Phytochemistry, Vol. 24, No. 3, pp. 622–624, 1985
Printed in Great Britain

0031–9422/85 $3.00 + 0.00

STILBENES OF *GNETUM ULA*

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(*Revised received* 14 *August* 1984)

Key Word Index—*Gnetum ula*; Gnetaceae; stilbenes; structure; synthesis; structure revision.

Abstract—Gnetin, a new stilbene isolated from *Gnetum ula* is assigned the structure 3,4-methylenedioxy-4'-methoxy-*trans*-stilbene, **3** on the basis of spectroscopic data and synthesis. The structure 3,3',4-trihydroxy-2-methoxy-*trans*-stilbene, **1a** earlier assigned to a trihydroxymonomethoxy stilbene is now revised to 3,4,5'-trihydroxy-3'-methoxy-*trans*-stilbene, **1b**.

INTRODUCTION

We have earlier reported [1, 2] the isolation of two stilbenes, together with bergenin, 2-hydroxy-4-benzyloxy acetophenone and bis-2-(2,2',4,4'-tetrahydroxy)-acetophenone. These were identified as 3,3',4-trihydroxy-2-methoxy-*trans*-stilbene (**1a**) and 2,3',5',6-tetrahydroxy-*trans*-stilbene (gnetol, **2**). A third stilbene, gnetin, has now been obtained in small amounts from the combined benzene eluates of several columns and identified as 3,4-methylenedioxy-4'-methoxy-*trans*-stilbene (**3**) on the basis of spectral data discussed below and synthesis. Some fresh observations made it necessary to check the structure **1a** assigned to the methoxy stilbene and it has now been revised to **1b**.

RESULTS AND DISCUSSION

The presence of methylenedioxy and OMe groups in gnetin was evident from 2 and 3H singlets at 5.93 and 3.80, respectively, in its ^{1}H NMR spectrum. While the pattern of multiplets of the aromatic protons definitely located the OMe group it left open the possibility of fusion of the methylenedioxy group to C-2 and C-3 of the stilbene nucleus. Confirmation of **3** was obtained by synthesis through condensation [3] of piperonal with *para*-methoxyphenylacetic acid.

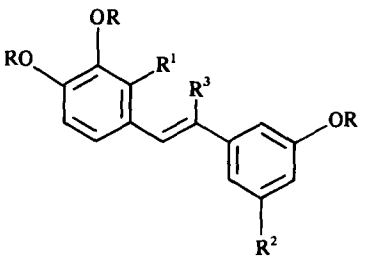
The structure of the methoxy stilbene reported earlier was based on the presence of a fragment at *m/z* 107 (100%) in the mass spectrum of the dihydro derivative and two *ortho* coupled doublets in the ^{1}H NMR spectrum. The mono substitution of one benzene ring and the presence of substituents on three contiguous carbon atoms in the other therefore did not seem open to doubt. The 360 MHz spectrum of gnetol obtained later made it possible to assign resonances of all the aromatic protons in gnetol (**2**) with certainty, the assignments being then checked through benzene induced shifts. Comparison of ^{1}H NMR spectra of the two compounds made structure **1a** doubtful for the methoxy stilbene. 2,3,3',4-Tetramethoxy-*trans*-stilbene (**1c**) was therefore synthesised and comparison revealed it to be different from the permethyl derivative of the natural compound. A similar comparison with synthetic 3,3',4,5'-tetramethoxy-*trans*-stilbene (**1d**) then showed that the trihydroxymonomethoxy stilbene had identical substitution. The only explanation of the parent peak at *m/z* 107 is that it arises through loss of formaldehyde. Also notable is that one of the *ortho* coupled doublets changes to a double doublet at 270 MHz. The green ferric colour suggested that the OMe group is located in the ring having a resorcinol type substitution and this was confirmed through formation of the diphenylmethylenedioxy derivative on reaction with dichloro diphenylmethane [4]. The structure of the stilbene must therefore be revised to **1b**. 3,3',4-Trimethoxy-*trans*-stilbene (**1e**) was also synthesised as a model compound and since it is not known is reported.

EXPERIMENTAL

Isolation of gnetin (**3**). Defatted stem-wood of *G. ula* (5 kg) was cut into small pieces and extracted in a Soxhlet with Me_2CO. The residue obtained after removal of solvent under red. pres. was taken up in H_2O and exhaustively extracted with EtOAc in a liquid–liquid extractor. The EtOAc sol fraction (25 g) was chromatographed and elution with C_6H_6 gave a viscous mass which was repeatedly fractionated on silica gel to give **3** (100 mg), light yellow plates from $CHCl_3$–petrol, mp 121–122°; MS $[M]^+$ *m/z* 254 ($C_{16}H_{14}O_3$); ν_{max} (Nujol) 1600, 1500, 1255, 1180, 1030, 965, 930 cm^{-1}; λ_{max} (MeOH) 205, 302 and 330 nm; ^{1}H NMR (CCl_4, 60 MHz) 7.40 (2H, *d*, *J* = 9 Hz, Ar H-2',6'), 6.87 (2H, *s*, –CH=CH–), 6.82 (2H, *d*, *J* = 9 Hz, Ar H-3',5'), 6.80–7.10 (3H, *m*, Ar H-2, 5, 6), 5.93 (2H, *s*, –O–CH_2–O–), 3.80 (3H, *s*, OMe); MS *m/z* 254 (100), 239 (23.5), 181 (17.7), 153 (15.8), 152 (12.5).

Dihydrognetin. **3** (50 mg) in MeOH (20 ml) was hydrogenated over Pd/C (10%, 50 mg) for 4 hr to give a colourless oil (40 mg). ν_{max} (Nujol) 1600, 1500, 1245, 1040 cm^{-1}, ^{1}H NMR (CCl_4, 60 MHz) 6.50–7.10 (7H, *m*, ArH), 5.80 (2H, *s*, –O–CH_2–O–), 3.73 (3H, *s*, OMe), 2.80 (4H, *s*, Ph–(CH_2–)$_2$).

Synthesis of **3**. Piperonal (1.5 g), *p*-methoxyphenylacetic acid (1.66 g) and piperidine (0.25 ml) were heated at 160–170° for 15 hr. The reaction mixture was cooled, dissolved in CH_2Cl_2 and filtered. The filtrate was first extracted with dil HCl to remove piperidine and then extracted with 5% aq NaOH (3 × 20 ml) to isolate the corresponding stilbene-*β*-carboxylic acid **4**. The CH_2Cl_2 layer was washed several times with H_2O and evapd to yield a gum (2.3 g) which was chromatographed on silica gel to give **3** (250 mg), found identical with the natural sample (co-TLC, IR, ^{1}H NMR).



1a $R = R^2 = R^3 = H$, $R^1 = OMe$

1b $R = R^1 = R^3 = H$, $R^2 = OMe$

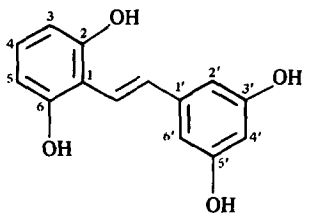
1c $R^2 = R^3 = H$, $R = Me$, $R^1 = OMe$

1d $R^1 = R^3 = H$, $R = Me$, $R^2 = OMe$

1e $R^1 = R^2 = R^3 = H$, $R = Me$

1f $R^1 = R^2 = H$, $R = Me$, $R^3 = COOH$

1g $R^1 = H$, $R = Me$, $R^2 = OMe$, $R^3 = COOH$



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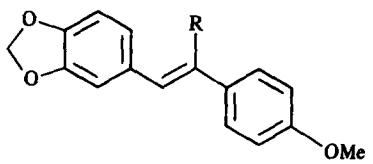

3 R = H

4 R = COOH

The NaOH extract was neutralised with dil HCl and ppted solid was collected and crystallised from MeOH to give colourless needles of **4** (500 mg), mp 252°; MS $[M]^+$ *m/z* 298 ($C_{17}H_{14}O_5$); ν_{max} (Nujol) 1660, 1610, 1600, 1505, 1420, 1375, 1350, 1290, 1240, 1180, 1100, 1030, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) 10.7 (1H, *br s*, COOH), 6.70–7.50 (8H, *m*, ArH and –CH=), 5.95 (2H, *s*, –O–CH_2–O–), 3.85 (3H, *s*, OMe); MS *m/z* 298 (100), 280 (90), 265 (50), 195 (46), 152 (70), 148 (65), 126 (45), 120 (55).

Decarboxylation of **4**. **4** (100 mg) was refluxed with quinoline (10 ml) and $CuCO_3$ [5] (100 mg) for 2 hr. The cooled reaction mixture was dissolved in Et_2O and extracted with dil HCl until free from quinoline. The solid obtained after usual work up of the Et_2O layer was crystallised from $CHCl_3$–petrol to give plates of **3** (50 mg), identical with the material obtained from plant.

3,4,5′-*Trihydroxy*-3′-*methoxy*-trans-*stilbene* (**1b**). Isolation according to the procedure in ref. [1]. ^1H NMR (DMSO-d_6, 270 MHz) 9.50 (3H, *br s*, exchangeable on addition of D_2O, 3 × –OH), 7.16 (1H, *d*, *J* = 2 Hz, ArH-5), 6.96 (1H, *dd*, *J* = 8, 2 Hz, ArH-6), 6.90 (2H, *dd*, *J* = 17 Hz, –CH=CH–), 6.75 (1H, *d*, *J* = 8 Hz, ArH-2), 6.40 (2H, *d*, *J* = 2 Hz, ArH-2′,6′), 6.12 (1H, *br s*, ArH-4′), 3.82 (3H, *s*, OMe); ^1H NMR (DMSO-d_6 + C_6D_6, 270 MHz) 9.40 (3H, *br s*, exchangeable on addition of D_2O, 3 × –OH), 7.20 (1H, *d*, *J* = 2 Hz, ArH-5), 6.99 (1H, *dd*, *J* = 8, 2 Hz, ArH-6), 6.98 (2H, *dd*, *J* = 17 Hz, –CH=CH–), 6.83 (1H, *d*, *J* = 8 Hz, ArH-2), 6.53 (2H, *d*, *J* = 2 Hz, ArH-2′,6′), 6.28 (1H, *dd*, *J* = 2 Hz, ArH-4′), 3.83 (3H, *s*, OMe).

2,3,3′,4-*Tetramethoxy*-trans-*stilbene* (**1c**). A mixture of 2,3,4-trimethoxybenzaldehyde (1.96 g), *m*-methoxyphenyl acetic acid (1.66 g) and piperidine (0.25 ml) was heated at 160–170° for 20 hr. The reaction mixture was dissolved in CH_2Cl_2 and worked up as before to give a gum (1.5 g). Chromatographic separation of this material on silica gel gave **1c** as a colourless oil (500 mg). MS $[M]^+$ *m/z* 300 ($C_{18}H_{20}O_4$); ^1H NMR ($CDCl_3$, 60 MHz) 6.2–7.4 (8H, *m*, ArH and –CH=CH–), 3.40, 3.50, 3.80 and 3.85 (3H each *s*, 4 × OMe).

Synthesis of 3,3′,4-*trimethoxy*-trans-*stilbene* (**1e**). Condensation of 3,4-dimethoxybenzaldehyde (1.66 g) and 3-methoxyphenyl acetic acid (1.66 g) as above gave **1e** (300 mg) along with the corresponding stilbene-β-carboxylic acid **1f** (700 mg) from the NaOH extract. **1e**: colourless oil; MS $[M]^+$ *m/z* 270 ($C_{17}H_{18}O_3$); ^1H NMR ($CDCl_3$, 60 MHz) 6.7–7.6 (9H, *m*, ArH and –CH =CH–), 3.60, 3.90 and 4.0 (3H each *s*, 3 × –OCH_3). **1f**: Colourless needles from MeOH, mp 200–201°; MS $[M]^+$ *m/z* 314 ($C_{18}H_{18}O_5$); ^1H NMR ($CDCl_3$, 60 MHz) 10.7 (1H, *br s*, exchangeable on addition of D_2O, COOH), 6.5–7.5 (9H, *m*, ArH and –CH=), 3.70, 3.90 and 3.95 (3H, each *s*, 3 × OMe).

Synthesis of 3,3′,4,5′-*tetramethoxy*-trans-*stilbene* (**1d**). Condensation of 3,4-dimethoxybenzaldehyde with 3,5-dimethoxyphenyl acetic acid [6] (1 mmol each) in presence of piperidine (0.25 ml) at 160–170° for 20 hr gave **1d** (300 mg) in the neutral and **1g** (600 mg) in the alkaline fraction. **1d**: colourless oil; MS $[M]^+$ *m/z* 300 ($C_{18}H_{20}O_4$); ^1H NMR ($CDCl_3$, 60 MHz) 6.0–7.0 (8H, *m*, ArH and –CH=CH–), 3.85 (3H, *s*, OMe), 3.80 (9H,

s, 3 × OMe). Found identical with the permethyl ether of natural **1b**. **1g**: colourless needles from MeOH, mp 180–182°; MS $[M]^+$ m/z 344 ($C_{19}H_{20}O_6$); ^1H NMR ($CDCl_3$, 60 MHz) 10.8 (1H, *br s*, exchangeable on addition of D_2O, –COOH), 6.0–7.5 (7H, *m*, ArH and –CH=), 4.10 (6H, *s*, 2 × OMe), 4.15 (6H, *s*, 2 × –OMe).

Diphenylmethylenedioxy derivative of **1b**. **1b** (50 mg) and diphenyldichloromethane (0.05 ml) were heated at 185° for 5 min. The reaction mixture was cooled, dissolved in C_6H_6 and passed through a small column of silica gel to give a solid (30 mg), crystallised from EtOH, mp 140–141°, MS $[M]^+$ m/z 410 ($C_{27}H_{22}O_4$).

Acknowledgements—The authors are grateful to Dr. Peerzada S. H. Khan, NBRI, Lucknow for his help in collection and identification of the plant material, to the instrumentation centre of IISC, Bangalore for some 270 MHz ^1H NMR spectra and CSIR, CCRUM and UGC, New Delhi for financial assistance.

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Phytochemistry, Vol. 24, No. 3, pp. 624–626, 1985.
Printed in Great Britain.

0031–9422/85 $3.00 + 0.00

THREE 3-BENZYL-4-CHROMANONES FROM *MUSCARI COMOSUM*

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(*Received* 26 *June* 1984)

Key Word Index—*Muscari comosum*; Liliaceae; bulbs; 3-benzyl-4-chromanones; homoisoflavanones; 5,8-dihydroxy-3-(4′-hydroxybenzyl)-6,7-dimethoxy-4-chromanone; 5,7-dihydroxy-3-(3′-hydroxy-4′-methoxybenzyl)-4-chromanone; 5,7-dihydroxy-3-(4′-hydroxybenzyl)-4-chromanone.

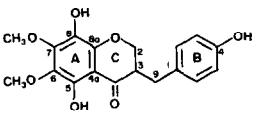
Abstract—Three novel 3-benzyl-4-chromanones have been isolated from the bulbs of *Muscari comosum*.

INTRODUCTION

We recently [1] described the structural elucidation of three components of the homoisoflavanone fraction extracted from the bulbs of *Muscari comosum*. In the present paper we report the spectral data which now allow us to assign structures **1**, **2** and **3** to a further three homoisoflavanones from the same source, named muscomin, 3′-hydroxy-3,9-dihydroeucomin and 4′-demethyl-3,9-dihydroeucomin, respectively. It is noteworthy that **1** and **2**, as compared to known 3-benzyl-4-chromanones [2], possess new oxygenation patterns. Compound **1** bears oxygen functions at both positions 6 and 8 of ring A in addition to the normally oxygenated functions 5 and 7, and compound **2** bears a hydroxyl group at the 3′ position like scillascillins, although it does not possess the 3-spirocyclobutene ring which is characteristic of these compounds.

RESULTS AND DISCUSSION

Compound **1** possesses the molecular formula $C_{18}H_{18}O_7$ (high-resolution mass spectrum). In the ^1H NMR spectrum the signals of the protons of rings B and C were clearly seen (Table 1). The remaining resonances were those of three hydroxyl and two methoxyl groups. The appearance of the hydroxytropylium fragment (m/z 107) in the mass spectrum indicated that one hydroxyl group was at the 4′ position. It was assigned the δ9.31 ^1H NMR signal because an NOE was measured between this and the 3′,5′ signals. The UV absorption at



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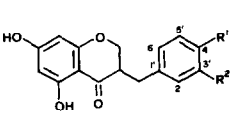

2 R¹ = OCH₃ R² = OH
3 R¹ = OH R² = H

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