50. *Methyl Ethers of Arabo-ascorbic Acid and their Isomerism.*

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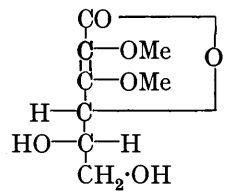
The behaviour of *d*-arabo-ascorbic acid on methylation with diazomethane has been studied with the view of comparing it with that of the stereochemically related *l*-ascorbic acid. It is found that the hydroxyl group at C_3 is the most acidic and reacts most readily, giving 3-*methyl* d-*arabo-ascorbic acid* (IV). The acid (IV) is convertible into the 2 : 3-*dimethyl* derivative (V), the lactone ring of which opens normally in the presence of alkali. Regeneration of 2 : 3-dimethyl *d*-arabo-ascorbic acid does not take place on acidification of the salts, the product being the iso-*derivative* (VII) containing a second ring system formed by the addition of the hydroxyl group at C_6 to the double bond. The *iso*-derivative behaves as a glucoside and in aqueous acid gives, after rearrangement, 2-*methyl* d-*arabo-ascorbic acid*. The latter in turn gives on methylation the normal 2 : 3-dimethyl derivative. There is therefore a close analogy with the behaviour of *l*-ascorbic acid.

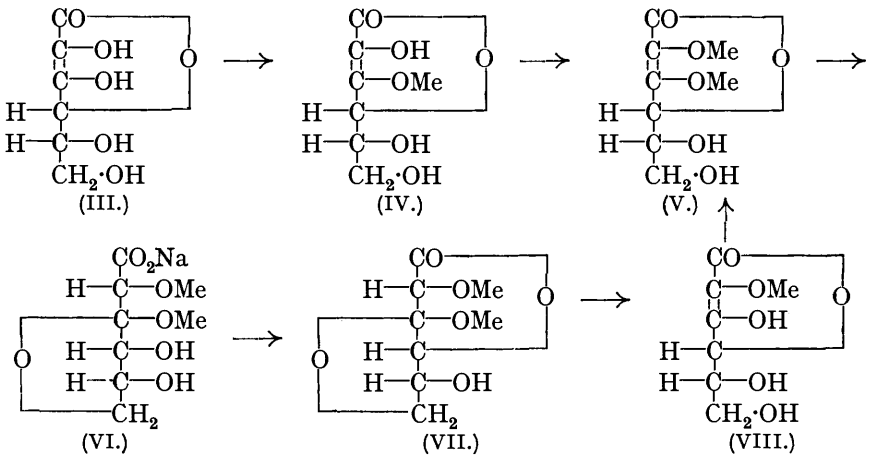
The lactone ring in 2 : 3-dimethyl ascorbic acid (I) opens in the usual way under the influence of alkalis, giving a salt of this acid. Acidification, followed by lactonisation of the free acid, no longer yields the original 2 : 3-dimethyl ascorbic acid but gives an isomeric modification (II) in which a new ring has been formed by the addition of the hydroxyl group at C_6 to the double bond (Haworth, Hirst, Smith, and Wilson, J., 1937, 829; compare Micheel, *Annalen*, 1935, **519**, 70; 1936, **525**, 66). Similar observations were made with 2 : 3-dimethyl gluco-ascorbic acid (Haworth, Hirst, and Jones, J., 1937, 549) and it appeared that this type of isomerisation might be a general feature of the ascorbic

(I.)  (II.)

acid group. In the present paper experiments on the methyl ethers of *d*-arabo-ascorbic acid are described. Since this analogue differs from ascorbic acid only in the configuration of the groups attached to C_5, an opportunity was presented to see what effects on the formation and stability of the new ring system might result from such a change in the stereochemical arrangement of the molecule.

The *d*-arabo-ascorbic acid (III) required was prepared by the action of sodium methoxide on methyl 2-keto-*d*-gluconate (Maurer and Schiedt, *Ber.*, 1933, **66**, 1054). The methylation of *d*-arabo-ascorbic acid with diazomethane proceeds in two well-marked stages. The first product, formed when the substance is titrated with diazomethane

(1 mol.), is 3-*methyl* d-*arabo-ascorbic acid* (IV), m. p. 102°, $[\alpha]_D$ — 26° in water. This acts as a monobasic acid towards alkali (without opening of the lactone ring), gives a blue colour with ferric chloride, thereby indicating that the hydroxyl at C_2 is not methylated, and displays a strong absorption band at λ 2450 A. (ε 9000) in slightly acidified water. In alkaline solution the head of the band moves to λ 2750 A. (ε *ca.* 7000). At this stage a difference between the behaviour of ascorbic acid and arabo-ascorbic acid manifests itself in that with the latter substance no trace is detectable of the isomeric ψ-derivative which accompanies the 3-methyl derivatives of both ascorbic acid and gluco-ascorbic acid when the methylation is carried out under these conditions.



The properties of 3-methyl arabo-ascorbic acid are very similar to those of 3-methyl ascorbic acid and on further methylation by diazomethane 2 : 3-*dimethyl* d-*arabo-ascorbic acid* (V) is produced as a syrup, $[\alpha]_D$ — 20° (in water), which shows a strong absorption band at 2380 A. In contrast with the behaviour of the monomethyl derivative, dimethyl *d*-arabo-ascorbic acid reacts towards alkali as a normal lactone, giving a salt by opening of the lactone ring. The salts display neither unsaturation nor selective absorption and we are inclined to the view that isomerisation with formation of the 3 : 6-oxide ring present in *iso*-dimethyl ascorbic acid takes place simultaneously with the fission of the lactone ring (VI). Lactonisation of the free acid does not result in regeneration of 2 : 3-dimethyl arabo-ascorbic acid and the product, *dimethyl* iso-d-*arabo-ascorbic acid* (VII), shows no selective absorption in the ultra-violet region and has properties exactly analogous with those of dimethyl *iso*-ascorbic acid. Occasionally, as is the case also with the latter substance, distillation of the *iso*-derivative results in rearrangement with formation of the normal 2 : 3-dimethyl arabo-ascorbic acid, but the conditions necessary for this could not be ascertained with any degree of certainty. An observation of special structural interest emerged from a study of the action of methyl-alcoholic hydrogen chloride on dimethyl *iso*-arabo-ascorbic acid. It has already been pointed out (Haworth, Hirst, Smith, and Wilson, *loc. cit.*) that the methoxyl group at C_3 in the *iso*-derivative is glucosidic in type and undergoes hydrolysis in the same way as that in ordinary glycosides. Strong confirmatory evidence of this comes from the observations that in anhydrous methyl-alcoholic hydrogen chloride (VII) remains unchanged, but when water is added, loss of methyl alcohol by hydrolysis takes place, accompanied by opening of the second ring and formation of 2-*methyl* d-*arabo-ascorbic acid* of normal structure (VIII). The latter, which resembles 2-methyl *l*-ascorbic acid in giving a red colour with ferric chloride, gives rise to the normal 2 : 3-dimethyl derivative (V) on methylation with diazomethane.

Experimental.

3-*Methyl* d-*Arabo-ascorbic Acid.*—To a solution of *d*-arabo-ascorbic acid (4 g.) in dry methyl alcohol, an ethereal solution of diazomethane was added slowly at — 10° until a faint yellow colour persisted. On removal of the solvent at 15° under diminished pressure, a syrup was

obtained which soon crystallised. The solid, after being triturated with acetone–light petroleum, was recrystallised from acetone, giving 3-*methyl* d-*arabo-ascorbic acid* in colourless needles, m. p. 102°, $[\alpha]_D^{20°}$ — 26° in water (*c*, 2·6). A further crop of crystalline material was obtained on concentration of the solvent used for trituration (total yield, 75%). The acid gave a blue colour with ferric chloride, required 1 equiv. of alkali for neutralisation of its aqueous solution (indicator, phenolphthalein), and reacted slowly with aqueous iodine in acid solution (Found: C, 44·1; H, 5·6; OMe, 16·5. $C_7H_{10}O_6$ requires C, 44·2; H, 5·3; OMe, 16·3%).

2 : 3-*Dimethyl* d-*Arabo-ascorbic Acid.*—This was obtained either by direct methylation of *d*-arabo-ascorbic acid by the above method, an excess of diazomethane being used, or by the treatment of the 3-methyl derivative in dry methyl alcohol with a slight excess of ethereal diazomethane at — 5°. It was a syrup (yield, quantitative) which could not be crystallised, $n_D^{20°}$ 1·4990, $[\alpha]_D^{20°}$ — 20° in water (*c*, 5·0), — 37° in methyl alcohol (*c*, 5·3) (Found: OMe, 30·5. $C_8H_{12}O_6$ requires OMe, 30·4%). It gave no colour with ferric chloride and did not react with iodine in aqueous solution. Its aqueous solution was neutral but reacted slowly with N/100-alkali, taking up finally 1 equiv. by opening of the lactone ring. The rotation of the sodium salt so formed was $[\alpha]_D^{20°}$ — 25° in water (*c*, 1·0). During the reaction with alkali the characteristic absorption band of 2 : 3-*dimethyl* d-*arabo-ascorbic acid* at λ 2380 A. (in water; ε, 9000) gradually disappeared and the sodium salt showed only general end-absorption.

Dimethyl iso-d-*Arabo-ascorbic Acid.*—2 : 3-Dimethyl *d*-arabo-ascorbic acid was allowed to react with a slight excess of N/20-barium hydroxide in an atmosphere of nitrogen, first at room temperature (30 mins.) and then at 50° for 30 minutes. The reaction was followed spectrophotometrically and its completion was indicated by the disappearance of the absorption band at λ2380 A. Sulphuric acid, equivalent to the barium hydroxide, was added and the precipitated barium sulphate was removed. The absorption spectrum of the solution at this stage had no trace of a band at λ2380 A. and consequently it was evident that no 2 : 3-dimethyl *d*-arabo-ascorbic acid had been regenerated. On evaporation of the aqueous solution *dimethyl* iso-d-*arabo-ascorbic acid* was obtained as a syrup, $n_D^{21°}$ 1·4980, which showed no tendency to crystallise. Its rotation in water was small ($[\alpha]_D$ *ca.* — 5°) and its absorption spectrum showed no band at λ2380 A. but merely end-absorption below λ2200 A. (Found: OMe, 28·4. $C_8H_{12}O_6$ requires OMe, 30·4%). It gave no colour with ferric chloride; its aqueous solution was neutral, but in presence of alkali it took up 1 equiv. Attempts were made to prepare from it an amide of the type so readily formed from dimethyl *iso-l*-ascorbic acid, but no crystalline derivative could be isolated.

On occasions simple distillation of the *iso*-derivative resulted in regeneration of normal 2 : 3-dimethyl *d*-arabo-ascorbic acid, b. p. *ca.* 140°/0·002 mm.; $[\alpha]_D^{20°}$ — 22° in water; OMe, 31·3%; absorption band at λ2380 A., which disappears in alkaline solution. On other occasions, however, the *iso*-derivative distilled unchanged at 145°/0·002 mm. and we were unable to determine the conditions governing the possibility of regeneration on distillation (compare Haworth, Hirst, Smith, and Wilson, *loc. cit.*).

When the *iso*-derivative (0·4 g.) was boiled with dry 3% methyl-alcoholic hydrogen chloride (30 c.c.), no absorption band appeared for some time. After 6 hours, a weak band corresponding to that of furfural (decomposition product) began to appear at λ2750 A. After neutralisation of the acid with silver carbonate, followed by filtration and removal of the solvent, dimethyl *iso-d*-arabo-ascorbic acid was recovered practically unchanged (no absorption band; no colour with ferric chloride; OMe, 28%). On the other hand, if the methyl-alcoholic hydrogen chloride contained 10% of water, an absorption band at λ2400—2450 A. quickly made its appearance and reached its maximum intensity in 8 hours. The product (yield, 75%), isolated in the usual way, was now a monomethyl derivative of normal structure, which, since it was not the 3-methyl derivative described above, must be the 2-*methyl* derivative. It gave a deep red colour with ferric chloride (compare 2-methyl *l*-ascorbic acid; *loc. cit.*) and its absorption spectrum had a single intense band at λ2400—2450 A. (Found: OMe, 16·5. $C_7H_{10}O_6$ requires OMe, 16·3%). On methylation with diazomethane (for conditions, see above) it gave normal 2 : 3-dimethyl *d*-arabo-ascorbic acid, characterised by the following properties: $n_D^{21°}$ 1·4985; $[\alpha]_D$ — 38° in methyl alcohol, — 19° in water; no colour with ferric chloride; neutral, but took up 1 equiv. of alkali when heated with N/10-sodium hydroxide; absorption band at λ2380 A. in neutral solution, no band in alkaline solution (Found: OMe, 29·9. Calc., 30·4%).

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