Tetrahedron Letters No.46, pp. 4735-4738, 1968. Pergamon Press. Printed in Great Britain.

BOROHYDRIDE REDUCTION OF PYRIDINIUM SALTS FORMATION OF TETRAHYDROPYRIDINES

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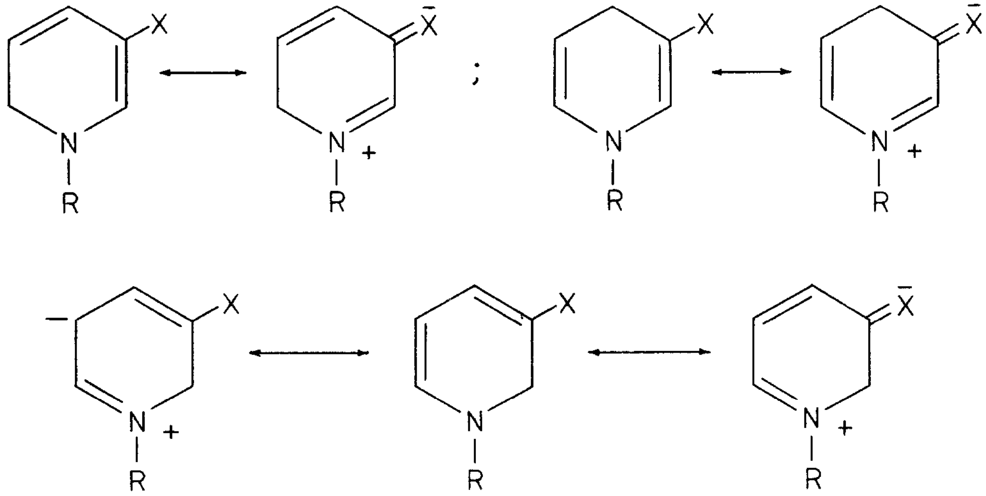
(Received in UK 29 July 1968; accepted for publication 14 August 1968)

The formation of 1,6-dihydropyridines and 1,2,5,6-tetrahydropyridines by borohydride reduction, in protic media, of pyridinium salts carrying electron-withdrawing group at carbon 3, has been reported (1,2).

The formation of 1,2,5,6-tetrahydropyridines has been related to further transformation of 1,2-dihydropyridines which are not normally obtained in this reduction (°). It should also be noted that the 1,6 and 1,4-dihydropyridines (6) have been said to be resistent to further reduction in protic solvents.

The peculiar behaviour of 1,2-dihydropyridines should be related to the fact that they have an enamine character in spite of the presence at carbon 3 of an electron-withdrawing group.

(°) 1,2-dihydropyridines has been obtained when the borohydride reduction of pyridinium salts was carried out in basic media (2,3) or when because of their insolubility (4,5) the 1,2-dihydropyridines escaped further reduction.



The borohydride reduction of pyridinium salts has been interpreted as a nucleophilic attack of BH_4^- upon the pyridinium ion and to proceed by hydride ion loss with contemporary formation of BH_3. Indeed it has been reported (6) that from these reactions the tetrahydropyridines are often isolated as the amine boranes.

A gross mechanism formulated by Lyle and coll. (7) in order to explain the formation of 1,2,5,6-tetrahydropyridines suggests that the intermediate 1,2-dihydropyridine is protonated at carbon 5 by "direct attack" (8) of the solvent (H_2O) and the resulting immonium cation is further reduced by borohydride.

In order to further elucidate the mechanism of 1,2,5,6-tetrahydropyridine formation, we have studied the borohydride reduction in the protic solvent water of the 1-methyl-3-cyano-1,6-dihydropyridine (1), 1-methyl-3-cyano-1,4-dihydropyridine (1) and 1-methyl-3-cyano-1,2-dihydropyridine (2).

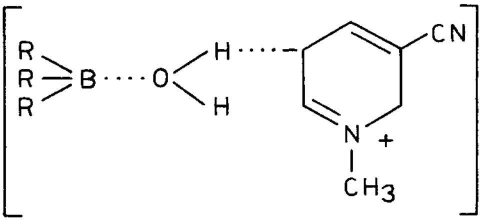
The 1-methyl-3-cyano-1,6-dihydro and 1-methyl-3-cyano-1,4-dihydropyridines were recovered unchanged after they were treated separately with borohydride in protic media. Identical results were also obtained when the 1-methyl-3-cyano-1,2-dihydropyridine was reacted under the same experimental conditions.

This result excludes, at least for the 1,2-dihydro-pyridines carrying an electron-withdrawing group at carbon 3, a direct protonation made by the solvent, such as has been postulated earlier (7).

The observed formation of the 1,2,5,6-tetrahydropyridines in the reduction of pyridinium salts toghether with the above result , clearly indicates the fundamental role of BH_3 species for the proceeding of the reduction. Obviously such a species is present only when the nucleophilic BH_4^- has attacked the suitable substrate.

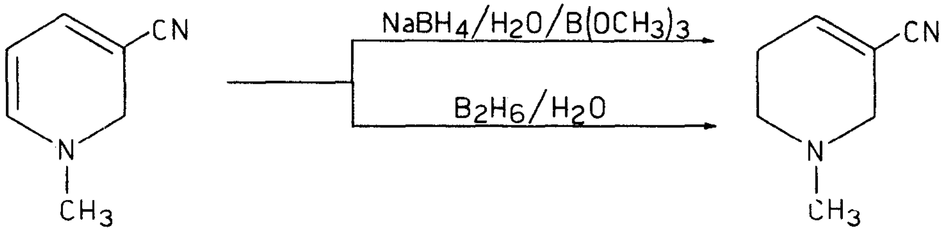
Lyle's experiences proved that a protonation at carbon 5 takes place, and therefore the problem is to identify the protonating species which obviously must arise from the interaction between borane and solvent (H_2O). Such protonating species is not boric acid, which is the final product of borane hydrolysis in water, as we have demonstrated by attempting the borohydride reduction of 1-methyl-3-cyano-1,2-dihydropyridine in protic solvent and in the presence of boric acid: also in these conditions the 1-methyl-3-cyano-1,2-dihydropyridine was recovered unchanged. On the other hand treatment of a water solution of the three dihydro pyridines with B_2H_6 externally generated left unchanged 1-methyl-3-cyano-1,6-dihydro-pyridine and the 1-methyl-3-cyano-1,4-dihydropyridine, while the 1-methyl-3-cyano-1,2-dihydropyridine was converted to 1-methyl-3-cyano-1,2,5,6-tetrahydropyridine, isolated as the amine-borane (m.p. 90-1°).

This result proves without any ambiguity the fundamental role of BH_3 in this conversion. It is possible that the protonating species could be one of the adducts which are formed in the gradual hydrolysis of BH_3, and it is known that this process is a multi-steps process implying the formation of borane-water adducts from which one proton and one hydride ion are expulsed (9). As an alternative hypothesis the protonation can be thought to proceed throught a borane-water-1,2-dihydropyridine transition state, the formation of which should be favoured either by the electrophilic character of borane either by the negative charge on the carbon 5 of the dihydropyridine.



If one assumes valid these hypothesis, then it should be possible to convert the 1,2-dihydropyridine to tetrahydropyridine carriyng out the reduction in water in the presence of any enough electrophilic borane which can easily undergo hydrolysis.

In fact we have proved that borohydride reduction of 1-methyl-3-cyano-1,2-dihydropyridine in the presence of trimethoxy-borane, yielded quickly and quantitatively the 1-methyl-3-cyano-1,2,5,6-tetrahydropyridine. Under the same conditions 1-methyl-3-cyano-1,6-dihydropyridine and 1-methyl-3-cyano-1,4-dihydropyridine did not undergo any transformation.



Acknowledgement. This work was supported by a research grant from "Consiglio Nazionale delle Ricerche" Rome, Italy.

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