Geometry of quinidine-like antiarrhythmic drugs

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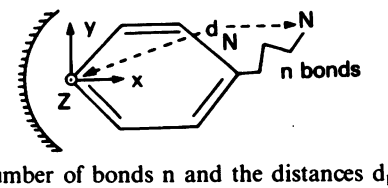
Antiarrhythmic drugs with quinidine-like action contain a wide variety of chemical groups. We have examined for similarities the available crystal-structure data. Data for the 2-*n*-propyl-4-anilino-1,2,3-benzotriazinium cation (I) and for the procaine cation in procaine penicillin monohydrate (II) were collected in our laboratory; other references are given in Table 1.

Two structural elements are believed important: a positively charged nitrogen and an aromatic ring (Petter & Engelmann, 1974). Atoms can be conveniently described in a coordinate system based on the aromatic ring:



The number of bonds n and the distances d_N vary considerably without evident correlation to activity. However, the coordinate x_N never exceeds 8.1 Å. If the ring touches the wall of a hydrophobic pocket, para substituents will push the whole molecule along +x. Such a CH_3 substituent is present in a promising member of the benzotriazinium series (French & Scott, 1978) with otherwise low x_N values, and an NH_2 group is tolerated in procaine with its moderate x_N. Large polar para substituents in practolol, INPEA, and sotalol would result in larger x_N values, and these antiarrhythmic drugs do not exhibit quinidine-like effects. There appears to be freedom in the y direction: single rings, ortho or meta substituents, and fused rings are all tolerated. The z_N coordinates span a fairly narrow range; CNDO-2 molecular orbital calculations for the benzotriaziniums suggest a smaller value at equilibrium than is tabulated. The presence of another heteroatom at a distance d_{NX} of ca. 3 Å from nitrogen appears to be helpful though not essential.

Table 1 Geometrical data from crystal structures (distances in Å)

Drug	*n*	d_N	x_N	z_N	d_{NX}	*Reference*
Quinidinium	3	6.51	6.25	1.81	2.84	(Carter, McPhail & Sim, 1967)
Diphenylhydantoin	3	5.93	5.64	1.29	2.31	(Camerman & Camerman, 1971)
Ajmaline (mol A)	4	6.61	6.07	0.77	3.25	(Prewo & Stezowski, 1978)
Ajmaline (mol B)	4	6.58	6.02	1.11	3.27	(Prewo & Stezowski, 1978)
N-*n*-Pr-*epi*-isoajmalinium	4	6.72	6.22	0.79	3.37	(Prewo & Stezowski, 1978)
(I)	4	6.04	5.03	2.52	3.46	—
Lignocaine·$(NO_2Ph)_2PO_4H$	4	7.49	7.23	1.67	2.85	(Yoo, Abola, Wood, Sax
Lignocaine·HA_5F_6	4	7.47	7.19	1.86	2.65	& Pletcher, 1975)
Alprenolol	5	8.17	8.09	0.87	2.93	(Barrans, Cotrait &
Propranolol	5	8.21	8.03	1.64	2.84	Dangomau, 1973)
Procaine·HCl	5	7.45	6.42	1.61	3.07	(Dexter, 1972)
(II)	5	7.62	6.72	2.39	3.20	—

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