Pak J Sci Ind Res 2003 ***46*** *(1) 27-30*

SYNTHESIS OF 2′ 4′-DIHYDROXY-6′-METHOXY-3, 4-METHYLENEDIOXYDIHYDRO CHALCONE AND 2′, 4′, 6′-TRIHYDROXY-4-METHOXYDIHYDROCHALCONE

Sayed Alam and Azizul Islam*

Department of Chemistry, University of Rajshahi, Rajshahi-6205, Bangladesh

(Received 24 June 2000; accepted 28 March 2002)

The world of nature abounds in organic compounds of every conceivable structural classes. Every year Organic Chemists isolate and characterize a lot of compound from medicinal plants all over the World. The isolation and characterization of 2′, 4′-dihydroxy-6′-methoxy-3, 4-methylenedioxy dihydrochalcone reported in 1990 from the bark of *Iryanthera sagotiana* (Benth.) *Warb.* In 1997 the isolation and characterization of 2′, 4′, 6′-trihydroxy-4-methoxydihydrochalcone from the woody part and the ripe fruit of *Iryanthera Laevis* reported. The syntheses of these two dihydrochalcones have not been reported yet. In this paper we wish to report the syntheses of the above two dihydrochalcones by Claisen – Schmidt reaction and other subsequent steps.

Key words: *Iryanthera sagotiana*, Myristicace, Dihydrochalcone.

Introduction

Iryanthera sagotiana (Benth) Warb., is a Myristicaceous family tree (Kawanishi *et al* 1990) which is collected at Belem, Brazil. *Iryanthera Laevis,* which is also a Myristicaceous family tree, called 'mamita' in the oriental Llanos of Colombia (Silva *et al* 1997). Its ripe fruit is used in the preparation of a sweet from consumption by the local population and its chemical analysis was thus deemed to be importance 2′, 4′, 6′-trihydroxy-4-methoxydihydrochalcone along with some other dihydrochalcones and flavonols. Now, we report the syntheses of the above two dihydrochalcones from 2-methoxy-4,6-dimethoxymethoxyacetophenone (**2**) and 2-hydroxy-4,6-dimethoxymethoxyacetophenone (7) respectively. Alkaline condensation of (**2**) with piperonal gave the chalcone (**4**), which on dimethoxymethylation yielded chalcone (**5**) (Scheme-1). This chalcone on hydrogenation using H_2-Pd/C in acetic acid medium gave the title dihydrochalcone (**6**). The required 2-methoxy-4, 6-dimethoxymethoxyacetophenone (**2**) was prepared by the methoxymethylation of 2-methoxy-4,6-dihydroxy acetophenone (Nagaranjan and Parmar 1978) (**1**).

Again, alkaline condensation of 2-hydroxy-4, 6-dimethoxymethoxyacetophenone (7) Sherif *et al* (1982) with p-methoxybenzaldehyde (**8**) yielded the corresponding chalcone (**9**), which on dimethoxymethylation furnished the chalcone (**10**) (Scheme-2). This chalcone (**10**) on hydrogenation produced the title dihydrochalcone (**11**). The structure of this two dihydrochalcones were determined on the basis of their spectral data (UV, IR and ^{1}H NMR) and elemental analysis.

Experimental

All melting points are uncorrected and were recorded on an electrothermal melting point apparatus (Gallenkamp). IR spectra were measured (KBr disc) using a DR-8001, SHIMADZU spectrophotometer. ^{1}H NMR spectra ($CDCl_3$) were recorded on a Brucker WH 200 MHz instrument with TMS as an internal standard and chemical shifts are given in δ values. UV spectra (λ_{max} in nm) were recorded on an UV-180, SHIMADZU, Double beam spectrophotometer in methanol. Column chromatography was packed with silica gel (Kiesel gel 60, 70-230 mesh, Merck). Completion of the reaction and purity of the compounds were checked by TLC. It was performed with silica gel GF_{254} (Fluka) and spots were developed by spraying 2% $FeCl_3$ solution and 1% H_2SO_4 and heating the plates at 100°C until coloration took place.

Methoxymethylation of 2-methoxy-4, 6-dihydroxyacetophenone (1). A mixture of 2-methoxy-4, 6-dihydroxyacetophenone[3] (Nagaranjan and Parmar 1978), (**1, 6g**), dry acetone (150 ml), methoxymethylchloride (Marvel and Porter 1951) (5 g) and ignited K_2CO_3 (50 g) was refluxed for 15 min. The progress of the reaction mixture was examined by TLC. Acetone was removed by distillation. The residue when chromatographed over silica gel and eluted with petroleum ether – ethyl acetate (10:1) gave semi-solid mass (5.5 g), yield 50%, R_f 0.52 (petroleum ether-ethyl acetate; (10 :1). It gave no color with alcoholic ferric chloride solution.

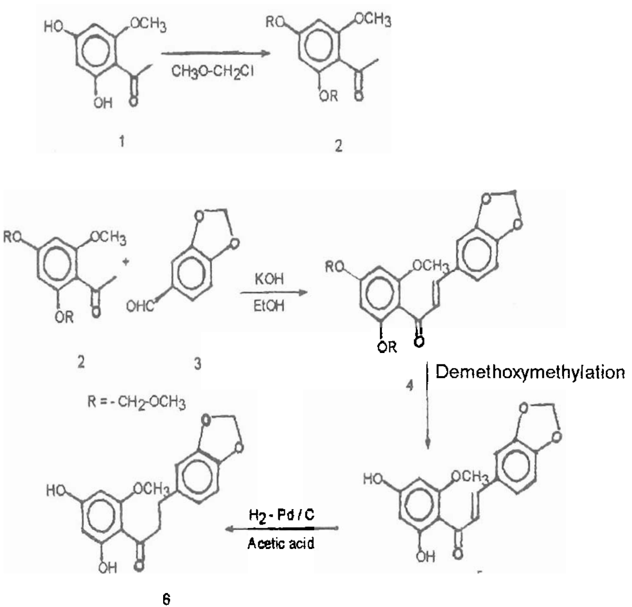
Anal found: C,57.91; H, 6.40% ; Calc. for $C_{13}H_{18}O_6$; C, 57.78; H,6.67% UV. λ_{max} : 255, 310 nm. IR. (KBr) υ_{max} : 3040, 2975, 2890, 1660, 1590, 1500, 1440, 1400, 1365, 1355,

---

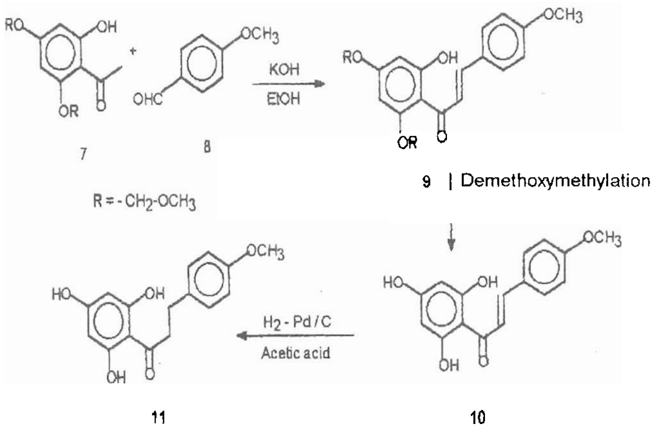
*Author for correspondence

1280, 1260, 1135, 1100, 940, 905, 840, 770 cm^{-1}. ^1H NMR: δ 2.48 (s, 3H, -COC$\underline{H}_3$), 3.54 (s, 6H, 2 X –CH_2-OC$\underline{H}_3$), 3.94 (s, 3H, OMe), 5.25 (s, 4H, 2 X –C$\underline{H}_2$-OCH_3), 6.18(1H, d, J=2.4 Hz, C_5-H). 6.24 (1H,d, J=2.4 Hz, C_3-H). It was identified as 2-methoxy-4, 6-dimethoxymethoxyacetophenone, (**2**).

Synthesis of 2′, 4′-dimethoxymethoxy-6′-methoxy -3, 4-methylenedioxychalcone (4). A mixture of 2-methoxy-4, 6-dimethoxymethoxyacetophenone (**2**, 5.5 g) and piperonal (**3**, 3.5 g) in ethanolic solution of KOH (20%, 25 ml) was kept at room temperature for about 75 h. The reaction mixture was diluted with ice cold water, acidified with dilute HCl and extracted with ether. The ether layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product, which was a mixture of chalcone, unreacted ketone and aldehyde were subjected to column chromatography over silica gel using n-hexane-chloroform (1:1) as developing solvent. The chalcone obtained as pale yellow needle (4.2 g), mp. 122°C, yield. 47%, R_f0.41(n-hexane-chloroform: 1: 1). It was insoluble in aq. alkali and showed no color with alcoholic ferric chloride solution.



Scheme-1



Scheme 2

Anal found: C,62.18; H,5.85%; Calc. for $C_{21}H_{22}O_8$; C, 62.69; H,5.47%.

UV. λ_{max}: 255, 345 nm. IR. (KBr) υ_{max}: 1650, 1595, 1490, 1440, 1370, 1310, 1255, 1200, 1160, 1130, 1105, 1020, 970, 930, 850, 835, 780 cm^{-1}. ^1H NMR: δ 3.56 (s. 6H, 2 X -CH_2-OC$\underline{H}_3$), 3.90 (s, 3H, OMe), 5.18 (s, 4H, 2 X-C$\underline{H}_2$-OCH_3), 5.96 (1H, d, J=3.0 Hz C_3′-H), 5.99 (s, 2H, -OCH_2O-), 6.03 (1H, d, J=3.0 Hz C_5′-H), 6.86 (1H, dd, J=8.0 and 2.0 Hz, C_6-H), 6.94 (1H, d, J=2.0 Hz, C_2-H), 7.01 (1H, d, J=8.0 Hz, C_5-H), 7.38 (1H, d, J=16Hz, C_α-H), 7.97 (1H, d, J=16 Hz, C_β-H).

Dimethoxymethylation of 2′, 4′-dimethoxymethoxy-6′-methoxy-3,4-methylenedioxy chalcone (4). To a solution of 2′, 4′-dimethoxymethoxy-6′-methoxy -3, 4- methylenedioxychalcone (**4**, 0.5 g) in absolute methanol (20 ml), 3N HCl (4 ml) was added. The solution was boiled for 15 min in water bath. It was diluted with water (50 ml) and extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried over anhydrous Na_2SO_4 and concentrated. The product was purified by preparative TLC using chloroform-methanol (9 : 1) as developing solvent. The chalcone crystallized as yellow crystals (175 mg) from chloroform, mp.139°C, yield 35%, R_f0.58 (chloroform-methanol: 9: 1). It gave deep brown color with alcoholic ferric chloride solution.

Anal found: C,64.49; H,4.82%; Calc. for $C_{17}H_{14}O_6$; C, 64.97; H,4.46%

UV. λ_{max}: 250, 315 nm. IR. (KBr) υ_{max} : 3330, 3100, 2855, 2810, 2775, 2680, 2400, 1645, 1610, 1490, 1445, 1375, 1305, 1260, 1205, 1155, 1130, 1100, 1015, 960, 925, 855, 825, 800, 775 cm^{-1}. ^1H NMR: δ 3.84 (s, 3H, OMe), 5.99 (1H, d, J=3.0 Hz, C_3′-H), 6.01 (s, 2H, -OCH_2O-), 6.06 (1H, d, J=3.0 Hz, C_5′-H), 6.50 (s, 1H, -OH), 6.75 (1H, d, J=8.0 and 2.0 Hz, C_6-H), 6.79 (1H, d, J=2.0 Hz, C_2-H), 6.82 (1H, d, J=8.0 Hz, C_5-H), 7.34 (1H, d, J=16Hz, Cα-H), 7.93 (1H, d, J=16 Hz, C_β-H), 13.57 (1H, s, -OH).

*Hydrogenation of 2′, 4′-dihydroxy-6′-methoxy-3,4-methylenedioxychalcone **(5)**.* The above chalcone (**5**, 0.5 g) was dissolved in acetic acid (25 ml) and Pd/C (5%, 40 mg) was added. Hydrogen gas was passed through the solution for 4 h with constant stirring using magnetic stirrer at room temperature. The mixture was neutralized by aq. K_2CO_3 (10%) and extracted with ethyl acetate. The organic layer was washed with water, dried over Na_2SO_4 and concentrated. The product was purified by preparative TLC over silica gel 60G using chloroform-methanol (9:1) as developing solvent. The dihydrochalcone crystallized and obtained as pale yellow needles (0.180 g) from chloroform, mp. 179°C, yield 36%, R_f 0.54 (chloroform-methanol; 9 : 1). It gave deep brown color with alcoholic ferric chloride solution.

Anal found: C,64.89; H, 4.87% ; Calc. for $C_{17}H_{16}O_6$; C, 64.56; H,5.06%

UV. λ_{max}: 240, 290 nm. IR. (KBr) υ_{max} : 3360, 3100, 2400, 1630, 1605, 1595, 1535, 1440, 1370, 1310, 1270, 1200, 1165, 1120, 1095, 1020, 970, 915, 860, 815, 795, 760 cm^{-1}. ^{1}H NMR: δ 2.93 (2H, t, J=7.5 Hz, C_β-H), 3.28 (2H, t, J=7.5 Hz, Cα-H), 3.88 (s, 3H, OMe), 5.97 (1H, d, J=3.0 Hz C_3'-H), 5.98 (2H, s, -OCH_2O-), 6.01 (1H, d, J=3.0 Hz, C_5'-H), 6.58 (1H, s, -OH), 6.73 (1H, dd, J=8.0 and 2.0 Hz, C_6-H), 6.78 (1H, d, J=2.0 Hz, C_2–H), 6.85 (1H, d, J=8.0 Hz, C_5-H), 13.66 (s, 1H, -OH). On the basis of the above spectral data (UV, IR & ^{1}H NMR) the structure **6** is assigned to 2′, 4′ -dihydroxy-6 -methoxy-3, 4-methylenedioxydihydrochalcone.

Preparation of 2′-hydroxy-4′, 6′-dimethoxymethoxy-4-methoxychalcone, (9). A mixture of 2-hydroxy-4, 6-dimethoxymethoxyacetophenone (7,5.5 g) and p-methoxybenzaldehyde (**8**, 3 g) in ethanolic solution of KOH (20%, 25 ml) was kept at room temperature for about 75 h. The reaction mixture was worked-up as usual and was purified by preparative TLC over silica gel using petroleum ether-ethyl acetate (5:1) as developing solvent. The chalcone was obtained as pale yellow solid (3.75 g), mp.96°C, yield, 44%, R_f=0.41 (petroleum ether-ethyl acetate; 5 : 1). It gave reddish brown color with alcoholic ferric chloride solution.

Anal found: C,64.52; H,5.49%; Calc. for $C_{20}H_{22}O_7$; C, 64.17; H,5.88%.

UV. λ_{max}: 240, 355 nm. IR. (KBr) υ_{max} : 3400, 3100, 3050, 2970, 2855, 1645, 1625, 1515, 1470, 1405, 1365, 1305, 1272, 1205, 1100, 1065, 975, 820 cm^{-1}. ^{1}H NMR: δ 3.58 (s, 6H, 2 X -CH_2-$OC\underline{H}_3$), 3.87 (s, 3H, OMe), 5.27 (s, 4H, 2 X-$C\underline{H}_2$-OCH_3), 5.94 (1H, d, J= 2.4 Hz, C_3'-H), 5.99 (1H, d, J=2.4 Hz, C_5'-H), 6.77 (2H, dd, J=8.6 & 2.4 Hz, C_3-H and C_5-H), 7.08 (2H, dd, J= 8.6 & 2.4 Hz, C_2-H and C_6-H) 7.35 (1H, d, J=16Hz, C_α-H), 7.96 (1H, d, J=16 Hz, C_β-H), 13.64 (1H, C_2'-OH).

Demethoxymethylation of 2′-hydroxy-4′, 6′-dimethoxymethoxy-4-methoxychalcone (9). Dimethoxy methylation of the above chalcone (**9**, 0.5 g) was carried out as previously described method and worked-up as usual. The product was purified by preparative TLC using n-hexane-benzene (6 :1) as developing solvent. The chalcone crystallized as yellow crystals (200 mg) from petroleum ether, mp. 209°C, yield 40%, R_f=0.46 (n-hexane-benzene; 6: 1). It gave deep brown color with alcoholic ferric chloride solution.

Anal found: C,67.43; H, 5.28% ; Calc. for $C_{16}H_{14}O_5$; C, 67.13 ; H,4.90%

UV. λ_{max}: 230, 295 nm. IR. (KBr) υ_{max} : 3360, 3095, 3045,2960, 2840, 1640, 1615, 1510, 1465, 1400, 1355, 11300, 1265, 1210, 1110, 1060, 970, 830 cm^{-1}. ^{1}H NMR: δ 3.78 (s, 3H, OMe), 5.94 (2H, s, C_3'-H and C_5'-H)) 6.54 (1H, s, C_4'-OH), 6.82 (2H, dd, J=8.6 & 2.4 Hz, C_3-H and C_5-H),7.06 (2H, dd, 8.6 & 2.4 Hz, C_2-H and C_6-H), 7.36 (1H, d, J=16Hz, Cα-H), 7.96 (1H, d, J=16 Hz, C_β-H), 13.66 (s, 2H, C_2'-OH and C_6'-OH),

Hydrogenation of 2′, 4′, 6′-trihydroxy-4-methoxychalcone (10). The above chalcone (**10**, 0.5 g) was hydrogenated as previously described method and worked-up as usual. The product was purified by preparative TLC over silica gel 60G using n-hexane-benzene (7:1) as developing solvent. The dihydrochalcone crystallized as yellow needles (200 mg) from methanol, mp. 203°C, yield 40%, R_f 0.44 (n-hexane-benzene; 7 : 1). It gave deep brown color with alcoholic ferric chloride solution.

Anal found: C,66.29; H, 5.62% ; Calc. for $C_{16}H_{16}O_5$; C,66.67; H,5.56%

UV. λ_{max} : 228, 287 nm. IR. (KBr) υ_{max} : 3330, 3070, 2960, 2845, 1640, 1620, 1520, 1480, 1405,1375, 1350, 1280, 1265, 1205, 1100, 1065, 980, 915, 830 cm^{-1}. ^{1}H NMR: δ 2.90 (2H, t, J= 7.5 Hz, C_β-H), 3.35 (2H, t, J= 7.5 Hz, C_α-H), 3.74 (s, 3H, OMe), 5.92 (2H, s, C_3'-H and C_5'-H)), 6.48 (1H, s, C_4'-OH), 6.80 (2H, dd, J=8.6 & 2.4 Hz, C_3-H and C_5-H), 7.18 (2H, dd, 8.6 & 2.4 Hz, C_2-H and C_6-H), 13.77 (s, 2H, C_2'-OH and C_6'-OH). On the basis of the above spectral data (UV, IR & ^{1}H NMR) the Structure **11** is assigned to 2′, 4′, 6′-trihydroxy-4–methoxydihydrochalcone.

Results and Discussion

In this paper the syntheses of the above two dihydrochalcones (**6** and **11**) are described. Methoxymethlylation of 2-methoxychloroacetophenone (**1**) gave 2-methoxy-4, 6-dimethoxymethoxyacetophenone (**2**). This ketone **2** could not be crystallized out and was a semi-solid mass. The structure of this ketone (**2**) has been confirmed by spectral data and elemental analysis. The IR absorption peak for hydroxy group in (**2**) was disappeared. The IR absorption frequency at n 1660 cm^{-1} indicated the presence of a carbonyl (>C=O) group. The pre-sence of two methoxymethyl groups was clearly indicated by two singlets at δ 3.54 (s, 6H, 2X-CH_2-$OC\underline{H}_3$) and 5.25 (s, 4H, 2X-CH_2-OCH_3). The acetyl protons (-$COCH_3$) and the methoxy protons (-OCH$_3$) were appeared as a singlet at δ 2.48 and 3.94 respectively integrating for three protons each. The C$_3$-H and C$_5$-H aromatic protons appeared as two doublets at δ 6.18 and 6.24 integrating for one proton each.

Alkaline condensation of 2-methoxy-4, 6-dimethoxymethoxyacetophenone (**2**) and piperonal (**3**, 3, 4-methylenedioxybenzaldehyde) gave 2′, 4′-dimethoxy-methoxy-6′-methoxy -3, 4-methylenedioxychalcone (**4**). It was obtained as pale yellow needles mp. 122°C. Spectral data and elemental analysis have confirmed the structure of chalcone (**4**). The UV absorption band of this chalcone (**4**) showed bands at λ$_{max}$ 255, 345 nm. The IR absorption frequency at ν 1650 cm^{-1} indicated the presence of a conjugated carbonyl group (>C=O). The ^{1}H NMR spectrum explained the presence of two methoxymethyl groups at δ 3.56 (s, 6H, 2 X-CH$_2$-O$\underline{CH}_3$) and 5.18 (s, 4H, 2 X-$\underline{CH}_2$-OCH$_3$) as a singlet integrating for six and four protons respectively. The three protons of the methoxy (-OCH$_3$) group appeared at δ 3.90 as a singlet integrating for three protons. The C′$_3$-H and C′$_3$-H protons of the A-ring appeared at δ 5.96 (1H, d, J=3.0 Hz) and 6.03 (1H, d, J=3.0 Hz) as a doublet integrating for one proton each. The methylene protons of the methylenedioxy group appeared as a singlet at δ 5.99 (s, 2H, -OCH$_2$-O-) integrating for two protons. The protons of the B-ring appeared as doublet at δ 6.94 (C$_2$-H), 7.01 (C$_3$-H) and a double doublet at δ 6.86 (C$_6$-H) integrating for one proton each. Two doublets at δ 7.38 (1H, d, J=16 Hz) and 7.97 (1H, d, J=16 Hz) showed the presence of C$_\alpha$-H and C$_\beta$-H protons respectively integrating for one proton each.

Dimethoxymethylation of chalcone (**4**) into corresponding 2′, 4′-dihydroxy-6′-methoxy-3, 4-methylenedioxychalcone (**5**) using 3N HCl was carried out. The chalcone **5** is a solid compound and the formation of which has been supported by spectral data (UV, IR and ^{1}H NMR) and elemental analysis. The chalcone (**5**) when hydrogenated using H$_2$-Pd/C in acetic acid medium furnished 2′, 4′-dihydroxy-6′-methoxy-3, 4-methylenedioxydihydro chalcone (**6**). The structure of this dihydrochalcone has been confirmed by spectral data (UV, IR and ^{1}H NMR) and elemental analysis.

Again, alkaline condensation of 2-hydroxy-4, 6-dimethoxymethoxyacetophenone (**7**) and p-methoxybenzal-dehyde (**8**) gave 2′-hydroxy-4′, 6′-dimethoxymethoxy-4-methoxy chalcone (**9**). It was obtained as a pale yellow solid, mp. 96°C. The structure of this chalcone (**9**) has been confirmed by spectral data and elemental analysis. The UV absorption band of chalcone (**9**) showed (λ$_{max}$) 240, 355 nm. The IR absorption frequency at ν 3400 cm^{-1} indicated the presence of a hydroxy group and ν 1645cm^{-1} showed the presence of a conjugated carbonyl group (>C=O). The ^{1}H NMR spectrum showed the presence of two methoxymethyl groups by two singlets at δ 3.58 (s, 6H, 2X-CH$_2$-O$\underline{CH}_3$) and 5.27 (s, 4H, 2X-CH$_2$-O$\underline{CH}_3$). The three methyl protons of the methoxy group (-OCH$_3$) appeared at δ 3.87 as a singlet integrating for three protons. The C′$_3$-H and C′$_3$-H protons of the A-ring appeared at δ 5.94 and 5.99 as two doublets integrating for one proton each. The C$_3$-H and C$_5$-H protons of the B-ring were indicated at δ 6.77 (2H, dd, J=8.6 & 2.0 Hz) as a double doublet integrating for two protons. The remaining C$_2$-H and C$_6$-H protons of the B-ring appeared at δ 7.08 as a double doublet integrating for two protons. The C$_\alpha$-H and C$_\beta$-H protons were shown by two doublets at δ 7.35 and 7.96 respectively. One hydroxy proton appeared as singlet at δ 13.64 integrating for one proton.

Dimethoxymethylation of chalcone (**9**) using 3N HCl gave the corresponding 2′, 4′, 6′-trihydroxy-4-methoxychalcone (**10**). The chalcone (**10**) was obtained as yellow crystals, mp. 209°C. The structure of chalcone (**1**)**0** has been confirmed by spectral data and elemental analysis. Hydrogenation of the chalcone (**10**) using H$_2$-Pd/C in acetic acid medium furnished the 2′, 4′ 6′-trihydroxy-4-methoxydihydrochalcone (**11**). On the basis of the above spectral data (UV, IR & 1H NMR) the structure (**11**) is assigned to 2′, 4′, 6′-trihydroxy-4-methoxydihydro-chalcone.

Acknowledgement

The authors are grateful to Dr. M. Abdul Mottaleb, Department of Chemistry, Strathclyde University, Glasgow for his help in connection with ^{1}H NMR spectroscopy and elemental analysis. They are also thankful to Professor Abul Hasem, Department of Chemistry, Jahangirnagar University for his help in connection with IR spectroscopy. The authors are grateful to Dr. Md. Rezaul Karim, Chairman, Department of Bio-chemistry, University of Rajshahi for recording UV spectra. One of the Authors (S. A.) is grateful to the Ministry of Science and Technology for providing him NST fellowship.

References

Kawanishi K, Takagaki T, Hashimotoy 1990 Flavonoids from *Iryanthera sagotiana. Phytochemistry* **29** (8) 2735.

Marvel C S, Porter P K 1951 Monochloromethyl ether. *Organic Synthesis* **1**, 2nd ed, pp 377.

Nagaranjan G R, Parmar VS 1978 New flavonoids of Prunuscerasus: Synthesis of cerasin, erasinone and crasidin. *Indian J Chem* **16B** 439.

Sherif E A, Islam A, Krishnamurti M 1982 A new synthesis of 4,5,7-trihydroxy-8-(3, 3-dimethylallyl) flavanone. *Indian J Chem* **2(B)** 478.

Silva DHS, Yoshida M, Kato MJ 1997 Dihydrocholcone from *Iryanthera sagotiana. Phytochemistry* **46**(3) 579.