THE SYNTHESIS OF 5-*O*-METHYL-L-ARABINOSE[1]

G. G. S. DUTTON, Y. TANAKA, AND K. YATES

ABSTRACT

5-*O*-Methyl-L-arabinose is thought to occur in the hydrolysis products of methylated wheat bran hemicellulose. This sugar has now been synthesized from ethyl 2,3-di-*O*-acetyl-5-*O*-trityl-α-L-arabinoside by detritylation, methylation, and hydrolysis. The free sugar was obtained as a sirup and was characterized by periodate oxidation together with the preparation of a crystalline osazone and a crystalline lactone.

In 1955 Adams (1) reported the probable occurrence of 5-*O*-methyl-L-arabinose, together with another monomethylarabinose, in the hydrolysis products of methylated wheat bran hemicellulose. It was not possible to separate these compounds and no constants for 5-*O*-methyl-L-arabinose were available so that positive identification was not possible.

We have now synthesized this compound from L-arabinose diethylmercaptal in 16% over-all yield by the following series of reactions:

L-arabinose diethyl mercaptal (I) → ethyl α-L-arabofuranoside (II) → ethyl 2,3-di-*O*-acetyl-5-*O*-trityl-α-L-arabinoside (III) → ethyl 2,3-di-*O*-acetyl-α-L-arabinoside (IV) → ethyl 2,3-di-*O*-acetyl-5-*O*-methyl-α-L-arabinoside (V) → 5-*O*-methyl-L-arabinose (VI).

Tritylation and acetylation of (II), which was readily obtained from (I) by the action of ethanol, mercuric chloride, and mercuric oxide, afforded (III) in high yield as a sirup. Although detritylation of (III) with hydrogen bromide in acetic acid was not satisfactory and gave positively rotating sirups the use of 80% acetic acid gave (IV) in high yield. Two treatments with Purdie's reagents gave a sirup which showed no hydroxyl band in the infrared. Successive hydrolyses with alkali and acid gave a sirup which showed a strong *p*-anisidine positive spot with R_f 0.30 (butanone–water azeotrope) and several weak spots which were not further examined. By chromatography on a column of cellulose–hydrocellulose (2) the component of R_f 0.30 was obtained pure.

A sample of this compound was oxidized with sodium metaperiodate and rapidly consumed 3 moles of periodate yielding 3 moles of formic acid. These results can be expected only from the 5-*O*-methyl derivative. Confirmation of this structure was obtained from the infrared spectrum of the lactone obtained by bromine oxidation. It has been reported that γ-lactones of aldonic acids show their C=O band in the range of 5.59–5.68 μ while for δ-lactones this is in the range of 5.68–5.79 μ (3). The C=O band of our mono-*O*-methyl-L-arabonolactone was at 5.62 μ, in agreement with the assigned structure of 5-*O*-methyl-L-arabinose. This was further supported by the fact that the lactone showed no change in rotation in aqueous solution after 20 hours.

It may be noted that the 5-*O*-methyl ether has a much higher R_f value than the corresponding 2-*O*-methyl derivative and that this is consistent with sugars which can only exist in the furanose form. Although sugar acetates may undergo acetyl migration even in the presence of such a weak base as silver oxide (4, 5) there was no indication of such migration in the preparation described here. It is obvious that this preparation might be shortened

[1]*Manuscript received June 22, 1959.*
Contribution from the Department of Chemistry, University of British Columbia, Vancouver, British Columbia. Presented at the 136th American Chemical Society meeting in Atlantic City, New Jersey, September, 1959.

by starting from an equilibrium mixture of arabofuranosides but we preferred to use a pure anomeric form in the hope that any intermediates would be crystalline. This hope was not realized. The ethyl furanoside was preferred to the methyl because of the hygroscopic nature of the latter (6, 7).

The related 2- and 3-*O*-methyl-L-arabinoses have been known for some time and only the 4-isomer remains to be synthesized.

EXPERIMENTAL

Ethyl α,L-Arabofuranoside (6)

L-Arabinose diethylmercaptal (4.90 g) was shaken for 4 hours at room temperature in absolute ethanol (50 ml) with mercuric chloride (11 g), yellow mercuric oxide (4.7 g), and drierite (1.5 g). The inorganic salts were removed by filtration and the filtrate was concentrated *in vacuo* to sirup. The sirup was dissolved in chloroform (60 ml) to remove inorganic salts and evaporation of the solution gave a light yellow sirup (3.05 g, 90%) which crystallized slowly on standing after seeding. R_f values of the sirup were 0.042 (very weak), 0.386 (very weak), and 0.543 (strong) (butanone–water azeotrope). M.p. 66–69° C, $[\alpha]_D^{25}$ −114.1° (*c*, 0.918 in water). Lit. (6) m.p. 68–69° C, $[\alpha]_D^{20}$ −116.0° (*c*, 7.055 in water).

Ethyl 2,3-Di-O-acetyl-5-O-trityl-α,L-arabinoside (8)

Ethyl α,L-arabofuranoside (3.05 g, 0.0172 mole) was dissolved in dry pyridine (20 ml) and the solution was kept at room temperature for 24 hours after addition of trityl chloride (5.25 g, 0.0188 mole). During this period pyridine hydrochloride precipitated out of the solution. Acetic anhydride (20 ml) was added and the solution was kept at room temperature for a further 24 hours. The acetylated solution was poured into ice water and extracted with chloroform (20 ml × 5). The chloroform solution was washed with aqueous sodium bicarbonate solution, washed with water, dried over anhydrous sodium sulphate, and evaporated *in vacuo* to give a yellow sirup (8.30 g, 96%), $[\alpha]_D^{25}$ −82.9° (*c*, 0.362 in chloroform).

Ethyl 2,3-Di-O-acetyl-α,L-arabinoside (8)

To ethyl 2,3-di-*O*-acetyl-5-*O*-trityl-α,L-arabinoside (8.30 g) were added water (62 ml) and glacial acetic acid (250 ml) and the mixture was heated for 1 hour in boiling water. The solution was concentrated *in vacuo* to give a mixture of tritanol and yellow sirup. The mixture was dissolved in chloroform (10 ml) and adsorbed on an alumina column (3.5×20 cm) which was washed with benzene. Tritanol was eluted first with benzene (800 ml) and the detritylated compound was eluted with chloroform (1500 ml). Evaporation of the eluate gave a yellow sirup (3.59 g, 83%) $[\alpha]_D^{25}$ −58.8° (*c*, 0.218 in chloroform). Lit. (8) $[\alpha]_D^{20}$ −30° (*c*, 1.7 in chloroform). Infrared spectrum of the sirup showed complete lack of aromatic character.

Ethyl 2,3-Di-O-acetyl-5-O-methyl-α,L-arabinoside

Ethyl 2,3-di-*O*-acetyl-α,L-arabinoside (3.59 g) and drierite (5 g) were stirred under reflux in methyl iodide (50 ml) for 6 hours. Silver oxide (10 g) was added in 10 portions at about 30-minute intervals. Excess methyl iodide was removed by distillation and the residue was extracted five times with 50 ml each of chloroform. Evaporation of the solvent gave a yellow sirup (2.99 g).

The procedure was repeated again under the same conditions and the yellow sirup (2.48 g, 65.5%), $[\alpha]_D^{25}$ −49.0° (*c*, 0.306 in chloroform), showed no free hydroxyl band on the infrared spectrum.

Hydrolysis of Ethyl 2,3-Di-O-acetyl-5-O-methyl-α,L-arabinoside

Ethyl 2,3-di-*O*-acetyl-5-*O*-methyl-α,L-arabinoside (2.48 g) was heated in a mixture of 2 *N* sodium hydroxide (20 ml), water (20 ml), and methanol (40 ml) for 1 hour in boiling water, and then neutralized with IR-120 resin (Rohm and Haas). The neutral solution was concentrated *in vacuo* to a volume of 65 ml and 1 *N* hydrochloric acid (65 ml) was added. The mixture was heated in boiling water and the hydrolysis was followed polarimetrically. The initial rotation (−1.440° in 1-dm tube) changed after 4 hours to a constant value (−0.155° in 0.5-dm tube). The acidic solution was neutralized with Duolite A-4 resin (Chemical Process Co.) and then concentrated *in vacuo* to a sirup (1.10 g, 74%). Paper chromatography (butanone–water azeotrope) of the sirup showed a strong spot of R_f 0.30 and weak spots of R_f's 0.64, 0.53, 0.22, and 0.12.

Separation of 5-O-Methyl-L-arabinose by Chromatography

The hydrolysis product (1.1 g) was dissolved in methanol (2 ml) and was chromatographed on a cellulose–hydrocellulose column (3×40 cm) using butanone–water azeotrope as developing solvent (rate of flow, 10 ml/30 minutes). Each fraction (10 ml) was checked by paper chromatography. In tubes No. 13–23 a compound with R_f 0.30 was found with others having R_f 0.64 and R_f 0.53, but in tubes No. 24–40 only the compound with R_f 0.30 was observed. On evaporation of the fractions No. 24–40 a colorless sirup (387 mg) was obtained. Rechromatography of fractions No. 13–23 under the same conditions gave a further quantity of sirup (120 mg). Both were chromatographically pure (R_f 0.30) and the total yield of the sirup was 507 mg (46%). Anal. calc. for $C_6H_{12}O_5$: OMe, 18.9%. Found: OMe, 18.8, 19.0%. $[\alpha]_D^{25}$ −32.0° (*c*, 0.484 in water). The R_f value in butan-1-ol–ethanol–water–ammonia (40:11:19:1) was 0.48.

Periodate Oxidation of 5-O-Methyl-L-arabinose

All reactions were carried out in the dark and at 5° C.

(*i*) *Determination of periodate consumed.*—5-*O*-Methyl-L-arabinose (7.5 mg) was dissolved in water (10 ml), and 0.23 *M* sodium metaperiodate solution (1 ml) was added to the solution. A blank was run concurrently. Aliquot portions (1 ml) were withdrawn at intervals and the consumption of periodate was determined by means of the arsenite method (8). The results are shown in Table I.

(*ii*) *Estimation of formic acid produced.*—After reacting overnight, an aliquot was titrated with 0.01 *N* sodium hydroxide solution using methyl red as an indicator. The results are shown in Table I.

TABLE I

Periodate oxidation of the mono-*O*-methyl-L-arabinose

	Periodate consumption					Formic acid production
Time, hour	0	1	2	3	Overnight	Overnight
Moles	1.97	2.68	2.70	2.86	2.86	3.09

5-O-Methyl-L-arabinose Phenylosazone

5-*O*-Methyl-L-arabinose (111 mg) was dissolved in 20% acetic acid (5 ml), and sodium bisulphite (110 mg) and phenylhydrazine (1 ml) were added. The solution was kept for 1 hour at 80° C and then at room temperature overnight. The precipitated yellow crystals (50 mg) were filtered and recrystallized from aqueous acetone, m.p. 154.5°, $[\alpha]_D^{25}$ −16.6°

(*c*, 0.4 in methanol). Dilution of the filtrate with water gave a further 70 mg of the crystals which showed m.p. 154.5° after recrystallization from aqueous acetone. Total yield of the phenylosazone was 120 mg (52%). Anal. calc. for $C_{18}H_{22}O_3N_4$: C, 63.1; H, 6.5; N, 16.4; OMe, 9.1%. Found: C, 62.9; H, 6.4; N, 16.3, 16.6; OMe, 9.0, 9.2%. (C, H, and N by Drs. Weiler and Strauss, Oxford).

*5-O-Methyl-*L*-arabonolactone*

5-*O*-Methyl-L-arabinose (120 mg) was dissolved in water (2 ml) and kept at room temperature in the dark, after addition of bromine (10 drops). The oxidation was complete after 30 hours (paper chromatography) and water (10 ml) was added. Excess bromine was removed by aeration, and the solution was treated with silver carbonate and centrifuged. After hydrogen sulphide was passed through the solution and after centrifugation, the solution was concentrated *in vacuo* to dryness to give a solid (77 mg) which by recrystallization from acetone–petroleum ether gave colorless needles, m.p. 135° C, $[\alpha]_D^{25}$ −76.2° (*c*, 0.22 in water) (no change after 20 hours); $[\alpha]_D^{25}$ −43.7° (*c*, 0.27 in acetone); γ Nujol max. 5.62 μ. Anal. calc. for $C_6H_{10}O_5$: OMe, 19.2%. Found: OMe, 19.1, 19.3%.

ACKNOWLEDGMENTS

The financial support of the National Research Council is gratefully acknowledged. We wish to thank Dr. F. Smith for a gift of ethyl α-L-arabofuranoside.

REFERENCES

1. Adams, R. A. Can. J. Chem. **33**, 56 (1955).
2. Geerdes, J. D., Lewis, B. A., Montgomery, R., and Smith, F. Anal. Chem. **26**, 264 (1954).
3. Baker, S. A., Bourne, E. J., Pinkard, R. M., and Whiffen, D. H. Chem. & Ind. 658 (1958).
4. Whistler, R. L. and Kazeniac, S. J. J. Am. Chem. Soc. **76**, 5812 (1954).
5. Bouveng, H. O., Lindberg, B., and Theander, O. Acta Chem. Scand. **11**, 1788 (1957).
6. Green, J. W. and Pacsu, E. J. Am. Chem. Soc. **60**, 2056 (1938).
7. Augestad, I. and Berner, E. Acta Chem. Scand. **8**, 251 (1954).
8. Goldstein, I. J., Smith, F., and Srivastava, H. C. J. Am. Chem. Soc. **79**, 3858 (1957).
9. Jackson, E. L. Organic reactions. Vol. 2. John Wiley & Sons, Inc., New York. 1944. p. 341.