

plays no appreciable temperature effect with both 2-nitro-1-butanol and tris-(hydroxymethyl)-nitromethane. Formic esters are produced by avoiding high reaction temperatures and by not

using sulfuric acid catalyst. Acetic esters are produced if vigorous conditions are maintained or if the sulfuric acid is present as catalyst.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

L-Fructose¹

BY M. L. WOLFROM AND ALVA THOMPSON²

Although L-fructose was reported by Fischer³ and characterized by its osazone (L-glucose phenylosazone), it was obtained only in solution and was never isolated. D,L-Glucose phenylosazone (α -acrosazone) had been isolated from the reaction mixture obtained by the action of alkali upon either dibromoacrolein⁴ or "glycerose,"⁵ an oxidation product of glycerol containing glyceraldehyde and dihydroxyacetone. Hydrolysis to the osone with subsequent reduction served to transform D,L-glucose phenylosazone into D,L-fructose.^{3,6} Treatment of the latter with yeast removed the D-fructose, leaving a solution of L-fructose. Crystalline D,L-fructose was obtained later by Schmitz⁷ through the action of very dilute alkali upon crystalline D,L-glyceraldehyde.

In the present work the synthesis of L-fructose was effected by the reaction sequence: L-arabonic acid tetraacetate \rightarrow L-arabonyl chloride tetraacetate \rightarrow 1-diazo-1-desoxy-*keto*-L-fructose tetraacetate \rightarrow *keto*-L-fructose tetraacetate \rightarrow L-fructose. This reaction series had been carried out in the D-configuration but new and improved details for these procedures are presently communicated. All of the products were isolated in crystalline form.

L-Fructose crystallized in long, fine needles emanating from a center and forming a spherical cluster. D-Fructose is described⁸ as crystallizing in the orthorhombic system and exhibiting prismatic or pyramidal habits of rather massive appearance. It is interesting to note that Jungfleisch and Lefranc,⁹ who first crystallized D-fructose, described it as crystallizing in the anhydrous form as long, fine needles emanating from a center to form a spherical cluster. The material meas-

ured by Schuster⁸ was furnished by Hönig and co-workers and consisted in large part of clear, individual crystals (maximum size 2×1.5 mm.) obtained by slow evaporation from ethanol of repeatedly crystallized material. Hönig also furnished Schuster with samples of the first lot of D-fructose that had crystallized in his laboratory. These were spherical clusters of fine needles. Schuster states¹⁰ that their appearance was identical with that cited by Jungfleisch and Lefranc⁹ for their preparation but that they were too small for measurement (by the methods then available). Hönig and Jesser¹¹ considered that this needle form was a hemihydrate but their evidence for such a conclusion was meager.

That the crystalline structure of the L-fructose herein reported is not enantiomorphous with that of the usual form of D-fructose is shown by comparative X-ray powder diagrams (Fig. 1) and by the tabulation of interplanar spacings and relative intensities of the X-ray diffraction lines (Table I).¹² Crystals that are enantiomorphous would exhibit identical X-ray powder diagrams. Single crystal diffraction photographs on D-fructose had been made and examined previously by Hengstenberg and Mark.¹³

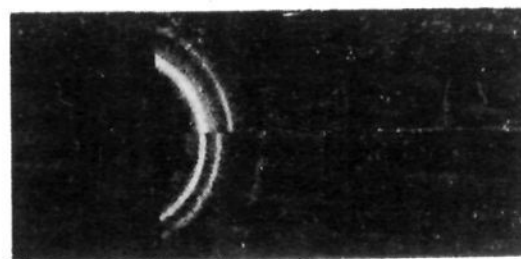


Fig. 1.—Comparative X-ray powder diagrams of L-fructose (upper) and D-fructose (lower) (cf. ref. 12 and Table I).

Analysis indicated that our preparation of L-fructose was anhydrous. The polarimetric and mutarotatory properties of this crystalline form of L-fructose, while not in exact numerical agreement with these difficultly determinable constants of D-fructose, are nevertheless sufficiently close to the accepted values to indicate that in

(1) Paper No. 8 in the series entitled "The Action of Diazomethane upon Acyclic Sugar Derivatives." Previous communication: M. L. Wolfrom, A. Thompson and E. F. Evans, *THIS JOURNAL*, **67**, 1793 (1945).

(2) Research Foundation Associate of the Graduate School.

(3) E. Fischer, *Ber.*, **23**, 389 (1890).

(4) E. Fischer and J. Tafel, *ibid.*, **20**, 1093, 2566, 3388 (1887).

(5) E. Fischer and J. Tafel, *ibid.*, **20**, 3384 (1887).

(6) E. Fischer and J. Tafel, *ibid.*, **22**, 97 (1889).

(7) E. Schmitz, *ibid.*, **46**, 2327 (1913).

(8) (a) M. Schuster, *Tschermak's mineralog. petrog. Mitt.*, **9**, 216 (1888); (b) M. Hönig, St. Schubert (and M. Schuster), *Monatsh.*, **8**, 555 (1887); (c) cf. F. J. Bates and Associates, National Bureau of Standards Circular C440, "Polarimetry, Saccharimetry and the Sugars," 541 (1942).

(9) Jungfleisch and Lefranc, *Compt. rend.*, **93**, 547 (1881).

(10) Ref. 8a, p. 222.

(11) M. Hönig and L. Jesser, *Monatsh.*, **9**, 563 (1888).

(12) For the X-ray photographs and measurements we are indebted to Professor P. M. Harris of this Laboratory.

(13) J. Hengstenberg and H. Mark, *Z. Krist.*, **72**, 301 (1929).

solution the two substances are enantiomorphous. We thus appear to be dealing with dimorphous modifications of fructose and it seems reasonable that our crystalline modification of L-fructose may be enantiomorphous with that form of D-fructose described by Jungfleisch and Lefranc.⁹ This may be an unstable dimorph, such as was encountered with xylitol.¹⁴

TABLE I
X-RAY DIFFRACTION PATTERNS^a (FIG. 1) OF D-FRUCTOSE
AND L-FRUCTOSE

D-Fructose		L-Fructose	
Interplanar spacing, Å.	Relative intensity ^b	Interplanar spacing, Å.	Relative intensity ^b
6.89	0.25	7.74	0.05
5.20	1.00	5.66	.10
4.38	0.75	5.26	1.00
3.49	.10	4.56	0.20
3.15	.30	3.96	.85
2.87	.20	3.73	.05
2.74	.05	3.31	.15
2.61	.10	2.98	.25
2.52	.15	2.82	.20
2.27	.10	2.64	.05
2.14	.05	2.50	.05
2.02	.05	2.37	.10
1.87	.10	2.29	.05
		1.97	.10
		1.94	.05
		1.83	.05

^a Cf. ref. 12. ^b Values visually estimated.

Experimental

D,L-Arabonic Acid Tetraacetate.—An amount of 2 g. each of the enantiomorphous forms¹⁵ of arabonic acid tetraacetate were mixed and crystallized from 15 parts of toluene; m. p. 141–143°, $[\alpha]^{25D} = 0^\circ$ (chloroform). The recorded melting point of the optically active forms is 135–136°.

Anal. Calcd. for $C_{15}H_{18}O_{10}$: C, 46.71; H, 5.43; sapon. value (5 equivs.), 14.96 cc. of 0.1 N sodium hydroxide per 100 mg. Found: C, 46.83; H, 5.49; sapon. value, 14.91 cc.

L-Arabonyl Chloride Tetraacetate.—L-Arabonic acid tetraacetate (5.0 g.) was suspended in 50 cc. of absolute ether and 3.5 g. of phosphorus pentachloride added. The mixture was shaken to effect solution and was then refluxed for one hour. The cooled solution was diluted with 200 cc. of petroleum ether (b. p. 30–60°) and placed at ice-box temperature. A solid gel formed that changed slowly into well-formed crystals over a period of several days. The crystals were filtered quickly, washed with petroleum ether and dried in a vacuum desiccator at room temperature; yield 3.7 g., m. p. 73.5–75°, $[\alpha]^{20D} = -45^\circ$ (c 3, abs. chloroform), in good agreement (opposite sign) with the constants reported (m. p. 74–75°, $[\alpha]^{22D} = +46^\circ$ in chloroform) for the enantiomorph.¹⁶

Anal. Calcd. for $C_5H_5O_5Cl(CH_3CO)_4$: C, 44.26; H, 4.86; Cl, 10.05; sapon. value (6 equivs.), 17.01 cc. of 0.1 N sodium hydroxide per 100 mg. Found: C, 43.94; H, 5.19; Cl, 10.02; sapon. value, 16.90 cc.

(14) M. L. Wolfrom and E. J. Kohn, *THIS JOURNAL*, **64**, 1739 (1942); F. J. Carroll, S. W. Waisbrot and F. T. Jones, *ibid.*, **65**, 1777 (1943).

(15) (a) C. D. Hurd and J. C. Sowden, *ibid.*, **60**, 235 (1938); (b) C. B. Robbins and F. W. Upson, *ibid.*, **62**, 1074 (1940).

(16) M. L. Wolfrom, R. L. Brown and E. F. Evans, *ibid.*, **65**, 1021 (1943).

1-Diazo-1-desoxy-keto-L-fructose Tetraacetate.—To an absolute ethereal solution (240 cc.) of diazomethane (2.07 g., 2.5 moles) was added slowly with stirring a solution of 6.93 g. (1 mole) of crystalline L-arabonyl chloride tetraacetate in 100 cc. of absolute ether. The resulting solution was kept at room temperature for two hours and was then concentrated to one-third volume. Upon the addition of petroleum ether and subsequent cooling, 1-diazo-1-desoxy-keto-L-fructose tetraacetate crystallized; yield 5.30 g., m. p. 87–88.5°. Pure material was obtained on further crystallization from absolute ethanol; light cream color, m. p. 93–94°, $[\alpha]^{20D} = +11^\circ$ (c 3, abs. chloroform) in agreement (opposite sign) with the constants reported (m. p. 93–94°, $[\alpha]^{23D} = -11^\circ$ in chloroform) for the enantiomorph.¹⁷

Anal. Calcd. for $C_6H_8O_5N_2(CH_3CO)_4$: C, 46.90; H, 5.06; N, 7.82; CH_3CO , 11.16 cc. of 0.1 N sodium hydroxide per 100 mg. Found: C, 47.04; H, 5.14; N, 7.75; CH_3CO , 11.12 cc.

1-Diazo-1-desoxy-keto-D,L-fructose Tetraacetate.—This was prepared by crystallizing from ethanol an equal mixture of the enantiomorphs; m. p. 113–114.5°, light cream color.

Anal. Calcd. for $C_{14}H_{18}O_9N_2$: C, 46.90; H, 5.06; N, 7.82. Found: C, 47.12; H, 5.35; N, 7.77.

keto-L-Fructose Pentaacetate.—A solution of 10 g. of 1-diazo-1-desoxy-keto-L-fructose tetraacetate and 0.01 g. of cupric acetate in 300 cc. of glacial acetic acid was heated gently in a 2-liter flask and brought just to the boiling point after the initial violent evolution of gas had subsided. The solvent was removed by distillation under reduced pressure, employing absolute ethanol as a co-distillation liquid for removal of the last portions. The residual sirup was dissolved in 15 cc. of ethanol, filtered and maintained at ice-box temperature overnight to effect crystallization; yield 4.2 g., m. p. 65°. The sirup obtained from the mother liquor on solvent removal was dissolved in 50 cc. of acetic anhydride containing 0.5 g. of zinc chloride (freshly fused), kept overnight at room temperature and then heated at 50° for ninety minutes (an adaptation of the D-fructose acetylation procedure of Cramer and Pacsu¹⁸). The excess acetic anhydride was hydrolyzed by pouring the solution into 200 cc. of cold water and the acetate was extracted with chloroform. The sirup obtained on solvent removal from the washed (with water) and dried extract was crystallized from 10 cc. of absolute ethanol; yield 3.15 (total yield 7.35 g.), m. p. 65°. Pure material was obtained on further crystallization from ethanol; m. p. 69–70°, $[\alpha]^{25D} = -35^\circ$ (c 4, abs. chloroform), in agreement (opposite sign) with the constants reported (m. p. 70°, $[\alpha]^{20D} = +35^\circ$ in chloroform) for the enantiomorph.¹⁹

Anal. Calcd. for $C_6H_7O_6(CH_3CO)_5$: C, 49.23; H, 5.68; CH_3CO , 12.81 cc. of 0.1 N sodium hydroxide per 100 mg. Found: C, 49.50; H, 5.71; CH_3CO , 12.69 cc.

keto-D,L-Fructose Pentaacetate.—This was obtained on crystallization of equal amounts of the enantiomorphs from ethanol; m. p. 99–100°, $[\alpha]^{25D} = 0^\circ$ (chloroform).

Anal. Calcd. for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.68. Found: C, 49.27; H, 5.86.

L-Fructose.—*keto-L-Fructose* pentaacetate (5.0 g.) was saponified as described¹ for the corresponding saponification of *keto-D-psicose* pentaacetate and the product was isolated in the same manner. The resultant sirup crystallized from ethanol on standing at ice-box temperature for several weeks; yield 2.0 g. It was recrystallized from the same solvent and was further purified by soaking overnight at room temperature in ethanol; m. p. 101–103°, $[\alpha]^{21D} = +128^\circ$ (extrapolated) $\rightarrow +93^\circ$ (c, 9.5 as determined by reducing value employing a modified Hagedorn-Jensen assay, 0.001 N potassium acid phthalate, pH 4.4, $k_{21} =$

(17) M. L. Wolfrom, S. W. Waisbrot and R. L. Brown, *ibid.*, **64**, 1701 (1942).

(18) F. B. Cramer and E. Pacsu, *ibid.*, **59**, 1148 (1937).

(19) C. S. Hudson and D. H. Brauns, *ibid.*, **37**, 2736 (1915).

0.066 expressed as minutes and decimal logarithms), $[\alpha]^{20D} +93^\circ$ (c 9.9, water, final value). The accepted values²⁰ for the usual crystalline form of D-fructose are: m. p. 102–104°; $[\alpha]^{20D} -132^\circ \rightarrow -93^\circ$ (c 4, water), $k_{20} = 0.0548$ expressed as minutes and decimal logarithms and in 0.001 *N* potassium acid phthalate (pH 4.4).

The material crystallized in spherical clusters of anhydrous needles. The X-ray powder diagram of this crystal is depicted in Fig. 1, and analyzed in Table I in comparison with the known orthorhombic form of D-fructose.

Anal. Calcd. for $C_6H_{12}O_6$: C, 40.00; H, 6.72. Found: C, 39.72; H, 6.64.

L-Fructose possessed a very sweet taste and was not fermentable by yeast. It readily formed a crystalline, slightly water-soluble compound with calcium hydroxide. It yielded L-glucose phenylosazone; m. p. 211–213° (dec.), a value within the accepted range for the melting point of D-glucose phenylosazone.

D,L-Fructose.—This substance was prepared by dissolving a portion of crystalline D-fructose in methanol and adding this to a solution of a like amount of sirupy L-fructose in methanol. The product crystallized on standing overnight at ice-box temperature; m. p. 132°. Schmitz⁷ recorded the m. p. 129–130° for racemic fructose.

Phenyl-L-glucosotriazole.—L-Glucose phenylosazone (4.0 g.) was converted to the phenylosotriazole according to the procedure of Hann and Hudson²¹ for the enantiomorph; yield 1.1 g. of m. p. 192°. Pure material was obtained on recrystallization from water; m. p. 194–195°. $[\alpha]^{20D} +81.3^\circ$ (c 1.1, pyridine). Hann and Hudson²¹ reported for the enantiomorph: m. p. 195–196°. $[\alpha]^{20D} -81.6^\circ$ (c 0.8, pyridine).

Anal. Calcd. for $C_{12}H_{15}O_4N_3$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.62; H, 5.72; N, 16.07.

(20) H. S. Isbell and W. W. Pigman, *J. Research Natl. Bur. Standards*, **20**, 773 (1938); W. C. Vosburgh, *THIS JOURNAL*, **42**, 1696 (1920); C. S. Hudson and D. H. Brauns, *ibid.*, **38**, 1222 (1916).

(21) R. M. Hann and C. S. Hudson, *THIS JOURNAL*, **66**, 735 (1944).

Phenyl-D,L-glucosotriazole.—This substance was prepared by crystallizing equal portions of the enantiomorphs from water; m. p. 185–187°, $[\alpha]^{20D} \approx 0^\circ$ (pyridine).

Anal. Calcd. for $C_{12}H_{15}O_4N_3$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.41; H, 5.52; N, 16.21.

Acknowledgment.—Preliminary work on this problem was carried out in this Laboratory by Messrs. Irving L. Miller and Evan F. Evans. One of us (A. T.) acknowledges a stipend from the funds of The Ohio State University Research Foundation administered by the Graduate School.

Summary

1. Syntheses are described for L-arabonyl chloride tetraacetate, 1-diazo-1-desoxy-*keto*-L-fructose tetraacetate and *keto*-L-fructose pentaacetate.

2. Saponification of *keto*-L-fructose pentaacetate led to the synthesis of L-fructose in crystalline form, further characterized by its crystalline phenylosazone, phenylosotriazole and racemate.

3. The crystalline structure of the L-fructose herein reported is not enantiomorphous with the presently known usual form of D-fructose.

4. Racemic forms of the following have been synthesized: arabonic acid tetraacetate, 1-diazo-1-desoxy-*keto*-fructose tetraacetate, *keto*-fructose pentaacetate, phenyl-glucosotriazole.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

Diazonium Borofluorides. V. A Study of Arylcopper Complexes

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The preceding article of this series³ recorded the preparation of organocopper compounds from diazonium borofluorides. Preparation was given of several phenylcopper compounds and their stable complexes with pyridine.

The present article describes a further study of this reaction and the compounds produced under varying conditions. Use of two rather than one equivalent of copper did not increase the yield. An important factor was the purity of the diazonium compound as reflected in the yield, the amount of tar formed and the quantity of boron trifluoride evolved. Apparently the reaction proceeds smoothly in any aromatic hydrocarbon of suitable boiling point. No arylcopper compound was formed when the decomposition was carried out in ligroin, diisopropyl ether or dioxane. The decomposition temperature in all cases was definite.

(1) Naval Research Laboratory, Washington, D. C.

(2) The Bunting Chemical Co., Baltimore, Md.

(3) Bolth, Whaley and Starkey, *THIS JOURNAL*, **65**, 1456 (1943).

Such basic substances as pyridine cause destruction of diazonium borofluorides and could not be used to stabilize copper compounds as formed. Since amides form stable complexes with organocopper compounds, they were added to the reaction mixture in an attempt to increase the yield. Use of formamide resulted in a definitely increased yield, while dry, powdered acetamide seemed even better. Urea gave an insoluble complex which could not be displaced by pyridine.

Addition of propionitrile to a solution of *p*-nitrophenylcopper resulted in a white compound, unstable in air. It was thought that addition had occurred at the triple bond of the nitrile, forming the cuprous salt of an imine (I), while its complex with pyridine (II) analyzed correctly and seemed to support the idea. Attempts to obtain *p*-nitropropionophenone by hydrolysis of I and II were attended with failure, thus reinforcing a previous report that phenylcopper does not react addi-