lized once from petroleum ether; 20 g (0.055 mol) of the semipure bromomethyl compound (*ca.* 90% by nmr) was dissolved in 500 ml of acetone and 10 g (0.15 mol) of KCN in 40 ml of H_2O was added to the solution. The reaction mixture was stirred and warmed at 50–60° for 12 hr. The solvent was removed under reduced pressure. The residue was extracted with Et_2O, washed (H_2O), and dried ($CaSO_4$), and the organic layer was evaporated under reduced pressure. The crude cyanomethyl compound **1** (14 g) was recrystallized from petroleum ether, mp 104–105°.

4-(*p*-chlorophenylthio)phenylacetonitrile was prepared in a similar manner from 4-chloro-4′-methyldiphenyl sulfide.[14] However, this acetonitrile was an oil which could not be recrystallized and was used as such in the next step.

α-Cyano-4-(2-naphthylthio)phenylacetaldehyde (2). The cyanomethyl compound **1** (16.5 g, 0.06 mol) was mixed with a NaOEt solution prepared from 1.5 g (0.065 mol) of Na and 100 ml of EtOH. Ethyl formate (45 g, 0.77 mol) was added to the solution and the mixture was refluxed for 2 hr. The solvent was removed, H_2O was added to the residue, and the aqueous mixture was acidified with HCl. The solution was extracted with Et_2O, washed (H_2O), dried ($CaSO_4$), and evaporated. A gummy solid remained, which on heating with petroleum ether turned into a solid (yield, 11 g). Recrystallization from petroleum ether–Et_2O gave a solid with mp 161–162°.

1-Cyano-1-[(4-chlorophenylthio)phenyl]butanone-2 (5). NaH Method. A solution of 30 g (0.065 mol) of the crude cyanomethyl compound (60% by nmr) in 100 ml of $PrCO_2Et$ was added dropwise to a suspension of 6.5 g (0.16 mol) of NaH (58% oil dispersion) in 50 ml of $PrCO_2Et$ at room temperature. After addition of about one-fourth of the cyanomethyl compound the reaction became exothermic and was placed in an ice bath. After the vigorous reaction subsided the remainder of the cyanomethyl compound was added to the mixture and stirring was continued overnight. The reaction was poured into ice–water and extracted with Et_2O, and the Et_2O layer was discarded. The clear aqueous layer was acidified with HCl and extracted with Et_2O, washed (H_2O), dried ($CaSO_4$), and evaporated to yield an oily substance which on standing overnight turned to a solid: yield, 10 g. Recrystallization was from petroleum ether, mp 75–77°.

NaOEt Method. Preparation of **5** was accomplished employing the procedure outlined for **2**; however, the yield was less than 10%. The material obtained for by the NaOEt method was identical with that obtained by the NaH method.

α-Cyano-β-isobutoxy-4-(2-naphthylthio)styrene (14). The formyl compound **2** (7.6 g, 0.025 mol) was dissolved in 150 ml of toluene to which was added 2.5 g of *i*-BuOH and 0.5 g of *p*-TsOH. The mixture was refluxed in a Dean-Stark apparatus for 10 hr. The solvent was removed under reduced pressure and the residue was extracted with Et_2O. The Et_2O layer was washed with $NaHCO_3$ and H_2O and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The oily residue was recrystallized from petroleum ether: the yield of **14** was 0.7 g, mp 109–110°. *Anal.* ($C_{23}H_{21}NOS$) C, H.

β-Isobutoxy-α-cyano-4-(*p*-chlorophenylthio)styrene (15) was prepared in a similar manner and recrystallized from petroleum ether, 99–100°. *Anal.* ($C_{19}H_{18}ClNOS$) C, H.

β-Isobutoxy-β-ethyl-α-cyano-4-(*p*-chlorophenylthio)styrene could not be prepared using the above conditions; however, refluxing the appropriate ketone in xylene for 48 hr produced about a 30% conversion to the enol ether as assessed by nmr. The crude mixture of enol ether gave the expected pyrimidine on treatment with guanidine (see below).

2,4-Diamino-5-[4-(2-naphthylthio)phenyl]pyrimidine (6). The isobutoxy ether **14** (4 g, 0.011 mol) was mixed with a suspension of 2 g (0.02 mol) of guanidine hydrochloride in a NaOEt solution prepared from 1 g (0.04 mol) of Na and 100 ml of EtOH. The mixture was refluxed for 2 hr and cooled, and the solid was filtered, washed with Et_2O, and crystallized from EtOH: yield, 2.0 g; mp 194–195°. The hydrochloride salt **7** was prepared by dissolving the base in Et_2O and adding concentrated HCl. The resulting solid was filtered and recrystallized from H_2O: mp 325–326°.

2,4-Diamino-5-[4-(*p*-chlorophenylthio)phenyl]-6-ethylpyrimidine (12). A solution of **5** (4.5 g, 0.014 mol) was allowed to react with CH_2N_2 in Et_2O, prepared from 8 g of *N*-nitrosomethylurea,[15] at 0° and allowed to warm to room temperature, with stirring, over a 5-hr period. The excess CH_2N_2 was decomposed with HOAc, the Et_2O was washed with H_2O, $NaHCO_3$, and again with H_2O, and dried ($CaSO_4$). The solvent was evaporated under reduced pressure and a liquid was obtained which failed to crystallize. The nmr of the oil was in accord with that expected of the *O*-methyl ether and the material was used directly. The *O*-methyl ether (3 g, 0.009 mol) was added to a solution of NaOEt (0.078 mol), prepared from 1.8 g of Na in 75 ml of EtOH, containing 4 g (0.04 mol) of guanidine hydrochloride and the mixture was refluxed for 2 hr. The EtOH was removed under reduced pressure and the residue was treated with H_2O and extracted with Et_2O. A white solid appeared at the interface and was removed by filtration and washed with H_2O and Et_2O. The solid was recrystallized from C_6H_6–EtOH, mp 215–216°.

2,4-Diamino-5-(2-naphthylsulfonyl)pyrimidine (8). H_2O_2 Method. The corresponding sulfide **6** (1 g, 0.003 mol) was dissolved in 20 ml of acetic acid and mixed with 10 ml of 30% H_2O_2, and the mixture was stirred 18 hr at room temperature. The mixture was poured into water, filtered, washed (H_2O), and crystallized from ethanol, mp 274–275°.

MCPA Method. The corresponding sulfide **6** (1.1 g, 0.0032 mol) was dissolved in 150 ml of CH_2Cl_2, 1.35 g (0.066 mol) of 85% MCPA was added, and the mixture was stirred at room temperature for 1 hr and at reflux for 15 min. The reaction mixture was treated with a dilute $NaHCO_3$ solution and a solid appeared at the interface which was separated by filtration. The solid was washed with H_2O, Et_2O, and finally with EtOH: yield, 0.25 g; mp 274–275°. A mixture melting point with a sample prepared by the above method showed no depression.

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Quinazolines and 1,4-Benzodiazepines. 64. Comparison of the Stereochemistry of Diazepam with That of Close Analogs with Marginal Biological Activity

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Numerous attempts have been made in recent years to correlate the biological activity of various anticonvulsants with their stereochemistry.[1] However, despite the pub-

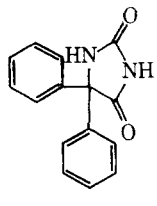
Table I. Pharmacological Activity[a]

Compd	Muscle relaxant and taming act. (mice)		Behavior (cat), MED	Anticonvulsant act. (mice)		
	Incl screen	Foot shock		Antipentylenetetrazole	Electroshock Max	Electroshock Min
1[b]	50[c]	>100	20[c]	>800	10.5	168
2[d]	30	10	0.2	1.4	6.4	64
3[b]	>200	>100	>50	>800	83	>800
4[b]	250	>100	>20	800	50	100

[a] A detailed description of the test methods and an extended discussion of the relationship between chemical structure and biological activity of 1,4-benzodiazepines can be found in ref 8 and 9. The figures indicate the orally administered dose (mg/kg) showing the desired effect in 50% of the mice used (ED_{50}). An exception is column 3 which shows the minimal effective dose (MED) in cats (high figures indicate low activity; low figures indicate high activity). [b] We are grateful to Drs. Randall and Pool for the pharmacological data. [c] Excitation. [d] See ref 8 and 9.

lished information dealing with active species, little is reported of the conformations of analogous compounds possessing little if any activity.

In recent papers, Camerman and Camerman have compared the stereochemistry of diphenylhydantoin (**1**) with that of diazepam (**2**).[2-4] They concluded that there might be a correlation between the anticonvulsant properties of these two compounds and their conformations.[2,†] Particular attention was drawn to the fact "that the relative positioning and space-filling characteristics of the two phenyl groups in each compound are very similar, lending a striking conformational resemblance to the two molecules."[3]



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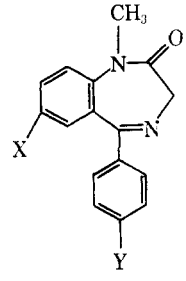

2, X = Cl; Y = H
3, X = Cl; Y = F
4, X = H; Y = H

Prompted by their conclusions and by our interest in 1,4-benzodiazepines we undertook a crystallographic study of two 1,4-benzodiazepines, **3** and **4**, which are structurally very closely related to diazepam (**2**) but have only minimal biological activity.

The pharmacological properties of these three benzodiazepines and those of diphenylhydantoin are summarized in Table I. These data show that 4′-fluorodiazepam (**3**) and 7-dechlorodiazepam (**4**) do not exhibit an interesting level of biological activity in mice, whereas diazepam (**2**) shows high pharmacological activity. On the other hand, the X-ray data show, as will be discussed below, that compounds **2**, **3**, and **4** have practically superimposable structures.

It is clear from these findings that while conformational similarities may indeed be a criterion for biological activity, generalizations based only on active species should be avoided. A systematic approach should be pursued with emphasis on both active and inactive compounds to determine if any correlation can be made.

† Publications in ref 2-4 were followed by two additional papers by the same authors discussing the stereochemistry of procyclidine hydrochloride[5a] and trihexyphenidyl.[5b]

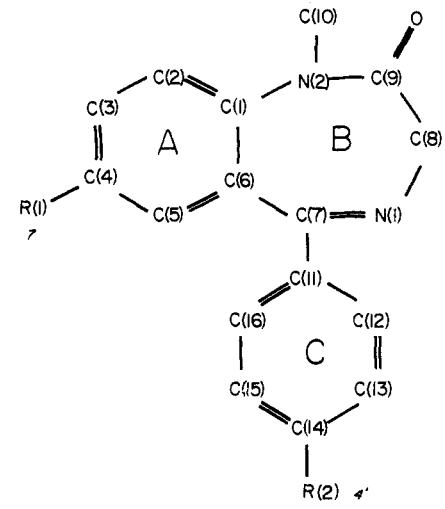

Figure 1. The atom numbering scheme. For **3**: R(1) = Cl, R(2) = F. For **4**: R(1) = H, R(2) = H.

Table II

	3	**4**
Formula	$C_{16}H_{12}ClFN_2O$	$C_{16}H_{14}H_2O$
Formula wt	302.736	250.286
Space group	$P2_12_12_1$	$P2_12_12_1$
a, Å	10.646 (2)	8.347 (2)
b, Å	15.191 (2)	11.086 (2)
c, Å	17.420 (4)	14.133 (2)
Z	8	4
d_{obsd} (KI–H_2O), g cm^{-3}	1.43	1.22
d_{calcd}, g cm^{-3}	1.43	1.27
μ (Cu Kα), cm^{-1}	25.2	6.5

Table III

	3	**4**
2θ max	133.5	133.5
No. of accessible reflections	3293	1577
No. of obsd reflections	2501	1480
Refinement	BDLS	FMLS
"Heavier" atoms	Aniso	Aniso
Hydrogens	Fixed	Iso
Final *R* (observed data)	0.041	0.043

Experimental Section

7-Chloro-1,3-dihydro-1-methyl-5-(4-fluorophenyl)-2*H*-1,4-benzodiazepin-2-one (3, 4′-Fluorodiazepam).‡ This compound was prepared from the corresponding 1-demethyl derivative[6] by methylation according to method S described in ref 6. After crystallization from ether, colorless prisms were obtained: mp 160–161.5°. *Anal.* ($C_{16}H_{12}ClFN_2O$) C, H.

1,3-Dihydro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one (4,7-Dechlorodiazepam). The compound, prepared as described in the literature,[6] was recrystallized from a mixture of methylene chloride and hexane to form colorless prisms, mp 156–157°.

Crystallography. The crystal data for **3** and **4** are shown in Table II.

Intensity data for compounds **3** and **4** were collected by a moving crystal-moving detector method on a Hilger-Watts Model Y290 four-circle diffractometer. Nickel-filtered Cu Kα radiation and pulse height discrimination were used. All data were corrected for absorption and Lorentz–polarization effects.

The structure of **3** was solved by the heavy atom method and the structure of **4** by a multiple solution procedure.[7] In each case, all hydrogen atoms were located in difference electron density maps, calculated near the conclusion of least-squares refinements. The final refinement of **3** was by block-diagonal least squares with the matrix partitioned into seven blocks; **4** was refined by full-matrix least squares. Details of the structure are summarized in Table III.

‡ We thank R. I. Fryer for the preparation of this compound.

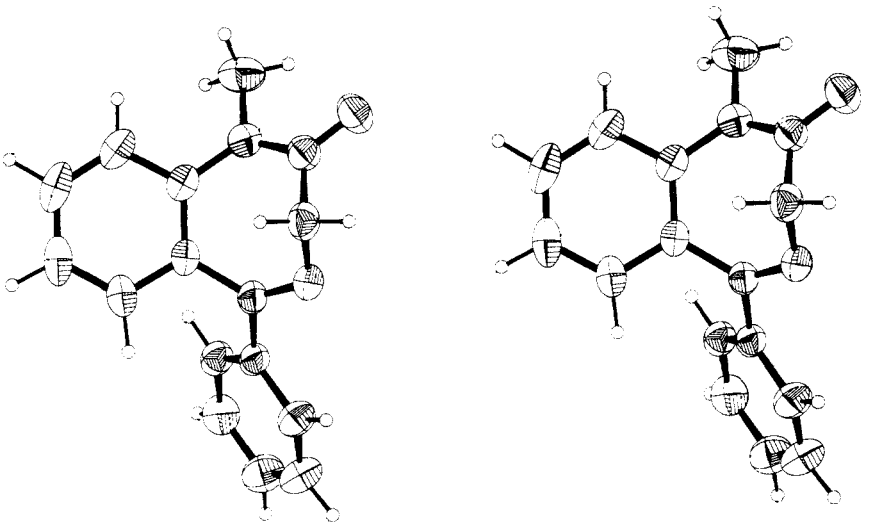

Figure 2. A stereoscopic drawing of 4. The thermal ellipsoids are scaled to 50% probability. The hydrogen atoms are shown as spheres of an arbitrary size.

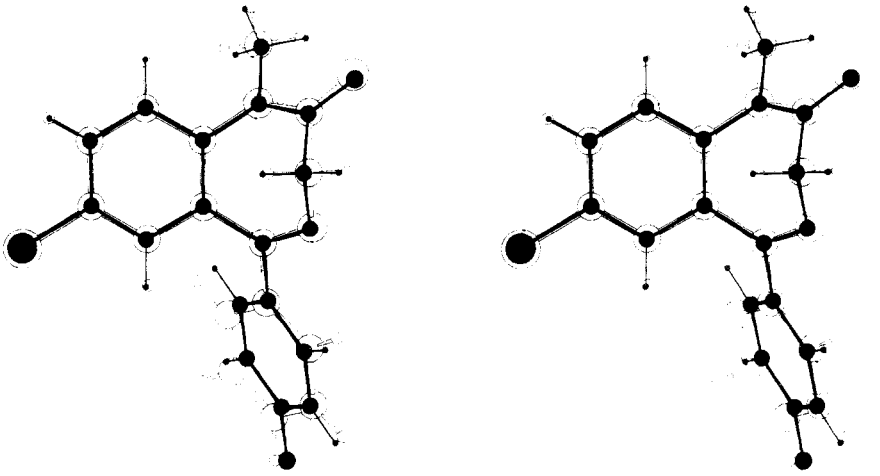

Figure 3. A stereoscopic drawing showing the structure of **3** (solid atoms and bonds) superimposed upon the structure of **2**[3] (open atoms and bonds).

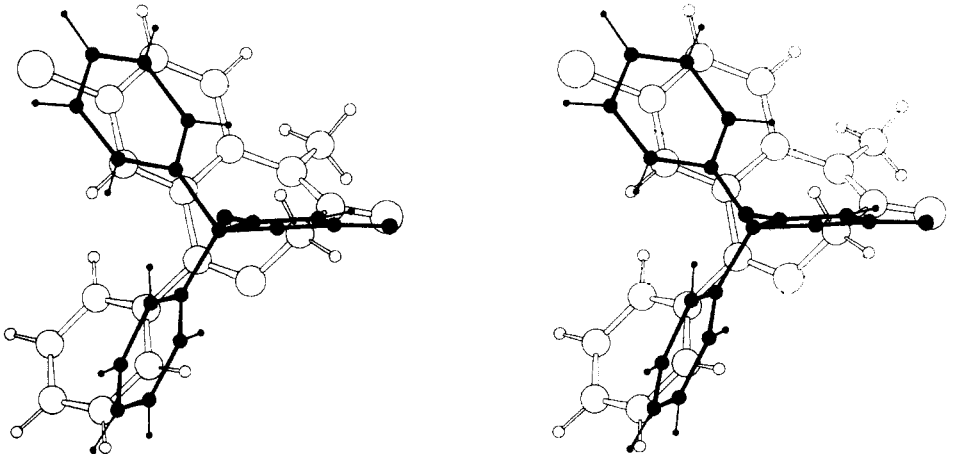

Figure 4. A stereoscopic drawing showing the structure of **1**[4] (solid atoms and bonds) superimposed upon the structure of **2**[3] (open atoms and bonds).

The bond lengths and angles in **3** and **4** are given in the microfilm addition of the journal with the atomic parameters and structure factors.§ The atom numbering scheme is shown in Figure 1.

A stereoscopic drawing showing the conformation of 4 is presented in Figure 2. A stereoscopic drawing of one of the crystallographically independent molecules of **3** is shown in Figure 3 superimposed on a drawing of **2**. Because the conformations of the two crystallographically independent molecules of **3** are nearly identical, only one has been illustrated.

Distances between the centroids of the two phenyl rings and the oxygen atoms and the angles between planes of the phenyl rings are given in Table IV for diphenylhydantoin (**1**) and the benzodiazepines 2–4.

Discussion

Several interesting observations emerge upon study of Tables I and IV.

§ See paragraph at end of paper regarding supplementary material.

Table IV. Distances (Å) between Ring Centroids and Oxygen Atoms and Angles (Degrees) between the Normals to the Phenyl Rings of Each Molecule

Compd	Ring A center to ring C center	Ring A center to oxygen	Ring C center to oxygen	Angle between normals
1[a]	4.84	5.68	5.51	90
2	5.06	5.34	6.68	125.3
3	5.06	4.99	6.46	118.4
3[b]	5.02	4.95	6.52	112.2
4	4.93	4.92	6.48	114.2

[a]References 1 and 2. [b]Values obtained for crystallographically independent molecule.

1. The separation of the ring centroids in 3 is the same as in 2 and only slightly greater than that found in 4; yet, the biological activity of 2 is much greater than that of 3 or 4.

2. The ring C to oxygen distances in 3 and 4 are about the same as those in 2, whereas the corresponding distance in 1 is about 1 Å shorter. On the other hand, the ring A to oxygen distances in 3 and 4 are both within 0.4 Å of that in 2.

3. Next consider the angles between the normals to the aromatic rings in these molecules. The angles in 2, 3, and 4 are approximately 120° whereas the angle in 1 is near 90°. Thus, there is no correlation between the anticonvulsant activity and this parameter (at least as observed in the crystalline state).

Figure 3 shows 3 superimposed upon 2 in such a manner as to have the rings coincident. It can be seen that the conformations of the two molecules are remarkably similar. There is only a small difference in the orientation of the C rings which is probably due to crystal packing forces. The only chemical difference between 2 and 3 is the 4′ substituent. It has been generally observed that 4′-substituted benzodiazepines show minimal pharmacological activity.[8,‡]

Although a separate figure showing 4 superimposed on 2 is not presented here, it is apparent from Figures 2 and 3 that the conformation of 4 is almost identical with that of 2 and 3.

For contrast, Figure 4 shows 1 superimposed on 2 so as to achieve the "best" overlap of the phenyl rings and corresponding oxygen atoms. It can be seen that there is a certain similarity in the conformation of these two active compounds, but the conformational similarity is by far not as pronounced as that found between 2 and 3.

Conclusion

Compounds 3 and 4 are more closely related, structurally and conformationally, to diazepam than diphenylhydantoin. Nonetheless, the three benzodiazepines exhibit marked differences in their anticonvulsant properties.

These findings show that conformational similarities of molecules do not necessarily indicate similar biological properties. Many other factors, many still unknown, play an important role in the biological activity of chemical entities.

Supplementary Material Available. Tables of the atomic parameters, observed and calculated structure factors, bond lengths, and angles will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-74-374.

‡ For a description of the tests, see ref 9.

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Determination of the Absolute Configuration of (+)-2-(6-Methoxy-2-naphthyl)propionic Acid†

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We have determined the absolute stereochemistry of the antiinflammatory agent (+)-2-(6-methoxy-2-naphthyl)propionic acid (naproxen,[1] 1) by degradation to (−)-2-phenyl-1-propanol (7), a substance of known[2] *S* chirality.

Reaction of (+)-2-(6-methoxy-2-naphthyl)propionic acid (1) with hydrogen bromide in acetic acid cleaved the methyl ether forming the phenolic acid 2, which was converted to the hexyl ester 3. Oxidation of 3 with sodium permanganate under buffered conditions gave the phthalic acid derivative 4, which was decarboxylated[3] by pyrolysis of the bis-*tert*-butyl peroxy ester 5 forming hexyl 2-phenylpropionate (6). Reduction of 6 with lithium aluminum hydride gave 2-phenyl-1-propanol (7) (Scheme I). Identification of 7 as the (−) antipode by measurement of the optical rotation was not considered conclusive on account of the small angles (7°) involved. However, identification was readily made by comparison with authentic samples of (−)- and (±)-7 by nmr in the presence of the chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium.[4] In the presence of 0.52 equiv of the shift reagent, a pair of doublets at 10.28 and 10.43 ppm was observed for the ortho protons of the phenyl group of (±)-7. The low-field doublet was shown to be due to the (−) antipode by addition of small amounts of authentic (−)-7. In the presence of 0.67 equiv of the shift reagent, only one doublet at 10.48 ppm was observed for 7 derived from naproxen. This was unambiguously identified as the (−) antipode by addition of authentic (−)-7.

Interconversions have been made[5-9] between optically resolved adjacent members of the series: tartaric acid, D-glyceraldehyde, serine, alanine, 2-phenylpropionic acid, and 2-phenyl-1-propanol, and the absolute configuration

† Publication No. 408 from the Syntex Institute of Organic Chemistry.