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THE REACTION OF AMMONIA WITH SOME ACETYLATED AND BENZOYLATED MONOSACCHARIDES. II. DERIVATIVES OF D-MANNOSE

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In the first paper of this series (1) we have reported on the action of ammonia on the two epimeric pentabenzoyl-D-glucoses and on hexaacetyl-D-gluco-D-*ido*-heptonic nitrile. The former gave rise to D-glucose dibenzamide, a compound previously prepared (2) by the action of ammonia on pentabenzoyl-*aldehydo*-D-glucose and related compounds. The latter (the nitrile) yielded N-acetyl-D-glucofuranosylamine. This substance was first prepared by Hockett and Chandler (3) by a similar treatment of the epimeric hexaacetyl-D-gluco-D-*gulo*-heptonic nitrile and also from pentaacetyl-*aldehydo*-D-glucose. Afterwards it was obtained by Niemann and Hays (4) by the action of ammonia on pentaacetyl-β-D-glucose.

An interpretation of the reaction was given following the mechanism proposed by Isbell and Frush (5), to explain the formation of products of the condensation of acetamide with aldoses in Wohl's degradation, or when acetylated-*aldehydo*-monosaccharides are treated with ammonia.

It was concluded that the products isolated in the reactions studied were the result of a series of competitive reactions, the capacity for forming an actual aldehyde group, and the ammonolysis of the different acyl groups playing an important part amongst them.

The reaction has now been extended to include acetyl and benzoyl derivatives of D-mannose. The fact that Brigl and co-workers (2) have studied the degradation of hexaacetyl- and hexabenzoyl-D-manno-D-*gala*-heptonic nitriles with ammonia gave a particular interest to this extension. The experiments with glucose derivatives have shown that the acylated nitriles give, by the action of methanolic ammonia, the same products as the acylated aldoses which can be formally derived from them by elimination of the cyano group.

This was confirmed in the mannose series. Pentaacetyl-β-D-mannose (I), when treated with methanolic ammonia, gave D-mannose diacetamide (IV) in 35% yield, identical with the compound obtained by Brigl and co-workers (2) by submitting hexaacetyl-D-manno-D-*gala*-heptonic nitrile to a Wohl's degradation.

The stereoisomerism of carbon atom 2 determines an important difference in the behavior of the acetylated derivatives of D-glucose and D-mannose. While the latter yields the open chain D-mannose diacetamide, the derivatives from D-glucose produced a cyclic compound, N-acetyl-D-glucofuranosylamine.

On the other hand, treatment of pentabenzoyl-α- or -β-D-mannose with ammonia yielded two different products, one containing two benzamide residues and the other containing one. The preparation of a pentabenzoyl-D-mannose dibenzamide confirms the open chain structure assigned to the first compound. The fact that the monobenzamide compound gives a tetraccetyl derivative

agrees with a cyclic structure, and except for the unknown nature of this ring, the compound is similar to N-acetyl-D-glucofuranosylamine.

Both substances were first prepared by Brigl and co-workers (2) when they degraded hexabenzoyl-D-manno-D-*gala*-heptonic nitrile with ammonia and silver nitrate. They believed that the monobenzamide derivative obtained was a secondary product of the reaction, resulting from the action of nitric acid on the dibenzamide derivative which was first formed. The nitric acid was formed when silver ions were precipitated with hydrogen chloride in the process of purification.

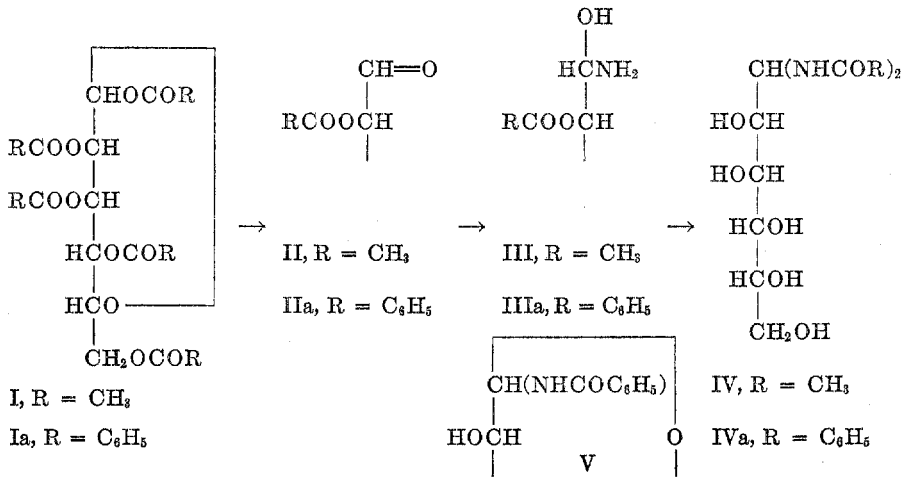

FIGURE 1. For the detail of the reactions leading from II to IV see the first part of this series (1).

Our experiments show that D-mannose monobenzamide is a primary product of the reaction. It does not derive from D-mannose dibenzamide. When pentabenzoyl-D-mannose dibenzamide was treated with ammonia, the original D-mannose dibenzamide was recovered in almost quantitative yield.

The formation of these compounds can be explained, as in the manner of the D-glucose derivatives, on the basis of the mechanism of Isbell and Frush (5). In the example of pentaacetyl-β-D-mannose (I), after the acetyl in carbon atom one is separated, an aldehyde group (II) is formed, which condenses with ammonia forming derivatives of type (III). Rearrangement of the remaining acetyl groups then produces D-mannose diacetamide (IV).

With the pentabenzoyl derivatives (Ia), the same series of reactions takes place in large measure, leading to the formation of D-mannose dibenzamide (IVa) in 20% yield. Part of the process, however, involves a change of IIIa to V rather than IIIa to IV. Here, one benzoyl rearranges so that one benzamide moiety becomes attached to carbon atom one. Almost simultaneously the hydroxyl present in the same carbon atom condenses with another hydroxyl in the molecule, giving an oxygen ring and forming a stable D-mannose monobenzamide (V) in 6–8% yield.

It is interesting to note that a rather large part of the pentabenzoyl-β-D-mannose employed loses all the benzoyl groups by ammonolysis. After separation of the benzamide compounds, 30% of the original mannose could be recovered as D-mannose phenylhydrazone from the mother liquors of the reaction.

It is evident that the different products obtained from the D-mannose derivatives, as from the D-glucose series, result from the balance of several competitive reactions.

EXPERIMENTAL

Methanolic ammonia always contained 16% ammonia. Ethanol when not specially stated was 96%.

D-*Mannose diacetamide* (IV) *from pentaacetyl-β-D-mannose.* The mannose (1 g.) was dissolved in 25 ml. of methanolic ammonia. After 24 hours at room temperature the solution was evaporated in a vacuum. The residue crystallized on the addition of a small amount of ethanol. After filtration, 250 mg. (35%) of IV, m.p. 218°, was obtained. By recrystallization from 80% ethanol, fine needles, m.p. 218–219°, $[\alpha]_D^{20}$ −13.8°, in water (*c*, 0.619) were obtained. This is identical with the IV of Brigl, Mühlschlegel, and Schinle (2) who give m.p. 219° and state no rotation.

D-*Mannose dibenzamide* (IVa) *from pentabenzoyl-α- or -β-D-mannose.* Pentabenzoyl-α- or -β-D-mannose (6) (10 g.) was dissolved, by shaking, in 250 ml. of methanolic ammonia. After 24 hours at room temperature, the solution was evaporated in a vacuum. The residue was dissolved in 160 ml. of ethanol and cooled to 0°. A crystalline precipitate formed that was filtered after 40 minutes. Yield: 1.20–1.17 g. (20.8–20.0%), m.p. 220°. Recrystallization from ethanol gave needles of m.p. 225–226°; $[\alpha]_D^{25}$ +2.8° in pyridine; Brigl and co-workers (2) list m.p. 226°, $[\alpha]_D^{25}$ +3.6°.

Anal. Calc'd for $C_{20}H_{24}N_2O_7$: C, 59.37; H, 5.98; N, 6.93.
Found: C, 59.02; H, 5.63; N, 7.17.

Pentabenzoyl-D-mannose dibenzamide (VI). Compound IVa (400 mg.) was dissolved in 5 ml. of boiling pyridine. The solution was cooled to room temperature and 1.4 g. of benzoyl chloride was added. It was then heated to 60° for 10 minutes and left overnight at 20°. Next morning the mass was poured into 200 ml. of ice-water. The gummy precipitate was washed well with water and dried. It was then washed many times with petroleum pentane, and it solidified during the treatment. The substance was then recrystallized from ethanol to form small prisms melting at 140–142°, $[\alpha]_D^{20}$ +25.3°, in chloroform (*c*, 0.632).

Anal. Calc'd for $C_{55}H_{44}N_2O_{12}$: C, 71.50; H, 4.76; N, 3.03.
Found: C, 71.12; H, 4.64; N, 3.22.

Ammonolysis of VI. Compound VI (4 g.) was dissolved in 100 ml. of methanolic ammonia. After 24 hours at room temperature the solution was evaporated *in vacuo*. The residue was dissolved in boiling ethanol from which 1.47 g. of IVa separated on cooling. The ethanolic solution remaining was evaporated again and the residue was extracted with boiling ethyl acetate to eliminate the benzamide. The new dry residue was dissolved again in boiling ethanol and by cooling a new crop of crystals of IVa weighing 200 mg. and melting at 225° was obtained. By concentration of the mother ethanolic liquors, 20 mg., m.p. 222–223°, resulted. Total yield, 1.69 g. (97%). Identification was by mixture melting point.

D-*Mannose monobenzamide* (V). The ethanolic mother liquors of the preparation of IVa from pentabenzoyl-D-mannose were left at room temperature; they deposited slowly a new crystalline precipitate. After four days 240–325 mg. (6–8%) of crystals melting at 252° was collected. After recrystallization from 70% ethanol, white needles melting at 253–254° were obtained, $[\alpha]_D^{26}$ +6.4°, in pyridine (*c*, 0.235). Brigl and co-workers (2) give m.p. 254° and record no rotation.

Anal. Calc'd for $C_{13}H_{17}NO_6$: C, 55.20; H, 6.01; N, 4.95.
Found: C, 55.27; H, 6.18; N, 5.07.

Tetraacetyl-D-mannose monobenzamide. A 310-mg. sample of V was dissolved by boiling with 10 ml. of a mixture (1:1) of pyridine and acetic anhydride. After 24 hours at 20° the solution was evaporated in a desiccator over sulfuric acid and potassium hydroxide. The residue crystallized when a small amount of ethanol was added. Recrystallization from ethanol gave prisms melting at 135–136°, $[\alpha]_D^{20}$ −28.8°, in chloroform (*c*, 1.267).

Anal. Calc'd for $C_{21}H_{25}NO_{10}$: C, 55.80; H, 5.54; N, 3.10.

Found: C, 56.08; H, 5.11; N, 3.46.

D-*Mannose phenylhydrazone.* After the separation of V, the remaining ethanolic mother liquor was evaporated to dryness and the residue was extracted with boiling ethyl acetate to eliminate the benzamide. It was then dissolved in 60 ml. of water, Norit was added, and the mixture was boiled and filtered. The filtrate on staying at 5° gave a few crystals (high-melting IVa or V) that were discarded. The solution was re-evaporated, dissolved in 16 ml. of water, and treated with 1.2 g. of phenylhydrazine and 1.2 g. of acetic acid in 6 ml. of water, according to van der Haar (7).

D-*Mannose phenylhydrazone* (1.08 g.), m.p. 189–190°, equivalent to 0.79 g. (30.4%) of D-mannose was isolated in the usual way.

SUMMARY

1. Treatment of pentaacetyl-β-D-mannose with methanolic ammonia gives D-mannose diacetamide.

2. Pentabenzoyl-α- or -β-D-mannose gives, under the same conditions, D-mannose monobenzamide and D-mannose dibenzamide in the same yields.

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