An Alternative Synthesis of 10*H*-Indolo[3,2-*b*]quinoline and its Selective *N*-Alkylation

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A new and a more efficient synthesis of 10*H*-Indolo[3,2-*b*]quinoline (quindoline) is reported. The synthesis involved *N*-arylation of 3-aminoquinoline with triphenylbismuth diacetate followed by oxidative cyclization using palladium(II) acetate. A selective *N*-alkylation methodology for quindoline was also developed. Alkylation on N-5 was obtained in sulpholane, while alkylation on N-10 was achieved in acetone in the presence of potassium hydroxide. A sequential N-5- and N-10 double alkylation procedure was also formulated.

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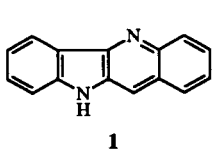
10*H*-Indolo[3,2-*b*]quinoline (quindoline, **1**) and cryptolepine **2** were isolated from *Cryptolepis sanguinolenta* [1-3], a plant native to West Africa and used in the treatment of malaria. Pharmacological investigations on cryptolepine have shown that it has antifungal and antibacterial activities among others [4-6]. We have also shown that cryptolepine possesses renal vasodilation and inhibition of platelet aggregation properties which are associated with the presence of N-5 alkyl groups on the quindoline nucleus [7]. Thus, it is of interest to investigate the structure-activity relationships associated with various alkyl groups at the 5 and 10 positions of the quindoline moiety.

Several synthetic procedures to obtain quindoline have been reported [1,8-10]. Most of these procedures require 5-9 steps with overall yields in the 13 to 20% range. We have singled out the Holt and Petrow method [8] for the synthesis of quindoline and its derivatives in the past because of its short reaction sequence (only 2 steps) and high yields (~70%). However, the latter method requires a condensation step which takes 10 days to complete. As a result, we began exploring other methods to obtain quindoline and its derivatives in order to evaluate their structure-activity relationships.

We now report a new alternative synthesis of quindoline which has several advantages over the available methods.



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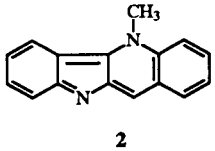

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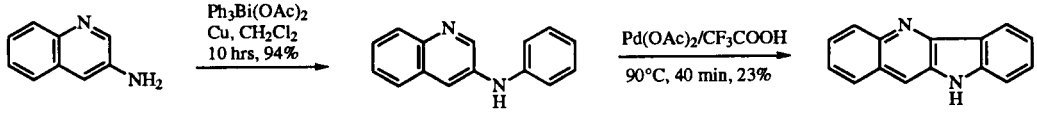
During the synthesis of the *N*-alkylated quindolines for structure activity relationship studies, we also explored conditions that could allow us to achieve selective N-5 or N-10 alkylation in the quindoline system. Thus, we also report that selective *N*-alkylation of quindoline can be achieved under different conditions. To our knowledge, no such results have been reported for this biologically important class of compounds.

The quindoline synthesis we devised involved only two steps that was completed in one day in an overall yield of 22% (Scheme 1). Thus, phenylation of 3-aminoquinoline with triphenylbismuth diacetate in the presence of metallic copper afforded 3-anilinoquinoline **3** in excellent yield [11]. A similar procedure, [12] using triphenylbismuth in the presence of copper diacetate also produced **3** but the yield was low (35%). Cyclization of **3** was effected by palladium(II) acetate in refluxing trifluoroacetic acid [13] to afford quindoline (**1**). The proton nmr data matched those of the authentic quindoline. The moderate yield of quindoline was attributed to the formation of a regioisomer resulting from cyclization at the 4-position of the quinoline ring. Compound **1** was readily separated from the undesired isomer by flash chromatography.

Scheme 1



Attempts were made to improve the yield in the cyclization step in Scheme 1. Thus, cyclization with palladium(II) acetate in acetic acid was slower and produced more side products than for trifluoroacetic acid. Boron trifluoride diethyl etherate in dichloromethane promoted little reaction at 50°. Change of oxidant to thallium(III) trifluoroacetate [14], which had been used extensively for intramolecular coupling of phenolic ethers, resulted in a complex mixture. Photochemical conditions also failed to produce the desired product as reported [15-16].

One strategy to direct the cyclization away from the 4-position of the quinoline ring would be by blocking the position. One ideal group would be chlorine which could be readily removed by catalytic hydrogenation afterwards. However, the preparation of 3-amino-4-chloroquinoline will require three to five steps starting with commercially available materials [17]. The current studies did not pursue this aspect in order to highlight the conciseness of the route. Despite the low yield in step 2 of Scheme 1, this procedure is more advantageous than the others because it requires only 2 steps, a shorter reaction time and has comparable yields.

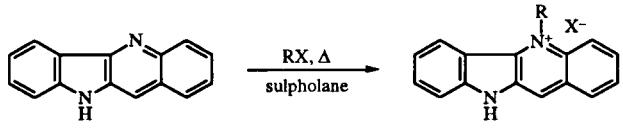
Studies on *N*-alkylation of quindoline, **1**, led to new and cleaner methods for obtaining either N-5 or N-10 alkylations. Previously, N-5 alkylation involved heating quindoline in the alkyl halides with drops of dimethyl sulfoxide or *N,N*-dimethylformamide in order to dissolve the quindoline. This method often led to low yields and the formation of substantial double alkylation products in addition to the desired N-5 alkylated products (Table 1). The former was often difficult to separate. Another shortcoming of the procedure is the need for excessive amounts of alkylating agents in order to drive the reaction to completion.

The new procedure for obtaining N-5 alkylations involved heating quindoline with excess amounts of the alkylating agents in sulpholane for 24 hours. Flash chromatography of the reaction mixture afforded the pure products as yellow solids which were purified further by recrystallization. From Table 1, good to moderate yields were obtained for a variety of halides. The poor yield of **5g** was perhaps due to the steric hindrance of the cyclohexane group in cyclohexylmethyl bromide. The moderate yields of **5b**, **5c** and **5e** were attributed to the formation of N-5 and N-10 double alkylation products. For compound **5c**, perhaps the yield was low because of competition from base-catalyzed dehydrohalogenation of phenylethyl bromide.

The choice of sulpholane as the solvent was originally intended to suppress the double alkylation encountered with some halides. We found that reaction in sulpholane led to a general increase in N-5 alkylation selectivity (Table 1, **5b**, **5c**, **5e** and **5g**). Other solvents tested did not have this effect. For example, quindoline reaction with ethyl bromoacetate yielded more double alkylation products when conducted in benzene, acetone or tetrahydrofuran. Also noticeable from Table 1 is the general increase in yield as a result of the use of sulpholane. Sulpholane was reported to prevent decomposition of some *N*-alkylation products and was a good solvent for certain *N*-quarternization reactions [18]. Our experience in working with alkylation of quindoline led us to conclude that sulpholane is more versatile than the more commonly employed solvents; dimethyl sulfoxide, dimethylformamide, acetone and ethanol.

Table 1

The Contribution of Sulpholane in the N-5 Alkylation of Quindoline



RX	Temperature	Product	Previous % Yield [a]	New % Yield [b]
CH_3I	50°C	**5a**		73
$PhCH_2Br$	90°C	**5b**	22 (0.8:1)	54 (2.2:1)
$PhCH_2CH_2Br$	105°C	**5c**	12 (7:1)	30 (>50:1)
$CH_2{=}CHCH_2Br$	90°C	**5d**		80
$BrCH_2CO_2Et$	85°C	**5e**	15 (2:1)	53 (46:1)
CH_3OCH_2I	rt	**5f** (c)		95
cyclohexylmethyl Br	120°C	**5g**	0	8

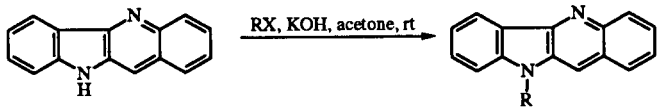
[a] Percent yield of the previous method; numbers in brackets are the ratio of N-5 to double alkylation on N-5 and N-10; ratios were estimated by comparing the nmr signals of N-5 and N-10 alkyl groups. [b] As for [a] but utilized the new method(in sulpholane). [c] Alkylation was conducted in benzene, which gave a cleaner reaction.

The N-10 alkylated quindolines were obtained by a modified literature method [19]. Quindoline was stirred in acetone and an excess amount of potassium hydroxide. Removal of solvent followed by flash chromatography yielded pure products. Excellent yields were obtained in general. However, attempts to alkylate quindoline under the same conditions with bromomethyl methyl ether using this procedure were unsuccessful.

We further demonstrated that a combination of the above N-5 and N-10 alkylation conditions can produce sequential double alkylated quindolines if desired. Thus, treatment of N-5 allylquindolium bromide **5e** with ammonia formed the corresponding anhydronium base, which was then alkylated at the N-10 position to form the double alkylated com-

Table 2

Selective Alkylation of the N-10 Atom in Quindoline

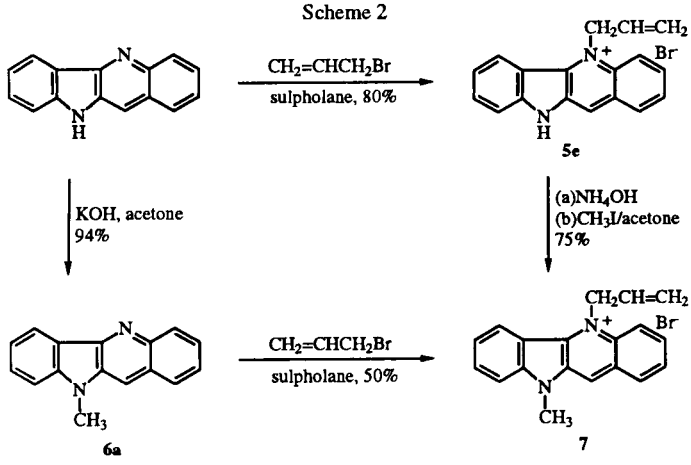


RX	Product	%Yield
CH_3I	**6a**	94
cyclohexyl methyl bromide	**6b**	86
$PhCH_2Br$	**6c**	97
$PhCH_2CH_2Br$	**6d**	68
$BrCH_2CO_2Et$	**6e**	87
$CH_2=CHCH_2Br$	**6g**	95

pound **7** (Scheme 2). The same product was also obtained in the reverse order, *i.e.*, N-10 alkylation prior to N-5 alkylation. The flexibility of the sequence is evident.

In summary, we have developed a short alternative synthesis and a selective *N*-alkylation methodology for quindoline. This method has advantage over the Holt and Petrow method in that quindoline can be obtained in a single day as opposed to the 10-11 days required in the previous method. In addition, the new method is ammenable to substitution on the quinoline moiety proposed as the pharmacophore in the natural product, cryptolepine. A variety of mono- and di-substituted quindolines can also be prepared by employing the current alkylation methodology. These alkylation conditions may also be extended to other heterocyclic compounds when similar *N*-alkylation selectivities are desired.

Scheme 2



EXPERIMENTAL

Proton nmr spectra were recorded on a Bruker AC300 270 MHz NMR instrument at Florida State University. Melting points were taken on a Gallenkamp (UK) digital melting point apparatus and were uncorrected. Elemental analysis data were determined by Atlantic Microlab, Inc., Norcross, GA 30091. Flash chromatography were performed with Davisil grade 633 type 60A 230-400 mesh silica gel as purchased from Aldrich Chemicals, Inc. All glassware were oven-dried at 120° prior to use. Dimethylformamide was distilled from anhydrous calcium sulfate and then stored over 4A molecular sieves. Sulpholane was dried over 4A molecular sieves. Other solvents were generally distilled from appropriate drying agents and then stored over molecular sieves. Triphenylbismuth diacetate was prepared from triphenylbismuth carbonate. Alkylating agents were purchased from either Aldrich or Fisher Scientific and used as such without further purification. All other chemicals were obtained from Aldrich Chemicals, Inc.

3-Anilinoquinoline (**3**).

A mixture of 3-aminoquinoline (0.288 g, 2 mmoles), triphenylbismuth diacetate (1.674 g, 3 mmoles) and Cu (0.030 g, 0.4 mmole) in dichloromethane (10 ml) was stirred overnight under a nitrogen atmosphere at room temperature. The resulting mixture was poured into 5% ammonia (100 ml) and extracted with ethyl acetate (4 x 25 ml). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated by rotary evaporation, and chromatographed with ethyl acetate:hexanes (1:1) as the eluent to yield **3** as a yellowish solid (0.415 g, 94%), mp 118-119.5°; ^{1}H nmr (deuteriochloroform): δ 6.27 (s, 1 H), 7.04 (m, 1 H), 7.17 (m, 1 H), 7.19 (m, 1 H), 7.34 (m, 2 H), 7.48 (m, 2 H), 7.62 (m, 1 H), 7.72 (d, 1 H, J = 2.6 Hz), 8.01 (dd, 1 H, J = 8.0, 1.0 Hz), 8.70 (d, 1 H, J = 2.7 Hz); ^{13}C nmr (deuteriochloroform): δ 116.8, 118.5, 122.2, 126.4, 127.1, 128.8, 128.9, 129.6, 137.1, 141.8, 143.5, 145.0.

Anal. Calcd. for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.51; H, 5.66; N, 12.47.

10*H*-Indolo[3,2-*b*]quinoline (Quindoline) (**1**).

A mixture of 3-anilinoquinoline **3** (0.080 g, 0.366 mmole) and palladium(II) acetate (0.164 g, 0.732 mmole) in trifluoroacetic acid (2 ml) was heated to 90° for 40 minutes. The mixture was cooled to room temperature and poured into 5% ammonia (50 ml). The mixture was extracted with ethyl acetate (3 x 50 ml). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated by rotary evaporation, and chromatographed with ethyl acetate:hexanes (1:1) and later with ethyl acetate alone. Two products were collected. The less polar product co-chromatographed with authentic quindoline and the melting point and proton nmr data matched those of the

natural product (0.018 g, 23%). A more polar product was identified as being isomeric with quindoline (0.040 g, 50%), mp, 244-246°; ^{1}H nmr (deuteriochloroform): δ 7.45 (m, 1 H), 7.59 (m, 1 H), 7.68 (m, 2 H), 7.75 (m, 1 H), 8.31 (dd, 1 H, J = 8.1, 1.3 Hz), 8.58 (d, 1 H, J = 8.1 Hz), 8.72 (dd, 1 H, J = 8.0, 1.4), 9.1 (s, 1 H), 9.25 (s, 1 H). Further characterization of this product is ongoing.

5-Methyl-10*H*-indolo[3,2-*b*]quinolinium Iodide (**5a**).

To a 10 ml round-bottomed flask was added quindoline (0.020 g, 0.09 mmole), methyl iodide (0.6 ml) and sulpholane (1 ml). The mixture was heated in a sealed flask overnight at 50°. At that time yellow precipitates were formed. The mixture was cooled to room temperature, precipitated further with methanol-ether, filtered, washed with ethyl acetate to afford **5a** as yellow solid (0.024 g, 73%), mp 271-272°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 5.04 (s, 3 H), 7.52 (m, 1 H), 7.86 (m, 1 H), 7.95 (dd, 2 H, J = 7.6, 7.6 Hz), 8.17 (m, 1 H), 8.58 (dd, 1 H, J = 8.0, 1.0 Hz), 8.77 (d, 1 H, J = 9.1 Hz), 8.81 (d, 1 H, J = 8.5 Hz), 9.30 (s, 1 H), 12.87 (s, 1 H).

Anal. Calcd. for $C_{16}H_{13}N_2I$: C, 53.35; H, 3.64; N, 7.78. Found: C, 53.33; H, 3.66; N, 7.69.

5-Benzyl-10*H*-indolo[3,2-*b*]quinolinium Bromide (**5b**).

To a 10 ml round-bottomed flask was added quindoline (0.020 g, 0.09 mmole), benzyl bromide (0.40 ml) and sulpholane (2 ml). The mixture was heated in a sealed flask overnight at 90°. It was then directly chromatographed with 5-15% methanol in methylene chloride (gradient elution) to give **5b** as a yellow solid (the second fraction, 0.015 g, 54%), mp 245-246° (recrystallized from methanol-ether); ^{1}H nmr (methanol-d_4): δ 6.85 (s, 2 H), 7.21 (m, 2 H), 7.40 (m, 4 H), 7.90 (m, 3 H), 8.10 (m, 1 H), 8.28 (d, 1 H, J = 8.5 Hz), 8.45 (d, 1 H, J = 9.1 Hz), 8.56 (dd, 1 H, J = 8.3, 1.2 Hz), 9.31 (s, 1 H).

Anal. Calcd. for $C_{22}H_{17}N_2Br$: C, 67.88; H, 4.40; N, 7.20. Found: C, 67.71; H, 4.48; N, 7.13.

5-(2'-Phenylethyl)-10*H*-indolo[3,2-*b*]quinolinium Bromide (**5c**).

To a 10 ml round-bottomed flask was added quindoline (0.020 g, 0.09 mmole), 2-phenylethyl bromide (0.40 ml) and sulpholane (2 ml). The mixture was heated in a sealed flask at 105° for 16 hours. After cooling to room temperature, the mixture was poured directly into a column of silica gel and eluted with 5-30% methanol in methylene chloride (gradient elution) to yield **5c** as yellow solid (0.011 g, 30%) and then recrystallized from absolute ethanol-ether, mp 255-257°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.47 (t, 2 H, J = 6.8 Hz), 5.81 (t, 2 H, J = 6.7 Hz), 7.21 (m, 5 H), 7.54 (dd, 1 H, J = 6.9, 6.9 Hz), 7.92 (m, 3 H), 8.06 (dd, 1 H, J = 7.2, 7.2 Hz), 8.58 (m, 3 H), 9.35 (s, 1 H), 13.01 (s, 1 H).

Anal. Calcd. for $C_{23}H_{19}N_2Br$: C, 68.49; H, 4.75; N, 6.95. Found: C, 68.42; H, 4.80; N, 6.99.

5-Allyl-10*H*-indolo[3,2-*b*]quinolinium Bromide (**5d**).

To a 10 ml round-bottomed flask was added quindoline (0.020 g, 0.09 mmole), allylbromide (1.0 ml) and sulpholane (1.0 ml). The mixture was heated to 90° for 24 hours. After cooling to rt, the mixture was poured directly into a column of silica gel and eluted with 5-20% methanol in methylene chloride (gradient elution) to yield **5d** as a yellow solid (0.025 g, 80%) and recrystallized from ethyl acetate-methanol; mp 255-257°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 4.81 (d, 1H, J = 16.2 Hz), 5.29 (d, 1 H, J = 10.5 Hz), 6.18 (s, 2 H, broad), 6.47 (m, 1 H), 7.51 (dd, 1 H, J = 6.8, 6.8 Hz), 7.91 (m, 3 H), 8.16 (dd, 1 H, J = 6.8, 6.8 Hz), 8.58 (m, 3 H), 9.41 (s, 1 H), 13.05 (s, 1H).

Anal. Calcd. for $C_{18}H_{15}N_2Br$: C, 63.73; H, 4.46; N, 8.26. Found: C, 63.48; H, 4.55; N, 8.18.

5-Ethoxycarbonyl-10*H*-indolo[3,2-*b*]quinolinium Bromide (**5e**).

To a 10 ml round-bottomed flask was added quindoline (0.020 g, 0.09 mmole), ethyl bromoacetate (0.5 ml) and sulpholane (1.5 ml). The mixture was heated to 85° for 24 hours. After cooling to room temperature, the mixture was poured directly into a column of silica gel and eluted with 5-25% methanol in methylene chloride (gradient elution) to yield **5e** as a yellow solid (0.019 g, 53%), mp 196-197°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.23 (t, 3 H, J = 6.4 Hz), 4.30 (q, 2 H, J = 6.4 Hz), 6.55 (s, 2 H, broad), 7.51 (dd, 1 H, J = 6.9, 6.9 Hz), 7.92 (m, 3 H), 8.18 (dd, 1 H, J = 6.6, 6.6 Hz), 8.39 (d, 1 H, J = 7.6 Hz), 8.68 (m, 2 H), 9.45 (s, 1 H).

Anal. Calcd. for $C_{19}H_{17}N_2O_2Br \cdot 0.5H_2O$: C, 57.88; H, 4.60; N, 7.11. Found: C, 58.03; H, 4.78; N, 7.09.

5-Methoxymethyl-10*H*-indolo[3,2-*b*]quinolinium Iodide (**5f**).

To a 25 ml round-bottomed flask was added quindoline (0.150 g, 0.688 mmole), methoxymethyl iodide (0.60 ml) and benzene (10 ml). The mixture was stirred at room temperature for 2 hours when a yellow precipitate was observed. The mixture was directly chromatographed with 5-15% methanol in methylene chloride (gradient elution) to afford **5f** as a yellow solid (0.034 g, 95%) which was subsequently recrystallized from methanol, mp: 232-235°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.54 (s, 3 H), 6.87 (s, 2 H), 7.53 (dd, 1 H, J = 6.8, 6.8 Hz), 7.92 (m, 3 H), 8.20 (dd, 1 H, J = 7.1, 7.1 Hz), 8.64 (m, 2 H), 8.90 (d, 1 H, J = 8.2 Hz), 9.44 (s, 1 H), 13.02 (s, 1 H).

Anal. Calcd. for $C_{17}H_{15}N_2IO$: C, 52.33; H, 3.87; N, 7.18. Found: C, 52.24; H, 3.85; N, 7.23.

5-Cyclohexylmethyl-10*H*-indolo[3,2-*b*]quinolinium Bromide (**5g**).

To a 25 ml round-bottomed flask was added quindoline (0.150 g, 0.688 mmole), cyclohexylmethylbromide (2.5 ml) and sulpholane (2.5 ml). The mixture was heated in a sealed flask at 120° for 2 days. The resulting mixture was then chromatographed over silica gel with 5-15% methanol in methylene chloride (gradient elution) to obtain **5g** as the product (0.019 g, 8%); which was recrystallized from absolute ethanol/ether, mp, 270-271°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.00-1.70 (m, 11 H), 5.48 (s, 2 H, broad), 7.57 (dd, 1 H, J = 7.9, 7.9 Hz), 7.93 (m, 3 H), 8.15 (dd, 1 H, J = 8.1, 8.1 Hz), 9.59 (m, 2 H), 8.85 (d, 1 H, J = 9.4 Hz), 9.35 (s, 1 H).

Anal. Calcd. for $C_{22}H_{23}N_2Br \cdot 0.5H_2O$: C, 65.35; H, 5.98; N, 6.93. Found: C, 65.31; H, 6.32; N, 6.96.

10-Methylindolo[3,2-*b*]quinoline (**6a**).

To a 10 ml round-bottomed flask was added potassium hydroxide (0.030 g), acetone (1.5 ml), quindoline (0.011 g, 0.05 mmole) and methyl iodide (0.3 ml). After stirring for 10 minutes at room temperature, the reaction mixture was charged with equal amounts of potassium hydroxide and methyl iodide. After a total of 20 minutes, acetone was removed by rotary evaporation and the crude product was chromatographed over silica gel with 15-30% ethyl acetate-hexanes (gradient elution) to obtain **6a** as a yellow solid (0.013 g, 94%), mp 110-112°; ^{1}H nmr (deuteriochloroform): δ 3.85 (s, 3 H), 7.32 (m, 1 H), 7.39 (d, 1

H, J = 9.0 Hz), 7.53 (m, 1 H), 7.64 (m, 2 H), 7.90 (s, 1 H), 7.95 (dd, 1 H, J = 9.4, 1.0 Hz), 8.32 (d, 1 H, J = 9.1 Hz), 8.55 (dd, 1 H, J = 8.7, 1.0 Hz).

Anal. Calcd. for $C_{16}H_{12}N_2 \cdot 0.3H_2O$: C, 80.85; H, 5.34; N, 11.79. Found: C, 80.60; H, 5.52; N, 11.64.

10-Cyclohexymethylindolo[3,2-*b*]quinoline (**6b**).

To a 10 ml round-bottomed flask was added potassium hydroxide (0.040 g), acetone (1.5 ml), quindoline (0.030 g, 0.137 mmole) and cyclohexylmethyl bromide (0.5 ml). After heating to 50° for 1 hour, acetone was removed *via* a rotary evaporation. The crude product was chromatographed over silica gel with 12-20% ethyl acetate in hexanes (gradient elution) to obtain **6b** as yellowish oil (0.037 g, 86%), mp (hydrochloride salt) 235-237°; ^{1}H nmr (deuteriochloroform): δ 1.2-1.4 (m, 7 H), 1.69 (m, 4 H), 4.09 (d, 2 H, J = 7.8 Hz), 7.3 (m, 1 H), 7.39 (d, 1 H, J = 9.2 Hz), 7.47-7.7 (m, 3 H), 7.89 (s, 1 H), 7.95 (dd, 1 H, J = 9.2, 0.9 Hz), 8.33 (d, 1 H, J = 9.3 Hz), 8.56 (d, 1 H, J = 8.8 Hz).

Anal. Calcd. for $C_{22}H_{22}N_2 \cdot HCl \cdot 0.2H_2O$: C, 74.54; H, 6.65; N, 7.90. Found: C, 74.59; H, 6.70; N, 7.82.

10-Benzylindolo[3,2-*b*]quinoline (**6c**).

To a 10 ml round-bottomed flask was added potassium hydroxide (0.030 g), acetone (1.5 ml), quindoline (0.032 g, 0.146 mmole) and benzyl bromide (0.4 ml). After stirring for 1 hour at room temperature, acetone was removed by rotary evaporation. The crude product was chromatographed over silica gel with 15-30% ethyl acetate in hexanes (gradient elution) to obtain **6c** as a yellowish solid (0.045 g, 97%), mp (hydrochloride salt) 248-250°; ^{1}H nmr (deuteriochloroform): δ 5.45 (s, 2 H), 7.1-7.3 (m, 5 H), 7.34 (dd, 2 H, J = 8.6, 8.6 Hz), 7.45-7.70 (m, 3 H), 7.83 (m, 2 H), 8.34 (d, 1 H, J = 9.6 Hz), 8.59 (dd, 1 H, J = 8.8, 1.0 Hz).

Anal. Calcd. for $C_{22}H_{16}N_2 \cdot HCl \cdot 0.3H_2O$: C, 75.44; H, 5.07; N, 8.00. Found: C, 75.44; H, 5.12; N, 7.93.

10-(2'-Phenylethyl)indolo[3,2-*b*]quinoline (**6d**).

To a 10 ml round-bottomed flask was added potassium hydroxide (0.030 g), acetone (1.3 ml), quindoline (0.030 g, 0.137 mmole) and 2-phenylethyl bromide (0.3 ml). After heating to 60° for 1 hour, the reaction mixture was charged with a second portion of equal amounts of potassium hydroxide and 2-phenylethyl bromide. Heating was continued for a total of 2 hours and acetone was removed by rotary evaporation. The crude product was chromatographed over silica gel with 12-20% ethyl acetate in hexanes (gradient elution) to obtain **6d** as yellowish oil (0.030 g, 68%) and converted to the hydrochloride salt, mp 203-206°; ^{1}H nmr (deuteriochloroform): δ 3.15 (t, 2 H, J = 8.0 Hz), 4.51 (t, 2 H, J = 7.9 Hz), 7.1-7.4 (m, 7 H), 7.59 (m, 3 H), 7.69 (s, 1 H), 7.86 (dd, 1 H, J = 8.3, 1.5 Hz), 8.32 (d, 1 H, J = 9.0 Hz), 8.55 (dd, 1 H, J = 9.0, 1.4 Hz).

Anal. Calcd. for $C_{23}H_{18}N_2 \cdot HCl \cdot 0.5H_2O$: C, 75.09; H, 5.48; N, 7.61. Found: C, 75.30; H, 5.51; N, 7.68.

10-Ethoxycarbonylindolo[3,2-*b*]quinoline (**6e**).

To a 10 ml round-bottomed flask was added potassium hydroxide (0.060 g), acetone (1.5 ml), quindoline (0.019 g, 0.087 mmole) and ethyl bromoacetate (0.5 ml). After stirring for 2 hours at room temperature, acetone was removed by rotary evaporation. The crude product was chromatographed over silica gel with 20-40% ethyl acetate in hexanes (gradient elution) to afford **6e** as a yellowish solid (0.023 g, 87%) and converted to the hydrochloride salt, mp 241-243°; ^{1}H nmr (deuteriochloroform): δ 0.98 (t, 3 H, J = 7.7 Hz), 4.18 (q, 2 H, J = 7.8 Hz), 4.96 (s, 2 H), 7.32 (m, 2 H), 7.48-7.68 (m, 3 H), 7.84 (s, 1 H), 7.90 (dd, 1 H, J = 9.3, 1.5 Hz), 8.54 (d, 1H, J = 8.5 Hz), 8.32 (d, 1 H, J = 9.2 Hz).

Anal. Calcd. for $C_{19}H_{16}N_2O_2 \cdot HCl$: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.75; H, 5.11; N, 8.11.

10-Allylindolo[3,2-*b*]quinoline (**6g**).

To a 10 ml round-bottomed flask was added potassium hydroxide (0.030 g), acetone (1.5 ml), quindoline (0.029 g, 0.133 mmole) and allyl bromide (0.3 ml). The solution was stirred for 1 hour at room temperature and the acetone was removed by rotary evaporation. The crude product was chromatographed over silica gel with 13-30% ethyl acetate in hexanes (gradient elution) to obtain **6g** as a yellowish oil (0.031 g, 95%). The hydrochloride salt was prepared and the melting point was determined, mp 253-254°; ^{1}H nmr (deuteriochloroform): δ 4.87 (m, 2 H), 5.13 (m, 2 H), 5.98 (m, 1 H), 7.31 (m, 2 H), 7.48-7.68 (m, 3 H), 7.85 (s, 1 H), 7.90 (d, 1 H, J = 9.5 Hz), 8.33 (d, 1 H, J = 9.7 Hz), 8.56 (d, 1 H, J = 9.2 Hz).

Anal. Calcd. for $C_{18}H_{14}N_2 \cdot HCl$: C, 73.34; H, 5.13; N, 9.50. Found: C, 73.24; H, 5.17; N, 9.46.

5-Allyl-10-methylindolo[3,2-*b*]quinolinium Bromide (**7**).

To a 10 ml round-bottomed flask was added **6a** (0.120 g, 0.517 mmole), allylbromide (1.0 ml) and sulpholane (2.0 ml). The mixture was heated to 95° for 24 hours. After cooled to rt, it was chromatographed with 5-20% methanol in methylene chloride (gradient elution) to yield **7** as yellow solid (0.090 g, 50%), mp 232-234° (recrystallized from methanol-ether); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 4.19 (s, 3 H), 4.76 (d, 1 H, J = 17.4 Hz), 5.28 (d, 1 H, J = 10.8 Hz), 6.20 (m, 2 H), 6.46 (m, 1 H), 7.56 (m, 1 H), 8.01 (m, 3 H), 8.18 (m, 1 H), 8.58 (m, 3 H), 9.68 (s, 1 H).

Anal. Calcd. for $C_{19}H_{17}N_2Br$: C, 64.60; H, 4.85; N, 7.93. Found: C, 64.67; H, 4.90; N, 7.89.

5-Allyl-10-methylindolo[3,2-*b*]quinolinium Bromide (**7**).

Compound **5e** (0.032 g, 0.094 mmole) was basified with concentrated ammonia (30 ml) and extracted with ethyl acetate (3 x 50 ml). The organic layer was separated, washed with water (30 ml), dried (sodium sulfate), and concentrated by rotary evaporation under reduced pressure. The deep reddish solid was dissolved in acetone (60 ml), methyl iodide (1.5 ml) was added and the mixture was refluxed at 70° for 24 hours. After cooling to room temperature, the solvent was removed and the residue was chromatographed over silica gel with 5-20% methanol in methylene chloride (gradient elution) as the eluent to yield **7** (0.025 g, 75%). Melting point and spectral characteristics were identical to that obtained from **6a** above.

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