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SYNTHESIS OF 5, 7-DIHYDROXY-6, 8-DI-C-PRENYL-4′-*O*-PRENYL-FLAVANONE

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The prenylated flavanone **(9)** has been synthesized from phloroacetophenone **(1)**. All the new products have been characterized by the spectral data and microanalysis.

Key words: Synthesis, Chalcone, Flavanone

Introduction

Flavones and their derivatives are naturally occurring and have a variety of biological properties, such as antibacterial (Mitscher *et al* 1993), antifungal (Conn 1981) and antitumour activity (Mizabuchi and Sato 1984). A large number of natural products including flavonoids are being reported in the literature every year and their structures need to be confirmed by synthesis. This paper reports the synthesis of 5,7-dihydroxy-6, 8-di-C-prenyl-4′-*O*-prenylflavanone **(9)** from phloroacetophenone **(1),** which may be used as a synthetic marker. Phloroacetophenone on treatment with methoxy-methyl chloride using K_2CO_3 and acetone afforded 2-hydroxy-4, 6-di (methoxymethoxy) acetophenone **(2)** (Hossain 1999), which on nuclear prenylation using well-cooled solution of KOH and prenyl bromide gave three products viz 2-hydroxy-4, 6-di (methoxymethoxy)-3-C-prenylacetophenone **(3),** 2-hydroxy-4, 6-di (methoxymethoxy)-5-C-prenylacetophenone **(4)** (Hossain and Islam 1993), and 2-hydroxy-4,6-di (methoxymethoxy)-3, 5-di-C- prenylaceto-phenone **(5)** and several other minor products. Similarly *O*-prenylation of p-hydroxybenzaldehyde using K_2CO_3/acetone/prenyl bromide gave 4-*O*-prenylbenzaldehyde **(6)**. Alkaline condensation of 2-hydroxy-4, 6-di(methoxy-methoxy)-3, 5-di-C-prenylac-etophenone **(5)** and 4-*O*-prenylbenzaldehyde **(6)** yielded 2′-hydroxy-4′, 6′-di (methoxymethoxy)-3′, 5′-di-C-prenyl-4-*O*-prenylchalcone **(7).** Compound **(7)** on treatment with NaOAc/EtOH furnished 5,7-di (methoxymethoxy)-6, 8-di-C-prenyl-4′-*O*-prenylflavanone **(8),** which upon demethoxymethylation afforded 5,7-dihydroxy-6, 8-di-C-prenyl-4′-*O*-prenylfla-vanone **(9).**

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 (ν_{max} in cm^{-1}), ^{1}H-NMR spectra on a Varian 300 MHz instrument in $CDCl_3$ with TMS as an internal standard (chemical shifts in δ, ppm) and UV spectra on Milton-Roy UV-visible spectrophotometer Ultrospeck in methanol (λ_{max} in nm). TLC was performed using silica gel 60G. Mass spectra were recorded on Time of Flight (GC-MS TOF). Satisfactory elemental analyses were obtained for all the compounds and structures are in accord with the UV, IR and ^{1}H-NMR data.

*Methoxymethylation of phloroacetophenone **(1)***. A mixture of phloroacetophenone (**1**, 10 g) in dry acetone (100 ml), methoxymethyl chloride (5.67 g) and anhydrous potassium carbonate (40 g) was refluxed for about 3 h. The progress of the reaction mixture was examined by TLC. On completion of the reaction acetone was distilled off and water was added and the mixture was then extracted with ether washed with water and dried over anhydrous Na_2SO_4. The organic layer was evaporated to dryness. The ether extract on silica gel column chromatography (mesh 60-120) using petrol (40-60°), petrol-benzene (4:1), petrol-benzene (4:3) and increasing quantities of benzene as eluent gave the major compound **(2)** and several other minor compounds. Compound **(2)** was purified from column and by preparative TLC over silica gel GF_{254} using benzene-petrol (25:1) as developing solvent. It was crystallized from petrol as colorless crystals (4.09g) R_f 0.69 (benzene-petrol; 25:1); m.p 80-81°C; IR: 3450, 2874, 1654, 1610, 1600, 1476, 1365, 1275, 1234, 1190, 1156, 1064, 1034, 966 984, 934, 886; 1H-NMR: 2.45 (s,1H,1-$COCH_3$), 3.45 (s,6H,-CH_2OCH_3x2), 5.55 (s,4H,-CH_2O-CH_3x2), 6.45 (s, 1H,H-3), 6.67 (s, 1H H-5), 12.76 (s, 1H, -OH).

*Nuclear prenylation of 2-hydroxy-4,6-di (methoxymethoxy) acetophenone **(2)***. 2-Hydroxy-4,6-di-(methoxymethyleneoxy) acetophenone (**2**, 1g) was added to a well cooled solution of KOH) (2 g) in absolute methanol (30 ml)

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and the whole solution was cooled to 0°C. Prenyl bromide (0.5 g) was added and the reaction mixture allowed to stand at room temperature for 24 h with constant stirring. The reaction mixture was diluted with water and acidified with cold diluted HC1. The mixture was then extracted with ethyl acetate. The ethyl acetate extract was dried over anhydrous Na_2SO_4 and concentrated. It was then subjected to column chromatography over silica gel (mesh 60-120) and eluted successively with petrol-benzene (5:1), petrol-benzene (1:3), petrol-benzene (1:5) and compounds **(3), (4)** and **(5)** were obtained.

*2-Hydroxy-4,6-di (methoxymethoxy)-3-C-prenylacetophenone **(3)**:* It was crystallized from ethanol as white needles (140 mg), m.p. 34°C, R_f 0.64 (benzene). It gave positive alcoholic ferric chloride test. UV: 229, 265, 285 nm; IR: 3476, 1645, 1605, 1595, 1472, 1424, 1370, 1365,1363,1205,1145 1105, 1040, 980, 945, 910, 835 cm^{-1}; ^{1}H-NMR: 1.72 [s, 6H, $>C(CH_3)_2$], 2.45 (s, 3H,-$COCH_3$), 3.53 (m, 8H,-C<u>H</u>$_2$-CH and -CH_2OCH_3), 5.25 (t, 1H,-CH_2-C<u>H</u>), 5.54 (s, 4H,-CH_2OCH_3), 6.68 (s,1H,H-5), 12.43 (s, 1H,-OH).

*2-Hydroxy-4,6-di (methoxymethoxy)-5-C-prenylacetophenone **(4)**.* It was crystallized from petrol as white needles (140 mg), m.p. 48°C, R_f 0.58 (benzene). It gave positive alcoholic ferric chloride test. UV: 229,268, 280 nm; IR: 3476, 1645, 1605, 1595, 1472, 1424, 1370, 1365, 1363, 1205, 1145,1105, 1040, 980, 945, 910, 835 cm^{-1},^{1}H-NMR: 1.75 [s, 6H, $>C(CH_3)_2$], 2.43 (s, 3H,-$COCH_3$), 3.55 (m, 8H,-C<u>H</u>$_2$-CH and - CH_2OCH_3), 5.30 (t, 1H,-CH_2-C<u>H</u>), 5.55 (s, 4H,-CH_2OCH_3), 6.45 (s, 1H, H-3).

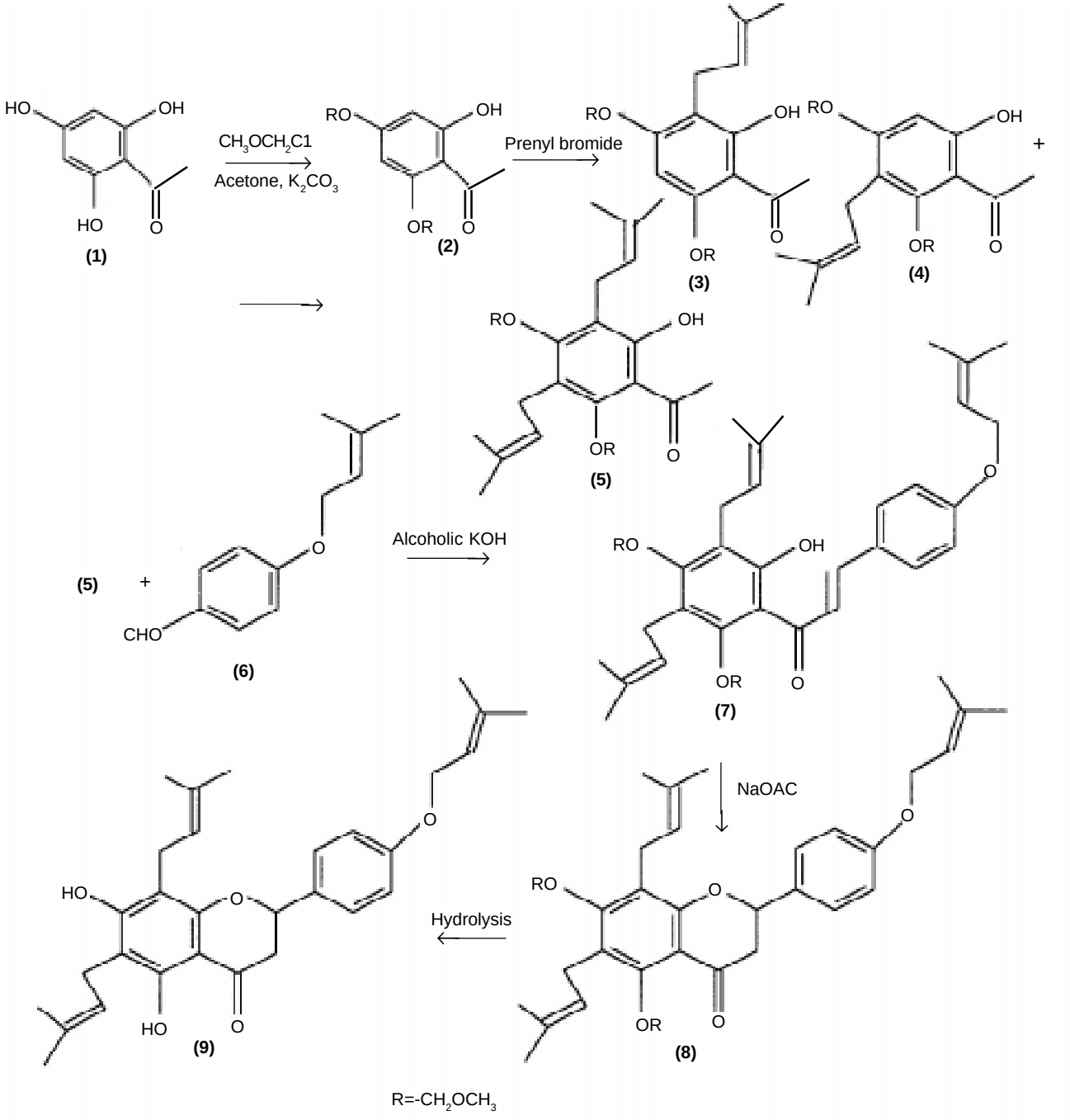
*2-Hydroxy-4,6-di (methoxymethoxy)-3,5-di-C-prenylacetophenone **(5)**.* It was a viscous liquid (675 mg) and was not crystallized from any solvent. UV: 225, 243, 288 nm; IR: 3455, 1645, 1600, 1590, 1420, 1375, 1365, 1325, 1240, 1205, 1100, 1050, 985, 910, 835, 725 cm^{-1}; ^{1}H-NMR: 1.70 [s, 12H,$>C(CH_3)_2$x2], 2.48 (s, 3H,-$COCH_3$), 3.52 (m, 8H, -C<u>H</u>$_2$-CH and -CH_2OCH_3), 5.22 (t, 1H,-CH_2-C<u>H</u>), 5.51 (s, 4H,-CH_2OCH_3), 12.10 (s, 1H,-OH).

*4-O-Prenylbenzaldehyde **(6)**.*A mixture of *p*-hydroxybenzaldehyde (1.20g), prenylbromide (1.46g) and K_2CO_3 (7g) in acetone (40ml) was refluxed for about 3 h and the progress of the reaction mixture was examined by TLC. After cooling, acetone was distilled off and water was added to the residue. The mixture was then extracted with ether, washed with water and dried over anhydrous Na_2SO_4. The organic layer was evaporated to dryness and the crude residue was passed through a small dry silica gel column. The product was crystallized from dilute alcohol and gave white needles (0.39g); m.p.52°C; (M^+,190); R_f 0.58 (benzene); UV: 229, 265; IR: 1760, 1645, 1605, 1410, 1372, 1368;^{1}H-NMR:1.75[s, 6H,$>C(CH_3)_2$], 4.51 (d, 2H, J 7Hz, -O-CH_2-CH), 5.52 (t, 1H, J 7Hz,-O-CH_2-CH), 6.43 (d, 2H, J 9Hz, H-2 and H-3), 6.98 (d, 2H, J 9Hz, H-5 and H-6), 9.78 (s, 1H,-CHO); [Found: C, 75.8; H, 7.4, $C_{12}H_{14}O_2$ requires: C, 75.4; H, 7.7%].

*2′-Hydroxy-4′,6′-di (methoxymethoxy)-3′, 5′-di-C-prenyl-4-O-prenylchalcone **(7)**.*A mixture of 2-hydroxy-4, 6-di (methoxymethoxy)-3, 5-di-C-prenylacetone (**5**, 1.87g) and 4-*O*-prenylbenzaldehyde (**6**,0.95g) in ethanolic KOH (50%, 20 ml) was kept at room temperature for 80 h, diluted with ice-cold water and acidified with diluted HC1. It was extracted with ether (100 ml). The ether extract was washed with water, dried over anhydrous Na_2SO_4 and ether was evaporated to dryness. The mixture was purified by preparative TLC over silica gel 60G using benzene as developing solvent. The product was crystallized from petrol as yellow crystals (0.78g); m.p. 112°C, (M^+,564); R: 0.71 (benzene-acetone; 5:2); UV: 235, 255, 265, 378; IR: 3470, 1760, 1645, 1605, 1590, 1478, 1370, 1362, 1040; ^{1}H-NMR: 1.72 [s, 6H, $>C(CH_3)_2$], 1.53 [s, 12H, $> C(CH_3)_2$x2], 3.41 (s,6H,-CH_2-OCH_3x2), 3.51 (d, 2H, J 7Hz,-CH_2-CHx2), 4.55 (d, 2H, J 7Hz, -O-CH_2-CH), 5.25-5.53 (m, 7H, -CH_2-OCH_3x2, -CH_2-CHx2,-O-CH_2-CH), 6.58 (d, 2H, J 9Hz, H-2 and H-3), 6.99 (d, 2H, J 9Hz, H-5 and H-6), 7,45 (d, 1H, J 9Hz,4 H-α), 8.01 (d, 1H, J 9Hz, H-β), 13.01 (s, 1H,-OH), [Found: C, 72.3; H, 7.8, $C_{34}H_{44}O_7$ requires: C, 72.6;H, 7.4%].

*5,7-Di(methoxymethoxy)-6,8-di-C-prenyl-4′-O-prenylflavanone **(8)**.* To a solution of **(7)** (1.78g) in ethanol (30 ml), sodium acetate (1.8g) 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 GF_{254} using benzene as developing solvent. It was crystallized from xylene as colorless crystals (0.82g); m.p. 129°C;(M^+,564); UV: 230, 245, 365, IR: 2944, 2845, 1645, 1600, 1590, 1540, 1410, 1370, 1360, 1255, 1040; ^{1}H-NMR: 1.72[s,6H,$>C(CH_3)_2$], 1.53 [s,12H,$> C(CH_3)_2$x2],2.92 (d, 2H, J 9Hz, H-3), 3.41 (s, 6H, -CH_2-OCH_3x2), 3.51 (d, 2H, J 7Hz,-CH_2-CHx2), 4.55 (d, 2H, J 7Hz, -O-CH_2-CH) 5.25-5.53 (m, 8H, H-2,-CH_2-OCH_3x2,-CH_2-CHx2),6.58 (d, 2H, J 9Hz, H-2 and H-3), 6.99 (d, 2H, J 9Hz, H-5 and H-6), 7,45 (d, 1H, J 9Hz, H-α),8.01 (d, 1H, J 9Hz, H-β), 13.01 (s, 1H, -OH), [Found : C, 72.4; H, 7.8, $C_{34}H_{44}O_7$ requires:C, 72.7; H, 7.4%].

*5,7-Dihydroxy-6, 8-di C-prenyl-4′-O-prenylflavanone **(9)**.* To a solution of the above methoxymethoxylated flavanone (**8**, 1g) in methanol (30 ml), HC1 (3N, 50ml) was added and boiled on a water bath for 15min. The reaction mixture



Scheme I

was diluted with water (150ml) and extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated. TLC examination of the residue showed several spots and the major product was purified by preparative TLC using ethyl acetate-benzene (10:7) as developing solvent. It was crystallized from petrol as white crystals (0.25g), m.p. 177°C, (M^+,476); UV: 225, 244, 265, 355; IR: 3520, 2945, 2810, 1645, 1605,1600, 1510, 1470, 1344, 1340; ^{1}H-NMR: 1.72 [s, 6H,>C$(CH_3)_2$], 1.53 [s, 12H, > C $(CH_3)_2$x2], 2.92 (d, 2H, J 9Hz, H-3), 3.41 (s, 6H, -CH_2-OCH_3x2), 3.51 (d, 2H, J 7Hz, -CH_2-CHx2), 4.55 (d, 2H, J 7Hz, -O-CH_2-CH), 5.25-5.53 (m, 8H, H-2, -CH_2-OCH_3x2,-CH_2 -CH x2), 6.58 (d, 2H, J 9Hz, H-2 and H-3), 6.99 (d, 2H, J 9Hz, H-5 and H-6), 7,45 (d, 1H, J 9Hz, H-α), 8.01 (d, 1H, J 9Hz, H-β), 13.01 (s, 1H, -OH), [Found : C, 75.6; H, 7.6, $C_{30}H_{36}O_5$ requires: C, 72.7; H, 7.4%].

Results and Discussion

The compound **(1)** was subjected to methoxymethylation (methoxymethyl chloride/K_2CO_3/acetone) to give compound **(2)** the formation of which was ascertained by spectral studies and elemental analysis. Infrared spectrum of **(2)** showed the absorption frequencies at 3450 and 1654 cm^{-1} indicating the presence of hydroxy and ketonic group in conjugation. In ^{1}H-NMR spectrum, a singlet at δ 2.45 indicated the presence of methyl protons of acetyl group. Two singlets at δ 3.45 and δ 5.55 indicated the presence of six protons of two -OCH_3 group and four protons of two-CH_2 group, respectively which confirmed that the methoxymethylation has taken place. Compound **(3)**, **(4)** and **(5)** were obtained by the nuclear prenylation (cool methanolic KOH/prenyl bromide) of **(2)** and the formation of which agreed with the data of spectral and elemental analysis. The ^{1}H-NMR spectrum of the prenylated compound **(7)** indicated the presence of C-prenyl unit. A sharp singlet at δ 1.70 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 multiplet at δ 3.52 and a triplet at δ 5.22, respectively. Similarly *O*-prenylation of *p*-hydroxybenzaldehyde using prenyl bromide/K_2CO_3/acetone gave compound **(6)**. The compound **(5)** on a cross-aldol condensation with **(6)** in the presence of 50% ethanolic KOH afforded the compound **(8)** after dehydration of the initial aldol product. The characteristic IR absorption frequencies at 1645 cm^{-1} showed the presence of conjugated ketonic group and the absorption peaks at 1600 and 1590 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 δ 7.45 and δ 8.01 appeared showing the presence of two vinylic protons (α and β protons; i.e cis isomer). The elemental analysis for C and H showed satisfactory results (within ± 0.4%). The NaOAc/EtOH treatment of **(7)** gave the corresponding flavanone **(8)**. Finally the compound **(9)** was obtained from **(8)** by demethoxymethylation (MeOH/3N HC1). The IR absorption frequencies at 3520 and 1645 cm^{-1} showed the presence of -OH (phenolic) group and ketonic group and the absorption peaks at 1605 and 1600 cm^{-1} indicated the presence of unsymmetric ethylenic double bond and the aromatic rings, respectively. One singlets at δ 13.01 indicated the presence of -OH protons which confirmed the completion demethoxymethylation. The B-ring protons have their usual chemical shift value.

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