

Effect of Sulfur Substitution on the Floral Odor of Tetrahydropyranyl and Tetrahydrofuran Ethers

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Sulfur-containing analogues of tetrahydropyranyl and tetrahydrofuran derivatives of selected alcohols and phenols have been prepared and their odor properties evaluated. The compounds include derivatives in which either one or both of the oxygen atoms had been replaced with sulfur. Derivatives with two sulfur atoms do not exhibit pleasant odors; those with an endocyclic oxygen and an exocyclic sulfur generally exhibit green notes. The floral character is found only in a few derivatives with an endocyclic sulfur and an exocyclic oxygen.

INTRODUCTION

The need for new floral odorants, to be used in perfumery and cosmetics as substitutes for unstable and unhealthy aldehydes so far employed, prompted us to study the relationships between chemical structure and the odor of white flowers, epitomized by the scent of muguet.

This particularly pleasant note is well reproduced by hydroxycitronellal, 3,7-dimethyl-7-hydroxyoctanal (which is not present in the natural muguet oil), and other synthetic aldehydes, such as lilyal [2-methyl-3-(*p*-*tert*-butylphenyl)propanal], lyral [4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxyaldehyde], cyclamen aldehyde [2-methyl-3-(*p*-isopropylphenyl)propanal], and bourgeonal [3-(*p*-*tert*-butylphenyl)propanal].

Our search for alternative floral odorants took into consideration 2-tetrahydropyranyl (THP) and 2-tetrahydrofuran (THF) derivatives of alcohols and phenols, because of their ease of preparation, that allowed a rapid screening of a great number of odorants (Anselmi *et al.*, 1992, 1993). Several of the synthesized compounds exhibited pleasant floral notes, suitable to be used as perfume additives.

As a further step in defining the relationships between odor and chemical structure, we decided to investigate the effect of oxygen/sulfur substitution on the floral note of THP and THF ethers. This idea was also suggested by the numerous literature reports concerning sulfur-containing compounds endowed with pleasant odors, of interest in food flavoring and perfumery.

Sulfur compounds are generally believed to have very unpleasant odors, and often they indicate decomposition processes in organic materials. Such a distinctive note is, however, typical of lower mercaptans and thioethers. Higher sulfur compounds, on the contrary, exhibit a variety of different odors, depending on size and shape parameters of the molecule, and may contribute pleasant and characteristic notes to the odors of foods and essential oils.

Besides the well-known heterocyclic compounds, such as the many thiazole derivatives with foodlike aromas (Maga, 1975), several thioesters, thioethers, and thiols have been described that present fruity and flower-like odors. Examples include thiobutyrate, thioisobutyrate, and

methyl thiobutyrate (Burrell *et al.*, 1971; Rivett, 1974; Campbell *et al.*, 1980; Hemlinger *et al.*, 1974) found in some essential oils, such as galbanum and agathosma, and contributing to their typical odors. Sulfur derivatives of ionone and irone exhibit fruity odors, such as raspberry, and floral notes (Hemlinger *et al.*, 1972, 1974, 1975a,b). Other interesting examples are thiogeraniol, thiolinalool, and 8-thiomenthone, endowed with floral and black currant odors (Sundt *et al.*, 1971; Demole *et al.*, 1982; Lamparsky and Schudel, 1971). The great number of patents describing the synthesis of these compounds or their uses in food flavoring and perfumery indicates the potential applications of these derivatives.

Here we report on the odor of several sulfur analogues of floral smelling THP and THF derivatives, in which either one or both oxygen atoms had been replaced by sulfur.

MATERIALS AND METHODS

Synthesis of Compounds. The synthesis of compounds 1-4, 7, and 8 has been described elsewhere (Giovani *et al.*, 1993). Compounds 5 and 6 have been prepared by direct addition of the appropriate thiophenol to 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran. All of the compounds were purified by column chromatography on silica gel, using 5% ethyl acetate in hexane as the eluant. Purity, as checked by GLC on a 25-m OV-1 capillary column, was always better than 99%. NMR spectra were recorded on a Bruker AC 200 instrument in CDCl₃. ¹H spectra (200 MHz) are referenced to TMS as internal standard; ¹³C spectra (50 MHz) are referenced to the internal line of CDCl₃ multiplet (77.7 ppm).

Odor Evaluation. Although the compounds were more than 99% pure by GLC, the presence of trace contaminants, with very low thresholds, such as mercaptans and disulfides, could still impair the odor test. Therefore, the compounds were dissolved in aqueous 0.1 M NaOH, containing 0.1 M NaBH₄, at concentrations around 10 mM (0.1-0.2%). The alkaline solution would thus keep traces of starting thiophenols and thiols in the ionized form, while the reducing medium could prevent the formation of strongly odoriferous disulfides or reduce them to thiols, in case they were already present. In some cases the odor became more pleasant after such treatment. Odors were evaluated by a panel of 10 expert perfumers. The odor descriptions obtained in the above conditions were consistent with the evaluations performed for each compound at the column exit port, in correspondence with the main chromatographic peak.

RESULTS AND DISCUSSION

Table 1 reports the NMR spectra of the compounds that, to the best of our knowledge, have not been previously described in the literature (5 and 6). Assignment of ¹³C

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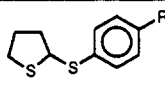
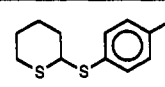
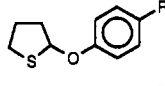
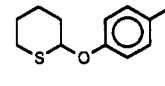
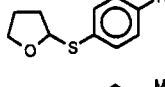
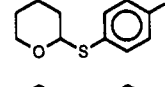
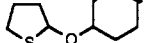
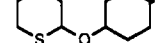
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Table 1. Spectral Properties of the New Thioacetals

compd	¹ H NMR (d, CDCl ₃ , 200 MHz)	¹³ C NMR (d, CDCl ₃ , 50 MHz)
5a	7.39 (d, <i>J</i> = 8.1 Hz, 2H, 2'-H, 6'-H), 7.10 (d, <i>J</i> = 8.1 Hz, 3'-H and 5'-H), 5.57 (dd, <i>J</i> = 3.6 and 7.1 Hz, 1H, 2-H), 3.86-4.08 (m, 2H, 5-H), 2.25-2.42 (m, 1H, 3-H), 2.31 (s, 3H, CH ₃), 2.03-1.76 (m, 3H, 4-H ₂ , 3-H)	137.64 (C-1'), 132.47 (C-2' and C-6'), 132.35 (C-4'), 130.23 (C-3' and C-5'), 88.20 (C-2), 67.83 (C-5), 33.20 (C-3), 25.48 (C-4), 21.74 (Me)
5b	7.45 (d, <i>J</i> = 8.2 Hz, 2H, 2'-H, 6'-H), 7.17 (d, <i>J</i> = 8.2 Hz, 2H, 3'-H, 5'-H), 5.61 (dd, <i>J</i> = 3.5 and 6.9 Hz, 1H, 2-H), 4.00 (m, 2H, 5-H ₂), 2.89 (heptuplet, <i>J</i> = 6.9 Hz, 1H, CHMe ₂), 2.40-2.30 (m, 1H), 2.06-1.81 (m, 3H), 1.24 (d, <i>J</i> = 6.9 Hz, 6H, CHMe ₂)	148.49 (C-1'), 132.78 (C-2' and C-6'), 132.37 (C-4'), 127.62 (C-3' and C-5'), 88.01 (C-2), 67.78 (C-5), 34.39 (CHMe ₂), 33.21 (C-3), 25.48 (C-4), 24.55 (CHMe ₂)
5c	7.44 (m, 2H, 2'-H, 6'-H), 7.31 (m, 2H, 3'-H, 5'-H), 5.61 (dd, <i>J</i> = 3.6 and 7.0 Hz, 1H, 2-H), 4.09-3.90 (m, 2H, 5-H ₂), 2.41-2.25 (m, 1H, 3-H), 2.17-1.80 (m, 3H, 3-H, 4-H ₂), 1.30 (s, 9H, CMe ₃)	150.76 (C-1'), 132.57 (C-4'), 132.03 (C-2' and C-6'), 126.57 (C-3' and C-5'), 88.06 (C-2), 67.84 (C-5), 35.18 (CMe ₃), 33.27 (C-3), 31.96 (CMe ₃), 25.52 (C-4)
6a	7.37 (d, <i>J</i> = 8.1 Hz, 2H, 2'-H, 6'-H), 7.08 (d, <i>J</i> = 8.1 Hz, 2H, 3'-H, 5'-H), 5.11 (dd, <i>J</i> = 5.8 and 3.7 Hz, 1H, 2-H), 4.17 (m, 1H, 6-H), 3.55 (m, 1H, 6-H), 2.31 (s, 3H, CH ₃), 1.99-1.94 (m, 1H), 1.92-1.69 (m, 2H), 1.66-1.53 (m, 3H)	137.50 (C-1'), 132.25 (C-2' and C-6'), 123.03 (C-2' and C-4'), 130.17 (C-3' and C-5'), 86.26 (C-2), 65.17 (C-6), 32.15 (C-5), 26.13 (C-3), 22.30 (C-4), 21.70 (Me)
6b	7.41 (d, <i>J</i> = 8.2 Hz, 2H, 2'-H, 6'-H), 7.14 (d, <i>J</i> = 8.2 Hz, 2H, 3'-H, 5'-H), 5.15 (dd, <i>J</i> = 3.7 and 5.6 Hz, 1H, 2-H), 4.18 (m, 1H, 6-H), 3.55 (m, 1H, 6-H), 2.87 (heptuplet, <i>J</i> = 6.9 Hz, 1H, CHMe ₂), 2.01-1.91 (m, 1H), 1.86-1.75 (m, 2H), 1.69-1.52 (m, 3H), 1.22 (d, <i>J</i> = 6.9 Hz, 6H, CHMe ₂)	148.34 (C-1'), 132.50 (C-4'), 132.08 (C-2' and C-6'), 127.56 (C-3' and C-5'), 86.20 (C-2), 65.07 (C-6), 34.34 (CHMe ₂), 32.20 (C-3), 26.15 (C-5), 24.52 (CHMe ₂), 22.26 (C-4)
6c	7.45-7.15 (m, 4H, ArH), 5.18 (dd, <i>J</i> = 5.6 and 3.7 Hz, 1H, 2-H), 4.20 (m, 1H, 6-H), 3.55 (m, 1H, 6-H), 2.12-1.72 (m, 3H), 1.68-1.43 (m, 3H), 1.32 (s, 9H, CMe ₃)	150.57 (C-1'), 132.29 (C-4'), 131.67 (C-2' and C-6'), 126.48 (C-3' and C-5'), 86.13 (C-2), 65.09 (C-6), 35.15 (CMe ₃), 32.22 (C-3), 31.90 (CMe ₃), 26.16 (C-5), 22.28 (C-4)

Table 2. Odor Properties of the Sulfur-Containing Odorants^a

structure	no.	odor	int	structure	no.	odor	int		
	1a	R + Me	mustard, green	S		2a	R = Me	sulfur, green	S
	1b	R = <i>i</i> -Pr	sulfur, green	S		2b	R = <i>i</i> -Pr	green, sulfur	S
	1c	R = <i>t</i> -Bu	garlic, green	VS		2c	R = <i>t</i> -Bu	sulfur, rancid	VS
	3a	R = Me	green, cabbage	VS		4a	R = Me	floral, green	VS
	3b	R = <i>i</i> -Pr	mushroom, floral	S		4b	R = <i>i</i> -Pr	green, minty	S
	3c	R = <i>t</i> -Bu	cabbage, green	VS		4c	R = <i>t</i> -Bu	floral, green	W
	5a	R = Me	green, fruity	M		6a	R = Me	green, fruity	W
	5b	R = <i>i</i> -Pr	fruity, green	M		6b	R = <i>i</i> -Pr	green, fruity	W
	5c	R = <i>t</i> -Bu	green, cabbage	M		6c	R = <i>t</i> -Bu	green, fruity	VW
	7a	cis	green, mushroom	VS		8a	cis	mushroom, green	S
	7b	trans	floral, green	VS		8b	trans	sulfur, green	S

signals to methyl, methylene, and methyne carbons was made by means of DEPT experiments. The synthesis of these odorants does not deserve any special comment, making use of a simple and well-known reaction routes.

The results of the odor evaluations of thioacetals (1-8) are shown in Table 2 and can be compared with the odor descriptions of their oxygen analogues previously reported (Anselmi *et al.*, 1992, 1993). The odors of thioacetals in which a single oxygen has been replaced by sulfur (3-8) are generally pleasant and rather similar to those of their oxygenated analogues. The sought floral note is actually present as the main character in some of these derivatives (4a, 4c, and 7b), containing the sulfur atom as part of the ring. The substitution of the exocyclic oxygen by sulfur, on the other hand, seems to enhance other characters, particularly the green note.

In the derivatives having both oxygen atoms substituted by sulfur (1 and 2), the odors are generally unpleasant and typical of lower sulfur compounds, with garlic- and mustard-like notes.

It is interesting to note that *cis/trans* isomerism of the cyclohexane derivatives (7a/7b and 8a/8b) gives rise to different odors. Such differences were also found with the corresponding oxygen derivatives (Anselmi *et al.*, 1992, 1993).

The similarity between the odor properties of mono-thioacetals and their oxygenated analogues correlates well with the similarity in their molecular shapes; indeed, the anomeric effect, which controls the conformation of the substituted heterocyclic rings, is also present in the sulfur-

containing derivatives, although the intensity of the effect tends to be lower when changing from oxygen to sulfur (Eliel and Giza, 1968). These data have been confirmed by preliminary conformational analysis, using molecular modeling.

The observed differences in odor properties can thus be related to the higher hydrophobicity of sulfur with respect to oxygen and to its corresponding scarce attitude to participate in hydrogen bonds. Sulfur substitution should progressively increase hydrophobic interactions with receptors but decrease, at the same time, the importance of hydrogen bonds. An exocyclic oxygen, which could be responsible for hydrogen bonding, on the other hand, seems to be important in preserving the floral character of these odorants.

In conclusion, new floral odorants have been synthesized in which oxygen is replaced with sulfur in THP and THF derivatives. The presence of at least one oxygen atom, preferentially the exocyclic one, is critical for the floral odor to be retained. Some of the described compounds, such as 4a and 7a, might find practical uses as additives in detergents and cosmetics. Odorants of the THP and THF series, previously described, are, however, to be preferred, being cheaper and easier to synthesize.

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