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THE AQUEOUS SOLUBILITY OF VARIOUSLY SUBSTITUTED BARBITURIC ACIDS. I. CHEMICAL EFFECTS

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ABSTRACT

The aqueous solubility of fourteen variously substituted barbituric acid was determined at 25°C. There was an approximate relationship between aqueous solubility and the duration of activity. The magnitudes of solubility varied substantially for these compounds and these results are based upon the net chemical grouping effect from compound to compound. While several compounds possessed rather similar melting points, the solubilities also varied to a large extent. These results are discussed further in this communication.

INTRODUCTION

The aqueous solubilities of fourteen variously substituted barbituric acids were studied at 25°C. The barbiturates used were substituted with groups on the barbituric acid molecule and were chosen in order to find the effects of these variants upon the solubility in water.

Several barbiturates were synthesized so that the effect of increasing n-alkyl at the C5 position could be determined and in one case, a positional variant was synthesized to determine its effect on solubility in another case.

The barbiturates utilized in this study were chosen to represent several examples with respect to the duration of activity of these compounds (1). Metharbital, 5, -5 diethyl 1-methyl (N-methyl) barbituric acid while possessing anti-convulsant properties was chosen since it is chemically quite similar to barbital, 5,-5' diethyl barbituric acid except for methylation at the 1-nitrogen position. Phenobarbital, 5 ethyl 5 phenyl barbituric acid was also chosen because of its importance as a sedative and to note the effect of the phenyl group upon solubility.

The solubility of many of the barbiturates in hydroalcoholic solutions (2) and in normal alkanols (3) has been previously given.

EXPERIMENTAL

Materials - The materials used in this study were as follows: barbituric acid,[1] m. p. 252-255°; metharbital,[2] m. p. 151-155°; butabarbital,[3] m. p. 166-168°; thiamylal,[4] m. p. 133-135°; barbital,[5] m. p. 189°; pentobarbital,[6] m. p. 131°; amobarbital,[7] m. p. 153°; phenobarbital USP, m. p. 176°, and vinbarbital, N. F., m. p. 160-163°. Thiopental was prepared from the sodium salt.[8] The sodium salt was dissolved in a quantity of distilled water, and the free acid precipitated by the addition of 1.0 M hydrochloric acid[9] solution. The slurry was filtered and washed with three portions of distilled water. The melting point range of the dried precipitate was 156-158°. Melting points of pooled and dried samples from the gravimetric procedure were also made and found not to vary more than ±1-2° outside the range of the original material. This was done to ascertain if any aberrant behavior such as hydrate formation or crystalline modification (polymorphism) occurred in the aqueous solvent.

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[1] Aldrich Chemical Co., Milwaukee, Wis., lot 072281.
[2] Gemonil, Abbott Laboratories, North Chicago, Ill., lot 685-7608.
[3] McNeil Laboratories, Fort Washington, Pa., lot 5086.
[4] Surital, Parke, Davis and Co., Detroit, Mich., lot 405838.
[5] Merck & Co., Rahway, N.J., lot 51115.
[6] Abbott Laboratories, North Chicago, Ill., lot 12130.
[7] Ruger Chemical Corp., N. J., lot 105 3180.
[8] Abbott Laboratories, North Chicago, Ill., lot 780-7657.
[9] Mallinckrodt Chemical Works, New York, N.Y.

There were three compounds that were synthesized for use in this study; the method of Fisher & Dilthey (4) was used for their preparation. The compounds synthesized were 5-ethyl 5-propyl barbituric acid, 5-ethyl 5-pentyl barbituric acid and 5-ethyl 5-(2 methylpropyl) barbituric acid. For these synthesized compounds purity and identification were evidenced by C, H, N analysis and IR spectra. Recrystallized samples from ethanol were dried to constant weight and melting points determined which were in excellent agreement with values found in the literature.

Equipment - A rotating apparatus was constructed which held 48 screw-capped glass vials of 21 ml volume and revolved at 32 r. p. m. The vials were rotated in such a way that the solute traversed the full length of the vial twice per revolution, thus causing sufficient agitation of the contents. No caking was observed in any of the samples. This apparatus was immersed in a 10 gal. water bath maintained at 25.0 ± 0.3° by a Tecan Tempunit.[10]

A Cary model 16 spectrophotometer,[11] a Mettler type H6T[12] analytical balance were utilized in the assay procedure.

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[10] Techne (Cambridge) Limited, Cambridge, England

[11] Cary Instruments, Belmont, Mass.

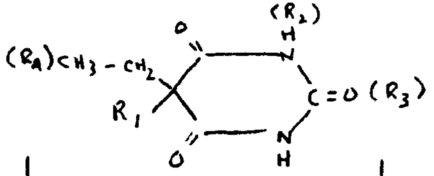
[12] Mettler Instrument Corp., Hightstown, N. J.

Procedure - The procedures used in this study have been previously given (5) and consist essentially of a gravimetric analytical technique with a spectrophotometric check run. Each solubility value represents the average values from at least three runs of triplicate samples.

RESULTS AND DISCUSSION

In Table 1, the compounds used in this study are enumerated, the chemical name and common name (if applicable) are also given. The chemical substituents are also shown for the various positions and the melting points are given. In Table II, the aqueous solubility at 25° is given in both the mg/ml and mole fraction notations. The solubility has been put in rank order for these substances although it should be pointed out that Metharbital (cpd. XII) has anticonvulsant activity rather than sedative properties. In the last column of this table, the duration of action is shown (1); for those compounds which were synthesized, compounds II, IV and VIII, it was assumed then duration of action would be similar to like chemical structures. It is interesting to note that as the duration of action decreases, the solubility in water decreases which implies greater lipophilicity with decreased duration of action.

Table I: A summary of the compound number, chemical name, common name and substituent groups and melting points of compounds used in this study.



Cpd. #	Chemical Name	R1 group	R2 group	R3 group	Common Name MP
I	5,5'diethyl barbituric acid	CH_3-CH_2-	H	O	Barbital MP 188-190°
II	5 ethyl, 5-propyl barbituric acid	CH_3-CH_2-CH_2-	H	O	Synthesized MP 146-147° Lit. 146-147°
III	5 ethyl, 5 butyl barbituric acid	CH_3-CH_2-CH_2-CH_2-	H	O	Butethal MP 126-128°
IV	5 ethyl, 5 pentyl barbituric acid	CH_3-CH_2-CH_2-CH_2-CH_2-	H	O	Synthesized MP 135-136° Lit. 135-136°
V	5 ethyl, 5 phenyl barbituric acid		H	O	Phenobarbital MP 156-157°

VI	5 ethyl 5-isopropyl barbituric acid	$\begin{matrix}CH_3\\CH_3\end{matrix}>CH-$	H	O	Probarbital MP 202-203°
VII	5 ethyl, 5-(1-methyl propyl) barbituric acid	$CH_3-CH_2\overset{H}{\underset{CH_3}{C}}-$	H	O	Butabarbital MP 165-166°
VIII	5 ethyl 5-(2-methyl propyl)-barbituric acid	$CH_3-\underset{CH_3}{CH}-CH_2-$	H	O	Synthesized MP 174-175° Lit. 174-176°
IX	5 ethyl 5-(1-methyl butyl) barbituric acid	$CH_3-CH_2-CH_2-\underset{CH_3}{CH}-$	H	O	Pentobarbital MP 129-130°
X	5 ethyl 5-(3 methyl butyl)-barbituric acid	$CH_3-\underset{CH_3}{CH}-CH_2-CH_2-$	H	O	Amobarbital MP 156-158°
XI	5 ethyl, 5-(1-methyl 1-butenyl)-barbituric acid	$CH_3-CH_2-CH=\underset{CH_3}{C}-$	H	O	Vinbarbital MP 160-163°
XII	5, 5'diethyl 1-Methyl barbituric acid	CH_3-CH_2-	CH_3	O	Metharbital MP 151-155°
XIII	5-ethyl 5-(1-methyl butyl)-2 thio barbituric acid	$CH_3-CH_2-CH_2-\underset{CH_3}{CH}-$	H	S	Thiopental MP 156-158°
XIV	5-alkyl 5-(1 methyl butyl)-	R_4 $CH_2=CH-CH_2-$ R_1 $CH_3-CH_2-CH_2-\underset{CH_3}{CH}$	H	S	Thiamylal MP 133-135°

Table II: A summary of the solubility in mg/ml and mole fraction at 25° in rank order and the duration of action.

	Solubility		
		$\times 10^5$	
Compound #	mg/ml	mole fraction	Duration of Action
I	7.31	72	Long
II	5.85	52	Long[a]
III	4.13	35	Long
XII	2.06	18	----
IV	1.33	12	Long[a]
VI	1.18	11	Long
V	1.21	9	Long
VII	0.90	7.6	Intermediate
VIII	0.84	7.2	Intermediate[a]
XI	0.69	5.7	Intermediate
X	0.56	4.8	Short to Intermediate
IX	0.50	4.0	Short to Intermediate
XIII	0.08	0.6	Ultra short
XIV	0.05	0.35	Ultra short

a: assumed duration of action of similarly structured compounds.

The relationship of the substituent group(s) and aqueous solubility could be obtained by considering either grouping several of these compounds or by pairing two compounds which differed by a definitive substituent.

Thus the solubility difference of the n-alkyl substituents could be determined by considering consecutive steps or as a group. In Figure 1, the mole fraction solubility of compounds I, II, III, and IV are shown and a straight line relationship is observed with a negative slope of 20×10^{-5} in terms of mole fraction.

When the solubility of phenobarbital (cpd. V) is plotted on this line, its value exists at greater than a linear 5-carbon chain with respect to the phenyl group since the remainder of the compound is constant. Thus, the phenyl group effectively acts between a 5 and 6 linear chain carbon. When the solubility of metharbital, compound XII, is plotted on this line, the N-methyl substitution is seen to effect a decrease in solubility about equal to 2.5 linear carbon atoms.

For the branched chain substituted barbiturates, their solubilities are shown in Figure 2. It is apparent that positional isomers have very little effect on the overall solubility in water. Thus, Compounds VII and VIII and Compounds IX and X which are a 1-methyl propyl and 2-methyl propyl pair and a 1-methyl butyl and 3-methyl butyl pair can be plotted together. In this case as well the solubility decreases with increasing size and the slope of a line has a negative value of 3×10^{-5} in terms of mole fraction. Vinbarbital, Compound XI,

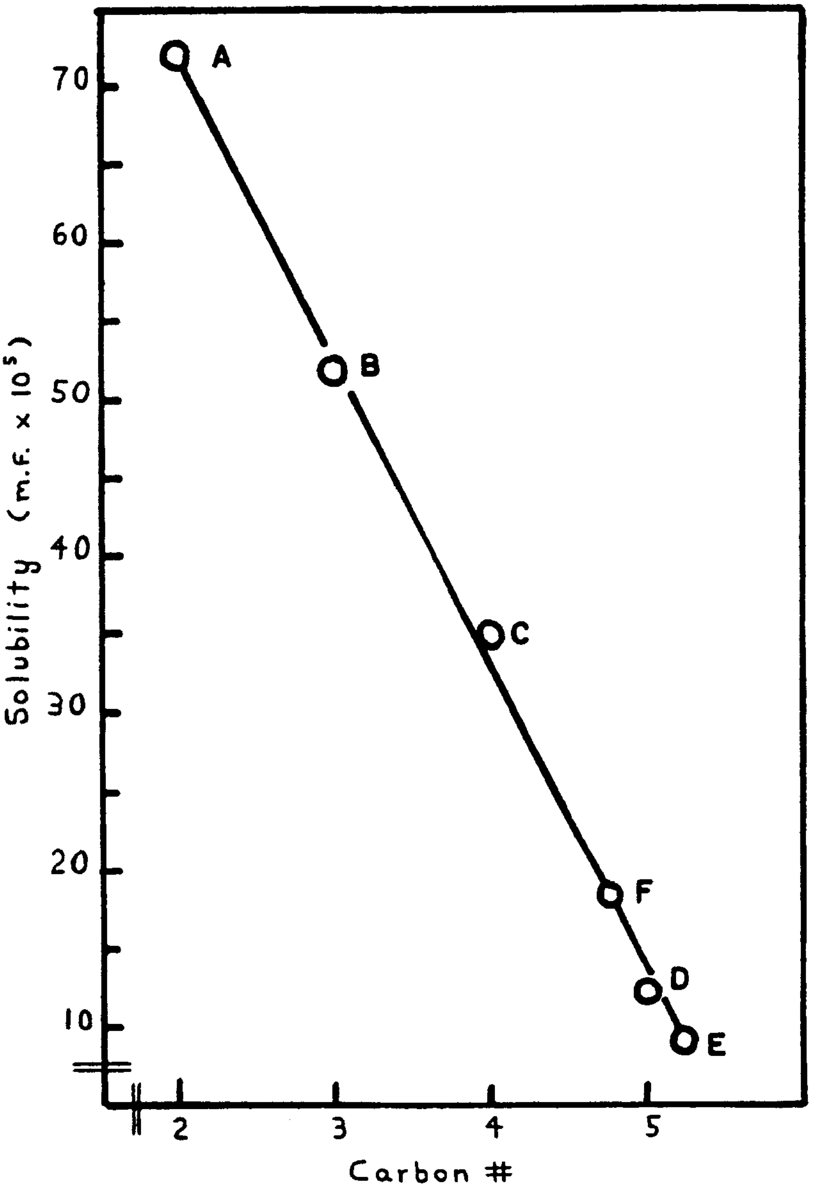


Figure 1. The mole fraction solubility versus the number of carbons in the n-alkyl C_5 substituents of barbituric acid. Point A, Compound I; Point B, Compound II; Point C, Compound III; Point D, Compound IV; Point E, Compound V; Point F, Compound XII.

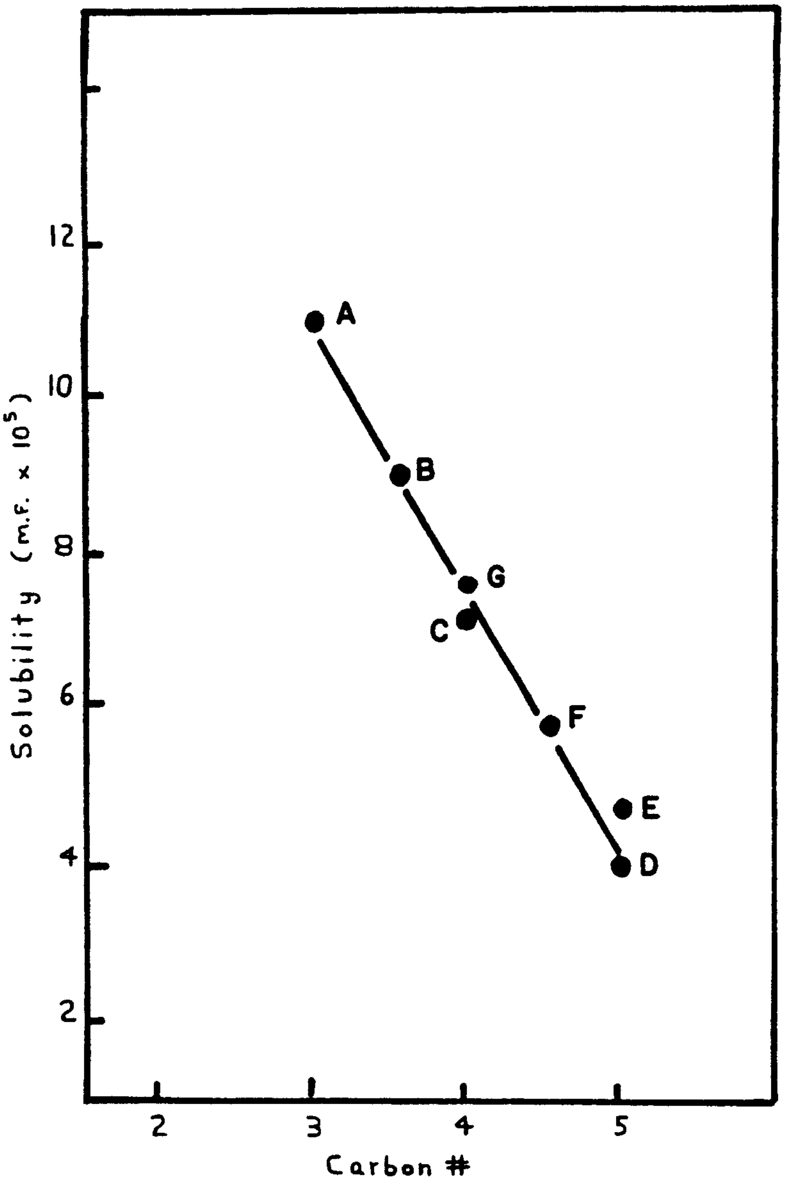


Figure 2. The mole fraction solubility versus the number of carbons in the branched chain alkyl C_5 substituent of barbituric acid. Point A, Compound VI; Point B, Compound V; Point C, Compound VIII; Point D, Compound IX; Point E, Compound X; Point F, Compound XI; and Point G, Compound VII.

possesses a 1-methyl 1-butenyl group in the C_5 position versus the 1-methyl butyl group in pentobarbital while the remainder of the molecule is constant. When the solubility is plotted on the line obtained for the branched chain barbiturates, it exists at a value of about 4.5 branched carbon chain and then the effect of the double bond in the 1-position increases the solubility but not to any great extent. Interestingly, if the solubility of phenobarbital is plotted on this line as well, the effect of the C_5 phenyl group occurs at 3.5 carbons, and the aromatic system effect is between an iso-propyl group and a 1 or 2 methyl propyl group.

The two thiobarbiturates, thiopental (Cpd. XIII) and Thiamylal (Cpd. XIV) showed dramatic decreases in solubility undoubtedly due to the thio substituent which substantially decreases the overall polarity of the molecule.

Thiopental, 5-ethyl 5-(1-methyl butyl) 2-thiobarbituric acid can be compared to Pentobarbital, 5-ethyl, 5(1-methyl butyl) barbituric acid and here the effect of the sulfur atom in position 2 causes about a sevenfold decrease in solubility.

Overall, the solubility of linear carbon chains is greater than branched chain with diminishing differences as the carbon number is increased. The solubility of positional isomers for the branched chain alkyl barbiturates does not change to any great extent. In general, solubility decreases with an increase in carbon number. A thio substituent in the 2 position causes a dramatic decrease in aqueous solubility and these ultrashort barbiturates possess greater lipophilicity than the other barbiturates used in this study.

Many of the compounds used in this study possessed melting points which were quite similar to one another. It was felt to be of interest to group these according to melting points such that the variation in solubility would be directly related to chemical effects of the various substituents.

In Table III, the melting points of compounds fitting into a melting point range of about 10° are shown for two subgroups of these compounds. Each compound is listed by number and common name and in rank order of mole fraction solubility.

In the first group which encompasses a melting point range of 151-163°, five of these solutes can be listed. While the melting points did not vary greatly from compound to compound, there are dramatic differences in the solubility of about thirtyfold in going from Thiopental to Metharbital. Obviously the magnitudes of the solubility is relatable to the chemical groupings or substituent variants from one compound to another. A subgroup of three in this melting point range can be considered further as their respective melting points

Table III: Summary of the barbiturates possessing similar melting points and the rank order of mole fraction solubility in water at 25°.

Compound #	Common Name	M. P. °C	Solubility m.f. x10^5
XII	Metharbital	151-155	18
V	Phenobarbital	156-157	9
XI	Vinbarbital	160-163	5.7
X	Amobarbital	156-157	4.8
XIII	Thiopental	156-158	0.6
III	Butethal	126-128	35
IV	---	135-136	12
IX	Pentobarbital	129-130	4
XIV	Thiomylal	133-135	0.35

were almost exactly the same. The compounds, Phenobarbital, Amobarbital and Thiopental (Cpds. V, X, XIII) which have melting points in the 156-158° range also gave striking differences in solubility. While Amobarbital possessed a solubility value of about one half that of Phenobarbital, Thiopental had a solubility value of about one-fifteenth as much.

In the second group which encompasses a melting point range of 126-135°, four additional compounds could be listed. The solubility for these four compounds varied one-hundred-fold in going from Thiamylal to Butethal which again illustrated the effect of chemical grouping or variants from one compound to another.

Further, Amobarbital from the first group is seen to have a melting point of 156-157° and Pentobarbital from the second group has a melting point of 129-130°. Yet, the magnitudes of solubility are quite similar although their melting points differ by almost 27°. The compounds are exactly similar except for the position of the methyl groups on a linear butyl chain, Amobarbital being the 3-methyl butyl and Pentobarbital the 1-methyl butyl substituent in the C_5 position.

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