LXXXIV.—*Constitutional Studies in the Monocarboxylic Acids derived from Sugars. Part IV. The Isomeric Lactones obtained from Arabinose.*

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WITH the view of accumulating more complete information regarding the isomeric forms of the pentose arabinose, we have continued our earlier investigations (Pryde, Hirst, and Humphreys, J., 1925, **127**, 348). Recently, Haworth and Nicholson (J., 1926, 1899) have had occasion to investigate related problems and in as far as our field and theirs have involved common ground we are able fully to corroborate their published findings.

We have now prepared 2 : 3 : 4-trimethyl arabonolactone from two different crystalline derivatives of arabinose, namely, the α- and β-stereoisomerides of trimethyl methylarabinoside. It has been shown by Hirst and Robertson (J., 1925, **127**, 358) that in the presence of acid methyl alcohol these two crystalline derivatives change in optical rotation until a final common equilibrium value of $[\alpha]_D + 150°$ is reached. Such evidence is generally accepted as showing that they are interconvertible α- and β-varieties of the same trimethyl methylarabinoside, possessing one and the same type of oxide linking. It has been clearly established that trimethyl α-methylarabinoside possesses an amylene-oxide linking (Hirst and Robertson, *loc. cit.*), but direct evidence regarding the β-compound is lacking. This evidence we are now able to supply in that it is shown that the crystalline β-compound yields on oxidation a lactone identical in optical rotation and in other physical properties with that obtained from the α-compound. The two stereoisomerides of the parent methylated sugar must therefore possess one and the same type of oxide linking. This is, so far as we are aware, the first *direct* chemical proof that two crystalline stereoisomeric sugars do in fact have a common oxide-linking structure.

The isomeric 2 : 3 : 5-trimethyl arabonolactone has also been prepared from two different sources, namely, by synthesis of the mixed methyl γ-arabinosides and subsequent methylation, followed by simultaneous hydrolysis and oxidation with hydrobromic acid and bromine, and alternatively by bromine oxidation of arabinose followed by methylation. The crystalline lactones obtained by both these processes again proved to be identical with each other, but sharply distinguished in their physical and chemical properties from the liquid 2 : 3 : 4-trimethyl lactone. After the completion of this work, similar results obtained by slightly different methods

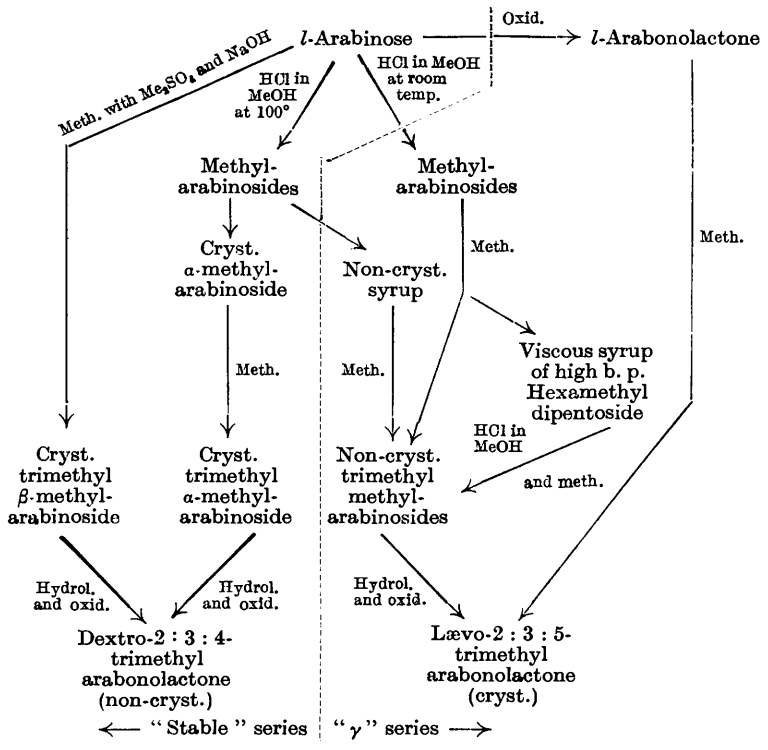
were recorded by Haworth and Nicholson (*loc. cit.*). Particulars of our own preparations are summarised in the following table:

Starting material.	$[\alpha]_D$ in water.	M. p.	Product.	Initial $[\alpha]_D$ in water.	M. p.
Trimethyl α-methyl-*l*-arabinoside.	+250°	44—46°	2 : 3 : 4-Trimethyl arabonolactone.	+176·5°	Liq.
Trimethyl β-methyl-*l*-arabinoside.	+ 26·2	46	,, ,,	+178·3	Liq.
Trimethyl methyl-*l*-γ-arabinosides.	— 56*	Liq.	2 : 3 : 5-Trimethyl arabonolactone.	— 42·5	29°
l-Arabonolactone.	— 62	Syrup.	,, ,,	— 43·0	30

* Equilibrium rotation.

The combined results of these four methods of preparing the two isomeric lactones afford clear proof that the stereoisomeric α- and β-derivatives of the normal form of arabinose have a common oxygen linking of the 1 : 5 type, and that a change in the position of this linking to the 1 : 4 type completely alters the nature of the derivatives obtained.

In the course of the foregoing investigations, two further observations of considerable interest were made. Pryde, Hirst, and Humphreys (*loc. cit.*) have already shown that the anomalous rotations obtained in various preparations involving the preliminary condensation of arabinose with methyl alcohol at 100° are to be ascribed to the formation of mixtures of amylene- and butylene-oxidic forms. Evidence has now been obtained which affords a direct proof of this, and of which details will be found in the experimental section of this paper. Levene and Simms (*J. Biol. Chem.*, 1926, **68**, 737) have investigated a similar simultaneous formation of 1 : 5- and 1 : 4-lactone rings in the instance of gluconic acid. The second observation referred to above clearly demonstrated the tendency of γ-arabinose derivatives to enter into an auto-condensation forming a compound apparently of the dipentoside type. The conditions which led to this interesting condensation are being further investigated and publication of the experimental details is deferred until a later date. This brief reference is made here for the purpose of including the observation in the scheme which follows. Of some 11 g. of mixed methyl-γ-arabinosides, which had been prepared by the cold acid methyl alcohol method, it was found that some 6—7 g. had undergone auto-condensation to form a dipentoside, which was eventually reconverted into the simple methylated monopentoside in very good yield.



EXPERIMENTAL.

Preparation of 2 : 3 : 4-Trimethyl Arabonolactone from Trimethyl α-Methylarabinoside.—This preparation has been described by Pryde, Hirst, and Humphreys (*loc. cit.*). It only remains to add that later preparations of the lactone yielded products with higher initial specific rotations in water, but with identical equilibrium values. Thus, initial values of + 176°, falling to + 21·4° and 21·95° on equilibration in water, and 21·55° from the sodium salt have been obtained (compare the earlier values of + 145°, equilibrating to 22·4° in water, and 22·9° from the sodium salt).

Preparation of 2 : 3 : 4-Trimethyl Arabonolactone from Trimethyl β-Methylarabinoside.—The crystalline trimethyl β-methylarabinoside was obtained by direct methylation of *l*-arabinose by sodium hydroxide and methyl sulphate as described by Hirst and Robertson (*loc. cit.*). It had an initial $[\alpha]_D$ + 26·17° in methyl alcohol, an equilibrium value, after heating in acid methyl alcohol, of $[\alpha]_D$ + 151·6°, and m. p. 46°. It was converted into the lactone by treatment with hydrobromic acid and bromine by the method

described by Pryde, Hirst, and Humphreys (*loc. cit.*). The lactone was obtained as a colourless, mobile syrup (Found: C, 50·4; H, 7·4; OMe, 47·9. Calc.: C, 50·5; H, 7·4; OMe, 48·9%), which had an initial $[\alpha]_D$ in water ($c = 1·12$) + 178·3°, falling in 24 hours to an equilibrium value $[\alpha]_D$ + 21·5°. The equilibrium value determined from the sodium salt ($c = 0·94$) was + 22·13°. 0·102 G. of lactone required 5·35 c.c. of N/10-alkali (calc., 5·40 c.c.).

Preparation of 2 : 3 : 5-*Trimethyl Arabonolactone from Trimethyl Methyl-*γ*-arabinosides.*—The trimethyl methyl-γ-arabinosides were obtained as a syrupy mixture by the method of Baker and Haworth (J., 1925, **127**, 365). During the formation of the methyl-γ-arabinosides a minimum specific rotation of − 42·8° was observed some 28 hours after the complete solution of the arabinose in the cold acid methyl alcohol, whilst in a second preparation a minimum value of − 47·14° was recorded. In the latter case, the syrupy product, when isolated, showed $[\alpha]_D$ − 47·55° ($c = 1·152$). Methylation with sodium hydroxide and methyl sulphate followed by Purdie's reagents yielded a syrup with the composition of trimethyl methylarabinoside, which, after distillation in a high vacuum, had $n_D^{15·5°}$ 1·4370 and $[\alpha]_D$ in water − 33·62 ($c = 0·81$), in methyl alcohol − 34·37° ($c = 0·91$), and an equilibrium rotation, after heating for 5 hours in acid methyl alcohol, of $[\alpha]_D$ − 56·33°. These results are all in good accord with those of Baker and Haworth. These authors isolated trimethyl-γ-arabinose by hydrolysis of the fully methylated arabinoside, and oxidised the free sugar to the corresponding monocarboxylic acid by means of nitric acid. In the present communication, simultaneous hydrolysis and oxidation of the arabinoside was achieved by using hydrobromic acid containing bromine. From 17 g. of trimethyl methyl-γ-arabinosides there were obtained, after vacuum distillation, 14 g. of a mobile liquid, b. p. 115°/2 mm., $n_D^{17°}$ 1·4452. This product soon solidified, yielding crystals which had m. p. 29° after being dried on porous tile (Found: C, 50·4; H, 7·3; OMe, 48·5. Calc.: C, 50·5; H, 7·4; OMe, 48·9%). 0·1355 G. of lactone required 7·15 c.c. of N/10-alkali (calc., 7·11 c.c.). $[\alpha]_D$ in water − 42·53°, after 10 days − 34·5° ($c = 1·12$). It is obvious from these figures that the lactone is identical with that obtained by Baker and Haworth by a different method. The lactone did not reduce Fehling's solution even on boiling, but instantly reduced alkaline permanganate in the cold.

Preparation of 2 : 3 : 5-*Trimethyl Arabonolactone from* l-*Arabonolactone.*—A similar preparation has been described by Haworth and Nicholson (*loc. cit.*), but the present work was completed prior to the publication of their results. Their methods differ somewhat

from our own, and the following brief description of the latter is given. 15 G. of *l*-arabinose in 80 c.c. of water were shaken with 30 g. of bromine for 3 hours until solution was complete. The solution was then heated on a water-bath at 40°, and after 20 hours all reducing action had disappeared. The excess of bromine and the hydrobromic acid were removed in the usual manner and finally there were obtained 14·3 g. of arabonic acid as a pale yellow, viscous syrup. Great difficulty was experienced in converting this completely into the lactone, for even after treatment over phosphorus pentoxide at 100°/1 mm. the value of the specific rotation was only — 62°, whereas Fischer and Piloty (*Ber.*, 1891, **24**, 4214) record — 73·9° for their crystalline lactone. We did not obtain the lactone in a crystalline condition, owing either to its content of some 10% of unchanged arabonic acid, or more probably to the fact that it was not allowed sufficient time to crystallise. It was decided to subject the non-crystalline product to methylation.

Methylation of l-*Arabonolactone.*—This was carried out by means of Purdie's reagents, methyl alcohol being used as extraneous solvent in the first two methylations. During the removal of solvent in the recovery of the methylated product after the first methylation, a little methyl oxalate distilled over, showing the presence of a small amount of oxalic acid in our original preparation of the lactone. After a third methylation in the absence of an extraneous solvent, some 12 g. of a pale yellow, mobile syrup were obtained which on distillation gave the following fractions :

Fractions	I	II	III
Weight (g.)	0·5	10	0·5
B. p. at 1 mm.	70°	95—105°	130—140°
$n_D^{14°}$	1·4150	1·4450	1·4462
OMe %	57·4	53·1	45·2

(Calc. for methyl tetramethylarabonate, methyl trimethylarabonate, and trimethyl arabonolactone : OMe, 65·7, 55·8, and 48·9%, respectively.)

Fraction I obviously contained some methyl tetramethylarabonate and hence fractions II and III only were submitted to a fourth methylation and again distilled. The main portion (8 g.) distilled at 100—105°/1 mm. It had $n_D^{15°}$ 1·4396, OMe 55·0%, and $[\alpha]_D$ in water — 8·4° (c = 1·21). This product is therefore essentially the methyl ester of trimethylarabonic acid.

Hydrolysis of the Ester and Preparation of 2 : 3 : 5-*Trimethyl Arabonolactone.*—7 G. of the ester were hydrolysed with approximately *N*-barium hydroxide at 85°. The barium was quantitatively precipitated as the sulphate and, the filtrate being worked up in the usual way, 5 g. of a colourless, mobile liquid were collected at 106°/1 mm. This had $n_D^{15°}$ 1·4452 and soon formed a solid mass

of white crystals, m. p. 30°, after drying (Found : C, 50·3; H, 7·4; OMe, 48·3. Calc. : C, 50·5; H, 7·4; OMe, 48·9%). 0·0989 G. of lactone required 5·26 c.c. of *N*-alkali (calc., 5·20 c.c.). It showed an initial $[\alpha]_D$ — 43·05° in water (c = 1·0), changing after 7 days to — 35·5° and after 20 days to — 25·46°. This aqueous solution still behaved essentially as a lactone on titration, showing that only partial conversion into the acid had occurred. The following alterations of specific rotation were observed on acidifying a solution of the sodium salt (c = 1·01); the times recorded are from the moment of adding excess of acid : 2 mins. — 4·1°; 3 mins. — 5·03°; 6 mins. — 7·58°; 60 mins. — 24·29°; 24 hours — 26·23° (t = 18°). The free acid must therefore have a specific rotation of the order — 2°. The same equilibrium mixture of acid and lactone is obtained whether one starts with the lactone or with an acidified solution of the sodium salt.

Direct Proof of the Simultaneous Formation of Amylene- and Butylene-oxidic Forms of Arabinose Derivatives.—From a mixture of methylarabinosides obtained by the initial condensation of *l*-arabinose in acid methyl alcohol at 100°, the α-methylarabinoside was separated in a crystalline form, and this on subsequent methylation and oxidation was found to yield *d*-2 : 3 : 4-trimethyl arabonolactone. The residual mother-liquor from the crystalline α-methylarabinoside was evaporated to a syrup, and the product (10 g.) was methylated twice with sodium hydroxide and methyl sulphate and once by Purdie's reagents. The methylated product was then distilled in a high vacuum, and the main fraction (about 6 g.) distilled at 94°/0·5 mm. It had OMe, 59·0% (calc., 60·2%). As the original syrup separated from the crystalline α-arabinoside was naturally thought to be in large part the corresponding β-derivative, the distilled, fully methylated product was expected to yield crystalline 2 : 3 : 4-trimethyl β-methylarabinoside. No crystallisation could, however, be induced even on nucleating with a crystal of trimethyl β-methylarabinoside. Nucleation with a crystal of the α-stereoisomeride likewise gave a negative result. The product had a specific rotation in water of — 15°, and this lævorotation was assumed to indicate the presence of the γ-, *i.e.*, the butylene-oxidic, form of the sugar. This was fully confirmed on subjecting the liquid to simultaneous hydrolysis and oxidation in the usual manner. There was obtained a final product which, on being cooled and nucleated with a crystal of 2 : 3 : 5-trimethyl arabonolactone, yielded about 4 g. of crystals. These were purified on a tile and were found to be identical in every way with 2 : 3 : 5-trimethyl arabonolactone, having m. p. 29° and $[\alpha]_D$ — 42·4° (c = 1·02). It is thus clear that the original condensation of arabin-

ose with methyl alcohol in the presence of hydrogen chloride at 100° must have resulted in the simultaneous formation of derivatives of the amylene- and butylene-oxidic types. It would also appear that only a relatively small amount of the β-stereoisomeride of the stable (amylene-oxidic) derivative was formed, since none could be separated from the fully methylated arabinoside product, and the final yield of butylene-oxidic lactone, allowing for experimental losses, was not far short of what might be expected had the whole of the non-crystalline syrup consisted of the butylene-oxidic form.

The expenses of this research were defrayed in part by a grant from the Medical Research Council, to whom we wish to express our grateful thanks. We are also indebted to the Department of Scientific and Industrial Research for a maintenance grant to one of us (R. W. H.).

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CARDIFF. [*Received, November 24th*, 1926.]