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THE REVISED STRUCTURE OF MORTONIN†‡

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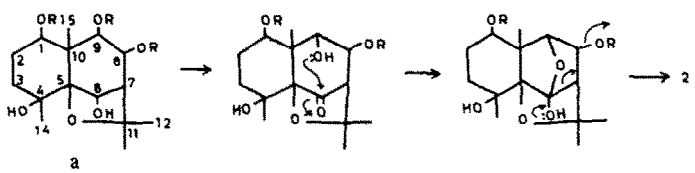
Abstract—The structure **1** previously proposed for mortonin, is revised to **2** based on spectroscopic and chemical evidence, and on biogenetic considerations.

Mortonin ($C_{22}H_{26}O_6$) is a natural product isolated from *Mortonia Gregii* (Gray), a shrub of the *Celastraceae* family, which grows in the northeastern arid region of Mexico.

In a previous work,[1] structure **1** was proposed for mortonin mainly based on spectroscopic data. In that work it was shown that mortonin possesses a benzoate group on a secondary C atom, and a tertiary OH group attached to a C atom which also supports a Me group. It was proved that these two groups are separated by two methylenes and flanked by fully substituted C atoms. It was also shown that mortonin has a saturated γ-lactone function. The hydrogen at the lactone closure is coupled to an ethylene moiety forming an ABX system in the NMR spectrum.

Biogenetic considerations prompted us to reinvestigate the structure **1** previously[1] proposed for mortonin. *Mortonia Gregii* (Gray) forms part of the Celastraceae family, in which there have been found several sesquiterpenes such as malkanguniol,[2a] malkangunin,[2b] celaparin,[2b] celapanigin,[2b] evonin,[2c] maytoline[2d] and others. The common feature of these compounds is that they are derivatives of β-dihydroagarofuran with different degrees of oxidation. The structure of mortonin could be derived from the above mentioned skeleton and satisfy, at the same time, all the spectroscopic data described previously. It is worth to mention the fact that the coupling constant found for the vinylic protons J = 11.5 Hz, is not in agreement with structure **1**. This value is not in accordance with that found in the literature for a double bond in a 6-membered ring,[3] or in a dihydropyran system,[4]§ in which J is not higher than 10.5 Hz. This fact induced us to think of a structure in which the double bond formed part of a larger ring, such as a tetrahydro oxepin. A possible structure is **2**, which can be derived biogenetically from a β-dihydroagarofuran derivative such as **a**, through the following sequence of transformations:



a

To our knowledge, structure **2** constitutes the first example of a natural product in which the ring B of the original eudesmane skeleton has suffered an oxidative cleavage to form the γ-lactone function.

The new structure **2** proposed for mortonin, was confirmed in the following manner. Ozonolysis of mortonin, followed by catalytic hydrogenation of the ozonide, gave a mixture of products, whose NMR spectrum showed the presence of two aldehyde protons at 9.5 and 9.7 ppm in a 4:1 ratio. We assumed that one of the expected aldehyde groups was partially hemiacetalised with the tertiary OH group. The oxidation of the reaction mixture with Jones reagent, afforded two products. One of them was formulated as the lactone aldehyde (**3a**, R = CHO), as it showed in the NMR the presence of an aldehyde proton at 9.5 ppm. The sharp signal at 4.43 ppm was assigned to the lactone closure. In the high field region, the NMR spectrum exhibited four singlets at 1.55, 1.60, 1.63 and 1.71 ppm indicative of four Me groups. Its IR spectrum did not show the absorption due to OH group; in the CO region there are observed bands at 1805 (saturated γ-lactone) and a broad absorption at 1745 cm^{-1} ascribed to the benzoate, aldehyde and δ lactone groups. The second product is an acid, which upon treatment with ethereal diazomethane, afforded the ester lactone (**3b**, R = COOMe). The spectroscopic data found for this compound are in accordance with the structure proposed (Experimental).

Treatment of mortonin with osmium tetroxide, gave a mixture of isomeric diols (α and β), which was treated with acetone in acid medium. The mixture of acetonides (**4a** and **4b**), was separated by chromatography. Dehydration of **4a** gave the anhydroacetonide (**5a**) which was ozonised to give the ketone (**5b**). The acetonide, in this last compound, could only be opened in drastic acidic conditions, which destroyed the molecule.

Catalytic hydrogenation of mortonin gave the dihydromortonin (**6a**), which showed in the NMR spectrum, the absence of the vinylic protons. The γ-lactone closure appeared as a broad doublet (J = 7 Hz) at 4.43 ppm. Dehydration of dihydromortonin gave the compound (**6b**, R = CH_2), which was also obtained when anhydromortonin (**7**)[1] was catalytically hydrogenated in the presence of Pd/C. In the NMR spectrum, the anhydrodi-

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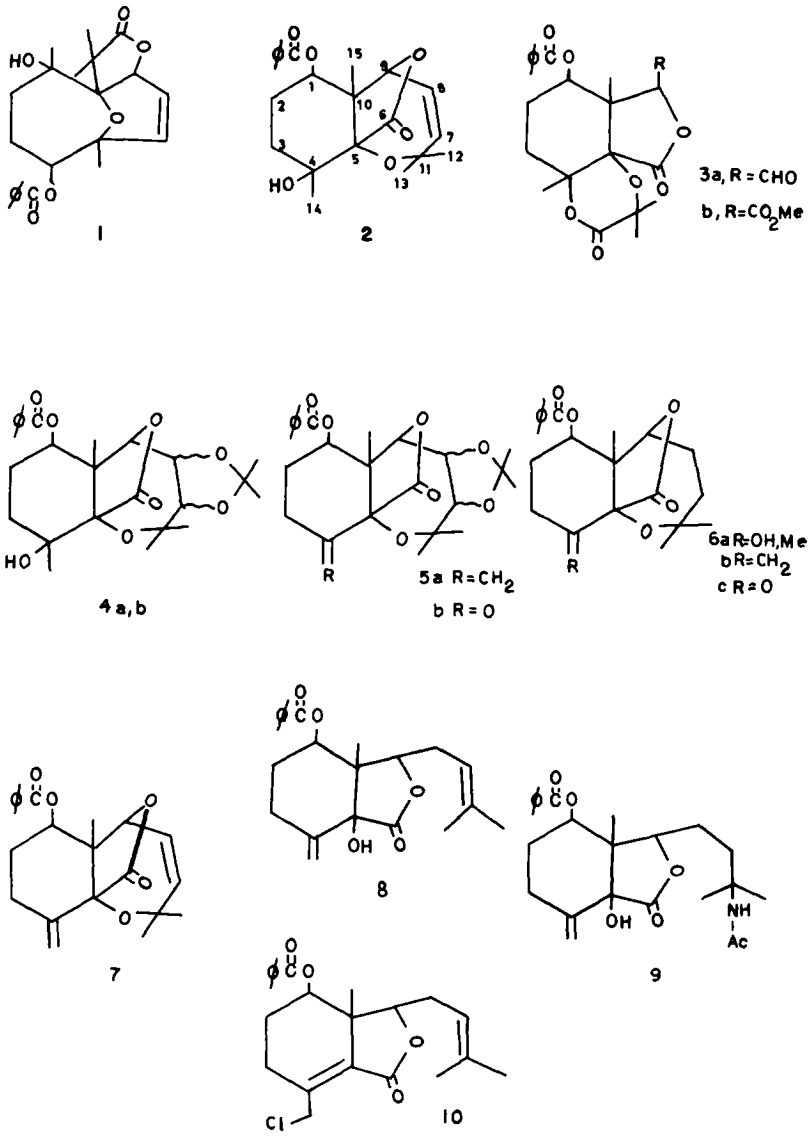

hydromortonin (**6b**, R = CH_2), showed two broad signals due to the exocyclic methylene group, at 5.01 and 5.42 ppm. In the high field region, there could be observed a signal at 1.37 ppm (6 H), assigned to the Me groups attached to the ethereal linkage, and a singlet at 1.2 ppm (3 H) due to the angular Me group. Ozonolysis of **6b** (R = CH_2), gave **6c** (R = O), which showed in the IR spectrum bands at 1790 (saturated γ-lactone) and 1715 cm^{-1} (benzoate ester and cyclohexanone).

Mazur *et al.*,[5] have found that the treatment of an ether with tosyl acetate (and with other mixed anhydrides), could open an ether linkage to give the acetate tosylate derivative of the corresponding diol. They also found that when the ether linkage is bound to a tertiary C atom, the anhydro derivative is obtained. On treatment of anhydrodihydromortonin (**6b**, R = CH_2) with tosyl acetate in acetonitrile, followed by chromatography, a product was obtained in which the ether linkage was opened. We assigned to this compound the structure **8** on spectroscopic grounds. In the IR spectrum it showed bands at 3400 (OH group), 1770 (saturated γ-lactone), 1705 (benzoate ester) and 910 cm^{-1} (exocyclic methylene). In the NMR spectrum a broad signal at 1.48 (6 H) was attributed to two vinylic Me groups. The base of the lactone appeared as a doublet of doublet at 4.22 (J = 5.5 and 9 Hz). Two signals (1 H each) at 5.1 and 5.6 were assigned to the protons of the exocyclic methylene; the vinylic proton of the isopropylidene moiety, appeared as a multiplet at 5.1 ppm. A second solid product could be isolated from the polar fractions of the chromatography of the reaction mixture. The spectroscopic data found for this compound,† suggested structure **9** for it.

When **8** was submitted to dehydration conditions (thionyl chloride in dry pyridine) an allylic rearrangement took place and a chloro derivative was isolated. The spectroscopic data found for this compound are in accordance with structure **10**. Its IR spectrum does not show an OH group, and the absorption due to the saturated γ-lactone function is shifted to 1750 cm^{-1} suggesting the formation of an α,β-unsaturated γ-lactone; the presence of a strong absorption at 1660 cm^{-1} can be attributed to a conjugated cisoid double bond. Its NMR spectrum showed a singlet at 1.46 (3 H) attributed to the angular methyl group, a broad signal at 1.53 ppm (6 H)

†See Experimental.

was assigned to the vinylic Me groups of the isopropylidene chain. The base of the lactone appeared at 4.23 ppm (dd J = 5.5 and 6.5 Hz). An AB pattern at 4.48 and 4.78 ppm (1 H each) could be assigned to an allylic chloromethylene group (J = 12 Hz). Its mass spectrum confirmed the presence of a Cl atom in the molecule.

The series of reactions presented support the structure **2** proposed for mortonin.†

EXPERIMENTAL

All m.ps were uncorrected. UV spectra were measured in EtOH on a Perkin–Elmer 202 Spectrophotometer. IR spectra were recorded with a Perkin–Elmer 337 Spectrophotometer. The NMR spectra were determined on a Varian A-60A and Varian HA-100 Spectrometers. Chemical shifts (δ) are given in ppm relative to internal TMS. The experiments of a double resonance were taken using a Radio Oscilator Hewlett–Packard 200 AB. The mass spectra were determined on a Hitachi Perkin–Elmer RMU 6D Mass Spectrometer using direct inlet system.

Isolation of mortonin **2**. Mortonin **2** was isolated from *Mortonia Gregii* (Gray) as previously described.[1]

Ozonolysis of mortonin. The mortonin **2** (1 g) in EtOAc was ozonised at low temp. for 0.5 hr. The soln was warmed to r.t. and the solvent removed under vacuum. The residue was dissolved in acetone and treated with Jones' reagent at 5°, poured onto ice and extracted with EtOAc. The organic soln was extracted with sat $NaHCO_3$aq. From the neutral fraction the **3a** could be isolated (200 mg). It showed m.p. 190–192° from acetone, ν_{max} 1800, 1745 (broad), 1605, 1595 cm^{-1}; δ: 1.55 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 4.43 (s, 1H, H_9), 5.6 (m, 1H, H_1), 7.3 and 8.2 (2m, 3H and 2H, aromatic protons), 9.5 ppm (br, s, 1H, aldehyde). (Found: C, 63.68; H, 5.85. Calc. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81%.)

The $NaHCO_3$ soln was acidified with dil HCl, extracted with EtOAc, washed with water, dried and the solvent removed. The residue, (460 mg), was treated with ethereal diazomethane. The oily product obtained, was passed through neutral alumina using benzene as eluent. The product **3b** was crystallized from acetone–isopropyl ether to constant m.p. 230–232°; ν_{max} 1800, 1745 (br.); δ: 1.58 (s, 6H, $2CH_3$), 1.70 (s, 3H, CH_3), 3.74 (s, 3H, COOMe), 4.62 (s, 1H, H_9), 5.8 (m, 1H, H_1), 7.30 and 8.2 ppm (2m, 3H and 2H, aromatic). (Found: C, 62.22; H, 5.73. Calc. for $C_{23}H_{26}O_9$: C, 61.87; H, 5.8%.)

Treatment of mortonin with osmium tetroxide. An ethereal soln (300 ml) of **2** (1.45 g), was treated with osmium tetroxide (1 g) and pyridine (0.5 ml), at 10°, for 72 hr. A black ppt was formed. The ethereal soln was decanted and concentrated to half its volume, MeOH was added and stream of H_2S was passed until saturation. The black ppt was filtered off. The solvents were removed, and the residue was dissolved in EtOAc, washed with water, $NaHCO_3$aq and water, dried and evaporated. The solid product so obtained, was dissolved in acetone (25 ml) and treated with conc. HCl for 18 hr at r.t. The solvent was removed in vacuum, the residue dissolved in chloroform, washed with sat $NaHCO_3$aq, and water, dried and evaporated. The crude product obtained, was chromatographed over SiO_2 using isopropyl ether as eluent. The first crystalline product obtained, (340 mg), was shown to be one of the acetonides, **4a**, m.p. 182–185°, from acetone–hexane; ν_{max} 3560, 1795, 1720, 1605 cm^{-1}; δ: 1.3 (s, 3H, C_{10}–CH_3), 1.42–1.54 (4s, 15H, $5CH_3$), 2.92 (br., signal dissapeared with D_2O, OH), 4.41 (d, J = 1.5 Hz, 1H, H_9), 4.41 (d, J = 1.5 Hz, 1H, H_7), 4.65 (t, J = 1.5 Hz, 1H, H_8), 5.78 (m, 1H, H_1), 7.25 and 8.20 ppm (m, 5H, aromatic). (Found: C, 65.34; H, 7.09; O, 27.72. Calc. for $C_{25}H_{32}O_8$: C, 65.20; H, 7.00; O, 27.80%.)

The following fractions gave 460 mg of recovered mortonin. The last fractions gave a solid product which was identified as **4b** (200 mg). The analytical sample was obtained from acetone–isopropyl ether and showed m.p. 207–208°; ν_{max} 3500, 1760, 1715, 1600 cm^{-1}; δ: 1.17 (s, 3H, C_{10}–CH_3), 1.41 (s, 6H, $2CH_3$), 1.46 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 4.17 (d, J = 6 Hz, 1H, H_7), 4.32 (d, J = 1.5 Hz, 1H, H_9), 4.65 (dd, J = 6 and 1.5, 1H, C_8), 5.65 (m, 1H, H_1), 7.3 and 8.2 ppm (m, 5H, aromatic). (Found: C, 65.00; H, 7.03; O, 27.60. Calc. for $C_{25}H_{32}O_8$: C, 65.20; H, 7.00; O, 27.80%.)

Ketone **5b**. The acetonide **4a** (m.p. 182–185°; 275 mg) was dehydrated with thionyl chloride in dry pyridine. The analytical sample of the product **5a** showed m.p. 182–182.5°; ν_{max} 1790, 1715, 1605, 920, 890 cm^{-1}; δ: 1.28 (s, 6H, $2CH_3$), 1.35 (s, 3H, CH_3), 1.50 (br. s, 6H, $2CH_3$), 4.41 (d, J = 3 Hz, 1H, H_7), 4.46 (s, 1H, H_9), 4.7 (d, J = 3 Hz, 1H, H_8), 5.12 and 5.65 (2m, 2H, C_4=CH_2), 5.9 (dd, J = 10 and 5 Hz, 1H, H_1), 7.3 and 8.2 ppm (m, 5H, aromatic). (Found: C, 68.04; H, 6.71; O, 25.15. Calc. for $C_{25}H_{30}O_7$: C, 67.85; H, 6.83; O, 25.31%.)

The anhydro **5a** (200 mg) in EtOAc, was ozonised at low temp. The ozonide was catalytically hydrogenated. The solid product obtained, was passed through alumina and crystallized from acetone–hexane. The ketone **5b**, showed m.p. 224–225°, (105 mg); ν_{max} 1800, 1715, 1600 cm^{-1}; δ: 1.32 (s, 6H, $2CH_3$), 1.45 (s, 3H, CH_3), 1.48 (s, 6H, $2CH_3$), 4.41 (dd, J = 3.5 and 7 Hz, 1H, H_8), 4.63 (d, J = 7 Hz, 1H, H_7), 4.70 (d, J = 3.5 Hz, 1H, H_9), 6.15 (dd, J = 6 and 10 Hz, 1H, H_1), 7.5 and 8.2 ppm (m, 5H, aromatic). (Found: C, 64.60; H, 6.38; O, 29.15. Calc. for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35; O, 28.80%.)

Catalytic hydrogenation of mortonin. Mortonin **2**, (500 mg) in EtOAc, was catalytically hydrogenated using 10% Pd/C (50 mg) as catalyst (8 hr). The catalyst was filtered off and the solvent removed under vacuum. The crystalline product **6a** (400 mg) showed m.p. 160–166°. The analytical sample showed m.p. 168–169°; ν_{max} 3570, 1785, 1720, 1605, 1595 cm^{-1}; δ: 1.38 and 1.42 (2s, 12H, $4CH_3$), 4.43 (dd, J = 6 and 2 Hz, 1H, H_9), 5.9 (m, 1H, H_1), 7.3 and 8.15 ppm (m, 5H, aromatic). (Found: C, 68.28; H, 7.23; O, 24.25. Calc. for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26; O, 24.72%.)

Anhydrodihydromortonin, **6b**. The **6a** (400 mg), in dry pyridine (10 ml), was treated in an ice bath, with thionyl chloride (2 ml) for 2 hr. The mixture was poured onto ice, extracted with EtOAc, washed with dil. HCl, and sat $NaHCO_3$aq, dried and the solvent removed. The solid product was crystallized from acetone–methanol to give **6b** (285 mg) m.p. 190–195°. The analytical sample showed m.p. 190–195°; ν_{max} 1790, 1725, 1605 cm^{-1}, δ: 1.2 (s, 3H, C_{10}–CH_3), 1.36 (s, 6H, $C_{11}(CH_3)_2$), 4.48 (t, J = 3.5 Hz, 1H, H_9), 5.02 and 5.45 (2m, 2H, C_4=CH_2), 6.1 (dd, J = 10 and 5 Hz, 1H, H_1), 7.3 and 8.2 (m, 5H, aromatic). (Found: C, 71.67; H, 6.93; O, 21.03. Calc. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08; O, 21.59%.)

Treatment of anhydrodihydromortonin, **6b**, *with tosyl acetate.* Compound **6b** (400 mg) in acetonitrile (50 ml), was treated with freshly prepared[5] tosyl acetate (1 g) at r.t. for 1 hr. The mixture was poured onto ice, extracted with EtOAc, washed with water $NaHCO_3$aq and water, dried and the solvent removed under vacuum. The crude product obtained, was chromatographed on silica gel. Elution with benzene gave **8**, which was crystallized from ether–hexane to constant m.p. 155–157°; ν_{max} 3500 (OH), 1770 (γ-lactone), 1705 (ester), 1610, 910 (CH_2=C) cm^{-1}; λ_{max} 230 (10,000), 212 (sh, 5000), 270 (4000); δ: 1.2 (s, 3H, C_{10}–CH_3), 1.48 (br., s, 6H, $C_{11}(CH_3)_2$), 4.22 (dd, J = 10 and 5 Hz, 1H, H_9), 5.15 and 5.55 (2m, 2H, C_4=CH_2), 5.10 (m, 1H, H_7), 5.83 (dd, J = 7.5 and 10 Hz, 1H, H_1), 7.5 and 8.2 ppm (m, 5H, aromatic). (Found: C, 71.33; H, 7.08; O, 21.60. Calc. for $C_{22}H_{26}O_5$: C, 71.02; H, 7.14; O, 21.73%.)

Elution with benzene–EtOAc gave **9**, (100 mg) which showed m.p. 218–220° from acetone–isopropyl ether; ν_{max} 3450 (OH, NH), 1760 (γ-lactone), 1702 (benzoate), 1645 ($NHCOCH_3$), 1600 (aromatic) cm^{-1}; δ: 1.15 (s, 3H, C_{10}–CH_3), 1.2 (s, 3H, C_{11}–CH_3), 1.25 (s, 3H, C_{11}–CH_3), 1.58 (s, 3H, $NHCOCH_3$), 4.2 (m, 1H, H_9), 5.15 and 5.55 (2m, 2H, C_4=CH_2), 5.15 (m, 1H, disappeared with D_2O, NH), 5.85 (dd, J = 10 and 6 Hz, 1H, H_1), 7.5 and 8.03 ppm (m, 5H, aromatic) *m/e*: M^+ 429 (2%), 412 (1%), 369 (3%), 354 (1%), 101 (100%), 100 (62%). Calc. for $C_{24}H_{31}O_6N$ MW 429.

Treatment of **8** *with thionyl chloride.* The compound **8**, (150 mg) in anhyd pyridine (3 ml), was treated with thionyl chloride (0.5 ml) at 5° for 0.5 hr, poured onto ice and extracted with chloroform, washed with dil. HCl, $NaHCO_3$aq and water. The product **10**, was obtained as an oil by tlc using benzene–EtOH (9:1) as eluent; ν_{max} 1750 (γ-lactone), 1715 (benzoate),

†A further support for structure **2** is given by the formation of photomortonin (see *Tetrahedron* **33**, 661 (1977)).

1675 (double bond) cm^{-1}; δ: 1.47 (s, 3H, C_{10}–CH_3), 1.53 (br., s, 6H, two vinylic Me groups), 4.23 (dd, J = 5.5 and 6.5 Hz, 1H, H_6), 4.48 (d, J = 12 Hz, 1H, CH_aCl), 4.78 (d, J = 12 Hz, 1H, CH_bCl), 5.06 (br., t, 1H, H_7), 5.13 (dd, J = 5 and 10.5 Hz, 1H, H_1), 7.46 and 8 ppm (m, 5H, aromatic), λ_{max} 232 (11,400), 215 sh (9080), 270 (1070), *m/e*: M^+ 388 (4%), M + 2 390 (1%), 319 (15%), 321. Calc. for $C_{22}H_{25}O_4Cl$ MW 388.5.

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