If the differences in the chromatographic behaviors of I, IIa, and III are due to solvation processes in the mobile phase, then analogous changes should occur when other types of polar sorbents are used. For example, for the column packed with Silasorb Diol, III has a lower retention volume than Ia in the mobile phase containing 2-propanol, while the relative retention of III is substantially increased in the ether-containing mobile phase (Fig. 4).

Thus, the use of n-hexane-diethyl ether-2-propanol eluant systems allows one to systematically vary the separation selectivity of the unsaturated alcohols I-III.

The use of the "Milikhrom" system for the quantitative analysis of solutions of IIa, in conjunction with the method given above, allows the mass fraction of IIa to be determined with a maximum relative error of 2.2% and a confidence level of 0.95. The relationship between the peak heights of IIa or the standard and their mass fractions is linear over at least the range indicated in this method. The drift in the retention volumes of all components was less than or equal to 2% over the course of 4 months. The use of this method for the determination of the mass fraction of compound IIa in products II and III is suggested for industrial applications.

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## ANALYSIS OF DIMETHOXYBENZYL CHLORIDE BY GAS-LIQUID

CHROMATOGRAPHY WITH IN SITU REACTION

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The chromomethylation of veratrole (I) to 3,4-dimethoxybenzyl chloride (II) is one of the key reactions in the production of papaverine from pyrocatechol.



In the reaction mixture, as well as the desired end product II, and unreacted I, compound III, which is a product of a deeper reaction, may also be present, and also anisole (IV) often detected in I, and its chloromethylation product (V).

Practically all the known methods of analysis of halogen derivatives are based on the hydrolytic splitting of the C-halogen followed by the determination of the halide ion by this

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Fig. 1. Chromatogram of dimethoxybenzyl chloride before (a) and after (b) reduction with potassium iodide. 1) Veratrole; 2) dimethoxybenzyl chloride.



Fig. 2. Chromatograms of products of reduction of dimethoxybenzyl chloride in the reaction mixture by zinc dust in a 10% solution of NaOH for 15 min (a) and 30 min (b). 1) Veratrole (I); 2) methylveratrole (IIa); 3) dimethoxybenzyl chloride (II), veratric alcohol (VI).



Fig. 3. Chromatograms of products of reduction of dimethoxybenzyl chloride by zinc dust in a 10% solution of ammonium chloride. a) Dimethoxybenzyl chloride distilled in vacuum; b) reaction mixture after chloromethylation of veratrole. 1) Solvent; 2) anisole (IV); 3) methylanisole (Va); 4) Veratrole (I); 5) methylveratrole (IIa); 6) dimethylveratrole (IIIa); 7) diphenyl (internal standard). or another method [4]. Among the several disadvantages of this method we should point out that the main one is its lack of selectivity: the presence in the reaction mixture of III and V, which also contain a chloromethyl group, inevitably leads to erroneous results. The same is also true of the method based on the formation of benzylthiuronium picrates [2, 3]. The most suitable with regard to selectivity, completeness of information, and objectiveness is in this case liquid chromatography. The chromatographic analysis of benzyl chloride is in particular dealt with in [1]. Its authors found that benzyl chloride partially polycondenses on the metallic parts of the apparatus during chromatography, leading to the appearance of false peaks and to a decrease in the sensitivity of detection. At the same time, solutions with a 30-40% and lower content of benzyl chloride gave normal chromatographic results.

In this investigation, we studied 15-20% solutions of II, i.e., solutions with a concentration close to that of the reaction mixture. According to our data, under chromatographic conditions, compound III is considerably more labile than unsubstituted benzyl chloride. With the first introduction of the sample at a column temperature of 160°C, a peak of II was obtained, which was much smaller than expected. This peak was not observed at all with the third introduction of the sample.

By diluting the initial solution to 1-1.5% and by decreasing the temperature of chromatography to the minimally possible one of 140°C, we were able to obtain satisfactory results. However, experience showed that after analysis of 25-30 samples, the characteristics of the sorbent change, and the times of elution of the mixture components and the peak of II decrease. A repeated conditioning of the column did not lead to positive results. Thus, direct chromatography of II is unsuitable for carrying out serial analyses. At the same time the high reactivity of II indicates that it can be chromatographed in the form of stable derivatives.

In particular, we studied the reduction of the Ch<sub>2</sub>Cl group to methyl:



It was assumed that the possible chloromethylated impurities of II and V would also be reduced to dimethylveratrole (IIIa) and methylanisole (Va), respectively. As the reducing agent, we used potassium iodide in acetone with the addition of acetic acid [5, 6] and zinc dust [7]. Reduction with potassium iodide led to a slightly volatile product with elution time double that of the starting II, and in addition, several peaks appeared on the chromatogram (Fig. 1), which could not be identified. This could be explained, for example, by the presence of acetone and acetic acid in the reaction mixture.

The reduction by zinc dust in 10-20% solutions of sodium hydroxide at 30-40°C for 15 min led to the formation of the desired IIa (Fig. 2a). However, on the chromatogram, not only peaks of IIa and I are observed, but also a peak with elution time of 6 min 15 sec, which we identified as unreduced II (from this point, the identification was carried out by comparison with authentic samples). Increase in the reduction time to 30 min or the temperature to 50-60°C resulted in the appearance of still another peak on the chromatogram of veratric alcohol (VI), formed as a result of the saponification of II (Fig. 2b). In some cases the unreacted II is completely saponified to VI. On the whole the conversion of II into IIa proceeds under these conditions only to the extent of 60-70%.

The  $CH_2Cl$  group can be practically completely reduced to the  $CH_3$  with zinc dust in 10-15% solutions of ammonium chloride at 50-60°C in the course of 15 min (Fig. 3). Besides the peaks of I, IV, IIa, and Va, a peak with an elution time of 3 min 35 sec is almost always observed on the chromatogram, which could not be identified by direct comparison. However, the fact that decrease in the chloromethylation time leads to a decrease in the peak, and sometimes to its disappearance, indicates that this is IIIa, formed as a result of the reduction of III, the product of a deeper chloromethylation of I. Its content in the mixture rarely exceeds 4-5%.

TABLE 1. Relative Retention Volumes  $(V_p^{rel})$  and Kovacs Indexes  $(I_K)$  of Mixture Components  $(t_{col} 150^{\circ}C, stationary liquid phase - 5\% Se-30$  on Chromaton NAW DMCS)

Compound	vre1 p	۶ĸ
Anisole (IV)	0,38	921
Methylanisole (Va)	0,50	1009
Veratrole (I)	0,71	1094
Methylveratrole (IIa)	1,00	1178
Dimethylveratrole (IIIa)	1,62	1278
Dimethoxybenzyl chloride (II)	2,74	1376
Veratric alcohol (VI)	3,14	1403

TABLE 2. Results of Determinations of Dimethoxybenzyl Chloride (II) in Distilled Sample in the Reaction Mixture

I in sam- p- mal.	al stics	I in sam- n- undard	al stics
und % ] stilled e; the i rnal non thod	trologic aracteri	und,%] stilled e; the j rnal st	trologic aracter
e to di e	che	S to to to to	che
96,52 96,75	n = 6 $\alpha = 0,95$	13,46 13,54	n=6 $\alpha=0,95$
96.13 96,11 96,41	$\bar{x} = 96, 43$ S = 0, 27 $S_{\bar{x}} = 0, 11$	12,36 13,03 12,87	$\bar{x} = 13,05$ S = 0,42 S = 0,17 $\bar{x} = 0,17$
96,66	$\Delta x = 0, 28$ Are1 = 0, 29 %	13,06	$\overline{\Delta x} = 0.44$ A <sub>rel</sub> = 3.4 %
		•	

TABLE 3. Results of the Determination of the Composition of the Reaction Mixture

No. of operations	Content of, %					
	anisole	methoxy- benzyl chloride	veratrole	dimethoxy- benzyl chloride	di(chloro-  methyl)-  veratrole	veratric alcohol
1 2 3 4 5 6 7	0,41 0,46 0,45 0,44 0,64 0,31	0,35 0,38 0,34 0,35 0,48 0,10	4,43 4,72 4,11 3,96 3,47 3,80 5,60	16,18 16,41 15,11 16,20 15,30 16,12 14,10	0,94 0,97 0,93 1,05 0,87 0,91 0,52	 0,42 0,22 

Table 1 shows the relative retention volumes  $V_p^{rel}$  [p = pure] and Kovacs indexes  $I_K$  for all the mixture components.

For quantitative determinations, we used the method of internal normalization without correction coefficients, or the method of internal standard. To monitor the quality of the distilled II or the course of the chloromethylation process, very satisfactory results are obtained by the internal normalization method. The internal standard method was used for accurate determination of the content of II in solutions. The results of the determination are given in Tables 2 and 3.

## EXPERIMENTAL

The investigation was carried out on a LKhM-80 model 6 chromatograph. Liquid Se-30 was used as the stationary liquid phase in an amount of 5%, deposited on Chromaton NAW DMCS; a stainless steel column (length 3 m, diameter 3 mm), temperature of the column 150°C, of detector 220°C, of evaporator 180°C, flow rate of carrier gas (He) 50 ml/min, a catharometer detector. detector current 110 mA were used in the investigation. Diphenyl was used as internal standard, the solvents were "pure" grade trichloroethylene or dichloroethane, zinc dust was of "technical" grade. Thoroughly distilled II, bp 124-125°C (20 mm Hg), the amount of impurities in which did not exceed 1% according to GLC, was used for the calibration.

Method of Determination of Dimethoxybenzyl Chloride in the Reaction Mixture. A 2 ml portion of the solution to be determined (concentration of the order of magnitude of 10-20%) is placed in a beaker or in a 50 ml conical flask. An accurately weighed sample (~ 0.30g) of diphenyl, 20 ml of a 10% solution of ammonium chloride, 1 drop of a dilute (1:1) HCl solution, and 2 g of zinc dust are added to the same flask. The contents are stirred with a magnetic stirrer at a temperature of 50-60°C for 15 min, cooled, and the liquid is decanted through cotton wool into a separatory funnel. The solid residue on the filter is washed twice with 5 ml portions of benzene, and the benzene washings are combined with the liquid in the separatory funnel. The funnel is shaken, the benzene layer is separated, slightly dried over calcined potassium chloride (~3-5 min), and 2 µl are chromatographed under the above indicated conditions.

To determine the calibration coefficient, a series of 6 experiments was carried out, precisely according to the above procedure, using an approximately 15% solution of pure II at an accurately known concentration, instead of the solution to be analyzed. The calculation was carried out according to the formula:

$$x = \frac{k \cdot g_m \cdot P_x}{V_x \cdot P_m} \cdot 100,$$

where x is the content of II, g/100 ml; k is the calibration coefficient of II, relative to diphenyl;  $g_m$  is the weight of diphenyl, g;  $V_x$  is the volume of the solution of II, taken for the analysis, m1; P<sub>x</sub>, P<sub>m</sub> are parameters of the chromatrographic peaks of II and diphenyl, respectively;  $P = l \cdot h$  was used, where h is the peak height, mm, l is the distance of the diagram tape from the site of elution of the nonsorbed component to the peak maximum, mm.

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