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THE SYNTHESIS OF 6C-METHYLNARINGENIN (PORIOL) AND AN UNAMBIGUOUS SYNTHESIS OF ITS 7,4'-DIMETHYL ETHER

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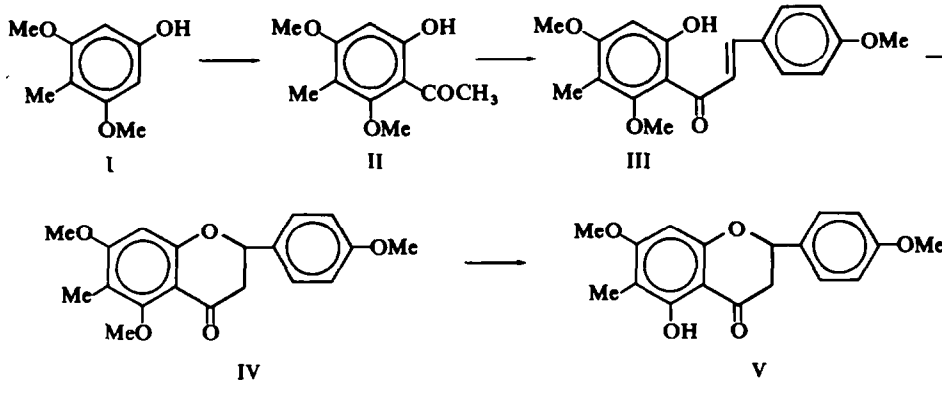
Abstract—An unambiguous synthesis of 6-C-methylnaringenin dimethyl ether (V) has been carried out starting from 4 methyl-3,5-dimethoxyphenol (I) and using 5-methyl-2-hydroxy-4,6-dimethoxyacetophenone (II) as the intermediate. It could not be demethylated to 6-C-methylnaringenin (poriol, IX). Therefore, an alternative method has been worked out; it involves condensation of C-methylphloracetophenone 6-methyl ether (VIb) with *p*-hydroxybenzaldehyde to the chalkone (VII), isomerization to the flavanone, poriol-5-methyl ether (VIII) and final demethylation.

PORIOL was isolated recently from the diseased (*Porii weirii* Murr) root-bark of Douglas fir (*Pseudotsuga menziesii*) and given the structure of 6-C-methylnaringenin (IX) on the basis of its colour reactions and spectral data (UV, IR, NMR and mass);[1] further its partial dimethyl ether agreed with 6-C-methyl-7,4'-di-O-methylnaringenin (V) which had earlier been made by nuclear methylation of naringenin.[2] Although the structure of the synthetic product (V) had been established by various transformations, its unambiguous synthesis has not so far been effected. This has now been done and together with the unambiguous synthesis of poriol itself fully confirms the proposed constitution.

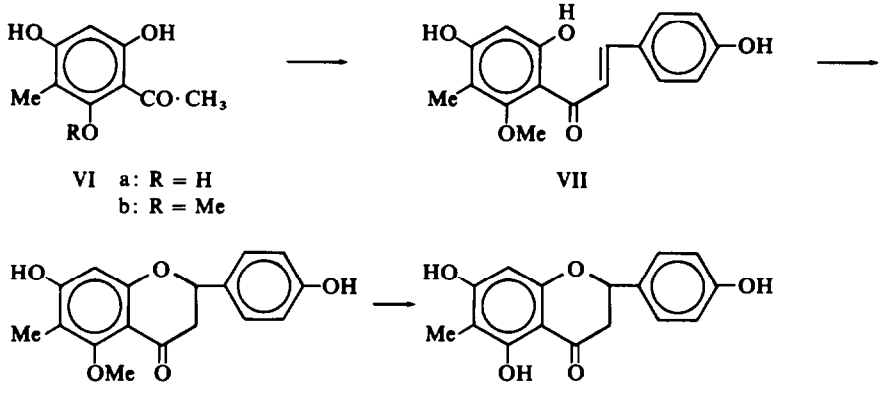
CHART 1. Synthesis of 7,4' di-O-methylporiol (V)



The synthesis of the dimethyl ether (Chart 1, V) starts from 4-methyl-3,5-dimethoxyphenol (I) the preparation of which was described recently.[3] Although the phenol (I) does not undergo Hoesch reaction, it readily condenses with acetyl chloride

under Friedel–Crafts' conditions to form 5-methyl-2-hydroxy-4,6-dimethoxyacetophenone (II) prepared earlier in another way.[4] Alkali condensation of the ketone (II) with anisaldehyde gives good yields of the corresponding chalkone (III) which undergoes cyclization to the flavanone (IV). This flavanone is unstable and undergoes ring opening to the chalkone during crystallization from methanol or chromatography over silica gel. However, after selective demethylation with anhydrous aluminium chloride in dry acetonitrile medium, the more stable 6-C-methyl-7,4′-di-O-methylnaringenin (V) is obtained in very good yields. Complete demethylation to poriol (6-C-methylnaringenin, IX) was unsuccessful; similar failure to demethylate simple 7,4′-di-O-methylnaringenin has been recorded earlier.[5]

CHART 2. Synthesis of poriol (IX)



Therefore, the synthesis of poriol itself has been achieved by an alternative method as shown in Chart 2. C-Methylphloracetophenone (VIa) was converted into 5-methyl-2,4-dihydroxy-6-methoxyacetophenone (VIb)[6] and condensed with *p*-hydroxybenzaldehyde to give 5′-methyl-4,2′,4′-trihydroxy-6′-methoxychalkone (VII). It may be noted that no flavanone (VIII) was formed directly in this condensation as was found in the condensation of the same ketone with benzaldehyde earlier.[7] This may be due to the stabilizing influence of 4-hydroxy in the chalkone (VII). Therefore, cyclization to the corresponding flavanone (VIII) has been brought about in an independent step, and the mixture of chalkone (VII) and flavanone (VIII) thus obtained separated by column chromatography. Final demethylation of the labile OMe group in the 5-position of the flavanone with anhydrous aluminium chloride in acetonitrile medium gave 6-C-methylnaringenin (IX) in good yield. It was found to be identical with poriol in all respects, such as m.p., UV, R_f value and finger-print region of the IR spectrum.

C-Methylphloracetophenone (VIa) the starting material for the synthesis of poriol, has been made by a number of methods. (1) The acetylation of C-methylphloroglucinol[8] which is difficult to prepare. (2) Methylation of phloracetophenone with methyl iodide in the presence of potassium carbonate and acetone and demethylation of the resulting C-methylphloracetophenone dimethyl ether.[8] (3)

Probably, the most satisfactory method is the formylation of phloroacetophenone by Gattermann–Adams' method and preferential reduction of the aldehyde with zinc amalgam and hydrochloric acid.[9] (4) An alternative method for the direct C-methylation of phloracetophenone in a single step was reported in an earlier paper.[10] It has now been examined in greater detail and good yields of C-methylphloroacetophenone were obtained by adopting details given in the Experimental. Its identity was established beyond doubt by further di-O-methylation and the NMR spectrum which agrees with the expected structure.

EXPERIMENTAL

Unless otherwise stated, m.p's are uncorrected; light petroleum had boiling range 60–80°; UV spectra were taken in methanolic soln, and the figures given in parenthesis represent log ε values; IR spectra were taken in nujol and NMR spectra in $CDCl_3$ using 60 mc spectrometer; analytical TLC was carried out on silica gel plates using the solvent systems:—(A) toluene:ethyl formate:formic acid (5:4:1) (B) Chloroform:methanol (7:3); silica gel was used as adsorbent for column chromatography.

5-Methyl-2-hydroxy-4,6-dimethoxyacetophenone (II). This was made earlier by Fries migration;[4] Friedel–Crafts has now been found more satisfactory. Acetyl chloride (1 ml) was added dropwise during 15 min, to a stirred mixture of I[3] (0·5 g), anhyd $AlCl_3$ (1·6 g) and dry ether (30 ml), cooled to 0°. It was then left at room temp for 72 hr with occasional shaking. The $AlCl_3$ complex was decomposed with ice and HCl, and the resulting mixture extracted with ether. The ether soln was washed with $NaHCO_3$ aq and concentrated to an oil. This was subjected to column chromatography. The eluate with benzene–light petroleum mixture (1:3) gave a yellow oil[4] (0·25 g), b.p. 120–122°/2 mm; TLC (solvent A) showed a single spot; violet ferric reaction and positive DNP test.

5'-Methyl-2'-hydroxy, 4,4',6'-trimethoxychalcone (III). A soln of the above acetophenone (II, 0·8 g, and anisaldehyde (0·6 ml) in alcohol (15 ml) was treated with KOH aq (1·2 g in 1·3 ml of water) and heated to a clear soln. After 24 hr at room temp, the resulting mixture was treated with water and acidified. The solid was filtered, washed with $NaHCO_3$ aq and then crystallized from MeOH when III separated as yellow needles (0·85 g), m.p. 107–108°; deep brown ferric reaction; λ_{max} 361 mμ (4·52); λ_{min} 271 mμ (3·38). (Found: C, 69·9; H, 6·4. $C_{19}H_{20}O_5$ requires: C, 69·5; H, 6·1%).

6-C-Methyl-5,7,4'-trimethoxyflavanone (poriol trimethyl ether, IV). A soln of III (0·6 g) in alcohol (60 ml) was refluxed with conc H_2SO_4 (2·4 ml) for 40 hr, concentrated *in vacuo* and the residue extracted with ether. The residue from the ether layer was subjected to column chromatography. The eluate from benzene–light petroleum mixture (1:5) gave the unchanged chalcone (200 mg, R_f 0·89 in solvent A); while the eluate from 100% benzene gave a white solid (170 mg, R_f 0·70 in solvent A) which was crystallized from MeOH. The desired IV separated as colourless plates, m.p. 112–113°; negative ferric reaction; λ_{max} 278 mμ (4·14); λ_{min} 251 mμ (3·46); ν_{max} 1675 (s), 1610 (s), 1546 (w), 1511 (s), 1414 (m), 1344 (br), 1311 (w), 1300 (w), 1250 (s), 1205 (w), 1183 (br), 1152 (s), 1117 (s), 1085 (s), 1026 (m), 1000 (w), 936 (w), 902 (w), 873 (w), 840 (br), 820 (w), 785 (w), 770 (w) cm^{-1}; δ (CCl_4), 1·96 (s, 3H of aromatic $C\underline{H}_3$), 2·72 (two quartets of two protons in 3 position), 3·71, 3·81, 3·83 (3 singlets of 9 protons of three $OC\underline{H}_3$ groups), 5·21 (quartet of one proton in the 2-position), 6·13 (singlet of one aromatic proton in the 8 position), 6·78 (doublet of two protons in 3',5'-positions, J = 8 c/s), 7·25 ppm (doublet of two protons in 2',6'-positions, J = 7 c/s). (Found: C, 69·6; H, 6·3. $C_{19}H_{20}O_5$ requires: C, 69·5; H, 6·1%).

6-C-Methyl-5-hydroxy-7,4'-dimethoxyflavanone (Poriol dimethyl ether, V). To a soln of IV (0·1 g) in dry acetonitrile (4 ml) was added anhyd $AlCl_3$ (0·15 g) at 0°. After 40 min at room temp, the mixture was refluxed on a boiling water bath for 1 hr; the solvent was evaporated *in vacuo* and the residue treated with ice and dil HCl to decompose the complex. The solid was collected and crystallized from MeOH yielding V as white needles (80 mg), m.p. 147–148° (lit.[2] 148°); green ferric reaction; λ_{max} 291 mμ (4·35), λ^{min} 253 mμ (3·40); ν_{max} 1640 (s), 1618 (s), 1582 (m), 1508 (m), 1346 (m), 1289 (s), 1250 (s), 1221 (w), 1202 (m), 1188 (w), 1159 (s), 1132 (b), 1081 (m), 1062 (w), 1031 (m), 987 (w), 933 (w), 901 (m), 868 (w), 820 (s), 805 (m), 769 (s), 753 (m) cm^{-1}; δ in $CDCl_3$ 1·98 (s, one $C\underline{H}_3$), 2·83 (two quartets of two protons in 3 position), 3·80 (s, two $OC\underline{H}_3$), 5·33 (quartet, one H in 2 position), 6·04 (s, 1 aromatic H in the 8 position), 6·92 (d, two aromatic protons in 3',5' positions, J = 7·8 c/s), 7·38 ppm (d, two aromatic protons in 2',6' positions, J = 9·6 c/s). (Found: C, 68·8; H, 6·3. $C_{18}H_{18}O_5$ requires: C, 68·8, H, 5·8%).

5'-Methyl-4,2',4'-trihydroxy-6'-methoxychalcone (VII). To a soln of VIb[6] (0·7 g) and *p*-hydroxybenzaldehyde (0·8 g) in alcohol (6 ml) was added KOH aq (5·1 g in 3·8 ml water). It was shaken and kept for 80 hr at room temp out of contact with air. The resulting soln was diluted with water, acidified and extracted with ether. The ether soln was washed with $NaHCO_3$ aq, concentrated and the residual solid subjected to column chromatography. Elution first with benzene gave the unchanged VI (R_f 0·65 in solvent A) and then with EtOAc–benzene (3:97) gave the chalcone as a yellow solid (R_f 0·55 in solvent A). The chalcone (VII) crystallized from MeOH aq as yellow needles (400 mg), m.p. 179–180°; deep brown ferric reaction; λ_{max} 360 mμ (4·30); λ_{min} 274 mμ (3·13). (Found: C, 67·9; H, 5·8. $C_{17}H_{16}O_5$ requires: C, 68·0; H, 5·3%).

6-C-Methyl-7,4'-dihydroxy-5-methoxyflavanone (*Poriol 5-methyl ether*, VIII). A soln of VII (0·4 g) in alcohol (3·2 ml) was refluxed with NaOH aq (6·0 ml, 1·5%) for 30 min and left at room temp for 16 hr. The resulting mixture was acidified with dil AcOH and the solid collected. TLC (solvent A) showed it to be a mixture of two compounds. Hence it was subjected to column chromatography. Elution first with EtOAc–benzene (3:97) gave the unchanged chalcone (R_f 0·55 in solvent A) and then with EtOAc–benzene (15:85) gave the flavanone as a colourless solid (R_f 0·46 in solvent A). 5-O-Methylporiol (VIII) crystallized from EtOAc–chloroform as white crystals (0·15 g), m.p. 198–199°; negative ferric reaction; λ_{max} 281 mμ (4·27); λ_{min} 251 mμ (3·61); ν_{max} 1658 (s), 1608 (s), 1513 (br), 1361 (w), 1282 (br), 1165 (s), 1100 (m), 1085 (br), 999 (w), 950 (w), 904 (w), 837 (m), 812 (w) cm^{-1}. (Found: (i) C, 66·0; H, 5·6; (ii) C, 66·0; H, 5·7. $C_{17}H_{16}O_5 . \frac{1}{2} H_2O$ requires: C, 66·0; H, 5·5%).

6-C-Methyl-5,7,4'-trihydroxyflavanone (*poriol*, IX). To a soln of VIII (0·1 g) in dry acetonitrile (5 ml) was added anhyd $AlCl_3$ (0·2 g) at 0°. After 1 hr at room temp, the mixture was refluxed on a boiling water bath for 1 hr. The product crystallized from EtOAc–chloroform as pale yellow plates (70 mg), sintering at 258° and melting at 264° (lit.[1] 255–265°); bluish green ferric reaction; R_f 0·90 in solvent B; λ_{max} 293 mμ (4·22); λ_{min} 254 mμ (3·27); ν_{max} 3000 (br), 1645 (s), 1608 (s), 1502 (br), 1452 (br), 1333 (w), 1314 (w), 1300 (w), 1245 (s), 1189 (w), 1175 (w), 1161 (w), 1111 (s), 1083 (w), 993 (w), 901 (w), 865 (w), 843 (w), 826 (s), 760 (w), 735 (w), 699 (w) cm^{-1}. (Found: C, 67·4; H, 5·2. $C_{16}H_{14}O_5$ requires: C, 67·1; H, 4·9%). In all these properties it agrees with poriol.[1]

3-Methyl-phloracetophenone (VIa). To a refluxing soln of phloracetophenone (6 g), abs MeOH (20 ml) and MeI (12 ml), was added 10% methanolic KOH (20 ml) in 6 lots during 3 hr. During this period, more of MeI (6 ml) was added. The solvent was distilled off *in vacuo* and the residue treated with dil HCl and extracted with ether (300 ml). The ether soln was in turn extracted successively with 7% $NaHCO_3$ aq (60 ml), 7% Na_2CO_3 aq (4 × 60 ml). Each lot was acidified separately and all the products examined on TLC (solvent A). The $NaHCO_3$ extract did not give any significant amount. The first extract with Na_2CO_3 contained mainly phloracetophenone; the second a mixture of phloracetophenone and C-methylphloracetophenone, whereas the third and fourth contained C-methylphloracetophenone as the major portions. The third and fourth lots were mixed and recrystallized from water when C-methylphloracetophenone separated as colourless crystals (1·5 g), m.p. alone or when mixed with authentic sample 205–206°. The second lot was again taken in ether and fractionally extracted with Na_2CO_3 (4 × 15 ml). The last two fractions gave a further amount of C-methylphloracetophenone (0·5 g). The identity of the product was established by O-methylation with 2 molecular equivts of Me_2SO_4 in the presence of K_2CO_3-acetone, when 2-hydroxy-3-methyl-4,6-dimethoxyacetophenone formed colourless needles, m.p. and m.m.p. 141–142°; δ (in $CDCl_3$): 2·00 (s, 3 protons of aromatic $C\underline{H}_3$), 2·60 (s, 3 protons of —$COC\underline{H}_3$), 3·90 (singlet of 6 protons of two $OC\underline{H}_3$ groups), 5·98 ppm (singlet of one aromatic proton).

REFERENCES

1 G. M. Barton, *Canad. J. Chem.* **45**, 1020 (1967).
2 R. N. Goel, A. C. Jain and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **48A**, 180 (1958).
3 A. C. Jain, Pyare Lal and T. R. Seshadri, *Ind. J. Chem.* under publication.
4 H. F. Birch and A. Robertson, *J. Chem. Soc.* 306 (1938).
5 R. N. Khanna, S. K. Mukerji, J. D. Ramanathan and T. R. Seshadri, *Ind. J. Chem.* **3**, 160 (1965).
6 W. B. Whalley, *J. Chem. Soc.* 105 (1955).
7 S. C. Bhrara, A. C. Jain and T. R. Seshadri, *Ind. J. Chem.* **2**, 399 (1964).
8 F. H. Curd and A. Robertson, *J. Chem. Soc.* 437 (1933).
9 A. Robertson and W. B. Whalley, *Ibid.* 3355 (1951).
10 A. C. Jain and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **42A**, 279 (1955).