BECKMANN REARRANGEMENT OF ADAMANTANONE OXIME AS A ROUTE TO DITOPIC AND TRITOPIC SECONDARILY SUBSTITUTED ADAMANTANE DERIVATIVES

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The reaction in mixtures of adamantanone with hydroxylamine hydrochloride was studied in hydrochloric, hydrobromic, and hydroiodic acid solutions. In hydrochloric and hydroiodic acids, mixtures of isomers of 4-chloroadamantan-2-one and of 4-iodoadamantan-2-one, respectively, are formed, whereas in hydrobromic acid in the presence of excess hydroxylamine hydrochloride, three stereoisomers of 4,8-dibromoadamantan-2-one appear. All the stereoisomeric haloketones were isolated by elution adsorption chromatography on silica gel or by crystallization. For the pure substances, their infrared, mass, and NMR spectra were measured.

Adamantane derivatives so far synthesized were mostly ones containing the substituents at the tertiary carbon atoms[1] which is due to the fact that the secondary carbon atoms of the adamantane skeleton are much less reactive than the tertiary ones. This also is the reason why, with few exceptions[2], adamantane is not used as the starting substance for the preparation of secondarily substituted ditopic or tritopic adamantane derivatives. Instead, adamantanone is employed and is subjected to oxidation[3], bromination[4,5], or — for the preparation of secondarily substituted ditopic derivatives — to Schmidt's reaction[6] or to Beckmann rearrangement[7,8,12]. Other routes to these compounds consist in closure of a suitable bicyclic skeleton[8] or in reactions of protoadamantene[9,10] or cyclohexane derivative[11]. We have shown[7,13] that the Beckmann rearrangement is a convenient route to 4-bromoadamantan-2-one, particularly in the one-stage variant proceeding immediately from adamantan-2-one. Haloketones containing the halogen at the secondary carbon atom of the adamantane molecule so far prepared have been obtained by considerably more involved procedures, starting, *e.g.*, from 4-oxahomoadamantan-5-one[14,15], dehydroadamantane[16], bicyclo[3,3,1]non-6-ene-3-carboxylic acid[17], or methyl adamantane-4,8-dione-2-carboxylate[18].

The synthesis of tritopic secondarily substituted adamantane derivatives is a complex problem, and up to now only procedures starting from various derivatives of bicyclo[3,3,1]nonane have been described[19–22].

The objective of this work was to gain a better insight into the reaction of adamantanone with hydroxylamine hydrochloride in hydrobromic acid solutions, and

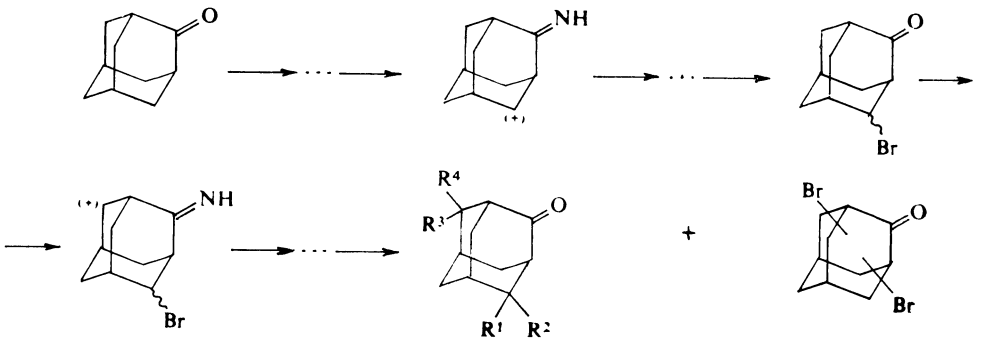
to make use of the results, combined with those for the reactions in hydrochloric and hydroiodic acids, for the synthesis of tritopic secondarily substituted adamantane derivatives.

RESULTS AND DISCUSSION

4-Chloroadamantan-2-one and 4-iodoadamantan-2-one were prepared from adamantan-2-one by procedure reported previously. Similarly as with the bromoderivative, in hydrochloric acid a mixture of 4-chloroadamantan-2-one isomers is formed in a 30% yield, with prevalence of the equatorial isomer. In hydroiodic acid, 4-iodoadamantan-2-one isomers are formed in an approximately 25% yield.

The pure stereoisomers (4^e- and 4^a-haloadamantan-2-ones) were isolated by separation of the reaction mixture on a silica gel column by adsorption elution chromatography; additional products of the Beckmann rearrangement (4-azatricyclo-[4,3,1,$1^{3,8}$]-undecan-5-one and 4-oxahomoadamantan-5-one) were identified by gas chromatography and mass spectrometry, while NMR spectroscopy was employed for the identification of the isomers of 4-chloro- and 4-iodoadamantan-2-one.

The possibility of adding two bromine atoms to the secondary carbon atoms of the adamantane skeleton by reacting adamantan-2-one with hydroxylamine hydrochloride in 48% hydrobromic acid was also examined. Using 100% excess of hydroxylamine hydrochloride with respect to adamantanone a reaction product was obtained in which four dibromoadamantan-2-ones were found by gas chromatography and mass spectrometry. The optimum temperature for the formation of the dibromoadamantan-2-ones was 140–150°C, reaction time 1·5 h. In 5–10 min heating, the mixture contained predominantly isomers of 4-bromoadamantan-2-one. Thus it can be supposed that the reaction starts by the formation of adamantan-2-one oxime, which undergoes fragmentation and recombination[8] to give 4-bromoadamantan-2-one[7,13]. In the presence of excess hydroxylamine hydrochloride, the latter transforms probably by the same pathway into 4-bromoadamantan-2-one oxime, which is subject to fragmentation and recombination, and the bromoiminocarbonium ion formed makes it possible for an additional bromine atom to add to the molecule of 4-bromoadamatan-2-one, namely, to the secondary carbon atom (β position with respect to the carbonyl group). In a simplified manner the pathway is shown in Scheme 1. The dibromoadamantan-2-ones were isolated from the reaction mixture by extraction with hexane; isomers *III* and *IV* were obtained by crystallization of the extract successively from methanol and methyl ethyl ketone (the labelling of the isomers corresponds to the order of their elution during the gas chromatographic treatment on the nonpolar SE-30 phase). Additional crystallization from a hexane–ethyl ether mixture afforded pure isomer *I*. The remaining isomer *II*, which makes about 10% of the dibromoadamantanone mixture, was not obtained in a sufficiently pure form. Isomer *I* predominates if the reaction temperature is



I, ($R^1 = R^3 = Br$, $R^2 = R^4 = H$)
III, ($R^2 = R^3 = H$, $R^1 = R^4 = Br$)
IV, ($R^2 = R^4 = Br$, $R^1 = R^3 = H$)

SCHEME 1

raised to 160°C and the reaction period is shortened to 30 min. Heated in 48% hydrobromic acid at 145°C, isomer *I* transforms into *III*.

The structure of the dibromoketones prepared was verified by ^1H NMR measurements employing a shift reagent[23], and by ^{13}C NMR measurements. The ^{13}C NMR spectra exhibited the following signals ($CDCl_3$, TMS): *I*: 207·5 (C=O), 55·6, 53·5, 34·2, 31·2, 24·6 ppm; *III*: 207·6 (C=O), 59·2, 55·7, 54·1, 53·5, 37·4, 34·9, 33·8, 31·6, 28·8 ppm; *IV*: 207·7 (C=O), 59·7, 54·4, 37·6, 35·5, 34·4 ppm.

It can be concluded that reacted with excess hydroxylamine hydrochloride in hydrobromic acid, adamantan-2-one transforms into a mixture of three isomers of 4,8-dibromoadamantan-2-one containing an additional, so far unidentified dibromoadamantan-2-one.

EXPERIMENTAL

The gas chromatographic analyses were carried out on a Chrom 5 apparatus using stainless steel columns 1·2 m long, 3 mm i.d., packed either with 5% FFAP on Chromosorb W or 5% SE-30 on Chromaton N. The mass spectra were measured on a single-focussing LKB 9000 Gas Chromatograph-Mass Spectrometer. The NMR spectra were scanned on a Varian XL-100 spectrometer in $CDCl_3$ solutions (1% TMS) at 37°C. $Eu(DPM)_3$ shift reagent was added in molar ratios to substrate of $R_p = 0·1—0·5$. The calculations for the structure verification were performed by using the P 1980 program. The ^{13}C NMR spectra were run on a Tesla BS 567 instrument at 30°C using the noise decoupling and the APT techniques. The infrared spectra were recorded on a Perkin-Elmer 325 spectrophotometer.

4-Chloroadamantan-2-one

5·0 g of adamantan-2-one (33·3 mmol) mixed with 2·32 g of hydroxylamine hydrochloride (33·3 mmol) and 130 ml of concentrated hydrochloric acid was boiled under reflux for 0·5 h

at the bath temperature 140°C. After the reaction, the mixture was diluted with the same volume of water and extracted with hexane (5 × 20 ml) and chloroform (3 × 20 ml). The hexane and chloroform extracts gave 2·2 g and 2·0 g of substance, respectively. From the latter, 1·1 g of 4-azatricyclo[4,3,1,$1^{3,8}$]undecan-5-one was precipitated with dry hydrogen chloride.

4^e-*Chloroadamantan-2-one*. The hexane fraction was introduced onto the column of 70 g of activated silica gel (5 h at 180°C) in hexane solution. 700 ml of hexane, 700 ml of hexane with 10% (*V*/*V*) benzene, 900 ml of hexane with 20% (*V*/*V*) benzene, and 550 ml of hexane with 50% (*V*/*V*) benzene were passed to isolate 1·44 g (23·5%) of 4^e-chloroadamantan-2-one, m.p. 207–208·5°C (ref.[16], 201–203°C). For $C_{10}H_{13}ClO$ (184·7) calculated: 65·0% C, 7·1% H, 19·2% Cl; found: 65·15% C, 7·2% H, 19·3% Cl. Infrared spectrum (CCl_4): 723, 844, 875, 908, 1 028, 1 085, 1 719, 1 735, 2 870, 2 940 cm^{-1}. Mass spectrum: M^+ 184 (17·2%), 79 (100%), 121 (82·8%), 149 (61·8%), 41 (53·5%), 93 (26·8%) *m*/*e*. NMR spectrum ($CDCl_3$) 3·90 ppm (s) (H_4a), others 1–2·8 ppm (12 H).

4^a-*Chloroadamantan-2-one*. By additional elution of the silica gel column with hexane with 3% (*V*/*V*) diethyl ether, 0·28 g (4·6%) of 4^a-chloroadamantan-2-one, m.p. 214·5–216°C, was isolated from 2 800 ml of the mixed solvent. For $C_{10}H_{13}ClO$ (184·7) calculated: 65·0% C, 7·1% H, 19·2% Cl; found: 65·1% C, 7·2% H, 19·3% Cl. Infrared spectrum (CCl_4): 1 055, 1 068, 1 120, 1 447, 1 457, 1 739, 2 865, 2 930 cm^{-1}. Mass spectrum: M^+ 184 (25%), 79 (100%), 78 (51%), 149 (48%), 121 (39%), 148 (36%), 39 (24%), 41 (23%). NMR spectrum ($CDCl_3$): 4·60 (H_4e), 2·82, 2·55, 2·62, 1·90–2·06 ppm.

4-Iodoadamantan-2-one

9 g (60 mmol) of adamantan-2-one and 4·2 g (60 mmol) of hydroxylamine hydrochloride were added to 100 ml of 56% hydroiodic acid and the mixture was stirred at 120°C for 1 h. After the reaction, 100 ml of water was added, and the system was neutralized with solid sodium carbonate. Hexane (3 × 40 ml) and chloroform (3 × 40 ml) were used for extraction. The combined extracts were decoloured with sodium sulphite solution and dried with anhydrous sodium sulphate. The solvents were removed by evaporation on a rotary vacuum evaporator. The hexane extract gave 3·72 g of substance, which was separated on a silica gel column. 160 g of silica gel (grain size 40–100 μm) activated at 160°C for 5 h was used in a column 102 cm long, i.d. 20 mm. Crude 4-iodoadamantan-2-one (3·5 g) was dissolved in 5 ml of chloroform and added onto the column and eluted with 500 ml of hexane, 250 ml of hexane with 1% (*V*/*V*) diethyl ether, 700 ml of hexane with 5% (*V*/*V*) diethyl ether, and 800 ml of hexane with 10% (*V*/*V*) diethyl ether. Evaporated on a rotary vacuum evaporator, the eluate afforded 1·58 g of crude 4^a-iodoadamantan-2-one. Additional 200 ml of eluate in hexane with 50% (*V*/*V*) diethyl ether gave 1 g of a yellow crystalline substance containing both stereoisomers, and 0·84 g of crude 4^a-iodoadamantan-2-one was obtained from additional 150 ml of hexane with 50% (*V*/*V*) diethyl ether.

4^e-*Iodoadamantan-2-one*. The crude product was purified by sublimation at 80°C/1·5 kPa to give 1·01 g of a yellow crystalline substance, m.p. 53·5–55°C. For $C_{10}H_{13}IO$ (276·2) calculated: 43·5% C, 4·7% H, 46·0% I; found: 44·8% C, 4·9% H, 34·9% I. Infrared spectrum (CCl_4): 480, 666, 873, 902, 929, 1 026, 1 708, 1 732, 2 875, 2 945 cm^{-1}. Mass spectrum: M^+ 276 (1·43%), 79 (100%), 121 (64·3%), 149 (46·4%), 67 (43%), 93 (38·6%), 41 (28%) *m*/*e*. NMR spectrum ($CDCl_3$): 4·70 (s) (H_4a), 1·4–1·9 ppm (m) (12 H).

4^a-*Iodoadamantan-2-one*. After purification by sublimation at 80°C/1·5 kPa, 0·29 g was obtained of a yellow crystalline substance, m.p. 85–87°C. For $C_{10}H_{13}IO$ (276·1) calculated: 43·5% C, 4·7% H, 46·0% I; found: 43·9% C, 4·9% H, 31·9% I. Infrared spectrum (CCl_4): 465,

669, 962, 1 065, 1 153, 1 732, 2 875, 2 945 cm^{-1}. Mass spectrum: M^+ 276 (1·37%), 149 (100%), 121 (97·3%), 79 (89%), 67 (41%), 93 (39·7%), 41 23·3%) *m/e*. NMR spectrum ($CDCl_3$): 4·92 (d) (H_4e), other 1·6—2·1 ppm (12 H).

Dibromoadamantan-2-ones

A mixture of 3 g (20·0 mmol) of adamantan-2-one, 2·78 g (40·0 mmol) of hydroxylamine hydrochloride, and 17·5 ml of hydrobromic acid (48%) was stirred under reflux at 145 to 148°C for 1 h. After the reaction the mixture was cooled, diluted with 20 ml of water, and extracted with hexane (6 × 15 ml), benzene (6 × 15 ml), and chloroform (4 × 15 ml). The extracts were dried with anhydrous sodium sulphate, and after solvent evaporation, 0·4, 1·7, and 1·22 g of substances were obtained. The benzene extract residue was crystallized multiply from methanol to give 0·35 g of pure isomer *IV*. The filtrate was evaporated and combined with the residue from the hexane extract (0·4 g). Crystallization of the combined fraction from ethyl methyl ketone yielded 0·66 g of isomer *III*, which then was purified by additional crystallization from methanol. Isomer *I* (0·3 g) was obtained by crystallization of the mother liquors from a hexane–ether mixture 1 : 1.

$4^e,8^e$-*Dibromoadamantan*-2-*one*. (I). M.p. (hexane–ethyl ether) 125—126°C. For $C_{10}H_{12}Br_2O$ (308·0) calculated: 39·0% C, 3·9% H, 51·9% Br; found: 39·25% C, 4·2% H, 51·7% Br. Infrared spectrum (CCl_4): 493, 640, 682, 915, 960, 1 072, 1 190, 1 710, 1 735, 2 870, 2 950 cm^{-1}. Mass spectrum: M^+ 308 (8·3%), 119 (100%), 91 (79·7%), 79 (72·2%), 41 (72·2%), 227· (69·4%), 229 (67·6%). NMR spectrum ($CDCl_3$): 4·45 (2 H), 1·60—2·86 ppm others.

$4^e,8^e$-*Dibromoadamantan*-2-*one* (III). M.p. (methanol) 123—125°C. For $C_{10}H_{12}Br_2O$ (308·0) calculated: 39·0% C, 3·9% H, 51·9% Br; found: 39·2% C, 4·2% H, 51·8% Br. Infrared spectrum (CCl_4): 693, 705, 856, 929, 985, 1 056, 1 743, 2 875, 2 955 cm^{-1}. Mass spectrum: M^+ 308 (3·3%), 119 (100%), 91 (78·2%), 227 (62·9%), 229 (62·7%), 79 (50·2%), 41 (49·2%). NMR spectrum ($CDCl_3$): 4·43 (1 H), 4·69 (1 H), 1·70—2·94 ppm others.

$4^a,8^a$-*Dibromoadamantan*-2-*one* (IV). M.p. (methanol) 241—242·5°C. For $C_{10}H_{12}Br_2O$ (308·0) calculated: 38·0% C, 3·9% H, 51·9% Br; found: 29·15% C, 4·2% H, 51·8% Br. Infrared spectrum (KBr disk): 699, 748, 821, 975, 1 053, 1 192, 1 730, 2 875, 2 950 cm^{-1}. Mass spectrum: M^+ 308 (8·8%), 227 (100%), 229 (91·2%), 41 (72·3%), 39 (70%), 119 (67·6), 91 (52·4%), 79 (33·5%). NMR spectrum ($CDCl_3$): 4·70 (2 H), 2·85 (2 H), 2·74 (2 H), 2·10 (2 H), 2·28 ppm others).

REFERENCES

1. Fort R. C. jr: *Studies in Organic Chemistry*, Vol. 5, *Adamantane: The Chemistry of Diamond Molecules*. Dekker, New York 1976.
2. Geluk H. W., Schlatmann J. L. M. A.: Rec. Trav. Chim. Pays-Bas *90*, 516 (1971).
3. Morat C., Rassat A.: Tetrahedron Lett. *45*, 4409 (1979).
4. Tabushi I., Aoyama, Yoshida Z.: J. Amer. Chem. Soc. *93*, 2077 (1971).
5. Mc Kervey M. A., Faulkner D., Hamill H.: Tetrahedron Lett. *1970*, 1971.
6. Sasaki T., Eguchi S., Toru T.: J. Org. Chem. *35*, 4109 (1970).
7. Vodička L., Tříska J., Hájek M.: This Journal *45*, 2670 (1980).
8. Korsloot J. G., Keizer V. G.: Tetrahedron Lett. *1969*, 3517.
9. Kervey M. A., Cuddy B. D., Grant D.: J. Chem. Soc. C *19*, 3173 (1971).
10. Lenoir D., Glaser R., Mison P., Schleyer P. v. R.: J. Org. Chem. *36*, 1821 (1971).
11. Stetter H., Thomas H. G.: Chem. Ber. *101*, 1115 (1968).
12. N. V. Philips' Gloeillampenfabrieken: Neth. Appl. 6904, 911.

13. Tříska J., Vodička L., Hlavatý J.: This Journal *44*, 1448 (1979).
14. Stetter H., Koch H.: Justus Liebigs Ann. Chem. *1975*, 1357.
15. Duddeck H., Wolff P.: Org. Magn. Resonance *9*, 528 (1977).
16. Udding A. C., Strating J., Wynberg H.: Tetrahedron Lett. *1968*, 1345.
17. Numan H., Troostwijk C. B., Wieringa J. H., Wynberg H.: Tetrahedron Lett. *1977*, 1761.
18. Snatzke G., Eckhardt G.: Chem. Ber. *101*, 2010 (1968).
19. Stetter H., Held H., Mayer J.: Justus Liebigs Ann. Chem. *658*, 151 (1962).
20. Stetter H., Thomas H. G.: Chem. Ber. *99*, 920 (1966).
21. Stetter H., Dorsch U. P.: Justus Liebigs Ann. Chem. *1976*, 1406.
22. McCabe P. H., Nelson C. R., Routledge W.: Tetrahedron *33*, 1749 (1977).
23. Hájek M., Horská A., Piccini-Leopardi C., Germain G.: 3rd NMR Symposium, Tábor 1982, Czechoslovakia.

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