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DITERPENES FROM *MARRUBIUM SERICEUM*, *MARRUBIUM SUPINUM* AND *MARRUBIUM ALYSSON*

GIUSEPPE SAVONA*, FRANCO PIOZZI*, LUISA M. ARÁNGUEZ† and BENJAMÍN RODRÍGUEZ†

* Institute of Organic Chemistry, University of Palermo, Italy and † Institute of General Organic Chemistry, C.S.I.C., Juan de la Cierva, 3, Madrid-6, Spain

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Key Word Index—*Marrubium sericeum*; *M. supinum*; *M. alysson*; Labiatae; new furanic and prefuranic labdane diterpenes.

Abstract—From some *Marrubium* species endemic in the Iberian Peninsula, four new diterpenoids, 6-acetyl-marrubenol, 19-acetyl-marrubenol, premarrubenol and 6-acetyl-premarrubenol, have been isolated. The previously known diterpenes marrubiin and marrubenol have also been obtained from the same sources.

INTRODUCTION

The genus *Marrubium* (Labiatae) contains some 40 species, but only a few of them have been investigated in the search for diterpenic compounds. Previous work has been reported on *M. vulgare* which contains the diterpenes marrubiin, peregrinol and vulgarol [1], marrubenol and its hemiacetal [2], and premarrubiin [3]. *M. peregrinum* contains peregrinone, tetrahydroperegrinone [4] and peregrinol [5], and *M. incanum* yielded marrubiin and peregrinone [6].

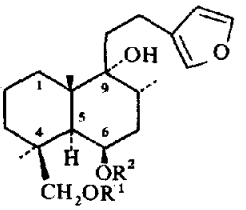
We now report our investigation on *M. sericeum* Boiss. (= *M. supinum* L. var. *boissieri* Rouy), *M. supinum* L. and *M. alysson* L., three species growing in Spain.

RESULTS AND DISCUSSION

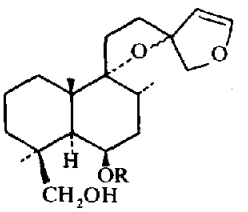
Besides the known diterpenoids marrubiin and marrubenol (**1**), two new labdane compounds have been isolated from the aerial part of *M. sericeum*, i.e. 19-acetyl-marrubenol (**2**) and 6-acetyl-marrubenol (**3**).

Compound **2** was an amorphous product with a $C_{22}H_{34}O_5$ molecular formula. Its IR spectrum had strong absorptions for an alcoholic function (3520 cm^{-1}) and acetate group (1720 and 1250 cm^{-1}), whereas the ^1H NMR spectrum showed signals for a β-substituted furan ring (three protons at δ 7.42, 7.31 and 6.35), a $-\overset{|}{\underset{|}{C}}-CH_2OAc$ group (AB system centred at 4.55, J = 12 Hz and a 3H singlet at 2.08), a secondary hydroxyl function (geminal proton as a narrow multiplet, $W_{1/2}$ = 6 Hz, at 4.35), two C-methyl singlets at 1.27 and 1.01 and a secondary methyl group at 0.95 (J = 7 Hz). All these data may be accommodated by structure **2** for 19-acetyl-marrubenol. This assignment was confirmed by the partial synthesis of **2** starting from marrubenol (**1**) by Ac_2O–pyridine treatment at room temperature for 6 hr. A mixture of two products was obtained, one of which was identical (IR, MS, ^1H NMR, $[\alpha]_D$) with natural 19-acetyl-marrubenol (**2**) and the other less polar substance, was identified with the previously described [7] 6,19-diacetyl-marrubenol (**4**).

The other new diterpenoid (**3**) isolated from *M. sericeum* was a highly unstable substance and isomerized slowly into 19-acetyl-marrubenol (**2**). The ^1H NMR spectrum of compound **3** was almost identical to the spectrum of **2**, the only differences being in the chemical shifts of the H-6 proton (now at δ 5.47) and the C-19 hydroxymethylene group (AB system centred at 3.78). These data are in agreement with the structure **3** of 6-acetyl-marrubenol. As compound **3** is unstable, it is possible that 19-acetyl-marrubenol (**2**) was an artefact arising from 6-acetyl-marrubenol (**3**) by transacetylation.



	R^1	R^2
1	H	H
2	Ac	H
3	H	Ac
4	Ac	Ac

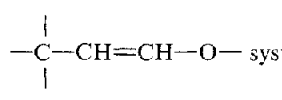


5 R = H
6 R = Ac

Marrubiin and two other new labdane diterpenoids, premarrubenol (**5**) and its 6-acetyl derivative (**6**), occurred also in the aerial part of *M. supinum*.

Premarrubenol (**5**) had the formula $C_{20}H_{32}O_4$ and its IR spectrum showed absorptions for an alcoholic —OH (3250 cm^{-1}) and an aliphatic double bond (1610 cm^{-1}). Signals in the ^1H NMR spectrum occurred at δ 1.05 and 1.25 (*s*, 3H each, tertiary Me), 0.85 (*d*, J = 6.5 Hz, 3H, secondary Me), 3.07 and 4.18 (AB system, J = 11 Hz, axial $-CH_2OH$; spin decoupling experiments showed that these two protons were coupled geminally); another AB system was indicated by signals at 3.95 and 4.35 (*dd*, J = 10 Hz, $-\overset{|}{\underset{|}{C}}-CH_2-O-$), whereas a

methyne proton, geminal to a secondary hydroxyl group, appeared at 4.12 (*m*, $W_{1/2}$ = 8 Hz). Irradiation at this last field caused a small doublet at δ 1.44 (1H, J = 1.8 Hz) to collapse to a sharp singlet which was assigned to the H-5 proton. Finally, two doublets at 5.15 and 6.35 (J = 3 Hz) corresponded to a



system. This ^{1}H NMR spectrum is very similar to that of marrubenol (**1**) [2], the differences being consistent with the occurrence of a β,β-disubstituted dihydrofuran instead of the β-monosubstituted furan ring of marrubenol. The fragments at *m/e* 96 and 82 in the MS of compound **5** further supported this attribution. On the basis of the molecular formula and the above ^{1}H NMR data, structure **5** of premarrubenol may be attributed to this new substance. This hypothesis was confirmed by the slow isomerization of **5** to marrubenol (**1**), identified by conventional methods (mp, IR, MS, ^{1}H NMR, $[\alpha]_D$): thus the absolute configuration of **5** was also proved.

6-Acetyl-premarrubenol (**6**) was a highly unstable uncrystallizable oil, that changed slowly into a mixture of prefuranic and furanic products, from which 19-acetyl-marrubenol (**2**) was isolated and identified. Compound **6** had the formula $C_{22}H_{34}O_5$ and the signals in its ^{1}H NMR spectrum were almost identical to those of premarrubenol (**5**); only the multiplet of the H-6 was shifted downfield at δ 5.35 and the double doublet of the axial —CH_2OH group occurred at 3.40 and 3.90, whereas an acetoxyl group appeared as a singlet at 2.02. These data can be rationalized with the occurrence of the acetate on the secondary hydroxyl group, and hence with structure **6** for 6-acetyl-premarrubenol.

It is notable that reports of the number of prefuranic diterpenes have been growing rather rapidly in the chemical literature during the last few years.

Finally, the aerial part of the third species studied by us, *M. alysson*, contained only marrubiin.

EXPERIMENTAL

Extraction of M. sericeum. The sample of *M. sericeum* was collected near Vélez Blanco (Almería). The powdered aerial part (1500 g) was extracted 3 × with Me_2CO (10 l.) at room temp. for 3 days. The extracts were evapd to dryness under red. pres. and low temp. (26°), dissolved in EtOAc and washed with H_2O. After evapn of the solvent, the residue (32 g) was chromatographed on Si gel (Merck, 7734, deactivated with 15% H_2O) column (750 g). Elution with petrol and petrol–EtOAc (9:1) gave, in order of elution, marrubiin (100 mg), 19-acetyl-marrubenol (**2**, 80 mg), 6-acetyl-marrubenol (**3**, 40 mg) and marrubenol (**1**, 3.1 mg). Marrubiin and marrubenol were identified by their physical and spectroscopic data (mp, $[\alpha]_D$, IR, MS, ^{1}H NMR), in full agreement with those reported in the literature. 19-Acetyl-marrubenol (**2**): a syrup; $[\alpha]_D^{20°}$ −3.3° (*c* 0.71, $CHCl_3$). IR ν_{max}^{NaCl} cm^{-1}: 3520, 2930, 2870, 1720, 1250, 1025, 880, 760. UV λ_{max}^{EtOH} nm (log ε): 218 (3.60). ^{1}H NMR ($CDCl_3$): see Discussion. MS (70 eV, direct inlet): M^+ at *m/e* 378 ($C_{22}H_{34}O_5$ requires 378), other strong peaks at *m/e* 360, 318, 305, 109, 81 (base peak). 6-Acetyl-marrubenol (**3**): ^{1}H NMR ($CDCl_3$): see Discussion, other signals at δ 7.45, 7.32 and 6.35 (1H each, *m*, $W_{1/2}$ = 4 Hz, furanic protons), 2.08 (3H, *s*, AcO), 1.25 and 1.04 (3H each, *s*, *t*-Me) and 0.95 (3H, *d*, J = 7 Hz, *s*-Me). A $CHCl_3$ soln of **3**, after 24 hr at room temp. gave a 1:1 mixture of 19-acetyl-marrubenol (**2**) and starting material.

Partial synthesis of **2** *and* **4** *from marrubenol* (**1**). Treatment of **1** (200 mg) with Ac_2O (2 ml) in Py (2 ml) for 6 hr at room temp. gave a mixture of two compounds easily separated on PLC (Si gel: $CHCl_3$–MeOH, 18:1) into a more polar substance (60 mg) identical (IR, MS, ^{1}H NMR, $[\alpha]_D$) with natural 19-acetyl-marrubenol (**2**), and a less polar compound (130 mg), identical in all respects with 6,19-diacetyl-marrubenol (**4**) [7].

Extraction of M. supinum. The sample of *M. supinum* was gathered near María (Almería). The powdered aerial part (800 g) was extracted 2× with Me_2CO (5 l.) at room temp. After the treatment described above for *M. sericeum*, the following compounds were isolated in order of elution: marrubiin (40 mg), 6-acetyl-premarrubenol (**6**, 300 mg), and premarrubenol (**5**, 400 mg). Premarrubenol (**5**): mp 162–164° (Me_2CO–*n*-hexane), thin rectangular platelets; $[\alpha]_D^{20°}$ −45° (*c* 0.33, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3250, 2980, 2960, 2920, 2895, 2880, 2845, 1610, 1460, 1380, 1340, 1310, 1270, 1220, 1140, 1065, 1030, 1010, 975, 945, 870, 860, 760. ^{1}H NMR ($CDCl_3$): see Discussion. MS (70 eV, direct inlet): M^+ at *m/e* 336, strong peaks at *m/e* 318, 235, 220, 193, 179, 167, 153 (base peak), 123, 109, 96 and 82. (Found: C, 71.15; H, 9.62. $C_{20}H_{34}O_4$ requires: C, 71.39; H, 9.59%). 6-Acetyl-premarrubenol (**6**): remained oily even after PLC purification (Si gel: petrol–EtOAc, 3:2), MS (70 eV, direct inlet) *m/e*: 378 (M^+), 360, 318, 123, 109, 96, 82. ^{1}H NMR ($CDCl_3$): see Discussion, other signals at δ 6.40 and 5.15 (1H each, *d*, J = 3 Hz, C-14 and C-15 protons), 4.42 and 4.02 (AB system, J = 10 Hz, C-16 protons), 1.25 and 1.01 (3H each, *s*, *t*-Me) and 0.82 (3H, *d*, J = 6.5 Hz, *s*-Me). When **6** was left for some days at room temp., several decomposition products were observed on TLC: one of these had an identical R_f to that of 19-acetyl-marrubenol (**2**). This compound was separated by PLC (Si gel: petrol EtOAc, 3:2) and its IR, ^{1}H NMR spectra and $[\alpha]_D$ were identical with the values for compound **2**.

Extraction of M. alysson. The sample of *M. alysson* was collected near Hellín (Albacete). The powdered aerial part (900 g) was extracted with Me_2CO as described for the other species. Chromatography gave only marrubiin (500 mg), identified by conventional methods.

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