The Chemistry of Fungi. Part 74.[1] Synthesis of (±)-5-Butyl-6,8-dihydroxy-3-pentyl-3,4-dihydroisocoumarin

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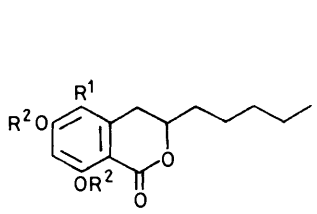
The title compound (1; $R^1 = Bu^n$ $R^2 = H$), which corresponds to the (+)-dihydro-derivative of fusamarin (2), a metabolite of an unidentified species of *Fusarium*, has been synthesised. (2-Butyl-3,5-dimethoxyphenyl)acetic acid (3; $R^1 = OH$, $R^2 = Bu^n$) was obtained from ethyl 3,5-dimethoxyphenylacetate by way of the corresponding 2-formyl derivative (3; $R^1 = OEt$, $R^2 = CHO$). Reaction of the acid chloride (3; $R^1 = Cl$, $R^2 = Bu^n$) with pentylmagnesium bromide furnished 1-(2-butyl-3,5-dimethoxyphenyl)heptan-2-one (4; $Ru = Bu^n$), which was reduced to the alcohol (5; $R^1 = H$, $R^2 = Bu^n$). Formylation of the acetate (5; $R^1 = Ac$, $R^2 = Bu^n$), followed by oxidation and hydrolysis of the ester residue, gave (±)-5-butyl-3-pentyl-6,8-dimethoxy-3,4-dihydroisocoumarin (1; $R^1 = Bu^n$, $R^2 = Me$), which was demethylated to (1; $R^1 = Bu^n$, $R^2 = H$). In model experiments (±)-6,8-dihydroxy-3-pentyl-3,4-dihydroisocoumarin (1; $R^1 = R^2 = H$) and related derivatives, together with associated isochromans of type (7), have been synthesised.

In 1970, Suzuki [2] isolated, from an unidentified species of *Fusarium*, a metabolite, fusamarin, to which he assigned structure (2) on the basis of chemical and spectroscopic evidence.

We became interested in this metabolite because of (*a*) its general structural similarity to sclerotiorin [3] and fusamarin (2). This we have now done, but alas 'the best laid schemes of mice and men . . . .' We have failed to locate specimens of fusamarin (2), dihydrofusamarin (1; $R^1 = Bu^n$, $R^2 = H$), or the relevant micro-organism. However it seems appropriate to record our work to date.



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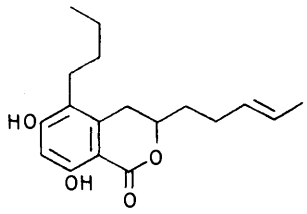

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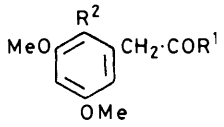

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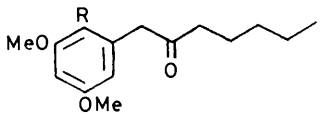

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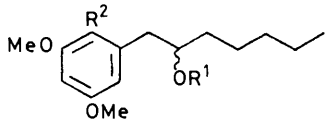

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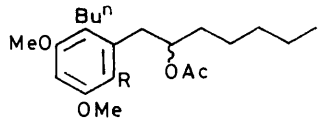

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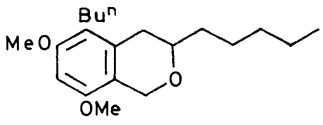

(7)

(*b*) its lack of congruence with a simple mode of biosynthesis. Thus, if by analogy with sclerotiorin and also in accord with general principles the nucleus of fusamarin were derived from acetate then the butyl side chain must arise (i) from a second, separate, acetate-derived chain, or (ii) from an isopentyl fragment which has lost a terminal *C*-methyl group, or (iii) by some other process. Paths (i) and (ii) would be atypical. Hence since we did not regard the structural definition of fusamarin as unequivocal we attempted first to elucidate this aspect of the problem by a synthesis of (±)-dihydro-

Commencing from 3,5-dihydroxyphenylacetic acid or 3,5-dihydroxybenzoic acid we failed, using a wide variety of processes to introduce the butyl substituent, or its equivalent, directly, and had to resort to an indirect process. Thus, ethyl 3,5-dimethoxyphenylacetate (3; $R^2 = H$, $R^1 = OEt$), was formylated by the Vilsmeier process, in high yield to give (3; $R^2 = CHO$, $R^1 = OEt$), the orientation of which was unequivocally defined by conversion into (3,5-dimethoxy-2-methylphenyl)acetic acid (3; $R^1 = OH$, $R^2 = Me$), which

[1] Part 73, A. R. Greenway and W. B. Whalley, *J.C.S. Perkin I*, 1976, 1385.

[2] Y. Suzuki, *Agric. and Biol. Chem.* (*Japan*), 1970, **34**, 760.

[3] See *e.g.* W. B. Whalley, G. Ferguson, W. C. Marsh, and R. J. Restivo, *J.C.S. Perkin I*, 1976, 1366, and references cited therein.

differed from the isomeric 3,5-dimethoxy-4-methylphenylacetic acid.[4]

Condensation of the aldehyde (3; R^1 = OEt, R^2 = CHO) with malonic acid furnished the cinnamic acid (3; R^1 = OEt, R^2 = $CH{:}CH{\cdot}CO_2H$) which was converted by way of the dihydro-derivative (3; R^1 = OEt, R^2 = $CH_2{\cdot}CH_2{\cdot}CO_2H$), the acid chloride (3; R^1 = OEt, R^2 = $CH_2{\cdot}CH_2{\cdot}COCl$), and the diazo-ketone (3; R^1 = OEt, R^2 = $CH_2{\cdot}CH_2{\cdot}CO{\cdot}CHN_2$), into the ketone (3; R^1 = OEt, R^2 = $CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_3$). This ketone, on Clemmensen reduction, followed by saponification of the product, gave (2-butyl-3,5-dimethoxyphenyl)acetic acid (3; R^1 = OH, R^2 = Bu^n), the acid chloride of which formed 1-(2-butyl-3,5-dimethoxyphenyl)heptan-2-one (4; R^1 = Bu^n) on reaction with pentylmagnesium bromide. The acetate (5; R^1 = Ac, R^2 = Bu^n), obtained by way of the alcohol (5; R^1 = H, R^2 = Bu^n), was converted into the aldehyde (6; R = CHO) by a second application of the Vilsmeier reaction. Oxidation of (6; R = CHO) to the intermediate acid (6; R = CO_2H) with potassium permanganate, followed by hydrolysis of the acetate residue, furnished (±)-5-butyl-6,8-dimethoxy-3-pentyl-3,4-dihydroisocoumarin (1; R^1 = Bu^n, R^2 = Me).

Demethylation of this ether with boron tribromide gave the corresponding dihydric phenol (1; R^1 = Bu^n, R^2 = H). The spectral properties of this phenol and of its dimethyl ether (1; R^1 = Bu^n, R^2 = Me) corresponded closely with the data recorded [1] for (−)-dihydrofusamarin, but in the absence of direct comparisons do not necessarily define unequivocally the structure of the metabolite.

In the course of preliminary, exploratory investigations (±)-6,8-dimethoxy-3-pentyl-3,4-dihydroisocoumarin (1; R^1 = H, R^2 = Me) was similarly synthesised, together with a number of derivatives (see Experimental section).

Condensation of several phenolic alcohols of type (5; R^1 = H) with aqueous formalin solution furnished the corresponding isochromans, of type (7).

EXPERIMENTAL

Ethyl 2-Formyl-3,5-dimethoxyphenylacetate.—(*a*) A solution of ethyl 3-5-dihydroxyphenylacetate (5 g) in triethyl orthoformate (38 ml) was saturated with hydrogen chloride during 2.5 h at 0 °C. The mixture was poured into water (250 ml) and stirred, and 12 h later the precipitate (4.5 g) was collected. Purification from benzene–light petroleum (b.p. 60—80 °C) gave *ethyl 2-formyl-3,5-dihydroxyphenylacetate* (4 g) in prisms, m.p. 114° (Found: C, 58.7; H, 5.2. $C_{11}H_{12}O_5$ requires C, 58.9; H, 5.4%).

Methylation of this phenol (0.45 g) by acetone–dimethyl sulphate–potassium carbonate during 12 h gave *ethyl 2-formyl-3,5-dimethoxyphenylacetate* (0.3 g) in prisms, m.p. 108—110° (from aqueous methanol) (Found: C, 61.9; H, 6.3. $C_{13}H_{16}O_5$ requires C, 61.9; H, 6.4%).

(*b*) Phosphoryl chloride (7 g) was added slowly to a stirred solution of ethyl 3,5-dimethoxyphenylacetate (10 g) in *NN'*-dimethylformamide (14 g) at 55 °C. The solution was then heated at 100 °C during 10 min. After 24 h at room temperature the mixture was added slowly (stir) to saturated aqueous sodium acetate (100 ml) at 0 °C. The resultant precipitate was purified from aqueous ethanol to yield ethyl 2-formyl-3,5-dimethoxyphenylacetate (6.1 g), m.p. 98°, identical with that prepared by method (*a*).

Reduction of this formyl derivative (1 g) in acetic acid (40 ml) containing 10N-hydrochloric acid (0.1 ml) and 10% palladium–charcoal (0.3 g) was complete after 1 h to yield ethyl 2-methyl-3,5-dimethoxyphenylacetate as an oil. Hydrolysis of this ester with 5% sodium hydroxide (15 ml) and methanol (5 ml) during 45 min at 100 °C gave *3,5-dimethoxy-2-methylphenylacetic acid* (0.8 g) in prisms, m.p. 137° (from ethanol) (Found: C, 62.7; H, 6.5. $C_{11}H_{14}O_4$ requires C, 62.8; H, 6.7%), mixed m.p. with an authentic specimen of 3,5-dimethoxy-4-methylphenylacetic acid (m.p. 130°) 115—130°.

Hydrolysis of a solution of 2-formyl-3,5-dimethoxyphenylacetate (0.6 g) in methanol (3 ml) containing 5% sodium hydroxide (25 ml) during 30 min at 100 °C gave *2-formyl-3,5-dimethoxyphenylacetic acid* (0.5 g) in needles, m.p. 176° (from acetone) (Found: C, 58.7; H, 5.5. $C_{11}H_{12}O_5$ requires C, 58.9; H, 5.4%).

2-Butyl-3,5-dimethoxyphenylacetic Acid (3; R^1 = OH, R^2 = Bu^n).—A solution of ethyl 2-formyl-3,5-dimethoxyphenylacetate (20 g) in pyridine (120 ml) and piperidine (20 ml) containing malonic acid (33 g) was maintained at 90 °C until evolution of carbon dioxide ceased (about 3 h). The cooled mixture was poured into iced water (500 ml) and the resultant solution acidified with 10N-hydrochloric acid. Purification of the precipitate from ethanol gave *2-ethoxycarbonylmethyl-4,6-dimethoxycinnamic acid* (11 g) in needles, m.p. 131° (Found: C, 61.3; H, 6.0. $C_{15}H_{18}O_6$ requires C, 61.2; H, 6.2%). Hydrogenation of this acid (10 g) dissolved in ethanol (125 ml) over platinic oxide (0.25 g) occurred rapidly to yield *2-ethoxycarbonylmethyl-4,6-dimethoxydihydrocinnamic acid* (8.5 g), which formed plates, m.p. 75° (from aqueous ethanol) (Found: C, 61.3; H, 6.8. $C_{15}H_{20}O_6$ requires C, 60.8; H, 6.8%).

A solution of this dihydrocinnamic acid (10 g) in benzene (35 ml) was treated with oxalyl chloride (13 g). After 12 h at 20 °C the solvent was removed *in vacuo*, more benzene (150 ml) was added to the residue, and the evaporation was repeated. A solution of the unpurified acid chloride in ether (50 ml) was added to an excess of a solution of diazomethane in ether (100 ml) at 0 °C. After 24 h the semi-crystalline, unstable diazo-ketone was isolated and dissolved in chloroform (80 ml). The resultant solution was shaken with 47% hydriodic acid (30 ml), and then washed with aqueous 5% sodium dithionite and water and evaporated to yield *ethyl 2-(3-oxobutyl)-3,5-dimethoxyphenylacetate* (6 g) in needles, m.p. 57° (from ether) (Found: C, 65.3; H, 7.8. $C_{16}H_{22}O_5$ requires C, 65.3; H, 7.5%)

A mixture of this ketone (10 g), zinc amalgam (200 g), ethanol (1 000 ml), and 10N-hydrochloric acid (200 ml) was refluxed during 72 h with the addition of 10N-hydrochloric acid (100 ml) every 12 h. The cooled, filtered mixture was diluted with water and extracted with ethyl acetate (3 × 300 ml). The extract was washed with 2N-sodium hydrogen carbonate and water, dried, and evaporated to yield an oil which was refluxed for 2 h with aqueous 10% sodium hydroxide (100 ml) and ethanol (100 ml). After isolation with ether from the cooled, acidified hydrolysate *2-butyl-3,5-dimethoxyphenylacetic acid* separated from ethanol in needles (6.5 g), m.p. 66° (Found: C, 66.5; H, 7.8. $C_{14}H_{20}O_4$ requires C, 66.6; H, 8.0%), τ 3.5 (2 H, s, ArH), 5.39 (6 H, s, OCH_3), and 6.21 (3 H, s, $ArCH_3$).

(±)-5-Butyl-6,8-dihydroxy-3-pentyl-3,4-dihydroisocoumarin (1; R^1 = Bu^n, R^2 = H).—A solution of the Grignard

[4] G. R. Birchall, M. N. Galbraith, R. W. Gray, R. R. King, and W. B. Whalley, *J. Chem. Soc.* (*C*), 1971, 3559.

reagent prepared from magnesium (1.3 g) and pentyl bromide (8.3 g) in ether (10 ml) was added gradually to a solution of 2-butyl-3,5-dimethoxyphenylacetyl chloride [from the acid (7 g) and oxalyl chloride (11 g)] in ether (300 ml) containing anhydrous iron(III) chloride (0.2 g). After an additional 0.5 h at room temperature followed by 1 h at reflux the product was isolated in the normal manner. The oily product was purified by chromatography on silica, from light petroleum (b.p. 40—60 °C)–ether (25 : 1), to yield 1-(2-*butyl*-3,5-*dimethoxyphenyl*)*heptan*-2-*one* as an oil (4 g) (Found: C, 74.0; H, 9.8. $C_{19}H_{30}O_3$ requires C, 74.4; H, 9.9%).

Reduction of this ketone (4 g) dissolved in ethanol (80 ml) with sodium borohydride (2.25 g) during 10 h at room temperature gave 1-(2-*butyl*-3,5-*dimethoxyphenyl*)*heptan*-2-*ol* (4 g) as an oil, after chromatography on silica from light petroleum (b.p. 40—60 °C)–ether (10 : 1) (Found: C, 74.0; H, 10.3. $C_{19}H_{32}O_3$ requires C, 74.0; H, 10.5%).

A solution of this alcohol (1 g) in ether (40 ml) was stirred with 40% formalin (0.35 ml) and 10N-hydrochloric acid (0.30 ml) during 48 h; reaction was then complete (t.l.c.). Purified from acetone–methanol (±)-5-*butyl*-6,8-*dimethoxy*-3-*pentylisochroman* (7) (0.5 g) formed prisms, m.p. 61° (Found: C, 75.1; H, 10.2. $C_{20}H_{32}O_3$ requires C, 75.0; H, 10.1%).

Prepared by the pyridine–acetic anhydride process, 1-(2-butyl-3,5-dimethoxybenzyl)hexyl acetate (1 g) formed an oil, which was converted by phosphoryl chloride (1 g) and *NN'*-dimethylformamide (2 g) at 55 °C during 30 min and then at 100 °C for 10 min into 1-(2-*butyl*-6-*formyl*-3,5-*dimethoxybenzyl*)*hexyl acetate* (0.7 g), a viscous oil (Found: C, 70.3; H, 8.8. $C_{22}H_{34}O_5$ requires C, 69.8; H, 9.1%).

Oxidation of this aldehyde (1 g) by addition of its solution in acetone (140 ml) to a refluxing solution of potassium permanganate (6.5 g) in acetone (200 ml) during 5 h, followed by removal of the inorganic residues by filtration, gave 1-(2-butyl-3,5-dimethoxy-6-carboxybenzyl)hexyl acetate (1 g) as an oil which was refluxed without purification in ethanol (10 ml), containing aqueous 20% potassium hydroxide (50 ml) for 2 h. After cooling, the mixture was acidified and the resultant product chromatographed on silica from light petrolum (b.p. 40—60 °C)–ether (20 : 1) to yield (±)-5-*butyl*-6,8-*dimethoxy*-3-*pentyldihydroisocoumarin* (1; R^1 = Bu^n, R^2 = Me) (0.5 g), which formed prisms, m.p. 75—76° (from the same solvent) (Found: C, 72.1; H, 9.0. $C_{20}H_{30}O_4$ requires C, 71.8; H, 9.0%). The dimethyl ether of (−)-dihydrofusamarin was an oil.[2]

A saturated solution (10 ml) of boron tribromide in dichloromethane was added to a solution of this isocoumarin (0.5 g) in the same solvent (50 ml) at −60 °C. The mixture was stirred during 36 h, and the product was isolated in the usual manner. Purified from light petroleum (b.p. 40—60 °C) (±)-5-*butyl*-6,8-*dihydroxy*-3-*pentyldihydroisocoumarin* (1; R^1 = Bu^n, R^2 = H) formed needles (0.3 g), m.p. 128° (Found: C, 70.5; H, 8.6. $C_{18}H_{26}O_4$ requires C, 70.6; H, 8.6%). (−)-Dihydrofusamarin [2] has m.p. 175°. The solution in ethanol exhibited an intense violet colour with iron(III). Remethylation of this dihydric phenol by methyl iodide–acetone–potassium carbonate regenerated (quantitatively) the dimethyl ether, m.p. and mixed m.p. 75—76°.

(±)-6,8-*Diacetoxy*-5-*butyl*-3-*pentyl*-3,4-*dihydroisocoumarin* formed prisms, m.p. 65—66° (from ether) (Found: C, 67.9; H, 7.8. $C_{22}H_{30}O_6$ requires C, 67.7; H, 7.7%). The corresponding natural compound was an oil.[2]

1-(2-*Butyl*-6-*formyl*-3,5-*dihydroxyphenyl*)*heptan*-2-*one*.—Demethylation of a solution of 1-(2-butyl-3,5-dimethoxyphenyl)heptan-2-one (3 g) in dichloromethane (120 ml) with a saturated solution (30 ml) of boron tribromide in dichloromethane at −60 °C during 1 h gave 1-(2-*butyl*-3,5-*dihydroxyphenyl*)*heptan*-2-*one* (1 g), which formed prisms, m.p. 102° [from benzene–light petroleum (b.p. 40—60 °C)] after chromatography from benzene–ether (25 : 1) (Found: C, 73.2; H, 9.4. $C_{17}H_{26}O_3$ requires C, 73.3; H, 9.4%). Hydrogen chloride was rapidly passed into a solution of this ketone (0.2 g) in triethyl orthoformate (1 ml). After 30 s the orange-coloured precipitate was rapidly collected and dissolved in a warm solution of sodium acetate in ethanol, to yield 1-(2-*butyl*-6-*formyl*-3,5-*dihydroxyphenyl*)*heptan*-2-*one* (0.1 g), which formed needles, m.p. 117° (from methanol) (Found: C, 70.4; H, 8.5. $C_{18}H_{26}O_4$ requires C, 70.6; H, 8.6%).

(±)-6,8-*Dihydroxy*-3-*pentyl*-3,4-*dihydroisocoumarin* (1; R^1 = R^2 = H).—The Grignard reagent prepared from pentyl bromide (7.5 g) and magnesium (1.2 g) in ether (100 ml) was added slowly with stirring to a solution of 3,5-dimethoxyphenylacetyl chloride [from oxalyl chloride (9.5 g) and 3,5-dimethoxyphenylacetic acid (5 g)] in ether (50 ml) containing anhydrous iron(III) chloride (0.1 g). After 15 min the mixture was refluxed for 1 h. Isolated in the normal manner, and purified by chromatography from light petroleum (b.p. 40—60 °C)–dichloromethane (25 : 2) on alumina, 1-(3,5-*dimethoxyphenyl*)*heptan*-2-*one* (2.2 g) formed an oil; $\nu_{max.}$ 1 715 cm^{-1} (C=O) (Found: C, 71.5; H, 9.0. $C_{15}H_{22}O_3$ requires C, 72.0; H, 8.9%). The 2,4-*dinitrophenylhydrazone* formed yellow needles, m.p. 111° (from dichloromethane) (Found: C, 59.1; H, 6.0; N, 12.6. $C_{21}H_{26}N_4O_6$ requires C, 58.6; H, 6.1; N, 13.0%).

Reduction of a solution of this ketone (1 g) in boiling ethanol (80 ml) containing sodium borohydride (0.5 g) during 1 h gave 1-(3,5-*dimethoxyphenyl*)*heptan*-2-*ol* (5; R^1 = R^2 = H) as an oil (0.8 g) after chromatography from light petroleum (b.p. 40—60 °C)–ether (25 : 1) on silica (Found: C, 70.9; H, 9.6. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.6%).

A solution of this alcohol (1 g) in ether (20 ml) was agitated with 40% formalin (0.4 ml) and 10N-hydrochloric acid (0.5 ml). Reaction was complete (t.l.c.) in 48 h, to yield (±)-6,8-*dimethoxy*-3-*pentylisochroman* (0.5 g), which formed needles, m.p. 122° (from dichloromethane) (Found: C, 72.9; H, 9.0. $C_{16}H_{24}O_3$ requires C, 72.7; H, 9.2%).

Prepared quantitatively by the pyridine–acetic anhydride method the *acetate* of 1-(3,5-dimethoxyphenyl)heptan-2-ol formed an oil (Found: C, 68.7; H, 9.3. $C_{17}H_{26}O_4$ requires C, 69.4; H, 8.9%). A mixture of this acetate (1.2 g), phosphoryl chloride (1.1 ml), and *NN'*-dimethylformamide (1.5 g) was stirred at 0 °C during 1 h, for a further 1 h at 40 °C, and then for 4 h at 70 °C. After decomposition of the cooled mixture with sodium acetate (2.5 g) in water (100 ml), the product was isolated with methylene chloride (3 × 100 ml) to yield 1-(2-*formyl*-3,5-*dimethoxybenzyl*)*hexyl acetate* (0.7 g) in needles, m.p. 70° (from hexane–ether) (Found: C, 66.9; H, 8.1. $C_{18}H_{26}O_5$ requires C, 67.1; H, 8.1%).

A solution of potassium permanganate (0.66 g) in acetone (100 ml) was added during 0.5 h to a refluxing solution of this formyl derivative (1 g) in acetone (100 ml). The mixture was refluxed for an additional 3 h, and the resultant carboxylic acid was isolated in the normal way and without purification was refluxed for 2 h in ethanol (20 ml) and water (5 ml) containing potassium hydroxide (1.5 g). The bulk of the solvent was removed *in vacuo* and the residue was dissolved in water and acidified with 2N-hydrochloric

acid; the product was extracted with ether. Chromatography from light petroleum (b.p. 40—60 °C)–ether (5 : 1) and then from hexane gave (±)-6,8-*dimethoxy*-3-*pentyl*-3,4-*dihydroisocoumarin* (1; R^1 = H, R^2 = Me) (0.5 g) in prisms, m.p. 78° (Found: C, 68.9; H, 8.0. $C_{16}H_{22}O_4$ requires C, 69.0; H, 8.0%).

Demethylation of a solution of this dihydrocoumarin (0.3 g) in 1,2-dichloroethane (12 ml) with a 10% solution (12 ml) of boron trichloride in the same solvent, at 70 °C during 3 h, gave (±)-8-*hydroxy*-6-*methoxy*-3-*pentyl*-3,4-*dihydroisocoumarin* (0.2 g) in needles, m.p. 38° (from methanol), which exhibited an intense red-brown colour with iron(III) in ethanol; $\nu_{max.}$ 1 663 cm^{-1} (lactone C=O); τ −1.21 (1 H, s, OH, replaceable with deuterium oxide), 3.67 (1 H, d, *J* 2 Hz, ArH), 3.75 (1 H, d, *J* 5.2 Hz, ArH), and 6.19 (3 H, s, OCH_3) (Found: C, 67.9; H, 7.6. $C_{15}H_{20}O_4$ requires C, 68.2; H, 7.6%).

When this reaction was performed on the di-*O*-methyldihydroisocoumarin (0.5 g) for 24 h, the product was (±)-6,8-*dihydroxy*-3-*pentyl*-3,4-*dihydroisocoumarin* (0.35 g), which formed prisms, m.p. 112° (from aqueous methanol) (Found: C, 67.1; H, 7.0. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.3%). The n.m.r. spectrum was devoid of OMe signals and showed τ −1.01 and 2.80 (2 H, s, 2 × OH, exchangeable with D_2O).

Remethylation of this phenol regenerated (almost quantitatively) (±)-6,8-dimethoxy-3-pentyl-3,4-dihydroisocoumarin.

(±)-6,8-*Bisbenzyloxy*-3-*n*-*pentylisochroman*.—(*a*) Demethylation of 1-(3,5-dimethoxyphenyl)heptan-2-one (2.5 g) with boiling acetic acid (80 ml) containing 48% hydrobromic acid (40 ml) occurred during 2 h to yield 1-(3,5-*dihydroxyphenyl*)*heptan*-2-*one*, which separated from dichloromethane in prisms (0.7 g), m.p. 87° (Found: C, 70.3; H, 8.3. $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.2%).

(*b*) Demethylation of this parent ether (2 g) dissolved in dichloromethane (80 ml) with a saturated solution of boron tribromide in dichloromethane (4.2 ml) during 1 h at −60° and 24 h at room temperature gave the same phenol (0.8 g) in prisms, m.p. 87°, identical with that prepared by method (*a*) and converted by methyl iodide–acetone–potassium carbonate into the parent 1-(3,5-dimethoxyphenyl)heptan-2-one, characterised as the 2,4-dinitrophenylhydrazone, m.p. 111°, identical with the previously prepared specimen.

Reduction of this phenolic ketone (1.1 g) in ethanol (25 ml) containing sodium borohydride (0.55 g) at room temperature during 24 h gave 1-(3,5-*dihydroxyphenyl*)-*heptan*-2-*ol* (0.8 g) in needles, m.p. 143° (from benzene) (Found: C, 69.7; H, 8.8. $C_{13}H_{20}O_3$ requires C, 69.6; H, 9.0%).

Benzylation of 1-(3,5-dihydroxyphenyl)heptan-2-one (2 g) in boiling acetone (40 ml) containing potassium carbonate (20 g) and benzyl bromide (3 g) during 6 h gave 1-(3,5-*bisbenzyloxyphenyl*)*heptan*-2-*one* (2.5 g) as an oil (Found: C, 80.8; H, 7.5. $C_{27}H_{30}O_3$ requires C, 80.6; H, 7.5%). Reduction of this ketone (1 g) with sodium borohydride (0.5 g) in boiling ethanol (80 ml) during 1 h gave 1-(3,5-*bisbenzyloxyphenyl*)*heptan*-2-*ol* (0.8 g) as an oil (Found: C, 80.3; H, 8.1. $C_{27}H_{32}O_3$ requires C, 80.2; H, 8.0%). The *acetate* was an oil (Found: C, 78.0; H, 7.7. $C_{29}H_{34}O_4$ requires C, 78.0; H, 7.7%).

Prepared from this acetate (1 g), phosphoryl chloride (0.6 ml), and *NN'*-dimethylformamide (7 g) in the normal manner, 1-(3,5-*bisbenzyloxy*-2-*formylbenzyl*)*hexyl acetate* (0.7 g) formed needles, m.p. 105° (from ethanol) (Found: C, 76.2; H, 7.4. $C_{30}H_{34}O_5$ requires C, 75.9; H, 7.2%).

Agitation of a solution of 1-(3,5-*bisbenzyloxyphenyl*)-*heptan*-2-*ol* (0.6 g) in ether (40 ml) with 40% formalin (0.2 ml) and 10N-hydrochloric acid (0.2 ml) during 48 h gave (±)-6,8-*bisbenzyloxy*-3-*pentylisochroman* (0.2 g) which formed needles, m.p. 160° (from ether) (Found: C, 80.8; H, 7.9. $C_{28}H_{32}O_3$ requires C, 80.7; H, 7.7%).

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