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[Dedicated to Professor Robert B. Woodward on the occasion of his 60th birthday.]

THE BIRCH REDUCTION OF QUERCETIN METHYL ETHERS

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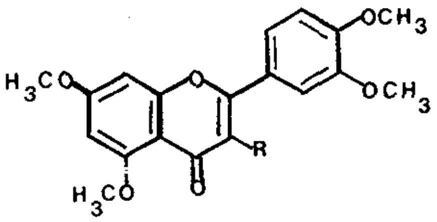
The sodium-ammonia reduction of 3,3',4',5,7-pentamethylquercetin (I) afforded the dihydrochalcone (II) in 54% yield. In contrast, the reduction of 3',4',5,7-tetramethylquercetin (III) yielded the α-hydroxydihydrochalcone (IV) (64% yield) as major product. The reactions are believed to proceed through the intermediary formation of 2,3-*trans*-dihydroquercetins.

Regiospecific 1,2-reductions of flavonols, either at the carbonyl or the $\Delta^{2,3}$-double bond, are known to proceed poorly as a result of electronic and steric interactions[1]. We would like to communicate that the heterocyclic ring of 3,3',4',5,7-pentamethylquercetin (I) is smoothly hydrogenolyzed by sodium in liquid ammonia to yield 2'-hydroxy-3,4,4',6'-tetramethoxydihydrochalcone (II), with the loss of the methoxy group originally attached to the flavone C_3-position.

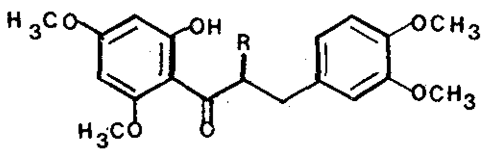
To a suspension of 1 g (2.7 mmoles) (I) in liquid ammonia (40 ml), sodium (400 mg, 17.4 mmoles) was added in three portions over 10 minutes. After stirring for one hour the mixture was quenched with ammonium chloride; the ammonia was evaporated, and the residue was partitioned between 1% acetic acid and chloroform. The organic layer afforded a brown oil, which was crystallized from methanol to yield 518 mg (54%) of II. m.p. 124-5° (lit.[2] 125-6°). NMR ($CDCl_3$): 4H m at δ 2.8-3.4 ppm (2 CH_2), 12H s at δ 3.8 ppm (4OCH_3), 2H q at

δ 6.0 ppm ($C_{3'}H$ and $C_{5'}H$) and 3H s at δ 6.8 ppm (C_2H, C_5H and C_6H). MS (m/e, relative intensity): M^+ 346 (57), 181 (100), 164 (85) and 151 (42).



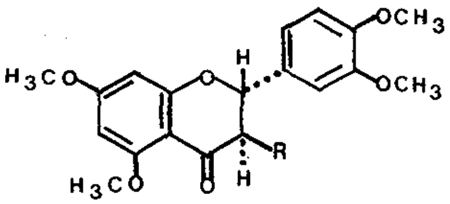
(I) R = OCH_3

(III) R = OH



(II) R = H

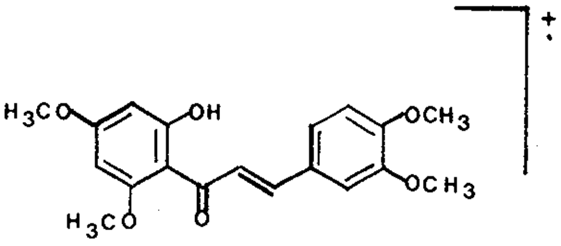
(IV) R = OH



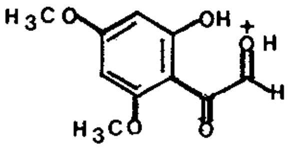
(V) R = OCH_3

(VI) R = OH

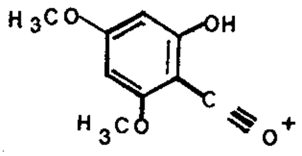
When 3',4',5,7-tetramethylquercetin (III)[3] was reduced with excess sodium as above, however, the corresponding 2',α-dihydroxy-3,4,4',6'-tetramethoxydihydrochalcone (IV) was isolated from preparative TLC on silica gel (eluant: 50% EtOAc-hexane) in 64% yield, m.p. 118-20° (MeOH). (Calc. for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12. Found: C, 62.75; H, 6.16.) The NMR ($CDCl_3$) of IV showed a 2H multiplet at δ 2.75-3.05 ppm for the benzyl CH_2 and a broad 1H quartet at δ 5.3-5.5 ppm for the proton α- to the keto group. The mass spectrum included fragments at m/e 344 (M^+-H_2O), 211, 181, and 151, which were assigned as follows:



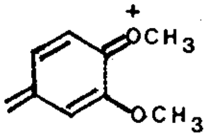
m/e 344



m/e 211



m/e 181



m/e 151

Furthermore, the Birch reduction of the corresponding 2,3-trans-dihydroquercetins V and VI afforded, as expected, the dihydrochalcones II and IV in 31 and 23% yield, respectively. From these results, one plausible mechanism would involve first the two-electron reduction of the flavonol to the 2,3-dihydro derivative, followed by base catalyzed opening to the α-substituted chalcone and further reduction to the final products.

α-Hydroxydihydrochalcones have been found in nature quite recently.[4,5] The Birch reduction of readily available flavonols seems a convenient route for the synthesis of specific members of this group of natural products.

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