572. *Monoalkyl Hexoses: Improved Procedures for the Preparation of 1- and 3-Methyl Ethers of Fructose, and of 3-Alkyl Ethers of Glucose.*

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The synthesis of 3-methyl D-glucose by way of glucose, 1 : 2-5 : 6-di*iso*propylidene D-glucose, and 3-methyl 1 : 2-5 : 6-di*iso*propylidene D-glucose has been studied in detail; improvements at all three stages have enabled a much increased overall yield to be obtained.

New methods have been developed for the alkylation of *iso*propylidene sugars and for the removal of the *iso*propylidene groups from the resultant alkylated products. Both these techniques represent advances over the methods hitherto described and are thought to be of wide application. These new methods have now been used for the preparations of three new monoalkyl glucoses and for the preparation of 3-methyl D-fructose.

Convenient procedures for the preparation of 1- and 3-methyl D-fructose have been developed, using sucrose or invert sugar as initial starting material.

Studies of its metabolism have demonstrated that 3-methyl glucose possesses interesting properties (Campbell and Danson, *Biochem. J.*, 1948, **43**, 426; Campbell, *ibid.*, 1949, **44**, 41; *Nature*, 1949, **164**, 365) and prompted an investigation of the synthesis of 3-methyl glucose and other 3-alkyl derivatives of glucose. It was thought that the non-glucosidic monomethyl derivatives of fructose might also be of pharmacological interest and accordingly 1- and 3-methyl D-fructose were selected for initial studies and synthesized by the procedures described in this paper.

The methods hitherto described for the preparation of 3-methyl D-glucose by way of the intermediate compounds 1 : 2-5 : 6-di*iso*propylidene and 3-methyl 1 : 2-5 : 6-di*iso*propylidene D-glucose cannot be considered wholly satisfactory in view of the low overall yields, and, accordingly, each of the three steps of the synthesis has now been examined in detail. The first stage has been considerably improved by the use of condensing agents which minimize side reactions, but it is at the two subsequent stages (methylation of di*iso*propylidene glucose and later removal of the *iso*propylidene groups) that improvement has been most marked. As a result of these studies a convenient laboratory method for the preparation of 3-methyl glucose has been developed and the overall yield has been raised to 60—65%.

Two new methods have been developed for the methylation of di*iso*propylidene glucose. Both give almost theoretical yields of 3-methyl di*iso*propylidene glucose and were designed with the economic utilization of the methylating agent as a primary objective. In the first method, a moderate excess (50%) of methyl sulphate is employed in presence of solid, pulverized sodium hydroxide and acetone; in the second method methyl chloride is used under pressure and in presence of acetone and solid sodium hydroxide. Both these procedures deviate considerably from established techniques employing alkylating agents such as methyl iodide and silver oxide (Irvine and Hynd, *J.*, 1909, **95**, 1220), an alkyl halide and metallic sodium (Freudenberg and Hixon, *Ber.*, 1923, **56**, 2119) or methyl sulphate and potassium hydroxide (Schmidt and Simon, *J. pr. Chem.*, 1939, **152**, 194).

The *iso*propylidene groups in 3-methyl di*iso*propylidene glucose are labile and readily removed by the action of dilute mineral acids, but despite this the methods hitherto described for the hydrolysis employ relatively large quantities of acid which must be eliminated from the final hydrolysate by, *e.g.*, barium carbonate (Loder and Lewis, *J. Amer. Chem. Soc.*, 1932, **54**, 1045), silver carbonate (Irvine *et al.*, *J.*, 1913, 569; 1914, 1390), or lead acetate (Schmidt and Simon, *J. pr. Chem.*, 1939, **152**, 194), and the methods are protracted. Two laboratory hydrolytic procedures have now been developed which avoid large quantities of acid. In the first an aqueous suspension of an acid-form ion-exchange resin is used as hydrolysing agent; in the second, water acidified to pH 2—3 is employed. Both avoid the usual tedious purifications and crystalline 3-methyl glucose is isolated from the hydrolysate, simply by concentration, in yields of at least 85%.

It is probable that these methods are of general application for the hydrolysis of sugar derivatives possessing labile *iso*propylidene groups. They have been found effective in the preparation of three new alkylated glucoses, namely, 3-ethyl, 3-*n*-propyl, and 3-*n*-butyl D-glucose.

The methods developed for the synthesis of 3-methyl glucose gave equally satisfactory results when applied to the preparation of 3- and 1-methyl fructose. Alkylations of " α "- and " β "-di*iso*propylidene fructose (respectively the 1 : 2-4 : 5- and 2 : 3-4 : 5-isomers; Wolfram, Shilling, and Blinkley, *J. Amer. Chem. Soc.*, 1950, **72**, 4544), by methyl sulphate in presence of solid sodium hydroxide, gave excellent yields (upwards of 90%) of 3- and 1-methyl di*iso*propylidene fructose and were superior to the methods described by Irvine and Hynd (*loc. cit.*), Freudenberg and Hixon (*loc. cit.*), and Ohle (*Ber.*, 1925, **58**, 2577). Hydrolysis of 3-methyl di*iso*propylidene fructose was effected smoothly by either of the hydrolytic procedures described for 3-methyl glucose, giving pure 3-methyl fructose in 85—90% yield without recourse to complex isolation procedures. Removal of the *iso*propylidene groups from 1-methyl di*iso*propylidene fructose necessitates relatively vigorous conditions but can be effected by 0·1N-sulphuric acid at 100°; the excess of acid can be eliminated from the hydrolysate by a suitable ion-exchange resin.

The intermediate " β "-di*iso*propylidene fructose required for these studies was prepared in 70—80% yield from sucrose and acetone by a process parallel to that described for the preparation of di*iso*propylidene glucose, a mixture of zinc chloride and phosphoric acid being used to effect fission of sucrose and introduction of the *iso*propylidene residues. The product was freed from concomitant di*iso*propylidene glucose by the methods outlined by Bell (*J.*, 1947, 1461).

Although " α "-di*iso*propylidene fructose can be prepared satisfactorily from fructose, a less expensive starting material seemed desirable and attempts were, therefore, made to develop processes starting from sucrose or invert sugar. The actions of condensing agents on glucose–acetone and fructose–acetone mixtures have been recorded by various workers but no attempt has been made to correlate the results and apply them to the preparation of the " α "-derivative. By using invert sugar and acetone as starting materials, and zinc chloride as condensing agent, it has been possible to prepare " α "-di*iso*propylidene fructose in satisfactory yields and of a quality which permits procedure to the next stage of the synthesis of 3-methyl fructose (methylation) without further purification. The preparation is based on the fact that under the conditions of the reaction, fructose is converted into " α "-di*iso*propylidene fructose, whereas the concomitant glucose forms little or no di*iso*propylidene derivative and can be removed from the product by partitioning between chloroform and water. An attempt to use sucrose as starting material gave less satisfactory results, but it has been possible to demonstrate that fission of sucrose and production of " α "-di*iso*propylidene fructose can be effected by using 0·3% sulphuric acid in presence of acetone. The series of reactions described above render 3-methyl fructose a readily available and comparatively inexpensive compound.

Our studies indicated that a mixture of approximately equal quantities of 3-methyl glucose and 1-methyl fructose might be of pharmacological interest. Accordingly such a mixture was prepared from sucrose by the four step process. In a similar manner mixtures of the corresponding ethylated and propylated hexoses were obtained.

EXPERIMENTAL.

Evaporation of solvents, when not otherwise stated, was conducted below 70° and under reduced pressure.

1 : 2-5 : 6-*Di*iso*propylidene Glucose from Glucose.*—To an efficiently stirred suspension of anhydrous glucose (150 g.) in acetone (1 l.) anhydrous pulverized zinc chloride (120 g.) was added, followed by 85% phosphoric acid (7·5 g.). This mixture was stirred at room temperature for 30 hours and the undissolved glucose (61·8 g.) was collected and washed with a little acetone. The filtrate and washings were cooled and made slightly alkaline with sodium hydroxide solution (85 g. of sodium hydroxide in 85 ml. of water), and the insoluble inorganic material removed by filtration and washed with acetone. The almost colourless filtrate and washings were concentrated and the residue was diluted with water (150 ml.) and extracted thrice with chloroform (3 × 150 ml.). The combined chloroform extracts were washed with a little water and concentrated to give a white crystalline residue of crude di*iso*propylidene glucose (115·4 g., 91% yield based on the glucose consumed), m. p. 95—101°. One crystallization from 1 : 2 chloroform–hexane raised the m. p. to 105—109°, but the crude product is satisfactory for the next step.

3-*Methyl* 1 : 2-5 : 6-*Di*iso*propylidene Glucose.*—(a) *By use of methyl sulphate.* A mixture of di*iso*propylidene glucose (78 g.), acetone (75 ml.), and pulverized sodium hydroxide (32 g.) was warmed under reflux to 45° with stirring and methyl sulphate (42·6 ml.) was added dropwise at this temperature during 90 minutes. The methylation was completed by warming the mixture to 50° for an additional 90 minutes and finally to 55—60° for 3 hours. The reaction mixture was diluted with water and the product extracted with chloroform (3 × 150 ml.). The chloroform extracts were washed with water and concentrated (finally at 1—3 mm. and on a steam-bath—in order to remove acetone polymers). The residual light amber-coloured crude liquid 3-methyl di*iso*propylidene glucose (83 g.) was suitable for hydrolysis to 3-methyl glucose without further purification.

(b) *By use of methyl chloride and sodium hydroxide.* A stainless-steel, rocking-type autoclave was cooled below −40° and charged with di*iso*propylidene glucose (52 g.), pulverized sodium hydroxide (24 g.), acetone (50 ml.), and liquid methyl chloride (26 ml.). The autoclave was then sealed and warmed with agitation to 145—150° for 8 hours. The mixture was then cooled and diluted with water and the 3-methyl di*iso*propylidene glucose (55 g.) isolated as in (a).

Hydrolysis of 3-*Methyl Di*iso*propylidene Glucose to* 3-*Methyl Glucose*.—(a) *With water at* pH 2·6. The crude 3-methyl di*iso*propylidene glucose obtained as above (*a*) (83 g.) was refluxed for 6 hours with water (150 ml.), adjusted to pH 2·6 with sulphuric acid. The warm amber-coloured hydrolysate was decolorized with charcoal ("Norit," 4 g.) and concentrated to a syrup from which final traces of water were removed by repeated evaporation with ethanol. The partly crystalline residue was warmed with methanol (45 ml.) and kept overnight at room temperature. The white crystalline 3-methyl glucose which separated (43 g.) was collected and washed with a little methanol; it had m. p. 166—168°. The mother-liquors gave a further quantity (7·1 g.; m. p. 164—167°). The total yield was 86%, based on the crude 3-methyl di*iso*propylidene glucose used.

(b) *By use of an acid ion-exchange resin*. A suspension of 3-methyl di*iso*propylidene glucose (133·8 g.) and ion-exchange resin (25 g. "IR-120," Rohm and Haas Co., Philadelphia, which was activated to the acid form by washing with 10% aqueous hydrochloric acid and then rinsing with distilled water), in water (135 ml.), was stirred at 100° for 4 hours. The resin was removed by filtration, the filtrate decolorized with charcoal, and the crystalline 3-methyl glucose isolated in good yield as in (a).

3-*Ethyl* 1 : 2-5 : 6-*Di*iso*propylidene Glucose*. A mixture of di*iso*propylidene glucose (78 g.), pulverized sodium hydroxide (32 g.), and acetone (75 ml.) was warmed with stirring to 45° and treated with ethyl sulphate (61 ml.) as described for the methyl analogue. The yield of crude amber-coloured liquid 3-ethyl di*iso*propylidene glucose (96 g.) was almost theoretical.

3-*Ethyl Glucose*.—Crude 3-ethyl di*iso*propylidene glucose (96 g.) was refluxed for 6 hours with 3 parts of water adjusted to pH 2·6 with sulphuric acid. The warm hydrolysate so obtained was decolorized with charcoal and concentrated, final traces of water being removed by evaporation with alcohol as described for 3-methyl glucose. The semi-solid residue was crystallized by warming it with acetone (150 ml.) and setting the mixture aside overnight at room temperature. The white, crystalline 3-*ethyl* D-*glucose* (51 g., 82%; m. p. 132—135°) was recrystallized several times from methanol–ether and then had m. p. 137—138° and $[\alpha]_{\mathrm{D}}^{25}$ + 26·1° (5 minutes) $\longrightarrow$ + 55·2° (constant after 24 hours) (*c*, 2 in water) (Found: C, 46·5; H, 7·9; OEt, 21·0. $C_8H_{16}O_6$ requires C, 46·2; H, 7·7; OEt, 21·6%).

3-n-*Propyl* 1 : 2-5 : 6-*Di*iso*propylidene Glucose*.—Di*iso*propylidene glucose (52 g.), acetone (50 ml.), *n*-propyl bromide (74 g.), and pulverized sodium hydroxide (32 g.) were warmed in an autoclave, with agitation, at 150° for 9 hours. The contents were cooled and extracted with chloroform, and the combined chloroform extracts washed with water and concentrated to a light amber-coloured liquid residue of crude 3-*n*-propyl di*iso*propylidene glucose (65 g.) which probably contained some high-boiling acetone polymers but was suitable for hydrolysis to 3-propyl glucose without further purification.

3-n-*Propyl Glucose*.—Crude 3-*n*-propyl di*iso*propylidene glucose obtained as above (65 g.) was boiled for 8 hours with 3 parts of water adjusted to pH 2·1 with sulphuric acid. The hydrolysate was then extracted with chloroform (2 × 75 ml.) to remove dark impurities, and the chloroform extracts were washed with a little water. The aqueous hydrolysate and water washings were combined, warmed, decolorized with charcoal (3 g.), and then concentrated: the final traces of water were removed by addition of alcohol to the residue and subsequently evaporation under reduced pressure in the usual manner. The solid crystalline residue of 3-n-*propyl* D-*glucose* was collected and washed with a little ether (38·3 g., 86% based on the di*iso*propylidene glucose used in the previous stage; m. p. 129—131°). Two recrystallizations from methanol–ether raised the m. p. to 130—131°; $[\alpha]_{\mathrm{D}}^{25}$ was +29·5° (5 minutes) $\longrightarrow$ +62·3° (constant after several hours) (*c*, 2 in water) (Found: C, 49·1; H, 8·25; OPr, 27·4. $C_9H_{18}O_6$ requires C, 48·6; H, 8·15; OPr, 26·8%).

3-n-*Butyl* 1 : 2-5 : 6-*Di*iso*propylidene Glucose*.—*n*-Butyl bromide (82·2 g.), di*iso*propylidene glucose (52 g.), pulverized sodium hydroxide (36 g.), and acetone (50 ml.) were warmed together in an autoclave at 150° for 9 hours. The crude 3-n-*butyl di*iso*propylidene* D-*glucose* (isolated as described for the 3-*n*-propyl analogue) was distilled and the fraction of b. p. 120—123°/1 mm. was collected {55·2 g., 87%; $[\alpha]_{\mathrm{D}}^{25}$ + 70·5° (*c*, 2 in chloroform); n_{D}^{27} 1·4513} (Found: C, 62·3; H, 8·9. $C_{16}H_{28}O_6$ requires C, 60·7; H, 8·9%).

3-n-*Butyl Glucose*.—The foregoing distilled compound (42 g.) was refluxed for 8 hours with 3 parts of water adjusted to pH 2·1 with sulphuric acid, and the 3-n-*butyl* D-*glucose* was isolated from the hydrolysate as described for 3-*n*-propyl glucose. The crude product (29·7 g., 98%; m. p. 130—134°), crystallized twice from methanol–ether, had m. p. 137—139° and $[\alpha]_{\mathrm{D}}^{25}$ +23·7° (5 minutes) $\longrightarrow$ +52·1° (constant after several hours) (*c*, 2 in water) (Found: C, 51·2; H, 8·6. $C_{10}H_{20}O_6$ requires C, 50·8; H, 8·55%).

"β"-*Di*iso*propylidene Fructose*.—(a) *From fructose*. A cold solution of phosphoric oxide (1·5 g.) in 85% phosphoric acid (3 g.) was added to a mixture of fructose (27 g.), anhydrous zinc chloride (36 g.), and acetone (180 ml.), and the resulting mixture was efficiently agitated at room temperature for 26 hours. The contents were then made alkaline with sodium hydroxide (35 g. of sodium hydroxide in 35 ml. of water), and the inorganic precipitate was filtered off and washed with acetone. The filtrate and washings were concentrated and the residue was diluted with water and extracted with chloroform. Evaporation of the chloroform gave crude β-di*iso*propylidene fructose (32·5 g.; m. p. 78—85°) which was purified by being stirred at room temperature for 8 hours with 0·1N-sulphuric acid (to hydrolyse any "α"-di*iso*propylidene fructose; Bell, *loc. cit.*). The product (24·4 g., 63%; m. p. 94·5—95°) was extracted from the hydrolysate with chloroform.

(b) *From sucrose*. To a well-stirred mixture of sucrose (150 g.) and acetone (1 l.) was added anhydrous zinc chloride (120 g.), followed by a cold solution of phosphoric oxide (10 g.) in 85% phosphoric acid (20 g.). The mixture, which warmed spontaneously to 40°, was stirred at room temperature for 24 hours by which time all the sugar had dissolved. A solution of sodium hydroxide (120 g. of sodium hydroxide in 120 ml. of water) was added dropwise with cooling, and the precipitated inorganic salts were collected and washed with acetone. The filtrate and washings were concentrated and the residue was diluted with water (800 ml.) and extracted with chloroform (4 × 200 ml.). The chloroform extracts were washed with water and concentrated. The residue so obtained was stirred for 6 hours with 0·1N-sulphuric acid (500 ml.) to hydrolyse the di*iso*propylidene glucose (and " α "-di*iso*propylidene fructose, if present). Extraction of the hydrolysate with chloroform in the usual manner gave " β "-di*iso*propylidene fructose (84 g., 74%; m. p. 90—93°). A sample twice crystallized from hexane melted at 94·5—95°.

1-*Methyl* Di*iso*propylidene *Fructose from " β "*-Di*iso*propylidene *Fructose*.—(a) *By use of methyl sulphate.* A mixture of " β "-di*iso*propylidene fructose (200 g.), acetone (200 ml.), and pulverized sodium hydroxide (135 g.) was treated at 45°, with stirring, with methyl sulphate (146 ml. added dropwise during 90 minutes). The mixture was then warmed to 50° for 1 hour and finally to 55—60° for 3 hours. The suspension was diluted with water and extracted with chloroform (4 × 200 ml.), and the chloroform extracts were washed with water and evaporated [1—2 mm., 100° (bath); removal of acetone polymers]. The residue of crude 1-methyl di*iso*propylidene fructose (215 g.) was crystallized at −40° from 3 : 2 methanol–water (475 ml.) to give a white crystalline product (182 g.; m. p. 48—48·5°). A second crop weighed 14 g. and had m. p. 46—47° (total yield, 93%).

(b) *By use of methyl iodide.* " β "-Di*iso*propylidene fructose (100 g.) in dry benzene (500 ml.) was added to metallic sodium (25 g.; powdered under toluene) and left for 24 hours at room temperature. The benzene solution was decanted from unchanged sodium, then concentrated, and the residue treated with methyl iodide (110 ml.). The mixture was kept, with occasional shaking, for 4 days at room temperature and finally diluted with ether, filtered to remove sodium iodide, and concentrated. The residue was crystallized from hexane and gave 96·5 g. (92%) of material, m. p. 45—47°.

1-*Methyl Fructose*.—A suspension of 1-methyl di*iso*propylidene fructose (411 g.) in three parts of 0·1N-sulphuric acid was warmed with stirring to 95—100° for 7 hours, by which time the sugar had dissolved and hydrolysis was complete. The warm, amber-coloured solution was decolorized with charcoal (12 g.; " Norit "), concentrated to 600 ml. and re-treated with charcoal. The sulphuric acid was then removed from the hydrolysate by stirring with either barium carbonate (40 g.) or an ion-exchange resin (Amberlite IRA-400, basic form; Rohm and Haas Co., Philadelphia). The final pH was adjusted to 5—5·5 since at this pH discoloration was minimized. The sugar solution was re-treated with charcoal, and concentrated to dryness in a water-bath at 60°, to give 1-methyl fructose as a sweet-tasting, honey-coloured, resinous syrup (270 g., 93%) (Found : OMe, 14·7. Calc. for $C_7H_{14}O_6$: OMe, 15·9%).

Crude " α "-Di*iso*propylidene *Fructose*.—(a) *From invert sugar.* Commercial invert sugar syrup (700 g.) was dried under reduced pressure on a steam-bath. To the viscous, almost solid resin so obtained (580 g.) acetone (4 l.) and anhydrous pulverized zinc chloride (700 g.) were added, together with coarse sand to facilitate disintegration of the resin. The mixture was stirred for 2 days at room temperature, by which time almost all the sugar had dissolved. Sodium hydroxide (450 g. in 450 ml. of water) was now added dropwise with cooling and the inorganic precipitate was collected and washed with acetone. The filtrate and washings were concentrated and the residue was diluted with water (500 ml.) and extracted with chloroform (4 × 200 ml.). The chloroform extracts were washed with water, dried (Na_2SO_4), and concentrated to give a residue of crude " α "-di*iso*propylidene fructose (250 g., 60% yield based on the fructose content of the invert sugar), m. p. 52—75°. This material was suitable for the preparation of 3-methyl di*iso*propylidene fructose as described below.

(b) *From sucrose.* A suspension of sucrose (250 g.) in acetone (1500 ml.) containing concentrated sulphuric acid (4·5 ml.) was stirred at room temperature for 2 days. The undissolved sugar (125 g.) was separated and the filtrate made alkaline with sodium hydroxide and concentrated. The residue was diluted with water and extracted with chloroform and the chloroform evaporated to give crude " α "-di*iso*propylidene fructose (137 g.) which probably contained considerable quantities of " β "-di*iso*propylidene fructose and di*iso*propylidene glucose but could be methylated as described below to give 3-methyl di*iso*propylidene fructose of good quality.

3-*Methyl* Di*iso*propylidene *Fructose*.—(a) *From pure " α "-di*iso*propylidene fructose.* A mixture of " α "-di*iso*propylidene fructose (52 g.; m. p. 115—117°), acetone (100 ml.), and pulverized sodium hydroxide (21·4 g.) was treated at 40—50°, with stirring, with methyl sulphate (28·4 ml., added dropwise during 75 minutes). Methylation was completed by warming at 50° for 90 minutes and finally at 55—60° for 3 hours. The sludge was diluted with water and extracted with chloroform, and the chloroform extracts were washed with water and concentrated to give 3-methyl di*iso*propylidene fructose (53 g.; m. p. 110—112°). One crystallization from hexane (200 ml.) gave 45 g. (82%), m. p. 113—117°.

(b) *From crude " α "-di*iso*propylidene fructose obtained from invert sugar.* The crude derivative (250 g.) was mixed with acetone (500 ml.) and sodium hydroxide (144 g.) and warmed with stirring to 45°. Methyl sulphate (183 ml.) was added at 40—50° during 75 minutes and methylation was completed by warming at 50° for 1 hour and finally at 55—60° for 3 hours. The crude product (272 g.), isolated as in (*a*), crystallized from hexane (300 ml.), to give 3-methyl di*iso*propylidene fructose (110 g., 42%; m. p. 115—117°).

(c) *From crude " α "-di*iso*propylidene fructose obtained from sucrose.* The crude material (137 g.) was methylated as in (*b*) with proportionate amounts of materials, and the crude product crystallized from hexane, to give 3-methyl di*iso*propylidene fructose (39·5 g.; m. p. 110—115°).

Hydrolysis of 3-*Methyl* Di*iso*propylidene *Fructose to* 3-*Methyl Fructose*.—(a) *By an acidic ion-exchange resin.* A mixture of 3-methyl di*iso*propylidene fructose (27·4 g.), ion-exchange resin (5 g.; Amberlite IR-120, acid form, Rohm and Haas Co., Philadelphia), and water (100 ml.) was stirred at 95—100° for 5—6 hours. The resin was then removed, and the solution decolorized with charcoal (4 g.) and concentrated to a syrup which crystallized on being rubbed with acetone (35 ml.). This crystalline 3-methyl fructose (17·2 g., 89%; m. p. 119—121°) recrystallized from methanol and melted at 124—126°.

(b) *With water at* pH 2·6. 3-Methyl di*iso*propylidene fructose (27·4 g.) was digested for 5 hours on a steam-bath with 3 parts of water acidified to pH 2·6 with sulphuric acid. The hydrolysate was decolorized with charcoal and refined as in (*a*), to give 3-methyl fructose (18·2 g., 93%; m. p. 119—121°).

Mixtures of Approximately Equal Proportions of 1- *and* 3-*Alkyl Glucose from Sucrose.*—Mixtures of the alkyl hexoses (methyl, ethyl, and propyl) were prepared from sucrose by fission, treatment with acetone, alkylation, and hydrolysis by methods similar to those described above.

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