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REDUCTION OF 1-SUBSTITUTED 3-OXIDOPYRIDINIUMS

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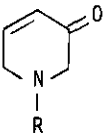
Abstract 1-Substituted 3-oxidopyridiniums are smoothly reduced by sodium borohydride in ethanol to give 1-substituted 3-hydroxypiperidines but much less efficiently by lithium aluminium hydride in hot tetrahydrofuran to give mainly, 1-substituted 5-hydroxypiperid-3-eines.

The reduction of pyridinium salts is well documented[1], however despite the considerable, recent structural[2a] and chemical[2b] interest in 1-substituted 3-oxidopyridiniums, in particular work[2b] by Katritzky and co-workers on cycloaddition reactions of such species, very little has been reported[3] on their reduction.

Simple 1-substituted 3-oxidopyridiniums have been catalytically reduced[3a,b] over platinum[3a] or rhodium[3b], to hexahydro derivatives, under some circumstances[3a] with concomitant hydrogenolysis of the 3-oxygen-substituent. Formic acid reduces[3c] 1-phenyl-3-oxidopyridinium to its hexahydro derivative. A study[3d] of electrolytic reduction of 3-oxidopyridiniums showed this to be complex, ring-fission as well as ring-contraction products being produced in addition to hexahydro derivatives. In two reports[3e,f] of complex metal hydride reductions the heterocyclic moiety was embedded in a polycyclic framework: in each case borohydride reduction was reported to give a tetrahydro-product in which the residual double bond was either[3e] part of an adjoining benzenoid ring or[3f] conjugated with an aromatic ring.

In the light of reports[4] of the partial reduction (addition of one hydride equivalent) by complex metal hydride of meso-ionic species, to which the six-membered 1-substituted 3-oxidopyridiniums are closely analogous, and in the hope of effecting comparable partial reduction and thereby producing species, such as 1, with potential as synthons[5] for alkaloid synthesis, we undertook an examination of the complex metal hydride reduction of some simple representative 1-aryl- and 1-alkyl-3-oxidopyridiniums.

Sodium borohydride treatment of the 3-oxidopyridiniums (2a-d) in ethanol at room temperature gave, cleanly, hexahydro derivatives[6] (3a-d) in high yield. The use of sodium borodeuteride in ethanol on 2c gave a trideuterio-3c in which the positions of the labelled atoms were established[7] as shown on 4 by (i) the absence of an ^{1}H n.m.r. signal at τ 4.8 for a C-3 proton, (ii) a reduction by two in the integrated intensity of signals in the region τ 7.2-7.6, corresponding to hydrogen on C-2 and C-6, and (iii) an increase of only one in the major spectral fragment ion at m/e 43, corresponding to $\mathrm{MeN^+{:}CH_2}$ ($\rightarrow \mathrm{Me\overset{+}{N}{:}CHD}$).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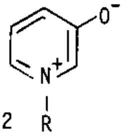
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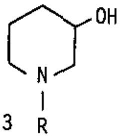
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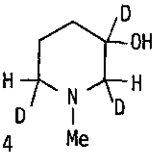
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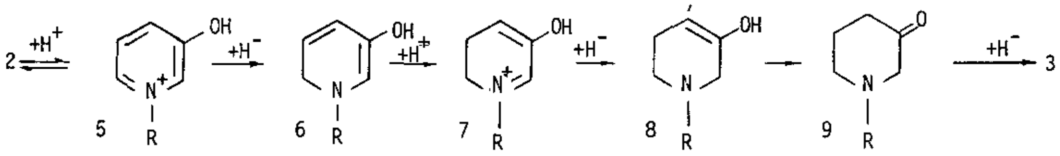
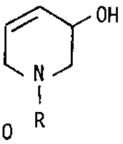
R : a) Ph ; b) indol-3-ylethyl; c) Me; d) pyrid-4-yl.

This labelling pattern and the facility of the borohydride reductions of 3-oxidopyridiniums, species which are overall neutral, are open to interpretation by several mechanistic sequences, varying only in detail, but certainly involving initial O-protonation and then, for example, intermediates (5-9).



Lithium aluminium hydride treatment of the 3-oxidopyridiniums (2a-c) yielded considerably more complex product mixtures and disappointingly did not lead to the desired addition of only one hydride equivalent and formation, after protonation, of species of the form 1. No reaction occurred in ether at room temperature or at reflux and prolonged reflux in tetrahydrofuran was necessary to achieve consumption of starting material.

In each case the major product was at a tetrahydro-oxidation-level, thus 2a and 2b gave 10a and 10b[8] respectively. From 2c a dimer (11) was obtained, the formation of which can be interpreted as involving strong base ($\mathrm{LiAlH_4}$) catalysed isomerisation[10] of allylamine to enamine and proton-catalysed dimerisation during aqueous work-up.



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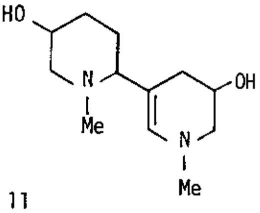

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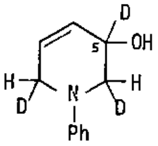

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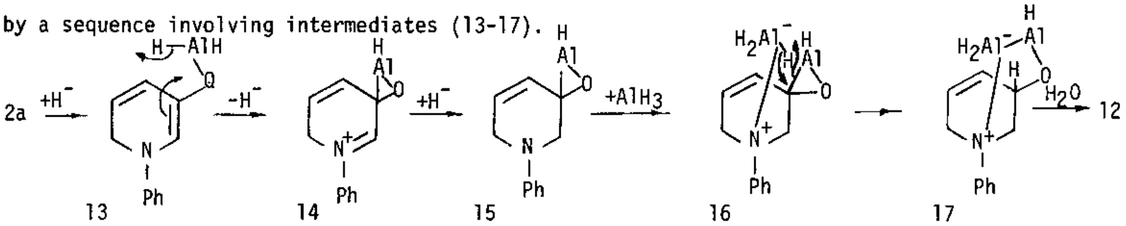
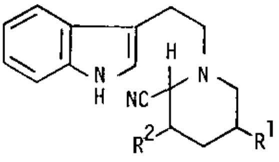
R : a) Ph ; b) indol-3-ylethyl

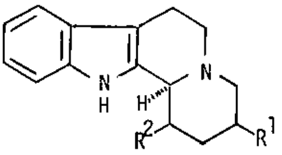
Labelling studies were carried out for the reduction of 2a, thus work-up of the hydride reduction with D_2O led to no incorporation of deuterium on carbon in product (10a). Conversely the use of lithium aluminium deuteride gave cleanly a trideuterio-10a in which the positions of the labelled atoms were established as shown on 12 by (i) the absence of a ^1H n.m.r. signal at τ 5.75 for a C-5-proton, (ii) the presence of signals for two olefinic protons, (iii) an increase of one in the mass spectral fragment ion at m/e 106, corresponding to $PhN^+H{:}CH_2$ ($\rightarrow PhN^+H{:}CHD$), and (iv) integration for "half" a proton in each case for the signals[11] for axial and equatorial protons at both C-2 and C-6. A rationalisation for this result is given by a sequence involving intermediates (13-17).



Although sodium cyanoborohydride was without effect on 2b, prolonged exposure (7 days) to a mixture[12] of potassium cyanide and sodium borohydride in water/methanol/ether gave the cyano-alcohol (18a) as major product together with its regio-isomer (18b). These cyano-alcohols could be utilised[12b,13] for the generation of immonium species and thereby of indolo-quinolizidines by treatment with 50 % aqueous acetic acid at room temperature; 18a gave 19a as major stereoisomer and 18b comparably produced 19b, again together with a minor amount of the stereoisomer.



(18)	R^1	R^2
a	OH	H
b	H	OH



(19)	R^1	R^2
a	β-OH	H
b	H	β-OH

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References and Notes

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5. *cf.* F. E. Ziegler and G. B. Bennett, *J. Amer. Chem. Soc.*, 1973, 95, 7458; T. Imanishi, H.Shin, M. Hanaoka, T. Momose, and I. Imanishi, *Heterocycles*, 1980, 1111.

6. All new compounds gave spectral and elemental or high resolution M.S. analyses consistent with the structures given.

7. Measurements made on the crystalline 3,5-dinitrobenzoate.

8. Further reduction, of the allylic alcohol double bond[9] was observed on prolonged reflux.

9. *cf.* F. A. Hochstein and W. G. Brown, *J. Amer. Chem. Soc.*, 1948, 70, 3484.

10. S. J. Martinez and J. A. Joule, *Tetrahedron*, 1978, 34, 3027; P. Beeken and F. W. Fowler *J. Org. Chem.*, 1980, 45, 1336.

11. Signals for the α-protons in 10a and 6.25 (1H, dd, J 3, 18 Hz, C-2-H_{eq}), 6.48 (1H, dd, J 1.5, 18 Hz, C-2-H_{ax}), 6.45 (1H, dd, J. 4.5, 14 Hz, C-6-H_{ax}), and 6.75 (1H, dd, J 3, 14 Hz, C-6-H_{eq}). These assignments assume a half-chair conformation with phenyl substituent equatorial and hydroxyl axial and thus able to hydrogen bond to nitrogen lone pair.

12. For earlier utilisations of this reagent mixture see (a) E. M. Fry, *J. Org. Chem.*, 1964, 29, 1647; (b) J. A. Beisler, *Tetrahedron*, 1970, 26, 1961; J. A. Beisler and E. M. Fry, *J. Org. Chem.*, 1970, 35, 2809; R. Besselièvre, C. Thal, H.-P. Husson, and P. Potier, *Chem. Comm.*, 1975, 90.

13. *cf.* D. S. Grierson, M. Harris and H.-P. Husson, *J. Amer. Chem. Soc.*, 1980, 102, 1064.

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