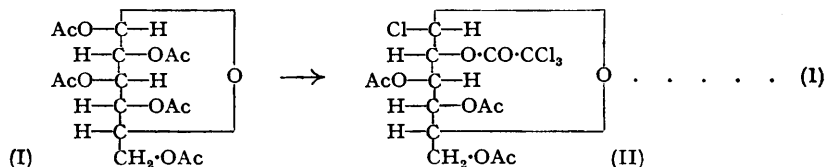


665. The Chlorination of β -D-Glucopyranose Penta-acetate. Abnormal Reactions of Phosphorus Pentachloride.

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The reaction of phosphorus pentachloride with β -D-glucopyranose penta-acetate, to give 3 : 4 : 6-triacetyl 2-trichloroacetyl β -D-glucosyl chloride, is assumed to proceed according to two mechanisms : the normal replacement of acetyl at C₍₁₎, and abnormal substitution into the 2-acetyl group. It is suggested that the latter follows dissociation of the phosphorus pentachloride, the chlorine thus obtained then acting as a substituting agent, probably catalysed by the acetyl chloride also present. The action of thionyl chloride and of phosphorus trichloride on β -D-glucopyranose is described.

3 : 4 : 6-TRIACETYL 2-trichloroacetyl β -D-glucosyl chloride (II) is obtained from β -D-glucopyranose penta-acetate (I) by the action of phosphorus pentachloride (Brigl, *Z. physiol. Chem.*, 1921, **116**, 1; Hickinbottom, *J.*, 1929, 1676). The structure of (II) is beyond doubt because hydrolysis with ammonia in dry ether gave trichloroacetamide and 3 : 4 : 6-triacetyl β -glucosyl chloride which with sulphuryl chloride yielded the 2-chlorosulphonate and with phosphorus pentachloride yielded the 2-chloro-derivative (Brigl, *loc. cit.*).



Reaction (1) presents two striking points : (i) Phosphorus pentachloride appears to react by two different mechanisms : first, replacement of the 1-acetyl group by chlorine, yielding phosphorus oxychloride and acetyl chloride as by-products; secondly, the abnormal chlorination of the 2-acetyl group. (ii) Only the 2-acetyl group appears to be attacked. The latter fact may be related to the configuration at C₍₂₎, and the reactions of the corresponding mannose and galactose derivatives are being examined. The halogen in position 1 may also favour the substitution by its -I effect, although this involves the assumptions that reaction at the 1-position precedes chlorination and that the influence would be sufficiently powerful to make itself felt along the rather long -C-C-O-C- chain. The low maximum yield (45%) suggests that other substitution products are also formed but examination of the final oil had negative results.

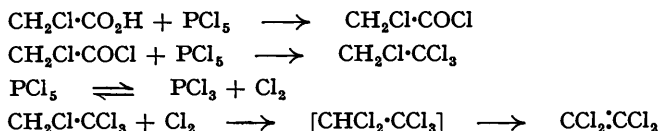
Chlorination by phosphorus pentachloride should lead to phosphorus trichloride as an end-product, and this was isolated in good yield from the reaction mixture. The pentachloride as such has no chlorinating action; this presumably arises by dissociation, $\text{PCl}_5 \rightleftharpoons \text{PCl}_3 + \text{Cl}_2$, which according to Smith and Lombard (*J. Amer. Chem. Soc.*, 1915, **37**, 2060) occurs to an appreciable extent under the reaction conditions used in the present work. The chlorinating action of chlorine on acids, and thus presumably on the acetoxy-group, is catalysed by acid chlorides, as in the Hell-Volhard reaction (cf. Watson and Roberts, *J.*, 1928, 2779; Watson and Gregory, *J.*, 1929, 1373).

The isolation of phosphorus trichloride favours this hypothesis, and it has been found that β -D-glucopyranose penta-acetate is unaffected by the trichloride. Further, removal of the catalysts (phosphorus trichloride and acetyl chloride) from the reaction mixture by conducting the reaction without a reflux condenser very greatly reduced the formation of trichloroacetyl derivative, whereas addition of a little acetyl chloride before or during the reaction accelerates it (although it does not affect the yield).

Finally, thionyl chloride, which resembles phosphorus pentachloride except that it does not dissociate to yield chlorine under the reaction conditions under consideration (Schenk, *Z. anorg. Chem.*, 1937, **233**, 385), does not afford any trichloroacetyl derivative from the glucose penta-acetate : it affords α -acetochloroglucose (with inversion) and an oil which also affords

tetra-acetyl methyl- α -D-glucoside on treatment with methanol and silver carbonate, and is probably a modified β -acetochloroglucose.

"Abnormal" (chlorinating) actions by phosphorus pentachloride have already been recorded in various cases. An excess of the boiling reagent slowly chlorinates acetyl chloride (Michael, *J. pr. Chem.*, 1887, **35**, 95; Friederici, *Ber.*, 1878, **11**, 1971), and with chloroacetic acid yields tetrachloroethylene and, probably, tetra- and penta-chloroethane (Michael, *loc. cit.*). Trichlorovinyl phenyl ether is obtained from phenyl acetate, resorcinol bistrichloroacetyl ether from resorcinol diacetate, and 1:2-dichlorobut-1-enyl phenyl ether from phenyl propionate (*idem, loc. cit.*). A possible mechanism for the formation of the chlorovinyl derivatives is exemplified by the following scheme for the formation of tetrachloroethylene:



Again, it is well known that phosphorus pentachloride reacts with many aldehydes and ketones. If the hydrocarbon radicals are simple, replacement of oxygen by chlorine takes place (*e.g.*, $\text{COMe}_2 \longrightarrow \text{CMe}_2\text{Cl}_2$). Frequently unsaturated monochloro-compounds, apparently formed by the loss of hydrogen chloride from the expected dichloro-compounds, are found among the products (*cf.* above). If the hydrocarbon radicals are complex, the pentachloride sometimes replaces an α -hydrogen atom and a chloro-ketone results (*e.g.*, $\text{COPr}^i_2 \longrightarrow \text{Pr}^i\text{CO}\cdot\text{CMe}_2\text{Cl}$). An excess of the halide has no effect on the carbonyl group (Gilman, "Organic Chemistry," Vol. I, p. 665). This suggests that the hydrocarbon radical is the influencing factor only insofar as the boiling point of the ketone increases with the complexity of the radical, so that the higher is the temperature of the boiling mixture the greater is the dissociation of phosphorus pentachloride. This is supported by the fact that phosphorus pentabromide dissociates more readily than the pentachloride and gives the α -bromo-compound in all cases (Gilman, *op. cit.*). This explanation is more suitable than that which assumes that the reactivity of the carbonyl group is affected by the attached hydrocarbon residues so considerably as to alter the course of the reaction.

EXPERIMENTAL.

All m. p.s are uncorrected.

For the chlorine determinations, advantage was taken of the easily hydrolysable nature of the compounds. Before carrying out the determinations, the method was checked on the known α -acetobromoglucose, twice recrystallised from *n*-amyl alcohol (Found: Br, 19.1. Calc. for $\text{C}_{14}\text{H}_{19}\text{O}_6\text{Br}$: Br, 19.45%).

A known weight of the compound was dissolved in methanol (free from halogen), and $\sim 2N$ -sodium hydroxide (AnalaR) methanol-water (1:1; v/v) was added. The whole was shaken occasionally during 2 days, after which the solution was exactly neutralized with nitric acid (AnalaR) to phenolphthalein. The solution thus obtained was rapidly titrated against standard silver nitrate (Mohr's method).

The acetyl groups were determined by hydrolysis with standard alkali (back-titration of the excess).

β -Penta-acetyl Glucose.—The method given by Vogel ("Practical organic chemistry," 1st edn., p. 439) was used. In all the following reactions, the crude compound, dried on a porous plate for about a month was found to be suitable.

3:4:6-Triacetyl 2-Trichloroacetyl β -Glucosyl Chloride.—(a) β -Penta-acetyl glucose (39 g.) and phosphorus pentachloride (104 g.) were heated on the water-bath under reflux (calcium chloride guard-tube), the mixture soon becoming liquid. Heating was continued till the evolution of hydrogen chloride was complete (2.5 hours). The liquid was distilled in a vacuum first at about 50°, then at 100° for a short period. The distillate (A) was collected. The residue was allowed to cool, covered with sodium-dried ether (50 ml.), shaken vigorously, and set aside, preferably in the ice-box. The crystals were filtered off and washed with a small amount of dry ether, and the filtrate (B) was put aside. The solid was washed with ice-cold methanol (25 ml.) and recrystallized from dry ether, yielding long white needles (14 g.), m. p. 140° (Brigl, *loc. cit.*, gives 142°).

These on hydrolysis with ammonia in dry ether gave 3:4:6-triacetyl β -glucosyl chloride, m. p. 156—158° (Brigl, *loc. cit.*; Winslow, Thesis, 1947).

(b) The preparation was carried out without a reflux condenser but using a calcium chloride guard tube. After 2.5 hours a dark brown oil remained. Occasionally, tar formation took place. The oil

were covered with a small amount of ether and shaken as before, then set aside. A very small amount of crystals appeared overnight, and these were treated as before.

In one case, acetyl chloride (10 c.c.) was added to the β -penta-acetyl glucose, and then phosphorus pentachloride was added. An uncontrollable reaction set in at once at room temperature and when it subsided a dark brown tar was left. When acetyl chloride was added through the condenser after the addition of phosphorus pentachloride, the reaction was complete in less than 2 hours.

Fractionation of the vacuum-distillate (A). Fractionation of (A) gave fractions: (i) b. p. 52—58°, (ii) b. p. 75—77°, and (iii) b. p. 106—107°. Refractionation of each showed (i) to be acetyl chloride, b. p. 55°, (ii) to be phosphorus trichloride, b. p. 76°, d 1.613, and (iii) to be phosphorus oxychloride, b. p. 107°. These were obtained in the approx. molecular ratio of 1 : 3 : 1.

Examination of the filtrate (B). The oil was poured with vigorous stirring into ice-water, extracted with ether, washed with dilute sodium hydrogen carbonate solution, then again with water, and dried (CaCl_2). The ether was removed and the oil left extracted with light petroleum (b. p. 60—80°). Decantation and cooling yielded fine needles, m. p. 130—133°, recrystallizing from dry ether as long needles, m. p. 140° undepressed when mixed with an original sample of 3 : 4 : 6-triacetyl 2-trichloroacetyl β -glucosyl chloride (Found: Cl, 30.0. Calc. for $\text{C}_{14}\text{H}_{18}\text{O}_9\text{Cl}$: Cl, 30.2%). The total yield after repeated extraction was 3 g.

The small amount of oil left was dissolved in methanol (40 ml.) and freshly prepared silver carbonate (2 g.) was added. The whole was shaken occasionally for 24 hours. Filtration and evaporation gave only an unidentified white oil.

Action of Phosphorus Trichloride on β -Penta-acetyl Glucose.—To β -penta-acetyl glucose (40 g.) was added phosphorus trichloride (44 c.c.), and the mixture was refluxed. The solid penta-acetate dissolved but the whole set to a solid mass on cooling. After 2.5 hours' boiling, the liquid fraction was distilled off at atmospheric pressure and was found to be unchanged trichloride (42 c.c., 95.4%). The solid, washed with ice-water and recrystallized from methyl, ethyl, or amyl alcohol or ether, had m. p. 130°, undepressed when mixed with authentic specimens of β -penta-acetyl glucose (Found: Ac, 54.9. Calc. for $\text{C}_{18}\text{H}_{22}\text{O}_{11}$: Ac, 55.1%). The amount of solid recovered after the reaction was almost 99%. The same result was obtained when the mixture was refluxed for 4 hours.

Action of Thionyl Chloride on β -Penta-acetyl Glucose.—To β -penta-acetyl glucose (39 g.), redistilled thionyl chloride (67 g.) was added. The mixture was then heated for 2.5 hours on the water-bath. Excess of thionyl chloride was removed in a vacuum, and the residue cooled, shaken with dry ether (50 c.c.), and set aside overnight. Only a small amount of dark impurities separated. The filtrate was diluted with ether, washed successively with ice-water, dilute sodium hydrogen carbonate solution, and water, and dried (CaCl_2). The ether was evaporated off and a yellowish brown oil was left. This was extracted with boiling light petroleum (b. p. 40—60°), and the hot supernatant liquid decanted. On cooling, a white oil (C) settled out. The clear, cold solution was decanted, scratched and set aside. Fine needle-like crystals appeared (2.6 g.) which were filtered off and dried (vacuum; soda-lime-phosphoric oxide) (m. p. 63—65°). These, after two recrystallizations from light petroleum (b. p. 40—50°), melted at 73° alone or mixed with α -acetochloroglucose (Found: Cl, 9.2. Calc. for $\text{C}_{14}\text{H}_{18}\text{O}_9\text{Cl}$: Cl, 9.7%). Dissolution in cold methanol, addition of silver carbonate, shaking occasionally during 24 hours, then filtration, evaporation, and crystallization from aqueous alcohol, gave tetra-acetyl methyl- β -D-glucoside, as long white needles, m. p. 105—106°. The oil (C) gave, on similar treatment, tetra-acetyl methyl- α -D-glucoside as needles, m. p. 100—101°. The initial crystals, m. p. 63—65°, were probably a mixture of the α - and the β -form, preponderating by the α -form. The total yield of α -acetochloroglucose after repeated extraction was 5 g., and of β -acetochloroglucose (calculated from the tetra-acetyl methylglucoside) 3 g. The pale brown oil left after complete extraction of acetochloroglucose could not be characterised by its methylglucoside since extensive hydrolysis occurred (Fehling's solution reduced easily), and only a small yield of a high-melting powder was obtained.

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