



An exploratory study on the peroxy-radical-scavenging activity of 2,6-dimethyl-5-hepten-2-ol and its heterocyclic analogues



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ABSTRACT

The structural properties and radical scavenging activity of 2,6-dimethyl-5-hepten-2-ol (**1**) and its new heterocyclic analogues, i.e. 2-methyl-4-(5-methylfuran-2-yl)-butan-2-ol (**2**) and 2-methyl-4-(5-methylthiophen-2-yl)-butan-2-ol (**3**) and have been studied by using the experimental and theoretical methods for the first time. Activity of title compounds against the peroxy radical was determined by using standard fluorimetric test, i.e. the Oxygen Radical Absorbance Capacity assay (ORAC_{FL}). Furthermore, the electron-donating ability of odorants has been evaluated by using colorimetric ABTS assay. According to the experimental results obtained from the ORAC_{FL} test 2,6-dimethyl-5-hepten-2-ol was characterized by the highest activity in comparison with the novel counterparts. Nevertheless, all investigated compounds exhibited pronounced anti-peroxy radical activity comparable to that exerted by the one of the most prominent antioxidant among the monoterpene alcohols, i.e. by linalool. On the other hand, the title compounds exerted relatively low capacity to quench the radical cation of ABTS. Theoretical calculations based on the Density Functional Theory (DFT) method with the hybrid functional B3LYP were carried out in order to investigate selected structural and electronic properties including the geometrical parameters as well as the energy of frontier molecular orbitals of parent molecules and the resulting radicals. Furthermore, the possible mechanism of peroxy-radical-scavenging has been determined by using the thermodynamic descriptors such as the bond dissociation enthalpies (BDEs) and ionization potentials (IPs). These theoretical data pointed out the relevance of HAT mechanism in the peroxy-radical-scavenging exhibited by 2,6-dimethyl-5-hepten-2-ol and its new heterocyclic analogues in polar and non-polar medium.

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1. Introduction

Numerous non-phenolic compounds that are abundant in the foodstuffs and the other commercial every-day products are well-known for their potent radical-scavenging capacity. The antioxidant activity of these compounds is, in principle, ascribed to the preventive and chain-breaking ability which efficiently slows down the air oxidation process of a substance [1]. In particular, some of powerful chain-breaking antioxidants were found among the non-phenolic cyclic and acyclic monoterpene hydrocarbons [2]. In most cases, these compounds possess the commercial importance as a

valuable aromatic material for the flavor and fragrance industry. Their beneficial anti-radical activity could be mainly attributed to the presence of the labile allylic C–H bond(s) [1]. From the practical point of view, the anti-radical activity such as the peroxy-radical-trapping ability of fragrant additives is extremely important factor in the cosmetics design and fabrication. Among the other, it will determinate the stability of odorant during the storage, its susceptibility towards auto-oxidation processes as well as its cytotoxicity and the allergising potential [3,4].

There are many precedents showing that substituting a phenyl for an isobutenyl moiety in the terpene structure gives sometimes excellent odoriferous effects. This case is good exemplified by Fenoxanol[®] and Doremox[®] the analogues of citronellol and rose oxide, respectively [5]. Another good example is the synthetic aromatic analogue of the currently investigated 2,6-dimethyl-5-hepten-2-ol, i.e. 2-methyl-4-phenylbutan-2-ol which was reported as an effective agent in supplying both the necessary

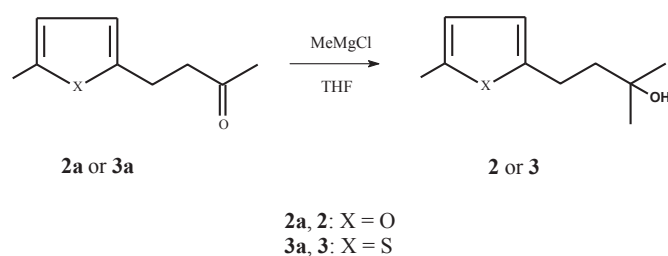
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fragrance as well as an anti-fungal properties of perfumes [6]. It is also worth mentioning that the replacing the isobutenyl moiety in a terpene alcohol by a furyl and thienyl substituent leads to increasing the substantivity of the new odorant [7,8]. Therefore, the search for the innovative (hetero)aromatic compounds structurally related to the natural or the natural-like terpenoids seems to be still in demand by the flavor and fragrance industry.

In the present study the peroxy-radical-scavenging activity and the computationally predicted structural features related to the possible antioxidant properties of fragrant 2,6-dimethyl-5-hepten-2-ol and its novel furyl and thienyl analogues were reported for the first time. 2,6-Dimethyl-5-hepten-2-ol (C₉H₁₈O) itself should be ascribed to the group of acyclic monoterpene alcohols. Because of its fresh, floral and lavender-woody like aroma this terpenoid can be re-used in various fragrance compositions as well as it can be utilized as the starting material for production of aroma chemicals [9]. Unfortunately, on the contrary to the well known lavender-scented terpene, i.e. linalool [10], the natural resources of 2,6-dimethyl-5-hepten-2-ol are very limited. In a consequence, this volatile could not be directly recovered from the available plant material but, instead of, it should be synthesized [11]. Novel analogues of 2,6-dimethyl-5-hepten-2-ol were produced from the adequate 4-(5-methylfuran/thiophen-2-yl)-butan-2-ones in the Grignard reaction shown in Scheme 1. As can be seen from the Fig. 1a, in these heterocyclic compounds the isobutenyl functionality of 2,6-dimethyl-5-hepten-2-ol (**1**) was replaced by the methyl-substituted furane or thiophene ring yielding 2-methyl-4-(5-methylfuran-2-yl)-butan-2-ol (**2**) and 2-methyl-4-(5-methylthiophen-2-yl)-butan-2-ol (**3**), respectively. According to our preliminary study, new synthetic compounds **2** and **3** were characterized by the lavender type scent but their odor tenacity was about seven and a half and twenty five times greater than that of 2,6-dimethyl-5-hepten-2-ol (**1**), respectively. Therefore, it could be expected that these new compounds characterized by both the low volatility and an interesting olfactory properties may possess the commercial importance as the fragrant additives applicable in fine fragrance compositions or various perfumed products.

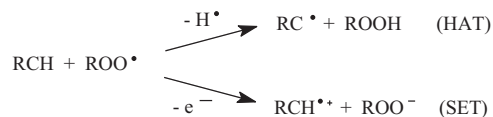
As it was mentioned previously, in the case of the currently studied synthetic odorants **2** and **3** the methyl-substituted furan or thiophene ring was incorporated into the terpenoid chain. It is well recognized that thiophene and furan itself are of great importance in the synthetic organic chemistry, biochemistry, pharmaceutical chemistry as well as in the flavor and fragrance chemistry [12,13]. These heterocycles were found in the numerous natural and synthetic products which are well known for the multifaceted pharmacological and therapeutic (bio)activity [14,15]. On the other hand, it should be also remembered that the modification of compound by the heterocyclic substitution may drastically change its overall chemical stability in some cases. For instance, the experimental and the DFT-derived results reported very recently by



Scheme 1. Synthesis of furyl (**2**) and thienyl (**3**) analogues of 2,6-dimethyl-5-hepten-2-ol from 4-(5-methylfuran-2-yl)-butan-2-one (**2a**) and 4-(5-methylthiophen-2-yl)-butan-2-one (**3a**), respectively.

Stobiecka et al. [16] revealed that the heterocyclic linalool analogues might possess significantly higher electron-acceptor ability as well as comparable or even lower resistivity towards an auto-oxidation in comparison with the parent molecule. Therefore, there is a great need for the in-depth comparative study on the anti-radical properties of both the new heterocyclic analogues of 2,6-dimethyl-5-hepten-2-ol as well as 2,6-dimethyl-5-hepten-2-ol itself. It should be stressed that the antioxidant capacity of the latter compound has not been evaluated so far.

The anti-peroxy radical activity of title compounds was explored by using the experimental and theoretical methods. On the one side, the ORAC_{FL} assay has been performed in order to determine antioxidant properties of odorant molecules. In this experimental method the free radical scavenging activity of compound was evaluated from the extent of fluorescein oxidation caused by the peroxy radicals in the aqueous medium [17]. In principle, the peroxy radicals (ROO[•]) could be quenched by studied compounds (RCH) *via* two different pathways associated with the hydrogen atom transfer (HAT) or the single electron transfer (SET) mechanism shown in the scheme below:



Beside the ORAC test, the electron-donor ability of compounds was evaluated directly by using typical SET-based assay, i.e. the ABTS test [18]. On the other side, due to the lack of experimental data describing the molecular structure as well as the overall reactivity of newly synthesized fragrances we attempted to characterize them by using the theoretical Density Functional Theory (DFT) method and the hybrid Becke three-parameter exchange-correlation functional (B3LYP). The DFT-computed quantities under consideration included the geometrical parameters such as the bond length and the bond angle as well as the energy of the highest occupied molecular orbital and the lowest unoccupied molecular orbital (thus the HOMO and LUMO energy) of parent molecules and resulting radical species. Furthermore, by using the DFT methodology the main thermodynamic descriptors of the HAT and SET mechanism, i.e. bond dissociation enthalpy (BDE) and the ionization potential (IP), respectively have been determined. It should be pointed out that the applied theoretical method has been proved to yield valuable information on the chemical stability and radical-scavenging activity of numerous compounds including naturally occurring terpenoids and their synthetic analogues [3,4,16,19]. Therefore, it is expected that the combined experimental and theoretical approach applied in this study could be relevant for the effective screening of synthetic fragrant molecules with the desired olfactory properties as well as the free radical scavenging capacity.

2. Experimental and theoretical details

2.1. Materials and methods

AAPH (2,2'-azo-bis(2-amidinopropane) dihydrochloride), ABTS (2,2'-azino-bis(3-ethylbenzo-thiazoline-6-sulfonic acid)), Trolox (6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid) and fluorescein were purchased from Sigma–Aldrich (Poznan, Poland). All reagents were generally of the best quality, commercial grade, and used without further purification. 2,6-Dimethyl-5-hepten-2-ol (GC purity > 97%) was synthesized from 6-methyl-5-hepten-2-one (Sigma–Aldrich, Poznan, Poland) according to the procedure reported elsewhere [11]. New compounds **2** (2-methyl-4-(5-

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