Unusual Behaviour of 2-Methyladamantane during Bromination

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As well as 1-bromo-2-methyladamantane and *cis*- and *trans*-1-bromo-4-methyladamantane the expected products of bridgehead substitution, bromination of 2-methyladamantane with hot bromine gives 4*eq*- and 4*ax*-bromo-2-(dibromomethylene)adamantane. The monobromides were not isolated as such, but were hydrolysed to the corresponding alcohols. The tribromides may be formed by an ionic mechanism involving an adamantane–protoadamantane–adamantane rearrangement.

DURING a recent investigation of adamantane rearrangements in sulphuric acid it became necessary to prepare 2-methyladamantan-1-ol (1) and the *cis*- and *trans*-isomers of 4-methyladamantan-1-ol (2).[1] The synthetic route chosen, for which there is ample precedent in adamantane methodology,[2] involved direct bromination of 2-methyladamantane (3) [3] with hydrolysis of the mixture of bromides produced. The direct approach to the functionalisation of the adamantane nucleus has found wide applicability because of its remarkable selectivity, giving exclusively bridgehead substitution, usually in very high yield.[2]

Dissolution of 2-methyladamantane in bromine at room temperature produced an immediate exothermic reaction with evolution of hydrogen bromide. The solution was heated under reflux for 4·5 hr. and then was processed (see Experimental section), yielding a mixture of products. Hydrolysis of the crude material with potassium carbonate in water–dioxan gave a mixture from which the desired alcohols (1) and (2) could be isolated by adsorption chromatography over alumina. At the same time substantial amounts (*ca.* 20%) of two isomeric compounds (ratio 3 : 1), each containing three bromo-substituents, were also isolated. Initially these compounds, hereafter referred to as (A) and (B), were thought to be tribromides of 2-methyladamantane, although this was considered unusual

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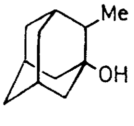
[1] M. A. McKervey, J. R. Alford, J. F. McGarrity, and E. J. F. Rea, *Tetrahedron Letters*, 1968, 5165.

[2] For a review see R. C. Fort, jun., and P. von R. Schleyer, *Chem. Rev.*, 1964, **64**, 277.

[3] P. von R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, 1961, **83**, 182.

insofar as tribromination of the adamantane nucleus usually requires aluminium bromide catalysis. However, a much more complex and exceptional bromination process was indicated when the molecular formula was found to be $C_{11}H_{13}Br_3$, since this required that the tribromides should be either tetracyclic or unsaturated. The presence of a strong i.r. absorption at 1590 cm.$^{-1}$ supported the latter alternative. Products (A) and (B) were separable by adsorption chromatography over silica gel, although the mixture sufficed for most of the experiments employed in the structure determination.



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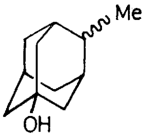

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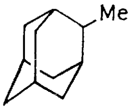

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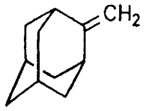

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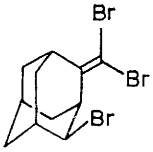

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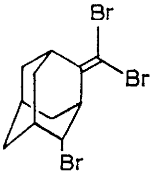

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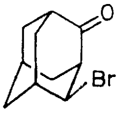

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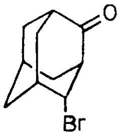

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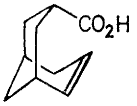

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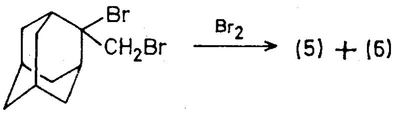

(10)

Attempts to replace the bromo-substituents by hydrolysis were not promising: use of silver nitrate in dioxan–water or silver sulphate in 50% sulphuric acid gave complex mixtures of products; milder conditions merely gave starting material. Hydrogenolytic debromination was much more satisfactory. Use of palladium and hydrogen at atmospheric pressure produced a smooth reaction, yielding 2-methyladamantane as the sole product, and this compound was also formed, though methyleneadamantane (4) was the major product, when the tribromide mixture was exposed to tri-n-butyltin hydride. These observations suggested that the adamantane skeleton was intact in both tribromides and, consequently, that the unsaturation was exocyclic. The n.m.r. spectra could be rationalised to some extent on the basis that (A) and (B) were stereoisomers, each with one bromine atom attached to a non-bridgehead position of adamantane nucleus and the two remaining substituents bonded to the carbon atom of the double bond as in (5) and (6). Thus the major isomer (A) displayed three one-proton absorptions at τ 5·38, 6·45, and 6·80, with the remaining protons represented by a complex multiplet at τ 7·45—8·50. The lowest field absorption was attributed to the C-4 proton and the signals at τ 6·45 and 6·80 to the bridgehead allylic protons. The corresponding signals in the spectrum of isomer (B) occurred at τ 5·65, 6·65, and 6·80, with the signals for the remaining protons enclosed in a multiplet at τ 7·40—8·50. These tentative assignments suggested that an ozonolysis experiment should be performed, since the bromo-ketones (7) and (8) were known compounds.[4] Ozonolysis of the mixture in methanol at −40° for 15 hr. followed by treatment of the solution with dimethyl sulphide [5] gave a crude product which showed ketonic i.r. absorption. Adsorption chromatography over alumina gave, in addition to unchanged (A) and (B), a compound the spectral properties of which left no doubt that it was 4*ax*-bromoadamantan-2-one (7).* The epimer, 4*eq*-bromoadamantan-2-one (8) * was not isolated. This may have been due to a complicating factor. It is known that the ketone (8) undergoes ready fragmentation to give bicyclo[3,3,1]non-6-ene-3-carboxylic acid (9).[6] A similar process may have occurred when the crude ozonolysis product was chromatographed over alumina. The ozonolysis reaction was repeated; this time the crude product was treated with silver perchlorate in acetone–water, yielding an acid identical with compound (9). Ozonolysis also established the relative stereochemistry of (A) and (B): a separate experiment with pure (A), the preponderant isomer, gave the axial bromo-ketone (7). Consequently, we concluded that (A) and (B) were 4*ax*- and 4*eq*-bromo-2-(dibromoethylene)adamantane, (5) and (6), respectively.

Any mechanistic account of this unusual bromination must explain why nuclear bromination occurs exclusively at the 4- (non-bridgehead) position. Evidence against direct bromination at this position is provided by the wealth of data on direct substitution reactions of substituted adamantanes; [2] with adamantanone, which partially resembles the present case, bromination occurs almost exclusively at the 5- (bridgehead) position.[7] One mechanism which accounts for this aspect of the reaction is shown in the Scheme. The key feature is an adamantane–protoadamantane–adamantane rearrangement in which the bromine substituent at C-4 is introduced at the protoadamantane stage. Although this mechanism requires at least temporary rearrangement of the adamantane skeleton, there are several recent indications that this process can occur readily.[8] The Scheme commences with the formation of methyleneadamantane (4) by proton elimination from the 2-methyl-2-adamantyl cation. Rearrangement then occurs during or subsequent to bromination of the

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* The symbols *ax* and *eq* denote the axial and equatorial positions with respect to that cyclohexane ring of the adamantane skeleton to which both substituents are attached.

[4] G. Snatzke and G. Eckhardt, *Chem. Ber.*, 1968, **101**, 2010.

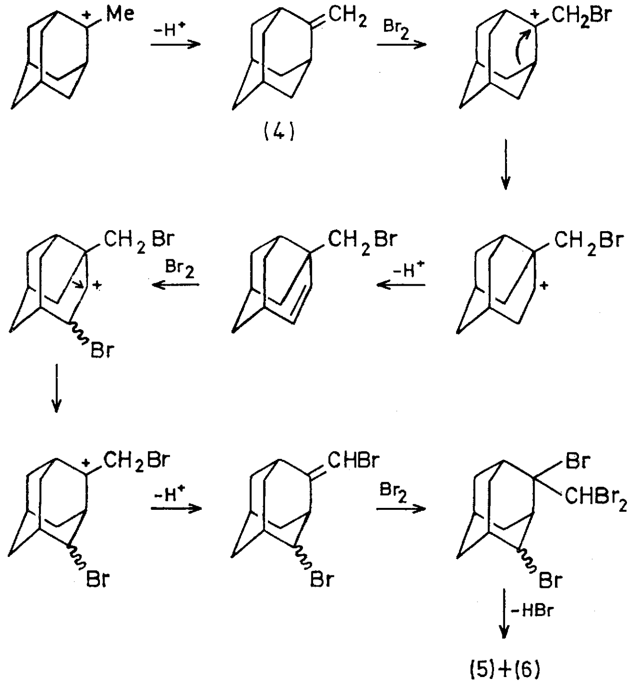
[5] J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Letters*, 1966, 4273.

[6] A. C. Udding, H. Wynberg, and J. Strating, *Tetrahedron Letters*, 1968, 5719.

[7] M. A. McKervey, D. Faulkner, and H. Hamill, *Tetrahedron Letters*, 1970, 1971.

[8] M. L. Sinnott, H. J. Storesund, and M. C. Whiting, *Chem. Comm.*, 1969, 1000; J. R. Alford and M. A. McKervey, *ibid.*, 1970, 615; D. Lenoir and P. von R. Schleyer, *ibid.*, 1970, 941.

olefin. The later stages involve sequential addition of bromine and elimination of hydrogen bromide. In separate experiments it was discovered that bromination of methyleneadamantane (4) in carbon tetrachloride proceeds without rearrangement, giving 2-bromo-2-bromomethyladamantane (10), but that further treatment of compound (10) with hot bromine gave the tribromides (5) and (6) in the same ratio as that observed in the bromination of 2-methyladamantane.



SCHEME

EXPERIMENTAL

M.p.s were determined for samples sealed in capillary tubes. I.r. spectral data relate to dispersions in potassium bromide discs. ^{1}H N.m.r. were measured at 100 MHz with tetramethylsilane as internal standard. Mass spectral data were obtained with an A.E.I. MS902 spectrometer, with an ionising beam of 70 ev. G.l.p.c. refers to analysis on a 2 m. Versamid 900 column. Light petroleum had b.p. 40—60°. Unless otherwise stated, the drying agent employed was magnesium sulphate.

Methyleneadamantane (4).—A solution of 2-methyladamantan-2-ol[3] (15·8 g.) in dry benzene (250 ml.) containing a few crystals of iodine was heated under reflux with continuous removal of water while the progress of the reaction was monitored by g.l.p.c. analysis at 120°. After 7 days, the cooled solution was washed with 5% aqueous sodium thiosulphate and water, dried and evaporated under reduced pressure. The residue was dissolved in light petroleum and run through a short column of alumina. Elution with light petroleum gave the olefin (4) (12 g., 86%), m.p. 132—134° (lit.,[3] 136—136·5°).

2-*Methyladamantane* (3).—Hydrogenation of methyleneadamantane over Adams catalyst at 20° and 3 atmos. gave the hydrocarbon (3) m.p. 144—146° (lit.,[3] 144—146°).

2-*Bromo*-2-*bromomethyladamantane* (10).—To a solution of methyleneadamantane (4·4 g.) in carbon tetrachloride (100 ml.) a 10% solution of bromine in carbon tetrachloride was added dropwise at room temperature until the first permanent red colour appeared. The solution was then washed with aqueous sodium disulphite (100 ml.) and water (100 ml.), dried, and evaporated to leave 2-*bromo*-2-*bromomethyladamantane* (8·7 g., 95%), m.p. 72° (from light petroleum) (Found: C, 42·65; H, 5·45; Br, 52·05. $C_{11}H_{16}Br_2$ requires C, 42·9; H, 5·25; Br, 51·9%), τ (CCl_4) 5·90 (2H, s, CH_2Br) and 7·51—8·35 (14H, m, adamantyl).

4ax- *and* 4eq-*Bromo*-2-(*dibromomethylene*)*adamantane* (5) *and* (6).—A solution of 2-methyladamantane (8 g.) in bromine (40 ml.) was heated under reflux (after the initial reaction had subsided) for 4·5 hr., then cooled. Water (100 ml.) and carbon tetrachloride (100 ml.) were added and the organic layer and carbon tetrachloride extracts (2 × 100 ml.) of the aqueous layer were shaken with aqueous disulphite, washed with water, and dried. Removal of the solvent under reduced pressure left an oil.

A solution of the crude product in 40% aqueous dioxan (350 ml.) containing potassium carbonate (20 g.) was heated under reflux for 24 hr. The cooled solution was diluted with water (1 l.) and extracted with ether (4 × 100 ml.). The extract was washed with water, dried, and concentrated, yielding an oil (13·2 g.). The crude product was divided into two fractions by chromatography in light petroleum on alumina. Fraction (i), eluted with light petroleum, was a mixture of the tribromides (5) and (6) (4·11 g., 20%). The isomer ratio as measured by g.l.p.c. analysis at 210° was 3 : 1. Fraction (ii), eluted with ether, was a mixture of the alcohols (1) and (2) (6·6 g.). Pure samples of (1) and (2) were obtained by a second chromatography of fraction (ii) on alumina and identified by comparison (m.p., i.r. and n.m.r. spectra, and g.l.p.c.) with authentic samples.[1]

The tribromide mixture [fraction (i); 4·11 g.] was subjected to a second chromatography on silica gel (900 g.). Elution with light petroleum gave 4eq-*bromo*-2-(*dibromomethylene*)*adamantane* (6) (0·90 g.) m.p. 128—128·5° (from methanol) [Found: C, 34·05; H, 3·55; Br, 62·4%; *m/e* (M^+), 385·85320. $C_{11}H_{13}Br_3$ requires C, 34·3; H, 3·4; Br, 62·25%; *m/e* (M^+), 385·85295], τ (CCl_4) 5·65 (1H, m CHBr), 6·65 (1H, m, allylic), 6·80 (1H, m, allylic), and 7·40—8·50 (10H, m, adamantyl), $\nu_{max.}$ 2875, 1590, 892, 885, 855, 800, 775, 760, and 752 cm.$^{-1}$. Further elution with light petroleum gave 4ax-*bromo*-2-(*dibromomethylene*) *adamantane* (5) (2·18 g.), m.p. 98—99° (from methanol) [Found: C, 34·25; H, 3·6; Br, 62·3%; *m/e* (M^+), 385·85244. $C_{11}H_{13}Br_3$ requires C, 34·3; H, 3·4; Br, 62·25%; *m/e* (M^+), 385·85295], τ (CCl_4) 5·38 (1H, m, CHBr), 6·45 (1H, m, allylic), 6·80 (1H, m, allylic), and 7·54—8·50 (10H, m, adamantyl), $\nu_{max.}$ 2875, 1590, 895, 880, 862, 776, 764, 755, and 695 cm.$^{-1}$.

Reaction of 2-*Bromo*-2-*bromomethyladamantane* (10) *with Bromine*.—A solution of the dibromide (12 g.) in bromine (40 ml.) was heated under reflux for 4 hr. Work-up as for the bromination of 2-methyladamantane gave a crude mixture of the tribromides (5) and (6) in the ratio 3 : 1 (15·4 g.). A portion (6 g.) of the product in light petroleum was placed on a column of silica gel (1200 g.). Elution with light petroleum gave the equatorial isomer (6) (1·07 g.), m.p. 128—128·5° (from methanol). Further elution with light petroleum gave the axial isomer (5) (3·11 g.), m.p. 98—99° (from methanol). G.l.p.c. and i.r. analysis indicated that the individual isomers were isomerically pure.

Debromination of the Tribromide Mixture (5) *and* (6).—

(a) *Over palladium*. A solution of the tribromide mixture (3 g.) in methanol (45 ml.) containing potassium hydroxide (4·5 g.) and 10% palladium on carbon (0·9 g.) was exposed to hydrogen at room temperature and atmospheric pressure. When hydrogen uptake had ceased, the catalyst was filtered off and the filtrate was diluted with water (100 ml.) and extracted with ether (3 × 100 ml.). The extract was washed with water and dried. Evaporation left 2-methyladamantane (1·1 g.), identified by comparison (g.l.p.c., n.m.r., and mass spectra) with an authentic sample.

(b) *With tri-n-butyltin hydride*.—Tri-n-butyltin chloride (0·75 g.) was added to a stirred solution of lithium aluminium hydride (0·25 g.) in ether (5 ml.). After 10 min., the tribromide mixture (0·70 g.) was added in a single portion and the solution was heated under reflux for 24 hr. The cooled solution was poured into water (30 ml.) and extracted with ether (4 × 40 ml.). Evaporation of the extract left an oil, which was taken up in light petroleum and placed on a column of alumina. Elution with light petroleum gave a 1 : 8 mixture of 2-methyladamantane and methyleneadamantane, as measured by n.m.r. and g.l.p.c. analysis.

Ozonolysis of the Tribromide Mixture (5) *and* (6).—(*a*) Ozonised oxygen was passed into a solution of the tribromides (500 mg.) in methanol (200 ml.) at −40° during 15 hr. The solution was then treated with excess of dimethyl sulphide [5] and diluted with ether (200 ml.). The resulting solution was washed with water (4 × 100 ml.), dried, and evaporated to leave an oil (360 mg.). The product in light petroleum was chromatographed on neutral alumina. Elution with light petroleum gave unchanged tribromides. Further elution, with ether, gave 4*ax*-bromoadamantan-2-one (7) (40 mg.). The i.r. spectrum (CCl_4) was identical with that of an authentic sample [4] and the n.m.r. spectral data were in close agreement with the published values.[4]

(*b*) Experiment (*a*) was repeated on the same scale and, after removal of the solvent, the crude product was added to a stirred mixture of acetone (10 ml.), water (5 ml.), and silver perchlorate (1 g.). After 14 hr. at room temperature the mixture was filtered and the filtrate was diluted with water and extracted with ether. The ethereal solution was shaken with N-sodium hydroxide and the alkaline solution was treated with 5N-hydrochloric acid. Extraction with ether then gave bicyclo[3,3,1]non-6-ene-3-carboxylic acid (9) (30 mg.), identified by comparison with an authentic sample.[6]

Ozonolysis of Tribromide (5).—Ozonolysis of the axial tribromide (5) (500 mg.) exactly as described under (*a*) gave 4*ax*-bromoadamantan-2-one (7) (40 mg.), identified by its i.r. spectrum.

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