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Conformational Properties of Benzodioxan Derivatives with *Alpha*-Adrenergic Blocking Activity

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SUMMARY

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Benzodioxan derivatives active on the *alpha*-adrenergic receptor are considered. The half-chair equilibrium of the dioxane ring was studied by ^{1}H-NMR spectroscopy for piperoxan **X** and quiloflex **XII**. The preferred conformation was also obtained by PCILO calculations for **X**. The results were evaluated in order to obtain information about the mechanism of the *alpha*-adrenergic drug-receptor interaction.

INTRODUCTION

Adrenergic agents represent a large class of drugs which are very important for clinical use. Moreover, the study of these drugs can help toward the understanding of the nature of their biological receptors; investigation of the mechanism of adrenergic drug-receptor interactions at the molecular level presently represents one of the active areas of pharmacological research.

The exact nature and structure of the adrenergic receptor sites remains undertermined, despite the great efforts directed at their isolation and analysis. All of the information on their topography and morphology has been obtained indirectly from comparative study of the molecular characteristics and the pharmacological activities of drugs which can stimulate (agonists) and block (antagonists) the various adrenergic responses.

Two types of adrenergic receptor, *alpha* and *beta*, are currently recognized. Adrenergic drugs can be related to the biological catecholamines structurally or on the basis of their pharmacological activity. With few exceptions, the *alpha*- and *beta*-agonists are derivatives of ethanolamine **I**, whereas the *beta*-antagonists are primarily derivatives of **I** or of oxypropanolamine **II**. The stimulant or blocking properties are determined in **I** by the nature and position of the phenyl (Ar) substituents, and in **II** by the aromatic group type. The *alpha*-antagonists are structurally atypical, having molecular structures which differ substantially from each other and from the structures of other adrenergic drugs.

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Compounds **III-VIII** represent examples of significant classes of *alpha*-adrenergic blocking drugs (1). Benzodioxans (**VIII**) comprised the first class to be synthesized. The marked antihypertensive actions of **IX** and **X** were demonstrated in 1933 (2) and 1937 (3), respectively. Other benzodioxan derivatives, such as dibozane (**XI**) and quiloflex (**XII**), were synthesized later.

The groups of *alpha*-adrenergic stimulant drugs which generally are believed to be involved in the interaction with the receptor are of the aromatic moiety, the amino group and the alcohol group of the side chain. Among the various *alpha*-adrenergic blockers, benzodioxan derivatives (**VIII**, **IX-XII**) approach the biological catecholamines more than other compounds, from a structural point of view. In fact, these molecules possess an aromatic ring, ethereal oxygen atoms that could be proton acceptors, and an aminic group.

One of first steps in explaining how structurally different drugs exhibit similar pharmacological behavior could involve a conformational study that shows the relative position of the groups that could interact in the drug-receptor complex.

The conformational flexibility of drug molecules provides a mutable 3-dimensional arrangement of the essential functional groups. Considerations about structure-activity relationships, simply deduced from conformational studies, could be misleading if the possibility that pharmacophore conformations differ from the preferred ones is not taken into account. However, conformational equivalence, which occurs between apparently dissimilar compounds, may be and has been invoked to explain the similarity of pharmacological activities.

To help in determining the existence of possible common structural features between the *alpha*-adrenergic

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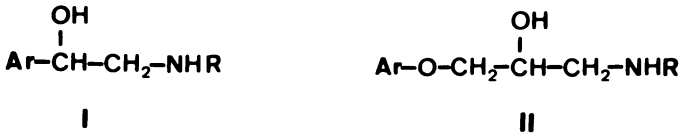


I II

STRUCTURES I AND II

stimulating drugs and the *alpha*-adrenergic blocking drugs and between the *alpha*-blocking agents themselves, we carried out an NMR study and a theoretical study on the conformation of two *alpha*-blocking benzodioxan derivatives, piperoxan (**X**) and quiloflex (**XII**).

NMR CONFORMATIONAL STUDY

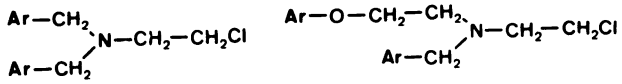
The first approach to the conformational analysis of **X** and **XII** is based on the values of the coupling constants of the vicinal dioxane ring protons H_A, H_B, and H_X, obtained from ^{1}H-NMR spectra. The **X** and **XII** compounds can exist in a mixture of two (**A** and **B**) rapidly interconverting half-chair conformations. In conformers **A** and **B**, the substituent CH_2R lies in an equatorial position and in an axial position, respectively. The observed coupling constants between the vicinal ring protons are given by the following expressions:

$$J_{trans} = \alpha J_{eq,eq} + (1 - \alpha)J_{ax,ax} \quad (1)$$

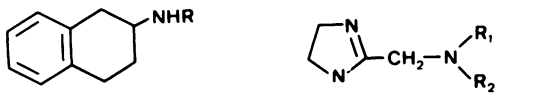
$$J_{cis} = \alpha J_{eq,ax} {}^{8}(1 - \alpha)J_{ax,eq} \quad (2)$$

where it is possible to calculate the **A** conformer fraction α and the **B** conformer fraction $(1 - \alpha)$ by taking the values of 1 Hz and 9.5 Hz for $J_{eq,eq}$ and $J_{ax,ax}$ respectively, from the literature (4).

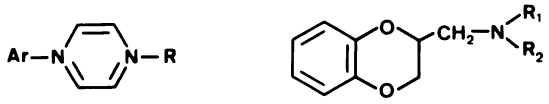
The spectra of compounds **X** and **XII** were well interpreted as an *ABXMM'* spin system and were well reproduced (Figs. 1 and 2). The signal of proton *X*, which appears as a multiplet, was decoupled from the side-chain protons, to confirm the proposed attribution. The spectral parameters used for the ring protons are summarized in Table 1. From J_{BX} values, through Eq. 1, we calculate that $\alpha = 0.30$ for both compounds **X** and **XII**.



III, β-Haloalkylamines IV, Phenoxybenzamines

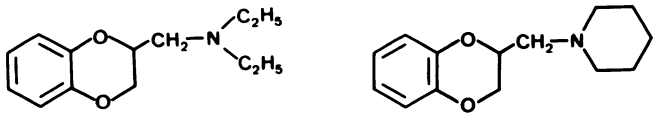


V, Tetralines VI, Imidazolines

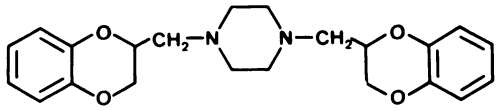


VII, Phenylpiperazines VIII, Benzodioxans

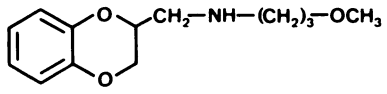
STRUCTURES III–VIII



IX, Prosympal X, Piperoxan



XI, Dibozane



XII, Quiloflex

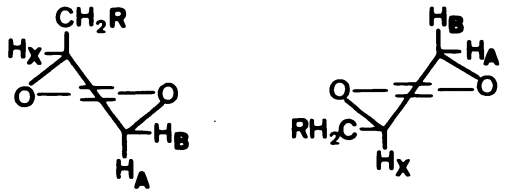
STRUCTURES IX–XII

The conformer with the CH_2R substituent in the equatorial position (**B**) is therefore the most favored, in agreement with what was previously found for other 2-substituted benzodioxans (5, 6).

THEORETICAL CALCULATIONS

Another approach to conformational analysis has been performed by theoretical calculations, using the PCILO method. This method was successfully used in evaluating the conformation of biological and pharmacological compounds (7, 8).

The first step in this method was the building of the conformational energy maps by changing the torsion angles α and β by amounts of 30°. The α and β angles are defined as in Fig. 3 for Compound **X**, and the piperidine



A **B**

STRUCTURES A AND B

ring is fixed in a chair position. The two conformers **A** and **B** have been considered separately.[4]

Unreported testing calculations showed that *N*-substitution of benzodioxan derivatives does not influence appreciably the conformation of the rest of the molecule. With this in mind and for the sake of brevity, we do not

[4] We have considered only one stereoisomer among the two generated by the optically active C_7 because in the conformational calculations this fact does not play any role.

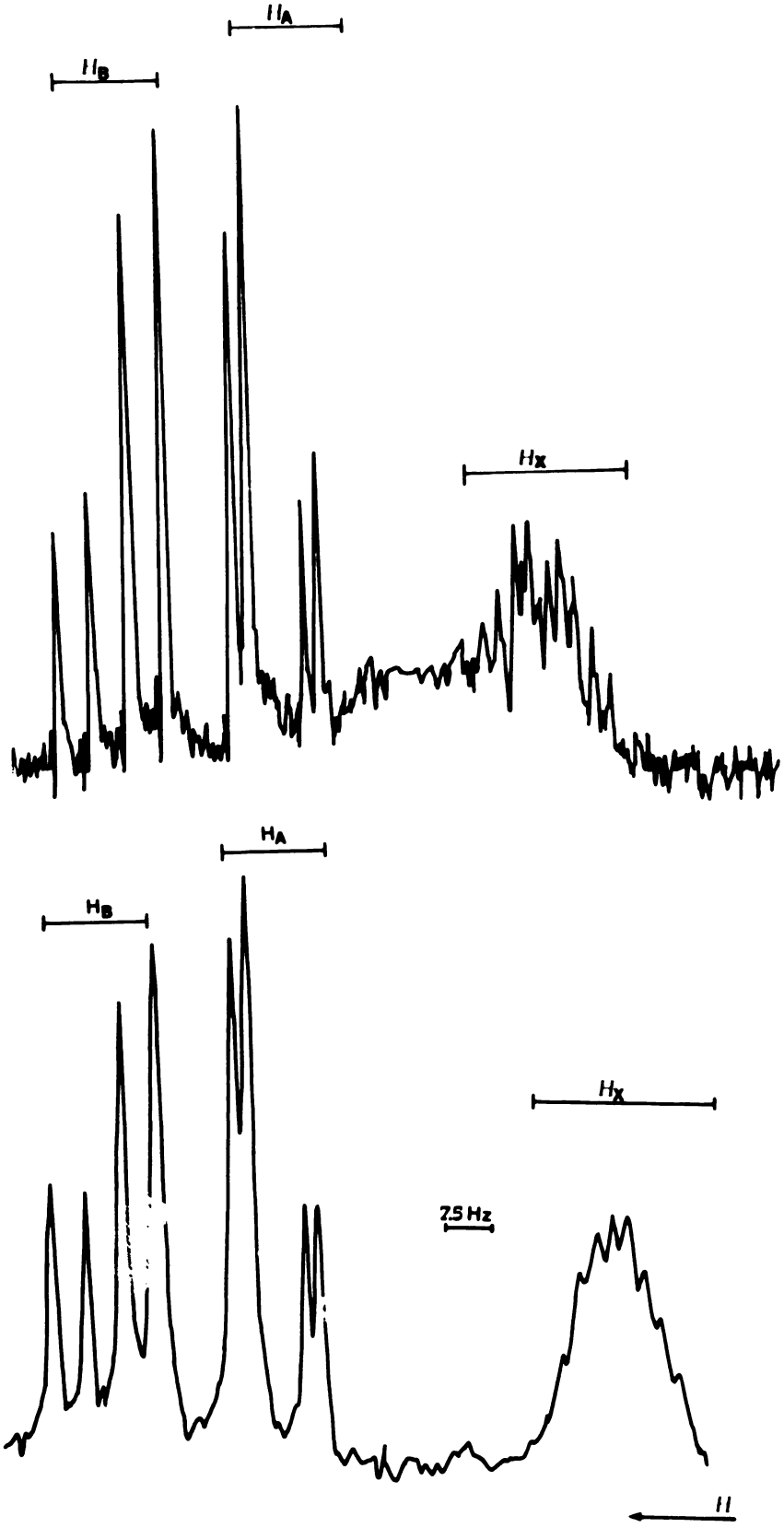


FIG. 1. *Spectra (100 MHz) of ABXMM' system in ^2H_2O*
Upper spectrum, piperoxan (X); lower spectrum, quiloflex (XII).

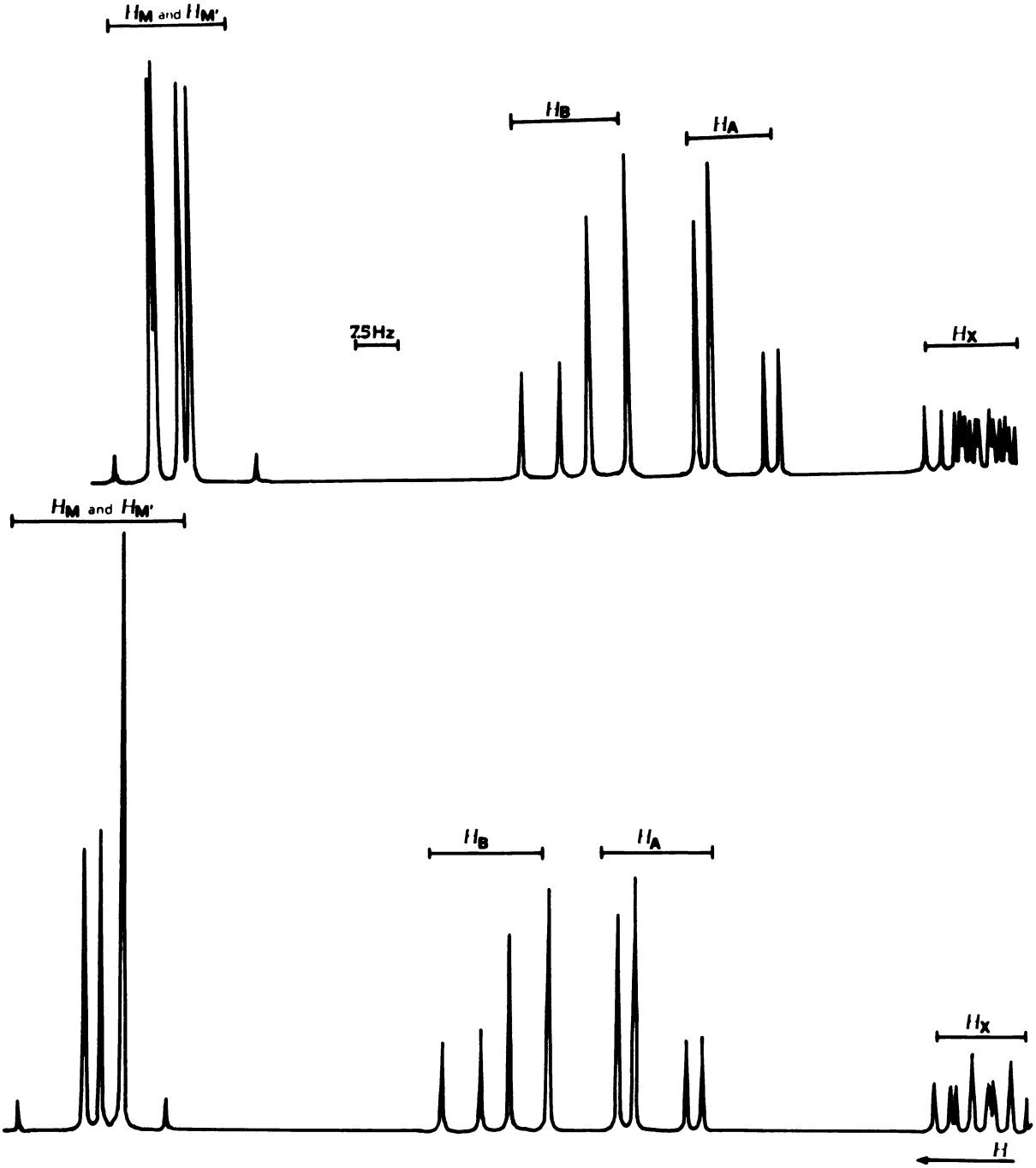


FIG. 2. *Simulated spectra (100 MHz) of ABXMM' system*
Upper spectrum, piperoxan (**X**); lower spectrum, quiloflex (**XII**).

consider here the possible conformations that the piperidine ring of **X** could assume, nor do we consider compound **XII**, which differs from **X** only in the *N*-substitution. Such a choice is also supported by the above-described NMR results.

Figure 4 shows the conformational energy maps obtained for the two conformers **A** and **B**: four minima can be seen for **B** and one minimum for **A**.

In Table 2 the energies relative to various values of the α and β angles are reported. The most favored conformation is the one with the side-chain equatorial (corresponding to conformer **B**), with $\alpha = 60°$ and $\beta = 21°$. Table 2 also shows the conformer population distribution computed using the Boltzmann equation with a temperature of 25°. We note that the total population of conformer **B** is 95% and that of conformer **A** is 5%.

The NMR results concerning the **A**⇄**B** conformational equilibrium for HCl salt in solution were in good agreement with those obtained by PCILO calculations which concern the "isolated" free base. This fact seems to indicate that the equilibrium between the two half-chair conformers **A** and **B** is neither greatly influenced by the solvent nor by the protonation of the nitrogen.

The results of Table 2 show that the energy differences

TABLE 1

Computer-refined values for the ABX part (Hertz) of piperoxan (X) and quiloflex (XII)

Compound	J_{AB}	J_{AX}	J_{BX}	$\Delta\nu_{AB}$	$\Delta\nu_{AX}$	$\Delta\nu_{BX}$
X	−12	2.7	7.0	27	86	59
XII	−12	2.7	6.8	27	71	44

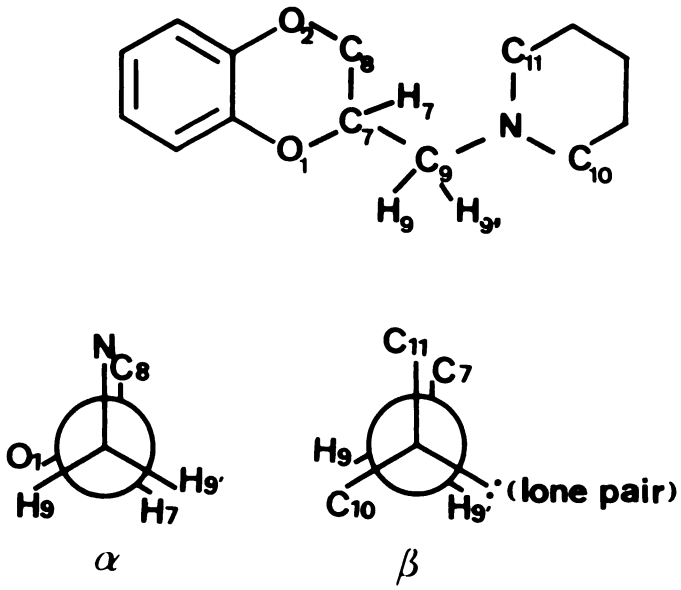


FIG. 3. *Torsion Angles*

The torsion angle α is the angle at which C_9 must be rotated counterclockwise around the C_9—C_7 bond starting from the shown position; the torsion angle β is the angle at which N must be rotated counterclockwise around the N—C_9 bond starting from the indicated position.

among the four preferred rotamers (1–4) having the side chain in an equatorial position are small. These conformers therefore have a comparable probability of existence, and therefore a strongly preferred conformation does not exist.

However, an analysis of Table 3 shows that intramolecular distances between "significant" molecular groups are very similar, at least for the three lowest minima. In other words, the O_1–N distance has a 78% probability of being about 2.9 A.

CONCLUSIONS

In Table 4, significant intramolecular distances are shown for the minimal conformations of piperoxan (X) compared with analogous distances of norepinephrine in its preferred conformation. The distances O_1–N are very close in both considered compounds. With regard to the distances between the aromatic portions and the other "significant" groups, we note that, if one considers the center of the phenyl ring as a reference point, the distances ϕ–N are closer than the distances ϕ–O_1. In fact, although the distance between the center of the phenyl ring and the nitrogen atom of X (5.5 A) is very close to that between the center of the phenyl ring and the aminic nitrogen atom of norepinephrine (5.1–5.2 A), the distance between the center of the phenyl ring and the O_1 atom of X (2.8 A) is shorter than that between the center of the phenyl ring and the alcohol oxygen atom of norepinephrine (3.7 A).

However, an alternative reasonable comparison between the ϕ–*N* and ϕ–O_1 distances could be made, using, as reference points, the most electron-rich areas of the aromatic π regions instead of the geometrical centers of

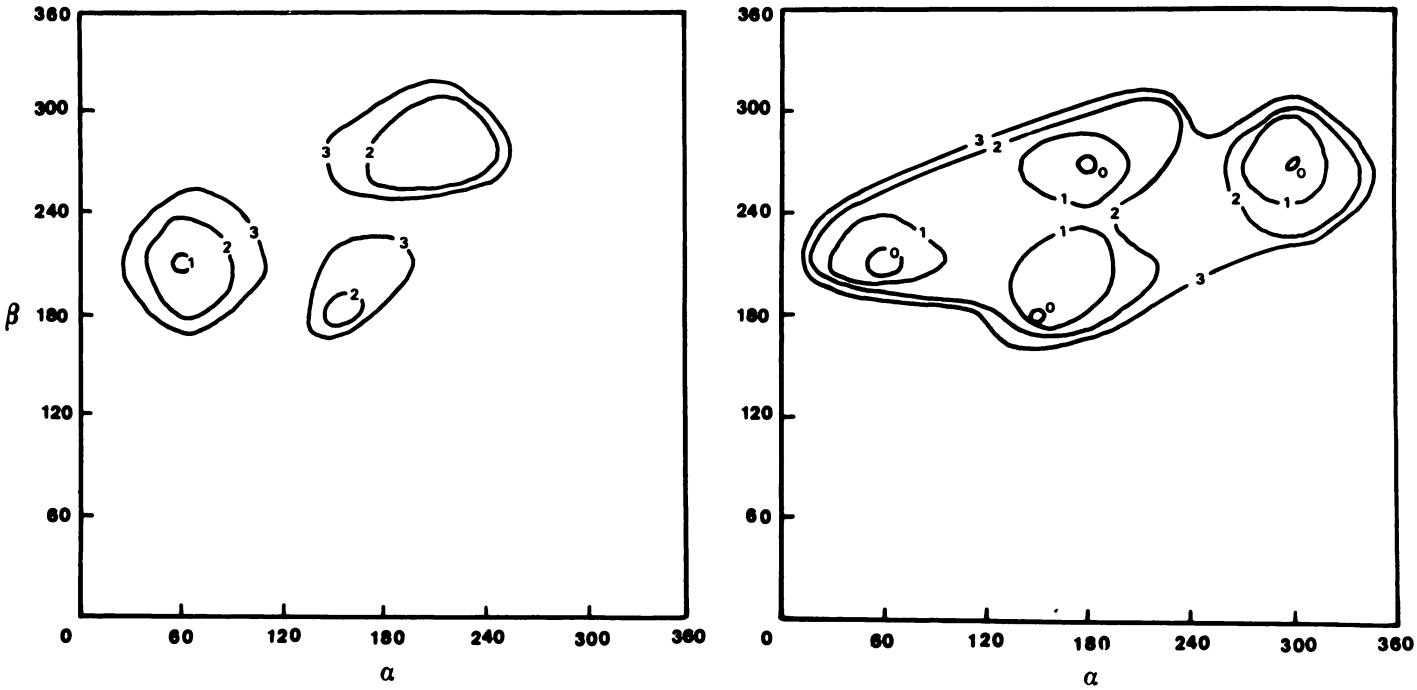


FIG. 4. *Conformational energy maps of conformers A (left) and B (right) of piperoxan*

Values indicate relative energies in kilocalories per mole.

TABLE 2

Side-chain conformation, torsion angle values (α, β), relative values of conformational energy (ΔE), and rotameric populations (P) of piperoxan

Conformer	Side chain	α	β	ΔE	P
				kcal mole^{-1}	%
1	Equatorial	60°	210°	0.00	32
2	Equatorial	150	180	0.38	25
3	Equatorial	180	270	0.43	21
4	Equatorial	300	270	0.49	17
5	Axial	60	270	1.66	5

the phenyl rings.[5] The electron-donor effect of the oxygen atoms bound to the ring moves π electrons away from the side chain of the phenyl ring for **X**, but, on the contrary, brings them nearer to the side chain for norepinephrine. By using this criterion, the ϕ–O_1 distance values become closer, whereas the ϕ–N distances become greater. In other words, if we superimpose the two centers of the phenyl rings of **X** and of norepinephrine, we find a correspondence of the two nitrogen atoms, whereas the two ϕ–O_1 distances differ by 0.9 A; alternatively, the superimposition of the two electron-rich areas of the aromatic regions makes the correspondence of the two O_1 atoms possible, the ϕ–N distances having a difference of about 1 A.

TABLE 3

Significant distances (A) of conformers of piperoxan

Conformer	ϕ–O[a]	O_1–N	O_2–N	ϕ–N[a]
1	2.77	2.86	4.28	5.40
2	2.77	2.97	4.80	5.41
3	2.77	2.94	4.80	5.56
4	2.77	3.73	4.06	5.96
5	2.77	3.73	3.12	4.98

[a] ϕ indicates the center of the phenyl ring.

TABLE 4

Comparison of significant distances (A) of the preferred conformers of piperoxan (X) and norepinephrine

Compound	ϕ–O_1[a]	O_1–N[a]	ϕ–N[a]
X	2.8	2.9	5.5
Norepinephrine[b]	3.7	2.9	5.1–5.2

[a] O_1 of norepinephrine indicates the alcohol oxygenatom; ϕ indicates the center of the phenyl ring.

[b] Distances for norepinephrine were obtained from data computed from theoretical studies (9, 10).

From the above data, it can be deduced that correspondences exist among the distances between the "significant" groups of piperoxan **X** and of norpinephrine in their preferred conformations.[6]

Taking into account considerations previously made (8, 11, 12) about possible mechanisms of interaction of benzodioxan derivatives at *alpha*-adrenergic receptor level, on the basis of our results it seems reasonable to us to suggest that the interaction of the *alpha*-adrenergic receptor sites can take place in a similar way for both biological catecholamines and benzodioxan derivatives. This could be a starting point in rationalizing the action of other *alpha*-blocking agents structurally more different with respect to catecholamines.

[5] The adrenergic drug-receptor interaction for these types of drugs generally involves rather weak bonds, such as ionic interactions, H-bonds, dispersion forces, and hydrophobic bonds, covalent bonds are probably not involved; this fact makes it reasonable to believe that the electronic structure of the isolated molecule is not greatly modified; therefore, the most electron-rich areas of the π regions could be preferentially involved in the interaction.

[6] From an inspection of their preferred conformations of **X** and norepinephrine, it can be seen that it is not possible to superimpose the three "significant" groups together, if one also wants a good superimposition of the molecular skeletons. In particular, there is a close analogy of the group O_1—C—C—N of **X** with the corresponding portion of the catecholamine side chain; however, the superimposition of these molecular moieties does not allow any correspondence between the two phenyl rings.

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