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

Alberto Aristeo-Dominguez, a Myriam Meléndez-Rodríguez, a,* Oscar R. Suárez Castillo, a,* Yaneth M. A. Contreras-Martínez, a Lizbeth Suárez-Ramírez, a Nayely Trejo-Carbajal, a Martha S. Morales-Ríos, b and Pedro Joseph-Nathan b

aÁrea Académica de Química, Universidad Autónoma del Estado de Hidalgo, Mineral de la Reforma, Hidalgo, 42184 Mexico. bDepartamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado 14-740, Mexico, D. F., 07000 Mexico

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(1H)-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[2H-indol]-3(1H)-one (spiro-indoxyl) moiety is found in the natural occurring mycotoxins brevianamide A (1) and B (2), isolated from Penicillium species, which have shown antifeedant and insecticidal effects. Other spiro-indoxyl molecules include rupicoline (3) and iboluteine (4) isolated from Tabernaemontana rupicola Benth, and Tabernanthe iboga, respectively, austamide (5) isolated from Aspergillus ustus, and the phytoalexin erucalexin (6) 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.\textsuperscript{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,\textsuperscript{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\textit{H},3\textit{H})-dione was treated with an aqueous KOH/benzene mixture.\textsuperscript{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\textsuperscript{9} and as anion receptors\textsuperscript{10} (Figure 1).

A number of reagents for the oxidation of the indole C2-C3 double bond to indoxyls have been reported,\textsuperscript{7} including NaIO\textsubscript{4},\textsuperscript{7d} N-chlorobenzotriazole,\textsuperscript{7e} OsO\textsubscript{4},\textsuperscript{11} oxodiperoxomolibdenum complexes,\textsuperscript{7f,12}...
Starting 2-methylindole derivatives 12a,b,d-f (Scheme 1) were obtained according to described methodologies, while indole 12e was obtained in 76% yield when 2-methylindole (12b) was reacted with Me₂CO₃/DBU.

RESULTS AND DISCUSSION

Starting 2-methylindole derivatives 12a,b,d-f (Scheme 1) were obtained according to described methodologies, while indole 12e was obtained in 76% yield when 2-methylindole (12b) was reacted with Me₂CO₃/DBU. In continuation with our studies aimed to shade light on the oxidation of N-protected-3-alkylindole derivatives with DMD to obtain exclusively 3-hydroxyoxindoles, we report herein an approach to indoxyl dimers based on oxidation of 2-methylindole derivatives.

We have already reported on the oxidation of 2-methylindole derivatives. Besides, it has been shown that the oxidation products depend on the nature of the substituents at the N1, C2, and C3 positions of the indole nucleus.

Starting 2-methylindole derivatives 12a,b,d-f (Scheme 1) were obtained according to described methodologies, while indole 12e was obtained in 76% yield when 2-methylindole (12b) was reacted with Me₂CO₃/DBU.

![Scheme 1](image-url)
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 1H and 13C 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,14 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. 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 bond21 to afford the ring-closed dimer 14a. Although dimer 13a has been obtained using oxidating agents like singlet oxygen,7b MoO$_5$·O=P(n-Pr)$_3$H$_2$O,7c m-CPBA7e-14 and H$_2$O$_2$,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$_2$Me) attenuate the internal nucleophilicity of the indole nitrogen atom11 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\textsuperscript{22} as is shown in Scheme 3.

Scheme 2
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/CHCl₃ solution afforded vinylogous N,N'-dialkylindigos trans-trans-27a,d in quantitative yields (Scheme 4).

Scheme 4

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

While the room temperature ¹H 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, the ¹H 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, W₁/₂ = 4.5 Hz) and the C2’-Me’ group (broad singlet at 2.27 ppm, W₁/₂ = 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 ¹H 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 CDCl₃ or to 70 °C in CDCl₃CDCl₂, the broad H4’ and C2’-Me’ resonances collapsed into sharp signals, while cooling below 0 °C in CD₂Cl₂ 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.
Figure 2. X-Ray crystal structures of dimers 13a,d,e, 14a,d and 15d.

Scheme 5
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\textsuperscript{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 ($E_{\text{rel}}$) for these four conformers are shown in Figure 4.

$\begin{align*}
13a_A & \quad E = -601719.4986 \text{ kcal mol}^{-1} \\
& \quad E_{\text{rel}} = 0 \text{ kcal mol}^{-1} \\
& \quad p = 73\%
\end{align*}$

$\begin{align*}
13a_B & \quad E = -601718.6465 \text{ kcal mol}^{-1} \\
& \quad E_{\text{rel}} = 0.85 \text{ kcal mol}^{-1} \\
& \quad p = 17\%
\end{align*}$

$\begin{align*}
13a_C & \quad E = -601718.0378 \text{ kcal mol}^{-1} \\
& \quad E_{\text{rel}} = 1.72 \text{ kcal mol}^{-1} \\
& \quad p = 6\%
\end{align*}$

$\begin{align*}
13a_D & \quad E = -601717.783 \text{ kcal mol}^{-1} \\
& \quad E_{\text{rel}} = 1.46 \text{ kcal mol}^{-1} \\
& \quad p = 4\%
\end{align*}$

**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.
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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$_2$Cl$_2$ or CDCl$_3$CDCl$_2$ as solvents. The chemical shifts of the residual hydrogen present in the deuterated solvents were used as reference. 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$_2$SO$_4$ 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-1H-indol-3-yl)-1,2-dimethyl-1,2-dihydro-3H-indol-3-one (13a).
Prepared from 12a as green crystals (177.0 mg, 34%); mp 187-188 °C (EtOAc/hexanes). Lit., $^{7b}$ 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) \(\delta\) 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) \(\delta\) 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'), 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\(^{1}\)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) \(\delta\) 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, \(\text{CH}_2\)CH3'), 3.33 (2H, q, \(J = 7.2\) Hz, \(\text{CH}_2\)CH3), 2.19 (3H, brs, CH3'), 1.95 (3H, s, CH3), 1.30 (3H, t, \(J = 7.2\) Hz, \(\text{CH}_2\)CH3'), 1.04 (3H, t, \(J = 7.2\) Hz, CH2CH3); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 204.0 (C3=O), 157.9 (C7a), 139.8, 137.8, 137.4, 137.3, 129.4, 129.3, 128.8, 128.8, 126.0, 125.4 (C4), 121.3, 120.3, 119.8, 119.6, 118.9, 110.2, 109.8, 72.6 (C2), 22.9, 12.90 (Me, Me'); IR (KBr) \(\nu_{\text{max}}\) 3014, 2969, 2931, 2869, 1690, 1610, 1595, 1499, 1478, 1466, 1454, 1371, 1319 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\(^{1}\)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) \(\delta\) 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) \(\delta\) 203.3 (C3), 157.9 (C7a), 139.8, 137.8, 137.4, 137.3, 129.4, 129.3, 128.8, 128.8, 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) \(\nu_{\text{max}}\) 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''(1H,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) \(\delta\) 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) $\nu_{\text{max}}$ 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$_2$O$_3$: 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$_2$O$_3$, 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, trd, $J = 8.6$ Hz, H7, H7’’), 3.71 (2H, dq, $J = 15.1$, 7.2 Hz, CH$_2$CH$_3$, CH$_2$''CH$_3$’’), 3.56 (2H, dq, $J = 15.1$, 7.2 Hz, CH$_2$CH$_3$, CH$_2$''CH$_3$’’), 2.80 and 2.11 (4H, AA’BB’, H3’, H4’’), 1.22 (6H, t, $J = 7.1$ Hz, CH$_2$CH$_3$, 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$_2$CH$_3$, CH$_2$''CH$_3$’’), 28.9 (C3’,C4’’). IR (KBr) $\nu_{\text{max}}$ 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$_2$O$_3$, 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 167-170 °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’’), 1.98 (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) $\nu_{\text{max}}$ 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$_{22}$H$_{22}$N$_2$O$_3$, 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, \(\text{CH}_2\text{CH}_3\)), 2.89 (2H, m, \(\text{CH}_2\text{CH}_3\)), 2.89 (2H, m, \(\text{CH}_2\text{CH}_3\)), 2.79 (1H, dq, \(J = 15.5, 7.5\) Hz, \(\text{CH}_2\text{CH}_3\)), 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, \(\text{CH}_2\text{CH}_3\)), 0.88 (3H, t, \(\text{CH}_2\text{CH}_3\)); 13C NMR (CDCl3, 100 MHz) \(\delta 201.7\) (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 (\(\text{CH}_2\text{CH}_3\)), 35.9 (\(\text{CH}_2\text{CH}_3\)), 22.2 (Me’); IR (KBr) \(\nu_{\max} 3372, 2970, 2918, 2850, 1715, 1674, 1619, 1490, 1481, 1326\) 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 (CDCl3, 400 MHz) \(\delta 7.98\) (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, Me’9), 1.62 (3H, s, Me’8); 13C NMR (CDCl3, 100 MHz) \(\delta 187.6\) (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) \(\nu_{\max} 3382, 2920, 2851, 1690, 1615, 1482, 1371, 1323, 1295\) cm\(^{-1}\). EIMS \(m/z\) 177 [M+\(^+] (8), 176 (80), 150 (15), 146 (11), 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 (CDCl3, 400 MHz) \(\delta 7.61\) (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, Me’8); 13C NMR (CDCl3, 100 MHz) \(\delta 187.6\) (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 (KBr) \(\nu_{\max} 3372, 2920, 2851, 1690, 1615, 1482, 1371, 1323, 1295\) 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 ºC (EtOAc/hexanes). \(^1\)H NMR (CDCl3, 400 MHz) \(\delta 8.24\) (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, CO2Me), 1.56 (3H, d, \(J = 7.1\) Hz, C2-Me); 13C NMR (CDCl3, 100 MHz) \(\delta 199.3\) (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 (CO2Me), 16.9 (C2-Me); IR (KBr) \(\nu_{\max} 3412, 3004, 2986, 2956, 2940, 1716, 1607, 1472, 1434, 1377, 1324, 1299, 1270\) 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) $\delta$ 7.63 (1H, dm, $J = 7.7$ Hz, H4), 7.50-7.40 (5H, overlapped, H10, H14, H11, H13, H6), 7.31 (1H, tt, $J = 1.7$, 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) $\delta$ 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) $\nu_{\text{max}}$ 3411, 3387, 1704, 1612, 1594, 1498, 1481, 1467, 1362 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) $\delta$ 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) $\delta$ 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) $\nu_{\text{max}}$ 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’-dialkylnindigos 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.
(2E,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 (CHCl₃). Although 27a is known,²⁻ it is spectroscopically not yet fully characterized. Thus, NMR data follow: ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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).

(2E,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 (CHCl₃). Although 27d is known,²⁻ it is spectroscopically not yet fully characterized. Thus, NMR data follow: ¹H NMR (CDCl₃, 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, 2CH₂), 1.35 (6H, t, J = 7.2 Hz, 2CH₃); ¹³C NMR (CDCl₃, 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 (2CH₂), 12.1 (2CH₃).

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 program included in the WINGX v1.6 package. 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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