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Summary

Alginic acid is converted into a nitrated alginic acid when in contact with nitric–sulfuric acid mixture. The ratio of nitrate groups per mannuronic unit, which varies from 0.49 to 1.2, largely depends upon the excess of nitric acid taken and upon the time of standing.

The failure to obtain higher nitration products is believed to be due to lactonization of the mannuronic units as the result either of drying the acid or of its coming in contact with concd. sulfuric acid.

When nitrated alginic acid is thoroughly dried lactonization of the carboxyl groups takes place.

Methylation of alginic acid by means of dimethyl sulfate and aqueous sodium hydroxide at 60° is not satisfactory since less than one methyl group per mannuronic unit is introduced, and degradation takes place.

Diazomethane is satisfactory as a methylating agent in that little or no degradation takes place. While the carboxyl group is undergoing methylation some methylation takes place on the hydroxyl group.

Nitrated alginic acid can be partially methylated but there is no replacement of nitrate by methoxyl groups.

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

Some Fully Acetylated Sugar Acids and their Derivatives

BY GORDON B. ROBBINS AND F. W. UPSON

Interest in the fully acetylated aldonic acids has been stimulated by Major and Cook[1,2,3] through the preparation and application to synthesis of acid chlorides of these acids. A general method of preparing fully acetylated sugar acids has been reported by Hurd and Sowden,[4] who prepared fully acetylated *d*-gluconic, *d*-galactonic and *l*-arabonic acids by treating an acetic acid solution of the acetylated acid amide with nitrous anhydride. Direct acetylation of aldonic acid amides has been shown to be a simple and general method for preparing the fully acetylated amides.[5] Various acetylated amides which had been prepared by this method have been treated according to the method of Hurd and Sowden[4] to give new fully acetylated aldonic acids.

Direct acetylation of gluconic acid has been reported to be unsuccessful by Major and Cook.[3] We have found, however, that some aldonic acids can be acetylated directly. Several of these are described in the following investigation. In addition some other fully acetylated acids hitherto unknown were prepared by the method of Hurd and Sowden. Thus tetraacetyl-*d*-arabonic, pentaacetyl-*d*-gulonic, and hexaacetyl-*d*-α-glucoheptonic acids were prepared by this procedure. A modification of the method was employed in the preparation of pentaacetyl-*d*-talonic acid and pentaacetyl-*d*-mannonic acid monohydrate. These acids were prepared by treating the reaction mixture from the acetylation of the corresponding aldonic amide with nitrous anhydride.

It was impossible to prepare hexaacetyl-*d*-α-galaheptonic acid from the corresponding amide by this method. The acetylated amide proved too insoluble in any solvents at suitable temperatures.

The unusual stability of *d*-α-galaheptonic acid suggested the possibility of direct acetylation to give the fully acetylated acid. Direct acetylation yielded hexaacetyl-*d*-α-galaheptonic acid as was indicated by comparison of the product with the acetylated lactone, analysis of the product, and its conversion into the methyl ester. Direct acetylation of *d*-arabonic, *d*-galactonic, and *d*-talonic acids likewise yielded the corresponding fully acetylated acids which were identified by comparison with the product obtained from the acetylated amide. The yields were too low to be satisfactory for the preparation of the fully acetylated *d*-galactonic and *d*-talonic acids, but proved to be the most successful method for obtaining tetraacetyl-*d*-arabonic acid.

Attempts were made to prepare fully acetylated *d*-mannonic, *d*-gulonic and *d*-α-glucoheptonic acids

(1) Major and Cook, THIS JOURNAL, **58**, 2477 (1936).
(2) Cook and Major, *ibid.*, **58**, 2410 (1936).
(3) Major and Cook, *ibid.*, **58**, 2474 (1936).
(4) Hurd and Sowden, *ibid.*, **60**, 235 (1938).
(5) Robbins and Upson, *ibid.*, **60**, 1788 (1938).

by treating the sodium salts of these acids with acetic acid–acetic anhydride mixtures, but the acetylated lactone was produced in each case.

Phenylhydrazides of the fully acetylated sugar acids were prepared by acetylation of the aldonic phenylhydrazide as Major and Cook[3] have done in preparing pentaacetyl-*d*-gluconic phenylhydrazide. Methyl esters were prepared by treating the fully acetylated acid with diazomethane.

d-Arabonamide and *d*-arabonic acid have been prepared in the course of this study and are reported for the first time. The acetylated *d*-arabonic and *d*-α-galaheptonic lactones are also reported.

Experimental

***d*-Arabonamide.**—*d*-Arabonic lactone was prepared by treating glucose with oxygen in 2 *N* potassium hydroxide according to the method of Spengler and Pfannenstiel.[6] The potassium salt was transformed to the calcium salt which was decomposed with oxalic acid to yield the lactone. The lactone was dissolved in liquid ammonia. The ammonia was allowed to evaporate, and the amide was heated at 60° *in vacuo* to remove the last of the ammonia. The amide was recrystallized several times from ethanol.

Fully Acetylated Aldonic Amides (Compounds 2–4).[7]—The aldonamide (7.5 g.) was acetylated with a solution of zinc chloride (4 g.) in 50 cc. of acetic anhydride at 0°. After the amide had dissolved, the mixture was stirred with ice water and neutralized with sodium bicarbonate. The product was obtained by extraction with chloroform and evaporation of the extract.

Compound 2 was recrystallized from absolute ethanol.

Compound 3 was prepared from *d*-talonamide.[8] It did not crystallize until the extract had stood *in vacuo* for a time. It was recrystallized twice from the butyl ethyl ether of ethylene glycol.

Compound 4 was prepared from *d*-α-galaheptonamide.[9] The product separated upon stirring with water. Filtration was substituted for chloroform extraction. The product was recrystallized twice from glacial acetic acid.

***d*-Arabonic Acid.**—The calcium salt was prepared by the method described in the preparation of *d*-arabonamide. It was converted to the sodium salt by treating the calcium salt with equivalent amounts of oxalic acid and sodium bicarbonate. The solution of sodium salt was concentrated to a sirup and treated with acetic acid according to the method of Brackenbury and Upson[10] for the preparation of *l*-arabonic acid. The acid was purified in the same manner as the *l*-form.

Fully Acetylated Aldonic Acids (Compounds 7–10).—The aldonamide was acetylated under the conditions described above. After acetylation was complete, the mixture was treated with nitrous anhydride at 8–10° until it remained yellowish-green. It was allowed to stand for four hours at room temperature. The mixture was diluted with 100 cc. of water, made alkaline with sodium bicarbonate, acidified with dilute hydrochloric acid, and warmed to 40°. The mixture was cooled and extracted with chloroform. The extract was evaporated to a sirup and crystallized from water. It was recrystallized twice from water.

Compounds 7 and 8 were best prepared by the above procedure.

Compounds 6–10 were prepared by a modification of the above procedure using a solution of the pure acetylated aldonamide in glacial acetic acid. This procedure was found to be the most satisfactory for compounds 9 and 10.

Compound 9 could not be crystallized. The sirupy extract was dissolved in ether and filtered from any unreacted amide. The ethereal filtrate was evaporated to a gum and dried in an Abderhalden drier for analysis and specific rotation.

Direct Acetylation of Aldonic Acids (Compounds 6 and 11).—The aldonic acid (10 g.) was treated with a solution of zinc chloride (4 g.) in 50 cc. of acetic anhydride at 0° for two or three days. The reaction mixture was stirred with ice water and extracted with chloroform. The extract was evaporated to a gum which crystallized.

In the preparation of compound 6, the product partially separated from the acetylation mixture and was filtered off before treatment with ice water. The product was recrystallized from toluene.

Compound 11 was recrystallized from water.

Acetylated Aldonic Lactones (Compounds 12 and 13).—The aldonic lactone (5 g.) was treated with 25 cc. of acetic anhydride at 0° and allowed to stand for a day. The mixture was stirred with ice water and extracted with chloroform. The extract was evaporated to a gum which crystallized on standing. The product was recrystallized from ethanol.

In the preparation of compound 12, zinc chloride (2 g.) was used as catalyst. The lactone was prepared as described under the preparation of the amide.

Compound 13 was prepared using concentrated sulfuric acid (1 cc.) as catalyst.

Fully Acetylated Aldonic Phenylhydrazides (Compounds 14–20).—The aldonic phenylhydrazide (7.5 g.) was treated with a solution of zinc chloride (4 g.) in 50 cc. of acetic anhydride at 0°. The mixture stood for a day at room temperature. It was stirred with ice water and extracted with chloroform.

Compounds 14, 15, 16, 17, 19 and 20 were obtained in crystalline form upon evaporation of the extract. The products were recrystallized by solution in ethanol and addition of ether.

Compound 18 failed to crystallize upon evaporation of the chloroform. The gum was dried in an Abderhalden drier for analysis and specific rotation.

Methyl Esters of Fully Acetylated Aldonic Acids (Compounds 21–27).—The fully acetylated aldonic acid was dissolved in a small amount of ethanol, cooled, and treated with the amount of an ethereal solution of diazomethane[11] which was necessary to produce a persistent yellow color. The solution was filtered and evaporated. The product

(6) Spengler and Pfannenstiel, German Patent 618,164.

(7) Numbers refer to those in the tabulation of compounds and constants.

(8) Renfrew and Cretcher, THIS JOURNAL, **54**, 4402 (1932).

(9) Hann, Merrill and Hudson, *ibid.*, **57**, 2100 (1935).

(10) Brackenbury and Upson, *ibid.*, **55**, 2512 (1933).

(11) "Organic Syntheses," Vol. 15, 1935, pp. 48, 3.

TABLE I

No.	Compound	M. p., °C.	$[\alpha]^{25}D$[a]	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
1	*d*-Arabonamide	138–139	+38.6°[b]	$C_5H_{11}O_5N$	36.34	6.72	36.37	6.73
2	Tetraacetyl-*d*-arabonamide	123	+24.3°	$C_{13}H_{19}O_9N$	46.83	5.75	46.76	5.82
3	Pentaacetyl-*d*-talonamide	104–106	+85.4°	$C_{16}H_{22}O_{11}N$	47.38	5.73	47.26	5.78
4	Hexaacetyl-*d*-α-galaheptonamide	185–187	+ 2.1°	$C_{18}H_{27}O_{13}N$	47.78	5.74	47.67	5.63
5	*d*-Arabonic acid	114–116	+10.5°[b]	$C_5H_{10}O_6$	36.13	6.07	36.12	6.00
6	Tetraacetyl-*d*-arabonic acid	135–136	+32.5°	$C_{13}H_{18}O_{10}$	46.69	5.43	46.69	5.42
7	Pentaacetyl-*d*-mannonic acid monohydrate	75–76	+24.8°	$C_{16}H_{22}O_{12}\cdot H_2O$	45.26	5.69	45.28	5.61[c]
8	Pentaacetyl-*d*-talonic acid	142–144	+78.3°	$C_{16}H_{22}O_{12}$	47.27	5.46	47.03	5.45
9	Pentaacetyl-*d*-gulonic acid	Sirup	+ 1.8°	$C_{16}H_{22}O_{12}$	47.27	5.46	47.07	5.50
10	Hexaacetyl-*d*-α-glucoheptonic acid hemihydrate	94	+10.7°	$C_{19}H_{26}O_{14}\cdot{}^1/_2H_2O$	46.80	5.59	46.73	5.64[d]
11	Hexaacetyl-*d*-α-galaheptonic acid	176–177	+15.3°	$C_{19}H_{26}O_{14}$	47.68	5.48	47.50	5.52
12	Triacetyl-*d*-arabonic lactone	68–69	+52.3°	$C_{11}H_{14}O_8$	48.16	5.15	48.18	5.15
13	Pentaacetyl-*d*-α-galaheptonic lactone	123–124	−16.9°	$C_{17}H_{22}O_{12}$	48.78	5.30	48.69	5.29
14	Tetraacetyl-*d*-arabonic phenylhydrazide	140–141	+ 8.4°	$C_{19}H_{24}O_9N_2$	53.76	5.71	54.04	5.74
15	Pentaacetyl-*d*-galactonic phenylhydrazide	220	+23.6°	$C_{22}H_{28}O_{11}N_2$	53.20	5.69	53.36	5.73
16	Pentaacetyl-*d*-mannonic phenylhydrazide	173	+13.0°	$C_{22}H_{28}O_{11}N_2$	53.20	5.69	53.37	5.67
17	Pentaacetyl-*d*-talonic phenylhydrazide	162–163	+35.0°	$C_{22}H_{28}O_{11}N_2$	53.20	5.69	53.52	5.75
18	Pentaacetyl-*d*-gulonic phenylhydrazide	Sirup	+37.7°	$C_{22}H_{28}O_{11}N_2$	53.20	5.69	53.13	5.63
19	Hexaacetyl-*d*-α-glucoheptonic phenylhydrazide	154	+27.4°	$C_{25}H_{32}O_{13}N_2$	52.80	5.68	52.82	5.68
20	Hexaacetyl-*d*-α-galaheptonic phenylhydrazide	112–114	+25.9°	$C_{25}H_{32}O_{13}N_2$	52.80	5.68	52.63	5.73
21	Methyl tetraacetyl-*d*-arabonate	136	+42.3°	$C_{14}H_{20}O_{10}$	48.25	5.79	48.20	5.73
22	Methyl pentaacetyl-*d*-gluconate	124	+ 9.2°	$C_{17}H_{24}O_{12}$	48.55	5.75	48.41	5.69
23	Methyl pentaacetyl-*d*-galactonate	126–127	+ 2.5°	$C_{17}H_{24}O_{12}$	48.55	5.75	48.42	5.64
24	Methyl pentaacetyl-*d*-talonate	78–79	+70.1°	$C_{17}H_{24}O_{12}$	48.55	5.75	48.41	5.70
25	Methyl pentaacetyl-*d*-gulonate	Sirup	+ 4.4°	$C_{17}H_{24}O_{12}$	48.55	5.75	48.64	5.82
26	Methyl hexaacetyl-*d*-α-glucoheptonate	93	+14.1°	$C_{20}H_{28}O_{14}$	48.76	5.73	48.47	5.70
27	Methyl hexaacetyl-*d*-α-galaheptonate	96–97	+18.8°	$C_{20}H_{28}O_{14}$	48.76	5.73	48.70	5.69

[a] Rotations taken in two-decimeter tube; concentration, 1.5–2.5 g./100 cc. Solvent is chloroform except as noted. [b] Solvent is water, concentration 6 g./100 cc. [c] Water of hydration: calcd., 4.25%; found, 4.24%. [d] Water of hydration: calcd., 1.88%; found, 1.84%.

crystallized during evaporation, and was recrystallized from ethanol with the addition of a small amount of petroleum ether.

Compounds 21, 22, 23, 24, 26 and 27 were prepared by the above directions, while compound 25, which failed to crystallize, was obtained by drying the gum in an Abderhalden drier for analysis and specific rotation.

Summary

1. The amides and phenylhydrazides of several fully acetylated aldonic acids have been prepared by direct acetylation of the aldonic acid derivative.

2. Pentaacetyl-*d*-mannonic acid monohydrate, pentaacetyl-*d*-talonic acid, pentaacetyl-*d*-gulonic acid and hexaacetyl-*d*-α-glucoheptonic acid hemihydrate have been prepared by treating the corresponding acetylated amide with nitrous anhydride.

3. Direct acetylation of aldonic acids to the fully acetylated acids has been reported for the first time. Tetraacetyl-*d*-arabonic and hexaacetyl-*d*-α-galaheptonic acids have been prepared in good yield by this method.

4. Methyl esters of several fully acetylated aldonic acids have been prepared by treating a solution of the acid with a solution of diazomethane.

5. *d*-Arabonamide, *d*-arabonic acid, triacetyl-*d*-arabonic lactone, and pentaacetyl-*d*-α-galaheptonic lactone have been prepared.

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