A NEW METHOD FOR THE PREPARATION OF D-ERYTHROSE AND OF L-GLYCERALDEHYDE[1]

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ABSTRACT

D-Glucose is degraded selectively to di-*O*-formyl-D-erythrose by oxidation with two moles of lead tetraacetate. The ester groups are easily hydrolyzed, giving D-erythrose in an over-all yield of at least 80% of theory. In like manner oxidation of L-arabinose, followed by hydrolysis, affords L-glyceraldehyde. It is suggested that D-erythrose can readily associate intermolecularly, a property previously ascribed among sugars only to the trioses.

INTRODUCTION

Among monosaccharides the tetroses constitute probably the most poorly characterized group. Only one preparation of a crystalline tetrose, that of D-threose, has been reported (6), but subsequent investigations by Hockett (9, 10) and Hockett *et al.* (11) have cast serious doubt on the identity of this preparation. The current importance of the tetroses is illustrated by the use of D-erythrose as a starting point for synthesis of 2-deoxy-D-ribose (20, 29) and of ribose-1-C^{14} (7, 18).

At least seven methods for preparing D-erythrose are recorded in the literature. Five of these have been evaluated by Overend, Stacey, and Wiggins (20), who recommended the Ruff procedure (26) as modified by Hockett and Hudson (12), and two additional methods have since been reported (30, 25, 16, 14). All of these procedures involve degradation of an appropriate sugar derivative—the acid, glucal, acetal, or mercaptal—which, however, is itself sometimes not obtained readily or in good yield. This communication now reports a convenient preparation of D-erythrose in high yield directly from D-glucose.

When aldohexoses are treated with lead tetraacetate they rapidly consume two moles of oxidant, after which the reaction becomes very slow (13, 24). Applied to D-glucose it is found that the initial rapid stage of the reaction corresponds to virtually complete conversion of the hexose to D-erythrose. With one mole of oxidant, D-arabinose as well as D-erythrose is obtained (23). The oxidation is carried out in acetic acid solution by the addition of two moles of the powdered oxidant per mole of glucose. Removal of the divalent lead and distillation of the solvent affords a clear, colorless sirup, in 90 to 95% yield, which exhibits the properties of a diformate ester of D-erythrose (24). The ester groups are easily hydrolyzed by heating in water or dilute acid, giving a product which has an equilibrium specific rotation of about $-30°$ and which is uncontaminated by hexose or pentose sugars (paper chromatogram). The infrared absorption spectrum of the free sugar, using the potassium bromide

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window technique (27), is identical with that of D-erythrose prepared from 4,6-*O*-ethylidene-D-glucose (25), and gives no indication of the presence of other compounds. The compound has been further characterized as D-erythrose by hydrogenation to erythritol, by oxidation with bromine to D-erythrono-γ-lactone, and by preparation of the crystalline 2,5-dichlorophenylhydrazone.

On paper chromatograms the new preparation of D-erythrose and the sample prepared from ethylidene glucose behave in identical fashion but show complex properties. For example, each gives a single equally-fast-travelling spot when the solvent is ethyl acetate/acetic acid/water (3/1/3) (15), but in butanol/ethanol/water (4/1/5) (2) much streaking from the origin almost to the solvent front is observed. When an aqueous solution of either preparation is frozen, then thawed, and examined on the chromatogram with the use of methyl ethyl ketone/water (4), at least two spots are found, the major component having an R_f of 0.22 and the other remaining close to the origin. The proportion of slow-moving component is, however, less if the solution is first heated on the boiling-water bath before chromatographing. This behavior may be related to gross changes in optical rotation which have been observed when a solution of the sugar is frozen and thawed. Thus, a solution of D-erythrose having an equilibrium specific rotation of $-31°$, after freezing for 18 hr. and thawing, had a specific rotation of about $-6°$, reverting to the original value during a period of four hours at room temperature. The specific rotation changed to $+2°$ when the solution was stored in the frozen state for 48 hr. These results suggest that D-erythrose in solution readily enters into loose intermolecular association possibly with formation of a dimer or other complex. Such behavior has long been recognized with glyceraldehyde (35), but appears not to have been reported for tetroses. The observed mutarotation changes might therefore correspond to a polymer ↔ monomerfuranose interconversion together with attainment of an α,β-anomer equilibrium for the latter. Perhaps this complexity in part accounts for the wide variation in specific rotations reported for erythrose, such as $-14.5°$ for the D-isomer and $+32.7°$ for the L-isomer (33). Further, the tendency of D-erythrose to associate or dimerize may explain why attempts to crystallize the compound have been unsuccessful.

Pentoses also quickly consume two moles of lead tetraacetate and it was therefore to be expected, by analogy with hexoses, that the degradation should yield the corresponding triose. D-Glyceraldehyde, first prepared by Wohl and Momber (34), is readily obtainable through the elegant method of Fischer and Baer (5), which involves periodate or lead tetraacetate oxidation of 1,2;5,6-di-*O*-isopropylidene-D-mannitol, and, more directly, through the procedure recently reported by Schöpf and Wild (28) in which D-glucose is oxidized with three moles of periodate. By contrast, L-glyceraldehyde is not as easily obtained since the methods just noted require the corresponding but rare L-sugars. Thus Baer and Fischer (2) prepare L-glyceraldehyde from 1,2;5,6-di-*O*-isopropylidene-L-mannitol which is first synthesized from L-arabinose *via* the cyanohydrin reaction and reduction. With lead tetraacetate oxidation, however, L-arabinose is degraded directly to L-glyceraldehyde in high yield. As with D-erythrose the product is recovered from the reaction as

a sirupy formate ester (24), which yields the free glyceraldehyde upon hydrolysis in water or dilute acid. The compound gives an elongated spot on the chromatogram (ethyl acetate/acetic acid/water solvent) with a rate of travel slightly smaller than D-erythrose, possibly due to its existence as a dimer. Traces of arabinose and erythrose were detected in some preparations. The butanol solvent causes much streaking of material on the chromatogram and several spots are discernible, but these are attributed at present to the various modifications possible for glyceraldehyde (2). It will be remembered that erythrose also behaved atypically with this solvent. The equilibrium specific rotation of the compound in water, $[\alpha]_D^{25}$ $-7°$, is close to the value of $+9°$ reported for a freshly-prepared solution of the D-isomer (3). The relatively high purity of the preparation is indicated by the fact that it gave a 73% yield of the L-glyceraldehyde dimedon, which agreed well with the yield of 75% obtained by Baer and Fischer from pure L-glyceraldehyde (2). The product was characterized further as the crystalline 2,4-dinitrophenylhydrazone.

Since oxidation of other aldohexoses and aldopentoses by lead tetraacetate parallels the foregoing oxidations, it is seen, for example, that D-threose may readily be prepared directly from D-galactose and D-glyceraldehyde from D-xylose. A description of their preparation is included in another communication (24), which considers the mechanism of the lead tetraacetate oxidation of reducing sugars.

EXPERIMENTAL

Lead tetraacetate was prepared according to the procedure of Vogel (31). A commercial sample (Matheson Co., Inc.) was also used. All other chemicals were reagent grade.

Spray reagents used for chromatography were triphenyltetrazolium chloride (32), silver nitrate (21), and aniline (22).

Solutions were concentrated *in vacuo* at 35° C.

*Di-O-formyl-*D*-erythrose*

D-Glucose (1.50 gm., 8.3 mM.) dissolved in 3 ml. of water was taken up in 150 ml. of glacial acetic acid. Lead tetraacetate[2] (7.7 gm., 17.4 mM.) was added over a period of three to four minutes to the rapidly stirred solution. Within five minutes' reaction time the lead tetraacetate had dissolved and the solution gave a faint potassium iodide – starch test. Oxalic acid dihydrate (1.9 gm.), dissolved in glacial acetic acid, was added,[3] and the suspension was stirred for an additional 30 min. The precipitate was filtered and washed with acetic acid and the filtrate was concentrated to a volume of a few milliliters. Ethyl acetate was added and the precipitate which formed was triturated with several portions of ethyl acetate. The extracts were combined, filtered, and concentrated to a sirup which was further purified twice by extraction with ethyl acetate. The product was a clear, pale yellow oil. Weight, 1.30 gm. This

[2]*If the compound was dark it was recrystallized before use from acetic acid. Or, it was dissolved in glacial acetic acid and the solution was filtered and added to the glucose solution.*

[3]*Excess lead tetraacetate was thereby decomposed and the divalent lead precipitated.*

compound, which is described in greater detail elsewhere (24), is found to contain two formate ester groups.

D-*Erythrose*

Di-*O*-formyl-D-erythrose (0.201 gm.) was dissolved in 20 ml. of 0.05 *N* hydrochloric acid (a slight turbidity was removed by filtering) and the solution was heated at 50° C., the hydrolysis being followed polarimetrically: $[\alpha]_D$ +0.55° (initial) → −0.40° (two hours, constant). The reducing power of the hydrolyzate, measured by hypoiodite oxidation (8), was equivalent to 0.122 gm. of tetrose (91%); $[\alpha]_D^{27}$ −32.7°. Acid was removed by use of a column (1 cm. × 10 cm.) of Amberlite IR4B resin with some loss of reducing power. The calculated weight of D-erythrose was 0.114 gm., an over-all yield from D-glucose of 80% of theory. $[\alpha]_D^{27}$ −30.0° (equilibrium) (*c*, 0.64).

Erythritol

Di-*O*-formyl-D-erythrose (1.0 gm.) was dissolved in absolute alcohol (40 ml.) and was hydrogenated at ambient temperature and pressure using reduced platinum oxide catalyst (1). Fifty milliliters of hydrogen was taken up, corresponding approximately to one mole per mole of erythrose, and the solution was then only faintly reducing to Fehling's solution. The catalyst was filtered and the filtrate concentrated to a colorless sirup which quickly crystallized. After washing with alcohol and drying the product weighed 0.25 gm. (73%); m.p. 114–116° C. Recrystallization from alcohol raised the melting point to 118° C.; the mixed melting point with an authentic specimen of erythritol (m.p. 118.5° C.) was 118–118.5° C. The X-ray diffraction pattern was identical with that of erythritol.

D-*Erythrono-γ-lactone*

Barium carbonate (10 gm.) was suspended in an aqueous solution of D-erythrose (2.0 gm. in 30 ml.), and bromine (3.4 ml.) was added dropwise with stirring. After three hours' reaction time excess bromine was removed by aeration, and there were added in succession silver carbonate to remove bromide, hydrogen sulphide gas to remove excess silver, and dilute sulphuric acid to precipitate excess barium. The final colorless solution was concentrated, giving a sirup which solidified when dried in high vacuum at 60° C. Weight, 1.3 gm. (65%). After one recrystallization from alcohol, m.p. 103–104° C., $[\alpha]_D^{27}$ −72.1° (*c*, 1, water); (m.p. 103° C., $[\alpha]_D$ −73.3° (26)).

D-*Erythrose 2,5-Dichlorophenylhydrazone*

D-Erythrose sirup (0.44 gm.), prepared by concentrating an aliquot of the neutral solution described above, was taken up in 20 ml. of methanol in an evaporating dish. 2,5-Dichlorophenylhydrazine (0.65 gm.) was added and the methanol was rapidly distilled on the steam bath (procedure of Mandl and Neuberg (17)). The product was dissolved in ether, filtered, and the ether was distilled. The residue was dissolved in ethyl acetate, treated with charcoal, and an equal volume of benzene was added. Crystallization was rapid in the cold. Weight, 0.68 gm. (68%), m.p. 101–105° C. Recrystallized twice from

ethyl acetate – benzene (1: 1), m.p. 110–112° C., $[\alpha]_D^{27}$ −12.5° (*c*, 1, methanol). (m.p. 110° C. (19)). Calc. for $C_{10}H_{12}O_3N_2Cl_2$: N, 10.04%; found: N, 10.06%.

By using an excess of the hydrazine reagent (1.6 moles per mole) and distilling off three successive additions of methanol containing a few drops of acetic acid, an osazone was obtained. Melting point after recrystallization from ethyl acetate – benzene (1: 1), 219–220° C. Calc. for $C_{16}H_{14}O_2N_4Cl_4$: N, 12.81%; found: N, 12.85%.

L-Glyceraldehyde

The method for preparation of the L-glyceraldehyde formate ester was the same as for di-*O*-formyl-D-erythrose differing only in the quantities of oxidant and oxalic acid used. L-Arabinose (1.5 gm.) was oxidized with 9.0 gm. of lead tetraacetate and most of the lead was removed by the addition of 2.5 gm. of oxalic acid dihydrate dissolved in acetic acid. The product obtained by ethyl acetate extraction was a clear, pale yellow oil. Weight, 1.2 gm. This compound, which is described in greater detail elsewhere (24), is found to contain about 1.5 formate ester groups.

The ester (0.201 gm.) was hydrolyzed to constant rotation in 10% acetic acid at 50° C. (7.5 hr.), and the acid was removed by distillation. The quantity of sugar estimated by hypoiodite oxidation was 0.102 gm., corresponding to a yield of L-glyceraldehyde from the ester of 83% $[\alpha]_D^{27}$ −7.15° (equilibrium) (*c*, 2).

Dimedon-L-glyceraldehyde

L-Glyceraldehyde formate ester (1.02 gm.) in 100 ml. of phosphate buffer (containing 10 ml. of 1 *M* monopotassium phosphate and 5.9 ml. of 1 *N* sodium hydroxide) was treated with 2.0 gm. of dimedon at room temperature. After 18 hr. reaction time the solution was concentrated and the crystalline product was recovered by filtration. Weight, 1.73 gm. (73%), m.p. 191–200° C. Two recrystallizations from 50% alcohol raised the melting point to 196.5–198.5° C.; $[\alpha]_D^{27}$ −208° (*c*, 0.5, ethanol), (m.p. 198° C., $[\alpha]_D$ −198° (2)). Calc. for $C_{19}H_{26}O_5$: C, 68.24%; H, 7.84%; found: C, 67.97%; H, 7.86%.

L-Glyceraldehyde-2,4-dinitrophenylhydrazone

To a solution of L-glyceraldehyde (0.71 gm.) in 25 ml. of water, cooled in an ice-bath, was added a slightly warm solution of 2,4-dinitrophenylhydrazine (1.6 gm.) in 2 *N* hydrochloric acid (90 ml.) over a period of 30 min. The reaction mixture was maintained at 0° C. for an additional 30 min. A copious yellow precipitate which formed was filtered, then washed with dilute hydrochloric acid and water, and dried. Weight, 0.97 gm., m.p. 120–140° C. Recrystallized three times from 50% alcohol, m.p. 146–148° (m.p. 147–148° (2)). Calc. for $C_9H_{10}O_6N_4$: C, 40.00%; H, 3.73%; found: C, 40.09%; H, 3.83%.

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