[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY, UNIVERSITY OF NEBRASKA]

The Preparation of Fully Acetylated Amides of Aldonic Acids

BY GORDON B. ROBBINS AND FRED W. UPSON

Acetylgluconic acid was prepared by Upson and Bartz[1] by direct acetylation of δ-gluconic lactone. Tetraacetylgluconic acid monohydrate which results on acetylation of δ-gluconic lactone was reported in the journal article but the 2,3,4,5,-6-pentaacetylgluconic acid was also prepared by further acetylation of the 2,3,4,6-product and is reported in the thesis of Bartz. More recently Major and Cook[2] report the pentaacetyl derivative prepared by the same method. This method, however, has not proved to be a general one for the preparation of fully acetylated acids since all other lactones with which we have worked have yielded acetylated lactones. It is necessary to start with a derivative such as the amide or ester which is not lactone in character.[2,3]

Major and Cook have made, from completely acetylated aldonic acids, the corresponding acid chlorides which offer a number of possibilities for the synthesis in the sugar series.

A method for the preparation of fully acetylated sugar acids has been reported by Hurd and Sowden[4] using the following sequence of reactions: aldose ⟶ aldose oxime ⟶ acetylated nitrile ⟶ acetylated amide ⟶ acetylated acid.

Acetylated amides of the aldonic acids have been prepared in this Laboratory by a method which is general in its application and is less complicated than that of Hurd and Sowden. The aldonic acid lactone is converted to the amide by solution in liquid ammonia followed by spontaneous evaporation of the excess ammonia.[5]

The amide results in pure condition and the yield is excellent. The amide is then subjected to direct acetylation using either sulfuric acid or zinc chloride as the catalyst. We have been able to explain a discrepancy between the work of Miksic[6] and that of Zemplén and Kiss.[7] Miksic reported the preparation of acetyl derivatives in which both the amide group and the hydroxyl groups are acetylated whereas the latter authors have obtained an acetyl derivative of an unacetylated amide group. Zemplén and Kiss used zinc chloride as the catalyst whereas Miksic used sulfuric acid. The work here reported indicates that the use of zinc chloride causes acetylation of the hydroxyl groups only whereas acetylation occurs in the amide group as well when sulfuric acid is the catalyst. This is illustrated in the acetylation of gluconamide and galactonamide using the two substances as catalysts.

The acetyl amides are readily converted to the corresponding acids by the method of Hurd and Sowden[4] through the action of nitrous acid in glacial acetic acid solution. We have shown that it is not necessary to isolate the acetyl amide. The acetylating mixture containing the amide may be treated directly with nitrous oxide giving excellent yields of the acetyl aldonic acid. Experiments with these acetyl aldonic acids will be reported in a later paper.

Experimental

Below is described the acetylation of the amides of several aldonic acids together with the properties of the resulting products. In all cases the rotatory power of the compounds was determined by means of a Bates saccharimeter using white light and a dichromate solution as a filter.

Pentaacetyl-*d*-gluconamide.—Fused zinc chloride (5 g.) was dissolved in acetic anhydride (50 cc.) and the mixture was cooled to 0°. Gluconamide (7.5 g.) was added with shaking, and the mixture was kept in an ice-bath for an hour. The reaction mixture stood at room temperature for twenty-four hours (or until all amide was dissolved).

The mixture was poured out into 200 cc. of ice and water, and stirred vigorously for forty-five minutes, giving a crystalline powder. The solid was filtered and washed with water. It was recrystallized from 95% alcohol: m. p. 184–185°; $[\alpha]^{25}D$ +23.6° (*c*, 0.9 in $CHCl_3$)[1,4,7].

Pentaacetyl-*d*-galactonamide.—Galactonamide was acetylated as described above. No solid separated upon stirring. Extraction with chloroform was followed by evaporation of solvent. Addition of ether gave a solid product which was filtered. Recrystallization from benzene yielded pure pentaacetyl-*d*-galactonamide: m. p. 165–166°; $[\alpha]^{25}D$ +26.7° (*c*, 1.8 in $CHCl_3$).[4]

Anal. Calcd. for $C_{16}H_{23}O_{11}N$: C, 47.38; H, 5.73. Found: C, 47.36; H, 5.74.

Pentaacetyl-*d*-mannonamide.—Mannonamide was acetylated as described above and the chloroform extract was evaporated to a gum which crystallized on standing. Recrystallization was accomplished from butyl ethyl ether

(1) Upson and Bartz, THIS JOURNAL, **53**, 4226 (1931).
(2) Major and Cook, *ibid.*, **58**, 2477 (1936).
(3) Major and Cook, *ibid.*, **58**, 2410 (1936).
(4) Hurd and Sowden, *ibid.*, **60**, 235 (1938).
(5) Glattfeld and McMillan, *ibid.*, **56**, 2481 (1934).
(6) Miksic, Ves Kral-Ces. Spal-Nauk Cl. 11 (1929).
(7) Zemplén and Kiss, *Ber.*, **60**, 165 (1927).

of ethylene glycol; m. p. 110°; $[\alpha]^{25}D$ +38.7° (*c*, 1.8 in $CHCl_3$).

Anal. Calcd. for $C_{16}H_{23}O_{11}N$: C, 47.38; H, 5.73. Found: C, 47.30; H, 5.75.

Pentaacetyl-*d*-gulonamide.—This compound was prepared from a sample of *d*-gulonic lactone ($[\alpha]^{20}D$ −54.4°), using the method described in the preparation of the galactonic derivative. Recrystallization several times from absolute alcohol gave crystals melting at 162–164°; $[\alpha]^{25}D$ +22.7° (*c*, 1.6 in $CHCl_3$).

Anal. Calcd. for $C_{16}H_{23}O_{11}N$: C, 47.38; H, 5.73. Found: C, 47.19; H, 5.68.

Hexaacetyl-*d*-gluconamide.—Acetic anhydride (50 cc.) and concentrated sulfuric acid (3 cc.) were mixed and cooled to 0°. Gluconamide (6 g.) was added and the reaction was completed as in the case of the pentaacetyl derivatives. The solution was poured into ice water and sodium bicarbonate (10 g.) was added. Chloroform extraction yielded a sirup which crystallized upon standing. Ether was added and it was filtered. Recrystallization from alcohol gave the hexaacetyl-*d*-gluconamide: m. p. 110°; $[\alpha]^{25}D$ +25.8° (*c*, 1.8 in $CHCl_3$).

Anal. Calcd. for $C_{18}H_{25}O_{12}N$: C, 48.31; H, 5.64. Found: C, 48.14; H, 5.70.

Hexaacetyl-*d*-galactonamide.—Galactonamide was acetylated in the same manner as for preparation of the hexaacetyl-*d*-gluconamide. A solid separated upon stirring with ice water and sodium bicarbonate. The material was filtered and recrystallized from benzene: m. p. 149.5–150°; $[\alpha]^{25}D$ +19.0° (*c*, 1.8 in $CHCl_3$).

Anal. Calcd. for $C_{18}H_{25}O_{12}N$: C, 48.31; H, 5.64. Found: C, 48.08; H, 5.71.

Summary

1. A general preparation of acetylated sugar acid amides has been indicated. This offers an easier route to obtain the fully acetylated sugar acids.

2. The product of acetylation of amides of sugar acids is governed by the catalyst used. Concentrated sulfuric acid gives a product in which both hydroxyl groups and amide nitrogen are acetylated. Zinc chloride gives a product in which only hydroxyls are acetylated.

3. The above methods have been applied to the preparation of several acetylated amides, of which four are new compounds.

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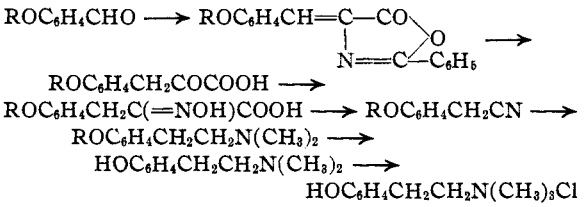
β-Phenylethylamine Derivatives.[1] Tertiary and Quaternary Salts

BY JOHANNES S. BUCK, RICHARD BALTZLY AND WALTER S. IDE

The present paper describes the preparation and properties of tertiary amine salts and quaternary salts containing the phenylethyl group. One series consists of alkoxy- and hydroxy-β-phenylethyldimethylamine hydrochlorides, of the type of hordenine, the other of the quaternary derivatives of these compounds.

Hordenine has received considerable attention in the literature, and a few related compounds also have been dealt with. For the most part the syntheses are unsatisfactory and not capable of being applied generally. The authors therefore worked out a series of reactions, a composite of various literature methods, which is generally applicable and which gives good yields at each stage. Starting with a substituted benzaldehyde, this is converted successively into the azlactone, the phenylpyruvic acid, the pyruvic acid oxime, and the phenylacetonitrile. This latter is then reduced, in one step, to the alkoxy-β-phenylethyldimethylamine, by catalytic reduction in the presence of excess dimethylamine. The tertiary amine may be converted readily into the quaternary salt, or O-dealkylated to give the hydroxy compound, which, in turn, easily forms the quaternary compound.

The series of reactions used is as follows



Experimental

The intermediates required were all prepared by the methods given below. A number of them have been described previously in the literature (many prepared by other methods). Only the ones not previously recorded are given (Table I).

Azlactones (2-Phenyl-4-(alkoxybenzal)-oxazolones).—These compounds were prepared in the conventional way from the appropriate benzaldehyde and hippuric acid,[2] and

(1) This work is part of a joint research being carried out in collaboration with a pharmacological group at the above laboratories.

(2) Kropp and Decker, *Ber.*, **42**, 1184 (1909); *Org. Syntheses*, **13**, 8 (1933).