338. *The Syntheses of Glycosides. Part XII. Fabiatrin.*

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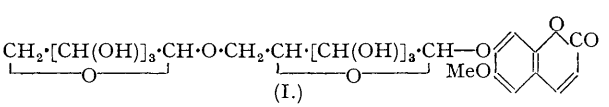
The syntheses of the β-gentiobioside and the β-primeveroside of 7-hydroxy-6-methoxycoumarin (scopoletin) are described; the latter substance is shown to be identical with the natural glycoside fabiatrin (cf. Merz, *loc. cit.*).

In the course of their examination of the constituents of *Fabiana imbricata* (Ruiz and Pavon), Edwards and Rogerson (*Biochem. J.*, 1927, **21**, 1010) isolated a glycoside fabiatrin, m. p. 226—228°, which, since it gave 7-hydroxy-6-methoxycoumarin (scopoletin) and glucose on hydrolysis, these authors regarded as a mono-glucoside of the coumarin, a conclusion in keeping with the then accepted view that scopolin, m. p. 215—217°, the known glycoside of scopoletin, contained two molecules of glucose as a disaccharide (see Van Rijin, " Die Glykoside ", 1931, p. 492; Armstrong and Armstrong, " The Glycosides ", 1931, p. 19). After having shown by synthesis that scopolin was the normal mono-β-glucopyranoside of scopoletin, Merz (*Arch. Pharm.*, 1932, **270**, 476), on the basis of Edwards and Rogerson's results and in spite of the considerable divergence in the melting points, concluded that fabiatrin was identical with scopolin. It appeared to us that the latter assumption was unjustified, and when, through the kindness of the late Mr. Rogerson, we were able to examine a small specimen of fabiatrin, it became clear that the two compounds were not identical. After purification we found that fabiatrin had m. p. 236—238°, forming an *acetyl* derivative, m. p. 172°, and in the first instance, accepting the conclusion that glucose was the only sugar formed by the hydrolysis of the glycoside and because the natural phenolic glucosides which have been completely investigated are invariably normal β-pyranosides, we envisaged the possibility of fabiatrin being a β-gentiobioside. Accordingly the O-*hepta-acetyl*-β-*gentiobioside* of scopoletin was synthesised by the quinoline–silver oxide method, and on deacetylation furnished the β-gentiobioside as a *trihydrate*, but comparison of the respective natural and synthetical specimens clearly showed that the two substances were not identical. We therefore re-examined the sugar solution obtained by the hydrolysis of a small amount of fabiatrin, and, finding that it gave the orcinol and phloroglucinol tests for a pentose, we concluded by analogy with other natural biosides that fabiatrin contained (in the following order of preference) either a xylose, a rhamnose, or an arabinose residue in addition to the glucose unit established by Edwards and Rogerson (*loc. cit.*). Consequently the β-primeveroside of scopoletin (I) was next synthesised, being obtained in good yield by the route employed for the corresponding gentiobioside, and was found to be identical in every way with fabiatrin.



(I.)

The identity of the compounds was confirmed by direct comparison of natural and synthetical specimens of the respective *acetyl* derivatives. Fabiatrin and the gentiobioside of scopoletin were obtained as hydrates from which the pure anhydrous substances could not be obtained by drying in a vacuum at elevated temperatures.

Attempts to utilise the general method for the synthesis of biosides (Robertson and Waters,

J., 1931, 1881) in the present series were unsuccessful because we were unable to form the 6-trityl derivative of scopolin by the usual methods.

Experimental.

Scopoletin.—The following synthesis gives better yields than the Perkin method employed by Head and Robertson (*J.*, 1931, 1241). The sodium salt of 2 : 4-dihydroxy-5-methoxybenzaldehyde (from 1 g. of aldehyde, 1·5 g. of sodium hydroxide, and 3 ml. of water) was treated at room temperature with cyanoacetic acid (10 ml. of a solution prepared according to Phelps and Tillotson, *Amer. J. Sci.*, 1908, **26**, 267), and 2 hours later the product was precipitated with hydrochloric acid and hydrolysed by being boiled with 4% hydrochloric acid (50 ml.) for ½ hour. The resulting *scopoletin-3-carboxylic acid* (1·15 g.) separated from warm alcohol in bright yellow needles, m. p. 260—263° after sintering at 250° (Found : C, 55·9; H, 3·7. $C_{11}H_8O_6$ requires C, 55·9; H, 3·4%). In alcoholic solution this acid exhibits an intense blue fluorescence. When a mixture of the acid (1 g.) and ethylene glycol (20 ml.) was kept at 160—170° until evolution of carbon dioxide had ceased and then cooled, scopoletin (0·6 g.) separated in tiny crystals, m. p. 202°, after purification from alcohol. When glycol was replaced by glycerol the evolution of carbon dioxide did not begin below 180° and the product was less pure.

Scopolin.—The following is an improved method for the preparation of the tetra-acetate of scopolin (compare Merz, *loc. cit.*). When scopoletin (1 g.), *O*-tetracetyl-α-glucosidyl bromide (5 g.), silver oxide (4 g.), and quinoline (10 ml.) were mixed, a mild reaction ensued. Next day the solid mixture was extracted with hot acetic acid (75 ml.) and the extract filtered and diluted with water. Crystallised from methyl alcohol, this material gave the tetra-acetate of scopolin in prisms, m. p. 166°, in agreement with Merz (*loc. cit.*). When a specimen of the crude material which had been kept for 2 weeks was crystallised as before, the tetra-acetate was obtained in flat plates, m. p. 184—185°. Since on deacetylation according to the directions of Merz (*loc. cit.*) both forms gave rise to scopolin, m. p. 217—219° (Merz gives m. p. 215—217°), they are regarded as being dimorphic.

β-Gentiobioside of Scopoletin.—Silver oxide (3·2 g.) was well mixed with a paste of scopoletin (1 g.), quinoline (10 ml.), and *O*-hepta-acetyl-α-gentiobiosidyl bromide (5·5 g.) and the mixture well stirred for 15 minutes. Next day the product was extracted with warm acetic acid (100 ml.) and filtered (charcoal), and the filtrate diluted with water (800 ml.). The solid (4·75 g.) was collected, well washed with water, dried, and crystallised from methyl alcohol and then alcohol, giving the 7-O-*hepta-acetyl-β-gentiobioside* of scopoletin in colourless needles, m. p. 190°, $[\alpha]_D^{20°}$ — 32° in chloroform (*c*, 0·43) (Found : C, 53·2; H, 5·5. $C_{36}H_{42}O_{21}$ requires C, 53·3; H, 5·2%).

The acetate (3·75 g.) was deacetylated with methyl alcoholic ammonia (500 ml.) at 0° in the course of 16 hours, and, after removal of the ammonia and the solvent under reduced pressure, a solution of the semi-solid residue in the minimum volume of water at 70° was diluted with 4 times its volume of warm alcohol. On cooling, the solution deposited the β-gentiobioside of scopoletin as a *trihydrate* in colourless needles, m. p. 158—162°, after repeated purification from aqueous methyl and ethyl alcohol, $[\alpha]_D^{20°}$ — 150° in water (*c*, 0·4) (Found : C, 46·1; H, 5·7. $C_{22}H_{28}O_{14},3H_2O$ requires C, 46·3; H, 5·9%).

Fabiatrin (1).—Interaction of scopoletin (1·5 g.), hexa-acetyl-α-primeverosidyl bromide (Zemplen, *Ber.*, 1939, **72**, 49) (7 g.), quinoline (10 ml.), and silver oxide (5 g.), followed by isolation of the product with the aid of acetic acid (60 ml.), gave the *hexa-acetate* of fabiatrin which separated from methyl alcohol in colourless, slender needles (4 g.), m. p. 173°, $[\alpha]_D^{20°}$ — 47° in chloroform (*c*, 0·6) (Found : C, 53·7; H, 5·2. $C_{33}H_{40}O_{19}$ requires C, 53·5; H, 5·4%). Deacetylation of this acetate (2·5 g.) with methyl alcohol (175 ml.) saturated with ammonia at 0° gave fabiatrin which, on crystallisation from dilute methyl alcohol, was obtained as a *dihydrate* in rosettes of needles, m. p. 236—238°, $[\alpha]_D^{20°}$ — 140° in water (*c*, 0·5) (Found : C, 48·8; H, 5·5. $C_{21}H_{26}O_{13},2H_2O$ requires C, 48·5; H, 5·7%). On being dried in a high vacuum at 100° the dihydrate lost only part of its water of crystallisation.

A specimen of fabiatrin dihydrate from natural sources was found to melt at 226—228° but on recrystallisation from dilute alcohol had m. p. 236—238°, and was identical with synthetical material (Found : C, 49·0; H, 5·7%). Acetylation of the natural compound (0·1 g.) with acetic anhydride (3 ml.) and sodium acetate (0·5 g.) on the water-bath for 2 hours gave the hexa-acetate which separated from methyl alcohol in slender needles, m. p. 172°, undepressed on admixture with a synthetical specimen (Found : C, 53·7; H, 5·2%).

The authors are indebted to Messrs. Imperial Chemical Industries Limited for a grant in aid of this work.

University of Liverpool. [*Received, November 22nd*, 1947.]