Hindawi Publishing Corporation
Research Letters in Organic Chemistry
Volume 2009, Article ID 684359, 5 pages
doi:10.1155/2009/684359

Research Letter

An Efficient Preparation, Spectroscopic Properties, and Crystal Structure of 1,1-Bis(4-[2-(dimethylamino)ethoxy]phenyl)-2-(3-guaiazulenyl)ethylene

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Received 24 November 2008; Accepted 20 February 2009

Recommended by William Ogilvie

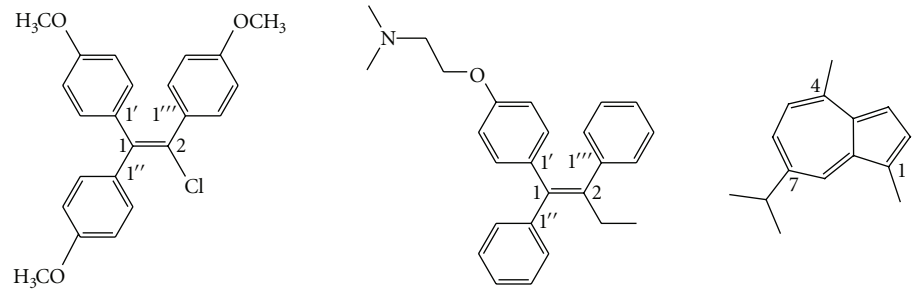
Reaction of 2-(3-guaiazulenyl)-1,1-bis(4-hydroxyphenyl)ethylene with 2-chloroethyldimethylammonium chloride in acetone in the presence of K_2CO_3 at reflux temperature for 24 hours gives a new title compound in 89% yield. Spectroscopic properties and crystal structure of the target molecule are reported.

1. Introduction

It is well known that chlorotrianisene [2-chloro-1,1,2-tris(4-methoxyphenyl)ethylene] (**1**) [1] exhibits significant estrogenic activity, while tamoxifen [(*Z*)-1-[4-(2-dimethylaminoethoxy)phenyl]-1,2-diphenyl-1-butene] (**2**) [1–4] exhibits significant antiestrogenic activity, owing to the difference between the substituents of **1** and those of **2** (see Figure 1). Furthermore, tamoxifen, which serves as a nonsteroidal antiestrogen [3], has become a widely used drug for a first-line endocrine therapy for all stages of breast cancer in pre- and postmenopausal women [5]. On the other hand, azulene, possessing a large dipole moment, is regarded as one of the representative examples of non-benzenoid aromatic hydrocarbons, and naturally occurring guaiazulene (7-isopropyl-1,4-dimethylazulene) (see Figure 1) [6] has been widely used clinically as an anti-inflammatory and antiulcer agent. However, none have really been used as other industrial materials. In relation to azulene chemistry, in 2004, we reported that the reaction of guaiazulene with 1,2-bis(4-methoxyphenyl)-1,2-ethanediol in methanol in the presence of hydrochloric acid at 60°C for 3 hours gave 2-(3-guaiazulenyl)-1,1-bis(4-methoxyphenyl)ethylene (**5**) (see Figure 2), possessing a similar structure to **1**, in 97% yield [7]. Similarly, the reaction of guaiazulene with 1,2-bis(4-hydroxyphenyl)-1,2-ethanediol under the same reaction conditions as the above afforded 2-(3-guaiazulenyl)-1,1-bis(4-hydroxyphenyl)ethylene (**3**) (see Figure 3) in 73% yield [7]. As a series of basic studies on our azulene chemistry [7–17], our interest has quite recently been focused on an efficient preparation and properties of new tamoxifen analogues with a 3-guaiazulenyl (7-isopropyl-1,4-dimethylazulen-3-yl) group, for example, the title compound **4**. We now wish to report a facile preparation as well as the spectroscopic properties and the crystal structure of the target compound **4** (see Figure 3).

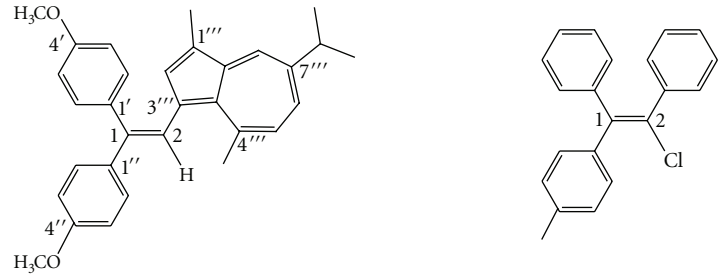
2. Results and Discussions

Compound **4** (89% yield) was prepared in acetone, according to the procedure shown in Figure 3, the molecular structure of which was established on the basis of elemental analysis and spectroscopic data [UV-vis, IR, exact FAB-MS, and ^{1}H and ^{13}C NMR including NOE and 2D NMR (i.e., H−H COSY, HMQC, and HMBC)]. ^{1}H NMR signals (δ and J values) were carefully assigned using computer-assisted simulation based on first-order analysis (^{1}H NMR signals were assigned using computer-assisted simulation (software:



1 **2** Guaiazulene

Figure 1



5 **6**

Figure 2

gNMR developed by Adept Scientific plc) on a DELL Dimension XPS T500 personal-computer with a Pentium III processor.).

The UV-vis spectrum of **4**, possessing a 1,1-bis(4-[2-(dimethylamino)ethoxy]phenyl)ethylene part, compared with that of structurally related π-electron system **5** [7] showed that the spectral pattern of **4** resembled that of **5**; however, the longest absorption wavelength of **4** (λ_{max} 632 nm, $\log\varepsilon = 2.72$) revealed a slight hyperchromic effect ($\Delta\log\varepsilon = 0.18$) in comparison with that of **5** (λ_{max} 635 nm, $\log\varepsilon = 2.54$). The IR spectrum showed specific bands based on the C−O, C−N, aromatic C=C, and C−H bonds. The protonated molecular formula $C_{37}H_{47}O_2N_2$ was determined by exact FAB-MS spectrum. The elemental analysis confirmed the molecular formula $C_{37}H_{46}O_2N_2$. The ^{1}H NMR spectrum showed signals based on a 3-guaiazulenyl group, signals based on two nonequivalent 4-[2-(dimethylamino)ethoxy]phenyl groups, and a signal based on an ethylene part (>C=CH−). The ^{13}C NMR spectrum exhibited 29 carbon signals, which could be assigned using HMQC and HMBC techniques. Thus, the elemental analysis and the spectroscopic data for **4** led to the title molecular structure.

The crystal structure of **4** was then determined by means of X-ray diffraction. Two molecules of **4** were found to exist in the unit cell of the crystal. The ORTEP drawing of **4** (one of the two molecules) with a numbering scheme is shown in Figure 4(a). The structural parameters of **4** revealed that the C1−C1′, C1−C1″, C2−C3‴, and C1=C2 bond lengths of **4** coincided with those of **5** [7]. Similarly, as in the case of **5**, the aromatic rings of the two 4′- and 4″-[2-(dimethylamino)ethoxy]phenyl and 3‴-guaiazulenyl groups of **4** twisted by 47.9°, 135.0°, and 47.4° from the plane of the >C=CH− part, owing to the influence of large steric hindrance and repulsion between the aromatic rings. The average C−C bond lengths for the seven- and five-membered rings of the 3‴-guaiazulenyl group of **4** (1.412 and 1.422 Å) coincided with those of **5** (1.405 and 1.427 Å) and the average C−C bond lengths for the benzene rings of the two 4′- and 4″-[2-(dimethylamino)ethoxy]phenyl groups of **4** (1.386 and 1.385 Å) also coincided with those of the two 4′- and 4″-methoxyphenyl groups of **5** (1.382 and 1.380 Å).

Comparing the bond lengths observed for **4** to those of **2** [4], it was found that the C1=C2 bond length of **4** coincided with that of **2** (1.34 Å) and the C1−C1′ and C1−C1″ bond lengths of **4** also coincided with those of **2** (1.50 Å each). The average C−C bond lengths observed for the 1′- and 1″-phenyl groups of **4** coincided with those of **2** (1.39 Å each), and the bond lengths observed for the two (dimethylamino)ethoxy groups of **4** also coincided with those of **2** (C4′–O:1.38, O–CH_2:1.44, CH_2–CH_2:1.51, CH_2–N:1.50, N–CH_3:1.34, and N–CH_3:1.26 Å). The (dimethylamino)ethoxy side chain of **2** is essential to the antiestrogenic action [1]. From the accurate structural parameters of **4**, a study on the antiestrogenic activity of **4**, compared with that of **2**, is noteworthy.

The crystal structure of the estrogenic drug **1** was not documented. For comparative purposes, the crystal

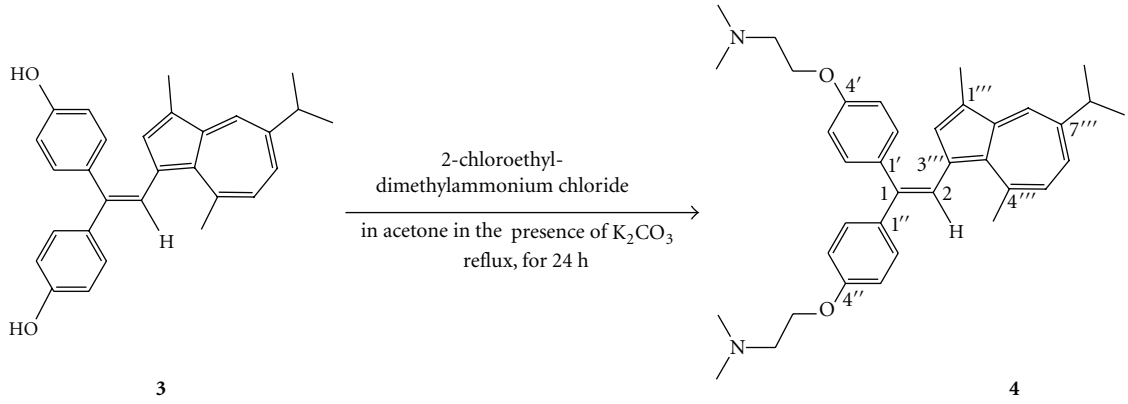


Figure 3: The reaction of **3** with 2-chloroethyldimethylammonium chloride in acetone in the presence of potassium carbonate at reflux temperature for 24 hours.

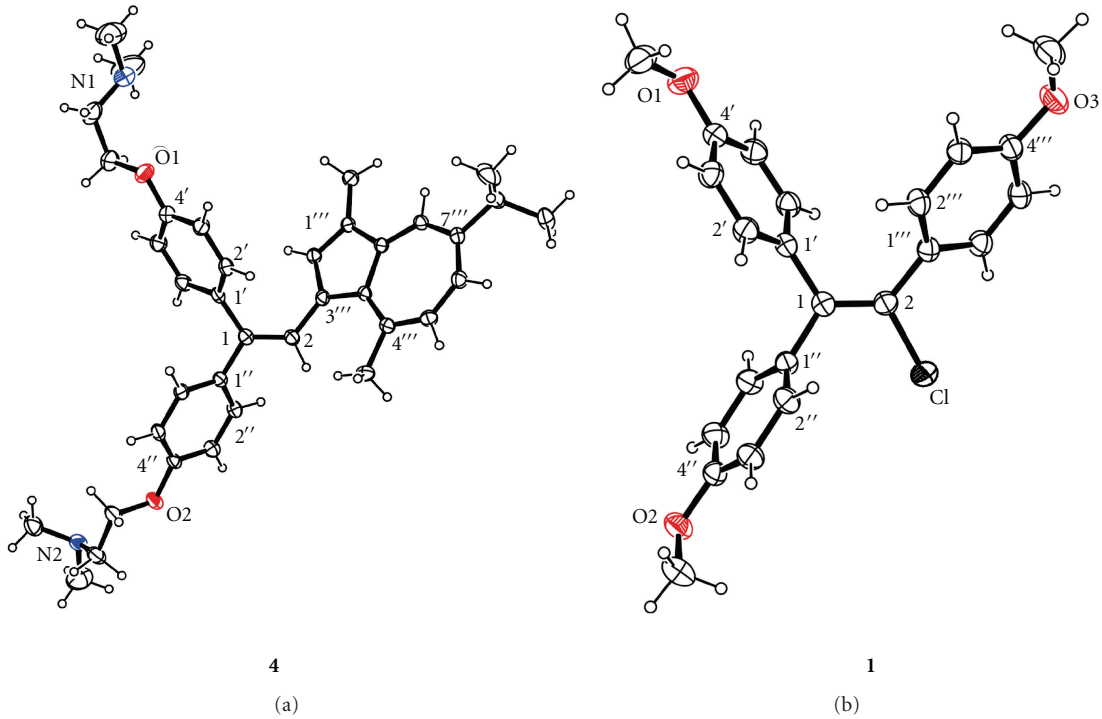


Figure 4: The ORTEP drawings with the numbering scheme (30% probability thermal ellipsoids) of **4** and **1**.

structure of **1** (Commercially available **1** was recrystallized from diethyl ether (several times) to provide stable single crystals (mp 114°C).) has been determined by means of X-ray diffraction (Crystallographic data for **1**: $C_{23}H_{21}O_3Cl$ (FW = 380.87), colorless prism (the crystal size, 0.50 × 0.40 × 0.40 mm^3), monoclinic, $C2/c$ (#15), a = 18.577(5) Å, b = 9.787(5) Å, c = 23.738(4) Å, β = 115.82(1)°, V = 3885(2) Å^3, Z = 8, D_{calcd} = 1.302 g/cm^3, μ(Mo Kα) = 2.17 cm^{-1}, scan width = (1.26 + 0.30 tan θ)°, scan mode = $\omega - 2\theta$, scan rate = 8.0°/min, measured reflections = 4882, observed reflections = 4461, No. of parameters = 244, $R1$ = 0.041, $wR2$ = 0.167, and goodness of fit indicator = 1.35. Deposition no. CCDC-252847 for compound no. 1.). The ORTEP drawing of **1** with a numbering scheme is shown in Figure 4(b). The structural parameters of **1** revealed that the C1=C2 bond length of **1** coincided with those of (*Z*)-2-chloro-1-(4-methylphenyl)-1,2-diphenylethylene (**6**) [1.340(3) Å] (see Figure 2) [18], **5** [7], and **4**. The C1−C1′, C1−C1′′, and C2−C1′′′ bond lengths of **1** also coincided with those of **4**–**6**. The benzene rings of the three 4′-, 4′′-, and 4′′′-methoxyphenyl groups of **1** twisted by 64.4°, 103.5°, and 41.3° from the plane of the >C=CCl− part, owing to the influence of large steric hindrance and repulsion between the benzene

rings. The average C−C bond lengths for the benzene rings of the 4′-, 4″-, and 4‴-methoxyphenyl groups of **1** (1.384 Å each) coincided with those of the 4′- and 4″-methoxyphenyl groups of **5** and the 4′- and 4″-[2-(dimethylamino)ethoxy]phenyl groups of **4**. The accurate crystal structure determination of **1** and **4**, along with that of **5**, is important from a viewpoint of computational study on the compounds' potential interactions with specific residues within the human estrogen receptor.

3. Experimental

Preparation of ***4***. Compound **4** was prepared according to the following procedure. To a solid of anhydrous K_2CO_3 (17 mg, 123 mmol) was added a solution of **3** (50 mg, 123 mmol) in acetone (10 mL). The mixture was stirred at 25°C for 12 hours, and then 2-chloroethyldimethylammonium chloride (36 mg, 250 mmol) was added to the mixture. The mixture was stirred at reflux temperature for 24 hours. After the reaction, distilled water was added to the mixture, and then the resulting product was extracted with diethyl ether (10 mL × 3). The extract was washed with distilled water, dried ($MgSO_4$), and evaporated in vacuo. The residue thus obtained was carefully separated by silica-gel column chromatography with methanol-dichloromethane (3:7, vol/vol) as an eluant. The crude product was recrystallized from petroleum ether to provide pure **4** (60 mg, 109 mmol, 89% yield) as stable crystals.

Compound **4**: dark-green needles [R_f = 0.10 on silica-gel TLC (solv. methanol:dichloromethane = 1:9, vol/vol)]; mp 100°C [determined by thermal analysis (TGA and DTA)]; found: C, 80.69; H, 8.41; N, 5.08%; calcd for $C_{37}H_{46}O_2N_2$: C, 80.69; H, 8.42; N, 5.09%; UV-vis λ_{max} (CH_3CN) nm (log ε), 271 (4.52), 329 (4.40), 357sh (4.30), 409 (4.27), and 632 (2.72); IR υ_{max}(KBr) cm^{-1}, 2955−2766 (C−H), 1605, 1508 (C=C), 1285 (C−N), and 1242, 1042 (C−O); exact FAB-MS (3-nitorobenzylalcohol matrix), found: *m*/*z* 551.3664; calcd for $C_{37}H_{47}O_2N_2$: $[M + H]^+$, *m*/*z* 551.3638; 500 MHz H NMR: (CD_3CN), signals based on the 3-guaiazulenyl group: δ 1.28 (6H, d, J = 7.0 Hz, (CH_3)$_2$CH-7‴), 2.38 (3H, s, CH_3-1‴), 2.94 (3H, s, CH_3-4‴), 2.97 (1H, sept, J = 7.0 Hz, $(CH_3)_2$C*H*-7‴), 6.81 (1H, d, J = 10.5 Hz, H-5‴), 6.89 (1H, s, H-2‴), 7.24 (1H, dd, J = 10.5, 2.5 Hz, H-6‴), and 7.92 (1H, d, J = 2.5 Hz, H-8‴); signals based on the (*Z*)-4-[2-(dimethylamino)ethoxy]phenyl group: δ 2.22 (6H, s, $(CH_3)_2N$), 2.60 (2H, t, J = 6.0 Hz, CH_2–N), 3.98 (2H, t, J = 6.0 Hz, CH_2–O), 6.74 (2H, dd, J = 8.5, 2.5 Hz, H-3′,5′), and 7.04 (2H, dd, J = 8.5, 2.5, Hz H-2′,6′); and signals of based on the (*E*)-4-[2-(dimethylamino)ethoxy]phenyl group: δ 2.24 (6H, s, $(CH_3)_2N$), 2.63 (2H, t, J = 6.0 Hz, CH_2–N), 4.03 (2H, t, J = 6.0 Hz, CH_2–O), 6.84 (2H, dd, J = 8.5, 2.5 Hz, H-3″,5″), and 7.22 (2H, dd, J = 8.5, 2.5 Hz, H-2″,6″); and a signal based on the >C=CH− part: δ7.52 (1H, s, H-2); 125 MHz ^{13}C NMR (CD_3CN), δ 159.3 (C-4″), 158.9 (C-4′), 147.1 (C-4‴), 141.5 (C-7‴), 140.2 (C-2‴), 139.5 (C-8a‴), 138.9 (C-1″), 137.5 (C-1′), 135.7 (C-6‴), 135.4 (C-3a‴), 134.4 (C-1), 134.1 (C-8‴), 133.4 (C-2′,6′), 129.6 (C-2″,6″), 127.2 (C-5‴), 127.1 (C-3‴), 125.8 (C-2), 125.4 (C-1‴), 115.1 (C-3″,5″), 115.0 (C-3′,5′), 67.2 (CH_2–O-4″), 67.1 (CH_2–O-4′), 59.0 (CH_2–N″), 58.9 (CH_2–N′), 46.1 (Me_2N × 2), 38.4 ((CH_3)$_2$ *C*H-7‴), 27.9 (Me-4‴), 24.6 ((*C*H_3)$_2$CH-7‴), and 12.9 (Me-1‴).

Crystallographic Data for ***4***. $C_{37}H_{46}O_2N_2$ (FW = 550.78), dark-green prism (the crystal size, 0.50 × 0.20 × 0.50 mm^3), triclinic, *P*-1 (#2), a = 16.904(3) Å, b = 20.322(4) Å, c = 10.372(1) Å, α = 103.00(1)°, β = 96.90(1)°, γ = 108.53(1)°, V = 3220.4(9) $Å^3$, Z = 4, D_{calcd} = 1.136 g/cm^3, μ(Mo Kα) = 0.69 cm^{-1}, scan width = (1.26 + 0.30 tan θ)°, scan mode = ω − 2θ, scan rate = 16.0°/min, measured reflections = 15303, observed reflections = 11731, no. of parameters = 739, $R1$ = 0.063, $wR2$ = 0.177, and goodness of fit indicator = 1.48. Crystallographic data of **4** have been deposited with Cambridge Crystallographic Data Center, Deposition no. CCDC-635049 for compound no. 4. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

4. Conclusions

We have reported the following three interesting points in this paper, namely, (i) the reaction of 2-(3-guaiazulenyl)-1,1-bis(4-hydroxyphenyl)ethylene (**3**) with 2-chloroethyldimethylammonium chloride in acetone in the presence of K_2CO_3 at reflux temperature for 24 hours gave a new title compound **4** in 89% yield; (ii) the elemental analysis and the spectroscopic data for **4** led to the target molecular structure; (iii) the crystal structure of **4** compared with those of structurally related compounds 2-(3-guaiazulenyl)-1,1-bis(4-methoxyphenyl)ethylene (**5**), tamoxifen (**2**), and chlorotrianisene (**1**) was documented. From the accurate structural parameters of **4**, a comparative study on the antiestrogenic activity of **4** with that of **2** is noteworthy.

Acknowledgment

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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