Short Communication

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SYNTHESIS OF 3,5,7,3′- TETRAMETHOXY -4′-HYDROXY-8-C-PRENYLFLAVONE

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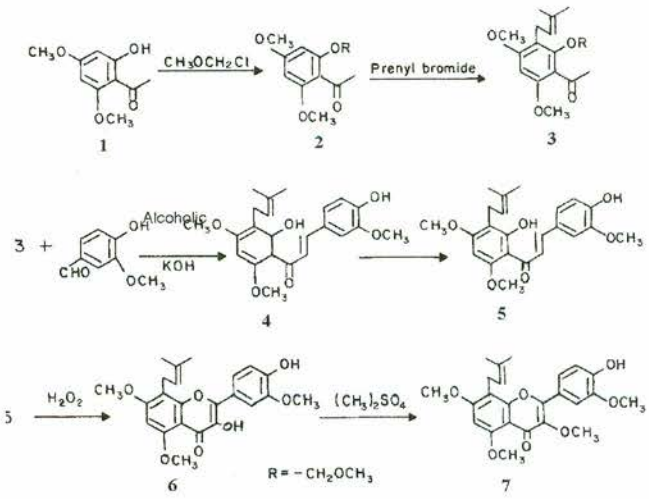
Flavonoids constitute an important group of natural products and some of possess a wide range of biological activities such as antibacterial antifungal anti-inflammatory, anti-microbial, anti-tumour (Hossain 2001), anti-cancer (Parmer *et al* 1988), prostaglandin binding (Hossain 2001) and insect antifeeddant (Parmer *et al* 1988). A large number of natural products including flavonoids are being reported in the literature every year and their structures need to be proved by synthesis. Here in this paper the synthesis of 3,5,7, 3′ -tetramethoxy-4′ -hydroxy-8-C-prenylflavone **(12)** has been reported which may be used as synthetic marker and it is also used as a polyphenolic standard of Gas Liquid Chromatography (GLC) for the identification of phenolic compounds. Alkaline condensation of 7 and 4-hydroxy-3 methoxy-benzaldehyde afforads 4′,6′,3-trimethoxy-4-hydroxy-2′-(methoxymethyleneoxy)-3′-C-prenylchalcone **(9)**. Dimethoxymethylation (Hossain and Islam 1993) of **(9)** gives 4′, 6′, 3-trimethoxy 2′, 4-dihydroxy-3′-C-prenylchalcone **(10)**. H_2O_2 treatment of 10 affords 5,7,3′-trimethoxy-3,4′-dihydroxy-8-C-prenylflavone **(11).** Finally partially methylation of **(11)** furnishes 3,5,7, 3′-tetramethoxy-4′-hydroxy-8-C-prenylfla--vone **(12)** (Scheme-I).

Melting points were determined using an electrothermal melting point apparatus (Gallenkamp) and are uncorrected. IR spectra were recorded (KBr discs) on a Pye-Unicam SP_3-300 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). Mass spectra were recorded on Jeol-300 analytical mass spectrometer.

Methoxymethylation of ***(1)***. A mixture of 2-hydroxy-4, 6-dimethoxyacetophenone (Nagaranjan and Parmer 1978) (**1**,2.5g) in dry acetone (25 ml), methoxymethyl chloride (**1**,0.5g) and anhydrous potassium carbonate (10 g) was refluxed for about 3 h. Usual work up and it was crystallized from benzene, m.p. 68°C; (M^+, 240); IR: 1642, 1603, 1598, 1400, 1380, 1364, 1214, 1200, 1040, 980 cm^{-1}; ^{1}H-NMR: 2.48 (s, 3H,-$COCH_3$), 3.42 (s, 3H, -CH_2OCH_3) 3.98 and 4.00 (2s, 6H, -OCH_3X_2), 5.55 (s, 2H, -CH_2OCH_3), 6.41 (s, 1H,H-3), 7.12 (s, 1H, H-5).



Scheme-1

Nuclear prenylation of 4, 6-dimethoxy-2-(methoxymethyleneoxy) acetophenone ***(2)***. 4, 6-Dimethoxy-2-(methoxymethyleneoxy) acetophenone (**2**, 1 g) was added to a well cooled solution of KOH (2 g) in absolute methanol (30 ml) and the whole solution was cooled to 0°C. Prenyl bromide (2.5 g) was added and the reaction mixture allowed to stand at room temperature for 24 h with constant stirring. Usual work up it was then subjected to column chromatography over silica gel and eluted successively with petrol-benzene (5:1), petrol-benzene (1:3) and petrol-benzene (1:5) compound **(3)** was obtained.

4,6-Dimethoxy-2-(methoxymethyleneoxy)-3-C-prenyla-cetophenone ***(3)***. It was a viscous liquid (675 mg) and was not characterized from any solvent. UV:225, 243, 280 nm; IR: 1645, 1600, 1590, 1420, 1375, 1365, 1325, 1240, 1205, 1100, 1050, 985, 910, 835, 725 cm^{-1},^{1}H-NMR: 1.70 [s, 6H,>$C(CH_3)_2$], 2.43 (s, 3H, -$COCH_3$), 3.51 (m, 5H, -CH_2-CH=and-CH_2OCH_3), 3.98 (s,3H-OCH_3), 4.00 (s,3H-OCH_3) 5.22 (t,1H,-C_2H-CH=) 5.51 (s, 2H, -CH_2OCH_3), 6.98 (s, 1H, H-5); [Found: C, 66.23; H,7.79; $C_{17}H_{24}O_5$ requires: C, 66.48; H, 7.57%]. It was identified as4,6-dimethoxy-2-(methoxymethyleneoxy)-3-C-prenylacetophenone (**3**).

4′,6′,3-Trimethoxy-4-hydroxy-2′ (methoxymethyleneoxy)-3′-C-prenylchalcone ***(4)***. A mixture of 4, 6-

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dimethoxy-2-(methoxymethyleneoxy)-3-C-prenylacetophenone (**3**, 0.50 g) and 3-methoxy-4- hydroxybenzaldehyde (0.340 g) in ethanolic KOH (50%, 20 ml) was kept at room temperature for 80 h. Usual work up and it crystallised from xylene as an orange crystals (0.104 g), m.p. 112°C; R_f 0.44 (benzene). It gave negative alcoholic ferric chloride test. UV:225, 243, 280 nm; IR: 1645, 1600, 1590, 1420, 1375, 1365, 1325, 1240, 1205, 1100, 1050, 985, 910, 835, 725 cm^{-1}; ^{1}H-NMR: 1.70 [s, 6H, >C(CH_3)$_2$], 2.43 (s, 3H, -COCH_3), 3.51 (m, 5H, -CH_2-CH=and -CH_2OCH_3), 3.96 (s, 3H, -OCH_3),3.98 (s, 3H, -OCH_3), 4.00 (s,3H, -OCH_3) 5.28 (t, 1H, -CH_2-CH=), 5.51 (s, 2H,-CH_2OCH_3), 6.94 (s, 1H, H-5), 7.41 (d, 1H, J=9Hz, H-α), 7.72 (m, 3H, H-2, H-5 and H-6), 8.03 (d, 1H, J= 9Hz, H-β), 12.01 (s, 1H, -OH); [Found : C, 67.87; H, 6.78. $C_{25}H_{30}O_7$ requires: C, 67.41; H, 6.41%].

4′, 6′, 3-Trimethoxy-2′4-dihydroxy-3′-C-prenylchalcone ***(5)***. To a solution of the above methoxymethylated chalcone (**4**,0.5g) in methanol (20 ml), HC1 (3N, 50 ml) was added and boiled in water bath for 15 min. Usual work up and it was crystallized from methanol as yellow needles (0.125 g), mp 124°C;(M^+,398); R_f 0.66 (acetone-benzene; 5:1). It gave positive ferric chloride test. UV: 232, 254, 365; IR: 3540, 1645, 1605, 1595, 1385, 1355; ^{1}H-NMR: 1.71 (s, 6H, >C(CH_3)$_2$], 3.53 (d, 2H, J=7Hz,-CH_2-CH=) 3.95 (s,3H,-OCH_3), 3.97 (s, 3H,-OCH_3), 3.99 (s,3H,-OCH_3) 5.50 (t,1H,J=7Hz,-CH_2-CH=) 6.94 (s,1H, H-5′), 7.45 (d, 1H,J=9Hz, H-α), 7.77 (m, 3H, H-2,H-5 and H-6), 8.01 (d, 1H, J=9Hz, H-β), 12.71 (s,2H,-OHx$_2$); [Found:C, 69.34; H, 6.53. $C_{23}H_{26}O_6$ requries: C, 69.41: H,6.81%].

3′, 5, 7-Trimethoxy-3, 4′-dihydroxy-8-C-prenylflavone ***(6)***. To the above chalcone (**5**, 0.250 g) in pyridine (20 ml) and NaOH (20%, 30 ml) kept at 60-70°C. H_2O_2 (30%, 30 ml) was added with stirring during 15 min. The reaction mixture was dissolved in benzene and crystallized methanol as yellow needles (0.109g), m.p. 129°C; (M^+, 412); R_f 0.54 (benzene); UV; 225, 274, 325; IR: 3520, 2910, 2875, 1645, 1600, 1510, 1472, 1375, 1365,; ^{1}H-NMR: 1.74 (s, 6H,>C(CH_3)$_2$], 3.51 (d, 2H, J=7Hz,-CH_2-CH=), 3.95 (s, 3H, -OCH_3), 3.97 (s, 3H, -OCH_3), 3.99 (s, 3H, -OCH_3), 3.99 (s, 3H, -OCH_3) 5.29 (t, 1 H, J=7Hz, -CH_2-CH=), 6.98 (s, 1H, H-6), 7.71 (m, 3H, H-2′, H-5′ and H-6′), 13.04 (s, 2H, -OHx$_2$); [Found: C, 66.99; H, 5.82. $C_{23}H_{24}O_7$ requires: C, 66.74; H, 5.73%].

3′, 3, 5, 7-Tetramethoxy-4′-dihydroxy-8-C-prenylflavone ***(7)***. A mixture of 3′, 5, 7-trimethoxy-3, 4′ -dihydroxy-8-C-prenylflavone (**6**,0.85 g), dimethyl sulphate (0.308g) and anhydrous K_2CO_3 (5 g) in acetone (20 ml) was refluxed for 2 h. Usual work up and was crystallized from petrol to give yellow crystals (0.200 g), m.p 144°C; R_f 0.61 (methanol-chloroform; 10:1), (M^+, 426), UV: 230, 262, 380; IR: 1645, 1605, 1590, 1470, 1372, 1365, 1147; ^{1}H-NMR; 1.72 [(s, 6H, >C(CH_3)$_2$], 3.99 (s, 3H, -OCH_3), 3.99 (s, 3H, -OCH_3), 4.01 (s, 3H, -OCH_3), 5.25 (t, 1H, J=7Hz, -CH_2-CH=),6.95 (s, 1H, H-6), 7.73 (m, 3H, H-2′, H-5′ and H-6′), 13.01 (s, ^{1}H, -OH); [Found: C, 66.99; H, 5.82. $C_{23}H_{24}O_7$ requires : C, 66. 74, H, 5.73%].

The compounds **1,2,3** and **4** have been prepared by following the literature procedure (Nagaranjan and Parmer 1978; Islam and Hossain 1992). The formation of these products has been confirmed by comparing their melting points with the reported values (Nagaranjan and Parmer 1978; Islam and Hossain 1992). The compound **1** was subjected to methoxymethylation (methoxymethyl chloride/ K_2CO_3/acetone) to give compound **2**. In ^{1}H-NMR spectrum a singlet at δ 2.48 indicated the presence of methyl protons of acetyl group. Two singlets at δ 3.42 and 5.5 indicated the presence of three protons of one-OCH_3 group and 2 protons of one-CH_2 group, respectively which confirmed that the methoxymethylation has taken place. Compound **3** was obtained by the nuclear prenylation (cool methanolic KOH/prenyl bromide) of **3** and the formation of which was agree with the data of spectral and elemental analysis. The ^{1}H-NMR spectrum of the prenylated compound **3** indicated the presence of C prenylunit. A sharp singlel 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 m (multiple) at δ 3.51and a triplet at δ 5.22, respectively. The compound **7** on a cross-aldol condensation with benzaldehyde in the presence of 50% ethanolic KOH afforded the compound **4** after dehydration of the initial aldol product. 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; i.e cis isomer). The elemental analysis for C and H showed satisfactory results (within ± 0.4%). The compound **5** was obtained from **4** by demethoxymethylation (MeOH/ 3N,HC1). H_2O_2 treatment of **5** gave the corresponding flavone **6**. Two doublets at δ 7.45 and δ 8.01 for vinylic protons disappeared. The title compound **7** was finally obtained by methylation of its precursor. The formation **7** was ascertained by spectral studies and elemental analysis.

Key words: Flavonoids, Gas Liquid Chromatography, Phenolic compounds

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