

1-(3,4-Dimethoxybenzylidene)-6,7-dimethoxyisochroman-3-one
with Lithium Aluminium Hydride: Formation of
1-(3,4-Dimethoxybenzylidene)-6,7-dimethoxyisochroman

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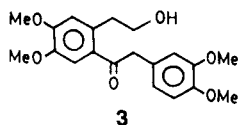
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Evidence is presented to indicate that the reductive reaction of the isochromanone derivative **1** by means of lithium aluminium hydride (LAH), yielded the isochroman **2** together with small amounts of naphthalene derivatives. All new compounds have been identified from spectroscopic and analytical data.

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As part of a program of research directed towards the preparation of benzo[*c*]phenanthridine derivatives [1], we were interested in a ready access to deoxybenzoin type compounds such as **3**, which after convenient hydroxylic protection, should be used as synthons of the already mentioned alkaloids *via* 3-arylisoquinoline formation [2] and final cyclization reaction to yield the corresponding tetracyclic derivatives.

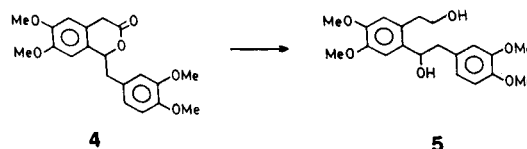
As starting material 1-(3,4-dimethoxybenzylidene)-6,7-dimethoxyisochroman-3-one (**1**) was selected [3]. This compound, under adequate reduction conditions, should afford the corresponding diol derivative, in tautomeric equilibrium with the desired aryl benzyl ketone **3**. Faced with



the problem of choosing a convenient reducing agent, the two complex hydrides (LAH and sodium borohydride) appeared to provide a simple and convenient route for the reduction of an organic functional group such as COOR [4]. However, it should be pointed out that in spite of its great convenience, the latter reagent suffers from certain limitations. For example, since its original discovery [5] it was generally accepted that sodium borohydride was a remarkably mild reducing agent, useful for the selective reduction of aldehyde and ketone groups [6]. Later, the reduction of esters by saline borohydrides was achieved in various solvents permitting the rapid reduction of the ester group in the presence of many substituents [7]. However, olefinic esters cannot be selectively reduced by borohydride without involvement of the double bond [8].

The above discussions prompted us to select LAH as the reducing agent for the conversion of the isochroman-3-one (**1**) to the desired deoxybenzoin **3**. Moreover, earlier inves-

tigations carried out by our research group showed that selective reduction of 1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (**4**), was converted into 2-[2-(3,4-dimethoxybenzylhydroxymethyl)-3,4-dimethoxyphenyl]ethanol (**5**), when treated with LAH under classical reduction conditions [9].



Application of the already mentioned procedure to the isochromanone **1** afforded the isochroman **2** as the major product, together with the aryl naphthalene derivatives **6** and **7** as side products. See Scheme.

Formation of the isochroman **2** could be rationalized by assuming that the formation of deoxybenzoin **3** has taken

Table 1
Synthetic Data for the Compounds Obtained

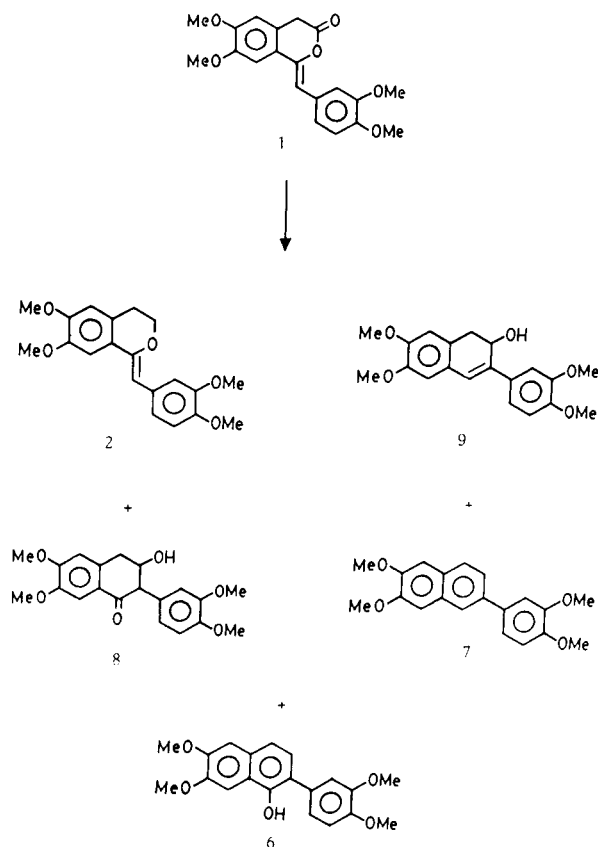
Product No.	Mp (°C) [a]	R _f [b]	Yield %	Formula	Calcd.(Found)	
					C	H (%)
2	173-175	0.24	60	C ₂₀ H ₂₄ O ₅	69.76 (69.73)	6.97 (7.00)
6	159-161	0.15	10	C ₂₀ H ₂₀ O ₅	70.58 (70.59)	5.88 (5.90)
7	168-170	0.30	19	C ₂₀ H ₂₀ O ₄	74.07 (74.06)	6.17 (6.19)
8	174-177	0.18	3	C ₂₀ H ₂₂ O ₆	67.03 (67.02)	6.14 (6.11)
9	186-189	0.33	7	C ₂₀ H ₂₂ O ₅	70.17 (70.20)	6.43 (6.40)

[a] Products **2**, **6** and **7** were recrystallized from ethanol, **8** and **9** from chloroform/hexane 9:1. [b] Eluent: dichloromethane/methanol 9.5:0.5.

place followed by intramolecular cyclization reaction leading to the corresponding hemiketal derivative, which after dehydration afforded the 1-(3,4-dimethoxybenzylidene)-6,7-dimethoxyisochroman (**2**). Considerable precedent for this behaviour exists for similar compounds [10].

Isolation of the aryl-naphthalene derivatives **6** and **7**, could be explained on the basis of a fragmentation reaction of the lactone ring, followed by subsequent cyclization through attack to the benzylic carbon atom, being the formation of a highly conjugated π -system, the driving force for the reaction.

Scheme



To support the above proposal, the tetrahydro compound **8** was also isolated (9%) from the reaction products. This compound, when submitted to an acetylation reaction, afforded quantitatively an acetyl derivative similar in all respects to the one obtained by direct acetylation of the naphthol derivative **6**.

Similarly, formation of 2-(3,4-dimethoxyphenyl)-6,7-dimethoxynaphthalene (**7**) (19%) could be explained through a classical dehydration reaction of alcohol **9**, also identified as a minor reaction product (7%).

Finally, from our results we may propose that even though the desired deoxybenzoin **3** was not isolated by the

Table 2

Spectral Data for the Compounds Obtained

Product	IR	PMR [a]	MS m/z (%)
2	1630 1335	2.89 (t, J = 5.5, 2H, H-4), 3.89 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.95 (s, 3H, OMe), 4.27 (t, J = 5.5, 2H, H-3), 5.92 (s, 1H, =CH-Ar), 6.62 (s, 1H, H-5), 6.85 (d, J = 8.2, 1H, H-5'), 7.12 (s, 1H, H-8), 7.27 (dd, J = 8.2, J = 2.2, 1H, H-6'), 7.42 (d, J = 2.2, 1H, H-2')	342 (100, M ⁺), 327 (83), 192 (2)
6	3450	3.91 (s, 3H, OMe), 3.94 (s, 3H, OMe), 4.01 (s, 3H, OMe), 4.03 (s, 3H, OMe), 5.87 (s, 1H, OH), 7.00 (d, J = 8.3, 1H, H-5'), 7.01 (d, J = 1.8, 1H, H-2'), 7.07 (dd, J = 8.3, J = 1.8, 1H, H-6'), 7.11 (s, 1H, H-5), 7.21 (d, J = 8.4, 1H, H-3), 7.33 (d, J = 8.4, 1H, H-4), 7.54 (s, 1H, H-8)	340 (100, M ⁺), 325 (9), 297 (6), 203 (2), 170 (10)
7		3.93-4.01 (4s, 12H, OMe), 6.97 (d, J = 8.0, 1H, H-5'), 7.13 (s, 1H, H-5), 7.17 (s, 1H, H-8), 7.21 (d, J = 2.0, 1H, H-2'), 7.24 (dd, J = 8.0, J = 2.0, 1H, H-6'), 7.57 (dd, J = 8.5, J = 1.8, 1H, H-3), 7.74 (d, J = 8.5, 1H, H-4), 7.85 (d, J = 1.8, 1H, H-1)	324 (100, M ⁺), 309 (99), 281 (49), 266 (69), 162 (89)
8	3490 1660	3.10 (dd, J = 3.8, J = 16.5, 1H, H-4a), 3.29 (dd, J = 2.5, J = 16.5, 1H, H-4b), 3.84 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.94 (s, 3H, OMe), 3.97 (s, 3H, OMe), 3.92 (d, J = 7.9, 1H, H-2), 4.03 (m, 1H, H-3), 4.49 (broad s, 1H, OH), 6.74 (s, 1H, H-5), 6.76 (dd, J = 8.1, J = 1.9, 1H, H-6'), 6.79 (d, J = 1.9, 1H, H-2'), 6.86 (d, J = 8.1, 1H, H-5'), 7.61 (s, 1H, H-8)	358 (3, M ⁺), 340 (100), 341 (20), 325 (10), 207 (25)
9	3460	2.72 (dd, J = 4.8, J = 17.0, 1H, H-4a), 3.01 (dd, J = 2.3, J = 8.0, 1H, OH), 3.10 (dd, J = 4.0, J = 17.0, 1H, H-4b), 3.77 (s, 3H, OMe), 3.81 (s, 6H, 2 × OMe), 3.83 (s, 3H, OMe), 4.30 (d, J = 2.7, 1H, H-3), 5.14 (dd, J = 5.2, J = 8.0, 1H, H-1), 6.55 (s, 1H, H-5), 6.79 (d, J = 8.2, 1H, H-5'), 6.83 (dd, J = 8.2, J = 1.8, 1H, H-6'), 6.85 (d, J = 1.7, 1H, H-2'), 7.04 (s, 1H, H-8)	

[a] J (Hz); s, singlet; d, doublet; dd, doublet of doublets; m, multiplet.

described reduction procedure, nevertheless, it allows the preparation of a isochroman derivative **2** in good yield. Thus, we have achieved a preparative route of this type of heterocycles, the isochromanes, which as it is well known have showed to be useful as antidepressants, analgesics,

diuretics, inflammation inhibitors, muscle relaxants and hipotensives [11].

EXPERIMENTAL

Melting points were determined on either Electrothermal 1A 6304 or Büchi apparatus and are uncorrected. All reactions were monitored by thin-layer chromatography (tlc) carried out on 0.2 mm silica gel 60 GF-254 (Merck) plates using uv light (λ 254 nm) as the developing agent. The flash column chromatography [12] was conducted on Merck Kieselgel 60 (0.040-0.063 mm, 230-400 mesh). Infrared spectra were recorded in potassium bromide on a Perkin-Elmer 1430 spectrophotometer and only noteworthy absorptions (cm^{-1}) are reported. Pmr spectra were measured at 250 MHz on a Bruker WM-250 spectrometer at ambient temperature. Chemical shifts are reported in parts per million (ppm) downfield (δ) from internal tetramethylsilane; the solvent was deuteriochloroform. Routine mass spectra were outlined using a Hewlett-Packard HP-5970 instrument. Combustion analyses were performed with a Perkin-Elmer model 240 B.

Reduction of 1-(3,4-dimethoxybenzylidene)-6,7-dimethoxyisochroman-3-one (**1**).

To a magnetically stirred suspension of lithium aluminium hydride (0.15 g, 4 mmoles) in dry ether (20 ml), a solution of isochromanone **1** (1.4 g, 4 mmoles) in dry ether-dichloromethane (100 ml, 8:2 ratio) was added dropwise. The whole was gently refluxed with stirring for 2 hours and then cooled to room temperature. The excess of the reagent was decomposed by the dropwise addition of cold water with vigorous stirring. The reaction mixture was then poured gradually into excess of ice-cold dilute sulphuric acid (10%). The organic phase was separated and the aqueous one was extracted with dichloromethane. The combined organic extracts were washed with 0.1 M sodium hydroxide, then with water, dried (sodium sulfate), and solvent evaporated under vacuum. The crude product was flash column chromatographed, eluting with dichloromethane/ethyl acetate 9:1, to afford the following compounds: 1-(3,4-dimethoxybenzylidene)-6,7-dimethoxyisochroman (**2**), 2-(3,4-dimethoxyphenyl)-6,7-dimethoxy-naphthol (**6**), 2-(3,4-dimethoxyphenyl)-6,7-dimethoxynaphthalene (**7**),

3-hydroxy-2-(3,4-dimethoxyphenyl)-6,7-dimethoxytetralone (**8**), 3-hydroxy-2-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydronaphthalene (**9**). Synthetic and spectral data of these products are given in Tables 1 and 2.

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