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THE DIRECT SYNTHESIS OF 5,7-DIHYDROXY-6-METHOXYFLAVONES I. SYNTHESIS OF 4',6-DIMETHOXY-3',5,7-TRIHYDROXYFLAVONE AND PECTOLINARIGENIN.+

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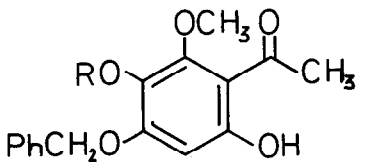
So far one has only succeded in synthetising 5,7-dihydroxy-6-methoxyflavones bearing not more than one substituent on the phenyl side chain /B-ring/[1-9]. We tried to solve this problem by alkaline ring isomerization[10-12].

With our new method 5,7-dihydroxy-6-methoxyflavones can be prepared in high yield without restrictions concerning the substitution of the B-ring and avoiding the production of the 5,7,8-substituted isomers. For illustration the synthesis of 4',6-dimethoxy-3',5,7-trihydroxyflavone, isolated from Centaurea nigrescens Willd. by Bohlman and Zdero[13] and pectolinarigenin is given.



I : R = H

II : R = OCH_3

The key intermediate of our syntheses 4-benzyloxy-2,5-dihydroxy-6-methoxyacetophenone /I/ was prepared from the readily accessible 4-benzyloxy-2-hydroxy-6-methoxyacetophenone by persulfate oxidation according to Elbs and subsequent careful decomposition of the primarily formed sulfate ester. The m.p. of I /109-110°/ differed significantly from the literature value /161-162°/[2]. The structure of I was confirmed by its NMR spectrum [δ, ppm, 2.67 /s, CH_3CO/, 3.96 /s, OCH_3/, 5.12 /s, $PhCH_2$/, 5.25 /s, C_5-OH/, 6.33 /s, C_3-H/, 7.39 /s, benzyl-aromatic

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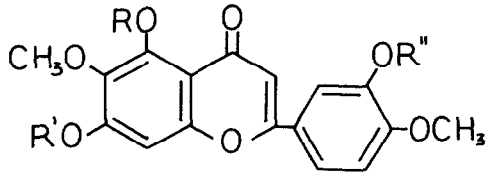
H/, 13.11 /s, C_2-OH/] and analysis /Found: C, 66.64; H, 5.69. $C_{16}H_{16}O_5$ required: C, 66.66; H, 5.69%/. I was converted to 4-benzyloxy-2-hydroxy-5,6-dimethoxyacetophenone /II, m.p. 84-85°/ by partial methylation.

Acylation of II with benzyl-isovanillic acid chloride yielded 4-benzyloxy-2-/3-benzyloxy-4-methoxybenzoyloxy-/-5,6-dimethoxyacetophenone /III/, that was isomerised to 3',4-dibenzyloxy-2-hydroxy-4',5,6-trimethoxydibenzoylmethane /IV, m.p. 136-137°/ by Baker-Venkataraman transformation[15,16]. Acid catalysed ring closure of IV gave 3',7-dibenzyloxy-4',5,6-trimethoxyflavone /V, m.p. 140-141°/. V was debenzylated by hydrogenation to 3',7-dihydroxy-4',5,6-trimethoxyflavone /VI, m.p. 211-213°/.

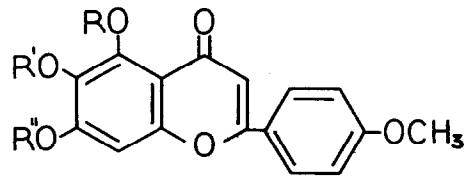


V : R = CH_3, R' = R" = CH_2Ph
VI : R = CH_3, R' = R" = H
VII : R = R' = R" = H

Demethylation of VI with $AlCl_3$ in acetonitrile furnished 4',6-dimethoxy-3',5,7-trihydroxyflavone /VII/ in good yield. The properties of VII [m.p. 269-270°, λ_{max} 273 and 342 nm, NMR /in DMSO-d_6/ δ, ppm, 3.90 /s, OCH_3/, 6.58 /s, C_3-H/, 6.73 /s, C_8-H/, 7.09 /d, C_5,-H/, 7.43 /d, C_2,-H/, 7.6-8.2 /m, C_6,-H/, 10.66 /s, C_3,-OH/, 9.40 /s, C_7-OH/ and 13.7 /C_5-OH/] and its triacetate / m.p. 186-188°/ were in good agreement with values for the natural product[16] [m.p. 269-272°, λ_{max} 273 and 342 nm, NMR /100 Mc, in DMSO-d_6/ δ, ppm, 6.58 /s, C_3-H/, 6.73 /s, C_8-H/, 7.08 /d, C_5,-H/, 7.41 /d, C_2,-H/, 7.52 /q, C_6,-H/] and its triacetate /m.p. 189-190°/ resp. Unfortunately natural VII was not available for direct comparison.

As the next member of the group pectolinarigenin was synthetised. Allan-Robinson condensation of I with anisic anhydride at 170° gave 7-benzyloxy-5,6-dihydroxy-4'-methoxyflavone /VIII, m.p. 233-234°/. VIII was methylated to 5,6,4'-trimethoxy-7-benzyloxyflavone /IX, m.p. 148-149°/. As the m.p.-s of both VIII and IX were significantly different from those published in the literature /197-

198° and 184-185° resp.[7,3]/ their structures were secured by NMR-spectra [δ, ppm, VIII: 3.87 /s, OCH_3/, 5.31 /s, $PhCH_2$/, 6.62 /C_3-H/, 6.83 /C_8-H/, 7.13 /d, C_3,-H, C_5,-H/, 7.47 /s, benzyl-aromatic-H/, 8.13 /d, C_2,-H, C_6,-H/, 8.85 /s, C_6-OH/ and 12.35 /C_5-OH/; IX: 3.85-3.99 /3 closely spaced singlets, 3xOCH_3/, 5.23 /s, $PhCH_2$/, 6.57 /s, C_3-H/, 6.87 /s, C_8-H/, 7.00 /d, C_3,-H, C_5,-H/, 7.47 /s, benzyl-aromatic-H/ and 7.83 /d, C_2,-H, C_6,-H/].



VIII: R = R' = H, R" = CH_2Ph

IX: R = R' = CH_3, R" = CH_2Ph

X: R = R" = H, R' = CH_3

The cautious treatment of IX with 40% HBr in AcOH provided 5,7-dihydroxy-4',6-dimethoxyflavone /X/, that was identical in every respect with an authentic sample of pectolinarigenin[17].

All new compounds prepared have correct elementary analyses and the expected NMR spectra.

The extension of our method to the synthesis of 5,7-dihydroxy-6-methoxyflavonols is in progress.

After the completion of this work a preliminary paper reporting a different approach to the synthesis of VIII has been published by Fukui et al.[18]

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