Solution Conformations of Barbituric Acid Derivatives: A $^3J(^{13}C,^1H)$ NMR Study[1]

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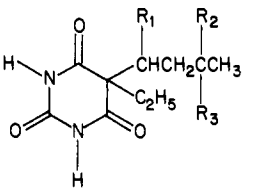
The conformations of the 5-alkyl chains of 5,5-dialkylbarbituric acid derivatives in polar and nonpolar media were determined from the magnitudes of the vicinal heteronuclear coupling constants between the α-alkyl hydrogens and the carbonyl carbons. The experimental ^3J values have been compared to theoretical values, and the conformational populations of the alkyl side chains with respect to the trioxopyrimidine ring have been determined. The results show that all these compounds have a very low barrier to rotation for both butyl and ethyl side chains. The barbiturates that do not have a 1′-methyl group in the butyl side chain, butobarbital and amobarbital, have no preferred conformation for either the butyl or ethyl side chains. However, the compounds with a 1′-methyl group, pentobarbital and α-methylamobarbital, exhibit preferred conformation for both alkyl chains. The significance of these results to the relationship between conformations and pharmacological activity is discussed.

Since the pharmacological activities of barbituric acid derivatives range from depressive to excitatory, the relationship between structure and activity has continued to be the subject of numerous in vivo and in vitro investigations.[2-4] Both the onset and the duration of hypnotic activity have been correlated with partition coefficients in a water/1-octanol system[2a] as well as with a high-pressure liquid chromatographic retention index.[5] However, lipid solubility can only partially account for activity of barbiturates since it is clear that metabolism and spatial configuration are also involved,[2,6-13] with optical isomers sometimes showing opposite types of pharmacological activity.[14,15] Specifically, it was reported in two separate studies that the (+) isomer of 5-(1′,3′-dimethylbutyl)-5-ethylbarbituric acid (α-methylamobarbital, 1) was a convulsant, whereas the (−) isomer caused anesthesia.[14,15] Thus, a change from convulsant to anesthetic activity occurs within the same structure due only to configurational differences.[14,15] These reports generated renewed interest in the configuration and conformation of the two 5-alkyl groups of barbiturates.

Investigations of the conformations of barbituric acid derivatives have been carried out by a wide variety of techniques. Crystal structure determinations revealed that in the solid state the 5-alkyl side chains of racemic 1 adopted a conformation different from that of the anticonvulsants 5-ethyl-5-(3′-methylbutyl)barbituric acid (amobarbital, 2) and 5-ethyl-5-(3′,3′-dimethylbutyl)-barbituric acid (γ-methylamobarbital, 3).[16] On the other hand, Daves and co-workers[17] concluded from ^1H NMR studies that the solution conformations of 1 and 2, as well as of the anticonvulsant 5-ethyl-5-(1′-methylbutyl)-barbituric acid (pentobarbital, 4), were all similar, resembling the solid-state conformations of 2 and 3. More recently Andrews and co-workers reported a computer-graphic-based pattern recognition analysis of 1, 3, 4, and 5-ethyl-5-*n*-butylbarbituric acid (butethal, 5).[18] This information was combined with earlier classical and molecular orbital potential energy calculations with a limited ^1H and ^{13}C NMR study to suggest specific conformations responsible for convulsant and anticonvulsant activity.[18] In this paper we report the use of $^3J(^{13}C,^1H)$ coupling constants to study the orientation of the alkyl side chains relative to the trioxopyrimidine ring for 1, 2, 4, and 5 in both polar and nonpolar solvents. The results obtained are compared to the solid-state conformations and to conformations suggested from theoretical calculations.



1. $R_1 = R_2 = CH_3$; $R_3 = H$
2. $R_1 = R_2 = H$; $R_3 = CH_3$
3. $R_1 = R_2 = R_3 = CH_3$
4. $R_1 = CH_3$, $R_2 = R_3 = H$
5. $R_1 = R_2 = R_3 = H$

Experimental Section

Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 267 grating spectrophotometer, ultraviolet spectra were recorded on a Cary 14 spectrophotometer, and mass spectra were obtained on an AEI MS-902 spectrometer. Proton NMR spectra were taken on a Varian HA-100 and a Bruker WM-250 spectrometer. The ^3J values were obtained at 25 MHz with a JEOL

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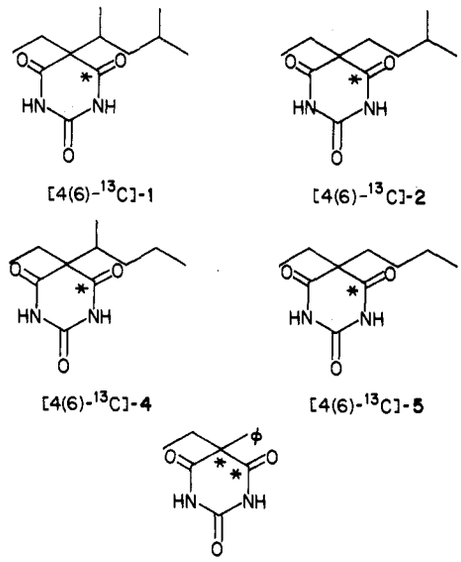
Table I. Magnitudes of Vicinal Coupling Constants ($^3J_{^{13}C,^1H}$) in Hertz[a] between the 1'-Hydrogen(s) and the Carbonyl Carbons 4 and 6 in Barbituric Acid Derivatives

		CD_3OD		$CDCl_3$	
entry	compd	$J_{C4,H1'}$	$J_{C6,H1'}$	$J_{C4,H1'}$	$J_{C6,H1'}$
1	[4(6)-^{13}C]-**2**[b]	4.64 ± 0.10		4.79 ± 0.10	
2	[4(6)-^{13}C]-**5**[b]	4.67 ± 0.10		4.78 ± 0.10	
3	[4(6)-^{13}C,*ethyl*-$^2H_5$]-**5**[b]	4.67 ± 0.10		4.70 ± 0.10	
4	[4(6)-^{13}C]-**1**	4.34 ± 0.20	5.27 ± 0.20	4.57 ± 0.20	5.65 ± 0.20
5	[4(6)-^{13}C]-**4**	4.34 ± 0.20	5.19 ± 0.20	4.13 ± 0.20	5.28 ± 0.20
6	[4(6)-^{13}C,*ethyl*-$^2H_5$]-**4**	4.15 ± 0.10	5.50 ± 0.10	4.52 ± 0.10	5.49 ± 0.10

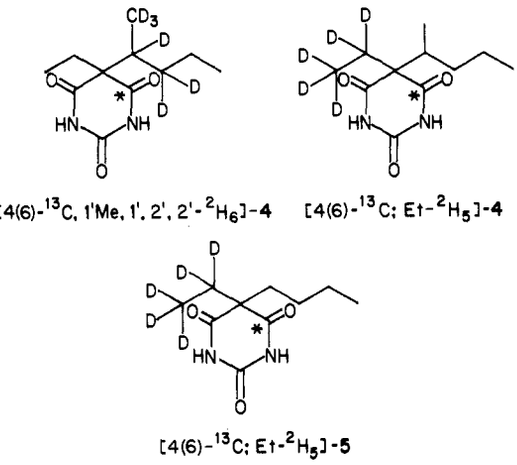
[a] Average of at least three measurements at 32 °C. [b] These compounds do not have a chiral center and therefore the chemical shifts for the carbonyl carbons 4 and 6 are the same.

Chart I[a]



[a] Asterisk designates ^{13}C enrichment.

Chart II[a]



[a] Asterisk designates ^{13}C enrichment.

JNM-PS-100FT NMR spectrometer or at 62.5 MHz on a Bruker WM-250 NMR spectrometer.

Barbituric Acid Derivatives. The ^{13}C-enriched compounds (Chart I) and ^{13}C-^{2}H-labeled compounds (Chart II) were prepared by using the procedures shown below.

Solvents and Reagents. Chloroform-*d* (99.8% D), methyl alcohol-d_4 (99% D), sodium borodeuteride (98% D), acetyl-d_3 chloride (99% D), and iodoethane (99% D) were purchased from Merck Co., Inc. Spectrograde methanol and chloroform were purchased from Fisher Scientific Co. 2-Pentanone, 4-methyl-2-pentanol, 2-pentanol, ethyl acetoacetate, diethyl malonate, bromoacetic acid, iodoethane, bromobutane, and 1-bromo-3-methylbutane were obtained from Aldrich Chemical Co.

Diethyl Malonate-*1*-^{13}*C*. Bromoacetic acid was treated with sodium cyanide-^{13}*C* to give cyanoacetic acid-^{13}*C*.[19] This product was treated with ethanolic hydrogen chloride to give diethyl malonate-*1*-^{13}*C*, bp 42 °C (0.15 mm). GLC analysis using a 6 ft × $^1/_8$ in. glass column packed with 3% SE-30 on 100–120-mesh Chromosorb W(AWS) showed one peak identical in retention time with that of diethyl malonate.

Deuterium-Labeled 2-Pentanol Compounds. 2-Pentanone-*1,1,1,3,3*-d_5 was prepared by base-catalyzed deuterium exchange of 2-pentanone. Pentanone-*1,1,1*-d_3 was prepared by treating acetyl-d_3 chloride with dipropylcadmium. Pentanol-*2*-*d* and pentanol-*1,1,1,2,3,3*-d_6 were prepared by reduction of 2-pentanone and 2-pentanone-*1,1,1,3,3*-d_5 with sodium borodeuteride. 3-Methyl-2-pentanol was prepared by the reduction of 4-methyl-2-pentanone with sodium borohydride.

The IR and ^{1}H NMR spectra of the labeled 2-pentanol samples were consistent with the assigned structures. Mass spectral analysis showed that each compound contained greater than 95% D.[20]

Each of the labeled 2-pentanol compounds as well as 3-methyl-2-pentanol were converted to their brosylate esters by treatment with *p*-bromobenzenesulfonyl chloride in pyridine.

5-Ethyl-5-alkylbarbituric-*4(6)*-^{13}*C* Acid Compounds. Alkylation of diethyl malonate-*1*-^{13}*C* with the appropriate 2-pentyl borsylate or bromoalkane in DMF with sodium hydride as the base followed by a second alkylation with iodoethane under similar conditions gave the expected diethyl ethyl(5-alkyl)malonate-*1*-^{13}*C* esters. Diethyl (ethyl-d_5)(5-alkyl)malonates-*1*-^{13}*C* was obtained by using iodoethane-d_5 in place of iodoethane. Condensation of these labeled diethyl malonate derivatives with urea using a procedure previously reported for the preparation of 5-ethyl-5-(1'-methylbutyl)barbituric acid gave the desired labeled compounds.[21] The products were recrystallized from an ethyl acetate and hexanes mixture and dried at 60 °C under vacuum.

The melting point and IR, UV, and ^{1}H NMR spectra of all the 5-ethyl-5-alkylbarbituric-*4(6)*-^{13}*C* acid derivatives were in agreement with the assigned structure. The purity of the compounds was determined by GLC analyses using a 6 ft × $^1/_8$ in. glass column packed with 3% OV-17 on 100–120-mesh Chromosorb W(AWS).

Results

The three bond coupling constants between the 4- and 6-carbonyl carbons and the 1'-hydrogen(s) and the 5-ethyl methylene hydrogens [$^3J(^{13}C,^1H)$] were measured in the

(19) We are grateful to Dr. Donald G. Ott, Los Alamos Scientific Laboratory, Los Alamos, NM, for supplying us with sodium cyanide-^{13}*C* (90.6% ^{13}C) and urea-^{13}*C* (91.3% ^{13}C).

(20) The present values were calculated by using a computer program. The computer program was developed by George Taylor, Research Triangle Institute, from a basic procedure described by Klaus Biemann in "Mass Spectrometry, Organic Chemical Applications", McGraw-Hill Book Co., New York, NY, 1962. Intensities of M^+, $M^+ + 1$, etc. for 2-pentanol were entered into a computer program along with the intensities of M^+, $M^+ + 1$, etc. for the deuterated sample of 2-pentanol. The percent of each deuterated species allowing for the natural abundance of ^{13}C could be calculated.

Table II. Magnitudes of Vicinal Coupling Constants ($^3J_{^{13}C,^1H}$) in Hertz[a] between Methylene Hydrogens of the 5-Ethyl Group and the Carbonyl Carbons 4 and 6

		CD_3OD		$CDCl_3$	
entry	compd	$J_{C4,H1}$ (= $J_{C6,H2}$)	$J_{C4,H2}$ (= $J_{C6,H1}$)	$J_{C4,H1}$ (= $J_{C6,H2}$)	$J_{C4,H2}$ (= $J_{C6,H1}$)
1	[4(6)-^{13}C]-**2**[b]	4.64 ± 0.10		4.79 ± 0.10	
2	[4(6)-^{13}C]-**5**[b]	4.67 ± 0.10		4.78 ± 0.10	
3	[2,4(6),5-^{13}C]-**6**[b]	5.00 ± 0.30		4.99 ± 0.30	
4	[4(6)-^{13}C]-**1**	2.66 ± 0.20	6.98 ± 0.20	3.40 ± 0.20	6.55 ± 0.20
5	[4(6)-^{13}C]-**4**	2.73 ± 0.20	6.91 ± 0.20	3.53 ± 0.20	6.52 ± 0.20
6	[4(6)-^{13}C,1′Me,-1′,2′,2′-$^2H_6$]-**4**	2.96 ± 0.10	6.81 ± 0.10	3.31 ± 0.10	6.73 ± 0.10

[a] Average of at least three measurements at 32 °C. [b] These compounds do not have a chiral center and therefore the chemical shifts for the carbonyl carbons 4 and 6 are the same.

following ^{13}C-enriched barbituric acids: [4(6)-^{13}C]-**1**, [4-(6)-^{13}C]-**2**, [4(6)-^{13}C]-**4**, [4(6)-^{13}C]-**5**, [2,4(6),5-^{13}C]-**6** (see Chart I), in deuterated methanol (CD_3OD) and deuterated chloroform ($CDCl_3$) (Tables I and II).

Accurate values for the $^3J(^{13}C,^1H)$ coupling constants between the carbonyl carbons 4 and 6 and either the 1′-hydrogens or the 5-ethyl methylene hydrogens were obtained from derivatives in which either the 1′-hydrogen(s) or the 5-ethyl methylene hydrogens were replaced by deuterium. For example, either [4(6)-^{13}C;*ethyl*-$^2H_5$]-**4** or [4(6)-^{13}C;*ethyl*-$^2H_5$]-**5** was used to obtain the 1′-hydrogen(s) coupling constant values to the carbonyl carbons 4 and 6 (numbers 6 and 3, respectively, in Table I). Similarly, coupling constants of the 5-ethyl methylene hydrogens to the carbonyl carbons 4 and 6 (number 6 in Table II) were obtained from [4(6)-^{13}C;1′Me,1′,2′,2′-$^2H_6$]-**4**. Since derivatives of [4(6)-^{13}C]-**2** or [4(6)-^{13}C]-**1** with either the 5-methyl group or the 1′-hydrogen(s) deuterated were not available, the $^3J(^{13}C,^1H)$ values for coupling of the 4- and 6-carbonyl carbons to H-1′ and to the methylene protons of the 5-ethyl group were determined by careful analysis of the coupling patterns of these undeuterated species. The validity of the values thus determined was confirmed by the observation that the values obtained for **4** and **5** are in good agreement with those of their deuterated analogues. In compounds **2** and **5** the 4- and 6-carbonyl carbons appear as a simple quintet (see Figure 1), consistent with a situation in which the coupling constants to the 1′-hydrogens and to the 5-ethyl methylene hydrogens are the same.

In compounds **1** and **4** the 4- and 6-carbonyl carbons exhibit an eight-line pattern, implying unequal coupling to the three protons involved. Analysis of the eight-line pattern allows the magnitude of the coupling constants to be determined; however, it does not permit the assignment of a particular coupling constant to a particular proton. These assignments are made from the simple spectra obtained for hexadeuterio **4** and pentadeuterio **4**. Assignment of specific coupling constants to the nonequivalent methylene hydrogens of the 5-ethyl group remains unresolved. Since the pattern for **1** is identical with that of **4**, the $^3J(^{13}C,^1H)$ values obtained from the eight-line pattern of **1** can be assigned to the individual hydrogens. The $^3J(^{13}C,^1H)$ results for **1** are the same as those for either **4**, [4(6)-^{13}C;1′Me,1′,2′,2′-$^2H_6$]-**4** or [4(6)-^{13}C;*ethyl*-$^2H_5$]-**4** (see Tables I and II). The $^3J(^{13}C,^1H)$ coupling constant value of the 5-ethyl methylene hydrogens for [4(6),5,2-$^{13}C_3$]-**6** in Table II is similar (within the experimental error) to those for **2** and **5** and is identical with the value obtained for **6** by Long and Goldstein.[22]

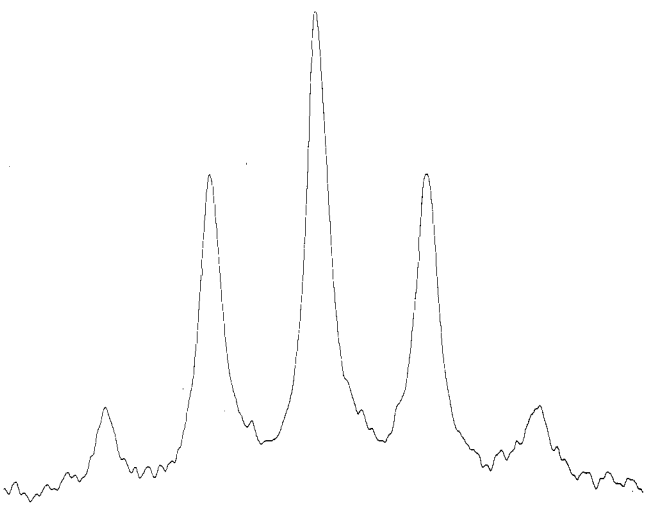


Figure 1. Carbon-13 NMR spectrum of carbonyl carbon 4(6) of 5-ethyl-5-*n*-butylbarbituric acid (**5**) at 62.5 MHz in CD_3OD at 32 °C. The spectrum was recorded at a spectral width of 1000 Hz.

Discussion

The observation that each of the four α-methylene hydrogens in the barbituric acids **2** and **5** is equally coupled (^3J = 4.7 Hz) to the carbonyl carbons 4 and 6 is uniquely consistent with the presence of equal populations of the three staggered conformations for each alkyl group and the absence of a significant barrier to rotation about the C-5 to alkyl group bonds. The magnitude of ^3J and the lack of a solvent effect on it further support this interpretation. A theoretical value for ^3J can be predicted from eq 1,[23]

$$^3J(^{13}C,^1H) = 4.26 - 1.00 \cos\theta + 3.56 \cos 2\theta \quad (1)$$

(θ = ^{13}C, ^{1}H dihedral angle)

which was originally derived from INDO MO calculations on propane and has been successfully applied, with some modifications, to a variety of compound classes.[24] For the case of rotation with no preferred conformation, eq 1 predicts ^3J = 4.3 Hz. Comparing this calculated value with the experimental ^3J results for either **2** or **5** and keeping in mind the experimental error (±3%), this deviation of 8–10% between the theoretical and experimental values is quite insignificant.

Similar results are obtained for **6** in which the 5-butyl group is replaced by phenyl. Thus, equal ^3J values (^3J = 5.0 Hz) for each of the methylene protons of the 5-ethyl group to the 4- and 6-carbonyl carbons are observed, indicating rotation with no preferred conformation. These results, together with those obtained for the barbiturates

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Table III. Calculated ^3J Values, Populations, and Relative Potential Energies for Conformations 4A, 4B, and 4C

conf	$J_{C4,H}$,[a] Hz	θ, deg	$J_{C6,H}$,[a] Hz	θ, deg	popultn[b]	rel potential[c] energy, kcal/mol
4A	2.0	60	8.8	180	0.51[d]	0
4B	8.8	180	2.0	60	0.32[d]	0.28
4C	2.0	60	2.0	60	0.17	0.68

[a] Calculated from eq 1. [b] Calculated from the experimental ^3J for 4 in CH_3OH and the calculated ^3J values. [c] Calculated from the conformational populations at 32 °C. [d] These may be interchanged (see text).

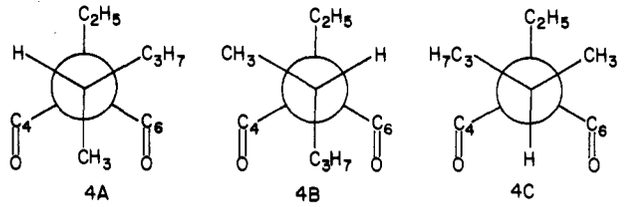
Table IV. Calculated ^3J Values, Populations, and Relative Potential Energies for Conformations 4D, 4E, and 4F

conf	$J_{C4,H1}$,[a] Hz	θ, deg	$J_{C6,H1}$,[a] Hz	θ, deg	$J_{C4,H2}$,[a] Hz	θ, deg	$J_{C6,H2}$,[a] Hz	θ, deg	popultn[b]	rel potential[c] energy, kcal/mol
4D	2.0	60	8.8	180	8.8	180	2.0	60	0.70	0
4E	2.0	60	2.0	60	2.0	60	8.0	180	0.15	1.0
4F	8.8	180	2.0	60	2.0	60	2.0	60	0.15	1.0

[a] Calculated from eq 1. [b] Calculated from the experimental ^3J for 4 in CH_3OH and the calculated ^3J values. [c] Calculated from the conformational populations at 32 °C.

2 and 5, justify the use of eq 1 for calculation of ^3J for the interaction of the α-hydrogens on the 5-alkyl chains with the 4- and 6-carbonyl carbons in all the barbiturates in this study.

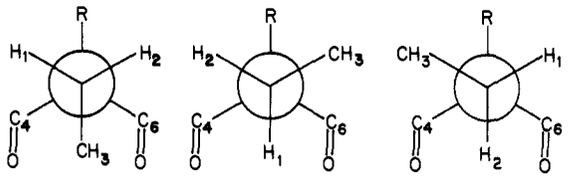
By contrast to the observed equal coupling constants between the methylene hydrogens and the 4- and 6-carbonyl carbons in 2 and 5, resulting from the rotation of all pendant alkyl chains, unequal couplings between H-1′ and the carbonyl carbons 4 and 6 are observed in the barbiturates 1 and 4. For 4 the ^3J values for the two carbonyl carbons are 4.15 ± 0.10 and 5.50 ± 0.10 Hz in CH_3OH and 4.52 ± 0.10 and 5.49 ± 0.10 Hz in $CHCl_3$ (see Table I, entry 6). This observation suggests that H-1′ is unsymmetrically disposed toward C-4 and C-6 in 4. In terms of the possible conformations 4A, 4B, and 4C of the 1′-methylbutyl side chain, this means that the populations of 4A and 4B must be nonzero and unequal. In order to determine the weighting factors for these conformers, theoretical ^3J values for the conformations 4A, 4B, and 4C were calculated by using eq 1 (Table III).



4A 4B 4C

In these conformers, the dihedral angles between the 1′-hydrogen and carbonyl carbons 4 and 6 are 60° ($^3J_{60°}$) and 180° ($^3J_{180°}$), giving $^3J_{60°}$ = 2.0 Hz and $^3J_{180°}$ = 8.8 Hz. Use of these calculated ^3J values and the experimental ^3J values for 4 in CH_3OH results in weighting factors of 17% for 4C, 51% (or 32%) for 4A, and 32% (or 51%) for 4B. With use of the same procedure for 4 in $CHCl_3$, the weighting factors are 12% for 4c 51% (or 37%) for 4A and 37% (or 51%) for 4b. Taking into consideration that the experimental ^3J values may be valid to about ±3% error and that the theoretical ^3J value may be in error by 8–10% implies that the difference in the results between the two solvents is probably not significant, and the average weighting factors of 15% for 4C, 51% (or 34%) for 4A, and 34% (or 51%) for 4B are adequate. The fact that the ^3J results for 1 are the same as that for 4 indicates that the conformation of the 1′,3′-dimethylbutyl chain of 1 is the same as that determined for the 1′-methylbutyl side chain in 4.

Comparison of the ^3J values for the interactions of the methylene hydrogens with the carbonyl carbons in barbiturates 1 and 4 with those of 2 and 5 reveals some striking differences. The fact that each of the two methylene hydrogens is unequally coupled to each carbonyl carbon immediately suggests restricted rotation and/or a preferred conformation. This conclusion is reinforced by the magnitude of the coupling constants. For example, for 4 values of 2.7 and 6.9 Hz are recorded (Table II); these values are close to $^3J_{60°}$ and $^3J_{180°}$ calculated from eq 1 (Table III), suggesting the predominance of a conformation in which each methylene hydrogen is gauche to one carbonyl carbon and anti to the other (4D). In fact, it has been found that based on potential energy calculations,[25] 4D is the minimum energy conformer of the 5-ethyl group, some 1–2 kcal/mol below 4E and 4F.



4D 4E 4F

R = C_5H_{11}

Using the ^3J values for conformations 4D, 4E, and 4F, calculated from eq 1 (Table IV) and the experimental ^3J values for 4 in CH_3OH, gives weighting factors of 70% for 4D and 30% for 4E and 4F. Following the same procedure for 4 in $CHCl_3$, the weighting factors obtained are 66% for 4D and 34% for 4E and 4F. Taking into account the experimental error, these conformational populations are the same, corresponding to an energy difference of 1.0 kcal/mol between the ground state, 4D, and the gauche conformations 4E and 4F, in reasonable agreement with calculated predictions.[25] The same situation obtained for the barbiturate 1.

Summary of Conformational Conclusions

For the series of barbituric acids investigated, the above analysis indicates that in the absence of a 1′-methyl group there are no preferred conformations of either of the alkyl groups at C-5 with respect to their attachment to the trixoypyrimidine ring. In other words, on the NMR time scale, rotation occurs around both C-5 to methylene bonds with the three staggered conformations (X, Y, Z) being equienergetic. This result is, in fact, unsurprising if one takes into consideration the near planarity of the trioxypyrimidine ring together with the rapid rate of pseudoaxial/pseudoequatorial interconversion. This situation is unaffected by γ substitution (2 vs. 5) or by replacement

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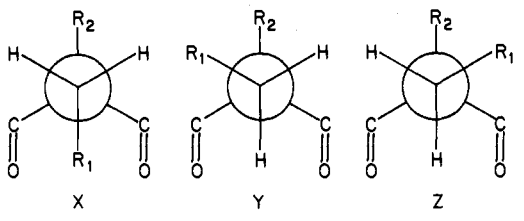

X Y Z

1, R_1=Me, R_2=4-Me-pentyl
2, R_1=Me, R_2=3-Me-Bu or R_1=*i*-Pr, R_2=Et
4, R_1=Me, R_2=2-Bu
5, R_1=Me, R_2=Bu or R_1=Pr, R_2=Et
6, R_1=Me, R_2=Ph

of one of the substituents by a phenyl group (**2**, **5** vs. **6**).

Conversely, the presence of a 1′-methyl group leads to conformational preferences for the alkyl groups. Thus, conformation 4C, in which both the methyl and the 2-pentyl groups are gauche to the ethyl group, is the least preferred, being some 0.68 kcal/mol higher in energy than the ground-state conformation. Conformations 4A and 4B differ by 0.28 kcal/mol, but our data do not allow us to determine which of the two is of lower energy.

Once again, as was observed for the derivatives **2** and **5**, the conformational situation around the linkages of C-5 to the alkyl groups is essentially unaffected by introduction of a γ substituent (**1** vs. **4**) and by the medium (CH_3OH vs. $CHCl_3$). These observations provide additional information about the conformation of the 2-pentyl chain. Structure determination of **1** by single-crystal X-ray crystallography[16] had shown that, in the solid state, the molecule is in conformation 4A with the 2-pentyl chain gauche to the methylene of the 5-ethyl group. In such a conformation the 2-pentyl chain must be fully extended to avoid steric interactions, as is observed in the solid-state structure.[16] Since no differences in conformational populations about C-5–C-1′ are observed between the γ-methyl-substituted barbiturates (**2** and **1**) relative to their unsubstituted analogues (**4** and **5**, respectively), it seems likely that both the 2-pentyl and the 4-methyl-2-pentyl chains are in extended conformation.

Structure–Activity Correlations

There have been numerous attempts to correlate the observed differences in pharmacological activities of barbituric acid derivatives with their molecular conformations. Most recently, it has been proposed[18] that the observed differences in activity may be due not to differences in ground-state conformations but to differences in conformations within 10 kcal/mol of the ground state. Specifically, it was calculated that convulsant barbiturates had a conformation with torsion angles 60° for the C-5–C-1′ bond (τ_1) and 140° for the C-1′–C-2′ bond (τ_2) within 10 kcal/mol of their global ground-state conformations; for anticonvulsant barbiturates such conformations were calculated to have energies exceeding 10 kcal/mol above their ground states. A conformation with $\tau_1 = \tau_2 = 180°$ was calculated to fall within 10 kcal/mol of the minimum energy conformation for anticonvulsant barbiturates; the energy of this conformation was more than 10 kcal/mol greater than the global minimum for some convulstants but was coincident with it for others.

Our experimental results deviate from these calculated values[18] by an order of magnitude. Thus, the ^3J values recorded by us for the barbiturates **1**–**5** unequivocally demonstrate that all possible staggered conformations for rotation about C-5–C-1′ lie within 1 kcal/mol of each other, making it very hard to accept the assertion that the convulsant conformation ($\tau_1 = 60°$, $\tau_2 = 140°$) for compound **1** has energy > 10 kcal/mol above the ground-state conformation.

The results of the present study provide direct experimental evidence that the difference in activity between **4** (anticonvulsant) and **1** (convulsant) is not related to any conformational difference relating to the linkage of the alkyl groups to C-5. It also shows that the slight conformational preference observed in the barbiturates **1** and **4** relative to **2** and **5** cannot account for the differences in pharmacological activities since **2**, **4**, and **5** are all anticonvulsants.

Because barbiturates possess both polar and nonpolar components and distribute between aqueous and lipid phases, their conformational populations could be medium dependent. Therefore, each barbiturate in this study was investigated in a polar solvent (methanol) and a relatively nonpolar medium (chloroform). No significant changes in conformational populations were observed. Thus, one can conclude that the conformational composition of the barbiturates studied is solvent independent, and therefore that conformation–activity results discussed above are valid for either polar or nonpolar media. All the above indicate that the observed differences in pharmacological activity of barbiturates is not related to their conformations. Since studies[14] using partially resolved **1** indicate that the convulsant activity resides in the (+) isomer whereas the (−) isomer shows anticonvulsant action similar to **2** and **5** and the (+) isomer of **4** has been reported[26] to cause convulsant action while the (−) isomer is anticonvulsant, the difference in the convulsant–anticonvulsant action of **1**, **2**, **4**, and **5** appears to be due to the sensitivity of the site of action to the absolute configuration of these barbiturates rather than to its conformation. This conclusion suggests the pharmacological evaluation of optically active γ-substituted barbiturates or their analogues, in which the asymmetric center is varied systematically. For example, the effect of altering the electronic and steric character of the center and its position along the alkyl chain could be investigated.

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Registry No. 1, 2964-06-9; 2, 57-43-2; 4, 76-74-4; 5, 77-28-1; cyanoacetic acid-^{13}C, 67121-16-8; diethyl malonate-*1*-^{13}C, 79341-48-3.

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