rats per group). The MES was examined 1 h after oral administration of the test compounds (in mice). The ED_{50} was determined as the dose that suppressed the manifestation of the tonic extensor convulsion in 50% of the animals used.

Pentylenetetrazol (PTZ) Clonic Convulsions in Rats.[6] Rats (six rats per group) were injected with 100 mg/kg ip of PTZ 2 (21), 4 (DPH), or 1 h (carbamazepine) after oral administration of the test drugs. The ED_{50} was defined as the dose that depressed the manifestation of clonic convulsions in 50% of the animals used.

Muscle-Relaxant Action (Vertical Screen Method) in Rats. Four limbs of rats (six rats per group) were placed (standing) on a vertical wire-meshed screen 1 h after oral administration of the test compounds. When the animals failed to climb up the screen, we judged a muscle-relaxant action to have occurred. The ED_{50} was defined as the dose that caused muscle relaxation in 50% of the animals used.

Acknowledgment. The authors thank M. Sugano and N. Hashimoto for their technical assistance and Drs. S. Hattori and S. Morita of this research center for their valuable advice and encouragement throughout this work. We are also indebted to members in the Systems Engineering and Analytical Laboratory, Mitsubishi Chemical Industries Ltd., for elemental analyses.

Registry No. 1, 89122-12-3; **2**, 89122-13-4; **3**, 89122-14-5; **4**, 89122-15-6; **5**, 89122-16-7; **6**, 89122-17-8; **7**, 89122-18-9; **8**, 89122-19-0; **9**, 89122-20-3; **10**, 89122-21-4; 11, 89122-22-5; **12**, 89122-23-6; **13**, 89122-24-7; **14**, 89122-25-8; **15**, 89122-26-9; **16**, 89122-27-0; **17**, 89122-28-1; **18**, 89122-29-2; **19**, 89122-30-5; **20**, 89122-31-6; **21**, 89122-32-7; **22**, 89122-33-8; **23**, 89122-34-9; **24**, 89122-35-0; **25**, 89122-36-1; **26**, 89122-37-2; **27**, 89122-38-3; **28**, 89122-39-4; **29**, 89122-40-7; **30**, 89122-41-8; **31**, 89122-42-9; **32**, 89122-43-0; **33**, 89122-44-1; **34**, 89122-45-2; **35**, 89122-46-3; **36**, 89122-47-4; **37**, 89122-48-5; **38**, 89122-49-6; **39**, 89122-50-9; **40**, 89122-51-0; 41, 89122-52-1; **42**, 89122-53-2; **43**, 89122-54-3; **44**, 89122-55-4; **45**, 89122-56-5; **46**, 89122-57-6; **47**, 89122-58-7; **48**, 89122-59-8; **49**, 89122-60-1; **50**, 89122-61-2; A (R_1 = 2-Cl; R_2 = H), 89122-63-4; A (R_1 = 3-Cl; R_2 = H), 89122-64-5; A (R_1 = 4-Cl; R_2 = H), 42224-51-1; A (R_1 = 2-F; R_2 = H), 89122-65-6; A (R_1 = 3-F; R_2 = H), 89122-66-7; A (R_1 = 4-F; R_2 = H), 89122-67-8; A (R_1 = 2-OMe; R_2 = H), 89122-68-9; A (R_1 = 2-Me; R_2 = H), 89122-69-0; A (R_1 = 3,4-Cl_2; R_2 = H), 89122-70-3; A (R_1 = H; R_2 = 5-Cl), 89122-71-4; B (R_1 = 2-Cl; R_2 = H), 89122-77-0; B (R_1 = 3-Cl; R_2 = H), 89122-78-1; B (R_1 = 4-Cl; R_2 = H), 89122-79-2; B (R_1 = 2-F; R_2 = H), 89122-80-5; B (R_1 = 3-F; R_2 = H), 89122-81-6; B (R_1 = 4-F; R_2 = H), 89122-82-7; B (R_1 = 2-OMe; R_2 = H), 89122-83-8; B (R_1 = H; R_2 = 3-OMe), 89122-84-9; B (R_1 = 2-Me; R_2 = H), 89122-85-0; B (R_1 = 3,4-Cl_2; R_2 = H), 89122-88-3; B (R_1 = H; R_2 = 5-Cl), 89122-89-4; D (R_1 = R_2 = H), 40473-60-7; D (R_1 = 2-Cl; R_2 = H), 89122-90-7; D (R_1 = 3-Cl; R_2 = H), 89122-91-8; D (R_1 = 4-Cl; R_2 = H), 89122-92-9; D (R_1 = 2-F; R_2 = H), 89122-93-0; D (R_1 = 3-F; R_2 = H), 89122-94-1; D (R_1 = 4-F; R_2 = H), 89122-95-2; D (R_1 = 2-OMe; R_2 = H), 89122-96-3; D (R_1 = 2-Me; R_2 = H), 89122-97-4; D (R_1 = 3,4-Cl_2; R_2 = H), 89122-98-5; D (R_1 = H; R_2 = 5-Cl), 89122-99-6; $Br(CH_2)_2Br$, 106-93-4; $Br(CH_2)_3Br$, 109-64-8; $Br(CH_2)_4Br$, 110-52-1; $Br(CH_2)_5Br$, 111-24-0; $PhCH_2Cl$, 100-44-7; *trans*-PhCH=CH-*o*-$C_6H_4O(CH_2)_4Br$, 89122-62-3; Me_2NH, 124-40-3; $MeNH_2$, 74-89-5; Et_2NH, 109-89-7; Pr_2NH, 142-84-7; $CH_3NH(CH_2)_2N(CH_3)_2$, 142-25-6; $PhCH_2CH(OH)$-*m*-C_6H_4OH, 32578-48-6; $PhCH_2CH(OH)$-*p*-C_6H_4OH, 73049-07-7; salicylaldehyde, 90-02-8; 2-hydroxy-*trans*-stilbene, 18493-15-7; 3-hydroxypiperidine, 6859-99-0; 3-hydroxy-*trans*-stilbene, 17861-18-6; 4-hydroxy-*trans*-stilbene, 6554-98-9; pyrrolidine, 123-75-1; piperidine, 110-89-4; morpholine, 110-91-8; 1-methylpiperazine, 109-01-3; 4-piperidinol, 5382-16-1; piperazine, 110-85-0; 1-ethylpiperazine, 5308-25-8; 1-propylpiperazine, 21867-64-1; 1-piperazineethanol, 103-76-4; 1-acetylpiperazine, 13889-98-0; 1-methylhexahydro-1*H*-1,4-diazepine, 4318-37-0; 3-methoxypiperidine, 4045-29-8; 3-ethoxypiperidine, 88536-17-8; 3-propoxypiperidine, 89122-72-5; 3-acetoxypiperidine, 89122-73-6; 3-piperidinemethanol, 4606-65-9; 3-piperidinecarboxamide, 4138-26-5; methyl 3-piperidinecarboxylate, 50585-89-2; 3-piperidinecarboxylic acid, 498-95-3; 3-methylpiperidine, 626-56-2; 2-(2-bromoethoxy)-*trans*-stilbene, 89122-74-7; 2-(3-bromopropoxy)-*trans*-stilbene, 89122-75-8; 2-(5-bromopentoxy)-*trans*-stilbene, 89122-76-9; 3-(4-bromobutoxy)-*trans*-stilbene, 89122-86-1; 4-(4-bromobutoxy)-*trans*-stilbene, 89122-87-2.

(6) T. Hirooka, K. Fujimoto, and S. Ose, *Arch. Int. Pharmacodyn. Ther.*, 156, 261 (1965).

Cyheptamide and 3-Hydroxy-3-phenacyloxindole: Structural Similarity to Diphenylhydantoin as the Basis for Anticonvulsant Activity

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The molecular structures of cyheptamide and 3-hydroxy-3-phenacyloxindole were determined by X-ray diffraction methods. The amide group in both compounds exhibits delocalization of the π-electrons over the three atoms (N, C, and O), while the bond linking the amide to the tetrahedral carbon atom is a single bond. These structural features are also present in two drugs used for the treatment of generalized tonic–clonic (GTC) seizures, namely, carbamazepine and diphenylhydantoin. The shapes of cyheptamide, 3-hydroxy-3-phenacyloxindole, and carbamazepine have three features that are the same and can be simultaneously overlapped, the amide and two hydrophobic regions, whereas diphenylhydantoin fits two of the three regions at one time. These structural and electronic features are analyzed in light of current models for anticonvulsant activity.

Elucidation of the mechanism of action of anticonvulsant drugs has been difficult because of the chemical diversity of the molecules and the complexity of the physiological and biochemical processes involved in the production of seizures. Although a variety of drugs are used for the control of seizures, the multiplicity of the effects of the drugs has frustrated attempts to correlate activity with chemistry so that the characteristics of anticonvulsants can be determined. One aid to mechanistic studies on these new drugs has been the development of tests that model different forms of epilepsy. For example, usually drugs that are most effective in preventing seizures after maximal electroshock (MES)[1] prevent generalized tonic–clonic seizures. In contrast, drugs that protect against seizures produced by pentylenetetrazol (metrazol, MET)[1] are effective as treatments for absence seizures. The discrimination between types of activity that is made

(1) Woodbury, D. M. In "Experimental Models of Epilepsy—A Manual for the Laboratory Worker"; Purpura, D. P.; Penry, J. K.; Tower, D. B.; Woodbury, D. M.; Walters, R. D., Eds.; Raven Press: New York, 1972; pp 557–601.

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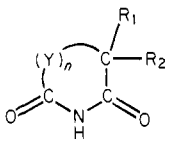
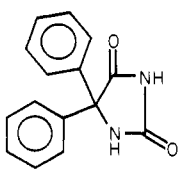
possible by the use of these tests allows the study of the sterochemical aspects of specific seizure-control mechanisms. Anticonvulsants can thus be studied as classes that have a specific action, and the precise structural features that determine their activity can be determined.

Ten years ago, anticonvulsant drugs all had very similar structures. Most drugs were patterned after phenobarbital, and, thus, had a five- or a six-membered heterocyclic ring (**1**) with carbonyl groups and a tetrahedral carbon atom whose substituents were alkyl or aromatic groups.



1, Y = C, N, O; n = 1, 2

Structure–activity data on these compounds predicted antigeneralized tonic–clonic activity (GTC) for the aromatic drugs and antiabsence activity for the fully alkyl-substituted compounds. A stereochemical model for anticonvulsant activity was developed by Camerman and Camerman[2] initially on the basis of their study of the similarities in shape between diphenylhydantoin (**2**) and



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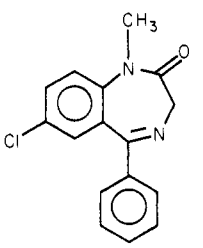
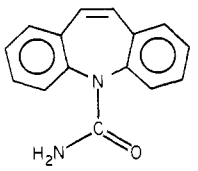


3

diazepam (**3**). With several structural analyses, they identified a specific geometrical arrangement between two hydrophobic groups and two electron-donating groups that are separated by 2.4–4.6 Å. This work had a major impact on studies of seizure-control drug mechanisms, yet the model does not differentiate antiabsence drugs from those effective against GTC seizures. As an example, drugs ineffective against MET-induced seizures have electron-donor separations that include both limits of the range of the model.[4] Also, the more recently developed drugs often lack either the chemical groups or the atomic separations required by the model, yet these compounds are active. Two examples are carbamazepine (**4**) and cyheptamide (**5**),



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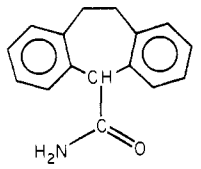


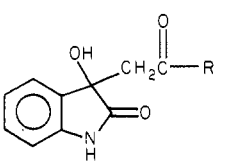
5

which are conformationally restricted and contain only one carbonyl group, yet they both are effective in preventing MES-induced seizures as compared to diphenylhydantoin.[5]

Table I. Crystallographic Data for Cyheptamide and 3-Hydroxy-3-phenacylindole

	cyheptamide	phenacyl-oxindole
mol formula	$C_{16}H_{15}NO$	$C_{16}H_{13}NO_3$
mol wt	273.30	267.25
space group, Z	$P2_1/c$, 4	$P2_1/c$, 4
a (esd), Å	5.671 (1)	8.571 (3)
b, Å	9.177 (1)	18.010 (2)
c, Å	23.650 (6)	8.504 (3)
β, deg	96.81 (1)	97.55 (2)
vol, Å^3	1222.24 (5)	1301.5 (6)
density (calcd), g cm^{-3}	1.30	1.36
crystal size, mm	0.20 × 0.20 × 0.35	0.10 × 0.35 × 0.45
radiation; wavelength, Å	Mo Kα, 0.71069	Cu Kα, 1.5418
monochromatization	graphite monochro-mator	nickel filter
maximum θ	30°	70°
unique data	3545	2480
R	0.048	0.035

Another example is the 3-hydroxyoxindole skeleton,[6] whose derivatives (**6a,b**) have activity against MES-induced



6a, R = C_6H_5
b, R = CH_3

seizures. The more potent acetonyl compound (**6b**) has only one bulky hydrophobic group, as does phenobarbital; however, the acetonyl compound is geometrically restricted due to the indole ring and cannot have the stereochemical similarity to diphenylhydantoin that was found for phenobarbital.[2]

The emphasis in the model for anticonvulsant activity has hitherto been on the stereochemical aspects of the drugs, while their electronic properties have received less consideration. This emphasis may be due to the lack of correlation between atomic charges and activity that was found in an early theoretical treatment using extended Hückel calculations and CNDO/2.[7] Unfortunately, these calculations had to use assumed average geometries and fully staggered conformations; these assumptions probably resulted in a loss of sensitivity to small changes in atomic charge and other electronic effects. With the current search for discrimination between types of anticonvulsant activity and for a model to explain differences in activity, it becomes essential to analyze in detail both accurate structural parameters and theoretical calculations on observed or computationally optimized geometries.

This work will present an analysis of two experimental compounds, cyheptamide[5] (**5**) and 3-hydroxy-3-phenacyloxindole[6] (**6a**), that are effective in preventing MES-induced seizures. The structures of these compounds will be compared to the structures of two anti-GTC seizure drugs, diphenylhydantoin[8] and carbamazepine.[9] The conformational features of these structures will be analyzed

(2) Camerman, A.; Camerman, N. In "Antiepileptic Drugs: Mechanisms of Action"; Glaser, G. H.; Penry, J. K.; Woodbury, D. M., Eds.; Raven Press: New York, 1980; pp 223–231.
(3) Camerman, A.; Camerman, N. *Science* **1970**, *168*, 1457–1458.
(4) Jones, G. L.; Woodbury, D. M. In "Antiepileptic Drugs"; Woodbury, D. M.; Penry, J. K.; Pippenger, C. E., Eds.; Raven Press: New York, 1980, pp 83–109.
(5) Wimbish, G. H.; Jones, G. L.; Amato, R. J.; Peyton, G. A. *Proc. West. Pharmacol. Soc.* **1980**, *23*, 75–79.
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(8) Camerman, A.; Camerman, N. *Acta Crystallogr., Sect. B* **1971**, *27*, 2205–2211.
(9) Terrence, C. F.; Sax, M.; Fromm, G. H.; Chang, C.-H.; Yoo, C. S. *Pharmacology*, in press.

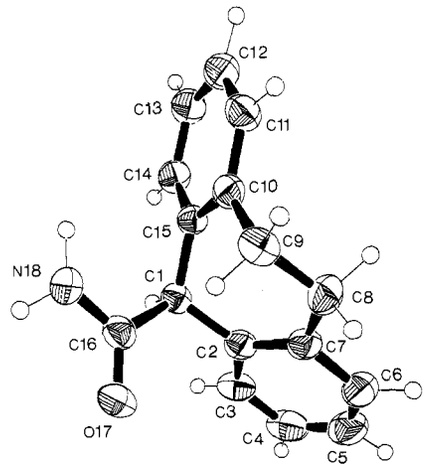

Figure 1. The conformation and atomic labeling scheme for cyheptamide. The drawing was done with the computer program ORTEP.[17] Atoms are represented by 50% probability ellipsoids, except for H atoms which are represented by spheroids of 0.1-Å radius.

in terms of the Camerman stereochemical model. In addition, further similarities in terms of bond lengths will be sought to strengthen the model for anti-GTC seizure activity.

Experimental Section

The sample of cyheptamide was a gift from Gary L. Jones of the Texas College of Oesteopathic Medicine. Cyheptamide was crystallized from an ethanol/CCl_4 mixture. Dr. Frank Popp of the University of Missouri-Kansas City provided the sample of 3-hydroxy-3-phenacyloxindole;[10] it was crystallized from a CCl_4/acetone mixture. The crystallographic and experimental data for both compounds are summarized in Table I. The unit cell parameters and orientation angles for each crystal were obtained by the method of least squares from the positional parameters of 25 reflections individually centered on an Enraf–Nonius CAD4 diffractometer. The diffracted intensities were collected by an ω–2θ scan. They were corrected for Lorentz and polarization effects, but corrections for absorption were deemed unnecessary.

The structures were solved by direct methods by the program MULTAN[11] and were refined by nonlinear least-squares analysis. Unit weights were used for **5** and $w = [\sigma(F_o)^2 + 0.002F_o^2]^{-1}$ for **6a**. The hydrogen atoms were identified in difference Fourier syntheses and were included in the models. In both structures, the coordinates of the hydrogen atoms were refined; in **5** their isotropic thermal parameters were also refined. The final values of the reliability indices are given in Table I. The scattering factors used in the refinement were those of Cromer and Mann.[12] The programs were those of the XRAY76[13] system of programs.

The positional and anisotropic thermal parameters for the carbon, nitrogen, and oxygen atoms, the positional and isotropic thermal parameters for the hydrogen atoms, and lists of structure factors for both structures are available (see the paragraph at the end of the paper regarding supplementary material).

Results

The structures and atomic labeling schemes of **5** and **6a** are shown in Figures 1 and 2, respectively. In cyheptamide (Figure 1), there is a concave hydrophobic surface made up of the three fused rings. The plane of the amide group is nearly perpendicular to each of the phenyl ring planes.

Table II. Bond Distances (Angstroms) and Angles (Degrees) for the C, N, and O Atoms of Cyheptamide and 3-Hydroxy-3-phenacyloxindole

cyheptamide		phenacyloxindole	
atoms	distances	atoms	distances
C1-C16	1.542 (5)	C1-C2	1.504 (2)
C1-C2	1.522 (5)	C1-O1	1.424 (2)
C1-C15	1.513 (5)	C1-C9	1.548 (2)
C2-C3	1.398 (5)	C1-C11	1.523 (2)
C2-C7	1.401 (5)	C2-C3	1.376 (2)
C3-C4	1.387 (6)	C2-C7	1.393 (2)
C4-C5	1.373 (7)	C3-C4	1.389 (3)
C5-C6	1.374 (7)	C4-C5	1.382 (3)
C6-C7	1.409 (6)	C5-C6	1.381 (3)
C7-C8	1.522 (6)	C6-C7	1.382 (2)
C8-C9	1.525 (5)	C7-N8	1.399 (2)
C9-C10	1.499 (5)	N8-C9	1.353 (2)
C10-C11	1.393 (5)	C9-O9	1.220 (2)
C10-C15	1.398 (5)	C11-C12	1.505 (2)
C11-C12	1.387 (6)	C12-O12	1.218 (2)
C12-C13	1.386 (6)	C12-C13	1.490 (2)
C13-C14	1.388 (6)	C13-C14	1.390 (2)
C14-C15	1.389 (5)	C14-C15	1.377 (3)
C16-O17	1.225 (5)	C15-C16	1.374 (3)
C16-N18	1.330 (5)	C16-C17	1.374 (3)
		C17-C18	1.386 (3)
		C18-C13	1.384 (2)
	angles		angles
C16-C1-C2	111.8 (3)		
C16-C1-C15	114.7 (3)	O1-C1-C2	112.9 (1)
C2-C1-C15	115.2 (3)	O1-C1-C11	104.6 (1)
C1-C2-C3	116.1 (3)	O1-C1-C9	109.7 (1)
C1-C2-C7	124.9 (3)	C2-C1-C11	115.8 (1)
C3-C2-C7	119.0 (3)	C2-C1-C9	101.6 (1)
C2-C3-C4	122.0 (4)	C11-C1-C9	112.3 (1)
C3-C4-C5	118.6 (4)	C1-C2-C3	131.2 (1)
C4-C5-C6	120.8 (4)	C1-C2-C7	109.0 (1)
C5-C6-C7	121.5 (4)	C3-C2-C7	119.8 (2)
C6-C7-C2	118.0 (4)	C2-C3-C4	118.9 (2)
C6-C7-C8	114.9 (3)	C3-C4-C5	120.5 (2)
C2-C7-C8	127.1 (3)	C4-C5-C6	121.4 (2)
C7-C8-C9	118.0 (3)	C5-C6-C7	117.4 (2)
C8-C9-C10	111.9 (3)	C2-C7-C6	122.0 (2)
C9-C10-C15	119.6 (3)	C6-C7-N8	128.7 (2)
C9-C10-C11	121.3 (3)	C2-C7-N8	109.3 (1)
C15-C10-C11	119.1 (3)	C7-N8-C9	111.9 (1)
C10-C11-C12	121.1 (4)		
C11-C12-C13	119.5 (4)		
C12-C13-C14	119.8 (4)	C1-C9-O9	125.5 (1)
C13-C14-C15	120.9 (4)	N8-C9-O9	126.6 (1)
C14-C15-C10	119.5 (3)	N8-C9-C1	107.8 (1)
C14-C15-C1	120.3 (3)	C1-C11-C12	114.9 (1)
C1-C15-C10	120.2 (3)	C11-C12-O12	120.2 (1)
C1-C16-O17	120.6 (3)	O12-C12-C13	121.0 (1)
C1-C16-N18	116.7 (3)	C11-C12-C13	118.8 (1)
O17-C16-N18	122.5 (3)	C12-C13-C14	118.5 (1)
		C12-C13-C18	122.6 (1)
		C14-C13-C18	118.9 (1)
		C13-C14-C15	120.6 (2)
		C14-C15-C16	120.2 (2)
		C15-C16-C17	119.7 (2)
		C16-C17-C18	120.6 (2)
		C17-C18-C14	119.9 (2)

The phenacyloxindole structure (Figure 2) also assumes a curved shape, which is achieved by rotation about the C11–C12 bond to position the phenacyl group over the indole ring; thus, the phenyl and indole rings are trans and perpendicular to each other. Apparently, this is a stable conformation of this molecule, as it is not determined by short intermolecular contacts or any intramolecular hydrogen bonds.

The bond distances and angles for both structures are given in Table II. In both structures, the carbonyl carbon atom to tetrahedral carbon atom bond distances are typical

(10) Popp, F. D.; Donigan, B. E. *J. Pharm. Sci.* **1979**, *68*, 519–520.
(11) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27*, 386–376.
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(13) Stewart, J. M. "The X-ray System of Crystallographic Programs"; Computer Science Center, University of Maryland: College Park, MD, 1976.

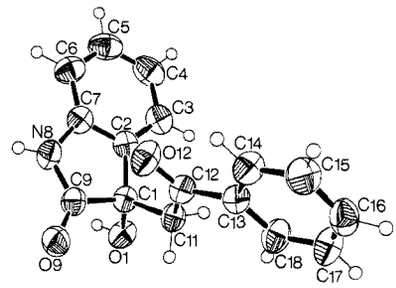

Figure 2. The conformation and atomic labeling scheme for 3-hydroxy-3-phenacyloxindole. The drawing was made as described for Figure 1.

single-bond values. The nitrogen atoms show considerable sp^2 character. In cyheptamide, the angles subtended by the nitrogen atom are all approximately 120°: C16–N18–H181 = 116 (3)°, C16–N18–H182 = 123 (3)°, H181–N18–H182 = 120 (4)°. Similarly, in **6a** the exocyclic angles are H8–N8–C7 = 127 (1)° and H8–N8–C9 = 120 (1)°, and in the ring the C7–N8–C9 angle is 111.9 (1)°.

The hydroxyphenacyloxindole crystal structure has one intermolecular hydrogen bond between the carbonyl oxygen atom O9 and the hydroxyl group of the molecule at $(x, -y, +z)$. This hydrogen bond determines only the orientation of the hydroxyl group, not the shape of the molecule. The O9···O1 distance is 2.732 (2) Å, the H1···O9 distance is 1.81 (2) Å, and the O9···H1–O1 angle is 172 (1)°, all typical values for an O–H···O hydrogen bond. Cyheptamide has a much weaker intermolecular hydrogen bond between the carbonyl oxygen O17 and the amine group at $(-x, -y, {}^3/_2-z)$. The dimensions are as follows, O17···N18 distance, 2.858 (4) Å; O17···H182 distance, 2.07 (5) Å; O17···H182–N18 angle, 131 (3)°.

The similarity of the shapes of the two molecules can be quantitatively measured by the angles between the planar rings of the structures. In cyheptamide, the angle between the two phenyl rings is 121.8°, and the amide plane forms angles of 96.3 and 101.3° to the two phenyl rings. In **6a**, the amide group is required to be in the plane of the indole ring. This plane is 92.3° from the plane of the phenyl ring, thus preserving one-half of the molecular arrangement found in cyheptamide; the plane of the amide is approximately 90° from one aromatic ring.

Discussion

Because both cyheptamide[5] and hydroxyphenacyloxindole[6] exhibit protection against MES-induced seizures, they are potential agents against generalized tonic–clonic seizures. At present, diphenylhydantoin (DPH) is one of the most frequently prescribed drugs for this disorder. The structures of these three compounds show some striking similarities both in bond distances and in overall shape. Table III compiles bond distances for four representative MES-protective compounds and, for comparison, a chemically related anti-MET drug, trimethadione.[14] The region of commonality in these compounds, as has been noted by Jones et al.,[15] is an amide group connected to a tetrahedral atom that has either phenyl or alkyl substituents. The four

Table III. Bond Distances in the N-C(O)-Cα Moiety of Anticonvulsants

compd	N-C	C=O	C-Cα
cyheptamide	1.330 (5)	1.225 (5)	1.542 (4)
phenacyloxindole	1.353 (2)	1.220 (2)	1.548 (2)
carbamazepine[a]	1.345 (4)	1.227 (4)	1.381 (4)[b]
diphenylhydantoin[c]	1.343 (8)	1.223 (8)	1.548 (8)
trimethadione[d]	1.357 (3)	1.210 (2)	1.510 (3)

[a] Reference 8. [b] The α-position is occupied by a nitrogen atom in carbamazepine. [c] Reference 7. [d] Reference 9.

anti-MES drugs show the same trend in distances for this segment, namely, a C–C bond distance near a single-bond value, a C=O distance which is lengthened, and a short C–N distance. This trend becomes more interesting when these structural parameters are compared to those in trimethadione, a compound with different antiseizure activity. In trimethadione, the C–C bond is short, as is the C=O double bond, while the C–N bond is lengthened. For the compounds with aromatic substituents on the tetrahedral or α-carbon atom, the electron-withdrawing properties of the phenyl ring apparently isolate the amide group so that the lone pair on the nitrogen atom and the π electrons of the carbonyl bond are delocalized over the three atoms (N–C=O). By comparison, in trimethadione, there is an increase in the bond order in the C–C bond, and the lone pair is isolated on the nitrogen atom. This difference must be taken as merely an indication of a trend, since structural data are available for only one example, trimethadione, of an antiabsence seizure drug. (Other drugs whose structures are known and that are effective against this type of seizure have been identified as carbonic anhydrase inhibitors.)

The geometry around the nitrogen atom in the phenacyloxindole molecule is planar, as is shown in the least-squares plane calculation through the atoms C7, C2, N8, C9, and O9. The standard deviation of this plane is 0.028 Å, and all atoms are closer than two standard deviations to the plane. In DPH[8] the hydantoin ring is also planar, with the largest deviations from the plane being those of the carbonyl oxygen atoms. Calculation of the planarity of the nitrogen atom geometry in carbamazepine and cyheptamide is precluded because of the imprecise positions of the hydrogen atoms in the amino group; however, the angles subtended by the nitrogen atoms in these structures also indicate sp^2 character in the bonding. In contrast to these examples of planar geometry, the least-squares plane of the oxazolidinedione ring (less the nitrogen atom) in trimethadione[14] shows a nearly planar, six-atom system with the nitrogen atom greater than 4 times the distance from the plane of any other atom, i.e, 0.083 Å. Thus, the trend seen in the bond distances of the two compounds, that the nitrogen atom in trimethadione had less s character and is thus more pyramidal, is also apparent in the calculation of least-squares planes. Again, there is an indication of a difference in these two drugs.

The general stereochemical features of anticonvulsants with aromatic substituents as described by Camerman and Camerman[2] are present to a limited extent in the two structures presented here, cyheptamide and phenacyloxindole. In the first four structures listed in Table III, the angles between the plane of the amide and the planes of aromatic rings fall in the range 92–114° (except the amide plane in **6a**, which is in the plane of the indole ring). In diphenylhydantoin and **6a**, the angles between the two aromatic groups are ca. 90°, while in the fused ring systems of carbamazepine and cyheptamide, the angles are 125 and 122°, respectively. The distances separating the elec-

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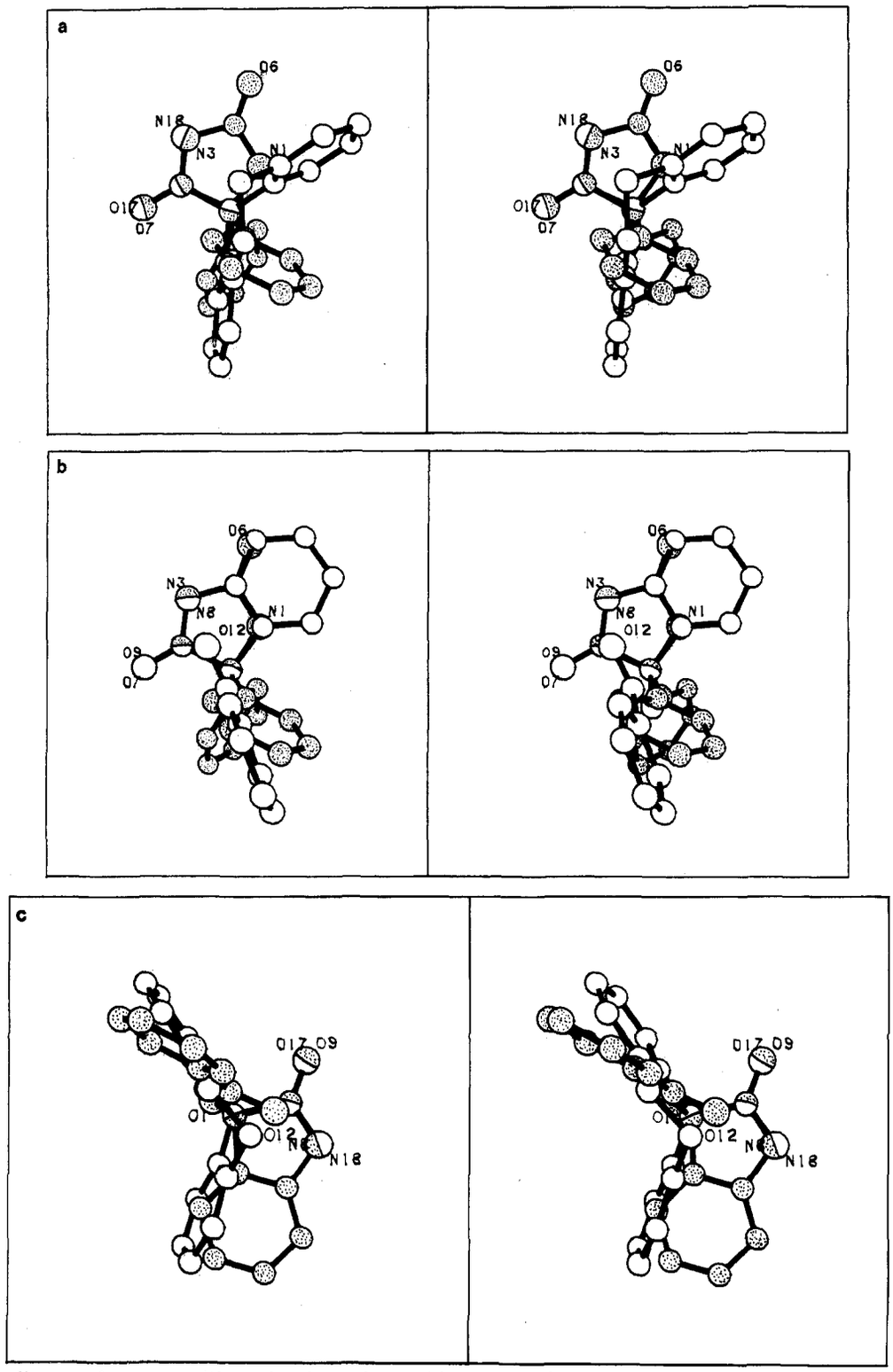

Figure 3. Stereo diagrams for superpositions of anticonvulsants, (a) cyheptamide and diphenylhydantoin, (b) hydroxyphenacyloxindole and diphenylhydantoin, and (c) cyheptamide and hydroxyphenacyloxindole, all drawn perpendicular to the plane of the amide group. These drawings were made with the computer program PLUTO.[18] In a and b, the atoms of diphenylhydantoin are dotted; in c, cyheptamide atoms are dotted.

tron-donating groups in cyheptamide and phenacyloxindole do not fall in the range previously identified as the necessary one for activity.[2] In cyheptamide, only two atoms, O17 and N18, can be identified as electron donating. Amide nitrogen atoms are more usually hydrogen-atom donors rather than acceptors; however, if the nitrogen atoms are taken as electron donors, the separation of O17 and N18 is only 2.25 Å, a value below the lower limit defined[2] as necessary for anticonvulsant activity. Both cyheptamide and carbamazepine have this short distance between the carbonyl oxygen atom and the nitrogen atom, yet both compounds have significant anticonvulsant effects.[5] In phenacyloxindole, the same caveat regarding amide nitrogen atoms is true, but the possible electron-donor groups with the same spatial relationship to the hydrophobic groups as in DPH and cyheptamide are N8 and O9. These atoms are separated by 2.30 Å, which is also shorter than the range for activity. If the two carbonyl

oxygen atoms are taken as the electron-donating atoms, the O9–O12 separation of 3.17 Å fits within the active range; however, the phenyl ring to O9 distance is long (5.96 Å), and the phenyl rings of DPH and **6a** do not superimpose in an orientation that places O9 and O12 over the carbonyl oxygen atoms of DPH.

Plots of the superpositions of the structures of cyhepatmide and DPH, as well as phenacyloxindole and DPH, show some striking differences in the shapes of the molecules. As shown in Figure 3a,b, the anticonvulsants studied in this work overlap nicely with DPH in the amide region and in the region of one hydrophobic group; however, overall it is evident that DPH has a different shape from the other molecules, because to superimpose both of the two hydrophobic portions of cyheptamide and diphenylhydantoin the planes of the amide portions of the two would have to be perpendicular to each other. Otherwise, when the amide groups are superimposed, the diphenylhydantoin has both phenyl rings in the general hydrophobic region occupied by one phenyl ring of cyheptamide and the phenacyl ring of the phenacyloxindole compound. The other hydrophobic region, which is occupied by a phenyl ring in cyheptamide and the indole in **6a**, is partially filled by the non-amide part of the hydantoin ring. A comparison of cyheptamide and phenacyloxindole (Figure 3c) shows that they occupy the same volume in space with one exception: the indole ring in **6a** is approximately perpendicular to the comparable phenyl ring in cyheptamide. The conclusions obtained from the comparisons in Figure 3 are enhanced by a superposition of the structures of carbamazepine and cyheptamide, which are nearly identical; the largest deviation of two similar atoms in the least-squares fit of the two structures is 0.6 Å. Thus, three structures, carbamazepine, cyheptamide, and phenacyloxindole, fit nearly the same three-dimensional molecular envelope for the amide group and one aromatic group and overlap partially for the other aromatic group.

A model that would accommodate *all four drugs* with anti-MES induced seizure activity would require an amide group with delocalized electrons and a planar nitrogen atom and would have only one binding site for an aromatic moiety. If both hydrophobic groups are required for binding, then it is probable that the stereochemical requirements for these compounds are imprecise because only a rather large hydrophobic pocket could accommodate both groups in all of the anti-MES anticonvulsants studied. Comparison of diphenylhydantoin to the other compounds indicates that the spatial requirement is probably for one hydrophobic group. It is possible that the main function of the hydrophobic groups is to assure bioavailability. Structure–activity studies[5,14] on anticonvulsants indicate that brain concentrations of the drugs are quite different from those in the blood; these differences may account for much of the data on activity in the literature and for the apparent need for two hydrophobic groups.

Clearly, further evaluation of the π-electron delocalization trends, as well as structural studies on a large number of similar anticonvulsants, are necessary for the development of a predictive model for anticonvulsant activity. Semiempirical calculations, as well as X-ray structural analyses, on several anticonvulsants are in progress.

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Supplementary Material Available: Positional and anisotropic thermal parameters for all non-hydrogen atoms, positional and isotropic thermal parameters and bond distances for hydrogen atoms, and lists of observed and calculated structure factor amplitudes (35 pages). Ordering information is given on any current masthead page.

Phosphorus Analogues of γ-Aminobutyric Acid, a New Class of Anticonvulsants

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A series of phosphorus compounds, designed as analogues of γ-aminobutyric acid (GABA) in that they possess a P=O moiety separated by three atoms from an amino or acetamido group, was synthesized and tested by using in vitro $GABA_A$ and $GABA_B$ receptor binding, GABA uptake assays, and was examined for anticonvulsant activity. Weak $GABA_B$ receptor affinity was noted for one agent, whereas six compounds displayed moderate to high potencies as inhibitors of electroshock- and pentylenetetrazol-induced seizures. The best anticonvulsant effect was found with the (*m*-aminophenyl)phosphinic acid compounds, with members of this class selected for further study.

Derivatives of γ-aminobutyric acid (GABA), an inhibitory central neurotransmitter, were synthesized and tested for in vitro and in vivo biological activities associated with convulsive disorders. Anticonvulsant drugs have been developed that mimic GABA at its brain receptor or elevate endogenous levels of the amino acid by inhibiting catabolic enzymes.[1] The success of these approaches led to the design and study of diverse chemical types of phosphorus compounds structurally related to GABA and potentially capable of producing similar therapeutic effects. Most of these agents are of the following general formula, which involves a P=O or P=S moiety in lieu of the carbonyl group present in GABA and a separation of these by three atoms from an amino or acetamido substituent:

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