The Reactions of 1-Acetamidoadamantane and 1-Acetamido-4-phenyl-bicyclo-[2,2,2]octane with Sodium Hydroxide in Ethylene Glycol or Diethylene Glycol

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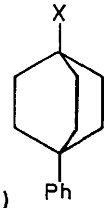
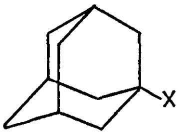
Summary The reaction of 1-acetamidoadamantane with sodium hydroxide in ethylene glycol gives 2-(1-adamantylamino)ethanol, and 1-acetamido-4-phenylbicyclo[2,2,2]-octane reacts in an analogous way, whereas the reactions with sodium hydroxide in diethylene glycol give the corresponding amines.

REQUIRING 1-amino-4-phenylbicyclo[2,2,2]octane, (Ib), for other work,[1] we hydrolysed[2] 1-acetamido-4-phenylbicyclo-[2,2,2]octane, (Ia), which was obtained in 70% yield by the Ritter reaction on (Ig).[1] Hydrolysis of (Ia) with sodium hydroxide in diethylene glycol (digol) at 170° for 48 h gave (Ib). The reaction of (Ia) with sodium hydroxide in ethylene glycol was also attempted, despite a report that the hydrolysis of (IIa) under these conditions is troublesome[3,4] because of the formation of 2-(1-adamantyloxy)-ethanol, (IIe), formed by reaction of the solvent with the bridgehead adamantyl carbonium ion. Since 1-bicyclo-[2,2,2]octyl bridgehead derivatives are 1000 times less reactive than the 1-adamantyl derivatives in solvolytic reactions,[3,5] we expected that C-1–N heterolysis in the amide, (Ia), would not interfere with the formation of the amine, (Ib). However, the reaction of (Ia) with sodium hydroxide in ethylene glycol at the b.p. for 48 h gave 2-(4-phenyl-1-bicyclo[2,2,2]octylamino)ethanol, (Ic), (60%); m.p. 126—127° [from light petroleum (b.p. 80—100°)]; i.r. (KCl) 3273 (sharp), 3112 (broad), 1602, 1495, 1447, 1215, 1134, 1068, 750, 690 cm^{-1}; n.m.r. ($CDCl_3$) τ 2·75 (m, 5H, phenyl), 6·38 (t, 2H, –C*H*$_2$–O), 7·27 (t, 2H, N–C*H*$_2$–), 8·00 (m, –N*H*– and –O*H*), overlapping 8·05—8·40 (sym m, bicyclo-octyl H; total 14H); M^+ 245, accurate mass measurement confirms $C_{16}H_{23}NO$. Acetylation of (Ic) gave the diacetyl derivative, (Id), m.p. 105–107° (from di-isopropyl ether); i.r. (KCl) 3080, 1729, 1640, 1600, 1495, 1229, 1050, 761, 697 cm^{-1}; n.m.r. ($CDCl_3$) τ 2·74 (m, 5H, phenyl), 5·84 (t, 2H, –C*H*$_2$–O), 6·42 (t, 2H, N–C*H*$_2$–), 7·73—8·13 (m, bicyclo-octyl H, with two singlets at 7·84, –COC*H*$_3$ and 7·94, –COC*H*$_3$; total 18H); M^+ 329.



(I) Ph



(II)

	X
(a)	NHAc
(b)	NH_2
(c)	$NH{\cdot}CH_2{\cdot}CH_2OH$
(d)	$NAc{\cdot}CH_2{\cdot}CH_2OAc$
(e)	$O{\cdot}CH_2{\cdot}CH_2OH$
(f)	$O{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2OH$
(g)	OH

We then re-investigated the reaction of (IIa) with sodium hydroxide in ethylene glycol at the b.p. for 48 h, which gave 2-(1-adamantylamino)ethanol, (IIc),[6] (65%), m.p. 98—100° [from light petroleum (b.p. 80—100°)]; n.m.r. ($CDCl_3$) τ 6·38 (t, 2H, –C*H*$_2$–O), 7·26 (t, 2H, N–C*H*$_2$–), 7·70 (m, 2H, –N*H*– and –O*H*), 7·92 (m, 3H, β-adamantyl H), 8·33 (m, 12H, α- and γ-adamantyl H); M^+ 195. Acetylation of this product gave (IId), m.p. 87—88° (from di-isopropyl ether).

G.l.c. analysis of samples taken during the reaction of (IIa) with sodium hydroxide in ethylene glycol showed that (IIe)[7] was not formed during the reaction and therefore ionisation of (IIa) with the acetamido-group as the leaving group to give the bridgehead carbonium ion does not appear to occur. When (IIa) was heated in ethylene glycol at the b.p. without sodium hydroxide (IIe) was not formed. Thus the acetamido-group does not behave as a leaving group under these conditions either, although it may do so under acidic conditions.[8]

1-Aminoadamantane, (IIb), was formed (80%) by the hydrolysis of (IIa) with sodium hydroxide in digol[9] and the reaction of (IIb) with sodium hydroxide in ethylene glycol produced (IIc).

It seems, therefore, that what was thought[3,4] to be an example of the ready solvolytic reaction of a bridgehead acetamido-compound to give (IIe) is really a reaction of the initial hydrolysis product, (Ib) or (IIb), with the solvent ethylene glycol in the presence of base. The long time advocated[2] for hydrolysing bridgehead acetamido-compounds is not necessary and with ethylene glycol this leads to a secondary product. A possible explanation is that ethylene oxide is formed reversibly by the action of sodium hydroxide on ethylene glycol under these anhydrous conditions and that the ethylene oxide then reacts with the amine. We are presently investigating these possibilities.

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[1] N. B. Chapman, S. Sotheeswaran, and K. J. Toyne, *J. Org. Chem.*, 1970, **35**, 917.

[2] E. I. du Pont de Nemours and Co., Netherlands Patent Application 6,507,151; *Chem. Abs.*, 1967, **67**, 53872a. We thank Dr. J. A. Snyder (E. I. du Pont de Nemours and Co., Newark, Delaware 19711) for helpful correspondence.

[3] R. C. Fort and P. von R. Schleyer, *Chem. Rev.*, 1964, **64**, 277.

[4] J. K. Chakrabarti, M. J. Foulis, and S. S. Szinai, *Tetrahedron Letters*, 1968, 6249.

[5] (a) P. von R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, 1961, **83**, 2700; (b) R. C. Bingham and P. von R. Schleyer, *ibid.*, 1971, **93**, 3189.

[6] See patent applications by E. I. du Pont de Nemours and Co., *Chem. Abs.*, 1965, **63**, P9838d; 1965, **63**, P14727a; 1966, **64**, P4970c; 1966, **64**, P15769e; 1967, **67**, P11275c; 1969, **71**, P123732p.

[7] S. S. Szinai and J. K. Chakrabarti. Patent application by Lilly Industries Ltd., *Chem. Abs.*, 1970, **72**, 66496j.

[8] (a) H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.*, 1959, **92**, 1629; (b) J.J. Ritter and P. P. Minieri, *J. Amer. Chem. Soc.*, 1948, **70**, 4045; (c) B. C. Challis and J. A. Challis in "The Chemistry of Amides", ed. J. Zabicky, Interscience, London, 1970, ch. 13, p. 731.

[9] (a) H. Stetter, J. Mayer, M. Schwarz, and K. Wulff, *Chem. Ber.*, 1960, **93**, 226; (b) With digol as solvent, one might have expected the formation of (IIf) if solvolysis of (IIa) occurred.