Conformational Analysis of Clinically Active Anticonvulsant Drugs

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A series of ureides active against grand mal epilepsy have been studied by using classical potential energy calculations. The series includes phenyl ethyl and diphenyl derivatives of hydantoins, succinimides, glutarimides, oxazolidine-2,4-diones, pyrimidine-2,6-diones, barbituric acids, and phenacemide. A thorough examination of the conformational possibilities did not reveal an exclusive conformation that could account for their activity. However, comparisons with diazepam and other benzodiazepines known to have the ability to competitively bind with drugs such as diphenylhydantoin at some sites show that there is a distinct conformational preference that may well account for their activity against grand mal epilepsy. The conformational studies led to the proposal of a general model for anticonvulsant activity comprising two aromatic rings or their equivalent in a favored orientation and a third region, usually a cyclic ureide, comprising a number of hydrogen-bond-forming functional groups. The specific placement of hydrogen-bonding groups in this region appears to be of less importance than the correct conformational arrangement of the hydrophobic elements.

Introduction

Drugs clinically active against tonic-clonic (grand mal) epilepsy include phenytoin, phenobarbitone, primidone, clonazepam, diazepam, valproic acid, acetazolamide, and some γ-aminobutyric acid (GABA) analogues.[1-3] Some of these drugs (such as the little used acetazolamide, which is a carbonic anhydrase inhibitor[2]) have specific modes of action, but others have not yet been linked with a specific binding site within the brain. As shown in Figure 1, however, those derived from hydantoins, oxazolidinediones, succinimides, and glutarimides do have important structural similarities. The most common structural elements appear to be a nitrogen heteroatomic system, usually a cyclic imide, and at least one carbonyl group. Compounds active against maximal electroshock (MES), the experimental model used for tonic-clonic epilepsy, also have at least one phenyl group and either another phenyl ring or an alkyl substituent attached to the heteroatomic system. Dialkyl-substituted cyclic ureides show activity[2] against absence seizures.

In addition to various structural elements, several physicochemical properties, including molecular dipole moment and partition coefficient, have been associated with anticonvulsant action,[4-6] but these are now thought to be primarily related to the ability of the drug to pass through the blood–brain barrier[2] in order to reach the site of action. Hydrogen bonding has been shown by theoretical[7] and experimental[8] studies to be necessary for activity, but there does not appear to be any correlation between the strength of hydrogen bonding and the type or extent of anticonvulsant action,[7,8] nor did molecular orbital calculations on a range of anticonvulsants and convulsants reveal any significant correlation between the electronic indices and either activity. Electrostatic potential calculations[9] on selected conformations of anticonvulsants suggested that the two minima on the potential surface, usually associated with the imide oxygens of diphenylhydantoin, were common to most of the drugs studied, indicating a major role for both these hydrogen-bond acceptors in binding. Subsequent structural modifications to diphenylhydantoin[10] and monophenylhydantoin[11] derivatives, however, revealed that replacing either of these oxygens with a methylene group results in a relatively slight reduction in anticonvulsant activity against MES. These and other structure–activity relationship data[2] make it difficult to assign a major role in anticonvulsant activity to any specific hydrogen-bonding group.

Binding studies indicate that several of the compounds in Figure 1 bind at sites within the GABA/benzodiazepine receptor–ionophore complex, though whether they all bind at exactly the same site is still not clear.[12-23] For diphenylhydantoin in particular, there is contradictory evidence as to whether it is capable of binding to the benzodiazepine binding site.[22-25] However, both diazepam and diphenylhydantoin have been shown to bind competitively against thyroxine at the thyroxine binding site,[26] showing

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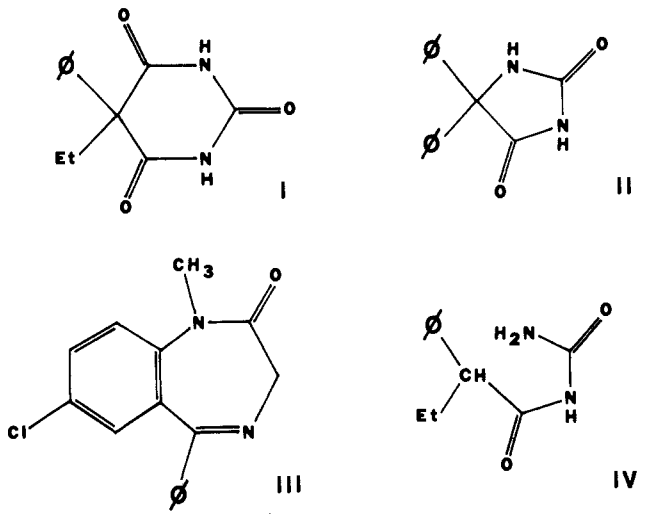

Figure 1. Representative anticonvulsant drugs showing activity against electroshock seizures: (I) phenobarbitone, (II) phenytoin, (III) diazepam, (IV) pheneturide. Compounds showing this type of anticonvulsant activity are likely to have clinical use in the treatment of tonic-clonic (grand mal) epilepsy.

that they do have sufficient structural similarity to bind at the same site in some instances. The sure identification of which binding sites are involved with anticonvulsant activity is difficult, especially as most anticonvulsant drugs interact with more than one receptor. Although saturatable binding sites have been found for several antiepileptic drugs, the binding levels at those sites do not always correlate well with the drug concentrations in the brain necessary for therapeutic action;[2] a significant proportion of the total drug concentration is usually bound to nonspecific membrane and soluble protein components, with the free concentration available for receptor binding being low. As all the antiepileptic drugs tested so far have relatively high levels of apparently nonspecific binding, this may conceivably include binding at the actual active site. It thus remains possible, but not proven, that the drugs shown in Figure 1 have a common receptor site for their antiepileptic activity. The fact that many of these compounds are structurally very similar tends to support this possibility.

Stereoisomeric data[27] also provide support for the existence of structurally specific receptors. Nirvanol, methoin, glutethimide, and pheneturide all show small but significant stereoisomeric differences in activity,[28-34] though data concerning enantiomeric activity against various test models for epilepsy are scarce. The largest enantiomeric difference against MES is shown by nirvanol, with the more potent (−) isomer being assigned the *R* configuration[35,36] by chemical correlation with *N*-(chloroacetyl)-isovaline, for which the absolute configuration has been determined by X-ray crystallography.[36] Interestingly, the (+) isomer is more active against pentylenetetrazole-induced seizures, the test used for antiabsence–seizure activity. For methoin, of which nirvanol is the N1-demethylated metabolite, the *S*-(+) isomer is more active against MES.[32,37] These results appear to be conflicting and should be retested by more accurate and modern methods. Tests on the activities of enantiomers of other anticonvulsant cyclic ureides are on sedative, hypnotic, and related properties.[32] However, it has been shown that these pharmacological actions are separable from the anticonvulsant action shown by these drugs, so that such enantiomeric differences as are seen for these properties do not necessarily give an accurate idea of which is the more active anticonvulsant enantiomer.

Pfeiffer's generalization[38] on the relationship between the potency and pharmacological effects of enantiomers binding at structurally specific receptors states that the more potent the drug, the greater the stereoisomeric difference. For anticonvulsant drugs in clinical use the differences between the enantiomers are not large. This implies that the specificity of the more active isomers for the target receptor is not as great as it might be and that more potent and specific anticonvulsant drugs could therefore be developed. On the other hand, the fact that the few enantiomeric activity differences available for anticonvulsants are of the order expected from Pfeiffer's generalization for drugs of their potency reinforces the view that these anticonvulsants are binding at stereospecific receptors.[32]

Provided the right chemical groups are present in the correct spatial configuration for binding, molecular conformation seems to be the most likely factor influencing the activity of these compounds. Camerman and Camerman[39-47] have suggested, on the basis of X-ray crystallographic studies, that molecular conformation is a key factor in the therapeutic activity of a number of anticonvulsant drugs although they are not closely related chemically. This approach is promising but restricted, as the crystal structure gives only one low-energy conformation of each molecule, although several alternate conformations of as low or even lower energy may exist in solution. Theoretical calculations have therefore been carried out to identify all low-energy conformations that could conceivably be involved in binding at the receptor. These conformations are then compared with those found in the

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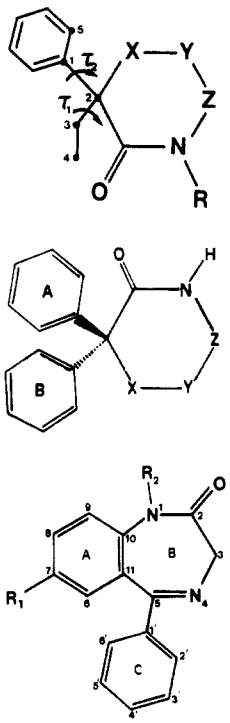
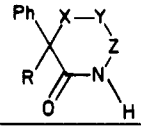


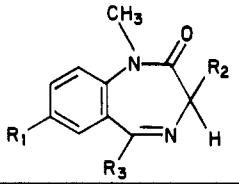
Figure 2. (Top) The definition of torsion angles used in conformational energy calculations: $\tau_1 = \tau(C1–C2–C3–C4)$; $\tau_2 = \tau(C3–C2–C1–C5)$. (Center) The definition of A and B rings in the cyclic ureides. Ring A has arbitrarily been defined as the ring coming out of the plane of the paper when the cyclic ureide is oriented as shown. Ring A is pro-*S* and ring B pro-*R*. (Bottom) The atom-numbering system and ring definition used in benzodiazepine systems.

solid state by X-ray crystallography[48–58] and those found in solution by NMR[59–61] and by previous calculations.[62–65]

Table I. Chemical Structure of Anticonvulsant Drugs Studied



compd		X	Y	Z	R
5-phenyl-5-ethylbarbituric acid	PEB	C=O	NH	C=O	Et
5-phenyl-5-ethylhydantoin	PEH	...	NH	C=O	Et
5-phenyl-5-ethyloxazolidine-2,4-dione	PEO	...	O	C=O	Et
3-phenyl-3-ethylsuccinimide	PES	...	CH_2	C=O	Et
3-phenyl-3-ethylglutarimide	PEG	CH_2	CH_2	C=O	Et
5-phenyl-5-ethylpyrimidine-4,6-dione	PEP	C=O	NH	CH_2	Et
5,5-diphenylbarbituric acid	PPB	C=O	NH	C=O	Ph
5,5-diphenylhydantoin	PPH	...	NH	C=O	Ph
5,5-diphenyloxazolidine-2,4-dione	PPO	...	O	C=O	Ph
5,5-diphenylsuccinimide	PPS	...	CH_2	C=O	Ph
(phenylethylacetyl)urea	PEA	H[a]	NH_2	C=O	Et
(diphenylacetyl)urea	PPA	H[a]	NH_2	C=O	Ph



compd	R_1	R_2	R_3
diazepam	Cl	H	phenyl
RO 11-6896	NO_2	CH_3	2′-fluorophenyl

[a] Alicyclic compound.

As a result of this, a new structure–activity relationship is proposed taking into account the therapeutic activities of drugs in clinical use.

Method

Conformational energies were calculated by using CONES (a three-torsion-angle version of the program COMOL[66]), on the Cyber 73 computer at the Royal Melbourne Institute of Technology. The program calculates classical conformational energies by pairwise summation of the van der Waals interactions between nonbonded atoms, together with the electrostatic and torsion potentials. The parameterization used was based on a series of amide and hydrocarbon structures[67] and gives results consistent with those obtained from semiempirical molecular orbital calculations.[68]

A minimum of two variable torsion angles has been taken into account for each compound studied. The torsion angles used are defined in Figure 2. Each torsion angle was varied, in 5° increments through 360°, to give a complete conformational energy picture for each molecule. In the noncyclic analogues, the acetylureas, there is a third torsion angle that was varied in steps of 30°. Low-energy conformations (all conformations within 10 kcal mol^{-1} of the global minimum) and high-energy conformations (>50 kcal mol^{-1}) were then compared throughout the set of anticonvulsants and related compounds.

The program HAYSTACK was used on a PDP 11/34 computer to ascertain which molecular conformations gave a reasonable fit to proposed geometric models. In this program each model is defined in terms of the distances

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Table II. Torsion Angles and Relative Energies of Anticonvulsant Energy Minima Conformations

compd	conformn 1			conformn 2		
	τ_1	τ_2	ΔE^a	τ_1	τ_2	ΔE^b
PEB	170	35	0	315	135	7
	40	50		190	155	0
PEH	55	50	1	190	115	2
	170	50	0	305	115	
PEO	50	50	2	185	110	0
	170	35	1	300	110	0
PES	165	30	0	300	160	9
	50	50	1			
PEG Ph ax	50	90	3	185	120	0
				330	120	0
PEG Ph eq	50	30	0	305	135	4
PEP Ph ax	50	70	2	320	105	0
PEP Ph eq	180	90	6	300	160	0
	60	20	0			
PPB	35	35	0	145	145	0
PPH	45	40	0	140	135	0
PPO	30	60	0	125	150	0
PPS	20	50	0	130	160	0

[a] Torsion angles for phenyl ethyl and diphenyl derivatives are τ_1 = τ C(1)-C(2)-C(3)-C(4) and τ_2 = τ C(3)-C(2)-C(1)-C(5). [b] ΔE is the energy difference between the global minimum and the local minimum.

between points in an extended drug molecule that includes dummy atoms built on as receptor points or alignment guides, ring centroids, etc. The conformation of a molecule, including points to be matched to the model, is then varied in a systematic manner through a specified range with a specified step size. Variables (up to 10) include torsion angles, bond angles, and bond lengths. The program reports the number of conformations that fit the model and the number of conformations that both fit the model and pass a test indicating that all nonbonded atoms are separated by more than the sum of their van der Waals radii. It also reports the conformations with the best and worst fit, the maximum and minimum separation between each target and guide pair, and the root-mean-square (RMS) difference between the desired and measured distances for each target guide pair.

Molecular geometries used for these calculations were based on molecular structure reports on barbiturates,[53-55,69-71] hydantoins,[45,49,56,72-76] oxazolidinedione,[77] succinimides,[78-84] glutarimides,[85-89] primidone,[52] benzodiazepines,[37,90-93] and triazolobenzodiazepines.[91-94] Standard geometries were used for aromatic and aliphatic

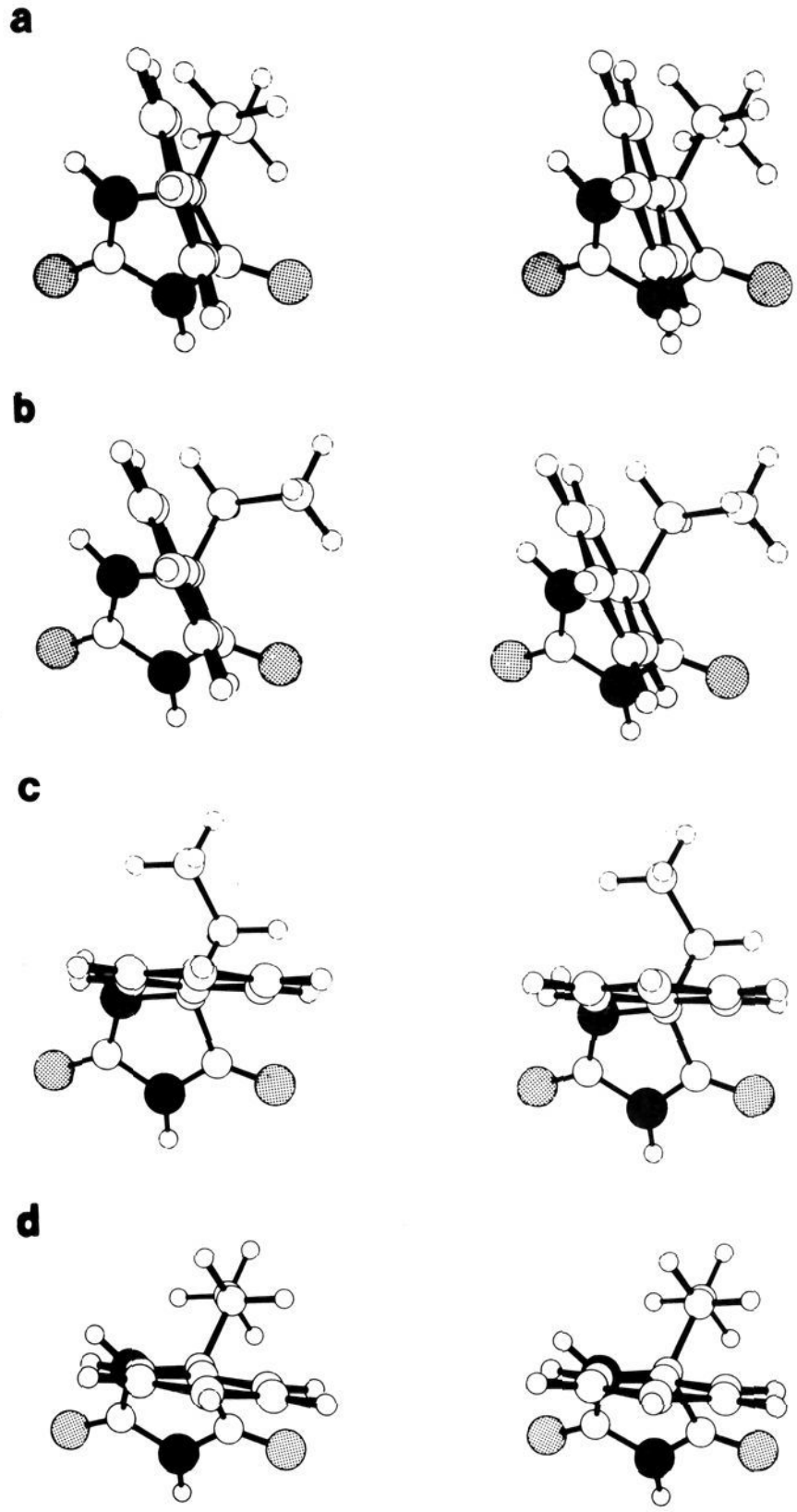

Figure 3. Stereoscopic views of the minimum energy conformations of phenylethylhydantoin. There are essentially two sorts of low-energy conformation of the phenyl ethyl cyclic ureides. Conformations a and b have the phenyl group oriented toward the carbonyl of the ureide ring, while conformations c and d have the phenyl group oriented toward the nitrogen (or analogous atom in the other ureides) of phenylethylhydantoin. Both low-energy conformations are found in conjunction with two ethyl group rotamers.

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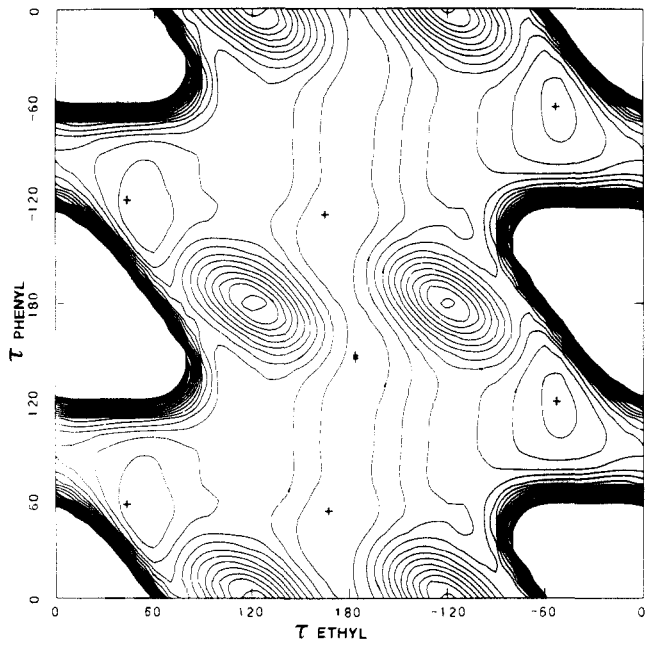

Figure 4. A typical conformational energy contour map of a phenyl ethyl cyclic ureide. This particular map is of phenylethylhydantoin. The x axis represents the ethyl group rotation (τ_1) and the y axis the phenyl group rotation (τ_2). Energy minima are marked +. The crystal structure conformation of methoin is marked ‡. The minima are at approximately 60°,60° and 300°,120°.

substituents.[95,96] Calculations were also carried out on the actual crystal structures of known antiepileptics and on geometries that included deviations from heterocyclic ring planarity in barbiturates, hydantoins, succinimides, and oxazolidinediones.

Results and Discussion

The compounds studied are shown in Table I. The values of the torsion angles giving minimum energy conformations are shown in Table II.

Phenylethyl Derivatives. Examination of lowest energy conformations of the phenyl ethyl substituted heterocycles found from the energy calculations showed two main types of conformations. The first type has the phenyl group oriented toward the adjacent carbonyl group. Here, the torsion angle of the phenyl ring is in the range of 30–90°, with the majority of torsion angles lying between 35 and 50°. The second type has the plane of the phenyl ring oriented toward the other side of the heterocyclic ring, where most of the phenyl ring torsion angles are in the range 110–135°. The ethyl group shows two orientations: (a) at 35–60°; (b) at 165–180° (essentially perpendicular to the ureide ring). These conformations are depicted in Figure 3, using phenylethylhydantoin as an example. A typical conformational energy map, also for phenylethylhydantoin, is shown in Figure 4. For each conformation of each of these compounds there is also a mirror image conformation of the same energy obtained from the enantiomer. In phenylethylbarbitone and primidone, however, the mirror image of the first type of conformation is identical with that of the second type, due to the symmetry of the heterocyclic ring.

Detailed conformational energy maps for each of the phenylethyl derivatives are not reproduced here, but examination of the low-energy regions (arbitrarily taken as <10 kcal mol^{-1} above the global minimum) shows quite clearly that the major low-energy conformations for phenyl ethyl derivatives are τ_1(ethyl) = 50 ± 10° and τ_2(phenyl) = 55 ± 15° [for its ethyl group rotamer τ_1(ethyl) = 180 ± 10° and τ_2(phenyl) = 55 ± 15°] and for the second type of low-energy conformation τ_1(ethyl) = −50 ± 20° and τ_2(phenyl) = 135 ± 20° [for its ethyl group rotamer τ_1(ethyl) = 180 ± 10° and τ_2(phenyl) = 135 ± 20°] as well as degenerate conformations corresponding to ~180° rotation of the phenyl ring, ie, of τ_2. A similar investigation of all the high-energy areas (>50 kcal mol^{-1} above the global minimum) also indicated which conformations were the least likely to be involved in the initial binding of these compounds to the active site. However, a combination of both these techniques did not uniquely determine which of the low-energy conformations was the most likely to be the active conformation.

In the crystal structures of these compounds, all the heterocyclic rings were nonplanar, but except for phenobarbital, primidone, and the glutarimides, the deviations from planarity were very slight. Calculations and superimpositions were therefore done assuming a planar ring for the hydantoins, oxazolidinediones, and succinimides, while nonplanar heterocyclic ring systems with both axial and equatorial orientations of the phenyl ring were considered for phenylethylglutarimide, primidone, and phenobarbital. Additional calculations were made assuming a planar heterocyclic ring for phenobarbital and diphenylbarbitone, since the pyrimidinetrione ring is nearly planar in the majority of barbiturates[71] and the energy barriers to ring buckling are slight. Although the minimum energy conformations were very similar, if not identical, for these minor ring deformations such differences need to be kept in mind when building receptor points. The minimum energy conformations for primidone with both phenyl axial and phenyl equatorial are shown in Figure 5. For the phenyl group axial form of primidone, there are no low-energy conformers with τ_1(ethyl) at ~180°, but there is another low-energy conformation, with the plane of the axial phenyl ring running across the pyrimidinedione ring from carbonyl group to carbonyl group. In all of those cases where there is a nonplanar heterocyclic ring, the derivative with the phenyl ring axial was found to be of slightly, though not significantly, lower energy, in accord with the observed crystal structures.[52,54,55] Bulkier substituents are found to be equatorial, as in the structurally related glutarimide thalidomide.[96] In primidone, phenylethylbarbitone, and phenylethylglutarimide, the phenyl axial minimum energy conformations are similar to those of the planar cyclic ureides. The phenyl equatorial analogues have minimum energy conformations that do not correspond particularly well with those of the planar systems. The alicyclic ureide (phenylethylacetyl)urea is also able to adopt both sorts of conformations. The crystal structure indicates that in the solid-state (phenylethylacetyl)urea is pseudocyclic due to intramolecular hydrogen bonding, so that both hydrophobic groups and heteroatoms can have similar spatial arrangements to the cyclic ureides.[42]

The conformations found in crystal structures all lie close to the energy minima found by calculation on com-

(92) Crystal structures obtained from the Cambridge Crystallographic Data Base, J. F. Blount [personal communication] and a literature survey covering 1983–1984.
(93) T. A. Hamor and I. L. Martin, In "X-Ray Crystallography and Drug Action"; A. S. Horn and C. J. de Ranter, Eds., Clarendon Press, Oxford, 1984, p 275.
(94) K. Kamiya, Y. Wada, and M. Nishikawa, *Chem. Pharm. Bull.*, 21, 1520 (1973).
(95) J. A. Pople and M. Gordon, *J. Am. Chem. Soc.*, 89, 4253 (1967).
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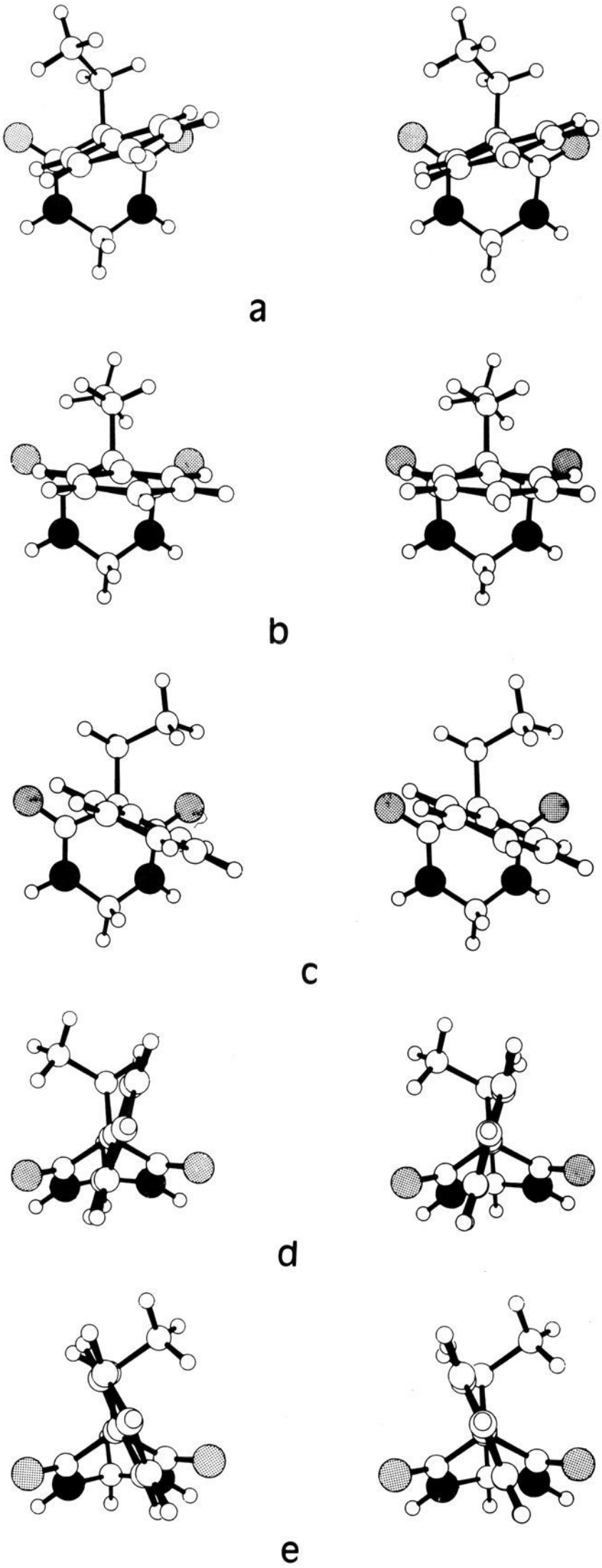

Figure 5. Stereoscopic views of the minimum energy conformations of primidone a, b, and c with the phenyl group axial and d and e with the phenyl group equatorial. Primidone demonstrates that one conformation is the mirror image of the other in those cyclic ureides that have a symmetric ureide ring.

pounds constructed from average geometries, except in the case of one of the crystal structures of phenobarbitone[55] that is distorted by intermolecular hydrogen bonding with a molecule of water in the unit cell of the crystal structure.

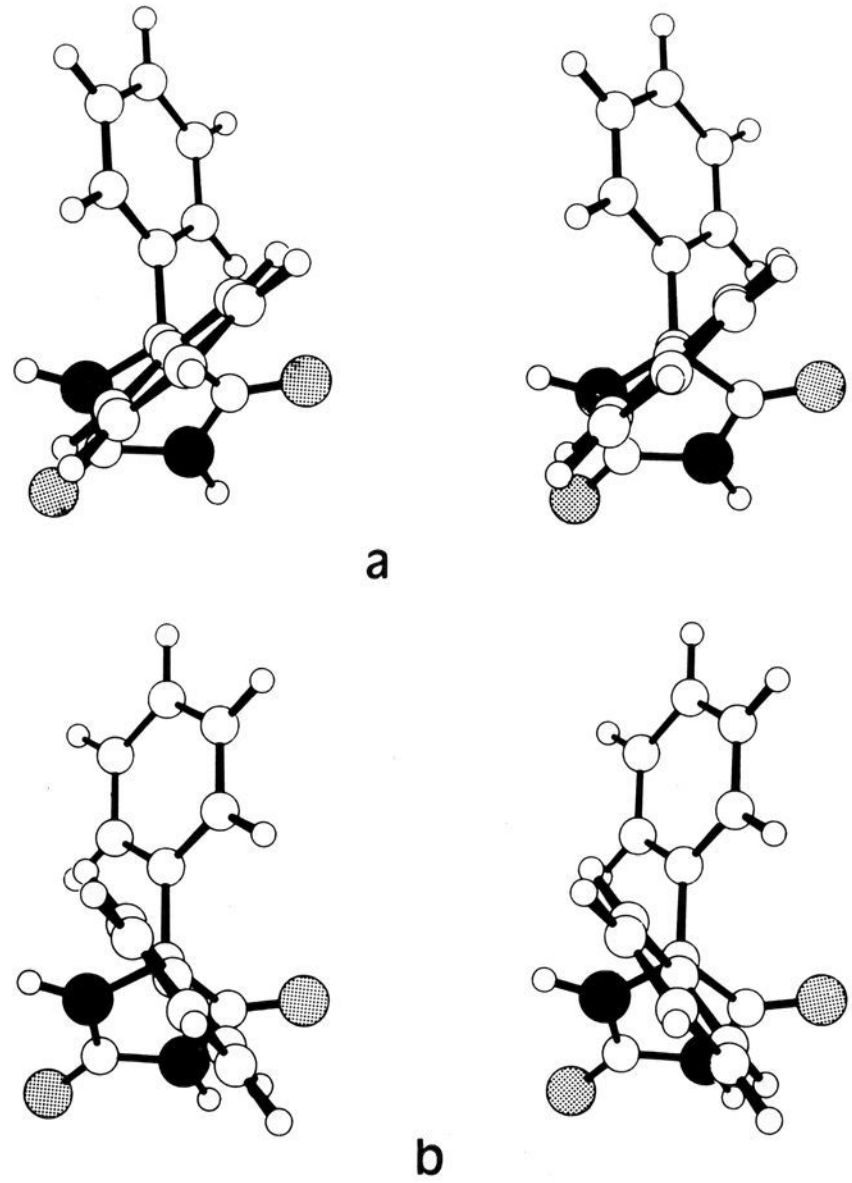

Figure 6. Stereoscopic views of the minimum energy conformations of diphenylhydantoin. As can be observed, a is the mirror image of b for cyclic ureides, as when ring A is oriented toward the carbonyl group, ring B is oriented toward the other side of the ureide ring, and vice versa.

Diphenyl Derivatives. The diphenyl derivatives also show two types of conformation, the types being assigned by comparison of the phenyl torsion angles with those of the analogous phenyl ethyl derivatives. However, this conformation definition is with respect to one ring, with the other phenyl ring invariably having the alternative conformation. That is, if ring A is oriented toward the carbonyl group, then ring B is oriented toward the other side of the ring, and vice versa. Ring A has been arbitrarily defined in Figure 2 as the ring coming out of the plane of the paper when the cyclic ureide is arranged as shown. Ring A is the pro-*S* ring and ring B the pro-*R* ring through all the cyclic ureides. Since one type of conformation is the mirror image of the other, either of these conformations could equally well be active.

The minimum energy conformations of diphenylhydantoin are illustrated in Figure 6 and the energy map in Figure 7. Detailed maps for the other diphenyl derivatives are not reproduced here, but the torsion angles are τ_1(phenyl) = 45 ± 20° and τ_2(phenyl) = 45 ± 15° for one type of conformation and τ_1(phenyl) = 135 ± 10° and τ_2(phenyl) = 145 ± 15° for the other, as well as degenerate conformations arising from rotation of a phenyl group through 180°. Calculations were also done on molecules with slightly nonplanar rings, again indicating similar minimum energy conformations. Other changes considered but found to make only minor energy minima changes were those in which the bond angle between the two phenyl rings was varied over a range of 105–120°. Here, as expected, the proportion of high-energy conformations increased as the angle between the rings decreased, though

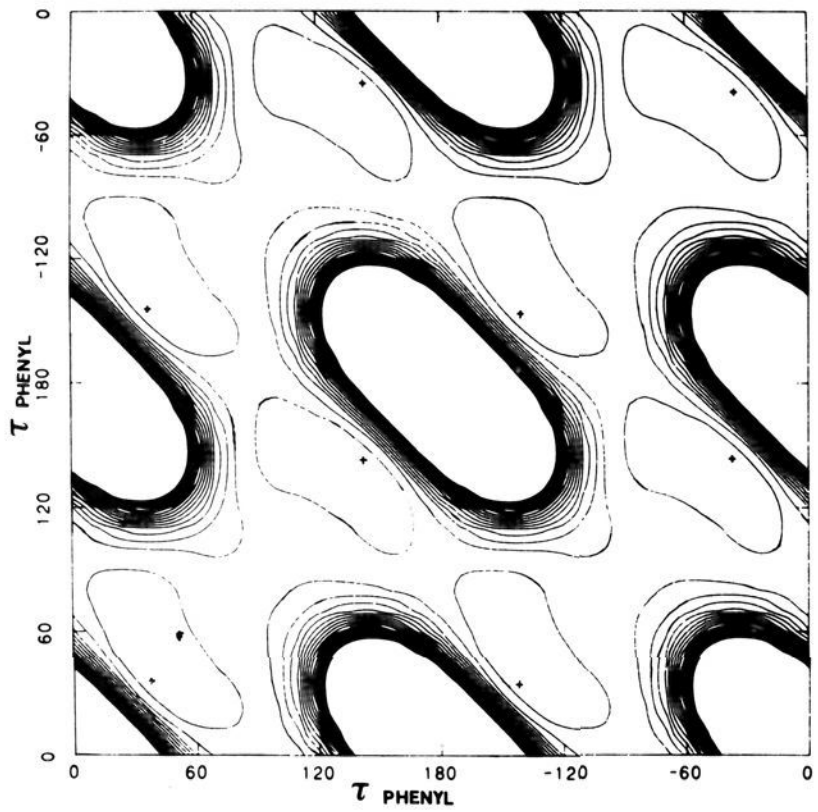

Figure 7. Typical conformational energy map of a diphenyl cyclic ureide, diphenylhydantoin. Energy minima are marked +. The crystal structure conformation is marked ‡.

the conformations of minimum energy were the same. In the crystal structure of diphenylhydantoin, this angle is approximately 112°.

Again, a consideration of both high- and low-energy conformations, and a comparison with those of the phenyl ethyl derivatives, does not define a unique conformation.

Benzodiazepine Derivatives. Since neither the phenyl ethyl nor diphenyl derivatives establishes a unique anticonvulsant conformation, we turned to the benzodiazepines, which also show activity against MES and have a somewhat more restricted geometry. Calculations based on functional group contributions indicate that diazepam provides an excellent match to the benzodiazepine receptor,[97] though its anticonvulsant and anxiolytic actions may not be mediated by a single receptor.[98] Diphenylhydantoin also shows a better than average match at its receptor.[97] Hopefully, the same receptor is responsible for the anticonvulsant action of both drugs.

The preferred conformations for diazepam and the conformational energy map obtained by rotation of the phenyl ring on C5 and the methyl group on N1 are shown in Figure 8. Ring inversion gives a mirror image conformation of the same energy. Crystal structures of benzodiazepines show only boat conformations of the diazepine ring, all remarkably similar in geometry, even when there is more than one molecule in the unit cell. In benzodiazepines that are not enantiomeric at C3, two mirror image boat forms may exist in the crystal, while in solution these two boat forms readily interconvert. However, in benzodiazpines substituted at C3, only the boat forms with the substituent pseudoequatorial are found, both in the solid state and in solution. Benzodiazepines enantiomeric at C3 show significant differences in activity. Both binding data[91,97] and in vivo activity data[20,99] indicate that the *S* enantiomers of 3-methylbenzodiazepines are significantly more active than the *R* enantiomers.

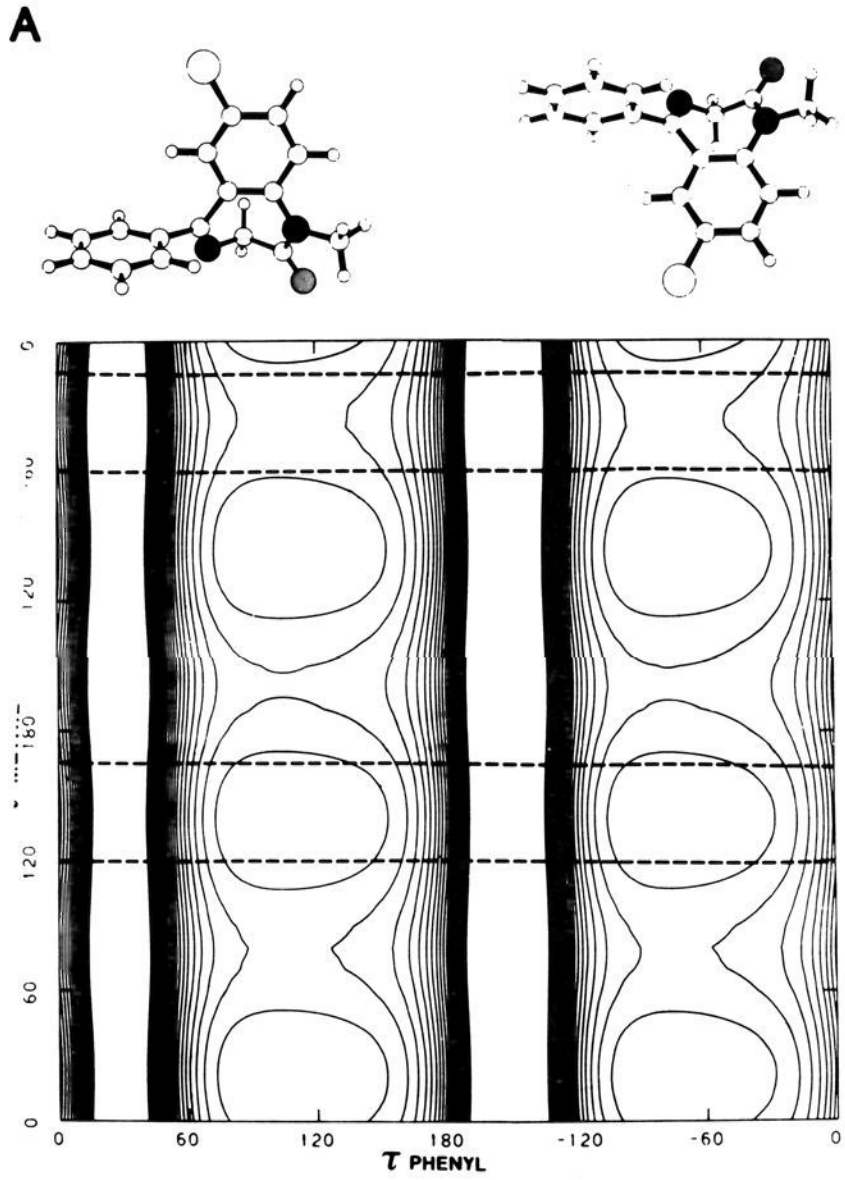

Figure 8. (A) Preferred conformation of diazepam (left) and the mirror image, ring-inverted conformation of the same energy (right). (B) Conformational energy map of the first conformation. This energy map is not strictly comparable with those of the cyclic ureides, which show the rotation of one hydrophobic group with respect to another off the same carbon. In order to demonstrate this effect for diazepam, a dotted line has been drawn across the conformational energy map that indicates the range of torsion angles for C10–C11–C5–C1′ (see Figure 2 for the torsion angle definition) found in the crystal structures of diazepines.

Empirical conformational calculations on the crystal structure of (*S*)-1,3-dimethyl-5-(2′-fluorophenyl)-7-nitro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (RO 11-6896) show that the boat form with the methyl group axial is of much higher energy than the form with the methyl group equatorial. The energy difference between the energy minima of the two forms is still significant in MINDO/3 calculations with fully optimized geometries, indicating that the boat conformation with the methyl group pseudoequatorial is the active form. This is the same conformation as that proposed by Blount et al.[91] based on the structural similarity between RO 11-6896 and the potent and almost rigid anthramycin-like benzodiazepine RO 14-5975. This geometry thus provides a basis for determining the most likely conformation for activity of the other anticonvulsants.

MINDO/3 calculations on RO 11-6896 with the 3-methyl group equatorial also gave the same torsion angle for the 5-phenyl group in the minimum energy conformation as that calculated via classical methods. This is in agreement with the minimum energy conformation found by other workers.[100] The preferred conformations and the energy maps of the forms obtained by rotation of the phenyl ring and the *C*3-methyl group while the *N*-

(97) P. R., Andrews, D. J. Craik, and J. L. Martin, *J. Med. Chem.*, **27**, 1648 (1984).
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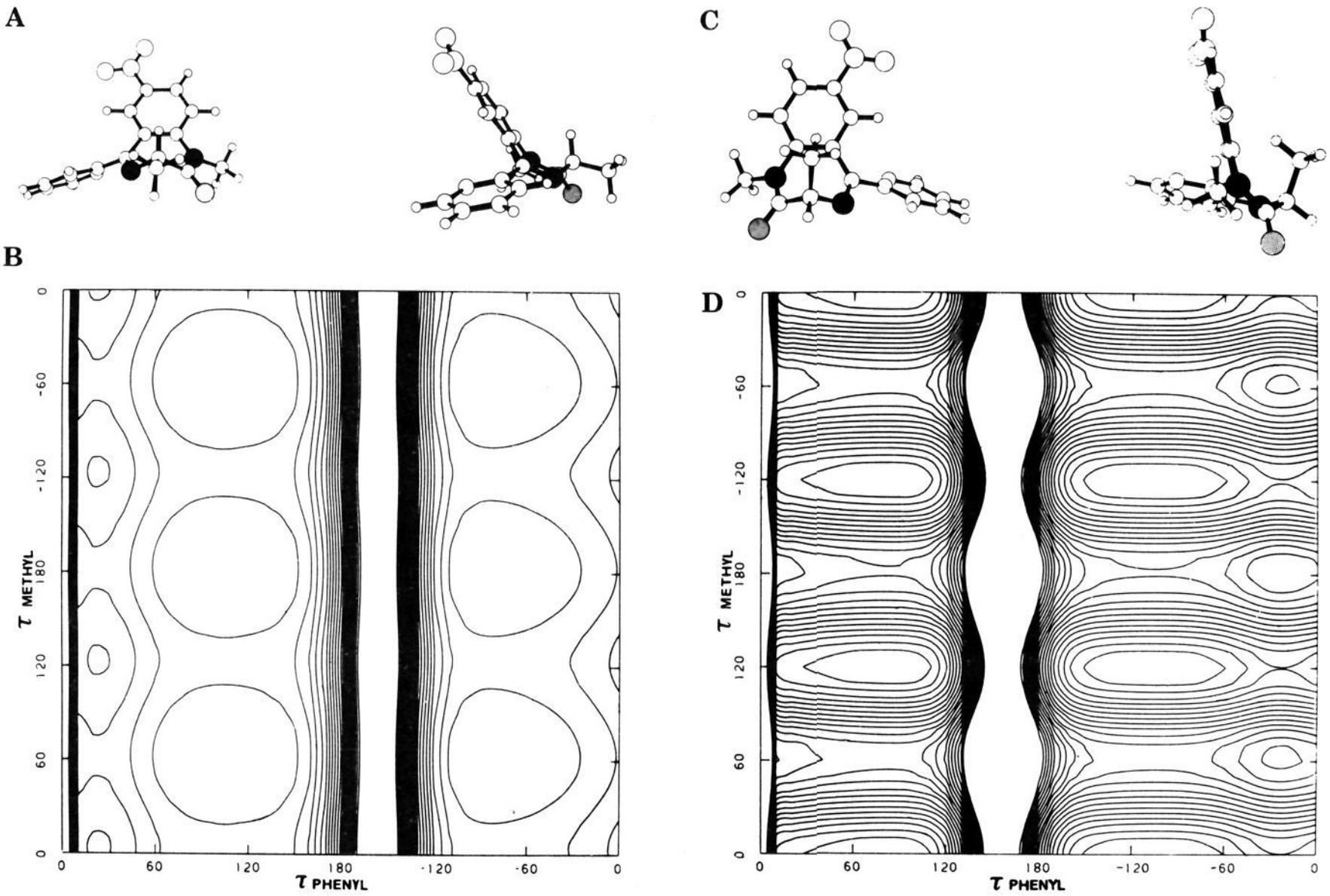


Figure 9. (A) Two views of RO 11-6896 with the methyl group at the C3 position equatorial. (B) Conformational energy map obtained by rotation of the phenyl group and methyl group on C3, while the methyl group on N1 was set at its most favored conformation (C). Two views of the same enantiomer of RO 11-6896, but with the benzodiazepine ring inverted and (D) the conformational energy map obtained as above. The two views of each stereoconformer demonstrate the interactions of the 3-methyl group with the annelated ring, the second view being a 90° rotation of the first.

methyl group is held in the most energetically favorable conformation are shown in Figure 9, which shows clearly the interaction of the axial methyl group and the annelated phenyl ring that causes the ring-inverted methyl axial form to be of higher energy than the form with the methyl group equatorial. The conformational energy maps also indicate much more conformational restriction in the form with the methyl group axial.

Molecular Superimpositions. The conformational energy maps of the benzodiazepines are not strictly comparable with those of the cyclic ureides, which really show the relationship of one hydrophobic group, a phenyl ring, with another hydrophobic group, either another phenyl or an ethyl off the same asymmetric carbon. Therefore, in order to simulate such a conformational energy map, the crystal structures of a number of benzodiazepines, dihydrobenzodiazepines, triazolobenzodiazepines, and anthramycin-like benzodiazepines were examined to ascertain the torsion angle range of C1′–C5–C11–C10,[92] which gives the orientation of the annelated benzene ring with respect to the 5-phenyl ring. This range, which is unlikely to be much larger in solution, is shown by the dotted lines across the conformational energy map for diazepam (Figure 8). This indicates, when *all* the conformational energy maps are superimposed and the low-energy conformations examined, that there are two types of low-energy conformation of the diphenyl cyclic ureides comparable with that of the benzodiazepines: these are the conformations $\tau_1 \sim 90 \pm 20°$ and $\tau_2 \sim 150 \pm 20°$ and its invert $\tau_1 \sim 150 \pm 20°$ and $\tau_2 \sim 90 \pm 20°$.

Figure 10 shows the correspondence of these low-energy conformations of diazepam, diphenylhydantoin, phenylethylhydantoin, diphenylsuccinimide, and diphenylbarbitone (in this case with a puckered ring) as a superimposition of the unoptimized 10-kcal contour line from the individual conformational energy maps, and the range of torsion angles, C1′–C5–C11–C10 of diazepam. There are only limited regions that are common to all the compounds, and these are marked on the map. All the other anticonvulsants studied also have conformations with energies of less than 10 kcal/mol in this region. Effectively, this map shows the three-dimensional overlap of the A phenyl ring of the cyclic ureides with the A phenyl ring of diazepam and of the B phenyl ring of the cyclic ureides with the C phenyl ring of diazepam. The opposite combination is equally possible and gives rise to the invert conformations not shown in this figure.

The validity of these findings was confirmed by systematically checking low-energy conformations of the diphenyl cyclic ureides to see whether any could be found that closely matched the low-energy conformation of diazepam and also had heteroatoms able to interact with the same receptor groups. For this purpose, it was assumed that both phenyl rings were interacting with lipophilic sites by hydrophobic and dispersion forces. Dummy atoms were therefore attached 3.5 Å above and below the phenyl ring centroids and perpendicular to the plane of the ring. This allowed the alignment of the rings to be matched with a reasonable degree of coplanarity. The cyclic ureide torsion angles τ_1 and τ_2 were then systematically varied, with the position of the dummy atoms in the cyclic ureide being matched with those of diazepam. The conformations with

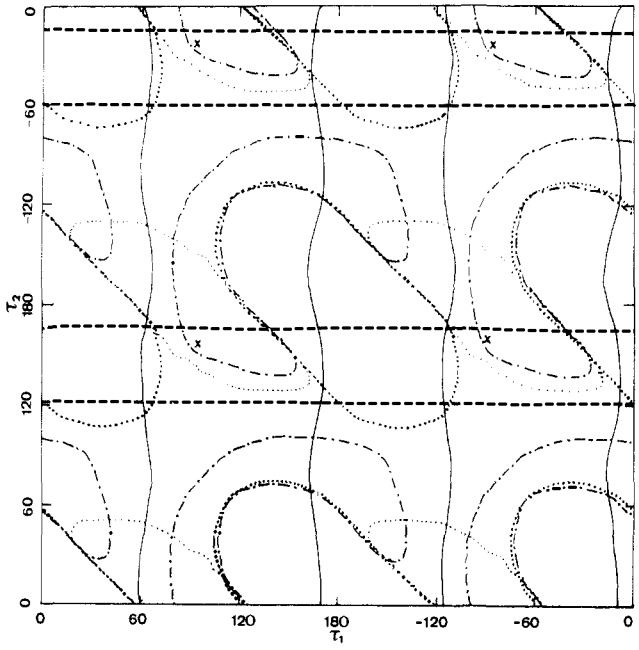


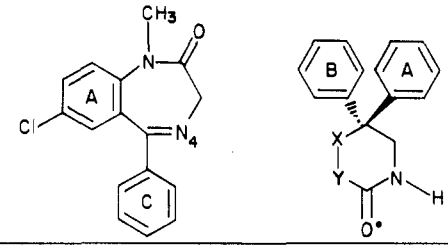
Figure 10. Superimposition of the 10 kcal/mol energy contour from the energy maps of diazepam, diphenylhydantoin, diphenylsuccinimide, and diphenylbarbitone and the range of torsion angles C10–C11–C5–C1′ (as Figure 8) found in benzodiazepine crystal structures. The stereoconformers chosen are those that overlap the A ring of the cyclic ureides with the A ring of diazepam and the B ring of the cyclic ureides with the C ring of diazepam (model B): diazepam (—), diphenylhydantoin (···), diphenylsuccinimide (–·–), diphenylbarbitone (light dots). The x axis is the rotation of a phenyl ring for all compounds; the y axis is the rotation of the other phenyl ring for the cyclic ureides and of the N-methyl group for diazepam.

the best match were then graphically superimposed on diazepam, the distances between corresponding heteroatoms and alignment guides through the phenyl rings measured, and the relative orientations of the heteroatoms noted. Two types of superimposition were shown to be possible and are depicted in Figure 11, with the relationships between the ureide phenyl rings and heteroatoms and the diazepam phenyl rings and heteroatoms being shown in Table III. There are thus two models for the interactions of the cyclic ureides and diazepam with a common receptor. All compounds were able to fit both models with a root mean square (RMS) of less than 0.8 Å, with compounds such as diphenylhydantoin fitting with a RMS of less than 0.2 Å. Minor ring puckering of the hydantoins, succinimides, and oxazolidinediones did not alter this value by more than ±0.1 Å. However, with the barbiturates a bent ring, similar to that found in phenobarbitone, was used as it gave a significantly better RMS value.

It did not prove possible to build a common model for action of these drugs based on a high-energy conformation of diazepam where the two phenyl rings were nearly coplanar. Even a model based on a 30° rotation of the 5-phenyl ring of diazepam from its minimum energy conformer, as has been suggested by Loew[100] for anxiolytic activity, provides a much less satisfactory basis for a common model for anticonvulsant action, as the energy differences between the cyclic ureides in their best fit conformations and their minimum-energy conformations is large. The RMS of fitted points also rose.

Structure–Activity Relations. The structural features of active benzodiazepines were examined in order to relate them to possible binding sites that might also be accessible to cyclic ureides. It has been demonstrated previously that N4 and the carbonyl group of diazepam

Table III. Relationship of the Proposed Anticonvulsant Models to the Benzodiazepine Structure



diazepam function	ureide function	
	model A	model B
ring A	ring B	ring A
ring C	ring A	ring B
N4	C=O	X
C=O	C=O	C=O*

are important in benzodiazepine bonding.[100-105] A role for N1 of diazepam has also been proposed.[106] Studies on the inhibition of [^{3}H]diazepam binding show this to be the only common heteroatom in all the active benzodiazepines tested to date,[97] although this does not necessarily imply that binding at this particular site is necessary for anticonvulsant activity. The other common features seen in active benzodiazepines are C=X (where X = O, S, N, or C) at the C2 position and the annelated aromatic ring. It may not be necessary for this ring to be annelated, as is shown by the structurally somewhat similar drug CGS 9896 (2-(*p*-chlorophenyl)pyrazolo[4,3-*c*]quinolin-3(5*H*)-one), at present undergoing trials as an anxioselective anxiolytic with anticonvulsant activity,[107] where the "free" phenyl ring appears to be analogous to the A ring of benzodiazepine. To date no active anticonvulsant benzodiazepines have been found with a nonaromatic system in this position. Some variation in the substituent at C5 seems possible with tetrazepam (cyclohexyl substituent) available for clinical use as a muscle relaxant. Some 5-alkoxy-substituted benzodiazepines have been prepared that show anticonvulsant activity similar to that of diazepam,[90] though none is in clinical use and none appears to have been tested against MES. 5-Phenylbenzodiazepines also show significant changes in activity according to the substituent pattern on the 5-phenyl ring. Optimum activity appears to be associated with electron-withdrawing substituents at the 2′-position. The nitrogen usually at the N4 may be "swapped" to the 5-position as in clobazam[90] or incorporated in a ring as in the anthramycin-like benzodiazepines[91] without loss of activity, possibly indicating a receptor interaction somewhat above or below the diazepine ring, rather than the position straight out from N4, which has been postulated previously[101,106] and would be expected if the nitrogen lone pair were involved in binding with normal directionality. Such a receptor interaction is consistent with that of several other CNS drug classes in the proposed common CNS pharmacophore.[108,109] An electron-with-

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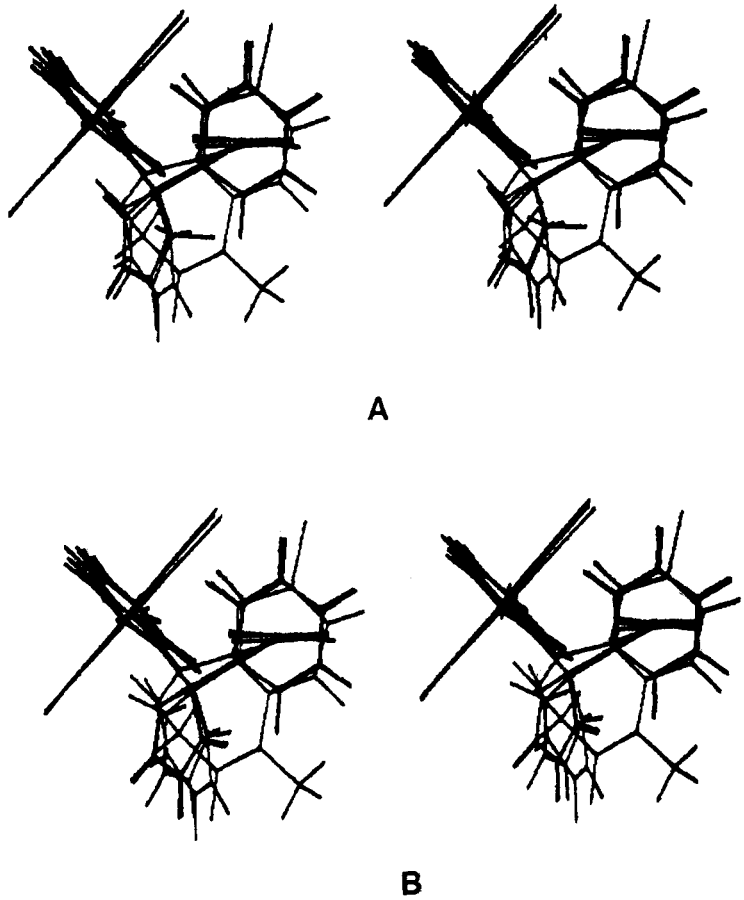

Figure 11. (A) Stereoscopic view of the superimposition (model A) of the compounds diphenylhydantoin, diphenyloxazolidinedione, diphenylsuccinimide, diphenylbarbiturate (with a bent ring) on diazepam. This superimposition has a carbonyl group of the cyclic ureide in the proximity of N4 of diazepam. (B) Superimposition (model B) of the same compounds with the cyclic ureide ring in a different orientation. Here the group in the position equivalent to N1 of diphenylhydantoin is in close proximity to N4 of diazepam.

drawing group such as chlorine in the 7-position gives significant enhancement of activity when compared to hydrogen and may interact electrostatically with a specific site in the receptor.[100] Chlorinated analogues of phenobarbital are known, and these compounds do show greater activity and longer duration of action than phenobarbital[110] although they have not been developed clinically.

An examination of the two superimposition models from the cyclic ureides and diazepam shows that model B has a slightly better match of all the cyclic ureides with diazepam. It provides a close match of the two hydrophobic pockets, i.e., the phenyl rings, and also has heteroatoms that may well be able to bind to the same groups on the receptor as the N4 and O2 atoms of diazepam. One heteroatom (except in the case of diphenylsuccinimide) is in close proximity to N4 of diazepam. The carbonyl groups of the cyclic ureides closest to O2 of diazepam may also be able to hydrogen bond to the same position of the receptor as O2 of diazepam, as indicated by a recent survey of the geometry of C=O to H—N hydrogen bonds[111-113] and by previous data.[114,115] This gives a four sites of interaction binding model that could still accommodate compounds such as diphenylsuccinimide at the same site, since the energy loss due to the loss of binding at one of the points of contact would be small (in the order of 2–4 kcal/mol).

Superimposition model A has a reasonable fit of the two hydrophobic phenyl groups, with the other possible sites of interaction being that of N4 and a carbonyl group of the cyclic ureides with the same receptor point as O2 of diazepam. Like model B, model A thus gives four possible sites of interaction, although the two heteroatomic groups do not provide as good a fit in terms of absolute distances between matched sites.

The phenyl ethyl cyclic ureides can also be superimposed on the diazepam-based models by matching of a phenyl ring and of heteroatoms, as in the analogous diphenyl compounds. Each ureide enantiomer can be superimposed in two ways, with the ureide phenyl ring overlapping either the annelated phenyl ring or the "free" ring of diazepam. Poor enantiomeric data for cyclic ureides give only a slight hint as to the more likely conformation. Using the more active *R* enantiomer of nirvanol and matching the phenyl ring with the annelated phenyl ring of diazepam suggests a model A superimposition, and supports the SAR data on benzodiazepines, indicating that an aromatic ring in this position is necessary for activity. Matching of the *R* enantiomer with the "free" phenyl ring would support a model B superimposition and indicate that occupation of

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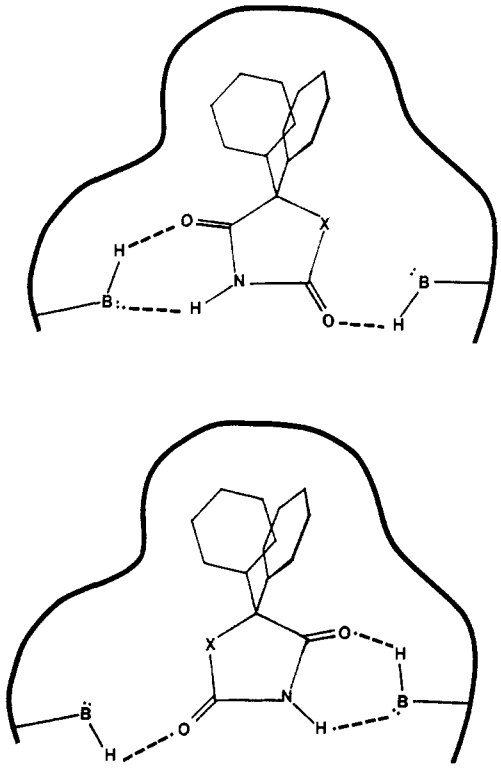

Figure 12. Illustration of a general anticonvulsant receptor site capable of accepting anticonvulsants in either of the binding modes, model A or model B, described in the text.

this hydrophobic pocket was necessary for activity against MES. However, the *S* enantiomer also has significant activity. This indicates either that both enantiomers bind with the same orientation of the cyclic ureide ring, and a phenyl ring in either hydrophobic pocket contributes to activity, or that occupation of one specific hydrophobic pocket of the receptor is necessary for activity the cyclic ureide ring can bind either way up. The conflicting stereoisomeric data for nirvanol, and scant enantiomeric data on MES activity for the other ureides, make it impossible to rule out either possibility.

Both models A and B require one phenyl ring, another hydrophobic region, and at least one heteroatom for activity. It is possible to match other anticonvulsants such as carbamazepine to both such models with a reasonable fit if only one aromatic region and two heteroatomic sites are considered to be essential for binding. Such a conclusion was previously reached by the comparison of carbamazepine, cyheptamide, 3-hydroxy-3-phenacyloxindole, and diphenylhydantoin.[116] However, either of our models would require the carbamazepine ring nitrogen and the amide oxygen or nitrogen to be involved in binding, in contradistinction to Codding's model,[116] where only the amide heteroatoms are thought to be important. It is also possible to fit carbamazepine to *both* hydrophobic pockets and two heteroatom binding sites, though the RMS is slightly above 1 Å. The oxindole also fits either model with both hydrophobic pockets occupied and interactions with two heteroatom receptor points derived from diazepam.

Both model A and B are open to criticism, as neither takes into full account the imide system in the ureides or the amide system in the benzodiazepines. Allowing some degree of lateral displacement between phenyl ring centroids while maintaining near coplanarity with the proposed receptor sites enables other models to be considered, including one intermediate between A and the Camermans' model, where there are again four sites of interaction, including two hydrophobic pockets and the N4 and O2 receptor points derived from diazepam. This leads to a significant increase in RMS from 0.2 to 0.8 Å for the compound of best fit, diphenylhydantoin. Similar manipulations with model B did not lead to any improvements of the model.

Conclusion

The consistent feature of all the data presented here is the key role played by the specific conformational arrangement of the two aromatic rings in the benzodiazepines and diphenyl cyclic ureides. There is, however, no firm indication of which aromatic group is more important for activity nor of which of these rings is matched by the single ring of the phenyl ethyl derivatives. The relatively minor and inconsistent stereoisomeric activity differences observed in the latter compounds could thus be explained by the ability of phenyl groups in either position to bind to the receptor. This in turn would imply that the cyclic ureides all bind in one or other of the binding modes, model A or model B, given in Table III.

There is, however, an alternative explanation suggested by the similarity in the fit of the cyclic ureides to the benzodiazepines provided by model A or model B. This similarity implies that any individual ureide could bind to the receptor site either way up, so that the phenyl rings of both stereoisomers of the phenyl ethyl derivatives would bind at the same site. This general possibility, which is illustrated in schematic form in Figure 12, is an attractive one in view of the very large number of variations in the position and number of hydrogen-binding groups in cyclic and other systems that have been synthesized without substantial loss of anticonvulsant activity. A receptor such as that illustrated in Figure 12 can clearly accommodate a diverse range of hydrogen-binding groups without unduly prejudicing the seemingly more specific conformational requirements of the two hydrophobic sites.

Registry No. PEB, 50-06-6; PEH, 631-07-2; PEO, 92288-54-5; PES, 3464-20-8; PEG, 77-21-4; PEP, 125-33-7; PPB, 21914-07-8; PPH, 57-41-0; PPO, 4171-11-3; PPS, 3464-15-1; PEA, 90-49-3; PPA, 81498-89-7; Ro 11-6896, 66855-85-4; diazepam, 439-14-5.

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