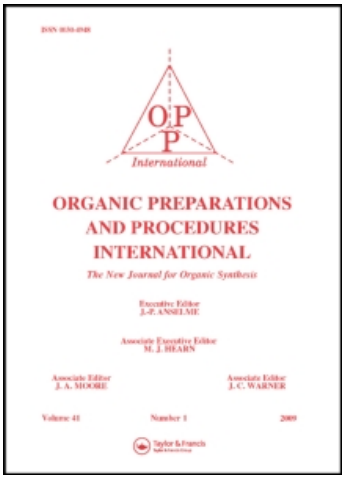

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A CONVENIENT METHOD FOR THE SYNTHESIS OF KAEMPFEROL

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Kaempferol (VI), 2-(4-hydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one, and quercetin, 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one,

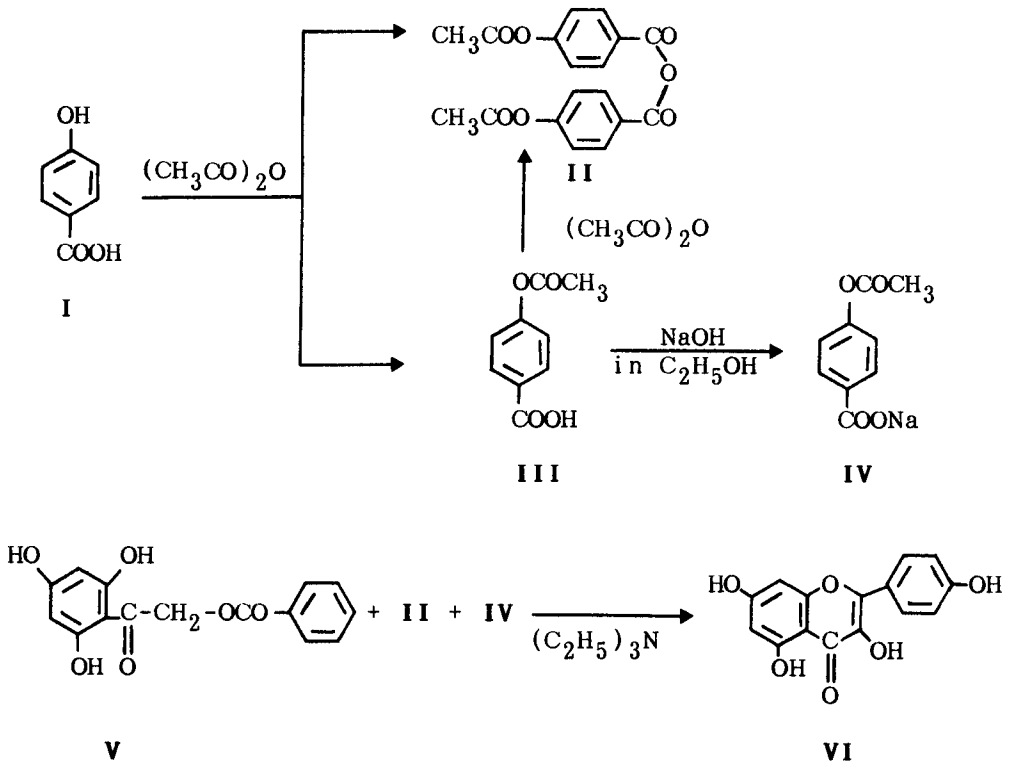

FIG. 1

occur in conjugated or free forms in many edible plants.[1-3] Oral administration of the plant bracken fern (Pteridium aquilinum) (BF) produced tumors at several sites in a variety of animals.[3,4] Kaempferol and quercetin were isolated from BF.[2,3] They displayed mutagenic activity in Salmonella typhimurium TA 98 and TA 100 strains.[5-7] We[3] recently demonstrated the carcinogenicity of quercetin for the rat intestine and urinary bladder, organs susceptible to tumor formation by oral BF.[3-5] Since kaempferol is present in larger concentrations in BF than is quercetin,[3] we required sufficient quantities of kaempferol to facilitate biological tests of this major plant flavonol.

A satisfactory method for the synthesis of kaempferol has not been reported. Quercetin was first synthesized in 1904 by Kostanecki et al.[8] An improved synthesis was reported in 1962 by Shakhova, et al.[9] Quercetin was obtained by the interaction of ω-methoxyphloracetophenone and the anhydride of O-benzylvanillic acid using triethylamine as the condensing agent.[8,9] Kaempferide, 2-(4-methoxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one, was prepared in an analogous process through the condensation of ω- benzoyloxyphloracetophenone (V), mp. 234-235° (lit. mp. 234-235°)[10] with anisic anhydride.[10] In preliminary studies, we found that neither of these methods led directly to the synthesis of VI. For example, to obtain VI from kaempferide, further hydrolysis of the methoxy group was necessary resulting in a low overall yield.

The synthesis of kaempferol in 35% overall yield is illustrated in Figure 1. Improvements over previously reported syntheses are described.

EXPERIMENTAL

Acetylation of p-Hydroxybenzoic Acid (I) to p-Acetyloxybenzoic Anhydride (II) and p-Acetyloxybenzoic Acid (III). - A suspension of 100 g. of I in 500 ml. of acetic anhydride (Ac_2O) was heated under reflux for 10 hrs. Excess Ac_2O was nearly completely removed in vacuo below 60°, and the residue was poured into 1,000 ml. of H_2O in an ice bath. The solid was collected by suction, washed with H_2O, and dried. The

crystalline mass was treated with 800 ml. of 2% aq. NaOH soln. below 10^{o} for 5 min. with shaking. The insoluble material was collected by suction, washed with H_2O, and dried. Recrystallization from ethanol-water (7/3) gave 63 g. of II as colorless prisms, mp. 91-92°; ir (KBr) cm^{-1}: 1730 and 1760 (C=O); MS: M^+ m/e: 342, calcd. 342; 299 (M^+ - CH_3CO) and 256 (M^+ - 2 CH_3CO). II gave no depression of mp. with p-acetyloxybenzoic anhydride, mp. 91-92°, prepared by the condensation of p-acetyloxybenzoyl chloride with p-acetyloxybenzoic acid in the presence of pyridine.[11]

Conversely, when the above alkaline filtrate was acidified with HCl, the crystalline precipitate was washed with H_2O, dried, and recrystallized from ethanol-water (3/7) to yield 45 g. of III as colorless needles, mp. 191-193°;[12] MS: M^+ m/e: 180, calcd. 180.

When the acetylation reaction was allowed to stand for 72 hrs. at 23° after heating for 10 hrs., II was obtained in an 85% yield by the described reaction treatment after the removal of Ac_2O.

Preparation of Sodium p-Acetyloxybenzoate (IV). - To a soln. of 45 g. of III in 300 ml. of ethanol, a soln. of 10 g. NaOH in 300 ml. of 95% ethanol was gradually added with stirring and the mixture was allowed to stand overnight at 5°-10°. The separated crystalline mass was collected by suction, washed with a small amount of ethanol, and dried. Recrystallization from 50% aq. ethanolic soln. gave the product (IV) as colorless needles, mp.> 300 in 85% yield; ir (KBr) cm^{-1}: 1740 (C=O). When IV was dissolved in H_2O and acidified with HCl, III was recovered almost quantitatively.

Reaction of p-Acetyloxybenzoic Acid (III) with Acetic Anhydride to Yield p-Acetyloxybenzoic Anhydride (II). - A suspension of 100 g. of III in 500 ml. of Ac_2O was heated under reflux for 10 hrs. and then allowed to stand for 72 hrs. at 23°. After the reaction was completed, the reaction soln. was treated in the same manner as that of the reaction of I with Ac_2O to give II in an 85% yield as colorless prisms; mp. and mixed mp. with II prepared as described above was 91-92°.

Reaction of p-Acetyloxybenzoic Anhydride (II) with ω-Benzoyloxyphloracetophenone (V) in the Presence of Sodium p-Acetyloxybenzoate (IV) and Triethylamine. - To a mixture of 102.6 g. (0.30 mol) of II, 28.28 g. (0.14 mol) of IV, and 28.8 g. (0.10 mol) of V, 14 g. (0.14 mol) of triethylamine was added. A molar ratio of between two to three of II to one of V was optimal in contrast to previously reported[8-10] molar ratios of 10 to 15 of methoxybenzoic anhydrides to phloracetophenones. The mixture was heated on an oil bath maintained at 160-165° for 8 hrs.; mechanical stirring was used for about 20 min. until the hardening of the mass prevented it. After the reaction was completed, the mass was crushed in 760 ml. of ethanol on a water bath and then dissolved in a soln. of 95.2 g. of KOH in 136 ml. of H_2O that was gradually added. The solution was heated under reflux for 30 min., and the ethanol was removed in vacuo below 40°. The residue was dissolved in 1,000 ml. of H_2O, and the filtered soln. was acidified with HCl. Previously described methods[8-10] using CO_2 (dry ice) for separation of 3-hydroxy-methoxy-flavones resulted in incomplete crystallization. The separated crystalline mass was collected by suction, washed with H_2O, and dried. The solid was dissolved by heating with a mixture of 100 ml. of HCl and 200 ml. of acetic acid on a water bath for 1 hr., and then poured into 1,000 ml. of H_2O to separate the crude product (VI). The precipitate (VI) was collected by suction, washed with H_2O, and dried. Recrystallization from ethanol-water (1/1) with active charcoal gave an analytical sample of the product (VI) as light yellow powder, mp. 278-280° (decomp.) in 43% yield (12.3 g.); ir (KBr) cm^{-1}: 1660 (C=O);[13] MS: M^+ m/e: 286, calcd. 286. VI gave no depression of the mp. with kaempferol [mp. 278-280° (decomp.)][14]. The ir, UV, and MS of VI were also identical in all respects with those of kaempferol.

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