57. *Synthesis of the Bismethylamides of 2-Hydroxy-3-methoxy-*d*- and -*l*-erythrosuccinic Acid.*

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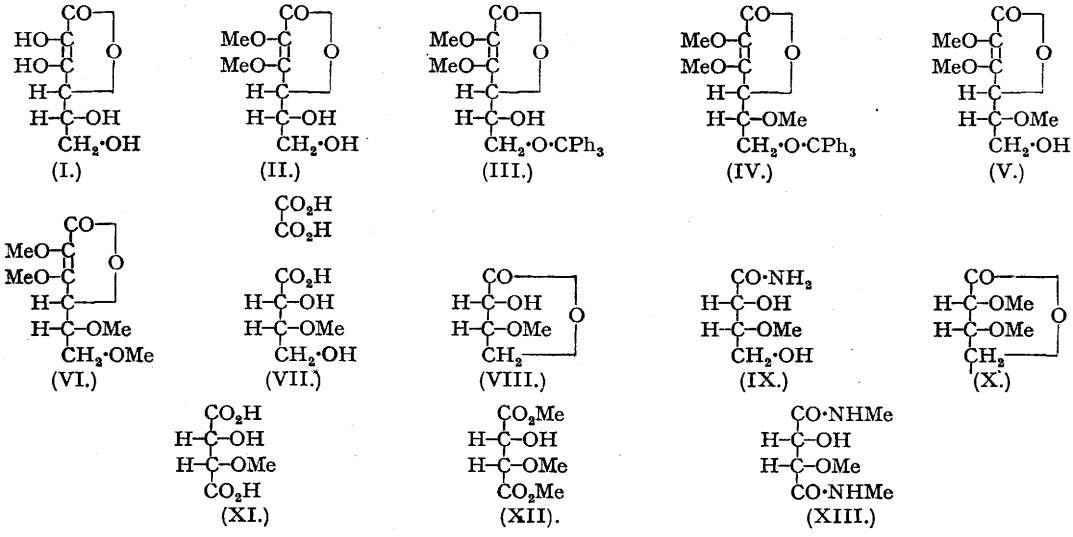
Methylation of mannosaccharodilactone either with diazomethane or with Purdie's reagents gives mainly 2 : 5-dimethyl Δ^4-mannosaccharo-3 : 6-lactone 1-methyl ester. The proof of the structure of this compound depended upon its transformation by ozonolysis and oxidation into a hitherto unknown hydroxymethoxyerythrosuccinic acid (see preceding paper). In order to determine the structure of the 2 : 5-dimethyl Δ^4-mannosaccharo-3 : 6-lactone 1-methyl ester it was necessary to establish the stereochemical configuration of the new hydroxymethoxyerythrosuccinic acid. This was achieved by the synthesis of the bismethylamides of the two enantiomorphic hydroxymethoxyerythrosuccinic acids.

The bismethylamide of 3-hydroxy-2-methoxy-*l*-erythrosuccinic acid (XIII), which may also be designated equally well as 2-hydroxy-3-methoxy-*d*-erythrosuccinic acid, was obtained from *d*-araboascorbic acid (I). The latter was transformed by successive stages into 2 : 3-dimethyl *d*-araboascorbic acid (II), 6-*trityl* 2 : 3-*dimethyl* d-*araboascorbic acid* (III), 6-*trityl* 2 : 3 : 5-*trimethyl* d-*araboascorbic acid* (IV), and thence into 2 : 3 : 5-*trimethyl* d-*araboascorbic acid* (V). Ozonisation of the last yielded 3-*methyl* d-*erythronic acid* (VII), which readily afforded a very stable *γ-lactone* (VIII). Oxidation of this lactone with nitric acid gave 2-hydroxy-3-methoxy-*d*-erythrosuccinic acid (or 3-hydroxy-2-methoxy-*l*-erythrosuccinic acid) (XI) and this, after esterification and treatment with methylamine, gave rise to the crystalline bismethylamide of 2-hydroxy-3-methoxy-*d*-erythrosuccinic acid (or 3-hydroxy-2-methoxy-*l*-erythrosuccinic acid) (XIII), m. p. 136°, $[\alpha]_D$ + 11° in water.

The *bismethylamide* of 3-hydroxy-2-methoxy-*d*-erythrosuccinic acid (XXIII), which may also be referred to as 2-hydroxy-3-methoxy-*l*-erythrosuccinic acid, was obtained from *meso*-tartaric acid (*i.e.*, dihydroxyerythrosuccinic acid). The latter was converted by means of methyl sulphate and sodium hydroxide solution into the racemic mixture of the hydroxymethoxyerythrosuccinic acids, which was resolved by means of brucine. The less water-soluble brucine salt afforded, upon treatment with alkali, followed by acid, 3-hydroxy-2-methoxy-*d*-erythrosuccinic acid (XXI), which after esterification, followed by treatment with methylamine, yielded the crystalline bismethylamide of 3-hydroxy-2-methoxy-*d*-erythrosuccinic acid (or 2-hydroxy-3-methoxy-*l*-erythrosuccinic acid) (XXIII), m. p. 135°, $[\alpha]_D$ −10·5° in water.

The bismethylamide of 2-hydroxy-3-methoxy-*d*-erythrosuccinic acid was obtained during the course of an investigation upon *d*-araboascorbic acid (I), which was obtained from methyl 2-keto-*d*-gluconate by the action of sodium methoxide (Maurer and Scheidt, *Ber.*, 1933, **66**, 1054). When *d*-araboascorbic acid (I) was allowed to react with an excess of ethereal diazomethane, the enolic hydroxy-groups in positions 2 and 3 underwent methylation, giving 2 : 3-dimethyl *d*-araboascorbic acid (II) (Hawkins, Hirst, and Jones, J., 1939, 246). Treatment of (II) in anhydrous pyridine with trityl chloride gave 6-*trityl* 2 : 3-*dimethyl* d-*araboascorbic acid* (III) and this upon complete methylation with silver oxide and methyl iodide yielded 6-*trityl* 2 : 3 : 5-*trimethyl* d-*araboascorbic acid* (IV). Saturation of a chloroform solution of the latter with hydrogen chloride readily removed the trityl group with the formation of 2 : 3 : 5-*trimethyl* d-*araboascorbic acid* (V), which yielded upon methylation with silver oxide and methyl iodide crystalline 2 : 3 : 5 : 6-*tetramethyl* d-*araboascorbic acid* (VI). The relationship of the 2 : 3-dimethyl (II), the 2 : 3 : 5-trimethyl (V) and the 2 : 3 : 5 : 6-tetramethyl *d*-araboascorbic acid (VI) is shown by the observation that all these substances exhibit an intense selective absorption band at λ 2350 A., as do the corresponding methyl derivatives of *l*-ascorbic acid (Haworth, Hirst, and Smith, *loc. cit.*; Haworth, Hirst, Smith, and Wilson, J., 1937, 829).



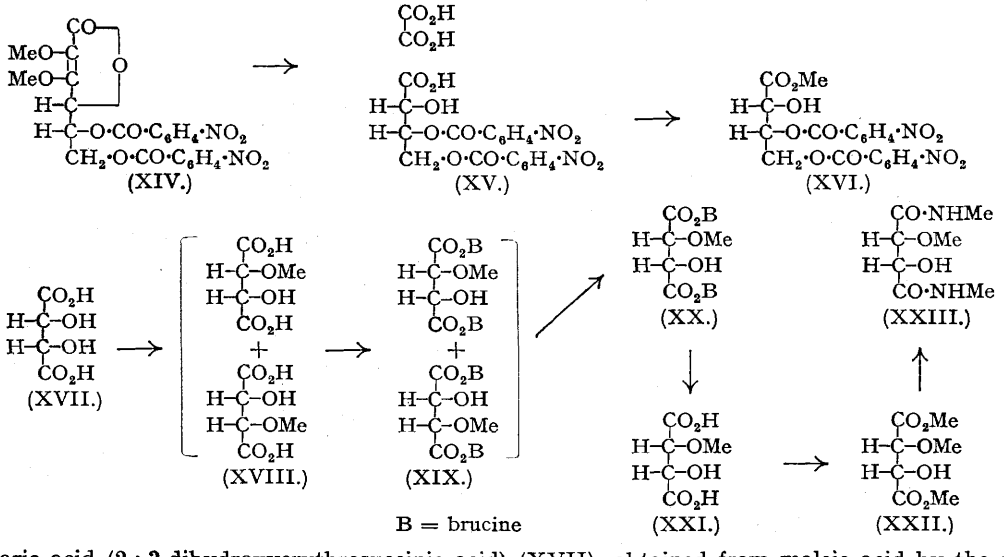
Ozonisation of 2 : 3 : 5-trimethyl *d*-araboascorbic acid (V), followed by hydrolysis, caused disruption of the double bond with the formation of oxalic acid and 3-methyl *d*-erythronic acid (VII), which upon esterification and subsequent distillation yielded crystalline 3-*methyl* d-*erythronolactone* (VIII). The presence of

the γ-lactone ring in the latter was supported by the fact that it showed no appreciable mutarotation in aqueous solution even after several months and reacted slowly in the cold with one equivalent proportion of sodium hydroxide. The 3-methyl *d*-erythronolactone (VIII) was characterised by its transformation into a crystalline *amide* (IX) and a crystalline *methylamide*. The positive Weerman test for α-hydroxy-amides (*Rev. Trav. chim.*, 1917, **36**, 16) shown by the amide (IX) proved that there must be a free hydroxy-group at C_2. The single methyl group is therefore located in position 3. These results lend strong support to the structure (I) assigned previously to *d*-araboascorbic acid by analogy with that proved for *l*-ascorbic acid (Baird, Haworth, Herbert, Hirst, Smith, and Stacey, J., 1934, **62**; Herbert, Hirst, Percival, Reynolds, and Smith, J., 1933, 1270). Further methylation of 3-methyl γ-*d*-erythronolactone (VIII) with silver oxide and methyl iodide gave 2 : 3-dimethyl γ-*d*-erythronolactone (X), characterised by its conversion into a crystalline *amide*.

The crystalline 3-methyl γ-*d*-erythronolactone (VIII) proved to be relatively stable to oxidation by nitric acid, probably because of the stability of the γ-lactone ring. Prolonged treatment with nitric acid, however, gave the corresponding dibasic acid (XI), from which the methyl ester (XII) was obtained by the action of either methyl-alcoholic hydrogen chloride or ethereal diazomethane. When this dimethyl ester (XII) was treated with methyl-alcoholic methylamine, the crystalline *bismethylamide* (XIII) of 2-hydroxy-3-methoxy-*d*-erythro-succinic acid (m. p. 136°; $[\alpha]_D$ + 11° in water) was obtained. This bismethylamide (XIII) was identical with that produced by the degradation of 2 : 5-dimethyl Δ^4-mannosaccharolactone methyl ester (see previous paper).

An attempt was then made to prepare the enantiomorph of 2-hydroxy-3-methoxy-*d*-erythrosuccinic acid, namely, 2-hydroxy-3-methoxy-*l*-erythrosuccinic acid, which is the same as 3-hydroxy-2-methoxy-*d*-erythro-succinic acid, from 5 : 6-*di*-p-*nitrobenzoyl* 2 : 3-*dimethyl* d-*araboascorbic acid* (XIV) as follows. Ozonisation of (XIV) in glacial acetic acid afforded a stable ozonide, which upon decomposition gave rise to oxalic acid and 3 : 4-di-*p*-nitrobenzoyl *d*-erythronic acid (XV), characterised as its crystalline *methyl* ester (XVI). It was expected that methylation of this methyl ester (XVI), followed by elimination of the *p*-nitrobenzoyl groups, would lead to the production of methyl 2-methoxy-*d*-erythronate and that this upon oxidation would give the required 3-hydroxy-2-methoxy-*d*-erythrosuccinic acid (XXI), the enantiomorph of 2-hydroxy-3-methoxy-*d*-erythrosuccinic acid. This scheme failed, however, because of the ease with which the *p*-nitrobenzoyl groups were split off from the methyl ester of 3 : 4-di-*p*-nitrobenzoyl *d*-erythronic acid (XVI) when it was methylated either with silver oxide and methyl iodide or with diazomethane. The ready removal of the *p*-nitrobenzoyl groups is probably dependent upon the weakening of the ester link caused by the electronic influence of the *p*-nitrophenyl group (Kindler, *Annalen*, 1926, **450**, 1; 1927, **452**, 90).

A successful isolation of 3-hydroxy-2-methoxy-*d*-erythrosuccinic acid (XXI) was achieved, however, by resolution of the *dl*-mixture of the monomethyl derivatives of *meso*-tartaric acid by means of brucine. The



meso-tartaric acid (2 : 3-dihydroxyerythrosuccinic acid) (XVII), obtained from maleic acid by the action of sodium chlorate in the presence of osmium tetroxide (Miles and Terry, *J. Amer. Chem. Soc.*, 1925, **47**, 1415), gave upon treatment with methyl sulphate and sodium hydroxide (cf. Haworth, J., 1915, **107**, 15), the *dl*-mixture (XVIII) of the hydroxymethoxyerythrosuccinic acids. This racemic mixture of acids (XVIII) was purified by crystallisation of the corresponding diamides, and from the *dl*-mixture of the latter the racemic mixture of acids was regenerated. The mixture of the neutral brucine salts (XIX) of the hydroxymethoxy-erythrosuccinic acids readily crystallised and repeated fractional crystallisation afforded the less soluble brucine salt (XX) of 3-hydroxy-2-methoxy-*d*-erythrosuccinic acid. Treatment of this brucine salt with barium hydroxide yielded the barium salt of 3-hydroxy-2-methoxy-*d*-erythrosuccinic acid (XXI) and this upon boiling

with methyl-alcoholic hydrogen chloride gave methyl 3-hydroxy-2-methoxy-*d*-erythrosuccinate (XXII). When the latter was allowed to react with methyl-alcoholic methylamine, there was obtained the required crystalline *bismethylamide* (XXIII) of 3-hydroxy-2-methoxy-*d*-erythrosuccinic acid (m. p. 135°; $[\alpha]_D$ — 10·5° in water), the enantiomorph of (XIII).

Experimental.

d-*Araboascorbic Acid* (I).—To a boiling solution of methyl 2-keto-*d*-gluconate (26 g.) in dry methyl alcohol (100 c.c.), through which a stream of nitrogen was bubbled, there was added with shaking a dry methyl-alcoholic solution (80 c.c.) of sodium methoxide (1 equiv.). The boiling was continued for 1—2 minutes and most of the precipitate of sodium *d*-araboascorbate appeared to have separated. The solution was cooled in ice and the sodium *d*-araboascorbate was converted into *d*-araboascorbic acid by the addition of methyl-alcoholic hydrogen chloride (1 equiv.). The solution was filtered, and evaporated to dryness under diminished pressure in an atmosphere of carbon dioxide, and the solid residue was extracted with ethyl alcohol until the insoluble sodium chloride was free from *d*-araboascorbic acid (tested with iodine and with Fehling's solution). Concentration of the filtrate gave *d*-araboascorbic acid (16 g.), m. p. and mixed m. p. 169°, $[\alpha]_D^{18°}$ — 14° in water (*c*, 0·8), after recrystallisation from ethyl alcohol (15·6 mg. reacted with 9·1 c.c. of N/50-iodine, corresponding to M = 172) (Found: C, 41·0; H, 4·2. Calc. for $C_6H_8O_6$: C, 40·8; H, 4·6%). Aqueous solutions of *d*-araboascorbic acid showed an intense band at λ *ca.* 2450 A., ε approx. 7500 (*c*, 3·2 mg. %).

2 : 3-*Dimethyl* d-*Araboascorbic Acid* (II).—A solution of *d*-araboascorbic acid (16 g.) in a small volume of dry methyl alcohol was treated for 2 days at — 5° with a slight excess of an ethereal solution of diazomethane. The volume of methyl alcohol should be sufficient to prevent precipitation of the *d*-araboascorbic acid when the ethereal solution of diazomethane is added. The persistent yellow colour of the solution, after evolution of nitrogen had ceased, indicated that an excess of diazomethane was present. Removal of a small amount of flocculent precipitate from the solution by filtration, followed by evaporation to dryness under diminished pressure, gave syrupy 2 : 3-dimethyl *d*-araboascorbic acid (18 g.), $[\alpha]_D^{20°}$ — 14° in water (*c*, 1·0) (Found: OMe, 33·0. Calc. for $C_8H_{12}O_6$: OMe, 30·4%). In aqueous solution 2 : 3-dimethyl *d*-araboascorbic acid shows a band at λ 2350 A., ε approx. 7000 (*c*, 4·0 mg./100 c.c.), disappearing upon the addition of a slight excess of sodium hydroxide.

6-*Trityl* 2 : 3-*Dimethyl* d-*Araboascorbic Acid* (III).—A solution of the syrupy 2 : 3-dimethyl *d*-araboascorbic acid (16·4 g.) in anhydrous pyridine (20 c.c.) was treated with triphenylmethyl chloride (25 g.) at room temperature for 5 days. After the reaction had been proceeding for 2 days the mixture was warmed for 5 minutes on the hot water-bath and this was again repeated on the third day. On the fifth day the reaction mixture was poured into water and the insoluble material was triturated to remove as much pyridine as possible. After purification by recrystallisation from methyl alcohol, followed by crystallisation from acetone–light petroleum, the 6-*trityl* 2 : 3-*dimethyl* d-*araboascorbic acid* had m. p. 174°, $[\alpha]_D^{18°}$ — 41° in chloroform (*c*, 1·0) (Found: C, 72·3; H, 6·85; OMe, 14·2. $C_{27}H_{26}O_6$ requires C, 72·5; H, 6·8; OMe, 13·9%). The crystals tend to retain methyl alcohol. Unlike the 6-trityl 2 : 3-dimethyl *l*-araboascorbic acid, this 6-trityl 2 : 3-dimethyl *d*-araboascorbic acid was not affected by treatment with methyl-alcoholic ammonia (cf. Micheel, *Annalen*, 1935, **510**, 70; Haworth, Hirst, Smith, and Wilson, *loc. cit.*).

6-*Trityl* 2 : 3 : 5-*Trimethyl* d-*Araboascorbic Acid* (IV).—Three treatments of 6-trityl 2 : 3-dimethyl *d*-araboascorbic acid (2 g.) with silver oxide and methyl iodide in the usual manner effected complete methylation of the compound. The methyl iodide was distilled off, and the product extracted with acetone. Removal of the solvent gave 6-*trityl* 2 : 3 : 5-*trimethyl* d-*araboascorbic acid* (2·0 g.) as a glass, $[\alpha]_D^{18°}$ — 28° in chloroform (*c*, 1·0) (Found: OMe, 20·4. $C_{28}H_{28}O_6$ requires OMe, 20·2%).

2 : 3 : 5-*Trimethyl* d-*Araboascorbic Acid* (V).—A solution of 6-trityl 2 : 3 : 5-trimethyl *d*-araboascorbic acid (12·0 g.) in a mixture of chloroform (200 c.c.) and methyl alcohol (10 c.c.) was cooled in an ice-bath and saturated with dry hydrogen chloride. After keeping for 1 hour at 0°, the ice-bath was removed and after a further 2 hours as much hydrogen chloride as possible was removed from the solution by aeration under diminished pressure. The chloroform solution was then exhaustively extracted with water; the aqueous extracts were combined, neutralised with lead carbonate, filtered, and evaporated to dryness under reduced pressure. The syrupy product was purified by extraction with acetone (yield, 3·8 g.) (Found: OMe, 41·0%). The product distilled as a colourless oil (3·0 g.), b. p. (bath temp.) 170°/0·02 mm., $n_D^{18°}$ 1·4880, $[\alpha]_D^{18°}$ + 9° in water (*c*, 1·0), absorption band at λ 2350 A. (ε, 10,000) (*c*, 3·4 mg. % in water) (Found: OMe, 42·3%). On cooling, the distillate crystallised; the crystals were separated by tiling and after recrystallisation from dry ether the 2 : 3 : 5-*trimethyl* d-*araboascorbic acid* had m. p. 74°, $[\alpha]_D^{22°}$ + 10° in water (*c*, 0·8) (Found: C, 49·6; H, 6·5; OMe, 43·1. $C_9H_{14}O_6$ requires C, 49·6; H, 6·4; OMe, 42·6%). Aqueous solutions of the crystalline 2 : 3 : 5-trimethyl *d*-araboascorbic acid show an intense band at λ 2350 A., ε approx. 11,000 (*c*, 3 mg. %).

2 : 3 : 5 : 6-*Tetramethyl* d-*Araboascorbic Acid* (VI).—Two methylations of crystalline 2 : 3 : 5-trimethyl *d*-araboascorbic acid (0·45 g.) with silver oxide (1 g.) and methyl iodide (3 c.c.) were sufficient to introduce the methoxyl group into position 6. After each methylation the product was isolated by means of acetone. The compound distilled as a colourless liquid (0·4 g.), b. p. (bath temp.) 130°/0·02 mm., $n_D^{22°}$ 1·4695, $[\alpha]_D^{20°}$ + 9·5° in water (*c*, 0·5), absorption band at λ 2350 A., ε approx. 10,000 (*c*, 3 mg.% in water) (Found: OMe, 53·0. $C_{10}H_{16}O_6$ requires OMe, 53·4%).

Ozonisation of 2 : 3 : 5-*Trimethyl* d-*Araboascorbic Acid.*—A solution of the acid (3·0 g.) in glacial acetic acid (30 c.c.) was subjected to the action of a stream of ozonised oxygen at room temperature. The solution showed $[\alpha]_D^{19°}$ — 1° (initial value); — 2·5° (after 3 hours); + 1° (6 hours); + 8° (8 hours); + 30° (12 hours); + 41° (14 hours); + 52° (17 hours). The solution was diluted with water, freed from water and acetic acid by evaporation under reduced pressure, and neutralised with barium hydroxide, and the barium oxalate (85% of the theoretical) removed. The filtrate containing the soluble barium salt of 3-methyl *d*-erythronic acid was evaporated under diminished pressure at 40°, and the dry residue (3·14 g.) boiled with methyl-alcoholic hydrogen chloride (200 c.c.). Sufficient hydrogen chloride was used to liberate the free acid from the barium salt and to give a solution of 1% hydrogen chloride with which to effect esterification, which was brought about by boiling the solution for 8 hours. The solution was neutralised with silver carbonate, filtered, and evaporated under reduced pressure to dryness. The product was purified by extraction with ether to remove inorganic impurity and then distilled, giving fraction I (0·6 g.), b. p. (bath temp.) 152°/0·04 mm., $n_D^{19°}$ 1·4565—1·4572, fraction II (0·51 g.), b. p. (bath temp. 200—210°/0·05 mm., $n_D^{19°}$ 1·4700.

Examination of fraction I. Isolation of 3-*methyl* d-*erythronolactone* (VIII). This fraction crystallised spontaneously and after 1 hour the crystals were freed from adhering syrup by trituration with ethyl alcohol–ether. After two recrystallisations from ethyl alcohol–ether the 3-*methyl* d-*erythronolactone* (0·1 g.) had m. p. 113°, $[\alpha]_D^{19°}$ — 108° in water (*c*, 4·0). No appreciable change in rotation took place after this solution had been kept for several months. The lactone reacted slowly when titrated directly with 0·01N-sodium hydroxide; on being kept for 1 hour with an excess of 0·01N-sodium hydroxide in the cold, followed by back-titration with 0·01N-sulphuric acid, one equivalent proportion was taken up (8·19 mg. required for neutralisation 7·14 c.c. of 0·01N-sodium hydroxide, corresponding to an equivalent weight of 127. Calc., 131) (Found: C, 45·1; H, 6·5; OMe, 23·4. $C_5H_8O_4$ requires C, 45·4; H, 6·1; OMe, 23·5%).

Treatment of the crystalline 3-methyl *d*-erythronolactone with methyl-alcoholic ammonia furnished the crystalline

amide (IX) of 3-methyl *d*-erythronic acid, which after recrystallisation from ethyl alcohol had m. p. 105°, $[\alpha]_D^{18°}$ + 36° in water (*c*, 1·0) (Found: C, 40·9; H, 7·6; N, 9·4; OMe, 20·6. $C_5H_{11}O_4N$ requires C, 40·3; H, 7·4; N, 9·4; OMe, 20·8%). When this amide (20 mg.) was treated for 30 minutes with 1·5N-sodium hypochlorite under the standard conditions for a Weerman reaction, it gave a positive test (see Smith, J., 1939, 753), because upon the addition of excess of solid sodium acetate and semicarbazide hydrochloride a precipitate of hydrazodicarbonamide, m. p. and mixed m. p. 254°, was obtained.

With methyl-alcoholic methylamine the 3-methyl *d*-erythronolactone gave the crystalline *methylamide* of 3-methyl *d*-erythronic acid, m. p. 82°, $[\alpha]_D^{17°}$ + 57·5° in methyl alcohol (*c*, 2·1) (Found: C, 44·5; H, 8·2; N, 8·6; OMe, 18·3. $C_6H_{13}O_4N$ requires C, 44·2; H, 8·0; N, 8·6; OMe, 19·0%).

Methylation of 3-*Methyl* d-*Erythronolactone*.—The crystalline 3-methyl *d*-erythronolactone (100 mg.) was dissolved in methyl iodide (3 c.c.) and refluxed for 7 hours in the presence of silver oxide (1 g.) with frequent shaking. The product was isolated by means of acetone and subjected to a second methylation in the same way. The product, a liquid which failed to crystallise after several days, was treated with methyl-alcoholic ammonia for 2 days at − 5°. Removal of the solvent gave the *amide* of 2 : 3-dimethyl *d*-erythronic acid, m. p. 72°, $[\alpha]_D^{21°}$ + 55·5° in water (*c*, 1·8), after recrystallisation from acetone–ether (Found: OMe, 38·3; N, 9·5. $C_6H_{13}O_4N$ requires OMe, 38·2; N, 9·4%).

Oxidation of 3-*Methyl* d-*Erythronolactone with Nitric Acid and the Isolation from the Bismethylamide of* 2-*Hydroxy*-3-*methoxy*-d-*erythrosuccinic Acid* (XIII).—Concentration of the mother-liquors from the crystallisation of the crystalline 3-methyl *d*-erythronolactone gave a syrupy crystalline product (0·5 g.). This was treated for 24 hours at 50° with nitric acid (10 c.c. of a solution made by mixing equal volumes of nitric acid, *d* 1·42, and water). The solution was then diluted with water, and the solvent removed by distillation under diminished pressure, methyl alcohol being added in the final stages to decompose any remaining traces of nitric acid. The dry syrupy acidic product was then boiled for 8 hours with 1% methyl-alcoholic hydrogen chloride (20 c.c.). Neutralisation of the mineral acid with silver carbonate, followed by removal of the solvent, gave a syrup, which was purified by extraction with ether and then distilled giving fraction I (0·1 g.), b. p. (bath temp.) 130°/0·04 mm., $n_D^{19°}$ 1·4466, $[\alpha]_D^{18°}$ − 34° in methyl alcohol (*c*, 2·0) (Found: OMe, 46·5; equiv., 97. $C_7H_{12}O_6$ requires OMe, 48·4%; equiv., 96), and fraction II, b. p. (bath temp.) 160°/0·04 mm., $n_D^{19°}$ 1·4560. This fraction readily crystallised and gave the unchanged lactone, m. p. and mixed m. p. 113° (after recrystallisation from ethyl alcohol).

Treatment of fraction I (40 mg.) with methyl-alcoholic methylamine for 24 hours at room temperature, followed by removal of the solvent, yielded the *bismethylamide* of 2-hydroxy-3-methoxy-*d*-erythrosuccinic acid, m. p. 136°, $[\alpha]_D^{18°}$ +11° in water (*c*, 2·5) (after recrystallisation from ethyl acetate). This bismethylamide gave no depression when mixed with that obtained from 2 : 5-dimethyl Δ^4-mannosaccharolactone methyl ester (previous paper) (Found: C, 44·3; H, 6·8; N, 14·8; OMe, 16·2. $C_7H_{14}O_4N_2$ requires C, 44·2; H, 7·4; N, 14·7; OMe, 16·3%).

In another experiment pure crystalline 3-methyl *d*-erythronolactone (0·1 g.) was oxidised for 48 hours at 60° with nitric acid (4 c.c. of a solution made by mixing equal volumes of nitric acid, *d* 1·42, and water). The solution was diluted with water and the product was freed from solvent and nitric acid as described above. In this way there was obtained a syrupy crystalline mass; the crystals and syrup were separated by means of alcohol. The crystals proved to be unchanged 3-methyl *d*-erythronolactone, m. p. and mixed m. p. 113°. The crystals and syrup were recombined and subjected to oxidation with the same amount of nitric acid for 5 hours at 90°. This reaction gave unchanged crystalline lactone (60 mg.) and a syrup (30 mg.) which reacted strongly acid to Congo-paper. This syrupy acid was dissolved in ether and esterified by treatment with a slight excess of an ethereal solution of diazomethane for 5 minutes at 0°. Removal of the solvent gave a neutral syrup which, when treated with methyl-alcoholic methylamine for 24 hours at room temperature, afforded the crystalline bismethylamide of 2-hydroxy-3-methoxy-*d*-erythrosuccinic acid (15 mg.), m. p. 135°, $[\alpha]_D^{18°}$ + 11° in water (*c*, 4·5) (after recrystallisation from ethyl acetate).

5 : 6-*Di*-p-*nitrobenzoyl* 2 : 3-*Dimethyl* d-*Araboascorbic Acid* (XIV).—A solution of 2 : 3-dimethyl *d*-araboascorbic acid (2·5 g.) in dry pyridine (5 c.c.) was allowed to react with *p*-nitrobenzoyl chloride (2·3 g.) for 48 hours at room temperature. The mixture was then warmed for 5 minutes at 60° in order to complete the reaction, cooled, and poured with stirring into water. The *p*-nitrobenzoyl derivative was extracted with chloroform, and the chloroform solution repeatedly washed with sodium bicarbonate solution to remove *p*-nitrobenzoic acid. After drying over anhydrous magnesium sulphate, the chloroform solution was evaporated to dryness under reduced pressure and there was obtained 5 : 6-*di*-p-*nitrobenzoyl* 2 : 3-*dimethyl* d-*araboascorbic acid* (4·2 g.) as a glass (Found: OMe, 8·9. $C_{22}H_{20}O_{12}N_2$ requires OMe, 8·9%).

Methyl 3 : 4-*Di*-p-*nitrobenzoyl* d-*Erythronate* (XVI).—A stream of ozonised oxygen was passed through a solution of the 5 : 6-di-*p*-nitrobenzoyl 2 : 3-dimethyl *d*-araboascorbic acid (4 g.) in glacial acetic acid (50 c.c.) for 15 hours at room temperature; the specific rotation changed from +15° to +23°. The presence of oxalate in the reaction mixture after 15 hours' ozonolysis could not be detected. The solution was diluted with water and freed from solvent by evaporation under diminished pressure. Methyl alcohol was added from time to time to the product during the last stages of the distillation to remove traces of acetic acid. The syrupy product thus obtained crystallised on keeping. After recrystallisation from aqueous ethyl alcohol, the *methyl* 3 : 4-*di*-p-*nitrobenzoyl* d-*erythronate* had m. p. 133°, $[\alpha]_D^{17°}$ + 29° in chloroform (*c*, 1·3) (Found: C, 50·9; H, 3·6; N, 6·4; OMe, 6·8. $C_{19}H_{16}O_{11}N_2$ requires C, 50·9; H, 3·6; N, 6·2; OMe, 6·9%).

Methylation of the methyl 3 : 4-di-*p*-nitrobenzoyl *d*-erythronate either with Purdie's reagents or with diazomethane effected the elimination of the *p*-nitrobenzoyl groups as methyl *p*-nitrobenzoate, m. p. and mixed m. p. 92° (after recrystallisation from ethyl alcohol).

Methylation of meso-*Tartaric Acid*.—*meso*-Tartaric acid (10 g.), prepared by the method of Miles and Terry (*J. Amer. Chem. Soc.*, 1925, **47**, 1415), was dissolved in sodium hydroxide (100 c.c. of a 30% solution) at 55°. Methyl sulphate (100 c.c.) and sodium hydroxide (200 c.c. of a 30% solution) were then added slowly during 3 hours to the solution at 55—60° with vigorous stirring. The reaction mixture was heated for 30 minutes at 90°, cooled, and made acid by the addition of 5N-sulphuric acid. The cold solution was filtered to remove sodium sulphate and, while still acid, was distilled under reduced pressure for a sufficient length of time to remove all carbon dioxide. It was then neutralised with sodium hydroxide, treated with 5N-sulphuric acid (20 c.c.) in order to liberate 60% of the organic acid, and concentrated to dryness under diminished pressure, and the organic acid extracted with acetone–ether. Removal of the solvent gave an acidic syrup, which was freed from a little sodium sulphate by extraction with ether. From the ethereal solution there was obtained an acidic syrup (4 g.). Further treatment of an aqueous solution of the residues of the sodium salt with more 5N-sulphuric acid (10 c.c.), followed by evaporation to dryness and extraction with acetone–ether, gave a further amount of the crude syrupy monomethyl derivative (2 g.).

The syrupy mixture (6 g.) of the monomethyl derivatives of *meso*-tartaric acid was esterified by boiling for 8 hours with 1% methyl-alcoholic hydrogen chloride (300 c.c.). The solution was cooled, neutralised with barium carbonate, filtered, and evaporated to dryness. The residue was extracted with acetone–ether and upon removal of the solvent there was obtained a mixture of syrup and crystals. The latter were separated by trituration with ether and after recrystallisation from acetone–ether the crystals (0·6 g.) had m. p. 114° alone or when mixed with methyl *meso*-tartrate. Concentration of the ethereal solution, after separation of the crystalline methyl *meso*-tartrate, yielded a syrup, which

was distilled, giving: Fraction I (a racemic mixture of the two forms of hydroxymethoxyerythrosuccinic acid) (2·6 g.), b. p. (bath temp.) 100—105°/0·04 mm., $n_D^{18°}$ 1·4400. Fraction II, methyl *meso*-tartrate (1·8 g.), b. p. (bath temp.) 130—140°/0·04 mm., $n_D^{18°}$ 1·4440, m. p. 114° (after crystallisation from acetone–ether).

Treatment of fraction I with methyl-alcoholic ammonia for 3 days at −5° gave the amide of the racemic hydroxymethoxyerythrosuccinic acid, m. p. 191° (after two recrystallisations from water). The free acid was then regenerated by heating the amide (2·3 g.) with N-sodium hydroxide (30 c.c.) for 45 minutes at 60°. Addition of N-sulphuric acid (198 c.c.), followed by removal of the solvent and extraction of the dry residue with acetone–ether, gave a syrupy racemic mixture (XVIII) of the hydroxymethoxyerythrosuccinic acids (2·3 g.).

Resolution of the Racemic Mixture of Hydroxymethoxyerythrosuccinic Acids.—An attempt to resolve the racemic acids by means of the half cinchonine salt had to be abandoned because the salt failed to crystallise.

The acid was therefore converted into the neutral brucine salt by adding an alcoholic solution of brucine to a solution of the hydroxymethoxyerythrosuccinic acid (2·1 g.) in ethyl alcohol (15 c.c.). Removal of the solvent gave a crystalline brucine salt, $[\alpha]_D^{18°}$ − 23° in water (*c*, 0·7) (after recrystallisation from water).

A further quantity of *meso*-tartaric acids (15 g.) was methylated as described above, methyl sulphate (100 c.c.) and sodium hydroxide (300 c.c. of a 30% solution) being used. Esterification of the partially methylated acid afforded an ester (6·0 g.), which was distilled, giving: Fraction I (0·47 g.), methyl dimethyl *meso*-tartrate, b. p. (bath temp.) 80—95°/0·01 mm., $n_D^{19°}$ 1·4390, recognised by its transformation into the crystalline bismethylamide, m. p. and mixed m. p. 202°. Fraction II, racemic methyl hydroxymethoxyerythrosuccinate (3·63 g.), b. p. (bath temp.) 96—98°/0·01 mm., $n_D^{19°}$ 1·4410. Fraction III, methyl *meso*-tartrate (1·85 g.), b. p. 130—140°/0·02 mm., $n_D^{19°}$ 1·4440, m. p. 114° (after crystallisation from acetone–ether).

Fraction II was treated with N-sodium hydroxide (50 c.c.) for 45 minutes at 60°; N-sulphuric acid (49·5 c.c.) was added, and the solution evaporated to dryness, giving the syrupy racemic mixture of the hydroxymethoxyerythrosuccinic acids. This acid was dissolved in ethyl alcohol and titrated with an alcoholic solution of brucine. Removal of the solvent yielded the crystalline brucine salt, $[\alpha]_D^{18°}$ − 23° in water (*c*, 1·0).

Fractional Crystallisation of the Brucine Salt of Racemic Hydroxymethoxyerythrosuccinic Acid.—One recrystallisation of the brucine salt (20 g.) from water gave the less soluble portion, $[\alpha]_D^{18°}$ − 22° in water. Concentration of the mother-liquors gave crystals, $[\alpha]_D^{17°}$ − 23° in water. Four more crystallisations of this, the more soluble fraction, gave crystals (4 g.), $[\alpha]_D^{18°}$ − 26° in water (*c*, 1·7), and no alteration of rotation occurred upon further crystallisation from water. Similarly, six crystallisations of the less soluble fraction of the brucine salt gave crystals, $[\alpha]_D^{17°}$ − 17° in water (*c*, 0·7).

3-*Hydroxy*-2-*methoxy*-d-*erythrosuccinobismethylamide* (XXIII).—A solution of the brucine salt (1·56 g.), $[\alpha]_D^{17°}$ − 17° in water) (15 c.c.) was treated with a slight excess of a solution of barium hydroxide. The brucine was removed and the solution neutralised with carbon dioxide, filtered, and evaporated to dryness. The barium salt was then boiled for 8 hours with 2% methyl-alcoholic hydrogen chloride (150 c.c.). Neutralisation of the solution with silver carbonate, followed by removal of the solvent, gave a neutral syrupy ester, which upon treatment with methyl-alcoholic methylamine yielded the crystalline *bismethylamide* of 3-hydroxy-2-methoxy-*d*-erythrosuccinic acid, m. p. 135°, $[\alpha]_D^{20°}$ − 10·5° in water (*c*, 1·0) (after recrystallisation from ethyl acetate) (Found: C, 44·3; H, 7·45; N, 14·8; OMe, 15·9. $C_7H_{14}O_4N_2$ requires C, 44·2; H, 7·4; N, 14·75; OMe, 16·3%). This was the enantiomorph of the bismethylamide obtained from *d*-araboascorbic acid (see above) and from 2 : 5-dimethyl Δ^4-mannosaccharolactone methyl ester (see previous paper).

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