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J. Nat. Prod., **1994**, 57 (1), 181-185• DOI:
10.1021/np50103a031 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 57, No. 1, pp. 181-185, January 1994

MONTBRETOL AND SALVINOLONE ARE IDENTICAL

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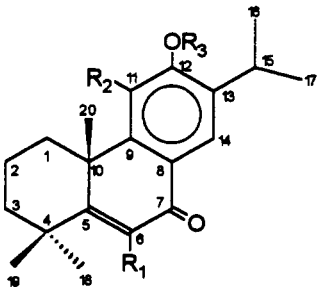
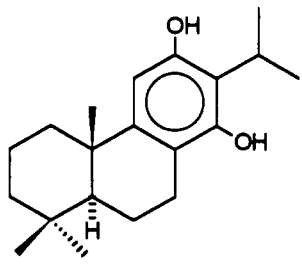
ABSTRACT.—Re-investigation of the structure of montbretyl methyl ether and montbretol by the selective INEPT nmr technique led to their identification as salvinolonyl 12-methyl ether [**5**] and salvinolone [**4**], respectively.

In 1992, two of us reported on the isolation of three new abietane diterpenoids from *Salvia montbretii*, which were assigned the structures **1**, **2** and **6** (1). Recently, Burnell and co-workers (2) synthesized montbretyl 12-methyl ether [**2**] through the oxygenation of sugiol methyl ether [**9**] in *t*-BuOK/*t*-BuOH and observed that the synthetic product showed significant spectroscopic differences from the reported natural substance (2). These authors went on to propose that the structure of compound **2** described by Ulubelen and Topçu (1) should be the 6-methyl ether, **3**. Although Burnell and co-workers did not make any definitive comment about the structure proposed for montbretol [**1**], they suggested that it should also be modified due to the great similarity between the spectral properties of **1** and **2**. Attempts to demethylate the synthetic compound **2** to afford **1** failed. Given these conflicts, we decided to reinvestigate the structure of compound **2** using higher-field nmr and the selective INEPT nmr technique (3–5).

In the ^{13}C-nmr spectrum (see Experimental), rerun on a more purified and concentrated sample of montbretyl 12-methyl ether, the chemical shift of the OMe group was observed to be too far downfield (61.9 ppm) for an isolated 12-OMe, which rarely falls outside the range of δ 55–56 unless C-11 also bears a hydroxyl or a methoxyl group. Some examples are compound **7** isolated from *Salvia candidissima* (6) and compound **8**



1 R_1=OH, R_2=R_3=H
2 R_1=OH, R_2=H, R_3=CH_3
3 R_1=OCH_3, R_2= R_3=H
4 R_1=R_3=H, R_2=OH
5 R_1=H, R_2=OH, R_3=CH_3



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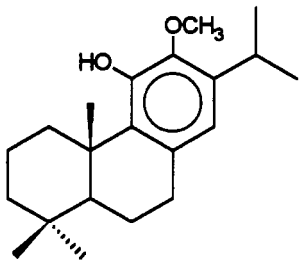

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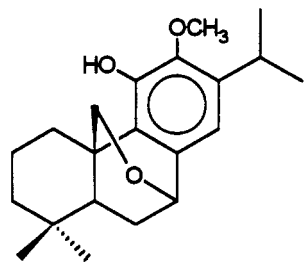

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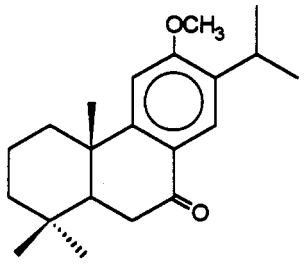

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isolated from *Salvia canariensis* (7), in which the chemical shifts of the OMe group are at 61.8 and 62.0 ppm, respectively. Additional examples are described by Burnell and co-workers (8).

The structure was solved using the selective INEPT technique (Table 1) and the critical experiment was the irradiation of the singlet at 6.45 ppm, which, in the literature (1), was assigned to H-11. Irradiation of this proton produced enhancement in the signals of the two quaternary aliphatic carbons (38.2 and 42.2 ppm), corresponding to C-4 and C-10, respectively. Enhancement of the signal at 127.4 ppm was also observed, and it was assigned to C-8. These results, together with the chemical shift of the OMe group, led us to suggest a change in the position of the OH group from C-6 to C-11 giving rise to structure **5** for montbretyl methyl ether. The singlet at 6.45 ppm was therefore assigned to H-6, which explained the presence of the signal at δ 175.4 ppm for a quaternary vinylic carbon in the β position of a

TABLE 1. Selective INEPT Experiments on Salvinolonyl 12-Methyl Ether [**5**].[a]

Proton irradiated	δ	Carbon enhanced
H-14	(7.72)	C-7 (185.4), C-9 (136.7), C-12 (148.2), C-15 (26.8)
OMe	(3.82)	C-12 (148.2)
OH	(6.29)	C-9 (136.7), C-11 (145.8), C-12 (148.2)
H-6	(6.45)	C-4 (38.2), C-8 (127.4), C-10 (42.2)
H-15	(3.22)	C-10 (42.2), C-12 (148.2), C-13 (139.7), C-14 (115.8), C-16 (23.6), C-17 (23.6)
H-20	(1.65)	C-5 (175.4), C-9 (136.7), C-10 (42.2)
H-19	(1.34)	C-4 (38.2), C-5 (175.4)
H-16, H-17, H-18	(1.25)	C-5 (175.4), C-4 (38.2), C-13 (139.7)

[a]Run in $CDCl_3$ at 90.8 MHz.

double bond conjugated with a carbonyl, and which was assigned to C-5. When the methyl proton signals H-19 and H-20 were irradiated, the signal at 175.4 ppm was enhanced, supporting the assignment of this resonance to C-5. Irradiation of the proton signals corresponding to the OMe and the OH enhanced the signal at 148.2 ppm (assigned to C-12) showing that both groups are vicinal in the aromatic ring. Irradiation at 1.25 ppm not only affects the resonances of the methyl groups H_3-16, H_3-17 and H_3-18, but also the resonances corresponding to some of the aliphatic protons in ring A. Hence, the results from this irradiation are ambiguous except for the enhancement of the signal at 139.7 ppm (C-13), which we are sure is due to the irradiation of H_3-16 and H_3-17. The other irradiations (Table 1) substantiated the proposed structure and permitted the unambiguous assignment of the carbon resonances. In a nOe experiment, irradiation of the singlet at 6.45 ppm caused a strong enhancement (13%) of the singlet at 1.25 ppm corresponding to the pseudo-equatorial methyl group at C-4 (H-18) and indicated the proximity between these two protons. An enhancement of 3% was also observed in the signal corresponding to H-19.

Regarding the ^{1}H-nmr spectra of this class of compounds, it is important to mention that a substantial deshielding is observed in the signal corresponding to H-1β when C-11 bears an oxygenated function (9,10). Normally, H-1 resonates at 2.3 ppm or less, but when a hydroxyl or a methoxy group is at C-11 the chemical shift for H-1β (equatorial) falls in the range of 3.1–3.8 ppm. In the previous study of the ^{1}H-nmr spectra (1), this signal was reported for montbretol at δ 3.30 (dt, J=13, 3 Hz), but was not taken into account in the structure elucidation; the chemical shift of H-20 at 1.68 ppm was considered more important in order to position the OH group at C-6 (11,12). In the present case, the spectra were taken at higher magnetic field (Table 2), and the signal of H-1β was found at 3.27 ppm for montbretyl methyl ether. At lower magnetic field it was not properly observed due to overlap with the heptet corresponding to H-15 at 3.22 ppm. This result not only supports the position of the OH group at C-11, but also shows that the chemical shift of H-20 is not indicative of the presence of an OH group at C-6 in this kind of abietane (5,8,11,13-abietatetraen-7-one). Furthermore, the higher magnetic field spectra and the nOe experiment run on the 12-methyl

TABLE 2. ^{1}H-NMR Spectra of Salvinolone [**4**] and Its 12-Methyl Ether [**5**].[a]

H	Compound **4**	Compound **4**[b]	Compound **5**
1β	3.25 (dt, 13, 3)	3.36 (dt, 13, 3)	3.27 (dt, 13, 3)
6	6.43 (s)	6.24 (s)	6.45 (s)
14	7.70 (s)	7.46 (s)	7.72 (s)
15	3.02 (hept., 7)	3.27 (hept., 6.8)	3.22 (hept., 7)
16	1.28 (d, 7)[c]	1.18 (d, 6.8)[c]	1.25 (d, 7)[c]
17	1.31 (d, 7)[c]	1.20 (d, 6.8)[c]	1.27 (d, 7)[c]
18	1.25 (s)	1.36 (s)	1.25 (s)
19	1.34 (s)	1.17 (s)	1.34 (s)
20	1.65 (s)	1.61 (s)	1.65 (s)
OMe	—	—	3.82 (s)
OH	—	—	6.29 (s)

[a]Run in $CDCl_3$ at 360 MHz. Chemical shifts given in ppm using TMS as an internal reference. Signal multiplicity and coupling constants (Hz) are in parentheses.

[b]Recorded in DMSO-d_6 at 300 MHz.

[c]The assignments corresponding to H-16 and H-17 may be interchangeable in all compounds.

ether led us to reassign the signals corresponding to the methyl protons H_3-16, H_3-17 and H_3-18.

Finally, it was found that the only differences between the respective ^{1}H-nmr spectra of montbretol and its methyl ether are the absence of a signal corresponding to the OMe group and the chemical shift of the protons H-15, H-16 and H-17; the remaining signals are almost superimposable (Table 2), thereby suggesting structure **4** for montbretol. Unfortunately, we could not acquire an adequate sample to obtain a good ^{13}C-nmr spectrum. Compound **4** is known as salvinolone, which, coincidentally, was previously isolated by one of our groups from *Salvia prionitis* (13). The ^{1}H-nmr spectra of salvinolone, reported in the literature as run in DMSO-d_6, is superimposable with that obtained for montbretol in the same solvent. It is important to note that in the selective INEPT experiment reported for salvinolone (13), the irradiation of H-6 also produced enhancement of carbons C-4, C-10 and C-8, as in the experiment run for its 12-methyl ether [**5**].

In conclusion, the structure of the compounds montbretol [**1**] and its 12-methyl ether [**2**] reported in the previous work (1) are corrected to salvinolone [**4**] and its new derivative salvinolonyl 12-methyl ether [**5**] respectively. As far as we can establish, compound **2** exists only as a synthetic product (2), but the structure **1** has been reported as being isolated from the wood of *Juniperus rigida* (14). Although the absolute stereochemistry of this compound was not given, the publication reports a positive specific rotation.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^{1}H-Nmr and ^{13}C-nmr (BB and DEPT) spectra were recorded in $CDCl_3$, with TMS as an internal standard, employing a Nicolet NMC-360 spectrometer, which was also used for the selective INEPT experiments. The ^{1}H-nmr spectrum of salvinolone recorded in DMSO-d_6 and the differential nOe experiments run on its 12-methyl ether were carried out using a Varian XL-300 instrument. For the selective INEPT experiments, data sets of 16K covering a spectral width of 10 KHz were acquired. Proton pulse widths were calibrated using a sample of HOAc in 10% C_6D_6 (^{1x}J=6.7 Hz) in a 5-mm nmr tube (15). The radio-frequency field strength for the soft pulse was on the order of 25 Hz for these experiments. We used 7 Hz as $^3J_{CH}$ for aromatic and vinylic protons and 5 Hz for aliphatic and hydroxyl protons.

Salvinolonyl 12-methyl ether [**5**].—Yellow, amorphous compound: uv λ max (MeOH) 342 (log ε 3.6), 248 (log ε 4.2) nm; ir ν max ($CHCl_3$) 3420 (OH), 3050, 1620, 1597, 1560 and 1505 (aromatic ring), 1665 (C=C-C=O); ^{1}H-nmr see Table 3; hrms *m/z* [M]$^+$ 328.2050 ($C_{21}H_{28}O_3$, calcd 328.2038) (10), [M−Me]$^+$ 313 (7), 278 (14), 257 (10), 217 (59), 113 (15), 71 (30), 57 (50); ^{13}C-nmr (DEPT, $CDCl_3$, 90.8 MHz) δ ppm 185.4 (s, C-7), 175.4 (s, C-5), 148.2 (s, C-12), 145.8 (s, C-11), 139.7 (s, C-13), 136.7 (s, C-9), 127.4 (s, C-8), 123.5 (d, C-6), 115.8 (d, C-14), 61.9 (q, OMe), 42.2 (s, C-10), 40.5 (t, C-1), 38.2 (s, C-4), 34.2 (t, C-3), 33.2 (q, C-20), 29.3 (q, C-19), 26.8 (q, C-15), 24.8 (q, C-18), 23.6 (q, C-16), 23.6 (q, C-17), 18.7 (t, C-2).

ACKNOWLEDGMENTS

We wish to acknowledge Dr. K. Zaw of the nmr laboratory of the Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago (UIC), for his expert help with the nmr experiments on the Varian XL-300. Thanks are also extended to the nmr laboratory of the Research Resources Center, UIC, for providing expert assistance and spectroscopic equipment used in this study and to Dr. George Doss (formerly A. N. Abdel-Sayed) for the initial implementation of the selective INEPT experiment at UIC (16). R.R.G. wishes to thank CONICET-Argentina for a post-doctoral fellowship.

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Received 28 July 1993