147. *Monomethyl Hexoses. Part II. A Revision of the Constitutions of the Supposed 4-Methyl Galactose and 4-Methyl Mannose of Pacsu, and their Formulation as 6-Methyl Galactose and 2-Methyl Mannose respectively.*

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SCHINLE (*Ber.*, 1931, **64**, 2361) proved that the monomethyl glucose prepared from glucose-dibenzylmercaptal was 2-methyl glucose and not 4-methyl glucose as stated by Pacsu (*Ber.*, 1925, **58**, 1455). Since a monomethyl galactose prepared by a similar method was described as 4-methyl galactose by Pacsu and Löb (*Ber.*, 1929, **62**, 3104), it became of importance to review this case also. The crystalline monomethyl galactose of Pacsu and Löb (*loc. cit.*) was prepared and a preliminary examination of the phenylosazone indicated that it was a true monomethyl galactosazone, thus excluding substitution in position 2. 3-Methyl galactose is excluded by the melting point of its phenylosazone, so that only positions 4, 5, and 6 remain available for the assignment of the methoxyl residue. Complete methylation afforded tetramethyl galactopyranose, isolated as the crystalline anilide, thus excluding substitution in position 5. Proof that position 4 also was unmethylated was obtained by oxidation of the free sugar and the isolation of a monomethyl γ-galactonolactone, easily recognised by its negative specific rotation and slow rate of hydrolysis (Haworth, "Constitution of Sugars," London, 1929). Further confirmation that both positions 4 and 5 were free was secured by following the progress of glycoside formation at 20° according to Levene, Raymond, and Dillon (*J. Biol. Chem.*, 1932, **95**, 699), which indicated that both galactofuranosides and galactopyranosides were formed (see Table II). Close agreement was observed between the physical constants of the free sugar, its phenylhydrazone and phenylosazone with those recorded by Freudenberg and Smeykal (*Ber.*, 1926, **59**, 100) for 6-methyl galactose and its corresponding derivatives, of which the structure appears to be well established by the method of preparation from diacetone galactopyranose. A direct comparison of the compounds concerned confirmed this view (see Table I) and it is considered therefore that the "4"-methyl galactose of Pacsu and Löb (*loc. cit.*) must now be described as 6-methyl galactose.

There is also dubiety about the assignment of the structure of 4-methyl mannose to the sugar isolated by Pacsu and v. Kary (*Ber.*, 1929, **62**, 2811) and an examination of their paper reveals the fact that the osazone prepared from this substance may have been glucosazone. There is no possibility that it is identical with 4-methyl glucosazone, since this has widely different properties (Munro and Percival, J., 1935, 873).

According to Pacsu and v. Kary (*loc. cit.*) a single methylation of diacetone mannose-dibenzylmercaptal, followed by hydrolysis to remove acetone, caused the separation of a crystalline product described as "4"-methyl mannosedibenzylmercaptal, m. p. 188°, $[\alpha]_D^{18°}$ — 106·6° (pyridine), together with a syrup. Many attempts to reproduce this result failed. In every case we obtained with the syrup crystalline products, m. p. 118,° $[\alpha]_D$ — 48°, which were apparently homogeneous but on analysis invariably showed a methoxyl content of about one-third of the theoretical for a monomethyl mannosedibenzylmercaptal. By repeated acetone condensation, methylation, and hydrolysis it was found possible to increase the methoxyl content of the crystals to 80% of the theoretical amount. Con-

TABLE I.

Substance.	M. p.	Rotatory power.	Reference.
(1) " 4 "-Methyl galactose	118°	$[\alpha]_D^{18°}$ +117° ⟶ +68° (after 3 hrs. in water)	(a) Pacsu and Löb, *loc. cit.*
(2) " 4 "-Methyl galactose	118—119	$[\alpha]_D^{20°}$ +120 ⟶ +70 (after 6 hrs. in water)	Present authors according to (a).
(3) 6-Methyl galactose	122—123	$[\alpha]_D^{20°}$ +112 (4 mins.) ⟶ +66 (after 6 hrs. in water)	Present authors according to (b).
(4) 6-Methyl galactose	128	$[\alpha]_{5780}^{20°}$ +114 (5 mins.) ⟶ +77 (after 3 hrs. in water)	(b) Freudenberg and Smeykal, *loc. cit.*
Mixture of (2) and (3)	120		
(5) " 4 "-Methyl galactose phenylosazone	194—195	$[\alpha]_D^{18°}$ +131 (in pyridine)	(a)
(6) " 4 "-Methyl galactose phenylosazone	200	$[\alpha]_D^{20°}$ +144 (in pyridine)	Present authors according to (a).
(7) 6-Methyl galactose phenylosazone	200—201	$[\alpha]_D^{20°}$ +141 (in pyridine)	Present authors according to (b).
(8) 6-Methyl galactose phenylosazone	204—205	$[\alpha]_{5780}^{20°}$ +135 (in pyridine)	(b)
Mixture of (6) and (7)	200		
(9) " 4 "-Methyl galactose phenylhydrazone	179	$[\alpha]_D^{20°}$ +24·4 ⟶ +14·1 (after 24 hrs. in pyridine)	Present authors.
(10) 6-Methyl galactose phenylhydrazone	179	$[\alpha]_D^{20°}$ +23·5 ⟶ +14·8 (after 24 hrs. in pyridine)	Present authors according to (b).
(11) 6-Methyl galactose phenylhydrazone	182—183	$[\alpha]_D^{20°}$ +14·5 (in pyridine)	(b)
Mixture of (9) and (10)	179		
(12) 3-Methyl galactose phenylosazone	176—179		Robertson and Lamb, J., 1934, 1321.

version into the free sugar yielded a product which was still contaminated with free mannose as shown by the isolation of pure mannosephenylhydrazone in quantity corresponding with the amount of mannose (20%) calculated from the analytical results. No methylated phenylhydrazone could be isolated during many attempts and there is thus reason to suppose that the " 4 "-methyl mannosephenylhydrazone (m. p. 179°) of Pacsu and v. Kary was indeed mannosephenylhydrazone (m. p. 183—184°). After removal of the mannosephenylhydrazone, heating produced three crops of an osazone of no methoxyl content, identical with glucosazone.

The results of Pacsu and v. Kary, however, do not depend on a study of the crystalline " 4 "-methyl mannosedibenzylmercaptal but are based on an examination of the sugar obtained on simultaneous removal of acetone and mercaptan residues from diacetone " 4 "-methyl mannosedibenzylmercaptal. The syrup obtained after one methylation, following the removal of the crystalline mixture of low methoxyl content previously described, had a slightly higher methoxyl content (17·5%) than is required for monomethyl mannose, but in this case also crystalline mannosephenylhydrazone was readily isolated. An examination of the osazones produced on heating after removal of the mannosephenylhydrazone revealed that they were specimens of glucosazone contaminated with small amounts of methylated by-products. It is considered, therefore, that the syrup was 2-methyl mannose admixed with mannose and some polymethylated derivatives.

The structures of the acetone compounds of the dibenzylmercaptals of glucose, galactose, and mannose, assigned by Pacsu, require revision in the light of the facts now known and this problem is under investigation.

EXPERIMENTAL.

Preparation of " 4 "-Methyl Galactosedibenzylmercaptal.—The methods described by Pacsu and Löb (*loc. cit.*) were followed for the preparation. Galactosedibenzylmercaptal (20 g.) yielded fine needles of " 4 "-methyl galactosedibenzylmercaptal (7 g.), m. p. 130°, $[\alpha]_D^{20°}$ − 27° in pyridine (*c*, 3·3) (Found: C, 59·5; H, 6·7; OMe, 6·7. Calc. for $C_{21}H_{28}O_5S_2$: C, 59·4; H, 6·6; OMe, 7·3%).

Isolation of " 4 "-Methyl Galactose.—The mercaptan residues were removed from " 4 "

methyl galactosedibenzylmercaptal (10 g.) as described for 4-methyl glucose (Munro and Percival, *loc. cit.*) to yield a syrup (3·6 g.) which slowly crystallised; m. p. 118° (Found: C, 43·7; H, 7·4; OMe, 13·9. Calc. for $C_7H_{14}O_6$: C, 43·4; H, 7·2; OMe, 16·0%).

" 4 "-Methyl Galactosephenylosazone.—" 4 "-Methyl galactose (0·3 g.), dissolved in water (1·5 c.c.), was heated at 100° for 1 hour with phenylhydrazine (1·5 g.) and acetic acid (0·5 g.). On recrystallisation from alcohol (needles) it showed m. p. 200°, $[\alpha]_D^{20°}$ + 144° in pyridine (*c*, 0·4) (Found: OMe, 7·9; N, 15·1. Calc. for $C_{19}H_{24}O_4N_4$: OMe, 8·3; N, 15·0%).

" 4 "-Methyl Galactosephenylhydrazone.—" 4 "-Methyl galactose (0·2 g.) was dissolved in water (0·5 c.c.), and phenylhydrazine (0·5 g.) added. Crystallisation began after a few hours and was complete in 2 days; m. p. 179° after recrystallisation from methyl alcohol, $[\alpha]_D^{20°}$ + 24·4° (initial value), falling to 14·1° in 24 hours, in pyridine (*c*, 0·8) (Found: OMe, 10·2; N, 9·8. Calc. for $C_{13}H_{20}O_5N_2$: OMe, 10·9; N, 9·85%).

Complete Methylation of " 4 "-Methyl Galactose.—In preparing the fully methylated galactose we employed a series of reactions precisely similar to that for the complete methylation of 4-methyl glucose (J., 1935, 873), namely, tetra-acetyl " 4 "-methyl galactose ⟶ triacetyl " 4 "-methyl galactosidyl bromide ⟶ triacetyl " 4 "-methyl methylgalactoside, in the hope of isolating some intermediate crystalline product, but without success.

Triacetyl " 4 "-methyl methylgalactoside (1·4 g.), dissolved in acetone (30 c.c.), was methylated with methyl sulphate (15 c.c.) and sodium hydroxide solution (40 c.c., 30%). The syrup obtained in the usual way was twice methylated with methyl iodide (10 c.c.) and silver oxide (2·5 g.) during 6 hours and gave on distillation at 115° (bath temp.)/0·04 mm. an oil (0·45 g.), $n_D^{15°}$ 1·4500. The galactoside (0·44 g.) was heated on a water-bath at 80° with 8% hydrochloric acid (4 c.c.) for 2 hours (cf. Irvine and Cameron, J., 1904, **85**, 1071), the acid neutralised with barium carbonate, and the filtered solution evaporated to dryness (diminished pressure). On extraction of the solid with boiling ether, a clear syrup (0·4 g.) of tetramethyl galactose was obtained. This (0·13 g.) was digested with aniline (0·4 g.) and alcohol (1 c.c.) at 100° for 3 hours. 2 : 3 : 4 : 6-Tetramethyl galactose anilide crystallised, on cooling, in long needles (0·1 g.), m. p., after recrystallisation from alcohol, 192—193°, unchanged by an authentic specimen; $[\alpha]_D^{20°}$ — 71° (initial) in acetone (*c*, 0·2) (Found: OMe, 40·8; N, 4·5. Calc. for $C_{16}H_{25}O_5N$: OMe, 39·9; N, 4·5%).

Oxidation of " 4 "-Methyl Galactose to " 4 "-Methyl γ-Galactonolactone.—" 4 "-Methyl galactose (1·5 g.), dissolved in water (10 c.c.), was oxidised with bromine (3 c.c.) at 35° until all reducing action had ceased (48 hours). The excess of bromine was removed by aeration, and the solution neutralised with silver carbonate. The lactone (1·0 g.) was obtained by precipitation of the silver with hydrogen sulphide, filtration, and evaporation to dryness (diminished pressure), followed by heating at 100° in a vacuum (2 hours); $[\alpha]_D^{20°}$ — 43° (10 mins.), — 40° (9 days; const.). 0·0183 G. required 1·32 c.c. 0·01*N*-sodium hydroxide for neutralisation of the free acid and 8·95 c.c. for complete neutralisation (calc., 9·5 c.c.), giving 85% lactone at equilibrium (cf. Freudenberg and Smeykal, *loc. cit.*) (Found: OMe, 14·4. Calc. for $C_7H_{12}O_6$: OMe, 16·1%).

Glycoside Formation with " 4 "-Methyl Galactose at 20°.—The method employed for examining the rate of glycoside formation at room temperature was essentially that described by Levene, Raymond, and Dillon (*loc. cit.*). From a 0·5% methyl-alcoholic hydrogen chloride solution containing " 4 "-methyl galactose (approximately 3 mg. per 0·5 c.c.), two samples of 0·5 c.c. were withdrawn at intervals. One was treated with 0·5 c.c. of 0·4*N*-sodium carbonate and water (3 c.c.), and kept for 15 minutes with 0·3*N*-sodium hydroxide (1 c.c.) and 0·03*N*-iodine (5 c.c.). The excess of iodine, liberated with 5*N*-sulphuric acid (0·2 c.c.), was titrated with 0·01*N*-sodium thiosulphate. The second sample was heated for 10 minutes at 100° with water (2 c.c.) and 0·26*N*-hydrochloric acid (1 c.c.). After immediate cooling, the acid was neutralised with the calculated amount of 0·4*N*-sodium carbonate, and the solution kept for 15 minutes with 0·3*N*-sodium hydroxide (1 c.c.) and 0·03*N*-iodine (5 c.c.). The excess of iodine was determined as before. The difference between these titrations and blank experiments carried out under similar conditions gave the figures for the reducing values. A correction of 21% had to be made on the reducing values obtained after hydrolysis with 0·1*N*-hydrochloric acid owing to the hydrolysis of the " 4 "-methyl methylgalactopyranoside under these conditions, this being determined by a separate experiment.

At the end of 48 hours, the sugar is transformed into a mixture of galactofuranosides and galactopyranosides in approximately equal amounts.

6-Methyl Galactose.—The compound was prepared as described by Freudenberg and Smeykal (*loc. cit.*). It was readily obtained crystalline, but repeated crystallisation from alcohol–ether failed to raise the m. p. above 123°. M. p. in admixture with " 4 "-methyl galactose 120°;

TABLE II.

	0·01*N*-$Na_2S_2O_3$, c.c.		Free sugar, %.					
Time.	Before hydrolysis.	After hydrolysis.	Before hydrolysis.	After hydrolysis.	Corrected.	Free sugar, %.	Furanoside, %.	Pyranoside, %.
0	2·13	2·39	100	100	100	100	—	—
15 mins.	1·68	2·46	78·9	102·9	100	78·9	21·1	—
30 ,,	1·60	2·31	75·1	96·6	95·8	75·1	20·7	4·2
1 hr.	1·38	2·24	64·8	93·7	92·1	64·8	27·3	7·9
2 hrs.	1·05	2·10	49·3	87·8	84·8	49·3	35·5	15·2
4 ,,	0·78	1·93	36·6	80·8	76·0	36·6	39·4	24·0
24 ,,	0·20	1·40	9·4	58·6	48·2	9·4	38·8	51·8
48 ,,	0·11	1·52	6·6	63·6	54·5	6·6	47·9	45·5

$[\alpha]_D^{20°}$ + 112° in water (*c*, 1), 4 minutes after dissolution, + 66° after 6 hours (constant). 6-Methyl galactosephenylhydrazone prepared in the usual way and recrystallised four times from methyl alcohol had m. p. 179°, unchanged by " 4 "-methyl galactosephenylhydrazone; $[\alpha]_D^{20°}$ +23·5° in pyridine (*c*, 1), +14·8° (after 24 hrs.; const.). 6-Methyl galactosephenylosazone, recrystallised from alcohol, showed m. p. 200° alone or in admixture with " 4 "-methyl galactosephenylosazone; $[\alpha]_D^{20°}$ +141° in pyridine (*c*, 0·5).

d-*Mannosedibenzylmercaptal.*—The method of preparation employed by Pacsu and v. Kary (*loc. cit.*) was followed, and the product obtained had the properties ascribed to it by those authors; m. p. 126°, $[\alpha]_D^{20°}$ −32·6° in pyridine (*c*, 0·7).

Preparation of the Acetone Compound of Mannosedibenzylmercaptal.—Mannosedibenzylmercaptal was condensed with acetone as described by Pacsu and v. Kary (*loc. cit.*). The acetone compound, after preliminary heating for some hours at 100°/15 mm., was heated for 20 minutes at 110° (bath temp.)/0·07 mm. The product gave $[\alpha]_D^{20°}$ +79° in acetylene tetrachloride (*c*, 2·0) ($[\alpha]_D^{20°}$ +66° in acetylene tetrachloride recorded by Pacsu and v. Kary, *loc. cit.*).

Methylation of the Acetone Compound of Mannosedibenzylmercaptal.—The methods of Pacsu and v. Kary (*loc. cit.*) were followed to yield a syrup, from which the acetone groups were removed as before. The white crystalline product was recrystallised from alcohol; m. p. 118°, and a mixed m. p. with mannosedibenzylmercaptal showed a depression of 1°. $[\alpha]_D^{20°}$ − 48° in pyridine (*c*, 1) (Found : OMe, 2·4. Calc. for $C_{21}H_{28}O_5S_2$: OMe, 7·3%). These results were twice confirmed.

Removal of the Mercaptan Residue and Isolation of the Reducing Sugar.—The mercaptan groups were removed, as described in the case of the galactose derivatives, to yield a reducing syrup which failed to crystallise (Found : OMe, 5·2. Calc. for $C_7H_{14}O_6$: OMe, 16·0%).

Attempted Separation of " 4 "-Methyl Mannose Derivatives.—The glycoside was prepared by the method of Bott, Haworth, and Hirst (J., 1930, 2653) and acetylated with pyridine and acetic anhydride in the usual way. The acetate, however, distilled in one fraction at 185° (bath temp.)/0·07 mm. and analysis showed it to be a mixture of tetra-acetyl methylmannoside and triacetyl monomethyl methylmannoside (Found : OMe, 11·1%).

Increase in the Methoxyl Content of the Partly Methylated Mannosedibenzylmercaptal.—Two consecutive methylations with methyl sulphate and sodium hydroxide without an intermediate hydrolysis to isolate the crystals of the methyl mannosemercaptal failed to produce any increase in the methoxyl content, but if the crystals and syrup formed after the methylation and hydrolysis of the acetone compound of mannosedibenzylmercaptal (1·5 g.) were condensed again with acetone and concentrated sulphuric acid and then remethylated and hydrolysed as before, the crystals (0·5 g.) had a higher methoxyl content. Pure monomethyl mannosedibenzylmercaptal, however, could not be produced by this method; the best sample obtained showed m. p. 117°, $[\alpha]_D^{20°}$ − 54° in pyridine (*c*, 0·5), m. p. on admixture with mannosedibenzylmercaptal 116° (Found : OMe, 5·8. Calc. for $C_{21}H_{28}O_5S_2$: OMe, 7·3%).

Preparation of the Partly Methylated Mannose.—The sugar was obtained as a reducing syrup after removal of the mercaptan residues with mercuric chloride; $[\alpha]_D^{20°}$ + 4·3° in water (*c*, 1·7) (Found : OMe, 11·7. Calc. for $C_7H_{12}O_6$: OMe, 16·0%).

Phenylhydrazone Formation.—The syrup (0·06 g.), dissolved in water (1 c.c.), was mixed with phenylhydrazine (0·5 g.) and glacial acetic acid (0·05 g.). In a few seconds a white crystalline precipitate appeared and was filtered off. After ½ hour a further crop was removed. No more crystals appeared after 2 days. The phenylhydrazone (0·02 g.) was washed with cold

acetone and dried; m. p. 183—184° alone or in admixture with a specimen prepared directly from mannose (Found: OMe, nil; N, 10·3. Calc. for $C_{12}H_{18}O_5N_2$: N, 10·4%).

If it be assumed that the phenylhydrazone formation from mannose is almost quantitative, 0·02 g. of phenylhydrazone would be produced from 0·013 g. of mannose. The monomethyl mannose is therefore present to the extent of 75—80%, which agrees with the previous analytical results.

After 2 days the clear solution was heated for 1 hour at 100° with glacial acetic acid (0·1 c.c.) and a crystal of sodium bisulphite (to retard tar formation). The osazone which formed (0·01 g.) was washed with cold acetone; m. p. 204° alone or in admixture with an authentic specimen of glucosazone (Found: OMe, nil). The filtrate on further heating yielded a second and a third crop of osazone, neither of which contained methoxyl (total yield, 0·02 g.). Since mannose gives a 30% yield of osazone under these conditions, it is clear that the glucosazone now isolated must have been formed from that portion of the syrup containing methoxyl.

Examination of the Syrup " 2 : 3-5 : 6 *"-Diacetone "* 4 *"-Methyl Mannosedibenzylmercaptal.*—The acetone compound of mannosedibenzylmercaptal (5 g.) was methylated once as before with methyl sulphate and sodium hydroxide. After extraction the product was hydrolysed with hydrochloric acid, and the crystalline, partly methylated, mannosedibenzylmercaptal obtained. The crystals (0·45 g.) were separated as completely as possible from syrup (1·8 g.) with ether and were identical with the mixtures of low methoxyl content (OMe, 2·8%) previously described; m.p. 117°, $[\alpha]_D^{20°}$ − 48° in pyridine (*c*, 1).

Removal of Mercaptan Residues from the Syrup.—The syrup (1·5 g.) was treated as before with mercuric chloride in acetone to yield a reducing syrup (0·5 g.) having $[\alpha]_D^{20°}$ + 9·6° in water (*c*, 3) (Found: OMe, 17·5. Calc. for $C_7H_{14}O_6$: OMe, 16·0%). The syrup (0·4 g.) on treatment with phenylhydrazine acetate rapidly gave mannosephenylhydrazone (0·1 g.), m. p. 183° (Found: OMe, nil; N, 10·6. Calc. for $C_{12}H_{18}O_5N_2$: N, 10·4%).

Preparation of Osazone.—The filtrate from the hydrazone was subjected to osazone formation. The two crops of osazone (0·07 g.), m. p. 180—185° (OMe, 2%), obtained proved to be glucosazone contaminated with a small amount of methylated material.

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