621. *Branched-chain Sugars. Part III.*[1] *The Introduction of Branching into Methyl* 3,4-O-*Isopropylidene*-β-L-*arabinoside and the Synthesis of* L-*Hamamelose*

By J. S. Burton, W. G. Overend, and N. R. Williams

Branched-chain sugars have been synthesised by the following route: (i) protection of a methyl glycoside at all sites except that at which branching is to be introduced; (ii) oxidation of the unprotected hydroxyl group to obtain a protected methyl glycopyranosidulose; (iii) treatment of the oxidation product with a Grignard reagent and removal of protecting groups. In this way methyl 3,4-*O*-isopropylidene-β-L-*erythro*-pentopyranosidulose has been prepared and treated with a range of Grignard reagents, and, after further conversions, it has been possible to obtain L-arabinose derivatives which have a methyl, hydroxymethyl, or formyl side-chain of the type which occurs in natural products. Stereochemical correlations have been carried out. The methods developed have been used to synthesise L-hamamelose and its epimer (2-*C*-hydroxymethyl-L-arabinose). Some attempts have been made to convert branched-chain glycosides into branched-chain deoxyglycosides by removal of the tertiary hydroxyl group.

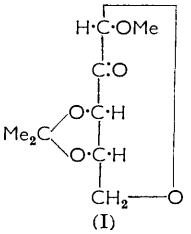
Until the extensive study in recent years of antibiotics the only known naturally-occurring branched-chain sugars were hamamelose and apiose, which are found as glycosides in plants; consequently, little attention was paid to this class of substance. However, the isolation from antibiotics of more branched-chain sugars has led to interest in the chemistry of this type of sugar.[2] For convenience branched-chain sugars may be divided into two groups since branching can occur in the carbon chain of a sugar either by substitution of a hydrogen atom (type A) or (less usual) of a hydroxyl group (type B), *e.g.*, $>$CHOH ⟶ $>$CR(OH) (A) or $>$CHR (B). Until recently the only groups (R) which had been found in natural products were $-CH_3$, $-CH_2{\cdot}OH$, or $-CHO$, but in 1962 a branched-chain trideoxyoctose was described in which the branching group is $-(OH)CH{\cdot}CH_3$.[3]

[1] Part II, W. G. Overend and G. Vaughan, *J.*, 1954, 2155.
[2] See F. A. Shafizadeh, *Adv. Carbohydrate Chem.*, 1956, **11**, 263.
[3] J. S. Webb, R. W. Broschard, D. B. Cosulich, J. H. Mowat, and J. E. Lancaster, *J. Amer. Chem. Soc.*, 1962, **84**, 3183.

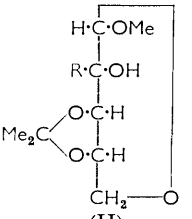
As part of a comprehensive study of branched-chain sugars we have examined methods for their synthesis and now report one general method for the preparation of type A sugars which we have applied to the synthesis of L-hamamelose (2-*C*-hydroxymethyl-L-ribose) and its epimer (2-*C*-hydroxymethyl-L-arabinose). Some experiments to make derivatives of type B sugars are also included. We describe now our work in the L-series; the synthesis of the natural D-hamamelose by an alternative route will be given in a subsequent Paper. Brief summaries of this work have already been reported.[4]

Essentially the method is simple, involving oxidation of a suitably protected methyl glycoside to a product with a carbonyl group in the sugar ring. This group can react with a number of reagents to lead to branching in the sugar, *e.g.*, >CH·OH ⟶ >C=O ⟶ >CR(OH). In this Paper we report on the action of Grignard reagents on the oxidation product. (Walton *et al.*[5] have used such a procedure in their synthesis of noviose, although in this case the carbonyl group was not in the sugar ring.) Subsequent communications will deal with the action of diazomethane and of organolithium compounds on the oxo-glycosides.

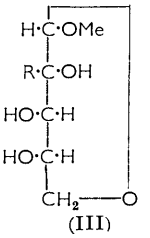
Theander *et al.*,[6] working with unprotected methyl glycosides, prepared sugar derivatives with endocyclic carbonyl groups but only in very low yields (*ca.* 5%). Consequently, we preferred to protect all hydroxyl groups except the one to be oxidised and carried out trial experiments with the 3,4-*O*-isopropylidene and 3,4-di-*O*-methyl derivatives of methyl β-L-arabinoside. Of a number of oxidants tested only chromic oxide in pyridine,[7] used according to a slight modification of Walton's procedure,[5] gave reasonable yields of oxidation product. Such oxidation of methyl 3,4-*O*-isopropylidene-β-L-arabinoside afforded crystalline methyl 3,4-*O*-isopropylidene-β-L-*erythro*-pentopyranosidulose (I) (over many preparations yields varied from 30—52%), which formed a solid 2,4-dinitrophenylhydrazone. [The D-isomer of (I) was likewise prepared from methyl 3,4-*O*-isopropylidene-β-D-arabinoside.] When the oxidation was carried out by heating the solution under reflux according to Korytnyk and Kris [8] only a 20% yield of compound (I) was obtained. Oxidation with t-butyl chromate in butanol [9] gave only 10% of (I). Attempts to use aqueous alkaline potassium permanganate, t-butyl hypochlorite in carbon tetrachloride,[10] or an Oppenauer oxidation with aluminium isopropoxide and either acetone or cyclohexanone all failed to yield crystalline products. The isopropylidene group in compound (I) is very sensitive to acid, and is hydrolysed even by water at room temperature to give a product which reduces Fehling's solution in the cold. This lability of the ketal may account for the failure of aqueous alkaline permanganate as an oxidising agent for the preparation of compound (I).



(I)



(II)



(III)

In Table 1 are listed the branched-chain glycosides of general formula (II) which have been prepared by treating compound (I) with Grignard reagents in ether solution. Some

[4] J. S. Burton, W. G. Overend, and N. R. Williams, (*a*) *Chem. and Ind.*, 1961, 175; (*b*) *Proc. Chem. Soc.*, 1962, 181.
[5] E. Walton, J. O. Rodin, C. H. Stammer, F. W. Holley, and K. Folkers, *J. Amer. Chem. Soc.*, 1958, **80**, 5168.
[6] See O. Theander, *Adv. Carbohydrate Chem.*, 1962, **17**, 223.
[7] G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[8] W. Korytnyk and E. J. Kris, *Chem. and Ind.*, 1961, 1834.
[9] A. Leo and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1952, **74**, 4383.
[10] C. A. Grob and H. J. Schmid, *Helv. Chim. Acta*, 1953, **36**, 1763.

of the compounds contained traces of methyl 3,4-*O*-isopropylidene-β-L-arabinoside formed as a by-product, presumably by reduction of the oxo-sugar by the Grignard reagent. This was conveniently removed after deacetonation when crystalline glycosides were formed. The vinyl compound (IId), which gives a syrupy glycoside after deacetonation, was purified

TABLE 1

Branched-chain glycosides with general formula (II)

No.	R	B. p. (mm.)	$[\alpha]_D$ (*c* in EtOH)	Yield (%)
1	(a) Me [1]	60°/0·1	+116 (0·6)	86
2	(b) Ph	115/10^{-3}	+169 (1·0)	95
3	(c) $CH_2{\cdot}CH{=}CH_2$	64—66/0·03	+86 (1·0 in $CHCl_3$)	78
4	(d) $CH{=}CH_2$ [2]	72/0·08	+138 (2·5 in MeOH)	70
5	(e) $C{\equiv}C{\cdot}[CH_2]_3{\cdot}CH_3$	99—100/0·04	+80·5 (1·4 in MeOH)	71
6	(f) *cis*-$CH{=}CH{\cdot}[CH_2]_3{\cdot}CH_3$ [3]	108—110/0·3	+106·4 (2·6 in MeOH)	91
7	(g) $C{\equiv}C{\cdot}Ph$	97—98 [4]	+100·5 (0·6)	62
8	(h) *cis*-$CH{=}CH{\cdot}Ph$ [5]	135—136/0·1	+125 (0·6)	95
9	(i) *cis*/*trans*-$CH{=}CH{\cdot}Ph$ [6]	131—133/0·03	—	60

	Found (%)					Required (%)			
No.	C	H	O	OMe	Formula	C	H	O	OMe
1	55·1	8·3	36·8	14·1	$C_{10}H_{18}O_5$	55·0	8·3	36·7	14·2
2	64·5	7·3	—	—	$C_{15}H_{20}O_5$	64·3	7·2	—	—
3	58·85	8·3	33·1	13·0	$C_{12}H_{20}O_5$	59·0	8·25	32·75	12·7
4	57·3	7·8	34·8	13·1	$C_{11}H_{18}O_5$	57·4	7·9	34·8	13·5
5	63·0	8·8	28·4	10·8	$C_{15}H_{24}O_5$	63·35	8·5	28·1	10·9
6	63·3	9·3	—	—	$C_{15}H_{26}O_5$	62·9	9·15	—	—
7	67·25	6·6	26·4	10·1	$C_{17}H_{20}O_5$	67·1	6·6	26·3	10·2
8	—	—	—	—	—	—	—	—	—
9	—	—	—	—	—	—	—	—	—

[1] D-Isomer (79%) was also prepared, b. p. 63—65°/0·2 mm., $[\alpha]_D$ −114·2° (*c* 0·82 in EtOH). [2] Prepared in tetrahydrofuran. [3] Prepared by hydrogenation of (IIe) with Lindlar's catalyst. [4] Recrystallised from light petroleum (b. p. 40—60°) as colourless needles. [5] Prepared by hydrogenation of (IIg) with Lindlar's catalyst. [6] Product contaminated with 1,4-diphenylbuta-1,3-diene, best removed after deacetonation.

by treatment with toluene-*p*-sulphonyl chloride in pyridine at room temperature; only the by-product is esterified under these conditions and unchanged (IId) can be obtained pure by distillation. In Table 2 details are given of the glycosides of general formula (III) which were obtained by deacetonation with methanolic hydrochloric acid of compounds listed in Table 1. All the compounds included in Tables 1 and 2 had infrared spectra in accordance with their proposed structures.

The preparation of a crystalline methyl 2-*C*-phenylethenylarabinoside is complicated by the formation of *cis*- and *trans*-isomers, which can form mixed crystals. The glycoside previously reported [4a] as having m. p. 150—151° has since been shown to be a mixture of these two isomers, which have been separated. Both of the isomers lead on ozonolysis to the same 2-*C*-formyl glycoside (see later) and on reduction give the same 2-*C*-phenylethyl derivative and are not, therefore, configurational isomers at C-2 of the glycoside. The assignment of configuration to these two geometrical isomers is based on (*a*) the alternative preparation of the *cis*-form by catalytic partial hydrogenation of the acetylenic compound (IIIf) and (*b*) their infrared spectra. The compounds (IIh) and (IIIg), which have been denoted as *cis*-forms, have an absorption peak at 6·10 μ [also shown by the *cis*-hex-1-enyl sugars (IIf) and (IIIe)] whereas the *trans*-compound (IIIh) has $\lambda_{max.} = 6{\cdot}00$ μ.

When either methyl 3,4-*O*-isopropylidene-2-*C*-vinyl-β-L-arabinoside or methyl 2-*C*-(*cis*-hex-1-enyl)-3,4-*O*-isopropylidene-β-L-arabinoside is ozonolysed the 2-*C*-formyl derivative (II; R = CHO) is obtained as a strongly reducing syrup, characterised as the crystalline toluene-*p*-sulphonylhydrazone. Reduction of compound (II; R = CHO) affords methyl 2-*C*-hydroxymethyl-3,4-*O*-isopropylidene-β-L-arabinoside (II; R = CH_2OH). Likewise, ozonolysis of methyl 2-*C*-(*cis*- or *trans*-phenylethenyl)-β-L-arabinoside yielded methyl 2-*C*-formyl-β-L-arabinoside (III; R = CHO) which can also be obtained by deacetonation

TABLE 2

Branched-chain glycosides with general formula (III)

No.	R	M. p.	$[\alpha]_D$ (c in EtOH)	Cryst. from	Yield (%)	R_F	M_G
1	(a) Me [1]	100°	+124 (0·5)	Ethyl acetate	80	0·50	0·36
2	(b) Ph	141—142	+168 (1·9)	Ethanol	52	—	—
3	(c) CH_2·CH=CH_2	81—82	+94·5 (0·5 in H_2O)	Ether	30	0·81	0·38
4	(d) CH=CH_2	B. p. 134/ 10^{-4} mm.	+169 (0·8)	—	94	0·66	0·38
5	(e) *cis*-CH=CH·[CH_2]$_3$·CH_3	54—55	+109 (0·2)	Ether–light petroleum (b. p. 40—60°)	24		
6	(f) C≡C·Ph	122—123	+40 (0·6)	Benzene	76	—	—
7	(g) *cis*-CH=CH·Ph	169—170	+97·5 (0·4)	Ethyl acetate	68 [2]	0·79	—
8	(h) *trans*-CH=CH·Ph	200—201	+38·6 (0·3)	Ethyl acetate–ethanol	28	0·81	—
9	(i) CH_2·CH_2Ph [3]	126—127	+42 (0·5 in MeOH)	Ethyl acetate	72—74	0·81	

	Found (%)					Required (%)			
No.	C	H	O	OMe	Formula	C	H	O	OMe
1	47·1	7·8	—	17·6	$C_7H_{14}O_5$	47·2	7·9	—	17·4
2	59·9	6·7	—	—	$C_{12}H_{16}O_5$	60·0	6·7	—	—
3	51·8	7·8	—	15·0	$C_9H_{16}O_5$	51·8	7·8	—	15·2
4	50·0	7·7	—	16·0	$C_8H_{14}O_5$	50·5	7·4	—	16·3
5	—	—	—	—	—	—	—	—	—
6	63·4	6·1	30·5	12·2	$C_{14}H_{16}O_5$	63·6	6·1	30·3	11·7
7	63·2	6·95	—	—	$C_{14}H_{18}O_5$	63·1	6·8	—	—
8	62·9	7·0	—	11·7	$C_{14}H_{18}O_5$	63·1	6·8	—	11·6
9	—	—	—	—	—	—	—	—	—

[1] Methyl 2-*C*-methyl-β-D-*arabino*-pentoside was also prepared as colourless rhombs, m. p. 99·5—100° (from ethyl acetate), $[\alpha]_D$ −126° (*c* 0·7 in EtOH) (Found: C, 47·3; H, 7·75; OMe, 17·9%). [2] Yield of *cis*-isomer based on deacetonation of (IIh). Catalytic reduction of (IIIf) gave 51% *cis*-isomer. Deacetonation of the *cis*-*trans*-mixture (IIi), after extraction of 1,4-diphenylbuta-1,3-diene with light petroleum (b. p. 40—60°) gave 32% of *cis*- and 28% of *trans*-isomer. [3] Prepared by hydrogenation of (IIIg), (IIIh), or (IIIf) in methanol using Adams catalyst.

of compound (II; R = CHO). It can be characterised as its *p*-nitrophenylhydrazone. Reduction of compound (III; R = CHO) or deacetonation of compound (II; R = CH_2·OH) afforded methyl 2-*C*-hydroxymethyl-β-L-arabinopyranoside (III; R = CH_2OH), characterised as its triacetate. Hence, these model experiments indicated routes for the synthesis of branched-chain sugars in which, in addition to other groups, a methyl, hydroxymethyl or formyl residue, as is found in natural products, is located at the branch point.

All the compounds have been discussed in terms of the L-*arabino*-configuration, and there are reasons for this assignment. The stereochemical implications of additions to oxo-sugars are interesting and will be discussed fully in a later Paper. As far as the action of the Grignard reagents on compound (I) is concerned, the reaction resulting in the formation of an asymmetric centre at C-2 is essentially stereospecific, for only one product could be detected. A very careful examination of the product from reaction of (I) with methylmagnesium iodide yielded a very small amount (4%) of a second isomer,[11] but analysis of compound (IId) by vapour-phase chromatography and the glycosides listed in Table 2 by paper chromatography and in some cases by electrophoresis in borate buffer, failed to reveal more than one component in each sample. The subsequent reactions of the unsaturated sugars to give products known not to be isomeric mixtures confirms this conclusion.

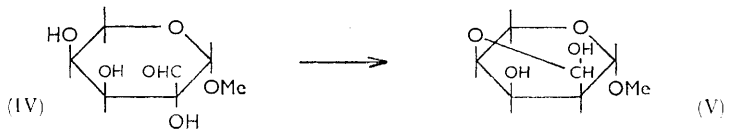
An examination of the ionophoresis in borate buffer of some of the glycosides listed in Table 2 showed that they conformed more closely in behaviour to methyl arabinopyranoside (M_G = 0·35) than to methyl ribopyranoside (M_G = 0·54).

Another lead concerning configuration at the branch point was obtained when methyl

[11] R. J. Ferrier, W. G. Overend, H. M. Wall, and N. R. Williams, unpublished results.

2-*C*-(*cis*-phenylethenyl)-β-L-(arabino)pentoside was subjected to ozonolysis. The 2-*C*-formyl derivative obtained was a syrup which showed a strong carbonyl absorption in the infrared region, but on storage it crystallised to give a substance A which was still strongly reducing, which showed mutarotation in water, but had no pronounced carbonyl absorption in its infrared spectrum. Subsequently substance A was prepared by ozonolysis of methyl 2-*C*-vinyl-β-L-pentoside, methyl 2-*C*-(*trans*-phenylethenyl)-β-L-pentoside, and methyl 2-*C*-(*cis*-hex-1-enyl)-β-L-pentoside [obtainable by partial reduction of the 2-*C*-hex-1-ynyl compound (IIe) and deacetonation], and so it follows that all these compounds have the same configuration at C-2. Since methyl 2-*C*-(*cis*-phenylethenyl)-β-L-pentoside can also be obtained by partial reduction of the corresponding 2-*C*-phenylethynyl compound, the configuration of this latter compound is also correlated with substance A. Correlation of the configuration of substance A and the 2-*C*-hydroxymethyl derivative (III; R = CH_2OH) follows from the preparation of the latter by direct reduction of compound A.

The following evidence about compound A is relevant regarding its configuration. Molecular-weight determinations showed that the substance was monomeric. With methanolic hydrogen chloride it gave a crystalline non-reducing mono-*O*-methyl derivative which did not exhibit mutarotation, and with aniline and *p*-toluidine it afforded respectively an *N*-phenylglycosylamine and an *N*-*p*-tolylglycosylamine, both crystalline. It was concluded that the initially-formed syrupy *C*-formyl derivative (IV) had undergone an intramolecular cyclisation to give the solid A (V) and this was supported by optical rotatory dispersion measurements (see later) and polarographic studies. Dr. A. Levy of this department showed that substance A behaves polarographically in a manner similar to normal free sugars in that the limiting current is independent of the height of the mercury reservoir and is determined by the rate of transformation of the αβ-equilibrium mixture from the ring form (V) to the " open-chain " reducible form (IV) at the mercury surface and not by the rate of diffusion of the sugar derivative to the mercury drop (see Overend *et al.*[12]). The rate of conversion of the αβ-equilibrium mixture (V) into the reducible form (IV), k_S, is $7{\cdot}05 \times 10^{-4}$ cm. sec.$^{-1}$ at pH 9·73: this value is higher than for ribose ($2{\cdot}65 \times 10^{-4}$ cm. sec.$^{-1}$) and much higher than for other simple sugars.[12] This work indicates that an intramolecular cyclisation of the 2-*C*-formyl compound (IV) had occurred to give compound A, and the high value of k_S indicates that the bicyclic system (V) is readily reconverted into the monocyclic system (IV). For the intramolecular cyclisation to occur it is necessary for the 2-*C*-formyl group and the 4-hydroxyl group in (IV) to be diaxial and this is only possible if the compound has the L-*arabino*-configuration as shown in the formulæ.

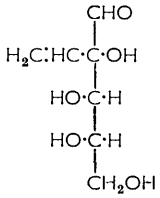


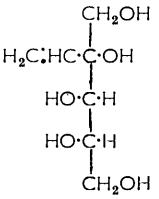
When compound A in dry dioxan was shaken with an excess of toluene-ω-thiol in the presence of an ion-exchange resin and the product was desulphurised with nickel, a crystalline compound was obtained which was identical with that produced when the main product of the action of methylmagnesium iodide on the oxo-sugar (I) was deacetonated. This established that the configurations of the 2-*C*-methyl derivatives (IIa) and (IIIa) were the same as that of the formyl derivative (IV ⇌ V). This conclusion has been confirmed by infrared-spectral studies [13] and by chromatography in solvents containing phenylboronic acid.[13] Direct proof was not obtained of the correlation of configuration of the 2-*C*-allyl (IIc) and (IIIc) and 2-*C*-phenyl (IIb) and (IIIb) derivatives with compound

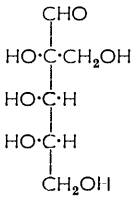
[12] W. G. Overend, J. B. Smith, and A. R. Peacocke, *J.*, 1961, 3487.
[13] R. J. Ferrier, W. G. Overend, G. A. Rafferty, H. M. Wall, and N. R. Williams, *Proc. Chem. Soc.*, 1963, 133.

(IV ⇌ V), but ionophoretic behaviour of compound (IIIc) indicated that the substance had the *arabino*-configuration.

The methods developed have been used to synthesise L-hamamelose. Methyl 2-*C*-vinyl-β-L-arabinoside (IIId) was hydrolysed to give 2-*C*-vinyl-L-arabinose (VI) as a syrup characterised as its toluene-*p*-sulphonylhydrazone, m. p. 159—161°. Borohydride reduction of compound (VI) afforded a mixture from which 2-*C*-vinyl-L-arabitol (VII) was


(VI)


(VII)


(VIII)

isolated and subjected to ozonolysis to yield 2-*C*-hydroxymethyl-L-ribose (VIII) (isolated as the α-form) (α-L-hamamelose). The same product could be obtained from 2-*C*-vinyl-L-arabinose in similar yield by effecting ozonolysis on the crude syrup from the borohydride reduction and then purifying the crude product by paper chromatography. The L-hamamelose was characterised as its *p*-nitrophenylhydrazone and toluene-*p*-sulphonylhydrazone. Oxidation of 2-*C*-hydroxymethyl-L-ribose was carried out by a modification of Freudenberg and Blümmel's method [14] and the 2-*C*-hydroxymethyl-L-ribono-γ-lactone so obtained was indistinguishable from a sample of the authentic material kindly supplied by Dr. R. J. Ferrier of this department.[15] Treatment of this lactone with ammonia solution gave crystalline ammonium L-hamamelonate identical with a sample provided by Dr. Ferrier.

When methyl 2-*C*-hydroxymethyl-β-L-arabinoside (III; R = CH_2OH) was hydrolysed it gave 2-*C*-hydroxymethyl-L-arabinose (the epimer of L-hamamelose), characterised as its toluene-*p*-sulphonylhydrazone and α,α-benzylphenylhydrazone. Oxidation of this branched-chain sugar with bromine water in the presence of lead carbonate [16] afforded 2-*C*-hydroxymethyl-L-arabinolactone which was converted into the phenylhydrazide of 2-*C*-hydroxymethyl-L-arabonic acid. These syntheses of L-hamamelose and its epimer provide further evidence for the *arabino*-configuration for the products from the action of Grignard reagents on compound (I).

Next, attention was directed to the conversion of some of the aforementioned type A branched-chain sugars into the corresponding type B derivatives. For the compounds described so far the tertiary hydroxyl group resisted normal esterification and, for example, methyl 3,4-*O*-isopropylidene-2-*C*-methyl-β-L-arabinoside did not react with toluene-*p*-sulphonyl chloride in pyridine at room temperature. However esterification was achieved by first preparing the sodio-derivative by treating the arabinoside with metallic sodium in boiling ether and treating this with toluene-*p*-sulphonyl chloride in ether. The 2-*O*-tosyl derivative so obtained was a very hygroscopic yellow gum which decomposed on exposure to air. This material was reduced, without further manipulation, with lithium aluminium hydride in ether to yield methyl 2-deoxy-3,4-*O*-isopropylidene-**2-*C*-**methyl-β-L-3,4-*erythro*-pentoside which could be deacetonated with methanolic hydrochloric acid. Unfortunately, an attempt to extend this method for the conversion of other branched-chain sugars of type A into type B was unsuccessful. Unstable gummy toluene-*p*-sulphonates were similarly prepared from methyl 3,4-*O*-isopropylidene-2-*C*-phenylethynyl-β-L-arabinoside and methyl 3,4-*O*-isopropylidene-2-*C*-(*cis*-phenylethenyl)-β-L-arabinoside but each, on treatment with lithium aluminium hydride, afforded the original

[14] K. Freudenberg and F. Blümmel, *Annalen*, 1924, **440**, 45.
[15] Cf. R. J. Ferrier, *J.*, 1962, 3544.
[16] J. W. E. Glattfeld and M. Hanke, *J. Amer. Chem. Soc.*, 1919, **40**, 989.

branched-chain sugar, and no deoxy-components were detected. When methyl 3,4-*O*-isopropylidene-2-*O*-tosyl-2-*C*-vinyl-β-L-arabinoside was reduced with lithium aluminium hydride in ether, a colourless mobile oil was obtained which infrared-spectral analysis indicated was a mixture of methyl 3,4-*O*-isopropylidene-2-*C*-vinyl-β-L-arabinoside and a deoxy-sugar derivative in which the vinyl double bond had undergone migration to give a compound with an exocyclic double bond attached directly to the sugar ring. The product had an absorption peak at 5·95 μ characteristic of a trisubstituted olefin and on ozonolysis it gave a 30% yield of the oxo-sugar (I).

Professor W. Klyne has kindly measured the optical rotatory dispersion curves of compounds prepared during this investigation and which contain a carbonyl group. In methanol solution compound (I) shows a curve with a strong negative Cotton effect and with a surprisingly large amplitude (10^{-2} *a* −64). Methyl 2-*C*-formyl-3,4-*O*-isopropylidene-β-L-arabinoside gave a negative Cotton-effect curve in chloroform, but a plain curve in ethanol suggesting that in the latter solvent the formyl group is converted into a hemiacetal. As expected, compound A, which is believed to exist as an intramolecular hemiacetal, also showed a plain curve in methanol solution.

Experimental

Unless otherwise stated all paper chromatography was carried out with the top phase of a mixture of n-butanol–ethanol–water (4 : 1 : 5, v/v) as developing solvent, on Whatman No. 1 (for qualitative analysis) or No. 3 (for preparations) paper. Spots were located by dipping the paper in aqueous saturated silver nitrate solution containing acetone and subsequently spraying with 0·5N-sodium hydroxide in ethanol. At room temperature reducing sugars were detectable immediately, and glycosides were revealed more slowly.

Electrophoresis (*ca.* 15 mA, 1200v, 2 hr.) was carried out with Whatman No. 3 paper in 0·2M-borate buffer, pH 10; the spots were located by the method of Trevelyan *et al.*[17]

Infrared-spectral measurements were made on substances in fused potassium bromide discs (liquids being applied as films) with a Perkin-Elmer " Infracord " Spectrometer.

Methyl 3,4-O-*Isopropylidene*-β-L-erythro-*pentopyranosidulose* (I).—(*a*) Chromic oxide (60 g.) was added slowly with stirring to dry pyridine (2 l.) at 0° to give a yellow solution of the chromic oxide–pyridine complex.[7] Methyl 3,4-*O*-isopropylidene-β-L-arabinoside[18] (42·0 g.), $[\alpha]_D^{20}$ +196° (in $CHCl_3$), in pyridine (100 ml.), was added and the solution was stirred for 20 hr. The pyridine was removed as far as possible by distillation under diminished pressure at 50°. The residue was extracted with ether (1 l.) and filtered. The filtrate and washings were evaporated to a brown syrup to which more ether was added. After filtration and re-evaporation the residue crystallised. On addition of di-isopropyl ether (15 ml.) crude oxidation product (13 g.) was obtained. A repeat oxidation of the residue (25 g.) from the mother-liquors by this procedure, with a similar mol. ratio of reagents, afforded a further batch (9 g.) of crystals. The combined crystals were recrystallised from di-isopropyl ether and the *methyl* 3,4-O-*isopropylidene*-β-L-erythro-*pentopyranosidulose* (I) (20·0 g.; 48%; over many preparations yields varied from 30—52%) obtained had m. p. 98—99°, $[\alpha]_D^{20}$ +166° (*c* 0·8 in EtOH); $\lambda_{max.}$ 5·7 μ (C=O), no O–H absorption (Found: C, 53·5; H, 7·1; O, 39·7. $C_9H_{14}O_5$ requires C, 53·4; H, 7·0; O, 39·6%). With 2,4-dinitrophenylhydrazine in ethanol–sulphuric acid the pentopyranosidulose gave a 2,4-*dinitrophenylhydrazone* which was recrystallised from ethanol as yellow crystals, m. p. 179° (Found: C, 47·3; H, 4·6; N, 14·4. $C_{15}H_{18}N_4O_8$ requires C, 47·1; H, 4·7; N, 14·7%).

(*b*) Chromic oxide (2·5 g.) was added cautiously to t-butyl alcohol (5 ml.) in light petroleum (b. p. 60—80°) (60 ml.) and after shaking the mixture vigorously, the supernatant solution was decanted, dried ($CaCl_2$), and cooled to −60°. Yellow-red crystals of t-butyl chromate appeared and were quickly filtered off and dissolved in benzene. The dried (Na_2SO_4) solution was diluted with t-butyl alcohol (15 ml.) and was used to oxidise methyl 3,4-*O*-isopropylidene-β-L-arabinoside (2·0 g.) in pyridine (3 ml.). After 18 hr. at room temperature methyl 3,4-*O*-isopropylidene-β-L-*erythro*-pentopyranosidulose (0·2 g., 10%) was isolated, m. p. 98—99° (from di-isopropyl ether), $[\alpha]_D^{20}$ +162° (*c* 0·5 in EtOH).

Methyl 3,4-O-*Isopropylidene*-β-D-erythro-*pentopyranosidulose* (11·1 g., 40%) was prepared by method (*a*) from methyl 3,4-*O*-isopropylidene-β-D-arabinoside (28 g.). After recrystallisation

[17] W. E. Trevelyan, D. P. Procter, and J. S. Harrison, *Nature*, 1950, **166**, 444.
[18] J. Honeyman, *J.*, 1946, 990.

twice from di-isopropyl ether it was obtained as colourless needles, m. p. 97—98°, $[\alpha]_D^{23}$ −161·2° (*c* 1·4 in EtOH) (Found: C, 53·5; H, 7·15. $C_9H_{14}O_5$ requires C, 53·4; H, 7·0%).

Grignard Reactions on Methyl 3,4-O-*Isopropylidene*-β-L-erythro-*pentopyranosidulose*.—The preparations of the compounds listed in Table 1 were accomplished by closely similar procedures which can be illustrated by a description of the synthesis of methyl 3,4-*O*-isopropylidene-2-*C*-methyl-β-L-*arabino*-pentoside (IIa). Methylmagnesium iodide (0·12 mole) in ether (40 ml.) was prepared in the usual way and cooled to 15°. The oxo-sugar (I) (8·08 g., 0·04 mole) in ether (50 ml.) was added slowly with stirring so that gentle boiling occurred. The stirred mixture was heated under reflux for 2 hr. (3 hr. for unsaturated Grignard reagents), cooled, and carefully diluted with water (20 ml.) to decompose the Grignard complex and excess of reagent. The ethereal layer was decanted and the aqueous layer was washed with ether (3 × 30 ml.). The combined extract and washings were shaken once with water, dried (Na_2SO_4) and evaporated under diminished pressure to a syrup which was obtained colourless on distillation.

The Grignard reagents from ethyl bromide, bromobenzene, and allyl bromide were made in the usual way. Vinylmagnesium bromide was prepared by the method of Nazarov *et al.*[19] and hex-1-yne and phenylacetylene were converted into Grignard reagents by Haynes and Jones's procedure.[20] Commercial β-bromostyrene in ether was added slowly to magnesium turnings suspended in ether heated gently under reflux for 2 hr. to give a solution of the Grignard reagent which was cooled before the oxo-sugar (I) was added. Distyryl by-product was partly removed by dissolving the crude methyl 3,4-*O*-isopropylidene-2-*C*-styryl-*arabino*-pentoside in ethanol and filtering from the crystalline distyryl, but the last traces could be removed only after deacetonation of the product.

The *cis*-hex-1-enyl and *cis*-styryl compounds (IIf) and (IIh) were prepared by reducing the corresponding acetylenic sugars (IIe) and (IIg) in ethanol (15 ml.) with hydrogen and a catalyst (Pd–$BaSO_4$) (0·02 g.) in the presence of quinoline (0·01 g.) until 1 mol. equiv. of hydrogen was taken up.

Hydrolysis of Branched-chain Glycosides with General Formula (II).—The glycosides listed in Table 2 were prepared from the corresponding compounds outlined in Table 1 by deacetonation. Compound (II) (5·0 mmole) was dissolved in methanol (40 ml.) containing 7N-hydrochloric acid (1·0 ml.), and the solution was heated under reflux for 3 hr. The cooled solution was neutralised ($PbCO_3$), filtered, and the filtrate evaporated under reduced pressure. The residue was extracted with boiling dry ethyl acetate (20 ml.), filtered from insoluble material, and concentrated *in vacuo*. The crystalline residue was recrystallised (see Table 2 for solvents) [the 2-*C*-vinyl glycoside (IIId) was obtained only as a syrup].

Methyl 3,4-*Di*-O-*acetyl*-2-C-*vinyl*-β-L-*arabinoside*.—Compound (IIId) (0·25 g.) in pyridine (10 ml.) was acetylated for 24 hr. at room temperature with acetic anhydride (3 ml.). The mixture was poured on to crushed ice (10 g.) and stirred for 2 hr. Ether (15 ml.) was added and stirring was continued for a further 15 min. The ethereal layer was separated and the aqueous residue was extracted with ether (3 × 10 ml.). The combined ethereal layers were dried (Na_2SO_4) and evaporated to a syrup. The *diacetate* was obtained by distillation as a colourless syrup (0·2 g., 55%), b. p. 113—114°/0·1 mm., $[\alpha]_D^{23}$ +104° (*c* 1·2 in MeOH) (Found: C, 52·7; H, 6·6; OMe, 11·45. $C_{12}H_{18}O_7$ requires C, 52·55; H, 6·6; OMe, 11·3%).

Methyl 2-C-*Formyl*-3,4-O-*isopropylidene*-β-L-*arabinoside*.—(*a*) Methyl 3,4-*O*-isopropylidene-2-*C*-vinyl-β-L-arabinoside (0·7 g.) was dissolved in dry ethyl acetate (40 ml.) and a stream of dry ozonised oxygen was passed through the solution. The solution was then shaken in an atmosphere of hydrogen at room temperature in the presence of platinum oxide catalyst (0·02 g.) until hydrogen uptake ceased. Removal of the catalyst and solvent gave *methyl* 2-C-*formyl*-, 3,4-O-*isopropylidene*-β-L-*arabinoside* (0·6 g., 86%) as a colourless syrup, b. p. 71—72°/0·05 mm. $[\alpha]_D^{22}$ +151° (*c* 0·62 in MeOH), $\lambda_{max.}$ 2·85 (OH), 5·75 μ (C=O), strongly reducing towards Fehling's solution (Found: C, 52·4; H, 7·0; OMe, 13·45. $C_{10}H_{16}O_6$ requires C, 51·7; H, 6·9; OMe, 13·4%).

(*b*) Ozonolysis of methyl 2-*C*-(*cis*-hex-1-enyl)-3,4-*O*-isopropylidene-β-L-arabinoside and of methyl 2-*C*-(*cis*-2-phenylethenyl)-3,4-*O*-isopropylidene-β-L-arabinoside afforded the 2-*C*-formyl compound in 65 and 60% yield, respectively.

[19] I. N. Nazarov, I. V. Torgov, and G. P. Verkholetova, *Doklady Akad. Nauk. S.S.S.R.*, 1957, **112**, 1067.

[20] L. J. Haynes and E. R. H. Jones, *J.*, 1946, 503.

Methyl 2-*C*-formyl-3,4-*O*-isopropylidene-β-L-arabinoside (0·12 g.) and toluene-*p*-sulphonylhydrazine (0·085 g.) in methanol (1·2 ml.) were heated together under reflux for 1·5 hr. to afford the *toluene*-p-*sulphonylhydrazone* (0·085 g., 41%) as colourless rhombs, m. p. 184·5—185·5° (decomp.) (from methanol), $[\alpha]_D^{22}$ +68·2° (*c* 0·3 in C_5H_5N) (Found: C, 51·1; H, 6·25; S, 7·2. $C_{17}H_{24}N_2O_7S$ requires C, 51·0; H, 6·0; S, 8·0%).

Methyl 2-C-*Formyl*-β-L-*arabinopyranoside*.—(*a*) Dry ozonised oxygen was passed through a solution of methyl 2-*C*-(*cis*-2-phenylethenyl)-β-L-arabinopyranoside (IIIg) (1·33 g.) in ethyl acetate (150 ml.) for 2 hr. The solution was then hydrogenated at room temperature over Adams catalyst (0·02 g.) until rapid uptake of hydrogen had ceased. After filtering off the catalyst, evaporation of the solution under reduced pressure afforded a viscous gum which was extracted with light petroleum (b. p. 60—80°) (3 × 10 ml.) to remove benzaldehyde, and then dried *in vacuo* to give methyl 2-*C*-formyl-β-L-arabinopyranoside as a colourless syrup, $\lambda_{max.}$ 2·85 (OH), 5·75 μ (C=O), no phenyl absorption. After storage for 5 days this syrup yielded crystals (0·52 g., 54%) which, recrystallised from ethyl acetate–ethanol (2 : 1, v/v), had m. p. 153—154°, $[\alpha]_D^{23}$ +132·8° (3 min.) ⟶ +124·6° (15 min., equilibrium value) (*c* 2·25 in H_2O), R_F 0·40, M_G 1·22, $\lambda_{max.}$ 2·85 μ (OH), no C=O absorption (Found: C, 43·7; H, 6·2; O, 50·3; OMe, 16·3%; *M* (Rast, camphor), 185. $C_7H_{12}O_6$ requires C, 43·75; H, 6·3; O, 50·0; OMe, 16·1%; *M*, 192). In a similar way methyl 2-*C*-(*trans*-2-phenylethenyl)-β-L-arabinopyranoside (IIIh) (in ethanol solution), methyl 2-*C*-(*cis*-hex-1-enyl)-β-L-arabinopyranoside (IIIe) and methyl 2-*C*-vinyl-β-L-arabinopyranoside (IIId) were ozonised to give crystalline methyl 2-*C*-formyl-β-L-arabinoside in 52, 33, and 40% yield, respectively.

(*b*) Methyl 2-*C*-formyl-3,4-*O*-isopropylidene-β-L-arabinoside (0·6 g.) in methanol (20 ml.) containing concentrated hydrochloric acid (0·2 ml.) and water (0·25 ml.) was heated under reflux for 2·5 hr. during which time the solution darkened. The solution was neutralised with lead carbonate, filtered, and the residue washed with methanol (3 × 5 ml.). The combined filtrate and washings were concentrated to a brown syrup, which was dissolved in water and decolourised with charcoal. Evaporation gave a syrup which crystallised on addition of ethyl acetate and storage for 1 week. Methyl 2-*C*-formyl-β-L-arabinoside (0·024 g., 4·8%) so obtained was shown to be identical with that prepared by method (*a*) by chromatography, m. p. and infrared spectrum.

Action of Methanolic Hydrogen Chloride on Methyl 2-C-*Formyl*-β-L-*arabinoside*.—The crystalline form of the 2-*C*-formyl-glycoside (0·19 g.) in methanol (10 ml.) containing 1% of hydrogen chloride was stored in a closed vessel at room temperature for 5 days, until a sample was no longer reducing to Fehling's solution. After neutralisation with lead carbonate and filtration the solution was evaporated under diminished pressure to a residue which on addition of ethyl acetate yielded the 2′-*monomethyl acetal*, (0·06 g., 33%), m. p. 214—215° (from ethyl acetate), $[\alpha]_D^{23}$ +106° (*c* 0·2 in EtOH) (Found: C, 47·1, 46·8; H, 6·8, 6·85; OMe, 30·8. $C_8H_{14}O_6$ requires C, 46·6; H, 6·8; OMe, 30·1%).

Glycosylamines Derived from Methyl 2-C-*Formyl*-β-L-*arabinoside*.—By the procedure of Ellis and Honeyman [21] the crystalline form of the 2-*C*-formyl-glycoside was treated in separate experiments with the base. The glycoside (0·096 g.), redistilled aniline (0·056 g.) and ethanol (1·0 ml.) were heated together under reflux for 2·5 hr. to give the 2′-N-*phenylglycosylamine* (0·122 g., 92%) which on recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) (2 : 1, v/v) was obtained as clusters of needles, m. p. 163—164° (decomp.), $[\alpha]_D^{23}$ −32° (*c* 0·31 in EtOH), $\lambda_{max.}$ 2·85 (OH); 3·00 (NH); 6·25, 6·68 μ (Ph); no C=N absorption (Found: C, 58·3; H, 6·45; N, 5·4. $C_{13}H_{17}NO_5$ requires C, 58·4; H, 6·4; N, 5·2%). In a similar way the 2′-N-p-*tolylglycosylamine* (0·081 g., 48%) was prepared from the 2-*C*-formyl compound (0·115 g.) and *p*-toluidine (0·07 g.) in ethanol (1·5 ml.). After recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) (2 : 1, v/v) it had m. p. 155—156° (decomp.), $[\alpha]_D^{22}$ −22·8° (*c* 0·48 in EtOH) (Found: C, 59·4; H, 7·15; N, 5·0. $C_{14}H_{19}NO_5$ requires C, 59·8; H, 6·8; N, 5·0%).

Methyl 2-C-*Formyl*-β-L-*arabinopyranoside* p-*Nitrophenylhydrazone*.—The glycoside (0·076 g.) and *p*-nitrophenylhydrazine hydrochloride (0·07 g.) were dissolved in ethanol (3 ml.) and set aside for 24 hr. at room temperature. Pale yellow crystals of the p-*nitrophenylhydrazone* (0·113 g., 93·5%) separated, m. p. 218—219° (from ethanol), $[\alpha]_D^{22}$ +136° (*c* 0·4 in C_5H_5N) (Found: C, 47·8; H, 5·2; N, 12·5. $C_{13}H_{17}N_3O_7$ requires C, 47·7; H, 5·2; N, 12·8%).

Conversion of Methyl 2-C-*Formyl*-β-L-*arabinoside into Methyl* 2-C-*Methyl*-β-L-*arabinoside*.—

[21] G. P. Ellis and J. Honeyman, *J.*, 1952, 1490.

The crystalline *C*-formyl glycoside (0·096 g.) and toluene-ω-thiol (0·15 g.) were dissolved in dry dioxan (15 ml.) and shaken in the presence of Amberlite IR-120(H^+) (*aci*-form) resin (1 g.) for 6 days. The resin was filtered and washed with dioxan (3 × 5 ml.). The combined dioxan solutions were concentrated under reduced pressure and the residue was extracted with light petroleum (b. p. 40—60°) (3 × 5 ml.) to remove any remaining thiol. Methyl 2-*C*-formyl-β-L-arabinopyranoside dibenzyl thioacetal (0·18 g.) was left as a pale yellow syrup which was dried *in vacuo*, $[\alpha]_D^{25}$ +18·3° (*c* 1·9 in MeOH), $\lambda_{max.}$ 2·85 (OH), 6·25, 6·68 μ (Ph), no C=O absorption: it was chromatographically pure, R_F = 0·81. This compound (0·17 g.) in methanol (30 ml.) was reductively desulphurised [22] by heating under reflux for 5 hr. with Raney nickel (2·0 g.). The yellow syrupy residue obtained from the methanol solution was extracted with ethyl acetate. Solvent was removed from the filtered extract and the dry residue crystallised on addition of ethyl acetate (1 ml.) and was recrystallised from the same solvent. Colourless rhombs (0·025 g., 35%) were obtained, m. p. 99—100° alone or in admixture with methyl 2-*C*-methyl-β-L-arabinoside, $[\alpha]_D^{22}$ +114° (*c* 0·2 in EtOH).

Methyl 2-C-*Hydroxymethyl*-3,4-O-*isopropylidene*-β-L-*arabinoside*.—(*a*) Methyl 2-*C*-formyl-3,4-*O*-isopropylidene-β-L-arabinoside (0·7 g.) in ether (20 ml.) was reduced by slowly adding the solution to lithium aluminium hydride (1·14 g.) in ether (20 ml.) followed by heating under reflux for 6 hr. Work-up of the solution in the usual way gave *methyl* 2-C-*hydroxymethyl*-3,4-O-*isopropylidene*-β-L-*arabinoside* (0·5 g., 71%) as a colourless viscous syrup, b. p. 70—71°/0·05 mm., $[\alpha]_D^{22}$ +90·5° (*c* 1·8 in MeOH) (Found: C, 51·8; H, 7·9; OMe, 13·05. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·75; OMe, 13·2%).

(*b*) Methyl 3,4-*O*-isopropylidene-2-*C*-vinyl-β-L-arabinoside (1·15 g.) in ether (30 ml.) at −5° was treated with a stream of ozonised oxygen for 1 hr. The solution was then added dropwise with stirring to lithium aluminium hydride (1·9 g.) in ether (20 ml.). The mixture was stirred and heated under reflux for a further 5 hr. (cf. Sousa and Bluhm [23]). Work-up gave methyl 2-*C*-hydroxymethyl-3,4-*O*-isopropylidene-β-L-arabinoside (0·72 g., 61%), b. p. 73—74°/0·07 mm., $[\alpha]_D^{22}$ +88·9° (*c* 1·1 in MeOH).

Methyl 2-C-*Hydroxymethyl*-β-L-*arabinopyranoside*.—(*a*) Methyl 2-*C*-formyl-β-L-arabinopyranoside (0·96 g.) in methanol (30 ml.) was shaken with hydrogen at room temperature and pressure in the presence of platinum oxide (0·02 g.) until hydrogen uptake ceased. After removal of the catalyst, the solution was evaporated *in vacuo* to give a syrup which crystallised on storage. After recrystallisation from ethyl acetate, needle-like crystals of *methyl* 2-C-*hydroxymethyl*-β-L-*arabinopyranoside* (0·72 g., 75%) were obtained, m. p. 122—123°, $[\alpha]_D^{24}$ +128·5° (*c* 0·7 in MeOH), R_F = 0·42 (Found: C, 43·4; H, 7·6; OMe, 15·6. $C_7H_{14}O_6$ requires C, 43·4; H, 7·3; OMe, 16·0%).

(*b*) Methyl 2-*C*-hydroxymethyl-3,4-*O*-isopropylidene-β-L-arabinoside (0·24 g.) in methanol (20 ml.) containing concentrated hydrochloric acid (0·2 ml.) and water (0·25 ml.) was heated under reflux for 3 hr. After neutralisation with lead carbonate, the product was isolated in the usual manner and the methyl 2-*C*-hydroxymethylarabinoside (0·08 g., 40%) so obtained had m. p. 122—123° (from ethyl acetate) alone or in admixture with the material prepared by method (*a*).

After treatment with excess of acetic anhydride (4 ml.) and pyridine (10 ml.) for 2 hr. at 100° and then for 24 hr. at room temperature, this glycoside (0·116 g.) yielded a 2′,3,4-*triacetate* (0·08 g., 42%), m. p. 144—145° (from ether), $[\alpha]_D^{23}$ +70·8° (*c* 0·34 in EtOH), $\lambda_{max.}$ 2·85 (OH, presumably tertiary OH at C-2), 5·75 μ (C=O) (Found: C, 48·35; H, 6·3; OMe, 10·0. $C_{13}H_{20}O_9$ requires C, 48·75; H, 6·3; OMe, 9·7%).

Methyl 3,4-O-*Isopropylidene*-2-C-(2′-*oxoethyl*)-β-L-*arabinoside*.—Methyl 2-*C*-allyl-3,4,*O*-isopropylidene-β-L-arabinoside (1·22 g.) in dry ethyl acetate (40 ml.) was treated with a stream of dry ozonised oxygen for 1·5 hr. The solution was then shaken in an atmosphere of hydrogen at room temperature in the presence of platinum oxide (0·02 g.) until hydrogen uptake ceased. Removal of both the catalyst and solvent gave *methyl* 3,4-O-*isopropylidene*-2-C-(2′-*oxoethyl*)-β-L-*arabinoside* (1·10 g., 90%), b. p. 88—89°/0·08 mm., $[\alpha]_D^{22}$ +110° (*c* 0·5 in MeOH), $\lambda_{max.}$ 2·85 (OH), 5·75 μ (C=O) (Found: C, 53·5; H, 7·5; O, 39·4; OMe, 12·9. $C_{11}H_{18}O_6$ requires C, 53·65; H, 7·3; O, 39·0; OMe, 12·6%).

2-C-*Vinyl*-L-*arabinose*.—Methyl 2-*C*-vinyl-β-L-arabinopyranoside (10 g.) was heated under reflux in water (350 ml.) containing Amberlite IR-120 H^+ (*aci*-form) resin (40 g.), with stirring,

[22] M. L. Wolfrom and J. V. Karabinos, *J. Amer. Chem. Soc.*, 1944, **66**, 909.
[23] J. A. Sousa and A. L. Bluhm, *J. Org. Chem.*, 1960, **25**, 108.

for 18 hr. The supernatant liquid was decanted and the resin washed with water (3 × 10 ml.). The combined aqueous solution was decolourised (charcoal), filtered, and evaporated under reduced pressure to leave 2-*C*-vinyl-L-arabinose (9·25 g.) as a pale yellow viscous syrup, $[\alpha]_D^{22}$ +41·2° (*c* 2·1 in MeOH), $R_F = 0{\cdot}42$, $M_G = 1{\cdot}06$. (A less-pure product was obtained by hydrolysis with 0·5N-sulphuric acid at the reflux temperature for 8 hr.) This syrup (0·14 g.) was treated with toluene-*p*-sulphonylhydrazine (0·14 g.) in methanol (2 ml.) at the reflux temperature for 1 hr. On cooling to 0° colourless crystals of the *toluene*-p-*sulphonylhydrazone* separated and were recrystallised twice from methanol (0·11 g., 44%), m. p. 159—161° (decomp.), $[\alpha]_D^{22}$ −48·1° (*c* 0·3 in MeOH) (Found: C, 48·6; H, 5·5; N, 7·9; S, 9·4. $C_{14}H_{20}N_2O_6S$ requires C, 48·8; H, 5·8; N, 8·1; S, 9·3%).

2-C-*Vinyl*-L-*arabitol*.—Sodium borohydride (1·14 g.) in water (10 ml.) was added dropwise with stirring to 2-*C*-vinyl-L-arabinose (2·67 g.) in water (20 ml.) cooled in an ice-bath. After stirring at room temperature for 8 hr. an aliquot showed no reaction with Fehling's solution and the excess of borohydride was then destroyed with Amberlite IR-120 H^+ (*aci*-form) resin (1·0 g.). The supernatant liquid was decanted, the resin washed with water, and the combined aqueous extracts evaporated to small bulk (5 ml.). Metal ions were removed on a column of Amberlite IR-120 H^+ (*aci*-form) (3 × 30 cm.) and the eluate was evaporated *in vacuo* to a semi-solid residue. Methanol was evaporated repeatedly over this residue to remove boric acid as methyl borate until finally a colourless syrup (2·2 g.) was obtained. Chromatography showed the presence of two major and one minor components ($R_F = 0{\cdot}76$, 0·51, and 0·37, respectively). These were best separated by preparative paper chromatography [Whatman No. 3 paper; 0·07 g. syrup per sheet (43 × 42 cm.)] eluting the relevant strips with methanol (80 ml.). In this way 2-*C*-vinyl-L-arabitol (0·24 g.) could be isolated from the crude syrup (0·5 g.) with $[\alpha]_D^{23}$ −35·8° (*c* 1·8 in MeOH), $R_F = 0{\cdot}51$. On acetylation with acetic anhydride (4·0 ml.) in dry pyridine (10 ml.) at 100° for 2 hr. and then at room temperature for 16 hr. this polyol (0·09 g.) gave the 1,3,4,5-*tetra-acetate* (0·05 g.), b. p. 142—145°/0·02 mm., $[\alpha]_D^{23}$ −28·2° (*c* 0·5 in MeOH), $\lambda_{max.}$ 2·85 μ (OH, presumably the tertiary hydroxyl) (Found: C, 52·3; H, 7·0. $C_{15}H_{22}O_9$ requires C, 52·0; H, 6·4%).

The other major component obtained (0·10 g.), $R_F = 0{\cdot}76$, m. p. 117—118°, $[\alpha]_D^{22}$ −114° (*c* 0·22 in EtOH), $\lambda_{max.}$ 2·85 (OH), 5·95w, 6·30 μ (very broad) (Found: C, 37·6; H, 6·45%) consumed no hydrogen when shaken with platinum catalyst at room temperature and atmospheric pressure: it has not yet been identified.

2-C-*Hydroxymethyl*-L-*ribose* (L-*Hamamelose*).—2-*C*-Vinyl-L-arabitol (0·15 g.) in ethanol (15 ml.) was treated with ozonised oxygen for 1·5 hr. The ozonide was decomposed by shaking the solution in hydrogen at room temperature and pressure with platinum oxide catalyst (0·01 g.) until rapid uptake of hydrogen ceased. The catalyst was removed and the filtrate concentrated to a viscous syrup (0·13 g.) which was chromatographically almost pure, containing no trace of 2-*C*-vinyl-L-arabitol. On standing at room temperature the syrup slowly crystallised, and recrystallisation from ethanol–ethyl acetate (2 : 1, v/v) gave 2-C-*hydroxymethyl*-α-L-*ribose* (0·03 g., 20%), m. p. 108—109°, $[\alpha]_D^{22}$ +1·3° (3 min.) ⟶ +7·1° (17 min., equilibrium) (*c* 2·0 in H_2O) (Found: C, 39·8; H, 6·5; O, 53·6. $C_6H_{12}O_6$ requires C, 40·0; H, 6·7; O, 53·3%). The compound had $R_F = 0{\cdot}18$ and was chromatographically indistinguishable from naturally-occurring D-hamamelose. The naturally-occurring material has not been obtained crystalline: it has $[\alpha]_{5780}^{21}$ −7·1°.[14]

2-C-*Hydroxymethyl*-L-*ribose* p-*Nitrophenylhydrazone*.—Syrupy 2-*C*-hydroxymethyl-L-ribose (0·22 g.) and *p*-nitrophenylhydrazine (0·17 g.) were heated together under reflux in methanol (2 ml.) for 1 hr. Water (1·5 ml.) was added and the mixture was set aside at room temperature for 4 days. The pale yellow crystals which separated were collected and recrystallised thrice from methanol. 2-C-*Hydroxymethyl*-L-*ribose* p-*nitrophenylhydrazone* (0·30 g., 80%) had m. p. 163—164°, $[\alpha]_D^{22}$ −145° (*c* 0·29 in C_5H_5N) (Found: C, 45·3; H, 5·2; N, 12·8. $C_{12}H_{17}N_3O_7$ requires C, 45·7; H, 5·4; N, 13·3%). (Freudenberg and Blümmel [14] give m. p. 165—166°, $[\alpha]_{5780}^{20}$ +144° for this derivative of D-hamamelose.)

2-C-*Hydroxymethyl*-L-*ribose* *Toluene*-p-*sulphonylhydrazone*.—Syrupy 2-*C*-hydroxymethyl-L-ribose (0·22 g.) and toluene-*p*-sulphonylhydrazine (0·21 g.) in methanol (2 ml.) were heated together under reflux for 1 hr. The solution was concentrated (to 1 ml.) and stored at room temperature. The crystalline deposit was collected and recrystallised twice from methanol to give the *toluene*-p-*sulphonylhydrazone* (0·28 g.) as colourless needles, m. p. 155—156°, $[\alpha]_D^{22}$ −78·1° (*c* 0·3 in C_5H_5N) (Found: C, 44·5; H, 5·9; N, 8·2; S, 9·4. $C_{13}H_{20}N_2O_7S$ requires C,

44·8; H, 5·75; N, 8·05; S, 9·2%). (For this derivative of D-hamamelose Freudenberg and Blümmel [14] report m. p. 155°, $[\alpha]_{5780}$ +76°.)

2-C-*Hydroxymethyl*-L-*ribonolactone* (L-*Hamamelonic Acid Lactone*).—Syrupy 2-*C*-hydroxymethyl-L-ribose (0·36 g.), yellow mercuric oxide (1·80 g.), and calcium carbonate (0·22 g.) in water (15 ml.) were heated under reflux for 24 hr. The cooled mixture was filtered and the residue was washed with water (3 × 5 ml.). Metallic ions were removed by passing the combined filtrate and washings down a column of Amberlite IR-120 H^+ (*aci*-form) resin (3 × 30 cm.). Concentration of the eluate furnished 2-*C*-hydroxymethyl-L-ribonolactone (0·30 g.) as a viscous syrup which was shown by paper chromatography to be practically pure, R_F = 0·35. On chromatography in butanol–acetic acid–water (4 : 1 : 5, v/v) the syrup (R_F = 0·30) was indistinguishable from the γ-lactone prepared from L-ribulose and hydrogen cyanide by Dr. R. J. Ferrier.[15]

Ammonium 2-C-*Hydroxymethyl*-L-*ribonate* (*Ammonium* L-*Hamamelonate*).—The above lactone (0·25 g.) was dissolved in excess of ammonia solution (*d* 0·88) and stored at room temperature for 18 hr. The filtered solution was concentrated under reduced pressure to a colourless syrup which crystallised on addition of methanol (1 ml.). Recrystallisation from aqueous methanol gave ammonium 2-*C*-hydroxymethyl-L-ribonate (0·15 g.) as needles, m. p. 151—152°, $[\alpha]_D^{22}$ +4·5° (*c* 2·0 in H_2O) (Found: C, 33·7; H, 6·7; N, 6·3. Calc. for $C_6H_{15}NO_7$: C, 33·8; H, 7·0; N, 6·6%). The melting point was not depressed when the product was admixed with a sample of the salt kindly supplied by Dr. R. J. Ferrier, who reported [15] m. p. 150—151°, $[\alpha]_D$ +4·8° (*c* 1·2 in N-NH_4OH). Ammonium D-hamamelonate prepared from naturally-occurring D-hamamelose has m. p. 152°, $[\alpha]_{5780}^{22}$ −3·9° (*c* 10 in H_2O).[14]

2-C-*Hydroxymethyl*-L-*arabinose*.—Methyl 2-*C*-hydroxymethyl-β-L-arabinopyranoside (0·92 g.) was hydrolysed by stirring in boiling water (40 ml.) with Amberlite IR-120 H^+ (*aci*-form) resin (5 g.) until chromatography indicated that no starting material remained (23 hr.). The supernatant liquor was decanted and the resin washed with water (3 × 5 ml.). The combined solutions were decolourised (charcoal), filtered, and concentrated under diminished pressure to give 2-*C*-hydroxymethyl-L-arabinose (0·80 g.) as a pale yellow gum, $[\alpha]_D^{22}$ +3·2° (*c* 5·0 in MeOH), R_F = 0·19, which was chromatographically pure apart from traces of reversion products. [Hydrolysis with 0·5N-sulphuric acid at the reflux temperature for 11 hr. gave a lower yield of a less-pure product.]

When heated under reflux for 1·25 hr. with toluene-*p*-sulphonylhydrazine (0·093 g.) in methanol (1·0 ml.) the 2-*C*-hydroxymethyl-L-arabinose (0·1 g.) gave a *toluene*-p-*sulphonylhydrazone* (0·104 g.) which was recrystallised from methanol, m. p. 158—159° (decomp.), $[\alpha]_D^{22}$ +70·8° (*c* 0·45 in C_5H_5N) (Found: C, 44·7; H, 6·2; S, 9·2. $C_{13}H_{20}N_2O_7S$ requires C, 44·8; H, 5·75; S, 9·2%).

2-C-*Hydroxymethyl*-L-*arabinose* α,α-*Benzylphenylhydrazone*.—2-*C*-Hydroxymethyl-L-arabinose (0·12 g.), α,α-benzylphenylhydrazine hydrochloride (0·14 g.) and sodium acetate trihydrate (0·082 g.) were dissolved in methanol (1·5 ml.) and water (0·1 ml.) and heated under reflux for 1 hr. Water (0·8 ml.) was added to the cooled solution to give faint turbidity. Fine needles of the α,α-*benzylphenylhydrazone* (0·13 g.) separated, m. p. 135·5—136·5° (from ethyl acetate), $[\alpha]_D^{22}$ −22·9° (*c* 0·3 in C_5H_5N) (Found: C, 63·1; H, 6·6; N, 7·6. $C_{19}H_{24}N_2O_5$ requires C, 63·3; H, 6·7; N, 7·8%).

2-C-*Hydroxymethyl*-L-*arabonic Acid Phenylhydrazide*.—2-*C*-Hydroxymethyl-L-arabinose (0·50 g.), bromine (0·56 g.), and water (20 ml.) were shaken together at room temperature for 18 hr. in the presence of lead carbonate (0·80 g.).[16] The bromine dissolved in about 30 min. The insoluble residue was filtered off and washed with water. The filtrate and washings were concentrated to a white amorphous solid. This was extracted with water (2 × 3 ml.), filtered, and the filtrate concentrated to 1 ml. and then passed down a column of Amberlite IR-120 H^+ (*aci*-form) resin to remove metal ions. Evaporation of the eluate yielded 2-*C*-hydroxymethyl-L-arabinolactone (0·4 g.) as a colourless syrup, R_F = 0·35. Paper chromatography showed that the product was substantially pure. This lactone could be distinguished from 2-*C*-hydroxymethyl-L-ribonic acid by using n-butanol–acetic acid–water (4 : 1 : 5, v/v) (top layer) as the solvent for development, when R_F = 0·29.

2-*C*-Hydroxymethyl-L-arabinolactone (0·3 g.) and phenylhydrazine (0·32 g.) were heated together under reflux in water (3 ml.) for 1·5 hr. The cooled solution was extracted with ether to remove unreacted phenylhydrazine. From the concentrated aqueous layer 2-C-*hydroxymethyl*-L-*arabonic acid phenylhydrazide* (0·12 g.) was obtained, m. p. 192—193° (from water),

$[\alpha]_D^{23}$ −81° (*c* 0·2 in H_2O) (Found: C, 50·5; H, 6·4; N, 9·7. $C_{12}H_{18}N_2O_6$ requires C, 50·4; H, 6·3; N, 9·8%). For the D-isomer the reported [24] m. p. is 194—195°, $[\alpha]_D^{18}$ +83° (in H_2O).

Methyl 2-*Deoxy*-3,4-O-*isopropylidene*-2-C-*methyl*-β-L-3,4-erythro-*pentopyranoside*.—Sodium metal (1·61 g.) was powdered in boiling xylene (30 ml.). After cooling the xylene was decanted through glass wool and the metal was washed with anhydrous ether (3 × 20 ml.). Methyl 3,4-*O*-isopropylidene-2-*C*-methyl-β-L-arabinoside (6·05 g.) in ether (50 ml.) was added slowly to a suspension of the powdered sodium in anhydrous ether (30 ml.) so that gentle boiling occurred. The mixture was stirred and heated under reflux for a further 2 hr. after the addition was completed. The cooled solution was decanted through glass wool and the residue was washed with dry ether (3 × 10 ml.). The ethereal extracts were combined and treated with toluene-*p*-sulphonyl chloride (5·90 g.) in dry ether (50 ml.) at the reflux temperature for 3 hr. The filtered solution and the ethereal washings of the residue were rinsed with water, dried (Na_2SO_4), and concentrated to a syrup. This was extracted with boiling light petroleum (b. p. 40—60°) (75 ml.) and the cooled to 0°. The supernatant liquor was decanted and the residue was dried *in vacuo* at 35° to give a yellow gum which was very hygrosopic and which presumably was methyl 3,4-*O*-isopropylidene-2-*C*-methyl-2-*O*-tosyl-β-L-arabinoside (6·4 g.), $\lambda_{max.}$ 6·25, 6·68 μ (Ph). The tosylate was stored under nitrogen at 0° since it decomposed on prolonged exposure to air.

This syrup (6·30 g.) in dry ether (50 ml.) was added slowly to a stirred solution of lithium aluminium hydride (3·8 g.) in ether (20 ml.) and heated under reflux for 5 hr. The excess of hydride was destroyed by cautious addition at 0° of ethyl acetate (20 ml.) and water (50 ml.). The mixture was filtered and the residue was washed thoroughly with ether (3 × 40 ml.). The ether phase was separated and the aqueous phase was extracted again with ether (3 × 15 ml.). The combined ether extracts were dried (Na_2SO_4) and evaporated to a yellow mobile oil which was fractionally distilled to give *methyl* 2-*deoxy*-3,4-O-*isopropylidene*-2-C-*methyl*-β-L-3,4-erythro-*pentoside* (1·7 g.) as a colourless hygroscopic syrup, b. p. 38—40°/0·1 mm., 113—115°/22 mm., $[\alpha]_D^{23}$ +36·8° (*c* 4·2 in MeOH), no OH or Ph infrared absorption (Found: C, 58·9; H, 9·0; O, 32·2; OMe, 16·2. $C_{10}H_{18}O_4$ requires C, 59·4; H, 8·9; O, 31·7; OMe, 15·3%).

Methyl 2-*Deoxy*-2-C-*methyl*-β-L-3,4-erythro-*pentoside*.—Methyl 2-deoxy-3,4-*O*-isopropylidene-2-*C*-methyl-β-L-*erythro*-pentoside (1·6 g.) was deacetonated with 7N-hydrochloric acid (0·7 ml.) in boiling methanol (30 ml.) for 3 hr. The solution was neutralised ($PbCO_3$), filtered, and evaporated. The residue was extracted with ether and the filtered extract was evaporated to a syrup which was distilled to afford *methyl* 2-*deoxy*-2-C-*methyl*-β-L-3,4-erythro-*pentopyranoside* (0·45 g.), b. p. 112—114°/0·5 mm., $[\alpha]_D^{23}$ +41·3° (*c* 1·1 in MeOH), R_F = 0·43 (Found: OMe, 19·7. $C_7H_{14}O_4$ requires OMe, 19·2%).

Attempt to Convert Methyl 3,4-O-*Isopropylidene*-2-C-*vinyl*-β-L-*arabinoside into Methyl* 2-*Deoxy*-3,4-O-*isopropylidene*-2-C-*vinyl*-β-L-3,4-erythro-*pentoside*.—According to the above procedure methyl 3,4-*O*-isopropylidene-2-*C*-vinyl-β-L-arabinoside (4·6 g.) was first converted into its 2-*O*-tosyl derivative which was obtained as an amber hygroscopic gum (3·8 g.), $\lambda_{max.}$ 6·05 (−CH=CH_2); 6·25 6·68 μ (Ph); very small OH peak, which decomposed in air, and which was stored under nitrogen at 0°. Treatment of this gum (3·76 g.) with lithium aluminium hydride (1·9 g.) in ether (60 ml.) and work-up in the usual way yielded a colourless mobile oil (1·5 g.), b. p. 40—42°/0·2 mm., 109—110°/15 mm., $\lambda_{max.}$ 2·85 (OH, small peak); 5·95 (>C=CH−) and 6·05 μ (−CH=CH_2). The latter two peaks were of equal intensity. A sample of this material (0·8 g.) was ozonolysed as before to yield a viscous syrup which, on addition of ether (1 ml.), afforded methyl 3,4-*O*-isopropylidene-β-L-*erythro*-pentopyranosidulose (0·25 g.), m. p. 98—99° (from di-isopropyl ether), undepressed on admixture with the authentic compound (I).

One of us (J. S. B.) thanks the D.S.I.R. for the award of a Research Studentship.

Department of Chemistry, Birkbeck College,
Malet Street, London W.C.1.

[*Received, August 14th*, 1964.]

[24] O. T. Schmidt and K. Heintz, *Annalen*, 1935, **515**, 77.