TABLE V

BASE STRENGTH MEASUREMENTS

Substance	Method[a]	Temp., °C.	Ionic strength approximate	pK_B	Investigator
Pyridine	s	24.3	0.02	8.80	Wieder, this lab.
	s	20.0	.028	8.88	Hughes, *et al.*[18]
	s	25.3	.01	8.84	Herington[20]
Piperidine	s	24.3		2.97	Corning, this lab.
	s	25.0	0.005	3.00	Semenow, this lab.
	p	25.0	0	2.94	Wynne-Jones, *et al.*[19]
Pyrrolidine	s	25.6	0.005	3.02	Semenow, this lab.
	p	25.0	0.005	2.99	Buckley, this lab.
	p			2.89	Craig and Hixon[21]
Piperazine	p	23.5	0.01	4.22 8.49	Wieder, this lab.
	p	15.0		4.02 8.34	Kolthoff[22]
		25.0		4.19	Bredig[23]

[a] s = spectrophotometric, p = potentiometric.

Pyrrolidine and piperidine are extremely strong bases while piperazine is not as strong even for the first ionization, showing that the second nitrogen atom has an inductive effect. Pyridine is a very weak base and pyrrole is not measurable in aqueous solution. No significant relation was found between the position of the absorption band and the base strength in aqueous solution.

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(20) E. F. G. Herington, *Disc. Faraday Soc.*, **9**, 26 (1950).

(21) L. C. Craig and R. M. Hixon, THIS JOURNAL, **53**, 4367 (1931).

(22) I. M. Kolthoff, *Biochem. Z.*, **162**, 289 (1925).

(23) G. Bredig, *Z. physik. Chem.*, **13**, 312 (1894).

SOUTH HADLEY, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE, AND THE OREGON FOREST PRODUCTS LABORATORY]

The Infrared Spectra of Lignin and Related Compounds. I. Characteristic Carbonyl and Hydroxyl Frequencies of Some Flavanones, Flavones, Chalcones and Acetophenones[1]

BY H. L. HERGERT AND E. F. KURTH

RECEIVED SEPTEMBER 2, 1952

The hydroxyl and ketone carbonyl infrared frequencies of a series of flavanones and related compounds have been measured. An *o*-hydroxyl group chelated to a carbonyl group effects a shift of 60 cm.$^{-1}$ to a longer wave length. Shifts to shorter or longer wave lengths were observed when electron-withdrawing or supplying constituents were introduced into ring positions conjugated with the carbonyl group. The effects of intramolecular and intermolecular hydrogen bonding upon the carbonyl frequency are shown and discussed.

Infrared spectroscopy has proved to be an especially useful tool in the field of lignin chemistry since it provides a rapid method of evaluating lignins isolated by different methods.[2a–f] Application of the infrared method toward the structural elucidation of lignin has been hindered, however, by the lack of sufficient data concerning certain functional group frequencies in solid organic compounds. This information is necessary, since lignin may be prepared only as a mull or a film because of its insolubility in the solvents ordinarily used in infrared analysis.

Examination of the infrared spectra of lignin and lignin derivatives prepared in this Laboratory indicates the presence of two bands, 1666–1668 cm.$^{-1}$ and 1705–1710 cm.$^{-1}$, which presumably originate from conjugated aldehyde and ketone carbonyl groups, respectively. Other materials related to lignin, such as tannin and phlobaphene, also show bands assignable to carbonyl groups. It seemed to be advantageous, therefore, to study a series of known solid compounds that may be related to lignin and contain hydroxyl, methoxyl and carbonyl groups. The results from the study of the first series of these compounds are presented here.

Experimental

Spectra.—The instrument used in this work is a model 12C Perkin–Elmer spectrometer and Brown recorder adapted to automatic, double-beam operation by the method of Savitsky and Halford.[3] Lithium fluoride optics were used in the 2500–4000 cm.$^{-1}$ region and sodium chloride in the 1550–1800 cm.$^{-1}$ region. Solid samples were mulled in mineral oil (Nujol) or perfluorokerosene and run against a salt plate as a blank.

Compounds.—Benzalacetophenone (chalcone) and the hydroxy acetophenones were purchased from the Eastman Kodak Company. Purification was effected by recrystallization or fractional distillation, whichever was appropriate. Derivatives were prepared by known methods.

Flavanone was prepared by the method of Kostanecki and Szabranski.[4] The method of Kurth[5] was used to prepare 2,4-dihydroxyflavanone and its corresponding chalcone. Douglas fir bark cork[6] was used as a source of *d*-3,3′,4′,5,7-pentahydroxyflavanone. The pentaacetate derivative, m.p. 128–129° from methanol, was prepared by the acetic anhydride–pyridine method. The 3′,4′,7-trimethoxy and pentamethoxy derivatives of this flavanone were prepared by diazomethane and dimethyl sulfate methylation, respectively, by Mr. Peter Coad and will be described in detail in a subsequent publication. The pentahydroxyflavanone was converted to the corresponding flavone (quercetin) by treatment with aqueous sodium bisulfite.[7] Pentamethoxy- and 3,3′,4′,7-tetramethoxyquercetin were prepared by the method of Gomm and Nierenstein.[8] The method of Pew[9]

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[1] From the Ph.D. thesis of H. L. Hergert to be submitted to the graduate school of Oregon State College. This paper was presented at the Northwest Regional Meeting of the American Chemical Society at Corvallis, Oregon, June 20, 1952.

(2) (a) G. de Stevens and F. F. Nord, THIS JOURNAL, **73**, 4622 (1951); (b, c) S. F. Kudzin and F. F. Nord, *ibid.*, **73**, 690, 4619 (1951); (d) S. F. Kudzin, R. M. DeBaun and F. F. Nord, *ibid.*, **73**, 4615 (1951); (e) E. J. Jones, *Tappi*, **32**, 167 (1949); (f) K. Freudenberg, *et al.*, *Ber.*, **83**, 533 (1950).

(3) A. Savitsky and R. S. Halford, *Rev. Sci. Instruments*, **21**, 203 (1950).

(4) V. Kostanecki and Szabranski, *Ber.*, **37**, 2635 (1904).

(5) E. F. Kurth, THIS JOURNAL, **61**, 861 (1939).

(6) H. L. Hergert and E. F. Kurth, *Tappi*, **35**, 59 (1952).

(7) E. F. Kurth and F. L. Chan, *J. Am. Oil Chem. Soc.*, **28**, 433 (1951).

(8) A. S. Gomm and M. Nierenstein, THIS JOURNAL, **53**, 4408 (1931).

(9) J. C. Pew, *ibid.*, **70**, 3031 (1948).

was used to prepare 3′,4′,5,7-tetrahydroxyflavanone. The 3′,4′,7-trimethoxy derivative was obtained by diazomethane methylation. Ponderosa pine bark was used as a source of 3,3′,4,5,8-pentahydroxyflavone.[10]

The carbonyl and hydroxyl frequencies of this series of compounds[11] are presented in Table I.

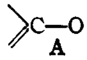
TABLE I

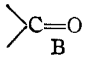
Compound	Frequency, cm.$^{-1}$ Carbonyl	Frequency, cm.$^{-1}$ Hydroxyl
Flavanone	1680	....
3′,4′-Dihydroxy-	1665	3395, 3105[a]
3′,4′-Diacetoxy-	1762, 1680	....
3′,4′,5,7-Tetrahydroxy-	1620	3260[a]
3′,4′,5,7-Tetraacetoxy-	1763, 1680	....
5-Hydroxy-3′,4′,7-trimethoxy-	~1610[b]	....
3,3′,4′,5,7-Pentahydroxy-	1642	3510, 3355[a]
3,3′,4′,5,7-Pentaacetoxy-	1764, 1703	....
3,3′,4′,5,7-Pentamethoxy	1649	....
3,5-Dihydroxy-3′,4′,7-trimethoxy-	~1606[b]	3380
Acetophenone	1687	....
2-Hydroxy-[c]	1635	....
2-Acetoxy-	1762, 1678	....
2-Benzoxy-	1736, 1684	....
2-Methoxy-[c]	1649	....
4-Hydroxy-	1638	3100[a]
4-Acetoxy-	1763, 1685	....
4-Methoxy-[c]	1657	....
4-Methoxy-2-hydroxy-	1615[b]	....
2,4-Dihydroxy-	1620	3260, 3150[a]
2,4-Dimethoxy-	1643	....
2,4-Diacetoxy-	1764, 1688	....
Chalcone (benzalacetophenone)	1659	....
2′,3,4-Trihydroxy-	1621	3280[a]
2′,3,4-Triacetoxy-	1762, 1661	....
2′,3,3′,4,4′-Pentahydroxy-	1619[b]	3250[a]
2′,3,3′,4,4′-Pentabenzoxy-	1744, 1656	....
Flavone		
3,3′,4′,5,7-Pentaacetoxy-	1763, 1640	....
3,3′,4′,5,7-Pentahydroxy-	1654	3290[a]
3,3′,4′,5,7-Pentamethoxy	1627	....
3′,4′,5,7-Tetramethoxy-5-hydroxy	1657	....
3′,4′,5,7-Tetrahydroxyflavone-3-rutinoside	1655	3270[a]
3,3′,4′,5,8-Pentahydroxy-	1655	3340
3,3′,4′,5,8-Pentaacetoxy-	1764, 1645	....

[a] Broad band, not sharply defined. [b] Exact position in doubt because of interference by phenyl band at 1605–1590 cm.$^{-1}$. [c] Liquid.

Discussion

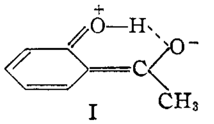
It is a well-known observation in infrared spectroscopy that conjugation of ethylenic double bonds, or a carbonyl group and double bonds causes a shift from the normal position to a longer wave length. Thus the unconjugated carbonyl group in acetone shows a band at 1718 cm.$^{-1}$ while conjugation with one phenyl group, as in acetophenone, lowers the frequency to 1687 cm.$^{-1}$ and conjugation with two phenyl groups, as in benzophenone, lowers the frequency to 1655 cm.$^{-1}$. Whether this shift is due to mesomerism or to an actual lengthening of the bond is not known. Our results indicate that whenever there is an increased opportunity for the contribution of the ionic resonance structure, A, to the carbonyl group, B, a shift to lower frequencies

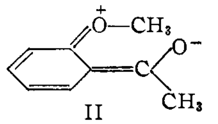

A


B

is observed. Generally, the shifted band also has a greater intensity, which would be expected from participation of A.

Acetophenones.—When a hydroxyl group is introduced ortho to the keto group in acetophenone, the carbonyl frequency is shifted from 1687 to 1635 cm.$^{-1}$. This effect has been previously noted by Gordy[12] who attributed it to hydrogen bonding between the hydroxyl group and the keto group. Rasmussen and co-workers[13] reinterpreted this shift as being due to a conjugate-chelate system. They suggested that such a system is necessary for the occurrence of extreme shifts. Careful examination of the 3500-2500 cm.$^{-1}$ region of the spectrum of *o*-hydroxyacetophenone indicates the absence of any band attributable to a hydroxyl group. This behavior was previously noted in the *o*-hydroxyanthraquinones[14] and attributed to intramolecular hydrogen bonding. Furthermore, acetylation of *o*-hydroxyacetophenone shifts the band back to 1678 cm.$^{-1}$ (the 1762–1764 cm.$^{-1}$ band in all the acetoxy derivatives is caused by the acetoxy carbonyl group). These three facts seem to indicate further that conjugated chelation is responsible for the shift to shorter wave length. However, *o*-methoxyacetophenone shows a band at 1649 cm.$^{-1}$; clearly neither hydrogen bonding nor chelation is possible in this case. It seems likely, therefore, that the lowering is due to the participation of resonance forms, such as I in the case of the hydroxyl derivative and II in the case of the methoxyl derivative. The increased stabilization in I, due to the chelate ring plus the presumedly greater ability of the hydroxyl group to donate electrons to the ring, is responsible for the lower carbonyl frequency in I than II. The ability of the acetoxy group to donate electrons is very meager and thus accounts for the acetoxy derivatives not markedly differing from unsubstituted acetophenone.


I


II

The hydroxyl band in *p*-hydroxyacetophenone occurs at 3250 cm.$^{-1}$, which indicates strong hydrogen bonding. Resonance structure III is likely responsible for the carbonyl shift to 1635 cm.$^{-1}$; structure III may be stabilized by hydrogen bonding as in IIIa.

The 2,4-derivatives of acetophenone require the same considerations as previously noted. The di-

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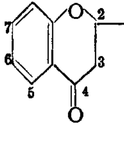
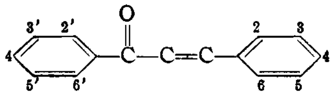
[10] E. F. Kurth and J. K. Hubbard, *Ind. Eng. Chem.*, **43**, 896 (1951).

[11] Flavanones, flavones and chalcones are numbered as follows

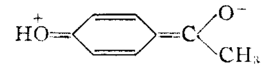




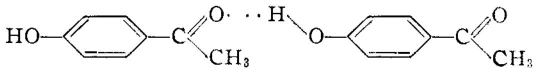
[12] W. Gordy, *J. Chem. Phys.*, **8**, 516 (1940).

[13] R. S. Rasmussen, D. Tunnicliff and R. Brattain, THIS JOURNAL, **71**, 1068 (1949).

[14] M. St. C. Flett, *J. Chem. Soc.*, 1441 (1948).

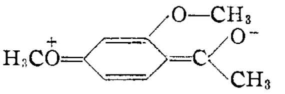


III

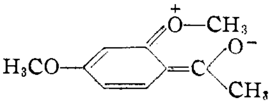


IIIa

methoxyl derivative shows a shift lower than either the para or ortho compound. Increased electron supply to the ring present in both forms IV and IVa is very likely responsible. It is interesting to note that the datum of Soloway and Friess[15] indicates that *m*-methoxylacetophenone shows a carbonyl band at 1681 cm.$^{-1}$. The meta position is not conjugated with the carbonyl group, which indicates that even though the methoxyl group is an electron donor, it must be in a conjugated position to affect the carbonyl frequency.

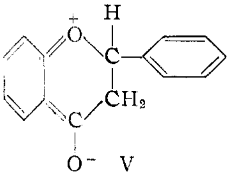


IV

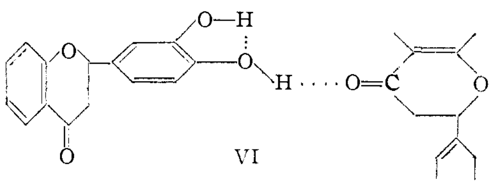


IVa

Flavanones.—Unsubstituted flavanone shows a band at 1680 cm.$^{-1}$ This is only a slightly longer wave length than that of acetophenone, indicating that the oxygen in the pyran ring does not have the same influence as the *o*-methoxyl group in acetophenone. Consequently, resonance structure V is of small importance. Introduction of hydroxyl groups in the 3′- and 4′-positions causes the carbonyl frequency to shift to 1665 cm.$^{-1}$. Acetylation of these groups causes a shift back to 1680 cm.$^{-1}$, a frequency identical with that of unsubstituted flavanone. Since these hydroxyl groups are not conjugated with the carbonyl group, their electron-donating character is not responsible for the shift to a lower wave number. This shift must be attributed to intermolecular hydrogen bonding of the type VI. Further evidence of this is found by examining the hydroxyl bands at 3395 and 3105 cm.$^{-1}$. The former indicates a moderately strong hydrogen bond. The latter is shifted further than normal for such phenols as catechol and is very likely due to hydrogen bonding to the keto group.[16]

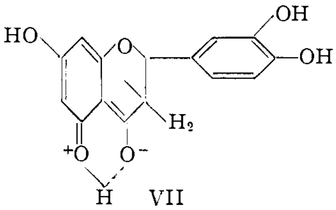


V

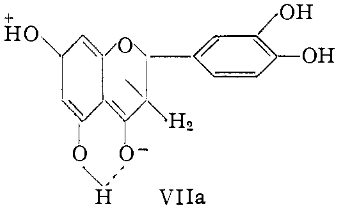


VI

Introduction of hydroxyl groups into the 5- and 7-positions shifts the carbonyl frequency to 1620 cm.$^{-1}$, which is identical with that of 2,4-dihydroxyacetophenone. It is concluded that VII and VIIa are important resonance structures. Hydrogen bonding between the 5-hydroxyl group and the keto group has previously been suggested to explain the resistance of the 5-hydroxyl group to methylation by diazomethane[8] and the stabilization of 5-hydroxyflavanones toward ring opening.[17] Methylation of 3′,4′,5,7-tetrahydroxyflavanone with diazomethane yields the 3′,4′,7-trimethoxy-5-hydroxy derivative, which has a carbonyl frequency of 1610 cm.$^{-1}$ and shows no band attributable to a hydroxyl group. Although this shift is very likely enhanced by the methoxyl group in the conjugated 7-position, the electron-donating property of the 5-hydroxyl group enhanced by chelation, as in VII, must be chiefly responsible for this shift.



VII



VIIa

Acetylation of 3,3′,4′,5,7-pentahydroxyflavanone shifts the carbonyl band from 1642 to 1703 cm.$^{-1}$. Since this acetoxy derivative has a higher carbonyl frequency than unsubstituted flavanone and 3′,4′,5,7-tetraacetoxyflavanone, it appears likely that the 3-substituent is responsible for this effect. Further work is necessary to verify this assumption.

Chalcones.—Unsubstituted chalcone (benzalacetophenone) shows a carbonyl band at 1659 cm.$^{-1}$ which is due to conjugation with a phenyl group and an aliphatic double bond. Introduction of a hydroxyl group in the conjugated-chelated 2′-position lowers the carbonyl frequency to about 1620 cm.$^{-1}$. Acetylation causes a return to the original unsubstituted position. The same considerations governing the carbonyl frequencies in acetophenone and flavanone derivatives apparently are operative in the chalcones, with the exception that enhancement due to the conjugated 2- and 4-positions is increased.

Flavones.—The flavone derivatives examined did not show marked lowering of carbonyl frequency when a hydroxyl group was present in the 5-position. Acetylation of the hydroxyl groups decreased, rather than increased, the carbonyl frequency. That the 5-hydroxyl group is involved in chelation is apparent, since the OH band is absent in 5-hydroxy-3,3′,4′,7-tetramethoxyflavone. Introduction of a methoxyl group in the 5-position causes a shift to 1627 cm.$^{-1}$ for 3,3′,4′,5,7-pentamethoxyflavone. This value is 22 cm.$^{-1}$ lower

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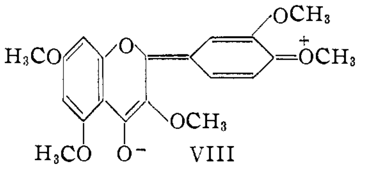
(15) A. H. Soloway and S. L. Friess, This Journal, **73**, 5000 (1951).

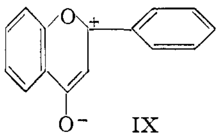
(16) It must be remembered that this shift is observed with crystalline material. The solution spectra in a non-proton-donor or -acceptor solvent probably would not show this effect.

(17) N. Narasimhachari and T. R. Seshadri, *Proc. Ind. Acad. Sci.*, **27A**, 223 (1948).

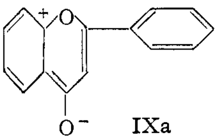
than that of the corresponding flavanone derivative. The lowering is due, at least partially, to increased conjugation, as in VIII, which is not possible in the flavanones. The chemical behavior of flavones (the formation of salts, difficulty of carbonyl derivative formation, etc.) and the infrared spectra indicate that flavones are not closely analogous to flavanones, chalcones or acetophenones. This may be due to the importance of resonance structures, such as IX and IXa, in which conjugation between the carbonyl group and the 5- and 7-position is not favored.



VIII



IX



IXa

Comparison of our results with studies of the polarographic reduction of the carbonyl group in flavones, flavanones and chalcones by Geissman and his co-workers[18] indicates that the same factors that are operative in altering the infrared frequency of the carbonyl group are responsible for the ease of reduction of this group.

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[18] Engelkemeir, Geissman, Crowell and Friess, THIS JOURNAL, **69**, 155 (1947); Geissman and Friess, *ibid.*, **71**, 3893 (1949).

CORVALLIS, OREGON

[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

The Synthesis of 2,3,4-Trimethoxybenzosuberene- and 2,3,4-Trimethoxybenzosuberancarboxylic Acids and Esters

BY JOHN KOO[1] AND JONATHAN L. HARTWELL

RECEIVED OCTOBER 9, 1952

The synthesis of several different types of 2,3,4-trimethoxybenzosuberene and -benzosuberancarboxylic acids and esters, which are of possible importance for the construction of the C-ring of colchicine and its related compounds, is described. The cyclization of these seven-membered ring compounds was accomplished with ease and in high yield by the use of polyphosphoric acid. The conversion of ethyl α-ethoxalyl-δ-(3,4,5-trimethoxyphenyl)-valerate to 2,3,4-trimethoxybenzosuber-5-ene-5-carboxylic acid in one operation, in good yield, is reported.

The successful synthesis of *dl*-colchinol methyl ether[2] and of deaminocolchinic acid anhydride[3] by two independent groups has eliminated any reasonable doubt as to the nature of ring B of colchicine. Our synthetic work on colchicine and its related compounds since then has been directed toward building ring C. One plan for this purpose consists in first preparing a compound containing the fused A/B ring system with ring A appropriately substituted, and with ring B bearing one or two reactive groups through which ring C may then be constructed. In this communication we wish to report the synthesis of a series of 2,3,4-trimethoxybenzosuber-5-ene and -suberancarboxylic esters and acids. Since these compounds contain the required fused A/B ring system and reactive groups, they are possible starting materials for the preparation of colchicine as well as of related compounds.

A search of the literature reveals that naphthalene or tetralin carboxylic acids and esters are relatively common, but little is known about the synthesis of their seven-membered analogs. Apparently, all types of bicyclic compounds described in this paper, containing three methoxyl groups on the benzene ring and with a mono- or dicarboxylic acid on one or both of the α- and β-positions of the seven-membered ring, are unreported. In the benzosuberene series, either mono- or diacids or their esters should prove applicable for subsequent work, and the position of the double bond may add to their suitability.

Condensation of ethyl δ-(3,4,5-trimethoxyphenyl)-valerate[3b] (I) with ethyl formate in the presence of dry potassium ethoxide yielded the formyl derivative (II) in 50% yield. Previously,[3,4] in connection with another study of the colchicine problem, many dimethoxy or trimethoxy five-membered, six-membered and seven-membered compounds were cyclized by a mixture of sulfuric acid and 85% phosphoric acid with difficulty and in varying yields. Our general experience with this reagent[4] is (1) that dimethoxy compounds are usually cyclized more easily than their trimethoxy analogs, and (2) that seven-membered compounds containing the same groups are more difficult to cyclize than their five- or six-membered analogs.[5] The difficulty in achieving cyclization of seven-membered compounds lies in the fact that it can be carried out only under certain rigid conditions (concentration of sulfuric acid, temperature and time), and the conditions used for one compound may not be applicable to another. Moreover, in many cases, sulfuric acid causes destruction or

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[1] Special Research Fellow of the National Cancer Institute, National Institutes of Health.

[2] H. Rapoport, A. R. Williams and M. E. Cisney, THIS JOURNAL, **73**, 1414 (1951).

[3] (a) E. C. Horning, M. G. Horning, J. Koo, M. S. Fish, J. A. Parker, G. N. Walker, R. M. Horowitz and G. E. Ullyot, *ibid.*, **72**, 4840 (1950); (b) J. Koo, *ibid.*, **75**, 720 (1953).

[4] E. C. Horning, J. Koo and G. N. Walker, *ibid.*, **73**, 5826 (1951); E. C. Horning and J. Koo, *ibid.*, **73**, 5828, 5830 (1951); J. Koo, *ibid.*, **75**, 723 (1953); J. Koo, *ibid.*, **75**, in press (1953).

[5] This phenomenon has also been found for the Friedel–Crafts cyclization. *Cf.* W. S. Johnson, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 117–118.