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Solubility Profiles for Several Barbiturates in Hydroalcoholic Mixtures

T. L. BREON and A. N. PARUTA

Abstract □ The solubilities of eight physiologically active barbiturates were determined in binary mixtures of alcohol and water. The solubility curves for these substances varied, showing either solubility maxima or asymptotic solubility isotherms. The dielectric requirement of the barbiturates investigated illustrated an approximate inverse relationship with the number of carbon atoms in the molecule. A similar correlation was found with the solubilities in pure water, with the ratios of the solubilities in ethanol, and at the dielectric requirement to the solubility in water. The therapeutic indexes of duration of action and the period of time involved between administration of the drug and the time when the activity is first manifested increased as the relative polarity of these barbiturates declined. An approximate correlation between activity and solubility ratios is considered.

Keyphrases □ Barbiturates, solubility—ethanol–water systems □ Dielectric requirement—barbiturates □ Polarity, barbiturates—activity correlation □ Solubility ratios—barbiturates, ethanol–water systems

The pharmacological action exerted by a drug molecule in contact with a biological system is the net result of the interactions and extent of interactions with the complex biological environment. The degree as well as the rate of interaction is governed by many parameters, many of which depend on the physical and chemical properties associated with the drug molecule.

To be physiologically active, a drug must be absorbed and distributed throughout the biological fluids. More specifically, it is noted that these actions occur on a molecular level; under these conditions, it would be assumed that solution properties and characteristics are operative. Many biologically active substances are weak electrolytes, and properties such as the pH of the medium, pKa of the drug, concentration gradients, surface tension, and the aqueous and lipid solubilities of the various species contribute to the overall extent of activity.

The biologically active species, to initiate a response, would be presumed to have interacted with cellular constituents; this process is involved with diffusion and permeability as well as those factors previously discussed. Thus, this study is an initial investigation into the possible approximate correlation between solubility characteristics of several barbiturates and therapeutic activity.

The wide variety of available barbiturates certainly attests to the importance of these materials, with a wide spectrum of uses such as sedatives and anticonvulsants. They are derivatives of barbituric acid with a variety of substitutions in the 5-position, and about 20 of these are presently available as therapeutic agents.

Although the general sedative action of all these barbiturates is about the same, they do vary in the duration of depressant action. Since these barbiturates are chemically different, it would be judicious to study them in attempting to relate known duration of action and chemical structure.

Thus, if in a series of barbiturates, a property such as solubility was determined as a function of polarity, there may be an indication of the relative lipoidal nature of these materials. It would be well to consider the solubility of these types of materials in a manner previously described (1). The cosolvent action on these barbiturates by mixtures of decreasing polarity should be instructive.

It might be expected that the position of the dielectric requirement (DR) and the magnitude of solubility at that point would be indicative of the effect of substituents and the relative polarity of the drug molecule. In view of this possibility, some eight barbiturates with a spectrum of values for the onset and duration of action were studied relative to their solubility behavior in hydroalcoholic solutions.

Several long-, intermediate-, and short-acting barbiturates (2) were chosen to test this hypothesis, including barbital as the comparing standard.

The very important work of Hansch and Anderson (3) should be mentioned here since they showed a definitive correlation of the activity of barbiturates with the log of the partition coefficients for various derivatives. This would suggest the importance of the hydrophobic character of substituted barbiturates in a wide variety of biochemical systems.

The model used by Hansch and Anderson (3) is a partitioning between phases to calculate the coefficients or a measure of lipophilicity of these drugs, *i.e.*, the

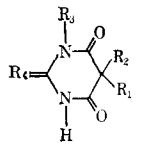


Table I—Summary of the Substituents Found in the Noted Positions for the Barbituric Acid Derivatives Used in this Study

Derivative	R_1	R_2	R_3	R_4
Barbituric acid	—H	—H	H	O
Barbital	$-CH_2CH_3$	$-CH_2CH_3$	H	O
Metharbital	$-CH_2CH_3$	$-CH_2CH_3$	CH_3	O
Butabarbital	$-CH_2CH_3$	$-CH(CH_3)CH_2CH_3$	H	O
Vinbarbital	$-CH_2CH_3$	$-C(CH_3)=CHCH_2CH_3$	H	O
Thiopental	$-CH_2CH_3$	$-CH(CH_2)CH_2CH_2CH_3$	H	S
Thiamylal	$-CH_2CH=CH_2$	$-CH(CH_3)CH_2CH_2CH_3$	H	S
Phenobarbital	$-CH_2CH_3$		H	O
Amobarbital	$-CH_2CH_3$	$-CH_2-CH_2-CH(CH_3)_2$	H	O
Pentobarbital	$-CH_2CH_3$	$-CH(CH_3)-CH_2-CH_2-CH_3$	H	O

greater the lipophilicity, the greater the partition coefficient. It is assumed that the partition coefficients in 1-octanol–water systems are additive in nature.

In the present study, the extent of lipophilicity is measured in a relative fashion, since it is assumed that the molecule possessing the greatest lipophilicity should have the least solubility in the most polar solvent. Further, the ratios of the solubilities, using a standard compound, should indicate the relative polarities of the molecules in a continuously varying spectrum of polarity.

In Table I, the pertinent chemical characteristics are shown for the barbiturates studied. Barbituric acid is also given in Table I and used to illustrate the parent compound.

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°; and phenobarbital USP, m.p. 176°. 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 these binary solvent mixtures.

Hydroalcoholic solvents were prepared volumetrically by the use of burets, previously determined densities for absolute ethyl alcohol,[10] and distilled water at ambient room temperature. These mixtures ranged from 0.0 to 100.0% w/w distilled water in 2.5% increments and represent a polarity range in terms of dielectric constant values of 24.3–78.5.

A pH 10.7 buffer was prepared with 71 g. of anhydrous sodium dibasic phosphate[11] (reagent grade) dissolved in 1000 ml. of distilled water and adjusted to pH 10.7 with 1.0 *M* sodium hydroxide[12] solution.

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.[13]

A Cary model 16 spectrophotometer,[14] a Mettler type H6T[15] analytical balance, a Leeds Northup model 7401 pH meter,[16] and a Sorvall model GLC-1[17] centrifuge were utilized in the assay procedure. Computational treatment of the data was aided through utilization of an IBM System 360 model 50 digital computer.[18]

Procedure—The procedures used in this study have been previously given (4) and consist essentially of a gravimetric analytical technique with a spectrophotometric check run. Each solubility curve represents the average values from at least three runs of the 41 samples comprising the total variation in solvent composition.

[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.
[10] U.S. Industrial Chemicals Co., New York, N. Y.
[11] Fisher Scientific Co., Fair Lawn, N. J.
[12] Mallinckrodt Chemical Works, New York, N. Y.
[13] Techne (Cambridge) Limited, Cambridge, England.
[14] Cary Instruments, Belmont, Mass.
[15] Mettler Instrument Corp., Hightstown, N. J.
[16] Leeds and Northup Co., Philadelphia, Pa.
[17] Sorvall, Newtown, Conn.
[18] International Business Machines, Armonk, N. Y.

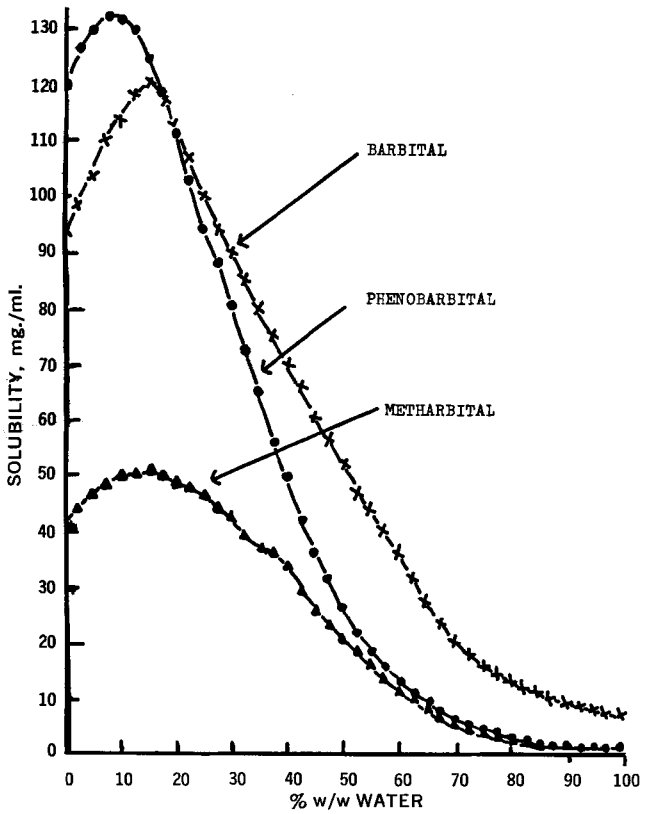


Figure 1—*Solubilities of the barbiturates noted are plotted in milligrams per milliliter at 25° as a function of the weight percent water.*

RESULTS AND DISCUSSION

In Fig. 1, the solubilities of barbital, phenobarbital, and metharbital in milligrams per milliliter as a function of the percent w/w water in binary mixtures are presented. The solubility curves show maxima at 10% w/w water for phenobarbital and 15% w/w water for barbital. Metharbital, on the other hand, shows a maximum at 15% w/w water and a shoulder at 35% w/w water. These values lead to DR (dielectric requirement) values of 29.0 for phenobarbital, 30.6 for barbital, and 30.6 and 41.3 for metharbital, respectively. The values for barbital and phenobarbital agree with those previously given (5–7).

The basic correlation of the interpretation of solubility phenomena in terms of dielectric constants is substantiated by considering Khalil and Martin's (5) value for barbital. The value of the solubility parameter is given as approximately 13.5 in their excellent work on model membranes. The DR of barbital in this present study was found to have a value of 31, which gives a solubility parameter value of 13.7 from a previously presented relationship (6), which has been modified slightly and presented in another communication (8).

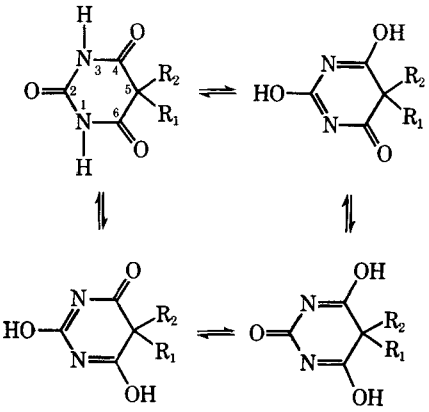
Further, Khalil and Martin (5) obtained a value for the solubility parameter of salicylic acid as 10.8, which coincides well with the value of 10.5 derived on a dielectric constant basis (8).

It is interesting to note the nature of these curves, since a crossover occurs in the magnitude of solubility. Barbital is seen to have greater solubility than phenobarbital over a wide range of polarity, *i.e.*, dielectric constant values of 33 to 78, whereas phenobarbital has greater solubility in the range of 24 to 33. These three barbiturates have been grouped together for convenience, since these materials possess a DR and approximately the same duration of action. The solubility of these substances varies about 5–13% w/v in pure alcohol to the maxima. The solubility of these substances are summarized in Table II.

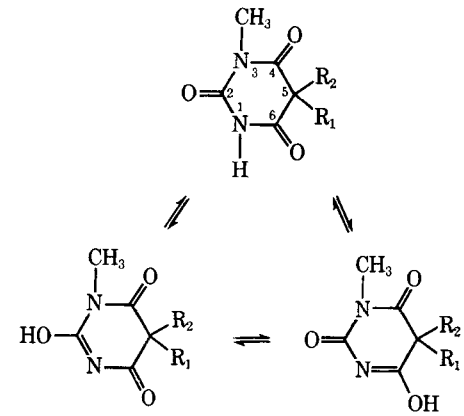
In the case of metharbital, it is noted from Fig. 1 that the addition of a methyl group to the R_3 position of the molecule dramatically reduces the maximum solubility as compared to barbital with a hydrogen at this position. A DR is observed at 30.6 and a solubility at this point of 51.2 mg./ml. It is also seen that a shouldering effect, unique to this derivative, is observed in the range of 40–44 in terms of dielectric constants. The pharmacological activity of this derivative is also unusual in that it not only produces sedation but possesses anticonvulsant properties.

A brief consideration of the chemical structure of the metharbital molecule will also yield some unusual characteristics relative to the nonmethylated analogs. It has been reported (9) that the barbituric acid derivatives undergo enol–keto tautomerism. Molecules devoid of alkyl substituents on the nitrogen atoms can provide a maximum of two (N—H) hydrogen atoms which would be available for contribution to monoenolized and dienolized structures with the three neighboring carbonyl groups.

Scheme I*a* illustrates the three possible dienolized structures as



a—derivatives devoid of *N*-alkyl substituents showing only the dienol combinations



b—*N*-alkyl derivatives showing all possible combinations of enol species

Scheme Ia,b—Enol–keto tautomerism of the barbituric acid derivatives

well as the keto form. It is noted from this illustration that the carbonyl group at carbon-2 has twice the number of chances of becoming enolized as those at carbon-4 or 6, due to its vicinal position to both nitrogen atoms. Metharbital, on the other hand, has only one (N—H) hydrogen available. With the methyl group on the nitrogen at position-3, only two possible monoenolized species can form, as shown in Scheme I*b*. Other effects being equal, the chances of the carbonyl group at position-2 or 6 being converted to the enol form are equal.

Tautomerism is not a static situation where tautomeric species of molecules exist in only keto or enol forms, but rather it is a dynamic equilibrium where active hydrogen atoms are rapidly interchanging between the various species.

It may be possible that the limitations imposed on the tautomerism of the metharbital molecule by the *N*-methyl group could cause the shouldering effect on the solubility profile. A second possibility for this unusual behavior for a barbiturate derivative is that the polarity of the various tautomeric forms is different. The assay procedure, not being specific for any particular species of this molecule, would detect the cumulative solubility of all the various species present.

Table II—Summary of the Solubility of the Barbiturate Noted in Ethanol–Water Mixtures in Milligrams per Milliliter at 25° as a Function of w/w Percent Water and Dielectric Constant

w/w % Water	Dielectric Constant, ε	Solubility, mg./ml. Barbital	Phenobarbital	Methabarbital
0.0	24.3	92.3	118.4	41.9
2.5	25.5	98.6	122.6	43.7
5.0	26.5	103.1	127.8	46.1
7.5	27.6	110.0	131.1	47.9
10.0	29.0	113.3	132.3	50.0
12.5	29.7	118.3	130.6	50.7
15.0	30.6	120.7	126.4	51.2
17.5	31.5	117.2	120.6	50.9
20.0	32.7	112.5	112.3	50.3
22.5	33.8	107.7	104.0	49.3
25.0	34.7	100.1	97.7	48.0
27.5	36.4	94.3	90.2	46.0
30.0	37.5	90.2	82.4	44.7
32.5	38.6	85.1	78.2	43.4
35.0	39.8	80.8	70.3	39.0
37.5	41.3	75.6	62.1	36.6
40.0	42.8	70.0	52.0	36.2
42.5	44.2	66.3	46.6	33.4
45.0	45.7	60.2	41.1	28.9
47.5	47.5	56.5	36.3	26.2
50.0	49.0	51.6	30.6	23.5
52.5	50.5	47.7	25.4	21.2
55.0	52.0	43.1	21.2	18.7
57.5	53.6	39.2	18.0	16.2
60.0	55.4	34.1	15.0	14.0
62.5	57.0	30.6	11.5	12.1
65.0	58.4	28.3	10.0	10.2
67.5	60.0	24.1	7.9	8.6
70.0	61.7	20.9	6.2	7.4
72.5	63.3	17.1	5.1	6.3
75.0	64.5	15.6	4.5	5.3
77.5	66.1	14.2	4.0	4.5
80.0	67.5	13.3	3.0	4.0
82.5	68.9	12.5	2.7	3.5
85.0	70.2	11.1	2.5	3.2
87.5	71.7	10.1	2.3	2.9
90.0	73.2	9.0	1.9	2.7
92.5	74.5	8.0	1.7	2.5
95.0	75.7	7.5	1.5	2.3
97.5	77.1	7.4	1.3	2.2
100.0	78.5	7.3	1.2	2.0

The solubility data for butabarbital are found in Table III. Figure 2 represents the isothermal data graphically as solubility in milligrams per milliliter as a function of solvent composition. This molecule is identical to barbital with the exception of the ethyl group on the R_2 position, which is replaced with a *sec*-butyl group. The addition of these two carbon atoms decreased the solubility over the entire range of the solvent composition.

Reber and Pathamanon (10) have determined the solubility of vinbarbital in ethanol–water mixtures. A tabulation of values derived from smoothing their data is found in Table III and plotted in Fig. 2, as described previously. This particular derivative has a fifth carbon atom and an olefinic bond added to the substituent at the R_2 position of the butabarbital molecule.

For the purpose of obtaining the solubility profiles for vinbarbital, special treatment of the data presented by Reber and Pathamanon (10) was necessary. Their profile consisted of 11 pieces of data, only one of which corresponded to an exact solvent composition used in this study. It was necessary, therefore, to analyze their data and determine the apparent solubility of vinbarbital in each of the 41 solvent systems employed for the remaining compounds. Rather than arbitrarily picking points off a plot of their data, the data were subjected to a polynomial regression. A previously compiled and published digital computer program (11) was employed in double precision. This program is based on a mathematical method presented by Ostle (12). The coefficients of an eighth-degree polynomial, representing the best fit of a curve to the data of Reber and Pathamanon (10), were computed. From this equation, the apparent solubilities of vinbarbital in hydroalcoholic solvents of identical composition to those used in this study were calculated. It is suggested by Ostle (12) that this particular method is not valid for data presented in uneven increments of the independent variable. However, it is felt that the published solubility data for vinbarbital closely approximate even increments of solvent composition and, therefore, a close approximation of the true equation describing the data should be rendered by this method. A comparison of the original data in Table IV may be made with the values computed by this method which are found in Table III.

Amobarbital, the third of the intermediate-acting barbiturates of this group, is also illustrated in Fig. 2. However, in this case, the solubility curve rises asymptotically toward a maximum value in pure ethanol. The DR would presumably have a value of about or less than the dielectric constant of pure ethanol, *i.e.*, 24.3. The solubility data for these compounds are given in Table III.

Three barbiturates of short to ultrashort duration were also studied. Pentobarbital, the 5-ethyl-5-(1-methyl butyl) derivative of barbituric acid, showed a solubility curve also running asymptotically toward pure alcohol. Again, it would be assumed that the DR would be about 24.3, that being the value for pure ethanol. Although there is a discrimination between amobarbital, the 5-ethyl-5-isopentyl derivative, and pentobarbital based on duration of action, both possess similar solubility curves and magnitudes of solubility. Certainly, there is considerable overlap in the duration

Table III—Summary of the Solubility of the Barbiturate Noted in Ethanol–Water Mixtures in Milligrams per Milliliter at 25° as a Function of w/w Percent Water and Dielectric Constant

w/w % Water	Dielectric Constant, ε	Solubility, mg./ml. Amobarbital	Butabarbital	Vinbarbital
0.0	24.3	219.6	84.0	62.3
2.5	25.5	217.1	85.9	62.7
5.0	26.5	213.4	87.9	63.1
7.5	27.6	210.3	89.3	63.3
10.0	29.0	205.6	90.1	63.0
12.5	29.7	196.6	90.6	62.2
15.0	30.6	191.9	89.6	61.0
17.5	31.5	182.2	88.5	59.2
20.0	32.7	172.1	85.9	56.9
22.5	33.8	160.1	82.6	54.2
25.0	34.7	145.8	79.2	51.3
27.5	36.4	137.5	73.4	48.1
30.0	37.5	123.6	68.6	44.8
32.5	38.6	110.9	63.6	41.3
35.0	39.8	104.2	58.6	37.9
37.5	41.3	88.2	53.7	34.4
40.0	42.8	81.0	48.2	31.1
42.5	44.2	67.0	43.0	27.8
45.0	45.7	62.3	38.4	24.7
47.5	47.4	51.8	33.4	21.8
50.0	49.0	40.0	29.4	19.0
52.5	50.5	33.4	24.8	16.4
55.0	52.0	25.5	21.1	14.0
57.5	53.6	19.5	17.7	11.8
60.0	55.4	16.4	14.5	9.8
62.5	57.0	11.2	11.9	8.1
65.0	58.4	9.6	9.6	6.6
67.5	60.0	7.8	7.5	5.3
70.0	61.7	7.4	6.4	4.2
72.5	63.3	5.3	4.8	3.3
75.0	64.5	2.6	3.7	2.6
77.5	66.1	2.2	2.9	2.1
80.0	67.5	1.7	2.4	1.7
82.5	68.9	1.2	2.0	1.4
85.0	70.2	1.1	1.7	1.2
87.5	71.7	0.96	1.5	1.1
90.0	73.2	0.84	1.4	1.0
92.5	74.5	0.70	1.2	0.9
95.0	75.7	0.68	1.1	0.8
97.5	77.1	0.64	1.0	0.7
100.0	78.5	0.56	0.9	0.7

Table IV—Summary of the Solubility of Vinbarbital in Ethanol–Water Mixtures in Milligrams per Milliliter at 25° as a Function of w/w Percent Water (10)

w/w % Water	Solubility, mg./ml.
0.16	62.3
7.56	63.3
20.96	55.8
28.77	46.6
38.62	32.8
48.85	20.20
58.26	11.38
67.62	5.03
79.87	1.76
90.20	0.96
100.00	0.71

of sedative effect for these materials; however, although amobarbital has an intermediate duration, it is closer to short-acting pentobarbital (especially chemically) than it is to intermediate-acting vinbarbital and butabarbital.

The following two compounds to be discussed differ from the previously mentioned derivatives, because the oxygen at the R_4 position has been replaced with a sulfur atom in the ultrashort-acting thiamylal and thiopental. The effect of this substitution may decrease the polarity of the molecule from its oxy-analog. On the electronegativity scale, the value for the oxygen atom is 1 unit higher than those for the sulfur and carbon atoms which are approximately equal. Thus, the chemical bond between the oxygen at the R_4 position and the adjacent carbon atom may be more polar in character than the similar situation with the sulfur atom.

Aside from this substitution, the chemical structure of thiopental varies from barbital by a 1-methylbutenyl group replacing an ethyl substituent on the R_2 position.

Table V and Fig. 3 tabulate and graphically illustrate the solubility data for thiopental, in the manner previously described.

The ultrashort-acting barbiturate thiamylal is similar in chemical structure to thiopental, with the exception of an allyl substituent replacing an ethyl group in the R_1 position. Data for this derivative are found in Table V. A plot of these data, in the usual fashion, is represented in Fig. 3. This curve is unique in that no maximum is observed, but the solubility profile rises sharply toward pure

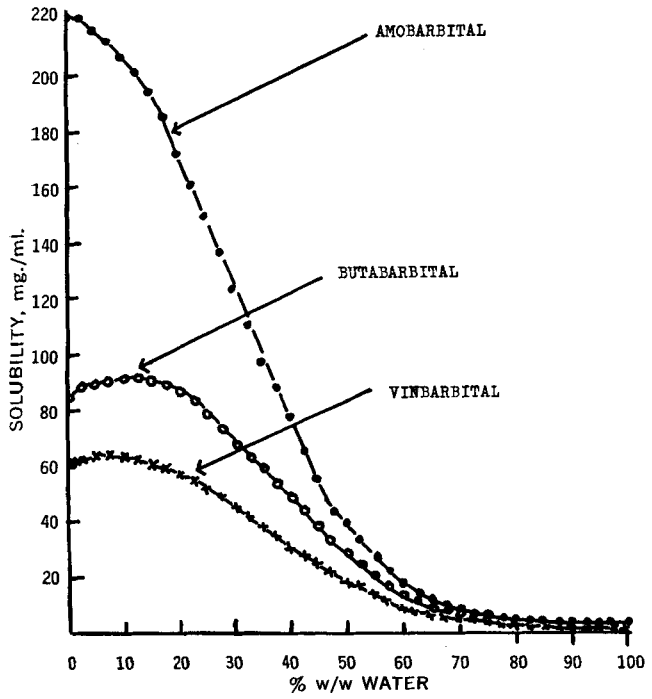


Figure 2—*This plot parallels that for Fig. 1 for the barbiturates noted.*

Table V—Summary of the Solubility of the Barbiturate Noted in Ethanol–Water Mixtures in Milligrams per Milliliter at 25° as a Function of w/w Percent Water and Dielectric Constant

w/w % Water	Dielectric Constant, ϵ	Solubility, mg./ml. Pentobarbital	Thiopental	Thiamylal
0.0	24.3	250.4	56.3	160.8
2.5	25.5	250.4	62.3	149.9
5.0	26.5	246.2	74.2	135.4
7.5	27.6	243.3	97.1	124.6
10.0	29.0	236.1	94.9	112.7
12.5	29.7	226.4	86.6	102.0
15.0	30.6	218.6	79.9	93.2
17.5	31.5	208.8	71.6	82.3
20.0	32.7	193.1	63.7	71.8
22.5	33.8	180.4	55.4	61.9
25.0	34.7	169.3	50.4	54.9
27.5	36.4	157.1	41.1	43.3
30.0	37.5	137.1	36.3	37.7
32.5	38.6	123.4	31.0	32.3
35.0	39.8	110.6	38.0	28.7
37.5	41.3	98.3	23.5	23.1
40.0	42.8	85.0	18.8	18.1
42.5	44.2	72.0	16.3	15.4
45.0	45.7	62.5	14.0	13.0
47.5	47.4	51.0	11.2	10.3
50.0	49.0	40.0	9.1	8.2
52.5	50.5	34.5	7.3	6.5
55.0	52.0	31.3	5.4	4.7
57.5	53.6	24.3	4.5	3.4
60.0	55.4	20.6	3.2	2.5
62.5	57.0	15.5	2.4	1.96
65.0	58.4	13.2	2.0	1.41
70.0	61.7	10.3	0.9	0.73
72.5	63.3	7.8	0.7	0.51
75.0	64.5	5.5	0.5	0.35
77.5	66.1	4.0	0.30	0.23
80.0	67.5	3.1	0.28	0.19
82.5	68.9	2.7	0.23	0.15
85.0	70.2	2.1	0.19	0.12
87.5	71.7	1.7	0.17	0.10
90.0	73.2	1.4	0.15	0.09
92.5	74.5	0.9	0.12	0.07
95.0	75.7	0.6	0.11	0.06
97.5	77.1	0.5	0.09	0.06
100.0	78.5	0.5	0.08	0.05

ethanol, having a dielectric constant of about 24.3. This would indicate that a DR of less than 24.3 would exist for this compound.

It was noted in the case of all the barbituric acid derivatives that some portion of the solubility isotherm possessed a fair degree of linearity relative to the solvent composition. The rates calculated as the slopes of the straight line best representing these approximately linear sections are summarized in Table VI, along with the ranges in solvent composition in which this relationship is valid.

The limits of solvent composition, within which these rates are operative, lie well within the range of pharmaceutical interest. It might be assumed then that there would be some pharmaceutical formulation advantages in this information.

It would be pertinent then to consider the changes in solubility produced by altering the substituent groups on the barbital molecule in a relative manner where barbital is used as the standard of comparison.

The ratios computed in this manner for metharbital are shown and the data plotted as a function of w/w percent water in Fig. 4. It can be seen in this illustration that the magnitude of solubility of metharbital is substantially lower than that of barbital over the entire range of solvent composition. The peak observed between 30 and 40% water by weight corresponds to the shoulder on the solubility profile. An inflection on this curve may be observed at 15% w/w water, which corresponds to the maximum solubility of both metharbital and barbital.

Phenobarbital, on the other hand, produces an interesting spectrum of values, wherein at low polarities the ratio is greater than

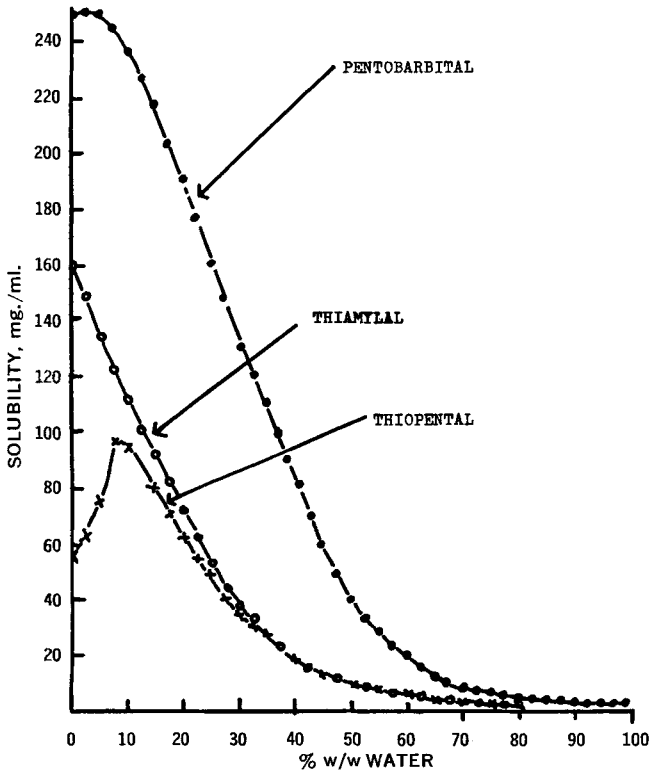


Figure 3—*Solubilities of the noted barbiturates are illustrated as described in Fig. 1.*

unity and is isodielectric at 20% w/w water. The fair degree of linearity for the ratio curve up to about 70% w/w water implies a unique discriminatory effect due to the phenyl substituent in the incremental polarity shifting due to the varying aqueous content. This would seem to support the concept of a continuous polarity spectrum in ethanol–water mixtures possessing constant forces of interaction or dissolution. The approximate slope for this line is

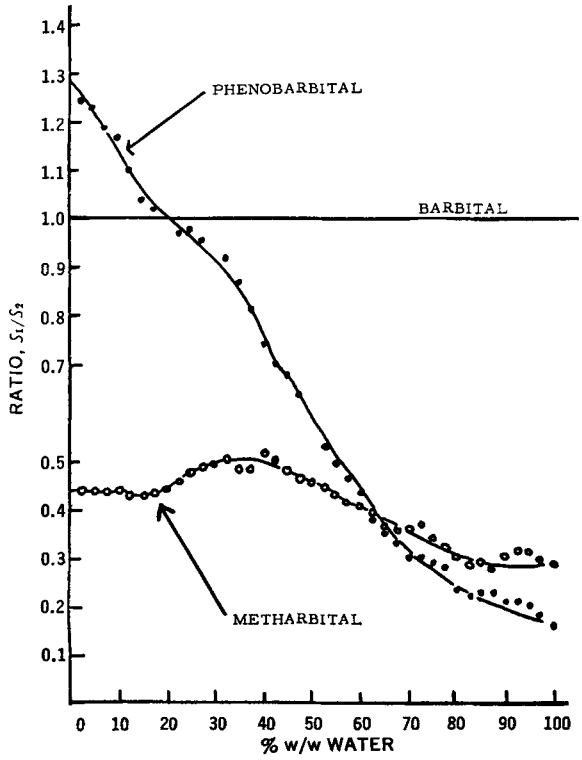


Figure 4—*Ratio of the solubility of phenobarbital and metharbital relative to barbital (defined as unity) is given as a function of the weight percent water.*

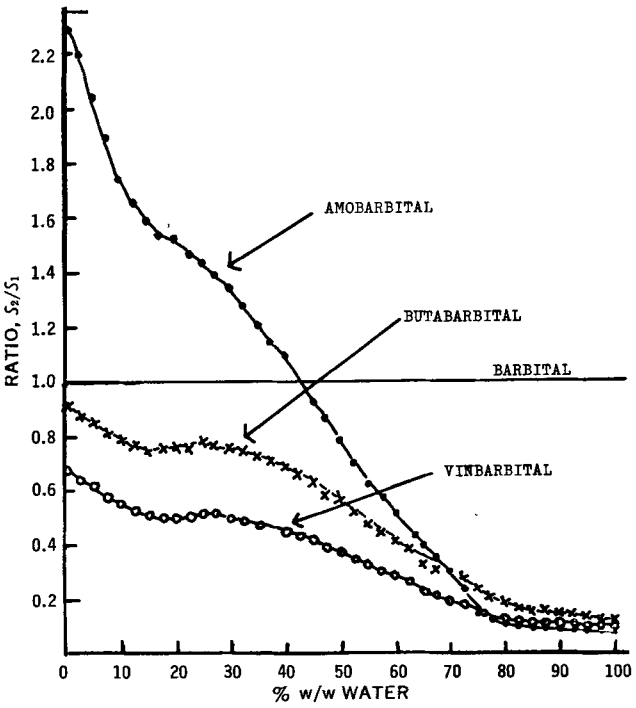


Figure 5—*This plot parallels that of Fig. 4 for amobarbital, butabarbital, and vinbarbital.*

1.4×10^{-2}/% change in water by weight. Thus a 10% change in water content from 10 to 20% would decrease the ratio by 0.14.

In Fig. 5, the ratio curves for amobarbital, butabarbital, and vinbarbital are shown. These three curves are similar in that there is an inflection point at about 15% w/w water and again, as expected, the curves converge from about 70–100% w/w water. Amobarbital also possesses an isodielectric point at 42.5% w/w water. In Fig. 6, the ratio curves are given for pentobarbital, thiamylal, and thiopental. Pentobarbital shows an inflection point at about 20% w/w water and an isodielectric point at 45% w/w water. A very large change in the ratio is seen, from a 270% increase in pure ethanol due to the 1-methyl butyl group to about a 300% reduction in pure water. This ninefold change in solubility ratio varies nonlinearly throughout the intermediate range.

The ratio curves for thiamylal and thiopental are also interesting, the "spike" for thiopental due to the sharp maximum in the solubility profile. Further, the convergence of these plots extends over a very wide spectrum of concentration values, *i.e.*, 30–100% w/w water.

To attempt to collate this information in a coherent fashion, the solubility values in pure water, pure ethanol, and at the DR (where applicable) were considered.

In Table VII, a summary of the duration and onset of action (13, 14) is shown for the compounds in this study, as well as the pertinent characteristics of the solubility profiles.

Table VI—Summary of Rates of Change in Solubility in Milligrams/Percent w/w Water, Calculated from the Linear Portion of the Solubility Profiles

Derivative	Range in % w/w Water	Rate in mg./% w/w Water
Barbital	15.0–55.0	−1.8
Phenobarbital	15.0–50.0	−2.9
Metharbital	20.0–60.0	−1.0
Butabarbital	20.0–55.0	−1.9
Vinbarbital	20.0–60.0	−1.2
Amobarbital	15.0–50.0	−4.4
Pentobarbital	10.0–50.0	−5.0
Thiopental	10.0–30.0	−3.0
Thiamylal	0.0–30.0	−4.0

Table VII—Summary of the Dielectric Requirement (DR), the Solubilities in Absolute Ethanol, in Water, and at the Dielectric Requirement in Milligrams per Milliliter, as a Function of the Duration and Onset of Action

Derivative	Duration of Action		Onset of Action	DR	Solubility in Ethanol, mg./ml.	Solubility at DR, mg./ml.	Solubility in Water, mg./ml.
	Reference 13	*Reference 14*	*Reference 13*				
Barbital	Long	Long	30–60 min.	30.6	92	121	7.3
Metharbital	Long	Long	30–60 min.	30.6	42	51	2.00
Phenobarbital	Long	Long	20–40 min.	29.7	118	132	1.20
Butabarbital	Intermediate	Short to intermediate	20–30 min.	29.7	84	91	0.86
Vinbarbital	Intermediate	Short to intermediate	20–30 min.	27.6	62	63	0.70
Amobarbital	Intermediate	Short to intermediate	20–30 min.	24.3	219	219	0.56
Pentobarbital	Short	Short to intermediate	20–30 min.	24.3	250	250	0.50
Thiopental	Ultrashort	Ultrashort	30 sec.	27.6	56	97	0.08
Thiamylal	Ultrashort	Ultrashort	20–60 sec.	24.3	161	161	0.05

Table VIII—Summary of the Therapeutic Action, and the Ratios of the Solubility in Ethanol and at the Dielectric Requirement (DR) to the Solubility in Water

Derivative	Duration (*Reference 13*)	Onset (*Reference 14*)	Sol. in Ethanol / Sol. in Water	Sol. at DR / Sol. in Water	Group
Barbital	Long	30–60 min.	12	16	I
Metharbital	Long	30–60 min.	21	25	I
Phenobarbital	Long	20–40 min.	98	110	II
Butabarbital	Intermediate	20–30 min.	98	104	II
Vinbarbital	Intermediate	20–30 min.	88	91	II
Amobarbital	Intermediate	20–30 min.	390	390	III
Thiopental	Ultrashort	30 sec.	670	1200	III
Thiamylal	Ultrashort	20–60 sec.	2300	2300	III
Pentobarbital	Short	20–30 min.	500	500	III

The onset of action for all the compounds listed is after the oral dose except with thiamylal and thiopental which are given intravenously. Intravenous administration of barbiturates other than thiamylal and thiopental would have an onset of action about 3–5 min., with barbital and phenobarbital at the upper value and the others at the lower. The DR's for these compounds shift to lower values as the duration of action decreases, indicating greater lipophilicity for the ultrashort barbiturates. The solubilities of these compounds in pure ethanol, pure water, or at the DR show no discernible pattern relative to direction and magnitude.

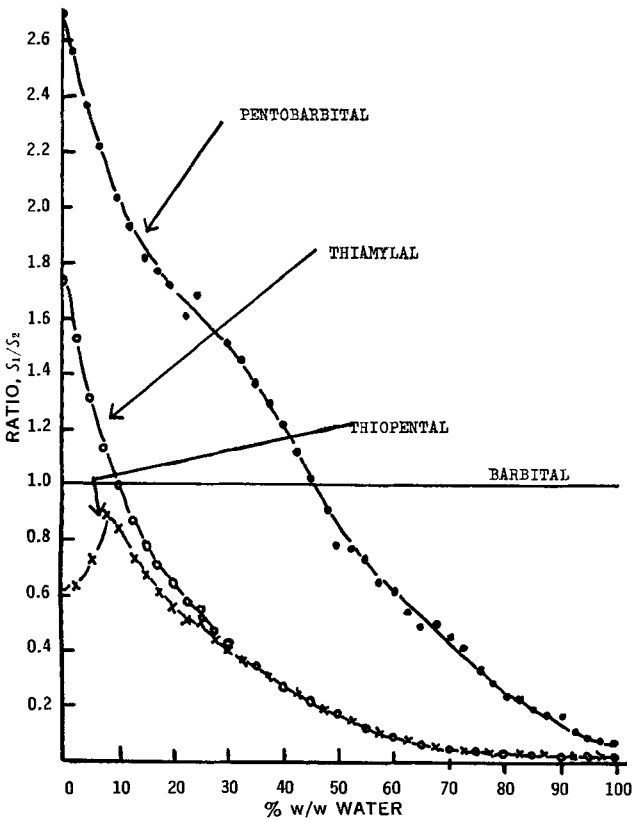


Figure 6—*This plot parallels that of Fig. 4 for pentobarbital, thiopental, and thiamylal.*

It was thought, however, that some sort of approximate correlation should exist relative to the pharmacological parameters and physical properties, although this relationship is undoubtedly complex (13). In Table VIII, the ratios of the solubilities of these compounds in pure ethanol and at the DR relative to water are shown. For compounds with a long duration of action, these ratios have values of about 10 to 100. However, if phenobarbital is omitted, the ratios vary from about 10 to 25. For the compounds listed as intermediate in action, these ratios vary from about 100 to 400 for butabarbital through amobarbital. Again, overlapping is suggested by these values since amobarbital is substantially greater than either butabarbital or vinbarbital. For those barbiturates possessing short or ultrashort action, the ratios are substantially larger, ranging in value from 500 to 2300, which indicates relatively greater lipophilicity for these substances. Since amobarbital is closer to pentobarbital in the properties of the solubility curves, they might also be considered in a given group.

Thus, a classification scheme for the barbiturates might be considered from both points of view, *i.e.*, pharmacological values and physical measurements. The last column of Table VIII breaks down the nine barbiturates in this study into three groups denoted by a Roman numeral. Although this type of classification would be very limited, it would provide a means by which exact and simple physical measurements could place a compound in the appropriate pharmacological range.

This correlation is rather good in view of the nature of the solvents. Such a relationship might be expected with pure water and ethanol which anchor the ends of the spectrum of solvent composition. Between these end-points, however, nonideal solvents are involved; this cosolvency phenomenon produces solubilities that deviate from those which may be expected of ideal solutions.

It may be conjectured that the magnitude of these ratios are an indication of the extent to which these compounds become concentrated in the less polar biological fluids. Thus, the derivatives

possessing a higher ratio, *i.e.*, thiopental and thiamylal, become concentrated to a higher degree in the body lipids than do barbital or metharbital and might be expected to be ultrashort acting.

In considering these solubility data in total, an approximate correlation has been observed between the lipophilic nature of the various barbiturate analogs and their therapeutic action. One must view this study with proper perspective in relation to the numerous other physical and chemical properties as well as the various biopharmaceutical parameters which all contribute to the variation in the final therapeutic activity possessed by the members of this series. The net result of the complex interaction of these and other factors determines the type and degree of the pharmacological activity involved.

The underlying concept of the pH-partition hypothesis as an approximate model would seem to be confirmed. However, such phenomena as binding, detoxification, active or passive diffusion, and complexation would play important roles in biological readouts which were not patternized or aberrant in behavior.

It is anticipated that several studies on the barbiturates and sulfonamides relative to solubility and partitioning will be undertaken in these laboratories and will be the subject of future communications.

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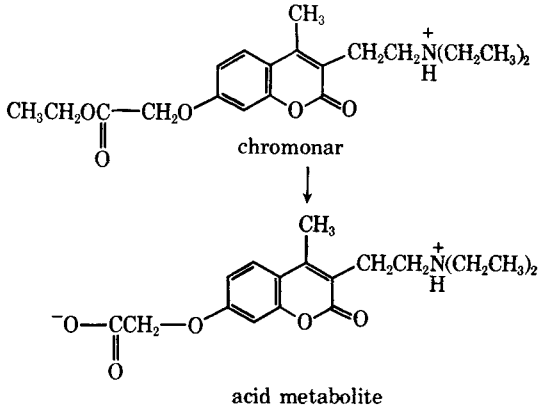
Metabolism and Excretion of Chromonar and Its Metabolite in Dog and Man

YVONNE C. MARTIN and RONALD G. WIEGAND

Abstract □ A simple method for the detection of chromonar and its acid metabolite by fluorescence techniques is described. Following oral or intravenous administration, chromonar is rapidly hydrolyzed to its metabolite, the corresponding acid. No further metabolism is observed. The metabolite distributes according to a single-compartment model. The plasma half-life is 1 hr. in man and dog. Excretion of the metabolite into the bile accounts for approximately 25% of the dose, and excretion into the urine accounts for the remainder.

Keyphrases □ Chromonar—metabolism, excretion □ Metabolite, chromonar—*in vitro, in vivo* determination □ Blood levels, chromonar and acid metabolite—human, dog □ Excretion—chromonar acid metabolite □ TLC—separation, identification □ Fluorometry—analysis

The coumarin compound chromonar[1] is used for the treatment of angina pectoris in Germany and Japan. The early report by Klarwein and Nitz (1) demonstrated that when the drug comes in contact with biological tissues, it is rapidly hydrolyzed to the corresponding acid (Scheme I), which exists as a zwitterion at the pH of the blood and urine. The present authors, therefore expected that the tissue distribution and further metabolism of the compound would be minimal and that the study of plasma and urine concentrations of the acid metabolite at various times after dosage would provide the information necessary to assess the way that chromonar is handled by the body.



Scheme I—Metabolism of Chromonar

[1] 3-(β-Diethylamino-ethyl)-4-methyl-7-carbethoxy-methoxy-2-oxo-(1,-2-chromene). Also known as Cassella 4489, Abbott-27053, and Intensain hydrochloride. Chromonar is marketed by the Cassella Co. of Germany.