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# THE STRUCTURE OF CASTANAGUYONE
## A BIISOCOUMARIN PLANT PRODUCT

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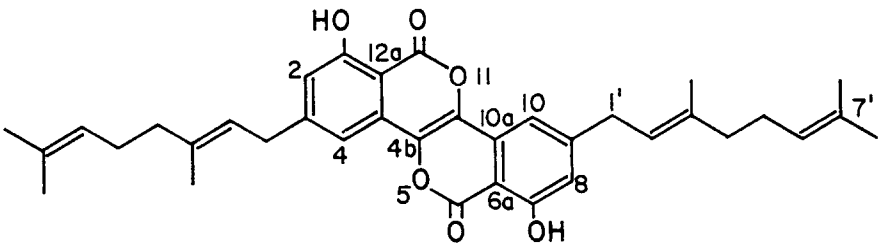
Summary: The fruit extract of the Mexican shrub Zanthoxylum fagara Sarg. has afforded castanaguyone 1; it is the first biisocoumarin encountered in nature.

Zanthoxylum fagara Sarg. (Rutaceae) is an evergreen shrub which has long been used medicinally in Mexico; the extract of its bark, leaves and fruit is used as a sudorific and nerve toxin.[1,2] The fruit (300 g, dry weight) was extracted under reflux for seven days with methanol and the extract was subsequently concentrated, upon which an orange-red precipitate (440 mg) was formed Although it was insoluble in water and various organic solvents, it was soluble to varying degrees in polar aprotic solvents capable of forming hydrogen bonds, such as DMSO, pyridine and dioxane. Recrystallization from dioxane yielded castanaguyone 1, m.p. > 320(dec), m/z 568.2823, calcd. for $C_{36}H_{40}O_6$, 568.2825;[3] UV(dioxane), 227nm (ε 24,100), 285 (4,680), 350 (7,190), 360 (sh, 6,970), 425 (6,200); UV(dioxane/aq. NaOH), 240 nm, 305, 373, 500.

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|---|---|---|---|
| 1 | castanaguyone | 3 | octahydro-1 (saturated side-chain) |
| 2 | diacetate | 4 | octahydro-2 (saturated side-chain) |

The simplicity of the NMR spectra (Fig. 1)[4] and the high molecular weight suggested a dimeric structure. The chelated hydroxyl function was clear from the 9.71 ppm $^{1}$H-NMR peak (exchangeable with $D_2O$), the IR bands at 3520(b)/ 1665 $cm^{-1}$, and the red-shifts induced in the UV upon addition of NaOH (see above) or $AlCl_3$ (in methanolic solution). The low solubility of 1 in DMSO and pyridine was a hindrance to detailed $^{13}$C-NMR studies.

Acetylation with $Ac_2O$/py yielded the diacetate 2, m.p. 158-160°C, UV (dioxane), 225 nm, 255, 263(sh), 272, 375, 410(sh), no shift in the UV upon basification; $^{1}$H-NMR, δ 2.34 (OAc); IR (KBr), 1763 $cm^{-1}$ (phenolic acetate), 1723 (lactone). The diacetate 2, although soluble in chloroform, was unstable to oxygen and decomposed to give a mixture of products; however, it was stable under nitrogen. Hydrogenation of 1, $H_2$/10%Pd-C in dioxane, gave the octahydro-derivative 3, which upon acetylation afforded the stable[5] and chloroform-soluble octahydro-castanaguyone diacetate 4, m.p. 151-152°C; m/z 660.3641, calcd. for $C_{40}H_{52}O_8$, 660.3662; UV (dioxane), 227nm (ε 19,900), 255 (9,680), 263 (sh, 7,590), 272 (sh, 5,880), 375 (12,400), 412 (sh, 7,760) (see Fig. 2 for NMR data of 4).[6]

The geranyl side chain was evident from the NMR data (Figs. 1 and 2) as well as characteristic EI-MS fragmentation pattern of 1: m/z 568 ($M^+$, 1.1%) 525 ($M^+-C_3H_7$, rearrangement peak, 0.8%), 499 ($M^+-C_5H_9$, 0.3%), 445 ($M^+-C_9H_{15}$, 0.6%), 429 ($M^+-C_5H_9-C_5H_9$, 0.8%), 375 ($M^+-C_9H_{15}-C_5H_9$, 16%), 123 ($C_9H_{15}$, 100%), and 69 ($C_5H_9$, 64%). Only two (or four) meta coupled aromatic protons are present. This evidence, in conjunction with the NMR coupling pattern of nuclea carbons (see Fig. 2 for undecoupled data), the long-range couplings of which were proven by single-frequency decoupling experiments, and the presence of an intramolecularly hydrogen bonded hydroxyl group, led uniquely to the biisocoumarin structure 1.

Although the unsubstituted and octachloroderivative of biisocoumarin have been prepared, to our knowledge, castanaguyone is the first natural product to possess this skeleton.[7] Biological testing for molluscicidal, herbicidal, insect anti-feedant, plant growth regulatory and anti-bacterial activities proved to be negative, thus the function of castanaguyone remains unclear.

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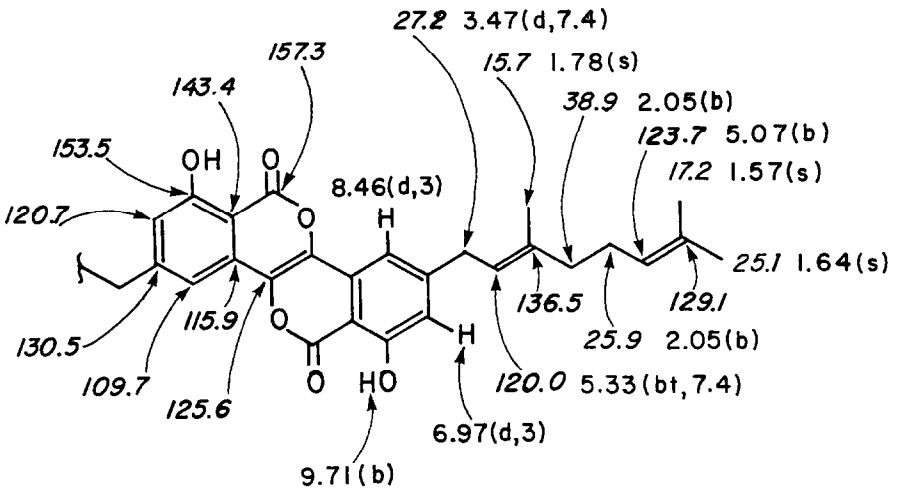


Fig. 1 NMR of castanaguyone 1, in DMSO-$d_6$; $^{13}$C-NMR data are in italics.

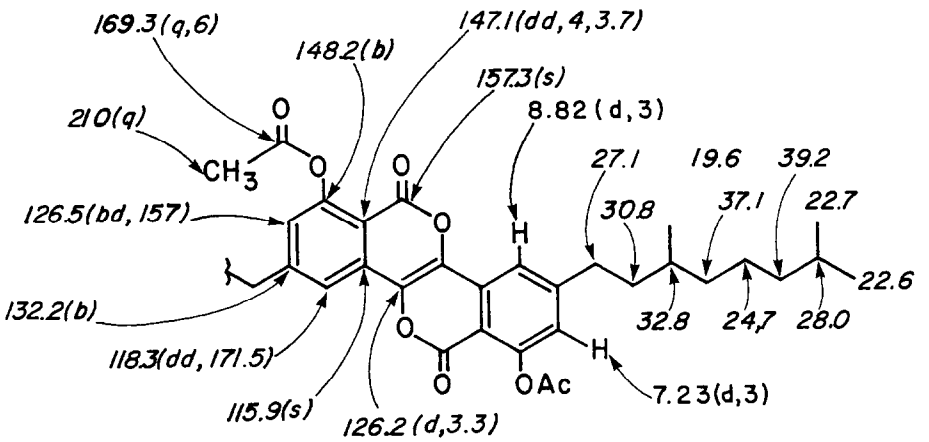


Fig. 2 NMR of octahydrocastanaguyone diacetate 4, in $CDCl_3$. Data for nuclea carbons are undecoupled; data for side-chain carbons are proton-noise decoupled (both in italics).

References

1. Martínez, M.; "Plantas Medicinales de Mexico," 4th edition, Editorial Botas, Mexico, p. 238, 448 (1959).
2. Roys, R.H.; "The Ethno-Botany of the Maya," Tulane University, New Orleans, p. 72 (1931).
3. High resolution mass spectra were measured on a JEOL JMS-01SG unit.
4. Most NMR spectra were measured with a Bruker WM 250 spectrometer.
5. Oxidation of 2 most likely occurs at the C-1' carbon of the geranyl side-chain which is both allylic and benzylic. The octahydro diacetate 4 is less susceptible to air oxidation as the allylic characteristics of this position are lost. Compounds 1 and 3 are stable in air due to the phenolic functionalities which are known to be excellent inhibitors of auto-oxidatio (see Pryor, W.A., "Free Radicals," McGraw-Hill, Inc.; New York, 1966). Acetylation or methylation ($AgO/CH_3I$ to give the corresponding dimethyl ether, $^1$H-NMR: $\delta^{CDCl_3}_{OCH_3}$=3.91) results in a loss of the phenolic function producing an air-sensitive compound.
6. The extreme low field shift of the C-4 (C-10) proton of 1 and 4 (see Figs. 1 and 2) due to the deshielding effect of the peri-oxygen is probably enhanced by the buttressing of the C-1' methylene.
7. Unsubstituted biisocoumarin, IR(KBr) 1722 $cm^{-1}$, was synthesized via acid-catalyzed rearrangement of biphthallyl which was produced from the triethyl phosphite dimerization of phthallic anhydride: Bird, C.W.; Wong, D.Y., Organometal. Org. Syn., 1, 421 (1972); Bird, C.W.; Wong, D.Y., Tetrahedron, 31, 31 (1975); Ramirez, F.; Yamanaka, H.; Basedow, O.H., J. Am. Chem. Soc., 83, 173 (1961); Ramirez, F.; Ricci, J.S.; Tsuboi, H.; Maracek, J.F.; Yamanaka, H., J. Org. Chem., 41, 3909 (1976). Triethyl phosphite dimerization of 3-hydroxyphthallic anhydride and 3-acetoxy-phthallic anhydride both failed to produce the desired 3,3'-dimethoxybiphthallyl, but in less than 3% yield.

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