Structure-odor relationship study of C-6 unsaturated acyclic monoterpene alcohols: A comparative approach

Shaimaa Awadain Elsharif[1] and ANDREA BUETTNER[1,2]

[1] Friedrich-Alexander-Universität Erlangen-Nürnberg, Professorship for Aroma Research, Emil Fischer Center, Department of Chemistry and Pharmacy, Henkestraße 9, 91054 Erlangen, Germany

[2] Fraunhofer Institute for Process Engineering and Packaging, Giggenhauser Straße 35, 85354 Freising, Germany

Abstract

Acyclic monoterpenes are a valuable class of compounds useful for the flavor and fragrance industries [1]. Among them are the C-6 unsaturated monoterpene alcohols, namely linalool, geraniol, nerol and β-citronellol. These substances exhibit pleasant smell properties, are prevalent in the essential oils of many plants and are pharmacologically and physiologically active. Thereby, it is interesting to note that linalool and geraniol, specifically, do not only activate olfactory receptors, but have also other physiological activities, e.g. acting as anti-cancerogens [2, 3]. Systematic elucidation of the sensory characteristics of metabolic derivatives of this substance group, however, is very limited as most work, until today, focused on the basic acyclic monoterpene compounds. Our studies demonstrated that a series of these metabolites are odor active compounds, at times exhibiting exceptionally pleasant smells [4, 5]. In the course of our studies, we started from the respective monoterpene alcohols and their corresponding acetates, yielding a total of 24 oxygenated derivatives via diverse synthetic strategies, and characterized their olfactory properties. Specifically, these compounds were tested with regards to their odor qualities, relative odor thresholds (OTs) in air, and potential inter-individual variations in human sensory perception for each single substance. Finally, a comprehensive substance library was established comprising the respective retention index data (RI values) as well as mass spectrometric and nuclear magnetic resonance data, to aid in future analytical studies on this sensorially fascinating substance class.

Introduction

Apart from being fragrant compounds, linalool, geraniol, nerol and citronellol are characterized by several pharmacological and physiological properties. Linalool, found in lavender plant, potentiates $GABA_A$ receptor modulatory activity in the central nervous system; this mechanism is supposed to be the underlying principle for sleep-inducing and balancing effects in humans [6]. Similarly, nerol, present in lemon balm, showed to exhibit an anxiolytic effect in mice [7]. Geraniol, found in palmarosa, is a plant-based insect repellent especially active against mosquitos [8]. β-citronellol, a main component of lemon grass leaves, has showed a vasodilatory effect and therefore is claimed to be a hypotensive agent [9]. These monoterpenes and their acetate esters have previously been studied in view of their odor characters, without comprehensively correlating these smell properties with their chemical structure. In addition, the metabolic derivatives of these compounds in plants and animals have been studied [10, 11]. The main metabolic pathway includes C-8 hydroxylation of these monoterpenes yielding 8-hydroxy compounds which are further oxidized to the corresponding 8-carboxy derivatives. Due to the lack of commercial availability of these metabolites, the present work aimed at the synthesis of a total of 24 C-8 oxygenated compounds, and the determination of their odor qualities and odor thresholds (OT) in air using gas chromatography-olfactometry (GC-O). It was found that most of these derivatives elicited distinct smells [4, 5, 12]. Therefore,

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a structure-odor relationship study was established in a comparative approach comprising all the aforementioned monoterpenes, their acetates and their derivatives, highlighting the main structural features and functional groups that impact the odor quality and potency of this substance class.

Experimental

Syntheses

General synthetic pathways are shown in Figure 1. Chemicals required for synthesis were purchased from Sigma-Aldrich or Fischer Scientific. Data comprising nuclear magnetic resonance spectra (^{1}H and ^{13}C), mass spectra as well as retention indices were recorded and are described in Elsharif, Banerjee [4], Elsharif and Buettner [5], Elsharif and Buettner [12].

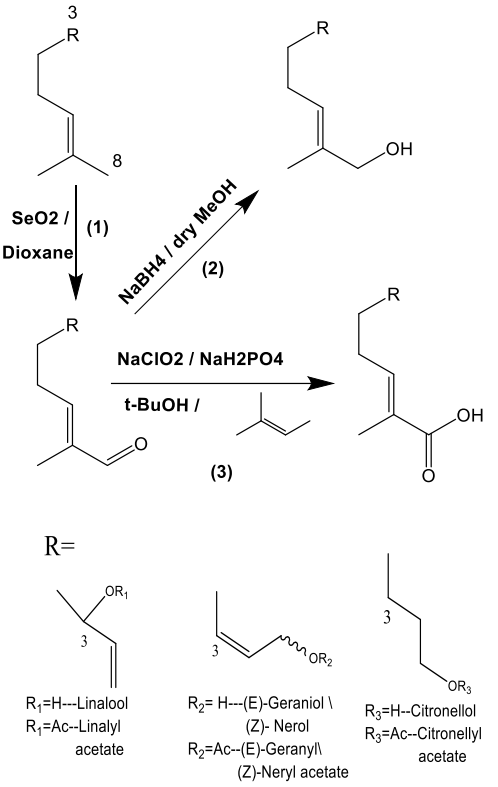

Figure 1: General synthetic pathways leading to the oxygenated derivatives.

Evaluation of odor quality and odor threshold

Odor qualities and thresholds in air were determined according to the procedure of Czerny, Brueckner [13] using GC-O involving five panelists who are trained volunteers from the University of Erlangen. Compounds were evaluated by each panelist repeatedly on different days on different capillary columns (DB-FFAP and DB-5). Panelists were asked to relate their sensory impression to an in-house developed flavor language.

Results and discussion

Tables 1 (monoterpene alcohols and their oxygenated derivatives) and 2 (monoterpene acetates and their oxygenated derivatives) show a comparison of the odor attributes perceived by at least 60% of the panel and group odor thresholds calculated as a geometric mean of the individual thresholds of panelists.

We found that parent monoterpene alcohols and their 8-hydroxy derivatives elicited citrus-like, fresh odor attributes (Table 1). Only two 8-oxo derivatives, 8-oxolinalool and 8-oxocitronellol showed similar odor attributes, i.e. citrus-like and fresh. On the other hand, 8-oxogeraniol and 8-oxonerol exhibited a fatty, musty odor. All 8-carboxy derivatives of this group were odorless with the sole exception of the 8-carboxynerol which elicits a fatty, waxy odor. Odor potencies of the parent monoterpene alcohols were much higher than that of their corresponding oxygenated derivatives. Although the additional OH group at C-8 preserved the citrus-like odor of the parent monoterpene alcohols, it tremendously decreased their potency. In case of 8-oxogeraniol and 8-oxonerol, the aldehyde group turned the odor to musty. A C-8 carboxy group added to linalool, geraniol or citronellol yielded odorless substances. To sum up: 1) the OH-group at C-1 or C-3 is responsible for the citrus-like odor and the low OT of the parent monoterpenes, 2) an additional OH at C-8 only retains the odor quality but not the potency, 3) oxidation of the OH at C-8 to the corresponding aldehyde group commonly turns the odor to musty and fatty, and 4) further oxidation of the aldehyde to the respective acid leads to odorless compounds.

Table 1: Odor qualities and thresholds for the acyclic monoterpene alcohols and their synthesized oxygenated derivatives

Name	*Odor quality*[a]	*% of panelists*	*Odor threshold*[b,c] *ng/L$_{air}$*
Linalool	Citrus	80	3.2
Geraniol	Citrus, fresh, fatty	80, 60	11.5
Nerol	Citrus, fresh	60	68
β-Citronellol	Citrus, floral, fresh	100, 40	11
8-Oxolinalool	Citrus, fatty	80, 60	50
8-Oxogeraniol	Fatty, musty	60	139
8-Oxonerol	Fatty, musty	80, 60	534.4
8-Oxocitronellol	Citrus, fresh	80, 60	879
8-Hydroxylinalool	Citrus, sweet	80, 40	123.6
8-Hydroxygeraniol	Citrus, fatty	60	310.2
8-Hydroxynerol	Citrus, sweet, vanilla	40, 60	451
8-Hydroxycitronellol	Citrus, fresh	100, 80	233
8-Carboxynerol[d]	Fatty, waxy	40	297

The parent monoterpene acetates elicited similar odor characters closely related to their monoterpene alcohols (citrus-like) with the sole exception of neryl acetate which smells sweet and phenolic (Table 2). Similarly, the 8-hydroxy acetates provoked citrus-like, soapy smell. 8-Oxogeranyl and 8-oxocitronellyl acetates were perceived as fatty, musty and rotten, musty. Interestingly, all 8-carboxy acetates were found to be odor active compounds with the sole exception of 8-carboxycitronellyl acetate. The panel described their smells as fatty for 8-carboxylinalyl acetate, sweet and coconut-like for 8-carboxygeranyl acetate, and green for 8-carboxyneryl acetate.

Table 2: Odor qualities and thresholds for the acyclic monoterpene acetates and their synthesized oxygenated derivatives

Name	*Odor quality*[a]	*% of panel*	*Odor threshold*[b,c] *ng/L$_{air}$*
Linalyl acetate	Citrus, fatty	60	134
Geranyl acetate	Citrus	60	57.1
Neryl acetate[d]	Phenolic, sweet	40	108
Citronellyl acetate	Citrus, soapy	60	665
8-Hydroxylinalyl acetate	Citrus, fresh	80, 60	120.3
8-Hydroxygeranyl acetate	Citrus, soapy	80, 60	62
8-Hydroxyneryl acetate[d]	Citrus	80	92
8- Hydroxycitronellyl acetate	Citrus, soapy	100, 80	1261
8-Oxolinalyl acetate	Citrus, fatty	60	6
8-Oxogeranyl acetate	Fatty, musty	60	20.5
8-Oxoneryl acetate	Citrus, fatty	80	26.1
8-Oxocitronellyl acetate	Musty, rotten	80, 60	346
8-Carboxylinalyl acetate	Fatty	100	7
8-Carboxygeranyl acetate	Sweet, coconut	60, 40	37.1
8-Carboxyneryl acetate	Green	40	24

[a]Common odor attributes given by the panel as perceived at the sniffing port. [b]Odor thresholds in air were determined as described by Ullrich and Grosch [14]. [c]Odor threshold was calculated as a geometric mean of the individual thresholds of panelists. [d]Anosmia observed.

The findings can be summarized as follows: 1) the acetate group at C-1 or C-3 decreases the odor potency at least by a factor of 5, but preserves the citrusy odor of the parent monoterpene alcohols with the sole exception of neryl acetate, 2) addition of an OH- group at C-8 enhances the citrus odor with an increase in potency, 3) the C-8 aldehyde group leads to the appearance of a musty odor for 8-oxogeranyl and 8-oxocitronellyl acetates, and 4) an acid moiety at C-8 of the acetates induces odor attributes other than citrusy, but with a further increase in odor potency. It is important to note that single cases of anosmia were observed for individuals with the following compounds: 8-hydroxynerol, neryl acetate and 8-hydroxyneryl acetate.

References

1. King, A.J. and J.R. Dickinson, (2003) FEMS Yeast Research, 3(1): p. 53-62.
2. Sun, X.-B., Wang, S.M., Li, T., and Yang Y.Q., (2015) Trop. J. Pharm. Res., 2015. 14(4): p. 619-625.
3. Madan, K.A. and T. Devaki, (2015) Int. J. Pharm. Pharm. Sci., 7(4): p. 67-70.
4. Elsharif, S.A., A. Banerjee, and A. Buettner, (2015) Frontiers in chemistry, 3: p. 57.
5. Elsharif, S.A. and A. Buettner, (2016) Journal of Agricultural and Food Chemistry,
6. Kessler, A., H. Sahin-Nadeem, S.C.R. Lummis, I. Weigel, M. Pischetsrieder, A. Buettner, and C. Villmann (2014) Mol Nutr Food Res, 58(4): p. 851-62.
7. Marques, T.H.C.,et.al., (2013) World Journal of Neuroscience, 2013. 03(01): p. 32-38.
8. Omolo, M.O., M.O.Omolo, D. Okinyo, I.O. Ndiege, W. Lwande, and A. Hassanali, (2004) Phytochemistry, 65(20): p. 2797-802.
9. Ribeiro-Filho, H.V., de Souza Silva C.M., de Siqueira R.J., Lahlou S., dos Santos A.A., and Magalhães P.J., (2016) European Journal of Pharmacology, 775: p. 96-105.
10. Luan, F., A. Mosandl, A. Degenhardt, M. Gubesch, and M.Wüst, (2006) Analytica Chimica Acta, 563(1-2): p. 353-364.
11. Chadha, A. and K.M. Madyastha, (1984) Xenobiotica, 14(5): p. 365-74.
12. Elsharif, S.A. and A. Buettner, (2017) Food Chemistry, 232: p. 704-711.
13. Czerny, M., R. Brueckner, E. Kirchhoff, R. Schmitt, and A., (2011) Chem Senses, 36(6): p. 539-53.
14. Ullrich, F. and W. Grosch, (1987) Zeitschrift für Lebensmittel-Untersuchung und Forschung, 184(4): p. 277-282.