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Action of the Reagent Pyridine–Acetic Anhydride on *d*-α-Glucoheptose, *d*-Glucosamine and *l*-Fucose Oximes

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The action of pyridine–acetic anhydride on aldose oximes was studied first by Behrend[1] with glucose oxime. He obtained an oxime hexaacetate at low temperature and the *d*-gluconononitrile pentaacetate at a higher temperature. Wolfrom and Thompson[2] showed that Behrend's acetylated glucose oxime was a cyclic form and that another isomer could be obtained when working with Wohl's method. This isomer was an open-chain or *aldehydo*-glucose oxime hexaacetate and was an intermediate in the formation of the acetylated nitrile.

Deulofeu, Wolfrom and co-workers[3] subjected galactose oxime to the action of pyridine–acetic anhydride at low temperature and obtained a mixture of *aldehydo*-galactose oxime hexaacetate, galactononitrile pentaacetate and cyclic galactose oxime hexaacetate. This work showed that galactose oxime reacted in the open-chain form to give the first two compounds and in the ring or cyclic form to give the last-named substance. Deulofeu, Cattaneo and Mendivelzúa[4] subjected a series of aldose oximes to the same reagent and found that even at very low temperatures, *l*-arabinose, *d*-xylose, *l*-rhamnose and *d*-mannose oximes reacted in the *aldehydo* structure. The first three gave the acetylated nitriles. Above 30° mannose oxime gave the acetylated nitrile but below that temperature *aldehydo*-mannose oxime hexaacetate was obtained. Similar results were obtained by Wolfrom and Georges[5] with mannose oxime. The application of the method to cellobiose oxime by Wolfrom and Soltzberg[6] and to *d*-α-galaheptose oxime by Hann and Hudson[7] gave n both cases the acetylated open-chain form.

We have studied now the behavior of three other aldose oximes, *viz.*, *d*-glucosamine oxime, *d*-α-glucoheptose oxime and *l*-fucose oxime, when treated with pyridine–acetic anhydride. The first two always reacted in the open-chain form but only gave acetylated nitriles, even at −10°. No open-chain or cyclic acetylated oximes could be detected among the products of the reaction. A very different result was obtained with *l*-fucose oxime. At −10°, there was obtained an oxime pentaacetate, melting at 116°, which was identical with the compound isolated by Votoček[8] on preparing *l*-fuconononitrile tetraacetate by Wohl's method. A sample of this substance, which gave no nitrile reaction, was found to have a rotatory power of +44.9° (*l*-series).[9] This is a cyclic compound because on fusion or on treatment with acetic anhydride and sodium acetate, it does not change to a nitrile. Its rotatory power is also of the same order as that of the closely related derivative of galactose oxime, which rotates −27.5° (*d*-series). At higher temperatures, part of the oxime reacted in the open-chain form and *l*-fuconononitrile tetraacetate was easily isolated and was finally the main product. The acetylated nitrile rotated at −22.4°, a value lower than that established for *d*-galactononitrile pentaacetate (+43.2°). The sign of the rotation was in agreement with the rule formulated by Deulofeu[10] that when the acetoyl group on carbon two is on the left in the projection formula the rotation is in the *levo* direction.

It is a very difficult matter to correlate the results obtained with the different oximes. Hann and Hudson[7] have pointed out that there is a similarity between the stereochemical constitution of *d*-mannose and *d*-α-galaheptose, and the reaction of their oximes with pyridine and acetic anhydride. It is evident that according to the structure of the sugar, its oxime tends to react at low temperatures in a cyclic form (*d*-glucose); in the *aldehydo* structure (*l*-arabinose, *d*-xylose, *l*-rhamnose, *d*-α-galaheptose, *d*-α-glucoheptose and *d*-glucosamine); or in a mixed form (*d*-galactose and *l*-fucose). When reacting in the open-chain form, the acetylated nitrile or the acetylated

(1) R. Behrend, *Ann.*, **359**, 109 (1907).

(2) M. L. Wolfrom and A. Thompson, THIS JOURNAL, **53**, 622 (1931).

(3) V. Deulofeu, M. L. Wolfrom, P. Cattaneo, C. C. Christman and L. W. Georges, *ibid.*, **55**, 3488 (1933).

(4) V. Deulofeu, P. Cattaneo and G. Mendivelzúa, *J. Chem. Soc.*, 147 (1934).

(5) M. L. Wolfrom and L. W. Georges, THIS JOURNAL, **58**, 1781 (1936).

(6) M. L. Wolfrom and S. Soltzberg, *ibid.*, **58**, 1783 (1936).

(7) R. M. Hann and C. S. Hudson, *ibid.*, **59**, 1898 (1937).

(8) E. Votoček, *Ber.*, **50**, 37 (1917).

(9) All rotations are specific rotations measured in chloroform solution at room temperature.

(10) V. Deulofeu, *Nature*, **131**, 548 (1933).

aldehydo oxime can be obtained as products. If we apply to the oximes of the aldoses the known information concerning the reactivity of aldoximes, then the formation of the acetylated nitrile or of the acetylated *aldehydo* oxime must be determined by preferential existence of *syn* or *anti* forms of the oxime, the first stabilizing as the oxime acetate. If we consider only the low temperature reaction, we find that *l*-rhamnose, *d*-mannose, *d*-α-glucoheptose and *d*-α-galaheptose oximes react in the open-chain form and are configurationally related in part, as their first three hydroxyl groups have the same spatial configuration. From their mutarotation, it has always been accepted that the aldose oximes have, at least in part, a cyclic structure, but it is evident that the oxygen rings must open easily under the action of the reagents.

l-Fucose and *d*-galactose are closely related in their configuration and their oximes react in the same manner to give derivatives of both the cyclic and open-chain forms. It must be noted that the acetate of the *aldehydo*-fucose oxime is unstable as only the acetylated nitrile can be isolated. On the other hand, *aldehydo*-galactose oxime hexaacetate can be obtained. Another difference is that, with fucose, the cyclic form predominates at low temperatures, while with galactose, the open-chain form predominates. The elimination of the fifth carbon atom of galactose, as in arabinose, determines an exclusive reaction in the open-chain form.

It is more difficult to relate the remaining oximes. Their different manner of reacting is a proof of the sensibility of the path of the reaction to the spatial constitution of the aldose. Glucose reacts at 0° exclusively in the cyclic form and the oxime hexaacetate is obtained, but the introduction of a glucose residue on the fourth carbon atom, as in cellobiose, or the transformation of the first hydroxyl into an amino group, as in glucosamine, or the elimination of the fifth carbon atom, as in xylose, determines that the reaction takes place exclusively in the *aldehydo* form.

Experimental

d-α-Glucoheptose Oxime.—*d*-α-Glucoheptose (1 g.) prepared by reduction of *d*-α-glucoheptonolactone,[11] was dissolved in 1 cc. of water and added to 10 cc. of alcoholic hydroxylamine solution prepared according to Wohl and List.[12] As no crystalline oxime separated spontaneously, the solution was concentrated under reduced pressure (20°) and a sirup was obtained that could not be induced to crystallize by drying with alcohol or by standing over sulfuric acid in a vacuum. A semi-crystalline solid was the best material obtained and this could not be purified by employing different solvents. The solid material could be used with success for the preparation of the acetylated nitrile.

d-α-Glucoheptononitrile Hexaacetate.—The oxime from 1 g. of *d*-α-glucoheptose was treated with a mixture (1:1) of 10 cc. of pyridine and acetic anhydride. In the several experiments the temperature was varied from −10 to 20°. The oxime dissolved more rapidly with increasing temperature of reaction. The solution was evaporated in a desiccator over sulfuric acid and potassium hydroxide, and crystals began to appear that when dried melted at 110–112° without purification. Pure material was obtained on recrystallization from alcohol; yield 1.5 g. (69%, basis *d*-α-glucoheptose), m. p. 113–114°, spec. rot. +24.1 (20°, D-line, $CHCl_3$). Zemplén and Kiss[13] record the constants: m. p. 112.5–113.5°, spec. rot. +24.6° (D-line, $CHCl_3$).

d-Glucosamine Oxime Hydrochloride.—Although this compound has been prepared by Winterstein,[14] the following method gave better yields. An alcoholic solution of hydroxylamine was prepared by dissolving 15 g. of hydroxylamine hydrochloride in 8 cc. of water, adding 15 g. of sodium dissolved in 100 cc. of absolute ethanol, filtering the precipitated sodium chloride and washing with 20 cc. of absolute ethanol (washings combined with filtrate). Glucosamine hydrochloride (20 g.), dissolved in the minimum quantity of warm water, was added to the above solution and, after twenty-four hours of standing, crystallization was initiated by seeding; yield 15 g. (70%), m. p. 166°. Impure crystals could be recovered from the mother liquor.

d-Glucosaminonitrile Pentaacetate.—Glucosamine oxime hydrochloride (1 g.) was treated with 12 cc. of the pyridine–acetic anhydride (1:1) mixture. In the several experiments the temperature was varied from −10 to 20°. After solution of the oxime, the reaction mixture was concentrated in a desiccator at 20° and crystals separated; m. p. 120°. Long prisms were obtained on recrystallization from alcohol; yield 1.8 g., m. p. 126°, spec. rot. +20.5° (20°, D-line, *c* 4.7, $CHCl_3$, 2-dm.). Neuberg and Wolff,[15] who prepared this substance by Wohl's method, recorded the melting point of 118–119° but gave no rotation.

Anal. Calcd. for $C_{16}H_{22}O_9N_2$: N, 7.25. Found: N, 7.25.

Mild Acetylation of *l*-Fucose Oxime.—*l*-Fucose oxime was prepared according to Votoček,[8] who recorded the melting point 188–189°; yield 1.8 g. from 2 g. of fucose, m. p. 185°. For the acetylation, lots of 0.5 g. of *l*-fucose oxime were treated with 5 cc. of the pyridine–acetic anhydride (1:1) mixture at the temperatures indicated in Table I. The solution obtained was concentrated under reduced pressure at room temperature. Concentration was continued for a short time after the appear-

(11) L. H. Philippe, *Ann. chim. phys.*, [8] **26**, 316 (1912).
(12) A. Wohl and E. List, *Ber.*, **30**, 3101 (1897).
(13) G. Zemplén and D. Kiss, *ibid.*, **60**, 165 (1927).
(14) E. Winterstein, *ibid.*, **29**, 1392 (1896).
(15) C. Neuberg and H. Wolff, *ibid.*, **35**, 4017 (1902).

ance of crystals, after which these were removed by filtration. These were crystals of *l*-fucononitrile tetraacetate; m. p. 176–177°. On further concentration, material was obtained which began to melt at about 115° and was a difficulty separable mixture of the cyclic-*l*-fucose oxime pentaacetate and the acetylated nitrile. Acetylation at −10° did not give crystals melting at 176°, but the nitrile was always present as the material isolated gave a faint nitrile reaction. Table I records the results of several experiments operated at different temperatures.

TABLE I

MILD ACETYLATION OF *l*-FUCOSE OXIME (0.5 G.) AT VARIOUS TEMPERATURES

Temp., °C.		−10	3	15	37	100
Wt., g., m. p.	115°	0.8	0.62	0.5	0.5	0.30
Wt., g., m. p.	176°	..	.12	.32	.36	.48

l-Fucononitrile Tetraacetate.—The material from several of the preparations described above was combined and recrystallized from alcohol, from which it was obtained as rectangular plates; m. p. 177°, sp. rot. −22.4° (20°, D-line, *c* 5.0, $CHCl_3$, 2-dm.).

l-Fucose Oxime Pentaacetate.—The product obtained by acetylation at −10° as described above, gave the nitrile test. Crystallization from alcohol did not separate the nitrile and the method of Deulofeu, Wolfrom and coworkers[3] for the purification of galactose oxime hexaacetate was employed. The crude preparation (1.5 g.) was recrystallized once from alcohol and this material was then boiled with 500 cc. of water, a portion dissolving. The mixture was cooled to 5°, maintained at this temperature for one hour, filtered and the filtrate extracted with chloroform. The crystalline material (plates) obtained on chloroform removal and recrystallization from alcohol gave a negative nitrile reaction; m. p. 116° (unchanged on further recrystallization), spec. rot. +44.9° (25°, D-line, *c* 3.35, $CHCl_3$, 1.894-dm.).

The acetylated oxime on heating at 135° for five minutes gave a sirup that crystallized on the addition of alcohol. The crystals melted at 115–116° and were the original substance. Unchanged material (m. p. 116°) also was returned on refluxing for fifteen minutes with acetic anhydride and sodium acetate.

Summary

1. A study has been made of the action of the reagent pyridine–acetic anhydride on the oximes of *d*-α-glucoheptose, *d*-glucosamine hydrochloride and *l*-fucose.

2. *d*-α-Glucoheptose oxime and *d*-glucosamine oxime react in an open-chain form to give the acetylated nitriles, even at low temperatures.

3. *l*-Fucose oxime reacts at low temperature in a cyclic form and cyclic-*l*-fucose oxime pentaacetate predominates among the substances obtained. At higher temperatures one part reacts in an open-chain form and *l*-fucononitrile tetraacetate is produced and predominates at 100°.

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Studies in the Thiamorpholine Series. II. N-Alkyl Substituted Derivatives

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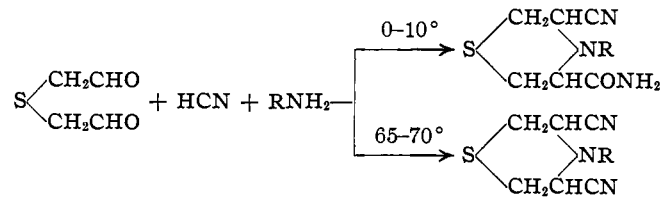
In the first paper of this series was described the reaction between thiodiacetaldehyde, hydrocyanic acid and ammonia to produce the half-amide, half-nitrile of thiamorpholine 3,5-dicarboxylic acid. The use of the Strecker reaction in this fashion for ring-closure in the thiamorpholine series has now been extended by using various aliphatic amines in place of the ammonia.

During the course of a study of the original synthesis in order to determine better reaction conditions, it was found that by allowing the reaction to proceed at temperatures of 65–70° instead of 0°, the dinitrile of the acid was obtained rather than the nitriloamide. This situation was also found to hold when methyl- or ethylamine was substituted for the ammonia, the dinitriles being formed at the elevated temperatures. These reactions can be expressed by the equations



In the cases of other amines, benzylamine formed only the dinitrile, while *n*-butyl-, *n*-amyl-, isoamyl- and *n*-heptylamine produced the nitriloamides. To date it has not been found possible to cause either reaction to take place with aniline.

Attempts have been made to hydrolyze these compound products to the corresponding N-alkyl

(1) This paper is constructed from the Dissertations of Helen I. Miner and Edwin O. Hook which were submitted in candidacy for the degree of Doctor of Philosophy at Yale University, June, 1939.

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