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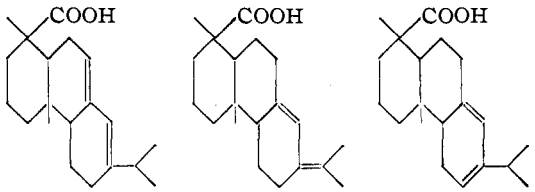
Kinetics of the Acid-catalyzed Isomerization of Levopimaric Acid in Anhydrous Ethanol

BY PAUL F. RITCHIE AND LANE F. MCBURNEY

For many years it has been known that certain constituents of wood rosin and oleoresin isomerize in the presence of strong acids or heat[1,2] and that the result of the preponderant reaction is an increase in the abietic acid content of the initial material.[3] The inadequacy of early techniques by which resin acids were isolated proved to be a serious handicap to investigators who attempted study of this isomerization reaction[4,5,6] and consequently the data acquired were incomplete or, in many cases, vitiated by the impurity of the resin acid specimens employed. Recent work established procedures by which resin acids were made available for study.[7] It is known now that the three isomeric, abietic-type acids—abietic (I), neoabietic (II), and levopimaric (III)—are the



I II III

resin acids participating in the isomerization and that the remaining components of oleoresin or rosin are relatively insensitive to strong acids or heat. The present communication is the result of an investigation, by a polarimetric method, of the kinetics of the acid-catalyzed isomerization of levopimaric acid in the solvent anhydrous ethanol.

Experimental

Preparation of Materials.—Anhydrous ethanol (Commercial Solvents Corp.) was purified from traces of aldehydes by the method of Dunlap.[8] The aldehyde-free alcohol was dried by the method of Lund and Bjerrum.[9] Levopimaric acid was isolated and purified by the method of Harris and Sanderson[7] $[\alpha]^{24}D$ −276° (C = 1%, ethanol), m. p. 150–152°. Hydrogen chloride was prepared by the method of Fieser.[10] Alcoholic hydrogen chloride was prepared by the absorption of dry hydrogen chloride in absolute ethanol until the concentration of the solution, as determined by weight, was approximately that desired. *p*-Toluenesulfonic acid was prepared from the monohydrate (Eastman Kodak Company, Eastman quality) by the methods of Gattermann[11] and Meyer,[12] melting point 105–105.5°. Methanesulfonic acid was prepared from "Indoil Methanesulfonic Acid," (Indoil Chemical Company) by the method of Smith and Hammett,[13] boiling point 136–138° at 0.4–0.6-mm. pressure. Trichloroacetic Acid (Eastman Kodak Company, Eastman quality, sulfate-free) was purified by the method of Jaeger.[14] The concentration of all ethanolic acid solutions was determined by titration of weighed samples with standard sodium hydroxide solution using methyl red as the indicator. Lithium ethylate solutions were prepared by the method of Elliott and Kilpatrick.[15] Lithium chloride (J. T. Baker Chemical Co., C.P. quality) was purified by the method of Elliott and Kilpatrick.[15]

Adequate precautions against acquisition of moisture by ethanolic solutions were taken at all stages in their preparation. In order to permit the withdrawal of a portion of a solution without exposing the bulk to the atmosphere, an all-glass apparatus—a modification of the automatic buret—was constructed and employed for the storage of solutions.

Apparatus.—A Pellin polarimeter sensitive to 0.02° was used in conjunction with a sodium-vapor lamp and a 5-dm. tube for all measurements. During experiments the temperature of the tube and contents was maintained constant within ±0.05° by water circulated from a thermostatically controlled bath through a jacket enclosing the tube.

Experimental Procedure.—Reaction mixtures were prepared by dispensing the desired volume of an ethanolic solution of levopimaric acid from an automatic buret into a 50-ml. volumetric flask, adding solutions of any other components, with the exception of the acid catalyst, from a weight buret and diluting with ethanol leaving only slightly more space than necessary to accommodate the catalyst solution. After placing the flask and contents in the water-bath at the temperature at which the experiment was to be conducted and allowing sufficient time for the attainment of thermal equilibrium, the proper amount of a solution of the acid catalyst was added from a weight

TABLE I

DATA FOR A TYPICAL REACTION, LOG $(\alpha - \alpha') = 0.785 - 0.00677t$

Concentration of reactants in moles per liter: levopimaric acid, 3.32×10^{-2}; hydrogen chloride, 4.20×10^{-3}.

t, min.	α	$t + \Delta t$, min.	α'	$(\alpha - \alpha')$ Obs.	$(\alpha - \alpha')$ Calcd.	$\Delta(\alpha - \alpha')$
4	(−)11.53°	64	(−)5.89°	(−)5.64°	(−)5.73°	+0.11°
9	10.91	69	5.61	5.30	5.30	.00
14	10.29	74	5.42	4.87	4.90	+ .03
19	9.75	79	5.17	4.58	4.53	− .05
24	9.20	84	4.98	4.22	4.20	− .02
29	8.69	89	4.76	3.93	3.88	− .05
34	8.23	94	4.57	3.66	3.59	− .07
39	7.76	99	4.44	3.32	3.32	.00
44	7.34	104	4.28	3.06	3.07	+ .01
49	7.00	109	4.18	2.82	2.84	+ .02
54	6.67	114	4.04	2.63	2.62	− .01
59	6.33	119	3.91	2.42	2.43	+ .01

Mean deviation ± .04°

(1) L. Ruzicka and H. Schinz, *Helv. Chim. Acta*, **6**, 662 (1923).
(2) S. Palkin and T. H. Harris, THIS JOURNAL, **55**, 3677 (1933).
(3) G. Dupont, *Bull. soc. chim.*, [4] **29**, 718 (1921).
(4) E. E. Fleck and S. Palkin, THIS JOURNAL, **59**, 1593 (1937).
(5) R. Lombard, *Bull. soc. chim.*, [5] **12**, 395 (1945).
(6) R. Lombard, *ibid.*, **745**, 1186 (1948).
(7) G. C. Harris and T. F. Sanderson, THIS JOURNAL, **70**, 334 (1948).
(8) F. L. Dunlap, *ibid.*, **28**, 395 (1906).
(9) H. Lund and J. Bjerrum, *Ber.*, **64B**, 210 (1931).
(10) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Company, New York, N. Y., 1941, p. 393.
(11) L. Gattermann, "Laboratory Methods of Organic Chemistry," Macmillan and Co., Ltd., London, 1941, p. 194.
(12) H. Meyer, *Ann.*, **433**, 327 (1923).
(13) L. C. Smith and L. P. Hammett, THIS JOURNAL, **67**, 23 (1945).
(14) F. M. Jaeger, *Z. anorg. allgem. Chem.*, **101**, 65 (1917).
(15) J. H. Elliott and M. Kilpatrick, *J. Phys. Chem.*, **45**, 454 (1941).

buret and the volume of the solution adjusted by the addition of ethanol. The flask was rotated to ensure thorough mixing of the contents, a portion of the solution transferred to the polarimeter tube, which had been brought to the desired temperature, and a stopper tightly fitted into the side tubulation.

Readings were taken in accordance with the directions of Guggenheim[16] and the constants of the general first order rate expression, $\log (\alpha - \alpha') = a - kt \log e$, calculated from the data by the method of averages. In Table I these methods have been applied to the data of a typical experiment for the purpose of deriving the rate constant, the calculated values of $(\alpha - \alpha')$ and the differences, $\Delta(\alpha - \alpha')$, between the observed and calculated values of $(\alpha - \alpha')$. The calculated mean deviation amounts to about 2% of the smallest observed value. Probable errors in the velocity constants were calculated and are represented by the radii of the circles in the graphs that follow. Unless otherwise noted, all measurements refer to 25°.

Results and Discussion

Preliminary investigations demonstrated that ethanolic solutions of levopimaric acid are perfectly stable for prolonged periods of time, but that in the presence of a strong acid catalyst the specific rotations of the solutions change rapidly from the initial value of −276°[7] to about −73° and, thereafter, very slowly to a final value of about −90°. The course of the rapid change was in strict accord with first order kinetics and examination of ultraviolet absorption spectra of reaction solutions of specific rotation −73° (Fig. 1) revealed that over 90% of the original levopimaric acid had been converted to abietic acid. It is not possible to determine levopimaric or neoabietic acid by absorption spectra in the presence of such large amounts of abietic acid. However, the fact that the same adduct, that of levopimaric acid, is formed when maleic anhydride reacts with either abietic or levopimaric acid in acidic media[17] is proof that levopimaric acid is present in the reaction solutions. The nature of the slow reaction is unknown although development of color in the solutions on standing for several hours may be an indication that the products of the isomerization are slowly oxidized by air under the experimental conditions. No detectable differences in the composition of the solutions of specific rotation −73° and −90° were exhibited by the ultraviolet absorption spectra. In the following discussion all measurements refer only to the rapid, relatively uncomplicated isomerization reaction.

A study of the effect of varying the initial concentration of levopimaric acid on the rate of isomerization was made using hydrogen chloride as catalyst. The results (Table II) show that the velocity of the reaction is independent of the initial concentration of levopimaric acid. Table III contains data obtained by measurement of the reaction velocity in solutions containing 1:1 trichloroacetic acid:lithium trichloroacetate buffers at 35.1°. The ionic strength of the medium was maintained constant at 7.02×10^{-2} by the addition of the proper amounts of lithium chloride.

(16) E. A. Guggenheim, *Phil. Mag.*, **I**, 538 (1926).

(17) L. Ruzicka and R. G. R. Bacon, *Helv. Chim. Acta*, **20**, 1542 (1937).

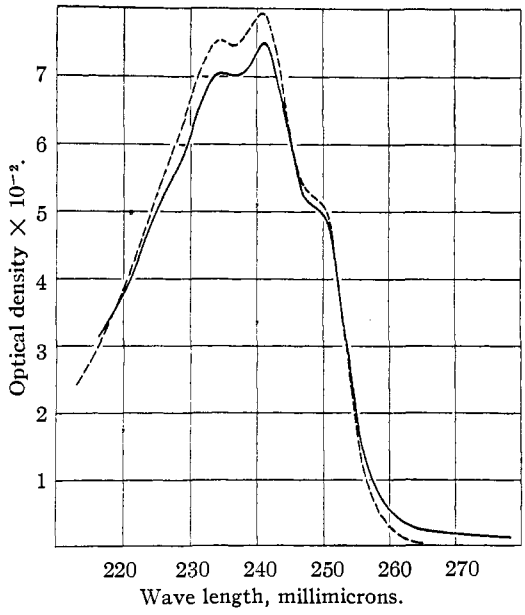


Fig. 1.—Ultraviolet absorption spectra of ethanolic solutions of resin acids: dotted curve, pure abietic acid, 10 g./liter; solid curve, acid-isomerized levopimaric acid, 10 g./liter.

Although the total buffer concentration was varied throughout a twelve-fold range, the rate of isomerization remained unaltered. Hence the reaction is catalyzed only by the solvated proton and not by undissociated acids or anions.

TABLE II

VELOCITY OF ISOMERIZATION AT VARIOUS INITIAL CONCENTRATIONS OF LEVOPIMARIC ACID

Concentration of hydrogen chloride: 4.48×10^{-3} mole/liter

Levopimaric acid, moles/liter × 10^2	Reaction velocity, $k \times 10^2$ (min.$^{-1}$)
1.11	1.53
1.88	2.02
2.33	1.88
2.77	2.07
4.01	1.60

TABLE III

ISOMERIZATION OF LEVOPIMARIC ACID IN 1:1 TRICHLOROACETIC ACID:TRICHLOROACETATE BUFFERS AT 35.1°

Concentration of levopimaric acid: 3.33×10^{-2} mole/liter.

Trichloroacetic acid, moles/liter × 10^3	Lithium trichloroacetate, moles/liter × 10^3	Lithium chloride, moles/liter × 10^2	Ionic strength, 1×10^2	Reaction velocity, $k \times 10^2$ (min.$^{-1}$)
2.66	2.66	6.75	7.02	6.78
12.6	12.6	5.76	7.02	6.93
19.2	19.2	5.10	7.02	7.05
31.6	31.6	3.86	7.02	6.82

The results of experiments in which three strong acids—hydrogen chloride, *p*-toluenesulfonic acid and methane sulfonic acid—were employed as catalysts are collected in Table IV. In Figs. 2 and 3 the values of k/c, where k is the reaction velocity

TABLE IV

ISOMERIZATION OF LEVOPIMARIC ACID CATALYZED BY STRONG ACIDS

Concentration of levopimaric acid: 3.32×10^{-2} mole/liter.

	Catalyst concentration, moles/liter $\times 10^4$	Reaction velocity, $k \times 10^3$ (min.$^{-1}$)
Hydrogen chloride	5.05	0.72
	10.2	1.50
	14.1	3.01
	21.8	5.96
	41.9	15.5
	68.3	34.2
	70.8	35.7
p-Toluenesulfonic acid	64.1	4.92
	140	12.0
	367	38.2
	599	70.1
Methanesulfonic acid	108	6.79
	288	17.0
	597	36.3
	928	57.0

and c the catalyst concentration, are plotted against c. Inspection of the plots reveals that, in the case of hydrogen chloride, a large primary electrolyte effect was found. Further evidence of the existence of a primary salt effect was obtained from experiments in which varying amounts of the uni-univalent salt lithium chloride were added to solutions containing constant amounts of levopimaric acid and hydrogen chloride. The plot of the ratio of the velocities at salt concentrations c and zero, k/k_0' *versus* c is linear (Fig. 4) in agreement with the Debye–Hückel theory.[18] A primary electrolyte effect was observed in connection with *p*-toluenesulfonic acid, but the values of

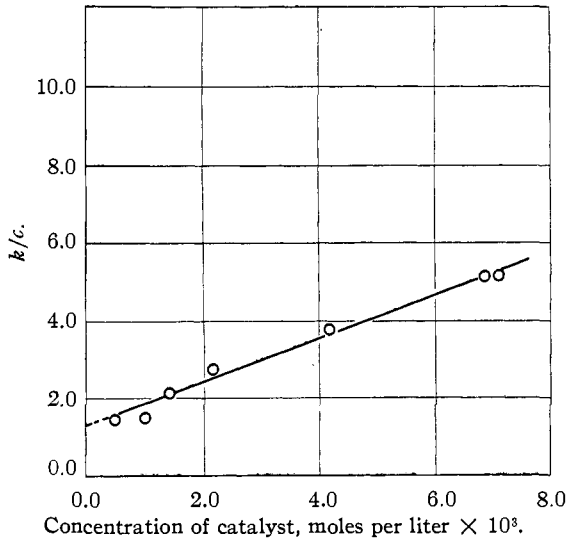


Fig. 2.—Hydrogen chloride-catalyzed isomerization of levopimaric acid: k is the reaction velocity and c the catalyst concentration in moles/liter.

(18) P. Debye and E. Hückel, *Physik. Z.*, **24**, 185 (1923).

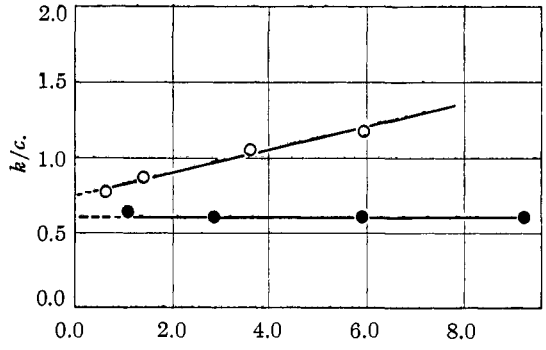


Fig. 3.—Isomerization of levopimaric acid catalyzed by (⊙) *p*-toluenesulfonic and (●) methanesulfonic acids. k is the reaction velocity and c the catalyst concentration in moles/liter.

k/c obtained with methanesulfonic acid were independent of the catalyst concentration.

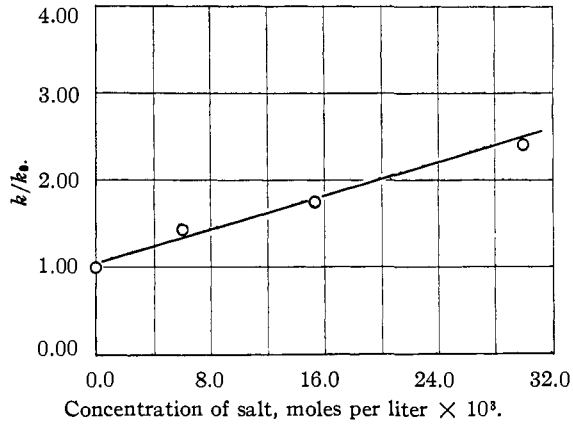


Fig. 4.—Neutral salt effect in the hydrogen chloride catalyzed isomerization of levopimaric acid: concentrations in moles/liter; hydrogen chloride, 4.62×10^{-3}; levopimaric acid, 3.33×10^{-2}; k/k_0 is the ratio of reaction velocities at salt concentrations c and zero.

Extrapolation of the curves of Figs. 2 and 3 leads to values of k/c at zero concentration with respect to each of the acid catalysts. The values thus obtained for *p*-toluenesulfonic acid (0.73) and methanesulfonic acid (0.61) are significantly lower than that corresponding to hydrogen chloride (1.23) and indicate that, at the concentrations employed, these two sulfonic acids are dissociated in ethanol to an extent less than hydrogen chloride. If it is assumed, in agreement, with the observations of Murray-Rust, and Hartley,[19] and Deyrup,[20] but contrary to the conclusions of Bezman and Verhoek[21] that hydrogen chloride is completely dissociated in ethanol, the value obtained for k/c at infinite dilution of hydrogen

(19) D. M. Murray-Rust and H. Hartley, *Proc. Roy. Soc.* (*London*), **A126**, 86 (1929).

(20) A. J. Deyrup, THIS JOURNAL, **56**, 60 (1934).

(21) I. I. Bezman and F. H. Verhoek, *ibid.*, **67**, 1330 (1945).

chloride is the catalytic coefficient $k_{C_2H_5OH_2^+}$ (in liters mole^{-1} min.$^{-1}$) of the reaction. From the catalytic coefficient and the data obtained in the experiments with trichloroacetic acid–trichloroacetate buffers (calculated to 25°) the dissociation constant of trichloroacetic acid was calculated. For purposes of comparison the dissociation constant at zero ionic strength was calculated from the Debye–Hückel limiting law, $\log_{10} K_0 = \log_{10} K_C - 5.6\sqrt{\mu}$, and found to be 6.9×10^{-6} in moderately good agreement with Deyrup's value of 3.5×10^{-6}.[20]

Both hydrogen chloride and *p*-toluenesulfonic acid were employed as catalysts in measuring the temperature coefficient of the reaction over the range 16 to 41°. The value obtained for the activation energy was 21.4 ± 0.5 kcal./mole and, as anticipated for a reaction catalyzed exclusively by solvated protons, independent of the nature of the strong acid catalyst (Fig. 5).

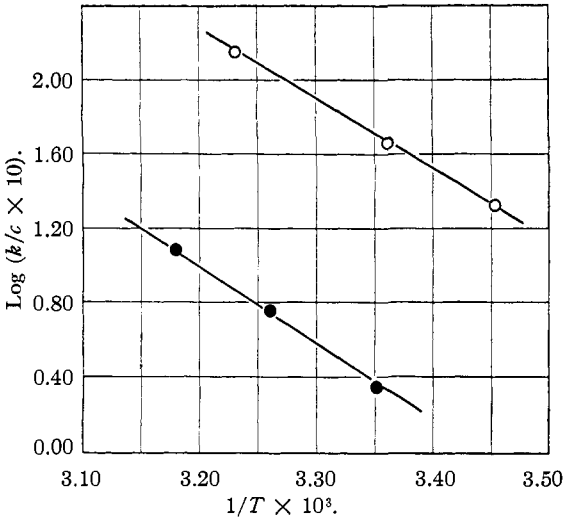


Fig. 5.—Temperature coefficient of the isomerization of levopimaric acid: concentrations in moles/liter; hydrogen chloride, ⊙, 6.01×10^{-3}; *p*-toluenesulfonic acid, ●, 2.05×10^{-2}; levopimaric acid, 3.32×10^{-2}; *k* is the reaction velocity; *c*, the catalyst concentration in moles/liter, and *T* the temperature (Å.).

Preliminary experiments indicated that the isomerization of levopimaric acid is retarded by the presence of even trace amounts of water in the medium. The reaction velocity was measured using solutions containing constant amounts of hydrogen chloride and levopimaric acid but varying amounts of water. Results of these experiments, collected in graphical form in Fig. 6, are very similar to those obtained by study of the inhibitive action of water in the acid-catalyzed formation of acetal,[20] in certain anionotropic rearrangements[22] and in many other reactions in anhydrous media as well as of the depressive effect of small amounts of water upon the activity coefficients of hydrogen chloride in ethanol.[23] Since water is considerably more basic than alcohols, the equilibrium

$$C_nH_{2n+1}OH_2^+ + H_2O \rightleftharpoons C_nH_{2n+1}OH + H_3O^+$$

very much favors the formation of the hydronium ion[24] which would be expected to function less efficiently as a proton donor than alkoxonium ions. A plausible explanation of the inhibitive effect of low concentrations of water upon acid-catalyzed reactions in alcoholic solution is thus afforded.

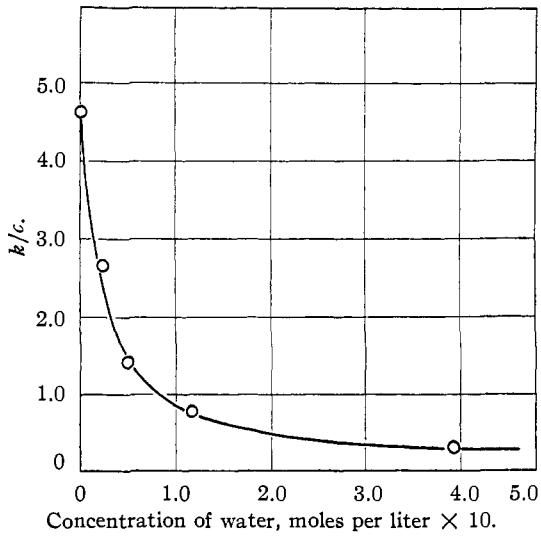


Fig. 6.—Inhibition by water of the hydrogen chloride-catalyzed isomerization of levopimaric acid: concentrations in moles/liter; levopimaric acid, 2.77×10^{-2}; hydrogen chloride, 4.46×10^{-3}; *k* is the reaction velocity, and *c* the catalyst concentration in moles/liter.

Acknowledgment.—The authors take this opportunity to thank Dr. George C. Harris of these laboratories who supplied the levopimaric acid used in this research.

Summary

Isomerization of levopimaric acid in the presence of an acid catalyst leads to reaction mixtures which contain over 90% of abietic acid and small amounts of the starting material. No evidence of the presence of the third isomer, neoabietic acid, in the reaction mixtures can be obtained from ultraviolet spectra.

The isomerization of levopimaric acid in ethanol is catalyzed exclusively by solvated protons and is first order with respect to both levopimaric acid and the catalyst. Assuming complete dissociation of hydrogen chloride in ethanol at the concentrations used, the catalytic coefficient of the reaction (in liters mole^{-1} min.$^{-1}$) is given by $k_{C_2H_5OH_2^+} = 6.3 \times 10^{15}\, e^{-21,450/RT}$. The reaction is inhibited by the presence of water in the medium.

The dependence of reaction velocity upon con-

(22) E. A. Braude, *J. Chem. Soc.*, 443 (1944).

(23) H. S. Harned and M. H. Fleysher, THIS JOURNAL, **47**, 82 (1925).

(24) H. Goldschmidt and O. Udby, *Z. physik. Chem.*, **60**, 728 (1907).

centration of the catalysts hydrogen chloride and *p*-toluenesulfonic acid is in accord with the predictions of the Debye–Hückel theory, but the behavior of methanesulfonic acid is anomalous. It appears that *p*-toluenesulfonic acid and methanesulfonic acids are incompletely dissociated in ethanol at concentrations of 1×10^{-2} to 1×10^{-1} mole/liter. The value calculated for the dissociation constant of trichloroacetic acid in ethanol is 6.9×10^{-6} and in reasonable agreement with previously published values.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, THE UNIVERSITY OF WISCONSIN]

Alkali-sensitive Glycosides of 3-Phenyl-4-hydroxycoumarin[1]

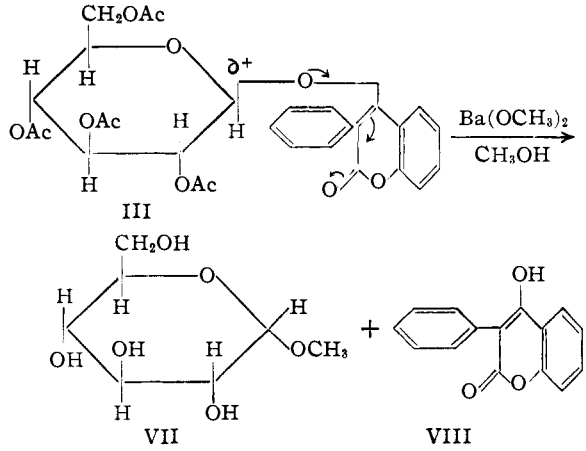
BY LEONARD SPERO,[2] CLINTON E. BALLOU AND KARL PAUL LINK

The synthesis and properties of some β-D-glucosides of 4-hydroxycoumarins were first reported from this Laboratory in 1944.[3] These compounds were made in connection with the biological studies on the hypoprothrombinemic effect of 3,3′-methylene-bis-(4-hydroxycoumarin) [Dicumarol] and related 4-hydroxycoumarins.[4] 4-Hydroxycoumarin D-glucoside tetraacetate (I), 4-hydroxy-6-methylcoumarin D-glucoside tetraacetate (II), 3-phenyl-4-hydroxycoumarin D-glucoside tetraacetate (III), and 3,3′-methylene-bis-(4-hydroxycoumarin) mono-D-glucoside tetraacetate (IV) were prepared by condensing the silver salt of the aglycon with tetraacetyl-D-glucosyl bromide. A modified Robertson method[5] was used in the preparation of 3,3′-methylene-bis-(4-hydroxycoumarin) diglucoside octaacetate (V), and 3-[6-oxo(1)-benzopyrano(4,3-b)(1)benzopyran-7-yl]-4-hydroxycoumarin D-glucoside tetraacetate (VI). Because of the method of preparation and the optical rotation of these glucosides the β-configuration was assigned.

As shown by Huebner, *et al.*,[3] these glucosides are extremely labile to alkali. Compounds I and II were deacetylated by the catalytic barium methoxide procedure. Attempts to deacetylate the glucosides in which there were substituents on position three of the coumarin residue resulted in cleavage of the glucoside linkage. This reaction is unique in that the starting compound is converted to the aglycon and methyl α-D-glucoside (VII). During attempted deacetylation of III, 80% of the starting material was converted to 3-phenyl-4-hydroxycoumarin (VIII) and VII.

Isbell's[6] interpretation of glycoside cleavage rationalizes the fact that the splitting may occur on either side of the glycosidic oxygen. An electrophilic aglycon promotes cleavage of the sugar–oxygen bond, while cleavage of the aglycon–oxygen bond occurs when the sugar residue is able to take electrons from the aglycon.

Cleavage of glycosides under anhydrous methanolic conditions could result in methanolysis, cyclization or unsaturation. This reaction demonstrates the methanolysis type. The formation of methyl α-D-glucoside (VII) indicates that a Walden inversion accompanies the cleavage of the glucosidic linkage, and this would be possible only if the sugar–oxygen bond were the one split. The following scheme, involving the indicated electronic shifts, may be used to rationalize this reaction.



A more involved mechanism is used to explain the products obtained during the alkaline cleavage of V [glucose, VII, and 3,3′-methylene-bis-(4-hydroxycoumarin) monomethyl ether]. For a detailed discussion see ref. 3.

It is conceivable that this reaction would be generally applicable to glycosides of this type.[7] One of the purposes of this study was to ascertain if the nature of the sugar residue played a role in determining the mechanism of the glycosidic cleavage. In order to study the reaction further,

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation. Part of this work is from the thesis submitted by Leonard Spero to the faculty of the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1948. This paper was presented before the Division of Sugar Chemistry and Technology at the 116th Meeting of the American Chemical Society, Atlantic City, September, 1949.

(2) Present address: Camp Detrick, Frederick, Maryland.

(3) Huebner, Karjala, Sullivan and Link, THIS JOURNAL, **66**, 906 (1944).

(4) Stahmann, Huebner and Link, *J. Biol. Chem.*, **138**, 513 (1941).

(5) Robertson and Waters, *J. Chem. Soc.*, 2729 (1930).

(6) Isbell, *Ann. Rev. Biochem.*, **XII**, 215 (1943).

(7) Dr. C. S. Hudson had originally suggested to one of us (K. P. L.) that this reaction might serve as the route through which certain inaccessible α-glycosides could be realized.