Correlation between Affinity toward Adrenergic Receptors and Approximate Electrostatic Potentials of Phenylethylamine Derivatives. 1. Effects of the Side Chain

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The molecular electrostatic potential (V_N) in the region of the nitrogen lone pair of a series of substituted propylamines is used in a correlation with the dissociation constants of parent phenylethylamine-type ligands obtained on β-adrenoceptors by Bilezikian et al. It is shown that V_N is a more effective index for quantitative structure–activity relationship studies than an optimal set of substituent constants used in additive, linear models. No significant correlation between the total electronic charge on the nitrogen and the binding potencies was obtained in the examined series. Protonation energies of the propylamines have been computed, but no meaningful correlation with the dissociation constants was obtained.

Qualitative considerations of the role of functional groups of phenylethanolamine (PEA) derivatives in their adrenergic activity have led to the conclusion that the ethanolamine side chain is the primary determinant for the receptor affinity, whereas the substituted phenolic moiety, though also involved in binding to the receptor, is more important for the type of activity (agonist or antagonist).[1] Quantitative structure–activity relationships (QSAR) for adrenergic drugs have been based on lipophilicity,[2] lipophilic–electronic, and steric substituent constants,[3] as well as on "group contributions" within the Free–Wilson[4] and Fujita–Ban approaches.[5-8] Quantum chemical indexes were also used for correlations with the pharmacological potency of PEA derivatives.[9] George et al.[10] have made EHT, CNDO/2, and ab initio calculations on the protonated ethanolamine side chain and found that substitution of the N-hydrogen with CH_3, CH_2CH_3, or $CH(CH_3)_2$ caused insignificant changes in the charge densities at N. Because of this, the authors concluded that β-adrenergic activity is influenced by dispersion forces between the alkyl group and the receptors.

Molecular electrostatic potential maps (MEP) of several PEA-type molecules were primarily used for differentiating between agonist and antagonist types of activities,[11] but Martin et al. also suggested that the charge around the amino nitrogen is important for the interaction between the side chain and the receptor.[12] Although in the last few years MEP's have become quite popular in attempts at defining the pharmacophoric pattern, they seem to be used less on larger series of drugs as a source of indexes for QSAR.[11-13] Calculations of MEP based on acceptable quality wave functions are expensive and thus have to be limited either in the number of calculated examples or to very modest size molecules. A possible alternative is to consider only one part of the molecule, provided that the pertaining charges are not appreciably perturbed by the neglected part and that such experimental data are available for which the part of the molecule considered may be taken to be relevant.

Starting with these premises, we have calculated the MEP's of a series of substituted 2-propanolamines as representing the side chain of adrenergic agonists. As for experimental data, we have taken the dissociation constants (K_D) of β_1 agonists determined by Bilezikian et al.[14] It is rather safe to assume that the influence of the aromatic part of the molecule on the potential in the vicinity of the side-chain nitrogen is negligible or, at least, constant throughout the series of agonists considered.[10-12] That the side chain mainly is responsible for the affinity is more hypothetical. However, recent results of Leclerc et al.,[15] who have synthesized powerful β-antagonists devoid of the aromatic moiety, support this hypothesis. Eventually, the results of our QSAR using the MEP of the side chain as an index accounting for at least 50% of the variance give more credence to it. We have also tried to correlate the dissociation constants with the calculated electronic charges on the nitrogen, but the charge turned out to be an inferior index to the potential (V_N). For β-receptor ligands the affinity increases with the (negative) potential, whereas for α-receptor ligands the opposite is true.

Results and Discussion

The computed V_N's are given in Table I, in which the corrected K_D values[14] of the agonists containing the respective side chain are also listed. It appears that increasing numerical values of K_D indicate a decreasing binding strength of the drug–receptor complex. For

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Table I. Results of ab Initio Calculations Using the Minimal STO-3G Basis Set

	side chain[a]	gross atomic charge on atom N	protonation energy, au	molec electrostatic potential, kJ/mol	adrenergic agonists[b]
I	$CH(OH)CH_2NHCH(CH_3)_2$	−0.3477	−0.43645	−90.8	1-10
II	$CH(OH)CH(CH_3)NH_2$	−0.4186	−0.41945	−89.1[c]	11-13
III	$CH(OH)CH(CH_3)NH_2$	−0.4115	−0.41895	−90.0[c]	11-13
IV	$CH(OH)CH_2NHCH_2CH_3$	−0.3411	−0.44131	−80.7	14, 15
V	$CH(OH)CH(CH_3)NHCH_3$	−0.3469	−0.42744	−74.5[d]	16, 17
VI	$CH(OH)CH(CH_3)NHCH_3$	−0.3483	−0.42677	−75.7[d]	16, 17
VII	$CH(OH)CH_2NHCH_3$	−0.3370	−0.43338	−74.9	18-21
VIII	$CH(OH)CH_2NH_2$	−0.4084	−0.41936	−64.4	22-24
IX	CH_2-$CH_2NHCH(CH_3)_2$	−0.3476	−0.44635	−70.3	25
X	$CH_2CH_2NHCH(CH_3)_2$	−0.3370	−0.43959	−65.3	26
XI	$CH_2CH_2NH_2$	−0.4091	−0.32119	−54.0	27-30

[a] The actual calculations were performed with a CH_3 group attached to the left-hand side of the side chains. [b] Figures in parentheses are the corrected values (see text) of $-\log K_D$. 1 = (−)-isoproterenol (0.47), 2 = PI 39 (−0.69), 3 = soterenol (−0.81), 4 = sulfonterol (−0.47), 5 = salbutamol (−0.20), 6 = MJ 6987 (−1.57), 7 = metaproterenol (−0.98), 8 = MI 39 (−0.37), 9 = dichloroisoproterenol (0.22), 10 = sotalol (−0.04, antagonist), 11 = cobefrine (0.80), 12, synephrine (−1.58), 13 = metaraminol (−0.90), 14 = ethylnorepinephrine (−0.65), 15 = S40032-7 (−1.24), 16 = hydroxyephedrine (−1.35), 17 = ephedrine (−1.22), 18 = epinephrine (−0.46), 19 = S 38537-9 (−1.76), 20 = phenylephrine (−1.27), 21 = metanephrine (−1.26), 22 = (−)-norepinephrine (−0.88), 23 = octapamine (−1.81), 24 = normetanephrine (−2.00), 25 = β-deoxyisoproterenol (−1.08), 26 = *N*-methyldopamine (−1.74), 27 = dopamine (−2.13), 28 = 5-hydroxydopamine (−2.01), 29 = tyramine (−2.30), 30 = methoxytyramine (−2.30). Data from ref 14. [c] For the actual calculations, the mean value −89.6 has been considered. [d] For the actual calculations, the mean value −75.1 has been considered.

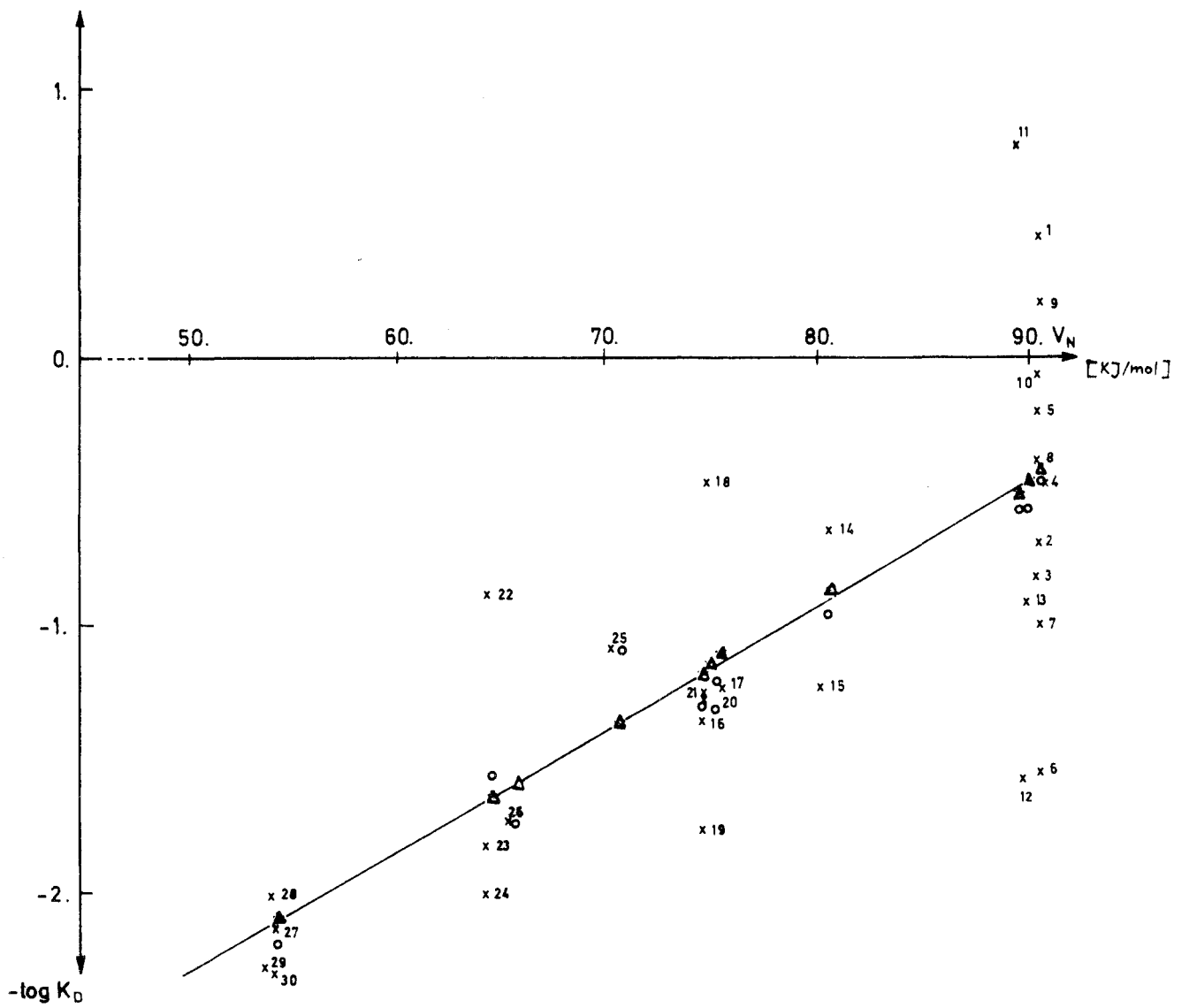

Figure 1. Correlation between $-\log K_D$ for binding[14] and the electrostatic potential (V_N, kJ/mol) of the side chain. Values are listed in Table I: x represents one compound; △ denotes the calculated values of $-\log K_D$; ○ denotes the average $-\log K_D$ of a given side chain.

molecules with identical substituents on the aromatic ring, the increase of the electrostatic potentials at the amino group is accompanied by lower values of K_D (Table I and Figure 1). From these data, the linear regression equation (eq 1) was obtained, where n denotes the number of

$$-\log K_D = -0.046V_N - 4.606 \quad (1)$$
$$(\pm 0.016) \quad (\pm 1.176)$$

$$n = 30;\ r = -0.753;\ s = 0.544;\ F = 36.66$$

molecules considered, s is the standard error of the estimate, r is the correlation coefficient, and the number in parentheses is the 95% confidence limit of the regression coefficient. Equation 1 is significant[16] even at the $p \leq 0.005$ level ($F_{1,28,p=0.005} = 9.28$). Obviously, the binding does not depend on V_N only, and the next factor to be considered is the presence or absence of the β-OH group. We have repeated the calculation by introducing a dummy variable, D, which was given a value of 1 if the β-OH group was present and 0 in its absence. This did not improve the correlation, the multiple correlation coefficient (R) being 0.753. Obviously, the electrostatic potential (V_N) already takes up the influence of this group. The correlation coefficient betweeen V_N and D is $r = -0.728$.

A reviewer suggested that the protonation energies could explain part of the variance. We have calculated the theoretical protonation energies, $E_p = E_{NH^+} - E_N$, and the results are given in Table I. Equation 2 indicates that the

$$-\log K_D = -12.925E_p - 3.601 \quad (2)$$
$$(\pm 8.414) \quad (\pm 3.080)$$

$$n = 30;\ r = 0.139;\ s = 0.645;\ F = 9.43$$

inclusion of E_p as a second independent variable would not improve the correlation over eq 1. The poor correlation of K_D with E_p should be considered by assuming two possible mechanisms of interaction of the aminic head with a receptor site. The assumption of an ionic interaction, i.e., via hydrogen bonding of the N^+–H···O^- type, requires the presence of water molecules necessary for the stabilization of the ionic form. If so, E_p is not a meaningful property, as shown by the well-known example of simple amines.[17] However, if the neutral groups were to interact, i.e., with the nitrogen acting as proton acceptor in the hydrogen bond of the N···H–O type, V_N should be determining the strength of the interaction.[18] Affinity data on tertiary amines would be useful for further argumentation along these lines, since they would offer a larger spread both of experimental and calculated properties.

In order to have a comparison of the value of V_N as an index for QSAR with "classical" approaches, we have also calculated the group contribution of the substituents β-OH, α-CH_3, N-CH_3, N-CH_2CH_3 and N-$CH(CH_3)_2$ in the Fujita–Ban scheme for the molecules in Table I. To begin with, we have not included the ring substituents; thus, the statistical indexes can be compared with those of eq 1. The F test indicates that this regression equation is significant at the $p \leq 0.005$ level ($F_{5,24} = 5.25$ vs. $F_{5,24,p=0.05} = 4.49$). The calculated group contributions are (integers in parentheses denote number of occurrence) as follows: β-OH, 0.709 (24); α-CH_3, 0.515 (5); N-CH_3, 0.042 (7); N-CH_2CH_3, 0.437 (2); N-$CH(CH_3)_2$, 0.945 (11). This limited Fujita–Ban approach yielded a multiple correlation coefficient of $R = 0.723$, which is lower than the absolute value of the simple correlation coefficient ($r = 0.753$) demonstrated between the V_N and –log K_D values (eq 1). Application of the Fujita–Ban approach for all substituents (in the side chain and aromatic ring) of the series of Ref 14 yields $R = 0.815$. The multiple correlation obtained by the Fujita–Ban[5] or the equivalent Free–Wilson[4] approach cannot be surpassed by any linear additive model.[7,8] Thus, the correlation coefficient for eq 1 appears satisfactory in comparison with the "limited" Fujita–Ban approach and even with the one considering all substituents, i.e., $R = 0.815$, where a set of 13 independent variables was considered.

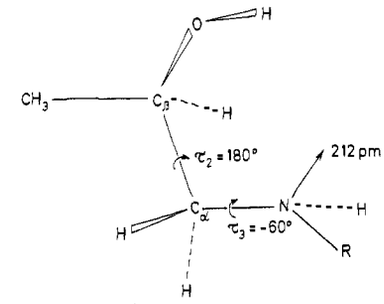

Figure 2. Ethanolamine side-chain conformation.

To show the superiority of V_N over the electronic charge on the nitrogen (q_N) we have tried to correlate the latter with the K_d values. Eq 3 is the regression derived. Comparison of the result of the F test with the theoretical value[16] indicates that eq 3 is not significant at the $p \leq 0.05$ level ($F_{1,28,p=0.05} = 4.20$). The demonstrated correlation between –log K_D and V_N values is also supported by qualitative trends observed with the binding potencies using (–)-[^{3}H]dihydroalprenolol[19] as a competitive antagonist.

$$-\log K_D = 8.545q_N + 2.098 \quad (3)$$
$$(\pm 8.907) \quad (\pm 3.930)$$

$$n = 30;\ r = 0.348;\ s = 0.775;\ F = 3.86$$

Encouraged by the significant correlation between V_N and K_D for β-receptor binding of agonists, we have also looked at the possibility of correlating V_N with K_D for binding to α-adrenoceptors using the experimental data of Lefkowitz and Williams.[1] However, here the increasing values of V_N associate with higher values of K_D. This might be taken as an indication that the nature of the interaction between ligands and α- and β-adrenoceptors, respectively, is different. However, before we accept this possibility, further work is necessary that would include ligands of different structural classes.

Since the primary goal of this work was to demonstrate the role of the MEP in the N-lone-pair region for the binding to the receptor, we did not search for other parameters that might explain the rest of the variance. This rest is likely to be due to the volume effect of the N-substituents, to the presence or absence of the β-OH group (although at least a part of its effect is reflected in V_N), and to the binding properties of the aromatic part. The role of the latter will be examined in a forthcoming paper.

Conclusions

The results of this work clearly indicate that the electrostatic potential in the region of the N-lone pair of

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phenylethylamines is important for the binding at the β-adrenergic receptor. The statistical analysis of the data shows that it accounts for 50% of the variance.

Experimental Section

Molecular Geometry. In our calculation we have considered only the $R(-)$ configuration, which is far more active than[20] the $S(+)$ configuration. In the case of C_α substitution, we have made calculations on both isomers, since the configuration on this atom also influences the pharmacological activity.[21,22]

The conformation around the C_α–C_β bond (dihedral angle τ_2, defined by atoms C_{Me}–C_β–C_α/C_β–C_α–N) has been the subject of many theoretical and experimental investigations. Ab initio calculations of the hydrated norepinephrine show the trans form to be energetically preferred,[23] which is in agreement with the NMR measurements.[24] However, the difference between this and the gauche form is of the order of 12–15 kJ/mol,[25] and the only indication that the trans form is preferred at the receptor is the activity of the semirigid agonists.[26] Therefore, we have based our calculation on this conformation and the standard bond lengths and angles.[27] In fixing the conformation about the C_α–N bond, we have followed the calculations of Martin et al.[12] and set the dihedral angle τ_3 (defined by the planes C_α–C_β–N/C_β–N–N_{LA}, where N_{LA} denotes the lone pair axis) to −60°. The axis of the nitrogen lone-pair orbital is thus parallel to the C_β–O bond, and the N-alkyl bond is at 180° to the C_β–C_α bond. The OH bond lies in the plane defined by the atoms C_{Me}–C_β–O and points toward the lone electron pair of atom N (Figure 2). No further optimization of the total energy with respect to the conformation of this bond has been performed, since a recent ab initio optimization of 2-aminoethanol geometry by Schäfer et al.[28] gave preference to this conformation.

MEP Computation. The molecular wave functions have been computed within the ab initio LCAO framework with the minimal STO-3G basis set[29] using the Gaussian 70 program.[30] The MEP has been computed in the point-charge approximation. Kollman et al.[31,32] have shown that this approximation is satisfactory in the region distant not less than 200 pm from the atomic centers. Recently, Baldwin et al.[13] have used this approximation within the semiempirical SCF framework for PEA derivatives. The potentials have been mapped in a plane at a distance of 200 pm parallel to the plane containing the C_β–C_α–N atoms. The values of V_N used for correlations were taken at the intersection of the vector pointing from the nitrogen center along the tetrahedral axis of the lone pair and the above defined plane. The intersection is at 212 pm from the center (Figure 2). This position does not correspond to the actual minimum V_N but has been chosen arbitratily so that (i) the point indicated in Figure 2 is in the direction of the least energy path of approach of a positive charge (e.g., a proton donor) and (ii) it is within the limits of validity of the point-charge approximation to the MEP.[31,32] In Figure 3 is presented a comparison between the results of calculating the MEP for noradrenaline without approximations and the point-charge approximation, respectively. The computations have been made for neutral molecules, although most of the models for catecholamine–receptor interactions assume the protonated form.[33] This stems from the fact that the catecholamines are predominantly protonated at pH 7.4. However, there is no direct evidence that the amines are indeed protonated when bound to the receptor. For the stabilization of the ionic form, the presence of water molecules is required,[17] and it is questionable whether they can be accommodated in the receptor cavity near the ligand's aminic head. In support of the present view, the case of butaclamol may be quoted, which is of low basicity (pK_a − 5.9) and is assumed to interact with the dopamine receptor via neutral hydrogen bonding.[34]

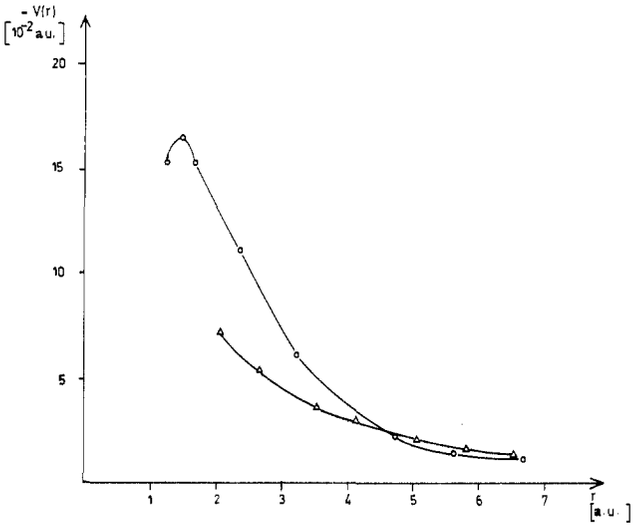

Figure 3. Comparison of electrostatic potentials of N-propylamine base obtained by two methods: (○) ab initio electrostatic potential without approximations,[11,12] STO-3G basis set; (△) ab initio electrostatic potential in point-charge approximation,[29,30] STO-3G basis set. All values are in atomic units. r denotes the distance between the point considered and the nitrogen atomic center in the lone-pair direction.

We have included in our calculations 11 out of 18 various side chains appearing in the data of Bilezikian et al.[14] Thus, protokylol, C-25, C-34, isoetharine, isoxyprine, nylidrin, ritodrine, dobutamine, AH 2923, 8798-1, MJ 9184, W 9803-A, W 10773, W 10470, fenoterol, S 35985, quinterenol, trimethoquinol, and S 35-179 were not considered because their N-substituents offer formidable conformational problems that cannot be rationally solved. Moreover, the aromatic rings in most of these cases offer additional binding possibilities and would thus blur the effect of the nitrogen MEP.

Protonation Energies E_p. The protonation energies (E_p), as defined by the difference between the total energies of the protonated species E_{NH^+} and the amine E_N, were computed under the ab initio scheme using the STO-3G basis set. The N–H distance was 101 pm,[27] and the angles at the nitrogen were tetrahedral. The internal geometry was not optimized.

Experimental Affinities. We used in the correlations the dissociation constants (K_D) obtained by Bilezikian et al.[14,35] with

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a series of agonists of membranes of the turkey erythrocyte containing mainly β-adrenoceptors.[36] Since the K_D values for pure isomers were available in a few cases only and our calculations were made for a definite configuration, we have used for correlations "corrected values", i.e., those given for the racemic mixture divided by two. This is justified, however, only for low receptor concentrations.[37]

Acknowledgment. One of the authors (I.L.) thanks the Slovenian Research Council for a postdoctoral fellowship.

(36) The formulas for metaraminol and ephedrine in ref 14 are incorrect. The K_D for PI 39 (9.7 μm) differs by a factor of 10 from what is given in a second paper[35] (0.97 μm). We have accepted the first value, but this does not affect the qualitative conclusion.

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β-Adrenergic Blocking Agents. 24. Heterocyclic Substituted 1-(Aryloxy)-3-[[(amido)alkyl]amino]propan-2-ols

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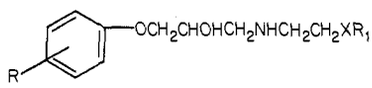
The synthesis of a series of 1-(aryloxy)-3-[[(amido)alkyl]amino]propan-2-ols where either the aryl moiety is heterocyclic or the amidic group is substituted by a heterocyclic moiety is described. Several of the compounds were more potent than propranolol when given intravenously to anesthetized rats. In contrast to previous findings with β-blockers based on heterocyclic moieties and with either an isopropylamino or *tert*-butylamino substituent on the side chain, several compounds proved to be cardioselective when further examined in anesthetized cats. The detailed structure–activity relationships shown by this series of compounds are discussed.

Heterocyclic moieties have been a structural feature of β-blockers for some considerable time; thus, pindolol[1] and timolol[2] are well-established β-blockers, and carazolol[3] and bufuralol[4] have undergone extensive clinical evaluation. All four compounds have either an isopropylamino or a *tert*-butylamino substituent on the side chain; none are cardioselective.

In earlier papers,[5-7] we have described the synthesis and structure–activity relationships of β_1-cardioselective blocking agents that incorporate an amidic moiety (X) into the side chain of an (aryloxy)propanolamine, **1**, or an arylethanolamine, **2**.



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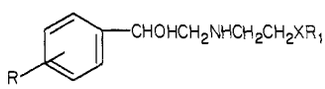
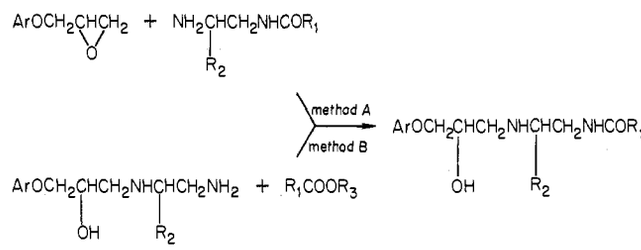


2

3, X = NHCO, NHCONH, $NHSO_2$

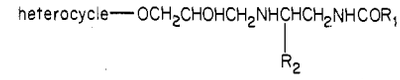
As an extension of this work, we considered it of interest to synthesize a further series of (aryloxy)propanolamines

Scheme I[a]

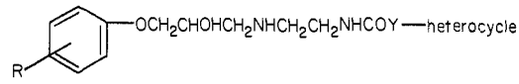


[a] Ar is a phenyl or heterocyclic moiety, R_1 relates to the substituents described in Tables I and II, R_3 is a suitable ester substituent, and R_2 is either a hydrogen atom or a methyl group.

in which either the aryl ring or the substituent R_1 in the above generic structure **1** is replaced by a heterocyclic moiety to give **4** and **5**, respectively.



4



5

We report here the β-blocking potency of these compounds in rats; some were also tested for β_1 cardioselectivity in cats.

Chemistry. The compounds listed in Tables I and II were synthesized by methods A and B illustrated in Scheme I.

Method A was the most frequently used procedure, since it is widely applicable for the variants Ar and R_1. Method B is particularly useful when R_1 is a complex heterocycle. The designation C in the tables refers to a separately described method of preparation. The amidoalkylamine

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