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ACYCLIC PRECURSORS OF THE UTEROTONIC OXEPANE DITERPENOIDS OF 'ZOAPATLE' (*MONTANOA TOMENTOSA*)*

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Key Word Index—*Montanoa tomentosa*; Compositae; uterotonic acyclic diterpenoids; oxepane diterpenoid precursors; pre-tomentol; pre-zoapatanol; pre-tomexanthol.

Abstract—Chemical analysis of *Montanoa tomentosa* yielded, in addition to the known biologically active oxepane diterpenoids zoapatanol, tomentol and tomexanthol, three new uterotonic acyclic diterpenoids, which are considered the precursors of the oxepane derivatives mentioned above. The structures of the new compounds were established by spectroscopic methods.

INTRODUCTION

In our previous papers we have described the isolation and structure elucidation of sesquiterpene lactones [1, 2] and the uterotonic oxepane diterpenoids tomentol (**1a**), tomexanthol (**1b**) besides the known zoapatanol (**1c**) and montanol (**1d**) [3] from the Mexican plant commonly called 'zoapatle' (*Montanoa tomentosa* Cerv.). In the course of our work on the isolation and identification of the components of 'zoapatle' diterpenoid mixture, we realized that tomentol (**1a**) and zoapatanol (**1c**) were the major components in our mixture, while montanol (**1d**) was the minor one. This observation suggested to us that montanol (**1d**) is an artefact formed during the isolation procedure used by the earlier authors [4]. In order to verify the above hypothesis we undertook a re-investigation of the plant using mild extraction conditions and, indeed, comparison of the results confirmed our hypothesis that montanol (**1d**) is an artefact derived from the isomerization of tomentol (**1a**). This report is on the results of this new study of the diterpenoid fraction which led to the isolation of three new acyclic compounds. These further components of 'zoapatle' plant which we have named pre-tomentol (**2a**), pre-zoapatanol (**2c**) and pre-tomexanthol (**2b**) were identified as the precursors of the known active oxepane diterpenoids mentioned above.

It is interesting to point out that these types of compounds had been suggested as suitable intermediates for the synthesis of the oxepane ring [5].

RESULTS AND DISCUSSION

In preliminary assays pre-tomentol and pre-zoapatanol were shown to be biologically less active than zoapatanol.

Pre-tomentol (**2a**), $C_{21}H_{36}O_4$, was a gum with an IR spectrum showing the presence of hydroxyl (3400 cm^{-1}) and carbonyl (1707 cm^{-1}) functions. The ^1H NMR spectrum of **2a** (Table 1) was very similar to the one of tomentol (**1a**), except for the different chemical shift associated with the replacement of the C-6 hydroxyl by an epoxy group. Accordingly, the H-6 signal located at δ3.54 in tomentol (**1a**) was shifted upfield to δ2.74 in pre-tomentol (**2a**). In addition, a paramagnetic shift of the H-2 triplet from δ5.45 to 5.75 was also observed. This downfield shift of H-2 is in agreement with the presence of a primary hydroxyl group at C-20 and the stereochemistry at Δ^2 which must be *E*.

Acetylation of pre-tomentol (**2a**) gave the diacetate **3**, which lacked the hydroxyl absorptions in the IR spectrum, but instead showed an additional carbonyl band at 1730 cm^{-1}. The ^1H NMR spectrum (Table 1) of **3** showed two three-proton singlets at δ2.05 and 2.07 and a downfield shift of the H-1 and H-20 signals, which appeared at δ4.61 and 4.51 respectively in the diacetate **3**. These paramagnetic shifts confirmed the presence of hydroxyl groups at C-1 and C-20 in compound **2a**.

Pre-zoapatanol (**2c**) and pre-tomexanthol (**2b**) were also isolated as gums, which exhibited mass spectral and ^1H NMR (Table 1) signals nearly identical to those of their corresponding oxepanes **1b** and **1c**, except for the same differences described above for pre-tomentol.

Based on the co-occurrence of these compounds, we think that the acyclic compounds **2a**, **2b** and **2c** are very likely the biogenetic precursor of the oxepane diterpenoids **1a**, **1b** and **1c** respectively.

Finally, the results of our study of seven individual plant collections of 'zoapatle', showed differences in the diterpenoids isolated from them. While five collections afforded mainly the (C_{20}) diterpenes zoapatanol (**1c**), tomexanthol (**1b**) and their precursors **2c** and **2b**, the other two afforded the C_{21} diterpenoids tomentol (**1a**) (montanol precursor) and pre-tomentol (**2a**). These results may be associated with botanical differences, which require further taxonomic investigation in order to establish whether this is due to varietial differences. Furthermore, our findings suggested that previous studies of 'zoapatle' were made with mixed collections of these two types of

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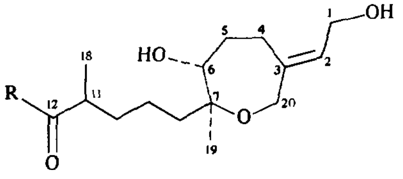

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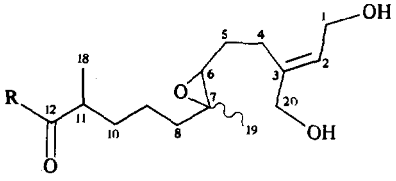

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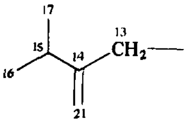

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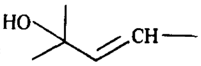

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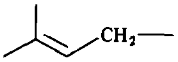

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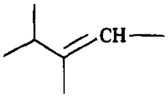

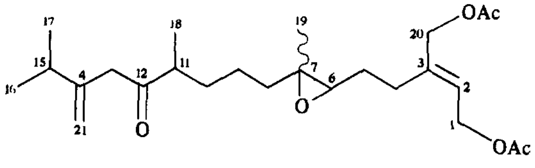

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Table 1. ¹H NMR data of pre-tomentol (**2a**), pre-zoapatanol (**2c**), pre-tomexanthol (**2b**) and pre-tomentol acetate (**3**) (80 MHz, $CDCl_3$, TMS as int. standard)

H	**2a**	**2c**	**2b**	**3**
1	4.21 *d* (7)*	4.20 *d* (7)	4.18 *d* (7)	4.63 *d* (7)
2	5.75 *br t* (7)	5.75 *br t* (7)	5.75 *br t* (7)	5.63 *br t* (7)
4	2.35 *t* (7)	2.33 *t* (7)	2.33 *t* (7)	†
6	2.74 *dd* (7, 5)	2.72 *dd* (7, 5)	2.72 *dd* (7, 5)	2.70 *dd* (7, 5)
13	3.17 *br s*	3.12 *br d* (7)	6.25 *d* (16)	3.17 *br s*
14	—	5.27 *br t* (7)	6.89 *d* (16)	—
16	1.10 *d* (7)	1.75 *d* (~ 1)	1.39 *s*	1.04 *d* (7)
17	1.04 *d* (7)	1.62 *d* (~ 1)	1.39 *s*	1.04 *d* (7)
18	†	1.07 *d* (7)	1.09 *d* (7)	1.07 *d* (7)
19	1.24 *s*	1.24 *s*	1.23 *s*	1.23 *s*
20	4.10 *br s*	4.09 *br s*	4.09 *br s*	4.53 *br s*
21a	4.77 *br s*	—	—	4.77 *br s*
21b	4.97 *br s*	—	—	4.96 *br s*
AcO	—	—	—	2.07, 2.09 *s*

*Figures in parentheses are coupling constants or line separations in Hz.
†Obscured by other signals.

plant material, since the diterpenoid fraction was isolated as a mixture of the C_{20} and C_{21} compounds [3, 4].

EXPERIMENTAL

Seven collections of different individual plants were made at UNAM Campus, México City, in March 1984. The fresh plant material (leaves) was extracted with CH_2Cl_2 for 10 min and the resulting extracts were roughly fractionated by CC on silica gel. Three fractions (100 ml) were collected using CH_2Cl_2, CH_2Cl_2–Me_2CO (4:1) and CH_2Cl_2–Me_2CO (1:1) as eluants. Fraction 3 was further chromatographed by prep TLC (silica gel G; 1 mm × 20 × 20 cm; CH_2Cl_2–Me_2CO, 3:1) to yield 2 bands. The less polar band contained the oxepane-diterpenoids. The more polar band was further separated by repeated TLC (silica gel G) using different solvent systems (CH_2Cl_2–Me_2CO, 4:1) and petrol–EtOAc, 1:1) to yield the acyclic precursors.

Collections No. 1 (47 g), No. 2 (54 g), No. 3 (30 g), No. 4 (273 g) and No. 5 (105 g) afforded zoapatanol (**1c**), tomexanthol (**1b**), pre-zoapatanol (**2c**) and pre-tomexanthol (**2b**). Collections No. 6 (98 g) and No. 7 (139 g) afforded tomentol (**1a**) and pre-tomentol (**2a**).

Pre-tomentol (**2a**). Colourless gum, UV λ_{max}^{MeOH} nm (ε): 209 (1760); IR ν_{max}^{film} cm^{-1}: 3403, 1707, 1460; EIMS (probe) 70 eV *m/z* (rel. int.): 334 $[M-H_2O]^+$ (0.3), 316 $[M-2H_2O]^+$ (0.1), 233 $[M-H_2O-C_5H_9]^+$ (1.3), 225 $[C_{14}H_{25}O_2]^+$ (5), 171 (4), 167 (4), 153 (6), 149 (11), 141 (6), 125 (15), 113 (20), 111 (37), 97 (37), 95 (33), 83 (25), 81 (25), 71 (30), 69 (43), 67 (23), 57 (41), 55 (75), 43 (100), 41 (48).

Pre-tomentol acetate (**3**). A 9 mg sample of **2a** was acetylated with Ac_2O/C_5H_5N. Usual work up and TLC (CH_2Cl_2–Me_2CO, 47:3) gave the diacetate **3**, colourless gum, IR ν_{max}^{film} cm^{-1}: 1730, 1700, 1630, 1230; EIMS (probe) 70 eV *m/z* (rel. int.): 376 $[M-AcOH]^+$ (0.4), 333 $[M-AcOH-Ac]^+$ (0.9), 316 $[M-2AcOH]^+$ (0.7), 251 $[M-C_5H_9O_2]^+$ (2.8), 225 $[C_{14}H_{25}O_2]^+$ (2), 153 (9), 141 (5), 125 (7), 113 (8), 111 (30), 97 (27), 95 (24), 83 (12), 81 (13), 79 (15), 69 (16), 67 (12), 55 (45), 43 (100).

Pre-zoapatanol (**2c**). Colourless gum, UV λ_{max}^{MeOH} nm (ε): 218 (3365); IR ν_{max}^{film} cm^{-1}: 3387, 1705, 1635, 864 cm^{-1}; EIMS (probe) 70 eV *m/z* (rel. int.): 338 $[M]^+$ (0.1), 320 $[M-H_2O]^+$ (0.6), 302 $[M-2H_2O]^+$ (1.2), 251 $[M-H_2O-C_5H_9]^+$ (1.2), 233 $[M-2H_2O-C_5H_9]^+$ (1.6), 211 $[C_{13}H_{23}O_2]^+$ (5.6), 135 (5.6), 125 (13), 113 (10), 109 (9), 107 (10), 97 (31), 95 (28), 83 (12), 81 (20), 79 (18), 69 (60), 55 (74), 43 (100), 41 (79).

Pre-tomexanthol (**2b**). Colourless gum, UV λ_{max}^{MeOH} nm (ε): 204 sh (2920), 223 (25530); IR ν_{max}^{film} cm^{-1}: 3386, 1688, 1460; EIMS (probe) 70 *m/z* (rel. int.): 354 $[M]^+$ (0.1), 336 $[M-H_2O]^+$ (0.2), 318 $[M-2H_2O]^+$ (0.2), 209 $[C_{13}H_{23}O_3–H_2O]^+$ (4), 141 (10), 126 (6), 113 (15), 111 (10), 97 (16), 95 (18), 85 (10), 83 (12), 81 (15), 71 (22), 69 (23), 67 (16), 55 (31), 43 (100).

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