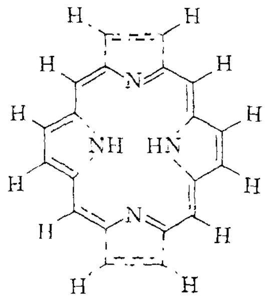
stabilize the lowest singlet state with respect to the triplet state. In fact, the n.m.r. spectrum of [24]annulene is incompatible with this molecule having a triplet ground state.[29]

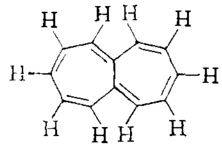
Although Hückel's rule was not formulated for the dehydro-annulenes, consideration of the underlying theory suggests that the rule should still be applicable although of diminished significance. Furthermore, the presence of triple bonds will produce bond alternation,[30] with a consequent lowering in the degree of aromaticity. In practice, monodehydro-[14]annulene (*e.g.*, II) and tridehydro-[18]annulene (VI), both of which comply with Hückel's rule (n = 3 and 4 out-of-plane π-electrons, respectively), are aromatic, whereas tetradehydro-[24]annulene (*e.g.*, IX), which does not obey the rule, is non-aromatic. Again, the origin of the lack of cyclic delocalization in the 24-membered ring is difficult to define; although the effects of hindrance to planarity, as well as adverse entropy factors, are less in this compound than in [24]annulene, the presence of the triple bonds introduces a further factor for consideration.

Table I gives the coupling constants between the inner protons and their two neighboring outer protons in the three dehydro-annulenes. The values for the analogous interactions in dimethyl *cis-trans*-muconate (IV)[16] are included for comparison. It is possible that the values of the coupling constants (J_{MX}) across the formal single bonds reflect the planarity of the diene system, and hence the aromaticity of the macrocycles.

It is pertinent to refer to two interesting systems in which recent n.m.r. investigations have revealed their degree of aromaticity. Analysis of proton spectra of a number of porphyrins and chlorins [*e.g.*, porphine (XI)] has shown that the peripheral protons are at low fields (*ca.* 0–1), whereas the imino protons are at very high fields (*ca.* 14).[32] These results are analogous to those for the aromatic macrocycles considered in this paper, and it is noteworthy that porphyrins (*e.g.*, XI) and chlorins contain a cyclic π-electron system isoelectronic with that of [18]annulene. However, a direct comparison of shifts is not justified because of the difference in geometry, the perturbation of the π-electron charge distribution by the nitrogen atoms, and the fact that the imino protons are attached directly to nitrogen.



XI



XII

The second example is the recently synthesized heptalene (XII).[33] Craig's generalization of Hückel's rule[34] predicts this compound to be non-aromatic, and indeed it has been pointed out[33] that the chemical shifts of its protons are characteristic of an olefinic rather than an aromatic molecule.

[29] A large chemical shift from the normal position of olefinic protons, or a broadening or splitting of the band, would be anticipated if [24]annulene possessed a paramagnetic ground state (*cf.* H. M. McConnell and C. H. Holm, *J. Chem. Phys.*, **27**, 314 (1957); **28**, 749 (1958)).

[30] In annulenes, this follows from the alternation in sign of the bond–bond polarizabilities, $\pi_{rs,tu}$, which indicate the way in which a change in the resonance integral, β_{rs}, of one bond affects the bond orders, p_{tu}, of the other bonds in the system.[31]

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Carbonyl Reactions. XIX. The Basicities of Substituted Chalcones[1,2]

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The basicities of a series of substituted *trans*-chalcones have been measured in sulfuric acid. The log K_{BH^+} values correlate well with σ^+, $\rho = 1.26$. In chalcone and substituted chalcones, there is a pronounced shift of the spectrum of the salt in more concentrated sulfuric acid manifested in both increased intensity of absorption and in a displacement of the maximum to longer wave lengths. Methods of correcting for these shifts in order to obtain accurate pK's are evaluated. The basicities of several substituted *cis*-chalcones have also been determined by measuring the frequency shift of phenol hydrogen-bonded to the ketone. The *cis*-ketone is uniformly less basic than its *trans* isomer.

Introduction

The basic characteristics of oxygen compounds manifested in fairly concentrated sulfuric acid solutions have been the subject of many investigations both qualitative and quantitative. The results of these investigations have been used in qualitative organic analysis, and they have also been used in establishing the acidity scale[4] (H_0) in

[1] Previous paper in this series, D. S. Noyce, H. S. Avarbock and W. L. Reed, *J. Am. Chem. Soc.*, **84**, 1647 (1962).

[2] Supported in part by a grant from the National Science Foundation, NSF G-13125, and in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of these funds.

[3] National Institutes of Health Postdoctoral Fellow, 1959–1961.

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aqueous sulfuric acid. Chalcone, β-benzoylnaphthalene, *p*-benzoylbiphenyl and anthraquinone are in the original set of Hammett indicators. Quantitative studies of the basicities of substituted acetophenones,[5,6] ω-arylacetophenones,[7] benzaldehydes[8] and benzoic acids[9] have been reported. Stewart and Yates find that the basicities of the aroyl compounds correlate well with σ^+.

The behavior of chalcone as a Hammett base has been the subject of some discussion.[10,11] Paul and Long[10] have pointed out that chalcone shows deviations from "ideal" behavior and have suggested that it be avoided as an indicator. Bascombe and Bell[11] found chalcone to be unsuitable as a Hammett base for aqueous solutions of methanesulfonic acid. In other studies, however, the use of chalcone has received no comment.[12] Other indicators also show similar shortcomings. The recent careful studies of Bascombe and Bell[11] have shown that the behavior of *p*-nitrodiphenylamine is likewise not "ideal" and that the use of this indicator is likely to lead to errors in assigning H_0 values.

In connection with a study of the acid-catalyzed isomerization of substituted *cis*-chalcones[13] it became desirable to determine the basicities of substituted *trans*- and *cis*-chalcones. The basicities of such cinnamoyl systems are also of inherent interest as a measure of the susceptibility of such systems to protonation. Aside from the measurement of acid dissociation constants of substituted cinnamic acids,[14] few other studies of the effect of substitution in the benzene ring on the electronic nature of the cinnamoyl moiety have been made. The determination of the H_0 scale in 5% dioxane–aqueous sulfuric acid[13] affords a very convenient solvent system for the measurement of the basicities of the very difficultly soluble chalcones. Our previous work in this solvent system has indicated that it gives results which are directly comparable to those obtained in completely aqueous systems.

It is the purpose of the present study to examine the *pK*'s of the substituted chalcones. We have also considered the detailed nature of the use of, and the proper *pK* for, chalcone itself as a Hammett indicator. In addition, we have found that the measurement of *pK* by the hydrogen bonding frequency shift method[15] is of great value with compounds which are not stable in the strong sulfuric acid which would be required to convert them to their conjugate acids.

Methods for Determining *pK*'s.—The use of the Hammett equation (1) by spectrophotometric

$$pK = H_0 + \log(C_{BH^+}/C_B) \qquad (1)$$

methods depends upon two properties of the organic base B: one, that there be suitable regions of the spectrum in which B and its conjugate acid BH^+ have markedly different absorptivities; and, secondly, that the spectra of both B and BH^+ be independent of the changing concentration of sulfuric acid in the medium. Though the first of these requisites is generally true, the second is rarely completely correct. The additional required assumptions regarding the activity coefficient terms will not be discussed in the present report.

In the case of the aniline bases used by Hammett, the long wave length band due to the free base is followed. The extent of protonation is determined simply by the decrease in the absorption maximum of the free base, the fully protonated base having negligible absorption in the region of this maximum. Generally, it is assumed that no displacement of the maximum occurs as the concentration of the sulfuric acid is changed. For the substituted aniline indicators used in defining the H_0 scale, this is usually a good assumption. In some cases, specific correction for a small lateral displacement of the absorption band has been made.[16,17] When the lateral displacement (medium shift) is small, corrections have been made, by using two wave lengths[16] in the calculations or the average of measurements at several wave lengths near the maximum which generally results in a cancellation of errors and a good value for the *pK*.[17]

In substances exhibiting a high intensity band for the protonated base, the medium shift is frequently much more troublesome. Hammett[18] first treated this problem in his pioneering studies, in measuring the pK_{BH^+} of acetophenone[19] and of benzoic acid. He used two methods: the first is the isobestic point method, in which lateral displacements of the absorption curves are made, constraining the curves measured in all acid concentrations to pass through an isobestic point. The second method involved treating ϵ_B or ϵ_{BH^+} (as appropriate) as an unknown in addition to the pK_{BH^+}, and then solving for the best values by least squares calculations.

Several variants of these methods have been used by subsequent investigators.[20–24]

One of the most convenient procedures has been suggested by Davis and Geissman[25] and has been widely used in recent years.[6–9] In this method, the difference in extinction coefficient at two selected wave lengths is plotted against H_0. This procedure has the advantage that it weights both

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the disappearance of one peak and the appearance of a new peak. However, it can be shown that the pK thus determined is still a function of the proper choice of the wave length pair used in the Geissman plot. This apparently has not been appreciated by some workers.[7] In addition, the Geissman method depends upon the two assumptions, *i.e.*, constant ϵ_{max} and constant λ_{max}, though it tends to compensate partially for errors resulting from the failure of these assumptions to hold.

None of the methods described above makes provision for dealing with medium effects which involve not only lateral displacements but also shifts in intensity over the protonation region. In the present study, it can be clearly shown that the latter effect also is present. Despite the claim made by some investigators[11] that the determination of accurate pK_{BH^+} values are impossible when such complex medium shifts occur, it can be shown in this work that if the detailed nature of the medium effect is studied (by measurement of the ultraviolet spectra at various acid concentrations over total region of absorption) an adequate provision for proper treatment of the data can be made so as to take into account these changes. In the present case, the absorption maxima of the protonated base is 100 mμ removed from the maximum of the free base, and, hence, the absorption due to free base at the wave length of the protonated base absorption is negligible. Medium effects (Tables II and III) are very pronounced and demanded a thorough treatment of the data.

One aspect of determination of pK's of weak bases by spectral methods has been overlooked. It has not been properly stressed that having an approximate pK_{BH^+}, then the spectrum in a solution of H_0 value two units more negative than the pK is that of 99.01% the acid form, and of only 0.99% of the basic form. Examination of the spectrum in this region and in more concentrated sulfuric acid solutions is very useful in revealing medium shifts.

In the case of benzylideneacetophenone (chalcone) such an evaluation of the data reveals the following: The position of the long wave length maximum is at 415 mμ (ϵ_{415} 37,000) in 80% sulfuric acid (H_0 −7.00). (The spectrum of chalcone in this region is also sensitive to a light-induced photodynamic equilibrium between the *cis* and *trans* isomer.[26] Suitable precautions must be taken to avoid this source of error.) When the acidity is raised to $H_0 = -8.00$, 88% sulfuric acid, the maximum shifts to 425 mμ, ε 43,000. Chalcone thus exhibits a pronounced medium shift, *both* in the position and intensity of the band of its conjugate acid. This, then, is the source of the difficulty in using chalcone as a Hammett indicator.

Experimental

Preparation of 2,4-Dimethoxychalcone.—A solution of 16.6 g. of 2,4-dimethoxybenzaldehyde, 12.0 g. of acetophenone, 5.1 g. of sodium hydroxide in 46 ml. of water and 30 ml. of 95% ethanol was stirred at room temperature for 5 hours. A yellow oil separated which did not crystallize after 2 days in the cold. Extraction with chloroform and work-up in the usual manner afforded 23.6 g. of yellow oil. Crystallization from ethanol proceeded slowly and afforded 13.0 g. (48.5%) of 2,4-dimethoxychalcone as stubby, yellow needles, m.p. 69.8–70.5°; λ_{max}^{EtOH} 256 mμ (ε 13,900), 365 mμ (ε 23,200).

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.83; H, 5.92.

Preparation of 2,4,6-Trimethoxychalcone.—A solution of 0.7 g. of 2,4,6-trimethoxybenzaldehyde[27] was treated by the above procedure with 0.6 g. of acetophenone. After 30 minutes, yellow crystals separated; these were collected after 20 hours, affording 1.2 g. (98%) of 2,4,6-trimethoxychalcone. Two recrystallizations from methanol gave yellow plates, m.p. 81–82°. Upon standing, change to a higher melting polymorphic form took place; m.p. 108–109°, λ_{max}^{EtOH} 255 mμ (ε 11,800), 368 mμ (ε 22,300).

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.19; H, 5.90.

***cis*-2-Methoxychalcone.**—A solution of 7.5 g. of *trans*-2-methoxychalcone in 1 liter of benzene was irradiated with a 275 watt sunlamp for a period of 3 days. At this time, the infrared spectrum indicated a high percentage conversion of the *trans* isomer to the *cis* isomer. The benzene solution was concentrated and hexane was added to precipitate a small amount of dark insoluble polymeric oil (about 1.0 g.). The clear solution was further concentrated and cooled to give crystals of the less soluble *trans* isomer. The process was repeated to enrich the mother liquors in the more soluble *cis* isomer, affording 4.5 g. of a yellow oil. Fractional distillation gave *cis*-2-methoxychalcone as a yellow oil, b.p. 130° (0.04 mm.). The infrared spectrum indicated that the material was almost entirely free of the *trans* isomer; λ_{max}^{EtOH} 250 mμ (ε 12,600), 294 mμ (ε 9,730), 345 mμ (ε 8,200).

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.93; H, 5.69.

Preparation of Other Chalcones Used in Measurements.—The other chalcones used have been previously reported. β-Phenylchalcone, m.p. 87–88° (lit.[28] 88–89°), was obtained by the dehydration of β,β-diphenyl-β-hydroxypropiophenone. 2-Methoxychalcone, m.p. 59.5–60.0° (lit.[29] 58–59°); 2-methylchalcone,[30] b.p. 183° (0.5 mm.); 2-chlorochalcone, m.p. 51–52° (lit.[31] 52–53°); 4-methylchalcone, m.p. 97–98° (lit.[32] 96.5°); and 4-fluorochalcone, m.p. 88–89° (lit.[33] 87°), were prepared by literature methods. Other chalcones used have been described in our previous publications.[13a]

H_0 Measurements.—Values of H_0 for sulfuric acid in 5% dioxane–95% H_2O up to 10.5 M H_2SO_4 ($H_0 = -5.42$) have been obtained in previous work.[13a] Additional values at higher acidities up to 77% sulfuric acid were obtained and are listed in Table I. The validity and continuity of this scale was demonstrated by overlap of indicator ratios obtained by two consecutive indicators. N,N-Dimethyl-2,4,6-trinitroaniline was shown to be an unsuitable indicator by this method.

At the highest acidities used it was important to employ freshly purified dioxane and to take precautions to avoid a temperature rise on mixing, since some decomposition and color formation took place otherwise. The solutions were mixed shortly before use and were found to be stable over the period of measurement in the long wave length region which was used for measurement. Some volume contraction occurred in mixing at the high acidities and the resulting solution was stronger by 1–2% than the value calculated by a simple correction for the presence of dioxane. At acidities below 50% H_2SO_4, this difference in concentration amounted to less than 0.5%. Despite the small difference in dioxane composition at the highest acidities (calculated 4.9% dioxane) resulting from this volume contraction, the mixed solvent system was employed throughout a pK determination in order to preserve continuity in the solvent system. A change to purely aqueous solvent in the region of high protonation, where solubility difficulties disappeared, was shown to have a considerable effect on the measured

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TABLE I

H_0 VALUES FOR SULFURIC ACID IN 5% DIOXANE–95% H_2O

H_2SO_4^{a}	log [BH^+/B]	H_0	ΔH_0^{b}
53.84	+0.59^c	−3.91	+0.12
53.84	− .58^d	−3.95	+ .16
57.35	− .20^d	−4.33	+ .16
61.11	+ .29^d	−4.82	+ .22
61.11	− .36^e	−4.46	(− .14)
64.43	+ .31^e	−5.12	(+ .16)
66.28	+ .69^e	−5.45	(+ .27)
68.05	+1.24^d	−5.78	+ .38
68.05	−1.01^f	−5.70	+ .30
71.96	+0.46^f	−6.25	+ .35
74.88	0.00^f	−6.71	+ .43

[a] Acidity of sulfuric acid after mixing. [b] H_0 in aqueous sulfuric acid − H_0 in 5% dioxane–95% aqueous sulfuric acid. [c] Indicator: 2,4-dichloro-6-nitroaniline, pK_a −3.32. [d] Indicator: 2,4-dinitroaniline, pK_a −4.53. [e] Indicator: N,N-dimethyl-2,4,6-trinitroaniline, pK_a −4.81. These values deviate from parallelism with plots of ionization ratio *vs.* H_0 for other indicators; this indicator has previously been shown to be unsuitable for measurement in acetic acid solution (ref. 10). [f] Indicator: 2-bromo-4,6-dinitroaniline, pK_a −6.71.

extinction coefficient. Since the change in dioxane composition generally affected only the optical density measurements beyond the principal protonation region, the error introduced was negligible. Furthermore, the pK_{BH^+} values obtained are in good agreement with those calculated from the least squares method, which did not utilize data at the highest acidities. In sulfuric acid, more concentrated than 80%, the salt of dioxane precipitated from solution; hence, the mixed solvent system was not employed at these acidities. The weakest base measured, 4-nitrochalcone, was measured in aqueous sulfuric acid for this reason.

Basicity Measurements: Sulfuric Acid Method.—Analytical solutions for measurement were prepared by either accurately weighing out individual samples of the chalcone or by pipetting aliquots of a solution of the chalcone in a low boiling solvent into a 100-ml. volumetric flask evaporating the solvent, dissolving the sample in 5 cc. of dioxane (whenever the 95% sulfuric acid–5% dioxane medium was used) and making up to volume with the requisite strength of sulfuric acid.

The basicity of *cis*-4-nitrochalcone was determined by measurement in 0.5% dioxane–99.5% aqueous sulfuric acid at low acidities with no corrections employed for the presence of dioxane. Since measurements were conducted at low temperature and mixing had to be rapid, the use of a small amount of dioxane to dissolve the chalcone hastened solution on addition of the cold acid. A thermostated cell compartment, flushed with nitrogen to effect defogging of the optics, was employed at 0–5°. Measurements were taken about 3 minutes after mixing, when the optics had defogged and the air bubbles, entrapped upon mixing in the cold viscous sulfuric acid, had dissipated. The measured values were constant over an additional period of several minutes even at the concentration where the isomerization[13b] of *cis*-4-nitrochalcone to *trans* was most rapid.

Measurements for the other chalcones were conducted at 25 ± 2°. A number of necessary experimental precautions became apparent after a few exploratory measurements.

(a) Even in 5% dioxane solution, solubility difficulties with most of the chalcones were experienced. A 10-cm. cell was used at acidities where protonation was slight; even so, the concentration often had to be kept to a minimum at that dilution.

(b) The *trans* isomer of a number of chalcones are isomerized to an equilibrium mixture of *cis* and *trans* isomers in solution by room light. The rate of isomerization was less pronounced in solutions in which protonation was negligible. In solutions in which the chalcone was appreciably protonated, and hence a high wave length maximum was available for the photochemical isomerization, the isomerization was so fast that it could not be avoided during the transfer of the solution to the cell for measurement, despite other precautions observed during the preparation of the solution. For chalcones whose rate of isomerization from *cis* to *trans* was slow at these acid concentrations, it was necessary to subject the solution to an isomerization period sufficiently long for complete reversion to the *trans* isomers. From fairly complete rate data over this acid concentration range obtained for a number of chalcones[13b] this time period was known and, in many cases, the optical density measurements were obtained from rate measurement experiments, after 10 half-lives. Thus, the rate in 95% sulfuric acid ranges from a few minutes for chalcone, to 2.5 hours for 2-chlorochalcone, to 5 hours for 4-nitrochalcone. The various methoxychalcones isomerized to the *trans* isomer immeasurably rapidly over the acid region of protonation, proceeding by a different mechanism[13b] and basicity measurements of these was not subject to this difficulty.

At concentrations corresponding to a small degree of protonation, some isomerization by room light also was apparent and adequate provision for complete isomerization to the *trans* isomer had to be made. Thus, without knowledge of the rate behavior of these chalcones of various acid concentrations, largely erroneous optical density measurements would have resulted.

In determining the basicity of *cis*-4-nitrochalcone, it was imperative that isomerization by room light to an equilibrium mixture of *cis* and *trans* isomers be avoided. Operations involving preparation and transfer of solutions were performed in the dark.

(c) The *trans*-chalcones were found to be stable in concentrated sulfuric acid (95%) over periods much longer than necessary for measurement, but showed changes in spectrum over many hours. Hence, solutions were prepared shortly before measurements were made. 2,4,6-Trimethoxychalcone was not stable over the period of measurement at the highest acid concentrations used and measurements were made at a lower temperature at these concentrations.

Methods for Determining pK's. Method I. Isosbestic Point Correction.—The lateral shift of each absorption curve moved each spectrum the amount necessary for overlap of all maxima at the same wave length, regardless of the acid concentration in which measurement was made. This procedure, therefore, amounts to evaluating the absorbance at each maximum, regardless of the bathochromic shift associated with the band as the medium changes. A plot of these values *vs.* H_0 gave curves which were not flat in the upper acidity region, but showed a continuing increase in absorbance beyond the region of complete protonation. This observation constituted evidence for the presence of a "vertical" component to the medium shift (Table II). The midpoint, equated to the pK, of such a plot was chosen at the absorbance one-half that observed at two H_0 units above the pK_{BH^+}. The pK thus determined is largely dependent upon the choice of the upper absorbance; it incorporates errors due to the "vertical" medium shift occurring throughout the region of partial protonation. As method II indicates, these errors are modest.

TABLE II

MEDIUM EFFECTS IN THE ULTRAVIOLET SPECTRA OF CHALCONE IN AQUEOUS SULFURIC ACID

H_2SO_4, %	H_0	λ_{max} B (ϵ)	λ_{max}, BH^+ (ϵ)
47	3.0	313 (21·800)	
56	4.0	320 (20·700)	390 (sh)
65	5.0	325 (13·000)	403 (19·100)
72	6.0	315 (7·500)	410 (31·600)
80	7.0	313 (7·000)	415 (36·700)
88	8.0	317 (6·000)	425 (39·500)
95	9.0	317 (7·000)	431 (43·200)

Method II.—Least squares calculations, using a modification of the method introduced by Hammett, were carried out, using eq. 2, in which ϵ_B is set equal to zero, and rearranged to eq. 3 in suitable analytical form. A preliminary plot of $1/\epsilon$ *vs.* h_0 afforded a rapid means of examining the data. Only points within 0.5 H_0 unit of the pK were used in this treatment, thus minimizing any medium shifts.

TABLE III

ABSORPTION MAXIMA FOR SUBSTITUTED CHALCONES

		λ_{max}, mμ, in 95% aq. H_2SO_4–5% dioxane Extent of protonation:		
Substituent	λ_{max}, mμ(ϵ) in ethanol	10%	50%	99%
Hydrogen	228 (9,800)	313		
	308 (24,300)	390(sh)	405	415
4-OCH_3	245 (11,700)	351		
	341 (24,000)	440(sh)	460	470
4-CH_3	231 (10,500)	330		
	322 (25,000)	410(sh)	425	439
4-Cl	230 (11,600)	333		
	315 (27,300)	400(sh)	414	428
4-NO_2	316 (28,000)	328[a]	353[a]	395[a]
2-OCH_3	245 (8,190)	355	385	395
	255 (9,200)	430(sh)	460	480
	297 (15,400)			
	348 (14,800)			
2-CH_3	232 (8,050)	325		
	314 (16,800)	405(sh)	415	430
2-Cl	231 (9,800)	315		
	297 (18,000)	395(sh)	402	410
cis-4-NO_2	250 (15,200)	300[a]		
	295 (9,300)	..	390[a]	390[a]
2,4,6-$(OCH_3)_3$	255 (11,800)	380		
	368 (22,300)	440(sh)	470	480
β-C_6H_5–	231 (16,100)	280–340[b]		
	250 (13,500)		375	395
	298 (10,500)	410(sh)	445	465

[a] Aqueous sulfuric. [b] Broad plateau.

$$H_0 = pK_{BH^+} + \log \frac{[B]}{[BH^+]} = pK_{BH^+} + \log \frac{\epsilon_B - {}_{BH^+}}{\epsilon_B - \epsilon} \qquad (2)$$

$$h_0 = -K + K\epsilon_{BH^+}/\epsilon$$

Method III.—It was of interest to examine the effect on the pK_{BH^+} that a conventional plot of ϵ *vs.* H_0 would have, ignoring any medium effects. It was found that well defined "titration curves" could only be obtained when the wave length chosen for measurement was that at which the maximum occurred at 50% protonation. The pK_{BH^+} value obtained in this manner was in excellent agreement with those obtained by the other methods. On the other hand, selecting the wave length for measurement as that at which the maximum occurred in the fully protonated species led to large errors in pK_{BH^+} and to ill-defined titration curves. This is illustrated in more detail in connection with the redetermination of the pK_{BH^+} of benzylideneacetophenone (Table IV) and is shown to be the cause of the erroneous value reported in the literature.

Method IV.—A Geissman[25] treatment of the data was also employed. Insofar as reliable pK^{BH+} data could be obtained by other methods, a determination of the pK_{BH^+} by the Geissman treatment constituted a test of the reliability of this method and of the validity of the assumptions made in its derivation. It was found that the pK_{BH^+} values obtained by this method depended on the choice of wave length pair. Though steep titration curves were obtained in each case, these curves were not flat in the upper region. The need for a judicious selection of wave lengths in this widely employed method is well illustrated in the case of chalcone (Table IV). When the long wave length maximum chosen for measurement was that at which the maximum appeared in the most concentrated acid, a pK_{BH^+} value too negative by 0.35 unit was obtained. When the long wave length selected was that of the maximum at 50% protonation, however, excellent agreement with the other methods was obtained. This method was relatively insensitive to the selection of the short wave length; a variation by 20 mμ in the location of the shorter wave length, keeping the long wave length maximum constant, produced only negligible difference in the pK value. Though the largest deviation observed is relatively small in the case of chalcone, it is to be expected that arbitrary selection of the long wave length for measurement as that at which the maximum is located in concentrated sulfuric acid, as is generally the practice, may have a large effect on the pK_{BH^+} of the most basic compound in the series.[34]

Table IV records values of the pK_{BH^+} for chalcone as determined by the various methods. In Table V the values for the substituted chalcones are presented.

TABLE IV

BASICITY OF CHALCONE DETERMINED BY VARIOUS METHODS

Method	Aq. H_2SO_4	5% Dioxane–95% aq. H_2SO_4
I	−5.10	−5.30
	−5.05[d]	
II	−5.00±0.035	−5.17
III	−5.00,[a] −4.95[a,d]	
	−5.35[b]	−5.30
	−5.70,[c] −5.68[c,d]	
IV	−5.04[a]	
	−5.15[b]	−5.25
	−5.30[c]	
Best value	−5.00	−5.17

Long wave length maximum employed at: [a] 50% protonation. [b] 99% protonation. [c] 95% sulfuric acid. [d] Values obtained from log *I* *vs.* % sulfuric acid plot (*cf.* Fig.1).

Hydrogen Bonding Method.—Infrared spectra were obtained with a Beckman IR-7 grating spectrophotometer, employing carbon tetrachloride solutions 0.10 *M* in the chalcone and 0.02 *M* in phenol, and a 0.3-cm. sodium chloride cell. No association of phenol could be discerned at this concentration, and a solution of the same concentration of chalcone in carbon tetrachloride showed absence of any appreciable absorption in the regions where the hydrogen-bonded peak and the phenolic stretching vibrations were found. Each determination was run in duplicate and the peak of the associated O–H stretching vibration could be reproduced to better than 5 cm.$^{-1}$; this error originated chiefly in the difficulty with which the peak of the broad maximum could be determined. Table VI presents a summary of the pK's measured in this fashion.

Results and Discussion

Basicity of *trans*-Chalcone (Benzylideneacetophenone).—Though values of −5.73,[4] −5.68,[12] and −5.17[35] have been reported for the pK_{BH^+} of chalcone, the uncertainties due to the medium shifts made it desirable to redetermine the value of the pK_{BH^+} for chalcone in water, as well as to determine it in the 5% dioxane–95% aqueous acid medium. In the present study, it was found that the pK_{BH^+} of chalcone is −5.00 in water, a value which we consider to be much more reliable for the following reasons. As previously noted,[11] extremely pronounced medium shift is present in the spectrum of the salt of chalcone. As Table II shows, the position of the long wave length maximum for the protonated species moves from 390 mμ (in 60% sulfuric acid) when it appears, to 431 mμ in concentrated sulfuric acid. Use of the absorption peak at 431 mμ in determination of the pK_{BH^+} results in measurements in which the ob-

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[34] A. Fischer, *et al.*,[7] have recently also demonstrated the dependence of pK_{BH^+} on the wave length pair selected for measurement with benzyl phenyl ketones; a range of values amounting to 0.5 unit was observed when the wave length was changed by 10 mμ. In this case, the shorter wave length was also varied by the same amount.

[35] This value at 20° has been reported for the pK_{BH^+} of chalcone in polyphosphoric acid (A. I. Geib'shtein, G. G. Shcheglova and M. I. Temkin, *Doklady Akad. Nauk SSSR*, **107**, 108 (1956)). Recent workers, however, have observed that this indicator is unstable in the 80% P_2O_5 region. (R. G. Downing and D. E. Pearson, *J. Am. Chem. Soc.*, **83**, 1718 (1961)).

served ϵ is too low throughout the protonation region. In Fig. 1, data obtained in this fashion (reproducing the reported pK_{BH^+} values[4,12]) are plotted. It is to be noted that a plot of log I *vs.* % sulfuric acid gives a curve which deviates considerably from parallelism with other indicators in this range. In contrast, a plot of the indicator ratios obtained by method I or method III gives excellent straight lines in which parallelism with other indicators in this region is excellent. Values determined by various methods are given in Table IV.

Basicities of Substituted Chalcones (Table V).—The basicities of *trans*-chalcone, *trans*-4-methoxychalcone, *trans*-4-methylchalcone and *trans*-4-chlorochalcone show excellent correlation with the σ^+-constants of Brown and Okamoto,[36] with a ρ of 1.26. The basicity of *trans*-4-nitrochalcone correlates very well with the above compounds when correction is made for the consistent, but small, difference in the pK's determined in purely aqueous acid and in the 5% dioxane medium.[37] When this correction (0.17 H_0 unit) is applied, the value for *trans*-4-nitrochalcone in the dioxane medium is −6.22; this value is included in calculating ρ.

TABLE V

BASICITIES OF SUBSTITUTED CHALCONES IN 5% DIOXANE–95% AQUEOUS SULFURIC ACID

Chalcone subst.	pK_{BH^+} Method I	Method II	Method III	Method IV	Best value
H	5.10^a	5.00^a	5.00^a	5.04^a	(5.00)^a
	5.30	5.17	5.30	5.25	5.17
4-OCH_3	4.35	4.25	4.35	4.28	4.25
4-CH_3	4.88	4.79	4.85	4.90	4.79
4-Cl	5.35	5.34	5.35	5.40	5.34
4-NO_2			6.05^a 6.22^e	6.04^a	6.22
2-OCH_3		4.63		4.60^c 4.50^d	4.63
2-CH_3		5.02		5.04	5.02
2-Cl		5.73		5.75	5.73
2,4,6-$(OCH_3)_3$				2.75	2.75
cis-4-NO_2				6.75^{a,b} 6.92^e	6.92
β-C_6H_5	5.55	5.65			5.65

^{a} Aqueous sulfuric. ^{b} 0.5% dioxane employed at low acidities. ^{c} For 475 mμ–330 mμ pair. ^{d} For 375 mμ–330 mμ pair. ^{e} Calculated value for 5% dioxane–95% aqueous H_2SO_4 medium.

The ρ-value of 1.26 should be compared with values of 2.17, 1.85 and 1.09 found for the basicities of acetophenones, benzaldehydes and benzoic acids, respectively. A lowered value was expected and is compatible with the interpretation that a substantial contribution to the stability of the protonated carbonyl group is afforded by the double bond in the side chain, making the contribution of substituents in the benzene ring of less import. Nevertheless, the fact that correlation with σ^+ rather than σ is obtained shows the presence of strong resonance interaction involving the substituent in the aromatic ring.

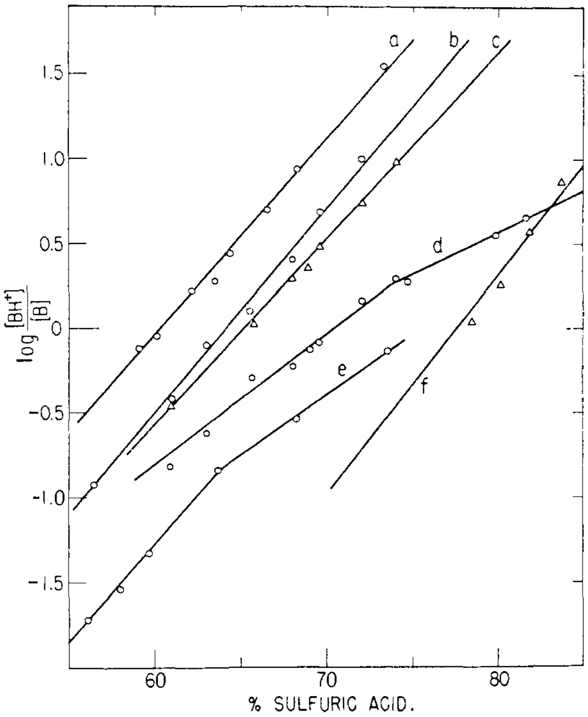

Fig. 1.—Ionization ratios (BH^+/B) for benzylideneacetophenone, as obtained by various methods, and for two aniline indicators plotted against % sulfuric acid. Benzylideneacetophenone: b, method III, λ 405 mμ; c, method I, λ λ_{max}; d, method III, λ 431 mμ; e, values by Hammett and Deyrup (ref. 4b). Aniline indicators: a, 2,4-dinitroaniline (ref. 4b); f, 2-bromo-4,6-dinitroaniline (ref. 4b).

It is interesting to note that Stewart and his coworkers observed that the basicities of p-methoxy- and p-hydroxyacetophenones and benzaldehydes deviated considerably, whether in either a ρ–σ or a ρ–σ^+ correlation. The suggestion was made that these deviations were the result of solvent interactions with the oxygen function. Based upon our experiences, it is possible that the spectra of substances are also subject to unusually large medium shifts, which result in the apparent deviation of the pK's.

***o*-Substituted Chalcones.**—The basicities of 2-methoxychalcone and 2-chlorochalcone were found to be less by about 0.40 pK unit than the corresponding 4-substituted chalcones. The effect is less in 2-methylchalcone; the basicity is lowered only by 0.20 pK unit. It is clear from a cursory examination of the ultraviolet spectra of these compounds that the *ortho* isomers show a considerable steric inhibition of resonance stabilization. This is manifested in two ways: the long wave length absorption (presumably due to the substituted cinnamoyl chromophore) is of considerably lessened intensity; and several new complexities appear in the spectra.

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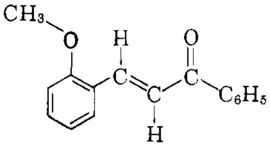
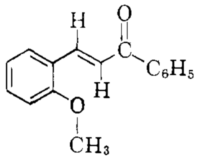
[36] H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **79**, 1913 (1957).

[37] The difference in pK_{BH^+} in aqueous solution and in 5% dioxane is presumably due to a medium effect caused by the presence of dioxane and protonated dioxane. Since the H_0 scale in this medium was determined by the use of aniline indicators, these values indicate that the effect of the change of medium on these ketone indicators is more pronounced by about 0.20 H_0 unit than on the aniline indicators.

The lessened intensity of absorption for the long wave length chromophore is similar to the characteristic effects found in *cis*-chalcones.[38]

The greater complexities of the spectrum of 2-methoxychalcone suggests additional electronic or geometrical effects. In contrast to the simple spectra of 4-substituted chalcones, this compound in ethanol shows two maxima in the 250 mμ region comparable in intensity and maxima at 300 and 350 mμ, also of equal intensity, but being solvent dependent in position and intensity. In cyclohexane a spectrum is obtained which shows pronounced fine structure of the long wave length maxima. Upon protonation both the 300 mμ band and the 350 mμ band give rise to a long wave length absorption band of approximately equal intensity, at 380 and 460 mμ, respectively. Calculation of pK_{BH^-} values, using either change, gave comparable results. The presence of two maxima may be attributable to the presence of rotational isomers, having grossly different electronic transitions. One type may rotate around the phenyl–carbon bond involving the pairs Ia, Ib in which dipole interactions destabilize one isomer over the other, leading to different absorption spectra.


Ia


Ib

Alternatively, the presence of a band at 300 mμ in 2-methoxychalcone and at 380 mμ in the conjugate acid, band positions very similar to those in chalcone itself, suggest that rotational isomerism about the methoxyl-aromatic ring bond may be responsible for the complex spectrum. Were the methoxyl group to be so oriented that electronic interaction is not possible with the unshared electrons on the ethereal oxygen, electronic transitions similar to those in chalcone itself would be expected.

Basicity of β-Phenylchalcone.—β-Phenylchalcone shows the presence of bands at 231, 250 and 298 mμ, which show similarity to the bands in both *cis*-chalcone and *trans*-chalcone. The spectral complexities are similar to those observed in α-phenylchalcone by Black and Lutz.[39]

The protonation equilibrium for β-phenylchalcone, $pK_{BH^+} = -5.65$, shows clearly that the additional phenyl ring does not provide any increased resonance stabilization for the cation but, instead, merely adds an inductive effect, which is destabilizing.

It is interesting to note that upon protonation two long wave length bands appear, one at 375 mμ, similar in position to the band in the conjugate acid of chalcone, and a more intense band at 450 mμ. The latter band is very similar to the long wave length band in benzhydryl cation.[40]

Basicity of *cis*-4-Nitrochalcone.—It was possible to measure directly the basicity of this chalcone, as the rate of isomerization[13b] to the *trans* isomer has a half-life at the *pK* of 9 minutes at 25°. By making measurements at reduced temperature, and extrapolating to zero time, the appropriate calculations could be made.

The observed pK_{BH^+} for *cis*-4-nitrochalcone in aqueous sulfuric acid is −6.75. Corrected to the 5% dioxane solvent mixture used for many of the other chalcones, the value for the pK_{BH^+} of *cis*-4-nitrochalcone is −6.92.

This value provides a very useful check on the consistency of data obtained by the hydrogen-bonding method for other *cis*-chalcones.

Basicities by Studies by Hydrogen Bonding.—It was originally suggested by Gordy and Stanford[15] that the position of the hydrogen stretching frequency of methanol hydrogen-bonded with other weak bases is a useful measure of relative basicity of the latter compounds. Subsequently, many investigators have made use of this proposal in a variety of studies. Cyclic ethers and aromatic ethers have been studied by Searles and Tamres,[41] and by Arnett and Wu.[42] Arnett and Wu report that a fairly good correlation of basicity and the shift of the stretching frequency is observed over a wide range of basicity. Recently, it has been suggested by West[43] that the use of phenol offers several advantages.

Table VI

Basicities of Substituted Chalcones Determined from the Shift of the O–H Stretching Vibration of Phenol in Carbon Tetrachloride Solution of the Chalcone

Chalcone substituent	O–H shift, cm.⁻¹	$-pK_{BH^+}$ (Table V)	$-pK_{BH^+}$[b]	ΔpK_{BH^+} *trans–cis*
H	207[a]	5.17		
4-Cl	205	5.34		
4-F	206		5.22	
4-CH_3	215	4.79		
4-OCH_3	225	4.25		
2-Cl	190	5.73		
2-CH_3	213	5.02		
cis-H	185		5.97	0.80
cis-2-OCH_3	200		5.39	.75
cis-4-NO_2	158	6.92	7.03	.81[c] (0.70)[d]
cis-4-Cl	187		5.89	.55
2,4-$(OCH_3)_2$	234		4.04	
2,4,6-$(OCH_3)_3$	255	2.75	3.22	

[a] $\nu_0 = 3627$ cm.$^{-1}$; $\nu_{bonded} = 3420$ cm.$^{-1}$. [b] Determined from the best slope correlating the *pK*'s measured in sulfuric acid with the frequency shifts in column 2; $pK = 0.039\Delta\nu - 13.23$, $r = 0.98$. [c] From infrared data. [d] From *pK*'s in sulfuric acid.

We have examined the basicities of the substituted chalcones by the latter procedure (Table VI). Several advantages accrue in the present study.

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[38] W. B. Black and R. E. Lutz, *J. Am. Chem. Soc.*, **77**, 5134 (1955).

[39] W. B. Black and R. E. Lutz, *ibid.*, **75**, 5990 (1953).

[40] N. C. Deno, J. J. Jaruzelski and A. Schriesheim, *ibid.*, **77**, 3044 (1955).

[41] S. Searles, Jr., and M. Tamres, *ibid.*, **73**, 3704 (1951).

[42] (a) E. M. Arnett and C. Y. Wu, Abstracts of Papers, 136th Meeting of the American Chemical Society, Atlantic City, N. J., September, 1959, p. 63P; (b) E. M. Arnett and C. Y. Wu, *J. Am. Chem. Soc.*, **82**, 4999, 5661 (1960); **84**, 1680, 1684 (1962); (c) E. M. Arnett, C. Y. Wu, J. N. Anderson and R. D. Bushick, *ibid.*, **84**, 1674 (1962).

[43] R. West, *ibid.*, **81**, 1614 (1959).

There is available a set of compounds, which varies in basicity by four powers of ten, and are of similar structure. For many of these compounds the basicities have also been measured by the usual Hammett acidity scale in sulfuric acid; there are therefore several independent checks on the quality of the correlation. In this fashion it has been possible to determine the pK_{BH^+} for several *cis*-chalcones, most of which undergo isomerization far too rapidly[13b] in moderately concentrated sulfuric acid for the Hammett procedure to be used.

It is to be noted (Table VI) that the *cis*-chalcones are uniformly less basic than the corresponding *trans*-chalcones. The average decrease in basicity is a factor of 5.

pK of *trans*-4-Fluorochalcone.—The basicity of 4-fluorochalcone was measured by the hydrogen bonding method, and a value of $pK_{BH^+} = -5.22$ obtained. An independent check of this value by the method of Fox, Levins and Taft,[44] the F^{19} nuclear magnetic resonance shift, was very kindly carried out by Professor Taft. The value by this procedure is $pK = -5.10$.[45]

[44] I. R. Fox, P. L. Levins and R. W. Taft, Jr., *Tetrahedron Letters*, No. **7**, 249 (1961).

[45] R. W. Taft, Jr., personal communication.

[CONTRIBUTION No. 179 FROM THE GRADUATE DEPARTMENT OF BIOCHEMISTRY, BRANDEIS UNIVERSITY, WALTHAM 54, MASS.]

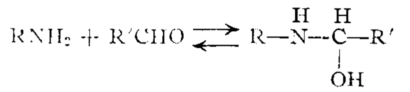
General Acid Catalysis of Semicarbazone Formation[1]

BY E. H. CORDES AND W. P. JENCKS

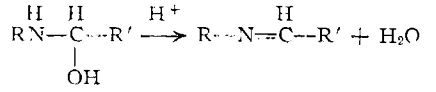
RECEIVED MAY 21, 1962

General acid catalysis of the attack of semicarbazide on a series of substituted benzaldehydes has been studied in aqueous solution at 25°. Protonated aldehydes do not appear to be intermediates in benzaldehyde semicarbazone formation, because the calculated rate constant for a reaction involving protonated p-nitrobenzaldehyde is larger than that for a diffusion-controlled reaction. From this and other arguments, based on the rates of proton transfer reactions, it is concluded that the general acid-catalyzed reaction involves concerted semicarbazide attack and proton transfer to the carbonyl group. The deuterium isotope effect on the catalytic constant for the hydrated proton is $k_H/k_D = 1.2$ and that for acetic acid is 1.6. The catalytic rate constants for chloroacetic acid, acetic acid and water are better correlated by σ^+ than by σ-substituent constants. Values of ρ^+ for these catalysts and the hydrated proton increase slightly with decreasing acid strength, from 0.71 for the hydrated proton to 0.94 for water. The Brönsted α-value was determined from the catalytic constants of several carboxylic acids and the hydrated proton for p-nitro-, p-chloro- and p-hydroxybenzaldehydes and acetophenone. Values of α near 0.25 were obtained in each case, indicating that α is insensitive to a moderate change in substrate reactivity. Relationships between the Brönsted α-value, the reactivity of the substrate and the reactivity of the nucleophilic reagent from the Hammett, Brönsted and Swain-Scott equations are discussed. In the case of p-chlorobenzaldehyde, the Brönsted plot was extended to include catalytic constants for thirty acids of varying structure and charge type.

Several investigations have established that the reaction of semicarbazide with aldehydes and ketones is subject to general acid catalysis.[2] Subsequent work has shown that, at neutral pH, the acid-catalyzed dehydration of the carbinolamine addition product (eq. 2) is the rate-determining step in semicarbazone formation, while under more acidic conditions the rate-determining step undergoes a transition to rate-determining semicarbazide attack[3,4] (eq. 1). The attack of semicarbazide on the carbonyl carbon atom obeys the rate law of eq. 3. Thus this reaction exhibits catalysis by general acids, the solvated proton and solvent.



$$RNH_2 + R'CHO \rightleftarrows R{-}\overset{H}{N}{-}\underset{OH}{\overset{H}{C}}{-}R' \qquad (1)$$



$$R\overset{H}{N}{-}\underset{OH}{\overset{H}{C}}{-}R' \xrightarrow{H^+} R{-}N{=}\overset{H}{C}{-}R' + H_2O \qquad (2)$$

$$v = \left[k_0 + k_H(H^+) + \sum_i k_{A_i}[A_i]\right][RNH_2][>C{=}O] \qquad (3)$$

Several aspects of the general acid-catalyzed attack of nucleophilic reagents on the carbonyl carbon atom, including the mechanism of the catalysis, the variation in susceptibility to general acid catalysis as a function of the reactivity of substrate and nucleophilic reagent, and the relationship of catalyst structure to catalytic efficiency are of particular chemical and biochemical interest. This work was undertaken in an attempt to obtain information pertinent to these questions.

Experimental

Materials.—All carbonyl compounds were either redistilled under nitrogen or twice recrystallized before use. Solutions of carbonyl compounds were prepared in water containing approximately 15% ethanol and 10^{-4} M ethylenediaminetetraacetic acid and were stored at 2°. These solutions are stable for several days under these conditions. Semicarbazide hydrochloride was recrystallized at least twice from aqueous ethanol and solutions were prepared just prior to use. Trimethylamine-N-oxide (m.p. 95–96°), N,N-dimethylhydroxylamine (m.p. 106°) and glycine hydroxamic acid (m.p. 141–143°) were prepared by known methods.[5-7] Formohydroxamic acid (m.p. 74–76°) and acetohydroxamic acid (m.p. 89.5–92°) were prepared by slight modifications of the method employed for the preparation of glycine hydroxamic acid.[7] Other reagents, except for reagent grade inorganic salts, were recrystallized or redistilled before use. Solutions of all nitrogen bases were prepared just prior to use. Deuterium oxide (>99%) was redistilled before use. Glass-distilled water was used throughout.

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[1] Supported by grants from the National Cancer Institute of the National Institutes of Health (C-3975) and the National Science Foundation. This investigation was carried out by E. C. during the tenure of a Predoctoral Fellowship from the National Heart Institute, U. S. Public Health Service.

[2] (a) J. B. Conant and P. D. Bartlett, *J. Am. Chem. Soc.*, **54**, 2881 (1932); (b) F. H. Westheimer, *ibid.*, **56**, 1962 (1934); (c) G. H. Stempel, Jr., and G. S. Schaffel, *ibid.*, **66**, 1158 (1944).

[3] W. P. Jencks, *ibid.*, **81**, 475 (1959).

[4] B. M. Anderson and W. P. Jencks, *ibid.*, **82**, 1773 (1960).

[5] W. R. Dunstan and E. Goulding, *J. Chem. Soc.*, **75**, 1004 (1899).

[6] H. Hepworth, *ibid.*, **119**, 251 (1921).

[7] S. R. Safir and J. H. Williams, *J. Org. Chem.*, **17**, 1298 (1952).