[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

A Polarographic Study of Some Oximes. I. Methyl 4,5-Dioxo-2-pentenoate-5-oxime[1]

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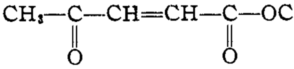
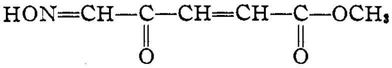
In connection with the problem of preparing ergothioneine, which was being carried on in this Laboratory by R. W. Wynn and A. H. Corwin, it was necessary to know whether methyl 5-amino-4-oxo-2-pentenoate could be prepared from the 5-oxime of methyl 4,5-dioxo-2-pentenoate (II). With the idea of using the technique of Lingane, Swain and Fields[2] to determine the appropriate reduction potential for reducing the oxime without destroying the ethylenic double bond, a polarographic study of II was initiated.



$CH_3-\underset{O}{\underset{\|}{C}}-CH=CH-\underset{O}{\underset{\|}{C}}-OCH_3$

I



$HON=CH-\underset{O}{\underset{\|}{C}}-CH=CH-\underset{O}{\underset{\|}{C}}-OCH_3$

II

In order to interpret the polarograms from II, it was necessary first to make a polarographic study of methyl 4-oxo-2-pentenoate (I). It was found, as will be shown later, that I in buffered acid solutions underwent a polarographic reduction corresponding to a two-electron change. Since this reduction was attributed to the hydrogenation of the double bond, the 5-isonitroso derivative (II) should show not only this same wave but, in addition, might show another wave due to the four-electron reduction of the isonitroso group to an amine. If this additional wave occurred at a more positive potential than the wave corresponding to the reduction of the double bond, it should be possible by an electrolytic reduction at a carefully controlled potential to reduce the oxime to an amine without destroying the ethylenic double bond.

Since some very peculiar observations were made during the preliminary polarographic study of II, a detailed investigation of this compound was carried out.

Experimental

Apparatus and Materials.—A Sargent Model XII polarograph was used for recording all the polarograms. An assembly of the polarographic cell and dropping mercury electrode similar to that described by Furman, Bricker and Whitesell[3] was employed throughout the investigation.

Two capillaries were used in this study. Capillary A had a drop time of 2.26 seconds in 0.1 *N* potassium chloride at an applied potential of zero volts and delivered 1.22 × 10^{-3} g. of mercury per second. Capillary B had a drop time of 3.22 seconds and delivered 1.65 × 10^{-3} g. of mercury per second. The capillary constant, $m^{2/3}t^{1/6}$, for capillary A was 1.31 mg.$^{2/3}$sec.$^{-1/2}$ and for capillary B the constant equaled 1.69 mg.$^{2/3}$sec.$^{-1/2}$.

The polarographic cell was not thermostated; all polarograms were made at room temperature, 23 ± 2°.

The galvanometer on the polarograph was calibrated by the method of Kolthoff and Lingane[4] and was found to have a value of 4.03 × 10^{-3} microampere per millimeter at a sensitivity of one.

A quiet pool of mercury was used as the anode. The potential of this electrode was measured *versus* a saturated calomel electrode by means of a Leeds and Northrup student-type potentiometer. All *p*H measurements were made with a Leeds and Northrup research-model *p*H meter.

The solutions used in this investigation, unless otherwise specified, were made up by precise analytical technique and should be accurate to two or three parts per thousand. In most cases, reagent-grade chemicals were used without further purification. Whenever necessary, polarographic blank runs were made on the supporting solutions. It was found satisfactory to use tank nitrogen without purification for removing dissolved oxygen from all solutions prior to the polarographic analysis. All solutions, unless otherwise indicated, were deaerated ten minutes with a slow stream of nitrogen before recording the polarogram.

The pipets which were used for removing aliquots of solution for analysis were calibrated and were reserved solely for this purpose.

The buffer which will be referred to in this investigation was prepared in a semiquantitative manner using 5.5 gram molecular weights of acetic acid and 0.1 gram formula weight of sodium acetate per liter of solution. In all cases the *p*H of this buffer was adjusted to 2.83 ± 0.02.

The methyl 4-oxo-2-pentenoate (I) was prepared by R. W. Wynn[5] from levulinic acid by a modification of the method of Pauly, Gilmour and Will.[6] The 5-oxime of methyl 4,5-dioxo-2-pentenoate (II) was prepared from I by a method developed by R. W. Wynn.[5]

Experiments with Methyl 4-Oxo-2-pentenoate (I).—A 0.00987 *M* solution of Compound I was prepared in the buffer of *p*H 2.83. Polarograms were recorded from solutions made by taking 0.486 ml. of this buffer solution and diluting with (a) 5.0 ml. of 0.1 *N* hydrochloric acid and 0.10 ml. of 0.1% gelatin solution, (b) 5.0 ml. of water, (c) 5.0 ml. of 0.50 *N* sodium hydroxide, (d) 5.0 ml. of *N* ammonia and (e) 5.0 ml. of *N* sodium hydroxide, respectively. The concentration of I in solution (a) was 8.56 × 10^{-4} *M*, and in the other solutions, 8.74 × 10^{-4} *M*. These polarograms are shown in Fig. 1 and the pertinent information is tabulated in Table I.

Since nearly the same value for the diffusion current was obtained from the two most acid solutions, the same electrode process was probably

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[2] J. J. Lingane, C. G. Swain and M. Fields, THIS JOURNAL, **65**, 1348 (1943).

[3] N. H. Furman, C. E. Bricker and E. B. Whitesell, *Ind. Eng. Chem., Anal. Ed.*, **14**, 333 (1942).

[4] I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941, pp. 227–229.

[5] R. W. Wynn, "Some Attempted Syntheses of Ergothionine," Doctor's Thesis, The Johns Hopkins University, Baltimore, Md., 1947. For details, see a forthcoming publication by R. W. Wynn and A. H. Corwin.

[6] H. Pauly, R. Gilmour and G. Will, *Ann.*, **403**, 150 (1914).

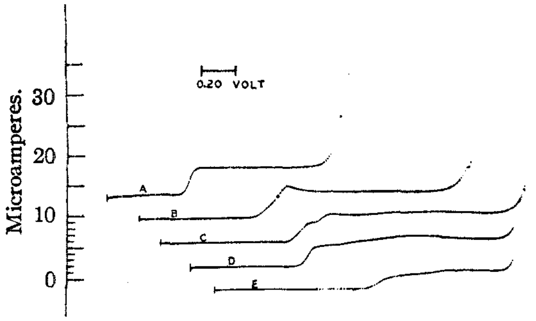

Fig. 1.—Polarograms of Compound I in solutions of various pH; all curves started at zero applied potential; a galvanometer setting of 1/100 and capillary A were used; data from these polarograms are recorded in Table I. An ink dot was placed at the middle of each current oscillation in order to make the polarograms visible when photographed.

TABLE I

Curve	pH	Wave height, microamperes/millimole/liter 1st wave	2nd wave	$E_{1/2}$ vs. S. C. E., volt 1st wave	2nd wave
A	1.85	5.08		−0.37	
B	2.85	4.98		−0.65	
C	5.53	3.69	1.48	−0.68	−0.82
D	9.02	3.91	0.89	−0.71	−0.97
E	11.0	2.77		−1.22	

taking place in both of these solutions. At a pH of 5.53, the total diffusion current of the two waves was very close to that obtained from the single waves in the more acid solutions. Since maleic and fumaric acids show identical reduction potentials in acid solutions but start to deviate at a pH of about 5, it might be postulated that the first wave in curve C was due to the *cis* isomer, and that the second wave was the result of the reduction of the *trans* isomer. However, in ammoniacal solution the ester may form an amide, and in sodium hydroxide solution the ester may partially saponify. These reactions may account for the different diffusion currents observed when I is reduced polarographically from basic solution.

At pH 1.85 the single diffusion current was directly proportional to concentration; the diffusion-current constant was 4.97/1.31 = 3.80 microamperes/millimole for a capillary having a constant of unity. The half-wave potential, −0.38 volt *vs.* S.C.E., was independent of the concentration.

Analysis of a Polarogram from Compound I.—An acetate-buffered solution of pH 2.86 was made $3.29 \times 10^{-3}M$ with I. This solution gave a single polarographic wave corresponding to 16.5 microamperes.

A plot of log $i/(i_d - i)$ *vs.* applied e.m.f. was made for this wave, and a value of 0.059 was obtained for the negative slope of the resulting straight line. For a reversible reduction this would correspond to a one-electron change. However, since the reduction of I was probably irreversible, little significance was placed on this method of determining the number of electrons involved in the polarographic reduction.

Using the Ilkovic equation, $i_d = 605\ nCD^{1/2}m^{2/3}t^{1/6}$, and assuming, from similar organic reductions, the diffusion coefficient of I to be 8.0×10^{-6}cm.^{2}/sec., a value of 3.45 microamperes/millimole/liter for a capillary constant of one was calculated for the theoretical diffusion current at zero volts. This value of 3.45 microamperes compares well with the theoretical value of 3.25 microamperes calculated by Kolthoff and Lingane[7] for the two-electron reduction of Cd^{++}. Kolthoff and Lingane observed a value of 3.51 microamperes for the reduction of cadmium ions. The observed value (calculated from 16.5 microamperes) for the reduction of I is 3.89 microamperes. Since the observed and calculated values agree with those for the reduction of Cd^{++}, the reduction of I in acid solution at the dropping-mercury electrode is probably a two-electron process and involves the hydrogenation of the ethylenic double bond.

Experiments with the 5-Oxime of Methyl 4,5-Dioxo-2-pentenoate (II).—A buffered solution of pH 2.86 which was theoretically 3.3×10^{-3} M with II gave two polarographic waves corresponding to only 4.03 and 1.21 microamperes, respectively. Since II should give at least the same wave for the reduction of the ethylenic double bond as did I and might be expected to give an additional wave twice as high for the four-electron reduction of the oxime group, it was necessary to explain these small waves. Another solution was prepared in exactly the same way from the same stock solution of II the following day, deaerated for ten minutes, and polarographed. The first wave now corresponded to only 1.4 microamperes, and the second wave was practically nonexistent. It was obvious, therefore, that II was decomposing in solution and that neither of the polarographed solutions were $3.3 \times 10^{-3}M$ with II.

A portion of a fresh preparation of II was dissolved in the buffer of pH 2.83 and studied immediately. The polarograms that were recorded in this study are shown in Fig. 2, and the pertinent information is summarized in Table II. These curves were recorded from solutions made by taking 0.486 ml. of the freshly prepared solution, which was 0.020 M with II, and diluting with 5.0 ml. of various reagents. The final concentration of II in each solution was $1.77 \times 10^{-3}M$.

The initial wave, which is nearly the same for curves A, B and C, corresponds to 6.2 microamperes/millimole/liter for a capillary constant of unity. The theoretical diffusion current for a one-electron change from the Ilkovic equation is 1.7 microamperes. It is apparent, therefore, that the first wave in these polarograms corresponds closely to a four-electron change.

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[7] I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941, p. 79.

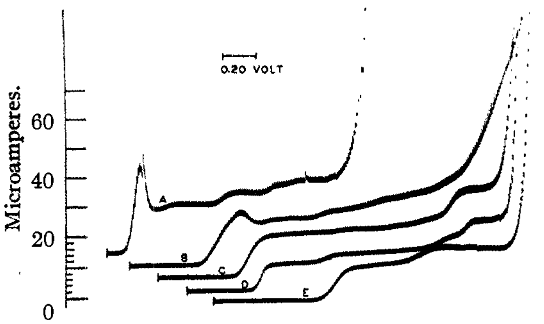


Fig. 2.—Polarograms of Compound II in solutions of various *p*H; all curves were started at zero volts applied; a galvanometer setting of 1/200 and capillary A were used; data from these polarograms are tabulated in Table II. Diluent for curve A was 0.1 *N* HCl; B, water; C, 0.5 *N* NaOH; D, 1.0 *N* NH_3; and E, 1.0 *N* NaOH.

TABLE II

Diluent	*p*H	Wave height, microamperes/ millimole/liter, for waves 1st	2nd	3rd	$E_{1/2}$ *vs.* S. C. E., volt, for waves 1st	2nd	3rd
0.1 *N* HCl	1.6	8.2	2.7	1.8	−0.06	−0.61	−0.90
H_2O	2.9	8.0	1.6	1.6	− .38	−1.02	−1.35
0.5 *N* NaOH	5.4	8.0	4.6		− .44	−1.65	
1 *N* NH_3[a]	9.1	4.5	1.4	2.3	− .46	−0.87	−1.53
1.0 *N* NaOH	12.3	6.2	2.3		− .92	−1.46	

[a] A fourth wave corresponding to 2.5 microamperes having a half-wave potential of −1.69 volts was observed from this solution.

The diffusion current for the first wave in D and E was considerably less than in the other polarograms. This is similar to the effect noted from the basic solutions of I.

Of the three curves recorded from acid solutions, only curve C shows a well-defined second wave which might be attributed to the two-electron reduction of the ethylenic double bond. The diffusion-current constant for this wave is 3.5 microamperes, which agrees well with the theoretical value for a two-electron change. Curve A shows two waves in addition to the initial wave, the combined height of which corresponds very closely to a two-electron reduction. Since a small second wave is obtained from the two most acid solutions, it may be postulated that the reduced oxime group (amino group) reacts rapidly but not quantitatively with the ester group to form a reducible lactam (acid-catalyzed reaction). Thus the amino group may react in the more acid solutions with the ester within the sphere of influence of the dropping mercury electrode to form 1,6-dihydro-2,5-pyridinedione. This compound should be reducible and may account for the second wave in these solutions. The third wave is probably due to the reduction of the ethylenic double bond in the unconverted amino compound.

At a *p*H of 1.6 the height of the first wave obtained in the polarographic reduction of II was found to be directly proportional to the concentration of this substance. Maxima in these waves prevented an accurate measurement of half-wave potentials.

The linearity of wave height *versus* concentration of II was determined, also, at a *p*H of 5.4. These polarograms are shown in Fig. 3. The diffusion-current constant for the first wave is 6.1 ± 0.05 microampere and for the second wave is 2.6 ± 0.1 microamperes. The half-wave potential *versus* the S.C.E. for the first wave is −0.39 volt and for the second wave −1.59 volts.

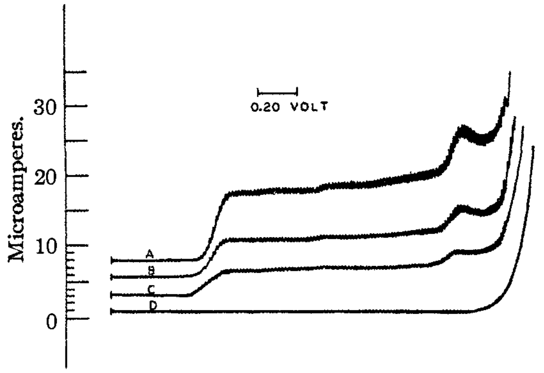


Fig. 3.—Polarograms of various concentrations of Compound II in the same background; curve D was obtained from the background alone (0.5 ml. buffer solution + 5.0 ml. 0.5 *N* NaOH; curve C from 3.29 × 10^{-4} *M* solution; curve B from 4.85 × 10^{-4} *M* solution; curve A from 9.26 × 10^{-4} *M* solution; capillary B was used. Because the original polarogram was too faint to photograph satisfactorily, this Fig. is a tracing of the original.

Kinetic Study with the 5-Oxime of Methyl 4,5-Dioxo-2-pentenoate (II).—Since II apparently decomposed slowly over a period of several days, it seemed to present an excellent opportunity for a kinetic study by means of the polarograph. The first problem was to determine the order of the decomposition reaction and, if possible, to calculate the energy of activation of this reaction. The second problem was to determine the mechanism and the possible decomposition products of the reaction.

Experimental

Approximately 0.01 *M* solutions of II were made in the acetate buffer of *p*H 2.83. All polarograms were made on solutions prepared by taking 0.486 ml. aliquots of these solutions of II and diluting them with 5.0 ml. of 0.50 *N* sodium hydroxide. This medium was selected for recording the polarograms because the heights of the well-shaped waves were proportional to the concentration of II.

The buffer solutions of the oxime were placed in constant-temperature baths operating at 50, 35, 30 and 25°, respectively. Aliquots from each of these solutions were polarographed as soon as the solution was prepared and at timed intervals thereafter. The polarograms of the study made at 35° are shown in Fig. 4. Only the first waves were considered in the study. When the logarithms of the wave heights in millimeters were plotted against time of withdrawal of sample, a straight line was obtained in each case, as is shown in Fig. 5. The decomposition proceeds, therefore, by a first-order reaction.

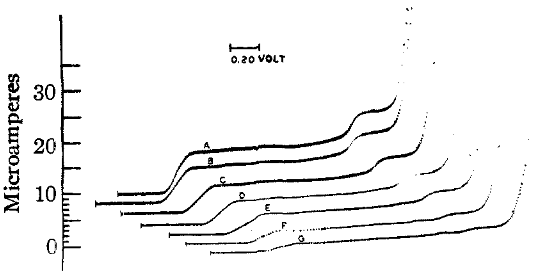


Fig. 4.—Polarograms of Compound II showing change of wave height on standing at 35°; curve A, started at −0.15 volt applied, obtained from aliquot taken immediately from fresh solution; all other curves started at zero volts applied; curve B, from aliquot taken after solution stood 5.5 hours; C, 14.5 hours; D, 21.3 hours; E, 28.3 hours; F, 50.3 hours; G, 62.3 hours; capillary A was used.

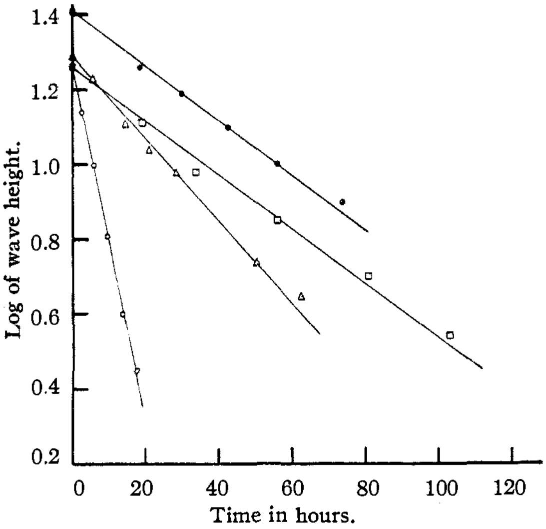


Fig. 5.—Results of decomposition studies plotted as logarithm of wave height *versus* time; squares, results at 25°; solid circles, results at 30°; triangles, results at 35°; open circles, results at 50°.

From the equation $\log C/0.4343\,t = k$, and from the data shown in Fig. 5, the rate constant for the decomposition is calculated to be 0.107 at 50°, 0.0253 at 35°, 0.0182 at 30° and 0.0160 at 25°. Plotting the logarithm of these constants against the reciprocal of the absolute temperature should give a straight line from which the energy of activation could be calculated. The plot of these data is shown in Fig. 6. Since a straight line is not obtained, the reaction rate is not a linear function of the temperature, and it is likely that more than one reaction is actually taking place in the decomposition.

A decomposition study similar to that described above was carried out at 0°. At the end of twenty days the first wave on the polarogram was 16 mm. high as compared to 18 mm. which was obtained from the solution at the beginning of the experiment. Obviously, Compound II at this temperature was quite stable.

Five additional decomposition studies were performed at 35° under various conditions, and the results of these studies are plotted in Fig. 7.

(a) Two solutions were allowed to decompose under the same conditions as previously described in order to check the reproducibility of the decomposition rate. The results of these studies are labeled "control runs" in Fig. 7. The negative slopes of these two lines are 0.0108 and 0.0110, respectively, as compared to a value of 0.0110 from the study at 35° shown in Fig. 5.

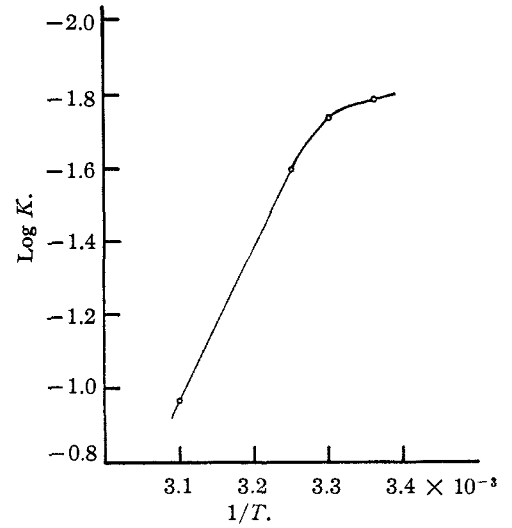


Fig. 6.—Logarithm of rate constant at various temperatures *versus* the reciprocal of the absolute temperatures.

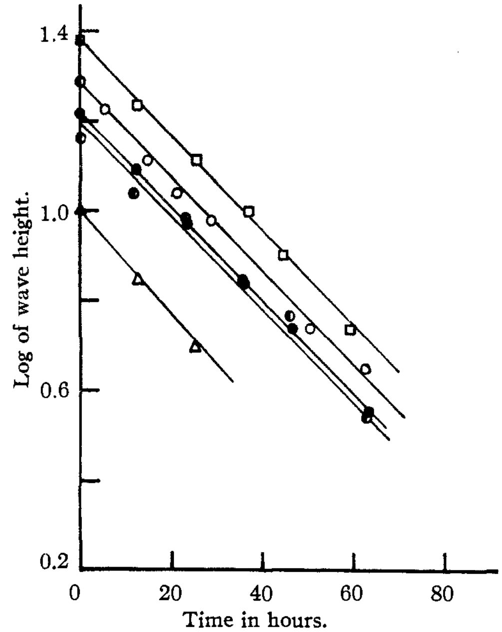


Fig. 7.—Results of decomposition studies at 35° under various conditions plotted as logarithm of wave height *versus* time; open and half-open circles, duplicate control runs; solid circles, in an oxygen atmosphere; squares, in a hydrogen atmosphere; triangles, in the presence of glass wool.

(b) A decomposition study was performed in an oxygen atmosphere in order to prove whether or not the decomposition reaction was actually an oxidation by the oxygen in the air. Oxygen was bubbled into the solution of II under a pressure of four inches of water during the entire decomposition period. The plotted results of the study give a negative slope of 0.0103 and indicate that oxygen has little effect on the rate of decomposition.

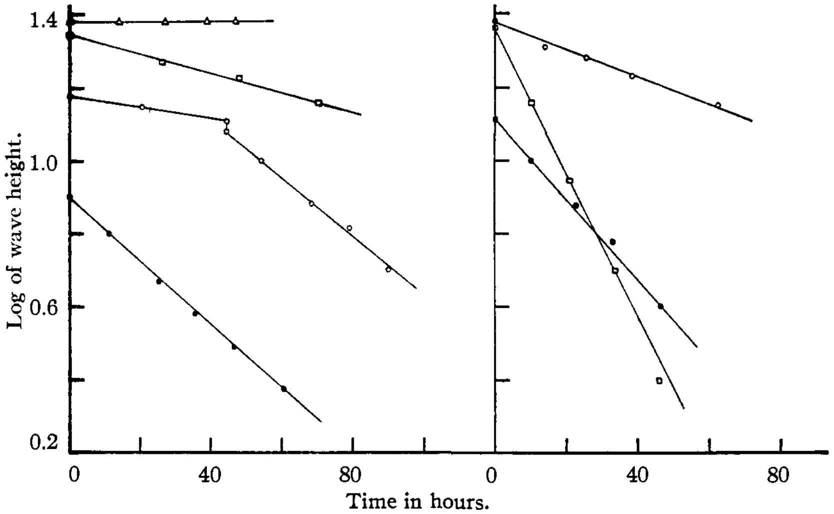


Fig. 8.—Results of decomposition studies at 35° in various buffers plotted as logarithm of wave height *versus* time; open circles on left-hand side, HCl solution of *p*H 2.8 followed by addition of glacial acetic acid after 45 hours; triangles, glacial acetic acid; solid circles on left-hand side, propionic acid buffer of *p*H 3.25 (lowered 0.5 log unit); squares on left-hand side, acetic acid–potassium acetate in 95% ethanol; solid circles on right-hand side, phosphoric acid buffer of *p*H 2.87; open circles on right-hand side, diluted acetic acid buffer of *p*H 2.85; squares on right-hand side, citric acid buffer of *p*H 2.86.

(c) A solution was allowed to decompose in a hydrogen atmosphere. The negative slope obtained from plotting these results is 0.0110. Obviously, hydrogen has no effect on the rate of decomposition and thereby eliminates the possibility of peroxide formation during the decomposition.

(d) A solution was allowed to decompose in the presence of a large amount of glass wool. Because the reaction flask was broken, only three polarograms were taken in this study. The negative slope from these three points is 0.0117 and deviates slightly more from the average slope of 0.0108 than do other runs at 35°. Nevertheless, it would appear that the decomposition is not a surface-catalyzed reaction.

Seven studies were made of the decomposition of II at 35° in different media:

(a) In hydrochloric acid solution having the same *p*H as that of the acetic acid buffer, followed by the addition of a small amount of glacial acetic acid to the solution.

(b) In glacial acetic acid.

(c) In a propionic acid–sodium propionate buffer of *p*H 3.25. This solution was 5.5 *M* with propionic acid and 0.1 *M* with sodium propionate.

(d) In an acetic acid–potassium acetate solution in 95% ethanol. This solution was 5.5 *M* with acetic acid and 0.1 *M* with potassium acetate.

(e) In a phosphoric acid–sodium dihydrogen phosphate buffer of *p*H 2.87. This buffer was prepared by adjusting the *p*H of a solution 2.5 *M* in sodium dihydrogen phosphate and 0.25 *M* in phosphoric acid.

(f) In an acetic acid–sodium acetate buffer of *p*H 2.85. This buffer was prepared by diluting by a factor of ten the standard buffer used throughout this study. The *p*H was adjusted with sodium hydroxide to 2.85.

(g) In a citric acid–monosodium citrate solution of *p*H 2.86. This buffer was prepared by adjusting the *p*H of a solution which was 0.1 *M* in monosodium citrate and 0.2 *M* in citric acid.

The logarithms of the observed wave heights *versus* time of each of these seven studies are plotted in Fig. 8. The negative slope of each line shown in Fig. 8 is listed in Table III. It appears that the hydronium ion concentration is not the determining factor in the rate of decomposition of II but that the concentration and nature of the buffer medium are important factors.

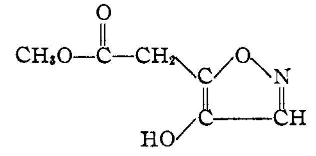
TABLE III

Study	Medium	Negative slope log of wave height *vs.* time
(a)	HCl	0.0013
	HAc added	.0085
(b)	Glacial HAc	.0000
(c)	Propionate buffer	.0088
(d)	Acetate in ethanol	.0024
(e)	Phosphate buffer	.0117
(f)	Diluted acetate	.0037
(g)	Citrate	.0205

Analysis of the Decomposed Solution of II.—Several attempts were made to determine the products of the decomposition. A solution of II in the acetic acid buffer was allowed to stand until no polarographically reducible material remained. This solution gave negative tests for ammonium salts, for hydroxylamine and for oximes, but when made alkaline with sodium hydroxide gave a positive test for cyanide ions. No cyanide test was ever obtained from a freshly prepared solution of II. In addition, since no hydrazone was obtained from the decomposed solution and since a yellow hydrazone was readily obtained from a fresh solution of II, the carbonyl group must have been changed or destroyed during the decomposition. Studies were made to determine whether carbon monoxide or carbon dioxide was liberated during the decomposition, and no evidence of either gas was detected.

A decomposed solution of II was made basic with 6 *N* sodium hydroxide and allowed to stand for a few minutes. A positive test for cyanide ion was obtained on one portion of this solution, and a polarographically reducible substance was found when another portion of this solution was reacidified with acetic acid. The wave obtained from this reduction corresponded to 2.08 microamperes/millimole/liter and had a half-wave potential of −1.60 volts *versus* the S. C. E. Since this half-wave potential differed from all others encountered in this study, it was believed that sodium hydroxide had reacted with the decomposition product of II to give a polarographically reducible substance.

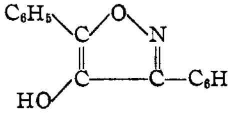
It was postulated that II might decompose in solution by rearranging to give an isoxazole derivative (III).



III

Since there is no literature on the polarographic behavior of such compounds, it was necessary to prepare and examine a known isoxazole derivative of similar structure.

Preparation of 3,5-Diphenyl-4-isoxazolol (IV).—This compound was prepared according to the method of Blatt



and Hawkins.[8] Although a decomposition point of 123° was given for the compound, this decomposition point was found to be inaccurate and to vary considerably with the rate of heating. However, the benzoate derivative was found to melt sharply at 158°, which agreed exactly with the reported melting point. The purity of IV was proved by analysis for carbon and hydrogen by combustion and for nitrogen by the Dumas method.[9]

	Calcd.	Found	Found
C, %	75.93	75.9	75.8
H, %	4.67	4.62	4.65
N, %	5.91	5.71	5.64

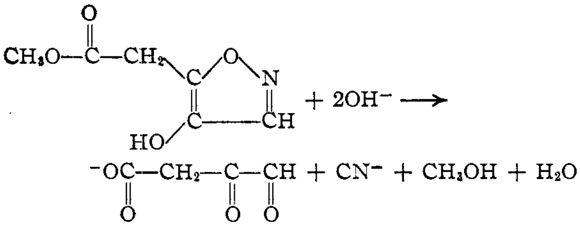
It was found that IV gave no hydrazone when treated with 2,4-dinitrophenylhydrazine.

Polarographic Study of Compound IV.—Compound IV is very difficultly soluble in water or acid solution but is readily soluble in sodium hydroxide solution. After a 6.7×10^{-4} *M* solution of this compound was prepared in 0.1 *N* sodium hydroxide, 10-ml. aliquots were diluted to 100 ml. with acetic or hydrochloric acid to give solutions of a desired acidity. As soon as this alkaline solution of IV became acid, a considerable portion of the compound separated from solution. Therefore, no quantitative calculations can be made from the polarograms of this material.

No polarographic wave was obtained from the alkaline solution of IV nor from the saturated solution of the compound in an acetate buffer of *p*H 4.95. However, in an acetate buffer of *p*H 3.55, a reduction occurred at a half-wave potential of −1.24 volts *vs.* the S. C. E. In a 0.1 *M* hydrochloric acid solution, the reduction occurred at −1.05 volts. When polarograms were made of solutions of this compound in acetic acid-potassium acetate buffers in 95% ethanol, no wave was obtained from *p*H's of 1.35 to 6.0.

The similar polarographic behavior of IV and the decomposed solution of II substantiated the assumption that an isoxazole derivative was formed during the decomposition.

Decomposition of Compound III.—When III is treated with sodium hydroxide, it might be expected to undergo the reaction



V

This would account for the positive cyanide test and also for the reducible substance which was found in a decomposed solution of II after treatment with sodium hydroxide.

Dakin[10] prepared the diethyl acetal of V and from this compound prepared the *p*-nitrophenylosazone, which he reported to have a melting point of 297–299°. In order to prove that V was obtained, a decomposed solution of II was refluxed for thirty minutes in the presence of 2.5 *N* sodium hydroxide. The refluxed solution was acidified with hydrochloric acid and treated with a solution of *p*-nitrophenylhydrazine in glacial acetic acid. A small amount of dark red precipitate was formed immediately. This precipitate was filtered, washed with warm methanol until the washings were colorless, and dried. This substance decomposed without melting; and although it was very difficult to observe the exact decomposition point, it was proved definitely that it did not decompose below 290° and that it had decomposed at 305°. Furthermore, a blue solution characteristic of adjacent nitrophenylhydrazine groups was obtained when a small amount of this dark red precipitate was treated with alcoholic potassium hydroxide.

Discussion

Mechanism of the Decomposition of Compound II.—The formation of an isoxazole from II is essentially the addition of the —OH group of the oxime across the ethylenic double bond. It was hoped from studies of the rate of decomposition in various media to determine the mechanism by which this process took place.

It is known that thioacetic acid adds to double bonds in propenoic acids.[11] It seems not unreasonable, therefore, to postulate that the buffer acid might add across the double bond to form an unstable intermediate. This might be the rate-determining step of the reaction. This step would be followed by the rapid formation of the isoxazole ring. The fact that decomposition did not occur in glacial acetic acid might be explained by the postulation either that the anion was necessary for the reaction or that ring closure did not proceed in that medium. The fact that decomposition was extremely slow in dilute hydrochloric acid, in a more dilute acetic acid–sodium acetate medium, and in an ethanol buffer would all seem to substantiate this mechanism. Although the rates of decomposition observed in the citric and phosphoric acid buffers are not readily explained, they do not exclude the possibility of the formation of an intermediate compound.

Another possible mechanism for the decomposition may be postulated in which the rate-determining step is the transfer of the proton from the acid molecule to II. This intermediate can then readily undergo ring closure by the loss of a proton. This mechanism is shown in the following equations and seems adequate to explain all the observed data.

With more dilute acetic acid, [HB] is reduced, and the rate is decreased. Since phosphoric acid is a stronger proton donor than acetic acid, it is not surprising that 0.25 *M* phosphoric acid would have the same effect as 5.5 *M* acetic acid. Citric acid can be considered to have three nearly equivalent proton-donating groups, and consequently its ability to give protons to II would be greatly enhanced in comparison to acetic acid. In glacial acetic acid and in ethanol solutions the dielectric constant of the medium is considerably changed. This would greatly affect the rate of the irreversible ring closure. Without this step, no apparent

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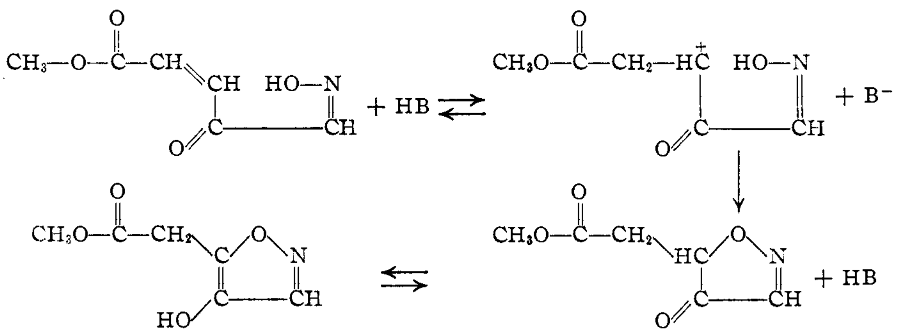
[8] A. H. Blatt and W. L. Hawkins, THIS JOURNAL, **56**, 2190 (1934).

[9] The authors gratefully acknowledge the assistance of Messrs. Robert Yale and Hilding Johnson of the Heyden Chemical Corporation of Garfield, N. J., for running these analyses.

[10] Dakin, *Biochem. J.*, **13**, 418 (1919).

[11] E. Schjånberg, *Ber.*, **74B**, 1751 (1941).



decomposition would be observed; or when ring closure becomes slow, this may become the rate-determining step. Also, the possibility of having two rate-determining steps may explain the non-linearity of the rate of decomposition with temperature.

One of us, E. D. H., wishes to acknowledge a grant-in-aid from the Hynson, Westcott and Dunning Research Fund.

Summary

1. Two compounds, methyl 4-oxo-2-pentenoate and the 5-oxime of methyl 4,5-dioxo-2-pentenoate, were studied polarographically. The former compound showed a polarographic wave corresponding to a two-electron reduction, whereas the latter compound gave two waves equal to a four- and a two-electron change, respectively,

2. The oxime was found to decompose in solution according to a first-order reaction. This decomposition was followed polarographically.

3. A polarographic study of 3,5-diphenyl-4-isoxazolol was made.

4. A mechanism for the decomposition of the oxime was proposed.

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

A Synthesis of *cis*-11-Octadecenoic and *trans*-11-Octadecenoic (Vaccenic) Acids[1]

BY KAMALUDDIN AHMAD, F. MERLIN BUMPUS AND F. M. STRONG

Vaccenic acid, *trans*-11-octadecenoic acid, was discovered in 1928 by Bertram,[2] who succeeded in isolating it from fats of animal origin and in establishing its structure. Interest in this substance was stimulated by the recent announcement of Boer, Jansen, Kentie and Knol[3] that vaccenic acid is one of the components of butter fat responsible for the superior nutritive value of butter as compared to vegetable fats when tested on certain diets.

Hart and co-workers in this laboratory[4] and Deuel, *et al.*,[5] have been unable to confirm this claim. In these studies solid mono-unsaturated fatty acid fractions obtained from butter and from hydrogenated vegetable fats by Bertram's method have been used as the source of vaccenic acid. In view of the well-known difficulty of isolating completely pure fatty acids from natural fats, it seemed possible that this discrepancy might be related to the quality of the vaccenic acid preparations being tested. In order to obtain an authentic sample of the acid for further feeding experiments it has been synthesized by a suitable application of the method recently reported.[6]

$$CH_3(CH_2)_5C{\equiv}CH + I(CH_2)_9Cl \xrightarrow[\text{liq. }NH_3]{Na}$$

$$CH_3(CH_2)_5C{\equiv}C(CH_2)_9Cl \xrightarrow[KOH]{NaCN}$$

$$CH_3(CH_2)_5C{\equiv}C(CH_2)_9COOH \xrightarrow[Ni]{H_2}$$

$$CH_3(CH_2)_5CH{=}CH(CH_2)_9COOH$$

Each of the indicated reactions was found to give excellent yields and the desired product was obtained without difficulty.

In contrast to natural vaccenic acid which was reported to melt at 39° and was regarded by Bertram as the *trans* form,[2] the synthetic acid melted at 10.5–12° and is probably the *cis* isomer. The production of *cis* olefins by catalytic partial hydrogenation of alkyl acetylenes has been reported.[7]

trans-11-Octadecenoic (vaccenic) acid was obtained by isomerization of the *cis* acid with selenium at 180–200°, and was found to melt at 43–44°. Each form was converted to the correspond-

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[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.

[2] Bertram, *Biochem. Z.*, **197**, 433 (1928).

[3] Boer, Jansen, Kentie and Knol, *J. Nutrition*, **33**, 356, 359 (1947).

[4] E. B. Hart, personal communication.

[5] Deuel, Greenberg, Straub, Jue, Gooding and Brown, *J. Nutrition*, **35**, 301 (1948).

[6] Ahmad and Strong, THIS JOURNAL, **70**, 1699 (1948).

[7] Campbell and Eby. *ibid.*. **63**, 216 (1941).