Stereospecific Synthesis of 2,4-Diaxial Adamantane and 2,4-Di-*endo*-protoadamantane Derivatives *via* a Nitrone Intermediate

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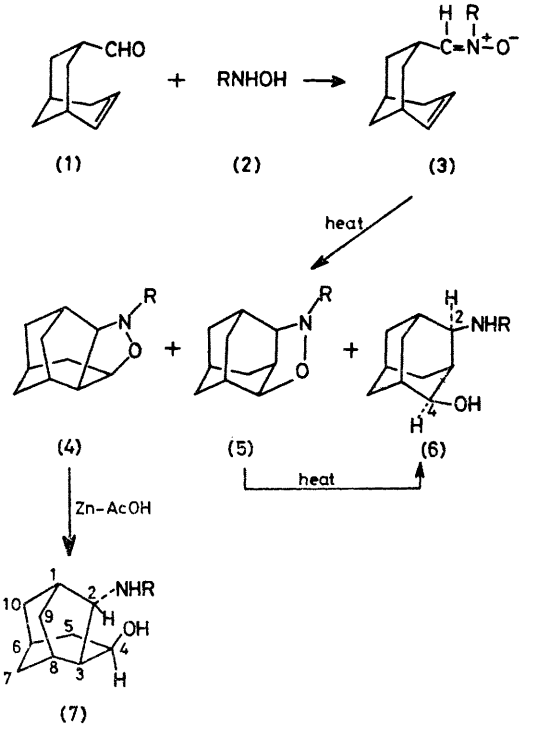
Summary An intramolecular 1,3-dipolar cycloaddition of the bicyclo[3.3.1]non-6-ene nitrone (**3**) yielded the 2,4-oxa-aza-bridged-protoadamantane (**4**), -adamantane (**5**), and 2-*ax*-amino-4-*ax*-hydroxyadamantane derivatives (**6**) in a ratio depending on the substituents and reaction conditions used; reduction of (**4**) gave the 2-*endo*-amino-4-*endo*-hydroxyprotoadamantane derivative (**7**) in good yield.

INTRAMOLECULAR 1,3-dipolar cycloadditions have proved to be of considerable value in the synthesis of novel fused ring heterocycles.[1] For example, nitrone-based syntheses of luciduline[2] and cocaine[3] have been reported recently. We now report a convenient stereospecific synthesis of 2,4-diaxial adamantane and 2,4-di-*endo*-protoadamantane derivatives *via* an intramolecular 1,3-dipolar cycloaddition of the bicyclo[3.3.1]non-6-ene nitrone (**3**).

The nitrone (**3**) was generated *in situ* simply by heating *endo*-bicyclo[3.3.1]non-6-ene-3-carbaldehyde (**1**),[4] readily available from 4-*eq*-methylsulphonyloxyadamantan-2-one, and a suitable hydroxylamine (**2**). When an equimolar mixture of (**1**) and benzylhydroxylamine (**2a**) was heated in the presence of a molecular sieve in toluene under reflux for 12 h, the adducts (**4a**) (31%), (**5a**) (3%), and 2-*ax*-benzylamino-4-*ax*-hydroxyadamantane (**6a**) (m.p. 111—112 °C; 8%)† were obtained after chromatography (Scheme). There was a distinct difference between the ^{1}H n.m.r. spectra ($CDCl_3$) of (**4a**) and (**5a**); (**4a**) showed a complex multiplet in the δ 3·5—2·8 region (2H), whereas (**5a**) showed a characteristic triplet in this region due to 2-H_{eq} (δ 3·0, J 4·5 Hz). Reduction of (**4a**) with zinc and acetic acid gave the aminoalcohol (**7a**) (oil; 64%), which showed a



a; R = $PhCH_2$
b; R = Me
c; R = 2-Adamantyl

SCHEME

† All new compounds described here have spectral (i.r., ^{1}H n.m.r., and mass spectra) and microanalytical properties in agreement with the assigned structures.

doublet of doublets at δ 3·26 (*J* 9·5 and 4·5 Hz), due to 2-H_{exo} supporting the proposed protoadamantane structure. The adduct (**5a**) was converted into the aminoalcohol (**6a**) (75%) on heating in toluene at 120 °C for 10 h. The adamantane structure of (**6a**) was confirmed by the similarity of its 2-H_{eq} and 4-H_{eq} n.m.r. signals (δ 3·0 and 3·81 respectively), to those of the known 2-*ax*-4-*ax*-dibromo- and -dihydroxy-adamantanes.[5]

TABLE. Intramolecular 1,3-dipolar cycloaddition of the bicyclo[3.3.1]non-6-ene nitrones (**3**).

Hydroxylamine	Solvent	Temperature (time)	Products (% yield)		
(**2a**)	Toluene	Reflux (12 h)	(**4a**) (31)	(**5a**) (3)	(**6a**) (8)
(**2a**)	Benzene	75—80 °C (8 days)	(**4a**) (38)	(**5a**) (20)	(**6a**) (8)
(**2a**)	Ethanol	75—80 °C (8 days)	(**4a**) (19)	(**5a**) (2)	(**6a**) (32)
(**2b**)	Toluene	Reflux (11 h)	(**4b**) (26)	(**5b**) (7)	
(**2c**)	Benzene	Reflux (10 h)	(**4c**) (40)	(**5c**) (30)	

The reaction of (**1**) and (**2a**) under other conditions and the reaction of (**1**) with (**2b**) and (**2c**) were also examined and the results are summarized in the Table. Several points emerge from the data. (i) The intramolecular cycloaddition of (**3**) proceeded nonregioselectively to afford both protoadamantane and adamantane skeletons but the ratio of these products depended on the conditions and the substituent R. (ii) The formation of the protoadamantane skeleton was favoured in aromatic solvents but that of the adamantane skeleton was favoured in ethanol. (iii) The stability of the adducts depended on the substituent R; the benzyl derivative (**5a**) was particularly unstable and afforded (**6a**) by reductive cleavage. This route therefore provides a simple stereospecific preparation of some 2,4-diaxial-adamantane and 2,4-di-*endo*-protoadamantane derivatives which are difficult to obtain otherwise, requiring multistep preparations and isomer separation.

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