170. *Isomerisation of 2 : 3-Dimethyl Ascorbic Acid.*

By W. N. Haworth, E. L. Hirst, F. Smith, and W. J. Wilson.

The physical and chemical properties of ascorbic acid (I), 3-methyl ascorbic acid (II), 2 : 3-dimethyl ascorbic acid (III), and 2 : 3 : 5 : 6-tetramethyl ascorbic acid (Haworth, Hirst, and Smith, J., 1934, 1556) show that each of these substances contains the normal ring system of ascorbic acid (Herbert, Hirst, Percival, Reynolds, and Smith, J., 1933, 1270). It is clear also that when 2 : 3-dimethyl ascorbic acid is made to react with alkali the product is the salt of the open-chain acid (IV), the only unexpected observation at this stage being the loss of selective absorption when the lactone ring is opened. What has hitherto been by no means certain is the structure of the product formed when the salt (IV) is acidified by addition of mineral acid. We have shown previously that it is possible to regenerate 2 : 3-dimethyl ascorbic acid directly from the acid so formed and this we have been able to confirm (see later). But subsequent work by Micheel (*Annalen*, 1935, **519**, 70; 1936, **525**, 66) has revealed that direct regeneration of dimethyl ascorbic acid is not the normal course of the reaction and that the product usually obtained consists mainly of a structural isomeride of dimethyl ascorbic acid characterised by absence of selective absorption and by the possession of only one free hydroxyl group. As the result of these and other experiments with 6-trityl dimethyl ascorbic acid, which showed that a free hydroxyl group at C_6 was necessary for the occurrence of isomerisation, Micheel suggested various structural formulæ. Of these he considered (XI) and (V) to be the most likely and indicated a definite preference for (XI). Our experiments on the other hand lead us to the conclusion that (V) best represents the properties of iso*dimethyl ascorbic acid.*

By repetition of our earlier experiments we have confirmed the observation that under certain conditions regeneration of 2 : 3-dimethyl ascorbic is possible from the product obtained on acidification of (IV). The presence of some catalyst is probably necessary and somewhat drastic conditions are required. Under ordinary conditions the product is always the *iso*dimethyl ascorbic acid. The latter substance reacts readily with alcoholic ammonia, giving almost quantitatively the amide, $C_8H_{15}O_6N,CH_3{\cdot}OH$ (m. p. 120°), which is obtainable also, but with greater difficulty and in smaller yield, from ordinary dimethyl ascorbic acid. We have previously commented on the unexpected resistance of this amide to ozonisation and further peculiarities have now been observed. For instance it loses ammonia very readily and in cold methyl-alcoholic solution it undergoes transformation with change of rotation and production of a substance showing strong absorption at λ2300 A., indicating the re-establishment of the true ascorbic acid structure. It is possible, therefore, that the amide may have the structure (VI*b*) or (VI*c*) instead of (VI*a*) as formerly supposed. With sodium hydroxide it reacts normally, giving the salt (IV).

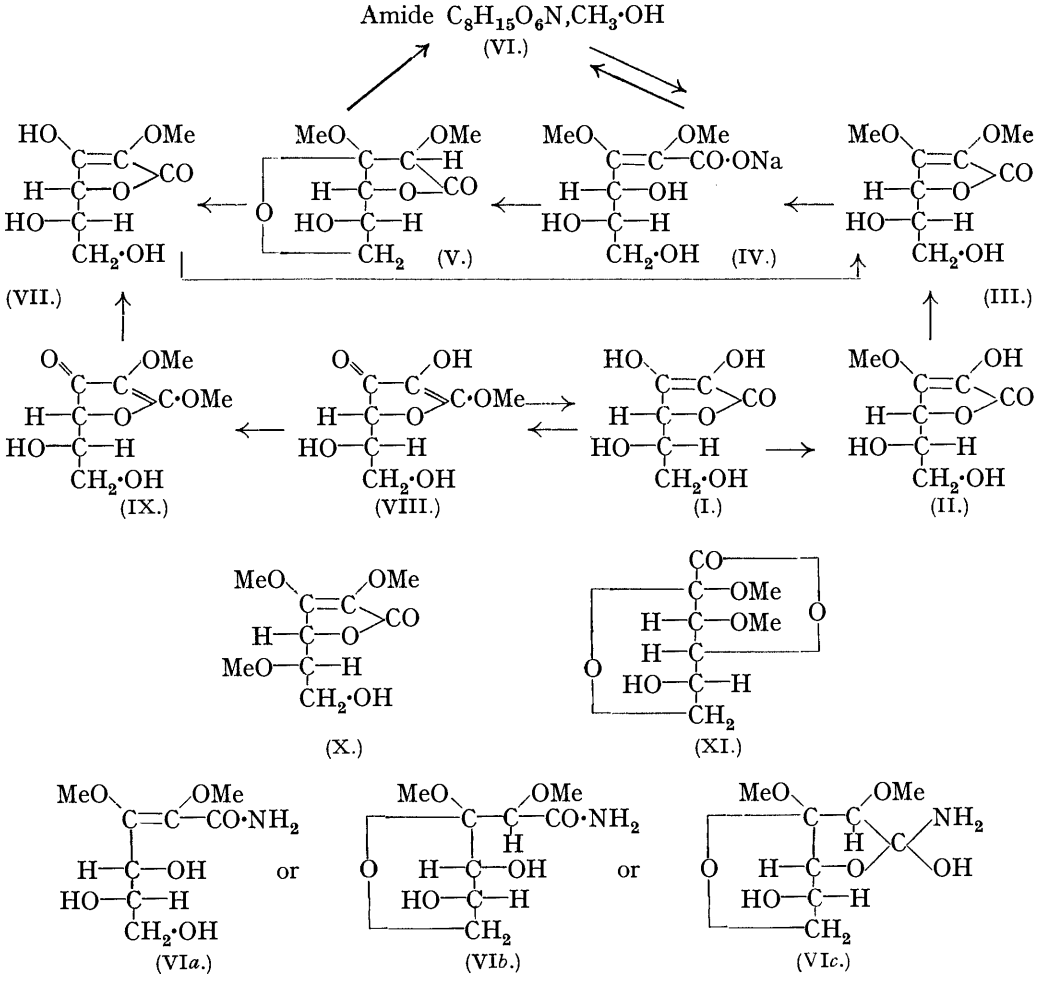
Inspection of the formula (V) reveals that the methoxyl group at C_3 is in reality glucosidic in type and is present in a ring system which is decidedly strained. It is to be expected, therefore, that this group would be labile in character and experiments show that this is indeed the case.

When boiled with methyl-alcoholic hydrogen chloride, *iso*dimethyl ascorbic acid gives a monomethyl ascorbic acid which has the true ascorbic acid structure. This substance has reducing properties, shows the type of absorption spectrum characteristic of ascorbic acid, and reacts smoothly with diazomethane, giving 2 : 3-dimethyl ascorbic acid. It differs from the known 3-methyl ascorbic acid in not giving a blue colour with ferric chloride and it must therefore be 2-*methyl ascorbic acid.*

Further information on this point is forthcoming from another source. When ascorbic acid reacts with one molecular proportion of diazomethane, two products can be isolated. One of these is the normal 3-methyl ascorbic acid, but the other possesses an absorption spectrum and a rotation value which indicate that it differs structurally from ascorbic acid. It was named tentatively 2(?)-methyl ascorbic acid (Haworth, Hirst, and Smith, J., 1934, 1560), but it now seems probable that it is the 1-methyl derivative (VIII) of one of the several possible tautomeric modifications of ascorbic acid and we propose to name it 1-methyl hetero-ascorbic acid. It loses methyl alcohol in cold aqueous solution, ascorbic

acid being regenerated. On methylation with diazomethane its structure remains unaltered and it yields a dimethyl derivative (IX) which again loses methyl alcohol in cold aqueous solution. The product is a monomethyl derivative which possesses the ordinary ascorbic acid structure and is identical with the monomethyl ascorbic acid (VII) derived from *iso*-dimethyl ascorbic acid by the action of methyl-alcoholic hydrogen chloride. There appears to be no question of enolisation involving a double bond between C_3 and C_4, since this would destroy the dissymmetry of C_4 and the products obtained from methyl hetero-ascorbic acid would in that event be expected to consist of derivatives of both ascorbic acid and its stereoisomeride, araboascorbic acid : only the former are found. No structure involving the usual double bond between C_2 and C_3 is possible and consequently we formulate methyl hetero-ascorbic acid with the double bond between C_1 and C_2 The labile methyl group in both the mono- and the di-methyl derivative of hetero-ascorbic acid must be on C_1, since hydrolysis of the dimethyl derivative gives 2-methyl ascorbic acid.

In the case of (VIII) and (IX) loss of the methyl group at C_1 results in rearrangement and re-formation of the valency system present in normal ascorbic acid. Such a reaction is by no means unusual and the most unexpected feature of the present series of experiments lies in the transformation from (IV) to (V) when lactonisation is accompanied by a second ring formation brought about by the saturation of the double bond between C_2 and C_3 by the hydroxyl group on C_6. Similar reactions have been recorded in the case of 2-carboxylic acids, but in the present instance the transformation is reversible. It appears, however,



that carlic acid (Clutterbuck, Raistrick, and Reuter, *Biochem. J.*, 1935, 873) provides a close analogy, for when the hydrated form of carlic acid is lactonised an additional ring is formed as the result of saturation of the double bond of the tetronic acid residue by a side-chain hydroxyl group. The reaction is reversible, the double bond being re-formed on hydration (for further comments on this reaction see Haworth, Hirst, and Jones, this vol., p. 549).

Micheel has already shown that the formation of the saturated *iso*-derivative does not take place if a triphenylmethyl ether group is substituted for the hydroxyl group at C_6. We have confirmed this, and also his observation that 6-trityl dimethyl ascorbic acid exists in two forms, and have further shown that isomerisation involves interaction between the double bond and the hydroxyl group at C_6.

The various reactions studied are summarised in the preceding schemes. In addition to the cycles of changes shown, transformations indicated by the stages (III)⟶(IV)⟶(V)⟶(VI) and (V)⟶(VII)⟶(III) have been completed also with 2 : 3 : 5-trimethyl ascorbic acid (X) as starting substance.

Experimental.

iso*Dimethyl* l-*Ascorbic Acid.*—In the following experiments crystalline dimethyl ascorbic acid, m. p. 63°, was employed as starting material. This can be obtained most conveniently by methylation of 3-methyl ascorbic acid with diazomethane (Haworth, Hirst, and Smith, *loc. cit.*). Direct transformation of ascorbic acid into the dimethyl derivative is also possible, but this procedure gives a product which crystallises more slowly. When dimethyl ascorbic acid was allowed to react with dilute barium hydroxide (1 mol. being taken up), the rotation changed to $[\alpha]_D^{20°}$ − 21° (concentration calculated on weight of dimethyl ascorbic acid), and the solution then displayed no selective absorption in the ultra-violet. The excess of barium hydroxide was removed by passing carbon dioxide, and the barium present as salt of the open-chain acid was exactly precipitated as sulphate by titration with dilute sulphuric acid. At this stage the rotation had the constant value − 14° and the solution showed only slight general absorption. Concentration of the solution under diminished pressure in absence of air left a stiff colourless syrup, which was slightly acid to litmus but titrated as a lactone. Its rotation varied in different experiments between $[\alpha]_D^{20°}$ − 10° and $[\alpha]_D^{20°}$ − 15° (both values in methyl alcohol). Usually it displayed no selective absorption, but occasionally a weak band at λ2300 A. was observed, the intensity of which corresponded to the presence of *ca.* 5% by weight of dimethyl ascorbic acid.

Purification of iso*dimethyl ascorbic acid* was effected by distillation in a high vacuum, b. p. 175°/0·03 mm. (bath temp.), $n_D^{18°}$ 1·4795, $[\alpha]_D^{22°}$ − 18° in methyl alcohol (*c*, 2·0). No selective absorption (Found : C, 46·8; H, 6·0; OMe, 30·3; equiv., by titration, 210. $C_8H_{12}O_6$ requires C, 47·0; H, 5·9; OMe, 30·4%; equiv., 204). The substance was non-reducing, behaved as a lactone, and readily gave the mono-*p*-nitrobenzoate, m. p. 180°, $[\alpha]_D^{21°}$ + 19° in chloroform (*c*, 1·7), described by Micheel (*loc. cit.*). Furthermore, on treatment with methyl-alcoholic ammonia, *iso*dimethyl ascorbic acid gave readily and in almost theoretical yield (contrast dimethyl ascorbic acid, which gives under similar conditions a yield of 25%), the amide $C_8H_{15}O_6N,CH_3{\cdot}OH$, m. p. 120° (Micheel and Kraft, *Z. physiol. Chem.*, 1933, **215**, 222; Herbert, Hirst, Percival, Reynolds, and Smith, *loc. cit.*) (Found : C, 42·7; H, 7·6; N, 5·3; OMe, 33·6. Calc. for $C_8H_{15}O_6N,CH_3{\cdot}OH$: C, 42·7; H, 7·5; N, 5·5; OMe, 36·8%).

When the amide (0·35 g.) was warmed with *N*/5-barium hydroxide at 60°, in an atmosphere of nitrogen, ammonia was evolved. When no more ammonia came over, carbon dioxide was passed to remove the excess of barium hydroxide. The solution now showed $[\alpha]_D$ − 16° (calc. on weight of amide used). A slight deficiency of sulphuric acid was added to remove almost all the barium and the solution was evaporated under reduced pressure. The syrup was dissolved in methyl alcohol, and ether added to precipitate the small remaining amount of barium salt. Evaporation of the solution then gave a syrup, $[\alpha]_D^{16°}$ − 14° in methyl alcohol (*c*, 1·7), which readily gave the mono-*p*-nitrobenzoate, m. p. 180°, and from which the amide, m. p. 120°, could easily be regenerated. The syrup did not display selective absorption. It was therefore *iso*-dimethyl ascorbic acid (Found : OMe, 30·6. Calc., 30·4%).

It was found also that the amide, although stable in cold aqueous solution, decomposes in boiling water with evolution of ammonia. After elimination of the ammonia and isolation of the product, *iso*dimethyl ascorbic acid was obtained. A solution of the amide in methyl alcohol had the initial value, $[\alpha]_D^{16°}$ − 24°, but the value was not constant and reached + 3° at the end of 3 days. The original solution showed no selective absorption (tested after dilution with methyl

alcohol such that the concentration was 10 mg. per 100 c.c.), but the final solution showed a strong absorption band at λ2300 A. (ε = 4000). It was observed also that when the amide was recrystallised from methyl alcohol, the mother-liquors had a positive rotation. It seems, therefore, that some transformation (possibly reversion to 2 : 3-dimethyl ascorbic acid) takes place in methyl alcohol and this may account for the observation that it is very difficult to raise the m. p. of the amide beyond 120° by recrystallisation from methyl alcohol. Samples which require little purification have m. p. 124°, as previously recorded.

Transformation of iso*Dimethyl Ascorbic into Dimethyl Ascorbic Acid.*—The direct transformation takes place somewhat capriciously. We have previously reported the regeneration of dimethyl ascorbic acid by heating the isomeric substance at 120°/0·1 mm. We have not been able to repeat this on all occasions, but in some experiments simple heating in a vacuum has resulted in regeneration of dimethyl ascorbic acid (yield, 80%). It is possible, however, that some catalyst was present, since specially purified and acid-free samples of *iso*dimethyl ascorbic acid could not be transformed in this way.

Action of Methyl-alcoholic Hydrogen Chloride on iso*Dimethyl Ascorbic Acid.*—It was shown in preliminary experiments that dimethyl ascorbic acid is recovered unchanged after being boiled for several hours with 3% methyl-alcoholic hydrogen chloride. When *iso*dimethyl ascorbic acid (2 g.) was boiled with 3% methyl-alcoholic hydrogen chloride for 12 hours, the rotation changed from $[\alpha]_D^{20°}$ — 14° to + 40° and a strong absorption band at λ2400 A. (ε = 8000) made its appearance. The solution was then divided into two portions, A and B (100 c.c. each). To the first portion (A) excess of an ethereal solution of diazomethane was added. After 24 hours at — 10° the solvent was removed, and the product extracted with ether containing a little water. On concentration of the ethereal solution the hydrate of dimethyl ascorbic acid crystallised, m. p. 59°, $[\alpha]_D^{23°}$ + 32° in methyl alcohol (*c*, 0·5) (Found : OMe, 27·5. Calc., 27·9%). It gave a di-*p*-nitrobenzoate, m. p. 171°, and on treatment with ammonia in methyl alcohol it gave (in the usual moderate yield) the amide, m. p. 119°.

The other portion (B) of the above solution was neutralised with barium carbonate. The neutral solution was evaporated to dryness, and the organic material dissolved in acetone. Removal of the acetone left a syrup, which was acidic and strongly reducing and gave a red colour with methyl-alcoholic ferric chloride. Its aqueous solution showed a strong absorption band at λ2450 A. (ε, 5000) (band at λ2600 A. in dilute alkali; ε, 6500). It consisted mainly of 2-*methyl ascorbic acid*, $[\alpha]_D$ + 10° in water (*c*, 1·5) (Found : OMe, 16·4. $C_7H_{10}O_6$ requires OMe, 16·3%). On methylation with diazomethane in the usual manner the monomethyl derivative gave quantitatively a syrup which had OMe 28%, $[\alpha]_D^{19°}$ + 23° in methyl alcohol (*c*, 0·3), showed a strong absorption band at λ2350 A. in aqueous solution, and gave the amide, m. p. 119°, on treatment with methyl-alcoholic ammonia. The syrup was extracted with ether, and the solution concentrated until a slight turbidity appeared. On cooling this solution, 2 : 3-dimethyl *l*-ascorbic acid monohydrate was deposited. This had m. p. 58°, $[\alpha]_D$ + 28° in water (*c*, 0·5), and an absorption band at λ2350 A. (ε, 10,000) which disappeared on addition of alkali. It was therefore mainly dimethyl ascorbic acid.

Monomethyl Hetero-ascorbic Acid (1 ?-*Methyl*).—It has already been shown (J., 1934, 1560) that methylation of ascorbic acid with diazomethane gives in small yield (besides 3-methyl ascorbic acid) another monomethyl derivative which has unusual properties and was provisionally named 2(?)-methyl ascorbic acid. This was prepared by the method described and had m. p. 162°, $[\alpha]_D^{20°}$ + 240° in methyl alcohol (*c*, 0·5), and showed in aqueous solution an intense absorption band at λ2800 A. (λ3200 A. in dilute alkali). An aqueous solution had $[\alpha]_D^{20°}$ + 200° (*c*, 1·5), but this value slowly fell to + 28° when the solution was kept at room temperature. Evaporation of the water at 40° in an atmosphere of nitrogen left *l*-ascorbic acid, m. p. 185° (no depression when mixed with an authentic sample of m. p. 189°) (Found : OMe, nil). The identity of the substance was confirmed by chemical and crystallographic examination.

Methylation of the methyl hetero-ascorbic acid with diazomethane gave the syrupy dimethyl derivative, $[\alpha]_D^{20°}$ + 107° in methyl alcohol; band at λ2700 A. in water (ε, 7000) (see J., 1934, 1560). When an aqueous solution of the dimethyl derivative was kept at 50° under nitrogen, the rotation decreased to + 9° and on removal of the water in an atmosphere of nitrogen (diminished pressure) a strongly acidic syrup was obtained which gave a red colour with methyl-alcoholic ferric chloride and showed an absorption band at λ2400—2450 A. in water (ε, 3600) (λ2600 A. in dilute alkali; ε, 4600), $[\alpha]_D^{19°}$ + 13° in water (*c*, 0·8) (Found : OMe, 21·0. Calc. for monomethyl ascorbic acid : OMe, 16·3%). It appeared to be mainly 2-methyl ascorbic acid (see above) and on methylation with diazomethane it gave syrupy 2 : 3-dimethyl ascorbic acid [band at λ2350 A. in water (ε, 5100), disappearing on addition of alkali] (Found : OMe, 28·9%).

The syrup was extracted with boiling ether and treated with light petroleum to give a turbid solution. After the latter had been kept for several hours at − 5°, crystalline 2 : 3-dimethyl *l*-ascorbic acid monohydrate separated. It had m. p. 58°, $[\alpha]_D^{15°}$ + 30° in water (*c*, 0·8), and an absorption band at λ2350 A. (ε, 10,000) which disappeared when the solution was made alkaline.

6-*Trityl* 2 : 3-*Dimethyl* l-*Ascorbic Acid.*—2 : 3-Dimethyl *l*-ascorbic acid (2·5 g.), prepared by the action of excess of diazomethane on *l*-ascorbic acid, was dissolved in pyridine (8 c.c.) and treated with trityl chloride (1·1 mols.). After being kept for 6—7 days at 20°, the mixture was poured into water. The insoluble syrup, after being triturated with water to remove pyridine, became solid and could be filtered off. It was thoroughly washed with water, dried, and recrystallised from methyl alcohol. Yield, after two recrystallisations, 3·3 g. M. p. 156°; $[\alpha]_D$ + 35° in chloroform (*c*, 1·0) (Found : C, 72·1; H, 6·4; OMe, 14·0. Calc. for $C_{27}H_{26}O_6$: C, 72·5; H, 5·9; OMe, 13·9%).

Examination of the mother-liquors revealed the presence of a small quantity of another crystalline substance, which had m. p. 178° after recrystallisation from methyl alcohol and $[\alpha]_D$ + 31° in chloroform (*c*, 0·8). It gave a depression of m. p. when mixed with the substance, m. p. 156° (Found : C, 72·6; H, 6·1; OMe, 13·9. Calc. for $C_{27}H_{26}O_6$: C, 72·6; H, 5·9; OMe, 13·9%).

Isomerisation of 6-trityl 2 : 3-dimethyl *l*-ascorbic acid (m. p. 156°) can be effected by boiling it for 5 minutes with a methyl-alcoholic solution of sodium hydroxide, potassium hydroxide, or sodium methoxide (3·5 mols.) (compare Micheel, *loc. cit.*). The solution is then nearly neutralised with methyl-alcoholic hydrogen chloride and poured into water, and the insoluble white precipitate filtered off. It was washed with water and recrystallised from methyl alcohol. The substance had m. p. 176° and gave no depression when mixed with the compound (m. p. 178°) obtained during tritylation of syrupy dimethyl *l*-ascorbic acid. The best method of bringing about the isomerisation was by dissolving 6-trityl 2 : 3-dimethyl *l*-ascorbic acid in methyl alcohol, followed by saturation with ammonia at room temperature. After 2 days the solution was evaporated and the crystalline isomeride, m. p. 178°, was isolated. It showed $[\alpha]_D$ + 36° in chloroform (*c*, 0·9) (Found : C, 72·7; H, 6·1; OMe, 14·1. Calc. for $C_{27}H_{26}O_6$: C, 72·6; H, 5·9; OMe, 13·9%).

The trityl residue could be removed from the two isomers by dissolving each in 10 parts of chloroform saturated with hydrogen chloride, and keeping the solution for 1 hour at 0° and 1 hour at 15°. The chloroform solution was then exhaustively extracted with water, and the combined aqueous extracts neutralised with silver carbonate, filtered, and evaporated to dryness under reduced pressure. The colourless syrup was extracted with ether; from the cooled ethereal solution, crystalline 2 : 3-dimethyl *l*-ascorbic acid monohydrate separated. It had m. p. 58—59°, $[\alpha]_D^{16°}$ + 30° in water (*c*, 1·0), and an absorption band at λ2350 A. (ε, 10,000).

Methylation of 6-*Trityl* 2 : 3-*Dimethyl* l-*Ascorbic Acid with Silver Oxide and Methyl Iodide.*—(a) The substance (m. p. 156°) (0·5 g.) was dissolved in methyl iodide (5 c.c.) and boiled in the presence of excess of silver oxide for 6 hours. The product was isolated by extraction with chloroform and after the chloroform solution had been dried over anhydrous magnesium sulphate the solvent was removed under diminished pressure. When recrystallised from alcohol–ether–light petroleum, the product had m. p. 133°, $[\alpha]_D$ + 31° in chloroform (*c*, 0·5) (Found : C, 73·2; H, 6·1; OMe, 20·2. $C_{28}H_{28}O_6$ requires C, 73·0; H, 6·1; OMe, 20·2%).

(b) The substance (0·2 g.), m. p. 174°, when treated as above gave rise to the same *trityl trimethyl* l-*ascorbic acid*, m. p. 131°, $[\alpha]_D$ + 31·5° in chloroform (*c*, 0·8) (Found : C, 73·4; H, 6·3; OMe, 19·5%). No depression in m. p. was observed when this material was mixed with the product from (a).

Preparation of 2 : 3 : 5-*Trimethyl* l-*Ascorbic Acid.*—6-Trityl 2 : 3-dimethyl *l*-ascorbic acid (1·3 g.) was dissolved in chloroform (10 c.c.) which had been saturated with hydrogen chloride at − 5°. After being kept for 1 hour at 0° and 1 hour at 15°, the solution was treated with water (20 c.c.), neutralised with silver carbonate, and filtered. The chloroform–water filtrate gave, on evaporation to dryness under diminished pressure at 35°, a crystalline residue containing triphenylcarbinol and 2 : 3 : 5-*trimethyl* l-*ascorbic acid*, from which the latter was extracted with water. Removal of the solvent under reduced pressure yielded a syrup (0·56 g.), which readily crystallised. 2 : 3 : 5-Trimethyl *l*-ascorbic acid separated well from ether–light petroleum and had m. p. 69—70°. It was readily soluble in water, alcohol, acetone, less soluble in ether, and insoluble in light petroleum. It did not reduce boiling Fehling's solution. In aqueous solution it showed selective absorption at λ2350 A. (ε, 11,200). The absorption disappeared on addition of alkali. $[\alpha]_D$ − 11·4° in water (*c*, 2·0) (Found : C, 49·3; H, 6·5; OMe, 42·7. $C_9H_{14}O_6$ requires C, 49·5; H, 6·5; OMe, 42·7%).

On treatment with *p*-nitrobenzoyl chloride in pyridine solution a *mono*-p-*nitrobenzoate* was obtained. This was recrystallised from aqueous alcohol and separated in needles, m. p. 118°. It was also obtained as plates, m. p. 103°, which subsequently solidified and remelted at 118°. A mixture of the two modifications had m. p. 118°. The substance showed no appreciable rotation in chloroform (*c*, 0·8) (Found : C, 52·6; H, 4·7; OMe, 24·2; N, 3·9. $C_{16}H_{17}O_9N$ requires C, 52·3; H, 4·7; OMe, 25·3; N, 3·82%).

iso*Trimethyl* l-*Ascorbic Acid*.—2 : 3 : 5-Trimethyl *l*-ascorbic acid (1 g.) in water (20 c.c.) was treated with a solution of 0·3*N*-barium hydroxide (20 c.c.). The specific rotation immediately changed from — 12° to — 47° and no further alteration in rotation occurred on warming for 30 minutes at 40°. The alkaline solution now showed no selective absorption in the ultra-violet. To the solution was then added a slight deficiency of 0·1*N*-sulphuric acid (59 c.c.) and after removal of barium sulphate the solvent was distilled under diminished pressure. The dry syrupy residue was taken up in ethyl alcohol, and excess of ether added. The small quantity of barium salt was filtered off, and the solution evaporated to dryness. The iso*trimethyl ascorbic acid* was a colourless, non-reducing, neutral syrup which had $[\alpha]_D^{15°}$ — 30° in methyl alcohol (*c*, 1·7) and showed no selective absorption in the ultra-violet (tested at 20 mg. %). The substance was distilled in a high vacuum, giving a colourless syrup, b. p. 115° (bath temp.)/0·01 mm., $n_D^{16°}$ 1·4655, which crystallised on keeping. After recrystallisation from ether–light petroleum the acid had m. p. 38°, $[\alpha]_D^{15°}$ — 34·8° in water (*c*, 2·3), and showed no selective absorption in the ultra-violet (tested at 20 mg. %). It was neutral and did not reduce Fehling's solution (Found : C, 49·4; H, 6·1; OMe, 42·3. $C_9H_{14}O_6$ requires C, 49·5; H, 6·5; OMe, 42·7%). When treated with methyl-alcoholic ammonia at 0° for 24 hours, the *iso*trimethyl ascorbic acid readily gave an *amide*, which could be crystallised from acetone; m. p. 115°, $[\alpha]_D^{16°}$ — 35·4° in methyl alcohol (*c*, 1·4), $[\alpha]_D$ — 39° in water (*c*, 1·3). It showed no selective absorption in water or methyl alcohol if examined immediately, but when a methyl-alcoholic solution of the amide was kept at 15° mutarotation took place and a band at λ2350 A. slowly made its appearance, showing that the ascorbic acid ring had been re-formed. In aqueous solution, however, the amide is quite stable, since no absorption band appears and the crystalline substance can be recovered unchanged by evaporation of the solvent under diminished pressure at 15°; m. p. 115° (Found : C, 45·7; H, 7·2; OMe, 38·0; N, 6·0. $C_9H_{17}O_6N$ requires C, 46·0; H, 7·3; OMe, 39·6; N, 5·96%).

Treatment of iso*Trimethyl* l-*Ascorbic Acid with Methyl-alcoholic Hydrogen Chloride*.—On boiling the *iso*trimethyl ascorbic acid (0·5 g.) with methyl-alcoholic hydrogen chloride (50 c.c. of 3%) the specific rotation changed from — 32° to + 3° (constant value) in 20 hours and an absorption band at λ2500 A. (ε, 7000) which had slowly been making its appearance reached a maximum. In alkaline solution this absorption moved to λ2600 A. (ε, 10,000). The acid methyl-alcoholic solution gave no colour with ferric chloride, but after neutralisation of the mineral acid a distinct red colour could be obtained. The removal of the methyl group on C_3 with the reformation of an ascorbic acid ring had therefore been effected. The solution was neutralised with silver carbonate, filtered, and divided into two portions, A and B.

Portion A gave after removal of solvent a syrup which had properties similar to those of 2-methyl *l*-ascorbic acid. Thus, it was acidic in nature, reduced boiling Fehling's solution, gave a red colour with ferric chloride, and had an absorption band at λ2500 A. which moved to λ2600 A. on addition of alkali. It had $[\alpha]_D^{15°}$ + 2·6° in water (*c*, 2·1) (Found : OMe, 34·0%). This high methoxyl value is probably due to the fact that the solution after refluxing with acid methyl alcohol still contains some unchanged *iso*trimethyl ascorbic acid. On methylation with diazomethane it yielded 2 : 3 : 5-trimethyl *l*-ascorbic acid; this displayed selective absorption at λ2350 A. (ε, 5500) which disappeared on the addition of alkali (Found : OMe, 40·0%).

Portion B was treated with excess of diazomethane and then evaporated under diminished pressure to a syrup. The latter was neutral, did not reduce Fehling's solution, and had $[\alpha]_D$ — 5° in water (*c*, 2·0). In aqueous solution it showed an absorption band at λ2350 A. (ε, 6600), which disappeared on addition of sodium hydroxide (Found : OMe, 41·0%). Portion B therefore consisted mainly of 2 : 3 : 5-trimethyl *l*-ascorbic acid. The syrup was extracted with boiling ether and kept at — 5° for 12 hours; crystalline 2 : 3 : 5-trimethyl *l*-ascorbic acid was then deposited. It had m. p. 68° and an absorption band at λ2320 A. (ε, 11,000).

The authors are indebted to the Department of Scientific and Industrial Research for grants to two of them (F. S. and W. J. W.).

THE UNIVERSITY OF BIRMINGHAM, EDGBASTON. [*Received, March 20th,* 1937.]