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β-Adrenergic Drugs: Analysis of Crystallographic and Theoretical Results

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SUMMARY

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Detailed crystallographic investigations of three chemically distinct families of drugs with β-adrenergic inhibiting activity have been compared with the results of PCILO calculations and three key features located. The presence of the same features in a β-adrenergic stimulating drug enables us to propose that they define the site responsible for binding to their receptor. In two recently synthesized compounds, the molecule folds in upon itself in order to preserve these features.

INTRODUCTION

Adrenergic receptors have been the subject of a number of recent studies in various parts of the world, with biologists trying to identify, isolate, and purify them. Pharmacologists have attempted to establish a quantitative relationship between adrenergic activity and structure (1–4).

Our aim is to approach the conformation of β-adrenergic receptors from an examination of drugs showing β-adrenergic activity. A model for these drugs has been established by the comparison of crystallographic (5–18) and theoretical studies (19).

COMPARATIVE RESULTS ON MOLECULAR STRUCTURES

Most of the drugs we have examined, which show activity toward β-adrenergic receptors, belong to two chemical families: PEA (phenylethanolamines)—salbutamol (β^+), pronethanol, dichloroisoproterenol, and sotalol (Fig. 1); and AOPA (aryloxypropanolamines)—bupranolol, oxprenolol, alprenolol, propranolol, penbutolol, pindolol, and timolol (Fig. 1).

Two original drugs (IPS 339 and IPS 345) were synthesized at the Institut de Pharmacologie de Strasbourg and have also been studied (20–22) (Fig. 2).

The molecular structures of these compounds found from single crystal X-ray diffraction measurements have been used to provide the geometrical input data for the calculation of conformational energy maps using the PCILO (perturbative configuration interaction using localized orbital) method (23–26). The same calculations were carried out by Pullman *et al.* (27) on some phenethylamines and related compounds with an α-adrenergic activity.

These molecules are most conveniently compared quantitatively in terms of the torsion angles defined in Table 1, since these angles allow the positions of different functional groups (N^+, OH, ϕ) to be defined accurately, giving a good representation of the active molecule (Fig. 3). Since in the AOPA family of molecules, τ_1 and τ_2 are always close to 0 and 180°, the only torsion angles which must be examined are those involving the asymmetric carbon atom, i.e., τ_3 and τ_4 for AOPA and τ_1 and τ_2 for PEA. Table 2 gives the values of torsion angles for each of the studied molecules.

PCILO calculations on the four PEA molecules give two interesting conformations (A and B) (Table 3). Only one (A) was found in the crystal structure, and the second one (B) differs in the sign of τ_1, the energy gap between the two solutions being less than 3 kcal/mol. The approximate value of τ_1 is 60° for A and 300° for B. For both A and B, τ_2 is about 180°.

In the case of the AOPA family, three stable conformations (A, B, and C) were computed (Table 4) and all have been found in actual crystal structures. The conformation with $\tau_1 \simeq 0°$ and $\tau_3 \simeq 60°$ always has the lowest energy; conformations A and B are identical to the A and B conformations for PEA.

(A) $\tau_3 \simeq 60°$, $\tau_4 \simeq 180°$.
(B) $\tau_3 \simeq 300°$, $\tau_4 \simeq 180°$.
(C) $\tau_3 \simeq 180°$, $\tau_4 \simeq 180°$.

Tables 1 to 4 make the point that these two classes of compounds probably exist in more than one conformation in solution, and the three determined conformations A, B, and C are the only ones possible.

A UNIFIED MODEL FOR β-BLOCKING AGENTS

Drugs in both the PEA and the AOPA families exist in

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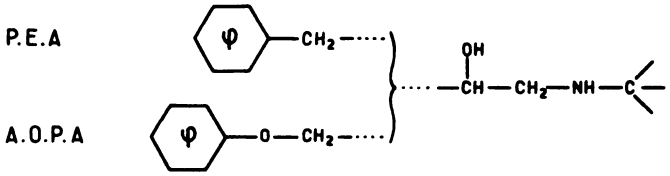

FIG. 1. *PEA and AOPA molecules*

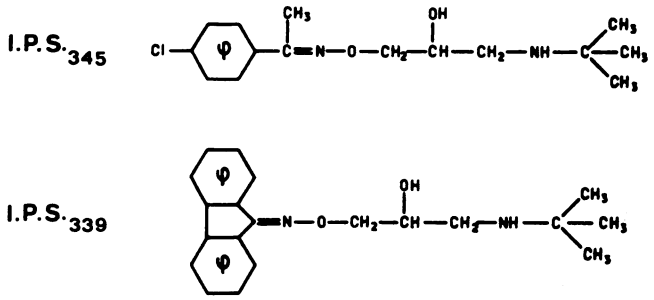

FIG. 2. *IPS molecules*

only three conformations, so we may present a unified model for these drugs.

Ammon *et al.* (28) suggested that conjugation between the aromatic ring and the extra —O—CH_2— group in AOPA molecules leads the side chain to simulate an aromatic ring. The crystallographic results confirm this, with τ_1 close to zero, so that the —O—CH_2— group is coplanar with the aromatic ring, and with C(1)–O(12) and O(12)–C(13) shorter than expected. Figure 4 shows the similarity between a PEA and an AOPA molecule in the same A or B conformation.

The π-electron system involves C(1)–O(12) and O(12)–C(13) for the AOPA drugs.

TABLE 1

Torsion angles used for the comparison of the molecules in the PEA and AOPA families

PEA

τ_1 = C(3)–C(4)–C(7)–C(9)
τ_2 = C(4)–C(7)–C(9)–N(10)

AOPA

τ_1 = C(2)–C(1)–O(12)–C(13)
τ_2 = C(1)–O(12)–C(13)–C(14)
τ_3 = O(12)–C(13)–C(14)–C(16)
τ_4 = C(13)–C(14)–C(16)–N(17)

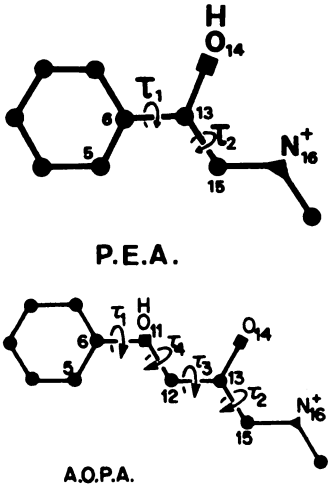

FIG. 3. *Torsion angles and positions of the three functional groups (N^+, OH, and ϕ) in PEA and AOPA molecules*

TABLE 2

Torsion angle values for each molecule in the PEA and AOPA families

Drugs	Torsion angle (°)			
	τ_1	τ_2	τ_3	τ_4
Pronethanol hydrochloride	65	168		
Sotalol hydrochloride	80	175		
Dichloroisoproterenol hydrochloride	100	175		
Dichloroisoproterenol free base	84	175		
Salbutamol[a] sulfate				
Molecule A	105	164		
Molecule B	101	171		
Penbutolol sulfate	341	184	183	171
Bupranolol hydrochloride	7	175	191	169
Oxprenolol chlorhydrate	15	178	304	184
Pindolol free base	4	198	184	178
Propranolol D hydrochloride	352	185	185	162
Propranolol D + L hydrochloride	6	175	302	184
Propranolol D + L free base	359	180	291	176
Timolol[a] maleate				
Molecule A	5	176	184	171
Molecule B	12	212	167	186
Acebutolol hydrochloride	17	176	56	177
Alprenolol hydrochloride	2	187	282	170

[a] Two independent molecules.

TABLE 3

Results of the PCILO calculations for PEA drugs

PEA	Conformation	τ_1 (°)		τ_2 (°)	
		Crystal	Free state	Crystal	Free state
Pronethanol hydrochloride	A	65	110	168	170
	B		300		180
Salbutamol free base	A	74	100	178	180
	B		280		180
Salbutamol sulfate	A	101	100	171	180
	B		280		180
Sotalol hydrochloride	A	79	100	175	180
	B		290		185
Dichloroisoproterenol hydrochloride	A	100	110	175	185
	B		290		185
Dichloroisoproterenol free base	A	84	110	176	185
	B		290		185

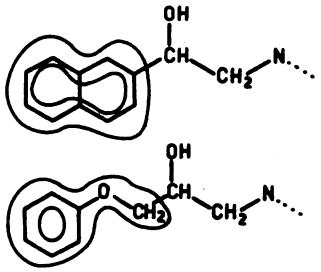

FIG. 4. *Similarity between a PEA and an AOPA molecule in the same conformation*

TABLE 4

Results of the PCILO calculations for AOPA drugs

AOPA	Conformation	τ_3 (°) Crystal	τ_3 (°) Free state	τ_4 (°), Crystal
Propranolol D hydrochloride	C	185	180	162
	A		55	162
	B		305	162
Propranolol D + L hydrochloride	B	302	305	184
	A		55	184
	C		180	184
Propranolol D + L free base	B	291	305	176
	A		55	176
	C		180	176
Pindolol free base	C	184	180	178
	A		60	178
	B		300	178
Bupranolol hydrochloride	C	191	180	169
	A		40	169
	B		300	169
Alprenolol hydrochloride	B	282	300	170
	A		60	170
	C		170	170
Penbutolol sulfate	C	183	180	171
	A		60	171
	B		310	171
Oxprenolol hydrochloride	B	304	300	184
	A		60	184
	C		170	184
Timolol maleate	C	184	180	171
	A		60	171
	B		300	171
Acebutolol hydrochloride	A	56	60	177
	B		300	177
	C		180	177

Due to difficulties in obtaining good single crystals of the IPS drugs, only two have been studied so far, but we are able to see some similarities to the AOPA drugs. The bond between the aromatic ring and the asymmetric carbon is shortened (Fig. 5) and the torsion angles show that the planar part of the molecule extends to C(13); Q_1 and Q_2 in IPS 339 and R_2 and R_3 in IPS 345 are close to zero, and R_1 is approximately 30°.

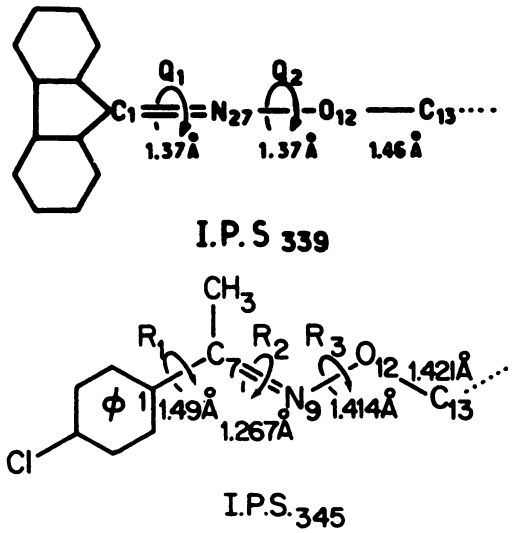

FIG. 5. *Interesting bond values in the IPS 339 and IPS 345 molecules*

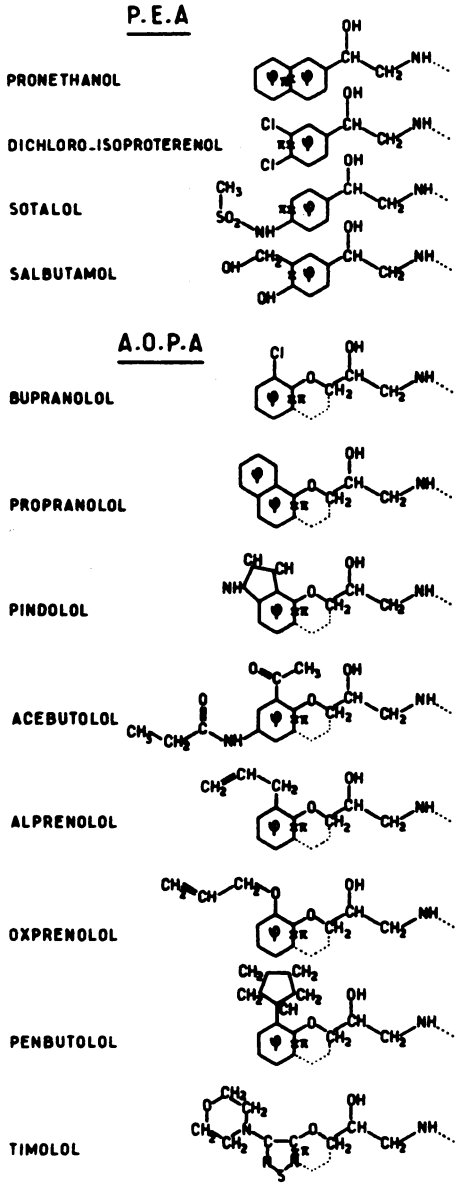

FIG. 6. *Introduction of the π point in each molecule*

For pronethanol it is easy to see that π is the center of the naphthalene ring. If we superimpose the side chains of all PEA, the π point must correspond to that of pronethanol. For the AOPA the correspondence arises from the simulation of an aromatic ring by the extra —O—CH_2— group.

$$Q_1 = 360°, \quad Q_2 = 175°.$$

$$R_1 = 30°, \quad R_2 = 183°, \quad R_3 = 184°.$$

Because there are too many torsion angles to be adjusted, PCILO calculations have not been made with the IPS drugs. However, using the experimental results, we are able to suggest some features involved in the activity of these drugs.

CONCLUSIONS

All the compounds with therapeutic activity have the (*l*) configuration, suggesting that the hydroxyl group on the asymmetric carbon is important; they all have the side-chain terminal nitrogen protonated. The planarity, and hence presumed electron delocalization, is also a

TABLE 5

Distances between the key features and φ angles in PEA drugs

PEA	Conformation	Distance (Å)			φ Angle (°)
		O–N⁺	N⁺–π	O–π	
Pronethanol	A	3.04	6.27	4.75	73
	B	2.90	6.30	4.49	28
Salbutamol	A	2.81	6.23	4.56	85
	B	2.81	6.17	4.93	33
Sotalol	A	2.92	6.18	4.73	73
	B	2.80	6.15	4.58	33
Dichloroisoproterenol	A	2.89	6.23	4.61	63
	B	2.80	6.15	4.92	28
Average	A	2.87	6.21	4.70	73
	B				30

TABLE 6

Distances between the key features and φ angles in AOPA drugs

AOPA	Conformation	Distance (Å)			φ Angle (°)
		O–N⁺	N⁺–π	O–π	
Propranolol	A	3.08	5.87	4.53	88
	B	3.08	5.80	4.92	27
	C	3.08	6.30	4.42	44
Pindolol	A	2.82	5.73	4.59	88
	B	2.82	5.96	4.95	17
	C	2.82	6.28	4.32	57
Bupranolol	A	3.00	5.94	4.52	68
	B	3.00	5.88	4.93	26
	C	3.00	6.31	4.49	60
Alprenolol	A	2.82	5.66	4.36	84
	B	2.82	5.64	4.97	26
	C	2.82	6.14	4.28	44
Penbutolol	A	2.95	5.90	4.52	89
	B	2.95	5.84	4.98	13
	C	2.95	6.32	4.43	32
Oxprenolol	A	2.78	5.90	4.38	84
	B	2.78	5.95	4.92	13
	C	2.78	6.27	4.42	40
Timolol	A	2.91	5.93	4.37	89
	B	2.91	5.81	4.83	25
	C	2.91	6.20	4.46	43
Acebutolol	A	2.81	5.97	4.52	82
	B	2.81	5.92	4.89	26
	C	2.81	6.35	4.54	43
Average	A	2.90	5.99	4.61	84
	B				22
	C				45

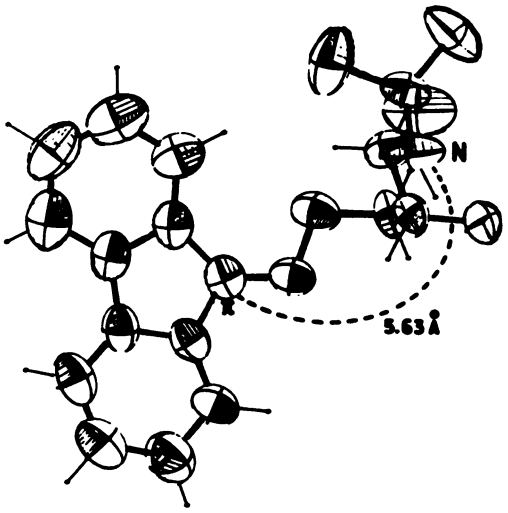

FIG. 7. *ORTEP view of the IPS 339 molecule*

prominent feature which has led us to define, for each molecule, a point π which is the "center of gravity" of the π electrons (Fig. 6). The distances between these three key features have been compared for each conformation A, B, and C (Tables 5 and 6) together with the angle φ between the best plane through the aromatic residue and the plane containing these key features.

Tables 5 and 6 show that the O–N⁺, N⁺–π, and O–π distances and φ angles for each conformation A, B, and C are similar for the PEA and AOPA compounds, thus confirming our belief that these features are necessary for the therapeutic activity. In particular, the N⁺–π dis-

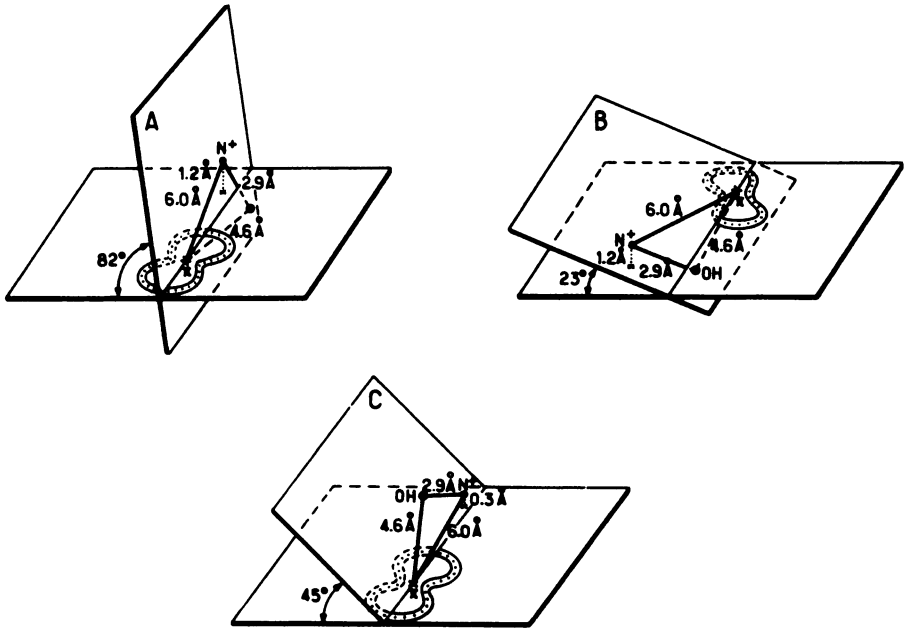

FIG. 8. *Unified model for β-blocking agents*

tance seems to be critical because the long side chain of the IPS molecules curls back on itself to preserve the N^+–π separation (Fig. 7).

Figure 8 shows our model of β-adrenergic drugs in the three conformations A, B, and C.

The β-stimulating drug salbutamol (14, 17) exhibits the same geometrical features as the β-inhibiting drugs. These common features will thus define the binding area of the substrate. Similarly, the parts of the molecules which cannot be changed without changing the mode of drug action must be responsible for the intrinsic activity. Comparison of salbutamol with the β inhibitors leads us to suggest that either or both of the hydroxyl and methanol functions on the phenyl ring are responsible for the β-stimulating action.

The PEA materials exist in two conformations (A and B) and the AOPA in three, two of which are similar to the PEA conformations. Materials existing in the third (C) conformation show the strongest drug activity. This leads us to suspect that there is a "best fit" between the substrate and molecules in the C conformation. With molecules in the A and B conformations, binding may not be so secure, due to deformation of the protein or the drug or to less satisfactory electronic interactions.

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