ART. XXVIII.—*On the Hydrolysis of Esters of Substituted Aliphatic Acids*; by E. W. DEAN.

[Contributions from the Kent Chemical Laboratory of Yale Univ.—clvi.]

7. *Hydrolysis in Acid and in Alkaline Solution of Ethyl Esters of Hydroxy Butyric Acids.*

ACID HYDROLYSIS.

Preliminary Discussion.

THE effect of the hydroxyl group upon the velocity of acid hydrolysis has been shown* to be somewhat irregular in the cases of acids of the acetic and propionic series. Ethyl glycolate is decomposed a little more rapidly than the acetate. Ethyl lactate, the alpha hydroxy propionate, has a greater reaction velocity at twenty-five degrees and a less at forty-five than has ethyl propionate. This is due to the lower temperature coefficient of the hydroxy ester, but makes it immediately impossible to state that the presence of this particular substituted group facilitates the hydrolytic cleavage. Ethyl glycerate, which is the alpha, beta, di-hydroxy propionate, has relatively a very low rate of hydrolysis, showing that the substitution of two groups may produce an effect differing in order of magnitude from that of one.

In view of the above facts it was thought desirable to obtain more data bearing upon this subject, and consequently measurements have been made of the rates of decomposition of several hydroxy butyric esters. Those which were examined comprise the following list:

Ethyl alpha hydroxy-butyrate, $\text{CH}_3\text{CH}_2\text{CH}(\text{OH})\text{COOC}_2\text{H}_5$,
 Ethyl beta hydroxy-butyrate, $\text{CH}_3\text{CH}(\text{OH})\text{CH}_2\text{COOC}_2\text{H}_5$, and
 Ethyl alpha hydroxy-iso-butyrate, $\text{CH}_3\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)\text{COOC}_2\text{H}_5$.

Ethyl normal butyrate and ethyl iso-butyrate were of course hydrolyzed at the same time with these esters in order that the comparisons made should deal with the results of measurements made under identical conditions.

Preparation of the Esters.

Ethyl butyrate was the Kahlbaum preparation of commerce which was carefully purified by washing and by fractional distillation. Boiling point, 118.5° to 119.5° . The figure given in Beilstein is 119.9° .

Ethyl iso-butyrate was prepared by the method of Pierre and

* This Journal, xxxiv, 293; xxxv, 486.

Puchot.* Iso-butyl alcohol was oxidized with chromic acid and the iso-butyl ester of iso-butyric acid thus formed. From this the ethyl ester was obtained by the successive processes of saponification by alkali, acidification, and treatment with ethyl alcohol. This last esterification was conducted according to the method of Wislicenus.† The purified product boiled at 110°, which is the figure given in the literature.

Ethyl alpha hydroxy-butyrate was obtained by the esterification of acid purchased from Kahlbaum. After obtaining unsatisfactory results from trials by most of the usual methods the method of Bogojawlensky and Narbut‡ was found to be well adapted to this case. The acid was boiled with absolute alcohol in the presence of finely powdered anhydrous copper sulphate. The resulting ester was purified by fractional distillation and a sample obtained boiling between 162° and 164° uncorrected. The temperature given in Beilstein is 165° corrected.

Ethyl beta hydroxy-butyrate was purchased from Kahlbaum and was used without special purification. Its boiling point was 178° to 180° uncorrected; no value is given in Beilstein. As a check upon the reliability of this commercial product a small quantity was prepared by esterifying some of the free acid by the copper sulphate method. One or two portions of this, when hydrolyzed, gave constants approximately the same as those of the Kahlbaum preparation. The freedom of the latter from impurities of any other esters was also proven by the regularity of its velocity constants. The presence of another ester having a different rate of reaction would have caused a progressive decrease in any series of these constants.

Ethyl alpha hydroxy-iso-butyrate was also purchased from Kahlbaum and was proven sufficiently pure by analysis and by determination of its boiling point. The latter was 146° uncorrected, that given in Beilstein is 150° corrected.

Procedure.

The unsubstituted esters of this list have rather low solubilities, so that it was found desirable to modify somewhat the procedure|| which had been used for acetates and propionates. In cases where a solution of the ester six hundredths or more normal can be prepared in decinormal hydrochloric acid, it is simplest to titrate twenty-five cubic centimeter portions directly

* Anal. de Chim. et Phys., (4), xxviii, 366.

† Ann. d. Chem. u. Pharm., clxiv, 181.

‡ Ber. xxxviii, 3344. See also Clemmenson and Heitman, Am. Chem. Jour., xlii, 319.

|| This Journal, xxxiv, 293; xxxv, 486.

with approximately tenth normal baryta water. The initial titration will then be about twenty-five cubic centimeters, the final at least fifteen cubic centimeters greater. With a range of this magnitude the constant error of titration does not cause undue irregularity among the constants obtained. Saturated solutions of ethyl butyrate or ethyl iso-butyrate (in decinormal hydrochloric acid) are only two to three hundredths normal, and the range in the titrations, measured in tenth normal barium hydroxide solution, is from five to seven and a half cubic centimeters. This is inconveniently small, and three modifications have been tried to increase it. First, fifteen cubic centimeter portions were titrated with twentieth normal alkali. The advantage here is slight but definite, the range increasing by one-fifth and the error remaining about the same.

Next, a modification of the method of De Hemptinne was tried.* A twenty-five cubic centimeter portion of the reaction mixture was treated with twenty-five cubic centimeters of tenth normal baryta water and the titration completed with a twentieth normal solution of the same alkali. This doubles the range, but unfortunately largely increases the error of titration.

The third and most satisfactory method involved the use of twentieth normal alkali and a hundred cubic centimeter burette. The latter was of the bore of the ordinary fifty cubic centimeter burette but was made with a top bulb that brought its capacity up to a hundred cubic centimeters. When twenty-five cubic centimeter portions of the reacting mixture were titrated with this it was possible to have a total range of from ten to fifteen cubic centimeters with a very slight increase in the error. One drop of twentieth normal alkali was sufficient to produce a perfectly definite color change in the indicator, and there was little increase of error due to the draining and reading of this burette.

The procedure may be briefly summarized as follows: Two hundred and fifty cubic centimeter flasks containing the solutions of the esters in decinormal hydrochloric acid were placed in an accurately regulated thermostat.† At measured intervals of time portions were removed by means of a twenty-five cubic centimeter pipette, run into cold water and their acidity determined by titration with twentieth normal barium hydroxide solution. Phenolphthalein was employed as an indicator.

Of the more insoluble esters, saturated solutions were prepared by shaking the acid vigorously with an excess of ester and then filtering. The paper was first moistened with the acid solution, which prevented the passage through it of any of the undissolved ester. The measurements of the final acidity were made upon portions of the mixtures, heated several days

* *Zeitschr. f. phys. Chem.*, xiii, 561.

† *This Journal*, xxx, 72.

in sealed tubes at about ninety degrees. The completion of the reaction was in this way assured.

Calculations were made by the use of the well-known titration formula* for reactions of the first order. In the tables are given values of the constants obtained and of the periods in minutes over which the courses of the various reactions were followed. Bracketed constants are not counted in the averages; their irregularity being undoubtedly caused by undue experimental error.

TABLE I.

Hydrolysis at 25°.			N/10 HCl.		
Ester	Ethyl Butyrate	Ethyl Iso-butyrate	Ethyl α -Oxy-butyrate	Ethyl α -Oxy-Iso-butyrate	Ethyl β -Oxy-butyrate
Time	3675	3675	4320	3675	3675
	53·3	40·5	37·2	19·9	10·2
	51·8	39·4	40·1	21·3	11·3
	49·2	40·2	40·4	20·4	11·0
	50·3	39·6	40·7	21·3	10·7
10°K	53·6	39·7	40·8	22·0	10·7
	55·5	39·4	40·7	21·8	10·7
	54·8	40·0	39·5	21·9	10·8
Average	52·6	39·8	39·9	21·2	10·8
Average (duplicate)	51·7	40·0	----	20·7	10·6
Hydrolysis at 35°.					
Time	2280	2940	1920	3000	5700
	107·	92·7	86·3	50·9	28·6
	108·	89·7	86·5	51·7	27·8
	109·	89·1	88·5	52·3	28·5
10°K	110·	93·3	87·2	51·7	27·6
	112·	91·4	84·8	51·4	27·4
	111·	94·1	88·8	51·3	27·3
	(117·)	92·3	(82·3)	51·2	27·4
Average	110·	91·8	87·0	51·5	27·8
Average (duplicate)	109·	90·9	----	50·9	27·4
Hydrolysis at 45°.					
Time	840	840	720	1560	1560
	248·	205·	203·	113·	61·7
	245·	204·	201·	109·	67·4
	243·	209·	203·	115·	64·2
10°K	240·	206·	198·	114·	64·1
	238·	205·	192·	116·	64·0
	234·	201·	186·	115·	63·5
	230·	(192·)	182·	113·	62·7
Average	239·	205·	195·	113·	63·9
Average (duplicate)	234·	201·	----	111·	64·1

* This Journal, xxxiii, 27.

Discussion of Results.

Perhaps the most noticeable fact set forth by the above figures is the marked and varying retardation caused by the hydroxyl group in esters of this series. The irregularity in effect of this group was indicated in the previous experiments with acetates and propionates and is now definitely established. The comparison of velocities of corresponding hydroxy and unsubstituted esters shows that the hydroxyl group may produce effects varying in different cases from a slight acceleration to a considerable retardation. Thus it seems to be definitely proven that the effect of the hydroxyl group upon the velocity of ester hydrolysis is not in any sense an additive property.

A second fact of interest is that substituted and unsubstituted iso-butyrate decompose more slowly than the corresponding normal esters. The difference here measured appears to be somewhat greater than that found by De Hemptinne* between the unsubstituted esters but is in the same direction.

The beta hydroxy ester hydrolyzes more slowly than the alpha, which is in accord with the rule indicated by all previous experiments.†

All the esters decompose more slowly than analogous ones of the propionic and acetic series. Temperature coefficients seem to be rather irregular, perhaps on account of experimental error. There are at least no conclusions to be drawn from their variations.

ALKALINE HYDROLYSIS.

In connection with the experiments recorded in the first half of this paper it was thought desirable to make measurements upon the reaction velocities of esters of the above list in alkaline solution. Previous work* has indicated that this velocity is controlled by the strength of the acid from which the ester is derived and by another factor called steric influence. No mathematical relation for the latter has yet been worked out, but it seems to be closely related to that which controls the velocity of acid hydrolysis. The strength of the acid in the latter case has at most only a minor influence.

Procedure.

Part of the measurements were made by the use of the titration method which has been carefully described in an earlier paper‡ of this series. Experiments were also made by a modi-

* Loc. cit.

† This Journal, xxxiv, 69; xxxv, 486.

‡ This Journal, xxxv, 605.

fication of the conductivity method of Walker* which has been employed in the experiments of Findlay and Hickmans† on the velocities of saponification of esters of hydroxy and alkyloxy acids. The modification devised by the author simply adapts the excellent procedure recommended by Walker to the cases of the somewhat insoluble esters here examined. This procedure was in outline as follows:

Fiftieth normal solutions of carbonate-free sodium hydroxide and of ester were first prepared. The conductivity apparatus was of the usual form with a cell of the narrow Ostwald type. The constant temperature bath was a mixture of cracked ice and water which was vigorously and efficiently agitated with a spiral stirrer operated by an electric motor. The initial conductivity was obtained by measurements made on hundredth normal sodium hydroxide solution. The cell was then carefully rinsed and dried. For the actual hydrolysis fifty cubic centimeters of the fiftieth normal alkali solution were placed in a clean and dry Erlenmeyer flask and suspended in the ice bath. The fiftieth normal ester solution was likewise cooled down to zero degrees in the same bath.

At the proper time fifty cubic centimeters of the latter were removed from its container by means of a pipette, run into the alkali and the mixture vigorously shaken for a second or two. The time at which the pipette was half empty was recorded as beginning the reaction. As soon as was convenient a portion of the reaction mixture was transferred from the flask to the conductivity cell and bridge readings were taken at appropriate intervals of time. The flask containing the remainder of the reacting mixture was tightly corked and warmed in a water bath for an hour or so to bring the action to completion. After this it was re-cooled and measurements made upon portions of its contents to obtain the final conductivity. Calculations were made in the same way as those of Walker except that his scheme for their simplification was not adopted. During all the measurements a constant resistance of two hundred ohms was kept in the box, thus eliminating the possibility of slight errors due to this source.

A trial experiment with ethyl glycollate showed that the results obtained checked almost exactly with those of the titration method. Measurements were made with the esters of alpha hydroxy-iso-butyric acid and of beta hydroxy-butyric acid. The constants recorded for the other three esters are from the results of titration experiments.

In Table II are values of the constants obtained and the time periods in minutes over which the reactions were followed.

* Proc. Royal Soc., Series A, lxxviii, 155, (1908).

† Jour. Chem. Soc., lxxvii, 747.

TABLE II.

Ester	Hydrolysis at 0°		N/101 NaOH		
	Ethyl Butyrate	Ethyl Iso-butyrate	Ethyl α -Oxy-butyrate	Ethyl α -Oxy-iso-butyrate	Ethyl β -Oxy-butyrate
Time	160	185	50	130	120
	·79	(·75)	6·7	1·5	2·5
	·67	·48	6·3	1·8	2·2
	·68	·46	7·1	1·7	2·1
	·65	·46	5·4	1·6	1·9
	·62	·45	6·4	1·6	1·9
		·46	5·8	1·6	1·9
		·45	5·7	1·6	
		·49		1·7	
Average	·68	·46	6·2	1·6	2·1
Average	·71	·47	6·5	1·7	2·0
(duplicate)					

Table III gives a summary of results from Tables I and II and has in addition some values of affinity constants of acids taken from tables of Landolt, Börnstein & Roth (fourth edition). Figures for ethyl acetate and for ethyl propionate are also tabulated for purposes of comparison.

TABLE III. SUMMARY.

Ester	Acid hydrolysis			Temp. Coefficients		Alkaline hydrolysis K (0°)	(10 ⁵)k(aff) (25°)
	10 ⁵ K 25°	10 ⁵ K 35°	10 ⁵ K 45°	25°-35°	35°-45°		
Ethyl butyrate.	52·1	110·	237	2·09	2·17	·68	1·49
Ethyl iso-butyrate	39·9	91·4	203	2·31	2·23	·46	1·44
Ethyl α -oxy-butyrate	39·8	87·0	195·	2·18	2·24	6·2	----
Ethyl oxy-iso-butyrate	21·0	51·2	112·	2·43	2·19	1·6	10·6
Ethyl β -oxy-butyrate	10·7	27·6	64·0	2·57	2·33	2·1	----
Ethyl acetate ..	64·7	163	374·	2·51	2·29	1·2	1·8
Ethyl propionate	71·6	179	406	2·50	2·26	1·1	1·34

SUMMARY.

I. When hydrolyzed in acid solution three hydroxy-butyrate were found to have considerably smaller velocities of reaction than the esters of the acids from which they were derived.

II. Ethyl iso-butyrate decomposes more slowly than the ester of the normal acid; a difference in the same direction but of greater magnitude occurs with the corresponding alpha hydroxy esters.

III. Ethyl beta-hydroxy-butyrate decomposes more slowly than the alpha ester.

IV. Esters of the butyric acid series appear in general to decompose more slowly than propionates and acetates.

V. The effect of the hydroxyl group upon the velocity of acid hydrolysis is not an additive property.

VI. The velocities of saponification, measured in centinormal sodium hydroxide at zero degrees, vary in the following order with the numerical values representing approximate ratios:

Ethyl alpha hydroxy-butyrate (13.5), ethyl beta-hydroxy-butyrate (4.5), ethyl alpha-hydroxy-iso-butyrate (3.4), ethyl butyrate (1.5) and ethyl iso-butyrate (1.0).

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