ether gave 0.6 g. of light yellow powder which decomposed at 277°. Two more recrystallizations resulted in a colorless powder of m.p. 281° dec. Silver bromide was precipitated when alcoholic solutions of this product and silver nitrate were mixed. From the first filtrate another 2.2 g. of the less pure substance was obtained of m.p. 275° dec.

Anal. Calcd. for $C_{12}H_{11}BrN_2OS$: C, 46.30; H, 3.54; N, 9.05. Found: C, 46.27; H, 3.84; N, 8.56.

3,4-Dihydro-6,8-dimethylpyrimido[1,2-a]pyrimidin-2-one Hydrobromide (VIII).—2-Amino-4,6-dimethylpyrimidine was prepared from guanidine carbonate and acetylacetone by adapting the procedure[17] for the preparation of 2-amino-4-methyl-6-methoxypyrimidine. The yield was 88% and the pure sample melted[18] at 150–151° (lit. 153°) after two recrystallizations from a mixture of chloroform and petroleum hexane.

When equivalent quantities (0.1 mole) of this amine and 3-bromopropionic acid were heated together on a steam-bath at first the mixture became a homogeneous melt. Then white solid began to appear and after 24 hours of heating the mixture became a hard mass. It was dissolved in 200 ml. of 90% methanol and its boiling point and then was diluted with excess ether to yield 5.7 g. of white powder which darkened at about 70° and melted with decomposition at 334–335°. One more crystallization from methanol–ether gave 4.0 g. of colorless needles (VIII) of m.p. 330° dec. Softening was noticed at about 245°.

Anal. Calcd. for $C_9H_{12}BrN_3O$: C, 41.85; H, 4.65; N, 16.28; neut. equiv., 258. Found: C, 41.95; H, 4.70; N, 16.03; neut. equiv., 256.

Processing of the first methanol–ether filtrate led to the recovery of 0.3 g. more of VIII and 3.3 g. of 2-amino-4,6-dimethylpyrimidine hydrobromide; m.p. 179–180°; neut. equiv., 209.6 (calcd. 204.0).

An attempt to effect interaction of 2-amino-4,6-dimethylpyrimidine and propiolactone in ether–acetone solution at 25° was negative. The clear solution turned dark brown in six days, but nothing precipitated. Actually, 99% of the pyrimidine was recovered.

3-(2,3-Dihydro-2-imino-6-methyl-3-benzothiazolyl)-propionic Acid.—2-Amino-6-methylbenzothiazole, m.p. 135–136° (lit.[19] 142°), was prepared by the general procedure[20] for the preparation of 6-substituted benzothiazoles.

To a clear yellow solution of 16.4 g. of this compound in 100 ml. of acetone was added 8.0 g. of propiolactone. After the first hour of refluxing, 4.35 g. of pale yellow crystals separated, m.p. 131–133° dec. after rinsing with acetone. From the filtrate was obtained another 5.5 g. of product by heating it 3 hours longer and allowing it to stand overnight. The solid was insoluble in ether, acetone or cold water, but it dissolved in cold methanol, hot water, dilute hydrochloric acid and aqueous sodium carbonate.

The acetone filtrate was evaporated and the resulting sirup treated with sodium carbonate solution and ether extracted. The ether removed 3.85 g. of unreacted benzothiazole. The aqueous layer was heated with Norit, then was taken to *p*H 6 (dil. HCl) to yield a yellow sticky solid, but addition of chloroform did away with the stickiness. The pale yellow solid weighed 2.65 g., thus making a total yield of 12.5 g.

The recrystallizations of either this last product or the first product of m.p. 131–133° from aqueous methanol caused hydration and brought the m.p. to 168° dec. These were white crystals of practically identical solubility behavior as the material of m.p. 131–133°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2S \cdot H_2O$: C, 52.0; H, 5.51; N, 11.0; neut. equiv., 254. Found: C, 52.35; H, 5.70; N, 11.0, 10.9; neut. equiv., 251.

The unpurified product of m.p. 131–133° probably contained a little of the original 2-amino-6-methylbenzothiazole. Its N content was 12.5–12.7% (calcd. for $C_{11}H_{12}N_2O_2S$: N, 11.9).

Acknowledgments.—Microanalyses were performed by Mrs. C. White and Miss H. Beck. Propiolactone was generously furnished by B. F. Goodrich Chemical Company. One of us (S. H.) was holder of a Swift and Company fellowship during a portion of this work.

(17) C. C. Price, N. J. Leonard and D. Y. Curtin, *J. Org. Chem.*, **10**, 318 (1945).

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EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

The Chemistry of 2,5-Anhydro-L-arabinose[1]

BY MARGARET CIFONELLI, J. A. CIFONELLI, R. MONTGOMERY AND F. SMITH

RECEIVED JUNE 28, 1954

Treatment of ethyl 5-*O*-tosyl-α-L-arabofuranoside (II, R = C_2H_3) with alkali affords ethyl 2,5-anhydro-α-L-arabofuranoside (III, R = C_2H_5); the corresponding anhydro methyl glucoside may be made in the same way. The structure of the 2,5-anhydro-L-arabinose was established by its transformation into 2,5-anhydro-L-arabitol, the enantiomorph of which was obtained from the known 3,6-anhydro-4,5-*O*-isopropylidene-D-mannitol. Although stable to alkali, the alkyl 2,5-anhydro-L-arabofuranosides are so sensitive to H^+ ions that they are hydrolyzed by distilled water giving 2,5-anhydro-L-arabinose (IV), which exists in the aldehydic form. Once the sugar ring is cleaved it would appear that it cannot be re-formed. methanolic hydrogen chloride, for example, affording the dimethyl acetal and not the methyl glycoside. The ease of conversion of 2,5-anhydro-L-arabinose into furfural by dilute acid favors the view that, in furfural formation, the hydrofuran ring is produced before unsaturation. It is also suggested that the enhanced reactivity at C_1 in III, induced by the strain of the 2,5-anhydro ring on the sugar ring, may parallel the manner in which an enzyme combines with and activates a substrate so that it may undergo facile cleavage.

The hydrofuranol (butylene oxide) type of ring system has been shown to have a marked effect upon the properties of hexose sugars and their derivatives. This deduction has been made as a result of investigation into 3,6-anhydro derivatives of D-galactose,[2–4] D-glucose[5] and D-mannose.[6] The conclusion was reached[5] that the anhydro ring assumes the character of the principal ring struc-

(1) This paper (No. 3173 Scientific Journal Series, Minnesota Agricultural Experiment Station), is based, in part, on a thesis submitted by Margaret Cifonelli to the University of Minnesota in partial fulfillment for the degree of M.S., 1952.

(2) W. N. Haworth, J. Jackson and F. Smith, *Nature*, **42**, 1075 (1938).

(3) W. N. Haworth, J. Jackson and F. Smith, *J. Chem. Soc.*, 620 (1940).

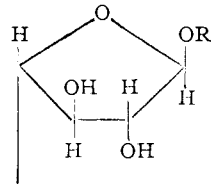
(4) P. A. Rao and F. Smith, *ibid.*, 229 (1944).

(5) W. N. Haworth, L. N. Owen and F. Smith, *ibid.*, 88 (1941).

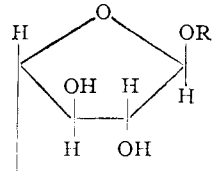
(6) A. B. Foster, W. J. G. Jones and F. Smith, unpublished work.

ture while the parent sugar ring plays a subsidiary role. The introduction of the planar hydrofuranol ring into a compound, which already possesses a furanose or a pyranose sugar ring system, results in the latter becoming strained and, as a consequence, the normal rules pertaining to pyranose and furanose single ring systems no longer operate. This mutual effect of fused ring systems also has been recognized in studies on the dilactones of D-mannaric (mannosaccharic)[7] and D-glucaric (glucosaccharic) acids.[8]

We have now sought to ascertain the effect of the hydrofuranol ring in the pentose series of sugars. An inspection of models will reveal that formation of an anhydro ring engaging C_2 and C_5 is stereochemically possible in arabinose and lyxose but not in ribose or xylose. This paper is concerned with the preparation and properties of 2,5-anhydro-L-arabinose.



I



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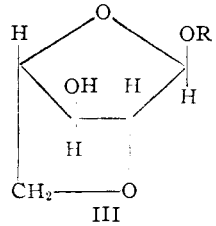


III

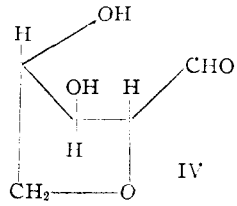
Ts = $-SO_2C_6H_4CH_3$-*p*

Treatment of ethyl α-L-arabofuranoside (I, R = C_2H_5) with *p*-toluenesulfonyl chloride in pyridine yields ethyl 5-*O*-tosyl-α-L-arabofuranoside (II, R = C_2H_5), which reacts with alkali to give a rather poor yield (15%) of ethyl 2,5-anhydro-α-L-arabofuranoside (III, R = C_2H_5). The corresponding methyl 2,5-anhydro-L-arabofuranoside (III, R = CH_3) was prepared in an analogous manner.

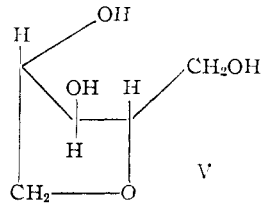
The structure of these alkyl 2,5-anhydro-L-arabinosides, which are colorless, mobile liquids, rests upon the following experimental facts.

The presence of a single hydroxyl group in III (R = CH_3) was shown by the fact that methylation gave a monomethyl derivative, methyl 2,5-anhydro-3-*O*-methyl-α-L-arabofuranoside. Moreover, treatment of III (R = CH_3) with phenyl isocyanate yielded the corresponding monocarbanilate.

Hydrolysis of either the methyl or the ethyl anhydroglycoside III, which proceeds with surprising ease (see later), followed by catalytic reduction of the resulting free sugar IV, gave the corresponding 2,5-anhydro-L-arabitol (V), which was characterized as the crystalline tri-*O*-*p*-toluenesulfonyl ester. The structure of the latter was proved by the following series of reactions. Oxidation of 3,6-anhydro-4,5-*O*-isopropylidene-D-mannitol (VI)[9]

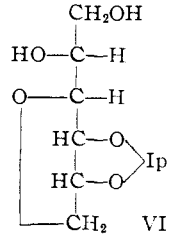


IV

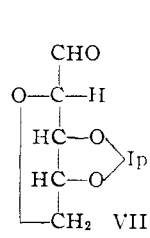


V

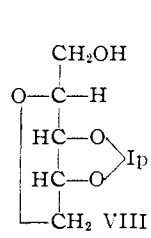
with periodate, furnished 2,5-anhydro-3,4-*O*-isopropylidene-D-arabinose (VII), which upon catalytic hydrogenation gave 2,5-anhydro-3,4-*O*-isopropylidene-D-arabitol (VIII). Hydrolysis of the latter gave 2,5-anhydro-D-arabitol (IX), which proved to be the enantiomorph of 2,5-anhydro-L-



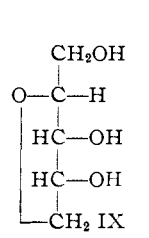
VI



VII



VIII



IX

arabitol (V) prepared above. It also was established that the tri-*O*-*p*-toluenesulfonyl derivative of IX was enantiomorphic with the tri-*O*-*p*-toluenesulfonate of V.

An examination of the molecular model of the alkyl 2,5-anhydro-L-arabofuranosides (III) shows that the two fused rings produce a condition of strain in the molecule. Many of the reactions displayed by these compounds lead to the relief of this strain. This is reflected also by the difficulty of introducing the hydrofuranol ring.

Similar though less marked conditions of strain are found in the 3,6-anhydro-2,4-di-*O*-methyl derivatives of the glucopyranosides[5] and galactopyranosides.[3] With these 3,6-anhydro sugar compounds, α,β-anomerizations occur in the presence of trace amounts of acid and under conditions in which the intermediate aldehydo-sugar cannot be formed. Under similar conditions, the methyl 3,6-anhydro-D-glucopyranosides can be directly transformed into the corresponding furanosides.[5]

Such a pyranoside–furanoside interconversion has not been encountered in the case of the 2,5-anhydro-L-arabofuranosides but, instead, the profound effect of strain is shown by the fact that solution of the glycosides in water results in their hydrolysis with the formation of the free anhydrosugar. The rate of hydrolysis is increased by the addition of acid and suppressed by alkali. The only other example known to the authors of a glycoside being hydrolyzed by water is theobromine glucoside.[10] This compound belongs to the class of glycosides, characterized by their ease of hydrolysis in alkaline solutions due to the presence of a double bond in the aglycon, which is adjacent to the aglycon-glycosidic oxygen linkage.[11] The labile nature of these compounds to alkali and, in the particular case cited to water, is due to an electronic effect, whereas in the 2,5-anhydro-L-arabofurano-

(7) Doreen Heslop and F. Smith, *J. Chem. Soc.*, 577 (1944).
(8) F. Smith, *ibid.*, 633, 637(1944).
(9) A. B. Foster and W. G. Overend, *ibid.*, 680 (1951).
(10) E. Fischer and B. Helferich, *Ber.*, **47**, 210 (1914).
(11) H. Gehman, L. C. Kreider and W. L. Evans, THIS JOURNAL, **58**, 2388 (1936).

sides, it is traced to the molecular strain in the fused ring system. The labile nature of groups in fused ring systems is also demonstrated by the behavior of 1,4;3,6-dianhydro-2,5-*O*-methylene-D-mannitol,[12] which loses its methylene group upon heating in aqueous solution and by 1,4-anhydro-3,5-*O*-benzylidene-6-chloro-6-deoxy-D-glucitol,[13] from which the benzylidene group can be removed under alkaline conditions. The condition of strain in 2,5-anhydro-L-arabofuranose is also indicated by the following additional experimental facts. The free 2,5-anhydro-L-arabinose gives an immediate test with Schiff reagent while the parent methyl glycoside gives a positive test within two minutes. On the other hand, 3,6-anhydro-D-glucose gives only a faint Schiff test after several minutes and the test with L-arabinose is negative. It would seem, therefore, that the 2,5-anhydro-L-arabinose must exist to a large extent in the open-chain aldehydic form. Once in this aldehydic form, it would appear that the sugar ring cannot be re-formed; for example, methanolic hydrogen chloride affords the dimethyl acetal and not the methyl glycoside. Also, the dimethyl acetal of 2,5-anhydro-L-arabinose did not give the corresponding methyl glycoside when treated with hydrogen bromide under conditions which were known[3] to achieve this result in the case of 3,6-anhydro-2,4-di-*O*-methyl-D-galactose dimethylacetal.

The ethyl 2,5-anhydro-α-L-arabofuranoside (III, R = C_2H_5) changed after four months from a mobile liquid to a glass with a concomitant small reduction in the ethoxyl content. The resulting material showed no Schiff test but reduced Fehling solution. The glass hydrolyzed easily with dilute acid to give 2,5-anhydro-L-arabinose but underwent decomposition when heated in high vacuum. The corresponding methyl 2,5-anhydro-α-L-arabofuranoside (III, R = CH_3) underwent a similar change from a mobile liquid to a glassy solid but after a much longer period of time.

The stability toward both acid and alkaline hydrolyzing agents has been a distinguishing characteristic of the hydrofuranol ring in the hexoses. This was not found to be true for the anhydro-pentose studied which in many respects behaved like a C_2-alkyl ether. For example, in the attempted preparation of 2,5-anhydro-L-arabinose phenylhydrazone, only L-arabinose phenylosazone was obtained. Similarly, benzylphenylhydrazine usually gave L-arabinose benzylphenylhydrazone although in some experiments a small amount of 2,5-anhydro-L-arabinose benzylphenylhydrazone was isolated. Attempts to prepare derivatives with hydroxylamine failed.

The anomalous behavior induced by the 2,5-anhydro ring is demonstrated further by the fact that 2,5-anhydro-L-arabonamide gave a positive Weerman reaction, a test that has been used extensively in diagnosing the presence of the OH group adjacent to the amide grouping. This observation further demonstrates that caution should be exercised when applying the normal tests for, and rules of, simple carbohydrate compounds to those substances which contain anhydro rings of the hydrofuranol type.

The 2,5-anhydro-L-arabinose readily gives furfural when gently warmed with 0.1 *N* sulfuric acid. It was found also that both 3,6-anhydro-D-glucose and 3,6-anhydro-D-galactose gave a positive test when boiled with 1 *N* hydrochloric acid. Furthermore, it has been shown previously[14] that a neutral aqueous solution of chitose, 2,5-anhydro-D-mannose (obtained from D-glucosamine), readily gives 5-hydroxymethyl-2-furfural when heated at elevated temperatures.

These facts, illustrating the ease with which anhydro-sugars containing a hydrofuranol ring are converted to furfural compounds, suggest that furfural formation from aldose and ketose sugars may not necessarily proceed through an unsaturated open chain compound before the formation of the anhydro ring.[15] On the contrary, the behavior of the anhydro-sugars would lend support to the view, first proposed by Nef[16] and more recently modified by Haworth[17] and Isbell,[18] that the hydrofuranol ring is formed first. Such a mechanism also explains more satisfactorily the greater ease with which 2-keto-hexoses are converted to 5-hydroxymethyl-2-furfural than are aldohexoses, when aqueous solutions of these sugars are autoclaved.[19] The 2-keto-hexoses, existing predominantly in the furanose form at elevated temperatures, already contain the furan ring system of the final product.

The extreme sensitivity displayed by the alkyl 2,5-anhydro-L-arabofuranosides toward the hydrogen ion concentration of water, as a result of the strain produced by the anhydro ring, has prompted the suggestion that the hydrolysis of a substrate by an enzyme may be produced by activation due to strain. The enzyme, in combining with specific points in the substrate molecule, may introduce a strained condition which is reflected by the substrate molecule becoming activated.

Experimental

Ethyl 2,5-Anhydro-α-L-arabofuranoside (III, R = C_2H_5). —To a solution of ethyl α-L-arabofuranoside[20] (9 g.) in dry pyridine (150 ml.) at 0°, was added *p*-toluenesulfonyl chloride (10.1 g., 1.1 moles) in small portions with shaking. The reaction mixture was maintained at 5° for three days and then at room temperature for one day after which time the solution was poured into ice-water. The tosyl derivative was extracted with chloroform and the chloroform extract washed with water, dried ($MgSO_4$) and filtered. Evaporation of the filtrate under reduced pressure at 40–50° yielded ethyl 5-*O*-tosyl-α-L-arabofuranoside (II, R = C_2H_5) as a sirup (16 g.) which did not crystallize. *Anal.* Calcd. for $C_{14}H_{20}O_7S$: OC_2H_5, 13.5. Found: OC_2H_5, 12.7.

Attempts to purify the tosyl derivative by distillation of its acetate under high vacuum (0.001 mm.) were not successful, decomposition occurring at 200° (bath temp.).

The sirupy ethyl 5-*O*-tosyl-α-L-arabofuranoside (16 g.) was dissolved in dry methanol (75 ml.) and treated with 0.58 *N* sodium methoxide in methanol (150 ml.). After 24 hours at room temperature, the sodium methoxide was decomposed with carbon dioxide and the solution evaporated to dryness under reduced pressure at 30–40°. The residue was

(12) S. Baker, *Can. J. Chem.*, **31**, 821 (1953).

(13) R. Montgomery and L. F. Wiggins, *J. Chem. Soc.*, 237 (1948).

(14) C. Tanaka, *Mem. Coll. Sci. Kyoto Imp. Univ.*, **13A**, 265 (1930).

(15) C. D. Hurd and L. L. Isenhour, THIS JOURNAL, **54**, 322 (1932).

(16) J. U. Nef, *Ann.*, **376**, 117 (1910).

(17) W. N. Haworth and W. G. M. Jones, *J. Chem. Soc.*, 667 (1944).

(18) H. S. Isbell, *J. Research Natl. Bur. Standards*, **32**, 45 (1944).

(19) R. Montgomery and L. F. Wiggins, *J. Soc. Chem. Ind.*, **66**, 31 (1947).

(20) J. W. Green and E. Pacsu, THIS JOURNAL, **60**, 2057 (1938).

extracted four times with dry acetone and the sirup from the acetone extract re-extracted once with dry ether. Distillation of the sirup (6 g.) from the ether extract gave fractions: (a) ethyl 2,5-anhydro-α-L-arabofuranoside (III, R = C_2H_5), a colorless mobile liquid, 2.5 g., b.p. (bath temp.) 85–100° (0.001 mm.), $n^{29}D$ 1.4541. *Anal.* Calcd. for $C_7H_{12}O_4$: C, 52.5; H, 7.5; OC_2H_5, 28.1. Found: C, 53.1; H, 7.8; OC_2H_5, 28.4; (b) a light yellow sirup, 0.8 g., b.p. (bath temp.) 130–140° (0.4 mm.), $n^{26}D$ 1.4731; found: OC_2H_5, 26.8; (c) a light brown sirup, 0.25 g., b.p. (bath temp.) 140–150° (0.001 mm.), $n^{26}D$ 1.4710; found: OC_2H_5, 18.9; (d) a brown sirup, 1.25 g., b.p. (bath temp.) 185–190° (0.001 mm.), $n^{26}D$ 1.5118; found: OC_2H_5, 12.0.

The nature of fractions b, c, and d is under investigation.

Properties of Ethyl 2,5-Anhydro-α-L-arabofuranoside (III, R = C_2H_5).—Ethyl 2,5-anhydro-α-L-arabofuranoside showed $[\alpha]^{26}D$ −81.7° (constant value) in 0.1 *N* sodium hydroxide (*c* 1.0). When dissolved in distilled water, it hydrolyzed to give 2,5-anhydro-L-arabinose (IV), the hydrolysis being indicated by a change from $[\alpha]^{29}D$ −127° (*c* 1.0) to +10° (constant value) in 96 hours. After standing for 4 months, the sirupy glycoside changed to a glass (A), $n^{28}D$ 1.4672, $[\alpha]^{26}D$ +6° in water (*c* 0.5), changing to +8° after 6 hours (found: OC_2H_5, 26.3). The glass A gave no Schiff test but reduced Fehling solution. Substance A did not revert to the sirupy state when maintained for 6 hours at 50° above the boiling point (at 0.01 mm. pressure) of the original glycoside. However, in a manner similar to the glycoside, the glass (A) hydrolyzed easily with dilute acid to give 2,5-anhydro-L-arabinose.

Methyl 2,5-Anhydro-α-L-arabofuranoside (III, R = CH_3).—Methyl α-L-arabofuranoside[21,22] was treated with *p*-toluenesulfonyl chloride (1.1 moles) as described previously for the ethyl glycoside. The resulting methyl 5-*O*-tosyl-α-L-arabofuranoside was a sirup showing $[\alpha]^{26}D$ −35° in methanol (*c* 2.0). *Anal.* Calcd. for $C_{13}H_{18}O_7S$: OCH_3, 9.7. Found: OCH_3, 8.1. Treatment of the tosyl compound in the usual way with sodium methoxide gave methyl 2,5-anhydro-α-L-arabofuranoside as a colorless, mobile liquid (yield 26%), b.p. 65–75° at 0.135 mm., $n^{23}D$ 1.4570. *Anal.* Calcd. for $C_6H_{10}O_4$: OCH_3, 21.2. Found: OCH_3, 21.3.

Methyl 2,5-anhydro-α-L-arabofuranoside hydrolyzed when dissolved in distilled water at room temperature. The progress of the hydrolysis was followed polarimetrically, $[\alpha]^{27}D$ −167° (initial value), −166° (after 40 min.), −159° (18 hours), −129° (42.5 hours), −116° (47.5 hours), +8° (167 hours).

Methyl 2,5-Anhydro-α-L-arabofuranoside 3-Carbanilate.—Methyl 2,5-anhydro-α-L-arabofuranoside (50 mg.), phenyl isocyanate (65 mg.) and dry pyridine (0.1 ml.) were heated together on a boiling water-bath for one hour. A small amount of methanol was added and on standing at room temperature diphenylurea separated. Petroleum ether (b.p. 30–60°) was added and the mixture filtered. The filtrate, containing an oily precipitate, was heated on a water-bath with shaking and the oil crystallized. The crystalline mass was triturated with petroleum ether and kept at 5° until no more crystals separated. After recrystallization from absolute ethanol, the methyl 2,5-anhydro-α-L-arabofuranoside 3-carbanilate had m.p. 137°, $[\alpha]^{25}D$ −141° in acetone (*c* 1.1). *Anal.* Calcd. for $C_{13}H_{15}O_5N$: C, 58.9; H, 5.7; N, 5.3; OCH_3, 11.7. Found: C, 58.6; H, 5.4; N, 5.4; OCH_3, 11.6.

An aqueous methanol solution of the carbanilate gave a positive Schiff test indicating hydrolysis of the glycosidic methyl group. In aqueous acetone (2.85 ml.) containing 1 *N* sulfuric acid (0.15 ml.), the hydrolysis of the carbanilate (30 mg.) was followed polarimetrically, $[\alpha]^{23}D$ −5° (after 8 min.), ±0° (10 min.), +8° (12 min.), +17° (18 min.), +21° (20 min.), +22° (28 min., constant value).

Methyl 2,5-anhydro-α-L-arabofuranoside 3-carbanilate (6 mg.), in methanol (1 ml.), water (0.5 ml.) and *N* sulfuric acid (0.1 ml.), was treated with 0.013 *N* potassium periodate (2 ml.) at room temperature for 17 hours. No oxidation of the compound occurred as shown by the fact that no periodate was consumed.

Methyl 2,5-Anhydro-3-*O*-methyl-α-L-arabofuranoside.—Methylation of methyl 2,5-anhydro-α-L-arabofuranoside with Purdie reagents in the usual way yielded a sirupy monomethyl ether, $n^{25}D$ 1.4540, $[\alpha]^{22}D$ −114° in water (*c* 2.0) changing in 24 hours to −55.0°, at which point the solution reduced Fehling solution and gave a positive Schiff test. *Anal.* Calcd. for $C_7H_{12}O_4$: OCH_3, 38.7. Found: OCH_3, 38.5.

2,5-Anhydro-L-arabinose (IV).—Ethyl 2,5-anhydro-α-L-arabofuranoside (1.7 g.) was dissolved in water (50 ml.) and three drops of *N* sulfuric acid were added. The specific rotation, observed as soon as possible, was $[\alpha]^{25}D$ +16° (constant value). The solution was neutralized with 0.01 *N* barium hydroxide, filtered and evaporated under reduced pressure at 35–40° (bath temp.) to give 2,5-anhydro-L-arabinose as a colorless sirup, $[\alpha]^{24}D$ +12° in water (*c* 0.5).

2,5-Anhydro-L-arabinose reduced Fehling solution and gave a strong Schiff test. With barely warm dilute acid (0.1 *N*), it gave furfural (aniline–acetate color test). 3,6-Anhydro-D-galactose and 3,6-anhydro-D-glucose gave positive tests under slightly more vigorous conditions (boiling with 1 *N* hydrochloric acid).

When the 2,5-anhydro-L-arabinose was treated with 0.08 *N* sodium periodate at 0° in the dark, it consumed 3 moles of periodate per mole of anhydro sugar after 10 minutes with the formation of 0.7 mole of formic acid.

A possible explanation of this reaction is[23]

$$\text{IV} \xrightarrow{IO_4} \text{CHO—CH}_2\text{—O—CH(CHO)}_2 \xrightarrow{IO_4} \text{CHO—CH}_2\text{—O—C(OH)(CHO)}_2$$

$$\xrightarrow{IO_4} \text{CHO—CH}_2\text{—O—CO—CHO} + \text{HCOOH}$$

2,5-Anhydro-L-arabinose Benzylphenylhydrazone.—Freshly prepared 2,5-anhydro-L-arabinose (100 mg.) was treated with benzylphenylhydrazine hydrochloride (160 mg.) and sodium acetate (140 mg.) in aqueous solution, enough ethanol being added to produce a clear solution. The solution was warmed for 30 minutes and the precipitated benzylphenylhydrazone was filtered, washed with water and recrystallized from aqueous ethanol to give colorless needles (20 mg.), m.p. 129–130°. *Anal.* Calcd. for $C_{18}H_{20}O_3N_2$: C, 69.2; H, 6.5; N, 9.0. Found: C, 68.9; H, 6.5; N, 9.1.

Several other attempts to prepare this derivative frequently resulted in the isolation of L-arabinose benzylphenylhydrazone, m.p. and mixed m.p. 165°.

Methyl 2,5-Anhydro-L-arabonate.—2,5-Anhydro-L-arabinose (0.35 g.) was oxidized with bromine in the usual way and the resulting sirupy acid (calcd. equiv. wt., 148; found: 140) was treated with ethereal diazomethane. Evaporation of the reaction solution gave the methyl ester of 2,5-anhydro-L-arabonic acid as a sirup. *Anal.* Calcd. for $C_6H_{10}O_5$: OCH_3, 19.1. Found: OCH_3, 19.3.

The methyl ester, when treated with methanolic ammonia, gave the corresponding amide as a sirup which did not crystallize. The amide gave a positive Weerman test, the hydrazodicarbonamide formed in the reaction having m.p. 254–255° (after recrystallization from water), undepressed on admixture with an authentic specimen.

2,5-Anhydro-L-arabitol.—2,5-Anhydro-L-arabinose (0.25 g.) in water (50 ml.) was reduced with hydrogen and Raney nickel catalyst at 120° and 500 lb. per square inch pressure for 5 hours. The resulting solution was filtered and evaporated under reduced pressure to give a sirup (0.23 g.), b.p. (bath temp.) 115–125° (0.09 mm.), $n^{25}D$ 1.4901, $[\alpha]^{23}D$ +0.2° in water (*c* 5.9). *Anal.* Calcd. for $C_5H_{10}O_4$: C, 44.8; H, 7.5. Found: C, 44.9; H, 7.2.

2,5-Anhydro-1,3,4-tri-*O*-*p*-toluenesulfonyl-L-arabitol, prepared in the usual manner and recrystallized from ethanol, had m.p. 128°, $[\alpha]^{23}D$ −27.4° in chloroform (*c* 5.9). *Anal.* Calcd. for $C_{26}H_{28}O_{10}S_3$: C, 52.4; H, 4.7. Found: C, 51.9; H, 5.3.

2,5-Anhydro-L-arabinose Dimethyl Acetal.—Ethyl 2,5-anhydro-α-L-arabofuranoside (0.65 g.) was boiled under reflux with 1.4% methanolic hydrogen chloride (22 ml.) for 2 hours, after which time the reaction solution showed $[\alpha]^{22}D$ +31° (constant value). The acid was neutralized with Duolite A4 ion exchange resin and the resulting solution evaporated to a sirup, which was distilled to yield a colorless

(21) S. Baker and W. N. Haworth, *J. Chem. Soc.*, **127**, 367 (1925).

(22) Although this glycoside and its derivatives are designated α, it is likely that some of the β anomer is also present.

(23) *Cf.* C. F. Huebner, R. Lohmar, R. J. Dimler, S. Moore and K. P. Link, *J. Biol. Chem.*, **159**, 503 (1945); T. G. Halsall, E. L. Hirst and J. K. N. Jones, *J. Chem. Soc.*, 1427 (1947).

liquid (0.5 g.), b.p. (bath temp.) 115–120° (0.005 mm.), $n^{25}D$ 1.4694, $[\alpha]^{26}D$ +30.5° in methanol (*c* 1.2). *Anal.* Calcd. for $C_7H_{14}O_5$: OCH_3, 34.8. Found: OCH_3, 34.0.

Action of Hydrogen Bromide on 2,5-Anhydro-L-arabinose Dimethyl Acetal.—2,5-Anhydro-L-arabinose dimethyl acetal (22 mg.) was exposed to an atmosphere of hydrogen bromide for 30 seconds during which time the sirup became very dark. It was dissolved in acetone and the solution neutralized with silver carbonate. After filtration, the solution was evaporated to leave a light brown sirup (18 mg.) which showed $[\alpha]^{26}D$ +80° in methanol (*c* 0.4).

Synthesis of 2,5-Anhydro-D-arabitol. 2,5-Anhydro-3,4-*O*-isopropylidene-D-arabitol.—3,6-Anhydro-4,5-*O*-isopropylidene-D-mannitol (VI), 6.7 g., m.p. 84°, prepared by the method of Foster and Overend,[9] was treated with 0.46 *N* sodium periodate (500 ml.) at 5° in the dark for approximately 48 hours, after which time 1.0 mole of periodate per mole of material had been consumed. To the resulting solution was added 1 *M* barium chloride (120 ml.) and the precipitate filtered. The filtrate was evaporated in the presence of strontium carbonate under reduced pressure to about 50 ml., the resulting mixture extracted with acetone and the aqueous acetone solution evaporated to dryness. The solid residue was extracted six times with boiling ethyl acetate and the combined extracts were evaporated to give sirupy 2,5-anhydro-3,4-*O*-isopropylidene-D-arabinose (VII), 4.29 g. A solution of the latter in thiophene-free benzene (100 ml.) showed the following changes in optical rotation: $[\alpha]^{20}D$ −126° (after 5 min.), −154° (20 min.), −160° (40 min.), −164° (46 hr.), −170° (51 hr.), −176° (73 hr., mutarotation incomplete). The benzene solution was evaporated to a sirup which was purified by extraction with ice-cold ethanol.

The solution of the sirupy 2,5-anhydro-3,4-*O*-isopropylidene-D-arabinose, in ethanol (100 ml.), was reduced using Raney nickel catalyst and 1000 lb. per square inch pressure of hydrogen at 120° for 7 hours. The resulting solution was evaporated under reduced pressure to give a crystalline residue which readily sublimed. Recrystallization of the material from benzene–ether–petroleum ether (b.p. 30–60°) at 5° gave 2,5-anhydro-3,4-*O*-isopropylidene-D-arabitol (VIII) as long colorless needles, m.p. 75–76°, $[\alpha]^{23}D$ −40.5° in water (*c* 5.4). *Anal.* Calcd. for $C_8H_{14}O_4$: C, 55.2; H, 8.1. Found: C, 55.0; H, 8.5.

2,5-Anhydro-3,4-*O*-isopropylidene-1-*O*-*p*-toluenesulfonyl-D-arabitol, prepared from the corresponding alcohol in the usual way, gave on recrystallization from aqueous ethanol, crystals, m.p. 67–68°, $[\alpha]^{23}D$ −33° in ethanol (*c* 1.6). *Anal.* Calcd. for $C_{15}H_{20}O_6S$: C, 54.9; H, 6.1. Found: C, 55.1; H, 6.3.

2,5-Anhydro-D-arabitol (IX).—2,5-Anhydro-3,4-*O*-isopropylidene-D-arabitol (0.1 g.), dissolved in *N* sulfuric acid (10 ml.), was heated on a boiling water-bath for two hours. The acid was neutralized with barium hydroxide, the solution filtered and the filtrate evaporated to dryness. The residue was extracted four times with boiling ethyl acetate and the combined extracts evaporated to a sirup (0.08 g.), which on distillation gave 2,5-anhydro-D-arabitol (IX), b.p. (bath temp.) 125–135° (0.24 mm.), $n^{23}D$ 1.4941, $[\alpha]^{23}D$ −1.4 ± 0.5° in water (*c* 0.9). *Anal.* Calcd. for $C_5H_{10}O_4$: C, 44.8 H, 7.5. Found: C, 44.4; H, 7.7.

2,5-Anhydro-1,3,4-tri-*O*-*p*-toluenesulfonyl-D-arabitol, prepared from the 2,5-anhydro-D-arabitol in the usual way, had m.p. 128–129°, $[\alpha]^{23}D$ +27.4° in chloroform (*c* 6.4) (after recrystallization from aqueous ethanol). When mixed with the L-isomer, the melting point was depressed to 110–111°.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, BRISTOL UNIVERSITY]

Methylene Derivatives of L-Rhamnose[1]

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The acid-catalyzed condensation of formaldehyde with L-rhamnose has yielded at least six methylene derivatives which have been separated and identified as 3,4-*O*-dimethyleneoxy-L-rhamnose, 2,3-*O*-dimethyleneoxy-L-rhamnose, 3,5-mono-*O*-methylene-L-rhamnose, 1,2;3,5-di-*O*-methylene-L-rhamnose, and *O*-dimethyleneoxy-mono-*O*-methylene-L-rhamnose and 2,3-mono-*O*-methylene-L-rhamnose. The first five crystallized.

Crystalline mono-*O*-methylene-L-rhamnose (m.p. 76°)[3] and mono-*O*-methylene-L-rhamnonolactone[4] (m.p. 151–152°) have been described but their structures are unknown. When L-rhamnose reacted with paraformaldehyde in the presence of sulfuric acid, at least six compounds were produced as indicated by paper chromatography. After neutralization the mixture was fractionated on a column of hydrocellulose,[5] giving five different crystalline methylene derivatives. None was identical with the compound (m.p. 76°) of Lobry de Bruyn and Alberda van Ekenstein.[3]

Three of the crystalline compounds (I, X, IX) reduced Fehling solution, sodium hypoiodite and sodium metaperiodate, whereas the other two (VIII, XII) did not. All were readily hydrolysed by acid to L-rhamnose and formaldehyde.

The main product of the condensation was 3,4-*O*-dimethyleneoxy-L-rhamnose (I). On hydrolysis it gave two moles of formaldehyde. It consumed one mole of metaperiodate with oxidative rupture to give one mole each of formic acid and of 5-deoxy-2,3-*O*-dimethyleneoxy-L-arabinose (II), thus showing the existence of an α-hydroxycarbonyl group in I. This was confirmed by methylation of I, followed by hydrolysis which gave 2-*O*-methyl-L-rhamnose (IV). The position of the *O*-dimethyleneoxy group in I was determined by reduction with sodium borohydride[6] to 3,4-*O*-dimethyleneoxy-L-rhamnitol (V). Methylation of V afforded the 1,2,5-tri-*O*-methyl derivative which on hydrolysis gave 1,2,5-tri-*O*-methyl-L-rhamnitol (VI). VI consumed one mole of metaperiodate, thus proving, in conjunction with the above evidence, that the *O*-dimethyleneoxy group was situated at C_3 and C_4 of L-rhamnopyranose.

2,3-*O*-Dimethyleneoxy-L-rhamnose (X) moved at a slower rate on the paper chromatogram than the 3,4-isomer I. It also yielded two moles of formaldehyde on hydrolysis but, on oxidation with meta-

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(6) B. Abdel-Akher, J. K. Hamilton and F. Smith, THIS JOURNAL, **73**, 4691 (1951).