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Note

Separation of diamantane-3-oneoxime stereoisomers by preparative high-performance liquid chromatography

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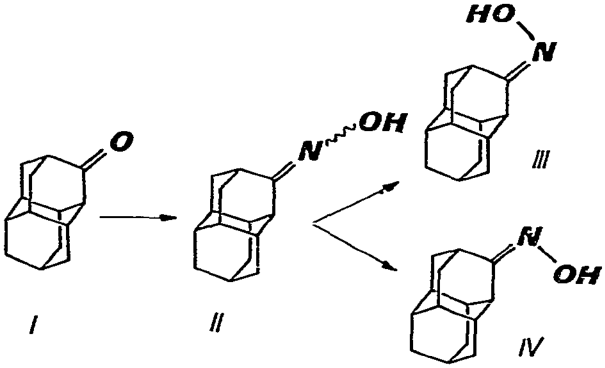
During the preparation of diamantane-3-oneoxime (II) by the reaction of diamantanone (I) with hydroxylamonium chloride and sodium hydroxide, a mixture of two stereoisomers[1] is formed, *viz.* the *E*-form (III) and the Z-form (IV).



As the oximes are thermally unstable and therefore cannot be subjected to gas chromatography, a method has been elaborated for their analysis using liquid chromatography. This paper describes a method for the separation of the above two stereoisomers by preparative high-performance liquid chromatography (HPLC).

EXPERIMENTAL

Separation of stereoisomers

The mixture of diamantane-3-oximes (II) was separated into individual compounds on a Chromatospac Prep 100 preparative chromatograph (Jobin Yvon, Longjumeau, France). A 200-g amount of silica gel of irregular shape (particle size 10–20 μm) was packed into a column of 40 mm I.D.; the height of the bed was 270 mm. The adsorbent was obtained from silica gel L-40 (Lachema, Brno, Czechoslovakia) by screening on a Zig-Zag classifier (Alpine, Augsburg, G.F.R.), washing out with methanol and drying at 200°C for 5 h before use.

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n-Pentane (Reakhim, U.S.S.R.) containing 4% (w/w) of 2-propanol was used as the mobile phase. The mobile phase was degassed before use by connecting its reservoir in the preparative chromatograph to a vacuum for 10 min. The flow-rate of the mobile phase was 18 ml/min at a pressure of 150 kPa. A 10% (w/w) solution of the sample in *n*-heptane–2-propanol (96:4, w/w) was injected using a sample injection reservoir. The amount of sample solution injected varied from 1 to 15 ml. Detection was effected with a refractive index (RI) (Varian, Palo Alto, CA, U.S.A.). Individual fractions were collected according to the shape of the chromatographic curve.

Analysis of fractions

HPLC analysis of fractions obtained by preparative separation was carried out on a Varian 8500 instrument with an RI detector. The column (250 × 3 mm I.D.) was packed with 10-μm spherical silica gel (Pragosil). The flow-rate of the mobile phase [*n*-heptane–2-propanol (98:2, w/w)] was 1 ml/min.

The crystal structure of the *Z*- and *E*-forms of diamantane-3-oneoxime was determined by three-dimensional X-ray diffraction analysis[2].

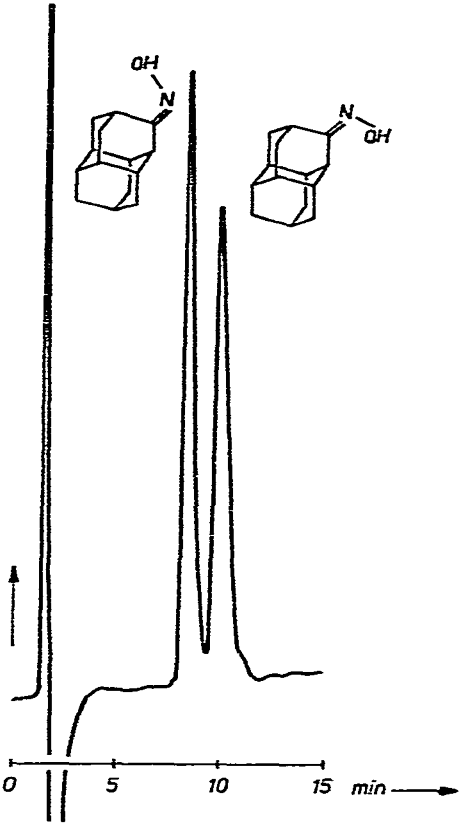

Fig. 1. Analytical separation of diamantane-3-oneoxime stereoisomers. Column: 250 × 3 mm I.D. packed with spherical silica (10 μm). Mobile phase: *n*-heptane–2-propanol (98:2, w/w), flow-rate 1 ml/min. Detection: RI detector.

RESULTS AND DISCUSSION

An analytical column of relatively high efficiency was used; the number of theoretical plates for naphthalene (capacity ratio, $k' = 1.6$) was 9000 (determined using *n*-pentane as the mobile phase) and 6000 for phenanthrene ($k' = 3.6$).

A chromatogram of the two diamantanone oximes is presented in Fig. 1. As the separation of these stereoisomers is difficult (separation factor, $\alpha \doteq 1.09$), the preparative parameters were chosen so as to achieve maximal efficiency for sufficiently large amounts of sample. Silica gel particles of size 10–20 μm were used, *i.e.*, the minimal size fraction that was obtainable from the original material in a sufficiently large amount. The use of 200 g of the silica gel resulted in a column of nearly the maximal length (275 mm), allowing the whole amount of stationary phase to be introduced into the column at once.

n-Heptane–2-propanol (98:2, w/w) was used as the mobile phase for the analytical separation, but for preparative purposes *n*-pentane was used instead of *n*-heptane as it is more readily available (particularly UV-grade material), is easily regener-

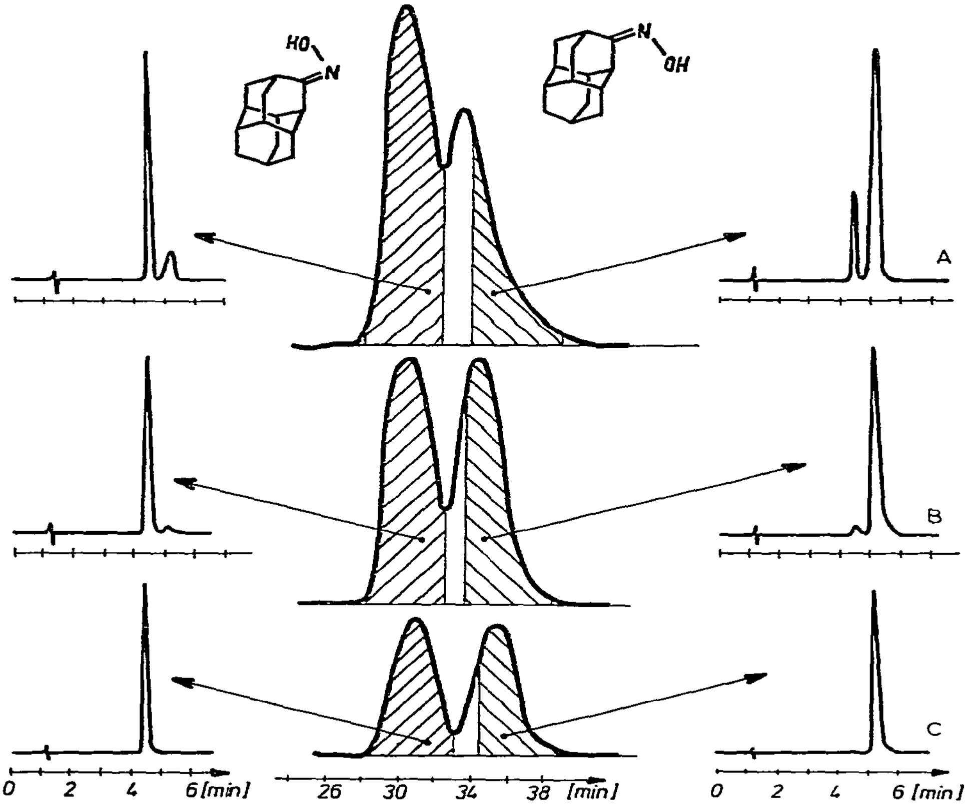

Fig. 2. Preparative chromatograms for various injection volumes, together with analytical chromatograms for the fractions obtained. Preparative run: column, 270 × 40 mm I.D. packed with irregular silica (10–20 μm); mobile phase, *n*-heptane–2-propanol (96:4, w/w), flow-rate 18 ml/min. Analytical run: column, 250 × 3 mm I.D. packed with spherical silica (10 μm); mobile phase, *n*-heptane–2-propanol (98:2, w/w), flow-rate 1 ml/min. Detection: RI detector. Amounts injected: A, 1.5 g; B, 0.9; C, 0.5 g.

ated, has a lower viscosity and is cheaper. Also, the separation of *n*-pentane from the fractions obtained is easy, owing to its low boiling point. It was also found that a much better separation during the preparation is possible when *n*-pentane was used instead of higher hydrocarbons with similar properties such as *n*-heptane and isooctane. In contrast to the analytical column separation, the contents of 2-propanol in the mobile phase had to be increased to 4%.

The flow-rate of the mobile phase was chosen on the basis of test experiments; the testing was carried out on a preparative column using dry *n*-pentane as the mobile phase. The number of theoretical plates for a column packed with an identical amount of the same silica gel (flow-rate 20 ml/min) was determined to be 5800 for naphthalene ($k' = 2.0$) and 6100 for phenanthrene ($k' = 4.1$).

When injecting the optimal amount of 0.5 g of the compound, it was possible to obtain both isomers sufficiently pure without further preparation. However, it is obvious that with increasing amount injected the separation becomes poorer and thus it is necessary either to collect only parts of the relevant peaks, or to repeat the preparation. Fig. 2 shows some preparative chromatograms for various the injected volumes, together with chromatograms of prepared fractions for comparison.

Of the total amount of 17.0 g of a mixture containing 52% of the *E*-form and 48% of the Z-form of diamantane-3-oneoxime, the preparation resulted in 6.0 g of the *E*-form and 4.5 g of the *Z*-form, respectively, in addition 3.5 g of a mixture of both compounds.

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