Carbon-13 Nuclear Magnetic Resonance Spectra of 5-Alkyl-5-(1-methylbutyl)barbituric Acids

By **F. Ivy Carroll,*** Chemistry and Life Sciences Division, Research Triangle Institute, Research Triangle Park, North Carolina 27709
Charles G. Moreland, Department of Chemistry, North Carolina State University at Raleigh, Raleigh, North Carolina 27607

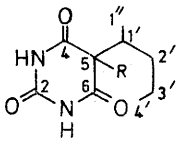
The natural-abundance ^{13}C n.m.r. spectra of 5-alkyl-5-(1-methylbutyl)barbituric acids have been obtained. All resonances were assigned by chemical shift comparisons including the analysis of deuteriated analogues and the use of single-frequency, off-resonance decoupling. Chemical shift nonequivalence was observed between the carbonyl C-4 and C-6 atoms. This chemical shift difference is very sensitive to changes in the 5-alkyl substituent, thus indicating that ^{13}C n.m.r. spectroscopy should be of considerable value in detecting steric effects and conformational changes in other optically active 5,5-dialkylbarbituric acids.

PREVIOUS studies have shown that both the barbituric acid ring and two C-5 lipophilic side chains are necessary for central nervous system (CNS) activity.[1] The detailed mechanism of the CNS activity of 5,5-dialkylbarbituric acids is not understood; however, it probably involves intramolecular interaction between the acids

[1] W. J. Doran in ' Medicinal Chemistry,' eds. F. F. Blicke and R. H. Cox, Wiley, New York, 1959, vol. IV, p. 1.

and the drug receptor site. Since the CNS activity may depend on factors which affect the transfer of the drug to its appropriate receptor, it is of considerable interest to investigate the possible conformational dependence of the C-5 alkyl side chains and the heterocyclic ring.

The molecular structure of 5,5-dialkylbarbituric acids has been investigated by a variety of physical methods including u.v.,[1,2] i.r.,[1,3,4] *X*-ray,[5,6] o.r.d.[7] or c.d.,[8] and ^{1}H n.m.r. spectroscopy.[4,9,10] However, no ^{13}C n.m.r. study has been reported for this medicinally important class of compounds.* Since proton-noise-decoupled ^{13}C n.m.r. has proved valuable in studies of the carbon framework, electronic structure, and conformational properties of other biologically interesting nitrogen heterocycles,[11-16] we have determined the ^{13}C n.m.r. spectra of a series of 5-alkyl-5-(1-methylbutyl)barbituric acids (1).



(1)

RESULTS AND DISCUSSION

The ^{13}C n.m.r. chemical shifts relative to tetramethylsilane for the 5-alkyl-5-(1-methylbutyl)barbituric acids studied are listed in the Table. The ^{13}C n.m.r. chemical shift assignments for the 1-methylbutyl side chain were made by comparing the spectra for the different compounds. Single-frequency, off-resonance decoupling experiments confirmed these assignments.[17] As can be seen from the Table, these assignments are straightforward and are consistent with general trends reported[17] for alkyl carbon atoms. In the case of C-1′ and C-2′ where R = H the signal multiplicity obtained from off-resonance experiments was used in making the chemical shift assignments. The ^{13}C chemical shift assignments for the R side chains were made by using deuteriated analogues, single-frequency, off-resonance experiments, and chemical shift comparisons.

^{13}C Chemical shifts of 5-alkyl-5-(1-methylbutyl)barbituric acids [a]

	Chemical shifts (p.p.m.) [b,c]												
Substituent	1″ 1′ 2′ 3′ 4′ $CH_3CHCH_2CH_2CH_3$					R			Ring	Carbonyl [d]			
R	C-1″(q)	C-1′(d)	C-2′(t)	C-3′(t)	C-4′(q)	C-1 [e]	C-2 [f]	CH_3(q)	C-5(s)	C-2(s)	C-4(s)	C-6(s)	$\delta_{C\text{-}4} - \delta_{C\text{-}6}$
H	16·69	35·91	35·77	20·09	13·87				52·32	151·04	170·75	169·97	0·78
CH_3 1	13·97 [g]	41·44	33·19	20·28	13·87 [g]			18·39	53·48	150·17	173·32	173·13	0·19
CH_3CH_2 2 1	14·12	41·25	33·58	20·33	13·92	27·66		9·46	59·31	150·03	173·03	172·69	0·34
CD_3CD_2 2 1	14·12	41·20	33·58	20·33	13·92	*h*		*h*	59·16	150·03	173·03	172·69	0·34
$CH_3CH_2CH_2$ 2 1	14·04 [i]	41·45	33·43	20·26	13·84	36·73	18·31	14·04 [i]	58·50	150·06	173·19	172·90	0·29
CH_3CHCH_3 2 1	14·17	37·32	32·80	20·23	13·92	33·78	17·56 [j]	17·47 [j]	60·77	150·02	172·74	172·59	0·15
CH_2=$CHCH_2$ 3 2 1	14·12	41·10	33·48	20·28	13·92	38·67	132·06	119·88 [k]	58·48	149·93	172·45	172·16	0·29

[a] Numbering of positions is shown in (1). [b] Shifts are in p.p.m. relative to tetramethylsilane. [c] Signal multiplicities obtained from single-frequency, off-resonance experiments are given in parentheses. [d] The designation C-4 and C-6 is arbitrary. [e] The 5-ethyl, 5-propyl, and 5-allyl derivatives showed a triplet, the 5-isopropyl a doublet. [f] The 5-propyl derivative showed a triplet, the 5-allyl a doublet, and the 5-isopropyl a quartet. [g] In the case where R = CH_3 the designation C-1″ and C-4′ is arbitrary. [h] The multiplet due to deuterium splitting was not resolved from the baseline noise. [i] The terminal methyl of the propyl group and 1″-methyl appeared as one peak with intensity approximately twice that of the 4′-methyl. [j] Chemical shift nonequivalence is observed for these methyl groups. [k] This resonance is for the terminal olefinic carbon atom.

The barbituric acid ring of all the 5-alkyl-5-(1-methylbutyl)barbituric acids listed in the Table show separate resonances for the C-5 quaternary atom and the 2-, 4-, and 6-carbonyl groups. The C-4 and C-6 carbonyl groups appear as separate resonances as a result of the molecular asymmetry in the 5-(1-methylbutyl) side chain. The chemical shift difference of the C-4 and C-6 atoms is exemplified by the ^{13}C n.m.r. spectrum of 5-ethyl-5-(1-methylbutyl)barbituric acid (1; R = Et) shown in Figure (A). In contrast the ^{13}C n.m.r. spectrum of 5-ethyl-5-isopropylbarbituric acid (1; R = Et,

* *Added in proof:* A communication (A. Fratiello, M. Mardirossian, and E. Chavez, *J. Magnetic Resonance*, 1973, **12**, 221) on the carbon-13 n.m.r. chemical shifts of seven barbiturates appeared in the literature after the submission of our paper.

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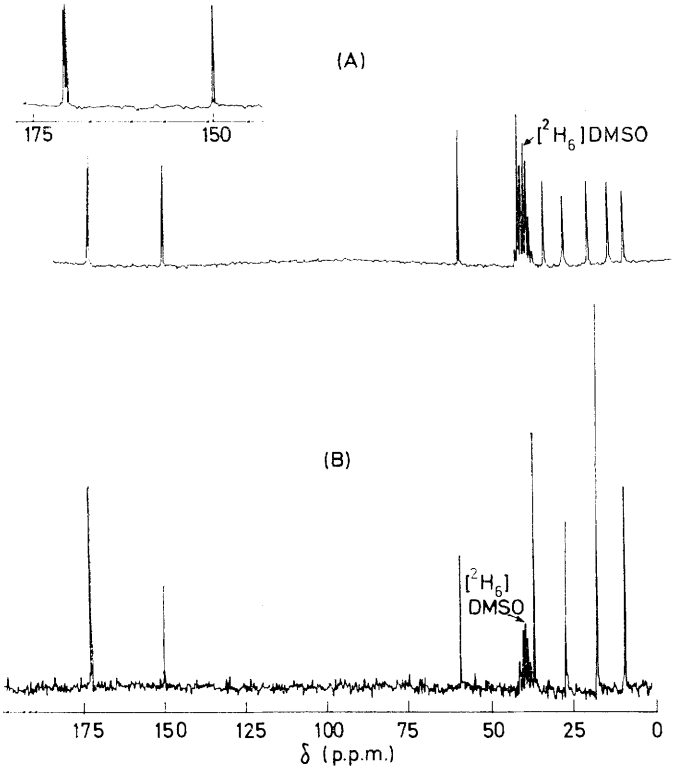
MeCHMe for MeCHPr) shown in Figure (B), which does not possess a centre of asymmetry, shows only one resonance for the C-4 and C-6 atoms. Carbon-13 chemical shift nonequivalence of methyl groups has been reported.[18-20] However, we present here the first



(A) $^{13}C-\{^1H\}$ Decoupled n.m.r. spectrum for 5-ethyl-5-(1-methylbutyl)barbituric acid (1; R = Et) in [$^2H_6$]DMSO. Insert shows the C-4, C-6, and C-2 signals on an expanded scale. (B) $^{13}C-\{^1H\}$ Decoupled n.m.r. spectrum for 5-ethyl-5-isopropylbarbituric acid (1; R = Et, MeCHMe for MeCHPr) in [$^2H_6$]DMSO. The C-4 and C-6 resonances appear as one signal

detection of chemical shift nonequivalence of carbonyl groups by ^{13}C n.m.r.

The results listed in the Table show that the degree of nonequivalence of the two carbonyl carbon atoms changes as the 5-alkyl group is varied. It is interesting that the chemical shift difference, $\delta_{C\text{-}4} - \delta_{C\text{-}6}$, of the biologically inactive 5-monoalkyl derivative (1; R = H) is quite different from the biologically active 5,5-dialkyl derivatives; also the difference between the unsubstituted derivative (1; R = H), and the other 5,5-dialkyl group is apparent from a comparison of the chemical shifts of the C-2 atoms of the barbituric acid ring. For example, even though C-2 is far removed from the 5-alkyl substituents, the resonance for (1; R = H) appears 1·11—0·87 p.p.m. downfield relative to the 5,5-dialkyl derivatives.

Since acids (1) contain an asymmetric centre, we had previously used o.r.d.[7] and c.d.[8] to probe their stereochemical structures. The c.d. curves of all the compounds studied showed three Cotton effects in the 200—260 nm range. The magnitude of the intermediate Cotton effect observed in the region 245—255 nm was extremely sensitive to changes in the 5-alkyl group indicating that the conformation of the heterocyclic ring, the 5-alkyl substituents, or both were changing as the 5-alkyl group was varied. In the case of the unsubstituted derivative, 5-(1-methylbutyl)-barbituric acid (1; R = H), the sign of all three Cotton effects was opposite from those found in all other 5-alkyl-5-(1-methylbutyl)barbituric acids. Thus, both the ^{13}C n.m.r. results reported in this paper and the previously reported o.r.d. and c.d. results indicate that steric relationships between the 5-alkyl substituents and the heterocyclic ring are apparently different in the monosubstituted acid (1; R = H) and 5-alkyl-substituted acids (1; R = alkyl).

EXPERIMENTAL

N.m.r. Spectra.—The ^{13}C n.m.r. spectra were determined on a JEOL JNM-PS-100 FT n.m.r. spectrometer interfaced with a Nicolet 1085 Fourier-transform computer system at 25·15 MHz. Because of the limited solubility of many barbiturates in [^2H]chloroform, [$^2H_6$]dimethyl sulphoxide was used as the common solvent for this study. The spectra were recorded at ambient temperature by using the deuterium resonance of [$^2H_6$]DMSO as the internal lock signal. All proton lines were decoupled by a broad band (*ca.* 2500 Hz) irradiation from an incoherent 99·998 MHz source. Interferograms were stored in 8K of computer memory (4K output data points in the transformed-phase, corrected, real spectrum), and chemical shifts were measured for 5000 Hz sweep width. Typical pulse widths were 12 μs, and the delay time between pulses was fixed at 1·0 s. Normally 512 data accumulations were obtained for 200 mg sample in 2 ml solvent. The chemical shifts are accurate to within ±0·1 p.p.m. Single-frequency, off-resonance experiments were performed in the CW mode on all the compounds listed in the Table.

Chemicals.—All the 5-alkyl-5-(1-methylbutyl)barbituric acids were prepared as described previously.[7,8]

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[3/1977 *Received*, 26*th September*, 1973]

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