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Identification of Alkylarene Chloromethylation Products Using Gas-Chromatographic Retention Indices

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Abstract—Gas-chromatographic retention indices on standard nonpolar polydimethylsiloxane stationary phases allow identification of products formed by known organic reactions even without using mass-spectrometric data. The efficiency of this approach was demonstrated by the example of identification of previously uncharacterized chloromethyl derivatives of alkylarenes, including structural isomers of compounds containing several chloromethyl groups, directly in reaction mixtures. Chromatographic analysis of such reaction mixtures allows identification of positional isomers of the starting alkylarenes even when they are present simultaneously. The retention indices were determined for the first time for more than 50 alkyl(chloromethyl)arenes, by-products of chloromethylation, and chloromethyl derivatives of the simplest alkyl phenyl ketones.

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The most widely used approach to identification of previously uncharacterized organic compounds involves their isolation followed by determination of various physicochemical constants (boiling and melting points, refractive indices, etc.) or of more informative spectral characteristics (primarily NMR and mass spectra). However, as applied to reaction mixtures containing a large number of components with similar properties (including isomers), the use of this approach is restricted by the possibilities of isolation and purification of the components. Therefore, for many relatively simple organic compounds the physicochemical constants and spectral characteristics are still unknown. Examples of such compounds are products of radical chlorination of alkylarenes RAr, (chloroalkyl)arenes, which can be obtained only as inseparable mixtures. Therefore, the physicochemical constants and even the mass spectra of the majority of such compounds with R $\geq$ C_3H_7 are unknown [1]. The same is true for many positional isomers of alkylarenes themselves, polyhalo derivatives, etc. Several important groups of ecotoxicants are so numerous that synthesis or isolation of their individual representatives is virtually impossible. For example, this problem was solved for all the 209 polychlorinated biphenyls $C_{12}H_{10-x}Cl_x$ ($1 \leq x \leq 10$), but for their metabolites, polychlorinated hydroxybiphenyls $C_{12}H_{9-x}\cdot$(OH)Cl_x ($1 \leq x \leq 9$) it is unfeasible to synthesize or isolate all the existing 839 congeners [2].

An alternative approach to identification of organic compounds is based on the use of modern methods of chromatography–spectroscopy and does not require isolation of components from complex mixtures. However, at present it is mostly applied to identification of compounds previously characterized by mass spectra and/or chromatographic retention indices. The "natural" limitation of this approach is the lack of the required reference data in the existing databases. This particularly concerns the retention indices, because the majority of these parameters are still "scattered" over original papers and have not been systematized, and the first universal computer database that included the retention indices of 25728 compounds on standard nonpolar polydimethylsiloxane stationary phases appeared only in 2005 [1]. Application of this approach to previously uncharacterized compounds was considered inadmissible until recently.

At the same time, in organic analytical chemistry there is a specific type of reactions for which isolation of products is considered unnecessary in identification of the starting compounds by chromatography–spectrometry: derivatization reactions used to optimize the conditions of chromatographic analysis of target analytes [3]. In this case, the reactions should be so specific that the structures of products, at known structures of the starting compounds, can be assumed without additional proof. Furthermore, it can be noted that the role of mass spectra in characterization of the products thus obtained is minor, and for isomers having identical mass spectra this method is useless. It becomes particularly important to determine the chromatographic retention indices of such compounds.

The use of unidimensional analytical parameters, chromatographic retention indices, is generally insufficient for unambiguous identification. However, in some particular cases it becomes possible, e.g., when the level of a priori chemical information about the samples being analyzed allows the number of alternative hypotheses about their component composition to be substantially reduced [4]. In other words, identification of products of well-known organic reactions solely on the basis of chromatographic data seems to be quite possible.

Just this approach was used for identification of products of radical chlorination of alkylarenes in various positions of alkyl substituents [5]. However, compounds of this class still remain insufficiently characterized by chromatographic parameters and deserve more detailed consideration. Among other synthetic routes to these compounds, the well-known and comprehensively studied reaction of arene chloromethylation is of interest:

$$\mathrm{ArH} + [\mathrm{CH_2O}] + \mathrm{HCl} \longrightarrow [\mathrm{ArCH_2OH}] \longrightarrow \mathrm{ArCH_2Cl} + \mathrm{H_2O}. \qquad (1)$$

The synthesis is usually performed with paraform, by passing dry HCl through reaction mixtures containing as catalysts Lewis acids ($AlCl_3$, $ZnCl_2$, etc.) [6] or nonvolatile inorganic acids (H_2SO_4, H_3PO_4) [7]. The reactant addition order can be inverse [6]. The reaction can also be performed with aqueous HCl solutions in the presence of phase-transfer catalysts (e.g., cetyltrimethylammonium bromide) [8]. The byproducts are bis(chloromethyl) derivatives and, in some cases, diarylmethanes $ArCH_2Ar$ formed by alkylation of hydrocarbons ArH with the intermediate carbinols $ArCH_2OH$ [6, 8].

Chromatographic data on the retention indices of (chloromethyl)arenes are limited. The simplest representative of this series, benzyl chloride, has been characterized in most detail [5, 9–12]. Data for isomeric (chloromethyl)toluenes are given in [12] and for 1,4-bis(chloromethyl)benzene, in [13]. The largest number of chloromethyl derivatives have been characterized in products of radical chlorination of methyl-substituted arenes [5].

This paper deals with gas-chromatographic identification of (chloromethyl)arenes synthesized by scheme (1) on the basis of their gas-chromatographic retention indices and well-known features of chloromethylation. In this case, it is basically unnecessary to record the mass spectra of the products, because compounds differing in the number of chloromethyl groups can be readily distinguished by the chromatographic retention parameters, and the mass spectra of isomers with different positions of these groups are virtually identical. This is illustrated in Fig. 1 by the mass spectra of 1-methyl-2-(chloromethyl)benzene and 1-methyl-3-(chloromethyl)benzene.

The 14 alkylarenes C_7–C_{12} whose chloromethylation products are considered in this paper are listed in Table 1 in the order of increasing molecular weights of the substrates. In addition, we included 1- and 2-methylnaphthalenes and three alkyl aryl ketones for which the chromatographic analysis of chloromethylation products is of particular interest, because for, e.g., acetophenone these products were isolated previously [6]. For the same purpose, we included cyclohexanone, because ketones also form products of chloromethylation at the α-position to the carbonyl group. For each of the starting compounds, we give the gas-chromatographic retention indices (RIs), and the reaction products are listed in the order of increasing retention indices on a standard nonpolar polydimethylsiloxane stationary phase, OV-101. For each of the products, we indicated their molecular weights (for ^{35}Cl) and the differences between the retention indices of the products and their precursors. In two cases, the poly(chloromethyl) derivatives can be formed from several precursors, and therefore for each of them we give two ΔRI values. Reference data on the retention indices are known for only three compounds given in Table 1: the simplest 1-methyl-4-(chloromethyl)benzene and two products formed from acetophenone, which clearly illustrates the existing level of chromatographic characterization of compounds of this class and the urgency of the problem under consideration.

The structures of chloromethylation products of some alkylarenes are unambiguously determined by the molecular structures of the starting compounds and hence can be established unambiguously. For example, durene and pentamethylbenzene can give a single mono(chloromethylation) product each; mesitylene can give one mono-, one bis-, and one tris(chloromethylation) products. Published data on isolation of the main reaction products simplify the identification of the positional isomers of chloromethyl derivatives of xylenes, 1,2,4-trimethylbenzene, etc. [6]. The retention indices of the simplest mono(chloromethyl) derivatives can be estimated with a fairly high accuracy by an additive scheme from the retention indices of the corresponding alkylmethylarenes and chromatographic increment of the reaction of replacement of primary hydrogen atoms with chlorine

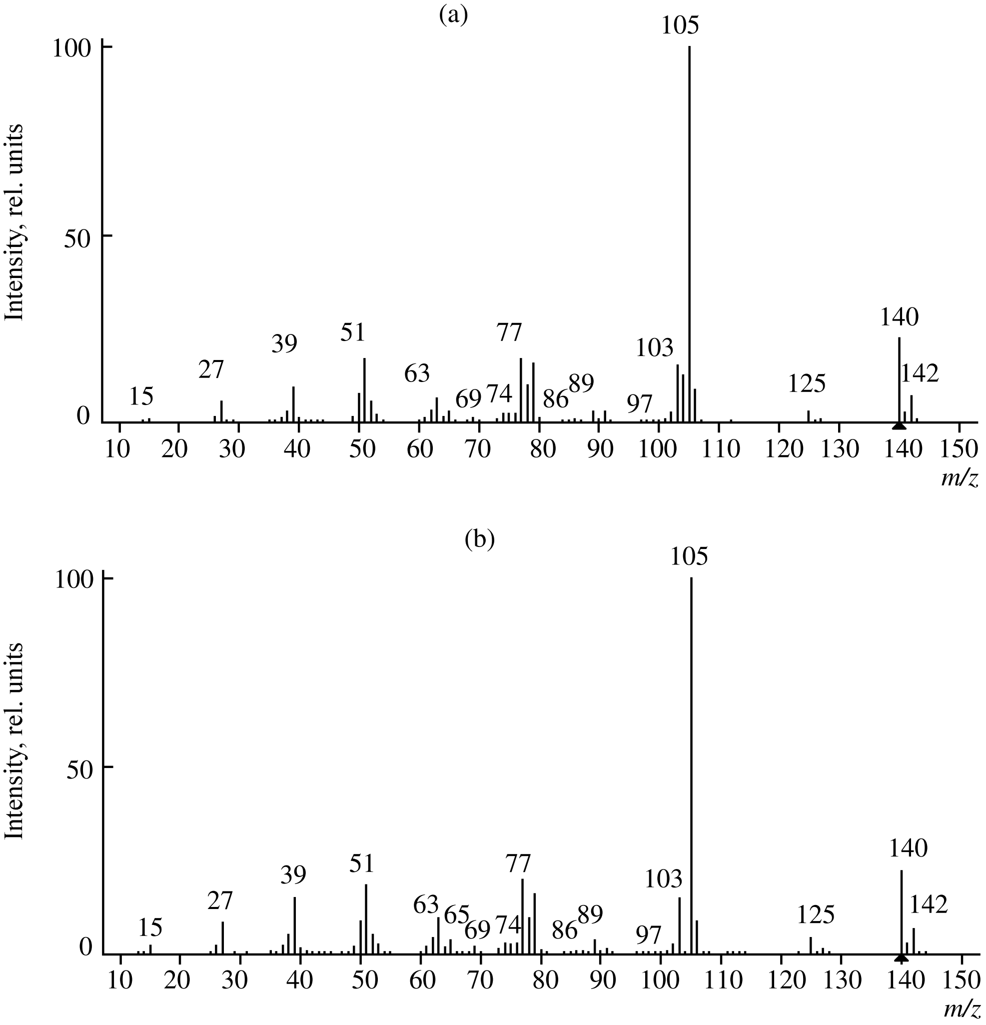


Fig. 1. Illustration of the identity of the mass spectra of (a) 1-methyl-2-(chloromethyl)benzene and (b) 1-methyl-3-(chloromethyl)benzene (from the NIST database [1] with the permission of S. Stine, director).

($ArCH_3 \rightarrow ArCH_2Cl$, ΔRI 228±14) [14]. As a result, we obtain the estimates of the retention indices given in Table 2. The mean deviation of the experimental retention indices from the additive estimates is ±5± 16 units, which is a good result for our simple calculation scheme, confirming the correctness of identification of all the chloromethylation products listed in Table 2.

Table 1. Retention indices (RIs) and results of identification of chloromethyl derivatives of alkylarenes and by-products in reaction mixtures

Starting compound (RI)	RI of product	Identification result (molecuilar weight)	ΔRI[a]
Toluene (760)	1096±4	1-Methyl-4-(chloromethyl)benzene (140) [1088][b]	336
	1412±3	1-Methyl-3,4-bis(chloromethyl)benzene (188)	316
	1463±2	1-Methyl-2,4-bis(chloromethyl)benzene (188)	367
	1616±3	4,4'-Dimethyldiphenylmethane (196) [*1616*]	–[c]
	1625±6	2,4'-Dimethyldiphenylmethane (196) [*1622*]	–
	1636±5	2,2'-Dimethyldiphenylmethane (196) [*1634*]	–

Table 1. (Contd.)

Starting compound (RI)	RI of product	Identification result (moleculiar weight)	ΔRI [a]
Ethylbenzene (854)	1184 ± 2	4-(Chloromethyl)-1-ethylbenzene (154)	330
	1550 ± 3	2,4-Bis(chloromethyl)-1-ethylbenzene (202)	366
p-Xylene (863)	1231 ± 2	1,4-Dimethyl-2-(chloromethyl)benzene (154)	368
	1518 ± 4	Unidentified product of reaction of *p*-xylene with [CH_2O] [*1518*]	
	1544 ± 3	1,4-Dimethyl-2,3-bis(chloromethyl)benzene (202)	313
	1605 ± 3	1,4-Dimethyl-2,6-bis(chloromethyl)benzene (202)	374
	1618 ± 3	1,4-Dimethyl-2,5-bis(chloromethyl)benzene (202)	387
	1861 ± 6	2,2',5,5'-Tetramethyldiphenylmethane (224) [*1868*]	–
	2166 ± 3	2,2',5,5'-Tetramethyl-*x*-(chloromethyl)diphenylmethane (272)	309
m-Xylene (865)	1207 ± 1	1,3-Dimethyl-4-(chloromethyl)benzene (154)	342
	1572 ± 3	1,3-Dimethyl-4,6-bis(chloromethyl)benzene (202)	365
	1808 ± 3	2,3',4,5'-Tetramethyldiphenylmethane (224) [*1806*]	–
	1823 ± 3	2,2',4,4'-Tetramethyldiphenylmethane (224) [*1822*]	–
	1953 ± 3	1,3-Dimethyl-2,4,6-tris(chloromethyl)benzene (250)	381
	2152 ± 3	1,3-Dimethyl-2,4,5,6-tetrakis(chloromethyl)benzene (298)	199
o-Xylene (885)	1233 ± 2	1,2-Dimethyl-4-(chloromethyl)benzene (154)	348
	1520 ± 3	Unidentified product of reaction of *o*-xylene with [CH_2O] [*1519*]	–
	1542 ± 2	1,2-Dimethyl-4,5-bis(chloromethyl)benzene (202)	309
	1578 ± 3	1,2-Dimethyl-3,4-bis(chloromethyl)benzene (202)	345
	1600 ± 5	1,2-Dimethyl-3,5-bis(chloromethyl)benzene (202)	367
	1618 ± 4	1,2-Dimethyl-3,6-bis(chloromethyl)benzene (202)	385
	1863 ± 3	3,3',4,4'-Tetramethyldiphenylmethane (224) [*1868*]	–
	1926 ± 5	1,2-Dimethyl-3,4,6-tris(chloromethyl)benzene (250)	395, 342
	2162 ± 2	3,3',4,4'-Tetramethyl-*x*-(chloromethyl)diphenylmethane (272)	299
	2198 ± 3	1,2-Dimethyltetrakis(chloromethyl)benzene (298)	272
1,3,5-Trimethylbenzene (963)	1312 ± 3	1,3,5-Trimethyl-2-(chloromethyl)benzene (168)	349
	1686 ± 2	1,3,5-Trimethyl-2,4-bis(chloromethyl)benzene (216)	374
	2073 ± 2	1,3,5-Trimethyl-2,4,6-tris(chloromethyl)benzene (264)	387
1,2,4-Trimethylbenzene (984)	**1335 ± 2**	1,2,4-Trimethyl-5-(chloromethyl) and/or 1,2,4-trimethyl-6-(chloromethyl)benzene (168)	351
	1392 ± 3	1,2,4-Trimethyl-3-(chloromethyl)benzene (168)	408
	1658 ± 3	1,2,4-Trimethyl-5,6-bis(chloromethyl)benzene (216)	323
	1710 ± 2	1,2,4-Trimethyl-3,5-bis(chloromethyl) and/or 1,2,4-trimethyl-3,6-bis-(chloromethyl)benzene (216)	375
1,2,3-Trimethylbenzene (1011) [d]	1375 ± 3	1,2,3-Trimethyl-4-(chloromethyl)benzene (168)	364
1,2,4,5-Tetramethylbenzene (1103)	1478 ± 3	1,2,4,5-Tetramethyl-3-(chloromethyl)benzene (182)	375
	1867 ± 3	1,2,4,5-Tetramethyl-3,6-bis(chloromethyl)benzene (230)	389
1,2,3,4-Tetramethylbenzene (1137) [d]	1517 ± 3	1,2,3,4-Tetramethyl-5-(chloromethyl)benzene (182)	380
1-Methyl-4-(1-methylethyl)-benzene (1013)	1328 ± 2	1-Methyl-4-(1-methylethyl)-3-(chloromethyl)benzene (182)	315
	1346 ± 2	1-Methyl-4-(1-methylethyl)-2-(chloromethyl)benzene (182)	333
	1670 ± 2	1-Methyl-4-(1-methylethyl)-2,3-bis(chloromethyl)benzene (230)	342, 324
	1696 ± 2	1-Methyl-4-(1-methylethyl)-2,5-bis(chloromethyl)benzene (230)	350
	1709 ± 3	1-Methyl-4-(1-methylethyl)-2,6-bis(chloromethyl)benzene (230)	363
Pentamethylbenzene (1269) [d]	1660 ± 3	Pentamethyl(chloromethyl)benzene (196)	391
1-Methyl-4-(1,1-dimethylethyl)-benzene (1080)	1426 ± 3	1-Methyl-4-(1,1-dimethylethyl)-2-chloromethylbenzene (196)	346

Table 1. (Contd.)

Starting compound (RI)	RI of product	Identification result (moleculiar weight)	ΔRI[a]
1,3,5-Trimethyl-2-(1-methylethyl)-benzene (1239)	1602±3	1,3,5-Trimethyl-2-(1-methylethyl)-4-(chloromethyl)benzene (210)	363
	1966±2	1,3,5-Trimethyl-2-(1-methylethyl)-4,6-bis(chloromethyl)-benzene (258)	364
1-Methylnaphthalene (1291)[e]	1678±5	1-Methyl-4-(chloromethyl)naphthalene (190)	387
2-Methylnaphthalene (1282)	1654±2	2-Methyl-*x*-(chloromethyl)naphthalene (190)	372
	2042±3, 2058±3, 2070±2	1(2)-Methyl-*x*,*y*-bis(chloromethyl)naphthalenes (238)	–
Acetophenone (1050)	**1147±2**	1-Phenyl-2-propen-1-one (132) [1138][b]	–
	1378±4	1-Phenyl-3-chloro-1-propanone (168) [1390][b]	328
	1410±2	1-[4-(Chloromethyl)phenyl]ethanone (168)	360
	1600±4	1-Phenyl-3-chloro-2-(chloromethyl)-1-propanone (216)	222
	1462±6	3-Hydroxypropiophenone (150)	–
	1814±3	1-Phenyl-3-chloro-2,2-bis(chloromethyl)-1-propanone (264)	214
Butyrophenone (1238)	1285±2	1-Phenyl-2-ethyl-2-propen-1-one (160)	–
	1485±2	1-Phenyl-2-(chloromethyl)-1-butanone (196)	247
	1540±6	1-Phenyl-2-ethyl-1-propanon-3-ol (178)	–
	1586±3	1-[4-(chloromethyl)phenyl]-1-butanone (196)	348
	1705±5	1-Phenyl-2,2-bis(chloromethyl)-1-butanone (244)	220
Isovalerophenone (1276)	**1351±2**	1-Phenyl-2-(1-methylethyl)-2-propen-1-one (174)	–
	1439±2	2,3-Dimethyl-1-phenyl-2-buten-1-one (174)	–
	1549±2	3-Methyl-1-phenyl-2-(chloromethyl)-1-butanone (210)	273
	1660±3	3-Methyl-1-[4-(chloromethyl)phenyl]-1-butanone (210)	384
Cyclohexanone (873)	1081±3	2-(Chloromethyl)cyclohexanone (146)	208
	2024±4	2,2,6,6-Tetrakis(chloromethyl)cyclohexanone (290)	–

[a] ΔRI values for chloromethylation products and their precursors (two figures correspond to two possible starting compounds). [b] In brackets are reference data or retention indices of specially synthesized compounds under the same conditions of analysis (printed italic). [c] Here and hereinafter, ΔRI values are not given for chloromethylation by-products and for compounds that cannot be identified unambiguously. [d] Hydrocarbons present as impurities in the durene fraction. [e] 1-Methylnaphthalene is an impurity in a 2-methylnaphthalene sample. For each group of isomeric products, the retention indices of the major isomers are printed bold.

The most difficult is structural interpretation of the chromatographic signals of several isomers differing in the retention parameters; these differences can reach 50–70 units. The differences in the retention indices of positional isomers of substituted arenes are associated with the presence or absence of *o*-substituents in their molecules. Using data from Table 1 for the unambiguously identified chloromethylation products, we can estimate the mean increments ΔRI of chloromethyl groups in various positions of the molecules.

Position of CH_2Cl group	RI
No *o*-substituents	339±9
One or two methyl groups in *o*-positions	369±18
One or two chloromethyl groups in *o*-positions (including CH_3 + CH_2Cl combination)	300±30
In alkyl fragments in α-position relative to carbonyl group	225±15

Determination of such increments is equivalent to the development and use of the simplest additive scheme for estimating the retention indices. Their more detailed structural differentiation is not appropriate, taking into account that the scheme itself is approximate. However, the ΔRI values obtained clear-

Table 2. Comparison of the retention indices (RIs) of the simplest (chloromethyl)arenes estimated by the additive scheme (RI_{add}) using the increment of the reaction $ArCH_3 \rightarrow ArCH_2Cl$, ΔRI 228 ± 14, with the experimentally determined retention indices (RI_{exp}) of components of reaction mixtures

Starting alkylmethylarene	RI	$ArCH_3 \rightarrow ArCH_2Cl$ substitution product	RI_{add}	RI_{exp}
Toluene	760	Benzyl chloride	988	986 ± 7
p-Xylene	863	1-Methyl-4-(chloromethyl)benzene	1091	1096 ± 4
1-Methyl-4-ethylbenzene	951	4-(Chloromethyl)-1-ethylbenzene	1179	1184 ± 2
1,2,4-Trimethylbenzene	984	1,4-Dimethyl-2-(chloromethyl)benzene	1212	1231 ± 2
		1,3-Dimethyl-4-(chloromethyl)benzene	1212	1207 ± 2
		1,2-Dimethyl-4-(chloromethyl)benzene	1212	1233 ± 2
1,2,3,5-Tetramethylbenzene	1107	1,3,5-Trimethyl-2-(chloromethyl)benzene	1335	1312 ± 3
1,2,4,5-Tetramethylbenzene	1103	1,2,4-Trimethyl-5-(chloromethyl)benzene	1331	1335 ± 2
1,2,3,4-Tetramethylbenzene	1137	1,2,4-Trimethyl-3-(chloromethyl)benzene	1365	1392 ± 3
		1,2,3-Trimethyl-4-(chloromethyl)benzene	1365	1375 ± 3
Pentamethylbenzene	1269	1,2,4,5-Tetramethyl-3-(chloromethyl)benzene	1497	1478 ± 3
		1,2,3,4-Tetramethyl-5-(chloromethyl)benzene	1497	1517 ± 3
Mean deviation, (RI_{add} – RI_{exp}), units			±5 ± 16	

ly reflect the observed scatter of the retention indices of isomeric (chloroalkyl)arenes depending on the positions of the other substituents and can be used for the identification of these products. The results of applying this criterion to identification of alkyl(chloromethyl)arenes in various groups of positional isomers are given in Table 3. It can be noted that in some cases this procedure allows unambiguous prediction of the

Table 3. Interpretation of the sequences of chromatographic elution of some isomeric alkyl(chloromethyl)arenes, based on the mean increments ΔRI and boiling points T_b estimated using ACD software

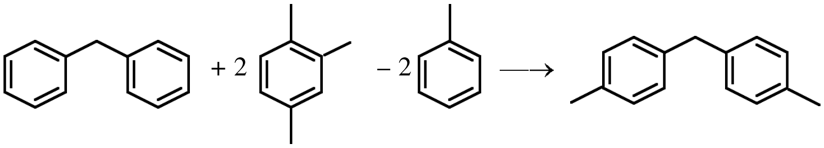
Starting compound	RI of product	Component	Estimation by ΔRI	Estimated T_b, °C
Toluene	1412 ± 3	1-Methyl-3,4-bis(chloromethyl)benzene	1396	264.8
	1463 ± 2	1-Methyl-2,4-bis(chloromethyl)benzene	1465	273.4
	1633 ± 3	4,4'-Dimethyldiphenylmethane	–	286.0
	1640 ± 3	2,4'-Dimethyldiphenylmethane	–	298.5
p-Xylene	1544 ± 3	1,4-Dimethyl-2,3-bis(chloromethyl)benzene	1531	284.8
	1605 ± 3	1,4-Dimethyl-2,6-bis(chloromethyl)benzene	1600	289.9
	1618 ± 3	1,4-Dimethyl-2,5-bis(chloromethyl)benzene	1600	291.5
o-Xylene	1542 ± 2	1,2-Dimethyl-4,5-bis(chloromethyl)benzene	1533	285.8
	1572 ± 3	1,2-Dimethyl-3,4-bis(chloromethyl)benzene	1533	288.1
	1600 ± 5	1,2-Dimethyl-3,5-bis(chloromethyl)benzene	1602	293.3
	1618 ± 4	1,2-Dimethyl-3,6-bis(chloromethyl)benzene	1602	297.3
1,2,4-Trimethylbenzene	1658 ± 3	1,2,4-Trimethyl-5,6-bis(chloromethyl)benzene	1635	304.5
	1710 ± 2	1,2,4-Trimethyl-3,5-bis(chloromethyl) and/or 1,2,4-trimethyl-3,6-bis(chloromethyl)benzene	1704	312.1 and 313.0
1-Methyl-4-(1-methylethyl)benzene	1328 ± 2	1-Methyl-4-(1-methylethyl)-3-(chloromethyl)benzene	1313	238.3
	1346 ± 2	1-Methyl-4-(1-methylethyl)-2-(chloromethyl)benzene	1313	246.8
	1670 ± 2	1-Methyl-4-(1-methylethyl)-2,3-bis(chloromethyl)benzene	1697	297.8
	1696 ± 2	1-Methyl-4-(1-methylethyl)-2,5-bis(chloromethyl)benzene	1697	303.4
	1709 ± 3	1-Methyl-4-(1-methylethyl)-2,6-bis(chloromethyl)benzene	1697	310.3
Isovalerophenone	1351 ± 2	2-(1-Methylethyl)-1-phenyl-2-propen-1-one	–	252.6
	1439 ± 2	2,3-Dimethyl-1-phenyl-2-buten-1-one	–	263.7

elution sequence for pairs (but not for larger groups) of isomers, e.g., for pairs of bis(chloromethyl) derivatives of toluene and pseudocumene, and hence their identification. In more complex cases, the estimated retention indices of several positional isomers are equal, and more structurally specific criteria are required for their identification.

Since the order of gas-chromatographic elution of isomers belonging to the same series on stationary phases of any polarity unambiguously corresponds to the ascending order of their boiling points, the most rational solution of the problem in hand is apparently that based on estimation of the boiling points (T_b) using the ACD software [15]. Although the accuracy of T_b estimation by this method is relatively poor, it can be assumed that, within a group of chemically similar compounds, the errors should be comparable, so that the relative order of T_b variation within a group of isomers should be fairly reliable. The estimated boiling points of isomers, arranged in Table 3 in ascending order within each group, are in all the cases consistent with the two other criteria considered above, which allows unambiguous prediction of the sequence of chromatographic elution of isomeric chloromethyl derivatives.

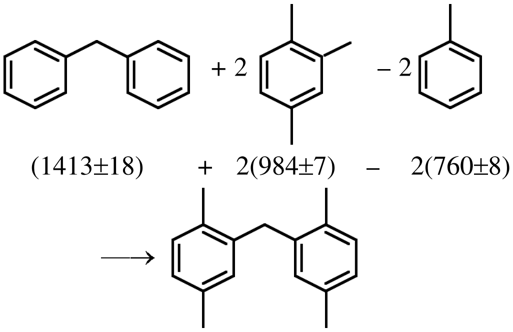
Small difference in the estimated boiling points of two bis(chloromethyl) derivatives of 1,2,4-trimethylbenzene, 312.1 and 313.0°C (Table 3), suggests joint elution of these compounds; this assumption eliminates the vagueness arising from the fact that there are three expected reaction products but only two observed chromatographic peaks.

The main side process accompanying the chloromethylation is the formation of substituted diphenylmethanes $ArCH_2Ar$ [6, 8]; for the majority of them, data on the retention indices are also unknown. However, such products can be readily revealed in reaction mixtures by theoretical estimation of their retention indices using a version of the additive scheme [2] involving "construction" of target molecules from simpler precursors and calculation of the retention indices without using any increments calculated beforehand. In accordance with this scheme, the retention index of 4,4'-dimethyldiphenylmethane (one of by-products of toluene chloromethylation) can be estimated from data for unsubstituted diphenylmethane, *p*-xylene, and toluene as follows:



(1413±18) + 2(863±8) – 2(760±8) = 1619±24
(experimental value 1616±3)

For 2,2',5,5'-tetramethyldiphenylmethane (by-product of *p*-xylene chloromethylation), the scheme is as follows:



(1413±18) + 2(984±7) – 2(760±8)

= 1861±23
(experimental value 1857±6)

In addition, the formation of all the diarylmethanes detected was confirmed experimentally by performing the reaction under similar conditions with H_2SO_4 used instead of HCl, which excludes formation of the chloromethylation products. For *o*- and *p*-xylenes, other products of unknown chemical nature were additionally detected in the reaction mixtures; without hypotheses on their structure, they cannot be identified using our approach. However, such products are readily revealed by the retention indices and do not interfere with the identification of the target components.

Among chloromethyl derivatives of methylnaphthalenes, only one component, the previously isolated [6] 1-methyl-4-(chloromethyl)naphthalene, can be identified. Ambiguous positions of the chloromethyl group and of several such groups in 2-methylnaphthalene chloromethylation products cannot be determined solely from the chromatographic data, and in this case our approach is inapplicable also.

The following fact is worth noting. Instead of pure 1,2,4,5-tetramethylbenzene, we had at our disposal only a durene fraction boiling in a relatively wide range (180–210°C) and containing about 80% main substances, with impurities of 1,2,3-trimethylbenzene, 1,2,3,4-tetramethylbenzene, and pentamethylbenzene. Naturally, chloromethylation of this sample yielded a multicomponent product mixture. However, this did not preclude unambiguous identification of the products on the basis of the above-considered chromatographic relationships of the reaction (the corresponding data are included in Table 1). It follows from these data that, first, chloromethylation cannot be classed with derivatization reactions, because the following important criteria are not observed: short reaction time, high degree of conversion (the conversion is particularly low for monoalkyl-substituted arenes and their derivatives containing acceptor substituents), and formation of no more than one or two products. However, on the other hand, just the latter feature allows determination of the molecular structure of positional isomers of alkylarenes, even present simultaneously, by chromatographic analysis of their chloromethylation products, which is impossible using other reactions of compounds of this class.

Interpretation of the composition of chloromethylation products formed from alkyl phenyl ketones is more difficult, because the substitution in the aromatic core can be accompanied by reactions in the α-position relative to the carbonyl group:

$$\mathrm{ArCOCH_2R} + [\mathrm{CH_2O}] + \mathrm{HCl} \longrightarrow \underset{\textbf{I}}{[\mathrm{ArCOCH(CH_2OH)R}]}$$

$$\longrightarrow \underset{\textbf{II}}{\mathrm{ArCOC(R){=}CH_2}} + \underset{\textbf{III}}{\mathrm{ArCOCH(CH_2Cl)R}}$$

$$\longrightarrow \underset{\textbf{IV}}{\mathrm{ArCOC(CH_2Cl)_2R}}. \qquad (2)$$

Nevertheless, this problem can also be successfully solved on the basis of chromatographic data. Virtually all the “anomalous” products in the reaction mixtures are readily revealed by their ΔRI values differing from those of the chloromethyl derivatives. For example, α,β-unsaturated carbonyl compounds **II** were detected with all alkyl phenyl ketones: acetophenone (retention index 1147 ± 2, identified by the reference value of the retention index, 1138), butyrophenone (1285 ± 2), and isovalerophenone (1351 ± 2). The ΔRI values of these products are considerably lower than those of the chloromethyl derivatives: 97, 47, and 75, respectively. In the reaction mixture obtained with isovalerophenone, we additionally identified 2,3-dimethyl-1-phenyl-2-buten-1-one formed by isomerization of the primary product, 2-(1-methylethyl)-1-phenyl-2-propen-1-one. In two cases (acetophenone and butyrophenone), the chromatograms contained broad asymmetrical peaks assignable to polar hydroxy ketones **I**. The product of acetophenone chloromethylation at the α-position relative to the carbonyl group, 1-phenyl-3-chloro-1-propanone, was identified by comparing its retention index with the available reference value (Table 1), and all the other α-chloromethyl derivatives **III** and **IV**, by the well reproducible increment ΔRI equal to 222 ± 15. With all the alkyl phenyl ketones, we detected single products of chloromethylation of the aromatic core, most probably at 4-position.

The mean value of ΔRI = 222 ± 15, determined for alkyl phenyl ketones, allows identification of the product of cyclohexanone chloromethylation at the α-position relative to the carbonyl group, 2-(chloromethyl)cyclohexanone (ΔRI = 1081 – 873 = 208). In the region of the chromatogram corresponding to bis- and tris(chloromethyl) derivatives, we observed several peaks, which does not allow their unambiguous assignment. However, in the region of the expected retention index of the exhaustive chloromethylation product, 2,2,6,6-tetrakis(chloromethyl)cyclohexanone, their is only one peak, so that its identification can be considered as unambiguous.

Thus, determination of chromatographic retention indices in combination with the a priori information about the chloromethylation features allowed identification of more than 50 chloromethyl derivatives of alkylarenes and alkyl phenyl ketones and of about ten by-products of this reaction. The suggested approach to identification of previously uncharacterized products of comprehensively studied organic reactions can also be applied to other processes.

EXPERIMENTAL

To prepare chloromethyl derivatives, we used available alkylarenes of pure or chemically pure grade. Isopropylmesitylene (d_4^{20} 0.890, n_D^{20} 1.5072) from the collection of Prof. B.V. Ioffe was synthesized by alkylation of mesitylene with isopropyl alcohol in the presence of $\mathrm{H_2SO_4}$. Instead of pure durene we used a durene fraction boiling in the range 180–210°C (main substance content about 80%, chromatographic monitoring). Samples of butyrophenone (d_4^{20} 0.987, n_D^{20} 1.519) and isovalerophenone (d_4^{20} 0.973, n_D^{20} 1.510) were kindly submitted by Cand. Sci. (Chem.) L.M. Kuznetsova. All the starting compounds were characterized by gas-chromatographic retention indices on a standard nonpolar phase; the data obtained coincided with the reference data.

Chloromethylation of alkylarenes was performed by a simplified procedure (without using phase-transfer catalysts). A 50-ml round-bottomed flask equipped with a reflux condenser was charged with 2 ml of alkylarene, 1.5 g of paraform, and 10 ml of concentrated HCl. The reaction mixture was refluxed for 2 h on a sand bath. After cooling, the organic phase was washed two times with 10–15 ml of water and analyzed. The degree of conversion for different alkylarenes ranged from 10 to 50% (estimated from the total areas of chromatographic peaks).

For additional identification of diarylmethanes in reaction mixtures, the process was performed under identical conditions but with HCl replaced with 10 ml of 30% H_2SO_4.

From unsubstituted benzene, benzyl chloride, and 4-chlorotoluene, no chloromethylation products were obtained under these conditions. Anisole forms with formaldehyde a polycondensation product, a white resinous substance. Extensive tarring was observed with cyclohexanone; the products were extracted from the reaction mixture with chloroform (15 ml).

Gas-chromatographic analysis of reaction mixtures was performed on a Biokhrom-1 chromatograph equipped with a flame ionization detector and a quartz capillary column (25 m × 0.20 mm, standard nonpolar polydimethylsiloxane stationary phase OV-101) in the linear programmed heating mode (from 60 to 240°C at a rate of 6 deg min^{-1}). The carrier gas was nitrogen; linear velocity 25 $\text{cm}^{-1}\,\text{s}^{-1}$, flow split ratio at sample injection (sample volume 0.5–1.0 μl) 1 : 30. The linear-logarithmic retention indices (RIs) were calculated from the retention times by formula (3) using the standard software (QBasic) [16]:

$$\mathrm{RI} = \mathrm{RI}_n + (\mathrm{RI}_{n+k} - \mathrm{RI}_n)[f(t_{R,x}) - f(t_{R,n})]/[f(t_{R,n+k}) - f(t_{R,n})], \qquad (3)$$

where RI_x, RI_n, and RI_{n+k} are the retention indices of the compound being characterized and reference *n*-alkanes with the numbers of carbon atoms (n) and ($n + k$) and retention times $t_{R,x}$, $t_{R,n}$, and $t_{R,n+k}$, respectively. The function $f(t_n)$ in the system of linear-logarithmic indices has the form $f(t_R) = t_R + q\log(t_R)$, where q is a variable coefficient calculated from the retention times of three reference *n*-alkanes [16].

As a source of information on the gas-chromatographic retention indices we used the NIST database [1] and the database of one of the authors (I.Z.).

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