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DIMETHYLDIOXIRANE OXIDATION OF *N*-SUBSTITUTED-2-METHYLINDOLES TO INDOXYLS AND BISINDOXYLS

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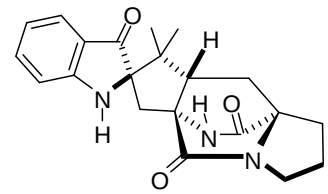
Abstract – Oxidation of 2-methylindoles **12a-f** with dimethyldioxirane (DMD) revealed that *N*-unprotected **12b**,**f** and protected *N*-carbamate 2-methylindole **12c** afforded indoxyls **16b**,**c** and *o*-(*N*-propionyl)aminobenzoic acid **17f** as the main products, while *N*-alkyl- or *N*-aryl-2-methylindoles **12a**,**d**,**e** gave 1,5'-diphenyl-4',5'-dihydro-3'*H*-spiro[indole-2,2'-pyrano[3,2-*b*]indol]-3(1*H*)-one (**10**), 2,3'-bisindolin-3-ones **13**, dispiro[indole-2,2'-furan-5',2"-indole]diones **14** or 2-[(3-oxoindolin-2-yl)methyl]-2-hydroxyindolin-3-ones **15**. The structure of dimers **10**, **13a**,**d**,**e**, **14a**,**d** and **15a**,**d** followed from NMR measurements, X-ray diffraction analysis confirmed those structures of **13a**,**d**,**e**, **14a**,**d** and **15d**, and some mechanistic implications are discussed.

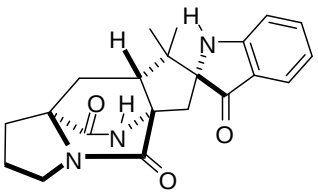
INTRODUCTION

The spiro[2*H*-indol]-3(1*H*)-one (spiro-indoxyl) moeity is found in the natural occurring mycotoxins brevianamide A (**1**) and B (**2**), isolated from *Penicillium* species, which have shown antifeedant and insecticidal effects.[1] Other spiro-indoxyl molecules include rupicoline (**3**) and iboluteine (**4**) isolated from *Tabernaemontana rupicola* Benth[2] and *Tabernanthe iboga*,[3] respectively, austamide (**5**)[4] isolated from *Aspergillus ustus*, and the phytoaliexin erucalexin (**6**)[5] isolated from *Erucastrum gallicum*. In turn, spiro indoxyl (**7**) has been prepared as an example of a conformationally restricted isoindolylpiperidine

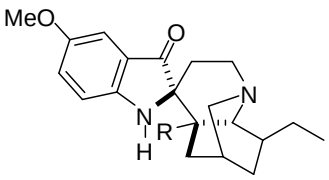
analogue, which inhibits the microsomal triglyceride-transfer protein function.[6] Structurally interesting indole dimers containing one or two indoxyl moieties such as **8**, **9** and **10** have been synthesized. Thus, compounds like **8** are the major products isolated after treatment of 2-alkyl- or 2-arylindole with a variety of oxidizing agents,[7] while spiroindole dimers **9** and **10** have only been obtained as by-products in 0.8% and 1%, respectively, when 3-hydroxy-3-methyl-1-phenylquinoline-2,4(1*H*,3*H*)-dione was treated with an aqueous KOH/benzene mixture.[8] Spiro-indoxyl **10** is structurally related to spiropyran derivative **11**, which belongs to a class of organic photochromic compounds that have extensively been studied for application in optical switches, memories[9] and as anion receptors[10] (Figure 1).



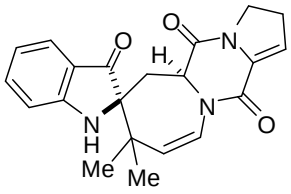
brevianamide A (**1**)



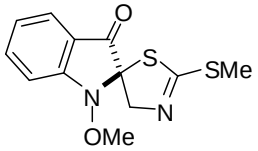
brevianamide B (**2**)



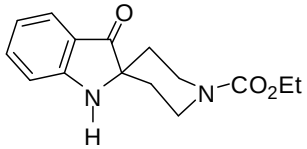
rupicoline (**3**) R = CO_2Me
iboluteine (**4**) R = H



austamide (**5**)



erucalexin (**6**)



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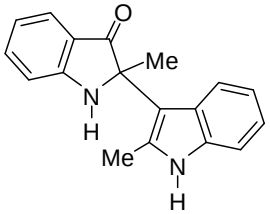

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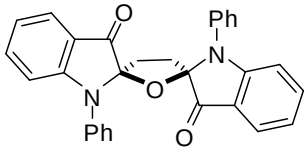

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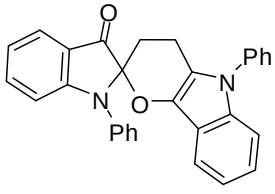

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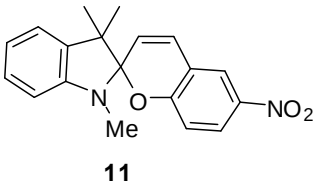

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Figure 1

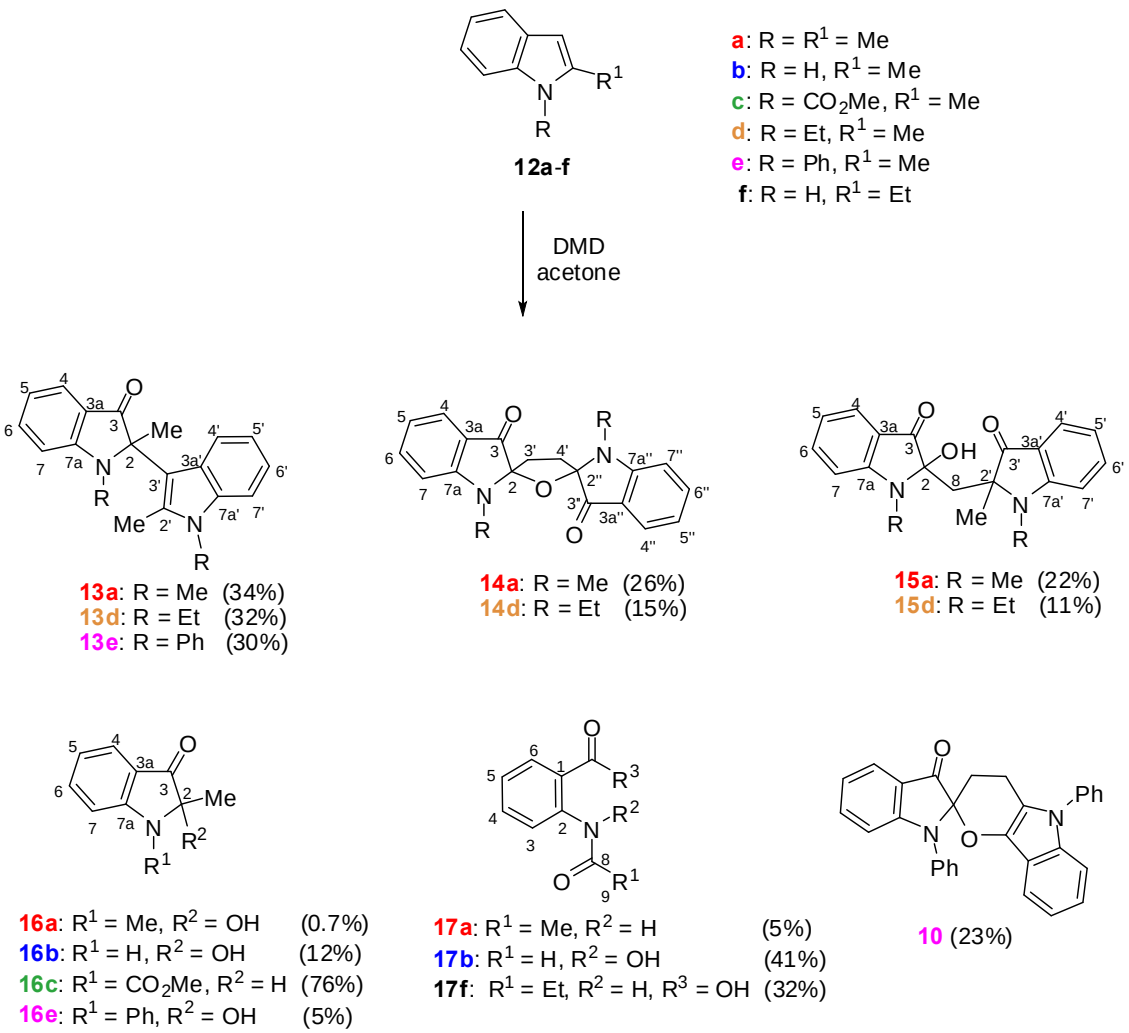
A number of reagents for the oxidation of the indole C2-C3 double bond to indoxyls have been reported,[7] including $NaIO_4$,[7d] *N*-chlorobenzotriazole,[7g] OsO_4,[11] oxodiperoxomolibdenum complexes,[7f,12]

bis(acetylacetonate)oxovanadium,[13] dimethyldioxirane (DMD),[12,14] singlet oxygen,[7e] *m*-CPBA,[7h,15] H_2O_2,[7h,16] HCl/MeOH[17] and $Pd(OAc)_2$.[18] Besides, it has been shown that the oxidation products depend on the nature of the substituens at the N1, C2, and C3 positions of the indole nucleus.

We have already reported on the oxidation of *N*-protected-3-alkylindole derivatives with DMD to obtain exclusively 3-hydroxyoxindoles.[19] In continuation with our studies aimed to shade light on the oxidation of indoles with this reagent, we report herein an approach to indoxyl dimers based on oxidation of 2-methylindole derivatives.

RESULTS AND DISCUSSION

Starting 2-methylindole derivatives **12a**,**b**,**d-f** (Scheme 1) were obtained according to described methodologies,[20] while indole **12c** was obtained in 76% yield when 2-methylindole (**12b**) was reacted with Me_2CO_3/DBU.[19a]



Scheme 1

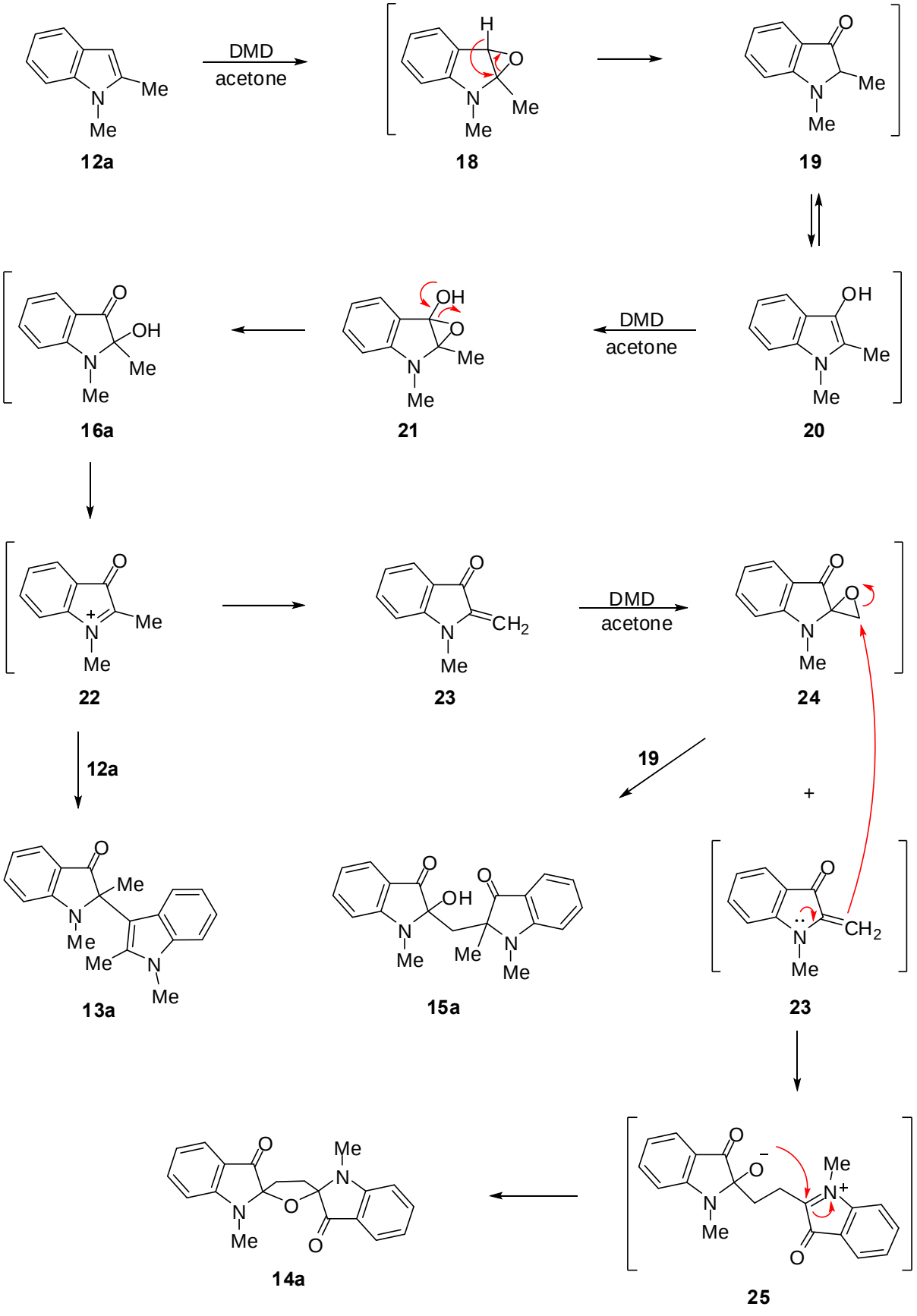
With compounds **12a-f** in hand, we firstly treated 1,2-dimethylindole **12a** with DMD/acetone (Scheme 1) giving rise to a mixture of five products identified as dimers **13a**, **14a** and **15a** in 34%, 26% and 22% yield, respectively, together with indoxyl **16a** and *o*-(*N*-acetyl)amino aldehyde (**17a**) in 0.7% and 5% yield, respectively. Compounds **13a-17a** were separated by column chromatography and characterized by detailed analysis of their ^{1}H and ^{13}C NMR spectra, including gHSQC and gHMBC experiments, and mass spectra.

Formation of dimers **13a-15a** and 2-hydroxyindoxyl **16a** may be rationalized as shown in Scheme 2. Thus, oxidation of **12a** with DMD afforded 2-hydroxyindoxyl **16a** through indoxyl **19**. At this respect, it is known that oxidation of 1,2-dialkyl indoles with DMD at low temperature affords oxindoles as the major products instead of indoxyls,[14a] but under our protocol indoxyl **16a** should preferentially be formed in order to obtain the iminium ion **22** which could then be attacked by a second indole moiety **12a** to afford the electrophilic aromatic substitution dimer **13a**.[7c] The iminium ion **22** could also rearrange to 2-methyleneindolinone **23** which is further oxidized with DMD to epoxide **24** with subsequent nucleophilic attack of a second molecule of indoxyl **19** to give dimer **15a**, or by 2-methyleneindolinone **23** to initially provide the zwitterionic intermediate **25**, followed by intramolecular nucleophilic addition of the alkoxide to the electron deficient carbon atom of the iminium bond[21] to afford the ring-closed dimer **14a**. Although dimer **13a** has been obtained using oxidating agents like singlet oxygen,[7b] $MoO_5 \cdot O{=}P(n\text{-}Pr)_3H_2O$,[7c] *m*-CPBA[7e,15] and H_2O_2,[7e] no such a compound has been reported in the oxidation of indoles with DMD. Besides, to the best of our knowledge, this is the first time dimers **14a** and **15a** are obtained by oxidation of indole derivatives.

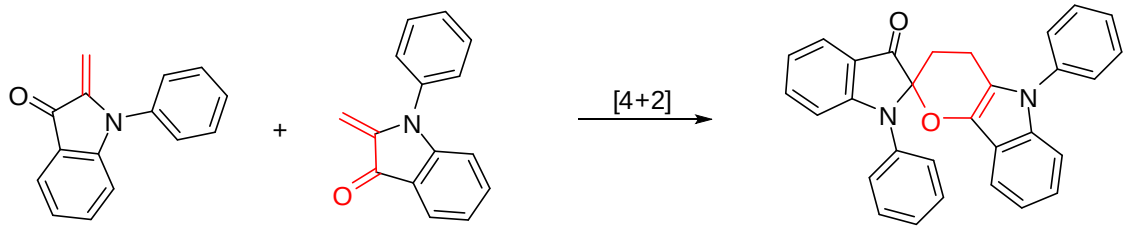
As oxidation products of indole derivatives depend on the nature of the substituents at the N1, C2, and C3 positions,[7] we decided to oxidize 2-methylindole (**12b**) under the same protocol, which afforded indoxyl **16b** and *o*-(*N*-acetyl)aminobenzoic acid (**17b**) in 12% and 41% yield, respectively. It is worth noting that no dimerization products were observed when **12b** was oxidized with DMD. Similarly, oxidation of *N*-carbomethoxy-2-methylindole (**12c**) gave indoxyl **16c** in 76%, and again dimerization products were absent. These results suggest iminium ion **19** is formed when the 2-methylindole is *N*-substituted with an electron rich group since a hydrogen atom or an electron attracting group (-CO_2Me) attenuate the internal nucleophilicity of the indole nitrogen atom[11] and consequently dimer products are not promoted.

In order to explore the scope and limitations of this reaction, the reactivity profiles of 1-ethyl-2-methylindole (**12d**), 1-phenyl-2-methylindole (**12e**) and 2-ethylindole (**12f**) were studied. When **12d** was reacted under the above reaction conditions, only dimers **13d**, **14d** and **15d** were obtained in 32%, 15% and 11% yield, respectively, while 1-phenyl-2-methylindole (**12e**) gave **10**, **13e** and **16e** in 23%, 30% and 5% yield, respectively. Oxidation of **12f** afforded *o*-(*N*-propionyl)aminobenzoic acid **17f** as the main product in 32% yield. Formation of compound **10** occurs through a hetero-Diels-Alder

reaction between two molecules of 2-methyleneindolinone **26**[22] as is shown in Scheme 3.



Scheme 2

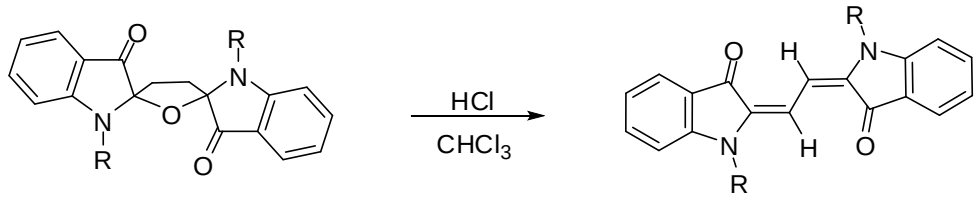


26 **10**

Scheme 3

Formation of adduct **10** could corroborate an indolinone intermediate like **23** shown in Scheme 2. Compounds **13a**,**d**,**e**, **14a**,**d** and **15d** provided single crystals suitable for X-ray diffraction analysis, the corresponding structures are shown in Figure 2 and the pertinent data are summarized in Table 1.

Finally, acid catalyzed tetrahydrofuran ring opening of dimers **14a**,**d** in an HCl/$CHCl_3$ solution afforded vinylogous *N*,*N*'-dialkylindigos *trans-trans*-**27a**,**d** in quantitative yields (Scheme 4).



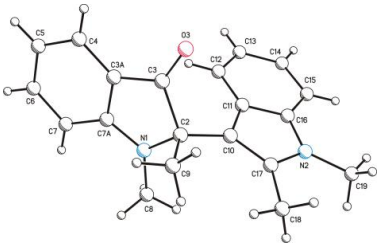
14a: R = Me
14d: R = Et

27a: R = Me
27d: R = Et

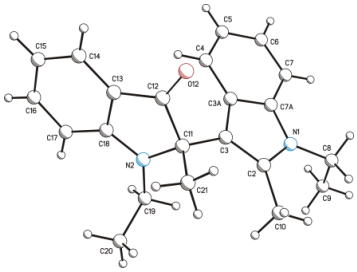
Sheme 4

The *trans-trans* geometry for **27a**,**d** follows from the chemical shift of the vinylic protons[23] of **27a** (δ = 8.04, s, 2H) and **27d** (δ = 8.15, s, 2H).

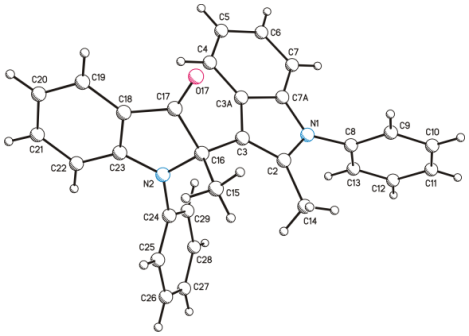
While the room temperature ^{1}H NMR spectrum of **14a** shows only four proton signals for the aromatic rings and a strongly coupled AA'BB' spin-spin system for the ethylene residue,[8] the ^{1}H NMR spectra of **13a** and **15a** evidenced eight signals for the aromatic ring protons, and dimer **13a** further exhibited line broadening for the aromatic H4' signal (broad doublet at 7.44 ppm, J = 7.7 Hz, $W_{1/2}$ = 4.5 Hz) and the C2'-Me' group (broad singlet at 2.27 ppm, $W_{1/2}$ = 2.0 Hz). This broadening suggests the presence of conformational isomers arising from slow rotation around the C2-C3' single bond (Scheme 5), a situation further evidenced when ^{1}H NMR spectra of **13a** were measured at temperatures other than the room temperature (20 °C) (Figure 3). When heating a solution of **13a** to 35 °C in $CDCl_3$ or to 70 °C in $CDCl_2CDCl_2$, the broad H4' and C2'-Me' resonances collapsed into sharp signals, while cooling below 0 °C in CD_2Cl_2 allowed observation of coalescence for the signals owing to H4' and H5' at -20 °C and -60 °C, respectively, while the C2'-Me' signal vanishes at -40 °C.



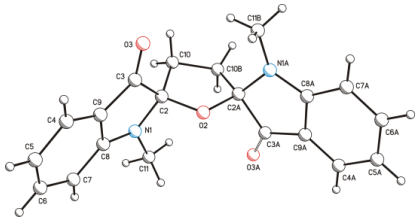
13a



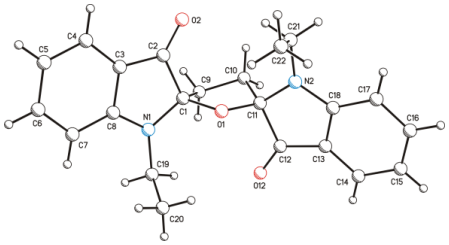
13d



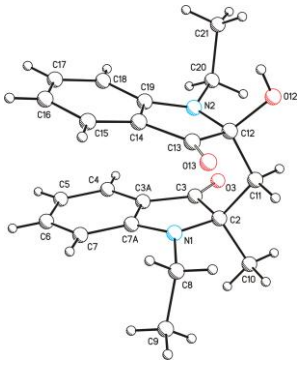
13e



14a

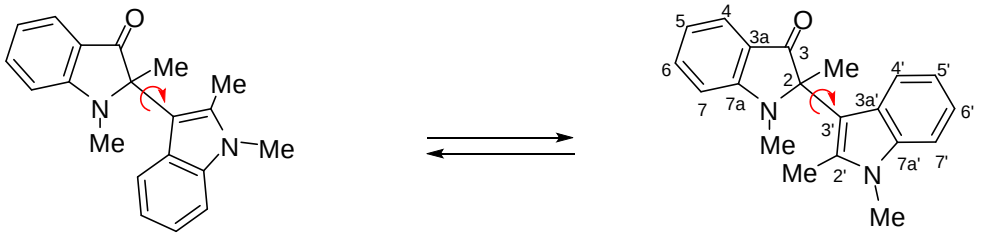


14d



15d

Figure 2. X-Ray crystal structures of dimers **13a**,**d**,**e**, **14a**,**d** and **15d**.



13a*A* **13a***B*

Scheme 5

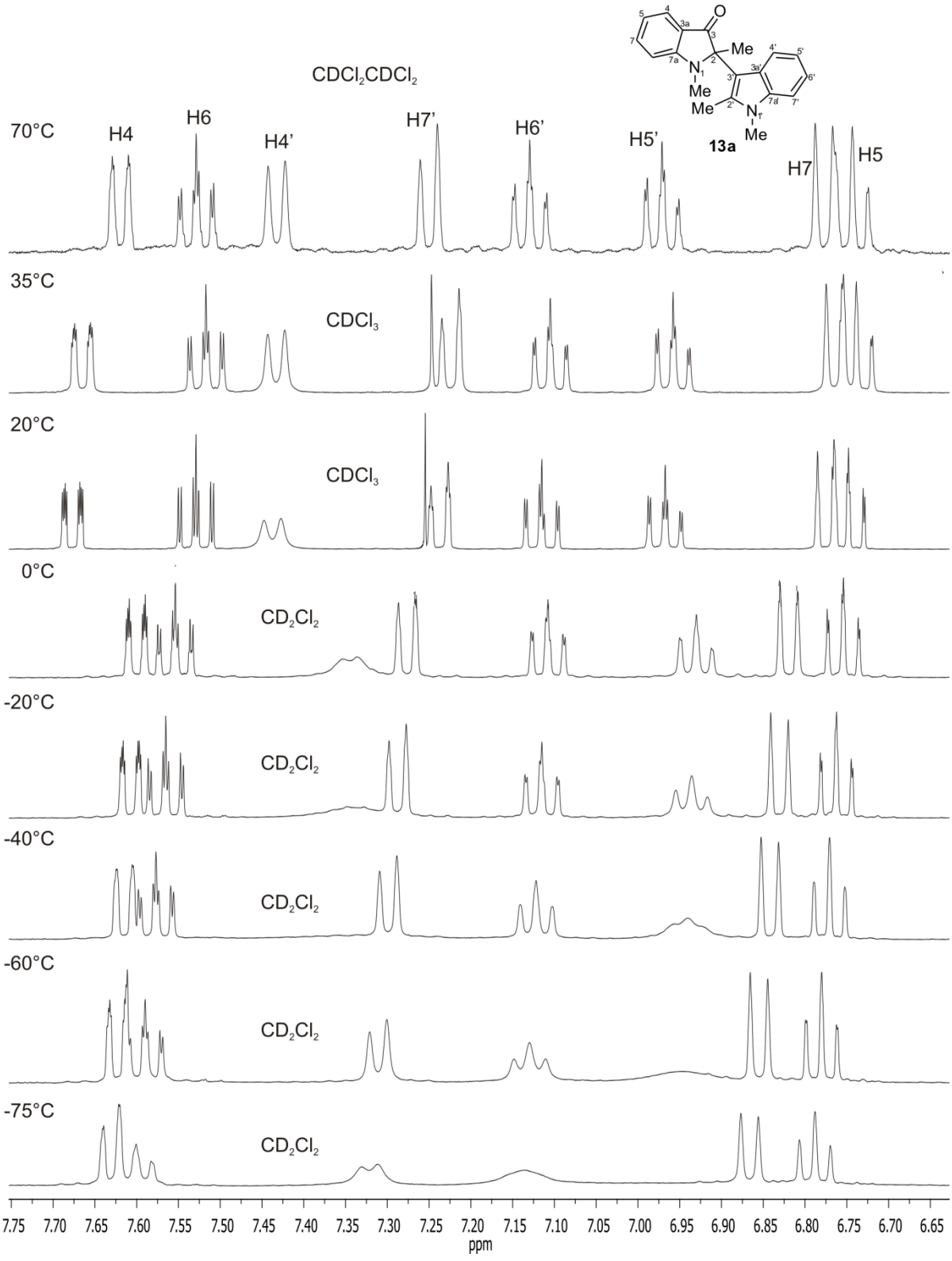
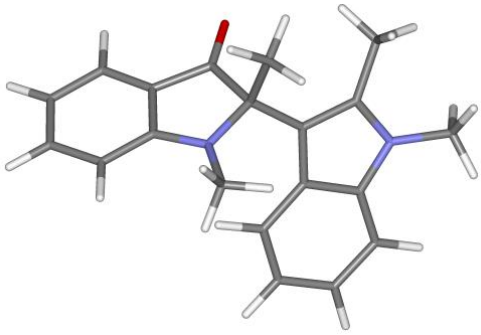


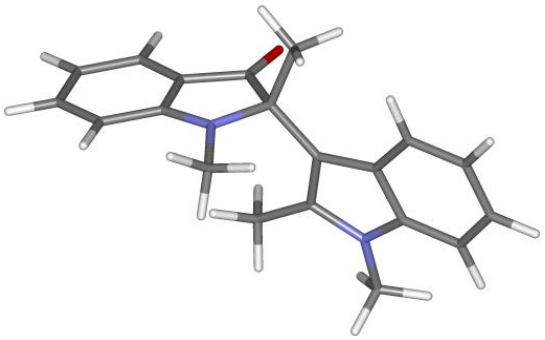
Figure 3. Partial ^{1}H NMR spectra of **13a** at different temperatures, 400 MHz.

As evidenced in Figure 3, when cooling a solution of **13a**, the broadening of the H4'-H7'signals is higher than that for the H4-H7 signals, which means the chemical environment for the protons of the indole

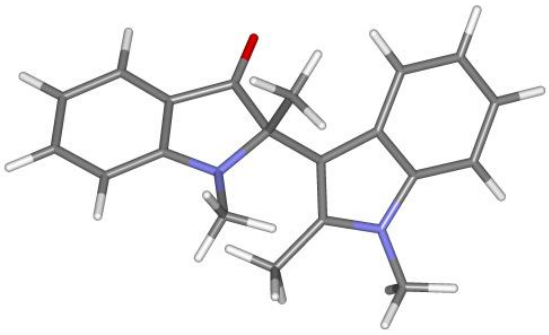
portion is more different than that for the indoxyl portion. Furthermore, conformational evaluations of **13a** were carried out by systematic and Monte Carlo search protocols within the Spartan 04 program[24] employing the MMFF94 molecular mechanics force field. According to the conformer distribution, only four models arose as relevant contributors, which were submitted to geometry optimization using DFT calculations at the B3LYP/6-31G(d) level of theory. The Boltzmann distribution (*p*) and relative energy (E_{rel}) for these four conformers are shown in Figure 4.



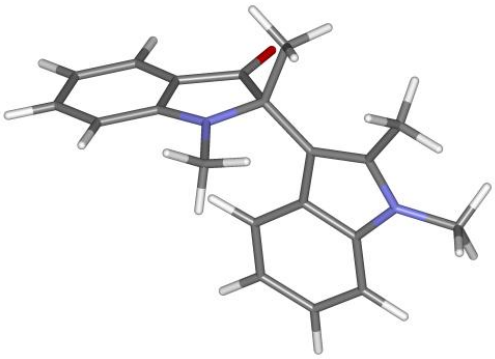
13a*A*
E = -601719.4986 kcal mol^{-1}
E_{rel} = 0 kcal mol^{-1}
p = 73%



13a*B*
E = -601718.6465 kcal mol^{-1}
E_{rel} = 0.85 kcal mol^{-1}
p = 17%



13a*C*
E = -601718.0378 kcal mol^{-1}
E_{rel} = 1.72 kcal mol^{-1}
p = 6%



13a*D*
E = -601717.783 kcal mol^{-1}
E_{rel} = 1.46 kcal mol^{-1}
p = 4%

Figure 4

In conclusion, we demonstrated that 2-methylindole derivatives **12a**,**d**,**e** are easily oxidized to indole dimers with DMD and that the N1 substituent influences the ratio and type of obtained monomers or dimers.

Table 1. Crystal data for dimers **13a**,**d**,**e**, **14a**,**d** and **15d**.

	13a	**13d**	**13e**	**14a**	**14d**	**15d**
Empirical formula	$C_{20}H_{20}N_2O$	$C_{22}H_{24}N_2O$	$C_{30}H_{24}N_2O \cdot C_2H_6SO$	$C_{20}H_{18}N_2O_3$	$C_{22}H_{22}N_2O_3$	$C_{22}H_{24}N_2O_3$
Formula weight	304.38	332.43	506.64	334.36	362.42	364.43
Crystal size (mm)	0.38 x 0.34 x 0.22	0.38 x 0.34 x 0.28	0.36 x 0.30 x 0.20	0.20 x 0.18 x 0.18	0.34 x 0.22 x 0.16	0.40 x 0.28 x 0.20
Crystal system	monoclinic	monoclinic	triclinic	orthorhombic	triclinic	orthorhombic
space group	$P2_1/c$	$P2_1/a$	P-1	Pba2	P-1	Pbca
Cell *a* (Å)	6.746(1)	16.856(2)	9.958(2)	13.594(9)	8.795(1)	14.792(3)
b (Å)	13.166(2)	8.932(4)	10.154(5)	13.712(3)	9.700(1)	13.879(3)
c (Å)	18.523(3)	24.562(4)	15.315(2)	8.767(4)	11.545(1)	18.522(4)
α (deg)	90	90	109.01(3)	90	73.618(9)	90
β (deg)	97.81(1)	99.22(1)	98.64(1)	90	80.998(2)	90
γ (deg)	90	90	107.84(3)	90	89.412(1)	90
Volume ($Å^3$)	1629.8(4)	3650.3(16)	1338.8(7)	1634.2(14)	932.7(2)	3802.8(13)
Z, ρ Calc (mg/mm^3)	4, 1.240	8, 1.210	2, 1.257	4, 1.359	2, 1.290	8, 1.273
μ (mm^{-1})	0.604	0.579	1.318	0.751	0.697	0.684
F(000)	648	1424	536	704	384	1552
Theta range (deg)	4.13 to 59.96	1.82 to 59.95	3.18 to 59.95	4.58 to 60.03	4.75 to 59.95	5.64 to 59.94
Limiting indices	-7<=h<=7, 0<=k<=14, 0<=l<=20	-18<=h<=18, 0<=k<=10, 0<=l<=26	-11<=h<=10, -11<=k<=10, 0<=l<=11	0<=h<=15, 0<=k<=15, -9<=l<=9	-9<=h<=9, -10<=k<=10, 0<=l<=12	0<=h<=16, 0<=k<=15, 2<=l<=20
Reflections collected	2728	6180	3567	5270	3030	2862
Reflections unique	2417	5381	3276	2430	2756	2514
Data / parameters	2127 / 208	4378 / 451	3000 / 372	2334 / 243	2440 / 244	2216 / 248
Goodness-of-fit on F^2	1.059	1.098	1.048	1.045	1.060	1.075
Final R1 (%)	3.8	4.9	4.9	2.8	3.9	3.3
wR2 (%)	10.8	14.8	13.6	7.1	10.9	8.1
Residual e^- ($e.Å^3$)	0.182 and -0.145	0.157 and -0.158	0.231 and -0.196	0.120 and -0.109	0.125 and -0.129	0.098 and -0.103
CCDC No.	924297	924298	924299	924300	924301	924302

EXPERIMENTAL

General experimental procedures

Melting points were determined on a Büchi B-540 apparatus. IR spectra were recorded on a Perkin-Elmer GX FT-IR spectrophotometer. The 400 and 100 MHz ^{1}H and ^{13}C NMR spectra were obtained on JEOL Eclipse + 400 and Varian VNMRS 400 spectrometers using $CDCl_3$, CD_2Cl_2 or $CDCl_2CDCl_2$ as solvents. The chemical shifts of the residual hydrogen present in the deuterated solvents were used as reference.[25] For complete assignments 2D NMR, gHSQC and gHMBC spectra were used. Data are reported as follows: chemical shift in ppm, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, AB = AB system, AA'BB' system), coupling constant (Hz), and assignment. GC/MS analyses were conducted on a Varian CP 3800 GC equipped with a Varian Saturn 2000 selective mass detector and a 30 m, 0.25 mm i.d., CP-SIL capillary column, using helium as the carrier gas (1 mL/min), programmed from 70 °C to 250 °C at a rate of 30 °C/min, with the injector temperature at 200 °C. MS analyses were obtained in the electron impact (EI) mode at an ionizing voltage of 70 eV on a Hewlett Packard 5989-A spectrometer. Microanalytical determinations were performed on a Perkin-Elmer 2400 series PCII apparatus. Analytical thin-layer chromatography (TLC) was done on silica gel F_{254} coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). Flash chromatography was done using Silica Gel 60 (230-400 mesh) from Aldrich.

General procedure for the oxidation of 2-alkylindoles 12a-f.

To a solution of 3.44 mmol of the appropriate indole **12a** (0.500 g), **12b** (0.452 g), **12c** (0.652 g), **12d** (0.548 g), **12e** (0.714 g) or **12f** (0.499 g) in acetone (50 mL) was added dropwise a solution of EDTA (0.031 g, 0.031 equiv) and $NaHCO_3$ (1.014 g, 3.5 equiv) dissolved in the minimum amount of water. The resulting thick mixture was treated dropwise with a solution of oxone monopersulfate complex (2.650 g, 2.5 equiv of $KHSO_5$) in water (5-10 mL) at room temperature over 10 min. After complete addition, the mixture was stirred at room temperature for 1 h, filtered off, the acetone was evaporated under reduce pressure and the residue was dissolved in EtOAc (50 mL). The organic phase was washed with brine (2 x 25 mL), dried over Na_2SO_4 and concentrated in vacuo. The resultant crude products were purified by flash column chromatography with EtOAc/hexane 1:3 for **13a-17a** and **13d-15d**, with EtOAc/hexane 1:4 for **10**, **13e**, **16b**,**c**,**e** and **17b**, and with EtOAc/MeOH 44:1 for **17f**.

2-(1,2-Dimethyl-1*H*-indol-3-yl)-1,2-dimethyl-1,2-dihydro-3*H*-indol-3-one (13a).

Prepared from **12a** as green crystals (177.0 mg, 34%); mp 187-188 °C (EtOAc/hexanes). Lit.,[7h] 155–157 °C, no crystallization solvent reported. Although **13a** is known for four decades,[7e] it is

spectroscopically not yet fully characterized. Thus, NMR data follow: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (1H, ddd, *J* = 7.7, 1.5, 0.8 Hz, H4), 7.53 (1H, td, *J* = 7.9, 1.3 Hz, H6), 7.44 (1H, brd, *J* = 7.7 Hz, H4'), 7.24 (1H, d, *J* = 8.4 Hz, H7'), 7.12 (1H, td, *J* = 7.4, 1.0 Hz, H6'), 6.97 (1H, td, *J* = 7.9, 1.1 Hz, H5'), 6.78 (1H, d, *J* = 8.1 Hz, H7), 6.75 (1H, t, *J* = 7.0 Hz, H5), 3.63 (3H, s, NMe'), 2.86 (3H, s, NMe), 2.27 (3H, s, Me'), 1.90 (3H, s, Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.0 (C=O), 159.1 (C7a), 137.9 (C6), 136.9 (C7a'), 135.8 (C2'), 127.5 (C3a'), 125.6 (C4), 120.8 (C6'), 119.8 (C4'), 119.7 (C5'), 118.5 (C3a), 116.9 (C5), 109.2 (C7'), 108.3 (C7), 106.8 (C3'), 71.4 (C2), 29.6 (NMe'), 28.0 (NMe), 22.2 (Me'), 12.1 (Me).

1-Ethyl-2-(1-ethyl-2-methyl-1*H*-indol-3-yl)-2-methylindolin-3-one (13d).

Prepared from **12d** as green crystals (183.2 mg, 32%); mp 107-108 °C (EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (1H, ddd, *J* = 8.2, 1.4, 0.7 Hz, H4), 7.51 (1H, ddd, *J* = 8.4, 7.1, 1.4 Hz, H6), 7.50 (1H, overlapped, H4'), 7.26 (1H, d, *J* = 8.2 Hz, H7'), 7.11 (1H, ddd, *J* = 8.2, 7.1, 1.1 Hz, H6'), 6.98 (1H, brt, *J* = 7.6 Hz, H5'), 6.77 (1H, d, *J* = 8.4 Hz, H7), 6.73 (1H, td, *J* = 7.4, 0.8 Hz, H5), 4.10 (2H, q, *J* = 7.3 Hz, CH_2'CH_3'), 3.33 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 2.19 (3H, brs, CH_3'), 1.95 (3H, s, CH_3), 1.30 (3H, t, *J* = 7.2 Hz, CH_2'CH_3'), 1.04 (3H, t, *J* = 7.2 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.0 (C3=O), 157.9 (C7a), 137.6 (C6), 135.6 (C7a'), 134.8 (C2'), 127.7 (C3a'), 125.6 (C4), 120.5 (C6'), 119.7 (C4'), 119.5 (C5'), 118.1 (C3a), 116.3 (C5), 109.0 (C7'), 108.1 (C7), 107.0 (C3'), 71.5 (C2), 37.5 (CH_2'CH_3'), 37.0 (CH_2CH_3), 23.4 (Me), 15.1 (CH_2'CH_3'), 14.1 (CH_2CH_3), 11.6 (Me'); IR (KBr) ν_{max} 3014, 2969, 2931, 2869, 1690, 1616, 1492, 1467, 1349, 1322 cm^{-1}; EIMS *m/z* 332 [M^+] (49), 317 (53), 289 (88), 213 (26), 173 (53), 158 (66), 144 (100), 130 (44), 117 (31), 103 (17), 77 (14).

2-Methyl-2-(2-methyl-1-phenyl-1*H*-inden-3-yl)-1-phenylindolin-3-one (13e).

Prepared from **12e** as orange crystals (219.2 mg, 30%); mp 121-122 °C (EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (1H, d, *J* = 7.6 Hz, H4), 7.55-6.85 (17H, overlapped, H5-H7, H4'-H7', H9-H13, H9'-H13'), 2.13 (3H, brs, Me or Me'), 1.83 (3H, brs, Me or Me'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.3 (C3), 157.9 (C7a), 139.8, 137.8, 137.4, 137.3, 129.4, 129.3, 128.8, 128.1, 126.0, 125.4 (C4), 121.3, 120.3, 119.8, 119.6, 118.9, 111.4, 110.2, 109.8, 72.6 (C2), 22.9, 12.90 (Me, Me'); IR (film) ν_{max} 3059, 2922, 2850, 1716, 1610, 1595, 1499, 1478, 1466, 1454, 1371, 1319 cm^{-1}; EIMS *m/z* 428 [M^+] (34), 414 (30), 400 (17), 386 (100), 324 (27), 310 (30), 233 (37), 223 (65).

1,1''-Dimethyl-3',4'-dihydrodispiro[indole-2,2'-furan-5',2"-indole]-3,3"(1*H*,1"*H*)-dione (14a).

Prepared from **12a** as yellow crystals (149.7 mg, 26%); mp 170-173 °C (EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (2H, d, *J* = 7.7 Hz, H4, H4''), 7.45 (2H, td, *J* = 7.8, 1.5 Hz, H6, H6''), 6.72 (2H, t, *J* = 7.3 Hz, H5, H5''), 6.67 (2H, d, *J* = 8.1 Hz, H7, H7''), 3.07 (6H, s, Me, Me''), 2.76 and 2.15

(4H, AA'BB', H3',H4'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.2 (C3, C3''), 161.2 (C7a, C7a''), 138.7 (C6, C6''), 125.2 (C4, C4''), 118.1 (C5, C5''), 117.6 (C3a, C3a''), 108.5 (C7, C7''), 97.1 (C2, C2''), 28.5 (C3', C4'), 26.9 (Me, Me''); IR (film) ν_{max} 2949, 1713, 1616, 1584, 1486, 1434, 1370, 1323 cm^{-1}; EIMS *m/z* 334 [M$^+$] (68), 199 (5), 175 (49), 159 (100), 133 (58), 105 (7); *Anal*. Calcd for $C_{20}H_{18}N_2O_3$: C 71.84; H 5.43; N 8.38. Found: C 71.71; H 5.54; N 8.38. FABHRMS *m/z* 334.1311 (calcd for $C_{20}H_{18}N_2O_3$, 334.1317).

1,1''-Diethyl-3',4'-dihydrodispiro[indole-2,2'-furan-5′,2"-indole]-3,3"(1*H*,1"*H*)-dione (14d).

Prepared from **12d** as yellow crystals (96.1 mg, 15%); mp 167-170 °C (EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (2H, ddd, *J* = 7.6, 1.4, 0.7 Hz, H4, H4''), 7.44 (2H, td, *J* = 7.1, 1.3 Hz, H6, H6''), 6.69 (2H, td, *J* = 7.4, 0.8 Hz, H5, H5''), 6.66 (2H, brd, *J* = 8.6 Hz, H7, H7''), 3.71 (2H, dq, *J* = 15.1, 7.2 Hz, CH_2CH_3, CH_2''CH_3''), 3.56 (2H, dq, *J* = 15.1, 7.2 Hz, CH_2CH_3, CH_2''CH_3''), 2.80 and 2.11 (4H, AA'BB', H3', H4'), 1.22 (6H, t, *J* = 7.1 Hz, CH_2CH_3, CH_2''CH_3''); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.6 (C3=O, C3''=O), 160.1 (C7a, C7a''), 138.4 (C6, C6''), 125.2 (C4, C4''), 117.4 (C5, C5''), 117.2 (C3a, C3a''), 108.4 (C7, C7''), 96.7 (C2, C2''), 35.0 (CH_2CH_3, CH_2''CH_3''), 28.9 (C3',C4'), 13.9 (CH_2CH_3, CH_2''CH_3''); IR (KBr) ν_{max} 2969, 2918, 2850, 1703, 1616, 1485, 1336, 1313 cm^{-1}; EIMS *m/z* 362 [M$^+$] (100), 345 (16), 188 (63), 172 (47), 173 (97), 158 (63), 147 (79), 130 (73), 117 (70), 104 (40), 77 (20), 51 (9). FABHRMS *m/z* 362.1639 (calcd for $C_{22}H_{22}N_2O_3$, 362.1630).

2-[(1,2-Dimethyl-3-oxoindolin-2-yl)methyl]-2-hydroxy-1-methylindolin-3-one (15a).

Prepared from **12a** as yellow crystals (127.4 mg, 22%); mp 146-149 °C (EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (1H, d, *J* = 7.3 Hz, H4'), 7.29 (1H, dd, *J* = 8.4, 2.2 Hz, H4), 7.00 (1H, td, *J* = 6.9, 1.4 Hz, H6'), 6.97 (1H, td, *J* = 7.2, 1.2 Hz, H6), 6.57 (1H, td, *J* = 7.3, 0.7 Hz, H5'), 6.50 (1H, td, *J* = 7.4, 0.7 Hz, H5), 6.01 (1H, d, *J* = 8.4 Hz, H7'), 5.87 (1H, d, *J* = 8.0 Hz, H7), 3.89 (1H, brs, OH), 2.74 and 2.63 (2H, AB, *J* = 14.7 Hz, H8), 2.48 (3H, s, NMe), 2.42 (3H, s, NMe'), 1.08 (3H, s, Me'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.6 (C3'), 198.8 (C3), 159.6 (C7a), 159.3 (C7a'), 136.4 (C6), 135.6 (C6'), 123.4 (C4), 123.2 (C4'), 121.8 (C3a'), 119.9 (C3a), 118.0 (C5, C5'), 109.7 (C7'), 109.3 (C7), 87.8 (C2), 67.6 (C2'), 45.0 (C8), 28.4 (NMe'), 27.5 (NMe), 20.5 (Me'); IR (film) ν_{max} 3386, 2927, 2883, 2825, 1698, 1617, 1485, 1361, 1320 cm^{-1}. EIMS *m/z* 336 [M$^+$] (36), 318 (4), 174 (100), 160 (46), 134 (10). FABHRMS *m/z* 336.1469 (calcd for $C_{20}H_{20}O_3N_2$, 336.1474).

1-Ethyl-2-((1-ethyl-2-hydroxy-3-oxoindolin-2-yl)methyl)-2-methylindolin-3-one (15d).

Prepared from **12d** as yellow crystals (69.0 mg, 11%); mp 158-160 °C (EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (1H, ddd, *J* = 7.7, 1.3, 0.6 Hz, H4'), 7.27 (1H, ddd, *J* = 7.6, 1.3, 0.6 Hz, H4),

6.89 (2H, td, *J* = 7.7, 0.6 Hz, H6, H6'), 6.46 (1H, td, *J* = 7.5, 0.7 Hz, H5'), 6.42 (1H, td, *J* = 7.5, 0.7 Hz, H5), 5.84 (1H, d, *J* = 8.3 Hz, H7'), 5.75 (1H, d, *J* = 8.3 Hz, H7), 3.09 (1H, dq, *J* = 15.5, 7.5 Hz, CH_2CH_3), 2.89 (2H, m, CH_2'CH_3), 2.79 (1H, dq, *J* = 15.5, 7.0 Hz, CH_2CH_3), 2.74 and 2.59 (2H, AB, *J* = 14.6 Hz, H8), 1.10 (3H, s, Me'), 0.93 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 0.88 (3H, t, CH_2CH_3'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.7 (C3'), 199.4 (C3), 157.6 (C7a), 157.3 (C7a'), 136.3 (C6), 135.3 (C6'), 123.6 (C4), 123.3 (C4′), 121.4 (C3a'), 119.5 (C3a), 117.3 (C5'), 116.9 (C5), 110.1 (C7'), 109.8 (C7), 88.1 (C2), 67.5 (C2'), 46.1 (C8), 36.1 (CH_2'CH_3'), 35.9 (CH_2CH_3), 22.2 (Me'), 12.4 (CH_2CH_3), 11.8 (CH_2'CH_3'); IR (KBr) ν_{max} 3372, 2970, 2918, 2850, 1715, 1674, 1619, 1490, 1481, 1326 cm^{-1}. EIMS *m/z* 364 [M$^+$] (9), 318 (6), 188 (61), 174 (100), 160 (23), 146 (20), 130 (21).

2-Hydroxy-1,2-dimethylindolin-3-one (16a).

Prepared from **12a** as red oil (4.2 mg, 0.7%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (1H, ddd, *J* = 7.9, 1.6, 0.5 Hz, H4), 7.50 (1H, ddd, *J* = 8.4, 7.3, 1.6 Hz, H6), 7.07 (1H, ddd, *J* = 7.9, 7.3, 0.9 Hz, H5), 6.81 (1H, brd, *J* = 8.4 Hz, H7), 3.25 (3H, s, Me9), 1.62 (3H, s, Me8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.6 (C3), 153.0 (C7a), 135.1 (C6), 128.6 (C4), 122.0 (C5), 117.2 (C3a), 112.6 (C7), 99.8 (C2), 40.6 (C9), 19.7 (C8); IR (film) ν_{max} 3382, 2920, 2851, 1690, 1615, 1482, 1371, 1323, 1295 cm^{-1}. EIMS *m/z* 177 [M$^+$] (8), 176 (80), 150 (25), 134 (20), 132 (100), 104 (31), 77 (12), 43 (9).

2-Hydroxy-2-methylindolin-3-one (16b).

Prepared from **12b** as yellow crystals (69.3 mg, 12%); mp 120 °C (EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (1H, dm, *J* = 7.8 Hz, H4), 7.49 (1H, ddd, *J* = 8.3, 7.0, 1,3 Hz, H6), 6.94 (1H, dt, *J* = 8.3, 0.8 Hz, H7), 6.81 (1H, ddd, *J* = 7.8, 7.1, 0.8 Hz, H5), 6.08 (1H, brs, NH), 1.66 (1H, brs, OH), 1.15 (3H, s, Me8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.1 (C3), 160.9 (C7a), 138.1 (C6), 124.7 (C4), 119.7 (C3a), 118.5 (C5), 112.2 (C7), 68.5 (C2), 18.2 (C8); IR (KBr) ν_{max} 3372, 3315, 2975, 2919, 1677, 1616, 1488, 1453, 1400, 1376, 1324, 1299, 1270 cm^{-1}; EIMS *m/z* 146 [M$^+$-17] (68), 117 (48), 104 (15), 89 (14).

Methyl 2-methyl-3-oxoindoline-1-carboxylate (16c).

Prepared from **12c** as white crystals (534.8 mg, 76%); mp 71-72 °C (EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.24 (1H, brs, H7), 7.74 (1H, brd, *J* = 6.9 Hz, H4), 7.67 (1H, td, *J* = 7.9, 1.4 Hz, H6), 7.18 (1H, td, *J* = 7.5, 0.8 Hz, H5), 4.29 (1H, brs, H2), 3.92 (3H, s, CO_2Me), 1.56 (3H, d, *J* = 7.1 Hz, C2-Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.3 (C3), 152.4 (C9, C7a), 137.2 (C6), 124.1 (C4), 123.4 (C5), 123.2 (C3a), 116.8 (C7), 61.5 (C2), 53.1 (CO_2Me), 16.9 (C2-*Me*); IR (KBr) ν_{max} 3412, 3004, 2986, 2956, 2940, 1716, 1607, 1472, 1434, 1377, 1324, 1299, 1270 cm^{-1}. EIMS *m/z* 205 [M$^+$] (100), 162 (35), 146 (39), 118 (73), 91 (20).

2-Hydroxy-2-methyl-1-phenylindolin-3-one (16e).

Prepared from **12e** as a green oil (43.8 mg, 5%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (1H, dm, *J* = 7.7 Hz, H4), 7.50-7.40 (5H, overlapped, H10, H14, H11, H13, H6), 7.31 (1H, tt, *J* = 7.0, 1.7, Hz, H12), 6.88 (1H, dd, *J* = 8.4, 0.5 Hz, H7), 6.83 (1H, ta, *J* = 7.7 Hz, H5), 3.40 (1H, brs, OH), 1.34 (3H, s, C8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.9 (C3), 158.3 (C7a), 138.3 (C9), 138.2 (C6), 129.5 (C10, C14), 126.7 (C12), 126.1 (C11, C13), 125.6 (C4), 119.4 (C5), 117.8 (C3a), 111.0 (C7), 89.1 (C2), 21.4 (Me8); IR (film) ν_{max} 3411, 3387, 1704, 1612, 1594, 1498, 1481, 1467, 1366, 1320 cm^{-1}. EIMS *m/z* 239 [M$^+$] (6), 221 (100), 192 (35), 165 (14), 89 (10), 77 (7), 63 (5), 51 (9).

***N*-(2-Formylphenyl)-*N*-methylacetamide (17a).**

Prepared from **12a** as a brown oil (32.1 mg, 5%). Although **17a** is known,[26] it is spectroscopically not yet fully characterized. Thus, NMR data follow: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.16 (1H, s, H7), 8.00 (1H, dd, *J* = 7.8, 1.5 Hz, H6), 7.73 (1H, td, *J* = 7.7, 1.7 Hz, H4), 7.56 (1H, ta, *J* = 7.6 Hz, H5), 7.32 (1H, dd, *J* = 7.9, 1.0 Hz, H3), 3.31 (3H, s, NMe), 1.82 (3H, s, COMe); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.4 (HC=O), 170.5 (MeC=O), 146.1 (C2), 135.8 (C4), 132.3 (C1), 130.3 (C6), 129.1 (C3), 129.0 (C5), 37.9 (NMe), 22.4 (MeC=O) IR (film) ν_{max} 2962, 2925, 2854, 2753, 1695, 1661, 1597, 1489, 1456, 1424, 1382, 1352, 1301, 1263; EIMS *m/z* 177 [M$^+$] (6), 148 (58), 135 (46), 106 (100), 77 (19), 51 (17), 43 (27).

2-Acetamidobenzoic acid (17b).

Prepared from **12b** as brown crystals (252.6 mg, 41%). ^{1}H NMR and ^{13}C NMR spectroscopic data match those reported.[27]

2-Propionamidobenzoic acid (17f).

Prepared from **12f** as a brown oil (215.0 g, 32%). ^{1}H NMR spectroscopic data match those reported.[28]

1,5'-Diphenyl-4',5'-dihydro-3'*H*-spiro[indoline-2,2'-pyrano[3,2-*b*]indol]-3-one (10).

Prepared from **12e** as orange crystals (176.0 mg, 23%); mp 192-193 °C (EtOAc/hexanes). Lit.,[8] 192 °C. ^{1}H NMR and ^{13}C NMR spectroscopic data match those reported.[8]

General procedure to obtain *N,N*'-dialkylindigos 27a,d.

To a solution of 0.15 mmol of the appropriate spirobisindoxyl **14a** (50 mg) or **14d** (54 mg) in $CHCl_3$ (10 mL) was added two drops of concentrated HCl (38%) and the mixture was stirred at room temperature for 1 h. The volatiles were evaporated under vacuum to afford **27a** or **27d**.

(2*E*,2'*E*)-2,2'-(Ethane-1,2-diylidene)bis(1-methylindolin-3-one) (27a).

Prepared from **14a** as a blue solid (47 mg, 99%); mp 274-275 °C ($CHCl_3$). Although **27a** is known,[23] it is spectroscopically not yet fully characterized. Thus, NMR data follow: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (2H, s, 2H8), 7.66 (2H, dm, *J* = 7.7 Hz, 2H4), 7.45 (2H, td, *J* = 7.7, 1.2 Hz, 2H6), 6.88 (2H, d, *J* = 8.1 Hz, 2H7), 6.89 (2H, t, *J* = 7.1 Hz, 2H5), 3.38 (6H, s, 2Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.7 (2C3), 151.6 (2C7a), 138.0 (2C2), 135.5 (2C6), 124.4 (2C4), 121.5 (2C3a), 119.5 (2C5), 111.7 (2C8), 108.9 (2C7), 28.8 (2Me).

(2*E*,2'*E*)-2,2'-(Ethane-1,2-diylidene)bis(1-ethylindolin-3-one) (27d).

Prepared from **14d** as a blue solid (51 mg, 99%); mp 237-239 °C ($CHCl_3$). Although **27d** is known,[23] it is spectroscopically not yet fully characterized. Thus, NMR data follow: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (2H, s, 2H8), 7.67 (2H, d, *J* = 8.3 Hz, 2H4), 7.46 (2H, td, *J* = 7.7, 1.3 Hz, 2H6), 6.91 (2H, d, *J* = 8.0 Hz, 2H7), 6.90 (2H, t, *J* = 7.5 Hz, 2H5), 3.89 (4H, q, *J* = 7.2 Hz, $2CH_2$), 1.35 (6H, t, *J* = 7.2 Hz, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 186.0 (2C3), 150.7 (2C7a), 136.6 (2C2), 135.5 (2C6), 124.6 (2C4), 121.7 (2C3a), 119.5 (2C5), 111.7 (2C8), 108.9 (2C7), 37.0 ($2CH_2$), 12.1 ($2CH_3$).

Single crystal X-ray diffraction analyses

Data collections for **13a**,**d**,**e**, **14a**,**d** and **15d** were done on an Enraf-Nonius CAD4 diffractometer using Cu Kα radiation (λ = 1.54184 Å). The structures were solved by direct methods using the SHELXS-97[29] program included in the WINGX v1.6 package.[30] Structural refinements were carried out by full-matrix least squares on F2. The non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Atomic coordinates, bond lengths, bond angles and anisotropic thermal parameters are in deposit at the Cambridge Crystallographic Data Center. Table 1 summarizes the relevant data and CCDC deposition numbers.

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