The regioselective hydrolysis or hydrolytic oxidation of indolo[3,2-*b*]quinolinium salts: a new synthetic approach to substituted indolo[3,2-*b*]quinolinones

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Abstract

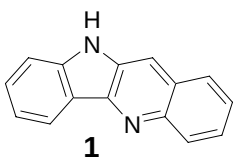
In this article, the regioselective hydrolysis or hydrolytic oxidation of indolo[3,2-*b*]quinolinium salts was examined, which lead to the formation of indolo[3,2-*b*]quinolinone as the major product or the sole product in different conditions. This work provided a new method for the preparation of substituted indolo[3,2-*b*]quinolinones.

Keywords: Indolo[3,2-*b*]quinolinium salt, indolo[3,2-*b*]quinolinone, hydrolysis, hydrolytic oxidation

Introduction

Indolo[3,2-*b*]quinolines **1** and indolo[3,2-*b*]quinolinones **2** are sometimes referred in the literature to as quindolines and quindolinone, respectively. (Figure 1) A number of indolo[3,2-*b*]quinoline and indolo[3,2-*b*]quinolinone alkaloids, such as quindoline **1**,[1,2] quindolinone **2**,[3] cryptolepine **3**,[4] 5-methylquindolinone **4**,[1] biscryptolepine **5**,[5] cryptoquindoline **6**,[1] cryptomisrine **7**[6] etc., had been isolated from a medicinal plant *Cryptolepis Sanguinolenta* in Africa. (Figure 2) Many indolo[3,2-*b*]quinoline and indolo[3,2-b]quinolinone derivatives, especially the 11-substituted indolo[3,2-b]quinoline, showed remarkable pharmaceutical activity. For example, 11-[2-methoxy-4-(methylsulfonyl)phenyl]amino indoloquinoline **8** has shown to exhibit antitumor activity,[7,8] while both 11-(4-diethylamino)-2-methylbutylamino indoloquinoline **9**[9] and 11-(4-hydroxylphenyl)amino indoloquinoline **10**[10] have comparable activity with chloroquine to inhibit a multi-resistant *Plasmodium falciparum* strain (Figure 3). Most of the known 11-substituted indoloquinoline derivates were prepared from nucleophilic substitution of 11-chloroindoloquinoline,[7,10,11] and the later compounds could be readily obtained by treatment of indoloquinolinones with $POCl_3$.[7,10,12] Therefore the substituted indolo[3,2-*b*]quinolinones became

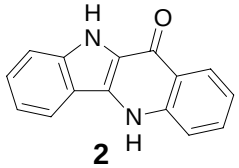
the key intermediates in the preparation of different types of 11-substituted indolo[3,2-*b*]quinoline.



1

10*H*-indolo[3,2-b]quinolines

quindoline

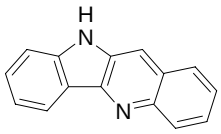


2

5*H,* 10*H*- indolo[3,2-b]quinolin-11-one

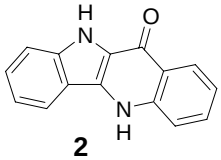
quindolinone

Figure 1



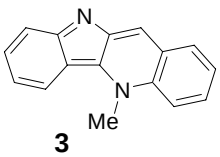
1

quindoline



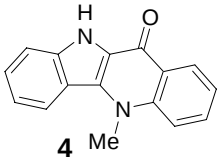
2

quindolinone



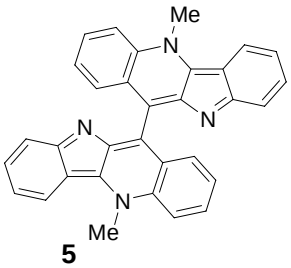
3

cryptolepine



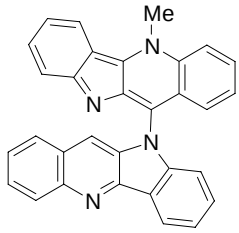
4

5-methylquindolinone



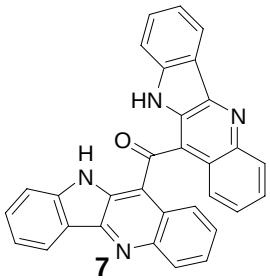
5

biscryptolepine



6

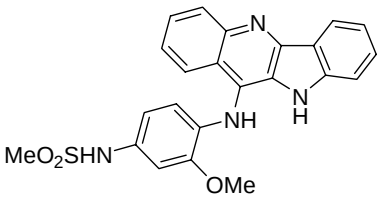
cryptoquindoline



7

Cryptomisrine

Figure 2



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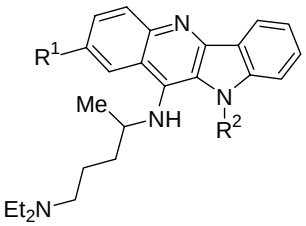

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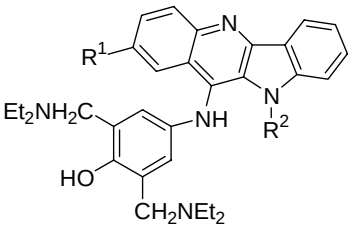

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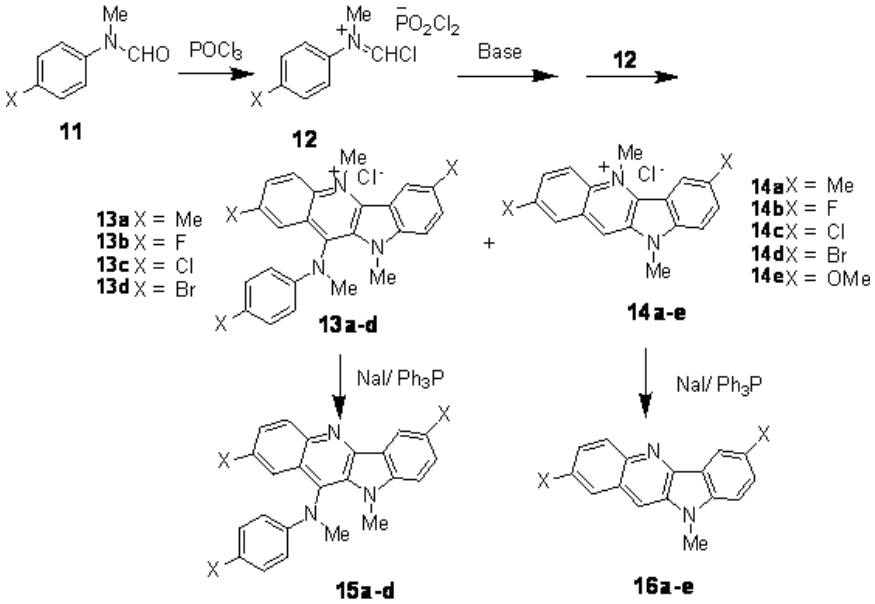
Figure 3

With the purpose to synthesize the analogues of alkaloid biscryptolepine **5**, cryptoquindoline **6** and cryptomisrine **7**, we first need to prepare some substituted indolo[3,2-*b*]quinolinones as starting materials. Although some synthetic methods for the preparation of indolo[3,2-*b*]quinolinones have been developed, most of them started from the condensation of two *o*-aminoaryl carbonyl compounds.[7,12, 13] Frequently encountered problems in these methods are the lack of commercially available starting materials. Several years ago,[14] we reported that the interaction of the Vilsmeier's reagents **12** and an organic base lead to the formation of 11-*N*-arylamino indolo[3,2-*b*]quinolinium salts **13** and /or indolo[3,2-*b*]quinolinium salts **14**, and the compounds **13** or **14** could be readily demethylated by sodium iodide/ triphenylphosphine to give quindolines **15** or **16** respectively in high yields. (Scheme 1) Considering their electrophilic nature, the hydrolysis of quindolinium ions **13** and **14** would give rise to substituted quindolinones. Here we report our study on the hydrolysis or hydrolytic oxidation of indolo[3,2-*b*]quinolinium salts.

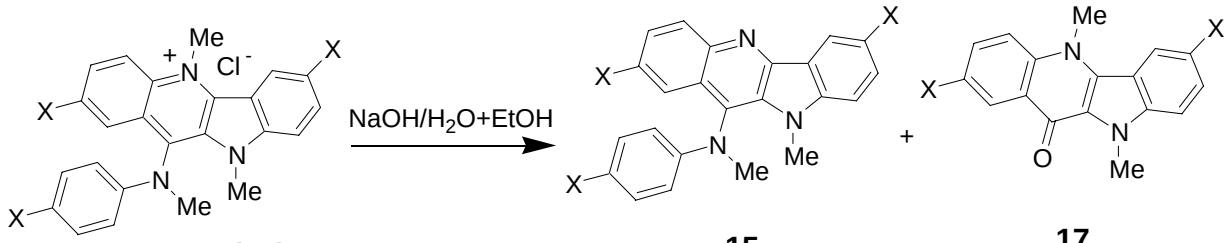


Scheme 1

Results and Discussion

In our earlier work,[14] we had noticed that the hydrolysis of indolo[3,2-*b*]quinolinium salt **13a** (X = Me) in 10% NaOH aqueous solution gave indoloquinolinone **17a** (X = Me) in good yield, but we did not examine the reactions of other quinolinium salts. Recently, during the preparation of halogen-substituted indolo[3,2-*b*]quinolinones, we found that the hydrolysis of halogen substituted quinolinium salts **13b-d** was not as satisfactory as their analogue **13a**. When

quinolinium salts **13b-d** were treated with 5% to 20% NaOH aqueous solution**,** the conversion of starting materials was lower than that of **13a** due to their lower solubility in aqueous solution. However, if a large amount of ethanol was used as co-solvent, both demethylation product **15** and hydrolysis product **17** were obtained. (Scheme 2 and Table 1) Quinolinone **17** should be yielded from the nucleophilic addition of hydroxide anion to the 11-position of quinolinium salt **13** followed by elimination of the amino substituent, while quinoline **15** was apparently the result of nucleophilic substitution to the 5-*N*-methyl group of **13.** (Scheme 3)

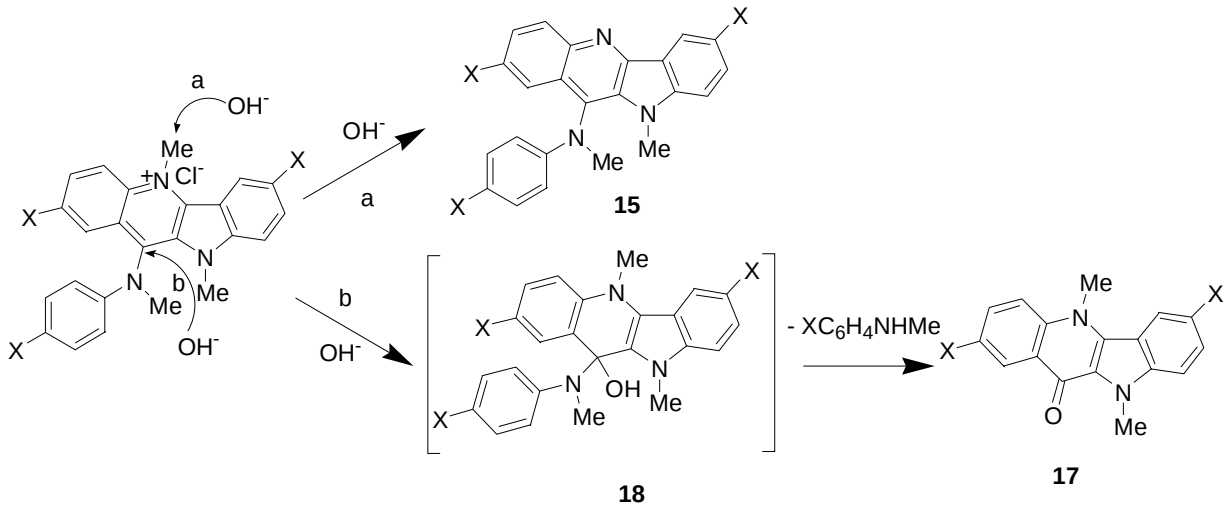


13a X = Me
13b X = F
13c X = Cl
13d X = Br

Scheme 2

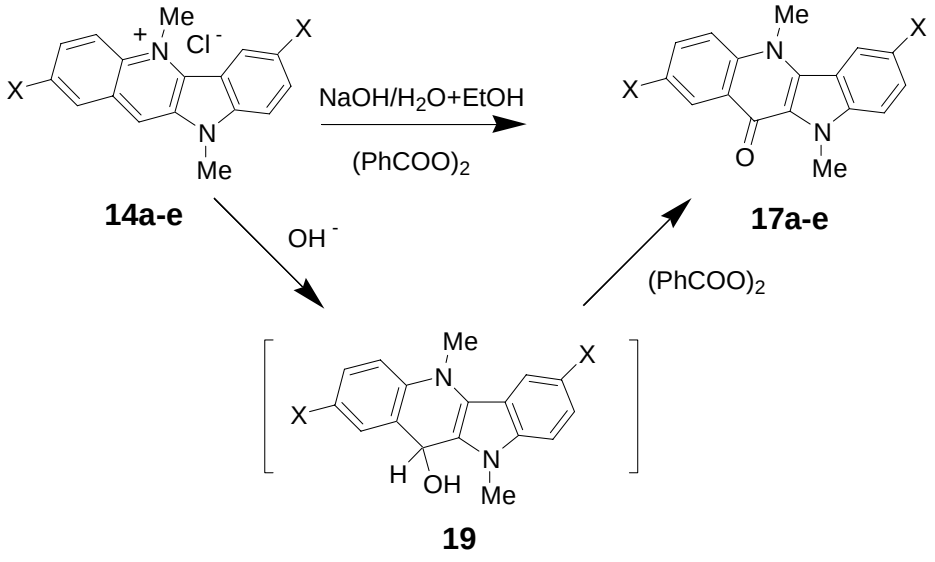
Table 1. Hydrolysis of quinolinium salts **13** in NaOH alcoholic aqueous solution

Starting material		Yield of product (%)		
13a	15a	30	17a	58
13b	15b	10	17b	40
13c	15c	22	17c	36
13d	15d	25	17d	35



Scheme 3

Comparing the structures of quinolinium salts **14** with that of **13,** we thought that quinolinium salts **14** could also be transformed into quinolinones by hydrolytic oxidation. Since compound **14** has much less steric hindrance at 11-carbon than **13**, the nucleophilic addition of hydroxide anion to the pyridine ring of **14** would be facilitated. Thus the hydrolytic oxidation of **14** was tried in refluxing sodium hydroxide alcoholic aqueous solution with benzoyl peroxide as an oxidant. As expected, the conversion of **14** proceeded quickly and efficiently to give the quinolinones **17** in moderate yields. (Scheme 4 and Table 2)



Scheme 4

Table 2. Hydrolytic oxidation of quindolinium salts **14** with benzoyl peroxide in NaOH alcoholic aqueous solution

Starting material	Yield of product (%)			
14a	17a	45	16a	-
14b	17b	48	16b	-
14c	17c	41	16c	-
14d	17d	47	16d	-
14e	17e	40	16e	23

In order to optimize the reaction conditions for the formation of quinolinones **17**, the hydrolysis of **13** and hydrolytic oxidation of **14** were performed in small scale and monitored by TLC. Weak bases such as Et_3N-H_2O and aqueous K_2CO_3 gave extremely low conversion of quinolinium salts. Aqueous NaOH solution in different concentrations (5-30% w/v) was found to be effective, but highly concentrated NaOH solution (>10%) increased the yield of demethylation product. The best selectivity for hydrolysis over demethylation was achieved utilizing 5% to 10% aqueous NaOH solution. The reaction was facilitated by adding ethanol as a co-solvent to increase the solubility of quinolinium salts in reaction media. But if a 50% ethanol aqueous solution was used as solvent, the reaction gave rise to the formation of demethylated product predominantly.

In summary, the regioselective hydrolysis of 11-(*N*-aryl-*N*-methylamino)-10*H*-indolo [3,2-*b*]quinolinium salts **13** and hydrolytic oxidation of 10*H*-indolo[3,2-*b*]quinolinium salts **14** afforded indolo[3,2-*b*]quinolinones in generally moderate yields. Combining the preparation of indolo[3,2-*b*]quinolinium salts from the one-pot reaction of the Vilsmeier's reagents with a nitrogen base,[14] this work provided a very simple two-step method for the synthesis of substituted 10*H*-indolo[3,2-*b*]quinol-11-ones.

Experimental Section

General Procedures. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance 500 or Varian Unity 200 NMR spectrometer. IR spectra were recorded using an AVATAR 360 FT-IR spectrometer. Mass spectra were recorded on a Kratos MS8ORF instrument (EI-MS) or Bruker APEX-2 (HRMS) and elemental analyses were performed on a GMBH Vario EL instrument. Indolo[3,2-*b*]quinolinium salts **13** and **14** were prepared according to our earlier report.[14]

General procedure for the preparation of substituted indolo[3,2-*b*]quinol-11-ones (17)

Method A. To compound **13** (1 mmol) in ethanol (10 mL) was added sodium hydroxide (100 mL, 10% w/v) and the mixture refluxed for 2h in a 100 ^{o}C oil bath. The cooled mixture was extracted with chloroform (50mL×5), and the extract was dried over $MgSO_4$. After removal of the solvent,

the residue was chromatographed on silica gel, eluting with light petroleum and ethyl acetate (3:1 to 1:1) to give indolo[3,2-*b*]quinoline **15** and indolo[3,2-*b*]quinolinone **17** as yellow solid.

Method B. A mixture of compound **14** (0.5 mmol) and benzoyl peroxide (0.5g) in the solution of ethanol (10 mL) with sodium hydroxide (50 mL, 10% w/v) refluxed for 1h in an 100 ^{o}C oil bath. The cooled mixture was extracted with chloroform (50mL×5), and the extract was dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel, eluting with light petroleum and ethyl acetate (1:1) to give indolo[3,2-*b*]quinolinone **17** as yellow solid.

2,7,10-Trimethyl-11-(*N*-4-methylphenyl-*N*-methylamino)-10*H*-indolo[3,2-*b*]quinoline (15a). 30% from method A, mp 188-190 ^{o}C. IR (KBr) ν_{max}/cm^{-1} 1635, 1610, 1565, 1520, 1510, 1500; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.46 (1H, brs), 8.36 (1H, d, *J* = 8.2 Hz), 7.56 (1H, brs), 7.44-7.52 (2H, m), 7.25 (2H, d, *J* = 8.6 Hz), 7.00 (2H, d, *J* = 8.4 Hz), 6.44-6.50 (2H, m), 3.70 (3H, s), 3.49 (3H, s), 2.57 (3H, s), 2.24 (3H, s); ^{13}C NMR (50MHz, DMSO-d_6) δ: 146.6, 146.5, 143.7, 143.3, 134.9, 130.8, 130.7, 129.7, 129.3, 128.8 (d), 128.4, 125.4, 125.3, 121.4, 120.7, 120.6, 111.6, 109.1, 30.0, 21.5 (d), 20.6, 19.7. MS (EI, m/z): 379 (M^+, 100%). Anal. Calcd for $C_{26}H_{25}N_3$: C, 82.29; H, 6.64; N, 11.07; Found C, 81.86; H, 6.89; N, 11.12.

2,7-Difluoro-10-methyl-11-(*N*-4-fluorophenyl-*N*-methylamino)-10*H*-indolo[3,2-*b*]quinoline (15b). 10% from method A, mp 261-263 ^{o}C (lit.[14] mp 261-262 ^{o}C).

2,7-Dichloro-10-methyl-11-(*N*-4-fluorophenyl-*N*-methylamino)-10*H*-indolo[3,2-*b*]quinoline (15c). 22% from method A, mp 295-296 ^{o}C (lit.[14] mp 295-298 ^{o}C).

2,7-Dibromo-10-methyl-11-(*N*-4-fluorophenyl-*N*-methylamino)-10*H*-indolo[3,2-*b*]quinoline (15d). 25% from method A, mp 275-277 ^{o}C. IR (KBr) ν_{max}/cm^{-1} 1623, 1589, 1556, 1489, 1457; ^{1}H NMR (200 MHz, DMSO-d_6) δ: 8.47 (1H, d, *J* = 2.0 Hz), 8.20 (1H, d, *J* = 9.2 Hz), 7.76-7.88 (3H, m), 7.65 (1H, d, *J* = 8.6 Hz), 7.30 (2H, d, *J* = 8.5 Hz), 6.49-6.55 (2H, m), 3.72 (3H, s), 3.49 (3H, s). ^{13}C NMR (125MHz, $CDCl_3$ + CF_3CO_2D) δ: 146.1, 145.5, 140.2, 138.5, 136.5, 134.4, 133.2, 132.6, 126.4, 126.1 125.8, 123.4, 121.8, 117.6, 116.1, 115.2, 113.1, 112.3, 110.8, 40.5, 31.5. MS (EI, m/z): 571 (M^+)/573 (100)/575/577. Anal. Calcd for $C_{23}H_{16}Br_3N_3$: C, 48.12; H, 2.80; N, 7.32. Found C, 47.56; H, 2.83; N, 7.15.

5,11-Dihydro-2,5,7,10-tetramethyl-10*H*-indolo[3,2-*b*]quinol-11-one (17a). 58% from method A and 45% from method B, mp 239-240 ^{o}C (lit.[14] mp 238-240 ^{o}C).

5,11-Dihydro-2,7-difluoro-5,10-dimethyl-10*H*-indolo[3,2-*b*]quinol-11-one (17b). 40% from method A and 48% from method B, mp 279-280 ^{o}C. IR (KBr) ν_{max}/cm^{-1} 1600, 1580, 1540, 1530; ^{1}H NMR (200 MHz, DMSO-d_6) δ: 8.18 (1H, dd, *J* = 10.5 and 2.0 Hz), 7.92-8.02 (2H, m), 7.58-7.70 (2H, m), 7.41-7.51 (1H, m), 4.25 (6H, s, 5-NMe and 10-NMe); ^{13}C NMR (50MHz, DMSO-d_6) δ: 167.3, 158.5,158.0, 155.0, 154.6, 136.8 (d), 124.9 (d), 122.8, 120.1, 119.8, 118.4 (d), 116.3, 116.0, 114.7, 111.9 (d), 109.3, 108.9, 108.3, 108.0, 107.9, 36.1, 31.2; MS (EI, m/z): 298 (M^+, 100%), 297 (M-1, 74), 299 (M+1, 20), 283 (M-Me, 62). Anal. Calcd for $C_{17}H_{12}F_2N_2O$: C, 68.45; H, 4.05; N, 9.39. Found C, 68.73; H, 3.92; N, 9.42.

5,11-Dihydro-2,7-dichloro-5,10-dimethyl-10*H*-indolo[3,2-*b*]quinol-11-one (17c). 36% from method A and 41% from method B, mp 318-319 °C. IR (KBr) ν_{max}/cm^{-1} 1620, 1590, 1520; ^{1}H NMR (200 MHz, DMSO-d_6) δ: 8.37 (1H, d, *J* = 1.2 Hz), 8.31 (1H, d, *J* = 2.4 Hz), 7.95 (1H, d, *J* = 9.4 Hz), 7.65-7.74 (2H, m), 7.54 (1H, dd, *J* = 8.8 and 1.8 Hz), 4.30 (6H, s, 5-NMe and 10-NMe); MS (EI, m/z): 330 (M^+, 100%)/332 (65), 329 (M-1, 55), 331 (M+1, 50), 315 (M-Me, 35); HRMS: Anal. Calcd for $C_{17}H_{12}Cl_2N_2O$ 330.0327. Found 330.0325.

5,11-Dihydro-2,7-dibromo-5,10-dimethyl-10*H*-indolo[3,2-*b*]quinol-11-one (17d). 35% from method A and 47% from method B, mp> 320 °C. IR (KBr) ν_{max}/cm^{-1} 1613, 1582, 1509; ^{1}H NMR (500 MHz, DMSO-d_6 +CF_3CO_2D) δ: 8.46 (1H, s), 8.28 (1H, s), 7.82 (2H, m), 7.62 (1H, d, *J* = 9.0 Hz), 7.28 (1H, d, *J* = 9.1 Hz), 4.46 (3H, s, NMe), 4.01 (3H, s, NMe).); ^{13}C NMR (125MHz, DMSO-d_6+CF_3CO_2D) δ: 156.5, 148.2, 141.3, 140.7, 140.1, 1302, 128.5, 126.2, 124.0, 122.1, 121.8, 119.5, 117.3, 116.2, 115.0, 42.1, 35.6. MS (EI, m/z): 418 (45)/420 (100)/422 (30), 403 (5)/405 (10); HRMS (FAB): Anal. Calcd for $C_{17}H_{13}Br_2N_2O$ 418.9395 (M+1). Found 418.9772.

5,11-Dihydro-2,7-dimethoxy-5,10-dimethyl-10*H*-indolo[3,2-*b*]quinol-11-one 17e). 40% from method B, mp 230-232 °C. IR (KBr) ν_{max}/cm^{-1} 1580, 1520, 1460; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.34-8.10 (6H, m), 4.37 (6H, s, 5-NMe and 10-NMe), 3.97 (3H, s, OMe), 3.95 (3H, s, OMe). ^{13}C NMR (125MHz, $CDCl_3$ + CF_3CO_2D) δ: 157.7, 153.8, 151.4, 141.6, 136.6, 133.5, 126.4, 118.1, 117.6, 115.3, 113.1, 110.8, 107.6, 100.0, 57.0, 55.7, 38.2, 31.9. MS (EI, m/z): 322 (M^+, 100%), 321 (M-1, 23), 323 (M+1, 20), 307 (M-Me, 20). Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found C, 70.40; H, 5.69; N, 8.85.

2,7-Dimethoxy-10-dimethyl-10*H*-indolo[3,2-*b*]quinoline (16e). 23% from method B, mp 125-126 °C. (lit.[14] mp 123-125.5 °C).

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