130. *Analogues of Ascorbic Acid containing Six-membered Rings.*

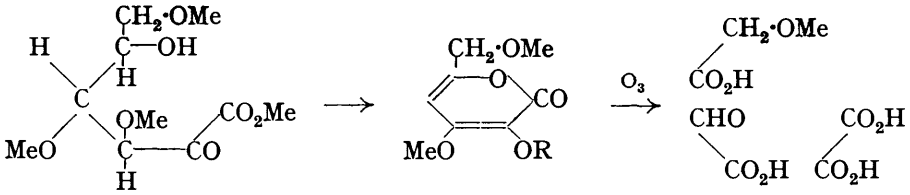
By W. N. Haworth, E. L. Hirst, and J. K. N. Jones.

It is shown that, by the action of sodium methoxide, or by continued heating under diminished pressure, esters (I) of methylated 2-ketogluconic acids having a free hydroxyl group at C_5 are converted into derivatives (II) of α-pyrone. These may be regarded as analogues of ascorbic acid containing six-membered rings and they have properties similar to those of 3-methyl ascorbic acid and absorption spectra generally resembling those displayed by members of the ascorbic acid series but with the heads of the bands situated at somewhat longer wave-lengths. The structure of the new substances is proved and a series of substituted α-pyrones has been prepared for comparison. It has now become possible to identify as the α-pyrone derivative (II, R = H) the substance, $C_8H_{10}O_5$, m. p. 89°, which is found consistently as one of the oxidation products of tetramethyl fructofuranose.

Several analogues of ascorbic acid possessing the normal five-membered ring structure have been prepared and for comparison with these we wished to obtain substances similar in constitution except as regards the nature of the lactone ring. Preliminary attempts to synthesise such compounds by the action of hydrogen cyanide on the osones of 3 : 5 : 6-trimethyl glucose and 3-methyl glucose were abandoned, in the former case because the osone was not readily obtainable from the osazone, and in the latter because of the unexpected behaviour of the addition product, which did not rearrange to form a substance analogous to ascorbic acid (compare Haworth, Hirst, Jones, and Smith, J., 1934, 1192).

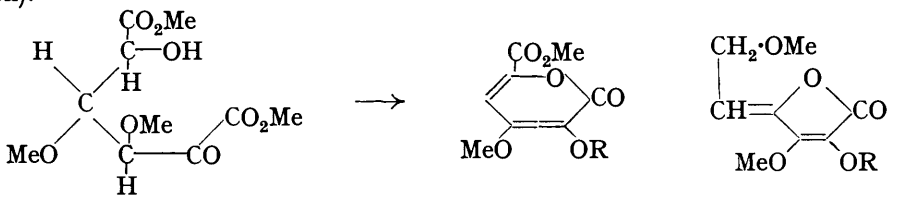
We then turned our attention to the action of sodium methoxide on the methyl esters of 3 : 4 : 6-trimethyl 2-ketogluconic acid (I). By analogy with the well-known reaction for the synthesis of ascorbic acid, this would be expected to give a methylated analogue of *d*-arabo-ascorbic acid containing a δ-lactone ring. It was found, however, that the reaction proceeds beyond this stage, with elimination of methyl alcohol between C_4 and C_5 and formation of the *α-pyrone* derivative (II, R = H). A similar procedure, starting from the ester of the dibasic acid (III), gives the corresponding *α-pyrone-6-carboxylate* (IV, R = H). The reactions of these towards diazomethane [which produces the corresponding *3-methyl* derivatives (II, R = Me) and (IV, R = Me)], acid iodine, Fehling's solution, sodium hypoiodite, and alkaline permanganate are closely similar to those previously observed with 3-methyl ascorbic acid (Haworth, Hirst, and Smith, J., 1934, 1556) except

that, as would be expected, some iodoform is produced by the action of sodium hypoiodite on (II, R = H). All the new substances are optically inactive.



(I.) (II.)

The presence of the α-pyrone ring structure in (II) and (IV) is supported by the following observations. The close similarities in mode of preparation, properties, and absorption spectra of (II, R = H) and (IV, R = H) point definitely to identity of ring structure, and since the latter has a terminal carboxy-group the presence of a 1 : 6-lactone ring is automatically ruled out. The formation of the five-membered ring (V) from (I) would involve the elimination of dimethyl ether between the CO·OMe group and the OMe at C_4, a reaction which is highly improbable when the much more facile elimination of methyl alcohol at C_5 can readily take place. Moreover, experiment showed that glyoxylic acid, recognised by its characteristic colour reaction, was one of the products of ozonisation of (II, R = H), and this can be formed on ozonisation only if the ring structure is the six-membered one shown in (IV). It cannot arise from (V). For these reasons we assign to all the above-mentioned substances the α-pyrone structure, and further support for this view was found in a comparison of the absorption spectra of the various substances with those of some typical hydroxylated α-pyrones and their methyl ethers, which were prepared specially for this purpose. Some of these, *e.g.*, (VII, R = Me), have not hitherto been described and in the course of the work we came across the open-chain *compound* (VI, R = H), which on treatment with diazomethane passes smoothly into the *methylated* derivative (VI, R = Me). The structure follows from the mode of preparation (see experimental section).

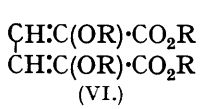


(III.) (IV.) (V.)

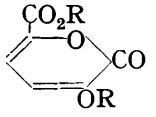
The absorption spectra of the α-pyrones resemble, in general, that of ascorbic acid in showing an intense band in the ultra-violet region, but owing to the increased conjugation the head of the band is situated closer to the visible spectrum. There are indications in some cases of the presence of a weaker band further in the ultra-violet, and coumalic acid (VIII), which is differently constituted, displays a markedly different absorption spectrum. Substance (VII, R = H), judging from the intensity of the band at λ 3200 A., exists in solution largely in the keto-form, this observation being in agreement with its behaviour towards ferric chloride. On methylation the enolic form is produced and the band is seen at its full intensity. Methyl 3 : 4 : 6-trimethyl 2-ketogluconate, which appears to exist mainly in the lactol form, does not display selective absorption in the ultra-violet.

Two other points of special interest emerge from the work described. The substance (II, R = H) is obtainable also by the slow distillation of (I) under diminished pressure, this fact being another argument in favour of the six-membered ring structure for (II). The reaction resembles that observed by Vŏtŏcek and Malachata (*Coll. Czech. Chem. Comm.*, **1936**, **8**, 66), who obtained α-pyrone derivatives by the distillation of lactones. Reference to the early work on the structure of sucrose shows that on oxidation of tetramethyl γ-fructose by nitric acid, a crystalline substance, $C_8H_{10}O_5$, m. p. 89°, was consistently obtained in small yield (Haworth and Linnell, J., 1923, **123**, 294; Haworth and Hirst, J.,

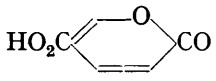
1926, 1858). The structural relationships of this material, which at the time was considered to be a furan derivative, have hitherto been uncertain, but it now appears that it is identical with the α-pyrone (II, R = H). The derivation of the substance from tetramethyl fructofuranose is now clear and a simple explanation becomes possible of the difficulties of interpretation commented upon in the earlier papers.



(VI.)



(VII.)



(VIII.)

The other point is that the *substance* (VII, R = Me), m. p. 215°, appears to be identical with a substance, $C_8H_8O_5$, m. p. 215°, encountered incidentally by Schmidt, Dippold, and Zeiser (*Ber.*, 1937, **70**, 2413) in the course of their work on the action of diazomethane on saccharic acid. These workers were unable to assign a definite structure to the substance, but a comparison of its properties with those of (VII, R = Me) indicates that in all probability it had the α-pyrone structure shown in (VII), a result which can be readily interpreted in the light of the other observations made by these authors.

Experimental.

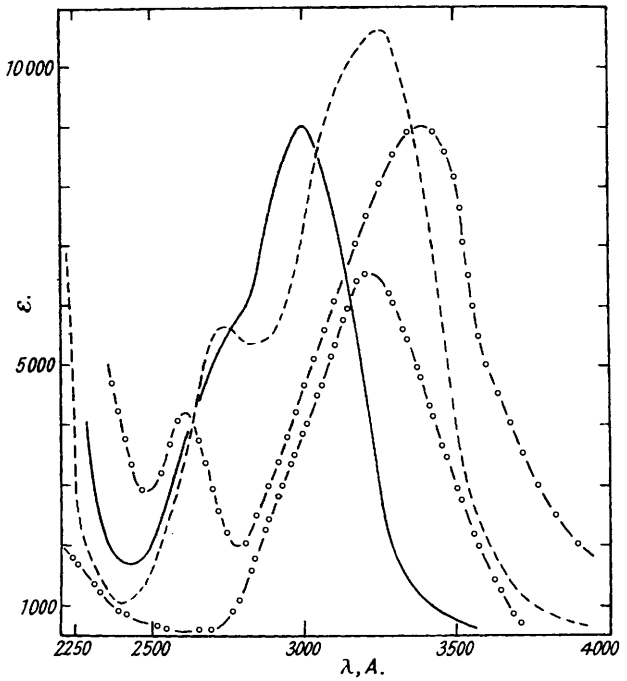
Addition of Hydrogen Cyanide to 3-*Methyl Glucosone.*—3-Methyl glucosazone (J., 1929, 1935) (50 g.) was stirred for 30 minutes at 20° with fuming hydrochloric acid (200 c.c.). The mixture was cooled (ice–salt), and the phenylhydrazine hydrochloride separated by filtration. The solution containing 3-methyl glucosone was neutralised with lead carbonate and filtered, lead acetate (50 g.) added, and sodium hydroxide stirred in until the solution was slightly alkaline. The lead hydroxide–osone complex was separated on the centrifuge and the osone was regenerated by addition of the requisite quantity of dilute sulphuric acid. The aqueous solution of 3-methyl glucosone so obtained gave the osazone rapidly on addition of phenylhydrazine at 40°. The osone did not reduce Fehling's solution in the cold, but did so readily on warming. Oxygen was displaced from the solution containing the osone by passing a rapid stream of nitrogen, and an excess of solid potassium cyanide and a little calcium chloride solution were then added. After 40 minutes the solution contained no material which reacted with iodine in acid solution. The product was isolated in the way described for the synthesis of ascorbic acid (Haworth, Hirst, Jones, and Smith, J., 1934, 1192) and was obtained as a brown syrup, which was acidic, reduced hot Fehling's solution, did not give 3-methyl glucosazone on treatment with phenylhydrazine, and did not react with iodine in acid solution. The methyl ester of this product was prepared and treated with sodium methoxide (compare Maurer and Schiedt, *Ber.*, 1933, **66**, 1054), but no material resembling ascorbic acid in its chemical properties was obtainable. In other experiments the addition of hydrogen cyanide was carried out in the presence of methyl chloroformate (compare Haworth and Peat, J., 1929, 354), but no substance analogous to ascorbic acid was encountered when the final product was isolated.

Preparation of Methyl 3-*Hydroxy*-4-*methoxy*-α-*pyrone*-6-*carboxylate from* 1 : 3 : 4 : 6-*Tetramethyl Fructose.*—1 : 3 : 4 : 6-Tetramethyl fructose (Menzies, J., 1922, 2238) was oxidised with nitric acid (*d* 1·42) (Haworth, Hirst, and Nicholson, J., 1927, 1520). The product contained monobasic and dibasic acids and was isolated as a syrup composed of the corresponding methyl esters. This crude syrup (without attempted purification by distillation: see below) (20 g.) was heated for 1 hour at 70° with methyl-alcoholic sodium methoxide (90 c.c., 1·4N). Yellow crystals separated, which were filtered off (filtrate A), washed rapidly with methyl alcohol, and dried in a vacuum. This sodium derivative was digested with methyl-alcoholic hydrogen chloride, giving in good yield *methyl* 3-*hydroxy*-4-*methoxy*-α-*pyrone*-6-*carboxylate* (IV, R = H) as colourless crystals, m. p. 207° after recrystallisation from methyl alcohol, sparingly soluble in the cold in water, methyl alcohol, acetone, and ether, readily in hot water and hot methyl alcohol (Found: C, 48·3; H, 4·2; OMe, 30·4. $C_8H_8O_6$ requires C, 48·0; H, 4·0; OMe, 31·0%). It was acid to litmus and Congo-paper, gave an orange colour in the presence of warm alkali, reduced hot Fehling's solution, and gave a greyish-blue colour with alcoholic ferric chloride. On treatment with alkaline potassium permanganate it gave oxalic acid (isolated as the calcium salt) in a yield of 80% of the theoretical calculated for formation of three molecules of oxalic

acid. Oxalic acid was formed also on ozonisation in glacial acetic acid. For the absorption spectrum, see Fig. 1.

Methyl 3 : 4-*Dimethoxy-α-pyrone-6-carboxylate* (IV, R = Me).—Substance (IV, R = H) was dissolved in dry methyl alcohol, and an excess of ethereal diazomethane added. After 12 hours at 0° the solution was concentrated under diminished pressure at 30°, giving a crystalline mass which on recrystallisation from methyl alcohol gave *methyl* 3 : 4-*dimethoxy-α-pyrone-6-carboxylate* in long needles, m. p. 93°, sparingly soluble in water and in ether; readily soluble in methyl alcohol and in acetone (Found : C, 50·6; H, 4·7; OMe, 42·1. $C_9H_{10}O_6$ requires C, 50·5; H, 4·7; OMe, 43·5%). It was neutral to Congo-red, gave no colour with alcoholic ferric chloride, was non-reducing to boiling Fehling's solution, and formed a yellow solution in hot alkali. For absorption spectrum, see Fig. 1.

FIG. 1.



— — — — 3-*Hydroxy-4-methoxy-6-hydroxymethyl-α-pyrone in methyl alcohol.*
———— 3 : 4-*Dimethoxy-6-hydroxymethyl-α-pyrone in water.*
— o — o — *Methyl 3-hydroxy-4-methoxy-α-pyrone-6-carboxylate in methyl alcohol.*
— oo — oo — *Methyl* 3 : 4-*dimethoxy-α-pyrone-6-carboxylate in methyl alcohol.*
(*Concentration in each instance* ca. 3 *mg.*/100 *c.c.*)

3-*Hydroxy-4-methoxy-6-methoxymethyl-α-pyrone* (II, R = H) *from* 1 : 3 : 4 : 6-*Tetramethyl Fructose*.—The filtrate (A) (p. 712) was rendered slightly acid with methyl-alcoholic hydrogen chloride, the sodium chloride removed, and the filtrate concentrated under diminished pressure. After some time a crystalline mass was deposited. This was extracted with ether, which dissolved substance (II, R = H), leaving a residue containing sodium chloride and a further quantity of substance (IV, R = H), m. p. 207° (see p. 712). The ethereal solution on evaporation gave 3-*hydroxy-4-methoxy-6-methoxymethyl-α-pyrone* (II, R = H), m. p. 88° after recrystallisation from methyl alcohol (Found : C, 51·9; H, 5·4; OMe, 33·9. $C_8H_{10}O_5$ requires C, 51·7; H, 5·3; OMe, 33·3%). For absorption spectrum, see Fig. 1. The pyrone was soluble in water and in the usual organic solvents except light petroleum. It was acid to litmus, reduced Fehling's solution, and gave a yellow colour with alkali, a red colour with a trace of alcoholic ferric chloride and a deep blue colour with larger quantities. With iodine in acidified aqueous solution it reacted slowly, using up 2 atomic proportions (0·100 g. required 11·4 c.c. of N/10-iodine. Calc., 11·1 c.c.). Sodium hypoiodite in slightly alkaline solution reacted with (II, R = H), giving iodoform (36·6 mg. gave 10·6 mg. of iodoform and required 14·1 c.c. of N/10-iodine; the conversion into oxalic acid, methoxyacetic acid, and iodoform is incomplete, since this requires 19·5 c.c. of

N/10-iodine and would liberate 77 mg. of iodoform). Ozonisation of the compound (1·76 g.) in purified glacial acetic acid (40 c.c.) gave oxalic acid (0·465 g.; isolated as the calcium salt; calc., 0·837 g.) and the filtrate after removal of the calcium oxalate then gave the characteristic colour reactions for glyoxylic acid (purple colour with casein and hydrochloric acid). In another experiment, pure carbon tetrachloride was used as solvent, and the same results obtained after ozonisation. The pyrone (II, R = H) reduced neutral alkaline potassium permanganate solution [20 mg. required 31·24 c.c. of N/25-neutral potassium permanganate at 0°; calc. for oxidation to oxalic acid (2 mols.) and methoxyacetic acid (1 mol.), 23·4 c.c. The yield of oxalic acid, isolated as the calcium salt, was 75% of the theoretical].

The above substance (II, R = H) could also be obtained by slow distillation at 200°/12 mm. of the mixed methyl esters (16·5 g.) prepared by the oxidation of 1 : 3 : 4 : 6-tetramethyl fructose (for method, see above). As distillation proceeded, the refractive index of the distillate rose from $n_D^{20°}$ 1·4385 to 1·5100. Three fractions were collected and the distillate gave a more intense blue colour with alcoholic ferric chloride as the b. p. and n_D increased: (*a*) b. p. 180°/12 mm., $n_D^{20°}$ 1·4500 (12 g.); (*b*) b. p. 190°/12 mm., $n_D^{20°}$ 1·4675 (6·3 g.); (*c*) b. p. 190°/12 mm., $n_D^{20°}$ 1·4812 (1·5 g.). Fractions (*a*) and (*b*) were united and redistilled, giving a further fraction similar in properties to fraction (*c*). On nucleation with substance (II, R = H), both fractions crystallised and on trituration with ether gave the crystalline solid, m. p. 88° (after recrystallisation from ether). A mixed m. p. with a specimen prepared by the first method showed no depression.

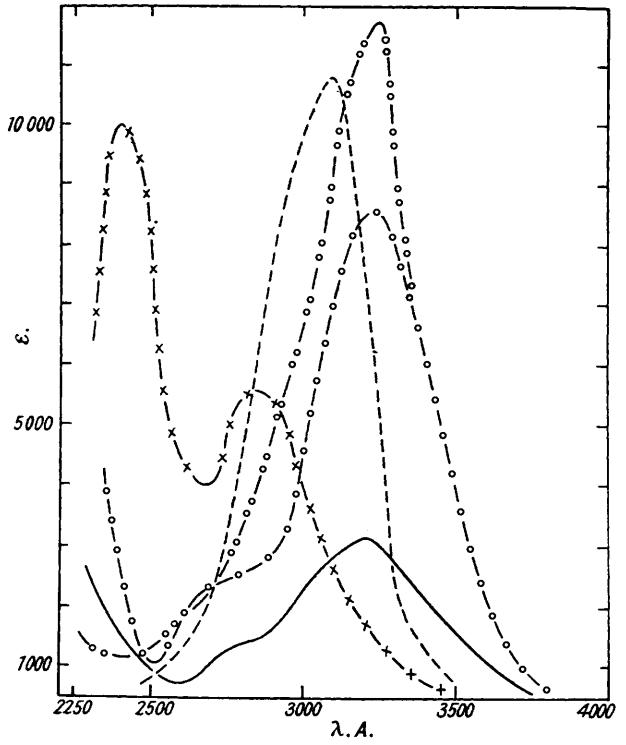
3 : 4-*Dimethoxy-6-methoxymethyl-α-pyrone* (II, R = Me).—Substance (II, R = H) (0·5 g.) was dissolved in dry methyl alcohol, and an excess of ethereal diazomethane added at 0°. After 20 hours at — 15°, the solution no longer gave a colour with alcoholic ferric chloride. The solvent was removed at 40°/12 mm., leaving a yellow syrup, $n_D^{20°}$ 1·5270 (Found: OMe, 46·0. $C_9H_{12}O_5$ requires OMe, 46·5%). The crude syrup was distilled at 135°/0·02 mm. (bath temp.), giving 3 : 4-*dimethoxy-6-methoxymethyl-α-pyrone* (II, R = Me) (0·46 g.), $n_D^{20°}$ 1·5280, $[\alpha]_D^{20°} \pm 0°$ in water (c = 1·2), as an orange syrup, soluble in all the usual solvents except light petroleum. In aqueous solution it reacted neutral to litmus and gave no colour with alcoholic ferric chloride (Found: C, 53·9; H, 6·4; OMe, 46·4. $C_9H_{12}O_5$ requires C, 54·0; H, 6·0; OMe, 46·5%). No free hydroxyl groups were present, since the substance was recovered unchanged after treatment with Purdie's reagents. The syrup (II, R = Me) reduced cold acid potassium permanganate solution (16·4 mg. required 22·22 c.c. of N/25-$KMnO_4$. Calc., 20·4 c.c. for oxidation to 2 mols. of oxalic acid and 1 mol. of methoxyacetic acid). For absorption spectrum, see Fig. 1.

αα'-Diketoadipic Acid.—Ethyl oxalate and ethyl succinate were condensed in ethereal solution by the method of Blaise and Gault (*Comp. rend.*, 1909, **148**, 177), sodium ethoxide at 15° being used. After 48 hours, the mixture was poured into water and acidified with hydrochloric acid and the oil which separated was extracted with ether. The syrup so obtained was dissolved in cold concentrated hydrochloric acid and left for 24 hours. It was then diluted with water and heated at 90° until evolution of carbon dioxide had ceased. Hydrochloric acid was removed by distillation with frequent additions of water. The concentrated solution finally obtained deposited oxalic and succinic acids, which were filtered off. On further concentration yellow crystals were deposited, which were triturated with ether. By continued extraction with ether the yellow material was separated into two portions: (*a*) (ether-soluble) 3-hydroxy-α-pyrone-6-carboxylic acid, (VII, R = H), m. p. 90°, solidifying at higher temps. (loss of carbon dioxide) and decomposing at 207° (Found: *M*, 158. Calc., 156), identical with the substance described by Blaise and Gault (for absorption spectrum, see Fig. 2); (*b*) (ether-insoluble) *αα'-diketoadipic acid* (VI, R = H), m. p. 227° (Found: C, 41·5; H, 3·26; *M*, 176. $C_6H_6O_6$ requires C, 41·4; H, 3·4%; *M*, 174). The latter was a yellow solid almost insoluble in water and in most organic solvents, but slightly soluble in chloroform. It gave a fleeting purple colour with alcoholic ferric chloride, reduced warm Fehling's solution, and was slowly oxidised by iodine in aqueous acid solution. In an excess of alkali it formed an orange-coloured solution. In aqueous solution the material showed an acidic reaction and gave a green colour with ferric chloride. For absorption spectrum, see Fig. 2. Titration of the material, dissolved in methyl alcohol, with ethereal diazomethane at — 10° gave the *tetramethyl* derivative (VI, R = Me), isolated on concentration of the solution at 30°/15 mm. as long needles, m. p. 116° (Found: OMe, 52·6. $C_{10}H_{14}O_6$ requires OMe 53·8%). For absorption spectrum, see Fig. 2.

Methyl 3-Methoxy-α-pyrone-6-carboxylate (VII, R = Me).—3-Hydroxy-α-pyrone-6-carboxylic acid (VII, R = H) reacted with diazomethane in methyl-alcoholic solution to give *methyl 3-methoxy-α-pyrone-6-carboxylate*, m. p. 215° (sublimes) (after recrystallisation from methyl

alcohol). This derivative was also prepared from (VII, R = H) by methylation with Purdie's reagent. It was isolated as a white crystalline solid, sparingly soluble in the cold in the usual organic solvents, soluble in hot methyl alcohol and hot water. It gave no colour with ferric

FIG. 2.



———— *3-Hydroxy-α-pyrone-6-carboxylic acid in water.*
— — — — *Methyl 3-methoxy-α-pyrone-6-carboxylate in methyl alcohol.*
— o — o — *αα′-Diketoadipic acid in methyl alcohol.*
— oo — oo — *Methyl O-dimethyl-αα′-diketoadipate (enolic form) in methyl alcohol.*
— x — x — *Coumalic acid in water.*
(*Concentrations* ca. 3 *mg.*/100 *c.c.*)

chloride solution, was neutral in reaction, and did not reduce Fehling's solution (Found : C, 51·9; H, 4·4; OMe, 32·9. $C_8H_8O_5$ requires C, 52·2; H, 4·4; OMe, 33·6%). For absorption spectrum, see Fig. 2. For comparison the absorption spectrum of coumalic acid (VIII) is shown in Fig. 2.

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