CHEMISTRY OF ADAMANTANE. VI.¹ REARRANGEMENT IN FRIEDEL-CRAFTS REACTION

OF 1-(2-CHLOROADAMANT-1-YL)-2-METHYLAMINOPROPANE.

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Normal nucleophilic or solvolytic displacement of halogen substituted at the 2-position of adamantane is expected to be severely hindered by steric factors due to the neighbouring axial hydrogens. The resistance to such reactions has been reported in an earlier paper.² Later work³ on solvolysis has also shown that, unlike normal secondary substrates, the effect of nucleophilic solvent participation in the 2-adamantane system is only minimal. On the other hand, it is possible to envisage that an intermediate trigonal carbonium ion⁴ should be reasonably accessible to a nucleophile. The substitution reactions resulting from such an intermediate should be feasible provided formation of further rearrangement products can be prevented. We examined the Friedel-Crafts reaction of 1-(2-chloroadamant- $1-y1)-2-methylaminopropane^{2}$ (I) in benzene in the presence of 3 equivalents of AlCl2. When the reaction was carried out with 1% w/v solution of (I) in benzene under reflux for 2-3 hours, the displacement of chlorine with the phenyl group occurred in almost quantitative yield. The reaction mixture on quenching and subsequent basification gave 1-(2-phenyladamant-1-y1)-2methylaminopropane (V), which was converted to its hydrochloride, m.p. $\sim 200^{\circ}$, n.m.r. δ (CDCl₂) 2.8 (lH,s, CHPh). The mixture of the two diastereoisomers, due to 2 asymmetric centres in the molecule, was separated in equal proportions by fractional crystallisation from iPrOH - petroleum ether to give isomer (1):¹¹ m.p. 210-25° (i PrOH-petrol); i.r. (KBr): 745, 700 cm⁻¹; $(\alpha)_{D}^{21} = 0$ (c, 1.6, EtOH); and isomer (2):¹¹ m.p. 210-15⁰ (EtOH-Et₂0); i.r.

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(KBr): 755, 740, 710 cm⁻¹ (a) $_{D}^{21} = 0(c, 1.0 \text{ EtOH})$. The n.m.r. spectra of the free bases of the isomers (1) and (2) revealed one proton singlet at 2.9 δ (CHPh). The main difference in the two spectra was exhibited due to the resonances of C-CH₃ and N-CH₃. These appeared at 0.95 (d) and 2.06 (s) in (1); 0.76 (d) and 2.26 (s) in (2) respectively. The protons of the side chain can be more clearly seen in n.m.r. studies with Eu(thd)₃. In addition, the quantitative chemical shifts induced with each isomer are very similar for analogous protons.⁵ Mass spectrum at 70ev in each case shows the same molecular ion (M⁺ 283). In both cases, the fragmentation pattern reveals an intact alkylamino side chain (m/e 211) and a phenyl substituent (m/e 205) to the adamantane nucleus. The similarity in both spectra indicates the two products as diastereoisomers rather than structural isomers.

The above reaction, when conducted in 20% w/v solution of (I) in benzene, led to a mixture of products from which a major component (<u>ca</u>. 50%), besides (V) (<u>ca</u>. 20%) and some dehalogenated product² (IV) (ca. 15%) was isolated by preparative glc. The rest (<u>ca</u>. 15%) consisted of minor constituents and polymeric material. The major product was characterised as a bridge head substituted derivative, 1-(3-phenyladamant-1-y1)-2-methylaminopropane (VII), on the basis of spectral evidence. N.m.r. $\S(CDCl_3)$: 1.07 (d, C-CH₃), 2.36 (s, N-CH₃); the absence of a low field proton adjacent to the phenyl group confirms that the phenyl is substituted on one of the equivalent tertiary positions. Hydrochloride,¹¹ m.p. 209-10^o (iPrOH- n-hexane).

The apparent intramolecular 1,2-shift in adamantane is prohibited due to the unfavourable stereochemical relationship between the migrating group and the vacant orbital of the adjoining carbonium centre.⁶ The formation of the bridgehead isomer (VII) can be rationalised by a process of intermolecular hydride shifts⁷ generating a tertiary adamantyl cation (III) (Scheme 1). 2-Adamantyl cation is also known⁸ to rearrange to its tertiary isomer in strong acidic solution. However, the variations in the concentration

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of (V) and (VII) with reaction time, as determined by glc,⁵ suggest that the normal product (V), initially derived from (II), also partially rearranges to (VII). The formation of a benzylic cation (VI) in this case would be greatly facilitated under the reaction conditions. 2-Methyladamantane is known⁹ to rearrange to 1-methyladamantane <u>via</u> a skeletal isomerisation involving an intermediate 2-methyl-2-adamantyl cation. 2-Phenyladamantane, obtained from a reaction of dehydroadamantane (tetracyclo (3,3,1,1,^{3,7} o^{2,4}) decane) with benzene and AlCl₃ at room temperature, is reported¹⁰ to rearrange to 1-phenyladamantane in boiling benzene under the influence of AlCl₃.



Intermolecular hydride shifts are second order and highly dependent on concentration. The presence of a considerable amount of disproportionation product (IV) coupled with the fact that the rearrangement can be suppressed in dilute solution indicates the intermolecular nature of the reaction as a major course.

REFERENCES

- Part V. <u>J.Med. Chem</u>., <u>15</u>, 853 (1972).
- 2. W.H.W. Lunn, W.D. Podmore, and S.S. Szinai, <u>J. Chem. Soc</u>., (c) 1657(1968).
- 3. (a) J.L. Fry, C.J. Lancelot, L.K.M. Lam, J.M. Harris, R.C. Bingham,
 D.J. Raber, R.E. Hall, P.v.R. Schleyer, <u>J.Amer.Chem.Soc</u>., <u>92</u>, 2538 (1970); (b) J.M. Harris, D.J. Raber, R.E. Hall, P.v.R. Schleyer,
 <u>1bid</u>., <u>92</u>, 5729 (1970); (c) J.A. Bone, M.C. Whiting, <u>Chem.Comm</u>.,
 115 (1970).
- 4. A number of reports appeared in the literature describing the chemistry and rearrangement of 2-adamantyl cation. For details and references, see Topics in Current Chemistry, Chemistry of Adamantane, by R.C. Bingham, and P.V.R. Schleyer, <u>Fortsch.Chem.Forsch.</u>, <u>18</u> (1971).
- 5. A.F. Cockerill, D.N.B. Mallen, D. Osborne and D.M. Rackham of this laboratory. (Private Communication.)
- 6. (a) P.v.R. Schleyer, <u>Angew.Chem.</u>, Int.Edn., <u>8</u>, 529 (1969).
 (b) D.M. Brouwer and H. Hogeveen, <u>Recl.Trav.Chim. Pays-Bas</u>, <u>89</u>, 211 (1970).
- P.v.R. Schleyer, L.K.M. Lam, D.J. Raber, J.L. Fry, M.A. McKervey, J.R. Alford, B.D. Cuddy, V.G. Keizer, H.W. Geluk, J.L.M.A. Schlatmann, J. Amer. Chem. Soc., 92, 5246 (1970) (references cited therein).
- (a) A.T. Balaban, D. Farcasiu, R. Bania, <u>Rev. Roumaine Chem.</u>, <u>11</u>, 1205 (1966); (b) C. Carpenter, Ph.D. Thesis, Pennsylvania State University, 1967.
- Z. Majerski, P.v.R. Schleyer, A.P. Wolf, <u>J. Amer.Chem.Soc</u>., <u>92</u>, 5731 (1970).
- 10. A.C. Udding, J. Strating and H. Wynberg, Tet.Lett., 1345 (1968).
- 11. Satisfactory elemental analyses were obtained for these compounds.