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Note

Gas chromatography of the acetate and nitrate esters of 1,4:3,6-dianhydro-D-sorbitol (isosorbide)

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Isosorbide 2-nitrate (IS-2N), 5-nitrate (IS-5N) and dinitrate (ISDN) are well known vasodilators[1–3]. One of the most popular routes for their synthesis is isosorbide → acetate esters → nitrate esters. Hence, in addition to the three above-mentioned nitrate esters, at certain stages of the synthesis it is possible for the reaction mixture to contain isosorbide 2-acetate (IS-2A), 5-acetate (IS-5A) and diacetate (ISDA), 2-nitrate-5-acetate (IS-2N5A), 2-acetate-5-nitrate (IS-2A5N) and the parent isosorbide (IS), *i.e.*, nine compounds in all.

The gas chromatographic (GC) analysis of the three nitrate esters of isosorbide has been reported[4–9]. Dimov *et al.*[10] analysed mixtures of nitrate and acetate esters of isosorbide. They identified all of the esters by thin-layer chromatography and determined only the nitrate esters by high-performance liquid chromatography. No work on the GC separation of mixtures of nitrate and acetate esters of isosorbide has been reported.

This study was carried out in an attempt to find the most suitable conditions for the GC separation, identification and determination of nitrate, acetate and nitrate–acetate esters of isosorbide in the above-mentioned reaction mixture.

EXPERIMENTAL

Apparatus

The instruments used were a Pye Unicam Model GCD chromatograph with packed glass columns and a Perkin-Elmer Model Sigma 2B chromatograph with an OV-101 WCOT quartz capillary column. Both instruments were equipped with flame-ionization detectors.

Operating conditions

Gas chromatography was carried out on the following columns.

The packed columns contained stationary phases of different polarity: (A) 1.5 m × 2 mm I.D. packed with 5% OV-101 on Gas-Chrom Q, 80–100 mesh (Carlo Erba), column temperature 105°C; (B) 1.5 m × 2 mm I.D. packed with 3% OV-17 (Varian Aerograph) on Gas-Chrom Q, column temperature 120°C; (C) 0.9 m × 2 mm I.D. packed with 3% OV-225 on Chromosorb W HP (Merck), column temperature 135°C; and (D) 1.5 m × 2 mm I.D. packed with 3% neopentyl glycol succinate

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(NPGS) (Varian Aerograph) on Chromosorb W HP, column temperature 150°C. All columns were operated isothermally, the detector temperature was 200°C and the injection port temperature was 160°C. The argon carrier gas flow-rate was 25 ml/min. On-column injection was used.

The capillary column was quartz, 25 m × 0.19 mm I.D., coated with OV-101 (WCOT). The oven temperature was 145°C (isothermal), injector temperature 160°C and detector temperature 200°C. The argon carrier gas flow-rate was 0.45 ml/min and the splitting ratio was 1:50.

All ester samples were synthesized in our laboratory.

RESULTS AND DISCUSSION

Using the packed columns, initially isothermal and temperature-programmed runs were made. As temperature programming did not give better separations, the isothermal mode was used in subsequent work.

Table I shows the retention times of the esters relative to that of isosorbide = 1.00 at the optimum temperature determined for each column. Columns C and D showed a definite selectivity for nitro esters with the nitro group at the C-5 position.

On the other hand, in spite of their selectivity, none of the four stationary phases could completely separate all the compounds in the mixture. Compounds 2 and 5 (see Table I) appeared as unresolved peaks on column A, compound 4 appeared as a shoulder with 7 and there was a poor separation of 7 and 9. Compounds 2 and 5 and 4 and 9 were eluted as common peaks on column. There was no separation between compounds 1 and 2, 6 and 8 or 3 and 4 on column C. A common peak of 6 and 9 was observed on column D.

Owing to the impossibility of separating all of the compounds on packed columns, a capillary column with OV-101 as the stationary phase was used. This phase

TABLE I

RELATIVE RETENTION TIMES OF ACETATE AND NITRATE ESTERS OF ISOSORBIDE ON FOUR PACKED COLUMNS

Retention times relative to that of isosorbide, taken as 1.00. Absolute retention times of isosorbide: column A, 4.35 min; B, 4.97 min; C, 4.53 min; and D, 14.33 min. The results are given at the optimum temperature for each column (see Experimental).

Peak No.	*Compound*	*Column*			
		A (OV-101)	*B (OV-17)*	*C (OV-225)*	*D (NPGS)*
1	Isosorbide	1.00	1.00	1.00	1.00
2	Isosorbide 2-nitrate	1.58	1.50	1.00	0.85
3	Isosorbide 5-nitrate	3.15	3.77	4.37	3.52
4	Isosorbide dinitrate	4.75	6.00	4.37	2.74
5	Isosorbide 2-acetate	1.77	1.50	0.83	0.59
6	Isosorbide 5-acetate	2.83	3.00	2.43	1.95
7	Isosorbide diacetate	5.21	4.98	2.04	1.14
8	Isosorbide 2-nitrate-5-acetate	4.44	4.52	2.43	1.43
9	Isosorbide 2-acetate-5-nitrate	5.36	6.00	3.44	1.95

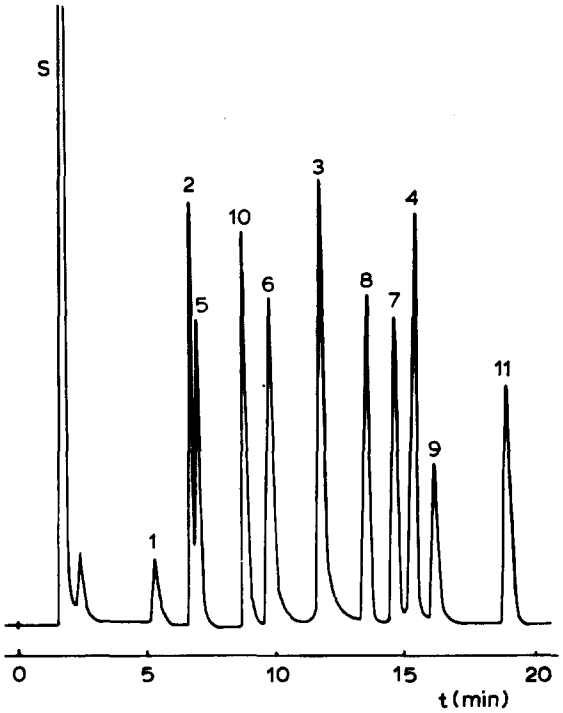

Fig. 1. GC of mixture of the nitrate and acetate esters of isosorbide, separated on an OV-101 quartz capillary WCOT column (25 m × 0.19 mm I.D. Column temperature, 145°C (isothermal); argon carrier gas flow-rate, 0.45 ml/min; splitting ratio, 1:50. S = solvent (chloroform); peaks identified as in Table II.

TABLE II

RELATIVE RETENTION TIMES OF ACETATE AND NITRATE ESTERS OF ISOSORBIDE ON OV-101 QUARTZ CAPILLARY COLUMN

Retention times relative to that of isosorbide, taken as 1.00 (absolute retention time = 5.34 min). Compounds 10 and 11 are internal standards.

Peak No.	*Compound*	*Relative retention time*
1	Isosorbide	1.00
2	Isosorbide 2-nitrate	1.28
3	Isosorbide 5-nitrate	2.21
4	Isosorbide dinitrate	2.87
5	Isosorbide 2-acetate	1.33
6	Isosorbide 5-acetate	1.86
7	Isosorbide diacetate	2.76
8	Isosorbide 2-nitrate-5-acetate	2.57
9	Isosorbide 2-acetate-5-nitrate	3.03
10	Isomanide nitrate	1.66
11	Isomanide dinitrate	3.53

was preferred because it was the only one on which all compounds had separate peaks, even though the separation was not the best. On the other three phases at least one pair of compounds appeared as a common peak.

As can be seen from Fig. 1, on the capillary column the individual esters were separated and only compounds 2 and 5 were partially resolved. The time for analysis is shorter than that when packed columns were used.

Using the established optimum chromatographic conditions, internal standards for quantitative determination were chosen, namely isomanide mono- and dinitrate. As can be seen from Fig. 1, they are completely separated from the other compounds in the mixture.

The retention times of the investigated esters on the OV-101 capillary column relative to isosorbide are given in Table II.

REFERENCES

1 M. Kaltenbach, W. D. Bussmann and A. Schrey, *Mononitrat,* Universitätsdruckerei und Verlag Dr. C. Wolf und Sohn, Munich, 1980.
2 K. Dietmann, G. Sponer and E. Voss, *Med. Welt,* 32 (1981) 481.
3 E. Heeg and A. Langner, *Med. Welt,* 32 (1981) 499.
4 I. W. F. Davidson, F. J. Dicarlo and E. I. Szabo, *J. Chromatogr.,* 57 (1971) 345.
5 K. H. Göbbeler, *Pharm. Ztg.,* 27 (1971) 961.
6 M.-T. Rosseel and M. G. Bogaert, *J. Chromatogr.,* 64 (1972) 364.
7 M. T. Rosseel and M. G. Bogaert, *J. Pharm. Sci.,* 62 (1973) 754.
8 J. O. Malbica, K. Monson, K. Neilson and R. Sprissler, *J. Pharm. Sci.,* 66 (1977) 384.
9 M. T. Rosseel and M. G. Bogaert, *J. Pharm. Sci.,* 68 (1979) 659.
10 N. Dimov, N. Agapova, Sh. Levy and Iv. Yanachkov, *J. Chromatogr.,* 285 (1984) 515.