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The Stereochemical Basis of Anticonvulsant Drug Action

III. The Structure of Procyclidine Hydrochloride

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SUMMARY

The crystal and molecular structure of procyclidine (α-cyclohexyl-α-phenyl-1-pyrrolidinepropanol) has been determined in order to investigate structural bases for its biological activity as an anticonvulsant drug. Crystals of procyclidine hydrochloride are monoclinic, space group $P2_1/c$, with cell dimensions $a = 5.891 \pm 0.006$, $b = 28.603 \pm 0.018$, $c = 11.314 \pm 0.004$ A, $\beta = 106.0$ degrees $\pm$ 15′, $Z = 4$ molecules/cell. The structure was determined by the symbolic addition procedure, utilizing data collected on an automated diffractometer (CuK_α radiation). Refinement was accomplished by an anisotropic full-matrix least-squares procedure, resulting in a final R value of 0.081.

Stereochemical features which the molecule has in common with other anticonvulsants, diphenylhydantoin and diazepam, and which may account for its anticonvulsant activity are analyzed and discussed.

INTRODUCTION

Procyclidine (α-cyclohexyl-α-phenyl-1-pyrrolidinepropanol) (Fig. 4) is an antiparkinsonism agent which has recently been shown to have clinical value as an anticonvulsant drug.

In laboratory trials procyclidine protected mice from maximal electroshock seizures, and in preliminary clinical tests with infants and children with generalized myoclonic spasms the drug demonstrated a degree of anticonvulsant activity against a seizure pattern usually refractory to conventional medications (1). This therapeutic efficacy, coupled with freedom from severe chronic toxicity, indicates that procyclidine may be a potentially valuable anticonvulsant agent for the treatment of epilepsy.

Widespread research on anticonvulsant drugs has led to numerous theories which ascribe their central nervous system activity to a variety of simple physicochemical properties (2), but none of these has satisfactorily accounted for the observed facts. We have determined the crystal and molecular structure of procyclidine hydrochloride as part of a program of investigation of the structures of anticonvulsant drugs in the hopes of discovering structural principles which will establish the relationships between the stereochemical features of these drugs and their anticonvulsant activities (3, 4).

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METHODS

Data collection. Crystals of procyclidine hydrochloride were obtained by slow evaporation of an ethanol–ethyl acetate solution, and are transparent needles elongated along a. The crystal data are given in Table 1.

The intensities were collected on an automated four-circle diffractometer (nickel-filtered copper radiation), and all independent reflections with 2θ (CuK_α) $\leqq$ 133 degrees (corresponding to a minimum interplanar spacing of 0.84 A) were measured. The moving-crystal moving-counter technique was employed (2θ scan), with stationary counts for background radiation on each side of the reflection. The crystal used was a needle mounted with the a^* axis parallel to the ϕ axis of the goniostat, and had a length of 0.8 mm parallel to a and a uniform cross-section of 0.06 mm perpendicular to a; absorption is fairly low and no corrections were applied. A total of 2524 reflections (of 3114 in the range collected) had intensities greater than the standard deviation of their measurements and were classified as being observed. Corrections were made for Lorentz and polarization factors, and structure amplitudes $|F|$ and normalized structure amplitudes $|E|$ were derived.

Structure determination. The phases of the structure amplitudes were determined by the symbolic addition procedure (5). Of 198 planes with $|E| > 1.9$, 181 had the index l = even, and only 17 were of the form l = odd; this immediately indicated that the chloride ion must be situated at $y = \frac{1}{4}$, as with that coordinate it contributes to the scattering from l = even planes only. This also indicated that since the l = odd reflections contributed to very few combinations in the $\sum 2$ relation and could not be used in the phase determinations, any electron density distribution calculated with the derived phases would necessarily contain a false mirror plane at $y = \frac{1}{4}$. In addition, the absence of l = odd reflections cuts the number of phases specifiable for origin determination to two instead of the usual three. Accordingly, phases for two origin-specifying planes were arbitrarily set as 0 degrees, and five more reflections were assigned symbolic values for their phases (Table 2). Several cycles of the $\sum 2$ formula, $s(E_h) \sim s \sum_k E_k E_{h-k}$ (where s means "sign of"), led ultimately to signs or symbolic phases (with probabilities of being correct $\geqq$ 0.98) for 345 reflections (all l = even) with $|E| \geqq 1.5$, with one of the symbols, a, being undetermined. Two E maps were therefore calculated; these had identical values of electron density, and differed from each other only by a translation in the crystal cell of $(a/2 + c/4)$. The chloride ion was easily identifiable as the largest peak on each map (at $y = \frac{1}{4}$ as expected), the phenyl ring was fairly well resolved, and although the rest of the molecule was unclear because of the false symmetry, it was possible, with the aid of models and imagination, to assign coordinates to the atoms of the cyclohexane ring, the central carbon atom (C_1), and the other 2 atoms attached to it. A Fourier summation, carried out using all the reflections with phases based

TABLE 1

Crystal data

Formula	$C_{19}NOH_{29}HCl$
Molecular weight	323.93
Crystal system	Monoclinic
a (A)	5.891 ± 0.006
b	28.603 ± 0.018
c	11.314 ± 0.004
β (deg.)	106.0 ± 0.25
Volume of unit cell (A^3)	1832.6
No. of molecules in cell	4
Calculated density (g/cm^3)	1.174
$F(000)$	704
Absorption coefficient, $\mu(CuK_\alpha)$ (cm^{-1})	18.1
Space group	$P2_1/c$

TABLE 2

Assigned phases and symbols

h			$E(h)$	$\phi(h)$
1	1	2	3.34	0
0	9	4	3.27	0
4	1	2	2.98	a
4	12	6	3.47	b
1	23	2	2.72	c
5	1	0	2.75	d
3	4	$\bar{1}0$	3.03	e

TABLE 3

Final positional parameters (fractional) and anisotropic thermal parameters ($\times 10^5$)

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl^-	0.3759	0.2500	0.1633	1682	168	713	52	38	56
C(1)	0.2016	0.1325	0.4702	1808	96	836	−38	319	−12
C(2)	0.1701	0.1100	0.3442	2406	89	765	50	222	−9
C(3)	−0.0221	0.0804	0.2955	3086	139	1054	−123	313	−63
C(4)	−0.0523	0.0599	0.1814	4220	146	1007	−93	50	−64
C(5)	0.1076	0.0665	0.1149	5100	140	782	128	197	−15
C(6)	0.2977	0.0963	0.1614	3989	209	825	183	567	18
C(7)	0.3277	0.1176	0.2758	2627	168	815	3	369	−6
O	0.4069	0.1619	0.4932	1860	122	993	−132	377	−34
C(8)	0.2386	0.0938	0.5712	2878	97	787	78	238	17
C(9)	0.2463	0.1128	0.6983	5968	144	822	297	688	51
C(10)	0.2861	0.0743	0.7969	7188	180	1032	305	999	93
C(11)	0.5104	0.0460	0.8012	6059	145	993	150	−24	29
C(12)	0.4984	0.0266	0.6743	6519	139	1217	391	134	50
C(13)	0.4618	0.0653	0.5780	4059	167	996	365	546	38
C(14)	−0.0115	0.1638	0.4685	1906	113	910	66	493	15
C(15)	−0.0501	0.2024	0.3718	2506	118	805	65	237	25
N	−0.0380	0.2493	0.4291	609	73	434	−7	133	16
C(16)	−0.2415	0.2607	0.4805	2476	134	842	36	775	29
C(17)	−0.2428	0.3136	0.4848	6318	147	1582	237	1724	3
C(18)	−0.0876	0.3307	0.4087	5798	133	1534	−1	1316	−3
C(19)	−0.0268	0.2889	0.3453	2810	133	880	15	525	38
H(3)	−0.144	0.077	0.345						
H(4)	−0.200	0.034	0.139						
H(5)	0.086	0.048	0.036						
H(6)	0.415	0.101	0.115						
H(7)	0.457	0.144	0.309						
H(O)	0.394	0.187	0.544						
H(8)	0.093	0.065	0.553						
H(9)	0.404	0.141	0.730						
H(9)	0.106	0.134	0.705						
H(10)	0.284	0.085	0.879						
H(10)	0.153	0.043	0.762						
H(11)	0.650	0.070	0.821						
H(11)	0.549	0.018	0.867						
H(12)	0.362	0.001	0.648						
H(12)	0.654	0.008	0.671						
H(13)	0.452	0.052	0.485						
H(13)	0.581	0.093	0.596						
H(14)	0.027	0.177	0.559						
H(14)	−0.145	0.141	0.454						
H(15)	−0.195	0.199	0.304						
H(15)	0.094	0.204	0.324						
H(N)	0.092	0.256	0.507						
H(16)	−0.216	0.245	0.560						
H(16)	−0.391	0.245	0.431						
H(17)	0.595	0.325	0.451						
H(17)	−0.187	0.323	0.575						
H(18)	0.111	0.339	0.479						
H(18)	−0.137	0.357	0.358						
H(19)	0.144	0.289	0.322						
H(19)	−0.150	0.285	0.262						
			Standard deviations						
Cl	0.0002	0.0000	0.0001	32	2	9	7	12	4
O	0.0004	0.0001	0.0003	97	5	31	16	41	10
N	0.0006	0.0001	0.0003	122	5	35	26	51	14
C[a]	0.0010	0.0002	0.0005	300	10	70	45	115	20
H[a]	0.009	0.002	0.004						

[a] Maximum values.

on these 16 atoms, clearly revealed the positions of the remaining 6 atoms.

Refinement of structure. The atomic coordinates and thermal parameters were refined by a full-matrix least-squares method, using a modified version of the ORLFS program (6). The function minimized was $\sum w(F_o - F_c)^2$, where w is inversely proportional to the estimated standard deviation of the observed intensity, and the atomic scattering factors were taken from "International Tables for X-ray Crystallography" (7). Two cycles of refinement with isotropic thermal parameters lowered R to 16.0%, and two anisotropic cycles resulted in R = 10.9%. The 31 hydrogen atoms were located from a succession of three three-dimensional difference Fourier syntheses, and were included in further refinement with the hydrogen atom positions allowed to vary but their thermal parameters held fixed at the values of the atoms to which they were bonded; the final R value was 0.081 for the observed reflections. The final atomic fractional coordinates and thermal parameters are given in Table 3, in which the anisotropic thermal parameters, β_{ij}, are the coefficients in the expression

$$\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{23}kl + 2\beta_{13}hl + 2\beta_{12}hk)]$$

Tables of the final observed and calculated structure factors are available from the authors on request.

RESULTS AND DISCUSSION

Figure 1 shows the conformation of the molecule. The phenyl ring is planar (maximum deviation of ring atoms from plane = 0.01 A), and the cyclohexyl ring is in the chair conformation. If one calculates the "best" least-squares plane through the 6 ring atoms of the cyclohexyl group (i.e., each atom of the ring deviates from this plane by ± 0.23 A alternately as we go around the ring), the angle between normals to this plane and to that of the phenyl group is 93 degrees. This value is similar to the angle of 90 degrees between the planes of the two phenyl groups of the anticonvulsant diphenylhydantoin (3).

The heterocyclic ring is puckered, but least-squares plane calculations through all

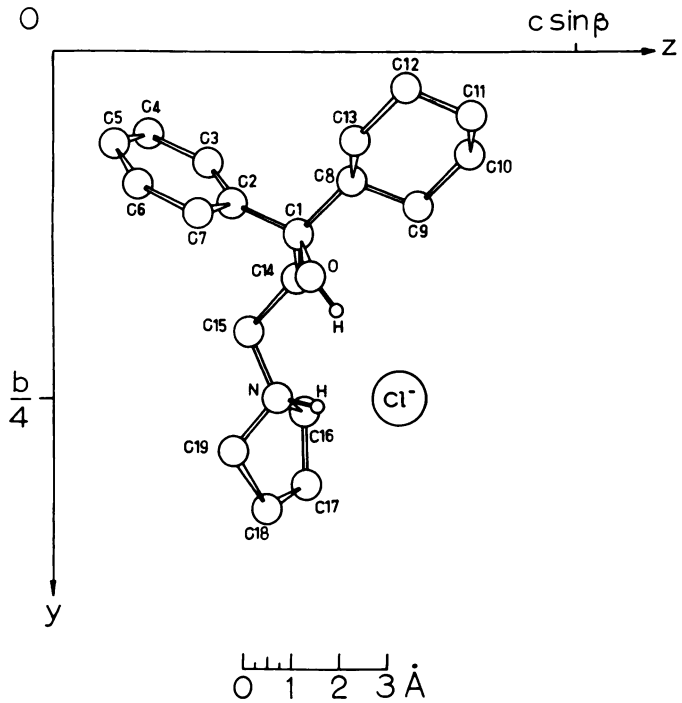


FIG. 1. *Perspective drawing of a molecule of procyclidine hydrochloride, viewed along [100]*

possible combinations of 4 atoms of the ring indicated that the 4 carbon atoms are relatively coplanar (maximum deviation = 0.05 A), with the nitrogen lying 0.51 A from this plane. The obtuse angles between normals to this plane and those of the phenyl ring and "best" cyclohexyl plane are 132 and 130 degrees, respectively; for comparison, the angles between the hydantoin ring and the two phenyl planes in diphenylhydantoin are 114 and 113 degrees.

The bond lengths and angles in procyclidine hydrochloride are shown in Fig. 2; the values are all near normal. The bond angles within the heterocyclic ring are shortened from tetrahedral values, probably because of steric requirements for ring formation. The exocyclic angles at the nitrogen atom are consequently increased, but the configuration at the nitrogen atom remains essentially tetrahedral. The carbon-carbon distances in the heterocyclic ring are somewhat shorter than expected for sp^3-sp^3 bonds; the lack of structural results for other compounds containing saturated 5-membered nitrogen heterocycles makes strict comparisons impossible at this time. The chloride ion is so situated that it forms hydrogen bonds with the hydrogen on the charged nitrogen and with the hydroxyl hydrogen ($N^+ \cdots Cl^-$ distance = 3.067 A, $O \cdots Cl^-$ distance = 3.206 A). The intermolecular separations correspond to normal van der Waals interactions.

Scale models constructed to fit the observed atomic positions (Fig. 3) show a high degree of similarity in the conformational structures of procyclidine, diphenylhydantoin, and diazepam. Similarities in the stereochemical features of the three anticonvulsants are especially striking in the following aspects. (a) The arrangement of two bulky hydrophobic groups with respect to each other (phenyl-phenyl, phenyl-chlorophenyl, and phenyl-cyclohexyl in diphenylhydantoin, diazepam, and procyclidine, respetively); models reveal that these groups have very similar space-filling characteristics and occupy similar areas of space in each compound. (*b*) When the models are superimposed so that these bulky groups approximate the same positions, all three molecules have an electron-donating group located in similar positions, between the two bulky groups: a ketonic oxygen in diphenylhydantoin, a trigonal nitrogen in diazepam,

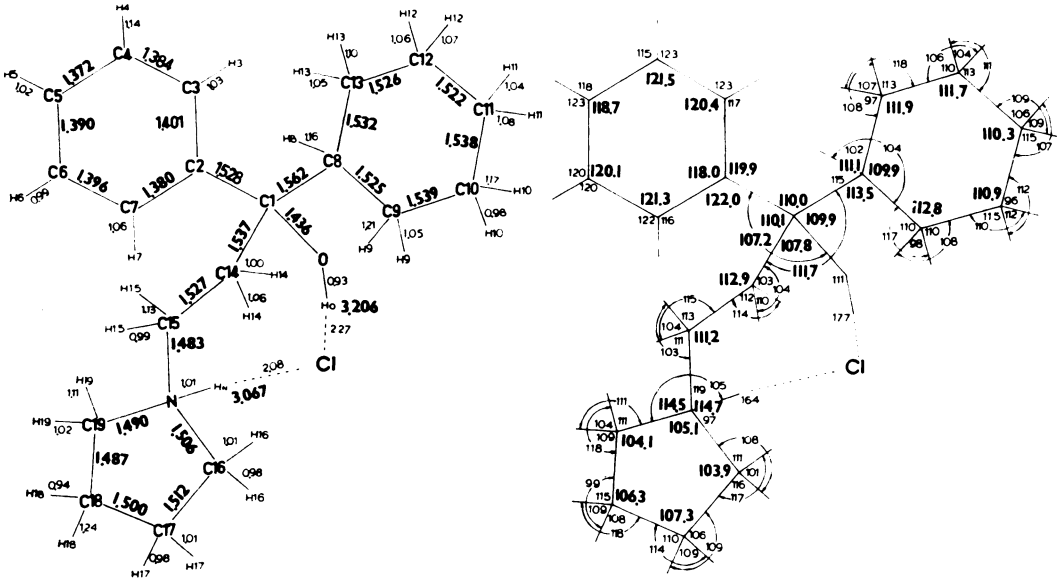


FIG. 2. *Bond distances (angstroms) and valency angles (degrees) in procyclidine hydrochloride*
Standard deviations are 0.006 A and 0.4 degree for bonds involving "heavy atoms," and 0.08 A and 3–5 degrees for bonds involving hydrogens.

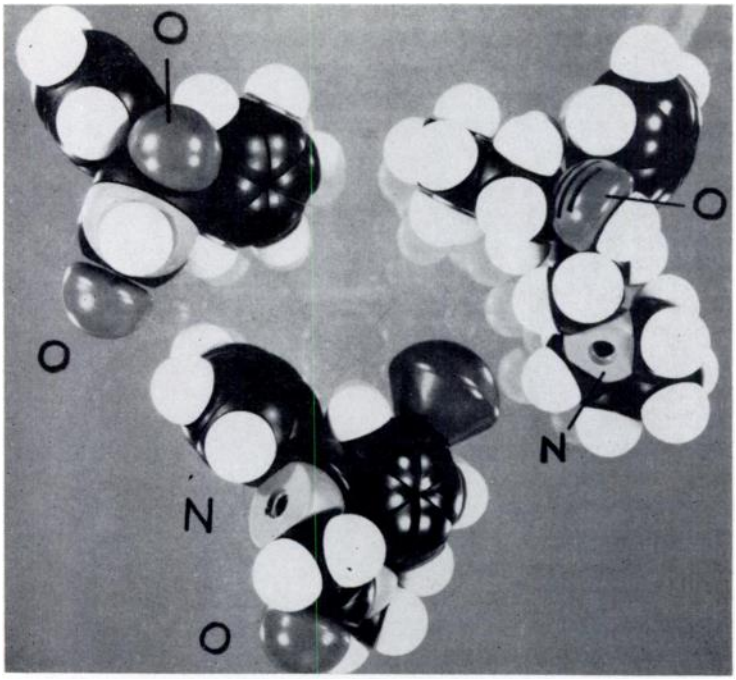


FIG. 3. *Photograph of space-filling models of diphenylhydantoin (left), diazepam (lower), and procyclidine (right)*

and the hydroxyl oxygen in procyclidine. (c) Another electron donor in each molecule also occupies a similar position in space: the second ketonic oxygen in diphenylhydantoin, a ketonic oxygen in diazepam, and the heterocyclic nitrogen of procyclidine. Distances beteen centroids of the phenyl and cyclohexyl rings and the electron-donating functional groups are listed in Table 4.

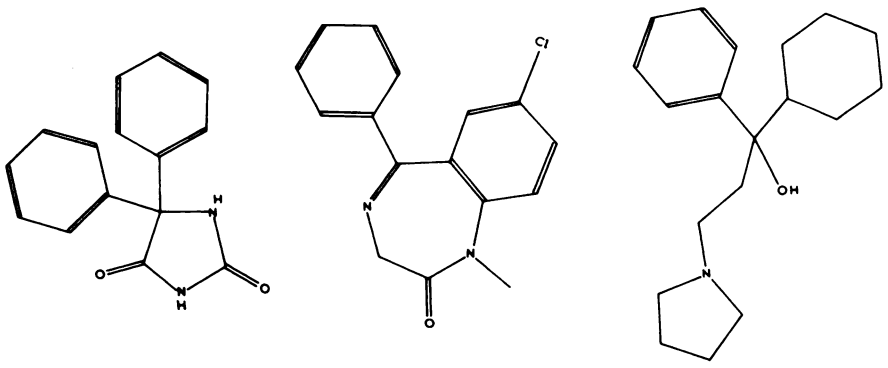
These three drugs, although chemically quite different (see Fig. 4), all possess high degrees of anticonvulsant activity; diphenylhydantoin and diazepam are clinically useful in the treatment of *grand mal* epilepsy, and the demonstrated ability of procyclidine to protect against maximal electrically and chemically induced seizures indicates that it is also potentially useful against this condition. It seems clear from our structural results that their similar anticonvulsant properties may be a result of their similar conformational features. How and why they act in the central nervous system to block seizures is not known, nor is the number or nature of the receptor sites for these agents established. Our results, however, indicate that a single class of receptor sites which accommodates the geometrical and stereochemical characteristics exhibited in common by these three drugs could be involved.

TABLE 4

Distances between ring centroids and electron-donating atoms in procyclidine hydrochloride

Functional groups	Distance
	Å
Phenyl-cyclohexyl	5.01
Nitrogen-cyclohexyl	6.07
Oxygen-phenyl	3.63
Nitrogen-phenyl	5.36
Oxygen-cyclohexyl	3.47
Oxygen-nitrogen	3.55

The search for antiepilepsy drugs has been directed, until now, along purely chemical avenues. We suggest that the seeking and testing of new therapeutic agents based on stereochemical similarities to present drugs may lead to greater progress in this field. This conformational approach may also be valuable in identifying receptor sites of anticonvulsant drugs, and thus in elucidating the mechanisms of seizures (8).



DPH DAZ PRO

FIG. 4. *Structural formulae of diphenylhydantoin (DPH), diazepam (DAZ), and procyclidine (PRO)*

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