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> ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis and Perfume Characteristics of Acetals Containing an Aromatic Ring

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Abstract—Aromatic acetals were prepared by condensation of 2-methyl-3-(4-R-phenyl)propanals (R = Me, *i*-Pr, *i*-Bu) with ethanol, methanol, ethylene glycol, 1,2-propanediol, methyl Cellosolve, and Cellosolve. The perfume characteristics of the acetals were studied.

Thanks to active development of synthetic organic chemistry, the set of available synthetic perfumes is rapidly extended, with new classes of compounds being involved. The use of new synthetic perfumes is characterized by two features: (1) as a rule, substances with interesting scent are discovered empirically; (2) the perfume characteristics are studied for as many structurally related compounds as possible, with the aim to apply the developed processes to synthesis of a wide set of perfumes.

Such an approach inevitably sets a task of revealing the structure–scent relationship for perfumes, with the aim to make a search for new perfumes purposeful. At the same time, to find such a relationship, it is necessary to prepare as many structural analogs as possible.

Such studies were performed previously [1] but became more active in the past years. For example, the structure–scent relationship was studied for the series of 7-oxanorbornanes [2], monoterpene lactones [3], and bicyclo[2.2.n]oximes [4].

In this work, starting from aldehydes in which the carbonyl group is located in a side chain of an aromatic ring, we prepared aromatic acetals and studied their perfume characteristics. The initial compounds were the aldehydes widely used in perfumery: jasmorange [2-methyl-3-(4-methylphenyl)propanal, **I**], cyclamenaldehyde [2-methyl-3-(4-isopropylphenyl)propanal, **II**], and lilial [2-methyl-3-(4-*tert*-butylphenyl)propanal, **II**]:





Acetals are widely used are synthetic perfumes. This mostly concernes diethyl, dimethyl, and ethylene acetals, although derivatives of some other alcohols (geraniol, isoamyl alcohol, 2-phenylethanol) are also used [5]. To systematically study the structure–scent relationship in the series of acetals derived from **I**–**III**, we prepared the acetals with methanol, ethanol, ethylene glycol, 1,2-propanediol, and also with methyl Cellosolve and Cellosolve (the two latter compounds were not used previously for these purposes).

The reaction is usually performed in the presence of an acid catalyst; from the viewpoint of process simplicity, it is convenient to use cation-exchange resins, e.g., granulated KU-2 cation exchanger. The reaction was performed in benzene in the presence of FIBAN K-1 fibrous sulfonic cation exchanger as catalyst. This resin was prepared by radiation-induced grafting ot styrene (98%)–1,4-divinylbenzene (2%) copolymer to a polypropylene thread, followed by sulfonation with sulfuric acid.

With this catalyst, owing to its developed surface [6], the reaction time was reduced by a factor of 1.5-2 as compared to KU-2. Furthermore, the fibrous ion exchanger did not noticeably lose its activity in repeated use, as demonstrated by the example of the reaction of aldehydes **I–III** with Cellosolve (Table 1).

The reaction progress was monitored by GLC. The structure of the acetals was confirmed spectroscopically. In the 1 H NMR spectra, a characteristic doublet

Alde-

hyde

at 4.3-4.8 ppm (J 5-8 Hz) corresponds to the HC(OR)₂ proton. The IR spectra exhibit a characteristic acetal pattern consisting of five bands in the range $1185-1030 \text{ cm}^{-1}$.

The synthesis conditions and yields of the target products are given in Table 2, and the perfume characteristics of the acetals, 1 in Table 3.

Certain similarity of the scents of the initial aldehydes **I**-III is undoubtedly due to their similar molecular structure, not only topological but also steric. It was suggested [7] that all these molecules have a "rolled-up" conformation of the side chain (A, B), which is stabilized owing to conjugation of the π orbitals of the aromatic ring and carbonyl group. This factor is also responsible for the similar scent of these aldehydes and of 7-hydroxy-3,7-dimethyloctanal (hydroxycitronellal, IV). As suggested in [7], the molecule of IV in the vapor phase can take the rolled-up conformation **C** owing to hydrogen bonding:



However, optimization of the molecular geometry of I-III in the MM-2 approximation [8] shows that for each aldehyde the energies of the molecule in all the possible conformations differ by no more than ± 0.8 kJ mol⁻¹. Thus, the rolled-up conformation affords no additional stabilization of the aldehyde molecule. Furthermore, calculation shows that the angle between the planes of the aromatic ring and CHO group in I-III in the rolled-up conformation is 41.3°, 43.2°, and 44.5°, respectively. Such orientation excludes any overlap "through space" of the orbitals of the two nonbonded molecular fragments. It should be noted also that in conformation C of IV the distance between the hydroxyl hydrogen and carbonyl oxygen is 4.87 Å, which is too long for hydrogen bonding, especially in the gas phase when the molecule acquires additional energy.

Catalyst

Ι	FIBAN K-1	130	95	93
	KU-2	180	90	65
Π	FIBAN K-1	150	95	91
	KU-2	220	92	58
III	FIBAN K-1	190	90	88
	KU-2	230	90	50

Table 1. Yield of acetals in reactions of aldehydes I–III with Cellosolve, as influenced by catalysis conditions

τ,

min

Table 2. Reaction time and yield of acetals from aldehydes I-III

Alde-	Alcohol used	τ, min	Conversion	Yield
hyde			%	
I	Methanol	45	100	94
	Ethanol	55	100	95
	Ethylene glycol	70	93	88
	Propylene glycol	90	92	85
	Methyl Cellosolve	120	95	91
	Cellosolve	130	95	87
II	Methanol	55	100	95
	Ethanol	60	100	95
	Ethylene glycol	80	92	90
	Propylene glycol	90	90	87
	Methyl Cellosolve	150	95	92
	Cellosolve	150	95	90
III	Methanol	60	100	94
	Ethanol	75	100	93
	Ethylene glycol	100	93	88
	Propylene glycol	120	90	85
	Methyl Cellosolve	180	93	86
	Cellosolve	190	90	82

These data cast doubt on the "conformational" approach to scent analysis. The obtained set of acetals allows us to correlate variations of the scent with variations of, e.g., the number of alkyl substituents, with the conformation of the molecular core being preserved.

When considering the relationship between the scent of the initial aldehydes and their molecular structure, it should be noted that, in going from the methyl to isopropyl and then *tert*-butyl substituent, the scent changes from fresh fruit to fresh flower. In the series of the corresponding dimethyl acetals, the

Aldehyde conversion, %

¹ The perfume characteristics of acetals, tested as 10% solutions in purified 96% ethanol, were evaluated by the Tasting Council (eight experts) at the Accredited Control and Analytical Laboratory of Perfumes and Cosmetics, Tereza-Inter Limited Liability Company (Accreditation Certificate of the State Committee for Standards of the Russian Federation no. ROSS RU.0001.512.312, July 6, 2000).

Table 3. Scent characteristics of the synthesized acetals

Compound	Scent		
2-Methyl-3-(4-methylphenyl)propanal dimethyl acetal	Green, flower, with a bittery tint		
2-Methyl-3-(4-isopropylphenyl)propanal dimethyl acetal	Green, of cyclamen, with a bitter grassy note		
2-Methyl-3-(4- <i>tert</i> -butylphenyl)propanal dimethyl acetal	Strong, flower, with a cold note of cyclamen and lily of the val- ley, light ozone		
2-Methyl-3-(4-methylphenyl)propanal diethyl acetal	Green, fresh watermelon, with a note of spice herbs Elower of cyclamen with a wood note		
2-Methyl-3-(4- <i>tert</i> -butylphenyl)propanal diethyl acetal 2-Methyl-3-(4- <i>tert</i> -butylphenyl)propanal diethyl acetal	Flower, of cyclamen and lily of the valley, with a wood note		
ethyl) acetal	Fresh, nower, of peony with a bright watermeion note		
2-Methyl-3-(4-isopropylphenyl)propanal di(2-methoxy- ethyl) acetal	Fresh, of cyclamen, with a watermelon-ozone note		
2-Methyl-3-(4- <i>tert</i> -butylphenyl)propanal di(2-methoxy-ethyl) acetal	Flower, with notes of cyclamen, lily of the valley, and sweet lime blossom		
2-Methyl-3-(4-methylphenyl)propanal di(2-ethoxy- ethyl) acetal	Flower, grassy, with a fresh note of watermelon and heady anise and wood tint		
2-Methyl-3-(4-isopropylphenyl)propanal di(2-ethoxy- ethyl) acetal	Flower, of cyclamen, with an anise–ozone note		
2-Methyl-3-(4- <i>tert</i> -butylphenyl)propanal di(2-ethoxy-ethyl) acetal	Flower, fresh, with a beewax and honey tint, with a light bittery note		
2-Methyl-3-(4-methylphenyl)propanal ethylene acetal	Flower-grassy with a tint of parsley, celery, and anise		
2-Methyl-3-(4-isopropylphenyl)propanal ethylene acetal	Flower, of cyclamen, with a fresh watermelon note		
2-Methyl-3-(4- <i>tert</i> -butylphenyl)propanal ethylene acetal	Flower, of cyclamen, with a sweet anise note		
2-Methyl-3-(4-methylphenyl)propanal propylene acetal	Grassy, heady, wood, with seaweed note		
2-Methyl-3-(4-isopropylphenyl)propanal propylene	Fresh, flower, sweet, with a beewax tint		
2-Methyl-3-(4- <i>tert</i> -butylphenyl)propanal propylene acetal	Flower, of cyclamen, sweet, powdery		

scent changes from green fruit–watermelon through flower-grassy with a bittery note to fresh flower with an ozone note. With diethyl acetals, very gentle heady and wood notes appear. With methoxy and ethoxy groups introduced into the ethyl acetal moiety, the scent changes more significantly: the fresh fruit– watermelon note is enhanced, ozone freshness components disappear, and a sweet wood or honey note appears. These trends are observed with derivatives of all the three aldehydes. Smooth variation of the scent of the initial aldehydes corresponds to smooth variation of the scent in the series of similar acetals with linear alkyl or alkoxy groups.

With compounds containing a cyclic acetal groups (ethylene or propylene acetals), the trend is reverse. In the series of ethylene acetals, the scent varies very sharply with increasing size of the substituent in the phenyl moiety: first a fairly pronounced sweet flower note appears, then it is enhanced, and a fresh watermelon note is added. In the series of propylene acetals, a wood scent gives way to a fresh flower scent subsequently acquiring a warm powdery tint.

The acetals obtained show promise as components of fragrant and perfume formulations, because they produce a fairly wide range of scents of various tints and, in contrast to the initial aldehydes, are stable to oxidation in ready perfumes and cosmetics.

EXPERIMENTAL

The ¹H NMR spectra were taken with a Tesla BS-567A spectrometer (CDCl₃, internal reference HMDS). The IR spectra were recorded on a Specord 75-IR spectrometer (thin films). The GLC analysis of reaction mixtures was performed with a Chrom-5 chromatograph [flame-ionization detector, 2000×3 -mm column, Chromaton N-AW-DMCS support (0.125– 0.160 mm), Reoplex-400 stationary phase, programmed heating from 100 to 180° C (4 deg min⁻¹), nitrogen carrier gas].

To prepare acetals, the catalyst (2 wt % relative to aldehyde) was added to a solution of 0.10 mol of aldehyde **I–III** and 0.11 mol of dihydric alcohol in 70 ml of benzene. The mixture was refluxed until the release of water ceased and the reaction was complete (monitored by GLC). The catalyst was separated by decanting, washed with benzene (2×5 ml), and reused; the wash solutions were combined with the reaction solutions. The solvent was distilled off. When necessary (if the acetal purity was less than 98%), the product was purified by chromatography (alumina, eluent hexane–diethyl ether with gradually increasing content of ether).

Monohydric alcohols were taken in a double amount. With dimethyl acetals, the released water was bound with a stoichiometric amount of triethyl orthoformate.

CONCLUSIONS

(1) A series of 2-methyl-3-(4-R-phenyl)propanal (R = Me, *i*-Pr, *t*-Bu) acetals was prepared; these compounds have pleasant scent and can be used as perfumes.

(2) In the series of acetals with the same monohydric alcohols, the scent changes smoothly depending on the substituent in the phenyl ring. In the series of diols, the scent changes more sharply.

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