219. *Deoxy-sugars. Part XV.* D-*Galactose-3 and -6 Phosphoric Acids and Their 2-Deoxy-analogues.*

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Syntheses of D-galactose-3 and -6 phosphoric acids and their 2-deoxy-analogues are described. Structures of intermediates are established. The phosporylating agent used, namely diphenyl phosphoryl chloride, has been characterised by reaction with ammonia, aliphatic and aromatic amines, alcohols, and phenols.

In the past a variety of reagents has been used for the phosphorylation of sugars, but many of these were extremely drastic in their action. Because of the lability and scarcity of most deoxy-sugars, many of these reagents were of little value for the preparation of deoxy-sugar phosphates. To synthesise 2-deoxy-D-galactose-3 and -6 phosphoric acids, two phosphorylating agents have been used, namely, phosphorus oxychloride in pyridine at −40° (Levene, *J. Biol. Chem.*, 1934, **106**, 113; 1935, **111**, 313; 1937, **121**, 131), and diphenyl phosphoryl chloride (diphenyl chlorophosphonate), $(PhO)_2POCl$, in pyridine at 0°. The former method, where successful, has the advantage of direct introduction into the sugar derivative of a free phosphate group in good yield, but does not readily afford crystalline compounds. The latter has been used by several workers (Gulland and Hobday, *J.*, 1940, 746; Brigl and Müller, *Ber.*, 1939, **72**, 2121; Bredereck *et al.*, *Ber.*, 1940, **73**, 269, 1124; Zeile and Meyer, *Z. physiol. Chem.*, 1938, **256**, 131; Baer and Fischer, *J. Biol. Chem.*, 1943, **150**, 213, 223; Baer and MacArther, *ibid.*, 1944, **153**, 451; Farrar, *J.*, 1949, 3131) but has never been systematically investigated. Diphenyl phosphoryl chloride has the advantages of being easily prepared and stored, and affords crystalline derivatives (Farrar, *loc. cit.*). It was prepared by a modification of Brigl and Müller's method (*loc. cit.*). Treatment of phenol with phosphorus oxychloride at 200° gave a mixture of three esters, namely, phenyl phosphoryl dichloride ($PhO{\cdot}POCl_2$), diphenyl phosphoryl chloride, and triphenyl phosphate. These were readily fractionated and diphenyl phosphoryl chloride isolated as a pungent colourless liquid. It reacts readily with both aliphatic and aromatic amines, although more smoothly with the former. For example, treatment of diphenyl phosphoryl chloride, in carbon tetrachloride at 0°, with gaseous ammonia gave diphenyl aminophosphonate (I; R = H). Replacement of ammonia by a primary amine such as *cyclo*hexylamine in carbon tetrachloride solution, or benzylamine,

(I.) $(PhO)_2P(=O)NHR$ $\qquad$ $(PhO)_2P(=O)OR$ (II.)

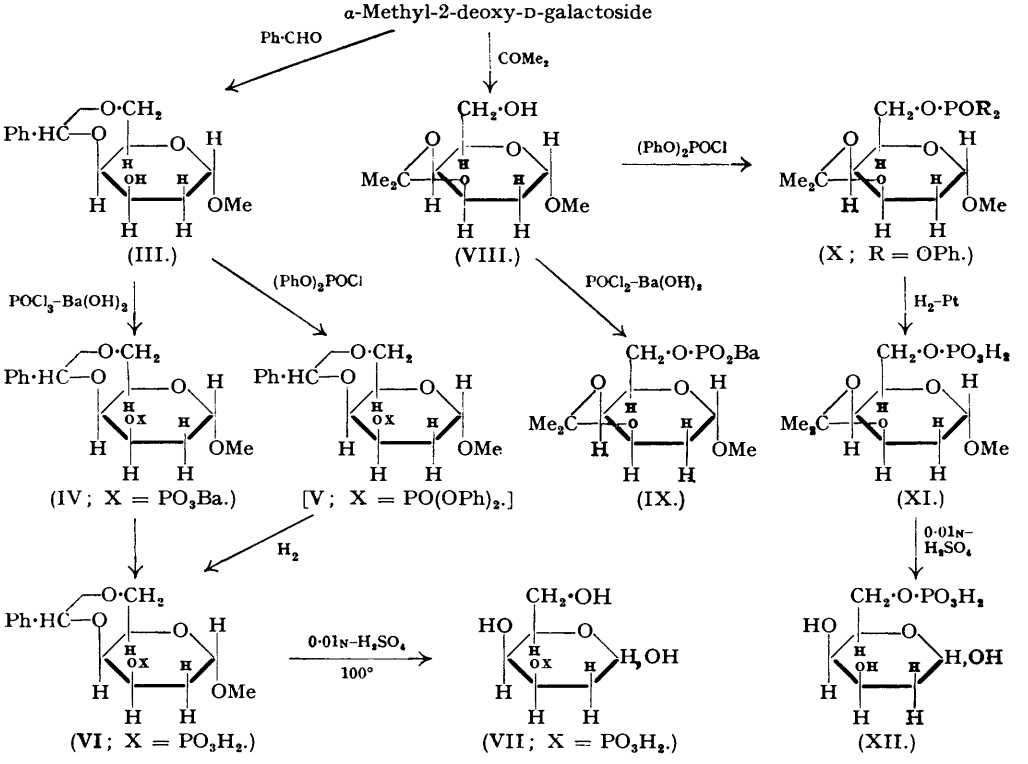
afforded diphenyl *cyclo*hexylaminophosphonate (I; R = C_6H_{11}) and diphenyl benzylaminophosphonate (I; R = $C_6H_5{\cdot}CH_2$) respectively. The secondary amine, morpholine, readily yielded diphenyl morpholinophosphonate (I; R = $O<[CH_2{\cdot}CH_2]_2>N-$. A solution of aniline in carbon tetrachloride with diphenyl phosphoryl chloride gave diphenyl anilinophosphonate (I; R = Ph), and diphenyl phenetidinophosphonate (I; R = *p*-$EtO{\cdot}C_6H_4$) and diphenyl phenylazoanilinophosphonate (I; R = $PhN{:}N{\cdot}C_6H_4$) were similarly prepared. The aminophosphonate derivatives were highly crystalline and well suited for the characterisation of diphenyl phosphoryl chloride.

Similarly diphenyl phosphoryl chloride reacts with aliphatic alcohols and phenols, most easily in the aliphatic series. *cyclo*Hexanol in solution in dry pyridine readily gave *cyclo*hexyl diphenyl phosphate (II; R = C_6H_{11}). Surprisingly, no crystalline products could be isolated from the reaction between diphenyl phosphoryl chloride and furfuryl alcohol or benzyl alcohol. Phenol gave triphenyl phosphate (II; R = Ph) identical with that isolated by Jacobsen (*Ber.*, 1875, **8**, 1522) after direct reaction of phenol and phosphorus oxychloride at 200°. Similarly β-naphthyl diphenyl phosphate (II; R = $C_{10}H_7$) and *p*-nitrophenyl diphenyl phosphate (II; R′ = *p*-$C_6H_4{\cdot}NO_2$) were prepared. The compounds obtained by treating diphenyl phosphoryl chloride with alcohols and phenols were not so characteristically crystalline as those obtained from amines, generally being viscid liquids or low-melting solids.

When 4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside (III) (see preceding paper) was treated with phosphorus oxychloride in pyridine at −40°, followed by barium hydroxide, it gave amorphous barium 4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside-3 phosphate (IV).

Treatment of (III) with diphenyl phosphoryl chloride in pyridine gave crystalline (4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside-3) diphenyl phosphate (V).

Before hydrogenolysis of this substance a solution in methanol of 4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside (III) was shown to be unchanged when shaken with Adams's catalyst in an atmosphere of hydrogen. Using a Raney nickel catalyst Tamm and Reichstein (*Helv. Chim. Acta*, 1948, **31**, 1630) succeeded in saturating the benzylidene substituent by shaking (III) in hydrogen under pressure and they isolated 4 : 6-hexahydrobenzylidene α-methyl-2-deoxy-D-galactoside; they did not observe any cleavage of the benzylidene residue under the conditions

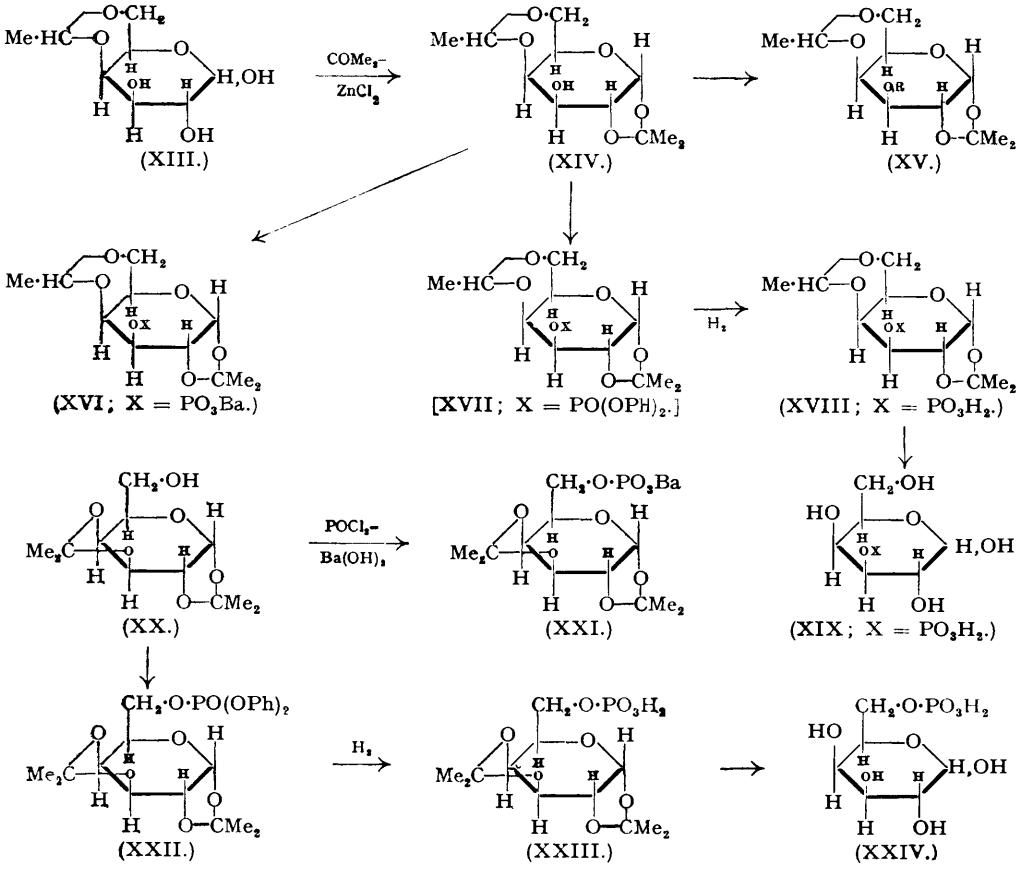


used. When (4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside-3) diphenyl phosphate (V) was subjected to hydrogenation in the presence of platinum oxide as already described, hydrogen was rapidly absorbed, corresponding to both cleavage and saturation of the phenyl groups, and it was possible to isolate 4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside-3 phosphoric acid (VI) as a colourless hygroscopic glass, which on treatment with a methanolic solution of acridine afforded a crystalline acridine salt. Treatment of (VI) with 2N-sulphuric acid under conditions identical with those which effected hydrolysis of α-methyl-2-deoxy-D-galactoside resulted in an extremely slow reaction, but at 45° there was smooth hydrolysis of the protecting groups. Unfortunately simultaneous hydrolysis of the phosphate residue also occurred. However, if a solution of (VI) in 0·01N-sulphuric acid was heated at 100° for 13 minutes, hydrolysis of the protecting groups was smooth and 2-deoxy-D-galactose-3 phosphoric acid was then isolated as its lead salt. Decomposition of the lead salt with hydrogen sulphide gave 2-deoxy-D-galactose-3 phosphoric acid (VII) as an amorphous white powder.

For the synthesis of 2-deoxy-D-galactose-6 phosphoric acid (XII), syrupy 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside (VIII) (see preceding paper) was treated with phosphorus oxychloride in pyridine at −40°, followed by barium hydroxide. Barium 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside-3 phosphate (IX) was obtained as an amorphous powder.

Treatment of (VIII) with diphenyl phosphoryl chloride in pyridine at 0° gave syrupy diphenyl (3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside-6) phosphate (X). A solution of this in aqueous ethanol, after removal of catalyst poisons by boiling under reflux with activated charcoal, absorbed hydrogen (8 mols.) in presence of platinum oxide. As before, this

corresponded to both saturation and cleavage of the phenyl groups and the formation of 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside-6 phosphoric acid (XI). No crystalline acridine salt of this compound has been obtained. Hydrolysis of (XI) with 0·01N-sulphuric acid at 100° for 30 minutes gave 2-deoxy-D-galactose-6 phosphoric acid (XII) as a fine white powder, strongly reducing towards Fehling's reagent.



For comparison of their properties (see following paper), D-galactose-3 and -6 phosphoric acids were also synthesised. Treatment of D-galactose with paraldehyde and concentrated sulphuric acid afforded a liquid ethylidene galactose. That this was 4 : 6-ethylidene D-galactose (XIII) was indicated by several facts. For example, it was strongly reducing towards Fehling's solution, indicating that $C_{(1)}$ of the sugar was not involved in the ethylidene linkage. Reaction with acetone and anhydrous zinc chloride afforded a syrupy compound (*A*), which was non-reducing and was subsequently shown to be 4 : 6-ethylidene 1 : 2-*iso*propylidene D-galactose.

Treatment of (*A*) with toluene-*p*-sulphonyl chloride in pyridine yielded crystalline ethylidene *iso*propylidene toluene-*p*-sulphonyl D-galactose, which when heated under standard conditions with sodium iodide in acetone underwent no reaction, showing that the toluene-*p*-sulphonyloxy-group was unlikely to be located at $C_{(6)}$ in galactose. Clearly the ethylidene residue was linked across positions 4 : 6 or 3 : 6. Normally the latter linkage is not formed if the former can take place, and so the ethylidene derivative is considered to be 4 : 6-ethylidene D-galactose (XIII). (*A*) would be 4 : 6-ethylidene 1 : 2-*iso*propylidene D-galactose (XIV), and its toluene-*p*-sulphonyl derivative, 4 : 6-ethylidene 1 : 2-*iso*propylidene 3-toluene-*p*-sulphonyl D-galactose (XV; R = ·SO_2·C_6H_4Me). The corresponding 3-methanesulphonyl derivative (XV; R = ·SO_2·Me) was obtained as a crystalline solid; this did not react with sodium iodide in dry acetone under standard conditions.

When 4 : 6-ethylidene 1 : 2-*iso*propylidene D-galactose (XIV) was treated with phosphorus oxychloride in pyridine at −40°, followed by barium hydroxide, barium 4 : 6-ethylidene 1 : 2-

*iso*propylidene D-galactose-3 phosphate (XVI) was obtained as an amorphous powder. Reaction of (XIV) with diphenyl phosphoryl chloride in pyridine solution at 0° gave syrupy (4 : 6-ethylidene 1 : 2-*iso*propylidene D-galactose-3) diphenyl phosphate (XVII) which, after removal of catalyst poisons in the manner already described, absorbed hydrogen (8·2 mols.) when in the presence of platinum oxide. 4 : 6-Ethylidene 1 : 2-*iso*propylidene D-galactose-3 phosphoric acid (XVIII) was isolated as a hygroscopic glass which readily gave a crystalline acridine salt. A dilute aqueous solution of this salt exhibited a characteristic green fluorescence. Treatment of (XVIII) with 0·01N-sulphuric acid at 100° for 1 hour afforded D-galactose-3 phosphoric acid (XIX) (42%) as a colourless glass which could be converted into a crystalline dipotassium or acridine salt.

D-Galactose-6 phosphoric acid was first described by Levene and Raymond (*J. Biol. Chem.*, 1931, **92**, 765). It was prepared by treating 1 : 2-3 : 4-di*iso*propylidene D-galactose (XX) with phosphorus oxychloride as already described, and then hydrolysing the protecting groups. Diphenyl phosphoryl chloride converted (XX) into syrupy (1 : 2-3 : 4-di*iso*propylidene D-galactose-6) diphenyl phosphate (XXII) from which 1 : 2-3 : 4-di*iso*propylidene D-galactose-6 phosphoric acid (XXIII) and D-galactose-6 phosphoric acid (XXIV) were obtained by successive hydrogenation in the presence of Adams's catalyst and hydrolysis with 0·01N-sulphuric acid. Both (XXIII) and (XXIV) were obtained as colourless glasses, but the former gave a crystalline acridine salt.

The properties and stabilities of these phosphoric acid derivatives of D-galactose and 2-deoxy-D-galactose are described in the following communication.

Experimental.

Diphenyl Phosphoryl Chloride.—Freshly distilled phosphorus oxychloride (150 g.) and phenol (200 g.) were mixed. A vigorous evolution of hydrogen chloride occurred. When the reaction had subsided the mixture was gradually heated and kept at 200° for 4 hours. Distillation then afforded fractions: (i) (112 g.), b. p. 105—110°/12—15 mm., n^{15} 1·5318 (this was phenyl phosphoryl dichloride, ($PhO{\cdot}POCl_2$); (ii) (75 g.), b. p. 180—190°/12—15 mm., n^{15} 1·5505 (diphenyl phosphoryl chloride); and (iii) (75 g.), b. p. 210—250°/12—15 mm. (triphenyl phosphate). Fraction (iii) was obtained originally as a colourless viscous liquid, but crystallised on storage. Recrystallisation from ether gave a product of m. p. 41—43° (Jacobsen, *loc. cit.*, gives m. p. 41—43°). The diphenyl phosphoryl chloride (fraction ii) was re-distilled twice and obtained as a colourless liquid with a characteristic pungent odour. It could be conveniently stored in the presence of phosphoric oxide, but in sunlight gradually became yellow.

Reaction of Diphenyl Phosphoryl Chloride with Amino-compounds.—(a) *Ammonia.* A rapid stream of ammonia was bubbled through a solution of diphenyl phosphoryl chloride (1·73 g.) in carbon tetrachloride (10 c.c.) cooled to −10°. After 5 minutes, when reaction was complete, excess of ammonia was removed by passing a rapid stream of nitrogen through the mixture. The crystalline material formed was collected and freed from inorganic material by being washed several times with water. Recrystallisation from aqueous methanol afforded diphenyl aminophosphonate, m. p. 148—149° (Atherton and Todd, *J.*, 1947, 674, record m. p. 149—150°).

(b) *Aliphatic amines.* A solution of diphenyl phosphoryl chloride (1·0 g.) in carbon tetrachloride (10 c.c.) was treated at room temperature with a solution of freshly distilled *cyclo*hexylamine (1·0 g.) in carbon tetrachloride (10 c.c.), and the reaction mixture was set aside overnight. After dilution with carbon tetrachloride (40 c.c.) the solution was washed successively with water, dilute hydrochloric acid, and again water. After drying ($MgSO_4$), evaporation of solvent afforded a crystalline residue. Recrystallization from aqueous methanol gave *diphenyl cyclohexylaminophosphonate* as colourless needles, m. p. 101—102° (Found: C, 65·3; H, 6·6; N, 4·1. $C_{18}H_{22}O_3NP$ requires C, 65·2; H, 6·6; N, 4·2%). By similar methods, using benzylamine and morpholine, were prepared *diphenyl benzylaminophosphonate*, large colourless needles (from aqueous methanol), m. p. 103—104° (Found: C, 67·2; H, 5·2. $C_{19}H_{18}O_3NP$ requires C, 67·2; H, 5·3%), and *diphenyl morpholinophosphonate*, colourless plates (from aqueous methanol), m. p. 71—72° (Found: 60·3; H, 5·6; N, 4·5. $C_{16}H_{18}O_4NP$ requires C, 60·2; H, 5·6; N, 4·4%).

(c) *Aromatic amines.* A solution of freshly distilled aniline (0·5 g.) in carbon tetrachloride (5 c.c.) was added to a solution of diphenyl phosphoryl chloride (0·5 g.) in the same solvent (10 c.c.). The solution was set aside at room temperature overnight, and then worked up in the usual manner. Recrystallisation of the product from aqueous methanol afforded *diphenyl anilinophosphonate* as colourless plates, m. p. 128—129° (Found: C, 65·8; H, 5·0. $C_{18}H_{16}O_3NP$ requires C, 66·5; H, 4·9%).

By similar methods were prepared *diphenyl phenetidinophosphonate*, colourless hexagonal plates (from aqueous methanol), m. p. 104—105° (Found: C, 65·3; H, 5·4. $C_{20}H_{20}O_4NP$ requires C, 65·1; H, 5·4%), and *diphenyl phenylazoanilinophosphonate*, stout orange needles (from aqueous methanol), m. p. 149—150° (Found: N, 9·8. $C_{24}H_{20}O_3N_3P$ requires N, 9·8%).

Reaction of Diphenyl Phosphoryl Chloride with Alcohols.—Redistilled *cyclo*hexanol (1·2 mols. 0·52 c.c.) was added to a solution of diphenyl phosphoryl chloride (1 g.) in dry pyridine (4 c.c.), and the mixture kept at room temperature for 20 hours. After dilution with chloroform or carbon tetrachloride (40 c.c), the mixture was washed twice with water and then dried ($MgSO_4$). Evaporation of the solvent afforded a syrupy product from which *cyclohexyl diphenyl phosphate* was obtained, having b. p. 175—180° (bath-

temp.)/0·03 mm., n^{21} 1·5350. It crystallised on storage, and after recrystallisation from ether–light petroleum (b. p. 40—60°) was obtained as colourless plates, m. p. 34—35° (Found: C, 65·1; H, 6·4. $C_{18}H_{21}O_4P$ requires C, 65·1; H, 6·3%).

Reactions of Diphenyl Phosphoryl Chloride with Phenols.—By use of *p*-nitrophenol and the procedure outlined above, *p-nitrophenyl diphenyl phosphate* was obtained as yellow plates [from ether–light petroleum (b. p. 60—80°)], m. p. 39—40°, b. p. 220—230° (bath-temp.)/0·15 mm., n^{20} 1·5803 (Found: C, 57·9; H, 3·7; N, 4·3. $C_{18}H_{14}O_6NP$ requires C, 58·2; H, 3·8; N, 3·8%).

If β-naphthol was used, *β-naphthyl diphenyl phosphate* was obtained as a viscous yellow liquid, b. p. 270—280° (bath-temp.)/0·03 mm., n^{18} 1·6050 (Found: C, 69·9; H, 4·6. $C_{22}H_{17}O_4P$ requires C, 70·2; H, 4·5%).

Diphenyl phosphoryl chloride and phenol yielded triphenyl phosphate, which formed colourless plates (from ether–light petroleum), m. p. 43—44° (Jacobsen, *loc. cit.*, gave m. p. 41—43° for this compound which he prepared by reaction of phosphorus oxychloride and phenol).

Phosphorylation of 4 : 6-*Benzylidene* α-*Methyl*-2-*deoxy*-D-*galactoside.*—(a) *With phosphorus oxychloride at* −40°. A solution of 4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside (1·0 g.) in dry pyridine (5 c.c.) was cooled to −40°. Phosphorus oxychloride (1·1 mols., 0·38 c.c.) in dry pyridine (2 c.c.) was then added during 20 minutes. The reaction mixture was kept at −40° for 2 hours, then at −10° for a further 2 hours. After recooling to −40°, 10% aqueous pyridine (3 c.c.) was added dropwise and then a small quantity of ice and water was added. When the reaction mixture had warmed, its pH was adjusted to 9·5 (thymolphthalein) by addition of aqueous barium hydroxide solution. The mixture was filtered through a carbon pad and then evaporated to dryness under diminished pressure. *Barium* 4 : 6-*benzylidene* α-*methyl*-2-*deoxy*-D-*galactoside*-3 *phosphate* was obtained as a white amorphous powder very soluble in water from which it could be precipitated by addition of acetone; it had $[\alpha]_D^{25}$ +22·8°, (*c*, 1·6 in water) (Found: P, 6·0; Ba, 29·1. $C_{14}H_{17}O_8PBa$ requires P, 6·5; Ba, 28·5%).

(b) *With diphenyl phosphoryl chloride.* A solution of the benzylidene derivative (3·06 g.) and diphenyl phosphoryl chloride (4 g.) in dry pyridine (16 c.c.) was kept at room temperature for 30 hours. After dilution with ether (75 c.c.), the reaction mixture was washed in turn with water, dilute hydrochloric acid, and again water, and then dried ($MgSO_4$). Evaporation of the solvent afforded a straw-coloured thick syrup (5·4 g., 93%; n^{21} 1·5527), which crystallised on storage. Recrystallisation from the minimum volume of ether gave *diphenyl* 4 : 6-*benzylidene* α-*methyl*-2-*deoxy*-D-*galactoside*-3 *phosphate* as large colourless plates, m. p. 77—78°, $[\alpha]_D^{20}$ +114° (*c*, 0·46 in ethanol) (Found: C, 62·4; H, 5·0. $C_{26}H_{27}O_8P$ requires C, 62·6; H, 5·4%).

4 : 6-*Benzylidene* α-*Methyl*-2-*deoxy*-D-*galactoside*-3 *Phosphoric Acid.*—A solution of diphenyl 4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside-3 phosphate (2 g.) in dry methanol (60 c.c.) was treated with hydrogen at a slight overpressure in the presence of platinum oxide (100 mg.). Uptake of hydrogen (8·9 mols.) was complete in 6 hours. Addition of more catalyst after this period failed to cause any further uptake of hydrogen. After filtration and evaporation of the solvent at 35° (bath-temp.), 4 : 6-*benzylidene* α-*methyl* 2-*deoxy*-D-*galactoside*-3 *phosphoric acid* (1·3 g.) was obtained as a colourless hygroscopic glass, $[\alpha]_D^{20}$ +98° (*c*, 1·3 in water) (Found: P, 9·1. $C_{14}H_{19}O_8P$ requires P, 8·9%).

A solution of this phosphoric acid derivative (50 mg.) in methanol (2 c.c.) was treated with acridine (1 mol., 26 mg.), and the bright yellow solution was evaporated to dryness. After 4 weeks the residue crystallised and when recrystallised from water containing a little ethanol gave the *acridine* salt, m. p. 166—167° (decomp.) (Found: P, 5·6; N, 2·4. $C_{14}H_{19}O_8P,C_{13}H_9N$ requires P, 5·9; N, 2·6%).

2-*Deoxy*-D-*galactose*-3 *Phosphoric Acid.*—4 : 6-Benzylidene α-methyl-2-deoxy-D-galactoside-3 phosphoric acid (0·087 g.) was dissolved in water (4·0 c.c.) and treated with 12N-sulphuric acid (0·8 c.c.) at room temperature. Changes in optical rotation {$[\alpha]_D^{18}$ +87·8° (after 1 minute) ⟶ +55·2° (after 115 minutes)} indicated that hydrolysis was proceeding slowly. The temperature was raised to 40—45° and changes in optical rotation re-observed:

Time (hours)	0	2	4	6
$[\alpha]_D$	+55·2°	+40·8°	+35·3°	+34·2°

The solution was neutralised to pH 8 with aqueous barium hydroxide and the insoluble barium salts were filtered off and washed with water. Addition to the filtrate of an aqueous solution of neutral lead acetate gave only a trace of the lead salt of the hydrolysis product.

In a trial experiment to determine better hydrolysis conditions, α-methyl-2-deoxy-D-galactoside (0·2 g.) dissolved in 0·01N-sulphuric acid (12 c.c.) was heated under reflux and the hydrolysis followed polarimetrically. The following observations were noted:

Time (minutes)	0	15	30
$[\alpha]_D$	+152°	+51·6°	+50·4°

The hydrolysis was essentially complete after 15 minutes and consequently 4 : 6-benzylidene α-methyl 2-deoxy-D-galactoside-3 phosphoric acid (0·22 g.) dissolved in 0·01N-sulphuric acid (12 c.c.) was boiled under reflux for 13 minutes and then the solution was neutralized (to pH 7) by addition of aqueous barium hydroxide. The insoluble barium residues were collected and washed with water. Addition of aqueous neutral lead acetate solution to the combined filtrate and washings gave a flocculent precipitate of the lead salt of 2-deoxy-D-galactose-3 phosphoric acid. This was filtered off, washed several times with water, and dried. It was obtained as a colourless, non-hygroscopic glass which was strongly reducing towards Fehling's solution (Found: P, 6·1. $C_6H_{11}O_8PPb$ requires P, 6·9%). This lead salt (98 mg.), finely ground in an agate mortar, was suspended in water (15 c.c.), and hydrogen sulphide passed through the suspension until decomposition was complete. The precipitated lead sulphide was

filtered off and washed with water and the combined filtrate and washings were freed from hydrogen sulphide by aeration. Evaporation of the solution under diminished pressure gave a straw-coloured glass which was dried with methanol, to yield *2-deoxy-D-galactose-3 phosphoric acid* (25 mg.) as an amorphous powder which strongly reduced Fehling's solution and showed $[\alpha]_D^{20}$ +25° (equilibrium; *c*, 0·5 in water) (Found: P, 12·5. $C_6H_{13}O_8P$ requires P, 12·7%).

Phosphorylation of 3 : 4-iso*Propylidene α-Methyl-2-deoxy-D-galactoside.*—(a) *With phosphorus oxychloride at* −40°. A solution of 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside (2 g.) in dry pyridine (10 c.c.) was cooled to −40° and treated during 30 minutes with a solution of phosphorus oxychloride (0·8 g.) in dry pyridine (4 c.c.), also cooled to −40°. The mixture was mechanically agitated throughout the addition. The product was subsequently isolated by the procedure described above and *barium* 3 : 4-iso*propylidene α-methyl-2-deoxy-D-galactoside-6 phosphate* (3·39 g., 84·6%) was obtained as a white amorphous powder. It was very soluble in water, giving a clear solution from which it could be precipitated by addition of acetone and had $[\alpha]_D^{20}$ +12° (*c*, 1·49 in water) (Found: P, 6·8; Ba, 30·6. $C_{10}H_{17}O_8PBa$ requires P, 7·2; Ba, 31·4%).

(b) *With diphenyl phosphoryl chloride.* 3 : 4-*iso*Propylidene α-methyl-2-deoxy-D-galactoside (0·93 g.) in dry pyridine (4 c.c.) was treated with diphenyl phosphoryl chloride (1·3 mols., 1·34 g.) at 0° for 10 minutes and then at room temperature overnight. The reaction mixture was then diluted with ether (40 c.c.) and washed successively with water (twice), 0·5N-sulphuric acid (thrice), water, and dilute aqueous sodium hydrogen carbonate. After being dried ($MgSO_4$), the solvent was evaporated and *diphenyl* (3 : 4-iso*propylidene α-methyl-2-deoxy-D-galactoside-6*) *phosphate* (1·69 g., 83·7%) was obtained as a pale yellow syrup, $[\alpha]_D^{20}$ +23·9° (*c*, 1·71 in ethanol), n^{17} 1·5140 (Found: C, 58·2; H, 6·2. $C_{22}H_{27}O_8P$ requires C, 58·7; H, 6·0%).

3 : 4-iso*Propylidene α-Methyl-2-deoxy-D-galactoside-6 Phosphoric Acid.*—A solution of the diphenyl phosphate (2·81 g.) in methanol (90 c.c.) and water (30 c.c.) was freed from catalyst poisons (traces) by being boiled under reflux for 10 minutes with activated charcoal (2 g.). The charcoal was filtered off and washed with a little hot methanol. The combined filtrate and washings were shaken in hydrogen at a slight overpressure with Adams's platinum oxide (150 mg.). Absorption of hydrogen (1220 c.c.) was complete in 3 hours. The solution was filtered from the catalyst and evaporated to dryness under diminished pressure. 3 : 4-iso*Propylidene α-methyl-2-deoxy-D-galactoside-6 phosphoric acid* (1·6 g.) was obtained as a colourless hygroscopic glass, $[\alpha]_D^{20}$ +53·7° (*c*, 1·2 in water) (Found: P, 11·0. $C_{10}H_{19}O_8P$ requires P, 10·5%). This compound rapidly coloured on storage. It did not yield a crystalline acridine salt.

2-Deoxy-D-galactose-6 Phosphoric Acid.—3 : 4-*iso*Propylidene α-methyl-2-deoxy-D-galactoside-6 phosphoric acid (1·8 g.) in solution in water (100 c.c.) was treated with 0·6N-sulphuric acid (1·7 c.c.). The solution was boiled gently under reflux and the ensuing hydrolysis was followed polarimetrically and was complete in 38 minutes. The solution was neutralised to pH 8 by the addition of aqueous barium hydroxide, the insoluble barium residues were collected and washed with water, and the washings added to the filtrate which was then treated with excess of neutral lead acetate solution. The flocculent precipitate was collected by centrifuging and washed five times by centrifuging with water. It was suspended in water and decomposed with hydrogen sulphide. The product was worked up in the usual manner and the colourless solution so obtained evaporated to dryness under diminished pressure. A colourless syrup (0·54 g.) was obtained which solidified on trituration with methanol. *2-Deoxy-D-galactose-6 phosphoric acid* was obtained as a non-hygroscopic white powder which strongly reduced Fehling's solution and showed m. p. 155—160° (decomp.), $[\alpha]_D^{20}$ +41° (equilibrium; *c*, 0·41 in water) (Found: P, 12·9. $C_6H_{13}O_8P$ requires P, 12·7%).

4 : 6-*Ethylidene* 1 : 2-iso*Propylidene* D-*Galactose.*—D-Galactose (30 g.) was mechanically agitated with freshly distilled paraldehyde (110 c.c.) and concentrated sulphuric acid (0·3 c.c.), at room temperature for 24 hours. The resulting semi-solid mass was filtered off, dissolved in dioxan, and, after cooling, filtered from unchanged D-galactose. Evaporation of the filtrate afforded syrupy 4 : 6-ethylidene D-galactose (21 g.) which was strongly reducing towards Fehling's reagent. It was dissolved in acetone (350 c.c.) containing anhydrous zinc chloride (35 g.) and shaken at room temperature for 24 hours. The reaction mixture was poured into water containing an excess of sodium carbonate, and the precipitated zinc residues were collected and washed with acetone. Evaporation of the acetone from the combined filtrate and washings left an aqueous solution which was extracted with chloroform (3 × 100 c.c.). After drying ($MgSO_4$), the extract was evaporated and the residue distilled. 4 : 6-Ethylidene 1 : 2-*iso*propylidene D-galactose was obtained as a colourless hygroscopic liquid, b. p. 125—130°/(bath-temp.)/0·05 mm., n^{17} 1·4710, $[\alpha]_D^{20}$ −55·7° (*c*, 2·06 in chloroform). Because of the hygroscopic nature of this compound it was not possible to obtain good results for elemental analysis, but its identity was fully substantiated by the following derivatives.

4 : 6-*Ethylidene* 1 : 2-iso*Propylidene* 3-*Toluene*-p-*sulphonyl* D-*Galactose.*—A solution of the ethylidene *iso*propylidene derivative (0·61 g.) in dry pyridine (2·5 c.c.) was treated with toluene-*p*-sulphonyl chloride (0·6 g., 1·2 mols.) at room temperature for 12 hours. The reaction mixture was poured into water, and an oil separated which soon solidified. Recrystallisation of it from aqueous ethanol gave 4 : 6-*ethylidene* 1 : 2-iso*propylidene* 3-*toluene*-p-*sulphonyl* D-*galactose* as colourless needles, m. p. 106—107°, $[\alpha]_D^{20}$ −67·3° (*c*, 1·3 in chloroform) (Found: C, 53·7; H, 5·9. $C_{18}H_{24}O_8S$ requires C, 54·0; H, 6·0%).

4 : 6-*Ethylidene* 3-*Methanesulphonyl* 1 : 2-iso*Propylidene* D-*Galactose.*—In a similar manner to that described, 4 : 6-*ethylidene* 3-*methanesulphonyl* 1 : 2-iso*propylidene* D-*galactose* was prepared from ethylidene *iso*propylidene D-galactose (0·33 g.) in dry pyridine (15 c.c.) and methanesulphonyl chloride (0·27 g., 1·2 mols.). When recrystallised from aqueous ethanol it was obtained as colourless needles, m. p. 98—99°, $[\alpha]_D^{20}$ −52·9° (*c*, 0·7 in chloroform) (Found: C, 44·3; H, 6·4. $C_{12}H_{20}O_8S$ requires C, 44·4; H, 6·2%).

The toluene-*p*-sulphonyl and methanesulphonyl derivatives (200 mg.) were separately dissolved in acetone (5 c.c.) containing excess of sodium iodide (500 mg.) and heated at 130—135° for 10 hours. There was no reaction in either case.

Phosphorylation of 4 : 6-*Ethylidene* 1 : 2-iso*Propylidene* D-*Galactose*.—(a) *With phosphorus oxychloride at* −40°. To a solution of 4 : 6-ethylidene 1 : 2-*iso*propylidene D-galactose (2·0 g.) in dry pyridine (10 c.c.) cooled to −40°, a solution of phosphorus oxychloride (0·8 c.c.) in dry pyridine (5 c.c.), also cooled to −40°, was added during 20 minutes with vigorous mechanical stirring. The product was isolated in the usual manner and *barium* 4 : 6-*ethylidene* 1 : 2-iso*propylidene* D-*galactose*-3 *phosphate* (3·5 g., 77%) was obtained as an amorphous white powder, soluble in water from which it could be precipitated by addition of acetone. Fractionation by this method gave a product showing $[\alpha]_D^{20}$ −24° (*c*, 1·4 in water) (Found : P, 6·8; Ba, 28·2. $C_{11}H_{17}O_9PBa$ requires P, 6·7; Ba, 29·7%).

(b) *With diphenyl phosphoryl chloride.* A solution of the ethylidene *iso*propylidene galactose (2·74 g.) in dry pyridine (11 c.c.) was cooled at 0° and treated with a solution of diphenyl phosphoryl chloride (3·5 g., 1·3 mols.) in dry pyridine (6 c.c.) for 10 minutes and then at room temperature for 24 hours. The mixture was diluted with ether (100 c.c.) and washed successively with water, 0·5N-sulphuric acid, water, and dilute aqueous sodium hydrogen carbonate. After drying ($MgSO_4$) it was evaporated and afforded (4 : 6-*ethylidene* 1 : 2-iso*propylidene* D-*galactose*-3) *diphenyl phosphate* (4·9 g., 76·5%), $[\alpha]_D^{20}$ −42·6° (*c*, 1·4 in ethanol), n^{17} 1·5200 (Found : C, 57·6; H, 5·5. $C_{23}H_{27}O_9P$ requires C, 57·7; H, 5·6%).

4 : 6-*Ethylidene* 1 : 2-iso*Propylidene* D-*Galactose*-3 *Phosphoric Acid*.—A solution of the above diphenyl phosphate (1·66 g.) in ethanol (60 c.c.) and water (20 c.c.) was freed from catalyst poisons, either by being shaken for 2 hours in an atmosphere of hydrogen at a slight overpressure in the presence of palladium black (2 g.) or, better, boiled under reflux with activated charcoal (2 g.) for 10 minutes. It was then shaken vigorously in an atmosphere of hydrogen at a slight overpressure in the presence of platinum oxide (100 mg.). Uptake of hydrogen (8 mols., 610 c.c.) was complete after 4·5 hours and the solution was filtered from catafyst and evaporated to dryness under diminished pressure. 4 : 6-Ethylidene 1 : 2-*iso*propylidene D-galactose-3 phosphoric acid (0·8 g.) was obtained as a water-soluble, hygroscopic glass, $[\alpha]_D^{18}$ −41·5° (*c*, 0·77 in water) (Found : P, 9·4. $C_{11}H_{19}O_9P$ requires P, 9·2%). This phosphoric acid derivative (100 mg.) was dissolved in methanol (1 c.c.) and treated with a solution of acridine (55 mg.) in methanol (1 c.c.). On addition of ether the *acridine* salt separated as very small bright yellow rods, m. p. 162—163° (with darkening), 171—172° (decomp.) (Found : P, 6·0; N, 2·7. $C_{11}H_{20}O_9P,C_{13}H_9N$ requires P, 6·1; N, 2·7%).

D-*Galactose*-3 *Phosphoric Acid*.—A solution of 4 : 6-ethylidene 1 : 2-*iso*propylidene D-galactose-3 phosphoric acid (1·57 g.) in water (100 c.c.) containing N-sulphuric acid (1 c.c.) was boiled under reflux for 1 hour. After neutralisation to pH 7·5 by addition of aqueous barium hydroxide and removal of the precipitated barium sulphate, the solution was treated with excess of aqueous neutral lead acetate solution. The flocculent precipitate was collected and washed by centrifuging with water. It was then suspended in warm water and decomposed by hydrogen sulphide. After removal of the lead sulphide, the filtrate was aerated to remove dissolved hydrogen sulphide and then evaporated to small bulk under diminished pressure. Dilute aqueous potassium hydroxide was added (to pH 7·2) and the solution re-evaporated. A colourless syrup (0·42 g., 42%) was obtained which crystallised in triangular plates on storage over phosphoric oxide. *Dipotassium* D-*galactose*-3 *phosphate dihydrate* was obtained as colourless small plates, $[\alpha]_D^{18}$ +25·2° (*c*, 0·81 in water) (Found : C, 18·7; H, 4·2; P, 8·4. $C_6H_{11}O_9PK_2,2H_2O$ requires C, 19·3; H, 4·1; P, 8·3%). It was very soluble in water and readily reduced Fehling's reagent.

The dipotassium salt (75 mg.) was converted into the lead salt by addition of excess of aqueous neutral lead acetate solution, and the lead salt in turn converted into the free phosphoric acid by hydrogen sulphide. The aqueous solution of the free phosphoric acid was shaken with solid acridine (200 mg.) for 5 hours. Undissolved solid material was filtered off and the filtrate evaporated to a syrup which crystallised on trituration with methanol. The *acridine* salt of D-galactose-3 phosphoric acid was obtained as fine yellow needles, m. p. 180—185° (Found : N, 2·7. $C_6H_{13}O_9P,C_{13}H_9N$ requires N, 3·1%).

Phosphorylation of 1 : 2-3 : 4-*Di*iso*propylidene* D-*Galactose*.—(a) *With phosphorus oxychloride at* −40°. A solution of the di*iso*propylidene derivative (2 g.) (Grunenberg *et al.*, *J. Amer. Chem. Soc.*, 1938, **60**, 1507) in dry pyridine (10 c.c.) was cooled to −40° and treated with a solution of phosphorus oxychloride (1·1 mols., 0·7 c.c.) in dry pyridine (5 c.c.), also cooled to −40°. The addition was made during 20 minutes to a vigorously stirred solution. The reaction mixture was then treated as already described, and barium 1 : 2-3 : 4-*iso*propylidene D-galactose-6 phosphate was obtained as an amorphous white powder, $[\alpha]_D^{20}$ −17·9° (*c*, 1·6 in water).

(b) *With diphenyl phosphoryl chloride.* 1 : 2-3 : 4-Di*iso*propylidene D-galactose (2 g.) was dissolved in dry pyridine (8 c.c.) cooled to 0°, and treated with diphenyl phosphoryl chloride (2·43 g.) also in solution in dry pyridine (4 c.c.) at 0°. After 10 minutes at 0° the mixture was kept overnight at room temperature, diluted with ether (50 c.c.), and worked up as previously described. (1 : 2-3 : 4-*Di*iso*propylidene* D-*galactose*-6) *diphenyl phosphate* (2·74 g., 76·5%) was obtained as a straw-coloured syrup, n^{17} 1·5150, $[\alpha]_D^{20}$ −30·9° (*c*, 1·4 in ethanol) (Found : C, 58·5; H, 5·9. $C_{24}H_{29}O_9P$ requires C, 58·4; H, 5·9%).

1 : 2-3 : 4-*Di*iso*propylidene* D-*Galactose*-6 *Phosphoric Acid*.—A solution of the above diphenyl 6-phosphate (2·2 g.) in ethanol (60 c.c.) and water (15 c.c.) was boiled under reflux with activated charcoal (2·5 g.) for 10 minutes. After filtration, the solution was shaken with platinum oxide (100 mg.) in an atmosphere of hydrogen at a slight overpressure. Hydrogen (830 c.c., 8·3 mols.) was absorbed during 6 hours. Filtration and evaporation of the solution afforded 1 : 2-3 : 4-di*iso*propylidene D-galactose-6 phosphoric acid (1·2 g.) as a colourless glass, $[\alpha]_D^{20}$ −20·1° (*c*, 1·6 in water). Treatment of this derivative (100 mg.) in methanol (3 c.c.) with acridine (55 mg.), followed by slow evaporation of the

solution, yielded the *acridine* salt as large yellow plates, m. p. 162—164° (Found: P, 6·4; N, 2·7. $C_{12}H_{21}O_9P,C_{13}H_9N$ requires P, 5·9; N, 2·7%).

D-*Galactose*-6 *Phosphoric Acid.*—1 : 2-3 : 4-Di*iso*propylidene D-galactose-6 phosphoric acid (1·2 g.) in solution in water (100 c.c.) containing 5N-sulphuric acid (6 c.c.) was boiled under reflux for 1 hour. Addition of aqueous barium hydroxide (to pH 8) and removal of the insoluble barium residues by filtration afforded a solution to which excess of aqueous neutral lead acetate solution was added. The lead salt was obtained as a gelatinous precipitate which was washed at the centrifuge several times with water. It was decomposed by hydrogen sulphide in the usual manner and D-galactose-6 phosphoric acid was obtained as a colourless glass (0·51 g., 50·9%), $[\alpha]_D^{20}$ +36·5° (*c*, 0·6 in water) (Found: P, 12·0. Calc. for $C_6H_{13}O_9P$: P, 11·9%). Levene and Raymond (*loc. cit.*) gave $[\alpha]_D^{25}$ +24·5° in water for the barium salt.

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