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CHEMISTRY OF ADAMANTANE. PART II.[1]

SYNTHESIS OF 1-ADAMANTYLOXYALKYLAMINES

J.K. Chakrabarti, M.J. Foulis and S.S. Szinai

Lilly Research Centre Limited, Erl Wood Manor,

Windlesham, Surrey, England.

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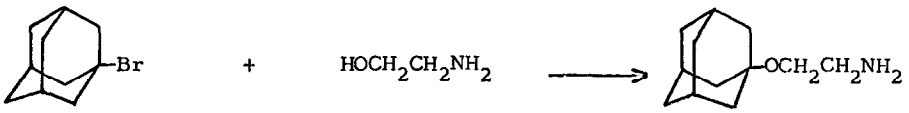
Contrary to mechanistic predictions, a carbonium ion process occurs with facility at a bridgehead position in adamantane. 1-Bromoadamantane is known to be highly reactive in nucleophilic substitution[2] despite the fact that such reactivity on a bridgehead carbon of a rigid ring system is entirely unexpected. 1-Adamantyl compounds solvolyse[2ab] quite readily and, in fact, ionic substitutions at the bridgehead are so facile as to lead sometimes to preparative complications. For example, 1-acetamidoadamantane on hydrolysis[2b] in ethylene glycol forms 1-adamantyloxyethanol[3] along with the desired amine.

We wish to report the unexpected reaction of 1-bromoadamantane with aminoalkanols leading mainly to the corresponding 1-adamantyloxyalkylamines as a result of preferential substitution on oxygen rather than nitrogen. When 1-bromoadamantane (I, 1 mole) was heated under reflux with an excess (10 fold) of hydroxyalkylamine (e.g., 2-hydroxyethylamine, II) in the presence of a base (triethylamine, 1 mole), 1-adamantyloxyalkylamine (III) was obtained in an excellent yield. The products were purified either by fractional distillation of the base or by crystallisation of the hydrochloride. These were characterised on the basis of spectral and chemical evidence. I.r. spectra showed a very strong absorption in the region 1120-1070 $cm.^{-1}$ (C-O-C frequencies) and were consistent with the other features of the respective structures. The 60 MHz n.m.r. spectra ($CDCl_3$) revealed the proton character of the 1-substituent (Table). The bridgehead 3γ protons appeared as an unresolved

broad resonance around 7.87τ and the remaining β and δ methylenes in the region of 8.1-8.5τ.[5]



I II III

On acetylation of the base with acetic anhydride and pyridine (Table, i, ii, iv, vi) only N-acetyl derivatives (νmax. 1645-1640; Amide I) were obtained. The crude base, when acetylated without purification, showed an additional weak carbonyl absorption ν max. 1725 cm.$^{-1}$ (ester) indicating the presence of a small amount of adamantylhydroxyalkylamine in the reaction mixture.[8] The formation of a similar product from n-propanolamine and 1-bromoadamantane under different conditions has been recently reported.[9]

Since nucleophilic substitution via an S_N2 pathway is impossible in this instance, it is obvious that facile ionic substitution has proceeded by way of a unimolecular S_N1 mechanism. The selectivity of the adamantonium ion for the oxygen of aminoalkanols is quite marked with the observed high yields of the resulting ethers. It is interesting to note that this reaction proceeded with equal ease in the case (ii), where an opposing steric factor is imposed by methyl substitution on the α-carbon of the hydroxyl and in the cases (x, xi, xiii), where the carbon chain is lengthened, or in the case of 3, 5, 7 - trimethyl substituted adamantane (vi and xii). Secondary and tertiary amino-alkanols served equally well as a reactant to afford the corresponding amino ethers. Thus, this reaction provides a direct one step synthesis of 1-adamantyloxyalkylamines, hitherto obtained only by an indirect route.[6]

The m.p.'s and b.p.'s are not corrected. All compounds in the Table are novel ones with the exception of (i). Satisfactory elemental analyses were obtained for all new compounds.

TABLE

Compound[a]	B.p./mm M.p. °C	Yield %	N.m.r. Chemical Shift(τ)	Hydrochloride M.p. °C	Acetate M.p. °C
i) [6] Ad.O.$CH_2CH_2NH_2$	89-90/0.1	90	6.54(unsym.t)(O.C$\underline{H}_2$-); 7.23 (unsym.t) (N-C$\underline{H}_2$-); 8.42 2P(s)(-N$\underline{H}_2$)[b]	206-208	66-68
ii) Ad.O.$CH(CH_3)CH_2NH_2$	100-101/0.2	79	6.25(m)(O.C$\underline{H}$-); 7.4 + 7.5(N-C$\underline{H}_2$-) 8.85 + 8.92(d)(-CH(C$\underline{H}_3$)-O) due to asym.centre; 8.27 2P(s)(-N$\underline{H}_2$)[b]	187-189	104-106
iii) Ad.O.$CH_2.C(CH_3)_2.N(CH_3)_2$	120-122/0.3	50		160-163(d.)	
iv) Ad.O.$CH_2CH_2NHCH_3$	108-110/0.3	77	6.48(unsym.t)(O-C$\underline{H}_2$); 7.32(unsym.t) N-C$\underline{H}_2$); 7.57 3P(s)(N-C$\underline{H}_3$); 8.15 1P(s)(-N$\underline{H}$)[b]	158-160	B.p. 150/0.4
v) [7] Ad.O.$CH_2CH_2N(C_2H_5)_2$	108-110/0.2	94		152-153	
vi) TMAd.O$(CH_2)_2NH_2$	94-95	89	6.39(unsym.t)(O-C$\underline{H}_2$); 7.28(unsym.t) (N-C$\underline{H}_2$); 9.13 9P(s)(3xC-C$\underline{H}_3$); 7.78 2P(s)(N$\underline{H}_2$)[b]	178-180	93-95
vii) Ad.O.$(CH_2)_2$.N 	-	87		195-198	
viii) Ad.O.$(CH_2)_2$.N 	132-134/0.1	91		246	
ix) Ad.O.$(CH_2)_2$.N 	-	90		225-227	
x) Ad.O.$(CH_2)_3NH_2$	100-102/0.2	75	6.49(unsym.t)(O-C$\underline{H}_2$); 7.25(unsym.t) (N-C$\underline{H}_2$); 8.57 2P(s)(N$\underline{H}_2$)[b]; (c)	155-157	
xi) Ad.O.$(CH_2)_4NH_2$	120/1.0	80	6.57(unsym.t)(O-C$\underline{H}_2$); 7.26(unsym.t) (N-C$\underline{H}_2$); 8.2 2P(s)(N$\underline{H}_2$)[b]; (c)	142-144	
xii) TMAd.O.$(CH_2)_4NH_2$	74-76	90	6.54(unsym.t)(O-C$\underline{H}_2$); 7.48(unsym.t) (N-C$\underline{H}_2$); 9.19 9P(s)(3xC-C$\underline{H}_3$); 6.77 2P(s)(N$\underline{H}_2$)[b]; (c)	281-283	
xiii) Ad.O.$(CH_2)_5NH_2$	158-160/5	72	6.72(unsym.t)(O-C$\underline{H}_2$); 7.39(unsym.t) (N-C$\underline{H}_2$); 8.80 2P(s)(N$\underline{H}_2$)[b]; (c)	179-181	

(a) Ad=1-Adamantyl-, TMAd=1-(3,5,7-trimethyl)adamantyl- (b) Removed on shaking with D_2O;
(c) Side chain methylene appearing in the region of other adamantane methylenes.

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3. We have prepared this compound, which was synthesised previously by a different route,[4] in almost quantitative yield by refluxing 1-bromoadamantane in ethylene glycol under the conditions reported here.

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7. This base and its hydrochloride were identical with those of an authentic sample prepared by reacting 2-diethylaminoethyl chloride with 1-hydroxyadamantane in the presence of NaH.

8. In the case (xiii), the corresponding adamantylhydroxyalkylamine was isolated as a solid crystalline material, m.p. 92-94°C, in about 15% yield.

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KEY WORDS

Unusual
Nucleophilic
Substitution
Tertiary carbon atom
Hydroxyalkylamines
Alkanolamine ethers