CXLIV.—*The Synthesis of Glucosides. Part IV. Alizarin Glucoside.*

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BY the interaction of tetra-acetyl-α-glucosidyl bromide and alizarin in the presence of quinoline and silver oxide, Takahashi (*J. Pharm. Soc. Japan*, 1925, **525**, 4) prepared the tetra-acetyl glucoside of alizarin, which on deacetylation with alkali yielded a monoglucoside, m. p. 230—231°. Glaser and Kahler (*Ber.*, 1927, **60**, 1349), using the acetone–alkali method, seem to have isolated the same tetra-acetyl glucoside, but on deacetylation by means of methyl-alcoholic ammonia they obtained alizarin and a red compound which they considered was the 1 : 2-diglucoside of 9 : 10-diamino-1 : 2 : 9 : 10-tetrahydroxyanthracene and was converted by cold hydrochloric acid into 1 : 2-diglucoalizarin, m. p. 214°. The production of a diglucoside in this manner was thought to be highly improbable, and, moreover, would restrict the use of this convenient method of deacetylation. In addition, the results were complicated by the fact that Fischer's method for the preparation of α-glucosides depends on the use of quinoline (*Ber.*, 1916, **49**, 2813). The experiments described in this communication were therefore undertaken.

Zemplén and Müller (*Ber.*, 1929, **62**, 2107), using Takahashi's method, have confirmed the results of this investigator. They also found that deacetylation of the tetra-acetyl glucoside as described by Glaser and Kahler gave a red compound of variable composition which on treatment with warm aqueous-alcoholic hydrochloric acid

afforded alizarin monoglucoside identical with that, m. p. 236—237°, obtained by deacetylation with alkali. The experimental results described below agree with the observations of Zemplén and Müller. A convenient procedure for the preparation of the tetra-acetyl glucoside by the acetone–alkali method is described (compare Glaser and Kahler, *loc. cit.*). Since acetylation of alizarin glucoside prepared by either method of hydrolysis and of the tetra-acetyl derivative gave the same penta-acetyl compound, it follows that migration of the glucose residue does not occur.

The fact that the red compound is not instantaneously decomposed by warm dilute acetic acid renders it unlikely that the substance is a simple ammonium salt. In support of this it may be noted that alizarin glucoside is liberated from its sodium salt by cold dilute acetic acid. Deacetylation of *O*-tetra-acetyl-2-β-glucosidoxyanthraquinone (compare Müller, *Ber.*, 1929, **62**, 2793) with methyl-alcoholic ammonia gave 2-β-*glucosidoxyanthraquinone* identical with that obtained by hydrolysis with alkali.

Previous investigators (Takahashi, *loc. cit.*; Glaser and Kahler, *loc. cit.*; Zemplén and Müller, *loc. cit.*) have suggested that the glucose residue of the tetra-acetyl glucoside of alizarin is attached at the 2-position. This conclusion was based on the well-known fact that in compounds like alizarin the hydroxyl group in the *o*-position to carbonyl is difficult to alkylate. Attempts to confirm this structure by the aid of boroacetic anhydride gave unsatisfactory results (compare Robertson and Waters, J., 1929, 2239). Although the addition of the glucoside or its acetyl compound to a solution of the reagent in acetic anhydride gave a red coloration indicating the formation of a boroacetate, a solid derivative could not be isolated; the red solutions became yellow on addition of water. The isolation of 1-methyl alizarin as a product of the hydrolysis of O-*tetra-acetyl*-2-β-*glucosidoxy*-1-*methoxyanthraquinone* (I) finally afforded conclusive proof of the constitutions of (I) and of alizarin glucoside; deacetylation of (I) gave the *glucoside* of 1-methyl alizarin.

Acetylation of the amorphous condensation product of *O*-hepta-acetylmaltosidyl bromide and alizarin gave a crystalline O-*octa-acetyl maltoside*, not identical with the octa-acetyl derivative of ruberythric acid.

The hydroxyxanthone glucosides (Robertson and Waters, *loc. cit.*) are readily decomposed by boiling 10% aqueous sodium hydroxide and in this respect resemble the compounds described in this communication.

EXPERIMENTAL.

2-β-*Glucosidoxyanthraquinone.*—*O*-Tetra-acetyl-α-glucosidyl bromide (8·2 g.) was added to a solution of 2-hydroxyanthraquinone

(6 g.) and potassium hydroxide (1·2 g.) in acetone (60 c.c.) and water (20 c.c.). The mixture was kept at room temperature for 16 hours and 12% aqueous potassium hydroxide (10 c.c.) and a further quantity of bromide (8·2 g.) were then added. After 24 hours, the reaction mixture was acidified with acetic acid, and on addition of water (300 c.c.) the tetra-acetyl glucoside (mixed with 2-hydroxyanthraquinone) separated. Repeated crystallisation from alcohol gave the substance (3·5 g.) in almost colourless, rectangular plates, m. p. 168° (Müller, *loc. cit.*, gives m. p. 164°) (Found in material dried at 100° : C, 60·6; H, 5·0. Calc. for $C_{28}H_{26}O_{12}$: C, 60·5; H, 4·7%).

The tetra-acetyl derivative (2 g.), suspended in warm methyl alcohol (80 c.c.), was treated with 10% aqueous sodium hydroxide (16 c.c.) at 60° for 5 minutes. The cooled mixture slowly deposited 2-β-*glucosidoxyanthraquinone* (1 g.), which crystallised from dilute alcohol in pale yellow needles containing $1H_2O$, m. p. 248—249° (Found : C, 59·5; H, 5·3. $C_{20}H_{18}O_8,H_2O$ requires C, 59·4; H, 5·0%. Found in material dried at 110° in a high vacuum for 2 hours : C, 62·2; H, 4·7. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7%). The compound tends to separate from warm dilute alcohol as a pale yellow gel which gradually crystallises. It is moderately easily soluble in warm water and sparingly soluble in hot alcohol. Acetylation with acetic anhydride and sodium acetate gave the tetra-acetyl derivative, m. p. 168°. In boiling 10% aqueous sodium hydroxide the glucoside decomposes with the formation of the red sodium salt of 2-hydroxyanthraquinone. It is readily hydrolysed by emulsin and by warm 15% hydrochloric acid to glucose and the anthraquinone.

Deacetylation of the tetra-acetyl glucoside by means of methylalcoholic ammonia during 22 hours at 0° afforded the glucoside in almost theoretical yield, m. p. and mixed m. p. 248—249° after crystallisation from dilute alcohol.

2-O-*Tetra-acetyl*-β-*glucosidoxy*-1-*hydroxyanthraquinone.*—A mixture of alizarin (18 g.), potassium hydroxide (2·8 g.), and 50% aqueous acetone (400 c.c.) was agitated for ¼ hour to ensure the formation of potassium alizarate. A solution of *O*-tetra-acetyl-α-glucosidyl bromide (20 g.) in ether (100 c.c.) was then introduced. The mixture was agitated for 12 hours and 7% potassium hydroxide solution (20 c.c.) and a further quantity of bromide (10·5 g.) were then added. After 16 hours, the faintly alkaline reaction mixture was acidified with acetic acid and the glucoside and unchanged alizarin were precipitated by addition of water (200 c.c.). A suspension of the solid in acetic acid (200 c.c.) was refluxed for 5 minutes, cooled, and filtered to remove alizarin. Addition of warm water (1 l. at 65°) to the filtrate precipitated the glucoside, con-

taminated with traces of alizarin. Recrystallisation from alcohol finally gave slender yellow needles, m. p. 206—207° after sintering at 204° (Found : C, 58·8; H, 4·9. Calc. for $C_{28}H_{26}O_{13}$: C, 58·9; H, 4·6%). Acetylation with acetic anhydride and pyridine during ¼ hour on the steam-bath yielded the penta-acetyl derivative, which separated from warm alcohol in pale yellow needles, m. p. 196—197° (Glaser and Kahler, *loc. cit.*, gave m. p. 192—193°) (Found : C, 59·1; H, 4·9. Calc. for $C_{30}H_{28}O_{14}$: C, 58·8; H, 4·6%).

2-β-*Glucosidoxy*-1-*hydroxyanthraquinone.*—(A) Deacetylation was effected by the addition of 5% aqueous sodium hydroxide (30 c.c.) to a suspension of the tetra-acetyl glucoside (1·1 g.) in warm methyl alcohol (80 c.c.). The solid rapidly dissolved and the cherry-red solution, maintained at 65° for 10 minutes, deposited the sodium salt of the glucoside in dark red needles. A warm aqueous solution of this salt was acidified with acetic acid and the yellow crystalline solid was collected, washed with water, and dissolved in boiling methyl alcohol (500 c.c.). After removal of the greater part of the alcohol by distillation the glucoside crystallised; repetition of this procedure with ethyl alcohol gave alizarin glucoside in rosettes of slender yellow needles, m. p. 237° (Found : C, 59·2; H, 4·5. Calc. for $C_{20}H_{18}O_9$: C, 59·7; H, 4·5%) (compare Zemplén and Müller, *loc. cit.*). Acetylation with acetic anhydride and pyridine on the water-bath gave the penta-acetyl derivative, m. p. 196—197°.

(B) Treatment of the tetra-acetyl glucoside (1·1 g.) with methyl-alcoholic ammonia at 0° for 24 hours gave a dark red solid (0·8 g.) (compare Glaser and Kahler, *loc. cit.*; Zemplén and Müller, *loc. cit.*) which crystallised from a large volume of ethyl alcohol in needles, m. p. 195—196° (decomp.) (Found : C, 53·8; H, 5·3; N, 3·9%). The red solution of this compound (0·2 g.) in hot 10% acetic acid (25 c.c.) was refluxed for 6 minutes. The colour gradually changed to orange-yellow, and alizarin glucoside separated from the cooled solution, m. p. 237° after purification (penta-acetyl derivative, m. p. 196—197°). The red compound dissolved in cold concentrated hydrochloric acid to a yellow solution, and after 5 minutes addition of water precipitated alizarin glucoside, m. p. 237° after purification.

This glucoside is hydrolysed by emulsin and by warm 10% hydrochloric acid to glucose and alizarin. The cherry-red solution of the glucoside in 10% aqueous sodium hydroxide becomes violet on boiling; acidification of the cooled solution gives a precipitate of alizarin.

2-O-*Tetra-acetyl*-β-*glucosidoxy*-1-*methoxyanthraquinone.*—A mixture of the tetra-acetyl glucoside (1·2 g.), methyl iodide (3 c.c.), active silver oxide (3 g.), and acetone (30 c.c.) was refluxed for 2 hours; a test with cold alcoholic alkali then showed that methylation

was complete. After separation from the silver salts (wash with acetone), the solvent was removed under diminished pressure. The residual *methyl* ether crystallised from methyl alcohol in elongated, pale yellow prisms, m. p. 155—156°, $[\alpha]_D^{17°}$ −71·72° in acetone (Found: C, 59·1; H, 5·1. $C_{29}H_{28}O_{14}$ requires C, 59·5; H, 4·8%). It is readily soluble in warm alcohol or acetone, and does not give a coloration with cold alcoholic sodium hydroxide. A solution of the ether (1·2 g.) in a mixture of methyl alcohol (30 c.c.) and concentrated hydrochloric acid (15 c.c.) was refluxed for 2 hours. Addition of water (50 c.c.) to the cooled solution precipitated 1-methyl alizarin, which crystallised from methyl alcohol in orange-yellow needles, m. p. 179°. Acetylation of the latter substance with acetic anhydride and sodium acetate gave 1-methyl-2-acetyl alizarin, yellow needles from methyl alcohol, m. p. 212° (Found: C, 69·1; H, 4·4. Calc. for $C_{12}H_{12}O_5$: C, 68·9; H, 4·1%).

2-β-*Glucosidoxy*-1-*methoxyanthraquinone*.—10% Methyl-alcoholic sodium hydroxide (15 c.c.) was added to a warm solution of the tetra-acetyl derivative (1 g.) in methyl alcohol (30 c.c.). The mixture became red owing to slight decomposition of the glucoside, and after 2 hours at room temperature 10% acetic acid (10 c.c.) was added. On evaporation of the methyl alcohol in a vacuum the *glucoside* gradually separated. After being kept for 12 hours in an ice-chest, the solid was separated from the faintly alkaline mother-liquor and washed with alcohol to remove traces of alkali. On crystallisation from methyl alcohol it formed clusters of slender yellow needles, m. p. 230—231° (Found: C, 60·2; H, 5·0. $C_{21}H_{20}O_9$ requires C, 60·6; H, 4·8%). The glucoside is sparingly soluble in cold alcohol, water, or acetone, and does not give a coloration with cold alcoholic sodium hydroxide. It is readily hydrolysed by emulsin to 1-methyl alizarin and glucose.

Alizarin Octa-acetyl Maltoside.—*O*-Hepta-acetylmaltosidyl bromide was prepared by the following method (compare Zemplén, *Ber.*, 1928, **61**, 927). Acetic anhydride (25 c.c.) was added to a solution of octa-acetyl maltose, m. p. 160° (50 g.) in acetic acid saturated at 0° with hydrogen bromide (100 g.). After 5 hours at room temperature the reaction mixture was diluted with chloroform (400 c.c.) and poured on ice (300 g.) in water (300 g.). The chloroform layer was separated, washed three times with ice-water (300 c.c.), and dried over calcium chloride. On removal of the solvent in a vacuum the bromide remained as a pale straw-coloured syrup (40 g.), which solidified on trituration with ligroin.

A solution of amorphous *O*-hepta-acetylmaltosidyl bromide (20 g.) in ether (150 c.c.) was added to a mixture of alizarin (8 g.), potassium hydroxide (1·2 g.), and 50% aqueous acetone (200 c.c.).

After agitation for 24 hours the faintly alkaline mixture was acidified with acetic acid, and the precipitate of alizarin removed by filtration. The ethereal layer was separated, and the aqueous solution extracted once with ether (100 c.c.). An acetic acid solution of the residue obtained on evaporation of the ether was kept in the ice-chest for 24 hours, filtered to remove alizarin which had crystallised, and then poured into water (500 c.c. at 50°). The orange solid which separated was immediately collected, washed with water, and dissolved in hot alcohol. On cooling, an amorphous, bright yellow solid separated. Purification by hot alcohol was repeated (five times) until a specimen gave a bright cherry-red colour in cold alcoholic sodium hydroxide. Acetylation of the purified amorphous solid with acetic anhydride and sodium acetate on the steam-bath during 6 hours gave *alizarin octa-acetyl maltoside*, which crystallised from alcohol in pale yellow needles (1·6 g.), m. p. 185°, $[\alpha]_D^{17°}$ −20·05° in acetone (Found: C, 55·8; H, 5·1. $C_{42}H_{44}O_{22}$ requires C, 56·0; H, 4·9%). The substance is readily soluble in warm alcohol or acetone and in cold acetic acid.

The author is indebted to the Chemical Society for a grant which has partly defrayed the cost of this investigation.

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[*Received, March 25th,* 1930.]