Sterically Hindered 5,11-Dicarbo Analogues of Clozapine as Potential Chiral Antipsychotic Agents[1]

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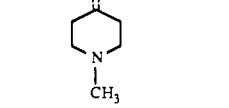
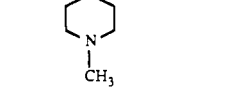
Sterically hindered 5,11-dicarbo analogues of clozapine were prepared as potential chiral antipsychotic agents, with the possibility that for a particular analogue the antipsychotic activity of clozapine may reside in one enantiomer of the analogue whereas other unwanted biological effects of clozapine may be caused by the other enantiomer. Variable-temperature proton nuclear magnetic resonance studies showed that although 5-methylene-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene exists at room temperature as configurational enantiomers, the activation energy for thermal racemization is 19 kcal mol^{-1} at 105 °C, and it is doubtful that the enantiomers of this analogue can be isolated under usual laboratory conditions. The (*Z*)-5-ethylidene and 5-isopropylidene analogues have activation energies greater than 23 kcal mol^{-1} at 160 °C, and thus there is a possibility that the analogues can be obtained as their respective enantiomers. 5-Methyl-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene incorporates a chiral center which is not thermally racemized, but it exists at room temperature as two diasteromers with an activation energy for inversion of the 5*H*-dibenzo[*a*,*d*]cycloheptene ring of 21 kcal mol^{-1}. When the 5,11-dicarbo analogues were tested in vitro for biological activity and their activities were compared to that of clozapine, the affinities for muscarinic and dopamine D-1 and D-2 sites were reduced but were still substantial. Thus the respective biological activities of the racemates indicate that the biological activities of the thermally stable enantiomers may be of importance in finding a clozapine derivative with fewer side effects than those shown by clozapine itself. Because of the susceptibility of the enamines to acid-catalyzed hydrolysis, resolution into respective enantiomers is not anticipated.

Many biologically active substances are chiral and their respective enantiomers have different pharmacological effects.[2-4] Frequently, a therapeutic action resides in one enantiomer while the other is biologically inactive or is associated with one or several unwanted side effects.[2-4]

One example of the biological stereoselectivity is shown by the enantiomers of 3-cyanocyproheptadine[5] [1-methyl-4-(3-cyano-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)piperidine, 1] and some of its analogues in which other



(pR_a,pS_b)-1



(pS_a,pR_b)-1

atoms (Br, I) or groups (SCF_3, OCH_3, SO_2CF_3) are substituted for the cyano group at C-3.[6,7] These 3-substituted cyproheptadines exist as configurational enantiomers as the result of the high activation energy for the conversion of one nonplanar chiral arrangement [(pR_a,pS_b)-1] to the other [(pS_a,pR_b)-1] by inversion of the seven-membered ring.[8-10] Significantly, enantiomers of 3-substituted cyproheptadines of the same absolute configuration show a similar biological profile.[5] In vitro, the muscarinic cholinergic antagonist [^{3}H]quinuclidinyl benzilate ([^{3}H]QNB) is uniformly more potently displaced from mammalian membrane cholinergic binding sites by the enantiomers with the pS_a,pR_b absolute configuration than by those with the pR_a,pS_b absolute configuration. The latter, however, more potently displace the α-adrenergic neurotransmitter [^{3}H]norepinephrine, the α-adrenergic antagonist [^{3}H]-[[[2-(2,6-dimethoxyphenoxy)ethyl]amino]methyl]benzodioxane (WB-4101), and the dopamine antagonist [^{3}H]-spiperone than do those with the pS_a,pR_b configuration.[5] In vivo experiments with racemic 1 and the two enantiomers of 1 show a similar pattern.[11] The classical neuroleptic (antiavoidance) and cholinolytic (mydriatic and oxotremorine antagonism) activities of racemic 1 reside in a different enantiomer, (pR_a,pS_b)-1 being a potent neuroleptic with weak or no anticholinergic properties and (pS_a,pR_b)-1 having significant anticholinergic activity but no neuroleptic properties.[11]

Clozapine [8-chloro-11-(4-methylpiperazino)-5*H*-dibenzo[*b*,*e*][1,4]diazepine, **2a**] is another tricyclic compound which also displays multiple central nervous system activities. It has been reported to be an antipsychotic agent which in clinical use produces practically no extrapyramidal side effects.[12] It has also been shown that, while clozapine in vitro does not readily displace [^{3}H]spiperone from rat caudate nuclei,[13] [^{3}H]clozapine does bind to sites in this tissue.[14,15] In such studies, binding in the presence

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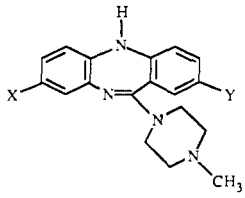
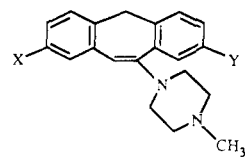


2a, X = Cl; Y = H
b, X = Y = H
c, X = H; Y = Cl



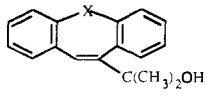
3a, X = Cl; Y = H
b, X = Y = H
c, X = H; Y = Cl

of atropine represents nonmuscarinic binding, and binding in the absence of atropine represents muscarinic plus nonmuscarinic binding.[14] While the identity of the nonmuscarinic clozapine binding sites and their relationship to the antipsychotic properties of clozapine are unknown, displacement of [^{3}H]clozapine from these sites by antipsychotic drugs[14,15] suggests a possible relationship of these sites to the antipsychotic activity of clozapine.

Since clozapine produces agranulocytosis as a rare but serious side effect in humans,[16] our attention was turned some years ago to the preparation of the clozapine analogues **3a–c**, in which the nitrogen atoms of the tricyclic system are replaced with carbon atoms,[13] 2-chloro-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene (**3a**) being the analogue with a chlorine atom in the same relative position as that in clozapine. These and other analogues were evaluated for their ability to inhibit muscarinic and nonmuscarinic [^{3}H]clozapine binding in rat forebrain and [^{3}H]spiperone binding to dopamine D-2 receptors in rat caudate nuclei.[13,17]

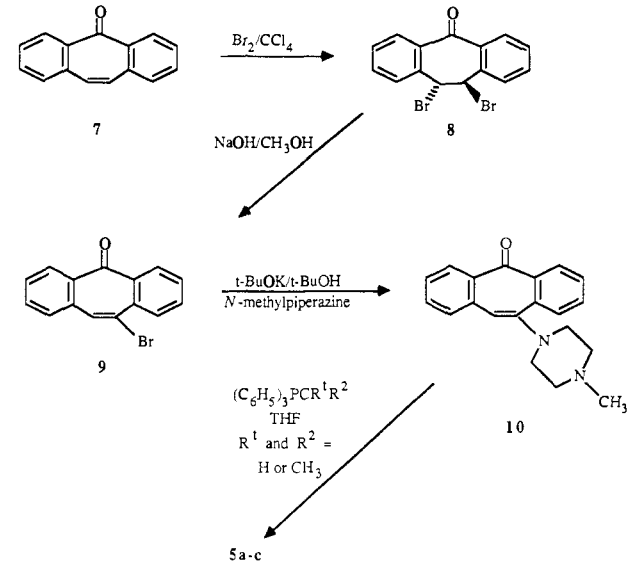
For binding to the nonmuscarinic clozapine binding sites in rat forebrain, the 5*H*-dibenzo[*a*,*d*]cycloheptene analogues **3a–c** are as effective as clozapine (**2a**) itself. Anticholinergic activity, as measured by binding to muscarinic sites, is somewhat decreased for **3a–c** as compared to that of **2a** but is still substantial. The analogues are somewhat more potent than clozapine in blocking [^{3}H]spiperone binding, and the deschloro analogue **3b** is the least potent.[13]

Since both the anticholinergic activity and affinity for [^{3}H]spiperone binding sites as well as binding affinity for nonmuscarinic [^{3}H]clozapine binding sites are present in **3b**, the possibility exists for the separation of these activities by separation of the configurational enantiomer of **3b**, much the same as is accomplished by the separation of configurational enantiomers of 3-cyanocyproheptadine[5] (**1**). Indeed, examination of a molecular model of **3b** shows that it does exist as a nonplanar dissymmetric arrangement, but as demonstrated by proton nuclear magnetic resonance (^{1}H NMR) studies with 10-(1-hydroxy-1-methylethyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (**4a**),[18] the enantiomeric forms of **3b** are easily interconverted at room temperature. For **4a** in chloroform-*d*, the activation energy (ΔG^*) for interconversion of its two enantiomers is 17.5 kcal mol^{-1} at 44 °C,[18] with a half-life of no more than 17 min at −23 °C,[9] a half-life of 17 min being considered the minimum for isolation of an enantiomer.[9] Since the tricyclic system in **3b** resembles that in **4a**, **3b** exists at room temperature as conformational enantiomers which cannot be separated under usual laboratory conditions. Thus we sought an alteration in the structure of **3b** which would increase the energy barrier for the conversion of one nonplanar form to its enantiomer and thus increase the possibility for the isolation of configurational enantiomers.

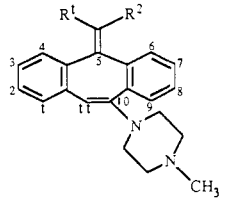


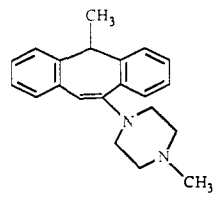
4a, X = CH_2
b, X = C=O
c, X = C=CH_2

Scheme I



We now report the synthesis of a number of 5-substituted 5,11-dicarbo analogues of clozapine, 5-methylene-, (*Z*)-5-ethylidene-, 5-(2-propylidene)-, and 5-methyl-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene (**5a–c**, **6**),





5a, $R^1 = R^2 = H$
b, $R^1 = H$; $R^2 = CH_3$
c, $R^1 = R^2 = CH_3$

6

each with a potential for separation into enantiomers. For **5a–c**, we have studied their ^{1}H NMR spectra and have estimated the activation energy (ΔG^*) or a lower limit of the activation energy for their thermal racemization. For **6**, the configurational stability is the result of the chiral center at C-5, and the enantiomers of **6** are not easily racemized by thermal energy.

Evaluation of the in vitro neuroreceptor affinity profiles was also done for each of the clozapine analogues **5a–c** and **6** in comparison to clozapine (**2a**), deschloroclozapine [11-(4-methylpiperazino)-5*H*-dibenzo[*b*,*e*][1,4]diazepine, **2b**],[19] and isoclozapine [2-chloro-11-(4-methylpiperazino)-5*H*-dibenzo[*b*,*e*][1,4]diazepine, **2c**].[19] Competition assays were done for binding to muscarinic,[20] dopamine D-1,[21] and dopamine D-2[22] binding sites in order to assess the degree to which the binding profiles are altered by an increase in the effective bulk size of a sub-

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stituent at C-5.

Results and Discussion

Synthesis. The syntheses of 5-methylene-, (*Z*)-5-ethylidene-, and 5-(2-propylidene)-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene (**5a–c**) are outlined in Scheme I. Bromination of dibenzodehydrosuberone (**7**) gave the dibromide **8**.[23] Dehydrobromination of **8** and substitution of the 4-methylpiperazino moiety for the bromine atom in **9** gave the key intermediate 10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one[24] (**10**). The formation of **5a** and **5c** by a Wittig reaction of **10** with methylidene- and isopropylidenetriphenylphosphine [$(C_6H_5)_3P{=}CH_2$ and $(C_6H_5)_3P{=}C(CH_3)_2$] was successful.

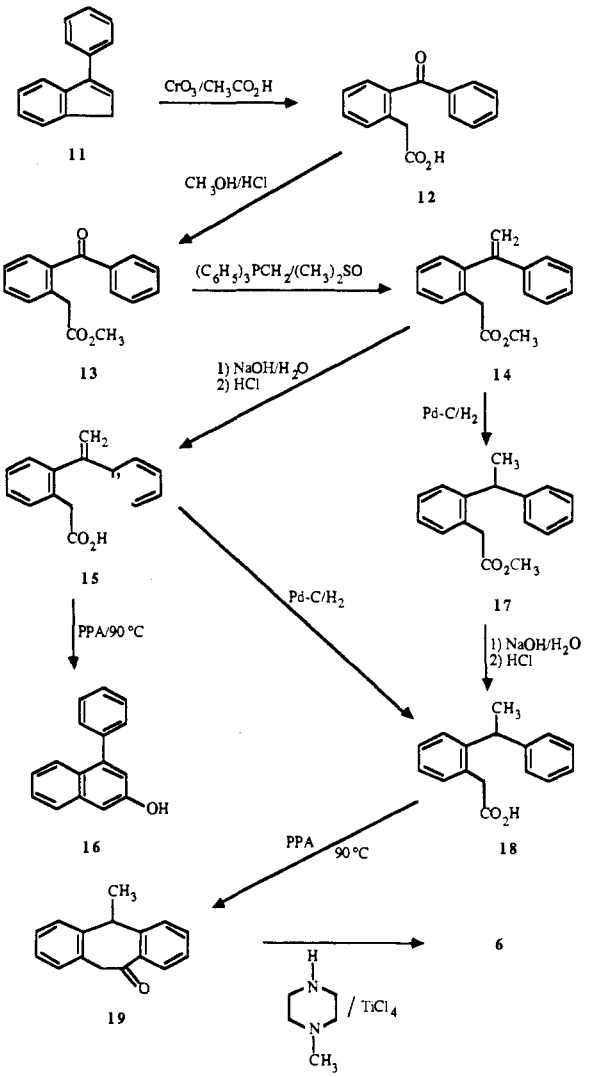
Subsequent variable-temperature ^1H NMR studies (vide infra) clearly show that **5a** occurs as nonplanar enantiomeric forms with a ΔG^* in nitrobenzene-d_5 for inversion of the seven-membered ring of 19 kcal mol^{-1} at 105 °C. The enantiomers of **5a** will not be thermally stable under usual laboratory conditions since the half-life of an enantiomer would be about 17 min at −23 °C.[9] In nitrobenzene-d_5 the ΔG^* for inversion of the seven-member ring of **5c** is greater than 23 kcal mol^{-1} at 160 °C, and the enantiomers will be thermally stable below 160 °C.

Reaction of ethylidenetriphenylphosphine [$(C_6H_5)_3P{=}CHCH_3$] with **10** gave (*Z*)-5-ethylidene-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene (**5b**) and the corresponding *E* isomer in a ratio of about 3:1 (^1H NMR), respectively. Isomerically pure **5b** crystallized from isopropyl ether while the *E* isomer slowly isomerized to **5b** in boiling isopropyl ether. Cooling of these solutions afforded additional amounts of **5b**. The *E* isomer could not be isolated free of contamination with **5b**.

The *Z* configuration for **5b** was established by 300-MHz ^1H NMR decoupling and nuclear Overhauser effect (NOE) experiments. In dimethyl sulfoxide-d_6, decoupling experiments allowed the identification of the signals due to protons on each of the aromatic rings: 7.68, 7.40, 7.32, and 7.18 ppm for one ring and 7.23 and 7.19 ppm (three protons) for the other. Saturation of the C-11 vinyl proton signal at 6.13 ppm gave a 17% intensity increase for the multiplet centered at 7.23 ppm thereby identifying this signal as that of the proximal proton at C-1. It follows that the signal at 7.19 ppm arises from the protons at C-2, C-3, and C-4. Finally, irradiation of the quartet at 5.59 ppm, assigned to the ethylidene vinylic hydrogen atom, gave an 8% intensity increase to the signal centered at 7.19 ppm. Since this vinylic proton at C-11 and that on the ethylidene group at C-5 have NOE effects on the proton signals of the same aromatic ring, the substance was assigned the *Z* configuration. Again, variable-temperature ^1H NMR studies show that ΔG^* for the interconversion of the enantiomers of **5b** in nitrobenzene-d_5 is greater than 23 kcal mol^{-1} at 160 °C and indicate that the enantiomers of **5b** will be configurationally stable under usual laboratory conditions.

As shown in Scheme II, the synthesis of 5-methyl-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene (**6**) began with 2-benzoylphenylacetic acid (**12**), which was prepared by oxidation of 1-phenylindene (**11**).[13] Esterification of **12** in methanolic hydrogen chloride gave **13**.

Scheme II



The latter in dimethyl sulfoxide reacted with methylidenetriphenylphosphine [$(C_6H_5)_3P{=}CH_2$)] to form methyl 2-(1-phenylethenyl)phenylacetate (**14**), the dimethyl sulfoxide solvent allowing a highly selective reaction of the ylide with the ketonic function of the keto ester **13**.[25] The ylide was formed by reaction of methyltriphenylphosphonium bromide with the conjugate base of dimethyl sulfoxide, the latter made by reaction of sodium hydride with dimethyl sulfoxide. An excess of the dimethyl sulfoxide anion over the amount of methyltriphenylphosphonium bromide must be avoided since the anion catalyzes the rapid addition of dimethyl sulfoxide to aryl-conjugated olefin **14**,[26] the product of the Wittig reaction itself. The ester **14** was an oil, but saponification and acidification gave 2-(1-phenylethenyl)phenylacetic acid (**15**) as a crystalline solid. Treatment of **15** with hot polyphosphoric acid[27] (PPA) did not lead to the desired 10,11-dihydro-5-methylene-5*H*-dibenzo[*a*,*d*]cyclohepten-10-one but gave 4-phenyl-2-naphthol[28] (**16**) prepared earlier by a different route.[28] Reduction of **14** with hydrogen over palladium on carbon gave methyl 2-(1-phenylethyl)-phenylacetate (**17**) as an oil, which was converted to the corresponding crystalline acid **18**, previously prepared by another synthetic scheme.[29] The same acid **18** was ob-

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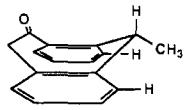
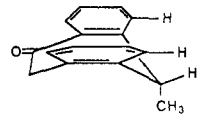
tained in the present work by reduction of **15** with hydrogen over palladium on carbon.

Cyclization of **18** in polyphosphoric acid gave 10,11-dihydro-5-methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-10-one[29] (**19**). In this present work, the sample of **19** first isolated from the cyclization reaction had spectral (^{1}H NMR, ^{13}C NMR, IR, MS) properties compatible with its assigned structure and a melting point that was the same as that previously reported[29] for **19** after recrystallization from petroleum ether. In our hands, however, attempts to recrystallize solid **19** from petroleum ether (bp 38–57 °C) were not successful. Complete removal of the petroleum ether gave an oil. Other solvents for recrystallization (benzene, ether) gave similar results.

The ^{1}H NMR spectrum of the oil not only had signals shown by solid **19** but also had a new set of signals. The latter, together with additional spectral (^{13}C NMR, MS) evidence, indicated the presence in the oil of two diastereomers with structure **19**. For structure **19**, the methyl



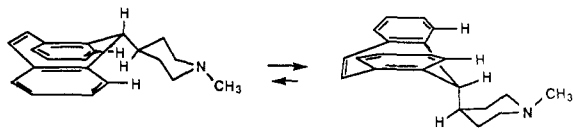
19a



19b

group is either quasiequatorial (**19a**) or quasiaxial (**19b**) with respect to the seven-membered ring, and the energy barrier for inversion of the seven-membered ring is sufficiently high so that the two diastereomers can be isolated. The initially formed diastereomer was stable as the crystalline solid during storage at room temperature over a year but was converted to a preponderance of the more stable diastereomer by sustained heating in petroleum ether (bp 38–57 °C).

The stereoisomerism of **19** is similar to that reported for 5-(1-methylpiperidin-4-yl)-5*H*-dibenzo[*a*,*d*]cycloheptene[30] (dihydrocyproheptadine, **20**). The quasiequatorial dia-



20a 20b

stereomer **20a** was initially formed[30] but underwent thermal isomerization to the more stable quasiaxial isomer **20b** with a ΔG^* of 25 kcal mol^{-1} at both 40 and 50 °C.[30] The configuration of **20b** was confirmed by single-crystal diffraction methods on the enantiomers of the 3-bromo derivatives of **20b**.[30] Similarly, the more thermodynamically stable diastereomer of **19** probably also has the methyl group in the quasiaxial conformation (**19b**). The only direct experimental evidence for this assignment is the downfield shift of the C-5 methyl group signal from 1.83 to 1.68 ppm when the solid diastereomer of **19** is converted to the more thermodynamically stable diastereomer.

Finally, the formation of 5-methyl-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene (**6**) was accomplished by condensation of the mixed diastereomers of **19** with *N*-methylpiperazine using titanium tetrachloride as catalyst and water scavenger.[31] After removal of impurities by flash chromatography, the reaction product was an oil. Its ^{1}H NMR spectrum in chloroform-*d* clearly showed the presence of two diastereomers with structure **6** in a ratio of about 4:1. In one, the methyl group at C-5 is quasiequatorial to the seven-membered ring, and in the other diastereomer, it is quasiaxial, similar to the stereoisomerism shown by **19** and reported[30] earlier for dihydrocyproheptadine (**20**). In contrast to compound **20**, for which the quasiaxial isomer **20b** is substantially more stable than the quasiequatorial isomer **20a**, the two diastereomers of **6** appear to differ only slightly in stability, and variable-temperature 300-MHz ^{1}H NMR observation with **6** in nitrobenzene-d_5 gave a ΔG^* of 21 kcal mol^{-1} for interconversion of the two diastereomers at 135 °C.

Since the more thermodynamically stable diastereomer of **6** in chloroform-*d* has its C-5 methyl group signal downfield (1.84 ppm) from that of the less stable diastereomer (1.39 ppm), the former is assigned the configuration with the C-5 methyl group in the quasiequatorial conformation and the latter is assigned with the C-5 methyl group in the quasiaxial conformation.

A sharp-melting, crystalline sample of **6** was isolated which on the basis of its sharp melting point may be a pure diastereomer but which on solution in chloroform-*d* showed the same 4:1 mixture of diastereomers as discussed above. Treatment of **6** with an equimolar amount of L-tartaric acid in methanol in an attempted resolution of **6** into its enantiomers revealed that these tertiary enamine structures are susceptible to acid-catalyzed hydrolysis since substantial amounts of the corresponding ketone **19** were detected by TLC. Further attempts to resolve **6** or **5b,c** were not made, and their pharmacological properties were evaluated with the racemates.

Variable-Temperature ^{1}H NMR Studies. At 400-MHz and 90 °C, the C-2 and C-6 and the C-3 and C-5 ^{1}H NMR signals of the piperazino ring of 10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**10**) in nitrobenzene-d_6 were triplets at 3.04 and 2.64 ppm, respectively, showing that inversion of the seven-membered ring, inversion of the piperazino ring, and rotation of the 4-methylpiperazino group about its attachment bond at C-10 are all rapid at this temperature. Cooling led to a gradual collapse of the triplets at 3.04 and 2.64 ppm, which at 40 °C were apparent singlets. Cooling of **10** in chloroform-*d* led to the broadening of the singlets, until at −10 °C, two broad peaks extended from 3.25 to 2.80 ppm and 2.80 to 2.30 ppm, respectively. At −20 °C, four broad peaks were observed, and at −40 °C, the four peaks for the piperazino ring protons had sharpened to a doublet at 3.26 ppm (2 equatorial H on C-2 and C-6) coupled to a triplet at 2.74 ppm (2 axial H on C-2 and C-6) and a second doublet at 2.96 ppm (2 equatorial H on C-3 and C-5) coupled to a second triplet at 2.38 ppm (2 axial H on C-3 and C-5). Further cooling to −70 °C did not change the spectrum.

The lowest temperature used in the ^{1}H NMR experiment caused only one of the three dynamic processes in **10** to become slow on the 400-MHz time scale. Both the rotation of the 4-methylpiperazino ring about its attachment bond and the inversion of the seven-membered ring are rapid at −70 °C. These observations are in agreement with those of variable-temperature ^{1}H NMR experiments with 10-(1-hydroxy-1-methylethyl)-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**4b**) in carbon disulfide, which gave $\Delta G^* <$ 9 kcal mol^{-1} at −90 °C for inversion of the seven-membered ring.[18] For **10**, inversion of the six-membered 4-methylpiperazino ring, however, was slowed with a coalescence temperature (T_c) for the 400-MHz ^{1}H NMR spectrum between −10 and −20 °C. With −15 °C for T_c and the difference in frequency of 220 Hz for the axial as opposed to equatorial protons, the ΔG^* for inversion of the 4-

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Figure 1. The piperazino proton signals in the 400-MHz nuclear magnetic resonance spectrum of 5-methylene-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene (**5a**) in chloroform-*d* at −50 °C.

methylpiperazino ring is calculated to be 12 kcal mol^{-1} by using the Gutowsky–Holm equation[32] together with the Eyring absolute reaction rate equation.[33] The magnitude of this activation energy is comparable to ΔG^* = 13 kcal mol^{-1} at T_c = −25[34] and −8 °C[35] for the ring inversions of 1,4-dimethylpiperazine in methylene chloride.

For 5-methylene-10-(4-methylpiperazino)-5*H*-dibenzo-[*a*,*d*]cycloheptene (**5a**), it was assumed that substitution of C-5 would not change greatly the activation energies for rotation of the 4-methylpiperazino group about its attachment bond and the ring inversion of the 4-methylpiperazino group in comparison to those of the ketone **10**. A C-5 substitution would, however, substantially increase the activation energy for inversion of the seven-membered ring. Indeed, at 400 MHz and 50 °C in nitrobenzene-d_5, the signals for the protons of the piperazino ring were in four envelopes of two protons each, 3.16, 2.96, 2.67, and 2.57 ppm, indicating that the seven-membered ring inversion was slow on the 400-MHz ^{1}H NMR time scale. The envelopes broadened on cooling in chloroform-*d* toward 0 °C. Between −10 and −30 °C, the interconversion of the piperazino ring was slowed so that eight distinct proton signals could be identified. Further cooling to −50 °C sharpened the signal multiplicities, and the eight proton envelopes were centered at 3.41, 3.13, 3.03, 3.00, 2.77, 2.41, 2.33, and 2.26 ppm (Figure 1). The presence of eight

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Table I. Affinity of Clozapine and Its Analogues for Binding Sites in Rat Brain

	IC_{50} ± SEM,[a] nM		
		dopaminergic	
compd	muscarinic ([^{3}H]QNB)	D-1 ([^{3}H]SCH 23390)	D-2 ([^{3}H]spiperone)
	Dibenzo[*b*,*e*][1,4]diazepines		
2a	51 ± 8 (2)	192 ± 37 (5)	2770 ± 380 (7)
2b	39 ± 11 (2)	895 ± 704 (2)	>10000 (2)
2c	55 ± 18 (2)	63 ± 17 (2)	218 ± 28 (3)
	Dibenzo[*a*,*d*]cycloheptenes		
5a	150 ± 40 (2)	21 ± 1 (2)	305 ± 54 (4)
5b	2600 ± 580 (2)	305 ± 89 (3)	6970 ± 860 (3)
5c	415 ± 15 (2)	540 ± 169 (3)	4750 ± 550 (2)
6	1020 ± 80 (2)	74 ± 6 (2)	2650 ± 350 (2)

[a] An IC_{50} value is the concentration of the compound necessary to displace 50% of specific radioligand binding. SEM is the standard error of the mean for the number of individual experiments, given in parentheses, conducted with triplicate determinations.

proton signals is possible only if both the piperazino and seven-membered-ring inversion are slow on the 400-MHz ^{1}H NMR time scale. Heating of **5a** in nitrobenzene-d_5 above 50 °C led to coalescence of the piperazino proton signals. Of the four proton envelopes at 50 °C, the two at 2.67 and 2.57 ppm, assigned to the protons at C-3 and C-5, began coalescence at 95 °C and completed coalescence at 105 °C. The two envelopes at 3.16 and 2.96 ppm assigned to the C-2 and C-6 protons completed coalescence at 120 °C. The 300-MHz ^{1}H NMR spectrum of **5a** in nitrobenzene-d_5 at 140 °C showed the C-3 and C-5 proton signals of the piperazino ring as a triplet and the C-2 and C-6 proton signals as a broad singlet. At 155 °C, the singlet had developed definite shoulders on its way to becoming a triplet at a higher temperature. By utilizing 105 and 120 °C as the coalescence temperature and the respective peak separations as 39 and 76 Hz, the ΔG^* for interconversion of the seven-membered ring is calculated to be 19 kcal mol^{-1} at both 105 and 120 °C. This ΔG^* is comparable to that of 21.2 kcal mol^{-1} at T_c 109 °C for inversion of the seven-member ring in 5-methylidene-10-(1-hydroxy-1-methylethyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (**4c**) in nitrobenzene.[18] An activation energy of 18.5 kcal mol^{-1} will give a half-life of 17 min to an enantiomer when the temperature is −23 °C.[9] Higher temperatures will give shorter half-lives. Thus it is doubtful if the enantiomers of **5a** can be isolated under usual laboratory conditions because of their ease of thermal racemization.

The 400-MHz ^{1}H NMR spectrum of (*Z*)-ethylidene-10-(4-methypiperazino)-5-*dibenzo*[*a*,*d*]cycloheptene (**5b**) in nitrobenzene-d_5 at 50 °C showed the proton signals of the piperazino ring in four poorly defined complex envelopes at 3.16, 2.94, 2.64, and 2.54 ppm of two protons each. On cooling in chloroform-*d*, these envelopes began to broaden and between −10 and −30 °C as the piperazino ring inversion became slow, and at lower temperatures, eight distinct proton signals centered at 3.42, 3.21, 3.05, 2.99, 2.78, 2.47, 2.38, and 2.29 ppm could be identified. Heating of **5b** in nitrobenzene-d_5 above 50 °C resulted in great improvement in the definition of the four 400-MHz proton signal envelopes, and at 80 °C, each of the four envelopes contained distinct peaks; the two envelopes centered at 3.16 and 2.94 ppm were more intense toward each other and the two centered at 2.64 and 2.54 ppm were more intense toward each other. Further heating to 130 °C gave no further changes in the 400-MHz spectrum. The 300-MHz spectrum was observed from 60 to 160 °C, but except for some sharpening of the signals on going from 60 to 90 °C, no change in the spectral appearance was observed up to 160 °C. Thus, with the maximum signal separation for

the C-3 and C-5 and for the C-2 and C-6 protons both as 23 Hz and the T_c greater than 160 °C, ΔG^* is calculated to be greater than 23 kcal mol^{-1} at 160 °C for the thermal racemization of the enantiomers of **5b**, with the distinct possibility that **5b** can be separated into enantiomers under usual laboratory conditions.

The 400-MHz ^{1}H NMR spectrum of 5-(2-propylidene)-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]-cycloheptene (**5c**) in nitrobenzene-d_5 was similar to that of **5b**, and no coalescence of the C-3 and C-5 and of the C-2 and C-6 protons was observed at 300 MHz at 160 °C. With a 21-Hz separation for these signals, ΔG^* is greater than 23 kcal mol^{-1} at 160 °C for interconversion of the two configurational enantiomers of **5c**. The enantiomers of **5c** thus have a thermal stability against racemization comparable to that of the enantiomers of 3-cyanocyproheptadine (**1**).

The 400-MHz spectrum of 5-methyl-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene (**6**) in nitrobenzene-d_5 showed an equilibrium for the two diastereomers in a ratio of about 4:1. Signals at 3.45 and 4.08 ppm for the methine proton at C-5 coalesced at 135 °C, giving a ΔG^* of 21 kcal mol^{-1} for interconversion of the two diastereromers. The signals for the vinyl protons on C-11 had a maximum separation of 24.5 Hz and coalesced at 135 °C, also giving a ΔG^* of 21 kcal mol^{-1} for the interconversion of the two diastereomers with structure **6**. Coalescences of signals for protons on the 4-methylpiperazino ring also gave a ΔG^* of 21 kcal mol^{-1} for the interconversion of the seven-member ring.

Biological Testing. As shown in Table I, some of the 5,11-dicarbo analogues (dibenzo[*a*,*d*]cycloheptenes) of clozapine (**5a–c**, **6**) do not differ greatly from clozapine (**2a**) in their binding to muscarinic ([^{3}H]QNB) and dopamine D-1 ([^{3}H]SCH 23390) and dopamine D-2 ([^{3}H]spiperone) receptor sites. As reported earlier,[17] deschloroclozapine (**2b**) has little or no affinity for dopamine D-2 binding sites, but as now shown in Table I, binding to the dopamine D-1 sites is still substantial. For isoclozapine (**2c**) the affinities for the D-1 and D-2 sites are higher than those for clozapine itself. The difference in affinity for D-2 binding sites between clozapine (**2a**) and isoclozapine (**2c**) is related to the observation that when clozapine is given in pharmacologically relevant doses to animals, it is devoid of cataleptic activity and does not inhibit apomorphine-induced sterotypes, whereas **2c** has the properties of a classical neuroleptic agent.[36]

For the 5,11-dicarbo analogues of clozapine **5a–c** and **6**, the affinities for the D-2 binding sites are substantial even though there is no chloro substituent on the tricyclic system. The 5-methylene analogue (**5a**) has an affinity similar to that of isoclozapine (**2c**) while the 5-isopropylidene and 5-methyl analogues (**5c** and **6**) are similar to clozapine (**2a**).

Conclusion

Clozapine (**2a**) displays affinity for both the dopamine D-1 and D-2 receptors as defined by using [^{3}H]SCH 23390 and [^{3}H]spiperone, respectively. It has not been established which of these receptor subtypes or if possibly both are implicated in the antipsychotic action of clozapine. The 5-methylene- and the 5-methyl-substituted carbocyclic analogues (**5a** and **6**) show affinities for the dopamine D-1 and D-2 receptor sites with potencies that are equal or superior to that of clozapine. Also the 5-ethylidene and 5-isopropylidene analogues (**5b** and **5c**) show considerable affinity for the dopamine D-1 and D-2 receptor sites as well as for the muscarinic receptor sites. Therefore, it seems possible that there exist a substantial difference in affinity for the particular binding site between the respective enantiomer of all the above compounds and, consequently, that the thermally stable enantiomers of **5b** and **5c** have substantial importance as model compounds in finding a clozapine-like agent with fewer side effects than clozapine. Because of the susceptibility of the enamines **5b** and **5c** to hydrolysis, resolution into their respective enantiomers is not anticipated.

Experimental Section

Melting points were taken in open capillary tubes and are corrected. Solvent evaporations were done at reduced pressure using a water pump and then an oil pump at 1 mmHg. Thin-layer chromatography (TLC) was done with silica gel on glass and were visualized with ultraviolet light and iodine vapor. Proton nuclear magnetic resonance (^{1}H NMR) spectra used for characterization of products were obtained with a JEOL FX-90Q spectrometer operating at 90 MHz. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were observed with a JEOL FX-90Q or Bruker Model AM-400-NB spectrometer operating at 22.5 MHz or 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane in chloroform-*d* or acetone-d_6. Infrared spectra were obtained with a Perkin-Elmer Model 727 spectrometer, and the ultraviolet spectrum was obtained with a Cary Model 14 spectrophotometer using the normal variable split and matched 1-cm cells. The mass spectra were obtained with an LKB 9000 mass spectrometer with 70-eV ionizing potential and a direct-introduction probe. Combustion analyses were done by Galbraith Laboratories, Knoxville, TN, and agreed to within 0.4% of the calculated values unless otherwise noted.

Nuclear Overhauser effect (NOE) and variable-temperature ^{1}H NMR were obtained with Bruker Model AC-300 and Bruker Model AM-400-NB spectrometers operating at 300 and 400 MHz, respectively. Chemical shifts are reported in ppm downfield from tetramethylsilane. For the variable-temperature experiments, the spectra were taken at 10 °C intervals from −70 to 30 °C in chloroform-*d* and from 40 to 160 °C at 400 MHz, and from 60 to 160 °C at 300 MHz in nitrobenzene-d_6. The 300-MHz spectrometer was used in an effort to observe the coalescence of some signals that had not coalesced at 160 °C at 400 MHz.

Deschloroclozapine (**2b**) and isoclozapine (**2c**) had respective melting points that were the same as those reported.[19]

5-Methylene-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]-cycloheptene (5a). *n*-Butyllithium (20.1 mL of a 1.55 M in hexanes, 31.2 mmol) was added dropwise to a stirred solution of methyltriphenylphosphonium bromide (10.2 g, 28.6 mmol) in dry ether (200 mL) under nitrogen. To the resulting orange solution was added 10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**10**; 6.75 g, 22.2 mmol) in tetrahydrofuran (80 mL). This solution was stirred and boiled for 3.5 h, cooled, and poured onto ice–water (200 mL). The organic layer was separated, and the aqueous layer was extracted with ether (2 × 90 mL). The combined organic layer and extracts were dried ($MgSO_4$) and evaporated. The residue consisted of **5a**, **10**, and triphenylphosphine oxide as determined by ^{1}H NMR. Most of the triphenylphosphine oxide was separated by trituration (3×) of the residue with hot hexane. Evaporation of combined hexane solutions and chromatography (350 g silica, 60–200 mesh) of the residue (7.88 g) using ethyl acetate as eluant separated **10** from **5a**, R_f (TLC, ethyl acetate) 0.04 and 0.08, respectively. Chromatography fractions containing only **5a** (TLC) were combined and evaporated, and recrystallization of the residue from ethyl acetate gave **5a** (4.02 g, 60%): mp 129–130 °C; ^{1}H NMR ($CDCl_3$) δ 7.70–7.10 (m, 8, aromatic H), 6.17 (s, 1, C-11 H), 5.24 (s, 2, methylene H), 2.96 (m, 4, piperazino C-2 and C-6 H), 2.56 (m, 4 piperazino C-3 and C-5 H), 2.34 ppm (s, 3, NCH_3); ^{13}C NMR ($CDCl_3$) δ 151.44, 150.65, 142.82, 141.22, 133.99, 133.04, 129.12, 128.57, 127.90, 127.63, 127.19 (2), 126.89, 126.73, 116.30 (methylene C on C-5), 110.78 (C-11), 55.55 (2, piperazino C-2 and C-6), 50.54 (2, piperazino C-3 and C-5), 46.20 ppm (NCH_3); off-resonance ^{13}C NMR ($CDCl_3$) δ 116.20 (t), 110.78 (d), 55.55 (t), 50.53 (t), 46.19 ppm (q). Anal. ($C_{21}H_{22}N_2$) C, H, N.

(*Z*)-5-Ethylidene-10-(4-methylpiperazino)-5*H*-dibenzo-[*a*,*d*]cycloheptene (5b) was formed as described above for the formation of **5a** from **10** except that ethyltriphenylphosphonium bromide was used in place of methyltriphenylphosphonium

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bromide. The crude reaction product, on the basis of its ^1H NMR spectrum, consisted of a 3:1 mixture of **5b**, the *E* isomer of **5b**, triphenylphosphine oxide, and a trace of the ketone **10**. Triphenylphosphine oxide was removed by trituration (3×) of the reaction product with hot isopropyl ether. After removal of the triphenylphosphine oxide, partial evaporation of the cooled solvent gave **5b** as a solid. Successive reduction of the solvent volume gave several more crops of **5b** (55% total yield): mp 165–166 °C; ^1H NMR ($CDCl_3$) δ 7.70–7.10 (m, 8, aromatic H), 6.13 (s, 1, C-11 H), 5.68 (q, 1, C=C*H*CH_3), 2.94 (m, 4, piperazino C-2 and C-6 H), 2.55 (m, 4, piperazino C-3 and C-5 H), 2.35 (s, 3, NCH_3), 1.73 ppm (d, 3, C=CHC*H*$_3$); ^{13}C NMR ($CDCl_3$) δ 150.76, 142.90 (2), 139.84, 134.26, 133.99, 128.41 (2), 128.30, 128.00, 126.68, 126.51 (3), 124.70 (C=*C*HCH$_3$), 110.04 (C-11), 55.47 (2, piperazino C-2 and C-6), 50.24 (2, piperazino C-3 and C-5), 46.18 (NCH_3), 14.40 ppm (C=CH*C*H$_3$); off-resonance ^{13}C NMR ($CDCl_3$) δ 124.70 (d), 110.04 (d), 55.47 (t), 50.24 (t), 46.18 (q), 14.40 ppm (q). Anal. ($C_{22}H_{24}N_2$) C, H, N.

Complete evaporation of the isopropyl ether mother liquors from the crystallization of **5b** gave an oil containing mostly **5b** and some of the *E* isomer: ^1H NMR ($CDCl_3$) δ 7.70–7.10 (m, 8, aromatic H), 6.17 (s, 1, C-11 H), 5.67 (q, 1, C=C*H*CH_3), 2.94 (m, 4, piperazino C-2 and C-6 H), 2.55 (m, 4, piperazino C-3 and C-5 H), 2.35 (s, 3, NCH_3), 1.75 ppm (d, 3, C=CHC*H*$_3$).

5-(2-Propylidene)-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene (5c) was formed as described above for the formation of **5a** from **10** except that isopropyltriphenylphosphonium iodide was used in place of methyltriphenylphosphonium bromide and the reaction mixture in which the ylide was formed was boiled for 3.5 h to ensure the complete formation of the ylide. After addition of **10** in ether, the reaction mixture was stirred overnight at room temperature, and triphenylphosphine oxide was removed by trituration (3×) of the crude product with hot pentane. The pentane solutions were combined and evaporated. Recrystallization of the residue from isopropyl ether gave **5c** (93%): mp 146–148 °C; ^1H NMR ($CDCH_3$) δ 7.70–7.10 (m, 8, aromatic H), 6.12 (s, 1, C-11 H), 2.95 (m, 4, piperazino C-2 and C-6 H), 2.55 (m, 4, piperazino C-3 and C-5 H), 2.34 (s, 3, NCH_3), 1.70 (s, 3, =C(CH_3)C*H*$_3$), 1.68 ppm (s, 3, =C(C*H*$_3$)CH$_3$); ^{13}C NMR ($CDCl_3$) 150.92, 142.69, 140.76, 135.64, 135.05, 133.83, 128.76, 128.47, 128.33, 128.17, 127.79, 127.68, 126.11, 125.83 (2), 109.67 (C-11), 55.55 (2, piperazino C-2 and C-6), 50.21 (2, piperazino C-3 and C-5), 42.26 (NCH_3), 20.77 ppm (2, C=C-(*C*H$_3$)$_2$); off-resonance ^{13}C NMR ($CDCl_3$) δ 109.66 (d), 55.55 (t), 50.20 (t), 46.26 (q), 20.77 ppm (q). Anal. ($C_{23}H_{26}N_2$) C, H, N.

5-Methyl-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene (6). A solution of titanium tetrachloride (2.52 g, 13.3 mmol) in dry benzene (100 mL) was slowly added to a stirred solution under nitrogen of 5-methyl-5*H*-dibenzo[*a*,*d*]cycloheptene-10-one (**19**; 2.95 g, 13.3 mmol) and 1-methylpiperazine (8.20 g, 81.9 mmol) in benzene (170 mL) at 20 °C. The solution was boiled for 2 h, and after cooling, it was poured into a mixture of sodium bicarbonate (4.20 g, 50.0 mmol) and water. The benzene layer was separated, and the aqueous layer was extracted with ether (3 × 125 mL). The combined organic solutions were dried (Na_2SO_4) and evaporated at reduced pressure. The residual oil (3.95 g) was subjected to flash chromatography on silica gel (400 g) using ethyl acetate–hexane (9:1) as eluant. Evaporation of the fractions containing product gave a mixture of diasteromers with structure **6** (2.22 g, 55%) in a ratio of 4:1 as an oil. No separation of the diastereomers by vartious TLC experiments or by HPLC using ethanol–hexane (1:19) as solvent was successful. The oil eventually formed an amorphous solid: ^1H NMR (major diastereomer) ($CDCl_3$) δ 7.70–7.05 (m, 8, aromatic H), 6.34 (s, 1, vinyl H), 3.45 (q, 1, C-5 H), 3.04 (m, 4, piperazino C-2 and C-6 H), 2.59 (m, 4, piperazino C-3 and C-5 H), 2.36 (s, 3, NCH_3), 1.84 ppm (d, 3, C-5 CH_3); ^1H NMR (minor diastereomer) ($CDCl_3$) δ 7.70–7.05 (m, 8, aromatic H), 6.23 (s, 1, vinyl H), 4.08 (q, 1, C-5 H), 3.04 (m, 4, piperazino C-2 and C-6 H), 2.59 (m, 4, piperazino C-3 and C-5 H), 2.36 (s, 38 NCH_3), 1.38 ppm (d, 3, C-5 CH_3); ^{13}C NMR ($CDCl_3$) δ 143.72, 141.81, 135.45, 133.73, 128.78, 128.22, 127.62, 126.41, 125.55, 125.14, 122.34, 122.11, 109.92 (C-11), 55.47 (2, piperazino C-2 and C-6), 50.29 (2, piperazino C-3 and C-5), 46.31 (NCH_3), 37.70 (C-5), 15.78 (CH_3 on C-5 on the minor isomer), 14.99 ppm (CH_3 on C-5 of the major isomer); IR (KBr pellet) 2900 (s), 1670 (m), 1620 (m), 1460 (m), 1390 (m), 1300 (m), 1210 (m), 1075 (w), 1010 (s), 760 cm^{-1} (s); MS *m*/*z* (relative intensity) 304 (M^+, 100), 289 (12), 274 (4), 246 (10), 191 (16), 189 (18).

A sample of the solid (1.50 g) was mixed with isopropyl ether (150 mL), and an insoluble solid (0.3 g) was removed by filtration. Evaporation of the solvent deposited crystals (0.293 g), and recrystallization of the latter from acetonitrile (12 mL) gave **6** (0.164 g, 11%) as a white, crystalline solid: mp 104–106 °C. Anal. ($C_{21}H_{24}N_2$) C, H, N. This solid in chloroform-*d* again showed the presence of the two diasteriomers in the same ratio (4:1) as found above.

***trans*-10,11-Dibromo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one (8).** Bromine (33 g, 0.21 mol) in carbon tetrachloride (100 mL) was added with stirring to dibenzodehydrosuberone (**7**; 37.0 g, 0.179 mol) in carbon tetrachloride (200 mL). White crystals began forming immediately. Stirring was continued for 1.5 h, and **8** (63.8 g, 97%) was collected by filtration: mp 204–207 °C (lit.[23] mp 211 °C); ^1H NMR (acetone-d_6) δ 8.10–7.95 (m, 2, C-4 and C-6 aromatic H), 7.68–7.55 (m, 6, aromatic H), 6.18 ppm (s, 2, C-10 and C-11 H).

10-Bromo-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one (9). *trans*-10,11-Dibromo-10,11-dihydro-5*H*-dibenzo[*a*,*b*]cycloheptene-5-one (**8**; 43.0 g, 0.117 mol) and sodium hydroxide (14.1 g, 0.352 mol) were mixed in methanol (800 mL), and the mixture was boiled for 1.5 h. Sodium bromide was removed by filtration of the hot solution. Cooling of the solution gave **9** (30.2 g, 90%) as a white solid: mp 116–117 °C (lit.[23] mp 116 °C); ^1H NMR (acetone-d_6) δ 8.15 (d, 1, C-9 H), 7.95 (s, 1, C-11 H), 7.87 (t, 2, C-4 and C-6 H), 7.77 (t, 1, C-1 H), 7.71–7.59 ppm (m, 4, C-2, C-3, C-7, and C-8 H).

10-(4-Methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one (10). To a solution of 10-bromo-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one (**9**; 33.3 g, 0.117 mol) and *N*-methylpiperazine (23.3 g, 0.233 mol) in *tert*-butyl alcohol (335 mL) was added potassium *tert*-butoxide (16.7 g, 0.149 mol). The mixture was boiled for 4 h. The solvent was evaporated, and the dark residual oil was mixed with water. The mixture was extracted with chloroform (3 × 120 mL), and the combined extracts were dried ($MgSO_4$). Evaporation of the chloroform and recrystallization of the residue gave **10** (28.6 g, 80%) as a white solid: mp 133–135 °C (lit.[24] mp 133–135 °C); ^1H NMR ($CDCl_3$) δ 8.00–7.30 (m, 8, aromatic H), 6.39 (s, 1, C-11 H), 2.99 (t, 4, piperazino C-2 and C-6 H), 2.59 (t, 4, piperazino C-3 and C-5 H), 2.37 ppm (s, 3, NCH_3); ^{13}C NMR ($CDCl_3$) δ 196.02 (C-5), 149.81, 140.95, 138.89, 134.72, 133.37, 131.17, 130.98, 129.58, 129.14, 128.44, 127.87, 127.73, 126.65, 112.17 (C-11), 55.53 (2, piperazino C-2 and C-6), 50.97 (2, piperazino C-3 and C-5), 46.04 ppm (NCH_3); off-resonance ^{13}C NMR ($CDCl_3$) δ 196.05 (s), 112.17 (d), 55.33 (t), 50.97 (t), 46.04 ppm (q). Anal. ($C_{20}H_{20}N_2O$) C, H, N.

Methyl 2-Benzoylphenylacetate (13). 2-Benzoylphenylacetic acid (**12**; 24.3 g, 0.101 mol), mp 129–131 °C (lit.[13] mp 127–129 °C), prepared by oxidation of 1-phenylindene (**11**), mp 25–27 °C (lit.[13] mp 25–28 °C), and 1.5 M methanolic hydrogen chloride (40.0 mL) were stirred at room temperature for 2 h. The solvent was evaporated, and the residual oil was dissolved in ether (100 mL). The ethereal solution was washed with 1.5 M sodium hydroxide (3 × 40 mL) and brine (2 × 50 mL). Evaporation of the ether gave **13** (23.8 g, 93%) as an oil: ^1H NMR ($CDCl_3$) δ 7.80–7.30 (m, 9, aromatic H), 3.89 (s, 2, CH_2CO_2), 3.54 ppm (s, 3, CO_2CH_3).

Methyl 2-(1-Phenylethenyl)phenylacetate (14). Under an atmosphere of nitrogen, dry dimethyl sulfoxide (50 mL) was added by syringe through a septum to sodium hydride (1.00 g, 41.6 mmol) prepared by washing (4×) of a 50% mineral oil dispersion with pentane. The mixture was stirred at 70 °C for 45 min, at which time the evolution of hydrogen ceased. The solution was then cooled to 0 °C, and methyltriphenylphosphonium bromide (16.1 g, 45.1 mmol) in warm dimethyl sulfoxide (50 mL) was added with stirring. The solution became yellow, and the stirring was continued for 15 min. Methyl 2-benzoylphenylacetate (**13**; 6.10 g, 24.0 mmol) in dimethyl sulfoxide (50 mL) was added with stirring. The stirring was continued at room temperature for 3 h, at 70 °C for 1.5 h, and finally at room temperature overnight. The mixture was poured into ice–water (200 mL), and this mixture was extracted with pentane (5 × 100 mL). The combined pentane layers were washed with water (2 × 50 mL) and dried ($MgSO_4$). Evaporation gave a 1:3 mixture, as indicated by ^1H NMR, of **13** and **14** (4.50 g) as an oil. Chromatography on silica gel (60–200 mesh) using methylene chloride as eluant gave **14** (2.57 g, 42%) as an oil: ^1H NMR ($CDCl_3$) δ 7.30–7.20 (m, 9, aromatic H), 5.80

(d, 1, vinylic H), 5.20 (d, 1, vinylic H), 3.50 (s, 3, CO_2CH_3), 3.47 ppm (s, 2, CH_2).

2-(1-Phenylethenyl)phenylacetic Acid (15). Potassium hydroxide (1.40 g, 25.0 mmol) in water (70 mL) was added to methyl 2-(1-methylethenyl)phenylacetate (14; 2.95 g, 11.7 mmol) in methanol (70 mL). The mixture was boiled for 1 h, cooled, and made acidic (pH 1) with concentrated hydrochloric acid. Evaporation of the methanol at reduced pressure resulted in precipitation of a small amount of solid. The heterogeneous mixture was extracted with ether (3 × 40 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated. Recrystallization of the solid residue from pentane–benzene gave **15** (2.07 g, 74%) as a white solid: mp 86–87 °C; ^{1}H NMR ($CDCl_3$) δ 9.40–9.00 (br s, 1, OH), 7.35–7.20 (m, 9, aromatic H), 5.80 (s, 1, vinylic H) 5.20 (s, 1, vinylic H), 3.47 ppm (s, 2, CH_2). Anal. ($C_{16}H_{14}O_2$) C, H.

4-Phenyl-2-naphthol (16). Finely powdered 2-(1-phenylethenyl)phenylacetic acid (**15**; 0.300 g, 1.26 mmol) was added to polyphosphoric acid (PPA, $H_6P_4O_{13}$, 10 g) with stirring at 90 °C. After the addition was complete, the mixture was stirred at 90 °C for 40 min when the appearance of a black color indicated the near completion of the reaction.[27] After cooling, ice–water (70 mL) was added, and the mixture was extracted with methylene chloride (3 × 40 mL). The combined methylene chloride extracts were washed with saturated sodium bicarbonate and dried (Na_2SO_4). Evaporation of the organic solvent gave **16** (0.190 g, 69%) as a solid: ^{1}H NMR ($CDCl_3$) δ 7.80–7.50 (m, 2, aromatic H), 7.30–6.95 ppm (m, 5, aromatic H and OH); UV max (CH_3OH) 337 (ε 2800), 291 (6200), 284 (6200), 228 nm (48 000) [lit.[28] UV max (CH_3CH_2OH) 338 (log ε 3.54), 292 (3.84) 286 (3.84), 230 nm (4.80)]; IR (film) 3600–3200 (s), 1625 (m), 1600 (s), 1460 (m), 1400 (m), 1165 (s), 925 (m), 865 (m), 780 (m), 740 (m), 660 cm^{-1} (m).

Methyl 2-(1-Phenylethyl)phenylacetate (17). Methyl 2-(1-phenylethenyl)phenylacetate (**14**; 3.06 g, 12.1 mmol) in methanol (60 mL) was stirred under an atmosphere of hydrogen over 10% palladium on carbon (0.40 g). Stirring was continued until the uptake of hydrogen ceased (4 h). The catalyst was removed by filtration, and evaporation of the methanol gave **17** (3.10 g, 101%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.30–7.20 (m, 9, aromatic H), 4.36 (q, 1, methine H), 3.58 (d, 2, CH_2), 3.54 (s, 3, CO_2CH_3), 1.57 ppm (d, 3, CCH_3).

2-(1-Phenylethyl)phenylacetic Acid (18). Potassium hydroxide (2.44 g, 43.5 mmol) in water (150 mL) was added to methyl 2-(1-phenylethyl)phenylacetate (**17**; 4.60 g, 18.1 mmol) in methanol (150 mL) and then was boiled with stirring for 1.5 h. The methanol was evaporated at reduced pressure, and the mixture was extracted with ether (1 × 50 mL) and then acidified (pH 1) with concentrated hydrochloric acid. The precipitate was collected by filtration, and recrystallization from benzene–pentane gave **18** (3.62 g, 83%): mp 87–89 °C (lit.[29] mp 93–94 °C); ^{1}H NMR ($CDCl_3$) δ 7.30–7.12 (m, 9, aromatic H), 4.36 (q, 1, methine H), 3.63 (q, 2, CH_2), 1.61 ppm (d, 3, CCH_3). Anal. ($C_{16}H_{16}O_2$) C, H.

2-(1-Phenylethenyl)phenylacetic acid (**15**; 1.10 g, 4.62 mmol) in methanol (95 mL) was stirred under an atmosphere of hydrogen over 10% palladium on carbon (2.00 g). Stirring was continued until the uptake of hydrogen ceased (1 h). The catalyst was removed by filtration, and evaporation of the methanol and recrystallization of the residue from benzene–pentane gave **18** (0.460 g, 41%): mp 89–90 °C.

10,11-Dihydro-5-methyl-5*H*-dibenzo[*a*,*d*]cyclohepten-10-one (19). Finely powdered 2-(1-phenylethyl)phenylacetic acid (**18**; 5.00 g, 20.8 mmol) was added with stirring to polyphosphoric acid (PPA, $H_6P_4O_{15}$; 350 g) at 90 °C. Stirring was continued at 90 °C for 2.5 h when the appearance of a black color indicated the near completion of the reaction.[27] Ice–water (600 mL) was added to the cooled reaction mixture, and the mixture was extracted with methylene chloride (3 × 150 mL). The combined methylene chloride layers were washed with 5% sodium hydroxide (2 × 50 mL) and then dried ($MgSO_4$). Evaporation of the methylene chloride at reduced pressure gave **19** (2.95 g, 64%) as a colorless oil, which soon solidified: mp 90–93 °C (lit.[29] mp 90–91 °C); ^{1}H NMR ($CDCl_3$) δ 8.00–7.10 (m, 8, aromatic H), 4.59 (q, 1, methine H), 4.26 (d, 2, $COCH_2$), 1.83 ppm (d, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 196.84 (C-10), 146.43, 143.62, 133.00, 132.62, 130.56, 129.85, 128.31, 127.39, 126.82 (2 C) 125.90, 125.20, 51.05 (C-11), 41.55 (C-5), 17.44 ppm (CH_3); off-resonance ^{13}C NMR ($CDCl_3$) δ 51.05 (t), 41.55 (d), 17.40 ppm (q); IR (film) 1780 (m), 1675 (s), 1600 (s), 1490 (w), 1455 (m), 1248 (m), 755 cm^{-1} (m); MS *m/z* (relative intensity) 222 (M^+, 100), 221 (13), 207 (85), 193 (12), 180 (25), 179 (32).

A sample of solid **19** was molecularly distilled at 95 °C (1 mmHg). The distillate crystallized on cooling: mp 96–97 °C with an ^{1}H NMR spectrum identical with that above. The ^{1}H NMR spectrum of the distillation residue was also unchanged from that reported above.

During attempted recrystallization of **19**, oils were obtained when the mother liquors were evaporated by distillation, and a diastereomer of solid **19** was identified in the residue by its spectral properties: ^{1}H NMR δ ($CDCl_3$) δ 8.00–7.10 (m, 8, aromatic H), 4.21 (q, 1, methine H), 2.08 (t, 2, $COCH_2$), 1.68 ppm (d, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 188.38 (C-10), 146.04, 134.59, 134.10, 133.67, 132.02, 130.69, 129.12, 128.25, 128.00, 127.65, 127.22, 125.83, 48.45 (C-11), 29.00 (C-5), 19.95 ppm (CH_3); off-resonance ^{13}C NMR ($CDCl_3$) δ 48.45 (d), 29.00 (q), 19.95 ppm (low signal to noise ratio; only observed as a singlet but possibly a triplet); MS *m/z* (relative intensity) 222 (M^+, 100), 221 (13), 207 (85), 193 (12), 180 (25), 179 (32).

Determination of Affinity for Muscarinic Binding Sites. By a modification of a method outlined earlier,[20] rat cerebral cortex was dissected from the rest of the brain and homogenized (Polytron, setting 5, 15 s) (Brinkman Instruments, Westbury, CN) in 40 vol (w/v) of Tris-HCl buffer (50 mM, pH 7.4 at 25 °C) containing 120 mM NaCl. The homogenate was centrifuged at 30 000*g* for 10 min, and the resulting pellet was resuspended in 40 vol of fresh buffer. The resuspension was incubated at 37 °C for 10 min and then centrifuged again. The final pellet was resuspended in 1000 vol of fresh buffer, and 0.4-mL aliquots (approximately 2 μg of tissue) were added to tubes containing [^{3}H]QNB (0.23–0.39 nM, final concentration), buffer, and one of eight concentrations of the respective drugs. The final assay volume was 2 mL. Assay tubes (in triplicate) were incubated at 25 °C for 60 min, and their contents were filtered over glass-fiber filters (30, Schleicher and Schuell, Keene, NH). Filters were rinsed three times with 4 mL of ice-cold buffer. The radioactivity remaining on the filters was determined by conventional liquid-scintillation spectrometry using a Beckman 3801 spectrometer. The counting efficiency was approximately 38%. Specific binding was defined as the difference in binding observed in the presence and absence of 1 μM atropine.

Determination of Affinity for Dopamine D-1 Binding Sites. As previously described,[21] rat striatum was dissected on ice and homogenized in 40 vol of Tris-HCl buffer (50 mM, pH 7.4 at 37 °C) containing 5 mM $MgSO_4$. The subsequent homogenate and the assay tubes were prepared as described above, but the final pellet was resuspended in 200 vol of the appropriate buffer. Assay tubes containing 0.4-mL aliquots of the tissue preparation were incubated with [^{3}H]SCH 23390 (0.45–0.76 nM, final concentration) at 37 °C for 30 min. Nonspecific binding was determined by the presence of 1 μM SCH 23390.

Determination of Affinity for Dopamine D-2 Binding Sites. The binding of [^{3}H]spiperone (0.95–1.4 nM, final concentration) to dopamine D-2 receptors in striatum was conducted by a modification of the methods described above, except ketanserin (40 nM) was included in all tubes to mask the binding of radioligand to serotonin (5HT-2) receptors.[37] In addition, [^{3}H]spiperone binding assays were conducted with Tris-HCl buffer (50 mM, pH 7.4 and 37 °C) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$. Nonspecific binding was determined in the presence of 1 μM haloperidol.

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