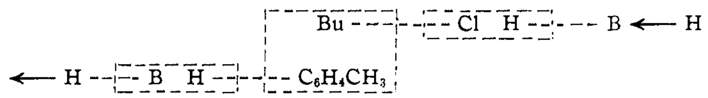
ture range 20–50°.[10] It is true, however, that certain catalysts such as aluminum chloride, hydrogen fluoride[11] and zinc chloride[8] will catalyze the reaction at temperatures at which it will not occur rapidly without an added catalyst.

Tertiary amyl chloride has also been condensed with phenol by refluxing for two and one-half hours without any added catalyst, to give a 72% yield of *p*-*t*-amylphenol.

Proof of Hydrogen Chloride Catalysis.—To actually demonstrate the catalytic activity of hydrogen chloride *t*-butyl chloride and toluene were heated at 235° for twenty-two hours, under a nitrogen pressure of approximately 575 pounds per square inch. At the end of this time, the contents of the bomb were treated in the usual manner and fractionated. Approximately 84% of the toluene and 55% of the *t*-butyl chloride were recovered unchanged, and a small quantity (approximately 10% of the theoretical) of higher boiling material (probably *t*-butyltoluene) was isolated. This is certainly not comparable to the 88% yield of *p*-*t*-butyltoluene obtained by use of hydrogen chloride as the catalyst. It can also be argued that due to prolonged heating at 235°, *t*-butyl chloride may have decomposed to give a small quantity of hydrogen chloride which was sufficient to catalyze the alkylation to some extent, but because of the dilution with nitrogen, could not be formed in sufficient quantity to give a good yield of the alkyl toluene.

Mechanism.—As this work followed from the kinetic study of the hydrogen fluoride catalyzed condensation of *t*-butyl chloride and toluene and as a similarity between the activity of hydrogen chloride and hydrogen fluoride as condensing agents has been found, a mechanism for these condensations, similar to that already proposed for hydrogen fluoride condensations, may be offered. Using the same reaction, which has been shown to give good yields of *p*-*t*-butyltoluene, the mechanism might be formulated as



The possibility of other substances, such as traces of water, supplying the basic species is quite strong. Although this mechanism is suggested without definite experimental proof, it seems to be at least subject to consideration.

Summary

1. The activity of hydrogen chloride as a condensing agent has been demonstrated. The alkylation of benzene and toluene has been accomplished using alkyl halides and olefins, and the acylation of benzene with an acyl halide has been accomplished, using hydrogen chloride as the condensing agent. The alkylation of an isoparaffin is also indicated.

2. Although the reactions are not as readily executed as those which use hydrogen fluoride or aluminum chloride as the catalyst, because of the pressure equipment required, the yields are good and the reactions take place without the formation of tarry residues.

3. Hydrogen chloride resembles hydrogen fluoride more than it does the metallic halides in its catalytic activity.

4. Phenol can be alkylated directly with active tertiary alkyl halides, without any added catalyst.

STATE COLLEGE, PA. RECEIVED MARCH 15, 1944

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(10) M. E. Putnam, E. C. Britton and R. P. Perkins, U. S. P. 2,039,344 (*C. A.*, **30**, 4176 (1936)).

(11) J. H. Simons, S. Archer and H. J. Passino, THIS JOURNAL, **60**, 2957 (1938).

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

Carbohydrate C-Nitroalcohols: 1-Nitro-1-desoxy-D-mannitol

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

Due to the present availability of the nitroparaffins, the reaction of these compounds with various types of aldehydes to produce nitroalcohols has received much attention in recent years.[1] Successful application of this reaction to the aldose sugars would produce carbohydrate C-nitroalcohols containing the grouping —C—NO₂, an interesting new type of derivative, differing from the well-known sugar nitrates containing the grouping —C—O—NO₂.

Apparently, the only recorded application of thenitro paraffin–aldehyde condensation reaction to the sugar series consists of the experiments described by Pictet and Barbier.[2] These authors treated glycolaldehyde, glyceraldehyde, L-arabinose and D-glucose with nitromethane and alkali but made no attempt to isolate the expected C-nitroalcohols. Their reaction mixtures were reduced and then treated with nitrous acid in an attempt to prepare the sugar alcohols containing one more carbon atom than the original sugars. However, no product could be identified from glyceraldehyde or L-arabinose, and the product isolated in low yield, from D-glucose, reported to be α-glucoheptitol, did not agree in every particu-

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(1) Excellent reviews on the chemistry of the nitroparaffins have recently appeared by Hass and Riley, *Chem. Rev.*, **32**, 373 (1943), and by Hass, *Ind. Eng. Chem.*, **35**, 1146 (1943).

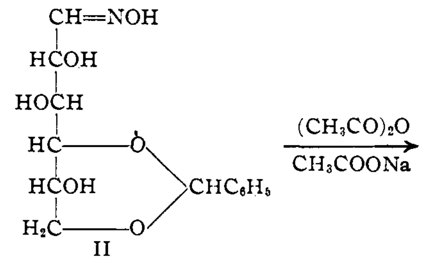
(2) Pictet and Barbier, *Helv. Chim. Acta*, **4**, 924 (1921).

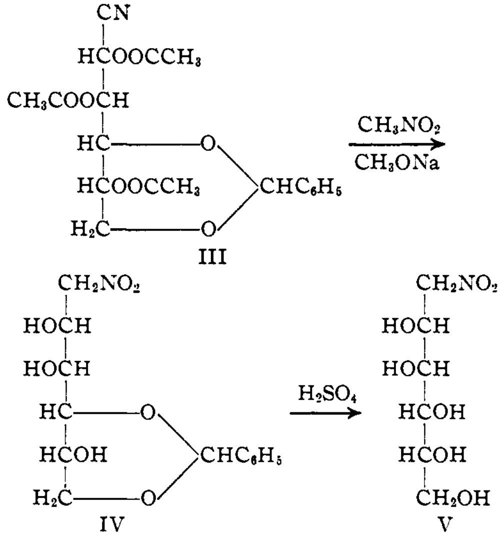
lar with this known substance. Thus, it must be concluded that Pictet and Barbier had no definite proof that the nitroparaffin–aldehyde condensation reaction occurred under the conditions employed, except in the case of glycolaldehyde. To be sure, in repeating their treatment of D-glucose with nitromethane in the presence of alkali we were able to confirm that little, if any, nitrogen-containing carbohydrate derivative is formed.

In order to bring about the condensation of nitromethane with an aldose, we have successfully employed, in place of the sugar itself, an acetylated cyanohydrin of the sugar. A similar technique was used by Helferich and Peters[3] for the condensation of ethyl glyoxylate with sugars to produce ascorbic acid and its analogs. When the acetylated cyanohydrin is treated with alkali in the presence of nitromethane, deacetylation and degradation of the cyanohydrin to the free aldose occurs. Thus, what may be called an aldehydo sugar *in statu nascendi* is available for condensation with the nitroparaffin.[3a]

Preliminary experiments consisted of treating the known acetylated L-arabono- and D-glucononitriles with alkali and nitromethane in methanol solution. Although it was possible in these instances to isolate and partially purify the sirupy products which apparently contained the desired C-nitroalcohols, we were unable to obtain any well-defined crystalline derivatives. For this reason, recourse was made to an acetylated cyanohydrin containing an alkali-stable grouping with good powers of crystallization.

The 4,6-benzylidene glucose I, described by Zervas,[4] was converted, by way of the oxime II, to the acetylated cyanohydrin III. When this substance was allowed to react with nitromethane and sodium methylate in methanol solution, the C-nitrodesoxymannitol derivative, IV, was obtained in pure crystalline form. The corresponding sorbitol derivative, whose simultaneous formation is to be expected, did not crystallize concurrently, thus simplifying the isolation of IV.





The benzylidene C-nitrodesoxymannitol is readily reduced to the corresponding amine by hydrogen and Raney nickel without cleavage or reduction of the benzylidene residue. Hydrolysis of the benzylidene group with dilute acid then gives the known[7] 1-amino-1-desoxy-D-mannitol. Treatment of the sodium salt of IV with sulfuric acid gives rise to the aldehyde, mannose, a reaction well-known for the simpler nitroalcohols.[1]

The crystalline 1-nitro-1-desoxy-D-mannitol, V, is obtained in good yield from IV, by hydrolysis of the benzylidene residue with dilute sulfuric acid.

Experimental

4,6-Benzylidene Glucose Oxime.—An alcoholic solution of hydroxylamine was prepared by the action of 1.83 g. of sodium in 50 cc. of absolute ethanol on 5.9 g. of hydroxylamine hydrochloride in 3 cc. of water. After filtration, the salt cake was washed with 75 cc. of absolute ethanol, and the filtrates were combined. This solution was added to 14.2 g. of 4,6-benzylidene glucose and the mixture was warmed to 70° in a water-bath. Complete solution occurred rapidly, and after a few minutes the oxime began to crystallize out in the form of long needles. Heating was continued at 65 to 70° for two hours after which the solution was cooled and the oxime filtered and washed with cold absolute ethanol; yield, 12.5 g. (83%). For analysis, the oxime was recrystallized from water. It then melted at 195° (dec.) and showed $[\alpha]^{27}\text{D}$ −72° in absolute pyridine, *c* 2.5.

Anal. Calcd. for $C_{13}H_{17}O_6N$ (283.3): C, 55.1; H, 6.05; N, 4.95. Found: C, 55.1; H, 6.33; N, 4.91.

4,6-Benzylidene-2,3,5-triacetylgluconononitrile.—A mixture containing 42 g. of 4,6-benzylidene glucose oxime, 300 cc. of acetic anhydride and 40 g. of fused sodium acetate was heated in an oil-bath at 120 to 125° for ninety minutes. The dark brown solution was cooled to about 80° and poured, with stirring, onto 2 liters of cracked ice and water. The sirup which precipitated crystallized after

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[3] Helferich and Peters, *Ber.*, **70**, 465 (1937); German Patent 637,448 (1936).

[3a] The condensation of nitroparaffins with mono- and di-carbonyl aldehydo sugars has also been accomplished in this Laboratory and will be described in the near future in publications by J. M. Grosheintz and H. O. L. Fischer.

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

standing overnight under ice-water. After filtration and thorough washing with water, the nitrile was purified by two recrystallizations from absolute ethanol with the aid of decolorizing carbon; yield, 38.4 g. (66%). The pure nitrile melted at 135.5–136° and showed $[\alpha]^{25}_{\mathrm{D}}$ +44° in absolute chloroform, *c* 4.

Anal. Calcd. for $C_{19}H_{21}O_8N$ (391.4): C, 58.3; H, 5.41; N, 3.58; CN, 6.65. Found: C, 58.4; H, 5.64; N, 3.72; CN,[5] 6.62.

4,6-Benzylidene-1-nitro-1-desoxy-D-mannitol.—An ice-cold solution of 4.5 g. of sodium in 275 cc. of absolute methanol was added to a cold solution containing 38.1 g. of 4,6-benzylidene-2,3,5-triacetylgluconназваниеonitrile and 70 cc. of nitromethane in 350 cc. of absolute methanol. After standing forty-two hours at about 5°, the solution was acidified by the addition of 17 cc. of glacial acetic acid and was then concentrated at reduced pressure to a thick sirup. The sirup was dissolved in 50 cc. of warm water, and the resulting solution after cooling in ice and rubbing with a glass rod, deposited fine needles of the sugar C-nitroalcohol. After two additional recrystallizations from a small volume of water, there was obtained 9.0 g. (31%) of the product in the form of colorless, silky needles. For analysis the nitro compound was further recrystallized from a large volume of absolute chloroform and finally from toluene. The pure substance melted at 146–147° and showed $[\alpha]^{21}_{\mathrm{D}}$ −70.4° in water, *c* 1.5. Further recrystallizations from the solvents indicated above did not alter these constants.

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, 5.92; N, 4.77.

Recrystallization of the sugar C-nitroalcohol from water only, yielded a product of the same melting point and approximately the same rotation as that described above from anhydrous solvents. Although carbon analyses of the substance so treated were invariably somewhat too low (C, 51.0 to 52.0), no appreciable weight loss, indicating water of crystallization, could be detected after drying *in vacuo* at 100°.

1-Nitro-1-desoxy-D-mannitol.—A solution of 1.0 g. of 4,6-benzylidene-1-nitro-1-desoxymannitol in 10 cc. of 0.1 *N* sulfuric acid was heated at 70° for one hour. After cooling, the solution was extracted three times with ether to remove benzaldehyde, and was then neutralized by the addition of an excess of barium carbonate. The solution was clarified by centrifuging and filtering. Following removal of the water *in vacuo*, recrystallization of the residue from a small volume of absolute ethanol yielded 0.55 g. (78%) of 1-nitro-1-desoxymannitol. After two further recrystallizations from absolute ethanol the product melted at 134.5–135° and showed $[\alpha]^{19}_{\mathrm{D}}$ −7.0° in water, *c* 5.8.

Anal. Calcd. for $C_6H_{13}O_7N$ (211.2): C, 34.1; H, 6.20; N, 6.63. Found: C, 34.3; H, 5.97; N, 6.66.

The C-nitroalcohol gave a brilliant red coloration when treated with the Greiss-Ilosvay reagent according to the directions of Bose.[6]

Hot Fehling solution is rapidly reduced by the C-nitroalcohol.

4,6-Benzylidene-1-amino-1-desoxymannitol Oxalate and 1-Amino-1-desoxymannitol Oxalate.—Four grams of 4,6-benzylidene-1-nitro-1-desoxymannitol in 60 cc. of water was shaken, at room temperature and pressure, with hydrogen in the presence of 4 g. of Raney nickel. The reduction was complete after approximately 3 moles of hydrogen had been absorbed.

After removal of the catalyst at the centrifuge, one-half of the above solution was treated with a slight excess of oxalic acid and concentrated to dryness at reduced pressure. Recrystallization of the residue from aqueous alcohol yielded 1.0 g. of 4,6-benzylidene-1-amino-1-desoxymannitol oxalate. After further recrystallization from aqueous alcohol, the pure amine oxalate melted at 208° (dec.) and showed $[\alpha]^{20}_{\mathrm{D}}$ −37° in water, *c* 6.

Anal. Calcd. for $C_{14}H_{20}O_7N$ (314.3): C, 53.5; H, 6.41; N, 4.46. Found: C, 53.3; H, 6.53; N, 4.36.

The remaining one-half of the 4,6-benzylidene-1-amino-1-desoxymannitol solution was acidified to a concentration of 0.2 *N* with sulfuric acid and was then heated at 70° for two hours. The solution was then distilled *in vacuo* until no more benzaldehyde appeared in the distillate. Sulfuric acid was removed from the residual solution by the addition of the exact amount of barium hydroxide and the filtered solution was treated with a slight excess of oxalic acid. After concentration of the solution to dryness *in vacuo*, recrystallization of the residue from aqueous alcohol yielded 0.77 g. of the known 1-amino-1-desoxymannitol oxalate. After further recrystallization from aqueous alcohol, the amine oxalate was obtained as thin quadrangular plates which melted at 183–184° (dec.) and showed $[\alpha]^{21}_{\mathrm{D}}$ +5.0° in water, *c* 10.

For D-mannamine oxalate, Maquenne and Roux[7] give m. p. 186° and $[\alpha]_{\mathrm{D}}$ +4.25° in water and for the corresponding D-glucamine oxalate, m. p. 180–182° and $[\alpha]_{\mathrm{D}}$ −15.2° in water.

Anal. Calcd. for $C_7H_{16}O_7N$ (226.2): C, 37.2; H, 7.13; N, 6.19. Found: C, 37.3; H, 7.12; N, 6.10.

Mannose from 4,6-Benzylidene-1-nitro-1-desoxymannitol.—A solution of 250 mg. of the substituted sugar C-nitroalcohol in 1.1 cc. of 1 *N* sodium hydroxide was added dropwise, with shaking, to 1 cc. of 50% sulfuric acid at 20°. The solution was diluted to 5 cc. and warmed at 35–40° for two hours in order to hydrolyze the benzylidene residue. After removal of the resulting benzaldehyde by ether extraction, the aqueous solution was treated with 3 g. of sodium acetate, followed by 0.25 cc. of phenylhydrazine. There resulted 68 mg. of mannose phenylhydrazone, m. p., after recrystallization, 197–198° (Calcd.: N, 10.4. Found: N, 10.3).

Similarly, using α-methylphenylhydrazine, 200 mg. of the substituted sugar C-nitroalcohol yielded 53 mg. of mannose α-methylphenylhydrazone, m. p. 181° (Calcd.: N, 9.86. Found: N, 9.73).

The authors wish to express their appreciation of the generous support received from the Corn Industries Research Foundation during the course of this research. The assistance of the National Research Council of Canada is also gratefully acknowledged.

Summary

The reaction of a nitroparaffin with a sugar cyanohydrin in the presence of alkali to produce the first known example of a carbohydrate C-nitroalcohol, is described. Certain reactions of the new type of sugar derivative are described. Further work is in progress in this Laboratory on the reaction of nitroparaffins with sugar derivatives.

TORONTO, CANADA RECEIVED APRIL 29, 1944

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[5] Zemplén, *Ber.*, **59**, 1259 (1926).

[6] Bose, *Analyst*, **56**, 504 (1931).

[7] Maquenne and Roux *Compt. rend.*, **132**, 980 (1901); Roux. *ibid.*, **138**, 503 (1904).