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A NEW SYNTHESIS OF HOMOISOFLAVANONES (3-BENZYL-4-CHROMANONES)

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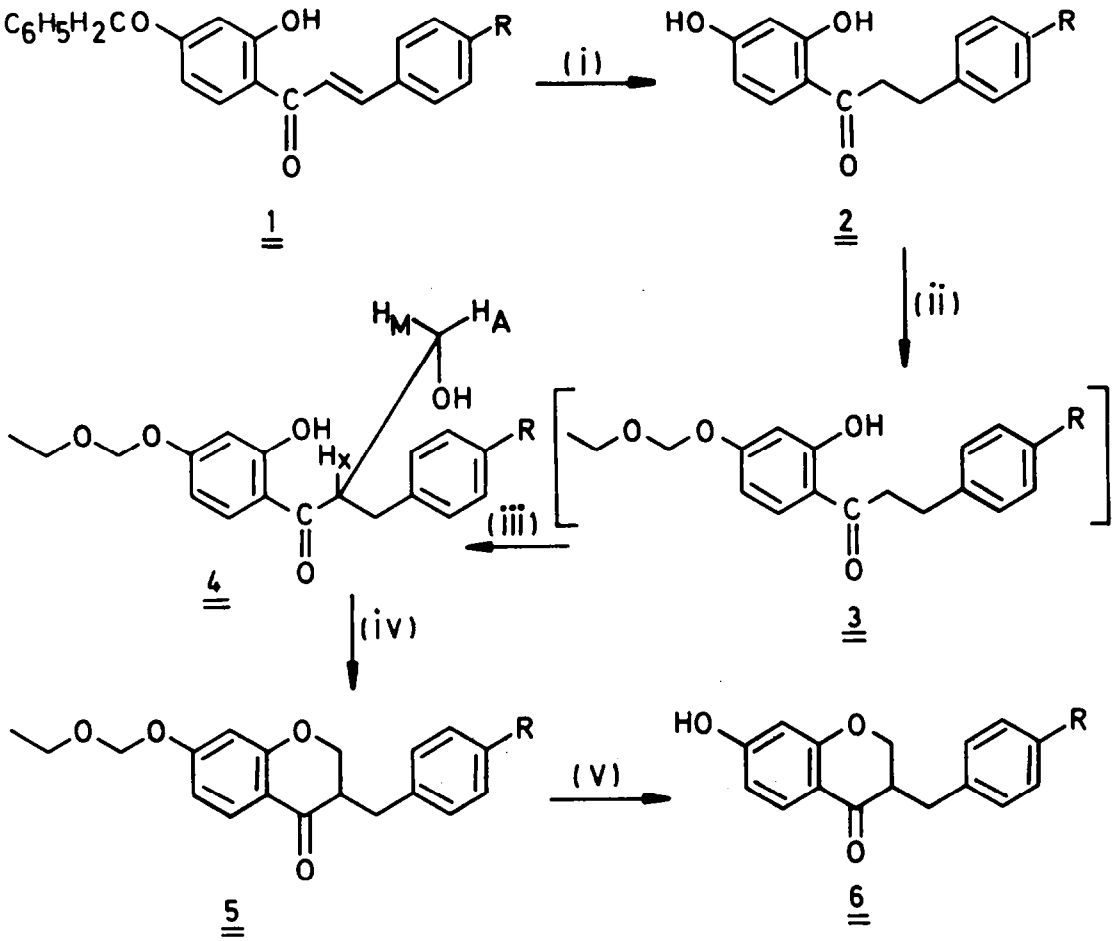
Abstract - Two 7-hydroxyhomoisoflavanones (6a/6b) have been synthesized from corresponding 2'-hydroxydihydrochalcones (2a/2b) in about 33% overall yields. The stages are : (i) selective protection of C_4'-hydroxyl in 2a/2b with $EtO.CH_2Cl$ (1 molar equiv.) in the presence of dry K_2CO_3 and acetone at r.t.; (ii) reaction with one more molar equiv. of $EtO.CH_2Cl$ at 60-70° without isolating products (3a/3b) (iii) cyclization of resulting α-hydroxymethyl derivatives (4a/4b) with 4% aq. alc. Na_2CO_3 and (iv) deprotection of resulting 7-ethoxymethoxy homoisoflavanones (5a/5b) with 10% CH_3OH-HCl. The explanations for the formation of 4a/4b and 5a/5b are given.

Homoisoflavonoids constitute an important group of plant polyphenols, among which four are homoisoflavanones (or 3-benzyl-4-chromanones) occurring in some species of Eucomis[1]. Related to them are five natural 3-benzylidene-4-chromanones, two 3-benzyl-3-hydroxy-4-chromanones and two spiro derivatives. Homoisoflavanones have been synthesised earlier by catalytic reduction of the corresponding 3-benzylidene-4-chromanones[2,3] or 3-benzyl chromones[3,4] which themselves are obtained from the corresponding chromanones[2,3,5-7] and dihydrochalcones[3,4,8,9] respectively. However, reduction of the double bond in each case is a slow reaction and is accompanied by reduction of the keto group as well. More recently, Grover et al.[10] reacted 2'-hydroxypolymethoxydihydrochalcones with methylene iodide in the presence of anhydrous potassium carbonate and acetone. However, this gave mostly bis(dihydrochalconyloxy)methanes; homoisoflavanones formed only in 2-10% yield. There is still another method in which 3-benzyl-4-hydroxycoumarins are hydroborated and subsequently oxidised by chromic acid[11]. But again, its scope is limited.

We report here a new method for the synthesis of homoisoflavanones from 2'-hydroxydihydrochalcones (See preliminary communication[12]). Since homoisoflavanones containing free hydroxyl(s) have now been synthesised, this method could be a general one. This method follows a similar approach as adopted recently by us for the synthesis of polymethoxy-as well as polyhydroxy-isoflavanones starting from o-hydroxydesoxybenzoins.[13,14,15] Further, the present synthesis follows a biogenetic pathway[16].

For the synthesis of 7-hydroxy-4'-methoxyhomoisoflavanone (6a), 2',4'-dihydroxy-4-methoxydihydrochalcone (2a) was first prepared from 4'-benzyloxy-2'-hydroxy-4-methoxychalcone[17] (1a) and then stirred at room temp. with one molar equiv. of ethoxymethyl chloride[18] in the presence of dry potassium carbonate and dry acetone in order to protect the 4'-hydroxy group by ethoxymethylation. Without isolating the product (3a), the above mixture was further treated with one more molar equivalent of ethoxymethyl chloride and then heated initially at 40-50° for 10-15 min and finally at 60-70° for 2.5 h. The product obtained in 93% yield was identified as 2'-hydroxy-α-hydroxymethyl-4-methoxy-4'-ethoxymethoxydihydrochalcone (4a) on the basis of a positive ferric chloride



For 1 to 6 : a, R = OMe ;
b, R = H

Reagents and Conditions

(i) H_2 – Pd (C)
(ii) $ClCH_2OEt$, K_2CO_3, Me_2CO at r.t.
(iii) $ClCH_2OEt$, K_2CO_3, Me_2CO, 60–70 °C
(iv) 4% aq. alc. Na_2CO_3
(v) 10 % Me OH – HCl

Chart 1. Synthesis of homoisoflavanones

test and ^1H- and ^{13}C-nmr data. Thus, the ^1H-nmr spectrum showed resonance signals of ethoxymethoxy protons and the ring protons of the starting meterial. Further, signals of α-benzylethyl -β-hydroxy keto group appeared as follows. α-Methine and β-hydroxymethyl protons resonated as a multiplet of three protons between δ 3.85 - 4.02; benzylic methylene separated as a multi--plet of 2 hydrogens at δ 3.0 ppm; and hydroxyl signal at δ 2.48 underwent exchange with D_2O. This carbinol structure (4a) was further confirmed by ^{13}C-nmr which showed one doublet due to -methine carbon at δ 49.56 and a triplet due to α-hydroxymethyl carbon at δ 62.70 besides other signals of the molecule (see experimental).

In the next step, α-hydroxymethyl dihydrochalcone (4a) was cyclised by refluxing with 4% aq. ethanolic sodium carbonate for 3 hours when 7-ethoxymethoxy-3-(4-methoxy)benzyl-4-chromanone (5a) was obtained in 41% yield. This was characterised by a negative ferric chloride test and ^{1}H nmr signals of three characteristic hydrogens of C-2, C-3 and C-9 as multiplets at δ 4.10-4.32 and δ 2.56-3.31 ppm.

Finally, the protecting group was removed by treating 5a with 10% methanolic hydrogen chloride for 10 min, when 7-hydroxy-4'-methoxyhomoisoflavanone (6a) was obtained in 94% yield. Its structure was supported by its ^{1}H-nmr spectrum showing no ethoxymethoxy group at position 7 but two multiplets of C-2, C-3 and C-9 at 4.37 and 2.70-3.20. The overall yield of 6a from starting dihydrochalcone (2a) is 35%.

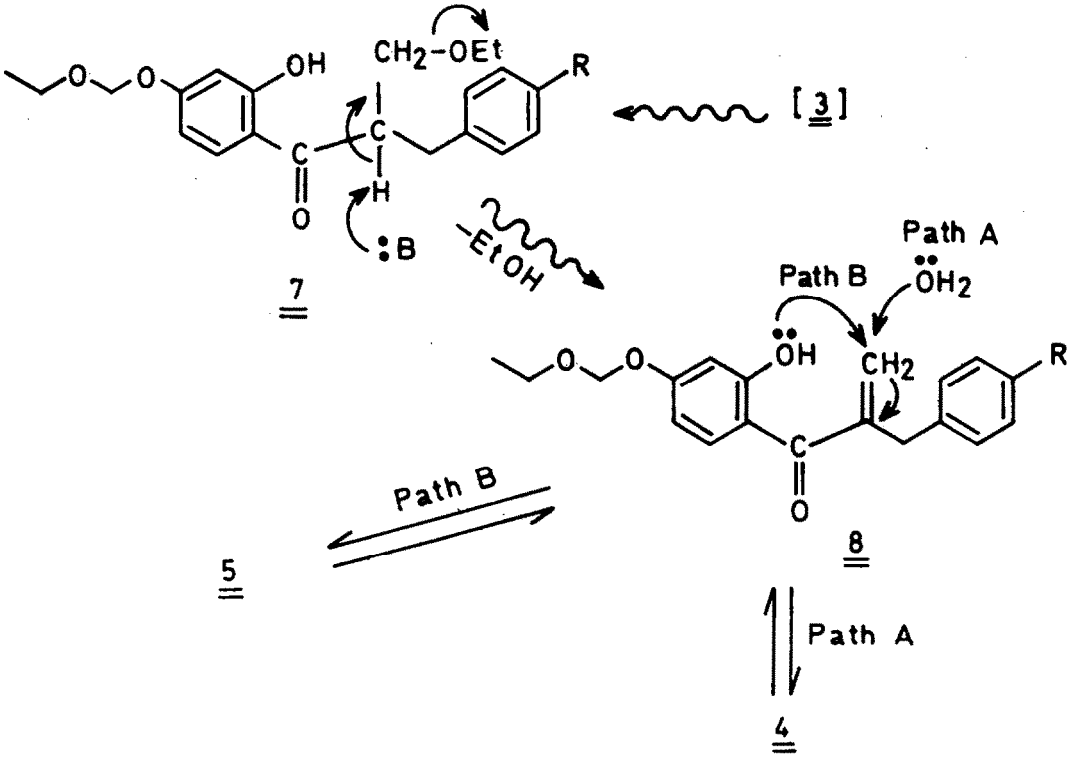


Chart 2. Explanation for formation of 4 and 5

The formation of α-hydroxymethyl derivative (4a) can be explained as follows. First, normal C-alkylation of α-methylene group of the dihydrochalcone (3a) occurs resulting in the formation of α-ethoxymethyl derivative (7a) followed by elimination of ethanol and Michael-type addition of water (path A) to the α,β -unsaturated ketone (8a). Similarly, the formation of isoflavanone (5a) from 4a may occur through 8 by intramolecular attack of 2'-hydroxyl (Path B). This explanation is similar to the one suggested by us during the synthesis of isoflavanones.

A parallel series of experiments were carried out with 2',4'-dihydroxy-dihydrochalcone (2b). Here, α-hydroxymethyl dihydrochalcone (4b) formed in 92% yield which underwent cyclisation with 4% aqueous alcoholic sodium carbonate during 4 h afforded 7-ethoxymethoxy-3-benzyl-4-chromanone (5b) in 38% yield. The final removal of the protecting group afforded 7-hydroxy-3-benzyl-4-chromanone (6b) in 94% yield. All these products were characterised in the same way as in a previous case. The overall yield of 6b from 2b is 32%.

EXPERIMENTAL

Unless stated otherwise, all m.ps are uncorrected; R_f values refer to t.l.c. on silica gel G using benzene - ethyl acetate (4:1) as solvent system and detecting the spots by spraying either

with dil H_2SO_4 followed by heating at 110°C for 5-10 min. or alcoholic ferric chloride. All products were routinely checked for homogeneity by t.l.c; pet. ether used had boiling range 60-80°C; ether refers to diethyl ether and ethoxymethyl chloride was always freshly distilled. IR spectra were recorded using KBr disc on a Perkin-Elmer infra-red 599-B or Shimadzu 435 spectrophotometer; UV data were recorded on Perkin-Elmer model 554 spectrophotometer in ethanol solutions. All ^{1}H-nmr spectra were recorded in $CDCl_3$ with tetramethyl silane as internal standard on either R-30 (90 MHz) Perkin-Elmer spectrophotometer or JNM FX 200 MHz Jeol Fourier transform; proton decoupling experiments were performed with computer-controlled homonuclear decoupling accessory to find out couplings in case of carbinols; the chemical shifts are expressed in ppm and J values in Hz.

2',4'-Dihydroxy-4-methoxydihydrochalcone (2a)

4'-Benzyloxy-2'-hydroxy-4-methoxychalcone[17] (1a, 2.5g) in ethyl acetate (75 ml) was hydrogenated over 10% palladised charcoal (250 mg). The catalyst was filtered, the filtrate concentrated and the residue crystallised from ethyl acetate - petroleum ether to give 2a as colourless crystals (1.7 g), mp 128°C; R_f 0.40 (C, 70.1; H, 5.7. $C_{16}H_{16}O_4$ requires C, 70.6; H,5.9%); UV: λ_{max}. 316(3.81), 276(4.00), 228(3.82), 214 nm (4.19); IR: ν_{max}. 1630 cm^{-1}; ^{1}H NMR: δ 2.70-3.28 (m, 4H, CH_2-CH_2), 3.74(s, 3H, OCH_3), 6.35(m, 2H, H-3',5'), 6.80(d, 2H, J=9.0, H-3,5), 7.11(d, 2H, J=9.6, H-2,6), and 7.60(d, 1H, J=9.6 Hz, H-6').

4'-Ethoxymethoxy-2'-hydroxy-α-hydroxymethyl-4-methoxydihydrochalcone (4a)

To a solution of 2',4'-dihydroxy-4-methoxydihydrochalcone (2a) (2.72 g, 10 mM) in dry acetone (200 ml) was added dry K_2CO_3 (6.9 g, 50 mM), followed by a solution of ethoxymethyl chloride[18] (1.32 ml, 10mM) in acetone (20 ml). The resulting mixture was stirred at room temp. for 20 min. after which TLC indicated full conversion of the starting material and formation of a new ferric positive product presumably 4'-ethoxymethoxy-2'-hydroxy-4-methoxy dihydrochalcone (3a). Next, more of ethoxymethyl chloride (1.45 ml, 11 mM) was added and the mixture heated initially at 40-50° for 10-15 min and finally at 60-70° for 2.5 h when TLC showed full conversion into another new product (ferric positive). The reaction mixture was filtered hot, acetone in the mother liquor was removed at room temp. and the residue treated with ice-cold water. The oil thus separated was extracted with ether. The ether residue on column chromatography yielded 4a as colourless viscous oil(3.3 g, 93%); Rf: 0.38; IR: ν_{max}. 3700-3100, 1620 cm^{-1}; UV: λ_{max}. 318(3.79) 276 (4.16) and 218 (4.26)nm; ^{1}H NMR.(200 MHz) : δ1.24(t, 3H, OCH_2CH_3). 2.48(bs, 1H, OH exchangeable with D_2O), 3.0(m, 2H, Ar-CH_2), 3.72(q, 2H, OCH_2CH_3), 3.80(s, 3H, OCH_3), 3.85-4.02(m, 3H, CH_2-OH, -H), 5.25(s, 2H, OCH_2O), 6.48(dd, 1H, J=2 and 9.6 Hz, H-5'), 6.63(d, 1H, J=2 Hz, H-3'), 6.83 (d, 2H, J=9.6 Hz, H-3,5), 7.12(d, 2H, J=9.6 Hz, H-2,6), 7.63(d, 1H, J=9.6 Hz, H-6'), and 12.72(s, 1H, chelated OH); ^{13}C-NMR : δ 15.08(q, OCH_2CH_3), 34.60(t, CH_2Ar), 49.56(d, β-CH), 55.20(q, OCH_3), 62.70(t, OCH_2CH_3), 64.88(t, α-CH_2), 92.85(t, OCH_2O), 104.04(d, C-3'), 108.54(d, C-5'), 114.08(s, C-1' , d of C-3,5), 129.95(d, C-6'), 130.68(s, C-1), 131.92(d, C-2,6), 158.41(s, C-4), 164.19(s, C-2'), 165.77(s, C-4'), and 207.5(s, CO).

3-(4-Methoxy) benzyl, 7-ethoxymethoxy-4-chromanone (5a)

4a (3.3 g) was refluxed with ethanol (20 ml) and 4% aq. ethanolic Na_2CO_3 (20 ml) for 3 h. Ethanol was distilled off in vacuo and the residue poured on crushed ice. The mixture was neutralised and the solid separated was collected. After chromatography on a small column of silica gel, 5a was obtained as a colourless solid (1.3 g, 41%), mp 96-97°C; R_f 0.50 (Found : C, 69.8; H, 6.6. $C_{20}H_{22}O_5$ requires C, 70.2; H, 6.4%); IR: ν_{max}.1660, 1600 cm^{-1}; UV: λ_{max}.(MeOH) 308(4.98), 270(5.37) and 224(1.34); ^{1}H-NMR (90 MHz): δ 1.25(t, 3H, OCH_2CH_3), 2.56-3.31 (m, 3H, H-3 and CH_2Ar), 3.62-3.90 (q, merged with s, 5H, OCH_2CH_3 ,OCH_3), 4.10-4.32(m, 2H, H-2), 5.26(s, 2H, OCH_2O), 6.51-6.76(m, 2H, H-6,8), 6.83(d, 2H, J=9,5 Hz, H-3',5'), 7.16(d,2H, J=9.5 Hz, H-2',6'), and 7.83(d, 1H, J=9.5 Hz, H-5).

3-(4-Methoxy)-benzyl-7-hydroxy-4-chromanone (6a)

A solution of 5a (1.3 g) in methanol (20 ml) was warmed slowly with 10% methanolic HCl (20 ml) for 10 min. Most of methanol was distilled in vacuo and the residue treated with crushed ice. The solid thus separated was collected, and crystallised from ethyl acetate - petrol mixture when 6a was obtained as a colourless solid (1 g, 94%), m.p. 147-48°, R_f : 0.44 (Found : C, 71.5; H, 5.4. $C_{17}H_{16}O_4$ requires C, 71.7; H, 5.6%); IR: ν_{max}. 3400-2500, 1671 cm^{-1}; UV: λ_{max}. 314(4.13), 275 (4.28), 222(sh) (4.43) and 217nm(4.53); ^{1}H-NMR (90 MHz) : δ 2.70-3.20(m, 3H, CH_2Ar, H-3), 3.87(s, 3H, OCH_3), 4.08-4.37(m, 2H, H-2), 6.36-6.70(m, 2H, H-6,8), 6.90(d, 2H, J=9.5 Hz, H-3',5'), 7.18(d, 2H, J=9.5 Hz, H-2',6'), and 7.85(d, 1H, J=9.5 Hz, H-5).

2',4'-Dihydroxydihydrochalcone (2b)

4'-Benzyloxy-2'-hydroxychalcone (1b, 2.0 g) in ethyl acetate (40 ml) was hydrogenated over 10% palladised charcoal (200 mg). The catalyst was filtered, the filtrate concentrated and residue crystallised from ethyl acetate - petroleum ether to give 2b as colourless needles (1.3 g), mp 83-85°, R_f 0.43; (Found: C, 74.8: H, 5.7. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%); IR: ν_{max}. 1620 cm^{-1} UV: λ_{max}. 284(3.79), 224(3.79), 214 nm (3.92); ^{1}H-NMR: δ 2.76-3.31(m, 4H, CH_2CH_2), 6.43(m, 2H, H-3',5'), 7.14(s, 5H, Ph), and 7.61(d, 1H, J=9.6 Hz, H-5).

4'-Ethoxymethoxy-2'-hydroxy-α-hydroxymethyldihydrochalcone (4b)

A solution of 2',4'-dihydroxydihydrochalcone (2b) (2.42 g, 10 mM) in dry acetone (200 ml) was first stirred with dry K_2CO_3 (6.9 g, 50 mM) and a solution of ethoxymethyl chloride (1.32 ml, 10 mM) in acetone (20 ml) at room temp. and next, again treated with more of ethoxymethyl chloride (1.45 ml, 11mM) in 20 ml of acetone. The mixture was heated initially at 40-50° for 10-15 min and then at 60-70° for 3 h. The product was chromatographed on a small column of silica gel when 4b was obtained as a colourless viscous oil (2.9 g, 92%); Rf: 0.41 ; IR: ν_{max}. 3700-3100, 1620 cm^{-1}; UV: λ_{max}. 316(3.82), 274(4,17), and 216 nm(4.64); ^{1}H-NMR (200 NHz) : δ1.22(t, 3H, OCH_2CH_3),

2.44(bs, 1H, exchangeable with D_2O), 3.0(m, 2H, Ar CH_2), 3.72(q, 2H, OCH_2CH_3), 3.80(m, 3H, CH_2OH, -H), 5.24(s, 2H, OCH_2O), 6.50(dd, 1H, J=2 and 9.6 Hz, H-5'), 6.60(d, 1H, J=2 Hz, H-3'), 7.12 (bs, 5H, C_6H_5), 7.64(d, 1H, J=9.5 Hz, H-6'), and 12.74(s, 1H, chelated OH).

3-Benzyl-7-ethoxymethoxy-4-chromanone (5b)

A solution of 4b (2.9 g) in ethanol (20 ml) and 4% aq. alc. Na_2CO_3 (20 ml) was refluxed for 3 h. The product after work-up and chromatography on silica gel column afforded 5b as colourless solid (1.0 5 g, 38%), mp 143-44°; R_f : 0.49 (Found: C, 72.7; H, 6.1. $C_{19}H_{20}O_4$ requires C, 73.1; H, 6.4%); IR: νmax. 1654, 1585 cm^{-1}; UV: λmax. 316(4.24), 277(4.24), and 215nm(4.54); ^{1}H-NMR (200 MHz): δ 1.22(t, 3H, OCH_2CH_3), 2.64-3.34(m, 3H, CH_2Ar, H-3), 3.70(q, 2H, OCH_2CH_3), 4.04-4.4(m, 2H, H-2), 5.24(s, 2H, OCH_2O), 6.58-6.14(m, 2H, H-6,8), 7.28(m, 5H, C_6H_5), and 7.86(d, J=9.5 Hz, 1H, H-5).

3-Benzyl-7-hydroxy-4-chromanone (6b)

A solution of 5b (1.05 g) in methanol (20 ml) was warmed slowly with 10% methanolic HCl for 12 min. The product crystallised from ethyl acetate - petrol mixture to give 6b as a colourless solid (800 mg, 94%),mp 154-55°; R_f: 0.43 (Found:C,74.4; H,5.9. $C_{16}H_{14}O_3$ requires C, 74.7; H, 5.5%); IR: λmax. 3800-2300, 1640, 1615 cm^{-1}; UV: λmax. 324(4.13), 276(4.11), and 214 nm (4.63). ^{1}H-NMR (90 MHz) : δ 2.72-3.20(m, 3H, ArCH_2, H-3), 4.15-4.32(m, 2H, H-2), 6.45-6.60(m, 2H, H-6,8), 7.24(s, 5H, C_6H_5), and 7.71(d, 1H, J=9.6 Hz, H-5).

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