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Synthesis of 5, 7-Dihydroxy-8-C-Prenylflavanone

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5,7-Dihydroxy-8-C-prenylflavanone (VII, glabranin) Mitscher *et al* 1983) isolated from the roots and stems of *Glycyrriza lepidota* has been synthesized by following unambigous route. All the new products have been characterized on the basis of spectral data.

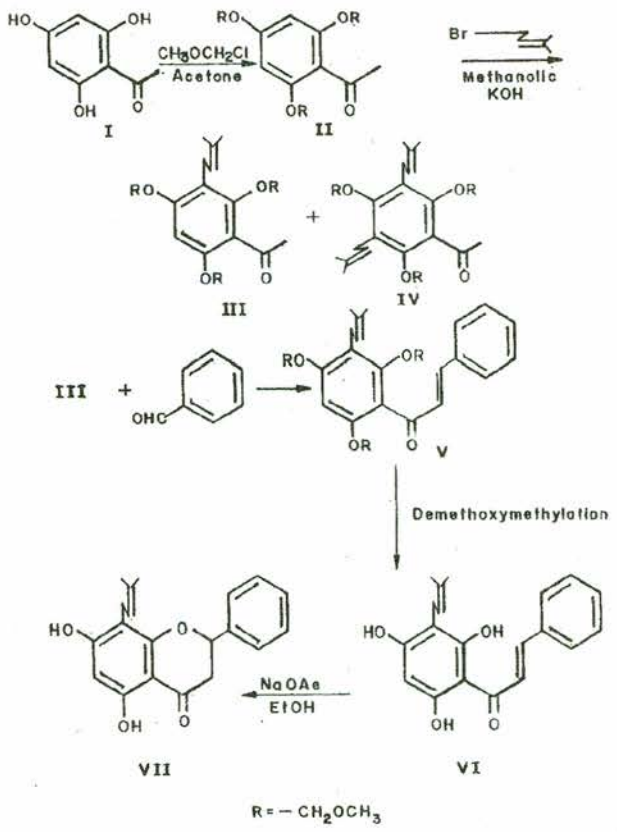
Key words: Synthesis, Chalcone, Flavanone.

Introduction

Chalcones and flavones are widespread components in all parts of the plants and are important as flower pigments, growth regulators, phytoalexins, animal toxins (Ghousal and Chaudhury *et al* 1975; Conn 1981) antibacterial and antifungal agents. The growing interest of synthesis of chalcones and flavones for the last few years may be easily explained by their pharamacological activitities e.g., anti-psychotic action, monoamine oxidase inhibition, anti-tubercular. L. A. Mitscher *et al* 1983 reported the isolation of 5, 7-dihydroxy-8-C-prenylflavanone (VII), glabranin) from the roots and stems of *Glycyrriza lepidota.* The structure for glabranin was assigned on the basis of spectral data but no synthetic proof was provided. In this paper, we describe the synthesis of 5, 7-dihydroxy-8-C-prenylflavanone (VII) starting from phloroacetophenone (Vogal 1956) (see Scheme-1). Methoxymethylation (Islam and Husain 1983) of I, using methoxymethyl chloride and potassium carbonate gave compound 2, 4, 6-tri (methoxymethoxy) acetophenone (II) which upon nuclear prenylation (Jain *et al* 1969) with prenyl bromide, in the presence of methanolic KOH, gives a mixture of 2, 4, 6-tri (methoxymethoxy)-3-C-prenylacetophenone (III) and 2, 4, 6-tri (methoxymethoxy)-3, 5-di-C-prenylacetophenone (IV). Alkaline condensation of III and benzaldehyde gave methoxymethylated chalcone (V). NaOAc/EtOH treatment of 2', 4', 6'-trihydroxy-3'-C-prenylchalcone (VI) obtained by the demethoxymethylation of V afforded the title compound (VII), whose m.p. and spectral characteristics agreed with those reported (Mitscher *et al* 1983) for the natural sample. A direct comparison was not possible since the isolated title compound was not available.

Experimental

Melting points were determined using an electrothermal melting point apparatus (Gallenkamp) and are uncorrected. IR spectra were recorded (KBr discs) on a Pye-Unicam SP3-300 IR spectrophotometer ($\gamma\square\square_{max}$ in cm^{-1}). ^{1}H-NMR spectra were recorded on a Perkin-Elmer R-32 (90MHz) instrument in $CDCl_3$ with TMS as an internal standard (chemical shifts in δ, ppm). UV spectra were recorded on LKB 4053 spectrophotometer Ultrospeck in methanol (λ_{max} in nm). TLC was performed using silica gel 60G. Satisfactory elemental analysis were obtained for all the compounds and structures are in accord with the UV, IR and ^{1}H-NMR data. Mass spectra were recorded on VG 7070E analytical mass spectrometer.



Scheme 1

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Methoxymethylation of phloroacetophenone(I). A mixture of phloroacetophenone (I, 1.56 g) in dry acetone (25 ml), methoxymethyl chloride (0.85 g) and anhydrous potassium carbonate (15 g) was refluxed for about 3 h. The progress of the reaction mixture was examined by TLC. After cooling acetone was distilled off, water was added to the residue. It was then extracted with ether, washed with water and dried over anhydrous Na_2SO_4. The organic layer was evaporated to dryness and the methoxymethylated product II (1.78 g) was obtained by crystallization from benzene, m.p. 58°C, yield 59.4%, (M^+, 300); R_f 0.76 (benzene-acetone; 9:1); IR : 2910, 2845, 1645, 1600, 1595; ^{1}H-NMR: 2.45 (s, 3H, -$COCH_3$), 3.51 (s, 9H, -CH_2OCH_3x3), 5.28 (s, 6H, -CH_2OCH_3x3), 6.43 (s, 1H, H-3), 6.98 (s, 1H, H-5),. [Found: C, 56.07; H, 6.66. $C_{14}H_{20}O_7$ requires: C, 56.31 ; H, 6.86%]. It was identified as 2, 4, 6-tri (methoxymethoxy) acetophenone (II).

Neuclear prenylation of 2, 4, 6-tri(methoxymethoxy) acetophenone (II). 2, 4, 6-Tri (methoxymethoxy) acetophenone (II, 1.5 g) was added to a well cooled solution of KOH (3.5 g) and absolute methanol (20 ml). The solution was treated with prenyl bromide (1.8 ml) slowly with shaking. After keeping the reaction mixture for 20 hr at room temperature, it was diluted with ice-cold water, acidified and extracted with ether. The ethereal solution was successively extracted with 7% sodium carbonate and 1% KOH solution. The sodium carbonate fraction gave unreacted 2, 4, 6-tri (methoxymethoxy) acetophenone (0.35 g), m.p. 58°C. The KOH fraction after acidification gave a solid product which after crystallization from benzene formed colourless shining plates (0.8 g), m.p. 62°C; yield 43.7%, (M^+, 368); IR : 1650, 1605, 1595, 1376, 1366; ^{1}H-NMR : 1.75 [s, 6H, >$C(CH_3)_2$], 2.45 (s, 3H, -$COCH_3$), 3.44 (s, 9H, -$CH_2OCH_3x_3$), 3.52 (d, 2H, J=7Hz, -CH_2-CH=), 5.25 (s, 6H, -CH_2OCH_3x3), 5.50 (t, 1H, J=7Hz, -CH_2-CH=), 6.89 (s, 1H, H-5), Found : C, 61.95; H, 7.60. $C_{19}H_{28}O_7$ requires: C, 61.77 ; H, 7.81 %]. These spectral data agree with the formation of 2, 4, 6-tri (methoxymethoxy)-3-C-prenylacetophenone (III). The compound 2, 4, 6-tri (methoxymethoxy)-3, 5-di-C-prenylacetophenone (IV) remaining in ethereal fraction was crystallized from ethyl acetate as colourless tiny needles (0.3 g), m.p. 38°C, yield 13.8%, (M^+, 436).

2', 4', 6'-Tri(methoxymethoxy)-3'-C-prenylchalcone (V). A mixture of 2, 4, 6-tri(methoxymethoxy)-3-C-prenylacetophe-none (III, 1.76 g) and benzaldehyde (0.58 g) in ethanolic solution of KOH (50%, 20 ml) was kept at room temperature for 3 days. The reaction mixture was diluted with ice cold water, acidified with dil. HCl and extracted with ether. The ether layer was washed with water dried over anhydrous sodium sulphate and evaporated to dryness. The residue was purified by preparative TLC over silica gel 60G using benzene-acetone (15:1) as developing solvent. The product was crystallized from petroleum spirit (b.p. 40-60°C) to give yellow crystals (1.55 g), m.p. 115°C, yield 71%, (M^+, 456); R_f 0.76 (benzene-acetone; 10:1); UV: 228, 254, 370; IR : 1642, 1605, 1595, 1375, 1365 ; ^{1}H-NMR : 1.70 [s, 6H, >$C(CH_3)_2$], 3.48 (s, 9H, -CH_2OCH_3 x3), 3.53 (d, 2H, J=7Hz, -CH_2-CH=), 5.30 (s, 6H, -CH_2OCH_3x3), 5.45 (t, 1H, J=7Hz, -CH_2-CH=), 6.95 (s, 1H, H-5'), 7.41 (d, 1H, J=9Hz, H-α), 7.65 (s, 5H, aromatic protons), 8.03 (d, 1H, J=9Hz, H-β). [Found : C, 73.68. ; H, 7.01. $C_{26}H_{32}O_7$ requires: C, 73.41, H, 6.92%].

2', 4', 6'-Trihydroxy-3'-C-prenylchalcone (VI). To a solution of the above methoxymethylated chalcone (V, 1 g) in methanol (30 ml), HCl (3N, 50 ml) was added and boiled in water bath for 15 min. It was diluted with water (150 ml) and extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated ten times. TLC examination of the residue showed several spots and the major product was purified by preparative TLC using ethyl acetate-benzene (1:1) as developing solvent. It crystallized from methanol as yellow needles (0.45 g), m.p. 140°C, (M^+, 324); R_f 0.76 (acetonebenzene; 4:1). It gave positive ferric chloride test. UV: 229, 255, 365; IR : 3540, 1650, 1610, 1590, 1385, 1355; ^{1}H-NMR : 1.69 (s, 6H, >$C(CH_3)_2$], 3.51 (d, 2H, J=7Hz, -CH_2-CH=), 5.50 (t, 1H, J=7Hz, -CH_2CH=), 6.91 (s, 1H, H-5'), 7.44 (d, 1H, J=9Hz, H-α), 7.69 (s, 5H, aromatic protons), 8.00 (d, 1H, J=9Hz, H-β), 8.75 (s, 1H, -OH), 12.75 (s, 2H, -OHx2). [Found : C, 74.07; H, 6.17. $C_{20}H_{20}O_4$ requires: C, 74.25; H, 6.34%].

5,7-Dihydroxy-8-C-prenylflavanone (VII, glabranin). To a solution of 2', 4', 6'-trihydroxy-3'-C-prenylchalcone (VI , 1 g) in ethanol (15 ml) sodium acetate (1.6 g) was added. The reaction mixture was left at room temperature for 3 days. It was diluted with water and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous Na_2SO_4 and concentrated. The product was purified by preparative TLC over silica gel 60G using benzene as developing solvent. It crystallized from benzene - petroleum spirit as colourless needles (0.65 mg), yield 62.9%, R_f 0.64 (benzene-acetone; 9:2), m.p. 170°C Lit[1]. m.p.169-170°C); M^+, 324); R_f 0.64 (benzene). UV:225, 370; IR : 3545, 1648, 1610, 1600, 1371, 1363; ^{1}H-NMR : 1.71 (s, 6H, >$C(CH_3)_2$], 2.95 (d, 2H, J=9Hz, H3), 3.50 (d, 2H, J=7Hz, CH_2-CH=), 5.28 (t, 1H, J=7Hz, H-2), 5.49 (t, 1H, J=7Hz, -CH_2-CH=), 6.88 (s, 1H, H-6), 7.67 (s, 5H, aromatic protons), 12.91 (s, 2H, -OHx2). [Found : C, 74.07 ; H, 6.17. $C_{20}H_{20}O_4$ requires: C, 74.25; H, 6.425].

Results and Discussion

The compounds I prepared following the literature procedure (Vogel *I* 1956) was subjected to methoxy-

methylation (methoxymethyl chloride/K_2CO_3/acetone) to give compound II, the formation of which was ascertained by spectral studies and elemental analysis. Infrared spectrum of II showed the absorption frequency at 1645 cm^{-1} indicating the presence of ketonic group. Two singlets at δ 3.51and 5.28 indicated the presence of 6 protons of two-OCH_3 group and 4 protons of two-CH_2 group, respectively which confirmed that the methoxymethylation has taken place. In addition, no peak for hydroxyl group was obtained which also confirms same. Compound III and IV were obtained by the nuclear prenylation (methanolic KOH/prenyl bromide) of II and the formation of which was agree with the data of spectral and elemental analysis. The ^{1}H-NMR spectrum of the prenylated compound III indicated the presence of C-prenyl unit. A sharp singlet at δ 1.75 revealed the presence of gem-dimethyl group and the presence of -CH_2- and -CH= protons attached to the aromatic ring was indicated by a doublet at δ 3.53 and a triplet at δ 5.50, respectively. The compound II on a cross-aldol condensation with benzaldehyde in the presence of ethanolic KOH afforded the compound V after dehydration of the initial aldol product. The characteristic IR absorption frequencies at 1642 cm^{-1} showed the presence of conjugated ketonic group and the absorption peaks at 1605 and 1595 cm^{-1} indicated the presence of unsymmetric ethylenic double bond and aromatic rings, respectively. The singlet for methyl protons of acetyl group disappeared while two new doublets at 7.41 and 8.03 appeared showing the presence of two vinylic protons (α and β protons). The elemental analysis for C and H showed satisfactory results (within + 0.4%). The compound VI was obtained from V by demethoxylation (MeOH/3N, HCl). IR absorption frequencies at 3540 and 1650 cm^{-1} showed the presence of -OH (phenolic) group and ketonic group and the absorption peaks at 1610 and 1590 cm^{-1} indicated the presence of unsymmetric ethylenic double bond and the aromatic rings, respectively. Two singlets at δ 8.75 and δ 12.75 indicated the presence of -OH protons which confirming the completion demethoxylation. The B-ring protons have their usual chemical shift value.The cyclized i.e, the title product VII was obtained by NaOAc/EtOH treatment of its precursor VI. In the mass spectrum of the final compound the following mass (m/e) peaks were observed : 69, 91, 92, 105, 147, 191, 192, 227, 228, 267, 282, 283, 324. The last one corresponds M^+. The formation of title compound VII was confirmed by comparing its spectral data and elemental analysis with that of the reported value of the natural sample.

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