The microscope is an Olympus Model BHB with vertical fluorescence illumination. Emitted fluorescent light, returning through the microscope objective, is directed to the camera port at the top of the microscope. A Farrand MSA microscope spectrum analyzer with an adapted Aminco potted 1P21 photomultiplier tube is mounted on the camera port. The photomultiplier is connected to an Aminco J-22A photometer. The movement of the image of the worm across the light-sensitive spot of the photometer is controlled by a small synchronous motor attached to the microscope stage controls. As the stage moves, the fluorescence as a function of distance across the specimen is recorded from the output of the photometer directly into a Hewlitt-Packard 9825A computer for interpretation. The computer automatically records 500 fluorescence values for each scan, locates the fluorescent peak, and determines the height and area of the fluorescent region of the scan.

The fluorescence labeling of the schistosome was evaluated as described previously.[7] Schistosomes are routinely scanned twice: once across the esophageal region (region 1) and once across the region of maximal brightness posterior to the esophagus (region 2). The data obtained include the peak height or maximum recorded fluorescence intensity at any point in the scanned region and the peak area or total fluorescence over the scanned region. Both the esophageal and central region of the head were evaluated by these parameters. Only male schistosomes were scanned, due to the small size of females.

Motor Activity Studies. A specially constructed "activity cage" described in previous reports[3,4] was used to measure the motor response of *S. mansoni* to test compounds. This apparatus contains four chambers mounted in a temperature-regulated block. Two worm pairs are placed in each glass-bottomed cell located above the array of fiber optics which are connected to photocells. Movement of the worms in the cells obscures a light beam. The photocells register the light-intensity fluctuations due to these movements. The resultant electronic changes are translated into numerical "counts" which are proportional to the amount of movement. The resulting counts for each chamber accumulate for a 2-min period and the data are automatically transferred to a Hewlett-Packard 9825A computer. The data are plotted automatically by the computer to give a graph of overall movement and patterns.

A typical experiment involves the use of two cells as control chambers and two cells as test chambers. The control chambers are perfused at 37 °C with FM solutions of serotonin (5HT) and carbachol (CCh) in the absence of test compound, and the test chambers are perfused with the same drugs in the presence of the test compound. The effects of various concentrations and lengths of exposure to the compounds are reported.

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Conformationally Restricted Tricyclic Antidepressants. 1. Octahydrodibenzazepinonaphthyridines as Rigid Imipramine Analogues

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The stereoselective synthesis and structure elucidation of the racemic 2-methyl-1,2,3,4,4a,8,9,15a-octahydro-15*H*-dibenz[*b,f*]azepino[5,4a,4-*bc*]-2,7-naphthyridine ring-fusion isomers (**1a** and **1b**) are described. Photocyclization of *N*-(1-methyl-1,2,5,6-tetrahydronicotinyl)-10,11-dihydro-5*H*-dibenzazepine (**3**) in methanol vs. tetrahydrofuran stereoselectively gave, respectively, the cis (moderate yield) or the trans (poor yield) pentacyclic lactams (**4a** or **4b**). Equilibration of **4a** in base gave a 1:2 mixture of **4a** and **4b**, which was separated by column chromatography. Borane reductions of **4a** and **4b** gave **1a** and **1b** without epimerization. The racemic ring-fusion isomers were compared with imipramine in rodents as inhibitors of (−)-norepinephrine uptake in vitro and in vivo, as inhibitors of serotonin uptake in vitro, and as inhibitors of the binding of the muscarinic cholinergic antagonist [^{3}H]quinuclidinylbenzilate (QNB), the α-adrenergic antagonist [[[2-(2′,6′-[^{3}H]dimethoxyphenoxy)ethyl]amino]methyl]benzodioxane (WB 4101), and the dopaminergic antagonist [^{3}H]spiperone at their respective membrane binding sites in homogenates obtained from rat brain. Both **1a** and **1b** inhibited (−)-norepinephrine uptake in a rat brain synaptosomal preparation; **1b** was slightly more potent than **1a** but somewhat less potent than imipramine. Imipramine was more than twice as effective as **1b** as an inhibitor of the neuronal uptake of the norepinephrine synthesis inhibitor 4,α-dimethyl-*m*-tyramine (H77/77) in vivo, while **1a** appeared to potentiate rather than prevent the norepinephrine depleting action of H77/77. Both **1a** and **1b** were virtually inactive as inhibitors of synaptosomal serotonin uptake. Imipramine and **1b** were nearly equipotent as inhibitors of [^{3}H]QNB binding and significantly more active than **1b**. In the [^{3}H]spiperone binding assay, **1a** was comparable to chlorpromazine in potency. Imipramine and **1b** were much less effective. The amine uptake and receptor binding results are rationalized on the basis of conformational structure–activity relationships.

The mechanism by which the clinically effective tricyclic antidepressants (thymoleptics) alleviate symptoms in depressed patients remains to be unequivocally established. The various tricyclics exhibit a bewildering variety of pharmacological properties,[1] which may include inhibition of neuronal uptake of norepinephrine and/or serotonin, antagonism of reserpine's actions, an anticholinergic (antimuscarinic) action, antihistaminic actions, cardiotoxic effects, and antipsychotic effects. The majority of thymoleptics in current clinical use are flexible molecules consisting of a condensed three ring system and a secondary or tertiary amino group connected by a three carbon chain. There is considerable freedom of rotation

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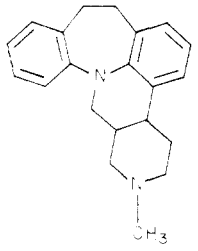
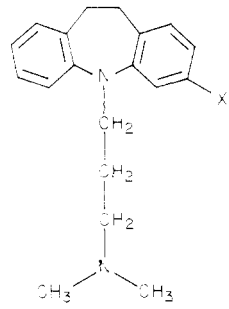
about the bonds separating the basic amino function and the tricyclic system, and thus numerous interconvertible side chain conformations differing only slightly in potential energy may exist. It is reasonable to assume that the diverse variety of pharmacological properties of the tricyclic neuroleptics may result, in part, from different receptors, wherein the basic amino group (or its protonated form) and the tricyclic ring system occupy different positions in space relative to each other.

In order to investigate the hypothesis put forth above and to seek more selective antidepressants, we have undertaken the design, synthesis, and pharmacological evaluation of a variety of analogues of the tricyclics where the three carbon side chain forms part of a rigid structure and the position of the amino function is therefore conformationally defined. The synthesis and preliminary pharmacological characterization of 2-methyl-1,2,3,4,4a,8,9,15a-octahydro-15*H*-dibenz[*b,f*]azepino-[5,4a,4-*bc*]-2,7-naphthyridine ring-fusion isomers **1a** and **1b**, as rigid analogues of imipramine (**2a**), represent our initial effort in this area.



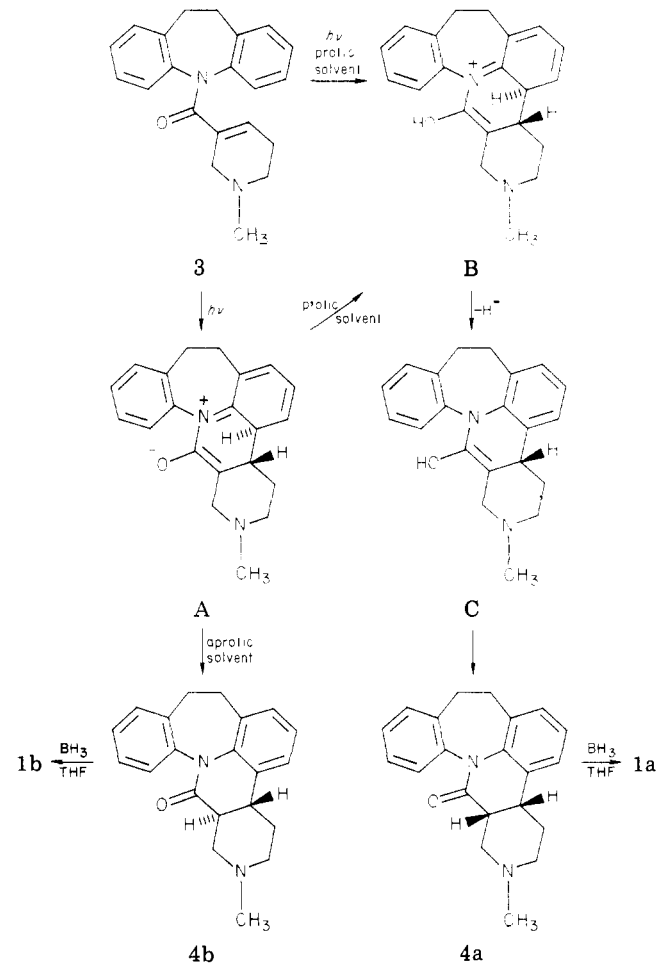
1a, cis
b, trans



2a, X = H
b, X = Cl

Hypotheses concerning the etiology of depression have largely centered around the levels of biogenic amines norepinephrine[2] and serotonin[3] in the central nervous system. The therapeutic effects of the tricyclics in depressive disorders have been thought to result primarily from their inhibition of neuronal membrane biogenic amine reuptake mechanisms, causing increased synaptic concentrations of norepinephrine[4,5] and/or serotonin[6,7] at postsynaptic receptors. The actions of the tricyclics in depressed patients have been categorized further as consisting of three components based on pharmacological tests: (1) psychomotor activation or increase in drive, which appears to correlate with the inhibition of norepinephrine uptake in adrenergic neurons;[5,6,8] (2) improvement of mood, which seems to correlate with increased serotonergic activity;[5,6] and (3) relief from anxiety or tranquilization, which may either be due to blockade or down regulation of catecholamine receptors in the brain similar to the action of the neuroleptics[9] or a central anticholinergic action.[8,10]

Scheme I



The use of inhibition of norepinephrine and/or serotonin uptake, in vitro or in vivo, as measures of potential clinical efficacy of antidepressants has been subjected to considerable criticism in recent years.[11-16] The principal complaint appears to center around the widely held belief that there is a significant delay in the onset of action of the tricyclic antidepressants clinically,[17] whereas the inhibition of amine uptake is manifested almost immediately. Recent investigations into the mechanism of antidepressant action of the tricyclics, therefore, have concentrated on their neurochemical effects, particularly adaptive changes,[18] following chronic administration. Thus far, the most compelling evidence points to a mechanism involving changes in the sensitivity of central noradrenergic receptors following prolonged treatment with the tricyclics. Thus,

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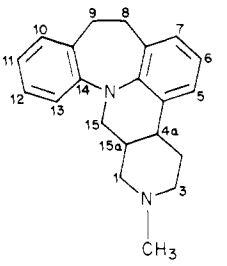
the sensitivity of the norepinephrine-activated adenylate cyclase system in the limbic forebrain[13,19] and the level of β-adrenergic receptors in the brain (measured as specific [^{3}H]dihydroalprenolol binding[15,20,21]) both decrease significantly following chronic, but not acute, treatment with the tricyclics. Electroconvulsive therapy (ECT) similarly brings decreases in norepinephrine-activated adenylate cyclase[13,19] sensitivity and in [^{3}H]dihydroalprenolol binding.[22] Furthermore, the subsensitivity of norepinephrine-activated adenylate cyclase induced by prolonged treatment with catecholamines is also accompanied by a parallel decrease in [^{3}H]dihydroalprenolol binding.[23,24] The inhibition of neuronal norepinephrine uptake therefore remains a logical first screening test for potential antidepressants, since uptake inhibitors are expected to increase postsynaptic concentrations of the neurotransmitter and thereby gradually bring about decreased receptor sensitivity.

The rigid imipramine analogues 1a and **1b** were evaluated as inhibitors of both norepinephrine and serotonin uptake in synaptosomal preparations obtained from rat brain. They were also screened as potential antagonists of muscarinic–cholinergic, α-adrenergic, and dopaminergic receptors in radioligand binding assays. Imipramine was employed as a standard of comparison in these tests.

Chemistry. The synthesis of racemic 2-methyl-1,2,3,4,4a,8,9,15a-octahydro-15*H*-dibenz[*b*,*f*]azepino-[5,4a,4-*bc*]-2,7-naphthyridine ring-fusion isomers 1a and **1b** is outlined in Scheme I. The pentacyclic lactams **4a** and **4b** were generated by stereoselective photocyclizations of the enamide *N*-(1-methyl-1,2,5,6-tetrahydronicotinyl)-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (**3**). Thus, photolysis of **3** in an aprotic solvent (ether or tetrahydrofuran) gave exclusively the trans-ring-fused lactam **4b**, but in poor yields (7–10%). On the other hand, when the protic solvent methanol was employed for the photolysis of **3**, moderate yields (40–50%) of only the cis-ring-fused lactam **4a** were obtained.

Photocyclizations of enamines of various types have been employed extensively for the synthesis of alkaloids and other polycyclic heterocycles.[25] It is generally accepted that such reactions proceed via a conrotary 6π electron electrocyclization to generate an intermediate such as A, wherein the substituents at the newly formed bond are trans to each other.[25,26] This intermediate is then believed to undergo a concerted 1,5-suprafacial shift leading to trans-ring-fused product **4b**. The exclusive formation of **4a** from the photolysis of **3** in methanol is not so easily explained. Some enamide photocyclizations are reported[27,28] to give mixtures of cis- and trans-fused products, the ratios of which are strongly solvent dependent. In these reactions, the trans product is strongly favored (15–20:1) in aprotic solvents, while the cis product seems to be favored (2–3:1) in protic solvents. Such results have been interpreted in terms of a partitioning of the intermediate in two reaction paths, one portion undergoing a deprotonation–reprotonation leading *primarily* to (in these cases) the thermodynamically more stable cis product, the other undergoing the 1,5-suprafacial shift leading *exclusively* to the trans product. Equilibrations of either **4a** or **4b** in base (ethanolic KOH) gave a mixture consisting of 30% **4a** and 70% **4b**, showing that the trans isomer is the more stable one in our case. Furthermore, **4b**, was recovered unchanged following its photolysis in methanol. Thus, the formation of **4a** from the photolysis of **3** in methanol must be kinetically and not thermodynamically controlled. We suggest that the photolysis of **3** in methanol proceeds through an enolization mechanism[28] (involving either direct protonation of **3**, followed by electrocyclization, or protonation of the intermediate A) to form the enolized intermediate B and loss of a proton to form the enol C. Tautomerization of C stereoselectively forms **4a**. Molecular models of C indicate that in its preferred conformation the trans face is sterically hindered, particularly by a nonbonding interaction from the C-13 hydrogen atom. Furthermore, the enolic hydroxyl group is oriented above the cis face. Thus, whether the ring fusion proton at C-15a is derived from the enolic hydroxyl group or from solvent, steric factors favor its addition at the cis face to form 1a.

Table I. ^{13}C Chemical Shifts (ppm from Me_4Si) in $CDCl_3$



no.	C-4a	C-15a
1a	35.72	30.78
1b	39.27	36.15
4a	38.91	40.54
4b	36.17	43.13

The lactams **4a** and **4b** were smoothly reduced to the corresponding amines 1a and **1b** with borane in tetrahydrofuran without affecting the ring-fusion geometry. Although ample precedent for assignment of ring-fusion geometry of **4** isomers seemed to be established by the numerous examples of products of similar enamide photocyclizations,[26] we sought further confirmation of our structural assignments by spectroscopic methods. Such confirmation was found in an examination of the carbon-13 nuclear magnetic resonance spectra of **1a** and **1b**. Thus, the signals for C-4a and C-15a are shifted to a much higher field in 1a as compared to **1b** (Table I).

This phenomenon has been consistently observed in saturated [6,6] ring-fused systems, e.g., in decalins,[29] decahydroquinolines,[30] decahydroisoquinolines,[31] and recently in a [5,6] hexahydropyridoindole system,[32] and has been

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Table II. Inhibition of Neurotransmitter Uptake and Displacement of Antagonist Binding

	IC_{50}, nM[a]				
	inhibn of neurotransmitter uptake		displacement of antagonist		
compd	(−)-[^{3}H]norepinephrine[b]	[^{3}H]serotonin[b]	(−)-[^{3}H]QNB[b,c]	[^{3}H]WB-4101[d,e]	[^{3}H]spiperone[b]
1a (cis)	3540 ± 870	19 600 ± 6000	2240 ± 1090	445 ± 110	112 ± 51
1b (trans)	1250 ± 510	14 200 ± 6160	449 ± 182	1760 ± 445	320 ± 13
imipramine	169 ± 54	384 ± 57	269 ± 58	160 ± 21	645 ± 130
atropine			4.84 ± 1.14		
phentolamine				5.20 ± 1.22	
chlorpromazine					111 ± 31

[a] Values are the averages of two experiments plus or minus the range. [b] Final concentration 100 pM (1×10^{-10} M). [c] (−)-3-Quinuclidinylbenzilate. [d] [[[2-(2',6'-Dimethoxyphenoxy)ethyl]amino]methyl]-1,4-benzodioxane. [e] Final concentration 200 pM.

ascribed to α-, β-, and γ-carbon (or nitrogen) shielding effects, the sum of which are greater for cis-fused as compared to trans-fused isomers. It will be noted that the effect does not apply to the lactams **4a** and **4b** where the chemical shifts of C-4a and C-15a are apparently dominated by deshielding from the C-15 carbonyl carbon.

Results and Discussion

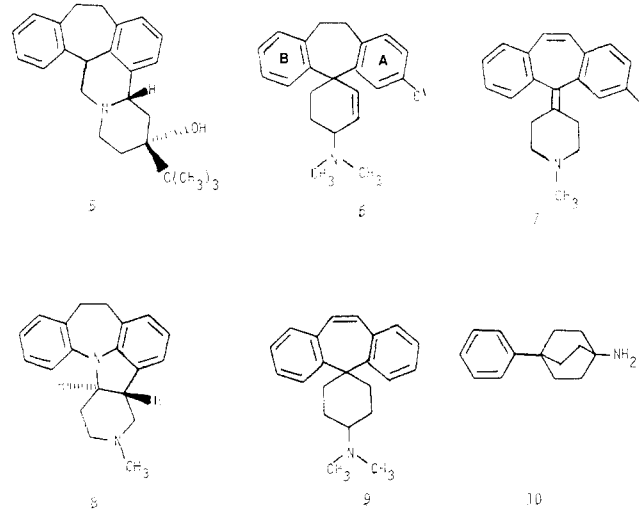
Pharmacology. The potencies of the rigid imipramine analogues 1a and **1b** were compared as racemates with imipramine as inhibitors of [^{3}H]norepinephrine and [^{3}H]serotonin uptake in synaptosomes obtained from rat brain and with imipramine and standard drugs as inhibitors of the binding of radiolabeled antagonists from membrane receptors in rat brain homogenates. The results, expressed as IC_{50} (concentration required to either inhibit 50% of the uptake or the binding of the radioligand) values, are shown in Table II. Additionally, 1a, **1b**, and imipramine were evaluated as inhibitors of 4,α-dimethyl-*m*-tyramine (H77/77) uptake in vivo.

Neurotransmitter Uptake Studies. Both 1a and **1b** were several orders of magnitude weaker than imipramine as inhibitors of serotonin uptake in vitro. They were significantly more active in blocking in vitro norepinephrine uptake but, nevertheless, somewhat less potent than imipramine. The trans isomer was about three times more effective than the cis isomer. When tested in vivo as inhibitors of 4,α-dimethyl-*m*-tyramine (H77/77) uptake[5] at equimolar doses of 20 mol/kg in mice, **1b** afforded 30%, and imipramine 55–62%, protection against the norepinephrine-depleting effects of the synthesis inhibitor in the brain. This result parallels the norepinephrine uptake inhibiting potencies of **1b** and imipramine in vitro. The cis-isomer 1a, on the other hand, synergized with the norepinephrine-depleting effects of H77/77 to bring about a *minus* 60% protection. It is possible that 1a exerts a reserpine-like effect and its inhibition of synaptosomal norepinephrine uptake may, thus, be due, in part, to inhibition of the storage granular uptake mechanism.

Receptor Binding Studies. The radioligand (±)-[^{3}H]-3-quinuclidinylbenzilate, [^{3}H]QNB, has been used to study muscarinic cholinergic receptors in central[33] and peripheral[34] tissue. The potencies of the tricyclic antidepressants as inhibitors of [^{3}H]QNB binding to receptors in rat brain and in the guinea pig ileum appears to roughly parallel their atropine-like side effects in man and other animals.[35] Furthermore, the central antimuscarinic activity of the tricyclics may contribute to their clinical antidepressant effects.[8,10,35] In this study the more active stereoisomer of QNB, (−)-[^{3}H]QNB, was employed to assess the central antimuscarinic potencies of the rigid imipramine analogues, imipramine and atropine. From the results (Table II) it can be seen that the trans-isomer **1b** is nearly equal to imipramine in potency, while 1a has about one-eighth the central antimuscarinic activity of **1b**.

Binding to central α-adrenergic receptors was determined using [[[2-(2',6'-[^{3}H]dimethoxyphenoxy)ethyl]-amino]methyl]benzodioxane (WB-4101)[36] as a radioligand. The potencies of tricyclic antidepressants as displacers of [^{3}H]WB-4101 binding have been correlated with their abilities to relieve psychomotor agitation in depressed patients and to cause sedation or hypotension.[37] In our study, the cis-isomer 1a was nearly four times as active as **1b** in displacing [^{3}H]WB-4101 and one-third as potent as imipramine (Table II).

Numerous examples of compounds bearing a formal structural relationship to the tricyclic antidepressants have been discovered to possess predominantly neuroleptic activity instead of, or in addition to, antidepressant activity. (+)-Butaclamol (**5**) and related compounds[38] represent the best known of such structural types, but many others are known, most notable among which are the rigid



5 6 7 8 9 10

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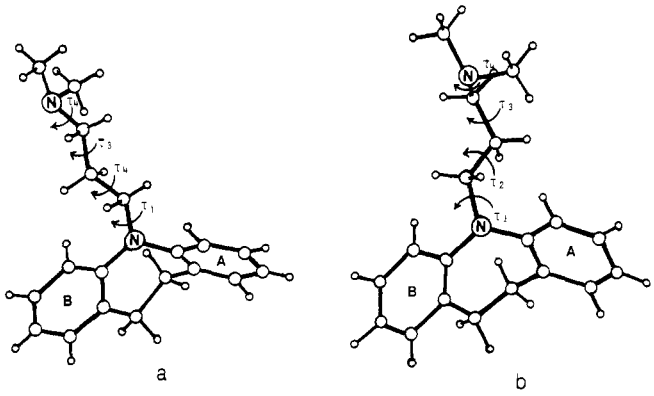

Figure 1. Imipramine hydrochloride solid-state conformations (reconstructed from Post et al.[45] with permission of the authors).

amitriptyline analogues represented by structures **6**[39,40] and **7**[41] and rigid imipramine analogues of type **8**.[42] The butyrophenone dopamine antagonist, spiperone (spiroperidol), has emerged as the current ligand of choice for studying the binding of neuroleptics (dopamine antagonists) to the dopamine receptor[43,44] and was, therefore, selected to evaluate the rigid imipramine analogues **1a** and **1b**. The results (Table II) indicate that the racemic cis-isomer 1a is equal to chlorpromazine in potency and is three times more active than the trans-isomer **1b** and six times more active than imipramine.

Structure–Activity Relationships. Recent speculations as to conformations of tricyclic antidepressants active at receptor sites for norepinephrine and serotonin uptake have centered around either the investigation of solid-state conformations of known, primarily flexible antidepressant compounds determined by X-ray crystallography[45–49] or the use of molecular models in the topological study of rigid and semirigid analogues.[50] Imipramine hydrochloride (**2a**), a potent inhibitor of both norepinephrine and serotonin uptake in vitro[51–53] and in vivo,[5,6] exists in two solid-state conformations, a and b (Figure 1).[45] In conformation a, the (dimethylamino)propyl side chain is nearly fully extended, with all torsion angles near ±180°, while in b the side chain folds back at τ_3. On the other hand, the 3-chloro analogue of imipramine, clomipramine (**2b**), exists in a single solid-state conformation[47] which closely resembles the imipramine b conformation. Although not highly selective, clomipramine is a much more potent inhibitor of serotonin uptake than is imipramine (five to eight times)[52,53] and a much weaker inhibitor of norepinephrine uptake (one-third times imipramine).[51,53] The rigid spiro compound **9**, a more selective inhibitor of norepinephrine uptake,[40] is conformationally unlike either a or b imipramine conformations.[45,50]

Table III.

compd	intramolecular distances, Å A-N[a]	B-N[a]
imipramine hydrochloride		
conformation a	6.24[b]	7.22[b]
conformation b	6.06[b]	6.54[b]
1a (cis)	5.5[c]	6.7[c]
1b (trans)	5.7[c]	7.2[c]
A 1866 (**9**)	5.53[b]	7.23[b]
EXP 561 (**10**)		7.0[c]
(+)-butaclamol hydrochloride		5.10[b]
(+)-isobutaclamol hydrobromide		6.45[b]

[a] A-N and B-N are the distances between the centers of the two benzene rings of the tricyclic nucleus and the nitrogen atom of the side chain. [b] Values determined by X-ray crystallography (see text for references). [c] Values estimated using Dreiding models.

On the other hand, Dreiding molecular models of the preferred conformations of the rigid imipramine analogues **1a** and **1b** reveal remarkable similarities of these molecules to the imipramine solid-state conformations. Thus, the trans-isomer **1b** resembles the extended imipramine conformation a, while the 4a-*pseudoaxial*, 15a-*equatorial* conformation of the cis-isomer 1a is similar to the folded imipramine conformation b. The major differences lie in the torsion angle τ_1 and the distance between the nitrogen atom and the center of the nearer aromatic ring A (see Table III for comparisons). Despite the close similarities in A–N and B–N distances between the trans-isomer **1b** and **9**, the two molecules are very different conformationally; **1b** is a relatively planar molecule, while **9** is a very nonplanar space-filling structure. The side-chain nitrogen atom of **9** lies well above the plane made by the nearer A ring,[46,50] while in **1b** it is much closer to this plane. However, the distance from the nitrogen to the plane made by the B ring is similar for **1b** and **9**. The B–N distances of imipramine conformation a, **1b**, and **9** all closely approximate the corresponding distance measured at 7.0 Å for the potent, but nonspecific, amine uptake inhibitor[49,54] EXP 561 (**10**). Assuming a single norepinephrine carrier receptor with highly specific binding requirements, it would thus appear that the more distant benzene ring B and the side-chain amino function may be the crucial determinants in the binding of these molecules to the receptor. To explain the potent norepinephrine-inhibiting potencies of the rigid desipramine analogue 11 and the corresponding tetralin derivative **12**,[48,49] it again seems probable that the distance between the methylamino and the B aryl ring functions is the crucial structural determinant. The low order of activity of 1a, **1b**, and **9** at the serotonin uptake site, on the other hand, suggests that the active conformation at the receptor may differ from both imipramine conformations a and b. Furthermore, the receptor site controlling serotonin uptake appears to im-

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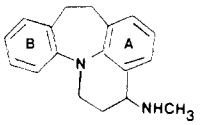

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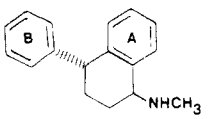

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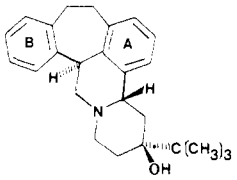

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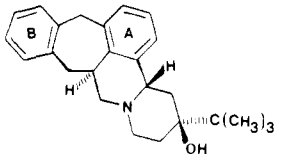

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pose greater steric demands for the binding of tricyclic-type inhibitors than does the norepinephrine uptake receptor.[49] The lack of activity of the rigid tricyclic analogues thus far examined coupled with the observed potency of **10** indicate that, while one aromatic ring is essential for the binding of serotonin uptake inhibitors to the receptor, steric demands at the receptor surface apparently place severe limitations on the number of orientations permitted for the binding of the second aromatic ring.

Because **1b** and imipramine displace [^{3}H]QNB with approximately equal potency, it appears that the extended imipramine conformation b may be responsible for its central antimuscarinic effects. On the other hand, a partially folded conformation like a seems to be involved in the binding of imipramine to α-adrenergic receptors, since 1a and imipramine displace [^{3}H]WB-4101 with much greater effectiveness than **1b**.

The discovery of apparent dopamine receptor antagonism by 1a is perhaps the most interesting result of this study. Thus, racemic 1a was found to equal chlorpromazine as an inhibitor of [^{3}H]spiperone binding in rat corpus striatum. The racemic trans isomer was about one-third as active as chlorpromazine and nearly twice as active as imipramine. Furthermore, mice treated with either **1a** or **1b** (as part of the experiment to measure protection of the compounds against the effects of the norepinephrine synthesis inhibitor H77/77) were observed to be visibly sedated. The sedative effect, which followed the order of potency 1a > **1b** > imipramine, is probably attributable to antagonism at either dopaminergic or α-adrenergic receptors or both.

It has been suggested[55-57] that the blockade of central dopaminergic receptors of neuroleptics of the tricyclic class results from a conformational complementarity between certain portions of these drugs and dopamine at receptors. X-ray crystallographic studies on several flexible[57] and a few semirigid[57-59] tricyclic neuroleptics indicate that the aminopropyl side chain is oriented asymmetrically with respect to the tricyclic nucleus in the solid state. Furthermore, in the more potent asymmetrically aryl-substituted analogues, the side-chain nitrogen is nearer the ring bearing the neuroleptic activity enhancing substituent in virtually every case, suggesting that the substituted aromatic ring and the side-chain nitrogen are complementary with the catechol system and the amino group of dopamine.[57,60] Crystallographic investigation of the semirigid dibenzodiazepines,[58] dibenzoxazepines,[58] and dibenzothiepins[59] and model studies of the spiro neuroleptic 6[61] indicate that the optimal aryl ring to side-chain nitrogen distance, A–N, is in the range of 5.7 to 6.1 Å. On the other hand, for dopamine[62] and the dopamine agonist apomorphine,[63] in the solid state, the distance from the center of the catechol ring to the nitrogen atom is around 5.1 Å. The corresponding distance (B–N_1) in the crystal structure of the potent dopaminergic antagonist (+)-butaclamol hydrochloride (**13**) is also around 5.1 Å,[64] supporting the theory that this compound binds to dopaminergic receptors in a *trans*-dopamine overlapping conformation. Interestingly, (+)-isobutaclamol hydrobromide (**14**), also a potent dopaminergic receptor antagonist, has a B–N_1 solid-state distance of 6.45 Å.[65] This value is near the B–N_1 distance of 6.7 Å estimated from Dreiding Models for 1a and also the B–N_1 distance of 6.54 Å in the b solid-state conformation of imipramine hydrochloride.[45] Perhaps the dopamine receptor binding properties of 1a and imipramine can both be attributed to a folded aminopropyl side-chain conformation similar to that of (+)-butaclamol, where the B aryl ring and the basic nitrogen are of primary importance in the binding. It will be noted, however, that the A–N_1 distances for the b imipramine conformation and **1b** of 6.06 and 5.7 Å, respectively, fall in the range of A–N_1 distances found in the solid state for several conformationally restricted neuroleptics.[57-59] The moderate neuroleptic potency of **1b**, and possibly also of imipramine, could be related to this correspondence.

Conclusion

The racemic trans-isomer **1b** is a moderately potent, potentially selective inhibitor or norepinephrine uptake in vitro and in vivo, lacking activity against serotonin uptake. (Additional studies on [^{3}H]dopamine uptake will be required to determine if its effect on catecholamine uptake is specific for norepinephrine.) It also exhibits some central anticholinergic and antidopaminergic activity in vitro but little α-adrenergic blocking activity. Thus, **1b** may find utility as an antidepressant, particularly in depressive states associated with anxiety or psychoses. The racemic cis-isomer 1a is a potential neuroleptic with significant antidopaminergic activity in vitro. It also appears to be moderately active in noradrenergic neurons (although this effect is, as yet, poorly characterized) and has some α-adrenergic receptor-blocking activity in vitro.

Experimental Section

Melting points were determined on a Fisher-Johns melting block or on a Mel Temp capillary apparatus and are uncorrected. Photolysis reactions were carried out under nitrogen in a glass

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photolysis apparatus using a Hanovia medium-pressure mercury lamp. Infrared spectra were obtained on a Beckman IR-33 spectrophotometer in KBr disks. Proton NMR spectra were recorded on a Varian EM360 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Broad-band proton-decoupled ^{13}C NMR spectra were obtained using a Bruker WH90FT spectrometer in deuteriochloroform solutions with tetramethylsilane as an internal standard. When it was required for structural assignment of chemical shifts, proton-coupled spectra were also obtained. Microanalysis were performed by Galbraith Laboratories, Knoxville, Tenn. Analytical results reported by symbols of the elements were within ±0.4% of the theoretical values.

***N*-Methyl-1,2,5,6-tetrahydronicotinic Acid (Arecaidine) Hydrochloride.** Arecoline hydrochloride (Columbia), 9 g, was refluxed 10 h in ethanolic hydrochloric acid solution (115 mL of 95% EtOH and 135 mL of concentrated HCl). The solvent was removed in vacuo (aspirator), leaving a white solid residue. The residue was dissolved in hot 95% ethanol and induced to crystallize by the addition of benzene, giving 7.4 g (67.6%) of arecaidine hydrochloride as colorless needles, mp 260–262 °C, lit.[66] mp 261–262 °C.

***N*-Methyl-1,2,5,6-tetrahydronicotinyl Chloride (Arecaidyl Chloride) Hydrochloride.** A mixture of 6.0 g (338 mmol) of arecaidine hydrochloride and 6 mL (68.7 mmol) of oxalyl chloride were refluxed with stirring in 80 mL of dry benzene for 6 h. The reaction mixture was cooled to 25 °C, and the arecaidyl chloride hydrochloride was collected on a filter, washed with dry petroleum ether, and dried under vacuum to be used in the preparation of *N*-(1-methyl-1,2,5,6-tetrahydronicotinyl)-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (**3**).

***N*-(1-Methyl-1,2,5,6-tetrahydronicotinyl)-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (3).** The crude arecaidyl chloride prepared from 6 g of arecaidine hydrochloride (above) was refluxed with 11.7 g (60 mmol) of iminodibenzyl (10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine) and 12 g of anhydrous K_2CO_3 in 150 mL of dry toluene for 15 h. The mixture was cooled to 25 °C and then extracted with 100 mL of distilled H_2O, followed by three 50-mL portions of cold 5% HCl solution. The acid extracts were combined, adjusted to pH 12 with ice-cold 10% NaOH solution, and extracted with two 75-mL portions of chloroform. The $CHCl_3$ extracts were combined, washed with 50 mL of distilled H_2O, and dried over anhydrous K_2CO_3. The solvent was removed in vacuo (aspirator) to give 5.55 g (51% based on arecaidine hydrochloride) of **3**, mp 101–102 °C (from Et_2O).

The hydrochloride salt was prepared by dissolving 1 g of **3** in dry Et_2O, followed by the addition of ethereal HCl. The white precipitate which formed was recrystallized from acetone to give colorless needles, mp 156 °C. Anal. ($C_{21}H_{22}N_2O$·HCl) C, H, N, Cl.

***cis*-2-Methyl-1,2,3,4,4a,8,9,15a-octahydro-15*H*-dibenz[*b*,*f*]azepino[5,4a,4-*bc*]-2,7-naphthyridin-15-one (4a).** A solution of 1.5 g (4.7 mmol) of **3** in 350 mL of spectroquality MeOH was irradiated under N_2 for 72 h using a Corex filter. The solvent was removed in vacuo (aspirator), the residue was dissolved in 50 mL of $CHCl_3$, and the $CHCl_3$ solution was extracted with three 50-mL portions of 10% HCl solution. The aqueous HCl extracts were combined, basified to pH 12 with 10% NaOH solution, and extracted with 100 mL of $CHCl_3$. The $CHCl_3$ solution was washed with 50 mL of distilled H_2O and dried over anhydrous K_2CO_3, and the solvent was evaporated in vacuo (aspirator) to give a yellow oil. Trituration of the oil in acetone gave a yellow solid, which was recrystallized from ethyl acetate to yield 570 mg (38%) of **4a**: mp 240 °C; IR (KBr) 1675 cm^{-1} (amide C=O); ^1H NMR ($CDCl_3$) δ 7.16 (s, 4 H, Ar H's), 6.9 (m, 3 H, Ar H's), 3.7–1.6 (7 m, 12 H, alicyclic H's), 2.30 (s, 3 H, NCH_3). Anal. ($C_{21}H_{22}N_2O$) C, H, N.

In a similar photolysis, but carried out in acidic MeOH wherein the pH was adjusted to 2 by the addition of 10% methanolic HCl, 500 mg of **3** gave after 10 h 250 mg (50%) of **4a**.

***trans*-2-Methyl-1,2,3,4,4a,8,9,15a-octahydro-15*H*-dibenz[*b*,*f*]azepino[5,4a,4-*bc*]-2,7-naphthyridin-15-one (4b).** A solution of 1 g (3.14 mmol) of **3** in 350 mL of dry THF (distilled from $LiAlH_4$) was photolyzed under N_2 using a Vycor filter for 90 min. The THF was removed in vacuo (aspirator), and the residue was chromatographed on acidic alumina (grade III) and eluted with $CHCl_3$ to give 80 mg (8%) of **4b** as pale yellow needles (from acetone): mp 180 °C; IR (KBr) 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25–6.75 (m, 7 H, Ar H's), 3.5–1.5 (7 m, 12 H, alicyclic H's), 2.32 (s, 3 H, NCH_3).

The hydrochloride salt, prepared in the usual manner, was obtained as fine pale yellow needles of the hemihydrate from acetone, mp 309 °C. Anal. ($C_{21}H_{20}N_2O$·HCl) C, H, N, Cl.

Equilibrations of 4a and 4b. A mixture consisting of 670 mg (2.1 mmol) of **4a**, 1 g (17.8 mmol) of KOH and 40 mL of MeOH was refluxed for 12 h. The reaction mixture was cooled to 25 °C, most of the MeOH was removed in vacuo (aspirator), and the residue was partitioned between 50 mL of distilled H_2O and 75 mL of $CHCl_3$. The $CHCl_3$ layer was separated, washed with 50 mL of distilled H_2O, and dried over anhydrous K_2CO_3. The solvent was removed in vacuo (aspirator), and the viscous oily residue was chromatographed on acidic alumina (grade III) and eluted with $CHCl_3$ at a flow rate of 1 mL/min to give first 473 mg (74.7%) of **4b** followed by 160 mg (25.3%) of **1a** for a total recovery of 94.5%. The separation was followed using silica gel G TLC plates with acetone as an eluting solvent. The eluting order on TLC was found to be opposite that for the column; thus, the R_f values were 0.34 for **4b** and 0.55 for **4a**.

***cis*-2-Methyl-1,2,3,4,4a,8,9,15a-octahydro-15*H*-dibenz[*b*,*f*]azepino[5,4a,4-*bc*]-2,7-naphthyridine (1a).** A mixture of 350 mg (1.57 mmol) of **4a**, 145 mg (3.82 mmol) of $NaBH_4$, and 35 mL of dry THF was stirred in a 250-mL three-necked flask equipped with a condensor, a pressure-equalizing addition funnel, and a N_2 inlet. Freshly distilled BF_3·Et_2O (0.75 mL, 6.09 mmol) in 10 mL of dry THF was added dropwise over 30 min. The reaction was heated at reflux for 18 h. After the flask had cooled to 25 °C, excess BH_3 was decomposed by the dropwise addition of MeOH. The mixture was then concentrated in vacuo (aspirator), 50 mL of fresh MeOH and 5 mL of concentrated HCl were added, and the mixture was refluxed for an additional 12 h. The reaction mixture was cooled to 25 °C and concentrated in vacuo (aspirator), and the residue was taken up in 50 mL of distilled H_2O and adjusted to pH 12 with the addition of ice-cold 10% NaOH solution. The aqueous alkaline mixture was extracted with three 50-mL portions of $CHCl_3$, and the $CHCl_3$ solutions were combined and dried over anhydrous K_2CO_3. Evaporation of the solvent in vacuo (aspirator) left a yellow oil, which was chromatographed on acidic alumina (grade III) using $CHCl_3$ as the eluting solvent to give 275 mg (82%) of a pale yellow (light sensitive!) oil: IR (film) no absorption at 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25–6.5 (m, 7 H, Ar H's), 4.3–1.8 (7 m, 14 H, alicyclic H's), 2.27 (s, 3 H, NCH_3).

The sulfate salt was immediately prepared [by adding a 10% solution of H_2SO_4 in MeOH dropwise to a solution of the free base in MeOH and concentrating the solvent in vacuo (aspirator)] as tiny pale yellow needles from acetone, mp 252 °C. Anal. ($C_{21}H_{22}N_2O$·H_2SO_4) C, H, N.

***trans*-2-Methyl-1,2,3,4,4a,8,9,15a-octahydro-15*H*-dibenz[*b*,*f*]azepino[5,4a,4-*bc*]-2,7-naphthyridine (1b).** Reduction of 140 mg (0.44 mmol) of **4b** with BH_3 in dry THF generated in situ from 60 mg (1.58 mmol) of $NaBH_4$ and 0.3 mL (2.4 mmol) of BF_3·Et_2O and then refluxed for 30 h gave, after the usual workup, a yellow oil. Trituration of the oil in MeOH gave 94 mg (70%) of a white solid: mp 135 °C (from acetone); IR (KBr) no absorption at 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.2–6.5 (m, 7 H, Ar H's), 4.0–3.2 (3 m, 5 H, alicyclic NCH_2, benzylic methine CH), 3.11 (s, 4 H, $ArCH_2CH_2Ar$), 2.33 (s, 3 H, NCH_3), 2.4–1.3 (3 m, 5 H, 15a-CH, alicyclic CH_2 and NCH_2).

The sulfate salt was prepared in the usual manner as colorless needles from CH_3CN·MeOH, mp 226–227 °C. Anal. ($C_{21}H_{22}N_2O$·H_2SO_4) C, H, N.

Neurotransmitter Uptake Studies. A modification of the procedure of Snyder and Coyle[67] was employed to study the effects of **1a**, **1b**, and imipramine hydrochloride on the uptake of

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[^{3}H]norepinephrine and [^{3}H]serotonin in synaptosomal preparations obtained from rat brain. Male Sprague–Dawley rats (200–250 g) were killed by cervical dislocation and immediately decapitated. Their brains were rapidly removed and immediately dissected on an ice-cold glass plate to remove the cerebella and corpus striatum (the latter was used in the preparation of membrane homogenates for [^{3}H]spiperone binding studies). The brains thus dissected were weighed and homogenized in 9 volumes of ice-cold 0.32 M sucrose with 10 strokes of a motor-driven Teflon pestle in a glass homogenizing tube. The homogenate was then transferred to plastic Sorvall centrifuge tubes and centrifuged at 1000g for 10 min at 0 °C to remove heavy nuclei. The supernatant (designated S_1) was decanted, thoroughly mixed to form a uniform suspension, and centrifuged at 11500g for 20 min to produce a p_2 pellet. The p_2 pellet was carefully resuspended in 9 volumes of ice-cold 0.32 M sucrose using a Pasteur pipet.

The incubation mixture consisted of 0.1 μM of [^{3}H]norepinephrine (or 0.1 μM serotonin) containing 1 mM ascorbic acid, 100 μL of the crude synaptosome preparation corresponding to 10 mg of original brain tissue, and the test compound made up to 1 mL with Krebs Ringer phosphate buffer (pH 7.4) containing 12.5 μM nialamide, 134 μM EDTA, and 5.56 mM glucose. Incubations were carried out in 1.5-mL plastic microfuge tubes at 0 and 37 °C. Drugs were preincubated with tissue for 5 min prior to the addition of labeled amine, which initiated the uptake process, and then incubated an additional 4 min. The uptake reaction was terminated by centrifuging the tubes for 30 s at 11000g, rapidly aspirating the supernatant, and carefully rinsing and aspirating the pellet twice with 1-mL portions of ice-cold 0.9% saline solution. The pellets were transferred to liquid scintillation vials and digested in 500 mL of NCS solubilizer (Amersham) overnight. Five milliliters of liquid scintillation cocktail (3 L of toluene, 16 g of omnifluor, and 7.7 mL of glacial acetic acid) was added to each tube, and the samples were counted on a Searle Mark III scintillation spectrometer at an efficiency of 45%.

Nonspecific uptake was defined as that portion of the uptake of labeled amine that was not inhibited by 300 μM cocaine at 37 °C. (The use of 100 μM concentrations of unlabeled amine at 37 °C to define nonspecific uptake gave similar results; however, the use of 0 °C incubations gave artificially low values for nonspecific uptake.) The concentration of drug producing a 50% inhibition of specific uptake (IC_{50}) values were calculated mathematically from Hill plots composed of at least five points.

Effect of Drugs on Mice Treated with 4,α-Dimethyl-*m*-tyramine (H77/77). A modification of the procedure of Waldmeier et al.[68] was employed. Two groups of four male Swiss Webster mice (30–40 g) received intraperotoneal (ip) injections of 20 μmol/kg of the test drug. Mice from one of the drug-treated groups and a third group of previously untreated mice were administered 6.25 mg/kg of H77/77 ip. All animals were sacrificed 4 h later by crushing the chest with a large scissor, their brains were removed, dissected on an ice-cold plate to remove the cerebella, divided into right and left hemispheres, placed in foil, and immediately frozen in liquid N_2.

The samples were analyzed for norepinephrine content fluorimetrically according to the procedure of Westerink and Korf.[69] Thus, the frozen samples were weighed, homogenized in 4 mL of 0.4 N perchloric acid, and transferred to plastic centrifuge tubes. The excess perchloric acid was precipitated by the addition of 0.4 mL of KOH/formate solution (final pH 2–3). After centrifugation (20 min, 4000g, 4 °C), the supernatants were transferred to glass tubes and two drops of 5% perchloric acid were added. The tissue extracts were passed through Sephadex G-10 columns prepared from long Pasteur pipets which had previously been washed with 3 mL of 0.01 N ammonia, followed by 3 mL of 0.01 N formic acid. After the tissue extracts had passed through the columns, 2 mL of 0.01 N formic acid was added; the norepinephrine first eluted with 1.5 mL of 0.01 N formic acid and then with 1 mL of phosphate buffer and collected in glass tubes. The samples were diluted 2.5 times with phosphate buffer, the norepinephrine was converted to a fluorophor by the trihydroxyindole method,[70] and 1-mL aliquots were subjected to fluorimetric analysis using an Auto Analyzer (Technicon). Values for the percentage of protection against the norepinephrine-depleting effects of H77/77 afforded by the test compound were calculated according to the formula:

$$\% \text{ protection} = \frac{NE_{drug + H77/77} - NE_{H77/77}}{NE_{drug} - NE_{H77/77}} \times 100$$

Receptor Binding Assays. Muscarinic Cholinergic Receptor Binding. Muscarinic cholinergic receptor binding in rat brain was characterized using (−)-[^{3}H]-3-quinuclidinylbenzilate (QNB) essentially according to the procedure of Yamamura and Snyder[33] who used racemic [^{3}H]QNB. Male Sprague–Dawley rats (150–250 g) were decapitated, and their brains were rapidly removed and dissected on a cold plate to remove the cerebella. The brain tissue was weighed and then homogenized in 29 volumes of ice-cold 0.05 M sodium potassium phosphate buffer (81 mM Na^+, 9 mM K^+, pH 7.4). After centrifugation at 48000g for 20 min at 0 °C (Sorvall RC2-B), the supernatant was discarded, the pellet was resuspended in buffer, and the process was twice repeated. The twice-washed pellet was resuspended in 29 volumes of ice-cold buffer. Aliquots of brain tissue (final concentration 0.825 mg/mL), (−)-[^{3}H]QNB (100 pM), and drugs were incubated in 0.05 M sodium potassium phosphate buffer (pH 7.4, final volume 2 mL) for 30 min at 37 °C. The binding reaction was terminated by filtration in vacuo over Whatman GF/B filters and rinsing with 2 × 5 mL of ice-cold buffer. The samples were counted and the results calculated as described below.

α-Adrenergic Receptor Binding. Central α_1-adrenergic receptor binding was characterized using [^{3}H]WB-4101.[36] Whole rat brains minus the cerebella were obtained as described above, weighed, and homogenized in 0.05 M ice-cold sodium potassium phosphate buffer (pH 7.4). After centrifugation (48000g, 20 min, 0 °C), the supernatant was discarded, the pellet was resuspended in buffer, and the process was twice repeated. The twice-washed pellet was resuspended in 9 volumes of ice-cold Tris-HCl buffer (pH 7.7). Aliquots of the homogenate (final concentration 10 mg/mL), [^{3}H]WB-4101 (200 pM), and drugs were incubated for 20 min at 25 °C in Tris-HCl buffer (pH 7.4 at 25 °C) in a final volume of 2 mL. The binding reaction was terminated by filtration in vacuo over Whatman GF/B filters and rinsing with 2 × 5 mL of ice-cold buffer. The samples were counted and the results calculated as described below.

Dopaminergic Receptor Binding. [^{3}H]Spiperone was utilized to characterize the binding of the test compounds to dopamine receptors in the rat striatum according to established procedures.[43,44] Male Sprague–Dawley rats (150–250 g) were decapitated and their brains were immediately removed and dissected on a cold plate to obtain the corpus striatum. The striatal tissue was weighed and homogenized in ice-cold 0.05 M sodium potassium phosphate buffer (pH 7.4). In some instances, the corpus striatum was frozen after weighing. No differences in [^{3}H]spiperone binding was observed between fresh and frozen striata. After centrifugation at 48000g for 20 min at 0 °C, the supernatant was discarded, the pellet was resuspended in buffer, and the process was repeated. The final pellet was resuspended in 20 volumes of ice-cold 0.05 M Tris-HCl buffer. Aliquots of brain tissue (final concentration 1.25 mg/mL), [^{3}H]spiperone (100 pM), and drugs were incubated in Tris-HCl buffer (pH 7.4) for 30 min at 37 °C in a final assay volume of 2 mL. The binding reaction was terminated by filtration in vacuo over Whatman GF/B filters and rinsing with 3 × 5 mL of ice-cold buffer.

Counting of Samples and Calculation of Results. The filters onto which the radioligand-bound membrane fragments were retained were collected in polyethylene liquid scintillation vials and extracted for 8 h with 8 mL of scintillation cocktail (prepared by dissolving 16 g of Omnifluor in 2 L of toluene and 1 L of Triton X-100). The samples were counted on a Searle Mark III liquid scintillation spectrometer at an efficiency of 45%. Specific binding for each of the tritiated ligands was calculated as the difference between total binding and nonspecific binding. To determine nonspecific binding, the following concentrations

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of unlabeled ligands were employed: 1 μM atropine for muscarinic cholinergic receptors, 1 μM phentolamine for α-adrenergic receptors, and 1 μM (+)-butaclamol for dopaminergic receptors. Logarithmic Hill plots were used to determine pIC_{50} (negative logarithm of the concentration required to inhibit specific binding by 50%) values, which were converted to IC_{50} values. At least 5 points on the decline of the curve were employed for each plot.

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6-(Substituted-amino)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines and 4-(Substituted-amino)-6*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines with Potential Antianxiety Activity

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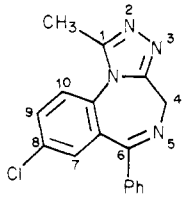
A series of 6-(substituted-amino)-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines was prepared for pharmacological evaluation, and, because of an interesting chemical isomerization, a similar series of 4-(substituted-amino)-6*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines was also obtained. Pharmacological evaluation of these compounds demonstrated that 8-chloro-1-methyl-6-piperidino-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (**10**) had interesting activity in tests useful for detecting antianxiety activity, while the corresponding 4-piperidino derivative (**15**) had little activity in these tests. A brief discussion of a possible mechanism for the isomerization is also included.

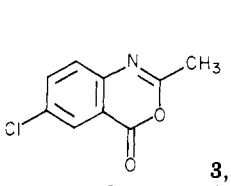
The 1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepines [viz., alprazolam (**1**)] have been shown to have



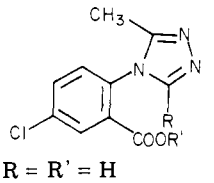
1

interesting antianxiety activity both in experimental animals[1] and in man.[2] Our discovery[3,4] that analogues of **1** with a variety of substituents at C-1 had an activity profile in the CNS screen that was different than that found for the anxiolytics prompted us to study the effect of substitution at other sites of the 4*H*-*s*-triazolo[4,3-*a*][1,4]-benzodiazepine ring system. This report details our preparation of a series of compounds with nitrogen substituents in place of the C-6 phenyl. Because of some interesting and unexpected chemistry associated with this system, a series of analogues with amino substituents at C-4 was also obtained.

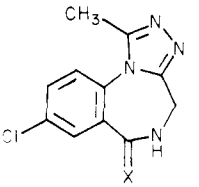
Entry into this series was provided by the reaction of 7-chloro-3-methyl-1*H*-2,4-benzoxazin-1-one[5] (**2**) with formic acid hydrazide to give the triazolobenzoic acid **3** using reaction conditions previously reported by Reid and Peters[6] for the unsubstituted system. The methyl ester (**4**), obtained from **3** with diazomethane, was hydroxymethylated in 74% yield with paraformaldehyde in xylene.[7] Thionyl chloride conversion of the resulting alcohol



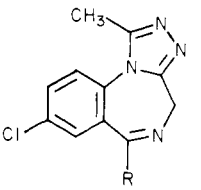
2



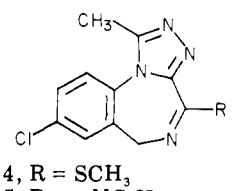
3, R = R' = H
4, R = H; R' = CH_3
5, R = CH_2OH; R' = CH_3
6, R = CH_2Cl; R' = CH_3



7, X = O
8, X = S



9, R = SCH_3
10, R = c-NC_5H_{10}
11, R = c-$N(CH_2CH_2)_2O$
12, R = c-NC_6H_{12}
13, R = $NH(CH_2)_5CH_3$



14, R = SCH_3
15, R = c-NC_5H_{10}
16, R = c-$N(CH_2CH_2)_2O$
17, R = c-NC_6H_{12}

(**5**) to the chloride (**6**) was followed by ammonolysis in the presence of potassium iodide to give the lactam (**7**). The electrophilic thiolactam (**8**) was then prepared by the reaction of **7** with phosphorus pentasulfide in refluxing pyridine. Amines reacted with **8** only with difficulty. Thus, the reaction of **8** with piperidine required 18 h at reflux with the amine as solvent. With the less nucleophilic morpholine, 20 h of reflux was required to give a 38% yield of the product (**11**). (Results for other amines in this reaction are recorded in Table I.) The reaction of **8** with hexamethylenimine was particularly difficult and, suprisingly, **13** was obtained in addition to the expected product **12**. The structure of **13**, which must have resulted from a reductive cleavage of the hexamethylenimine ring, was confirmed by an independent condensation of **8** with *n*-hexylamine to give **13** in 80% yield. In an attempt to increase the reactivity of the thiolactam system and perhaps also avoid the hexamethylenimine ring cleavage reaction, **8** was alkylated with methyl iodide and sodium

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