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. ($C_{13}H_{17}NO$·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. [$(C_{14}H_{19}NO)_2$·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.

Acknowledgment. The author wishes to thank Dr. R. K. Kullnig for spectral data and Mrs. A. K. Pierson for biological data.

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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*]cycloheptene-5-yl)-4-[(arylmethylene)amino]piperazines

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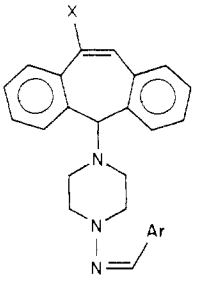
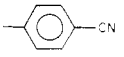
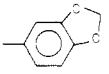
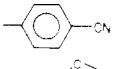
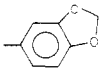
Since the potent anticonvulsant activity against electroshock seizures in mice for a novel series of hydrazone derivatives of benzhydrylpiperazines (1) was first reported by Craig,[1] much effort has been expended in these laboratories seeking to characterize and improve this activity. For one compound 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]

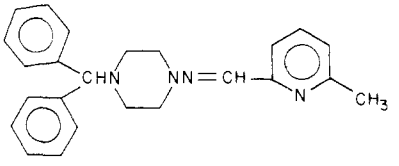
The present communication describes the synthesis and anticonvulsant activity of a series of highly active hydrazones derived from 10-substituted 5*H*-dibenzo[*a*,*d*]-cycloheptene-5-ylpiperazines. These compounds were prepared in order to define the effect of substitution of the

Table I. 1-(10-Cyano- and -10-bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)-4-[(arylmethylene)amino]piperazines



Compd	X	Ar	Crystn solvent[a]	Mp, °C	% yield	Analyses	λ_{max}	ϵ_{max}
10a	Br		A	166.5-168	61	C, H, N	305[c]	28700
10b	Br		B	208-211.5	70	C, H, N	310[c]	28900
10c	Br		C	162.5-165	60	C, H, N	297[c]	25200
10d	Br		C	160.5-163	50	C, H, N	307[c]	27200
10e	Br		B	218-221	67	C, H, N	322[d]	28500
10f	Br		D	95-135[b]	60	C, H, N	289,[c] 308	27300, 26300
10g	CN		E	182-184	62	C, H, N	306[c]	35400
10h	CN		B	226.5-229	53	C, H, N	311[c]	32700
10i	CN		B	250-253	53	C, H, N	302[d]	29400
10j	CN		B	200-202	61	C, H, N	308[c]	34800
10k	CN		F	231-234	64	C, H, N	319[d]	35300
10l	CN		B	183-185.5	70	C, H, N	295,[c] 310	27000, 28400

[a] A, *i*-PrOH; B, THF-hexane; C, EtOH; D, *i*-PrOH-EtOH; E, $CHCl_3$-hexane; F, THF-pentane. [b] Compound became a glass at 95° and had melted by 135°. [c] Run in MeOH. [d] Run in dioxane.



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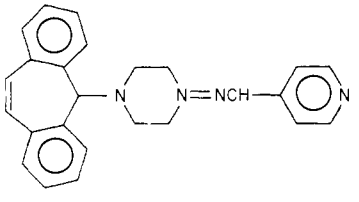


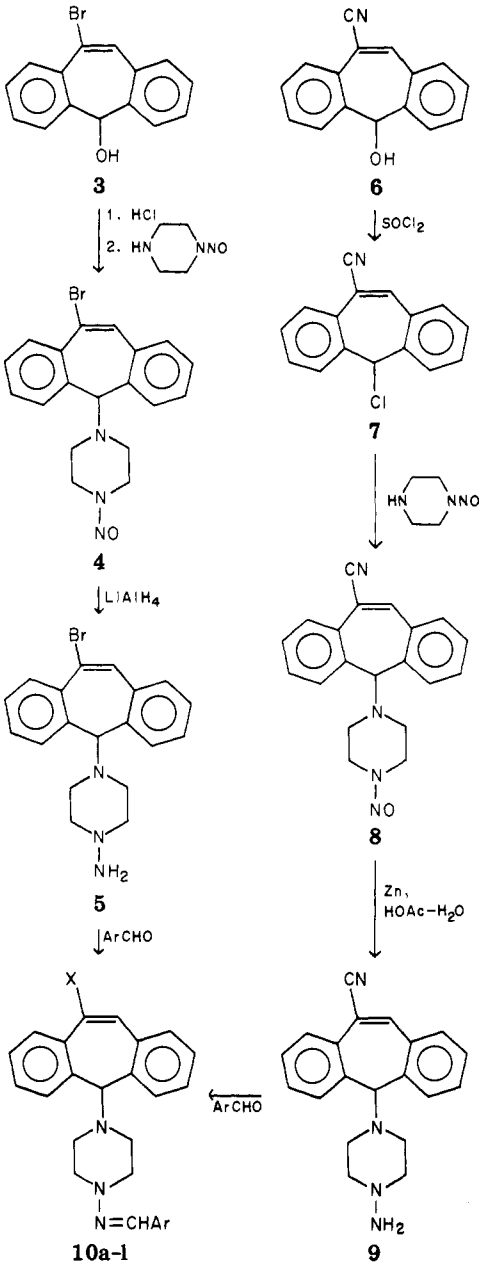
2

10 position of 2 on the anticonvulsant activity and side effects.

New compounds were prepared as outlined in Scheme I. Details of the general methods of preparation are given in the Experimental Section. Details of the characteristic uv spectra that were useful for the identification and characterization of the hydrazones (**10a**–l) and other physical properties are given in Table I.

Biology. The title compounds (**10**) were assessed for anticonvulsant activity in mice by the maximal electroshock seizure (MES) test as described by Swinyard et al.[8] In this assay each mouse is challenged with a current of 50 mA delivered via corneal electrodes for 0.2 s, 2.5 h following intragastric administration of the test compound in saline. The current is sufficient to induce maximal electroshock seizures in 100% of control animals. The ED_{50} is determined as the dose of compound protecting 50% of the animals. Acute neurotoxicity was used as a measure of side effects and was estimated by determining the inability of mice to maintain equilibrium on a rotating horizontal rod (rotar). Mice were placed on a rotating rod 2.5 h after intragastric administration of the test compound in saline. Untreated mice can remain on the rod indefinitely. The ED_{50} is the dose affecting 50% of the animals. Groups of ten mice were used per dose level and ED_{50}'s were calculated by the method of Litchfield and Wilcoxon.[9] The results are summarized in Table II along with the data for 1 as reported in Craigs' paper,[1] 2, diphenylhydantoin,

Scheme I



and phenobarbital. A protective index (PI) was also calculated by the method of Litchfield and Wilcoxon[9] and is included in Table II.

The 10-bromo and 10-cyano compounds do, indeed, represent a series of compounds that were highly active in blocking the seizures associated with maximal electroshock (MES). The pyridylhydrazones were consistently as active or more active than the two standard drugs in these tests. The 10-bromo compounds were, in general, slightly more active than the 10-cyano compounds. As in the benzhydryl series,[1] it was only the pyridylhydrazones that possessed significant activity and the arylhydrazones (**10e,f,k,l**) possessed only slight activity or were inactive at screening doses. Even though the anticonvulsant activity of these compounds seemed improved by the 10-substituent, no reduction in side effects (rotar) was observed. There was no improvement in the PI as compared to **1** or the standard compounds.

The blockade of pentylenetetrazole (Metrazol, MET) induced seizures is another assay commonly employed as an animal model for testing potential anticonvulsants.[10]

Table II. Anticonvulsant (MES), Rotar Activity, and PI[a] for **10a-l** and Standard Drugs

Compd	MES ED_{50}	Rotar ED_{50}	PI[a]
Diphenylhydantoin	7	47	7
Phenobarbital	10	37	3.7
1	6	93	15.5
2[b]	18	300	16.6
10a	4	7	1.8
10b	6	11	1.8
10c	3	7	2.3
10d	3	3	1
10e	i[c]	i[c]	
10f	16	17	1
10g	7	9	1.3
10h	6	15	2.5
10i	6	11	1.8
10j	7	10	1.4
10k	i[c]	i[c]	
10l	a[d]	a[d]	

[a] PI = ED_{50} rotar/ED_{50} MES. [b] See ref 7. [c] Inactive at 50 mg/kg. [d] Active in three of ten mice at 50 mpk.

Antiepileptic drugs like diphenylhydantoin are active in the MES test but inactive in the MET test. Other drugs such as phenobarbital are active in both assays. A selected group of our compounds were tested against Metrazol seizures; 1.5 h following intragastric administration of the test compound in saline, each mouse was challenged with an intravenous infusion of 35 mg/kg of Metrazol. A dose of compound is considered active if the clonic component of the Metrazol-induced convulsion is blocked. Compounds **10a,b,h,j** were inactive at 25 mg/kg and **10c** was inactive at 100 mg/kg. These compounds appear to behave more like diphenylhydantoin in the two assays. Compounds **10a,f,j** were also tested against minimal electroshock and oxotremorine- and strychnine-induced convulsions and were inactive at screening doses.

Experimental Section

The infrared spectra were determined using a Beckman IR-12 and ultraviolet spectra were determined using a Beckman DK2. Meltings points were determined in open capillary tubes in a Melt-Temp apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for the elements were within 0.4% of the theoretical values.

1-(10-Bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)-4-nitrosopiperazine (4). Anhydrous hydrogen chloride was bubbled for 1 h into a solution of 5.0 g (0.017 mol) of 5-hydroxy-10-bromo-5*H*-dibenzo[*a*,*d*]cycloheptene (**3**)[11] in 40 ml of benzene. The benzene solution was decanted from the water that had formed and was dried over Drierite. The solvent was removed under reduced pressure and the solid residue, 5-chloro-10-bromo-5*H*-dibenzo[*a*,*d*]cycloheptene, was dissolved in 70 ml of methyl ethyl ketone. A solution of 3.0 g (0.026 mol) of *N*-nitrosopiperazine[12] in 20 ml of methyl ethyl ketone was added followed by 6 g of powdered anhydrous potassium carbonate and the reaction mixture was stirred at reflux for 7 h. The mixture was filtered and concentration of the filtrate to dryness left a solid that on warming first with boiling ethanol and then cooling and washing with hexane gave 4.57 g (70%), mp 191–198°. Recrystallization from tetrahydrofuran–hexane produced almost colorless crystals, mp 197.5–199.5°. Anal. ($C_{19}H_{18}BrN_3O$) C, H, N.

1-(10-Bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)-4-aminopiperazine (5). Lithium aluminum hydride (7.0 g, 0.18 mol) was added to a suspension of 20.0 g (0.052 mol) of 1-(10-bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)-4-nitrosopiperazine (**4**) in 2 l. of anhydrous ether. The mixture was stirred at room temperature for 5 h and cooled in an ice bath, and the following solutions were added successively: (1) 14 ml of water in 28 ml of tetrahydrofuran, (2) 14 ml of 25% NaOH, and (3) 14 ml of water. The salts were removed by filtration and washed with tetrahydrofuran. The

combined filtrate and washes were dried over anhydrous magnesium sulfate. Removal of the solvents left 18.0 g (93%) of pale yellow solid. Recrystallization from tetrahydrofuran–hexane yielded pure white crystals, mp 187.5–190.5°. Anal. ($C_{19}H_{20}BrN_3$) C, H, N.

5-Chloro-10-cyano-5*H*-dibenzo[*a*,*d*]cycloheptene (7). A solution of 55 ml of thionyl chloride in 100 ml of chloroform was added dropwise with stirring to a solution of 56 g (0.24 mol) of 5-hydroxy-10-cyano-5*H*-dibenzo[*a*,*d*]cycloheptene (**6**)[11] in 250 ml of chloroform. The reaction solution was stirred under reflux for 5 h; then the solvent was removed by distillation under reduced pressure. The solid residue was recrystallized from ethyl acetate–hexane yielding 25.4 g (42%) of white crystals: mp 147.5–150.5°; ir ν ($CHCl_3$) 2225 cm^{-1}. A second crop of 18.6 g (31%), mp 144–148°, was obtained by concentrating the filtrate and addition of more hexane. These products were used without further purification.

1-(10-Cyano-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)-4-nitrosopiperazine (8). A solution of 12.0 g (0.104 mol) of *N*-nitrosopiperazine[12] in 50 ml of methyl ethyl ketone was added dropwise to a mixture of 20.0 g (0.0797 mol) of 5-chloro-10-cyano-5*H*-dibenzo[*a*,*d*]cycloheptene (**7**) and 20 g of powdered anhydrous potassium carbonate in 400 ml of methyl ethyl ketone. The mixture was heated under reflux with stirring for 5 h and then was left standing at room temperature overnight. Filtration and concentration of the filtrate to dryness gave a solid that was washed with cold ethanol yielding 23.0 g (87%) of off-white solid, mp 182–184.5°. An analytical sample was prepared by recrystallization from absolute ethanol: mp 185–187.5°; ir ν ($CHCl_3$) 2220 cm^{-1}. Anal. ($C_{20}H_{18}N_4O$) C, H, N.

1-(10-Cyano-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)-4-aminopiperazine (9). Zinc dust (15 g) was slowly added to a solution of 9.80 g (0.0297 mol) of 1-(10-cyano-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)-4-nitrosopiperazine (**8**) in 125 ml of glacial acetic acid and 50 ml of water, keeping the temperature at 30–35°. After the mixture was stirred at 30° for 1 h the zinc was removed by filtration and washed with a solution of 30 ml of 70% (v/v) acetic acid in water. The combined filtrate and wash were diluted to 600 ml with water and, after cooling in an ice bath, the solution was made alkaline by the addition of concentrated ammonia. The oil that separated was extracted into chloroform, washed with water, and dried over anhydrous potassium carbonate. Removal of the solvent under reduced pressure left an oil that solidified on scratching. The solid was washed with petroleum ether yielding 9.20 g of white powder, mp 137–146°, that was used for the preparation of the hydrazones without further purification: ir ν ($CHCl_3$) 2210 cm^{-1}.

General Procedure for the Preparation of 1-(10-Cyano- and -10-bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)-4-[(arylmethylene)amino]piperazines (10). A mixture of 0.01 mol of 1-(10-cyano- or -10-bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)-4-aminopiperazine and 0.015–0.03 mol of the arylcarboxaldehyde and 1–2 drops of glacial acetic acid in 30 ml of 2-propanol was stirred at reflux for 5 h and then left standing at room temperature. If crystals separated they were collected and purified by recrystallization. If no crystals separated on standing, the solvent was removed under reduced pressure and the residue was triturated with hexane. The solid that formed was then purified by recrystallization. Data for the compounds are given in Table I. Two specific examples are given below.

1-(10-Cyano-5*H*-dibenzo[*a*,*d*]cycloheptene-5-yl)-4-[(6-methyl-2-pyridylmethylene)amino]piperazine (10j). A mixture of 3.0 g (0.010 mol) of 1-(10-cyano-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-yl)-4-aminopiperazine (**9**) and 2.1 g (0.017 mol) of 6-methyl-2-pyridinecarboxaldehyde and 2 drops of glacial acetic acid in 30 ml of 2-propanol was stirred at reflux for 4 h and on standing at room temperature overnight no crystals formed. The solution was reduced to near dryness under reduced pressure. The addition of hexane to the residue produced 3.19 g of light brown solid that was recrystallized from tetrahydrofuran–hexane yielding 2.57 g (61%) of beige crystals: mp 200–202°; ir ν ($CHCl_3$) 2220 cm^{-1}; uv λ_{max} (MeOH) 308 nm (ϵ 34 800). Anal. ($C_{27}H_{25}N_5$) C, H, N.

1-(10-Bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)-4-[(2-pyridylmethylene)amino]piperazine (10a). A mixture of 4.0 g (0.011 mol) of 1-(10-bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)-4-aminopiperazine and 1.6 g (0.015 mol) of 2-pyridinecarboxaldehyde and 1 drop of glacial acetic acid in 40 ml of 2-propanol was stirred under reflux for 6 h. The crystals that formed on standing were collected and washed with hexane yielding 3.43 g of brown crystals that were recrystallized from 2-propanol yielding 3.0 g (61%) of beige crystals: mp 166.5–168°; uv λ_{max} (MeOH) 305 nm (ϵ 28 700). Anal. ($C_{25}H_{23}BrN_4$) C, H, N.

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