of only mannose units, this question is left unanswered by the present investigation.

Guar galactomannan absorbs comparatively large quantities of water at room temperature. For example, at 58% relative humidity and 25°, the water content on a dry basis is 16.5% and at 96% R.H. the water content is 48%. In order to determine the variation in interchain distance with water content, X-ray photographs were taken of both wet and dry guar galactomannan films. The latter was dried in an Abderhalden drying apparatus at 70° for forty-eight hours and then sealed in a thin-walled glass capillary. The wet film was left several days in an atmosphere saturated with water vapor and then sealed in a thin-walled glass capillary. The results obtained are recorded in Table III. These results show that the major

TABLE III

UNIT CELL SIZE AT DIFFERENT MOISTURE CONTENTS

	Dry	16.5% H_2O	48% H_2O
a	13.5	15.49	16.6
b	10.3	10.32	10.4
c	8.66	8.65	8.80

change occurs in the *a* axis direction *i. e.*, the direction of the side chains. The *c* axis does not change for water contents between zero and 16.5%, but shows a small increase by the time the water content has reached 48%. The *b* axis is invariant, as is to be expected since it is a measure of the identity period in the direction of the completely extended polymannose chains.

In contrast to sodium pectate,[18] there is no marked change in crystallinity when the guar galactomannan film becomes dehydrated.

Acknowledgments.—We wish to express our thanks to Dr. John F. Carson for supplying us with the pectin esters and the guar galactomannan used in this investigation; to Dr. Harry S. Owens for the equilibrium moisture data, and to Dr. F. T. Jones for the index of refraction measurements.

(18) K. J. Palmer, T. M. Shaw and M. Ballantyne, *J. Polymer Science*, **2**, 318 (1947).

Summary

The small angle diffraction from pectin acetate, propionate, butyrate, laurate, myristate and palmitate esters are recorded. The increase in interchain separation per carbon atom in the ester chain is 0.78 Å. This has been interpreted to indicate that the aliphatic chains are perpendicular to the plane of the pyranose rings and make an angle of 35° with the polygalacturonide chain axis.

The measured densities of the esters are in good agreement with densities calculated on the assumption that the volumes of the pectinic acid and aliphatic acids are additive.

A method is described for producing highly oriented films from the galactomannan obtained from guar. The X-ray diffraction investigation of these oriented films shows that the galactomannan chains have a fiber identity period of 10.3 Å.

A polymannose chain with side chains of one galactose unit on every second mannose unit is in best accord with the X-ray data. The chains appear to be arranged in sheets with all of the side chains in one sheet pointing in the same direction, while adjacent sheets have the side chains pointing in the opposite direction. The chains are randomly distributed with regard to chain direction. When the moisture content is 16.5% of the dry weight, an orthorhombic unit cell with a = 15.5 Å., b = 10.3 Å., and c = 8.65 Å. satisfactorily accounts for all of the observed X-ray reflections. The density is 1.44 g./cc. when the water content is 16.5%, and there are therefore six hexopyranoside units in this orthorhombic unit cell. The unit cell size is given for water contents of 0%, 16.5% and 48%.

RECEIVED MAY 18, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

The Action of *Acetobacter suboxydans* upon ω-Desoxy Sugar Alcohols

BY G. N. BOLLENBACK AND L. A. UNDERKOFLER

The oxidation of sugar alcohols by *Acetobacter suboxydans* has proven to be of both practical and theoretical importance.[1] Although only a few ω-desoxy sugar alcohols have been subjected to the oxidative action of the organism, the results obtained have indicated variance from the regular and predictable action of the organism on the pentitols and hexitols.[1] The extension of Bertrand's[2] rule as applied to these compounds evidently requires further modification when applied to the ω-desoxy alcohols. Bertrand originally specified the action of *A. xylinum* on polyhydric alcohols to be restricted to those having contiguous secondary hydroxyl groups in *cis* configuration. Extending this rule to *A. suboxydans*, Hann, Tilden and Hudson,[3] found this organism more selective and indicated that for fully hydroxylated alcohols having four or more carbon atoms, if oxidation by *A. suboxydans* is to occur the two contiguous secondary alcohol groups must be adjacent to a primary alcohol group, the secondary hydroxyls must be *cis* in relation to each other and of D-configuration. If these specific require-

(1) For a recent review of the oxidative action of *A. suboxydans* on polyhydric alcohols see Fulmer and Underkofler, *Iowa State Coll. J. Sci.*, **21**, 251 (1947).

(2) Bertrand, *Compt. rend.*, **126**, 762 (1898); *Ann. chim. phys.*, [8] **3**, 181 (1904).

(3) Hann, Tilden and Hudson, THIS JOURNAL, **60**, 1201 (1938).

TABLE I

OXIDATION OF ω-DESOXY SUGAR ALCOHOLS BY A. SUBOXYDANS

Désoxy alcohol		Reducing compound formed mg./100 mg. of alcohol 5 days	10 days	21 days
L-Lyxomethylitol	$CH_2-\perp-\top-\top CH_2OH$	9.5	17.7	25.0
D-Lyxomethylitol	$CH_3-\top-\perp-\top-CH_2OH$	82.0	85.7	..
D-Allomethylitol[a]	$CH_3-\top-\top-\top-\top-CH_2OH$	14.2	21.4	..
L-Fucitol	$CH_3-\perp-\top-\top-\perp-CH_2OH$	6.6	14.3	27.0
L-Glucomethylitol[a]	$CH_3-\perp-\perp-\top-\perp CH_2OH$	2.4	2.0	..
D-Gulomethylitol	$CH_3-\top-\perp-\top-\top CH_2OH$	No reduction		..
L-Gulomethylitol	$CH_3-\perp-\top-\perp-\perp CH_2OH$	60.0	85.2	..
D-Idomethylitol[a]	$CH_3-\top-\perp-\top-\perp CH_2OH$	..	No reduction	..
D-Rhamnitol	$CH_3-\top-\top-\perp-\perp CH_2OH$	26.4	87.5	..
L-Rhamnitol	$CH_3-\perp-\perp-\top-\top CH_2OH$	No reduction		..

[a] Media contained 0.5% yeast extract plus 0.025% sorbitol; all other media contained only 0.5% yeast extract.

ments are fulfilled, the organism will oxidize to a ketone the secondary alcohol group next to the primary alcohol group.

A program has been initiated in these Laboratories with the purpose of producing the rare ω-desoxy sugar alcohols and testing the action of *A. suboxydans* upon them in order to clarify the behavior of this organism upon this type of compound.[4]

The number of avenues for preparing the ω-desoxy alcohols is limited. For small scale operations (up to 5 g.) we have found the method of Wolfrom and Karabinos[5] quite satisfactory. This procedure involves the hydrogenolysis of sugar mercaptals or their acetates by refluxing with rather large amounts (10 to 1 by weight) of Raney nickel in dilute ethanol. In our experience adsorption of product is too great to make larger runs practicable. Other methods include the classical ω-tosylation, iodination and reduction;[6] the reaction of diazomethane with acid chlorides or their esters[7] or with acyclic sugar esters,[8] treatment with hydrogen iodide, and subsequent reduction of the resulting ketose; and the reaction of methylmagnesium halide with *aldehydo* compounds.[9]

By the various methods we have prepared a number of the ω-desoxy alcohols and at present are able to report observations on the oxidation of ten of them by *A. suboxydans*, as shown in Table I. It will be noted that the production of a substantial amount of reducing compound from D-rhamnitol corroborates the findings of Anderson and Lardy.[4] The results obtained with L-fucitol and L-rhamnitol are in agreement with the respective reports of Hann, Tilden and Hudson[3] and Dunning, Fulmer and Underkofler.[10]

A much more complete oxidation of L-gulomethylitol by *A. suboxydans* was obtained than that reported by Müller and Reichstein[11] (15% in three weeks) by *A. xylinum*.

The oxidation of the new D-lyxomethylitol, while lacking the confirmatory isolation and identification of the ketose, is not unexpected considering its configurational relationship to L-gulomethylitol.

Production of an unidentified reducing compound from the new L-lyxomethylitol may not be too surprising considering its configurational relation to L-fucitol. These compounds might be considered as deriving from an homomorphous series and the results provoke curiosity as to the response of the third derived member of the series, L-talomethylitol, to action of *A. suboxydans*.

Two other known ω-desoxy alcohols, D-allomethylitol and L-glucomethylitol, have been tested for response to the oxidative action of *A. suboxydans* for the first time. As shown in Table I the D-allomethylitol yielded a small but definite amount of reducing compound while L-glucomethylitol apparently remained unattacked by the organism.

Of the newly prepared and characterized ω-desoxy hexitols neither D-idomethylitol nor D-gulomethylitol gave significant amounts of reducing compounds.

In an attempt to increase the yield of reducing compound from L-fucitol a basal medium containing 0.5% yeast extract and varying amounts of the fucitol was fortified with low concentrations of sorbitol. Such a procedure is not new. Dunning, Fulmer, Guymon and Underkofler[12] showed in their work on inositol that the production of reducing compound from inositol could be substantially increased by supplying *A. suboxydans* with small amounts of an available carbon source, such as sorbitol. In Table II are recorded data anent the effect of variation of the concentration of sorbitol and L-fucitol upon the production of reducing compound by the action of *A. suboxydans* on L-fucitol. Concentrations of sorbitol varying

(4) The oxidizing action of *Acetobacter* species toward some ω-desoxy sugar alcohols has recently been reviewed by Anderson and Lardy, THIS JOURNAL, **70**, 594 (1948).

(5) Wolfrom and Karabinos, *ibid.*, **66**, 909 (1944).

(6) *Cf.* Hann, Ness and Hudson, *ibid.*, **66**, 73 (1944), and Fischer and Zach, *Ber.*, **45**, 3761 (1912).

(7) Wolfrom and Brown, THIS JOURNAL, **65**, 1516 (1943).

(8) Wolfrom, Weisblat, Zophy and Waisbrot, *ibid.*, **63**, 201 (1941).

(9) Gätzi and Reichstein, *Helv. Chim. Acta*, **21**, 914 (1938).

(10) Dunning, Fulmer and Underkofler, *Iowa State Coll. J. Sci.*, **15**, 39 (1940).

(11) Müller and Reichstein, *Helv. Chim. Acta*, **21**, 271 (1938).

(12) Dunning, Fulmer, Guymon and Underkofler, *Science*, **87**, 72 (1938).

from 25 to 75 mg. per 10 ml. of medium were equally effective. The rate of production of reducing compound notably decreased with increasing concentration of L-fucitol.

TABLE II

EFFECT OF VARIATION OF CONCENTRATION OF SORBITOL AND L-FUCITOL ON THE ACTION OF A. SUBOXYDANS ON L-FUCITOL

Mg. sorbitol per 10 ml.	Mg. L-fucitol per 10 ml.	Mg. reducing compound per 100 mg. L-fucitol 5 days	10 days
25	100	22.5	43.1
25	200	23.2	34.2
25	300	..	4.2
50	100	32.2	41.1
50	200	26.3	29.4
50	300	..	15.5
75	100	30.1	43.0
75	200	18.0	24.8
75	300	..	19.1

TABLE III

EFFECT OF RE-INOCULATING MEDIA ON THE ACTION OF A. SUBOXYDANS ON L-FUCITOL AND L-LYXOMETHYLITOL

Time in days of re-inoculation[a]	Total time in days before analysis	Mg. reducing compound per 100 mg. alcohol L-Fucitol	L-Lyxomethylitol
5	10	55.5	34.2
10	15	61.8	42.5
10	20	68.0	47.4

[a] Re-inoculated with 1 ml. saline suspension of organism containing 0.025% sorbitol.

A further attempt to increase the yields of reducing compounds from both L-fucitol and L-lyxomethylitol consisted of re-inoculating the test media at given intervals with 1 ml. of *A. suboxydans* cells suspended in sterile saline containing 0.025% sorbitol. The results of this experiment, as given in Table III, show the possibility of producing up to 68% reducing compound from L-fucitol and 47% reducing compound from L-lyxomethylitol.

Some of the mercaptals which served as intermediates in the preparation of the desoxy alcohols were also subjected to *A. suboxydans*. The results are given in Table IV. Small amounts of reducing compounds, none of which was identified, were obtained from each of the mercaptals tested. Such results are not in agreement with Hann, Tilden and Hudson[3] who detected no reducing compound when D-mannose diethyl mercaptal was present in a medium acted upon by *A. suboxydans* nor with Iselin[13] who obtained similar negative results with D-glucose diethyl mercaptal.

TABLE IV

ACTION OF A. SUBOXYDANS ON SOME MERCAPTALS

Diethyl mercaptal of[a]	Mg. reducing compound per 100 mg. mercaptal 5 days	10 days
D-Arabinose	23.7	30.3
L-Arabinose	15.3	17.0
D-Galactose	15.4	17.2
D-Glucose	..	22.2
D-Mannose	17.7	25.4
D-Xylose	17.1	17.4

[a] All media contained 0.5% yeast extract and 0.025% sorbitol.

Experimental

The culture of *Acetobacter suboxydans*[14] was grown on sterile medium containing 0.5% Difco yeast extract and 5% sorbitol, employing 10-ml. portions of the medium in each 50-ml. Erlenmeyer flask. Transfers (1 ml.), using aseptic procedures, were made at twenty-four-hour intervals. To serve as inoculum for the experimental runs, the cells from a twenty-four-hour culture were centrifuged, washed three times with 10 ml. of sterile isotonic saline solution, and resuspended in 10 ml. of saline.

Compounds tested were included, in concentrations varying from 1 to 5%, in an aqueous medium containing 0.5% Difco yeast extract. The media were distributed in 10-ml. portions in 50-ml. Erlenmeyer flasks, autoclaved at 15-lb. steam pressure for fifteen minutes, cooled and inoculated with 1 ml. of suspension of *A. suboxydans*. Incubation was at 28°. After five days, 1 ml. samples were tested for the presence of reducing compound using a modified Shaffer–Somogyi method.[15] After ten days samples were diluted to 25 ml. and 1-ml. subsamples subjected to the same test. The amount of reducing compound reported is based on glucose as the reference substance. Where small amounts of sorbitol were present in the media, corrections were made for the reducing sugar obtained from this source.

D-Lyxomethylitol Tetraacetate.—D-Arabinose diethyl mercaptal tetraacetate[3] (12 g.) was subjected to treatment with 120 g. of Raney nickel[16] after the procedure of Wolfrom and Karabinos.[5] The resulting D-lyxomethylitol tetraacetate was isolated in crystalline form. Repeated crystallizations from absolute ethanol gave 2.3 g. (26%) of product melting 115–116°; $[\alpha]^{30}D$ + 27.30° in chloroform (*c*, 1.00).

Anal. Calcd. for $C_{13}H_{20}O_8$: C, 51.32; H, 6.58. Found: C, 51.59; H, 6.77.

D-Lyxomethylitol.—A solution of 1.5 g. of the tetraacetate in 15 ml. absolute methanol was refluxed with 0.01 ml. of 0.5 *N* barium methylate for ten minutes. After cooling, anhydrous ether was added until crystals started to form on the sides of the flask. After refrigeration for twenty-four hours, filtration gave a product melting 131–132°. Several recrystallizations from methanol–ether yielded 0.6 g. (90%) of the D-lyxomethylitol, m. p. 131–132°; $[\alpha]^{29}D$ +2.46° in water (*c*, 1.02).

Anal. Calcd. for $C_5H_{12}O_4$: C, 44.12; H, 8.82. Found: C, 44.25; H, 9.21.

L-Lyxomethylitol Tetraacetate.—In manner similar to that for the preparation of its enantiomorph, the L-lyxomethylitol tetraacetate was prepared by hydrogenolysis of L-arabinose diethyl mercaptal tetraacetate[17] using Raney nickel.[5] The yield (4.3 g. from 12 g. of mercaptal acetate) of pure product obtained after several recrystallizations from absolute ethanol was 50%; m. p. 115°, $[\alpha]^{30}D$ −26.37° in chloroform (*c*, 1.29).

Anal. Calcd. for $C_{13}H_{20}O_8$: C, 51.32; H, 6.58. Found: C, 51.37; H, 6.57.

L-Lyxomethylitol.—The alcohol was prepared by barium methylate deacetylation of the tetraacetate and crystallized from methanol–ether to constant melting point; yield 0.42 g. (93%) from 1 g. of ester; m. p. 129–131°; $[\alpha]^{30}D$ −1.46° in water (*c*, 1.02).

(13) Iselin, *J. Biol. Chem.*, **175**, 997 (1948).

(14) The culture was originally obtained from the American Type Culture Collection as No. 621.

(15) Underkofler, Guymon, Rayman and Fulmer, *Iowa State Coll. J. Sci.*, **17**, 251 (1943).

(16) Pavlic and Adkins, THIS JOURNAL, **68**, 1471 (1946).

(17) Fischer, *Ber.*, **27**, 673 (1894).

Anal. Calcd. for $C_6H_{12}O_4$: C, 44.12; H, 8.82. Found: C, 44.02; H, 8.92.

L-Fucitol (L-Galactomethylitol) Pentaacetate.—D-Galactose diethyl mercaptal pentaacetate[18] (10 g.) was subjected to hydrogenolysis in the usual manner and the L-fucitol pentaacetate isolated in 48% (3.4 g.) yield. The constants, m. p. 127–128°, and $[\alpha]^{30}D$ +22.00° in chloroform (*c*, 2.00), are in good agreement with the constants recorded[19] for L-fucitol pentaacetate, m. p. 127° and $[\alpha]^{25}D$ +20.5° in chloroform (*c*, 3.0).

L-Fucitol (L-Galactomethylitol).—Hydrolysis of the L-fucitol pentaacetate (1.0 g.) with barium methylate gave an 87% (0.4 g.) yield of L-fucitol, melting 154–156° $[\alpha]^{30}D$ +4.00° in satd. borax solution (*c*, 2.00). The recorded constants[20] for L-fucitol are m. p. 153–154°, $[\alpha]^{20}D$ +4.7° in 10% borax solution (*c*, 3).

L-Gulomethylitol Pentaacetate.—In like manner, 12 g. D-glucose diethyl mercaptal pentaacetate[21] yielded 3.4 g. (40%) of L-gulomethylitol pentaacetate, m. p. 102–104°; $[\alpha]^{30}D$ +21.00 in methanol (*c*, 2.00). The recorded constants[9] for this compound are m. p. 105–106°, $[\alpha]^{21}D$ +21° in methanol (*c*, 2).

L-Gulomethylitol.—Hydrolysis of 1.0 g. of the L-gulomethylitol pentaacetate with barium methylate gave 0.3 g. (65%) of L-gulomethylitol, melting 133–134°; $[\alpha]^{29}D$ +4.50° in water (*c*, 2.00). The recorded constants[22] are m. p. 131–132°, $[\alpha]^{20}D$ +3.97 in water.

D-Rhamnitol (D-Mannomethylitol).—In an identical manner 5 g. of D-mannose diethyl mercaptal pentaacetate[23] yielded a sirupy compound which was hydrolyzed directly with barium methylate to give 0.6 g. of D-rhamnitol (36%) melting at 120–121°; $[\alpha]^{28}D$ −10.0 in water (*c*, 1.00). M. p. 123° and $[\alpha]D$ −12.4° in water have been reported on this compound.[24]

D-Gulomethylitol and L-Mannomethylitol (L-Rhamnitol).—After the procedure of Gätzi and Reichstein[9] an excess of methylmagnesium iodide was treated with 5 g. of 2,3:4,5-diacetone-*aldehydo*-L-arabinose.[25] The resulting mixture of diastereoisomeric diacetone derivatives (4.2 g., 78.5% crude) was dissolved in light petroleum ether (Skelly A) and immersed in a Dry Ice–acetone bath. By scratching with a glass rod crystals were obtained. This product was filtered immediately after removal from the freezing mixture and washed with equally cool petroleum ether. At this point the solid product could be crystallized at room temperature from petroleum ether. The melting point remained constant at 62–64°; $[\alpha]^{28}D$ 0.00 in methanol (*c*, 1.00). Gätzi and Reichstein[9] give for the 1,2:3,4-diacetone-D-rhamnitol, the enantiomorph of the product obtained; m. p. 66.5–67° and $[\alpha]^{19}D$ +1.0 in methanol (*c*, 1.4). The yield of 1,2:3,4-diacetone-L-rhamnitol was 1.5 g. (28%).

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.54; H, 8.94. Found: C, 58.68; H, 8.95.

From the mother liquor of the rhamnitol derivative was obtained 2.1 g. (39%) of a light yellow sirup of $[\alpha]^{28}D$ −1.00° in methanol (*c*, 1.00). This compound was considered to be the 1,2:3,4-diacetone-D-gulomethylitol. Gätzi and Reichstein[9] give $[\alpha]^{19}D$ +3.0° in methanol (*c*, 0.68) for the enantiomorph.

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.54; H, 8.94. Found: C, 58.56; H, 8.97.

L-Rhamnitol was obtained in 74% yield (0.5 g.) by warming 1 g. of the diacetone derivative in 15 ml. of 10% acetic acid at 100° for four hours. The solvent was removed *in vacuo*, the sirupy residue dissolved in absolute ethanol, and acetone added to incipient turbidity. After a few hours at room temperature the L-rhamnitol crystallized. The product melted at 120–121° and had a specific rotation of $[\alpha]^{28}D$ +9.50 in water (*c*, 1.00). Such constants were in agreement with m. p. 123° and $[\alpha]^{20}D$ +12.4 in water given by Fischer and Piloty[26] for the same compound.

Hydrolysis of the diastereoisomeric D-gulomethylitol derivative (1.2 g.) in the same manner gave 0.54 g. (62.5%) of the D-gulomethylitol of m. p. 130–132° and $[\alpha]^{28}D$ −2.30 in water (*c*, 1.01). The constants recorded[22] for the enantiomorph are m. p. 131–132° and $[\alpha]^{20}D$ +3.95° in water.

Anal. Calcd. for $C_6H_{14}O_5$: C, 43.37; H, 8.43. Found: C, 43.52; H, 8.49.

D-Idomethylitol and L-Glucomethylitol.—A solution of 10 g. (0.031 mole) of aldehydo-D-xylose tetraacetate[27] in 50 ml. of anhydrous benzene was added with stirring in a nitrogen atmosphere to 250 ml. of an ethereal solution of excess (0.372 mole) of methylmagnesium iodide (prepared from 9.0 g. atoms of magnesium and 54 g. or 0.38 mole of methyl iodide) over ten minutes. After completing the addition the mixture was refluxed for half an hour. The complex was hydrolyzed by pouring into 500 ml. of an ice-cold 5% sulfuric acid solution. After removal of ether and benzene in an air stream, the iodide ion was precipitated by addition of silver carbonate. Filtration was followed by treatment with hydrogen sulfide to remove excess silver ions. Following aeration to remove excess hydrogen sulfide an excess of barium hydroxide was added to the heated solution and the mixture was gently boiled for an hour. The magnesium hydroxide and the barium sulfate were then centrifuged off and excess barium ions removed from the supernatant by exactly neutralizing with dilute sulfuric acid. Centrifugation of the barium sulfate was followed by concentration of the filtrate to dryness *in vacuo* to give 5 g. (96%) of crude sirupy product.

This sirup was dissolved in 150 ml. of dry pyridine, 75 ml. of acetic anhydride added, and the solution allowed to stand at room temperature for three days. After removal of solvents *in vacuo* the residual sirup was dissolved in 60 ml. of ether and extracted five times with 20-ml. portions of 10% hydrochloric acid, then with saturated potassium carbonate solution, and with water. The ethereal layer was then dried over anhydrous sodium sulfate. After filtration, evaporation of the ether gave 1.9 g. (16.1%) of a sirupy mixture of acetates. The sirup was dissolved in petroleum ether and the solution cooled in a Dry Ice–acetone bath. The resultant gummy crystals were filtered rapidly, washed with cold petroleum ether, and recrystallized several times from petroleum ether at room temperature. The crystalline D-idomethylitol pentaacetate thus obtained amounted to 1.1 g. (9.2%), m. p. 100°; $[\alpha]^{28}D$ +10.5° in chloroform (*c*, 1.00). The constants given for the enantiomorphous compound[28] are m. p. 102–103°, $[\alpha]^{19}D$ −13.1 in chloroform.

Anal. Calcd. for $C_{18}H_{24}O_{10}$: C, 51.06; H, 6.43. Found: C, 51.18; H, 6.38.

The D-idomethylitol pentaacetate (800 mg.) was hydrolyzed by adding to a methanolic solution of the compound 1 ml. of 0.5 *N* barium methylate and allowing the solution to stand in the refrigerator for twenty-four hours. The barium was removed by the addition of anhydrous ether, filtering, evaporating to dryness, dissolving the residue in absolute methanol, and repeating the process until 200 mg. (56.5%) of a clear light yellow sirup were obtained, $[\alpha]^{28}D$ +1.43° in water (*c*, 1.00). $[\alpha]^{17}D$ −2.6° in water has been reported[28] for the enantiomorph.

Anal. Calcd. for $C_6H_{14}O_5$: C, 43.37; H, 8.43. Found: C, 43.49; H, 8.50.

The sirupy mother liquors from the D-idomethylitol pentaacetate (625 mg.) were hydrolyzed in a similar manner. The L-glucomethylitol (200 mg., 79%) obtained as

(18) Wolfrom, THIS JOURNAL, **52**, 2467 (1930).

(19) Wolfrom, Burke and Waisbrot, *ibid.*, **61**, 1828 (1939).

(20) Votoček and Potměšsil, *Ber.*, **46**, 3653 (1913).

(21) Schneider and Sepp, *ibid.*, **51**, 226 (1918; Wolfrom, THIS JOURNAL, **51**, 2190 (1929).

(22) Müller and Reichstein, *Helv. Chim. Acta*, **21**, 251 (1938).

(23) Pirie, *Biochem. J.*, **30**, 374 (1936).

(24) Votoček, Valentin and Rác, *Collection Czechoslov. Chem. Communs.*, **2**, 402 (1930).

(25) English and Griswold, THIS JOURNAL, **67**, 2039 (1945).

(26) Fischer and Piloty, *Ber.*, **23**, 3102 (1890).

(27) Wolfrom, Olin and Evans, THIS JOURNAL, **66**, 204 (1944).

(28) Meyer and Reichstein, *Helv. Chim. Acta*, **29**, 139 (1946).

a sirup had $[\alpha]^{28}D$ +7.21° in water (*c*, 1.00). Votoček and Miksic[29] give $[\alpha]^{20}D$ +9.18° in water for this compound. The amount of material available was too small to allow further purification by means of a solid derivative.

D-**Allomethylitol.**—This compound was prepared by the sodium amalgam reduction[30] of D-allomethylose[31] and melted at 60°; $[\alpha]^{30}D$ −8.62° in water (*c*, 1.00). The constants recorded[30] for this compound are m. p. 62–63°; $[\alpha]^{16}D$ −11 in water.

Summary

D-Lyxomethylitol, L-lyxomethylitol, L-fucitol, L-gulomethylitol and D-rhamnitol have been prepared through their respective acetates by hydrogenolysis of the corresponding mercaptal acetates with Raney nickel. D-Gulomethylitol, L-rhamnitol, D-idomethylitol and L-glucomethylitol were prepared by the addition of methylmagnesium iodide to the appropriate acyclic compounds. D-Allomethylitol was prepared by sodium amalgam reduction of D-allomethylose.

Each of the ω-desoxy sugar alcohols was subjected to the oxidative action of *Acetobacter suboxydans*. An oxidative specificity of uncertain character was displayed by the organism toward the desoxy compounds. D-Lyxomethylitol, L-gulomethylitol and D-rhamnitol were oxidized rapidly and almost completely. L-Lyxomethylitol, D-allomethylitol and L-fucitol were oxidized slowly and gave small but definite amounts of reducing compounds. L-Glucomethyltiol, D-gulomethylitol, D-idomethylitol and L-rhamnitol were not oxidized by the organism.

Amounts of reducing compounds obtained from L-fucitol and L-lyxomethylitol were markedly increased by adding small quantities of assimilable sorbitol to the media and by re-inoculating with active cells of *A. suboxydans* after an initial growth period.

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(29) Votoček and Miksic, *Bull. soc. chim. France*, [4] **43**, 220 (1928).

(30) Iwadare, *Bull. Chem. Soc. Japan*, **17**, 296 (1942).

(31) Levene and Compton, *J. Biol. Chem.*, **116**, 169 (1936).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MONSANTO CHEMICAL CO., ST. LOUIS 4, MISSOURI]

Antihistaminic Agents Containing a Thiophene Nucleus

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Interest in amine derivatives which contain a thiophene nucleus has resulted in the development of two useful antihistaminic agents, N,N-dimethyl-N′-phenyl-N′-(2-thenyl)-ethylenediamine,[3] and N,N-dimethyl-N′-(2-pyridyl)-N′-(2-thenyl)-ethylenediamine (I).[4] The results reported in this paper are an extension of previous studies[5] in the thiophene series. Several phenyl analogs of the thienyl compounds were made for comparison.

Among the new products prepared (Table II), N,N-dimethyl-N′-(5-chloro-2-thenyl)-N′-phenylethylenediamine proved to be the most potent, approximately 125% as active as Antergan in animal tests. In this case the introduction of chlorine into the thiophene ring had a potentiating effect on antihistaminic activity, similar to the observations of previous workers[6] in the pyridine series; Diatrin has been reported by one group to be two-thirds[5] as active as Antergan, while other workers reported it to be as active[7] as Antergan. When chlorine was introduced into the phenyl ring, the activity dropped markedly. The *o*-chlorophenyl derivatives had negligible activity, the *m*-chlorophenyl derivatives were slightly active and the *p*-chlorophenyl derivatives were the most active, but the best compound in this series, N,N-dimethyl-N′-(*p*-chlorophenyl)-N′-(2-thenyl)-ethylenediamine, was only one-half as active as Antergan.

Introduction of a third methyl group in place of the aryl or pyridyl groups, or replacement of the 2-thenyl group by methoxybenzyl practically eliminated activity. Substitution of chlorine or the 4-morpholinyl group for the dimethylamino group produced inactive compounds.

In the Antistin[8] series, the tetrahydropyrimidine analog, 2-(N-benzylanilinomethyl)-1,4,5,6-tetrahydropyrimidine, and the corresponding 2-thenyl derivative, were found to have insignificant activity.

The products were tested for pharmacological activity in the Lilly Research Laboratories.

Several intermediate trisubstituted-ethylenediamines, Table I, were prepared by treating N,N-dimethyl-2-chloroethylamine hydrochloride with the required substituted aniline or aminoheterocycle using known procedures.[9] The secondary

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(3) This compound is the thiophene analog of Antergan, and is known in this country as "Diatrin." For literature references, see (a) Leonard and Solmssen, THIS JOURNAL, **70**, 2064 (1948). The toxicology and pharmacology of Diatrin were discussed recently by (b) Ercoli, Schachter, Hueper and Lewis, *J. Pharmacol.*, **93**, 210 (1948).

(4) This product is the thiophene analog of Pyribenzamine, and is known in this country under the names, "Histadyl" and "Thenylene." For literature references, see Leonard and Solmssen, ref. 3.

(5) Kyrides, Meyer and Zienty, THIS JOURNAL, **69**, 2239 (1947).

(6) Clapp, Clark, Vaughn, English and Anderson, *ibid.*, **69**, 1549 (1947).

(7) Ercoli, Schachter, Leonard and Solmssen, *Arch. Biochem.*, **13**, 487 (1947).

(8) Antistin is 2-(N-benzylanilinomethyl)-2-imidazoline; *cf.* Meier and Bucher, *Schweiz. med. Wochschr.*, **76**, 294 (1946).

(9) Huttrer, Djerassi, Beears, Mayer and Scholz, THIS JOURNAL, **68**, 2001 (1946).