a period of 4.5 hours. The 30-Ghz trace provides a useful indication of the amount of liquid water in the direction of the sun. Time proceeds from left to right at two major divisions per hour. Early in the period shown, the sky was clear. Soon broken, dark-bottomed cumulus clouds moved in, however, and in the middle of the picture a rain shower occurred.

The records from 28 October 1968 to 30 July 1969 were analyzed to determine the percentage of the time that the attenuation exceeded 10, 20, and 30 db. The results were 48, 43, and 34 percent. I conclude that, if the 10-μm atmospheric window is to be useful for earth-space communication, the earth station will have to be in a climate very different from the New Jersey climate; alternatively, the system will have to work through attenuations much greater than 30 db.

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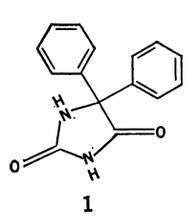
29 January 1970

Diphenylhydantoin and Diazepam: Molecular Structure Similarities and Steric Basis of Anticonvulsant Activity

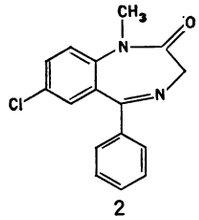
Abstract. *Diphenylhydantoin and diazepam are two useful antiepileptic drugs. Though not obviously related chemically, their molecular conformations exhibit marked similarities. These similarities indicate a steric basis for their anticonvulsant activity and lead to conclusions about the receptor sites for this type of pharmaceutical.*

Differently substituted barbiturates, hydantoins, and oxazolidinediones exhibit different hypnotic and anticonvulsant properties. Compounds with ethyl or other aliphatic groups substituted at C-5 are commonly used as sedatives, whereas C-5 phenyl substitution is necessary to obtain effective activity against grand mal epilepsy. These facts indicate to us a possible steric basis of behavior of this type of drug: that is, that conformational structure may be a primary factor in determining pharmacological properties. In order to test the validity of this hypothesis, we have determined the crystal and molecular structures of diphenylhydantoin (Dilantin) and diazepam (Valium), two clinically useful antiepileptic drugs which are not closely related chemically.



1

Diphenylhydantoin



2

Diazepam

Since its introduction into medicine in 1938 (*1*), diphenylhydantoin (DPH) has been an extremely effective and widely used drug for the treatment of grand mal epilepsy. Diazepam (DAP) and other benzodiazepines, first introduced as tranquilizing agents, possess specific anticonvulsant action to varying degrees against grand mal, psychomotor, and petit mal epilepsies (*2*). Indeed, after extensive research and clinical investigation (*3*), DAP has been praised as the "drug of choice for the emergency treatment of all cases of status epilepticus" (*4*).

Diphenylhydantoin was obtained as the sodium salt and crystallized as the free acid from aqueous solution at *p*H 11. The crystals are orthorhombic with $a = 6.230$, $b = 13.581$, $c = 15.523$ Å; space group $Pn2_1a$ with $Z = 4$ molecules per unit cell. Intensities of 1210 reflections to $2\theta = 50°$ for MoKα were measured on a manual four-circle diffractometer. Preliminary statistics indicated a centrosymmetric space group and the 13 atoms comprising the hydantoin group and one phenyl ring were located by the symbolic addition procedure (*5*) applied to space group *Pmna*. This space group restricts the central hydantoin ring so that it lies in a mirror plane at $y = \frac{1}{4}$ and the two phenyl groups so that they are related through the mirror. When this structure failed to refine, space group $Pn2_1a$ was chosen and the atoms of the second phenyl ring were located in a Fourier map calculated from the 13 atomic positions previously determined in space group *Pmna*. After refinement by least-squares methods, the discrepancy index R was shown to be 0.052.

Diazepam crystals were grown from

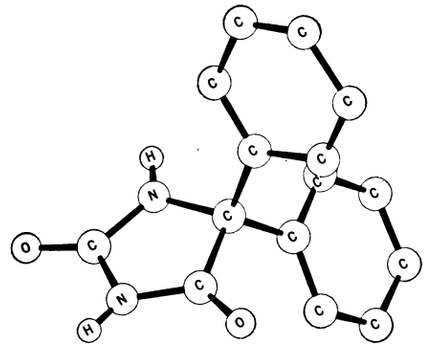


Fig. 1 (left). Perspective drawing of the diphenylhydantoin molecule.

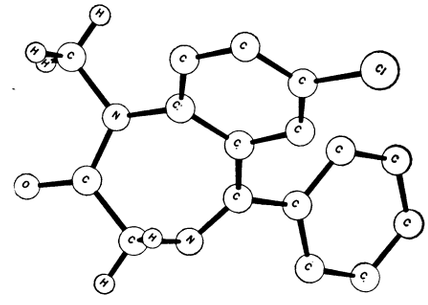


Fig. 2 (right). Perspective drawing of the diazepam molecule.

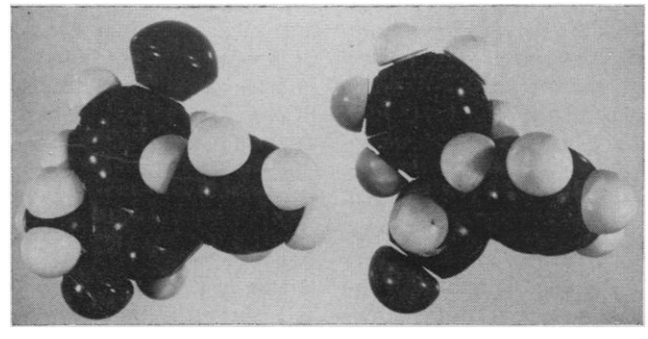


Fig. 3. Photograph of space-filling models of diazepam (left) diphenylhydantoin.

a water-acetone solution. They crystallize in space group $P2_1/a$ with $a = 12.928$, $b = 13.354$, $c = 7.976$ Å, and $\beta = 90.01°$. Intensities of 3171 reflections to $2\theta = 55°$ were measured as for DPH. The crystal structure was solved by the symbolic addition procedure, and all of the nonhydrogen atoms were located in the first E map. After refinement of the atomic positions and anisotropic thermal parameters, the discrepancy index R was found equal to 0.039.

Perspective drawings of DPH and DAP molecules are shown in Figs. 1 and 2, respectively. The two phenyl groups of DPH lie at angles of 114° and 113° to the hydantoin ring, and at an angle of 90° to each other. The phenyl group in DAP makes an angle of 124° with the chlorophenyl ring. Scale models constructed to fit the observed atomic positions (Fig. 3) reveal a high degree of similarity in the conformational structures of the two anticonvulsants. Similarities in the space-filling features of the two molecules are especially striking in two aspects: (i) the arrangement of the two phenyl rings in each molecule with respect to each other, and (ii) the similar positioning in each molecule of two electron-donating groups. When the DPH and DAP molecules are superimposed so that the two phenyl rings of DPH approximately match the orientation of the phenyl and chlorophenyl rings of DAP, a ketonic oxygen of DPH and the ketonic oxygen of DAP occupy the same position in space as do the second ketonic oxygen of DPH and a trigonal nitrogen of DAP.

The role of DAP as a most important antianxiety agent and at the same time as one of the most important anticonvulsant drugs in experimental epilepsy seemingly contradicts the general rule that desynchronizing drugs are also good antiepileptics, while synchronizing drugs may have a facilitating role on seizure discharge (*6*). It may be that the various therapeutic activities of the benzodiazepines and other drugs that act upon the central nervous system are functions of two distinct molecular features—chemical composition and molecular shape. Either one or both of these features may be the determining factor in the effectiveness of drugs in the treatment of different pathological conditions. It seems clear from our structural results that the anticonvulsant properties of DAP and DPH are a consequence, to a large degree, of the three-dimensional molecular configuration of these compounds, particularly the orientational relation between the bulky rings and the electron-donating functional groups. How the steric configuration influences the exact mechanism of seizure suppression is not known. Two possible structure-dependent modes of action are that (i) the drugs may inhibit enzyme reactions that facilitate transfer of electrical energy in the brain or activate other enzyme systems that hinder such transfer, or that (ii) they may interact with membrane walls and alter the diffusion characteristics of brain cells, thus radically affecting the concentrations of sodium and potassium ions inside and outside cell membranes. An analogous mode of behavior has been independently proposed for the action of DDT (*7*).

The search for antiepilepsy agents has heretofore been directed along purely chemical lines. We suggest that a conformational approach to this problem, that is, the choosing of experimental medications on the basis of their conformational rather than chemical similarities to existing drugs, may be useful in developing new and more effective therapies. The conformational similarities between **1** and **2** also suggest that this approach may be valuable in identifying receptor sites of anticonvulsant drugs and thus elucidating the mechanism of seizures. The biological relevance of our findings can best be assessed from evidence on the question of whether other compounds with diphenylhydantoin-diazepam steric conformations always have antiepileptic activity.

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Plasmalemmal and Subsurface Complexes in Human Leukemic Cells: Membrane Bonding by Zipperlike Junctions

Abstract. *After a brief exposure to agents that provoke phagocytosis, monocytic cells from patients with acute leukemia exhibit pentalaminar and septate membranous complexes. These structures connect plasma membranes of adjacent cells and join surfaces of approximating pseudopodia on the same cell; they also appear to be present in cortical areas of the cytoplasm.*

In the course of studies of the ultrastructure and function of leukemic cells during chemotherapy, junctional surface specializations were elicited in monocytic cells from several patients with acute monocytic and monomyelocytic leukemia. To our knowledge such specializations in hematopoietic cells have not been reported (*1*). However, intercellular junctions with a multiplicity of fine-structured subunits are present in normal, differentiated, solid tissues of vertebrate and nonvertebrate species (*2*) and have been associated with functions of selective permeability (*3*), electrical coupling (*4*), cell adhesion, and contact inhibition (*5*). Intercellular adhesion sites have also been demonstrated in studies of dissociated normal cells and cells transformed by viruses and carcinogens (*6*).

Our experiments were designed to test phagocytic competence. Specimens of peripheral blood were obtained at various times during treatment and were aspirated into heparin-rinsed plastic syringes (*7*). Chemotherapeutic agents varied from patient to patient. In most instances specimens were obtained when patients were in regression, just before a new course of treatment was initiated. After gravity sedimentation of erythrocytes, the cell-rich plasma was diluted (1:1) with Hanks base medium containing 10 percent calf serum. Samples (4 ml) containing 1×10^6 to 5×10^6 cells were incubated for 15 minutes at 37°C. To each tube, 0.2-ml suspensions of thorium dioxide or *Pseudomonas aeruginosa* (*8*) were added and incubation was continued for 15 or 20 minutes. Controls were set up