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Note

Preparative high-performance liquid chromatography in the synthesis of diamantane derivatives*

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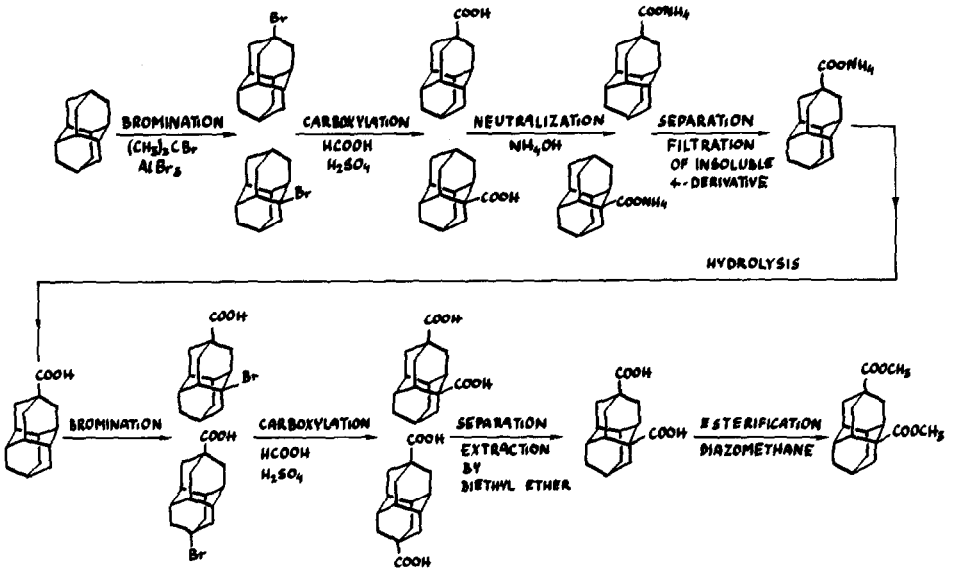
In many organic syntheses complex mixtures of products are often obtained, the separation of which into individual components may be very difficult, particularly when it is necessary to prepare pure isomers. In the case of diamantane, 3 mono- and 23 disubstituted derivatives with identical substituents may be formed. In order to obtain individual isomers, it is often necessary to devise a multi-stage synthesis, for example dimethyl diamantane-1,4-dicarboxylate was prepared according to the procedure shown in Scheme 1.



Scheme 1.

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Preparative high-performance liquid chromatography (HPLC) may be used to simplify the preparation of pure isomers significantly. Instead of a time-consuming multi-stage synthesis of an individual isomer, simple reactions resulting in a mixture of isomers are utilized. The resulting mixture is then separated into individual compounds by means of preparative HPLC.

We have applied HPLC to the preparation of individual isomers from two mixtures of dibromodiamantanes (mixtures A and B) and one mixture of dimethyl diamantanedicarboxylates (mixture C).

EXPERIMENTAL

Synthesis of diamantane derivative mixtures

Mixture A. Bromination of diamantane by refluxing with dry bromine for 38 h yields mixture A. The individual isomers in the mixtures are listed in Table I.

Mixture B. Mixture B was synthesized from diamantanone in four steps: (i) bromination of diamantanone, catalysed by $AlBr_3$, by refluxing with bromine; (ii) hydrolysis of 9- and 11-bromodiamantanones by 65% nitric acid at 80°C; (iii) reduction of hydroxyketones by $LiAlH_4$ in diethyl ether; and (iv) reaction of 1,5- and 3,9-diamantanediols with $SOBr_2$, yielding the coresponding dibromodiamantanes.

Mixture C. Mixture C was synthesized from mixture A in two steps: (i) dicarboxylic acids were prepared by Koch–Haaf carboxylation of mixture A; and (ii) the resulting acids were esterified with diazomethane in diethyl ether.

Separation of individual isomers

The mixtures of dibromodiamantanes and dimethyl diamantanedicarboxylates were 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. to a bed height of 270 mm. The adsorbent was obtained from silica gel L-40 (Lachema, Brno, Czechoslovakia) as described previously[2]. The mobile phase used for the separation of dibromodiamantanes was *n*-pentane (Reakhim, U.S.S.R.), dried by per-

TABLE I

COMPOSITION OF SYNTHESIZED MIXTURES

Mixture	*Compound*	*Amount (%, w/w)*
A	1-Bromodiamantane	2.6
	1,4-Dibromodiamantane	12.0
	1,6-Dibromodiamantane	52.7
	1,7-Dibromodiamantane	32.7
B	1,5-Dibromodiamantane	25.6
	3,9-Dibromodiamantane	59.2
	Unknown	15.2
C	Methyldiamantane-1-carboxylate	23.6
	Dimethyldiamantane-1,4-dicarboxylate	34.9
	Dimethyldiamantane-1,6-dicarboxylate	12.9
	Dimethyldiamantane-1,7-dicarboxylate	28.6

TABLE II

CONDITIONS FOR PREPARATIVE HPLC SEPARATIONS

Mixture	*Mobile phase (%, v/v)*	*Flow-rate (ml/min)*	*Amount introduced (g)*	*Injection mode*	*No. of compounds isolated*
A	Dry *n*-pentane	23	2 × 0.8	Solid introduction[4]	4
B	Dry *n*-pentane	23	2 × 0.6	Solid introduction[4]	2
C	*n*-Pentane–diethyl ether (90:10, v/v)	22–24	0.3–0.4	Solid introduction*	4

* The sample was mixed with silica in a mortar in the presence of chloroform. The chloroform was partially evaporated and the mixture was introduced as described previously[4].

colation through a glass column (40 mm I.D.), which was packed with coarse silica activated by heating at 200°C for 5 h. The composition of the mobile phase was chosen on the basis of analytical HPLC of separated compounds[3]. A refractive index (RI) detector (Varian, Palo Alto, CA, U.S.A.) was used. Table II lists further conditions used for the preparative HPLC separations.

Analysis of fractions

Gas–liquid chromatographic analyses of the fractions obtained by preparative separation were carried out on a Chrom 4 gas chromatograph (Laboratory Instruments, Prague, Czechoslovakia) at 180°C. The column used (1200 × 3 mm I.D.) was packed with 3% GE XF-1150 (General Electric, U.S.A.) on Chromosorb W HMDS (Lachema).

RESULTS AND DISCUSSION

Mixture A

In order to achieve the efficient separation of low-polarity halogen derivatives, it was necessary to use a chromatographic system in which the stationary and mobile phases did not contain even trace amounts of water or other polar compounds (*e.g.*, alcohols). The presence of such compounds resulted in such a rapid elution of the derivatives concerned (dibromodiamantanes in this instance) that an adequate separation is not attained. For preparation, we used mixture A from which 1,6-dibromo derivatives had been partially removed via crystallization. Fig. 1 shows the analytical chromatogram of this mixture. Two preparations yielded the following: 0.15 g of 1-bromodiamantane, 0.4 g of 1,4-dibromodiamantane (both of purity over 98%), 0.15 and 0.2 g of 1,7-dibromodiamantane (purity 97% and 90%, respectively) and 0.1 and 0.15 g of 1,6-dibromodiamantane (purity 97% and 80%, respectively). Further, 0.2 g of a mixture of 1,6- and 1,7- derivatives was obtained. The chromatogram of this preparation is shown in Fig. 2.

Mixture B

The conditions for the separation of mixture B were analogous to those used

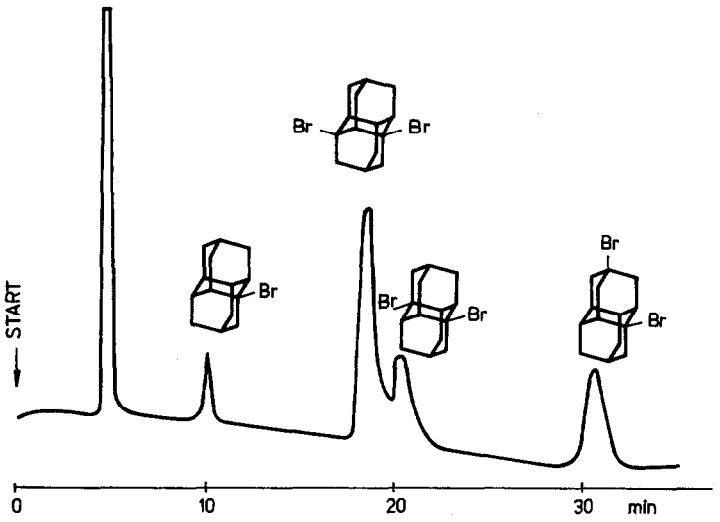

Fig. 1. Analytical chromatogram of dibromodiamantanes (mixture A after partial removal of 1,6-dibromodiamantane by crystallization). Column, 250 × 8 mm I.D., packed with 7.5 μm silica gel. Mobile phase: moisture-controlled *n*-pentane; 0.5% water in MCS (= moisture-control system)[3]. Flow-rate, 100 ml/h. Refractive index (RI) detector.

for mixture A. A dry system (*i.e.*, both the mobile phase and silica) was used. The separation of mixture B yielded 0.25 g of 1,5-dibromodiamantane and 0.35 g of 3,9-dibromodiamantane. Figs. 3 and 4 illustrate the analytical and preparative separations of these compounds.

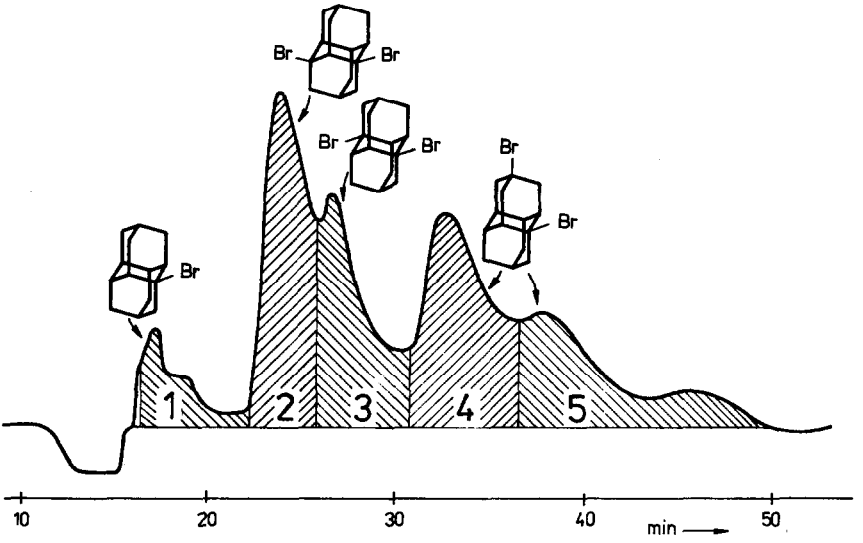

Fig. 2. Preparative separation of mixture A. Column, 270 × 40 mm I.D., packed with irregular silica (10–20 μm); mobile phase, dry *n*-pentane. Flow-rate, 23 ml/min. RI detector.

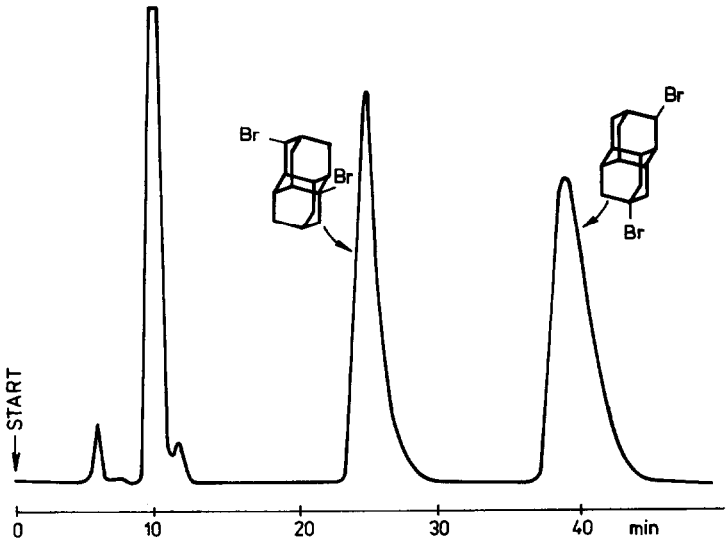

Fig. 3. Analytical chromatogram of 1,5- and 3,9-dibromodiamantanes (mixture B). Column, 250 × 8 mm I.D., packed with 7.5 μm silica gel. Mobile phase: moisture-controlled *n*-pentane; 0.5% water in MCS (= moisture-control system). Flow-rate, 100 ml/h. RI detector.

Mixture C

The strategy for the preparative separation of mixture C was established on the basis of the chromatogram shown in Fig. 5. In order to achieve the highest possible efficiency of the separation, the amount of the sample introduced was rela-

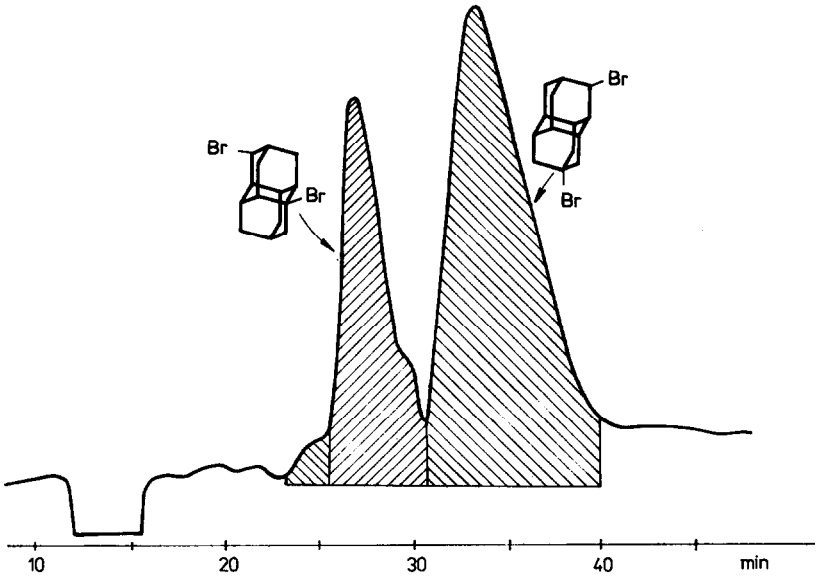

Fig. 4. Preparative separation of mixture B. Column, 270 × 40 mm I.D., packed with irregular silica (10–20 μm); mobile phase, dry *n*-pentane. Flow-rate, 23 ml/min. RI detector.

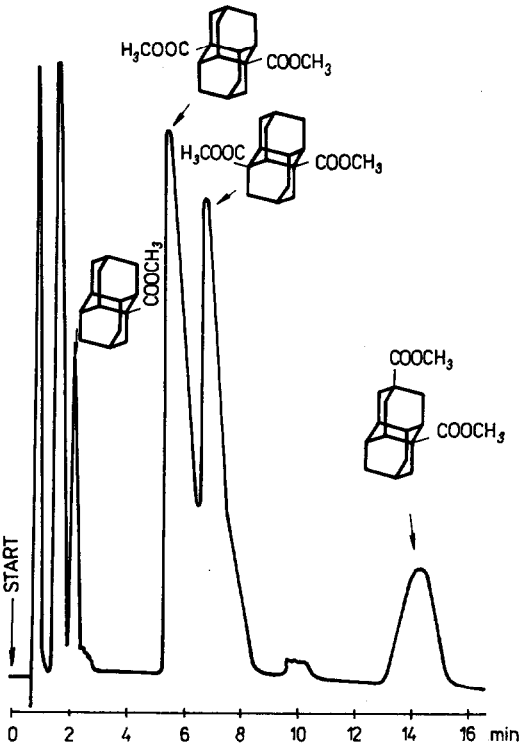

Fig. 5. Analytical chromatogram of dimethyl diamantanedicarboxylates. Column, 250 × 4 mm I.D., packed with 8 μm silica gel. Mobile phase: *n*-heptane–diethyl ether (95:5, w/w). Flow-rate, 100 ml/h. RI detector.

tively low, *i.e.*, 0.3–0.4 g. The preparative chromatogram of the original mixture C and the chromatogram of the second separation are both shown in Fig. 6. Fraction 1 consisted of nearly pure methyl diamantane-1-carboxylate. Repeated preparation of fractions 2 and 5 yielded dimethyl diamantanedicarboxylates in positions 1,6- and 1,4-, respectively.

The combined fraction 4, consisting of a mixture of 30% of the 1,6-isomer and 70% of the 1,7-isomer, was again prepared in order to obtain pure 1,7-isomer. The separation was carried out with 0.5 g of sample for a single preparation. As a result of these repeated preparations, another unidentified dimethyl ester of a diamantanedicarboxylic acid was obtained (verified by mass spectrometry). Owing to the small amount of the compound (0.07 g), its structure was not determined by means of ^{13}C NMR spectroscopy.

A total of 2.3 g of mixture C was separated. Seventeen preparations resulted in the following compounds: 0.15 g of methyl diamantane-1-carboxylate, 0.5 g of the 1,6- derivative, 0.55 g of the 1,7- derivative and 0.35 g of dimethyl diamantane-1,4-dicarboxylate.

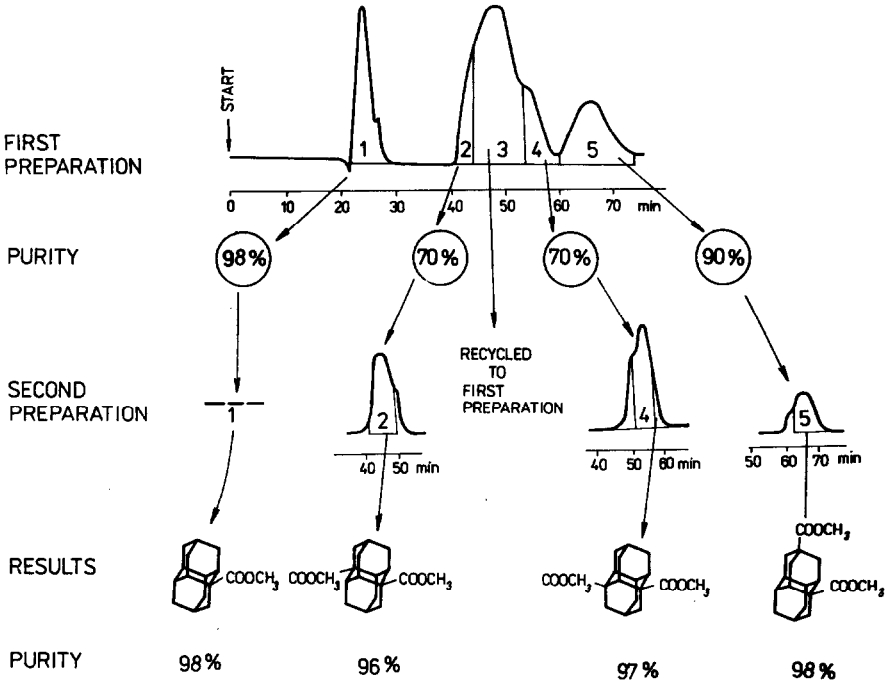

Fig. 6. Preparative separation of mixture C. Column, 270 × 40 mm I.D., packed with irregular silica (10–20 μm); mobile phase, *n*-pentane–diethyl ether (90:10, v/v). Flow-rate, 22–24 ml/min. RI detector.

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