[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF CREIGHTON UNIVERSITY]

NEW METHOD FOR THE SYNTHESIS OF LONG CARBON-CHAIN SUGARS.[1] CONDENSATION OF DIETHYL ACETONEDICARBOXYLATE WITH 1,2-*O*-ISOPROPYLIDENE-D-XYLOPENTADIALDOSE, 4,6-BENZYLIDENE-GLUCOSE AND 2,3,4,5-TETRA-*O*-ACETYL-GALACTARICDIALDEHYDE

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The condensation of aldehydo or monoaldehydo-*O*-isopropylidene dialdehyde sugars with 5-(*p*-hydroxy or acetoxyphenyl)cyclohexanedione-1,3 was reported in a recent publication (1). Diethyl acetonedicarboxylate is also a 1,3-dicarbonyl compound having two methylene groups, both of which could condense with the aldehydo form of aldoses or dialdoses giving derivatives of long carbon chain sugars. Hitherto the lengthening of the carbon chain in sugars was done stepwise, one, two, or three carbons at a time (2–5).

The present report deals with the condensation of diethyl acetonedicarboxylate with: (a) 1,2-*O*-isopropylidene-D-xylopentadialdehyde, (b) 4,6-*O*-benzylidene glucose, and (c) 2,3,4,5-tetra-*O*-acetyl-galactaricdialdehyde. The ester and the respective sugar were refluxed in benzene or in 75% methanol using piperidine as catalyst. Details of the procedure are given in the experimental part.

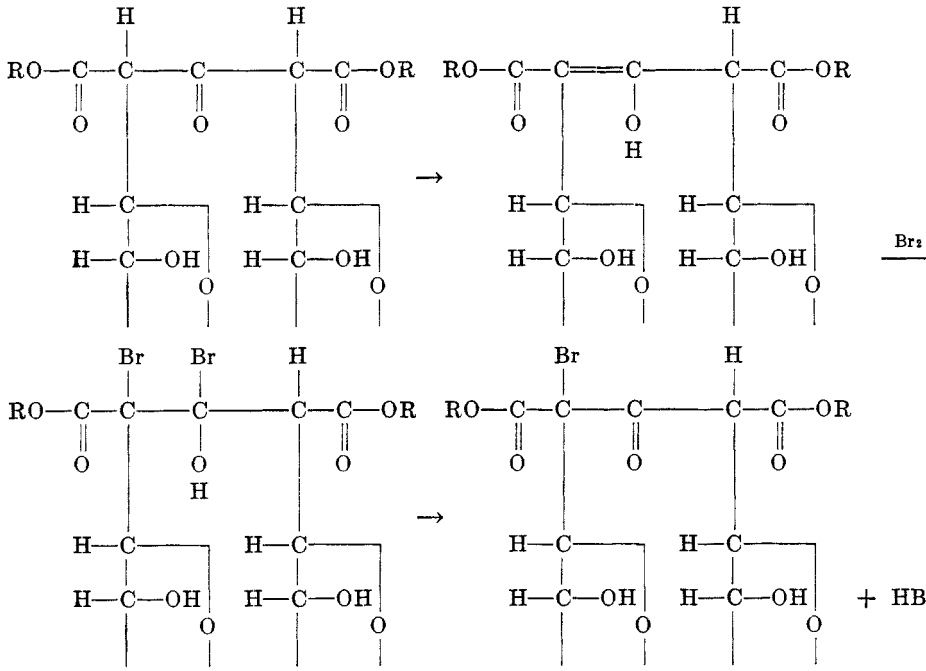
In condensation (a), two moles of 1,2-*O*-isopropylidene-D-xylotrihydroxyglutaric dialdehyde reacted with one mole of diethyl acetonedicarboxylate to produce one mole of a product $C_{25}H_{34}O_{13}$ and two moles of water. Since the xylopentodialdehyde used in (a) possesses only one functional aldehydic group, the condensation has been assumed to occur between this aldehyde group at C_5 and the active methylene group of diethyl acetonedicarboxylate, giving structure I, Table I.

The hydroxylation of the double bonds or other transformations in this type of condensation products will give sugars which may be of physiological, industrial, and scientific interest. Hydrolysis of the isopropylidene groups in structure I, for example, could give rise to two aldehydes and might open the way for a chain polymerisation with diethyl acetonedicarboxylate or other appropriate compounds. It could also open the field for glycoside or polysaccharide formation of longer carbon-chain sugars. By blocking the ketonic group, hydrolyzing the carbethoxy groups, and lactonizing the products, *alpha-beta* unsaturated lactones may be formed.

Condensation (b) is assumed to follow the same pattern as (a), giving III and IV, Table I as initial products of the aldol condensation, although subsequent reactions due to resonance or pyranose ring formation may give rise to isomeric

[1] An attempt to condense glucose with diethyl malonate and diethyl acetonedicarboxylate, with the object of making longer carbon-chain sugars, was made by the present author at Washington Square College, New York University, Jan. 20, 1932. Because of unusual conditions and other interests the problem was shelved, but it was resumed in this laboratory along with other projects.

structures. In a preliminary experiment where a sample of III in carbon tetrachloride was brominated until the solution became light brown, a derivative was obtained, m.p. 173°, the carbon and hydrogen analysis of which indicated that it was a monobromo derivative. This result may be accounted for if one assumes that III had rearranged to a structure of the pyranose type and that the bromination took place as follows:



Under the experimental conditions the products in condensation (c) lost acetic acid, resulting in conjugated double bonded compounds. The results suggest that the following reactions may have taken place:

(*1*) Ester + acetylated dialdehydo sugar → $2H_2O$ + 2HOAc + Product VI

(*2*) 2 Esters + acetylated dialdehydo sugar → $2H_2O$ + 2HOAc + Product VII.

In reaction (*1*) other cyclic polymeric products having the same percentage composition are possible, but such cyclizations may be unlikely. The work on condensation (c) is preliminary. Further investigation with varying conditions and catalysts will follow.

There is evidence (6) that the product of the alcoholic alkaline hydrolysis of dimethyl tetra-*O*-acetyl mucate is α,α'-dihydroxy muconic acid having a *trans-trans* structure

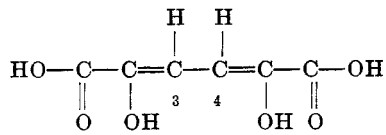
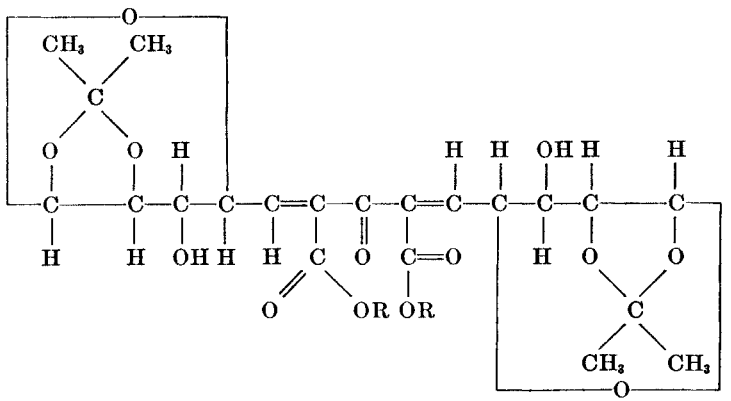
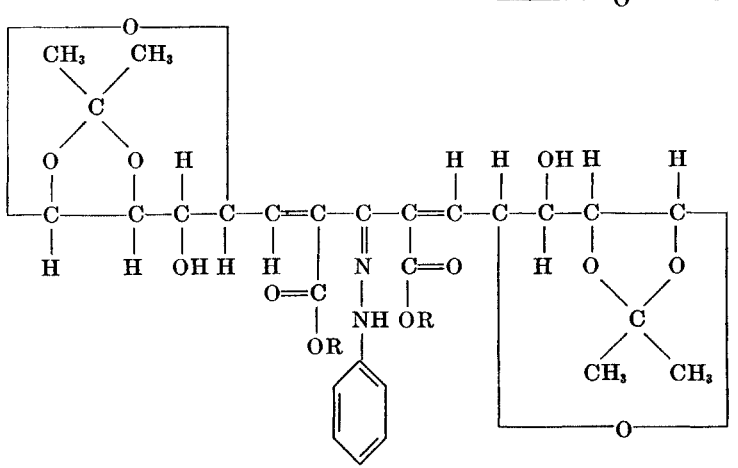


TABLE I

Long Carbon-Chain Sugars

Number	Structure	Formula	Analyses			
			Calc'd		Found	
			C	H	C	H
I		$C_{25}H_{34}O_{13}$	55.35	6.31	55.86 55.66	6.56 6.19
II		$C_{31}H_{40}N_2O_{12}$		4.43[a]		4.71[a]

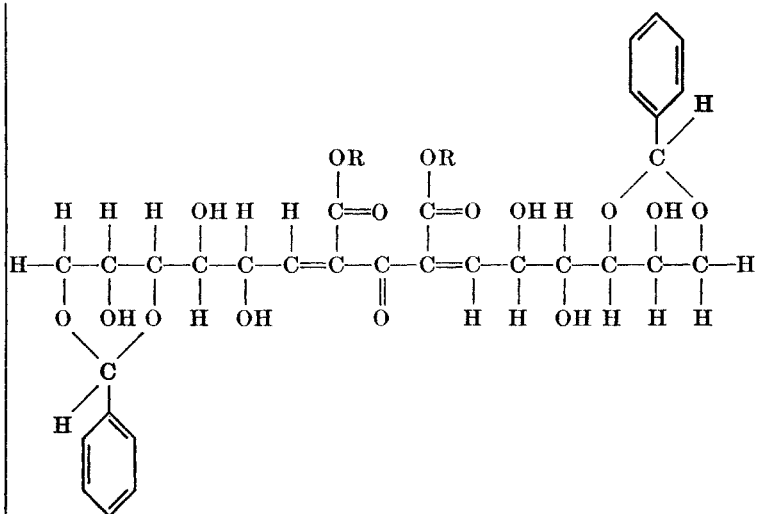
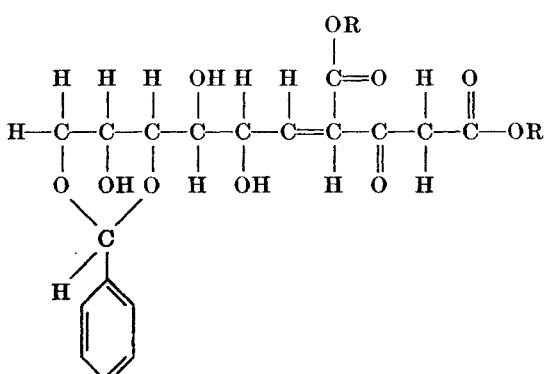
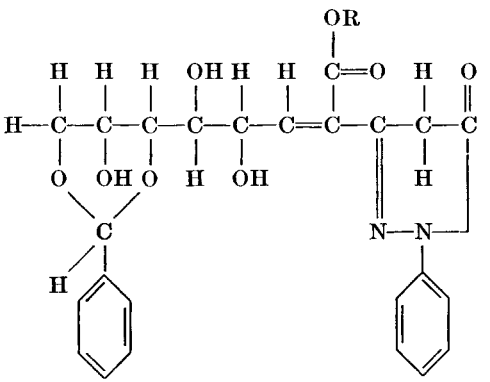
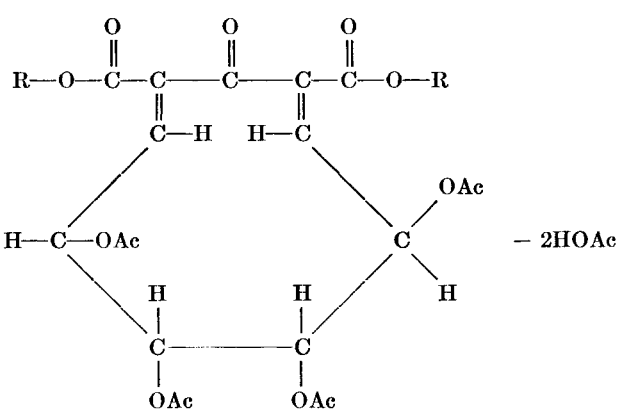
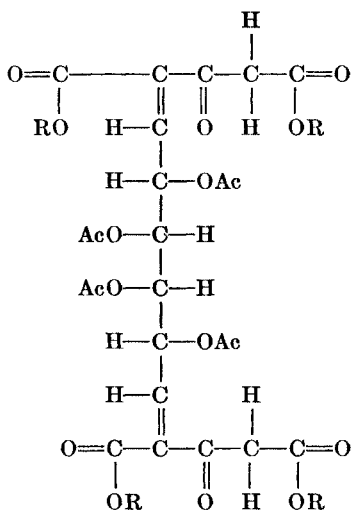
III		$(C_{35}H_{42}O_{15})_2 \cdot H_2O$	59.06	6.09	59.20 59.52	6.25 6.47
IV		$C_{22}H_{28}O_{10}$	58.33	6.19	58.44	6.20

TABLE I (*Continued*)

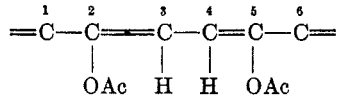
Number	Structure	Formula	Analyses			
			Calc'd		Found	
			C	H	C	H
V		$C_{26}H_{28}N_2O_8$	62.89	5.68	63.12	6.15
VI		$C_{19}H_{20}O_9$	57.86	5.00	57.71	4.72

VII		– 2HOAc	$C_{32}H_{42}O_{18}$ – 2HOAc	56.56	5.72	56.80	6.18

[a] These are values for nitrogen.

The inversion of C_3 and C_4 may have resulted from change of the enol to the keto and back to the *trans-trans* enol which is the more stable form.

The elimination of two molecules of acetic acid in each of the products VI and VII, Table I may take place in a similar way as in the case of the dimethyl tetra-*O*-acetyl mucate giving



As the two acetoxy groups, presumably the C_2 and C_5 in VI and VII, have not been hydrolyzed, it is assumed that ketonization followed by enolization did not take place; and therefore C_3 and C_4 may not have inverted to give structures of the α,α'-dihydroxy muconic acid type.

Condensation of glucose with methyl acetoacetate and other 1,3-dicarbonyl compounds has been done in the past in connection with the problem of anti-ketogenesis. The theory that glucose or its metabolic products combine in the body with acetoacetic acid or other acetone bodies to produce substances which can be oxidized faster than the acetone bodies themselves has been advanced by various authors. To test this theory *in vitro* glucose and its metabolic products were condensed (7, 8) with methyl acetoacetate by heating the reactants with anhydrous zinc chloride in alcohol. The zinc chloride method has been used also to condense carbohydrates with other 1,3-dicarbonyl compounds (6, 9–11). The zinc chloride acted as condensing agent and to some extent as a dehydrating agent. The products obtained were substituted furan type of compounds in which one substituent was a polyhydroxyalcohol.

The compounds in Table I may be named as derivatives of dicarbethoxy acetone or each of their formulae may be separated into segments and named accordingly. For long chain carbon sugars a scientific name should be given descriptive of the structural configuration and including some of the features of the Geneva system as well as features of the conventional carbohydrate nomenclature and the suggestions of well-known authors (12, 13), whenever such suggestions are applicable.

The structures shown in Table I are assumed. Formulae III and IV may represent the initial products of the respective aldol condensations. Chemical proof of the structure of the final products will be the object of future investigation.

EXPERIMENTAL

Product I was prepared as follows: To a benzene solution of 6.7 g. of 1,2-*O*-isopropylidene-D-xylotrihydroxyglutaric dialdehyde (14), 4 ml. of diethyl acetonedicarboxylate and two drops of piperidine were added. The mixture was allowed to stand at room temperature overnight and then it was refluxed for an hour. To the benzene solution distilled water was added and the mixture was subjected to distillation until all the benzene was distilled off. A viscous syrup of amber color settled. The water was decanted and the syrup was boiled again with fresh distilled water to extract any unreacted 1,2-*O*-isopropylidene-D-xylotrihydroxyglutaric dialdehyde. Since the product of the condensation is less soluble than the reagent acetonedicarboxylate in each of the following two-component mixtures (a)

benzene-petroleum ether, (b) ether-petroleum ether, and (c) alcohol-water, it was purified as follows. The viscous syrup was dissolved in benzene and then precipitated with petroleum ether. The benzene-petroleum ether was decanted and the residue was dissolved in ether. To the ether solution petroleum ether was added. After decanting the supernatant liquids the residue was dissolved in alcohol and then it was reprecipitated with distilled water. Decanting the alcohol-water mixture left a residue that was of light amber color. When it was dried it was resin-like and could be pulverized to an amorphous powder. It sintered at 80° and melted at 110°. A sample of the viscous syrup kept in a little vial since Nov. 1953 has not crystallized.

In another experiment the ester, the sugar, and the piperidine were dissolved in 75% methanol and the mixture was refluxed for half an hour. The solvents were evaporated and the remaining syrup was boiled with distilled water. The water-insoluble material was dissolved in methanol and reprecipitated with distilled water. The residue was filtered then dried in a vacuum desiccator. The product of this experiment had the same physical appearance, the same physical constants, and gave practically the same analysis for carbon and hydrogen as the previous experiment.

Phenyl hydrazone derivative (II) was prepared from I and phenylhydrazine. The hydrazone was recrystallized from 50% methanol. It sintered at 66°, turned to a viscous dark material adhering to one side of the inner wall at 88°, and settled at the bottom of the capillary at 110°.

Product (III) was prepared as follows: One gram of 4,6-*O*-benzylidene glucose (15), 0.36 g. of diethyl acetonedicarboxylate, one drop of piperidine, and 25 ml. of 50% methanol were refluxed for eight hours. The solution concentrated to a thick, brownish-amber-colored syrup, which was purified as follows. The syrup was washed with ether to extract any unreacted diethyl acetonedicarboxylate. The ether was decanted and the residue was boiled with distilled water to dissolve any unreacted 4,6-*O*-benzylideneglucose. After decanting, the residue was dissolved in methyl alcohol. To the solution distilled water was added. An orange-brown syrup separated which solidified. The brown-orange precipitate was filtered and then dissolved in ethanol. The solution was filtered and allowed to vaporize. The brown-orange amorphous residue was washed with ether, then boiled again with distilled water. The insoluble part was dried in a vacuum desiccator. It sintered at 86° and melted at 120°.

A monobromo derivative of III was obtained by treating a sample of III with bromine in carbon tetrachloride till the solution became light brown. After evaporation of the carbon tetrachloride the product was recrystallized from methanol, m.p. 173°.

Anal. Calc'd for $C_{35}H_{42}BrO_{15}$: C, 53.71; H, 5.24.

Found: C, 54.04; H, 5.15.

Product (IV) was prepared in the same way as compound III except that the molar proportions of the ester to the sugar were 1:1. The product was amorphous. It sintered at 85° then bubbled and began to rise in the capillary at 86°.

The phenylpyrazolone derivative (V) was made from IV and phenylhydrazine. The product had an orange color. It was recrystallized from 50% methanol. It sintered at 100° and melted at 105–110°. On further heating it bubbled at 140°.

2,3,4,5-Tetra-O-acetyl-galactaricdialdehyde was prepared by the Rosenmund's catalytic reduction (16) of tetraacetyl-*o*-galactaryl chloride. It melted at 189°.

Anal. Calc'd for $C_{14}H_{18}O_{16}$: C, 48.55; H, 5.23.

Found: C, 48.51; H, 5.68.

Product (VI) was prepared as follows: 0.350 g. of 2,3,4,5-tetra-*O*-acetyl-galactaric-dialdehyde, 0.4 ml. of diethyl acetonedicarboxylate, a third of a drop of piperidine, and 10 ml. of 50% methanol were refluxed for half an hour. The alcohol and excess ester were removed. The remaining dark syrup was dissolved in methyl alcohol, and the solution was filtered and allowed to vaporize slowly. Brownish crystals were formed which sintered at 65° and melted at 70–75°.

Product VII was prepared in the same way as product (VI) except that the molar pro-

portions of the reagents were 1:1. The product sintered at 58° and melted at 65–70° and bubbled at 75°. We intend to extend this work to prepare other long carbon-chain sugars by varying the initial sugar as well as the type of dicarbonyl compounds.

SUMMARY

A new method for the synthesis of long carbon-chain sugars is described.

Condensation of diethyl acetonedicarboxylate with 1,2-*O*-isopropylidene-D-xylopentadialdehyde, using piperidine as catalyst, gave a derivative of an unsaturated 13 carbon-chain dialdehydo-7-keto sugar assumed to be (1,2–12,13)$_\alpha$ - *O* - diisopropylidene-6,8 - dicarbethoxy - 7-oxo - (3,11)$_\beta$ - dihydroxy-5,8-diene-D-tridecadialdoxylofuranose or 1,3-dicarbethoxy-1,3-[bis-(4′,5′-*O*-isopropylidene-D-xylofuranosylidene)]acetone (I).

A phenylhydrazone, (1,2–12,13)$_\alpha$-*O*-diisopropylidene-6,8-dicarbethoxy-7-(phenylhydrazone) - (3,11)$_\beta$ - dihydroxy - 5,8 - diene - D - tridecadialdoxylofuranose ((II), was prepared from (I) and phenylhydrazine.

Condensation of diethyl acetonedicarboxylate with 4,6-*O*-benzylideneglucose gave a derivative of a 15 carbon-chain 8-keto sugar (III). With molar proportions of 1:1 of the ester to the sugar, product IV was obtained. A phenylpyrazolone derivative V was prepared from IV and phenylhydrazine. Bromination of III gave a monobromo derivative which may have resulted from the enol form of the pyranose rather than from the glucosylidene isomer.

The products of condensation of diethyl acetonedicarboxylate with 2,3,4,5-tetra-*O*-acetyl-galactaricdialdehyde lost acetic acid, rendering derivatives of unsaturated cyclic or open chain compounds with acetoxy, keto, and carbethoxy groups, VI and VII.

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