in water (c = 3.7). These constants agree with those reported by Ohle[8] for the same compound (m. p. 176–177°, $[\alpha]^{20}\text{D}$ −7.02° in water, (c = 5.01)).

(9) **1,2,3,5-Diacetone-6-amino-6-desoxy-D-glucose *p*-Toluenesulfonate.**—An amount of 1.05 g. 1,2,3,5-diacetone-6-nitro-6-desoxy-D-glucose (m. p. 106–107°) was dissolved in 60 cc. of dioxane and reduced as under (8). The reduction was complete within forty-five minutes and the free amine was obtained as a viscous sirup after centrifuging off the catalyst and evaporating the dioxane *in vacuo* at 40°. This sirup was dissolved in 20 cc. of water, neutralized exactly with 0.5 N *p*-toluenesulfonic acid and filtered. On evaporating the water *in vacuo*, 1.3 g. (83%) of the salt was obtained and was crystallized once from benzene and once from dry ethyl acetate. *Anal.* Calcd. for $C_{19}H_{29}O_8NS$ (431): C, 52.8; H, 6.72; N, 3.25; acetone, 26.9. Found: C, 52.9; H, 6.62; N, 3.12; acetone, 26.7.

Since the melting point found for this substance did not entirely agree with that reported by Ohle, the physical constants of the salt were thoroughly examined by Mr. D. L. MacDonald of this Laboratory, who reports as follows:

"The melting point of this compound varied considerably with the rate of heating, and melting was accompanied by decomposition; as these characteristics were not reported by Ohle and v. Vargha, the compound was also prepared according to their method from 6-tosyl-1,2-monoacetone-D-glucose *via* 6-tosyl-1,2,3,5-diacetone-D-glucose.[9,10] The amine salt prepared by the two different methods was found to be identical as regards melting point (with decomposition), solubilities in various solvents, crystal form, optical rotation and dependence of melting point on rate of heating, as shown in the table. From the data, it can be concluded that the compound under consideration is identical with Ohle and v. Vargha's 1,2,3,5-diacetone-6-amino-6-desoxy-D-glucose *p*-toluenesulfonate. The slightly low rotation may indicate the presence of a small amount of the corresponding L-idose compound."

	Prepared according to: Ohle and v. Vargha	Grosheintz and Fischer	Mixed melting point, °C.
From dry ethyl acetate:			
(1) Standing in bath for 20 minutes at	160°	160°	
(2) Heating at 1°/minute	172–172.5°	171.5–172°	171.5–172°
(3) Heating at 10°/minute	177–179°	176–179°	
(4) $[\alpha]\text{D}$ (1 dm. tube, H_2O)	+30.5° (c = 5.4, t = 25°)	+29.1 (c = 4.0, t = 24°)	

(10) **1,2,3,5-Diacetone-6-amino-6-desoxy-L-idose *p*-Toluenesulfonate.**—An amount of 2.35 g. of 1,2,3,5-diacetone-6-nitro-6-desoxy-L-idose (m. p. 150–151°) was dissolved in 100 cc. of dioxane, reduced, and the resulting amine was neutralized with *p*-toluenesulfonic acid as under (9). The crude salt was dissolved in a little warm methanol, treated with charcoal, and filtered. On addition of about 5 volumes of absolute ether to this solution 2.8 g. (80%) of substance crystallized immediately in long fine needles, m. p. 198–200° (dec.), $[\alpha]^{25}\text{D}$ +5.8° in 0.1 N NaOH (c = 3.8), $[\alpha]^{26}\text{D}$ +0.84° in absolute ethanol (c = 3.5), $[\alpha]^{26}\text{D}$ −7.0° in dry pyridine (c = 5.3). No optical rotation could be observed in water. *Anal.* Calcd. for $C_{19}H_{29}O_8NS$ (431): C, 52.8; H, 6.72; N, 3.25; acetone, 26.9. Found: C, 52.7; H, 6.55; N, 3.24; acetone, 26.8.

Acknowledgment.—We are pleased to acknowledge gratefully the generous support of a section of this work by the Nutrition Foundation, Inc.

Summary

The preparation of a new type of sugar derivative is described. 1,2-Acetone-D-*xylo*-trihydroxyglutaric dialdehyde was condensed with nitromethane to yield a mixture of 1,2-acetone-6-nitro-6-desoxy-D-glucose and 1,2-acetone-6-nitro-6-desoxy-L-idose. Separation of the two diastereoisomers could be effected. The free nitrodesoxysugars were obtained on desacetonation with dilute sulfuric acid.

The constitution and configuration of the glucose derivatives were established by the reduction of the mono- and diacetone-6-nitro-6-desoxy-D-glucose to the known 1,2-acetone-6-amino-6-desoxy-D-glucose and to 1,2,3,5-diacetone-6-amino-6-desoxy-D-glucose and subsequent isolation of their *p*-toluenesulfonates.

This leaves for the other isomer the L-idose configuration.

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[10] H. Ohle and E. Dickhäuser, *Ber.*, **58,** 2602 (1925); H. Ohle and L. v. Vargha, *ibid.*, **61,** 1208 (1928).

[CONTRIBUTION FROM THE BANTING AND BEST DEPARTMENT OF MEDICAL RESEARCH, UNIVERSITY OF TORONTO]

Cyclization of 6-Nitrodesoxyaldohexoses to Nitrodesoxyinositols

BY J. M. GROSHEINTZ AND HERMANN O. L. FISCHER

When an aldose, in which the primary hydroxyl group is replaced by a nitro group, is exposed to a mild alkali, condensation of the aldehyde group into the $—CH_2NO_2$ group may be expected[1] forming the group $—CH(NO_2)—CH(OH)—$ with two new asymmetric carbon atom centers. Such a reaction, reminiscent of an aldol condensation, could produce either straight-chain or cyclic polymers or produce cyclic monoisomers. In the latter case the aldehyde group would condense with the nitromethylene group of the same molecule. It was with this reaction in mind that we synthesized 6-nitro-6-desoxy-D-glucose and 6-nitro-6-desoxy-L-idose,[2] since we expected intramolecular condensation, *i. e.*, cyclization of these nitrodesoxysugars to a number of nitrodesoxyinositol stereoisomers. We found our expectations confirmed and we were able to isolate some of these nitrodesoxyinositols under certain controlled conditions.

Evidence for the cyclohexane ring structure of our condensation products is shown by the quantitative transformation of these compounds to a known aromatic compound. Thus, on dissolving a pentaacetylnitrodesoxyinositol in warm pyridine

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[1] L. Henry, *Compt. rend.*, **120,** 1265 (1895).

[2] Grosheintz and Fischer, THIS JOURNAL, **70,** 1476 (1948).

it is immediately and quantitatively transformed to diacetyl-5-nitroresorcinol. Similarly, on dissolving any of the nitrodesoxy inositols in warm pyridine and acetic anhydride the diacetyl-5-nitroresorcinol is immediately formed in a quantitative yield. This transformation is in principle the same as that of inosose and its pentaacetate to the tetraacetate of 1,2,3,5-tetrahydroxybenzene as described by Posternak.[3] On ring closure the aldehyde group disappears with the formation of a new hydroxyl group. This was evidenced by the preparation of pentasubstituted nitrodesoxyinositol derivatives and by the absence of any carbonyl reaction. Thus, after reduction of the nitro group to an amino group, the amino sugars give a strong Fehling test, whereas the amino inositols give none whatever. Also characteristic for our condensation products is the absence of any optical activity. This property points to the formation of symmetrically built molecules, or the presence of equal amounts of enantiomorphs.

The cyclization process, which was followed polarimetrically, is induced by very small amounts of alkali, as was already observed during the investigation of the mutarotation of 6-nitro-6-desoxy-D-glucose.[2] It takes place, in water, *via* the nitronium salts, as evidenced by an initial (numerical) increase in the optical rotation, and it can be arrested at any stage by acidification of the reaction solution or by precipitation of the nitronium salts; on restoring the initial *p*H of the solution or on redissolving the precipitated salts in water the cyclization continues where it had been interrupted, until the optical activity had disappeared. The rate of cyclization and the end-products are dependent, within limits, on the alkalinity to which the nitrodesoxysugars are exposed.

For one series of experiments the nitrodesoxysugars were dissolved in the calculated amount of 0.1 to 0.16 *N* barium hydroxide. Approximately half of the theoretical amount of barium salts of the cyclic compounds would crystallize overnight and the other half could be precipitated by the addition of ethanol. A slight excess of barium hydroxide solution did not affect the reaction, but tends to discoloration of the barium salts, whereas a great excess and especially greater concentration of the alkali induces strong discoloration and subsequent lower yields of the free nitrodesoxyinositols. On dissolving the barium salts in acetic acid and eliminating the barium in the usual manner, a mixture of the crystalline isomers was obtained in excellent yield. Thus from the cyclization of crystalline nitrodesoxy-D-glucose two individual substances could be isolated in approximately equal amounts. The separation could be effected due to the fact that one isomer, which we shall call **Nitrodesoxyinositol I,** crystallized from pure 1,4-dioxane with one half mole of solvent, was practically insoluble in acetone and could not be acetonated under the usual conditions, whereas the other isomer, which we shall call **Nitrodesoxyinositol II,** crystallized only in very small amounts, when pure, from dioxane, and was very easily acetonated to a diacetone derivative. In a similar manner, but in somewhat smaller yields, two nitrodesoxyinositols could be isolated from the mixture of stereoisomers obtained from the cyclization of amorphous nitrodesoxy-L-idose. These two isomers proved to be identical with those obtained from the cyclization of nitrodesoxyglucose.

An altogether different mixture of nitrodesoxyinositols was obtained when a molar solution of nitro glucose was made alkaline with one-third of the calculated amount of normal sodium hydroxide. The cyclization proceeded slowly and a main product, which we will call **Nitrodesoxyinositol III,** was obtained in a yield of about 65% of the theoretical. This material did not represent a pure isomer, since products of slightly differing melting points were isolated on fractional crystallization, but no clear separation of individual compounds could be effected. It did not form acetone derivatives under the usual conditions. Moreover, the reaction mixture contained some nitrodesoxyinositol II, which could be isolated due to its ready formation of a diacetone derivative, and we believe, therefore, that it also contained smaller amounts of nitrodesoxyinositol I.

These results lead to the following considerations with regard to the steric configuration of our compounds: on ring closure of 6-nitro-6-desoxy-D-glucose four isomers may be formed theoretically, of which two would possess symmetrical and two asymmetrical molecular structure; the same is the case for 6-nitro-6-desoxy-L-idose. The isomers with asymmetrical molecular structure which would be thus obtained by cyclization of one of the sugars are the enantiomorphs of those to be expected by cyclization of the other sugar, whereas all the expected isomers with symmetrical molecular structure would have a different steric configuration from one another. Therefore, having obtained two nitrodesoxyinositols from one of the sugars under certain experimental conditions, one should expect two different nitrodesoxyinositols from the other sugar under the same experimental conditions, while the absence of optical activity would, in general, indicate the absence of asymmetrical structure in these compounds. Since we obtained only two different compounds in all, under similar experimental conditions, we conclude that, in alkaline medium, an equilibrium is established between the cyclic and open-chain forms of the nitrodesoxysugar derivatives (Table I) resulting in a transformation of these derivatives, whether originally of the D-glucose or L-idose configuration, to an identical mixture of nitrodesoxyinositol isomers.[4] This would therefore not ex-

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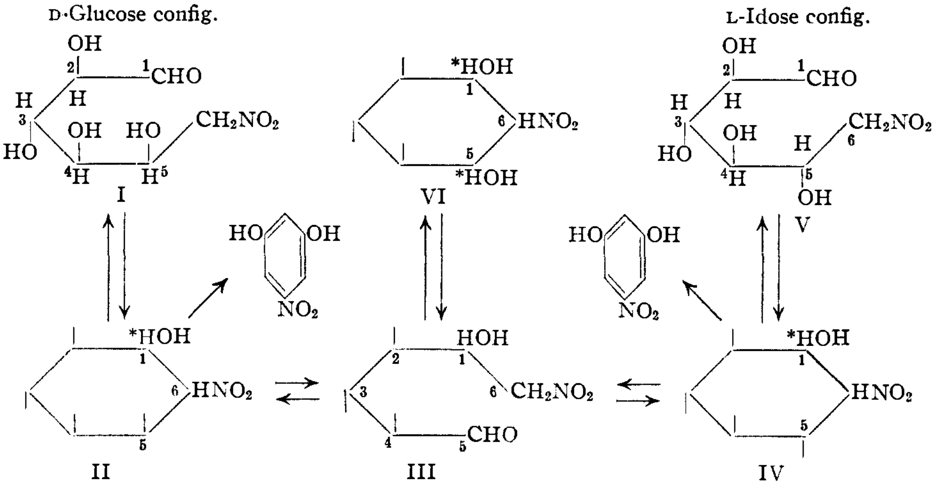
[3] Th. Posternak, *Helv. Chim. Acta*, **19**, 1333 (1936).

[4] This, of course, does not exclude other reaction mechanisms in the alkaline medium, *e. g.*, cleavage of the nitrohexoses into nitromethane and D-xylo-trihydroxyglutaric dialdehyde, and the recondensation to nitrohexoses and/or nitroinositols.

TABLE I



clude the formation of racemates and one may not rule out any of the eight possible steric configurations on the grounds of optical inactivity. We believe that in the case of cyclization experiments with mild and dilute alkali, such as one-tenth normal barium hydroxide, the reaction indicated in the table is the main reaction. Thus, the conversion into one another of the two nitrodesoxyinositols I and II was easily effected under the same conditions as their preparation from the nitrodesoxysugars. This conversion may, of course, simply indicate an isomerization due to the intermediate formation of a nitronium salt, but we are more inclined to believe that a symmetrical arrangement of the hydroxyl groups is achieved prior to the precipitation of the salts and that upon reconversion of the salts to the free nitro compounds the nitro group is guided into the *trans* position with regard to the neighboring hydroxyl groups. Such an arrangement would agree with all observed reactions as well as with previous experience.[5] In the case of the cyclization experiments which led to the formation of nitrodesoxyinositol III, a much greater concentration of alkali prevailed. Therefore, one cannot dismiss completely the possibility of far reaching enolization such as the sugars are known to undergo in alkaline solution as evidenced in the reduction of glucose at ordinary temperature and *p*H 10–13.[6]

Such a reaction would leave the way open to all theoretically possible steric rearrangements. The non-occurrence of isomers is not surprising in such a labile system where certain molecular structures would naturally be preferred.

From the aforesaid it is evident that for the preparation of these cyclic compounds one need not start from the individual 6-nitro-6-desoxy-D-glucose or 6-nitro-6-desoxy-L-idose, but may use their equimolecular mixture, which is readily available by desacetonation of "mixture A," as described in our previous publication.[2]

All cyclic nitro compounds were reduced and in most cases the corresponding amino compounds could be isolated. The desamination of the amino compounds to the inosityls and the transformation of the nitro compounds to inososes by means of the Nef reaction[7] has not yet been realized.

We wish to stress the fact that the significance of our observations lies not so much in the purity or final identification of individual isomers, but rather in the ease with which ring closure is effected[8] under mild conditions. We feel that such a model experiment gives validity to the belief that inositol is formed in nature through cyclization of glucose.[9] The easy transformation of a sugar *via* an inositol derivative to an aromatic compound as demonstrated by us in the laboratory might well have its counterpart in an enzymatic process in nature.

Experimental

A. Cyclization of 6-Nitro-6-desoxy-D-glucose. (1) **Barium Salts of Nitrodesoxyinositols.**—To a solution of 12.0 g. of nitrodesoxy-D-glucose (m. p. 154–156°)[2] in 100 cc. of water was added 352 cc. of 0.163 *N* barium hydroxide. Crystallization of barium nitrodesoxyinositol started within a few minutes; 8.7 g. or 55% of the theoretical of the salts separated within twelve hours and 7.2 g. or 45% of the theoretical of crystalline salts precipitated on addition, in portions, of 600 cc. of ethanol within the next thirty-six hours. The first crystals formed were colorless, whereas those formed later were usually light brown. *Anal.* Calcd. for $C_{12}H_{20}O_{14}N_2Ba$ (553): Ba, 24.77. Found: Ba, 24.6.

(2) **Nitrodesoxyinositols.**—An amount of 8.65 g. of the above barium salts was dissolved in 40 cc. of 2 *N* acetic acid by shaking at room temperature. The resulting solution was freed from the barium by addition of 95% of the theoretical amount of *N* sulfuric acid and balanced

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[5] H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **19**, 519 (1936).

[6] M. L. Wolfrom, B. W. Lew and R. Max Goepp, Jr., THIS JOURNAL, **68**, 1443 (1946), and preceding papers.

[7] Nef reaction: J. U. Nef, *Ann.*, **280**, 263–291 (1894); *cf.* also J. C. Sowden and H. O. L. Fischer, THIS JOURNAL, **69**, 1963 (1947).

[8] For literature on attempted ring closure by chemical means *cf.* F. Micheel, *Ann.*, **496**, 77 (1932); "Chemie der Zucker und Polysaccharide," Leipzig, 1939, p. 329.

[9] For further support of this contention *cf.* H. O. L. Fischer, Harvey Lectures, Series XL, 1944–1945, pp. 156–178.

out exactly with 0.1 *N* sulfuric acid. On evaporation, *in vacuo*, of the filtered solution a mixture of isomeric nitrodesoxyinositols was obtained as a partly crystalline mass. After drying this mixture over phosphorus pentoxide and sodium hydroxide and dissolving it in 50 cc. of boiling 1,4-dioxane, 3.7 g. or 47% of the theoretical of substance (**Nitrodesoxyinositol** I) crystallized with one-half mole of dioxane on cooling to room temperature. Twice recrystallized from the same solvent, this substance melted at 147–148°. *Anal.* Calcd. for $(C_6H_{11}O_7N)_2 \cdot C_4H_8O_2$ (506): C, 37.94; H, 5.93; N, 5.53. Found: C, 38.10; H, 5.97; N, 5.55.

The mother liquors were collected and evaporated *in vacuo* and the residue was dissolved in a little hot methanol. On partial evaporation of the solvent over phosphorus pentoxide 3.0 g. or 46% of the theoretical of crystalline substance (**Nitrodesoxyinositol** II) was obtained. Crystallized from absolute ethanol with addition, in portions, of about 20% of absolute ether this substance melted at 185–186° (dec.). *Anal.* Calcd. for $C_6H_{11}O_7N$ (209): C, 34.5; H, 5.27; N, 6.70. Found: C, 34.5; H, 5.26; N, 6.72.

(3) **Nitrodesoxyinositol** I.—This substance, as obtained under (2), contained some isomers which could not be eliminated satisfactorily by repeated crystallization. However, separation was partially effected due to the fact that this substance could not be acetonated under standard conditions, whereas the contaminating isomers were easily acetonated. Thus 2 g. of this powdered substance was shaken for five hours in 50 cc. of absolute acetone containing 0.5% of concentrated sulfuric acid, whereupon the undissolved material was filtered off, washed with a few drops of absolute acetone and crystallized from dry 1,4-dioxane. This operation was repeated (3–5 times) until the substance showed a constant melting point. After filtration from the acetonation solution it melted at 182–183° (dec.). *Anal.* Calcd. for $C_6H_{11}O_7N$ (209): C, 34.5; H, 5.27; N, 6.70. Found: C, 34.6; H, 5.23; N, 6.82. After crystallization from 1,4-dioxane the nitrodesoxyinositol I contained one half mole of dioxane and melted at 162–163°. *Anal.* Calcd. for $(C_6H_{11}O_7N)_2 \cdot C_4H_8O_2$ (506): C, 37.94; H, 5.93; N, 5.53. Found: C, 38.10; H, 5.81; N, 5.52. The acetone mother liquor contained some diacetone-nitrodesoxyinositol II, as described under (6), and small amounts of not acetonated nitrodesoxyinositols, which were not further investigated.

(4) **Aminodesoxyinositol** I **Hydrochloride**.—An amount of 1.02 g. of nitrodesoxyinositol I, as obtained under (2), was dissolved in 50 cc. of distilled water and reduced with hydrogen at 26° and 752 mm. pressure in the presence of 2 g. of freshly prepared Raney nickel. Within the first ten minutes 250 cc. of hydrogen was absorbed, and 15 cc. within the next fifty minutes (calcd. 263 cc.). The catalyst was centrifuged off and the solution was neutralized with 0.5 *N* hydrochloric acid, and concentrated to about 25 cc., filtered with a little charcoal, and further concentrated to about 10 cc. On addition of about 80 cc. of acetone the solution turned slightly turbid and the hydrochloride crystallized within thirty minutes in long needles with one mole of water in a yield of about 75%. *Anal.* Calcd. for $C_6H_{14}O_5 \cdot HCl \cdot H_2O$ (233.5): C, 30.9; H, 6.85; N, 6.01. Found: C, 31.3; H, 6.80; N, 6.00. This compound sintered at 211° and slowly fused under decomposition on further heating to 230°. It did not reduce Fehling solution, which is a characteristic difference between the aminoinositols and the aminosugars, nitrosugars or nitroinositols.

(5) **Nitrodesoxyinositol** II.—This substance, as obtained under (2), appeared to be free of isomers, since its melting point did not change on repeated crystallization from ethanol or methanol and ether. Moreover, this procedure is wasteful. Pure substance in best yields is obtained by acetonation of the crude mixture of isomers and subsequent desacetonation, as described under (6).

(6) **Diacetone-nitrodesoxyinositol** II.—An amount of 2.4 g. of nitrodesoxyinositol II was added to 50 cc. of dry acetone containing 0.25 cc. of concentrated sulfuric acid, in which it dissolved on shaking, within thirty minutes. The solution was kept at room temperature overnight and was then neutralized with the calculated amount of concentrated ammonium hydroxide; the precipitate of ammonium sulfate was centrifuged off and the solution was evaporated, *in vacuo*, to about 5 cc. Then 100 cc. of ether was added and the ethereal solution was washed and dried and the ether was evaporated. Crystallization from *n*-butanol gave 2.8 g. or 85% of the theoretical of the diacetone compound, which showed a constant melting point of 186–186.5° after one more crystallization from the same solvent. *Anal.* Calcd. for $C_{12}H_{19}O_7N$ (289): C, 49.8; H, 6.58; N, 4.84; acetone, 40.1. Found: C, 49.7; H, 6.62; N, 4.74; acetone, 40.4.

Desacetonation of this substance by dissolving 2.0 g. of it in 20 cc. of boiling ethanol, refluxing for one hour with 20 cc. of *N* sulfuric acid, eliminating the sulfuric acid with the exact amount of barium acetate, evaporating the solvent *in vacuo* and crystallizing the residue from ethanol and ether, gave the nitrodesoxyinositol II, m. p. 185–186° (dec.), in a yield of 83% of the theoretical.

(7) **Monoacetyl-diacetone-nitrodesoxyinositol** II.—This was obtained by acetylating 0.5 g. of diacetone-nitrodesoxyinositol II in a mixture of 2 cc. of pyridine and 2 cc. of acetic anhydride and keeping the reaction mixture at room temperature for two hours, then evaporating the solvents *in vacuo* and crystallizing the residue twice from ethanol; m. p. 226°; yield about 87% of the theoretical. *Anal.* Calcd. for $C_{14}H_{21}O_8N$ (331): C, 50.7; H, 6.35; N, 4.23; acetone, 35.0. Found: C, 50.6; H, 6.35; N, 4.24; acetone, 34.9.

(8) **Diacetone-aminodesoxyinositol** II ***p*-Toluenesulfonate**.—An amount of 0.929 g. of diacetone-nitrodesoxyinositol II was dissolved in 25 cc. of 1,4-dioxane and reduced with hydrogen at 28° and 756 mm. pressure in the presence of 1 g. of freshly prepared Raney nickel. Within the first ten minutes 210 cc. of hydrogen was absorbed and 40 cc. within the next twenty minutes (calcd. 248 cc.). The catalyst was centrifuged off, the dioxane was evaporated *in vacuo* to about 5 cc. and 20 cc. of water was added, whereupon the solution was neutralized with 0.5 *N* *p*-toluenesulfonic acid, filtered with a little charcoal and evaporated to dryness *in vacuo*. On dissolving the residue in a little cold absolute ethanol and adding about five times the amount of absolute ether, long colorless needles of the salt formed immediately in a yield of 82% of the theoretical; decomposition point 225°. *Anal.* Calcd. for $C_{19}H_{29}O_8NS$ (431): C, 52.8; H, 6.72; N, 3.25; acetone, 26.9. Found: C, 52.8; H, 6.64; N, 3.22; acetone, 26.9.

(9) **Nitrodesoxyinositol** III.—To a solution of 12.3 g. of nitrodesoxy-D-glucose in 90 cc. of water was added 30.0 cc. of 1.003 *N* sodium hydroxide. This reaction mixture was kept at room temperature until the optical rotation had disappeared (forty-eight hours), and was then acidified with 32 cc. of *N* acetic acid. After the addition of 1.030 *N* sulfuric acid the solution was evaporated to dryness *in vacuo*. The dry, crystalline residue was extracted three times with 100 cc. of absolute ethanol. On cooling the alcoholic extract, 4.0 g. of nitrodesoxyinositol III, m. p. 215° (dec.) crystallized. From the mother liquor an additional 4.1 g. of the same substance was collected on evaporation of the solvent and boiling the residue in a little dioxane. On dissolving this substance in boiling ethanol only 20% of it crystallized on cooling, m. p. 212–213° (dec.); still less was obtained on using dioxane, from which it crystallized with a m. p. of 218–219° (dec.). *Anal.* Calcd. for $C_6H_{11}O_7N$ (209): C, 34.5; H, 5.27; N, 6.70. Found: C, 34.8; H, 5.14; N, 6.84. This compound did not form acetone derivatives under standard conditions, but some diacetone-nitrodesoxyinositol II, m. p. 184–185°, was isolated on acetonation of the mother liquor residues, as under (6).

(10) **Aminodesoxyinositol** III.—An amount of 1.04 g. of nitrodesoxyinositol III was dissolved in 50 cc. of distilled water and reduced with hydrogen at 24° and 760 mm. pressure in the presence of freshly prepared Raney nickel; 265 cc. of hydrogen or 71% of the theoretical were absorbed within two and one-half hours. The

catalyst was then centrifuged off and the solution filtered with a little charcoal, and evaporated to about 10 cc. *in vacuo*, whereupon crystallization of the amine began; yield 69% of the theoretical. *Anal.* Calcd. for $C_6H_{13}O_5N$ (179): C, 40.2; H, 7.26; N, 7.82. Found: C, 40.1; H, 7.09; N, 7.74. This substance started decomposing at about 255° and melted under decomposition at 280–285°.

(11) **Pentaacetyl-nitrodesoxyinositol III.**—This was obtained by mixing 0.5 g. of nitrodesoxyinositol III with 10 cc. of acetic anhydride containing one drop of concentrated sulfuric acid and keeping the mixture at 20–22°; the nitrodesoxyinositol went quickly into solution and the pentaacetate crystallized immediately. After standing for two hours the crystals were filtered with suction and washed with water, yielding 90% of the theoretical. After crystallization from dioxane this substance melted at 258–259° (dec.). *Anal.* Calcd. for $C_{16}H_{21}O_{12}N$ (419): C, 45.7; H, 5.01; N, 3.34. Found: C, 45.7; H, 4.88; N, 3.63.

(12) **Sodium Salts of Nitrodesoxyinositols.**—These were isolated in an almost quantitative yield by dissolving 2.0 g. of nitrodesoxyinositol I or nitrodesoxyinositol II in 7 cc. of water and adding the theoretical amount of 2 *N* sodium hydroxide. Small colorless needles formed quickly; 30 cc. of ethanol was added, in portions, and the crystals were filtered with suction and washed with a little ethanol and ether. These salts could be recrystallized from water alone, or better by dissolving 1 g. in 25 cc. of warm water and adding 50 cc. of acetone in portions. *Anal.* Calcd. for $C_6H_{10}O_7NNa$ (231): Na, 9.95. Found: 9.78. From a concentrated aqueous solution of these sodium salts the barium nitrodesoxyinositols could be precipitated quantitatively by a molar solution of the calculated amount of barium chloride.

(13) **Conversion of Nitrodesoxyinositol I into Nitrodesoxyinositol II.**—To a solution of 0.010 mole (2.09 g.) of pure nitrodesoxyinositol I, as obtained under (3), in 64 cc. of water, was added 0.0050 mole of barium hydroxide dissolved in 36 cc. of water. Crystals appeared within two minutes; 2.66 g. of barium nitrodesoxyinositol was isolated after fifteen hours and 0.10 g. from the mother liquor, on addition of 200 cc. of ethanol, or a total of 99.7% of the theoretical. On treating this salt as described under (2), (5) and (6), the diacetonenitrodesoxyinositol II was isolated in a yield of 58% of the theoretical.

(14) **Conversion of Nitrodesoxyinositol II into Nitrodesoxyinositol I.**—On repeating as under (12) with nitrodesoxyinositol II, barium nitrodesoxyinositol was isolated in a nearly quantitative yield. On treating this salt as under (2), nitrodesoxyinositol I was isolated in a yield of 43% of the theoretical.

B. **Cyclization of 6-Nitro-6-desoxy-L-idose.**—(15) To a solution of 9.2 g. of nitrodesoxy-D-idose[2] in 100 cc. of water was added 188 cc. of 0.235 *N* barium hydroxide. The solution was kept at room temperature for sixteen hours, during which time only a very small precipitate formed.[10] On addition, in portions, of 700 cc. of ethanol, 8.5 g. or 70% of the theoretical of finely precipitated barium nitrodesoxyinositol was obtained. On eliminating the barium, as described under (2), a mixture of nitrodesoxyinositols was obtained in a yield of 83% of the theoretical. From this mixture identical compounds were isolated as described under (2)–(8).

(16) **Change of the Optical Rotation during Cyclization.**—This was observed on the following solutions—Solution A: 104.5 mg. crystalline nitrodesoxy-D-glucose, m. p. 156°, dissolved in 5.0 cc. of 0.126 *N* sodium hydroxide. **Solution B**: 2.50 cc. of an 0.20 molar solution of the same sample of nitrodesoxy-D-glucose, prepared twenty hours in advance and made alkaline with 2.50 cc. of 0.252 *N* sodium hydroxide. **Solution C**: 68.7 mg. of crystalline nitrodesoxy-D-glucose dissolved in 0.4 *N* sodium hydroxide. **Solution D**: 5.00 cc. of a solution of nitrodesoxy-L-idose, prepared by deacetonation of 3.563 g. of diacetone-6-nitro-6-desoxy-L-idose with 8.00 cc. of *N* sulfuric acid, as described previously (2), made up to 100.0 cc., made alkaline with 1.00 cc. of 1.20 *N* sodium hydroxide. The following changes in rotation were observed:

TABLE II

Time	Soln. A. $[\alpha]^{24}D$	Soln. B. $[\alpha]^{24}D$	Soln. C. $[\alpha]^{25}D$	Soln. D. $[\alpha]^{25}D$
Before addition of NaOH	(+45.5)	+36.4	(+44.3)	−27.3
After addition of NaOH				
2 minutes	+56.1	....	+57.8	−60.7
3 minutes	+56.3	+56.3	....	....
4 minutes	+56.8	+56.8	....	....
5 minutes	+56.1	+56.3	+49.8	−56.3
6 minutes	+55.5	+56.0	....	....
7 minutes	+54.7	....	....	....
8 minutes	+53.5	+54.7	....	....
9 minutes	+52.5	....	....	....
10 minutes	....	+53.0	+44.1	−50.7
11 minutes	+51.3	....	....	....
15 minutes	+49.0	+48.5	....	....
20 minutes	....	+45.4	+36.8	−44.6
25 minutes	+40.6	+40.6	....	....
48 minutes	+27.9	....	....	....
50 minutes	....	+25.2	....	....
60 minutes	....	....	....	−19.7
1.5 hours	....	....	+11.6	−14.2
2 hours	+10.1	+10.3	....	....
2.5 hours	+ 2.9	+ 2.5	0	− 8.8
3 hours	+ 1.2	+ 1.2		....
3.5 hours	0	0		....
5.5 hours				− 3.9
8 hours				0

C. **Cyclization Products Obtained from "Mixture A."**[11]—(17) An amount of 50 g. of "Mixture A" was dissolved in 300 cc. of 0.1 *N* sulfuric acid and kept for about seventy-five minutes at 75–80°. The warm solution was then freed from the sulfuric acid by addition of the exact amount of barium acetate; the precipitate was centrifuged off and the solution was concentrated to dryness *in vacuo*. The residue was dissolved in 100 cc. of water and 2100 cc. of 0.1 *N* barium hydroxide was added. Crystallization of barium nitrodesoxyinositols started within a few hours and the optical activity of the supernatant solution disappeared after twenty hours. The solution was acidified with glacial acetic acid and stirred until all crystals had dissolved. On processing this solution, as described under (2), a crystalline mass was obtained from which 25 g. of nitrodesoxyinositol I (50% of the theoretical) was obtained on crystallization from dioxane, and 18 g. of diacetone nitrodesoxyinositol II (31% of the theoretical) was obtained on acetonation of the dioxane soluble material, as described under (5) and (6).

D. **Aromatization of the Nitrodesoxyinositols.**—(18) Acetylation of any of the foregoing nitrodesoxyinositols by dissolving 0.5 g. of these substances in a mixture of 2 cc. of pyridine and 2 cc. of acetic anhydride and warming the solution to 70° for one minute, then evaporating the solvents *in vacuo* and crystallizing the residue twice from ethanol, gave **diacetyl-5-nitroresorcinol**, m. p. 105°, in an almost quantitative yield. *Anal.* Calcd. for $C_{16}H_9O_6N$

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(10) The failure of the barium salts to precipitate directly from the aqueous solution, as in the case of the cyclization of the 6-nitro-6-desoxy-D-glucose, may be due to the fact that the starting material was amorphous and perhaps less pure. This is also indicated by the considerably lower yield in which the mixture of nitrodesoxyinositols was obtained.

(11) This "mixture A" represents the crude mixture of 1,2-acetone-6-nitro-6-desoxy-D-glucose and 1,2-acetone-6-nitro-6-desoxy-L-idose as described in our preceding publication.[2]

(239): C, 50.2; H, 3.76; N, 5.85; CH_3CO-, 36.0. Found: C, 50.1; H, 3.72; N, 5.81; CH_3CO-, 36.9. Propionylation of the nitroinositols gave in a similar manner, **the dipropionyl-5-nitroresorcinol**, m. p. 115°, from 70% ethanol. *Anal.* Calcd. for $C_{12}H_{13}O_6N$ (267): C, 53.9; H, 4.86; N, 5.24. Found: C, 53.7; H, 4.90; N, 5.20. On hydrolysis of the two above substances with 50% alcoholic 0.5 *N* potassium hydroxide, the known 5-nitro resorcinol, m. p. 157–159°, was isolated in the usual manner and gave, on methylation, the known 3,5-methoxynitrobenzene, m. p. 89.5°.

On dissolving 0.5 g. of pentaacetyl-nitrodesoxyinositol III, as described under (11), in 5 cc. of hot pyridine, it was transformed almost quantitatively into diacetyl-5-nitroresorcinol.

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Summary

The cyclization of 6-nitro-6-desoxy-D-glucose and 6-nitro-6-desoxy-L-idose to a mixture of nitrodesoxyinositols is described. Starting from either of the nitrodesoxy hexoses, the same mixture of nitrodesoxyinositols was obtained. A reaction mechanism for the cyclization is proposed.

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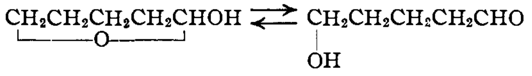
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Hydroxylation of 2,3-Dihydropyran and the Application of Desoxyaldopentoses in the Browning Reaction[1]

BY CHARLES D. HURD AND CHARLES D. KELSO

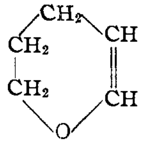
The reaction of reducing sugars with amino acids, leading to the evolution of carbon dioxide and the development of an intense brown color was studied by Maillard.[2] This general subject of the "browning reaction" has been one of considerable interest in recent years, since it seems to be intimately associated with the color changes observed in many foodstuffs during processing or storage.

To extend our knowledge of the fundamentals of this reaction, two model aldoses were synthesized for test purposes. One was tetrahydropyran-2-ol, made by hydration of dihydropyran (I), following the directions[3] of Schniepp and Geller. This is stated to exist in equilibrium (95:5) with 5-hydroxypentanal

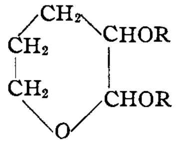


$$\underbrace{CH_2CH_2CH_2CH_2CHOH}_{O} \rightleftarrows \underset{\overset{|}{OH}}{CH_2}CH_2CH_2CH_2CHO$$

This material may be regarded as a 2,3,4-tridesoxyaldopentose. The substance is similar to

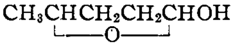


I



II (R = H)
III (R = Ac)

4-hydroxypentanal, $CH_2CHOHCH_2CH_2CHO$, which was synthesized by Helferich[4] and shown to exist primarily in the cyclic modification



$$\underbrace{CH_3CHCH_2CH_2CHOH}_{O}$$

The second model sugar was tetrahydropyran-2,3-diol (II). This substance is new. It may be regarded as a 3,4-didesoxyaldopentose, thereby providing an aldose molecule with inert beta and gamma positions. In solution the cyclic alpha and beta forms of II should be in equilibrium with the open-chain structure, $HOCH_2CH_2CH_2CHOH$-CHO, just as the alpha and beta forms of a glycose are in equilibrium with the glyconaldehyde.

Synthesis of II was readily accomplished from I by use of hydrogen peroxide in *t*-butyl alcohol using osmium tetroxide as catalyst. This follows the type of synthesis devised by Milas and co-workers[5] for such syntheses as these: isobutylene glycol from isobutylene, ethylene glycol from ethylene, racemic acid from fumaric acid, glycerol from allyl alcohol, glycolaldehyde from vinyl acetate or vinyl ether, etc. Glycals, according to Hockett and co-workers,[6] behave analogously.

Although hydroxylation of double bonds by hydrogen peroxide ordinarily produces *cis* glycols,[5] it seems reasonable to think that both *cis* and *trans* hydroxyls are present in II because of the equilibration reaction mentioned above. Besides II, the reaction product also contained a considerable C_{10}-fraction revealing both non-reducing and reducing isomers. The non-reducing compound was shown to be 3,4-didesoxyaldopentosyl 3,4-didesoxyaldopentoside (IV). Products II and IV accounted for half of the I used. An additional 10–15% was accounted for by reducing disaccharide and 6% by a fraction, some of which is reducing, which may contain trisaccharide.

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(2) Maillard, *Compt. rend.*, **154**, 66 (1912); *Ann. chim.*, [9] **5**, 258 (1916).

(3) Schniepp and Geller, THIS JOURNAL, **68**, 1646 (1946).

(4) Helferich, *Ber.*, **52**, 1128, 1802 (1919).

(5) Milas and Sussman, THIS JOURNAL, **58**, 1302 (1936); **59**, 2345 (1937); Milas, Sussman and Mason, *ibid.*, **61**, 1844 (1939); Milas and Maloney, *ibid.*, **62**, 1842 (1940).

(6) Hockett, Sapp and Millman, *ibid.*, **63**, 2051 (1941); Hockett and Millman, *ibid.*, **63**, 2587 (1941).