Tetrahedron Letters No. 43, pp. 3987 - 3990, 1971. Pergamon Press. Printed in Great Britain.

BRIDGEHEAD REACTIVITY IN PROTOADAMANTANE

By Amna Karim and M.A. McKervey

Department of Chemistry, The Queen's University, Belfast BT9 5AG

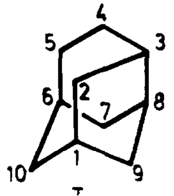
Edward M. Engler and Paul v. R. Schleyer

Department of Chemistry, Princeton University, Princeton, N.J. 08540

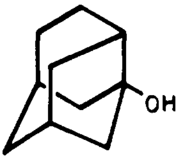
(Received in UK 1 September 1971; accepted for publication 22 September 1971)

The solvolytic reactivities of bridgehead substrates have recently been placed on a quantitative basis through the application of computer conformational analysis calculations.[1] It is desirable to test the predictive power of this treatment for other reactions involving carbocations, e.g., ionic bromination. Protoadamantane (I), with four different bridgehead positions, appeared to afford a suitable complex substrate for this purpose, especially since direct substitution of I has not been reported.

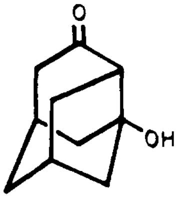
Exposure of protoadamantane (I)[2] to bromine at 80° for three hours gave predominately (∿95%) a single tertiary monobromide, m.p. 80-81°, for which the 8-protoadamantyl bromide structure could readily be dismissed. The alcohol, m.p. 235-236°, obtained on hydrolysis of the bromination product with hydrochloric acid-dimethylformamide was distinctly different from 8-hydroxyprotoadamantane (II), m.p. 258-259°, prepared by Wolff-Kishner reduction of 8-hydroxyprotoadamantan-4-one (III).[3]



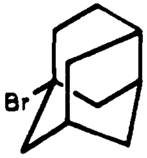
I



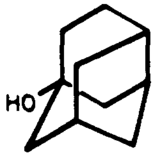
II



III



IV



V

The formation of essentially a single monobromide is in agreement with the conformational analysis calculations, Table I, which indicate that the 6-position should be most reactive, appreciably more reactive than the 3-position and much more reactive than either the 1- or the 8-positions. These calculations evaluate the change in strain energy (Δ strain) in going from ground state (approximated by the parent hydrocarbon) to the transition state (approximated by the appropriate carbonium ion).

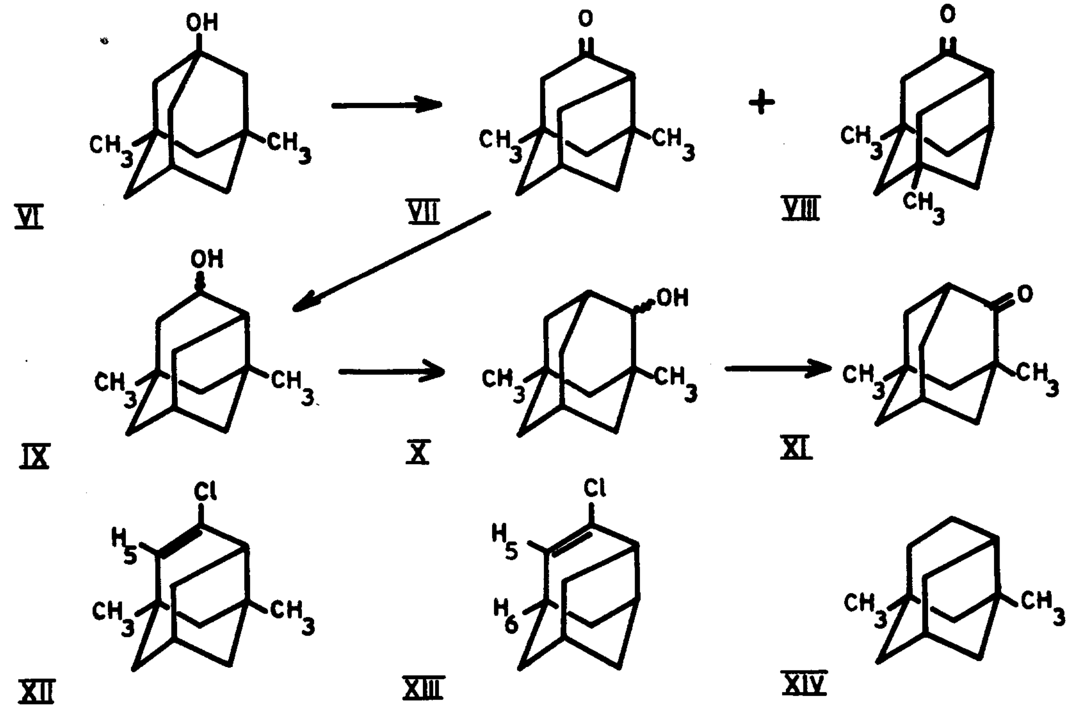
Table I. Calculated Bridgehead Reactivities 80% Ethanol, 70° [a]

Position	Δ Strain, kcal/mole	k_{Br}(calc)sec^{-1} [b]	k_{Br}rel(calc)[b]	k_{Br}(Obs)[c],sec^{-1}
6-Protoadamantyl	10.8	4.7×10^{-5}	1.00	1.50×10^{-4}
3-Protoadamantyl	12.9	6.6×10^{-6}	0.14	-
8-Protoadamantyl	17.7	7.4×10^{-8}	1.6×10^{-3}	-
1-Protoadamantyl	18.3	4.2×10^{-8}	9.5×10^{-4}	-
1-Adamantyl[a]	12.3	1.2×10^{-5}	0.26	7.24×10^{-5}

[a] For details of the approach used, see ref. 1. [b] Based on equation (3) from ref. 1: $-\log k_{bromide}$, 80% EtOH, 70° = 0.41 Δ Strain(calcd) - 0.12. [c] Calculated from experimental data.

That the bromination product was 6-bromoprotoadamantane (IV) (hydrolysis product, V), was confirmed through the following chemical argument: if the product is IV then under similar reaction conditions 6-methylprotoadamantane should be significantly less reactive (see Table I) towards bromination. This argument involves the reasonable assumption that replacement of a bridgehead hydrogen atom by a methyl group will have a negligible effect on the relative reactivity towards bromination of the three remaining bridgehead positions. In practice it was more convenient to have two bridgeheads blocked with methyl groups, but one of these methyls was at the 8-position, already excluded as a possible bromination site.

Reaction of 3,5-dimethyl-1-hydroxyadamantane (VI) with lead tetraacetate and iodine in benzene afforded an unstable iodo-ketone mixture (ca. 30% yield) which was converted with pyridine into a 9:1 mixture of liquid dimethylprotoadamantanones, (VII)(dinitrophenylhydrazone m.p. 162-163°) and (VIII) (dinitrophenylhydrazone m.p. 171-172°)[4,5] which were separated by preparative g.l.p.c. The methyl groups in the preponderant isomer VII were located as follows. The ketone was reduced with lithium aluminium hydride, the alcohol mixture IX so produced was exposed to hot 25% sulphuric acid whereupon a protoadamantane → adamantane rearrangement occurred[6,7] giving a new alcohol mixture X which upon oxidation with chromic acid gave as the major product 1,5-dimethyladamantan-2-one(XI), identified by comparison with an authentic sample prepared by cobalt naphthenate - catalysed air oxidation of 1,3-dimethyladamantane.[8] This result fixes the location of the C-8 methyl group. The position of the second methyl group followed from the observation that treatment of VII with PCl_5/PCl_3 gave as major product



chloroolefin XII. The nmr spectrum of XII was very similar to that of 4-chloroprotoadamantene (XIII),[7] but lacked the H_5-H_6 coupling present in the latter. H_5-H_3 coupling was present in both XII and XIII. Wolff-Kishner reduction of VII gave 6,8-dimethyl protoadamantane (XIV), b.p. 67° (12 mm).

When XIV was treated with bromine under conditions whereby protoadamantane (I) undergoes complete bromination, only 6% reaction was observed and the remainder of the starting hydrocarbon (XIV) could be recovered.[9] Thus, we conclude that the 6-position of protoadamantane (I) is the most reactive towards ionic bromination.

The solvolysis rates of 6-bromoprotoadamantane (IV) in 80% ethanol were: 49.65°, 1.42×10^{-5} sec^{-1}; 75.15°, 2.60×10^{-4} sec^{-1} ($\Delta H^{\ddagger}$ 24.8 kcal/mole, $\Delta S^{\ddagger}$ -4 e.u.). The interpolated value at 70°, 1.50×10^{-4} sec^{-1} agreed within a factor of three with the value predicted on the basis of the strain calculations (Table I). Experimentally, 6-protoadamantyl bromide (IV) solvolyzes two times faster than 1-adamantyl bromide (Table I).

Competitive experiments showed protoadamantane (I) to be slightly less reactive towards bromination than adamantane. This observation is easily reconciled with the relative solvolysis rates when statistical factors are taken into consideration. Adamantane has four equivalent bridgehead positions available for bromination while protoadamantane (I) has only one 6-position. Thus on a per bridgehead basis, adamantane is less reactive towards bromination than protoadamantane.

These results, and prior indications[10] show that the strain calculations, which work so well for solvolytic reactivities, can be applied as well to the prediction of bridgehead brominations, and very likely to other substitution processes as well.[1]

References and Footnotes

(1) R.C. Bingham and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, 93, 3189 (1971).

(2) Prepared by Wolff-Kishner reduction of protoadamantan-4-one (4).

(3) J.R. Alford and M.A. McKervey, *Chem. Commun.*, 1970, 615.

(4) *Cf.* W.H.W. Lunn, *J. Chem. Soc.* (C), 1970, 2134; R.M. Black and G.B. Gill, *Chem. Commun.*, 1970, 972.

(5) The structure proof of the minor ketone VIII will be described in the full paper.

(6) D. Lenoir, P. von R. Schleyer, C.A. Cupas, and W.E. Heyd, *Chem. Commun.*, 1971, 26.

(7) B.D. Cuddy, D. Grant, and M.A. McKervey, *Chem. Commun.*, 1971, 27.

(8) A. Schneider, U.S. Patent 3,356,741 (1967); *Chem. Abstr.*, 68, 62536p (1968).

(9) Our calculations (Table I) indicate that the 3-position of XIV should be most readily attacked. We are investigating this experimentally.

(10) P. v. R. Schleyer, P.R. Isele, and R.C. Bingham, *J. Org. Chem.*, 33, 1239 (1968); R.C. Bingham and P. v. R. Schleyer, *ibid.*, 36, 1198 (1971); R.C. Bingham and P. v. R. Schleyer, *Fortschr. Chem. Forschung*, 18, 1 (1971).

Acknowledgements. This work was supported at Princeton by grants from the National Institutes of Health (AI-07766), the National Science Foundation, and Hoffmann-La Roche, Inc., Nutley, N.J. We thank Dr. A. Schneider, Sun Oil Company, for a generous gift of 1,3-dimethyladamantane.