# Structure–Activity Relations and Receptor Modelling of Convulsant and Anticonvulsant Barbiturates from Crystallographic Data

**Graham P. Jones***
*Waite Agricultural Research Institute, University of Adelaide, Glen Osmond, South Australia, 5064, Australia*
**Peter R. Andrews**
*School of Pharmaceutical Chemistry, Victorian College of Pharmacy Ltd., Parkville, Victoria 3052, Australia*

The crystallographic structures of 14 convulsant and anticonvulsant barbiturates in a variety of crystalline environments are used to determine their molecular geometries and preferred conformations together with their optimal hydrogen bonding and molecular packing arrangements. These data suggest distinct structural requirements for barbiturate convulsant and anticonvulsant activity, and provide information on the likely molecular environment at the barbiturate target site.

The introduction of methyl groups and double bonds into the 5-butyl side chain of 5-ethyl-5-butylbarbituric acid leads to compounds whose pharmacological activities range from anaesthetics and anticonvulsants to convulsants.[1,2] The salient features of these molecules are the trioxopyrimidine ring, which has been shown to form strong hydrogen bonds with biologically important molecules both in solution[3] and in crystals,[4–14] and the 5,5-dialkyl or aryl substituents. Whilst the lipophilicities of the latter are important in determining pharmacological activity (little or no activity is observed when both 5-alkyl substituents are smaller than ethyl groups[15]) there is a large body of data which suggests that differences in molecular conformation caused by changes in the substitution pattern of the 5-butyl group rather than changes in lipid solubility mediate the pharmacological activities of these compounds.[16–19] In studies of the structure–activity relationships of barbiturates related to 5-ethyl-5-butylbarbituric acid, conformational energy calculations[18–20] together with a pattern recognition study[21] and n.m.r. experiments,[22–25] have been used to determine preferred conformations in the gas phase and in solution. We report here a survey of molecular conformations determined by *X*-ray crystal structure analyses for the convulsant and anticonvulsant barbiturates listed in Table 1. These include all structures determined to date for 5-ethyl-5-alkyl (aryl) barbiturates which are not *N*-methylated. Also included is the structure determined for the anticonvulsant and anaesthetic compound 5,5-diallylbarbituric acid.[17] It is pointed out that all these structures are non-ionic, with intermolecular forces being purely of a hydrogen-bond or van der Waals nature. The intermolecular forces between adjacent alkyl groups are solely of the van der Waals type. This suggests that the observed molecular conformations are unlikely to be more than 1 or 2 kcal mol$^{-1}$ above the global minimum, and should therefore also be extensively populated.[26]

## Experimental

Barbiturate *X*-ray crystal data were obtained using the Cambridge Crystal Data File Abstracting Service.[27] Molecular geometries were computed from the crystal co-ordinates using

**Table 1.** Structure and CNS activities of barbiturates surveyed†

| Compound | $R^1$ | $R^2$ | Generic or common name | Activity |
|---|---|---|---|---|
| **(1a)*** | Ethyl | Butyl | Butethal | Anticonvulsant |
| **(1b)** | Ethyl | 1-Methylbutyl | Pentobarbital | Anticonvulsant |
| **(1c)*** | Ethyl | 3-Methylbutyl | Amobarbital | Anticonvulsant |
| **(1d)*** | Ethyl | 1,3-Dimethylbutyl | DMBB | Convulsant (*R* isomer)<br>Anticonvulsant (*S* isomer) |
| **(1e)*** | Ethyl | 3,3-Dimethylbutyl | | Anticonvulsant |
| **(2a)*** | Ethyl | But-1-enyl | | Anticonvulsant |
| **(2b)*** | Ethyl | 1-Methylbut-1-enyl | Vinbarbital | Anticonvulsant |
| **(2c)** | Ethyl | 3-Methylbut-1-enyl | | Anticonvulsant |
| **(2d)*** | Ethyl | 1,3-Dimethylbut-1-enyl | | Convulsant |
| **(3a)** | Ethyl | But-2-enyl | | Anticonvulsant |
| **(3b)** | Ethyl | 1-Methylbut-2-enyl | | Anticonvulsant |
| **(3c)*** | Ethyl | 3-Methylbut-2-enyl | | Convulsant |
| **(3d)*** | Ethyl | 1,3-Dimethylbut-2-enyl | | Convulsant |
| **(4a)*** | Ethyl | Ethyl | Barbital | Anticonvulsant |
| **(4b)*** | Ethyl | Phenyl | Phenobarbital | Anticonvulsant |
| **(4c)*** | Ethyl | 1-Cyclohex-1-enyl | Cyclobarbital | Anticonvulsant |
| **(4d)*** | Ethyl | 1-Cyclohept-1-enyl | Heptabarbital | Anticonvulsant |
| **(4e)*** | Allyl | Allyl | | Anticonvulsant |

* These compounds for which crystal structures have been determined are the only ones appearing in subsequent Tables.
† Compound numbers (**1**)—(**3**) refer to the presence of a butyl, but-1-enyl, and but-2-enyl side chain at the $R^2$ position, respectively. The letters **a**—**e** following these numbers refer to the number and position of methyl substituents in the $R^2$ substituent. The final group of compounds (**4**) are a series of clinically useful barbiturates.

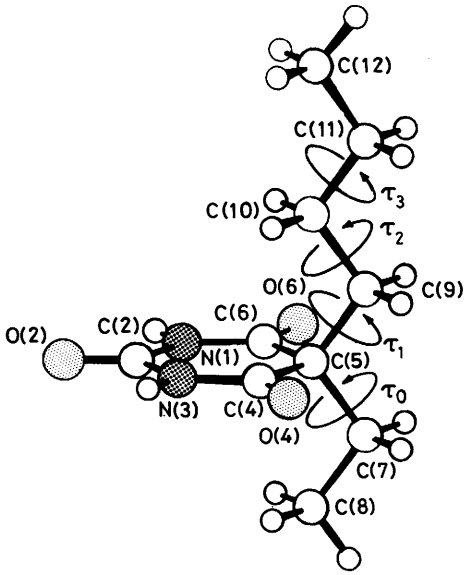


**Figure 1.** Observed molecular conformation of butethal (**1a**) showing atomic numbering and conformational variables used in this study. Torsion angles are defined by clockwise rotations about the appropriate bonds; in this illustration $\tau_0 = \tau_1 = \tau_2 = \tau_3 = 180°$. Light and dark shadings represent oxygen and nitrogen atoms respectively

the computer program TORSION which computes bond distances, bond angles, torsion angles, and least-squares planes together with their standard deviations. Molecular structures were drawn using PLUTO.[28]

*Molecular Conformations.*—Four torsion angles are required to describe the conformations of 5-ethyl-5-butylbarbituric acid and its analogues. These are illustrated in Figure 1 together with the atomic numbering system used in this study. Only two of these, $\tau_0$ and $\tau_1$, are required to describe barbital (**4a**), for which crystal structures have been determined as the free acid,[29,30] as its sodium and potassium salts,[31] and in molecular complexes with nitrogen-containing compounds.[4–12] In all these structures the terminal methyl groups are situated above and below the plane of the trioxopyrimidine ring with $\tau_0 \cong \tau_1 \cong 180°$ (Table 2), as shown in Figure 2. Also shown in Figure 2 are the observed conformations of all barbiturates surveyed in this work. Where the conformations of more than one independent structure of a particular compound are similar only one illustration is made. This applies to barbital (**4a**) (17 independent structures), amobarbital (**1c**) (four independent structures), phenobarbital (**4b**) (two independent structures), and cyclobarbital (**4c**) (two independent structures). The conformation of the ethyl groups in barbital (**4a**) is consistent with the observed conformation of the ethyl group in all structures of 5-ethyl-substituted barbituric acids, where $\tau_0 \cong 180°$ (see Table 2). These findings are supported by classical potential energy[18] and MO calculations[19] and by an early n.m.r. study.[23] However, a later n.m.r. study using C–H vicinal coupling constants to determine barbiturate solution conformations has shown that conformations with $\tau_0 \cong \pm 60°$ are also very likely to occur.[25] It was suggested that in solution pseudoaxial–pseudoequatorial interconversion of the substituents at C(5) may reduce the potential barrier for rotations about $\tau_0$ and $\tau_1$.[25] However, compounds (**2a**), (**3d**), (**4b**), and (**4e**) all display such a distortion in crystals and in all cases $\tau_0 \cong 180°$. On the other hand, the conformation of the other 5-alkyl (aryl) substituent, determined primarily by the rotation about the C(5)–C(9) bond ($\tau_1$), is dependent on the nature of this substituent.

**Table 2.** Torsion angles (°) describing molecular conformations†

| Compound | $\tau_0$[a] | $\tau_1$[b] | $\tau_2$[c] | $\tau_3$[d] | $\tau_{-1}$[e] | $D$‡ (Å) | Reference |
|---|---|---|---|---|---|---|---|
| (**1a**) | −171 | 179 | −177 | 155 | 71 | 0.44 | 32 |
| (**1c**$_1$)[f] | −174 | −179 | 178 | −168 | 68 | 0.40 | 33 |
| (**1c**$_2$)[f] | −173 | −176 | 178 | −177 | 68 | 0.32 | 33 |
| (**1c**$_3$)[f] | −172 | −178 | −175 | −168 | 69 | 0.23 | 33 |
| (**1c**$_4$)[f] | −179 | −176 | 169 | −174 | 62 | 0.25 | 13 |
| (**1d**)[g] | −175 | −45 | 161 | 172 | 65 | 0.05 | 34 |
| (**1e**) | −180 | −180 | −175 | −180 | 63 | 0.32 | 35 |
| (**2a**) | −178 | −138 | −178 | −2 | 61 | 1.09* | 36 |
| (**2b**) | −176 | 8 | 180 | −122 | 64 | 0.05 | 37 |
| (**2d**) | −176 | −7 | 179 | −111 | 65 | 0.06 | 38 |
| (**3c**$_1$)[h] | −176 | −175 | −118 | −178 | 67 | 0.41 | 39 |
| (**3c**$_2$)[h] | −176 | 166 | 109 | −171 | 67 | 0.50 | 39 |
| (**3d**)[g] | 173 | −176 | 103 | 177 | 59 | 0.94* | 40 |
| (**4a**)[i] | −178 | −178 | | | 65 | 0.03 | 4—12, 29, 30 |
| (**4b**$_1$)[j] | −180 | −128 | 179 | 1 | 61 | 1.44* | 41 |
| (**4b**$_2$)[j] | −179 | −104 | 179 | 0 | 61 | 1.82* | 42 |
| (**4c**$_1$)[k] | −177 | 175 | 171 | 39 | 62 | 0.67 | 43 |
| (**4c**$_2$)[k] | −178 | −180 | 179 | 24 | 63 | 0.30 | 14 |
| (**4d**) | −174 | −175 | 117 | 79 | 65 | 0.16 | 44 |
| (**4e**) | −178 | −175 | 3, 125[l] | | 61 | 0.72* | 45 |

* See text.

† Mirror image conformations will also apply.

‡ $D$ is defined as the difference in distance of C(7) and C(9) from the least-squares plane containing the barbiturate ring atoms and is a measure of ring puckering at C(5).

[a] C(8)–C(7)–C(5)–C(9). [b] C(7)–C(5)–C(9)–C(10). [c] C(5)–C(9)–C(10)–C(11). [d] C(9)–C(10)–C(11)–C(12). [e] C(4)[C(6)]–C(5)–C(7)–C(8). [f] Four independent structures of (**1c**) have been determined. [g] Data are given for the (*S*)-(−)-enantiomer. [h] Two independent structures of (**3c**) have been determined. [i] These values represent the average values of 17 independent structures of (**4a**). [j] Two independent structures of (**4b**) have been determined. [k] Two independent structures of (**4c**) have been determined. [l] These values are for the two 5-allyl groups in (**4e**).

Barbiturates which contain non-1′-methyl-substituted saturated chains (**1a**,**c**,**e**) adopt extended conformations with $\tau_1 \cong \tau_2 \cong \tau_3 \cong 180°$ (Table 2). The C(10) methylene group, analogous to the terminal methyl group in (**4a**), is again situated over the barbiturate ring. Four crystallographically independent structures of (**1c**) have been determined and in each example the conformation of the 3′-methylbutyl group is the same although in each case some disorder of the terminal isopropyl group is observed. The data suggest that conformations with $\tau_3 \cong 60°$ may also be present in the crystals, which is in agreement with results obtained from molecular energy calculations[18,19] and n.m.r. experiments.[22] Incorporation of a 1′-methyl group into the chain as in (**1d**) causes the alkyl chain to move away from a position over the barbiturate ring. The preferred conformation places the 1′-methyl group over the ring with the isobutyl group directed away from the ring [*cf.* (**1c** and **d**)].

Incorporation of a double bond in the 1′-position of the butyl group causes $\tau_1$ to move away from the ~180° value observed in the saturated derivatives. In (**2a**) $\tau_1$ −138° with C(10) situated over a ring carbonyl group, while in the somewhat analogous compound phenobarbital (**4b**) values of $\tau_1$ −128 and −104° are observed. If a 1′-methyl group is substituted at C(9) of (**2a**) the alkenyl chain is again forced away from a position above the barbiturate ring as observed in (**2b** and **d**) with $\tau_1 \sim 0°$. Cyclohex-1-enyl and cyclohept-1-enyl derivatives (**4c** and **d**), where a ring methylene group substitutes for the 1′-methyl group, also display similar conformational preferences. If on the other hand the double bond is present in the 2′-position $\tau_1$ again approaches a value of 180°, even if a 1′-methyl substituent is present, but $\tau_2$ is no longer close to 180°. The

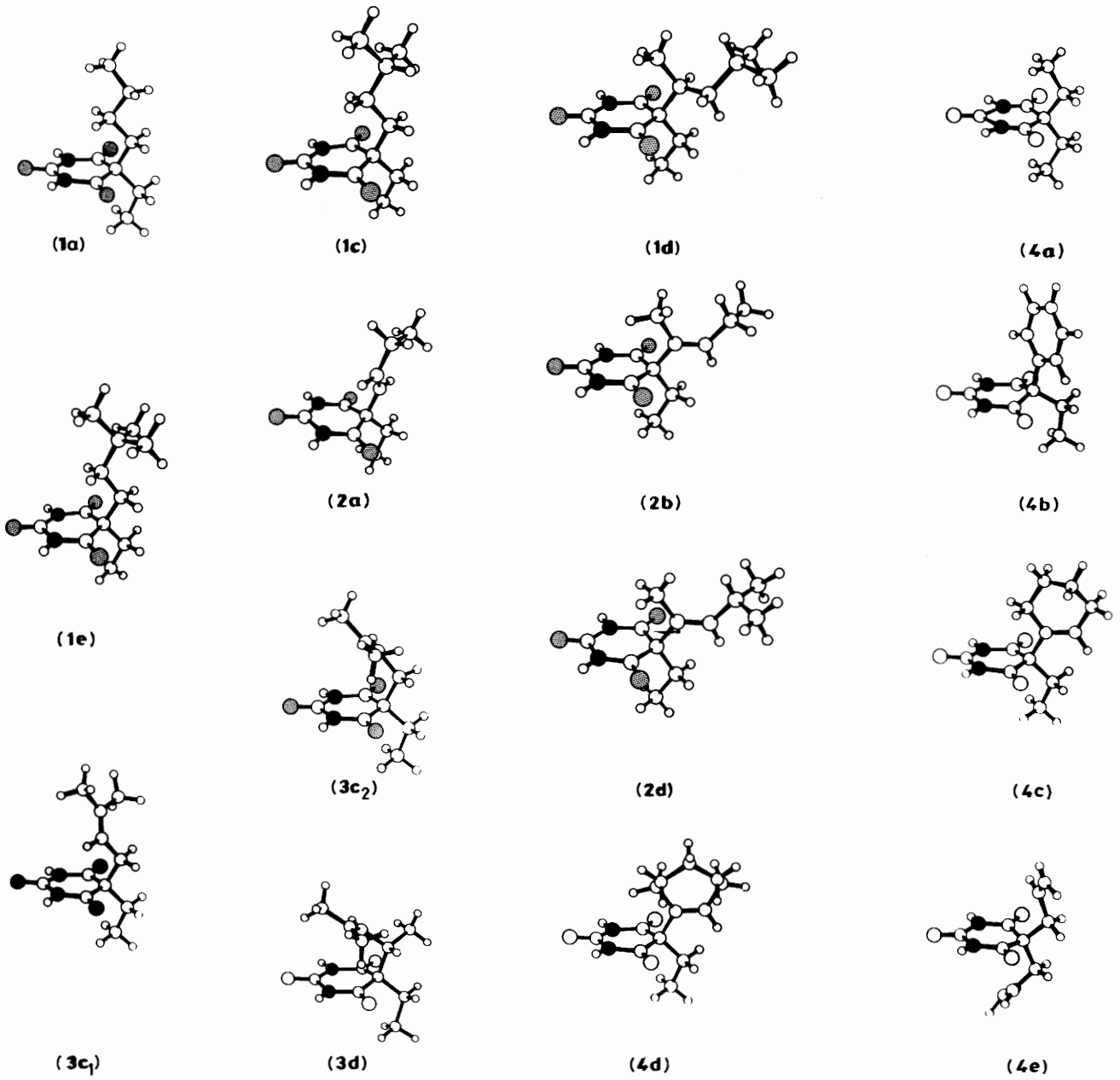


**Figure 2.** Observed molecular conformations in crystals of compounds (**1**)—(**4**). Where the conformations of more than one independent structure of a particular compound are similar only one illustration is made. In all compounds mirror image conformations will also apply. Hydrogen atoms have been added to the structures in theoretical positions (where these were not present in original data)

values observed for (**3d**) and two independent structures of (**3c**) are 103, −118, and 109° respectively (it is pointed out however that in the latter structure molecular disorder is observed[39] which is consistent with contributions from conformations with $\tau_2 \cong -120°$). The 3′-methylbut-2-enyl group forms an extended chain above the barbiturate ring in ($\mathbf{3c_1}$) whereas in ($\mathbf{3c_2}$) the plane of the terminal isobutenyl group is rotated to lie more closely parallel to the plane of the barbiturate ring. The latter conformation is also observed in (**3d**) and it has been suggested that a π interaction between the isobutenyl group and the delocalised trioxypyrimidine ring stabilises this structure.[40] A similar conformation is observed for one of the allyl groups in 5,5-diallylbarbituric acid (**4e**). The second allyl group in this structure is extended and directed away from the barbiturate ring. These observations indicate that there are several preferred conformations of but-2-enyl-substituted barbiturates. This is supported by conformational energy calculations[18,19] which suggest that conformations of (**3c**) with $\tau_1 \cong \pm 60, \tau_2 \cong \pm 120°$ might also be significantly populated.

*Barbiturate Ring Geometry.*—Figure 3 illustrates the average observed bond distances and angles of the trioxopyrimidine ring, the data being taken from 17 independent structures of (**4a**). Quoted estimated standard deviations for these structures vary between 0.002 and 0.008 Å for bond lengths with most being in the range 0.002—0.003 Å, and 0.1—0.5° for bond angles with most being in the range 0.1—0.2°. Standard deviations for bond distances and bond angles in Figure 3 are *ca.* 0.005 Å and 0.4°, respectively. The apparent deviations from mirror plane symmetry through C(2) ··· C(5), whilst not highly significant in

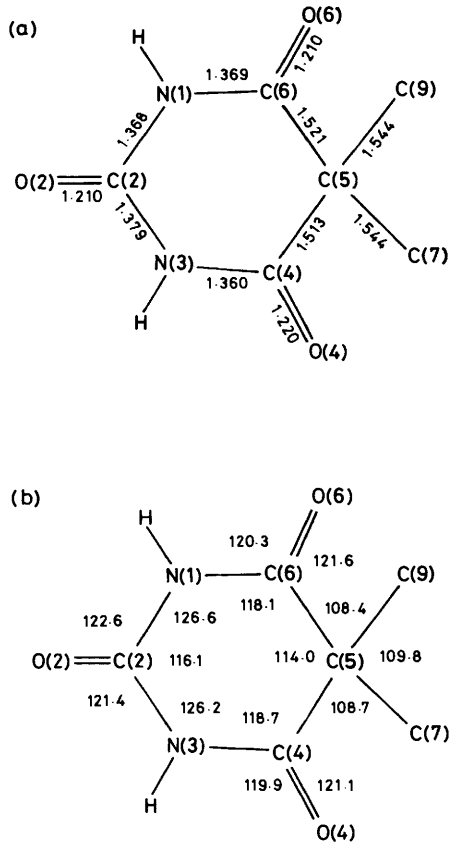


**Figure 3.** Bond distances (Å) and bond angles (°) defining the geometry of the trioxopyrimidine ring. The data are the mean of 17 independent structures of barbital (**4a**). The small deviations from two-fold symmetry of the ring are a function of hydrogen bond formation in which the ring participates (see text)

terms of standard deviations in bond lengths and angles, have been frequently observed and have been attributed to the asymmetry in hydrogen bonding arrangements which the barbiturate ring usually enters into. Quite frequently only one carbonyl group flanking C(5) is involved in hydrogen bonding. Using the convention adopted by Craven and his co-workers[30] this carbonyl is labelled C(4)=O(4). It has been observed previously[46] that carbonyl bond lengths increase by *ca.* 0.01 Å when the oxygen atom is involved in hydrogen bond formation. This is illustrated in Figure 3 by the difference in average C(4)=O(4) and C(6)=O(6) bond distances where nine out of the 17 barbital structures adopt an asymmetric hydrogen bonding arrangement. Barbituric acid derivatives show deviations from planarity of the trioxopyrimidine ring. These deviations produce a variety of ring shapes but these may be roughly divided into (a) skew form where C(2)—C(5) lie on the least-squares plane containing the ring atoms and adjacent atoms are either above or below this plane (see ref. 30), (b) envelope form where C(5) is out of the plane, or (c) envelope form where N(1) or N(3) is out of the plane. In most examples these deviations are small and have been ascribed to differences in hydrogen bonding in the crystals. Thus, in all the barbiturates studied other than (**2a**), (**3d**), (**4b**), and (**4e**), the deviations of ring atoms from the least-squares plane containing all nine non-hydrogen ring atoms are never greater than 0.10 Å with the largest *D* value [the difference in distances of C(7) and C(9) from this plane, which is a measure of ring puckering at C(5)] being 0.67 Å (see Table 2). In each of these structures the groups substituted at the 5-position which lie over the ring have almost mirror plane

**Table 3.** Trioxopyrimidine ring hydrogen bonding involved in barbiturate–barbiturate interactions

| Compound | Structure type[a] | Hydrogen bond distances (Å) N···O(2) | N···O(4)[b] | N···O(6) |
|---|---|---|---|---|
| (**1a**) | 2 | 2.87 | 2.86 | |
| (**1c**$_1$) | 2 | 2.92 | 2.89 | |
| (**1c**$_2$) | 2 | 2.92 | 2.91 | |
| (**1c**$_3$) | 2 | 2.88 | 2.86 | |
| (**1d**) | 1 | 2.88 | 2.87 | |
| (**1e**) | 5 | 2.88 | 2.82 | |
| (**2a**) | 1 | 2.89 | 2.87 | |
| (**2b**) | 4 | | 2.87, 2.92 | |
| (**2d**) | 1 | 2.88 | 2.85 | |
| (**3c**$_1$) | 2 | 2.95 | 2.89 | |
| (**3c**$_2$) | 2 | 2.92 | 2.90 | |
| (**3d**) | 1 | 2.89 | 2.86 | |
| (**4a**$_1$) | 6 | 2.89 | 2.87 | |
| (**4a**$_2$) | 3 | | 2.87 | 2.87 |
| (**4a**$_3$) | 4 | | 2.85—2.91, 2.90—2.92[c] | |
| (**4b**$_1$) | 3 | | 2.89 | 2.91 |
| (**4c**$_1$) | 2 | 2.90 | 2.87 | |
| (**4d**) | 4 | | 2.87, 2.89 | |
| (**4e**) | 1 | 2.90 | 2.89 | |

[a] See test. [b] In cases where either O(4) or O(6) is hydrogen bonded, O(4) is taken to be involved in hydrogen bonding by convention (see text). [c] These are the ranges of values observed for four independent molecules in the asymmetric unit.

symmetry, *i.e.* $\tau_1 \cong 0$ or 180° [this plane passing through O(2), C(5), C(7), C(9)]. Conversely in (**2a**), (**3d**), (**4b**), and (**4e**), where this symmetry does not exist, deviations from the least-squares plane are as large as 0.44 Å with *D* values up to 1.82 Å (**4b**$_2$).

Since there is a wide range of molecular packing arrangements in the crystal structures of both symmetric and non-symmetric barbiturates the data suggest that intramolecular rather than intermolecular effects are the major factors affecting the ring planarity. The energy barriers for rotation about the C(5)–C(9) bond ($\tau_1$) calculated for these compounds, assuming a rigid planar barbiturate ring, may therefore be somewhat overestimated. This possibility has been previously suggested when comparing results from classical and molecular orbital conformational energy calculations.[19]

*Hydrogen Bonding and Molecular Packing.*—An important feature of barbiturates is their ability to form strong hydrogen bonds, acting either as hydrogen bond donors *via* the amide nitrogen atom or as hydrogen bond acceptors *via* the carbonyl groups. This hydrogen bonding has been studied in crystals of barbiturates themselves and in molecular complexes with nitrogen-containing compounds by Garland and Craven.[6] These authors point out that changes in barbiturate structure, electronic charge, and molecular environment appear to have at most a small effect on the strength of hydrogen bonded interactions involving barbiturates as either donors or acceptors as measured by the observed N···O distances. The hydrogen bond distances observed for the compounds in the present study are given in Table 3. The hydrogen bonding arrangements in non-*N*-alkylated 5,5-dialkyl (aryl) barbituric acids can be divided into six categories (see Table 3 and Figure 4). The single ribbon arrangement with the 5-alkyl groups projecting on alternate sides of the ribbon as in (**1d**) and (**2a**), where both O(2) and O(4) are involved in the formation of NH···O=C hydrogen bonds, constitutes Type 1. These infinite ribbons of trioxopyrimidine rings are held together by van der

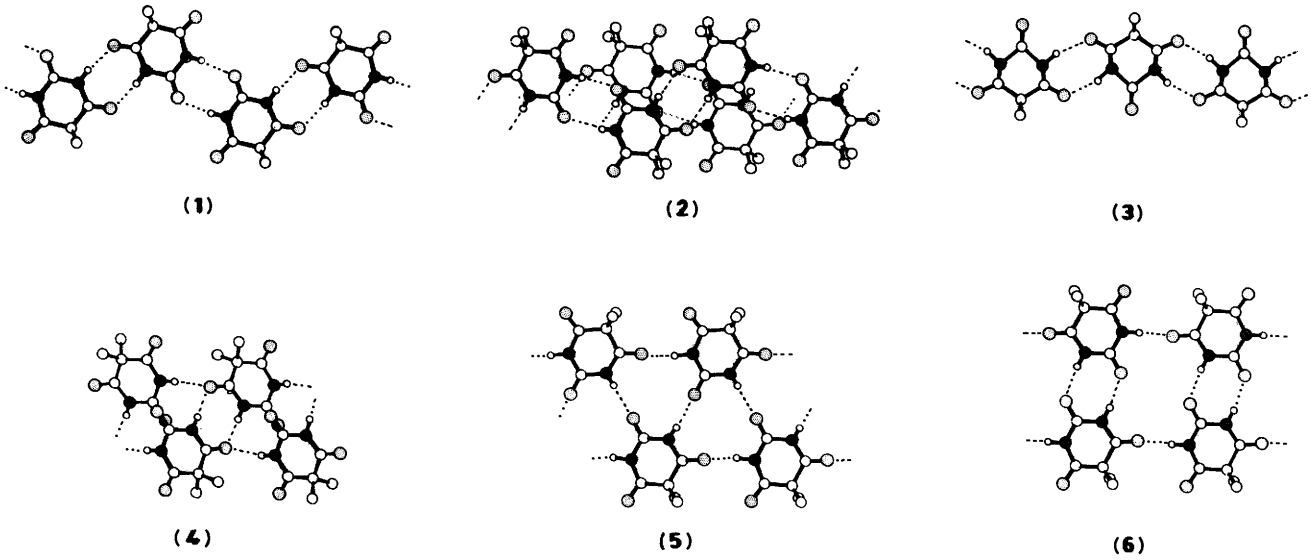


**Figure 4.** Arrangements of hydrogen bonds between trioxopyrimidine rings observed in crystal structures of barbiturates. Hydrogen bonds are indicated by broken lines.

Waals forces between the 5-alkyl substituents. Other structures belonging to this class are (**2d**), (**3d**), and (**4e**). A simple variant (Type 2) on this arrangement is where the 5-ethyl groups project on one side of the ribbon with the 5-alkyl groups on the opposite side. A double ribbon is then formed by the close stacking of one ribbon on top of the other and is observed in crystal structures of (**1a**), (**1c**) (two polymorphs), (**3c**), and (**4c**). The inter-ribbon spacing is dictated by the dimensions of the ethyl group and is in the range 3.59—4.13 Å. Single ribbons of trioxopyrimidine rings are also formed when O(4) and O(6) are involved in hydrogen bond formation (Type 3). O(2) is not involved in hydrogen bonding. This arrangement of hydrogen bonds is observed in the crystal structures of (**4a**$_2$) and (**4b**$_1$). A further hydrogen bond arrangement is found in (**2b**) where O(4) is involved in the formation of two hydrogen bonds with imino nitrogen atoms of two separate molecules. The remaining two oxo groups are not involved in hydrogen bonding. The resulting structure (Type 4) is in the form of sheets of barbiturate rings linked together by hydrogen bonds. The interaction between adjacent trioxopyrimidine rings is also enhanced by van der Waals interactions between adjacent C(2)=O(2) carbonyl groups in this structure. A similar arrangement of hydrogen bonds is also observed in (**4a**$_3$) and (**4d**). A fifth structure is formed where two adjacent hydrogen bonded ribbons of barbiturate rings are interlinked by additional hydrogen bonds to form a trigonal arrangement (Type 5). The resultant structure is in the form of a twin ribbon where O(2) and O(4) are involved in the formation of linear N–H • • • O=C hydrogen bonds. This arrangment is observed in (**1e**). A somewhat similar twin ribbon arrangement (Type 6) is found in (**4a**$_1$) where the second ribbon is displaced in the direction of the ribbon.

In all these hydrogen bonding arrangements the ribbons or sheets of barbiturate rings are localised in distinct regions of crystal space and are separated from the regions occupied by the 5,5-dialkyl substituents. Since the intra-ribbon forces are predominantly due to hydrogen bonding whilst the inter-ribbon forces are due to van der Waals interactions between the 5,5-dialkyl groups, the barbiturate–barbiturate interactions in crystals are effectively partitioned. The van der Waals interactions responsible for binding the barbiturate ribbons into the three-dimensional structures observed in crystals are also responsible for determining conformations for the 5-alkyl substituents, but in view of the large number of molecular packing arrangements available to any given barbiturate it seems unlikely that the molecular conformations observed in crystals are dictated by molecular packing. Indeed, a number of barbiturates have been observed as different polymorphs, and as different molecular complexes, and in all examples the observed molecular conformations are very similar (see Table 2). It thus appears that the molecular packing arrangement adapts to the molecular conformation rather than *vice versa*.

*Structure–Activity Relationships.*—Solid-state studies of drugs and other biologically active molecules usually detect only the single conformation which predominates under a specific set of experimental conditions, and *X*-ray crystallography is therefore not generally regarded as the method of choice for investigating all likely biologically active conformations. In the present case, however, many structures have been determined for compounds in different polymorphs or in molecular complexes with other biologically important molecules. The observation of the same molecular conformations under these various conditions clearly increases the relevance of the crystal data. The relevance of these data is further enhanced when one recognizes that the necessary structural features for an ideal 'barbiturate receptor' are all present within the barbiturates themselves, *viz.* a combination of hydrogen bond acceptors and donors to bind the barbiturate ring, and hydrophobic groups to bind the hydrocarbon side chains. The environment in the crystal may thus provide a useful representation of the actual biological target site.

The structural requirements of the convulsant 'receptor' are very demanding, as illustrated by the action of (*R*)-(+)-(**1d**) as a convulsant and (*S*)-(−)-(**1d**) as an anticonvulsant. The major conformational feature of the convulsant barbiturates is the rotation of the substituted butyl group about the C(5)–C(9) bond away from the barbiturate ring such that $\tau_1$ is $0 \pm 60°$. This is the observed conformation of (**1d**) and (**2d**), and it is the predicted[18] preferred conformation of (**3d**). Furthermore, this conformation is a low energy conformation of (**3c**) and of the structurally related convulsant barbiturate 5-ethyl-5-(2-cyclohexylethylidene)barbituric acid (CHEB).[18,21] The difference in activities of (*R*)-(+)-(**1d**) and (*S*)-(−)-(**1d**) as convulsant and anticonvulsant respectively illustrates the high degree of specificity of the convulsant receptor for the active conformation of the 1,3-dimethylbutyl group. Such specificity cannot, however,

explain the lack of convulsant activities of the appropriate enantiomers of (**1b**)—(**3b**) since the data presented here and elsewhere [18] suggest that these compounds adopt conformations similar to the corresponding 3′-methylated compounds, all of which are convulsants. The changes in action of these compounds must therefore result from some difference in binding due to the introduction of the 3-methyl group, although the likely increase in binding energy due to attractive van der Waals interactions would only be 0.5—1 kcal $mol^{-1}$.

The structural requirements for anticonvulsant activity are less stringent, *e.g.* barbital (**4a**), containing only 5,5-diethyl substituents, possesses anaesthetic and anticonvulsant activities. Indeed, the potency of barbital as an anticonvulsant is comparable with those of the remainder of this series of barbiturates and its molecular structure may represent both a minimum and maximum structural requirement for anticonvulsant action. The observed and calculated conformations of barbital are invariant with the ethyl groups situated above and below the plane of the trioxopyrimidine ring. Since all the 5,5-disubstituted barbiturates discussed in this work are observed in conformations which contain this structural feature the anticonvulsant action of these barbiturates (including the convulsant barbiturates which show anticonvulsant action at subconvulsant doses) is to be anticipated.

*Receptor Modelling.*—The barbiturates and related compounds with anaesthetic and anticonvulsant activities have generally been classified as structurally nonspecific drugs, but a number of arguments in favour of structurally specific target sites for these agents have recently been advanced.[47,48] It is also likely, as noted above, that a direct parallel may be drawn between the situations of barbiturates in crystals and at their biological target sites.

In addition to allowing direct examination of molecular conformation, the crystal structures provide information on barbiturate–barbiturate interactions, which can be partitioned into the hydrogen bonded interactions between the trioxopyrimidine rings, and the lipophilic interactions of the 5,5-dialkyl substituents. It is thus possible to gain some insight into the relative importance of the likely structural requirements of barbiturate 'receptors' from the observed crystal structures.

The potential for tautomerism of the amide groups in the barbiturate ring limits the number of strong hydrogen bonds which the ring can enter into to four (weak dipole–dipole interactions have been observed involving the third carbonyl group). It is predominantly this situation which is observed in the crystal structures where N(1) and N(3) act as hydrogen bond donors and O(2) and O(4) (Types 1, 2, 5, and 6) or O(4) and O(6) (Type 3) act as hydrogen bond acceptors. A similar arrangement would presumably apply at an ideal barbiturate 'receptor'.

The crystalline environments of the convulsant barbiturates (**1d**) and (**2d**) are shown in Figure 5(A) and (B), respectively. In each case there is a well defined binding pocket for the substituted butyl chain in addition to the four hydrogen bonding interactions (indicated in Figure 5 by heavy shading of the atoms involved in hydrogen bond formation). A similar binding pocket for the 5-ethyl group is also observed (data not shown) in both structures. It is evident from Figure 5 that these two convulsant barbiturates and their corresponding 'binding sites' are stereochemically interchangeable. The crystal data may therefore be used to derive a convulsant barbiturate receptor model, which although directly applicable only to the two convulsant barbiturates used to derive it, provides some insight into the probable structural characteristics of the convulsant barbiturate receptor. In particular, in addition to the four N–H ••• O=C hydrogen bonds (N ••• O distances 2.85—2.88 Å), each of the methyl groups in the molecules are flanked by methyl groups of adjacent molecules with $C_{methyl}$ ••• $C_{methyl}$ distances in the range 3.96—4.48 Å (Table 4). The 1-methyl groups are located in pockets formed by four adjacent methyl groups. Similarly the 3-methyl groups and the 3′-methyl and 5-ethyl methyl groups of (**1d**) are each flanked by three adjacent methyl groups. In (**2d**) there are two such groups flanking the 3′-

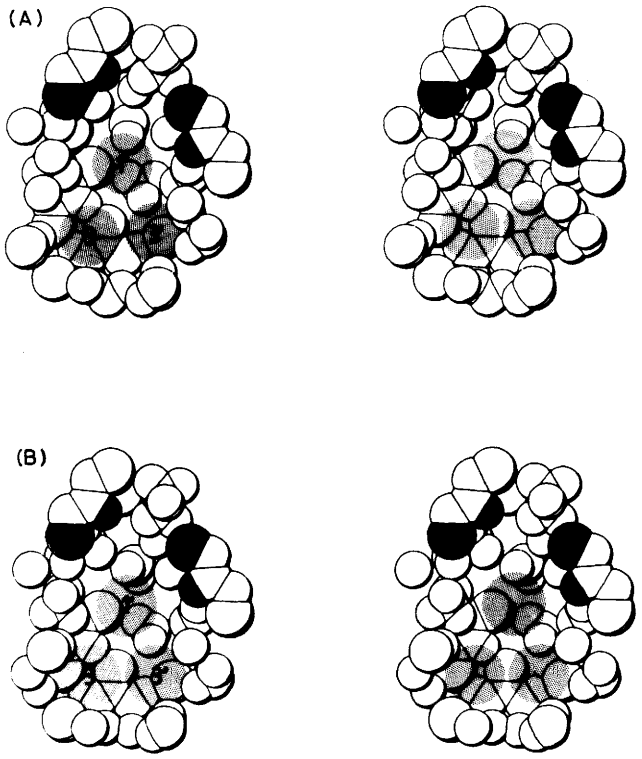


**Figure 5.** Crystal packing environments observed for (**1d**)[34] (A) and (**2d**)[38] (B). Views, sectioned in the plane of the barbiturate ring and observed in the direction of the substituted butyl groups, are shown in stereo for each structure. Only those atoms which are <4.5 Å from the non-hydrogen atoms of the original molecule are shown. The original molecule is omitted in each case. The atoms involved in hydrogen bond formation with the original molecules are shown by heavy shading. The locations of the 1′-methyl, 3-methyl, and 3′-methyl groups of the original molecules are indicated by light shading which assumes a van der Waals radius for the methyl group of 1.8 Å

**Table 4.** Short intermolecular methyl ••• methyl group distances† observed in the crystal structures of (a) (**1d**) and (b) (**2d**)

| (a) | Original Neighbour | 1′-Methyl | 3-Methyl | 3′-Methyl | Et-Methyl |
|---|---|---|---|---|---|
| | 1′-Methyl | 4.22 | 4.41 | 4.00 | 4.28 |
| | 3-Methyl | 4.41 | 4.15 | | 4.23 |
| | 3′-Methyl | 4.00 | | 3.96 | 4.31 |
| | Et-methyl | 4.28 | 4.23 | 4.31 | |

| (b) | Original Neighbour | 1′-Methyl | 3-Methyl | 3′-Methyl | Et-Methyl |
|---|---|---|---|---|---|
| | 1′-Methyl | 4.09 | 4.48 | 4.06 | 4.39 |
| | 3-Methyl | 4.48 | 4.14 | | 4.18 |
| | 3′-Methyl | 4.06 | | 3.98 | |
| | Et-methyl | 4.39 | 4.18 | | |

† Distances (in Å) between methyl group carbon atoms are presented.

methyl and 5-ethyl methyl groups with additional pocket boundaries defined by adjacent barbiturate ring atoms at distances > 3.4 Å. The short $C_{methyl} \cdots C_{methyl}$ group distances observed in these structures are consistent with the minimum in the potential energy curves for such groups (see ref. 49). The importance of these van der Waals interactions thus provides a direct explanation for the role of the alkyl side chains in *specifying* the type of pharmacological activity exhibited by the barbiturates.

*Conclusions.*—Current theories on the action of convulsant, anticonvulsant, and anaesthetic drugs[50] mainly relate to their effects on the GABA–benzodiazepine receptor–ionophore complex, although studies of the influence of the present series of barbiturates on GABA and benzodiazepine binding suggest that their anaesthetic, anticonvulsant, and convulsant activities arise from actions at different loci.[51] These could include alternative conformational states of the same receptor. The structural and conformational findings described here support the view that convulsant and anticonvulsant activity are exerted at similar but conformationally distinct sites. They are also consistent with our previous observation of a conformational similarity between convulsant barbiturates[21] and structurally unrelated convulsants such as picrotoxinin,[52] on the one hand, and between anticonvulsant barbiturates and other classes of anticonvulsant drugs[53] on the other. The prospect of a similar structural basis underlying the inherently less powerful anaesthetic activities of the barbiturates seems less likely, although the stereoisomeric activity ratios of the anaesthetics are, like those of the anticonvulsants, fully consistent with their acting at structurally specific receptors.[48]

## References


1 P. R. Andrews, G. P. Jones, and D. Lodge, *Eur. J. Pharmacol.*, 1979, **55**, 115.
2 P. R. Andrews, G. P. Jones, and D. B. Poulton, *Eur. J. Pharmacol.*, 1982, **79**, 61.
3 R. F. Novak and T. J. Swift, *Mol. Pharmacol*, 1976, **12**, 263.
4 B. M. Craven and G. L. Gartland, *Acta Crystallogr.*, 1974, **B30**, 1191.
5 I.-Nan Hsu and B. M. Craven, *Acta Crystallogr.*, 1974, **B30**, 998.
6 G. L. Gartland and B. M. Craven, *Acta Crystallogr.*, 1974, **B30**, 980.
7 I.-Nan Hsu and B. M. Craven, *Acta Crystallogr.*, 1974, **B30**, 974.
8 I.-Nan Hsu and B. M. Craven, *Acta Crystallogr.*, 1974, **B30**, 1299.
9 I.-Nan Hsu and B. M. Craven, *Acta Crystallogr.*, 1974, **B30**, 994.
10 I.-Nan Hsu and B. M. Craven, *Acta Crystallogr.*, 1974, **B30**, 988.
11 D. Voet, *J. Am. Chem. Soc.*, 1972, **94**, 8213.
12 S. Kiryu, *J. Pharm. Sci.*, 1971, **60**, 699.
13 I.-Nan Hsu and B. M. Craven, *Acta Crystallogr.*, 1974, **B30**, 843.
14 S. Kiryu, H. Fumitoshi, and S. Iguchi, *Chem. Pharm. Bull.*, 1974, **22**, 1588.
15 W. J. Doran, 'Barbituric Acid Hypnotics,' in 'Medicinal Chemistry,' eds. F. F. Blicke and R. H. Cox, Wiley, New York, 1959, vol. VI, pp. 1—327.
16 H. Downes, R. S. Perry, R. E. Ostlund, and R. Karler, *J. Pharmacol. Exp. Ther.*, 1970, **175**, 692.
17 L. Velluz, J. Mathieu, and R. Jequier, *Ann. Pharm. Fr.*, 1951, **9**, 271.
18 G. P. Jones and P. R. Andrews, *J. Med. Chem.*, 1980, **23**, 444.
19 P. R. Andrews and G. P. Jones, *Eur. J. Med. Chem.*, 1981, **16**, 139.
20 B. Pullman, J. L. Coubeils, and P. H. Courrière, *J. Theor. Biol.*, 1972, **35**, 375.
21 P. R. Andrews, L. C. Mark, D. A. Winkler, and G. P. Jones, *J. Med. Chem.*, 1983, **26**, 1223.
22 P. R. Andrews, A. J. Jones, G. P. Jones, A. Marker, and E. A. Owen, *Eur. J. Med. Chem.*, 1981, **16**, 145.
23 G. D. Daves Jr., R. B. Belshee, W. R. Anderson Jr., and H. Downes, *Mol. Pharmacol.*, 1975, **11**, 470.
24 G. A. Neville and D. Cook, *Can. J. Chem.*, 1969, **47**, 743.
25 F. I. Carroll, A. H. Lewin, E. E. Williams, J. A. Berdasco, and C. G. Moreland, *J. Med. Chem.*, 1984, **27**, 1191.
26 P. Murray-Rust, in 'Molecular Structure and Biological Activity,' eds. J. F. Griffin and W. L. Duax, Elsevier, Amsterdam, 1982, pp. 117—133.
27 O. Kennard, 'Molecular Structure and Dimensions,' Cambridge Crystallographic Data Centre, 1970—1984, vols. 1—15.
28 W. D. S. Motherwell, 'PLUTO, a Plotting Program for Molecular Structures,' University of Cambridge, 1975.
29 B. M. Craven, E. A. Vizzini, and M. M. Rodrigues, *Acta Crystallogr.*, 1969, **B25**, 1978.
30 B. M. Craven and E. A. Vizzini, *Acta Crystallogr.*, 1971, **B27**, 1917.
31 B. Berking and B. M. Craven, *Acta Crystallogr.*, 1971, **B27**, 1107.
32 J.-P. Bideau, *C. R. Acad. Sci. (Paris)*, 1971, **C272**, 757.
33 B. M. Craven and E. A. Vizzini, *Acta Crystallogr.*, 1969, **B25**, 1993.
34 P. H. Smit and J. A. Kanters, *Acta Crystallogr.*, 1974, **B30**, 784.
35 G. L. Gartland and B. M. Craven, *Acta Crystallogr.*, 1971, **B27**, 1909.
36 G. P. Jones and P. R. Andrews, *J. Cryst. Mol. Struct.*, 1981, **11**, 125.
37 B. M. Craven and C. Cusatis, *Acta Crystallogr.*, 1969, **B25**, 2291.
38 P. R. Andrews and G. P. Jones, *J. Cryst. Mol. Struct.*, 1981, **11**, 135.
39 G. P. Jones and P. R. Andrews, *J. Cryst. Mol. Struct.*, 1981, **11**, 145.
40 G. P. Jones and E. Horn, *J. Crystallgr. Spectrosc. Res.*, 1986, **16**, 629.
41 P. P. Williams, *Acta Crystallogr.*, 1973, **B29**, 1572.
42 P. P. Williams, *Acta Crystallogr.*, 1974, **B30**, 12.
43 J.-P. Bideau and M. Artaud, *C. R. Acad. Sci. (Paris)*, 1970, **C271**, 806.
44 J.-P. Bideau, F. Leroy, and J. Housty, *C. R. Acad. Sci. (Paris)*, 1969, **C268**, 1590.
45 C. Escobar, *Acta Crystallogr.*, 1975, **B31**, 1059.
46 B. M. Craven, C. Cusatis, G. L. Gartland, and E. A. Vizzini, *J. Mol. Struct.*, 1973, **16**, 331.
47 F. S. LaBella, *Can. J. Physiol. Pharmacol.*, 1981, **59**, 432.
48 P. R. Andrews and L. C. Mark, *Anesthesiology*, 1982, **57**, 314.
49 J. L. de Coen, G. Elefante, A. M. Liquori, and A. Damiani, *Nature (London)*, 1967, **216**, 910.
50 J. H. Skerritt and G. A. R. Johnston, *Neurochem. Res.*, 1983, **8**, 1351.
51 J. H. Skerritt, G. A. R. Johnston, T. Katsikas, J. Tabar, G. M. Nicholson, and P. R. Andrews, *Neurochem. Res.*, 1983, **8**, 1337.
52 P. R. Andrews and G. P. Jones, *Int. J. Quantum Chem.*, 1979, **6**, 439.
53 M. G. Wong, J. A. Defina, and P. R. Andrews, *J. Med. Chem.*, 1986, **29**, 562.


*Received 2nd October* 1985; *Paper* 5/1706