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SYNTHESIS OF ALPINUM ISOFLAVONE, OSAJIN AND WARANGALONE

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Genistein (1) when heated with prenyl bromide in the presence of methanolic methoxide yielded 7,4'-di-O-prenyl- (2), 6,8-di-CC-prenyl- (3) and 6-C-prenyl- (4) genisteins. Structures of these compounds were established by NMR spectra of themselves and their derivatives. Oxidative cyclisation of (4) with DDQ afforded natural alpinum isoflavone (6); whereas that of (3) gave a mixture of natural osajin (8) and warangalone (7) which were separated by chromatography and identified by mass spectra.

Four isopentenylated derivatives of genistein are known to occur in Nature. They are alpinum isoflavone[1], osajin[2], warangalone[3] (scandenone)[4] and chandalone[3]. Their constitutions as 5,4'-dihydroxy-6",6"-dimethylpyrano- (2",3" : 7,6)-isoflavone (6), 5,4'-dihydroxy-6-C-prenyl-6",6"-dimethylpyrano- (2",3" : 7,8)-isoflavone (8), 5,4'-dihydroxy-8-C-prenyl-6",6"-dimethylpyrano-(2",3" : 7,6)-isoflavone (7) and 5,4'-dihydroxy-3'-C-prenyl-6",6"-dimethylpyrano- (2",3" : 7,6)-isoflavone respectively has been established on the basis of their degradation products, spectral data and in the first three cases by synthesis of their 4'-methyl ethers[5]. However none of them has been synthesised so far. The synthesis of the first three isoflavones themselves has now been accomplished.

Genistein[6] (1) when reacted with γ,γ-dimethylallyl (or prenyl) bromide in the presence of methanolic methoxide gave a mixture of several products as shown by TLC but only three compounds could be obtained in pure form after column chromatography. The first eluate yielded an oily liquid which resisted crystallisation but was TLC[7] homogeneous (R_f 0.70, solvent B) and identical with the product obtained by prenylation of genistein with two moles of prenyl bromide in the presence of K_2CO_3 and acetone. It is identified as 7,4'-di-O-prenylgenistein (2) on the basis of its NMR[7] in $CDCl_3$: δ 1.77, 1.82 (2s, 12H, $(CH_3)_2.C=$), 4.63 (m, 4H, $-OCH_2-$), 5.53 (m, 2H, $-CH=$), 6.38, 6.42 (2d, J = 2Hz, 2H in positions 6 and 8), 6.95 (d, J=9Hz, 2H in positions 3' and 5'), 7.47 (d, J =9Hz, 2H in positions 2' and 6') and 7.73 ppm (s, 1H in position 2).

The second eluate afforded colourless crystals, m.p. 140°; which formed triacetatem m.p. 190°; R_f 0.80 (solvent C) and dimethyl ether, m.p. 86°; R_f 0.67 (solvent A); positive ferric reation. The following NMR data of the prenylation

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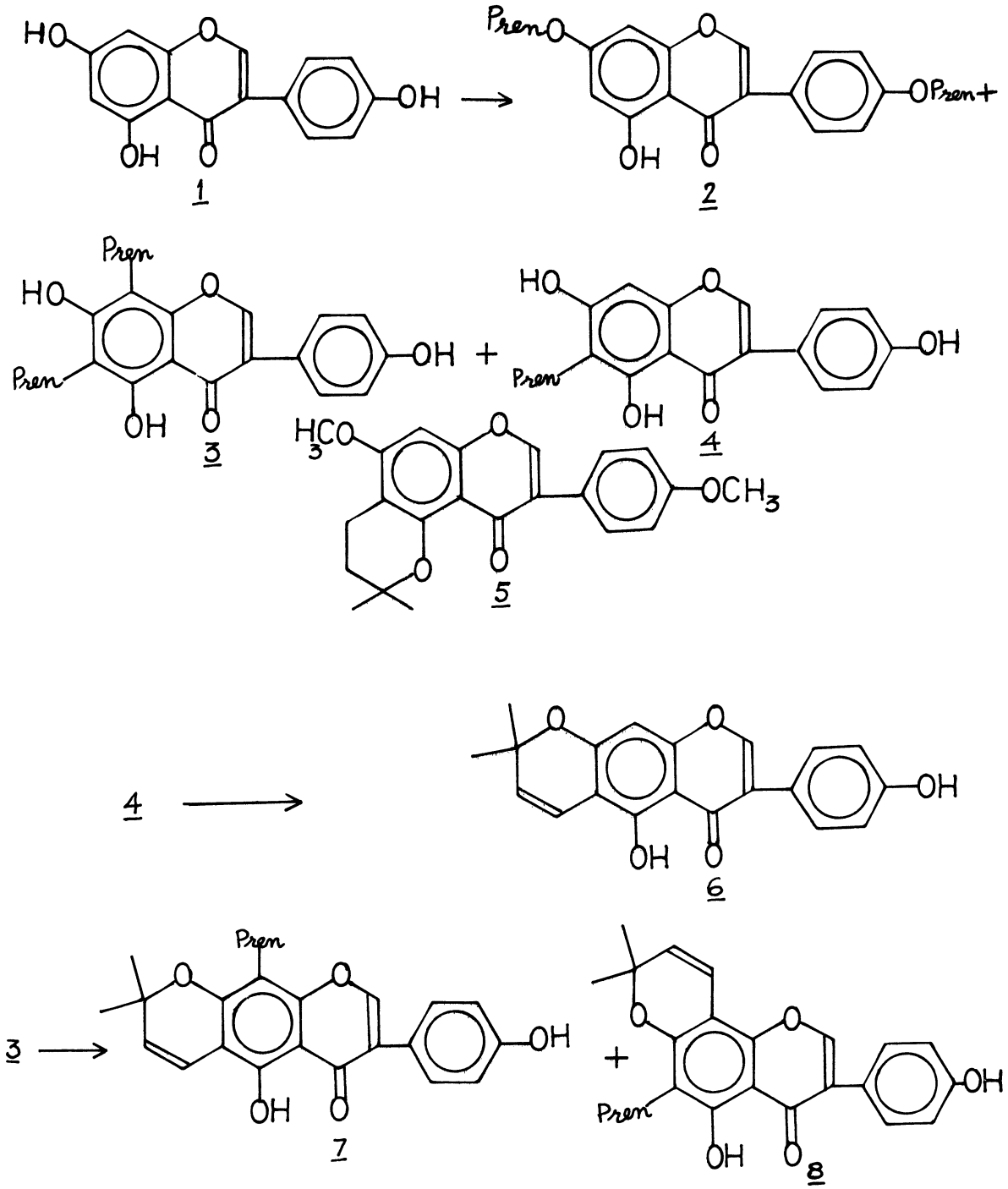
product itself, its triacetate and dimethyl ether indicated it as 6,8-di-C-prenylgenistein (3): NMR of hydroxy compound in $CDCl_3$: δ 1.87, 1.98 (2 broad s, 12H, $(CH_3)_2$.C=), 3.55, 3.68 (2d, J = 3Hz, 4H, Ar-CH_2), 5.42 (m, 2H, -CH=), 6.95 (d, J = 9Hz, 2H in positions 3' and 5'), 7.50 (d, J = 9Hz, 2H in 2' and 6' positions) and 8.08 ppm (s, 1H in position 2); NMR of triacetate in $CDCl_3$: δ 1.69, 1.79 (2 broad s, 12H, $(CH_3)_2$.C=), 2.31, 2.37 and 2.43 (3s, 9H, -OCO.CH_3), 3.25, 3.46 (2d, J = 10Hz, 4H, Ar-CH_2), 5.11 (m, 2H, -CH =), 7.19 (d, J = 9Hz, 2H in positions 3' and 5'), 7.55 (d, J = 9Hz, 2H in positions 2' and 6') and 7.97 ppm (s, 1H in 2 position); NMR of 7,4' -dimethyl ether in CCl_4: δ 1.70, 1.80 (2s, 12H, $(CH_3)_2$. C =), 3.40 (m, 4H, Ar-CH_2), 3.78, 3.83 (2s, 6H, -OCH_3), 5.20 (m, 2H, -CH =), 6.87 (d, J = 9Hz, 2H in positions 3' and 5'), 7.44 (d, J = 9Hz, 2H in positions 2' and 6') and 7.94 ppm (s, 1H in position 2). The structure 3 was further confirmed by comparing its 7,4'-dimethyl ether with an authentic sample prepared from 6,8-di-C-prenylbiochanin-A[5] by methylation with diazomethane.

The third eluate was obtained as colourless crystals, m.p. 221°, R_f 0.52 (solvent B). It formed triacetate, m.p. 160°; R_f 0.60 (solvent D) and dimethyl ether, m.p. 123° (lit[5]. m.p. 122-23°); R_f 0.50 (solvent A); positive ferric reaction. The following NMR data of hydroxy compound and acetate suggested it to be mono C-prenylgenistein: NMR of the parent compound in $CD_3.CO.CD_3$: δ 1.68, 1.80 (2s, 6H, $(CH_3)_2$. C =), 3.34 (d, J = 7Hz, 2H, Ar-CH_2), 5.27 (m, 1H, -CH =), 6.44 (s, 1H in position 8), 6.85 (d, J = 9Hz, 2H in positions 3' and 5'), 7.40 (d, J = 9Hz, 2H in positions 2' and 6') and 7.95 ppm (s, 1H in position 2); NMR of the triacetate in $CDCl_3$: δ 1.74, 1.82 (2s, 6H, $CH_3)_2$.C =), 2.35, 2.38 and 2.45 (3s, 9H, -O.CO.CH_3), 3.39 (d, J = 7Hz, 2H, Ar-CH_2), 5.08 (m, 1H, -CH =), 7.01 (d, J = 10Hz, 2H in positions 3' and 5'), 7.33 (s, 1H in position 8), 7.56 (d, J = 10Hz, 2H in positions 2' and 6') and 7.97 ppm (s, 1H in position 2). Since the dimethyl ether on acid cyclisation with HCOOH gave 7,4'-dimethoxy-6",6"-dimethyl-4",5"-dihydropyrano-(2", 3" : 5,6)-isoflavone (5) as shown by negative ferric reation and the following NMR data, the structure of the third prenylation product is established as 6-C-prenylgenistein (4); NMR in CCl_4 of (5): δ 1.40 (s, 6H, $(CH_3)_2$.C<), 1.75, 2.60 (2t, J = 6.5Hz, 4H, -CH_2 -), 3.78, 3.83 (2s, 6H, -OCH_3), 6.20 (s, 1H in position 8), 6.82 (d, J = 9Hz, 2H in positions 3' and 5'), 7.40 (d, J = 9Hz, 2H in positions 2' and 6') and 7.62 ppm (s, 1H in position 2). Had it been 8-C-prenylgenistein, cyclisation would not have taken place. Finally structure (4) was established by the identity of its 7,4'-dimethyl ether with an authentic sample prepared from 5, 7-dihydroxy-4'-methoxy-6-C-prenylisoflavone.[5]

6-C-prenylgenistein (4) has been cyclodehydrogenated with DDQ in benzene when the product formed was found identical with the description of natural alpinum isoflavone (6) in m.p. TLC, IR spectrum, diacetate (a marked diamagentic shift of +0.3-0.4 of the peri proton in 4" position and a small paramagentic shift of of 0.01 of the second olefinic proton in 5" position) and mass spectrum[7].

Similar oxidative cyclization of 6,8-di-C-prenylgenistein (3) with DDQ yielded two products. The first fraction yielded a crystalline compound identical in all respects with the description of natural warangalone[3] (7). The linear


HO
OH
OH
1
PrenO
OPren+
OH
2
Pren
HO
Pren
OH
OH
3
HO
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OH
OH
4
H3CO
OCH3
O
5
4
OH
OH
6
3
Pren
OH
OH
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+
Pren
OH
OH
8

nature of the chromene was established by its mass spectrum which showed fragment of mass ion m/e 349 $(M-55)^+$ characteristic of p-prenyl phenols[8], besides other fragments at m/e 404, 389, 351, 231, 121, 118 and 55. The second fraction afforded a pale yellow crystalline compound identical in all respects with the description of natural osajin (8). The angular nature of the chromene was established by its mass spectrum which did not show $(M-55)^+$ fragment but instead showed $(M-56)^+$ mass ion fragment at m/e 348, characteristic of o-prenyl phenols[8], besides other fragments at m/e 404, 389, 351, 333, 231, 181, 121 and 56.

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7. Solvents used for TLC, (A) benzene, (B) benzene: ethyl acetate(75:25), (C) toluene: ethyl formate: formic acid (5:4:1) and (D) benzene:ethyl acetate (1:1). NMR spectra were taken in 60 MHz spectrophotometer with TMS as internal standard. Mass spectra were taken by MS-72 spectrometer, 70 ev ionising voltage, 900x10 trap current and 2.0 Kv accelerating voltage.
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