Synthesis of 3,4-Dihydro-8-hydroxy-6-methoxy-7-methylisocoumarin and (±)-6,8-Dimethoxy-1,7-dimethylisochroman

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(Received 10th January, 1993, revised 27th June, 1993)

Summary: 6,8-Dimethoxy-7-methylisochroman(6) was obtained by boron trifluoride catalysed cyclocodensation of the phenylethanol(5) with diethoxymethane. Chromic acid oxidation of the isochroman (6) gave 6,8-dimethoxy-7-methylisocoumarin (8) which on selective demethylation of the 8-methoxy group, afforded the title dihydroisocoumarin (1) related to the fungal metabolite stellatin (2). Similar, cyclocondensation of phenylethanol (5) with diethoxyethane furnished the title isochroman (7) as the 1-methyl homologoue of isochroman (6).

Introduction

A large number of 3,4-dihydroisocoumarin and isochromans have been isolated from a variety of natural sources [1]. Since, most of the natural dihydroisocoumarins are derived biosynthetically from acetate *via* the acetate-polymalonate pathway, the C-3 carbon substitution and C-6, C-8 oxygenation is nearly always present. The C-7 carbon (or oxidized carb-' on), like the C-4, or C-5 carbon substituents is introduced from C-1 pool, at a later stage, as evidenced by the biosynthetic studies on oospolactone, canescin and ochratoxin A etc. A few dihydroisocoumarins possess a C-7 carbon substituent and these include the plant growth regulating substances sclerotinin A and B, dihydrocitrone, 7-methylmellein, 7-carboxymellein, stellatin and isocoumarins like lunatinin. The title dihydroisocoumarin (1) differs from stellatin [2] (2) in having a 7-methyl instead of the 7-hydroxy methyl group in the latter. Stellatin was isolated from mycelium of *Aspergillus variecolor* (Syn. *A. stellatus*) and its structure was established using fully ^{1}H-coupled ^{13}C-NMR spectrum. Both dihydroisocou marins (1) and (2) are unique in being unsubstituted at C-3 or C-4.

Results and Discussion

The 6,8-dimethyoxy-7-methylisochroman [7], like the (±)-6,8-dihydroxy-3-isopropyl-7-methylisochroman is a possible intermediate towards synthesis of rotiorin nucleus [3]. Rotiorin, is an important member of the sclerotiorin group of fungal metabolites, possessing a unique pyrano-quinone structure (3). The (±)-1,7-methyl-6,8-dimethoxyisochroman (6) was prepared with a view to synthesize the 1-alkyl derivatives of (7), but due to the shortage of arylethanol (5), the higher 1-alkyl homologues could not be prepared. The arylethanol (5) is relatively inaccessible as it is prepared from 2-(3,5-dimethoxy-4-phenyl) ethanoic acid (4) which is itself obtained from a series of low-yielding steps [4].

Thus, a high yield process for 2-(3,5-dimethoxy-4-methylphenyl) ethanol (5) has been needed and was found by the lithium aluminium hydride redu -ction of 2-(3,5-dimethoxy-4-methylphenyl) ethanolic acid (4) *via* the acid chloride. Cyclocondensation of alcohol (5) in nitromethane with diethoxymethane under the catalysis of boron trifluoride etherate, afforded the isochroman (6). The isochro man (7) was obtained [5] by a similar condensation of alcohol (5) with diethoxyethane. The ^{1}H-NMR spectra of the isochromans showed characteristic peaks for the C-1 protons. Thus a 2H singlet (δ 4.5 ppm) and a 1H quartet (δ 4.95 ppm J=6.5 Hz) were observed for the C-1 protons of (6) and (7) respectively. Chromic acid oxidation of isochroman [6] (6) gave the 3,4-dihydro-6,8-dimethoxy-7-methylisocoumarin (8). The IR spectrum showed a strong absorption at 1695 cm^{-1} due to lactonic carbonyl. ^{1}H-NMR showed a 2H, doublet of triplet for the benzylic hydrogens (C-4) at δ 2.93-3.0 and a 2H triplet at δ 4.37 for the C-3 methylene protons. Selective demethylation [7] of the 8-methoxy group of (8) using borontrichloride in dichloromethane at -78°C afforded the title dihydroisocoumarin (1;R=H). The lactonic carbonyl absorption in IR was lowered from 1695 to 1656 cm^{-1} due to strong intramolecular H-bonding with 8-hydroxylic proton. The demethylation was further confirmed by the disappearance of 3H singlet at δ 3.67 for C-8 methoxy and by the preparation of 8-acetoxy derivative (1;R=Ac) using acetic anhydridepyridine method.

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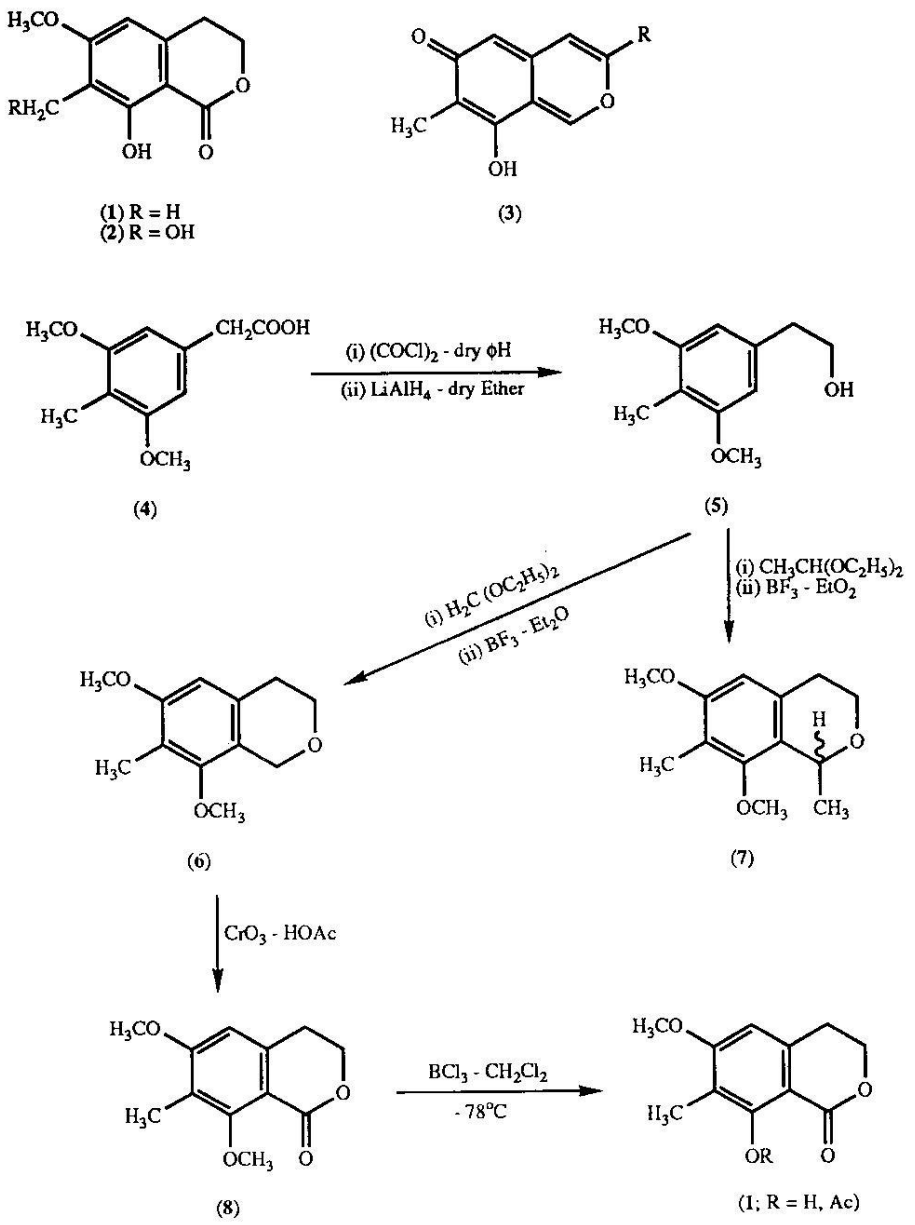

Synthetic Scheme

Experimental

Melting points determined using a MEL-TEMP MP-D apparatus are uncorrected. IR spectra were recorded on a Hitachi Model 270 spectrophotometer as neat liquids or KBr discs. ^{1}H-NMR (300 MHz) recorded on a Bruker AM-300 and the EIMS on MAT 112 S machine.

2-(3,5-Dimethoxy-4-methylphenyl)ethanol (5)

To a stirred suspension of lithium aluminium hydride (0.38 g, 0.01 mol.) in sodium dried ether (30 ml) was added, at such a rate to maintain a gentle reflux, a solution of the (3,5-dimethoxy-4-methyl-phenyl)ethanoyl chloride (2.3 g, 0.01 mol) in dry ether (15 ml). After further reflux for one hour, the

reaction mixture was cooled and ethylacetate (10 ml) was added cautiously. The reaction mixture was poured onto ice, and acidified with aqueous sulphuric acid. The organic phase separated and the aqueous phase extracted with ether (3 x 100 ml). The combined extracts were washed, dried and the solvent evaporated *in vacuo* to leave yellowish oil which was adsorbed on silica. Elution with ether: light petroleum (40-60°) (8:100) gave the 2-(3,5-dimethoxy-4-methyl -phenyl) ethanol (5) (1.66 g, 0.0085 mol, 85%) as colourless oil. ν_{max}: 3400, 2932, 1587, 1182 cm^{-1}; δ ($CDCl_3$): 2.2 (3H, s, CH_2-Ar), 2.48 (1H, s, OH, exchangeable), 2.8 (2H, t, Ar-CH_2, J=6Hz), 3.81 (6H, s, OCH_3 x 2), 4.3 (2H, t, -CH_2OH, J=7.5Hz), 6.35 (1H, s, Ar-*H*); m/z : 196 (M^+).

6,8-Dimethoxy-7-methylisochroman (6)

To a stirred solution of 2-(3,5-dimethoxy-4-methyl phenyl) ethanol (5) (1.96 g, 0.01 mol), diethoxymethane (1.63 g, 0.008 mol) and nitromethane (10 ml) was added dropwise, borontrifluoride etherate (0.27 ml). The mixture was stirred at 22° for 3-4 hours. After the completion of reaction (analytical TLC), the mixture was partitioned between aqueous sodium hydrogen carbonate (5%) and dichloromethane. The organic phase was separated, dried (anhydrous $MgSO_4$), evaporated, and purified by the thick layer chromatography to leave a viscous oil (6) (1.66 g, 0.008 mol, 80%). IR (Neat): 2914, 1590, 1116, 1068 cm^{-1}; δ ($CDCl_3$): 2.19 (3H, s, C_7-CH_3), 2.75 (2H, t, C_4-CH_2, J=5.1 Hz), 3.67 (3H, s, C_6-OCH_3), 3.69 (3H, s, C_8- OCH_3), 4.22 '2H, t, C_3-CH_2 J=6.0 Hz), 4.94 (2H, s, C_1-CH_2), 6.37 (1H, s, C_5-H); m/z 210 (M+2), 209(M+1), 208 (M^+) 177, 166 (base), 151, 119.

(±)-6,8-Dimethoxy-1,7-dimethylisochroman (7)

To a stirred solution of 2-(3,5-dimethoxy-4-methylphenyl) ethanol (5) (1.96 g, 0.01 mol), diethoxyethan (1.04 g, 1.24 ml, 0.01 mol) and nitromethane (20 ml) was added borontrifluoride eherate (0.27 ml). The mixture was stirred at 22° for 3 h. and then partitioned between 5% sodium bicarbonate and dichloromethane. The organic phase was separated, dried and solvent evaporated to leave a yellow oil which on PTLC from ethylacetate-petroleum ether afforded (7) (1.33 g, 0.006 mol, 60%) ν_{max}: 2950, 1594, 1120, 1070 cm^{-1}; δ ($CDCl_3$): 1.21 (3H, d, C_1-CH_3 J=6.5 Hz), 2.21 (3H, s, C_7-CH_3), 2.72 (2H, t, C_4-CH_2 J=5.2Hz), 3.67 (3H, s, C_6OCH_3), 3.69 (3H, s, C_8-OCH_3), 4.23 (2H, t, C_3-CH_2 J=6.0Hz), 4.94 (1H, q, C_1-H J=6.5Hz), 6.37 (1H, s, C_5-H); m/z 222 (M^+), 207 (base), 192, 177.

3,4-Dihydroxy-6,8-dimethoxy-7-methylisocoumarin (8)

To a stirred solution of 6,8-dimethoxy-7-methylisochroman (6) (1.0 g, 0.005 mol) in acetic acid (10 ml) was added dropwise at 30-35° a solution of CrO_3 (1.75 g, 0.0175 mol) in acetic acid (10 ml) and water (3 ml). The mixture was stirred for 2 hrs, warmed on water bath at 60° for 15 minutes. The reaction mixture was cooled, diluted with water and extracted with chloroform (3 x 50 ml). The extracts were dried (Na_2SO_4 anhyd.) evaporated *in vacuo* to leave an oil which was purified by thick layer chromatography to yield the title isocoumarin (8) (0.61 g, 0.003 mol 60%) as colourless oil. ν_{max} 2896, 1695, 1584, 1116, 783 cm^{-1}; δ $CDCl_3$: 2.19 (3H, s, C_7-CH_3), 2.97 (2H, dt, C_4-CH_2 J_1, J_2=7.0 Hz), 3.83 (3H, s, C_6-OCH_3), 3.87 (3H, s, C_8-OCH_3), 4.36-4.40 (2H, t, C_3-CH_2 J=5.5 Hz), 6.45 (1H, s, C_5-H); m/z 222 (M), 207, 192, 162 (base), 134.

3,4-Dihydro-8-hydroxy-6-methoxy-7-methylisocoumarin (1)

1.0 Molar solution of borontrichloride in dichloromethane (0.95 ml, 0.006 mol) was added dropwise to a stirred solution of isocoumarin (8) (0.33 g, 0.0015 mol) at -78° for 4 hours. After stirring overnight the mixture was poured into ice-water, filtered and extracted with dichloromethane (3x20 ml). The combined extracts were washed, dried and concentrated. Purification on PTLC and recrystallization using ethylacetate afforded the isocoumarin (1) (0.25 g, 0.0012 mol, 81%) as colourless crystals m.p. 116-117°C. ν_{max} (KBr): 2902, 1656, 1584, 1131, 798 cm^{-1}; δ ($CDCl_3$): 2.19 (3H, s, C_7-CH_3), 2.97 (2H, dt, C_4- CH_2 J_1, J_2=7.0Hz), 3.83 (3H, s, C_6-OCH_3), 4.36-4.40 (2H, t, C_3- CH_2 J=5.5Hz), 6.45 (1H, s, C_5-H), 11.23 (1H, s, *OH*, exchangeable); m/z 208 (M^+), 193, 162, 134.

3,4-Dihydro-8-Acetoxy-6-methoxy-7-methylisocoumarin (1;H=Ac)

A solution of 3,4-dihydro-8-hydroxy-6-methoxy-7-methylisocoumarin (1) (0.25 g, 0.0012 mol) in dry pyridine (4 ml) and acetic anhydride (0.24 g, 0.0024 mol) was stirred overnight. Water was added

and the reaction mixture extracted with ether (3 x 50 ml), extracts being washing dried and concentrated. Purification of the residue by PTLC followed by recrystallization from ethylacetate furnished the title acetate (1,H-Ac) (0.26 g, 0.001 mol, 90%) m.p. 161-162°; ν_{max} 1735, 1720, 1600, 1595 cm^{-1}.

Acknowledgement

We are thankful for the financial assistance from NSRDB under the project No. PAEC-24.

References

1. (a) R.A. Hill, *Fortschr. Chem. Org. Naturst.*, **49**, 1-78 (1986)
   (b) R.D. Barry, *Chem. Rev.*, **64**, 229 (1964) and references therein.
2. T. J. Simpson, *Chem. Commun.*, 627 (1978).
3. E.Alice, S. M. Macmanus, J.W. Powel, W. B. Whalley, *J. Chem. Research(S)*, **77** (1987).
4. N.H. Rama, E. Turner, W.B. Whalley, *J. Chem. Research(S)*, 149 (1981).
5. J.M. McCall, R.B. McCall, R.E. Tenbrink, B. V. Kamdar, S.J. Humphery, V. H. Sethy, D.W. Harris and C. Daenzer, *J. Med. Chem.*, **25**, 75 (1982).
6. M. Yamato, K. Hashigaki, M. Ikedo, H. Ohtake and K. Tasaka, *Chem. Pharm. Bull.*, **29**(2), 402 (1981).
7. S.M. Afzal, R. Pike, N. H. Rama, E.S. Turner, W. B. Whalley, *J. Chem. Soc.Perkin Trans I.*, 81 (1978).