Adrenergic Agents. 5.[1] Conformational Analysis of 1-Alkylamino-3-aryloxy-2-propanols by Proton Magnetic Resonance Studies. Implications Relating to the Steric Requirements of Adrenoreceptors

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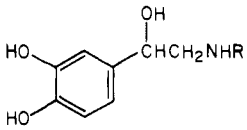
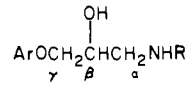
Two distinct chemical classes, namely, phenylethanolamines resembling the natural biogenic catecholamines and 1-alkylamino-3-aryloxy-2-propanols (aryloxypropanolamines), exert a distinct action as agonists and/or antagonists of adrenergic receptors. To explore the possibility that these two different kinds of chemicals might share a common ground-state conformation as an essential structural feature that satisfies the specific steric requirements for the active site of the receptor, a conformational analysis of some aryloxypropanolamines and related compounds was performed. On the basis of this NMR conformational analysis it is suggested that salts of 1-alkylamino-3-aryloxy-2-propanols in a nonpolar solvent may exist in a stable "rigid" conformation involving two intramolecular hydrogen bonds to form a 6–5 bicyclic chelated structure. Comparison of stereomodels of this "rigid" bicyclic conformer with the conformationally preferred trans (phenyl to amino) rotamer of adrenergic phenylethanolamines, such as isoproterenol, indicates that all positions of the phenyl ring, the phenyl to oxygen or phenyl to carbon bonds, and the ammonium groups of both chemical classes may be superimposed nearly exactly. A major difference between the two species is the relative steric orientation of the alcoholic hydroxyl groups which are about 2 Å removed when models of the two classes of adrenergic agents are superimposed. That a specific steric orientation of this alcoholic functionality may not be an absolute requirement for adrenergic activity is supported by the recent observation of significant activity in the homologue of *N*-*tert*-butylnorepinephrine in which a methylene group is inserted between the benzylic carbon and the hydroxyl group. Possibly the different steric location of the alcoholic hydroxyl group may be involved in the altered β_1- and β_2-adrenoreceptor selectivity of phenylethanolamines and phenoxypropanolamines.

Conformational studies of biologically active molecules have played an important role in probing the mechanism of drug action. One of the areas which has been widely investigated involves adrenergic (sympathomimetic) agents,[2] i.e., compounds structurally related to the natural hormones epinephrine (**1a**) and norepinephrine (**1b**).



1a, R = Me
b, R = H
c, R = $CHMe_2$



2a, Ar = 1-naphthyl; R = $CHMe_2$
b, Ar = 3,4-$(HO)_2$Ph; R = CMe_3
c, Ar = 3-$PhCH_2N(SO_2Me)$-4-$PhCH_2OPh$; R = CMe_3

The pharmacological actions of adrenergic agents almost certainly are elicited as a consequence of their interaction with macromolecular bioreceptors. Relatively strict structural requirements are observed in adrenergic drugs. That their activity is highly dependent upon their stereostructure [being confined almost exclusively to the D (−) antipodes] suggests that induction of their effects depends upon an interaction of these substances with preformed molecular sites, i.e., adrenergic receptors. The main structural difference between adrenergic agonist and antagonist agents depends upon the nature and substitution of the aromatic ring.[3,4] Quantum mechanical calculations led to the suggestion that the difference in the action of these closely related agents may be explained on the basis of their electrostatic molecular potentials.[5]

Two types of adrenoreceptors, namely, α and β, have been proposed to explain the diverse pharmacological actions of **1a** and **1b**[6-8], although evidence favoring the existence of a single adrenergic receptor which is influenced in different ways has also been advanced.[9] Isoproterenol (**1c**), a bronchodilator used for treating asthmatic conditions, was the first synthetic analogue to demonstrate a clear-cut separation of β-adrenoreceptor agonist activity from α effects. Further research has led to the postulation of at least two subtypes of β-receptors, i.e., β_1- and β_2-adrenoreceptors, in different organs.[10-13] The existence of other adrenergic receptors, namely, γ and δ, has also been suggested.[14] Some of the more recently developed bronchodilators, such as carbuterol,[15] sulfonterol,[16] and salbutamol,[17] are selective β_2-adrenoreceptor agonists. As the structures of these compounds resemble those of the natural hormones in that they retain the phenylethanolamine backbone, their interaction with β-receptors likely occurs in a similar manner. A distinctly different chemical class of compounds, 1-alkylamino-3-aryloxy-2-propanols, however, also acts on the β-adrenoreceptors as agonists and/or antagonists. The antianginal agent propranolol (**2a**)[18] is an antagonist whereas **2b**[1] is a β-adrenergic receptor agonist.

The basic structure of 1-alkylamino-3-aryloxy-2-propanols appears dissimilar from that of the adrenergic phenylethanolamines. It is conceivable, however, that both of these chemical classes may share a certain ground-state conformation as an essential structural feature that satisfies the specific steric requirements for the active site of the receptor. That the two classes of β-adrenergic agents act at the same receptor site(s) is indicated by the competitive inhibition caused by the antagonists, i.e., a surmountable antagonism which implies a dynamic equilibrium between the antagonist and receptor that can be reversed by excess agonist.[4] Consequently, determination of the thermodynamically favored conformation of 1-alkylamino-3-aryloxy-2-propanols may provide evidence relating to the mode of interaction between adrenergic drugs and the receptors. In this article are described the results of a conformational analysis of some of these compounds by NMR spectroscopic methods and a consideration of the possible implication of these results on the steric requirements of adrenoreceptors.

Conformational Analysis. Propranolol (**2a**) and **2c** were selected as representatives of the 1-alkylamino-3-aryloxy-2-propanols for NMR spectral studies of the conformation of this class of compounds. The NMR chemical shifts for various protons of the free bases and hydrochloride salts of these compounds and various other propyl- and ethylamine derivatives are presented in Table

Table I. Proton Chemical Shifts for the Free Bases and Hydrochloride Salts of Propylamine and Ethylamine Derivatives[a]

			H_α[a]			H_β[a]			H_γ[a]			C-CH_3 or N-CH_3			OH and/or NH	
No.	Structure[b]	Solvent	Base	Salt	Δ[c]	Base	Salt	Δ[c]	Base	Salt	Δ[c]	Base	Salt	Δ[c]	Base	Salt
2a	*d*	$CDCl_3$[e]*	2.88 m[f]	3.36 d[f]	0.48	4.10 br s	4.80 m	0.70	4.10 br s	4.10 m	0.00	1.07 d	1.48 d	0.41		
		Me_2SO-d_6*	2.8[f]	3.2[f]	0.4	4.08 br s	4.40 m	0.32	4.12 br s	4.10 m	−0.02	1.00 d	1.33 d	0.33	3.46 br (2 H)	6.03 br (1 H), 9.06 br (2 H)
2c	*g*	$CDCl_3$	2.70 m[h]	3.13 m[h]	0.43	3.80 br s[i]	4.50 m	0.70	3.76 br s	3.87 m	0.11	1.09 s	1.44 s	0.35	2.38 s (2 H)	
		Me_2SO-d_6[j]	*k*	*k*		3.69 m	4.07 m	0.38	3.83 m	3.82 d	−0.01	1.00 s	1.27 s	0.27	3.25 br (2 H)[l]	
3	$Ph(CH_2)_3NH_2$	$CDCl_3$*	2.71 br[f,m]	2.96 t	0.25	1.72 m	2.05 q	0.33	2.65 t[m]	2.66 t	0.01				1.11 s (2 H)	8.15 br (2 H)
4	$Ph(CH_2)_2NHMe$	$CDCl_3$*	2.80 s	3.19 s	0.39	2.80 s	3.19 s	0.39				2.41 s	2.70 s	0.29	1.04 s (1 H)	
5	$MeOCH_2CH(OH)CH_2$-$NHCMe_3$[n]	$CDCl_3$	2.64 m[h]	3.05 m	0.41	3.72 m	4.36 m[i]	0.64	3.37 m	3.48 m[i]	0.11	1.08 s	1.46 s	0.39	2.25–3.80 br[o] (2 H)	4.95[p] (1 H), 8.20[q] (1 H), 9.45[q] (1 H)
		Me_2SO-d_6	2.4 m[h,r]	2.84 m	0.44	3.55 m	3.96 m[s]	0.41	3.23 d	3.34 d	0.11	0.99 s	1.29 s	0.30		5.62 s (1 H), 8.63 br (1 H), 0.20 br (1 H)
		D_2O[t]		(2.9, 3.1) m[h]		3.73 m	3.96 m	0.23	3.36 m[h]	3.42 d	0.06					
6	$HO(CH_2)_2NHMe$	$CDCl_3$	2.69 t	3.28 t	0.60	3.65 t	3.92 m	0.27				2.43 s	2.85 s	0.42	3.55 (2 H)[l]	
		Me_2SO-d_6	2.50 t	2.92 t	0.42	3.43 t	3.68 t	0.25				2.26 s	2.52 s	0.26	3.01 s[l]	7.06 s[l]
		D_2O[u]	2.63 t	3.04 t	0.61	3.64 t	3.84 t	0.20				2.30 s	2.74 s	0.44		
7	$HO(CH_2)_2NMe_2$	$CDCl_3$	2.46 t	3.24 m	0.78	3.62 t	4.02 m	0.40				2.27 s	2.93 s	0.66	3.36 s[l]	
8	$MeO(CH_2)_3NH_2$	$CDCl_3$*	2.77 t	3.17 t	0.40	1.68 m	2.05 m	0.37	3.44 t	3.55 t	0.11				1.19 s (2 H)[l]	8.07 br s (3 H)
9	$MeOCH_2CH(OH)CH_2$-NMe_2[v]	$CDCl_3$	*k*	*k*		3.81 m	4.29 m	0.48	*k*	*k*		2.25 s	2.98 s	0.73		

[a] The NMR spectra were obtained on a Perkin-Elmer R-32 90-MHz spectrometer except for those compounds marked with an asterisk (*) which were obtained on a Perkin-Elmer R-24 60-MHz spectrometer. Chemical shifts are presented in δ units (ppm) downfield from an internal reference of Me_4Si at ambient temperature unless otherwise noted. A multiplet signal is reported by measuring its center position. The protons are designated as α, β, or γ according to the positions of the carbon atoms relative to the nitrogen atom. The following abbreviations of signal appearances are used: s, singlet; d, doublet; m, multiplet; br, broad hump; q, quartet. [b] Obtained from commercial source unless indicated otherwise. Physical properties of the base and HCl salts in all cases were consistent with literature values. In cases where crystalline hydrochloride could not be obtained, an Et_2O solution was treated with HCl and was evaporated to dryness. [c] $\Delta = \delta$ (salt) − δ (base). [d] Structure given in text; see ref 18. [e] Because of the limited solubility of the salt in $CDCl_3$, spectral data for the salt were obtained on a Varian CFT-20 NMR spectrometer with a proton probe (80 MHz). [f] Overlaps multiplet of $CH(CH_3)_2$ and H_α. [g] Structure given in text; see ref 1. [h] AB of ABX pattern. [i] Position determined by spin decoupling. [j] The salt was examined in Me_2SO-d_6 with D_2O added. [k] Chemical shift cannot be determined because of overlapping signals. [l] This signal was lost in a sample of the base treated with D_2O. [m] Because of the similarities of chemical shifts these assignments may be either H_α or H_γ. [n] Prepared from epichlorohydrin via H_2SO_4-catalyzed addition of MeOH, followed by ring closure (NaH in Et_2O) to 3-methoxy-1,2-epoxypropane to which is added *t*-$BuNH_2$ in MeOH (6-h reflux); lit.[19] bp 92-93 °C (10 Torr); hydrochloride mp 132-133 °C, prepared in Et_2O. Anal. Calcd for $C_8H_{19}NO_2$·HCl: C, 48.60; H, 10.20; N, 7.08. Found: C, 48.94; H, 9.40; N, 7.08. [o] Overlapping H_α signal. Exchanged with D_2O. [p] Observed as a sharp singlet or a broad hump, depending on the concentration of the solution; see Conformational Analysis section. [q] Observed only in concentrated solution; see Conformational Analysis section. [r] Overlapping solvent absorption. [s] On addition of D_2O to the solution and decoupling with H_α, this multiplet collapsed to a triplet. [t] MeCN was used as an internal standard locked in at 0.00 ppm. The chemical shifts are corrected by addition of 1.98, the chemical shift of MeCN in CCl_4 with Me_4Si as the internal reference, to the observed values. [u] Using sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal reference. [v] Prepared by addition of Me_2NH to 3-methoxy-1,2-epoxypropane (footnote *n*) in MeOH (reflux, 2 h).[26] The hydrochloride was prepared by addition of HCl to an Et_2O solution and evaporation to dryness to give an amorphous residue; M^+ 133.

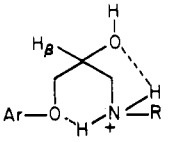
I. An abnormally large NMR downfield shift of the proton (β proton, H_β) attached to the hydroxylated β-carbon atom of the hydrochloride salts of **2a** and **2c** was observed. The chemical shifts of H_β of the free bases of **2a** and **2c** (δ 4.10 and 3.80, respectively) in $CDCl_3$ solution are within the normal range; however, those of the corresponding hydrochloride salts (δ 4.80 and 4.50, respectively) in the same solvent are shifted significantly downfield. Thus, the base to salt shift [$\Delta = \delta$(salt) - δ(base)] is 0.7 for both **2a** and **2c**. As smaller Δ's, within the expected range, were obtained for H_β in **3** and **4** (Δ = 0.33 and 0.39, respectively), the large Δ's noted for H_β in **2a** and **2c** cannot be attributed solely to the inductive effect of the protonated nitrogen atom which is two carbon atoms removed from the β proton. Further, in Me_2SO-d_6 solution the Δ's for **2a** and **2c** (Δ = 0.32 and 0.38, respectively) were within the normal range. Several interpretations may be advanced for these results. For example: (a) there may be large conformational differences between the free base and the hydrochloride salt in $CDCl_3$ solution, (b) a diamagnetic anisotropic effect (C–C, C–O, C–N, or aromatic ring current) might contribute to the large net deshielding of H_β, or (c) *intra*molecular hydrogen bonding (intra H bonding) may play an important role in the conformation of the salt in $CDCl_3$ solution but be displaced in Me_2SO-d_6 solution by *inter*molecular hydrogen bonding (inter H bonding) with the solvent. Additional studies were undertaken to examine the validity of these possibilities.

To examine the possibility that aromatic ring currents in **2a** and **2c** might produce a large net deshielding of H_β, a 1-methoxy analogue **5**[19] was examined. In this case, however, the Δ (0.64) for H_β was similar to that of **2a** and **2c**, suggesting that the 2-propanolamine chains of the hydrochloride salts of **2a**, **2c**, and **5** assume similar conformations. The aromatic ring currents of the former compounds apparently have an insignificant effect on the abnormal deshielding of H_β. Furthermore, the decreased Δ values of H_β for **5** in both Me_2SO-d_6 and D_2O solutions are consistent with previous findings. On this basis it seems probable that the abnormally large Δ values for H_β in the salts of 1-alkylamino-3-aryloxy-2-propanols are intimately related to conformational changes that are associated with intra H bonding in these systems. For this reason a study of the type and strength of intra H bonds in these systems was undertaken.

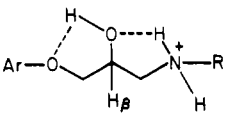
Important factors[20-22] that influence H bonding are (a) the steric conditions or geometry of the molecule, (b) the competition between intra and inter H bonding, (c) the nature of proton donors and acceptors, and (d) the polarity (dielectric constant) of the solvent. In open-chain compounds the degree of collinearity (bond angle) of AH···B (A = donor, B = acceptor) determines the strength (proportional to collinearity) and type, e.g., five-membered vs. six-membered ring, of the intra H bond, all other factors being equal. Competition between intra vs. inter H bonding is influenced by their relative strengths and the concentration of the compound in solution. Conventional techniques for detection of intra H bonding generally entail high dilution of the compound (ca. 0.005 M) to measure A–H absorption or resonance by IR or NMR spectroscopy. Both techniques have some limitations in conformational analysis. IR spectral methods may reveal the thermodynamically favored conformation, but the result cannot be extrapolated to predict the stable conformation at higher concentrations, e.g., 0.01 M or greater. Moreover, interference of salt bands precludes application of IR spectral methods to ammonium ions such as those involved in the present study. The conventional NMR spectral technique is hampered by the required high dilution of the compound and it is complicated by the proton exchange and rapid chemical shift averaging phenomenon. Therefore, an alternative NMR method for detecting strong intra H bonding that reflects the predominant thermodynamically favored conformation of the molecule at moderate concentrations (ca. 0.1 M) would be of value.

The somewhat unfavorable equilibrium for intra H bonding in the 0.01 M **2c**, and **5–8** in $CDCl_3$ solution, can be deduced from NMR chemical shifts of hydroxyl and amino protons and reported IR spectral data for similar compounds. These chemical shifts are only slightly larger (1.11–2.83 ppm) than those for **3** and **4** which are incapable of intra H bonding. That the observed differences are probably due to different inter H bonding (OH···N and OH···OH vs. NH···N) rather than contributions from intra H bonding seems probable as the amino protons of **8** resonate at δ 1.19. A series of 1,2-, 1,3-, and 1,4-amino alcohols was investigated[23] to determine the strength of intra H bonding involving OH···N. The results of this IR spectral study indicated that 1,2-amino alcohols form substantially weaker intra H bonds than inter H bonds and that the intra H bond strength was enhanced as the distance between the alcohol and amino groups was increased. Only the 1,4-amino alcohols had intra H-bond strengths comparable to those of corresponding inter H bonds. Intra H bonds involving alcohols and ether oxygen (OH···O)[24] and amino–oxygen bonding (NH···O) are generally weaker than the alcohol–amino (OH···N) type.[25] These data indicated that at the concentrations at which our NMR experiments were performed, inter H bonding predominates in the free bases.

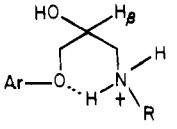
In amine salts, as a consequence of the formal positive charge, the nitrogen atom becomes an excellent donor for hydrogen bonding. Four types (**10a–d**) of intra H bonding are possible for **2a**, **2c**, and **5**.



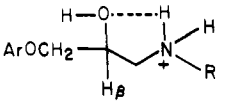
10a



10b



10c

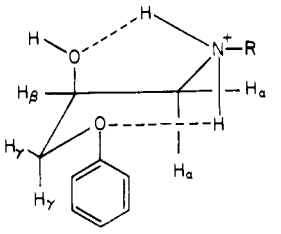


10d

Types **10a** and **10b** involve bicyclic chelates and are expected to be more stable than the monocyclic forms **10c** and **10d**. The normal Δ values for H_β in **7** and **8** which are incapable of H bonding to form bicyclic forms suggest that monocyclic conformers are suppressed by inter H bonding and therefore they do not exist in a significant population under the NMR experimental conditions. The high Δ value (0.48) for **9**[26] is an enigma. The bicyclic conformer **10a** might be expected to be more stable than **10b**. According to the well-established correlation of collinearity with H-bond strength the 6–5 bicyclic structure **10a** should be more stable than the 5–5 bicyclic structure **10b**. Also, **10a** has two ammonium protons whereas **10b** involves mixed proton donors, one of which (the oxygen atom) is a less effective donor than the positively charged nitrogen. Additionally, the geometry of **10a** is more favorable than that of **10b**. In general, a 5–5 bicyclic structure infers greater ring stain than a 6–5 bicyclic structure. Exami-

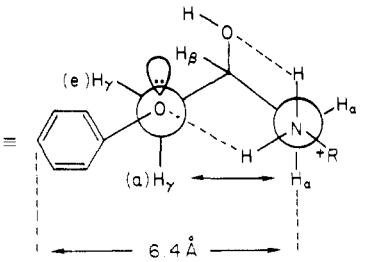
nation of molecular models suggests that **10a** may assume a "rigid" conformation as illustrated in the two projections **11a** and **11b**.

10a ≡



11a

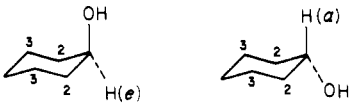
≡



11b

The six-membered ring approximates a chair form where the two bulky substituents (Ar and R) are in equatorial positions. In this conformation there is only one 1,3-diaxial proton–proton (*a* H_α vs. *a* H_γ) interaction which might, in reality, be minimized by distortion of the chair form. The hydroxyl group *must* be in an axial position to form the five-membered ring and thus H_β must be in an equatorial position. In contrast to type **10a**, type **10b** would involve various modes of proton–proton interaction.

The stereochemistry of H_β, thus deduced, provides a rational explanation of the "abnormally" large NMR downfield shift of the H_β signal when it is compared to the analogous chair form of cyclohexanol.



The difference in the chemical shifts of the axial and equatorial protons is attributed to the diamagnetic anisotropies of the 2:3 C–C bonds and the directions of their shift are dependent on the angle between the proton and the electrical center of gravity of these bonds.[27] The equatorial proton is generally deshielded whereas the axial proton is shielded; the experimental Δae for cyclohexanol is 0.60 ppm.[28] As the equatorial proton is slightly more removed from the 2:3 C–C bonds than is the axial proton, the deshielding effect for the equatorial proton should be ≤0.3 ppm. Thus the large Δ value for H_β of 1-alkylamino-3-aryloxy-2-propanols **2a** and **2c** in $CDCl_3$ may be attributed to the sum of two deshielding effects in the salt form, an inductive effect (E_I) due to the ammonium ion and a diamagnetic anisotropic effect (E_A) due to N–C and C–O bonds. The magnetic anisotropy of the C–O bond approximates that of a C–C bond,[27] whereas that of a C–N bond is not certain. Although calculation of the net E_A on H_β is precluded by the uncertainty of the center of gravity of C–O and C–N bonds, E_A may be deduced from the experimental results. The inductive component (E_I) should be Δ for H_β in Me_2SO-d_6 (Table I) whereas the anisotropic component may be calculated by subtracting E_I from the Δ value for H_β in $CDCl_3$; i.e., $E_A = \Delta(CDCl_3) - \Delta(Me_2SO)$. E_A's deduced in this manner for the salts of **2a**, **2c**, and **5** are 0.38, 0.32, and 0.24, respectively. These figures are in agreement with the E_A for the equatorial proton in cyclohexanol (<0.30 ppm). The variation of E_A among the compounds may reflect distortion of the chair form. The small Δ's for H_β in **6**, **7**, and **8** indicate the absence of E_A and intra H bonding in the corresponding salts.

Further evidence to support strong intra H bonding in **5**·HCl was discerned from an experiment in which a drop of D_2O was added to a $CDCl_3$ solution of the salt. In the NMR spectrum of this preparation a new multiplet (δ 4.12) emerged while the H_β signal at δ 4.36 was proportionately decreased so that the combined signals integrated for one proton. Similarly, a new singlet of lower intensity appeared (δ 1.31) adjacent to the *tert*-butyl signal. Additionally, the H_γ signal was transformed into a complex splitting pattern. These data suggest that a mixture of two species of the same compound was present in the $CDCl_3$–D_2O mixture; one is the intra H-bonded "rigid" bicyclic conformer (**10a**, **11**) and the other is a "random" conformer solvated by inter H bonding with D_2O.[29] The interconversion rate of these two species must be slow on the NMR time scale. In principle, the difference in chemical shifts for the two multiplets (δ 4.12, 4.36) should represent E_A for H_β. This value (0.24 ppm) is identical with E_A for H_β previously deduced for **5**·HCl. It is also noteworthy that three distinct signals, corresponding to three nonequivalent acidic protons, appear in the downfield region. The signal at δ 4.95 is assigned to the *free* OH. The downfield shift (increased acidity) is probably promoted by $^+NH\cdots O$ bonding rather than by participation of OH as a donor. The two remaining broad signals at δ 8.20 and 9.45 suggest two different types of $^+NH\cdots O$ bonding. These data support the intra H-bonding "rigid" bicyclic conformer (**10a**, **11**).

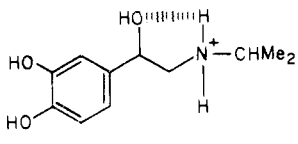
The insignificant Δ value for H_γ in **2a**, **2c**, and **5** may be rationalized in terms of E_A. In **10a** (**11**) the axial H_γ would be shielded by the C_α–C_β bond, but deshielded by the C_β–O bond to nullify the partial E_A. The same result would apply for the equatorial H_γ except that the direction of partial E_A produced by each bond would be reversed. The Δ values for *C*-methyl protons in **2a**, **2c**, and **5** are consistent with the expected E_I. The variation in Δ's for H_α is associated with factors having little bearing on the present study. It is interesting to note that the hydrochloride salts of **2c** and **5** are extraordinarily more soluble in $CDCl_3$ than are the salts of **3**, **4**, and **6**–**8**. Except for **2a**, the solubility properties of these compounds appear to reflect the presence or absence of intra H bonding.

On the basis of our NMR conformational analysis, we suggest that the salts of 1-alkylamino-3-aryloxy-2-propanols in a nonpolar solvent may exist in a stable "rigid" conformation which involves two intramolecular hydrogen bonds forming a bicyclic chelated structure **10a** (**11**). The selection of the 6–5 (**10a**, **11**), rather than the 5–5 (**10b**), bicyclic chelated structure as the preferred conformation is based on the described theoretical considerations.

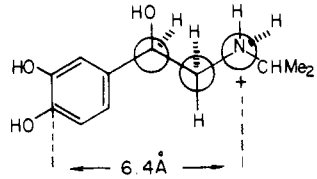
Discussion

The actual chemical nature of adrenergic receptors is a matter of speculation,[30] although attempts have been made to isolate them[31] and considerable attention has been directed toward constructing hypothetical models.[32-37] Determination of the preferred conformation of adrenergic agents might be of value in deciphering the topography of macromolecular receptors[38-41] and has been the subject of extensive investigation.[42,43] The conformation of many phenylethanolamines, e.g., norepinephrine, isoproterenol, ephedrine, and related compounds, has been studied by

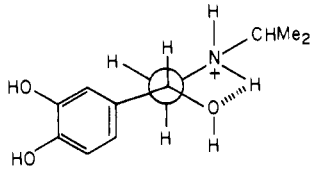
a variety of methods.[2,44-55] Most of these investigations indicate that the preferred rotamer of isoproterenol hydrochloride may be assigned, with reasonable certainty, to that indicated by **12** in which the ammonium group is trans to the aromatic ring and gauche to the benzylic hydroxyl. In an NMR study in solution this conformation was preferred with a fractional population of about 0.8.[49] The major interaction leading to this rotamer preference was attributed to an intra H bonding between the amino and hydroxyl groups.



12a

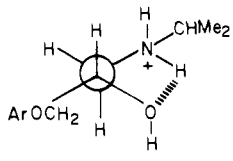


12b

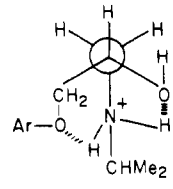


12c

Considerably less information is available for adrenergic 1-alkylamino-3-aryloxy-2-propanols.[56] Solid-state x-ray crystallographic analysis of propranolol (**2a**), a related phenoxypropanolamine type β-adrenergic antagonist alprenolol,[57] and propranolol hydrochloride indicates a conformation in which the nitrogen is approximately antiperiplanar or trans to the aryloxymethylene group; i.e., **13**. This contrasts to our proposed bicyclic chelated structure which would have the indicated gauche or synclinal conformation **14**. This difference may be attributed to different conformations in the solid state, perhaps due to crystal packing forces, and in the NMR spectral studies in $CDCl_3$ solution.



13

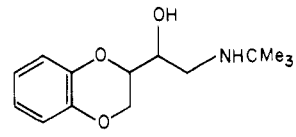


14

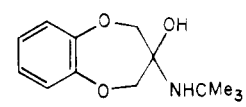
It appears likely that both arylethanolamines, e.g., **1**, and 1-alkylamino-3-aryloxypropanols **2** act at the same receptor, although suggestions to the contrary have been advanced.[58] The reversible and competitive nature of the inhibition,[4] coupled with the strict stereoselectivity of action which is restricted to the D antipodes[59] in both adrenergic agonists and/or antagonists of the type **1**[60-62] and **2**[63-66] strongly suggests that they interact with similar receptors. Although the structure-activity relationships for both classes of adrenergic agents have been extensively studied, there is no completely satisfactory explanation[1] for the way in which the aryloxymethylene moiety of the aryloxypropanolamines **2** can replace the single aromatic nucleus of the arylethanolamines **1** in the drug-receptor interaction.[3,4,30,67,68] It has been suggested that 1-alkylamino-3-aryloxy-2-propanols, by virtue of the oxymethylene group which is interposed between the aromatic and ammonium groups, may interact with accessory receptors.[3,69] This supposition is supported somewhat by the observation that aryloxypropanolamines, in general, have ten times greater affinity for isolated adrenergic tissue than do the arylethanolamines;[68] however, it fails to explain the conformational relationship between the two classes.

On the basis of solid-state studies, others[56] have proposed that the ether oxygen-carbon 1-carbon 2 moiety of the aryl group of 1-alkylamino-3-aryloxy-2-propanols, because of conjugation of the oxygen with the aromatic ring, can electronically and sterically simulate a portion of the aromatic ring and therefore take the place of the aryl group in arylethanolamines. This explanation, however, fails to attribute significance to the carbon bearing the aryloxy group in the aryloxypropanolamines.

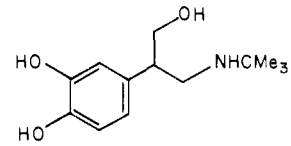
The proposed intra H-bonded "rigid" bicyclic conformer (**10a**, **11**) is supported by the relative lack of adrenergic activity of the tertiary amine, the thioether,[70] and the methylene[71] isosteric analogues of propranolol[18] which are less likely or incapable of double intra H bonding. It may also be significant that several compounds that have some of the structural features of **1** and **2** and which seem capable of double intra H bonding have significant adrenergic activity. For example, **15**[72,73] is a potent β-adrenoreceptor antagonist and the related benzodioxepin **16** is a potent agonist.[74] The pharmacological results described in our study[1] of ring-substituted phenoxypropanolamines also support the proposed conformer (**10a**, **11**).



15



16



17

In comparison of models of the "rigid" bicyclic doubly intra H-bonded structure (**10a**, **11**) with the preferred trans rotamer of isoproterenol all positions of a phenyl ring, the phenyl to oxygen or phenyl to carbon bonds, and the ammonium groups may be superimposed almost precisely. For example, the distance between the ammonium ion and all positions on a phenyl group is precisely the same for the two classes. Thus, the distance between the ammonium nitrogen and the carbon in the *p*-phenyl position is 6.4 Å in both the 1-alkylamino-3-phenoxy-2-propanol (**11b**) and isoproterenol (**12b**). A major point of departure in comparison of the two species is the relative steric orientation of the alcoholic hydroxyl groups. When **11b** and **12b** are superimposed relative to the phenyl ring, the bond of attachment to the side chain, and the ammonium groups, the oxygen atoms of the alcoholic hydroxyl groups are about 2.0 Å apart. This may indicate that this functionality need not be critically oriented for adrenergic activity. Support for this notion is provided by the observation that the homologue **17** of *N*-*tert*-butylnorepinephrine has potent β-adrenergic agonist activity.[75] Conceivably, this difference in steric location of the alcoholic hydroxyl group may account for the relatively greater β_1- vs. β_2-adrenergic activity of compounds such as **2b**[1] and other 1-alkylamino-3-aryloxy-2-propanols with selective myocardial β-adrenergic agonist activity.[66]

The proposed conformational similarity between adrenergic phenylethanolamines, e.g., **12b**, and phenoxypropanolamines, e.g., **11b**, makes it unnecessary to invoke the possibility of allosteric or conformational changes at

the receptor[76] to account for their similar actions.

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