

CCCLXIII.—*Syntheses of Glucosides. Part VI. The Preparation of β -Glucosides of Phenols.*

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THE most general method hitherto available for the preparation of β -glucosides of phenolic compounds depends on the interaction of an alkali salt of the phenol and *O*-tetra-acetyl- α -glucosidyl bromide. The procedure is somewhat tedious and the yields, which vary with the nature of the phenol, are generally poor. Moreover, the method is frequently inapplicable to partly acylated derivatives of polyhydric phenols. By the interaction of *O*-tetra-acetyl- α -glucosidyl bromide and hydroxyanthraquinones in the presence of silver oxide and quinoline, Takahashi (*J. Pharm. Soc. Japan*, 1925, **525**, 4) obtained the corresponding glucosidoxyanthraquinones. A modification of this method has been extended to other members of this

series by Zemplén and Müller (*Ber.*, 1929, **62**, 2107) and by Müller (*ibid.*, p. 2793) (compare Jones and Robertson, this vol., p. 1708). This reaction has now been applied to the preparation of phenylglucosides and appears to be a general one. In view of the economy both in time and in materials it seems to us that this procedure is superior to those described by previous authors (for references, see Armstrong, "The Simple Carbohydrates and Glucosides," 1924, pp. 282 and 283).

Fischer's method (*Ber.*, 1916, **49**, 2813) which depends on the use of quinoline gives rise to both α - and β -glucosides and can be applied to the preparation of the glucosides of alcohols and phenols. The present method, however, gives only the β -form (compare Robertson, this vol., p. 1136). Careful search has failed to reveal even traces of the α -forms in our products. Attempts to apply the reaction to the preparation of glucosides of alcohols (*e.g.*, methyl, benzyl, etc.) were wholly unsuccessful. It has been found in general that when pyridine is substituted for quinoline in the mixture the reaction is much more vigorous and the product, although identical, is highly contaminated with dark-coloured impurities.

In carrying out the reaction it is essential that the materials should be pure and dry, otherwise the product is difficult to purify. For the same reason, where the temperature of the mixture rises above 50—60° the reaction should be moderated by cooling in tap-water. The use of acetic acid in working up the products has proved convenient and the somewhat tedious process of extracting the reaction mixture with chloroform and subsequently removing the quinoline from the extract by means of mineral acid is thus avoided (compare Takahashi; Zemplén and Müller; Müller, *loc. cit.*). From the fact that resorcinol yields only a diglucoside by this method (compare Müller; Robertson and Jones, *loc. cit.*), it seems desirable, in order to obtain the monoglucoside of a polyhydric phenol, to protect one (or more) of the hydroxyl groups by partial acylation, as is exemplified in the new synthesis of arbutin described below.

Experiments on the preparation of α -glucosides by this method by means of Brigl's β -glucosidyl chlorides (*Z. physiol. Chem.*, 1921, **116**, 1) are in progress.

EXPERIMENTAL.

β -Phenylglucoside.—Dry "active" silver oxide (5 g.) was added with stirring to a paste of phenol (1 g.), *O*-tetra-acetyl- α -glucosidyl bromide (9 g.), and quinoline (10 c.c.). The mixture, which became warm and at first less viscous, was agitated for 15 minutes and the resulting stiff paste was kept in a desiccator for 1 hour. A solution

of the product in acetic acid (40 c.c.) was filtered to remove undissolved silver salts and poured into ice-water (200 c.c.). The tetra-acetyl compound thus precipitated, on crystallisation from alcohol, formed colourless needles (3.5 g.), m. p. 128°, $[\alpha]_D^{20} - 28.7^\circ$ (in acetone) (Found: C, 56.7; H, 5.8. Calc. for $C_{20}H_{24}O_{10}$: C, 56.6; H, 5.7%) (Fischer and Mechel, *Ber.*, 1916, 49, 2813, give m. p. 128° and $[\alpha]_D^{20} - 28.9^\circ$).

A solution of the tetra-acetate (2 g.) in methyl alcohol (40 c.c.) cooled to 0° was saturated with dry ammonia and then kept in the ice-chest for 16 hours. After removal of the ammonia and methyl alcohol in a vacuum, the residue was dissolved in warm water; on cooling, the solution deposited β -phenylglucoside as a hydrate in colourless needles (0.7 g.), m. p. 176°, $[\alpha]_D^{20} - 72.0^\circ$ (in water) (Found: C, 49.3; H, 7.0. Calc. for $C_{12}H_{16}O_6 \cdot 2H_2O$: C, 49.3; H, 6.9%) (Fischer and Mechel, *loc. cit.*, give m. p. 176—177° and $[\alpha]_D^{20} - 71.7^\circ$). The glucoside is hydrolysed by emulsin to glucose and phenol.

β -2-Naphthylglucoside.—The vigorous interaction between β -naphthol (4 g.) and *O*-tetra-acetyl- α -glucosidyl bromide (10 g.) in the presence of silver oxide (5 g.) and quinoline (10 c.c.) was moderated by cooling the containing vessel in tap-water for 10 minutes. The mixture, having been kept in a desiccator for $\frac{1}{2}$ hour, was extracted with acetic acid, and the filtered extract poured into ice-water (400 c.c.). The light brown, crystalline tetra-acetate, on recrystallisation from methyl alcohol (charcoal) and then ligroin, formed colourless prisms (13 g.), m. p. 135°, $[\alpha]_D^{20} - 12.67^\circ$ (in acetone) (Found: C, 60.8; H, 5.4. Calc. for $C_{24}H_{26}O_{10}$: C, 60.8; H, 5.5%) (Fischer and Armstrong, *Ber.*, 1901, 34, 2900, give m. p. 135° but do not record the rotation).

Deacetylation of the tetra-acetate by means of methyl-alcoholic ammonia gave an almost theoretical yield of β -2-naphthylglucoside, which crystallised from water as a monohydrate in elongated colourless prisms, m. p. 188°, $[\alpha]_D^{20} - 26.7^\circ$ (in 95% acetone) (Found: C, 59.3; H, 6.0. Calc. for $C_{16}H_{18}O_6 \cdot H_2O$: C, 59.3; H, 6.2%) (Ryan, J., 1899, 75, 1055, gives m. p. 184—186° but does not record the rotation). The glucoside on hydrolysis by emulsin gave glucose and β -naphthol.

O-Octa-acetyl β -*m*-Phenylenediglucoside.—When resorcinol (1 g.), *O*-tetra-acetyl- α -glucosidyl bromide (9 g.), quinoline (10 c.c.), and silver oxide (5 g.) were mixed, a mild reaction took place. After 15 minutes, the product was dissolved in warm acetic acid, and the filtered solution poured into ice-water (250 c.c.). The solid octa-acetate crystallised from alcohol in plates (4 g.), m. p. 203°, $[\alpha]_D^{20} - 83.1^\circ$ (in acetone) (Found: C, 53.0; H, 5.4. $C_{34}H_{42}O_{20}$ requires

C, 53.0; H, 5.5%). The compound is moderately easily soluble in hot alcohol, readily soluble in chloroform, and insoluble in ether.

O-Monobenzoylquinol.—Into a solution of quinol (15 g.) in 2% aqueous potassium hydroxide (280 c.c.) cooled to -5° in an atmosphere of hydrogen, benzoyl chloride (14 g.) was introduced in twelve portions, vigorous shaking being maintained until the odour of the chloride had disappeared. The mixture was poured into saturated aqueous sodium bicarbonate solution (300 c.c.) and after $\frac{1}{2}$ hour the solid was collected and washed with water. Crystallised from 70% alcohol, the *monobenzoate* formed colourless, slender needles (15 g.), m. p. 161° (Found: C, 73.1; H, 5.0. $C_{13}H_{10}O_3$ requires C, 72.9; H, 4.7%).

Arbutin.—A mixture of *O*-monobenzoylquinol (2.5 g.), *O*-tetra-acetyl- α -glucosidyl bromide (5 g.), silver oxide (3 g.), and quinoline (10 c.c.) gave rise to the *tetra-acetyl glucoside* of quinol monobenzoate (6 g.). The compound (isolated by the aid of acetic acid) separated from warm alcohol in colourless leaflets, m. p. $154-155^{\circ}$, $[\alpha]_D^{20} - 63.97^{\circ}$ (in acetone) (Found: C, 59.7; H, 5.2. $C_{27}H_{28}O_{12}$ requires C, 59.7; H, 5.1%).

Removal of the benzoyl and acetyl groups was effected by means of methyl-alcoholic ammonia. The glucoside (yield, 70% of the theoretical) on crystallisation from water and then from moist ethyl acetate, formed colourless elongated prisms containing $1H_2O$, m. p. 199° , after sintering at $163-164^{\circ}$, alone or mixed with a specimen of the natural glucoside, $[\alpha]_D^{30} - 60.3^{\circ}$ (in water) (Found: C, 49.9; H, 6.1. Calc. for $C_{12}H_{16}O_7 \cdot H_2O$: C, 49.7; H, 6.2%) (Mannich, *Arch. Pharm.*, 1912, **250**, 547, gives $[\alpha]_D^{17.5} - 60.34^{\circ}$). Acetylation of the synthetic glucoside by means of acetic anhydride and sodium acetate during $\frac{1}{2}$ hour at 160° (oil-bath) gave the penta-acetate, which crystallised from alcohol in slender needles, m. p. $145-146^{\circ}$, alone or mixed with a specimen prepared from the natural glucoside (Mannich, *loc. cit.*), $[\alpha]_D^{20} - 28.18^{\circ}$ (in acetone) (Found: C, 54.8; H, 5.5. Calc. for $C_{22}H_{26}O_{12}$: C, 54.8; H, 5.4%). Synthetic arbutin is hydrolysed by emulsin to glucose and quinol.

Attempts to prepare the tetra-acetyl glucoside directly from quinol were unsuccessful.

Helicin.—The solid mixture obtained from salicylaldehyde (3 g.), *O*-tetra-acetyl- α -glucosidyl bromide (22 g.), silver oxide (12 g.), and quinoline (20 c.c.) was extracted with cold 25% acetic acid (400 c.c.), and the extract rejected. The solid was then dissolved in hot alcohol, and the solution filtered to remove silver salts. On cooling, tetra-acetyl helicin crystallised in thick needles (10.5 g.), m. p. 142° , $[\alpha]_D^{20} - 37.0^{\circ}$ (in acetone) (Found: C, 55.8; H, 5.3. Calc. for

$C_{21}H_{24}O_{11}$: C, 55.8; H, 5.3%) (Fischer and Slimmer, *Sitzungsber. K. Akad. Wiss. Berlin*, 1902, p. 597, give m. p. 142° and $[\alpha]_D^{20} - 37.2^{\circ}$).

Deacetylation of the tetra-acetate and purification of the glucoside by Fischer and Slimmer's procedure (*loc. cit.*) gave synthetic helicin, which formed fine needles, m. p. 175° , $[\alpha]_D^{20} - 60.1^{\circ}$ (in water) (Found in a specimen dried in a vacuum at 100° : C, 55.0; H, 5.8. Calc. for $C_{13}H_{16}O_7$: C, 54.9; H, 5.7%) (Fischer and Slimmer give $[\alpha]_D^{20} - 60.4^{\circ}$). Hydrolysis of the compound was readily effected by emulsin at $35-37^{\circ}$ with the formation of salicylaldehyde and glucose.

O-Tetra-acetyl- β -glucovanillin.—The interaction of vanillin (5 g.) and *O*-tetra-acetyl- α -glucosidyl bromide (12.2 g.) in the presence of silver oxide (7 g.) and quinoline (10 c.c.) gave a solid which partly dissolved in acetic acid (50 c.c.). Water (300 c.c.) was then added and the solid was collected, washed, and extracted with hot alcohol. On cooling, the filtered extract deposited the tetra-acetyl glucoside in colourless prisms (14 g.), m. p. $143-144^{\circ}$, $[\alpha]_D^{20} - 50.68^{\circ}$ (in acetone) (Found: C, 54.8; H, 5.4. Calc. for $C_{22}H_{26}O_{12}$: C, 54.8; H, 5.4%) (Fischer and Raske, *Ber.*, 1909, **42**, 1465, give m. p. 143°).

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