Methyl Valerenate, a New Sesquiterpenoid in the Essential Oil from Underground Parts of *Valeriana officinalis* L. *s.l.*

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A new valerenane sesquiterpenoid, methyl valerenate (**1**), was found in the essential oil from underground parts of *Valeriana officinalis* L. *s.l.* Spectral data of methyl valerenate, which was synthesized from valerenic acid (**2**), are given in this paper.

Introduction

The roots and rhizomes of *Valeriana officinalis* L. *s.l.*, family Valerianaceae, are used for the preparation of phytomedicines that are employed as mild sedative (Bos *et al.*, 1994, 1996a). Valerenic acid (**2**) and its derivatives acetoxyvalerenic acid and hydroxyvalerenic acid are characteristic constituents of *Valeriana officinalis* and have been isolated and characterized (Bos *et al.*, 1986). Together with the valepotriates, these valerenane sesquiterpenoids are held responsible for the mild sedative action of valerian-derived phytomedicines. Additionally, the essential oil might play a role in the biological activity of valerian (Bos *et al.*, 1997a).

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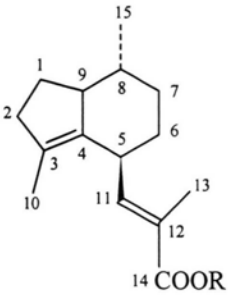

1 Methyl valerenate
R = CH_3

2 Valerenic acid
R = H

In continuation of our studies on the essential oil components of underground parts of *V. officinalis* (Bos *et al.*, 1997b) we now report on the occurrence of methyl valerenate in the oil. This valerenic acid derivative has not been found in nature before and is completely given in the paper.

Materials and Methods

Plant material

Seeds of *Valeriana officinalis* L. *s.l.* (Valerianaceae) were obtained from different botanical gardens in Europe and from VNK (Verenigde Nederlandse Kruidencoöperatie, Elburg, The Netherlands) (Bos *et al.*, 1997b). After germination, the plants were grown in an experimental field in Elburg, where the underground parts were harvested. The essential oils were isolated from air-dried and freshly ground material by hydrodistillation. Voucher specimens have been deposited at the Department of Pharmaceutical Biology, Groningen, The Netherlands.

General experimental procedures

Essential oil samples were isolated using the apparatus described in the Dutch Pharmacopoeia (Bos *et al.*, 1996; 1997b). Optical rotation was measured on a Perkin-Elmer 241 polarimeter. UV and IR spectra were obtained with a Spectroflex III (Pharmacia) spectrophotometer and an ATI Mattson Genesis Series FTIR spectrometer, respectively. ^{1}H- and ^{13}C-NMR (APT) spectra were recorded on a Varian-500 Unity spectrometer (500 and 125.72 MHz).

Before measuring the 2D spectra, the exact 90° pulse width was determined. The shift-correlated

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2D NMR (COSY), incoherence transfer (NOESY) and C-H correlation by polarization transfer (HETCOR) spectra were recorded using standard Varian microprograms. GC was carried out on a Hewlett-Packard 5890 Series II gas chromatograph with a CP-Sil 5 WCOT fused-silica column (Bos *et al.*, 1996b; 1997b). GC-MS (EI and CI) was performed on a Unicam 610/Automass 150 GC/MS system with a CP-Sil 5 WCOT fused-silica column (Bos *et al.*, 1996b; 1997b).

Methyl valerenate (**1**) (synthetic)

Valerenic acid (2.1 mmol, was dissolved in 10 ml diethyl ether and treated with 27 mL of a solution of diazomethane in diethyl ether (0.76 mmol/ml). After evaporation of the solvent and the reagent, 2.0 mmol methyl valerenate (**1**) was obtained as a colourless fluid.

$[\alpha]_D^{20}$: -96.6° (c = 3.08, EtOH); UV (EtOH) $\lambda_{max.}$ (log ε) 219 nm (4.119); IR $\nu_{max.}$ (film) 2928, 2858 (OCH_3), 1714, 1642, 1435, 1379 ($COCH_3$), 1292, 1240, 1208, 1131, 1105, 1061, 840–752 (C=C) cm^{-1}. EI-GC/MS *m/z* (rel int) 39 (35), 40 (7), 41 (90), 42 (7), 43 (23), 44 (1), 45 (6), 50 (1), 51 (11), 52 (6), 53 (30), 54 (4), 55 (49), 56 (5), 57 (3), 58 (2), 59 (15), 63 (2), 64 (2), 65 (11), 66 (4), 67 (7), 68 (1), 69 (2), 77 (12), 78 (4), 79 (14), 80 (3), 81 (10), 82 (1), 87 (1), 88 (6), 89 (2), 90 (1), 91 (65), 92 (12), 93 (41), 94 (11), 95 (28), 96 (4), 97 (3), 99 (1), 100 (4), 101 (5), 102 (4), 103 (10), 104 (6), 105 (100), 106 (23), 107 (83), 108 (21), 109 (14), 110 (1), 111 (3), 112 (37), 113 (4), 114 (2), 115 (22), 116 (12), 117 (33), 118 (10), 119 (56), 120 (15), 121 (37), 122 (51), 123 (9), 125 (6), 126 (3), 127 (8), 128 (12), 129 (15), 130 (7), 131 (57), 132 (16), 133 (94), 134 (17), 135 (16), 136 (2), 137 (2), 138 (3), 139 (9), 140 (19), 141 (4), 142 (3), 143 (9), 144 (5), 145 (47), 146 (22), 147 (44), 148 (41), 149 (10), 151 (2), 154 (2), 156 (2), 157 (4), 158 (8), 159 (36), 160 (25), 161 (67), 162 (9), 163 (2), 165 (2), 166 (10), 172 (1), 173 (23), 174 (17), 175 (3), 177 (2), 183 (6), 187 (10), 188 (12), 189 (32), 190 (5), 191 (4), 192 (2), 193 (5), 196 (1), 199 (1), 201 (23), 202 (3), 205 (6), 206 (2), 215 (2), 216 (38), 217 (15), 218 (2), 219 (1), 233 (8), 247 (1), 248 $[M^+]$ (74), 249 $[M+1]^+$ (13); CI-GC/MS (NH_4+) 249 $[M+1]^+$ (5), 266 $[M+18]^+$ (100).

Results and Discussion

Using GC-MS, we detected an unknown valerenane sesquiterpenoid with a molecular weight of 248 in the essential oil of several *V. officinalis* samples (Bos *et al.*, 1997b) . The fragmentation pattern of its mass spectrum was largely similar to that of valerenic acid, but it showed a clear difference of 14 *m/z* and a fragment of *m/z* of 233 which corresponds with $[M-1]^+$ of valerenic acid (**2**). This could be indicative for an extra methyl group, which was readily lost. In addition, the observation that the peak of the component in the gas chromatogram did not show tailing, in contrast to valerenic acid (**2**), suggested that the methyl group was esterified to the acid function. The isolation of the unknown component was hampered by its low content, i.e. 0.1–0.2% of the essential oil. Therefore, methyl valerenate (**1**) was synthesized by treating compound **2** with diazomethane.

Both the synthesized compound **1** and the unknown component had a retention index of 1785 in the gas chromatogram and their mass spectra were identical. On the base of the collected data, methyl valerenate (**1**) is most probably a genuine constituent of the essential oil from underground parts of *V. officinalis*. Compound **1** had already been mentioned as an intermediate in the chemical structure identification of valerenic acid (**2**) (Büchi *et al.*, 1960).

Table I. ^1H- (500 MHz) and ^{13}C-(125 MHz) NMR data of the synthetic methyl valerenate (δ ppm), $CDCl_3$ as solvent and TMS as internal standard.

position	δH (*J*, Hz)	δC
1	1.80 + 1.52, m	24.3
2	2.17, br t (7.6)	37.2
3		130.8
4		133.2
5	3.51, dd (9.7, 5.0)	34.1
6	1.74 + 1.39, m	25.2
7	1.83 + 1.39, m	28.5
8	1.97, m	32.8
9	2.94, m	47.2
11	6.99, dq (9.7, 1.46)	143.5
12		125.5
14		168.9
CH_3-10	1.61, m	11.8
CH_3-13	1.87, d (1.46)	13.2
CH_3-15	0.76, d (7.0)	12.1
Methoxy	3.70, s	51.4

In the ^{1}H-NMR spectrum of compound **1** (Table I) only small differences were found in comparison with the spectrum of valerenic acid (**2**) (Bos *et al.*, 1986). An additional singlet at δ 3.70 clearly indicated the presence of the esterified methyl group. The ^{13}C-NMR spectrum of compound **1** (Table I) revealed the presence of 16 carbon atoms: 8 secondary and quaternary, and 8 primary and tertiary carbon signals were seen. Compared with compound **2**, compound **1** had an additional tertiary carbon atom at δ 51.4 (esterified methyl) and further differences between the spectra of both compounds were small. Additional proof of the structure and identity of methyl valerenate (**1**) were obtained by combining COSY, NOESY and HETCOR with the 1D ^{1}H- and ^{13}C-NMR techniques.

Bos R., Hendriks H., Bruins A. P., Kloosterman J. and Sipma G. (1986), Isolation and identification of valerenane sesquiterpenoids from *Valeriana officinalis*. Phytochemistry **25**, 133–135.

Bos R., Woerdenbag H. J. and Zwaving J. H. (1994), Valeriaan en valeriaanpreparaten. Pharm. Weekbl. **129**, 37–43.

Bos R., Woerdenbag H. J., Hendriks H., Zwaving J. H., De Smet P. A. G. M., Tittel G., Wikström H. V. and Scheffer J. J. C. (1996a), Analytical aspects of phytotherapeutic valerian preparations. Phytochem. Anal. **7**, 143–151.

Bos R., Woerdenbag H. J., Hendriks H., Sidik, Wikström H. V. and Scheffer J. J. C. (1996b), The essential oil and valepotriates from roots of *Valeriana javanica* Blume grown in Indonesia. Flavour Fragr. J. **11**, 321–326.

Bos R., Woerdenbag H. J., De Smet P. A. G. M. and Scheffer J. J. C. (1997a), *Valeriana species*. In Adverse Effects of Herbal Drugs, Vol. 3. (De Smet P. A. G. M., Keller K., Hänsel R.and Chandler R. F. Eds.) Springer-Verlag: Berlin, Heidelberg, pp 165–180.

Bos R., Woerdenbag H. J., Hendriks H. and Scheffer J. J. C. (1997b), Composition of the essential oil from subterranean parts of *Valeriana officinalis* L. *s.l.* and several closely related taxa. Flavour Fragr. J. **12**, 359–370.

Büchi G., Popper T. L. and Stauffacher D. (1960), The structure of valerenic acid. J. Am. Chem. Soc. **82**, 2962–2963.