Synthesis of some Benzo[*h*]quinoline Derivatives

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Reaction between 6-methoxy-1-tetralone, methyl propiolate and an ammonia-saturated methanolic solution led to 5,6-dihydro-8-methoxybenzo[*h*]quinolin-2(1*H*)-one in good yields. Subsequent aromatization, chlorination, substitution and demethylation enabled us to prepare 2-amino-substituted benzo[*h*]quinoline derivatives. These compounds, which are structurally related to the antitumor benzo[*c*]phenanthridine alkaloids by deletion of a ring, were tested on cultured murine lymphoblastic leukaemia cells (L1210). Results showed that they are devoid of cytotoxicity.

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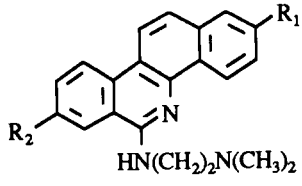
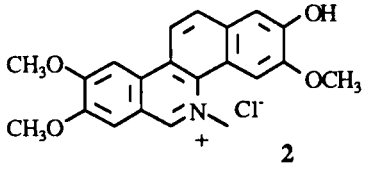
In the course of our research on new antitumor heterocyclic derivatives, we recently synthesized the benzo[*c*]-phenanthridine derivatives **1a-b** [1], as analogs of the antitumor [2] and antiviral [3] alkaloid Fagaronine **2**. These two derivatives displayed a significant cytotoxicity with an IC_{50} of 0.5 μM on L1210 cells and compound **1a** only was weakly active in the *in vivo* P388 murine model.

In order to further study the structure-activity relationship of these series, we undertook the synthesis of 2-substituted benzo[*h*]quinolines **3a-d**, structurally related to the former ring system by deletion of ring A.



1a : $R_1 = OH$, $R_2 = OH$
1b: $R_1 = OH$, $R_2 = H$



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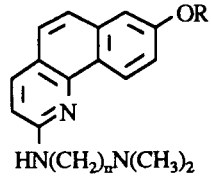


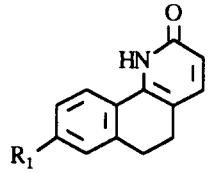
3a : R = CH_3, n = 2
3b : R = CH_3, n = 3
3c : R = H, n = 2
3d : R = H, n = 3

Although literature reports that some derivatives of benzo[*h*]quinoline display a central nervous system action [4-5], little has been published about the preparation [6-11] and properties of this heterocycle. Recently, the preparation of 5,6-dihydrobenzo[*h*]quinolin-2(1*H*)-one (**4a**) has been achieved through the Michael addition of 1-tetralone (**5a**) on methyl propiolate and concomitant cyclisation in an ammonia-saturated medium at 100° [12]. However, this communication did not mention the yield obtained in this case.

In our hands, starting with 6-methoxytetralone (**5b**) and using the reported conditions, 8-methoxy-5,6-dihydrobenzo[*h*]quinolin-2(1*H*)-one (**4b**) was obtained in a 10% yield. By increasing the temperature to 135°, the yield rose to 46% and at the highest possible temperature (150°), compound **4b** was obtained in a 72% yield (Scheme 1).

Scheme 1

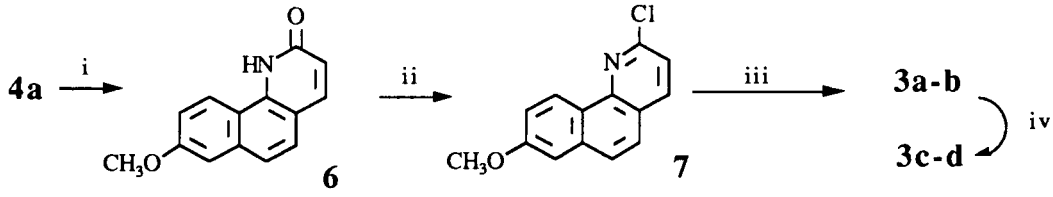
5 a $R_1 = H$
5 b $R_1 = CH_3O$



4 a $R_1 = H$
4 b $R_1 = CH_3O$

Four complementary steps allowed us to achieve the synthesis of the projected analogs: (i) aromatization, performed with 10% Pd/C in boiling diphenyl ether, to give compound **6**. (ii) Chlorination of **6** turned out to be rather difficult. When using either phosphorus oxychloride or an-

Scheme 2



i : Pd/C, diphenyloxyde, Δ. ii : $PhPOCl_2$, 160°C. iii : $Me_2N(CH_2)_nNH_2$, Δ. iv : HBr 47%, Δ.

other method generally proven to be more efficient [13] yields were in the 10-15% range. However the use of phenylphosphonic dichloride at 160° led to compound **7** in a 68% yield. (iii) Substitution of **7** gave **3a-b** and (iv) demethylation gave **3c-d**. These last two transformations were performed under the usual conditions (Scheme 2).

Cytotoxicity of the bismaleic salts of compounds **3a-d** were measured on L1210 cultured cells. Except compound **3c** which displayed an IC_{50} of 5 μM, these compounds were inactive at 10 μM concentration.

In conclusion, reaction of 6-methoxy-1-tetralone, methyl propiolate and ammonia at 150° provides an improved procedure for the preparation of the benzo[*h*]quinolines from readily available compounds which could be useful for further pharmacological investigation of this ring system. Unfortunately, the new benzo[*h*]quinolines synthesized which are related to the cytotoxic benzo[*c*]phenanthridines derivatives **1a-b** we recently prepared are devoid of significant cytotoxicity.

EXPERIMENTAL

Melting points are uncorrected, ^1H nmr spectra were recorded on a Bruker AC-200 MHz spectrometer in deuteriochloroform, unless stated otherwise. Chemical shifts are reported in parts per million relative to tetramethylsilane as the internal standard. Elemental analyses were performed by the Service Central de Micronalyses (ICSN-CNRS, Gif-sur-Yvette, France) on the isolated products. Pure commercially available solvents were used, without further treatment. Compounds **3a-d** were tested on cultured murine lymphoblastic leukaemia cells (L1210), using the usual conditions. The cells were counted after 48 hours of incubation with the drugs.

5,6-Dihydro-8-methoxybenzo[*h*]quinolin-2(1*H*)-one (**4**).

6-Methoxy-1-tetralone (10.56 g, 0.06 mole) and methyl propiolate (10 g, 0.12 mole) were mixed in an ammonia-saturated methanol solution (190 ml) in a 500 ml stainless steel vessel (maximum pressure 300 atomospheres). The reaction was heated at 150° with shaking for 14 hours. After cooling, the crude mixture was evaporated to dryness, diluted with methylene chloride, filtered, concentrated again and recrystallized twice from toluene. Thus 9.8 g (72%) of **4** was obtained as yellow crystals, mp 220°; ^1H nmr: δ 2.66 (m, 2H, H-6), 2.8 (m, 2H, H-5), 3.84 (s, 3H, OCH_3), 6.47 (d, 1H, J = 9.0 Hz, H-3), 6.77 (d, 1H, J = 2.6 Hz, H-7), 6.92 (dd, 1H, J = 2.6 Hz, 8.7, H-9), 7.34 (d, 1H, J = 9.0 Hz, H-4), 7.95 (d, 1H, J = 8.7 Hz, H-10).

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.00; H, 5.50; N, 5.90.

8-Methoxybenzo[*h*]quinolin-2(1*H*)-one (**6**).

Compound **4** (16.29, 0.072 mole) was heated in boiling phenyl ether (100 ml) in the presence of 10% Pd on charcoal (3.8 g) during 40 minutes. The reaction mixture was then evaporated to dryness and the residue was extracted repeatedly with boiling xylene. The filtered organic solution was concentrated to a 100 ml volume and left to crystallize, yielding 13.1 g (81%) of **6** as pale yellow crystals, mp 280°; ^1H nmr (DMSO-d_6): δ 3.90 (s, 3H, OCH_3), 6.54 (d, 1H, J = 9.3 Hz, H-3), 7.25 (dd, 1H, J = 2.6, 9.2 Hz, H-9), 7.41 (d, 1H, J = 2.6 Hz, H-7), 7.55 (d, 1H, J = 8.6 Hz, H-6), 7.63 (d, 1H, J = 8.6 Hz, H-5), 7.98 (d, 1H, J = 9.3 Hz, H-4), 8.79 (d, 1H, J = 9.2 Hz, H-10), 12.03 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.80; H, 5.10; N, 6.30.

2-Chloro-8-methoxybenzo[*h*]quinoline (**7**).

Compound **6** (6 g, 26.4 mmoles) was dissolved under an inert atmosphere in phenylphosphonic dichloride (60 ml, 0.42 mole) and heated in an oil bath at 160° for 2.5 hours. The mixture is then poured on crushed ice (250 g), basified with concentrated ammonia and left to precipitate. The solid obtained was filtered, washed with water, dried and chromatographied on alumina (neutral, 5% water) eluting with cyclohexane. After concentration and recrystallization in hexane, 4.4 g (68%) of **7** were obtained as fine needles, mp 100°; ^1H nmr: δ 3.94 (s, 3H, OCH_3), 7.21 (d, 1H, J = 2.6 Hz, H-7), 7.31 (dd, 1H, J = 2.6 Hz, 9.1, H-9), 7.39 (d, 1H, J = 8.4 Hz, H-3), 7.60 (d, 1H, J = 8.8 Hz, H-6), 7.70 (d, 1H, J = 8.8 Hz, H-5), 8.03 (d, 1H, J = 8.4 Hz, H-4), 9.07 (d, 1H, J = 9.1 Hz, H-10).

Anal. Calcd. for $C_{14}H_{10}ClNO$: C, 69.00; H, 4.16; N, 6.16; Cl, 14.55. Found: C, 69.00; H, 4.10; N, 5.80; Cl, 14.80.

Compounds **3a-b**.

The chlorinated compound **9** (0.5 g, 2 mmoles) was dissolved in the required amine (5 ml) and heated at boiling temperature under an inert atmosphere for a 24 hour period. The crude mixture was evaporated to dryness, dissolved in methylene chloride, washed with water, dried (sodium carbonate) and evaporated to dryness. The crude crystals obtained were recrystallized from hexane to yield the corresponding bases. The bismaleic salts were obtained by adding an acetone solution of the bases to maleic acid (2.1 equivalents) dissolved in dry acetone. The salts were precipitated upon standing, filtered, washed with dry acetone and air dried.

8-Methoxy-2-{[2-(dimethylamino)ethyl]amino}benzo[*h*]quinoline (**3a**).

This compound was obtained in 76% yield, mp 104°; ^1H nmr: δ

2.36 (s, 6H, $N(CH_3)_2$), 2.71 (t, 2H, J = 6.2 Hz, CH_2-2'), 3.74 (m, 2H, CH_2-1'), 3.95 (s, 3H, OCH_3), 5.40 (s, 1H, NH), 6.67 (d, 1H, J = 8.6 Hz, H-3), 7.17 (d, 1H, J = 2.5 Hz, H-7), 7.23 (dd, 1H, J = 2.5, 8.8 Hz, H-9), 7.42 (d, 1H, J = 8.6 Hz, H-6), 7.50 (d, 1H, J = 8.6 Hz, H-5), 7.80 (d, 1H, J = 8.6 Hz, H-4), 9.03 (d, 1H, J = 8.8 Hz, H-10). Bismaleic salts of **3a**, mp 146°.

Anal. Calcd. for $C_{26}H_{29}N_3O_9$: C, 59.2; H, 5.54; N, 7.97. Found: C, 59.30; H, 5.50; N, 7.80..

8-Methoxy-2-{[3-(dimethylamino)propyl]amino}benzo[*h*]quinoline (**3b**).

This compound was obtained in 77% yield, mp 83°; ^1H nmr: δ 1.94 (m, 2H, CH_2-2'), 2.32 (s, 6H, $N(CH_3)_2$), 2.54 (t, 2H, J = 6.8 Hz, CH_2-3'), 3.69 (m, 2H, CH_2-1'), 3.95 (s, 3H, OCH_3), 5.55 (s, 1H, NH), 6.64 (d, 1H, J = 8.7 Hz, H-3), 7.17 (d, 1H, J = 2.6 Hz, H-7), 7.22 (dd, 1H, J = 2.6, 8.8 Hz, H-9), 7.41 (d, 1H, J = 8.7 Hz, H-6), 7.49 (d, 1H, J = 8.7 Hz, H-5), 7.79 (d, 1H, J = 8.7 Hz, H-4), 9.03 (d, 1H, J = 8.8 Hz, H-10). Bismaleic salts of **3b**, mp 127°.

Anal. Calcd. for $C_{27}H_{31}N_3O_9$: C, 59.88; H, 5.77; N, 7.76. Found: C, 58.80; H, 5.70; N, 7.60.

Compounds **3c-d**.

The bases **3a-b** (1.6 mmoles) were dissolved in 47% hydrobromic acid (20 ml) and heated at reflux for 3 hours. The mixture was evaporated to dryness, dissolved in 5% aqueous sodium hyroxide (30 ml), washed with methylene chloride and the aqueous layer was then acidified with 35% hydrochloric acid. The suspension which appeared after basification with 33% aqueous ammonia was extracted with methylene chloride. This organic layer was washed once with water, dried (sodium carbonate) and evaporated to dryness. The gummy solids obtained were characterized as crystalline bismaleic salts.

Bismaleate of 8-Hydroxy-2-{[2-(dimethylamino)ethyl]amino}benzo[*h*]quinoline (**3c**).

This compound was obtained in 83% yield, mp 170°; ^1H nmr (DMSO-d_6): δ 2.93 (s, 6H, $N(CH_3)_2$), 3.46 (m, 2H, CH_2-2'), 3.92 (m, 2H, CH_2-1'), 6.19 (s, 4H, maleate), 6.81 (d, 1H, J = 8.7 Hz, H-3), 7.18 (m, 3H, H-7, H-9, OH), 7.43 (d, 1H, J = 8.7 Hz, H-6), 7.58 (d, 1H, J = 8.7 Hz, H-5), 7.96 (d, 1H, J = 8.7 Hz, H-4), 8.89 (d, 1H, J = 9.6 Hz, H-10).

Anal. Calcd. for $C_{25}H_{27}N_3O_9$: C, 58.47; H, 5.30; N, 8.18. Found: C, 58.20; H, 5.10; N, 8.00.

Bimaleate of 8-Hydroxy-2-{[3-(dimethylamino)propyl]amino}benzo[*h*]quinoline (**3d**).

This compound was obtained in 62% yield, mp 143°; ^1H nmr (DMSO-d_6): δ 2.08 (m, 2H, CH_2-2'), 2.83 (s, 6H, $N(CH_3)_2$), 3.25 (m, 2H, CH_2-3'), 3.63 (m, 2H, CH_2-1'), 6.21 (s, 4H, maleate), 6.78 (d, 1H, J = 8.7 Hz, H-3), 7.17 (m, 3H, H-7, H-9, OH), 7.39 (d, 1H, J = 8.7 Hz, H-6), 7.55 (d, 1H, J = 8.7 Hz, H-5), 7.91 (d, 1H, J = 8.7 Hz, H-4), 8.89 (d, 1H, J = 9.5 Hz, H-10).

Anal. Calcd. for $C_{26}H_{29}N_3O_9 \cdot H_2O$: C, 57.24; H, 5.73; N, 7.70. Found: C, 57.60; H, 5.60; N, 7.60.

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