essential that the temperature during the exothermic reaction is not allowed to get out of control which will lead to a black reaction mixture and ultimately to a much reduced yield.) Water (800 ml) was cautiously added and the cake crushed until a homogenous slurry is formed. The mixture was filtered and washed with water. The wet solid was suspended in EtOH (400 ml) and heated to boiling. The mixture was cooled, filtered, washed with EtOH until the filtrate was almost colorless and dried in vacuum to give **1** (77 g, 81%) as a grey solid. Mp >260°C. The material was identical to **1** prepared by other routes.[14] IR (KBr): 3398, 1442, 1395, 1341, 775, 749 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO-$d_6$): 11.55 (s, 2H), 7.56 (d, 2H), 7.40 (d, 2H), 7.11 (t, 2H), 7.00 (t, 2H), 6.93 (s, 2H). $^{13}$C-NMR (400 MHz, DMSO-$d_6$): 136.9, 131.4, 128.4, 121.7, 120.0, 119.4, 111.0, 98.4. MS *m/e* 232 ($M^+$, 100%).
Recrystallization from dioxan/$Ac_2O$ (5:3) gave an analytically pure sample. Anal. Calcd. for $C_{16}H_{12}N_2 \cdot C_4H_8O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.33 H, 6.36; N, 8.75. Drying this sample at 140°C, $10^{-2}$ mm Hg gave an off white solid free from dioxane. Anal. Calcd. for $C_{16}H_{12}N_2$: C, 82.27; H, 5.20; N, 12.06. Found: C, 82.47; H, 5.27; N, 11.87.

Acidification of the alkaline aqueous mother liquor with 4M HCl gave a precipitate which was collected by filtration and recrystallized from MeCN to give **12** (4.90 g, 8%), mp 270-1°C (lit mp 266-8°C)[43] This material was identical with a sample prepared by ring-expansion of isatin with diazomethane.[43] IR (KBr): 3267, 3162, 1654, 1575, 1399, 1289, 1249, 757, 603 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO-$d_6$): 12.0 (br s, 1H), 9.7 (br s, 1H), 7.47 (d, 1H), 7.25 (m, 2H), 7.08 (m, 2H). $^{13}$C-NMR (400 MHz, DMSO-$d_6$): 158.6, 146.4, 133.5, 126.2, 125.7, 122.0, 120.8, 114.7, 112.4.
MS *m/e* 161 ($M^+$, 100%).

**3-Acetoxy-2-quinolinone (12).**
A mixture of 3-hydroxy-2-quinolinone (**11**) (1.16 g, 10 mmol) and $Ac_2O$ (15 ml) was heated at reflux for 10 min. The mixture was allowed to cool and the solid formed was filtered off and dried to give **13** (1.65 g, 81%) as white needles, mp 220-2°C (lit mp 214-5°C; 223-5°C).[29,30] IR (KBr): 3150-2700 (br), 1766, 1674, 1578, 1440, 1374, 1207, 1162, 902, 761 $cm^{-1}$. $^1$H-NMR (400 MHz, $CDCl_3$): 11.8 (br s, 1H), 7.59 (s, 1H), 7.53 (d, 1H), 7.49 (t, 1H), 7.36 (d, 1H), 7.23 (t, 1H), 2.41 (s, 3H). $^{13}$C-NMR (400 MHz, $CDCl_3$): 168.6, 158.7, 140.6, 136.4, 130.1, 129.3, 127.7, 123.1, 119.1, 115.8, 20.7. MS *m/e* 203 ($M^+$), 161 (100%).

**1,1'-Carbonyl-2,2'-biindolyl (10).**
A mixture of **1** (1.16 g, 5 mmol), 1,1'-carbonyldiimidazole (0.90 g, 5.5 mmol) and DMF (25 ml) was refluxed for 5h. The mixture was allowed to cool and the precipitated solid filtered off, washed with DMF followed by MeOH and dried to give **10** (1.04 g, 81%) which was identical to **10** prepared by literature methods.[14] Mp 293-4°C (lit mp 293-4°C).[14] IR (KBr): 1759, 1747, 1640, 1439, 1378, 1309, 1219, 1139, 826, 803, 737 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO-$d_6$): 7.76 (d, 2H), 7.65 (d, 2H),

7.36 (t, 2H), 7.24 (t, 2H), 6.99 (s, 2H). $^{13}$C-NMR (400 MHz, DMSO-$d_6$): 133.6, 132.3, 130.0, 125.8, 123.6, 122.8, 111.7, 102.8.[44] MS *m/e* 258 ($M^+$, 100%), 229.

**1,1'-Diacetyl-2,2'-biindolyl (15).**
A mixture of **1** (4.64 g, 20 mmol), $Ac_2O$ (75 ml) and $Et_3N$ (75 ml) was refluxed for 18h. The mixture was allowed to cool, filtered and poured into water (400 ml) The oil which formed solidified on cooling and was purified by chromatography ($CH_2Cl_2$) to give **15** (5.10 g, 81%) as pale yellow crystals. Mp 170-1°C, (lit. mp 208°C[37], 70-2°C[45]).[46] IR (KBr):[47] 3060(w), 2925(w), 1698, 1445, 1372, 1297(s), 1199, 1005(w), 932(w), 744 cm$^{-1}$. $^1$H-NMR (400 MHz, $CDCl_3$): 8.29 (d, 2H, 7-H), 7.61 (d, 2H, 4-H), 7.41 (t, 2H, 5-H), 7.35 (t, 2H, 6-H), 6.82 (s, 2H, 3-H), 2.29 (s, 6H, $COCH_3$); $J_{4-5}\approx J_{5-6}\approx J_{6-7}\approx 8.5$ Hz. $^{13}$C-NMR (400 MHz, $CDCl_3$): 169.6, 136.9, 130.8, 128.7, 125.8, 123.8, 121.1, 116.4, 114.2, 25.5.
MS *m/e* 316 ($M^+$), 274, 232 (100%), 204.

**3,3'-Dibenzoyl-2,2'-biindolyl (16a).**
A mixture of **1** (2.32 g, 10 mmol) and benzoyl chloride (8.0 ml) was heated at 220°C for 10 min. A clear solution was formed which rapidly solidified. The cooled mixture was treated with EtOH, filtered and washed thouroughly with EtOH to give crystalline **16a** (3.74g, 85%), mp 290-2°C. (lit. mp 267°C)[37] IR (KBr): 3200-2700 (br), 1587, 1570, 1494, 1465, 1441, 1402, 1338, 1204, 915, 746, 697 cm$^{-1}$. $^1$H-NMR (400 MHz, $CDCl_3$): 7.83 (d, 4H), 7.64 (m, 4H), 7.50 (t, 4H); 7.26 (t, 2H), 6.99 (t, 2H), 6.79 (d, 2H). $^{13}$C-NMR (400 MHz, $CDCl_3$): 195.2, 141.0, 135.4, 135.0, 132.5, 129.6, 128.9, 128.5, 124.1, 121.9, 121.8, 114.2, 112.8. MS *m/e* 440 ($M^+$), 335 (100%), 305, 229, 105.

**3,3'-Di-(4-methylbenzoyl)-2,2'-biindolyl (16b).**
A mixture of **1** (2.32 g, 10 mmol) and 4-methylbenzoyl chloride (8.0 ml) was heated at 220°C for 10 min. A clear solution was formed which rapidly solidified. The cooled mixture was treated with EtOH, filtered and washed thoroughly with EtOH to give crystalline **16b** (4.21g, 90%), mp 284-5°C. IR (KBr): 3200-2700 (br), 1604, 1591 (sh), 1494, 1465, 1410, 1399, 1336, 1175, 920, 748 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-$d_6$): 12.22 (s, 2H), 7.44 (d, 2H), 7.44 (d, 4H), 7.37 (d, 2H), 7.18 (t, 2H), 7.07 (t, 2H), 7.01 (d, 4H). $^{13}$C-NMR (400 MHz, DMSO-$d_6$): 190.5, 141.4, 137.1, 135.7, 134.3, 128.8, 128.1, 126.8, 123.0, 121.3, 120.6, 115,2, 111.8, 20.9. MS *m/e* 468 ($M^+$), 349 (100%).

**3,3'-Di-(4-methoxybenzoyl)-2,2'-biindolyl (16c).**
A mixture of **1** (2.32 g, 10 mmol) and 4-methoxybenzoyl chloride (8.0 ml) was heated at 220°C for 10 min. A clear solution was formed which rapidly solidified. The cooled mixture was treated with EtOH, filtered and washed thoroughly with EtOH to give yellow crystalline **16c** (4.90g, 98%), mp 272-4°C. IR (KBr): 3200-2700 (br), 1603(s), 1595(sh), 1507, 1500, 1394(s), 1338, 1251, 1229, 1167(s), 1025, 921, 842, 751, 746 cm$^{-1}$. $^1$H-NMR (400 MHz, DMSO-$d_6$): 12.18 (s, 2H), 7.56 (d, 2H), 7.49 (d, 2H,), 7.38 (d, 2H), 7.19 (t, 2H), 7.08 (t, 2H), 6.74 (d, 2H), 3.64 (s, 6H). $^{13}$C-NMR (400 MHz, DMSO-$d_6$): 189.6, 161.9, 135.7, 134.0, 132.2, 131.0, 127.0, 122.9, 121.1, 120.6, 115.3, 112.9, 111.8, 55.2. MS *m/e* 500 ($M^+$), 365 (100%), 135.

**2,2'-Biindolyl-3,3'-dicarboxaldehyde (19).**

$POCl_3$ (4 ml, 44 mmol) was added slowly to dry DMF (20 ml) at 0°C. After 10 min a solution of **1** (4.64 g, 20 mmol) in DMF (100 ml) was added dropwise over 1h at 0°C. The mixture was stirred at rt for 40h and poured into 2M NaOH (500 ml). The mixture was heated at 100°C for 30 min and allowed to cool. The yellow precipitate was filtered off, washed with water and dried leaving **19** (5.68 g, 98%) as a yellow solid. Mp >260°C. IR (KBr): 3700-3100 (br), 3048, 2802, 1652, 1601, 1584, 1470, 1426, 1380, 1339, 1238, 1075, 1010, 825, 742 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO-$d_6$): 12.94 (s, 2H), 10.03 (s, 2H), 8.28 (d, 2H), 7.60 (d, 2H), 7.39 (t, 2H), 7.33 (t, 2H). $^{13}$C-NMR (400 MHz, DMSO-$d_6$): 185.6, 136.6, 136.2, 125.3, 124.8, 123.1, 121.3, 116.5, 112.5. MS *m/e* 288 ($M^+$), 259 (100%), 231.
An analytically pure sample was obtained by recrystallization from pyridine. Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.63; H, 4.19; N, 9.66.

**3,3'-Bis-dimethylaminocarbonyl-2,2'-biindolyl (20).**

Phosgene iminium chloride (2.00 g, 12 mmol) was added to a stirred mixture of **1** (1.16 g, 5 mmol) in MeCN (30 ml) at rt. The mixture was stirred at 60°C for 1h and quenched with water. The crude solid product was filtered off and purified by flash chromatography ($CH_2Cl_2$/1% MeOH) to give **20** (0.90 g, 48%) as a tan solid. Mp 290-2 °C. IR (KBr): 3210 (br), 1625, 1585, 1509, 1445, 1386, 1339, 1136, 748, 704 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO-$d_6$): 11.92 (s, 2H), 7.51 (d, 4H), 7.21 (t, 2H), 7.13 (t, 2H), 2.99 (br s, 6H), 2.78 (br s, 6H). $^{13}$C-NMR (400 MHz, DMSO-$d_6$): 166.2, 135.3, 129.2, 126.1, 122.8, 120.8, 119.9, 112.0, 110.2, 38.6 (br), 34.7 (br). MS *m/e* 374 ($M^+$, 100%), 329, 284, 257, 229.

**3,3'-Bis-dimethylaminomethyl-2,2'-biindolyl (22).**

A solution of **1** (4.64 g, 20 mmol) in THF (50 ml) was added slowly to an ice-cooled stirred mixture of formaline (37%; 43 mmol, 3.2 ml), aqueous $HNMe_2$ (40%; 45 mmol, 5.6 ml), AcOH (10 ml) and THF (10 ml). The mixture was stirred at rt 20 h and filtered through celite. On addition of 2M NaOH a precipitate formed which was filtered off, washed with water and dried to give **22** as a light brown solid (4.79 g, 73%). The compound could be recrystallized from EtOAc (mp 233°) but could not be obtained analytically pure. IR (KBr): 2818 (br), 1503, 1460, 1338, 1003, 738 $cm^{-1}$. $^1$H-NMR (400MHz, $CDCl_3$): 13.0 (br s, 2H), 7.63 (d, 2H), 7.40 (d, 2H), 7.18 (t, 2H), 7.12 (t, 2H), 3.73 (s, 4H), 2.44 (s, 12H). $^{13}$C-NMR (400MHz, $CDCl_3$): 136.0, 131.7, 129.6, 121.5, 119.2, 117.8, 111.4, 108.3, 53.3, 44.0. MS *m/e* 346 ($M^+$), 257 (100%).

**Diethyl 2,2'-biindolyl-3,3'-diacetate (23b).**

Ethyl diazoacetate (0.70 ml, 6.7 mmol) was added in three portions at 1h intervals to a mixture of **1** (0.50 g, 2.2 mmol) a little Cu-powder and xylene (25 ml) at reflux. After an additional hour at reflux the mixture was allowed to cool and was filtered. The filtrate was concentrated and the residue purified by flash-chromatography (hexanes/EtOAc, 9:1) to give **23b** (0.36 g, 41%), mp 150-1°C. IR (KBr): 3287, 1708, 1665, 1450, 1318, 1250, 1191, 1143, 1026, 739 $cm^{-1}$. $^1$H-NMR (200 MHz, DMSO-$d_6$): 11.36 (s, 2H), 7.50 (d, 2H), 7.42 (d, 2H), 7.18 (t, 2H), 7.06 (m 2H), 4.03 (q, 4H), 3.75

(s, 4H), 1.12 (t, 6H). $^{13}$C-NMR (200 MHz, DMSO-$d_6$): 171.6, 136.4, 127.8, 127.6, 122.1, 119.1, 117.0, 111.4, 107.9, 60.3, 30.5, 14.1. MS *m/e* 404 ($M^+$), 331, 268, 257, 107 (100%).

**Ethyl 2,2'-biindolyl-3-acetate (25).**

Ethyl diazoacetate (0.70 ml, 6.7 mmol) was added in three portions at 1h intervals to a refluxing mixture of **1** (1.16 g, 5.0 mmol), a little Cu-powder and toluene (70 ml). After an additional hour at reflux the mixture was allowed to cool and was filtered. The filtrate was concentrated and the residue (which also contained starting material and **23b**) was purified by flasch-chromatography (hexanes/EtOAc, 9:1) to give **25** (0.26 g, 16%), mp 148-9°C. IR (KBr): 3383, 3290, 3060(w), 2930(w), 1705(s), 1454, 1417, 1366, 1333, 1211, 1183, 1021, 778, 736, 645 $cm^{-1}$. $^1$H-NMR (200 MHz, DMSO-$d_6$): 11.35 (s, 1H), 11.29 (s, 1H), 7.65-7.05 (m, 8H), 6.86 (s, 1H). 4.10 (q, 2H), 4.03 (s, 2H), 1.16 (t, 3H). $^{13}$C-NMR (200 MHz, DMSO-$d_6$): 171.4, 136.7, 135.9, 130.2, 128.7, 128.6, 128.3, 121.9, 121.7, 120.0, 119.5, 119.1, 118.5, 111.3, 111.1, 105.2, 101.0, 60.2, 30.5, 14.0. MS *m/e* 318 ($M^+$), 245 (100%), 122.

**References and Notes**


1. Bergman, J. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, p 3.
2. Gribble, G. W.; Berthel, S. J. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1993; Vol. 12, p 365.
3. Chakraborty, D. P. *The Alkaloids* **1993**, *44*, 258.
4. Bergman, J.; Pelcman, B. *J. Org. Chem.* **1989**, *54*, 824.
5. Bergman, J.; Pelcman, B. *Tetrahedron Lett.* **1987**, *28*, 4441.
6. Gribble, G. W.; Pelcman, B. *J. Org. Chem.* **1992**, *57*, 3636.
7. Napolitano, A.; Corradini, M. G.; Prota, G. *Tetrahedron Lett.* **1985**, *26*, 2805.
8. Black, D. St. C. *Synlett* **1993**, 246.
9. Madelung, W. *Ber.* **1912**, *45*, 1128.
10. Madelung, W. *Ann. Chem.* **1914**, *405*, 58.
11. Seidel, P. *Ber.* **1944**, *77B*, 788.
12. Faseeh, S. A.; Harley-Mason, J. *J. Chem. Soc.* **1957**, 4141.
13. Capuano, L.; Drescher, S.; Hammerer, V.; Hanisch, M. *Chem. Ber.* **1988**, *121*, 2259.
14. Bergman, J.; Eklund, N. *Tetrahedron* **1980**, *36*, 1439.
15. Somei, M.; Kodama, A. *Heterocycles* **1992**, *34*, 1285.
16. Labadie, S. S.; Teng, E. *J. Org. Chem.* **1994**, *59*, 4250.
17. Palmisano, G.; Santagostini, M. *Helv. Chim. Acta* **1993**, *76*, 2356.
18. Amat, M.; Hadida, S.; Bosch, J. *Tetrahedron Lett.* **1993**, *34*, 5005.
19. Beddoes, R. L.; Cheeseright, T.; Wang, J.; Quayle, P. *Tetrahedron Lett.* **1995**, *36*, 283.
20. Jesudoss, K.; Srinivasan, P. C. *Synth. Commun.* **1994**, *24*, 1701.
21. Britten, A. Z.; Smith, G. F. *J. Chem. Soc., Perkin Trans. I* **1972**, 418.
22. Berti, G.; Da Settimo, A.; Segnini, A. *Tetrahedron Lett.* **1960**, 13.

23. Bergman, J.; Koch, E.; Pelcman, B., Manuscript in preparation.
24. Saito, I.; Morii, T.; Matsugo, S.; Matsuura, T. *J. Chem. Soc., Chem. Commun.* **1982,** 977.
25. Kubo, A.; Uchino, K. *Heterocycles* **1981,** *16,* 1441.
26. Houlihan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981,** *46,* 4511.
27. Steinmetzer, H.-C. Diss., Universität Würzburg, 1971.
28. Madelung, W. *Ber.* **1912,** *45,* 3521.
29. Heller, G. *Ber.* **1919,** *52,* 741.
30. Kobayashi, K.; Suzuki, M.; Suginome, H. *J. Org. Chem.* **1992,** *57,* 599. These authors seem to be unaware of the previous work in this area.
31. Bergman, J.; Eklund, N. *Chem. Scripta* **1982,** *19,* 193.
32. Fränkel, J. Diss., Technische Hochschule Aachen, 1965.
33. Pindur, U.; Kim, Y.-S.; Schollmeyer, D. *Heterocycles* **1994,** *38,* 2267.
34. Pindur, U.; Kim, Y.-S.; Schollmeyer, D. *J. Heterocycl. Chem.* **1994,** *31,* 377.
35. Barry, J. F.; Wallace, T. W.; Walshe, N. D. A. *Tetrahedron Lett.* **1993,** *34,* 5329.
36. Kaneko, T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett* **1985,** *26,* 4015.
37. Madelung, W.; Hager, F. *Ber.* **1916,** *49,* 2039.
38. Bergman, J.; Pelcman, B. *Tetrahedron Lett.* **1986,** *27,* 1939.
39. Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L.; Pellicciari, R.; Cogolli, P. *J. Org. Chem.* **1977,** *42,* 3945. and references cited therein.
40. Bitancourt, A. A. *Nature* **1963,** *200,* 548.
41. Bergman, J.; Renström, L.; Sjöberg, B. *Tetrahedron* **1980,** *36,* 2505.
42. The best results were obtained using a fluidized sand bath (Tecam, SBL-2) as the heat source. Good yields were also obtained by using a salt bath, especially on a smaller scale.
43. Greibrock, T.; Undheim, K. *Acta Chem. Scand.* **1971,** *25,* 2935.
44. A peak corresponding to the carbonyl-carbon was not detected due to the poor solubility of **10** in DMSO-$d_6$.
45. Barry, J. F. Diss., Univ. of Salford, 1992.
46. These melting points are not in agreement with the one reported in this work. However by using the reaction conditions reported by Madelung and Hager (ref 37) we found that the mp of the compound obtained (170-1°C) matched ours. Interestingly, although we have not studied 1-acetyl-2,2'-biindolyl ourselves, there is an unaccounted discrepancy of the mp reported by Madelung and Hager (212 °C) and the one reported by Barry (98-9 °C), ref 45.
47. Although the reported $^1$H-NMR data are in agreement with ours there are some discrepancies in the IR signals (2925, 2854, 1704,1248 $cm^{-1}$) reported in ref 45 and those reported here.

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