Preparation of Benzo[g]quinolines from 1-Methyl-5,6-dimethoxy-2-naphthylamine (1)

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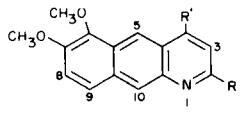
As a part of a program of preparation of antimalarial agents, it was necessary to investigate methods of synthesis of benzo[*g*]quinolines (**1**) having methoxy groups at positions 6 and 7, with a provision for variation of the substituent at the 2-position, and with a group at position 4 which would allow further elaboration of that position.



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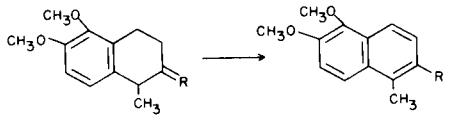
2-Naphthylamine participates in a variety of cyclization reactions leading to benzoquinolines (3); however, most of these reactions lead to the angularly annelated benzo[*f*]quinolines through cyclization into the 1-position of the 2-naphthylamine. Even when the 1-position was blocked with halogen or nitro groups, it was found, with few exceptions (4), that cyclization afforded benzo[*f*]-quinolines (5) or mixtures of benzo[*f*]- and benzo[*g*]-quinolines (6). The known (7,8) efficacy of a methyl blocking group prompted our selection of 1-methyl-2-aminonaphthalene derivatives as intermediates in the synthesis of benzo[*g*]quinoline derivatives.

1-Methyl-5,6-dimethoxy-2(1*H*)naphthalenone (**3**) (9) was aromatized to the phenol **4**, but this could not be converted to the naphthylamine **2** by a Bucherer reaction. The oxime **5** of **3** was converted directly to the amine **2** by an extremely useful general method developed by Rosen and Green (10).



3 R = O
5 R = NOH

4 R = OH
2 R = NH_2

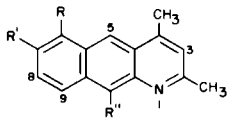
The relative ease of preparation of 1-methyl-2-tetralones and the good yields realized in their conversion into 1-methyl-2-naphthylamines demonstrates a method of potentially great synthetic utility, which may be applicable to a variety of 2-naphthylamines.

Only tars were obtained when **2** was subjected to the conditions of the Doebner pyruvic acid reaction, and no improvement (11) was obtained by use of the benzylidene derivative of the amine.

While Johnson, *et al.* (8,12) were able to use ultraviolet spectroscopy to demonstrate that a benzo[*g*]quinoline derivative is formed when 2-naphthylamine is used in a Combes synthesis, it is clear from the work of Clemo and Legg (13) that such evidence is not unambiguous. Fortunately, it is now clear that the nmr spectra of benzo[*g*]-quinolines are readily distinguishable from those reported (14,15) for benzo[*f*]- and benzo[*h*]quinolines. Table I lists chemical shifts of the aromatic protons of some benzo[*g*]quinolines. The signal at δ 7.20 of the spectrum of compound **6** was assigned to the proton at position 8, because of the shielding effect of the methoxyl groups; it then follows that the δ 8.00 signal represents the proton at position 9. The relative positions of the protons at 5 and 10 in compounds **7** and **8** was proposed on the basis

TABLE I

Chemical Shifts of the Aromatic Protons of Some Benzo(*g*)quinoline Products of Combes Cyclizations (a)



6 R = R′ = OMe; R″ = Me
7 R = R″ = H; R′ = OMe
8 R = R′ = R″ = H

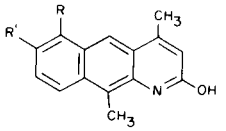
	Compound **6**	Compound **7**	Compound **8**
H_3	s, δ 7.03	s, 7.05	s, 7.01
H_5	s, 8.50	s, 8.23	s, 8.40
$H_{6,7,8,9}$			m, 7.40 and 7.98
H_{10}		s, 8.50	s, 8.58
$H_{6,8}$		m, 7.10	
H_9	d, 8.00	d, 7.96	
H_8	d, 7.20		

(a) Signal positions are measured from the center of the multiplet.

of molecular orbital calculations (16,17), which indicate that position 5 is more electron-rich than 10; thus, the proton at 5 would be expected to be more shielded than the one at 10. The ultraviolet spectra for **6** and **7** are quite similar to that reported (8,12) for compound **8**.

TABLE II

Chemical Shifts of the Aromatic Protons of Some Benzo(g)quinoline Products of Knorr Cyclizations (a)



9 R = R′ = OMe
10 R = R′ = H

	Compound **9**	Compound **10**
H_3	s, δ 6.56	s, 7.15
H_5	s, 8.45	s, 8.50
H_8	d, 7.45	
H_9	d, 7.80	
$H_{6,7}$		m, 7.70
$H_{8,9}$		m, 8.17

(a) Signal positions are measured from the center of the multiplet.

Huisgen (7) converted 1-methyl-2-naphthylamine to a benzo[*g*]quinoline *via* a Knorr reaction, but he did not report spectral data. In the present work, 1-methyl-2-acetoacetylaminonaphthalene and its 5,6-dimethoxy congener were cyclized with concentrated sulfuric acid. Chemical shifts of the aromatic protons of the Knorr products, assigned by analogy with the data on the Combes products (Table I), are shown in Table II. The difference in positions of the H_3 signal for compounds **9** and **10** is probably referrable to the fact that chloroform was the solvent for **9**, whereas trifluoroacetic acid was the solvent for **10**.

EXPERIMENTAL

Boiling points are uncorrected. Melting points are uncorrected and were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Nuclear magnetic resonance spectra were recorded with a Varian Associates T-60 instrument at 60 Mc. relative to an internal standard of tetramethylsilane. Infrared spectra were obtained on Beckman IR 5A and IR 10 spectrophotometers. Ultraviolet spectra were recorded on a Beckman DK-2 instrument.

1-Methyl-5,6-dimethoxy-2(1*H*)naphthalenone (**3**).

This was prepared by the procedure of Elmore and King (9), except that the 2,3-dimethoxycinnamic acid intermediate was reduced to β-(2,3-dimethoxyphenyl) propionic acid in quantitative yield, using 5% palladium on charcoal at an initial pressure of 10.8 Kg./cm^2. b.p. of **3**, 125-127° (2 mm.) [lit. (9) b.p. 115-116° (2mm.)].

1-Methyl-5,6-dimethoxy-2-naphthol (**4**).

Compound **3** (10.04 g., 0.045 mole) in 100 ml. of practical grade mesitylene was refluxed and stirred with 2.0 g. of 10% palladium on charcoal for 96 hours while a stream of carbon dioxide was passed through the reaction mixture. Upon cooling to room temperature, a large amount of material crystallized; this was collected on a filter and was treated with acetone to separate the product from the catalyst. Removal of the acetone under reduced pressure gave light tan crystals. The mesitylene filtrate was extracted with 5% aqueous sodium hydroxide and this extract was washed with ether. Addition of solid carbon dioxide to the basic extract induced formation of a solid which was combined with the product of the acetone wash, and the combined material was recrystallized from xylene to give 7.65 g. (76%) of light brown crystals. An analytical sample was recrystallized from ethanol-water, m.p. 138-139°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.50; H, 6.42. Found: C, 71.42; H, 6.51.

1-Methyl-5,6-dimethoxy-2(1*H*)naphthalenone Oxime (**5**).

A procedure of Nelson and Sinclair (18) was utilized. Compound **3** (9.21 g., 0.042 mole) in 50 ml. of methanol was added slowly with stirring to an ice cold solution of 2.94 g. (0.042 mole) of hydroxylamine hydrochloride and 3.15 g. (0.023 mole) of potassium carbonate in 50 ml. of 50% aqueous methanol. After two hours stirring, the crystalline oxime was collected on a filter; additional product was obtained by diluting the reaction solution with water. The oil which separated was taken up in ether, this solution was dried over sodium sulfate, and the oxime hydrochloride was precipitated with anhydrous hydrogen chloride. The solid salt was washed with ether, was dissolved in water, and the free oxime was precipitated with 5% sodium bicarbonate solution. The combined product (8.33 g., 85%) was sufficiently pure for the next step. An analytical sample was recrystallized from hexane, m.p. 138-139°; nmr (deuteriochloroform) δ 1.36 (s, 1H): 1.56 (s, 2H); 2.96 (m, 4H); 3.53 (m, 1H); 3.64 (m, 1H); 3.88 (s, 3H); 3.95 (s, 3H); 6.9 (d, 2H).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.38; H, 7.23; N, 5.96. Found: C, 66.75; H, 7.41; N, 5.94.

1-Methyl-5,6-dimethoxy-2-naphthylamine (**2**).

Compound 5 (0.94 g., 0.004 mole) was refluxed for 1 hour in 40 ml. of methanol which had been saturated with anhydrous hydrogen chloride. The methanol was then removed, the residue was dissolved in water, and the free amine was precipitated with excess 5% aqueous sodium bicarbonate. The product was collected on a filter, dried under reduced pressure, and chromatographed on silica gel and eluted with benzene-ethyl acetate (85:15). Yield, 0.61 g. (66%) of red crystals, m.p. 148-149°; nmr (deuteriochloroform δ 2.4 (s, 3H); 3.34 (broad s, 2H); 4.00 (d, 6H); 7.2 (m, 4H).

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.90; H, 6.92; N, 6.45. Found: C, 71.76; H, 6.87; N, 6.30.

N-Benzal-1-methyl-5,6-dimethoxy-2-naphthylamine (**11**).

Benzaldehyde (3.2 g., 0.03 mole) and 2.29 g. (0.01 mole) of **2** were refluxed in 10 ml. of anhydrous ethanol for 2 hours. Upon cooling, the Schiff base product crystallized; it was recrystallized

from 95% ethanol to afford 2.7 g. (84%) of a yellow solid, m.p. 114-115°; ir (chloroform) 1630 cm^{-1} (C=N); nmr (deuteriochloroform) δ 2.7 (s, 3H); 3.98 (s, 3H); 4.00 (s, 3H); 7.4 (m, 4H); 7.9 (m, 4H); 8.47 (s, 1H). A sample for analysis was prepared by sublimation.

Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.69; H, 6.23; N, 4.59. Found: C, 78.52; H, 6.26; N, 4.47.

1-Methyl-2(1*H*)naphthalenone (**12**).

This was prepared in 41% yield by the procedure of Elmore and King (9), beginning with 1-(2*H*)naphthalenone (Aldrich Chemical Co.) b.p. 126° (6 mm.) [lit. (19) b.p. 138-142° (20 mm.)].

1-Methyl-2-naphthylamine (**13**).

This was prepared as described for **2**, except that the crude, oily oxime was treated with methanolic hydrogen chloride without purification, yield, 10.1 g. (63%), m.p. 47° (hexane), [lit. (8) m.p. 49-50°].

N-Benzal-1-methyl-2-naphthylamine (**14**).

This was prepared in 78% yield as described for **11**, and it was purified by sublimation at room temperature, m.p. 88-90°; ir (chloroform) 1630 cm^{-1} (C=N); nmr (deuteriochloroform) δ 2.76 (s, 3H); 7.60 (m, 11H); 8.45 (s, 1H).

Anal. Calcd. for $C_{18}H_{15}N$: C, 88.16; H, 6.12; N, 5.71. Found: C, 87.96; H, 6.22; N, 5.63.

4-(1-Methyl-5,6-dimethoxy-2-naphthylimino)pentanone-2 (**15**).

Compound **2** (1.0 g., 0.0046 mole) was refluxed in 5 ml. of pentane-2,4-dione (Aldrich Chemical Co.) in the presence of several pieces of Drierite for 2 hours, then the excess pentane-2,4-dione was removed by distillation. The solid residue was recrystallized from ether to afford 0.910 g. (68%) of material, m.p. 91.5-93°; ir (chloroform) 1660 cm^{-1} (C=N); nmr (deuteriochloroform) δ 1.82 (s, 3H); 2.21 (s, 3H); 2.57 (s, 3H); 4.00 (s, 6H); 5.25 (s, 1H); 7.09-8.03 (m, 5H).

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.24; H, 7.02; N, 4.69. Found: C, 71.99; H, 7.02; N, 4.57.

2,4,10-Trimethyl-6,7-dimethoxybenzo[*g*]quinoline (**6**).

A solution of 0.75 g. (0.0025 mole) of **15** in 5 ml. of concentrated sulfuric acid was stirred for 2 minutes while immersed in an ice bath. The mixture was then stirred at 60° for 3 minutes, and the green solution was poured over ice, whereupon it turned red. Excess 10% aqueous sodium hydroxide was added; the mixture turned a deep blue-green and a solid separated. The entire mixture was extracted with ether in a liquid/liquid extractor, and the ethereal extract was dried over magnesium sulfate. Removal of the ether afforded a yellow solid which was chromatographed on silica gel and eluted with benzene. Fractions which showed the same R_f value on thin layer chromatographic analysis were combined; the solvent was removed and the residue was recrystallized from hexane to yield 0.220 g. (29%) of product, m.p. 110-111°, λ max (ethanol) 260 mμ; nmr (deuteriochloroform) δ 2.72 (s, 3H); 2.75 (s, 3H); 3.25 (s, 3H); 4.02 (s, 3H); 4.10 (s, 3H); 7.07 (s, 1H); 7.20 (d, 1H); 8.10 (d, 1H); and 8.50 (s, 1H).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98. Found: C, 76.79; H, 6.60; N, 4.83.

2,4-Dimethylbenzo[*g*]quinoline (**8**).

This was prepared in 66% yield by method (b) of Johnson and Matthews (8), m.p. 92-93°, [lit. (8) m.p. 92-93°]; nmr (deuteriochloroform) δ 2.7 (s, 6H); 7.1 (s, 1H); 7.4 (m, 2H); 7.92 (m, 2H); 8.40 (s, 1H); 8.58 (s, 1H).

6-Methoxy-2-naphthol (**16**).

To a refluxing solution of 21.6 g. (0.078 mole) of 6-hydroxy-2-naphthyl benzoate (20) and 42.5 g. (0.38 mole) of potassium carbonate in 240 ml. of reagent grade acetone was slowly added 18 ml. (0.11 mole) of dimethyl sulfate. The reaction mixture was refluxed overnight; it was then poured over ice and the solid which separated was dissolved in 100 ml. of methanol, and 11.5 g. (0.21 mole) of potassium hydroxide in 40 ml. of water was slowly added to this solution. It was refluxed for 5 minutes, poured into an excess of water, and the solid which separated was dried under reduced pressure. Recrystallization from ethanol-water gave 5.95 g., (41%) of colorless crystals, m.p. 148-149°, [lit. (21) m.p. 150-151°].

6-Methoxy-2-naphthylamine (**17**).

Concentrated ammonium hydroxide (27.4 ml.), 5.95 g. (0.034 mole) of **16**, and 6.45 g. (0.062 mole) of sodium bisulfite were heated at 160° with shaking in a bomb for 48 hours. The granular contents of the bomb were extracted with ether in a Soxhlet apparatus. The ether extract was concentrated and the residue was extracted with petroleum ether in a Soxhlet apparatus. When this extract was cooled, red crystals were deposited which were recrystallized from petroleum ether to give 3.75 g. (63%) of red crystals, m.p. 153°, [lit. (22) m.p. 156-157°].

4-(6-Methoxy-2-naphthylamino)pentanone-2 (**18**).

This was prepared in 57% yield as described for **15**, and was recrystallized from hexane (charcoal), m.p. 79-80°; ir (chloroform) 1610 cm^{-1} (C=N); nmr (deuteriochloroform) δ 2.00 (s, 3H); 2.1 (s, 3H); 3.89 (s, 3H); 5.24 (s, 1H); 7.40 (m, 6H); and 12.7 (broad s, 1H).

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.67; N, 5.49. Found: C, 75.28; H, 6.70; N, 5.37.

2,4-Dimethyl-7-methoxybenzo[*g*]quinoline (**7**).

This was prepared in 66% yield by the method described for **6**, except that the chromatography step was omitted. The crude solid product was recrystallized from hexane to yield 0.33 g. of yellow crystals, m.p. 139-141°; λ max (ethanol) 265 mμ nmr (deuteriochloroform) δ 2.67 (s, 6H); 3.94 (s, 3H); 7.05 (s, 1H); 7.10 (m, 2H); 7.96 (d, 1H); 8.23 (s, 1H); 8.50 (s, 1H).

Anal. Calcd. for $C_{16}H_{15}NO$: C, 81.01; H, 6.33; N, 5.91. Found: C, 81.26; H, 6.42; N, 5.80.

2-Hydroxy-4,10-dimethylbenzo[*g*]quinoline (**10**).

This was prepared by the sulfuric acid method of Huisgen (7), m.p. 251-252°, [lit. (7) m.p. 253°]; ir (chloroform) 3410 cm^{-1} (NH) and 1660 (C=O); nmr (trifluoroacetic acid) δ 2.90 (s, 3H); 2.93 (s, 3H); 7.1 (s, 1H); 7.70 (m, 2H); 8.17 (m, 2H); 8.50 (s, 1H).

N-Acetoacetyl-1-methyl-5,6-dimethoxy-2-naphthylamine (**19**).

Compound **2** (1.0 g., 0.0046 mole) was heated for 2 hours at 100° with ethyl acetoacetate. The excess ester was then removed under reduced pressure, and the residual solid was washed with ether, then was recrystallized from methanol to give 0.810 g. (58%) of a light brown powder, m.p. 145-146.5°; ir (potassium bromide) 3200 cm^{-1} (NH) and 1710 (C=O).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.77; H, 6.31; N, 4.65. Found: C, 67.86; H, 6.21; N, 4.62.

2-Hydroxy-4,10-dimethyl-6,7-dimethoxybenzo[*g*]quinoline (**9**).

Compound **19** (0.400 g., 0.0013 mole) was permitted to stand in 5 ml. of concentrated sulfuric acid at room temperature for

0.25 hour, then the green solution was poured over ice. The resulting mixture was basified with ammonium hydroxide and this mixture was extracted with chloroform; the extract was dried over sodium sulfate and the solvent was removed to leave a yellow-green powder which was recrystallized from methanol-water to give 0.150 g. (39%) of material, m.p. 225° dec., ir (chloroform) 3420 cm^{-1} (NH) and 1660 (C=O); nmr (deuteriochloroform) δ 2.66 (d, 6H); 4.03 (d, 6H); 6.56 (s, 1H); 7.26 (s, 1H); 7.45 (d, 1H); 7.80 (d, 1H); 8.14 (s, 1H).

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.01; N, 4.95. Found: C, 71.90; H, 6.03; N, 4.93

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(1) This work was performed, in part, under Contract DA-49-193-2944 with the U.S. Army Medical Research and Service Command, Office of the Surgeon General, under the Army Research Program on Malaria.

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