

### Benzo[*g*]quinolines. 3. Influence of Carbon-5 Substituents on Narcotic Antagonist and Antiwrithing Activities of Derivatives of *cis*-1,2,3,4,4a,5,10,10a-Octahydrobenzo[*g*]quinolin-7-ol

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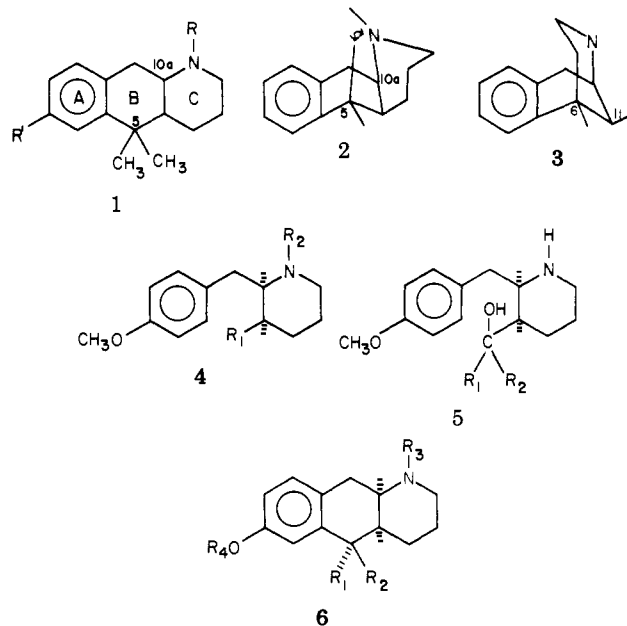
The synthesis of new C-5 substituted derivatives of *cis*-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolin-7-ol is described. For a given N-substituent narcotic antagonism generally increases and antiwrithing activity generally decreases with decreasing substitution on C-5.

The results of earlier work<sup>1,2</sup> established that certain *N*-alkyl derivatives of 1,2,3,4,4a,5,10,10a-octahydro-5,5-dimethylbenzo[*g*]quinoline (1) possessed narcotic antagonist activity. For a given R (methyl, allyl, propyl, cyclopropylmethyl) maximum activity was observed when (a) the B/C ring fusion was *cis* and (b) R' = OH rather than H. These compounds contained a quaternary carbon atom at position 5 because it had been postulated that such a highly substituted central atom was an essential feature of strong analgesic molecules.<sup>3</sup> The higher activity of the *cis*-fused compounds was explained by the possibility of these isomers assuming a conformation in which the C-10a-N bond is axial on ring B (2). Such a conformation is superimposable on the 6,11-*trans*-dialkyl-2,6-methano-3-benzazocine ring system (compare partial stereostructures 2 and 3), derivatives of which are known to be potent analgesics and narcotic antagonists.<sup>4</sup> However, this conformation is expected to be destabilized by a 1,3-diaxial interaction (arrow in 2) between the nitrogen atom and the C-5β methyl group. Removal of this or both of the C-5 methyl groups should reduce this interaction and thereby increase the population of this conformation and its associated narcotic antagonist activity. Coincidental removal of the quaternary substitution at C-5 may be of minor consequence since it has been shown that quaternary substitution of C-6 in the 2,6-methano-3-benzazocine series is not necessary for analgesic activity.<sup>5,6</sup>

**Chemistry.** The required *cis*-fused norbases **6h** and **6i** were obtained by 48% HBr cyclizations of the alcohols **5f** and **5g**, respectively. These alcohols were in turn prepared in the following manner: **5f** by hydrogenolysis of **4a** to give **4b** which was reduced with LiAlH<sub>4</sub>; **5g** by hydrolysis of **4a** to the acid **4c**, reaction of **4c** with CH<sub>3</sub>Li to give the ketone **4d**, controlled reduction of **4d** with LiAlH<sub>4</sub> to give **4e** as a mixture of C-α epimers, and finally hydrogenolysis of the mixture. Cyclization of the **5g** epimers gave a major crystalline product **6i** which was homogeneous on thin-layer chromatography. Lacking the other C-5 epimer for comparison, we could not assign the relative configuration of C-5 with certainty. However, a study of models showed that the sterically less crowded cyclization transition state of **5g** would result in **6i** with R<sub>1</sub> = CH<sub>3</sub> and R<sub>2</sub> = H.

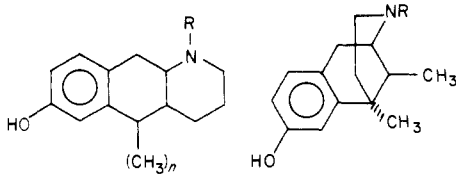
We then prepared by the usual procedures the *N*-methyl, *N*-allyl, *N*-propyl, *N*-cyclopropylmethyl, and *N*-(3-methyl-2-butenyl) derivatives of the norbases **6h** and **6i** (7-11 and 12-16, respectively) and the latter derivative (**21**) of norbase **6j**. Compounds 17-20 were available from previous work.

**Pharmacology and Discussion.** Compounds 7-21 were tested for narcotic (meperidine) antagonism by the



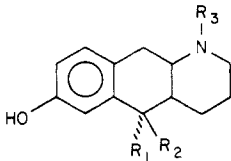
- a, R<sub>1</sub> = CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>; R<sub>2</sub> = CO<sub>2</sub>CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>  
 b, R<sub>1</sub> = CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>; R<sub>2</sub> = H  
 c, R<sub>1</sub> = COOH; R<sub>2</sub> = CO<sub>2</sub>CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>  
 d, R<sub>1</sub> = COCH<sub>3</sub>; R<sub>2</sub> = CO<sub>2</sub>CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>  
 e, R<sub>1</sub> = CH(OH)CH<sub>3</sub>; R<sub>2</sub> = CO<sub>2</sub>CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>  
 f, R<sub>1</sub> = R<sub>2</sub> = H  
 g, R<sub>1</sub> = CH<sub>3</sub>; R<sub>2</sub> = H  
 h, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = R<sub>4</sub> = H  
 i, R<sub>1</sub> (or R<sub>2</sub>) = CH<sub>3</sub>; R<sub>2</sub> (or R<sub>1</sub>) = R<sub>3</sub> = R<sub>4</sub> = H  
 j, R<sub>1</sub> = R<sub>2</sub> = CH<sub>3</sub>; R<sub>3</sub> = R<sub>4</sub> = H

method of Harris and Pierson<sup>7</sup> and for activity in the acetylcholine-induced writhing test of Collier et al.<sup>8</sup> The results are shown in Table I along with comparative data for some 6,11-*trans*-dimethyl-2,6-methano-3-benzazocines. In Table I the benzo[*g*]quinolines are divided into three groups according to the number of CH<sub>3</sub>'s on C-5. While the narcotic antagonist potencies are generally less than those of 22-25, a comparison of the AD<sub>50</sub>'s for compounds 7-21 with the same R shows a trend of increasing activity with decreasing substitution of C-5, even though in a few cases the 95% confidence limits overlap. On the other hand, a comparison of the antiwrithing ED<sub>50</sub>'s for compounds with the same R shows an opposite trend, namely, decreasing activity with decreasing substitution of C-5.<sup>9</sup> These results show that the phenomena of narcotic antagonism and protection against acetylcholine-induced writhing are probably elicited by different mechanisms and that the structural requirements for each phenomenon are

Table I. Biological Activities of *cis*-Benzo[*g*]quinolin-7-ols as a Function of N-Substituent (R) and Number (*n*) of CH<sub>3</sub>'s on C-5


No.	R	Meperidine antagonism <sup>a</sup>	Antiwirthing act. <sup>b</sup>	<i>n</i>
7	CH <sub>3</sub>	1.1 (0.7-1.8)	Inactive <sup>c</sup>	0
8	CH <sub>2</sub> CH=CH <sub>2</sub>	0.16 (0.12-0.22)	Inactive <sup>c</sup>	0
9	C <sub>3</sub> H <sub>7</sub>	0.11 (0.06-0.20)	15 (13-17)	0
10	CH <sub>2</sub> - <i>c</i> -C <sub>3</sub> H <sub>5</sub>	0.16 (0.11-0.22)	Inactive <sup>c</sup>	0
11	CH <sub>2</sub> CH=C(CH <sub>3</sub> ) <sub>2</sub>	0.8 (0.5-1.3)	11 (8-14)	0
12	CH <sub>3</sub>	1.1 (0.7-1.8)	15 (13-17)	1
13	CH <sub>2</sub> CH=CH <sub>2</sub>	0.5 (0.2-0.9)	14 (12-17)	1
14	C <sub>3</sub> H <sub>7</sub>	0.6 (0.3-1.0)	12 (9.5-15)	1
15	CH <sub>2</sub> - <i>c</i> -C <sub>3</sub> H <sub>5</sub>	0.5 (0.3-0.8)	12 (9.6-15)	1
16	CH <sub>2</sub> CH=C(CH <sub>3</sub> ) <sub>2</sub>	2.9 (1.5-5.5)	5.8 (4.0-8.6)	1
17	CH <sub>3</sub>	7.9 (4.6-13.4)	7.1 (5.9-8.7)	2
18	CH <sub>2</sub> CH=CH <sub>2</sub>	0.5 (0.2-0.9)	4.6 (3.7-5.7)	2
19	C <sub>3</sub> H <sub>7</sub>	1.0 (0.7-1.6)	9.6 (7.8-11.6)	2
20	CH <sub>2</sub> - <i>c</i> -C <sub>3</sub> H <sub>5</sub>	0.3 (0.2-0.4)	6.6 (5.4-8.5)	2
21	CH <sub>2</sub> CH=C(CH <sub>3</sub> ) <sub>2</sub>	6.7 (4.3-10)	8.2 (6.7-9.7)	2
22	CH <sub>2</sub> CH=CH <sub>2</sub>	0.019 <sup>d</sup>	1.3 (0.9-1.8)	
23	C <sub>3</sub> H <sub>7</sub>	0.056 <sup>d</sup>		
24	CH <sub>2</sub> - <i>c</i> -C <sub>3</sub> H <sub>5</sub>	0.014 (0.009-0.020)		
25	CH <sub>2</sub> CH=C(CH <sub>3</sub> ) <sub>2</sub>	3.3 (1.8-5.9)		

<sup>a</sup> AD<sub>50</sub> (95% confidence limits), mg/kg sc. <sup>b</sup> ED<sub>50</sub> (95% confidence limits), mg/kg sc. <sup>c</sup> At screening dose of 100 mg/kg sc. <sup>d</sup> Dose response too flat (seven-point assay) to determine valid confidence limits.

Table II. Physical Properties of *cis*-Benzo[*g*]quinolin-7-ols


Compd no.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Formula	Mp, °C	Analyses
7	H	H	CH <sub>3</sub>	C <sub>14</sub> H <sub>19</sub> NO	213-216	C, H, N
8	H	H	CH <sub>2</sub> CH=CH <sub>2</sub>	C <sub>16</sub> H <sub>21</sub> NO·HCl	270-272	C, H, N
9	H	H	C <sub>3</sub> H <sub>7</sub>	C <sub>16</sub> H <sub>23</sub> NO	139-142	C, H, N
10	H	H	CH <sub>2</sub> - <i>c</i> -C <sub>3</sub> H <sub>5</sub>	C <sub>17</sub> H <sub>23</sub> NO	176-178	C, H, N
11	H	H	CH <sub>2</sub> CH=C(CH <sub>3</sub> ) <sub>2</sub>	C <sub>18</sub> H <sub>25</sub> NO	131-133	C, H, N
12	CH <sub>3</sub>	H	CH <sub>3</sub>	C <sub>15</sub> H <sub>21</sub> NO	203-205	C, H, N
13	CH <sub>3</sub>	H	CH <sub>2</sub> CH=CH <sub>2</sub>	C <sub>17</sub> H <sub>23</sub> NO·C <sub>7</sub> H <sub>8</sub> O <sub>3</sub> S	165-170	C, H, N
14	CH <sub>3</sub>	H	C <sub>3</sub> H <sub>7</sub>	C <sub>17</sub> H <sub>25</sub> NO·C <sub>7</sub> H <sub>8</sub> O <sub>3</sub> S	214-215	C, H, N
15	CH <sub>3</sub>	H	CH <sub>2</sub> - <i>c</i> -C <sub>3</sub> H <sub>5</sub>	C <sub>18</sub> H <sub>25</sub> NO·CH <sub>4</sub> O <sub>3</sub> S	207-210	C, H, N
16	CH <sub>3</sub>	H	CH <sub>2</sub> CH=C(CH <sub>3</sub> ) <sub>2</sub>	C <sub>19</sub> H <sub>27</sub> NO·HCl	130 dec	C, H, N
21	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>2</sub> CH=C(CH <sub>3</sub> ) <sub>2</sub>	C <sub>20</sub> H <sub>29</sub> NO	170-173	H, N; C <sup>a</sup>

<sup>a</sup> C: calcd, 80.22; found, 80.67.

different. On the one hand, narcotic antagonism may depend more on conformational factors (i.e., the shape of the antagonist molecule), whereas antiwrithing activity may depend more on lipophilicity in the region of space around C-5. We conclude that the balance between the two types of biological activity of the benzo[*g*]quinolines can be varied at least to some extent by varying the substitution of C-5. We are currently applying this observation to other more rigid structures in order to determine its scope and limitations.<sup>10</sup>

### Experimental Section

Melting points were determined by the capillary method and are uncorrected. Ir (Perkin-Elmer Model 257) and NMR (Varian Associates Model A-60, Me<sub>4</sub>Si) substantiated all structures. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ±0.4% of the theoretical values.

**Ethyl *cis*-2-(4-Methoxyphenylmethyl)-3-piperidine-carboxylate (4b).** A mixture of 6 g of ethyl *cis*-1-benzyloxy-carboxyl-2-(4-methoxyphenylmethyl)-3-piperidinecarboxylate (4a),<sup>1</sup> 0.5 g of Pd/C, 1 ml of concentrated HCl, and EtOH to a total volume of 60 ml was shaken under 50 psi of H<sub>2</sub> until uptake ceased. The catalyst was removed by filtration and the EtOH removed in vacuo. The residue was dissolved in H<sub>2</sub>O and washed with Et<sub>2</sub>O. The aqueous layer was basified with NH<sub>4</sub>OH and extracted with Et<sub>2</sub>O. The Et<sub>2</sub>O layer was washed with H<sub>2</sub>O, dried, filtered, and concentrated to give 3.5 g (88%) of a syrup of adequate purity for chemical purposes. A sample was converted to its HCl salt with HCl-Et<sub>2</sub>O and recrystallized from EtOH-Et<sub>2</sub>O to give 4b·HCl: mp 139-142°. Anal. (C<sub>16</sub>H<sub>23</sub>NO<sub>3</sub>·HCl) C, H, N. *cis*-2-(4-Methoxyphenylmethyl)-3-piperidinemethanol (5f). A 12.5-g sample of 4b·HCl on treatment with dilute NH<sub>4</sub>OH followed by drying in Et<sub>2</sub>O yielded 10.1 g of syrupy 4b. This was reduced with 1.4 g of LiAlH<sub>4</sub> in 200 ml of THF at room temperature for 5 h. Quenching with 2.8 ml of H<sub>2</sub>O followed by filtration and evaporation left 8.7 g (100%) of a syrup. This was

converted to its *p*-TSA salt, mp 174–176°. Anal. (C<sub>14</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>·C<sub>7</sub>H<sub>5</sub>O<sub>3</sub>S) C, H, N.

*cis*-1,2,3,4,4a,5,10,10a-Octahydrobenzo[*g*]quinolin-7-ol (6h). A solution of 10.4 g of 5f *p*-TSA in 52 ml of 48% HBr was refluxed for 24 h and decanted from a small amount of tarry material. The decanted liquid crystallized on cooling. Filtration, washing with H<sub>2</sub>O, and recrystallization from EtOH gave 2.0 g (28%) of 6h·HBr, mp 274–278°. Anal. (C<sub>13</sub>H<sub>17</sub>NO·HBr) H, N; C: calcd, 54.96; found, 54.29.

A suspension of 38 g of 6h·HBr in 570 ml of warm H<sub>2</sub>O was treated with 790 ml of concentrated NH<sub>4</sub>OH, stirred on a steam bath 0.5 h, cooled, filtered, and washed with H<sub>2</sub>O. The moist product was recrystallized from EtOH to give 21.5 g (79%) of 6h base, mp 233–235° dec. Anal. (C<sub>13</sub>H<sub>17</sub>NO) C, H, N.

*cis*-1-Benzoyloxycarbonyl-2-(4-methoxyphenylmethyl)-3-piperidinecarboxylic Acid (4c). A mixture of 4.1 g of 4a, 10 ml of EtOH, and 10 ml of 1 N NaOH was heated on a steam bath for 15 min and evaporated until only H<sub>2</sub>O distilled. More H<sub>2</sub>O was added to obtain a single phase which was washed with Et<sub>2</sub>O and acidified with 1 N HCl to precipitate the crystalline product (78%). Two recrystallizations from EtOH afforded material with mp 176–178°. Anal. (C<sub>22</sub>H<sub>25</sub>NO<sub>5</sub>) C, H, N.

*cis*-3-Acetyl-1-benzoyloxycarbonyl-2-(4-methoxyphenylmethyl)piperidine (4d). A suspension of 7.7 g of 4c in 150 ml of Et<sub>2</sub>O was stirred at 0° under N<sub>2</sub> while 19 ml of 2.3 M CH<sub>3</sub>Li-Et<sub>2</sub>O was added dropwise. Stirring was continued at 0° for 4 h. The reaction mixture was poured into cold aqueous NH<sub>4</sub>Cl, and the Et<sub>2</sub>O layer was washed with saturated NaHCO<sub>3</sub>. After drying and removal of the solvent, there was left 3.0 g (39%) of a residue which crystallized from EtOH. Repeated crystallization from EtOH afforded pure 4d, mp 83–84°. Anal. (C<sub>23</sub>H<sub>27</sub>NO<sub>4</sub>) C, H, N.

*cis*-1,2,3,4,4a,5,10,10a-Octahydro-5-methylbenzo[*g*]quinolin-7-ol (6i). A suspension of 7.2 g of LiAlH<sub>4</sub> in 250 ml of Et<sub>2</sub>O was stirred at 0° while a solution of 73 g of 4d in 1500 ml of Et<sub>2</sub>O was added dropwise. After addition, stirring was continued at 0° for 4 h. The reaction mixture was poured into ice-1 N HCl and a small amount of CHCl<sub>3</sub> added. The organic layer was washed with saturated NaHCO<sub>3</sub>, dried, and concentrated to give 61 g of 4e epimers. This was diluted to 600 ml with EtOH, 6 g of Pd/C and 15 ml of 5.9 N HCl-EtOH were added, and the mixture was shaken under 50 psi of H<sub>2</sub> at room temperature for 4 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was partitioned between H<sub>2</sub>O and Et<sub>2</sub>O, and the H<sub>2</sub>O layer was made basic with NH<sub>4</sub>OH and K<sub>2</sub>CO<sub>3</sub>. Extraction with Et<sub>2</sub>O, drying, and removal of the solvent left 31 g of 5g epimers as a syrup. A solution of this syrup in 300 ml of 48% HBr was refluxed for 24 h and allowed to cool. With ice cooling 300 ml of concentrated NH<sub>4</sub>OH was added. The product was filtered, washed with H<sub>2</sub>O, and dried to give 17.5 g (35% yield from 4d) of 6i hemihydrobromide, mp > 300°. An analytical sample was obtained by recrystallization from DMF. Anal. [(C<sub>14</sub>H<sub>19</sub>NO)<sub>2</sub>·HBr] C, H, N.

*N*-Methyl Derivatives of Norbases 6h and 6i (7 and 12).

A suspension of 6h or 6i in EtOH containing 1 equiv of 40% aqueous formaldehyde was shaken with H<sub>2</sub> (400 psi) in the presence of Pd/C until uptake ceased. Filtration of the catalyst and evaporation of the filtrate left a residue. For 7, crystallization from EtOH gave the product. For 12, the residue was first slurried with dilute NH<sub>4</sub>OH, filtered, washed with H<sub>2</sub>O, and then crystallized from EtOH. Yields ranged from 50 to 70%. The properties of 7 and 12 are given in Table II.

*N*-Allyl, *N*-Propyl, *N*-(Cyclopropylmethyl), and *N*-(3-Methyl-2-butenyl) Derivatives of Norbases 6h–j (8–11, 13–16, 21). These compounds were prepared by heating on a steam bath for 2 h a solution of the norbase in DMF containing slight excesses of the alkyl halide and NaHCO<sub>3</sub>. Evaporation of the DMF, dissolution of the residue in CHCl<sub>3</sub>, washing with H<sub>2</sub>O, drying, filtration, and evaporation of the CHCl<sub>3</sub> gave the crude products. Bases were recrystallized from EtOH and salts from EtOH or EtOH-Et<sub>2</sub>O. Yields ranged from 50 to 75%. The requisite physical data are given in Table II.

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## References and Notes

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- It would be of interest to determine the biological activity of the corresponding N derivatives of 6-noralkyl-11β-methyl-2,6-methano-3-benzocin-8-ol since our work suggests that these compounds would be potent narcotic antagonists with weak antiwrithing activity. The *N*-methyl derivative has been reported: H. Inoue, T. Oh-ishi, and E. L. May, *J. Med. Chem.*, **18**, 787 (1975). To our knowledge no derivatives bearing antagonist side chains on nitrogen have appeared in the literature.

## Synthesis and Anticonvulsant Properties of 1-(10-Cyano- and -10-bromo-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)-4-[(arylmethylene)amino]piperazines

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Since the potent anticonvulsant activity against electroshock seizures in mice for a novel series of hydrazone derivatives of benzhydrylpiperazines (1) was first reported by Craig,<sup>1</sup> much effort has been expended in these laboratories seeking to characterize and improve this activity. For one compound of the original series, 1 (SC 13504), anticonvulsant activity has also been demonstrated in cat,<sup>2,3</sup> dog,<sup>4</sup> and *Papio papio*<sup>5</sup> models. When the two

phenyl rings were bridged as in the dibenzocycloheptene analogue 2,<sup>6</sup> mild anticonvulsant activity was retained but it was decreased as compared to 1.<sup>7</sup>

The present communication describes the synthesis and anticonvulsant activity of a series of highly active hydrazones derived from 10-substituted 5*H*-dibenzo[*a,d*]cyclohepten-5-ylpiperazines. These compounds were prepared in order to define the effect of substitution of the