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A SUBSTITUTED 1,2-DIARYLETHANE FROM *CYMBIDIUM GIGANTEUM**

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Key Word Index—*Cymbidium giganteum*; Orchidaceae; 1,2-diarylethane; 1-(3′-hydroxy-5′-methoxyphenyl)-2-(4″-hydroxy-5″-methoxyphenyl)ethane.

Abstract—In addition to sitosterol and taraxerone, a new substituted 1,2-diarylethane, gigantol, has been isolated from *Cymbidium giganteum* and characterized as 1-(3′-hydroxy-5′-methoxyphenyl)-2-(4″-hydroxy-5″-methoxyphenyl)ethane on the basis of physicochemical data and through synthesis of its derivative.

INTRODUCTION

Cymbidium giganteum Wall. is an epiphytic herb belonging to the Orchidaceae. The genus is considered to be purgative and is used as a nutrient and a demulcent. In a research programme directed towards the chemical investigation of medicinal plants, *Cymbidium giganteum* was found to possess spasmolytic activity in its ethanolic extract. Despite the fact that this plant has attracted the attention of Dahmen and Leander [1], no biological activity either in the crude plant material or in the isolated glycoside named cymbidoside has been reported. The alcoholic extract of this plant material was further fractionated into hexane, chloroform, *n*-butanol and aqueous parts. The activity was distributed in the hexane and chloroform fractions. Chromatography of the hexane-soluble fraction yielded sitosterol and taraxerone. Column chromatography of the chloroform fraction yielded a new substituted 1,2-diarylethane (bibenzyl), gigantol (**1**).

RESULTS AND DISCUSSION

The hexane-soluble fraction was chromatographed over silica gel and crude **1** was obtained from the chloroform–ethyl acetate (19:1) eluate and purified by preparative thin-layer chromatography. The brown-coloured material so obtained was crystallized from chloroform–petrol (mp 94–95°) and was found to be optically inactive. The compound gave a pink spot on TLC when sprayed with a 2% solution of ceric sulphate in 8% sulphuric acid and showed a positive Gibb's test [2].

The IR spectrum of **1** had characteristic bands at 3500 (OH), 2900, 1600, 1520 (aromatic C–H) and 1220 cm^{-1} (C–O–C). The presence of a phenolic group was evident from the appearance of a blue spot on TLC when sprayed with ferric chloride solution. The UV spectra of **1**, its acetate and the fully methylated product were characteristic of 1,2-diarylethane derivatives (Table 1) [3]. The ^1H NMR spectrum of **1** showed the presence of two methoxyl signals at δ3.77 and 3.85 and a signal for four equivalent benzylic protons at δ2.83. The six aromatic proton signals appeared at δ6.81 (1H, *d*, J = 9 Hz, 3″-H), 6.77 (1H, *dd*, J = 2 and 9 Hz, 2″-H), 6.65 (1H, *d*, J = 2 Hz, 6″-H) and 6.29 (3H, *br s*, A-ring protons). Two hydroxyl protons appeared at δ5.57 and were confirmed by D_2O exchange. The signal for aromatic protons in the ^1H NMR spectrum of **1** indicated that at least one of the two aromatic rings has a symmetrical arrangement of substituents at C-3′ and C-5′ with respect to the benzylic linkage as evident from a broad singlet at δ6.29 for three protons.

The NOE experiments on **1** indicated a 21.8% increase in the intensity of the signals for 4′-H, 6′-H and 6″-H at δ6.29 and 6.65 after irradiation of the signals attributable to the methoxyl groups.

1 gave a molecular ion peak $[M]^+$ at m/z 274 ($C_{16}H_{18}O_4$) and a base peak at m/z 137 which arises from the tropylium ion formed by the C-1 and C-2 bond (benzylic) cleavage arising from both aromatic rings each containing one hydroxyl and one methoxyl group.

The diacetate of **1** obtained by usual methods and purified by preparative TLC showed a single spot on TLC but remained as a gummy product. The UV and ^1H NMR spectra of the acetate given in Tables 1 and 2 were further

Table 1. UV spectral data of 1,2-diarylethane and its derivatives

1,2-Diarylethane	λ_{max}/nm (log ε)
1 3′,4″-Dihydroxy-5′,5″-dimethoxy	206 (4.3) 224 sh (3.97) 274 (3.51) 300 sh (3.08)
2 Diacetate	204 (4.34) 224 sh (3.5) 272 (3.35) 278 sh (3.33)
4 Tetramethoxy	208 (4.36) 226 sh (4.00) 278 (3.63) 300 sh

*CDRI communication No. 3510.

Table 2. Assignment of chemical shifts (δ) in the ^{1}H NMR spectra of 1,2-diarylethanes*

1,2-Diarylethane	OMe	OAc or OH†	2′,4′,6′-H	3″-H	2″-H	6″-H	1,2-Protons
1 3′,4″-Dihydroxy 5′,5″-dimethoxy	3.85 3.77	5.57	6.29 (*br s*)	6.81 (*d*, J = 9)	6.77 (*dd*, J = 9, 2)	6.65 (*d*, J = 2)	2.83
2 3′,4″-Diacetoxy 5′,5″-dimethoxy	3.81 3.79	2.31 2.33	6.56 (*d*, J = 2)	6.98 (*d*, J = 9)	6.86 (*dd*, J = 2)	6.73 (*d*, J = 2)	2.90
4 Tetramethoxy	3.86 (6H) 3.78 (6H)		6.34 (*br s*)	6.83 (*d*, J = 9)	6.75 (*dd*, J = 9, 2)	6.7 (*br s*)	2.86

*Unless indicated otherwise, all signals are singlets and have the appropriate integrated intensities; J in Hz.
†Signal exchanged on shaking with D_2O.

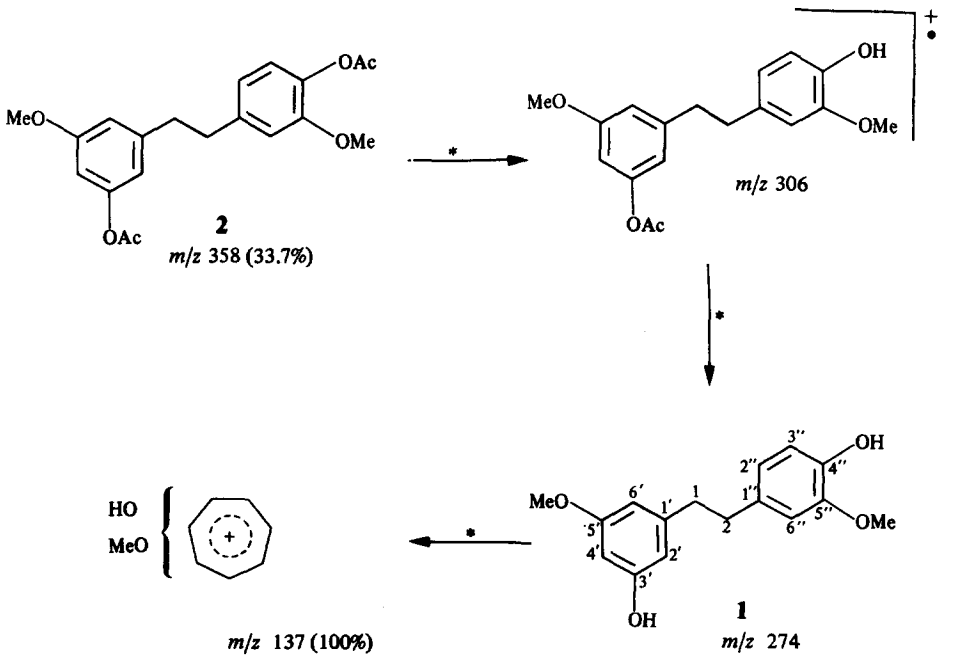
in accordance with the 1,2-diarylethane compound having two hydroxyl and two methoxyl groups. The mass spectrum ($[M]^+$ at m/z 358, $C_{20}H_{22}O_6$) indicated that the substance lost ketene (two molecules) and fragmented into two equivalent stable portions (Scheme 1) as the base peak (m/z 137).

The C-1 and C-2 protons (δ2.90) in the ^{1}H NMR spectrum remained unaffected on acetylation, thereby eliminating the possibility of hydroxyl substituents at C-2′,2″ or C-6′,6″. The positive Gibb's test further suggested that the position of one or both hydroxyl groups is present at positions in which the *para* positions are free. The downfield shift of 3″-H with respect to 6″-H indicated a hydroxyl group *para* to a benzylic linkage. Thus on the basis of the spectral data and chemical tests, three probable structures (**1**, **6** and **7**) were postulated.

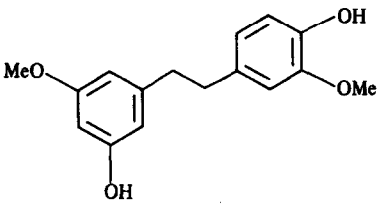
1 was methylated with ethereal diazomethane to give the tetramethyl ether (**4**); the UV and ^{1}H NMR spectral data (given in Tables 1 and 2) have been discussed earlier in the text.

The structure for **1** was finally confirmed by synthesizing the tetramethyl ether by condensing 3,5-dimethoxyphenylacetic acid and 3,6-dimethoxybenzaldehyde in the presence of piperidine to give **5**. This, on decarboxylation and further hydrogenation, afforded the dimethyl ether of **6**. This compound, 1-(3′,5′-dimethoxyphenyl)-2-(3″,6″-dimethoxyphenyl)ethane, was found to be different from gigantol tetramethyl ether (**4**) on TLC and ^{1}H NMR spectral comparison.

Another approach involving condensation of 3,4-dimethoxyphenylacetic acid with 3,5-dimethoxybenzaldehyde in the presence of piperidine resulted in compound **3**, which on decarboxylation with Cu–bronze and quinoline and then hydrogenation with Pd–C at room temperature afforded tetramethoxy-1,2-diarylethane. This compound was found to be completely



Scheme 1.



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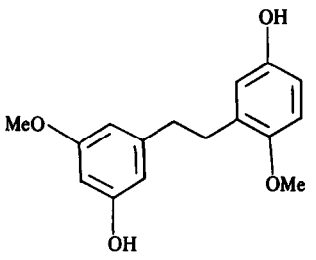

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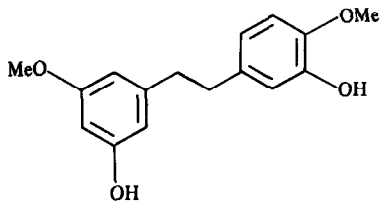

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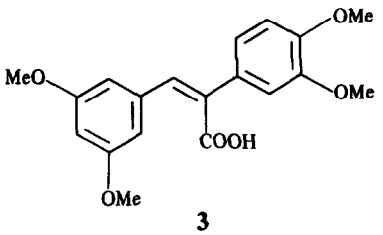

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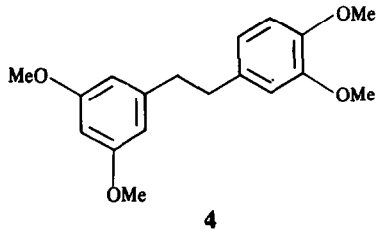

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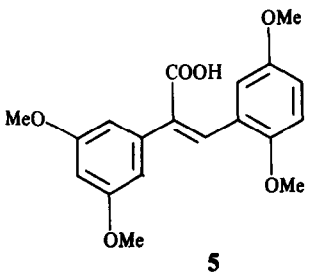

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identical (mp, co-TLC, IR, ^{1}H NMR and MS) with the tetramethyl ether of gigantol (**4**). Thus gigantol (**1**) has been assigned as 1-(3′-hydroxy-5′-methoxyphenyl)-2-(4″-hydroxy-5″-methoxyphenyl)ethane.

A literature survey revealed that a number of substituted bibenzyls (1,2-diarylethanes) have been reported, such as lunularic acid and lunularin [4], dihydropinosylvin [5], pellipiphyllin [6] and 3,4′-dihydroxy-4,5′-dimethoxybibenzyl [2]. From *Radula* species, about seven new bibenzyls have been reported by Asakawa *et al.* [7], some of them having a fused seven-membered heterocyclic ring and a few having extended isoprene units. Occurrence in a few higher plant families, such as the Combretaceae, Dioscoreaceae, Leguminosae and Pinaceae, is also known. This is the second report of a bibenzyl in the Orchidaceae. Previously, Takagi *et al.* [8] found bibenzyls in *Bletilla striata* (Orchidaceae). Some of these bibenzyls exhibit antibacterial [8] or growth inhibitory properties [9].

EXPERIMENTAL

All mps are uncorr. UV spectra were taken in MeOH and ^{1}H NMR spectra were recorded with TMS as an external standard. Plant material was collected from Phata, Chamoli District, U.P. and verified by S. K. Palvi. A herbarium specimen (No. 11895) has been deposited at The Medicinal Plants Herbarium, Central Drug Research Institute, Lucknow.

Isolation of gigantol (**1**). The whole dried plant of *Cymbidium giganteum* (3 kg) was ground and exhaustively extracted with 95% EtOH (3 × 5 l.). The residue obtained after concn was defatted with hexane and then extracted with $CHCl_3$. The $CHCl_3$–soluble fraction (9 g) was chromatographed over silica gel. Elution with $CHCl_3$–EtOAc (19:1) gave a brownish residue (150 mg), which was further purified by prep. TLC (120 mg), mp 94–95° ($CHCl_3$–petrol); IR ν^{CHCl_3} cm^{-1}: 3500, 3000, 2900, 1600, 1520, 1460, 1430, 1260, 1220, 1150, 1060, 1040 and 930; MS *m/z*: 274 $[M]^+$ and 137 (base peak).

Diacetoxy-gigantol (**2**). Gigantol (40 mg) was kept overnight with pyridine–Ac_2O at room temp. Usual work-up gave a viscous compound which was purified by prep. TLC but could not be crystallized from any solvent; IR ν^{neat} cm^{-1}: 3000, 1760, 1600, 1520, 1460, 1380, 1223, 1040 and 910; MS *m/z*: 358 $[M]^+$, 306, 274 and 137 (base peak).

Gigantol tetramethyl ether (**4**). A soln of gigantol (50 mg) in dry Et_2O was treated with excess CH_2N_2 and the reaction continued overnight below 4°. Usual work-up gave a viscous product which was purified by prep. TLC and afforded a pure compound (**4**, 8 mg), mp 52° (petrol–MeOH); IR ν^{CHCl_3} cm^{-1}: 2950, 1600, 1520, 1470, 1270, 1210, 1160, 1080, 1040, 940, 820 and 770; MS *m/z*: 302 $[M]^+$, 288, 151 (base peak) and 137.

3,5,3′,6′-*Tetramethoxybibenzyl* (**6**). 3,5,3′,6′-Tetramethoxystilbene-8-carboxylic acid (**5**) and 3,5,3′,6′-tetramethoxystilbene: 3,5-dimethoxyphenylacetic acid (1 g), 3,6-dimethoxybenzaldehyde (0.83 g) and piperidine (0.25 ml) were heated on an oil bath at 160° for 20 hr. The reaction product was dissolved in CH_2Cl_2 (80 ml) and washed with 10% HCl. The organic layer was extracted with 10% NaOH soln. The alkaline layer was acidified with conc. HCl and extracted with petrol (40–60°) which on evapn afforded **5** as viscous material. This was purified by prep. TLC and identified by TLC, mass and IR ν^{neat} cm^{-1}: 3400, 2900, 1700, 1600, 1470, 1440, 1300, 1240, 1220, 1170 and 1080. **5** (1 g) on decarboxylation with Cu–bronze (1 g) and quinoline (40 ml) under heating at 260° for 4 min and 240° for 3 min under N_2 with stirring afforded a gummy mass which was diluted with Et_2O, filtered and the filtrate washed with 5% HCl and then with 5% NaOH. Evapn of solvent gave an oil (1 g) which on purification by CC gave 3,5,3′,6′-tetramethoxystilbene identified by TLC, IR ν^{neat} cm^{-1}: 2900, 1600, 1500, 1470, 1430, 1300, 1210, 1160, 1060, 980, 730 and 700; ^1H NMR: δ3.5 (6H, *s*, 2 × OMe), 3.75 (6H, *s*, 2 × OMe), 6.2–6.7 (6H, *m*, Ar–H), 7.05 (1H, *d*, J = 16 Hz, H-7), 7.37 (1H, *d*, J = 16 Hz, H-8); MS *m/z*: 300 $[M]^+$, 269 (base peak) and 238.

Hydrogenation of 3,5,3′,6′-tetramethoxystilbene with Pd–C in MeOH at room temp. afforded dihydrostilbene (**6**), which was different from the tetramethoxy derivative of the original compound (**1**).

3,5,4′,5′-*Tetramethoxystilbene*-8-*carboxylic acid* (**3**). 3,5-Dimethoxybenzaldehyde (0.83 g), 3,4-dimethoxyphenylacetic acid (1 g) and piperidine (0.25 ml) were heated on an oil bath at 160° for 20 hr. The reaction product was dissolved in CH_2Cl_2, washed with 10% HCl and extracted with 10% NaOH. The alkaline layer was acidified with conc. HCl and extracted with petrol (40–60°). Removal of solvent and crystallization of the residue from Me_2CO afforded **3** as colourless crystals (1.3 g), mp 170–172° (Me_2CO–petrol); IR ν^{KBr} cm^{-1}: 3400 (broad) 2900, 1690, 1600, 1520, 1460, 1430, 1350, 1280, 1260, 1210, 1160, 1090, 1030, 930, 850, 820 and 760; MS *m/z*: 344 $[M]^+$ and base peak, 300 and 151.

3,5,4′,5′-*Tetramethoxystilbene*. **3** (1 g), Cu–bronze (1 g) and quinoline (40 ml) were heated at 260° for 4 min and at 240° for 3 min under N_2 with stirring. The reaction product was diluted with petrol (40–60°), filtered and the filtrate washed with 5% HCl followed by 5% NaOH. Evapn gave a dark-coloured oil (1 g) which was purified by CC to afford tetramethoxystilbene (250 mg); IR ν^{neat} cm^{-1}: 2900, 1600, 1510, 1470, 1430, 1270, 1230, 1160, 1070, 1030 and 680; MS *m/z*: 300 $[M]^+$ and base peak and 166; ^1H NMR: δ3.7 (6H, *s*, 2 × OMe), 3.82 (6H, *s*, 2 × OMe), olefinic protons were observed as an AB*q* (7.1 and 6.85, J = 17 Hz) and at δ6.35–6.85 (6H, *m*, Ar-H).

3,5,4′,5′-*Tetramethoxydihydrostilbene*. On hydrogenation of 3,5,4′,5′-tetramethoxystilbene (100 mg) in the presence of Pd–C in MeOH (20 ml) at room temp. for 3 hr, the dihydro product was obtained as colourless needles, mp 55° (Me_2CO); IR ν^{KBr} cm^{-1}: 2950, 2850, 1600, 1520, 1460, 1360, 1340, 1300, 1240, 1220, 1160, 1080, 1040, 930, 880, 850, 820, 780 and 700; UV λ_{max} nm (log ε): 280 (3.58), 226 (4.17) and 208 (4.49); ^1H NMR: δ2.86 (4H, *s*, benzylic protons), 3.78 and 3.86 (each 6H, *s*, 4 × OMe), 6.34 (3H, *br s*, A-ring protons), 6.7–6.83 (3H, *m*, B-ring protons); MS *m/z*: 302 $[M]^+$ 151 (base peak) and 137.

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