This compound was also obtained when 13.0 g. of 4-bromo-2,3,5,6-tetramethylbenzophenone was treated with the Grignard reagent prepared from 30 cc. of *t*-butyl chloride, using the same procedure as in the reaction of benzoyldurene with benzylmagnesium chloride. There was obtained 6.1 g. (40%) of a product shown by the method of mixed melting points to be identical with that produced by the bromination method.

Anal. Calcd. for $C_{21}H_{25}OBr$: C, 67.56; H, 6.75; Br, 21.41. Found: C, 67.79; H, 6.86; Br, 21.25.

In addition, 1.1 g. (8%) of the original ketone was recovered by fractional crystallization.

Summary

Benzoyldurene has been found to react with benzyl- and *t*-butylmagnesium chloride to undergo para alkylation, yielding the corresponding duryl *p*-alkylphenyl ketones. The introduction of the alkyl groups into the para position of the benzoyl group corresponds to 1,6 addition of the Grignard reagent followed by loss of a molecule of hydrogen or its equivalent.

URBANA, ILLINOIS RECEIVED OCTOBER 14, 1942

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Ring Structure of Polygalitol

BY NELSON K. RICHTMYER AND C. S. HUDSON

Polygalitol is an anhydrohexitol which was discovered by Chodat[1] in an extract of *Polygala amara*, L. It has been isolated also from *P. vulgaris*, L.,[2] from *P. tenuifolia*,[3] and from *P. Senega*, L.[4] According to Shinoda, Sato and Sato,[3] polygalitol is the epimer of styracitol, a 1,5-anhydro-D-hexitol which was isolated from *Styrax Obassia*, Sieb and Zucc., by Asahina,[5] and later synthesized by Zervas.[6] The 1,5-ring structure of styracitol is based upon the reasonable assumption that no shift in the size of the ring has occurred during the synthesis from acetobromoglucose. Although this synthesis by the addition of hydrogen to the 1,2 double bond in tetraacetylhydroxyglucal does not enable one to distinguish between the mannitol and sorbitol configurations for this compound, evidence has been presented by Zervas and Papadimitriou[7] to prove that styracitol is 1,5-anhydro-D-mannitol. Consequently, if polygalitol is the epimer, it must be 1,5-anhydro-D-sorbitol.

However, W. Freudenberg and Sheehan[8] have claimed that tetramethylstyracitol is identical with their synthetic tetramethyl-1,5-anhydrosorbitol. Tetramethylpolygalitol, on the other hand, appeared to be quite different from their synthetic tetramethyl-1,5-anhydromannitol and especially from their tetramethyl-1,5-anhydrosorbitol. They have concluded, therefore, that polygalitol is neither 1,5-anhydro-D-sorbitol nor 1,5-anhydro-D-mannitol, and also that styracitol is 1,5-anhydro-D-sorbitol.

In view of these conflicting opinions and the lack of satisfactory experimental evidence concerning the structure and configuration, especially of polygalitol, we have decided to examine these substances by the application of some new methods of study.

The present communication deals with the oxidation of styracitol and polygalitol by periodic acid[9] and by sodium metaperiodate.[10] These reagents can be used to determine directly and conclusively the ring structures of such compounds. With each of the two anhydrohexitols (I) the reaction with sodium metaperiodate consumed two equivalents of oxidant, and liberated one equivalent of formic acid; the rotations of the resulting solutions had the same value, indicating the formation of the same dialdehyde (II). The reactions with periodic acid likewise consumed two equivalents of oxidant. In each case, the presumed dialdehyde (II), upon further oxidation with bromine water and strontium carbonate, yielded a crystalline, hydrated strontium salt; the salts were identical, as could be shown by analyses for carbon, hydrogen, strontium and water of crystallization and by their rotations in water and in excess hydrochloric acid. The strontium salt (III), named in accordance with the established terminology,[9] is strontium D-hy-

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[1] Chodat, *Arch. sci. phys. nat.*, [3] **18**, 228 (1887); [3] **19**, 290 (1888).

[2] Picard, *Bull. soc. chim. biol.*, **9**, 692 (1927).

[3] Shinoda, Sato and Sato, *Ber.*, **65**, 1219 (1932).

[4] (a) W. Freudenberg and Rogers, THIS JOURNAL, **59**, 1602 (1937); (b) Carr and Krantz, *J. Am. Pharm. Assoc.*, **27**, 318 (1938).

[5] Asahina, *Arch. Pharm.*, **245**, 325 (1907); **247**, 157 (1909).

[6] Zervas, *Ber.*, **63**, 1689 (1930).

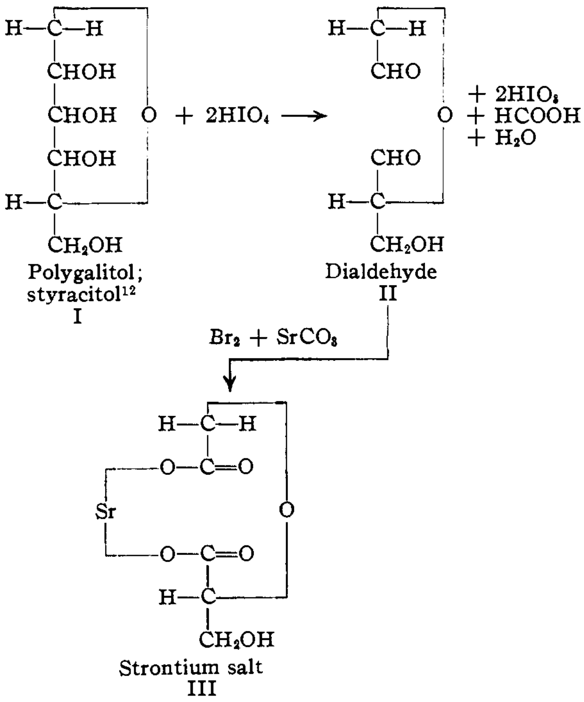
[7] Zervas and Papadimitriou, *ibid.*, **73**, 174 (1940).

[8] W. Freudenberg and Sheehan, THIS JOURNAL, **62**, 558 (1940).

[9] Jackson and Hudson, *ibid.*, **59**, 994 (1937).

[10] Jackson and Hudson, *ibid.*, **61**, 1530 (1939).

droxymethyldiglycolate.[11] The designation as a member of the D-series is based upon the fact that styracitol was synthesized from D-glucose.



Polygalitol; styracitol[12] I

Dialdehyde II

Strontium salt III

Inasmuch as there is only one possible ring structure which will permit the consumption of two equivalents of periodic acid, the liberation of one equivalent of formic acid, and the formation of a dialdehyde containing five carbon atoms, the data reported above prove conclusively that polygalitol and styracitol are isomeric 1,5-anhydro-D-hexitols as generally believed. The application of new methods to a study of the configuration of polygalitol is now in progress.

From the leaves of *Acer ginnala*, Maxim., Perkin and Uyeda[13] isolated a crystalline tannin, which, upon hydrolysis, yielded aceritol, an anhydrohexitol. W. Freudenberg and Rogers[4a] have established the identity of aceritol and polygalitol by a comparison of rotations and melting points, and especially by a determination of the melting point of a mixture of the two substances; the melting points of the tetraacetates were also in agreement. We are now able to confirm their identification through the kindness of Dr. and Mrs. George Tunell of the Geophysical Laboratory of the Carnegie Institution of Washington, who have made a crystallographic study of polygalitol and have compared their data with the precise measurements of aceritol by Miss M. W. Porter, as reported by Perkin and Uyeda.[13]

Experimental Part

Polygalitol.—A 1000-g. portion of powdered Senega root, N. F. was covered with about 3500 cc. of water and heated for six hours at 60–80°. The "soup" was cooled, mixed with "Filter-cel" and filtered through a Büchner funnel precoated with a layer of "Filter-cel." The residue was extracted twice more in similar fashion. To the combined extracts (12 liters; *p*H 4.9) was added 100 g. of bakers' yeast; fermentation proceeded readily in a warm room, and overnight the reading on a Brix spindle dropped from 3.2 to 2.0 (constant), indicating the loss of about 144 g. of fermentable sugar.[14] The mixture was filtered with the aid of "Filter-cel," and the filtrate was treated with basic lead acetate followed by hydrogen sulfide in the usual manner.[3] The aqueous solution was concentrated *in vacuo* to a sirup which was extracted thoroughly with methyl alcohol. By the cautious addition of ether to the methyl alcohol solution,[3] the less soluble impurities could be precipitated fractionally. The several fractions containing the more soluble material were concentrated, inoculated with seed crystals,[15] and the product was allowed to crystallize for a week or more in a desiccator. The crude polygalitol was granular, and could be separated readily from the residual sirup with the aid of methyl alcohol. The melting point was 139–141°, and the yield averaged nearly 12 g. from each 1000 g. of Senega root. Twice recrystallized from hot methyl alcohol, as clusters of thin, more or less hexagonal plates, the polygalitol melted at 141–142° in agreement with the value 142–143° as usually reported. The rotation,[16] +42.5° in water (*c*, 2), agrees with the rotations of +42.86 and +42.0° reported by W. Freudenberg.[4a,8] The rotation +47.8°, which was published by Shinoda, Sato and Sato,[3] appears to have been calculated from an incorrect formula, in which the reciprocal of the density has been used instead of the density; recalculation of their data, on such an assumption, leads to the $[\alpha]^{16}\mathrm{D}$ value of +42.87°.

Crystallographic Examination of Polygalitol and Confirmation of its Identity with Aceritol.—The following report on polygalitol which had been recrystallized from water was furnished by Ruth P. Tunell.

"Of the crystals of polygalitol sent by you, I have

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(11) Dr. Robert C. Hockett and Miss Maryalice Conley, of the Massachusetts Institute of Technology, have obtained independently this same strontium salt by the oxidation of styracitol with lead tetraacetate followed by strontium hypobromite. Their work will be described in a later article in THIS JOURNAL [private communication].

(12) As explained above, the configurations of the hydrogen atoms and hydroxyl groups on carbon atoms 2, 3 and 4 in polygalitol are in doubt but in styracitol the configuration at carbon 2 alone is doubtful, since the hydroxyls of carbon atoms 3 and 4 are unquestionably the same as in D-glucose. The asymmetry of carbon atoms 2, 3 and 4 is lost during the oxidations with periodic acid.

(13) Perkin and Uyeda, *J. Chem. Soc.*, **121**, 66 (1922).

(14) The presence of sucrose in *Senega* root was demonstrated conclusively by Bienfang [*J. Am. Pharm. Assoc.*, **23**, 396 (1934)]. We also isolated crystalline sucrose in a preliminary experiment, and accordingly decided to remove all fermentable sugars in the manner described above.

(15) Furnished through the courtesy of Dr. C. Jelleff Carr of the University of Maryland School of Medicine.

(16) Throughout the article the rotations are specific rotations at 20° for sodium light; *c* designates concentration in grams per 100 cc of solution, and *l* the length of the tube in decimeters.

TABLE I

COÖRDINATE ANGLES OF POLYGALITOL AND ACERITOL CRYSTALS

Face	φ Polygalitol (R. P. Tunell)	φ Aceritol (M. W. Porter)	φ Calculated[a]	ρ Polygalitol (R. P. Tunell)	ρ Aceritol (M. W. Porter)	ρ Calculated[a]
a	89°53'	90°02'	90°00'	89°55'	89°58'	90°00'
m	51°44'	51°56'	51°56'	89°50'	89°59'	90°00'
q	32°09'	32°53'	32°35'	34°10'	34°02'	34°02'
b	. . .	00°34'	00°00'	. . .	89°57'	90°00'
c	90°25'	88°51'	90°00'	20°08'	19°59'	19°59'

[a] Calculated by Miss Porter from her axial elements for aceritol.

mounted 4 crystals, 2 that had been dipped in methyl alcohol and 2 from the mother liquor. The coördinate angles of the faces of these crystals were then measured on the two-circle reflection goniometer.[17] The results agree closely with those obtained previously by Miss Porter,[13] on crystals of aceritol, as shown by Table I. The agreement is within the accuracy of the measurements, which in this case is limited by the quality of the signals yielded by the crystal faces. The crystals sent by you exhibit the same habit as the one shown by Miss Porter in her Fig. 2, except that on some of the polygalitol crystals the base c is missing. The probability that the crystals of polygalitol are chemically identical with the aceritol crystals is strong.

"The crystals of polygalitol were observed in this study to have a perfect cleavage parallel to the base c (001)."

Tetraacetylpolygalitol.—Acetylation of polygalitol with acetic anhydride and sodium acetate produced the expected compound in an almost theoretical yield. Tetraacetylpolygalitol crystallized from a mixture of ether and isopentane in two distinct forms, either of which could be obtained by suitable inoculation of the solution. The form first isolated, in diamond-shaped prisms melting at 65–67°, is probably the one described by Shinoda, Sato and Sato[8]; they reported a melting point of 60° at first, rising later to 73–75°. The second form, in long, flat, prismatic needles melting at 73–74°, is undoubtedly the compound described by Perkin and Uyeda[13] as tetraacetylaceritol, melting at 74–75°. The rotation has not been recorded by previous investigators; we found $[\alpha]^{20}D$ to be +38.9° in chloroform (c, 2), and identical for each of the two forms. The tetraacetate apparently exhibits dimorphism.

Anal. Calcd. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: (needles), C, 50.75; H, 6.11; (prisms), C, 50.69; H, 6.05.

Oxidation of Styracitol with Sodium Metaperiodate.—To 0.3693 g. of recrystallized styracitol,[15] of rotation −50.6° in water (c, 2), was added 12 cc. of 0.412 molal aqueous sodium periodate (2.2 equivalents), and the solution was diluted exactly to 50 cc. with water. Overnight the rotation changed to −1.5°, calculated as the expected dialdehyde, and titration of a 10-cc. sample indicated that 2.00 equivalents of oxidant had been consumed. The rotation, however, continued to change, and became constant at −9.7° after ten days at 20°. A titration of the periodate in excess at the end of nineteen days showed that 2.01 equivalents of oxidant had been consumed. The titration of another 10-cc. portion with 0.1 N sodium hydroxide, in the presence of methyl red, indicated that 0.99 equivalent of formic acid had been liberated.

Oxidation of Polygalitol with Sodium Metaperiodate.—To 0.1843 g. of pure polygalitol, of rotation +42.5° in water (c, 2), was added 6 cc. of 0.412 molal aqueous sodium periodate (2.2 equivalents), and the solution was diluted exactly to 25 cc. with water. The rotation dropped overnight to −1.5°, calculated as the dialdehyde, and became constant at −9.9° in about ten days. After three days, the consumption of oxidant was 2.01 equivalents, a value which was found to be practically unchanged after nineteen days. At that time titration with alkali indicated the presence of 0.98 equivalent of formic acid in the oxidation mixture.

Oxidation of Styracitol with Periodic Acid.—To 4.548 g. of styracitol in 50 cc. of water was added 100 cc. of 0.614 molal periodic acid (2.2 equivalents), and the solution was diluted exactly to 200 cc. with water. After three days the rotation had become constant at −9.0°, calculated as the dialdehyde. Titration of an aliquot portion for excess periodic acid showed that 2.03 equivalents had been consumed. The remainder of the solution was neutralized with strontium hydroxide, and the dialdehyde was separated from the strontium salts and oxidized with bromine water and strontium hydroxide, in the usual manner. A crystalline strontium salt (3.1 g.) was obtained without difficulty. This salt was recrystallized from water by the addition of alcohol, and then from water alone, as small, chunky prisms. The air-dried product has the composition of a tetrahydrate of the expected salt, and accordingly is to be named **strontium D-hydroxymethyldiglycolate tetrahydrate.**[11] The rotation of the hydrated salt was −10.8° in water (c, 1.6; l, 4), equivalent to −13.9 ± 0.4° for the anhydrous salt (c, 1.2). The rotation of the hydrated strontium salt was +23.2° in an excess of N hydrochloric acid (c, 2; l, 4), equivalent to +45.4 ± 0.4° for the liberated dibasic acid (c, 1.0).

Anal. Calcd. for $C_5H_6O_6Sr \cdot 4H_2O$: C, 18.66; H, 4.38; Sr, 27.23; H_2O, 22.39. Found: C, 18.92; H, 4.49; Sr, 27.19; H_2O (dried at 110° *in vacuo*), 22.23.

Oxidation of Polygalitol with Periodic Acid.—A 3.411-g. portion of polygalitol was oxidized with 75 cc. of 0.614 molal periodic acid in a total volume of 200 cc. in the same manner as described above. The rotation of the dialdehyde in the reaction mixture was −8.3° (constant), and 2.05 equivalents of oxidant were consumed. The dialdehyde was oxidized with bromine water and strontium carbonate to a crystalline strontium salt (2.6 g.) which appeared identical in all respects with the **strontium D-hydroxymethyldiglycolate tetrahydrate** derived from styracitol. The rotation of the twice recrystallized hy-

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(17) These measurements were carried out in the Geophysical Laboratory and valuable advice was received from Dr. George Tunell.

drated salt was $-10.8°$ in water (c, 1.6; l, 4), equivalent to $-13.9 \pm 0.4°$ for the anhydrous salt (c, 1.2). The rotation of the hydrated strontium salt was $+23.3°$ in an excess of N hydrochloric acid (c, 1.9; l, 4), equivalent to $+45.6 \pm 0.4°$ for the liberated dibasic acid (c, 0.98).

Anal. Calcd. for $C_6H_6O_6Sr \cdot 4H_2O$: C, 18.66; H, 4.38; Sr, 27.23; H_2O, 22.39. Found: C, 18.76; H, 4.52; Sr, 27.05; H_2O (dried at 130° *in vacuo*), 22.47.

The authors express their indebtedness to Dr. C. Jelleff Carr, of the University of Maryland School of Medicine, for his generous gift of synthetic styracitol; to Dr. and Mrs. George Tunell, of the Geophysical Laboratory of the Carnegie Institution of Washington, for their measurements of the polygalitol crystals; and to Dr. Arthur T. Ness, of this Laboratory, for carrying out the microanalyses. One of the authors (N. K. R.) desires to thank the Chemical Foundation, of New York, for a Research Associateship which he held while completing a portion of this research.

Summary

1. An improved method has been described for the isolation of polygalitol from *Polygala Senega*, L.

2. The identity of aceritol and polygalitol has been confirmed by crystallographic examination.

3. Polygalitol and styracitol have been oxidized by periodic acid, followed by bromine water and strontium carbonate, to strontium D-hydroxymethyldiglycolate. Polygalitol and styracitol have thus been proved to possess the same 1,5-ring; the D-configuration of polygalitol follows from the known D-configuration of styracitol.

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[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

2,3,4,5-Dimethylene-D-mannitol and a Second Dimethylene-D-mannitol

BY W. T. HASKINS, RAYMOND M. HANN AND C. S. HUDSON

In a study of the products that result from the condensation of formaldehyde with D-mannitol in the presence of strong hydrochloric acid, we have isolated the known trimethylene-D-mannitol (m. p. 227°, $[\alpha]_D$ $-103.9°$ in chloroform)[1] and a new substance, the analysis of which shows that it is a dimethylene-D-mannitol (m. p. 204–208°, $[\alpha]^{20}$D $-91.0°$ in water).

Trimethylene-D-mannitol and a New Dimethylene-D-mannitol from Formaldehyde, D-Mannitol and Concentrated Hydrochloric Acid.—A solution of 100 g. of D-mannitol in a mixture of 100 cc. of 37% formaldehyde and 100 cc. of concentrated hydrochloric acid was heated on the steam-bath for forty-five minutes; the reaction mixture was cooled and the precipitated trimethylene-D-mannitol (47 g., 39%) was separated by filtration, and upon recrystallization from 100 parts of 50% alcohol it was obtained in needles which melted sharply at 232° (cor.) and rotated $[\alpha]^{20}$D $-104.0°$ in chloroform (c, 2.2)[2] in agreement with the recorded values of Schulz and Tollens. The strongly acid filtrate remaining after the separation of the trimethylene-D-mannitol was neutralized with 64 g. of sodium carbonate and the solution was concentrated *in vacuo;* the crystalline residue was extracted with hot absolute alcohol and as the extract cooled it deposited tufts of plates which, after recrystallization from 8 parts of alcohol, melted at 204–208° (cor.) and rotated $[\alpha]^{20}$D $-91.0°$ in water (c, 0.9). The yield was 14.3 g. (12.6%).

Anal. Calcd. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.47; H, 6.82.

No dimethylene-D-mannitol has been reported previously, but Micheel[3] has established the structure for a 1,6-di-iodo-2,3,4,5-dimethylene-D-mannitol and some derivatives of it; our first effort was therefore directed toward determining whether our dimethylene-D-mannitol is to be regarded as the corresponding diacetal in Micheel's series of compounds. A test showed that the dimethylene-D-mannitol (m. p. 204–208°) was not oxidized by per-iodic acid, which proves that the substance contains no α-glycol grouping; the possibility of its belonging in Micheel's series of compounds was therefore not excluded. A decisive answer to the question was obtained through the preparation, by structurally interpretable syntheses, of the hitherto unknown 2,3,4,5-dimethylene-D-mannitol; the properties of this substance (m. p. 139° (cor.); $[\alpha]^{20}$D $+71.1°$ in water) show that the two dimethylene-D-mannitols are different compounds. In naming them we designate the one of melting point 139° as 2,3,4,5-

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(1) Schulz and Tollens, *Ann.*, **289**, 21 (1896).

(2) All of the crystalline compounds described in the experimental part were recrystallized to constant melting point and specific rotation, $[\alpha]^{20}$D; c is the concentration in grams in 100 cc. of solution; the tube length was 4 dm.

(3) Micheel, *Ann.* **496**, 93 (1932).