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A Novel Ring Expansion Reaction in the Reduction of Benzylic Methoxyamines with Lithium Aluminium Hydride

Susan E. Booth, a Paul R. Jenkins* and Christopher J. Swain b

^a Department of Chemistry, The University, Leicester LE1 7RH, UK ^b Merck, Sharp and Dohme, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK

Reduction of the N–O bonds of benzylic hydroxylamines with lithium aluminium hydride gives a novel ring expansion reaction that can be explained by a radical mechanism.

We recently reported the intramolecular cyclisation of vinyl and aryl radicals on to oxime ether acceptors to give five-, sixand seven-membered rings.¹ Part of these studies was the reduction of the N–O bond of the methoxyamine products to produce the corresponding amines. Several methods are available for the reduction of the N–O bond,² but initial attempts at reduction using aluminium amalgam,³ samarium diiodide⁴ and zinc-acetic acid were unsuccessful. The attempted reduction of the N–O bond of 1 with lithium aluminium hydride (LiAlH₄) resulted in an unexpected rearrangement which is the subject of this communication.

4a-Methoxyaminocyclohex[a]indan 1 in anhydrous diethyl ether was reacted with LiAlH₄ at reflux temperature for 2 h under nitrogen. Chromatography of the product mixture gave two pure solids (19:6 ratio) in 96% overall yield.[†] Mass

spectrometry indicated that the two products were isomers (M = 147), but neither of the products were the expected 4a-aminocyclohex[a]indan 2. The IR spectra showed, in each case, only a single N-H stretching vibration instead of the expected two strong bands for the primary amine 2. The ¹H NMR spectra showed all the aromatic protons appearing at higher field than those of the starting material, strongly suggesting that a rearrangement had occurred bringing the nitrogen into conjugation with the aromatic ring. The spectroscopic evidence indicated that the products were trans and cis 1,2,3,4,4a,9,9a,10-octahydroacridine 3 and 4 with the trans isomer as the major product. The melting point for the trans compound 3 was 80-82 °C which was in agreement with the literature value.5 In the same way 1-methoxyamino-1methylindan 5 gave 2-methyl-1,2,3,4-tetrahydroquinoline 6⁵† and ethyl 3a-methoxyaminocyclopent[a]indan 7 was converted into 1,1a,1b,3-tetrahydro-1b-hydroxymethylcyclopenta[b]quinoline 8 (Scheme 1).†

[†] Compounds **3**, **4**, **6** and **8** were fully characterised by ¹H and ¹³C NMR spectroscopy and high-resolution mass spectrometry.



LiAlH₄ usually behaves as a hydride donor when used as a reducing group for carbonyl groups. However, in some cases, such as the reduction of carbon-halogen bonds of aryl and vinyl halides, a mechanistic study has shown that these are not simple S_N2 substitution reactions.⁶ Reduction of vinyl halides can result in a geometrical isomerism that might suggest the involvement of a radical intermediate.7 It is suggested that in these cases the reaction involves a single electron transfer mechanism.

A similar electron-transfer process could explain the reaction of 4a-methoxyaminocyclohex[a]indan 1 with LiAlH₄ (Scheme 2). A radical anion 9 could be formed by a one electron-transfer, subsequent decomposition leading to the stabilised radical 11, ring opening of the strained threemembered ring would either produce the aminyl radical 10 or result in ring expansion to the six-membered ring tertiary radical 12 where the aromaticity of the benzenoid ring has also been re-established. Reaction with hydride would then give 1,2,3,4,4a,9,9a,10-octahydroacridine as a mixture of the cis and trans isomers 3 and 4 as the tertiary radical 12 can be attached by the hydride from either face. This mechanism offers a rational explanation of the observed reaction, but it can only be regarded as speculative in the absence of definitive evidence. This ring expansion of benzylic methoxyamines is related to the Beckmann type rearrangement of oximes with LiAlH₄.⁸ A somewhat related reaction has been reported by Curran.9

The combination of this new rearrangement reaction with the facile synthesis of hydroxylamines by intramolecular



radical cyclisation reactions promises to be a useful method for the synthesis of a number of N-heterocyclic natural products.

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