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MECHANISM OF THE FORMATION OF LEVOGLUCOSAN

MARINUS P. BARDOLPH[1,2] AND GEORGE H. COLEMAN[3]

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Montgomery, Richtmyer, and Hudson (1, 2) have shown that many phenyl β-D-glycosides are converted to 1,6-anhydro sugars under alkaline treatment, while the corresponding α-isomers are either unaffected or degraded to tars. In the case of the single exception, that of the conversion of phenyl α-D-galactoside to D-galactosan <1,5> β <1,6>, the reaction time was 2,688 hours as compared with eight or nine hours for most of the β-glycosides studied. Subsequently, McCloskey and Coleman (3) proposed a double inversion mechanism to explain the retention of configuration of the number one carbon atom. The reaction is pictured as proceeding through two steps. First, the inversion of carbon one with the simultaneous removal of the phenoxyl group and the formation of a 1,2-anhydro sugar; and second, the addition of the hydroxyl group on carbon six to the ethylene oxide ring when it is sterically possible. When the second step is not sterically possible, as in the case of 1,2-anhydromannose, tars are formed. To test this mechanism they treated phenyl tetramethyl-β-D-glucoside, phenyl 2,3-dimethyl-β-D-glucoside, and phenyl 3-methyl-β-D-glucoside with hot alkali. The first two compounds were recovered unchanged, presumably because the formation of the 1,2-anhydro ring is prevented by the methoxyl group on carbon two. The third compound, in which the number two hydroxyl group is free, reacted, yielding the theoretical amount of phenol and an unidentified sirup. The work with phenyl 3-methyl-β-D-glucoside has been repeated and will be described in a later paragraph. In the further study of this mechanism the present authors have made the following observations.

Hickinbottom (4) has shown that Brigl's anhydride (3,4,6-triacetyl-1,2-anhydro-D-glucose) is readily attacked at room temperature by alcohols alone, yielding the corresponding β-glucosides. In view of this, treatment of phenyl β-D-glucoside with hot alcoholic alkali should produce either the glucoside or levoglucosan. It was found that the latter product was formed in good yield in hot *n*-propanolic, ethanolic, and methanolic alkali. Either sodium hydroxide or the corresponding sodium alkoxide may be used with the same effect. Thus, if the proposed mechanism is correct, the primary hydroxyl group on carbon six rather than the solvent adds to the ethylene oxide ring.

Since Brigl's anhydride is the triacetyl derivative of the proposed intermediate, its use in testing the validity of the mechanism is at once apparent. Accordingly, Brigl's anhydride was subjected to treatment with aqueous alkali under the same conditions used for phenyl β-D-glucoside. The result was the formation of levoglucosan, isolated as the triacetate, in 25% yield. It is known

[1] From the Ph.D. Thesis of Marinus P. Bardolph.

[2] Present address: Department of Chemistry, University of Omaha, Omaha, Nebraska.

[3] Present address: Institute of Textile Technology, Charlottesville, Virginia.

that Brigl's anhydride reacts with water to give 3,4,6-triacetyl-D-glucose. It seems safe then to conclude that the alkali stabilizes the ring sufficiently to permit deacetylation to occur prior to the reaction of the hydroxyl group on the number six carbon atom with the 1,2-anhydro ring. That the 1,2-anhydro sugar can act as an intermediate in the formation of levoglucosan from phenyl β-D-glucoside now seems quite probable. This is consistent with the contention of Ohle and Wilcke (5) that methyl 2,3-anhydroalloside, in which the ethylene oxide ring is *trans* with respect to the primary hydroxyl group, is an intermediate in the formation of methyl 3,6-anhydroglucoside. They showed that when methyl 2-acetyl-3,5,6-tritosylglucofuranoside, from which the tosyl groups at positions five and six are difficult to remove, is treated with alkali, the product is methyl 2,3-anhydro-5,6-ditosylallofuranoside. But when methyl 3-tosyl-2,5,6-triacetylglucofuranoside, from which all three acetyl groups are easily removed, is treated with alkali, the product is methyl 3,6-anhydroglucofuranoside. However, when 3-tosyl-5,6-diacetyl-1,2-isopropylidene-D-glucose, in which the formation of a 2,3-anhydro ring is hindered by the isopropylidene group, is so treated, the only effect is deacetylation at the five and six positions. No anhydro ring is formed.

When the alkaline treatment of Brigl's anhydride was carried out in ethyl alcohol, the result was likewise the formation of levoglucosan, in 30% yield. This is consistent with our finding that phenyl β-D-glucoside is converted to levoglucosan under the action of hot ethanolic alkali.

Phenyl 3-methyltriacetyl-β-D-glucoside was treated with 2.6 *N* ethanolic alkali. Upon benzoylation of the sirupy product, a crystalline compound was obtained. Simultaneous debenzoylation and methylation of this compound by the Haworth method yielded trimethyllevoglucosan. Thus, the compound was the dibenzoyl derivative of 3-methyllevoglucosan.

The synthesis of phenyl 2-methyl-β-D-glucoside was accomplished. This compound was unaffected by boiling for forty-eight hours in aqueous alkali. A 92% recovery of the original compound was obtained.

EXPERIMENTAL

Action of alcoholic alkali on phenyl β-D-glucoside. Phenyl β-D-glucoside (2 g.) was added to 100 ml. of 2.6 *N* sodium hydroxide or sodium ethoxide in ethyl alcohol, and refluxed for forty hours. At the end of this time the solution was neutralized to methyl orange with 4 *N* sulfuric acid. The salts were separated by filtration, and the alcoholic solution evaporated under reduced pressure to a sirup. This sirup was acetylated by adding 12 ml. of acetic anhydride and heating at 100° for one hour. The excess acetic anhydride was decomposed with water and the solution was evaporated to dryness under reduced pressure. The residue was taken up with 25 ml. of chloroform. After washing with two 5-ml. portions of water, the chloroform was removed by distillation under reduced pressure. The residue (triacetyllevoglucosan) was crystallized from a small amount of ethyl alcohol. Yield, 1.3 g. (60%). The identity of the product was confirmed by a mixed melting point with an authentic sample of triacetyllevoglucosan.

When methyl alcohol was substituted for ethyl alcohol, using either sodium hydroxide or sodium methoxide in a 1.3 *N* solution, the mixture was heated for three days in an oven set at 98°. The yield was 67%.

When 1.3 *N* sodium hydroxide or sodium *n*-propoxide in *n*-propyl alcohol was used, the mixture was heated at reflux temperature for 24 hours. The yield was 60%.

Action of aqueous alkali on Brigl's anhydride. Two grams of 3,4,6-triacetyl-1,2-anhydro-D-glucose (4, 6) was heated in 100 ml. of 1.3 *N* aqueous sodium hydroxide at 90° in an oil-bath for twenty-four hours. The solution was neutralized to methyl orange with 4 *N* sulfuric acid and evaporated to dryness under reduced pressure. The salts were extracted with hot ethyl alcohol. From this point on, the procedure was the same as for the extraction of triacetyllevoglucosan from the alkaline treatment of phenyl β-D-glucoside. The yield of triacetyllevoglucosan was 0.5 g. (25%). The identity of the product was confirmed by a mixed melting point.

Action of ethanolic alkali on Brigl's anhydride. Four grams of 3,4,6-triacetyl-1,2-anhydro-D-glucose was heated in 200 ml. of 2.6 *N* sodium hydroxide in ethyl alcohol at reflux temperature for twenty-four hours. The solution was neutralized to methyl orange with 4 *N* sulfuric acid and evaporated to dryness under reduced pressure. The salts were extracted with hot ethyl alcohol. From this point on, the procedure was the same as for the preceding experiment. The yield of triacetyllevoglucosan was 1.2 g. (30%). The identity of the product was confirmed by a mixed melting point.

3-Methyl-2,4-dibenzoyllevoglucosan. A mixture of 3 g. of phenyl 3-methyl-triacetyl-β-D-glucoside (7) in 100 ml. of 2.6 *N* ethanolic sodium hydroxide was refluxed for forty hours. After neutralizing the solution and evaporating the solvent, as above, the remaining sirup was benzoylated in 13 ml. of anhydrous pyridine with 11 ml. of benzoyl chloride. The mixture was allowed to stand in an oven at 60° for two hours, and then at room temperature overnight. The next day the mixture was triturated with enough water to decompose the excess benzoyl chloride. The mixture was extracted with 80 ml. of chloroform followed by 25 ml. of water. The aqueous extract was extracted with 25 ml. of chloroform, and the chloroform extracts were combined. The chloroform solution was washed successively with 25 ml. of 6 *N* hydrochloric acid, 25 ml. of 4 *N* sodium hydroxide, and 25 ml. of water. The solvent was removed by distillation, leaving a sirup which was crystallized from glacial acetic acid. The yield was 2.4 g. (82%). After several recrystallizations from glacial acetic acid, the melting point was 134–136° (corr.)

$[\alpha]_D^{25}$ −36.0° (*c*, 1.44, USP chloroform).

Anal. Calc'd for $C_{21}H_{20}O_7$: C, 65.61; H, 5.25; OCH_3, 8.08.

Found: C, 65.57; H, 5.40; OCH_3, 8.19.

Methylation of 3-methyl-2,4-dibenzoyllevoglucosan. A mixture of 5 g. of 3-methyl-2,4-dibenzoyllevoglucosan and 65 ml. of acetone was placed in a 3-necked flask fitted with two burettes, a stirrer, and a tube arranged for downward distillation. While heating the flask in a water-bath at 50°, 33 ml. of methyl sulfate and 36 ml. of 50% sodium hydroxide were added from the burettes dropwise in ten portions at 10-minute intervals. After the last addition the temperature was raised to 75° and maintained for one hour. Then 50 ml. of water was added, and the temperature kept at 75° another hour. After cooling, the salts were removed by filtration, and the filtrate was extracted with four equal volumes of chloroform. The chloroform solution was evaporated to a sirup. Distillation of the sirup at 4 mm. (107°) yielded 1.7 g. (64%) of trimethyllevoglucosan. The distillate crystallized immediately upon inoculation with a seed crystal of trimethyllevoglucosan. The identity of the product was confirmed by a mixed melting point with an authentic sample.

Action of alkali on phenyl 2-methyl-β-D-glucoside. A solution of 2 g. of phenyl 2-methyl-β-D-glucoside in 100 ml. of 2.6 *N* aqueous potassium hydroxide was refluxed for forty-eight hours. The solution was neutralized to methyl orange with sulfuric acid and evaporated to dryness under reduced pressure. The residue was extracted with hot ethyl alcohol and evaporated to dryness. This residue was crystallized from a small amount of water and found to be identical with the original glucoside. The recovery was 92%.

2-Methyl-D-glucose. (8, 9). A mixture of 2.5 l. of water, 100 g. of mercuric chloride, and 125 g. of cadmium carbonate was heated to 50°. Under vigorous stirring, 50 g. of 2-methylglucose diethyl mercaptal was added. The stirring was maintained at 50° for three hours. The solid was then removed by filtration and washed well with water. Then 65 g. of silver carbonate was added to the aqueous solution and the suspension was stirred for two hours at room temperature. After the solid was removed by filtration, the filtrate was saturated

with hydrogen sulfide and again filtered through charcoal. Upon evaporation of the solvent a heavy sirup remained.

2-Methyltetrabenzoyl-D-glucose. The dry sirupy 2-methyl-D-glucose was benzoylated in the manner described in the paragraph headed "3-methyl-2,4-dibenzoyllevoglucosan." The proportions were: 125 ml. of anhydrous pyridine, 100 ml. of benzoyl chloride, 650 ml. of chloroform, and 220 ml. of water, etc. The product was not crystallized.

Phenyl 2-methyltribenzoyl-β-D-glucoside. The dried 2-methyltetrabenzoyl-D-glucose sirup was placed in a flask along with 185 ml. of a solution of anhydrous hydrogen bromide in glacial acetic acid (saturated at 0°), 510 ml. of dry benzene, and 140 ml. of dry ether, and allowed to stand overnight. The next day the solution was poured into ice, washed with a saturated solution of potassium bicarbonate and then dried with powdered calcium chloride. The solution was filtered and put into a flask containing 370 g. of phenol and 185 g. of powdered Drierite. After stirring the solution for about fifteen minutes, 75 g. of powdered silver carbonate was added and the mixture was stirred for 24 hours, with exclusion of moisture. The salts were separated by filtration and the solution was washed with sufficient alkali to remove the unchanged phenol, and then with water. This solution was evaporated to a sirup.

Phenyl 2-methyl-β-D-glucoside. The sirupy phenyl 2-methyltribenzoyl-β-D-glucoside was boiled for one minute in a solution of 375 ml. of methyl alcohol and 150 ml. of dioxane to which 15 ml. of a 10% solution of potassium methoxide was added. About 1 liter of water was added and the mixture was distilled until the volume of the residue was about 150 ml. Enough methyl alcohol was added to the sirup and water to effect complete solution on boiling. To the hot solution was added a solution of 23 g. of potassium hydroxide in 25 ml. of water. This solution was allowed to cool and stand overnight. The next day the solution was neutralized to litmus with 4 *N* sulfuric acid. The salts were removed by filtration and washed with hot methyl alcohol. This solution was evaporated to dryness and the residue was taken up with about a liter of water. The aqueous solution was acidified with sulfuric acid so that it was just acid to Bromophenol Blue. The precipitated benzoic acid was removed by filtration, and the last traces removed by extraction with ether. Enough potassium hydroxide was then added to the solution to render it alkaline to Bromophenol Blue. The solution was evaporated to a sirup, which was taken up with a small amount of hot water. On cooling, short needles of phenyl 2-methyl-β-D-glucoside formed. After several recrystallizations from Dimethyl Cellosolve, the melting point was 167–168° (corr.). Yield, 7 g., $[\alpha]_D^{25}$ −63.0° (*c*, 1, 95% alcohol).

Anal. Calc'd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71; OCH_3, 11.48.
Found: C, 57.93; H, 6.70; OCH_3, 12.48.

SUMMARY

Treatment of 3,4,6-triacetyl-1,2-anhydroglucose with hot alkali led to the formation of levoglucosan, showing that a 1,2-anhydrosugar is a possible intermediate in the conversion of phenyl β-D-glucoside to levoglucosan.

The action of hot alcoholic alkali on phenyl β-D-glucoside was shown to be as effective as aqueous alkali.

The dibenzoyl derivative of 3-methyllevoglucosan was prepared from phenyl 3-methyl-β-D-glucoside.

The preparation of phenyl 2-methyl-β-D-glucoside was accomplished. It was not affected by hot alkali.

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CHARLOTTESVILLE, VIRGINIA

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