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The Preparation of Some Fully Acetylated Aldonic Acids and Nitriles[1]

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Fully acetylated aldonic acids may be prepared from the corresponding aldoses by the methods of Major and Cook[2] and of Hurd and Sowden[3] or from the corresponding aldonic acids or lactones.[4,5,6,7,8] The choice of a suitable procedure for the preparation of an acetylated aldonic acid would depend on the relative availability of the aldose and the corresponding aldonic acid. Ordinarily the aldoses are more readily available as starting materials than the aldonic acids, but for reactions where the glyconic acid is accessible, the method of widest application is that reported by Robbins and Upson[5] which involves the series of reactions: aldonic acid → lactone → acid amide → acetylated amide → acetylated acid.

In search for a simple and direct method for preparing tetraacetyl-*d*-ribonic acid we applied the method of Robbins and Upson,[6] consisting of acetylating free aldonic acids to *d*-ribonic acid. Aside from the difficulties in preparing *d*-ribonic acid, this procedure gave poor results. The desired acetylated acid was obtained in 15% yield along with triacetyl-*d*-ribonolactone and an intractable oil. As triacetyl-*d*-erythronic acid may be prepared from potassium erythronate and acetyl chloride,[9] we subjected the potassium *d*-ribonate to the same reaction with poor results. However, the nature of the acetylating agent as well as the nature of the cation seem to play important roles in this type of acetylation reaction. A mixture of acetic anhydride and hydrogen chloride was found to be an excellent acetylating agent and when used with cadmium ribonate, tetraacetyl-*d*-ribonic acid was obtained in 85% yield. In a similar manner cadmium arabonate was also converted to the fully acetylated acid in the same yield.

The importance of the nature of the cation in the acetylation is borne out by the yields obtained with the following salts of *d*-ribonic acid: Ba, 4%; Ca, 22%; K, 25%; NH_4, 46%; and Cd, 85%. The striking differences in yields among these salts may be related to the ease with which the cation is neutralized by the stronger inorganic acid and to the activity of the resulting salt as a promoter of acetylation.

As to the mechanism of the acetylation reaction, the following facts must be considered. Triacetyl-*d*-ribonolactone is formed in good yields when *d*-ribonolactone is acetylated with acetic acid and hydrogen chloride. Free *d*-ribonic acid, as stated previously, does not form the fully acetylated acid in significant amounts. Salts of ribonic acid lead to triacetyl-*d*-ribonolactone when acetylated with acetic anhydride and zinc chloride.

Although many methods are now known for preparing the acetylated aldonic acids, only one[10] exists for the synthesis of the fully acetylated aldonic nitriles. As this well-known method starts with aldoses, a general scheme which utilizes the sugar acids is of importance. Zemplén and Kiss[11] prepared α-*d*-hexaacetylglucoheptonic nitrile from the corresponding amide by dehydration with phosphorus oxychloride. We have found that this method can be applied to the fully acetylated gluconamide, ribonamide, and arabonamide. This procedure, undoubtedly, has wide application and should find utility in those instances where the sugar acids are readily available.

Experimental

Salts of *d*-Ribonic Acid.—The barium and calcium salts were prepared by treating a hot water solution of *d*-ribonolactone with barium or calcium hydroxide, removing the excess base by treatment with carbon dioxide, concentrating the resulting solution and adding methanol. Potassium ribonate was made similarly in methanol and crystallized by removing most of the methanol by distillation. Ammonium ribonate was made in water, heated, concentrated, and the residue recrystallized from water and methanol.

Acetylation of Cadmium *d*-Ribonate, Tetraacetyl-*d*-ribonic Acid.—A suspension of 50 g. of dry cadmium ribonate in 250 cc. of acetic anhydride was cooled to 10° and dry hydrogen chloride was passed through the suspension with stirring until the mixture was saturated with hydrogen chloride. The temperature of the reaction mixture was raised to 50° and maintained for one hour. The mixture was concentrated *in vacuo* and the residue slurried with about 300 cc. of ice-water to dissolve the inorganic salts. A good quality product (m. p. 137–139°) was obtained by filtering the mixture and washing with cold water yield 85% (64.5 g.).

Tetraacetyl-*d*-ribonic acid is sparingly soluble in cold benzene, ether, water and acetic acid. It may be recrystallized from hot acetic acid from which it separates as needles melting, when pure, at 139–140°; $[\alpha]^{25}D$ − 27.5° (*C*, 5% in acetic acid).

Anal. Calcd. for $C_{13}H_{18}O_{10}$: C, 46.71; H, 5.43. Found: C, 46.50; H, 5.20.

The other salts of *d*-ribonic acid were acetylated and worked up in the same manner.

Tetraacetyl-*d*-arabonic Acid.—Cadmium arabonate (prepared from arabonolactone and cadmium hydroxide) was acetylated in the same way as cadmium ribonate. The yield of acetylated acid (m. p. 135–136°) was 86%.

***d*-Ribonic Acid.**—We were unable to prepare *d*-ribonic acid by the procedure of Robbins and Upson[6] used for arabonic acid and other free acids. The following method

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[1] Presented in part at the meeting of the Division of Organic Chemistry, American Chemical Society, held in Detroit, Michigan, April 12, 1943.

[2] Major and Cook, THIS JOURNAL, 58, 2477 (1936).

[3] Hurd and Sowden, *ibid.*, 60, 235 (1938).

[4] Major and Cook, *ibid.*, 58, 2474 (1936).

[5] Robbins and Upson, *ibid.*, 60, 1788 (1938).

[6] Robbins and Upson, *ibid.*, 62, 1074 (1940).

[7] Wolfrom, Konigsberg and Weisblat, *ibid.*, 61, 574 (1939).

[8] Pasternack and Brown, U. S. Patent 2,237,263.

[9] Glattfeld and Kribben, THIS JOURNAL, 61, 1720 (1939).

[10] Wohl, *Ber.*, 26, 732 (1893).

[11] Zemplén and Kiss, *ibid.*, 60, 168 (1927).

works well: A mixture of 10 g. of potassium ribonate and 80 cc. of glacial acetic acid was heated at 60° for twenty minutes. The mixture was filtered and kept at 15° for three hours. The resulting acid (6 g.), m. p. 110–112°, was purified by recrystallization from methanol (m. p. 112–113°).

Anal. Calcd. for $C_6H_{10}O_6$: C, 36.15; H, 6.07. Found: C, 36.33; H, 6.25; $[\alpha]^{25}D$ −17.0° (*C*, 4% in water); $[\alpha]^{25}D$ −17.3° (*C*, 4% in methanol).

d-Ribonic acid is unstable at room temperature as indicated by a lowering of the melting point of several degrees after twenty-four-hour storage. Acetylation of the acid by the procedure of Robbins and Upson[6] gave tetraacetyl-*d*-ribonic acid (15%), triacetyl-*d*-ribonolactone (about 10%), and an intractable oil.

Triacetyl-*d*-ribonolactone.—Dry hydrogen chloride was passed into a suspension of 20 g. of *d*-ribonolactone in 100 cc. of acetic anhydride at 10° until saturation was complete. The solution was heated to 50° for one hour and then concentrated to dryness under reduced pressure. The residue was recrystallized from a mixture of acetic acid and water; yield 88% (81.5 g.), m. p. 54–56°.

Anal. Calcd. for $C_{11}H_{14}O_8$: C, 48.17; H, 5.15. Found: C, 48.36; H, 5.44; $[\alpha]^{D}_{25}$ + 27° (*C*, 2% in chloroform).

Tetraacetyl-*d*-ribonitrile.—A mixture of 5 g. of tetraacetyl-*d*-ribonamide, 6 g. of phosphorus oxychloride and 20 cc. of alcohol-free chloroform was refluxed for three hours. The cooled solution was cautiously stirred into 50 cc. of ice-water and the organic layer separated. The aqueous fraction was extracted with three 20-cc. portions of chloroform and the combined chloroform extracts were washed with ice water and aqueous sodium bicarbonate solution. After drying over anhydrous sodium sulfate, the chloroform was removed completely by distillation *in vacuo* and the crystalline residue was recrystallized from 10 cc. of ether; weight 4.4 g., melting at 66–68°. A second recrystallization from ether or methanol gave analytically pure product melting at 71–72°. *Anal.* Calcd. for $C_{13}H_{17}O_8N$: C, 49.52; H, 5.39; N, 4.44. Found: C, 49.58; H, 5.37; N, 4.51; $[\alpha]^{25}D$ +34.45° (*C*, 3% in chloroform).

Tetraacetyl-*d*-arabononitrile was prepared by heating the acetylated amide with 3 parts of phosphorus oxychloride at 80° for thirty minutes. The product was isolated by removing the phosphorus oxychloride under reduced pressure, dissolving the residue in chloroform and washing the latter with ice water to remove acidic constituents. From this point on, the procedure described above was used. From 10 g. of amide, 9 g. of product (94% yield), melting at 116–118° was obtained. Recrystallization from benzene gave an analytically pure product (m. p. 120–121°). *Anal.* Found: C, 49.66; H, 5.61; N, 4.29; $[\alpha]^{25}D$ −3.5° (in chloroform).

Pentaacetyl-*d*-gluconitrile was prepared in the same manner as was tetraacetyl-*d*-arabononitrile; yield of pure nitrile 89% (m. p. 84–85°).

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Summary

1. The direct acetylation of salts of *d*-ribonic acid and *d*-arabonic acid to the corresponding fully acetylated acids is described.

2. Acetylated aldonic amides may be converted to the corresponding nitriles in excellent yields by the action of phosphoryl chloride; this step constitutes a general method for preparing fully acetylated aldonic nitriles.

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The Effect of Bases on the Hydrogenation of Alkylphenols in the Presence of Raney Nickel

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It has been shown previously that small amounts of 40% aqueous sodium hydroxide will promote the hydrogenation of ortho disubstituted alkylphenols, *p*-phenylphenol and acylphenols in the presence of Raney nickel. The behavior of simple alkyl phenols was anomalous since aqueous alkali did not appreciably affect their hydrogenation.[1]

Further investigation has shown that phenol and alkylphenols are hydrogenated more rapidly and at lower temperatures when a small amount of the corresponding phenoxide is present during the hydrogenation. This effect is masked by water, which hinders the hydrogenation, and thus could not be observed with aqueous base.

The hydrogenations were carried out as described previously, with carefully purified compounds. Sodium or sodium hydroxide was added to the hot melted phenols. After the reaction was complete, 3 g. of Raney nickel catalyst[2] was added to the hot liquid and mixed thoroughly. The mixture was immediately hydrogenated at 130–150 atm.[3]

The ease of hydrogenation (or activity of the catalyst) was determined by observing the temperature of initial hydrogen absorption and by comparison of the isothermal rates. The relative order was the same for both methods.

The hydrogenation products were washed from the liner with benzene and then distilled under atmospheric pressure through a one-foot column packed with Pyrex helices. The constants of the cyclohexanols are given in Table I. The yields were quantitative except for mechanical losses.

The results of fourteen hydrogenations carried out at 100° with 0.53 mole of phenol each show the following:

A quantitative conversion to cyclohexanol can be accomplished in 0.6 hr. with 0.4 mole % of so-

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[1] Ungnade and McLaren, THIS JOURNAL, **66**, 118 (1944).

[2] The catalyst was dried by blotting with filter paper. Portions of catalyst were used from the same preparation within a short period of time in order to minimize the effect of age. All catalysts were found to change in activity with time. The activity decreased most rapidly when the catalyst was stored under 95% ethanol, least rapidly when absolute alcohol was used.

[3] The catalyst was partially inactivated if the mixture was allowed to stand at this point.