SYNTHESIS AND SEPARATION OF STEREOISOMERS OF 1,4- AND 2,4-DIHYDROXYADAMANTANES

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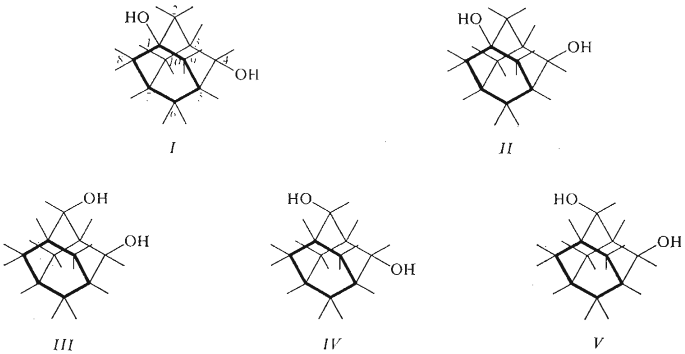
Mixture of isomers of 1,4-dihydroxyadamantane has been prepared by reduction of 5-hydroxyadamantane-2-one, the isomeric 2,4-dihydroxyadamantanes have been prepared by reduction of adamantane-2,4-dione. The mixtures of 1,4- and 2,4-dihydroxyadamantanes have been separated into pure stereoisomers by elution chromatography on a silica gel column using benzene and diethyl ether as eluents. Structures of the individual isomers have been confirmed by NMR spectroscopy.

Compounds with adamantane structure are used nowadays for preparation of medicaments, thermostable polymers, special lubricating oils and a number of other compounds, and, therefore, preparation and study of properties of basic adamantane derivatives are given increased attention. Out of the group of double-substituted oxygen derivatives of adamantane, properties of some pure stereoisomers have not yet been studied due to their difficult separation from isomeric mixtures. The aim of the present paper is to describe the separation of 1,4-dihydroxyadamantanes and 2,4-dihydroxyadamantanes into pure stereoisomers (Scheme 1). In the following text the individual sterical isomers are denoted by the letters *a*, *e* meaning axial and equatorial position of the respective substituent.

Preparation of isomer mixtures of the mentioned dihydroxyadamantanes is described in literature, so far, however, not all the isomers have been prepared in pure form. Only $2^a,4^a$-dihydroxyadamantane was prepared by direct method (without separation of the isomers). It is formed by epoxidation of protoadamantene with *m*-chloroperbenzoic acid in dichloromethane and subsequent splitting of the epoxide by acidification and boiling in 80% acetone[1]. It can be prepared[2] from 4^a-hydroxyadamantane-2-one by reduction with $LiAlH_4$.

Mixture of the isomeric 1,4-dihydroxyadamantanes (*I*, *II*) can be prepared by action of 70% sulphuric acid on 2-hydroxyadamantane[3] or by oxidation of adamantane with 18—25% oleum[4]. For preparation of the mixture of isomeric 1,4-dihydroxyadamantanes we chose the not yet described reduction of 5-hydroxyadamantane-2-one with respect to simplicity of the reaction and availability of 5-hydroxyadamantane-2-one from adamantane-2-one[5,6].

Mixture of the isomeric 2,4-dihydroxyadamantanes (*III*, *IV*, *V*) can be prepared by reduction of 4-hydroxyadamantane-2-one with zinc(II) borohydride[7,8] or by reduction of adamantane-2,4-dione with $LiAlH_4$[2].



SCHEME 1

In literature there are no reports giving detailed procedure of separation of the stereoisomeric mixtures of 1,4- and 2,4-dihydroxyadamantanes. Separation of the mixture of 2,4-dihydroxyadamantanes is only briefly mentioned in a recent paper by Duddeck[9]. The separation was carried out on a silica gel column using ligroin–acetone mixture as eluent.

For preparation of the isomeric mixture of 2,4-dihydroxyadamantane we chose adamantane-2,4-dione as the starting raw material which was obtained by oxidation of 4-hydroxyadamantane-2-one with the Jones reagent[10]. 4-Hydroxyadamantane-2-one is produced by rearrangement of 4-oxahomoadamantane-5-one in sulphuric acid [11–13] or by Beckmann rearrangement of adamantane-2-one oxime in sulphuric or polyphosphoric acid[14,15].

EXPERIMENTAL

Methods

The gas chromatography analyses were carried out with a Chrom IV apparatus equipped with a flame ionization detector using nitrogen as the carrier gas. Glass column 120 cm × 3 mm was packed with Chromosorb W (170—250 μm) with 5% FFAP (Supelco, USA), temperature 190°C.

The individual fractions from column chromatography were checked also by liquid chromatography using a Varian 8500 apparatus equipped with a differential refractometer (column of 250 mm length packed with silica gel with chemically bound phase CH-10 (Varian, USA), eluent phase $CH_3OH + H_2O$ (3 : 7), flow rate 10 ml/h, pressure 6·06 MPa).

Molecular mass and structure of the isolated compounds were determined with a mass spectrometer connected with a gas chromatograph type Gas-Chromatograph Mass-Spectrometer LKB 9000.

The NMR spectra were measured with a Varian XL/100—15 apparatus (100 MHz) at 37°C, using tetramethylsilane (TMS) as internal standard. For the measurements the samples were weighed and dissolved in deuteriochloroform or deuteriopyridine (for less soluble substances).

For separation of isomer mixtures of 1,4- and 2,4-dihydroxyadamantanes we used a glass column 140 cm × 30 mm packed with 460 g silica gel (grain size 140 μm) activated at 180°C for 6 hours.

All the solvents used for the elution chromatography were dried before use over molecular sieves (4 Å) for 24 hours. The melting points were determined in sealed capillaries and are not corrected.

1,4-Dihydroxyadamantanes

Mixture of the isomers *I* and *II* was prepared by reduction of 5-hydroxyadamantane-2-one with $LiAlH_4$ in absolute ether with the yield 92%. Crystallization from ethyl acetate and sublimation (200°C, 2·0 kPa) gave crystalline solid melting at 340—341°C (ref.[3] m.p. 327—331°C). For $C_{10}H_{16}O_2$ (168·3) calculated: 71·36% C, 9·58% H; found: 71·38% C, 9·56% H. Liquid chromatography showed that the substance contained 2 isomers at a ratio 3 : 2. The mixture *I* + *II* (2·15 g) was dissolved in 400 ml mixture benzene–diethyl ether (1 : 1), the solution was introduced on a silica gel column and eluted with total 26455 ml of the mentioned solvent mixture. The solvents were distilled off, and the residue was purified by sublimation (130°C, 2·0 kPa) to give 1·23 g white crystalline solid m.p. 336—337°C (the isomer *I*). For $C_{10}H_{16}O_2$ (168·3) calculated: 71·36% C, 9·58% H; found: 71·35% C, 9·54% H. ^{1}H-NMR (δ): H_2 — 4·18, $H_{8a,10a}$ — 2·48, $H_{1,3}$ — 2·26, $H_{8a,10c}$ — 1·46, the rest — 2·04—2·20.

Further elution of the column with 4910 ml mixture benzene–diethyl ether (1 : 1) gave 0·1 g intermediate fraction (mixture of the isomers *I* and *II*). Then the elution was continued with 3125 ml pure diethyl ether to give 0·70 g product. The latter was purified by sublimation (180°C, 2·0 kPa) and gave 0·42 g crystalline solid m.p. 352—353°C (the isomer *II*). For $C_{10}H_{16}O_2$ (168·3) calculated: 71·36% C, 9·58% H; found: 71·30% C, 9·51% H. ^{1}H-NMR (δ): H_2 — 3·98, $H_{4a,9a}$ — 2·54, $H_{1,3}$ — 2·27, H_7 — 1·97, $H_{4e,9e}$ — 1·72, the rest — 1·5—1·9.

2,4-Dihydroxyadamantanes

Mixture of the isomers *III*, *IV* and *V* was prepared by reduction of adamantane-2,4-dione with $LiAlH_4$ in absolute ether with the yield 93%. After sublimation (150°C, 2·0 kPa) the crystalline solid melted at 343—347°C. For separation of the mixture of isomeric 2,4-dihydroxyadamantanes (*III*, *IV*, *V*) we used a glass column 140 cm × 30 mm packed with 370 g silica gel (grain size 140 μm) activated at 180°C for 5 hours. The solvents were dried with sodium metal and with molecular sieves (4 Å) before use. The mixture *III* + *IV* + *V* (2·1 g) was dissolved in 300 ml benzene and introduced on the column. Elution of the column with 2900 ml benzene washed out the impurities only. In the course of further elution (total 7000 ml) the diethyl ether content was gradually increased by 5% until final benzene : diethyl ether ratio 1 : 1, when the first component began to be eluated. From the total 8760 ml eluate (benzene : diethyl ether = 1 : 1) we isolated 0·90 g product which was further purified by sublimation (160°C, 2·0 kPa) to give 0·80 g crystalline solid m.p. 359—360·5°C (the isomer *III*); ref.[1] and ref.[2] give m.p. 305—310°C and 312—326°C, respectively. ^{1}H-NMR (δ): H_2 — 3·98, $H_{4a,9a}$ — 2·54, $H_{1,3}$ — 2·27, H_7 — 1·97, $H_{4e,9e}$ — 1·72, the rest — 1·5—1·9. For $C_{10}H_{16}O_2$ (168·3) calculated: 71·36% C, 9·58% H found: 71·29% C, 9·52% H.

Further elution of the column with the 1 : 1 mixture of benzene and diethyl ether (1055 ml total) gave two intermediate fractions from which total 0·07 g mixture of isomers *III* and *IV* was obtained. Next portion (3 880 ml mixture benzene–diethyl ether 1 : 1) gave 0·33 g crystalline solid; its sublimation (150°C, 2·0 kPa) and crystallization from benzene gave 0·24 g substance melting at 333—334°C (isomer *IV*). ^{1}H-NMR (δ): $H_{2a,4a}$ — 4·14, the rest — 1·4—2·8. For $C_{10}H_{16}O_2$ (168·3) calculated: 71·36% C, 9·58% H; found: 71·30% C, 9·52% H.

Continuing in the elution (1 100 ml mixture benzene–diethyl ether 1 : 1) we isolated two intermediate fractions of overall weight 0·06 g containing the isomers *IV* and *V*. Then the column was eluted with 8 620 ml of the mixture benzene–diethyl ether 1 : 1. The solvents were distilled off and the residue was purified by sublimation (170°C, 2·0 kPa) to give 0·56 g white crystalline solid m.p. 350·5—352°C (the isomer *V*). For $C_{10}H_{16}O_2$ (168·3) calculated: 71·36% C, 9·58% H; found: 71·32% C, 9·56% H. ^{1}H-NMR (δ): H_{2e} — 4·86, H_{4a} — 4·32, the rest — 1·4—2·8.

DISCUSSION

As preparation of 2,4-dihydroxyadamantanes by reduction of 4-hydroxyadamantane-2-one with $LiAlH_4$ gives only small amount of $2^a,4^e$-dihydroxyadamantane (*V*), we used adamantane-2,4-dione as the starting material for reduction. In this way mixture of isomers was obtained containing the compounds *III*, *IV* and *V* in approximate ratio 5 : 2 : 3.

All the three isomers (*III*, *IV*, *V*) can be separated on a silica gel column by gradual elution with a solvent mixture of the same elution power (benzene–diethyl ether 1 : 1). The diaxial isomer is eluted first, followed by the diequatorial isomer; the compound *V* is eluted as the last. The mentioned order agrees with the data by Duddeck[9].

Different polarity of the isomers *III*, *IV* and *V* is evident from their different solubility in non-polar solvents. Whereas the compound *III* is well soluble *e.g.* in cyclohexane, the compounds *IV* and *V* dissolve in this solvent very little. With respect to limited solubility of the compounds *IV* and *V* in deuteriochloroform their ^{1}H-NMR spectra were measured in deuteriopyridine.

Mixture of the isomeric 1,4-dihydroxyadamantanes contains the compounds *I* and *II* in approximate ratio 3 : 2. Polarity difference of the two isomers is somewhat higher than that of the isomeric 2,4-dihydroxyadamantanes, so that by their separation by elution chromatography on silica gel the more polar eluent (diethyl ether) for elution of the second isomer (*II*) from the column should be used.

Except for the compound *III*, melting points of the compounds *I* – *V* have not yet been published. The compound *III* isolated by us has the melting point higher by 25°C and 50°C than that given in ref.[2] and ref.[1], respectively, which indicates that in the both cases mixtures of isomers were investigated instead of the pure substance *III*.

Constitution of the studied dihydroxyadamantanes was confirmed by measurement of their ^{1}H-NMR spectra in the presence of shift reagents[16] and by ^{13}C- and ^{29}Si-NMR spectra of the respective bis-(trimethylsiloxy) derivatives[17,18].

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