[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

Some Products Arising from the Condensation of D-Ribose with Benzaldehyde. 2,3-*O*-Benzylidene-β-D-ribofuranose and Di-(2,3-*O*-benzylidene-D-ribofuranose)-1,5′:1′,5-dianhydride

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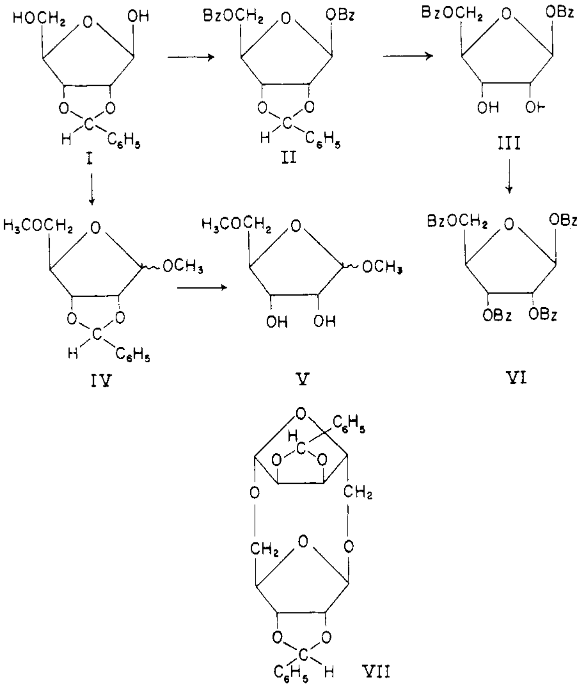
Benzylideneation of D-ribose at +5° in the presence of zinc chloride–acetic acid gives a crystalline product which is shown to be 2,3-*O*-benzylidene-β-D-ribofuranose. When the reaction is carried out at 80° a benzylidene-D-ribosan is formed. Hydrogenolysis converts this substance to the previously known di-D-ribofuranose-1,5′:1′,5-dianhydride.

The condensation of D-ribose with benzaldehyde in the presence of the zinc chloride–acetic acid complex[1] at +5° has been found to give a crystalline monobenzylidene-D-ribose in 29% yield.[2] This substance reduces Fehling solution and is, therefore, unsubstituted at C_1. Its crystalline dibenzoate was hydrogenolyzed to give a crystalline dibenzoyl-D-ribose; further benzoylation then produced the known[3] β-D-ribofuranose tetrabenzoate (VI). Assuming that no migration of benzoyl groups has occurred in this sequence of reactions, we may conclude that the benzylidene group is attached C_2–C_3, C_2–C_5 or C_3–C_5 and that all of these substances belong to the β-series. If the benzylidene group forms a C_2–C_3 bridge, the derived di-*O*-benzoyl-β-D-ribofuranose should possess a pair of vicinal hydroxyl groups while the other possible isomers with C_2–C_5 or C_3–C_5 bridges would give rise to dibenzoates lacking vicinal hydroxyls. The D-ribofuranose dibenzoate obtained was found to consume 1.07 moles of lead tetraacetate, the reaction being a rapid one as would be expected for a substance having a locked *cis*-glycol grouping. The dibenzoate therefore is 1,5-di-*O*-benzoyl-β-D-ribose (III) and the starting material 2,3-*O*-benzylidene-β-D-ribose (I).



The above findings were confirmed in an independent fashion. Methylation of the benzylidene-D-ribose gave an amorphous, non-reducing methyl ether (IV); hydrogenolysis of this latter afforded an amorphous methyl mono-*O*-methyl-D-riboside (V) which consumed 1.02 moles of periodate. The glycoside (IV) is certainly a mixture of anomers. Barker, Noone, Smith and Spoors[4] have recently obtained a similar mixture through condensation of methyl D-ribofuranoside with benzaldehyde and subsequent methylation; comparison of physical constants indicates that the relative proportions of anomers differ in the two cases, however.

It seems probable that 2,3-*O*-benzylidene-β-D-ribofuranose (I) with free hydroxyl groups at C_1 and C_5 might serve as a useful intermediate in the synthesis of 1,5-di-substituted ribofuranose derivatives.

In the course of exploratory experiments in our studies of the benzylideneation of D-ribose, considerably more vigorous conditions than those mentioned above were tried. It was found that when the reaction temperature was increased to 80°, there was readily obtained in 27% yield a crystalline, non-reducing substance which melted at 197–198° and had the composition of a benzylidene-anhydro-D-ribose. Removal of the benzylidene residue through hydrogenolysis gave an anhydro-D-ribose melting at 230–232°[5] and rotating +9.5°[5] in water. Only one unsubstituted anhydride of D-ribose has been reported in the literature. Some sixteen years ago Bredereck, Köthnig and Berger[6] reported that detritylation of 1,2,3-tri-*O*-acetyl-5-*O*-trityl-D-ribofuranose with hydrogen bromide in glacial acetic acid at 0° gave an acetate which, upon hydrolysis, afforded a ribosan. Later inves-

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(1) This complex, discovered by H. Meerwein [*Ann.*, **455**, 227 (1927)], was apparently first used as a catalyst in the preparation of cyclic acetals by G. Dangschat [*Naturwissenschaften*, **30**, 146 (1942)].

(2) Other crystalline products from this reaction are currently under investigation in this Laboratory. While this communication was in press G. R. Barker and J. W. Spoors [*J. Chem. Soc.*, 1192 (1956)] published a description of the benzylideneation of D-ribose in the presence of zinc chloride alone. One of the products obtained by these authors is shown by them to be 2,3-*O*-benzylidene-D-ribofuranose; the cause of the disparity between their physical constants for this acetal and those reported here remains to be investigated.

(3) R. K. Ness, H. W. Diehl and H. G. Fletcher, Jr., THIS JOURNAL, **76**, 763 (1954).

(4) G. R. Barker, T. M. Noone, D. C. C. Smith and J. W. Spoors, *J. Chem. Soc.*, 1327 (1955).

(5) Melting points are corrected. Rotations are specific rotations for the D-line of sodium at 20°, concentration being expressed in g. of substance per 100 ml. of solution.

(6) H. Bredereck, M. Köthnig and E. Berger, *Ber.*, **73**, 956 (1940).

tigations by Barker and Lock[7] and by Jeanloz[8] showed that the substance is "dimeric," *i.e.*, made up of two ribose units and most probably is di-D-ribofuranose-1,5′:1′,5-dianhydride. The constants which these authors reported for the substance (m.p. 231–232°; $[\alpha]^{20}\text{D}$ +8.6 ± 0.5°) agreed closely with those found for our substance; the identification was confirmed through preparation of the tetraacetate and comparison of the latter with an authentic specimen kindly provided by Dr. Barker. We conclude, therefore, that our new benzylidene derivative is di-(2,3-*O*-benzylidene-D-ribofuranose)-1,5′:1′,5-dianhydride (VII).[9]

While the over-all yield of the dimeric ribosan by the procedure described here is not large, the method is probably more convenient than that described earlier[6] for those requiring small quantities of this interesting substance.

The close relationship of I to VII tempts one to suspect that the former may be the precursor of the latter. No evidence is available at present, however, to support such a speculation.

Experimental[5]

2,3-*O*-Benzylidene-β-D-ribofuranose (I).—Five grams of D-ribose, 2.5 g. of freshly fused zinc chloride, 30 ml. of benzaldehyde (redistilled and protected from atmospheric oxygen) and 2 ml. of glacial acetic acid were mixed and shaken at +5° for 24 hr. The mixture was then poured into 200 ml. of ice-water and extracted thrice with 50-ml. portions of ether. The combined ether extracts were dried with sodium sulfate and concentrated to a thin sirup. From a mixture of 50 ml. of benzene and 60 ml. of pentane at −5° a crystalline product (2.3 g., 29%) melting at 114–118° and rotating −21.6° in chloroform (*c* 1.1) was obtained. After recrystallization from 35 ml. of hot benzene, the material melted at 123–124° and showed $[\alpha]^{20}\text{D}$ −22.4° ($CHCl_3$, *c* 1.4), no mutarotation being observed in 17 hr.[9a] Further recrystallization failed to change these constants significantly. When dissolved in warm ethanol and added to warm Fehling solution the 2,3-*O*-benzylidene-β-D-ribofuranose thus prepared gave a positive test after being heated for 5 minutes.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.35; H, 6.09.

1,5-Di-*O*-benzoyl-2,3-*O*-benzylidene-β-D-ribose (II).—2,3-*O*-Benzylidene-β-D-ribofuranose (150 mg.) was benzoylated with benzoyl chloride in pyridine solution at 0° in the conventional manner. After removal of the excess reactants, a sirupy residue was obtained; from its solution in ether 197 mg. (70%) of crystalline material melting at 110–120° was deposited. One recrystallization from ethanol-pentane and then repeated recrystallization from methanol afforded a product which melted at 110–117° and rotated −62.7° ($CHCl_3$, *c* 1.5) after drying at 78° and 0.5 mm. pressure. While this melting range is a broad one, as is often the case with benzylidene derivatives of the sugars, the rotation was unaffected by further recrystallization.

Anal. Calcd. for $C_{26}H_{22}O_7$: C, 69.94; H, 4.97. Found: C, 69.87; H, 5.24.

1,5-Di-*O*-benzoyl-β-D-ribose (III).—One gram of 1,5-di-*O*-benzoyl-2,3-*O*-benzylidene-β-D-ribose was dissolved in 40 ml. of methanol and reduced under a slight pressure of hydrogen, 10% palladium-on-charcoal being used as a catalyst. After the calculated quantity of hydrogen had been consumed, the catalyst was removed and the solution concentrated *in vacuo* to a sirup which crystallized spontaneously. From a mixture of 10 ml. of ethyl acetate and 11 ml. of pentane, the 1,5-di-*O*-benzoyl-β-D-ribose (430 mg., 54%) was obtained as fine needles melting at 122–126°. Three recrystallizations from ethanol–pentane gave pure material of m.p. 125–126° and $[\alpha]^{20}\text{D}$ −6.8° ($CHCl_3$, *c* 0.9).

Anal. Calcd. for $C_{19}H_{18}O_7$: C, 63.68; H, 5.07. Found: C, 63.75; H, 5.26.

A sample (39.1 mg.) of the above ester was oxidized with lead tetraacetate in glacial acetic acid solution using the technique of Hockett and McClenahan.[10] After 5 hr. at room temperature the substance was found to have consumed 1.07 moles of oxidant. No further quantity was consumed in 22 hr.

β-D-Ribofuranose Tetrabenzoate (VI) from 1,5-Di-*O*-benzoyl-β-D-ribose (III).—The dibenzoate (100 mg.), prepared as described above, was benzoylated in pyridine solution at 0° with benzoyl chloride in the usual fashion to yield from ethanol solution 120 mg. (76%) of handsome needles melting at 119–120°. Recrystallized from ethanol the product rotated +17.2° ($CHCl_3$, *c* 1.3) and melted at 121°; mixed with authentic β-D-ribofuranose tetrabenzoate[3] it melted at 120–121°. A rotation of +17.0° ($CHCl_3$) has been reported[3] earlier for this substance.

Methyl 5-*O*-Methyl-D-riboside (V).—2,3-*O*-Benzylidene-β-D-ribofuranose (2.4 g.) was dissolved in a mixture of 20 ml. of methyl iodide and 5 ml. of anhydrous dioxane. To the boiling solution 5 g. of silver oxide was added in 1-g. portions at 0.5-hr. intervals. After the addition was complete the solution was boiled 0.5 hr., cooled, filtered and concentrated to a sirup which was remethylated in the same fashion save for the omission of the dioxane. The clear, light-yellow sirup (2.3 g.) was distilled *in vacuo* (0.075 mm.) at 137–148° (bath) to give a clear, colorless sirup rotating −40.5° in chloroform (*c* 4.3).[11]

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81; OCH_3, 23.3. Found: C, 63.25; H, 7.05; OCH_3, 23.4.

Two grams of the amorphous methyl 2,3-*O*-benzylidene-5-*O*-methyl-D-riboside was dissolved in 25 ml. of ethanol and reduced in the presence of 1 g. of 10% palladium-charcoal. When the theoretical quantity of hydrogen had been consumed the catalyst and solvent were removed to give a clear sirup which, dried at 78° and 1 mm. pressure for 2 hr., rotated −32.4° in methanol (*c* 1.5) and failed to reduce Fehling solution.

Anal. Calcd. for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 46.68; H, 7.94.

A sample (68.5 mg.) of the above-described glycoside was treated with aqueous sodium metaperiodate in the usual fashion. After 22 hr. at room temperature, analysis showed the substance to have consumed 1.02 molar equivalents of oxidant.

Di-(2,3-*O*-benzylidene-D-ribofuranose)-1,5′:1′,5-dianhydride (VII).—To a mixture of 250 ml. of benzaldehyde, 25 g. of freshly fused zinc chloride and 25 ml. of glacial acetic acid, heated to 80° and vigorously stirred, was added 5.0 g. of D-ribose. The mixture became homogeneous after approximately 5 min. and was then held at 80° for 1 hr. The amber solution was then poured into a mixture of 300 ml. of ice and water and 200 ml. of ether. After separation of the organic layer, the aqueous layer was extracted with 2 × 50 ml. of ether. The combined extracts, washed successively with water and sodium bicarbonate solution, were dried over sodium sulfate, treated with carbon and concentrated *in vacuo*, finally at 60–70° (bath) and 1 mm. pressure. The residue, which crystallized on cooling, was rubbed with 50 ml. of ethanol, cooled to 0° and filtered to yield 4.0 g. (27.2%) of product melting at 190–195° and rotating −35.7° ($CHCl_3$, *c* 1.7). Recrystallization from 30 parts of boiling acetone gave pure material melting at 197–198° and rotating −36.3° ($CHCl_3$, *c* 1.1).

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[7] G. R. Barker and M. V. Lock, *J. Chem. Soc.*, 23 (1950); 1323 (1955).

[8] R. W. Jeanloz, G. R. Barker and M. V. Lock, *Nature*, **167**, 42 (1951).

[9] While no direct evidence is available, considerations of symmetry and the known "preference" of ribose derivatives for the β-configuration suggest that both C_1 carbon atoms have the β-configuration as indicated in VII.

[9a] In methanol (*c* 0.6) the substance showed $[\alpha]^{20}\text{D}$ −26.6° (no change in 1/2 hr.). Barker and Spoors (reference 2) found m.p. 98–101° and $[\alpha]^{19}\text{D}$ −16.5° (CH_3OH) for their preparation of 2,3-*O*-benzylidene-D-ribofuranose.

[10] R. C. Hockett and W. S. McClenahan, This Journal, **61**, 1667 (1939).

[11] Barker and his co-workers (reference 4) condensed sirupy methyl D-ribofuranoside with benzaldehyde and methylated the product. The amorphous methyl 2,3-*O*-benzylidene-5-*O*-methyl-D-ribofuranoside which they obtained rotated −55.6° in chloroform (*c* 4.1) and thus probably differs somewhat from our product in the proportions of anomers present.

Anal. Calcd. for $C_{24}H_{24}O_8$: C, 65.44; H, 5.49. Found: C, 65.17; H, 5.62.

The substance gave a negative Fehling test and its infrared absorption spectrum indicated the absence of free hydroxyl groups.

Di-D-ribofuranose-1,5′:1′,5-dianhydride.—Two grams of the benzylidene derivative was reduced in the presence of palladium black, absolute ethanol being used as a solvent. When the theoretical quantity of hydrogen had been absorbed, the catalyst was removed and the solution concentrated *in vacuo* at 40° to yield 1.10 g. of crystalline residue. Recrystallization from ethanol–hexane gave the pure dianhydride melting at 230–232° and rotating +9.5° (H_2O, *c* 1.4). Jeanloz, Barker and Lock[8] reported m.p. 231–232° and $[\alpha]^{20}\mathrm{D}$ +8.6° ± 0.5° in water (*c* 1.4).

Di-D-ribofuranose-1,5′:1′,5-dianhydride Tetraacetate.—A sample (250 mg.) of the anhydride was acetylated with acetic anhydride in pyridine in the usual manner to yield, from ethanol–pentane 405 mg. (99%) of crude product. Recrystallization from ethanol–pentane gave the pure ester melting at 171–172° and rotating +53.5° in chloroform (*c* 1.03). Mixed with a sample of the ester kindly provided by Dr. G. R. Barker, the material melted at 170–172°.

Acknowledgment.—We are indebted to the Institutes' Microanalytical Laboratory for elementary analyses performed under the direction of Dr. W. C. Alford.

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

Sedoheptulose—Its Rotation, Reducing Power, Equilibrium with Sedoheptulosan in Acid Solution, and Crystalline Hexaacetate; Also Crystalline 2,7-Anhydro-β-D-*altro*-heptulofuranose

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Sedoheptulose (= D-*altro*-heptulose) has been purified by transformation to a crystalline hexaacetate and subsequent deacetylation; the liberated sugar showed $[\alpha]^{20}\mathrm{D}$ +8.2° in water and had 80% of the reducing power of D-glucose toward the Hagedorn–Jensen–Hanes ferricyanide reagent. A reinvestigation of the equilibrium between sedoheptulose and sedoheptulosan (= 2,7-anhydro-β-D-*altro*-heptulopyranose) in dilute acid solution has shown that the amount of anhydride varies from 91% at 20° to 84.5% at 80°; loss of material due to the formation of dihydroxyethylfurfural was insignificant at 20–80° but became appreciable quickly at 100°. The new anhydride of sedoheptulose that was isolated first by Zill and Tolbert in 1954 has now been obtained in crystalline form (melting point 199–200°, $[\alpha]^{20}\mathrm{D}$ +3.5° in water); its structure has been confirmed as 2,7-anhydro-β-D-*altro*-heptulofuranose.

Sedoheptulose (= D-*altro*-heptulose, I) was discovered in 1917 by LaForge and Hudson[1] in *Sedum spectabile* Bor. This seven-carbon ketone sugar was long considered a curiosity in nature; recently, however, it has become of great importance in biochemical studies, particularly because of its roles in the pentose phosphate pathway of carbohydrate metabolism, in the synthesis of other carbohydrates during photosynthesis,[2] and in the biosynthesis of shikimic acid (and hence of the benzene ring of the aromatic amino acids).[3] Although sedoheptulose can be identified readily through its crystalline anhydride, sedoheptulosan[1] (= 2,7-anhydro-β-D-*altro*-heptulopyranose,[4] IIa, IIb) and especially through sedoheptulosan tetrabenzoate,[5] the sugar itself has never been separated in crystalline form.[6] Furthermore, no derivative was known from which sedoheptulose could be recovered quantitatively. Consequently, no satisfactory data on either the specific rotation or the reducing power of sedoheptulose have been available.

We have now converted crystalline sedoheptulosan with acetic anhydride and pyridine to a sirupy tetraacetate ($[\alpha]^{20}\mathrm{D}$ −110°). The acetolysis of this compound with acetic anhydride, in the presence of a small amount of perchloric acid as catalyst, led to the successful preparation of a crystalline sedoheptulose hexaacetate melting at 98–99.5° and showing $[\alpha]^{20}\mathrm{D}$ +59.0° in chloroform. A comparison of its molecular rotation ($[M]^{20}\mathrm{D}$ +27,300) with that of α-D-altropyranose pentacetate ($[M]^{20}\mathrm{D}$ +24,600),[7] together with the fact that the ultraviolet spectrum of the new acetate shows no absorption band in the region of 280 mμ (indicating the absence of a ketone group[8]), is evidence that our hexaacetate is a cyclic form with the α-D-*altro* configuration and may be designated hexa-*O*-acetyl-α-D-*altro*-heptulopyranose. Cautious deacetylation of the hexaacetate yielded sedoheptulose whose rotation was determined as $[\alpha]^{20}\mathrm{D}$

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[1] F. B. LaForge and C. S. Hudson, *J. Biol. Chem.*, **30**, 61 (1917).

[2] See B. L. Horecker and A. H. Mehler, *Ann. Rev. Biochem.*, **24**, 229, 249 (1955), for pertinent references.

[3] See P. R. Srinivasan, M. Katagiri and D. B. Sprinson, THIS JOURNAL, **77**, 4943 (1955), for a recent paper and pertinent references.

[4] J. W. Pratt, N. K. Richtmyer and C. S. Hudson, *ibid.*, (a) **73**, 1876 (1951); (b) **74**, 2200 (1952).

[5] W. T. Haskins, R. M. Hann and C. S. Hudson, *ibid.*, **74**, 2198 (1952).

[6] Note, however, that L. Ujejski and E. R. Waygood [*Can. J. Chem.*, **33**, 687 (1955)] have reported "the beginnings of crystallization of sedoheptulose" although "complete crystallization of a large quantity of sedoheptulose was not obtained." Personal communications from those authors in March 1956 reveal that because of lack of material they were unable to obtain any physical data on their sedoheptulose.

[7] N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **63**, 1727 (1941). The corresponding rotations for α-D-*gluco*-heptulose hexaacetate and α-D-glucose pentaacetate are +40,200 and +39,700, respectively, and for α-D-*manno*-heptulose hexaacetate and α-D-mannose pentaacetate are +19,200 and +21,500, respectively. The molecular rotation of α-D-*manno*-heptulose hexaacetate has been calculated from a new value for its specific rotation, $[\alpha]^{20}\mathrm{D}$ +41.5°, as determined recently by Mr. E. Zissis in this Laboratory.

[8] *Cf.* Y. Khouvine and G. Arragon [*Compt. rend.*, **206**, 917 (1938)], who found that hexa-*O*-acetyl-*keto*-perseulose, of $[\alpha]^{20}_{578}$ +0.57° in chloroform, showed absorption at 280 mμ, whereas the hexaacetate of $[\alpha]^{20}_{578}$ −113.4° in chloroform showed no absorption at 280 mμ, could not be hydrogenated, and must therefore be a cyclic form. The corresponding cyclic α-L-galactopyranose pentaacetate shows $[\alpha]^{20}\mathrm{D}$ −106.7°.