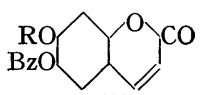
268. *Syntheses of Glycosides. Part XI. Cichoriin.*

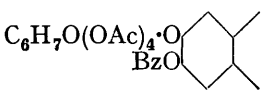
By Frank S. H. Head and Alexander Robertson.

Benzoylation of æsculetin gave rise to 6-*O*-benzoyl- and 6 : 7-*O*-dibenzoyl-æsculetin. On condensation with *O*-tetra-acetyl-α-glucosidyl bromide by the silver oxide–quinoline method the monobenzoate gave the *O*-tetra-acetyl-β-glucoside of 6-*O*-benzoyl-æsculetin, which yielded cichoriin on deacylation.

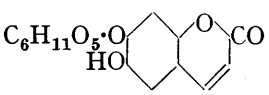
Contrary to the claims of Glaser and Kraus (*Biochem. Z.*, **1923**, **138**, 185; *Arch. Pharm.*, 1928, **266**, 573) Seka and Kallir (*Ber.*, **1931**, **64**, 909) have found that the condensation of æsculetin with *O*-tetra-acetyl-α-glucosidyl bromide in alkaline solution gives rise to the tetra-acetate of the glucoside (III) isomeric and not identical with æsculin, which we have shown to have the glucose residue in the 6-position (J., 1930, 2434). Similarly Merz (*Arch. Pharm.*, **1932**, **270**, 476) has found that methylation of æsculetin with diazomethane yields 7-*O*-methyl- and 6 : 7-*O*-dimethyl-æsculetin. It therefore seemed reasonable to expect that the monobenzoylation of the coumarin would give rise to 7-*O*-benzoylæsculetin, which would be a suitable intermediate for the synthesis of æsculetin : from the mixture obtained by treatment of æsculetin with molecular proportions of aqueous sodium hydroxide and benzoyl chloride, however, we have been able to isolate only 6-O-*benzoylæsculetin* (I, R = H) in addition to the dibenzoate. The orientation of (I, R = H) was effected by methylation to the ether (I, R = Me), which on debenzoylation gave 7-*O*-methylæsculetin.



(I.)



(II.)



(III.)

The tetra-acetylglucoside (II) was prepared from (I, R = H) by the quinoline–silver oxide method and on treatment with methyl-alcoholic ammonia gave rise to (III), identical in every way with natural cichoriin, which was shown to have formula (III) by Merz (*loc. cit.*).

Experimental.

Benzoylation of Æsculetin.—2% Aqueous sodium hydroxide (40 c.c.) was added to water (180 c.c.) containing a suspension of powdered æsculetin (3·5 g.), the mixture vigorously agitated for 1 hour, and the resulting solution cooled to 0°. Benzoyl chloride (2·8 g.) was then introduced in three portions with very vigorous shaking, which was continued until the odour of the chloride

had almost disappeared (½ hour). The mixture was stirred with aqueous sodium bicarbonate for 15 minutes, and the solid collected, washed, ground to a paste with a little water, and thoroughly extracted with 5% aqueous sodium carbonate (150 c.c.). The extract was filtered to separate the insoluble dibenzoate (1·5 g.) and on acidification with hydrochloric acid gave 6-O-*benzoylæsculetin* (2·7 g.), which was probably contaminated with traces of unchanged æsculetin, since it gave a dark green ferric reaction. Crystallisation of the product from alcohol served to remove the impurity and finally gave the benzoate in colourless needles, m. p. 198° after sintering at 185°, having a negative ferric reaction (Found : C, 68·2; H, 3·8. $C_{16}H_{10}O_5$ requires C, 68·1; H, 3·6%).

The dibenzoate formed rosettes of slender needles, m. p. 186°, from hot acetic acid, sparingly soluble in hot alcohol (Found : C, 71·3; H, 3·8. Calc. for $C_{23}H_{14}O_6$: C, 71·5; H, 3·6%) (Merz, *loc. cit.*).

6-*Benzoyloxy*-7-*methoxycoumarin*.—The afore-mentioned monobenzoate (1·2 g.) was methylated with methyl iodide (10 c.c.) and potassium carbonate (5 g.) in boiling acetone for 1 hour; the pale yellow solution became colourless in the course of 15 minutes, indicating that the reaction was complete. On isolation the product separated from warm acetic acid in hexagonal prisms, m. p. 217—218°, sparingly soluble in benzene (Found : C, 68·7; H, 4·2. Calc. for $C_{17}H_{12}O_5$: C, 68·9; H, 4·1%). The same compound was obtained by the benzoylation of 6-hydroxy-7-methoxycoumarin (Head and Robertson, *loc. cit.*), m. p. and mixed m. p. 217—218° after purification (compare Seka and Kallir, *loc. cit.*, who give m. p. 211°).

A solution of the ether (0·8 g.) in methyl alcohol (150 c.c.), saturated with ammonia, was kept at 0° for 24 hours and the residue left on removal of the solvent was treated with warm dilute hydrochloric acid, giving 7-*O*-methylæsculetin, which formed needles from methyl alcohol, m. p. 185°, identical with an authentic specimen (Head and Robertson, *loc. cit.*).

7-O-*Tetra-acetyl*-β-*glucosidoxy*-6-*benzoyloxycoumarin* (II).—Active silver oxide (2 g.) was added, with vigorous stirring, to a paste of 6-*O*-benzoylæsculetin (0·5 g.) and *O*-tetra-acetyl-α-glucosidyl bromide (2·5 g.) and the mixture, which became warm, was stirred for 15 minutes, kept in a desiccator for 1 hour, and extracted with hot acetic acid (50 c.c.). The filtered extract (charcoal) was poured into water, and the precipitated *glucoside* crystallised from methyl or ethyl alcohol, forming elongated slender needles (0·8 g.), m. p. 218° (Found : C, 58·8; H, 4·8. $C_{30}H_{28}O_{14}$ requires C, 58·8; H, 4·6%).

6-*Hydroxy*-7-β-*glucosidoxycoumarin* (*Cichoriin*) (III).—Methyl alcohol (300 c.c.) containing a suspension of the foregoing compound (2·5 g.) was saturated with ammonia at 0°, and the solution kept for 24 hours and evaporated in a vacuum. The residue was boiled for 1 minute with 20% acetic acid and, on cooling, the filtered solution deposited the dihydrate of cichoriin in glistening needles which on recrystallisation from water had m. p. 213—214°, identical in every way with a natural specimen, $[\alpha]_D^{20°}$ — 104° (*c*, 3 g. of air-dried material in 100 c.c. of 50% aqueous dioxan) (Found in air-dried specimen : C, 47·9; H, 5·2. Calc. for $C_{15}H_{16}O_9,2H_2O$: C, 47·9; H, 5·3%. Found in material dried in a high vacuum at 100° : C, 52·4; H, 4·8. Calc. for $C_{15}H_{16}O_9$: C, 52·9; H, 4·7%) (Merz, *loc. cit.*, gives m. p. 213—215°). Acetylated with acetic anhydride (10 c.c.) and sodium acetate (5 g.) on the steam-bath, synthetic cichoriin (0·5 g.) gave rise to the penta-acetate, which separated from alcohol in slender needles, m. p. 218°, undepressed by admixture with a natural specimen (Found : C, 54·7; H, 4·8. Calc. for $C_{25}H_{26}O_{14}$: C, 54·5; H, 4·7%).

The authors are indebted to Professor Merz for specimens of natural cichoriin and its penta-acetate.

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