Summary

1. Tetraacetyl-*d*-gluconic acid has been prepared by the oxidation of tetraacetyl-*d*-glucose with bromine.
2. Pentaacetyl-*d*-gluconic acid was obtained by the oxidation of aldehydo-*d*-glucose pentaacetate and by acetylation of tetraacetyl-*d*-gluconic acid.
3. Ethyl pentaacetyl-*d*-gluconate and pentaacetyl-*d*-gluconic phenylhydrazide were prepared.
4. The ring form of *d*-xylose semicarbazone tetraacetate was isolated.
5. Aldehydoxylose tetraacetates have been prepared by the treatment of the corresponding semicarbazones with nitrous acid.
6. Tetraacetylxylonic acids have been obtained by the oxidation of aldehydoxylose tetraacetates.

RAHWAY, N. J. RECEIVED SEPTEMBER 17, 1936

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

Preparation and Properties of Pentaacetyl-2-keto-*d*-glucoheptonic Acid

BY RANDOLPH T. MAJOR AND ELMER W. COOK

The 2-keto-sugar acids have acquired in recent years considerable interest due to the fact that the enol forms of these acids have been shown to be vitamin C and its homologs.[1]

A new method of preparing the acetyl derivatives of these acids has become possible since the recent synthesis of the fully acetylated sugar acids.[2]

The acetyl sugar acid was converted into its acid chloride with phosphorus pentachloride; it is noteworthy that thionyl chloride was not a satisfactory agent for the purpose. The chloride was converted into the corresponding cyanide by means of silver cyanide. This was hydrolyzed in turn to the corresponding acid. This acid could be esterified readily.

The series of reactions described above has been carried through to completion starting with pentaacetyl-*d*-gluconic acid and through, except for the last step, with tetraacetyl-*d*,*l*-xylonic acid.

Attempts are being made to hydrolyze the acetyl groups and enolize the keto group of pentaacetyl-2-ketoglucoheptonic acid and its ester to give a homolog of vitamin C.

Experimental

Acetylated Sugar Acid Chloride.—The dry fully acetylated sugar acid was added with cooling to a suspension of one molecular equivalent of phosphorus pentachloride in ten times its weight of dry ether. The reaction was soon complete as shown by disappearance of the phosphorus pentachloride.

Pentaacetyl-*d*-gluconyl Chloride.—After the solution had stood at room temperature for two or three hours the ether was evaporated *in vacuo*. Dry xylene was then added. This and the phosphorus oxychloride formed in the reaction were removed by evaporation at 45 to 50° *in vacuo*. The addition of xylene followed by evaporation *in vacuo* was repeated twice. The residual gum was dissolved in dry ether. Upon evaporation in a slight vacuum beautiful white crystals separated; m. p. 68–70°; yield, 88%; $[\alpha]^{20}_{D}$ +2° (alcohol-free chloroform, *c*, 2).

Anal. Calcd. for $C_{16}H_{21}O_{11}Cl$: C, 45.22; H, 4.99; Cl, 8.35. Found: C, 45.60; H, 4.90; Cl, 8.27.

With water the acid chloride gave pentaacetyl-*d*-gluconic acid monohydrate, m. p. 72–73°.[2]

Tetraacetyl-*d*,*l*-xylonyl Chloride.—White crystals appeared soon after solution of the phosphorus pentachloride. The precipitate was recrystallized from dry ether; m. p. 90–92°; yield, 71%; $[\alpha]^{20}_{D}$ 0° (alcohol-free chloroform, *c*, 2).

Anal. Calcd. for $C_{13}H_{17}O_9Cl$: C, 44.26; H, 4.86; Cl, 10.08. Found: C, 44.25, 44.33; H, 4.80, 5.03; Cl, 10.18, 10.32.

Ethyl Ester of Acetylated Sugar Acids.—When a solution of an acetylated sugar acid chloride in absolute alcohol was evaporated *in vacuo* a crystalline residue was left which was washed with cold water and recrystallized from absolute alcohol.

Ethyl pentaacetyl-*d*-gluconate melted at 103–104°.[3]

Ethyl tetraacetyl-*d*,*l*-xylonate melted at 70–72°; $[\alpha]^{20}_{D}$ 0° (alcohol, *c*, 0.06).

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.70; H, 6.12. Found: C, 49.53; H, 6.13.

Pentaacetyl-*d*-gluconamide.—Dry ammonia was bubbled through a solution of pentaacetyl-*d*-gluconic acid chloride in dry ether. The white precipitate which formed was washed with water to remove ammonium chloride. The pentaacetyl-*d*-gluconamide which remained melted at 183–184°.[4]

Tetraacetyl-*d*,*l*-xylonamide.—This compound was prepared in the same way as pentaacetyl-*d*-gluconamide except that it did not precipitate from the ether with the

---

[1] Hirst, *Chemistry and Industry*, 221 (1933); Haworth, *ibid.*, 482 (1933).

[2] Major and Cook, THIS JOURNAL, **58**, 2474 (1936).

[3] Volpert, *Ber.*, **19**, 2622 (1886), gives 103.5° as the melting point of ethyl pentaacetyl-*d*-gluconate.

[4] Zemplén and Kiss, *Ber.*, **60**, 170 (1927), give 183.5–184° as the melting point of pentaacetyl-*d*-gluconamide.

ammonium chloride but could be recovered from the ether filtrate by evaporation. It was recrystallized from benzene; m. p. 130–132°; $[\alpha]^{20}_{\mathrm{D}}$ 0° (alcohol-free chloroform, *c*, 0.05).

Anal. Calcd. for $C_{13}H_{19}O_9N$: C, 46.83; H, 5.75; N, 4.20. Found: C, 46.82; H, 5.76; N, 4.11.

Pentaacetyl-2-keto-*d*-glucoheptonitrile.—Pentaacetylgluconyl chloride (10 g.) was heated for one hour with 4.7 g. of silver cyanide in a closed tube at 120 to 125°. The fused contents were shaken frequently to ensure good contact of the acid chloride with the silver cyanide. After cooling the gummy material was extracted thoroughly with anhydrous ether and filtered from the silver salts. Petroleum ether was added carefully to precipitate a part of the product as a dark colored sirup, thereby removing most of the color. Then an excess of petroleum ether was added with cooling. A gum was precipitated along with some crystalline product. The supernatant liquor was poured off and on evaporation yielded crystalline pentaacetyl-2-keto-*d*-glucoheptonitrile. The gum was dissolved in a small quantity of absolute alcohol and upon standing in the ice box for twenty-four hours yielded a quantity of pentaacetyl-2-keto-glucoheptonitrile. The product was purified by recrystallizing it from absolute alcohol; yield 34%; m. p. 116°; $[\alpha]^{20}_{\mathrm{D}}$ +7° (alcohol-free chloroform, *c*, 2). When this compound was heated in water with either dilute acid or base, hydrogen cyanide was evolved.

Anal. Calcd. for $C_{17}H_{21}O_{11}N$: C, 49.14; H, 5.10; N, 3.37. Found: C, 49.32; H, 5.24; N, 3.16.

Tetraacetyl-2-keto-*d*,*l*-gulononitrile.—This nitrile was prepared from tetraacetyl-*d*,*l*-xylonyl chloride in the same way as pentaacetyl-2-keto-*d*-glucoheptonitrile except that the filtrate obtained after the addition of sufficient petroleum ether to the ether extract to produce slight turbidity was treated with another larger portion of petroleum ether which precipitated a gum. Trituration of this gum with absolute alcohol yielded a solid precipitate. It was recrystallized from alcohol; m. p. 125–126°.

Anal. Calcd. for $C_{14}H_{17}O_9N$: N, 4.08. Found: N, 3.83.

Pentaacetyl-2-keto-*d*-glucoheptonic Acid.—Pentaacetyl-2-keto-*d*-glucoheptonitrile (7.55 g.) was dissolved in 20 cc. of pure dioxane. To this 13.1 cc. of 1.39 normal hydrogen chloride in dioxane was added. The solution was cooled and 0.33 cc. of water added. After this had stood in the ice box for twenty-four hours an additional 0.33 cc. of water was added. The solution was allowed to stand for another twenty-four hours, by which time ammonium chloride had precipitated. Ether was added and the ammonium chloride filtered. The filtrate was evaporated *in vacuo* to a gum. The gum was dissolved in ether and evaporation *in vacuo* repeated. The gum that remained crystallized upon scratching; m. p. 136–138°. After recrystallization from water the product melted at 160–161°; $[\alpha]^{20}_{\mathrm{D}}$ 0° (alcohol, *c*, 2); yield 40%. A solution of the keto acid in water was acid to congo red paper. It was extremely soluble in alcohol, ether, chloroform and acetone.

Anal. Calcd. for $C_{17}H_{22}O_{13}$: C, 46.98; H, 5.11. Found: C, 46.98; H, 5.05.

Ethyl Pentaacetyl-2-keto-*d*-glucoheptonate.—A solution of 1 g. of pentaacetyl-2-keto-*d*-glucoheptonic acid in 10 cc. of absolute alcohol containing 2% hydrogen chloride was warmed at 55–60° for five minutes. The solution was cooled quickly to nearly room temperature and then allowed to crystallize; yield, 60%; m. p. 97–98°; $[\alpha]^{20}_{\mathrm{D}}$ 0° (alcohol, *c*, 2).

Anal. Calcd. for $C_{19}H_{26}O_{13}$: C, 49.33; H, 5.67. Found: C, 49.19, 49.38; H, 5.91, 5.67.

Methyl Tetraacetyl-2-keto-*d*-gluconate.—One gram of methyl 2-keto-*d*-gluconate[5] was added to 5 cc. of acetic anhydride containing 0.4 g. of zinc chloride at 0°. As soon as solution was complete (about thirty minutes) the mixture was allowed to come to room temperature and remain there for twenty-four hours. It was then poured into 25 cc. of ice water; a white solid separated which was recrystallized from absolute alcohol; m. p. 168–169°; yield, 61%; $[\alpha]^{20}_{\mathrm{D}}$ −133° (alcohol-free chloroform, *c*, 2).[6]

Anal. Calcd. for $C_{15}H_{20}O_{11}$: C, 47.90; H, 5.36. Found: C, 47.79; H, 5.30.

Summary

1. Pentaacetyl-*d*-gluconyl chloride and tetraacetyl-*d*,*l*-xylonyl chloride have been prepared from the corresponding acids.

2. Ethyl pentaacetyl-*d*-gluconate and ethyl tetraacetyl-*d*,*l*-xylonate have been prepared from the corresponding acid chlorides.

3. Pentaacetyl-*d*-gluconamide and tetraacetyl-*d*,*l*-xylonamide have been prepared from the corresponding acid chlorides.

4. Pentaacetyl-2-keto-*d*-glucoheptonitrile and tetraacetyl-2-keto-*d*,*l*-gulononitrile have been prepared from the corresponding chlorides.

5. Pentaacetyl-2-keto-*d*-glucoheptonic acid has been synthesized by hydrolysis of the corresponding nitrile.

6. Ethyl pentaacetyl-2-keto-*d*-glucoheptonate has been prepared by esterification of the corresponding acid.

7. Methyl tetraacetyl-2-keto-*d*-gluconate has been prepared by acetylation of methyl 2-keto-*d*-gluconate.

RAHWAY, N. J. RECEIVED SEPTEMBER 17, 1936

---

(5) Ohle and Wolter, *Ber.*, **63B**, 843 (1930).

(6) Ohle and Wolter[5] reported that the methyl tetraacetyl-2-keto-*d*-gluconate they obtained was an oil; $[\alpha]^{18}_{\mathrm{D}}$ −38.8° (chloroform, *c*, 2.552). Since this was formed in pyridine it is possible that this was an acetyl derivative of an enol form of methyl 2-keto-*d*-gluconate.