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CARBON-CARBON CLEAVAGE WITH POTASSIUM BOROHYDRIDE - A PROPOSED MECHANISM

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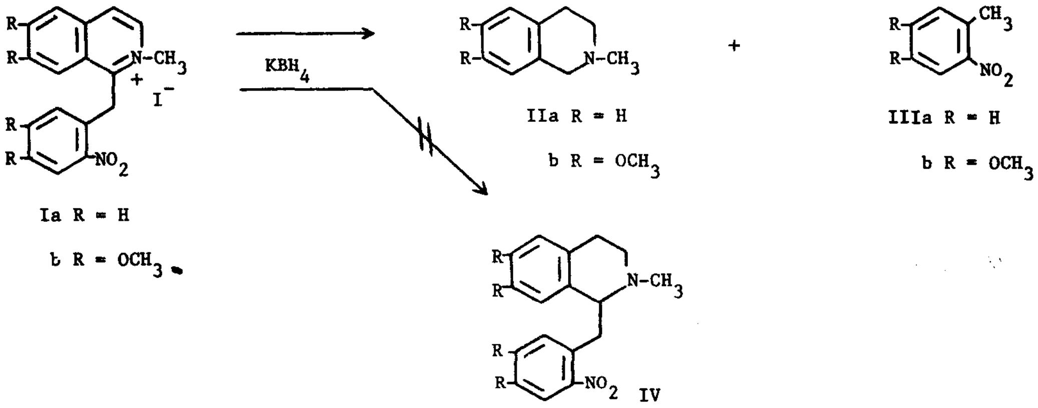
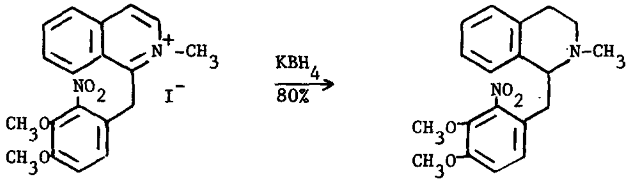
The reduction of pyridinium, quinolinium and isoquinolinium ions to the dihydro-and tetrahydro-N-substituted bases has been extensively investigated and recently reviewed.$^{(1)}$ The reduction of 2-substituted isoquinolinium salts has been reported by Torossian$^{(2)}$ with potassium borohydride (KBH_4) in water; by Miraza;$^{(3)}$ and by Durmond, et al.,$^{(4,5)}$ using sodium borohydride in aqueous methanol to yield 1,2,3,4-tetrahydroisoquinolines. Panouse$^{(6,7)}$ reported that in the reduction of various pyridinium salts the dihydropyridine results from a strongly basic cold solution, while the tetrahydropyridine results from a weakly basic hot solution. Lyle and Anderson$^{(1)}$ support Panouse in stating that the reduction in a strongly basic solution will form the dihydropyridine, and in the absence of a protonating species the dihydropyridines are stable.

We wish to report the unusual cleavage of a carbon-carbon bond in two 1-benzylisoquinolinium salts Ia and Ib when treated with KBH_4 in refluxing aqueous ethanol, and to suggest a mechanism for this reaction. However, under identical conditions 1-(2-nitro-3,4-dimethoxybenzyl) isoquinoline methiodide (V), mp 190-193°,$^{(8)}$ was reduced with KBH_4 to 1-(2-nitro-3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (VI), mp 97-98.5°, in 80% yield. This "normal" reduction can be rationalized by the proposed mechanism.

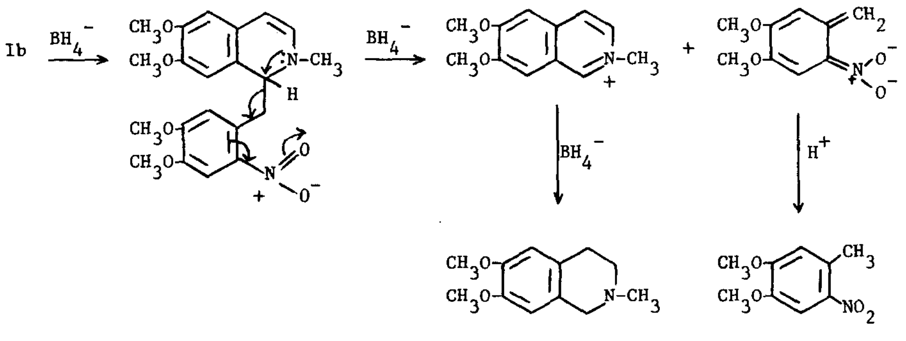




V VI

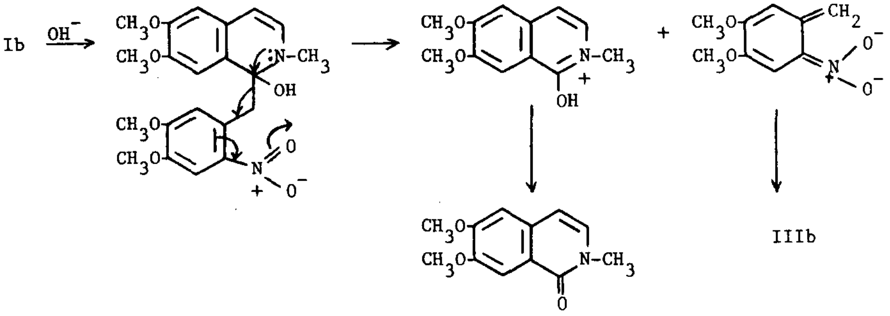
Papaverine was nitrated by nitric acid in acetic acid by the method of Shamma.(9) The resulting 1-(3,4-dimethoxy-6-nitrobenzyl)-6,7-dimethoxyisoquinoline was converted to the methiodide Ib, mp 230° (dec) (lit(10) 235°). Similarly, 1-(2-nitrobenzyl)isoquinoline, mp 110-111°, picrate mp 182°, was converted to the methiodide Ia, mp 223° (dec).(11) The borohydride reduction of Ia and b and of V was carried out in an excess of potassium borohydride in refluxing ethanol:water (3:1). In the case of Ia, 2-methyl-1,2,3,4-tetrahydroisoquinoline IIa was isolated and characterized as the picrate, mp 156° (dec) (lit(2) mp 160°). Similarly, the reduction of Ib yielded 68% of 2-nitro-4,5-dimethoxytoluene (IIIb), mp 117.5-119° (lit(10) mp 118°), and 2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IIb) identified as the picrate, mp 158-159° (lit(12) mp 158-159°; mixed mp 158.5-159.5°(13)). The nmr spectra of IIb and IIIb also confirmed their structures. The 1-benzyltetrahydroisoquinoline derivative IV, the "normal" product of a borohydride reduction, was not isolated in either case.

The following mechanism is presented to rationalize the formation of the cleavage products II and III and to explain the behavior of V in failing to undergo carbon-carbon cleavage and undergoing the course of "normal" borohydride reduction.



IIb IIIb

In the case of the reaction of Ia and b with KBH_4, the nitro group is coplanar with the benzene ring and is able to stabilize the formation of the nitrotoluene through its resonance contribution to the ring. In the reaction of V with KBH_4, the nitro group is forced out of the plane of the benzene ring because of the additional steric interaction of the ortho methoxy group. The necessary resonance stabilization for the cleavage reaction is not provided, precluding the formation of the nitrotoluene. A similar mechanism can explain the observations of Pschorr,(10) who found that boiling the nitropapaverine methiodide Ib with 33% potassium hydroxide yielded the nitrotoluene IIIb and the isoquinolone VII.



VII

The scope of this borohydride cleavage will be the subject of future communications.

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References

1. R. E. Lyle and P. S. Ar n, "Reduction of Nitrogen Heterocycles with Complex Metal Hydrides," Advances in erocyclic Chemistry, Vol. 6, A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, 1966, pp. 46-55, 68-70.
2. R. Torossian, Compt. Rend., 235, 1312 (1952).
3. R. Mirza, J. Chem. Soc., 1957, 4400.
4. S. Durmond, X. Lusinchi, and R. C. Moreau, Bull. Soc. Chim. France, 1961, 270.
5. X. Lusinchi, S. Du ad, and R. Delaby, Compt. Rend., 248, 426 (1959).
6. J. Panouse, ibid., 233, 260 (1951).
7. J. Panouse, ibid., 233, 1200 (1951).
8. Satisfactory elemental analyses were obtained for all new compounds reported and the structures were supported by nmr and IR analyses. Melting points are uncorrected.

9. We are indebted to Professor Shamma, Pennsylvania State University, for communicating to us the conditions used for nitrating O-benzylcodamine.

10. R. Pschorr, Ber., 37, 1926 (1904).

11. We wish to thank Mr. Bernard R. Neustadt for the preparation of Ia.

12. R. Forsyth, C. I. Kelley, F. L. Pyman, J. Chem. Soc., 127, 1659.

13. An authentic sample of N-methyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline was kindly supplied by Dr. A. Brossi, Hoffmann-LaRoche, Inc.