

BENZOYLATED NITRILES OF ALDONIC ACIDS. DEGRADATION ACCORDING TO WOHL AND ZEMPLÉN METHODS

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The degradation of acylated nitriles of aldonic acids, with ammonia, known in sugar chemistry as Wohl's method of degradation, has been usually applied to acetyl derivatives, with the exception of the work of Brigl, Mühlischlegel, and Schinle (1) who prepared hexabenzoyl mannoheptonic nitrile, and obtained by the action of silver nitrate in methanolic ammonia, mannose dibenzamide and mannose monobenzamide.

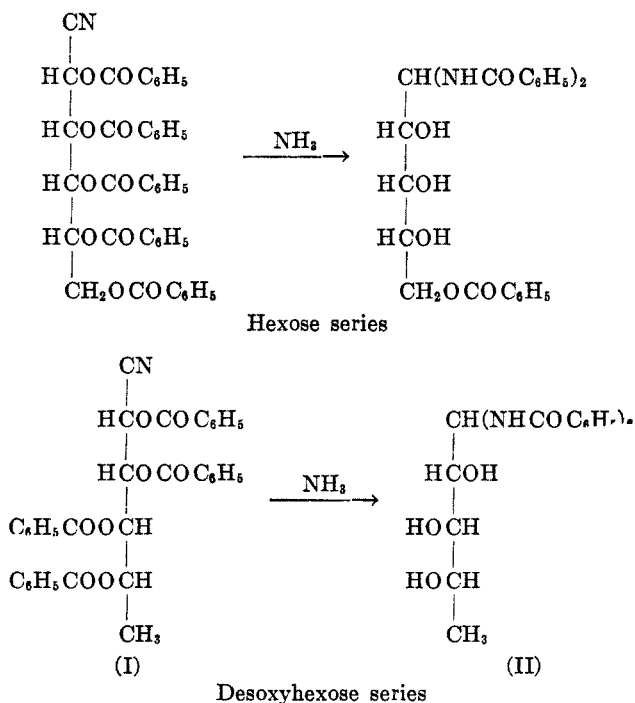
According to Brigl *et al.*, the dibenzamide is produced during the degradation, and the monobenzamide is a secondary product arising from the action of nitric acid, produced during working up the reaction products, on the dibenzamide already formed. The formation of a monoacylamide compound in the Wohl degradation can be viewed from another point after Hockett and Chandler (2) obtained glucose monoacetamide by the degradation of hexaacetyl-D- α -glucoheptonic nitrile without employing silver nitrate or oxide, but only ammonia, and Niemann and Hays (3) obtained the same compound by treating β -D-glucose pentaacetate with methanolic ammonia. It is evident that variations of the classical products obtained in the Wohl degradation can be expected with different aldonic acids, and that also some variation might result from employing acids with different acylating residues. Our work is related to this latter possibility.

We now describe the preparation of the benzoylated nitriles of the four aldonic acids derived from D-glucose, D-galactose, D-mannose, and L-rhamnose. They were easily prepared by the action of benzoyl chloride on the oximes of the sugars suspended in pyridine.

It was found that the nitriles can be degraded by treatment with 96% ethanol saturated with ammonia. They were left unattacked by lower concentrations of ammonia and by concentrated aqueous ammonia, in this last case seemingly because of their insolubility.

In all cases, the dibenzamides of the lower sugars were obtained in smaller yields than is usual with the acetylated nitriles. The dibenzamides obtained from pentabenzoyl-D-gluconic acid nitrile, pentabenzoyl-D-mannonic acid nitrile, and pentabenzoyl-D-galactonic acid nitrile, when analyzed, revealed the presence of three benzoyl residues, while from tetrabenzoyl-L-rhammonic acid nitrile (I), 5-desoxy-L-arabinose dibenzamide (II) was obtained.

It is evident that in the case of the former nitriles, one of the esterifying benzoyl groups remains, and resists the action of the ammonia. Although we have not a direct proof, the difference in reaction between benzoylated nitriles with a primary alcoholic hydroxyl, and tetrabenzoyl-L-rhammonic acid nitrile, where there is none, justifies the hypothesis that the remaining benzoyl is attached to the 5



carbon atom in the pentoses produced, and that the products obtained by degradation are: 5-benzoyl-D-arabinose dibenzamide and 5-benzoyl-D-lyxose dibenzamide.

The preparation of some acetylated and benzoylated derivatives of the benzamides has confirmed their formulas.

This resistance of the primary benzoyl group to hydrolysis by alcoholic ammonia has been described also by Todd, who found that methanolic ammonia hydrolysis of 5-benzoyl-2,3,4-triacetyl-L-arabinose derivatives removes the acetyl groups, leaving the benzoyl group unaffected (4).

In the experiments of Brigl, Mülschlegen, and Schinle (1), all the benzoyl groups were removed, and only new experimental work can decide if this difference can be attributed to the silver salt used in the degradation, together with slightly different conditions.

When Zemplén's method of degradation with sodium methoxide was applied, all benzoyl groups were removed, and D-arabinose was isolated from pentabenzoyl-D-gluconic and pentabenzoyl-D-mannonic nitriles.

EXPERIMENTAL

Pentabenzoyl-D-galactonic acid nitrile. Five grams of D-galactose oxime, finely divided, was suspended in 30 ml. of pyridine and 28.2 ml. of benzoyl chloride slowly added. Heat developed and the oxime dissolved. After 24 hours the partly solidified mass was poured into water, and a sirup precipitated, which by washing many times with cold water solidified.

This solid was filtered, well dried, and recrystallized from acetic acid. Sixteen and two-tenths grams (98% yield) of pentabenzoyl-D-galactonic acid nitrile, melting at 142-144°,

was obtained. Recrystallized many times from ethanol, long needles melting at 144° were obtained. It is very soluble in cold chloroform, ether, acetone, and benzene, sparingly soluble in cold methanol and ethanol, insoluble in petroleum ether and water. $[\alpha]_D^{20}$ in chloroform +9.7° (c, 1.33).

Anal. Calc'd for $C_{41}H_{51}NO_{10}$: C, 70.30; H, 4.44; N, 2.00.

Found: C, 70.15; H, 4.46; N, 2.31.

5-Benzoyl-D-lyxose dibenzamide. Three grams of pentabenzoyl-D-galactonic acid nitrile was suspended, finely divided, in 90 ml. of 96% ethanol saturated with ammonia, and shaken at room temperature. After 2 hours, the nitrile had dissolved, and shaking was continued for one hour. The solution was concentrated to dryness in a vacuum, and the dried residue washed well with cold ethanol until no more color was removed. The remaining 5-benzoyl-D-lyxose dibenzamide melted at 210–218° and could be purified by recrystallization from a large volume of ethanol; long needles melting at 222–224°; sparingly soluble in all common organic solvents except pyridine. $[\alpha]_D^{25}$ +36.1° in pyridine (c, 0.71).

Anal. Calc'd for $C_{26}H_{26}N_2O_7$: C, 65.27; H, 5.43.

Found: C, 65.77; H, 5.35.

5-Benzoyl-2,3,4-triacetyl-D-lyxose dibenzamide. 5-Benzoyl-D-lyxose dibenzamide (0.35 g.) was treated with 2.5 ml. of pyridine and 2.5 ml. of acetic anhydride and heated until all dissolved. After 24 hours, the solution was poured into ice-water, and a sirup precipitated that crystallized easily. The crystals (yield 0.42 g.) were recrystallized from ethanol; fine needles melting at 189°; $[\alpha]_D^{25}$ +36.2° in chloroform (c, 0.95).

Anal. Calc'd for $C_{32}H_{32}N_2O_{10}$: C, 63.57; H, 5.29.

Found: C, 63.10; H, 5.21.

Tetrabenzoyl-D-lyxose dibenzamide. 5-Benzoyl-D-lyxose dibenzamide (0.5 g.) was treated with 5 ml. of pyridine and 3.5 ml. of benzoyl chloride. The reaction mass after 24 hours was poured into ice-water and purified in the usual way. The crude product, recrystallized from acetic acid, gave needles melting at 227–229°. $[\alpha]_D^{19}$ +39.1° in chloroform (c, 0.88).

Anal. Calc'd for $C_{47}H_{48}N_2O_{10}$: C, 71.39; H, 4.81.

Found: C, 71.78; H, 5.74.

Pentabenzoyl-D-gluconic acid nitrile. Five grams of glucose oxime was suspended in 30 ml. of pyridine and treated with 28 cc. of benzoyl chloride. The semi-solid reaction product stood for 24 hours, and then was treated as described for pentabenzoyl-D-galactonic acid nitrile. From acetic acid it was obtained in prisms melting at 114–115°, yield 12 g., 71%. By recrystallization from acetic acid the melting point 118° was attained. It is very soluble in chloroform, ether, acetone, and benzene, less so in methanol and ethanol. $[\alpha]_D^{20}$ +15.1° in chloroform (c, 2.09).

Anal. Calc'd for $C_{41}H_{51}NO_{10}$: C, 70.30; H, 4.44.

Found: C, 70.31; H, 4.95.

5-Benzoyl-D-arabinose dibenzamide. Five grams of pentabenzoyl-D-gluconic acid nitrile, finely ground, was suspended in 150 ml. of ethanol saturated with ammonia, and shaken for 2.5 hours, when all the solid dissolved. The solution was then concentrated in a vacuum, the residue very well dried, and then washed with cold methanol. Nine-tenths gram of residue melting at 205–208° was obtained. This product, when dissolved in various organic solvents, precipitated on cooling as a gel-like solid. This property was not changed by many solutions and precipitations from methanol, and the product had the constant melting point 206–208°. An X-ray analysis, for which we are indebted to Ing. Galloni, showed that it has a crystalline structure. It has low solubility in cold methanol, ethanol, and ethyl acetate, but is more soluble at higher temperatures; almost insoluble in benzene and water, soluble in pyridine; $[\alpha]_D^{21}$ +8.5° in pyridine (c, 1.17).

Anal. Calc'd for $C_{26}H_{26}N_2O_7$: C, 65.27; H, 5.43.

Found: C, 64.90; H, 5.57.

5-Benzoyl-2,3,4-triacetyl-D-arabinose dibenzamide. 5-Benzoyl-D-arabinose dibenzamide (0.5 g.), melting at 205–207° was dissolved in 5 ml. of pyridine, and 5 ml. of acetic anhydride added. After 24 hours at room temperature, the solution was poured into ice-water. The

precipitated sirup crystallized on washing, and recrystallized from methanol gave rhombic plates melting at 193°; $[\alpha]_D^{25} +69.0^\circ$ in chloroform (*c*, 0.81).

Anal. Calc'd for $C_{32}H_{42}N_2O_{10}$: C, 63.57; H, 5.29.

Found: C, 63.83; H, 5.80.

5-Benzoyl-D-arabinose dibenzamide from 5-benzoyl-2,3,4-triacetyl-D-arabinose dibenzamide. A small amount of 5-benzoyl-2,3,4-triacetyl-D-arabinose dibenzamide was dissolved in an excess of ethanol saturated with ammonia, and shaken for three hours at room temperature. The solution was evaporated, and the well-dried residue washed with water and methanol; recrystallization from methanol gave a product melting at 207–208° which gave no depression when mixed with the original 5-benzoyl-D-arabinose dibenzamide. It maintained the property of giving gel-like precipitates when its solution in a hot organic solvent was cooled.

Pentabenzoyl-D-mannonic acid nitrile. One gram of finely-divided mannose oxime was suspended in 6 ml. of pyridine and 5.5 ml. of benzoyl chloride added slowly. After 24 hours at room temperature, the semi-solid mass was poured into ice-water. The precipitated sirup solidified slowly on washing with water. The solid was well dried and dissolved in the minimum amount of acetic acid with a little heating. After 24 hours, 3 g. (93%) of crystals melting at 120° was collected. By recrystallization from methanol or ethanol, plates melting at 130° were obtained, but large losses took place in the purification; soluble in chloroform, ether, acetone, and benzene, less so in methanol and ethanol; $[\alpha]_D^{17} +10.2^\circ$ in chloroform (*c*, 1.37).

Anal. Calc'd for $C_{41}H_{51}NO_{10}$: C, 70.30; H, 4.44.

Found: C, 70.63; H, 4.70.

5-Benzoyl-D-arabinose dibenzamide from pentabenzoyl-D-mannonic acid nitrile. One gram of pentabenzoyl-D-mannonic acid nitrile was shaken for 3 hours with 30 ml. of ethanol saturated with ammonia. In the usual way, 0.1 g. (much less than from the gluconic acid nitrile) of residue melting at 200° was obtained. Recrystallization from methanol gave the m.p. 205–207°. The solid gave no depression in melting point when mixed with a sample of 5-benzoyl-D-arabinose dibenzamide from gluconic acid nitrile, and precipitated from its solutions in methanol in a gel-like condition.

Tetrabenzoyl-L-rhammonic acid nitrile. Three grams of rhamnose oxime was dissolved at room temperature in 18 ml. of pyridine and treated with 16.5 ml. of benzoyl chloride. After 24 hours, the semi-solid mass was poured into ice-water, and the sirup that precipitated solidified by washing. It was filtered, dried, and recrystallized from methanol, 9 g. (91% yield) of long prisms melting at 110°. By further recrystallization, the melting point 114° was obtained; very soluble in chloroform, ether, acetone, and benzene, much less so in methanol or ethanol, insoluble in water. $[\alpha]_D^{25} +4.7^\circ$ in chloroform (*c*, 1.14).

Anal. Calc'd for $C_{34}H_{47}NO_9$: C, 70.71; H, 4.68.

Found: C, 70.79; H, 4.77.

5-Dexosyl-L-arabinose dibenzamide. Five grams of tetrabenzoyl-L-rhammonic acid nitrile was suspended in 150 ml. of ethanol saturated with ammonia and shaken for two hours; all the solid had then dissolved. The solution was distilled in a vacuum, and the dried residue washed well with methanol. Four-tenths gram of 5-dexosyl-L-arabinose dibenzamide was obtained, that recrystallized from acetic acid or methanol gave needles melting at 225–226°; very sparingly soluble in water and in all cold organic solvents except pyridine. $[\alpha]_D^{18} -2.1^\circ$ in pyridine (*c*, 0.71).

Anal. Calc'd for $C_{19}H_{22}N_2O_5$: C, 63.18; H, 6.14.

Found: C, 62.85; H, 6.28.

Triacetyl-5-desoxy-L-arabinose dibenzamide. Five-tenths gram of the dibenzamide was treated with 5 ml. of pyridine and 5 ml. of acetic anhydride, and gently heated until the solid dissolved. After 24 hours at room temperature, the solution was poured into ice-water, and the precipitated sirup crystallized very easily. Recrystallized from chloroform-petroleum ether, rhombic plates melting at 193° were obtained. $[\alpha]_D^{19} -92.9^\circ$ in chloroform (*c*, 0.92).

Anal. Calc'd for $C_{26}H_{28}N_2O_8$: C, 61.98; H, 5.78.

Found: C, 61.71; H, 5.66.

Tribenzoyl-5-desoxy-L-arabinose dibenzamide. The dibenzamide (0.15 g.) was treated with 0.9 ml. of pyridine and 0.8 ml. of benzoyl chloride. After 24 hours standing at room temperature, the crude benzoyl derivative was isolated in the usual way, and recrystallized from methanol; rhombic plates melting at 212° .

Anal. Calc'd for $C_{40}H_{44}N_2O_8$: C, 71.64; H, 5.07.

Found: C, 70.96; H, 5.33.

Degradations with Sodium Methoxide

Pentabenzoyl-D-gluconic acid nitrile. The nitrile (8.25 g.) was dissolved in 7 ml. of chloroform and cooled to -5° . A solution of 0.82 g. of sodium in 7 ml. of methanol was then added with vigorous shaking. A reddish gel-like mass was formed. After 5 minutes, 20 ml. of ice-water and 2 ml. of acetic acid were added, and the aqueous solution concentrated to dryness. The residue was treated with 20 ml. of absolute ethanol, the ethanol evaporated, and this operation repeated once. The residue gave a clear solution when dissolved to 26 ml. with water. From 13 ml. of this solution, 0.32 g. of D-arabinose diphenylhydrazone was isolated, melting at $202-204^\circ$; yield as arabinose, 31%.

Pentabenzoyl-D-mannonic acid nitrile. The nitrile (8.25 g.) was dissolved in 10 ml. of chloroform (a larger amount than in the previous degradation) and treated exactly as the gluconic nitrile. A yield of 18% of arabinose, isolated as diphenylhydrazone was obtained.

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