To derive discriminant functions, one can use various sets of physicochemical parameters. Here, we used the experimentally determined log P value as one parameter. Others were selected from parameters which have been used to correlate the log P or π values for each of the series, as shown in eq 12,[23] 13,[24] and 14a-c.[10] In these equations,

benzoguanamines

$$\log P = \underset{(0.038)}{0.913}\sum\pi(\text{monosubstituted benzene}) + \underset{(0.087)}{0.510}\sum\sigma + \underset{(0.069)}{0.602}E_s(\text{ortho}) - \underset{(0.165)}{0.974}\mathcal{F}(\text{ortho}) + \underset{(0.043)}{1.466}$$

$$n = 35;\ s = 0.133;\ r = 0.978 \qquad (12)$$

phenylacetic acids

$$\log P = \underset{(0.057)}{0.954}\pi(\text{monosubstituted benzene}) + \underset{(0.143)}{0.294}\sigma^\circ + \underset{(0.059)}{0.012}$$

$$n = 20;\ s = 0.079;\ r = 0.993 \qquad (13)$$

aminouracils

$$\pi_{R_1} = \underset{(0.212)}{0.815}\pi(\text{monosubstituted benzene}) - \underset{(0.616)}{0.698}\sigma^* - \underset{(0.312)}{1.020}$$

$$n = 8;\ s = 0.182;\ r = 0.976 \qquad (14a)$$

$$\pi_{R_2} = \underset{(0.342)}{0.762}\pi(\text{monosubstituted benzene}) - \underset{(1.103)}{1.142}\sigma^* - \underset{(0.538)}{0.445}$$

$$n = 9;\ s = 0.345;\ r = 0.940 \qquad (14b)$$

$$\sum\pi(R_3 + R_4) = \underset{(0.441)}{0.674}\sum\pi(\text{aliphatic}) - \underset{(0.758)}{0.866}\sum\sigma^*(R_3 + R_4) - \underset{(0.817)}{0.801}$$

$$n = 9;\ s = 0.262;\ r = 0.921 \qquad (14c)$$

n is the number of compounds, s is the standard deviation, r is the correlation coefficient, and the figures in parentheses are the 95% confidence intervals. It is generally acknowledged that log P is a very important parameter, especially for activities in vivo. Other effects should also participate in the variation of activity. The significance of parameters other than log P in discriminant functions may be that they adjust differences in various physicochemical effects between the partitioning process and in vivo behavior.

In this work, we limited our approach to utilizing the linear elementary discriminant procedures. When the equicovariance model does not hold between populations, we could use the quadratic discriminant analysis. The nonelementary discriminant functions may allow a mechanistic interpretation more clearly than the present procedure, especially for the simultaneous classification of three potency groups. Comparisons of the present results with those from these alternative procedures, as well as appropriate pattern-recognition techniques, will offer us useful information about application methodology of multivariate analysis to structure-activity studies, which will be reported elsewhere.

Acknowledgment. We are grateful to Professor Ikuo Moriguchi and Dr. Yvonne Martin for their helpful discussions and to Drs. Masashi Goto and Takaji Teranishi for their invaluable advice on admissible discriminant analysis. We also thank one of the reviewers for his suggestions to improve the presentations.

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Convulsant and Anticonvulsant Barbiturates. 1. Molecular Conformations from Classical Potential-Energy Calculations

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Conformational energy calculations are reported for a series of convulsant and anticonvulsant barbiturates derived from 5-ethyl-5-(1'-methylbutyl)barbituric acid (pentobarbital) by minor structural changes to the butyl side chain. A number of low-energy conformations are identified for each barbiturate. In each case substantial barriers to rotation exist between the alternative conformations, and the magnitudes of these barriers suggest that the barbiturates may be conformationally restricted even at physiological temperatures. Fully extended conformations, with both side chains perpendicular to the plane of the barbiturate ring, are favored. In the 1'-methyl derivatives, conformations with the 1'-methyl group located directly above the barbiturate ring are equally low in energy.

Minor structural changes to barbiturates and related drugs frequently result in dramatic switches between convulsant and anticonvulsant activity,[3-6] but no structural explanation for these differences is yet available. In an effort to obtain definitive structure-activity relationships for the convulsant and anticonvulsant barbiturates, we have undertaken a theoretical and experimental study of

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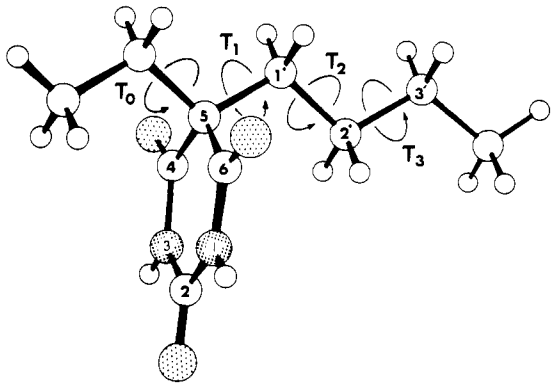
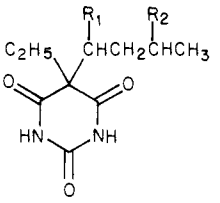
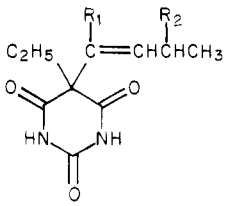


Figure 1. Conformational variables and atom numbering for barbiturates under study. Torsion angles are defined by clockwise rotations around the appropriate bonds; in this illustration $\tau_0 = \tau_1 = \tau_2 = \tau_3 = 180°$. Light and dark shadings represent oxygen and nitrogen atoms, respectively.

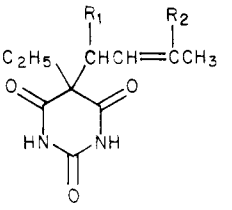
the molecular conformations of the series of barbiturates **1–3**, in which maximal variations in biological activity are



1a, $R_1 = R_2 = H$ (butethal)
b, $R_1 = CH_3$; $R_2 = H$ (pentobarbital)
c, $R_1 = H$; $R_2 = CH_3$ (amytal)
d, $R_1 = R_2 = CH_3$



2a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$ (vinbarbital)
c, $R_1 = H$; $R_2 = CH_3$
d, $R_1 = R_2 = CH_3$



3a, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = H$; $R_2 = CH_3$
d, $R_1 = R_2 = CH_3$

combined with minimal changes in physicochemical properties.[7] In this paper, we report the results of classical calculations of the potential-energy surfaces for all the major conformational variables in this series of barbiturates. Subsequent papers will deal with molecular orbital, NMR, and crystallographic studies of the same compounds.

Experimental Section

The calculations were done on the neutral triketo form of the barbiturates. This form predominates under physiological conditions and is thought to be the active species. The molecular geometries were taken from standard compilations,[8] and the barbiturate ring was assumed to be planar; the justification for this assumption is our observation (unpublished) that the slight deviations from planarity observed in barbiturate crystal structures

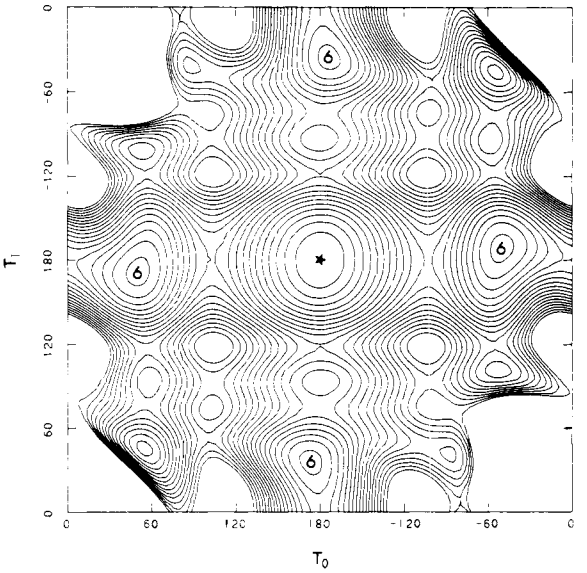


Figure 2. Contour map showing the relative energies of conformations defined by rotations τ_0 and τ_1 in butethal (**1a**). The contour interval is 2.5 kcal/mol and the first 20 contour lines are shown. τ_2 and τ_3 are set at 180°. The global minimum is marked by a star. Energies (in kcal/mol) of key secondary minima are as indicated.

vary from one barbiturate to another. Preliminary calculations demonstrated that their effects on the calculated potential-energy surfaces were insignificant.

The calculations were performed with a Univac 1100/42 computer using the program COMOL.[9] The program performs classical conformational calculations by pairwise summation of the van der Waals interactions between nonbonded atoms, together with electrostatic and torsional potentials. The paramerization, which was developed by Giglio on the basis of a series of hydrocarbon and amide structures,[10] has been used to study a number of systems of biological interest.[11,12]

The calculations were carried out at fixed values of all bond lengths and bond angles; preliminary calculations indicated that relaxation of this condition did not affect the qualitative nature of the potential-energy surfaces, although the barriers to rotation between alternative conformations were reduced by relaxation of nontorsional degrees of freedom.

Four torsion angles are required to describe the conformations of the barbiturates, and these are defined in Figure 1. Initially, these variables were considered two at a time, and approximate potential-energy surfaces were computed for each barbiturate using rotational intervals of 5°. The calculations for each pair of variables were then repeated for alternative values of the other conformational parameters until a complete picture of the conformational surface was built up. Conformational energy maps were prepared using a modification of the contouring program KONTOR.[13]

Results

Saturated Derivatives (1). The calculated relative energies for rotations τ_0 and τ_1 in butethal (**1a**) are given in the form of a contour map in Figure 2. It is apparent that the extended conformation ($\tau_0 = \tau_1 = 180°$) is significantly more stable than other alternative conformations, of which the most stable are those with either τ_0 or τ_1 in the region of ±60°. The barriers to rotation between

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Table I. Relative Energies of Alternative Conformations of Substituted 5-Ethyl-5-butylbarbituric Acids (1)

torsion angle[b]	relative energy, kcal/mol[a,c]					
	0°	60°	120°	180°	-120°	-60°
τ_0	15 (40, 40)	7 (8, 25)	30	0	30	7 (25, 8)
τ_1	20	7 (12, 3)	30	0	30	7 (3, 12)
τ_2	>100	~100	2 (2, 30)	0 (3, 3)	2 (30, 2)	~100
τ_3 (no 3'-Me)	20	2	3	0	3	2
τ_3 (3'-Me)[d]	30	7	30	0	4	0

[a] Quantities given are averages for the four saturated barbiturates (1). Energies for the individual barbiturates are within 50% of values given. [b] In each case, torsion angles other than that being varied are fixed at their optimum values. Values given in each column refer to the topographical feature (minimum, maximum) which is near, but not necessarily at, the appropriate torsion angle. [c] Values in parentheses refer to *S* and *R* isomers, respectively, of the 1'-methyl derivatives. [d] The torsion angle for the additional 3'-methyl group is defined as $\tau_{3'} = \tau_3 - 120°$.

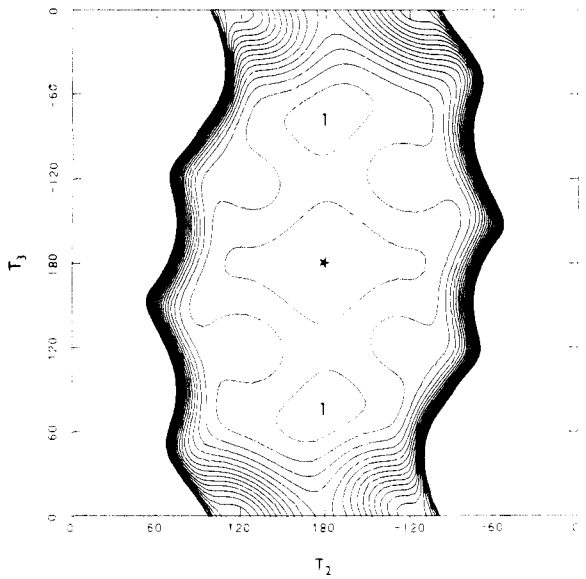

Figure 3. Contour map describing relative energies for rotations τ_2 and τ_3 in butethal (**1a**). τ_0 and τ_1 are set to 180° and the first 20 2.5 kcal/mol contour intervals are shown. The global minimum is marked by a star. Energies (in kcal/mol) of key secondary minima are as indicated.

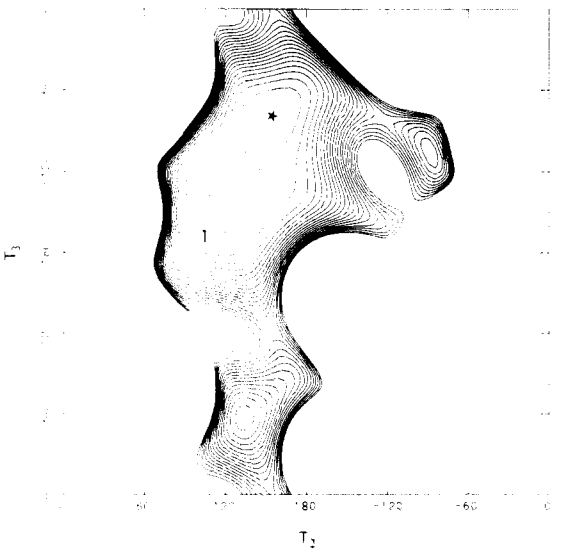

Figure 4. Contour map obtained for rotations τ_2 and τ_3 in the *S* isomer of the dimethyl derivative **1d**. τ_0 and τ_1 are fixed at 180° and the first 20 2.5 kcal/mol contour intervals are shown. The global minimum is marked by a star. Energies (in kcal/mol) of key secondary minima are as indicated.

these alternative conformations are also high, being of the order of 30 kcal/mol.

The corresponding energies for rotations τ_2 and τ_3 in butethal are given in Figure 3, where the preference for a fully extended conformation ($\tau_2 = \tau_3 = 180°$) is again evident, although conformations with τ_2 between 180° and ±120°, or τ_3 between 180° and ±60°, all fall within 5 kcal/mol of the global minimum. The barrier to rotation τ_2 is prohibitive (>100 kcal/mol at $\tau_2 = 0°$), while that for τ_3 is relatively low (12 kcal/mol at $\tau_3 = 0°$).

Introduction of a 1'-methyl group, as in pentobarbital (**1b**) or 5-ethyl-5-(1',3'-dimethylbutyl)barbituric acid (**1d**), has relatively little effect on τ_3 but changes the relative energies obtained for rotations τ_0, τ_1, and τ_2. Thus, conformations in which the 1'-methyl group is situated over the barbiturate ring ($\tau_1 = -60°$ for *S* isomers; in this and following examples, the corresponding angle for *R* isomers is minus that for *S* isomers) now lie less than 3 kcal/mol above the global minimum, while the other alternative conformers ($\tau_1 = 60°$, *S* isomers) are destabilized to approximately 12 kcal/mol. Conformations with $\tau_2 = 180°$ are also destabilized, and the global minimum moves to the region of $\tau_2 = +150°$ (*S* isomers) in response to the presence of the 1'-methyl group. This effect is evident in Figure 4, which shows the relative energies obtained for rotation around τ_2 and τ_3 in **1d** (*S* isomer).

The effects of introducing an additional methyl substituent at C-3' ($\tau_3 = \tau_3 - 120°$), as in amytal (**1c**) and **1d**, are also shown in Figure 4. The major changes are the destabilization of the region around $\tau_3 = 60°$, where both methyl groups occupy synclinal orientations, and the corresponding increase in the barrier at $\tau_3 = 120°$.

The energies of all four saturated barbiturates, and of their optical isomers, are summarized in Table I. It is clear that, in general, fully or almost fully extended conformations are favored, and substantial barriers exist between these and alternative conformations.

But-1'-enyl Derivatives (2). In each of these derivatives, τ_2 is defined as 180°, and the 5-ethyl group favors the extended conformation ($\tau_0 = 180°$); there are barriers of approximately 30 kcal/mol between this and the secondary minima at ±50° (6 kcal/mol). The calculated energies for rotations τ_1 and τ_3 are given for 5-ethyl-5-(but-1'-enyl)barbituric acid (**2a**) in Figure 5. As in the saturated derivatives, the extended conformation, $\tau_1 = 180°$, is favored, but now by less than 2 kcal/mol relative to the minima at $\tau_1 = \pm 50°$. The $\tau_1 = 0°$ region is also stabilized relative to the saturated derivatives, with a barrier of only 3 kcal/mol between the synclinal conformations. Rotation around τ_3 is virtually free, with barriers of 2 and 4 kcal/mol at $\tau_3 = 180°$ and $\tau_3 = 0°$, respectively.

Introduction of 1'-methyl group further stabilizes $\tau_1 = 0°$, in which the 1'-methyl group occupies the region above the barbiturate ring. As shown in Figure 6, this conformation is now equal in energy to that with $\tau_1 = 180°$. Rotation τ_0 is not substantially affected by the presence of the 1'-methyl group, but τ_3 is severely restricted; the

Table II. Relative Energies of Alternative Conformations of Substituted 5-Ethyl-5-(but-1′-enyl)barbituric Acids (2)

torsion angle[b]	relative energy, kcal/mol[a,c]					
	0°	60°	120°	180°	−120°	−60°
τ_0	20 (30)	5 (8)	30	0	30	5 (8)
τ_1	5 (0)	2 (5)	20	0	20	2 (5)
τ_2			defined as 180°			
τ_3 (no 3′-Me)	4 (50)	0 (4)	0	1	0	0 (4)
τ_3 (3′-Me)[d]	6 (50)	0 (10)	6 (50)	4	0	4

[a] Quantities given are averages for the four but-1′-enyl barbiturates (2). Energies for individual barbiturates are within 50% of values given. [b] As for Table I. [c] Values in parentheses refer to 1′-methyl derivatives. [d] As for Table I.

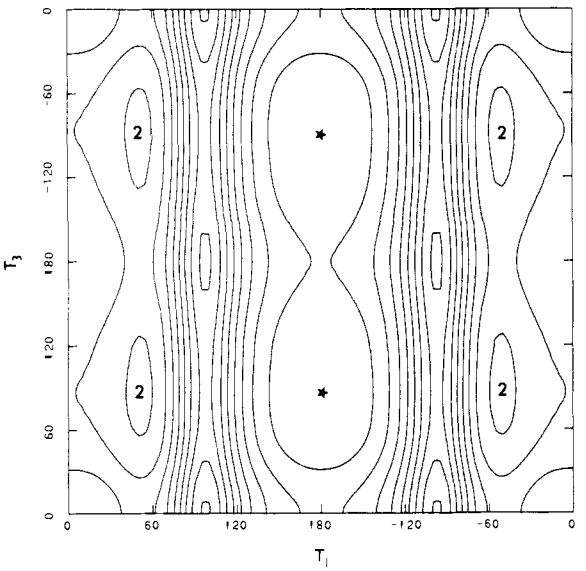

Figure 5. Contour map showing the relative energies of conformations defined by rotations τ_1 and τ_3 in 5-ethyl-5-(but-1′-enyl)barbituric acid (**2a**). The contour interval is 2.5 kcal/mol. τ_0 is set at 180° and τ_2 is defined as 180° by the presence of the double bond. There are two global minima, marked by stars. Energies (in kcal/mol) of key secondary minima are as indicated.

barrier at τ_3 = 0° is approximately 50 kcal/mol.

Rotation around τ_3 is further limited by the introduction of a 3′-methyl group ($\tau_{3'} = \tau_3 - 120°$), which results in another 50 kcal/mol barrier at τ_3 = 120°, as shown for **2d** in Figure 6.

The relative energies of all four but-1′-enyl derivatives are summarized in Table II. The preference for fully extended conformations in these compounds is plainly less than in the corresponding saturated derivatives, with τ_3 favoring conformations in the vicinity of ±90° and τ_1 = 0° jointly favored with τ_1 = 180° in the 1′-methyl derivatives.

But-2′-enyl Derivatives (3). In common with the saturated and but-1′-enyl derivatives, these barbiturates favor the conformation in which the 5-ethyl group is extended above the barbiturate ring (τ_0 = 180°); rotation between this and alternative conformations (τ_0 = ±50°, 6 kcal/mol) is hindered by barriers of the order of 30 kcal/mol. τ_3 for these derivatives is fixed at 180°, and Figure 7 gives details of the calculated relative energies for τ_1 and τ_2 in **3a**. Again, τ_1 = 180° is marginally favored over the alternative conformations near ±50°, but the barrier to rotation around τ_1 is relatively low, reaching a maximum of 10 kcal/mol at τ_1 = ±120°. Rotation τ_2 is more restricted, with a barrier of 40 kcal/mol at τ_2 = 0°, but the entire region between 180° and ±60° lies below 1 kcal/mol.

As in saturated and but-1′-enyl derivatives, the introduction of a 1′-methyl group further stabilizes the τ_0 = 180° region, and conformations in which the 1′-methyl group is situated above the barbiturate ring (−60°, *S* isomers) are slightly favored over those in which C-2′ of the but-2′-enyl side chain occupies this location. For *S* isomers, conformations with τ_2 between 180° and −60° are significantly destabilized by the 1′-methyl group, and the global minimum moves to the region of +120°. This effect is illustrated in Figure 8, which gives the relative energies for variations of τ_1 and τ_2 in 5-ethyl-5-(1′,3′-dimethylbut-2′-enyl)barbituric acid (**3d**; *S* isomer). Also evident in Figure 8 is the effect of introducing an additional 3′-methyl substituent ($\tau_{3'}$ = 0°), which further enhances the

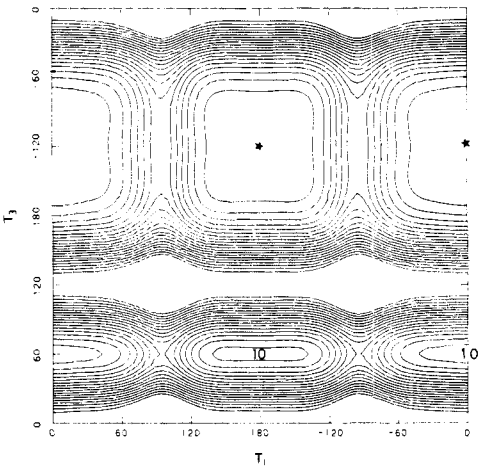

Figure 6. Contour map obtained for rotations τ_1 and τ_3 in 5-ethyl-5-(1′,3′-dimethylbut-1′-enyl)barbituric acid (**2d**). τ_2 is defined as 180° by the double bond and τ_0 is also set at 180°. The first 20 2.5 kcal/mol contour lines are shown. There are two global minima, marked by stars. Energies (in kcal/mol) of key secondary minima are as indicated.

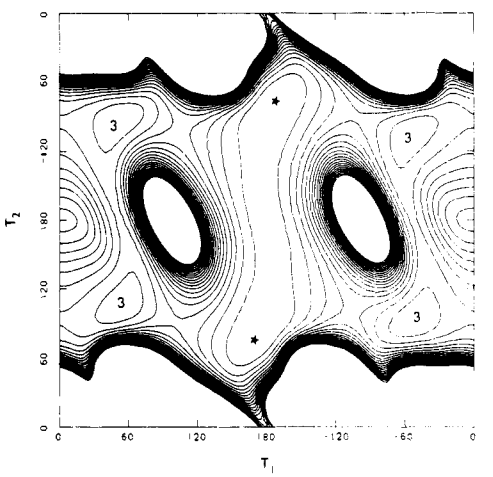

Figure 7. Contour map showing the relative energies of conformations defined by rotations τ_1 and τ_2 in 5-ethyl-5-(but-2′-enyl)barbituric acid (**3a**). The contour interval is 2.5 kcal/mol and the first 20 contour lines are shown. τ_0 is set at 180° and τ_3 is defined as 180° by the presence of the double bond. There are two global minima, marked by stars. Energies (in kcal/mol) of key secondary minima are as indicated.

Table III. Relative Energies of Alternative Conformations of Substituted 5-Ethyl-5-(but-2'-enyl)barbituric Acids (3)

	relative energy, kcal/mol[a,c]					
torsion angle[b]	0°	60°	120°	180°	−120°	−60°
τ_0	20 (40, 40)	6 (7, 30)	30	0	30	6 (30, 7)
τ_1	10 (20, 20)	5 (5, 0)	10 (10, 20)	0 (2, 2)	10 (20, 10)	5 (0, 5)
τ_2 (no 3'-Me)	50	1 (8, 8)	0 (0, 15)	0 (1, 1)	0 (15, 0)	1 (8, 8)
τ_2 (3'-Me)[d]	>100	40	3 (0, 120)	0 (10, 10)	3 (120, 0)	40
τ_3			defined as 180°			

[a] Quantities given are averages for the four but-2'-enyl barbiturates (**3**). Energies for individual barbiturates are within 50% of values given. [b,c] As for Table I. [d] $\tau_{3'} = 0°$.

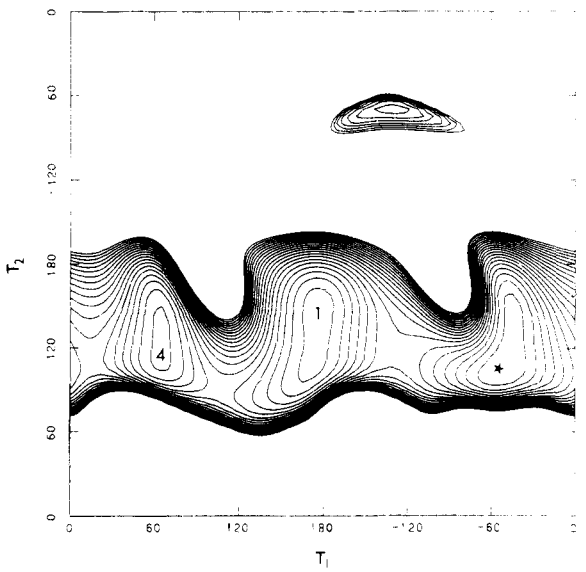

Figure 8. Countour map obtained for rotations τ_1 and τ_2 in the *S* isomer of 5-ethyl-5-(1',3'-dimethylbut-2'-enyl)barbituric acid (**3d**). τ_3 is defined at 180° by the double bond and τ_0 is also set at 180°. The first 20 2.5 kcal/mol contour lines are shown. The global minimum is marked by a star. Energies (in kcal/mol) of key secondary minima are as indicated.

already substantial barrier at $\tau_2 = 0°$.

The potential energies of all four but-2'-enyl barbiturates, and of their optical isomers, are summarized in Table III. Apart from a marginal preference for τ_1 values near −60° in the 1'-methylated derivatives (*S* isomers), the fully or almost fully extended conformations are clearly favored.

Discussion and Conclusions

Three general conclusions concerning the conformations of the barbiturates may be drawn from the preceding analysis: (1) Several alternative low-energy conformations are available to each of the barbiturates studied. (2) Substantial barriers to rotation exist between these alternative conformations. The magnitude of the barriers suggests that the barbiturates may be conformationally restricted even at physiological temperatures. (3) Fully extended conformations (i.e., all torsion angles 180°) are generally favored.

In addition to these general conclusions, the following detailed conclusions may be drawn regarding the individual rotational variables: (4) Rotation of the 5-ethyl moiety (τ_0) is restricted by substantial barriers (ca. 30 kcal/mol) and clearly favors the orientation in which the methyl group lies directly above the barbiturate ring ($\tau_0 = 180°$). (5) Rotation of the 5-butyl or 5-butenyl side chain (τ_1) is constrained by similar barriers in all but the but-2'-enyl derivatives (**3**), in which repulsive interactions are relieved by rotation around τ_2. In the absence of a 1'-methyl group, the orientation in which C-2' of the side chain lies directly above the ring ($\tau_1 = 180°$) is favored; otherwise, either C-2' or the 1'-methyl group may occupy this location. (6) The conformation with $\tau_2 = 180°$ is favored unless there is a 1'-methyl substituent, in which case τ_2 shifts toward 120° (*S* isomers). The barrier at $\tau_2 = 0°$ is always insurmountable. (7) Rotation of the terminal ethyl or isopropyl group (τ_3) is restricted by a barrier of 20 kcal/mol or more at $\tau_3 = 0°$ in all but **2a** and **2c**. In the presence of a 3'-methyl group, a second barrier appears at $\tau_3 = 120°$.

The preceding conclusions define the alternative conformations available to each of the convulsant and anticonvulsant barbiturates studied and provide, in addition, a first estimate of the relative stabilities of these alternatives. These data do not, however, indicate which conformation of any particular barbiturate is the "biologically active conformation", since interaction with the receptor may equally involve modest binding by a low-energy conformation or tighter binding by a higher energy alternative. Any conformation within reasonable range of the global minimum may therefore be the active species.

The selection of conformations available to the individual compounds does not vary markedly between one barbiturate and the next or between convulsant and anticonvulsant barbiturates. Nor is there any specific conformation or conformational region which is accessible to either convulsant or anticonvulsant barbiturates alone. The results thus imply that these barbiturates are probably capable of interacting at both convulsant and anticonvulsant binding sites, with the observed activity being determined by the more powerful of the two interactions. This mechanism would also be consistent with our observation of underlying anticonvulsant activity in the convulsant barbiturates.[6,7]

Of the two classes of activity, the convulsant property appears to be the more sensitive to minor structural changes, which suggests that the conformational specifications for convulsant activity are tighter than those for the depressant barbiturates. This conclusion is also suggested by the fact that the total number of convulsant barbiturates is very much smaller than that of depressant barbiturates. The present data, by supplying complete conformational potential-energy surfaces for each barbiturate, define a limited range of alternative conformations within which the biologically active conformation(s) of the convulsant barbiturates should fall and a somewhat broader conformational range for the anticonvulsant barbiturates. In forthcoming papers, the detailed geometries and relative energies of these alternative conformations will be further refined using MINDO/3, and the resulting structures will be compared with those obtained from X-ray crystallography and NMR conformational analysis.