First Thermodynamic Dissociation Constants of 5,5-Disubstituted Barbituric Acids in Water at 25 °C. Part 1. 5,5-Dialkyl-,5-Alkenyl-5-alkyl-, 5-Alkyl-5-aryl-, 5,5-Dialkenyl-, 5,5-Diaryl-, and 5,5-Dihalogeno-barbituric Acids

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First thermodynamic dissociation constants (K_1) [expressed as pK_1 values ($-\log K_1 = pK_1$)] have been determined for a series of 14 acids (Ia; R^1 = Me; R^2 = Me, Et, Pr^i, Ph; R^1 = Et; R^2 = Et, Pr^i, Ph, 3-NO_2.C_6H_4, 4-NO_2.C_6H_4; R^1 = allyl, R^2 = Pr^i; R^1 = R^2 = allyl, Ph, Br, Cl) with C(5)-substituents (R^1 and R^2) having widely differing polar (R^1 = R^2 = Me, Et, Ph, Br, or Cl) and steric (R^1 = R^2 = Me to R^1 = Et and R^2 = Pr^i) effects. Thermodynamic dissociation constants, expressed as pK_1 values, cover the range 8.51—5.55 for the derivatives studied. The R^1 = Me; R^2 = Me, Et, Pr^i or Ph derivatives are observed to be weaker acids than the corresponding series in which Me is replaced by Et, *i.e.* R^1 = Et; R^2 = Et, Pr^i or Ph. This reversal of the order of the acid strengths from the order anticipated for polar effects alone for C(5)-substituents is believed to be due to steric effects. The steric effects are acid strengthening.

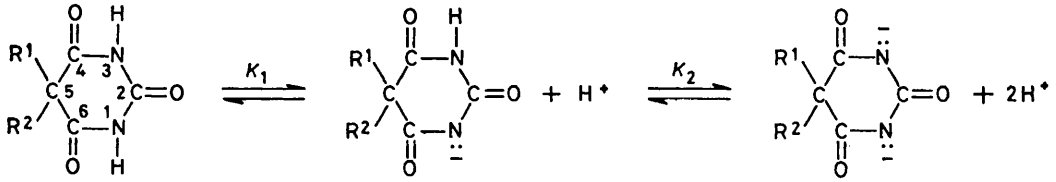
PREVIOUSLY reported pK_1 values [1-8] have covered a relatively narrow range of acid strengths (*ca.* pK_1 = 7.0 to 8.2) for 5,5-disubstituted barbituric acids. The present work endeavours to expand this range of acid strengths of derivatives and to provide pK_1 values which are accurate enough to allow effects of C(5)-substituents on acidity to be determined reliably. The present paper is concerned with the accuracy and precision of the pK_1 values determined. Structure–reactivity effects will be considered only briefly and qualitatively here, a quantitative treatment will follow in Part 2 and subsequent parts of this series.

Earlier measurements of conductance in aqueous solutions which have been made on some of the compounds [9,10] reported in this paper are not suitable for derivation of thermodynamic pK_1 values. The reasons for this will be given in the discussion to follow.

The original series of 15 derivatives contained 5,5-di-isopropylbarbituric acid, but the compound described as such was in fact found to be 4-isopropoxy-5-isopropyl-barbituric acid and it was dropped from the series to give 14 derivatives.†

First thermodynamic dissociation constants were measured by a refined potentiometric titration procedure where possible and, for derivatives which were not soluble enough for titration, by a spectrophotometric method.

5,5-Disubstituted barbituric acids (Ia) are weak dibasic acids [equation (1)‡] which owe their acidic character to dissociation of the protons bonded to the 1- and the 3-nitrogen atoms in imide (CONHCO) functions, in the heterocyclic nucleus. The two stages in the dissociation of these acids are well separated [3] with $\Delta pK = (pK_2 - pK_1) < 4$.§¶ Therefore, for practical purposes the first and second dissociation steps may be regarded as mutually exclusive, successive processes. In the neutralization of these acids with base in potentiometric titrations, the first dissociation constants may be reliably derived from calculations based on the behaviour of a weak monobasic acid. Care must be taken and the calculated pK_1 values should remain constant, as the second stage for dissociation is approached, near the first equivalence point in the neutralization reaction. In this region any interference due to overlap in dissoci-



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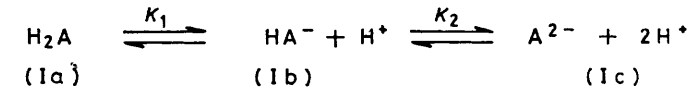

(Ia) (Ib) (Ic)

† Authentic 5,5-di-isopropylbarbituric acid has since been synthesized in the author's laboratory, by two methods, and the pK_1 value has been determined very recently.

‡ Additional canonical structures for (Ia), (Ib), and (Ic) have been omitted in this Part. Also, symmetry corrections for statistical effects arising from the equivalence of the imide functions in (Ia) have been deferred for the time being.

§ Spectrophotometrically determined pK_2 values in water at 25 °C, although not reported in detail in the present paper, have been shown in support of this in Table 5.

¶ pK_2 Values determined in water at 38 °C and ionic strength I = 0.1M,[11] although found under somewhat different conditions, from those given above,[3] also support this large difference, ΔpK, between first and second dissociation constants.

ation steps, if it is significant, will become apparent by lack of constancy in the pK_1 values calculated, relative to those found in the buffer region, $pH = pK_1 \pm 1$, for the weak acid. Errors in the method also become more significant in this region of the titration. 5,5-Disubstituted barbituric acids are too weak, as acids, for the second thermodynamic dissociation constants to be determined satisfactorily by potentiometric titration and the spectrophotometric method was always employed.

In the spectrophotometric determination of pK_1 values, where compounds were too insoluble for potentiometric titration, a buffer solution of suitable pH was used to obtain the maximum concentration of the univalent anion (Ib). Also, for the same molar concentration of barbituric acid derivative, a solution with pH (0.1M-HCl) which will give the undissociated molecule only, and a further buffer solution, intermediate in pH, which allows both the undissociated molecule (Ia) and the univalent anion (Ib) to be present simultaneously, are necessary. The optical absorbance (D) of each of these solutions is measured at a suitable fixed wavelength. For the buffer solution containing both the undissociated molecule and the univalent anion, the ionic strength, I, must also be known for the calculation of thermodynamic pK_1 values. The spectrophotometric procedure follows that used by Biggs,[2] except that in the present work the pH value of the intermediate buffer was measured with a pH-meter, and a later modification of the Davies equation [12] was used in estimating activity coefficients.

Benzoic acid and 5,5-diethylbarbituric acid were used as reference substances in testing the potentiometric titration procedure for pK_1 determinations and the pK_1 value for 5-ethyl-5-phenylbarbituric acid was determined by both the potentiometric titration and the spectrophotometric procedure.

EXPERIMENTAL

I.r. spectra were recorded for solids in Nujol and hexachlorobutadiene mulls, or potassium chloride and potassium bromide discs, and for liquids as films between sodium chloride windows, on Perkin-Elmer 421, Perkin-Elmer 021, and Unicam SP200G (grating) spectrometers. N.m.r. spectra were recorded on Varian H.A. 60 and Varian H.A. 100 spectrometers with tetramethylsilane (TMS) as the internal standard in all deuteriated solvents used. These were deuteriochloroform ($CDCl_3$), deuteriodimethyl sulphoxide [$(CD_3)_2SO$], and deuteriopyridine (C_5D_5N). Mass spectra were obtained on AEI MS9 mass spectrometers. Melting points were determined with an Electrothermal melting-point apparatus 1A 6304 Mark II.

Thin Layer Chromatography.—Final products obtained for all 5,5-disubstituted barbituric acids synthesized or obtained from various sources were examined for impurities by t.l.c. Activated silica gel G (Merck) was used as the support, on glass plates. Two distinct developing solvent systems, one more suitable for 5,5-disubstituted and the other for 5-monosubstituted barbituric acid derivatives, were used for each compound examined. Two visualizing sprays were employed; one specific for imides and the other a general oxidizing agent for detecting non-barbituric acid organic impurities.

Materials and Solvents.—All esters were redistilled and dried ($MgSO_4$) before use and alkyl halides were dried over the same reagent. Ethanol employed as a solvent in reactions and in the preparation of sodium ethoxide was 'super-dry'.[13a] Urea was dried at 60 °C (4 h) [13b] and stored in a desiccator over silica gel.

Substituted Diethyl Malonates.—All these ester intermediates were prepared by alkylation of diethyl malonate with alkyl iodides in the presence of sodium ethoxide. Details are given in Tables 1 and 2.

Diethyl Dimethylmalonate (II).[14]—Methyl iodide–diethyl malonate–sodium ethoxide (300 ml ethanol), 1.0 : 0.5 : 1.09 molar; reflux time: until neutral to litmus.

Diethyl Ethylmethylmalonate (III).[15]—Ethyl iodide–diethyl methylmalonate (Fluka)–sodium ethoxide (600 ml ethanol), 1.92 : 1.38 : 1.39 molar; reflux time as for (II).

Diethyl Isopropylmalonate (IV).—Isopropyl iodide–diethyl malonate–sodium ethoxide (1 200 ml ethanol), 2.0 : 2.0 : 2.0 molar; reflux time as for (II).

Barbituric Acid Syntheses.—5,5-Dimethyl- (Ia; $R^1 = R^2 = Me$), 5-ethyl-5-methyl- (Ia; $R^1 = Me$, $R^2 = Et$), and 5-isopropyl-barbituric acid (Ia; $R^1 = H$, $R^2 = Pr^i$) were prepared by condensation of the corresponding ester intermediates, (II), (III), and (IV) respectively, with urea in the presence of sodium ethoxide solution.[14] The barbituric acid derivative formed in this reaction appears as the ethanol-insoluble sodium salt. The sodium salt may be filtered off and the free acid isolated from it by acidifying the salt with hydrochloric acid. Where the barbituric acid derivative is very unstable in bases, *e.g.* (Ia; $R^1 = R^2 = Me$), the free acid is best isolated by adding the salt to an ice-cold solution of hydrochloric acid. Otherwise the free acid may be isolated from an ice-cold aqueous solution of the sodium salt by addition of hydrochloric acid. The free acid is washed with small portions of water until free of chloride, dried in a desiccator over silica gel, and finally recrystallized to constant m.p. from a suitable solvent.

5,5-Dimethylbarbituric Acid (V).[14]—[Ester (II)–urea–sodium ethoxide (300 ml ethanol)] 0.32 : 0.32 : 0.67 molar; reflux time 5.5 h; recrystallized from water.

5-Ethyl-5-methylbarbituric Acid (VI).[14]—[Ester (III)–urea–sodium ethoxide (270 ml ethanol)] 0.21 : 0.30 : 0.63 molar; reflux time 5.5 h; recrystallized from water.

5-Isopropylbarbituric Acid (VII).[14]—[Ester (IV)–urea–sodium ethoxide (1 l ethanol)] 1.00 : 1.42 : 3.13 molar; reflux time 4 h; recrystallized from ethanol.

5-Isopropyl-5-methylbarbituric Acid (VIII).[16,*]—[Methyl iodide–5-isopropylbarbituric acid–sodium hydroxide [76 g of a 6.7% (w/w) aqueous solution] 0.13 : 0.13 : 0.13 molar; reaction time 24 h at 40 °C with vigorous stirring. The barbituric acid derivatives were precipitated from the cold reaction mixture by acidification with dilute hydrochloric acid, and were filtered off, and washed free of chloride. The dry crude product (15.6 g) melted over a wide range (168—192 °C) and was shown by t.l.c. to contain much (VII). The acidic filtrate was shaken five times with ether and the combined ethereal extracts, after being washed with a small volume of water, were evaporated to give a small amount of residue, m.p. 130—160 °C. This residue (C) contained (VII) (t.l.c.) but the n.m.r. spectrum showed it was substantially (VIII). On recrystallization of (C) twice

* This method of synthesis gave a poor result in the author's hands. The derivative (VIII) has since been prepared without difficulty by the ester intermediate route (diethyl isopropylmethylmalonate) in good yield.[17]

TABLE 1

Compound	Found B.p./mmHg	Found η_D^t	Found M.p. (°C)	Lit. B.p./mmHg	Lit. η_D^t	Lit. M.p. (°C)	Yield (%)	Formula	Found (%) C	H	N	O	Halogen	Required (%) C	H	N	O	Halogen	*m/e*	$\nu_{max.}$/cm^{-1}
(II)	83—84/17	1.4260 [a]			1.425 28 [a,*]		71	$C_9H_{16}O_4$	57.1	8.6				57.4	8.6					2 990, 2 940sh, 2 900sh, 2 870sh, (alkyl), 1 758, 1 730sh, 1 710sh (CO)
(III)	98—101/20	1.4195 [a]			1.418 96 [b,†]		45	$C_{10}H_{18}O_4$	59.2	8.9				59.4	9.0					2 980, 2 940, 2 900, 2 880 (alkyl), 1 750, 1 730, 1 727sh, 1 717sh (CO)
(IV)	120—122/22						65	$C_{10}H_{18}O_4$	59.7	8.9				59.4	9.0					2 975, 2 935, 2 900, 2 875 (alkyl), 1 750, 1 734, 1 715sh (CO)
(V)			273—274			279 [14] 278 [‡]	46	$C_6H_6N_2O_3$	46.1	5.2	17.9			46.2	5.2	17.9			156 (M^+)	3 200, 3 070 (NH), 2 860 (alkyl), 1 750, 1 726, 1 690 (CO)
(VI)			210—212			212 [14]	28	$C_7H_{10}N_2O_3$	49.2	5.9	16.6			49.4	5.9	16.5				3 210, 3 100 (NH), 2 990sh, 2 940sh, 2 860 (alkyl), 1 742, 1 700sh, 1 682 (CO)
(VII)			216—218			216 [14]	85	$C_7H_{10}N_2O_3$	49.7	6.0	16.6	28.2		49.4	5.9	16.5	28.2		170 (M^+), 128 [M — (CH_3–CH=CH_2)]	3 210, 3 090 (NH), 2 990vw, 2 960, 2 930vw, 2 880, 2 810vw (alkyl), 1 737, 1 705, 1 692 (CO)
(VIII)			186—188			186—187 [16]	6.7	$C_8H_{12}N_2O_3$	52.1	6.5	15.2			52.2	6.6	15.2			142 [M — (CH_3–CH=CH_2)]	3 220, 3 110sh (NH), 2 975sh, 2 955sh, 2 870sh (alkyl), 1767sh 1 750, 1 720, 1 690sh (CO)
(IX)			283.5—285 [c] 286—288 [d]			283—284 [c,19]	95	$C_{12}H_{11}N_3O_5$	51.8	4.0	15.2			52.0	4.0	15.2				3 220m, 3 175m, 3 095s (NH), 2 975vw, 2 960vw, 2 880m (alkyl), 1 760, 1 718, 1 680, 1 650sh (CO), 1 528, 1 353 (nitro)
(X)			212—216 [c]			216—217 [19]	0.57	$C_{12}H_{11}N_3O_5$	52.1	4.1	15.3			52.0	4.0	15.2				3 210, 3 090 (NH), 2 875 (alkyl), 1 760, 1 735, 1 710, 1 690, 1 677sh (CO), 1 535sh, 1 525, 1 350 (nitro)
(XI)			286—288			290—292 [20]	8.8	$C_{16}H_{12}N_2O_3$	68.8	4.3	9.8			68.5	4.3	10.0			280 (M^+)	3 240, 3 170sh, 3 120sh, 3 070sh (NH), 2 830vw (alkyl), 1 765, 1 735, 1 693sh, 1 675, 1 660sh (CO)
(XII)			234—236			235—237 [21]	48	$C_4H_2Br_2N_2O_3$	16.7	0.77	9.8		55.6 [d]	16.8	0.71	9.8		55.9 [d]	284 (M^+), 286 (M^+ + 2) 288 (M^+ + 4) (1.13 : 2 : 0.91) [d,f]	3 310vw, 3 200, 3 080 (NH), 2 870 (NH),[g] 1 760sh, 1 750sh, 1 733, 1 708, 1 695 (CO)
(XIII)			215—217			209—211 [22] 219—220 [§]	56	$C_4H_2Cl_2N_2O_3$	24.3	1.2	14.2		36.2 [e]	24.4	1.0	14.2		36.0 [e]	196 (M^+), 198 (M^+ + 2), 200 (M^+ + 4) (9 : 6 : 1) [e,f]	3 290vw, 3 200, 3 100 (NH), 2 950sh, 2 870 (NH),[g] 1 770sh, 1 755sh, 1 735, 1 720, 1 695, 1 685sh (CO)
(XIV)			191—193			188—192 [¶] 188—190 [**]															
(XV)			140—141.5			200—203 [**] 197—198 [††]															
(XVI)			140—141.5			137—138 [16]															
(XVII)			171—172			171—173 [‡‡]															
(XVIII)			226—228			226 [§§]															
(XIX)			176.5—177.5			174—178 [¶¶]															

(II) *a*, t = 24.5 °C. (III) *a*, t = 18 °C; *b*, 18.2 °C. (IX) *c*, recrystallized from ethanol (95%); *d*, recrystallized from acetone. (X) *c*, recrystallized from ethanol (95%). (XII) *d*, $C_4H_2Br_2N_2O_3$ requires 284, 286, 288 (1 : 2 : 1). (XIII) *e*, $C_4H_2Cl_2N_2O_3$ requires 196, 198, 200 (9 : 6 : 1). (XII) and (XIII) *f*. The intensity ratios and pattern for the molecular ion clusters *m/e* values persisted through the loss of two HCNO groups in fragmentations. (XII) and (XIII) *g*, The band near 2 800 cm^{-1} in spectra, commonly assigned to alkyl functions in barbituric acid derivatives, is an intense band in these structures. Deuteriation of the NH does not completely remove this band in spectra. Therefore, alkyl assignments for this band (*ca.* 2 880 cm^{-1}) in other derivatives are tentative and most likely of different origin.

* I. M. Heilbron and H. M. Bunbury, ' Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1943, vol. 1, p. 930. † See footnote *, vol. 2, p. 698. ‡ R. E. Stuckey, *Quart. J. Pharm. Pharmacol.*, 1942, **15**, 377. § H. Biltz and T. Hamberger, *Ber.*, 1916, **49**, 635; A. K. Macbeth, T. H. Nunan, and D. Trail, *J. Chem. Soc.*, 1926, 1248. ¶ ' The Merck Index,' P. G. Stecher (ed.), Merck and Co., Rahway, 1968, p. 119. ** C. P. Stewart and A. Stolman, ' Toxicology,' Academic Press, New York, 1960 and 1961, vol. 2, p. 163. †† See footnote ¶, p. 865. ‡‡ See footnote ¶, p. 33. §§ See footnote ¶, p. 818. ¶¶ See footnote ¶, p. 809.

from ethanol a product (300 mg), m.p. 190—192 °C [lit.,[16] m.p. 186—187 °C for (VIII)], free from (VII) by t.l.c., with the required structure (VIII) (Tables 1 and 2) was obtained. This sample was used as a reference in the separation of (VIII) from the residue in the above filtration, and for the physical measurements described in this paper. The crude residue after two recrystallizations from ethanol had m.p. 212—215 °C and it was found, by t.l.c. and n.m.r.

TABLE 2

^{1}H N.m.r. data

Cmpd.	Solvent	δ (Chemical shift downfield from Me_4Si)
(II)	$CDCl_3$	4.18 (4 H, q, *J* 6—7 Hz, CH_3–CH_2), 1.41 [6 H, s, $(CH_3)_2C$], 1.24 (6 H, t, *J* 6—7 Hz, CH_3–CH_2)
(III)	$CDCl_3$	4.17 (4 H, q, *J* 7 Hz, CH_3–CH_2–O), 1.90 (2 H, q, *J* 7 Hz, CH_3–CH_2–C), 1.37 (3 H, s, CH_3–C), 1.22 (6 H, t, *J* 7—8 Hz, CH_3–CH_2–O), 0.87 (3 H, t, *J* 5—7 Hz, CH_3–CH_2–C)
(IV)	$CDCl_3$	4.18 (4 H, q, *J* 7 Hz, CH_3–CH_2–O), 3.09 [1 H, d, *J* 8 Hz, $(CH_3)_2CH$–CH], *ca.* 2.38 [1 H, o, *J* 7 Hz, $(CH_3)_2CH$–CH)], 1.25 (6 H, t, *J* 6—7 Hz, CH_3–CH_2–O), 0.99 [6 H, d, *J* 8 Hz, $(CH_3)_2CH$]
(V)	$(CD_3)_2SO$	10.99 (2 H, s, NH, D_2O exchanged), 1.38 [6 H, s, $(CH_3)_2C$]
(VI)	$(CD_3)_2SO$	11.08 (2 H, s, NH, D_2O exchanged), 1.84 (2 H, q, *J* 7—7.5 Hz, CH_3–CH_2–C), 1.37 (3 H, s, 5-Me), 0.79 (3 H, t, *J* 7—7.5 Hz, CH_3–CH_2–C)
(VII)	$(CD_3)_2SO$	11.20 (2 H, s, NH, D_2O exchanged), 3.20 (H, d, *J* 3.5 Hz, 5-H, D_2O exchanged), 2.20 [H, o, *J* 4 Hz, $(CH_3)_2CH$], 1.00 [6 H, d, *J* 6.5 Hz, $(CH_3)_2CH$]
(VIII)	$(CD_3)_2SO$	11.30 (2 H, s, NH, D_2O exchanged), 2.05 [H, sept., *J* 6.5 Hz, $(CH_3)_2CH$], 1.29 (3 H, s, 5-Me), 0.90 [6 H, d, *J* 6 Hz, $(CH_3)_2CH$]
(IX)	C_5D_5N	7.73 (4 H, m, Ar), 2.65 (2 H, q, *J* 7 Hz, CH_3–CH_2), 1.08 (3 H, t, *J* 7 Hz, CH_3–CH_2)
(X)	C_5D_5N	7.96 (4 H, m, Ar), 2.64 (2 H, q, *J* 7 Hz, CH_3–CH_2), 1.08 (3 H, t, *J* 7 Hz, CH_3–CH_2)
(XI)	$(CD_3)_2SO$	11.7 (2 H, s, NH, D_2O exchanged), 7.30 (10 H, s, Ar)

spectroscopy, that recrystallization was concentrating (VII). This crude product, after recrystallization, was divided into two parts: (A) the residue from the recrystallizations, and (B) the solid recovered from the filtrates from (A). These solids (A) and (B) were then treated with portions of ether. Each portion of ether was evaporated and the residue further recrystallized from ethanol. In this way a further 1.3 g of (VIII) (Tables 1 and 2) was recovered.

5-Ethyl-5-(3-nitrophenyl)- (IX) *and 5-Ethyl-5-(4-nitrophenyl)-barbituric Acid* (X).[18,19]—These isomeric nitro-derivatives of 5-ethyl-5-phenylbarbituric acid (XIX) are formed in the nitration of the parent compound (XIX),[18] with the 3-nitro-derivative (IX) predominant. A smaller amount of the 4-nitro-derivative (X) is also formed and is recovered by partial neutralization [19] (3/4) of the residue recovered by evaporation of the mother-liquors from recrystallization of (IX).[18]

Procedure.—Compound (XIX) (0.22 mol) was dissolved with stirring in concentrated sulphuric acid (200 ml) cooled in ice–salt. The nitrating mixture [11 ml fuming nitric acid (*d* 1.50) in concentrated sulphuric acid (50 ml)] was added dropwise to the rapidly stirred mixture the temperature being kept between −10 and 3 °C; stirring was continued for a further hour. The reaction mixture was then added to ice–water (3 l) and filtered when cold. The precipitated crude product, washed free of mineral acids, was dried *in vacuo* (silica gel). Recrystallization of the crude product from ethanol (25 g required 2 l of solvent) (four times, to constant m.p.) gave a product (IX) (Table 1), m.p. 283.5—285 °C. Two recrystallizations of the crude product from acetone * (25 g in 2 l of solvent) gave a product (IX) (Table 1) with constant m.p., 286—288 °C.

Filtrates from recrystallizations of the crude product, in obtaining (IX), were combined and the solvent was evaporated. The residue obtained (5 g) was dissolved in a minimum amount of sodium hydroxide solution (23.5 ml of 1M). Hydrochloric acid (17.6 ml of 1M) was slowly added to the solution with rapid stirring. The precipitate formed was filtered off, washed free of chloride, and dried *in vacuo* (silica gel) before being recrystallized from 95% ethanol. After three recrystallizations the 4-nitro-compound (X) (150 mg) (Table 1) was obtained.

5,5-Diphenylbarbituric Acid (XI).[20]—This derivative was prepared by arylation of alloxan monohydrate (5,5-dihydroxybarbituric acid), in fuming sulphuric acid, with benzene. The reaction mixture is fairly viscous and the stirrer was fitted with a large semi-circular Teflon blade. Finely powdered alloxan monohydrate (50 g, 0.31 mol) was added in small portions to ice-cold fuming sulphuric acid (20% w/w SO_3) (110 g) with constant stirring. The ice-bath was then replaced by an oil-bath. Benzene (150 ml, 1.69 mol) was added through the condenser to the stirred reaction mixture, the temperature of which did not exceed 60 °C during the addition, and when all of it had been added the oil-bath temperature was raised and maintained in the range 75—80 °C for 3 h. The unchanged benzene was decanted from the cooled product and the reaction mixture was poured into crushed ice. The light brown solid which separated was filtered off (No. 541 Whatman filter paper), and then washed twice by stirring it into 500-ml portions of water. The dried final residue weighed 41 g (0.15 mol) (47%), m.p. 277—283 °C. A portion (2.13 g) of this product was then sublimed at 230 °C/4 mmHg, and although a non-volatile residue remained, the off-white crystalline sublimate, m.p. 263—282 °C, did not give a single spot by t.l.c. Further purification was achieved by dissolving the solid in the minimum amount of 6% (w/v) sodium hydroxide solution, filtering the solution, and then diluting it to 800 ml with water before reprecipitating the free acid with carbon dioxide. The acid was filtered off, the process was repeated, and the precipitated acid (XI) (Table 1) was finally recrystallized twice from glacial acetic acid and dried *in vacuo* at 40 °C (KOH).

5,5-Dihalogenobarbituric Acid Derivatives.—5,5-Dibromo- (XII) [21] and 5,5-dichloro-barbituric acid (XIII) [22] were prepared by direct halogenation of barbituric acid (Ia; $R^1 = R^2 = H$) in aqueous solution as previously described; [21,22] both were recrystallized from water (Table 1).

5,5-Diethylbarbituric Acid (XIV).—A commercial grade (B.D.H.) was recrystallized, from ethanol.

5-Ethyl-5-isopropylbarbituric Acid (XV)—A sample of the compound (XV), donated by E. R. Squibb & Sons, Inc., was recrystallized from ethanol.

5-Allyl-5-isopropylbarbituric Acid (XVI).—A sample of compound (XVI), donated by Sandoz Ltd., was recrystallized from ethanol–water (2 : 3).

5,5-Diallylbarbituric Acid (XVII).—Tablets containing (XVII) as the only drug substance, were treated with dry

* Acetone is to be recommended over ethanol in the author's experience.

ether in a Soxhlet apparatus. The extract, on removal of ether, gave a solid, which on recrystallization from ethanol–water (1 : 1) gave (XVII) as glistening plates.

5-Methyl-5-phenylbarbituric Acid (XVIII).—A sample of compound (XVIII), donated by May & Baker Ltd., was recrystallized from ethanol–water (1 : 4).

5-Ethyl-5-phenylbarbituric Acid (XIX).—A sample (XIX), donated by Kempthorne Prosser & Co. Ltd., Dunedin, New Zealand, was recrystallized from ethanol–water (1 : 4).

Benzoic Acid.—Benzoic acid B.D.H. (certified by the National Physical Laboratory) for use as a thermochemical standard [23] was used. It was prepared from AnalaR material by a slow fractional freezing method of purification.[24]

Physical Measurements.—Temperatures were recorded with a calibrated (±0.02 °C) −5 to 50 °C mercury-in-glass solid-stem thermometer graduated to 0.1 °C which could be read to within 0.02 of a 0.1 °C scale division under magnification. Corrections for partial immersion of the thermometer at temperatures near 25 °C were unnecessary. Boiled-out distilled water protected from carbon dioxide was always used. Calibrated volumetric flasks and pipettes were used as were a 50-ml burette (0.1-ml graduations) and a 5-ml burette (0.02-ml graduations). Carbonate-free potassium hydroxide solution was used in titrations,[25] and was standardized against AnalaR potassium hydrogen phthalate with phenolphthalein as indicator. In replicated titrations end-points were obtained for matched colours. The potassium hydroxide solution was restandardized on completion of the work and no significant change in molarity was found. Sodium hydroxide solutions were standardized by the same procedure. Hydrochloric acid solutions were standardized against AnalaR disodium tetraborate (borax) by using Methyl Red as indicator. Buffer solutions were prepared by weighing analytical grades of the recommended commercial salts, where possible, and the pH values of the final solutions were determined relative to the pH standards,[26,27] 0.05M-potassium hydrogen phthalate and 0.05M-borax, employed in standardizing the pH-meter at 25.00 ± 0.02 °C.

pH *Value Determinations.*—pH Values were determined with a Beckman Research pH-meter fitted with glass (G.P.) and saturated calomel (Fibre Junction Reference Electrode) electrodes. On stabilization of the instrument and after calibration (standard cell 1 019.25 mV at 25 °C), a 0.05M-solution of potassium hydrogen phthalate maintained at 25.00 ± 0.02 °C under an atmosphere of nitrogen was used to set the pH-meter to a pH value of 4.005. The phthalate solution was then replaced by a 0.05M-borax solution, under the same conditions, and provided the pH value found for this solution differed not more than ±0.01 pH units from pH = 9.185, the pH-meter and electrodes [28] were considered ready for further pH measurements on solutions. Where sodium ion concentrations in solutions were significant, pH values were corrected for sodium ion errors * arising at the glass electrode, from a nomograph provided by the manufacturers (Beckman).

Potentiometric Titrations.—The titrations were carried out in a 120-ml water-jacketted cell maintained at 25.00 ± 0.02 °C. A known volume of water, pre-equilibrated at 25.00 ± 0.02 °C, was added to the cell from a calibrated pipette. The barbituric acid derivative, accurately weighed, was added and dissolved with stirring. When dissolution was complete, glass and calomel electrodes, a calibrated thermometer, and the semimicro-burette containing the standard potassium hydroxide solution were inserted through a plastic cap covering the thermostatted cell. The cell contents were maintained under an atmosphere of nitrogen during all operations. pH Values found after each addition of base were rechecked at 5-min intervals until no change was evident between successive measurements.

Experimental quantities used in the terms described for calculations are defined as in relation (2) where N denotes

$$[K^+] = \frac{NV_t}{(V_o + V_t)} \quad (2)$$

the normality of the standard potassium hydroxide solution, V_o the initial volume of the solution containing the barbituric acid derivative and V_t the volume of added potassium hydroxide solution at any point in the titration. The solutions have been assumed ideal in that volumes have been taken as additive. In equation (3) V_o and V_t have the

$$[Y] = \frac{M_oV_o}{(V_o + V_o)} \quad (3)$$

same significance as in equation (2) and M_o is the initial molarity of the barbituric acid solution.

Spectrophotometric Determinations.—Preliminary spectra were obtained with an SP800 Unicam recording spectrophotometer and precise absorbance measurements were obtained with a Hilger Uvispek H700 spectrophotometer. Both instruments were fitted with jacketted cell-assembly blocks for temperature control by water circulation from a constant-temperature bath (Haake). The cuvettes were maintained at 25.00 ± 0.02 °C and matched silica cuvettes were employed. For spectra of barbituric acid derivatives with maximum concentrations of the univalent anions, a borax–sodium hydroxide buffer [29] for pH values between 9 and 11 was employed. Absorbance was plotted against buffer composition between pH 9 and 11 to obtain maxima corresponding to the maximum concentrations of the univalent anions in these solutions. These plots were broad and flat with relatively wide ranges for which absorbances remained constant within the limits of error in measurement. The borax–sodium hydroxide buffer [29] (pH 10.4) was used for the determination of D_1 values in the spectrophotometric pK_1 measurements [equation (13)]. D_0 Values were determined in 0.1M-hydrochloric acid and D values, at intermediate pH, in buffer solutions which each contained sodium dihydrogen phosphate, disodium hydrogen phosphate, and sodium chloride in the molar ratios (1 : 1.529 : 1) at dilutions corresponding to 0.01, 0.005, 0.0025, and 0.001 25M with respect to sodium dihydrogen phosphate. Ionic strengths for these solutions were calculated, at each dilution, and employed in estimating activity coefficients from the Davies equation [12] in calculating pK_1 values.

DISCUSSION

In attempting to obtain thermodynamic pK_1 values by the methods described procedures can be designed and results refined so as to approach an ideal. If pH is defined according to the British Standard [30,31], pH = $-\log\{[H^+]f_\pm\} \pm 0.02$, in the range pH 2—12, for aqueous solutions with ionic strength, $I \leqslant 0.1$M. Also,

* Sodium-ion error corrections were not necessary for any of the pK_1 values reported in this paper. However they will be considered further in reporting details for the determination of pK_2 values.

for $I \leqslant 0.1$, log $f_{\pm}$ for 1 : 1-electrolytes may be represented by the Debye–Hückel equation or a suitable modification of it [12,32,33] to an accuracy of at least ± 0.02 or better for lower ionic strengths. Therefore, for the conditions stipulated and within the limits of accuracy given, a suitable estimate of the mean activity coefficient, $f_{\pm}$, may be used to convert $\{[H^+]\ f_{\pm}\}$ into $[H^+]$. Also, from the ionic product for water, equation (10), $\{[OH^-]\ f_{\pm}\}$ may be calculated from the measured pH value and converted into $[OH^-]$ in the same way. In deriving thermodynamic pK_1 values in equation (6), the mean activity coefficient ($f_{\pm}$), is similarly estimated, *e.g.* equation (7). The mean activity coefficient ($f_{\pm}$) is defined by the geometrical mean of the activity co-efficients of the separate species, *i.e.* $f_{\pm} = (f_{H^+} \cdot f_{HA^-})^{\frac{1}{2}}$, for reaction (4). These relationships provide the basis for the derived thermodynamic pK_1 values in the present paper.

A further limitation on the significance of pH for the cell, glass electrode || saturated calomel electrode, used for pH measurements is a residual liquid-junction potential which contributes to the overall e.m.f. There is no simple or satisfactory way of allowing for this liquid-junction potential, caused by the use of the calomel reference electrode, and its uncertain contribution to the measured pH value. However, although the effect will be inherent in all pK_1 values determined in the present work, the magnitude of errors due to this factor is not great.[30,34–36] In the pH range 3—9 the uncertainty in the meaning of measured pH values, due to liquid-junction potential errors, is believed to remain within 0.01 unit. Outside this pH interval the magnitude of the errors may increase to as much as 0.05 unit. Also at high ionic strengths liquid-junction potentials may become considerable and the possible error in applying the interpretation of the British Standard is of the same order of magnitude as that for the uncertainty in the value of the mean activity coefficient of a typical 1 : 1 electrolyte in a solution of high ionic strength.

The rationale in the present work has been to accept the above imposed limitations in theoretical calculations and then to compare the results obtained for pK values with those reported in fundamental pK studies capable of achieving or being close to the ultimate precision for the method. This comparison was taken as a check on the overall procedure employed. Benzoic and 5,5-diethylbarbituric acids were selected as the reference substances for comparison of pK values with those obtained in the present work (Table 5).

Activity Coefficients.—Of the various modifications of the Debye–Hückel expression,[37] a parameter-free equation capable of providing accurate estimates of activity coefficients for 1 : 1 electrolytes at ionic strengths up to $I = 0.1$ was needed for the iterative calculations involved in refining the potentiometric titration results. An equation due to Güntelberg [37] was initially employed * for this purpose in refining the potentiometric titration data. However, an earlier modification of the Davies equation [38] had been used in a previous spectrophotometric study of barbituric acid pK_1 values.[2] It was, therefore, decided to adopt the presently accepted form of the Davies equation [12] in all calculations for pK_1 values by both methods used for their determination. This served to provide for a consistent comparison between pK_1 values obtained by the two methods and gave a more accurate estimate of activity coefficients than the Güntelberg equation, when judged from the differences between measured values for a typical 1 : 1 electrolyte (NaCl) and the values calculated from each equation.[12,39]

pK_1 *Equations.*—It is from the dissociation reaction

Dissociation

$$\underset{(1-\alpha)c}{H_2A} \rightleftharpoons \underset{\alpha c}{H^+} + \underset{\alpha c}{HA^-} \qquad (4)$$

Neutralization

$$KOH + H_2A \rightleftharpoons K^+ + HA^- + H_2O \qquad (5)$$

(4) and equation (7), for $-\log f_{\pm}$, that equation (6) is arrived at, and from it pK_1 values are derived for the potentiometric and spectrophotometric procedures.

$$pK_1 = pH - \log \frac{[HA^-]}{[H_2A]} + 0.5 \left\{ \frac{I^{\frac{1}{2}}}{1 + I^{\frac{1}{2}}} - 0.3I \right\} \qquad (6)$$

In equation (6) the activity coefficient of the undissociated species $f_{H_2A} = f \sim 1$ for $I \leqslant 0.1$M. The mean activity coefficient ($f_{\pm}$) is given by the Davies equation,[12] equation (7).

$$-\log f_{\pm} = 0.5\ |z_+ z_-| \left\{ \frac{I^{1/2}}{1 + I^{1/2}} - 0.3I \right\} \qquad (7)$$

The ionic strength (I) is given by $I = \frac{1}{2} \sum_{i=1}^{S} c_i Z_i^2$ where c_i is the molar concentration of the ionic species i and Z_i the associated charge.

Potentiometric Titration Equation.—Equation (8) is

$$pK_1 = pH - \log \left\{ \frac{[K^+] + [H^+] - [OH^-]}{[Y] - [K^+] - [H^+] + [OH^-]} \right\} + 0.5 \left\{ \frac{I^{\frac{1}{2}}}{1 + I^{\frac{1}{2}}} - 0.3I \right\} \qquad (8)$$

derived from equation (6) where $[HA^-]$ and $[H_2A]$ are obtained from the condition of electroneutrality ($\sum_{i=1}^{S} c_i Z_i = 0$) ($[HA^-] = [K^+] + [H^+] - [OH^-]$) and the mass balance equation ($[Y] = [H_2A] + [HA^-] = c$) respectively. [Y] is the total concentration of the acid species expressed as the sum of the concentrations of all species of the acid, *viz.* the undissociated molecule $[H_2A]$ and the univalent anion $[HA^-]$ as applied to reaction (4). The ionic strength is given by equation (9) and is estimated by successive approximations.

$$I = [K^+] + [H^+] \qquad (9)$$

Since activities for hydrogen and hydroxy ions are related through the *ionic product for water*, equation

* The Güntelberg equation has been retained in the computer program and a set of pK_1 values are also provided. Use of this equation will be central to pK_1 value determinations in a later part of this series.

(10) $\{[OH^-]f_{\pm}\}$ may be calculated from the observed pH value. $[K^+]$ is known from the amount of KOH

$$K_w = [H^+][OH^-]f_{H^+} \cdot f_{OH^-} = [H^+][OH^-]f_{\pm}^2 \quad (10)$$

added in the titration, pH is measured, but the concentration terms $[H^+]$, $[OH^-]$ and ionic strength (I) have to be estimated by successive approximations. As a first approximation $[H^+]$ is replaced by $\{[H^+]f_{\pm}\}$ in equation (9) to obtain I_1, and $f_{\pm(1)}$ may then be estimated from equation (7). First approximations $[H^+]_{(1)}$ and $[OH^-]_{(1)}$ may then be obtained:

$$[H^+]_{(1)} = \frac{\{[H^+]f_{\pm}\}}{f_{\pm(1)}} \quad (11)$$

and

$$[OH^-]_{(1)} = \frac{K_w}{\{[H^+]f_{\pm}\}} \cdot f_{\pm(1)} \quad (12)$$

By repetitive approximations $f_{\pm(1)}$ was found to assume a constant value quickly and in no instance was it necessary to recycle through more than three approximations for convergence within strict limits with the final cycle merely confirming that the preceding approximation had reached this limit. The calculations have been programmed for computer calculation. Equation (8) is exact for the entire titration of a weak monobasic acid within the limits of the non-thermodynamic assumptions made in its derivation and provided $\{[Y] - [K^+] - [H^+] + [OH^+]\} > 0$.

Spectrophotometric Equation.—For the dissociation reaction (4) the thermodynamic dissociation constant, K_1, expressed as pK_1, is obtained as shown in equation (13) [which is equivalent with equation (6)].

TABLE 3

pK_1 Values for 5,5-disubstituted barbituric acids found by potentiometric titration at 25 °C

(Ia)	R¹	R²	pK_1 (mean value)	Set number	Range of pK_1 in set	Titration
(V)	Me	Me	8.51	39	8.53—8.48	1
	Me	Me	8.52	23	8.53—8.50	2
	Me	Me	8.51	62	8.53—8.48	(1 + 2)
(VI)	Me	Et	8.28	23	8.29—8.26	1
	Me	Et	8.28	24	8.29—8.26	2
	Me	Et	8.28	47	8.29—8.26	(1 + 2)
(VIII)	Me	Pr^i	8.45	19	8.45—8.44	1
	Me	Pr^i	8.45	16	8.46—8.44	2
	Me	Pr^i	8.45	35	8.46—8.44	(1 + 2)
(XVIII)	Me	Ph	7.78	12	7.79—7.77	1
	Me	Ph	7.78	14	7.79—7.77	2
	Me	Ph	7.78	26	7.79—7.77	(1 + 2)
(XIV)	Et	Et	7.99	13	8.00—7.98	1
	Et	Et	7.97	10	7.98—7.96	2
	Et	Et	7.98	13	8.00—7.97	3
	Et	Et	7.98	36	8.00—7.96	(1 + 2 + 3)
	Et	Et	7.99	32	8.00—7.97	Final check titration
(XV)	Et	Pr^i	8.15	11	8.15—8.14	1
	Et	Pr^i	8.14	16	8.14—8.13	2
	Et	Pr^i	8.14	27	8.15—8.13	(1 + 2)
(XIX)	Et	Ph	7.48	13	7.50—7.47	1
	Et	Ph	7.47	14	7.48—7.46	2
	Et	Ph	7.48	27	7.50—7.46	(1 + 2)
(XVII)	Allyl	Allyl	7.81	16	7.83—7.81	1
	Allyl	Allyl	7.81	18	7.82—7.80	2
	Allyl	Allyl	7.81	34	7.83—7.80	(1 + 2)
(XVI)	Allyl	Pr^i	8.02	16	8.04—8.00	1
	Allyl	Pr^i	8.02	15	8.04—8.00	2
	Allyl	Pr^i	8.02	31	8.04—8.00	(1 + 2)
(XII)	Br	Br	5.68	14	5.70—5.65	1
	Br	Br	5.68	15	5.71—5.65	2
	Br	Br	5.68	29	5.71—5.65	(1 + 2)
(XIII)	Cl	Cl	5.55	11	5.57—5.54	1
	Cl	Cl	5.54	9	5.55—5.52	2
	Cl	Cl	5.55	20	5.57—5.52	(1 + 2)
	Benzoic acid		4.211	5	4.215—4.210 [pH < (pK − 1)]	
			4.208	15	4.213—4.205 [(pK − 1) < pH < (pK + 1)]	
			4.203	6 *	4.220—4.187 [pH > (pK + 1)]	

* Final value in a set of seven values, $pK_1 = 4.011$, was not included.

The concentration ratio, $[HA^-]/[H_2A] = \alpha/(1 - \alpha)$, in equation (6) can be measured spectrophotometrically when the total concentration of the acid (C) is constant for all solutions. pK_1 Determinations at different ionic strengths may be made by dilution of the solutions. The ionic strength of the solution was calculated from the composition of the buffer solution, in the present work, and the pH was measured.

$$pK_1 = pH - \log \frac{(D - D_0)}{(D_1 - D)} - \log f_{\pm} \quad (13)$$

pK_1 *Values: Accuracy and Precision.*—Constancy in pK_1 values has been taken as the first criterion for acceptance in determinations. In the potentiometric titrations, a pK_1 value is calculated for each volume increment of standard potassium hydroxide added in the titration. The total number of pK_1 values accepted (on the basis of constancy) in a titration, from which the

mean value is calculated [pK_1 (mean value)],* is described in Table 3 as the *set number*. The total range of pK_1 values in a *set* is also given in Table 3 as the *range of* pK_1 *in set*. In the computer-programmed calculations, already described, pH values and V_t are the grouped variable quantities which appear in the printout with the corresponding computed pK_1 values. It was therefore convenient to use V_t to divide the data into three regions between commencement of the titration and the first equivalence point. The latter overall boundaries in V_t may be expressed as:

$$0 < V_t < \frac{M_o V_o}{N} \qquad (14)$$

where all terms in the inequality (14) have the meaning previously given in equations (2) and (3). The course of the titration was then divided into three regions: (*a*) the pre-buffer region; (*b*) the buffer region; (*c*) the post-buffer region up to the first equivalence point. These regions are then defined by limits involving V_t. For

$$pK_1 \sim pH - \log\left\{\frac{[K^+]}{[Y] - [K^+]}\right\} \qquad (15)$$

this purpose it has been assumed that equation (8) without correction terms for $[H^+]$, $[OH^-]$ and $f_\pm$, *viz.* equation (15), leads to pK_1 values to a first approximation.

Also, in the buffer region for the acid (pH = p$K_1 \pm 1$) the concentration ratio of the anion to undissociated molecule $[HA^-]/[H_2A] \sim [K^+]/([Y] - [K^+])$ corresponds to 0.1 and 10 for the lower limit (p$K_1 - 1$) and the upper limit (p$K_1 + 1$) respectively of the buffer range.

Region

(*a*) $0 < V_t < 0.091\frac{M_o V_o}{N}$; $1/2(pK_1 - \log M_o) < pH < (pK_1 - 1)$.

(*b*) $0.091\frac{M_o V_o}{N} < V_t < 0.909\frac{M_o V_o}{N}$; $(pK_1 - 1) < pH < (pK_1 + 1)$.

(*c*) $0.909\frac{M_o V_o}{N} < V_t < \frac{M_o V_o}{N}$; $(pK_1 + 1) < pH < 1/2(pK_w + pK_1 + \log M_o)$

pK_1 Values obtained in *sets* for potentiometric titrations of benzoic acid and 5,5-diethylbarbituric acid were examined for precision up to the first equivalence point.

TABLE 4

pK_1 Values for 5-phenyl-5-substituted barbituric acid derivatives at 25 °C [all concentrations (*c*) in mol l^{-1} in Table 4]

(Ia)		D	$-\log\frac{(D - D_0)}{(D_1 - D)}$	pH	$-\log f_\pm$	pK_1	pK_1 (mean value)
$c = 1.106 \times 10^{-4}$ 5-Ethyl-5-phenylbarbituric acid (XIX) (λ = 240.5 nm, slit width 0.725 mm)							
NaH_2PO_4	0.01M	0.556	0.105	7.18_5	0.092	7.38_2	7.40
NaH_2PO_4	0.005M	0.580	0.058	7.27_5	0.072	7.40_5	
NaH_2PO_4	0.002 5M	0.617	−0.014	7.36_1	0.054	7.40_1	
NaH_2PO_4	0.001 25M	0.708	−0.192	7.57_0	0.040	7.41_8	
Buffer pH = 10.4	D_1 =	1.061					
0.1M-HCl	D_0 =	0.159					
$c = 0.799\,6 \times 10^{-4}$ 5-Ethyl-5-(3-nitrophenyl)barbituric acid (IX) (λ = 243 nm, slit width 0.710 mm)							
NaH_2PO_4	0.01M	0.754	−0.225	7.18_2	0.092	7.04_9	7.04
NaH_2PO_4	0.005M	0.777	−0.297	7.27_2	0.072	7.04_7	
NaH_2PO_4	0.002 5M	0.796	−0.360	7.34_2	0.054	7.03_6	
NaH_2PO_4	0.001 25M	0.814	−0.422	7.42_7	0.040	7.04_5	
Buffer pH = 10.4	D_1 =	0.980					
0.1M-HCl	D_0 =	0.375					
$c = 0.799\,6 \times 10^{-4}$ 5-Ethyl-5-(4-nitrophenyl)barbituric acid (X) (λ = 243 nm, slit width = 0.71 mm)							
NaH_2PO_4	0.01M	0.750	−0.349	7.18_3	0.092	6.92_6	6.94
NaH_2PO_4	0.005M	0.759_5	−0.384	7.26_9	0.072	6.95_7	
NaH_2PO_4	0.002 5M	0.779	−0.467	7.34_3	0.054	6.93_0	
NaH_2PO_4	0.001 25M	0.793	−0.531	7.42_8	0.040	6.93_7	
Buffer pH = 10.4	D_1 =	0.913					
0.1M-HCl	D_0 =	0.386					
$c = 0.790\,9 \times 10^{-4}$ 5,5-Diphenylbarbituric acid (XI) (λ = 244.5 nm, slit width 0.695 mm)							
NaH_2PO_4	0.01M	0.483	0.018	7.18_2	0.092	7.29_2	7.30
NaH_2PO_4	0.005M	0.503	−0.052	7.27_1	0.072	7.29_1	
NaH_2PO_4	0.002 5M	0.519	−0.109	7.35_0	0.054	7.29_5	
NaH_2PO_4	0.001 25M	0.538	−0.177	7.44_4	0.040	7.30_7	
Buffer pH = 10.4	D_1 =	0.735_5					
0.1M-HCl	D_0 =	0.241					

For benzoic acid, 20 volume increments in regions (*a*) and (*b*) gave pK_1 = 4.21 without deviation. In region (*c*) pK_1 values found remained within 4.21 ± 0.01 except for the last two of seven values for V_t which led to pK_1 values of 4.19 and 4.01 respectively. All pK_1 values were calculated from equation (8). A similar comparison was made for the data obtained in the three titrations of 5,5-diethylbarbituric acid. In region (*b*) the last two pK_1 values in *sets* did not maintain the precision found in the previous values for this region, where p$K_1 = 7.99 \pm 0.01$. For region (*a*), the pK_1 values were found to have the same average value and high precision as those for (*b*). However, in region (*c*), pK_1 values followed the pattern found finally in region

* For the set (N = set number); pK(mean) = $\log N - \log \sum_{i=1}^{N} K_i$.

(*b*) with the values progressively decreasing and finally exceeding the limits of precision and accuracy regarded as acceptable in results.

For the remaining barbituric acid derivatives, where pK_1 values found in region (*a*) had the same mean value and precision, within the limits found for acceptable values in region (*b*), they were grouped with those for region (*b*) in obtaining mean values. The final one or two pK_1 values found in region (*b*) were not retained when they deviated markedly from preceding values. For region (*c*), pK_1 values calculated generally did not maintain the level of precision found in regions (*a*) and (*b*), and systematically decreased with increase in V_t with deviations finally exceeding $\Delta\ pK_1 = -0.06$.

Good precision was observed in pK_1 values obtained in single titrations and between duplicates. The uncertainty as judged from the range for pK_1 values in a *set* and between *sets*, in duplicate titrations, was between ± 0.03 and ± 0.01 in all derivatives examined in regions (*a*) and (*b*) (Table 3) and the precision was most often nearer the lower limit. pK_1 Values found for benzoic acid and 5,5-diethylbarbituric acid (XIV) agreed very well with the reference values,[1,40,41] obtained by very precise measurements in cells without liquid-junction potentials (Table 5). Therefore, the potentiometric procedure and calibrated equipment employed led to results which can be accepted with confidence. In fact the pK_1 values obtained for the reference substances appear to be well within the errors which might have been calculated from assumptions involved in defining pH values, estimating activity coefficients and allowing for liquid-junction potentials. The ionic strengths of solutions in both procedures for pK_1 values remained well within the limits $I \leqslant 0.1$M, specified for these assumptions. For the titration $I < 0.02$M and for the spectrophotometric procedure $I < 0.07$M and the precision for pK_1 values in the latter determinations (Table 4) always remained within a range of 0.04 and most often nearer 0.02 to 0.01 in pK_1. The pK_1 values found for 5-ethyl-5-phenylbarbituric acid (XIX) by potentiometric titration and by spectrophotometry differ by 0.08 units. The pK_1 value found by the latter method appears to be low when compared with other values reported for the same method.[2,4] The levels of accuracy attainable for the potentiometric titration and spectrophotometric procedures are generally given wider limits than the precision in results might suggest. In the titration procedure the results are likely to be within 0.04 pK units of the true thermodynamic value for the range $pK = 2$ to $pK = 10$ determined at concentrations in the range 0.002 5—0.050M.[42] For the spectrophotometric procedure somewhat wider limits might be expected since a measured pH is involved, as in the potentiometric titration method, in addition to other new sources of error in the analytical procedure and a range of up to ± 0.06 pK units for precision has been proposed.[42] The accuracy of such a result would probably be even less. However, these ranges for accuracy would account for the differences noted in the pK_1 determinations for (XIX) and it seems possible at this stage that a further factor * might be involved which would explain this difference.

Error functions were investigated for equation (13) and also for equation (15) which is an approximation for equation (8), to gauge the sensitivity of the thermodynamic pK_1 values to small changes in the independent variables in these equations. This allowed the effect of errors of the order that would be anticipated in the measurement of these independent variables to be judged. With the computer programme available for pK_1 values from titrations, it is easier to judge the effect of errors by introducing data with known incremental changes made in the variables.

pK_1 *Values: Comparison with Values in the Literature.*—The pK_1 values, and three approximate pK_2 values,† measured in the present work have been compared with previously reported values, in Table 5. For five derivatives, (VI), (VIII), (IX), (X), and (XI), pK_1 values are reported for the first time in this paper. Three further derivatives, (V), (XII), and (XIII), for which pK_1 values, by conductance, have been reported show very large deviations from pK_1 values found in the present work. These three derivatives were first investigated in early attempts to determine dissociation constants of barbituric acids before the theories of ionic activities had been established. Since for meaningful results, a knowledge of these theories and an experimental design consistent with limitations involved in applying corrections for activity effects are necessary [4a] most of the conductance work is now of only historical significance. Therefore, the pK_1 values previously reported for (V), (XII), and (XIII) are not regarded as a challenge to the values found in the present work. Also the pK_1 value for (XIV), by conductance, to which the above remarks also apply, clearly does not agree with any of the numerous thermodynamic values subsequently reported. The very accurate study on (XIV), between 0 and 60 °C, in a cell without liquid-junction potentials made by Manov *et al.*[1] is regarded [4a] as providing the most reliable pK_1 value at 25 °C, *viz.* 7.980, and in all subsequent work [2-4] including the present, close agreement with this pK_1 value has been taken as confirmation that the method used is satisfactory. pK_1 Values for (XIV) determined previously have been summarized [1] and with the possible exception of the value determined by Britton and Robinson ($pK_1 = 7.89$) [43] remain of historical interest only. Biggs notes [2] that with the exception of (XVII), the pK_1 values reported by Krahl [5] were less by *ca.* 0.06 in pK_1, for the seven derivatives which could be compared, than those obtained in his work. This difference, it was suggested,[2] may be due to liquid-junction potentials in the cell, which contained a saturated calomel reference electrode, in the e.m.f. method used by Krahl. In a similar comparison of pK_1 values for five derivatives, (XIV), (XV), (XVI), (XVII),

* A factor which will be discussed in a later part for this series.

† Details for the determination of pK_2 values have not been provided in this paper but will appear in a later part in this series.

and (XIX), found by potentiometric titration in the present work, with those of Krahl [5] the average difference was 0.08 lower in pK_1 for the latter. Errors due to liquid-junction potentials cannot be precluded, although they are believed to be small (< 0.01 in pK_1) for any of the pK_1 values in the present work. Therefore, Krahl's [5] pK_1 values are still low even when compared with results obtained by an e.m.f. method with a cell in which liquid-junction potentials can be present. For five derivatives, (XIV), (XVI), (XVII), (XVIII), and (XIX), for which pK_1 values were found by potentiometric titration in the present work, comparison with Biggs' [2] spectrophotometric pK_1 values gives an average 'a_i' values in equation (16) which gave the best agreement between pK_1 values at every ionic strength, up to $I = 2.00$, for each derivative investigated. Reliable estimates of activity coefficients could not be expected from the procedure employed in refining the data and, further, no attempt was made to allow for hydrogen and hydroxide ion concentrations in calculation of the stoicheiometric concentration ratio term in the form of the Henderson equation used to define pK_1 values derived. No attempt has been made to recalculate Krahl's data since for all derivatives the range of ionic strengths employed included only two values at which theoretical expressions for activity coefficients could be used within

TABLE 5

Summary of pK_1 values at 25 °C for all derivatives

No.	(Ia)	R[1]	R[2]	pK_1 (mean value) [a]	pK_2	pK_1 (lit.)	pK_2 (lit.)
1	(V)	Me	Me	8.51 ± 0.03(P)		7.14(C) [10]	
2	(VI)	Me	Et	8.28 ± 0.02(P)			
3	(VIII)	Me	Pr^i	8.45 ± 0.01(P)			
4	(XVIII)	Me	Ph	7.78 ± 0.01(P)		7.73(S) [2]	
5	(XIV)	Et	Et	7.98 ± 0.02(P) 7.97 (*ca.* I = 0.3M)(S)	12.4(S)	7.43(C),[10] 7.91(P) [5] 7.980(P),[1] 8.00(P) [3] (7.97(S),[2] 8.019(S) [4]	12.8(S)[3]
6	(XV)	Et	Pr^i	8.14 ± 0.01(P)		8.01(P) [5]	
7	(XVII)	Allyl	Allyl	7.81 ± 0.02(P)		7.79(P),[5] 7.77(S) [2]	
8	(XVI)	Allyl	Pr^i	8.02 ± 0.02(P)		7.91(P),[5] 7.99(S) [2]	
9	(XIX)	Et	Ph	7.48 ± 0.02(P) 7.40 ± 0.02(S) 7.39 (*ca.* I = 0.3M)(S)	12.2(S)	7.41(P) [5] 7.45(S),[2] 7.441(S) [4]	
10	(XI)	Ph	Ph	7.30 ± 0.01(S) 7.30 (*ca.* I = 0.3M)(S)	11.9(S)		
11	(IX)	Et	3-NO_2Ph	7.04 ± 0.01(S)			
12	(X)	Et	4-NO_2Ph	6.94 ± 0.02(S)			
13	(XIII)	Cl	Cl	5.55 ± 0.03(P)		4.77(C) [9]	
14	(XII)	Br	Br	5.68 ± 0.03(P)		5.08(C) [9]	
		Benzoic acid [$(pK - 1) < pH < (pK_1 + 1)$]		4.208 ± 0.005(P)		4.201(P) * 4.204 ± 0.005(P) †	
	(final check)	Et	Et	7.99 ± 0.02		See No. 5 (XIV) above	

[a] (C) Conductance method; (P) potentiometric method; (S) spectrophotometric method. * A. V. Jones and H. N. Parton, *Trans. Faraday Soc.*, 1952, **48**, 8; and R. A. Robinson and R. H. Stokes, 'Electrolyte Solutions,' Butterworths, London, 1959, p. 522 [for a summary of pK_1 values reported for various methods (C), (P), and (S)]. † The most recent pK_1 values for benzoic acid are given and reviewed in J. G. Travers, K. G. McCurdy, D. Dolman, and L. G. Hepler, *J. Solution Chem.*, 1975, **4**, 267; and Takeki Matsui, Hon Chung Ko, and L. G. Hepler, *Canad. J. Chem.*, 1974, **52**, 2906, 2912

difference of 0.03 pK_1 units lower for the latter derivatives. This difference remains within the experimental error for the determinations.

The main question that may be raised about Krahl's procedure is the high ionic strength of the solutions employed in the majority of the pK_1 determinations. Ionic strengths up to $I = 2.00$ were used and liquid-junction-potential errors would be increased over those normally present when $I \leqslant 0.10$. Also, these high ionic strengths are beyond the known predictive range of the Debye-Hückel equation (16) used in the work.[5]

$$-\log f_{A^-} = \frac{A\,I^{\frac{1}{2}}}{1 + Ba_iI^{\frac{1}{2}}} \qquad (16)$$

In equation (16) A and B depend on the dielectric constant and temperature of the solution and 'a_i' is an adjustable parameter—*the distance of closest approach between ions*—which may be chosen to give the best fit for the data. Equation (16) for activity coefficient corrections is known to apply at ionic strengths up to *ca.* $I = 0.1$ to a good approximation with the correct choice of 'a_i'. In determining pK_1 values, Krahl used their known range of usefulness. The 'a_i' values reported by Krahl were unrealistically small and ranged from (1.5 to 2.7) $\times 10^{-8}$ cm. Estimated values for $-\log f_{A^-}$ in equation (16) would, under these circumstances, be expected to be too large, and result in pK_1 values which are falsely high. Comparison of the pK_1 values obtained with those subsequently reported by other workers,[1,2,4] including the present work, suggests that the values are too low, and additional factors in the concentration ratio term and in the observed pH values, with the saturated calomel reference electrode present, at the high ionic strengths used could be involved. Moreover, Briggs *et al.*[4] used a buffer system with $0.20 \leqslant I \leqslant 0.25$, under conditions outside the range of application of the activity coefficient equation employed, equation (17).

$$-\log f_{\pm} = AI^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}). - 0.2\,I \qquad (17)$$

In equation (17) A is given [4] as 'the parameter in the Debye–Hückel–Onsager equation' and presumably it has a value of $A = 0.509\,2$ [44] or is so close to this value that no significant difference would arise in the cal-

culation of $-\log f_{\pm}$. Also, differences in $-\log f_{\pm}$ calculated from equation (7), in the present work, and from an earlier modification of this equation [2] and equation (17) [4] are not significant since they differ only in the third place of decimals.

Finally, the spectrophotometric procedure for pK_1 value determinations used by Biggs [2] differs from that employed in the present work and by other workers referred to.[3,4] This difference arises from the use [45] of National Bureau of Standards buffers for which $pH = -\log [H^+]f_{H^+}$ is known, and for slight changes on adding the acid a calculated correction can be made.[46] The thermodynamic pK_1 values derived do not involve a measured pH, with a pH meter.

Structure–Reactivity Effects.—The accuracy of the pK_1 values determined in the present work (Table 5) allow differences in acid strengths for these compounds to be clearly distinguished. The C(5)-substituents in these derivatives influence the acid strengths and the differences in pK_1 values observed. It is clear, from Table 5, that acid strengths do not follow the expected qualitative order for electronic effects due to C(5)-substituents. These departures are evident for (V; $R^1 = R^2 =$ Me), (VI; $R^1 =$ Me, $R^2 =$ Et), and (XIV; $R^1 = R^2 =$ Et) and for (XVIII; $R^1 =$ Me, $R^2 =$ Ph) and (XIX; $R^1 =$ Et, $R^2 =$ Ph) where an increase in acid strength occurs in a direction opposite from that anticipated for electronic effects in substituents. In fact the acid strength in these derivatives shows an increase which qualitatively follows the increase in the steric effects for substituents. For (XVIII; $R^1 =$ Me, $R^2 =$ Pr^i) and (XV; $R^1 =$ Et, $R^2 = Pr^i$) the same trend is observed. However, comparison of (XVIII; $R^1 =$ Me, $R^2 = Pr^i$) with other 5-alkyl-5-methyl-derivatives shows that it does not follow the observed direction in accordance with expected steric requirements for the 5-Pr^i group. An increased electronic effect ($+I$) over that usual for the Pr^i group, which seems unlikely, or a reduced steric effect, over that for a 5-Et group, would be required to explain the relatively low acid strength of (VIII; $R^1 =$ Me, $R^2 = Pr^i$) in the 5-alkyl-5-methyl-barbituric acid derivatives in the series. With the 5-Et group constant, (XIX; $R^1 =$ Et, $R^2 =$ Ph), (IX; $R^1 =$ Et, $R^2 =$ 3-NO_2·C_6H_4), and (X; $R^1 =$ Et, $R^2 =$ 4-NO_2·C_6H_4 follow the direction in acid strengths, expected from the ancitipated order of electronic effects in the phenyl and nitrophenyl substituents. Moreover, the dihalogen derivatives (XII; $R^1 = R^2 =$ Br) and (XIII; $R^1 = R^2 =$ Cl) are the strongest acids and also follow in the order for acid strengths that would be anticipated from the electronic effects of their 5-substituents.

The factors determining reactivity of the above series of fourteen 5,5-disubstituted barbituric acids (Table 5) will be considered further, on a quantitative basis, in the following paper.

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