# First Thermodynamic Dissociation Constants of 5,5-Disubstituted Barbituric Acids in Water at 25 °C. Part 2.[1] Structure–Reactivity Relationships (SRR). Linear Free Energy Relationships which Correlate C(5)-Substituent Effects with Acid Strength

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First thermodynamic dissociation constants have been examined for the effect of C(5)-substituents on acid strength in a series of 14 5,5-disubstituted barbituric acids (Ia; $R^1$ = Me, $R^2$ = Me, Et, $Pr^i$ or Ph; $R^1$ = Et, $R^2$ = Et, $Pr^i$, Ph, 3-$NO_2C_6H_4$ or 4-$NO_2C_6H_4$; $R^1$ = allyl, $R^2$ = $Pr^i$; $R^1$ = $R^2$ = allyl, Ph, Br, or Cl). Taft polar substituent constants, $\sigma^*$, have been calculated for a number of groups. Steric factors have been investigated as an additional effect on reactivity in these derivatives: Taft steric substituent constants, $E_s$, and the Newman six-number measure of steric effects have been used. A linear free-energy relationship (LFER) is established by multiple correlation, with the independent variables polar and steric substituent constants, and its significance for the reaction series is discussed.

PART 1[1] of this series was concerned with the measurement of the first thermodynamic dissociation constants of 14 5,5-disubstituted barbituric acids making up the reaction series for the present structure–reactivity relationship (SRR) study. Acid strengths in these derivatives were in the range $pK_1 = 8.51—5.55$; the range of reactivity thus provided for the dependent variable allowed significant correlations to be obtained, the reactivity being determined by the relevant independent variables. The $pK_1$ values determined[1] are considered to be accurate to within ±0.05 units in $pK$ and are quite adequate for the quantitative investigation of linear free-energy relationships (LFER). The object of this study is to see whether reactivity in structure (Ia) can be related to the C(5)-substituents in the heterocyclic nucleus.

TABLE 1

Polar substituent constants

| | $RCH_2$ | $R^1CH_2$ | $R^2CH_2$ | $R^1R^2CH$ ($\sigma^*$ calc.) | $R^1R^2CH$ ($\sigma^*$ expt.) | % Error $\frac{100(\sigma^* \text{ expt.} - \sigma^* \text{ calc.})}{\sigma^* \text{ expt.}}$ |
|---|---|---|---|---|---|---|
| (1) | $MeCH_2$ | | | | −0.100 | |
| (2) | $Me(CH_2)_2$ | | | | −0.115 | |
| (3) | $Me_2CHCH_2$ | | | | −0.125 | |
| (4) | $Me_3CCH_2$ | | | | −0.165 | |
| (5) | $Me_2CH$ | $MeCH_2$ | $MeCH_2$ | −0.200 | −0.190 | −5.26 |
| (6) | $MeCH_2(Me)CH$ | $Me(CH_2)_2$ | $MeCH_2$ | −0.215 | −0.210 | −2.38 |
| (7) | Ph | | | | +0.600 | |
| (8) | $PhCH_2$ | No. (7) ÷ (2.8) | | +0.214 | +0.215 | +0.46 |
| (9) | $Ph(CH_2)_2$ | No. (7) ÷ $(2.8)^2$ | | +0.077 | +0.080 | +3.75 |
| (10) | $Ph(CH_2)_3$ | No. (7) ÷ $(2.8)^3$ | | $+0.02_7$ | +0.02 | −8.75 |
| (11) | $Ph_2CH$ | $PhCH_2$ | $PhCH_2$ | +0.430 | +0.405 | −5.68 |
| (12) | $Ph(Me)CH$ | $PhCH_2$ | $MeCH_2$ | +0.115 | +0.11 | −4.54 |
| (13) | $Ph(Et)CH$ | $PhCH_2$ | $Me(CH_2)_2$ | +0.100 | +0.04 | −150.00 |
| (14) | $Et_2CH$ | $Me(CH_2)_2$ | $Me(CH_2)_2$ | −0.230 | −0.225 | −2.22 |
| (15) | $Me_3C(Me)CH$ | $Me_3CCH_2$ | $MeCH_2$ | −0.265 | −0.28 | −5.36 |
| (16) | $Me_3C$ | $Me_2CH$ | $MeCH_2$ | −0.290 | −0.300 | +3.33 |
| (17) | $CH_2{=}CH(CH_2)_2$ | | | +0.06 | | |
| (18) | $(CH_2{=}CH{-}CH_2)_2CH$ | $CH_2{=}CH(CH_2)_2$ | $CH_2{=}CH(CH_2)_2$ | +0.12= | | |
| (19) | $Me_2CH(CH_2{=}CHCH_2)CH$ | $Me_2CHCH_2$ | $CH_2{=}CHCH_2)_2$ | −0.065= | | |
| (20) | $Me_2CH(Et)CH$ | $Me_2CHCH_2$ | $Me(CH_2)_2$ | −0.240 | | |
| (21) | $FCH_2$ | | | | +1.10 | |
| (22) | $F_2CH$ | $FCH_2$ | $FCH_2$ | +2.04 | +2.05 | $+0.48_7$ |
| (23) | $ClCH_2$ | | | | +1.050 | |
| (24) | $Cl_2CH$ | $ClCH_2$ | $ClCH_2$ | +1.94 | +1.940 | 0.00 |
| (25) | $BrCH_2$ | | | | +1.000 | |
| (26) | $Br_2CH$ | $BrCH_2$ | $BrCH_2$ | +1.84 | | |
| (27) | 3-$NO_2C_6H_4CH_2$ | | | $+0.42_8$ | | |
| (28) | 3-$NO_2C_6H_4(Et)CH$ | 3-$NO_2C_6H_4CH_2$ | $Me(CH_2)_2$ | +0.313 | | |
| (29) | 4-$NO_2C_6H_4CH_2$ | | | +0.499 | | |
| (30) | 4-$NO_2C_6H_4(Et)CH$ | 4-$NO_2C_6H_4CH_2$ | $Me(CH_2)_2$ | +0.384 | | |
| (31) | $Me_2CH(Me)CH$ | $Me_2CHCH_2$ | $MeCH_2$ | −0.225 | | |

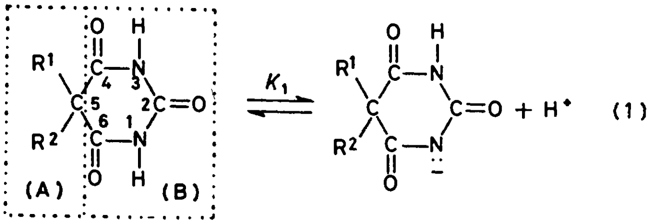
In the first instance the $R^1R^2CH$ group has been taken as the substituent (or its equivalent) in the barbituric acid structure (Ia).

Therefore, the division into substituent (A) and reaction centre (B) in structure (Ia) involves the 5-carbon atom of the barbituric acid nucleus as part of the substituent. Substituent (A) [$(R^1R^2C)$] differs from $R^1R^2CH$ by one proton and this difference remains constant, for all substituents.

If the effect of change in molecular structure on the standard free-energy change for dissociation ($\Delta G^\circ$) in reaction (1), equation (2), is considered to arise from the sum of independent polar, steric, resonance, and possibly hyperconjugative contributions, these factors must be investigated separately to see which of them is important for the reaction series. For this series equation (2) holds and with the polar and steric substituent constants

$$\Delta G^\circ = 2.303\, RT\, pK_1 \qquad (2)$$

as the independent variables in the LFER, reactivity can largely be accounted for. Remaining deviations, $\Delta pK = pK_{1(\text{pred.})} - pK_{\text{obs.}}$, will be discussed in detail since they have prompted further investigations, to test hypotheses arising from the present work, the results of which will appear in a later paper.



(Ia) (Ib)

Polar substituent constants, σ*, can usually be calculated from suitable empirical rules. Where multiple substituents, *e.g.* $R^1R^2CH$, are present additive relationships starting from simpler groups can usually be found [equation (3)]. No such simple procedures are known for Taft steric substituent constants, $E_s$, and the experimentally determined values available are limited and this restricts investigations involving steric effects. E Values were not available for all substituents in the series being investigated, as may be seen from Table 2. However, it may be noted that the availability of $E_s$ values for $R^1R^2CH$ groups corresponding to ten of the compounds in the reaction series was a primary reason for selection of this group as the substituent [*i.e.* equivalent to (Ia; $R^1R^2C$)] at the outset. The Newman rule of six[2,3] has also been investigated as an alternative to $E_s$ values as a quantitative measure of steric effects for 5-substituents.

TABLE 2

Polar and steric substituent constants

| | ($R^1R^2CH$)§ | σ* [a] | $E_s$ | $n$ [b] | $pK_i$ |
|---|---|---|---|---|---|
| (1) | $Me_2CH$ | $-0.190^e$ | $-0.47^e$ | 0 | 8.51 |
| (2) | Et(Me)CH | $-0.210^e$ | $-1.13^e$ | 3 | 8.28 |
| (3) | $Pr^i$(Me)CH | $-0.225^e$ | | 6 | 8.45 |
| (4) | Ph(Me)CH | $+0.11^e$ | $-1.19^e$ | 4 | 7.78 |
| (5) | $Et_2CH$ | $-0.225^e$ | $-1.98^e$ | 6 | 7.98 |
| (6) | $Pr^i$(Et)CH | $-0.240^c$ | | 9 | 8.14 |
| (7) | $(allyl)_2CH$ | $+0.12^c$ | $-1.80^e$ † | 4 | 7.81 |
| (8) | $Pr^i$(allyl)CH | $-0.065^c$ | $-2.71^e$ † | 8 | 8.02 |
| (9) | Ph(Et)CH | $+0.04^e$<br>$(0.100^c)$ | $-1.50^e$ | 7 | 7.40; 7.48<br>(7.44) ¶ |
| (10) | $Ph_2CH$ | $+0.405^e$ | $-1.76^e$<br>$(-143)^e$ ‡ | 8 | 7.30 |
| (11) | $3\text{-}NO_2C_6H_4$(Et)CH | $+0.313^c$ | | 7 | 7.04 |
| (12) | $4\text{-}NO_2$(Et)CH | $+0.384^c$ | | 7 | 6.94 |
| (13) | $Cl_2CH$ | $+1.940^e$ | $-1.54^e$ | 0 | 5.55 |
| (14) | $Br_2CH$ | $+1.84^c$ | $-1.86^e$ | 0 | 5.68 |

[a] e = Experimental and c = Calculated. [b] Newman six-number.[2,3] ¶ Meanvalue ($pK_{\text{mean}} = \log N - \log \sum_{i=1}^{N} K_i$. † Lamb.[8] ‡ $E_s$ (minimum value in the literature; K. Bowden, N. B. Chapman, and J. Shorter, *J. Chem. Soc.*, 1963, 5239. § The numbering of the derivatives in Table 2 is followed in Tables 3—5, but is not the same as in Table 1.

## EXPERIMENTAL AND CALCULATIONS

(a) *Calculation of Polar Substituent Constants* (σ*).—The σ* values for the $R^1R^2CH$ group were calculated from the additivity relationship, equation (3).

$$\sigma^*R^1R^2CH = \sum_{i=1}^{2} \sigma^*R^iCH_2 \qquad (3)$$

*The polar constant for the* 5-*allyl group* [$CH_2{=}CH\text{-}(CH_2)_2 = R^1CH_2$]. The σ* value for the $CH_2{=}CH(CH_2)_2$ group was calculated from the polar constant for the $CH_2{=}CH{-}CH_2$ group by multiplication by the factor[4] (1/2.8). This factor allows for the introduction of a methylene group between substituent and the reaction centre. For the $CH_2{=}CH{-}CH_2$ group, σ* was calculated from the most recently determined $pK_a$ value of vinylacetic acid (but-3-enoic acid)[5] in a revised LFER for dissociation of carboxylic acids.[6] The value σ* = +0.17 was obtained for the $CH_2{=}CHCH_2$ group and for the $CH_2{=}CH(CH_2)_2$ group σ* = +0.06 (Table 1).

*The polar constants for the* 5-(3-*nitrophenyl*), 5-(4-*nitrophenyl*), *and* 5-*phenyl groups*. Polar constants for the $3\text{-}NO_2C_6H_4CH_2$, $4\text{-}NO_2C_6H_4CH_2$ and $C_6H_5CH_2$ groups were estimated from the pK values[5] of the corresponding carboxylic acids, 3-nitrophenyl-, 4-nitrophenyl- and phenyl-acetic acid by using a LFER for carboxylic acids.[6] The σ* values for these groups (Table 1) were then used to calculate polar constants for the $3\text{-}NO_2$Ph(Et)CH, $4\text{-}NO_2$Ph(Et)CH and Ph(Et)CH groups for the corresponding barbituric acid derivatives, from equation (3) (Table 1).

*The polar constant for the* 5,5-*dibromo-group* ($Br_2CH$). In calculating σ* for the $Br_2CH$ group it was found that equation (4) gave calculated values within 0.5% of the

$$\sigma^*_{X_2CH} = (2\sigma^*_{XCH_2} - 0.16);\ X = F \text{ or } Cl \qquad (4)$$

experimental values for the $F_2CH$ and the $Cl_2CH$ group when the corresponding values (σ*) for the $FCH_2$ and the $ClCH_2$ group were used (Table 1). By using the experimental value for the $BrCH_2$ group, σ* = +1.00, the polar constant calculated for the $Br_2CH$ group is +1.84 (Table 1).

(b) *Steric Substituent Constants*.—For Taft $E_s$ values it has been necessary to rely totally on available experimental values,[7,8] which are listed in Table 2.

An empirical rule, the *rule of six*[2,3] has been applied in correlations of steric effects in a number of instances[2,9,10] and the six-number, *n*, for each $R^1R^2CH$ group corresponding to the barbituric acid series is also given (Table 2) for all 14 derivatives studied. Six-numbers have been calculated with respect to the oxygen atoms of the 4-carbonyl group (or the equivalent 6-carbonyl group) (Figure 1).

(c) *The Correlation of Dissociation Constants*.—The data in Table 2 were investigated for a multiple correlation, in independent variables, involving electronic and steric effects by use of equation (5). In equation (5), $K_i$ is the first dissociation constant for any acid, *i*, in the series, and $K_0$ the

$$\log K_i = \log K_0 + \rho^*\sigma^* + \delta E_s \qquad (5)$$

dissociation constant corresponding to the acid, hypothetical for the present *series*, where both the Taft electronic (σ*) and steric ($E_s$) constants have values of zero. The constants ρ* and δ give the susceptibility of the compounds to electronic and steric effects respectively. Equation (5) may be transformed to give p$K_i$ values directly, *viz.* equation (6).

$$\mathrm{p}K_i = \mathrm{p}K_0 - \rho^*\sigma^* - \delta E_s \qquad (6)$$

p$K_1$ Values found for the 5,5-disubstituted barbituric acid series in the present work, σ* values available from the literature [11] and calculated in the present work, and available $E_s$ values [7,8] for $R^1R^2CH$ groups are summarised in Table 2. These data have been fitted to equation (6) in calculations initially involving only σ* and $E_s$ for which experimental values were available (3A1—3G1, Table 3). Calculations were then extended to include calculated σ* values, where experimentally determined values were not available (3H1 and 3I1, Table 3), and finally for all data for which $E_s$ values were available including approximations thereto. The approximations to $E_s$ values involved the assumption that for the 3- and 4-nitrophenyl groups in $3\text{-}NO_2C_6H_4(Et)CH$ and $4\text{-}NO_2C_6H_4(Et)CH$ the $E_s$ values could be taken to be identical with that for the parent, non-nitrated compound Ph(Et)CH, which was available. The effect of giving σ* for the Ph(Et)CH group the calculated value, σ* = +0.10, in place of the experimentally determined value,[11] σ* = +0.04, was also determined in carrying out the above calculations. Data were fitted to equation (6) by the method of least squares. All calculations were carried out on a computer using an OMNI TAB program. For each calculation the value for p$K_1$ predicted [p$K_i$(pred.)] from the multiple regression equation, for each derivative, has been compared with the observed value, p$K_i$(obs.), the difference, Δp$K$(obs.) is given. Standard errors (S.E.) for the constants p$K_0$, ρ*, and δ are recorded and the multiple correlation coefficient, $R$, for the regression equation is given. The numbering for derivatives in all Tables, which include the above information, follows that used in Table 2. The calculations described for the data in Table 2 when applied to equation (6), even on taking $E_s$ values for compounds (11) and (12) as identical with that for (9), could only be extended to 12 of the 14 compounds in the series.

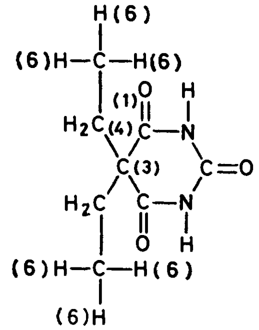


FIGURE 1 5,5-Diethylbarbituric acid, six-number, $n$ = 6

Six-numbers,[2,3] $n$, have been used in place in $E_s$ values in the correlations and equation (6) then becomes equation (7). In equation (7) $h$ is a constant giving the susceptibility of the reaction series to steric effects. The remaining terms in the equation have the same significance as in equations (5) and (6). Since $n \geqslant 0$, when an increased steric effect produces an increased acid strength $h$ will be positive, and for a decreased acid strength $h$ will be negative. Clearly, $h$ will be of opposite sign to δ in equations (5) and (6). All steps in the analysis described for the data in Table 2 with equation (6) were repeated with equation (7). Since six-numbers can be arrived at for all derivatives in the series no restrictions exist for the amount of data that can be employed in the analysis. In fitting the data in Table 2 to equations (6) and (7) in the way described 23 Tables resulted, and these are summarised in Table 3.

$$\mathrm{p}K_i = \mathrm{p}K_0 - \rho^*\sigma^* - hn \qquad (7)$$

DISCUSSION

*Polar Substituent Constants.—The* 5-*ethyl*-5-*phenyl group* [Ph(Et)CH]. The experimental value of σ* = +0.04 for the Ph(Et)CH group alone, contrasts with the calculated value σ* = +0.100 obtained in Table 1 from the additivity rule.† Further the polar constant for the $PhCH_2$ group, σ* = +0.215, calculated from the carboxylic acid ‡ LFER [6] and the p$K_\alpha$ of phenylacetic acid,[5] when combined with the σ* value for $Me(CH_2)_2$ (= −0.115, Table 1) according to equation (3) also leads to σ* = +0.100 for the Ph(Et)CH group. The same value for this group is obtained again when it is calculated from the σ* value for the $PhCH_2$ group derived from that for the Ph group § with the (1/2.8) factor for introducing a methylene group [no. (8), Table 1]. In addition to the agreement between these independently derived values the actual use of σ* = +0.100 for the Ph(Et)CH group in correlation equations, Table 3, always led to an improved fit over that for σ* = +0.04. On this basis then, σ* = +0.100 is considered to be a better estimate of the polar effect, for the Ph(Et)CH group, than σ* = +0.04.

*The* 5-*allyl group* [$CH_2{=}CH(CH_2)_2 = R^1CH_2$]. A value of σ* = +0.17, identical with that calculated in the present work, for the $CH_2{=}CHCH_2$ group had previously been reported.[12] However, the method of arriving at σ* for $CH_2{=}CH(CH_2)_2$ from the $CH_2{=}CHCH_2$ group differs from that used in the present work. In this previously reported derivation, available σ* values [11] for MeCH=CH (σ* = +0.360) and $MeCH{=}CHCH_2$ (σ* = +0.13) were used in obtaining the difference ($\sigma^*_{MeCH=CH} - \sigma^*_{MeCH=CHCH}$) = +0.23 which was attributed to the effect of methylene group introduction. This value was then combined, as a difference, with σ* = +0.17 for the allyl group to give σ* = −0.06 for the $CH_2{=}CH(CH_2)_2$ group. This value for σ* has the same magnitude but is of opposite sign to the value found in the present work (Introduction and Table 1) where the introduction of a methylene group was calculated by an established rule,[4] for −$I$ groups, and must therefore be regarded as more reliable.¶ Also alkenyl groups would be expected to be −$I$ in character and have positive σ* values as indeed the MeCH=CH and MeCH=

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† Both $\sigma^*_{R^iCH_2-(i = \text{Et and Ph})}$ values were originally derived from ester hydrolyses rates.[11]

‡ $\sigma^*_{PhCH_2}$ is therefore derived independently from that in Table 1.[11]

§ $\sigma^*_{Ph}$ is derived from ester hydrolysis rates but for an independent member in the reaction series.

¶ The satisfactory nature of this rule is further demonstrated by the agreement between calculations shown in Table 1, compounds (8)—(10), and the corresponding experimental values.

$CHCH_2$ groups do for the incorrectly derived $\sigma^*$ value obtained in the difference procedure.[12] $\sigma^* = +0.360$ for the $CH_3CH{=}CH$ group [11] and when multiplied by the (1/2.8) factor $\sigma^* = +0.13$ for the $CH_3CH{=}CH{\cdot}CH_2$ group which agrees with the observed value ($\sigma^* = +0.13$).[11] Introduction of a further methylene group leads to a calculated value of $\sigma^* = +0.05$ for the $MeCH{=}CH(CH_2)_2$ group which would be expected to be very close to the value for the $CH_2{=}CH(CH_2)_2$ group in the present work. A slight diminishment in the $\sigma^*$ value due to the methyl group at the double bond, over $CH_2{=}CH(CH_2)_2$, would also be expected and this is seen to be the case for the calculated $\sigma^*$ value for the $MeCH{=}CH(CH_2)_2$ group. Therefore, the $CH_2{=}CH(CH_2)_2$ group would have a $-I$ effect, albeit weak, and $\sigma^*$ should be positive as is found by the method used in the present work.

TABLE 3

The correlation equations (LFER). Values of the S.E. for $pK_0$, $\rho^*$, $\delta$, and $h$ are in parentheses

| Equation | Reaction series [a,b] | $pK_0$ | $\rho^*$ | $\delta$ | $R$ |
|---|---|---|---|---|---|
| (3A1) | 1, 2, 4, 5, 9 (+0.04, −1.50, 7.44), 10, 13 | $8.43_2$ (0.215) | $1.16_2$ (0.098) | −0.418 (0.153) | 0.9887 |
| (3B1) | 1, 2, 4, 5, 9 (+0.100, −1.50, 7.44), 10, 13 | $8.43_0$ (0.179) | $1.17_3$ (0.082) | $-0.40_8$ (0.127) | 0.9922 |
| (3C1) | 1, 2, 4, 5, 9 (+0.100, −1.50, 7.40), 10, 13 | $8.43_0$ (0.200) | $1.17_0$ (0.091) | $-0.41_3$ (0.142) | 0.9903 |
| (3D1) | 1, 2, 4, 5, 9 (+0.100, −1.50, 7.48), 10, 13 | $8.43_0$ (0.158) | $1.17_6$ (0.072) | −0.403 (0.112) | 0.9939 |
| (3E1) | 1, 2, 4, 5, 9 (+0.04, −1.50, 7.40), 10, 13 | $8.43_2$ (0.237) | $1.15_9$ (0.108) | $-0.42_3$ (0.168) | 0.9864 |
| (3F1) | 1, 2, 4, 5, 9 (+0.04, −1.50, 7.48), 10, 13 | $8.43_1$ (0.195) | $1.16_6$ (0.089) | −0.414 (0.138) | 0.9908 |
| (3G1) | 1, 2, 4, 5, 9 (+0.04, −1.50, 7.44), 10 (+0.405, −1.43, 7.30), 13 | $8.45_2$ (0.215) | $1.16_3$ (0.096) | $-0.44_9$ (0.157) | 0.9892 |
| (3H1) | 1, 2, 4, 5, 9 (+0.04, −1.50, 7.44), 10, 13, 7, 8, 14 | $8.13_2$ (0.199) | $1.20_6$ (0.086) | $-0.15_2$ (0.119) | 0.9835 |
| (3I1) | 1, 2, 4, 5, 9 (+0.100, −1.50, 7.44), 10, 13, 7, 8, 14 | $8.14_4$ (0.180) | $1.21_4$ (0.078) | $-0.15_3$ (0.107) | 0.9865 |
| (3J1) | 1, 2, 4, 5, 9 (+0.04, −1.50, 7.44), 10, 13, 7, 8, 14, 11, 12 | $8.01_2$ (0.261) | $1.20_5$ (0.115) | $-0.12_8$ (0.159) | 0.9628 |
| (3K1) | 1, 2, 4, 5, 9 (+0.100, −1.50, 7.44), 10, 13, 7, 8, 14, 11, 12 | $8.02_1$ (0.253) | $1.21_1$ (0.112) | $-0.12_9$ (0.154) | 0.9651 |
| | | | | $h$ | |
| (3A2) | 1, 2, 4, 5, 9 (+0.04, 7, 7.44), 10, 13 | $8.18_9$ (0.116) | $1.33_8$ (0.091) | $0.07_0$ (0.022) | 0.9911 |
| (3B2) | 1, 2, 4, 5, 9 (+0.100, 7, 7.44), 10, 13 | $8.18_6$ (0.099) | $1.33_9$ (0.078) | $0.06_7$ (0.019) | 0.9935 |
| (3C2) | 1, 2, 4, 5, 9 (+0.100, 7, 7.40), 10, 13 | $8.18_9$ (0.107) | $1.34_0$ (0.084) | $0.06_9$ (0.020) | 0.9924 |
| (3D2) | 1, 2, 4, 5, 9 (+0.100, 7, 7.48), 10, 13 | $8.18_4$ (0.092) | $1.33_8$ (0.072) | $0.06_5$ (0.017) | 0.9944 |
| (3E2) | 1, 2, 4, 5, 9 (+0.04, 7, 7.40), 10, 13 | $8.19_2$ (0.126) | $1.33_8$ (0.098) | $0.07_2$ (0.024) | 0.9896 |
| (3F2) | 1, 2, 4, 5, 9 (+0.04, 7, 7.48), 10, 13 | $8.18_7$ (0.107) | $1.33_7$ (0.084) | $0.06_8$ (0.020) | 0.9924 |
| (3G2) | Not comparable with (3G1) | | | | |
| (3H2) | 1, 2, 4, 5, 9 (+0.04, 7, 7.44), 10, 13, 7, 8, 14 | $8.16_6$ (0.109) | $1.34_3$ (0.076) | $0.05_6$ (0.019) | 0.9908 |
| (3I2) | 1, 2, 4, 5, 9 (+0.100, 7, 7.44), 10, 13, 7, 8, 14 | $8.16_5$ (0.095) | $1.34_5$ (0.067) | $0.05_4$ (0.017) | 0.9929 |
| (3J2) | 1, 2, 4, 5, 9 (+0.04, 7, 7.44), 10, 13, 7, 8, 14, 11, 12 | $8.21_5$ (0.125) | $1.38_3$ (0.088) | $0.07_5$ (0.021) | 0.9841 |
| (3K2) | 1, 2, 4, 5, 9 (+0.100, 7, 7.44), 10, 13, 7, 8, 14, 11, 12 | $8.21_5$ (0.120) | $1.38_5$ (0.084) | $0.07_4$ (0.020) | 0.9855 |
| (3L2) | 1, 2, 4, 5, 9 (+0.04, 7, 7.44), 10, 13, 7, 8, 14, 11, 12, 6, 3 | $8.23_2$ (0.137) | $1.41_4$ (0.096) | $0.06_7$ (0.022) | 0.9789 |
| (3M2) | 1, 2, 4, 5, 9 (+0.100, 7, 7.44), 10, 13, 7, 8, 14, 11, 12, 6, 3 | $8.23_3$ (0.132) | $1.41_6$ (0.092) | $0.06_6$ (0.021) | 0.9806 |

[a] Numbering for derivatives as in Table 2. [b] In column 2, substituent constants and $pK_i$ values used are given in parentheses [$\sigma^*$, steric constant ($E_s$ or $n$), $pK_i$], see Table 2, where necessary

*The 5,5-dibromo-group* ($Br_2CH$). For the $BrCH_2$-group [11] $\sigma^* = +1.00$ and when doubled by addition, according to equation (3), gives for the $Br_2CH$ group $\sigma^* = +2.00$ which makes this a stronger $-I$ group than $Cl_2CH$; this is the reverse of the order expected from the electronegativities of the halogen substituents. Further, the same anomaly can be seen for the corresponding fluoro- and chloro-derivatives.[11] To allow for this a correction term $a$ was introduced, into the additivity equation (3), to obtain equation (4) and the fluorine and chlorine derivatives were used to evaluate the value of the constant ($a = 0.16$).

*The Correlation Equations, Table* 3.—The development of these equations may be seen in Table 3. From the outset compound (9; $R^1 = Et$, $R^2 = Ph$), showed deviations, $\Delta pK$ being between +0.35 and +0.23. For all other derivatives (3A1)—(3G1), $|\Delta pK| \leqslant -0.16$. Extension of the reaction series by inclusion of (7; $R^1 = R^2 =$ allyl), (8; $R^1 =$ allyl, $R^2 = Pr^i$), and (14; $R^1 = R^2 = Br$) resulted in $\Delta pK = +0.35$ for compound (9; $R^1 = Et$, $R^2 = Ph$); the next largest deviation was −0.21 for compounds (1; $R^1 = R^2 = Me$) and (8; $R^1 =$ allyl, $R^2 = Pr^i$). Further, the S.E. ($\delta$) assumed a magnitude approaching that for $\delta$ itself [see (3H1) and (3I1)]. However, it is on the introduction of the isomeric 3-nitro- and 4-nitro-phenyl derivatives (11; $R^1 = Et$, $R^2 = 3\text{-}NO_2C_6H_4$) and (12; $R^1 = Et$, $R^2 = 4\text{-}NO_2C_6H_4$) [see (3J1) and (3K1)] that the five derivatives (1), (9), (8), (11), and (12) have deviations $\Delta pK = +0.42$ to −0.27 and the S.E. ($\delta$) becomes larger than $\delta$ itself [see (3K1)]. This was clearly unsatisfactory for a correlation and the analysis was repeated with the six-number ($n$) in place of $E_s$ [equation (7)].

With the Newman six-number ($n$) as a measure of steric effects (3I2) provides a convenient point to commence the comparison. The largest deviation is again for compound (9; $R^1 = Et$, $R^2 = Ph$), $\Delta pK = +0.21$ followed by (8; $R^1 =$ allyl, $R^2 = Pr^i$), $\Delta pK = -0.20$ and then (5; $R^1 = R^2 = Et$), $\Delta pK = +0.16$. Then in (3K2) the largest deviations are due to compounds (8; $R^1 =$ allyl, $R^2 = Pr^i$), $\Delta pK = -0.31$, (10; $R^1 = R^2 = Ph$), $\Delta pK = -0.24$, (12; $R^1 = Et$, $R^2 = 4\text{-}NO_2C_6H_4$), $\Delta pK = +0.23$, (11; $R^1 = Et$, $R^2 = 3\text{-}NO_2C_6H_4$), $\Delta pK = +0.22$, (9; $R^1 = Et$, $R^2 = Ph$), $\Delta pK = +0.12$, and the S.E.($h$) is less than one-third of ($h$). The order and distribution of deviations ($\Delta pK$) between derivatives is different from that in the corresponding Table 3K1 for $E_s$ values. In the Table, (3K1) was the final correlation with $E_s$ values in which all assumptions and approximations had been made and then it had been possible to include only 12 of the 14 derivatives in the series. The remaining two derivatives, for which $E_s$

values were not available, were (6; $R^1$ = Et, $R^2$ = Pr$^i$), and (3; $R^1$ = Me, $R^2$ = Pr$^i$). Six-numbers may be calculated for these compounds [for (6) and (3)] and the analysis extended to all 14 derivatives. This result is shown in Tables 4 and 5 where all details have been tabulated. In every respect the correlation with the six-number measure of steric effects, for all 14 derivatives is more satisfactory than that obtained with $E_s$ values [Table 3, (3K1)]. Although in (3K1) S.E. $(\delta) > \delta$, $\delta$ remained negative as was found in all previous correlations (3A1)—(3J1), where this objection was generally less significant. On this basis the sign for ($h$) would be expected to be positive which is seen in (3M2). Therefore an acid-strengthening effect is consistently observed for each measure of steric effects ($E_s$ and $n$) although basic differences may be seen in the scales. Also the sign for $\rho^*$ (positive) conforms with the direction in which substituents would be expected to influence reactivity, with electron-withdrawing groups ($-I$, $\sigma^*$ positive) and electron-donating groups ($+I$, $\sigma^*$ negative) having acid-strengthening and acid-weakening effects respectively. Multiple correlation coefficients ($R$) are not directly comparable for (3K1) and (3M2) (Table 3) since the number of data points, in addition to scatter, determine the magnitude of $R$. In any case $R$ is a relatively insensitive measure of change even when there is no difference in the number of data points and direct comparisons are valid. In (3M2) (Table 4) the standard errors for all constants in equation (7) remain small enough for significant correlations with polar and steric effects to be accepted.

TABLE 4

Final correlation table (3M2) [see also Table 3 (3M2)]

| Compound no [a] | $R^1$ | $R^2$ | $pK_{i\,(obs.)}$ | $pK_{i\,(pred.)}$ | $\Delta pK$ [b] | $\sigma^*$ | $n$ |
|---|---|---|---|---|---|---|---|
| (1) | Me | Me | 8.51 | 8.50 | −0.01 | −0.190 | 0 |
| (2) | Me | Et | 8.28 | 8.33 | +0.05 | −0.210 | 3 |
| (4) | Me | Ph | 7.78 | 7.81 | +0.03 | +0.11 | 4 |
| (5) | Et | Et | 7.98 | 8.15 | +0.17 | −0.225 | 6 |
| (9) | Et | Ph | 7.44 | 7.62 | +0.18 | +0.100 | 7 |
| (10) | Ph | Ph | 7.30 | 7.13 | −0.17 | +0.405 | 8 |
| (13) | Cl | Cl | 5.55 | 5.49 | −0.06 | +1.94 | 0 |
| (7) | Allyl | allyl | 7.81 | 7.80 | −0.01 | +0.12 | 4 |
| (8) | Allyl | Pr$^i$ | 8.02 | 7.79 | −0.23 | −0.065 | 8 |
| (14) | Br | Br | 5.68 | 5.63 | −0.05 | +1.84 | 0 |
| (11) | Et | 3-$NO_2C_6H_4$ | 7.04 | 7.32 | +0.28 | +0.313 | 7 |
| (12) | Et | 4-$NO_2C_6H_4$ | 6.94 | 7.22 | +0.28 | +0.384 | 7 |
| (6) | Et | Pr$^i$ | 8.14 | 7.97 | −0.17 | −0.240 | 9 |
| (3) | Me | Pr$^i$ | 8.45 | 8.15 | −0.30 | −0.225 | 6 |

$pK_i = 8.23_3 - 1.41\sigma_6{}^* - 0.06_6 n$; $\rho^* = 1.41_6$ S.E. $(\rho^*) = 0.092$

$h = 0.06_6$ S.E. $(h) = 0.021$

$pK_0 = 8.23_3$ S.E. $(pK_0) = 0.132$

[a] Numbering for derivatives as in Table 2. [b] $\Delta pK = pK_{(pred.)} - (pK_{obs.})$ $R = 0.9806$

The magnitude of the deviations $\Delta pK$ obtained in correlations with equations (6) and (7) must be considered in the light of likely errors arising in the analysis. For one independent variable ($\sigma^*$) only, such LFER usually allow experimental $pK_i$ values to be fitted within ±0.1 unit.[6] The fit in multiparameter equations, (6) and (7), would have a wider latitude and ±0.2 to ±0.3 perhaps would seem not unreasonable for equation (6), in view of the origin of $E_s$, on account of the further independent variable $E_s$. It is difficult to be certain about equation (7) where ($n$) is an exact number calculated from the structural formula and short-comings in the six-number concept or in its application will be the factor in determining deviations here. Also in obtaining $\sigma^*$ values for the series (Table 1) it was necessary to calculate some of these values [for derivatives (7), (8), (11) and (12)] from the LFER for the carboxylic acids [6,13] and this might be expected to introduce up to a further ±0.1 units in uncertainty in $pK_1$ values estimated from

TABLE 5

' Relative contributions of polar and steric substituent effects on reactivity

$pK_{(pred.)} = 8.23_3 - 1.41_6\sigma^* - 0.06_6 n$ [Equation (3M2)]

| Compound no. [a] | $R^1$ | $R^2$ | * | $n$ | $pK_{(obs.)}$ | $pK_0$ | $-1.41_6\sigma^*$ | $-006_6 n$ | $pK_{i(pred.)}$ | $\Delta pK$ [b] |
|---|---|---|---|---|---|---|---|---|---|---|
| (1) | Me | Me | −0.190 | 0 | 8.51 | $8.23_3$ | +0.269 | 0.00 | $8.50_2$ | −0.01 |
| (2) | Me | Et | −0.210 | 3 | 8.28 | $8.23_3$ | $+0.29_7$ | $-0.19_8$ | $8.33_2$ | +0.05 |
| (4) | Me | Ph | +0.11 | 4 | 7.78 | $0.23_3$ | $-0.15_5$ | $-0.26_4$ | $7.81_4$ | +0.03 |
| (5) | Et | Et | −0.225 | 6 | 7.98 | $8.23_3$ | $+0.31_8$ | $-0.39_6$ | $8.15_5$ | +0.17 |
| (9) | Et | Ph | +0.100 | 7 | 7.44 [c] | $8.23_3$ | $-0.14_1$ | $-0.46_2$ | $7.63_0$ | +0.18 |
| (10) | Ph | Ph | +0.405 | 8 | 7.30 | $8.23_3$ | $-0.57_3$ | $-0.52_8$ | $7.13_2$ | −0.17 |
| (13) | Cl | Cl | +1.94 | 0 | 5.55 | $8.23_3$ | $-2.74_7$ | 0.00 | $5.48_6$ | −0.06 |
| (7) | Allyl | Allyl | +0.12 | 4 | 7.81 | $8.23_3$ | $-0.16_9$ | $-0.26_4$ | $7.80_0$ | −0.01 |
| (8) | Allyl | Pr$^i$ | −0.065 | 8 | 8.02 | $8.23_3$ | $+0.09_2$ | $-0.52_8$ | $7.79_7$ | −0.23 |
| (14) | Br | Br | +1.84 | 0 | 5.68 | $8.23_3$ | $-2.60_5$ | 0.00 | $5.62_8$ | −0.05 |
| (11) | Et | 3-$NO_2C_6H_4$ | +0.313 | 7 | 7.04 | $8.23_3$ | $-0.44_3$ | $-0.46_2$ | $7.32_8$ | +0.28 |
| (12) | Et | 4-$NO_2C_6H_4$ | +0.384 | 7 | 6.94 | $8.23_3$ | $-0.54_3$ | $-0.46_2$ | $7.22_8$ | +0.28 |
| (6) | Et | Pr$^i$ | −0.240 | 9 | 8.14 | $8.23_3$ | $+0.33_9$ | $-0.59_4$ | $7.97_8$ | −0.17 |
| (3) | Me | Pr$^i$ | −0.225 | 6 | 8.45 | $8.23_3$ | $+0.31_8$ | $-0.39_6$ | $8.15_5$ | −0.30 |

[a] Numbering for compounds as in Table 2. [b] $\Delta pK = pK_{(pred.)} - pK_{(obs.)}$ [c] Mean value.

equations (6) and (7). It therefore seemed reasonable to anticipate deviations from equation (6) which would approach $\pm0.3$ or $\pm0.4$ in p$K_i$ and for equation (7) $\pm0.2$ p$K_i$. In Table 4 (3M2), for deviations exceeding $\pm0.2$ for equation (7), it has been tentatively presumed that they are significant. Equation (7) as applied to the data in Table 4 has, therefore, been taken as (i) having some value as a predictive relationship, (ii) demonstrating that acid strength in 5,5-disubstituted barbituric acid derivatives is increased because of steric effects of 5-substituents, and (iii) that deviations ($\Delta$p$K$) for derivatives (8), (11), (12), and (3) (Table 4) are due to causes inadequately accounted for in the application of equation (7) to the data in Table 4. Each of these conclusions will now be considered in further detail.

(i) *Predictive Relationship.*—Further improvement in the correlation of the data in Table 3 with equations (6) and (7) over that given [equation (7), (3M2), Table 4] largely depends on further understanding of the cause of the deviations ($\Delta$p$K$), (iii) above.

(ii) *Steric Acid-strengthening Effects.*—Equation (3M2) (Table 4) has been taken to demonstrate that a correlation between steric effects, in addition to electronic effects, of 5-substituents is significant. The equation (3M2) demonstrates, empirically, that acid strength in derivatives increases with increasing steric effects in 5-substituents. Except for the derivatives noted in (iii), equation (3M2), by its inclusion of an allowance for steric effects, accounts fairly well for acid strengths in the reaction series. The 5,5-dimethyl- and 5,5-diethyl-barbituric acids [compounds (1) and (5) respectively, Tables 4 and 5] showed this most convincingly. 5,5-Dimethylbarbituric acid would be expected to be a stronger acid than 5,5-diethylbarbituric acid if electronic effects of substituents alone determined acid strength. Although the difference is greatest for compounds (1) and (5), similar trends may be seen in all other examples in which 5-methyl is replaced by 5-ethyl. Moreover, this steric acid-strengthening trend is less with the isopropyl group than the ethyl group as can be seen for the series (1; $R^1 = R^2 =$ Me), (2; $R^1 =$ Me, $R^2 =$ Et), and (3; $R^1 =$ Me, $R^2 =$ Pr$^i$) in Table 4. The difference in electronic effects for the Pr$^i$ and the Et group is altogether too small to account for the weak acid character of (3; $R^1 =$ Me, $R^2 =$ Pr$^i$) and it appears that the Pr$^i$ group is less effective than the Et group in increasing acid strength.

Generally, proton-transfer dissociation has been regarded as the simplest reactivity characteristic of organic acids. Most often acid strengths in aqueous solutions have followed the anticipated order for electronic effects in substituents. Steric effects have been found to be important in dissociation in some instances.[14-21] In these instances, for larger groups, increased steric effects of substituents have been observed to have an acid-weakening effect. In aliphatic carboxylic acids, this weakening effect is attributed [15,18] to steric hindrance of solvation (solvent exclusion) in the anion of the acid, which is thus less stable with respect to the acid $RCO_2H$; this results in an increase in the standard free-energy change for dissociation.

The small size of the hydrated proton would be expected to offer the least possible steric dependence in the dissociation of acids in aqueous solvents. Failure of structure–reactivity relationships, or anomalies within a reaction series, may arise from discontinuities in the degree of solvation of species involved in equilibria, or as a result of a change in reaction mechanism. For dissociation of 5,5-disubstituted barbituric acid derivatives, a change of mechanism may be discounted. Therefore, a steric effect influencing solvation development, by hydrogen-bonding of water molecules, at the polar heterocyclic barbituric acid nucleus which, in turn, has an acid-strengthening effect, seemed a reasonable explanation. This steric effect, due to 5-substituents, is considered to be more important in the undissociated molecule where solvation due to weaker dipole–dipole interactions would be more susceptible to disruption than in the anion, where the stronger ion–dipole interactions are relatively less affected. This steric hindrance would result in a reduction of stabilization by dipole–dipole solvation (solvent exclusion in the undissociated molecule) relative to the less affected anion and decrease the standard free-energy change for dissociation. In structure (II) the reduced steric effect would result in the most solvated species in the series. For (III) the 5-ethyl groups may project over the heterocyclic nucleus, both above and below the ring, and hinder solvation. In the solid state the plane connecting the 5-ethyl groups cuts the ring plane almost perpendicularly along an axis intersecting the C(2)- and C(5)-carbon atoms in both the free acid [22] and its potassium salt.[23] Rotation of the ethyl groups about the 5-carbon atom should be possible in solution and it is likely that the above proposed orientations fall within wells in the potential energy-rotation function for these groups. An explanation for the consequences of this hypothesis can be put forward also. If for (II) in Figure 2 the 4- and 6-carbonyl groups are more highly solvated than in (III) this would reduce the effective dipole in these groups and the $-I$ effect for these groups in (II) would be less than in (III) where solvation is diminished because of steric effects. The reduced $-I$ effect of the carbonyl groups in (II) would then be less effective in promoting dissociation at the adjacent N–H groups than in (III).

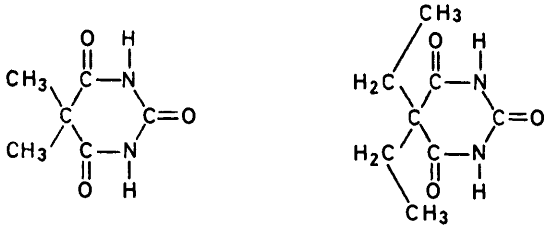
(II) (Solvated) (III) (less solvated)

FIGURE 2

As in all analyses of structure–reactivity relationships, for electronic or steric or other effects, it is the difference between the magnitude of the effect in the initial and final states in the critical process or reaction under study which is important. For acid dissociation, the undissociated molecule in solution is taken as the initial state and the products formed on dissociation as the final state. Substituent effects on this difference may occur in several ways to produce: (*a*) a significant change in the final state relative to the initial state, (*b*) a significant effect in the initial state relative to the final state, and (*c*) similar effects on both initial and final states. For the hypothesis so far developed, the low acid strength of compound (1; $R^1 = R^2 =$ Me) is attributed to a higher degree of solvation in the undissociated molecule relative to all other derivatives in the series. Introduction of ethyl groups in place of methyls, hinders solvation in the undissociated molecule (solvent exclusion) relative to the anion to have an acid-strengthening effect, case (*b*) above. This is essentially the converse of the argument, *i.e.* case (*a*), used to account for acid-weakening in the highly hindered carboxylic acids previously referred to. It has been proposed that in the 5,5-disubstituted barbituric acid derivatives a transition from an acid-strengthening to an acid-weakening effect might be possible.[24] A suitable substituent might, therefore, have a steric effect in both the initial and the final states thus cancelling itself out so far as overall reactivity is concerned. This is visualised as a substituent which desolvates, by steric hindrance, both the undissociated molecule (acid-strengthening effect) and the anion (acid-weakening effect) to such an extent that the $pK_1$ value does not depend on steric effects, case (*c*). Attention is drawn to this last possibility since the 5-isopropyl substituent clearly does not increase reactivity in derivatives in the reaction series in proportion to the steric effect anticipated for the group on a six-number basis.* Also in the only instance where an $E_s$ value for an isopropyl derivative (8; $R^1 =$ allyl, $R^2 = Pr^i$) is available [see Table 3 (3H1)], $\Delta pK = -0.22$, suggesting that a similar situation exists with these values. Therefore, the ' effective steric effect ' of the isopropyl group may be much less than originally anticipated because it falls between case (*b*) and case (*c*) as given above. This will be considered further in the following section on $\Delta pK$ values. Attention has previously been drawn to the need to allow not only for the orientating effect of ions, but also for the interaction of the uncharged molecules with the solvent in the dissociation of acids.[25]

(iii) *The Deviations* ($\Delta pK$), *Table* 4.—Further work is being carried out to confirm and, if necessary, advance reasons for the deviations referred to previously [compounds (8), (11), (12), and (3)].

A major interest developed for compound (3; $R^1 =$ Me, $R^2 = Pr^i$) (Tables 4 and 5) which had the largest deviation ($\Delta pK = -0.30$) in the series. This was surprising since derivatives with alkyl substituents generally appeared to fit equation (7) well. Also it may be noted that this derivative is isoelectronic, isosteric (six-number) and isohyperconjugative with compound (5; $R^1 = R^2 =$ Et). Although the polar effect allowed for compound (3; $R^1 =$ Me, $R^2 = Pr^i$) rests on a calculated $\sigma^*$ value (Table 1) this value lies within the range ($-0.3$ and $+1.5$) where the additive rule is known to be correct, within limits of error, for these values.[26] Therefore, the overestimation of the acid strength for compound (3; $R^1 =$ Me, $R^2 = Pr^i$) is unlikely to be significantly connected with this polar constant which, in any case, will make an acid-weakening contribution in the calculation. Overestimation of the steric effect (six-number) for the isopropyl group in 5,5-disubstituted barbituric acids seems a much more likely cause of the deviation. This overestimation may arise in two ways at least: (*a*) the isopropyl group in its orientations over the heterocyclic nucleus has an ' effective six-number ' of less than six [referred to in (ii) above] or (*b*) conformations that can develop in the heterocyclic ring hold the isopropyl group in a position (time-averaged) where it cannot exert its full steric influence. For (*a*) an adjustment of *n* to a smaller value, corresponding to the ' effective six-number ' (e.s.n.) for steric effects, would be expected to be consistent when applied to all isopropyl derivatives in the reaction series. For (*b*) simple corrections may be much more difficult, requiring a knowledge of a conformer ratio for each derivative. It is proposed, as an addition to the acid-weakening solvation hypothesis already put forward, that rapidly inter-changing half-chair conformers exist in equilibrium (Figure 3). The conformer in which solvation is greatest will be the thermodynamically more stable one and it will be the weaker acid of the two conformers in equilibrium. The measured $pK_1$, based on the dissociation of a weak monobasic acid, will, therefore, be a 'weighted value ' and the more solvated conformer [the weaker acid ($H_2A$)] will dominate the value found. If this follows then the deviation observed for compound (3; $R^1 =$ Me, $R^2 = Pr^i$) might be accounted for. From Dreiding models with the substituent least capable of hindering solvation (Me) in the equatorial position and the other ($Pr^i$) in the axial position, it seems that this structure would correspond to the conformer which is the weaker acid. Clearly when $R^1 = R^2$ the conformers are indistinguishable and only with such substituents would the best correlations with equations (6) and (7) result, unless a correction for the conformational isomer ratio can be introduced into the LFER.

Finally it may be noted that, whether conformations of the half-chair type are important or not in these 5,5-disubstituted barbituric acid structures, it is clear that any particular 5-substituent, as a consequence of the $sp^3$-hybridization at the 5-carbon atom, can develop a greater steric effect on one face of the heterocyclic nucleus than the other.

Work is in progress which should confirm, quite independently of the present empirical correlation (Table 4), the acid-strengthening steric effects (ii), and

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* Nor, for the present reaction series, is it possible to test $E_s$ values for a large substituent $R^2$ and a methyl group ($R^1 =$ Me).

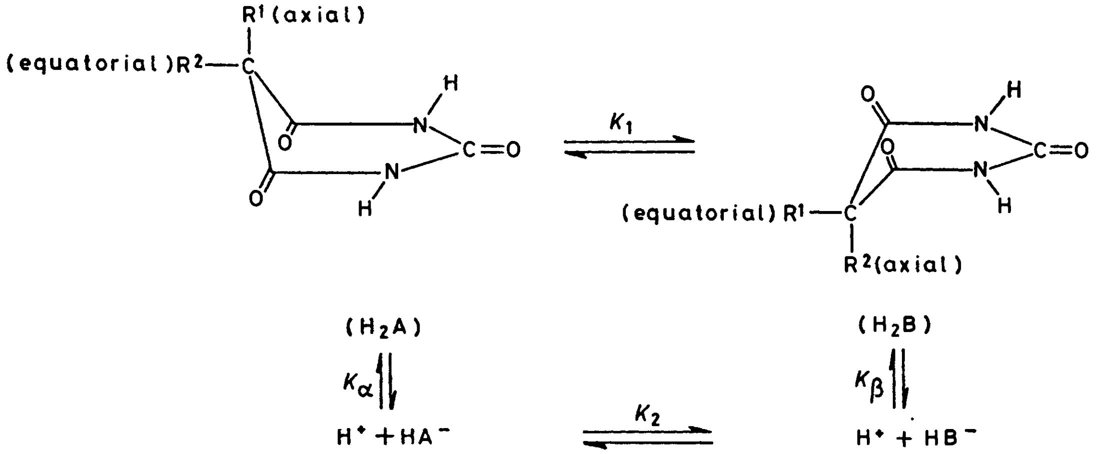

FIGURE 3

discriminate between (*a*) and (*b*) in (iii). The desirability of obtaining independent evidence that correlations with reaction constants in multi-parameter analyses are significant has been stressed.[27] Also further independent experimental evidence for solvation in the undissociated molecule of the less sterically hindered barbituric acid derivatives will appear in following Parts of this series.

*Steric Substituent Constants*.—The use of six-numbers in place of $E_s$ values has the obvious attraction of allowing the extension of structure-reactivity relationships beyond reaction series for which $E_s$ values are available. However, it may be noted that six-numbers imply that for compounds (1; $R^1 = R^2 = Me$), (13; $R^1 = R^2 = Cl$), and (14; $R^1 = R^2 = Br$) electronic effects alone determine the acid strength for these compounds. While this may not represent a significant departure from the $E_s$ value scale of steric effects for compound (1) there is a fundamental difference for compounds (13) and (14).

[8/1936 *Received, 7th November*, 1978]

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