SYNTHESIS OF (±)-6,8-DIMETHOXY-3-PENTADECYLISOCHROMAN, ITS 1-HYDROXY DERIVATIVE AND (±)-3,4-DIHYDRO-6,8-DIMETHOXY-3-PENTADECYLISOCOUMARIN RELATED TO PENIOLACTOL

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الخلاصة :

استخدمت الطريقة المباشرة ذات المردود الوفير لتحضير ٦ر٨ دايميثلوكسي - ٣ - بنتاديسل - أيزوكرمان (٥) و ٦ر٨ - دايميثلوكسي - ٣ - بنتاديسل - هيدروكسي أزوكومارين (٦) وكذلك ٣ر٤ - دايهيدرو - ٦ر٨ - دايميثوكسي - ٣ - بنتاديسل أيزوكومارين (٧) وهذه لها علامة بمادة بنيولاكتول (المخبرية) الناتجة عن أيض الفطريات . وبما أن التكيف الدوري لـ ١ - (٣ر٥ - دايميثوكسيفينيل) هيبتاديكان - ٢ - أو إلـ - (٢ر٢=R) ينتج باي أيزوكرمان (٨) فقد تم تحويل الكحول إلى فورميل أسيتيت (٣) . وإختزال المركب (٣) يُنتج هيدروكسيميثيل أستيت (٤) والذي ينتج بالتَحَلْمُؤ (التحليل المأئي) أيزوكرومان (٥) . كما أن تحلمؤ فورميل أستيت (٣) المباشر أنتج ١ - هيدروكسي أيزوكرومان والذي بدوره تأكد لينتج داي هيدرو أيزوكومارين (٧) .

ABSTRACT

Straightforward high yield syntheses of the 6,8-dimethoxy-3-pentadecyl-isochroman (**5**), 6,8-dimethoxy-3-pentadecyl-1-hydroxyisochroman (**6b**) and hence of 3,4-dihydro-6,8-dimethoxy-3-pentadecylisocoumarin (**7**), related to the fungal metabolite peniolactol (**1ab**) are reported. Since direct cyclocondensation of 1-(3,5-dimethoxyphenyl)heptadecan-2-ol (**2**,R=H) invariably afforded the bis-isochroman (**8**), the alcohol was converted to the formyl acetate (**3**). Reduction of compound (**3**) afforded the hydroxymethyl acetate (**4**) which on hydrolysis gave isochroman (**5**). Direct hydrolysis of formyl acetate (3) afforded the 1-hydroxyisochroman (**6b**) which was readily oxidized to the dihydroisocoumarin (**7**).

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SYNTHESIS OF (±)-6,8-DIMETHOXY-3-PENTADECYLISOCHROMAN, ITS 1-HYDROXY DERIVATIVE AND (±)-3,4-DIHYDRO-6,8-DIMETHOXY-3-PENTADECYLISOCOUMARIN RELATED TO PENIOLACTOL

1. INTRODUCTION

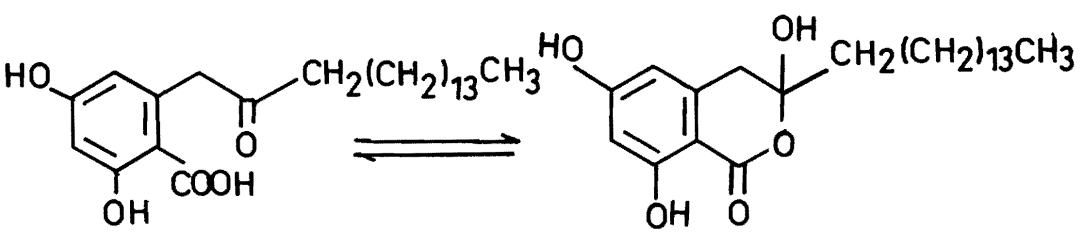
Peniolactol [1] is a fungal metabolite, isolated from decaying wood attacked by the fungus *Peniophora sanguinea*. It can exist in two tautomeric forms *viz.*, the keto acid form, 2,4-dihydroxy-6-(2-oxoheptadecyl)benzoic acid (**1a**) and the lactol form (3,4-dihydro-3,6,8-trihydroxy-3-pentadecylisocoumarin) (**1b**). Spectroscopic and X-ray crystallographic evidence [2] indicates that it is present in the lactol form both in organic solvents and in the crystalline state (Figure 1).

We have carried out previously [3] the total synthesis of peniolactol; in this article we wish to report the syntheses of (±)-6,8-dimethoxy-3-pentadecylisochroman (**5**) and 6,8-dimethoxy-1-hydroxy-3-pentadecyl-isochroman (**6b**) and the conversion of the latter to (±)-6,8-dimethoxy-3-pentadecyl-3,4-dihydroisocoumarin (**7**), related to the peniolactol.

2. SYNTHESIS OF COMPOUNDS

The (±)-1-(3,5-dimethoxyphenyl)heptadecan-2-ol (**2**, R=H) was obtained by sodium boron hydride reduction of 1-(3,5-dimethoxyphenyl)heptadecan-2-one prepared by anhydrous iron(III) chloride catalyzed coupling [4] of 3,5-dimethoxyphenylacetyl chloride with pentadecylmagnesium bromide. The attempts to synthesize the (±)-6,8-dimethoxy-3-pentadecylisochroman (**5**) by the cyclization of alcohol (**2**, R=H) using standard procedures, *i.e.* the reaction of alcohol (**2**, R=H) with either formalin–hydrochloric acid or boron trifluoride catalyzed [5] treatment with diethoxymethane in nitromethane as solvent, resulted in the synthesis of the corresponding bis-isochroman (**8**) [6]. It was therefore decided to synthesize the simple isochroman (**5**) by a modified route. The acetylation of alcohol (**2**, R=H) gave the acetate (**2**, R=Ac) which underwent Vilsmeier Haack formylation to afford the formyl acetate (**3**). Reduction of (**3**) with sodium borohydride in ethanol afforded the hydroxymethyl acetate (**4**) which on alkaline hydrolysis directly furnished the (±)-6,8-dimethoxy-3-pentadecylisochroman (**5**) probably *via* the unstable diol [7], 2,4-dimethoxy-6-(2-hydroxyheptadecyl)benzyl alcohol (**5a**), which could not be isolated. (Scheme 1).

Direct hydrolytic removal of the acetate group in (**3**) provided an alcohol. This compound is probably present in solution as 2,4-dimethoxy-6-(2-hydroxyheptadecyl)benzaldehyde (**6a**), since the IR spectrum run as a thin film shows the carbonyl absorption at 1662 cm, whereas in the crystalline state it is present mainly as the cyclic



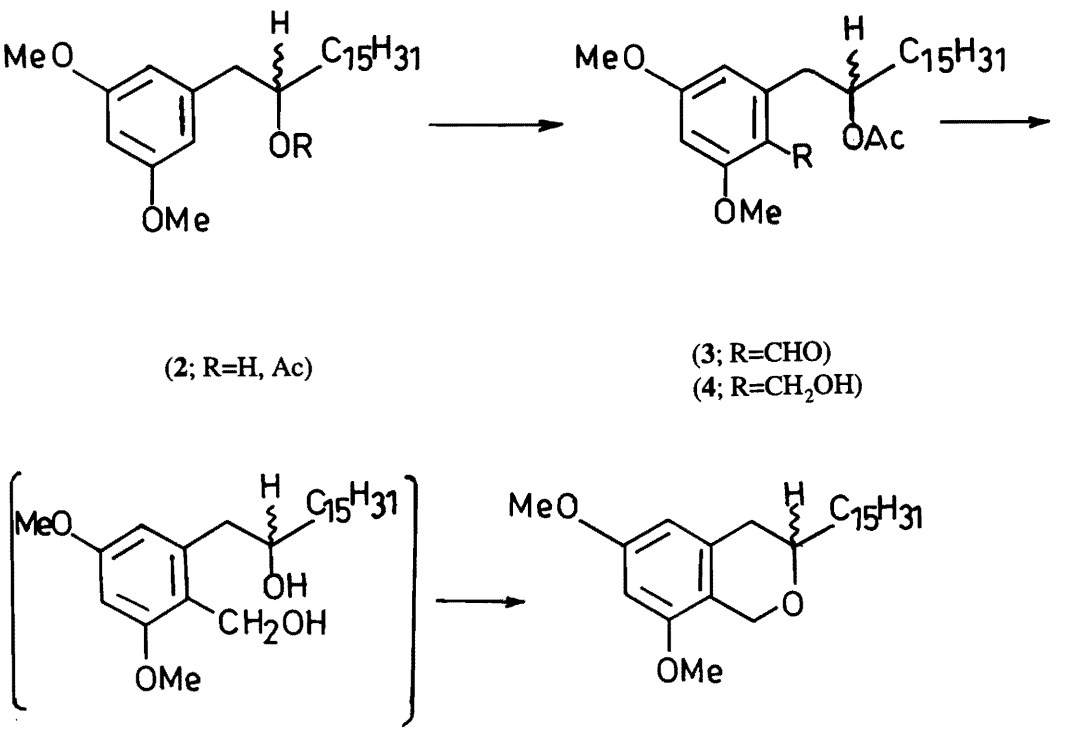
(**1a**) (**1b**)

Figure 1.

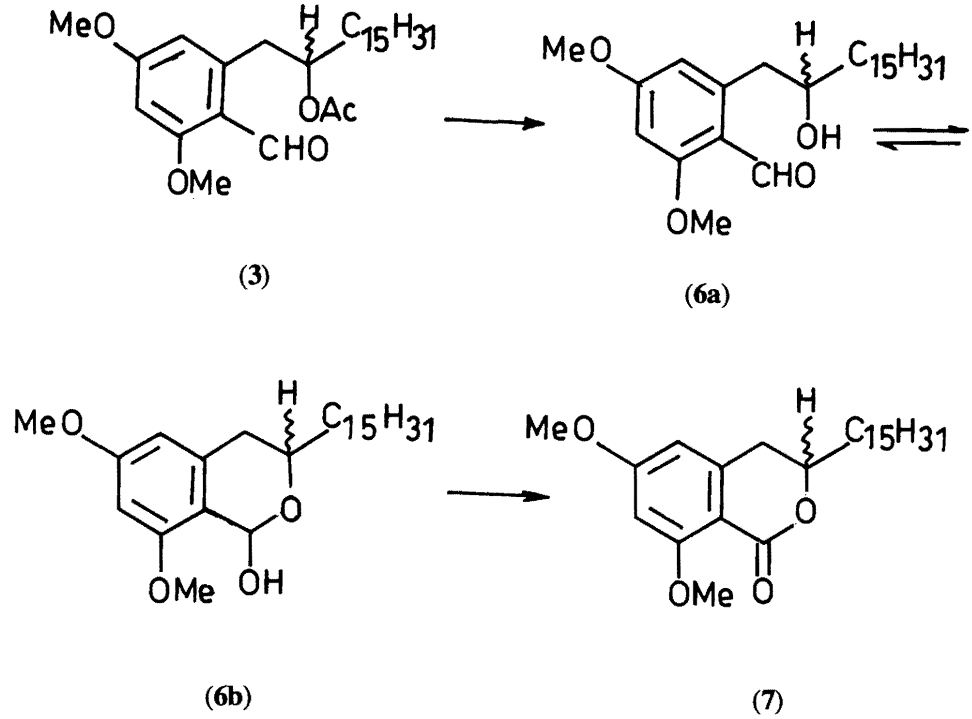
tautomeric hemiacetal 6,8-dimethoxy-1-hydroxy-3-pentadecylisochroman (**6b**) [8] because the IR spectrum taken as KBr pellets shows the absence of carbonyl absorption and a presence of weak broad band at 3242 cm for hydroxyl function. The ^{1}H-NMR spectrum showed a signal for C_1–H in tautomer (**6b**) at δ 5.61 ppm and a very weak signal at δ 10.4 ppm for formyl proton in tautomer (**6a**).

Chromic acid oxidation [9, 10] of 1-hydroxyisochroman (**6ab**) afforded readily (±)-6,8-dimethoxy-3-pentadecyl-3,4-dihydroisocoumarin (**7**) identical in all respects to that obtained previously through oxidation of formyl acetate (**3**) to corresponding carboxy acetate using potassium permanganate in neutral aqueous acetone followed by hydrolytic removal of protective acetyl group with spontaneous lactonization. (Scheme 2).

The structures of all purified compounds were established by their IR, ^{1}H-NMR, and mass spectra and elemental analyses.



Scheme 1.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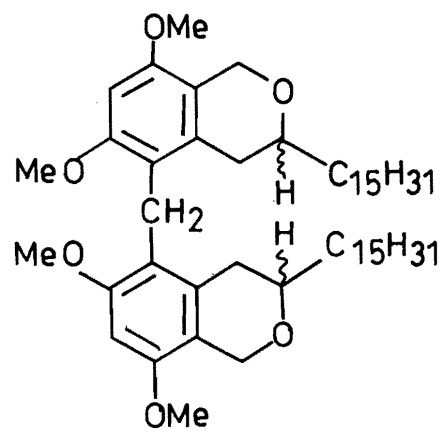
H
C15H31
OAc
CHO
OMe
(3)
MeO
H
C15H31
OH
CHO
OMe
(6a)
MeO
H
C15H31
O
OMe
OH
(6b)
MeO
H
C15H31
O
OMe
O
(7)

Scheme 2.


OMe
O
MeO
C15H31
H
CH2
H
MeO
C15H31
O
OMe

(8)

3. EXPERIMENTAL

Melting points were determined using MEL-TEMP MP-D apparatus and are uncorrected. IR spectra were recorded on a Hitachi spectrophotometer Model-270 as KBr discs or as neat liquids. The ^{1}H-NMR (360 MHz) spectra for compounds (4–6) were recorded on a Bruker AM-300 instrument and the 500 MHz spectrum for compound (**7**) using a Bruker AM-500 instrument. The E.I.M.S. were obtained using a MAT-112-S machine.

(±)-1-(3,5-Dimethoxy-2-hydroxymethylphenyl)-heptadecan-2-yl acetate (4)

1-(3,5-dimethoxy-2-formylphenyl)-heptadecan-2-yl acetate (**3**) [2] (2.31 g, 0.005 mol) and sodium borohydride (0.2 g, 0.005 mol) in absolute ethanol (50 ml) were heated under reflux for 2 hours. The ice-cooled solution was treated with dilute sulfuric acid and then extracted with ether (3×75 ml). The combined ethereal extracts were dried (Na_2SO_4 anhydrous) and the solvent evaporated to leave a colorless oil which solidified on standing. Recrystallization from diethyl ether and petroleum ether (40–60) (1:10) afforded the (±)-1-(3,5-dimethoxy-2-hydroxymethylphenyl)-heptadecan-2-yl acetate (**4**) (1.97 g, 0.00425 mol, 85%) as colorless crystals. M.p. 32–33°C; IR(KBr): 3346, 2908, 1731, 1596, 1233, 1149 cm^{-1}; δ($CDCl_3$): 0.88(3H, t, H17′; J = 6.5 Hz), 1.25(26H, s, H4′–H16′), 1.59(2H, m, H3′) 1.91(3H, s, CH_3COO), 2.76–2.82(1H, d, AB, $H1_B$′; J_{gem} = 13.5 Hz; J_{vic} =9.0 Hz), 3.61–3.65(1H, d, AB, $H1_A$′; J_{gem} = 13.3 Hz; J_{vic} = 3.3 Hz), 3.84(3H, s, C-3 OCH_3), 3.86(3H, s, C-5 OCH_3), 4.25(2H, s, CH_2OH), 5.55–4.88 (1H, m, H2′) 6.31(1H, d, C-4; J = 2.2 Hz), 6.34(1H, d, C-6; J=2.3 Hz) ppm; MS(*m/z*): 464, (M^+), 462, 432, 418(base), 404, 207, 164, 152.

Analysis; Found: C,72.40, H 10.31; $C_{28}H_{48}O_5$ requires C 72.41, H 10.34.

(±)-6,8-Dimethoxy-3-pentadecylisochroman (5)

A solution of the hydroxymethyl acetate (**4**) (1.40 g, 0.003 mol) in ethanol (40 ml) was heated under reflux for 2 hours with 10% aqueous potassium hydroxide (20 ml). The mixture was concentrated (to 20 ml), diluted with water and acidified with dilute hydrochloric acid. Extraction with ether (3×150 ml), followed by drying and evaporation of the solvent afforded directly the (±)-6,8-dimethoxy-3-pentadecylisochroman (**5**) (0.90 g, 0.00225 mol, 75%) as colorless crystals from diethyl ether. M.p. 46–47°C; IR(KBr): 2842, 1584, 1140, 831 cm^{-1}; δ($CDCl_3$): 0.88(3H, t, H17′; J = 6.5 Hz), 1.25(26H, s, H2′–H15′), 1.59(2H, m, H1′), 2.72–2.78(1H, d, AB, $H4_B$; J_{gem} = 16.1 Hz; J_{vic} = 3.7 Hz, H4), 2.79–2.88(1H, d, AB, $H4_A$; J_{gem} = 16.0 Hz, J_{vic} = 10.5 Hz,), 3.82(3H, s, 6-OCH_3), 3.88(3H, s, 8-OCH_3), 4.42–4.53(1H, m, H3), 5.2(2H, s, H1), 6.27(1H, d, H5; J = 2.3 Hz), 6.30(1H, d, H7; J = 2.3 Hz)ppm; *m/z*: 405(M^++1), 404(M^+, base), 193, 164.

Analysis; Found: C 77.14, H 10.81; $C_{26}H_{44}O_3$ requires C 77.22, H 10.89.

6,8-Dimethoxy-1-hydroxy-3-pentadecylisochroman (6ab)

A solution of formyl acetate (**3**) (1.85 g, 0.004 mol) in ethanol (80 ml) was heated under reflux for 2 hours with 10% aqueous potassium hydroxide (20 ml) and worked up as for compound (**5**) to afford 6,8-dimethoxy-1-hydroxy-3-pentadecylisochroman (**6ab**) as colorless prisms from diethylether (1.0 g, 0.0026 mol, 65%). M.p. 80–82°C; IR(KBr): 3242, 3160, 2842, 1593, 1146 cm^{-1}; IR(Neat): 3160, 2842, 1662, 1593, 1146 cm^{-1}; δ($CDCl_3$): 0.88(3H, t, H15′, J = 6.5 Hz), 1.25(26H, s, H2′–H14′), 1.59(2H, m, H1′), 2.53–2.59(1H, d, AB, $H4_B$; J_{gem} =16.1 Hz; J_{vic} = 3.7 Hz, H4), 2.71–2.89(1H, d, AB, $H4_A$; J_{gem} = 16.0 Hz; J_{vic} = 10.5 Hz,), 3.79(3H, s, 6-OCH), 3.84(3H, s, 8-OCH_3), 4.45(1H, m, H3), 5.61(2H, s, H1), 6.27(1H, d, H5; J=2.3 Hz), 6.30(1H, d, H7; J=2.3 Hz)ppm; MS *m/z*: 421(M^++1), 420(M^+), 404, 403, 402(base), 209, 191, 164.

Analysis; Found: C 74.32, H 10.38; $C_{26}H_{44}O_4$ requires C 74.28, H 10.47%.

(±)-3,4-Dihydro-6,8-dimethoxy-3-pentadecylisocoumarin (7)

To a cooled, stirred solution of 6,8-dimethoxy-1-hydroxy-3-pentadecylisochroman (**6**) (0.84 g,0.002 mol) in acetic acid (10 ml) was added dropwise a solution of chromium trioxide (0.59 g,0.006 mol), in acetic acid (6 ml) and water (1.5 ml). The mixture was stirred for one hour then warmed on a water bath at 60°C for 15 minutes. The

reaction mixture was cooled, diluted with water and extracted with chloroform (3×50ml). The combined extracts were dried, and concentrated. Recrystallization from diethyl ether, afforded (±)-3,4-dihydro-6,8-dimethoxy-3-pentadecylisocoumarin (**7**) (0.47 g, 0.0011 mol, 56%) as colorless crystals. M.p. 46–48°C; IR(KBr): 2908, 1716, 1605, 1599, 831 cm^{-1}; δ ($CDCl_3$)(500 MHz): 0.86(3H, t, H15′; J =7.0 Hz), 1.25(26H, brs, H2′–H14′), 1.62(2H, td, H1′; J_1 =7.0 Hz; J_2 =2.8 Hz), 2.20–2.34(1H, d, AB; J_{gem} = 14.0 Hz; J_{vic} = 4.0 Hz, $H4_B$), 2.80–2.89(1H, d, AB; J_{gem} = 14.0 Hz; J_{vic} = 7.0 Hz, $H4_A$), 3.85(3H, s, 6-OCH_3), 3.90(3H, s, 8-OCH_3), 4.48–4.57 (1H, m, H3), 6.30(1H, d, H5; J = 2.7 Hz), 6.46(1H, d, H7; J =2.7 Hz)ppm; *m/z*:419, 418(M^+), 382, 207(base), 179, 164, 152.

Analysis; Found: C 74.61, H 9.98; $C_{26}H_{42}O_4$ requires C 74.64, H 10.04%.

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Paper Received 12 July 1993; Revised 20 April 1994; Accepted 3 July 1994.