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## Gas chromatographic–mass spectrometric identification of impurities in 1,2-diethoxybenzene

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### ABSTRACT

Impurities in a 1,2-diethoxybenzene sample were identified based on mass spectral interpretation. To confirm the tentative structural assignment and also to identify the isomers of ethyl(diethoxy)benzenes, authentic 3,4-ethyl(diethoxy)benzene was synthesized. The suspected presence of an unreacted OH group in one of the compounds was confirmed by derivatization. Retention indices of the compounds present were measured.

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### INTRODUCTION

1,2-Diethoxybenzene (1,2-DEB) is an intermediate product in the synthesis of certain pharmaceuticals (*e.g.*, Drotaverin, Perparin). It is generally prepared by alkylation of pyrocatechol with ethyl halides, ethyl sulphate or ethyltoluene sulphate [1].

The identification of contaminants in intermediate product(s) of a multi-step synthesis is of special interest as it makes it possible to predict the composition of homologous impurities in the end product. It is obvious that gas chromatography–mass spectrometry (GC–MS) is an excellent method for determining any volatile reaction product or intermediate, as it is capable of separating and quantifying the impurities possibly present. Moreover, it provides the ability to identify separated compounds if their mass spectra are known or can be interpreted.

Here we report a study directed toward the identification of impurities present in 1,2-DEB, obtained by reaction of pyrocatechol with diethyl sulphate.

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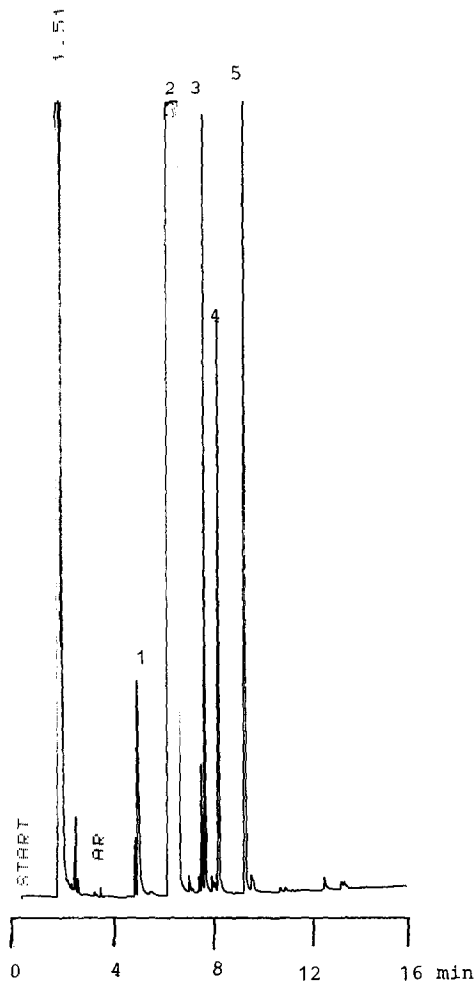


Fig. 1. Gas chromatogram of 1,2-diethoxybenzene sample. Column, 20 m  $\times$  0.25 mm I.D. glass capillary coated with OV-1 stationary phase; carrier gas, hydrogen; splitting ratio, 1:30; injection temperature, 250°C; flame ionization detector temperature, 250°C; oven temperature, 90°C isothermal for 2 min, then increased to 170°C at 6°C/min. For peak labels see Fig. 2 and text.

#### EXPERIMENTAL

1,2-DEB was synthesized by reaction of pyrocatechol with diethyl sulphate [1] on an industrial scale. The total amount of impurities in the sample was 0.4%.

GC analyses were conducted using a Hewlett-Packard Type 5830 gas chromatograph equipped with split injection system and a flame ionization detector.

GC-MS measurements were performed on a computerized Hewlett-Packard 5985A system. The spectra were taken in the electron-impact mode with an electron energy of 70 eV. The operating conditions are given in the legend to Fig. 1.

Silylation was performed under standard conditions using N,O-bis(trimethyl-

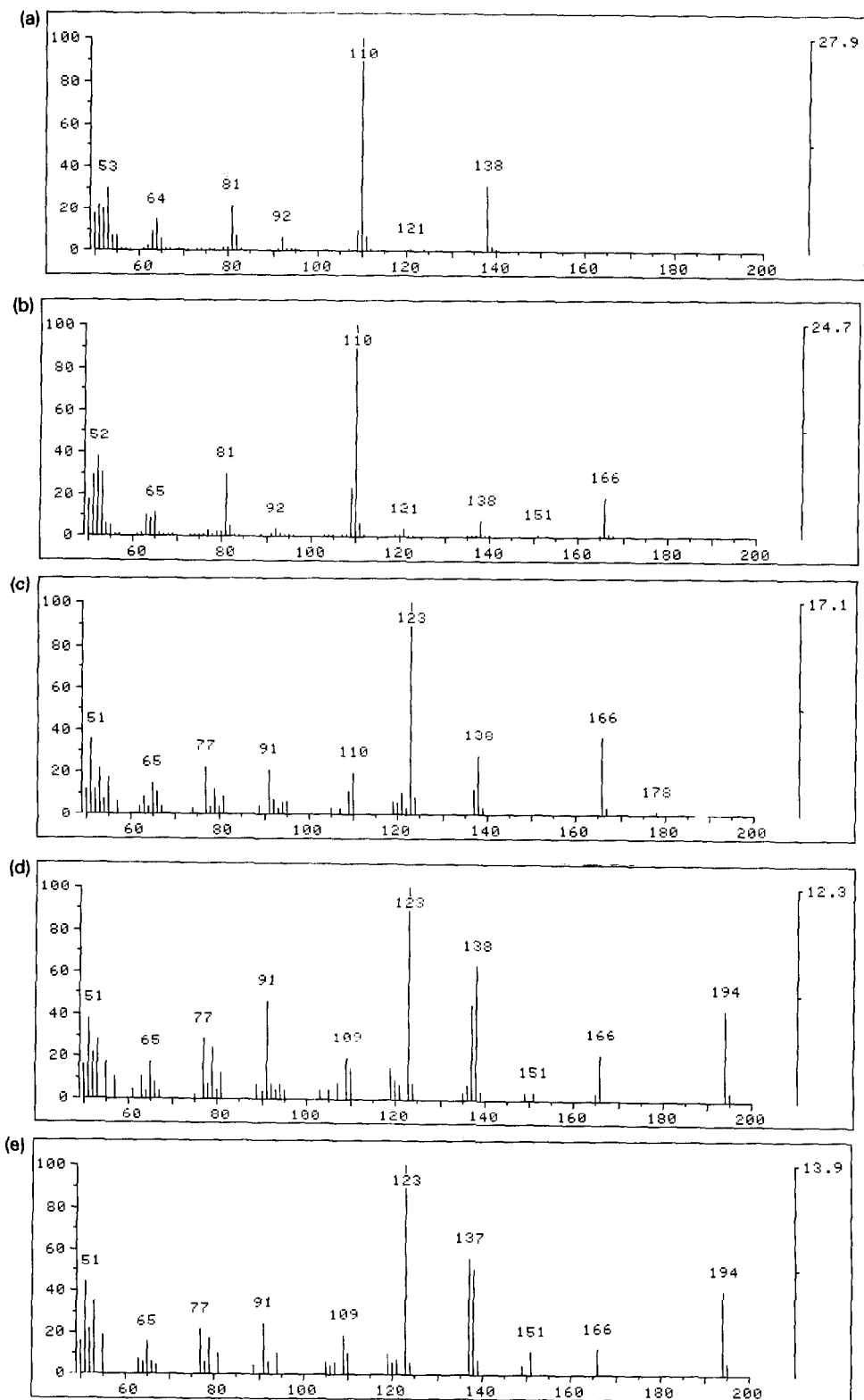


Fig. 2. Mass spectra of peaks 1-5 in Fig. 1. (a) peak 1; (b) peak 2; (c) peak 3; (d) peak 4; (e) peak 5.

silyl)acetamide (BSA) as silylating agent: 10  $\mu$ l of BSA were added to 20  $\mu$ l of sample and the mixture was allowed to stand at 70°C for 15 min.

## RESULTS AND DISCUSSION

In Fig. 1 the gas chromatogram of the 1,2-DEB sample is shown. In addition to the main product (peak 2) there are four minor peaks corresponding to impurities. The mass spectra of species eluted in the peaks in Fig. 1 are shown in Fig. 2.

It was surprising that, in spite of the presumably simple structures of the impurities, we were not able to identify them by comparison with several mass spectral libraries [2–5]. The computerized mass spectral library search offered only one positive result: the main product 1,2-DEB (peak 2) was identified as its isomer 1,4-diethoxybenzene. This result was to be expected, as it is well known that isomeric molecules possess mass spectra that closely resemble each other and the spectrum of 1,2-DEB was not included in the library. Moreover, the three isomers of diethoxybenzene exhibit virtually identical spectra [6].

As can be seen in Fig. 2b, highly characteristic odd-electron-numbered fragments are present in the mass spectrum of 1,2-DEB, which is typical of the mass spectral behaviour of ethoxyaryl compounds [6–8]. Abundant ions at  $m/z$  138 and 110 are formed through the subsequent losses of two ethylenes, which correspond to  $M - 28$  and  $M - 56$  fragments respectively.

The first-eluting compound (peak 1, Fig. 1) was identified as 2-ethoxyphenol (guaiethol), as both the retention time and the mass spectrum (see Fig. 2a) corresponded to those of the authentic standard. Thus peak 1 represents the amount of partly reacted pyrochatecol present in the sample. In the mass spectrum the most intense peak is displayed at  $m/z$  110, corresponding to the loss of ethylene ( $M - 28$ ).

In Fig. 2d and e mass spectra corresponding to peaks 4 and 5 are shown. These spectra show that both compounds have a molecular mass of 194. In addition, the spectra are very similar, suggesting that the species eluting in these peaks are isomers. The fragments in the mass spectra at  $m/z$  138 and 166 clearly indicate the presence of two ethoxy substituents in the benzene ring, giving rise to the  $M - 28$  and  $M - 56$  ions (in both spectra an intense fragment at  $m/z$  137 is also present). As molecular ions of these species are 28 daltons higher than the molecular mass of 1,2-DEB, it was presumed that they corresponded to the two possible isomers of ethyl(diethoxy)benzene. If this assumption were correct, it would indicate that no matter how mild were the conditions applied during the preparation of 1,2-DEB, the benzene ring was unavoidably alkylated (of course, only to a minute extent). The presence of a highly intense ion at  $m/z$  123 (base peak) may be explained by methyl loss from the alkyl side-chain, similarly to that which occurs with ethylphenols (in the mass spectra of ethylphenols there is a base peak at  $m/z$  107, *i.e.*, at  $M - 15$ ).

Based both on mass spectral interpretation and retention behaviour, one can hardly identify the isomers of the compounds of interest. In order to confirm the tentative structural assignment and also to identify the isomers, we synthesized 3,4-diethoxyethylbenzene. Because the authentic standard co-eluted with peak 4 and had virtually the same mass spectrum, we concluded that they were identical; its isomer (peak 5) was consequently identified as 1,2-diethoxyethylbenzene.

The mass spectrum of the compound eluted in peak 3 is shown in Fig. 2c. Like

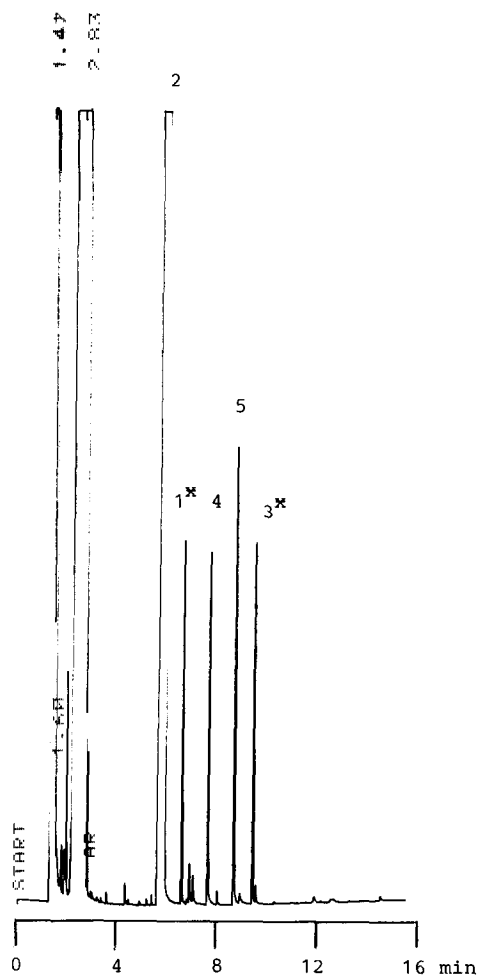


Fig. 3. Gas chromatogram of 1,2-diethoxybenzene sample after silylation. Chromatographic conditions as in Fig. 1. For peak labels see Figs. 2 and 4 and text.

1,2-DEB, this constituent has a molecular mass of 166. The probability that it was an isomeric DEB was excluded, because the mass spectra shown in Fig. 2b did not correspond to that of DEBs [6]. As only one odd-electron-numbered fragment was found in the mass spectrum (at  $m/z$  138), we concluded that there had to be only one ethoxy substituent. Further, the most intense fragment in the mass spectrum was found at  $m/z$  123, which indicates a close structural similarity to the compounds discussed above (peaks 4 and 5, Fig. 1).

Based on the considerations outlined above, a possible structure of the impurity eluting in peak 3 (Fig. 1) was considered to be ethoxy(ethyl)phenol. The formation of a compound having an alkyl side-chain and an unreacted OH group in the benzene ring seemed, however, to be very unusual. Therefore, the assumption based on mass

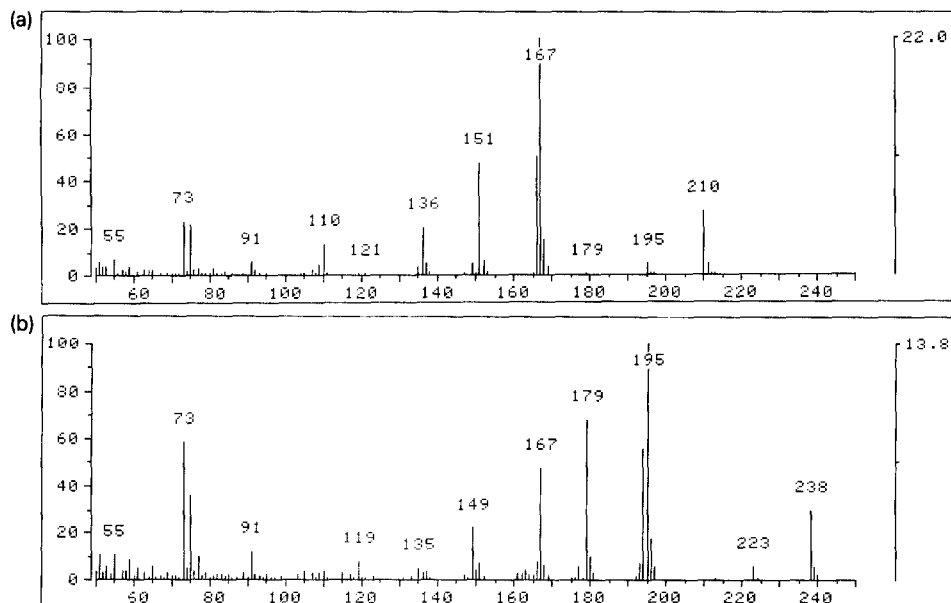


Fig. 4. Mass spectra of peaks (a) 1\* and (b) 3\*.

<i>J</i>	Compound	Peak label
1	<chem>CCOC1=CC=C(O)C=C1</chem>	1132
1*	<chem>CCOC1=CC=C(OC(C)(C)C)C=C1</chem>	1270
2	<chem>CCOC1=CC=C(CC(=O)OC)C=C1</chem>	1214
3	<chem>CCOC1=CC=C(CC(=O)OC)C=C1O</chem>	1296
3*	<chem>CCOC1=CC=C(CC(=O)OC)C=C1OC(C)(C)C</chem>	1424
4	<chem>CCOC1=CC=C(CC(=O)OC)C=C1CC(C)C</chem>	1327
5	<chem>CCOC1=CC=C(CC(=O)OC)C=C1CC(C)C</chem>	1384

Fig. 5. Kováts retention indices (*J*) of the compounds studied on OV-1 at 110 C.

spectral speculation [*i.e.*, peak 3 corresponds to ethoxy(ethyl)phenol] had to be confirmed. This confirmation was easily achieved by derivatization of the free OH group. For this purpose the simple and widely used silylation reaction was applied.

Fig. 3 shows the chromatogram obtained after silylation. By comparing Figs. 1 and 3 it is clear that two peaks have shifted: peak 1 to peak 1\* and peak 3 to peak 3\*. This is clear evidence that compounds 1 and 3 (and only these) were subject to silylation.

In Fig. 4 the mass spectra of compounds 1\* and 3\* are shown. The molecular ions in both spectra correspond to derivatives containing one TMS group. In addition, the fragments at  $M - 15$  and  $M - 89$  clearly indicate the presence of TMS group [9]. Consequently, both the chromatographic and mass spectrometric data support the assumption that compound 3 contains a free OH group, *i.e.*, it is ethyl(ethoxy)phenol. Based on available data, the positions of substitutions in the benzene ring cannot be determined.

By matching retention times or retention indices, confidence in the identification is greatly increased. The relative retention times for substituted anisole (methoxybenzene) and veratrole (dimethoxybenzene) compounds are available [10]; however, in spite of a detailed search of the literature, we could not find any indication of retention data regarding the species present in the investigated mixture. In Fig. 5 we report the Kováts retention indices all of the compounds studied.

## CONCLUSIONS

Impurities in a 1,2-DEB sample were identified. It has been shown that species which form during the preparation of 1,2-DEB contain an ethyl substituent in the benzene ring.

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