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D-APIOSE[1]

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ABSTRACT

Naturally-occurring apiose is shown by synthesis to be the D-isomer in the open-chain form. In this synthesis 3-*O*-benzyl-D-fructose is cyanohydrated and the resulting heptonic lactones are reduced to 3-*O*-benzyl-2-*C*-(hydroxymethyl)-D-*arabo*-hexitol. The latter is oxidized with lead tetraacetate affording 2-*O*-benzyl-3-*C*-(hydroxymethyl)-D-*glycero*-tetrose which, on debenzylation, gives 3-*C*-(hydroxymethyl)-D-*glycero*-tetrose (D-apiose).

INTRODUCTION

Apiose was first isolated by Vongerichten (1), who recognized it as a component sugar of the parsley flavone glycoside, apiin. The sugar has since been found in still other glycosides present in parsley (2, 3, 4, 5) and more recently in *Posidonia australis* (6) and in the rubber plant, *Hevea brasiliensis* (7). The researches of Vongerichten and later work by Schmidt (8), which have been reviewed by Hudson (9), established that apiose is a branched-chain pentose whose structure is represented by I. The synthesis of DL-apiose (10) provides additional confirmation of this structure. In the open-chain form the compound possesses only one asymmetric center, at carbon atom 2, for which the D-configuration has been assigned (8) by application of the salt–acid (11, 12) and phenylhydrazide and amide (12, 13) rules to the derived apionic acid and its derivatives. The present study furnishes an alternative proof for the configuration at C-2 through synthesis of D-apiose, which is found to be identical with the naturally-occurring sugar.

A ready synthetic pathway to D-apiose was suggested by the preparation of 4-*C*-(hydroxymethyl)-D-*threo*-pentose[2] (II) by Woods and Neish (14). It was apparent that D-apiose could be obtained by a one-step descent of the sugar series. However, attempts to achieve this by the Weerman degradation (15) or by partial lead tetraacetate oxidation (16) resulted in the production of only trace amounts of the desired product.

An alternative synthetic pathway, starting with 3-*O*-benzyl-D-fructose (III), was more successful. 1,2;4,5-Di-*O*-*iso*propylidene-D-fructose (17) was benzylated to give 3-*O*-benzyl-1,2;4,5-di-*O*-*iso*propylidene-D-fructose. The acetone groups were removed by acid hydrolysis, affording sirupy 3-*O*-benzyl-D-fructose (III), which was characterized by formation of 3-*O*-benzyl-D-glucose phenylosazone (18) on treatment with phenylhydrazine acetate. The 3-*O*-benzyl-D-fructose was cyanohydrated, the nitrile was hydrolyzed under alkaline conditions, and the product was acidified, yielding a mixture of the corresponding *O*-benzyl-α- and -β-D-fructoheptonic lactones (e.g., IV); the β-isomer was isolated as the crystalline γ-lactone. Reduction of the mixture with sodium borohydride (19, 20) gave the sirupy alcohol, 3-*O*-benzyl-2-*C*-(hydroxymethyl)-D-*arabo*-hexitol (V). The structure of V was confirmed by its conversion, on catalytic hydrogenolysis with palladium oxide followed by acetylation, to the known hepta-*O*-acetyl-2-*C*-(hydroxymethyl)-D-*arabo*-hexitol ("D-fructoheptitol" heptaacetate (21)).

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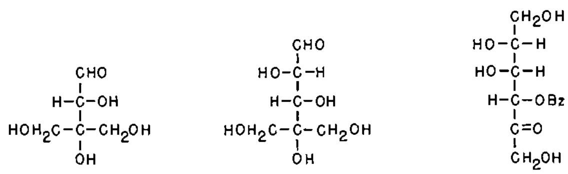
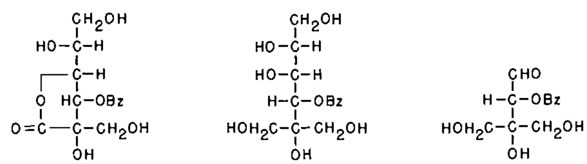
[2]*The nomenclature of the branched-chain sugar has recently been discussed by F. Shafizadeh, Advances in carbohydrate chemistry,* ***11****, 263 (1956).*

The alcohol (V) rapidly consumed approximately 2 moles of oxidant when treated with lead tetraacetate in acetic acid or aqueous periodate, but a moderately rapid over-oxidation followed, which was more pronounced with the latter reagent. Consumption of 2 moles of oxidant was expected to correspond to cleavage of the 1,2,3-triol of V affording 2-*O*-benzyl-3-*C*-(hydroxymethyl)-D-*glycero*-tetrose (2-*O*-benzyl-D-apiose) (VI), in preference to attack at the tertiary hydroxyl group (22). Accordingly, V was oxidized



(I) (II) (III)



(IV) (V) (VI)

with 2 moles of lead tetraacetate in acetic acid and the product was treated with methanolic hydrogen chloride to promote formation of the methyl glycosides. The latter were debenzylated with hydrogen – palladium oxide and the product hydrolyzed with aqueous acid. The final material was found by paper chromatography to contain three components present in approximately equal proportions, the central component corresponding in its rate of travel to D-apiose (I). Presence of the faster- and slower-moving components suggests that over- and under-oxidation occur in addition to the desired reaction on treatment of IV with lead tetraacetate.

The product corresponding to D-apiose was separated as a sirup from the mixture by column chromatography on cellulose (23). Its rate of travel on a paper chromatogram was identical with that of authentic D-apiose isolated from parsley. Detected on the chromatogram with the aniline oxalate spray (24) the natural and synthetic sugars each gave a faint yellow-brown spot which exhibited a strong yellow fluorescence under ultraviolet light, a characteristic of tetroses (25). The identity of the two compounds was demonstrated further by the fact that they gave identical infrared absorption spectra and 2,5-dichlorophenylosazones (6). The specific rotation of the synthetic specimen was $[\alpha]_D$ +6.4°, which is in good agreement with the values of $[\alpha]_D$ +3.8° found by Vongerichten and Müller (26) and $[\alpha]_D$ +5.8° found by Schmidt (8) for D-apiose obtained by regeneration from the 1-benzyl-1-phenylhydrazone.

Since the configuration of carbon atom 2 of synthetic D-apiose, originally carbon atom 3 of D-fructose, is known, the present results confirm Schmidt's assignment of the D-configuration to naturally-occurring apiose.

EXPERIMENTAL

Paper chromatography was carried out on Whatman No. 1 paper using *n*-butanol–ethanol–water (40:11:19, v/v) as solvent. Chromatograms were developed with aniline oxalate (24) and ammoniacal silver nitrate (27) sprays. The distance travelled by compounds on chromatograms (R_{Rh}) was measured relative to the distance travelled by L-rhamnose. Evaporations were carried out *in vacuo* at 40° C.

*3-O-Benzyl-1,2;4,5-di-O-isopropylidene-*D*-fructose*

1,2;4,5-Di-*O*-*iso*propylidene-D-fructose (17) (45 g.) was dissolved in a mixture of benzyl chloride (75 ml.) and xylene (50 ml.). The solution was agitated vigorously with an Ultra-Turrax stirrer (28) and powdered potassium hydroxide (180 g.) was added during a period of 0.5 hour, the reaction temperature being maintained at 85°–95° C. during this time and for an additional 1.5 hours' reaction period. The mixture was cooled, washed with water three times, and concentrated. Water was added to the resulting sirup and the suspension heated on the steam bath at 1 mm., more water was added, and the evaporation repeated. The residue was taken up in acetone, filtered through a bed of filter-cel, and concentrated, yielding a yellow, viscous sirup; n_{D}^{24} 1.5080. Weight 59.0 g. After distillation (135°–155° C. at 0.05 mm.) the product was colorless and had n_{D}^{24} 1.5033, $[\alpha]_{\mathrm{D}}^{25}$ −95.0° (*c*, 4.6, ethanol). Calculated for $C_{19}H_{26}O_6$: C, 65.12%; H, 7.48%. Found: C, 65.00%; H, 7.43%.

*3-O-Benzyl-*D*-fructose*

3-*O*-Benzyl-1,2;4,5-di-*O*-*iso*propylidene-D-fructose (55 g.), dissolved in 50% acetic acid (200 ml.), was heated on a steam bath for 18 hours. After evaporation of the solvent, the product was found (infrared absorption) still to contain some *iso*propylidene groups and was therefore treated on a steam bath for 2 hours with 0.1 *N* sulphuric acid. The hydrolyzate was neutralized with barium carbonate and the solution filtered and concentrated, affording a pale yellow amorphous solid $[\alpha]_{\mathrm{D}}^{25}$ −24.9° (*c*, 4.1, water). Weight 30.4 g. On a paper chromatogram the product gave a single spot (R_{Rh} 2.4) detected by silver nitrate. Calculated for $C_{13}H_{18}O_6$: C, 57.77%; H, 6.71%. Found: C, 57.78%; H, 6.81%.

As expected for a 3-substituted ketose, the compound consumed lead tetraacetate slowly (29).

*3-O-Benzyl-*D*-fructose-(*D*-glucose)-phenylosazone*

3-*O*-Benzyl-D-fructose (400 mg.) was dissolved in water (10 ml.) containing acetic acid (1.5 ml.) and phenylhydrazine (1 ml.). The solution was kept at 50° C. for 18 hours and the red-brown mass which formed was taken up in methanol. On addition of water, crystals were deposited and these were recrystallized from aqueous ethanol and then benzene. The light-yellow product (37 mg.) had m.p. 151°–152° C. Calculated for $C_{25}H_{28}O_4N_4$: C, 66.94%; H, 6.29%. Found: C, 67.14%; H, 6.20%. (Melting point of 3-*O*-benzyl-D-glucose-phenylosazone 149°–150° C. (18).)

*3-O-Benzyl-2-C-hydroxymethyl-*D*-glucono- and -*D*-mannono-γ-lactones (3-O-Benzyl-α- and -β-*D*-fructoheptonic lactones)*

In preliminary tests, cyanohydration of 3-*O*-benzyl-D-fructose with aqueous sodium cyanide at pH 9.3 was approximately 95% complete within 40 hours' reaction time, as measured by evolution of ammonia after alkaline hydrolysis. Accordingly, 3-*O*-benzyl-D-fructose (14.7 g.) in water (25 ml.) was added to a solution (200 ml.) of sodium cyanide (4.1 g.) buffered to pH 9.3 with acetic acid. The pH of the solution rose rapidly to pH 9.8 and more acetic acid was added, further additions of the acid being required during the first 5 hours' reaction time to maintain the pH at 9.3. After 48 hours at room temperature, the reaction mixture was diluted with water (200 ml.) and then concentrated, water was added again and evaporated, the procedure being repeated three times, with the last evaporation at 70° C. to promote complete hydrolysis of the nitrile. The sirup obtained was dissolved in water, treated with Amberlite IR-120, and the hydrocyanic and acetic acids released were removed upon evaporation. After the residue was heated at 100° C. *in vacuo* over phosphorus pentoxide for 4 hours, a pale yellow amorphous solid was obtained. Weight 11.1 g. The infrared absorption spectrum of the product showed a predominance of the γ-lactone form to be present (strong absorption band at 1770 cm.$^{-1}$ (30)). The product (46.5 mg.), in water, consumed 0.26 ml. of 0.1 *N* sodium hydroxide by direct titration to a stable end point. Excess of the alkali was added, the solution heated, and back-titrated with acid. The total alkali consumed was 1.57 ml. (required, 1.55 ml.), indicating that approximately 85% of the material existed as the γ-lactone.

*3-O-Benzyl-2-C-hydroxymethyl-*D*-mannono-γ-lactone (3-O-Benzyl-β-*D*-fructoheptonic lactone)*

Partial crystallization of the lactone mixture occurred after several months. The sirup was taken up in ethyl acetate and the crystals were filtered off and recrystallized from ethyl acetate. Weight, 120 mg. from 500 mg. of the mixture. Melting point 150.5°–152.0° C., $[\alpha]_D^{27}$ +45.5° (*c*, 1.2, alcohol). Calculated for $C_{14}H_{18}O_7$: C, 56.38%; H, 6.08%. Found: C, 56.16%; H, 6.05%. The compound absorbed strongly in the infrared region at 1770 cm.$^{-1}$, which, together with the stability exhibited to alkaline hydrolysis, showed the presence of a γ-lactone structure (30). The non-crystalline fraction showed $[\alpha]_D^{27}$ +89.3° (*c*, 1.6, alcohol).

The crystalline lactone was treated with one equivalent of hot sodium hydroxide solution; the resulting sodium salt showed $[\alpha]_D^{27}$ +11.6° (*c*, 1.4). This value was altered to $[\alpha]_D^{27}$ +15.4° (*c*, 1.3) by liberation of the free acid through addition of one equivalent of hydrochloric acid. Likewise, the salt and acid prepared from the non-crystalline material had $[\alpha]_D^{27}$ −1.1° (*c*, 1.9) and $[\alpha]_D^{27}$ −5.7° (*c*, 1.7), respectively. These data are in close agreement with the results obtained (31) by application of the salt–acid rule (11, 12) to α- and β-D-fructoheptonic lactones, and indicate that the crystalline lactone is the β-(*mannono*)-isomer.

*3-O-Benzyl-2-C-(hydroxymethyl)-*D*-arabo-hexitol*

The crude mixture of *O*-benzyl-D-fructoheptonic lactones (7.5 g.) in water (15 ml.) was added slowly to a solution of sodium borohydride (1.5 g.) in water (25 ml.) (19). After 2 hours, excess of acetic acid was added, the solution passed through a column of Amberlite IR-120, and the solvent evaporated. The resulting sirup was taken up in methanol, the methanol was evaporated, and this procedure repeated five times to ensure removal of boric acid. The product contained some free acid and lactone (infrared spectrum). Accordingly the material was neutralized in methanol with ethereal diazomethane, again treated with sodium borohydride, and the product was worked up as described above. A small quantity of acid and lactone still present was removed by dissolving the product in excess hot 0.05 *N* sodium hydroxide and then treating with a mixed-bed resin of Amberlite IR-120 and IR-4B. (Reduction of the lactone was more efficient when, in a separate run, the reaction was carried out in cold methanol in the presence of sodium methoxide (20).) The final product was a colorless glass which gave a single spot (R_{Rh} 1.9) on a paper chromatogram using the ammoniacal silver nitrate spray, and was shown by its infrared spectrum to contain neither carboxyl nor lactone groups; $[\alpha]_D^{25}$ +13.7° (*c*, 2.9, water). Weight 3.0 g. Calculated for $C_{14}H_{22}O_7$: C, 55.62%; H, 7.34%. Found: C, 55.66%; H, 7.34%.

*2-C-(Hydroxymethyl)-*D*-arabo-hexitol ("*D*-Fructoheptitol")*

The *O*-benzyl heptitol was dissolved in ethanol (20 ml.) and treated at ambient temperature and pressure with hydrogen in the presence of palladium black catalyst (0.10 g.).

Approximately 1 mole of hydrogen was taken up in 2 hours' reaction time; ultraviolet absorption analysis then showed complete absence of the benzyl group. Removal of the catalyst and evaporation of the solvent afforded a sirupy product having the same R_{Rh} (0.53) on a paper chromatogram as authentic "D-fructoheptitol" (21), and an infrared absorption spectrum indistinguishable from that of the latter compound. The material was acetylated with hot acetic anhydride – sodium acetate. The sirupy acetate formed gave an infrared absorption spectrum which, except for the added presence of a weak hydroxyl band, was indistinguishable from that of "D-fructoheptitol" heptaacetate (21), and had the same specific rotation; $[\alpha]_D^{25}$ +31.0° (*c*, 6.0, chloroform) (authentic material has $[\alpha]_D^{24}$ +31.6° (21)). The product crystallized with difficulty, however, and after repeated recrystallization from ethanol–water the acetate (10 mg.) melted at 63°–67° C., undepressed by admixture with an authentic specimen (69°–70° C.). The X-ray diffraction pattern of the compound was indistinguishable from that of "D-fructoheptitol" heptaacetate. Calculated for $C_{21}H_{30}O_{14}$: C, 49.80%; H, 5.97%; acetyl, 60.8%. Found: C, 50.15%; H, 6.35%; acetyl, 60.5%.

*Glycol-Cleavage Oxidations of 3-O-Benzyl-2-C-(hydroxymethyl)-*D*-arabo-hexitol*

Oxidation of the *O*-benzyl polyol was examined using excess lead tetraacetate in acetic acid and excess sodium metaperiodate in water. At intervals, aliquots were removed from each reaction mixture and the consumption of oxidant was measured: lead tetraacetate (moles per mole)—1.85 (10 minutes), 2.20 (25 minutes), 2.55 (40 minutes); periodate (moles per mole)—2.45 (5 minutes), 2.60 (15 minutes), 2.77 (25 minutes).

*3-C-(Hydroxymethyl)-*D*-glycero-tetrose* (D-*Apiose*)

3-*O*-Benzyl-2-*C*-(hydroxymethyl)-D-*arabo*-hexitol (1.5 g.) was dissolved in acetic acid (20 ml.) and lead tetraacetate (4.2 g., 1.9 molar equivalents) in acetic acid (140 ml.) was added. After the oxidant has been consumed, oxalic acid (0.8 g.) in acetic acid (8.0 ml.) was added with stirring, the precipitate was filtered off, and the solvent evaporated. The sirup was extracted with ethyl acetate and the extract concentrated yielding a sirup (1.0 g.) which was treated under reflux with methanolic hydrogen chloride (0.5%, 20 ml.) for 2 hours and at room temperature for 18 hours. Acid was removed with silver carbonate and the methanolic filtrate evaporated yielding a sirup (0.88 g.) non-reducing to Fehling's solution. The product was catalytically debenzylated as described above, and then hydrolyzed with 0.3 *N* sulphuric acid for 1 hour at 95° C. The hydrolyzate was neutralized with Dowex-1 resin (bicarbonate form) and concentrated. The resulting sirup (0.40 g.), which was found by paper chromatography to contain three components (R_{Rh} 1.3, 0.9, and 0.5, respectively), was chromatographed on a cellulose column (23) using *n*-butanol half-saturated with water. The fraction corresponding to D-apiose (R_{Rh} 0.9) was collected, filtered through a Seitz bacterial filter, and concentrated. The residue was taken up in water, and the solution filtered through charcoal and concentrated giving a clear colorless sirup (94 mg.); $[\alpha]_D^{25}$ +6.4° (*c*, 1.0, water). The infrared absorption spectrum was identical with that of D-apiose isolated from parsley. Treated with 2,5-dichlorophenylhydrazine according to the procedure of Bell *et al.* (6), the product (50 mg.) gave an osazone which after two recrystallizations from aqueous ethanol (weight 47 mg.) had m.p. 194°–195.5° C. (corr.) (Bell *et al.* (6) report m.p. 188.5°–190.5° C. for D-apiose-2,5-dichlorophenylosazone). The X-ray diffraction pattern of the osazone was identical with that of the 2,5-dichlorophenylosazone prepared from D-apiose isolated according to the procedure of Vongerichten (1) from parsley. Calculated for $C_{17}H_{16}O_3N_4Cl_4$: C, 43.80%; H, 3.46%. Found: C, 44.04%; H, 3.43%.

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