[CONTRIBUTION FROM THE RESEARCH LABORATORY OF PHYSICAL CHEMISTRY, NO. 485, AND FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, NO. 299, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Thermal Rates and Activation Energies for the Aqueous Acid Hydrolysis of α- and β-Methyl, Phenyl and Benzyl-D-glucopyranosides, α- and β-Methyl and β-Benzyl-D-fructopyranosides, and α-Methyl-D-fructofuranoside

BY LAWRENCE J. HEIDT AND CLIFFORD B. PURVES[1]

This study is a continuation of our earlier work[2] to determine the effects of molecular structure upon the hydrolysis of the hemiacetal oxygen bridge linking the aglycone with the sugar residue of glycosides. Several new facts are revealed and their significance is discussed.

The Haworth formulas of the glycosides hydrolyzed are sketched in Fig. 1. The atoms attached above the carbon atoms in the rings are to be considered above the plane of the ring and those attached below are to be considered below the plane of the ring. The α forms only are sketched in Fig. 1. The β forms are obtained simply by interchanging the two groups attached to carbon atom 1 of the glucosides and carbon atom 2 of the fructosides.

The hydrolysis results in the formation of glucose from the glucosides and fructose from the fructosides by the replacement of the aglycone, A in Fig. 1, by hydrogen. At the same time an AOH molecule is formed which in the cases studied was either an alcohol or phenol.

The reaction vessel is sketched in Fig. 2. Stirring was accomplished by raising and lowering the plunger with an electromagnet. Temperatures were maintained within 0.01°.

The hydrolyses were followed by withdrawing samples of the hydrolyzing solution in the reaction vessel by means of a pipet thrust through the opening which is capped in Fig. 2. These samples were immediately neutralized by caustic soda solution at 0° which stopped the hydrolysis.

The concentration of sugar in the neutralized sample was determined as in our earlier work[2] by means of the copper reduction method devised by Shaffer, Hartman, and Somogyi.[3] Several minor improvements, noted elsewhere,[4] were employed. The method is a convenient one not subject to correction for mutarotation of the liberated sugars. A very careful study of the hydrolysis of sucrose by this method demonstrated[5] that the method is as reliable, accurate, and sensitive as any of its predecessors and that the activation energy of the hydrolysis does not vary with temperature between 0 and 60° within the limits of probable error of 1.2% in the rate constants. The data obtained on that occasion were analyzed by the method of least squares instead of by the graphical method we previously used.[2] This improvement was applied in the present work.

The glucose and fructose used in calibrating the Shaffer–Hartman–Somogyi reagent,[3] and the fructosides were the remains of samples used previously.[2] The glucosides were synthesized by standard procedures. All these compounds were prepared as white crystalline specimens whose water solutions were neutral to brom thymol blue. Their melting points and specific rotations checked the published values and are given in Table I, columns 10 and 11. The compounds contained less than 0.1% impurities which, if present, were probably salts of the alkaline earths. Other reagents were of "Analytical Reagent" or "C. P." quality.

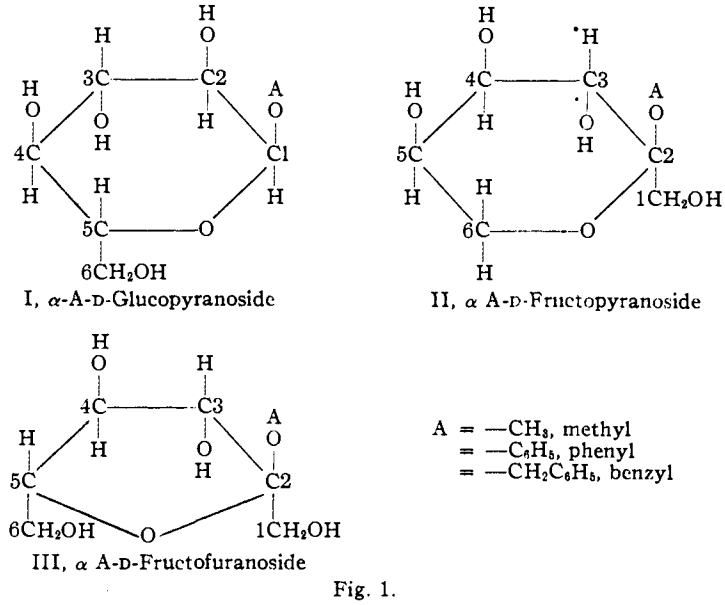

Fig. 1.

The glucosides were hydrolyzed in roughly 0.1 and the fructosides in 0.01 *N* hydrochloric acid. The choice of these acid concentrations made it possible to follow the reactions conveniently in every case over a temperature range of at least 20°. The particular acid concentrations and

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(2) L. J. Heidt and C. B. Purves, THIS JOURNAL, **60**, 1206 (1938).

(3) (a) P. A. Shaffer and A. F. Hartman, *J. Biol. Chem.*, **45**, 377 (1920–21), and (b) P. A. Shaffer and M. Somogyi, *ibid.*, **100**, 695 (1933).

(4) L. J. Heidt, *J. Franklin Inst.*, **234**, 473 (1942).

(5) L. J. Heidt and C. B. Purves, THIS JOURNAL, **62**, 1006 (1940).

TABLE I

RATES, ACTIVATION ENERGIES, AND OTHER PERTINENT DATA FOR THE HYDROLYSIS OF SEVERAL CLOSELY RELATED GLUCOSIDES AND FRUCTOSIDES INITIALLY AT 0.01 *M*. LOG a^* IS THE VALUE OF LOG a FOR $k^* = k/(HCl)$, IN MIN.$^{-1}$ THE "*C*" RATIO IN COLUMN 8 = $E/1.987$ LOG a^*

Column 1	2	3	4	5	6	7	8	9	10	11
Glycoside in hydrochloric acid	Experimental Temp. range, °C.	Experimental Half life range in min.	Half life in min. in 0.05 *N* HCl at 60°	Probable error in k^* and half lives, %	Activation energy, E = 0.004576*b* kcal./mole	Log a^*	"*C*" Ratio	ϕ	M. p., °C.	α_D in water at 21°
D-Glucopyranosides in 0.097 *N* HCl										
1 α-methyl	75 to 96	11,100 to 634	207,000	3.3	34.78±0.36	18.639±0.223	939		166	+159°
2 β-methyl	75 to 96	6,050 to 386	104,000	2.0	33.46±0.20	18.074±0.130	932		110	− 34°
3 α-benzyl	75 to 96	6,790 to 411	116,000	2.0	34.13±0.25	18.443±0.150	931	0.018	122	+134°
4 β-benzyl	75 to 96	4,640 to 348	69,700	3.0	31.46±0.35	16.935±0.214	935	.018	122	− 56°
5 α-phenyl	44 to 75	17,300 to 214	3,150	3.8	31.12±0.27	18.055±0.179	867	.008	174	+180°
6 β-phenyl	55 to 75	12,400 to 728	11,500	4.0	32.20±0.43	18.201±0.274	890	.008	174	− 71°
D-Fructopyranosides in 0.00965 *N* HCl										
7 α-methyl	30 to 50	2,040 to 118	6.2	1.2	27.79±0.13	18.578±0.089	753		102	+ 44°
8 β-methyl	30 to 60	5,390 to 66	12.8	2.2	29.42±0.14	19.335±0.095	766		120	−172°
9 β-benzyl	30 to 60	2,440 to 38	7.4	3.0	27.78±0.22	18.491±0.150	756	.019	157	−131°
D-Fructofuranoside in 0.00965 *N* HCl										
10 α-methyl	14 to 50	7,690 to 40	2.2	2.6	26.95±0.12	18.481±0.082	734		81	+ 93°

temperatures employed are given in Table I, columns 1 and 2.

The reactions were followed until 60 to 90% complete. First order rate constants, k, were obtained and put on a comparable basis by calculating $k^* = k/(HCl)$ in reciprocal minutes. The dependences of the rate constants k^* upon temperature are given by equations of the form $\log k^* = \log a^* - b/T$, where $\log a^*$ and b are constants characteristic of the glycoside; $T = 273.16 + °C$. The constant k^* probably increases slightly with the acid concentration[5] but the difference between k^* at 0.01 and 0.1 *N* HCl is, no doubt, trivial. The constants for the fructosides were calculated from our old and from much new data and differ somewhat from our previously published values[2] largely because of the difference between the graphical and least square methods of treating the results. The activation energies equal 4.576b calories per mole and do not vary with the temperature.

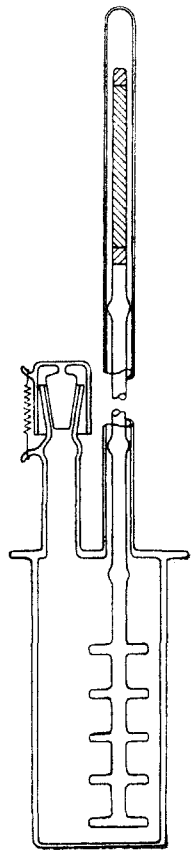


Fig. 2.—Reaction vessel

Results.—The data are summarized in Table I, which records also the probable errors in the various constants. In order to compare the rates of hydrolyses of the various glycosides under conditions near those actually employed, we have recorded in column 4 the half lives in minutes—$0.693/k$—calculated for an acid concentration of 0.05 *N* HCl and a temperature of 60°.

The quantum efficiencies, ϕ, are recorded in Table I, column 9, in order to compare the photochemical with the thermal hydrolyses. The values of ϕ are taken from an earlier publication by the first named author[4] and refer to 10% hydrolysis by light of λ, 254 mμ of 0.02 molar solutions of the aryl glycosides in water buffered with acetate at *p*H 3.5.

Table II records the effects of changes in the molecular structures of the glycosides upon the activation energies and the more familiar rate ratios under the specified conditions.

Discussion.—In attempting to evaluate the effects of changes in molecular structure upon the kinetics of a reaction, it is better to consider the variations in the temperature independent factors $\log a^*$ and b (or the activation energy) rather than the variations in the rate ratios under certain chosen conditions. The rate ratios, of course, will change with temperature except in the rare event of the activation energies being equal.

In the absence of sufficient kinetic data to evaluate $\log a^*$ and b conclusions based on rate ratios at a single temperature have been of great use. Among these very useful conclusions are (1) glucosides hydrolyze much slower than fructosides and (2) pyranosides hydrolyze much slower than furanosides. The differences between these rates are usually so great that no exceptions to these generalizations have yet been found under any experimental environment in which the slower rate is conveniently measurable. In fact even the smaller differences in rates encountered in the present research between, *e. g.*, α and β forms,

TABLE II

COMPARISON OF THE PHYSICAL CONSTANTS OF THE D-GLYCOSIDES

Glycosides compared	ΔE in kcal./mole	Rate ratio in 0.05 N HCl at 60°
A. Gluco- compared with Fructo-pyranosides		
α-methyl	+7.0	3.0×10^{-5}
β-methyl	+4.0	12.0×10^{-5}
β-benzyl	+3.7	11.0×10^{-5}
α-methylglucoside with β-methylfructoside	+5.4	6.2×10^{-5}
β-methylglucoside with α-methylfructoside	+5.7	6.0×10^{-5}
α-benzylglucoside with β-benzylfructoside	+6.4	6.4×10^{-5}
B. Pyranoside compared with Furanoside Form of Fructosides		
α-methyl	+0.8	3.6×10^{-1}
C. α Compared with β-Forms		
Glucopyranosides methyl	+1.3	5.0×10^{-1}
Glucopyranosides benzyl	+2.7	6.0×10^{-1}
Glucopyranosides phenyl	−1.1	3.7
Fructopyranoside, methyl	−1.6	2.1
D. Methyl Compared with Benzyl Compounds		
Glucopyranosides α compounds	+0.7	5.6×10^{-1}
Glucopyranosides β compounds	+2.0	6.7×10^{-1}
Fructopyranoside, β-compounds	+1.6	5.8×10^{-1}
E. Benzyl Compared with Phenyl Glucopyranosides		
α-compounds	+3.0	0.27×10^{-1}
β-compounds	−0.7[a]	1.7×10^{-1}

[a] This value of ΔE is less than the limits of error.

have not been found to reverse sign over the entire temperature ranges we employed.

There is, however, a temperature for every environment at which the rates of hydrolysis of any given pair of glycosides will become equal and at this temperature, their relative rates reach an inversion point. It also happens that the rates of hydrolysis of *all* the methyl and benzyl glycosides of the *same* sugar become equal ($k = 1$) at a single temperature because the log a^* factor of each of them equals the *same* fraction of the respective activation energy. This fact will be amplified later in this text.

It happens that the calculated rates in 0.05 N HCl at 60° exhibit the same *trends* as those observed under all the other conditions employed. Thus one notes by comparing the entries in columns 4 and 6, Table I, that the glycosides which hydrolyze slowest—longest half lives—require the largest activation energies. No similar trend exists, however, among the log a^* factors recorded in Table I, column 7; in fact, the first and last values of log a^* in this column are equal, within the limits of error, while the rates differ by nearly 100,000 fold. This fact might suggest that all the values of log a^* are or should be equal. Thus one might take for all these glycosides a value of log a^* equal to the average of the values recorded in Table I, column 7, and proceed to calculate the values of the activation energies which best fit the data. This procedure, however, yields equations giving values of k^* which do not agree well with many of the observed rates. Much better agreement is obtained when both log a^* and the activation energy are allowed to vary.

Table IIA reveals that the activation energy differences become equal to 5.8 ± 0.5 kcal./mole when one compares gluco- and fructo-pyranosides of *opposite* glycosidic configuration whereas no obvious relationship exists between pairs of the same configuration. The same is borne out by the ratios of the calculated rates in 0.05 N HCl at 60°. This fact suggests that α-methyl-D-glucopyranoside, for example, is stereochemically more similar to β methyl-D-fructopyranoside than to the α-D isomer of the latter.

Hudson[6] already has pointed out that the α-D form of one monosaccharide is sometimes stereochemically more similar to the corresponding β-L rather than the α-D form of another sugar. The α form of an α-β pair is considered to be the one more dextrorotatory among the D sugars and glycosides and the one more levorotatory among the L sugars and glycosides. The β-L and β-D isomers of the *same* sugar are mirror images; hence they exhibit identical behavior toward nonasymmetric chemical reagents like hydrochloric acid. Thus a correspondence might well exist between α-D and β-D forms of the glycosides of *different* sugars as far as hydrolysis by acid is concerned.

The Haworth formulas IV, V, VI, Fig. 3, for the methyl glycosides of gluco- and fructopyranosides do indeed show that the α-D-*gluco*-pyranoside, IV, formulated[6] on the basis of Hudson's rules regarding α and β isomers is stereochemically more similar to β-L-*fructo*-pyranoside, V, *and its mirror image the* β-D *form*, than to its α-D isomer, VI.

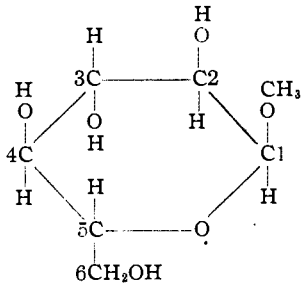
The closest stereochemical analog to α-D-fructopyranoside in the aldohexose series is β-L-galactopyranoside VII, Fig. 3, its mirror image is the β-D form; hence one might expect a constant difference to exist also between the activation energies of galacto- and fructo-pyranosides of *opposite* glycosidic configuration.

Table IIB reveals that the activation energy difference of −0.84 ± 0.25 kcal./mole between fructo-furanoside and -pyranoside is small as well as the previously observed[7] rate ratio. The rate ratio of the same ring structures in glucosides at 95 to 100° in 0.01 N HCl has a value of 200.[8]

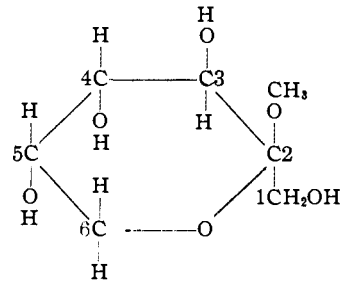
(6) C. S. Hudson, THIS JOURNAL, **60**, 1537 (1938). The authors are indebted to Professor Hudson for a private communication setting forth the explanation summarized here for the α-D, β-D correspondence.

(7) C. B. Purves and C. S. Hudson, *ibid.*, **59**, 1170 (1937).

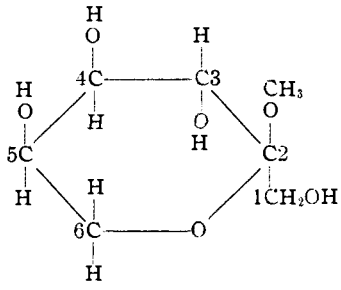
(8) (a) W. N. Haworth, C. R. Porter, and A. C. Waine, *J. Chem. Soc.*, 2256 (1932); (b) W. N. Haworth, *Ber.*, **65A**, 50 (1932).



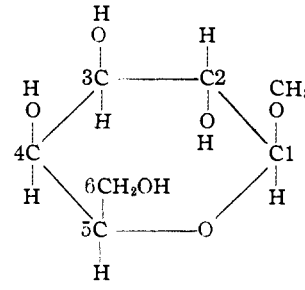
IV, α-Methyl-D-glucopyranoside



V, β-Methyl-L-fructopyranoside



VI, α-Methyl-D-fructopyranoside



VII, β-Methyl-L-galactopyranoside

Fig. 3.

The remainder of Table II reveals that changes in the aglycone have little effect on the thermal hydrolysis compared to the change from glucoside to fructoside. Although the energy differences are small, all are larger than the probable error except that between β-benzyl- and phenyl-glucopyranosides.

Table IIC reveals that among methyl and benzyl gluco pyranosides, the activation energy required is greater for α than β forms, but the reverse is the case among phenyl glucopyranosides and methyl fructopyranosides. No constant difference exists between the activation energies of α and β forms.

Tables IID and E reveal that the activation energies in both the α and β series of the glycosides decrease in the order methyl, benzyl, phenyl and the same order represents the increase in the rates of hydrolyses. The activation energy difference between β-benzyl- and phenyl-glucopyranosides, however, is less than the probable error so the possibility remains that in the β series the order of the activation energy decrease is methyl, phenyl, benzyl.

The relationship existing between the activation energies and the log a^* factors will now be considered. Moelwyn-Hughes[9] was the first to note that log a^* is nearly a constant fraction of the activation energy, E, for gluco- and fructopyranosides differing only in the aglycone. He denoted the quantity $2.3b/\log a^*$ as C and found C to be 857 for the glucosides and 743 for the fructosides he studied. The present work gives—Table I, Column 8—C the values 934 ± 5 (E varies 10%) for methyl- and benzyl-, and 879 ± 11 (E varies 3.5%) for phenyl-glucopyranosides, 758 ± 8 (E varies 5.8%) for methyl- and benzylfructopyranosides, and 734 for α-methylfructofuranoside. In every case a decrease in the average value of C is accompanied by a decrease in the average value of the activation energy. $\bar{C}$ is 19% and $\bar{E}$ is 15% smaller for fructo- than for glucopyranosides; $\bar{C}$ is 6% and E is 5% smaller for phenyl- than for methyl- and benzyl-glucopyranosides; and C is 3% and E is 5% smaller for the furanoside than for the pyranoside form of fructosides.

The constancy of C implies that the rate constants, k^*, of glycosides can be expressed by the equation $k^* = e^{E/C}e^{-E/RT}$ suggested originally by Moelwyn-Hughes.[9] This makes it possible to calculate the activation energy and the rate of hydrolysis at any reasonable temperature of a glycoside whose rate has been measured at but a single temperature provided the proper value of C is known. This value of C will be within 1% of that pertaining to any other glycoside of the same sugar. The phenyl glycosides, however, cannot be used for this purpose because they have, as noted above, a significantly lower value of C, 6% in the case of the glucopyranosides.

An earlier article[4] presented evidence that the photolyses of the aryl glycosides yield the same products as the acid hydrolysis. The ultraviolet light of λ 254 mμ used in that work is practically all absorbed by the phenyl part of the aglycone so it was not surprising perhaps to find the photochemical hydrolysis affected most by changes in the structure of the aglycone, see Table I column 9, whereas the thermal hydrolysis is affected most by changes in the structure of the glycosyl or sugar residue.

Perhaps photolysis involves scission in the sense G—O—A + HOH = GOH + AOH where G represents glycosyl and A an aryl aglycon; whereas, the thermal hydrolysis involves scission in the sense G—O—A + HOH = GOH + AOH.

The photochemical hydrolyses unlike the thermal hydrolyses were found, as expected, to increase little with temperature—ϕ increased 10% for a 10° rise compared to over a 400% increase in k—and to be practically independent of the pH. ϕ was also independent of the light intensity when stirring was adequate.

The transfer of the light energy absorbed to the hydrolyzable linkage appears to be hindered when CH_2 groups intervene because ϕ decreases from 0.018 for benzyl glucosides and fructosides to 0.015 for β phenylethyl glucosides. The small value for ϕ of 0.008 for phenyl glucosides was at-

(9) E. A. Moelwyn-Hughes, "The Kinetics of Reactions in Solution," Oxford University Press, London, 1933, p. 167.

tributed therefore to factors such as the strengthening of the O–C linkage when it becomes oxygen-phenyl. This conclusion[4] is supported by the following observations.

The hydrolyzable O–C link in benzyl-glycosides is quantitatively cleaved to toluene and reducing sugar by hydrogenation with palladium as catalyst under very mild conditions[10] which produce no detectable cleavage of the phenylglucosides. Also, hydriodic acid quantitatively cleaves phenyl-alkyl-ethers into *alkyl* iodide and phenol through scission of the oxygen-*alkyl* rather than the oxygen-phenyl link. The relative strengths of the oxygen-alkyl and oxygen-phenyl links in glycosides is probably of the same order of magnitude as in phenyl-alkyl ethers and may be responsible also for the unusual alkaline cleavage of phenyl-glycosides to glycosans.[11]

Summary

1. The copper reduction method of Shaffer, Hartman and Somogyi was used to follow the hydrolyses by aqueous hydrochloric acid of initially 0.01 molar solutions of the glycosides identified in the title. The fructosides were hydrolyzed in 0.01 *N* HCl at 15 to 60° and the glucosides in 0.1 *N* HCl at 45 to 96°.

2. The dependences of the first order rate constants, $k^* = k_{obs}/(HCl)$, upon temperature are given within the limits of error by the equation $\log k^* = \log a^* - b/T$ where a^* and b are constants. The activation energies are greatest for the glycosides which hydrolyze slowest.

3. A constant difference of 5.8 ± 0.5 kcal./mole exists between the activation energies of gluco- and fructo-pyranosides of *opposite* glycosidic configuration whereas no obvious relationship exists between pairs of the same configuration. The significance of this fact is discussed.

4. Among methyl- and benzyl-glucopyranosides, the activation energy required is greater for α than β forms, but the reverse is the case among phenyl-glucopyranosides and methyl-fructopyranosides.

5. The activation energies in both the α and β series of gluco- and fructo-pyranosides decrease in the order methyl, benzyl, phenyl and the same order represents the increase in the rates of hydrolyses.

6. The ratio, $2.3b/\log a^*$, equals 934 ± 5 for methyl- and benzyl-, and 879 ± 11 for phenyl-glucopyranosides, 758 ± 8 for methyl- and benzyl-fructopyranosides, and 734 for α methyl-fructofuranoside. The constancy of this ratio within a group enables one to calculate the activation energy and the rate of hydrolysis at any reasonable temperature of a glycoside whose rate of hydrolysis has been determined at but a single temperature provided that the value of $2.3b/\log a^*$ is known for some glycoside in its group.

7. The activation energies, the ratios, $2.3b/\log a^*$, and the relative rates of hydrolyses depend primarily upon the structure of the sugar residue rather than, as in the photochemical hydrolyses, upon the structure of the aglycone

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(10) N. K. Richtmyer, THIS JOURNAL, **56**, 1633 (1934).

(11) E. M. Montgomery, N. K. Richtmyer and C. S. Hudson, *ibid.*, **65**, 1848 (1943).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF THE ETHYL CORPORATION]

Hexamethylethane[1]

BY GEORGE CALINGAERT, HAROLD SOROOS, VINCENT HNIZDA AND HYMIN SHAPIRO

Hexamethylethane has long attracted the attention of chemists and physicists because of its unusually branched and symmetrical structure, and the effect of this structure on its physical properties. This branched octane melts above 100°, or 157° above the normal isomer, and as high as hexacontane ($C_{60}H_{122}$), while retaining the volatility to be expected of its low molecular weight.

While there have been a number of publications of its preparation[2] and properties,[3] only one of these[4] has reported data on samples of known high purity. This leaves considerable doubt as to its exact physical properties, especially since the melting point reported by Henry,[2b] 103–104°,

(1) Presented before the Organic Division of the American Chemical Society at Cleveland, Ohio, April 6, 1944.

(2) (a) Krakau (report of Chrapowicki's work), *Bull. soc. chim.*, **35**, 165 (1881); (b) Henry, *Comp. rend.*, **142**, 1075 (1906), *Bull. Acad. roy. Belg.*, Cl. sci., 256 (1906); 352 (1906); *Rec. trav. chim.*, **26**, 84 (1907); **26**, 106 (1907); (c) Richards, *Ann. chim. phys.*, **21**, 323 (1910); (d) Whitmore, Stehman and Herndon, THIS JOURNAL, **55**, 3807 (1933); (e) Flood and Calingaert, *ibid.*, **56**, 1211 (1934); (f) Marker and Oakwood, *ibid.*, **60**, 2598 (1938); (g) Greenwood, Whitmore and Crooks, *ibid.*, **60**, 2028 (1938); (h) Whitmore and Wheeler, *ibid.*, **60**, 2899 (1938).

(3) (a) Brackett, *Proc. Natl. Acad. Sci.*, **14**, 857 (1928); (b) Parks and Todd, *Ind. Eng. Chem.*, **21**, 1235 (1929); (c) Parks, Huffman and Thomas, THIS JOURNAL, **52**, 1032 (1930); (d) Linder, *J. Phys. Chem.*, **35**, 532 (1931); (e) Lovell, Campbell and Boyd, *Ind. Eng. Chem.*, **23**, 26 (1931); (f) West, *Z. Krist.*, **88**, 195 (1934); (g) Hoog, Smittenberg and Visser, *Congrès Mondial du Petrol*, Paris, June (1937); (h) Calingaert and Soroos, *J. Org. Chem.*, **2**, 535 (1938); (i) Maman, *Comp. rend.*, **207**, 1401 (1938); (j) Smittenberg, Hoog and Henkes, THIS JOURNAL, **60**, 17 (1938); (k) Lambert and Lecomte, *Ann. phys.*, **10**, 503 (1938); (l) Smittenberg, Hoog, Moerbeck and Zijden, *J. Inst. Pet.*, **26**, 294 (1940); (m) Maman, *Chimie et industrie*, **44**, 299 (1940); (n) Whitmore, Marker and Plambeck, THIS JOURNAL, **63**, 1626 (1941); (o) Day and Pease, *ibid.*, **63**, 912 (1941); (p) Bauer and Beach, *ibid.*, **64**, 1142 (1942).

(4) Whitmore, Marker and Plambeck[3n] report the melting point and boiling point of material which they estimated had a purity of above 99.4 mole per cent., based on the melting point range of 250 to 300 milligram samples of every fourth sample of fifty fractions obtained by fractional distillation.