[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

The Action of Diazomethane on the Tetraacetates of *aldehydo*-D(and L)-Arabinose[1]

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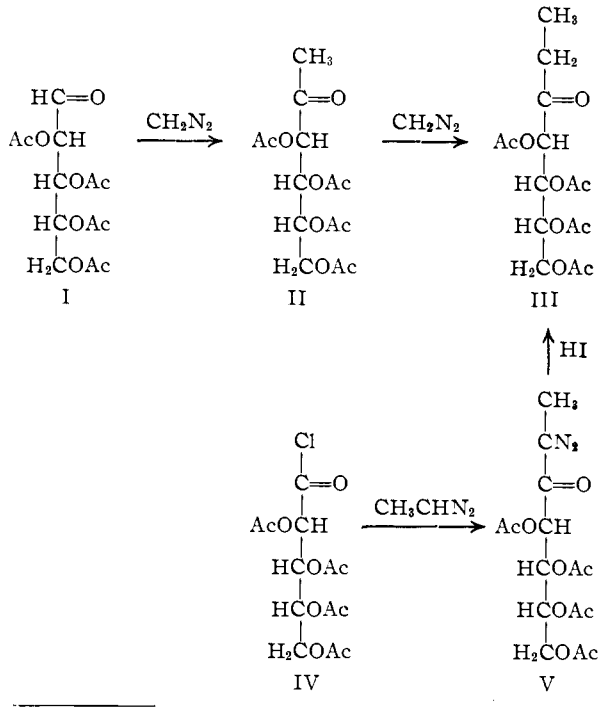
The action of two moles of diazomethane on the tetraacetates of *aldehydo*-D-arabinose and *aldehydo*-L-arabinose has produced the corresponding enantiomorphous 1,2-dideoxy-3-*keto*-*arabino*-heptulose tetraacetates. These dideoxy structures have been established by functional group tests and by the synthesis of 1,2-dideoxy-3-*keto*-D-*arabino*-heptulose tetraacetate from tetra-*O*-acetyl-D-arabinonoyl chloride and diazoethane.

In previous reports from this Laboratory, we have shown that *keto*-D-fructose pentaacetate and *keto*-L-sorbose pentaacetate react with diazomethane to yield epoxy derivatives.[4] On the other hand, *aldehydo*-D-glucose pentaacetate, on like reaction, gave 1-deoxy-*keto*-D-*gluco*-heptulose pentaacetate and this on further reaction produced 1,2-*dideoxy*-3-*keto*-D-*gluco*-octulose pentaacetate; an analogous octulose derivative was obtained from *aldehydo*-D-galactose pentaacetate.[5]

These studies have now been extended to *aldehydo*-D(and L)-arabinose tetraacetate (I). It had been previously shown[6] that these substances reacted initially with diazomethane to yield the 1-deoxy-*keto*-D(and L)-fructose tetraacetate (II). We have now found that further reaction leads to the formation of 1,2-dideoxy-3-*keto*-D(and L)-*arabino*-heptulose tetraacetate (III).



Substance III was a crystalline solid that was reducing to Fehling solution and gave negative tests toward hypohalite (no iodoform) and Schiff aldehyde reagents; it formed a crystalline oxime. As with the corresponding 1,2-dideoxy-3-*keto*-D-*gluco*-octulose,[5] the structure of III was proved unequivocally by reaction of tetra-*O*-acetyl-D-arabinonoyl chloride (IV)[7] with diazoethane to yield the diazomethyl ketone V which on reduction yielded III with nitrogen loss.

Using the low temperature technique of Wilds and Meader,[8] we still failed to obtain the diazo product V in crystalline form. The diazo compound effervesced on acidification and showed the expected absorptions in the 4.75, 6.1 and 7.2 μ regions.[9,10] The reduction of diazo compounds with hydriodic acid, which gives good yields in the case of the analogous diazomethyl ketones,[11-13] proceeded poorly in the present case and crystalline material was obtained only after silicate column chromatography. A further explanation of the over-all poor yield of the ethyl ketone from the acid chloride and diazoethane might be found in the further reaction of the diazo compound with diazoethane,[14] as follows.

$$RCOCl + 2CH_3CHN_2 \longrightarrow RCOCN_2CH_3 + CH_3CH_2Cl + N_2$$

$$RCOCN_2CH_3 + CH_3CHN_2 \longrightarrow RCOC(CH_3)=NN=CHCH_3 + N_2$$

Experimental

1,2-Dideoxy-3-*keto*-D-*arabino*-heptulose Tetraacetate. (a) **From *aldehydo*-D-Arabinose Tetraacetate.**—A cold (0–5°) solution of 6 g. of *aldehydo*-D-arabinose tetraacetate[6] in absolute chloroform was treated with an ethereal solution of diazomethane (about 2.1 moles), prepared by the action of methanolic potassium hydroxide on ethyl *N*-methyl-*N*-nitroso-carbamate according to the procedure of von Pechmann.[15] There was a steady, vigorous evolution of nitrogen

(1) Paper No. 20 in the series entitled "The Action of Diazomethane upon Acyclic Sugar Derivatives"; previous communication: D. L. MacDonald, J. D. Crum and R. Barker, THIS JOURNAL, **80**, 3379 (1958).

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as the reaction progressed and finally the solution acquired a permanent yellow color. After standing overnight at room temperature, the colorless solution was filtered and the sirup obtained on solvent removal at reduced pressure crystallized on scratching; yield 5.3 g., m.p. 88–92°. Pure material, in the form of elongated plates, was obtained after four recrystallizations from 50% ethanol; yield 3.5 g., m.p. 93–94°, $[\alpha]^{27}D$ + 53° (*c* 3.2, abs. $CHCl_3$), a pronounced absorption maximum at 2800 Å.[16] in U.S.P.[17] chloroform: log ϵ_{max} 1.60 (282 mμ, 1.8 × 10^{-2} *M*), log ϵ_{max} 1.63 (282 mμ, *c* 9 × 10^{-3} *M*); X-ray powder diffraction data[18]: 9.88 m (2), 7.25s(1), 5.29s(1), 4.68m(2), 4.20m(2), 4.01w, 3.80m(2), 3.58w, 3.47w, 3.33w, 2.78w. The compound showed no mutarotation in U.S.P. chloroform, gave a negative Schiff aldehyde test, reduced Fehling solution and exhibited the usual solubility properties of a sugar acetate.

Anal. Calcd. for $C_7H_{10}O_5(CH_3CO)_4$: C, 51.98; H, 6.41; CH_3CO, 11.56 ml. of 0.1 *N* NaOH per 100 mg. Found: C, 52.14, H, 6.41; CH_3CO,[19] 12.15 ml.

(b) From Tetra-*O*-acetyl-D-Arabinonoyl Chloride and Diazoethane.—D-Arabinose was oxidized with bromine according to the procedure of Hudson and Isbell,[20] employing barium benzoate as a buffer, and the resulting D-arabinonic acid was isolated as the crystalline potassium salt. D-Arabinonic acid was prepared from the potassium salt by recrystallization from acetic acid and on acetylation with zinc chloride and acetic anhydride, according to the procedure of Upson and associates,[21] gave D-arabinonic acid tetraacetate. D-Arabinonyl chloride tetraacetate was prepared from D-arabinonic acid tetraacetate by treatment with phosphorus pentachloride in anhydrous ether by the method of Wolfrom, Brown and Evans.[7] Pure material was obtained on crystallization from dry ether by the addition of petroleum ether; m.p. 74–75°, $[\alpha]^{20}D$ + 46° (*c* 2.5, abs. $CHCl_3$) in agreement with the constants reported by these workers.

N-Ethyl-*N*-nitrosourea was prepared from ethylamine hydrochloride and urea according to the procedure for the preparation of the homologous *N*-methyl-*N*-nitrosourea.[22] An ethereal solution of the urea derivative gave diazoethane on treatment[23] with a solution of potassium hydroxide in 2-(2-ethoxyethoxy)-ethanol (8% yield).

To a solution of 700 mg. of diazoethane in 80 ml. of ether, cooled in an ethanol–(solid carbon dioxide) bath, was added slowly, with stirring, a solution of 1.8 g. of tetra-*O*-acetyl-D-arabinonoyl chloride dissolved in 50 ml. of anhydrous ether. The reaction mixture was allowed to remain at room temperature for 30 min. and the solvent was then removed by evaporation under reduced pressure. The resulting bright yellow sirup was dissolved in 20 ml. of benzene and chromatographed in 10-ml. portions on two Magnesol[24]–Celite[25] (5:1 by wt.) columns (4.4 × 21.5 cm.) using 500 ml. of benzene–*tert*-butyl alcohol (100:1 by vol.) as developer. Alkaline permanganate streaking[26] indicated the presence of a zone located 5–9 cm. from the column top. The sectioned zones from the two columns were combined, eluted with acetone, and the eluate evaporated to a thick, bright yellow sirup which effervesced on acidification and which showed absorption[9,10] at 4.77, 6.1 and 7.2 μ.

This sirupy 1,2-dideoxy-2-diazo-3-*keto*-D-*arabino*-heptulose tetraacetate was dissolved in 40 ml. of U.S.P. chloroform and 10 ml. of 47% hydriodic acid was added. The reaction mixture was shaken until nitrogen evolution ceased (about 5 min.) and the dark red chloroform solution was washed with water, saturated aqueous sodium thiosulfate solution, and again with water. The bright yellow chloroform solution was dried with sodium sulfate and the solvent removed by evaporation under reduced pressure. The resulting bright yellow sirup was dissolved in 20 ml. of benzene, the benzene solution divided in half, and each portion chromatographed on Magnesol[24]–Celite[25] (5:1 by wt.) columns (4.4 × 20.5 cm.) using 500 ml. of benzene–*tert*-butyl alcohol (100:1 by vol.) as developer. Alkaline permanganate streaking[26] indicated the presence of three zones: 0–3 cm., 8–12 cm. and 15–16 cm., from the column top.

The middle zones from both columns were sectioned and combined, eluted with acetone, and the eluate evaporated under reduced pressure to yield a light yellow sirup of 1,2-dideoxy-3-*keto*-D-*arabino*-heptulose tetraacetate which crystallized from ether–petroleum ether (b.p. 30–60°); yield 160 mg., m.p. 86–88°. Recrystallization was effected from the same solvent mixture, $[\alpha]^{20}D$ + 54.4° (*c* 2.6, U.S.P. $CHCl_3$), m.p. 93–94° unchanged on admixture with 1,2-dideoxy-3-*keto*-D-*arabino*-heptulose tetraacetate prepared in part (a), X-ray powder diffraction pattern identical with that reported in (a) above.

1,2-Dideoxy-3-*keto*-L-*arabino*-heptulose Tetraacetate from *aldehydo*-L-Arabinose Tetraacetate.—*aldehydo*-L-Arabinose tetraacetate[27] (6 g.) was treated with an excess of diazomethane (about 2 moles) and the product was isolated as described above for the enantiomorph; m.p. 93–94°, $[\alpha]^{23}D$ −53° (*c* 3.2, abs. $CHCl_3$), no mutarotation in U.S.P. chloroform. The substance reduced Fehling solution and displayed the same solubility as its enantiomorph.

Anal. Calcd. for $C_7H_{10}O_5(CH_3CO)_4$: C, 51.98; H, 6.41; CH_3CO, 11.56 ml. of 0.1 *N* NaOH per 100 mg. Found: C, 52.05; H, 6.19; CH_3CO, 12.08 ml.

4,5,6,7-Tetra-*O*-acetyl-1,2-dideoxy-3-*keto*-D-*arabino*-heptulose Oxime.—To a solution of 2.0 g. of 1,2-dideoxy-3-*keto*-D-*arabino*-heptulose tetraacetate (prepared from *aldehydo*-D-arabinose tetraacetate) in 20 ml. of absolute ethanol was added a solution of 0.63 g. of hydroxylamine hydrochloride and 1.2 g. of freshly fused potassium acetate in 20 ml. of 50% ethanol. The reaction mixture was allowed to remain at room temperature for 2 hr. whereupon the solvent was evaporated by a stream of dry air. The solid material obtained was extracted with several portions of warm methanol (total vol., 25 ml.), the extract concentrated to 15 ml. and 90 ml. of water was added. Upon standing at 15°, the oxime crystallized in transparent plates; yield 1.32 g., m.p. 92–103°. Pure material was obtained on recrystallization from ether–petroleum ether; m.p. 116–117°, $[\alpha]^{30}D$ + 22.4° (*c* 3.2, abs. $CHCl_3$).

Anal. Calcd. for $C_7H_{11}O_5N(CH_3CO)_4$: N, 3.88; CH_3CO, 11.07 ml. of 0.1 *N* NaOH per 100 mg. Found: N, 3.85; CH_3CO,[28] 11.07 ml.

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(17) United States Pharmacopoeia: contains ethanol.

(18) Relative intensity, estimated visually; s, strong; m, medium; w, weak. First three strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities.

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