After keeping the reaction mixture at 70° for three additional hours, the product was isolated as described for the preparation of compound III; yield 46.5 g. of gray-brown solid or 69.4%. The compound was purified by crystallization from a mixture of 500 cc. of dioxane and 200 cc. of water; yield 31 g. of small, bright yellow needles; m. p. 261° (dec.).

Anal. Calcd. for $C_{13}H_{13}N_5O_4S$: C, 46.56; H, 3.91; N, 20.89; S, 9.56. Found: C, 46.78; H, 3.93; N, 20.74; S, 9.41.

Deacetylation was accomplished in a mixture of ethanol and hydrochloric acid by essentially the same procedure given for the deacetylation of 2-(N^4-acetylsulfanilamido)-3-carbomethoxypyrazine. The yield from 28.7 g. of 3-(N^4-acetylsulfanilamido)-pyrazinamide was 20.0 g. or 79.6%. The compound was purified by crystallization from ethanol. Large, straw-yellow crystals which exhibit a blue-yellow fluorescence in solution were produced; m. p. 203° (cor.).

Anal. Calcd. for $C_{11}H_{11}N_5O_3S$: C, 45.04; H, 3.78; N, 23.88; S, 10.93. Found: C, 44.77; H, 3.88; N, 23.84; S, 10.78.

3-Sulfanilamidopyrazinoic Acid (VIII).—Two grams of 3-sulfanilamidopyrazinamide (VII) was dissolved in 14 cc. of *N* sodium hydroxide and warmed on the steam-bath for three and one-half hours. After dilution of the clear brown solution with 50 cc. of water, the *p*H was adjusted to about 2 by the addition of hydrochloric acid. The yellow solid was collected and dried; yield 1.9 g. or 95%. The compound was purified by crystallization from 50 parts of water; large, straw-yellow plates; m. p. 178–180° (dec.).

Anal. Calcd. for $C_{11}H_{10}N_4O_4S$: C, 44.89; H, 3.42; N, 19.04; S, 10.89. Found: C, 44.74; H, 3.50; N, 19.95; S, 11.02.

3-Sulfanilamidopyrazinoic acid (VIII) was decarboxylated to 2-sulfanilamidopyrazine in an 89% yield by boiling a solution of the acid in 10 parts of Carbitol acetate. The product melted at 257–259° with decomposition and showed no depression on mixed melting with an authentic sample of 2-sulfanilamidopyrazine.

Acknowledgment.—We appreciate the assistance and encouragement Dr. Charles E. Bills has given us in this work.

Summary

1. The synthesis of four new pyrazine derivatives, 2-amino-3-carbomethoxypyrazine, 3-aminopyrazinamide, 3-acetamidopyrazinamide and 3-aminopyrazinenitrile, is described.

2. The synthesis of three new pyrazine sulfonamides, 2-sulfanilamido-3-carbomethoxypyrazine, 3-sulfanilamidopyrazinamide and 3-sulfanilamidopyrazinoic acid, is described.

3. Two of the aminopyrazines, 3-aminopyrazinoic acid and 3-aminopyrazinenitrile, contrary to expectation, do not condense with acetylsulfanilyl chloride.

4. 2,3-Diaminopyrazine is not obtained when 3-aminopyrazinamide is subjected to the Hofmann degradation.

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

Carbohydrate C-Nitroalcohols: 6-Nitro-6-desoxy-D-sorbitol. A Convenient Source of L-Gulose

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

In a previous publication[1] from this Laboratory, we described the preparation of 1-nitro-1-desoxy-D-mannitol. This substance, a carbohydrate C-nitroalcohol, was obtained by treating an acetylated sugar cyanohydrin, in methanol solution, with alkali in the presence of nitromethane. Under these conditions, deacetylation and degradation of the cyanohydrin occurs and the newly-formed aldose sugar reacted with the nitroparaffin to yield the carbohydrate C-nitroalcohol.

The condensation of nitromethane with certain substituted aldose sugars containing the hemiacetal ring structure, to produce carbohydrate C-nitroalcohols, has now been accomplished. Thus, the direct condensation of nitromethane with 2,4-benzylidene L-xylopyranose is described in the present communication.

When the substituted xylose I, prepared from 2,4-benzylidene sorbitol, by cleavage with lead tetraacetate, according to the directions of v. Vargha[2] was treated in methanol solution, at room temperature, with sodium methoxide in the presence of nitromethane, a smooth condensation reaction occurred, yielding 2,4-benzylidene 6-nitro-6-desoxy-D-sorbitol II. The substituted nitrodesoxysorbitol apparently was obtained as a pure individual substance and the corresponding isomer possessing the L-iditol configuration, whose concurrent formation may be expected, was not isolated. Hydrolysis of the benzylidene residue of II with dilute sulfuric acid yielded the crystalline 6-nitro-6-desoxy-D-sorbitol III.

The configuration of III was proved by converting it to L-gulose. When a solution of the sodium salt of 6-nitro-6-desoxy-D-sorbitol was added dropwise to an excess of moderately concentrated sulfuric acid, it was possible to isolate L-gulose IV, as its crystalline benzylphenylhydrazone, from the resulting solution in a yield of about 50%. This elimination of the aliphatic nitro group to produce an aldehyde was discovered by Nef[3] for the simple primary nitroparaffins and was first applied for the production of an aldose sugar by the authors.[1]

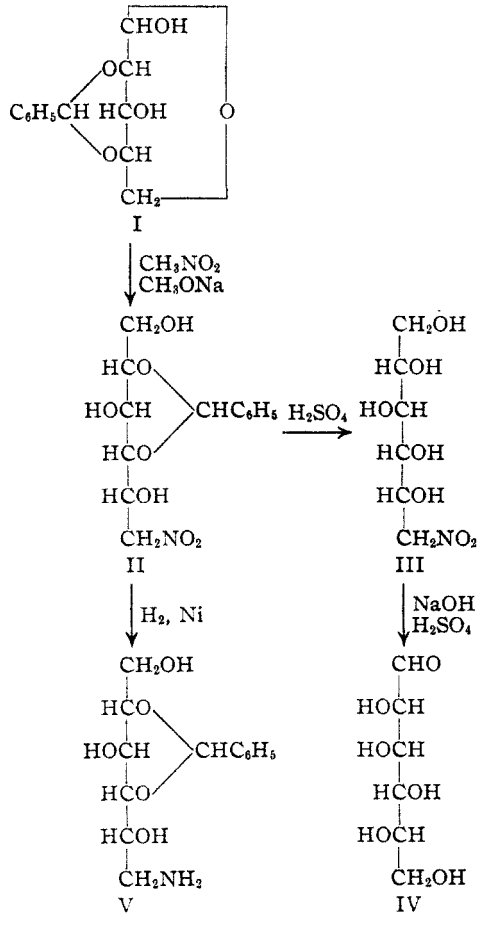
L-Gulose was prepared originally by Emil Fischer and O. Piloty[4] by the following series of

(1) Sowden and Fischer, THIS JOURNAL, **66**, 1312 (1944).

(2) v. Vargha, *Ber.*, **68**, 18, 1377 (1935).

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

(4) E. Fischer and Piloty, *Ber.*, **24**, 521 (1891).



successive reductions with sodium amalgam: D-saccharic acid → D-glucuronic acid → L-gulonolactone → L-gulose. The yield of L-gulonolactone from D-saccharic acid amounted to 15%. The sodium amalgam reduction of D-glucuronic acid to L-gulonolactone, in a yield of 25%, had previously been accomplished by Thierfelder.[5] No new methods of obtaining L-gulose have been recorded up to the present time and thus the preparation of this hexose, even in small amounts, has remained a laborious and costly operation. In the synthesis described herein, the benzylidene L-xylose of v. Vargha[2] may be obtained readily, in good yield, from commercially-available D-sorbitol. The subsequent operations producing L-gulose benzylphenylhydrazone, from which the sirupy free hexose is obtainable readily, can be carried out in a relatively short period of time in a yield of about 25%. Thus, at least for the preparation of laboratory amounts of L-gulose, the present synthesis has obvious advantages. The use of the costly benzylphenylhydrazine, however, could not be recommended for large-scale preparations.

Free L-gulose was obtained as a colorless sirup from the hydrazone, by cleavage with benzaldehyde, and showed $[\alpha]^{23}D$ +20.0°. For D-gulose obtained in a similar manner, from its phenylhydrazone, Blanksma and v. Ekenstein[6] recorded $[\alpha]D$ −20.4°. The L-gulose was characterized further by oxidation with bromine water to the known[4,5] L-gulonolactone, $[\alpha]^{23}D$ +55°. Treatment of the sirupy L-gulose with an alcoholic solution of calcium chloride yielded a crystalline coordination compound with the composition α-L-gulose–$CaCl_2$–H_2O corresponding to the enantiomorphic compound described for D-gulose by Isbell.[7] The mutarotation values obtained from a 5% aqueous solution of the L-gulose–calcium chloride compound were approximately equal in magnitude and were opposite in sign to those recorded by Isbell for the D-gulose–calcium chloride compound.

The benzylidene 6-nitro-6-desoxy-D-sorbitol was reduced to the corresponding amine V, without cleavage or reduction of the benzylidene residue, by hydrogen in the presence of Raney nickel.

Experimental

2,4-Benzylidene-6-nitro-6-desoxy-D-sorbitol.—2,4-Benzylidene L-xylose was prepared from 2,4-benzylidene D-sorbitol according to the directions of v. Vargha.[2] For the condensation with nitromethane, it is not necessary to isolate the substituted L-xylose in crystalline form. The sirup obtained by concentrating the benzylidene sorbitol–lead tetraacetate cleavage mixture was dissolved in ethyl acetate and the solution was washed with water, then with sodium bicarbonate solution to remove the last traces of acetic acid and finally, again, with water. The resulting solution was dried with anhydrous sodium sulfate and was concentrated at reduced pressure. The last traces of ethyl acetate were removed from the resulting sirup by concentration at reduced pressure with absolute ethanol and, finally, with absolute methanol.

A solution of 53.7 g. of the sirupy benzylidene L-xylose, dissolved in 1 liter of absolute methanol and 160 cc. of nitromethane, was treated with a solution of 10 g. of sodium in 800 cc. of absolute methanol. After twenty-two hours at room temperature, the reaction mixture was acidified by the addition of a slight excess of glacial acetic acid and then was concentrated at reduced pressure. Crystallization of the product began during this concentration. Methanol and unchanged nitromethane were removed by the addition of water, followed by further concentration at reduced pressure. The resulting moist crystalline mass was filtered with the aid of ice-water and, finally, washed with small portions of ice-water. There was obtained 34.0 g. (50.4%) of crude 2,4-benzylidene-6-nitro-6-desoxy-D-sorbitol, m. p. 178–181°. No appreciable difference in yield was observed when *crystalline* 2,4-benzylidene L-xylopyranose was employed for the reaction.

For analysis, the substituted C-nitroalcohol was recrystallized from water and then from anhydrous ethyl acetate. In the recrystallization from water, prolonged heating of the aqueous solution must be avoided since the product is somewhat unstable under such conditions. The purified substance melted at 192–194° and showed $[\alpha]^{25}D$ +2.5° in absolute ethanol, *c* 3.5 and $[\alpha]^{22}D$ −4.4° in water, *c* 1.

Further recrystallizations did not appreciably alter these values and the substance was therefore assumed to consist of a single isomer.

Anal. Calcd. for $C_{13}H_{17}O_7N$ (299.3): C, 52.2; H, 5.73; N, 4.68. Found: C, 52.3; H, 5.84; N, 4.65.

(5) Thierfelder, *Z. physiol. Chem.*, **15**, 71 (1891).

(6) Blanksma and v. Ekenstein, *Chem. Weekblad*, **5**, 777 (1908); *Chem. Zentr.*, **79**, II, 1583 (1908).

(7) Isbell, *Bur. Standards J. Research*, **5**, 741 (1930).

6-Nitro-6-desoxy-D-sorbitol.—Ten grams of 2,4-benzylidene-6-nitro-6-desoxy-D-sorbitol was heated at 75–80° with 100 cc. of 0.1 *N* sulfuric acid for one hour. After cooling, the solution was extracted three times with ether to remove benzaldehyde and then was neutralized by stirring with an excess of barium carbonate. The precipitated inorganic salts were removed by centrifuging and filtering through a precoated filter and the resulting clear solution was concentrated at reduced pressure. The residual sirup crystallized spontaneously after several days. Recrystallization from ethyl acetate containing a little methanol yielded 5.56 g. (79%) of 6-nitro-6-desoxy-D-sorbitol, m. p. 78–80°.

For analysis, the C-nitroalcohol was recrystallized several times from dry ethyl acetate and then several times from dry butanol. Two types of crystals were obtained from successive recrystallizations from either solvent: soft needles, m. p. 81–83°, and hard, compact prisms, m. p. 89–91°. The two forms were interchangeable by appropriate conditions of concentration, rate of cooling or inoculation of their solutions and both showed $[\alpha]^{24}D$ −7.9° in water, *c* 5.

Anal. Calcd. for $C_6H_{13}O_7N$ (211.2): C, 34.1; H, 6.20; N, 6.63. Found: C, 34.5, 34.3; H, 6.35, 6.47; N, 6.70, 6.63.

L-Gulose Benzylphenylhydrazone.—For the preparation of L-gulose it is not necessary to isolate the 6-nitro-6-desoxy-D-sorbitol in crystalline form. The sirup obtained from the hydrolysis, as described above, of 13.6 g. of benzylidene nitrodesoxysorbitol was dissolved in 55 cc. of 1 *N* sodium hydroxide. This solution was added dropwise to 20 cc. of a vigorously stirred, 60% by weight, sulfuric acid solution. After dilution with water, the resulting solution was neutralized with excess barium carbonate. Acetic acid (3 or 4 cc.) was then added and the precipitated inorganic salts removed by centrifuging and filtering. The sirup resulting from the concentration of the solution at reduced pressure was dissolved in 100 cc. of 75% ethanol, filtered from a slight amorphous precipitate, and treated with about 10 g. of benzylphenylhydrazine.[8] The mixture was allowed to evaporate in an open dish, with occasional additions of small amounts of methanol, until crystallization was complete. The resulting crystals were freed from sirup by washing at the centrifuge with water and ether. There was obtained 8.5 g. (52%) of crude L-gulose benzylphenylhydrazone, m. p. 124–128°. Recrystallization from a mixture of 110 cc. of chloroform and 15 cc. of methanol yielded the pure, colorless hydrazone, m. p. 130–131°, $[\alpha]^{23}D$ +29° in absolute methanol, *c* 2.8.

For D-gulose benzylphenylhydrazone, v. Ekenstein and Lobry de Bruyn,[9] recorded m. p. 124°, and $[\alpha]D$ −24°, in methanol.

Anal. Calcd. for $C_{19}H_{24}O_5N_2$ (360.4): C, 63.3; H, 6.71; N, 7.77. Found: C, 63.2; H, 6.98; N, 7.97.

The conversion of the nitroalcohol to its sodium salt for the above reaction was demonstrated to have no apparent effect on the configuration of the adjacent secondary alcohol group. Thus, 2,4-benzylidene-6-nitro-6-desoxysorbitol was recovered in good yield and purity from its solution in aqueous sodium hydroxide by the addition of a slight excess of acetic acid.

L-Gulose.—An amount of 6.8 g. of L-gulose benzylphenylhydrazone was refluxed for three hours with 100 cc. of water and 20 cc. of ethanol containing 7.5 cc. of benzaldehyde and 0.8 g. of benzoic acid. After cooling, the solution was decanted from the separated benzaldehyde benzylphenylhydrazone and extracted several times with ether to remove benzaldehyde and benzoic acid. After decolorizing, the solution was concentrated at reduced pressure to a colorless sirup. When this sirup was made up to 25.0 cc. with water, the solution showed $\alpha^{23}D$ +2.72°, in a 1-dc. tube. This corresponds to $[\alpha]^{23}D$ +20° for the sirupy L-gulose.

α-L-Gulose–$CaCl_2$–H_2O.—One gram of L-gulose sirup was treated with 1.7 g. of pure calcium chloride dihydrate dissolved in 10 cc. of 95% ethanol. The solution was warmed gently, filtered from a slight amorphous precipitate, and then was concentrated at reduced pressure to a sirup. After several days, crystallization began and was completed by the addition of ethanol. There was obtained 1.13 g. (66%) of the crystalline coördination compound. For analysis, the substance was dissolved in a small amount of water, the solution was filtered, and concentrated to a sirup. Seeding and addition of ethanol then yielded the recrystallized product, m. p. 200–203° with decomposition. A 5% aqueous solution of the product showed the following specific rotations, at 24°: 6 min., −18.7°; 10 min., −10.2°; 15 min., −3.5°; 20 min., +1.3°; 30 min., +5.7°; 60 min., +10.2°; 240 min., + 11.2° (constant).

For a 5.15% aqueous solution of α-D-gulose–$CaCl_2$–H_2O at 20°, Isbell[7] recorded a similar mutarotation, opposite in direction, to a constant value of $[\alpha]^{20}D$ −11.1°.

Anal. Calcd. for $C_6H_{12}O_6 \cdot CaCl_2 \cdot H_2O$ (309.1): C, 23.3; H, 4.57; Ca, 12.96; Cl, 22.9. Found: C, 23.2; H, 4.50; Ca, 12.90; Cl, 22.8.

Treatment of the calcium chloride addition compound with silver oxalate as described by Isbell[7] for the D-gulose enantiomorph, yielded L-gulose as a colorless sirup.

L-Gulonolactone.—A solution of 1.4 g. of sirupy L-gulose in 20 cc. of water was shaken with 1 cc. of bromine at room temperature for twenty hours. From the resulting solution, bromine was removed by aeration, hydrobromic acid then was removed by treatment with silver carbonate and filtration and, finally, dissolved silver ions were removed by precipitation with hydrogen sulfide. The filtered, colorless solution was concentrated at reduced pressure to a sirup. On seeding this sirup with authentic L-gulonolactone,[10] rapid crystallization ensued. Recrystallization from 60% ethanol yielded 0.56 g. of the known[4,5] L-gulonolactone, m. p. 186–188° (cor.) and $[\alpha]^{23}D$ +55.4, in water, *c* 8.9.

2,4-Benzylidene-6-amino-6-desoxy-D-sorbitol Oxalate.—A suspension of 1.5 g. of 2,4-benzylidene-6-nitro-6-desoxysorbitol in 75 cc. of water was shaken, at ordinary temperature and pressure, with hydrogen in the presence of 1 g. of Raney nickel. The reduction was complete in forty minutes with the absorption of 3 moles of hydrogen. The resulting soapy solution was freed from the catalyst by filtration and, after the addition of 0.35 g. of oxalic acid dihydrate, was concentrated to dryness at reduced pressure. Recrystallization of the residue from water by the addition of absolute ethanol yielded 1.3 g. (82.5%) of 2,4-benzylidene-6-amino-6-desoxy-D-sorbitol oxalate. After further recrystallization from aqueous alcohol, the pure amine oxalate showed m. p. 235–236°, with decomposition, and $[\alpha]D$ 0° in water, *c* 1.

Anal. Calcd. for $C_{14}H_{20}O_7N$ (314.3): C, 53.5; H, 6.41; N, 4.46; Found: C, 53.5; H, 6.10; N, 4.48.

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Summary

Nitromethane has been condensed with benzylidene L-xylopyranose to produce benzylidene nitrodesoxy-D-sorbitol. Nitrodesoxy-D-sorbitol has been converted to L-gulose by treatment of its sodium salt with sulfuric acid. Further work is in progress in this Laboratory on the reaction of nitroparaffins with sugar derivatives.

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(8) Prepared from phenylhydrazine and benzyl chloride, *cf.* H. Meyer, "Lehrbuch der organish-chemischen Methodik," Erster Band, Julius Springer, Berlin, 1922, p. 794.

(9) v. Ekenstein and Lobry de Bruyn, *Rec. trav. chim.*, **19**, 178 (1900).

(10) From a sample of "*d*"-gulonolactone prepared by I. W. Fay; *cf.* E. Fischer and I. W. Fay, *Ber.*, **28**, 1975 (1895).