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Stereo-electronic Effects in the Alkaline Hydrolysis of Benzamides and Benzonitriles[1]

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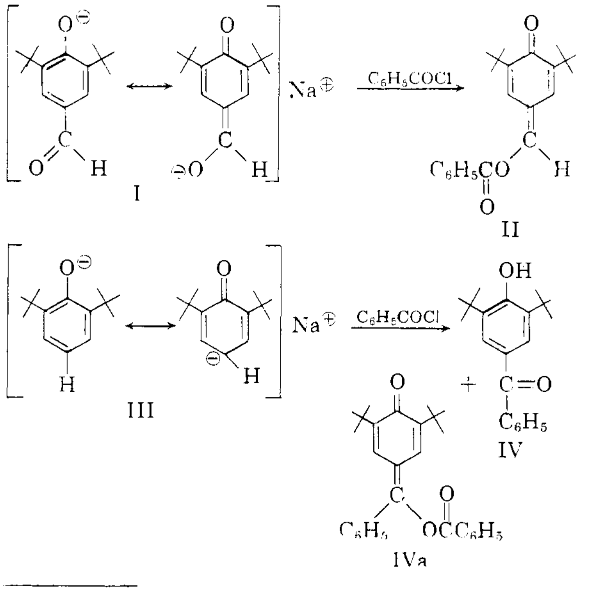
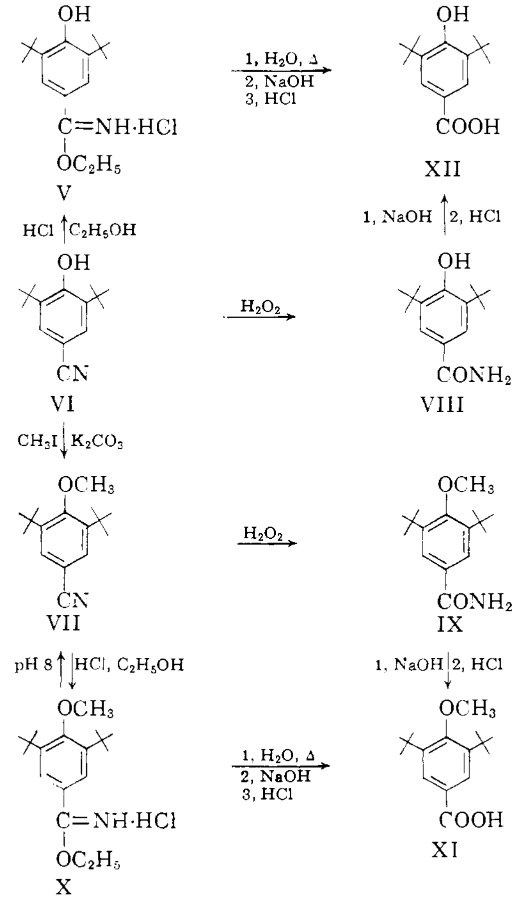
(Pseudo)-first-order rate constants for the alkaline hydrolysis of *p*-substituted benzonitriles and benzamides are reported. Values for k_1 in the consecutive series $RCN \xrightarrow{k_1} RCONH_2 \xrightarrow{k_2} RCOOH + NH_3$ were obtained by automatic approximation and curve-fitting on an electronic calculator. Introduction of *t*-butyl groups *ortho* to the hydroxyl of *p*-hydroxybenzonitrile and *p*-hydroxybenzamide decreases the hydrolysis rate 30-fold. The phenomenon is attributed to a highly increased density of negative charge at the site of nucleophilic attack; the latter is, in turn, the result of steric hindrance to solvation of the charge at the phenolate anion.

The negative charge of a phenolate anion is generally considered to reside partly on oxygen and partly on the *ortho* and *para* carbon atoms of the aromatic ring. When the ring carries an unsaturated functional group in the *o*- or *p*-position, further resonance structures may be written for the anion, in which the charge is dispersed by an additional heteroatom. In an earlier paper of this series,[2] it was suggested on the basis of physical data that the introduction of bulky substituents *ortho* to the phenolate anion could alter the distribution of negative charge so that less hindered regions of the resonance hybrid would command a larger share of the electron density. The phenomenon was considered to be due to steric hindrance to charge dispersion by the solvent at the phenolate anion. The existence of high electron density in the *p*-position is also suggested by chemical evidence. Thus, from the benzoylation of I there was obtained an enol-benzoate II[3] and from III, both the benzophenone IV and its enol-benzoate IVa.[4] However, simple steric hindrance to acylation at the phenolic site would account for such data equally as well. A test of the concept was sought, therefore, by studying the rates of reactions occurring at the *p*-position, where the effect of charge distribution could be observed in the absence of direct steric interference by the *t*-butyl groups. Indeed, we have already shown that, in an electrophilic reaction such as the acid-catalyzed decarboxylation of *p*-hydroxycinnamic acid,[1] the introduction of *t*-butyl groups *ortho* to the phenolic hydroxyl effects a moderate *increase* in the rate of decarboxylation. Because of electrostatic repulsion, however, the same structural changes should lead to a *decrease* in the rate of a reaction involving nucleophilic attack at or near a center of negative charge.





To test the hypothesis, we have examined the rates of alkaline hydrolysis of a series of *p*-substi-

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[1] Paper III of a series on phenol–dienone tautomerism; for paper II, *cf.* L. A. Cohen and W. M. Jones, *J. Am. Chem. Soc.*, **82**, 1907 (1960).

[2] L. A. Cohen, *J. Org. Chem.*, **22**, 1333 (1957).

[3] K. Ley, *Angew. Chem.*, **70**, 74 (1958).

[4] T. H. Coffield, A. H. Filbey, G. G. Ecke and A. J. Kolka, *J. Am. Chem. Soc.*, **79**, 5019 (1957).

tuted benzonitriles[5] and benzamides,[6] both with and without *t*-butyl substitution, and have observed impressive changes in reaction rate in the expected direction.

Experimental[7]

Materials.—Where available, commercial materials were used and recrystallized when necessary. *p*-Hydroxybenzonitrile (Aldrich) was recrystallized from hot water; m.p. 113–114°. *p*-Methoxybenzamide was prepared from anisoyl chloride and concentrated ammonium hydroxide and recrystallized from water; m.p. 164–165°. *p*-Aminobenzamide was prepared from *p*-aminobenzonitrile by oxidation with aqueous hydrogen peroxide[8] and recrystallized from hot water; m.p. 183–184.5°. *p*-Hydroxybenzamide was prepared from *p*-hydroxybenzonitrile and hydrogen peroxide by a similar procedure and recrystallized from water. After the solvated product had been dried at 100° *in vacuo*, it melted at 161–162°. *p*-Carboxybenzamide (*p*-phthalamic acid) was prepared from *p*-cyanobenzoic acid and hydrogen peroxide.[9]

3,5-Di-*t*-butyl-4-methoxybenzonitrile (VII).—To a solution of 23.1 g. (0.1 mole) of 3,5-di-*t*-butyl-4-hydroxybenzonitrile (VI)[1] in 200 ml. of dioxane was added 60 ml. of methyl iodide and 40 g. of powdered, anhydrous potassium carbonate. The mixture was heated at reflux for 48 hours, filtered and the residue was washed with 100 ml. of methylene chloride. The combined filtrate and washings were concentrated to a yellow sirup which was dissolved in 50 ml. of methanol. The methanol solution was diluted with 250 ml. of *N* sodium hydroxide and the precipitate of methoxynitrile was collected by filtration. The crude product was recrystallized from methanol–water after treatment with charcoal to give 19.7 g. (80%) of material melting at 75–76° (lit.[1] 73–75°). In a number of similar preparations, yields varied from 75–88%.

3,5-Di-*t*-butyl-4-hydroxybenzamide (VIII).—To a solution of 4.62 g. (0.02 mole) of 3,5-di-*t*-butyl-4-hydroxybenzo nitrile (VI) in 150 ml. of ethanol was added 40 ml. of water and 20 ml. of 30% hydrogen peroxide. The solution was adjusted to *p*H 8.5 with 4 *N* sodium hydroxide and kept at 50–60° for 24 hours. After acidification to *p*H 1, the solution was concentrated to one-fourth the original volume and the product was collected by filtration. The colorless solid was washed thoroughly with ether and recrystallized from methanol–water; 3.5 g. (70%), m.p. 266–266.5°. The solvated product was dried *in vacuo* at 100° for 24 hours; m.p. 266–266.5°.

Anal. Calcd. for $C_{15}H_{23}O_2N$: C, 72.25; H, 9.30; N, 5.62. Found: C, 71.98; H, 9.48; N, 5.63.

3,5-Di-*t*-butyl-4-methoxybenzamide (IX).—The methoxynitrile VII was converted into the methoxy-amide by oxidation with hydrogen peroxide as described above for the hydroxy-amide. In this case, the crude, dried product was washed with hot benzene prior to recrystallization from methanol–water. A yield of 4.2 g. (80%) of needles, m.p. 244–246°, was obtained. The solvated product was dried *in vacuo* at 100° for 24 hours; m.p. 245–246°.

Anal. Calcd. for $C_{16}H_{25}O_2N$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.96; H, 9.67; N, 5.37.

3,5-Di-*t*-butyl-4-methoxybenzoic Acid (XI).—A solution of 4.90 g. (0.02 mole) of 3,5-di-*t*-butyl-4-methoxybenzonitrile (VII) in 50 ml. of ethanol was saturated with hydrogen chloride and the mixture was stored at room temperature for 48 hours. The solvent was removed under reduced pressure, leaving a colorless, crystalline residue which was triturated with ether, filtered and dried. The yield of imino-ester hydrochloride X, m.p. 247–248°, was 5.85 g. When an aqueous solution of the imino ester hydrochloride was neutralized with sodium bicarbonate and heated, the oily imino ester gradually solidified, the product being identified as the original methoxy-nitrile. Apparently, even under conditions as mild as *p*H 8, the imino ester lost the elements of ethanol readily to re-form the nitrile.[10] Only by heating a solution of the imino ester hydrochloride in water alone could hydrolysis be effected, the oily ester separating within a few minutes. The mixture was then made alkaline with 10–12 equivalents of 2 *N* sodium hydroxide, enough ethanol added to effect complete solution and the mixture refluxed for several hours. After removal of ethanol under reduced pressure and acidification of the clear, aqueous solution, a crystalline precipitate of the methoxy acid separated. It was filtered, dried and recrystallized from ligroin (90–100°), affording a 90% yield of colorless granules, m.p. 192.5–194.5°.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.45; H, 9.06.

Kinetic Runs.—Reaction mixtures were made up by adding 0.01 mole of compound to 100 ml. of 2 *M* sodium hydroxide in 60% ethanol. The solutions were thus 0.1 molar with respect to compound and contained a twenty-fold quantity of alkali. Corning alkali-resistant glass, No. 7280, was used for the reaction vessel. The solutions were heated at reflux (82°) in an oil-bath kept at 125° while dry nitrogen was passed through the system at the rate of approximately 20 ml. per minute. Control experiments showed no significant loss of solvent from the reaction vessel after flushing with nitrogen for 48 hours at such a rate. The effluent gas was bubbled through 25 ml. of 2% boric acid containing Tashiro indicator.[11] At various time intervals the boric acid solution was titrated back to the end-point with 0.5 *M* hydrochloric acid. Blank experiments were performed by adding weighed quantities of ammonium chloride to the alkaline solution in the reaction flask. In each case, at least 90% of the theoretical ammonia titer was realized within 5 minutes, suggesting that only in the case of very rapid hydrolyses could a time lag introduce significant error. Several kinetic runs were repeated using increased rates of nitrogen flow without significant change in the results. Hydrolysis was carried to 70–80% completion except for the two very slow cases, VI and VIII, in which the reaction was stopped after 20% completion.

The mixture resulting from hydrolysis of VI was worked up for product recovery. The alkaline solution was acidified and concentrated to dryness. The residue was extracted with ether and the ether solution was extracted with aqueous sodium bicarbonate. The hydroxy acid XII[2] was obtained by acidification of the bicarbonate extract. The ether solution was taken to dryness and the residue was extracted with hot ligroin (90–100°) to dissolve the hydroxy-nitrile VI, leaving the hydroxy-amide VIII as a residue. In a similar manner XII was recovered from the hydrolysis of VIII. Recovery results agreed satisfactorily with data obtained from ammonia titration as well as from spectrophotometric assay (see below).

Several attempts were made to analyze mixtures of nitrile, amide and acid by gas chromatography. Despite the use of silicone columns operated as high as 250°, only benzonitrile and anisonitrile could be volatilized and the method was abandoned for the present study. For VI and VIII, differences in ultraviolet spectra were useful for following hydrolysis rates. Aliquots of the reaction mixture were withdrawn, diluted as required with the same alkaline solvent, and the intensity measured at 340 mμ. In the alkaline medium, VIII had an ϵ value of 13,000 at 340 mμ, whereas VI and XII had intensities below 50.

Results

For all amides studied, second-order or (pseudo)-first-order rate laws were obeyed equally as well (the ratio of alkali to amide being 19:1 or 20:1) up to 70% hydrolysis. Rate constants were determined graphically and are summarized in Table I.

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(5) For an earlier study of the kinetics of alkaline hydrolysis of benzonitriles, *cf.* Y. Ogata and M. Okana, *J. Chem. Soc. Japan*, **70**, 32 (1949).

(6) *Cf.* I. Meloche and K. J. Laidler, *J. Am. Chem. Soc.*, **73**, 1712 (1951); E. E. Reid, *Am. Chem. J.*, **21**, 284 (1899); **24**, 397 (1900).

(7) Melting points are uncorrected. Ultraviolet spectra were run on a Cary recording spectrophotometer, model 14. The authors thank Mr. H. G. McCann and his associates of this Institute for carrying out the microanalyses.

(8) M. T. Bogert and L. Kohnstamm, *J. Am. Chem. Soc.*, **25**, 483 (1903).

(9) P. Kattwinkel and R. Wolffenstein, *Ber.*, **37**, 3223 (1904).

(10) Similar difficulties were encountered in the preparation of XII from V. The procedure described below should be substituted for that reported in the earlier paper (ref. 2).

(11) N. C. Davis and E. L. Smith, "Methods of Biochemical Analysis," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1955, p. 232.

TABLE I

(PSEUDO)-FIRST-ORDER RATE CONSTANTS FOR THE ALKALINE HYDROLYSIS OF BENZAMIDES[a]

Benzamide	$k_2 \times 10^5$, min.$^{-1}$ H series	Di-*t*-butyl series
p-Carboxy	3100	..
p-Hydrogen	2460	..
p-Methoxy	963	505
p-Amino	285	..
p-Hydroxy	63	2

[a] Reaction mixtures were composed of 0.01 mole of compound in 100 ml. of 2 *M* sodium hydroxide in 60% ethanol; hydrolysis rates were measured at reflux (82°).

Since the hydrolysis of nitriles involves a set of consecutive reactions following, in this case, (pseudo)-first-order kinetics, the set of integrated equations derived by Esson[12] for the reaction sequence

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C\,(+D)$$

may be applied, where

$$A = A_0e^{-k_1t} \quad (1)$$

$$B = \frac{A_0k_1}{k_2 - k_1}\{e^{-k_1t} - e^{-k_2t}\} \quad (2)$$

and

$$A + B + C = A_0 \text{ or } A_0 - C = A + B$$

Then

$$A_0 - C = A_0e^{-k_1t} + \frac{A_0k_1}{k_2 - k_1}\{e^{-k_1t} - e^{-k_2t}\} \quad (3)$$

By setting $A_0 = 1$ and C = per cent. of theoretical amount of ammonia released/100

$$1 - C = e^{-k_1t} + \frac{k_1}{k_2 - k_1}\{e^{-k_1t} - e^{-k_2t}\} \quad (4)$$

Using the values of k_2 recorded in Table I and tentative values for k_1, eq. 4 was solved at various values of t and the results compared with the experimentally measured values of C or D. By successive approximations for the value of k_1, a satisfactory fit to each experimental curve was realized. Computation was greatly facilitated by programming eq. 4 for an IBM 650 computer which performed successive approximations and curve-fitting automatically.[13] A representative comparison of experimental and calculated results is shown in Fig. 1. Values for k_1 are collected in Table II.

TABLE II

(PSEUDO)-FIRST-ORDER RATE CONSTANTS FOR THE ALKALINE HYDROLYSIS OF BENZONITRILES[a]

Benzonitrile	$k_1 \times 10^5$, min.$^{-1}$ H series	Di-*t*-butyl series
p-Carboxy	12000	..
p-Hydrogen	7250	..
p-Methoxy	3000	2000
p-Amino	630	..
p-Hydroxy	125	4

[a] Reaction mixtures were composed of 0.01 mole of compound in 100 ml. of 2 *M* sodium hydroxide in 60% ethanol; hydrolysis rates were measured at reflux (82°).

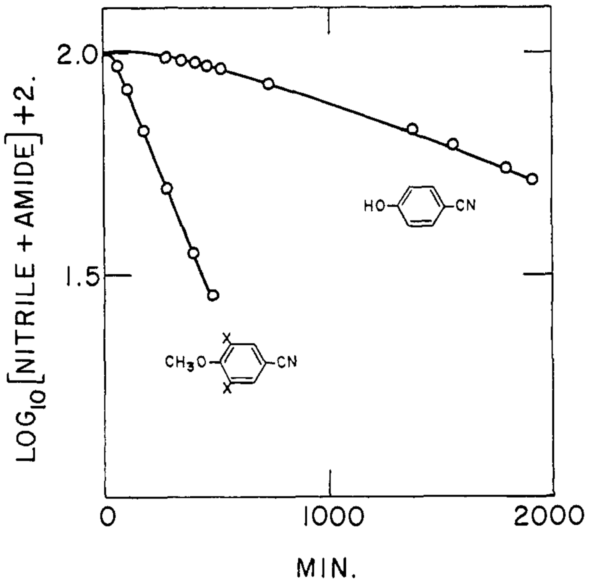

Fig. 1.—Comparison of experimental and calculated rates of hydrolysis of benzonitriles: —, calculated curve; O, experimental values.

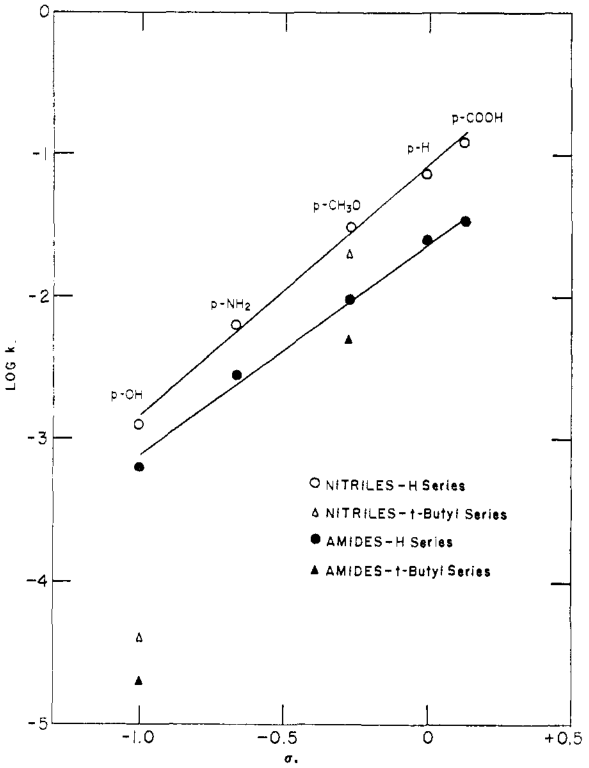

Fig. 2.—Hammett plot for alkaline hydrolysis of benzonitriles and benzamides.

When log k was plotted against σ[14] for each series of *unhindered* compounds, an approximately linear relationship was obtained (Fig. 2). The value of ρ for the hydrolysis of benzamides was found to be 1.5, while that for benzonitriles was 1.75.

Discussion

The alkaline hydrolysis of propionitrile has been shown to proceed at a rate one-tenth that of pro-

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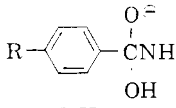
[12] W. Esson, *Phil. Trans. Roy. Soc. (London)*, **156**, 220 (1866); A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 153.

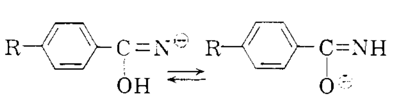
[13] We are indebted to Dr. N. Z. Shapiro and Mr. R. H. Brunelle, Computation and Data Processing Branch, National Institutes of Health, for performing the necessary computation.

[14] H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

pionamide.[15] Aromatic nitriles, on the other hand, appear to hydrolyze from 2–4 times as fast as the corresponding amides, according to the data of Tables I and II. The inverted sequence may be due to resonance factors. As the result of the formation of a tetrahedral intermediate in benzamide hydrolysis (XIII), resonance coupling between the amide and the aromatic ring is totally lost; however, the trigonal intermediate in nitrile hydrolysis (XIV) is still capable of resonance interaction with the ring. Consequently, benzamides might be expected to show a higher energy of activation for hydrolysis.

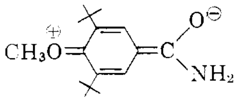


XIII



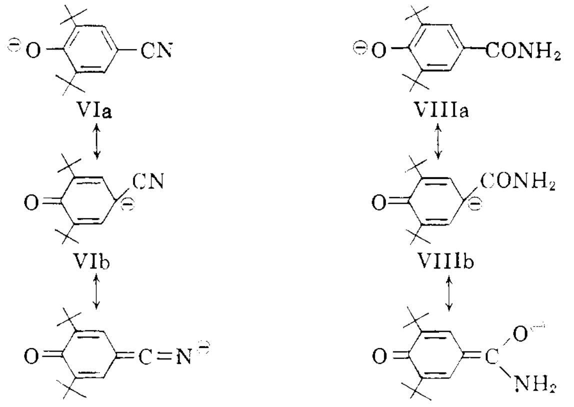
XIV

From a comparison of the rate data (Tables I and II) for *p*-methoxybenzamides as well as for *p*-methoxybenzonitriles, it is evident that *t*-butyl groups affect the hydrolysis rate to a relatively small extent. The observed difference may result from a small steric effect of the bulky *t*-butyl group *meta* to the site of nucleophilic attack or, more likely, from increased contributions of forms such as XV in addition to a small inductive effect. However, the introduction of *t*-butyl groups into the phenolic derivatives VI and VIII serves to reduce the rates of alkaline hydrolysis by a factor of 30.[16] Undoubtedly, the increased contributions of VIb and VIc and of VIIIb and VIIIc to the



XV

respective resonance hybrids are reflected in the rates of hydrolysis. The effect may be attributed to (a) greater electrostatic repulsion of hydroxide ion by VIb and VIIIb; (b) a similar repulsion by VIc and VIIIc; (c) impaired ability of hydroxide ion to add to the quinonemethine structures VIc and VIIIc in a Michael fashion, as compared with the unhindered analogs. Although no rigid assessment of the relative importance of each factor can be made at present, it is instructive to examine the effect of *t*-butyl groups on the ultraviolet spectra of the compounds in question. The data of Table III suggest that VIc and VIIIc contribute measurably to the structures of the phenolate anions and may affect reaction rates to a greater extent than VIb or VIIIb.[17] Preliminary experiments on the alkaline hydrolysis of ethyl *p*-hydroxybenzoate at 25°, both with and without *t*-butyl substitution *ortho* to the phenol, indicate that a considerable stereo-electronic hindrance to saponification exists in this series as well.



VIa VIIIa

VIb VIIIb

VIc VIIIc

TABLE III

EFFECT OF ALKALI ON ULTRAVIOLET SPECTRA OF PHENOLS

Compound	Wave length, mμ H series Neutral	Wave length, mμ H series Alkaline[a]	Wave length, mμ Di-*t*-butyl series Neutral	Wave length, mμ Di-*t*-butyl series Alkaline
p-Hydroxybenzonitrile	252	281	252	305
p-Hydroxybenzamide	257	294	262	325
p-Hydroxybenzoic acid	259	281	262	308
Ethyl *p*-hydroxybenzoate	258	300	262	330

[a] Neutral spectra were measured in 95% ethanol; alkaline spectra in 2 *M* sodium hydroxide (60% ethanol).

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[15] B. S. Rabinovitch and C. A. Winkler, *Can. J. Rerearch*, **20B**, 185 (1942).

[16] During the course of this investigation, the resistance of VIII to alkaline hydrolysis was also observed by E. Müller, A. Rieker, K. Ley, R. Mayer and K. Schieffier, *Chem. Ber.*, **92**, 2278 (1959).

[17] G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 292.