Letters to the Editor

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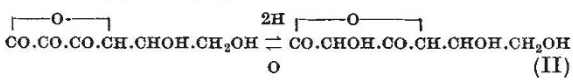
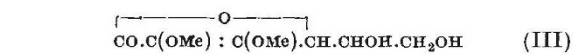
Constitution of Ascorbic Acid

WE have now confirmed the accuracy of the structure (I) COOH.CO.CO.CHOH.CHOH.CH_2OH which we had previously assigned to the first (reversible) oxidation product of ascorbic acid on the ground that it yields oxalic acid and trihydroxybutyric acid (*l*-threonic acid) on further oxidation[1]. The above formulation represents an open chain acid, but it is now evident that at the moment of formation the substance behaves as a lactone of (I) and not as the free acid. We have already advanced a constitutional formula for ascorbic acid (represented by (II) and its tautomerides) which shows the relationship between (I) and (II) to be as follows:[2]



(II)

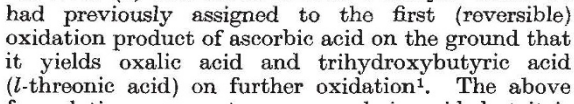
Strong evidence in favour of these views has been obtained from a study of the properties of the methylated derivatives of ascorbic acid. We find that dimethyl ascorbic acid (III), obtained by the action of diazomethane on ascorbic acid, is a neutral substance which reacts with one equivalent of warm $N/10$ alkali without elimination of methyl alcohol. The formation of the sodium salt appears to involve the opening up of the lactone ring in (III). Both methoxy groups are therefore enolic in character (contrast Karrer[3] and Micheel and Kraft[4]). Profound decomposition occurs when the dimethyl derivative is warmed with strong alkali. In this respect the tetramethyl derivative (see below) is much less stable and on continued heating with $N/10$ alkali it breaks down with elimination of at least three molecules of methyl alcohol.



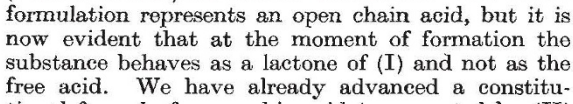
(III)

The crystalline substance, m.p. 123°, obtained by Micheel and Kraft[5] by the action of methyl alcoholic ammonia on dimethyl ascorbic acid is apparently formed in an analogous manner by the addition of ammonia to the lactone group of (III). The two methoxyl groups of dimethyl ascorbic acid are retained in the product, which we find behaves as an amide. It contains one molecule of combined methyl alcohol and has an empirical formula $C_9H_{19}O_7N$ (not $C_8H_{15}O_6N$).

The nature of the ring system (1 : 4) present in dimethyl ascorbic acid has been determined by the degradative oxidation of tetramethyl ascorbic acid, obtained by the action of methyl iodide and silver oxide on the dimethyl derivative. On treatment with ozone the tetramethyl derivative gives rise to a neutral substance (V) which reacts immediately with ammonia giving quantitatively oxamide and 2-hydroxy 3 : 4-dimethoxybutyramide. Detailed examination of the hydroxy dimethoxybutyric acid has revealed that it consists of two isomerides, the main portion (80 per cent) being 3 : 4-dimethyl-threonic acid, which we have characterised by its conversion into 2 : 3 : 4-trimethyl *l*-threonic acid (amide, m.p. 77°, $[\alpha]_D$ + 66° in water). The remainder was found to be 3 : 4-dimethyl *l*-erythronic acid (amide, m.p. 113°, $[\alpha]_D$ − 34° in water). The amides of both hydroxy acids gave sodium isocyanate on treatment with sodium hypochlorite (Weerman's reaction) and are therefore α-hydroxy derivatives. The isolation of the two epimeric acids suggests that at some stage during the series of reactions enolisation has occurred at C_4. The observation is of special interest in that any possibility of such a change taking place in the plant or animal or during the process of isolating ascorbic acid has great significance from the biological point of view.

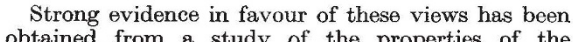


(IV)



(V)

The present observations are incompatible with the furane carboxylic acid structure for ascorbic acid advocated by Micheel[4] (which we had previously rejected for crystallographic reasons) and with the formulæ recently suggested by Karrer[6]. The oxidation results demand for tetramethyl ascorbic acid either (IV) or the structure



but apart from its inherent improbability on account of the propylene oxide ring, the latter formula is unable to explain the non-acidic character of the newly-formed first oxidation product of ascorbic acid or the behaviour of the methylated derivatives towards alkali and towards ammonia. On the other hand, all the observations offer strong support to (IV) for tetramethyl ascorbic acid and to (II) and its various tautomeric modifications for free ascorbic acid.

We wish to thank Prof. A. Szent-Györgyi for his kindness in placing at our disposal the ascorbic acid used in this work.

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April 7.

[1] NATURE, **130**, 888; 1932.
[2] *J.S.C.I. (Chemistry and Industry)*, **52**, 221; 1933.
[3] *Helv. Chim. Acta*, **16**, 181; 1933.
[4] NATURE, **131**, 274, Feb. 25, 1933.
[5] *Z. physiol. Chem.*, **215**, 222; 1933.
[6] *Helv. Chim. Acta*, **16**, 302; 1933.

Vitamin B_4 and Adenine

IN a recent preliminary communication, R. Tschesche[1] has directed attention to the similarity between adenine hydrochloride and the crystals isolated by Barnes, O'Brien and Reader[2]. These crystals were specifically stated by them to have vitamin B_4 activity (10γ per diem per rat), but no claim was made that they were actually vitamin B_4. Tschesche does not state whether the specimen of crystals obtained by him was biologically active.

The general resemblance in many respects between the isolated crystals and adenine hydrochloride has been familiar knowledge in this laboratory for a considerable time. Before leaving the work in September, V. Reader tested a specimen of adenine