Synthesis and Receptor Binding Studies Relevant to the Neuroleptic Activities of Some 1-Methyl-4-piperidylidene-9-substituted-pyrrolo[2,1-*b*][3]benzazepine Derivatives

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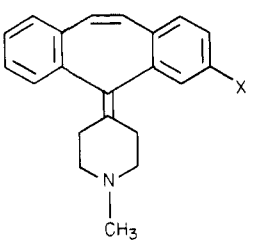
The synthesis of a series of 1-methyl-4-(9-substituted-11*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ylidene)piperidines (**4a–f**) and 1-methyl-4-(9-substituted-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ylidene)piperidines (**4g–l**) is described. As with the 3-substituted cyproheptadine compounds **1b–e**, atropisomerism exists in **4b–f**, but unlike the enantiomers of **1b–e**, the pyrrolobenzazepine enantiomers racemize at room temperature. Thus, the bromo compound (+)-**4b** has a half-life of 128 ± 1 min at 25 °C, while the chloro compound (−)-**4c** has a half-life of 114 ± 9 min at 25 °C. Compounds **4a–l** have been examined for receptor binding affinities in assays that have been recognized as predictive for antipsychotic activity. The displacement of specifically bound tritiated ligands, comprising the dopamine antagonist [^{3}H]spiperone, the dopamine agonist [^{3}H]apomorphine, the muscarinic cholinergic antagonist [^{3}H]quinuclidinyl benzilate (QNB), the α-adrenergic antagonist [^{3}H]prazosin, the α-adrenergic agonist [^{3}H]clonidine, the serotonin-1 binding agent [^{3}H]serotonin, and the mixed serotonin agonist–antagonist [^{3}H]lysergic acid diethylamide (LSD), by **4a–l** has been measured utilizing membrane preparations of mammalian brain. Certain of the features of the receptor binding of these compounds have been shown to be common to several of the receptor sites. Data from these binding studies have been compared to corresponding data previously obtained for a series of chiral 3-substituted cyproheptadine analogues, and the receptor binding data of the two classes of compounds are discussed with respect to their molecular geometries.

Cyproheptadine (**1a**) has a diverse profile of pharmacological properties that includes antihistaminic, antiserotonergic, antidopaminergic, anticholinergic, and appetite-stimulatory (orexigenic) activities.[1,2] Studies with analogues of **1a** have sought to separate these pharmacological properties either by selective enhancement of one effect or diminution of the other properties. One successful approach to this objective has involved the introduction of an appropriate nuclear substituent into the 3-position of the cyproheptadine molecule and resolution of the resulting enantiomers.[3,4] Thus, the antidopaminergic as well as the antiserotonergic and orexigenic activities of such compounds have been selectively enhanced and separated from central and/or peripheral anticholinergic activities by this method.[5,6]

Recently, the synthesis of an analogue of **1a** in which



1a, X = H
b, X = Br
c, X = CN
d, X = SCF_3
e, X = Cl

one of the benzene rings has been replaced by a pyrrole nucleus, **4a**, as well as of its dihydro analogue **4g**, was reported.[7] In a preliminary pharmacological evaluation, both **4a** and **4g** were found to have biological profiles similar to that observed for the clinically useful H-1 histamine and serotonin antagonist **1a**. In order to examine the influence of nuclear substituents on the stereochemical, biochemical, and pharmacological properties of the parent 1-methyl-4-piperidylidenepyrrolo[2,1-*b*][3]benzazepine systems **4a,g**, a series of compounds having nuclear substituents located at the 9-positions of **4a,g** was prepared. It is now well acknowledged that antipsychotic agents are potent inhibitors of [^{3}H]haloperidol and [^{3}H]spiperone binding to dopamine receptors and that such binding affinity correlates reasonably well with in vivo pharmacological effects in animals[8] as well as with clinical efficacy in humans.[9–11] Moreover, the ancillary pharmacological properties of many neuroleptic drugs may be determined by their interactions at cholinergic, serotonergic, and α-adrenergic receptors using radioligand binding techniques.[12] Therefore, the binding affinities of each of the nuclear-substituted compounds **4b–f** and **4h–l**, as well as of the unsubstituted parent compounds, to receptor

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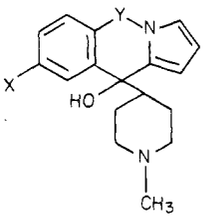
Table I. Grignard Product Intermediates



compd	X	Y	yield, %	mp, °C
3a	H	CH=CH	78	151-153
3b	Br	CH=CH	57	135-140
3c	SCF_3	CH=CH	57	158-166
3d	H	CH_2CH_2	68	175-177
3e	Br	CH_2CH_2	48	214-216
3f	Cl	CH_2CH_2	53	217-218
3g	CN	CH_2CH_2	49	218-222
3h	SCF_3	CH_2CH_2	49	210-212

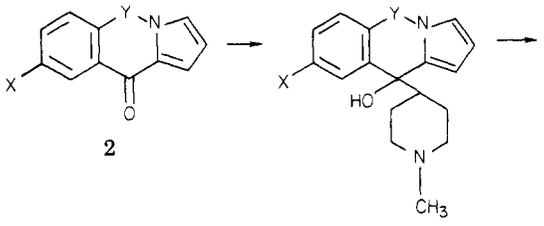
membrane sites were determined. The displacement of specifically bound tritiated ligands, comprising the dopamine antagonist [^{3}H]spiperone, the dopamine agonist [^{3}H]apomorphine, the muscarinic cholinergic antagonist [^{3}H]quinuclidinyl benzilate (QNB), the α-adrenergic antagonist [^{3}H]prazosin, the α-adrenergic agonist [^{3}H]clonidine, the serotonin-1 binding agent [^{3}H]serotonin, and the mixed serotonin agonist–antagonist [^{3}H]lysergic acid diethylamide (LSD), by **4a–l** was measured utilizing membrane preparations of mammalian brain.

The synthesis, stereochemistry, and receptor binding characteristics of the pyrrolobenzazepine derivatives **4a–l** are reported in this paper. The neuroleptic activities and ancillary pharmacological properties of these compounds will be reported in a subsequent publication.

Chemistry. The pyrrolobenzazepine derivatives **4a,b,e,g–k** were all prepared by the addition of 1-methyl-4-piperidylmagnesium chloride to the appropriate ketones **2**[13,14] followed by dehydration of the resulting tertiary carbinols **3a–h**, respectively. For those carbinols having a double bond in the 5,6-positions, **3a–c**, dehydration was carried out with a chloroform solution of hydrogen chloride gas at room temperature, while for those carbinols having a saturated bridge in the 5,6-positions, **3d–h**, dehydration was carried out with oxalic acid in refluxing ethanol. The chloro- and cyanopyrrolobenzazepines **4c,d** were prepared from the corresponding bromo compound **4b** by exchange reactions with cuprous chloride and cuprous cyanide, respectively.

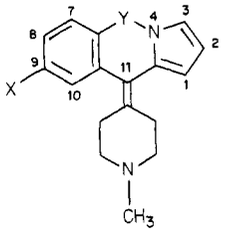
It is now well established that nuclear substitution at the 3-position of cyproheptadine (**1a**) results in the atropisomerism of such compounds[3] and that the resulting enantiomers have distinct biological activities.[4-7] The structural similarity of the 9-substituted pyrrolobenzazepines **4b–f** to the 3-substituted cyproheptadines therefore prompted an investigation into the resolution of these compounds. As with the 3-substituted cyproheptadines, both di-*p*-toluoyl-*d*- and -*l*-tartaric acids provided crystalline, optically active salts with either **4b** or **4c**. Conversion of these salts to the free bases afforded optically active products that racemized rapidly at room temperature. For example, (+)-**4b** was found to have a half-life ($t_{1/2}$) of 128 ± 1 min at 25.0 °C, while (−)-**4c** had a $t_{1/2}$ of 114 ± 9 min at 25.0 °C. Thus, the barrier to inversion, and hence racemization, is far lower in compounds **4b,c** than it is in the corresponding cyproheptadine derivatives,[3] and, therefore, no attempt was made to assess biological properties of individual enantiomers.

Scheme I



2 3

a, X = H; Y = CH=CH
b, X = Br; Y = CH=CH
c, X = SCF_3; Y = CH=CH
d, X = H; Y = CH_2CH_2
e, X = Br; Y = CH_2CH_2
f, X = Cl; Y = CH_2CH_2
g, X = CN; Y = CH_2CH_2
h, X = SCF_3; Y = CH_2CH_2



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a, X = H; Y = CH=CH
b, X = Br; Y = CH=CH
c, X = Cl; Y = CH=CH
d, X = CN; Y = CH=CH
e, X = SCF_3; Y = CH=CH
f, X = CO_2H; Y = CH=CH
g, X = H; Y = CH_2CH_2
h, X = Br; Y = CH_2CH_2
i, X = Cl; Y = CH_2CH_2
j, X = CN; Y = CH_2CH_2
k, X = SCF_3; Y = CH_2CH_2
l, X = CO_2H; Y = CH_2CH_2

Results and Discussion

Radioligand Displacement Assays. All radioligand displacement assays were conducted by incubating a constant concentration of radioligand with brain membrane suspensions in the presence of three to five triplicate concentrations of the compounds under investigation. The receptor–radioligand complex was isolated by rapid filtration and quantitated by liquid scintillation spectrometry. Specific binding of each radioligand was defined as the difference in radioligand bound in the absence and presence of a saturating concentration of an unlabeled ligand specific for the receptor. Information concerning the receptor type, radioligand, tissue, and saturating ligand is collected in Table III. This table also contains references to the detailed procedures used for each radioligand displacement assay.

The IC_{50} concentration required to displace 50% of the specifically bound radioligand was determined for each compound from the percent inhibition–concentration data using regression techniques. The corresponding inhibition constants, K_I, were then calculated by means of the Cheng–Prussof relationship (eq 1).[15] In this equation, c

$$K_I = IC_{50}/(1 + c/K_D) \quad (1)$$

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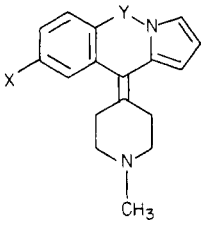
Table II



compd	X	Y	starting material	method[a]	yield, %	mp, °C	formula	analyses
4a	H	CH=CH	3a	*b*	89	222 dec	$C_{19}H_{20}N_2 \cdot C_2H_2O_4$	
4b	Br	CH=CH	3b	B	64	150-152	$C_{19}H_{19}BrN_2$	C, H, Br, N
4c	Cl	CH=CH	4b	C	71	113-114.5	$C_{19}H_{19}ClN_2$	C, H, Cl, N
4d	CN	CH=CH	4b	D	94	158-161	$C_{20}H_{19}N_3$	C, H, N
4e	SCF_3	CH=CH	3c	B	75	124-126	$C_{20}H_{19}F_3N_2S$	C, H, F, N, S
4f	CO_2H	CH=CH	4d	*b*	74	214 dec	$C_{20}H_{20}N_2O_2 \cdot HCl$	
4g	H	CH_2CH_2	3d	*b*	84	238-243 dec	$C_{19}H_{22}N_2 \cdot C_2H_2O_4$	
4h	Br	CH_2CH_2	3e	E	78	170-172	$C_{19}H_{21}BrN_2$	C, H, Br, N
4i	Cl	CH_2CH_2	3f	E	70	146.5-148	$C_{19}H_{21}ClN_2$	C, H, Cl, N
4j	CN	CH_2CH_2	3g	E	45	177-179	$C_{20}H_{21}N_3$	C, H, N
4k	SCF_3	CH_2CH_2	3h	E	50	139-140	$C_{20}H_{21}F_3N_2S$	C, H, F, N, S
4l	CO_2H	CH_2CH_2	4j	*b*	65	265 dec	$C_{20}H_{22}N_2O_2 \cdot HCl \cdot 0.25H_2O$	

[a] See Experimental Section. [b] Reference 7.

Table III. Radioligand Displacement Assays

	[^{3}H]radioligand				displacing ligand		
receptor	name	sp act., Ci/mmol	assay concn, nM	tissue	name	assay concn, nM	ref
dopamine antagonist	spiperone	40	0.1	rat caudate	(+)-butaclamol	100	16
dopamine agonist	apomorphine	25-35	0.2	rat caudate	(+)-butaclamol	10 000	17
α_1 adrenoceptor	prazosin	33	0.14	calf cerebral cortex	prazosin	1 000	18
α_2 adrenoceptor	clonidine	23	0.2	calf cerebral cortex	clonidine	100	19
serotonin-1	serotonin	30	4	rat cortex	serotonin	10 000	20
serotonin-1 and -2	LSD	30	2	rat cortex	LSD	10 000	20
muscarinic-cholinergic	QNB	40	0.06	rat brain S_1	oxotremorine	100 000	21

is the concentration of radioligand and K_D is the dissociation constant of the radioligand–receptor complex.

Receptor Binding Studies. Data for the displacement of specifically bound radioligands to mammalian brain membrane suspensions are summarized in Table IV. The compounds were active in all seven of the listed binding assays but were devoid of significant activity ($K_I > 50000$ nM) in binding assays for adenosine A-1, γ-aminobutyric acid, benzodiazepine, opiate, and β-adrenergic receptors.[22]

Certain of the features of the receptor binding of these compounds were common to several of the binding sites. The presence of a 9-carboxy substituent in both **4f** and **4l** dramatically reduced the observed affinity of the compound at the binding site. The series of unsaturated pyrrolobenzazepines **4a–f** had a higher affinity for the labeled quinuclidinyl benzilate, prazosin, clonidine, and serotonin receptor binding sites than did the corresponding saturated compounds **4g–l**. Such an affinity difference was much less evident for displacement of labeled spiperone, LSD, and apomorphine. Indeed, comparison of displacement results for the radiolabeled dopamine antagonist [^{3}H]spiperone and the dopamine agonist [^{3}H]apomorphine revealed a marked similarity. In both cases, introduction of an uncharged substituent at the 9-position led to an increase in binding affinity, and there was little difference in the affinities between the saturated and unsaturated series. One difference, however, was the lack of increase in binding affinity produced by the trifluoromethylthio-substituted compounds **4e,k** at the [^{3}H]apomorphine binding site compared to that shown at the [^{3}H]spiperone site. Examination of the 9-chloro (**4c,i**) and 9-bromo (**4b,h**) derivatives in each series for dopamine agonist activity in the carp retinal adenylate cyclase assay showed that while these compounds had significant affinity for the apomorphine binding site, they were unable to stimulate cyclic AMP production in this dopamine-responsive system.[23] Indeed, they were potent inhibitors of dopamine with K_I's in the 1–10 nM range.[24]

Displacement of the α-adrenoceptor antagonist [^{3}H]-prazosin was enhanced by the presence of a 9-halogen or 9-trifluoromethylthio substituent for both the saturated and unsaturated series. Indeed, all of the pyrrolobenzazepine derivatives tested revealed a substantially greater affinity (6- to 30-fold) for the [^{3}H]prazosin binding site than for the corresponding α-adrenoceptor binding site of the radiolabeled agonist [^{3}H]clonidine. For both adrenoceptors, the presence of a 9-cyano substituent (**4d,j**),

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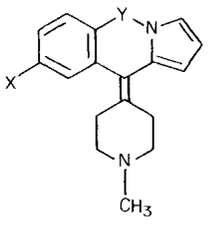
Table IV. Displacement of Radioligand Binding by 9-Substituted Pyrrolobenzazepines 4a–l



			K_I, nM, of displaced radioligand						
			dopamine binding		α adrenergic binding		serotonin binding		muscarinic-cholinergic binding
compd	X	Y	[^{3}H]spiperone	[^{3}H]apomorphine	[^{3}H]prazosin	[^{3}H]clonidine	[^{3}H]LSD	[^{3}H]serotonin	[^{3}H]QNB
4a	H	CH=CH	114 ± 4[a]	185 ± 20	29 ± 2	226 ± 10	13 ± 7	210 ± 60	14.5 ± 4.4
4b	Br	CH=CH	7 ± 1	6.6 ± 1.0	19 ± 3	210 ± 20	8.7 ± 1.5	250 ± 60	18 ± 7
4c	Cl	CH=CH	11 ± 1	6.8 ± 0.4	20 ± 3	310 ± 20	7.6 ± 50	300 ± 50	20 ± 5
4d	CN	CH=CH	27 ± 4	33 ± 10	30 ± 3	1 030 ± 70	12 ± 2	310 ± 20	21 ± 8
4e	SCF_3	CH=CH	17 ± 3	180 ± 30	13 ± 3	230 ± 20	24 ± 4	260 ± 70	88 ± 4
4f	CO_2H	CH=CH	43 500 ± 3 700	23 000 ± 5 000	1 200 ± 200	77 000 ± 20 000	1 320 ± 16	4 200 ± 900	9 800 ± 400
4g	H	CH_2CH_2	210 ± 90	150 ± 30	130 ± 20	730 ± 50	25 ± 3	1 360 ± 260	49 ± 7
4h	Br	CH_2CH_2	11.1 ± 0.6	7.2 ± 1.5	44 ± 4	430 ± 20	7.8 ± 0.5	1 400 ± 300	60 ± 7
4i	Cl	CH_2CH_2	20 ± 1	11 ± 2	80 ± 14	600 ± 70	8.2 ± 1.6	1 940 ± 60	48 ± 6
4j	CN	CH_2CH_2	32 ± 4	15.5 ± 2.7	140 ± 10	2 050 ± 120	14 ± 3	1 150 ± 160	270 ± 20
4k	SCF_3	CH_2CH_2	12 ± 1.5	87 ± 14	36 ± 10	330 ± 30	18 ± 4	1 100 ± 400	250 ± 20
4l	CO_2H	CH_2CH_2	80 000 ± 10 000	18 000 ± 12 000			12 000 ± 1 600[b]	10 700[b]	>50 000
spiperone			2.0 ± 0.6						49 600 ± 660
1a			63 ± 11						4.0 ± 0.1
(+)-butaclamol			0.2 ± 0.02						5 200 ± 990

[a] Mean plus or minus standard deviation. [b] Single determination.

Table V. Substituent Affinity Contributions[a]

	$-\ln [K_I (X)/K_I (H)]$											
	dopamine antagonist receptor			α_1 adrenoceptor			α_2 adrenoceptor			muscarinic-cholinergic receptor		
substituent	1	4 Y = CH=CH	4 Y = CH_2CH_2	1	4 Y = CH=CH	4 Y = CH_2CH_2	1	4 Y = CH=CH	4 Y = CH_2CH_2	1	4 Y = CH=CH	4 Y = CH_2CH_2
Br	2.76	2.78	2.96	0.75	0.42	1.08	0.41	0.07	0.53	0.69	−0.23	−0.20
CN	2.53	1.43	1.90	0.21	−0.03	−0.07	−1.03	−1.52	−1.03	1.39	−0.38	−1.72
SCF_3	1.75	1.89	2.90	0.02	0.80	1.28	0.31	−0.02	−0.79	−0.69	−1.80	−1.63
Cl		2.34	2.37		0.37	0.49		−0.32	0.20		−0.34	0.03

[a] Since the observed affinity for a racemic mixture would be dominated by the high-affinity enantiomer, we have compared the inhibition constants found for the unsaturated series 4b-e and the saturated series 4h-k to the inhibition constant of the higher affinity enantiomer of the corresponding cyproheptadine series.

however, substantially reduced binding affinity.

Comparison of the displacement results of the radioligand [^{3}H]serotonin, which binds to the serotonin-1 site,[20] with the corresponding results for the displacement of [^{3}H]LSD, which binds to both serotonin-1 and serotonin-2 sites,[20] showed a marked preference of all of the pyrrolobenzazepines for the serotonin-2 site. For both the saturated and unsaturated series, substitution at the 9-position with an uncharged substituent led to only minor changes in affinity at either serotonin site.

The binding affinity at the site labeled by the muscarinic–cholinergic radioligand [^{3}H]quinuclidinyl benzilate averaged about fivefold greater for the unsaturated series **4a–e** than for the corresponding saturated analogues **4g–k**, the largest difference being seen for the 9-cyano-substituted compounds **4d,j**. For both series, no compound produced a significant increase in binding affinity relative to the unsubstituted compounds **4a,g**.

Overall, therefore, the 9-substituted pyrrolobenzazepines **4b–e,h–k** have significant dopaminergic, α-adrenergic, serotonergic, and muscarinic–cholinergic[10] activities as reflected by radioligands specific for each of the putative receptor classes.

These compounds display several features thought to be favorable for neuroleptic activity. They are potent inhibitors of the dopamine antagonist [^{3}H]spiperone, with a binding affinity 2–3 times greater than that of chlorpromazine in this assay. For a large number of neuroleptics, the relative affinity of receptor binding at the closely related [^{3}H]haloperidol binding site has been shown to correlate well with their clinical efficacy.[8] The compounds also display a pronounced affinity for the serotonin-2 binding site, as indicated by their affinity for the [^{3}H]LSD binding site. This latter property has been predicted to be favorable for neuroleptic activity.[25] The intrinsic antimuscarinic–cholinergic activity of these compounds is also a property that may be of importance in reducing the potential for extrapyramidal side effects associated with neuroleptic usage. The ratio of affinities for the α-adrenergic antagonist and the dopamine antagonist receptor, as indicated by the ratio K_I (WB-4101)/K_I (spiperone), has been shown to correlate with the tendency of a drug to elicit sedation and orthostatic hypotension,[26] with a value of 2 indicating a high and a value of 10 indicating a low propensity. Calculation of the equivalent ratio K_I (prazosin)/K_I (spiperone) for the 9-halo-substituted pyrrolobenzazepines yields ratios of 2–3 for the unsaturated series, while the corresponding saturated compounds have a ratio of 4.

Comparison with 3-Substituted Cyproheptadines. The pyrrolobenzazepine derivatives **4a–f,g–l** were synthesized as analogues of the corresponding 3-substituted cyproheptadines, for which receptor binding data have previously been published.[5] It was therefore of interest to compare the receptor binding data of the three classes of compounds. The inhibition constants of **1a** were found to be 123 ± 3 and 1500 ± 250 nM at the α_1 and α_2 adrenoceptors, respectively, 63 ± 11 nM at the dopamine ([^{3}H]spiperone) receptor, and 4.0 ± 0.1 nM at the muscarinic–cholinergic receptor. For the cyproheptadine series, the α_1 and α_2 adrenoceptors were labeled by the alternate antagonist radioligand WB-4101 and agonist radioligand (−)-norepinephrine, respectively. Studies have indicated a generally good agreement between inhibition constants obtained with labeled clonidine or (−)-norepinephrine[19,27] and prazosin or WB-4101.[18,28] Comparison with Table IV shows that, relative to **1a**, the unsubstituted compounds **4a,g** display a greater affinity toward the α_2 adrenoceptor, weaker affinities at the dopamine and muscarinic–cholinergic receptors, and a greater or nearly equal affinity at the α_1 adrenoceptor.

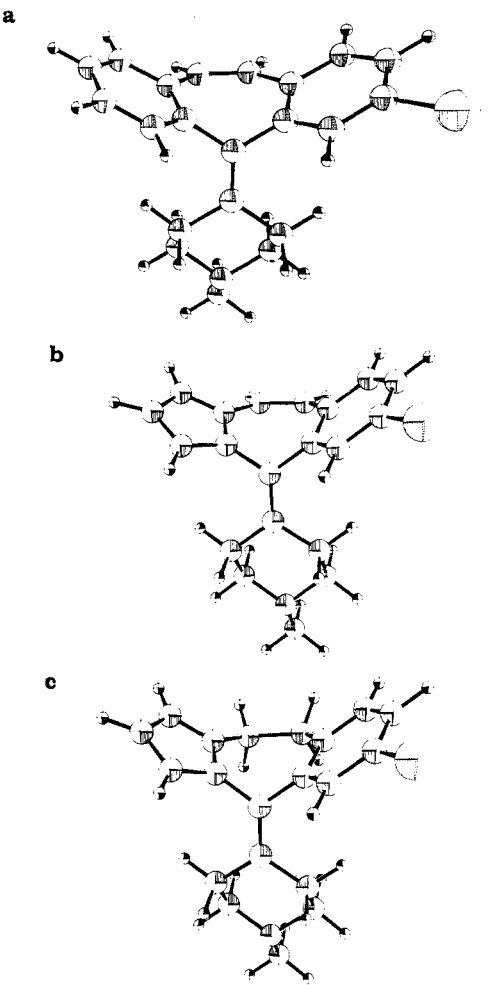


Figure 1. (a) (pR_apS_b)-(−)-1-Methyl-4-(3-bromo-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)piperidine [(−)-**1b**] (structure according to X-ray analysis[5]). (b) Computer-generated perspective drawing of **4b**. (c) Computer-generated perspective drawing of **4h**.

Substitution of the nitrogen-containing pyrrole ring for one of the benzene rings in the cyproheptadine series will clearly lead to marked changes in the molecular electronic distribution. Additional changes, however, will also be expected in the conformation and conformational flexibility of such pyrrolobenzazepine compounds. Further changes in conformation and flexibility would be expected upon saturation at the 5,6-positions. Each of these changes could lead to differences in the interactions of the compounds with the central receptors under consideration.

We have previously reported the X-ray structure of (pR_apS_b)-(−)-3-bromocyproheptadine[5] (Figure 1a). Using this structure as a starting point, it is possible to employ a classical force field minimization program[29] within the Merck molecular modeling system[30] to obtain estimates

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of the conformations of the corresponding 9-bromopyrrolobenzazepine analogues **4b,h**. These structures are shown in Figure 1b,c. As shown in Figure 1a–c, the three structures resemble each other fairly closely, a conclusion supported by the following quantitative comparisons.

For (–)-3-bromocyproheptadine (Figure 1a), the benzene–benzene interplane angle is 125°. The corresponding calculated angles between the benzene and pyrrole rings become somewhat more acute for the pyrrolobenzazepines, having values of 120.5 and 113° for the unsaturated and saturated derivatives, Figure 1b,c, respectively. If the central seven-membered rings of the cyproheptadine and pyrrolobenzazepine derivatives are superimposed using a Merck molecular modeling system least-squares superposition of appropriate atoms, the relative displacements of certain atoms or groups may be calculated. Relative to (–)-3-bromocyproheptadine, **1b**, the bromine atom moves 0.08 and 0.28 Å, the piperidine nitrogen moves 0.28 and 0.26 Å, and the *N*-methyl carbon moves 0.52 and 0.32 Å for **4b** and **4h**, respectively.

The relative conformational flexibilities of these compounds may be estimated by a comparison of the rates of racemization of their respective atropisomers. We have shown the half-lives for racemization of (+)-**4b** and (–)-**4c** to be 128 and 114 min, respectively, at 25 °C. The corresponding 3-substituted cyproheptadine compounds show negligible racemization at this temperature, but by extrapolation from work conducted at elevated temperatures,[3] the corresponding racemization half-life for 3-chlorocyproheptadine (**1e**) at 25 °C may be calculated to be 12×10^6 min or approximately 100 000 times slower than the corresponding 9-chloro compound **4c**. 10,11-Dihydro-3-chlorocyproheptadine was also shown to have a racemization half-life roughly 2 million times shorter than the corresponding unsaturated compound.[3] Analogously, those pyrrolobenzazepine derivatives having a saturated bridge in the 5,6-positions are certain to have a much faster racemization half-life than those compounds having a double bond in the 5,6-positions. These results strongly suggest that the compounds increase in flexibility in the order **4h** ≫ **4b** ≫ **1b**.[31]

These factors clearly can influence the receptor binding affinities, as was shown for the unsubstituted members of the three series. They can also influence the orientation in which the compounds bind to a given receptor. Such a change in orientation would also change the binding position of the nuclear substituent. If one assumes that the major contribution (positive or negative) of a substituent to the binding affinity for a receptor is due to a local interaction with its immediate receptor environment, then an alteration of this environment would change the contribution of the substituent. It is therefore possible, but not proven, that a change in the contribution of a substituent to receptor affinity for one series of compounds relative to another would indicate a relative difference in orientation of binding for the two series.

The contribution of the substituent to the receptor binding affinity, relative to the unsubstituted member of the series, may be represented by the expression $-\ln [K_I (X)/K_I (H)]$. These values were calculated for the four substituents (X) Br, CN, SCF_3, and Cl, and the results are tabulated in Table V. As was reported previously, the enantiomers of the 3-substituted cyproheptadines **1b–e** display significantly different receptor affinities.[5] Since the observed affinity for a racemic mixture would be dominated by the high-affinity enantiomer, we have compared the inhibition constants found for the unsaturated series **4b–e** and the saturated series **4h–k** to the inhibition constant of the higher-affinity enantiomer of the corresponding cyproheptadine series.

Table VI. Correlation Coefficients for Substituent's Affinity Contributions

Receptor	Correlation Coefficients
Dopamine	(1b-e) 0.390 (4b-e); (1b-e) -0.251 (4h-k); (4b-e) 0.689 (4h-k)
α-1 adrenoceptor	(1b-e) -0.203 (4b-e); (1b-e) 0.132 (4h-k); (4b-e) 0.928 (4h-k)
α-2 adrenoceptor	(1b-e) 1.00 (4b-e); (1b-e) -0.666 (4h-k); (4b-e) 0.642 (4h-k)
muscarinic cholinergic	(1b-e) 0.912 (4b-e); (1b-e) 0.133 (4h-k); (4b-e) 0.584 (4h-k)

In Table V, each column represents the relative contribution of a substituent to the binding affinity for a specified receptor and class of compound. For a given receptor these contributions may be compared by calculating the correlation coefficients between columns. The resulting coefficients are displayed in Table VI. The results of the correlations displayed in Table VI are not conclusive, since they are based on too few examples for statistical significance to be demonstrated. The existence of a correlation coefficient greater than 0.9, therefore, only suggests a similar binding orientation for **1b–e** and the unsaturated pyrrolobenzazepines **4b–e** at the α_2 adrenoceptor and muscarinic–cholinergic receptor binding sites, and for **4b–e,h–k** at the α_1 adrenoceptor site. There is no evidence for a common binding orientation between **1b–e** and **4h–k** at any of the four receptors.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. NMR spectra were recorded for the compounds given in Tables I and II on Varian A-60 and T-60 spectrometers employing $(CH_3)_4Si$ as an internal standard and were compatible with the assigned structures of the compounds. All compounds listed in Tables I and II were homogeneous by TLC analysis. TLC's were performed on (1) fluorescent silica gel plates with 10% methanol in chloroform and on (2) fluorescent alumina plates with chloroform. Spots were detected by UV and by exposure to I_2 vapor or Dragendorff's reagent. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Method A. General Procedure for the Addition of 1-Methyl-4-piperidylmagnesium Chloride to Ketones 2. 11-Hydroxy-11-(1-methyl-4-piperidyl)-9-bromo-11*H*-pyrrolo[2,1-*b*][3]benzazepine (3b). A suspension of 33.1 g (0.121 mol) of **2b**[13] in 330 mL of dry THF was cooled in an ice bath. While stirring, a solution of 1-methyl-4-piperidylmagnesium chloride in THF was added dropwise until the ketone was completely consumed. The mixture became homogeneous as the Grignard

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(31) A referee has pointed out that "**4a** is formally subject to resolution as a result of atropisomerism although the kinetics of racemization may make this impractical".

reagent addition proceeded. The THF was removed on a rotary evaporator. The red oily residue was dissolved in benzene, and water 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 50-mL portions of hot benzene. The combined benzene phases were washed with water, dried ($MgSO_4$), and filtered, and the benzene was removed on a rotary evaporator. The residue was triturated with acetonitrile, and the product was collected by filtration to afford 26.0 g (57%) of **3b**, mp 135–140 °C. The Grignard product intermediates prepared by this method are listed in Table I.

Method B. 1-Methyl-4-(9-bromo-11*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ylidene)piperidine (4b). Dry hydrogen chloride gas was bubbled into an ice-cooled solution of 25.7 g (0.0688 mol) of the tertiary alcohol **3b** in 2250 mL of chloroform until the solution darkened noticeably and became acidic to moist litmus paper. The solution then was allowed to stir at room temperature for 3 h. The chloroform phase was washed with a saturated sodium carbonate solution, water, and brine. After the solution was dried ($MgSO_4$) and the solvent was evaporated, the residue was triturated with acetonitrile to afford 17.64 g (72%) of crude **4b**. This product was readily purified by chromatography on a silica gel column with 7% methanol in chloroform as an eluant. Thus, from 12.2 g of crude **4b**, 10.8 g (64%) of analytically pure, TLC homogeneous **4b** was obtained, mp 150–152 °C.

The properties of **4a,e**, prepared in a similar manner, are given in Table II.

Method C. 1-Methyl-4-(9-chloro-11*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ylidene)piperidine (4c). A mixture of 17.8 g (0.05 mol) of **4b**, 25 g (0.25 mol) of cuprous chloride, and 300 mL of DMF was stirred and heated in an oil bath at 160 °C for 1.5 h. An additional 8.0 g (0.081 mol) of cuprous chloride was then added, and the mixture was stirred and heated for an additional 0.5 h. The reaction mixture was concentrated on a rotary evaporator, and 200 mL each of toluene and a saturated aqueous sodium cyanide solution were added to the residue. The mixture was stirred vigorously for 1 h. The toluene layer was then separated and washed with brine, dried ($MgSO_4$), and filtered, and the toluene was evaporated. The residue was purified by chromatography on silica gel with 5% methanol in chloroform as eluant. There was thus obtained 11.1 g (71%) of HPLC homogeneous **4c**. An analytical sample was prepared by recrystallization from acetonitrile: mp 113–114.5 °C.

Method D. 1-Methyl-4-(9-cyano-11*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ylidene)piperidine (4d). A mixture of 6.3 g (0.017 mol) of **4b** and 3.2 g (0.035 mol) of cuprous cyanide in 25 mL of dry dimethylformamide was stirred and refluxed under a nitrogen atmosphere for 5 h. The mixture was cooled to 50 °C and then treated with 60 mL each of benzene and aqueous saturated sodium cyanide solution. After the mixture was stirred for 1 h, the contents were transferred to a separatory funnel with the aid of additional benzene and water. The aqueous phase was extracted twice with benzene, and the combined benzene extracts were washed with dilute sodium cyanide, water, dilute ammonium hydroxide, and water. After the solution was dried (Na_2SO_4) and the solvent was evaporated, there was obtained 5.0 g (94%) of product that crystallized on trituration with acetonitrile. Recrystallization from acetonitrile gave pure **4d**, mp 158–161 °C.

Method E. 1-Methyl-4-(9-cyano-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ylidene)piperidine (4j). A solution of 3.32 g (0.0103 mol) of **3g** and 2.70 g of oxalic acid in 100 mL of absolute ethanol was stirred and refluxed for 6 h. The ethanol was removed on a rotary evaporator, saturated sodium carbonate solution was added to the residue, and the free base that precipitated was extracted into chloroform. The crude product was purified by chromatography on alumina with chloroform as the eluant. Evaporation of the chloroform gave 1.5 g (45%) of an oil that rapidly crystallized. An analytical sample was prepared by recrystallization from acetonitrile, mp 177–179 °C.

The properties of compounds **4g–i,k**, prepared in a similar manner, are given in Table II.

Resolution and Racemization Rate Studies of Compounds 4b,c. To a solution of 0.50 g (0.0014 mol) of (±)-**4b** in 12 mL of hot ethanol was added 0.504 g (0.0013 mol) of di-*p*-toluoyl-*l*-tartaric acid in 5 mL of ethanol. The solution was allowed to cool to room temperature, and the salt that crystallized was collected by filtration, washed with cold ethanol, collected, and dried at 65 °C to give 0.65 g of a crystalline material, $[\alpha]^{25}_{589}$ +113° (*c* 0.85, pyridine). The rotation of this material did not change after recrystallization from ethanol. A 0.50-g sample of this salt was converted to the free base with a saturated aqueous sodium bicarbonate solution. The oil that precipitated was extracted into 25 mL of chloroform, and this solution was washed with water, dried ($MgSO_4$), and filtered. Within an hour after converting to the free base, an aliquot of this chloroform solution was placed in a polarimeter cell that was thermostatically controlled at 25.0 ± 0.5 °C. Optical rotation measurements were determined with a Perkin-Elmer 141 automatic polarimeter, and readings were taken at 5-min intervals over a 2-h period and then at 10- or 15-min intervals over an additional 4-h period. The observed optical rotation vs. time data were fitted by nonlinear least squares to eq 2, where α_0 is the initial rotation and k_{app} is the apparent

$$\alpha = \alpha_0 e^{-k_{app}t} \quad (2)$$

rate constant for disappearance of the observed rotation. This apparent rate constant is twice the value of the rate constant for interconversion of the atropisomers. The half-life for (+)-**4b** was found to be 128 ± 1 min at 25.0 ± 0.5 °C.

By the same procedure as described for **4b**, but substituting di-*p*-toluoyl-*d*-tartaric acid and (±)-**4c**, (−)-**4c** was found to have a half-life of 114 ± 9 min at 25.0 ± 0.5 °C.

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Registry No. **2a**, 62541-74-6; **2b**, 62541-75-7; **2c**, 69624-22-2; **2d**, 62541-43-9; **2e**, 85664-83-1; **2f**, 69624-15-3; **2g**, 69624-17-5; **2h**, 62541-65-5; **3a**, 70684-09-2; **3b**, 70684-04-7; **3c**, 70684-01-4; **3d**, 70538-85-1; **3e**, 85664-84-2; **3f**, 70683-88-4; **3g**, 70683-90-8; **3h**, 70683-89-5; (±)-**4a**, 85664-85-3; (±)-**4a** oxalate, 85664-86-4; (±)-**4b**, 85664-87-5; (+)-**4b**, 85664-88-6; (+)-**4b** di-*p*-toluoyl-*l*-tartrate, 85664-89-7; (±)-**4c**, 85664-90-0; (−)-**4c**, 85664-91-1; (±)-**4d**, 85664-92-2; (±)-**4e**, 85664-93-3; (±)-**4f**, 85664-94-4; (±)-**4f**·HCl, 85664-95-5; (±)-**4g**, 85664-96-6; (±)-**4g** oxalate, 85664-97-7; (±)-**4h**, 85664-98-8; (±)-**4i**, 85664-99-9; (±)-**4j**, 85665-00-5; (±)-**4k**, 85665-01-6; (±)-**4l**, 85665-02-7; (±)-**4l**·HCl, 85665-03-8; 1-methyl-4-piperidyl chloride, 5570-77-4.