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SYNTHESIS OF LICOFLAVONE-A AND 6″,6″-DIMETHYLPYRANO(2″,3″:7,8)FLAVONE

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Abstract—Licoflavone-A assigned structure of 6-*C*-prenyl-7,4′-dihydroxyflavone 5 has been synthesized by condensing 5-*C*-prenyl-2-hydroxy-4-prenyloxyacetophenone 2 with p-prenyloxybenzaldehyde in the presence of alkali. The resulting chalcone 3 on cyclodehydrogenation with DDQ gave 6-*C*-prenyl-7,4′-diprenyloxyflavone 4 which on boiling with aqueous morpholine afforded the natural product. This synthesis uses, for the first time, protection of phenolic hydroxyls by *O*-prenylation and DDQ for conversion of chalcone to flavone. 6″,6″-Dimethylpyrano(2″,3″:7,8)flavone 8 has been synthesized by the Hlubucek reaction of 7-hydroxyflavone 6 with 2-chloro-2-methyl-3-butyne.

Licoflavone-A assigned structure as 7,4′-dihydroxy-6-*C*-prenylflavone 5 was mentioned to have been isolated from *Glycyrrhiza echinata* by Saitoh *et al.*[1] and by Furuya *et al.*[2] However, no publication giving data has appeared so far. Its synthesis having some novel features has now been accomplished.

Since *C*-prenylation of 7-hydroxyflavone[3] 6 failed using 2-methyl-but-3-en-2-ol in the presence of BF_3-etherate, synthesis of licoflavone-A was projected by using 5-*C*-prenylresacetophenone 1. As the natural compound is a dihydroxy compound, *O*-prenylation was chosen to protect free hydroxyl groups of the ketone because the preayl ether is stable during chalcone condensation and can subsequently be deprotected by heating with aqueous morpholine under which conditions the *C*-prenyl group does not undergo cyclisation with the *ortho* hydroxyl group.[4]

5-*C*-Prenylresacetophenone[5] 1 was selectively *O*-prenylated in the 4-position with 1 mole equivalent of prenyl bromide in the presence of K_2CO_3, KI and acetone. The resulting ketone 2 was condensed with 4-prenyloxybenzaldehyde[6] in the presence of alcoholic alkali to give 2′-hydroxy-5′-*C*-prenyl-4,4′-diprenyloxychalcone 3 which structure was established by its UV and NMR spectra. The chalcone 3 was converted into the corresponding flavone 4 by heating with DDQ in benzene. This conversion by the use of DDQ has been accomplished for the first time and goes smoothly. The structure of flavone 4 was established by its NMR spectrum (see Experimental section). Final boiling of the flavone 4 with aqueous morpholine removed the *O*-prenyl groups and afforded 7,4′-dihydroxy-6-*C*-prenylflavone 5. The synthetic compound was compared with the natural sample of licoflavone-A in mp, mmp, TLC and IR when both the samples were found identical in all respects.

In connection with prenylation experiments, 7-hydroxyflavone 6 was converted into 6″,6″-dimethylpyrano(2″,3″:7,8)flavone 8 by treating with 2-chloro - 2 - methyl - 3 - butyne in the presence of K_2CO_3, KI, acetone and DMF which gave a mixture of two products separable by column chromatography. The major product proved to be 7-(1,1-dimethylpropargyloxy)flavone 7 and the minor product proved to be the desired compound 8 which represents the alkali rearranged compound of the major product. The propargyl ether 7 when treated with *N,N*-dimethylaniline gave the same angular chromene 8.

EXPERIMENTAL

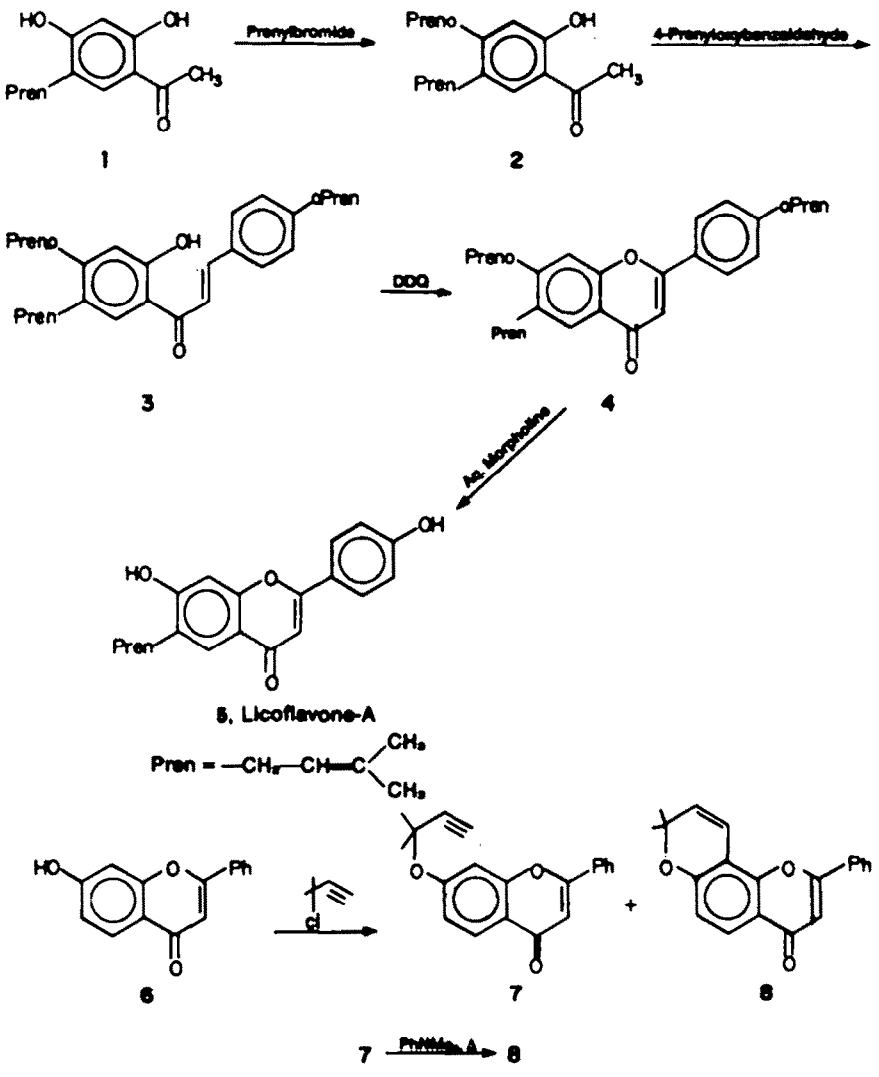
All melting points are uncorrected, unless stated otherwise. UV spectra were measured in MeOH (figures in parenthesis are log ε values); NMR spectra were recorded on BS487C spectrometer (80 MHz) in $CDCl_3$ with reference to tetramethylsilane as an internal standard; the chemical shifts are expressed in δ values; light petroleum ether used had boiling range 60–80°; silica gel was used for column chromatography and silica gel G for TLC; R_f values recorded for TLC using one of the following solvent systems: (A) light petroleum:benzene (1:4), (B) ethyl acetate:benzene (1:9), (C) ethyl acetate:benzene (1:4), (D) toulene:ethyl formate:formic acid (6:4:1); spraying of TLC plates was carried out with 10% aqueous H_2SO_4 and/or 1% alcoholic $FeCl_3$.

5-C-Prenyl-2-hydroxy-4-prenyloxyacetophenone 2

To a solution of 5-*C*-prenylresacetophenone[5] (1, 550 mg) in acetone (20 ml) was added prenyl bromide (0.3 ml), anhd. K_2CO_3 (1.4 g), and KI (0.25 g). The resulting mixture was refluxed for 7 h, the solvent distilled off and water added to the residue. The whole mixture was extracted with ether and the ether extract evaporated to dryness. The residue on column chromatography using light petroleum as eluant afforded 5-*C*-prenyl-2-hydroxy-4-prenyloxyacetophenone 2 as a colourless oil (600 mg), brownish ferric reaction; R_f 0.78 (solvent A); λ_{max} 278 and 318 nm (4.16 and 3.78 respectively); NMR: 1.75, 1.73, 1.70 (3s, 12H, two$(CH_3)_2C$=), 2.49 (s, 3H, $COCH_3$), 3.18 (d, J = 8Hz, 2H, Ar-CH_2-CH=), 4.49 (d, J = 7Hz, 2H, Ar-O-CH_2-CH=), 5.15–5.33 (m, 2H, two-CH_2-CH=), 6.30 (d, J = 1.5Hz, 1H, H-3), 7.32 (d, J = 1.5Hz, 1H, H-6).

5′-C-Prenyl-2′-hydroxy-4,4′-diprenyloxychalcone 3

To a solution of the above ketone (2, 0.5 g) in ethanol (10 ml) was added 4-prenyloxybenzaldehyde[6] (0.35 g), followed by KOH (0.7 g in 1 ml water). The resulting solution was warmed on a water bath for 30 sec and kept at room temperature for 48 h with occasional shaking. The orange coloured solution was diluted with excess water, extracted with light petroleum ether to remove the unreacted 4-prenyloxybenzaldehyde and the remaining aqueous solution acidified with dil HCl. The yellow viscous mass was washed with 5% aqueous Na_2CO_3, followed by water, dried and subjected to column chromatography. Elution with



benzene–light petroleum (1:4) gave 3 as orange-yellow semi-solid (0.37 g), dark brown ferric reaction; R_f 0.62 (solvent A); λ_{max} 236 and 365 nm (4.08 and 4.37 respectively); NMR (CCl_4): 1.75 (br s, 18H, three $(CH_3)_2C$=), 3.23 (d, J = 7.5Hz, 2H, Ar-CH_2-CH=), 4.53 (d, J = 8Hz, 4H, two Ar-O-CH_2-CH=), 5.08–5.57 (m, 3H, three-CH_2-CH=), 6.35 (d, J = 1.5Hz, 1H, H-3'), 6.82 (d, J = 9Hz, 2H, H-3 and 5), 7.86 (d, J = 9Hz, 1H, H-2 and 6), 7.37 (d, J = 15Hz, 1H, H-α), 7.50 (d, J = 15Hz, 1H, H-β), 7.70 (d, J = 1.5Hz, 1H, H-6').

6-C-Prenyl-7,4'-diprenyloxyflavone 4

The above chalcone (3, 240 mg) was refluxed with DDQ (240 mg) in dry benzene (20 ml) for 15 h. The reaction product was filtered while hot. The filtrate was evaporated to dryness and the residue purified by column chromatography. Elution with C_6H_6–light petroleum (4:1) gave a solid which crystallized from ethyl acetate–light petroleum mixture to give 6-*C*-prenyl-7,4'-diprenyloxy - flavone 4 as almost colourless crystals (130 mg), mp 155° (decomp.); R_f 0.72 (solvent B) (Found: C, 78.2; H, 7.6. $C_{30}H_{34}O_4$ requires: C, 78.6; H, 7.4%); λ_{max} 238 and 326 nm (3.95 and 4.25 respectively); NMR: 1.82, 1.90, 2.05 (3s, 18H, three $(CH_3)_2C$=), 3.45 (d, J = 8 Hz, 2H, Ar-CH_2-CH=), 4.53, 4.62 (2d, J = 7.5Hz, 4H, two Ar-O-CH_2-CH=), 5.30–5.65 (m, 3H, three-CH_2-CH=), 6.38 (s, 1H, H-8), 7.06 (d, J = 10Hz, 2H, H-3' and 5'), 7.10 (s, 1H, H-3), 7.40 (s, 1H, H-5), 7.72 (d, J = 10Hz, 2H, H-2' and 6').

Licoflavone-A 5

The above flavone (4, 60 mg) was refluxed with 50% aqueous morpholine (8 ml) for 45 h. It was concentrated *in vacuo* and treated with cold dil HCl. The solid thus collected was found to be mixture of two compounds. The fraction soluble in 10% aqueous NaOH crystallized from ethyl acetate–light petroleum mixture to afford licoflavone-A 5 as pale yellow crystals (35 mg), m.p. and m.m.p. 230–1°; R_f 0.46 (solvent D) (Found: C, 74.1; H, 5.3. Calc. for $C_{25}H_{26}O_6$: C, 74.5; H, 5.6%); λ_{max} 330 (4.54); NMR [$(CD_3)_2CO$]: 1.72 (s, 6H, $(CH_3)_2C$=), 3.38 (d, J = 8Hz, 2H, Ar-CH_2-CH=), 5.25–5.45 (m, 1H, Ar-CH_2-CH=), 6.55 (s, 1H, H-8), 6.97 (d, J = 9Hz, 2H, H-3' and 5'), 7.08 (s, 1H, H-3), 7.77 (s, 1H, H-5), 7.82 (d, J = 9Hz, 2H, H-2' and 6'). Superimposable IR spectrum with the natural sample.

The alkali insoluble fraction (20 mg) proved to be starting material 4.

Reaction of 7-hydroxyflavone 6 with 2-chloro-2-methyl-3-butyne

To a solution of 7-hydroxyflavone (6, 2 g) in acetone (250 ml) was added 2-chloro-2-methyl-3-butyne (1.01 ml), DMF (4 ml), anhydrous K_2CO_3 (10 g), KI (3 g) and the resulting mixture refluxed for 65 h. After the removal of the solvent water was added, when a viscous mass was obtained. TLC showed it to be a mixture of three components. Hence it was subjected to column chromatography. Successive elution with benzene:light petroleum (1:4), benzene:light petroleum (3:7) and benzene alone gave three fractions labelled A, B and C respectively.

Fraction A. Crystallized from methanol to give 7-(1,1-dimethyl - propargyloxy)flavone 7 as colourless shining needles (0.8 g), mp 150–51°; white ppt. with alcoholic silver nitrate; R_f 0.6 (solvent C) (Found: C, 79.0; H, 5.5. $C_{20}H_{16}O_3$ requires: C, 78.9; H, 5.3%); λ_{max} 253 and 300 nm (4.41 and 4.21 respectively); 60 MHz NMR: 1.74 (s, 6H, $(CH_3)_2C$), 2.70 (s, 1H, -C≡CH),

6.68 (s, 1H, H-3), 7.25 (d, J_{ac} = 3Hz, 1H, H-8), 7.40 (d, J_o = 10Hz, J_{ac} = 3Hz, 1H, H-6), 7.50-7.90 (m, 5H, $C_6\underline{H}_5$), 8.04 (d, J = 10Hz, 1H, H-5).

Fraction B. Crystallized from benzene–light petroleum mixture to afford 6",6'-dimethylpyrano(2",3":7,8)flavone 8 as colourless needles (0.1 g), m.p. 130-31°; R_f 0.5 (solvent C) (Found: C, 78.9; H, 5.8. $C_{20}H_{16}O_3$ requires: C, 78.9; H, 5.3%); λ_{max} 224, 253 and 306 nm (4.27, 4.32 and 4.38 respectively); NMR: 1.72 (s, 6H, $(C\underline{H}_3)_2C$<), 5.48 (d, J = 10Hz, 1H, H-5"), 6.45 (d, J = 10Hz, 1H, H-4"), 7.07 (s, 1H, H-3), 7.23 (d, J = 10Hz, 1H, H-6), 7.35-7.85 (m, 5H, C_6H_5), 8.16 (d, J = 10Hz, 1H, H-5).

Fraction C. Proved to be starting material (0.8 g), m.p. and m.m.p. 238-39°.

Thermal rearrangement of 7

The propargyloxyflavone (7, 0.15 g) was refluxed in *N,N*-dimethylaniline (10 ml) for 2 h, cooled and poured on ice-cold dil. HCl. The solid was collected and crystallized from benzene–light petroleum mixture when the pyrano flavone 8 was obtained as colourless needles (0.12 g), m.p. and m.m.p. with the sample prepared earlier 130-31°.

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