Polyalkoxybenzenes from plant raw materials
1. Isolation of polyalkoxybenzenes from CO_2 extracts of *Umbelliferae* plant seeds

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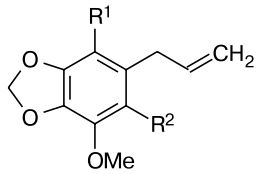
For the search for a domestic natural source of allylpolyalkoxybenzenes and development of an effective process for their isolation, CO_2 extracts of several varieties of parsley, dill, celery, caraway, and nutmeg were analyzed systematically for the first time by GC/MS and GLC techniques. The varieties with high contents of myristicin, elemicin, allyltetramethoxybenzene, apiol, and dillapiol were identified. The conditions of CO_2 extraction for obtaining concentrates with minimum contents of the distillation residues were selected. Using high performance fractional distillation, polyalkoxyallylbenzenes with 98—99% purity were isolated from the concentrates on a pilot unit. By isomerization of some allylbenzenes followed by ozonolysis under specially selected conditions, apiol- and dillapiolaldehydes were obtained in 75—80% yields.

Key words: allylpolyalkoxybenzenes, myristicin, elemicin, apiol, dillapiol, benzaldehydes, essential oils, extraction, ozonolysis.

This communication opens a series of works dealing with the chemistry of polyalkoxybenzenes, which we use as the basis for the development of analogs of natural food components and natural antimitotic antitumor agents. The isolation of valuable components from plant sources for fine organic chemistry and pharmaceutics is especially topical provided that this process is economically and environmentally more efficient than the synthetic manufacture. For the development of such processes, it is necessary, first of all, to find plants with high contents of the required metabolites. Second, it is necessary to use raw materials produced on a large scale; in this respect agricultural crops with well-developed growing and harvesting processes are cheaper than the wild-growing plants. Third, the existing industrial processes for plant raw material processing should be employed.

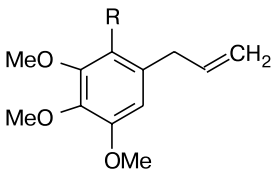
The efficient and environmentally safe extraction with both supercritical and liquid CO_2 (in particular, ultrasound-assisted) has long been used in Russia for the industrial manufacture of spices: allspice, cinnamon, pepper, dill, nutmeg, caraway, anise, parsley, celery, mint, and so on.[1] These extracts are widely used as food additives, dressings, and antioxidants, especially in the fish canning industry. In the world practice CO_2 extraction of plants has been studied in recent years[2] in relation to the search for natural antioxidants[3] and the limitations on the use of conventional solvents in food and pharmaceutical industries.

Analysis of the recent publications[4] and databases* on the compositions and biological properties of more than 30000 plants showed that umbelliferous crops (parsley, celery, dill, caraway, *etc*.) contain considerable amounts of diverse allylpolyalkoxybenzenes **1**—**5**.



1—3

R^1 = OMe, R^2 = H (apiol, **1**),
R^1 = H, R^2 = OMe (dillapiol, **2**),
R^1 = R^2 = H (myristicin, **3**)



4, **5**

R = H (elemicin, **4**), OMe (allyltetramethoxybenzene, **5**)

* http://www.ars-grin.gov/dulce/

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Within the framework of the USA National Genetic Resources Program,* 10 to 30 types of pharmacological activity were identified for each of these components, in particular, antiinfectious activity and the action on the cardiovascular, urogenital, and central nervous system. Antimicrobial and antifungal activities of polyalkoxybenzenes have been patented.[5] Dillapiol (**2**) is also promising for the use in combination with many anticancer drugs, because it markedly decreases the cell resistance against antimitotic drugs.[6]

Owing to the presence of reactive allyl group and activated aromatic ring, polyalkoxybenzenes could also serve as versatile promising building blocks for fine organic synthesis.

Analysis of 28 varieties of parsley seeds from European countries showed that the content of polymethoxybenzenes changes appreciably (from 10 to 70%) depending on the growing region and the phenotype. Three parsley phenotypes exist, namely, the apiol (58—80%), myristicin (49—77%), and myristicin-containing (26—37%) allyltetramethoxybenzene (52—57%) phenotypes.[7] The distribution of these compounds between parsley seeds, leaves, and roots is fairly variable.[7—9] Different essential oil contents of these parts should also be noted, the highest content of oils, 3.5 to 6.7%, being found in the seeds.**

The extracts of leaves of 104 varieties of parsley from different countries were analyzed.[8] The variety from Yugoslavia was found to contain a lot of myristicin (**3**) (50—60%),[8] much more than the nutmeg, which is the main source of this compound. In Iranian and Turkish parsley, *p*-mentha-1,3,8-triene is the main metabolite.[8] The extracts of Indian caraway[3] and dill[10,11] seeds were found to contain 30—50% dillapiol (**2**), while northern varieties (*e.g.*, caraway from the Krasnoyarsk Territory[12] or dill from Finland[13]) did not contain dillapiol (**2**) at all.

The relative composition of the volatile components in the parsley[14] and dill[13] leaves at different growth stages was considered. The contents of phellandrene, *p*-mentha-1,3,8-triene, and apiol were the highest at the seventh week of the parsley growth.

Unfortunately, no systematic research of the composition of essential oils of parsley and dill from different regions has been carried out in the former USSR. Only in one study[15] was the composition of the essential oil of the root variety of parsley seeds from the Tashkent region studied. According to GLC, it contained myristicin (**3**, 10.8%), apiol (**1**, 57.6%), and allyltetramethoxybenzene (**5**, 0.8%). The composition of the parsley and dill extracts produced in Russia is still unknown. None of the foreign publications presents the names of the analyzed varieties of parsley. Therefore, it was impossible to find particular varieties with high contents of polyalkoxybenzenes for their preparative extraction.

The purpose of this study is to analyze agricultural crops growing in Russia in order to find varieties with the highest contents of polyalkoxybenzenes and optimization of the process for isolation of essential oils from the best varieties by CO_2 extraction followed by component separation using high performance fractional distillation. The solution of this problem would create conditions for extensive investigation of the polyalkoxybenzene chemistry.

Experimental

Samples were analyzed using a GC/MS instrument comprising a Finnigan MAT ITD-700 ion trap (UK) and a Varian 3400 gas chromatograph (USA) equipped with a 25-m long HP-101 capillary column with an inner diameter of 0.2 mm and with 0.2-μm thick stationary grafted phase, injector temperature of 250—270 °C, helium as the carrier gas, 1 mL min^{-1}, thermostat temperature programming mode: from 80 °C (1 min isotherm), linear heating at 10 °C min^{-1} to 290 °C, and sample injection in 1 μL of chloroform. The Finnigan MAT ITD-700 mass spectrometer (ion trap) was adjusted for scanning at m/z from 50 to 500, scanning frequency of 1 scan s^{-1}, recording delay of 150 s, EI with an ionization potential of 70 eV, interface temperature of 220 °C, and peak recording threshold of 1. The ITDS software (Finnigan MAT) was used, version 4.10, the files were converted into the HPChem format. The compounds were identified using the Wiley275 database. Direct inlet mass spectra were run on a Finnigan MAT INCOS50 instrument (ionizing voltage 70 eV). In the mass spectra of allylpolymethoxybenzenes, the molecular ion peak is most intense in line with the previously reported mass spectra of dillapiol (**2**)[16] and myristicin (**3**).[17]

Quantitative GLC analysis of the extracts was carried out on a Biochrom-1 chromatograph with a flame ionization detector and a 25-m long quartz capillary column, stationary phase SE-54, injector and detector temperature 250 °C, initial temperature of the column thermostat 100 °C, temperature programming mode: heating at 12 °C min^{-1} to 230 °C followed by isothermal mode, sample volume 0.2 μL. Chromatographic data were processed using ECOCHROM software. The results of GC/MS analysis were also compared with published data.[13,14,18,19]

The ^1H NMR spectra of polyalkoxybenzenes were recorded for solutions in $CDCl_3$ on a Bruker DRX-500 spectrometer (500.13 MHz) using Me_4Si as the internal standard.

CO_2 Extraction. The industrial liquid-CO_2 extraction* of the varieties chosen based on the results of analysis was carried out at a temperature below 28 °C in the workshop of the Karavan company. For each sort of raw material, extraction conditions (temperature, pressure, time, raw material preparation, *etc.*) for a laboratory setup were selected to recover most fully allylpolyalkoxybenzenes and to minimize the amount (not more than 20%) of the heavy fraction hampering the subsequent fractional distillation.

* http://www.ars-grin.gov/duke/

** http://www.eda-server.ru/prjan/045.shtml

* http://www.karawan.ru//

Variation of the process operation parameters on the laboratory setup, in particular, the extractant flowrate through the raw material layer and successive recovery of up to seven fractions of the CO_2 extract during a single extraction cycle allowed us to select the process conditions and determine the time for the highest recovery of apiol (**1**), dillapiol (**2**), and myristicin (**3**) in industrial CO_2 extracts.

High performance fractional distillation of CO_2 extracts. The CO_2 extracts were treated on a rotary evaporator with a 10-L vessel at a residual pressure of 0.20—0.26 kPa and temperature of 100—140 °C. The principal fraction was separated from the distillation residue (various unsaturated acids and high-boiling compounds).

The principal fraction was separated into components *in vacuo* at a residual pressure of 0.20—0.26 kPa on a batch distillation column with a 6-L external vessel. The 3-m high packed column of diameter 50 mm (packed with triangular helices made of nichrome thread, d = 0.3 mm, size 3×3 mm) was equipped with a temperature compensation heating and had efficiency of 30—40 theoretical plates. The column efficiency was determined using a reference mixture, benzene—carbon tetrachloride, at atmospheric pressure. The fractional distillation was carried out at high reflux ratios (R = 30—50).

In some experiments, the CO_2 extracts of parsley and dill were directly subjected to separation in the distillation column. In particular, this refers to the separation of the parsley extract from Germany (Natur Extract), Kudryavaya (Karavan), and Bogatyr´ (Karavan). It was shown that preliminary distillation on a rotary film evaporator increases the yield of the target products. The physicochemical parameters and NMR spectra of these compounds that we measured coincide with published data (Table 1).

The fractional distillation modes and the material balances of some operations for the recovery of particular components in a pure state are summarized in Tables 2—7.

Table 1. Physicochemical properties of allylpolyalkoxybenzenes

Compound	B.p./°C (p/kPa) [M.p./°C]	d_4^{20} /g cm^{-3}	n_D^t	Ref.	^{1}H NMR (500 MHz), δ (J/Hz)
Apiol (**1**) (1-allyl-3,4-methylenedioxy-2,5-dimethoxybenzene)	294 (101.3); 126—128 (0.13); 179 (4.39); [30.0]	1.176* 1.015**	1.5330—1.5619	20, 21d	3.30 (d, 2 H, CH_2, J = 6.8); 3.85, 3.88 (both s, 3 H each, OMe); 5.04 (br.d, 2 H, H_2C=); 5.93 (m, 1 H, HC=); 5.95 (s, 2 H, OCH_2O); 6.3 (s, 1 H, H arom.)
Dillapiol (**2**) (1-allyl-4,5-methylenedioxy-2,3-dimethoxybenzene)	285 (101.3); 162 (1.46) [29.5]	1.1644	1.5278	21e	3.30 (d, 2 H, CH_2, J = 6.4); 3.75, 4.02 (both s, 3 H each, OMe); 5.04 (d, 1 H, H_2C=, J = 10.0); 5.05 (d, 1 H, H_2C=, J = 12.8); 5.87 (s, 2 H, OCH_2O); 5.91 (m, 1 H, HC=); 6.35 (s, 1 H, H аром.)
Myristicin (**3**) (1-allyl-4,5-methylenedioxy-3-methoxybenzene)	149.5 (1.99); 157 (2.79); 282 (101.3); 107 (0.13)	1.1437	1.5403	20, 21a	3.29 (d, 2 H, CH_2, J = 6.6); 3.88 (s, 3 H, OMe); 5.05 (d, 1 H, J = 10.0); 5.08 (d, 1 H, H_2C=, J = 13.8); 5.95 (m, 1 H, HC=); 5.93 (s, 2 H, OCH_2O); 6.35, 6.38 (both s, 1 H each, H arom.)
Elemicin (**4**) (1-allyl-3,4,5-trimethoxybenzene)	144—147 (1.33)	1.0630	1.5288	21b	6.42 (s, 2 H, 2 CHAr); 5.96 (m, 1 H, CH=); 5.12 (d, 1 H, H_2C=, J = 15.4); 5.07 (d, 1 H, H_2C=, J = 10.0); 3.86 (s, 6 H, 2 OMe); 3.83 (s, 3 H, OMe); 3.34 (d, 2 H, CH_2, J = 6.5)
1-Allyl-2,3,4,5-tetramethoxybenzene (**5**)	[25.0]	1.0870	1.5146	21c	3.36 (d, 2 H, CH_2, J = 6.6); 3.79, 3.82, 3.88, 3.93 (all s, 3 H each, OMe); 5.08 (2 d, 2 H, H_2C=, J = 13.4, J = 10.0); 5.96 (m, 1 H, HC=); 6.54 (s, 1 H, H arom.)

* The d_4^{14} value is given.
** The d_4^{30} value is given.

Table 2. Fractional distillation of the Bogatyr´ parsley oil (residual pressure 0.20—0.26 kPa)

Loaded			Recovered			
Components	Composition (wt %)	m/g	Fraction	B.p. /°C	Weight /g	Composition (wt %)
Light impurities	19.5	980	I	106	1020	Pinenes (62), limonene (25)
Myristicin (**3**)	25.8	1300	II	106—107	1130	**3** (98)
Elemicin (**4**)	4.2	210	III	107—116	600	**3** (22), **4** (35), **5** (43)
Allyltetramethoxybenzene (**5**)	11.1	560	IV	116	270	**5** (96)
Apiol (**1**)	28.4	1430	V	116—125	62	**5** (48), **1** (52)
			VI	125	1234	**1** (98)
Heavy impurities	10.9	550	Bottoms	—	714	—
Total:	100.0	5030			5030	

Table 3. Fractional distillation of the Kudryavaya parsley oil (residual pressure 0.20—0.26 kPa)[a]

Loaded			Recovered			
Components	Composition (wt %)	*m*/g	Fraction	B.p. /°C	Weight /g	Composition (wt %)
Light impurities	12.6	126	I	≤106	146.0	Pinenes (45), limonene (32), **3** (14)
Myristicin (**3**)	25.0	250	II	106—107	225.0	**3** (98)
Elemicin (**4**)	5.4	54	III [b]	107—124	224.0	**3** (2), **4** (24), **5** (69), **1** (5)
Allyltetramethoxybenzene (**5**)	16.5	165				
Apiol (**1**)	17.0	170	V	124	150.0	**1** (99)
Heavy impurities	23.5	235	Bottoms		255	
Total:	100.0	1000			1000	

[a] The starting mixture was pre-distilled on a rotary film evaporator in a vacuum of 0.665—0.798 kPa at 120—140 °C.
[b] Fraction III is recycled for repeated fractional distillation for the recovery of pure allyltetramethoxybenzene **5**.

Table 4. Fractional distillation of the Natur Extract parsley oil (residual pressure 0.20—0.26 kPa)

Loaded			Recovered			
Components	Composition (wt %)	*m*/g	Fraction	B.p. /°C	Weight /g	Composition (wt %)
Light impurities	12	60	I	≤106	70.0	Pinenes (60), limonene (30)
Myristicin (**3**)	28	140	II	106—107	120.0	**3** (96.6)
Elemicin (**4**)	5	25	III*	107—123	54.0	**3** (18), **4** (46.5), **5** (23), **1** (12)
Allyltetramethoxybenzene (**5**)	2.5	12.5				
Apiol (**1**)	47.5	237.5	IV	124—125	230.0	**1** (99)
Heavy impurities	5	25	Bottoms		26.0	
Total:	100.0	500.0			500.0	

* Fraction III is recycled for repeated fractional distillation for the recovery of pure components.

Table 5. Fractional distillation of the parsley oil (Goro) obtained by supercritical CO_2 extraction (residual pressure 0.20—0.26 kPa)

Loaded			Recovered			
Components	Composition (wt %)	*m*/g	Fraction	B.p. /°C	Weight /g	Composition (wt %)
Light impurities	18	108	I	≤106	113	Pinenes (40), limonene (25)
Myristicin (**3**)	4.3	25.8	II*	106—124	29.2	**3** (72), **4** (20.5), **5** (7.5)
Elemicin (**4**)	1.7	10.2				
Allyltetramethoxybenzene (**5**)	0.7	4.2				
Apiol (**1**)	0.3	1.8	III	124—125	1.8	**1** (96)
Heavy impurities	75	450	Bottoms		456	
Total:	100.0	600.0			600.0	

* Fraction II is recycled for repeated fractional distillation for the recovery of pure components.

Preparation of polyalkoxybenzaldehydes. Isoapiol (**6**) and isodillapiol (**7**) were prepared by isomerization of appropriate polyalkoxyallylbenzenes[1,2] in alkaline media[22,23] in the presence of tetraalkylammonium salts as phase transfer catalysts.

A mixture of apiol (**1**) or dillapiol (**2**) (0.25 mol), tetrabutylammonium bromide (2.5 g), and finely powdered KOH (10 g) was heated on a boiling water bath for 40 min. The reaction mixture was cooled and extracted with ether, and the ethereal extract was washed with water (2×140 mL) and dried over sodium sulfate. After removal of the ether, the residue was distilled *in vacuo* or recrystallized from petroleum ether. The yields of isoapiol (**6**) and isodillapiol (**7**) were 90—95%. According to ^{1}H NMR spectroscopy, the content of the *trans*-isomers in the isolated products was ~80—85%.

Ozonolysis was carried out using specially designed ozonizer (Scientific and Technological Park of the St. Petersburg State

Table 6. Fractional distillation of the Karavan dill oil (India) (residual pressure 0.53—0.66 kPa)

Loaded			Recovered			
Components	Composition (wt %)	*m*/g	Fraction	B.p. /°C	Weight /g	Composition (wt %)
β-Pinene	1.23	92.3	I	28—63	181.4	Pinenes (51), limonene (49)
Limonene	14.4	1080	II	68	901.8	Limonene (98)
			III	68—87	221.5	Limonene (40), Carvone (60)
Carvone	23.5	1765.3	III	90	1500.4	Carvone (98)
Dihydrocarvone	5.5	417	IV	90—115	163.7	Carvone (81), Dihydrocarvone (19)
			V	115	354.4	Dihydrocarvone (97)
Dillapiol (**2**)	36.7	2756.4	VI	115—141	270.1	Dihydrocarvone (11), **2** (89)
			VII	141	2387.7	**2** (97)
Heavy impurities	18.5	1389	Bottoms		1519	
Total:	100.0	7500			7500	

Table 7. Fractional distillation of the Kornevaya Sakharnaya parsley oil (residual pressure 0.20—0.26 kPa)

Loaded			Recovered			
Components	Composition (wt %)	*m*/g	Fraction	B.p. /°C	Weight /g	Composition (wt %)
Light impurities	10.6	1060	I	≤106	1130	Pinenes (42), limonene (38)
Myristicin (**3**)	1.34	1340	II*	106—124	1470	**3** (13), **1** (71)
Apiol (**1**)	64.24	6424	III	124—125	5180	**1** (98)
Heavy impurities	20.82	2082	Bottoms	—	2230	—
Total:	100.0	10000			10000	

* Fraction II is recycled for repeated fractional distillation for the recovery of pure components.

Polytechnic University) with an infrared sensor of ozone concentration and electronic control system to switch off the device after a specified amount of ozone has been passed. The maximum output was 10 g of ozone per h for operation with oxygen.

3,4-Methylenedioxy-2,5-dimethoxybenzaldehyde (apiolaldehyde, 8). Ozone (2 g, 0.04 mol according to the ozonizer gage) was passed for 1—2 h at −25 °C through a solution of isoapiol (**6**) (6.66 g, 0.03 mol) in chloroform (80 mL), methanol (20 mL), and pyridine (3 mL) and the mixture was left in a refrigerator for ~14 h. The solution was concentrated on a rotary evaporator at ~20 °C, the residue was treated with water (50 mL) and acidified with concentrated HCl, and the solution was cooled and filtered. Drying gave 4.8 g (76%) of apiolaldehyde identical to an authentic sample,[24] m.p. 102 °C. ^{1}H NMR, δ: 3.83 (s, 3 H, 5-OMe); 3.99 (s, 3 H, 2-OMe); 6.20 (s, 2 H, OCH_2O); 7.00 (s, 1 H, H(6)); 10.12 (s, 1 H, CHO). MS, *m/z*: 210 $[M]^+$.

4,5-Methylenedioxy-2,3-dimethoxybenzaldehyde (dillapiolaldehyde, 9) was prepared in a similar way, yield 80%, m.p. 75 °C (*cf.* Ref. 24: m.p. 75 °C). ^{1}H NMR, δ: 3.87 (s, 3 H, 3-OMe); 3.98 (s, 3 H, 2-OMe); 6.13 (s, 2 H, OCH_2O); 6.85 (s, 1 H, H(6)); 10.08 (s, 1 H, CHO). MS, *m/z*: 210 $[M]^+$.

Results and Discussion

In order to find a potential source of polyalkoxybenzenes as industrial raw materials, we collected and analyzed, using GC/MS and GLC methods, the CO_2 extracts of the following plants: 12 varieties of parsley, three varieties of dill, one variety each of celery, caraway, and nutmeg from various regions. For comparison, some of the extracts were separated by fractional distillation (Table 8). We analyzed the relative contents of volatile compounds. The actual content is found by subtracting the percentage of the distillation residue determined by fractional distillation (see Tables 2—8), which mainly comprises undistillable and GLC-nondetectable unsaturated fatty acids.[14]

It was found that the main natural source of myristicin (**3**), the nutmeg extract,* from the Indonesian raw material contains only minor amounts of elemicin (5.3%) and myristicin (**3**, 12.8%). The caraway extract from the Krasnodar Territory (see Table 8) almost does not contain polyalkoxybenzenes (less than 1% myristicin (**3**), apiol (**1**), and dillapiol (**2**)). The same is true for the caraway essential oil from the Krasnoyarsk suburb where even no traces of polyalkoxyallylbenzene were previously found.[12] However, the essential oil of the Indian caraway was found to contain dillapiol (**2**, 29.9%) and nosapiol (4-allyl-1,2-methylenedioxy-3,5,6-trimethoxybenzene) in 5.8% amount (see Ref. 3). According to our data, the dill seed

* http://www.ars-grin.gov/duke/

Table 8. Relative contents of volatile components (%) in the CO_2 extracts from seeds of several varieties of dill, caraway, parsley, celery, nutmeg

Culture (source region, extract manufacturer)	Method	α-Pinene	β-Pinene	β-Phellandrene	Limonene	Carvone	Dihydrocarvone	Myristicin (**3**)	Elemicin (**4**)	Allyltetramethoxybenzene (**5**)	Apiol (**1**)	Dillapiol (**2**)	Distillation residue
Dill (India, Karavan)	GLC*	1.5	—	—	31	29	8.6	—	—	—	—	30	—
	Distillation**	1.2	—	—	14.2	23.2	5.4	—	—	—	—	33.1	20.3
Dill (Krasnodar, Karavan)	GLC	—	—	2.5	60.7	34.6	1.9	—	—	—	—	—	—
Dill leaves (Krasnodar, Karavan)	GLC	—	—	13.6	28	44.2	9.8	—	—	—	—	—	—
Caraway (Krasnodar, Karavan)	GLC	—	—	—	48.2	49.3	—	0.7	—	—	0.8	0.8	—
Celery (Krasnodar, Karavan)	GLC	6.1	3.7	—	19	—	—	15.4	3.4	7	16.6	—	***
Parsley (Germany,	GLC	6.2	4.1	—	2	—	—	27	4.4	1.3	52	—	—
Natur Extract)	Distillation*	8.4		—	4.2	—	—	25.1	5	2.5	46.8	—	5.2
Parsley (Rostov,	GLC	6.9	3.9	—	1.8	—	—	29.8	7.8	24	25.9	—	—
Goro supercritical)	Distillation*	1.5		—	4.7	—	—	3.5	1	0.4	0.3	—	76
Parsley Kudryavaya,	GLC	6.7	5.9	—	1.8	—	—	32	5.1	21.3	24.4	—	—
Slavyanovskaya variety (Krasnodar, Karavan)	Distillation*	6.6		—	4.7	—	—	25	5.4	15.3	16	—	25.5
Parsley Kudryavaya, Astra variety (Krasnodar, Karavan)	GLC	10.6	10.2	—	6	—	—	46.1	12.9	3.6	5.8	—	—
Parsley Universal´naya,	GLC	6.9	4.2	—	1.2	—	—	30.6	3.7	17	36.2	—	—
Bogatyr´ variety (Krasnodar, Karavan)	Distillation*	12.6		—	5.07	—	—	24.6	4.2	10.9	24.7	—	14.2
Parsley Listovaya, Obyknovennaya variety (Krasnodar, Karavan)	GLC	4.6	4.9	—	3.7	—	—	32.8	2.4	11.4	40	—	—
Parsley Kornevaya,	GLC	8.6	7.7	—	1.6	—	—	4.3	0.4	0.2	74.6	—	—
Sakharnaya variety (Krasnodar, Karavan)	Distillation*, 70 kg of extract	4.7		—	4.3	—	—	1.9	—	—	61.2	—	22.3
Parsley, specimen 5557 (Florachim)	GLC	29.4	24.9	—	8.8	—	—	12.3	0.6	7.6	15	—	—
Parsley, specimen 5551 (Florachim)	GLC	33.5	23.5	—	10.5	—	—	25.7	0.5	2	1.1	—	—
Nutmeg (Indonesia, Karavan)	GLC	14.3	7.6	—	8.4	—	—	12.8	5.3	—	—	—	—

* The relative content of volatile compounds was determined. For estimating the real percentage, it is necessary to subtract the content of the distillation residue determined by fractional distillation.

** The percentages of the isolated components were calculated taking into account their contents in all three distilled fractions.

*** Additionally 20.2% of a compound (unsaturated fatty acid) with the formula $C_{11}H_{12}O_3$ was isolated, and in total 4.9% of sesquiterpenes.

extracts from India and the Krasnodar Territory are also markedly different in composition, dillapiol (**2**, ~30%) and carvone (~30%) being the major metabolites of the former, whereas the latter contains up to 60% limonene and 35% carvone but no dillapiol (**2**). In the extract of dill leaves from the Krasnodar Territory, carvone is the major component (44.2%).

Among many varieties of the umbelliferous (see Table 8), the domestic parsley Kornevaya, the Sakharnaya variety, is the main source of apiol (**1**, content more than 70%) (see Table 2). However, its essential oil content (3.7%) is about half that of other varieties of parsley (6—7%). The parsley extract produced by the German company Natur Extract is a rather good, although expensive, source of apiol (**1**) and myristicin (**3**). These compounds, which differ by 19 °C in boiling points, can be readily separated by distillation (see Table 4), and the closely boiling elemicin (**4**) and allyltetramethoxybenzene (**5**), which are present in minor amounts (≤5%), do not interfere with the separation. The domestic parsley Kudryavaya, the Astra variety, is well suited for the preparation of myristicin (**3**, 46%), which can be separated from elemicin by high performance fractional distillation (see Table 8), despite close boiling points.

For industrial use, both the state of CO_2 (either liquid or supercritical) and the extraction duration are important aspects. In the case of supercritical CO_2, not only volatile components are extracted from seeds but also much higher-boiling and poorly soluble fatty acids, which are present in parsley in large amounts.[14] These acids were of no interest for us because they are produced more easily by other methods. The distillation of the parsley oil of the Goro company prepared by supercritical CO_2 extraction resulted in up to 76% (see Table 8) of a hardly separable mixture remaining in the bottoms, the overall amount of isolated target polyalkoxybenzenes being less then 5%.

Thus, the extraction with supercritical CO_2 for targeted isolation of polyalkoxybenzenes is inefficient. The industrial liquid CO_2 extracts of the Karavan company contain on average 15 to 25% of the distillation residues of fatty acids (see Table 8), and polyalkoxybenzenes can be easily distilled off using a rotary film evaporator. For targeted production of polyalkoxybenzenes, the extraction time can be reduced, which decreases significantly the amount of the distillation residue, as for example, in the Natur Extract product (5.2%) (see Table 8).

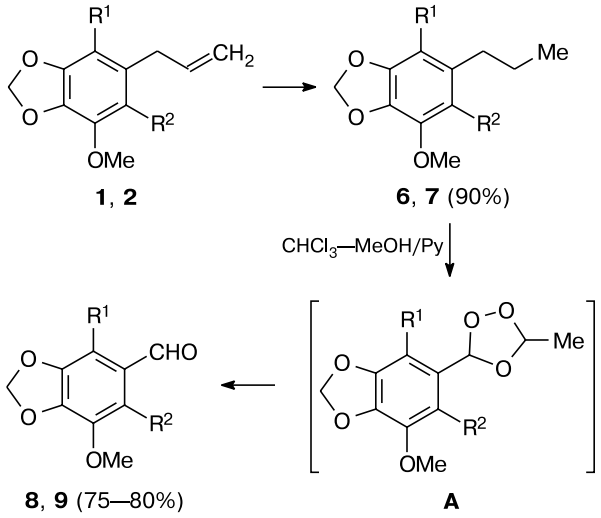
The multistage fractional distillation (see Table 2—7) is a key stage of the recovery of polyalkoxyallylbenzenes.

In the separation of CO_2 extracts of parsley, it was shown that isolation and purification are better performed as two stages comprising, first, evaporation of the target fraction on a rotary evaporator and, second, isolation of the target compounds from this fraction by fractional distillation. The distillation residue of the rotary evaporation stage contains high-boiling compounds, in particular, organic fatty acids (see Table 2—7).

Optimization of the fractional distillation process at the pilot units of the N. D. Zelinsky Institute of Organic Chemistry included processing of ~100 L of CO_2 extracts obtained from 2.5 tons of parsley and dill seeds of several varieties. This gave ~40 kg of apiol (**1**, purity 98—99%), 3 kg of dillapiol (**2**, 98—99%), 5.5 kg of myristicin (**3**, 98%), and 0.3 kg of allyltetramethoxybenzene (**4**, 97%).

For transformation of allylpolyalkoxybenzenes into various classes of organic compounds, it was necessary to develop efficient methods for the synthesis of "key building blocks" such as aldehydes, acids, alcohols, *etc.* According to published data, ozonolysis[23] or oxidation of isoapiol (**6**) and isodillapiol (**7**) with permanganates and dichromates[15,22,24,25] would be the most practically feasible route to polymethoxybenzaldehydes **8** and **9** (Scheme 1).

Scheme 1



R^1 = OMe, R^2 = H (**1**, **6**, **8**); R^1 = H, R^2 = OMe (**2**, **7**, **9**)

Allylbenzenes are isomerized in alkaline media to give propenylbenzenes[22,23] in high yields. Note that with heterogeneous catalysts this process can be performed in a continuous mode[26] to obtain products in quantitative yields.

In the oxidation of propenylbenzenes with dichromates and permanganates, the yields of the target aldehydes usually do not exceed 40—50% and the manganese dioxide precipitate and benzoic acids formed as by-products hamper the isolation of aldehydes.

We were unable to reproduce the results of studies on isoapiol (**6**) and isodillapiol (**7**) ozonolysis in acetic acid solutions[23] where the yields of aldehydes were postulated

to be 75—80%. In our experiments, the yields did not exceed 20—40%. However, the use of $CHCl_3$—MeOH solvent mixture at low temperature and in the presence of pyridine, which efficiently destroys the intermediate molozonide (**A**), gives pure apiolaldehyde and dillapiolaldehyde in high yields.

It is noteworthy that passing of excess ozone destroys the benzene ring activated by the polyalkoxy groups, thus substantially decreasing the yields of the target aldehydes. To prevent this process, we ordered a special ozonizer equipped with an infrared sensor of ozone concentration and an electronic control system that stops the operation after the specified amount of ozone has been passed. Using this equipment, we attained yields of apiolaldehyde (**8**) and dillapiolaldehyde (**9**) of 75—80% for up to 100 g scales.

On the basis of these aldehydes, we synthesized aromatic food additives and analogs of the natural antimitotic drugs, which will be reported elsewhere.

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