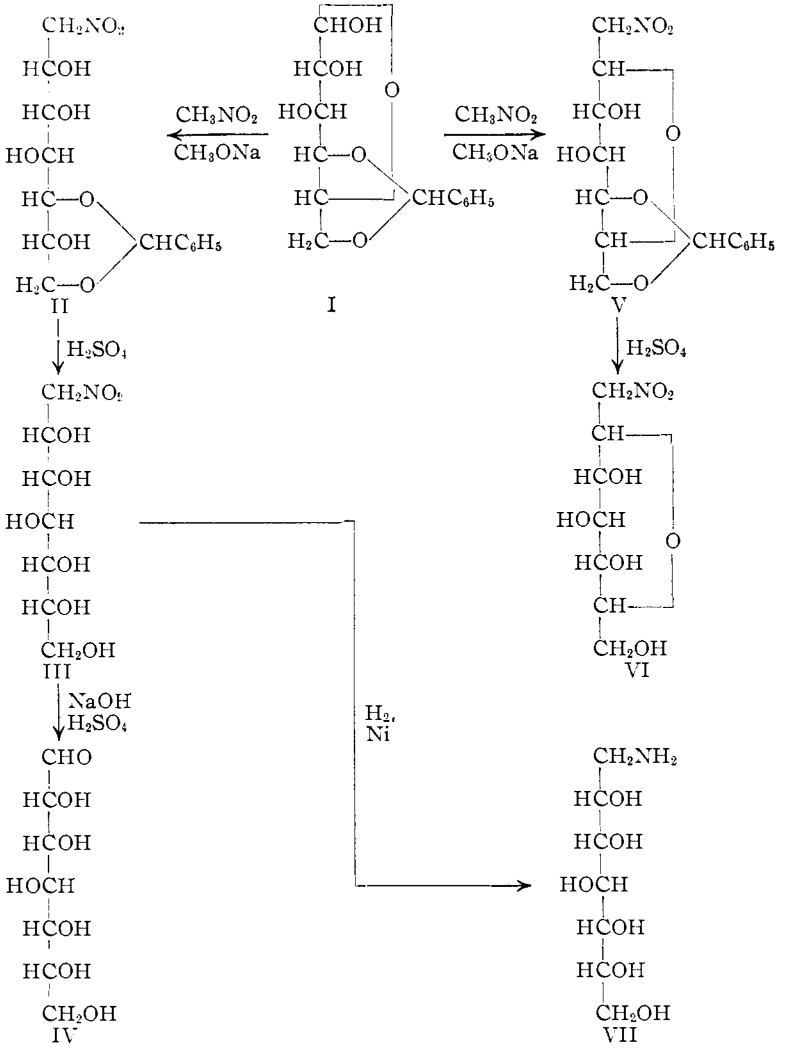
[Contribution from the Department of Chemistry, Banting Institute, University of Toronto]

Carbohydrate C-Nitroalcohols: 1-Nitro-1-desoxy-D-α-glucoheptitol and a 2,6-Anhydro-1-nitro-1-desoxyheptitol

By John C. Sowden and Hermann O. L. Fischer

In the continuation of our study of the reaction between nitroparaffins and carbohydrate derivatives under the influence of alkali[1] we wish to report concerning the products of the reaction of nitromethane and 4,6-benzylidene glucose, I.



When a solution of 4,6-benzylidene glucose[2] in methanol was treated with nitromethane and sodium methoxide at room temperature, the change in optical rotation of the solution, rapid at first, became quite slow after two hours. Acidification of the reaction mixture with a slight excess of acetic acid after eight hours at room temperature then resulted in the isolation of 5,7-benzylidene-1-nitro-1-desoxy-D-α-glucoheptitol, II, in a yield of about 20%. As in the instances previously recorded,[1] the substituted carbohydrate C-nitroalcohol was apparently obtained as a pure isomer and the epimeric D-β-glucoheptitol derivative was not isolated. Hydrolysis of the benzylidene residue of II with dilute sulfuric acid yielded the crystalline 1-nitro-1-desoxy-D-α-glucoheptitol, III.

The configuration of III, and hence of II, was established by converting it through treatment of its sodium salt with sulfuric acid[1,3] to D-α-glucoheptose, IV, isolated as the benzylphenylhydrazone.

It is apparent that the condensation reaction between nitromethane and a substituted aldose, followed by elimination of the nitro group to produce an aldehyde, constitutes a means of lengthening the sugar chain comparable to the familiar cyanohydrin synthesis. In the present instance, the new method is not attractive as a source of D-α-glucoheptose because of the low yields encountered in preparing benzylidene glucose from glucose and in the condensation reaction itself. However, in some instances, as in the preparation of L-gulose,[1] the new method may involve less time and effort than the cyanohydrin synthesis.

When the alkaline condensation reaction mixture containing benzylidene glucose and nitromethane was allowed to stand twenty-four hours at room temperature before acidification, it was possible to isolate, in low yield, a second reaction product. This product showed qualitatively the presence of a C-nitro group and a benzylidene group but differed sharply from II in being practically insoluble in cold water and in being indifferent to hot Fehling solution. Analysis indicated a compound differing from II by the absence of one mole of water.

This secondary product has been assigned the

---

[1] Sowden and Fischer, This Journal, **66**, 1312 (1944); **67**, 1713 (1945).

[2] Zervas, *Ber.*, **64**, 2289 (1931).

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

structure V, a 5,7-benzylidene 2,6-anhydro-1-nitro-1-desoxyheptitol, in view of the following observations: Hydrolysis of the benzylidene group with dilute sulfuric acid gave a crystalline product which did not reduce Fehling solution and which gave correct analytical data for the nitrodesoxyanhydroheptitol, VI. Neither V nor VI reduced aqueous osmium tetraoxide, indicating the absence of an olefinic double bond. Acetylation of V and VI yielded crystalline acetates which were unaffected by boiling, in benzene solution, with solid sodium bicarbonate, indicating the absence, in either compound, of an acetoxy group on the carbon atom adjacent to the -CH_2-NO_2 group.[4] Thus carbon atom two of each substance is involved in an anhydro ring. When dissolved in a standard solution of sodium metaperiodate, VI consumed two equivalents of the oxidant and yielded one equivalent of formic acid, as determined by back-titration, but *no* formaldehyde. The 2,6-position is therefore assigned to the anhydro ring in VI. When dissolved in a standard solution of lead tetraacetate in acetic acid, V slowly consumed one mole of the oxidant. Thus the 2,6-position is also assigned to the anhydro ring in V.[5] No configuration has been assigned to carbon atoms two or six of the anhydro-nitrodesoxyheptitol or its benzylidene derivative.

It is of interest to speculate on the origin of compound V. Although no supporting evidence is available, it is possible that this anhydro compound is the result of direct elimination of water between nitromethane and benzylidene glucopyranose without disruption of the hemi-acetal ring, in contrast to the usual aldehyde–nitroparaffin condensation reaction. The anhydro compound would then have the configuration of a D-α- or D-β-glucoheptitol derivative.

Reduction of the nitrodesoxy-α-glucoheptitol, III, with hydrogen in the presence of Raney nickel yielded the corresponding amine, VII, isolated as its crystalline *p*-toluenesulfonate.

Experimental

5,7-Benzylidene-1-nitro-1-desoxy-D-α-glucoheptitol.—One hundred grams of 4,6-benzylidene glucose dissolved in a mixture of 1500 cc. of absolute methanol and 250 cc. of nitromethane, was treated with 1 liter of methanol containing 17.3 g. of sodium. After eight hours at room temperature, the solution was acidified with 47 cc. of glacial acetic acid and was concentrated at reduced pressure to a thin sirup. Water (200 cc.) was added and the concentration at reduced pressure was continued, to remove methanol and nitromethane. On cooling the resulting concentrated aqueous solution, the product crystallized and was collected by filtration and washed with ice-water. There was obtained 25.9 g. (21%) of the crude benzylidene nitroalcohol.

For analysis, the product was recrystallized first from water and then several times from ethyl acetate by the addition of petroleum ether. The purified substance showed m. p. 160–162° and $[\alpha]^{28}\mathrm{D}$ $-42.5°$ in water, *c* 1.1. Further recrystallizations did not alter these values and it was assumed that a single isomer was in hand.

Anal. Calcd. for $C_{14}H_{19}O_8N$ (329.3): C, 51.1; H, 5.82; N, 4.25. Found: C, 51.1; H, 5.83; N, 4.39.

1-Nitro-1-desoxy-D-α-glucoheptitol.—A solution of 5.0 g. of the benzylidene nitrodesoxyglucoheptitol in 50 cc. of 0.1 *N* sulfuric acid was heated, with stirring, at 70–75° for forty-five minutes and then at 100° for fifteen minutes. After cooling, the solution was extracted three times with ether to remove benzaldehyde and then was neutralized by stirring with barium carbonate. Concentration of the filtered solution to dryness at reduced pressure yielded the crystalline product. Recrystallization from absolute ethanol gave 2.82 g. (77%) of the pure nitroalcohol, m. p. 138–139° and $[\alpha]^{23}\mathrm{D}$ $+ 3.1°$ in water, *c* 6.4.

Anal. Calcd. for $C_7H_{15}O_5N$ (241.2): C, 34.9; H, 6.27; N, 5.81. Found: C, 34.9; H, 6.24; N, 5.56.

Both the benzylidene substituted and the unsubstituted nitrodesoxyglucoheptitol vigorously reduced hot Fehling solution.

D-α-Glucoheptose Benzylphenylhydrazone.—A solution of 0.3 g. of 1-nitro-1-desoxy-α-glucoheptitol in 2 cc. of 1 *N* sodium hydroxide was added dropwise, at room temperature, to a stirred solution of 1 cc. of sulfuric acid in 1.6 cc. of water. After dilution, the resulting solution was neutralized with an excess of barium carbonate, a few drops of acetic acid were added, and the precipitated salts were removed by centrifuging and filtering. The sirup resulting from concentration of the clear solution at reduced pressure was dissolved in 8 cc. of 65% ethanol, 0.3 cc. of benzylphenylhydrazine was added and the solution was heated at 65–70° for one hour. Water was then added to turbidity and the solution was allowed to evaporate in an open dish. There resulted 0.29 g. (60%) of the colorless D-α-glucoheptose benzylphenylhydrazone. For analysis, the hydrazone was recrystallized from ethyl acetate containing a little ethanol. It then showed m. p. 158–159° and $[\alpha]^{29}\mathrm{D}$ $-20.4°$ in methanol, *c* 2, after a slight downward mutarotation.

The recorded values for this hydrazone are m. p. 155–156°[6] and $[\alpha]\mathrm{D}$ $-21.6° \rightarrow -22.2°$ in methanol.[7]

Anal. Calcd. for $C_{20}H_{26}O_6N_2$ (390.4): C, 61.5; H, 6.71; N, 7.17. Found: C, 61.1; H, 6.76; N, 7.06.

1-Amino-1-desoxy-D-α-glucoheptitol *p*-Toluenesulfonate.—Two grams of the nitrodesoxy-α-glucoheptitol in 40 cc. of water was shaken with hydrogen at ordinary temperature and pressure in the presence of 1 g. of Raney nickel. The reduction was complete in fifty-five minutes with the absorption of 3 moles of hydrogen. The filtered solution was made just acid to litmus by the addition of 1.65 g. of *p*-toluenesulfonic acid and was concentrated to dryness at reduced pressure. Recrystallization of the residue from absolute ethanol yielded 2.67 g. (84%) of the amine *p*-toluenesulfonate. The pure amine salt showed m. p. 149–150° and $[\alpha]^{22}\mathrm{D}$ $-4.2°$ in water, *c* 4.

Anal. Calcd. for $C_{14}H_{25}O_9NS$ (383.4): C, 43.9; H, 6.57; N, 3.65. Found: C, 44.0; H, 6.52; N, 3.53.

5,7-Benzylidene 2,6-Anhydro-1-nitro-1-desoxyheptitol.—A condensation mixture containing 126 g. of benzylidene glucose, 250 cc. of nitromethane, 3160 cc. of methanol and 21.7 g. of sodium was acidified with a slight excess of acetic acid after standing for twenty-four hours at room temperature. Concentration at reduced pressure then yielded

---

(4) The reaction of α-acetoxynitroparaffins with sodium bicarbonate to produce nitroölefins was discovered by Schmidt and Rutz (*Ber.*, **61**, 2142 (1928)) for the simple α-hydroxynitroparaffins and has been applied recently by the authors for the preparation of several acetylated carbohydrate C-nitroölefins. Details will be given in a future publication.

(5) It was necessary to establish the position of the anhydro ring independently for V and VI, since the treatment with acid for the hydrolysis of the benzylidene residue is capable of causing a shift of the oxide ring. Thus, Vargha and Puskas (*Ber.*, **76**, 859 (1943)) observed that the acid hydrolysis of 1-tosyl-2,4-benzylidene 5,6-anhydrosorbitol yielded 1-tosyl-2,5-anhydro-L-iditol.

(6) Glaser and Zuckermann, *Z. physiol. Chem.*, **167**, 37 (1927).

(7) Votoček, Valentin and Leminger, *Coll. Czechoslov. Chem. Comm.*, **3**, 250 (1931); *cf.* Tollens-Elsner, "Kurzes Handbuch der Kohlenhydrate," Johann Ambrosius Barth, Leipzig, 1935, p. 397.

a sirupy residue containing a small amount of crystalline material. The latter was separated by the addition of water followed by filtration. The crude crystals were recrystallized from methanol by the addition of water to give 7.22 g. (5%) of the benzylidene anhydronitroalcohol, m. p. 208–210°. Further recrystallization from aqueous methanol yielded the pure substance, m. p. 211–212° and $[\alpha]^{31}D$ −35.4° in methanol, *c* 1.3.

Anal. Calcd. for $C_{14}H_{17}O_7N$ (311.3): C, 54.0; H, 5.50; N, 4.50. Found: C, 54.1; H, 5.40; N, 4.55.

In the above experiment, the benzylidene nitroalcohol, II, failed to crystallize from the sirupy mother liquor. However, in another experiment where the reaction time before acidification was eighteen days at 6–8° the anhydro compound, V, was obtained in 3% yield and II in a yield of 19%.

The benzylidene anhydronitroalcohol did not reduce hot Fehling solution or aqueous osmium tetraoxide.

When dissolved in an excess of 0.1 *N* lead tetraacetate in 98% (by volume) acetic acid, the benzylidene anhydronitroalcohol showed the following consumption of the oxidant at room temperature: 20 hr., 0.51 mole; 48 hr., 0.84 mole; 68 hr., 0.96 mole; 115 hr., 1.22 moles.[8]

5,7-Benzylidene 2,6-Anhydro-1-nitro-1-desoxyheptitol Diacetate.—The benzylidene anhydronitroalcohol (0.4 g.) was acetylated with 5 cc. of acetic anhydride and 0.4 g. of fused sodium acetate, for five minutes at 100°. The product, which crystallized at once when the acetylation mixture was poured onto crushed ice, was filtered, washed with water and recrystallized from absolute ethanol. There was obtained 0.35 g. (69%) of the diacetate. After further recrystallization from ethanol the pure substance showed m. p. 192–193° and $[\alpha]^{23}D$ −60° in absolute chloroform, *c* 2.

Anal. Calcd. for $C_{18}H_{21}O_9N$ (395.4): C, 54.7; H, 5.35; N, 3.54. Found: C, 54.7; H, 5.29; N, 3.52.

The diacetate was recovered unchanged in 93% yield from its solution in benzene after being refluxed for two hours with solid sodium bicarbonate.

2,6-Anhydro-1-nitro-1-desoxyheptitol.—A solution of 1.2 g. of the benzylidene anhydronitroalcohol in 10 cc. of 0.1 *N* sulfuric acid, was heated at 100° for one hour. After cooling, benzaldehyde was removed from the solution by extraction with ether and sulfuric acid was removed by stirring with barium carbonate. The filtered solution was concentrated to dryness at reduced pressure and the resulting crystalline residue was recrystallized from absolute ethanol. There was obtained 0.66 g. (77%) of the anhydronitroalcohol, m. p. 177–177.5° and $[\alpha]^{22}D$ +8.2° in water, *c* 3.7.

Anal. Calcd. for $C_7H_{13}O_7N$ (223.2): C, 37.7; H, 5.87; N, 6.28. Found: C, 37.7; H, 5.96; N, 6.00.

The substance was indifferent to hot Fehling solution and to aqueous osmium tetraoxide.

When the anhydronitroalcohol was dissolved in an excess of 0.2 *M* sodium metaperiodate solution at room temperature, it was found to have consumed 2.05 moles of the oxidant after six hours. This value was unchanged after twenty-three hours. Back-titration of an aliquot of the solution with 0.1 *N* sodium hydroxide solution, to the methyl red end-point, then showed that 0.99 mole of formic acid had been produced.[9] Another aliquot of the solution was distilled to dryness at reduced pressure. Water was added to the residue and the distillation was repeated twice. No formaldehyde could be detected in the distillate on treatment with dimethyldihydroresorcinol. When a similar procedure was applied to the nitrodesoxyglucoheptitol, III, formaldehyde was detected readily in the distillate as the characteristic formaldimedon.

2,6-Anhydro-1-nitro-1-desoxyheptitol Tetraacetate.—A solution of 0.5 g. of the anhydronitroalcohol in 5 cc. of acetic anhydride containing a trace of sulfuric acid (1 drop to 50 cc. of acetic anhydride) was allowed to stand two days at room temperature. Ice-water was then added and the resulting crystalline precipitate was filtered and washed with water. Recrystallization from absolute ethanol yielded 0.75 g. (85%) of the pure tetraacetate, m. p. 144–145° and $[\alpha]^{25}D$ + 4.2° in absolute chloroform, *c* 4.2.

Anal. Calcd. for $C_{15}H_{21}O_{11}N$ (391.3): C, 46.0; H, 5.41; N, 3.58. Found: C, 46.0; H, 5.50; N, 3.46.

The tetraacetate was recovered unchanged in 94% yield from its solution in benzene after being refluxed for two hours with solid sodium bicarbonate.

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

Summary

Nitromethane has been condensed, under the influence of alkali, with 4,6-benzylidene glucose to produce 5,7-benzylidene 1-nitro-1-desoxy-D-α-glucoheptitol. Hydrolysis of the latter yielded the 1-nitro-1-desoxyheptitol which in turn was converted to the 1-amino 1-desoxyheptitol and to D-α-glucoheptose.

A slight modification of the original condensation conditions also gave, in low yield, a 5,7-benzylidene 2,6-anhydro-1-nitro-1-desoxyheptitol. Hydrolysis of the benzylidene group yielded the 2,6-anhydro-1-nitro-1-desoxyheptitol. The anhydro ring in these substances occupied the second position, since the fully acetylated derivatives were stable toward sodium bicarbonate. Lead tetraacetate and periodic acid oxidations showed that the anhydro ring also engaged the sixth position. Configurations about the second and sixth carbon atoms of the anhydro compounds were not determined.

TORONTO, CANADA RECEIVED APRIL 8, 1946

---

[8] The slowly continuing reduction of lead tetraacetate after consumption of the theoretical one mole may be due to incipient hydrolysis of the benzylidene group or to a slow oxidation of some non-glycol portion of the molecule. Thus, a solution of 2,4-benzylidene 6-nitro-6-desoxysorbitol (ref. 1) in 0.1 *N* lead tetraacetate in glacial acetic acid was found to have reduced 0.26 mole of the oxidant after 115 hours at room temperature.

[9] Malaprade, *Bull. soc. chim.*, [5] **4**, 906 (1937); Jackson and Hudson, THIS JOURNAL, **61**, 1530 (1939).