mixture of pyridine and phenol at time zero, giving a 5:1 pyridine–phenol solvent. In the case of B, a 1:1 pyridine–phenol solvent was employed.

Isomer **A**: (a) concn., **1**.683 g./100 ml.; (b) t, $[\alpha]^{25}D$: 1, −40.0°; 3, −22.2°; 4, −15.1°; 6, −5.9°; 10, +2.4°; 15, +8.3°; 20, +9.8°; final, +10.7°; (c) α_0 approximately −53.0° (from corresponding mutarotation in pyridine above); (d) k''_A, 0.218 min.$^{-1}$.

Isomer B: (a) concn., 0.737 g./100 ml.; (b) t, $[\alpha]^{25}D$: 2, −80°; 60, −67.8°; 130, −57.0°; 200, −47.4°; 555, +10.8° (at this point the solution had darkened extensively, and further polarimetric observations were impossible).

3,4,6-Tri-*O*-acetyl-β-D-mannose 1,2-(methylorthoacetate) (IV) was prepared from sirupy tetra-*O*-acetyl-α-D-mannopyranosyl bromide by treatment with a suspension of silver carbonate in methanol after the procedure of Dale.[13] After recrystallization from a 1:6 chloroform–ether mixture the product had m.p. 101–102°, $[\alpha]^{25}D$ −29.0° (*c* 2.4, $CHCl_3$), in substantial agreement with the m.p. 105°, $[\alpha]^{20}D$ −26.6° ($CHCl_3$) reported.[13]

Infrared Absorption Studies.—Chloroform solutions of the substances listed in Table II were made up at a concentration of 0.025 *M* each. These solutions were in turn placed in a 0.105-mm. sodium chloride cell, and the infrared spectrum of each was scanned in the region 5.0–6.2 μ, using a Perkin–Elmer model 21 double-beam infrared spectrophotometer. Chloroform solvent was used in a 0.107-mm. cell in the I_o beam, and a slit-width of 57 μ was employed. Since the carbonyl absorption band in each of these compounds proved almost completely symmetrical, the areas under each band were approximated by multiplying the peak height by the half-peak height width. The areas so measured were 5.25, 6.53, 6.90, 6.90 and 8.26 cm.^{2}, respectively, for compounds 1 through 5 in Table II. The molar extinction coefficients, calculated in the usual way from the peak heights and the relationship $\epsilon = (\log I_0/I_t) \times (1/lc)$ were 903, 1165, 1195, 1195 and 1476, respectively, for compounds 1 through 5 in Table II.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY, AND THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

The Synthesis of D-*erythro*-Pentulose Tetrabenzoate[1]

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The synthesis of 1,3,4,5-tetra-*O*-benzoyl-*keto*-D-*erythro*-pentulose is described. The fully benzoylated aldotetronic acid was converted to the acyl chloride and this with diazomethane yielded the diazomethyl ketone. The latter was transformed directly into the ketopentose tetrabenzoate and the identity of the keto ester was demonstrated by reduction and isolation of known arabinitol and ribitol derivatives.

In continuation of our work on the general method for the preparation of ketoses from the lactones of the sugar acids with one less carbon atom,[3] we wish to describe the application of this method to the synthesis of D-*erythro*-pentulose ("ribulose") as the crystalline tetrabenzoate. The reaction sequence employed was

$$RCO_2H \xrightarrow{PCl_5} RCOCl \xrightarrow{CH_2N_2} RCOCHN_2 \xrightarrow[Cu]{C_6H_5COOH} RCOCH_2OCOC_6H_5$$

R = $CH_2OCOC_6H_5(CHOCOC_6H_5)_2$–

The starting point for our synthesis was D-erythrono-1,4-lactone prepared by the selective degradation of D-glucose by lead tetraacetate[4] and subsequent bromine oxidation of the D-erythrose to D-erythronolactone or, more conveniently for larger quantities, by the oxidative scission of D-*erythro*-2-hexulosono-1,4-lactone 2,3-*cis*-enediol ("D-araboascorbic acid") with *p*-toluenediazonium sulfate.[5] The lactone was converted to the amide with liquid ammonia[6] and subsequent benzoylation in anhydrous pyridine with benzoyl chloride gave 2,3,4-tri-*O*-benzoyl-D-erythronamide.[7]

The benzoylated amide was converted to 2,3,4-tri-*O*-benzoyl-D-erythronic acid with nitrosyl chloride in dioxane, and then to 2,3,4-tri-*O*-benzoyl-D-erythronyl chloride with phosphorus pentachloride. Reaction with diazomethane and silicate column chromatography of the reaction product gave 1-deoxy-1-diazo-*keto*-D-*erythro*-pentulose tribenzoate. Treatment of the diazomethyl ketone with benzoic acid and copper bronze yielded 1,3,4,5-tetra-*O*-benzoyl-D-*erythro*-pentulose.

The free keto structure of this tetrabenzoate was demonstrated by reduction of the carbonyl group with sodium borohydride to the corresponding diastereoisomeric pentitol tetrabenzoates which, after saponification with aqueous sodium hydroxide and treatment with hydrochloric acid,[8a] were separated by paper chromatography and identified as D-arabinitol (and D-arabinitol pentaacetate) and 1,4-anhydro-DL-ribitol (and 2,3,5-tri-*O*-benzoyl-1,4-anhydro-DL-ribitol). The treatment of D-arabinitol and ribitol with hydrochloric acid under like conditions has been shown[8a] previously by paper chromatography to yield unchanged D-arabinitol and 1,4-anhydro-DL-ribitol, respectively. The separation of these compounds and the synthesis of the latter are herein described on a preparative basis.[8b] The isolation of the two 2-epimeric pentitols thus establishes the free keto nature of the second carbon atom in the crystalline ketopentose tetrabenzoate.

D-*erythro*-Pentulose ("ribulose") was first synthesized by Glatthaar and Reichstein[9] by the pyridine interconversion of D-arabinose and isolated as

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its *o*-nitrophenylhydrazone. Cohen[10] isolated the free sugar by the action of the B_{a15} strain of *Escherichia coli* on D-arabinose. The ketopentose has received more attention, however, as the phosphate esters produced in the enzymic conversions of D-gluconic acid 6-(dihydrogen phosphate) ("6-phosphogluconate")[11] and as a primary product in the photosynthetic cycle.[12]

Experimental

2,3,4-Tri-*O*-benzoyl-D-erythronic Acid.—Controlled oxidation of D-glucose with lead tetraacetate in acetic acid according to Perlin and Brice[4] gave sirupy D-erythrose of $[\alpha]^{25}D$ −28° (*c* 1, water), in agreement with the value (−30°) cited by these workers. Oxidation of the aldose with hypobromite in the presence of calcium carbonate[13] yielded D-erythrono-1,4-lactone of m.p. 103–104° and $[\alpha]^{20}D$ −73° (*c* 4, water); X-ray powder diffraction data[14]: 7.53m, 6.20s(2), 4.78m, 4.32s(1), 4.03m, 3.78w, 3.56w, 3.23w, 3.07m(3), 2.87w, 2.75w, 2.67w, 2.51m. These data are in agreement with the values (103° and −73°) cited by Ruff.[15] This lactone was prepared more conveniently, for relatively larger amounts, from D-*erythro*-2-hexulosono-1,4-lactone 2,3-*cis*-enediol ("D-araboascorbic acid") according to the procedure of Weidenhagen and co-workers.[5] D-Erythronamide was prepared quantitatively, according to Glattfeld and Macmillan,[6] by the action of liquid ammonia upon the lactone. The constants of the amide were in agreement with those (m.p. 95°, $[\alpha]^{20}D$ +28° in water) cited by these workers; X-ray powder diffraction data[14]: 5.21m, 4.26s(1), 3.84m, 3.63m(3), 3.39m, 3.28m(3), 3.07s(2), 2.92w, 2.85w, 2.73w, 2.63m, 2.45w, 2.41w.

Benzoylation of the amide, according to Jelinek and Upson,[7] gave a 95% yield of tri-*O*-benzoyl-D-erythronamide with the constants: m.p. 205-206°, $[\alpha]^{25}D$ +10° (*c* 0.8, chloroform); X-ray powder diffraction data[14]: 9.41m, 8.91m, 5.51w, 5.30m(3), 5.10m(3), 4.77m, 4.42s(2), 4.04s(1), 3.77w, 3.51m, 3.22w.

To 18.0 g. of 2,3,4-tri-*O*-benzoyl-D-erythronamide, dissolved in 200 ml. of dioxane and cooled to 0°, was added slowly, with stirring, 30 ml. of nitrosyl chloride. The mixture was allowed to stand overnight at 0° and then was warmed slowly to room temperature. The resulting semi-solid gum that formed upon pouring the reaction mixture into water was dissolved in absolute ethanol and evaporated to a heavy sirup which was crystallized from 15 ml. of benzene; yield 14.3 g. (80%), m.p. 133–135°. Recrystallization from benzene gave colorless 2,3,4-tri-*O*-benzoyl-D-erythronic acid, m.p. 138–139°, $[\alpha]^{21}D$ +27° (*c* 0.5, chloroform); X-ray powder diffraction data[14]: 9.22m(2), 5.22m(2), 4.80m, 4.44s(1), 3.99m(2), 3.75w, 3.53w, 3.22w.

Anal. Calcd. for $C_{25}H_{20}O_8$: C, 66.96; H, 4.50. Found: C, 67.19; H, 4.60.

2,3,4-Tri-*O*-benzoyl-D-erythronyl Chloride.—To 9.0 g. of 2,3,4-tri-*O*-benzoyl-D-erythronic acid, dissolved in 100 ml. of dry ether, was added 4.2 g. of phosphorus pentachloride. The reaction mixture was stirred at room temperature for 4 hr. and then 250 ml. of petroleum ether (b.p. 30–60°) was added. After standing overnight at 10–15°, the crystals were filtered rapidly and placed in a vacuum desiccator; yield 7.5 g. (81%), m.p. 94-95°, $[\alpha]^{21}D$ −14° (*c* 2.0, chloroform); X-ray powder diffraction data[14]: 9.36s(2), 5.26s(2), 4.84m, 4.56m, 4.46m, 4.29w, 4.14s(1), 3.97w, 3.63m, 3.48w.

Anal. Calcd. for $C_{25}H_{19}ClO_7$: C, 64.33; H, 4.10; Cl, 7.59. Found: C, 64.40; H, 4.21; Cl, 7.47.

1-Deoxy-1-diazo-3,4,5-tri-*O*-benzoyl-*keto*-D-*erythro*-pentulose.—A solution of 4.7 g. of 2,3,4-tri-*O*-benzyl-D-erythronyl chloride in 50 ml. of dry ether was added slowly, with stirring, to a solution of 1 g. of diazomethane in 50 ml. of dry ether. The mixture was maintained overnight at 10–15°, whereupon the addition of petroleum ether (b.p. 30–60°) gave a crude yellow product; yield 3.8 g. (81%), m.p. 79–81°.

One gram of the above product was dissolved in 10 ml. of benzene and chromatographed on a 230 × 35 mm. (diam.)[16] column of Magnesol[17]–Celite[18] (5:1 by wt.) by development with 100 ml. of benzene–*t*-butyl alcohol (500:1 by vol.). An alkaline permanganate streak[19] showed a large zone near the bottom of the extruded column. The sectioned bottom zone was extracted with acetone and the sirup obtained on solvent removal was crystallized from ether (warming)–petroleum ether. The crystals possessed a slight yellow color; yield 0.64 g., m.p. 95–96°, $[\alpha]^{21}D$ −28° (*c* 2.0, chloroform); X-ray powder diffraction data[14]: 10.07m(2), 7.80w, 5.91w, 5.37s(1), 4.63w, 4.10s(1), 3.79m, 3.36m.

Anal. Calcd. for $C_{26}H_{20}N_2O_7$: C, 66.10; H, 4.27; N, 5.93. Found C, 66.01; H, 4.19; N, 5.74.

1,3,4,5-Tetra-*O*-benzoyl-*keto*-D-*erythro*-pentulose.—A mixture of 200 mg. of 1-deoxy-1-diazo-3,4,5-tri-*O*-benzoyl-*keto*-D-*erythro*-pentulose, 1 g. of benzoic acid and a trace of copper bronze was heated in an oil-bath at 125° for 2 min. After the rapid evolution of gas had ceased, the mixture was cooled in an ice-bath and the resulting solid material was dissolved in 25 ml. of chloroform. The chloroform solution was washed with 50 ml. each of *N* potassium carbonate, *N* sulfuric acid and water and, after drying over sodium sulfate, was evaporated under reduced pressure. Repeated evaporation from methanol solution gave a crystalline product; yield 98.6 mg. (42%), m.p. 139–140°. Recrystallization was effected from 5 ml. of *n*-butyl ether; yield 88 mg., m.p. 142-143°, $[\alpha]^{20}D$ +31.5° (*c* 3.4, chloroform), X-ray powder diffraction data[14]: 10.88s(2), 7.01m(3), 5.49m, 5.17m, 4.44s(1), 4.20w, 3.98m, 3.63m, 3.43m.

Anal. Calcd. for $C_{33}H_{26}O_9$: C, 70.0; H, 4.6. Found: C, 69.8; H, 4.7.

1,4-Anhydro-DL-ribitol.—A solution of 2 g. of ribitol in 100 ml. of 2.1 *N* hydrochloric acid was heated at 110° for 27 hr. and the resulting solution was evaporated under reduced pressure at 55°. Repeated vacuum evaporation (5 times) at this temperature from small volumes of water served to remove the hydrochloric acid. Paper chromatography, using 1-butanol saturated with ammonium hydroxide as developer and periodate-benzidine as indicator,[20] gave a single spot and indicated that the resulting sirup contained only one component. Crystalline material was obtained by solution of the sirup in 20 ml. of hot 1-butanol followed by the addition of 4 ml. of hot hexane; yield 1.5 g., m.p. 76-77°. Recrystallization gave pure material; m.p. 76.5–77°, in agreement with the value (74–75°) reported.[8b]

Anal. Calcd. for $C_5H_{10}O_4$: C, 44.7; H, 7.5. Found: C, 44.6; H, 7.3.

The product consumed one mole of sodium metaperiodate (after 3 hr., no further consumption after 24 hr.) and no acid or formaldehyde could be detected.

2,3,5-Tri-*O*-benzoyl-1,4-anhydro-DL-ribitol.—To a solution of 100 mg. of 1,4-anhydro-DL-ribitol in 5 ml. of pyridine was added, at 0°, 0.25 ml. of benzoyl chloride and the mixture was allowed to remain overnight at room temperature. After the addition of ice and 25 ml. of chloroform, the chloroform layer was washed with 50 ml. each of *N* sulfuric acid, saturated aqueous sodium bicarbonate and water. The solvent was removed under reduced pressure from the dried extract and the residual sirup was dissolved in 10 ml. of hot 1-butanol, decolorized (carbon) and filtered. Crystals were obtained on cooling; yield 300 mg. (89%), m.p. 115–116°.

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(11) B. L. Horecker and P. Z. Smyrniotis, *ibid.*, **196**, 135 (1952).

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(14) Interplanar spacing, Å., CuKα radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak. Parenthetical numerals indicate the order of the three most intense lines: 1, most intense.

(15) O. Ruff, *Ber.*, **32**, 3679 (1899); see also J. W. E. Glattfeld and L. R. Forbrich, This Journal, **56**, 1209 (1934).

(16) Adsorbent dimensions.

(17) A synthetic magnesium silicate produced by the Westvaco Chemical Division of the Food Machinery and Chemical Corp., South Charleston, W. Va.

(18) No. 535, a siliceous filter-aid produced by the Johns-Manville Co., New York, N. Y.

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Three recrystallizations from the same solvent gave pure material, m.p. 116–117°, in agreement with the value (114°) reported.[8b]

Anal. Calcd. for $C_{26}H_{22}O_7$: C, 69.9; H, 4.9. Found: C, 69.6; H, 4.9.

D-Arabinitol (1.0 g.), treated under the same conditions, was recovered unchanged; yield 0.85 g., m.p. 102° unchanged on admixture with authentic D-arabinitol of like melting point. Paper chromatography (as described above for 1,4-anhydro-DL-ribitol) of the crystalline substance, as well as the mother liquor material, showed only one component.

Proof of Structure of 1,3,4,5-Tetra-*O*-benzoyl-*keto*-D-*erythro*-pentulose. (a) **Catalytic Reduction.**—The tetrabenzoate (32.9 mg.), dissolved in 10 ml. of redistilled glacial acetic acid, with 150 mg. of prereduced Adams catalyst[21] took up 16.6 ml. (S.T.P.) of hydrogen in 25 min.; calcd. 16.9 ml.

(b) **Sodium Borohydride Reduction.**—To 3.0 g. of the tetrabenzoate in 60 ml. of pure dioxane and 20 ml. of water was added a solution of 200 mg. of sodium borohydride in 4 ml. of water and the whole was allowed to stand at room temperature for 1 hr. The solution was concentrated under reduced pressure at 50° and the resultant sirupy residue was dissolved in chloroform, washed with 50 ml. each of *N* sulfuric acid, saturated aqueous sodium bicarbonate and water, dried over sodium sulfate, and evaporated to dryness. The residue was dissolved in 100 ml. of acetone, treated with 10 ml. of 5 *N* sodium hydroxide and allowed to stand at room temperature for 2 hr. The acetone was removed by evaporation at reduced pressure, the sodium ions were removed with Dowex 50[22] (acid form), and the benzoic acid by extraction with ether. Some of the benzoic acid crystallized in the resin but this did not interfere with the removal of the carbohydrate product from the resin. The resulting nonreducing solution was evaporated to dryness under reduced pressure and the residue was dissolved in methanol and decolorized (carbon). No crystals were obtained after 24 hr. at 0–5°. Dry heptane (15 ml.) was added and crystallization was effected after 12 hr. at 0–5°; yield 366.5 mg. More product formed on further addition of heptane; total yield 417 mg., m.p. 65–80°.

(c) **Periodate Oxidation of Mixed Pentitols.**—A sample of the above mixed pentitols (51.9 mg., 0.34 mM.) consumed 1.33 mM. of sodium metaperiodate (4.0 mM. per mM. of substrate) in 2 hr., this value remaining unchanged after 24 hr. An aliquot titrated for acid produced showed 3.1 mM. of acid per mM. of pentitol and treatment of half of the reaction mixture with dimedon (5,5-dimethyl-1,3-cyclohexanedione) aqueous solution gave a derivative; yield 89 mg. (1.8 mM. per mole of substrate), m.p. 182°. Pure material was obtained on recrystallization from methanol; yield 61 mg., m.p. and mixed m.p. with authentic dimedon derivative of formaldehyde, 191–192°.

(d) **Separation of Mixed Pentitols.**—To 300 mg. of the crystalline mixed pentitols was added 30 ml. of 2 *N* hydrochloric acid and the mixture was heated at 100° for 28 hr. The solution was evaporated at reduced pressure and the residue was chromatographed on sheets of Whatman 3 MM paper (46.4 × 58.2 cm.) using 1-butanol saturated with ammonium hydroxide as developer. Two bands were identified by spraying strips cut from the edges of each paper with periodate–benzidine spray.[20] The two bands containing the bulk of the material were eluted with water and the eluates were concentrated under reduced pressure.

The residue from the top band (R_f 0.24) was dissolved in 1 ml. of absolute ethanol and 2 ml. of 1-butanol added. After remaining overnight at ice-box temperature, the solution deposited crystals, yield 41 mg., m.p. 94–96°. Recrystallization from the same solvent gave pure material, m.p. 102° unchanged on admixture with authentic D-arabinitol of like melting point.

The mother liquor from the first crop of crystals was evaporated to dryness and the residue obtained was treated with 5 ml. of dry pyridine and 2 ml. of acetic anhydride. After 5 hr. at room temperature, excess ice and 25 ml. of chloroform were added. The chloroform was washed with 50 ml. each of *N* sulfuric acid, saturated aqueous sodium bicarbonate solution and water, then dried over sodium sulfate. The sirup obtained on evaporation of the chloroform was dissolved in 5 ml. of dry ethyl ether and 15 ml. of dry heptane was added. Crystals were obtained after standing overnight at 0–5°; yield 107 mg., m.p. 74–75° unchanged on admixture with authentic penta-*O*-acetyl-D-arabinitol of like melting point.

The presence of D-arabinitol in the mixed pentitols could also be shown by the marked increase in rotation of the sample on the addition of ammonium molybdate and sulfuric acid.[23] In this manner, it was estimated that the pentitol mixture was about 45% D-arabinitol.

The residue from the second band (R_f 0.39) was dissolved in 1 ml. of 1-butanol and dry heptane was added to incipient turbidity. A crop of rather gummy crystals was obtained which were recrystallized in the same manner; yield 32 mg. Recrystallization (twice) gave pure material, m.p. 75–76° and m.p. 76–77° on admixture with authentic 1,4-anhydro-DL-ribitol (m.p. 76–77°).

The combined mother liquors from the crystallizations were evaporated to dryness under reduced pressure and treated with 3 ml. of benzoyl chloride in 10 ml. of anhydrous pyridine. After 0.5 hr., ice was added and the product was extracted with chloroform, washed twice with 50 ml. each of *N* sulfuric acid, saturated aqueous sodium bicarbonate solution and water. The dried chloroform layer was evaporated under reduced pressure and the resultant sirup was dissolved in 2 ml. of hot 1-butanol. Crystals were obtained on cooling; yield 160 mg., m.p. 114–116°. Pure material formed on recrystallization from 1-butanol–heptane; m.p. 116–116.5° and m.p. 115–116° on admixture with authentic 2,3,5-tri-*O*-benzoyl-1,4-anhydro-DL-ribitol of like melting point.

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