Notes

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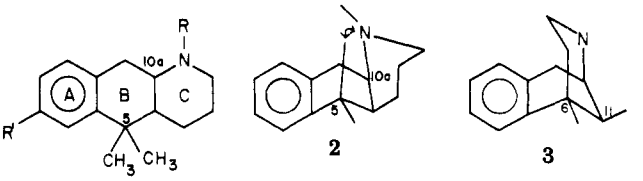
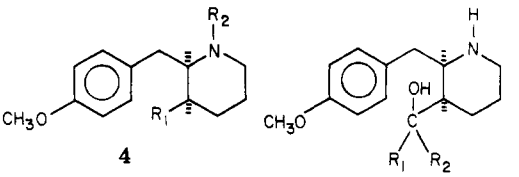
The synthesis of new C-5 substituted derivatives of *cis*-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolin-7-ol is described. For a given N-substituent narcotic antagonism generally increases and antiwrithing activity generally decreases with decreasing substitution on C-5.

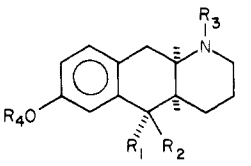
The results of earlier work[1,2] established that certain *N*-alkyl derivatives of 1,2,3,4,4a,5,10,10a-octahydro-5,5-dimethylbenzo[g]quinoline (**1**) possessed narcotic antagonist activity. For a given R (methyl, allyl, propyl, cyclopropylmethyl) maximum activity was observed when (a) the B/C ring fusion 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.[3] 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 analgetics and narcotic antagonists.[4] 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 analgetic activity.[5,6]



1 **2** **3**



4 **5**



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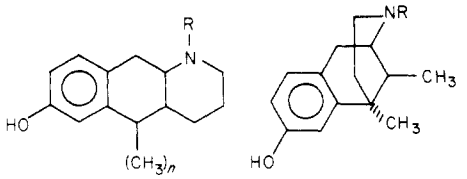
a, $R_1 = CO_2C_2H_5$; $R_2 = CO_2CH_2C_6H_5$
b, $R_1 = CO_2C_2H_5$; $R_2 = H$
c, $R_1 = COOH$; $R_2 = CO_2CH_2C_6H_5$
d, $R_1 = COCH_3$; $R_2 = CO_2CH_2C_6H_5$
e, $R_1 = CH(OH)CH_3$; $R_2 = CO_2CH_2C_6H_5$
f, $R_1 = R_2 = H$
g, $R_1 = CH_3$; $R_2 = H$
h, $R_1 = R_2 = R_3 = R_4 = H$
i, R_1 (or R_2) $= CH_3$; R_2 (or R_1) $= R_3 = R_4 = H$
j, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$

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 $LiAlH_4$; **5g** by hydrolysis of **4a** to the acid **4c**, reaction of **4c** with CH_3Li to give the ketone **4d**, controlled reduction of **4d** with $LiAlH_4$ 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 $R_1 = CH_3$ and $R_2 = H$.

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 method of Harris and Pierson[7] and for activity in the acetylcholine-induced writhing test of Collier et al.[8] 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_3's on C-5. While the narcotic antagonist potencies are generally less than those of **22–25**, a comparison of the AD_{50}'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_{50}'s for compounds with the same R shows an opposite trend, namely, decreasing activity with decreasing substitution of C-5.[9] 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_3's on C-5

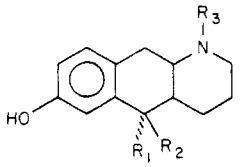


7-21 22-25

No.	R	Meperidine antagonism[a]	Antiwrithing act.[b]	*n*
7	CH_3	1.1 (0.7-1.8)	Inactive[c]	0
8	$CH_2CH=CH_2$	0.16 (0.12-0.22)	Inactive[c]	0
9	C_3H_7	0.11 (0.06-0.20)	15 (13-17)	0
10	CH_2-c-C_3H_5	0.16 (0.11-0.22)	Inactive[c]	0
11	$CH_2CH=C(CH_3)_2$	0.8 (0.5-1.3)	11 (8-14)	0
12	CH_3	1.1 (0.7-1.8)	15 (13-17)	1
13	$CH_2CH=CH_2$	0.5 (0.2-0.9)	14 (12-17)	1
14	C_3H_7	0.6 (0.3-1.0)	12 (9.5-15)	1
15	CH_2-c-C_3H_5	0.5 (0.3-0.8)	12 (9.6-15)	1
16	$CH_2CH=C(CH_3)_2$	2.9 (1.5-5.5)	5.8 (4.0-8.6)	1
17	CH_3	7.9 (4.6-13.4)	7.1 (5.9-8.7)	2
18	$CH_2CH=CH_2$	0.5 (0.2-0.9)	4.6 (3.7-5.7)	2
19	C_3H_7	1.0 (0.7-1.6)	9.6 (7.8-11.6)	2
20	CH_2-c-C_3H_5	0.3 (0.2-0.4)	6.6 (5.4-8.5)	2
21	$CH_2CH=C(CH_3)_2$	6.7 (4.3-10)	8.2 (6.7-9.7)	2
22	$CH_2CH=CH_2$	0.019[d]	1.3 (0.9-1.8)	
23	C_3H_7	0.056[d]		
24	CH_2-c-C_3H_5	0.014 (0.009-0.020)		
25	$CH_2CH=C(CH_3)_2$	3.3 (1.8-5.9)		

[a] AD_{50} (95% confidence limits), mg/kg sc. [b] ED_{50} (95% confidence limits), mg/kg sc. [c] At screening dose of 100 mg/kg sc. [d] 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_1	R_2	R_3	Formula	Mp, °C	Analyses
7	H	H	CH_3	$C_{14}H_{19}NO$	213-216	C, H, N
8	H	H	$CH_2CH=CH_2$	$C_{16}H_{21}NO\cdot HCl$	270-272	C, H, N
9	H	H	C_3H_7	$C_{16}H_{23}NO$	139-142	C, H, N
10	H	H	CH_2-c-C_3H_5	$C_{17}H_{23}NO$	176-178	C, H, N
11	H	H	$CH_2CH=C(CH_3)_2$	$C_{18}H_{25}NO$	131-133	C, H, N
12	CH_3	H	CH_3	$C_{15}H_{21}NO$	203-205	C, H, N
13	CH_3	H	$CH_2CH=CH_2$	$C_{17}H_{23}NO\cdot C_7H_8O_3S$	165-170	C, H, N
14	CH_3	H	C_3H_7	$C_{17}H_{25}NO\cdot C_7H_8O_3S$	214-215	C, H, N
15	CH_3	H	CH_2-c-C_3H_5	$C_{18}H_{25}NO\cdot CH_4O_3S$	207-210	C, H, N
16	CH_3	H	$CH_2CH=C(CH_3)_2$	$C_{19}H_{27}NO\cdot HCl$	130 dec	C, H, N
21	CH_3	CH_3	$CH_2CH=C(CH_3)_2$	$C_{20}H_{29}NO$	170-173	H, N; C[a]

[a] 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.[10]

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_4Si) 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-piperidinecarboxylate (4b). A mixture of 6 g of ethyl *cis*-1-benzyloxycarbonyl-2-(4-methoxyphenylmethyl)-3-piperidinecarboxylate (**4a**),[1] 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_2 until uptake ceased. The catalyst was removed by filtration and the EtOH removed in vacuo. The residue was dissolved in H_2O and washed with Et_2O. The aqueous layer was basified with NH_4OH and extracted with Et_2O. The Et_2O layer was washed with H_2O, 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_2O and recrystallized from EtOH–Et_2O to give **4b**·HCl: mp 139–142°. Anal. ($C_{16}H_{23}NO_3\cdot HCl$) C, H, N.

***cis*-2-(4-Methoxyphenylmethyl)-3-piperidinemethanol (5f).** A 12.5-g sample of **4b**·HCl on treatment with dilute NH_4OH followed by drying in Et_2O yielded 10.1 g of syrupy **4b**. This was reduced with 1.4 g of $LiAlH_4$ in 200 ml of THF at room temperature for 5 h. Quenching with 2.8 ml of H_2O 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. ($C_{14}H_{21}NO_2 \cdot C_7H_8O_3S$) 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_2O, and recrystallization from EtOH gave 2.0 g (28%) of **6h**·HBr, mp 274–278°. Anal. ($C_{13}H_{17}NO \cdot HBr$) H, N; C: calcd, 54.96; found, 54.29.

A suspension of 38 g of **6h**·HBr in 570 ml of warm H_2O was treated with 790 ml of concentrated NH_4OH, stirred on a steam bath 0.5 h, cooled, filtered, and washed with H_2O. The moist product was recrystallized from EtOH to give 21.5 g (79%) of **6h** base, mp 233–235° dec. Anal. ($C_{13}H_{17}NO$) C, H, N.

cis-**1-Benzyloxycarbonyl-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_2O distilled. More H_2O was added to obtain a single phase which was washed with Et_2O and acidified with 1 N HCl to precipitate the crystalline product (78%). Two recrystallizations from EtOH afforded material with mp 176–178°. Anal. ($C_{22}H_{25}NO_5$) C, H, N.

cis-**3-Acetyl-1-benzyloxycarbonyl-2-(4-methoxyphenylmethyl)piperidine (4d).** A suspension of 7.7 g of **4c** in 150 ml of Et_2O was stirred at 0° under N_2 while 19 ml of 2.3 M CH_3Li–Et_2O was added dropwise. Stirring was continued at 0° for 4 h. The reaction mixture was poured into cold aqueous NH_4Cl, and the Et_2O layer was washed with saturated $NaHCO_3$. 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. ($C_{23}H_{27}NO_4$) 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 $LiAlH_4$ in 250 ml of Et_2O was stirred at 0° while a solution of 73 g of **4d** in 1500 ml of Et_2O 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 $CHCl_3$ added. The organic layer was washed with saturated $NaHCO_3$, 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_2 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_2O and Et_2O, and the H_2O layer was made basic with NH_4OH and K_2CO_3. Extraction with Et_2O, 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_4OH was added. The product was filtered, washed with H_2O, 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. [$(C_{14}H_{19}NO)_2 \cdot HBr$] 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_2 (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_4OH, filtered, washed with H_2O, 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 $NaHCO_3$. Evaporation of the DMF, dissolution of the residue in $CHCl_3$, washing with H_2O, drying, filtration, and evaporation of the $CHCl_3$ gave the crude products. Bases were recrystallized from EtOH and salts from EtOH or EtOH–Et_2O. 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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(10) It would be of interest to determine the biological activity of the corresponding N derivatives of 6-noralkyl-11β-methyl-2,6-methano-3-benazocin-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,[1] 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,[2,3] dog,[4] and *Papio papio*[5] models. When the two phenyl rings were bridged as in the dibenzocycloheptene analogue **2**,[6] mild anticonvulsant activity was retained but it was decreased as compared to **1**.[7]

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