Phenyl α- and β-D-Allopyranosides and Their Behavior toward Aqueous Alkali

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Earlier studies in this Laboratory[1] have shown that phenyl β-D-glucopyranoside, the configurationally related phenyl 3-deoxy-β-D-*ribo*-hexopyranoside, phenyl β-D-galactopyranoside, and phenyl β-D-mannopyranoside were converted readily by hot aqueous alkali into the corresponding 1,6-anhydro-β-D-hexopyranoses. The anomeric glycosides behaved differently, for phenyl α-D-glucopyranoside and phenyl 3-deoxy-α-D-*ribo*-hexopyranoside appeared to be completely stable toward alkali; phenyl α-D-galactopyranoside was attacked slowly (sixteen weeks), and the product was the same 1,6-anhydro-β-D-galactopyranose that was obtained from the β-anomer (nine hours)[2]; phenyl α-D-mannopyranoside was attacked readily, but most of the material underwent extensive destruction, and only a very small amount of 1,6-anhydro-β-D-mannopyranose could be isolated.

In continuing the study of the behavior of anomeric pairs of phenyl glycosides toward aqueous alkali, we have prepared the anomeric phenyl allopyranoside tetraacetates by suitable modifications of the Helferich and Schmitz-Hillebrecht synthesis,[3] and then deacetylated to obtain the free glycosides. When phenyl β-D-allopyranoside was heated with 0.6*N* aqueous sodium hydroxide, it was transformed readily into the known 1,6-anhydro-β-D-allopyranose.[4] It thus behaved like phenyl β-D-glucopyranoside and phenyl β-D-galactopyranoside; all three of these have the hydroxyl group at C-2 *trans* to the β-D-phenoxyl group at C-1. For such an arrangement, McCloskey and Coleman[5] proposed a mechanism that was supported by the subsequent experimental work of Bardolph and Coleman[6] and of Dyfverman and Lindberg.[7] They suggested that the reaction consisted of two steps with a double Walden inversion, involving a 1,2-anhydrohexopyranose as an intermediate.[8] The behavior of the anomeric phenyl α-D-allopyranoside, however, with its phenoxyl and hydroxyl groups at C-1 and C-2 in a *cis* position, stands in contrast to that of the corresponding glucoside (stable) and galactoside (converted slowly into the 1,6-anhydride). It is attacked readily by hot aqueous alkali with much decomposition, and no 1,6-anhydro-β-D-allopyranose could be detected, even by paper chromatography.

EXPERIMENTAL

Penta-O-acetyl-β-D-allopyranose. Acetylation of 10 g. of D-allose[4] with acetic anhydride and fused sodium acetate yielded 15.4 g. (71%) of the β-pentaacetate. Seed crystals were obtained by slow evaporation of an aqueous acetone solution of the sirup. The pentaacetate, after two recrystallizations from aqueous ethanol, melted at 96–98° and showed $[\alpha]_D^{20}$ −14.8° in chloroform (*c*, 1), in good agreement with the m.p. 97–100° and $[\alpha]_D$ −14.6° recorded by Lemieux and Brice.[9]

Anal. (not previously reported) Calcd. for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.68; CH_3CO, 55.1. Found: C, 49.10; H, 5.66; CH_3CO, 54.5.

Phenyl β-D-allopyranoside. A mixture of 10.7 g. of penta-*O*-acetyl-β-D-allopyranose, 10 g. of phenol, and 0.6 g. of *p*-toluenesulfonic acid monohydrate was fused and then heated at 75–80° in a water pump vacuum for 1.25 hr. The dark brown product was dissolved in 200 ml. of chloroform, and the phenol and most of the color were removed by two washings with 3% aqueous sodium hydroxide. The chloroform solution was washed once with water, dried with sodium sulfate, filtered with carbon, and concentrated to a sirup (10.5 g.; theory, 11.6 g.). The sirup could not be induced to crystallize and so was deacetylated with a catalytic amount of methanolic sodium methoxide. The resulting crystalline product weighed 4.8 g. (68% over-all yield from the pentaacetate). Two recrystallizations from hot water followed by four recrystallizations from methanol afforded 190 mg. of phenyl β-D-allopyranoside as rectangular prisms with m.p. 176–178° and $[\alpha]_D^{20}$ −54.0° in pyridine (*c*, 1).

Anal. Calcd. for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.39; H, 6.43.

Phenyl tetra-O-acetyl-β-D-allopyranoside. Acetylation of 100 mg. of phenyl β-D-allopyranoside with acetic anhydride and pyridine yielded 145 mg. (88%) of phenyl tetra-*O*-acetyl-β-D-allopyranoside. It was recrystallized from aqueous ethanol and then from chloroform-pentane; stout prisms, m.p. 121–122° and $[\alpha]_D^{20}$ −26.7° in chloroform (*c*, 1).

Anal. Calcd. for $C_{20}H_{24}O_{10}$: C, 56.60; H, 5.70; CH_3CO, 40.6. Found: C, 56.60; H, 5.60; CH_3CO, 40.0.

Phenyl tetra-O-acetyl-α-D-allopyranoside. When the condensation of penta-*O*-acetyl-β-D-allopyranose (5 g.) with

(1) E. M. Montgomery, N. K. Richtmyer, and C. S. Hudson, *J. Am. Chem. Soc.*, **64**, 1483 (1942); **65**, 3, 1848 (1943); J. W. Pratt and N. K. Richtmyer, *J. Am. Chem. Soc.*, **79**, 2597 (1957).

(2) E. M. Montgomery, N. K. Richtmyer, and C. S. Hudson [*J. Org. Chem.*, **10**, 194 (1945)] reported that the compound presumed to be 1,3-anhydro-β-D-galactopyranose, because of its stability toward periodate [R. M. Hann and C. S. Hudson, *J. Am. Chem. Soc.*, **63**, 2241 (1941)], could not be an intermediate in the alkaline degradation of either phenyl α- or β-D-galactoside. The structure of that anhydride was proved later by B. H. Alexander, R. J. Dimler, and C. L. Mehltretter [*J. Am. Chem. Soc.*, **7** , 4658 (1951)] to be 1,6-anhydro-α-D-galactofuranose.

(3) B. Helferich and E. Schmitz-Hillebrecht, *Ber.*, **66**, 378 (1933); E. M. Montgomery, N. K. Richtmyer, and C. S. Hudson, *J. Am. Chem. Soc.*, **64**, 690 (1942).

(4) J. W. Pratt and N. K. Richtmyer, *J. Am. Chem. Soc.*, **77**, 1906 (1955).

(5) C. M. McCloskey and G. H. Coleman, *J. Org. Chem.*, **10**, 184 (1945).

(6) M. P. Bardolph and G. H. Coleman, *J. Org. Chem.*, **15**, 169 (1950).

(7) A. Dyfverman and B. Lindberg, *Acta Chem. Scand.*, **4**, 878 (1950).

(8) For a comprehensive review of this and alternative mechanisms, see C. E. Ballou, *Advances in Carbohydrate Chem.*, **9**, 59 (1954); *cf.* B. Capon and W. G. Overend, *Advances in Carbohydrate Chem.*, **15**, 38 (1960).

(9) R. U. Lemieux and C. Brice, *Can. J. Chem.*, **34**, 1006 (1956).

phenol was repeated, using *p*-toluenesulfonic acid as catalyst, the washed and dried chloroform solution showed $[\alpha]_D^{20}$ +44° calculated as phenyl tetra-*O*-acetyl-D-allopyranoside. The chloroform was removed *in vacuo*, and the resulting sirup was dissolved in ethanol, diluted with water, and inoculated with the β-anomer. The 1.3 g. of sticky crystals thus obtained consisted principally of the β-anomer as shown by the m.p. 110–120° obtained after one recrystallization from chloroform-pentane. The aqueous alcohol mother liquor deposited an additional 2.2 g. of product (total yield 3.5 g., 64%) consisting principally of the α-anomer. This, after recrystallization once from aqueous ethanol and thrice from chloroform-pentane, gave 160 mg. of the pure phenyl tetra-*O*-acetyl-α-D-allopyranoside as elongated prisms, m.p. 97–98°, and $[\alpha]_D^{20}$ +160° in chloroform (*c*, 1).

Anal. Calcd. for $C_{20}H_{24}O_{10}$: C, 56.60; H, 5.70; CH_3CO, 40.6. Found: C, 56.76; H, 5.77; CH_3CO, 40.3.

When fused zinc chloride was used as catalyst, the chloroform solution showed $[\alpha]_D^{20}$ +64°, and the first three fractions of crystals (2.8 g.) consisted principally of the α-anomer while the fourth fraction (0.3 g.) consisted principally of the β-anomer; the total yield was 3.1 g. (73%) from 3.9 g. of the β-D-allose pentaacetate.

Phenyl α-D-allopyranoside. A 526-mg. sample of phenyl tetra-*O*-acetyl-α-D-allopyranoside was deacetylated catalytically with methanolic sodium methoxide. The product was a sirup; on solution in absolute ethanol and dilution with pentane a waxy substance was produced. Fine needles were finally obtained by dissolving a small sample in 95% ethanol and allowing the solution to concentrate slowly at room temperature. The main fraction was then crystallized from ethanol-pentane; weight 219 mg. (69%); m.p. 102–106°, unchanged by recrystallization from acetone-pentane. The observed rotation $[\alpha]_D^{20}$ + 179° in water (*c*, 1) was probably about 5% low because the crystalline material appears to be solvated to a variable degree; thus, samples of the air-dried product lost 3.5 and 6.2% when dried at 70° in a high vacuum for 2 hr. and 1 hr., respectively. The samples melted during the drying and were then analyzed.

Anal. Calcd. for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.47, 56.36; H, 6.33; 6.30.

Transformation of phenyl β-D-allopyranoside into 1,6-anhydro-β-D-allopyranose by alkali. A 395-mg. sample of phenyl β-D-allopyranoside was refluxed with 40 ml. of 0.6*N* aqueous sodium hydroxide in a silver flask for 8 hr.; the solution had then reached a constant rotation $[\alpha]_D^{20}$ −93° calculated as 1,6-anhydro-β-D-allopyranose, which is known to show $[\alpha]_D^{20}$ −75.8° in water.[4] The solution was deionized, extracted with chloroform to remove phenol, and concentrated to a sirup (150 mg.; theory 250 mg.). The sirup, when dissolved in absolute ethanol and inoculated, deposited 136 mg. (54%) of 1,6-anhydro-β-D-allopyranose, identified by melting point, mixed melting point, and paper chromatography in three different solvents.

Reaction of phenyl α-D-allopyranoside with alkali. When 90 mg. of phenyl α-D-allopyranoside in 30 ml. of 0.8*N* aqueous sodium hydroxide was refluxed the solution developed color slowly, and the rotation dropped from $[\alpha]_D^{20}$ +186° to +151° in 7 hr. At the end of an additional 6 hr. the solution was so dark that the rotation could no longer be read in the polarimeter, and consequently it was decolorized with carbon. The colorless solution was concentrated and its rotation found to be nearly zero; neither phenyl α-D-allopyranoside nor 1,6-anhydro-β-D-allopyranose could be detected by paper chromatography. The decolorizing carbon was extracted with hot acetone and a total of 35 mg. of sirup recovered; from this, 23 mg. of unchanged crystalline phenyl α-D-allopyranoside was obtained, but again no anhydro compound could be detected by paper chromatography.

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Halogenated Progesterones. A Preferential Reaction of Perchloryl Fluoride

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Quite recently various analogs of progesterone having biological activity greatly enhanced over that of the parent hormone have been prepared.[2] Our efforts in this area were initially directed toward the preparation of representative 17α-fluoroprogesterone derivatives. These compounds were potentially of interest, since 21-fluoroprogesterone is reported to be two to four times more active than progesterone.[3]

It was our intention to use the recently discovered[4] reaction of perchloryl fluoride with enol acetates for the preparation of the 17α-fluoro analogs. We initially investigated the reaction of this reagent with 3,20-diacetoxy-3,5,17(20)-pregnatriene (I).[5] The ability of this bisenol acetate to react with cationoid reagents at both C-6 and C-17 was demonstrated by treatment of I with sodium hypochlorite to give the known 6β,17α-dichloroprogesterone (II)[6] in 74% yield. When the bisenol acetate I was treated with perchloryl fluoride in dioxane for three and one-half hours, an amorphous product resulted. The infrared spectrum of this material had bands ascribable to a Δ^4-3-ketone, but it also exhibited strong bands at 5.72 and 8.20 μ, indicative of an enol acetate. Notable by its complete absence was a 20-carbonyl band in the 5.85 μ region. Accordingly, the product was regarded as being essentially 20 - acetoxy - 6 β- fluoro - 4,17(20) - pregnadiene - 3 - one (III).[7] Without purification III was treated successively with *N*-bromosuccinimide and hydrogen chloride in acetic acid to give the

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