

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

Ying Cheng^{a*}, Jian Wang^a, and Otto Meth-Cohn^b

^a Department of Chemistry, Beijing Normal University, Beijing 100875, China

^b Chemistry Department, University of Sunderland, Sunderland SR1 3SD, U.K.

E-mail: ycheng2@bnu.edu.cn

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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 cryptomisine **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-hydroxyphenyl)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 derivatives were prepared from nucleophilic substitution of 11-chloroindoloquinoline,^{7,10,11} and the later compounds could be readily obtained by treatment of indoloquinolinones with POCl₃.^{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.

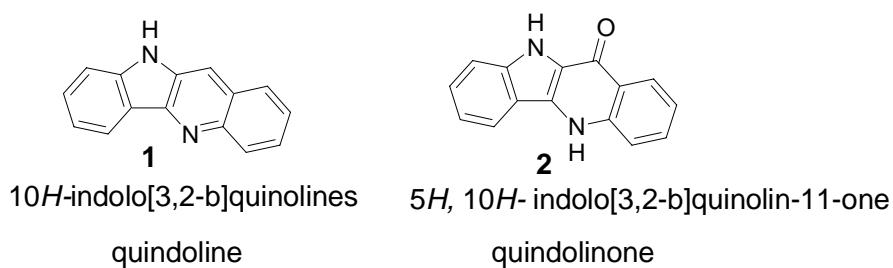


Figure 1

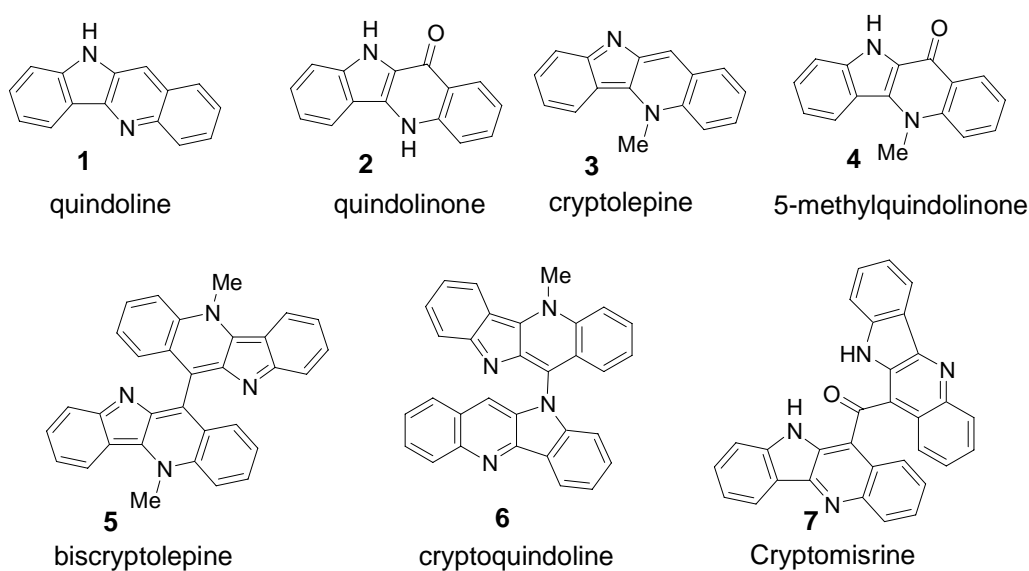


Figure 2

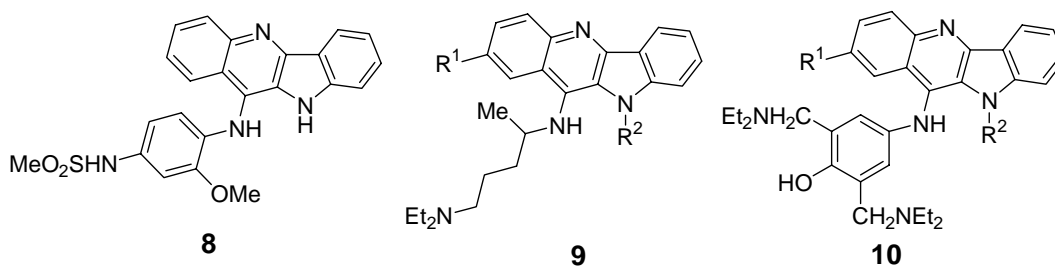
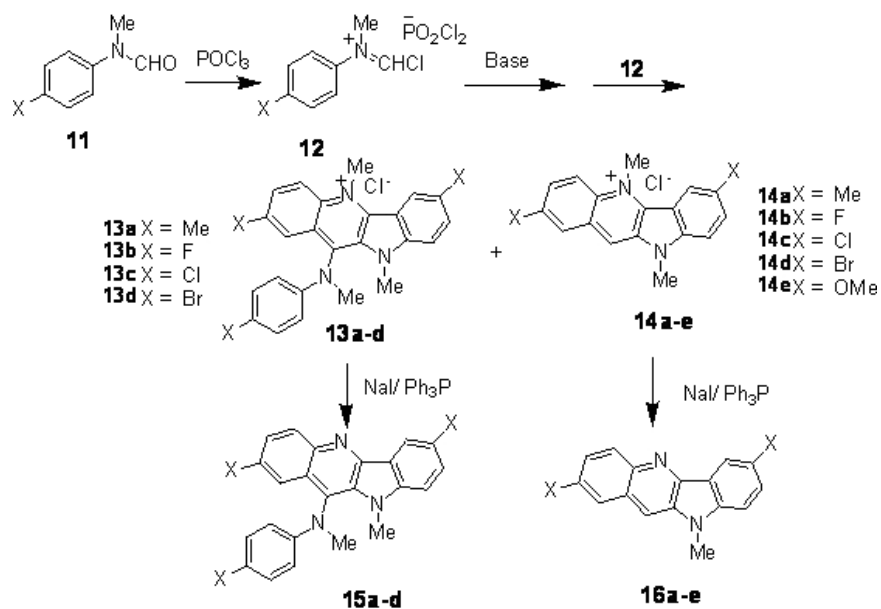


Figure 3

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.

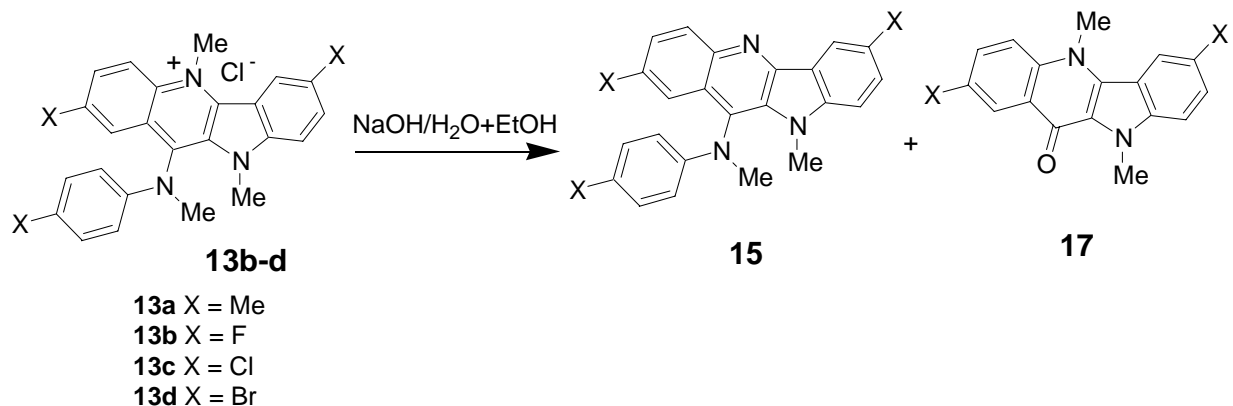


Scheme 1

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

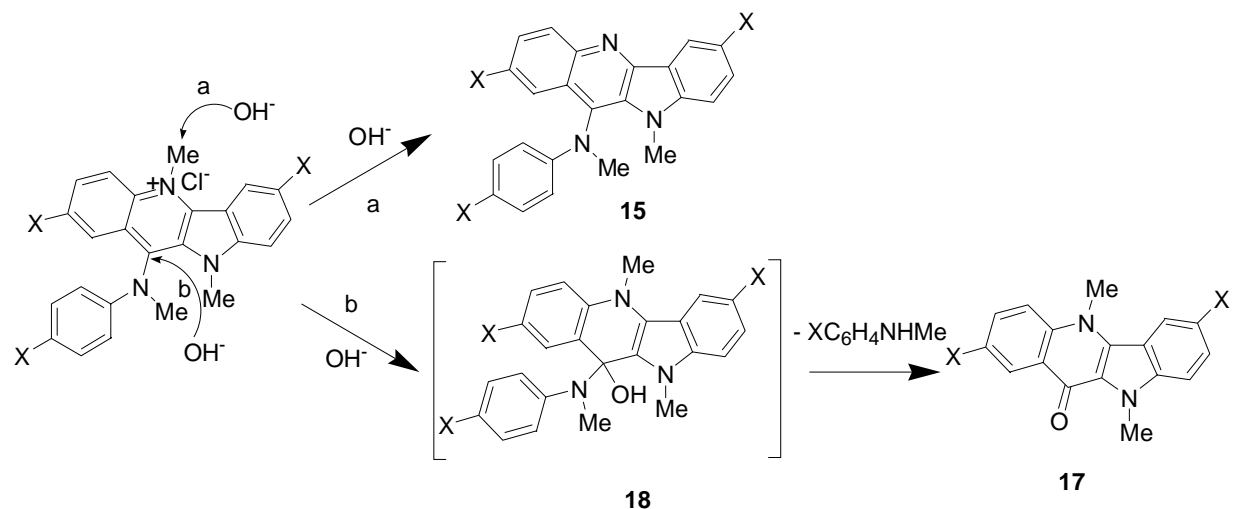
quinolinium salts **13b-d** were treated with 5% to 20% NaOH aqueous solution, the conversion of starting materials was lower than that of **13a** due to their lower solubility in aqueous solution. However, if a large amount of ethanol was used as co-solvent, both demethylation product **15** and hydrolysis 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)



Scheme 2

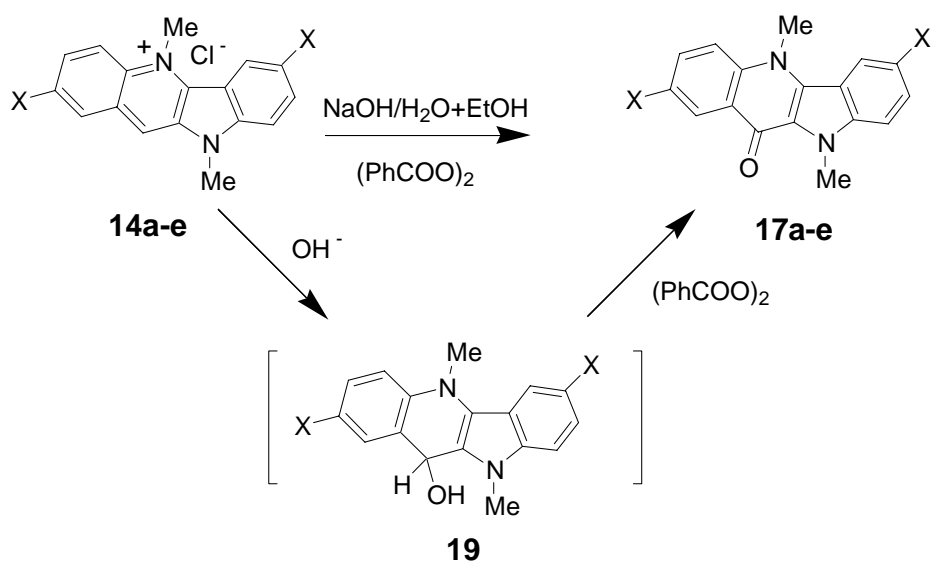
Table 1. Hydrolysis of quinolinium salts **13** in NaOH alcoholic aqueous solution

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 Et₃N-H₂O and aqueous K₂CO₃ 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. ¹H NMR and ¹³C 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 °C oil bath. The cooled mixture was extracted with chloroform (50mL×5), and the extract was dried over MgSO₄. 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 °C oil bath. The cooled mixture was extracted with chloroform (50mL×5), and the extract was dried over MgSO₄. 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 °C. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1635, 1610, 1565, 1520, 1510, 1500; ¹H NMR (200 MHz, CDCl₃) 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); ¹³C 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 C₂₆H₂₅N₃: 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 °C (lit.¹⁴ mp 261-262 °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 °C (lit.¹⁴ mp 295-298 °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 °C. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1623, 1589, 1556, 1489, 1457; ¹H 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). ¹³C NMR (125MHz, CDCl₃ + CF₃CO₂D) 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 C₂₃H₁₆Br₃N₃: 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 °C (lit.¹⁴ mp 238-240 °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 °C. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1600, 1580, 1540, 1530; ¹H 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); ¹³C 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 C₁₇H₁₂F₂N₂O: 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-10H-indolo[3,2-b]quinol-11-one (17c). 36% from method A and 41% from method B, mp 318-319 °C. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1620, 1590, 1520; ^1H 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 $\text{C}_{17}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}$ 330.0327. Found 330.0325.

5,11-Dihydro-2,7-dibromo-5,10-dimethyl-10H-indolo[3,2-b]quinol-11-one (17d). 35% from method A and 47% from method B, mp > 320 °C. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1613, 1582, 1509; ^1H NMR (500 MHz, DMSO- d_6 + $\text{CF}_3\text{CO}_2\text{D}$) 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 + $\text{CF}_3\text{CO}_2\text{D}$) 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 $\text{C}_{17}\text{H}_{13}\text{Br}_2\text{N}_2\text{O}$ 418.9395 (M+1). Found 418.9772.

5,11-Dihydro-2,7-dimethoxy-5,10-dimethyl-10H-indolo[3,2-b]quinol-11-one (17e). 40% from method B, mp 230-232 °C. IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 1580, 1520, 1460; ^1H 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 + $\text{CF}_3\text{CO}_2\text{D}$) 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 $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3$: C, 70.79; H, 5.63; N, 8.69. Found C, 70.40; H, 5.69; N, 8.85.

2,7-Dimethoxy-10-dimethyl-10H-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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