

Synthesis of Ethers Related to Some Floral Odorants: Effect of Oxygen/Carbon Replacement

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A series of ethers has been prepared whose structures are related to tetrahydropyranyl and tetrahydrofuran derivatives with floral odors by replacement of either one of the two oxygen atoms with a methylene group. 2-Substituted tetrahydropyrans and tetrahydrofurans, as well as cyclohexyl and cyclopentyl ethers, have thus been obtained by substitution of the exocyclic or the endocyclic oxygen, respectively. None of the compounds exhibited a pure floral odor, although in several of them this note was present as a secondary character. The data contribute to a better understanding between structure and floral odor.

Keywords: Structure/odor relationships; floral odor; tetrahydropyran; tetrahydrofuran

INTRODUCTION

The importance of floral odorants in perfumery and cosmetics prompted us to investigate the relationships between molecular structure and the odor of white flowers. The aim was to find new compounds that are more stable or easier to synthesize as compared to the known floral odorants, such as hydroxycitronellal (3,7-dimethyl-7-hydroxyoctanal), linal [2-methyl-3-(*p*-*tert*-butylphenyl)propanal], and other synthetic compounds (Boelens *et al.*, 1980; Olhoff and Giersch, 1980). Therefore, we have designed, synthesized, and evaluated several 2-tetrahydropyranyl (THP) and 2-tetrahydrofuran (THF) ethers of alcohols and phenols, varying the size, shape, and stereochemistry of the hydrocarbon region (Anselmi *et al.*, 1992, 1993).

This approach proved to be satisfactory, as we were able to synthesize several odorants with the desired character and strong intensity. In particular, the odor of white flowers was reproduced to different degrees in both THP and THF derivatives of *p*-alkylphenols (alkyl groups being methyl, ethyl, isopropyl, and *tert*-butyl), as well as in derivatives of cyclohexanols substituted with a methyl group in different positions or with a bulkier group (isopropyl and *tert*-butyl) in position 4. It was also found that in some cases diastereoisomers exhibited different odors, both in quality and in intensity.

The odor of several of these compounds was judged rather close to that of hydroxycitronellal, so their use could be proposed as a substitute for this compound in formulations of perfumes, cosmetics, and detergents. However, their acetalic nature limited any possible application to neutral and alkaline media. In fact, their hydrolysis affords phenols and alcohols of strong unpleasant odor.

In this paper we report the synthesis and odor properties of compounds related to the 2-THP and 2-THF above described by substitution of either one of

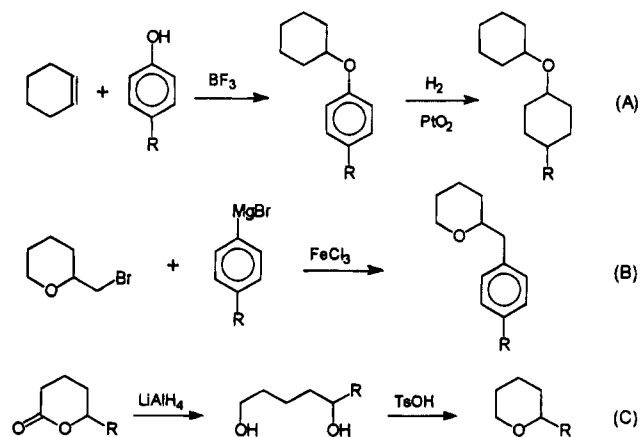


Figure 1. Synthetic routes used in the preparation of the odorants described. The same reactions were applied to cyclopentene (route A), 2-chloromethyltetrahydrofuran (route B), and γ -lactones (route C) for the synthesis of the homologous five-membered ring derivatives.

the two oxygen atoms with carbon. These new odorants are therefore tetrahydropyran and tetrahydrofuran alkyl derivatives or cyclopentyl and cyclohexyl ethers. The interest in these additional compounds was motivated by the possibility of designing and synthesizing new floral odorants that could be stable at pH below neutrality and therefore find wider applications in perfumery and cosmetics.

The effect of the substitution of one or two oxygen atoms of the THP and THF ethers with sulfur (Giovani *et al.*, 1993) is discussed in a previous paper (Napolitano *et al.*, 1994).

MATERIALS AND METHODS

Synthesis of the Odorants. Compounds were prepared according to method A, B, or C (Figure 1).

Compounds 1-6 (Method A). To a stirred solution of the alkylphenol (0.1 mol) in 10 mL of benzene was added 1.08 mL of 50% boron trifluoride in diethyl ether. After cooling at 0 °C, the mixture was treated with a benzene solution of the cycloalkene (50 mmol). The mixture was stirred for 40 min at 0 °C and then hydrolyzed with ice-cold water. The organic phase was washed with 20% potassium hydroxide, and the

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Table 1. NMR and Mass Spectra of the New Odorants^a

no.	¹ H NMR (200 MHz, CDCl ₃), δ	MS (70 eV), m/z (rel intensity)
3a	7.03–7.11 (2H, m, Ar); 6.78–6.85 (2H, m, Ar); 4.12–4.22 (1H, m, CHO); 2.51–2.63 (2H, q, $J = 7.5$ Hz, CH ₂ Ar); 1.24–2.01 (10H, m, (CH ₂) ₅); 1.20 (3H, t, $J = 7.5$ Hz, CH ₃)	204 (24), 150 (9), 135 (44), 122 (100), 107 (97), 91 (8), 71 (19), 55 (16), 41 (21)
3b	7.08–7.12 (2H, m, Ar); 6.80–6.86 (2H, m, Ar); 4.15–4.22 (1H, m, CHO); 2.70–2.95 (1H, heptuplet, $J = 6.9$ Hz, (CH ₃) ₂ CH); 1.24–2.00 (10H, m, (CH ₂) ₅); 1.22 (6H, d, $J = 6.9$ Hz, (CH ₃) ₂ CH)	218 (19), 136 (52), 121 (100), 103 (8), 91 (10), 77 (10), 55 (13), 41 (14)
3c	7.24–7.29 (2H, m, Ar); 6.80–6.85 (2H, m, Ar); 4.12–4.28 (1H, m, CHO); 1.25–2.00 (10H, m, (CH ₂) ₅); 1.29 (9H, s, CH ₃)	232 (22), 217 (3), 150 (30), 135 (100), 107 (13), 91 (8), 77 (6), 55 (16), 41 (12)
5a	3.52–3.59 (1H, m, CHO); 3.20–3.30 (1H, m, CHO); 1.16–1.90 (19H, m, CH ₂ and CHCH ₃); 0.89 (3H, d, $J = 5.8$ Hz, CH ₃)	196 (24), 139 (8), 114 (48), 100 (68), 97 (87), 96 (65), 82 (40), 70 (22), 67 (24), 57 (35), 55 (100), 41 (13)
5b	3.18–3.34 (2H, m, CHO); 0.94–1.97 (19H, m, CH ₂ and CHCH ₃); 0.86 (3H, d, $J = 6.4$ Hz, CH ₃)	196 (21), 139 (6), 114 (43), 100 (52), 97 (68), 82 (32), 70 (18), 67 (20), 55 (100), 41 (44)
4a	7.03–7.11 (2H, m, Ar); 6.74–6.82 (2H, m, Ar); 4.66–4.75 (1H, m, CHO); 2.57 (2H, q, $J = 7.6$ Hz, CH ₂ Ar); 1.51–1.91 (8H, m, (CH ₂) ₄); 1.20 (3H, t, $J = 7.6$ Hz, CH ₃)	190 (22), 133 (3), 122 (78), 107 (100), 91 (6), 77 (14), 41 (16)
4b	7.07–7.23 (2H, m, Ar); 6.77–6.83 (2H, m, Ar); 4.69–4.74 (1H, m, CHO); 2.70–2.95 (1H, heptuplet, $J = 6.9$ Hz, (CH ₃) ₂ CH); 1.53–1.91 (8H, m, (CH ₂) ₄); 1.22 (6H, d, $J = 6.9$ Hz, (CH ₃) ₂ CH)	204 (19), 136 (38), 121 (100), 103 (8), 91 (11), 77 (11), 41 (16)
4c	7.23–7.31 (2H, m, Ar); 6.75–6.84 (2H, m, Ar); 4.67–4.77 (1H, m, CHO); 1.52–1.93 (8H, m, (CH ₂) ₄); 1.29 (9H, s, CH ₃)	218 (17), 150 (20), 135 (100), 107 (13), 91 (8), 77 (5), 41 (17)
6a	3.93–4.00 (1H, m, CHO); 3.41–3.48 (1H, m, CHO); 1.24–1.83 (17H, m, CH ₂ and CHCH ₃); 0.89 (3H, d, $J = 5.8$ Hz, CH ₃)	182 (15), 125 (12), 114 (46), 97 (92), 96 (47), 81 (25), 69 (26), 55 (100), 41 (55)
6b	4.01–4.08 (1H, m, CHO); 3.10–3.25 (1H, m, CHO); 0.90–2.05 (17H, m, CH ₂ and CHCH ₃); 0.86 (3H, d, $J = 6.4$ Hz, CH ₃)	182 (31), 125 (19), 114 (51), 97 (100), 96 (57), 81 (32), 69 (32), 55 (87), 41 (41)
7a	7.09 (4H, s, Ar); 3.92–4.02 (1H, m, CHO); 3.33–3.51 (1H, m, OCH ₂); 2.84 (1H, dd, CH ₂ Ar); 2.63 (1H, dd, CH ₂ Ar); 2.31 (3H, s, CH ₃); 1.20–1.83 (6H, m, CH(C ₂) ₃)	190 (9), 105 (20), 85 (100), 67 (17), 57 (19), 43 (14)
7b	7.20–7.24 (2H, m, Ar); 7.03–7.08 (2H, m, Ar); 3.85–3.95 (1H, m, CHO); 3.27–3.47 (1H, m, OCH ₂); 2.78 (1H, dd, $J = 6.3$ and 14.4 Hz, CH ₂ Ar); 2.53 (1H, dd, $J = 6.6$ and 14.4 Hz, CH ₂ Ar); 1.16–1.76 (6H, m, CH(C ₂) ₃); 1.23 (9H, s, CH ₃)	232 (8), 148 (13), 133 (9), 117 (11), 91 (8), 85 (100), 67 (13), 57 (16), 41 (14)
8a	7.09 (4H, s, Ar); 3.95–4.09 (1H, m, CHO); 3.82–3.93 (1H, m, OCH); 3.65–3.78 (1H, m, OCH); 2.86 (1H, dd, $J = 6.4$ and 13.5 Hz, CH ₂ Ar); 2.67 (1H, dd, $J = 6.6$ and 13.5 Hz, CH ₂ Ar); 2.30 (3H, s, CH ₃); 1.48–1.98 (4H, m, CH(C ₂) ₂)	176 (14), 115 (5), 107 (11), 105 (25), 91 (9), 77 (11), 71 (100), 51 (5), 43 (41)
8b	7.24–7.33 (2H, m, Ar); 7.13–7.18 (2H, m, Ar); 4.01–4.09 (1H, m, CHO); 3.84–3.99 (1H, m, OCH); 3.67–3.79 (1H, m, OCH); 2.89 (1H, dd, $J = 6.6$ and 13.5 Hz, CH ₂ Ar); 2.70 (1H, dd, $J = 6.4$ and 13.5 Hz, CH ₂ Ar); 1.51–2.01 (4H, m, CH(C ₂) ₂); 1.30 (9H, s, CH ₃)	218 (9), 148 (9), 133 (8), 117 (9), 91 (5), 71 (100), 43 (22)

^a Numbers in the first column refer to structures reported in Table 2.

crude product, thus obtained, was purified by column chromatography on silica gel, using pure petroleum ether as the eluent. Yields were in the range 30–40%.

Aromatic ethers **1c** and **2c** (10 mmol in 10 mL of acetic acid) were hydrogenated over platinum oxide (50 mg) at room temperature and atmospheric pressure for 24 h. The mixture was then diluted with diethyl ether and neutralized with sodium bicarbonate. The crude product was purified by column chromatography on silica gel and pure petroleum ether as the eluent, obtaining at the same time the separation of the *cis/trans* isomers produced by the reaction. Yields were better than 90%.

Compounds 7 and 8 (Method B). To the Grignard solution, prepared from 0.5 g of magnesium (20.5 mmol) and 20.5 mmol of *p*-alkylbenzene bromide, was added 0.15 mL of 8% ferric chloride at 0 °C, followed by 20.5 mmol of 2-(bromomethyl)-tetrahydropyran or 2-(chloromethyl)tetrahydrofuran in diethyl ether. After refluxing for 3 h, the mixture was cooled to 0 °C and hydrolyzed with a saturated aqueous solution of ammonium chloride. After working up, the crude product was purified by column chromatography on silica gel, using 1% diethyl ether in petroleum ether as the eluent. Yields were around 60%.

Compounds 9 and 10 (Method C). To a suspension of lithium aluminum hydride (250 mg) in dry diethyl ether was added 5 mmol of the lactone, and the mixture was stirred for 2.5 h. The excess lithium aluminum hydride was hydrolyzed by subsequent addition of moist diethyl ether, water, and 1 N sodium hydroxide. After working up, the crude glycol was purified by filtration on silica gel and elution with 20% diethyl ether in petroleum ether followed by pure diethyl ether. The glycol was then cyclized by refluxing in dichloromethane for 8 h in the presence of traces of *p*-toluenesulfonic acid. The final compound was purified by column chromatography on silica

gel, eluting with 1% diethyl ether in petroleum ether. Yields were in the range 20–30%.

Purity of all the final products was checked by GLC on a DB-1 capillary column, in the following conditions: injector temperature 250 °C; detector temperature, 250 °C; oven temperature, 50–200 °C.

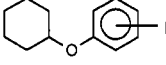
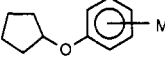
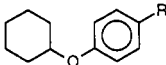
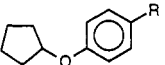
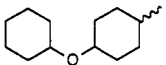
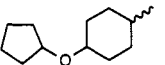
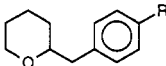
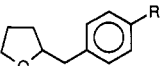
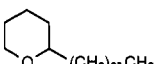
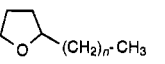
Odor Evaluation. Odor quality of the undiluted samples was judged by a panel of 10 expert perfumers.

RESULTS AND DISCUSSION

Synthesis of the Odorants. The preparation of the compounds reported was performed along classical routes described in the literature for the synthesis of ethers, which are summarized in Figure 1. Cresols, cyclohexyl ethers **1a–c** as well as cyclopentyl ethers **2a–c**, had been already described in the literature (Lefebvre and Levas, 1945; Levas, 1948; Pajean and Begue, 1962); also, the synthesis of cyclohexyl ethers of 4-methylcyclohexanol has been reported (Volkov *et al.*, 1962), but their *cis/trans* isomers (**5a/5b**) have not been previously separated and independently characterized. Finally, 2-*n*-heptyltetrahydropyran (**9**) and the 2-alkyl-tetrahydrofurans **10a** and **10b** have been described in the literature (Normant *et al.*, 1989; Bailey and Bischoff, 1985; Montaudon *et al.*, 1979). All of the other compounds, to the best of our knowledge, have not been previously synthesized.

Compounds containing an exocyclic oxygen (**1–4**) were prepared by addition of alkylphenols to cyclohexene or cyclopentene in the presence of boron trifluoride (Figure

Table 2. Odor Properties of the Ethers Prepared^a

structure	no.	odor	intensity	structure	no.	odor	intensity
	1a <i>ortho</i>	rubber, <i>green</i>	S		2a <i>ortho</i>	rubber, <i>leather</i>	M
	1b <i>meta</i>	fruity, <i>phenol</i>	VS		2b <i>meta</i>	<i>green, mushroom</i>	S
	1c <i>para</i>	rubber, <i>green</i>	W		2c <i>para</i>	<i>green, rubber</i>	M
	3a R = Et	ethereal, <i>floral</i>	M		4a R = Et	fruity, <i>green</i>	S
	3b R = <i>i</i> -Pr	ethereal, <i>green</i>	S		4b R = <i>i</i> -Pr	fruity, <i>mushroom</i>	W
	3c R = <i>t</i> -Bu	sulfur	VW		4c R = <i>t</i> -Bu	<i>green, fruity</i>	W
	5a <i>cis</i>	<i>green, floral</i>	S		6a <i>cis</i>	ethereal, <i>green</i>	VS
	5b <i>trans</i>	<i>green, floral</i>	S		6b <i>trans</i>	fruity, <i>green</i>	VS
	7a R = Me	leather, <i>almond</i>	S		8a R = Me	medicinal, <i>quinoline</i>	S
	7b R = <i>t</i> -Bu	medicinal, <i>lether</i>	W		8b R = <i>t</i> -Bu	fruity, <i>green</i>	M
	9	<i>green, floral</i>			10a n = 5	fruity, <i>green</i>	
					10b n = 7	fruity, <i>waxy</i>	

^a VS, very strong; S, strong; M, medium; W, weak; VW, very weak. Secondary notes are in italics.

1A), following general procedures (Lefebvre and Levas, 1945). Cycloaliphatic derivatives (**5** and **6**) were obtained in turn from their aromatic equivalents by hydrogenation on platinum oxide.

Benzyl derivatives of 2-THP (**7**) and 2-THF (**8**) were obtained by reaction of 2-(bromomethyl)tetrahydropyran or 2-(chloromethyl)tetrahydrofuran with the appropriate Grignard reagent in the presence of ferric chloride (Figure 1B), along with general procedures (Lefebvre and Levas, 1945). Yields in these cases were rather poor, owing to a side dimerization reaction. The compounds obtained, however, could be easily purified by column chromatography.

2-Heptyltetrahydropyran (**9**) as well as 2-hexyl- (**10a**) and 2-octyltetrahydrofuran (**10b**) was prepared by reduction of the corresponding lactones, followed by cyclization of the glycols thus obtained (Figure 1C).

NMR and mass spectra of the new compounds are reported in Table 1 and are in agreement with the expected structures.

All of the odorants were purified by column chromatography. Their purity, as checked by GLC, was between 99.7 and 99.9%. Particular care was taken when performing odor evaluation in detecting traces of the starting compounds that, particularly in the cases of phenols, could modify the odor quality, even at very low concentration.

Odor Properties. The odor quality and intensity for all of the compounds examined are reported in Table 2.

None of the odorants exhibits the floral note as the main character; only in four compounds (one of the 2-THP series and three among the cyclohexyl ethers) is it present as secondary note. This fact requires an explanation, as in the series of 2-THP and 2-THF ethers, several members were found to have a strong distinct floral character. The replacement of one of the two oxygen atoms with a carbon not only modifies the hydrophilicity of the odorant but also induces important conformational changes affecting the oriented profile of the molecule.

It is well-known (McKelvey *et al.*, 1981) that in the tetrahydropyranyl ethers the anomeric effect, that is, the repulsion of the lone pairs present on the two oxygen atoms, stabilizes the conformation where the substituent in position 2 is linked with an axial bond; therefore, the shape of the resulting molecule is rather bent

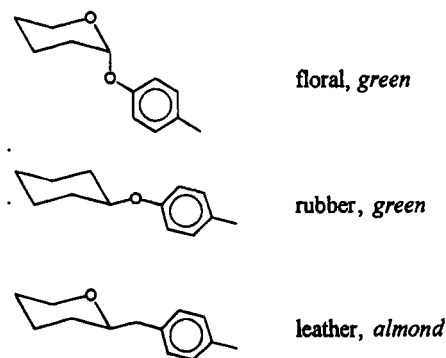


Figure 2. Preferred conformations of three homologous odorants. The anomeric effect is present only in the first compound, where it is responsible for a rather bent shape.

around carbon-2 of the tetrahydropyran ring. In our previously described tetrahydropyranyl ethers (Anselmi *et al.*, 1992, 1993) the presence of the anomeric effect is supported by ¹³C NMR data (Anselmi *et al.*, unpublished results). In the compounds where a single oxygen atom is present, such repulsion does not occur and the equatorial conformation is the most stable; the overall shape of the molecule becomes more flat and extended. In the benzyl derivatives of tetrahydropyran (**7**) the substituent has been assigned to the equatorial position on the basis of the NMR values for the proton in position 1 of the tetrahydropyran ring ($\delta = 3.85\text{--}3.95$; $J_{a,a} \text{H1-H2} = 12.3 \text{ Hz}$), whose coupling constant is close to the value (11.2 Hz) reported for the axial proton in position 1 of C-glycopyranosides (Brakta *et al.*, 1993). Concerning cyclohexyl ethers **1** and **3**, the equatorial position of the substituent is indicated by the coupling constants of the proton in position 1 with those in positions 2 and 6 ($J_{a,a} = 8.5 \text{ Hz}$; $J_{a,e} = 4.5 \text{ Hz}$), which are close to the literature values for an axial proton in similar compounds (Gaudemer *et al.*, 1977).

These considerations can be visualized by the models of Figure 2, in which the most stable conformations are indicated for three homologous odorants. Molecular modeling and NMR data are in agreement with this explanation of the olfactory data.

Due to analogous stereoelectronic effects, 2-tetrahydrofuran ethers and their carbon analogues are likely to adopt different conformations, which could account for their different odors.

These results give a further contribution toward the definition of the stereochemical parameters associated with a floral odor and indicate that only molecules that can assume a bent shape similar to the first of Figure 2 can exhibit the typical floral note. This model should be further supported by an olfactory study of analogues of these compounds, in which one or the other conformation is "frozen" in more rigid structures.

ACKNOWLEDGMENT

This work was supported by the National Research Council of Italy, Special Project "Chimica Fine".

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Received for review April 18, 1994. Accepted August 4, 1994.®

® Abstract published in *Advance ACS Abstracts*, September 1, 1994.