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LABDANE DITERPENES FROM *BRICKELLIA VERNICOSA*

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Key Word Index—*Brickellia vernicosa*; Eupatorieae; Compositae; new labdane derivatives.

Abstract—The investigation of *Brickellia vernicosa* afforded, in addition to the known 3α-hydroxycativic acid, three new labdane derivatives. The structures and stereochemistry have been established by spectroscopic methods and chemical transformations.

INTRODUCTION

As a continuation of our biochemical systematic study of the genus *Brickellia* Ell. we here report the isolation of five labdane diterpenes, including three novel compounds, from the leaves of *Brickellia vernicosa* B. L. Robins., a member of the section *Gemmipedium*. Although only a relatively small number of species in this large genus (*ca* 100 species) have been examined, the presence of labdane diterpenes is common in *Brickellia* [1–6].

RESULTS AND DISCUSSION

The principle diterpene constituent of the leaves of *B. vernicosa* was the known labdane 3α-hydroxycativic acid (**1a**), isolated previously from *Chrysothamnus nauseosus* [7]† and *Eupatorium maretiana* (= *Ageratina maretiana* (DC) King and H. Robins.) [Calderon *et al.*, unpublished]. The structure of **1a** was confirmed by comparison of its mass, ^{1}H NMR and IR spectra with those reported in the literature [7]. The previously unreported ^{13}C NMR spectral data of 3α-hydroxycativic acid (**1a**) are given in Table 2. Additional proof of the structure was provided by the conversion of **1a** to the known 3-keto compound **2a** [1] by Jones oxidation. Optical rotation measurements at five wavelengths were in accord with those reported by Bohlmann *et al.* [1]. In the previous study [1] the absolute configuration of **2a** was determined by chemical conversion to dihydromethylcativate, a compound of known absolute stereochemistry [8]. In order to correlate **2a** with other related diterpenes we obtained the CD curve of the methyl ester **2b**. A negative Cotton effect was observed for the ketone chromophore at 291 nm. As expected, this is opposite that found for the *ent*-labdane, 3-keto methyl lithofellate (**5**), a compound of known absolute configuration [9]. Interestingly, a positive Cotton effect was also reported for the normal labdane, 3-keto evillosin (**6**), isolated from *Eupatorium villosum* (= *Koanophyllon villosum* (Sw.) King and H. Robins.) [10]. The relative configuration of this compound's 3α-hydroxy analogue (evillosin) was determined by X-ray [10], but our results indicate both compounds may belong to the *ent* series. Alternatively, the additional lactone and ester chromophores in evillosin or conformational differences may explain the opposite Cotton effect. Additional evidence will be required to determine the absolute configuration of evillosin.

A second less polar compound (**1b**) isolated in trace amounts had an ^{1}H NMR spectrum nearly identical to that of 3α-hydroxycativic acid (**1a**), with the exception of an additional singlet at δ3.67 integrating for three protons. Further, the molecular ion for **1b** in the MS was fourteen mass units higher than that of compound **1a**. That **1b** is the methyl ester of 3α-hydroxycativic acid [7], was confirmed by methylation of **1a** with diazomethane to form a compound identical in every respect to **1b**. Since methanol was used in the extraction and work-up (see Experimental) of this species the natural methyl ester **1b** may be an artifact.

Compound **3a** also had a similar ^{1}H NMR spectrum to compound **1a**. One apparent difference was the absence of the ABX pattern (the A and B parts centred δ2.36 and δ2.18, see Table 1) for H-14a and H-14b. An additional two proton resonance at δ3.70, approximating a narrowly split triplet ($J = 6$ Hz)‡, indicated that the carboxylic acid group terminating the side chain was replaced by a hydroxymethylene function. This was supported by a molecular ion in the mass spectrum at m/z 308. Thus, the third compound is formulated as the diol **3a**. The structure of **3a** was confirmed when it was formed by reduction of **1a** with lithium aluminium hydride. Although compound **3a** is new as a natural product, it has previously been synthetically prepared by lithium aluminium hydride reduction of the corresponding 2α-tosyl-3α-hydroxy analogue [6].

The fourth compound (**3b**) was similar to **3a**. In the

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†Bohlmann *et al.* [7] reported both the 3α- and 3β-hydroxy epimers. An examination of Dreiding models clearly shows that the ^{1}H NMR data of the two compounds were interchanged. The H-3 signal in the 3β-hydroxy epimer should exhibit one large coupling and a second smaller coupling, while the 3α-hydroxy epimer should show two smaller, nearly equal couplings.

‡The appearance of this signal (*ca dt* with additional lines and the absence of geminal coupling) suggested it was probably second order.