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Note

Determination of the content of 2-chlorobenzenesulphonamide and bis(*p*-chlorophenyl) sulphone in 4-chlorobenzenesulphonamide

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4-Chlorobenzenesulphonamide (I) is used as raw material for the synthesis[1] of chlorpropamide, which is extensively employed in hypoglycaemia. One of the most important processes used in the manufacture of I consists of two steps, a chlorosulphonation of chlorobenzene followed by treatment of the product obtained with ammonia[2]. Side reactions also occur, forming undesirable substances, some of which are difficult to eliminate. The two most important by-products are 2-chlorobenzenesulphonamide (II) and bis(*p*-chlorophenyl) sulphone (III).

Therefore, suitable analytical procedures are required for testing the purity of compound I. This is very difficult to achieve as compounds I–III have very similar functional and structural properties. In spite of some limitations, it is possible to use ultraviolet (UV) spectroscopy[3], but the absorbance maxima of those compounds present differ only slightly in their positions. Extinction coefficients and complicated equations must be used. This make the method unsuitable for the determination of low levels of compounds II and III in I. Thin-layer chromatography is another method generally employed to measure this type of contamination. By using two independent analyses in different systems, semi-quantitative values can be obtained[3]. However, the results are unsatisfactory in terms of the requirements of specificity and accuracy.

Trials performed by gas chromatographic procedures showed that the use of a wide variety of stationary phases in single columns did not results in the separation of the three compounds. Intermediate polarity columns separated III from a mixture of I and II and polar columns resolved I from II and III. Therefore, a dual column system was employed, with good results. This paper describes the procedure employed.

EXPERIMENTAL

Reagents

Reagent grade acetone was employed. Compounds II and III were prepared by controlled procipitation of reaction mixtures at different pH values, and purified by successive recrystallizations.

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Sample preparation

A 1-g amount of contaminated I was dissolved in 10 ml acetone and 1 μl was injected into the gas chromatograph.

Standard preparation

Starting from the pure compounds, solutions of I (1 g per 10 ml acetone) were prepared containing the following additions of contaminants (II and III with respect to I): 0.1, 0.2, 0.3, 0.4, 0.5, 0.75 and 1.0%. A 1-μl volume of each solution was injected into the gas chromatograph.

Gas–liquid chromatography (GLC)

A Perkin-Elmer Model 3920B gas chromatograph was equipped with a hydrogen flame ionization detector. The two columns were connected according to the following sequence: injector, column 1, 2, detector. Glass column 1 (37 cm × 2 mm I.D.) was packed with Chromosorb W AW DMCS (80–100 mesh) coated with 5% polyphenyl ether (6 rings) (Applied Sciences Cat. 19, 1976, No. 08152) and glass column 2 (180 cm × 2 mm I.D.) was packed with Chromosorb W AW DMCS coated with 5% Carbowax 20M (Applied Sciences Cat. 19, 1976, No. 08006). Nitrogen was used as the carrier gas at a flow-rate of 27 ml/min. The air and hydrogen flow-rates were 370 and 40 ml/min respectively. The injection port, oven and detector temperatures were 250, 225 and 260°C respectively.

RESULTS AND DISCUSSION

Separation

Under the described GLC conditions, compounds I, II and III were eluted with retention times of 11.2, 9.0 and 16.4 min respectively (Fig. 1). The solvent did not produce any interfering peaks with retention times similar to those of the analyzed compounds.

Standard curve

The standard curves of peak areas, measured by conventional triangulation by drawing imaginary tangents to the minima, *versus* percentage of contamination in the range 0–1% were linear for contaminants II and III.

The least-squares fitting of a plot of the mean of the peak areas obtained for three assays of the same standards *versus* the percentage of compound II gave a coefficient of determination, $r = 0.999$ for seven data and the regression equation $y = 139.2x + 0.4$, where y is the area in mm^2 and x is the percentage concentration. For compound III the r value was 0.992 for $n = 7$ and the corresponding equation was $y = 276.2x - 11.4$. The standard deviations were 139.2 ± 1.8 and 276.2 ± 4.6 respectively, and the confidence limits (95%) were 139.2 ± 6.2 and 276.2 ± 16 respectively[4,5].

The described GLC method has several advantages over previously methods. It is fast, specific and sensitive to 0.05% contamination levels of II and III in I under the described conditions. In the case of mixtures of similar quiantities of the three compounds, their proportions can be determined directly by area normalization taking into consideration the detector responses, which are equal for isomers I and II and slightly higher in the case of III. In the present study, standards with a known contamination of II and III in a fixed amount of I were used because the matrix peak

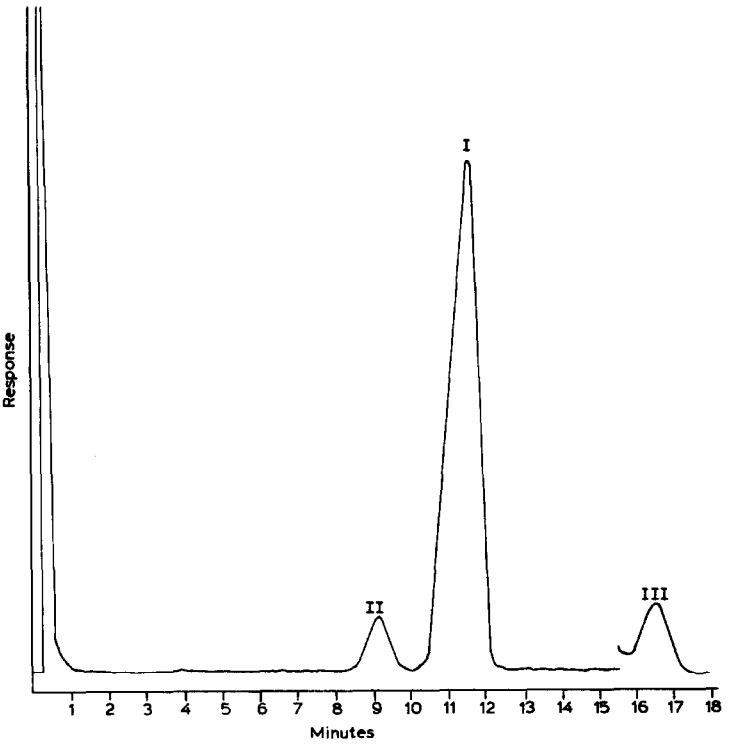

Fig. 1. Typical gas chromatogram of a sample of compound I containing 0.3% II and 0.3% III. The attenuation for I was 128 and for II and III, 2.

of this component has a notable effect on the area of the small peaks of the impurities, hindering the utilization of the area normalization method or the preparation of standards without I.

The method shows a good reproducibility; repeated injections, with the same syringe and made by the same operator, of each of the different standard solutions, showed deviations of approximately 4% between area readings. This indicates that it is not necessary to use an internal standard, but for such purposes one could use the matrix peak of I or any other available compound.

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