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Structure–Odor Activity Studies on Derivatives of Aromatic and Oxygenated Monoterpenoids Synthesized by Modifying *p*-Cymene

Linda Schreiner,[§] Johannes Bauer,[§] Eva Ortner, and Andrea Buettner*

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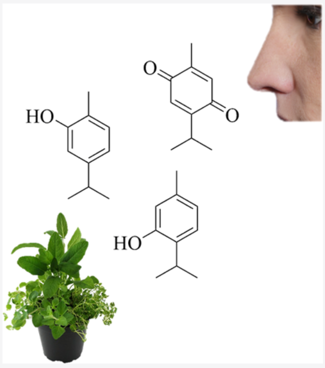
ABSTRACT: Thymoquinone was recently reported as having a unique pencil-like odor and being the impact compound for the cedar-like and cedar wood-based product smell such as pencils. The compounds thymol and carvacrol are structurally related odorants commonly found in plants and foods such as thyme and oregano, also having a significant contribution to their overall aroma. However, a systematic elucidation of the sensory properties in this class of oxygenated, aromatic monoterpenoids has not been carried out. To close this gap and gain new insights into structure–odor relationships leading to pencil-like and woody odors, 19 structurally related derivatives of *p*-cymene starting from thymol and carvacrol were synthesized and characterized. The compounds had odor thresholds ranging from 2.0 ng/L air to 388.8 ng/L air, being lowest for thymol and carvacrol and highest for thymohydroquinone. The compounds smelled mostly thyme-like, oregano-like, and pencil-like with phenolic, earthy, and medicinal variations in their odor character, which could be successfully linked to structural motifs.



Monoterpenes are a natural class of compounds comprising 10 carbon atoms. They are of great diversity, as they can consist of acyclic, monocyclic, or bicyclic structures and unsaturated, saturated, or aromatic structural elements, as well as being decorated with different functional groups, yielding alcohols, aldehydes, or ketones. By adding an oxygen function, the molecules are commonly called monoterpenoids. Monoterpenes and monoterpenoids are naturally synthesized by many plants, including conifers and often have pharmacological effects, such as antifungal, antibacterial, or antioxidant activities.[1] Furthermore, they are of interest for the perfume and food industry due to their aroma properties.[2]

Thymol (**1**), with its thyme-like, rosemary-like, ethereal smell and its structural isomer carvacrol (**2**), with an oregano-like, wood-like, and pencil-like odor, are monoterpenoids and well known for their occurrence in various aromatic plants such as thyme and oregano, thereby representing the main components of the essential oil.[3] They can also be found in basil,[4] eyebright,[5] black cumin,[6] and seafennel.[7] In addition, thymol is present in lettuce,[8] whereas carvacrol can be found in savory[2,9] and majoram.[2,9] The essential oils of aromatic plants containing thymol and carvacrol as well as the pure substances themselves are used as flavoring agents for food, e.g., baked goods, chewing gums, beverages, or hard candy.[10] Furthermore, both compounds show antimicrobial activity and can therefore act as food preservatives.[11−14] Owing to their antioxidative, antibacterial, and anticancer activity, both compounds are considered with regard to medical applications, either as auxiliary agents in cancer treatment or as an alternative remedy in the treatment of antibiotic-resistant bacteria.[15−17]

Thymol and carvacrol are hydroxylated derivatives of *p*-cymene (**3**). *p*-Cymene itself is also a common aroma-active compound in essential oils having a wood-like, citrus-like odor, and can be found in numerous plants such as thyme and horsemint, as well as cinnamon, cypress, eucalyptus, or turpentine (Table S1, Supporting Information).[2,18] All three molecules share the following core moiety: a benzene ring alkylated at C-1 and C-4 with a methyl and an isopropyl group, respectively. This structural similarity can also be found in the corresponding benzoquinone thymoquinone (**4**). Thymoquinone is one of the main components in black cumin (*Nigella sativa* L.) seed oil and has been reported to exert many positive physiological properties[19] relating to, for example, hepatoprotective,[20] anti-inflammatory,[21] antioxidant,[22] and anticancer[23,24] effects. Despite its potential for medical purposes, thymoquinone is an odor-active molecule with a unique medicinal, pencil- and leather-like odor, thereby being a natural molecule that had been reported for the first time to elicit this odor impression. Apart from that, we recently found that thymoquinone is an important odorous constituent of cedar and pine wood.[25,26] Thymol, carvacrol, and *p*-cymene, on the other hand, have been reported with various smell descriptors

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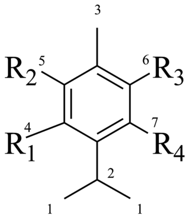
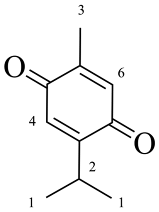


1-3, 5, 7-17

Compound	R_1	R_2	R_3	R_4
1	OH	H	H	H
2	H	OH	H	H
3	H	H	H	H
5	OH	OH	H	H
7	OH	H	OH	H
8	OCH_3	H	H	H
9	H	OCH_3	H	H
10	OH	H	OCH_3	H
11	H	OH	H	OCH_3
12	OCH_3	H	OCH_3	H
13	$OCOCH_3$	H	H	H
14	H	$OCOCH_3$	H	H
15	$OCOCH_3$	H	$OCOCH_3$	H
16	OH	H	$COCH_3$	H
17	H	OH	H	$COCH_3$



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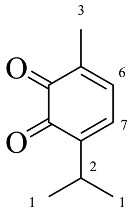

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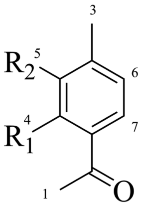

18-19

Compound	R_1	R_2
18	OH	H
19	H	OH

Figure 1. Chemical structures of compounds **1**−**19**. The numbering (1−7) corresponds to the ^{1}H NMR data in Tables S1−S4, Supporting Information.

such as wood-like, leaf-like (for thymol),[27] spicy (for carvacrol and thymol),[27,28] fuel-like (for *p*-cymene), and thyme-like, oregano-like (for carvacrol and thymol).[29]

From our numerous studies in the field of smell research it becomes evident that, despite decades of intense research in odorant discovery and on structure−smell activity relationships, there still is a lot to be unveiled. Nowadays, odorants are still discovered, commonly those that are very odor potent, yet hard to detect in nature due to their occurrence in traces or in complex substance mixtures. This is especially true in the case of terpenoid and sesquiterpenoid substances, as these molecules tend to be buried in complex mixtures of structurally related, but less odorous molecules, bringing about special challenges in chromatographic separation and unequivocal mass spectrometric detection. An example of this kind was our recent discovery of mustakone as a potent odorant in frankincense that required sophisticated chromatographic separation and enrichment steps in the course of structural identification of this substance.[30] Such studies demonstrate the need for establishing systematic databases in a bottom-up approach to ease future discovery of odor molecules.

According to this concept, an extended database in a series of recent studies comprising, among others, acyclic monoterpenes and their oxygenated derivatives had been established.[31−33] Using a systematic approach for odor threshold determination and for the recording of the respective smell descriptors it was demonstrated that structurally related monoterpenes are often similar in smell (e.g., citrus-like smells for linalool and its derivatives) with some of them being highly odor-active. Accordingly, this concept was extended in the present study to the investigation of structurally related substances of thymol, carvacrol, *p*-cymene, and thymoquinone. We hypothesized that targeted synthesis of related compounds might reveal further still unknown odorants, potentially even with related odor qualities, namely, wood- or pencil-like smells.

Structurally related substances that had previously been reported as natural compounds are thymol methyl ether, carvacrol methyl ether, *O*-acetylthymol, and *O*-acetylcarvacrol as well as thymohydroquinone dimethyl ether. Those substances were found, inter alia, in thyme,[34] oregano,[35] willowleaf yellowhead,[36] aya-pana,[37] seafennel,[7] and lettuce[8] (detailed information, cf. Table S1, Supporting Information). Despite knowledge of the presence of those substances as constituents in natural plants, there has been no comprehensive data provided regarding their sensory properties. Likewise, no further oxygenated aromatic monoterpenoids had been described. Thus, the aim of the present study was to synthesize structurally related derivatives and set up a database providing detailed sensory and analytical data for these substances. Therefore, 19 structurally related derivatives of thymol and carvacrol were synthesized, and their odor qualities and odor thresholds in air were determined. Furthermore, the MS data and retention indices on two chromatographic capillaries of different polarity as well as NMR spectra were compiled. The data generated will facilitate future identification of molecules belonging to this substance class and contribute to the analysis of structure−odor relationships in general, but also with regard to woody smells.

■ RESULTS AND DISCUSSION

Syntheses. Nineteen compounds (Figure 1) were investigated, and 15 of these compounds were synthesized following general synthetic procedures (cf. Figures S1−S6, Supporting Information). Thymol (**1**), carvacrol (**2**), *p*-cymene (**3**), and thymocatechol (**5**) were obtained from commercial sources.

Thymoquinone (**4**) was synthesized by catalytic oxidation of either thymol (**1**) or carvacrol (**2**) using Co(II)salen as catalyst and molecular oxygen as oxidant (Figure S4, Supporting Information).[38] The advantage of this reaction compared to stoichiometric oxidations is the decrease of the amount of chemicals used as well as the high yield. The thymo-1,2-quinone (**6**) was also successfully obtained via oxidation (Figure S6, Supporting Information). To this end, $NaIO_4$ was

Table 1. Retention Indices (RI), Odor Thresholds in Air (OT, Median, Range, and Factor between Highest and Lowest OT), and Odor Qualities of the Investigated Monoterpenoids

		RI[b] on			OT[d] (ng/L air)			
no.[a]	odorant	DB-FFAP	DB-5	N[c]	median	range	factor (high/low)[f]	odor qualities[e]
1	thymol	1950	1293	6	2.0	0.7–10.8	16	thyme-like, rosemary-like, ethereal
2	carvacrol	1984	1303	6	2.7	0.3–10.8	32	oregano-like, wood-like, pencil-like
3	*p*-cymene	1200	1030	9	43.2	21.6–345.6	16	wood-like, citrus-like
4	thymoquinone	2825	1257	4	24.3	1.4–345.6	256	medicinal, pencil-like, leather-like
5	thymocatechol	nd[g]	nd	2	nd	nd	nd	thyme-like, ethereal[h]
6	thymo-*o*-quinone	nd	nd	2	nd	nd	nd	thyme-like, pencil-like and ethereal[h]
7	thymohydroquinone	2818	1562	8	388.8	1.4–345.6	640	smoke-like, pencil-like
8	thymol methyl ether	1462	1232	6	10.8	2.7–86.4	32	thyme-like, rosemary-like, medicinal
9	carvacrol methyl ether	1482	1241	6	8.1	2.7–21.6	8	pencil-like, bergamot-like, oregano-like
10	*p*-methoxythymol	2222	1482	6	8.1	2.7–43.2	16	oregano-like, pencil-like, resin-like
11	*p*-methoxycarvacrol	1709	1414	6	8.1	2.7–172.8	64	oregano-like, pencil-like, resin-like
12	thymohydroquinone dimethyl ether	2252	1490	4	32.4	10.8–43.2	4	earthy, moldy
13	*O*-acetylthymol	1667	1349	4	8.1	2.7–10.8	4	thyme-like, ethereal-like, rosemary-like
14	*O*-acetylcarvacrol	1700	1368	4	12.2	2.7–43.2	16	oregano-like, thyme-like
15	di-*O*-acetyl-thymohydroquinone	2222	1664	9	172.8	0.7–691.2	1024	pencil-like, medicinal
16	*p*-acetylthymol	2749	1676	9	43.2	10.8–1728	160	phenolic, leather-like, faecal
17	*p*-acetylcarvacrol	2752	1656	9	21.6	2.7–86.4	32	phenolic, rubber-like
18	2-hydroxy-4-methyl-acetophenone	2807	1500	4	5.4	2.7–21.6	8	plastic-like, rubber-like
19	3-hydroxy-4-methyl-acetophenone	2811	1521	4	32.4	21.6–172.8	8	smoke-like, ham-like, phenolic

[a] Numbers chosen according to structural relation and used within the whole publication. [b] RI = retention index. [c] *N* = number of panelists determining the odor thresholds in air. [d] OT = odor threshold in air determined according to the literature.[28−30] [e] Odor qualities determined by the trained sensory panel. [f] Factor of variation between highest and lowest individual value. [g] nd = not determined due to instability of the compounds. [h] Due to instability only determined directly after synthesis by two trained panelists.

Table 2. Odor Thresholds (OT) of All Panelists of Thymol, Carvacrol, and Its Derivatives in Air Determined by GC-O

		OT[b] in ng/L air	panelists[c]									
no.	odorant	geometric mean	P1-A	P2-A	P3-A	P4-A	P5-A	P6-A	P1–B	P2–B	P3–B	P4–B
1	thymol	1.9	0.7	2.7	2.7	1.4	10.8	0.7	n.i.[a]	n.i.	n.i.	n.i.
2	carvacrol	3.0	0.3	10.8	2.7	10.8	2.7	2.7	n.i.	n.i.	n.i.	n.i.
3	*p*-cymene	74.1	43.2	172.8	345.6	43.2	n.i	21.6	21.6	172.8	172.8	43.2
4	thymoquinone	18.2	n.i.	1.4	345.6	5.4	n.i.	43.2	n.i.	n.i.	n.i.	n.i.
7	thymohydro-quinone	172.3	5.4	691.2	3456	432	n.i.	n.i.	43.2	10.8	345.6	864
8	thymol methyl ether	9.6	10.8	2.7	10.8	10.8	86.4	2.7	n.i.	n.i.	n.i.	n.i.
9	carvacrol methyl ether	7.6	5.4	21.6	10.8	10.8	5.4	2.7	n.i.	n.i.	n.i.	n.i.
10	*p*-methoxythymol	10.8	5.4	2.7	10.8	43.2	172.8	5.4	n.i.	n.i.	n.i.	n.i.
11	*p*-methoxycarvacrol	13.6	10.8	2.7	5.4	43.2	43.2	5.4	n.i.	n.i.	n.i.	n.i.
12	thymohydro-quinone dimethyl ether	25.7	10.8	43.2	21.6	43.2	n.i.	n.i	n.i.	n.i.	n.i.	n.i.
13	*O*-acetylthymol	6.4	5.4	2.7	10.8	10.8	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
14	*O*-acetylcarvacrol	9.1	2.7	2.7	21.6	43.2	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
15	di-*O*-acetylthymo- hydroquinone	93.3	0.7	345.6	691.2	43.2	345.6	n.i.	43.2	86.4	345.6	172.8
16	*p*-acetylthymol	90.8	43.2	43.2	1728	43.2	n.i.	21.6	10.8	345.6	864	43.2
17	p-acetylcarvacrol	13.6	43.2	2.7	21.6	10.8	21.6	n.i.	2.7	5.4	86.4	21.6
18	2-hydroxy-4-methyl-acetophenone	6.4	2.7	5.4	5.4	21.6	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
19	3-hydroxy-4-methyl-acetophenone	43.2	21.6	43.2	172.8	21.6	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.

[a] n.i. = not investigated (by the respective panelist). [b] OT geometric mean values determined in air by GC-O. [c] Panelists investigated the compounds partially two times (A and B); in total the values of panelists 1–6 (P1–P6) in investigations A and B are displayed.

added to thymocatechol (**5**). As both substances readily decompose, especially when being dissolved or during gas chromatography, sensory properties and mass spectra could not be determined. In these cases, two trained panelists smelled the pure substances directly after synthesis to gain an immediate odor impression. Thymohydroquinone (**7**) was obtained by reducing thymoquinone with elemental Zn and HOAc.

Thymol methyl ether (**8**), carvacrol methyl ether (**9**), *p*-methoxythymol (**10**), *p*-methoxycarvacrol (**11**), and thymohydroquinone dimethyl ether (**12**) were generated applying a Wiliamson etherification on thymol (**1**), carvacrol (**2**), and thymohydroquinone (**7**) with CH_3I as methylation agent (Figure S1, Supporting Information). The syntheses of the mono methyl ethers were conducted with KOH as base. For the synthesis of thymohydroquinone dimethyl ether (**12**) the reaction was carried out stepwise using the stronger base potassium *tert*-butoxide (Figure S5, Supporting Information). The acetylated substances *O*-acetylthymol (**13**), *O*-acetylcarvacrol (**14**), and di-*O*-acetylthymohydroquinone (**15**) were

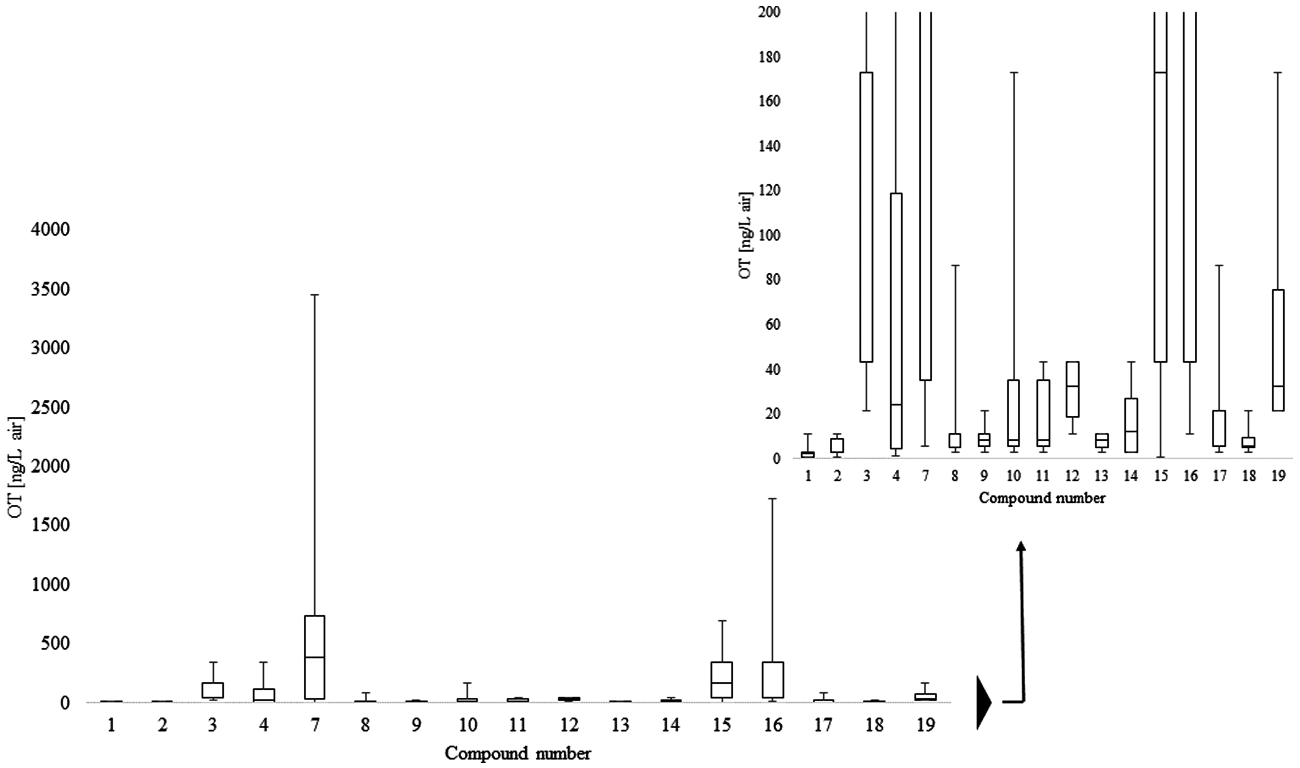

Figure 2. Odor thresholds for thymol and carvacrol derivatives shown as median value of all panelists.

formed by reaction with $(Ac)_2O$ (Figure S2, Supporting Information).

For further changes of the structural motifs related to the carbon skeletons of **1**, **2**, and **7**, a Fries rearrangement reaction was applied. First, *p*-acetylthymol (**16**) and *p*-acetylcarvacrol (**17**) were obtained via the readily formed phenolic esters, followed by the Fries rearrangement,[39] which converted the phenolic esters into hydroxyacetophenones (Figure S3, Supporting Information). Based upon steric considerations, acylation in the *para*-position was preferred. When adjusting the conditions to favor the *o*-acetylated products by using a nonpolar solvent (cyclohexane) and increased temperature (80 °C) the substances 2-hydroxy-4-methylacetophenone (**18**) and 3-hydroxy-4-methylacetophenone (**19**) were obtained. Steric and electronic effects led to *ipso*-substitution instead of the common reaction pathway. All the compounds were synthesized in high purity, as was verified by GC-MS and NMR measurements.

Determination of Odor Thresholds (OTs). For the determination of odor thresholds in air, a state-of-the-art gas chromatography−olfactometry (GC-O) method was chosen.[40] The use of GC-O allows for the separation of possible odor-active impurities accompanying the target compound during gas chromatography so that such potential impurities cannot influence the results of smell characterization. Furthermore, the determination of OTs in air rules out any influence of matrix constituents, as it would be the case when OTs are determined, e.g., in water, oil, or cellulose.[41] OT values in air were calculated both as median (cf. Table 1) and as geometric mean (cf. Table 2). In the following, mainly the median values will be discussed, since both the geometric mean and the corresponding median values showed the same overall tendency in OTs. This approach is proposed by Lorber et al.[42] in the case of a limited panel size. Nevertheless, it has to be noted that although the panel size might seem to be small, numerous studies investigating OT values in air consisted of only 1−3 panelists, as the method is time-consuming.[41,43,44]

The OTs ranged from 2.0 ng/L air to 388.8 ng/L air (Table 1). A graphical overview is provided in Figure 2. Thereby, the lowest OTs were obtained for thymol (**1**, 2.0 ng/L air) and carvacrol (**2**, 2.7 ng/L air), followed by 2-hydroxy-4-methylacetophenone (**18**, 5.4 ng/L air). Their acetates **13** and **14** and their mono methyl ethers **8** and **9** as well as the mono methyl ethers of thymohydroquinone **10** and **11** showed comparable OTs of around 10 ng/L air. The OTs of *p*-cymene (**3**), *O*-acetylcarvacrol (**14**), 3-hydroxy-4-methylacetophenone (**19**), *p*-acetylthymol (**16**), *p*-acetylcarvacrol (**17**), thymohydroquinone dimethyl ether (**12**), and thymoquinone (**4**) ranged between 21.6 ng/L air and 43.2 ng/L air. The highest OTs were obtained for di-*O*-acetylthymohydroquinone (**15**) and thymohydroquinone (**7**) with 172.8 and 388.8 ng/L air, respectively. The latter two molecules have a higher degree of *p*-oxygenation, resulting in a more hydrophilic character and being the likely reason for their higher OTs in comparison to thymoquinone (**4**) and thymohydroquinone dimethyl ether (**12**), which are comparable in structure but comprise more *p*-located lipophilic groups. The nasal mucosa is lipophilic in nature; accordingly, it has been hypothesized that more lipophilic substances might more easily interact with the nasal mucosa, and other groups stated that, accordingly, more lipophilic substances have enhanced odor potency.[45,46] On the other hand, one needs to keep in mind that odorous molecules first need to pass an aqueous mucus layer, and may, furthermore, undergo biotransformation at the periphery prior to interaction with the receptor sites.[47] Accordingly, without any factual biochemical and nasal and olfactory tissue studies, such considerations remain mostly speculative. With the sole exception of the higher OTs in the case of

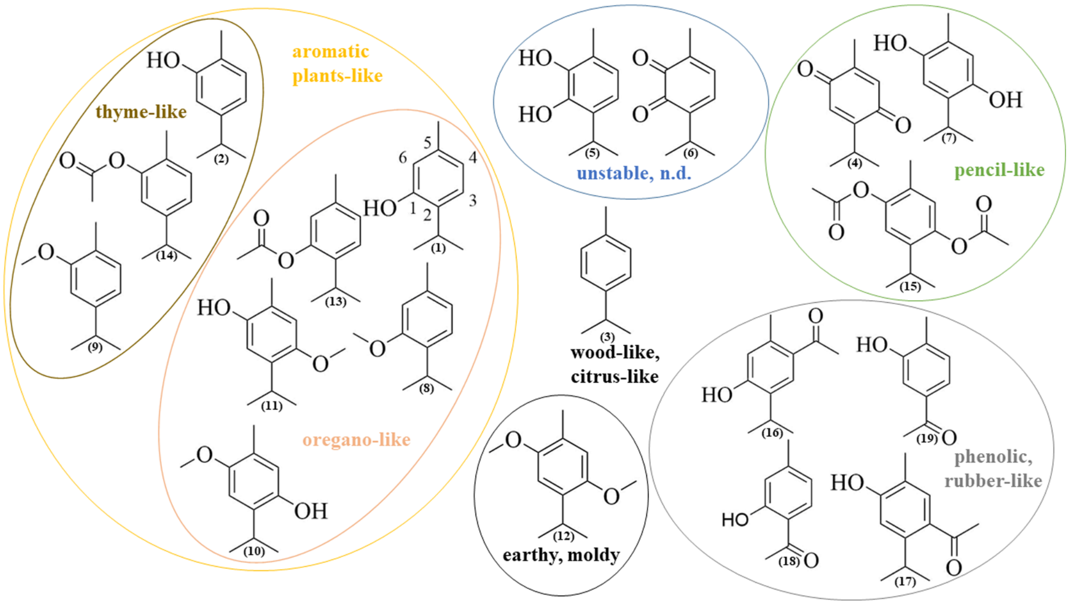

Figure 3. Overview of the odor qualities of the synthesized compounds (n.d.: not determined, due to instability of the compounds).

thymohydroquinone (**7**) and di-*O*-acetylthymohydroquinone (**15**), the remaining substances showed relatively similar OTs. It is especially interesting to note that there was no clear relationship between odor threshold value and the different structural motifs that were present in the *p*-cymene derivatives. Neither an acetyl, hydroxy, or methoxy group nor having two or one substituents (*p*-positioned) influenced the OT values of the resulting molecules. Likewise, it had no effect on the OT values whether the molecule was a structurally modified derivative of thymol (hydroxy group in *ortho*-position relative to the isopropyl group) or of carvacrol (hydroxy group in *meta*-position relative to the isopropyl group).

In the present study, the compounds were always modified in either position 1 or 3 regarding the substitution pattern in *p*-cymene (**3**) (hydroxy groups in *ortho*- and *meta*-positions with regard to the methyl and isopropyl groups) or in combined patterns, implying substituents occurring in 1,4-*para*-locations. Only in the case of thymocatechol (**5**) and thymo-*o*-quinone (**6**) did the compounds have a 1,2-disubstitution relative to the methyl group and hence were *ortho* to each other. In accordance with catechol and benzo-1,2-quinone, both substances were unstable and decomposed readily.[48] Therefore, an attempt to synthesize further derivatives of compounds **1**, **2**, and **7** substituted in 1,2-locations to the methyl group might be challenging, even though the sensory properties of such unstable intermediates would be of interest.

Odor threshold single values (Table 2) were only slightly variable between individual panelists. To provide a better visualization of the breadth of the range covered by the individual values, calculated factors between the highest and lowest individual value are provided for each substance in Table 1. Generally, this factor was in the range of 16 (typically ranging from 4 to 64), which might appear to be high but is, in comparison to other findings of our group on interindividual variation in smell sensitivity to terpenoid and sesquiterpenoid substances, surprisingly low.[30,33] The highest factors, however, between individual extremes were obtained for di-*O*-acetylthymohydroquinone (factor 1024) and thymohydroquinone (factor 640). Such deviations in odor thresholds between individuals have repeatedly been reported.[42,49] Humans differ in their individual olfactory receptor patterns; in view of this, it is noteworthy that the olfactory receptor repertoire is, generally speaking, one of the most diverse in the human genome.[50,51] Based on individual expression patterns and levels, the activation of one or several receptors by one or several odorants can be divergent between individuals, which might be one of the reasons for the observed threshold variations. Furthermore, odorants may be biotransformed (e.g., by nasal enzymes) before reaching the respective receptor site.[47,52] This biotransformation can, inter alia, occur in the course of cytochrome P450 metabolization and has previously been reported to be relevant for phenolic compounds.[53] For both substances with highest extremes between individuals, namely, di-*O*-acetylthymohydroquinone (**15**) and thymohydroquinone (**7**), the same panelist (P-3A) perceived the substance with very high OTs, which might indicate that this panelist is more insensitive to the substances because of the receptor disposition.

In general, the OT values from the present study correspond well with those of other terpenes. The OTs determined in air of α-pinene, myrcene, and limonene,[54] as well as (+)-(4S)-carvone,[55] were also in the range of 5−450 ng/L air. On the other hand, comparable phenolic structures such as alkylated phenols or guaiacol derivatives had OT values between around 0.05 ng/L air and 502 ng/L air.[43,56] Thereby, monomethylation of phenols in the *meta*-position showed the lowest OTs with below 0.5 ng/L air, whereas additional methyl groups as well as a prolongation of the alkyl group increased the OTs, leading to values in the range of those of the investigated substances (2−500 ng/L air).[43]

Odor threshold information on the investigated substances is rare. Matrix-based odor thresholds are only reported for carvacrol, thymol, and *p*-cymene.[57−59] Moreover, no literature odor threshold values in air are known. OTs in water have been reported in a study on mango volatiles,[57] with values of 2.29 and 1.7 ppb for carvacrol and thymol, respectively. In another study targeting the characterization of odor-active and physiologically active compounds in thyme, oregano, and majoram,[60] odor thresholds in water were determined for thymol and carvacrol, as well as for *p*-cymene. In that study, thymol has been reported with the lowest OT in water with a value of 0.08 μg/L water, followed by carvacrol with 5 μg/L water and *p*-cymene with 5.1 μg/L water. Our results of 2.0 ng/L air for thymol, 2.7 ng/L air for carvacrol, and 43.2 ng/L air for *p*-cymene align well in rank order. In contrast to that, a further study on sensory thresholds of phenolic compounds reports the OTs of carvacrol and thymol in sunflower oil with 31 mg/kg for carvacrol and 124 mg/kg for thymol, thus being ranked in reverse order. Since a determination of odor thresholds is matrix-dependent and can differ in several orders of magnitude between the applied methods, these discrepancies are not surprising.[61]

Determination of Odor Qualities. In contrast to the determined OTs, where the differences in structures had little effect on the respective odor thresholds, the structural modifications in the investigated molecules apparently influenced their smell character. For a better comparison, all descriptors selected by the trained panel during sensory evaluation of the compounds are provided in Table 1.

The unsubstituted *p*-cymene (**3**) was primarily described as smelling wood-like and citrus-like. Most of the substances showed similar odor impressions with thyme-, oregano-, and pencil-like smells. Nevertheless, it became evident that the substances can be clustered into groups according to their common olfactory properties (cf. Figure 3). Generally, the panelists reported that thymol (**1**), carvacrol (**2**), thymol methyl ether (**8**), carvacrol methyl ether (**9**), *O*-acetylthymol (**13**), *O*-acetylcarvacrol (**14**), *p*-methoxythymol (**10**), and *p*-methoxycarvacrol (**11**) predominantly elicited odors that were reminiscent of aromatic plants. The substances smelled mainly thyme-, rosemary-, oregano-, and bergamot-like, at times accompanied by pencil-like, resin-like, and ethereal notes. Moreover, the substances can be subgrouped, according to their core structures, into thymol and its derivatives thymol methyl ether (**8**), *O*-acetylthymol (**13**) comprising substances with a substitution in *meta*-position to the isopropyl group, and carvacrol and its derivatives carvacrol methyl ether (**9**) and *O*-acetylcarvacrol (**14**) with substitution with a hydrophilic group in *ortho*-position to the isopropyl group. The compounds with the thymol core structure elicited smells that were dominated by a clear thyme-like impression, whereas those with a carvacrol core moiety tended to smell oregano-like. This corresponds with the fact that the essential oil of thyme is dominated by thymol, while the essential oil of oregano has a higher carvacrol content.[3] It is interesting to note that *p*-methoxythymol (**10**) and *p*-methoxycarvacrol (**11**) have substitutions in both *meta*- and *ortho*-position relative to the isopropyl group; these compounds were perceived with smell that appeared to be rather a blend of oregano-like, pencil-like, and resin-like odors.

Thymohydroquinone (**7**), thymoquinone (**4**), and di-*O*-acetylthymohydroquinone (**15**), which have electronegative functional groups in positions 1 and 4, elicited pencil-like smells, accompanied by smoky and medicinal notes. A smoky odor is known for guaiacol and guaiacol dervivatives such as 4-methylguaiacol, 2,6-dimethoxyguaiacol, and plenty of other alkylated and alkenylated guaiacols.[56,62] In the case of a medicinal odor, previous studies showed that phenols substituted in an *ortho*-position elicit this odor impression regardless of the substituent being a halogen or an alkyl group.[43,63] This specific substitution pattern of an oxygenated functional group and an alkyl group in an *ortho*-position can also be found in thymohydroquinone (**7**), thymoquinone (**4**), and di-*O*-acetylthymohydroquinone (**15**), which all have an oxygen atom *ortho* to the methyl group. Yet, the odor qualities of these substances are accompanied by a pencil-like odor. Accordingly, the proximity of the substituents to the isopropyl group appears to be related to more pencil-like odors, which is also the case for the *p*-methoxythymol (**10**) and *p*-methoxycarvacrol (**11**). An exception was observed for the thymohydroquinone dimethyl ether (**12**), which was reported with an earthy, moldy odor, despite its substitution with an electronegative group in the *para*-position.

In the case of 2-hydroxy-4-methylacetophenone (**18**), 3-hydroxy-4-methylacetophenone (**19**), *p*-acetylthymol (**16**), and *p*-acetylcarvacrol (**17**), the characteristic aromatic plant-like and pencil-like odors were not perceivable; instead, plastic-like, rubber-like, smoky, phenolic, and leather-like notes characterized the smell of these substances. The common structural element in those substances is an acetyl group being located *para* to either the hydroxy (**16**, **17**) or the methyl group, giving the respective *ipso*-isomers (**18**, **19**). In a study on the odor properties of alkylated phenols, various alkylated phenolic compounds were rated with similar attributes as smelling leather-like (e.g., 3-ethylphenol), medicinal (e.g., *o*-cresol), fecal (e.g., *p*-cresol), or rubber-like (4-isopropylphenol).[43] Moreover, various derivatives of guaiacol are characterized by smoke-, ham-, and plastic-like odors,[56] which appear to be, consequently, common odor qualities in the class of phenolic substances, as previously observed, and now being confirmed by further derivatives. In addition, a plastic-like smell is reported for acetophenone, 1-hexen-3-one, and 1-octen-3-one[64] as well as for various mono- or diunsaturated carbonyl compounds.[65] The common substitution pattern is the α,β-unsaturated carbonyl group, which is also present in the synthesized compounds **18**, **19**, **16**, and **17** and could give a hint of plastic-like odors.

The synthesized products with a 1,2-substitution pattern, thymocatechol (**5**) and thymo-*o*-quinone (**6**), respectively, were, as mentioned above, unstable, and gas chromatographic analyses could not be performed. In order to still get some insights into their smell properties, the following approach was applied: directly after synthesis, two panelists evaluated the immediately perceived odor qualities, coupled with immediate NMR experiments that confirmed the successful synthesis and high purity of the obtained compounds. The smell impressions reported by the panelists were thyme-like, ethereal for thymocatechol (**5**) and thyme-like, pencil-like, and ethereal for thymo-*o*-quinone (**6**). This indicates that the modified 1,2-substitution pattern also leads to olfactorily interesting molecules that are related to pencil-like odors and provide further insights into structure−odor relationships of oxygenated, aromatic monoterpenoids.

In summary, the investigations on structure−odor relations showed that the different substituents clearly influence the odor character of the target molecules of the present study. We could show that the odor quality changed from woody, citrus-like (unsubstituted *p*-cymene) to thyme- and oregano-like (for the monosubstituted molecules). The position of the hydrophilic group and the isopropyl group also had an impact on the odor quality: a substitution in the *meta*-position resulted in a thyme-like smell, whereas the substitution in *ortho*-position to the isopropyl group yielded oregano-like odors. In the case of *p*-methoxythymol (**10**) and *p*-methoxy-carvacrol (**11**), disubstitution in *p*-position led to comparable odor qualities, which is likely due to the fact that both compounds share a substitution motif in the *meta*- and *ortho*-position. In addition to the prevalent oregano-like impression, those two substances were additionally described as smelling pencil- and resin-like. In the case of thymohydroquinone (**7**), thymoquinone (**4**), and di-*O*-acetylthymohydroquinone (**15**), disubstitution in the *p*-position likewise provoked pencil-like smells, which was replaced by more plastic-like, rubber-like smells for the acetophenone derivatives. Whereas differences in odor qualities could be assigned, the structural modifications did, however, not influence the odor thresholds to a larger extent.

Thus, we provide with this study comprehensive analytical and sensory data, comprising routes for synthesis, retention indices, NMR and mass spectra, odor thresholds in air, and odor qualities, on derivatives of thymol and carvacrol. The data generated further extends common knowledge on substances that elicit woody, aromatic, and pencil-like odors. Further studies on the interaction of those substances with the specific odorant receptors will help to fully resolve the structure−odor relationships.

■ EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise stated, all solvents and reagents were purchased from commercial sources (Sigma-Aldrich, VWR, Grüssing GmbH Analytica, Acros, Carl Roth, Fluka); they were analytically pure and used without further purification. All solvents were freshly distilled prior to use. All reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere, and the solvents were dried before use to remove moisture using appropriate drying solvents. For column chromatography silica gel with a size of 40−60 μm, purchased from Carl Roth, was used. Thin-layer chromatography (TLC) was conducted on silica gel 60 F254 TLC plates from Macherey-Nagel (Düren, Germany) with a pore diameter of 60 Å.

All reactions were monitored by TLC using cyclohexane and EtOAc (5:1) as separation agents. The visualization of the reaction components was achieved using UV fluorescence (254 nm) and $KMnO_4$ stain. If not stated otherwise, column chromatography over silica gel 60 was carried out for purification. The yields reported here are those obtained after purification.

^{1}H NMR spectra were recorded in $CDCl_3$ on Avance 360 and Avance 600 spectrometers (Bruker Biospin, Rheinstetten, Germany) at room temperature operated at 360 or 600 MHz with TMS as internal standard. Chemical shifts (δ) are quoted in parts per million (ppm) calibrated to TMS (1H). Coupling constants (J) were measured in hertz (Hz). The following abbreviations are used to describe multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The identity of all intermediates and synthetic products was additionally determined by GC-MS in EI-mode as described in the following.

Gas Chromatography−Olfactometry and Gas Chromatography−Mass Spectrometry (GC-MS). GC-FID/O analyses were performed with a Trace GC Ultra (Thermo Fisher Scientific GmbH, Dreieich, Germany) housing a DB-FFAP or a DB-5 fused silica capillary both with dimensions 30 m × 0.32 mm, 0.25 μm (both Agilent J&W, Santa Clara, CA, USA). The samples were injected manually by the cold on-column technique at 40 °C with an injection volume of 2 μL. After 2 min, the oven temperature was raised at 10 °C/min to a final temperature of 240 °C (DB-FFAP) or 280 °C (DB-5). The final temperature was held for 10 min. The flow rate of the carrier gas helium was 2.5 mL/min. At the end of the capillary column, the effluent was split into a ratio of 1:1 (by volume) into an FID and a sniffing port using two deactivated uncoated fused silica capillaries (50 cm × 0.32 mm) of the same length. The FID and the sniffing port were held at 250 °C, respectively.

GC-MS analyses were performed using an Agilent MSD quadrupole system (GC 6890 and MSD 5973, Agilent Technologies, Waldbronn, Germany), equipped with a Gerstel MPS 2 autosampler and a Gerstel CIS 3 injection system (Gerstel, Duisburg, Germany). The samples were injected automatically with a total volume of 2 μL. The analyses were conducted using the same capillaries and temperature programs as described above with a flow rate of 1.0 mL/min. Mass spectra were generated in the electron impact mode (EI-MS) at 70 eV.

Retention indices (RI) for all compounds were calculated based on a series of homologous *n*-alkanes (C_6−C_{31}) according to van den Dool and Kratz.[66]

Panelists. Panelists were trained volunteers from the Chair of Aroma and Smell Research of the Friedrich-Alexander-University Erlangen-Nürnberg (Erlangen, Germany) and the Fraunhofer Institute for Process Engineering and Packaging IVV (Freising, Germany), exhibiting no known illness at the time of examination and with audited olfactory function. In preceding weekly training sessions, the assessors were trained prior to participation in the experiments for at least half a year to correctly recognize, identify, and name the odor qualities of reference substances and natural products according to an in-house developed odor language. Moreover, no anosmia of the chosen assessors was known and they showed no clearly deviating olfactory sensitivity.

Odor Quality Determination. The characteristic odor qualities of all synthesized compounds (except nos. **5** and **6** due to instability) were evaluated following a systematic procedure for sensory analysis. Therefore, the substances were dropped onto a filter paper and put into glass vessels. The purity of all compounds was ascertained by ^{1}H NMR and GC-MS analyses prior to the sensory experiments. All synthesized compounds were further checked for olfactory purity using GC-O. The substances were presented to the trained sensory panel (cf. panelists) in covered glass vessels coded with a random three-digit number in a sensory room, at 21 °C. The panel consisted of four males and six females in the age range of 23 to 33 years. First, the panelists were asked to name the individual odor qualities of the compounds based on the in-house odor language and weekly training sessions (cf. 2.5), and then the characteristic attributes for each substance were chosen in consensus.

Odor Threshold Values. Odor thresholds in air were determined by GC-O using (E)-dec-2-enal as internal standard.[40,43,67] A stock solution of the target substances and the internal standard in known concentrations (1000 μg/mL) was prepared in CH_2Cl_2 and diluted stepwise 1:1 (v:v). Every dilution was then injected into the GC-O system and analyzed by each panelist. The thresholds were determined by 4−6 panelists (four male, two female), with each experiment being conducted at least once by each panelist. GC-O analyses for RI determination were performed on DB-5 and DB-FFAP capillaries as described in the section Gas Chromatography−Olfactometry and Gas Chromatography−Mass Spectrometry (GC-MS). The purity of all commercially available and synthesized compounds was ensured by ^{1}H NMR and GC-MS analyses prior to the GC-O experiments. All synthesized compounds were further checked using GC-O for potential odor-active impurities during the sniffing process to exclude any interferences.

Ethics Statement. The study was conducted in agreement with the Declaration of Helsinki. The study (registration number 180_16B) was approved by the Ethical Committee of the Medical Faculty, Friedrich-Alexander Universität Erlangen-Nürnberg. Informed consent was obtained from all subjects participating in the study.

Syntheses. The synthetic procedures are general procedures. The reader is referred to the Supporting Information for a detailed description.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.9b00339.

General synthetic routes and ^{1}H NMR spectroscopic data of all synthesized compounds, information on previous identification sources, mass spectrometric data of all synthesized compounds, individual odor thresholds of all panelists (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Andrea Buettner – *Aroma and Smell Research, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), 91054 Erlangen, Germany; Department of Sensory Analytics, Fraunhofer Institute for Process Engineering and Packaging (IVV), 85354 Freising, Germany;* orcid.org/0000-0002-6205-5125; Email: andrea.buettner@ivv.fraunhofer.de

Authors

Linda Schreiner – *Aroma and Smell Research, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), 91054 Erlangen, Germany; Department of Sensory Analytics, Fraunhofer Institute for Process Engineering and Packaging (IVV), 85354 Freising, Germany*

Johannes Bauer – *Aroma and Smell Research, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), 91054 Erlangen, Germany*

Eva Ortner – *Department of Sensory Analytics, Fraunhofer Institute for Process Engineering and Packaging (IVV), 85354 Freising, Germany*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.jnatprod.9b00339

Author Contributions

[§]L. Schreiner and J. Bauer contributed equally.

Notes

The authors declare no competing financial interest.

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