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THE PREPARATION OF D-α-FRUCTOHEPTOSE[1]

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ABSTRACT

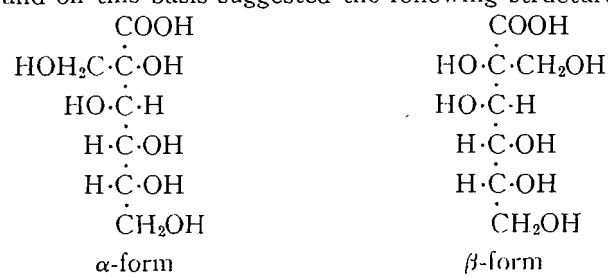
Crystalline D-α-fructoheptose (2-C-hydroxymethyl-D-glucose) has been obtained by the sodium amalgam reduction of D-α-fructoheptonic lactone. Some crystalline derivatives of the sugar are described and also the crystalline heptacetate of D-fructoheptitol (1,1-C-di(hydroxymethyl)-D-arabitol).

INTRODUCTION

During the course of his work upon the configuration of the sugars, Kiliani (5) condensed fructose with hydrogen cyanide and isolated a crystalline cyanhydrin which he hydrolyzed to a heptonic acid and subsequently reduced to 2-methyl hexanoic acid, thus establishing the position of the carbonyl group in fructose.

The crystalline cyanhydrin and the heptonic acid derived from it were made the subject of further research by Kiliani and Düll (2, 6, 7, 8, 9), the acid being characterized by the formation of several salts (see also 11) and a crystalline lactone, m.p. 126–130° C. Later, the acids obtained by hydrolysis of the crystalline fructose cyanhydrin and by hydrolysis of the whole of the fructose – hydrogen cyanide addition product were examined by Schmidt and Weber-Molster (12). The crystalline cyanhydrin was found to yield only the heptonic acid obtained by Kiliani while the hydrolyzate of the total addition product gave a mixture of acids, which were separated, one as the brucine salt and the other as the phenylhydrazide. The former gave a lactone identical with that obtained by Kiliani while the latter gave the epimeric acid which could be dehydrated to a crystalline anhydro lactone. The two acids were designated D-α- and D-β-fructoheptonic acid respectively, following the order of their isolation.

By comparison of the rotations shown by the free acids, the sodium salts, the amides, and the phenylhydrazides, Schmidt and Weber-Molster showed that the *alpha* and *beta* acids behaved similarly to gluconic and mannonic acids respectively and on this basis suggested the following structures:



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If these structures are correct the sugar obtained by reduction of the alpha lactone is 2-C-hydroxymethyl-D-glucose; the trivial name D-α-fructoheptose is used in this paper.

Fischer (3) noted in an early paper on the sodium amalgam reduction of sugar lactones that fructoheptonic lactone could be reduced to a sugar by this method, though he isolated no pure products. He stated that further work was in progress but we have not been able to find any subsequent references to the preparation of D-α-fructoheptose. We have repeated the reduction of D-α-fructoheptonic lactone with sodium amalgam to give solutions containing D-α-fructoheptose in up to 65% of the theoretical yield.

In the first instance the sugar was obtained as a syrup or amorphous, very deliquescent, solid from which it was very difficult to isolate any pure derivative. However, 2: 5-dichlorophenylhydrazine was found to give a hydrazone that formed readily and was easily purified. Regeneration from this derivative led to a sugar syrup that finally crystallized, subsequent reductions yielding the crystalline sugar directly on seeding. The crystalline sugar was stable and nondeliquescent. Neither the α-fructoheptonic lactone nor the sugar itself showed any evidence of anhydride formation as described for the β-lactone. Assuming aqueous D-α-fructoheptose solutions to mutarotate similarly to the straight chain sugars, the change in rotation to give a less dextrorotatory solution indicated that the crystalline sugar isolated was an α-D-anomer (4). No evidence concerning the ring size was obtained.

The sugar was catalytically hydrogenated to give the corresponding sugar alcohol, isolated as the crystalline heptacetate. The free alcohol has not yet crystallized.

EXPERIMENTAL

Melting points were determined on a heating stage microscope and, unless otherwise stated, are corrected.

Fructose Cyanhydrin

The method of Zervas and Sessler (16) was followed. It proceeded smoothly once seeds of the cyanhydrin had been obtained to promote crystallization of the condensation product. The fructose cyanhydrin was washed with cold methanol and dried in a vacuum desiccator for 18–20 hr. over calcium chloride before being hydrolyzed. It was obtained as a white crystalline solid, m.p. 108–109° C. (uncorr.), in yields of 50 to 65%; usually one mole was prepared at a time.

D-α-*Fructoheptonic Lactone*

The cyanhydrin was hydrolyzed by hydrochloric acid and the product worked up essentially as described previously (8, 12). Removal of the hydrogen chloride was greatly expedited by use of an evaporator similar to that described by Bartholomew (1), arranged to recycle automatically. Remaining inorganic materials were removed as previously described (12) and final traces of cations by passage through a column of ion-exchange resin (Amberlite IR-120). Yields of heptonic acid of 85–90% (by titration) were obtained with

a hydrolysis period of two and one-half hours and yields of 68–78% with a hydrolysis period of four hours. A purified acid was obtained, by regeneration from the once-recrystallized brucine salt, and lactonized by heating to 130° C. for five hours. The syrup crystallized on cooling to give the lactone, m.p. 118–119° C. (uncorr.) in 57% over-all yield (two and one-half hours hydrolysis). One crystallization from ethanol raised the melting point to 129.5° C., unchanged by further crystallization.

Reduction D-α-*Fructoheptonic Lactone*

A solution of sodium hydrogen oxalate was prepared by dissolving oxalic acid dihydrate (126 gm.) in warm water (1100 ml.) and adding sodium hydroxide solution (100 ml.; 10 *N*). D-α-Fructoheptonic lactone (180 gm.; m.p. 118–119° C.) was added and the solution cooled to 5° C. Sodium amalgam (2800 gm.; 3%) was stirred into the solution in four equal portions, keeping the temperature below 15° C. and keeping the pH below 4.0 by the addition of powdered oxalic acid. The mixture was then stirred for 45 min. and filtered while still cold. The solid was washed with a little cold water and the filtrate treated with an excess of calcium acetate, the precipitated calcium oxalate being filtered off and the filtrate passed through a column of cation exchange resin (Amberlite IR-120). The amount of aldose present in the solution, estimated by the reduction of hypoiodite, corresponded to a 65% yield of the required sugar. The solution was concentrated under reduced pressure.

The crude reduction mixture could not be crystallized and did not form any derivatives readily. Phenylhydrazine and *as*-diphenylhydrazine did not give solid hydrazones although a crystalline derivative was later obtained with 2:5-dichlorophenylhydrazine.

Reduction of D-α-fructoheptonic lactone with sodium borohydride by a method similar to that described by Wolfrom and Wood (14), but in the presence of a sodium hydrogen oxalate buffer, gave a solution containing 49% of the theoretical quantity of aldose, estimated by hypoiodite. Since this reagent appeared to offer no advantage over the use of sodium amalgam the reduction employing it was not studied further.

D-α-*Fructoheptose 2,5-Dichlorophenylhydrazone*

The syrupy D-α-fructoheptose obtained above was dissolved in methanol (750 ml.) (cf. Mandl and Neuberg (10)) and treated with an excess (15%) of 2,5-dichlorophenylhydrazine. The crude derivative was washed with ethanol and water and crystallized once from aqueous pyridine (201 gm., m.p. 188° C., uncorr.), further crystallization gave the pure *hydrazone* as white plates, m.p. 190° C. Found: C, 42.45; H, 5.05; Cl, 19.25. $C_{13}H_{18}O_6N_2Cl_2$ requires: C, 42.3; H, 4.9; Cl, 19.2%, $[\alpha]_D^{22.2°}$ 7.9° (*c*, 3.6 in pyridine) changing to $[\alpha]_D^{22.3°}$ 5.05°.

D-α-*Fructoheptose*

A solution of the sugar 2,5-dichlorophenylhydrazone (178 gm.; obs. m.p. 188°) in ethanol (1500 ml.) and water (2500 ml.) was refluxed with benzaldehyde (500 ml.) and benzoic acid (50 gm.) for 18 hr. (cf. Sowden and Fischer (13)). After cooling, the aqueous layer was separated and thoroughly washed

with chloroform and ether and evaporated to give the sugar as a pale yellow syrup (79 gm.), which crystallized from an ethanolic solution after several weeks as needles (70.5 gm.), m.p. 171.5° C. A sample was recrystallized by dissolving it in a minimum of water and adding glacial acetic acid or ethanol (about five volumes). The pure *sugar* separated slowly as sweet white needles, very soluble in water, m.p. 172.5–173.5° C. Found: C, 40.0; H, 6.7. $C_7H_{14}O_7$ requires: C, 40.0; H, 6.7%, $[\alpha]_D^{18.2°}$ 51.9° (*c*, 5 in water) mutarotating to $[\alpha]_D^{20.5°}$ 42.95°.

In later experiments, in which seed was available, the sugar could be crystallized directly from the syrupy reduction product by diluting with several volumes of glacial acetic acid and seeding. About 80% of the sugar present crystallized directly and the greater part of the remainder could be recovered by treating the mother liquors with 2,5-dichlorophenylhydrazine.

An attempt to regenerate the sugar by treating the hydrazone above with acetaldehyde, as suggested by Mandl and Neuberg (10), was unsuccessful and neither the sugar nor the hydrazone could be recovered.

Other Hydrazones of D-*α-Fructoheptose*

The pure sugar formed a *phenylhydrazone*, obtained as unstable, transparent plates from methanol, m.p. 144.5°. Found: C, 52.2; H, 6.75; N, 9.4. $C_{13}H_{20}O_6N_2$ requires: C, 52.0; H, 6.7; N, 9.35%, $[\alpha]_D^{22.2°}$ 9.81° (*c*, 1.6 in ethanol) changing to $[\alpha]_D^{22.2°}$ 1.46° after 40 hr. No osazone could be detected under the usual conditions of osazone formation. The *p-nitrophenylhydrazone* crystallized from water as golden plates and needles, discoloring slightly in light, m.p. 178.5° C. Found: C, 45.3; H, 5.5; N, 12.10. $C_{13}H_{19}O_8N_3$ requires: C, 45.2; H, 5.55; N, 12.15%, $[\alpha]_D^{22.2°}$ −26.3° ± 0.8° (*c*, 0.5 in water) changing to $[\alpha]_D^{21.5}$ −21.6° ± 0.4° after 95 hr. The melting point fell to 150° when the derivative was stored in the dark for six weeks. Though the phenylhydrazone and *p*-nitrophenylhydrazone decomposed on keeping the 2,5-dichlorophenylhydrazone appeared to be quite stable.

D-*Fructoheptitol Heptacetate*

Crystalline D-α-fructoheptose (20 gm.) in water (60 ml.) was shaken in an atmosphere of hydrogen in the presence of a Raney nickel catalyst (1–2 gm.) until the uptake of hydrogen ceased (four hours at 100° C. and 2500 lb./sq. in.). The catalyst was filtered off and the filtrate concentrated to give a pale yellow syrup (21.7 gm.) containing less than 5% aldose (estimated by hypoiodite).

A portion of the syrupy alcohol (13.3 gm.) was refluxed with anhydrous sodium acetate (12 gm.) and acetic anhydride (150 ml.) for three and one-half hours. The gummy acetate, isolated by chloroform extraction, was dissolved in benzene (30 ml.) and filtered through a column of activated aluminum oxide (400 gm.; Merck, washed with 10% acetic acid and water and dried at 180°) and eluted with the same solvent. Fractions (50 ml.) were collected and evaporated, those constituting the main band solidified and were crystallized from ethanol to give D-*fructoheptitol heptacetate* as white needles (24.8 gm.) m.p. 70.5° C. Found: C, 49.85; H, 6.05; $CH_3.CO$, 59.25. $C_{21}H_{30}O_{14}$ requires: C, 49.8; H, 5.95; $CH_3.CO$, 59.5%, $[\alpha]_D^{24.2}$ 31.6° (*c*, 7 in chloroform). The chro-

matographic purification could be omitted in later preparations in which the crude acetate solidified on seeding.

Acetylation in pyridine solution gave a mixture of products from which the heptacetate could be isolated by chromatography, though in poorer yield than described above.

D-*Fructoheptitol* [*1,1-C-di(hydroxymethyl)*-D-*arabitol*]

The alcohol was regenerated from the heptacetate (15.0 gm.) by solution in anhydrous methanol (70 ml.) containing a little sodium (0.05 gm.) (15). The solution was evaporated under reduced pressure after standing at room temperature (23° C.) overnight and yielded a colorless syrup (7.23 gm.), $[\alpha]_D^{21.8}$ −5.69° (*c*, 11 in water).

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