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Pyrimidine *N*-Oxides. V*
Ionization Constants of *N*-Hydroxybarbiturates

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Abstract

The ionization constants, pK_a, of a number of *N*-hydroxy 5-substituted barbituric acids and their *O*- and *N*-alkylated derivatives are reported. For practical comparisons under physiological conditions, pK_a values were also determined at I 0·15 M KNO_3 and 37° for the clinically useful barbiturates metharbital, phenobarbital and veronal, and for their mono-*N*-hydroxy derivatives. The pK_a values for *N,N'*-dihydroxyphenobarbital and the corresponding veronal were also measured.

This work was prompted by continuing interest in the *N*-hydroxybarbituric acids[1,2] and pyrimidine *N*-oxides in general.[3–5] The barbiturate drugs have pK_a values ranging from *c.* 7·2 to 8·3.[6] It was decided to determine the ionization constants of some *N*-hydroxybarbiturates, substances which are potential metabolites of the parent drugs. The pK_a values for some related substances were also determined.

There are only a few literature references to pK_a values of *N*-oxidized pyrimidines.[3,4,7,8] Two examples have been reported in which *N*-oxidized pyrimidines were stronger acids than the corresponding parent compounds: 1-hydroxy-4,6-dimethylpyrimidin-2(1*H*)-one, pK_a 6·1 as against 9·9 for the parent pyrimidinone,[7] and cytosine 3-oxide, pK_a 10·3 as against 12·2 for cytosine.[8]

Approximate pK_a values are now reported for a number of *N*-hydroxybarbituric acids ($I \leqslant 0{\cdot}01$ M, 25°). These measurements at low ionic strength gave values which are comparable with the 'thermodynamic' values quoted in much of the early literature. Such values are of somewhat limited utility to those interested in drug behaviour in biological systems, where the ionic strength is comparatively higher. We have therefore measured the pK_a values in 0·15 M KNO_3 at 37° for the clinically

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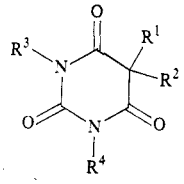
significant barbiturate drugs: metharbital and its *N*-hydroxy derivative, phenobarbital and veronal and their *N*-mono- and *N,N'*-di-hydroxy derivatives. The results, plus some literature data,[6,9–11] are given in Table 1.

Table 1. pK_a values of barbiturates and their *N*-hydroxy derivatives



Compound	Substituents R¹	R²	R³	R⁴	pK_a[A] 25°C	Method[B]	pK_a[C] 37°C	2nd pK_a[C] 37°C
(1)	Et	Et	H	H	7·9[6]		7·68	12·3[D]
(2)	Et	Et	H	OH	6·5	pot	6·24	8·89
(3)	Et	Et	H	OMe	6·8	pot		
(4)	Et	Et	H	OCH_2Ph	6·9	sp		
(5)	Et	Et	Me	H	8·2[9]		8·10	—
(6)	Et	Et	Me	OH	6·5	pot	6·39	—
(7)	Et	Et	OH	OH	—		5·60	7·07
(8)	Et	Pr^i	H	H	8·0[6]			
(9)	Et	Pr^i	H	OH	6·6	pot		
(10)	Pr	Pr	H	OH	6·4	pot		
(11)	Me	Pr^i	H	OH	6·9	pot		
(12)	Et	Ph	H	H	7·4[6]	pot	7·18	11·8[D]
(13)	Et	Ph	H	OH	—		5·96	8·57
(14)	Et	Ph	OH	OH	—		5·43	6·86
(15)	Et	H	H	H	3·9	pot		
(16)	Et	H	H	OH	3·4	sp		
(17)	Et	H	H	OCH_2Ph	3·8	sp/pot		
(18)	H	H	H	H	3·9[11]			
(19)	H	H	H	OCH_2Ph	3·7	sp		

[A] *I* 0·01 M. [B] sp, Spectrophotometry; pot, potentiometry. [C] *I* 0·15 M (KNO_3), potentiometry. [D] *I* 0·1 M, 38°C, see ref. 10.

Results and Discussion

The 5,5-dialkylbarbituric acids with simple substituents in the 5-position have an average pK_a of around 8·0;[6,9] 5-ethyl-5-phenylbarbituric acid is somewhat more acidic. The influence of *N*-substituents on the pK_a values of barbiturates can be judged by comparing compounds (1)–(6). The introduction of a non-protic *N*-oxygen function increases the acidity by *c.* 1 pK_a unit [compare compounds (3) and (4) to (1)]. This effect can be attributed to the inductive influence of the oxygen function. The pK_a values of compound (3) (NH group) and compound (6) (*N*-OH group) are comparable. Compound (2), which contains both of these acidic groups, has a similar pK_a. Thus, deprotonation can occur on either group; in fact both processes may contribute to the observed first deprotonation of compound (2) (pK_a 6·5). (The

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same, of course, is true for the second deprotonation.) Introduction of a second *N*-hydroxy group into the barbiturates increases the acidity further [cf. compounds (7) and (14)]. Much of this effect is attributable to the presence of two identical ionizable groups (statistical factor 0·3).

The second deprotonation of the unsubstituted barbiturates (1) and (12)[10] creates a dianion in which the charges are separated by only two bonds. In the dianions of the monohydroxy derivatives (2) and (13) the charge separation, three bonds, is greater and the four-bond separation in the dianions of the dihydroxy derivatives (7) and (14) is greater still. This affects the relative closeness of the first and second pK_a values of the compounds in question. Thus, the second deprotonation of the *N,N'*-dihydroxybarbiturates (7) and (14), where charge separation is greatest, takes place at 1·47 and 1·43 pK_a units above the first, respectively. The second deprotonation of the mono-*N*-hydroxybarbiturates (2) and (13) takes place less readily, 2·65 and 2·61 pK_a units respectively above the first. The unsubstituted barbiturates (1) and (12), with the smallest charge separation in the dianions, show the greatest differences, 4·6 pK_a units each between first and second ionizations. It should be noted that the second deprotonation is of biological significance only for the *N,N'*-dihydroxybarbiturates.

The deprotonation of the 5-monoalkyl- and 5-unsubstituted-barbituric acids is likely to occur at position 5.[11] This different behaviour is reflected in the considerably increased acidity of compounds (15) and (18) and in the smaller influence of the oxygen functions on the pK_a values of compounds (16), (17) and (19).

Experimental

Barbituric acid, veronal, metharbital and phenobarbital were purchased commercially. The mono-*N*-hydroxybarbiturates, *N*-benzyloxy- and *N*-hydroxy-5-ethylbarbituric acids were previously reported,[1] as were the *N,N'*-dihydroxybarbiturates.[2] *N*-Benzyloxybarbituric acid was prepared according to the method of Kloetzer.[12]

The pK_a values determined in this work are 'practical' constants:

$$pK_a = -\log([L]\{H\}/[HL])$$

where the quantities in square brackets are the molar concentrations of the protonated [HL] and deprotonated [L] ligands and {H} is the activity of the hydrogen ion. (Thermodynamic pK_a values are expressed entirely in activities.)

The potentiometric measurements at low ionic strength were done at 25°C on solutions 0·005–0·01 M of the respective ligand without addition of an inert electrolyte.[13] The spectrophotometric pK_a determinations were done at 25° in buffers of ionic strength 0·01 M.[14]

The method, instrumentation and computer evaluation of pK_a values from alkalimetric titrations with 0·15 M KNO_3 as inert electrolyte at 37°C have been reported previously.[15]

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