(−)-(1*S*,4*R*,5*R*)-Guaia-6,9-diene from Geranium Bourbon

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A sesquiterpene from Geranium Bourbon has been found to be guaia-6,9-diene in accordance with the report of Pesnelle *et al.*; it had previously been erroneously assigned as 3,7-diene by Herout *et al.* The details of the evidence on the structure, along with its stereochemistry, are described.

In the course of the study of Geranium oil[1] (Geranium Bourbon), we have isolated guaia-6,9-diene (I), which was identical with the compound previously reported[2] as "guaia-3,7-diene." This had been pointed out by Pesnelle *et al.*[3] In this paper, we wish to report the evidence for the correction of the structure, together with its stereochemistry, since we have not yet seen any detailed publication relating to the revised structure, I.

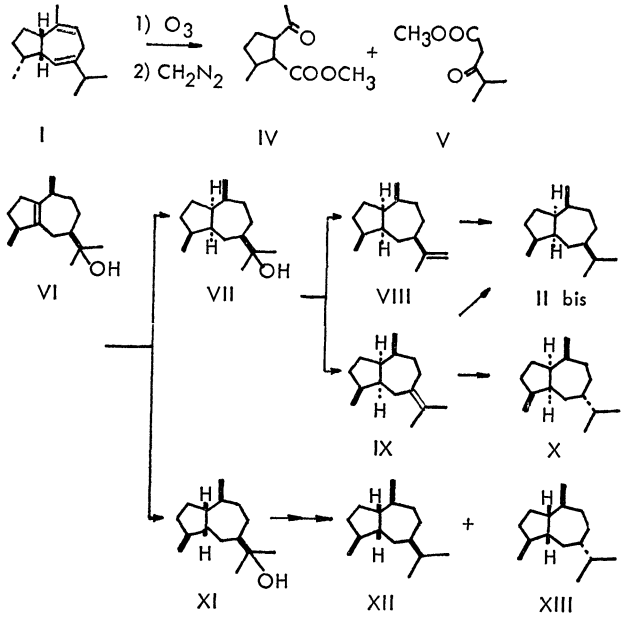
Commercial Geranium oil* was subjected to separation by column chromatography and preparative glc to obtain Compound I. Compound I, $[\alpha]_D$ −50.9°, was a colorless oil which exhibited its molecular ion peak at *m/e* 204 ($C_{15}H_{24}$) in its mass spectrum. Its IR spectrum revealed the absorptions of the isolated double bond and the trisubstituted ethylenes. In addition, no UV absorption maxima were observed in the region of 215—280 nm. The PMR spectrum exhibited two doublets, at δ 0.93 (6H, J=6.0) and at 1.02 (3H, J=6.0), which were assignable to an isopropyl and a secondary methyl group respectively; a broad singlet at 1.53 (3H) and a complex signal at around 5.35 (1H), accounting for the CH_3C=CH− system, as was confirmed by spin-spin decoupling, and a broad signal at around 5.16 (1H) coupled with a broad signal around 2.86 (1H), which was attributable to a vinyl proton adjacent to a methine.

The catalytic hydrogenation of I over PtO_2 in acetic acid afforded a mixture of two tetrahydro derivatives in the ratio of three to one. The IR spectrum of the major product (II), $[\alpha]_D$ +40.6°; M^+, *m/e* 208 ($C_{15}H_{28}$), was identical with that of Šorm's "guaiane."[4] On the other hand, in methanol over the same catalyst, I was reduced to a complex mixture of the dihydro isomers, accompanied by a small amount of II. The examination of the PMR spectrum of the main dihydro compound (III), M^+, *m/e* 206 ($C_{15}H_{26}$), revealed that CH_3C=CH had been reduced and that another trisubstituted double bond remained.

I was ozonized in ethyl acetate at −40 °C, followed by oxidative degradation. Its acidic fraction was treated with diazomethane-etherate. The methyl esters thus obtained were determined to be (IV) and (V) by an examination of their physical data. Compound IV exhibited the molecular ion peak at *m/e* 184 ($C_{10}H_{16}O_3$) in its mass spectrum. Its IR spectrum revealed the absorptions arising from nonconjugated C=O vibrations and the C–O bands of the methyl ester. The PMR spectrum exhibited a doublet at δ 0.9 (3H, J=6.5), indicating a secondary methyl; a singlet at 2.19 (3H) corresponding to $-COC\underline{H}_3$, and a signal at 3.69 (3H) which was assigned to $-COOC\underline{H}_3$. From all the above data, it seems that IV should contain a cyclopentane skeleton. Compound V, M^+, *m/e* 144 ($C_7H_{12}O_3$), obtained in a small amount, exhibited the absorption bands of carbonyl and methyl ester in its IR spectrum. Its PMR spectrum exhibited a doublet at δ 1.18 (6H, J=6.0), accounting for an isopropyl group, and a singlet at 3.67 (3H) which was assigned to a methyl ester group. Therefore, V should be methyl 4-methyl-3-oxopentanoate.

Now, in order to obtain the physical data of "guaiane" with definitely established stereochemistry, it was prepared from (−)-guaiol[5] (VI) *via* crystalline (−)-dihydroguaiol[6] (VII), with its known stereochemistry. VII was dehydrated by thionyl chloride–pyridine to afford two hydrocarbons, with isopropenyl (VIII) and isopropylidene (IX) groups respectively, in the ratio of three to two. The major hydrocarbon, VIII, was reduced to a saturated hydrocarbon (II *bis*), $[\alpha]_D$ −58°, which was found to be identical with "guaiane"[4] by a comparison of their IR spectra.

Hydrogenation of IX afforded a mixture of (II *bis*) and its isomer at C_7 (X) in the same ratio. On the other hand, oily (+)-dihydroguaiol[7] (XI), with a known stereochemistry, prepared from (−)-guaiol, afforded saturated (+)-hydrocarbon isomers (XII) and (XIII) in a similar manner. The IR spectra of X, XII, and XIII differed from that of (II *bis*), though



* Commercial Geranium oil was produced by Soda Aromatic Co., Ltd., in the Shodo island in 1974.

they exhibited quite similar mass spectra. Consequently, the structure including the absolute configuration of I was concluded to be (−)-(1*S*,4*R*,5*R*)-guaia-6,9-diene.

Experimental

The IR spectra were measured using a Hitachi EPI-G2 spectrometer. The UV spectra were taken on a Jasco Model ORD/UV-5 spectrometer. Measurements of optical rotation were carried out with a Perkin-Elmer 141 polarimeter. The mass spectra were measured using a Hitachi RMU-6 spectrometer with a indirect-inlet system operating at 80 eV. The PMR spectra were taken by a Hitachi R-20 B spectrometer at 60 MHz in CCl_4. The chemical shifts were expressed in δ downfield from TMS as an internal standard and coupling constants in Hz. The preparative glc conditions, using a model 920 Varian Aerograph fitted with a thermal-conductivity detector, were as follows: a 10-ft×3/8 in. aluminum column containing 20% Carbowax 20M on 60—80 mesh Diasolid-L. Nitrogen was used as the carrier gas, and the column temperature was set at 170—200 °C. All the melting points are uncorrected.

Isolation of I. Commercial geranium oil* (400 g) was successively chromatographed on SiO_2 and $AgNO_3$-SiO_2 (15%) columns and then eluted with *n*-hexane. On further purification by preparative glc, Compound (I) (400 mg) was obtained. Compound I was a colorless oil; $[\alpha]_D$ −50.9° (*c* 1.49, EtOH); IR (liq.) 1658 (C=C), 1360, 1375 (-CH(CH$_3$)-CH$_3$), 854, 828 cm^{-1} (-C=C-); PMR (CCl_4) δ 0.93 (6H, d, J=6.0, an isopropyl group), 1.02 (3H, d, J=6.0: 4-CH$_3$), 1.53 (3H, br. s) and 5.35 (1H, m): a system of CH$_3$C=CH, 2.23 (1H, m) and 2.98 (1H, br. signal): protons at 8-C, 2.86 (1H, br. signal) coupled with 5.16 (1H, br. signal): protons at 5-C and 6-C, and 1.0—2.4 (7H, complex signals: methines and methylenes); mass spectrum *m/e* 204(38%, M$^+$, $C_{15}H_{24}$), 105(100%), 119(62%), and 161(52%).

Hydrogenation of I in Acetic Acid. I was reduced catalytically (PtO_2) in acetic acid at room temperature. After the filtration of the catalyst, the filtrate was diluted with water and extracted with ether. The evaporation of the ether gave a residue, which was purified on preparative glc (CW-20M, at 180 °C) to afford two compounds, (II) and (II′), in the ratio of three to one. The major product, II, was a colorless oil; $[\alpha]_D$ +40.6° (*c* 1.45, EtOH); δ 0.82 (6H, d, J=6.0), 0.83 (3H, d, J=6.0), 0.90 (3H, d, J=6.0), 1.0—2.3 (16H, complex signals); *m/e* 208 (9%, M$^+$, $C_{15}H_{28}$), 109(100%), 95(70%), 81(60%); the IR spectrum agreed with that of "guaiane."[4] The minor product, II′, was a colorless oil; δ 0.85 (6H, d, J=6.0), 0.88 (3H, d, J=6.0), 0.94 (3H, d, J=6.0), and 1.0—2.2 (16H, complex signals). Its IR spectrum was identical with that of the (X) prepared from guaiol (VI).

Hydrogenation of I in Methanol. A solution of I in methanol was hydrogenated in the presence of PtO_2 at room temperature. The filtration of the catalyst and the evaporation of the solvent left a residue, which was purified by preparative glc (CW-20M, at 180 °C) to afford (III), accompanied by a small amount of II. III was a colorless oil; ν_{max} 1655 cm^{-1} (C=C); δ 0.86 (3H, d, J=6.0), 0.95 (6H, d, J=6.0), 1.02 (3H, d, J=6.0), 1.1—2.5 (13H, complex signals), and 5.13 (1H, br. d, J=3.5); *m/e* 206 (5%, M$^+$, $C_{15}H_{26}$), 107(100%), 163(76%), 81(76%), 93(50%), and 121(22%).

Ozonolysis of I. A solution of I in ethyl acetate was ozonized at −40 °C. When the reaction was completed, hydrogen peroxide (30%) and a potassium bicarbonate solution (5%) were added to the ozonide for degradation. The solution was then allowed to stand overnight at 0 °C. The organic layer was further treated as usual to obtain acidic compounds. The acids thus obtained were treated with diazomethane-etherate to give the methyl esters, (IV) and (V). Compound IV was a colorless oil; ν_{max} 1710, 1725 (sh) (C=O), 1200, 1170 cm^{-1} (C-O); δ 0.9 (3H, d, J=6.5), 2.19 (3H, s), 3.69 (3H, s), 3.0—3.5 (2H, m), and 1.3—2.5 (5H, m); *m/e* 184 (3%, M$^+$, $C_{10}H_{16}O_3$), 81 (100%), 43(96%).

Compound V was obtained in a very small amount as a colorless oil; ν_{max} 1730 (C=O), 1200, 1170 cm^{-1} (C-O); δ 1.18 (6H, d, J=6.0), 3.67 (3H, s), 2.0—3.5 (3H, complex signals); *m/e* 144 (4%, M$^+$, $C_7H_{12}O_3$), 143(21%), 55(100%).

Hydrogenation of Guaiol VI.[8] A solution of 1.86 g of (−)-guaiol (VI)** in 30 ml of ethanol and 0.69 g of a Raney nickel catalyst was shaken for 20 hr at 100 °C under a hydrogen pressure of 100 atm. The filtration of the catalyst and the evaporation of the solvent yielded a mixture of dihydroguaiols. They were both diastereomers at the ring juncture and were revealed on the gas chromatogram in the ratio of 2 : 3. Separation by preparative glc (CW-20M, at 200 °C) led to the dihydroguaiol (VII)[6] (major) and (XI),[7] with known stereochemistries. VII was a colorless needle; mp 76—76.5 °C; $[\alpha]_D$ −44.8° (*c* 1.06, acetone); ν_{max} 3325 (-OH), 1166, 1134 cm^{-1} (C-O); δ 0.86 (3H, d, J=6.0), 0.95 (3H, d, J=6.0), 1.07 (3H, s), 1.10 (3H, s), and 1.2—2.4 (16H, m, including -OH); *m/e* 224 (M$^+$, trace, $C_{15}H_{28}O$), 206 (2%, M$^+$−18), 164(10%), 81(19%), and 59(100%). XI was a colorless oil; $[\alpha]_D$ +73.5° (*c* 0.93, acetone); ν_{max} 3380 (-OH), 1158, 1120 cm^{-1} (C-O); δ 0.95 (6H, br. d, J=9.5), 1.10 (6H, s), 1.2—2.0 (15H, complex signals), and 2.51 (1H, s, -OH); *m/e* 224 (M$^+$, trace, $C_{15}H_{28}O$), 206 (3%, M$^+$−18), 163(7%), 81(22%), and 59 (100%).

Dehydration of (−)-Dihydroguaiol VII with Thionyl Chloride-Pyridine. Thionyl chloride (1.38 equiv) was stirred, drop by drop into a solution of (−)-dihydroguaiol VII in pyridine at 5—10 °C. After observation by tlc of the completion of the reaction, the mixture was poured over ice and then extracted with pet. ether. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a brown oil, which was purified on preparative glc to afford (VIII) and (IX). Compound VIII was a colorless oil; $[\alpha]_D$ −47.0° (*c* 0.57, EtOH); ν_{max} 3070, 888 cm^{-1} (=CH$_2$); *m/e* 206 (M$^+$, 14%, $C_{15}H_{26}$), 163(52%), 81(100%). Compound IX was a colorless oil; *m/e* 206 (M$^+$, 12%, $C_{15}H_{26}$), 163(44%), 81(100%).

Dehydration of (+)-Dihydroguaiol XI with Thionyl Chloride-Pyridine. (+)-Dihydroguaiol XI was worked up with thionyl chloride (1.38 equiv.) and pyridine as has been described above, affording two products, (VIII′) and (IX′). Compound VIII′ was a colorless oil; ν_{max} 3070, 888 cm^{-1} (=CH$_2$); *m/e* 206 (M$^+$, 25%, $C_{15}H_{26}$), 163(60%), 81(100%). Compound IX′ was a colorless oil; *m/e* 206 (M$^+$, 22%, $C_{15}H_{26}$), 163(48%), and 81(100%).

Hydrogenation of VIII in Ethanol. VIII in ethanol was hydrogenated over PtO_2 at room temperature. After the completion of the reaction, the catalyst and the solvent were removed. (II *bis*) was obtained as the sole product and identified with II by a comparison of their IR spectra;

** (−)-Guaiol was kindly presented by Inabata Koryo Co., Ltd.

a colorless oil; $[\alpha]_D$ −58.1° (*c* 0.74, EtOH); δ 0.82 (6H, d, J=6.0), 0.83 (3H, d, J=6.0), 0.90 (3H, d, J=6.0), and 1.0—2.3 (16H, complex signals); *m/e* 208 (M^+, 12%, $C_{15}H_{28}$), 109 (100%).

Hydrogenation of IX in Acetic Acid. IX was hydrogenated in acetic acid over PtO_2 at room temperature. After the filtration of the catalyst, water was added to the reaction mixture, extracting with *n*-pentane. The evaporation of the solvent left a mixture of (II *bis*) and X, in the ratio of 1 : 1; those substances were separated by preparative glc (CW-20M, at 170 °C). Compound X was a colorless oil; $[\alpha]_D \fallingdotseq 0°$ (*c* 0.13, EtOH); δ 0.85 (6H, d, J=6.0) 0.88 (3H, d, J=6.0), 0.94 (3H, d, J=6.0), 1.0—2.2 (16H, complex signals); *m/e* 208 (M^+, 14%, $C_{15}H_{28}$), 109 (100%).

Hydrogenation of VIII′ in Ethanol and IX′ in Acetic Acid. VIII′ was hydrogenated over the PtO_2 catalyst in ethanol in a way similar to that as in the case of VIII to afford a colorless oil (XII); $[\alpha]_D$ +58.1° (*c* 0.91, EtOH); δ 0.86 (6H, d, J=6.0), 0.92 (3H, d, J=6.0), 0.95 (3H, d, J=6.0), 1.1—2.0 (16H, complex signals); *m/e* 208 (M^+, 10%, $C_{15}H_{28}$), 109(100%). IX′ was reduced over the PtO_2 catalyst in acetic acid in a way similar to that in the case of IX to give XII and (XIII) on purification by preparative glc (CW-20M, at 180 °C). Compound XIII was a colorless oil; $[\alpha]_D$ +34.7° (*c* 0.23, EtOH); δ 0.84 (6H, d, J=6.0), 0.92 (3H, d, J=6.0), 0.97 (3H, d, J=6.0), 1.1—2.0 (16H, complex signals); *m/e* 208 (M^+, 12%, $C_{15}H_{28}$), 109(100%).

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