SYNTHESIS, SEPARATION, AND IDENTIFICATION OF 4-BROMOADAMANTAN-2-ONE STEREOISOMERS

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A one-step synthesis of mixture of stereosiomers of 4-bromoadamantan-2-one based on the reaction of adamantan-2-one with hydroxylamine hydrochloride in hydrobromic acid is described. The pure stereoisomers were isolated by elution chromatography on silica gel, and their NMR spectra with the $Eu(FOD)_3$ shift reagent, mass spectra, IR spectra, and dipole moments were measured.

The published procedures developed for preparation of the 4-bromoadamantan-2-one stereoisomers comprise complex, multistep syntheses giving very low yields. Snatzke and Eckhardt[1] started from adamantan-4,8-dione-2-carboxylic acid methyl ester, which in three stages afforded the equatorial stereoisomer of adamantan-2-one-4-carboxylic acid; the latter gave *via* the Hunsdiecker degradation a mixture of the 4-bromoadamantan-2-one equatorial and axial steroisomers in the ratio 2 : 1. The mixture was then separated by elution chromatography. The method of Udding and coworkers[2] starts from dehydroadamantane, which reacts with N-bromosuccinimide in wet dimethyl sulphoxide to give 2^e-bromo-4^e-hydroxyadamantane, converting on oxidation to 4^e-bromoadamantan-2-one in a 84% yield. Tabushi and coworkers[3] studied the radical bromination of adamantan-2-one, resulting in a mixture of five bromoadamantan-2-ones, difficult to separate.

In our previous work[4] we have studied the rearrangement of 2-oximinoadamantane in hydrobromic acid and have found conditions in which the oxime converts to 4-bromoadamantan-2-one in a roughly 70% yield.

In the present work, which is a continuation of the above study, a simplified method is described for the preparation of a mixture of the 4-bromoadamantan-2-one stereoisomers. The reaction is conducted in one step so that adamantan-2-one reacts directly with hydroxylamine hydrochloride in hydrobromic acid. The aim of this work was to prepare the two individual stereoisomers. For this purpose, the effect of the reaction conditions on the ratio of the two stereoisomers in the product was examined. The isomers were separated by elution chromatography on a silica gel column, and their physicochemical properties were determined.

EXPERIMENTAL

Measurements

The gas chromatographic analyses were performed on a Chrom IV apparatus using a glass column 1·2 m long, i.d. 3 mm, with 5% FFAP stationary phase on Chromosorb. The mass spectra were measured on a single-focus LKB 9000 Gas Chromatograph-Mass Spectrometer instrument. The IR spectra were scanned on a Perkin–Elmer 325 spectrophotometer. The NMR spectra were run on a Varian XL 100 spectrometer in $CDCl_3$ solutions (1% TMS) at 37°C. The $Eu(FOD)_3$ shift reagent was added directly in the cell, and the induced shifts were measured for the R_p values (reagent-to-substrate molar ratios) 0·05—0·5. The limiting shift values were obtained by applying the optimization method PSEUDO II (ref.[5]). The course of the reaction for various reaction conditions were monitored analogously as in the previous work[4].

4-Bromoadamantan-2-one

2·0 g (13·3 mmol) of adamantan-2-one prepared according to[6] was mixed with 0·93 g (13·3 mmol) of hydroxylamine hydrochloride and 20 ml of 48% hydrobromic acid in a 50 ml flask. The reaction mixture was heated at 140°C for 2 h, after cooling, diluted with the same volume of water, and extracted with benzene (6× 20 ml). The combined extracts were washed with water and dried with anhydrous sodium sulphate. The solvent was evaporated to give 2·2 g of the substance, which was twice recrystallized from n-pentane. 4-Bromoadamantan-2-one, m.p. 160·5—162·5°C, was obtained (1·7 g, hence 62%).

Isolation of the 4-Bromoadamantan-2-one Stereoisomers

The mixture of the 4-bromoadamantan-2-one stereoisomers was separated on a silica gel column. The column used, 110 cm long, i.d. 40 mm, was packed with 570 g of silica gel (grain size 125 to 150 μm) activated at 180°C for 5 h. 10 g of the crude 4-bromoadamantan-2-one was dissolved in 30 ml of n-hexane and transferred onto the silica gel column. n-Hexane with 5% vol. diethyl ether served as the eluting agent. The composition of the fractions was monitored gas chromatographically. 2·10 g of pure 4^e-bromoadamantan-2-one was isolated from the total 12·4 l of n-hexane with 5% diethyl ether, and 5·30 g of pure 4^a-bromoadamantan-2-one from additional 9·9 l of n-hexane with 10% vol. diethyl ether.

4^e-Bromoadamantan-2-one

The first fraction from the elution column chromatography was resublimed (120°C, 1·33 kPa) to give the crystalline substance, m.p. 165—165·5°C. Ref.[3] gives 159·5—161°C for the equatorial stereoisomer. For $C_{10}H_{13}BrO$ (229·1) calculated: 52·42% C, 5·72% H, 34·87% Br; found: 52·28% C, 5·79% H, 35·0% Br. IR spectrum: 1022, 1045, 1079, 1195, 1270, 1450, 1708, 1731, 2855, 2925 cm^{-1}. Mass spectrum: M^+ 149 (100%), 121 (100%), 79 (67%), 67 (32%), 93 (31%) *m/e*. NMR spectrum: 4·48 (H_{4a}), 2·82 (H_3), 2·60 (H_1), 2·50 (H_{9a}), 1·6—2·4 ppm others. Dipole moment (C_6H_6): $\mu_{20°C} = 2{\cdot}97$ D.

4^a-Bromoadamantan-2-one

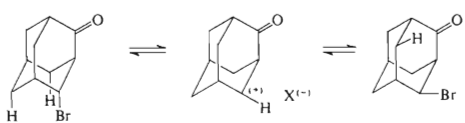
The second fraction from the elution column chromatography was resublimed (120°C, 1·33 kPa) to give the pure axial stereoisomer; m.p. 172·0—173·0°C, ref.[3] gives 156·5—159·5°C. For

$C_{10}H_{13}BrO$ (229·1) found: 52·48% C, 5·75% H, 34·65% Br. IR spectrum: 1060, 1180, 1228, 1242, 1278, 1450, 1694, 1732, 2855, 2920 cm^{-1}. Mass spectrum: M^+ 149 (100%), 121 (94%), 79 (63%), 93 (28%), 67 (28%) *m/e*. NMR spectrum: 4·75 (H_4[e]), 2·91 (H_3), 2·59 (H_1), 2·67 (H_9[a]), 1·90—2·4 ppm others. Dipole moment: (C_6H_6): $\mu_{20\,°C} = 4{\cdot}35$ D.

RESULTS AND DISCUSSION

The product of reaction of adamantan-2-one with hydroxylamine hydrochloride in the molar ratio 1 : 1 in hydrobromic acid (48·4%) at 100—160°C represents in all cases mixture of 4[e]-bromoadamantan-2-one (*I*) with 4[a]-bromoadamantan-2-one (*II*). The proportions of the two stereoisomers are affected by the temperature and duration of the reaction. The fractions of the two stereoisomers in dependence on the reaction period for different temperatures are given in Table I; as can be seen, the content of the stereoisomer *II* in the product increases with the reaction period and the temperature, the highest yield being attained at the temperature 140°C and reaction period 4 h. When the temperature is risen above 140°C, the total yield of 4-bromoadamantan-2-one decreases on account of side products. A similar effect results if the reaction is conducted longer than for 4 h. The rearrangement of the stereoisomer *I* to the stereoisomer *II* during the reaction was proved by a check experiment, in which a sample of 4-bromoadamantan-2-one containing 20·6 wt.% *II* exposed to 48·4% hydrobromic acid for 24 h at various temperatures; the changes in the proportions of the two stereoisomers are given in Table II.

The conversion of the stereoisomer *I* to the stereoisomer *II* in hydrobromic acid can be explained in terms of the higher thermodynamic stability of the latter stereoisomer, which is obviously due to the smaller number of nonbonding interactions between the bromine atom and the hydrogen atoms of the adamantane skeleton.



I *II*

The substances *I* and *II* were separated by using elution column chromatography on silica gel. The purity and conformation of the stereoisomers obtained were checked by measuring their ^{1}H-NMR spectra. The chemical shifts were attributed to the individual protons based on a comparison of the values for the compounds *I* and *II* with those for adamantane halo derivatives[7]. For the compound *II*, the value of the shift for the proton H_{4e} in the equatorial position is lower than for the proton H_{4a} of the compound *I*. This effect is accounted for by the anisotropy of the C=O bond, similarly as in the case of other bromo ketones[8]. Addition of the shift reagent resulted

TABLE I

Proportions (%) of the Substances *I* and *II* for Various Temperatures and Reaction Periods

For each temperature, the first row pertains to the substance *I*, the second row to the substance *II*.

Temperature °C	Time, min					
	15	30	60	120	180	240
100	95·54	71·52	61·95	47·43	26·52	28·21
	4·46	28·48	38·05	52·57	73·48	71·79
120	55·62	41·68	41·68	33·51	27·76	28·52
	44·38	58·32	58·32	66·49	72·24	71·48
140	34·04	25·11	28·79	30·11	28·95	21·38
	65·96	74·89	71·21	69·89	71·05	78·62
160	38·06	34·79	33·73	32·53	34·71	33·65
	61·94	65·21	66·27	67·47	65·29	66·35

TABLE II

Isomerization of the Substances *I* and *II* in 48·4% Hydrobromic Acid

Temperature, °C	Ratio *II*/*I*
30	0·304
60	0·517
90	0·705
120	2·22
150	3·00

TABLE III

Relative Limiting Induced Shifts for the Compounds *I* and *II* with $Eu(FOD)_3$ in $CDCl_3$

Compound	Shift for the proton													
	1	3	4[a]	4[e]	5a	6[a]	6[e]	7	8[a]	8[e]	9[a]	9[e]	10[a]	10[e]
I	4·3	4·1	2·3	—	1·1	1·1	1	1	1·6	1·1	1·6	1·1	1·6	1·1
II	3·9	4·6	—	1·6	1	1	1	1	1·4	1	2·1	1·4	1·5	1

in such a resolution of the signals belonging to the various protons that they could be identified by decoupling and by calculation based on the limiting induced shifts emerging from the solution of the pseudocontact shift equation. The relative limiting induced shifts are given in Table III.

The values of the relative limiting induced shifts of the protons 1 and 3 in the two compounds are different, which cannot be so far explained uniquely. The optimization calculation, however, confirmes unambiguously the assignment shown. The identification is corroborated also by the long-range interactions in the case of H_4^e.

In addition to the observed and calculated limiting shifts, the correctness of the assignment was confirmed also by dipole moment measurements of the two stereoisomers. The C—Br and C=O bonds in the stereosiomer *II* form a relatively small acute angle, and thus the resulting dipole moment can be expected to exceed that of the stereoisomer *I*, in which the dipoles of the two bonds compensate each other to a high extent[1]. This assumption was confirmed by dipole moment measurements of the two stereoisomers: the substance *II* exhibits a higher dipole moment value ($\mu_{20°C} = 4{\cdot}35$ D) than the substance *II* ($\mu_{20°C} = 2{\cdot}97$ D).

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