Preparation of 5-Substituted Benzylbarburituric Acids and Investigation of the Effect of the Benzyl and Substituted Benzyl Groups on the Acidity of Barbituric Acid

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The acidity of 5-benzylbarbituric acid and a series of 5-substituted benzylbarbituric acids has been determined in 50% ethanol/water and they were found to be more acidic than barbituric acid. The pK_as of these derivatives obey Hammett's equation indicating that their acidity is affected by substituents in the same manner as the benzoic acid ionization constants. A synthesis of these acids is described.

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Introduction.

The knowledge of the dissociation constants of barbiturates is necessary for interpreting more adequately their efficiency as drugs and their mode of action [3]. For example, the 5,5-disubstituted barbituric acids and their salts have proved useful as buffers in the biologically important *p*H range from about 6 to 9, and unionized barbituric acids have been postulated to penetrate living cells more readily than the constituent ions [4].

Our continuing interest in the effect of substituents on the acidity of barbituric acids has led us recently to synthesize and measure pK_a values for several 5-substituted benzylbarbituric acids. Initially, we attempted to prepare these compounds by treating barbituric acid, **1**, with appropriately substituted benzyl halides and aqueous sodium bicarbonate. However, this reaction produced only 5,5-disubstituted barbituric acids even if an excess of **1** was used. That the first-formed 5-substituted benzylbarbituric acids undergo benzylation faster than **1** in the presence of sodium bicarbonate indicates that they are more acidic than **1**. One would expect the opposite on the basis of the +I nature of the benzyl group ($\sigma_p = -0.09$ [5]). Koffer [6,7], Okada and Esaki [8], and Buckingham and coworkers [9] also found that barbituric acids possessing 5-alkyl-substituents having no branching at the alpha carbon were more acidic than **1**. The C-5 acidity of 5-methylbarbituric acid and 5-*n*-butylbarbituric acid has been correlated with the rates of proton transfer to and from that carbon atom [7,9].

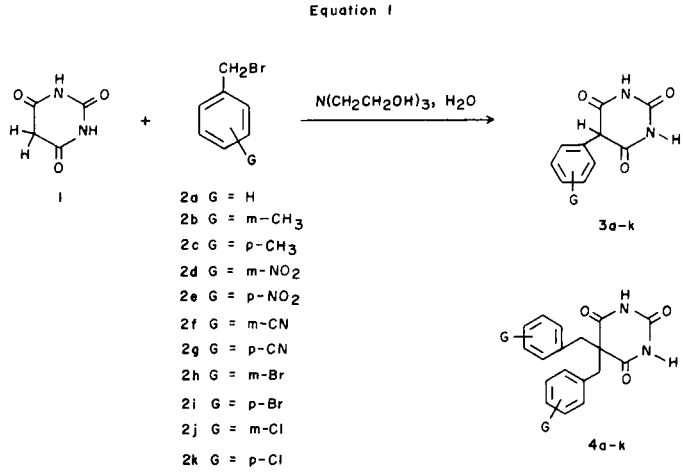
This paper reports the synthesis of a series of 5-substituted benzylbarbituric acids and their pK_a values in ethanol-water. In addition, the pK_as of 5-benzyl-, 1-benzyl-, and 1,3-dibenzylbarbituric acids in water are presented. The evaluation of these pK_as should allow one to assess electronic substituent effects on C-5 acidities.

Results and Discussion.

Synthesis of 5-Substituted Benzylbarbituric Acids.

5-Substituted benzylbarbituric acids, **3a-k**, were prepared by the reaction of barbituric acid, **1**, with the appropriate benzyl bromide, **2a-k**, in the presence of triethanolamine in water.

Equation I



The results are listed in Table 1. 5,5-Disubstituted benzylbarbituric acids, **4a-k**, were also produced; however, they were readily separated from the mono-substituted compounds by extracting the reaction mixture with sodium bicarbonate solution. The 5-substituted benzylbarbituric acids were precipitated from the basic mother liquor by the addition of excess 10% hydrochloric acid.

pK_a Determinations.

The pK_as of barbituric acids **3a-k** were determined by the titration-graphical method described by Roberts [10]. Since several of these acids were insoluble in water, their pK_as were determined in water/ethanol solution (50% w/w). Nitrogen gas was bubbled gently into the solution throughout the titrations to prevent autooxidation of the acids [11]. The pK_a of 5-benzylbarbituric acid, **3a**, and 1-benzyl- and 1,3-dibenzylbarbituric acids, **5** and **6**, respectively, were determined in water spectrophotometri-

Table 1

Preparation of 5-Substituted Benzylbarbituric Acids, **3a-k** [a]

Entry	G	Mp, °C	Yield, [b] %	Elemental Analysis, % Calcd./Found C	H	N	Halogen
3a	H	213-215	40	60.54	4.62	12.84	
				60.47	4.70	12.89	
3b	*m*-CH_3	203-204	45	62.06	5.21	12.06	
				61.80	5.08	12.03	
3c	*p*-CH_3	229-231	56	62.06	5.21	12.06	
				62.14	5.23	12.22	
3d	*m*-NO_2	198-200	31	50.20	3.45	15.96	
				50.10	3.33	15.74	
3e	*p*-NO_2	265-266	48	50.20	3.45	15.96	
				50.22	3.60	15.74	
3f	*m*-CN	228-229	36	59.26	3.73	17.28	
				59.29	3.63	17.36	
3g	*p*-CN	248-249.5	40	59.26	3.73	17.28	
				58.77	3.62	16.87	
3h	*m*-Br	205-207	45	44.46	3.05	9.43	26.89
				44.72	2.99	9.24	27.13
3i	*p*-Br	211-212	58	44.46	3.05	9.43	26.89
				44.30	2.77	9.24	27.09
3j	*m*-Cl	204-205	20	52.30	3.59	11.09	14.03
				52.20	3.39	11.36	13.74
3k	*p*-Cl	214-215	49	52.30	3.59	11.09	14.03
				52.25	3.39	10.75	13.93

[a] See experimental. [b] All melting points are uncorrected.

Table 2

pK_as for Benzylbarbituric Acids and 5-Substituted Benzylbarbituric Acids at 20°

Acid	Solvent	pK_a
Barbituric, **1**	Water	4.01 [a]
5-Benzyl, **3a**		3.33
1-Benzyl, **5**		4.00
1,3-Dibenzyl, **6**		4.01
5-Benzyl, **3a**	Ethanol/Water	3.90
m-Methyl, **3b**		3.94
p-Methyl, **3c**		4.00
m-Nitro, **3d**		3.62
p-Nitro, **3e**		3.52
m-Cyano, **3f**		3.58
p-Cyano, **3g**		3.57
m-Bromo, **3h**		3.68
p-Bromo, **3i**		3.73
m-Chloro, **3j**		3.69
p-Chloro, **3k**		3.73

[a] Values are within + 0.02.

cally [12]. The results of the pK_a determinations are listed in Table 2.

In water, the acidity of the 5-benzylbarbituric acid, **3a** (pK_a = 3.03), is approximately 10 times higher than **1** (pK_a = 4.00). However, the nitrogen-substituted derivatives, **5** and **6**, have about the same pK_a value as **1**, which indicates that benzyl substitution at nitrogen does not influence C-5 acidity significantly. Moreover, compound **3a** (pK_a as = 3.90) and the 5-substituted benzylbarbituric acids, **3b-k** (p$K_a$as = 3.52-3.94) are more acidic than **1** (pK_a = 4.41) in ethanol/water. The influence of the *m*- and *p*-substituents on the acidity of C-5 is in accord with their electron-releasing or electron-attracting nature. For example, 5-(*p*-methylbenzyl)barbituric acid, **3c**, (pK_a = 4.00) is

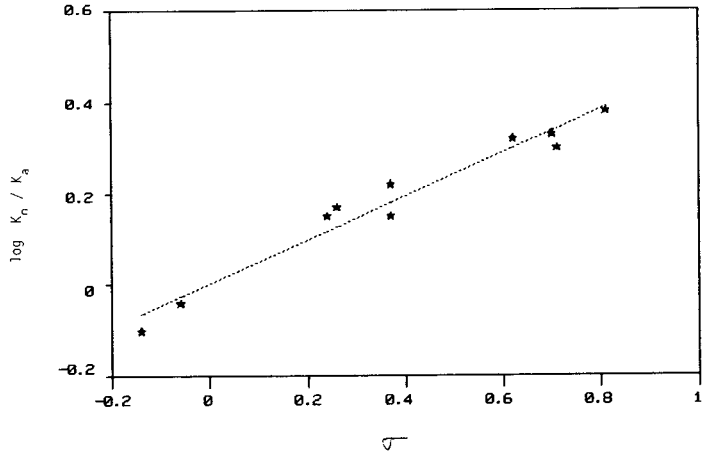


Figure 1. Hammett plot of log K/K_o *vs.* for series of 5-substituted benzylbarbituric acids.

less acidic than **3a**, whereas 5-(*p*-nitrobenzyl)barbituric acid, **3e**, (pK_a = 3.52) is more acidic than **3a**. A Hammett plot of the pK_a as of the meta- and para-substituted acids *vs.* σ shown in Figure 2 yields a straight line with ρ = 0.39 (correlation coefficient = 0.980) confirming that the ionization of 5-substituted benzylbarbituric acids are affected by substituents in the same manner as benzoic acid ionization; that is, their acidities are increased by electron-attracting groups and decreased by electron-releasing groups. We are investigating currently how benzyl substituents effect C-5 acidity.

EXPERIMENTAL

Materials.

Barbituric acid was obtained from Matheson, Coleman, and Bell and recrystallized from water and vacuum dried over sulfuric acid before use. Benzyl bromide and substituted benzyl bromides were obtained from Aldrich Chemical Co. and triethanolamine was purchased from the Matheson Company whose compounds were distilled under vacuum prior to use.

Instrumentation.

The uv spectra were run on a Cary Model spectrophotometer, melting points were taken on a Fisher-Johns melting point apparatus and *p*H measurements were made using a Beckman Xeromatic *p*H meter. pK_a measurements were carried out in a constant temperature bath and temperature controlled by Haake-Buchler heating unit to within + 0.1°C.

pK_a Determinations.

a. Graphical Titration Method.

Sodium hydroxide was used as the titrant and was prepared according to the method of Kenner [13] and standardized against potassium biphthalate. Exactly 0.200-0.400 meq of each acid was dissolved in 60 ml of 50% w/w ethanol/water and titrated with standardized sodium hydroxide. Dry nitrogen gas was bubbled gently into the solution to prevent autooxidation of the acids and to aid in stirring. After each increment of base, an equal weight of absolute ethanol was added to maintain a 50% w/w ethanol/water solution. The Sargent's combination glass-calomel electrode was standardized before and after titration against a 5.40 *p*H buffer consisting of 0.1326 g of glacial acetic acid, 0.0906 g of sodium acetate and 0.0322 g of sodium chloride in 100 g of 52 wt % aqueous ethanol-water. Titrations were repeated if standardizations deviations were > 0.02 *p*H units.

b. Spectrophotometric Method.

The following 0.01 *M* buffer solutions with their effective *p*H range were used in this study: hydrochloric acid, *p*H > 3.2; formic acid, 3.2-4.4 *p*H; acetic acid, 4.2-5.4 *p*H; potassium dihydrogen phosphate, 6.5-7.7; tris(aminotrishydroxymethylmethane), 7.5-9.0; and potassium hydroxide > 9.0 were used. The uv scans from 340 to 218 nm were made on solutions of varying *p*Hs of each acid in order to obtain the absorbances of the ionized and molecular forms of the acids and the absorbances of solutions containing both forms. Approximate pK_as were then calculated from the equation:

$$pK_a = pH + \log (A_i - A)/(A\text{-}A_m)$$

where A_i is the absorbance of the ionized form, A_m is the absorbance of the molecular form and A is the absorbance of a solution of known *p*H containing both forms. Seven solutions of each acid ranging in *p*H from 0.7 units above and below the approximate pK_a value of the appropriate acid were prepared and the absorbance of the solutions were taken at wavelength of maximum absorption. The accurate pK_a was obtained by taking the average of the seven determinations. In all cases, the average deviation was no greater than + 0.03 *p*H units.

Synthesis of 5-Substituted Benzylbarbituric Acids, **3a-k**.

The preparation of 5-(*p*-nitrobenzyl)barbituric acid, **3e**, is given as a typical example. A mixture of 0.08 mole of barbituric acid, 0.04 mole (5.97 g) of triethanolamine, and 160 ml of water was stirred at room temperature until dissolved. Then, 0.04 mole (8.65 g) of *p*-nitrobenzyl bromide, **2e**, was added over a period fo 10 minutes and the mixture was stirred at room temperature for 3 days at which time the reaction mixture was acidified to *p*H 2 with hydrochloric acid and the precipitate removed by suction filtration. In order to separate *p*-nitrobenzylbarbituric acid, **3e**, from the 5,5-di-*p*-nitrobenzyl derivative, **4e**, the precipitate was treated with excess 10% sodium bicarbonate solution and filtered. The sodium bicarbonate insoluble compound, **4e**, was washed repeatedly with water until no precipitate was obtained upon acidification of the filtrate. Barbituric acid **3e** was precipitated upon acidification of the filtrate, and collected by suction filtration, dried and recrystallized from water-acetone to yield pure crystals, mp 265°.

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