N-Alkyl Derivatives of *trans*-6,7-Dihydroxy-1,2,3,4,4a,5,10,10b-octahyrobenzo[*g*]quinoline A Congener of Apomorphine Lacking the Non-Oxygenated Aromatic Ring

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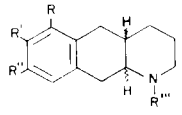
A synthetic sequence leading to the title compounds began with methyl 5,6-dimethoxy-2-tetralone-3-carboxylate and involved a multi-step construction of the heterocyclic ring. The *trans*-fused isomer was isolated from the cyclization step. However, the possibility of formation of some *cis*-fused isomer cannot be precluded.

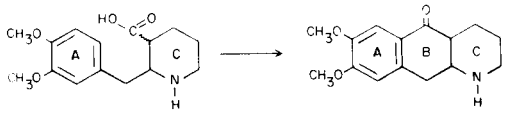
J. Heterocyclic Chem., **17**, 1633 (1980).

The literature reveals a paucity of accounts of synthesis of linear octahydrobenzoquinolines **1** bearing oxygen substituents on the aromatic ring. Walsh and Smissman (**1**) prepared a *trans*-7,8-dimethoxy system (**1**: R = R‴ =



1

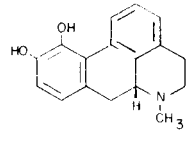
H; R′ = R″ = OCH_3) by a strategy involving formation of the linear tricyclic system by closure of the saturated carbocyclic B ring (**2** → **3**):



2 3

It was proposed that the cyclization reagent used (polyphosphoric acid) provided only the *trans*-fused ring system.

Preparation of methoxyl group positions isomers of **3** (*e.g.*, **1**: R = R′ = OCH_3; R″ = H; R‴ = H or alkyl) seemed of interest, in that such systems are congeners of the potent pharmacologic agent apomorphine **4**, lacking the non-oxygenated aromatic (D) ring.



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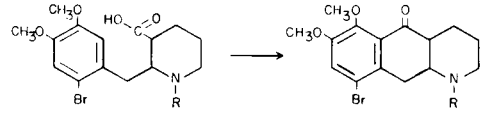
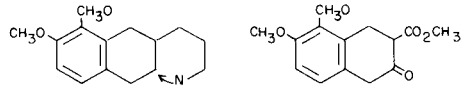
When a modification of the Walsh-Smissman synthetic route was considered for the 6,7-dimethoxy position isomer system described above, it seemed necessary to introduce a bromo substituent onto position 6 of the benzene ring (structure **5**) to direct cyclization into the sterically less favored ortho position (**5** → **6**) and prevent the alternate cyclization to produce system **3** (2).



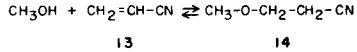
5 6

This cyclization provided extremely poor (less than 5%) yields of tricyclic material, which was not homogeneous; the cyclizing reagent appeared to effect partial cleavages of the methyl ether groups (2). These defects in the synthetic method, coupled with the considerable number of steps contemplated to be necessary to convert the bromo ketone **6** into the target compounds, led to a search for an alternate synthetic route. The possibility of a method in which a tetralin derivative **7** could be utilized in construction of the piperidine ring C was investigated.



7 8

A prior communication (3) from this laboratory described a practical synthesis for 5,6-dimethoxy-3-carbomethoxy-2-tetralone **8**. This compound was used as the starting material for preparation of *trans*-6,7-dimethoxyoctahydrobenzo[*g*]quinoline, as shown in Scheme I. In the Michael reaction of **8** with acrylonitrile, methanol was included in the reaction mixture, to take advantage of the equilibrium reaction between primary alcohols and acrylonitrile (**13** → **14** (4).

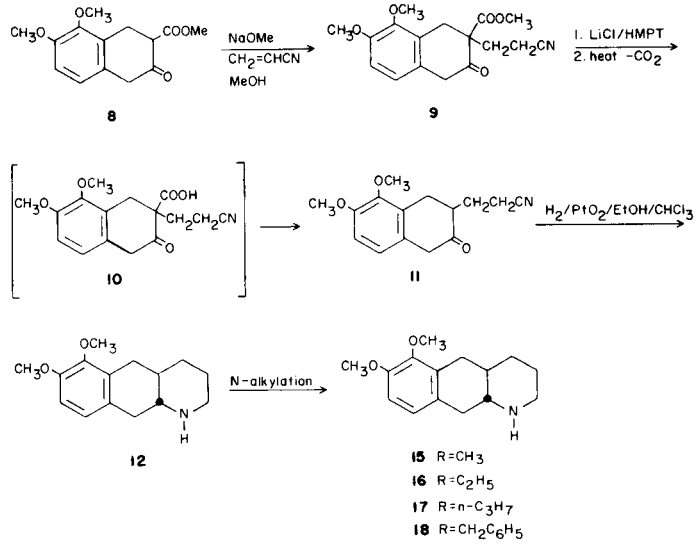


13 14

Compound **14** liberates small amounts of acrylonitrile for the Michael reaction, but high concentrations of free acrylonitrile are avoided, thus minimizing polymerization of the acrylonitrile. Rigorous exclusion of oxygen was necessary in the Michael reaction, to prevent aromatization of the β-keto ester **8** in the presence of base. The ester

0022-152X/80/071633-04$02.25

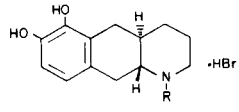
Scheme I
Preparation of trans-6,7-Dimethoxy-1,2,3,4,4a,5,10,10b-octahydrobenzo[g]quinoline



group of **9** was cleaved, preliminary to *in situ* decarboxylation, using a nucleophile reagent rather than an acid- or base catalyzed ester hydrolysis. Sodium cyanide/hexamethylphosphoric triamide ("HMPT") reagent induced ester cleavage of **9**, but the product was always heavily contaminated by products of side reactions. The use of lithium chloride/HMPT required a longer reaction time, but the reaction seemed cleaner. However, results with this latter reagent combination were inconsistent and capricious. The free carboxylic acid **10** could not be isolated, but the decarboxylated system **11** was obtained from the ester cleavage reaction mixture. This was reductively cyclized to afford a poor yield of the tricyclic product **12** (10% overall, from **8**). The material isolated from this reaction mixture was found to be the *trans*-fused isomer (*vide infra*), and all attempts to isolate *cis*-fused product failed. However, it cannot be stated that only *trans*-ring fusion occurred in conversion of **11** to **12**. The *trans*-stereochemistry of **12** was established by noting the presence of strong "Bohlmann bands" in the 2700-2900

Table I

trans-6,7-Dihydroxy-1,2,3,4,4a,5,10,10b-octahydrobenzo[*g*]quinoline Derivatives



Compound No.	R	Yield, %	M.p. °C (a)	Formula	Analysis Calculated	Found
19	H	82	>300	$C_{13}H_{18}BrNO_2$	C 52.00 H 6.04 N 4.66	C 51.96 H 5.98 N 4.62
20	CH_3	65	307-310	$C_{14}H_{20}BrNO_2$	C 53.51 H 6.42 N 4.46	C 53.61 H 6.29 N 4.48
21	C_2H_5	88	>300	$C_{15}H_{22}BrNO_2$	C 54.88 H 6.71 N 4.27	C 54.93 H 6.66 N 4.25
22	*n*-C_3H_7	95	>300	$C_{16}H_{24}BrNO_2$	C 56.13 H 7.06 N 4.09	C 56.28 H 7.22 N 4.00

(a) From methanol-ether.

cm^{-1} region of the infrared spectra of the free base of **12** and of its *N*-methyl and *N*-benzyl homologs (5,6). In addition, the *N*-benzyl homolog **18** provided a nuclear magnetic resonance spectrum in which the N-CH_2-C_6H_5 protons displayed magnetic non-equivalence. Walsh and Smissman (1) have described spectra of some *cis*- and *trans*-octahydrobenzo[*g*]quinolines in which the N-CH_2-C_6H_5 protons appear as an AB quartet with the *cis*-fused isomer exhibiting a small chemical shift difference (23.7 Hz) and the *trans*-fused isomer exhibiting a much larger chemical shift difference (60.3 Hz). In the present work, the nuclear magnetic resonance spectrum of the *N*-benzyl homolog **18** revealed an AB quartet centered at δ 3.72 with $\Delta\nu$ = 82.7 Hz. These data seem to confirm the *trans*-geometry of ring fusion.

The *trans*-secondary amine **12** was *N*-alkylated using literature procedures, and the ether linkages were cleaved using 48% hydrobromic acid (see Table I).

EXPERIMENTAL

General.

Melting points are uncorrected and were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus. Infrared spectra were obtained with a Beckman IR 4240 instrument, and nuclear magnetic resonance spectra were recorded with a Varian Associates T-60 instrument with internal tetramethylsilane reference. Mass spectra were recorded on a Finnigan 1010 S/L spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

3-Carbomethoxy-3-(2-cyanoethyl)-5,6-dimethoxy-2-tetralone (**9**).

3-Carbomethoxy-5,6-dimethoxy-2-tetralone (3) (5.28 g., 0.02 mole) in 43 ml. of toluene and 30 ml. of methanol was treated with 0.8 g. (0.015 mole) of acrylonitrile. A catalytic amount of sodium hydride (50% mineral oil dispersion) was added, and the mixture was degassed and stirred under nitrogen at ambient temperature for 20 hours. The resulting mixture was then treated with a slight excess of methanolic hydrogen chloride, the volatiles were removed under reduced pressure, and the oily residue was taken up in ether. This solution was filtered and the ether was evaporated to give a thick paste which soon deposited yellow crystals. Methanol was added and the resulting yellow solid was collected on a filter to afford 1.27 g. (24%) of recovered starting material. Methanol was removed from the filtrate and the residue was chromatographed on silica and eluted with chloroform to afford 3.17 g. (50%) of a bright yellow oil; ir (film): 1715 cm^{-1} (C=O), 1735 (ester C=O), 2240 (CN); ms: m/e 317 (M^+); nmr (deuteriochloroform): δ 6.77 (s, 2H, arom H), 3.86 (s, 6H, OCH_3), 3.65 (d, 2H, ArCH_2CO), 3.62 (s, 3H, CO_2CH_3), 3.25 (q, 2H, $ArCH_2$-C-CO), 2.43 (m, 2H, CH_2CN), 2.12 (m, 2H, CH_2CH_2CN).

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.43; H, 5.99; N, 4.42. Found: C, 64.80; H, 6.04; N, 4.32.

2-(2-Cyanoethyl)-5,6-dimethoxy-2-tetralone (**11**).

a)

A mixture of 0.63 g. (0.002 mole) of **9**, 0.17 g. of (0.004 mole) of lithium chloride, and 56 ml. of hexamethylphosphoric triamide was heated at 75-80° for 23 hours, during which time the initially yellow solution became orange-brown. The cooled solution was diluted with 240 ml. of water, extracted four times with ether, and the pooled extracts were washed four times with water. Evaporation of the ether gave 0.5 g. of a brown oil which was estimated from tlc to be 70% pure. This material was chromatographed on silica and eluted with chloroform to afford 0.180 g. (35%) of a nearly colorless oil; ir (film): 1710 cm^{-1} (C=O), 2240 (CN); ms: m/e 259 (M^+); nmr (deuteriochloroform): δ 6.77 (s, 2H, arom H), 3.81, 3.85 (2s, 6H, OCH_3), 3.53 (s, 2H, ArCH_2CO), 2.90-2.23 (m, 5H), 1.5-2.23 (m, 2H, CH_2CH_2CN).

b)

A mixture of 1.9 g. (0.006 mole) of **9**, 0.59 g. (0.012 mole) of sodium cyanide, 12 drops of water, and 130 ml. of hexamethylphosphoric triamide was heated at 75° for 50 minutes. The reaction mixture was worked up as described above in a), to afford approximately 35% yield of product.

trans-6,7-Dimethoxy-1,2,3,4,4a,5,10,10b-octahydrobenzo[*g*]quinoline Hydrochloride (**12**).

A mixture of 1.6 g. of crude **11** (estimated by tlc to be 40-50% **11**), 0.2 g. of platinum oxide, and 3.5 ml. of chloroform in 175 ml. of absolute ethanol was hydrogenated for 16 hours at an initial pressure of 30 psig. The reduction mixture was filtered and volatiles were removed from the filtrate under reduced pressure. The residue was partitioned between water and ether. The water layer was extracted with ether once more and the ether washings were discarded. The water layer was treated with excess sodium hydroxide and the resulting mixture was extracted with ether. Removal of the ether left a dark red oil which was converted to its hydrochloride salt. This was recrystallized from methanol-ether to yield 0.171 g. (10% overall yield, from **8**), m.p. 272-273°, ir (film, free base): 2831, 2846 cm^{-1} (strong, "Bohlmann bands"); nmr (deuteriochloroform, free base): δ 6.72 (s, 2H, arom H), 3.80, 3.83 (2s, 6H, OCH_3), 3.40-0.80 (m, 13H, aliphatic H); ms: m/e 247 (M^+).

Anal. Calcd. for $C_{15}H_{22}ClNO_2$: C, 63.48; H, 7.72; N, 4.94. Found: C, 63.65; H, 7.99; N, 5.07.

trans-*N*-Methyl-6,7-dimethoxy-1,2,3,4,4a,5,10,10b-octahydrobenzo[*g*]-quinoline Hydrochloride (**15**).

A mixture of 0.142 g. (0.0006 mole) of **12**, 0.25 ml. of 37% aqueous formaldehyde solution, and 0.189 g. (0.0015 mole) of sodium cyanoborohydride in 6 ml. of methanol was stirred overnight at ambient temperature. Acetic acid was added dropwise from time to time to maintain the *p*H at 6-7 (*p*H paper). The product was isolated according to Borch's procedure (7), and was recrystallized from ethanol-ether to give 0.132 g. (88%) of product, m.p. 210-215°; ir (chloroform, free base): 2787, 2835, 2847 cm^{-1} (strong, "Bohlmann bands"), ms: m/e 261 (M^+); nmr (deuteriochloroform): δ 6.74 (s, 2H, arom H), 3.79, 3.82 (2s, 6H, OCH_3), 3.7-1.1 (m, 12H), 2.88 (s, 3H).

Anal. Calcd. for $C_{16}H_{24}ClNO_2$ (including experimentally determined 2.00% water): C, 63.24; H, 8.15; H, 4.60. Found: C, 63.44; H, 8.17; N, 4.59.

trans-*N*-ethyl-6,7-dimethoxy-1,2,3,4,4a,5,10,10b-octahydrobenzo[*g*]-quinoline Hydrochloride (**16**).

This was prepared from 0.20 g. (0.0007 mole) of **12**, 0.134 g. (0.0035 mole) of sodium borohydride, and 0.72 g. (0.012 mole) of acetic acid in 25 ml. of benzene, according to a method of Marchini and co-workers (8), to give 0.178 g. (82%) of product, m.p. 198-201° (from methanol-ether); nmr (deuteriochloroform): δ 6.77 (s, 2H, arom H), 3.77, 3.81 (2s, 6H, OCH_3), 3.8-1.0 (m, 12H), 1.40 (t, 3H), 3.37 (q, 2H), 3.37 (q, 2H); ms: m/e 275 (M^+ -HCl).

Anal. Calcd. for $C_{17}H_{26}ClNO_2$: C, 65.47; H, 8.34; N, 4.49. Found: C, 65.60; H, 8.40; N, 4.39.

trans-N-n-Propyl-6,7-dimethoxy-1,2,3,4,4a,5,10,10b-octahydrobenzo[*g*]-quinoline Hydrochloride (**17**).

This was prepared from 0.224 g. (0.00079 mole) of **12**, 0.15 g. (0.0039 mole) of sodium borohydride, and 0.99 g. (0.0134 mole) of propionic acid in 25 ml. of benzene according to a method of Marchini and co-workers (8), to give 0.205 g. (80%) of product, m.p. 218-221° (from methanol-ether); nmr (deuteriochloroform): δ 6.72 (s, 2H, arom H), 3.78, 3.82 (2s, 6H, OCH_3), 3.8-1.0 (m, 16H), 1.05 (t, 3H); ms: m/e 289 (M^+ - HCl).

Anal. Calcd. for $C_{18}H_{28}ClNO_2$: C, 66.30; H, 8.60; N, 4.30. Found: C, 66.11; H, 8.74; N, 4.21.

trans-*N*-Benzyl-6,7-dimethoxy-1,2,3,4,4a,5,10,10b-octahydrobenzo[*g*]quinoline (**18**).

A mixture of 0.160 g. (0.0006 mole) of **12**, 0.3 g. (0.005 mole) of sodium cyanoborohydride, and 0.250 g. (0.002 mole) of benzaldehyde in 8 ml. of methanol was stirred at ambient temperature for 3 days. During this time, acetic acid was added from time to time to maintain the *p*H at 7 (*p*H paper). The reaction mixture was treated with excess concentrated hydrochloric acid and volatiles were removed under reduced pressure. The residue was taken up in water and the solution was washed twice with ether. The aqueous layer was treated with excess sodium hydroxide, extracted twice with ether, and the pooled dried (magnesium sulfate) ethereal extracts were treated with anhydrous hydrogen chloride. The resulting solid was fractionally crystallized from methanol-ether to afford a sizeable amount of starting material **12** and 0.021 g. (10%) of product, m.p. 242-245°; ir (chloroform, free base): 2838, 2795 cm^{-1} (medium, "Bohlmann bands"); nmr (deuteriochloroform, free base): δ 7.30 (broad, 5H, arom H), 6.77 (m, 2H, arom H), 3.80, 3.83 (2s, 6H, OCH_3), 3.72 (q, $\Delta\nu$ = 82.7 Hz, J = 13.5 Hz, 2H, $CH_2C_6H_5$), 3.5-1.0 (m, 14H); ms: m/e 337 (M^+).

Ether Cleavage Reactions.

The amine salt (0.001 mole) was heated in 30 ml. of 48% hydrobromic acid under nitrogen at 135-145° for 3 hours. Volatiles were removed under reduced pressure and the residue was recrystallized (see Table I).

Acknowledgement.

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