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Abstract

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SYNTHESIS OF RUTIN

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Rutin, quercetin-3-rutinoside (VII)—the active principle of vitamin P—together with hesperidin, eriodictyol, and certain catechins, is of great importance, since it has the ability (especially in combination with ascorbic acid) to reduce the permeability and fragility of capillaries.

The presence of five hydroxyl groups in the quercetin (V) molecule makes the preparation of its 3-glycosides very difficult. In addition, the reactivity of the hydroxyl group in position 3 of quercetin is weakened by its hydrogen bond with the oxygen of the pyran carbonyl group ([1,2]).

Formation of a glycosidic bond in position 3 by the Koenigs—Knorr method, through the action of α-acetobromoglucose in the presence of active silver oxide in quinoline, succeeds only for the simplest flavonols and is accompanied by substitution of the free phenolic groups ([3,4]).

In 1952, Aisy and Vender ([5]) succeeded in obtaining isoquercitrin, quercetin 3-glucoside, by the action of α-acetobromoglucose on the 3-potassium salt of quercetin in a solution of liquid ammonia. The synthesis of rutin itself or of other quercetin 3-disaccharides had not been known until recently.

In the present work we describe the preparation of rutin from quercetin and α-acetobromorutinose according to the scheme:

$$(\mathrm{V}) \xrightarrow[\text{pH 8}]{\mathrm{CH_3COOK}} (\mathrm{VI}) \longrightarrow$$

$$(\mathrm{VI}) \xrightarrow[\text{liquid ammonia}]{\mathrm{BrC_{12}H_{15}O_3(OOCCH_3)_6}} (\mathrm{VII})$$

The starting quercetin was obtained by the Allan—Robinson method ([6]), with the difference that protection of the hydroxyl group in vanillic acid was achieved by benzylation; triethylamine was used as the condensing agent ([7]).

$$(\mathrm{I}) + (\mathrm{II}) \xrightarrow{\mathrm{N(C_2H_5)_3}} (\mathrm{III}) \xrightarrow{\text{a) debenzylation}} (\mathrm{IV}) \xrightarrow{\text{b) demethylation}} (\mathrm{V})$$

The disaccharide α-acetobromo-β-1-L-rhamnosido-6-D-glucose, α-acetobromorutinose, was synthesized by Zemplén’ s method (8) from acetobromorhamnose and acetochloroglucose.

The data of paper chromatography and comparison of the ultraviolet absorption spectra (Fig. 1) showed the complete identity of the synthetic and natural rutin.

At the same time, treatment of quercetin with liquid ammonia is accompanied by partial decomposition of the latter; therefore, upon paper chromatography of synthetic rutin, impurities are detected with ultraviolet absorption maxima characteristic of the decomposition products of quercetin.

The preparation of rutin carried out by us represents the completion of its total synthesis.

Fig. 1. Ultraviolet absorption spectrum of rutin (in 96% alcohol): 1 –synthetic, 2 –natural

Experimental Part

A. 5,7,4′-Trioxy-3,3′-dimethoxyflavone (IV). 2.5 g (0.0126 mole) of ω-methoxyfluoroacetophenone (I) and 31.5 g (0.063 mole) of o-benzylvanillic acid anhydride (II) are ground, mixed with 7.65 g of triethylamine, and heated for 4 hours at 150–160°. The cooled melt is dissolved in 200 ml of alcohol and 35 ml of water containing 25 g of caustic potash, boiled for 30 min., and the alcohol is removed under reduced pressure. The residue is dissolved in 200 ml of water and saturated with carbon dioxide. A yellow-green precipitate (3.41 g) of 5,7-dioxy-4′-benzyloxy-3,3′-dimethoxyflavone (III) separates. The entire precipitate is heated for 1 hour on a boiling water bath with 135 ml of glacial acetic acid and 63 ml of concentrated hydrochloric acid. The solution is poured into water and left overnight. 5,7,4′-Trioxy-3,3′-dimethoxyflavone (IV) separates in the form of small crystals. After three crystallizations from alcohol the yield is 1.32 g (31.6% based on ω-methoxyfluoroacetophenone). M.p. 258–259°.

Found, %: C 61.72; H 4.56
$C_{17}H_{14}O_7$. Calculated, %: C 61.82; H 4.27.

B. 3,5,7,3′,4′-Pentaoxyflavone (quercetin) (V). 420 mg of 5,7,4′-trioxy-3,3′-dimethoxyflavone (IV) and 18 ml of freshly distilled hydriodic acid (b.p. 125–126°) are heated for 2 hours on an oil bath to 150–155°. The bright-yellow small crystals are filtered off and crystallized from 70% alcohol. Yield 300 mg (78.1%). M.p. 311–312°. A mixed sample with natural quercetin gives no depression. λ_{max} 375 and 255 mμ, $E^{1\%}_{1\mathrm{cm}}$ 719 and 671, respectively. R_f 0.38 –in 60% acetic acid.

Found, %: C 59.48; H 3.56
$C_{15}H_{10}O_7$. Calculated, %: C 59.61; H 3.34.

B. Quercetin-3-rutinoside (rutin) (VII). a. Potassium salt of

quercetin (VI). 0.7 g (0.00232 mole) of quercetin (V) is dissolved in 50 ml of alcohol and added to 14 ml of alcohol containing 0.84 g (0.00857 mole) of potassium acetate. During precipitation, the pH of the solution is maintained at about 8 by adding an alcoholic solution of caustic potash. The precipitated potassium salt of quercetin is filtered off and washed with alcohol. Yield 0.74 g.

b. Quercetin-3-rutinoside (VII). To 75 ml of distilled liquid ammonia are added 0.3 g (0.00088 mole) of the potassium salt of quercetin (VI) and 0.85 g (0.00132 mole) of α-acetobromorutinose (α-acetobromo-β-1-L-rhamnosido-6-D-glucose). The ammonia is removed; to the residue 75 ml of dry methyl alcohol is added and it is left for 24 hours. The mineral precipitate is filtered off; methyl alcohol is distilled from the filtrate under reduced pressure, and 0.83 g of technical synthetic rutin is obtained. For purification, a 60-mg sample of the substance is dissolved in 20 ml of ethyl alcohol and subjected to paper chromatography (filter paper of density 120, manufactured by the Volodarskii factory). Development is carried out with 22% isopropyl alcohol and the spots are located with a fluoroscope. R_f 0.53. The substance is eluted with ethyl alcohol.

Fig. 2. Paper chromatogram of synthetic and natural rutin and their mixture in 15% acetic acid: 1 –synthetic rutin (R_f 0.60), 2 –mixture of synthetic and natural rutin (R_f 0.59), 3 –natural rutin (R_f 0.60)

For comparison of synthetic and natural rutin, spots of alcoholic solutions of rutins are applied to the paper: 1) synthetic, 2) a mixture of synthetic and natural, and 3) natural. Development is carried out with 15% acetic acid, and visualization with a 1% alcoholic solution of aluminum chloride. In the light of the fluoroscope, spots of intense yellow color are obtained, the R_f values of which for the natural and synthetic samples are 0.60, and for their mixture 0.59 (Fig. 2).

For synthetic rutin and its mixture with natural rutin, two additional weak spots were detected on the chromatogram in the light of the fluoroscope: a green one, fluorescing with R_f 0.145 (Fig. 2, *1a* and *2a*), and yellow ones with R_f 0.77 (*1b* and *2b*).

The spots with R_f 0.145 contain the starting sugars, and those with R_f 0.77 contain substances possessing intense absorption of ultraviolet light with a maximum in the region of 290–295 mμ.

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Note: Figure translations are in progress. See original paper for figures.