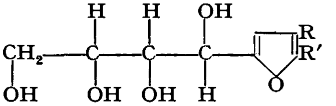
30. *The Condensation of Glucose and β-Diketones.*

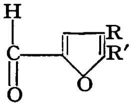
By J. K. N. Jones.

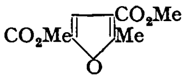
Glucose condenses with β-diketones in the presence of anhydrous zinc chloride to give derivatives of furan. These are converted into derivatives of pyran on heating with dilute aqueous acid. The ultra-violet absorption of several of these derivatives has been examined.

In view of the publications of Müller and Varga (*Ber.*, 1939, **72**, 1993) and of Szeki and Laszlo (*Ber.*, 1940, **73**, 924) on the condensation products of glucose and β-diketones, it is opportune to summarise work in which the results of Szeki and Laszlo are confirmed and extended.

Glucose condenses with acetoacetic ester (West, *J. Biol. Chem.*, 1925, **66**, 63; Moore, Erlanger, and West, *ibid.*, 1936, **113**, 43), benzoylacetic ester, and acetonedicarboxylic ester (Szeki and Laszlo, *loc. cit.*) in the presence of anhydrous zinc chloride, with the formation of furan derivatives, (I; R = CO_2Et, R′ = Me, Ph, and $CH_2{\cdot}CO_2Et$ respectively). The constitution of these substances was proved by oxidation with lead tetra-acetate to the corresponding derivatives (II). Owing to war conditions, these publications were not available to the author, who had reached a similar conclusion from a study of the products of oxidation by periodic acid, of (I; R = CO_2Et, R′ = Me) and (I; R = COMe, R′ = Me), the latter having been prepared by condensation of glucose and acetylacetone. These two compounds react quantitatively with 3 moles of periodic acid, with the formation of formaldehyde, formic acid, and the aldehydes (II; R = CO_2Et, R′ = Me and R = COMe, R′ = Me, respectively). The constitution of the aldehyde (II; R = CO_2H, R′ = Me) was proved by decarboxylating it to ω-methylfurfuraldehyde, identified as its oxime and 2 : 4-dinitrophenylhydrazone. Further proof was furnished by the isolation of the compound (III) after oxidative methylation of (I; R = CO_2H, R′ = Me) with silver oxide and methyl iodide. This showed an absorption band in water at 2620 A. The constitution of the new *substance* (I; R = COMe, R′ = Me) is inferred from its reactions, which are similar to those of (I; R = CO_2H, R′ = Me). The *aldehyde* (II; R = COMe, R′ = Me) showed an absorption band in water at 2850 A.

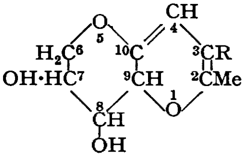

(I.)

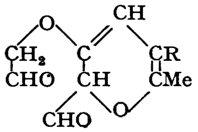

(II.)


(III.)

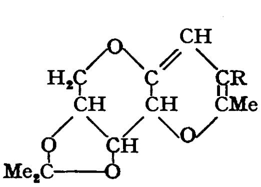
Substances (I; R = CO_2H, R′ = Me and R = COMe, R′ = Me) in boiling dilute acid solution rearrange with the elimination of the elements of water: substance (I, R = CO_2H) gives a pyran derivative (IV, R = CO_2H) (7 : 8-d-erythro-*dihydroxy-2-methyl-*1 : 5 : 6 : 7 : 8 : 9-*hexahydro-*1 : 5-*dioxanaphthalene-3-carboxylic acid*) and, by analogy, substance (I, R = COMe) is considered to give the pyran derivative (IV, R = COMe). Substances (IV, R = CO_2H and R = COMe) contain two alcoholic hydroxyl groups adjacent to each other, since they are oxidised by periodic acid with the formation of optically active dialdehydes (IV*a*) without loss of carbon atoms; one mole of (IV) consumes one mole of periodic acid. No selective absorption in the ultra-violet region could be detected when either of these substances (IV; R = CO_2H and R = COMe) was examined in aqueous solution. (IV*a*, R = COMe) showed an absorption band in water at 2700 A. (IV*a*, R = CO_2H) gave, on oxidative methylation with silver oxide and methyl iodide, a crystalline derivative in insufficient yield for complete characterisation; it may be (X). (IV, R = CO_2H) reacts with acetone in the presence of anhydrous copper sulphate with the formation of the iso*propylidene* derivative (V, R = CO_2H), which is converted by silver oxide and methyl iodide into the *methyl* ester (V, R = CO_2Me). Similarly, (IV, R = COMe) reacts with acetone in the presence of anhydrous copper sulphate with the formation of (V, R = COMe). Oxidation of this product with sodium hypoiodite gives iodoform and the sodium salt of (V, R = CO_2H). Methylation of (IV, R = CO_2H) with silver oxide and methyl iodide gives a mixture of syrup and crystals. This crystalline

(IV.)




(IV*a*.)

product of unknown constitution shows no observable rotation in methyl alcohol and appears to be formed from (V, R = CO_2H) by oxidation and methylation, since it possesses an extra oxygen atom. A possible



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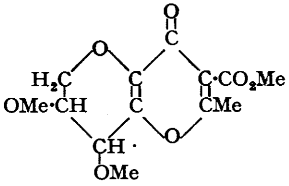
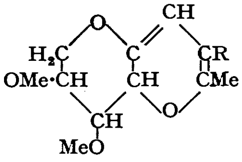


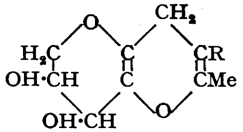
(VI.)



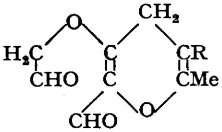
(VII.)

formula is (VI). The *dimethyl* derivative (VII) of (IV, R = CO_2H) is more readily prepared by methylation with caustic soda and methyl sulphate. The corresponding *methyl* ester (VII, R = CO_2Me) results on methylation of the acid with silver oxide and methyl iodide. Both the ester and the acid, on oxidation with nitric acid, give *meso*-dimethoxysuccinic acid, which is also similarly produced from (VI).

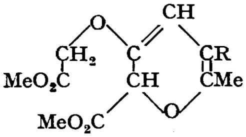
The possibility that substance (IV, R = CO_2H or COMe) may have structure (VIII) is excluded because oxidation of this with periodic acid would give an optically inactive derivative (IX). The hydroxyl groups which are free in (IV) must be on C_4 and C_5 of the original glucose unit, since they are adjacent (periodic acid



(VIII.)



(IX.)



(X.)

oxidation), an *iso*propylidene derivative is readily prepared, and *meso*-dimethoxysuccinic acid is isolated after oxidation of (VII) with nitric acid.

EXPERIMENTAL.

Oxidation of 2-*Methyl*-5-(d-arabo-*tetrahydroxybutyl*)*furan*-3-*carboxylic Acid* (I; R = CO_2H, R′ = Me).—The acid (217 mg.) was oxidised with aqueous periodic acid at 30°; it reduced 32·2 c.c. of 0·1N-periodic acid in 10 mins. (constant value) (Found: equiv., 42·4. Calc. for $C_{10}H_{14}O_7$: equiv., 40·6, on the assumption that three atoms of oxygen are consumed per mole of the carboxylic acid).

During the oxidation crystals of the aldehyde (II; R = CO_2H) separated; they were recrystallised from acetone and water. The product, 5-formyl-2-methylfuran-3-carboxylic acid (70 mg.), m. p. 176°, $[\alpha]_D^{20°}$ 0° (in acetone; *c*, 1·2), gave no colour with aqueous ferric chloride (Found: C, 54·4; H, 4·6; equiv., 157. Calc. for $C_7H_6O_4$: C, 54·6; H, 3·9%; equiv., 154).

Decarboxylation of the Aldehyde (II; R = CO_2H, R′ = Me).—The aldehyde (1 g.) was dissolved in quinoline (25 c.c.), copper chromite (0·2 g.) added, and the solution boiled for 4 hrs. (evolution of carbon dioxide). The cooled solution was poured into water and extracted with ether (twice), and the combined extracts shaken successively with 2N-hydrochloric acid (twice), sodium carbonate solution, and water. The ethereal extract was dried (anhydrous sodium sulphate) and evaporated to a syrup (0·6 g.). This syrup with hydroxylamine gave the oxime of ω-methylfurfuraldehyde, identical with the oxime prepared from ω-methylfurfuraldehyde obtained from rhamnose. The oxime was isolated in its two forms, m. p. 110° and m. p. 50°. The 2 : 4-dinitrophenylhydrazone of the aldehyde also was obtained in two forms, a red form, m. p. and mixed m. p. with a synthetic specimen 173°, and a purple-black form which was not obtained pure.

Oxidation of the Ethyl Ester (I; R = CO_2Et, R′ = Me).—The ester (97 mg.) at 20° reduced 20·5 c.c. of 0·1N-periodic acid in 15 mins. (constant value) (Found: equiv., 47·3. Calc. for $C_{12}H_{18}O_7$: equiv., 45·7) (assuming three atoms of oxygen are consumed). During the reaction the crystalline ethyl ester (II, R = CO_2Et) separated, m. p. 59° after recrystallisation from ether–light petroleum (b. p. 40—60°). With dinitrophenylhydrazine hydrochloride solution this gave the red *dinitrophenylhydrazone*, m. p. 234° (decomp.) after recrystallisation from dioxan (Found: C, 49·6; H, 3·97; N, 15·85. $C_{15}H_{14}O_7N_4$ requires C, 49·7; H, 3·9; N, 15·5%).

From the dioxan mother-liquor a small quantity of formaldehyde-2 : 4-dinitrophenylhydrazone was obtained, m. p. (after recrystallisation from methyl alcohol) and mixed m. p. with an authentic sample 165°.

Methylation of 2-*Methyl*-5-(d-arabo-*tetrahydroxybutyl*)*furan*-3-*carboxylic Acid*.—The acid (0·7 g.), dissolved in acetone, was methylated with silver oxide and methyl iodide. After the initial vigorous reaction had subsided, the mixture was refluxed for 6 hrs. and then worked up in the usual manner. The syrup (0·6 g.) was distilled in a vacuum and gave a small quantity of crystals mixed with syrup [b. p. 100°/0·1 mm. (bath temp.)]. The crystals (III) were collected on a tile and recrystallised from light petroleum (b. p. 40—60°); m. p. 53°, $[\alpha]_D^{20°}$ ±0° (*c*, 1·79 in methyl alcohol) (Found: C, 54·5; H, 5·5; OMe, 31·4; equiv., 98. Calc. for $C_9H_{10}O_5$: C, 54·6; H, 5·1; OMe, 31·3%; equiv., 99).

Acidification of the solution used for the determination of the equivalent weight gave, after extraction with ether, the free acid, m. p. 270° (decomp.) after recrystallisation from ethyl acetate (Found: C, 49·4; H, 3·7; equiv., 85. Calc. for $C_7H_6O_5$: C, 49·4; H, 3·5%; equiv., 85).

7 : 8-d-erythro-*Dihydroxy*-2-*methyl*-1 : 5 : 6 : 7 : 8 : 9-*hexahydro*-1 : 5-*dioxanaphthalene*-3-*carboxylic Acid* (IV, R = CO_2H).—(*a*) The acid (I, R = CO_2H) (10 g.) was dissolved in water (100 c.c.) and boiled under reflux: $[\alpha]_D^{20°}$ −17° (initial value); −34° (½ hr.); −57° (1 hr.); −67° (1½ hrs.); −72° (2 hrs.); −74° (2½ hrs.); −74° (3 hrs.). The solution was then cooled and evaporated, under reduced pressure; the crystals which separated were recrystallised from the minimum quantity of hot water or from ethyl acetate. Yield 6 g., m. p. 142° (Found: equiv., 233. Calc. for $C_{10}H_{12}O_6$: equiv., 228).

(*b*) The acid (I, R = CO_2H) (1 g.) was heated at 170° for 5 mins. and then cooled to 20°. Water and gas were evolved during the heating. Recrystallisation of the residue from ethyl acetate gave (IV, R = CO_2H) in 54% yield, m. p. and mixed m. p. 142°.

iso*Propylidene Derivative* (V, R = CO_2H).—The acid (IV, R = CO_2H) (5 g.) was shaken with dry acetone (100 c.c.) and anhydrous copper sulphate (25 g.) for 24 hrs. The filtered solution was evaporated under reduced pressure at 30°, and the crystalline residue (5·5 g.) recrystallised from benzene–light petroleum (b. p. 40—60°). Yield 5·2 g., m. p. 118°, $[\alpha]_D^{20^\circ}$ −95° (*c*, 0·52 in ethyl alcohol) (Found : C, 58·3; H, 6·5; equiv., 274. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%; equiv., 268).

Methylation of this product with silver oxide and methyl iodide gave quantitatively the corresponding *methyl* ester (V, R = CO_2Me), m. p. 99° after recrystallisation from absolute alcohol, $[\alpha]_D^{20^\circ}$ −89° (*c*, 1·5 in absolute alcohol) (Found : C, 59·6; H, 6·0; OMe, 11·6; equiv., 279. $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4; OMe, 11·0%; equiv., 282).

Oxidation of the Acid (IV, R = CO_2H).—The acid (113 mg.) was oxidised with aqueous periodic acid, and the change of rotation followed : $[\alpha]_D^{20^\circ}$ −120° (initial value); −31° (4 mins.); −23° (25 mins., constant value). The solution reduced 9·8 c.c. of 0·1N-periodic acid [Found : equiv., 115. Calc. for $C_{10}H_{12}O_6$: equiv., 113, assuming one oxygen atom is consumed per mole of (IV)]. No crystals separated and no formaldehyde could be detected in the solution. Dinitrophenylhydrazine hydrochloride solution, however, gave an orange precipitate which could not be obtained crystalline.

Oxidation of (IV, R = CO_2H) (755 mg.) with periodic acid in concentrated aqueous solution (5 c.c.) at 0° caused the precipitation of a *substance* (IV*a*, R = CO_2H) (540 mg.), m. p. 146°, $[\alpha]_D^{20^\circ}$ −25° (*c*, 0·44 in water) (Found : C, 53·3; H, 4·6. $C_{10}H_{10}O_6$ requires C, 53·2; H, 4·5%). Methylation of this material (50 mg.) with silver oxide and methyl iodide in the usual manner gave a crystalline *substance* [X (?), R = CO_2Me] (14 mg.), m. p. 119° after recrystallisation from methyl alcohol (Found : OMe, 31·3. $C_{13}H_{16}O_8$ requires OMe, 31·0%).

Methylation of the Acid (IV, R = CO_2H).—(a) *With silver oxide and methyl iodide.* The acid (2 g.), dissolved in methyl alcohol, was methylated with silver oxide and methyl iodide; after the initial reaction had subsided, the mixture was refluxed for 6 hrs. and then worked up in the usual manner. The resultant syrup (2·1 g.), $n_D^{17^\circ}$ 1·4978, was distilled in a vacuum and the following fractions obtained : 1 g., b. p. 140°/0·1 mm. (bath temp.), $n_D^{18^\circ}$ 1·4938; 0·4 g., b. p. 150°/0·1 mm. (bath temp.), $n_D^{17^\circ}$ 1·4926; 0·2 g., b. p. 160°/0·1 mm. (bath temp.), $n_D^{17^\circ}$ 1·4918.

The first fraction partly crystallised. The crystals [VI (?)] were collected on a tile and recrystallised from methyl alcohol; m. p. 126°, $[\alpha]_D^{20^\circ}$ ±0° (*c*, 1·0 in methyl alcohol) (Found : C, 54·6; H, 6·3; OMe, 32·5; equiv., 244. $C_{13}H_{18}O_7$ requires C, 54·6; H, 6·3; OMe, 32·5%; equiv., 286). After determination of the equivalent weight the solution was acidified and extracted with ether. Concentration of the extracts gave a crystalline *acid*, m. p. 151° (Found : C, 52·9; H, 5·7; OMe, 23·4; equiv., 278. $C_{12}H_{16}O_7$ requires C, 52·9; H, 5·9; OMe, 22·8%; equiv., 272).

(b) *With methyl sulphate and* 30% *sodium hydroxide solution.* The acid (10 g.) was dissolved in water (10 c.c.) and acetone (10 c.c.) and methylated at 30° by the gradual addition (1 hr.) of sodium hydroxide solution (30%, 200 c.c.) and methyl sulphate (95 c.c.). The mixture was stirred for 3 hrs., heated at 60° for 15 mins., cooled, acidified with dilute sulphuric acid, and extracted with ether (50 c.c.) (twice) and then with chloroform (50 c.c.) (twice). The combined extracts were washed with water, dried (anhydrous sodium sulphate), and evaporated under reduced pressure at 40° to a syrup (10 g.). The syrup was dissolved in methyl iodide (30 c.c.), and silver oxide added. The reaction was moderated by cooling, and the mixture then kept at 20° for 48 hrs. The product was worked up in the usual manner, and the resultant syrup (VII, R = CO_2Me) (10 g.), $n_D^{19^\circ}$ 1·4972, was distilled under reduced pressure; b. p. 140° (bath temp.)/0·01 mm., $n_D^{20^\circ}$ 1·4973, $[\alpha]_D^{20^\circ}$ −105° (*c*, 2·6 in methyl alcohol) (Found : C, 57·6; H, 6·9; OMe, 33·6; equiv., 273. $C_{13}H_{18}O_6$ requires C, 57·8; H, 6·7; OMe, 34·4%; equiv., 270).

This material (7·5 g.) was heated with N-sodium hydroxide (30 c.c.) on the boiling water-bath for 6 hrs., and N-sulphuric acid (30 c.c.) then added to the cooled solution. The light brown oil which separated was extracted with ether, and the extract dried over anhydrous sodium sulphate. Solvent was removed in a vacuum, and the residual *acid* (VII, R = CO_2H) distilled; b. p. 180° (bath temp.)/0·01 mm., $n_D^{20^\circ}$ 1·5130, $[\alpha]_D^{20^\circ}$ −97° (*c*, 1·8 in methyl alcohol) (Found : C, 56·0; H, 6·4; OMe, 23·0; equiv., 254. $C_{12}H_{16}O_6$ requires C, 56·1; H, 6·3; OMe, 24·2%; equiv., 256). The acid formed in concentrated hydrochloric acid a deep blue solution, the colour of which was destroyed on heating with the separation of a brown oil.

This syrup (2·3 g.) was oxidised with nitric acid (*d* 1·42) (10 c.c.), and the solution worked up as described below. From the residual syrup a product (0·6 g.), b.p. 90° (bath temp.)/0·01 mm., $n_D^{20^\circ}$ 1·4462, was obtained by fractional distillation. This crystallised on standing and, after trituration with ether–light petroleum (b. p. 40—60°), the methyl ester of *meso*-dimethoxysuccinic acid was isolated, m. p. 67° not depressed by an authentic specimen. With methyl-alcoholic ammonia this gave *meso*-dimethoxysuccinamide, m. p. and mixed m. p. with an authentic specimen, 244°.

Oxidation of the Crystalline Methylated Derivative [VI (?)].—The crystals (200 mg.) were oxidised with nitric acid (*d* 1·42) (2 c.c.) at room temperature and then at 70—80°, the reaction being moderated by cooling. After standing at 20° for 12 hrs., the solution was concentrated under reduced pressure, and methyl alcohol distilled through the residue to remove nitric acid and water. The residual syrup was esterified with methyl-alcoholic hydrogen chloride, and the mixed neutral esters isolated after neutralisation with silver carbonate. Fractional distillation of the syrup in a vacuum gave the dimethyl ester of *meso*-dimethoxysuccinic acid (20 mg.), m. p. and mixed m. p. with an authentic specimen, 66—67°.

Condensation of Glucose and Acetylacetone. Preparation of 2-*Methyl*-5-(d-arabo-*tetrahydroxybutyl*)-3-*furyl Methyl Ketone* (I; R = COMe, R′ = Me).—Glucose (25 g.) was heated with acetylacetone (12 g.) in methyl alcohol (12 c.c.) and anhydrous zinc chloride (12 g.) on the boiling water-bath until a clear solution was obtained (30 mins.). The solution was poured into water, and the precipitated crystals (3 g.) collected after 12 hrs. The *product* (I; R = COMe, R′ = Me) was recrystallised from hot methyl alcohol; m. p. 152°, $[\alpha]_D^{20^\circ}$ −18° in water (*c*, 5·0) (Found : C, 54·1; H, 6·8. $C_{11}H_{16}O_6$ requires C, 54·1; H, 6·6%). With dinitrophenylhydrazine hydrochloride solution it gave a scarlet *derivative*, m. p. 142° (Found : C, 48·2; H, 4·8; N, 14·3. $C_{17}H_{20}O_9N_4$ requires C, 48·1; H, 4·7; N, 13·2%).

The substance (122 mg.) reduced 0·1N-periodic acid (30 c.c.), whence the equivalent weight is 40·7 (calc., 40·6 on the assumption that 1 mole reduces 3 moles of periodic acid). During the reaction crystalline 5-*formyl*-2-*methyl*-3-*furyl methyl ketone* (II; R = COMe, R′ = Me) separated, m. p. 104—105° after recrystallisation from acetone and water (Found : C, 63·2; H, 5·2. $C_8H_8O_3$ requires C, 63·2; H, 5·3%). This gave an orange *dinitrophenylhydrazone*, m. p. 202° after recrystallisation from dioxan (Found : C, 49·2; H, 3·9; N, 17·9. $C_{14}H_{12}O_6N_4$ requires C, 49·1; H, 3·5; N, 16·4%).

7 : 8-d-erythro-*Dihydroxy*-2-*methyl*-1 : 5 : 6 : 7 : 8 : 9-*hexahydro*-1 : 5-*dioxa*-3-*naphthyl Methyl Ketone* (IV, R = COMe).—(I; R = COMe, R′ = Me) (2·5 g.) was boiled with 10% aqueous acetic acid (50 c.c.), and the change of rotation observed : $[\alpha]_D^{20}$ −17·6° (initial); −58° (¾ hr.); −81° (1 hr.); −91° (2½ hrs.); −94° (3 hrs.; constant value). The solution was then concentrated under reduced pressure, and the residual crystals (IV, R = COMe) recrystallised from acetone–light petroleum (b. p. 40—60°). Yield 2·2 g., m. p. 102°, $[\alpha]_D^{20^\circ}$ −104° (*c*, 0·41 in methyl alcohol) (Found : C, 58·2; H, 6·2. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%). This *substance* gave neither crystalline oxime nor dinitrophenylhydrazone.

Substance (IV, R = COMe) was readily oxidised with periodic acid, 1 mole reducing 1 mole of the acid to iodic acid. During the reaction a *product*, m. p. 128—129° (*ex* acetone–light petroleum, b. p. 40—60°) separated, $[\alpha]_D^{20^\circ}$ −23° (*c*, 0·2 in methyl alcohol) (Found : C, 54·6; H, 5·6. $C_{11}H_{12}O_5,H_2O$ requires C, 54·5; H, 5·8%).

Preparation of the iso*Propylidene Derivative* (V, R = COMe).—A solution of (IV, R = COMe) (1 g.) in acetone (20 c.c.) was shaken with anhydrous copper sulphate (10 g.) for 24 hrs., filtered, and concentrated under reduced pressure. The residual crystalline solid (1 g.), recrystallised from aqueous methyl alcohol, had m. p. 96° (Found: C, 63·4; H, 7·3. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·9%).

This *product* (129 mg.) was dissolved in methyl alcohol (10 c.c.) and oxidised with an excess of 0·1N-iodine (50 c.c.) in 2N-sodium hydroxide (30 c.c.). After standing for 30 mins. at 20°, the precipitated iodoform was collected (141 mg.; 80%). The filtrate was acidified with dilute sulphuric acid, the excess of iodine removed with sulphur dioxide, and the solution extracted with ether (20 c.c. portions; thrice). The extracts were dried (anhydrous sodium sulphate) and evaporated to dryness. The crystalline residue (110 mg.), recrystallised from ether–light petroleum (b. p. 40—60°), had m. p. and mixed m. p. with an authentic specimen of the acid (V, R = CO_2H), 118°.

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