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Biomimetic Synthesis of Some Novel Coumarin Dimers

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Abstract: 7,7'-dimethoxy-4,4'-dimethyl -3,3'-bicoumarin;7,7'-dimethoxy-4,4'-dimethyl-3,6'-bicoumarin; 7,7',8,8'-tetramethoxy-4,4'-dimethyl-3,3'-bicoumarin and 7,7',8,8'-tetramethoxy-4,4'-dimethyl-3,5'-bicoumarin have been synthesized by the oxidation of 7-methoxy-4-methyl-coumarin and 7,8-dimethoxy-4-methylcoumarin with $Mn(OAc)_3/HClO_4$ respectively.

The coumarins are a large group of naturally occuring oxygen heterocycles. Many natural coumarins have been reported[1] for their wide range of biological activities.[2-4] Bi- and tri-coumarins are comparatively new group which have recently been encountered in nature.[5-10] Most of them are bridged through C-O-C and C-C linkage.

Mn(III) or Fe(III) acetates in the presence of strong acid, such as perchloric acid are the most efficient salts for the formation of biaryls.[11] A coumarin dimer 3,3'-umbelliferone has only been synthesized by the oxidation of umbelliferone with ferric chloride.[12] Therefore, it was planned to synthesize certain other coumarin dimers by the oxidative coupling reactions. On oxidative coupling with $Mn(OAc)_3/HClO_4$, 7-methoxy-4-methyl coumarin(1) gave a mixture of two coumarin dimers namely 7,7'-dimethoxy-4,4'-dimethyl-3,3'-bicoumarin (2, 17%) and 7,7'-dimethoxy-4,4'-dimethyl-3,6'-bicoumarin (3, 11%), the ratio depending markedly on the reactivity of the 3 and 6'-positions. 7,8-Dimethoxy-4-methyl-coumarin(4), on oxidation with the same reagent, gave 7,7',8,8'-tetramethoxy-4,4'-dimethyl-3,3'-bicoumarin (5,16%) and 7,7',8,8'-tetramethoxy-4,4'-dimethyl-3,5'-bicoumarin(6, 12%). The formation of the 3,5'-dimer (6) can only be accounted for, on the basis of steric together with electronic factors. In both cases the expected dicoumaryl methanes were not isolated.

The reaction may proceed by the transfer of one electron from the coumarin molecule to $Mn(OAc)_3$ resulting in the formation of a radical cation. The dimers are formed by electrophilic attack of the cation on another molecule of coumarin.

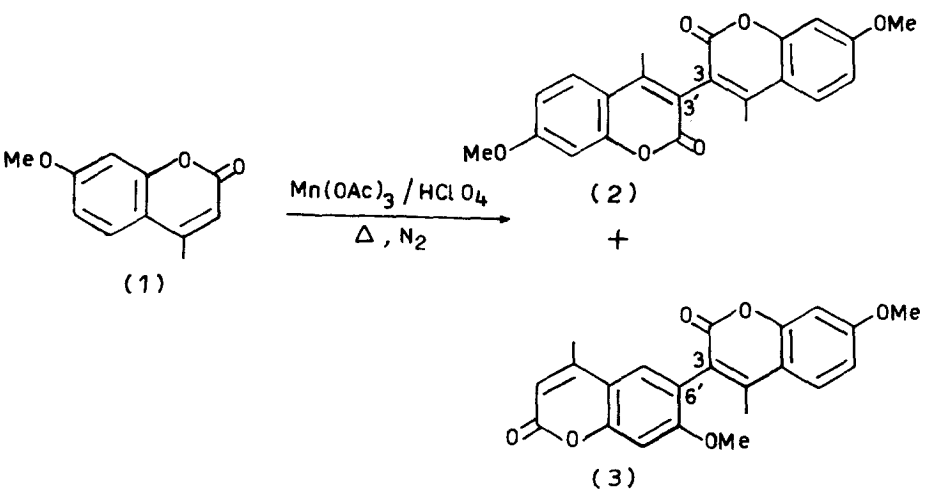
Results and Discussion

7-Methoxy-4-methyl-coumarin (1) was treated with manganese(III) acetate in acetic acid containing perchloric acid under nitrogen. The reaction mixture was refluxed with stirring at 114°C for 3 hrs. After usual work up and elution from silica gel column, a mixture was obtained which was resolved by

preparative t.l.c. into compounds (2) and (3) characterized as 7,7'-dimethoxy-4,4'-dimethyl-3,3'-bicoumarin and 7,7'-di-methoxy-4,4'-dimethyl-3,6'-bicoumarin respectively by analytical and spectral techniques.

The 3,3'-bicoumarin (2), m.p.284-85°C, was unequivocally characterized by its IR, ^{1}H NMR and Mass spectral data. The absence of 3-H and 3'H signals in its ^{1}H NMR spectrum (Table) indicates that linkage is between C-3 and C-3'. In its mass spectrum the molecular ion peak was observed at m/z 378.

In compound (3) mp. 260°C, H-3 was evidenced by one proton singlet at δ 6.19 in its ^{1}H-NMR spectrum (Table). A doublet (J = 2.5 and 9Hz) for one proton centered at δ 6.89-6.90 corresponded to H-6. Two independent singlets at δ 6.93 and 7.41 integrating for one proton each were assigned to H-8' and H-5' respectively. A *meta*-coupled doublet (J = 2.5 Hz) centered at δ 6.91 was attributed to H-8, while an *ortho*-coupled doublet (J=9 Hz) of one proton at δ 7.60 was assigned to H-5. The absence of signals for H-3 and H-6' indicates the linkage between C-3 and C-6'. Its assignment was compared with the starting material (1, Table) in which the H-5 proton appeared at δ 7.55 while in 3-6' dimer (3) it was located at δ 7.41, an unfield shift of 0.14 ppm due to C-3-6' linkage. The mass spectrum showed molecular ion peak at m/z 378.



Treatment of 7,8-dimethoxy-4-methyl coumarin (4) with $Mn(OAc)_3/HClO_4$ by the earlier procedure gave compounds (5, 16%) and (6, 12%) which were identified as 7,7',8,8'-tetramethoxy-4,4'-dimethyl-3,3'-bicoumarin and 7,7',8,8'-tetramethoxy-4,4'-dimethyl-3,5'-bicoumarin respectively by means of their spectral data. The increase in the concentration of manganese(III) acetate and percholoric acid increases the formation of polymeric tar.

The 3,3'-bicoumarin (5) mp 281°C was chracterized by means of its IR, ^{1}H-NMR and mass spectral data. The lack of 3-H and 3'-H signals in its ^{1}H-NMR spectrum (Table) supporting the C-3-3'-linkage. The mass spectrum exhibited the molecular ion at m/z 438.

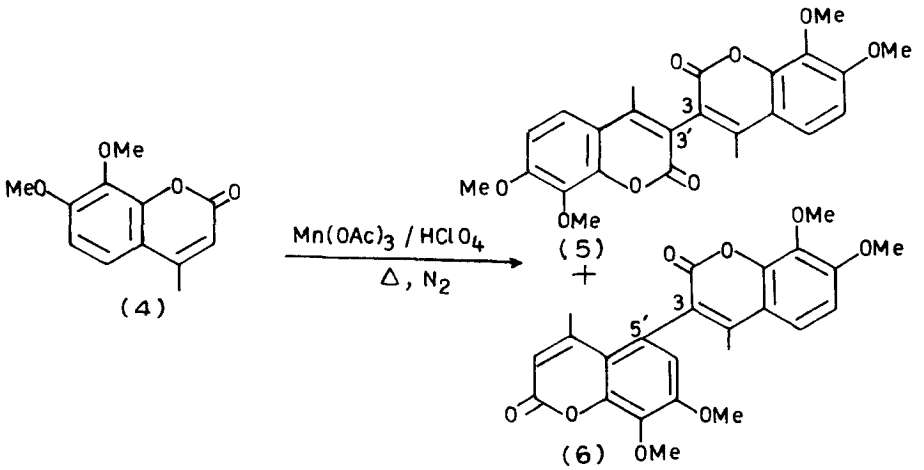
TABLE

^{1}H-MNR assignments of compounds 1-6 (δ-scale)

Protons	Compunds					
	(1)	(2)	(3)	(4)	(5)	(6)
CH_3	2.11 (3H,s)		2.21 (3H,s)	2.56 (3H,s)		2.11 (3H,s)
		2.31 (6H,s)			2.32 (6H,s)	
CH_3	-		2.40 (3H,s)	-		2.17 (3H,s)
OCH_3	3.68 (3H,s)		3.84 (3H,s)			3.91 (3H,s)
		3.91 (6H,s)		4.25 (6H,s)	3.99 (6H,s)	
OCH3	-		3.90 (3H,s)			4.00 (3H,s)
OCH3	-	-	-	-		4.01 (3H,s)
					4.10 (6H,s)	
OCH3	-	-	-	-		4.02 (3H,s)
H-3	6.35 (1H,s)	-	-	6.41 (1H,s)	-	-
H-3'	-	-	6.19 (1H,s)	-	-	6.1 (1H,s)
H-5	7.55 (1H,d,J=9Hz)		7.60 (1H,d,J=9Hz)	7.60 (1H,d,J=9Hz)		7.41 (1H,d,J=9Hz)
		7.61 (2H,d,J=9Hz)			7.39 (2H,d,J=9Hz)	
H-5'	-		7.41 (1H,s)	-		-
H-6	6.86-7.00 (1H,dd,J=2.5&9Hz)		6.89-6.90 (1H,dd,J=2.5&9Hz)	7.20 (1H,d,J=9Hz)		6.99 (1H,d,J=9Hz)
		6.87-6.94 (2H,dd,J=2.5&9Hz)			6.93 (2H,d,J=9Hz)	
H-6'	-		-	-		6.6 (1H,s)
H-8	6.83 (1H,d,J=2.5Hz)		6.91 (1H,d,J=2.5Hz)	-	-	-
		6.86 (2H,d,J=2.5Hz)				
H-8'	-		6.93 (1H,s)	-	-	-

Multiplicity and coupling constant are shown in parentheses recorded in $CDCl_3$.

The ^{1}H-NMR spectrum of 3,5'-bicoumarin (6) mp 236-7°C, showed a pair of *ortho*-coupled doublets (J = 9 Hz) integrating for one proton each at δ 6.99 and δ 7.41 for H-6 and H-5 respectively. A one proton singlet at δ 6.1 was attributed to H-3'. The absence of any signal for H-3 indicated the linkage from C-3 The remaining one proton singlet at δ 6.6 can be accounted for H-5' or H-6'. As observed in 3-6' dimer (3) the C-5' proton suffers an upfield shift of low magnitude (0.14 ppm) as compared with the starting material (1). However, in this case (6) an upfield shift of 1.0 ppm (7.6 - 6.6) was observed. Hence the singlet at δ 6.6 is ascribed to the C-6' proton. The upfield shift of such a high magnitude (7.6-6.6) is dueto the shielding effect of *ortho*-OCH_3 substituent. On the basis of the above facts the compound (6) can be rationalized by considering it to be a case of 3-5' coupling to give the dimer.



This is further substantiated by measuring the benzene induced shift of methoxyl resonance in th ^{1}H NMR spectrum in which only two methoxy groups out of four moved upfield 4.01 - 3.48, 4.02-3.48 on changing the solvent from $CDCl_3$ to C_6D_6 indicating the presence of two *ortho*- protons with respect of both methoxyl groups. This can only be possible when the linkage is from C-5'. It was also confirmed through the N.O.E. difference spectroscopy. Irradiation of the signal at δ 4.02 for methoxyl group resulted in an N.O.E. enhancement of the singlet at δ 6.6. These facts can be accounted by the formation of compound (6) as dimer resulting from the coupling between C-3 and C-5'. It was further supported by a mass spectrum which displayed the molecular ion peak at m/z 438.

Experimental Section

General: The melting points were determined on a Reichert microscope hot stage apparatus and are uncorrected. The IR spectra were recorded on Shimadzu IR-408 and UV on Pye Unicam 8800. The ^{1}H NMR spectra were run on Brucker WM-400 using $CDCl_3$ and C_6D_6 as the solvents and TMS as internal standard. The mass spectrum was obtained by the direct inlet method at 70 eV ionization potential on a JEOL JMS-300 mass spectrometer. Manganese(III) acetate was prepared by the reported method[13].

Reaction of 7-hydroxy-4-methyl coumarin (1) with manganese(III) acetate in acetic acid in the presence of perchloric acid :

A mixture of 7-methoxy-4-methyl-coumarin (1.90 g, 10 mmol) and manganese(III) acetate (0.774 g, 1 mmol) was stirred at room temperature, then 70% perchloric acid (0.8 g, 6 mmol) was added. The reaction mixture was heated under reflux at 114°C with stirring under nitrogen for 3 hrs. The reaction mixture was cooled and diluted with 50 ml of benzene. The benzene solution was washed with water and aq. $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated. The residue was chromatographed over silica gel column. Elution of the column with benzene afforded a mixture of two compounds along with some minor impurities which were separated by preparative thin layer chromatography (Benzene:EtOAc, 9:1) followed by crystallization into compounds (2), (325 mg, 17% yield) and (3) (200 mg, 11%).

7,7'-Dimethoxy-4,4'-dimethyl-3,3'-bicoumarin (2):

Mp 284-5°C (Found: C 69.85; H 4.77; $C_{22}H_{18}O_6$ Req. C 69.84; H 4.76%). ν_{max} 1715 (C=O), 1600 (arom), 1510 (C=C) cm^{-1} λ_{max} 230, 321 nm. $^{\delta}H$ 2.31(6H, s, 2xCH_3), 3.91 (6H, s, 2xOCH_3), 6.86 (2H,d, J=2.5 Hz, H-8,8'), 6.87-6.94 (2H, dd, J=2.5 and 9Hz, H-6,6'), 7.61 (2H, d, J=9Hz, H-5,5'). m/z 378 (46, M^+), 363 (35, M^+- CH_3), 350 (19, M^+-CO), 335 (21, 350-CH_3), 319 (18, 363-CO_2), 307 (15, 335-C_2H_4), 278 (13, 307-CH_2CH_3).

7,7'-Dimethoxy-4,4'-dimethyl-3,6'-bicoumarin (3):

Mp. 260°C (Found C 69.83; H 4.75; Req. C 69.84, H 4.76%) ν_{max} 1720 (C=O), 1605 (arom), 1566 (C=C) cm^{-1}. λ_{max} 225, 318 nm. $^{\delta}H$ 2.21 (3H, s, CH_3), 2.40 (3H, s, CH_3), 3.84 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.19 (3H, s,H-3'), 6.89-6.90 (1H, dd, J=2.5 and 9Hz, H-6), 6.91 (1H, d, J=2.5 Hz , H-8), 6.93 (1H, s, H-8'), 7.41 (1H, s, H-5'), 7.60 (1H, d, J=9Hz, H-5). m/z 378 (100, M^+), 363 (95, M^+-CH_3), 350 (15, M^+-CO),335(15,350-CH_3), 307 (13, 335-C_2H_4), 278 (14, 307-CH_2CH_3).

Reaction of 7,8-dimethoxy-4-methyl coumarin (4) with Manganese(III) acetate in presence of perchloric acid:

7,8-dimethoxy-4-methyl coumarin (4, 2.20 g, 10 mmol) was treated with $Mn(OAc)_3$ in acetic acid containing perchloric acid by the procedure described earlier. The reaction mixture showed two major compounds which were separated by column chromatography followed by preparative thin layer chromatography (Benz:EtOAc 9:1) into compounds (5), (360 mg, 16%) and (6) (260 mg, 12%).

7,7',8,8'-Tetramethoxy-4,4'-dimethyl-3,3'-bicoumarin (5):

Mp. 281°C (Found: C 65.76; H 5.1; $C_{24}H_{22}O_8$, Req. C 65.75, H 5.0%). ν_{max} 1710 (C=O), 1600 (arom), 1560 (C=C) cm^{-1}.λ_{max} 214, 228, 335 nm. $^{\delta}H$ 2.32 (6H, s, 2xCH_3), 3.99 (6H,s,2xOCH_3), 4.10 (6H, s, 2xOCH_3), 6.93 (2H, d, J=9Hz, H-6,6'),7.39 (2H, d, J=9Hz, H-5,5'). m/z 438 (39, M^+), 423 (100, M^+-CH_3), 410 (18, M^+-CO), 395 (16, 410-CH_3), 379 (11, 423-CO_2), 367 (13, 395-C_2H_4), 352 (14, 367-CH_3),

337 (11, 352-CH_3).

7,7',8,8'-Tetramethoxy-4,4'-di-methyl-3,5'-bicoumarin (6):

Mp. 236-7°C (Found: C 65.77, H, 5.1; $C_{24}H_{22}O_8$, Req. C 65.75; H 5.0%) ν_{max} 1715 (C=O), 1610 (arom), 1590 (C=C) cm^{-1}.λ_{max} 227, 328 nm. H 2.11 (3H, s, CH_3), 2.17 (3H, s, CH_3), 4.0 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 6.1 (1H, s, H-3'), 6.6 (1H, s, H-6'), 6.99 (1H, d, J=9Hz, H-6), 7.41 (1H, d, J=9Hz, H-5), m/z 438 (100, M^+), 423 (50, M^+-CH_3), 408 (12, 423-CH_3), 395 (26, 423-CO), 379 (18, 423-CO_2), 367 (16, 395-C_2H_4), 352 (14, 367-CH_3), 337 (21, 352-CH_3).

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