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Structures of Suaveolic Acid and Suaveolol[1]

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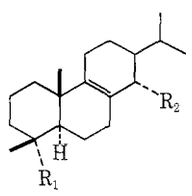
Several species of *Hyptis* have been found to possess significant pharmacological properties.[3] An investigation of *Hyptis suaveolens* (L) Point (Labiatae), a species widespread throughout tropical America[4] and reputed to possess medicinal properties,[5] has led to the isolation of two novel diterpenes for which the names suaveolic acid and suaveolol are proposed.

Suaveolic acid (**1**) was obtained by extraction of the dried leaves and stems of *H. suaveolens* with either acetone or methanol, and its infrared spectrum revealed the presence of both COOH and OH groups. Although its nmr spectrum showed that no vinyl protons were present, a strong absorption in the Raman spectrum of **1** at 1650 cm^{-1} indicated that the structure contained a C=C bond. The nmr spectrum, in addition to confirming the presence of two exchangeable hydrogens, indicated that suaveolic acid contained an isopropyl group and two quaternary methyl substituents. Furthermore, a one-proton signal at δ 3.81 (d, J = 7 Hz) suggested that the alcohol function was secondary.



1, R_1 = CO_2H; R_2 = OH
2, R_1 = CO_2Me; R_2 = OH
3, R_1 = CO_2Me; R_2 = OAc
4, R_1 = CO_2Me; R_2 = =O
5, R_1 = CH_2OH; R_2 = OH
6, R_1 = CH_2OAc; R_2 = OAc

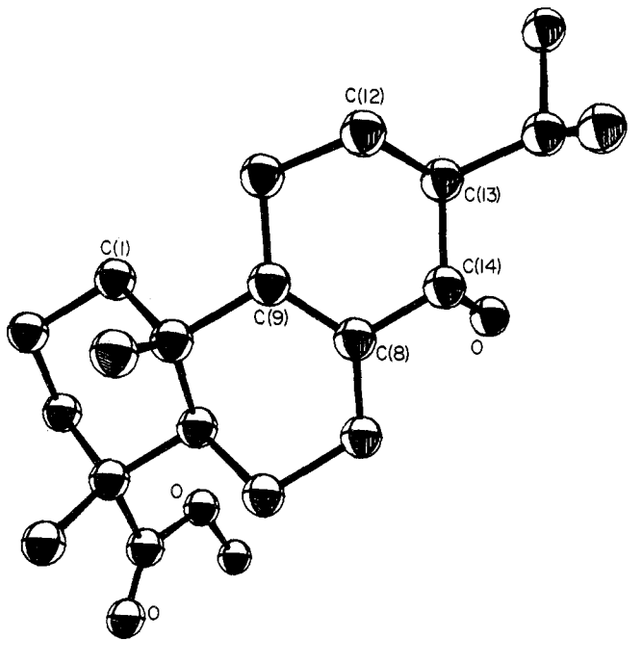


Figure 1. A perspective drawing of methyl suaveolate (relative configuration). All atoms are drawn with the same radius and hydrogens are omitted for clarity.

Treatment of **1** with diazomethane gave methyl suaveolate (**2**), which, upon exposure to acetic anhydride in pyridine, produced a secondary acetate (**3**) showing a one-proton doublet (J = 7 Hz) at δ 5.33. The low-field position of this signal[6] suggested that the CHOH proton in suaveolic acid might be allylic, and this was confirmed by oxidation of methyl suaveolate with Jones reagent to an α,β-unsaturated ketone **4**.[7] The chemical evidence implies a structure for **1** based upon 8-abieten-18-oic acid,[8] with placement of the OH at C-14 rather than C-11 dictated by the fact that in **1**, **2**, and **3** the CHOH proton appears as a well-defined doublet.

Suaveolol (**5**) was isolated after chromatography of the *Hyptis* extract on alumina and also by direct crystallization from the extract. It showed no carbonyl absorption, but its nmr spectrum revealed both primary and secondary alcohol functions. As in the case of **1**, the Raman spectrum (1670 cm^{-1}) of **5** clearly indicated the presence of a tetrasubstituted double bond. Treatment of suaveolol with acetic anhydride in pyridine gave a gummy diacetate **6**. The relationship between suaveolic acid and suaveolol was established by reduction of methyl suaveolate with lithium aluminum hydride, which gave **5** in high yield.

In order to confirm the structural hypothesis and to establish the relative stereochemistry of **1** and **5**, an X-ray determination of the structure of methyl suaveolate was undertaken. A computer-generated drawing of the final X-ray model is shown in Figure 1.[9] A double bond is clearly indicated between C-8 and C-9 in **2**. The OH group at C-14 is in the α configuration and hydrogen bonded to the methanol of crystallization, with an O–O distance of 2.65 Å. The isopropyl group at C-13 is in the β configuration.

Although oxygen substitution at C-12 of the abietane skeleton is commonplace,[10] oxygenation at C-14 is rare.[11] The structures of suaveolic acid (**1**) and suaveolol (**5**) are also unusual in that the oxygenated C ring is nonaromatic.

Experimental Section

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Ultravio-

let and infrared spectra were measured on Perkin-Elmer 402 and 257 spectrophotometers, respectively. Raman spectra were obtained on a Spex 1401 double-monochromator spectrophotometer with a Spectrophysics 164 argon-krypton double-headed laser beam. Mass spectra were measured (at 70 eV, direct inlet) on CEC 21-110 and Varian (MAG) CH-5 spectrometers. Nmr spectra were measured on either a Varian T-60 or HA-100 instrument, with tetramethylsilane as internal standard. Thin layer chromatograms were run on silica gel plates and were developed with either phosphomolybdic acid (10% in ethanol) or ceric sulfate (10% in 10% sulfuric acid).

Isolation of Suaveolic Acid (1). One kilogram of the dried leaves and terminal stems of *Hyptis suaveolens* (L.) Point (collected at Wallerfield, Trinidad) was steeped in 10 l. of methanol for 60 hr, and the mixture was decanted through a filter funnel. The mixture was concentrated to 1.2 l., stirred twice with 30 g of decolorizing charcoal (3 hr each time), filtered, and evaporated to give 29.4 g of a light brown gum. This material was dissolved in 50 ml of methanol and 750 ml of methylene chloride, followed by 750 ml of 5% sodium hydroxide. The aqueous phase was separated, acidified with ice-cold sulfuric acid (5%) and extracted with 1 l. of ethyl acetate. The extract was washed with saturated brine, dried (Na_2SO_4), and evaporated to give 10.3 g of a semisolid. Repeated crystallization from 90% aqueous methanol gave 1.16 g of suaveolic acid: mp 198–201° dec; $[\alpha]^{25}D$ +68.2° (*c* 1.18, $CHCl_3$); ir (Nujol) 3330, 2640, 1695, 1380, 1270, 1050 and 945 cm^{-1}; Raman (neat) 1650 and 645 cm^{-1}; nmr ($CDCl_3$) δ 0.76 (3 H, d, J = 7 Hz), 0.88 (3 H, d, J = 7), 0.96 (3 H, s), 1.16 (3 H, s), 3.81 (1 H, d, J = 7 Hz), and 6.16 (2 H, broad s, disappears on addition of D_2O); mass spectrum m/e 320.2365 (M^-).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.17. Found: C, 75.06; H, 10.37.

Isolation of Suaveolol (5). One kilogram of the dried leaves of *H. suaveolens* was extracted with 10 l. of acetone as previously described. The residue (33.2 g), which was obtained after treatment with decolorizing charcoal, was stirred with 1 l. of hexane for 3 hr and filtered. The filtrate was evaporated and the residue was dissolved in 50 ml of benzene and left at room temperature for 2 days. The deposited solid was collected by filtration, giving 364 mg of crude suaveolol (**5**), mp 182–184°. Repeated crystallizations from methylene chloride–hexane gave an analytical sample as colorless prisms: mp 186–187°; $[\alpha]^{25}D$ +81.3° (*c* 1.02, $CHCl_3$); ir (Nujol) 3240, 1660, 1050, 970, 872 and 720 cm^{-1}; Raman (neat) 1670 cm^{-1}; nmr (10% DMSO-d_6 in $CDCl_3$) δ 0.73 (3 H, s), 0.81 (3 H, d, J = 7 Hz) 0.94 (3 H, d, J = 7 Hz), 1.00 (3 H, s), 2.90 (1 H, d, J = 11 Hz), 3.49 (1 H, d, J = 11 Hz), 3.76 (1 H, d, J = 7 Hz), and 3.05 (2 H, broad, exchanges with D_2O); mass spectrum m/e 306 (M^+).

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.50, H, 11.09.

After the first crop of suaveolol was removed the mother liquor was chromatographed on 1 kg of neutral alumina (Woelm grade II) with increasing percentages of ethyl acetate in benzene as eluent. This gave a further 304 mg of suaveolol (eluted with 70–90% ethyl acetate).

Methyl Suaveolate (2). A solution of 160 mg (0.5 mmol) of suaveolic acid in 10 ml of methylene chloride was esterified with an excess of ethereal diazomethane. Removal of the solvents and crystallization of the residue from 95% aqueous methanol at 0° gave 146 mg of **2** as colorless needles: mp 102–103° (after drying *in vacuo* at 40° overnight); $[\alpha]^{25}D$ +66.7° (*c* 1.01, $CHCl_3$); ir ($CHCl_3$) 3580, 3400–3500, 1712, 1430, 1380, 1312, 1250, 1160, 1110, 1035, 965, and 940 cm^{-1}; Raman (neat) 1650 and 645 cm^{-1}; nmr ($CDCl_3$) δ 0.81 (3 H, d, J = 7 Hz), 0.91 (3 H, d, J = 7 Hz), 1.01 (3 H, s), 1.15 (3 H, s), 3.66 (3 H, s) and 3.83 (1 H, d, J = 7 Hz); mass spectrum m/e 334 (M^-).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.38; H, 10.39.

Acetylation of Methyl Suaveolate. A solution of 66.8 mg (0.2 mmol) of **2** in 1.0 ml of acetic anhydride and 0.2 ml of pyridine was left at room temperature overnight. The mixture was diluted with 25 ml of water and extracted with 30 ml of ether. The extract was washed, dried (Na_2SO_4), and evaporated to give a gum, which crystallized from 90% aqueous methanol at 0° to give 51 mg of **3** as colorless prisms: mp 132–133°; $[\alpha]^{25}D$ −44.5° (*c* 1.00, $CHCl_3$); ir ($CHCl_3$) 1730, 1715, 1365 and 1245 cm^{-1}; Raman (neat) 1655 and 645 cm^{-1}; nmr ($CDCl_3$) δ 0.76 (3 H, d, J = 7 Hz), 0.90 (3 H, d, J = 7 Hz), 0.98 (3 H, s), 1.16 (3 H, s), 2.05 (3 H, s), 3.63 (3 H, s), and 5.33 (1 H, d, J = 7 Hz); mass spectrum m/e 376 (M^+).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.67; H, 9.64. Found: C, 73.49; H, 9.57.

Oxidation of Methyl Suaveolate. A stirred solution of 33.4 mg (0.1 mmol) of **2** in 3 ml of acetone was cooled to 5° and treated with 0.10 ml of Jones reagent. The mixture was stirred for 3 min, diluted with 40 ml of water, and extracted with 50 ml of ethyl acetate. The extract was washed four times with 50 ml of saturated brine, dried (Na_2SO_4), and evaporated to give a gum, which was purified by thick layer chromatography (PF_{254} silica gel, 10% ethyl acetate in benzene). Collection of the main band (which was visible under short-wavelength uv light) gave **4** as a semisolid, which resisted crystallization: $[\alpha]^{25}D$ +115.2° (*c* 1.01, $CHCl_3$); uv (methanol) λ_{max} 246 nm (ϵ 12,700); ir ($CHCl_3$) 1715, 1655, 1615, 1430, 1250, 1110, and 895 cm^{-1}; nmr ($CDCl_3$) δ 0.78 (3 H, d, J = 7 Hz), 0.95 (3 H, d, J = 7 Hz), 1.10 (3 H, s), 1.21 (3 H, s), and 3.70 (3 H, s); mass spectrum m/e 332.2355 (M^+).

Acetylation of Suaveolol. A 30.6-mg (0.1 mmol) sample of suaveolol (**5**) was acetylated under conditions described for the preparation of **3**. The acetate (**6**), although homogeneous by tlc (silica gel, 15% ethyl acetate in benzene, R_f 0.57), was obtained as an oil which failed to crystallize: $[\alpha]^{25}D$ −39.1° (*c* 1.1, $CHCl_3$); ir ($CHCl_3$) 1725, 1370, 1250, 1025, and 950 cm^{-1}; nmr ($CDCl_3$) δ 0.81 (3 H, d, J = 7 Hz), 0.90 (3 H, s), 0.94 (3 H, d, J = 7 Hz), 1.02 (3 H, s), 2.06 (6 H, s), 3.68 (1 H, d, J = 7 Hz), 3.88 (1 H, d, J = 7 Hz), and 5.34 (1 H, d, J = 7 Hz); mass spectrum m/e 330 ($M^+ - C_2H_4O_2$), the molecular ion peak was not observed.

Conversion of Methyl Suaveolate (2) into Suaveolol (5). A solution of 66.8 mg (0.2 mmol) of **2** in 3.5 ml of ether was added to a stirred mixture of 100 mg of lithium aluminum hydride in 7.5 ml of ether. The mixture was heated under reflux for 4.5 hr, cooled to 5°, and cautiously treated with 10 ml of ethyl acetate followed by 5 ml of 2 *N* sulfuric acid. The mixture was extracted with 25 ml of ethyl acetate, washed with brine, dried (Na_2SO_4), and evaporated to give a colorless solid. Repeated crystallizations, first from methylene chloride–hexane and then from ethyl acetate, gave **5** mp 185–186°. A mixture melting point with authentic suaveolol was not depressed; a mixed chromatogram (tlc, silica gel, 70% ethyl acetate in benzene) showed no separation, and both samples had identical spectral properties (ir, nmr, and mass spectra).

X-Ray Structure Determination of Methyl Suaveolate (2). Methyl suaveolate (**2**) crystallizes in the uniquely determined space group $P2_12_12_1$ with a = 7.465 (4), b = 24.89 (1), and c = 11.773 (6) Å. A density measurement indicated that the asymmetric unit was one molecule of methyl suaveolate and one methanol of crystallization. A total of 1331 independent diffraction maxima with $\theta \leq 50°$ were measured on a computer-controlled, four-circle diffractometer using Ni-filtered Cu Kα radiation (1.5418 Å). There was a 30% decline in periodically monitored reflection, indicating substantial crystal decomposition. After correction for Lorentz, polarization, and decay effects, 1153 reflections were judged observed, $|F_o| \geq 3\sigma(|F_o|)$. Normalized structure factors were computed and phases were assigned to the largest 184 by an iterative application of a weighted tangent formula.[12] Careful investigation of the resulting E-synthesis revealed all nonhydrogen atoms in methyl suaveolate. Full-matrix, least-squares refinements smoothly converged to a conventional discrepancy index of 0.085.[13]

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Registry No.—**1**, 51593-38-5; **2**, 51635-64-4; **3**, 51593-39-6; **4**, 51593-40-9; **5**, 51593-41-0; **6**, 51593-42-1.

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On the Nuclear Bromination in the Kojic Acid Series

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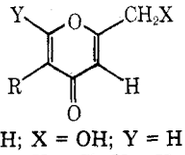
We recently corrected previous reports on the Friedel–Crafts acylation and aroylation reactions of kojic acid (1),[1] and as we contemplate no further work in the area we now wish to describe some observations concerning the ring bromination in this series.



1, R = OH; X = OH; Y = H
2, R = OH; X = Cl; Y = H
3, R = OH; X = Cl; Y = Br
4, R = X = OH; Y = Br
5, R = X = $OCOCH_3$; Y = H
6, R = X = $OCOC_6H_5$; Y = H
7, R = X = $OCOCH_3$; Y = Br
8, R = X = $OCOC_6H_5$; Y = Br
9, R = OH; X = $OCOCH_3$; Y = H
10, R = OH; X = $OCOC_6H_5$; Y = H
11, R = OH; X = $OCOCH_3$; Y = Br
12, R = OH; X = $OCOC_6H_5$; Y = Br

Woods described the reaction of chlorokojic acid (2) with *N*-bromosuccinimide (NBS) in benzene and tentatively assigned the 2-chloromethyl-5-hydroxy-6-bromo-4*H*-pyrone structure (3) to the product, mp 163°.[2] However, his compound was characterized only by its elemental analysis and a $FeCl_3$ test, and there was no additional chemical or spectroscopic data in support of the proposed structure.

When the reaction was repeated following the published procedure, a product, mp 162–163°, was obtained in 22% yield after two recrystallizations from ethanol. That it was not the starting material, mp 165–166°, was shown by mixture melting point depression, mass spectroscopy (mol wt 238), and the nmr (Table I), which clearly indicated that the ring proton absorbing at 8.13 ppm in **2** had been substituted. We previously showed that this signal corresponded to H-6,[1] and Woods' tentative structural assignment is therefore confirmed. The same product was also obtained by brominating **2** in a phosphate buffer.

We could not improve on Woods' results with kojic acid itself,[2] which consistently yielded a black tar when treated with NBS. Likewise, we did not observe the ring bromination with NBS of either its diacetate (**5**) or dibenzoate (**6**), which would have yielded **7** and **8**, respectively. Molecular bromine in water or in a phosphate buffer was not effective either. Treatment of either the monoacetate **9** or the monobenzoate **10** with NBS, on the other hand, yielded the products of ring bromination, **11** and **12**, respectively.

The bromination of kojic acid with bromine water was described by Yabuta,[3] who obtained a product, mp 159–160°, alleged to be a monobromokojic acid, and yielding a diacetyl derivative, mp 94–95°, and a dibenzoyl derivative, mp 133–134°. These values are to be compared to 165–166, 101–102, and 133–134° for **1**, its diacetate, and its dibenzoate, respectively.[1] When Yabuta's procedure was repeated, a black tar was always formed, but the desired bromokojic acid (**4**) was also obtained in *ca.* 1% yield. It melted at 171–172° and was characterized by its mass spectrum (mol wt 221) and nmr, which indicated that bromination had taken place in the ring and supported the assignment of the bromine to the 6 position in preference to the 3 position.[1] The same product **4** was also obtained in good yield by brominating **1** in a phosphate buffer.[4] It gave a diacetate **7**, mp 67–68°, and a dibenzoate **8**, mp 123–125°. The discrepancy between these values and those reported by Yabuta is noteworthy, but in the absence of direct comparison no definitive conclusion may be drawn concerning the nature of his compound melting at 159–160°. Yabuta also claimed to have converted in poor yield his bromokojic acid into an otherwise unidentified hydroxykojic acid, but we could not duplicate this reaction when **2** was treated with either barium hydroxide or potassium hydroxide, where extensive decomposition took place.[5]

Finally, Woods and Dix reported the dibromination of **1** in trifluoroacetic acid,[6] but this result could not be duplicated and the only product which we succeeded in isolating was the monobromokojic acid (**4**), obtained in low yield.

Table I
Nmr Spectra of Kojic Acids

Compd	Solvent	$-CH_2R$	H-3	H-6	Phenyl	CH_3CO	OH
1	DMSO-d_6	4.50	6.60	8.10			5.68, 9.09
2	DMSO-d_6	4.67	6.70[a]	8.13			9.26
3	DMSO-d_6	4.74	6.66				10.18
4	DMSO-d_6	4.32	6.40				10.46
7	$CDCl_3$	4.97	6.52			2.20, 2.37	
8	DMSO-d_6	5.13	6.53		7.40–8.20		
11	$CDCl_3$	4.93	6.50			2.17	10.15
	DMSO-d_6	4.93	6.51			2.08	10.17
12	DMSO-d_6	5.20	6.57		7.43–8.03		10.20

[a] This value was erroneously printed as 7.70 in ref 1.