[CONTRIBUTION FROM THE ORGANIC CHEMISTRY SECTION, DIVISION OF CHEMISTRY, NATIONAL BUREAU OF STANDARDS]

Branched-chain Higher Sugars. III. A 4-C-(Hydroxymethyl)-pentose[1]

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The applicability of a mixed aldol reaction for carbohydrate synthesis is demonstrated by the reaction of 5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose (I) with formaldehyde. 4-*C*-(Hydroxymethyl)-1,2,-*O*-isopropylidene-L-*threo*-pentofuranose (II) is isolated in 75% yield, and probably results from reduction of the condensation product by a second molecule of formaldehyde through a crossed-Cannizzaro reaction. Hydrolysis of II gives the new branched-chain hexose. Oxidation of the sugar led to isolation of a crystalline calcium hexonate, and degradation of the latter yields previously unreported L-apiose. An alternative procedure involving I and formaldehyde, co-products of periodate oxidation of 1,2-*O*-isopropylidene-D-glucofuranose and used without intermediate crystallization of I, gives II in an over-all yield of 58%.

Earlier papers in this series[2] have shown that aldol "self-condensations" take place with carbohydrates larger than triose, if these substances are modified by alkali-stable substituent groups which prevent (a) existence of the reactant in an intramolecular hemiacetal form, and (b) enol migration below the carbon atom adjacent to the carbonyl group of the reactant. The products, double the size of the self-condensing substances, have branched carbon chains; thus, from a substituted pentose, there was obtained a derivative of 9-aldo-4-*C*-formyl-L-*xylo*-L-*ido*-nonose,[2a,b] and, from a substituted tetrose, there resulted a 3-*C*-formyl-D-*glycero*-D-*talo*-heptitol derivative.[2c] In order to examine the possibility of enlarging the applicability of the aldol reaction for carbohydrate synthesis, a mixed aldol reaction was investigated.

5-Aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose,[3] which has been found to undergo aldol self-condensation,[2a,b] was employed as one of the reactants. Formaldehyde was selected as the second reactant for the mixed aldol reaction because self-additions, as well as mixed-additions, are possible in an aldol synthesis involving unlike carbonyl-containing substances; however, if one of the reactants (formaldehyde) has no α-hydrogen atoms, it is restricted to the role of adding to the activated α-carbon atom of the other reactant.[4]

A molar ratio of one part of I, 2.6 parts of formaldehyde and two parts of sodium hydroxide was employed. After six days of reaction at room temperature, about half of the alkali remained to be neutralized. Upon working up the reaction mixture, a 75% yield of a crystalline product (II) was isolated.

Acid hydrolysis of II, and quantitative hypoiodite oxidation of the hydrolysis product III, demonstrated the presence of but one aldehyde group per molecule of III. In addition, the oxidation of III led to isolation of a crystalline salt IV, whose composition corresponded to that of a calcium hexonate. These properties showed that the product isolated was a *reduced* form of the anticipated acetonated dialdehyde condensation product (V). Reduction of V probably resulted from interaction with the extra formaldehyde present, through a mixed-Cannizzaro reaction. Evidence for this is found in the neutralization of about one molar equivalent of the alkali present in the reaction mixture. Other examples involving formaldehyde in mixed-aldol syntheses that are followed by crossed-Cannizzaro reactions are known.[5]

The structure and configuration of II could at once be predicted to be that of 4-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-L-*threo*-pentofuranose, because (a) the probable site of condensation on I would be at carbon atom 4, (b) the asymmetry at this position would be lost by the subsequent reduction, and (c) the alkaline condition of the reactions would not be expected to affect the remainder of the molecule. That II was the product obtained was proved by preparation of its phenylosazone VI. The enantiomorph of VI had been reported by Utkin,[6] who had prepared the phenylosazone of 4-*C*-(hydroxymethyl)-D-*glycero*-pentulose. The enantiomorphic properties of VI corresponded to this previously described derivative. Further corroboration was obtained by degrading IV, by the Ruff[7] method, to L-apiose. While D-apiose[8] is known only as a sirup, it has been characterized by its crystalline N^2-benzyl-N^2-phenylhydrazone.[8a,b] The corresponding hydrazone was prepared from the L-apiose, and its properties were correct for the enantiomorph of the known product. Sirupy L-apiose was regenerated, by the benzaldehyde method, from the hydrazone, and showed $[\alpha]^{20}\text{D}$ of $-5°$ (in water). Values of $+3.8$ to $6.4°$ are recorded for the D-sugar.[8]

The two reactants for synthesis of II are co-products of periodate oxidation of 1,2-*O*-isopropylidene-D-glucofuranose.[3] It was of interest to de-

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(1) (a) This work was conducted as part of a project on the development of methods for the synthesis of radioactive carbohydrates, sponsored by the Division of Research, Atomic Energy Commission; H. S. Isbell, project leader. (b) ADDED IN PROOF.—The recent paper of F. Weygand and R. Schmiechen [*Ber.*, **92**, 535 (1959)] reports a synthesis of calcium 4-*C*-(hydroxymethyl)-L-*threo*-pentonate *di*hydrate by additions of diazomethane to an L-threaric acid derivative followed by degradation of the branched-chain hexonate to sirupy L-apiose.

(2) (a) R. Schaffer and H. S. Isbell, THIS JOURNAL, **80**, 756 (1958); (b) **81**, 2178 (1959); (c) R. Schaffer, *ibid.*, **81**, 2838 (1959).

(3) (a) K. Iwadare, *Bull. Chem. Soc. Japan*, **16**, 40 (1941); (b) V. Brocca and A. Dansi, *Ann. chim. (Rome)*, **44**, 120 (1954); (c) R. Schaffer and H. S. Isbell, *J. Research Natl. Bur. Standards*, **56**, 191 (1956); (d) R. Schaffer and H. S. Isbell, THIS JOURNAL, **79**, 3864 (1957).

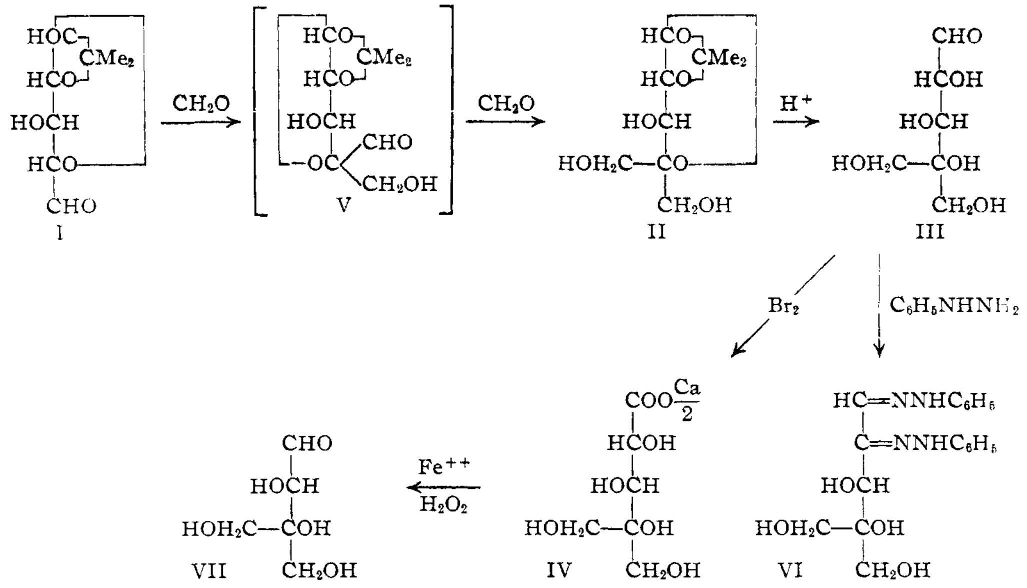
(4) An aldol-like self-condensation of formaldehyde occurs giving "formose" [A. Butlerow, *Compt. rend.*, **53**, 145 (1861); *Ann.*, **120**, 295 (1861); O. Loew, *J. prakt. Chem.*, [2] **33**, 321 (1886)], but this reaction appears to be preceded by an acyloin condensation to glycolaldehyde, which catalyzes the aldol addition reaction [W. Langenbeck, *Naturwissenschaften*, **30**, 30 (1942)].

(5) T. A. Geissman, in "Organic Reactions," R. Adams, ed., John Wiley and Sons, Inc., New York, N. Y., 1944, Vol. 2, p. 100.

(6) L. M. Utkin, *Doklady Akad. Nauk S.S.S.R.*, **67**, 301 (1949).

(7) (a) O. Ruff and G. Ollendorff, *Ber.*, **32**, 550 (1899); (b) R. C. Hockett and C. S. Hudson, THIS JOURNAL, **56**, 1632 (1934).

(8) (a) E. Vongerichten and F. Müller, *Ber.*, **39**, 235 (1906); (b) O. T. Schmidt, *Ann.*, **483**, 115 (1930); (c) P. A. J. Gorin and A. S. Perlin, *Can. J. Chem.*, **36**, 480 (1958).



termine how satisfactorily II could be made from this readily available D-glucose derivative, without intermediate crystallization of I. The synthesis was therefore carried out from the monoisopropylidene-D-glucose, using the sirupy mixture of I and formaldehyde (after separation of the inorganic products of the periodate oxidation). Alkali and additional formaldehyde were added. The yield of II by this procedure was 58% on the basis of the monoisopropylidene-D-glucose.

Experimental

Preparation of 4-*C*-(Hydroxymethyl)-1,2-*O*-isopropylidene-L-*threo*-pentofuranose (II).—A stirred, ice-cold solution of 28.8 g. of hydrated, crystalline, dimeric 5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose (bis-[5-aldo-1,2-*O*-isopropylidene-D-*xylo*-pentofuranose]-3,5′:5′,5-cyclic acetal, hemihydrate)[3c,d] in 320 ml. of water was treated with 30 ml. of a 37% aqueous solution of formaldehyde and with 300 ml. of 1 *N* sodium hydroxide. After 6 days at room temperature, the colorless solution was neutralized with formic acid (about 0.15 mole), and then concentrated under reduced pressure, and dehydrated further by adding abolute ethanol and reconcentrating several times. The sodium formate which crystallized during this process was removed by filtration from the ethanol-soluble material. Concentration of the filtrate left a sirup, which was incompletely soluble in acetone. The acetone solution was concentrated under reduced pressure, and the sirupy material was finally taken up in chloroform. The product crystallized from this solvent. The yield of II was 24.7 g., m.p. 97–99°, $[\alpha]^{20}_D$ −11.8° (*c* 2, water), $[\alpha]^{20}_D$ −7.5° (*c* 4, ethanol). The product did not react with boiling Fehling solution and was not affected by treatment with sodium borohydride.

Anal. Calcd. for $C_9H_{16}O_6$: C, 49.1; H, 7.3. Found: C, 48.9; H, 7.2.

4-*C*-(Hydroxymethyl)-L-*threo*-pentose (III).—At 22°, the initial levorotation of 10 ml. of a 0.2 *N* hydrochloric acid solution containing 0.55 g. of II changed in less than 4 hr. to an $[\alpha]^{22}_D$ of +63° (calculated for 0.45 g. of III). (At 90°, hydrolysis of a similar solution is complete in less than 10 min.) The acid was removed with anion-exchange resin,[9] and the solution was concentrated under reduced pressure and twice reconcentrated after addition of water. The sirupy sugar was soluble in methanol, pyridine and acetic acid, but insoluble in ethanol or 2-propanol. The product reduced boiling Fehling solution. Bakers' yeast did not ferment the sugar. Paper chromatography with 1-butanol–ethanol–water (4:1:1.2), and aniline hydrogen oxalate as developer, showed the sugar as a violet spot with an R_f slightly less than that of glucose. The crystalline sugar has not been obtained.

A sample of 0.231 g. of II was hydrolyzed as described above, neutralized with dilute sodium hydroxide, and concentrated to remove acetone. The hydrolysis product, oxidized with iodine by the method of Kline and Acree,[10] consumed 99.3% of the theoretical amount of iodine required for oxidation of 0.105 mmole of an aldohexose.

Calcium 4-*C*-(Hydroxymethyl)-L-*threo*-pentonate Pentahydrate (IV).—Hydrolysis of 4.4 g. of II in 50 ml. of 0.2 *N* hydrochloric acid was carried out as described above. The mixture was neutralized with barium carbonate and then freed of acetone by concentration under reduced pressure. Bromine oxidation of the sugar was conducted by the method of Hudson and Isbell.[11] The concentrate was treated with 200 ml. of ice-cold water, 12 g. of barium benzoate monohydrate and 1.2 ml. of bromine. The mixture was worked up in the usual way, except that the solution of silver salts was treated with 50 ml. of cation-exchange resin.[12] The acid solution thus obtained was boiled for 0.5 hr. with 2 g. of calcium carbonate. After cooling, the mixture was filtered and the filtrate was concentrated at reduced pressure. Calcium 4-*C*-(hydroxymethyl)-L-*threo*-pentonate pentahydrate crystallized from the aqueous concentrate; yield 4.0 g., $[\alpha]^{20}_D$ +13.7° (*c* 1.3, water), m.p. 137° (gas evolution).

Anal. Calcd. for $(C_6H_{11}O_7)_2Ca.5H_2O$: C, 27.7; H, 6.2; Ca, 7.7. Found: C, 27.8; H, 6.3; Ca, 7.9.

The $[\alpha]^{20}_D$ of 4-*C*-(hydroxymethyl)-L-*threo*-pentonic acid, prepared by addition of 0.5 ml. of 1 *N* hydrochloric acid to 10 ml. of a solution of 0.13 g. of IV, was +7.2° (initial value, extrapolated). The specific rotation of the solution increased to a maximum of +27° in 2 hr. and then slowly decreased during the next 5 days to +5° (all values are calculated as the acid).

4-*C*-(Hydroxymethyl)-L-*glycero*-pentose Phenylosazone (VI).—Hydrolysis of 1.1 g. of II, neutralization, and removal of acetone were carried out as described above. The phenylosazone was prepared in the usual way. The crude product, washed with chloroform to remove adhering colored material, weighed 0.73 g. It was recrystallized first from ethanol–water and then from methanol–water; m.p. 167°, $[\alpha]^{20}_D$ −43.7° (*c* 1, acetone). Utkin[6] reported m.p. 166° and $[\alpha]^{19}_D$ +43.7° for the enantiomorph.

Anal. Calcd. for $C_{18}H_{22}N_4O_4$: C, 60.3; H, 6.2. Found: C, 60.5; H, 6.4.

L-Apiose [3-*C*-(Hydroxymethyl)-L-*glycero*-tetrose] (VII).—Ruff degradation[7a] of IV was carried out according to the directions of Hockett and Hudson.[7b] The reaction mixture

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(9) Duolite A-4, Chemical Process Co., Redwood City, Calif.

(10) G. M. Kline and S. F. Acree, *Bur. Standards J. Research*, **5**, 1063 (1930).

(11) C. S. Hudson and H. S. Isbell, THIS JOURNAL, **51**, 2225 (1929).

(12) Amberlite IR-120H, Rohm and Haas Co., Philadelphia, Pa.

was worked up by deionization with cation[12] and anion exchange[9] resins. In this way, from 0.88 g. of IV there was obtained 0.22 g. of sirupy degradation product. The 3-*C*-(hydroxymethyl)-L-*glycero*-tetrose N^2-benzyl-N^2-phenylhydrazone was prepared, m.p. 136–137°, $[\alpha]^{20}_{5460}$ +94° and $[\alpha]^{20}_{5790}$ +79.5° (*c* 1, pyridine). For the enantiomorph,[8a] the m.p. was reported[8b] as 137–138° and $[\alpha]^{20}_{5460}$ −94° and $[\alpha]^{25}_{5790}$ −78.5°.

Anal. Calcd. for $C_{19}H_{24}N_2O_6$: C, 65.4; H, 6.7. Found: C, 65.6; H, 6.7.

The benzylphenylhydrazone was treated with benzaldehyde, to give L-apiose, $[\alpha]^{20}D$ −5° (*c* 8, water). For naturally occurring, sirupy D-apiose[8a,b] the following values are given: $[\alpha]^{20}D$ +3.8°, $[\alpha]^{15}D$ +5.6° and, for a synthetic[8c] D-apiose, $[\alpha]^{25}D$ +6.4°.

Preparation of II from 1,2-*O*-Isopropylidene-D-glucofuranose.—A solution of 50 g. of sodium metaperiodate in 400 ml. of water was treated with 50 g. of 1,2-*O*-isopropylidene-D-glucofuranose, then freeze-dried, extracted with chloroform, and concentrated as previously described.[3c] The sirupy product was dissolved in 500 ml. of water. The solution was treated with 45 g. of a 37% formaldehyde solution (aqueous) and then, after cooling, with 450 ml. of 1 *N* sodium hydroxide solution. After 6 days at room temperature, the mixture was treated for isolation of II as described above. The weight of product was 29 g. and its m.p. was 97–99°.

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WASHINGTON 25, D. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

The Conversion of D-Xylose-1-C^{14} into 2-Furaldehyde-α-C^{14}

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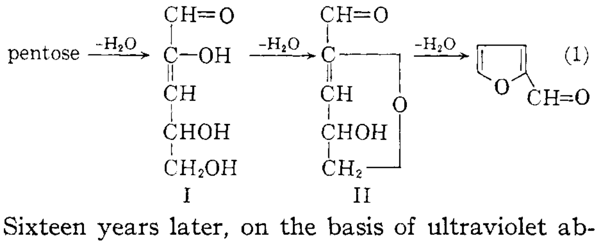
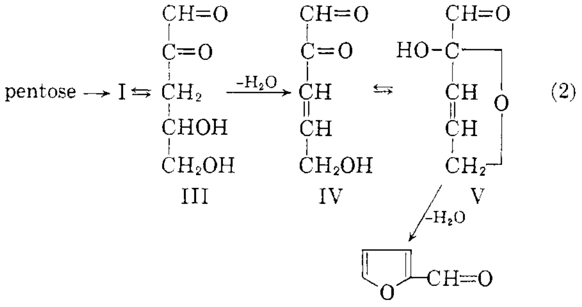
D-Xylose-1-C^{14} has been prepared and converted by acid into 2-furaldehyde-α-C^{14}. This product has been oxidized to 2-furoic-α-C^{14} acid, which was converted into 2-chloromercurifuran and $C^{14}O_2$. The latter furan derivative contained less than 2% of the radioactivity of its 2-furoic-α-C^{14} acid precursor, indicating that substantially all of Cl in the pentose starting material appeared as the aldehydic carbon in the 2-furaldehyde conversion product. These results accord with the predictions of speculative mechanisms for the pentose → 2-furaldehyde conversion, as well as with the results of a radiochemical investigation of the conversion of hexose to levulinic acid under similar acid conditions.

The world production of 2-furaldehyde (furfural) runs to the order of 100 million pounds per year,[2] ranking it about 67th[3] in annual volume among major organic chemicals. In view of this importance of 2-furaldehyde it is rather surprising that so relatively little has been established regarding the intimate mechanism of its production from pentoses and related substances under the usual acidic conditions. Arguing that the aldehyde group at C-1 in pentoses was essential to 2-furaldehyde production on the basis that *meso*-erythritol failed to yield furan under comparable conditions, Hurd and Isenhour, in 1932, proposed[4] the following mechanism for the pentose → 2-furaldehyde conversion.



(1)

Sixteen years later, on the basis of ultraviolet absorption spectra studies on solutions of D-glucose under acidic conditions, Wolfrom and co-workers arrived at an alternative explanation for the conversion of D-glucose to 4-hydroxymethyl-2-furaldehyde,[5] an explanation which was extended on the basis of similar evidence to the pentose → 2-furaldehyde conversion in 1949.[6] Wolfrom's mechanism for the latter conversion is illustrated in (2).



(2)

Similar intermediates have been postulated by Isbell[7] to explain the conversion of 2,3,4-tri-*O*-methylpentoses into 2-furaldehyde, as well as other related transformations.

While mechanisms 1 and 2 are plausible ones, they remain unsupported by way of isolation of any of the postulated intermediates as such, although Wolfrom and coworkers do report the isolation of the phenylosazone of the analog of IV formed during the related hydrochloric acid-catalyzed conversion of 2,3,4,6-tetra-*O*-methyl-D-glucose-en-1,2 into 5-(methoxymethyl)-2-furaldehyde.[8]

According to both mechanisms 1 and 2 the aldehydic carbon at C-1 in pentose does not change its oxidation state during the transformation to 2-furaldehyde and appears unaltered as the free alde-

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[1] Quaker Oats Co. Post-doctoral Fellow, 1956–1958. The authors are indebted to the Quaker Oats Co. for its generous support of their research.

[2] H. R. Duffey and P. A. Well, Jr., *Ind. Eng. Chem.*, **47**, 1408 (1955).

[3] "Chemical Economics Handbook," Stanford Research Institute, Vol. VI, 600.10a, Sept., 1955.

[4] C. D. Hurd and L. L. Isenhour, THIS JOURNAL, **54**, 317 (1932).

[5] M. L. Wolfrom, R. D. Schuetz and L. F. Cavalieri, *ibid.*, **70**, 514 (1948).

[6] M. L. Wolfrom, R. D. Schuetz and L. F. Cavalieri, *ibid.*, **71**, 3518 (1949).

[7] H. S. Isbell, *J. Research Natl. Bur. Standards*, **32**, 45 (1944); *cf.* also A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, p. 289 ff.

[8] M. L. Wolfrom, E. G. Wallace and E. A. Metcalf, THIS JOURNAL, **64**, 265 (1942).