(6) **5-(β-Picolyl)-5-*n*-butylbarbituric Acid.**—The synthesis was essentially the same as for the lower homologs. Two and one-half grams of the substituted malonic ester gave 0.71 g. of the product when recrystallized three times from 95% alcohol.

(7) **5-(β-Picolyl)-5-isoamylbarbituric Acid.**—The method of preparation was the same as above. Four grams of the substituted malonic ester gave 1.4 g. of the product when recrystallized three times from alcohol.

## Summary

1. The synthesis of four new heterocyclic derivatives of barbituric acid which contain the β-picolyl group in the 5-position is described.

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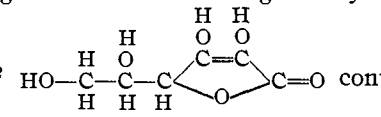
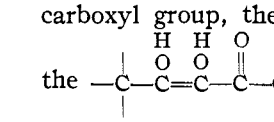
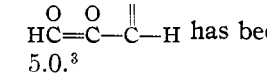
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA AND THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

# Titration Curves and Dissociation Constants of *l*-Ascorbic Acid (Vitamin C) and Diethyl Dihydroxymaleate

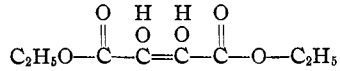
BY W. D. KUMLER AND T. C. DANIELS

Birch and Harris[1] using a micro method found the $pK_a$ values of *l*-ascorbic acid at 16–18° to be $pK_{a_1}$ = 4.17 and $pK_{a_2}$ = 11.57. We have redetermined these constants at 22–23° using a macrohydrogen electrode and find values in agreement with theirs, namely, $pK_{a_1}$ = 4.12 and $pK_{a_2}$ = 11.51.

Although *l*-ascorbic acid is about four times as strong as acetic acid the generally accepted formula[2]  contains no carboxyl group, the acidity being attributed to the  grouping.[2] As evidence that a structure of this type may give rise to relatively strong acid properties the case of reductone (glucose-reductone, gluco-reductone)  has been cited[2] which has a $pK_a$ = 5.0.[3]

Reductone is the enol form of a 1,3-dialdehyde and these compounds like the enol forms of 1,3-diketones are undoubtedly much stronger acids than the enol form of the β-ketonic esters to which type of compound the structure assigned to *l*-ascorbic acid belongs. The enol form of acetylacetone has a $K_{a_{enol.}}$ = 1.3 × $10^{-5}$ and the enol form of ethyl acetoacetate has a $K_{a_{enol.}}$ = 5 × $10^{-9}$.[4] Thus for comparing acid strength reductone is not a correct analog of *l*-ascorbic acid.

We have measured the $pK_a$ values of a β ketonic ester, diethyldihydroxymaleate



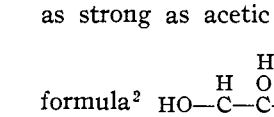
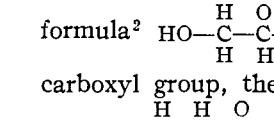
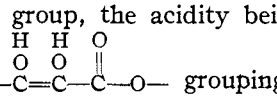
which contains the grouping to which the acidity of *l*-ascorbic acid has been attributed[2]  . Since the negativity of the  group is considerably greater than that of the  group and the ester has two equivalent hydrogens it should actually be a stronger acid than *l*-ascorbic. However, from the $pK_a$ values in Table I it is seen that *l*-ascorbic is much the stronger acid, its first dissociation constant being 1000 times as great as that of the other compound.

TABLE I

ALCOHOL–WATER SOLUTION

| | $pK_{a_1}$ | $pK_{a_2}$ |
|---|---|---|
| *l*-Ascorbic acid | 4.85 | 12.0 |
| Diethyl dihydroxymaleate | 7.88 | 12.3 |
| Dimethyl dihydroxymaleate | 7.85 | 12.3 |
| WATER | | |
| *l*-Ascorbic acid | 4.12 | 11.51 |

The second dissociation constants have very nearly the same value, and in both cases are un-

(1) Birch and Harris, *Biochem. J.*, **27**, 595 (1933).

(2) Herbert, Hirst, Percival, Reynolds, Smith, *J. Chem. Soc.*, 1270 (1933).

(3) Von Euler and Martins, *Ann.*, **505**, 73 (1933).

(4) Acetylacetone $K_a \approx 1.5 \times 10^{-9}$, ethyl acetoacetate $K_a = 2 \times 10^{-11}$ (Landolt–Börnstein), acetylacetone $K_{enolization} = 0.132$, ethyl-acetoacetate $K_{enolization} = 0.004$ (Rice, "Mechanism of Homogeneous Organic Reactions," Chemical Catalog Co., p. 92). The $K_{a_{enol.}}$ constants were calculated from the above $K_a$'s by use of the equation

$$K_{a_{enol.}} = K_a \frac{(K_{enolization} + 1)}{K_{enolization}}$$

doubtedly due to an enolic type of structure. The first constant of *l*-ascorbic acid is too strong to be attributed to an enolized α-hydroxy-β-ketonic ester but might be due to some other grouping such as the enol form of a hydroxy, 1,3-diketone, a free carboxyl group, or the opening of the lactone ring. We are aware of the various arguments which have been advanced against these types of structures[2] but in view of inability of the enolized α-hydroxy-β-ketonic ester structure to account for the first dissociation constant these arguments should be checked.

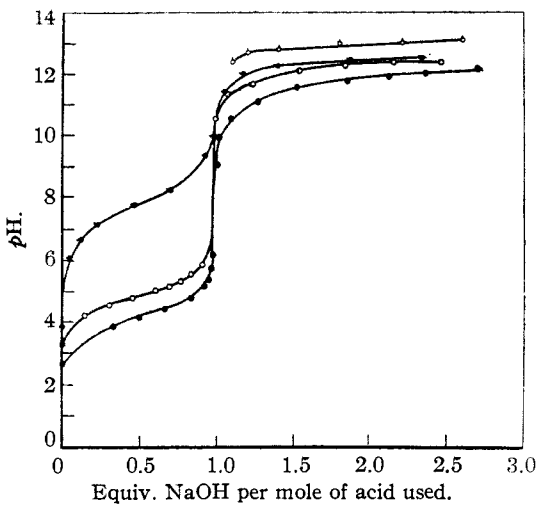



Fig. 1.—*l*-Ascorbic acid, ○: 0.0574 g. of acid, 4 ml. of alcohol, 4 ml. of water at beginning. Diethyldihydroxymaleate, -●: 0.0436 g. of compound, 4 ml. of alcohol, 4 ml. of water at beginning. No evidence of hydrolysis after thirty minutes at end of titration. Blank salt solution, ☉: 0.109 g. of $NaC_2H_3O_2 \cdot 3H_2O$, 4 ml. of alcohol, 4 ml. of water. *l*-Ascorbic acid, ●: 0.0647 g. of acid, 5 ml. of water at beginning.

## Experimental

A Hildebrand type hydrogen electrode and saturated calomel cell were used. These were checked against a standard phosphate buffer. A potentiometer–galvanometer circuit was used in obtaining the electromotive forces.

Due to the insolubility of the diethyl dihydroxymaleate in water the titrations were made in ethyl alcohol–water solutions which were 50% by volume at the start of the titration. Although the $pK_a$ values are higher[5] in the alcohol solutions than in pure water they are strictly comparable with each other. The $pK_{a_1}$ of *l*-ascorbic acid is 0.73 higher in the alcohol solution than in pure water.

As a check on the $pK_a$ values of diethyl dihydroxymaleate the dimethyl ester was measured. Theoretically one would expect very little difference in the acidity of these two compounds and very little was observed as is shown by the $pK_a$ values in Table I. However, since in the case of the dimethyl compound it was necessary to start with a 60% alcohol solution the values are not strictly comparable with the other two compounds but the errors thus introduced are less than 0.06 of a $pK_a$ unit.

To demonstrate that the second $pK_a$ is real and not an apparent effect due to the dilution of the 0.1 *N* sodium hydroxide, the curve for a sodium acetate blank is shown which falls definitely above the other curves.

### Materials

**Synthetic *l*-ascorbic acid** was obtained from Hoffmann-LaRoche, Inc., and was used without further purification, m. p. 190°; literature m. p. 189, 190, 192°; molecular weight by titration 175.7, theoretical 176.1.

**Dimethyl dihydroxymaleate** was prepared by dissolving anhydrous dihydroxymaleic acid in the least quantity of anhydrous methyl alcohol and passing dry hydrogen chloride into the solution;[6] m. p. 150–151°, literature m. p. 151°.

**Diethyl dihydroxymaleate** was prepared by dissolving anhydrous dihydroxymaleic acid in anhydrous ethyl alcohol and passing dry hydrogen chloride into the solution;[7] m. p. 71–73°, literature 72–73°.

**Dihydroxymaleic acid** was prepared by oxidizing tartaric acid with hydrogen peroxide in the presence of ferrous iron[6] (p. 899).

## Summary

The titration curves of *l*-ascorbic acid in water and of *l*-ascorbic acid and diethyl dihydroxymaleate in alcohol–water solution have been determined. The $pK_a$ values of these compounds and of dimethyl dihydroxymaleate were measured. *l*-Ascorbic acid is 1000 times as strong as diethyl dihydroxymaleate. The apparent inability of the enolized α-hydroxy-β-ketonic ester type of compound to account for the acid properties of *l*-ascorbic acid suggests that some other grouping is responsible for its large first dissociation constant.

BERKELEY, CALIF.
SAN FRANCISCO, CALIF. RECEIVED JUNE 25, 1935

(5) Branch, Yabroff and Bettman, THIS JOURNAL, **56**, 937 (1934).

(6) Fenton, *J. Chem. Soc.*, **65**, 905 (1894).

(7) Fenton, *ibid.*, **69**, 555 (1896).