Substituent Effects on 6-Substituted 3-Hydroxy-4-pyrones

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Acidity and basicity constants, heats of ionization, and electronic and nmr spectra of a series of 6-substituted 3-hydroxy-4-pyrones (HA) have been determined. The acidity and basicity constants and the chemical shifts of C_2 and C_5 protons have been correlated with Hammett σ_p values. As with phenols the correlation between heats of ionization and acidity constants is unsatisfactory. The wavenumber shifts $\Delta\nu = \nu_A - \nu_{HA}$, where ν_A and ν_{HA} are the electronic absorption frequencies, correlate well with the heats of ionization but poorly with the acidity constants.

The effect of substituents in the aromatic and aliphatic series, as measured by σ constants, has been evaluated through dissociation constants, respectively of substituted benzoic acids[1,2] and acetic acids.[3] The substituent effect in the 4-pyrone series, where the transmission of the substituents effect is likely to be different, was investigated by measuring the pK values of 3-hydroxy-4-pyrones (HA) and establishing correlations with other properties. The relative contributions of enthalpy and entropy to the acid ionization process were determined for comparison with previous results on phenols[4] where there is no simple relation between pK and $\Delta H°$. The ultraviolet maximum absorption frequencies of the HA and A^- forms, expressed as wavenumber shifts $\Delta\nu = \nu_A - \nu_{HA}$, were obtained in an attempt to check the relation between $\Delta\nu$ and pK or $\Delta H°$ proposed[5] in the case of disubstituted phenols.

Results and Discussion

The acidity constants of eight substituted 3-hydroxy-4-pyrones were measured by spectrophotometric and potentiometric methods at 0.50 M ionic strength[6]. As some charged substituents (6-CO_2^- and 2,6-CO_2^-) were included in the series, the pK values were extrapolated to zero ionic strength to correct for different activity effects. The pK values of kojic acid (6-CH_2OH) were measured for different ionic strengths, from $\mu^{1/2} = 0.7$ to 0.1. Extrapolation of pK *vs.* $\mu^{1/2}$ to $\mu = 0$ gives a pK_0 value corrected for activity. The relation found was pK_0 = p$K_{0.50}$ + 0.30. The same correction was used for other uncharged acids. For comenic acid (6-CO_2^-) pK_0 = p$K_{0.50}$ + 0.46 was obtained. This correction is similar to that determined for 4-CO_2^- p-hydroxy benzoic acid of similar structure, pK_0 = p$K_{0.50}$ + 0.48. As expected, with meconic acid (2,6-CO_2^-), the activity correction is larger: pK_0 = p$K_{0.50}$ + 0.95. The acidity constants are shown in Table I and are compared with values already known.[7]

A correlation between pK_0 values and Hammett σ_p constants can be established for 6-substituted 3-hydroxy-4-pyrones, as shown in Figure 1. Equation 1

$$\mathrm{p}K_0 = 8.01 - 1.63\sigma_p \tag{1}$$

is obtained by a least-squares treatment with a correlation coefficient $r = -0.978$ and a standard deviation from regression $s = 0.02$.

TABLE I

ACIDITY CONSTANTS OF 3-HYDROXY-4-PYRONES

No.	Name	Substituent	p$K_{0.50}$	pK_0	pK_0[a]	σ_p[b]
1	Allomaltol	6-CH_3	7.98 ± 0.03	8.28	8.28	−0.170
2	Pyromeconic acid	6-H	7.69 ± 0.03	7.99	7.91	0
3	Kojic acid	6-CH_2OH	7.66 ± 0.03	7.96	7.90	0.08[c]
4	Iodokojic acid	6-CH_2I	7.50 ± 0.03	7.80	...	...
5	Chlorokojic acid	6-CH_2Cl	7.40 ± 0.03	7.70	...	0.184
6	Comenic acid	6-CO_2^-	7.29 ± 0.03	7.75	7.67	0.132
7	Meconic acid	2,6-CO_2^-	9.35 ± 0.03	10.30	10.81	...
8	Maltol	2-CH_3	8.36 ± 0.03	8.66	...	...

[a] See ref 7. [b] See ref 2. [c] From phenols, $\rho = -2.11$,[2] $\sigma_p = (9.99 - 9.82)/2.11 = 0.08$; p$K_0$ values for phenol and p-methylolphenol from G. Kortum, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solutions," Butterworth and Co. Ltd., London, 1961, p 457.

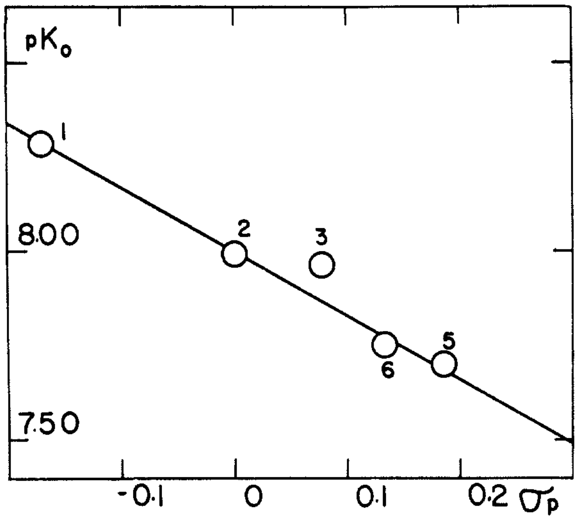

Figure 1.—The relationship between pK_0 and σ_p for 6-substituted 3-hydroxy-4-pyrones. Numbers refer to Table I.

A σ_p value can thus be deduced for the CH_2I substituent, $\sigma_p = (8.01 - 7.80)/1.63 = 0.128$. The -1.63ρ value, is higher than that found in the phenols series, −2.11.[2] The transmission of the substituent effect is apparently decreased in the pyrones because of decreased resonance.

The pK_0 values may be considered as a first measure of the substituent effect on the pyrone ring, but the pK_0 *vs.* σ_p correlation indicates that the Hammett constants may be used to advantage, so that other properties of 3-hydroxy-4-pyrones could be correlated with σ_p values.

When the reaction site changes, R may be either in *meta* or *ortho* positions and σ_m or Taft's σ_0 should be

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(1) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p 188.

(2) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(3) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).

(4) L. G. Hepler, *J. Am. Chem. Soc.*, **85**, 3489 (1961).

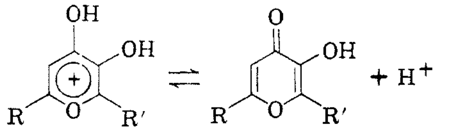
(5) M. Rapoport, C. K. Hancock, and E. A. Meyers, *ibid.*, **83**, 3489 (1961).

(6) G. Choux and R. L. Benoit, *Bull. Soc. Chim. France*, in press.

(7) K. Tsuji, *J. Sci. Res. Inst.* (Tokyo), **48**, 126 (1954); *Chem. Abstr.*, **49**, 4379 (1955).

used. However, as the constants σ_m or σ_o are not available in the literature for most of our substituents, σ_p will be used even in these cases. As the resonance contribution of these substituents to the σ values is not very important, the linearity of the relationships will not be affected, although the ρ values will depend on the position of the substituents.

In strongly acid medium, the ultraviolet spectra of 3-hydroxy-4-pyrones show protonation of the carbonyl group.[8]



$$K_B = \frac{(H^+)\ (HA)}{(H_2A^+)}$$

The protonation constants K_B were measured by spectrophotometric methods. (H^+) is given by the Hammett acidity function H_0;[9] (HA) and (H_2A^+) are obtained from the absorbance of 10^{-3} M solutions of 4-pyrones, for different concentrations of sulfuric acid. The pK_B values are shown in Table II. They are correlated with σ_p values as shown in Figure 2 and eq 2, with $r = -0.968$ and $s = 0.06$.

TABLE II
BASICITY CONSTANTS AND NMR AND INFRARED SPECTRA OF 3-HYDROXY-4-PYRONES

Substituent	pK_B	δ 5 H, ppm	δ 2 H, ppm	δ 3 OH, ppm	ν_{OH}, cm^{-1}	σ_p
6-CH_3	−0.72 ± 0.10	6.10	7.82	8.56	3385	−0.170
6-H	−1.28 ± 0.10	6.36	8.00	8.95	3409	0
6-CH_2OH	−1.38 ± 0.10	6.30	7.96	8.90		0.08
6-CH_2I	−1.60 ± 0.10	6.54	8.00		3391	0.128
6-CH_2Cl	−1.71 ± 0.10	6.60	8.08		3405	0.184
6-CO_2H[b]	−2.34 ± 0.10	6.96	8.17	10.00		0.265
2,6-CO_2H						
2-CH_3	−0.71 ± 0.10[a]	6.30	7.98	8.40	3386	

[a] A. Beauchamp and R. L. Benoit, *Can. J. Chem.*, **44**, 1615 (1966). [b] The carboxylic group of comenic acid has a pK 1.7 value in water and is not appreciably ionized in dimethyl sulfoxide.

$$pK_B = -3.39\sigma_p - 1.23 \qquad (2)$$

The transmission of the substituent effect on the carbonyl group, as measured by $\rho = -3.38$, is more important than for the 3-hydroxyl group. The substituent is nearer and its effect can be transmitted more easily on the oxygen of the carbonyl through conjugated double bonds and a more aromatic structure.

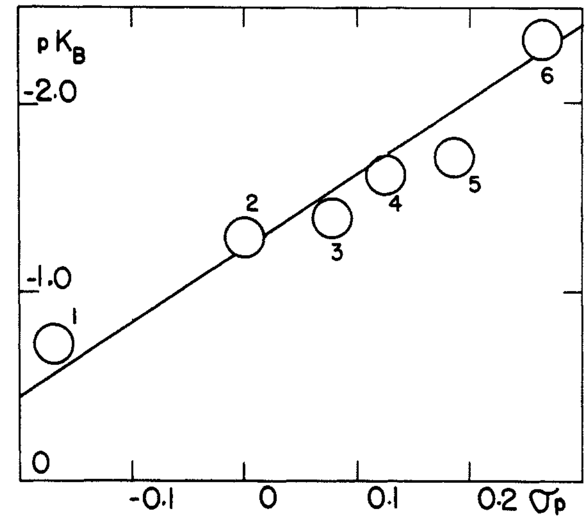


Figure 2.—The relationship between pK_B and σ_p for 6-substituted 3-hydroxy-4-pyrones. Numbers refer to Table I.

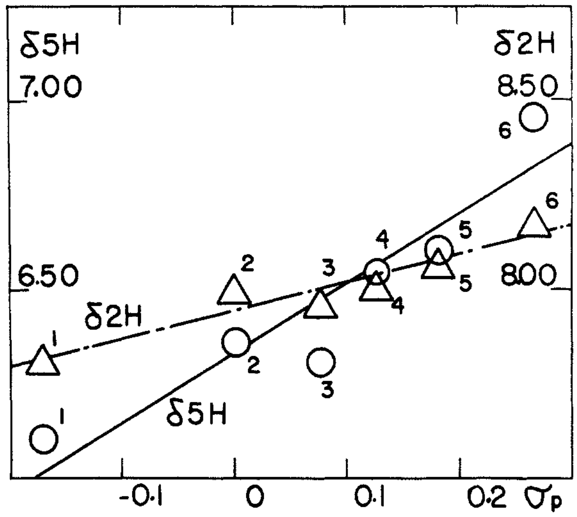


Figure 3.—The relationships between δ 5 H (ppm), δ 2 H (ppm), and σ_p for 6-substituted 3-hydroxy-4-pyrones. Numbers refer to Table I.

Among other properties of 4-pyrones affected by substituents is the nmr chemical shift of the different protons. Protons of the 4-pyrones are sensitive to the effect of the oxygen heteroatom, and appear at different fields. The chemical shifts of C_2 and C_6 protons appear at lower field than those of C_3 and C_5 protons.[10] In 3-hydroxy-4-pyrones, the substituent on C_6 position affects the chemical shifts of other protons. The nmr spectra of our derivatives in deuterated dimethyl sulfoxide were recorded and the values of the chemical shifts of C_2, C_5, and C_3 OH protons are given in Table II. The values found for maltol (2-CH_3) are comparable to those reported using deuterated chloroform.[11] The chemical shifts of C_2 and C_5 protons are correlated with σ_p values in Figure 3 and eq 3 and 4, with $r = 0.945$, $s = 0.02$ (eq 3), and $r = 0.924$, $s = 0.04$ (eq 4), with units in parts per million.

$$\delta\,2\,H = 0.73\sigma_p + 7.95 \qquad (3)$$

$$\delta\,5\,H = 1.80\sigma_p + 6.33 \qquad (4)$$

The positive values of ρ indicate that an electron withdrawing substituent displaces the chemical shifts of C_2 and C_5 protons to low fields. The substituents have a stronger effect on the chemical shift of the conjugated *ortho* C_5 proton, than on that of the C_2 proton. The chemical shift of C_3 OH cannot be measured accurately, and it is expected that δ 3 OH is modified by hydrogen bonding.

The free energy of ionization, calculated from pK_0 values is expressed as $\Delta F° = \Delta H° - T\Delta S°$, where $\Delta H°$ is the heat of ionization. For many compounds $\Delta H°$

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(8) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworth and Co. Ltd., London, 1963, p 82.

(9) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

(10) J. Jonas, W. Derbyshire, and M. S. Gutowsky, *J. Phys. Chem.*, **69**, 1 (1965).

(11) C. T. Mathis and J. H. Goldstein, *Spectrochim. Acta*, **20**, 871 (1964).

TABLE III

FREE ENERGY, HEAT OF IONIZATION, AND ELECTRONIC SPECTRA OF 3-HYDROXY-4-PYRONES

Substituent	$\Delta F°$, kcal mole^{-1}	$\Delta H°$, kcal mole^{-1}	λ_A, mμ	λ_{HA}, mμ	ν_{HA}, cm^{-1}	ν_A, cm^{-1}	$\Delta\nu$, cm^{-1}
6-CH_3	11.25 ± 0.05	4.27 ± 0.10	266	308	37740	32470	−5270
6-H	10.85 ± 0.05	3.82 ± 0.10	270	315	37040	31750	−5290
6-CH_2OH	10.82 ± 0.05	3.37 ± 0.10	268	314	37310	31850	−5460
6-CH_2I	10.62 ± 0.05	1.42 ± 0.10	273	330	36630	30300	−6330
6-CH_2Cl	10.47 ± 0.05	2.67 ± 0.10	273	322	36630	31000	−5570
6-CO_2^-	10.53 ± 0.05	2.76 ± 0.10	289	345	34600	28990	−5610
2,6-CO_2^-	14.00 ± 0.05	3.47 ± 0.10	305	365	32790	27400	−5390
2-CH_3	11.80 ± 0.05	4.54 ± 0.10	275	319	36360	31350	−5010

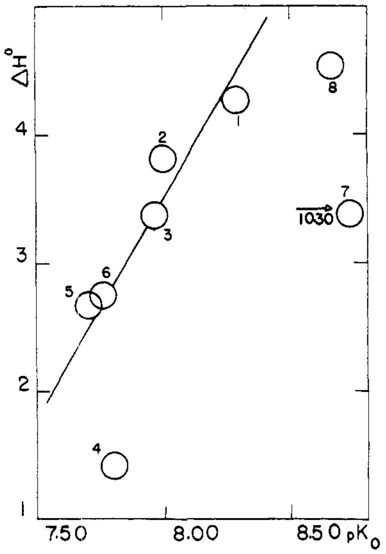

Figure 4.—The relationship between $\Delta H°$ (kcal mole^{-1}) and pK_0 for 3-hydroxy-4-pyrones. Numbers refer to Table I.

cannot be correlated with σ values even if the substituent effect is mainly of inductive nature. Hepler has offered an interesting explanation to account for this. $\Delta H°$ is separated in two terms: one represents the external contribution to enthalpy and is related to the entropy change; the other term is the internal contribution and is dependent on σ values. The heats of ionization of the 3-hydroxy-4-pyrones, $\Delta H°$, are shown in Table III, with the corresponding $\Delta F°$ values.

A rough correlation is observed in Figure 4 between $\Delta H°$ and pK_0 or $\Delta F°$ for 6-substituted 3-hydroxy-4-pyrones. Iodokojic acid (6-CH_2I) and maltol (2-CH_3) fall badly off the line. However, the substituent effect is found here mainly in the enthalpy part of $\Delta F°$. $\Delta H°$ cannot be simply considered as the result of the ionization of 3 OH, because of hydrogen bonding. The hydrogen-bond contribution to the heat of ionization is likely to be affected by the substituents through a change of the electronic density on the *ortho* carbonyl, and the heat of ionization may remain small or nearly constant. The result will be a global change in $\Delta H°$ depending on the substituent. Hydrogen bonding is evidenced by the infrared spectra in CCl_4. The OH band is very wide and the frequencies shown in Table III indicate important intramolecular hydrogen bonding, especially for methyl-substituted compounds.

A general relationship between electronic spectra and acidity constants has been established in the case of disubstituted phenols.[5] Assuming that all compounds in the series considered undergo the same electronic transitions, the relation is eq 5 or 6 where

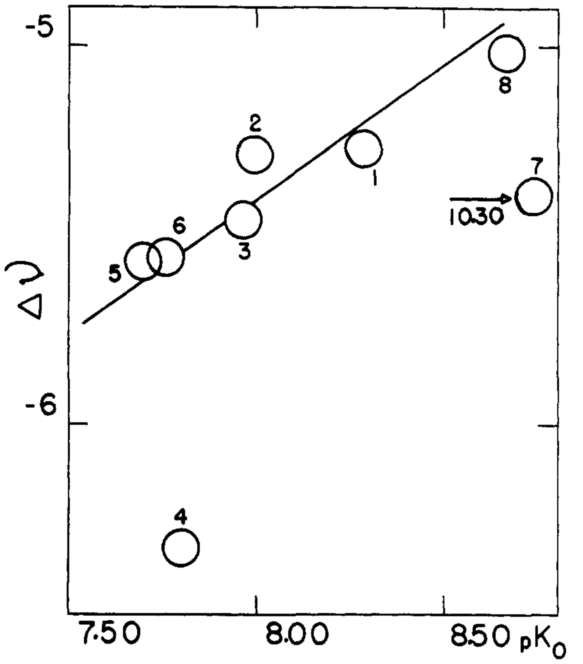

Figure 5.—The relationship between $\Delta\nu$ (cm^{-1} × 10^{-3}) and pK_0 for 3-hydroxy-4-pyrones. Numbers refer to Table I.

$$\Delta\nu = 350\,(\Delta E^* - \Delta H°) \tag{5}$$

$$\Delta\nu = \frac{-2.30\,RT}{2.86}\,\mathrm{p}K + \frac{\Delta E^* - T\Delta S - H°(\mathrm{H}^+)}{2.86} \times 10^3 \tag{6}$$

$\Delta\nu = \nu_A - \nu_{HA}$ is the difference between the electronic absorption frequencies of A^- and HA expressed in cm^{-1}, $\Delta E^* = E_A^* - E_{HA}^*$ is the difference between the energies of the excited states of A^- and HA expressed in kcal mole^{-1}, and $H°(\mathrm{H}^+)$ is the standard enthalpy of the proton. Hancock and Meyers[5] have stated that, if $\Delta E^* - T\Delta S° - H°(\mathrm{H}^+)$ is either constant or has a small variation, $\Delta\nu$ should be linearly related to pK with a negative slope. The absence of such a relation with the disubstituted phenols led these authors to conclude that the last term in eq 6 was a variable. $\Delta\nu = \nu_A - \nu_{HA}$ were measured here in aqueous acidic and basic solutions and are given in Table III. Although, Figure 5 shows only a poor correlation between $\Delta\nu$ and pK_0, $\Delta\nu$ and $\Delta H°$ are well correlated in Figure 6, through the relation given in eq 7, with r = 0.966 and s = 122. Equation 7 is even in-

$$\Delta\nu = -6725 + 375\,\Delta H° \tag{7}$$

dependent of the position of the substituent and may be applied to all 3-hydroxy-4-pyrones studied. Meconic acid (2,6-CO_2^-), maltol, and iodokojic acid which did not follow the correlation $\Delta\nu$ *vs.* pK_0 can now be included in $\Delta\nu$ *vs.* $\Delta H°$. However, the slope obtained is positive (this is in disagreement with the value pre-

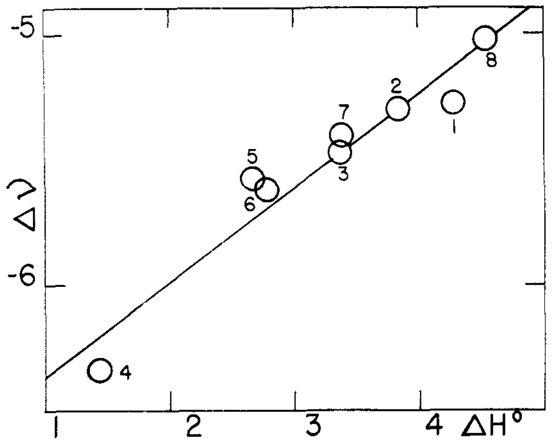

Figure 6.—The relationship between $\Delta\nu$ (cm^{-1} × 10^{-3}) and $\Delta H°$ (kcal mole^{-1}) for 3-hydroxy-4-pyrones. Numbers refer to Table I.

dicted by eq 5 assuming constant ΔE^*) as in the previous correlations $\Delta\nu$ *vs.* pK_0.[5,12] The $T\Delta S°$ term which might have accounted largely for the nonobservance of eq 6, has been supressed here in the $\Delta\nu$ *vs.* $\Delta H°$ correlation, but the slope remains positive. It seems therefore preferable to interprete these results in terms of an experimental relation between ΔE^* and $\Delta H°$ (eq 8). The application of eq 5 to substituted phenols[4] was also attempted and failed.

$$\Delta E^* = 2.06\Delta H° - 19.2 \qquad (8)$$

Equation 8 implies that the excited states are sensitive to the substituents effect in the same way as are the ground states. A better knowledge of the nature of the electronic transitions in these compounds is required to explain these experimental conclusions.

Experimental Section

Materials.—The 3-hydroxy-4-pyrones were obtained from commercial sources or prepared by methods previously described in the literature or modifications thereof, as indicated by footnotes in Table IV. The compounds were purified by vacuum sublimation.

Ultraviolet Spectra and Measurements of pK_0 and pK_B Values.—All measurements were carried out at 25.0°. The ionic strength was adjusted with weighed amounts of NaCl. The pH values were measured with a Radiometer pH Meter 22, and standardization was made with potassium bitartrate (pH = 3.56). The acidity constants were determined from ionic strength 0.01 to 0.50 *M* by potentiometric neutralization of 100 ml of 10^{-2} *M* solutions of 3-hydroxy-4-pyrones. A 1 *M* sodium hydroxide solution was added by means of a microburet. Plotting (Na$^+$)·(H$^+$) *vs.* (Na$^+$) gives a straight line whose slope is *K*, (Na$^+$) being the concentration of sodium hydroxide added. The p*K* values were also determined for ionic strength 0.50 by measuring at several wavelengths the absorbance of 10^{-3} *M* solutions, ranging in pH from 2 to 12. A Bausch and Lomb 505 spectrophotometer was used. The pK_B values were calculated from the absorbance at several wavelengths for 10^{-3} *M* solutions of the compounds in sulfuric acid ranging in concentration from 0.1 to 17 *M*. p$K_{0.50}$ and pK_B were calculated in the same way. Plotting ΔA(H$^+$) *vs.* ΔA or $\Delta A 10^{H_0}$ *vs.* ΔA gives a straight line whose slope is $K_{0.50}$ or K_B^{-1}. ΔA is the difference of absorbance between solutions of nonionized and partially neutralized pyrone; H_0 is the Hammett acidity function.[9]

TABLE IV

ANALYSIS AND MELTING POINTS OF 3-HYDROXY-4-PYRONES

	Calcd, %		Found, %			Lit.
Substituent	C	H	C	H	Mp, °C	mp, °C
2-CH_3	57.20	4.80	57.09	4.83	158–159	159[a]
6-CH_3	57.20	4.80	57.40	4.87	149–150	152[b]
6-H	53.51	3.57	53.70	3.68	116–117	118[a]
6-CH_2OH	50.71	4.23	50.72	4.24	153–154	152–153[c]
6-CH_2I[d]	28.60	1.98	30.29	2.19	176–177	
6-CH_2Cl	44.90	3.12	44.83	3.00	166–167	166–167[c]
6-CO_2H	46.17	2.56	45.98	2.57	284–285	. . .

[a] See ref 8. [b] M. G. Brown, *J. Chem. Soc.*, 2558 (1956). [c] V. Grignard, G. Dupont, and J. B. Locquin, Traité de Chimie Organique, Vol. 18, Masson et Cie., Editeurs, Paris 1945, p 351. [d] From chlorokojic acid dissolved in acetone, by adding a solution of sodium iodide in acetone. Sodium chloride precipitates, and iodokojic acid is recrystallized twice in 95% ethanol.

Infrared and Nmr Spectra.—Infrared spectra of the compounds 2.10^{-3} *M* in dried CCl_4 were recorded on a Perkin-Elmer 621 spectrophotometer. Nmr spectra were taken at 30° with an A-60 Varian spectrometer. The solutions of the compounds were 10% in deuterated dimethyl sulfoxide with tetramethylsilane added as an internal standard.

Calorimetric Measurements.—The Tian–Calvet microcalorimeter used[13] was standardized in the range 0 to 0.200 cal by the Joule effect; 2.10^{-3} *M* solutions of 3-hydroxy-4-pyrones were prepared, adjusted to pH 4.5, and thermostated at 25.0°. The inside compartment of the cell was filled with 1.500 ml of a 10^{-2} *M* NaOH solution; about 5 g of the acidic solution was introduced in the outside compartment and accurately weighed. The cell was placed in the microcalorimeter and thermostated at 25.0° and thermal equilibrium was attained after 5 hr. The microcalorimeter was then turned to mix the acidic and basic solutions inside the working cell, and the heat effect was recorded until there was a return to thermal equilibrium. The heat effect was measured, then calculated for a molar acid concentration, and substracted from 13.52 kcal mole^{-1} [14] to give $\Delta H°$ values. Each value given in Table III is the result of at least two measurements with different amounts of acid.

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(12) H. N. Simpson, C. K. Hancock, and E. A. Meyers, *J. Org. Chem.*, **30**, 2673 (1965).

(13) E. Calvet and H. Prat, "Microcalorimétrie, applications physicochimiques et biologiques," Masson et Cie., Editeurs, Paris, 1956, p 126.

(14) H. M. Papée, W. J. Canady, and K. J. Laidler, *Can. J. Chem.*, **34**, 1677 (1956).