Table VI. Hydrogen Bond Lengths and Angles

Bond A-H···B	Symmetry[a] code for B	Distance, Å A···B	Distance, Å A-H	Distance, Å H···B	Angle, deg A-H-B
N(1)-H···O(5′)	I	2.901	0.83	2.10	158
O(2′)-H···O(5′)	II	2.824	0.82	2.01	173
O(3′)-H···O(6)	III	2.884	0.74	2.17	162
O(5′)-H···N(7)	IV	2.772	0.84	1.96	165

[a] Symmetry code: I, $-1/2 + x$, $1/2 - y$, $-z$; II, $1 + x$, y, z; III, $1/2 - x$, $1 - y$, $1/2 + z$; IV, $1\,1/2 - x$, $1 - y$, $1/2 + z$.

dimethyl group plays a predominant role in stacking interactions.

Interactions between guanine derivatives in aqueous solution have been found to be unusually strong.[45-47] Hypochromism values from uv spectral studies and fluorescence and phosphorescence emission spectral studies on model dinucleoside compounds containing N^2-dimethylguanine or guanine or adenine linked to adenine or cytosine through a trimethylene bridge instead of the sugar–phosphate backbone indicate that the stacking interactions in solution between N^2-dimethylguanine and adenine or cytosine is greater than those between guanine and adenine or cytosine.[20] These results suggest that the intimate stacking observed in the crystal may also occur in solution and that the N(2) dimethyl group is implicated in the increased stacking. It should be pointed out that the stacking patterns observed in Figure 4 could serve as a reasonable model for the association of dimethylguanosine molecules in solution.

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The Stereochemical Basis of Anticonvulsant Drug Action. IV.[1a] The Crystal and Molecular Structure of Trihexyphenidyl[1b]

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Abstract: The molecular structure of trihexyphenidyl (α-cyclohexyl-α-phenyl-1-piperidinepropanol) has been elucidated as part of a series of conformational determinations of anticonvulsant drugs in order to investigate stereochemical bases for drug action. Crystals of trihexyphenidyl are monoclinic with cell dimensions $a = 31.059 \pm 0.004$, $b = 5.713 \pm 0.002$, and $c = 21.889 \pm 0.004$ Å; $\beta = 112.67 \pm 0.02°$; space group $C2/c$. Crystal data were collected on an automated diffractometer and the structure was solved by the symbolic addition procedure. Refinement was by least squares to an R value of 0.051. The molecule has stereochemical features in common with other anticonvulsants which have demonstrated clinical or laboratory efficacies against grand mal epilepsy. These stereochemical similarities are analyzed and discussed, and may account for the ability of chemically different drugs to block grand mal seizures.

Trihexyphenidyl (α-cyclohexyl-α-phenyl-1-piperidinepropanol) (I) is a pharmacological agent which has been widely used in the treatment of the symptoms of Parkinsonism. Its effects resemble those of atropine, and it is generally believed that it acts by blocking acetylcholine at certain cerebral synaptic sites.[3a] The potency of trihexyphenidyl and related drugs against nicotine-induced tremors and electroencephalographic abnormalities in animals has recently led to successful trials of the drug as an anticonvulsant,

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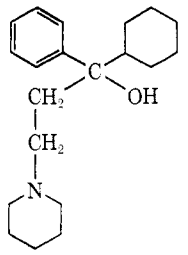

I

with some indications of efficacy against epileptic seizures which have been refractory to conventional medications.[3b]

Widespread research into anticonvulsant drugs has so far failed to lead to any satisfactory theory correlating chemical or physical properties of anticonvulsants with activity. Determinations of the crystal and molecular structures of diphenylhydantoin[4a] and diazepam,[4b] two clinically useful anticonvulsants for the treatment of grand mal epilepsy, have revealed that although the drugs are chemically unrelated they have striking stereochemical similarities.[5] These results have indicated a steric basis for anticonvulsant activity and point to a need for structural investigations of other effective agents to discover stereochemical principles of drug action. We have recently elucidated the molecular structure of procyclidine hydrochloride, an anti-Parkinsonism drug with anticonvulsant action, which is chemically dissimilar to both diphenylhydantoin and diazepam and found that it has stereochemical features in common with both.[6] Trihexyphenidyl resembles procyclidine chemically, but differs in anticonvulsant efficacy,[3b] and it is of interest to compare its three-dimensional structure with those of these other agents to ascertain (a) if the conformational features of procyclidine are maintained in trihexyphenidyl and are characteristic of this class of drugs, and (b) if differences in anticonvulsant potency between procyclidine and trihexyphenidyl can be correlated with stereochemical differences. Therefore, we have determined the conformational structure of trihexyphenidyl in order to compare it with the other agents and to seek relationships between structure and biological activity in the anticonvulsant drugs.

Experimental Section

Data Collection. Crystals of trihexyphenidyl were prepared by dissolving trihexyphenidyl hydrochloride in water, adding NaOH to attain a basic pH, and allowing the solution to slowly evaporate. Cell dimensions and space group information were obtained from Weissenberg photographs and diffractometer measurements, and crystal data are given in Table I. A lath-shaped crystal, approximately 0.12 × 0.25 × 0.5 mm, was used for data collection, and intensities were measured on a four-circle automated diffractometer (Ni-filtered Cu radiation) employing a $\theta/2\theta$ scan with stationary background counts on each side of the reflection. The intensities of all independent reflections with $0 < 2\theta$ (Cu Kα) $\leq 100°$ were recorded (preliminary photographs had revealed no significant intensity values at larger angles); of 1851 reflections in this range, 1665 had intensities above background greater than twice their standard deviations. These were classified as observed and were subsequently used in the structure refinement. Lorentz and polarization corrections were applied and structure amplitudes, $|F|$, and normalized structure amplitudes, $|E|$, were derived.

Table I. Crystal Data for Trihexyphenidyl

Formula	$C_{20}H_{31}NO$
Mol wt	302.47
Crystal system	Monoclinic
a, Å	31.059 ± 0.004
b, Å	5.713 ± 0.002
c, Å	21.889 ± 0.004
β, deg	112.67 ± 0.02
Volume of unit cell, Å^3	3583.7
Measured density, g cm^{-3}	1.113
No. of molecules in unit cell	8
Calculated density, g cm^{-3}	1.113
$F(000)$	1328
Absorption coefficient, μ (Cu Kα), cm^{-1}	5.2
Space group	$C2/c$

Structure Determination. The structure was elucidated by the symbolic addition procedure.[7] Two reflections were arbitrarily assigned phases of 0° in order to specify the cell origin, four additional reflections were assigned symbolic phases, and this set was then employed to obtain additional phase information *via* the $\Sigma 2$ formula

$$\text{sign of } E_h \sim \text{sign of } \sum_k E_k E_{h-k}$$

New phases were accepted only if their various contributors in the $\Sigma 2$ formula gave consistent indications of sign, and only if their probabilities were at least 0.98. Several cycles of application of the $\Sigma 2$ procedure led to signs or symbolic phases accepted for 199 reflections with $|E| \geq 1.9$; among the relationships indicated between the symbols by the $\Sigma 2$ results the most ubiquitous were $a = b = c = -$, and $d = +$. Accordingly, a three-dimensional Fourier map was computed, with the above choice of signs for the coefficient E values; all of the 22 nonhydrogen atoms were clearly visible in this map.

Refinement of the Structure. Refinement was carried out by full-matrix least squares, using a modified version of ORFLS.[8] The function minimized was $\Sigma w(|F_o| - |F_c|)^2$ with weights inversely proportional to the square of the standard deviations of the structure factors, and scattering factors were taken from the International Tables for X-Ray Crystallography.[9]

Two cycles of refinement with individual isotropic thermal parameters (R, all reflections, = 0.147) and two cycles with anisotropic thermal parameters (R = 0.123) were followed by calculation of a three-dimensional difference Fourier map, from which positions of all 31 hydrogen atoms were obtained. The hydrogens were assigned isotropic temperature factors B = 6.0 Å^2, and three cycles of least squares, varying everything but the hydrogen B values, resulted in a final discrepancy factor R (observed reflections only) = 0.051. Final coordinates and anisotropic thermal parameters are given in Table II, in which β_{ij} are coefficients in the expression

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

The final observed and calculated structure factors have been deposited in the microfilm edition of this volume of the journal.[10]

Results and Discussion

The conformation of the trihexyphenidyl molecule is shown in Figure 1. The phenyl ring is planar, with a maximum ring-atom deviation from the plane of 0.003

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(10) The final observed and calculated structure factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JACS-72-8553. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

Table II. 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}
C(1)	0.4102	0.2656	0.3326	114	1915	223	−57	61	−28
C(2)	0.3882	0.2801	0.2566	76	2284	239	10	56	−38
C(3)	0.3976	0.4699	0.2240	123	2753	244	−17	59	90
C(4)	0.3783	0.4820	0.1552	146	3624	281	72	71	184
C(5)	0.3496	0.3045	0.1181	126	4804	245	176	53	−20
C(6)	0.3401	0.1176	0.1502	117	4162	279	−96	46	−285
C(7)	0.3590	0.1027	0.2191	106	2972	275	−69	61	−131
C(8)	0.4643	0.2424	0.3553	96	2696	193	−52	49	−80
C(9)	0.4903	0.2524	0.4305	118	4882	232	31	37	−254
C(10)	0.5431	0.2202	0.4513	119	6314	271	−16	16	−266
C(11)	0.5544	−0.0080	0.4242	112	5714	268	159	39	36
C(12)	0.5298	−0.0144	0.3488	110	5115	261	102	63	−50
C(13)	0.4764	0.0159	0.3289	96	3446	237	67	48	−178
O	0.3945	0.0587	0.3555	125	1936	302	−40	100	77
C(14)	0.3966	0.4817	0.3635	143	1954	328	−35	116	−150
C(15)	0.3434	0.5096	0.3423	140	2542	345	80	125	152
N	0.3235	0.3180	0.3689	105	2845	211	65	58	29
C(16)	0.3329	0.3511	0.4395	134	4414	196	−84	59	−54
C(17)	0.3161	0.1408	0.4663	119	5437	242	−72	59	228
C(18)	0.2635	0.1040	0.4282	123	5867	278	−68	72	215
C(19)	0.2531	0.0891	0.3545	116	5033	303	−115	60	−11
C(20)	0.2724	0.2992	0.3309	103	4746	223	55	41	90

Atom	x	y	z	Atom	x	y	z
H(3)	0.418	0.615	0.252	H(13)	0.465	−0.128	0.348
H(4)	0.387	0.627	0.130	H(O)	0.365	0.097	0.363
H(5)	0.337	0.316	0.067	H(14)	0.413	0.470	0.419
H(6)	0.319	−0.021	0.122	H(14)	0.408	0.624	0.351
H(7)	0.353	−0.042	0.243	H(15)	0.339	0.680	0.360
H(8)	0.475	0.389	0.335	H(15)	0.325	0.507	0.288
H(9)	0.486	0.412	0.445	H(16)	0.368	0.368	0.467
H(9)	0.476	0.121	0.453	G(16)	0.317	0.508	0.448
H(10)	0.556	0.223	0.503	H(17)	0.335	−0.021	0.463
H(10)	0.558	0.360	0.431	H(17)	0.323	0.178	0.514
H(11)	0.543	−0.153	0.449	H(18)	0.252	−0.047	0.448
H(11)	0.592	−0.028	0.434	H(18)	0.244	0.245	0.440
H(12)	0.537	−0.175	0.329	H(19)	0.219	0.089	0.325
H(12)	0.541	0.126	0.325	H(19)	0.268	−0.067	0.347
H(13)	0.460	0.010	0.278	H(20)	0.269	0.272	0.282
				H(20)	0.254	0.470	0.335

Å, and a deviation of 0.02 Å for atom C(1). The cyclohexyl ring is in the chair conformation, with the ring atoms lying at distances of 0.22–0.25 Å alternately above and below the "best plane" through all six cyclohexyl carbons as one progresses around the ring. The angle between normals to this "best plane" and that of the phenyl group is 96°, as compared to 93° between similar groups in procyclidine hydrochloride[6] and 90° between the two phenyl rings in the anticonvulsant diphenylhydantoin.[4a] The nitrogen heterocycle is also in the chair conformation, with ring atoms lying alternately ±0.22–0.26 Å above and below a mean plane through all six atoms. The normal to this mean plane makes obtuse angles of 152 and 106° with normals to the plane of the phenyl ring and to the mean plane through the cyclohexyl group, respectively.

The bond lengths and angles in trihexyphenidyl are shown in Figure 2. The values are all near normal; the average of the aromatic carbon bond lengths and angles is 1.388 Å and 120.0°, and the sp^3 carbons have interatomic distances and angles averaging 1.534 Å and 110.6°. The nitrogen atom in the saturated six-membered heterocyclic ring displays a tetrahedral configuration with its lone pair of electrons in an sp^3 orbital; the protonated nitrogen in the saturated five-membered heterocyclic ring in procyclidine hydrochloride also exhibits a tetrahedral configuration; thus no significant change in the heterocyclic nitrogen atom configuration occurs upon protonation in these compounds. There is an intramolecular hydrogen bond between the hydroxyl group and the heterocyclic nitrogen in trihexyphenidyl; the hydrogen–nitrogen

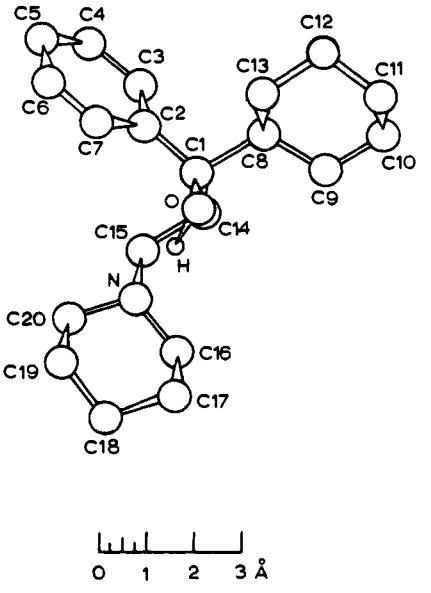

Figure 1. Perspective drawing of one molecule of trihexyphenidyl, viewed along [010].

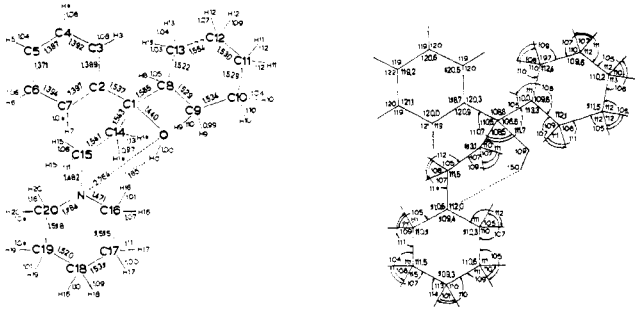

Figure 2. Bond distances (ångströms) and valency angles (degrees) in trihexyphenidyl. Estimated standard deviations are 0.005 Å and 0.4° for bonds and angles involving nonhydrogen atoms, and 0.06 Å and 2–4° for bonds and angles involving hydrogens.

separation is 1.85 Å, and the O–H···N angle is 150° (a value closer to linearity is prevented by the geometry of the molecule and the intramolecular nature of the contact). The intermolecular distances correspond to normal van der Waals interactions.

It is of interest to compare the structural features of trihexyphenidyl with those of the other anticonvulsants examined thus far: diphenylhydantoin, diazepam, and procyclidine. A study of scale models constructed to fit the observed atomic positions reveals that those stereochemical features found to be similar in these anticonvulsants are also present in trihexyphenidyl. Like the others, trihexyphenidyl has two bulky hydrophobic groups at approximately right angles (96° *vs.* 90, 124, and 93° in diphenylhydantoin, diazepam, and procyclidine, respectively) with an electron donor (OH) situated between the two rings. Again, like the other drugs, trihexyphenidyl has a second electron donor (the heterocyclic nitrogen) lying below and behind the molecule from the first, although the separation of the two electron-donating atoms is somewhat less in trihexyphenidyl than in the other pharmaceuticals (2.764 *vs.* 3.4–4.6 Å) because of the intramolecular hydrogen bonding. As mentioned above, this hydrogen bond is nonlinear (N···H–O angle = 150°) and possibly could be disrupted by the approach to a receptor site bearing a geometrically more favorable arrangement for hydrogen bonding, causing somewhat of a greater separation of the two electron donors in trihexyphenidyl. (Alternatively, if the nitrogen is protonated *in vivo*, then we would expect the hydrogen-bonding scheme present in the free base to be altered and an enlarged separation to occur between the nitrogen and oxygen atoms.) Distances between centroids of the phenyl and cyclohexyl rings and the electron-donating functional groups are listed in Table III.

Table III. Distances (Å) between Ring Centroids and Electron-Donating Atoms in Trihexyphenidyl

	Å
Cyclohexyl–phenyl	4.99
Cyclohexyl–nitrogen	5.75
Cyclohexyl–oxygen	3.39
Phenyl–nitrogen	4.69
Phenyl–oxygen	3.70
Nitrogen–oxygen	2.76

Trihexyphenidyl and procyclidine differ chemically only in the occurrence of a six-membered nitrogen heterocycle in the former *vs.* a five-membered nitrogen heterocycle in the latter. In laboratory trials of potency of the drugs against electroshock-induced seizures in mice, the anticonvulsant ED_{50} doses required and the minimum time for protection were significantly smaller for procyclidine.[3b] Though one cannot rule out chemical or physical reasons for this difference in potency, *e.g.*, differences in solubility, metabolism rates, etc., the great chemical similarity of these two agents minimizes these possibilities. If stereochemical differences play the dominant role in the differing efficacies, then the conformational differences of the two heterocyclic rings must of course be the major factor. Procyclidine was studied structurally as the hydrochloride, in which form the heterocyclic nitrogen is protonated, and trihexyphenidyl was studied as the free molecule; from these results we can by simple analogy deduce the orientations of the nitrogen containing rings in the two drugs in the absence or presence of intramolecular O–H···N hydrogen bonding. Examination of the scale models shows that in *both* cases the nitrogen in trihexyphenidyl is considerably more buried within the molecule than is the case with procyclidine. The heterocycle in trihexyphenidyl is in the chair conformation, while that in procyclidine (with the nitrogen protonated) is best described as a planar arrangement of the carbons, with the nitrogen out of this plane; this latter conformation leaves the nitrogen well exposed, while the chair conformation in trihexyphenidyl results in steric shielding of the nitrogen by axial hydrogens, and restricts the ease with which the nitrogen may form intermolecular contacts. Since the presence of an electron donor in this position is one of the stereochemical similarities among the anticonvulsants we have studied, and is probably essential for receptor binding, the steric inhibition of the nitrogen in trihexyphenidyl could well account for the greater drug potency of procyclidine.

The stereochemical features determined to be common to the other anticonvulsants we have studied are maintained in trihexyphenidyl. The conformational structure of trihexyphenidyl is very similar to that observed for procyclidine, and we may conclude that it is likely the favored one for this type of chemical agent. These results therefore reinforce our conclusions that the drugs we have studied so far derive their anticonvulsant efficacies against grand mal seizures from their similar stereochemical characteristics, and that a single class of receptor sites accommodating these common features could be involved.

These conclusions are dependent, of course, on the premise that it is possible for these drugs to adopt conformations at the receptor sites in which the stereochemical similarities present in the solid state conformations of each are maintained. The evidence that this is possible is very extensive; to give just one example pertinent to our studies on anticonvulsants, it has been shown by protein-binding studies[11] that the stereochemical features common to diphenylhydantoin and diazepam[5] in their crystal structures are maintained under physiological conditions.

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