Synthesis of Spiro[2*H*-indole-2,1'-1*H*-isoindole]-3,3'-diones, Spiro[1*H*-isobenzofuran-1,2'-2*H*-indole]-3,3'-diones and Spiro[benzofuran-2,1'-isobenzofuran]-3,3'-diones *via* Transannular Reactions of Eight Membered Ring Intermediates

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An auto oxidation-rearrangement product **4** was isolated from a high dilution reaction of ninhydrin with 3,4,5-trimethoxyaniline in water. A general synthesis of this compound and its derivatives **4-6** was devised by oxidation of tetrahydroindeno[1,2-*b*]indol-10-ones **1-3** with sodium periodate to give isoindolo[2,1-*a*]-indole-6,11-diones **4-6** in good yield. Compounds **4-6** can be easily transformed into spiro[1*H*-isobenzofuran-1,2'-2*H*-indole]-3,3'-diones **8-10**, spiro[2*H*-indole-2,1'-1*H*-isoindole]-3,3'-diones **11-13** and isoindole[1,2-*a*:2',1'-*b*]pyrimidine-5,15-diones **15, 16** in high yields. Analogous reactions were performed on 3-amino-5a,10a-dihydroxybenzo[*b*]indeno[2,1-*d*]furan-10-one (**17**) to give a dibenzoxocintrione **18**, spiro-[benzofuran-2,1'-isobenzofuran]-3,3'-dione **19** and an isoindol-1-one **20**.

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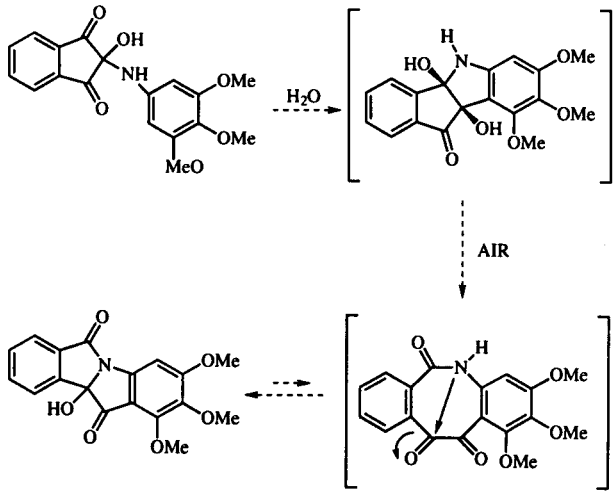
In a previous article [1] we reported the reaction of ninhydrin with various aromatic amines to form tetrahydroindeno[1,2-*b*]indol-10-ones **1-3**. In that article we stated that the reaction of 3,4,5-trimethoxyaniline with ninhydrin in water precipitated only 2-phenylamino-2-hydroxy-1,3-indanedione, even after stirring for several days [2]. In examining this reaction further we have found that an interesting oxidation-rearrangement product precipitates when this reaction is carried out in high dilution. This precipitate has been identified by nmr, ^{13}C nmr, HETCOR and NOESY experiments in deuterated dimethyl sulfoxide or deuterated pyridine, as 10b-hydroxy-1,2,3-trimethoxyisoindolo[2,1-*a*]indole-6,11-dione (**4**).

Isoindolo[2,1-*a*]indole-6,11-diones were first described by Hooper and Imam in 1985 [3]. Our compound differs from those of Hooper and Imam by the hydroxy group at the 10b position which appears to be unprecedented in the literature. In this communication we will show how this carbinolamine has a prominent effect on the reactivity of this ring system facilitated by the tautomeric structure which forms a reactive dibenzazocinetrione intermediate.

Attempts to improve the low and erratic yields of the auto oxidation-rearrangement reaction by introducing air or varying the dilution ratio did not prove fruitful. To circumvent these uncertainties a general synthesis of 10b-hydroxyisoindolo[2,1-*a*]indole-6,11-diones **4-6** was desired. One possible mechanism of this auto oxidation-rearrangement reaction proceeds through an indeno-indolone intermediate, which then undergoes auto-oxidation of the *cis* diol to form a dibenzazocinetrione. The amide nitrogen of this azocine can then transannularly add to the carbonyl, forming a hydroxyisoindolo[2,1-*a*]-indole-6,11-dione (Scheme 1).

Transannular addition of amide nitrogens with ketones of medium sized rings has been reported in the literature

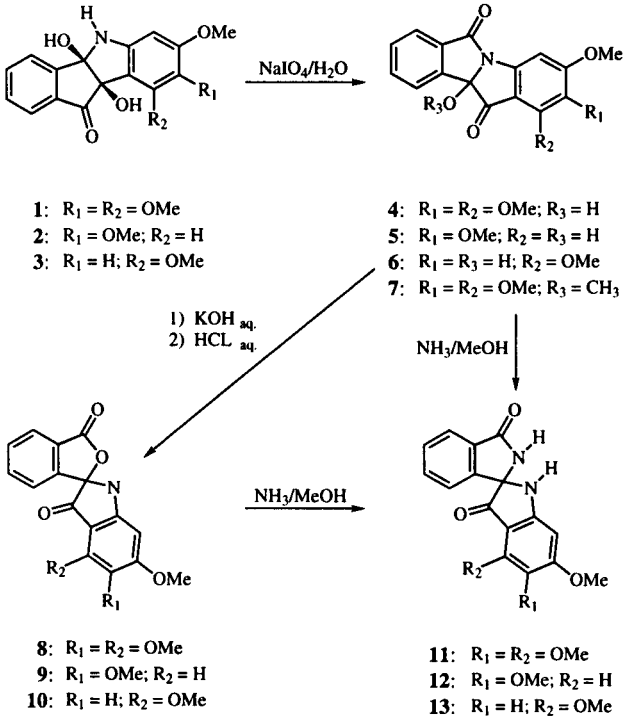
Scheme 1



by other workers [4,5,6,7,8]. Based on their findings, a general synthesis of these compounds was developed by oxidation of the proposed intermediate dihydroxyindeno[1,2-*b*]indolones **1-3** with sodium periodate in water to give hydroxyisoindolo[2,1-*a*]indole-6,11-diones **4-6** in excellent yields (Scheme 2).

In our initial structural investigation of compound **4**, we found that when **4** was treated with sodium hydride and quenched with methyl iodide, methylation occurs on the alcohol group to give the methoxy product **7**. Attempted exchange of the hydroxy group of hydroxyisoindoloindoldiones **4-6** with ammonia in methanol resulted in a rearrangement to give spiro[2*H*-indole-2,1'-1*H*-isoindole]-3,3'-diones **11-13**. When shorter reaction times are used, spiro[1*H*-isobenzofuran-1,2'-2*H*-indole]-3,3'-diones **8-10** may be observed in addition to the spiro[2*H*-indole-2,1'-1*H*-isoindole]-3,3'-dione products **11-13**.

Scheme 2



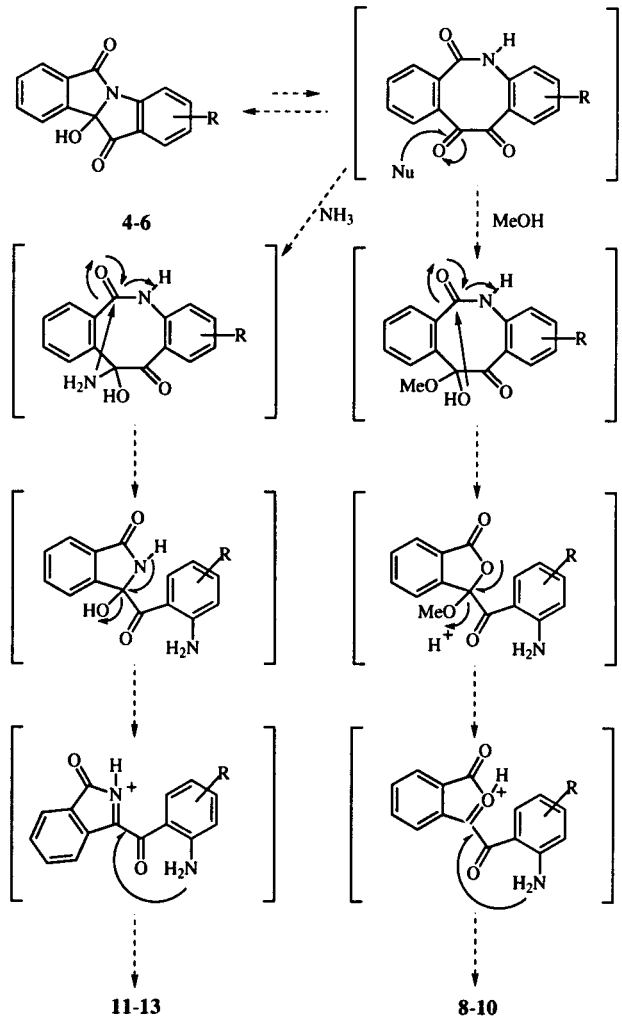
The spiro intermediate **10** was reported by Black *et al.* in which they synthesized **10** directly from the corresponding tetrahydroindeno[1,2-*b*]indol-10-one **3** in one step [9]. Our intermediate **10** has consistent physical and spectral data to that reported by Black *et al.* and therefore analogs **8** and **9** are assigned structures based on the similarity of their spectra to **10**.

It is not clear whether compounds **8-10** are intermediates to compounds **11-13** or simply reversible side products. This reaction to form **8-10** can be explained by a competing addition reaction of methanol under basic conditions. To explore this side reaction, **4** was stirred at room temperature in methanol saturated with dimethylamine to yield the spiro product **8** as the major product. This reaction can also be carried out with a catalytic amount of sodium methoxide as the base or preferably by treating **4-6** with aqueous hydroxide which upon acidification precipitates product **8-10** in good yield. We observed no reaction when compound **4** was refluxed in methanol or methanol containing a catalytic amount of tosic acid. We also observed no reaction when ammonium chloride was used in place of ammonia for the reaction of **4** in methanol. Based on these observations, we have shown that formation of these spiro products is base catalyzed.

Numerous mechanisms can be envisioned for these transformations to form spiro products **8-13**. Ring opening of the lactam *via* nucleophilic attack followed by cyclization to the spiro product is one possibility. Previous reports by Cohen and Witkop suggest that base can reverse the transannular carbinol formation in medium sized rings which can subsequently re-close in a different fashion to form new rings [4]. On the basis of these published data, a base catalyzed mechanism which opens the two five membered rings to a dibenzazocinetrione is proposed. The newly formed carbonyl of the dibenzazocinetrione intermediate can either form a hemi-ketal with methanol or react with ammonia to form the amino alcohol. The resulting amine (or alcohol) can then transannularly close onto the amide carbonyl which eliminates the aromatic amine breaking the amide bond. A second ring closure forming the spiro product is then achieved after protonation of the resulting alcohol and dehydration to form the protonated imine, which is then susceptible to amine addition (Scheme 3).

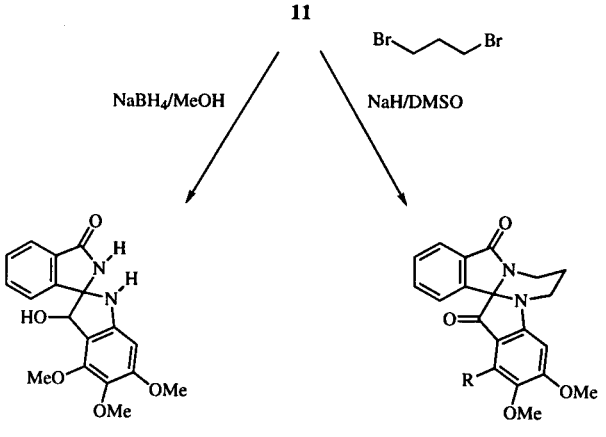
Scheme 3

Proposed Mechanism of Spiro Products Formation



Examination of the literature shows only one reference to spiro[2*H*-indole-2,1'-1*H*-isoindole]-3,3'-diones. In an article by Cheung *et al.* [10] a spiro[2*H*-indole-2,1'-1*H*-isoindole]-3,3'-dione was prepared by a temperature dependent reaction of aniline with benzylidene(methyl)-dioxodibenzoazocine. This reaction gives a similar product to ours but with both the amide and aniline nitrogens substituted. Our synthesis represents the first example of unsubstituted nitrogen analogs of this spiro ring system.

Scheme 4



14

15: R = OMe
16: R = H

To help confirm the structure of the spiro product we reduced **11** with sodium borohydride to give the corresponding alcohol **14** as a single diastereomer. To examine the special relationship of the two nitrogens we alkylated **11** and **12** with 1,3-dibromopropane. This resulted in the formation of a six membered ring to give 9*H*-7,8-dihydro-12,13,14-trimethoxyindoloisoindolo[1,2-*a*:2',1'-*b*]pyrimidine-5,15-dione (**15**) and 9*H*-7,8-dihydro-12,13-dimethoxyindoloisoindolo[1,2-*a*:2',1'-*b*]pyrimidine-5,15-dione (**16**) respectively. This represents the first report of the indoloisoindolo[1,2-*a*:2',1'-*b*]pyrimidine ring system in the literature. We have confirmed the structure of **16** by obtaining a single crystal X-ray of this product (Figure 1).

Further exploration of the mechanism and scope of these rearrangement reactions was done by treating 3-amino-5a,10a-dihydroxybenzo[*b*]indeno[2,1-*d*]-furan-10-one (**17**) with sodium periodate in water (Scheme 5). This reaction also oxidizes the *cis* diol in high yield, but without the amide nitrogen to transannularly close to a tetracyclic product, a dibenzoxocin **18** is isolated. Since we had proposed a similar eight membered ring in the mechanism of the nitrogen analogs (Scheme 3), we speculated that similar chemistry could be performed on **18**. When the dibenzoxocin **18** is treated with aqueous

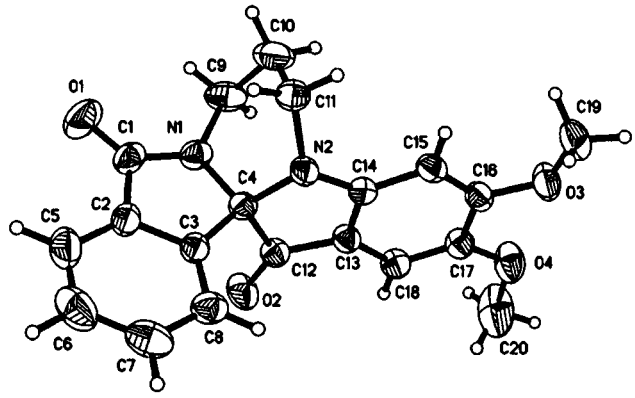
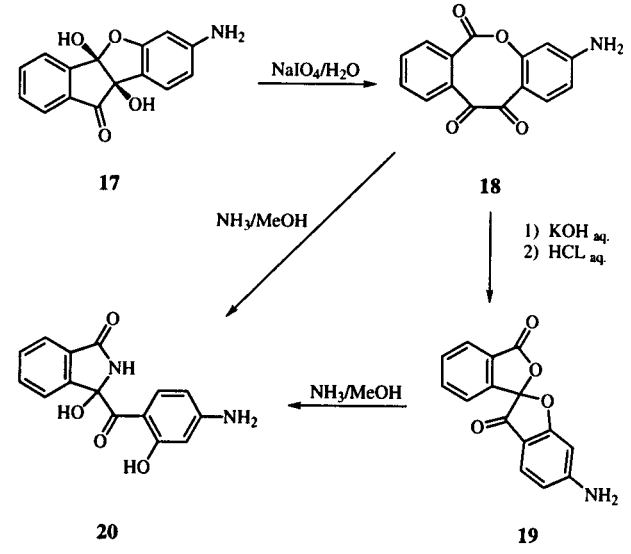


Figure 1. ORTEP drawing of 9*H*-7,8-dihydro-12,13-dimethoxyindoloisoindolo[1,2-*a*:2',1'-*b*]pyrimidine-5,15-dione (**16**).

base, a rearrangement similar to the one observed for isoindolo[2,1-*a*]indole-6,11-diones occurs to give spiro[6-aminobenzofuran-2(3*H*),1'(3'*H*)-isobenzofuran]-3,3'-dione (**19**). The first synthesis of this ring system was in 1992 by Letcher *et al.* in which the unsubstituted analog was prepared using an alternate synthetic scheme [11]. When **18** or **19** is treated with alcoholic ammonia an isoindole product **20** is formed. This product was dissolved in aqueous base and acidified in order to treat it in the same fashion as used in forming the spiro precursor **18**. Only compound **20** was recovered from this procedure showing that the equilibrium of this product lies toward the open hydrated form instead of closing to the spiro product. Product **20** was identified by nmr, cmr and two-dimensional cHSQC, nHSQC, cHMBC experiments.

Scheme 5



20

19

Table 1

Crystal and Refinement Data for **16**

formula	$C_{20}H_{18}N_2O_4$
dimensions	0.52 x 0.55 x 0.83 mm
crystal system	monoclinic
space group	$P2_1/c$-C^5_{2h} (No. 14)
a, Å	7.253 (2)
b, Å	15.363 (5)
c, Å	15.672
α	90.00°
β	6.36 (2)°
γ	90.00°
V, Å^3	1736 (1)
Z	4
F(000)	736.0
calcd density	1.341
total reflections	4133
independent data	2765
parameters refined	242
GoF	1.61
R1	0.046
R2	0.064
μ abs coef	0.09

Table 2

Atomic Coordinates (x 10^4) and Equivalent Isotropic Thermal Parameters (Å x 10) for **16**

	x	y	z	B
O_1	4687 (3)	-2106 (1)	2090 (1)	54 (1)
O_2	6112 (2)	586 (1)	764 (1)	38 (1)
O_3	-1409 (2)	2905 (1)	451 (1)	38 (1)
O_4	1025 (2)	3082 (1)	-567 (1)	44 (1)
N_1	3688 (2)	-774 (1)	1564 (1)	29 (1)
N_2	2184 (2)	552 (1)	1936 (1)	25 (1)
C_1	4738 (3)	-1313 (1)	2108 (2)	33 (1)
C_2	5887 (3)	-744 (1)	2718 (1)	29 (1)
C_3	5397 (2)	114 (1)	2547 (1)	25 (1)
C_4	3951 (2)	143 (1)	1777 (1)	24 (1)
C_5	7185 (3)	-969 (2)	3398 (2)	43 (1)
C_6	7975 (3)	-312 (2)	3901 (2)	48 (1)
C_7	7497 (3)	552 (2)	3737 (2)	44 (1)
C_8	6207 (3)	781 (1)	3048 (1)	33 (1)
C_9	1998 (3)	-1033 (2)	1029 (1)	39 (1)
C_{10}	276 (3)	-722 (2)	1420 (2)	46 (1)
C_{11}	760 (3)	-68 (1)	2138 (1)	34 (1)
C_{12}	4604 (2)	681 (1)	1021 (1)	26 (1)
C_{13}	3132 (2)	1293 (1)	768 (1)	26 (1)
C_{14}	1749 (2)	1183 (1)	1304 (1)	24 (1)
C_{15}	157 (2)	1704 (1)	1219 (1)	27 (1)
C_{16}	18 (2)	2332 (1)	591 (1)	27 (1)
C_{17}	1409 (3)	2441 (1)	22 (1)	29 (1)
C_{18}	2960 (3)	1924 (1)	115 (1)	29 (1)
C_{19}	-2716 (3)	2922 (2)	1072 (2)	47 (1)
C_{20}	2439 (5)	3301 (2)	-1087 (2)	71 (1)

Table 3

Bond Angles for Compound **16**

$C_{16}O_3C_{19}$	117.0 (2)	$C_4N_2C_{11}$	114.0 (1)
$C_1N_1C_4$	113.3 (2)	$C_4N_2C_{14}$	108.0 (1)
$C_1N_1C_9$	124.7 (2)	$C_{11}N_2C_{14}$	119.7 (1)
$C_4N_1C_9$	118.4 (2)	$C_4C_{12}C_{13}$	106.1 (1)
$N_1C_1C_2$	106.2 (2)	$C_{12}C_{13}C_{14}$	108.4 (2)
$C_1C_2C_3$	108.9 (2)	$N_2C_{14}C_{13}$	113.1 (2)
$C_2C_3C_4$	108.9 (2)	$N_2C_4C_{12}$	104.2 (1)
$N_1C_4C_3$	102.5 (1)	$C_3C_4C_{12}$	112.3 (1)
$N_1C_4N_2$	110.9 (1)	$N_1C_4C_{12}$	112.5 (1)
$N_2C_4C_3$	114.7 (1)	$C_{12}C_{13}C_{18}$	130.7 (2)
$C_1C_2C_5$	129.4 (2)	$N_2C_{14}C_{15}$	125.8 (2)
$C_4C_3C_8$	130.3 (2)	$O_2C_{12}C_4$	123.2 (2)
$O_1C_1N_1$	125.5 (2)	$O_2C_{12}C_{13}$	130.7 (2)
$O_1C_1C_2$	128.2 (2)	$C_{14}C_{13}C_{18}$	120.9 (2)
$C_3C_2C_5$	121.6 (2)	$C_{13}C_{14}C_{15}$	121.1 (2)
$C_2C_3C_8$	120.8 (2)	$C_{14}C_{15}C_{16}$	117.7 (2)
$C_2C_5C_6$	117.8 (2)	$O_3C_{16}C_{15}$	124.4 (2)
$C_5C_6C_7$	121.2 (2)	$O_3C_{16}C_{17}$	113.7 (2)
$C_6C_7C_8$	121.1 (2)	$C_{15}C_{16}C_{17}$	122.0 (2)
$C_3C_8C_7$	117.4 (2)	$O_4C_{17}C_{16}$	113.8 (2)
$N_1C_9C_{10}$	110.8 (2)	$O_4C_{17}C_{18}$	126.7 (2)
$C_9C_{10}C_{11}$	111.8 (2)	$C_{16}C_{17}C_{18}$	119.5 (2)
$N_2C_{11}C_{10}$	112.3 (2)	$C_{13}C_{18}C_{17}$	118.9 (2)
$C_{17}O_4C_{20}$	117.1 (2)		

Table 4

Bond Lengths for Compound **16**

O_1-C_1	1.219 (3)	C_3-C_8	1.382 (3)
O_2-C_{12}	1.216 (2)	C_5-C_6	1.366 (4)
O_3-C_{16}	1.358 (2)	C_6-C_7	1.389 (4)
O_4-C_{17}	1.357 (3)	C_7-C_8	1.393 (3)
O_3-C_{19}	1.432 (3)	C_3-C_4	1.509 (2)
O_4-C_{20}	1.419 (4)	C_9-C_{10}	1.528 (3)
N_1-C_1	1.361 (3)	C_{12}-C_{13}	1.444 (3)
N_2-C_{14}	1.396 (2)	C_{13}-C_{14}	1.389 (3)
N_1-C_4	1.455 (2)	C_{13}-C_{18}	1.405 (3)
N_2-C_4	1.473 (2)	C_{14}-C_{15}	1.399 (2)
N_1-C_9	1.461 (3)	C_{15}-C_{16}	1.374 (3)
N_2-C_{11}	1.465 (3)	C_{16}-C_{17}	1.429 (3)
C_1-C_2	1.482 (3)	C_{17}-C_{18}	1.372 (3)
C_2-C_3	1.383 (3)	C_4-C_{12}	1.561 (3)
C_2-C_5	1.385 (3)	C_{10}-C_{11}	1.519 (3)

In summary, we have identified a new reaction product from the reaction of ninhydrin and an aromatic amine. Employing the use of sodium periodate results in a high yielding synthesis of this product and its analogs. This enabled us to synthesize several different and novel heterocycles through proposed transannular reactions of eight membered ring intermediates. Structural assignments were made by 2 dimensional nmr experiments on key products and a single crystal X-ray of the end product.

EXPERIMENTAL [12]

5,5a,10,10a-Tetrahydro-5a,10a-dihydroxy-2,3-dimethoxyindeno[1,2-*b*]indol-10-one (**2**).

Compound **2** was prepared by literature procedures using 1% acetic acid in water (81% yield) [1]. It was recrystallized from ethyl acetate to give an analytical sample, mp 119-123°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.90 (d, J = 7.7 Hz, 1H), 7.84-7.81 (m, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.53-7.50 (m, 1H), 7.04 (s, 1H), 6.81 (s, 1H), 6.12 (s, 1H), 6.06 (s, 1H), 6.00 (s, 1H), 3.64 (s, 3H), 3.62 (s, 3H); ^{13}C nmr (dimethyl sulfoxide-d_6): 202.5 (C=O, ketone), 154.3, 153.7, 144.4, 143.5, 137.6, 135.7, 131.1, 126.7, 124.1, 116.6, 111.8, 95.7, 94.3, 85.7, 58.2, 57.1.

Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.79; H, 5.53; N, 4.44.

General Method for Compounds **4-6**.

A suspension of appropriately substituted 5,5a,10,10a-tetrahydro-5a,10a-dihydroxyindeno[1,2-*b*]indol-10-one **1-3** and 2 equivalents of sodium *meta*-periodate were stirred in water (100 ml/g of iodate) for 2 hours. The resulting solid was isolated by filtration, washed with water and dried.

Rearrangement of 2-(Amino-*N*-3,4,5-trimethoxybenzene)-2-hydroxy-1,3-indanedione. Formation of 10b-Hydroxy-1,2,3-trimethoxyisoindolo[2,1-*a*]indole-6,11-dione (**4**).

A suspension of 2-phenylamino-2-hydroxy-1,3-indanedione (1.5 g, 44 mmoles) in water (150 ml) was stirred in an Erlenmeyer flask open to the atmosphere for 16 hours. The precipitate was filtered, washed with distilled water and dried to give 0.3 g (20%) of **4**.

Reaction of Ninhydrin and Trimethoxyaniline to form 10b-Hydroxy-1,2,3-trimethoxyisoindolo[2,1-*a*]indole-6,11-dione (**4**).

Ninhydrin (1.00 g, 5.6 mmoles) and 4,5,6-trimethoxyaniline (1.03 g, 5.6 mmoles) were stirred with water (900 ml) in an Erlenmeyer flask open to the atmosphere for 16 hours. The resulting solid was filtered, washed with distilled water and dried to give 0.2 g (10%) of **4**.

10b-Hydroxy-1,2,3-trimethoxyisoindolo[2,1-*a*]indole-6,11-dione (**4**).

The general method gave compound **4** in an 89% yield. A small sample was recrystallized from ethyl acetate to give an analytical sample of colorless needles, mp 249-250°, MW 341.32; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.95 (s, OH), 7.88-7.70 (m, 4H), 7.17 (s, 1H), 4.01 (s, 3H), 3.97 (s, 3H), 3.70 (s, 3H); ^{1}H nmr (perdeuteriopyridine): δ 10.48 (br s, OH), 8.30 (d, J = 7.6 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.72-7.67 (m, 1H), 7.56-7.51 (m, 1H), 7.47 (s, 1H), 4.12 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H); ^{13}C nmr (perdeuteriopyridine): 191.3 (C=O, ketone), 169.6 (C=O, amide), 162.4, 153.1, 149.7, 145.0, 139.0, 134.8, 132.6, 131.1, 125.1, 124.9, 112.9, 97.6, 92.8, 62.0, 61.4, 56.6; ^{13}C nmr (dimethyl sulfoxide-d_6) 191.6 (C=O, ketone), 170.3 (C=O, amide), 163.3, 153.7, 150.2, 145.0, 139.7, 136.4, 132.8, 132.7, 126.1, 126.0, 113.1, 98.5, 93.1, 63.4, 62.7, 58.5.

Anal. Calcd. for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.43; N, 4.10. Found: C, 63.26; H, 4.52; N, 4.08.

10b-Hydroxy-2,3-dimethoxyisoindolo[2,1-*a*]indole-6,11-dione (**5**).

The general method gave compound **5** in a 91% yield, mp 235-237°, MW 311.30; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.94 (s, 1H), 7.88-7.67 (m, 4H), 7.34 (s, 1H), 7.22 (s, 1H), 4.00 (s, 3H), 3.81 (s, 3H); ^{13}C nmr (dimethyl sulfoxide-d_6): 193.9 (C=O, ketone), 170.6 (C=O, amide), 159.1, 149.5, 149.2, 144.9, 136.5, 132.9, 132.8, 126.1, 126.0, 119.6, 107.4, 102.7, 93.3, 58.2, 57.7.

Anal. Calcd. for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.19; H, 4.40; N, 4.35.

10b-Hydroxy-1,3-dimethoxyisoindolo[2,1-*a*]indole-6,11-dione (**6**).

The general method gave compound **6** in a 88% yield, mp 248-250°, MW 311.30; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.85-7.78 (m, 4H), 7.70-7.65 (m, 1H), 6.87 (d, J = 1.9 Hz, 1H), 6.45 (d, J = 1.9 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H); ^{13}C nmr (dimethyl sulfoxide-d_6): 190.7 (C=O, ketone), 170.6, 170.4, 161.8, 155.1, 145.3, 136.5, 132.8, 132.7, 126.1, 126.0, 109.7, 97.2, 96.9, 93.2, 58.1, 57.8.

Anal. Calcd. for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.29; H, 4.11; N, 4.55.

1,2,3,10b-Tetramethoxyisoindolo[2,1-*a*]indole-6,11-dione (**7**).

Sodium hydride (0.2 g) was washed with hexane three times and then treated with **4** (0.5 g) in tetrahydrofuran (100 ml). Iodomethane was added and the resulting mixture was stirred for 5 hours. After quenching with water, the solution was extracted into ethyl acetate and washed with water three times. The organic layer was dried over sodium sulfate and evaporated *in vacuo* to give a solid. Recrystallized from ethyl acetate to give light yellow crystals (51% yield), mp 125-127°, MW 355.35; ^{1}H nmr (deuteriochloroform): δ 7.94-7.61 (m, 4H), 7.21 (s, 1H), 4.12 (s, 3H), 4.06 (s, 3H), 3.81 (s, 3H), 3.21 (s, 3H); ^{13}C nmr (deuteriochloroform): 188.6 (C=O, ketone), 169.5 (C=O, amide), 162.0, 152.6, 149.4, 140.2, 138.4, 134.6, 132.2, 131.3, 124.8, 124.6, 111.8, 96.7, 94.8, 62.0, 61.4, 56.8, 52.1.

Anal. Calcd. for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 64.17; H, 4.77; N, 3.89.

General Method for Compounds **8-10**.

The appropriately substituted 10b-hydroxyisoindolo[2,1-*a*]-indole-6,11-dione **2** was stirred in 1*N* potassium hydroxide until a solution forms. This solution was acidified with 1*N* hydrochloric acid to precipitate a solid which was filtered, washed with water and dried.

Spiro[1*H*-isobenzofuran-1,2'-2*H*-4,5,6-trimethoxyindole]-3,3'-dione (**8**).

The general method gave a 93% yield of yellow crystals, mp 176-177°, MW 341.32; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.36 (s, NH), 7.95 (d, J = 7.5 Hz, 1H), 7.81-7.72 (m, 2H), 7.54 (d, J = 7.5 Hz, 1H), 6.30, (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.65 (s, 3H); ^{13}C nmr (dimethyl sulfoxide-d_6): 190.6 (C=O, ketone), 169.9 (C=O, lactone), 165.6, 161.2, 153.6, 145.8, 136.9, 135.5, 132.9, 128.6, 126.8, 124.4, 103.8, 96.9, 91.9, 63.0, 62.8, 58.4.

Anal. Calcd. for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.43; N, 4.10. Found: C, 63.36; H, 4.39; N, 4.03.

Spiro[1*H*-isobenzofuran-1,2'-2*H*-5,6-dimethoxyindole]-3,3'-dione (**9**).

The general method gave an 89% yield of yellow crystals, mp 228-230°, MW 311.30; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.16 (s, NH), 7.97 (d, J = 7.3 Hz, 1H), 7.80-7.73 (m, 2H), 7.49 (d, J = 7.5 Hz, 1H), 7.01 (s, 1H), 6.59 (s, 1H), 3.93 (s, 3H), 3.75 (s, 3H); ^{13}C nmr (dimethyl sulfoxide-d_6): 193.2 (C=O, ketone), 170.0 (C=O, lactone), 161.5, 161.2, 146.0, 136.9, 132.8, 128.6, 126.9, 124.1, 109.5, 107.1, 97.1, 96.8, 58.1, 57.6.

Anal. Calcd. for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.65; H, 4.14; N, 4.44.

Spiro[1*H*-isobenzofuran-1,2'-2*H*-5,7-dimethoxyindole]-3,3'-dione (**10**).

The general method gave a 96% yield of yellow crystals, mp 233-235°, MW 311.30; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.46 (s, NH), 7.94 (d, J = 7.5 Hz, 1H), 7.80-7.70 (m, 2H), 7.51 (d, J = 7.5, 1H) 6.06 (d, J = 1.7 Hz, 1H), 6.00 (d, J = 1.8 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H); ^{13}C nmr (dimethyl sulfoxide-d_6): 189.4 (C=O, ketone), 172.4, 169.9 (C=O, lactone), 165.3, 162.1, 146.0, 136.9, 132.8, 128.6, 126.7, 124.3, 101.7, 96.8, 92.5, 90.1, 57.9, 57.5.

Anal. Calcd. for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.50. Found: C, 65.34; H, 4.13; N, 4.50.

General Method for Compounds **11-13**.

A suspension of the appropriately substituted 10b-hydroxyisoindolo[2,1-*a*]indole-6,11-dione **4-6** in methanol was cooled to 5° and ammonia gas bubbled through the solution until saturated and allowed to stir at room temperature for 16 hours. The solvent was removed by evaporation to give compounds **11-13** as a solid.

Spiro[2*H*-4,5,6-trimethoxyindole-2,1'-1*H*-isoindole]-3,3'-dione (**11**).

The general method gave a 97% yield of yellow crystals, mp 284-286°, MW 340.34; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.88 (s, NH, amide), 7.85 (s, NH, amine), 7.71-7.69 (m, 1H), 7.57-7.54 (m, 2H), 7.27-7.24 (m, 1H), 6.21 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.64 (s, 3H); ^{13}C nmr (dimethyl sulfoxide-d_6): 192.1 (C=O, ketone), 169.4 (C=O, amide), 163.2, 159.8, 151.4, 144.1, 133.1, 132.4 (2C), 129.5, 123.0, 121.2, 103.3, 89.5, 80.1, 61.2, 61.1, 56.3.

Anal. Calcd. for $C_{18}H_{16}N_2O_5$: C, 63.53; H, 4.74; N, 8.23. Found: C, 63.31; H, 4.65; N, 7.93.

Spiro[2*H*-5,6-dimethoxyindole-2,1'-1*H*-isoindole]-3,3'-dione (**12**).

The general method gave a 95% yield of yellow-green crystals, mp 298 dec, MW 310.31; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.93 (s, NH), 7.73-7.70 (m, 1H), 7.66 (s, NH), 7.57-7.54 (m, 2H), 7.21-7.18 (m, 1H), 6.96 (s, 1H), 6.51 (s, 1H), 3.91 (s, 3H), 3.74 (s, 3H); ^{13}C nmr (dimethyl sulfoxide-d_6): 196.2 (C=O, ketone) 171.2 (C=O, amide), 161.2, 161.0, 145.9, 145.3, 134.2, 134.1, 131.2, 124.7, 122.8, 110.7, 106.7, 96.6, 81.8, 57.9, 57.6.

Anal. Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.46; H, 4.44; N, 8.97.

Spiro[2*H*-5,7-dimethoxyindole-2,1'-1*H*-isoindole]-3,3'-dione (**13**).

The general method gave a 95% yield of a light yellow solid, MW 310.31, mp 282-284° dec; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.88 (s, NH), 7.94 (s, NH), 7.70-7.67 (m, 1H), 7.57-7.53 (m, 2H), 7.23-7.20 (m, 1H), 5.98 (d, J = 1.7 Hz, 1H), 5.89 (d, J = 1.7 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H); ^{13}C nmr (dimethyl sulfoxide-d_6): 192.5 (C=O, ketone), 171.6, 171.1, 165.6, 161.6, 145.9, 134.1, 134.1, 131.2, 124.6, 123.0, 102.8, 91.4, 89.1, 81.6, 57.6, 57.2.

Anal. Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.66; H, 4.55; N, 8.78.

Spiro[2*H*-3-hydroxy-4,5,6-trimethoxyindole-2,1'-1*H*-isoindole]-3'-one (**14**).

Compound **11** (0.5 g) was dissolved in methanol (60 ml), sodium borohydride was added and allowed to stir for 1 hour, then evaporated *in vacuo* to give a solid. The product was extracted into ethyl acetate and washed with water three times. Evaporation of the solvent *in vacuo* gave an off-white solid in 82% yield, mp 227-229°, MW 342.36; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 9.00 (s, NH), 7.62-7.47 (m, 4H), 6.41 (s, NH), 5.98 (s, 1H), 5.55 (d, J = 7.5 Hz, OH), 4.93 (d, J = 7.4 Hz, 1H), 3.90 (s, 3H), 3.72 (s, 3H), 3.60 (s, 3H); ^{13}C nmr (dimethyl sulfoxide-d_6): 169.84 (C=O, amide), 156.6, 152.8, 149.3, 146.6, 134.6, 134.1, 132.8, 130.6, 128.1, 123.8, 112.0, 90.5, 86.3, 79.6, 62.2, 61.1, 57.5.

Anal. Calcd. for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 62.85; H, 5.57; N, 8.02.

9*H*-7,8-Dihydro-12,13,14-trimethoxyindoloisoindolo-[1,2-*a*:2',1'-*b*]pyrimidine-5,15-dione (**15**).

Sodium hydride (0.15 g) was washed with hexane three times and then treated with **11** (0.5 g) in dimethyl sulfoxide (5 ml) at 5°. Dibromopropane (0.16 ml) was added and the resulting solution was stirred at 25° for 1 hour. The solution was then poured into water (100 ml) and the resulting solid was removed by filtration and washed with water. This solid was dried under vacuum to yield 0.33 g (59% yield) of a yellow solid **15**, mp 212-213°, MW 380.4; ^{1}H nmr (benzene-d_6): δ 7.93-7.90 (m, 1H), 7.06-6.98 (m, 3H), 5.71 (s, 1H), 4.28-4.18 (m, 1H), 4.02 (s, 3H), 3.71 (s, 3H), 3.23 (s, 3H), 2.82-2.75 (m, 1H), 2.47-2.40 (m, 1H), 2.30-2.25 (m, 1H), 1.32-1.0 (2m, 2H).

Anal. Calcd. for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.14; H, 5.27; N, 7.28.

9*H*-7,8-Dihydro-12,13-dimethoxyindoloisoindolo[1,2-*a*:2',1'-*b*]-pyrimidine-5,15-dione (**16**).

Sodium hydride (0.3 g) was washed with hexane three times and then treated with **12** (1.0 g) in dimethyl sulfoxide (10 ml) at 5°. Dibromopropane (0.35 ml) was added and the resulting solution was stirred at 25° for 1 hour. The solution was then poured into water (200 ml) and the resulting solid was removed by filtration and washed with water. This solid was dried under vacuum to yield 1.03 g (94% yield) of a yellow-green solid **16**. Compound **16** was recrystallized from acetonitrile to obtain yellow-green crystals suitable for X-ray crystallography, mp 301-302°, MW 350.38; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.92-7.90 (m, 1H), 7.57-7.50 (m, 2H), 7.23-7.21 (m, 1H), 7.13 (s, 1H), 6.58 (s, 1H), 4.4-4.30 (m, 1H), 4.04 (s, 3H), 3.90 (s, 3H), 3.63-3.57 (m, 1H), 2.92-2.79 (m, 2H), 1.90-1.85 (m, 2H); ^{13}C nmr (dimethyl sulfoxide-d_6): 197.0 (C=O, ketone), 169.8, 163.4, 161.2, 146.9, 144.8, 134.5 (CH), 133.9, 131.8 (CH), 124.9 (CH), 123.9 (CH), 115.5, 106.2 (CH), 99.1 (CH), 85.3, 58.3 (CH), 57.6 (CH), 34.2 (CH_2), 21.7 (CH_2).

Anal. Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.58; H, 5.23; N, 8.02.

2-Amino-1*H*-dibenz[*b*,*f*]oxocin-6,11,12-trione (**18**).

A suspension of 3-amino-5a,10a-dihydroxybenzo[*b*]indeno-[2,1-*d*]furan-10-one **17** and 2 equivalents of sodium *meta*-periodate was stirred in water (100 ml/g of iodate) for 2 hours. The resulting solid was isolated by filtration, washed with water, followed by ethyl acetate and air dried to give a colorless solid **18** (78% yield), mp 226-230° dec, MW 267.24; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.03 (d, J = 7.7 Hz, 1H), 7.97 (dd, J = 7.6, 7.6 Hz, 1H), 7.85 (dd, J = 7.6, 7.6 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.10 (br s, NH_2), 6.65 (dd, J = 8.6, 2.0 Hz, 1H), 6.61 (d, J = 2.0 Hz, 1H); ^{13}C nmr (dimethyl sulfoxide-d_6): 201.2 (C=O, ketone), 190.8 (C=O, ketone), 166.9 (C=O, lactone), 160.0, 157.5, 141.1, 137.9, 134.6, 133.1, 132.6, 129.9, 128.7, 116.1, 114.6, 107.2.

Anal. Calcd. for $C_{15}H_9NO_4$: C, 67.42; H, 3.39; N, 5.24. Found: C, 67.21; H, 3.18; N, 5.17.

Spiro[6-aminobenzofuran-2(3*H*),1'(3'*H*)-isobenzofuran]-3,3'-dione (**19**).

Compound **18** was stirred in 1*N* potassium hydroxide until dissolution was complete. This solution was acidified with 1*N* hydrochloric acid and extracted into ethyl acetate. The organic layer was washed with water three times and dried over sodium sulfate. After evaporation *in vacuo* a solid was recovered. Trituration with ethyl acetate gave compound **19** isolated as off-white crystals (44% yield), mp 269-271°, MW 267.24; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.03 (d, J = 7.0 Hz, 1H), 7.87-7.80 (m, 2H), 7.64 (d, J = 7.4 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.25 (br s, NH_2), 6.50 (dd, J = 8.6, 1.7 Hz, 1H), 6.29 (d, J = 1.7 Hz, 1H); ^{13}C nmr (dimethyl sulfoxide-d_6): 187.6 (C=O, ketone), 174.6, 168.7 (C=O, lactone), 162.2, 144.5, 137.7, 133.9, 128.9, 127.7, 127.3, 124.8, 113.5, 107.2, 106.7, 95.1.

Anal. Calcd. for $C_{15}H_9NO_4$: C, 67.42; H, 3.39; N, 5.24. Found: C, 67.12; H, 3.43; N, 5.40.

2,3-Dihydro-3-hydroxy-3-[1-oxo-1-(4-amino-2-hydroxyphenyl)-methyl]-1*H*-isoindol-1-one (**20**).

A suspension of compound **18** in methanol was cooled to 5° and ammonia gas bubbled through the solution until saturated. This was allowed to stir at room temperature for 2 hours. The solvent was removed by evaporation to give compound **20** as a tan solid. Purification was accomplished by dissolving in ethyl acetate and diluting with dichloromethane (82% yield), mp 145-148° dec, MW 284.27; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 12.73 (s, OH), 9.28 (s, NH), 8.34 (d, J = 9.1 Hz, 1H), 7.66 (dd, J = 7.3, 1.4 Hz, 1H), 7.60 (dd, J = 7.4, 1.1 Hz, 1H), 7.54 (dd, J = 7.4, 1.1 Hz, 1H), 7.53 (dd, J = 7.4, 1.1 Hz, 1H), 7.43, (br s, OH), 6.60 (s, NH_2), 6.17 (dd, J = 9.1, 2.2 Hz, 1H), 5.95 (d, J = 2.2 Hz, 1H); ^{13}C nmr (dimethyl sulfoxide-d_6): 195.2 (C=O, ketone), 168.6 (C=O, amide), 166.5 ,156.7, 146.8, 134.9 (CH), 131.8 (CH), 131.0, 129.3 (CH), 123.6 (CH), 122.5 (CH), 106.3, 106.2 (CH), 97.8 (CH), 90.4.

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.26; N, 9.85. Found: C, 63.15; H, 4.18; N, 9.67

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