[Contribution from the Laboratorio de Química Orgánica, Facultad de Ciencias Exactas, Físicas, y Naturales, and the Instituto de Fisiología, Facultad de Ciencías Médicas]

THE PREPARATION AND DEGRADATION OF SOME PROPIONYLATED NITRILES OF ALDONIC ACIDS

VENANCIO DEULOFEU and FRANCISCO GIMÉNEZ

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The degradation of the acetylated or benzoylated nitriles of aldonic acids, the only acylated types known to date, by application of the Wohl reaction, was considered to give in all cases the diacetamide or dibenzamide derivatives of the lower aldose sugar, until Hockett and Chandler (1), treating hexaacetyl-D-gluco-D-*gulo*-heptonic acid nitrile with 29% aqueous ammonia, obtained as the only degradation product N-acetyl-D-glucofuranosylamine.

The formation of the "diamide" derivatives was always expected and it is not surprising that, when Brigl and co-workers (2) in 1931 by the degradation of hexabenzoyl-D-manno-D-*gala*-heptonic acid nitrile, isolated D-mannose dibenzamide and a small amount of D-mannose benzamide, they announced without further proof that this substance was a secondary reaction product, formed from the original D-mannose dibenzamide, — a possibility that requires experimental confirmation. Hexaacety-D-manno-D-*gala*-heptonic acid nitrile gave instead only D-mannose diacetamide.

Although N-acetyl-D-glucofuranosyl amine has been obtained by Niemann and Hays (3) by the direct action of ammonia on pentaacetyl-D-glucose, a circumstance that shows how complicated is the interpretation of its formation in the Wohl reaction, it is evident that in the case of the two acetylated heptonic nitriles so far employed, whatever the details of the mechanism that favors the production of the monoacetamide compound, the change in the configuration of the aldose has determined an important difference in the type of the reaction product obtained.

Isbell and Frush (4) have proposed an interpretation of the mechanism of the Wohl reaction based on the formation of intermediate cyclic orthoesters of acetic acids, an interpretation that has received experimental support from the work of Hockett, Deulofeu, and Defarreri (5) who employed labelled ammonia (N^{15}) to ascertain the origin of the acetamide that combines with the newly formed aldose molecule. The Isbell and Frush interpretation allows for the formation of diacetamide or monoacetamide compounds.

To determine the influence of the acylating radical on the reaction, we have begun in our laboratory the preparation of nitriles of aldonic acids acylated with different radicals. Some benzoylated nitriles have been prepared (6) and, although by treatment with ammonia the dibenzamide derivatives of the lower sugars were always obtained, it was found that when a primary alcoholic hydroxyl is benzoylated the benzoyl group is retained through the degradation and appears in the dibenzamide compounds.

In this paper we present data on the preparation and degradation of some propionylated nitriles of aldonic acids. Propionic acid derivatives were selected because of the availability of propionic anhydride and the hope that if they could not be crystallized easily, distillation could be applied as a method of purification (7).

It is well known that when aldose oximes are treated at low temperatures with a mixture of pyridine-acetic anhydride the type of product obtained varies with the nature of the sugar (8). In some cases acetylated cyclic or open-chain oximes are obtained, while in others the acetylated nitriles are the main or only product of the reaction. When open-chain acetylated oximes are produced, they can be transformed into nitriles by simple heating.

By employing a mixture of pyridine-propionic anhydride this reaction has been applied to the preparation of the propionylated nitriles.

From L-rhamnose oxime a crystalline *aldo*-pentapropionyl-L-rhamnose oxime was obtained in high yield, showing that the free oxime reacts almost quantitatively in the open-chain form under the conditions applied for propionylation. By heating, propionic acid was lost, and the oxime transformed into tetrapropionyl-L-rhamnonic acid nitrile.

The other oximes studied gave, even when treated with the reagent at low temperatures, syrups that did not crystallize. It was then decided to treat them with the mixture of pyridine-propionic anhydride at 100°. The impure nitriles obtained were in all cases purified by molecular-distillation at 0.001 mm. Previous heating transformed all the open-chain propionylated oximes that could be present in the reacting syrup into nitriles.

Pentapropionyl-D-gluconic acid nitrile, pentapropionyl-D-galactonic acid nitrile, and tetrapropionyl-L-rhamnonic acid nitrile were obtained as crystalline solids. The pentapropionyl-D-mannonic acid nitrile always remained a syrup.

Pentapropionyl-D-gluconic acid nitrile and pentapropionyl-D-galactonic acid nitrile when submitted to a classical Wohl degradation gave what can be considered the normal degradation products: D-arabinose dipropionamide and D-lyxose dipropionamide. Degradation of the pentapropionyl-D-gluconic acid nitrile by the Zemplén method gave D-arabinose. This nitrile when treated with hydrobromic acid in acetic acid solution yielded pentaacetyl-D-gluconic acid amide.

As shown in Table I certain regularities emerge when the rotatory power of the propionyl aldonic acid nitriles and their degradation products are compared with the corresponding acetylated compounds. Those regularities are not of a general character.

In the case of the first three nitriles noted in Table I, there is a constant difference between the rotatory powers of the acetyl and propionyl derivatives. This constancy disappears in the case of L-rhamnonic acid nitrile. With the first two nitriles the molecular rotatory power is almost the same, larger differences being encountered with the last two.

The molecular rotatory powers are practically identical in the case of the diacetamide and dipropionamide derivatives of D-arabinose and D-lyxose. It is remarkable that this identity of value of the molecular rotatory power is retained when the D-arabinose diacetamide and dipropionamide are acetylated, and the solvent for the determination is changed from water to chloroform.

NOTE ON THE MOLECULAR-DISTILLATION OF ACYLATED ALDONIC NITRILES

Molecular-distillation has been employed by Hurd and co-workers (7) for the separation and purification of propionyl derivatives of the sugars. We have found it very useful for the purification of propionylated aldonic nitriles as described in the experimental part. A still of the Washburn type (9) was employed for the distillation of solid nitriles and a horizontal-flask molecular still similar to that described by Morton (10) for the syrups.

TABLE I

ROTATORY AND MOLECULAR ROTATORY POWER OF ACETYLATED AND PROPIONYLATED ALDONIC ACID NITRILES AND THEIR DEGRADATION PRODUCTS

SUBSTANCE	$[\alpha]_D^{\circ}$	Δ°	$[M]_D^{\circ}/100$	Δ°
Pentaacetyl-D-gluconic acid nitrile	+47.8		+177.3	
Pentapropionyl-D-gluconic acid nitrile	+40.1	+7.7	+183.2	−5.9
Pentaacetyl-D-galactonic acid nitrile	+43.2		+160.3	
Pentapropionyl-D-galactonic acid nitrile	+36.7	+6.5	+167.7	−7.4
Pentaacetyl-D-mannonic acid nitrile	−1.8		−6.7	
Pentapropionyl-D-mannonic acid nitrile	+5.7	−7.5	−25.5	−33.0
Tetraacetyl-L-rhamnonic acid nitrile	−4.0		−14.8	
Tetrapropionyl-L-rhamnonic acid nitrile	−6.0	+2.0	−27.4	−12.6
D-Arabinose diacetamide	−9.5		−23.7	
D-Arabinose dipropionamide	−9.8	+0.3	−27.2	+3.5
Tetraacetyl-D-arabinose diacetamide	+72.5		+303.0	
Tetraacetyl-D-arabinose dipropionamide	−67.7	+4.8	+301.9	+1.1
D-Lyxose diacetamide	−9.2		−23.0	
D-Lyxose dipropionamide	−8.5	+0.7	−23.4	+0.4

When pure acetylated nitriles of aldonic acids were submitted to molecular-distillation they sublimed without passing into the liquid state, and at temperatures lower than the melting point a solid began to collect in the condenser.

The following acetylated nitriles were sublimed at 0.001 mm; the temperature in parentheses is the temperature of the outside bath: D-arabonic, m.p. 119° (85–100°): L-rhamnonic, m.p. 65° (50–55°); D-xylonic, m.p. 81° (70°); D-gluconic, m.p. 83° (70°); D-galactonic, m.p. 137° (110°); D-mannonic, m.p. 93° (70–85°).

Benzoylated nitriles (6) required higher temperatures for distillation, and decomposition took place. As an example pentabenzoyl-D-gluconic acid nitrile, m.p. 117°, could be distilled only above 200° (0.001 mm) and the collected solid melted at 65° and had a yellow tinge. After two recrystallizations from methanol the melting point of the pure nitrile was again obtained.

Separation of a mixture of an acetylated and a benzoylated nitrile can be realized by heating at the temperature of sublimation of the acetylated nitrile. By heating at 110–120° (0.001 mm) a 1:1 mixture of pentaacetyl-D-galactonic acid nitrile and pentabenzoyl-D-galactonic acid nitrile, the acetylated nitrile was collected in the sublimate and purified by a second sublimation (m.p. 137°); the benzoylated nitrile remained in the residue (m.p. 144°).

EXPERIMENTAL

Pentapropionyl-D-gluconic acid nitriles. D-Glucose oxime (20 g.) was dissolved in 100 ml. of pyridine, 100 ml. of propionic anhydride was added, and the mixture was heated to 100° for one hour. It was then poured into iced-water, and a heavy oil precipitated. This oil was washed well with water, dissolved in ether, and the ether washed with sodium bicarbonate, then with water, dried, and evaporated. The residue was a syrup that was distilled at 0.001 mm. and 140–150° bath temperature; 14.1 g. of a solid, m.p. 58–60°, was collected (yield 60%). Recrystallized from ethanol, 9.7 g. of small prisms, m.p. 67–69°, was obtained. By further recrystallization the melting point 68–70° was attained. Insoluble in water and petroleum ether, very soluble in ether, chloroform, less in methanol and ethanol; $[\alpha]_D^{20}$ +40.1° in chloroform (*c*, 1.7).

Anal. Calc'd for $C_{21}H_{31}NO_{10}$: C, 55.14; H, 6,78; −CN, 5.68; Propionyl, 62.36.

Found: C, 55.62; H, 6.92; −CN, 5.63; Propionyl, 62.23.

The propionyl groups were determined according to Gerzenstein (11).

D-*Arabinose dipropionamide.* Pentapropionyl-D-gluconic acid nitrile (5 g.) was dissolved in 25 ml. of ethanol and 35 ml. of ammonia water (28–29%) containing silver oxide (from 2.5 g. of silver nitrate) was added. After 48 hours the precipitated silver cyanide was filtered and the filtrate evaporated in a vacuum. The residue was a syrup that solidified on addition of a small amount of water. It was then dissolved in 250 ml. of water, the silver eliminated with hydrogen sulfide, and the filtered solution decolorized with Norit and evaporated to dryness. The residue crystallized on the addition of a small amount of ethanol and 1 g. of D-arabinose dipropionamide (yield 33%), m.p. 168–170°, was collected. Recrystallized from ethanol, fine needles, m.p. 177–178°, were obtained. The compound has a low solubility in methanol and ethanol and is insoluble in ether and chloroform. It is soluble in water but less so than the corresponding diacetamide compounds. $[\alpha]_D^{22}$ −9.8° in water (*c*, 0.76).

Anal. Calc'd for $C_{11}H_{22}N_2O_6$: C, 47.48; H, 7.91; N, 10.07.

Found: C, 47.18; H, 8.09; N, 9.95.

D-Arabinose dipropionamide was also obtained, but with a lower yield, by treating 5 g. of the nitrile with 50 ml. of conc'd ammonia, and heating to dryness in a boiling-water bath (12). The reaction seems less rapid than with acetylated nitriles; 0.76 g. (yield 25%) of crude D-arabinose dipropionamide was obtained. After recrystallization the melting point 175–177° was attained.

Tetraacetyl-D-arabinose dipropionamide. D-Arabinose dipropionamide (0.58 g.) was treated with 7 ml. of pyridine and 7 ml. of acetic anhydride was added; the mixture was heated to solution and left overnight at room temperature. The solution was then evaporated at 30° and the residue crystallized first from chloroform-petroleum ether and then from ethanol to give long prisms, m.p. 171–172°; soluble in chloroform, less soluble in ether and in water, insoluble in petroleum ether. $[\alpha]_D^{22}$ +67.7° in chloroform (*c*, 0.72).

Anal. Calc'd for $C_{19}H_{30}N_2O_2$: C, 51.11; H, 6.72; N, 6.27.

Found: C, 51.42; H, 6.95; N, 6.07.

Degradation of pentapropionyl-D-gluconic acid nitrile according to Zemplén. Pentapropionyl-D-gluconic acid nitrile (5 g.) was dissolved in 7 ml. of chloroform and cooled to −5°. A solution of 0.84 g. of sodium in 10 ml. of absolute methanol was added, and by shaking, a jelled mass was produced. After five minutes, 14 ml. of water and 2.5 ml. of acetic acid were added, and the aqueous solution was separated from the chloroform and evaporated in a vacuum at 70–80°. Absolute ethanol (20 ml.) was added; the residue almost dissolved and it was evaporated again. The new residue was brought to 26 ml. with water. From 13 ml. of the solution, 0.97 g. of D-arabinose diphenylhydrazone, m.p. 204°, was obtained in the usual way, corresponding to a total yield of 0.88 g. of D-arabinose (54%).

*Pentapropionyl-*D*-gluconic amide.* The nitrile (2 g.) was dissolved in 10 ml. of glacial acetic acid saturated with hydrobromic acid. After five hours the solution was poured into iced-water, no precipitate being formed. The solution was then extracted with chloroform, the chloroform washed with sodium carbonate solution and water, dried, and evaporated. The resulting syrup crystallized on standing for some days in a desiccator. Recrystallized from ether-petroleum ether, long needles, m.p. 67–69°, were obtained. Mixed with the original nitrile (m.p. 68–70°), the m.p. 56–69°, was obtained. $[\alpha]_D^{20}+20.7°$ in chloroform (*c*, 0.85).

Anal. Calc'd for $C_{21}H_{33}NO_{11}$: C, 53.05; H, 6.94.
Found: C, 53.32; H, 7.12.

*Pentapropionyl-*D*-galactonic nitrile.* D-Galactose oxime (6 g.) was dissolved in 30 ml. of pyridine and 30 ml. of propionic anhydride was added. The solution was heated at 100° for one hour and poured into iced-water. A syrup precipitated that was washed well with water, dissolved in ether, the ether washed with sodium bicarbonate solution and water, dried, and evaporated. The resulting syrup was evaporated at 0.001 mm. (bath temperature 110°). An oil distilled that crystallized easily; 9.5 g. (yield 65%) of a substance, m.p. 48–50°, was collected and was purified by recrystallization from *n*-butanol. Large prisms, m.p. 60–61°, were obtained. Insoluble in water, soluble in chloroform, ether, benzene, toluene, methanol, and ethanol. $[\alpha]_D^{22}+36.7°$ in chloroform (*c*, 0.83).

Anal. Calc'd for $C_{21}H_{31}NO_{10}$: C, 55.14; H, 6.78; N, 3.06; –CN, 5.68.
Found: C, 55.70; H, 7.01; N, 3.33; –CN, 5.62.

D*-Lyxose dipropionamide.* Pentapropionyl-D-galactonic acid nitrile (5 g.) was treated with ammonia-silver oxide in the same way as has been described for the pentapropionyl-D-gluconic acid nitrile. The D-lyxose dipropionamide crystallized easily. Yield, 0.91 g. (30%); m.p. 173–176°. Recrystallized from ethanol, it formed very long needles, m.p. 180–182°; $[\alpha]_D^{24}-8.5°$ in water (*c*, 1.0).

Anal. Calc'd for $C_{11}H_{22}N_2O_2$: C, 47.48; H, 7.91; N, 10.07.
Found: C, 47.69; H, 7.82; N, 10.28.

*Pentapropionyl-*D*-mannonic acid nitrile.* D-Mannose oxime (5 g.) was finely divided and suspended in 25 ml. of pyridine and 25 ml. of propionic anhydride was added. The suspension was heated at 100°; the oxime dissolved and heating was continued for one hour. The solution was then poured into iced-water. The insoluble syrup was washed with water, dissolved in ether, and the ether washed with sodium bicarbonate solution and water, dried, and evaporated. The residue was distilled at 0.001 mm. (bath temperature 100°). Yield, 5 g. (43%) of an oil which could not be induced to crystallize even by repeated distillation and separation into several fractions. Insoluble in water, very soluble in ether, chloroform, methanol, ethanol, benzene, and toluene. For analysis one of the middle fractions was employed. $[\alpha]_D^{24}+5.6°$ in chloroform (*c*, 0.13).

Anal. Calc'd for $C_{21}H_{31}NO_{10}$: C, 55.14; H, 6.78; N, 3.63; –CN, 5.68.
Found: C, 55.57; H, 6.60; N, 3.35; –CN, 5.74.

*Pentapropionyl-*D*-rhamnose oxime.* L-Rhamnose oxime (3 g.) was dissolved in 15 ml. of pyridine and 15 ml. of propionic anhydride was added slowly, keeping the temperature at 40–50°. After solution of the oxime the solution was left at room temperature 24 hours and then poured into iced-water. The oil that separated crystallized very easily on agitation. The solid was filtered, washed well with water, dried, and recrystallized from the minimum amount of petroleum ether. Yield 7.5 g. (97%) of fine needles, m.p. 47–49°. By further recrystallization from petroleum ether the m.p. 50–52° was attained. Insoluble in water, very soluble in ether, chloroform, benzene, toluene, ethanol, and methanol. $[\alpha]_D^{22}+4.0°$ in chloroform (*c*, 2.12).

Anal. Calc'd for $C_{21}H_{23}NO_{10}$: C, 54.90; H, 7.18; Propionyl, 62.09.
Found: C, 55.15; H, 7.07; Propionyl, 61.75.

Tetrapropionyl-L-rhamnonic nitrile. Pentapropionyl-L-rhamnose oxime (2 g.) was placed in a molecular-still and heated with a bath above the melting point. Propionic acid was evolved. The temperature was then slowly raised to 100° and an ordinary vacuum applied, until liberation of the acid had ceased. The remaining oil was distilled at a bath temperature of 100°, and 0.001 mm. Yield, 1.44 g. (87%) of an oil that on long standing at 5° crystallized. The crystals, m.p. 26–28°, were suspended in petroleum ether and filtered, but could not be recrystallized owing to their high solubility in all solvents employed. By adding petroleum ether to the solutions or by diluting with water, oils were always obtained from the crystals. The original crystals were then employed for analysis. $[\alpha]_D^{24}$ −6.0° in chloroform (*c*, 2.31).

Anal. Calc'd for $C_{18}H_{27}NO_8$: C, 56.10; H, 7.01; −CN, 6.75; Propionyl, 59.22.
Found: C, 55.85; H, 7.11; −CN, 6.87; Propionyl, 59.40.

SUMMARY

1. By the action of pyridine-propionic anhydride on some oximes of monosaccharides a series of propionylated nitriles of aldonic acids have been prepared.

2. The oximes employed reacted with preference in an aldo form, as shown by the high yields of nitriles obtained. L-Rhamnose oxime reacted only in the aldo form.

3. Degradation of the nitriles with ammonia-silver oxide gave the usual dipropionamide derivative of the lower sugar.

4. Molecular distillation was found to be a good method for the purification of the propionylated nitriles of aldonic acids. Acetylated nitriles can be sublimed without decomposition, but the benzoylated nitriles, while distillable, are partially decomposed.

BUENOS AIRES, ARGENTINA

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