general fundamental principles which may be applicable to many other chemotherapeutic or biological actions. Anionic antiseptics in general, if their action is reversible, may fit equations analogous to those derived above. The equations describing the action of cationic reagents can also be derived very readily. When comprehensive quantitative data on drug activities in these various cases are available, it may be possible to throw some light on the mechanism of their action by analyzing the results from the point of view described above.

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Summary

The inhibition of bacterial growth by sulfonamides may be accounted for quantitatively by assuming that the action is due to a reversible combination between the basic form of the drug and the neutral form of the protein, and that the law of mass action is applicable. Equations may be derived which relate drug potency to the acid ionization constant of the sulfonamide and to the *p*H of the solution.

The reversal of sulfonamide bacteriostasis by addition of *p*-aminobenzoic acid may be considered from the same point of view. Expressions may be obtained which account for variations in the ratio of sulfonamide to *p*-aminobenzoic acid from drug to drug and from one *p*H to another.

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The Structure of Styracitol[1]

BY ROBERT C. HOCKETT AND MARYALICE CONLEY[2]

In a recent paper,[3] it was indicated that the behavior of styracitol when oxidized by lead tetraacetate in acetic acid under standard conditions points clearly to the 1,5-anhydro-D-mannitol structure assigned to this compound by Zervas and Papadimitriou.[4] It was stated further that because the configuration of styracitol has been the subject of so much controversy[5] and because this oxidation method is relatively new, we would seek other evidence concerning the configuration of this substance. The rate-of-oxidation measurement would appear to offer an extremely simple and rapid method of solving such structural problems as this, provided that it can be depended upon invariably to give the right answer. Hence the establishment of the styracitol structure beyond question was essential to any extension of the oxidation procedure to other problems.

In 1931, Asahina and Takimoto[5] reported the complete methylation of this anhydro-alcohol and claimed the isolation of *d*-dimethoxysuccinic acid from the products of oxidation of tetramethyl styracitol by nitric acid. The formation of this acid is entirely incompatible with the 1,5-anhydromannitol structure assigned by Zervas and Papadimitriou[4] and provided the basis for Asahina's claim that styracitol is 1,5-anhydro-D-sorbitol. Zervas' synthesis of the compound[5] appears to establish the position of the ring and to limit the structural possibilities to the two alternatives mentioned.

We have undertaken to repeat the work of Asahina and Takimoto in order to discover the cause of this disagreement. Styracitol has been prepared synthetically by the method of Zervas.[5] Methylation by the procedure of West and Holden[6] yielded a tetramethyl ether of the expected composition and whose properties agreed well with those reported by the Japanese workers and by Freudenberg and Sheehan.[5] On oxidation of this ether with nitric acid, we obtained two substances that were definitely identified by means of well-known derivatives. These were oxalic acid and *l*-(−)-dimethoxysuccinic acid. None of the *d*-(+)-dimethoxysuccinic acid was found and the mother liquor left after separation of the two acids described above was somewhat levorotatory. Therefore, the experimental observations of Asahina and Takimoto were erroneous.

It should be noted that while the formation of the *d*-dimethoxysuccinic acid would be definitive, the levo isomer could be produced from either structure proposed for styracitol. Hence, the present work must be regarded as only removing a puzzling discrepancy and not in itself a structure proof. The isolation of *meso*-dimethoxysuccinic acid, D-arabotrimethoxyglutaric acid or of D-xylotrimethoxyglutaric acid would be necessary to complete the proof. Since, however, Richtmyer

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(3) Hockett, Dienes and Ramsden, THIS JOURNAL, **65**, 1474 (1943).

(4) Zervas and Papadimitriou, *Ber.*, **73**, 174 (1940).

(5) Asahina and Takimoto, *ibid.*, **64**, 2032 (1931); Freudenberg and Rogers, THIS JOURNAL, **59**, 1602 (1937); Freudenberg and Sheehan, *ibid.*, **62**, 559 (1940); *cf.* Zervas, *Ber.*, **63**, 1689 (1930).

(6) West and Holden, THIS JOURNAL, **56**, 930 (1934).

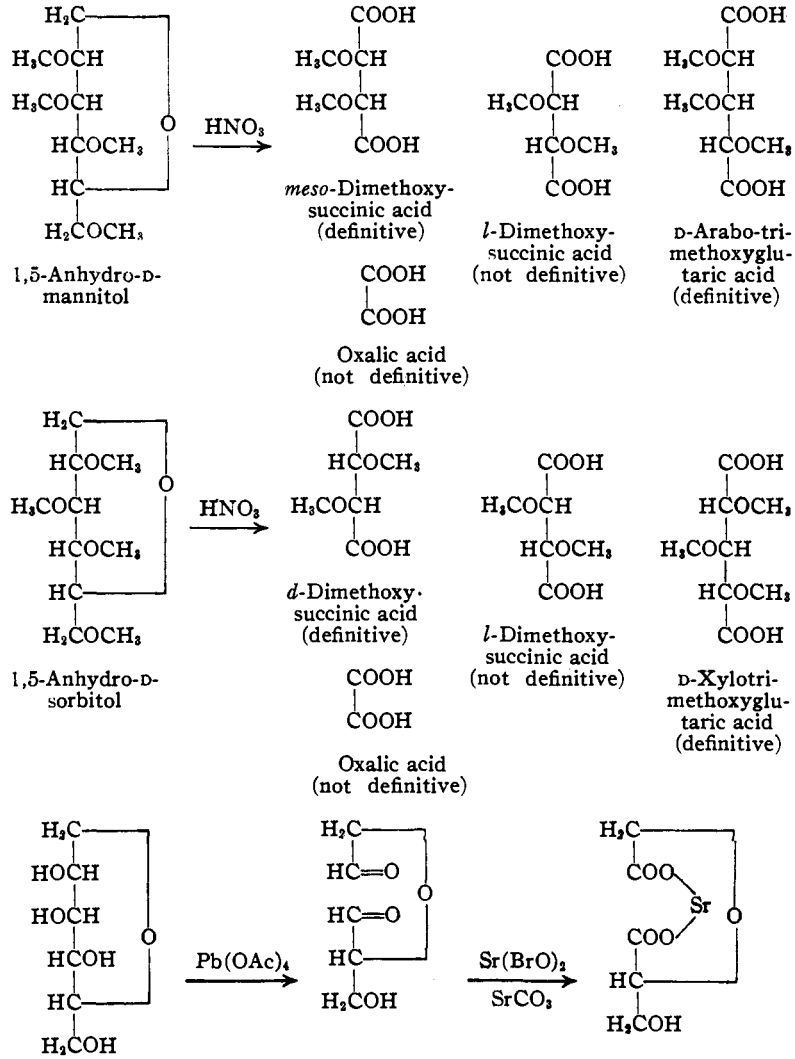
and Hudson have further confirmed the conclusions of Zervas and Papadimitriou first by demonstrating that polygalitol and styracitol are epimers and then by synthesis of polygalitol,[7] a search for these acids among the oxidation products is now unnecessary.

By oxidation of styracitol with lead tetraacetate in acetic acid and then further oxidation by strontium hypobromite in aqueous solution, we have obtained the strontium salt of a dibasic acid corresponding in composition to that calculated for D-hydroxymethyl diglycolate. The same salt has been obtained by Richtmyer and Hudson[8] from both styracitol and polygalitol following oxidation by periodic acid. The formation of this substance constitutes independent proof that these compounds are 1,5-anhydrohexitols.

In one experiment, we substituted Adams platinum oxide catalyst[9] in an alcoholic medium for palladium in acetic acid for the hydrogenation of tetraacetylhydroxyglucal to tetraacetyl-1,5-anhydrohexitol. The hydrogen absorption occurred normally but the main product was not tetraacetylstyracitol. Instead, a sirup of opposite sign of rotation[10] +37.1 (*C*, 1.2037; alcohol; 25°) was obtained. Richtmyer and Hudson[8] have reported a rotation of +38.9° (in $CHCl_3$) for tetraacetylpolygalitol. This experiment not only supports the claim that these two anhydro alcohols are epimers[11] but suggests the possibility of controlling the course of hydrogenation. This possibility will be explored further.

We report also the properties of a mono-*m*-nitrobenzylidenestyracitol prepared by Dr. Mortimer H. Nickerson, formerly of this Laboratory.[12]

POSSIBLE OXIDATION PRODUCTS OF TETRAMETHYLSTYRACITOL



Experimental

Tetraacetylstyracitol.—Tetraacetylhydroxyglucal was prepared by the method of Maurer and Mahn[13] and palladium black by the method of Willstätter and Waldschmidt-Leitz.[14] A sample of 13.2 g. (0.08 mole) of the former and 2.0 g. of the latter was placed with 100 cc. of pure acetic acid in a modified Adams hydrogenation apparatus[9] and shaken in contact with hydrogen at 23 lb. pressure. The pressure fell about 4.5 lb. (900 cc. of hydrogen absorbed) within a few hours (calcd. 895 cc.). After eight hours at room temperature, the catalyst was filtered and the solution was diluted with an equal volume of water. Three extractions with 75-cc. portions of chloroform were made and the combined extracts were washed free of acetic acid with 3% aqueous sodium bicarbonate, dried with sodium sulfate and concentrated under reduced pressure to a sirup.

Styracitol.—The sirupy tetraacetylstyracitol was dissolved in 40 cc. of dried methanol in which a tiny piece of sodium had been dissolved and the mixture was heated under reflux at 70° bath temperature for one hour. On cooling, 3.2 g. of styracitol separated, and 0.5 g. more was recovered after concentrating; yield, 57%. The product melted 154–155° and rotated[10] −50.9° (*C*, 0.4900; H_2O). Asahina gives m. p. 155° and rotation −49.9° (H_2O; 17°) as the constants for styracitol from *Styrax obassia*.

Hydrogenation of Tetraacetylhydroxyglucal with Platinum Catalyst.—Adams platinum oxide[9] (0.3 g.) was reduced with hydrogen in the presence of 10 cc. of dry

(7) Richtmyer and Hudson, THIS JOURNAL, **65**, 64 (1943); Richtmyer, Carr and Hudson, *ibid.*, **65**, 1477 (1943).

(8) Richtmyer and Hudson, *ibid.*, **65**, 64 (1943).

(9) Adams, "Organic Syntheses," Coll. Vol. I, New York, N. Y., 1941, p. 463; see also p. 61.

(10) All rotations cited in this paper are specific rotations of the D line of sodium at 20° unless exception is noted.

(11) Shinoda, Sato and Sato, *Ber.*, **65**, 1219 (1932).

(12) *Cf.* Bleyer, Diemair and Lix, *Z. Untersuch. Lebensm.*, **65**, 37–41 (1933).

(13) Maurer and Mahn, *Ber.*, **60**, 1316 (1927); Maurer, *ibid.*, **62**, 332 (1929).

(14) Willstätter and Waldschmidt-Leitz, *ibid.*, **54**, 130 (1921).

methanol. Then 2 g. of acetylated hydroxyglucal in 40 cc. of methanol was added and the mixture was shaken in contact with hydrogen in a low-pressure hydrogenator[9] until absorption of hydrogen ceased at the end of two hours. Then the flask was removed and shaken for four hours more while warmed under reflux. The filtered solution when concentrated dry under reduced pressure yielded a trace of crystalline styracitol and 1.05 g. of a sirup which rotated[10] +37.1° (*C*, 1.2037; absolute ethanol; 25°). Tetraacetylstyracitol rotates −20.86°.

Strontium D-Hydroxymethyldiglycolate.—A sample of 1.5 g. of styracitol was suspended in 150 cc. of dry chloroform in a 500-cc. three-necked flask and stirred mechanically during the gradual addition of 9.4 g. of lead tetraacetate over the period of an hour. After three hours, lead diacetate was filtered and the chloroform was removed under reduced pressure. The residue was dissolved in water and lead was removed with hydrogen sulfide. The filtrate was aerated free of excess hydrogen sulfide and was concentrated to a sirup under reduced pressure. Sulfur-free toluene was twice added and removed by distillation under reduced pressure in order to remove acetic acid as completely as possible. The sirup was then dissolved to 250 cc. with water and treated with 1.5 cc. of bromine in the presence of 10 g. of strontium carbonate. The flask was shaken until the bromine dissolved and kept in the dark for eighteen hours. Excess bromine was removed by aeration and excess strontium carbonate by filtration. The filtrate was shaken overnight with 10 g. of silver carbonate and the resulting mixture of silver bromide and carbonate was removed by filtration. Silver ions were precipitated as sulfide. Then, after aeration free of hydrogen sulfide, the solution was made neutral with a little strontium hydroxide solution. After concentration to 10 cc. and addition of alcohol to turbidity, crystals separated overnight. Dried at 120°, the anhydrous salt weighed 1.04 g. or 44% of the calculated yield. It rotated[10] −14.1° (*C*, 1.2; H_2O). Richtmyer and Hudson[7] found −10.8° for the hydrated salt equivalent to −13.9 ± 0.4° for the anhydrous form (*C*, 1.2; 1, 4).

Tetramethylstyracitol.—A sample of 9.0 g. of synthetic styracitol, when methylated by the technique of West and Holden[6] yielded 9.8 g. or 85% of the theoretical quantity of a colorless oil which distilled from 88–93° at 2 mm. pressure and rotated[10] −35.0° (no solvent). This showed $n^{23}D$ 1.4520 and $d^{26.5}_4$ 1.0895.

Anal. Calcd. for $C_4H_8O(OCH_3)_4$: OCH_3, 56.4. Found: OCH_3, 55.7.

Asahina and Takimoto[5] found: −35.63° (14°); $n^{14}D$ 1.45162; d^{18}_4 1.1092. Freudenberg and Sheehan[6] found: −36.5°(23°); n^{25} 1.4520; *d* 1.0849.

Oxidation of Tetramethylstyracitol by Nitric Acid.—A mixture of 5 g. of tetramethylstyracitol and 33 cc. of concentrated nitric acid (d. 1.42) was digested on the steam-bath for five hours. Then the mixture was diluted with water and concentrated under reduced pressure to a sirup. Water was added and reëvaporated six times to remove most of the nitric acid. The residue weighed about 2.5 g. and was a mixture of sirup and large flat crystals which remained undissolved when the sirup was extracted with chloroform. The crystals weighed about 0.5 g. and were identified by melting point, optical inactivity, and insolubility of the calcium salt in acetic acid, as oxalic acid. The chloroform extract was evaporated to a sirup which was redissolved in dry ether and mixed with an ethereal solution of diazomethane[15] in large excess. The ether and excess reagent were evaporated to leave a colorless oil distilling from 70–85° at 0.5 mm. The liquid weighed 1.6 g. and rotated[10] −8.4° (*C*, 2.3; CH_3OH). The ester was dissolved in dry methanol (10 cc.) and saturated with gaseous ammonia. Almost at once a fine powder separated which was filtered and dried. It melted at 270° and rotated −78.2° (*C*, 0.0192; H_2O). It was considered to be slightly impure *l*-dimethoxysuccinamide.[16] Since this substance is not definitive, it was not purified further.

The filtrate when evaporated dry yielded a sirup rotating[10] −11.3° (*C*, 1.7288; CH_3OH). The low rotation suggested that it contained a little more *l*-dimethoxysuccinamide mixed with inactive material. The weight of this sirup was 0.6634 g.

***m*-Nitrobenzylidenestyracitol.**—A sample of 0.4 g. of styracitol was dissolved in 1 cc. of water and 1 cc. of 50% (by weight) sulfuric acid was added. Then 1 g. of *m*-nitrobenzaldehyde in 3.5 cc. of butyl acetate was added and the mixture was shaken mechanically for about forty-eight hours. After two more days in a refrigerator, a crystalline product was filtered, washed with 50% alcohol, 80% alcohol and dry ether. Recrystallized from a 1:3 mixture of ethanol and ethyl acetate, the substance formed fine white needles melting 175–175.5°.

Anal. Calcd. for $C_{13}H_{15}O_7N$: C, 52.6; H, 5.05. Found: C, 52.9, 52.5; H, 5.60, 5.72.

Summary

1. The oxidation of styracitol by lead tetraacetate and by strontium hypobromite to D-hydroxymethyl diglycolate is described.

2. Tetramethylstyracitol has been oxidized with nitric acid to oxalic acid and *l*-dimethoxysuccinic acid, showing that the experimental observations of Asahina are incorrect and removing the obstacle to acceptance of the Zervas structure for styracitol.

3. A *m*-nitrobenzylidene derivative of styracitol is described.

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(15) Arndt, "Organic Syntheses," **15**, 3 (1935).

(16) Purdie and Irvine, *J. Chem. Soc.*, 957 (1901).