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Chemistry of Adamantane. VIII.[1] Synthesis of 1,2-difunctional Adamantanes using Protoadamantane-4-spirooxirane as a novel intermediate.

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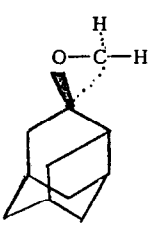
During the course of our work on 1,2-disubstituted adamantanes[2], we were interested in certain 2-substituted adamantane derivatives with a functional methyl group ($-CH_2-X$) at the position 1. Such a system cannot be directly obtained by intramolecular insertion reactions. We reported previously the preparation of 2-substituted adamantane-1-methylamine using Hofmann degradation on the corresponding acetamide [2a]. Here we describe a direct and convenient route to such 1,2-difunctional adamantane derivatives.

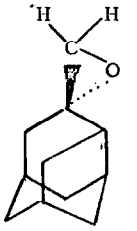
The protoadamantane ring system rearranges to the thermodynamically more stable adamantane nucleus. The relative ease with which such a conversion occurs has been illustrated and the principle has been applied to synthetic advantage[3]. It is thus possible to consider a suitable protoadamantane system bearing two functional groups which would rearrange to 1,2-disubstituted adamantanes. Such a situation could be ideally envisaged in a system like protoadamantane-4-spiro oxirane, which should provide a versatile reactive intermediate offering a wide range of possibilities in the synthesis of protoadamantane as well as adamantane derivatives. We have thus prepared this oxirane from the readily available 4-protoadamantanone[4] and examined various reactions involving opening of the oxirane ring and rearrangement of the corresponding products into 1,2-difunctionalised adamantanes.

4-Protoadamantanone on reaction with dimethylsulphonium methylide

in dimethylsulphoxide at ~54° gave essentially a quantitative yield of the spiro oxirane (I) as a mixture of epimers (m.p. 62-64°) (endo: exo = 2:3, determined by analysis of the n.m.r. spectrum). The mixture on treatment with dilute mineral acids in aqueous dioxane at low temperature (<10°) rearranged cleanly to 2-hydroxy-1-adamantanemethanol (IIa, m.p. 172-74°). The reaction of (I) with anydrous HBr led to 2-bromo-1-adamantanemethanol (IIb, m.p. 138°). The protonation of the oxirane oxygen by the acidic reagents results in a selective cleavage of the C-O bond to the more substituted carbon (Markownikoff). The process also simultaneously involves the protoadamantane-adamantane rearrangement leading to the product (II). Nucleophilic attack on (I) by methylamine occurred, as expected, by an S_N2 process at the least substituted terminal carbon leading to the aminol (III, B.maleate, m.p. 160-62°). The rearrangement of this aminol with anhydrous acids (HBr, HCl) produced the corresponding 2-halo-1-adamantanemethylamines (IVa, X=Br, B.HBr, m.p. 260-65°; IVb, X=Cl, B.HCl m.p. 216-26°).



I (endo-)



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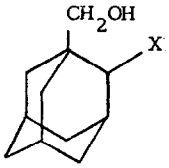
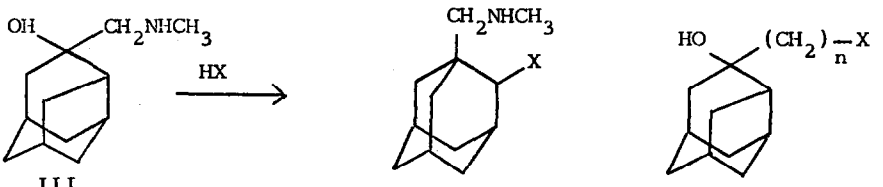


II (a) X = OH
(b) X = Br

The selectivity of the oxirane ring opening reactions coupled with the facile rearrangement, as described above, makes this route attractive for the synthesis of various 1,2-difunctional adamantane derivatives. These in turn could be easily converted to compounds otherwise only accessible by lengthy multistep syntheses. For example, 2-oxo-1-adamantane-carboxylic acid[5a] (m.p. 167-69°) has been prepared by Jones' oxidation of the oxirane (I) or the diol (IIa). Similarly, oxidation of 2-bromo-1-adamantanemethanol has afforded crystalline 2-bromo-1-adamantanecarboxylic acid[5b] (m.p.160°).



III IV (a) X = Br (b) X = Cl V

The reactions reported here proceeded smoothly with good yields. The products had satisfactory spectral data and microanalyses. Synthetic use of this route could be further extended to schemes where the carbon chain at the 1-position may be lengthened. For example, compounds of the type (V), where X is an optionally masked functional group can be obtained by addition of an anion $^{\ominus}(CH_2)_n$-X to 4-protoadamantanone. These on rearrangement should lead to 2-substituted 1-admantanealkyl derivatives, which we previously prepared by insertion reactions[2].

References

1. Part VII: See reference 2(d).

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(b) This bromoacid was reported (I.Tabushi and Y.Aoyama, J.Org. Chem., (1973) 38, 3447) as an oil, obtained by a four stage process from the 2-oxoadamantane-1-carboxylic acid prepared as in reference 5(a).