Substituent and Solvent Effects on Tautomeric Equilibria of Barbituric Acid Derivatives and Isoterically Related Compounds

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N-Mono and *N,N*-dialkyl/diarylbarbituric acids exist in solution as a single tautomer. The ^{13}C nmr spectroscopy shows that they are present in the triketo form in a number of polar and non-polar solvents. 2-Thiobarbituric acid derivatives, however, show extensive tautomerization. Their ^{13}C chemical shift assignments were achieved by utilizing models **11a**, **11c**, **12b** and **12d** and from which relative tautomer distribution ratios were determined. These ratios were correlated with the dielectric constant of the various solvents (ϵ). Thiobarbituric acids also formed adducts with solvents having carbonyl groups, characteristic observed only with barbiturates possessing the thione or thiophenolic group. 6-Amino and 6-methyluracils and thiouracils exist in DMSO solution as stable "*ene*" forms as do orotic acid, **24**, and its thio analogue **25**. Compound **25** undergoes disproportionantion and tautomerization when heated or on prolonged standing in solution. Literature contradictions regarding the structure of "4,6-dihydroxypyrimidine," **26**, were resolved and its tautomers in solution correctly assigned by ^{13}C nmr.

Anions of barbiturics and related systems exist in one of the two possible types A and B, depending on whether ring nitrogens are substituted (type A), or not (type B). Rapid H/D exchange at C_5 was evident from C-deuterium coupling. The redistribution of charge through $C_4(C_6)$ carbonyl groups shown by ^{13}C shifts of carbonyl carbon atoms of up to 10 ppm as compared to the CO carbons of the neutral species was evident.

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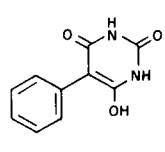
Introduction.

Barbituric acid derivatives are a well-known class of compounds many of which are widely-used drugs having such disparate pharmacological activities as depressants, hypnotics and stimulants. Hence, they have been the subject of numerous reports and investigations which have attempted to interpret their mode of action [1-5]. Additional incentives for studying these compounds stem from observations that (a) they closely resemble several nitrogenous bases found in nucleic acids and (b) some bacteria metabolize certain pyrimidines to barbituric acid derivatives [6]. This paper reports on the study of the effect of solvents and substituents on the tautomeric equilibria of barbituric acid and some of its derivatives and isoterically related compounds.

The trioxo form of barbituric acid, **1a**, in the solid state has been confirmed by X-ray [7,8] and ^{14}N-NQR [9] methods. On the basis of ultraviolet spectroscopy, Rosen and Sandberg [10] postulated an equilibrium in water between the keto (trioxo) and enol (monohydroxy-dioxo) forms, and Fox and Shugar [11] demonstrated the predominance of the former. The uv studies subsequently carried out on barbituric acids substituted at the 5-position by chloro, bromo, or methyl groups indicated that the position of tautomeric equilibrium of these acids was dependent upon the nature of the solvent [12,13]. The enol form of all these acids was absent in aprotic solvents but appeared in amphiprotic solvents, sometimes to such an extent that it predominated over the keto form.

Most of the ^{13}C nmr studies of barbiturates capable of undergoing enolization at C_5 were done during the early 1970's on spectrometers which were much less sensitive than the various FT spectrometers presently used. Consequently, there appear to be some inconsistancies in these studies. For example, the conclusions of ^{13}C nmr spectral studies of **1** [14,15] and 5-alkyl derivatives of **1** [14,16,17] in DMSO were that these barbiturates exist only in the keto form. However, Jones and coworkers [18] reported that the ^{13}C nmr spectrum of 1-(β-D-ribofuranosyl)barbituric acid, **2**, in DMF showed a low intensity signal at 87.2 ppm which they ascribed to a C_5 vinyl carbon atom [18]. The weak ab-



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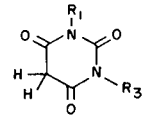
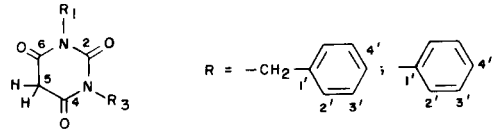


1 $R_1 = R_3 = H$
4 $R_1 = CH_3$, $R_3 = H$
5 $R_1 = CH_2C_6H_5$, $R_3 = H$
6 $R_1 = C_6H_5$, $R_3 = H$
7 $R_1 = R_3 = CH_3$
8 $R_1 = R_3 = CH_2C_6H_5$
9 $R_1 = R_3 = C_6H_5$

Table 1

^{13}C NMR Chemical Shifts of some *N*-Alkyl and *N*-Arylbarbituric Acids at Ambient Temperature (25°)



Compound No.	Substituent(s)	Solvent	Chemical Shifts (in ppm) [a,b] C_2	C_4	C_5	C_6	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	Other
1 [c,d]	$R_1 = R_3 = H$	d_6-DMSO	151.7	167.8	40.0 [e]	167.8					—
4	$R_1 = CH_3$, $R_3 = H$	d_6-DMSO	151.8	166.4	39.7 [e]	166.9					26.8
		$CDCl_3$ [f,g]	150.6	164.3	39.3	165.3					27.9
		d_6-acetone [h]	151.9	166.0	39.5	166.9					26.9
		CH_3OD [i]	153.4	168.2	39.8	168.7					27.7
		D_2O [j]	152.6	168.7	38.4 [e]	168.4					27.0
		$HCONHCH_3$ [k]	152.7	167.7	39.9	167.4					27.1
5	$R_1 = CH_2C_6H_5$; $R_3 = H$	d_6-DMSO	151.8	166.5	39.9 [e]	167.0	137.0	128.3	127.5 [*l*]	127.5 [*l*]	43.1
		$CDCl_3$ [f,g]	150.4	165.0	39.3	164.3	135.7	129.2	128.6	128.2	44.4
		d_6-acetone [h]	151.9	166.9	39.9	166.0	137.6	128.7 [*l*]	128.7 [*l*]	127.7	44.0
		CH_3OD [i]	153.2	168.4	40.3	168.0	138.2	129.5 [*l*]	129.5 [*l*]	128.6	44.9
		$HCONHCH_3$ [k]	152.7	167.7	40.3	167.4	137.5	128.7	128.3	127.7	44.1
6	$R_1 = C_6H_5$, $R_3 = H$	d_6-DMSO	151.5	166.5 [m]	41.6	166.6 [m]	135.0	128.8 [*l*]	128.8 [*l*]	128.2	—
7	$R_1 = R_3 = CH_3$	d_6-DMSO	152.3	165.8	39.8 [e]	165.8					27.7
		$CDCl_3$ [g]	151.8	164.6	39.3	164.6					28.3
		d_6-acetone [h]	153.1	166.1	40.0	166.1					28.0
		CH_3OD [i]	154.0	167.7	40.2	167.7					28.6
		D_2O [j]	153.1	167.9	38.9 [n]	167.9					27.9
		$HCONHCH_3$ [k]	153.1	[e]	40.3	[e]					28.0 [e]
8	$R_1 = R_3 = CH_2C_6H_5$	d_6-DMSO	151.9	165.7	40.2 [e]	165.7	136.7	128.1	127.4	127.1	44.1
		$CDCl_3$ [g]	151.5	164.4	39.7	164.4	136.0	129.1	128.5	128.0	45.1
		d_6-acetone [h]	153.0	166.2	40.1 [n]	166.2	137.9	128.9 [*l*]	128.9 [*l*]	128.0	45.2
		CH_3OD [i]	153.6	167.3	[o]	167.3	138.2	129.5 [*l*]	129.5 [*l*]	128.7	45.9
9	$R_1 = R_3 = C_6H_5$	d_6-DMSO	151.6	165.7	41.0	165.7	135.3	128.8 [*l*]	128.8 [*l*]	128.3	—
		$CDCl_3$ [g]	151.1	164.3	40.3	164.3	133.9	129.3	128.3	129.2	—
		d_6-acetone [h]	152.5	166.0	41.3	166.0	136.3	129.4	129.4	129.4	—
		$HCONHCH_3$ [k]									

[a] Downfield from TMS and using a solvent as a double reference standard unless indicated otherwise; d_6-DMSO = 39.5 ppm. [b] δ (ppm). [c] Reference compound reported previously [8]. [d] Chemical shifts of major tautomer (see text for further discussion). [e] ^{13}C resonance obscured by solvent peak(s) but clearly visible in other solvents. [f] Partially soluble in the solvent listed. [g] Deuteriochloroform = 77.0 ppm. [h] CO signal at 206.0 ppm. [i] Monodeuteriomethanol = 50.0 ppm. [j] Referenced to external chloroform standard (77.0 ppm). [k] Referenced to the CO resonance at the lower field of the *trans* isomer (166.7 ppm), and using external deuterium oxide as reference deuterium lock. [*l*] Overlapping signals. [m] Clearly resolved and assigned by relaxation times and comparison with models (see text). [n] Estimated value. [o] Signal not resolved.

sorbance exhibited by that nucleoside was indicative of enol-keto tautomerism. These investigators noted that the vinyl absorbance was obscured by the DMSO peak in the ^{13}C nmr spectrum of a solution of the acid in DMSO. Interestingly, Fox, *et al.* [19] had reported in a previous pmr study that 1-(β-D-ribofuranosyl)barbituric acid, **2**, exists essentially in the triketo form in DMSO.

To our knowledge, no other barbiturate was shown to be in the enol form by ^{13}C nmr spectroscopy until we reported recently, that 5-phenylbarbituric acid, **3**, exists as a mixture of enol and keto tautomers in DMSO [20]. During the course of that study, we obtained the ^{13}C nmr spectrum of barbituric acid, **1**, in DMSO-d_6. This spectrum exhibited a weak absorbance at 87.0 ppm indicating that **1** exhibited tautomerism in that solvent (*ca.* 1% of **1** is in enol form). A previous pmr studies indicated that **1** adopted only in the keto form in DMSO [21,22]. Thus, ^{13}C nmr spectroscopy should provide a convenient method for evaluating tautomerism in barbiturates. These studies also should give useful information about the role of substituents on acidities of barbituric acids and an increased understanding of their mode of action. For example, barbituric acid and its derivatives act as buffers in the biologically important *p*H range of 6-9; indicating that unionized barbituric acids penetrate living cells more readily than their constituent ions [23].

In light of the previous comments, we elected to study the effect of substituents and solvent on the tautomeric equilibria of various barbiturates and the influence of substituents on the structure of these acids and their con-

Table 2

^{13}C NMR Chemical Shifts of Thiobarbituric Acids [a]

Compound No.	Solvent	Substituent(s)	Chemical Shifts (in ppm) [b] C_2	C_4	C_5	C_6	Other
10a	d_6-DMSO	—	181.0	165.6	40.0 [c,d]	165.6	—
10c	d_6-DMSO	—	175.3	162.6	82.2	162.6	—
10a	CH_3OD	—	181.8	167.3	39.6	167.3	—
10c	CH_3OD	—	176.9	165.2	82.5	165.2	—
10 [e]	d_6-DMSO/D_2O (50:50)	2-OH (**1**)	150.7	167.0	[c]	167.0	—
10 [f]	$HCONHCH_3$	$2SCH(OH)NHCH_3$ (**17**)	177.7	166.7	86.5	166.7	104.2 (CH), 22.9 (CH_3)
11a	$CDCl_3$	$R_1 = R_3 = CH_2CH_3$	180.0	163.0	40.5	163.0	43.3 (CH_2), 12.2 (CH_3)
11a	d_6-acetone	$R_1 = R_3 = CH_2CH_3$	182.3	164.6	41.4	164.6	43.4 (CH_2), 12.3 (CH_3)
11 [f]	d_6-acetone	$2SC(\alpha CH_3)_2O^-$ [g] [18] $R_1 = R_3 = CH_2CH_3$	180.0	160.9	92.0	160.9	120.3 (C), 28.6 (αCH_3), 43.7 (CH_2), 12.6 (CH_3)
11a	CH_3OD	$R_1 = R_3 = CH_2CH_3$	182.5	165.8	41.3	165.8	44.1 (CH_2), 12.6 (CH_3)
11c	CH_3OD	$R_1 = R_3 = CH_2CH_3$	177.7	163.2	83.5	163.2	44.7 (CH_2), 12.4 (CH_3)
11a [h]	d_6-DMSO/D_2O (50:50)	$R_1 = R_3 = CH_2CH_3$	177.6	162.9	83.5	162.9	43.6 (CH_2), 12.6 (CH_3)
11 [e]	D_2O	2-OH (**38**) [i] $R_1 = R_3 = CH_2CH_3$	149.1	165.3	57.5	165.3	58.3 (CH_2), 18.2 (CH_3)
11 [f]	$HCONHCH_3$	$2SCH(NH\alpha CH_3)O^-$ (**39**) [g] $R_1 = R_3 = CH_2\beta CH_3$	178.5	160.9	87.0 [d]	160.9	104.7 (CH), 23.7 (αCH_3) 43.3 (CH_2), 12.1 (βCH_3)
12b	d_6-DMSO	$2\text{-}SCH_3$	163.6	167.3	54.3	167.3	12.9 (CH_3)
12d	d_6-DMSO	$2\text{-}SCH_3$	165.0	169.7	85.6	166.3	12.8 (CH_3)
12d [j]	CH_3OD	$2\text{-}SCH_3$	164.5	169.8	87.4	169.8	13.5 (CH_3)
16	CH_3OD (Y = O)	$2\text{-}OCH_3$	171.7	168.0	87.1	168.0	55.4 (CH_3)
12b	d_6-DMSO/D_2O (50:50)	$2\text{-}SCH_3$ [i]	171.3	167.3	56.3	167.3	14.0 (CH_3)
12d	d_6-DMSO/D_2O (50:50)	$2\text{-}SCH_3$	164.6	168.9	87.3	168.9	13.9 (CH_3)
12e	$HCONHCH_3$	$2\text{-}SCH_3$	170.8	[c]	54.6	[c]	13.0 [k] CH_3
12d	$HCONHCH_3$	$2\text{-}SCH_3$	160.4	168.7	86.4	168.7	13.0 [k] CH_3

[a] Nomenclature and numbering system is the same as in Table 1. [b] δ (ppm) downfield from TMS and using a solvent as a double reference standard (see Table 1). [c] Resonance obscured by solvent peak(s) but clearly visible in other solvents. [d] Estimated value. [e] Hydrolyses in deuterium oxide. [f] Forms an adduct with the solvent. [g] Zwitterionic adduct. [h] Undergoes slow hydrolysis in deuterium oxide. [j] Covalent hydrate. [j] Undergoes partial alcoholysis in the solvent listed. [k] Overlapping signals.

jugate bases. In addition, the structures of some isosterically related compounds in solution were reexamined and the results compared with those obtained from x-ray diffraction studies.

Results and Discussion.

The *N*-alkyl and *N*-aryl substituted barbituric acids, **4-9**, were studied first to see if substituents at nitrogen influenced the proton transfer equilibria of barbituric acid. The ^{13}C nmr of these compounds are listed in Table 1 and show that they all exhibit C_5 methylene carbon signals (40 to 50 ppm) of the keto form in DMSO, deuteriochloroform, hexadeuterioacetone, monodeuteriomethanol, deuterium oxide, and *N*-methylformamide. The characteristic absorption of the C_5 "vinyl" group of the enol form, which is in the range of 80 to 90 ppm, [13,20,24] could not be detected. Thus, the *N*-alkyl and *N*-aryl compounds, **4-9**, adopt the triketo form in the polar and non-polar solvents used in this study.

The other ^{13}C chemical shifts were assigned in the following manner. The non-equivalent C_4 and C_6 carbonyl carbon atoms in the asymmetric compounds **4-6** were assigned by analogy with monomethyl and dimethylurea [25,26]; the downfield and upfield signals were assigned to C_6 and C_4, respectively [16,27]. In all cases, the former signal has a longer relaxation time than the latter. Generally, the C_2 carbonyl carbon appears upfield from the C_4 and C_6 resonances [27] and waas distinguished from the other carbonyl resonances by the absence of α-coupling to C_5-methylene protons [28] (see Table 5). Phenyl carbon atoms in **5**, **6**, **8**, and **9**, were easily assigned from proton-coupled ^{13}C spectra. For example, $C_{1'}$ and

Table 3

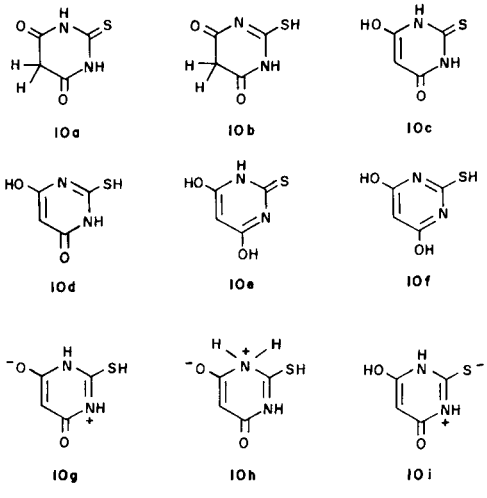
Relative Tautomer Distribution of some Barbituric Acid and 2-Thiobarbituric Acid Derivatives in Different Solvents

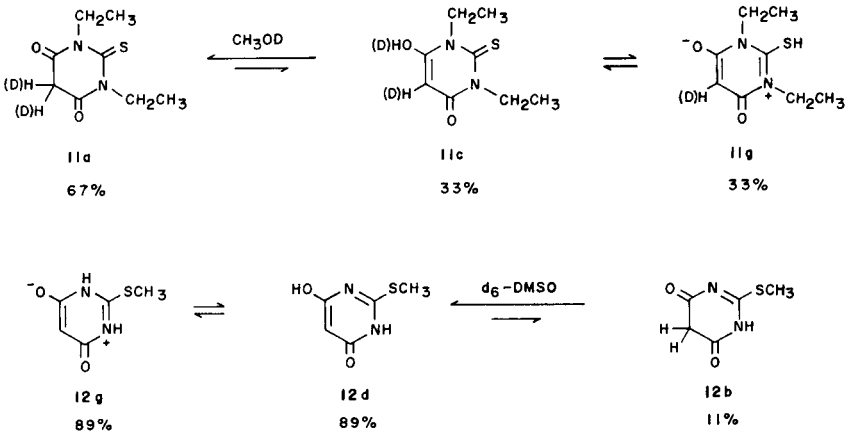
Compound No.	Substituent(s)	Solvent	Dielectric const (ε) [a]	Tautomer keto	Tautomer enol/zwitterion
10	R_2 = SH	CH_3OH	33.62 (20°) 32.63 (25°)	46% (**10a**)	54% (**10c/10g**)
10	R_2 = SH	DMSO	46.65 (25°)	35% (**10a**)	65% (**10c/10g**)
10	R_2 = SH	$HCONHCH_3$	>120 [b]	none	100% [c] (**17**)
11	R_2 = SH R_1 = R_3 = CH_2CH_3	$CHCl_3$	4.81 (20°)	100% (**11a**)	none
11	R_2 = SH R_1 = R_3 = CH_2CH_3	acetone	20.7 (25°)	98% (**11a**)	2% [c] (**18**)
11	R_2 = SH R_1 = R_3 = CH_2CH_3	CH_3OH	33.62 (20°) 32.63 (25°)	67% (**11a**)	33% (**11c/11g**)
11	R_2 = SH R_1 = R_3 = CH_2CH_3	DMSO/D_2O (50:50)	64 [d]	55% (**11a**)	45% (**11c/11g**)
11	R_2 = SH R_1 = R_3 = CH_2CH_3	$HCONHCH_3$	>120 [h]	none	100% [c]
12	R_2 = SCH_3	CH_3OH	33.62 (20°) 32.63 (25°)	none	100% (**12d**)
12	R_2 = SCH_3	DMSO	46.65 (25°)	11% (**12b**)	89% (**12d**)
12	R_2 = SCH_3	DMSO/D_2O (50:50)	64 [d]	15% (**12b**)	85% (**12d**)
12	R_2 = SCH_3	$HCONHCH_3$	>120 [b]	21% (**12b**)	79% (**12d**)
16	R_2 = OCH_3	CH_3OH	33.62 (20°) 32.63 (25°)	none	100% (**16d**)
1 [e]	R_2 = OH	DMSO	46.65 (25°)	99%	1%
4-9	R_2 = OH R_1,R_3 = H, alkyl, aryl	$CHCl_3$ acetone CH_3OH	4.81 (20°) 20.7 (25°) 33.62 (20°) 32.63 (25°)	100% 100% 100%	none none none
		DMSO	46.65 (25°)	100%	none
		H_2O	80.37 (20°) 78.54 (25°)	100%	none
		$HCONHCH_3$	>120 [b]	100%	none

[a] Source: CRC Handbook of Chemistry and Physics and National Bureau of Standards. [b] Estimated from $HCONH_2$ (ε = 109 at 20°). [c] Exists as an adduct with the solvent listed. [d] Estimated value from the dielectric constant of DMSO and deuterium oxide (ε = 78.25 at 25°).

substituted $C_{4'}$ carbon atoms show no *ipso* J_{CH} coupling and appear as a narrow triplet, whereas $C_{2'(6')}$, $C_{3'(5')}$ and $C_{4'}$ appear as two sets of doublet of doublets and a doublet of triplets, respectively.

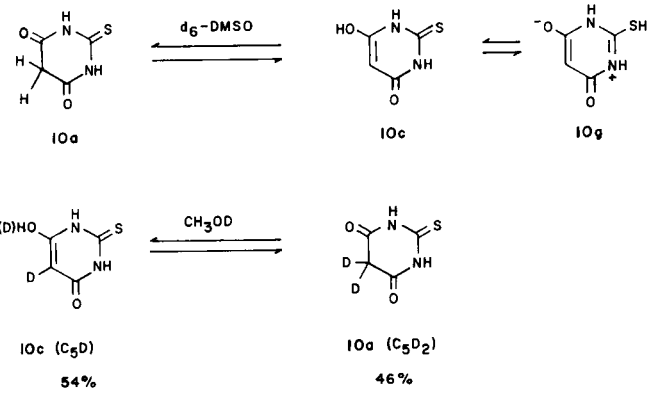
Next, the influence of substituents at the C_2 carbon on tautomeric equilibria was examined. Replacing a carbonyl group by thiocarbonyl group yields 2-thiobarbituric acid, **10**, which can exist in six possible neutral tautomeric forms, **10a-f**, and three zwitterionic forms, **10g-i**, of which one, **10g**, has to be seriously considered. The results of previous studies on the structure of **10** have been inconclusive [29-31]. One study suggested that **10** probably exists either as dioxothione **10a** or hydroxy-oxo-thione **10c** [29]. The x-ray structure of **10** was investigated but no definitive choice was made as to which tautomer is present in





the solid state [30]. A parallel study of 1,3-diethyl-2-thiobarbituric acid, **11**, was also inconclusive even though the choice was narrowed to only two tautomers, *i.e.* **11a** and **11c** [31].

In order to establish which tautomer(s) is(are) present in solution, the ^{13}C spectra of *N*-alkyl, **11**, and *S*-alkyl derivative, **12**, were recorded and they are discussed first. Compound **11**, exists as dioxothione **11a** in deuteriochloroofrm and d_6-acetone as evident by the presence of the C_5-methylene carbon resonance at ~40 ppm (Table 2). In monodeuteriomethanol, however, it exists as a tautomeric mixture of dioxothione, **11a**, and hydroxy-oxo-thione, **11c**, or zwitterion **11g**, in a ratio of about 2:1, respectively. Zwitterion **11g** would most likely be formed by intramolecular neutralization of the hydroxyoxothione form, **11c** [32].



That the ^{13}C nmr spectrum of **11** exhibits only one set of resonances of the non-keto forms indicates that the equilibrium between these two forms is rapid on the NMR time scale [32]. All the acidic hydrogens exchange with deuterium so that C_5 resonance in **11a** appears as a pentet and C_5 signal in **11c/11g** as a triplet due to carbon-deuterium coupling. (Table 5 gives J_{CD} and H/D isotope shifts on nuclear shielding of C_5). Unfortunately, compound **11** decomposes in DMSO, and only residual broad signals are

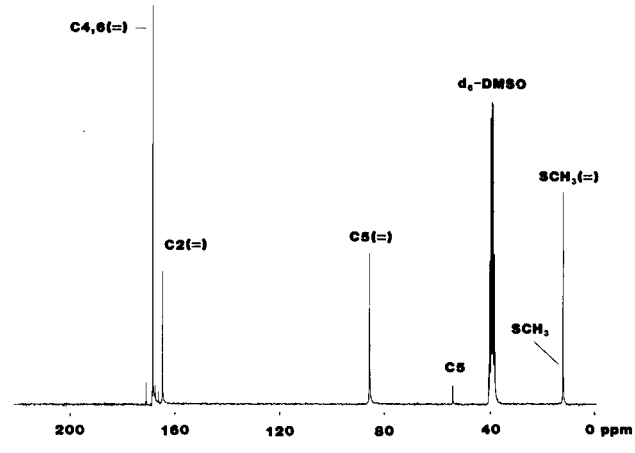


Figure 1a. 50.3 MHz ^{13}C-nmr ^1H-decoupled spectrum of 4,6-dihydroxy-2-methylmercaptopyrimidine, **12**, in hexadeuteriomethylsulfoxide (spectral width 220 ppm).

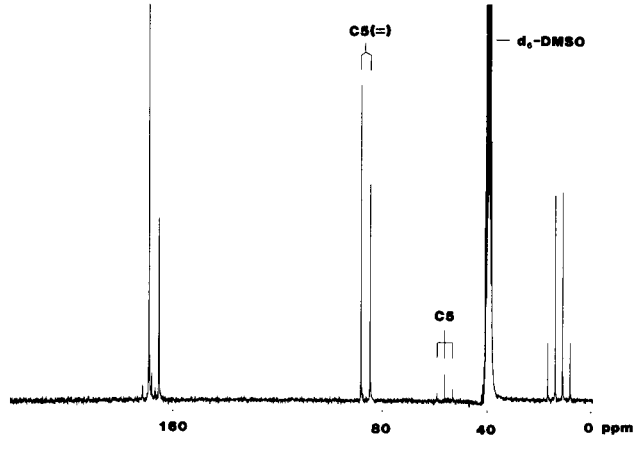


Figure 1b. 50.3 MHz ^{13}C-nmr ^1H-coupled spectrum of 4,6-dihydroxy-2-methylmercaptopyrimidine, **12**, in hexadeuteriomethylsulfoxide (spectral width 220 pm).

detected. Another possible interpretation could be that a number of other species are formed which provide a set of broad averaged ^{13}C resonances which cannot be interpreted adequately.

4,6-Dihydroxy-2-methylmercaptopyrimidine, **12**, is insoluble in deuteriochloroform and hexadeuterioacetone and undergoes partial alcoholysis in monodeuteriomethanol. In hexadeuteriomethylsulfoxide it exists as a mixture of diketo, **12b**, and hydroxy-keto, **12d**, (or the zwitterion, **12g**) forms, in a tautomer ratio of 11:89, respectively (Figures 1a and 1b). Structural assignment of **12b** was straightforward since it is the only isomer (of the two possible choices) which has the methylene C_5 carbon and thiophenolic methylmercapto substituent (-N=C-SR). The "vinylic" C_5 carbon resonance was assigned to the **12d/12g** tautomer(s) since the only other possible isomer would be the aromatic dihydroxymethylmercapto compound (as in **10f**) which has been ruled out by uv studies [29].

In order to ascertain the importance of zwitterionic structures **11g** and **12g** and to make a distinction between these species and their neutral non-ionized forms **11c** and **12d**, we attempted to prepare *N,N'*-1,3-diethyl-4,6-dihydroxy-2-methylmercaptopyrimidine, **13**. Alkylation of 1,3-diethyl-2-thiobarbituric acid, **11**, with excess amounts of methyl iodide in a sealed tube and under pressure failed to produce a salt. However, reaction of **11** with one equivalent of trimethyloxonium tetrafluoroborate in dichloroethane at gentle reflux in a sealed tube did produce **13** as translucent, low melting crystals. Treatment of this tetrafluoroborate salt with one equivalent of aqueous sodium hydroxide yields a resonance stabilized common anion **14** for both tautomers **13a** and **13b**. This anion is isoelectronic with zwitterion **11g** and should therefore have the same uv absorption as **14**. Indeed, adding small aliquots of 0.01 *N* solution of sodium hydroxide to **14** until a 1:1 ratio was achieved, we were able to reproduce a uv spectrum which closely resembled that of **11**. This strongly suggests that forms **11g** and **12g** are probably the correct representations for the enol tautomers of **11** and **12**.

With four out of six tautomeric models on hand, the remaining two identified by uv spectroscopy and by other methods [29], and the reference model for zwitterion **10g**, we were now able to study the tautomerism of 2-thiobarbituric acid, **10**. Proton-decoupled ^{13}C spectrum of **10** in d_6-DMSO has four absorptions in the region 160-185 ppm, one resonance at 82.2 ppm, and one in the methylene region (40 ppm). Furthermore, the signals are of unequal intensity and they can be further subdivided into two groups; those appearing at 175.3, 162.6 and 82.2 ppm, and the set of signals with ^{13}C chemical shifts at 181.0, 165.6 and 40 ppm (Table 2). Carbon resonance at 181 ppm must be that of C_2 thione based on the C_2 chemical shift of **11a** (182.5 ppm) and the corresponding ^{13}C chemical shifts of dimethyl- and diethylthiourea at 182.7 and 182.8 ppm, respectively [33]. Furthermore, this tautomer has a C_5 methylene group and therefore must have the structure of dioxothione **10a**.

The second set of signals has a "vinylic" C_5 carbon at 82.2 ppm and thus it limits the choice to four tautomers **10a-f** and one zwitterionic form **10g**. Of these possible tautomeric forms, **10e** and **10f** are ruled out by uv studies and on theoretical grounds [29]. Of the three remaining tautomers, **10d** can be eliminated by chemical shift comparison with model compounds, **11c** and **12d**. The C_2 carbon substituted with a methylmercapto group in **12d** has a chemical shift of 165.0 ppm, whereas the chemical shifts of the C_2 atom containing the unsubstituted thione group in **11c** is 177.7 ppm. Since the SCS (substituent chemical shift) additivity parameters for SH and SCH_3 for an *ipso* carbon are +2.1 and +10.0 ppm, respectively, the C_2 chemical shift of **10d** would be predicted to be around

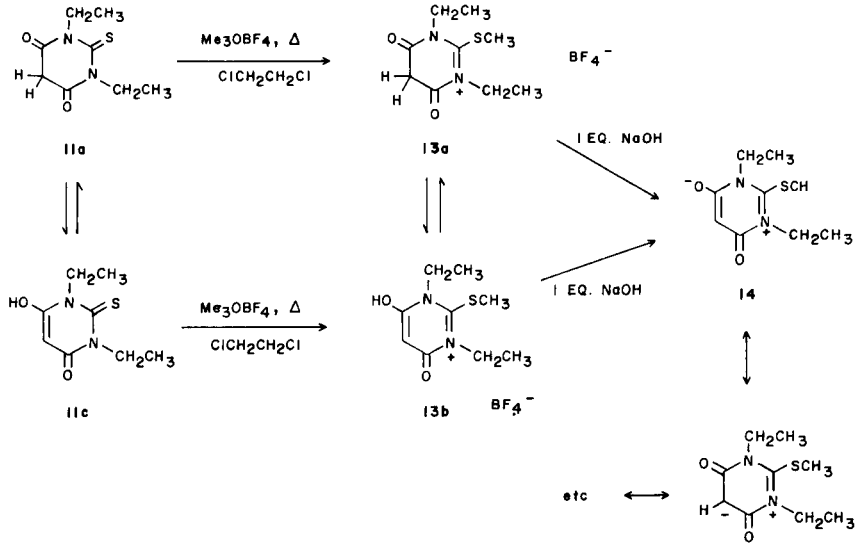
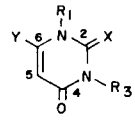


Table 4

^{13}C NMR Chemical Shifts of some Uracils and Related Compounds at Ambient Temperature (25°)



Compound No.	Substituent(s)	Chemical Shifts (in ppm) [b] C_2	C_4	C_5	C_6	Other
20	X = O, Y = NH_2, R_1 = R_3 = H	151.0	164.5	74.2	155.3 [b]	—
21	X = O, Y = NH_2, R_1 = R_3 = CH_3	151.6	161.4	74.9	154.9 [b]	27.0 (N_3-CH_3), 29.2 (N_1-CH_3)
22	X = O, Y = CH_3, R_1 = R_3 = H	151.5	164.1	98.7	152.9 [c]	18.2 (CH_3)
23	X = S, Y = CH_3, R_1 = R_3 = H	175.8	160.9	103.6	153.1 [c]	18.0 (CH_3)
24	X = O, Y = CO_2H, R_1 = R_3 = H	150.9	164.1	103.3	142.6	161.8 (CO_2H) [d]
25	X = S, Y = CO_2H, R_1 = R_3 = H	176.0	160.9	107.3	142.7	161.1 (CO_2H) [d]
25b [e]	X = $^+$SH, Y = CO_2^-, R_1 = R_3 = H	175.7	161.1	106.4	143.5	164.5 (CO_2^-)
25c	X = SH, Y = CO_2H, R_1 = R_3 = H	167.3	155.5	113.6	152.2	160.0 (CO_2H)
26a [f]	X = H, Y = OH, R_1 = R_3 = H	149.8	166.2	90.0	166.2	—
26b	X = H, Y = OH, R_1 = R_3 = H	149.9	167.6	98.4	162.3	—
26a [f,g]	X = H; Y = OH; R_1 = R_3 = H	149.9	166.2	90.1	166.2	—
26b [g]	X = H; Y = OH, R_1 = R_3 = H	149.7	167.4	99.3	162.6	—

[a] δ (ppm) downfield from TMS and using a solvent as a double reference standard; d_6-DMSO = 39.5 ppm. [b] ^{14}N quadrupole broadening of ^{13}C signals. [c] Assigned on the basis of C_6-CH_3 benzylic J_{CH} coupling. [d] Assigned by H/D isotope shift. [e] Zwitterionic species of compound **25**. [f] Could be betaine **26f** (see text for further discussion). [g] 50:50 d_6-DMSO/d_6-acetone solvent mixture.

157.1 which is significantly different than the observed value of 175.3 ppm. Thus, the remaining two tautomers are the hydroxy-keto-thione, **10c**, and its zwitterion, **10g**. The two forms are most likely in equilibrium with each other in DMSO since we observed only very broad ^{13}C resonances indicating a slow equilibrium and overlaps of two sets of signals.

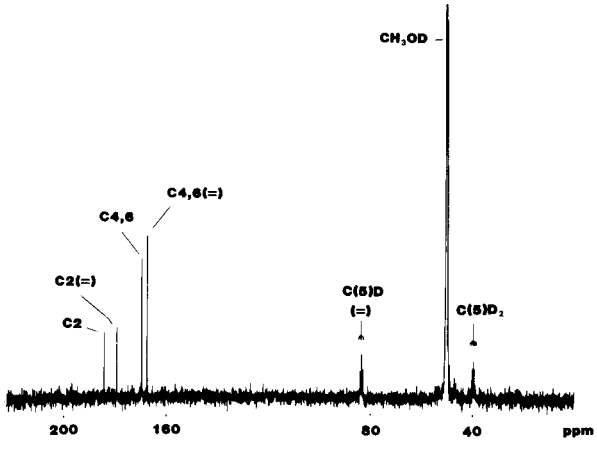


Figure 2. 50.3 MHz ^1H-decoupled ^{13}C spectrum of 2-thiobarbituric acid, **10**, in monodeuteriomethanol (220 pm); C_5-D carbon-deuterium coupling is clearly visible. Enol carbon atoms are denoted as (=).

The ^{13}C nmr spectrum of a solution of **10** in monodeuteriomethanol indicates the presence of **10c** and **10c/10g** except that the ratio of dioxothione to the hydroxy-keto-thione/zwitterion pair is more evenly distributed in monodeuteriomethanol (54:46) than in d_6-DMSO (65:35). As was the case with 1,3-diethyl-2-thiobarbituric acid, **11**, all acidic hydrogens of **10** are exchanged by deuterium giving rise to a triplet for C_5-D of **10c/10g** and a pentuplet for $C_5\langle^{D}_{D}$ of **10a** (Figure 2). The chemical shifts of these tautomers are almost identical to ^{13}C chemical shifts reported for **11a** and **11c/11g**.

Since it appeared that more polar solvents favor and stabilize the enol/zwitterionic pair *over* the keto form, we obtained the ^{13}C spectra of compounds **1**, **4-12** and **15** in solvents with wide range of dielectric constants. The data presented in Table 3 show that significant enolization, self-ionization and subsequent zwitterion formation occurs only with barbiturates possessing the thio-oxo group or alkylmercapto substituents. The lack of enolization of non-sulfur containing barbiturates listed in Table 3 probably reflects the lower propensity for -OH formation as compared to -SH formation [13,29]. The data in Table 3 also show that the relative concentration of the enol forms of **10** and **11** increases as the dielectric constant of the solvent is increased. This direct relationship is consistent with enol-zwitterion formation of thiobarbiturates **10** and

Table 5

Typical ^{13}C-^{1}H, ^{13}C-^{2}H Coupling Constants [a] and Hydrogen-deuterium Isotope Shifts [b] for some Barbituric Acids and Related Compounds [c,d]

Compound No.	C_2	C_4	C_5	C_6	CH_2	CH_3
6	[e]	[f] 7.0 (t, H_5)	132.9 (t) [g]	— 7.0 (t, H_5)		
7	[e]	— 7.0 (t, H_5)	132.3 (t) 3.4 (NH)	— 7.5 (t, H_5)		142.2 (q)
8	—	— 6.7 (t, H_5)	133.1 (t) 2.5 (NH)	— (m) [j]	141.4 (t)	
9	—	— [k]	133.8 (t) [k]	— [k]		
10	[e]	[e]	125.1 (t)	[e]		140.8 (q)
11	— 3.2 (CH_2)	— 6.9 (H_5) 3.2 (CH_2)	[l]	— 6.9 (H_5) 3.2 (CH_2)	141.9 (t)	
12	—	— 6.9 (t, H_5)	133.3 (t)	— 6.9 (t, H_5)		
13a	[m]	[m]	[l]	[m]		
13c	[m]	[m]	169.3 (d) [k]	[m]		
15b	— [k]	—	142.0 (t)	—		141.9 (q)
15d	— 5.2 (q, SCH_3)	[e]	168.0 (d)	[e]		142.4 (q)
20	[e]	[e]	168.6 (d)	[e]		
21	– 3.3 (m, NCH_3)	[e]	169.3 (dt) 3.6 (NH_2)	[e]		141.0 (q) [n] 140.5 (q) [o]
22	—	—	172.5 3.9 (CH_3)	— 3.8 (q, CH_3)		129.5 4.5 (H_5)
23	—	— [k]	173.8 3.7 (CH_3)	— 4.1 (q, CH_3)	129.5	4.0 (H_5)
24	—	—	177.6 (d)	—		
25	—	— 3.1 (d, H_5)	179.3 (d)	—		
25b [g]	—	— 3.6 (d, H_5)	181.1 (d)	—		
26	203.4 (d)	— 9.5 (d, OH)	166.4 (d)	— 9.5 (d, OH)		
27	[e]	—	—	—		
28	— 3.7 (CH_3)	—	—	[e]		139.5 (q)
29	—	—	—	—	[l]	
30	—	—	—	—		142.2 (q)
31	— 3.0 (t, CH_3)	—	—	—	138.2 (t)	
32	—	—	—	—		
33	—	—	—	—		
34	— 4.0 (m, CH_2) [u]	[e]	—	[e]	141.8 (t)	127.6 (q)
35	— 3.8 (q, SCH_3)	—	—	—		140.5 (q)
36	[e]	—	—	—		
37	— 3.5 (d, NH)	—	—	—		

Table 5 (Continued)

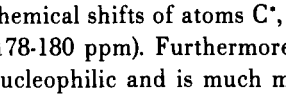
Compound No.	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$J_{C,D}$	ΔC_5D^b [b]
6					24.8 [i] (p)	0.18 [i]
7					20.4 [b] (m) 20.3 [i] (p)	0.14 [h]
8	— (m) [j]	160.0 [k]	157.7 [k]	160.1 (dt) 6.8 ($H_{2'}$, $H_{6'}$)		
9	— 9.8 (t, $H_{3'}$, $H_{5'}$)	163.0 (dd) 7.3 ($H_{4'}$)	162.7 (dd) 6.9 ($H_{5'}$)	161.3 (dt) 7.2 ($H_{2'}$, $H_{6'}$)		
10					20.1 [h] (p)	
11	— (m) [j]	159.9 [k]	159.2 (dd) 7.0 ($H_{5'}$)	161.0 (dt) 7.4 ($H_{2'}$, $H_{6'}$)		
12	— 9.1 (t, $H_{3'}$, $H_{5'}$)	164.3 (dd) 5.2 ($H_{4'}$)	162.2 (dd) 7.0 ($H_{5'}$)	162.0 (dt) 7.4 ($H_{2'}$, $H_{6'}$)		
13a					20.7 [h] (p)	
13c					26.5 [h] (t)	
15b						
15d					20.0 [h] (t)	0.13 [h]
20						
21						
22						
23						
24						p (CO_2H)
25						p (CO_2H)
25b [g]						p (SH)
26						p (OH)
27					24.8 [r] (t)	0.18 [r]
28					21.7 [r] (t)	0.19 [r]
29	— (m) [j]	160.7 (dd) 7.0 ($H_{4'}$)	159.0 [k]	161.0 (dt) 7.0 ($H_{2'}$, $H_{6'}$)	s (t)	
30					22 [t] (t)	
31	— (m) [j]	160.8 [k]	157.3 [k]	160.1 [k]	21 [t] (t)	0.16 [r]
32	— (m) [k]	162.7 (dd) 6.7 ($H_{4'}$)	163.0 (dd) 6.3 ($H_{5'}$)	162.9 (dt) 8.0 ($H_{2'}$, $H_{6'}$)	18.3 [r] (t)	0.17 [r]
33					24.4 [r] (t)	
34					s (t)	
35					26.8 [r] (t)	
36					25.2 [r] (t)	0.22 [r]
37					23.2 [r] (t)	

[a] All values in Hz (DMSO). [d] Given in Δ ppm. [c]Nomenclature and the numbering system is the same as those given in Tables 1 and 6. [d] All enolate anion are sodium salts in deuterium oxide. [e] Line broadening indicates presence of coupling which under the experimental conditions used appears to be less than 1 Hz. [f] Long-range ^{13}C-^1H couplings are listed below the one-bond couplings with the coupled hydrogen atoms listed in parentheses. [g] Notation used: d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, p = pentaplet. [h] Solvent monodeuteriomethanol. [i] Solvent, deuterium oxide. [j] Broadening of resonance due to benzylic coupling. [k] Unresolved long range coupling. [l] Obscured by solvent peaks. [m] Broadening of resonance due to tautomeric exchange equilibria. [n] N_1-CH_3. [o] N_3-CH_3. [p] H/D exchange to fast for isotope shift to be observed. [q] J CO_2^-, H_5 = 3.7 Hz. [r] Solvent, 2*M* sodium deuteroxide. [s] Burried in the noise. [t] Estimated value. [u] Two non-equivalent CH_2 groups.

11. With sulfur atom blocked, as in methylmercapto derivative **15**, the effect is exactly the opposite with the enol form completely predominating in monodeuteriomethanol. In this instance, the amide linkages are better stabilized by hydrogen bonding interactions with *N*-methylformamide (ϵ = 120) and water (ϵ = 80) and it reverts completely to the conjugated enol in methanol (ϵ = 33.6). The same observations apply to 2-methoxy-4,6-dihydroxypyrimidine, **16**, which is present in methanol only as hydroxy-oxo tautomer **16d**. The reason for this behavior is presently unknown.

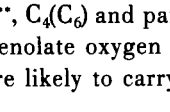
Further support for zwitterion formation is that the barbituric acids listed in Table 3 which contain a 2-thione group form adducts with the carbonyl-containing solvents, such as acetone and *N*-methylformamide. For example, the ^{13}C nmr spectrum of a solution of **10** in *N*-methylformamide (NMF) revealed that **10** was converted nearly quantitatively to adduct **17** which most likely arises from nucleophilic attack by the SH group of zwitterion **10g** onto the carbonyl group of NMF and provides further evidence for the existence of **10g**. Similarly, **10** yields the zwitterionic complex **18** in acetone solution although it is present in much lower concentration (Table 3). The two adducts are depicted as *S*-adducts based on the ^{13}C chemical shifts of atoms C*, C**, $C_4(C_6)$ and particularly C_2 (178-180 ppm). Furthermore, enolate oxygen atom is less nucleophilic and is much more likely to carry a negative charge than sulfur atom. Because of this, we feel that compounds **17** and **18** as depicted above are probably the *only* correct forms for the two adducts. None of the other barbiturates without the thiocarbonyl group formed adducts with carbonyl-containing solvents.

"2-Amino-4,6-dihydroxypyrimidine", **19**, is insoluble even in hot *N*-methylformamide and is therefore not suitable for solution measurements. However, based on the knowledge that the amino form has 12 kcal/mole greater stabilization energy than the imino tautomer [29], it is reasonable to suggest that compound **19** is best represented as the 2-amino-4,6-dioxopyrimidine.



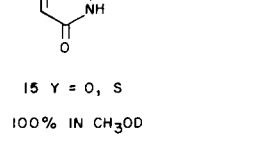
15 Y = O, S

100% IN CH_3OD

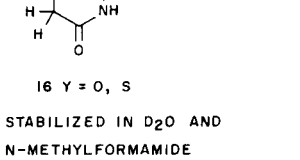


16 Y = O, S

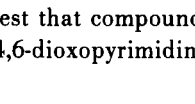
STABILIZED IN D_2O AND N-METHYLFORMAMIDE



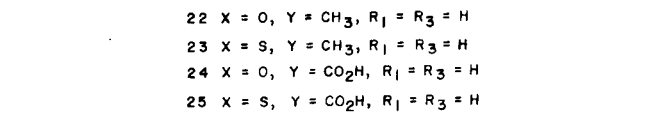
17



18



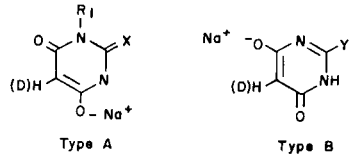
20 X = O, Y = NH_2, R_1 = R_3 = H
21 X = O, Y = NH_2, R_1 = R_3 = CH_3
22 X = O, Y = CH_3, R_1 = R_3 = H
23 X = S, Y = CH_3, R_1 = R_3 = H
24 X = O, Y = CO_2H, R_1 = R_3 = H
25 X = S, Y = CO_2H, R_1 = R_3 = H



25a 25b Etc

Table 6

^{13}C NMR Chemical Shifts of some Barbiturate Enolate Anions and Related Compounds at Ambient Temperature (25°) [a,b]



Type A Type B

Compound No.	Substituent(s)	Type	Chemical Shifts (in ppm) [c] C_2	C_4	C_5	C_6	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	Other
27	X = O, R_1 = R_3 = H	A									
28	X = O, R_1 = CH_3, R_3 = H	A	160.4	175.8	78.3	167.4					26.1 (CH_3)
29	X = O, R_1 = $CH_2C_6H_5$, R_3 = H	A	160.2	176.2	78.2	167.1	137.8	127.3	124.8	125.4	42.0 (CH_2)
30	X = O, R_1 = R_3 = CH_3	A	153.2	165.0	77.1	165.0					26.3 (CH_3)
31	X = O, R_1 = R_3 = $CH_2C_6H_5$	A	152.4	164.7	76.8	164.7	136.5	127.2	125.3	125.7	42.5 (CH_2)
32	X = O, R_1 = R_3 = C_6H_5	A	153.0	165.3	77.3	165.3	134.5	128.3	127.6 [d]	127.6 [d]	—
33	Y = SH [e]	B	172.3	171.2	82.5	171.2					—
34	X = S, R_1 = R_3 = CH_2CH_3	A	174.4	163.4	82.5	163.4					41.8 (CH_2), 10.7 (CH_3)
35	Y = SCH_3	B	168.2	175.6	85.1	175.6					11.9 (CH_3)
36	Y = NH_2	B	162.6	176.5	80.7	176.5					—
37	Y = H	B	157.2	175.4	89.5	175.4					—

[a] Recorded in 2*M* sodium deuteroxide with d_6-DMSO as external reference standard. [b] Nomenclature and numbering system is the same as in Table 1. [c] δ (ppm) downfield from TMS and using the external reference as a double standard (d_6-DMSO = 39.5 ppm). [d] Overlapping signals. [e] Could be S⁻.

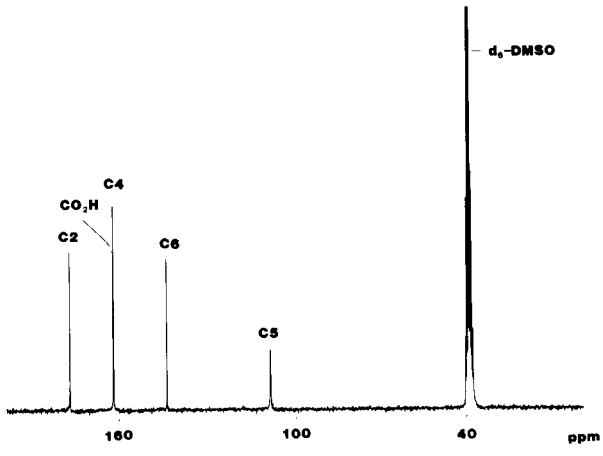


Figure 3a. 50.3 MHz ^{1}H-decoupled ^{13}C spectrum of freshly prepared d_6-DMSO solution of 2-thioorotic acid, **25** (200 ppm).

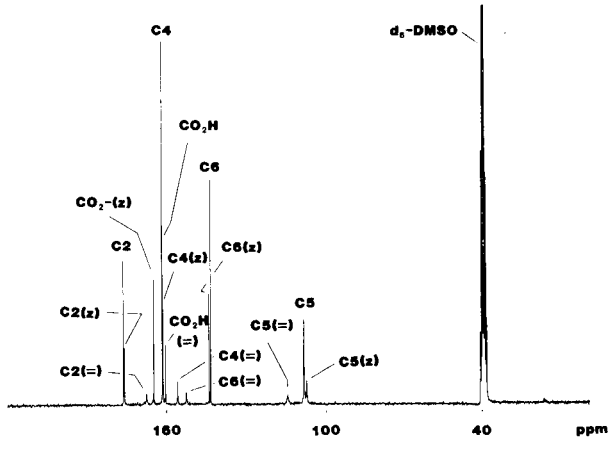


Figure 3b. 50.3 MHz ^{1}H-decoupled ^{13}C spectrum of **25** after 48 hours or when heated (50°C), 200 ppm width. Carbon atom notation for **25** is plain, for zwitterion **25b** is numbered carbon followed by (z) and for enol **25c** is numbered carbon followed by (=).

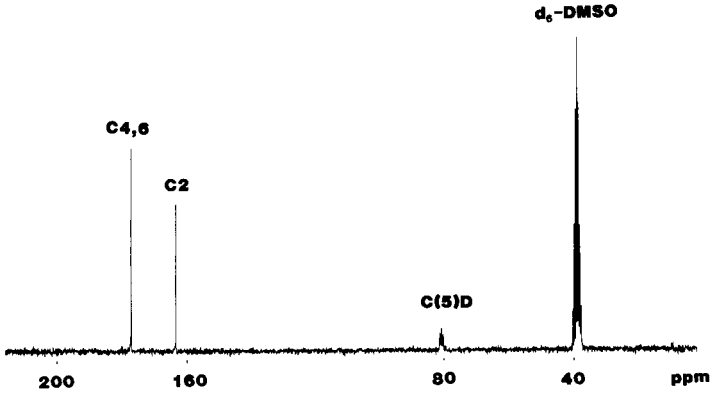
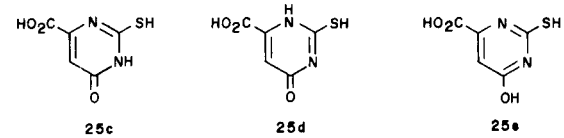


Figure 4. 50.3 MHz ^{1}H-decoupled ^{13}C spectrum of 2-amino-4,6-dihydroxypyrimidine enolate anion, **37**, in 2*M* sodium deuteroxide at ambient temperature (spectral width 220 ppm).

Compounds with tautomeric groups at 4(6) position also have a potential to appear in several tautomeric forms. Table 4 lists the ^{13}C chemical shifts of several such compounds, **20-25**, all of which are unmistakably the "*ene*" tautomers in d_6-DMSO solution since they all have ^{13}C absorptions characteristic of vinyl carbon atoms (C_5) [24]. The proton-decoupled ^{13}C spectra of 6-aminouracil, **20**, and its 1,3-dimethyl derivative, **21**, were almost superimposable, thus eliminating from consideration any tautomerism with amide linkages. Similarly, 6-methyluracil, **22**, and 6-methyl-2-thiouracil, **23**, exist in DMSO solutions as methyl-diketo tautomers and not in the alternative methylene, methide or methine forms. This is in accord with known trends and the general tendency for potential methyl compounds to exist as methyl groups and not in alkylidene forms mentioned ($K_T > 12$) [29].

Orotic acid, **24**, exists in DMSO solution as the acid-dione, deriving an increase in stabilization energy from the extended conjugation and from the extensive hydrogen bonding with amide groups. Its 2-thio analogue, 2-thioorotic acid, **25**, however, shows considerable tautomerization when left standing in solution for extended periods or when heated. Fortuitously, freshly prepared solution of **25** has only five ^{13}C peaks at 176.0, 161.1, 160.9, 142.7 and 107.3 which were assigned to C_2, -CO_2H, C_4, C_6 and C_5, respectively. The assignments were made as previously described for C_2, C_5 and C_6 by utilizing chemical shifts, C-H coupling constants and SCS parameters (for -CO_2H, C_{ipso} = +2.1 ppm [24,33]). The distinction between the C_4 keto and -CO_2H carbons was made by selective H/D exchange and by observing the deuterium isotope shift of the acid carbon. Figures 3a and 3b show proton-decoupled ^{13}C spectra of pure **25** and of the tautomeric mixture. The mixture consists of 72% of the original tautomer, 25% of a tautomer, whose ^{13}C nmr spectrum (175.7, 164.5, 161.1, 143.5, and 106.4 ppm) is only slightly different than that of the initial tautomer, and 3% of another tautomer, whose ^{13}C nmr spectrum (167.3, 160.0, 155.5, 152.2 and 113.6 ppm) is distinctly different than the other two forms. Hence, ^{13}C nmr results point to lactim/lactam tautomerism as well as inter/intramolecular proton transfer from the carboxyl group to one of the heteroatoms. Of the two possible zwitterions, **25a** and **25b**, **25a** can be eliminated on the grounds of proton affinities, number of resonance stabilizing forms (there are three for **25b** and only two for **25a**), and by the fact that oxo analogue **24** shows no such betaine in DMSO. Thus, freshly prepared solutions of **25**

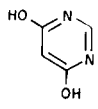


show that it exists in the ene form, **25c/25d** and upon standing undergoes self-neutralization to yield the corresponding zwitterion **25b**. Since the spectra of these two tautomers are seen in solutions of **10** in DMSO it indicates that their interconversion is slow on the nmr time scale. There is literature evidence for the existence of similar zwitterionic forms of picolinic acids and other pyridine carboxylic acids which actually exceed the concentrations of zwitterions formed from self-dissociation of amino acids [34].

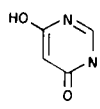
The tautomer present in smallest concentration has a thio group (δ ^{13}C 167.3 ppm), and thus has to have one of the three structures given. The fully aromatic form, **25e**, is eliminated by uv data [29] whereas **25c** is somewhat favored over the " *p*-quinoidal" form **25d** because of extended conjugation in **25c**. The C_4 carbonyl carbon is shielded by 5.4 ppm which is what one would expect for conjugated carbonyl groups [13,20,24,35].

Finally, the deoxy analogue of barbituric acid, "4,6-dihydroxypyrimidine", **26** was studied. Much controversy has been generated in the literature about the structure of this compound and since the conclusions of many authors differ substantially from each other, we present our results herein.

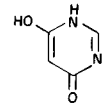
There are six possible tautomeric forms which could represent **26**: dihydroxy form **26a**, 3,4- and 1,4-dihydrohydroxy-oxo compounds **26b** and **26c**, hydroxy-oxo-C_5-methylene form **26d**, dioxo-C_5-methylene form **26e**, and mesomeric betaine **26f**. Early infrared studies of **26** *in the solid state* suggested that it existed in one of the hydroxy-oxo forms **26b**, **26c** or **26d** [36,37]. Ultraviolet spectra [38] and relatively high acidity of **26** (p*K*a = 5.4) [39] were also considered consistent with such a structure. More recent reports, however, disagree sharply with each other. Brown and Teitei concluded from the uv studies of *N*-alkyl, *O*-alkyl, and 5,5-dialkyl derivatives with "fixed structures"



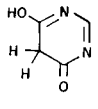
26a



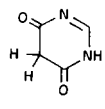
26b



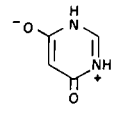
26c



26d



26e



26f

that aqueous solutions of **26** are an equilibrium mixture of dioxo **26e** and 1,4-dihydro-hydroxy-oxo tautomer **26c**, with the former predominating [40]. Y. Inoue, *et al.* [41] also has concluded from proton nmr measurements that the main species in DMSO and 50% aqueous DMSO is the 3,4-dihydro-hydroxy-oxo form **26b** with small amounts of **26e**, which is the same conclusion reached by other workers [42]. Katritzky and his group have proposed that in aqueous solution "4,6-dihydroxypyrimidine" exists mainly as the mesomeric betaine **26f** together with appreciable amount of 6-hydroxy-4(3*H*)pyrimidinone, **26b** [43]. Finally, the ^{1}H nmr spectra of **26** and of its *O*- and *N*-methyl derivatives indicated that, in dimethyl sulphoxide, **26** exists predominately (?) in the oxo-hydroxy form **26b** and, in aqueous solution, in the bipolar-ionic form similar to **26f** [44].

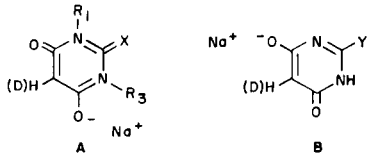
Our results, which are reported in Table 4, differ markedly from those mentioned above. Thus, a dimethylsulfoxide solution of **26** contains 99% of a tautomer *A* with ^{13}C chemical shifts at 166.2 (large), 149.8 and 90 ppm, and 1% of a dissymmetric tautomer **B** with chemical shifts at 167.6, 162.3, 149.9, and 98.4 ppm. A 50:50 mixture of DMSO/acetone and DMSO/water also contains the major tautomer **A** and 20% of the minor tautomer **B** in addition to trace amounts of at least 4 or 5 other structures. The low solubility of **26** precluded any further attempts to study this complex equilibrium mixture. Nevertheless, some important deductions can be made from the analysis of the data presented. The lack of sp^2 carbons eliminates the methylene forms **26d** and **26e** mentioned in earlier reports [40-42]. Of the remaining structures, tautomers **26a** and **26f** are symmetric. Of these, **26a** appears unlikely in aqueous solution since Katritzky has presented strong evidence from uv data against it [43]. The ^{13}C nmr spectrum in d_6-DMSO could support **26d** or zwitterion **26f**. For example, the resonance at 166.2 ppm is at least twice as large as the other two and it appears as a narrow doublet in a proton-coupled spectrum (J_{CH} = 9.5 Hz). The ^{13}C peaks at 149.8 and 90.5 ppm show large one-bond C-H couplings of 203.4 Hz, typical of C_2 unsubstituted carbon in pyrimidines [45], and 166.4 Hz for the vinylogous carbon atom, respectively. Since a narrow doublet at 166.2 ppm disappears in DMSO/D_2O and $^2J_{CH}$ are seldom larger than 1.5-2.0 Hz (except with α-carbonyl compounds [46]), it follows that this resonance represents two equivalents $C_4(C_6)$ enolate positions in **26a** or **26f** [47].

The second tautomer *B* can be either **26b** or **26c**. Based on the overwhelming chemical and spectroscopic evidence [40-44] it must be the 3,4-dihydro-hydroxy-oxo tautomer **26b**, which is also supported by the fact that extended conjugation is preferred over "*p*-quinoidal" forms (as in **25e** *vs.* **25d**). Carbonyl carbons were assigned as C_6 (167.6 ppm) and C_4 (162.3 ppm) by the analogy with hydroxy-oxo compound **12d**.

^{13}C NMR and Structure of Barbiturate Anions.

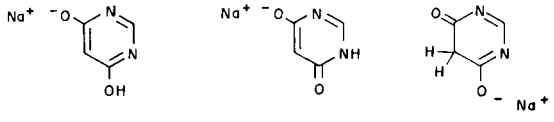
The ^{13}C chemical shifts of enolate anions of compounds **1**, **4-12**, **19** and **26** were recorded in 2*M* sodium deuterox-

ide (see Experimental) and are reported in Table 6. There are two features which are evident from these data. Base-catalyzed H/D exchange at C_5 is very fast so that all enolate anions are partially or completely deuterated at C_5. One such example is shown in Figure 4 where C_5 appears as a narrow triplet due to carbon-deuterium coupling. (J_{CD} and H/D isotope shifts are tabulated in Table 5). There are two general structures attributed to these anions, **A** and **B**. In each, a rapid exchange and redistribution of charge



between the C_4 and C_6 carbonyl groups in both systems occurs. The resulting electronic equivalence gives rise to a single carbon resonance twice to three times the intensity of C_2 signal. This is also typified with shifts of +9-10 ppm for *all* carbonyl groups of anions adjacent to unsubstituted ring nitrogens as compared to the neutral species (Table 6). These shifts compare favorably with the similar -OH -> -O⁻ transition of +12.7 ppm in the phenol series [48,49].

The anion of 4,6-dihydroxypyrimidine, **37**, could have any of the three possible structures **37a-c**, one of which was eliminated by uv data (**37a**) [43]. Structure **37c** *does not* contribute and *is not* present in the sodium deuteroxide solution of **37** since no C_5-methylene carbon signal is observed. Thus, structure **37b** is the one adopted by **37** which is contrary to the previous report [43] which suggested that **37c** may be present in the equilibrium mixture of **37**.



EXPERIMENTAL

Starting Materials.

Several of the compounds studied (**1**, **4**, **7**, **10**) were available from previous studies [20,35]. The remainder (**5**, **6**, **8**, **9**) were prepared by literature methods [50,51], or were purchased from Aldrich Chemical Company and Lancaster Synthesis (**11**, **12**, **20-26**).

^{13}C NMR Spectra.

The ^{13}C nmr spectra in Tables 1, 2 and 4 were determined as 1*M* solutions in deuteriochloroform, d_6-acetone, CH_3OD, d_6-DMSO, deuterium oxide, *N*-methylformamide (NMF) or in mixtures of these solvents (see footnotes). In all cases solvent peaks were used for deuterium lock and as reference unless indicated otherwise. They are as follows: deuteriochloroform, 77.0 ppm; d_6-acetone, 206.0 ppm (CO); deuterium oxide, 50.0 ppm; d_6-DMSO, 39.5 ppm; and NMF, 166.7 ppm (CO carbon resonance at the lower field of the *trans* isomer). The samples in deuterium oxide were referenced to the external chloroform and samples in NMF were recorded with external deuterium oxide used for deuterium lock. The ^{13}C spectra in sodium deuteroxide (Table 6) were obtained as 0.5 *M* solutions in 2*M* sodium deuteroxide contained in a 10 mm Wilmad nmr tube with 5 mm coaxial nmr tube containing d_6-DMSO as an external reference standard. The spectra were recorded at ambient temperature (35°) on a WP 200-SY Bruker spectrometer operating in a Fourier transform mode at the frequency of 50.327 MHz. The spectrometer was interfaced with Winchester 24 MFD data system and was equipped with PTS 160 frequency synthesizer. The following spectral parameters were used: data set = 1000-2000 transients for pure compounds, 2500 scans for enolate anions and 3000-5000 for tautomeric mixtures for proton-noise decoupled ^{13}C spectra and 2-4 times as many counts for ^1H-coupled spectra; pulse width 10 μs (33° flip angle); interpulse delay = 1-2 seconds, typically 2.0 seconds, sweep width = 10 KHz, line broadening = 0.3 Hz, acquisition time = 0.5407 seconds, data size = 16k output data points (8K real). Expanded spectra with smaller spectral widths (2.5 KHz, ± 0.3 Hz resolution) were used for evaluation of ^{13}C-^1H spin-spin coupling constants in Table 5.

Assignments of unsymmetrical barbiturates such as **4**, **5**, **6**, *etc.*, were accomplished by the methodology described in ref [13]. In addition, several other criteria were used to confirm the ^{13}C chemical shift assignments of C_4/C_6 carbonyl groups. For instance, decreasing relaxation delays from 4 seconds to 0.5 seconds decreased dramatically the intensity of ^{13}C signals adjacent to *N*-substituted sites analogous to the observations made for *N*-substituted ureas referenced in the text.

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