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5,6-DIACETYL-L-ASCORBIC ACID

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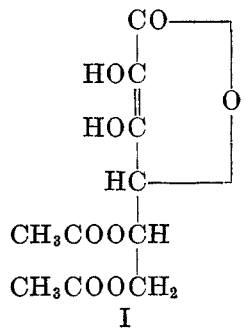
Soon after its isolation, L-ascorbic acid was shown to be related to sugars, and during determination of its structure the usual reactions in sugar chemistry were studied. One of the most useful of those reactions is acetylation. Converting the reactive free hydroxyl groups into acetoxyl groups allows degradation studies impossible with the free sugars.

Consequently Svirbely and Szent-György tried to obtain an acetyl derivative of L-ascorbic acid (2). They were not able to isolate a crystalline acetyl derivative. Ohle (1) likewise could not prepare crystalline acetyl derivatives of D-isoascorbic acid. It seems that other attempts to acetylate L-ascorbic acid also were unsuccessful since the extensive literature on L-ascorbic acid published within the last fifteen years fails to mention an acetyl derivative. That efforts to acetylate L-ascorbic acid were never abandoned is evident from a paper published by Vestling and Rebstock in 1944 (3), where the authors report the preparation of 3-acetyl-5,6-isopropylidene-L-ascorbic acid.

Several years ago we reinvestigated the acetylation of L-ascorbic acid. In the course of this work 5,6-diacetyl-L-ascorbic acid was isolated; however, it is very difficult to obtain in crystalline form. This is obviously the reason why previous investigators failed to isolate acetyl derivatives of L-ascorbic acid. It took months to obtain the compound in crystalline form, but once crystals were isolated, it proved to be easy to prepare large amounts of the compound by a simple procedure.

The treatment of L-ascorbic acid with hot acetic anhydride yielded a non-crystallizable syrup, which did not decolorize iodine. This behavior indicates that the compound may represent a tri- or tetra-acetyl derivative. On prolonged standing, crystals formed in the syrup, which proved to be 5,6-diacetyl-L-ascorbic acid. The structure is represented by formula I which is in agreement with the properties. The diacetyl derivative consumes the calculated amount of iodine, and it titrates as a monobasic acid with alkali. Both reactions are proof that the enediol system must be free.



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The method by which the compound was obtained for the first time is not of any preparatory importance. A satisfactory method of preparation was later found in the use of sulfuric acid as catalyst. At the time when these experiments were carried out, the use of conc'd sulfuric acid was not an obvious method, because sulfuric acid caramelizes and destroys ordinary sugars easily. Addition of small amounts of conc'd sulfuric acid to a cold suspension of L-ascorbic acid in acetic anhydride causes a spontaneous rise in temperature, and solution of the L-ascorbic acid. On seeding, 5,6-diacetyl-L-ascorbic acid crystallizes slowly.

The yield of 5,6-diacetyl-L-ascorbic acid is about 50%. An excellent solvent for the recrystallization was found in nitromethane, which surprisingly enough, is not reduced by 5,6-diacetyl-L-ascorbic acid at the temperatures necessary for recrystallization. 5,6-Diacetyl-L-ascorbic acid is stable when kept protected from air and moisture. It keeps indefinitely in an evacuated desiccator containing a drying agent. In ordinary stoppered bottles even the carefully dried compound decomposes slowly, and the characteristic odor of acetic acid appears soon. At the same time, the originally colorless material turns yellow and cakes, but such samples may still contain more than 90% of unchanged material.

In water the compound is not very stable. However, small amounts may be recrystallized from hot water, yielding beautiful prisms.

It is noteworthy that the same procedure did not succeed in attempts to prepare an acetyl derivative of D-isoascorbic acid.

EXPERIMENTAL

First isolation of crystallized 5,6-diacetyl-L-ascorbic acid. Seventeen and six-tenths grams of L-ascorbic acid (0.1 mole) was heated in 40.8 g. of acetic anhydride (0.4 mole) on an oil-bath to about 130° for 20 minutes. At about 110° a vigorous reaction occurred and the L-ascorbic acid dissolved completely. Heating was continued for an additional two hours at 110–115°. The solvent was then removed *in vacuo*. A thick, light amber syrup remained, which did not reduce iodine. It was triturated with absolute ethanol and the solvent was removed *in vacuo*. This procedure was repeated twice. The syrup was kept in a desiccator for about a month, when it smelled strongly of acetic acid and a sample reduced iodine. On prolonged standing in an evacuated desiccator for several more weeks, crystals started to form. Scratching induced crystallization throughout the syrup. It was then placed in the refrigerator, and after one day a solid mass of crystals had formed. They proved to be 5,6-diacetyl-L-ascorbic acid.

Preparation of 5,6-diacetyl-L-ascorbic acid. In a five-liter three-necked flask equipped with a condenser, stirrer, and thermometer were introduced 880.6 g. (5 moles) of L-ascorbic acid and 1123 g. (11 moles) of acetic anhydride. One drop of concentrated sulfuric acid was added to the stirred mixture. A vigorous reaction took place, the temperature rising to 125° within approximately 10 minutes after the addition of the sulfuric acid. The L-ascorbic acid dissolved at the same time. The resulting solution contained 5,6-diacetyl-L-ascorbic acid. The compound did not, however, crystallize from this solution, even after standing for months. The failure of previous investigators to obtain an acetyl derivative of L-ascorbic acid was obviously due to these poor crystallization properties.

If the solution was seeded at room temperature with crystals of 5,6-diacetyl-L-ascorbic acid and set aside, crystallization started within a few days. After about three weeks approximately 25% of the theoretical amount of the diacetyl derivative had crystallized and was filtered. From the mother liquor, 5,6-diacetyl-L-ascorbic acid continued to crystallize slowly, yielding approximately another 25% of the theoretical amount in two

months. The crude compound was triturated with ether to remove the thick syrupy mother liquor. The crude diacetyl derivative was dried *in vacuo* over sulfuric acid. This crude material melted at 151–154° (uncorr.) and gave the following analysis:

100 mg. used 7.4 cc. $N/10$ iodine (calc'd 7.68 cc.)
100 mg. used 3.87 cc. $N/10$ sodium hydroxide (calc'd 3.84 cc.)

Recrystallization. Five grams of crude 5,6-diacetyl-L-ascorbic acid was dissolved in 6 cc. of boiling nitromethane. From the filtered solution 4.5 g. (about 90%) crystallized on cooling. The melting point is 156–157° (uncorr.).

Anal. Calc'd for $C_{10}H_{12}O_8$: C, 46.16; H, 4.65; mol. wt. 260.20.
Found: C, 46.45; H, 4.81.

Iodine Titration: 100 mg. used 7.75 cc. $N/10$ iodine
Calc'd 7.68 cc. $N/10$ iodine

Acid Titration: 100 mg. used 3.87 cc. $N/10$ sodium hydroxide
Calc'd 3.84 cc. $N/10$ sodium hydroxide

Recrystallization is also possible from 10 parts of ethyl acetate, giving about 55% recovery in beautiful prisms, and from 0.6 parts of water, yielding large crystals in about 60% yield. Specific Rotation: $[\alpha]_D^{27}$ 64.15° (*c*, 4.9, water). Acidity: *p*H = 2.44 (*c*, 5, water). Solubility at 24°: acetic acid approx. 10%; alcohol approx. 25%; ether approx. 0.4%; ethyl acetate approx. 4.5%; nitromethane approx. 5%; water approx. 25%.

Stability. The stability of the compound was determined by iodine titrations and acid titrations. When stored in an evacuated desiccator over calcium chloride or sulfuric acid, the titrations showed no change after a period of 6 months. Under all other conditions (in stoppered bottles, under nitrogen) the acetyl groups are slowly split off.

SUMMARY

L-Ascorbic acid yields, on treatment with acetic anhydride and small amounts of sulfuric acid, the easily-crystallized 5,6-diacetyl-L-ascorbic acid of m.p. 156–157° (uncorr.).

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REFERENCES

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