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MUCRONUSTYRENE, MUCRONULASTYRENE AND VILLOSTYRENE, CINNAMYLPHENOLS FROM *MACHAERIUM MUCRONULATUM* AND *M. VILLOSUM**

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Key Word Index—*Machaerium mucronulatum*; *M. villosum*; Leguminosae–Lotoideae; cinnamylphenols; isoflavonoids; chalcones.

Abstract—The wood of *Machaerium mucronulatum* contains, in addition to chalcones and isoflavonoids, the cinnamylphenols mucronustyrene [*E*-1-(4-hydroxy-2,3-dimethoxybenzyl)-2-phenylethylene], mucronulastyrene [*Z*-1-(4-hydroxy-2,3-dimethoxybenzyl)-2-phenylethylene] and villostyrene [*Z*-1-(4-hydroxy-2,3-dimethoxybenzyl)-2-(2-methoxyphenyl)-ethylene. Isoflavonoids and villostyrene were also found in the heartwood of *M. villosum*. The structural determination of the cinnamylphenols relied on spectra, degradations and syntheses.

INTRODUCTION

The benzene extract of the trunkwood of *Machaerium mucronulatum* Mart. ex Benth. gave, besides the isoflavonoids (−)-duartin, (−)- and (±)-mucronulatol, (−)-mucroquinone, (+)-mucronucarpan and 3′-hydroxyformononetin, the chalcones butein and isoliquiritigenin, and the simple benzene derivative 2,6-dimethoxyphenol, the cinnamylphenols mucronustyrene and mucronulastyrene. An ethanolic extract of the root was also examined and found to contain, besides isoflavonoids, the same cinnamylphenols, accompanied by villostyrene. Villostyrene was isolated additionally, again together with mucronulatol and other isoflavonoids, from the benzene extract of the heartwood of *M. villosum* Vog. [2]. Indeed, the two species are morphologically similar, the distinction being based chiefly on the characteristics of branches [3].

The elucidation of structure and the synthesis of the cinnamylphenols, subject of a preliminary communication [4], are reported in the present paper. The isoflavonoids of both species will be described in a forthcoming publication [5].

ANALYSIS OF CINNAMYLPHENOLS

Mucronustyrene

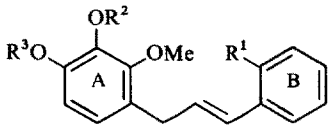
The molecular formula, $C_{17}H_{18}O_3$, and the spectral characteristics (IR and PMR) are consistent with a *E*-cinnamylphenol structure (ABX_2 system, J_{AB} = 16 Hz) [6] with two methoxy (τ 6.10, 6.18) and one hydroxy (ν_{max} 3500 cm^{-1}) substituents situated at positions 2, 3 and 4 of one aromatic ring (AB system, J_{AB} = 8.5 Hz). The other ring is formed by a C_6H_5 (τ 2.80) group. The cinnamylphenol **1a**, compatible with these data, had been synthesized by the *para*-Claisen rearrangement of the cinnamyl ether of 2,3-dimethoxyphenol [6] and, indeed direct comparison proved the identity of this derivative with mucronustyrene.

Mucronulastyrene

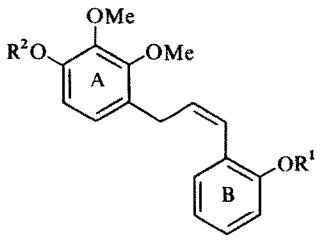
The molecular formula, $C_{17}H_{18}O_4$, and the IR and PMR spectra are consistent with a *Z*-cinnamylphenol structure (ABX_2 system, J_{AB} = 11.5 *Hz*) [1] with two methoxy and two hydroxy substituents. Accordingly, a dimethyl ether, a diethyl ether and a dihydromethyl ether could be obtained. One aromatic ring of mucronulastyrene and its derivatives is disubstituted (4 H, τ 2.7–3.4) and the other ring is 1,2,3,4-tetrasubstituted (AB system, J_{AB} = 8.5 Hz). The positions of the substituents were determined by the hydroxylation of the diethyl ether with OsO_4, followed by oxidation of the resulting glycol with $NaIO_4$ to *o*-ethoxybenzaldehyde, identified by comparison with an authentic synthetic sample. Since the substitution patterns of the aromatic rings A of mucronustyrene and mucronulastyrene may be identical, these data suggest structure **2a** for the latter compound. Indeed treatment of mucronulastyrene diethyl ether (**2b**) with $KMnO_4$, followed by CH_2N_2-esterification of the acidic oxidation products, gave methyl 4-ethoxy-2,3-dimethoxyphenylacetate (**3**), identified by direct comparison with a synthetic sample.

The synthetic ester **3** was prepared by the oxidation of 3-(4-ethoxy-2,3-dimethoxyphenyl)propene (**4a**) with $KMnO_4$, followed by methylation of the acidic reaction product. The 3-arylpropene **4a** was obtained by ethylation of the phenol **4b** which, together with the phenol **4c**, was produced by the Claisen rearrangement of 2,3-dimethoxyphenyl allyl ether (**4d**). The required phenol **4b** was distinguished from the *ortho*-Claisen product **4c** by the failure of **4b** to produce a non-phenolic cyclization product on traetment with HCl/EtOH, and by the

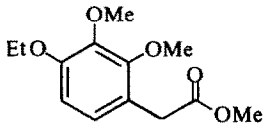
* Part 7 in the series 'The Neoflavonoid Group of Natural Products'. For Part 6 see ref. [1].



1a $R^1 = R^3 = H$, $R^2 = Me$
1b $R^1 = R^2 = H$, $R^3 = Me$
1c $R^1 = OMe$, $R^2 = R^3 = Me$
1d $R^1 = H$, $R^2 = CH_2Ph$, $R^3 = Me$



2a $R^1 = R^2 = H$
2b $R^1 = R^2 = Et$
2c $R^1 = R^2 = Me$
2d $R^1 = Me$, $R^2 = H$
2e $R^1 = Me$, $R^2 = Ac$
2f $R^1 = H$, $R^2 = Me$
2g $R^1 = H$, $R^2 = CH_2Ph$
2h $R^1 = Me$, $R^2 = CH_2Ph$



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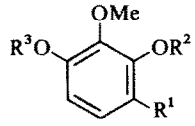
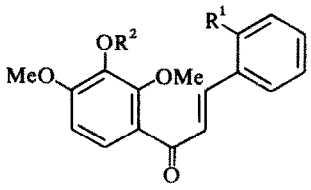
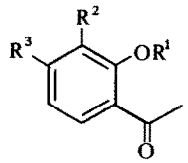


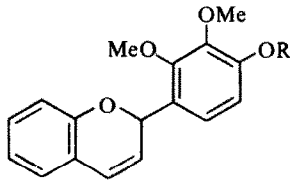
4a $R^1 = allyl$, $R^2 = Me$, $R^3 = Et$
4b $R^1 = allyl$, $R^2 = Me$, $R^3 = H$
4c $R^1 = allyl$, $R^2 = H$, $R^3 = Me$
4d $R^1 = H$, $R^2 = allyl$, $R^3 = Me$



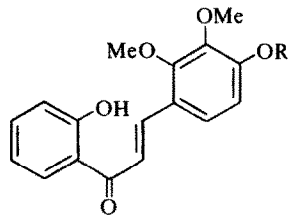
5a $R^1 = H$, $R^2 = CH_2Ph$
5b $R^1 = OMe$, $R^2 = Me$



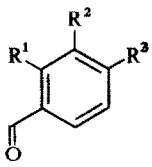
6a $R^1 = Me$, $R^2 = OCH_2Ph$, $R^3 = OMe$
6b $R^1 = Me$, $R^2 = R^3 = OMe$
6c $R^1 = R^2 = R^3 = H$
6d $R^1 = H$, $R^2 = OCH_2Ph$, $R^3 = OMe$



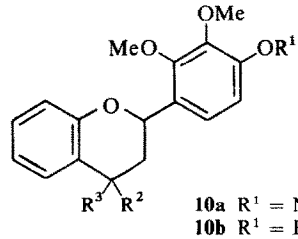
7a R = Me
7b R = H
7c R = CH_2Ph



8a R = Me
8b R = H
8c R = CH_2Ph



9a $R^1 = R^2 = R^3 = H$
9b $R^1 = OMe$, $R^2 = R^3 = H$
9c $R^1 = R^2 = OMe$, $R^3 = OMe$
9d $R^1 = R^2 = OMe$, $R^3 = OH$
9e $R^1 = R^2 = OMe$, $R^3 = OCH_2Ph$



10a $R^1 = Me$, $R^2 - R^3 = O$
10b $R^1 = H$, $R^2 - R^3 = O$
10c $R^1 = CH_2Ph$, $R^2 - R^3 = O$
10d $R^1 = Me$, $R^2 = H$, $R^3 = OH$
10e $R^1 = R^2 = H$, $R^3 = OH$
10f $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = OH$
10g $R^1 = Me$, $R^2 = H$, $R^3 = Cl$
10h $R^1 = R^2 = H$, $R^3 = Cl$
10i $R^1 = CH_2Ph$, $R^2 = H$, $R^3 = Cl$

identity of **4c** with a sample of 3-(2-hydroxy-3,4-dimethoxyphenyl)propene prepared by a thermal rearrangement of the ether **4d**, conducted at lower temperature in accord with an established procedure [7].

Villostyrene

Spectral data characterized this compound, $C_{18}H_{20}O_4$, as a Z-cinnamylphenol with three methoxy and one hydroxy substituents. Accordingly, a monoacetate, a monomethyl ether and a dihydro-derivative could be obtained. When the monomethyl ether was shown to be identical with the dimethyl ether of mucronulastyrene (**2c**), only the relative positions of the substituents remained to be established.

The hydroxy group cannot be located on ring B, since $KMnO_4$-oxidation of villostyrene gave *o*-methoxybenzoic acid. Indeed, it can be only *ortho* or *para* related with H-5 on ring A, since it was the H-5 ($\Delta\tau$ −0.16 ppm) and not the H-6 ($\Delta\tau$ −0.02 ppm) PMR doublet which suffered a significant paramagnetic shift upon acetylation of the compound. In the *para*-case, villostyrene would be expected to give a positive Gibbs test. The reaction product with 2,6-dichlorobenzoquinone chlorimide, however, showed only a feeble absorption in the 700 nm region of the spectrum, in contradistinction to an intense absorption at 462 nm. Data of this type are characteristic of *p*-hydroxyallylbenzenes [8].

Structure **2d** which thus can be proposed for villostyrene, as well as the proposed structures **1a** and **2a** for, respectively, mucronustyrene and mucronulastyrene were, subsequently confirmed by synthesis.

SYNTHESIS OF CINNAMYLPHENOLS

The Claisen rearrangement [9], mentioned above with reference to the synthesis of mucronustyrene (**1a**), has limited applications for the synthesis of cinnamylphenols [6, 10] for general structural reasons, and also because it results usually in the formation of *ortho* and *para* rearrangement products which require separation and identification. The direct cinnamylation of phenols is more convenient, and was employed for the preparation of natural [11, 12] and synthetic [13, 14] derivatives, and, in particular, also for the preparation of mucronustyrene (**1a**) [11]. Finally, the reduction of chalcones with $LiAlH_4/AlCl_3$ was reported to give cinnamylphenols [15] in which the 1-aryl substituent is less oxygenated than the 3-aryl substituent, and used in the preparation of violastyrene and isoviolastyrene [4, 10].

As part of the investigation on the general applicability of this method, the synthesis of the mucronustyrene isomer **1b** and of the 2′-oxygenated *E*-cinnamylphenol **1c** was undertaken.

The chalcones **5a** and **5b**, to be used as starting materials, were prepared by the base catalysed condensations of, respectively, 3-benzyloxy-2,4-dimethoxyacetophenone (**6a**) with benzaldehyde and 2,3,4-trimethoxyacetophenone (**6b**) with 2-methoxybenzaldehyde. Upon $LiAlH_4/AlCl_3$-reduction, **5a** gave the cinnamylphenol derivative **1d**, whose debenzylation with HCl/EtOH gave the required mucronustyrene isomer **1b**. Reduction of **5b** gave the cinnamylphenol **1c**. Catalytic hydrogenation of **1c** led to a 1,3-diarylpropane, identical with dihydromucronulastyrene dimethyl ether. This result proved that the oxygenation pattern of mucronulastyrene and villostyrene, deduced from analytical data, is correct.

All three methods, the Claisen rearrangement, the direct cinnamylation of phenols [11] and the reduction of chalcones, gave only *E*-cinnamylphenols, and the synthesis of *Z*-cinnamylphenols, e.g. mucronulastyrene (**2a**) and villostyrene (**2d**), required the development of an alternative synthetic method. Fortunately all the natural *Z*-cinnamylphenols which have been recognized [4] are characterized by the presence of a 2′-oxygen substituent. This suggested the hydrogenolysis of flavenes (**7**) as a suitable general method for the synthesis of this type of *Z*-cinnamylphenol (**2**).

The required flavene precursors (**7a–c**) were obtained from chalcones according to a described reaction sequence: HCl/EtOH cyclization to flavanones (**10a–c**), $NaBH_4$ reduction to flavonols (**10d–f**), PCl_5 chlorination to 4-chloroflavans (**10g–i**) and C_5H_5N dehydrochlorination to flavens (**7a–c**) [16]. $LiAlH_4/AlCl_3$ hydrogenolysis of the 1,2-bond of the flavenes gave the *Z*-cinnamylphenols in good yield and free from *E*-isomers, as shown by PMR spectra.

The chalcones **8a** and **8b**, to be used as starting materials in this reaction sequence, were prepared by the base catalysed condensations of 2-hydroxyacetophenone (**6c**) with, respectively, 2,3,4-trimethoxybenzaldehyde and 4-hydroxy-2,3-dimethoxybenzaldehyde. The chalcone **8a** gave the *Z*-cinnamylphenol **2f**, whose methyl ether (**2c**) was shown to be identical (IR, PMR) with the dimethyl ether of mucronulastyrene and the monomethyl ether of villostyrene, confirming the proposed oxygenation pattern of these compounds. The chalcone **8b** gave mucronulastyrene (**2a**). The synthesis of villostyrene (**2d**) required that the 4′-oxygen function of the flavene be protected, and 4-benzyloxy-2′-hydroxy-2,3-dimethoxychalcone (**8c**) had to be used as starting material. Consecutive methylation and debenzylation of the resulting *Z*-cinnamylphenol **2g** gave **2d**, identical with villostyrene.

EXPERIMENTAL

Unless otherwise stated spectra were measured in EtOH (UV), $CHCl_3$ (IR) and $CDCl_3$ (60 MHz PMR). All evapns of volatile material were performed under diminished pressure.

Isolation of the constituents of M. mucronulatum. A specimen was collected near Diamantina, MG, Brasil, and identified by Apparício Pereira Duarte. Ground heartwood and sapwood (19.8 kg) were continuously extracted with hot C_6H_6 and then hot EtOH. During evap of C_6H_6 separated a solid (fraction A, 4.8 g). Complete removal of C_6H_6 gave a residue (319 g). A portion (50 g) was triturated with cold C_6H_6, giving insoluble material (fraction B, 7.1 g). The C_6H_6 soln was then chromatographed on Si gel (1 kg), giving, with the indicated eluants, various fractions: C_6H_6 (C_1), C_6H_6–$CHCl_3$ mixtures (8:2, C_2 and C_3; 1:1, C_4; 2:8, C_5), $CHCl_3$ (C_6, C_7 and C_8), MeOH (C_9). Evapn of EtOH gave a residue (208 g). A portion (50 g) was chromatographed on Si gel (1 kg), giving, with the identicated eluants, various fractions: C_6H_6–$CHCl_3$ mixtures (2:8, D_1; 1:9, D_2), $CHCl_3$ (D_3), $CHCl_3$–MeOH mixtures (99:1, D_4; 98:2, D_5; 97:3, D_6), MeOH (D_7). Fraction A was separated chromatographically (Al_2O_3, $CHCl_3$–MeOH). Cryst. of the fractions gave (−)-duartin (2.0 g), (−)-mucronulatol (130 mg) and (±)-mucronulatol (2.25 g). Fraction B was separated similarly giving (−)-duartin (1.9 g) and (−)-mucronulatol (200 mg). C_1 (7.8 g) was an oil of fatty nature. C_2 (0.5 g) was dissolved in Et_2O and shaken with 10% aq. NaOH. The alkaline soln was acidified (ice cooling) and extracted with Et_2O. Evapn of the Et_2O soln gave an oil which was fractionated by TLC (Si gel, $CHCl_3$). The major band was then extracted. Distillation of the extract under diminished pressure gave **1a** (20 mg). C_3 (1.3 g) was chromatographed (Al_2O_3, $CHCl_3$), and further fractionation by TLC

(Al_2O_3, $CHCl_3$), followed by distillation under diminished pressure, gave **1a** (150 mg). Later fractions gave 2,6-dimethoxyphenol (20 mg). C_4 (11.1 g) contained a mixture of **2a** and (−)-duartin. C_5 (12.4 g) was cryst. from EtOH giving (−)-duartin (5.1 g). Evapn of the mother liquors and chromatography (Al_2O_3, $CHCl_3$), followed by distillation under diminished pressure, gave **2a** (2.5 g). C_6 (5.2 g) was separated by multiple chromatography and fractional cryst. into (−)-mucroquinone (50 mg) and (+)-mucronucarpan (185 mg). C_7 (3.5 g) was a mixture of (−)-duartin and (−)-mucronulatol. C_8 (0.9 g) and C_9 (2.8 g) were examined but nothing useful could be isolated. D_1 (4.2 g) was cryst. from EtOH to (−)-duartin (1.3 g). D_2 (1.5 g) was cryst. from EtOH to (±)-mucronulatol (0.1 g). D_3 (0.8 g) was cryst. from MeOH to a small quantity of a low melting solid which was not further examined. D_4 (2.7 g) was cryst. from MeOH to 3′-hydroxyformononetin (30 mg). Evapn of the mother liquors and chromatography of the residue (1 g) (sephadex LH-20, 50 g, MeOH), followed by cryst. of the intermediate fraction, gave 3′-hydroxyformononetin (8 mg). From later fractions isoliquiritigenin (4 mg) was isolated by TLC (Si gel, $CHCl_3$–MeOH, 95:5). D_5 (1.2 g) was cryst. from MeOH giving a small quantity (5 mg) of a solid (mp 280°) which was not further examined. D_6 (2.8 g) was chromatographed (sephadex LH-20, 200 g, MeOH). The final fractions were purified by TLC (Si gel, $CHCl_3$–MeOH, 9:1) to butein (4 mg). D_7 (32 g) was a dark resin. Ground root (4.6 kg) was continuously extracted with hot C_6H_6 and with hot EtOH. Evapn of the EtOH gave a residue (64.5 g). A portion (63 g) was triturated with $CHCl_3$ (400 ml) in a Waring blender. The soluble fraction (12 g) was separated by multiple chromatography and cryst. into **1a** (10 mg), **2a** (30 mg), **2d** (63 mg) and (−)-mucronulatol (50 mg).

Identifications. For (−)-duartin, (−)- and (±)-mucronulatol, (−)-mucronuquinone, (+)-mucronucarpan, 3′-hydroxyformononetin, isoliquiritigenin and butein see ref [5]. 2,6-Dimethoxyphenol was identified by comparison with an authentic sample [17].

Mucronustyrene (**1a**). Oil, bp 190° (bath temp., 0.2 mm). [Found: M (MS), 270. $C_{17}H_{18}O_3$ requires: M, 270]. λ_{max}^{MeOH} (nm): 255, 283 infl., 294 (ε 16 600, 4260, 1800). ν_{max} (cm^{-1}): 3500, 1600. PMR (CCl_4, τ): 2.8 (*m*, C_6H_5), 3.25 (*d*, H-6), 3.43 (*d*, H-5) (AB system, J_{AB} = 8.5 Hz), 3.54 (*dd*), 3.77 (*dt*), 6.58 (*dd*) (ABX_2 system, J_{AB} = 16 Hz, J_{BX} = 6.5 Hz, J_{AX} = −2 Hz, $CH_A{=}CH_B{-}CH_{2X}$), 6.10, 6.18 (2*s*, 2OMe). The cmpd was identical with a synthetic sample [6].

Mucronulastyrene (**2a**). Oil, bp 200–201° (bath temp., 0.5 mm). [Found: M (MS), 286. $C_{17}H_{18}O_4$ requires: M, 286] λ_{max}^{MeOH} (nm): 240, 284 (ε 18 500, 7200). ν_{max} (cm^{-1}): 3450, 1600. PMR (CCl_4, τ): 2.7–3.6 (*m*, 4ArH), 3.35 (*d*, H-6), 3.48 (*d*, H-5) (AB system, *J* = 8.5 Hz), 4.6 (*br. s*, 2OH), 3.63 (*br. d*), 4.11 (*dt*), 6.70 (*dd*) (ABX_2 system, J_{AB} = 11.5 Hz, J_{BX} = 7 Hz, J_{AX} = −1.4 Hz, $CH_A{=}CH_B{-}CH_{2X}$), 6.17, 6.28 (2*s*, 2OMe). *Diethyl ether* (**2b**) (**2a**, EtI, K_2CO_3, Me_2CO, refl., 20 hr, evapn, extraction of the residue with Et_2O followed by evapn and purification by TLC gave an oil, bp 190–200° (bath temp., 0.2 mm). [Found: C, 73.23; H, 7.48. $C_{21}H_{26}O_4$ requires: C, 73.66; H, 7.65%]. λ_{max}^{MeOH} (nm): 239, 283 (ε 15 000, 4500). ν_{max} (cm^{-1}): 1585. *Dimethyl ether* (**2c**) (**2a**, MeI etc as above), oil, bp 180–190° (bath temp., 0.2 mm). [Found: C, 72.49; H, 7.06; M (MS), 314. $C_{19}H_{22}O_4$ requires: C, 72.59; H, 7.05; M, 314]. λ_{max}^{MeOH} (nm): 240, 282 (ε 13 500, 6750). ν_{max} (cm^{-1}): 1595. PMR (CCl_4, τ): 3.27 (*d*, H-6), 3.51 (*d*, H-5) (AB system, J_{AB} = 9 Hz), 2.7–3.6 (*m*, 4ArH), 3.51 (*d*), 4.28 (*dt*), 6.56 (*dd*) (ABX_2 system, J_{AB} = 11.5 Hz, J_{BX} = 7.4 Hz, J_{AX} = −1.5 Hz, $CH_A{=}CH_B{-}CH_{2X}$), 6.23 (*s*, 4OMe). *Dihydromucronulastyrene dimethyl ether* [**2c** (50 mg), EtOAc (20 ml), 10% Pd/C (35 mg), H_2 (room temp., 1 atm.)] oil, bp 180–190°, 0.2 mm. [Found: C, 72.21; H, 7.41. $C_{19}H_{24}O_4$ requires: C, 72.13; H, 7.65%]. ν_{max} (cm^{-1}): 1595. *OsO_4–$NaIO_4$ Oxidation of* **2b**. **2b** (150 mg) was treated with OsO_4 (250 mg) in anh. dioxan (48 hr). H_2S was then passed through the mixture. The OsS_4 was collected. The dioxan was evapd and the residual glycol and $NaIO_4$ (200 mg) in 50% MeOH (15 ml) were kept at room temp. (3 days). $CHCl_3$ extraction and fractionation by TLC (Si gel, $CHCl_3$) gave 2-ethoxybenzaldehyde (30 mg), ν_{max} (cm^{-1}). 1675. PMR (τ): −0.5 (*s*, CHO), 2.10–3.20 (*m*, 4ArH), 5.84 (*q*), 8.50 (*t*) (*J* = 7 Hz, OEt). 2,4-Dinitrophenylhydrazone, red needles, mp 269° ($CHCl_3$). [Found: C, 54.50; H, 4.23; N, 17.22. $C_{15}H_{14}O_5N_4$ requires C, 54.54; H, 9.27; N, 16.95%] identical with an authentic sample prepared from 2-ethoxybenzaldehyde. *$KMnO_4$ oxidation of* **2b**. $KMnO_4$ (700 mg) in H_2O (10 ml) was added to **2b** (160 mg) in Me_2CO (10 ml). After 3 hr at room temp. SO_2 was passed through the mixture which was then extracted with Et_2O. The Et_2O soln was treated with CH_2N_2 in Et_2O. The product was purified by TLC (Si gel, $CHCl_3$) to **3** (20 mg), oil, bp 140–145° (bath temp., 0.3 mm) identical (IR and PMR) with the synthetic sample described below.

Synthesis of methyl 4-ethoxy-2,3-dimethoxyphenylacetate (**3**). **6** (2.8 g) [18] in *N,N*-dimethylaniline was heated (200–210°, 2 hr) and the product separated by column chromatography (Si gel, $CHCl_3$) into two phenolic compounds. A small portion of each was treated with HCl/EtOH. The bulk of the sample which was recovered unchanged was purified by distillation to **4b** (600 mg), oil (bp 115–120°, 0.03 mm). [Found: C, 68.23; H, 7.38. $C_{11}H_{14}O_3$ requires: C, 68.02; H, 7.27%]. The other sample was identified with the known **5**, also prepared by the thermal rearrangement of **6** [6]. **4b**, EtI, K_2CO_3, Me_2CO (reflux, 48 hr) gave **4a**, oil, bp 130–135° (bath temp., 0.05 mm). [Found: C, 70.30; H, 8.46. $C_{13}H_{18}O_3$ requires: C, 70.24; H, 8.16%]. **4a** (160 mg), $KMnO_4$ (1 g), Me_2CO (20 ml) were kept at room temp. (30 min). Then SO_2 was passed, the Me_2CO evapd and the residue extracted with Et_2O and methylated with CH_2N_2 in Et_2O. TLC (Si gel, $CHCl_3$), followed by distillation, gave **3** (12 mg), oil, bp 120–125° (bath temp., 0.1 mm). [Found: C, 61.58; H, 7.33. $C_{13}H_{18}O_5$ requires: C, 61.41; H, 7.14%]. ν_{max}^{film} (cm^{-1}): 1730. PMR (CCl_4, τ): 3.33 (*d*, H-6), 3.50 (*d*, H-5) (AB system, J_{AB} = 9 Hz), 5.98 (*q*), 8.58 (*t*) (*J* = 7 Hz, OEt), 6.20 (*s*, 3OMe), 6.51 (*s*, CH_2).

Villostyrene (**2d**). Oil, bp 180–190° (bath temp., 0.05 mm). [Found: C, 71.72; H, 6.56. $C_{18}H_{20}O_4$ requires: C, 71.98; H, 6.71%]. λ_{max} (nm): 245, 286 (ε 26 400, 9000). Gibbs test [8], λ_{max} (nm): 462 (intense), 645. ν_{max}^{film} (cm^{-1}): 3460, 1600, 1580, 1500, 1290, 1070, 755. PMR (τ): 2.6–3.5 (*m*, 4ArH), 3.12 (*d*, H-6), 3.38 (*d*, H-5) (AB system, J_{AB} = 8.5 Hz), 4.30 (*br.s*, OH), 3.35 (*d*), 4.15 (*dt*), 6.50 (*dd*) (ABX_2 system, J_{AB} = 12 Hz, J_{BX} = 7 Hz, J_{AX} = −1.5 Hz, $CH_A{=}CH_B{-}CH_{2X}$), 6.12, 6.18, 6.22 (3*s*, 3OMe). MS (*m/e*): 300 (35%) M, 285 (25), 269 (31), 167 (18), 165 (25), 153 (25), 152 (33), 147 (18), 133 (23), 131 (54), 121 (38), 118 (46), 115 (81), 106 (17), 103 (34), 91 (100). *Monomethyl ether* (**2c**), identical (IR, PMR) with mucronulastyrene dimethyl ether. *Monoacetate* (**2e**), oil. [Found: M (MS), 342. $C_{20}H_{22}O_5$ requires: M, 342]. ν_{max}^{film} (cm^{-1}): 1775, 1600, 1580, 1500, 775. PMR (τ). 3.10 (*d*, H-6), 3.22 (*d*, H-5) (AB system, *J* = 8.5 Hz, 2.6–3.10 (*m*, 4 ArH), 3.28 (*d*), 4.15 (*dt*), 6.40 (*dd*) (ABX_2 system, J_{AB} = 12 Hz, J_{BX} = 7 Hz, J_{AX} = −1.5 Hz, $CH_A{=}CH_B{-}CH_{2X}$), 6.10, 6.15, 6.25 (3 *s*, 3 OMe), 7.70 (*s*, OAc). *Dihydrovillostyrene* [**2d** (100 mg), EtOH (20 ml), 10% Pd/C (50 mg), H_2 room temp. 1 atm.)], oil [Found: M (MS), 302. $C_{18}H_{22}O_4$ requires: 302] ν_{max}^{film} (cm^{-1}): 3425, 1600, 1495, 1250, 755. λ_{max} (nm): 222 infl., 263, 279 (ε 36 800, 17 500, 7200); λ_{max}^{NaOH} (nm): 229, 245, 279, 295 (ε 17 500, 19 900, 6000, 4800). *$KMnO_4$ oxidation of* **2d**. $KMnO_4$ (550 mg) in H_2O (10 ml) was added to **2d** (100 mg) in Me_2CO (10 mg). Treatment of the mixture as described above gave *o*-methoxybenzoic acid, identified by direct comparison (IR, mmp) with an authentic sample.

Synthesis of starting materials. (a) *Methylation of 3-benzyloxy-2-hydroxy-4-methoxyacetophenone* (**6d**) [19] with MeI etc. gave 3-benzyloxy-2,4-dimethoxyacetophenone (**6a**), oil, bp 164–170°, 0.2 mm. ν_{max} (cm^{-1}): 1675, 1600. PMR (CCl_4, τ): 2.70 (*m*, Ph), 2.63 (*d*, H-6), 3.42 (*d*, H-5) (AB system, J_{AB} = 9 Hz), 5.10 (*s*, CH_2), 6.13, 6.21 (2 *s*, 2 OMe), 7.55 (*s*, OAc). 2,4-Dinitrophenylhydrazone, red microcrystals, mp 145° ($CHCl_3$–petrol). [Found: C, 59.11; H, 4.57; N, 12.30. $C_{23}H_{22}N_4O_7$ requires: C, 59.22; H, 4.75; N, 12.01%]. (b) *Preparation of 4-benzyloxy-2,3-dimethoxybenzaldehyde* (**9e**). $CHCl_3$ (140 ml) was added dropwise to a boiling soln of 2,3-dimethoxyphenol (44 g) [20] and NaOH (120 g) in H_2O (400 ml) under N_2. The mixture was heated under reflux (1 hr), acidified with HCl and extracted with Et_2O. Distillation at 115–123°, 0.1 mm, gave a mixture of aldehydes

which was separated by column chromatography (Si gel, $CHCl_3$). Slow cryst. of the later fractions gave 4-hydroxy-2,3-dimethoxybenzaldehyde (**9d**, 7.1 g), cream coloured prisms, mp 73° (C_6H_6–petrol). [Found: C, 59.57; H, 5.41. $C_9H_{10}O_4$ requires: C, 59.34; H, 5.53%]. ν_{max} (cm^{-1}): 3500, 1665, 1595. PMR (τ): −0.02 (*s*, CHO), 2.45 (*d*, H-6), 3.19 (*d*, H-5) (AB system, J_{AB} = 9 Hz), 5.97, 6.02 (2 *s*, 2 OMe). **9d** (10 g), $PhCH_2Br$ (18 g), anh. K_2CO_3 (20 g) in Me_2CO (120 ml, reflux, 3.5 hr), evapn, addition of H_2O, extraction with Et_2O and distillation at 168–178°, 0.02 mm, gave 4-benzyloxy-2,3-dimethoxybenzaldehyde (**9e**, 13.5 g), oil. [Found: C, 70.56; H, 6.09. $C_{16}H_{16}O_4$ requires: C, 70.58; H, 5.92%]. ν_{max} (cm^{-1}): 1670, 1600.

Synthesis of chalcones. The mixture of benzaldehyde (0.01 mol) and acetophenone (0.01 mol) in EtOH (30 ml), added to KOH (30 g) in H_2O (40 ml), was stirred (room temp., *ca* 18 hr). The neutral chalcones pptd and were collected by filtration. The phenolic chalcones were obtained by acidification of the reaction mixture and extraction with Et_2O. 3-Benzyloxy-2',4'-dimethoxychalcone (**5a**) (from **9a** and **6a**), yellow needles, mp 87° (MeOH). [Found: C, 77.01; H, 6.16. $C_{24}H_{22}O_4$ requires: C, 76.99; H, 5.92%]. ν_{max} (cm^{-1}): 1645, 1600. PMR (τ): 2.0–3.0 (*m*, Ph and PhCH=CH), 2.50 (*d*, H-6'), 3.35 (*d*, H-5') (AB system, J_{AB} = 9 Hz), 5.05 (*s*, CH_2), 6.05, 6.15 (2 *s*, 2 OMe). 2,2',3',4'-Tetramethoxychalcone (**5b**) (from **9b** and **6b**), yellow needles, mp 77° (MeOH). [Found: C, 69.51; H, 6.17. $C_{19}H_{20}O_5$ requires: C, 69.50; H, 6.14%]. ν_{max} (cm^{-1}): 1645, 1590. 2'-Hydroxy-2,3,4-trimethoxychalcone (**8a**) (from **9c** and **6c**), yellow needles, mp 79° (MeOH). [Found: C, 69.43; H, 5.80. $C_{18}H_{18}O_5$ requires: C, 69.78; H, 5.77%]. ν_{max} (cm^{-1}): 1640. 4,2'-Dihydroxy-2,3-dimethoxychalcone (**8b**) (from **9d** and **6c**), yellow crystals, mp 122° (C_6H_6–petrol). [Found: C, 67.97; H, 5.25. $C_{17}H_{16}O_5$ requires: C, 67.99; H, 5.37%]. ν_{max} (cm^{-1}): 3500, 1640, 1570. 4-Benzyloxy-2'-hydroxy-2,3-dimethoxychalcone (from **9e** and **6c**), yellow needle clusters, mp 76° (EtOH). [Found: C, 73.78; H, 5.98. $C_{24}H_{22}O_5$ requires: C, 73.83; H, 5.68%]. ν_{max} (cm^{-1}): 1645, 1585.

Synthesis of E*-cinnamylphenols.* $LiAlH_4$ (resp. 104 and 250 mg) was added to the chalcone (**5a** 500 mg, **5b** 2.1 g) in Et_2O (resp. 15 and 20 ml) and the mixture was stirred (10 min) at 0°. $AlCl_3$ (resp. 175 and 400 mg) was then added at 0°. The mixture was allowed to warm to room temp. during 30 min and then chromatographed directly on Si gel (20 g), eluting with Et_2O. The chalcone **5a** gave the intermediate *E*-1-(3-benzyloxy-2,4-dimethoxybenzyl)-2-phenylethylene (**1d**) (310 mg), ν_{max} (cm^{-1}): no OH absorption, 1600, which was treated with satd HCl/EtOH (20 ml) at room temp. Evapn gave a residue which was separated by TLC (Si gel, $CHCl_3$) into *E*-1-(3-hydroxy-2,4-dimethoxybenzyl)-2-phenylethylene (**1b**) (169 mg), oil, bp 195–204°, 0.2 mm. [Found: C, 75.77; H, 6.74. $C_{17}H_{18}O_3$ requires: C, 75.53; H, 6.71%]. λ_{max} (nm): 256, 282 (ε 10500, 3650). ν_{max} (cm^{-1}): 3500, 1620, 1600. PMR (CCl_4, τ): 2.80 (*m*, Ph), 3.35 (*d*, H-6), 3.45 (*d*, H-5) (AB system, J_{AB} = 9 Hz), 3.4–3.8 (*m*, 2 H), 6.51 (*m*, 2 H) (ABX_2 system, CH_A=CH_B—CH_{2X}), 6.13, 6.19 (2 *s*, 2 OMe). The chalcone **5b** gave *E*-1-(2,3,4-trimethoxybenzyl)-2-(2-methoxyphenyl)ethylene (**1c** 1.2 g), oil, bp 210–215°, 0.2 mm. [Found: C, 72.60; H, 7.06. $C_{19}H_{22}O_4$ requires: C, 72.59; H, 7.05%]. λ_{max} (mm): 258, 300 (ε 15700, 4650). ν_{max} (cm^{-1}): 1585. PMR (τ): 2.5–3.7 (*m*, 6 ArH), 3.5 (*m*), 3.7 (*dt*), 6.49 (*br. d*) (ABX_2 system, J_{AB} = 15.7 *Hz*, J_{BX} = 6.5 *Hz*, J_{AX} = *ca* 0 Hz, CH_A = CH_B—CH_{2X}), 6.12 (*s*, 2 OMe), 6.20 (*s*, 2 OMe). **1c** (100 mg) in EtOAc (20 ml) was hydrogenated (room temp., 4 hr) over 10% Pd/C (50 mg) to an oil (60 mg), identical (IR, PMR) with dihydromucronulastyrene dimethyl ether.

Synthesis of Z*-cinnamylphenols.* (a) *Flavanones.* The chalcone (**8a** 12 g, **8b** 7.4 g), EtOH (resp. 250 and 50 ml) and conc HCl (1 ml) were heated under reflux (resp. 24 and 6 hr). The soln was concd to half vol., cooled and the cryst. ppt. collected. Further concn yielded more material, resp. 2',3',4'-trimethoxyflavanone (9.3 g), crystals, mp 117° (EtOH). [Found: C, 68.71; H, 6.09. $C_{18}H_{18}O_5$ requires: C, 68.78: H, 5.77%]; and 4'-hydroxy-2',3'-dimethoxyflavanone (1.67 g), plates, mp 149° (C_6H_6–petrol). [Found: C, 68.21; H, 5.43. $C_{17}H_{16}O_5$ requires: C, 67.99; H, 5.37%]. The chalcone (**8c** 12.3 g), EtOH (100 ml) and NaOH (125 mg) were heated under reflux (3 hr). Repeated concn as above, gave 4'-benzyloxy-2',3'-dimethoxyflavanone (7.4 g), needles, mp 107° (EtOH). [Found: C, 74.06; H, 5.74. $C_{24}H_{22}O_5$ requires: C, 73.83: H, 5.68%]. (b) *Flavan-4-ols.* $NaBH_4$ (resp. 2.1 and 3.7 g) was added to a stirred soln of the flavanone (**12a** 8.3 g, **12b** 1.5 g, **12c** 7.3 g) in EtOH (resp. 300, 50 and 150 ml) at room temp. After resp. 16, 2 and 4.5 hr) the EtOH was evapd and H_2O and 2N HCl cautiously added. $CHCl_3$ extraction and evapn of the solvent gave the flavan-4-ol. (*cis*-2,4)-2',3',4'-Trimethoxyflavan-4-ol (**10d**, 6.35 g), crystals, mp 146° (C_6H_6–petrol). [Found: C, 68.78; H, 6.43. $C_{18}H_{20}O_4$ requires: C, 68.34; H, 6.37%]. ν_{max} (cm^{-1}): 3550, 1600, 1575. PMR (τ): 2.4–3.4 (*m*, 6 ArH), 4.58 (*dd*, J = −11, 2.7 Hz, H_{ax}-2), 4.92 (*dd*, J = −9, 7 Hz, H_{ax}-4), 7.4–8.3 (*m*, 2 H-3), 6.07, 6.12, 6.14 (3 *s*, 3 OMe). 4'-Hydroxy-2',3'-dimethoxyflavan-4-ol (**10e**, 1.23 g), microcrystals, mp 128–134° (C_6H_6). [Found: C, 67.75; H, 6.06. $C_{17}H_{18}O_5$ requires: C, 67.54; H, 6.00%]. ν_{max} (cm^{-1}): 3500, 1600, 1575. PMR indicates that the product is a mixture of 2H, 4H *cis* and *trans* isomers, (τ): 2.4–3.4 (*m*, 6 ArH), 4.4–5.3 (*m*, H-2, H-4), 7.5–8.2 (*m*, 2 H-3), 6.12, 6.13 (2 *s*, 2 OMe). (*cis*-2,4)-4'-Benzyloxy-2',3'-dimethoxyflavan-4-ol (**10f** 6 g), plates, mp 94° (C_6H_6). [Found: C, 74.00; H, 6.58. $C_{24}H_{24}O_5$ requires: C, 73.45; H, 6.16%]. ν_{max} (cm^{-1}): 3500, 1605, 1585. PMR (τ): 2.4–3.4 (*m*, 11 ArH), 4.69 (*dd*, J = 10.5, 2.5 Hz, H_{ax}-2), 5.00 (*s*, CH_2), 5.0–5.3 (*m*, H_{ax}-4), 6.14 (*s*, 2 OMe), 7.3–8.3 (*m*, 2 H-3). (c) *Flav-3-enes.* The flavan-4-ol (**10d** 6.58 g, **10f** 5.2 g) was treated with PCl_5 (resp. 6.58 g, 5.2 g) in resp. C_6H_6 (250 ml, room temp., 2 hr) and $CHCl_3$ (50 ml, 0°, 2 hr). The reaction mixture was poured into iced H_2O. Extraction with CH_2Cl_2 and evapn gave crude 4-chloroflavan (resp. **10g**, **10i**). Alternatively, the flavan-4-ol (**10e**, 278 mg) was treated with $SOCl_2$ (0.33 ml) in $CHCl_3$ (10 ml, reflux, 30 min). $CHCl_3$ and excess $SOCl_2$ were evapd giving crude 4-chloroflavan (**10h**). The 4-chloroflavan and C_5H_5N were heated under reflux (2 hr). After evapn the residue was (i) rapidly shaken with ether and ice-cold 2N HCl, then with satd aq. NaCl and the EtOH soln evapd to give, after purification by TLC (Si gel, $CHCl_3$) followed by distillation, **7a** (2.8 g); (ii) separated by TLC (Si gel, $CHCl_3$, under N_2) giving **7b** (47 mg); (iii) shaken with H_2O–Et_2O, the Et_2O soln evapd and the re idue distilled at 225–260° (bath temp., 0.35 mm) to **7c** (2.48 g). 2,3',4'-Trimethoxyflav-3-ene (**7a**), oil bp 190–200°, 0.3 mm. [Found: C, 71.90; H, 5.60. $C_{18}H_{18}O_4$ requires: 72.47, H, 6.08%]. PMR (τ): 2.8–3.5 (*m*, 6 ArH), 3.52 (*dd*), 3.80 (*dd*), 4.32 (*dd*) (ABX system, J_{AB} = −1.9 Hz, J_{AX} = 10.3 Hz, J_{BX} = 3.7 Hz, CH_A=CH_X—CH_B), 6.05, 6.14, 6.24 (3 *s*, 3 OMe). 4'-Hydroxy-2',3'-dimethoxyflav-3-ene (**7b**), oil which is rapidly oxidized; it may be kept under N_2 at 0° for short periods, ν_{max} (cm^{-1}): 3500, 1580. 4'-Benzyloxy-2',3'-dimethoxyflav-3-ene (**7c**), oil. [Found: C, 77.17; H, 5.98. $C_{24}H_{22}O_4$ requires: C, 76.99; H, 5.92%], ν_{max} (cm^{-1}): 1600. (d) *Z-Cinnamylphenols.* $LiAlH_4$ (resp. 125, 187 and 1000 mg) was added to a soln of the flav-3-ene (**7a** 330 mg, **7b** 143 mg, **7c** 2300 mg) in anh. Et_2O (0°). Then $AlCl_3$ (resp. 161, 166 and 1600 mg) was added to the stirred soln (0°) and after 3 hr cold 2N HCl was cautiously added. Extraction with Et_2O gave phenolic products. The product from **7a** was methylated (MeI, K_2CO_3, Me_2CO, reflux, 12 hr). Purification by TLC (Si gel, $CHCl_3$) gave **2c** (171 mg), identical (IR, PMR) with the dimethyl ether of mucronulastyrene. The products from **7b** and **7c** were purified by TLC (Si gel $CHCl_3$) and distilled resp. to **2a** (33 mg), identical (IR, PMR) with mucronulastyrene, and to *Z*-1-(4-benzyloxy-2,3-dimethoxybenzyl)-2-(2'-hydroxyphenyl)-ethylene (**2g**, 570 mg), oil. ν_{max} (cm^{-1}): 3500, 1590, 1575. PMR (τ): 2.5–3.5 (*m*, 9 ArH), 3.26 (*d*, H-6), 3.36 (*d*, H-5) (AB system, J_{AB} = 8.5 Hz), 3.55 (*br. d*), 4.05 (*dt*), 6.62 (*dd*) (ABX_2 system, J_{AB} = 12 Hz, J_{BX} = 6.5 Hz, J_{AX} = −1.5 Hz, CH_A=CH_B—CH_{2X}), 6.12, 6.17 (2 *s*, 2OMe). Methylation of **2g** (MeI etc.) gave, after purification by TLC (Si gel, $CHCl_3$), *Z*-1-(4-benzyloxy-2,3-dimethoxybenzyl)-2-(2'-methoxyphenyl)-ethylene (**2h**), oil, ν_{max} (cm^{-1}): 1595, 1575. PMR (τ): 2.5–3.5 (*m*, 11 ArH), 3.5 (*d*), 4.17 (*dt*), 6.48 (*dd*) (ABX_2 system, J_{AB} = 12 Hz, J_{BX} = 7 Hz, J_{AX} = −2 Hz, CH_A=CH_B—CH_{2X}), 4.92 (*s*, CH_2), 6.10, 6.18, 6.19 (3 *s*, 3 OMe). Debenzylation of **2h** (260 mg) by $AlCl_3$ (100 mg) in C_6H_6 (10 ml, reflux, 1 hr) gave a mixture which was poured into cold 2N HCl and extracted with

Et_2O. Distillation gave **2d** (98 mg), identical (IR, PMR) with villostyrene.

REFERENCES

1. Ollis, W. D., Redman, B. T., Roberts, R. J., Sutherland, I. O., Gottlieb, O. R. and Magalhães, M. T. (1978) *Phytochemistry* **17**, 1383.
2. Braga, A. da S., Gottlieb, O. R., Eyton, W. B., Kurosawa, K. and Ollis, W. B. (1968) *Ann. Acad. Brasil. Ciênc.* **40**, 33; Oliveira, A. B. de, Gottlieb, O. R. and Ollis, W. D (1968) *Ann. Acad. Brasil Ciênc.* **40**, 147.
3. Hoehne, F. C. (1941) *Flora Brasilica*, Vol. XXV. fasc. III, p. 90. Secretaria da Agricultura, Indústria e Comércio de São Paulo, Brasil.
4. Gregson, M., Kurosawa, K., Ollis, W. D., Redman, B. T., Roberts, R. J., Sutherland, I. O., Oliveira, A. B. de, Eyton, W. B., Gottlieb, O. R. and Dietrichs, H. H. (1968) *Chem. Commun.* 1390.
5. Kurosawa, K., Ollis, W. D., Sutherland, I. O., Gottlieb, O. R. and Oliveira, A. B. de (1978) *Phytochemistry* **17**, 1405.
6. Barnes, M. F., Ollis, W. D., Sutherland, I. O., Gottlieb, O. R and Magalhães, M. T. (1965) *Tetrahedron* **21**, 2707.
7. Trikojus, V. M. and White, D. E. (1949) *J. Chem. Soc.* 436.
8. Mesquita, A. A. L., Corrêa, D. de B., Gottlieb, O. R. and Magalhães, M. T. (1968) *Anal. Chim. Acta* **42**, 311.
9. Tarbell, D. S. (1944) *Org. Reactions* **2**, 1; Jefferson, A. and Scheinmann, F. (1968) *Quart. Rev.* **22**, 391.
10. Gregson, M., Ollis, W. D., Sutherland, I. O., Gottlieb, O. R. and Magalhães, M. T. (1978) *Phytochemistry* **17**, 1375.
11. Mageswaran, S., Ollis, W. D., Roberts, R. J. and Sutherland, I. O. (1969) *Tetrahedron Letters* 2897.
12. Larkin, J., Nonhebel, D. C. and Wood, H. C. S. (1970) *Chem. Commun.* 455.
13. Jurd, L. (1968) *Experientia* **24**, 858; (1969) *Tetrahedron Letters* 2863; (1969) *Tetrahedron* **25**, 1407, (1976) US Patent 3973040.
14. Cardillo, G., Cricchio, R. and Merlini, L. (1969) *Tetrahedron Letters* 907.
15. Verma, P. M. and Bokadia, M. M. (1964) *Chem Ind. (London)* 807
16. Clark-Lewis, J. W., Jackman, L. M. and Williams, L. R. (1962) *J. Chem. Soc.* 3858. Clark-Lewis, J. W. and Williams, L. R. (1965) *Australian J. Chem.* **18**, 90.
17. Krauss, R. B. and Crede, E. (1917) *J. Am. Chem. Soc* **39**, 1433.
18. Baker, W. and Smith, H. A (1931) *J. Chem. Soc.* 2542; Baker, W. and Savage, R. I. (1938) *J. Chem. Soc.* 1602.
19. Baker, W. and Evans, C. (1938) *J. Chem Soc.* 372.
20. Meltzer, R. I. and Doczi, J. (1950) *J. Am. Chem. Soc.* **72**, 4986.