Influence of the Regio- and Stereochemistry on the Floral Odor of THP and THF Ethers

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The relationships between chemical structure and the odor of white flowers in a new series of tetrahydropyranyl and tetrahydrofuranyl derivatives of substituted cyclohexanols and phenols was investigated, with particular reference to the stereochemistry of the odorants. Several of these compounds exhibit a pleasant floral odor, two of them being very similar in their odor profiles to hydroxycitronellal, taken as a reference for the odor of white flowers. They represent interesting alternatives to the currently used additives for cosmetics and detergents.

INTRODUCTION

In a previous paper (Anselmi et al., 1992) we discussed the relationships between chemical structure and floral odor, with particular reference to the note of muguet, which may be reproduced by hydroxycitronellal (3,7-dimethyl-7-hydroxyoctanal), lilial [2-methyl-3-(p-tert-butylphenyl)-propanal], and other synthetic compounds (Boelens et al., 1980; Olhoff and Giersch, 1980). We also emphasized the need in perfumery for new chemicals endowed with this type of odor, because of problems related to the chemical instability and skin incompatibility of the aldehydic compounds so far employed (Ford et al., 1988).

In the same paper, we also reported the synthesis of new floral odorants belonging to the class of 2-tetrahydropyranyl (THP) derivatives of alcohols and phenols. A comparison of the molecular profiles of the best odorants synthesized (THP of p-alkylphenols and cis-4-methylcyclohexanol) with those of hydroxycitronellal and lilial had indicated the structural parameters required to produce the odor of white flowers, thus contributing to a better definition of the relationships between chemical structure and odor. In particular, it was found that the alcoholic group of hydroxycitronellal only provides the necessary bulkiness and can therefore be replaced by a methyl group, while the aldehyde group of hydroxycitronellal, lilial, and other floral odorants could be replaced by other polar moieties, such as the THP radical, thus avoiding problems of instability and unsafeness characteristic of aldehydic compounds.

Therefore, we have prepared additional 2-THP derivatives and a new series of 2-tetrahydrofuranyl (THF) ethers, homologous with those members in the THP series, that best reproduced the odor of white flowers.

In the present paper we report how the odor is affected by two types of structural modifications: (a) the position and the size of the substituent on the cyclohexane ring in the series of cyclohexanol 2-THP derivatives; (b) the replacement of the 2-tetrahydropyranyl group with the smaller 2-tetrahydrofuranyl.

The results give the basis for a more detailed definition of the stereochemical parameters associated with the odor of white flowers and provide, at the same time, two

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derivatives that reproduce very closely the odor of lilial and could find practical uses in cosmetics and toiletries.

MATERIALS AND METHODS

Synthesis of Compounds. Both the 2-THP and 2-THF derivatives were prepared by addition of the appropriate alcohol or phenol with 3,4-dihydro-2H-pyran or 2,3-dihydrofuran, in the presence of traces of p-toluenesulfonic acid. The reaction is known to give the corresponding tetrahydro-2-pyranyloxy or tetrahydro-2-furanyloxy derivative, respectively. Some of the compounds were best synthesized according to the modified procedure of Bongini et al. (1979), as described also in our previous paper (Anselmi et al., 1992).

All of the products were purified by column chromatography on silica gel, using 1% diethyl ether in petroleum ether as the eluent. This procedure allowed, in most cases, separation of diastereoisomers and gave better confidence in the purity of the synthesized odorants. The chemical purity of the final samples was better than 99% by GLC on a 12-m DB-1 capillary column. The odorants were also subjected to an informal smell test to detect traces of the starting alcohols and phenols, if present.

Odor Evaluation. A panel of 10 expert perfumers was employed for all of the odor measurements. Odor descriptors have been defined on all the undiluted samples, while odor profiles have been determined only for the best compounds, using 10% solutions in diethyl phthalate.

RESULTS AND DISCUSSION

Chemical Characterization. Table I lists the compounds that, as far as we could determine, were not previously reported in the literature. NMR and mass spectra have been used for their characterization. Only the mass spectra run at the ionization potential of 15 eV are reported, as at the standard value of 70 eV the molecular ions could not be detected, because of an extensive fragmentation, and the spectra were not very informative. NMR spectra confirm the expected structures and can be used to differentiate between diastereoisomers that are obtained with certain alcohols.

Odor Properties. The structures of the compounds synthesized are reported in Table II with their odor descriptions. Some of them had been previously synthesized, but their odor properties had not been evaluated; they are the 2-THP ethers of 1-methylcyclohexanol (Wellmann and Steckhan, 1980), 3-methylcyclohexanol (Goering and Serres, 1952), and 4-tert-butylcyclohexanol (Morizawa et al., 1981) and the 2-THF ethers of 1-methylcyclohexanol (Kruse et al., 1979), p-methylphenol (Dusek et al., 1981), and p-tert-butylphenol (Loewen and Brown, 1972). Most of these odorants belong to two classes

Table I. ¹H NMR and Mass Spectra of 2-Tetrahydropyranyl (THP) and 2-Tetrahydrofuranyl (THF) Derivatives Not Previously Reported in the Literature

alcohol	¹H NMR (100 MHz, CDCl₃)	MS (15 eV), m/z (% relative intensity)
cyclohexanols-2-THP		
cis-2-methyl (I)	4.63 (1 H, m); 3.90 (1 H, m); 3.64 (1 H, m); 3.48 (1 H, m); 1.20–1.90 (15 H, m); 0.89 (3 H, d, J = 7.0 Hz)	198 (M, 10), 114 (10), 96 (75), 85 (90), 68 (76), 55 (100), 41 (43)
cis-2-methyl (II)	4.73 (1 H, m); 3.90 (1 H, m); 3.72 (1 H, m); 3.48 (1 H, m); 1.20–1.90 (15 H, m); 1.02 (3 H, d, J = 7.0 Hz)	198 (M, 7), 114 (13), 96 (78), 81 (95), 68 (80), 55 (100), 41 (35)
trans-2-methyl (I)	4.56–4.65 (1 H, m, OCHO); 3.88–4.02 (1 H, m, CH₂O); 3.39–3.54 (1 H, m, CH₂O); 2.94–3.09 (1 H, dt, CHO); 0.95–2.15 (15 H, m, CH₂CHCH₃); 0.94 (3 H, d, CH₃)	198 (M, 12), 114 (10), 96 (63), 85 (82), 68 (73), 55 (110), 41 (42)
trans-2-methyl (II)	4.76–4.84 (1 H, m, OCHO); 3.84–3.98 (1 H, m, CH₂O); 3.42–3.56 (1 H, m, CH₂O); 3.13–3.28 (1 H, dt, CHO); 0.95–2.12 (15 H, m, CH₂ + CHCH₃); 1.04 (3 H, d, CH₃)	198 (M, 5), 114 (12), 97 (70), 85 (100), 68 (62), 55 (96), 41 (38)
cis-3-methyl	4.55–4.65 (1 H, m, OCHO); 3.75–3.95 (2 H, m, OCH + 1CH₂O); 3.50–3.35 (1 H, m, CH₂O); 0.90–1.90 (15 H, m, CH₂ + CHCH₃); 0.80 (3 H, d, CH₃, J = 6.6 Hz)	198 (M, 10), 113 (14), 96 (88), 81 (92), 71 (100), 55 (98), 41 (47)
trans-3-methyl (I)	4.67–4.75 (1 H, m, OCHO); 3.83–3.98 (1 H, m, CH₂O); 3.38–3.65 (2 H, m, OCH₂ + CHO); 0.70–2.06 (15 H, m, CH₂ + CHCH₃); 0.89 (3 H, d, CH₃, J = 6.6 Hz)	198 (M, 10), 113 (13), 96 (80), 81 (88), 71 (100), 55 (96), 41 (43)
trans-3-methyl (II)	4.67–4.75 (1 H, m, OCHO); 3.83–3.98 (1 H, m, CH₂O); 3.38–3.65 (2 H, m, OCH₂ + CHO); 0.70–2.06 (15 H, m, CH₂ + CHCH₃); 0.89 (3 H, d, CH₃, J = 6.5 Hz)	198 (M, 8), 113 (18), 96 (100), 81 (93), 71 (97), 55 (50)
cis-4-isopropyl	4.65–4.78 (1 H, m, OCHO); 3.85–4.00 (1 H, m, CH₂O); 3.40–3.62 (2 H, m, OCH₂ + OCH); 0.96–2.15 (16 H, m, CH₂ + 2 × CH); 0.86 (6 H, d, 2 × CH₃, J = 6.7 Hz)	226 (M, 8), 183 (10), 124 (37), 109 (25), 81 (100), 67 (22), 55 (46), 43 (21)
trans-4-isopropyl	4.63–4.68 (1 H, m, OCHO); 3.81–3.97 (2 H, m, CH₂O + OCH); 3.41–3.55 (1 H, m, OCH₂); 1.00–2.00 (16 H, m, CH₂ + 2 × CH); 0.89 (6 H, d, 2 × CH₃, J = 6.7 Hz)	226 (M, 4), 124 (32), 109 (25), 81 (100), 67 (22), 55 (42), 43 (21)
cis-4-tert-butyl	4.60–4.68 (1 H, m, OCHO); 3.83–3.98 (2 H, m, CH₂O + CHO); 3.39–3.53 (1 H, m, OCH₂); 0.90–2.03 (15 H, m, CH₂ + CH); 0.86 (9 H, s, 3 × CH₃)	240 (M, 3), 139 (16), 123 (25), 82 (48), 67 (40), 57 (100), 41 (22)
trans-4-tert-butyl	4.66–4.75 (1 H, m, OCHO); 3.84–3.98 (1 H, m, CH₂O); 3.40–3.58 (2 H, m, OCH₂ + CHO); 0.90–2.12 (15 H, m, CH₂ + CH); 0.85 (9 H, s, 3 × CH₃)	240 (M, 4), 138 (18), 123 (24), 81 (45), 67 (28), 57 (100), 41 (15)
cyclohexanols-2-THF		
cis-2-methyl	5.15–5.25 (1 H, m, OCHO); 3.75–4.00 (3 H, m, CH₂O + CHO); 3.65–3.71 (1 H, m, CH₂OO); 3.55–3.65 (1 H, m, CH₂O); 1.15–2.10 (13 H, m, CH₂ + CHCH₃); 0.95 (3 H, d, CH₃, J = 6.7 Hz); 0.91 (3 H, d, CH₃, J = 6.8 Hz)	184 (M, 18), 114 (10), 96 (50), 81 (52), 71 (100), 57 (54), 41 (60)
trans-2-methyl (I)	5.15 (1 H, m); 3.75–3.95 (2 H, m); 2.94 (1 H, dt, J_d = 4.6 Hz, J_t = 9.7 Hz); 1.0–2.1 (13 H, m); 0.88 (2 H, d, J = 6.7 Hz)	184 (M, 4), 114 (13), 96 (56), 81 (68), 71 (100), 57 (73), 41 (70)
trans-2-methyl (II)	5.22 (1 H, m); 3.75–3.95 (2 H, m); 3.09 (1 H, dt, J_d = 4.0 Hz, J_t = 10.1 Hz); 1.0–2.1 (13 H, m); 0.88 (2 H, d, J = 6.7 Hz)	184 (M, 3), 114 (15), 96 (64), 81 (80), 71 (100), 57 (78), 41 (80)
cis-3-methyl	5.15–5.25 (1 H, m, OCHO); 3.75–3.95 (3 H, m, CH₂O + CHO); 0.95–2.1 (13 H, m, CH₂ + CHCH₃); 0.88 (3 H, d, CH₃, J = 6.6 Hz)	184 (M, 9), 96 (58), 81 (56), 71 (100), 55 (37), 41 (58)
trans-3-methyl	5.25–5.35 (1 H, m, OCHO); 3.77–3.97 (2 H, m, CH₂O + CH-O); 3.41–3.58 (1 H, m, CH₂O); 1.00–2.10 (13 H, m, CH₂ + CHCH₃); 0.94 (3 H, d, J = 6.6 Hz)	184 (M, 13), 141 (10), 113 (17), 96 (64), 81 (55), 71 (100)
cis-4-methyl	5.15–5.30 (1 H, m, OCHO); 3.65–3.95 (3 H, m, OCH + 1CH₂O); 1.15–2.10 (13 H, m, CH₂ + CHCH₃); 0.90 (3 H, d, CH₃, J = 5.8 Hz)	184 (18), 141 (14), 97 (73), 71 (100)
trans-4-methyl	5.22–5.29 (1 H, m, OCHO); 3.74–3.95 (22, m, CH₂O); 3.35–3.53 (1 H, m, CHO); 0.89–2.06 (14 H, m, CH₂ + CH); 0.83 (3 H, d, CH₃, J = 6.4 Hz)	184 (M, 5), 97 (30), 71 (100), 55 (17), 43 (13)
cis-4-isopropyl	5.18–5.28 (1 H, m, OCHO); 3.73–3.95 (3 H, m, CH₂O + OCH); 0.95–2.10 (14 H, m, CH₂ + 2 × CH); 0.87 (6 H, d, 2 × CH₃, J = 6.6 Hz)	212 (M, 3), 124 (28), 109 (15), 81 (100), 71 (65), 55 (17), 41 (28)
trans-4-isopropyl	5.25–5.31 (1 H, m, OCHO); 3.75–3.95 (2 H, m, CH₂O); 3.35–3.53 (1 H, m, OCH); 0.90–2.10 (14 H, m, CH₂ + 2 × CH); 0.84 (6 H, d, 2 × CH₃, J = 6.7 Hz)	212 (M, 4), 169 (10), 124 (33), 109 (25), 81 (100), 70 (32), 55 (21), 41 (34)
cis-4-tert-butyl	5.12–5.23 (1 H, m, OCHO); 3.71–3.95 (3 H, m, CH₂O + CHO); 0.85–2.08 (14 H, m, CH₂ + CH); 0.80 (5 H, s, 3 × CH₃)	226 (M, 3), 156 (14), 123 (44), 99 (37), 82 (61), 67 (48), 57 (100), 41 (24)
trans-4-tert-butyl	5.22–5.28 (1 H, m, OCHO); 3.74–3.95 (2 H, m, CH₂O); 3.32–3.50 (1 H, m, CHO); 0.88–2.10 (14 H, m, CH₂ + CH); 0.82 (9 H, s, 3 × CH₃)	226 (M, 3), 138 (32), 123 (36), 99 (21), 81 (58), 70 (40), 57 (100), 41 (45)
phenols-2-THF		
p-ethyl	7.09 (2 H, d, 2 × ar CH); 6.95 (2 H, d, 2 × ar CH); 5.72–5.80 (1 H, dd, OCHO); 3.86–4.10 (2 H, m, CH₂O); 2.58 (2 H, q, CH₂CH₃); 1.83–2.15 (4 H, m, CH₂); 1.20 (3 H, t, CH₃)	192 (M, 11), 122 (47), 107 (100), 91 (8), 77 (21), 70 (20), 41 (24)
p-isopropyl	7.12 (2 H, d, 2 × ar CH); 6.95 (2 H, d, 2 × ar CH); 5.74–5.81 (1 H, dd, OCHO); 3.86–4.11 (2 H, m, CH₂O); 2.83 (1 H, h, CH₃CHCH₃); 1.85–2.23 (4 H, m, CH₂); 1.23 (6 H, d, 2 × CH₃)	206 (M, 8), 136 (42), 121 (100), 103 (15), 91 (17), 77 (18), 70 (18), 41 (27)

of compounds, THP and THF of substituted cyclohexanols, chosen on the basis of the structure/odor relationships defined for derivatives of this type in our previous paper. Taking as a reference the THP ether of cis-4-methylcyclohexanol, which proved to be the best odorant in the first series, we investigated how the odor was affected

Table II. Odor Properties of 2-Tetrahydropyranyl (THP) and 2-Tetrahydrofuranyl (THF) Ethers of Alcohols and Phenols

alcohol	no. of C	main odor	secondary notes	intensity
cyclohexanols–2-THP				
1-methyl	7	floral/green	moldy	w
cis-2-methyl (I)	7	floral	musk/aldehyde	m
cis-2-methyl (II)	7	floral	musk/aldehyde	m/s
trans-2-methyl (I)	7	floral	phenol	s
trans-2-methyl (II)	7	floral	rubber	s
cis-3-methyl	7	floral	fruity	m
trans-3-methyl (I)	7	floral	green/fruity	s
trans-3-methyl (II)	7	floral	green/fatty	m/s
cis-4-isopropyl	9	green	floral	s
trans-4-isopropyl	9	fruity	green/floral	m
cis-4-tert-butyl	10	floral	green/musk	vw
trans-4-tert-butyl	10	odorless		
cyclohexanols–2-THF				
1-methyl	7	mushroom/moldy	floral/green	s
cis-2-methyl	7	floral (hyacinth)	phenol	m
trans-2-methyl	7	phenol	floral/green	vs
cis-3-methyl	7	fruity	phenol	s
trans-3-methyl	7	floral (rose)	phenol	vs
cis-4-methyl	7	floral	green/fruity	m
trans-4-methyl	7	anise	floral	vs
cis-4-isopropyl	9	floral	green/fruity	vs
trans-4-isopropyl	9	floral	fruity	s
cis-4-tert-butyl	10	floral	musk/green	vs
trans-4-tert-butyl	10	fruity	green	vs
phenols–2-THF				
p-methyl	7	green/fruity	floral	m
p-ethyl	8	fruity/green	floral	s
p-isopropyl	9	floral	fruity/green	vs
p-tert-butyl	10	green	floral	vw

a w, weak; m, medium; s, strong; v, very.

by the following structural modifications: (a) regio- and stereochemistry of the methyl group on the cyclohexane ring; (b) substitution of a methyl with the bulkier isopropyl or *tert*-butyl in position 4 of the ring, with cis or trans configuration; and (c) substitution of the THP radical with a THF radical.

The last four compounds, the THF ethers of phenols, were synthesized because the corresponding THP derivatives had all been previously found to be good floral odorants (Anselmi et al., 1992).

From the data obtained, a few pertinent facts can be pointed out.

(a) In the series of the THP ethers, all of the derivatives exhibit a floral odor as their main character, although associated with secondary notes that are not always very pleasant. The last two members, the two isomers of 4-*tert*-butylcyclohexanol–THP, are extremely weak or odorless, indicating a strong steric influence of the *tert*-butyl group. The position of the methyl group on the cyclohexanol ring seems not to have a marked effect, apart from the 1-methyl derivative. No significant differences are found between the odors of cis/trans isomers, when the methyl group is in position 2 or 3 of the cyclohexane ring, unlike the 4-substituted isomers, as reported in our previous paper (Anselmi et al., 1992). These facts indicate that the floral odor is associated more with the size of the alcohol part of the THP ether than with its particular shape. The floral odor is present in almost all of the methylcyclohexanol derivatives, regardless of the position of the methyl group and without major differences between isomers. The shape only becomes critical for the 4-methylcyclohexanol derivatives. Moreover, increasing the size of the substituent in position 4 drastically reduces the odor intensity, the *tert*-butyl-substituted compounds being almost odorless. This effect is most pronounced with the trans isomers, in both the isopropyl and the *tert*-butyl derivatives.

(b) The THF derivatives of alkylcyclohexanols markedly differ from their THP homologues. The floral note is the
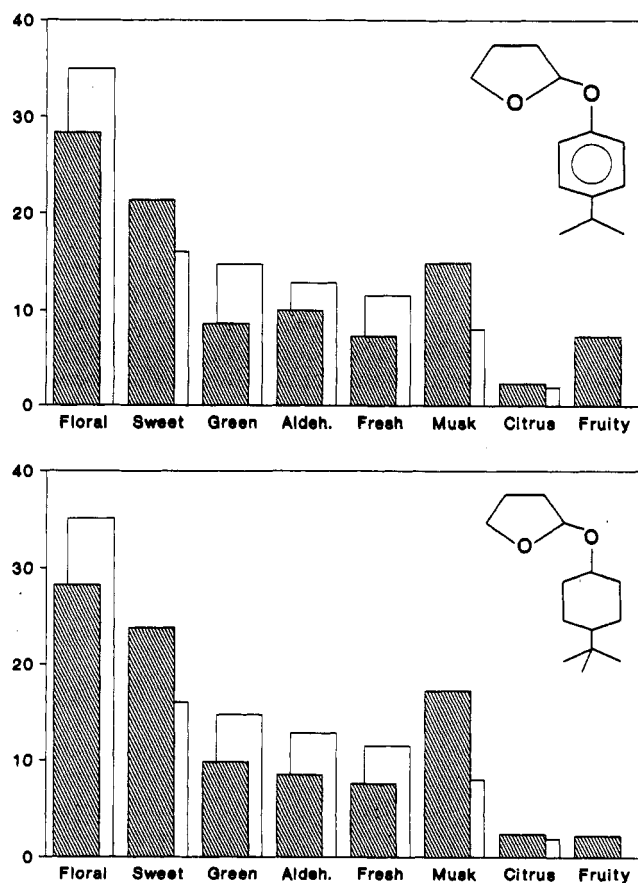

Figure 1. Odor profiles of the best rated floral odorants (structures shown) compared with that of hydroxycitronellal (blank bars in the background). The intensities of the different notes are indicated as percent of total odor.

main character in only some of them, although it is often present as secondary note, while almost all of the THP ethers are floral in their main character. This result points

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to a major effect following the substitution of the six-membered THP ring with the homologous five-membered THF ring and cannot be explained only by the different sizes of the two rings, as discussed below.

(c) The phenol–THFs also show a great variability in their odor, according to the size of the hydrocarbon radical in the para position, unlike the corresponding THP derivatives, all mainly floral.

Differences between the odors of THP derivatives and those of the corresponding THF derivatives can be pointed out by comparing the data here reported with those of our previous paper (Anselmi et al., 1992). While the THP ethers of *p*-alkylphenols are more floral than the corresponding THF derivatives, the reverse has been observed with the 4-substituted cyclohexanols. The differences in both cases are a consequence of substituting the THP ring with the THF ring. However, they cannot be accounted for only by the different sizes of the two rings, as indicated above, and other factors should be considered. One of these is certainly the different orientations of the bonds in the THP and the THF rings. In particular, the anomeric effect, present only in the THP ring, stabilizes the conformation where the external oxygen is linked with an axial bond to the THP ring. As a consequence, the THP ethers assume a more bent conformation than the corresponding THF derivatives. Another element to be considered is the greater flexibility of the THP ring with respect to the THF ring, which could make easier the necessary adjustments in the conformation of the odorant molecule for a good fitting to the protein binding site.

In both the THP and the THF derivatives, the stereochemistry seems to largely affect the olfactory properties, as can be easily seen by comparing the odors of cis and trans isomers.

It is rather difficult to give an exact account of the interactions occurring between odorants and binding proteins in the nose, not only due to our limited knowledge of the biochemistry of olfaction but also because of the great complexity of the system. In fact, any molecule can interact with a variety of different binding protines and receptors, each interaction producing a different odor sensation. Therefore, when studying structure/odor relationships, some facts would only be explained if we could take into account all of the possible interactions between odorants and olfactory receptors.

Although we are not able to solve such multivariable problems, the data obtained in studies such as the present one can be of practical use for designing new structures with the desired odor.

The THP and THF ethers synthesized and reported in this paper and in our previous paper include a few members endowed with the pleasant odor of white flowers, which could be used as substitutes of hydroxycitronellal or lilial.

In particular, two of these compounds, the THF derivatives of *p*-isopropylphenol and *cis*-4-*tert*-butylcyclohexanol, showed odor profiles (Figure 1) that were very similar to that of hydroxycitronellal. They can therefore be employed to replace this compound and other aldehydes of similar odor in formulations for toiletries and cosmetics, provided the medium is neutral or alkaline.

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