

A study of ethoxymethylation in the 3-position of chroman-4-ones

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Abstract. Ethoxymethylation of 7-hydroxy- (1) and 7-methoxy (6a) -chroman-4-ones with ethoxymethyl chloride in the presence of anhydrous potassium carbonate and acetone results in formation of 3,3-bis-hydroxymethyl derivatives (3 and 7) in very good yields, and not the expected 3-hydroxymethyl derivatives. But 5,7-dimethoxychroman-4-one (6b) does not react with ethoxymethyl chloride under the same conditions.

Keywords. Hydroxy- and methoxy-chromanones; 3-bis-hydroxymethyl chromanones; ethoxymethylation.

1. Introduction

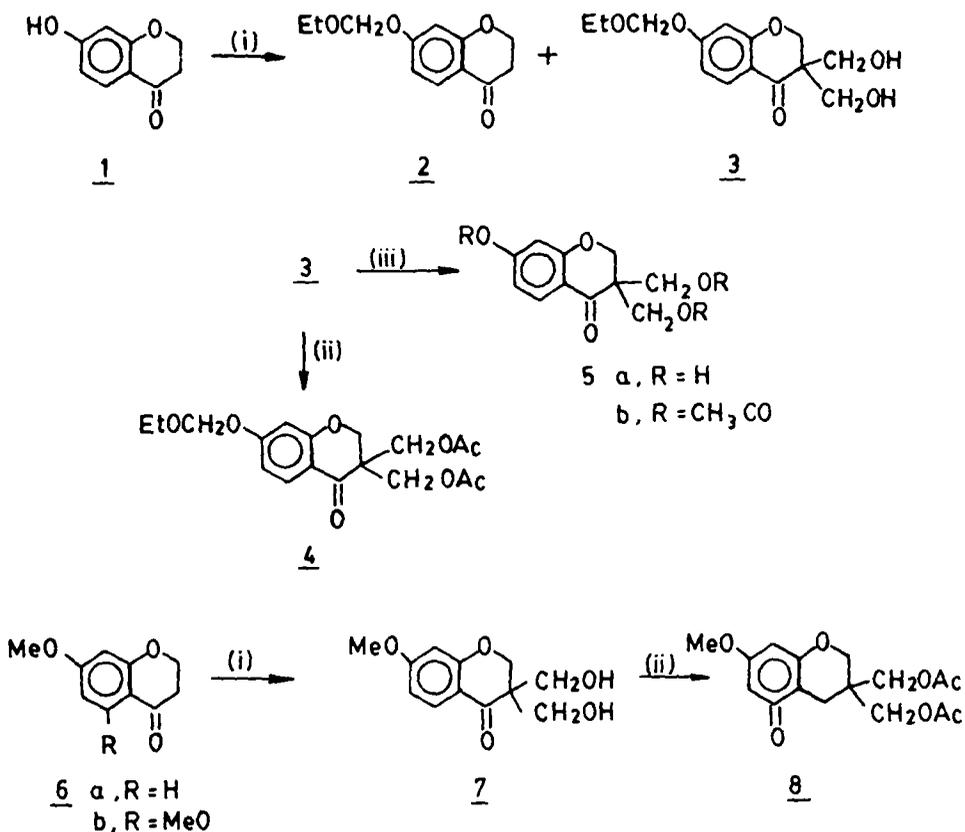
Ethoxymethylation of benzyl- and ethyl-2-hydroxyphenyl ketones with ethoxymethyl chloride in the presence of anhydrous potassium carbonate and dry acetone has been found earlier to result in the formation of α -hydroxymethyl derivatives, which have subsequently been cyclised to isoflavanones (Jain and Sharma 1984) and 3-methylchroman-4-ones (Jain *et al* 1989) respectively. Since chroman-4-ones also possess an active methylene group at the 3-position, similar treatment with ethoxymethyl chloride should result in the formation of 3-hydroxymethyl derivatives. With this objective in mind, the ethoxymethylation of some hydroxy- and methoxy-chroman-4-ones was studied.

2. Results and discussion

2.1 Reaction with 7-hydroxychroman-4-one

7-Hydroxychroman-4-one (1) was first reacted with ethoxymethyl chloride (one molar equivalent) at room temperature in the presence of freshly ignited potassium carbonate and dry acetone. After an hour, one more molar equivalent of ethoxymethyl chloride was added and the stirring continued at room temperature for 15 h. The product was a mixture of two compounds. One was 7-ethoxymethoxy-4-chromanone (2) (35% yield) as shown by its PMR spectrum. Thus, it showed a methyl group as a triplet at δ 1.37, a methylene group as a quartet at δ 3.74, at methylenedioxy group at δ 5.17 and the

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Reagents

(i) EtOCH_2Cl , dry $\text{K}_2\text{CO}_3 + \text{Me}_2\text{CO}$

(ii) Ac_2O , pyridine

(iii) $\text{MeOH} - \text{HCl}$

protons at C-2 and C-3 as two triplets at δ 4.44 and δ 2.83 respectively. The other product was characterised as 7-ethoxymethoxy-3,3-bis-hydroxymethylchroman-4-one (3) (60% yield) on the basis of its spectral data and by conversion into its diacetyl derivative (4). Thus, in its PMR spectrum, 3 showed a methyl group as a triplet at δ 1.25, a methylene group as a quartet at δ 3.71, a methylenedioxy group at δ 5.25, the two protons at C-2 as a singlet at δ 4.40 and two hydroxymethyl groups as a singlet at δ 3.87. The diacetyl derivative (4) showed six aliphatic protons at δ 2.06 due to the two acetoxy groups.

When 7-ethoxymethoxy-3,3-bis-hydroxymethyl chroman-4-one (3) was warmed with 10% methanolic hydrochloric acid, the deprotected compound, 3,3-bis-hydroxymethyl-7-hydroxychroman-4-one (5a) resulted (95% yield), and was characterised by its spectral data and conversion into its triacetyl derivative (5b). Thus, in its PMR spectrum, 5a showed the two hydroxymethyl groups as a singlet at δ 3.08 and the two protons at C-2 as another singlet at δ 4.55. The triacetyl derivative, 3,3-bis-acetoxy-

methyl-7-acetoxychroman-4-one (**5b**) showed the three acetoxyl groups as two singlets at δ 2.04 and δ 2.42.

2.2 Reaction with 7-methoxychroman-4-one

7-Methoxychroman-4-one (**1a**) was next treated with one molar equivalent of ethoxymethyl chloride under the same conditions as above. On stirring at room temperature for eight hours, conversion into a single product occurred. This product was identified as 3,3-bis-hydroxymethyl-7-methoxychroman-4-one (**7**) (82% yield) on the basis of its spectral data and by conversion into its diacetyl derivative (**8**). Thus in its PMR spectrum, **7** showed two hydroxymethyl groups as a singlet at δ 3.48 and the two protons at C-2 as another singlet at δ 4.43. The diacetyl derivative, 3,3-bis-acetoxymethyl-7-methoxychroman-4-one (**8**) showed two acetoxyl groups as a singlet at δ 2.11.

2.3 Reaction with 5,7-dimethoxychroman-4-one

Finally, 5,7-dimethoxychroman-4-one (**6b**) was treated with one molar equivalent of ethoxymethyl chloride in the presence of anhydrous potassium carbonate and dry acetone at room temperature. It was observed that no change in reaction occurred even after a fortnight. The reaction mixture was therefore refluxed at 60° for another week and when still no change occurred, one more molar equivalent of ethoxymethyl chloride was added. 5,7-Dimethoxychroman-4-one (**6b**), however, failed to react.

3. Experimental

All melting points are uncorrected. This light petroleum used had a boiling range 60–80°. R_f values refer to TLC; the solvent systems used for TLC are indicated in table 1. The following spectrometers were used for spectral measurements; UV Shimadzu 260; IR Shimadzu 435; $^1\text{H-NMR}$ 90 MHz Perkin-Elmer R-32; UV data were recorded in methanol; IR values were recorded using KBr disc or nujol thin film. NMR data were recorded in CDCl_3 using TMS as internal standard. Silica gel-G was used for TLC and silica gel for column chromatography.

3.1 Reaction of 7-hydroxychroman-4-one (**1**) with ethoxymethyl chloride

To a solution of 7-hydroxychroman-4-one (Naylor *et al* 1958) (**1**, 4.92 g; 30 mmol) in dry acetone (100 ml), anhydrous potassium carbonate (20.85 g, 150 mmol) followed by ethoxymethyl chloride (4.36 ml, 33 mmol) was added and the resulting mixture stirred at room temperature for 15 h and then filtered. The filtrate was concentrated at room temperature and the residue subjected to purification by column chromatography. Successive elution with ethyl acetate-petroleum ether (1:19) and ethyl acetate-petroleum ether (1:9) afforded two fractions (A and B).

Fraction A: 7-Ethoxymethoxychroman-4-one (**2**) was obtained as a colourless oil (2.33 g, 35% yield).

Table 1. Physical and spectral data of the compounds.

Compound	m.p. (°C)	R_f (solvent) ^a	IR absorption peaks of characteristic groups (cm ⁻¹)	UV absorption maxima (nm) (log)	Analysis %				Molecular formula
					Found	Calculated	C	H	
2	Colourless oil	0.62(A)	1675, 1600 and 1565	211, 223(sh), 266 and 306	—	—	—	—	C ₁₂ H ₁₄ O ₄
3	Colourless oil	0.54(B)	3380, 1660 and 1600	209, 223(sh), 266 and 309	—	—	—	—	C ₁₄ H ₁₈ O ₆
4	Pale yellow oil	0.61(A)	1740, 1675 and 1608	208, 224(sh), 266 and 305	—	—	—	—	C ₁₈ H ₂₂ O ₈
5a	133°	0.48(C)	3200, 1650 and 1602	208(4.44), 229 sh (4.09), 268(4.25) and 305(3.99)	58.8	5.5	58.9	5.4	C ₁₁ H ₁₂ O ₅
5b	Colourless oil	0.58(A)	1737, 1680 and 1605	200 sh, 208, 256, 312	—	—	—	—	C ₁₇ H ₁₈ O ₇
7	125–26° ^b	0.49(B)	3250, 1660, 1600	206(4.34), 226(sh) (4.05), 269(4.13) and 307(4.13)	60.4	6.0	60.5	5.9	C ₁₂ H ₁₄ O ₅
8	Colourless oil	0.58(A)	1740, 1680, 1605 and 1575	208, 224, 268 and 308	—	—	—	—	C ₁₆ H ₁₈ O ₇

^aA, benzene – ethyl acetate (9:1); B, benzene – ethyl acetate (3:1); C, benzene – ethyl acetate (1:1); ^bagrees with that of Hofmann *et al* 1970.

Fraction B: It gave 7-ethoxymethoxy-3,3-bis-hydroxymethyl chroman-4-one (**3**) as a colourless oil (5.1 g, 60% yield).

3.2 3,3-Bis-acetoxymethyl-7-ethoxymethoxychroman-4-one (**4**)

7-Ethoxymethoxy-3,3-bis-hydroxymethylchroman-4-one (**3**) (1.0 g) was dissolved in acetic anhydride (10 ml), a drop of pyridine added and the solution allowed to stand at room temperature. After 1 h, TLC showed conversion into two new products suspected to be the mono- and di-acetyl derivatives of **3**. The reaction mixture was allowed to stand overnight and then poured over crushed ice. It was extracted with ether, the ether extract dried over anhydrous sodium sulphate and evaporated to dryness. Purification by preparative TLC yielded 3,3-bis-acetoxymethyl-7-ethoxymethoxychroman-4-one (**4**) as a pale yellow oil. The NMR data of the compounds are given in table 2.

3.3 3,3-Bis-hydroxymethyl-7-hydroxychroman-4-one (**5a**)

A solution of 7-ethoxymethoxy-3,3-bis-hydroxymethylchroman-4-one (**3**) (4.1 g) in methanol (20 ml) was warmed slowly with 10% methanolic hydrochloric acid (20 ml) for 10 minutes. The solution was concentrated to half the bulk, treated with an equal amount of cold water and extracted with ether (50 ml). The ether extract was dried over anhydrous sodium sulphate and evaporated to dryness. The residue obtained was crystallised from acetone-petroleum ether to afford 3,3-bis-hydroxymethyl-7-hydroxychroman-4-one (**5a**) as colourless, shiny plates (3.1 g, 95% yield).

3.4 3,3-Bis-acetoxymethyl-7-acetoxychroman-4-one (**5b**)

3,3-Bis-hydroxymethyl-7-hydroxychroman-4-one (**5a**) was dissolved in acetic anhydride (10 ml), a drop of pyridine added and the solution allowed to stand at room temperature. After 1 h, TLC showed conversion into three new products, suspected to be the mono-, di- and triacetyl derivatives of **5**. The reaction mixture was allowed to stand overnight and was then poured over crushed ice. It was extracted with ether, the ether extract dried over anhydrous sodium sulphate and evaporated to dryness. Purification by preparative TLC afforded 3,3-bis-acetoxymethyl-7-acetoxychroman-4-one (**5b**) as a colourless oil (1.53 g).

3.5 Reaction of 7-methoxychroman-4-one (**6a**) with ethoxymethyl chloride

To a solution of 7-methoxychroman-4-one (**6a**) (Loudon and Razdan 1954) (3.56 g, 20 mmol) in dry acetone (100 ml), freshly ignited potassium carbonate (13.9 g, 100 mmol) was added followed by ethoxymethyl chloride (2.90 ml, 22 mmol) and the reaction mixture stirred at room temperature for 8 h. It was then filtered, the filtrate concentrated at room temperature and the residue purified by column chromatography. Elution with ethyl acetate-petroleum ether (1:9) afforded 3,3-bis-hydroxymethyl-7-methoxychroman-4-one (**7**) which crystallised from acetone-petroleum ether as colourless needles (3.90 g, 82%).

Table 2. ¹H NMR data of the compounds.

Compound	2-H ₁	3-H ₂	5-H	6-H	8-H	OCH ₂ -O	CH ₃ -CH ₂	O-CH ₂ -CH ₃	3-(CH ₂ OH) ₂	3-(CH ₂ OAc) ₂	OCH ₃	OCOCH ₃
2	4.44 <i>t</i> <i>J</i> = 8.5	2.83 <i>t</i> <i>J</i> = 8.5	7.75 <i>d</i> <i>J</i> = 9.5	6.57 <i>dd</i> <i>J</i> = 9.5	6.49 <i>d</i> <i>J</i> = 2.25	5.17	1.37 <i>t</i> <i>J</i> = 8	3.74 <i>q</i> <i>J</i> = 8	—	—	—	—
3	4.40	—	7.77 <i>d</i> <i>J</i> = 9.5	6.99 <i>dd</i> <i>J</i> = 2.5, 9.5	6.64 <i>d</i> <i>J</i> = 2.5	5.23	1.25 <i>t</i> <i>J</i> = 8	3.71 <i>q</i> <i>J</i> = 8	3.87	—	—	—
4	4.64	—	7.96 <i>d</i> <i>J</i> = 9.5	6.81 <i>dd</i> <i>J</i> = 2.5, 9.5	6.73 <i>d</i> <i>J</i> = 2.5	5.33	1.24 <i>t</i> <i>J</i> = 8	3.86 <i>q</i> <i>J</i> = 8	—	4.42	—	2.06 (6H)
5a	4.55	—	7.80 <i>d</i> <i>J</i> = 9.5	6.59 <i>dd</i> <i>J</i> = 2.5, 9.5	6.42 <i>d</i> <i>J</i> = 2.5	—	—	—	3.08	—	—	—
5b	4.54	—	8.04 <i>d</i> <i>J</i> = 9.5	6.96 <i>dd</i> <i>J</i> = 2.5, 9.5	6.89 <i>d</i> <i>J</i> = 2.5	—	—	—	—	4.41	—	2.04, (6H) 2.42 (3H)
7	4.43	—	7.54 <i>d</i> <i>J</i> = 9.5	6.34 <i>dd</i> <i>J</i> = 9.5, 2.5	6.22 <i>d</i> <i>J</i> = 2.5	—	—	—	3.48	—	4.20	—
8	4.60	—	8.12 <i>d</i> <i>J</i> = 9.5	6.85 <i>dd</i> <i>J</i> = 9.5, 2.5	6.65 <i>d</i> <i>J</i> = 2.5	—	—	—	—	4.50	3.97	2.11

3.6 *3,3-Bis-acetoxymethyl-7-methoxychroman-4-one* (8)

3,3-Bis-hydroxymethyl-7-methoxychroman-4-one (7) (1.0 g) was dissolved in acetic anhydride (10 ml), a drop of pyridine added and the solution allowed to stand at room temperature overnight and then poured over crushed ice. It was then extracted with ether, the ether extract dried over anhydrous sodium sulphate and evaporated to dryness. Purification by preparative TLC afforded *3,3-bis-acetoxymethyl-7-methoxychroman-4-one* (8) as a colourless oil (1.33 g).

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