Synthesis of Higher Ketoses by Aldol Reactions. I. Three D-Heptuloses

ROBERT SCHAFFER AND HORACE S. ISBELL

Division of Physical Chemistry, National Bureau of Standards, Washington 25, D. C.

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The 5,7-O-ethylidene acetals of D-*altro*-, D-*manno*-, and D-*gluco*-heptulose have been prepared directly from reaction of 2,4-O-ethylidene-D-erythrose with 1,3-dihydroxy-2-propanone. The ethylidene acetals of D-*altro*-heptulose and D-*manno*-heptulose were separated and isolated in crystalline form. The product having the D-*gluco* configuration was hydrolyzed to crystalline D-*gluco*-heptulose. The over-all yield of crystalline products was 44.5%. The synthesis demonstrates the utility of aldehydo-aldoses (having alkali-stable substituents) for the preparation of higher ketoses by the aldol synthesis.

The alkaline aldol reaction of trioses and smaller sugar fragments to form carbohydrates (up to and including the hexoses) is well documented.[1] Only recently has it been shown that the aldol reaction can be employed for the synthesis of higher aldoses (more than six carbon atoms). Certain β-hydroxy aldehydo-aldoses (having alkali-stable substituents that served to preclude the existence of these molecules in intramolecular, hemiacetal ring-forms) were found to undergo self-aldol reaction to yield branched-chain aldoses of double the original size.[2,3] In addition, one of these aldehydo-aldoses was successfully employed in a mixed-aldol reaction, yielding another branched-chain sugar.[4] The present paper concerns the application of the aldol reaction for synthesis of *higher ketoses* by utilizing such aldehydo-aldoses.[5]

Heretofore, higher ketoses have been prepared by (a) the Lobry de Bruyn-Alberda van Ekenstein rearrangement of isomeric higher aldoses[6] usually produced from a lower aldose by prior application of the cyanohydrin synthesis[7]; (b) the diazomethane reaction sequence[8] that lengthens the carbon chain by one carbon atom to afford the next higher ketose; (c) Sowden's nitroethanol procedure[9] that adds two carbon atoms to the chain; (d) selective degradation[10] of a 3-C-formylheptitol to a 3-heptulose[3]; and (e) biosynthetic, aldol reactions which employ a tetrose or pentose and D-fructose 1,6-diphosphate in the presence of an aldolase.[11]

1,3-Dihydroxy-2-propanone (I) would be required in forming a higher ketose by mixed-aldol reaction with an aldehydo-aldose [2,4-O-ethylidene-D-erythrose[3] (II) is used in this paper.] A nucleophilic attack on the carbonyl-carbon atom of II by the anionic form of I present in the alkaline solution would result in the formation of higher ketoses having a *normal* carbon chain. This would be analogous to the mixed-aldol reactions of compound I with 2- and 3-carbon hydroxy aldehydes, which have been shown to give a mixture of reducing sugars containing pentuloses[12] and hexuloses,[13] respectively. As new asymmetric centers would be produced at the carbon atoms where the chains are joined, four isomeric ketoses may result. These would be restricted to forming hemi-acetal pyranoid rings only, because the O-ethylidene substituent would block the hydroxyl groups at C-5 and C-7. In the synthesis, the pyranoid ring would probably serve to stabilize the aldols produced, with respect to the reactants. The system would be complicated, however, because the reactants could conceivably interact in the reverse manner, with the aldehydo-aldose serving as the enediol and the triose as the acceptor; also, additional products might arise from (a) reaction of C-2 of the triose enediol instead of C-3, (b) self-aldol reactions, and (c) isomerization[6b] and degradation[6b,14] reactions.

Preliminary experiments (using dilute aqueous calcium hydroxide, as well as barium hydroxide, to catalyze the reaction) gave evidence, obtained by paper chromatography, of the formation of at least two normal-chain O-ethylideneheptuloses and of dendroketose,[15] 4-*C*-(hydroxymethyl)-DL-*glycero*-pentulose. The latter is the product of self-aldol reaction of I. To compensate for this side reaction, the molar ratio of reactants I to II in the

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[1] (a) J. C. Sowden, "The Carbohydrates," W. W. Pigman, ed., Academic Press, Inc., New York, 1957, pp. 113–114. (b) L. Hough and J. K. N. Jones, *Advan. Carbohydrate Chem.*, **11**, 185 (1956).

[2] R. Schaffer and H. S. Isbell, *J. Am. Chem. Soc.*, **80**, 756 (1958); **81**, 2178 (1959).

[3] R. Schaffer, *ibid.*, **81**, 2838 (1959).

[4] R. Schaffer, *ibid.*, **81**, 5452 (1959).

[5] A statement that a heptulose is formed by an aldol reaction of D-erythrose with 1,3-dihydroxy-2-propanone is found in a paper by L. Hough and J. K. N. Jones, *Nature*, **167**, 180 (1951). This was based on work by K. B. Taylor of their laboratory, who detected on a paper chromatogram a spot that resembled that for a heptulose. No further information has been found in the literature.

[6] (a) E. M. Montgomery and C. S. Hudson, *J. Am. Chem. Soc.*, **52**, 2101 (1930); (b) J. C. Speck, Jr., *Advan. Carbohydrate Chem.*, **13**, 63 (1958).

[7] C. S. Hudson, *ibid.*, **1**, 1 (1945).

[8] (a) K. Gatzi and T. Reichstein, *Helv. Chim. Acta*, **21**, 186 (1938); (b) M. L. Wolfrom, R. L. Brown, and E. F. Evans, *J. Am. Chem. Soc.*, **65**, 1021 (1943).

[9] J. C. Sowden, *ibid.*, **72**, 3325 (1950).

[10] A. S. Perlin and Carol Price, *Can. J. Chem.*, **34**, 541 (1956).

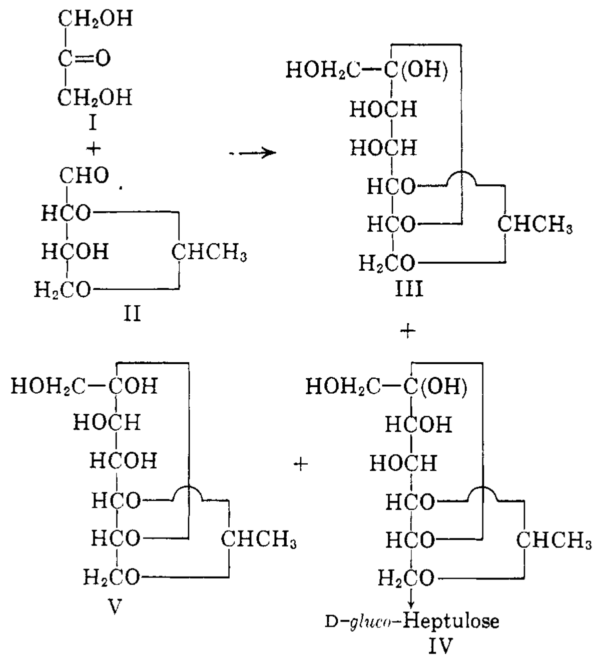
[11] (a) B. L. Horecker and P. Z. Smyrniotis, *J. Am. Chem. Soc.*, **74**, 2123 (1952); (b) L. Hough and J. K. N. Jones, *J. Chem. Soc.*, 342 (1953); (c) J. K. N. Jones and H. H. Sephton, *Can. J. Chem.*, **38**, 753 (1960).

[12] L. Orthner and E. Gerisch, *Biochem. Z.*, **259**, 20 (1933).

[13] E. Schmitz, *Ber.*, **46**, 2327 (1913).

[14] J. U. Nef, *Ann.*, **357**, 293 (1907); **376**, 1 (1910); **403**, 204 (1913).

[15] L. M. Utkin, *Dok. Akad. Nauk SSSR*, **67**, 301 (1949).



described preparation was raised to about 1.4 to 1. This ratio was selected by determining the proportion of reactants that, on reaction, produced the maximum dextrorotation per mole of II. The reaction time was prolonged beyond that required for attaining this optical rotation in order to allow excess compound I to be transformed into dendroketose, which, in contrast with I, could be readily separated from the O-ethylideneheptuloses by chromatography. Separation of the reaction products was effected by chromatography on high-capacity paper. Three ketose bands were detected. The slowest, *A*, contained dendroketose. Two closely situated bands, *B* and *C*, contained O-ethylideneheptuloses. From the slower of these two, *B*, a crystalline product, 5,7-O-ethylidene-D-*manno*-heptulose (III), was isolated in 7.2% yield. The structure of III was deduced from (a) its elementary composition, (b) isolation of D-*manno*-heptulose[16] on hydrolysis, and (c) the known stability of the ethylidene acetal linkage to alkaline conditions.[17] Upon acid hydrolysis, the mother liquor (from which compound III had been crystallized) yielded crystalline D-*gluco*-heptulose[18] (IV) in 20.1% yield. The fastest ketose band, *C*, yielded crystalline 5,7-O-ethylidene-D-*altro*-heptulose (V) in 17.2% yield. The structure of V was assigned from knowledge of the starting material and the fact that it gave sedoheptulosan hydrate[19] on hydrolysis. Although a specimen of D-*allo*-heptulose,[20] the anticipated fourth isomer, was available, to aid in identification, unequivocal evidence for the presence of this isomer was not obtained. The preponderance (about 5 to 1), obtained in the present synthesis, of the isomers (IV and V) having *trans* configurations at C-3 and C-4, relative to the *cis* isomer (III), corresponds in general with the findings of Fischer and Baer[21] and Hough and Jones[22] regarding the ratios of yields of *cis* and *trans* isomers obtained in their related syntheses of hexuloses and pentuloses.

The O-ethylideneheptuloses reported here are new derivatives of these sugars. Presumably, a variety of ketoses can be prepared by condensation of suitable aldehydo-aldose derivatives with 1,3-dihydroxy-2-propanone. The subject is being investigated further.

In our original preparation[3] of crystalline 2,4-O-ethylidene-D-erythrose, an *anhydrous* "dimer" was obtained. Only a slightly lower melting modification will now crystallize in our laboratory, and this form is solvated with half a molecule of ethanol per molecule. The properties of this material are reported. Dr. A. S. Perlin[23] has obtained yet another crystalline modification, which is hydrated.

Experimental

Bis(2,4-O-ethylidene-D-erythrose)-1,1′:1′,3-cyclic Acetal or [2,4-O-Ethylidene-1,3-O-(2,4-O-ethylidene-D-*erythro*-2,3-4-trihydroxybutylidene)-(1-hydroxy-D-erythritol)] Hemiethanolate.—The crystalline dimer of 2,4-O-ethylidene-D-erythrose was prepared from 4,6-O-ethylidene-D-glucose by the procedure previously described.[3] The product differed from that previously described in that it contained ethanol of crystallization. It melted at 144–144.5° and had $[\alpha]^{22}\text{D}$ −34° (initial)→−40° (4 hr.; *c* 1, water).

Anal. Calcd. for $C_{26}H_{46}O_{17}$: C, 49.3; H, 7.4. Found: C, 49.3; H, 7.1.

The average of several determinations of equivalent weight by hypoiodite oxidation was 98% of the value required for the "dimer" hemiethanolate.

Synthesis of O-Ethylideneheptuloses.—A 200-ml. aqueous solution of 3.8 g. of "dimeric" 2,4-O-ethylidene-D-erythrose hemiethanolate and 4.0 g. of 1,3-dihydroxy-2-propanone was mixed at 23° with 54 ml. of 0.232 *N* barium hydroxide; after 45 min., the mixture was treated with an excess of gaseous carbon dioxide. The suspension was filtered, the filtrate concentrated to a low volume under diminished pressure, and additional insoluble material was filtered off. Two drops of acetic acid were added and the remaining water was removed under diminished pressure, with several additions of absolute ethanol. The sirupy residue was chromatographed on four separate 18 × 22.5 in. sheets of Whatman seed-testing paper during 2.5 days, using 4:1:1.2 butanol–ethanol–water as irrigant. The bands of sugars were made visible by pressing each wet chromatogram[24] between two sheets of Whatman No. 1 paper of the above size until the latter were wet through and then spraying one transfer with silver nitrate and sodium

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[16] F. B. LaForge, *J. Biol. Chem.*, **28**, 517 (1916).

[17] S. A. Barker and E. J. Bourne, *Advan. Carbohydrate Chem.*, **7**, 137 (1952).

[18] W. C. Austin, *J. Am. Chem. Soc.*, **52**, 2106 (1930).

[19] J. W. Pratt, N. K. Richtmyer, and C. S. Hudson, *ibid.*, **74**, 2200 (1952).

[20] J. W. Pratt and N. K. Richtmyer, *ibid.*, **77**, 6326 (1955). The authors are indebted to Dr. N. K. Richtmyer for supplying a sample of this compound.

[21] H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **19**, 519 (1936).

[22] L. Hough and J. K. N. Jones, *Nature*, **167**, 180 (1951).

[23] Private communication from Dr. A. S. Perlin.

[24] H. H. Brownell, J. G. Hamilton, and A. A. Casselman, *Anal. Chem.*, **29**, 550 (1957).

hydroxide[25] and the other with Bial's orcinol reagent.[26] Three ketose bands were detected. Two of these were close to each other and were situated in the 1,3-dihydroxy-2-propanone region; the third was in the region usually occupied by hexoses. The similar bands from the four chromatograms were combined and eluted. Fraction A, the effluent from the slowest band, on concentrating to dryness, weighed 0.7 g. This sirupy material was identified as containing 4-C-(hydroxymethyl)-DL-*glycero*-pentulose (dendroketose)[15] from its similarity in behavior to the product prepared by the action of dilute alkali on compound I. The dendroketose from the two sources showed similar chromatographic behavior, and both gave a gray color with the orcinol spray.

5,7-O-Ethylidene-D-*manno*-heptulose (III).—The material in fraction *B*, which reacted with the orcinol spray to give a blue-green color, weighed 4.2 g. on drying. Compound III crystallized from methanol; weight 0.41 g., m.p. 200.5–201.5°, $[\alpha]^{20}\text{D}$ +4.4° (*c* 3, water). No mutarotation was observed.

Anal. Calcd. for $C_9H_{16}O_7$: C, 45.8; H, 6.8. Found: C, 45.6; H, 6.8.

A solution of 0.05 g. of compound III in 2 ml. of water containing 0.5 ml. of Amberlite IR-120(H$^+$) was agitated with a gentle stream of nitrogen and hydrolyzed by heating for 0.5 hr. in a boiling water bath. On removal of the resin, D-*manno*-heptulose[16] was obtained; it was identified by its infrared spectrum,[27] m.p. 151–152°, mixed m.p. with authentic material 151–152°, and $[\alpha]^{20}\text{D}$ +29°. Compound III and the parent sugar were found to produce a green color in the orcinol test, in accordance with observations by Richtmyer.[28]

D-*gluco*-**Heptulose** (IV).—The mother liquor (from which III had crystallized) was hydrolyzed as described above and, from the hydrolyzate, was crystallized 1.025 g. of compound IV,[18] identified by its infrared spectrum, m.p. 171–174°, mixed m.p. 171–174°, $[\alpha]^{20}\text{D}$ +67.6°, and a blue color[26] with the orcinol reagent.

5,7-O-Ethylidene-α-D-*altro*-heptulose (V).—A sirupy residue resulted on concentrating the effluent from band *C;* wt. 1.9 g. Crystalline compound V, wt. 0.98 g., was obtained from a 2-propanol solution of the material, m.p. 149–151°, $[\alpha]^{20}\text{D}$ +55° (*c* 1; water), $[\alpha]^{20}\text{D}$ +50° (1 min.) $\rightarrow$ +40° (7 min.; *c* 1; methanol). From the mutarotation in methanol, an α-D configuration is assigned to the crystalline acetal.

Anal. Calcd. for $C_9H_{16}O_7$: C, 45.8; H, 6.8. Found: C, 45.7; H, 6.9.

A sample (0.05 g.) of compound V, on hydrolysis as described above, yielded 2,7-anhydro-D-*altro*-heptulose hydrate,[20] which was identified by its infrared spectrum,[27] m.p. 99–101°, mixed m.p. with authentic material 99–101°, and $[\alpha]^{20}\text{D}$ −134°.

All melting points are uncorrected.

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[25] W. E. Trevelyan, D. P. Proctor, and J. S. Harrison, *Nature*, **166**, 444 (1950).

[26] A. Bevenue and K. T. Williams, *Arch. Biochem. Biophys.*, **34**, 225 (1951).

[27] R. S. Tipson and H. S. Isbell, *J. Res. Natl. Bur. Std.*, **66A**, 31 (1962).

[28] Private communication from Dr. N. K. Richtmyer.

2-Chloro-3-dimethylamino-6-phenylsulfonylphenyllithium

HERMAN E. ZIEGER[1] AND GEORG WITTIG

The Organic Chemistry Institute, The University of Heidelberg, Heidelberg, Germany

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By the metalation of 3-chloro-4-dimethylaminodiphenyl sulfone (I) using *n*-butyllithium, 3-chloro-4-dimethylamino-6 phenylsulfonylphenyllithium (II) was prepared. At temperatures higher than −10°, II eliminates lithium chloride forming 3-dimethylamino-6-phenylsulfonylbenzyne (III). This intermediate reacts readily with furan yielding 5-dimethylamino-8-phenylsulfonyl-1,4-dihydronaphthalene 1,4-endoxide (V). The consumption of the organolithium compound II with time was used to measure the rate of formation of III. The elimination of lithium chloride by II was shown to be a first-order process.

An elimination-addition mechanism has been discussed to explain reactions of *o*-halophenyllithium compounds proceeding through a dehydrobenzene[2] intermediate.[3] It has been shown that *o*-halophenyllithium compounds can be prepared and are stable at temperatures ranging from −60 to −110°.[4] For example, *o*-chlorophenyllithium is stable at −90°. We hoped to modify the properties of both the halophenyllithium compounds and the short-lived benzyne intermediate by the introduction of the dimethylamino and the phenylsulfonyl groups at positions 3 and 6. These groups were chosen because of their respective mesomeric and inductive effects. The expected stabilization of this 3,6-disubstituted *o*-chlorophenyllithium compound was observed.

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[1] Fulbright Fellow 1960–1961; present address, Department of Chemistry, Brooklyn College, Brooklyn, New York.

[2] The authors feel that dehydrobenzene is a more general name than benzyne, because the name benzyne implies the presence of a triple bond in the symmetrical intermediate. Experimental evidence is not available to substantiate this implication. For the sake of conformity with the current usage of this journal, we shall use the term benzyne to mean dehydrobenzene.

[3] For the reviews of the field see G. Wittig, *Naturwissenschaften*, **30**, 696 (1942); G. Wittig, *Angew. Chem.*, **69**, 245 (1957); E. F. Jenny, M. C. Caserio, and J. D. Roberts, *Experientia*, **14**, 349 (1958); R. Huisgen in H. Zeiss, "Organometallic Chemistry," Reinhold Publishing Corp., New York, 1960, pp. 36–87.

[4] H. Gilman and R. D. Gorsich, *J. Am. Chem. Soc.*, **79**, 2625 (1957); *ibid.*, **78**, 2217 (1956); H. Gilman and T. S. Soddy, *J. Org. Chem.*, **22**, 1715 (1957).