temperature range 80–90° in agreement with the observation of Utermohlen.[16] The reaction temperature was allowed to rise to 120–125° with the formation of only small quantities of low-boiling materials which may have been hydrogenolysis products. Utermohlen[16] reported some cleavage at 125° in the hydrogenation of β-alkoxypropionitriles and Wiedemann and Montgomery[17] obtained substantial quantities of hydrogenolysis products from the reduction of di-(β-cyanoethyl)-ether at 100–110°.

TABLE I

SALTS OF 1,4-(γ-AMINOPROPOXY)-PENTANE

Salts	Method of preparation	M. p., °C.	Nitrogen, %[a] Calcd.	Found
Disulfamate	B	*ca.* 65[b]		
Diacetate	A	Oil		
Dipropionate	A	Oil		
Dibutyrate	A	Oil		
Dilevulinate	A	Gum		
Dibenzoate	A	Gum		
Oxalate	A	196–198	9.09	9.65
Malonate	A	Gum		
Succinate	A	121–122	8.33	8.42
Glutarate	B	Gum		
Adipate	A	136–138	7.69	7.92
Sebacate	A	*ca.* 50[c]		
Maleate	B	129–131	8.38	8.62
Itaconate	C	Gum		
Phthalate	B	125–126	7.29	7.38
Dioxalate	D	108–110	7.04	7.26
Dimalonate	C	Gum		
Disuccinate	C	92–94	6.17	6.33
Diglutarate	C	Gum		
Diadipate	C	102–103	5.49	5.53
Dimaleate	C	80–85[c]		
Diphthalate	B	Gum		

[a] By micro Dumas. [b] White, deliquescent solid which darkened and exhibited a lower melting point after recrystallization from an absolute ethanol–ether mixture. [c] Soft solid which separated as an oil when recrystallized and could not be obtained in a satisfactorily crystalline state.

The salts of 1,4-di-(γ-aminopropoxy)-pentane were obtained as solids only when the acid was dibasic and contained an even number of carbon atoms. Although the compounds were white powders which appeared amorphous, X-ray examination[21] of the oxalate and succinate showed well defined powder diagrams indicating microcrystallinity. These salts were hygroscopic substances, easily soluble in water or absolute ethanol with the exception of the oxalate which was insoluble in ethanol. They were insoluble in ether and other non-polar solvents.

Summary

1. γ-Valerolactone has been prepared in good yield by hydrogenation of levulinic acid in the presence of Raney nickel.

2. α-Methyltetrahydrofuran has been identified as a by-product from the reduction of γ-valerolactone over copper–chromium oxide.

3. Levulinic acid has been hydrogenated directly to 1,4-pentanediol using copper–chromium oxide catalyst.

4. 1,4-Di-(β-cyanoethoxy)-pentane and 1,4-di-(γ-aminopropoxy)-pentane have been prepared and characterized.

5. A series of salts of 1,4-di-(γ-aminopropoxy)-pentane has been prepared.

[21] Kindly carried out by Mr. Harvey Dube.

AMES, IOWA RECEIVED APRIL 1, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BANTING INSTITUTE, UNIVERSITY OF TORONTO]

The Condensation of Nitromethane with D- and L-Arabinose: Preparation of L-Glucose and L-Mannose

BY JOHN C. SOWDEN AND HERMANN O. L. FISCHER

In a recent publication from this Laboratory[1] we described the condensation of nitromethane with several aldopentoses and with D-glucose, under the influence of alkali, to give sirupy mixtures containing the corresponding pairs of carbohydrate C-nitroalcohols. These crude sirups were converted, on acetylation and subsequent treatment of the sirupy acetates in benzene solution with sodium bicarbonate, to the corresponding crystalline, acetylated carbohydrate nitroölefins in yields of from 5 to 40%.

It now has been found possible to isolate and separate the crystalline nitroalcohols themselves which result from the condensation of nitromethane with D- and L-arabinose. The first products of the condensation of nitromethane with the arabinoses, as described previously,[1] were mixtures of the amorphous sodium salts of the nitroalcohols. Following removal of the sodium from these crude products by means of ion-exchange, the mixed nitroalcohols were obtained in crystalline condition and could be separated readily into the pure epimeric pairs of nitroalcohols by fractional crystallization from ethanol. The yield of mixed, crystalline carbohydrate C-nitroalcohols was about 60% while the combined yield of the pure, separated isomers was about 40%. Unlike the addition of hydrocyanic acid to the arabinoses, which gives mainly the mannonic acid lactones, the addition of nitromethane seems to give the nitroalcohols with the glucose and mannose configurations in nearly equal amounts.

The isomeric carbohydrate C-nitroalcohols re-

---

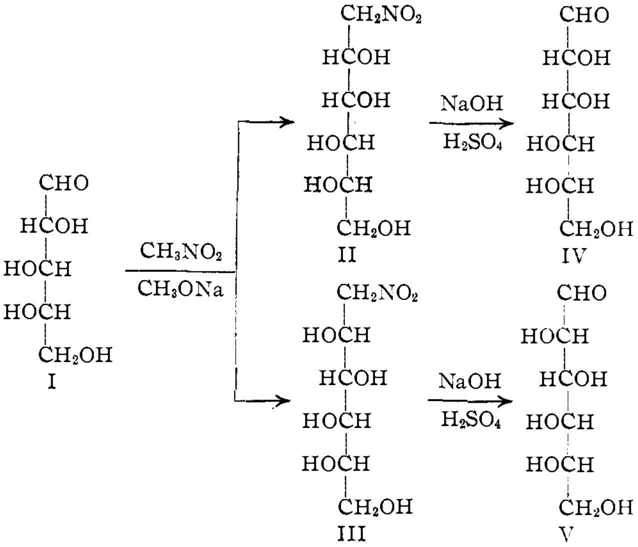
[1] Sowden and Fischer, THIS JOURNAL, **69**, 1048 (1947).

sulting from L-arabinose, I, and nitromethane: 1-nitro-1-desoxy-L-mannitol, II, and 1-nitro-1-desoxy-L-glucitol, III, are of particular interest because of their ready conversion to the corresponding sugars: L-mannose, IV, and L-glucose, V, by means of the Nef reaction.[1,2,3]

L-Mannose is fairly accessible *via* the cyanohydrin synthesis from L-arabinose.[4,5] However, the present synthesis *via* nitromethane from L-arabinose is preferable to the cyanohydrin method in that the necessary operations are simpler, the time required for the preparation is much shorter and the yield of L-mannose is of the same order of magnitude. Due to the ease of separating L-mannose from other carbohydrates as the insoluble phenylhydrazone, no separation of the isomeric nitroalcohols from L-arabinose is necessary for the preparation of L-mannose and thus the mixed, amorphous sodium nitroalcohols can be used directly in the Nef reaction. In this way, L-mannose phenylhydrazone, from which L-mannose is easily obtainable, can be prepared from L-arabinose in 20 to 25% yield in about one day.

L-Glucose has aroused considerable interest in the past because of its possible occurrence in nature.[6,7,8] Moreover, its relationship to D-glucose has prompted some experiments to ascertain any possible significance it may have in biological processes.[9,10] While these latter experiments have thus far indicated a negative biological role for L-glucose, no doubt such experiments have been largely handicapped with regard to scope by the difficult accessibility of the sugar itself. The preparation of L-glucose by the cyanohydrin synthesis[9] is long and tedious and the final yield is small. In contrast, by the present synthesis, using nitromethane and L-arabinose, it is possible to prepare comparatively large amounts of pure L-glucose with a reasonable outlay of material and time.

The preparation of D-glucose and D-mannose from D-arabinose by the nitromethane synthesis possesses, of course, similar advantages over their preparation by the cyanohydrin method. This should prove of value in the synthesis, for biological studies, of D-glucose and D-mannose containing isotopic C^{13} or C^{14} in the aldehydic carbon.



Experimental

D-Arabinose and Nitromethane

A suspension of 50 g. of D-arabinose in 100 cc. of methanol and 180 cc. of nitromethane was shaken with a solution of 10.5 g. of sodium in 350 cc. of methanol. The mixture became noticeably cooler, the sugar dissolved rapidly and the amorphous sodium salts of the sugar nitroalcohols began to precipitate after a few minutes. After shaking for eighteen hours, the sodium salts were collected by filtration and washed with cold methanol, ether and petroleum ether. There resulted 83 g. of amorphous, hygroscopic powder containing 9.1% of sodium and 5.7% of nitrogen (theory for the pure sodium nitroalcohols: Na, 9.9; N, 6.1).

The sodium salts were dissolved in 400 cc. of cold water and the solution immediately passed through a column containing about 1 kg. of moist Amberlite-IR-100-AG. Concentration of the effluent at reduced pressure followed by concentration with absolute ethanol yielded a crystalline residue. Fractional crystallization of this residue from absolute ethanol yielded the following fractions: 28.2 g., m. p. 124–129°; 8.3 g., m. p. 105–107°; 12.1 g., m. p. 95–135°.

Recrystallization of the first fraction from absolute ethanol yielded 18.2 g. of pure 1-nitro-1-desoxy-D-mannitol,[3a] m. p. 133–134° and $[\alpha]^{26}\text{D}$ −6.8° in water, *c* 5.7.

Recrystallization of the second fraction from absolute ethanol yielded 7.6 g. of pure 1-nitro-1-desoxysorbitol, m. p. 107–108° and $[\alpha]^{25}\text{D}$ −9.7° in water, *c* 6.6.

Anal. Calcd. for $C_6H_{13}O_7N$ (211.2): C, 34.1; H, 6.20; N, 6.63. Found: C, 34.2; H, 6.33; N, 6.64.

The mother liquors from the above recrystallizations were concentrated to dryness and the residue combined with the third crystalline fraction above. The crude, mixed nitroalcohols thus obtained were converted by acetylation followed by treatment with sodium bicarbonate, as previously described,[1] to the corresponding acetylated nitroölefin. There was obtained 23.3 g. of D-*arabo*-tetraacetoxy-1-nitrohexene-1, m. p. 115–116°.

The yield of the crude, crystalline nitroalcohols was 69%, while the combined yield of pure products, including the acetylated nitroölefin, was 56%.

L-Arabinose and Nitromethane

When 25 g. of L-arabinose was treated with nitromethane and alkali as described above for D-arabinose, the two nitroalcohols again crystallized readily and were separated by fractional crystallization from absolute ethanol. The following products were obtained.

---

(2) Nef, *Ann.*, **280**, 263 (1894).

(3) (a) Sowden and Fischer, THIS JOURNAL, **66**, 1312 (1944); (b) **67**, 1713 (1945); (c) **68**, 1511 (1946).

(4) Fischer, *Ber.*, **23**, 370 (1890); *ibid.*, **24**, 2683 (1891).

(5) van Ekenstein and Blanksma, *Chem. Weekblad*, **11**, 902 (1914), *cf. Chem. Zentr.*, **85**, II, 1265 (1914).

(6) Power and Tutin, *Pub. Wellcome Chem. Research Lab.*, **57**, 1 (1905).

(7) Saha and Choudhury, *J. Chem. Soc.*, **121**, 1044 (1922).

(8) Beek, THIS JOURNAL, **63**, 1483 (1941); *J. Research Natl. Bur. Standards*, **27**, 507 (1941).

(9) Fischer, *Ber.*, **23**, 2611 (1890).

(10) Rudney, *Science*, **92**, 112 (1940).

(1) **1-Nitro-1-desoxy-L-mannitol.**—Yield was 6.5 g. (18.5%). Recrystallized from absolute ethanol, the pure product melted at 133–134° and showed $[\alpha]^{25}D$ +7.0° in water, *c* 6.2.

Anal. Calcd. for $C_6H_{13}O_7N$ (211.2): C, 34.1; H, 6.20; N, 6.63. Found: C, 34.4; H, 6.22; N, 6.41.

(2) **1-Nitro-1-desoxy-L-glucitol.**—Yield was 6.6 g. (18.8%). Recrystallized from absolute ethanol, the pure product melted at 107–108° and showed $[\alpha]^{25}D$ +9.5° in water, *c* 6.7.

Anal. Calcd. for $C_6H_{13}O_7N$ (211.2): C, 34.1; H, 6.20; N, 6.63. Found: C, 34.3; H, 6.19; N, 6.25.

(3) **L-*arabo*-Tetraacetoxy-1-nitrohexene-1.**—After separation of the nitroalcohols described above, the residual crude product was converted by acetylation and subsequent treatment with sodium bicarbonate, as previously described,[1] to the corresponding acetylated nitroölefin. There resulted 3.9 g. (6.5%) of L-*arabo*-tetraacetoxy-1-nitrohexene-1. After recrystallization from absolute ethanol, the product melted at 115–116° and showed $[\alpha]^{28}D$ −31.8° in absolute chloroform, *c* 5.

Anal. Calcd. for $C_{14}H_{19}O_{10}N$ (361.3): C, 46.5; H, 5.30; N, 3.88. Found: C, 46.5; H, 5.39; N, 3.86.

When considerably larger amounts of L-arabinose were condensed with nitromethane, the two nitroalcohols were obtained in percentage yields almost identical with those quoted above. In working with larger amounts it was found advantageous to extract the crude crystalline nitroalcohols first obtained away from the small amount of unchanged L-arabinose present, with dry acetone in a Soxhlet extractor. On cooling, the acetone extract then deposits relatively pure nitrodesoxy-L-mannitol. After filtration, the nitrodesoxy-L-glucitol is separated by concentrating and cooling the filtrate. A single recrystallization of each of the two isomers from absolute ethanol then gives the pure products.

1-Nitro-1-desoxysorbitol Pentaacetate.—Acetylation of 0.5 g. of 1-nitro-1-desoxysorbitol with acetic anhydride containing a trace of sulfuric acid[1] yielded 0.7 g. (70%) of the crystalline pentaacetate. After recrystallization from absolute ethanol, the product melted at 90–91° and showed $[\alpha]^{25}D$ +25.5° in absolute chloroform, *c* 5.

Anal. Calcd. for $C_{16}H_{23}O_{12}N$ (421.3): C, 45.6; H, 5.50; N, 3.32. Found: C, 45.4; H, 5.68; N, 3.53.

When the pentaacetate was refluxed in benzene solution with sodium bicarbonate, as previously described,[1] there was obtained, in 85% yield, D-*arabo*-tetraacetoxy-1-nitrohexene-1, m. p. 114–115° and $[\alpha]^{28}D$ +33.4° in absolute chloroform, *c* 2.4.

1-Amino-1-desoxysorbitol.—One gram of 1-nitro-1-desoxysorbitol in 40 cc. of water was shaken at ordinary temperature and pressure with hydrogen in the presence of 1 g. of Raney nickel. The reduction was soon complete with the absorption of 3 moles of hydrogen. The solution was filtered onto a slight excess of oxalic acid and then concentrated to dryness at reduced pressure. Recrystallization of the residue from a small volume of water by the addition of ethanol yielded 0.6 g. of 1-amino-1-desoxy sorbitol oxalate, m. p. 175–176° (dec.) and $[\alpha]^{25}D$ −14.6° in water, *c* 3.7.

The recorded constants for this salt, ("D-glucamine" oxalate),[11] are m. p. 180–182° and $[\alpha]_D$ −15.2° in water.

Anal. Calcd. for $C_7H_{16}O_7N$ (226.2): N, 6.19. Found: N, 6.24.

L-Mannose.—A suspension of 30 g. of L-arabinose in 110 cc. of nitromethane and 150 cc. of methanol was shaken for eighteen hours at room temperature with a solution of 6.9 g. of sodium in 200 cc. of methanol. The resulting amorphous sodium salts of the nitroalcohols, after drying in high vacuum over phosphorus pentoxide, weighed 52 g. and contained 9.4% of sodium. The sodium salts were dissolved in 200 cc. of cold water and the resulting solution was added dropwise at room temperature to a stirred solution containing 40 cc. of sulfuric acid and 50 cc. of water. The resulting solution was neutralized to congo red with solid sodium carbonate, treated with decolorizing carbon and filtered. The pale amber solution was then made just alkaline to litmus with sodium bicarbonate solution and again acid to litmus with a few drops of acetic acid. A solution of 20 cc. of phenylhydrazine in 40 cc. of 25% acetic acid was then added. The precipitation of L-mannose phenylhydrazone began after a few minutes. After standing overnight, the hydrazone was collected and washed successively with water, 60% ethanol, absolute ethanol and acetone. The colorless product weighed 12.2 g. (22.6%) and melted at 186–188°.

Four grams of the hydrazone was refluxed for two and one-half hours with a solution containing 50 cc. of water, 10 cc. of ethanol, 5 cc. of benzaldehyde and 0.5 g. of benzoic acid. The cooled solution was decanted from benzaldehyde phenylhydrazone, extracted three times with chloroform, decolorized with carbon and concentrated at reduced pressure. The resulting sirup crystallized readily. Filtration with absolute ethanol then yielded 2.2 g. (82.4%) of L-mannose, m. p. 128–132° and $[\alpha]^{25}D$ −14.5° (equil.) in water, *c* 3.4.

The above procedure can be simplified by adding the dry amorphous sodium nitroalcohols directly to the aqueous sulfuric acid. Thus, when the sodium salts obtained from 5 g. of D-arabinose and nitromethane were added, with stirring, to 25 cc. of 40% (by weight) sulfuric acid, there was obtained, after neutralization and addition of phenylhydrazine, 1.9 g. (21%) of D-mannose phenylhydrazone.

L-Glucose.—Forty-five grams of 1-nitro-1-desoxy-L-glucitol, m. p. 104–106°, was dissolved in 125 cc. of 2 *N* sodium hydroxide and the solution added dropwise to a stirred solution containing 63 cc. of sulfuric acid and 73 cc. of water, at room temperature. The resulting solution was neutralized to congo red with warm barium hydroxide solution. The barium sulfate was removed by centrifuging and the remaining sulfate ion was then precipitated from the solution by the addition of a slight excess of barium acetate solution. The finely divided barium sulfate was removed by filtration through Super-Cel and the resulting solution was then passed through a column containing about 1 kg. of moist Amberlite-IR-100-AG, to remove sodium and barium ions. The effluent was concentrated at reduced pressure and the resulting sirup transferred to a crystallizing dish with the aid of a little ethanol. Slow evaporation of the ethanol in a desiccator over sulfuric acid gave a crystalline mass. Adhering sirup was removed from the product by grinding with cold 95% ethanol and filtering. There was obtained 20.6 g. of L-glucose, m. p. 146–147° and $[\alpha]^{22}D$ −52.6° (equil.) in water, *c* 2.6. From the alcoholic mother liquor was obtained 1.5 g. of L-glucose of comparable purity. Yield was 22.1 g. (58%).

The above constants for L-glucose compare favorably with the corresponding constants for D-glucose of highest purity.

Acknowledgment.—The authors are pleased to acknowledge the support of the Corn Products Refining Company during the course of this research.

Summary

The epimeric carbohydrate C-nitroalcohols resulting from the condensation of D- and L-arabinose with nitromethane under the influence of alkali have been isolated and separated into their pure, crystalline forms.

Treatment of the sodium salts of these nitroalcohols with sulfuric acid yields the corresponding aldohexoses: D- and L-glucose, D- and L-mannose.

The comparatively rare sugars, L-glucose and L-mannose, are made more easily available by this new method of synthesis.

TORONTO, CANADA

RECEIVED MARCH 24, 1947

---

[11] Maquenne and Roux, *Compt. rend.*, **132**, 980 (1901).