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Neurotoxins of *Karwinskia humboldtiana*. Atropisomerism and Diastereomeric Oxidation Products

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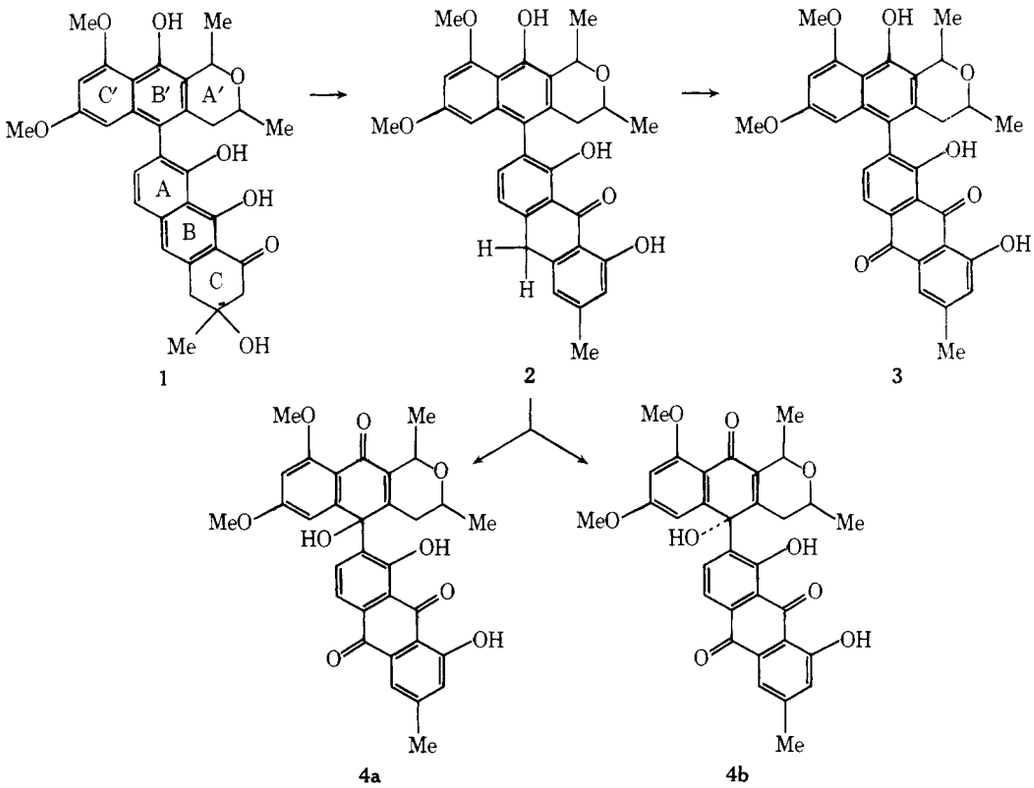
A previous report from this laboratory[2] described the isolation and structure elucidation of several polyphenolic components of the neurotoxic fruit of *Karwinskia humboldtiana*, Zucc. (Rhamnaceae). These polyphenolic neurotoxins include four C_{15} "dimers" which have since been isolated from the roots of the plant by Dominguez and students.[3] We now report evidence from proton nuclear magnetic resonance (^1H NMR) studies that, as isolated from seeds of *K. humboldtiana* following extensive fractionation,[2] one of the "dimeric" polyphenolic neurotoxins (1) exists as a mixture of two conformational isomers (i.e., atropicisomers) of the biphenyl type.[4-6] In addition, we report the formation of two oxidation products of **1** which are isomeric at a newly formed chiral center (C-5′, see structures **1**, **4a**, **4b**) and exhibit ^1H NMR spectra which are individually quite similar to the spectra of the respective conformational isomers of **1** (and its transformation products **2** and **3**).

The ^1H NMR spectrum of **1**, a major component of the neurotoxic extract of *K. humboldtiana*, exhibits a number of features which made initial interpretation difficult.[2] Thus, chromatographically homogeneous samples of **1** exhibited ^1H NMR spectra in which the number of hydrogen resonances exceeded the number of hydrogens (32) established by high resolution mass spectrometry. In these spectra, and in spectra of transformation products **2**, derived by dehydration of **1**,[2] and **3**, formed by oxidation of **2**[2] (see Figure 1A for the spectrum of **3**), several specific resonances failed to integrate for an integral number of hydrogens. It became clear that the nonintegral resonances occur in pairs, i.e., they arise from hydrogens which, owing to the existence of two conformational isomers, experience two different magnetic environments. For quinone **3**, this "doubling" of resonance signals was observed for the 1′-methyl, H-5, H-6, H-6′ and the 1- and 8-hydroxyl hydrogen resonances (see Figure 1A). The spectra of **1** and **2** are similar.[2]

When samples of **2** or **3** in $CDBr_3$ were heated, the equilibrium between the conformational isomers was altered. In each case, heating resulted in an increase in the intensity of signals owing to the minor conformational isomer. After heating solutions of **2** and **3** in $CDBr_3$ at 100 °C for ~1 h, the isomer concentrations were approximately equal in each case; heating beyond 1.5 h caused sample decomposition.

When a wet methanol solution of **2** was allowed to stand at room temperature in air for several months, two new products were formed. The products were shown by mass spectrometry to be isomers of empirical formula $C_{32}H_{28}O_9$. The spectral properties of the newly formed isomers were very similar to each other and showed many similarities to those of **3**. Thus, the ultraviolet–visable spectra of the isomers were essentially identical and assignable as an anthraquinone chromophore with a long wavelength band at 435 nm. The ^1H NMR spectrum of each (Figures 1B and 1C) showed typical anthraquinone 1,8-dihydroxy resonances at about δ 12, but the characteristic phenolic hydroxy signal associated with the 10′-



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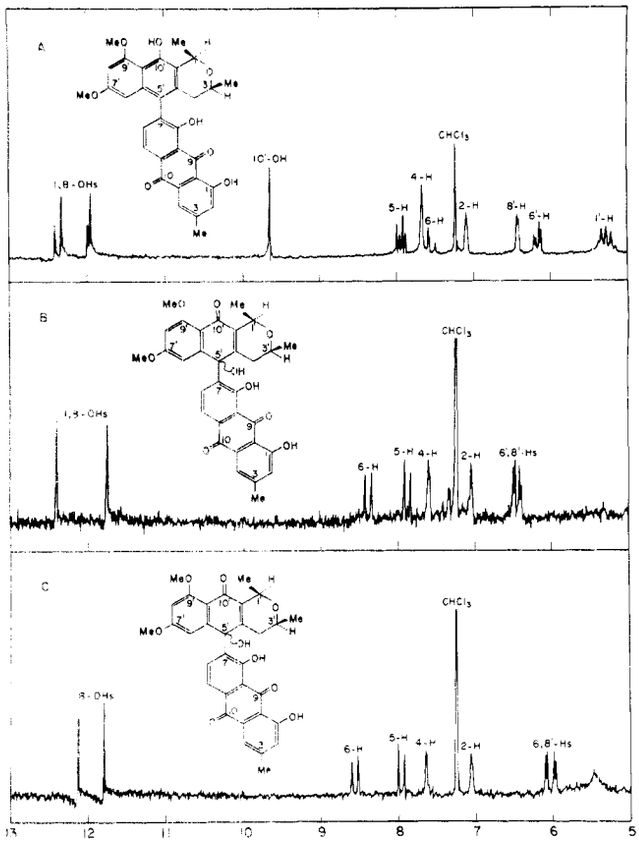

Figure 1. (A) Partial ^1H NMR spectrum of **3** exhibiting resonances of two atropisomers; (B) partial ^1H NMR spectrum of the nonpolar isomer of the diasteriomeric alcohol pair (**4**) obtained by air oxidation of **2**; (C) the partial ^1H NMR of the corresponding polar isomer (**4**).

hydroxy in the starting material[2] (see Figure 1A) was absent. The resonances due to two methoxy groups and the A′-ring aromatic AB system as well as signals due to the corresponding protons in the A′,C′, and C rings of **3** were present in each and could be related to the corresponding signals in **3**.

These results lead us to assign general structure **4** to the new products, designated nonpolar and polar in accord with their relative chromatographic mobilities (see Experimental Section). The existence of two very similar isomers is then due to (a) air oxidation of the ABC system with creation of an anthraquinone moiety and (b) the creation of a new chiral center with hydroxylation at the 5′ position. Since it has been established[2] that the two C-methyl substituents of ring A′ are cis diequatorially related to one another, a chiral center at the 5′ position would place the 5′-hydroxy either cis or trans to the C-methyls (**4a** and **4b**, respectively).

The differences in the ^1H NMR spectra of the nonpolar and polar 5′-hydroxy isomers (**4**) are appreciable (compare Figures 1B and 1C) and must result from differences in hydrogen bonding (5′-OH to O-8)[7] and/or conformational differences. We have been unable to account for the observed differences by inspection of molecular models and, therefore, have not assigned stereochemistries at C-5′ to the isolated isomer pair.

Experimental Section

Isolation of Isomeric 7-[3′,4′-Dihydro-7′,9′-dimethoxy-1′,3′-dimethyl-5′-hydroxy-10′-oxo-1′*H*-naphtho[2′,3′-*c*′]pyran-5′-yl]-1,8-dihydroxy-3-methylanthracene-4,10-diones (4). A methanol filtrate retained following recrystallization of **2**[2] was allowed to stand at room temperature in contact with air for ~4 months. At the end of this time thin layer chromatography showed the presence of several new products. By chromatography on silica gel using chloroform for elution, two components, assigned general structure **4**, were isolated in approximately equal amounts (~5 mg).

The first compound to elute, designated the nonpolar isomer, exhibited spectral data: MS *m/e* 556.1719 ($C_{32}H_{28}O_9$, M^+ ·), *m/e* 541, 526, 511, 496, 482; UV λ_{max} (MeOH) 228, 258, 290, 330, 435 nm; IR ν_{max} (KBr) 3440, 1630, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.44, 11.79 (1, 8-OH's), 8.38 (d, J = 8 Hz, 6-H), 7.87 (d, J = 8 Hz, 5-H), 7.59 (d, J = 1 Hz, 4-H), 7.05 (d, J = 1 Hz, 2-H), 6.49, 6.40 (both d, J = 2 Hz, 6′, 8′-H's), 4.90 (m, 1′-H), 3.90, 3.71 (OMes), 2.42 (3-Me), 1.47 (d, J = 6 Hz, 1′-Me), 1.17 (d, J = 6 Hz, 3′-Me).

The polar isomer exhibited: MS *m/e* 556.1711 ($C_{32}H_{28}O_9$, M^+ ·), 541, 526, 511, 496, 482; UV λ_{max} (MeOH) 228, 258, 290, 330, 435 nm; IR ν_{max} (KBr) 3390, 1625, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.18, 11.84 (1,8-OHs), 8.57 (d, J = 8 Hz, 6-H), 7.96 (d, J = 8 Hz, 5-H), 7.64 (d, J = 1 Hz, H-4), 7.07 (d, J = 1 Hz, H-2), 6.09, 5.98 (both d, J = 2 Hz, 6′-,8′-H's), 5.48 (m, 1′-H), 3.69, 3.65 (OMes), 2.45 (3-Me), 1.43 (d, J = 6 Hz, 1′-Me), 1.21 (d, J = 6 Hz, 3′-Me).

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Registry No.—**2**, 56709-27-4; **3**, 56678-20-7; 4 isomer 1, 64957-52-4; 4 isomer 2, 65024-71-7.

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Voleneol Diacetate: a New Sesquiterpenoid from *Lepidotrichilia volensii* Leroy (Meliaceae)

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As the result of a phytochemical investigation of the chloroform extract of the stem bark of *Lepidotrichilia volensii* Leroy (Meliaceae),[1] the diacetate of a new sesquiterpenediol was obtained and characterized as I.

Discussion

One of the constituents of the chloroform extract of *Lepidotrichilia volensii* Leroy was an oil which on acetylation yielded a beautifully crystalline new substance with the molecular formula $C_{19}H_{30}O_4$. The mass spectrum of this diacetate indicated a parent peak at *m/e* 322. The fragmentation pattern was consistent wih successive losses of acetic acid [*m/e* 262 and 202 (base)] and the loss of a methyl (187) and isopropyl radical (159) from the base fragment.

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