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The Synthesis of Isoquercitrin

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Sufficient quantities of isoquercitrin (3,3′,4′,5,7-pentahydroxyflavone-3-glucoside) are needed for biological studies involving the possible value of this compound, as compared with rutin, in alleviation of capillary fragility and irradiation injury. No report, however, of the synthesis of isoquercitrin has been found in the literature. Previously described methods for the synthesis of other flavonoid glycosides by use of the aglycone with acetobromoglucose have been tried without success for the synthesis of isoquercitrin. This paper reports a synthesis of isoquercitrin based on the reaction of acetobromoglucose with the potassium salt of quercetin, using liquid ammonia as solvent.

Introduction

Certain flavone and flavanone glycosides have been synthesized by treating an acetone solution of the aglycone with acetobromoglucose in the presence of aqueous potassium hydroxide.[1] The resulting product is then deacetylated to yield the free glycoside.

The Koenigs–Knorr synthesis, with minor modifications, has also been employed in the preparation of flavone and flavanone glycosides.[2] In accordance with this method, the aglycone in a suitable solvent is treated with acetobromoglucose in the presence of silver oxide. Finally, the product is deacetylated in alkaline solution.

Flavanone glycosides also have been synthesized by the condensation of hydroxyacetophenone glycosides with benzaldehyde.[3]

By the treatment of *o*-hydroxychalcone glycosides with hydrogen peroxide in alkaline solution, Reichel[4] was able to prepare the corresponding flavonol glycoside.

The authors, however, have been unable to find any reference in the literature to the synthesis of a pentahydroxyflavonol glycoside, or to the synthesis of any flavonol glycoside by the reaction of the aglycone with acetobromoglucose.

In a long series of experiments, the methods previously described for the reaction of an aglycone with acetobromoglucose have been thoroughly investigated. In no case was there any evidence of the formation of isoquercitrin from the reaction of quercetin and acetobromoglucose. Consequently, a different method suitable for the synthesis of isoquercitrin was sought. Such a method involving the use of liquid ammonia has been found and is described below.

Experimental

Preparation of Acetobromoglucose.—Acetobromoglucose (tetraacetyl α-D-glucopyranosyl bromide) was prepared according to the method of MacKenzie.[5]

Preparation of the Potassium Salt of Quercetin.—A 10-g. sample of quercetin was dissolved in 400 ml. of 95% ethanol. This solution was added to 200 ml. of 95% ethanol containing 12 g. of potassium acetate. The *p*H of the solution was maintained at approximately 8 during the precipitation by the addition of alcoholic potassium hydroxide. The precipitated potassium salt was filtered off and washed with ethanol; yield 11 g. Analysis showed the material to be a monopotassium salt.

Anal. Calcd. for $C_{15}H_9O_7K$: K, 11.48. Found: K, 11.71.

Synthesis of Isoquercitrin.—To the reaction vessel were added 0.2 g. of the potassium salt of quercetin, 50 ml. of liquid ammonia and 0.4 g. of acetobromoglucose. The ammonia was allowed to evaporate (approximately 1 hour) and the residue was then treated with 50 ml. of anhydrous methanol. The reaction mixture was let stand for 24 hours, protected from moisture. After filtering through a sintered glass filter, the methanol was removed from the filtrate by distillation at reduced pressure. The residue was then dissolved in 10 ml. of methanol and the solution passed through a 1-inch magnesol column.[6] The column was eluted with ethyl acetate saturated with water and the brown glucoside band collected as a separate fraction. This fraction was taken to dryness by distillation at reduced pressure; yield 25 mg.

The yields from several runs were combined and rechromatographed on the magnesol column. Finally, the product was recrystallized from hot water, and dried at 110°, m.p. 230° uncor. When a mixed melting point was run with authentic isoquercitrin, there was no depression of the melting point.

The R_f values for the synthetic isoquercitrin were determined in 15% acetic acid, 60% acetic acid and in butanol–acetic acid–water (40–10–50% by volume).[7] The results agreed with the values given by authentic isoquercitrin. The ultraviolet absorption spectrum was identical with that of known isoquercitrin.

A sample of the synthetic isoquercitrin was methylated with dimethyl sulfate and potassium carbonate in acetone solution. The resulting product was then hydrolyzed to yield 3′,4′,5,7-tetramethoxyquercetin, m.p. 195–196°, which agrees with the value previously reported for this compound.[8]

Discussion

Since quercetin and acetobromoglucose are readily available, this method makes the synthesis of isoquercitrin, in gram quantities, feasible. The conditions given for the reaction are considered to be optimum. Further investigation, however, may well discover means of increasing the yield.

From the results of a number of experiments, it seems clear that the reaction between acetobromoglucose and the potassium salt occurs only in the liquid ammonia. The product is then deacetylated upon standing in ammoniacal methanol.

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