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GAS CHROMATOGRAPHIC DETERMINATION OF CAMPHORSULPHONIC ACID AND ITS SALTS IN PHARMACEUTICAL PREPARATIONS

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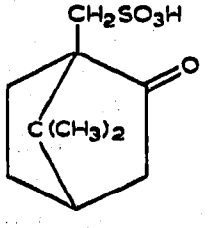
SUMMARY

A gas chromatographic procedure has been developed for the quantitative determination of camphorsulphonic acid and its salts. The free acid (which can be obtained from its salts by passing them through a column of strongly acid cation-exchange resin) is methylated with diazomethane; the determination is made using a 210 cm × 4 mm I.D. glass column packed with 5% SE-30 on Chromosorb W, isothermally operated at 173°. The method has been successfully applied even to complex pharmaceutical preparations which may contain substances interfering with the usual chemical methods described for determination of the compound.

INTRODUCTION

d-Camphorsulphonic acid (2-oxo-10-bornane-sulphonic acid)(I), also known as Reychler's acid, is an active component of many pharmaceutical preparations. These products often contain (I) as the calcium or sodium salt, but it may also be found as a salt with other bases, such as ephedrine, theophylline, etc. In spite of its wide use, only relatively few analytical methods are reported in the literature which allow its specific quantitative determination.



(I)

In fact, apart from indirect assay methods, such as the determination of calcium or sodium in the respective salts[1–4] and another method[5] based on the reaction with potassium ferrocyanide (which shows poor sensitivity, however, and is extremely time-consuming), only two methods are available for application to the analysis of

pharmaceutical products. The first is based on the spectrophotometric determination of 2,4-dinitrophenylhydrazone camphorsulphonate, formed by treatment with 2,4-dinitrophenylhydrazine[6–8]. The second method is based on the formation of salts between sulphonic ions and basic fuchsin, which can be determined photometrically[9].

Both procedures are lengthy, and other substances may interfere in these assays; in the fuchsin method, moreover, a series of five extractions is required to allow a recovery of about 86%.

Gas chromatography can offer an excellent alternative method for the analysis of camphorsulphonic acid. In this communication a quantitative gas chromatographic procedure is described which allows the determination of this compound and its salts, even in complex pharmaceutical formulations.

The method consists in obtaining the free acid, its methylation with diazomethane and analysis of the methyl ester by gas chromatography under suitable operating conditions.

EXPERIMENTAL

A Pye dual-column gas chromatograph (Series 104, Model 64) fitted with a hydrogen-flame detector (FID) was used. Glass columns (210 cm × 4 mm I.D.) packed with 5% w/w SE-30 on 60–80 mesh Chromosorb W (Carlo Erba, Milan) and pre-conditioned before use were employed. During the analysis they were operated isothermally at 173°, while the FID temperature was 200°.

Nitrogen (80 ml/min) was used as the carrier gas, while hydrogen (80 ml/min) and air (320 ml/min) fed the detector. An attenuator setting of 5×10^2 and a backing-off range of × 100 were adopted.

The apparatus was equipped with a Philips PM 8000/01 recorder (1 mV f.s.d.) and the chart speed was 2.5 mm/min. The samples (3–5 μl) were injected with a 10 μl Terumo microsyringe.

Preparation of the calibration curve

d-Camphorsulphonic acid (BDH, Poole, Great Britain) was accurately weighed and dissolved in ether–methanol (9:1) in order to obtain a concentration of 1 mg/ml. Aliquots of this solution (*e.g.*, 1.0; 1.5; 2.0; 2.5; and 3.0 ml) were adjusted to the volume of 3.0 ml with the same mixture of ether–methanol in calibrated test tubes. They were then methylated with diazomethane, prepared according to SCHLENK AND GELLERMAN[10] from *N*-methyl-*N*-nitroso-*p*-toluene-sulphonamide (commercially available as "Diazald" from Aldrich Chem. Co., Inc., Milwaukee, Wisc., U.S.A.), until a yellow-coloured solution was obtained. The volume of the mixture was checked (if not constant, it was readjusted to 3.0 ml with ether–methanol), and 1 ml of internal standard solution (methyl palmitate, Applied Science Lab., Inc., State College, Pa., U.S.A., at a concentration of 2 mg/ml in ether) was added to each tube.

Samples of 3–5 μl were injected, and Fig. 1 shows a typical gas chromatogram. The retention times are respectively 4 min 15 sec for camphorsulphonic acid methyl ester, and 8 min 15 sec for methyl palmitate.

The calibration curve was obtained by plotting the peak height ratios (PHR) of camphorsulphonic acid methyl ester to internal standard against concentrations of camphorsulphonic acid in the final solution.

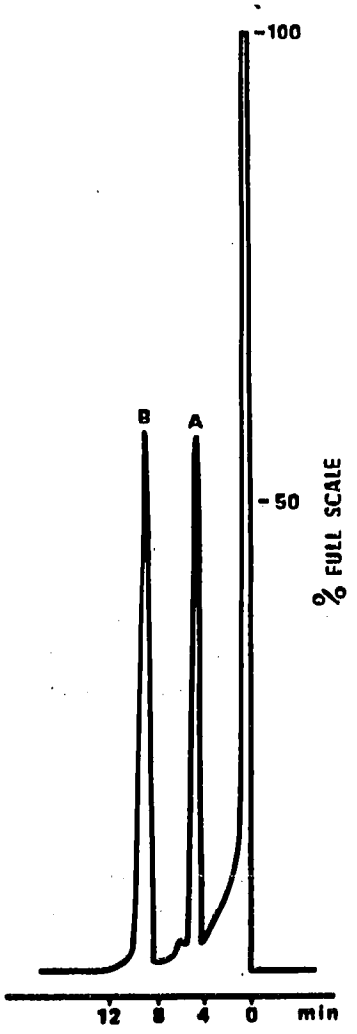


Fig. 1. Gas chromatogram of: A, camphorsulphonic acid methyl ester; and B, methyl palmitate (internal standard). Conditions are reported in the text.

The relationship between detector responses and quantities injected was linear over the whole range of concentrations considered (0.75–3.75 μg of camphorsulphonic acid injected into the column).

PROCEDURE

When camphorsulphonic acid is present as a salt, it is necessary to obtain the free acid. This is done with the use of an ion-exchange resin.

In a typical experiment, a sample containing about 50 mg of calcium camphorsulphonate was diluted to 10 ml with water. Of this solution 8 ml was added to a short column (10 × 1 cm I.D.) filled with strongly acid cation-exchange resin Type I (E. Merck AG, Darmstadt, G.F.R.), suspended and eluted with water.

The first 25 ml of the effluent were collected and an aliquot of this solution (corresponding to about 1.5 mg of camphorsulphonic acid) was evaporated to dryness at room temperature over phosphorus pentoxide, if necessary with the aid of a vacuum pump. Of the ether–methanol mixture (9:1) 3 ml was added to the residue. After

TABLE I

CALCIUM CAMPHORSULPHONATE RECOVERIES

Sample	*Theoretical (mg)*	*Found (mg)*	*Percentage of theoretical*
1	200.0	193.8	96.9
2	200.0	190.0	95.0
3	200.0	190.0	95.0
4	200.0	193.2	96.6
5	200.0	195.0	97.5
6	200.0	193.6	96.8
7	200.0	193.8	96.9
8	200.0	196.8	98.4
9	200.0	193.8	96.9
10	200.0	193.4	96.7
Average recovery: 96.7% (S.D. ± 1.0)			

treatment with diazomethane and checking of the volume (as previously described), 1 ml of internal standard solution (methyl palmitate) was added. Of this final solution 3–5 μl was injected into the column. The PHR was calculated and the concentration of camphorsulphonic acid was determined from the calibration curve.

RESULTS AND DISCUSSION

As shown in Table I, replicate analyses on accurately weighed samples of calcium camphorsulphonate gave a recovery value of 96.7 ± 1.0 (mean of ten analyses ± standard deviation).

TABLE II

ANALYSIS OF CAMPHORSULPHONIC ACID AND ITS SALTS IN COMMERCIAL PHARMACEUTICAL PREPARATIONS

Sample	*Component(s)*	*Label claim*	*Found*[a]	*% found of declared*
Ampoules[b]	Calcium camphorsulphonate	90.0 mg/ml	87.3 mg/ml	97.0
Ampoules[c]	Calcium camphorsulphonate	100.0 mg/ml	94.6 mg/ml	94.6
Drops[d]	Calcium camphorsulphonate and ephedrine camphorsulphonate corresponding to camphorsulphonic acid	144.4 mg/ml	144.1 mg/ml	99.8
Drops	Diethylaminoethyltheophylline camphorsulphonate	250.0 mg/ml	267.5 mg/ml	107.0
Tablets[e]	Calcium camphorsulphonate	100.0 mg/tab.	100.3 mg/tab.	100.3
Suppositories[f]	Calcium camphorsulphonate	200.0 mg/sup.	198.0 mg/sup.	99.0

[a] Mean of three analyses.
[b] 1 ml also contained magnesium chloride (10 mg), vitamin C (6 mg), K (0.6 mg) and P (2 mg).
[c] 1 ml also contained vitamin C (20 mg), cystein chloride (5 mg), and phenyltoloxamine (1 mg).
[d] 1 ml also contained ethanol (0.02 ml).
[e] Each tablet also contained aminopyrine gentisate (250 mg), quinine diascorbate (50 mg), magnesium stearate (22 mg), stearic acid (18 mg) and starch (14 mg).
[f] Each suppository also contained aminopyrine gentisate (400 mg), quinine diascorbate (100 mg), mono-, di- and triglycerides (2 g).

Moreover, the proposed method can be adopted successfully even for the analysis of complex pharmaceutical mixtures.

Table II shows data obtained by assaying a few pharmaceutical preparations produced and commercially available in Italy, some of which contain one of the substances (*i.e.* ascorbic acid) which most commonly interferes with the usual colorimetric assays of camphorsulphonic acid. A prior washing with anhydrous ether was performed in the last sample only (suppositories), in order to remove the fatty components.

In addition to its simplicity and rapidity, a further advantage of this method lies in its specificity, so that it is also suitable for studies of stability.

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