The Formation of Polyhydroxy-dialdehydes. II.[1] *d*-Lyxo-trihydroxy-glutaric Dialdehyde and its Derivatives.

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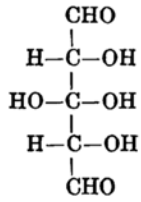
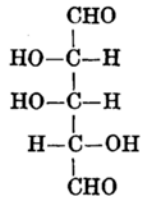
(Received April 7, 1941.)

Theoretically there should exist four dialdo-pentonoses, that is, trihydroxy-glutaric dialdehydes, and, among them, it was reported in the first paper about xylo-trihydroxy-glutaric dialdehyde (I). This communication concerns with the formation of *d*-lyxo-derivatives[2] (or *d*-arabo-derivatives) (II).



(I)

Xylo-trihydroxy-glutaric dialdehyde (described arbitrarily in chain formula)



(II)

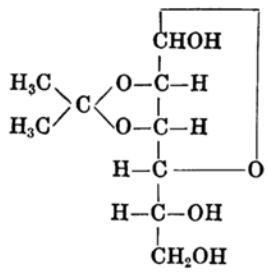
d-Lyxo-trihydroxy-glutaric dialdehyde (described arbitrarily in chain formula)

For obtaining xylo-trihydroxy-glutaric dialdehyde, 1,2-monoacetone-*d*-glucofuranose was used as the starting substance, and so monoacetone-*d*-mannose, whose constitution had not yet been ultimately determined, was analogically used for obtaining *d*-lyxo-trihydroxy-glutaric dialdehyde and was proved to be suitable for its formation. And the constitution of monoacetone-*d*-mannose was decided at the same time. This compound was first obtained as impure sirup by K. Freudenberg[3] by the partial hydrolysis of 2,3,5,6-diacetone-*d*-mannofuranose which has no substituent at 1 position. And it was identified as crystalline triacetyl-monoacetone-*d*-mannose by acetylating it with pyridine and acetic anhydride, and assumed to be 2,3-monoacetone-*d*-mannofuranose (III). It might, however, be 5,6-monoacetone-*d*-mannofuranose (IV), or, although less probable, 2,3-monoacetone-*d*-mannopyranose (V). But it was now proved to be 2,3-monoacetone-*d*-mannofuranose as supposed before. For formaldehyde was obtained by oxidizing it with lead tetracetate, and this certificated the presence of $-C(OH)-CH_2OH$ linkage. And the fact that the derivative of trihydroxy-glutaric dialdehyde was obtained by oxidizing monoacetone-*d*-mannose with lead tetraacetate was another evidence of its structure.

(1) This Bulletin, **16** (1941), 40.

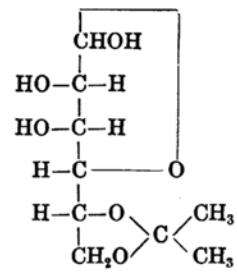
(2) The author reported briefly on these on the annual meeting of the Chemical Society of Japan in July 1940 at Sapporo.

(3) K. Freudenberg, W. Durr, and H. v. Hochstetter, *Ber.*, **61** (1928), 1740.



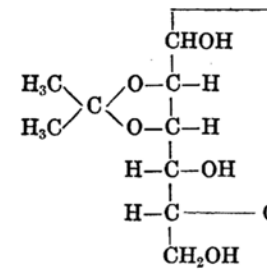
(III)

2,3-monoacetone-*d*-mannofuranose



(IV)

5,6-monoacetone-*d*-mannofuranose



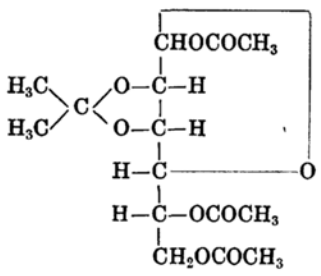
(V)

2,3-monoacetone-*d*-mannopyranose

2,3,5,6-Diacetone-*d*-mannose is dissolved in biphthalate buffer solution (*p*H 4.4), and the solution is distilled by heating in an oil bath at 140–150° for 1.5 hours, the necessary quantity of water being added during the time to keep the volume of the solution constant[3]. Then the buffer solution containing diacetone-*d*-mannose and monoacetone-*d*-mannose which is obtained by partial hydrolysis of diacetone-derivative is neutralized (phenolphthalein) and evaporated to small volume under diminished pressure, and extracted with ether for 48 hours. The ether extract is evaporated to sirup and thoroughly washed with boiling petroleum benzine to remove diacetone-mannose. The remaining sirup of monoacetone-mannose crystallizes spontaneously on standing. It is recrystallized from ether. It crystallizes in fine colourless needles. Melting point, 80.5–82° (corrected). $[\alpha]_D^{15}=+4.5°$ in water (5 minutes after solution). $[\alpha]_D^{15}=-3.7°$ (40 hours after solution). It is soluble in ether, glacial acetic acid, ethyl acetate, acetone, etc. It does not reduce Fehling's solution, or, if does, quite feebly.

Monoacetone-mannose is dissolved in glacial acetic acid, equivalent quantity of lead tetracetate is added and the mixture is warmed on a water bath at 60–65° for half an hour[4]. The evolved formaldehyde is water-distilled under diminished pressure and estimated as formaldimedon. About 70% of the theoretical quantity of formaldehyde is obtained. Thus the structure of monoacetone-*d*-mannose (III) is now established.

The crystalline 2,3-monoacetone-*d*-mannose is acetylated by pyridine and acetic anhydride in usual manner, and the same triacetyl-derivative (58.5–59°) is obtained as from sirupy one[3]. And so this derivative is ascertained to be 1,5,6-triacetyl-2,3-monoacetone-*d*-mannofuranose (VI).



(VI)

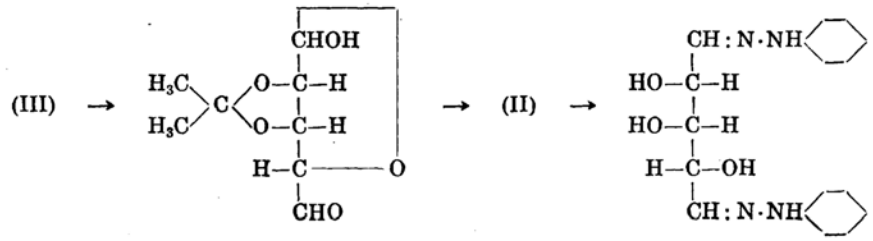
1,5,6-triacetyl-2,3-monoacetone-*d*-mannofuranose

2,3-Monoacetone-*d*-mannofuranose is dissolved in benzene and oxidized with lead tetraacetate. The mixture is filtered, filtrate evapo-

(4) Criegee, *Ann.*, **495** (1932), 211.

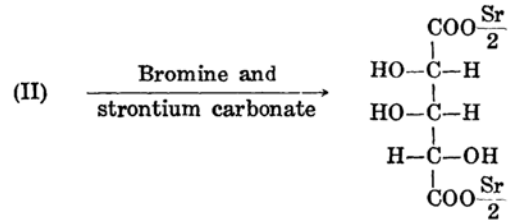
rated under diminished pressure, and the remaining sirup is hydrolized by warming with dilute sulphuric acid. Phenylhydrazine is added to the solution and *bis*-phenylhydrazone of *d*-lyxo-trihydroxy-glutaric dialdehyde soon precipitates on standing. It is recrystallized from acetone and petroleum ether, and then from alcohol. It crystallizes in fine needles. $[\alpha]_D^{15} = -72°$ in pyridine. Melting point, 168.5–169° (corrected, decomposing). *d*-Lyxo-trihydroxy-glutaric dialdehyde is obtained as sirup by decomposing its *bis*-phenylhydrazone with benzaldehyde, phenylhydrazine groups being removed as benzaldehyde-phenylhydrazone. The specific rotation of this dialdehyde is calculated by directly measuring the rotation of its water solution, which is obtained by decomposing the known quantity of its *bis*-phenylhydrazone, on the assumption that the conversion is quantitative. Thus, the specific rotatory power of *d*-lyxo-trihydroxy-glutaric dialdehyde, $[\alpha]_D^{15}$, is found to be +5°.

Bis-*p*-nitro-phenylhydrazone of *d*-lyxo-trihydroxy-glutaric dialdehyde is obtained by adding acidic aqueous solution of *p*-nitro-phenylhydrazine to the aqueous solution of the dialdehyde. Orange leaflets. Melting point, 207–207.5° (decomposing, corrected).



Bis-phenylhydrazone of *d*-lyxo-trihydroxy-glutaric dialdehyde (described arbitrarily in chain formula)

By oxidizing the aldehyde groups of *d*-lyxo-trihydroxy-glutaric dialdehyde with bromine, the corresponding carboxylic acid is obtained. Thus, strontium salt of *d*-lyxo-trihydroxy-glutaric acid is obtained by oxidizing the dialdehyde with bromine, generated acids being neutralized by excess of strontium carbonate.



Strontium *d*-lyxo-trihydroxy-glutarate

Experimental.

2,3-Monoacetone-d-*mannofuranose.* For preparing this substance, 2,3,5,6-diacetone-*d*-mannofuranose was first obtained by the slight modi-

fication of the usual method[5]. That is, 15 g. of *d*-mannose were mechanically shaked with 600 c.c. of acetone containing 10.5 c.c. of concentrated sulphuric acid. The greater part of *d*-mannose disappeared after half an hour, and all but coarce grains dissolved after an hour. The mixture was shaked for two hours, and then the colour of the solution was orange. It was neutralized with excess of anhydrous sodium carbonate after two hours standing, and then filtered from inorganic substances. Filtrate, now coloured in light lemon-yellow, was boiled on a water bath with a few grams of sodium carbonate and active charcoal. It was filtered after an hour, and the filtrate was concentrated first at ordinary pressure to a small volume and then evaporated to dryness under diminished pressure. The crystalline residue was recrystallized from benzine. Yield, 16 g. Ten grams of diacetone-*d*-mannose were dissolved in 250 c.c. of biphthalate buffer solution of *p*H 4.4, and the mixture was distilled in an oil bath at 140–150° for about two hours, adding water from time to time to maintain the initial volume. The distillate, received in an ice-cooled receiver, was made up to 250 c.c. with water. The acetone-content of the solution was measured by iodine-method[6], and it was found that 51% of acetone (calculated from the initial quantity of diacetone-*d*-mannose) had come to the distillate. The cooled buffer solution, which contained *d*-mannose and monoacetone- and diacetone-*d*-mannose, was neutralized to phenolphthalein, evaporated to about 25 c.c. under diminished pressure, and extracted with ether for 48 hours. The ether extract was concentrated to sirup. In order to remove diacetone-derivative completely from the sirup, 70 c.c. of petroleum benzine (70–90°) were added to it, and the mixture was heated on a boiling water bath, and stirred mechanically for one or two hours. Benzine extract was removed by decantation, and the remaining sirup was again extracted with benzine just like above-mentioned method. This procedure was repeated ten times and then the remaining sirup crystallized slowly on standing. It was recrystallized from ether. Fine colourless Needles. Melting point, 80.5–82°. (Found: C 48.64, H 7.49. Calc. for $C_9H_{16}O_6$: C 49.09, H 7.33%). $[\alpha]_D^{15}=+4.5$ in water (5 minutes after solution).→−1° (30 minutes)→−2° (one hour)→−3.7° (40 hours) (c=2.42).

*The oxidation of monoacetone-*d*-mannose.* Monoacetone-*d*-mannose (46.3 mg.) was dissolved in 3 c.c. of glacial acetic acid, 95.1 mg. of lead tetracetate were added to it, and the mixture was warmed for 30 minutes on a water bath at 60–65°. Then it was steam-distilled at 55° under reduced pressure (50 mm.), and 120 c.c., of distillate were obtained in an ice-cooled receiver. The alkaline solution of 0.5 g. of dimethylcyclohexandion-1,3 (dimedon) was added to the distillate, and the mixture was made slightly acidic by adding acetic acid. Then the colourless crystalline needles appeared at once. It was filtered after standing overnight in a refrigerator. Thus, 46.8 mg. of formal-dimedon was obtained. Melting point, 189–190° (corr.). This corresponds to 74% of the theoretical yield of formaldehyde from 2,3-monoacetone-*d*-mannofuranose.

(5) K. Freudenberg and A. Wolf, *Ber.*, **60** (1927), 232.
(6) K. Freudenberg, *Ber.*, **60** (1927), 241.

Bis-*phenylhydrazone of* d-*lyxo-trihydroxy-glutaric dialdehyde*. Mono-acetone-*d*-mannose (1.2 g.) was dissolved in 60 c.c. of benzene and lead tetracetate (2.4 g.) was added. The mixture was warmed on a water bath at 70° for ten minutes, cooled and then filtered. The precipitate was washed with acetone, and combined filtrate and washings were evaporated in vacuo to sirup, the temperature of the bath being kept below 30°. The sirup was dissolved in 50 c.c. of N/20-sulphuric acid, and warmed on a water bath for half an hour. It was warmed in vacuo to remove the isolated acetone, and phenylhydrazine (1.5 g.) was added to it. Light yellow precipitate soon appeared from the mixture. It was filtered, dried, and dissolved in acetone. Acetone solution was filtered, if necessary, and *bis*-phenylhydrazone was precipitated by adding petroleum ether. It was recrystallized from alcohol. Fine colourless needles. $[\alpha]_D^{15} = -72°$ in pyridine. Melting point, 168.5–169°. (Found: N 17.36. Calc. for $C_{17}H_{20}O_3N_4$: N 17.06%).

d-*Lyxo-trihydroxy-glutaric dialdehyde*. *Bis*-phenyhydrazone of *d*-lyxo-trihydroxy-glutaric dialdehyde (1 g.) was suspended in 30 c.c. of water, 1 g. of benzaldehyde added, and the mixture was mechanically stirred for an hour, heating on a water bath at 90°. After cooling, it was extracted with ether and the aqueous solution was filtered with charcoal and evaporated in vacuo to sirup. *d*-Lyxo-trihydroxy-glutaric dialdehyde thus obtained reduces Fehling's solution after several minutes at room temperature, but at once reduces it strongly when heated. The equilibrium rotatory power of *d*-lyxo-trihydroxy-glutaric dialdehyde was calculated from the rotatory power of its aqueous solution obtained by decomposition of the known quantity of its *bis*-phenylhydrazone. That is, 0.418 g. of *bis*-phenylhydrazone was suspended in 6 c.c. of water and decomposed by benzaldehyde as mentioned above. The aqueous solution was made up to 10 c.c. by adding water and its rotatory power was measured with 1 dm. tube. $\alpha_D^{15} = +0.10°$. As 0.188 g. of free dialdehyde should be obtained from 0.418 g. of its *bis*-phenylhydrazone, the specific rotatory power, $[\alpha]_D^{15}$, of *d*-lyxo-trihydroxy-glutaric dialdehyde is about +5°.

Bis-p-*nitro-phenylhydrazone of* d-*lyxo-trihydroxy-glutaric dialdehyde*. To the aqueous solution of *d*-lyxo-trihydroxy-glutaric dialdehyde, obtained as mentioned above, acidic solution of *p*-nitro-phenylhydrazine was added. Fine orange yellow precipitate soon appeared. It was filtered, and recrystallized from alcohol containing a small quantity of pyridine. Melting point, 207–207.5° (decomposing, corrected). (Found: N, 20.06. Calc. for $C_{17}H_{18}O_7N_6$ N, 20.09%).

Strontium d-*lyxo-trihydroxy-glutarate*. To the aqueous solution of *d*-lyxo-trihydroxy-glutaric dialdehyde (containing about 0.2 g. of it), 4 g. of strontium carbonate and 0.7 g. of bromine were added. The mixture was frequently shaked for several hours and then kept standing for two days. Excess bromine was removed by airing under reduced pressure, and the mixture was filtered from strontium carbonate. Then the solution was stirred on adding silver carbonate to remove bromine ion, and filtered. Sulphuretted hydrogen was passed in the filtrate to eliminate silver ion and the mixture was again filtered. The filtrate was evaporated under

reduced pressure to a small volume, and white precipitate of strontium *d*-lyxo-trihydroxy-glutarate was obtained on adding alcohol to it. (Found: Sr, 33.28. Calc. for $C_5H_6O_7Sr$: Sr, 32.98%).

1,5,6-triacetyl-2,3-monoacetone-d-*mannofuranose.* Crystalline 2,3-monoacetone-*d*-mannofuranose (0.4 g.) was dissolved in 2 c.c. of pyridine and 1 g. of acetic anhydride was added to it. The mixture was evaporated in vacuum desiccator with soda-lime and sulphuric acid, and a small quantity of dilute methyl alcohol was added to the remaining sirup, which solidified spontaneously on standing. It was recrystallized from dilute methyl alcohol. Melting point, 58.5–59°.

Summary.

(1) Monoacetone-*d*-mannose was now obtained as colourless crystalline needles and its structure was established as 2,3-monoacetone-*d*-mannofuranose (III). Melting point, 80.5–82°. $[\alpha]_D^{15}=+4.5°$ (5 minutes)$\rightarrow$ $-3.7°$ (40 hours) in water. And triacetyl-monoacetone-*d*-mannose[3] was ascertained to have the constitution (VI).

(2) *Bis*-phenylhydrazone of *d*-lyxo-trihydroxy-glutaric dialdehyde was obtained as colourless needles, starting from 2,3-monoacetone-*d*-mannofuranose. Melting point, 168.5–169°. $[\alpha]_D^{15}=-72°$ in pyridine. Equilibrium rotation of *d*-lyxo-trihydroxy-glutaric dialdehyde was measured. $[\alpha]_D^{15}=+5°$ in water. *Bis-p*-nitrophenylhydrazone of *d*-lyxo-trihydroxy-glutaric dialdehyde was obtained as orange-yellow leaflets. Melting point, 207–207.5°.

Strontium salt of *d*-lyxo-trihydroxy-glutaric acid was obtained by oxidizing the dialdehyde with bromine in presence of strontium carbonate.

In conclusion the author wishes to express his hearty thanks to Prof. B. Kubota for his kind advice for this experiment.

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