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Review article

Synthesis and odour properties of some saturated and unsaturated ketones and their derivatives

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Abstract: *Five ketones, both unsaturated and saturated, which have phenyl and/or t-butyl groups as substituents located at the end of a molecule have been prepared. They were used as starting materials in the synthesis of ethylene and propylene acetals, alcohols and their acetates. Thirteen from twenty three synthesized compounds (all ethylene and propylene acetals, an alcohol and two acetates) have not been described yet. The odour properties for all the prepared compounds have been determined. Most of them have pleasant, fruity-floral odours.*

Keywords: *ketones, acetals, alcohols, esters, synthesis, odour.*

Introduction

Recently the interest in finding new chemical compounds which possess interesting odour properties has increased. The main route for the development of perfumery is organic synthesis, which offers a wide range of synthetic compounds. These, in turn, can replace the ones obtained from natural sources.

The intensity and the type of odour of a compound strongly depends on the shape of its molecule, its conformation, configuration and also on the kinds of functional groups present [1,2].

One of the main groups of compounds having floral-fruity type of odours are compounds which contain the aromatic ring in their structure, e.g. 4-methylacetophenone with mimosa-coumarin odour, 4-methoxyacetophenone with a hawthorn odour, 2-phenylethanol with a strong rose odour or 4-(4-hydroxyphenyl)-butan-2-one with an intense raspberry odour [3-5]. Many compounds belonging to this group are found in some plants as the components of their essential oils [6,7]. Anethol appears in anise, cinnamaldehyde in cinnamon bark, benzyl acetate and benzyl alcohol in jasmine flowers, almonds contain benzaldehyde, used as a flavourant in confectionery [8].

The goal of this work was to synthesize a series of derivatives (alcohols, acetates, ethylene and propylene acetals) of a group of five ketones having phenyl and/or *t*-butyl groups at both ends of the molecule, and to compare their odours. We also report the physical properties and spectral data of the obtained compounds.

Experimental

Materials

Ketones: Three α,β-unsaturated ketones were prepared using the appropriate carbonyl compounds as substrates in the aldol condensation reaction in the presence of basic catalysts according to methods described in literature. Two of them were further hydrogenated by cyclohexene as the hydrogen donor in the presence of a Pd/C catalyst yielding the saturated ketones.

Other reagents: Ethane-1,2-diol (p.a. POCH Gliwice), propane-1,2-diol (p.a. VEB Laborchemie APOLDA), p-toluenesulfonic acid (pure, Fluka), sodium borohydride (98%, Aldrich), triethyl orthoformate (98%, Aldrich), pyridine (99,8%, Aldrich), cyclohexene (99,7, Fluka), acetic anhydride (p.a. International Enzymes Ltd) and 2-propanol (p.a. POCH Gliwice) were used as received.

Methods

Gas chromatography: GC Carlo-Erba Instruments, GC 6000, VEGA series with FID detector was used, equipped with a column CPSIL 5 CB, length 30 m, i.d. 0,32 mm, film thickness 0,25 µm.

^{1}H-NMR spectra were recorded on a Bruker 250 DPX spectrometer, in $CDCl_3$ using TMS as the internal standard. The IR spectra were measured using Specord Shimadzu IR 408 spectrometer (film or KBr pellet).

Melting points (uncorrected) were determined on Boetius apparatus. The purity of compounds were confirmed by GC-MS, IR, ^{1}H NMR and the measurements of refractive indices.

Odour characteristics of the studied compounds (10% solutions in ethanol) were defined according to a well known method, that is by a group of twelve specialists with extensive odour evaluation training (age 20–55, both sexes) from the Institute of Food Chemistry, Lodz Technical University.

Synthesis of ketones (A1-E1): Pivalidenepinacolone, 2,2,6,6-tetramethylhept-4-en-3-one (**A1**) was prepared by the aldol condensation of pivalaldehyde with pinacolone in diethyl ether in the presence of ethanolic solution of sodium hydroxide according to the procedure described elsewhere [9]. The crude product was isolated from the reaction mixture by fractional distillation under reduced pressure. The obtained semi-solid product was further purified by crystallization from methanol at -30ºC. After two crystallizations a colourless solid (**A1**) was obtained (m.p. 44°C), yield 23%, purity 99,9% (GC).

Dihydropivalidenopinacolone, 2,2,6,6-tetramethylheptan-3-one (**B1**) and dihydrobenzylidenepinacolone, 4,4-dimethyl-1-phenyl-pentan-3-one (**D1**) were prepared by catalytic transfer hydrogenation of (**A1**) or (**C1**) with cyclohexene as the hydrogen donor in the presence of a palladium catalyst**.** To a solution of an unsaturated ketone (100 mmol) in 40 cm^3 of cyclohexene 300 mg of 5wt% Pd/C catalyst was added. The suspension was heated under reflux for 12 h. After cooling the catalyst was separated by filtration. Evaporation of the solvent in a rotatory evaporator yields the crude product which was distilled under reduced pressure. (**B1**) – colourless liquid**,** yield 92%, purity 98.3% (GC). (**D1**) - colourless liquid, yield 82%, purity 99.4% (GC).

Benzylidenepinacolone, 4,4-dimethyl-1-phenyl-pent-1-en-3-one (C**1**) was prepared by the aldol condensation of benzaldehyde with methyl-t-butyl ketone in the presence of water-ethanolic solution of sodium hydroxide, according to the procedure described elsewhere [10]. The crude product was purified by distillation under reduced pressure. The resulted yellow solid (m.p. 40-1ºC) was crystallized twice from 95% ethanol. Almost pure white crystals were obtained. Yield 71% (m.p. 43°C), purity 99,5% (GC).

Pivalideneacetophenone, 4,4-dimethyl-1-phenyl-pent-2-en-1-one (**E1**) was prepared by the aldol condensation of acetophenone with pivalaldehyde in the presence of water-ethanolic solution of sodium hydroxide, according to the procedure described elsewhere [11]. The crude product was purified by distillation under reduced pressure. **E1** – yellow liquid, yield 48%, purity 99,4% (GC).

Table 1. Physical properties of ketones and their ethylene and propylene acetals

Code No.	Y/P^{x} [%]/[%]	M.p. [°C]	B.p. [°C/mm Hg]	n^{20}_{D} (exp)
A1	23/99.9	43-44	–; 62/5 [12]	–
B1	92/98.3	–	57/0.4; 108/2 [14]	1.4243
C1	71/99.5	43; 42-43 [10]	–	–
D1	82/99.4	–	84-6/5; 65/0.04 [15]	1.4972^{xx}
E1	48/99.4	–	95/0.4; 92-8/0.1 [16]	1.5329
A2*	76/92.9	–	50-1/1.0	1.4359
B2*	93/98.0	–	47-9/0.7	1.4685
C2*	74/99.3	97-8	–	–
D2*	82/98.5	56-8	–	–
E2*	65/96.2	39-40	–	–
A3*	65/97.9	–	58-60/0.6	1.4365
B3*	94/99.9	–	51-2/0.8	1.4355
C3*	82/99.9	71-2	–	–
D3*	85/98.6	42-3	–	–
E3*	49/97.8	–	71-4/0.7	1.4436

* – newly prepared compound; ^{x} – Y/P = yield/purity (GC); ^{xx} – 1.4972 (lit) [13]

Synthesis of ethylene (A2-E2) and propylene acetals (A3-E3): A mixture of a ketone (50 mmol), ethylene glycol (3.72 g, 60 mmol) or propylene glycol (4.56 g, 60 mmol), 100 mg of p-toluenosulfonic acid and triethyl orthoformate (14.82, 100 mmol) in 100 cm^3 of methylene chloride was heated under reflux for 10 h. After cooling, water (100 cm^3) was added to the reaction mixture and the layers were separated. The organic layer was washed with brine and with 5% Na_2CO_3 solution and dried over $MgSO_4$. After evaporation of the solvent in a rotatory evaporator, the crude product was distilled under reduced pressure.

Synthesis of alcohols (A4-D4): To the stirred solution of a ketone (100 mmol) in 100 cm^3 of 2-propanol a solution of $NaBH_4$ (1.00 g, 26 mmol) in 30 cm^3 50/50 v/v water – 2-propanol was ***added*** dropwise at room temperature. The mixture was stirred for 11 h, 150 cm^3 of water were added and 2-propanol was distilled off in a rotatory evaporator. The resulted mixture was separated, the water layer was extracted with hexane (3x20 cm^3), and the extracts were collected. The organic layer was washed with brine, then with water until neutral, and dried over $MgSO_4$. After evaporation of hexane in a rotatory evaporator the crude product was distilled under reduced pressure.

Table 2. Physical properties of alcohols and their acetates

Code No.	Y/P^x [%]/[%]	M.p. [°C]	B.p. [°C/mm Hg]	n^{20}_D (exp)
A4	95/97.0	–	79-82/1.0	1.4382
B4	94/96.0	56-8; 58-9 [17]	–	–
C4*	71/98.6	–	104/1.5	1.5362
D4	68/98.8	–	78-9/0.4; 72-3/1.0 [18]	1.5086^{xx}
A5	96/96.3	–	81-3/1.5	1.4867
B5	92/98.7	–	79-81/1.6	1.4849
C5*	93/98.7	–	82-5/2.0	1.4804
D5*	80/98.4	–	86-89/1.4	1.4796

* – newly prepared compound; ^{x} – yield/purity (GC); ^{xx} – 1.5080 (lit) [18]

Synthesis of acetates (A5-D5): A mixture of an alcohol (8 mmol), acetic anhydride (1.40 g, 14 mmol) and 1 cm^3 pyridine was stirred for 3 h and left for 24 h. To the cold mixture 50 cm^3 of water was added and the layers were separated. The organic layer was washed with 10 cm^3 1% hydrochloric acid, then with water and dried over $MgSO_4$. The crude product was distilled under reduced pressure.

The physical properties of ketones and their ethylene and propylene acetals are presented in Table 1. The physical properties of alcohols and their acetates are presented in Table 2. The spectral data of ketones and their ethylene and propylene acetals are collected in Table 3. The spectral data of alcohols and their acetates are collected in Table 4.

Table 3. Spectral data of ketones and their ethylene and propylene acetals

Code No.	IR [cm^{-1}]	^{1}H-NMR δ [ppm], J [Hz]
A1	3000; 1690; 1630	1.09 (s, 9H); 1.17 (s, 9H); 6.41 (d, 1H, J = 15,5); 6.94 (d, 1H, J = 15.5)
B1	3030; 1710	0.96 (s, 9H); 1.15 (s, 9H); 1.42-1.48 (m, 2H); 2.41-2.47 (m, 2H)
C1	3030; 1730; 1620; 1580	1.23 (s, 9H); 7.13 (d, 1H, J = 15.7); 7.36-7.57 (m, 5H, ar.); 7.69 (d, 1H, J=15.7)
D1	3030; 1730; 1620	1.13 (s, 9H); 2.77-2.83 (m, 2H); 2.84-2.95 (m, 2H); 7.19-7.29 (m, 5H)
E1	3030; 1670; 1650; 1620; 1580	1.06 (s, 9H); 6.78 (d, 1H, J = 15.5); 7.06 (d, 1H, J = 15.5); 7.39-7.47 (m, 3H); 7.90-793 (m, 2H)
A2	3030; 1660; 1480; 1360; 1210	0.93 (s, 9H); 1.01 (s, 9H); 3.73-3.90 (m, 4H); 5.28 (d, 1H, J = 15.8); 5.75 (d, 1H, J = 16.8)
B2	3030; 1460; 1210; 1160	0.85 (s, 9H); 0.95 (s, 9H); 1.20-1.32 (m, 4H); 3.97-4.06 (m, 4H)
C2	3030; 1630; 1560; 1170	1.05 (s, 9H); 3.75-3.99 (m,.4H); 6.20 (d, 1H, J = 16.0); 6.65 (d, 1H, J = 16.0); 7.25-7.43 (m, 5H)
D2	3030; 1620; 1180	0.97 (s, 9H); 1.99-2.05 (m, 2H); 2.63-2.70 (m, 2H); 4.02-4.15 (m, 4H); 7.17-7.31 (m, 5H)
E2	3100; 3000; 1660; 1300; 1260; 1160	0.99 (s, 9H); 3.86-4.07 (m, 4H); 5.54 (d, 1H, J = 16.0); 5.74 (d, 1H, J = 16.0); 7.25-7.35 (m, 3H); 7.46-7.50 (m, 2H)
A3	3020; 2900; 1590; 1210; 1150; 1080	0.94 (s, 9H);1.02 (s, 9H); 1.24-1.27 (m, 3H); 3.29-3.35 (t, 1H, J = 7.3); 3.92-4.15 (m, 2H); 5.34 (2d, 1H, $J_1 = J_2 = 15.8$); 5.78 (2d, 1H, $J_1 = J_2 = 8.0$)
B3	3000; 2900; 1480; 1360; 1300; 1210; 1160	0.88 (s, 9H); 1.03 (s, 9H); 1.24-1.32 (m, 4H); 1.64-1.71(m, 3H); 3.33-3.47 (m, 1H); 4.06-4.35 (m, 2H)
C3	3000; 1490; 1170	1.01 (s, 9H); 1.29 (2d, 3H, $J_1 = J_2 = 2.4$); 3.36-3.41 (m, 1H); 4.00-4.21 (m, 2H,); 6.25 (2d, 1H, $J_1 = J_2 = 15.9$); 6.67 (2d,1H, $J_1 = J_2 = 7.4$); 7.24-7.43 (m, 5H ar.)
D3	3030; 1590; 1570	0.97 (d, 9H, J = 1.1); 1.32 (t, 3H, J = 5.8); 1.98-2.05 (m, 2H); 2.67-2.74 (m, 2H); 3.41-3.57 (m, 1H); 4.16-4.22 (m, 1H); 4.32-4.39 (m, 1H); 7.20-7.29 (m, 5H)
E3	3000; 1490; 1170	1.04 (s, 9H); 1.26 (2d, 3H, J = 2.4); 3.37-3.41 (m, 1H); 4.00-4.23 (m, 2H); 6.48 (2d, 1H, $J_1 = J_2 = 15.9$); 6.75 (2d, 1H, $J_1 = J_2 = 7.4$); 7.24-7.43 (m, 5H ar)

Table 4. Spectral data of alcohols and their acetates

Code No.	IR [cm^{-1}]	^{1}H-NMR δ [ppm], J [Hz]
A4	3500; 3090; 2990; 1590; 1480; 1220	0.89 (s, 9H); 1.02 (s, 9H); 1.51 (s, 1H); 3.68 (2d, 1H, $J_1 = J_2 = 0.75$); 5.40 (2d, 1H, $J_1 = 5.0$, $J_2 = 7.5$); 5.67 (2d, 1H, $J_1 = J_2 = 15.5$)
B4	3500; 3010; 1210	0.89 (s, 9H);0.91 (s, 9H); 1.14-1.20 (m, H); 1.31 (s, 1H); 1.49-1.56 (m, 2H); 3.11 (d, 1H, J = 8.75)
C4	3490; 3000; 1610; 1580; 1240	1.00 (s, 9H); 1.84-1.91 (m, 1H); 3.95 (2d, 1H, $J_1 = J_2 = 1.0$); 6.27-6.37 (2d, 1H, $J_1 = J_2 = 7.0$); 6.60 (d, 1H, J = 16.0); 7.27-7.44 (m, 5H)
D4	3490; 3030; 1620; 1100	0.90 (s, 9H); 1.53-1.87 (m, 3H); 2.63-2.94 (m, 2H); 3.24 (2d, 1H, $J_1 = J_2 = 1.8$); 7.19-7.30 (m, 5H)
A5	3090; 1730; 1250; 1215	0.87 (s, 9H); 1.00 (s, 9H); 2.05 (s, 3H); 4.96 (2d, 1H, $J_1 = J_2 = 0.75$); 5.31 (2d, 1H, $J_1 = J_2 = 7.8$); 5.70 (2d, 1H, $J_1 = J_2 = 0.75$)
B5	3080; 1730; 1260	0.91 (s, 9H); 1.11 (s, 9H); 1.81-1.89 (m, 2H); 2.11 (s, 3H); 2.51-2.60 (m, 2H); 4.79-4.84 (m, 1H)
C5	3030; 1760; 1610; 1590; 1250	0.98 (s, 9H); 2.10 (s, 3H); 5.18 (2d, 1H, $J_1 = J_2 = 1.0$); 6.20 (2d, 1H, $J_1 = J_2 =7.0$); 6.61 (d, 1H, J = 15.9); 7.24-7.40 (m, 5H)
D5	3490; 3030; 1610; 1260	0.92 (s, 9H); 1.79-1.89 (m, 2H); 2.10 (s, 3H); 2.54-2.63 (m, 2H); 4.83 (2d, 1H, $J_1 = J_2 = 2.5$); 7.18-7.30 (m, 5H)

Results and Discussion

Ketones, their ethylene and propylene acetals, alcohols and their acetates were prepared using commonly known methods. The details of the synthesis are summarized for each group of compounds in four procedures given below. The yields of the products, as well as their physical and spectral data are also given.
For all five groups of the prepared compounds, i.e. the ketones, their ethylene and propylene acetals, alcohols and their acetates the olfactory properties have been determined. Odour characteristics of ketones and their ethylene and propylene acetals are presented in Table 5. Odour characteristics of alcohols and their acetates are presented in Table 6.

All ketones have fruity odours which are intense irrespective of the substituents surrounding the carbonyl group. Most of alcohols preserve a fruity note with the exception of 4,4-dimethyl-1-phenylpentan-3-ol, for which a floral note was detected. The odours of alcohols are less intensive compared to the odours of ketones, probably due to their lower volatility, which is caused by the formation of a hydrogen bond between alcohol molecules. A fruity note is dominant among acetates with the exception of 4,4-dimethyl-1-phenylpent-2-en-3-yl acetate, for which a fine honey note appears. Many ethylene and propylene acetals have fruity odours, although the intensity is weak. The most interesting odours are exhibited by ethylene acetals of 4,4-dimethyl-1-phenyl-pent-1-en-3-one and 4,4-dimethyl-1-phenylpentan-3-one. The former has a pleasant fresh, sweet fruity-citrus odour and the latter a pleasant, fresh fruity-citrus odour with a lime note.

Table 5. Odour characteristics of ketones and their ethylene and propylene acetals

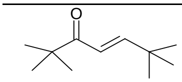
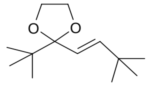
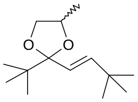
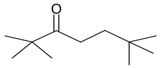
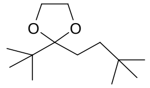
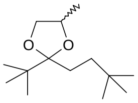
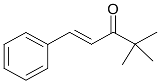
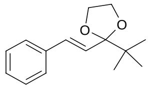
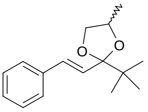
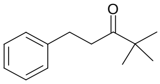
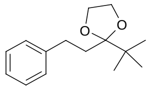
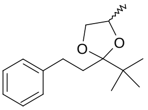
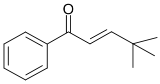
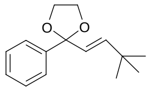
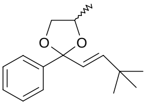
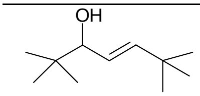
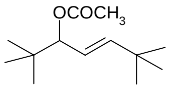
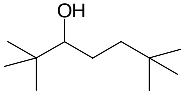
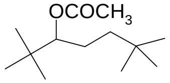
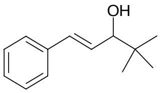
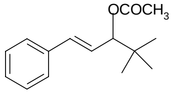
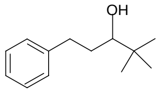
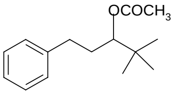
Compound Code No. Odour characteristics	Compound Code No. Odour characteristics	Compound Code No. Odour characteristics
 A1 Intense, fruity with a dried raspberry note	 A2 Very faint, pleasant with a floral-fruity note	 A3 Faint, herbaceous-spicy note
 B1 Intense, fresh with a banana-minty note	 B2 Very faint with a fine sour fruity note	 B3 Fruity with an apple purée note
 C1 Intense with a floral-citrus note	 C2 Pleasant, fresh, sweet fruity-citrus	 C3 Faint, lemon-like with a candied orange peel note
 D1 Fine, green with a matured blackberry note	 D2 Pleasant, fresh fruity-citrus with a lime note	 D3 Fruity with a matured currant note
 E1 Sweet, fruity-citrus with banana and strawberry notes	 E2 Unpleasant, mouldering wood with a cresol note	 E3 Milky-fruity note

Table 6. Odour characteristics of alcohols and their acetates

Compound Code No. Odour characteristics	Compound Code No. Odour characteristics
 A4 Intense, pleasant fruity-citrus with a grapefruit stone note	 A5 Pleasant, floral with apple and strawberry notes
 B4 Pleasant, fruity-citrus note	 B5 Fine, floral with a matured wild strawberry note
 C4 Fine with a bitter anise-almond note	 C5 Fine, floral with a gerber note
 D4 Sweet, floral with a fine honey note	 D5 Faint, with a fine honey note

Analysis of the structure of the studied compounds using computer methods reveals that the presence of a carbonyl group (ketones, esters) is responsible for fruity notes. An introductory analysis of the structure of the studied compounds reveals that for most of them the osmophoric group has a rigid structure and possesses a well exposed position in the molecule which strengthens its interaction with a receptor. In these compounds the presence of a carbon-carbon double bond, as well as a t-butyl group or exchange of the latter with a phenyl group has only a weak influence on the type of odour.

The odours of the studied compounds have been compared with the odours of compounds of a similar structure known from literature. It has been found that the presence of a t-butyl group as a substituent at the end of a molecule leads to a shift of the type of its odour from floral to fruity.

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