tallized from CH_2Cl_2–hexane to give 2.83 g of resolved 7: mp 138–140 °C; $[\alpha]^{25}_D$ +7.7 ± 0.1° (c 0.0121, MeOH).

The crude salt remaining was converted to the free acid, mp 139–141 °C, and showed $[\alpha]_D$ of −1.25 ± 0.15°.

Biological. Male rats (Sprague–Dawley derived) weighing 150–160 g were employed in the study. The compounds were dissolved in acetone and taken up on silica gel (3 × weight of drug) and the solvent was evaporated. The silica gel drug mixture was mixed with commercial ground rat chow to yield concentrations of 0.125 or 0.25% (w/w) of drug in the feed. This treated feed was administered to the rats ad libitum over a 14-day period. Control groups were given feed alone. At the end of the experimental period, the animals were weighed and killed by decapitation. Blood samples were collected; the liver was removed, weighed, and frozen for future analysis. The serum cholesterol and triglyceride levels were measured by methods previously described.[11,12]

The data are presented as milligram percent in the serum along with the standard deviation for each group. The significance level (p) was determined using Student's t test. The mean and standard deviation for the test groups and control groups was used to calculate t.

Acknowledgment. The authors sincerely appreciate the initial screening results from Phil Shea of the Pharmacology Department and the spectroscopic analyses of Werner Braun of the Pharmacokinetics Group, The Dow Chemical Co.

References and Notes

(1) Presented in part at the 4th International Symposium on Medicinal Chemistry, Noordwijkerhout, The Netherlands, Sept 9–13, 1974, and the 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 6–11, 1975.
(2) D. T. Nash, *J. Clin. Pharmacol.*, **14** (8 and 9), 470 (1974).
(3) M. S. Newman and H. A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966).
(4) R. Pajeau and J. P. Begue, *Bull. Soc. Chim. Fr.*, 1923 (1962).
(5) W. L. Mosby, *J. Org. Chem.*, **24**, 421 (1959).
(6) J. L. Wood, *Org. React.*, **3**, 240 (1946).
(7) A. N. Tischler, F. M. Thompson, L. J. Libertini, and M. Calvin, *J. Med. Chem.*, **17**, 948 (1974). The principal difference in our TLC system was that acetic acid was added and the ratios were altered in the developing solvent mixture to give rounder shaped spots and less streaking.
(8) J. B. Peterson and M. Dexter, U.S. Patent 3 249 632.
(9) M. Knell, U.S. Patent 3 455 994 (July 1969).
(10) R. J. Laufer, U.S. Patent 3 129 262 (April 1964).
(11) A. A. Henly, *Analyst*, **82**, 286 (1957).
(12) E. E. VanHandel and D. B. Zilversmit, *J. Lab. Clin. Med.*, **50**, 152 (1957); E. E. VanHandel, *Clin. Chem.*, **7**, 249 (1961).

Synthesis and Stereospecific Antipsychotic Activity of (−)-1-Cyclopropylmethyl-4-(3-trifluoromethylthio-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)piperidine

David C. Remy,* Kenneth E. Rittle, Cecilia A. Hunt, Paul S. Anderson, Byron H. Arison, Edward L. Engelhardt, Ralph Hirschmann,

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

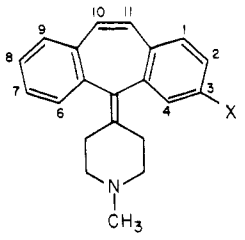
Bradley V. Clineschmidt, Victor J. Lotti, Patricia R. Bunting, Ruby J. Ballentine, Nan L. Papp, Lars Flataker, John J. Witoslawski, and Clement A. Stone

Merck Institute for Therapeutic Research, West Point, Pennsylvania 19486. *Received February 2, 1977*

The synthesis and resolution of 3-iodocyproheptadine [(±)-**5a**] and 1-cyclopropylmethyl-4-(3-iodo-5*H*-dibenzo-[*a*,*d*]cyclohepten-5-ylidene)piperidine [(±)-**5b**] are described. The resulting atropisomers undergo reaction with trifluoromethylthiocopper to give optically active products without extensive racemization. In this manner, optically pure (+)- and (−)-3-trifluoromethylthiocyproheptadine [(+)-**6a** and (−)-**6a**, respectively] and (+)- and (−)-1-cyclopropylmethyl-4-(3-trifluoromethylthio-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)piperidine [(+)-**6b** and (−)-**6b**, respectively] have been prepared. The influence of a chiral europium shift reagent on the proton and fluorine resonance signals as a diagnostic tool for the determination of the optical purities of these atropisomers is discussed. The four compounds, (+)-**6a**, (−)-**6a**, (+)-**6b**, and (−)-**6b**, were studied in squirrel monkeys for their ability to block conditioned avoidance responding. All of the antiavoidance activity was found to reside solely in the levorotatory compounds (−)-**6a** and (−)-**6b**. Further comparison of the enantiomers (−)-**6b** and (+)-**6b** showed that the ability to antagonize apomorphine-induced stereotyped behavior is confined to the levorotatory isomer (−)-**6b** while weak central anticholinergic activity resides solely in the dextrorotatory isomer (+)-**6b**. Neither (−)-**6b** nor (+)-**6b** has significant peripheral anticholinergic activity.

The introduction of nuclear substituents into the 3 position of cyproheptadine (1, X = H) results not only in significant changes in the biological profiles of the resulting compounds but also results in the introduction of atropisomerism into the series. Ebnöther et al.[1] have shown that nonbonded interactions between the protons in the 4 and 6 positions of the aromatic rings and the allylic protons of the piperidine ring restrict the inversion of the central, nonplanar, seven-membered ring of these 3-substituted cyproheptadine derivatives. As a consequence of these interactions, the free-energy barriers to inversion are sufficiently high as to confer a relatively high degree of thermal stability on these chiral conformers (atropisomers).[1]

During the course of investigating structure–activity relationships in a series of 3-substituted cyproheptadine derivatives and analogues, 3-iodocyproheptadine [(±)-**5a**]

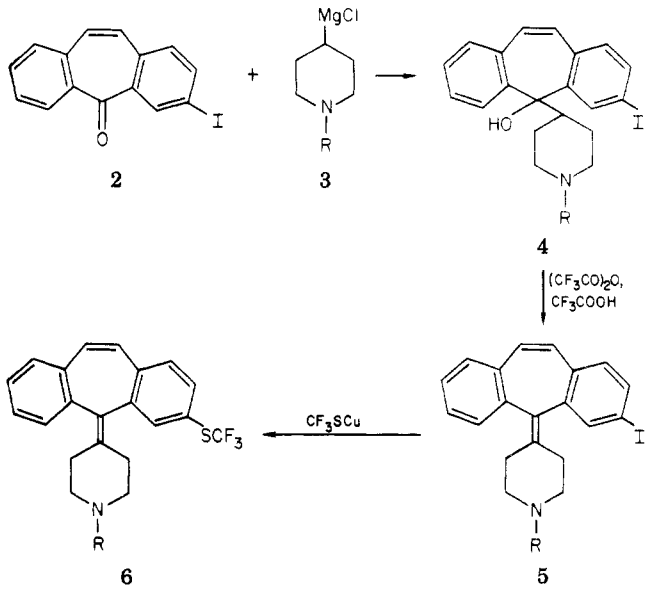


1

and 1-cyclopropylmethyl-4-(3-iodo-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-ylidene)piperidine [(±)-**5b**] were prepared and resolved into their optical antipodes.

Trifluoromethylthiocopper, generated in situ by the reaction of bis(trifluoromethylthio)mercury with copper, has recently been shown to react with aromatic iodides and bromides to give aryltrifluoromethyl sulfides.[2] The re-

Scheme I



3-6a, R = CH_3
b, R = CH_2-c-C_3H_5

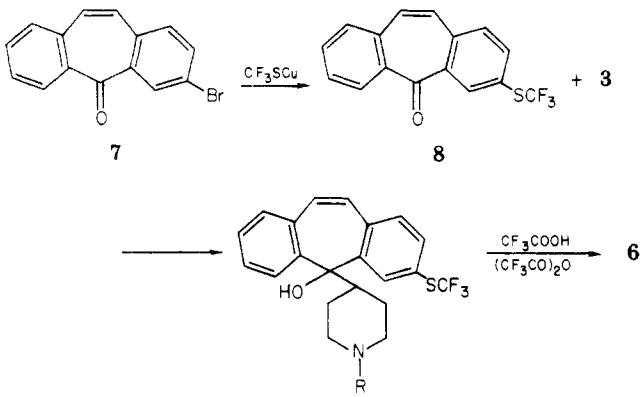
action of aromatic iodides proceeds under particularly mild, neutral conditions. In view of the mild conditions available for the preparation of trifluoromethylthio derivatives, it became of interest to study the reaction of trifluoromethylthiocopper with (+)- and (−)-**5a** and (+)- and (−)-**5b**.[3] We now wish to report that these enantiomers undergo nuclear substitution reactions with trifluoromethylthiocopper to give optically active products without extensive racemization. In this manner, optically pure (+)- and (−)-**6a** and (+)- and (−)-**6b** have been prepared. Since antipsychotic activity has been reported for certain piperidylidene derivatives of thioxanthenes, xanthenes, dibenzoxepins, and acridans,[4] an examination of the neuropharmacological activities of (+)- and (−)-**6a** and (+)- and (−)-**6b** was carried out. In view of the recent reports of chiral neuroleptic agents exhibiting stereospecificity of biological activity,[5] it was of particular interest to examine the antipsychotic potential of these compounds to ascertain whether there were enantiomeric differences in activity.

Chemistry. The tricyclic carbinols **4a** and **4b** were prepared by addition of the Grignard reagents derived from 1-methyl-4-chloropiperidine[6] or 1-cyclopropylmethyl-4-chloropiperidine to ketone **2**. A mixture of trifluoroacetic acid and trifluoroacetic anhydride smoothly converted these carbinols to the racemic cyproheptadine analogues (±)-**5a** and (±)-**5b** (Scheme I).

These racemates, (±)-**5a** and (±)-**5b**, were readily resolved via crystallization of the diastereomeric di-*p*-toluoyl-*d*- or -*l*-tartaric acid (DPT-*d*-TA and DPT-*l*-TA, respectively) salts from ethanol. Both isomers of the resolving agent were used in each case. For example, reaction of (±)-**5a** with DPT-*d*-TA gave, after five crystallizations, the (−)-**5a**·DPT-*d*-TA salt, $[\alpha]^{25}_{589}$ −129°. The partially resolved free base (+)-**5a** that was isolated from the mother liquors was treated with DPT-*l*-TA to give, after five crystallizations, (+)-**5a**·DPT-*l*-TA, $[\alpha]^{25}_{589}$ +128°. Treatment of these salts with dilute sodium hydroxide afforded the pure enantiomeric bases (−)-**5a**, $[\alpha]^{25}_{589}$ −142°, and (+)-**5a**, $[\alpha]^{25}_{589}$ +142°.

When the optically pure iodides (+)-**5a**, (−)-**5a**, (+)-**5b**, and (−)-**5b** were allowed to react with trifluoromethylthiocopper at 100 °C for 4–6 h, the optically active derivatives (+)-**6a**, (−)-**6a**, (+)-**6b**, and (−)-**6b**, respectively,

Scheme II



9a, R = CH_3
b, R = CH_2-c-C_3H_5

were formed without extensive racemization. In a typical experiment, the iodo compound (−)-**5b**, $[\alpha]^{25}_{589}$ −145°, was allowed to react with trifluoromethylthiocopper at steam bath temperature for 6 h to give a 63% yield of (−)-**6b** that was 89% optically pure ($[\alpha]^{25}_{589}$ −56.3°). Three recrystallizations of this material from acetonitrile gave optically pure (−)-**6b**, $[\alpha]^{25}_{589}$ −63.5°, in an overall yield of 57%. In a similar maner, (+)-**5b**, $[\alpha]^{25}_{589}$ +143°, after reaction with trifluoromethylthiocopper and three recrystallizations of the product from acetonitrile, gave optically pure (+)-**6b**, $[\alpha]^{25}_{589}$ +63.5°, in an overall yield of 57%.

The stereochemical homogeneity of (+)-**6b** and (−)-**6b** was demonstrated by phase solubility analysis. Both (+)-**6b** and (−)-**6b** showed percent slopes of 0.0% (±0.2 and ±0.1%, respectively) when their solubility was measured in acetonitrile. When a sample of (+)-**6b** was admixed with 6.2% of the racemate (±)-**6b**, the expected slope of 3.1% was found experimentally.

Racemic **6b**, prepared by the procedure shown in Scheme II, was resolved using di-*p*-toluoyl-*d*-tartaric acid. The levorotatory isomer thus obtained was identical with material prepared from the reaction of trifluoromethylthiocopper with (−)-**5b**. As expected, the enantiomeric pairs (+)-**6a**, (−)-**6a**, and (+)-**6b**, (−)-**6b** had equal but opposite circular dichroism spectra.

The direct determination of enantiomeric purity or composition during resolution or reaction using chiral lanthanide shift reagents is now a well-established procedure.[7,8] Except for one report, however, these shift reagents do not appear to have been used in a study of enantiomerism resulting from atropisomerism. Yang and Lui[9] examined a series of atropisomeric *cis*-β-alkylstyrene derivatives in the presence of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) and observed a small doubling of a methoxymethyl singlet at low temperatures. It was of interest, therefore, to examine the influence of a chiral shift reagent on the chiral atropisomers discussed in this paper in order to determine whether magnetic nonequivalence of diastereotopic nuclei would result and, thus, lead to an analytical procedure useful in the study of these compounds.

The ^{1}H NMR spectra of (±)-**5a**, (±)-**5b**, (±)-**6a**, and (±)-**6b** were examined in the presence of tris[3-(heptafluorobutyryl)-*d*-camphorato]europium (III), [Eu(hfbc)$_3$].[7] Concentrations of the shift reagent were varied from 0.3 to 1.0 mol of reagent per mole of substrate. Only in the case of (±)-**6a** was any enantiomeric shift differential observed. In this racemate, the doublet signals for the H_{10}–H_{11} vinyl protons each showed a doubling (1.5 Hz) at 0.5 mol of Eu(hfbc)$_3$ per mole of substrate. This was not a sufficient shift difference to be useful in establishing

Table I. Behavioral Effects. Inhibition of Conditioned Avoidance Response in Squirrel Monkeys by (−)-6a and (−)-6b

Compd	Dose,[a] mg/kg po	Time interval, min, postdosing	N^b	No. of responses[c]	Shocks No.	Shocks % max[d]
(−)-6a	1.0	0-30	3	202	0	0
		30-60		197	0.33	0.66
		60-90		312	4.0	8.0
	3.0	90-120		187	38.7	77.4
		120-150		19	50	100
		150-180		8	50	100
(−)-6b	0.25	0-30	6	401	0.17	0.34
		30-60		374	0.17	0.34
		60-90		344	0.34	0.68
	0.50	90-120		305	8.7	17.4
		120-150		203	19.8	39.4
		150-180		44	48.7	97.4
	1.0	180-210		24	50	100
		210-240		6	50	100
		240-270		5	50	100

[a] The animals were dosed at intervals of 90 min. [b] Number of animals. [c] The values represent the averages for the number of animals. [d] Maximum number of shocks possible per 30-min interval was 50.

Table II. Reversal of Antiavoidance Effect of (−)-6b in Squirrel Monkeys by Administration of Benztropine

Treatments[a]		Shocks received (% max),[b] hours after treatment I								
I, mg/kg po	II, mg/kg im	0-0.5	0.5-1	1-1.5	1.5-2	2-2.5	2.5-3	3-3.5	3.5-4	4-4.5
1. (−)-6b[c] (1)	Saline	0	9.6	61.3	62	65	69	66.7	90	82
2. (−)-6b (1)	Benztropine (0.75)	2	7.6	5.7	5.3	8.7	4.3	4.	3	3.7
3. (−)-6b (1)	Saline	0	1.7	42	52.7	69.3	42.7	70.3	73	64.3

[a] The test compound was administered by gavage to the same group of six monkeys on three occasions. Line 1: the test compound was administered followed by saline 15 min later. Line 2: 6 days later the animals received test compound followed by benztropine 15 min later. Line 3: 10 days later, the animals were tested with (−)-6b and saline again. [b] All values are averages of six animals. [c] Phosphate salt.

enantiomeric compositions or optical purity.

The ^{19}F NMR spectra of (±)-6a and (±)-6b were also examined in the presence of $Eu(hfbc)_3$. The ^{19}F chemical shifts observed for the trifluoromethylthio groups of these compounds are sharp singlets occurring in a part of the spectrum unoccupied by fluorine signals arising from the fluorinated chiral shift reagent. The ^{19}F signal of the trifluoromethylthio group of (±)-6b occurs at δ +42.2 ($CDCl_3$). Addition of 0.25 mol of $Eu(hfbc)_3$ per mole of (±)-6b to the solution causes a shift to δ +42.7 ppm while the signal remains an apparent singlet. The addition of another 0.25 mol of $Eu(hfbc)_3$ causes a further shift to δ +43.1 ppm with a simultaneous doubling of the signal into two equal trifluoromethylthio peaks separated by 3.0 Hz. This represents an enantiomeric shift difference, $\Delta\Delta\delta$, of 0.05 ppm. This separation was increased to 5.2 Hz ($\Delta\Delta\delta$ = 0.09 ppm) when the ratio of shift reagent to substrate was increased to unity. The ^{19}F NMR spectra of both (+)-6b and (−)-6b, measured in a similar fashion, showed only single trifluoromethylthio resonance signals. Excessive line broadening was not observed in any of these spectra.

The ^{19}F NMR spectrum of a mixture of 45 mg of (+)-6b, 5.0 mg of (−)-6b, and 140 mg of $Eu(hfbc)_3$ showed two trifluoromethylthio resonance signals with a $\Delta\Delta\delta$ of 0.09 ppm. For (−)-6b or (+)-6b, therefore, minimum optical purities of 80% can be determined by this procedure.

Similar results were obtained during a study of the ^{19}F NMR spectra of (±)-6a, (+)-6a, and (−)-6a.

Pharmacological Results. Inhibition of a conditioned avoidance response (antiavoidance activity) is a property common to neuroleptics and other CNS depressants. When the enantiomers (+)-6a, (−)-6a and (+)-6b, (−)-6b were tested for their ability to inhibit conditioned avoidance response in squirrel monkeys, the dextrorotatory compounds (+)-6a and (+)-6b were found to be inactive at oral doses of 9 and 27 mg/kg, respectively. As seen in Table I, all of the antiavoidance activity resides solely in the levorotatory compounds (−)-6a and (−)-6b.

Table III. Comparison of (±)-6b with Thioridazine and (−)-6b with Haloperidol for Blocking Conditioned Avoidance Response in Monkeys

Compd compared[a]	ED_{50}, mg/kg po (95% confidence limits)[b]
(±)-6b[c]	0.99 (0.64-1.52)
Thioridazine[d]	0.97 (0.55-1.74)
(−)-6b[c]	0.51 (0.19-1.35)
Haloperidol[e]	0.29 (0.23-0.37)

[a] Two groups of six monkeys per group were used, with one being employed for comparing (±)-6b with thioridazine and the other for studies with (−)-6b and haloperidol. The experimental design was that of a Latin square, with three dose levels (noncumulative) per compound and at least 7 days between treatments. [b] ED_{50} for each compound was determined via regression analysis at the time of peak activity. [c] Phosphate salt. [d] Hydrochloride salt. [e] Haldol (McNeil).

Neuroleptics can be distinguished from other CNS depressants, such as chlordiazepoxide, pentobarbital, and chloral hydrate, by the use of anticholinergic agents such as benztropine.[10] Anticholinergic compounds markedly antagonize the antiavoidance effects of neuroleptics, while having no effect or increasing the antiavoidance actions of other types of depressants.[10] That (−)-6b has true neuroleptic activity was shown by the antagonism of its antiavoidance effect by benztropine (Table II). When (−)-6b was compared with its racemate (±)-6b for their ability to block conditioned avoidance response in squirrel monkeys (Table III), the racemate was observed to be one-half as active as the enantiomer (−)-6b.

Stereotyped behavior, that is, compulsive licking, gnawing, and sniffing, elicited by apomorphine depends on a direct stimulation of receptors for dopamine in the CNS.[11] Antagonism of apomorphine-induced stereotypies,

Table IV. Blockade of Apomorphine-Induced Stereotypies[a] and Peripheral Anticholinergic Activities[a]

Compd	Blockade of apomorphine-induced stereotypies, ED_{50}, mg/kg po[d]	Peripheral anticholinergic act., $ED_{1.5}$,[b] mg/kg po[d] 2 h	5 h
(−)-6b	3.8 (3.1-4.6)	>120	>120
(+)-6b	>60	>120	>120
(±)-6b	9.8 (6.6-13.6)	>120	>120
Haloperidol[c]	0.32 (0.08-1.22)		
1 (X = H)		6.0 (4.6-8.1)	

[a] See Pharmacology in the Experimental Section for details. [b] The $ED_{1.5}$ is defined as the dose level required to produce dilation of the pupil to 1.5 μm units in 50% of the mice, see ref 16; 20 mice per group. [c] Haldol (McNeil). [d] 95% confidence limits are given in parentheses.

therefore, provides a useful in vivo test for dopamine receptor-blocking activity. Not only is this a selective and sensitive test for neuroleptic activity,[12] but it is consistent with a potential antipsychotic utility in man.[13] The activities of (±)-**6b**, (−)-**6b**, and (+)-**6b** against apomorphine-induced stereotyped behavior in rats are summarized in Table IV. The results of this test show distinct differences in activity between the enantiomers. The dextrorotatory isomer, (+)-**6b**, at 60 mg/kg orally, administered 5 h prior to apomorphine, failed to protect the rats; that is, stereotypies occurred in all of the animals. The levorotatory enantiomer was orally active with an ED_{50} of 3.8 mg/kg.

As indicated in Table IV, (+)-**6b** and (−)-**6b**, as well as the racemate (±)-**6b**, produced little pupillary dilation at 2 or 5 h after oral administration. Cyproheptadine tested concurrently caused a considerable increase in pupil size consistent with its well-known peripheral anticholinergic property.

Central anticholinergic activity as shown by the ability to protect against lethality in mice induced by physostigmine was found only with (+)-**6b**; (−)-**6b** was inactive at doses four times the minimally effective dose of the former (Table V).

Blockade of central dopamine receptors by octoclothepin[5c] and butaclamol[5b] recently has been shown to be stereoselective in the sense that only one of the optical isomers of these chiral molecules has antiapomorphine and amphetamine antagonist activity. The results reported in this paper are in accord with this finding in that the central dopamine receptor blocking activity resides solely in (−)-**6b**. In addition, however, we find that the optical antipode (+)-**6b** has stereoselective central anticholinergic activity. This would suggest that blockade of central dopamine and cholinergic receptors not only has rigid selective stereochemical requirements but also that these requirements may have the opposite stereochemical sense. Further work to explore the significance of this intriguing possibility is in progress.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. Optical rotation measurements were determined with a Perkin-Elmer 141 automatic polarimeter; at least two readings were recorded at each wavelength and showed a deviation of ±0.005°. Gas–liquid phase chromatographic analyses were carried out on a Hewlett-Packard, Model 5700A/3370B gas chromatograph using a column (6 ft × 2 mm) packed with 1% OV-17 on 100–120 Gas-Chrom Q. ^1H NMR spectra were determined on Varian T-60 and HA-100 spectrometers in $CDCl_3$, and all shifts are relative to tetramethylsilane as an internal standard. ^{19}F NMR spectra were determined on a Varian T-60 spectrometer in $CDCl_3$, and all shifts are relative to fluorotrichloromethane as an internal standard. Circular dichroism measurements were made with a Jasco J-41A automatic recording spectropolarimeter; all CD measurements were made in absolute ethanol and the results are expressed in terms of molecular ellipticity, $[\theta]_T$, in (deg cm^3)/dmol. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

3-Iodo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one[14] (2). 3-Bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one[3] (7) (30.0 g, 0.105 mol), Cu turnings (1.40 g, 0.022 mol), CuCl (1.10 g, 0.016 mol), and concentrated NH_4OH (75 mL) were agitated together at 195 °C in a steel bomb for 24 h. The cooled mixture was removed from the bomb, and the large solid mass was dissolved in hot $CHCl_3$. The blue aqueous residue from the reaction was extracted with $CHCl_3$, the combined $CHCl_3$ fractions were washed with H_2O, dried (Na_2SO_4), and filtered, and the solvent was removed by evaporation to give 22.8 g (98%) of crude 3-amino-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one.

3-Amino-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (60.02 g, 0.27 mol) was slurried with 250 mL of concentrated HCl. Ice (150 mL) was added, and the stirred mixture was cooled in an ice bath and

Table V. Central Anticholinergic Activities of (−)-6b and (+)-6b

Treatment I,[a] mg/kg po	Treatment II,[b] mg/kg ip	Treatment III, mg/kg sc	No. of deaths[c] / no. tested[d]
Methylcellulose	Methylcellulose	Saline	0/20
Methylcellulose	Methylcellulose	Physostigmine (1.6)	20/20 (100%)
Methylcellulose	Atropine methyl nitrate (2)	Physostigmine (1.6)	16/20 (80%)
1 (X = H) (10)	Atropine methyl nitrate (2)	Physostigmine (1.6)	0/20[e] (0%)
(+)-6b (240)	Atropine methyl nitrate (2)	Physostigmine (1.6)	1/19[e] (5%)
(120)	Atropine methyl nitrate (2)	Physostigmine (1.6)	4/20[e] (20%)
(60)	Atropine methyl nitrate (2)	Physostigmine (1.6)	4/18[e] (22%)
(30)	Atropine methyl nitrate (2)	Physostigmine (1.6)	12/19 (63%)
(15)	Atropine methyl nitrate (2)	Physostigmine (1.6)	17/20 (85%)
(7.5)	Atropine methyl nitrate (2)	Physostigmine (1.6)	16/20 (80%)
(3.75)	Atropine methyl nitrate (2)	Physostigmine (1.6)	19/19 (100%)
(−)-6b (240)	Atropine methyl nitrate (2)	Physostigmine (1.6)	16/20 (80%)
(120)	Atropine methyl nitrate (2)	Physostigmine (1.6)	15/20 (75%)
(60)	Atropine methyl nitrate (2)	Physostigmine (1.6)	18/20 (90%)
(30)	Atropine methyl nitrate (2)	Physostigmine (1.6)	17/20 (85%)
(15)	Atropine methyl nitrate (2)	Physostigmine (1.6)	19/19 (100%)
(7.5)	Atropine methyl nitrate (2)	Physostigmine (1.6)	19/20 (95%)
(3.75)	Atropine methyl nitrate (2)	Physostigmine (1.6)	20/20 (100%)

[a] 5 h before treatment III. [b] 0.5 h before treatment III. [c] Mice dead within 20 min after injecting physostigmine. [d] An occasional death occurred in mice treated with (+)-6b before injecting physostigmine. [e] $p < 0.05$ (Fisher's exact test; one tailed) vs. methylcellulose + atropine methyl nitrate + physostigmine.

diazotized by dropwise addition of a solution of 20.49 g (0.297 mol) of $NaNO_2$ in 100 mL of H_2O over 1 h. The internal temperature was held at 0 °C throughout the addition. The mixture was stirred for an additional 15 min and then was poured slowly into a stirred solution of 224 g (1.35 mol) of KI in 180 mL of H_2O. The mixture was stirred for 1 h at room temperature and then filtered to collect a brown solid. The solid was dissolved in $CHCl_3$, this solution was washed with H_2O, 10% sodium bisulfite, and H_2O, dried (Na_2SO_4), and filtered, and the solvent was removed by evaporation. The residual brown gum was dissolved in benzene and chromatographed on a silica gel column packed in benzene. Elution of the column with benzene gave, after removal of the solvent, 53.06 g (59%) of **2**. An analytical sample was prepared by recrystallization from MeOH: mp 97.5–99 °C. Anal. ($C_{15}H_9IO$) C, H, I.

(±)-1-Methyl-4-(3-iodo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)piperidine [(±)-5a]. To an ice-cooled solution of 10.0 g (0.301 mol) of **2** in 100 mL of dry THF was added dropwise 64 mL of 0.47 M **3a** in THF. The solution was stirred 1 h at room temperature and then the THF was removed on a rotary evaporator. The remaining red oily residue was dissolved in benzene and H_2O was added dropwise until a clear benzene supernatant and a gelatinous aqueous phase were obtained. The benzene phase was decanted and the gelatinous aqueous phase was extracted with two 100-mL portions of hot benzene. The combined benzene extracts were concentrated. The residue that remained was triturated with CH_3CN, and the product that crystallized was collected by filtration, washed with cold CH_3CN, and dried to give 5.95 g (46%) of **4a**. A solution of 3.23 g of **4a**, 30 mL of CF_3CO_2H, and 10 mL of $(CF_3CO)_2O$ was refluxed for 6 h. The solution was concentrated on a rotary evaporator and the residue was made basic with 5% NaOH. The oil that precipitated was extracted into ether, and this ether phase was washed with H_2O, dried, and filtered and the ether removed. The residue was triturated with CH_3CN, collected, and dried to give 2.36 g (76%) of (±)-**5a**. An analytical sample was prepared by recrystallization from ethyl acetate: mp 166–170 °C; NMR ($CDCl_3$) 1.9–2.6 [m, with a peak at 2.13 (NCH_3), 11 H, aliphatic CH], 6.80 (d, J = 1 Hz, 2 H, vinyl CH), 7.0–7.4 (m, 7 H, ArH). Anal. ($C_{21}H_{20}IN$) C, H, I, N.

Resolution of (±)-1-Methyl-4-(3-iodo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)piperidine. A. Levorotatory Isomer (-)-5a. To a solution of 4.60 g (0.0111 mol) of (±)-**5a** in 100 mL of hot EtOH was added 4.30 g (0.0111 mol) of di-*p*-toluoyl-*d*-tartaric acid dissolved in 45 mL of warm EtOH. The solution was stirred and allowed to cool slowly to room temperature. The salt that crystallized was removed by filtration, washed with cold EtOH, collected, and dried to give 2.36 g of material designated A. The clear EtOH filtrate and washings were combined and the solvent was removed to give a residue, B.

The 2.36 g of A was recrystallized from EtOH four times to give a product with a constant rotation: $[\alpha]^{25}_{589}$ −129°, $[\alpha]^{25}_{578}$ −136°, $[\alpha]^{25}_{546}$ −162°, $[\alpha]^{25}_{436}$ −371° (*c* 0.407, pyridine); mp 156–157 °C. This salt, 0.35 g, was converted to the free base (-)-**5a** using 5% NaOH and extracting it into ether. The ether extract was washed with H_2O, dried ($MgSO_4$), and filtered, and the ether was removed to give 0.12 g of material. An analytical sample was prepared by recrystallization from CH_3CN: mp 190.5–193 °C; $[\alpha]^{25}_{589}$ −142°, $[\alpha]^{25}_{578}$ −151°, $[\alpha]^{25}_{546}$ −182°, $[\alpha]^{25}_{436}$ −443° (*c* 0.356, $CHCl_3$); GLC homogeneous. Anal. ($C_{21}H_{20}IN$) C, H, I, N.

B. Dextrorotatory Isomer (+)-5a. Residue B was treated with a saturated Na_2CO_3 solution. The free base that precipitated was extracted into ether. Evaporation of the ether gave 2.23 g of a solid that was dissolved in 75 mL of hot EtOH and was treated with 2.18 g of di-*p*-toluoyl-*l*-tartaric acid monohydrate dissolved in 20 mL of hot EtOH. The solution was stirred, concentrated by boiling to 45 mL, and allowed to cool slowly to room temperature. The salt that crystallized was removed by filtration, washed with cold EtOH, and dried to give 2.00 g of material. After five recrystallizations from EtOH there was obtained 0.53 g of salt having a constant rotation: $[\alpha]^{25}_{589}$ +128°, $[\alpha]^{25}_{578}$ +136°, $[\alpha]^{25}_{546}$ +162°, $[\alpha]^{25}_{436}$ +372° (*c* 0.181, pyridine); mp 155–157 °C. This salt was converted to the free base (+)-**5a** as described for the enantiomer (-)-**5a**. Recrystallization from CH_3CN gave 0.18 g of pure (+)-**5a**: mp 189–193 °C; $[\alpha]^{25}_{589}$ +142°, $[\alpha]^{25}_{578}$ +151°, $[\alpha]^{25}_{546}$ +181°, $[\alpha]^{25}_{436}$ +443° (*c* 0.738, $CHCl_3$); NMR ($CDCl_3$) 2.0–2.7 [m, with a peak at 2.25 (NCH_3), 11 H, aliphatic CH], 6.85 (d, J = 1 Hz, 2 H, vinyl CH), 6.9–7.6 (m, 7 H, ArH); GLC homogeneous. Anal. ($C_{21}H_{20}IN$) C, H, I, N.

(-)-1-Methyl-4-(3-trifluoromethylthio-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)piperidine [(-)-6a]. A mixture of 1.42 g (0.0224 mol) of Cu (electrolytic dust), 2.47 g (0.00615 mol) of bis(trifluoromethylthio)mercury, 1.27 g (0.00307 mol) of (-)-**5a**, and 15 mL of DMF was stirred and heated on a steam bath for 4 h. The mixture was cooled in an ice bath and 25 mL of $CHCl_3$ was added. Then, 25 mL of concentrated NH_4OH was added slowly. After stirring overnight, the mixture was filtered through Celite. The inorganic residues were washed with $CHCl_3$. The filtrate and washings were combined and the $CHCl_3$ phase was separated from the deep blue aqueous phase. The $CHCl_3$ was washed with H_2O, dried ($MgSO_4$), and filtered, and the solvent was removed by evaporation. The residue was triturated with CH_3CN and removed by filtration to give 0.40 g (34%) of solid having $[\alpha]^{25}_{589}$ −58.0°; mp 130–132 °C. Two recrystallizations from CH_3CN gave 0.30 g of optically pure (-)-**6a**: mp 130–132 °C; $[\alpha]^{25}_{589}$ −58.4°, $[\alpha]^{25}_{578}$ −62.4°, $[\alpha]^{25}_{546}$ −76.9°, $[\alpha]^{25}_{436}$ −206° (*c* 0.498, $CHCl_3$); GLC homogeneous; the NMR spectrum was identical with the NMR spectrum of (+)-**6a**; CD (3×10^{-4} M) $[\theta]_{287}$ -1.60×10^4, $[\theta]_{250}$ $+3.27 \times 10^4$, $[\theta]_{233}$ $+2.50 \times 10^4$, $[\theta]_{221}$ -7.15×10^4, $[\theta]_{206}$ $+7.25 \times 10^4$. Anal. ($C_{22}H_{20}F_3NS$) H, F, N; C: calcd, 68.19; found, 68.67.

(+)-1-Methyl-4-(3-trifluoromethylthio-5*H*-dibenzo-[*a*,*d*]cyclohepten-5-ylidene)piperidine [(+)-6a]. Starting with 2.00 g (0.00484 mol) of (+)-**5a**, 3.90 g (0.0097 mol) of bis(trifluoromethylthio)mercury, 2.24 g (0.0353 mol) of Cu (electrolytic dust), and 20 mL of DMF, and following the procedure as described for the preparation of (-)-**6a**, there was obtained 0.45 g (39%) of (+)-**6a**: mp 130–132 °C; $[\alpha]^{25}_{589}$ +58.7°, $[\alpha]^{25}_{578}$ +63.0°, $[\alpha]^{25}_{546}$ +76.8°, $[\alpha]^{25}_{436}$ +204° (*c* 0.79, $CHCl_3$); NMR ($CDCl_3$) δ 2.0–2.7 [m, with a peak at 2.23 (NCH_3), 11 H, aliphatic CH], 6.95 (d, J = 1 Hz, 2 H, vinyl CH), 7.2–7.6 (m, 7 H, ArH), 42.1 (s, CF_3); GLC homogeneous; CD (3×10^{-4} M) $[\theta]_{287}$ $+1.57 \times 10^4$, $[\theta]_{250}$ -3.13×10^4, $[\theta]_{233}$ -2.33×10^4, $[\theta]_{221}$ $+7.09 \times 10^4$, $[\theta]_{206}$ -6.99×10^4. Anal. ($C_{22}H_{20}F_3NS$) C, H, F, N.

1-Cyclopropylmethyl-4-piperidylmagnesium Chloride (3b). To an ice-cooled solution of 21.97 g (0.143 mol) of 4-piperidone hydrochloride hydrate in 80 mL of H_2O was added dropwise 15.0 g (0.143 mol) of cyclopropanecarboxylic acid chloride. Simultaneous with the addition of the acid chloride, 37.53 g (0.236 mol) of potassium carbonate(s) was added in small portions and at such a rate as to maintain an alkaline mixture. After the additions were complete, the solution was stirred 1 h and then saturated with K_2CO_3(s). The mixture was extracted with five 100-mL portions of benzene. The combined benzene phases were dried ($MgSO_4$) and filtered, and the benzene was removed. The residue crystallized to give 20.78 g (87%) of 1-(cyclopropanecarbonyl)-4-piperidone, mp 69–72 °C. A solution of 20.10 g (0.120 mol) of 1-(cyclopropanecarbonyl)-4-piperidone in 75 mL of THF was added dropwise over 1 h to a slurry of 9.12 g (0.24 mol) of $LiAlH_4$ in 100 mL of dry THF. The mixture was allowed to warm spontaneously and then was stirred overnight at room temperature. After cooling in an ice bath, 40% NaOH was added dropwise until a clear, colorless organic phase over a semigranular, solid aqueous phase was obtained. The organic phase was decanted, and the residue was washed with warm THF. Evaporation of the combined THF fractions gave 17.81 g of 1-cyclopropylmethyl-4-piperidinol. This material was used immediately in the next reaction.

A solution of 16.78 g (0.141 mol) of $SOCl_2$ in 160 mL of benzene was cooled in an ice bath, and, while stirring, a solution of 17.55 g (0.063 mol) of 1-cyclopropylmethyl-4-piperidinol in 100 mL of benzene was added dropwise over 0.5 h. The mixture was stirred for 1 h in the ice bath, 3 h at room temperature, 2.5 h at reflux, and overnight at room temperature. The crystalline precipitate was removed by filtration and washed well with ether. After drying, there was obtained 19.61 g (83%) of 1-cyclopropylmethyl-4-chloropiperidine hydrochloride. A solution of 39.71 g of this salt in 100 mL of cold H_2O was saturated with solid K_2CO_3. The mixture was extracted with three 300-mL portions of ether. The combined ether extracts were dried ($MgSO_4$) and filtered, and the ether was removed in vacuo. The residue was distilled to give 28.64 g of 1-cyclopropylmethyl-4-chloropiperidine, bp 93–109 °C (17–18 mm). This water-soluble, slightly unstable

amine was used immediately in the Grignard reagent preparation.

Into a dry, nitrogen-flushed flask was placed 4.01 g (0.165 mol) of Mg turnings and 20 mL of dry THF. The flask was warmed to 50 °C and, while stirring, a solution of 28.64 g (0.165 mol) of 1-cyclopropylmethyl-4-chloropiperidine in 60 mL of THF was added dropwise at such a rate that when the external heating was removed, gentle refluxing occurred. After the reaction subsided, it was refluxed for 1 h. The solution, 1-cyclopropylmethyl-4-piperidylmagnesium chloride in THF, was found to be 1.20 M by magnesium analysis.

(±)-1-Cyclopropylmethyl-4-(3-iodo-5*H*-dibenzo[*a,d*]-cyclohepten-5-ylidene)piperidine [(±)-5b]. To an ice-cooled solution of 10.00 g (0.030 mol) of **2** in 60 mL of dry THF was added dropwise 30 mL of 1.20 M **3b** in THF. The solution was stirred 2 h, and then the THF was removed on a rotary evaporator. The red oily residue that remained was dissolved in benzene and H_2O was added dropwise until a clear benzene supernatant and a gelatinous aqueous phase were obtained. The benzene phase was decanted and the gelatinous aqueous phase was extracted with two 100-mL portions of hot benzene. The combined benzene extracts were washed with five 200-mL portions of H_2O, dried ($MgSO_4$), and filtered, and the benzene was removed in vacuo. The residue was placed on a silica gel column (1 × 24 in.) packed in $CHCl_3$. The column was washed with $CHCl_3$ which causes a by-product of the reaction, 3-iodo-5*H*-dibenzo[*a,d*]cyclohepten-5-ol, to be eluted. The column was eluted with 2% MeOH in $CHCl_3$. This eluate was concentrated to give 6.03 g of an oil that is mainly **4b**. A solution of 4.67 g of this oil in 45 mL of CF_3COOH and 35 mL of $(CF_3CO)_2O$ was refluxed for 20 h. The solution was concentrated on a rotary evaporator and the residue was made basic with 20% NaOH. The oil that precipitated was extracted into benzene, washed with H_2O, dried ($MgSO_4$), and filtered. After removal of solvent, the residue was triturated with CH_3CN and collected by filtration. There was obtained 2.58 g of product, which, when recrystallized from CH_3CN, gave 2.54 g (18.6% from **2**) of (±)-**5b**: mp 139–141 °C; NMR ($CDCl_3$) δ 0.1–0.85 (m, 4 H, cyclopropyl $-CH_2CH_2-$), 1.9–4.0 (m, 11 H, aliphatic CH, NCH_2, and cyclopropyl CH), 6.84 (d, J = 1 Hz, 2 H, vinyl CH), 7.0–7.6 (m, 7 H, ArH). Anal. ($C_{24}H_{24}IN$) C, H, I, N.

Resolution of (±)-1-Cyclopropylmethyl-4-(3-iodo-5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)piperidine. Levorotatory Isomer (-)-5b. The resolution of (±)-**5b** was carried out in a manner similar to that described for the resolution of (±)-**5a**. Starting with 63.98 g (0.1411 mol) of (±)-**5b** and 54.53 g (0.1411 mol) of di-*p*-toluoyl-*d*-tartaric acid, there was obtained after four recrystallizations from EtOH 24.60 g of crystalline salt having a constant rotation: $[\alpha]^{25}_{589}$ −129°, $[\alpha]^{25}_{578}$ −136°, $[\alpha]^{25}_{546}$ −162°, $[\alpha]^{25}_{436}$ −368° (*c* 0.948, pyridine); mp 147–149 °C. The crystalline free base (−)-**5b**, generated from the salt by treatment with Na_2CO_3, was recrystallized from CH_3CN to give pure (−)-**5b**: mp 136–138 °C; $[\alpha]^{25}_{589}$ −145°, $[\alpha]^{25}_{578}$ −153°, $[\alpha]^{25}_{546}$ −182°, $[\alpha]^{25}_{436}$ −435° (*c* 0.743, $CHCl_3$). Anal. ($C_{24}H_{24}IN$) C, H, I, N.

Dextrorotatory isomer (+)-**5b** was obtained from either racemic compound (±)-**5b** or from the mother liquors obtained above which were rich in (+)-**5b**. For example, when 10.0 g (0.0221 mol) of (±)-**5b** and 8.92 g (0.022 mol) of di-*p*-toluoyl-*l*-tartaric acid monohydrate were allowed to crystallize from 100 mL of EtOH and the product was recrystallized three times from EtOH, there was obtained 5.06 g of crystalline salt having $[\alpha]^{25}_{589}$ +129°, $[\alpha]^{25}_{578}$ +137°, $[\alpha]^{25}_{546}$ +163°, $[\alpha]^{25}_{436}$ +370° (*c* 0.663, pyridine); mp 146–147 °C. The crystalline free base (+)-**5b**, generated from the salt by treatment with Na_2CO_3, was purified by recrystallization from CH_3CN: mp 136–138 °C; $[\alpha]^{25}_{589}$ +143°, $[\alpha]^{25}_{578}$ +151°, $[\alpha]^{25}_{546}$ +181°, $[\alpha]^{25}_{436}$ +432° (*c* 0.99, $CHCl_3$). Anal. ($C_{24}H_{24}IN$) C, H, I, N.

(+)-1-Cyclopropylmethyl-4-(3-trifluoromethylthio-5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)piperidine [(+)-6b]. A mixture of 11.54 g (0.0255 mol) of (+)-**5b**, 30.77 g (0.0764 mol) of bis(trifluoromethylthio)mercury, 17.61 g (0.277 mol) of Cu powder (electrolytic dust), and 150 mL of DMF was stirred vigorously and heated on a steam bath for 6 h. The mixture was cooled in an ice bath and 175 mL of $CHCl_3$ was added. Then, 150 mL of 5% NaOH was added dropwise. The mixture was stirred vigorously for 2 h, after which time it was filtered through a pad of Celite. The cake of inorganic salts was washed with $CHCl_3$. The $CHCl_3$ filtrate and washings were separated from the aqueous phase, and after washing with H_2O the $CHCl_3$ phase was dried ($MgSO_4$) and filtered, and the solvent was removed by evaporation. The residue was triturated with CH_3CN and removed by filtration to give 8.41 g of pale yellow solid, mp 142–144 °C. This material was recrystallized from CH_3CN (Norite) to give 7.30 g of material having $[\alpha]^{25}_{589}$ +60.6°. Two more recrystallizations from CH_3CN gave 6.16 g (57%) of optically pure (+)-**6b**: mp 143.5–144.5 °C; $[\alpha]^{25}_{589}$ +63.5°, $[\alpha]^{25}_{578}$ +68.3°, $[\alpha]^{25}_{546}$ +82.1°, $[\alpha]^{25}_{436}$ +209° (*c* 0.630, $CHCl_3$); NMR ($CDCl_3$) δ 0.1–1.0 (m, 4 H, cyclopropyl $-CH_2CH_2-$), 1.8–2.7 (m, 11 H, aliphatic CH, NCH_2, and cyclopropyl CH), 6.92 (d, J = 1 Hz, 2 H, vinyl CH), 7.2–7.5 (m, 7 H, ArH), 41.9 (s, SCF_3); GLC homogeneous; CD (3×10^{-4} M) $[\theta]_{285}$ $+1.51 \times 10^4$, $[\theta]_{250}$ -2.91×10^4, $[\theta]_{233}$ -2.31×10^4, $[\theta]_{221}$ $+6.6 \times 10^4$, $[\theta]_{205.5}$ -6.2×10^4.

Phase solubility analysis showed a percent slope of 0.0 ± 0.2% in acetonitrile. A sample of (+)-**6b** was admixed with 6.2% of (±)-**6b**. Phase solubility analysis showed a percent slope of 3.1%. Anal. ($C_{25}H_{24}F_3NS$) C, H, F, N.

(-)-1-Cyclopropylmethyl-4-(3-trifluoromethylthio-5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)piperidine [(-)-6b]. Starting with 67.00 g (0.148 mol) of (−)-**5b**, 151.92 g (0.377 mol) of bis(trifluoromethylthio)mercury, 86.99 g (1.37 mol) of Cu (electrolytic dust), and 610 mL of DMF, and following the procedure as described for the preparation of (+)-**6b**, there was obtained 39.05 g (63%) of crystalline product, $[\alpha]^{25}_{589}$ −56.3°. Three recrystallizations from CH_3CN gave optically pure (−)-**6b**: 30.38 g (57%); mp 143.5–144.5 °C; $[\alpha]^{25}_{589}$ −63.5°, $[\alpha]^{25}_{578}$ −67.0°, $[\alpha]^{25}_{546}$ −81.4°, $[\alpha]^{25}_{436}$ −209° (*c* 0.397, $CHCl_3$); the NMR spectrum was identical with the NMR spectrum of (+)-**6b**; GLC homogeneous; CD (3×10^{-4} M) $[\theta]_{285}$ -1.46×10^4, $[\theta]_{250}$ $+3.06 \times 10^4$, $[\theta]_{233}$ $+2.46 \times 10^4$, $[\theta]_{221}$ -6.8×10^4, $[\theta]_{205.5}$ $+7.1 \times 10^4$.

Phase solubility analysis showed a percent slope of 0.0 ± 0.1% in acetonitrile. The extrapolated solubility of (−)-**6b** in acetonitrile at 25 °C was 2.1 mg/g of CH_3CN. Anal. ($C_{25}H_{24}F_3NS$) C, H, F, N.

3-Trifluoromethylthio-5*H*-dibenzo[*a,d*]cyclohepten-5-one (8). A mixture of 40.0 g (0.140 mol) of **7**, 97.0 g (0.28 mol) of bis(trifluoromethylthio)mercury, 64.81 g (1.02 mol) of Cu (electrolytic dust), and 220 mL of HMPA was stirred and heated at 175–180 °C for 2 h. The reaction was cooled in an ice bath, and, after adding 400 mL of benzene, 250 mL of 10% NaOH was added dropwise. The mixture was stirred for an additional 1 h and then was filtered through a pad of Celite. The benzene phase was separated and the aqueous phase was extracted with three 100-mL portions of benzene. The combined benzene phases were washed with four 250-mL portions of H_2O, dried ($MgSO_4$), and filtered, and the benzene was removed on a rotary evaporator. The residue, dissolved in 30 mL of benzene, was placed on a silica gel column (1.5 × 25 in.) packed in benzene. The column was eluted with benzene. Evaporation of the eluate gave 40.16 g (94%) of **8**, mp 87–88 °C. An analytical sample was prepared by sublimation at 100 °C (0.05 mm): mp 94.5–95 °C; NMR ($CDCl_3$) δ 41.4 (s, SCF_3). Anal. ($C_{16}H_9F_3OS$) C, H, F.

(±)-1-Methyl-4-(3-trifluoromethylthio-5*H*-dibenzo-[*a,d*]cyclohepten-5-ylidene)piperidine [(±)-6a]. The addition of 50 mL of 0.35 M **3a** to 5.00 g (0.0163 mol) of **8** was carried out in a manner similar to that described for the preparation of **4a**. There was obtained 2.81 g of crystalline alcohol **9a**. A solution of 2.81 g of **9a** in 50 mL of 6 N HCl and 10 mL of 1-butanol was stirred and refluxed for 21 h. The bulk of the solvent was removed on a rotary evaporator. The residue was made basic by adding 5% sodium hydroxide and the oil that precipitated was extracted into chloroform. This extract was washed with water and dried ($MgSO_4$) and the solvent removed. Recrystallization from acetonitrile gave 1.90 g (30% from **8**) of (±)-**6a**: mp 115–116.5 °C; NMR ($CDCl_3$) δ 1.9–2.7 [m, with a peak at 2.20 (NCH_3), 11 H aliphatic CH], 7.0 (d, J = 1 Hz, 2 H, vinyl CH), 7.3–7.6 (m, 7 H, ArH), 42.1 (s, SCF_3). Anal. ($C_{22}H_{20}F_3NS$) C, H, F, N, S.

(±)-1-Cyclopropylmethyl-4-(3-trifluoromethylthio-5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)piperidine [(±)-6b]. The addition of 29 mL of 1.14 M **3b** to 10.0 g (0.0326 mol) of **8** was carried out in a manner similar to that described for the preparation of **4b**. There was obtained 7.0 g of an oil that was predominantly **9b**. A solution of this oil in 40 mL of CF_3COOH and 50 mL of $(CF_3CO)_2O$ was refluxed overnight. The solution

was concentrated on a rotary evaporator and the residue was made basic with 5% NaOH. The oil that precipitated was extracted into ether, the ether phase was washed with H_2O and dried ($MgSO_4$), and the solvent was removed. Recrystallization from CH_3CN gave 4.26 g (31% from 8) of (±)-**6b**: mp 122–123 °C; NMR ($CDCl_3$) δ 0.1–1.0 (m, 4 H, cyclopropyl $-CH_2CH_2-$), 1.9–2.7 (m, 11 H, aliphatic CH, NCH_2, and cyclopropyl CH), 6.9 (d, J = 1 Hz, 2 H, vinyl CH), 7.2–7.5 (m, 7 H, ArH), 42.2 (s, SCF_3). Anal. ($C_{25}H_{24}F_3NS$) C, H, N, S.

This material, (±)-**6b**, was also prepared from (±)-**5b**. A mixture of 7.42 g (0.016 mol) of (±)-**5b**, 11.33 g (0.178 mol) of Cu dust, 19.77 g (0.049 mol) of bis(trifluoromethylthio)mercury, and 85 mL of DMF was stirred and heated on a steam bath for 6 h. Work-up and recrystallization as described for (−)-**6b** gave 4.88 g (70%) of (±)-**6b**, mp 120–123 °C.

(−)-1-Cyclopropylmethyl-4-(3-trifluoromethylthio-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)piperidine [(−)-6b] Prepared by Resolution of (±)-6b. To a solution of 19.81 g (0.0463 mol) of (±)-**6b** in 70 mL of benzene was added 8.95 g (0.0232 mol) of di-*p*-toluoyl-*d*-tartaric acid. The mixture was stirred and warmed on a steam bath until a homogeneous solution was obtained. On standing for several days, a total of 6.31 g of the salt crystallized. The crystalline free base, generated from the salt by treatment with Na_2CO_3 and extraction into benzene, weighed 2.94 g and had $[\alpha]^{25}_{589}$ −48.8°. Three recrystallizations of this material from CH_3CN gave 1.80 g of (−)-**6b**: mp 143.5–144.5 °C; $[\alpha]^{25}_{589}$ −64.3°.

Pharmacological Testing Methods. Antiavoidance studies were carried out in squirrel monkeys (*Saimiri sciureus*) of both sexes trained to press a lever in order to avoid an electric shock. All compounds, as the base, were suspended in 1% methylcellulose and administered by gavage. The animals were trained and tested while restrained in a chair in an isolation chamber. The electric shock (600 V ac, 2 mA, 1 s) was given via leads placed on the seat of the chair and a ring around the animal's neck. Background noise was supplied with a Grason Stadler noise generator. A modified Sidman avoidance schedule (RS-36; SS-36) was used,[15] programming 36 s of shock-free time after each lever press (avoidance response). A lever press made during a shock (escape response) immediately terminated the shock, resetting the shock–shock interval timer to 36 s. The avoidance schedule also contained an "alarm" system to shut off the schedule for 30 min, if an animal received ten consecutive shocks without a lever press. This prevented the animals from receiving an excessive number of shocks. Following the 30-min alarm period, the schedule resumed again. An animal was assigned the maximum number of shocks (50/30 min), if the alarm system was activated during a trial.

Antiapomorphine activities were carried out in 160–190-g female Sprague–Dawley rats that were pretreated orally (0.2 mL/100 g of body weight) with vehicle, diluted phosphoric acid control solution, or the test compounds and placed in individual cages for later injection and observation. At 5 h after pretreatment (predetermined to coincide with the time of maximum activity), apomorphine hydrochloride (dissolved in saline) or saline was administered subcutaneously. Thirty minutes after the apomorphine, 1 mg/kg, the animals were observed under random and blind conditions for the presence of stereotyped behavior. Stereotyped behavior, defined as continuous sniffing, licking, gnawing, or biting, was scored as either present or absent. When appropriate, the ED_{50} value (dose preventing stereotypes in 50% of the animals) was ascertained by regression analysis of log dose and percent inhibition. The dose of apomorphine selected was just adequate to elicit stereotypes in 100% of the rats. The test compounds (−)-**6b**, (+)-**6b**, and (±)-**6b** were administered in dilute phosphoric acid solution (30 mg/mL) after appropriate dilution. All dose levels refer to the free base.

Anticholinergic activity in Carworth CF_1 female mice weighing 18–22 g was assessed by determining mydriatic potency (peripheral cholinergic blockage) and the ability of the compounds to protect against physostigmine-induced lethality after treatment with atropine methyl nitrate (central cholinergic blockade). Mydriatic activity was evaluated by measuring the diameter of the pupil with the aid of an ocular micrometer 2 and 5 h after treatment with the test compound using a method previously described.[16] A positive control, 1 (X = H), was included in the study which was conducted under random and blind conditions.

For central anticholinergic activity studies, preliminary dose–response studies with physostigmine in atropine methyl nitrate pretreated animals were performed to estimate the dose required to cause death in approximately 95% of the animals. Physostigmine sulfate was dissolved in saline for subcutaneous injection, and atropine methyl nitrate was dissolved in distilled water and injected intraperitoneally. All other compounds were administered orally. Cyproheptadine hydrochloride was dissolved/suspended in 1% methylcellulose; (−)-**6b**, (+)-**6b**, and (±)-**6b** were prepared by appropriately diluting with distilled water the stock solutions containing 30 mg of compound/mL of dilute phosphoric acid. All doses refer to the base.

Acknowledgment. The authors are indebted to Mr. K. Streeter and Mr. Y. Lee for the microanalyses, Dr. G. Smith and his associates for the phase solubility analyses, Mr. A. Augenblick for the GLC analyses, Mr. W. R. McGaughran for the ^1H NMR spectra, and Dr. W. Randall for the CD spectra.

References and Notes

(1) A. Ebnöther, E. Jucker, and A. Stoll, *Helv. Chim. Acta*, **48** (6), 1237 (1965).
(2) D. C. Remy, K. E. Rittle, C. A. Hunt, and M. B. Freedman, *J. Org. Chem.*, **41**, 1644 (1976).
(3) The use of (+)- and (−)-**5a** as synthons for the preparation of other chiral 3-substituted cyproheptadine analogues of biological interest is in progress.
(4) C. Kaiser, P. J. Fowler, D. H. Tedeschi, B. M. Lester, E. Garvey, C. L. Zirkle, E. A. Nodiff, and A. J. Saggiomo, *J. Med. Chem.*, **17**, 57 (1974).
(5) (a) W. Aschwanden, E. Kyburz, and P. Schonholzer, *Helv. Chim. Acta*, **59**, 1245 (1976); (b) L. G. Humber, F. T. Bruderlein, and K. Voith, *Mol. Pharmacol.*, **11**, 833 (1975); (c) T. J. Petcher, J. Schmutz, H. P. Weber, and T. G. White, *Experientia*, **31**, 1389 (1975); (d) B. Carnmalm, L. Johansson, S. Rämsby, N. E. Stjernström, S. B. Ross, and S.-O. Ogren, *Nature (London)*, **263**, 519 (1976).
(6) E. L. Engelhardt, H. C. Zell, W. S. Saari, M. E. Christy, C. D. Colton, C. A. Stone, J. M. Stavorski, H. C. Wenger, and C. T. Ludden, *J. Med. Chem.*, **8**, 829 (1965).
(7) H. L. Goering, J. N. Eikenberry, G. S. Koermer, and C. J. Lattimer, *J. Am. Chem. Soc.*, **96**, 1493 (1974).
(8) M. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, *J. Am. Chem. Soc.*, **96**, 1038 (1974).
(9) C. S. C. Yang and R. S. H. Liu, *Tetrahedron Lett.*, 4811 (1973).
(10) H. M. Hanson, C. A. Stone, and J. J. Witoslawski, *J. Pharmacol. Exp. Ther.*, **173**, 117 (1970).
(11) N.-E. Anden, A. Rubenson, K. Fuxe, and T. Hokfelt, *J. Pharm. Pharmacol.*, **19**, 627 (1967); A. M. Ernst, *Psychopharmacology*, **10**, 316 (1967).
(12) P. A. J. Janssen, C. J. E. Niemegeers, K. H. L. Schellekens, and F. M. Lenaerts, *Arzneim.-Forsch.*, **17**, 841 (1967).
(13) J. M. van Rossum, *Arch. Int. Pharmacodyn. Ther.*, **160**, 492 (1966); H. Rollema, B. H. C. Westerink, and C. J. Grol, *J. Pharm. Pharmacol.*, **28**, 321 (1976).
(14) The procedure for the preparation of this ketone was kindly provided by Dr. B. E. Evans of these laboratories.
(15) H. M. Hanson, J. J. Witoslawski, E. H. Campbell, and A. G. Itkin, *Arch. Int. Pharmacodyn. Ther.*, **161**, 7 (1966).
(16) C. A. Stone, K. L. Meckelnburn, and M. L. Torchiana, *Arch. Int. Pharmacodyn. Ther.*, **117**, 419 (1958).