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THE REDUCTION OF KETONES WITH LITHIUM BOROHYDRIDE IN PYRIDINE

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In the course of an investigation of solvent effects on the relative reactivities of ketones with borohydride[1], we have observed some unusual features of reductions in pyridine solvent which are relevant to recent discussions of the mechanism and stereochemistry of metal hydride reductions[2,3,4,5] and to the suggested use of borohydride reductions as models for carbonium ion processes[6,7].

The reactions of cyclohexanone and of 3,3,5-trimethylcyclohexanone with sodium and lithium borohydrides in pyridine solvent have been studied. Sodium borohydride was found to give no measurable reaction with either ketone until aqueous work-up. The reductions with lithium borohydride proceed at easily measurable rates, and the reaction produces pyridine-borane, which does not further react with the ketones. The rates and stereochemistry of the lithium borohydride reductions

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[1] C.D. Ritchie and A.L. Pratt, submitted to J. Am. Chem. Soc.

[2] H. Haubenstock and E.L. Eliel, J. Am. Chem. Soc., 84, 2368 (1962).

[3] M.G. Combe and H.B. Henbest, Tetrahedron Letters, 1961, 404.

[4] P.T. Lansbury and R.E. MacLeay, J. Org. Chem., in press.

[5] W.G. Dauben, G.J. Fonken, and D.S. Noyce, J. Am. Chem. Soc., 78, 2579 (1956).

[6] H.C. Brown and K. Ichikawa, Tetrahedron, 1, 221 (1957).

[7] H.C. Brown and K. Ichikawa, J. Am. Chem. Soc., 83, 4372 (1961).

were determined, and the results are compared to those obtained in other metal hydride reactions, and with data for corresponding carbonium ion processes.

RESULTS

In initial attempts to measure the competitive reactions of cyclohexanone and dihydroisophorone with sodium borohydride in pyridine solution, it became apparent that a great deal of the reduction was taking place during work-up of the reaction mixture in aqueous solution. This conclusion was confirmed when the reaction of cyclohexanone with sodium borohydride was studied by infrared spectrophotometry. A solution containing 0.1 molar cyclohexanone and 0.1 molar sodium borohydride in pyridine showed no appreciable decrease in the absorbance of the carbonyl group after 72 hours at room temperature. Brown[7] has also reported no observable reaction between sodium borohydride and acetone in more dilute pyridine solution.

Dihydroisophorone is even more slowly reduced by lithium borohydride than is cyclohexanone, and no reduction with sodium borohydride was observed by infrared spectrophotometry. However, on mixing sodium borohydride with dihydroisophorone in pyridine solution and immediately pouring the reaction mixture into water, followed by acidification and extraction, a product mixture was obtained which contained 33.5% of cis-3,3,5-trimethylcyclohexanol, 66.5% of the trans-alcohol, and only 9% unreacted ketone.

Attempts to quench the reactions of the ketones with lithium borohydride by pouring the reaction mixtures into aqueous base, aqueous acid, or aqueous potassium iodate solution[8] were similarly unsuccessful. For example, 10 ml. of a pyridine solution containing 0.96×10^{-1} molar $LiBH_4$, 1.0×10^{-1} molar cyclohexanone, and 1.0×10^{-1} molar dihydroisophorone, two minutes after mixing, was poured into 10 ml. of basic 0.4 molar

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[8] D.A. Lyttle, E.H. Jensen, and W.A. Struck, Anal. Chem., 24., 1843 (1952).

aqueous KIO_3. The mixture was diluted to 50 ml. with water and extracted with 3-20 ml. portions of ether. The ether solution was washed with dilute HCl, dried, and the ether evaporated on the steam bath. Analysis of the product showed 49% cyclohexanol, 27.5% dihydroisophorone, 13.5% trans-alcohol, 9.7% cis-alcohol, and a trace of cyclohexanone.

The addition of a five-fold excess of propionaldehyde to the reaction mixture prior to pouring into water also failed to stop the reduction of the ketones.

The results of the kinetic study of the lithium borohydride reductions reported below leave no doubt that in each of these cases the entire reaction took place after the addition of water.

Although sodium borohydride does not react with either ketone in pyridine solution at a measurable rate, lithium borohydride reacts at a reasonable rate and the reactions may be conveniently followed by infrared spectrophotometry.

One mole of cyclohexanone is reduced by each mole of lithium borohydride. During the course of the reduction, the carbonyl infrared band at 1705 cm^{-1} and the borohydride band at 2240 cm^{-1} decrease, while new bands at 2380 cm^{-1} and 1165 cm^{-1} increase in intensity. These latter bands may be compared to the reported[9] Raman bands of ammonia borane at 2409 cm^{-1} and 1209 cm^{-1}, and to the infrared bands of pyridine phenylborane[10] at 2420 cm^{-1} and 1160 cm^{-1}. Both the stoichiometry and infrared spectrum of the reaction mixture therefore indicate the reaction to be as shown in (1):

$$C_6H_{10}O + LiBH_4 + C_5H_5N = C_6H_{11}OLi + C_5H_5N^+BH_3^- \qquad (1)$$

Kinetic experiments based on the change in absorption at 1705 cm^{-1}, 2240 cm^{-1}, and 2380 cm^{-1} with time show the reaction to be first order with respect to ketone and first order with respect to lithium borohydride. The second order rate constant

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[9] A.R. Emery and R.C. Taylor, J. Chem. Phys., 28, 1029 (1958).

[10] J.E. Douglass, J. Am. Chem. Soc., 84, 121 (1962).

for the reaction of cyclohexanone is 4.2×10^{-1} l-moles^{-1}-mins.$^{-1}$, and that for dihydroisophorone is 1.5×10^{-2} l-moles^{-1}-mins.$^{-1}$.

In order to determine the stereochemistry of the reduction of dihydroisophorone, a solution containing 5×10^{-1} molar $LiBH_4$ and 2.5×10^{-1} molar dihydroisophorone was allowed to stand at room temperature for 30 hours. (The reaction is calculated to be 90% complete after 11 hours.) The reaction mixture was poured into water, acidified with dilute HCl, and extracted with ether. After evaporation of the ether, the product was analyzed by gas chromatography. The product contained 90.9% cis (equatorial)-alcohol and 9.1% trans (axial)-alcohol.

That the products do not undergo equilibration under the reaction conditions is indicated by the fact that identical reaction mixtures worked up at the end of 30, 48, and 62 hours gave the same ratio of cis to trans alcohol. Since the equilibration mixture of the two isomers has been shown by Eliel[2] to be nearly pure cis-isomer, this result strongly argues against equilibration of products. It was also found that a sample of the pure trans-alcohol was unaffected by the work-up procedure[11].

DISCUSSION

The stereochemical result obtained in the reduction of dihydroisophorone with lithium borohydride in pyridine solution is surprising when compared with other hydride reductions of this ketone. Lansbury[4] reported that the reduction with lithium aluminum hydride in pyridine solution produced 71% trans-alcohol and 29% cis-alcohol. Haubenstock and Eliel found that borohydride reduction in hydroxylic solvents gave 55-73% trans-alcohol[2]. Considering the differences in the reactions in detail, however, the stereochemical results are quite reasonable.

The simplest and most reasonable explanation of the differences of the borohydride and aluminohydride reductions is that the transition state for the borohydride reaction

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[11] I am indebted to Dr. P.T. Lansbury, and indirectly to Prof. E.L. Eliel, for a sample of the pure alcohol.

is much closer to products than is that for the aluminohydride case. This explanation is in accord with the usual observation that the more reactive reagent gives the less product-like transition state[12], and with further discussion below. One might also argue that the smaller size of borohydride as compared to aluminohydride[13] plays an important role.

The difference in the stereochemical result of reduction with lithium borohydride in pyridine and sodium borohydride in hydroxylic solvents must be due in large part to the fact that borohydride reductions in hydroxylic solvents involve alkoxyborohydrides which are formed and must account for 75% of the total reduction. These species are more reactive than borohydride (and also larger), and would therefore be expected to be less selective[1,2].

The stereochemical result obtained in this study is in direct opposition to that obtained by Dauben for sodium borohydride reductions of steroidal ketones[5]. Dauben reported that borohydride reduction in pyridine solution results in a predominance of attack at the least hindered side of the ketone, and this result has been quoted in recent discussions of the mechanism of borohydride reductions[2].

We believe that this discrepancy is due to the fact that reduction occurred only after the addition of water to the reaction mixture during work-up. As reported above, we have found no reaction of sodium borohydride with either cyclohexanone or dihydroisophorone in 0.1 molar pyridine solution in 72 hours. Work-up of the reaction in aqueous solution, however, leads to appreciable reduction, and more important, <u>a completely different stereochemical result than is obtained by reduction in the pyridine solution.</u>

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[12] G.S. Hammond, J. Am. Chem. Soc., 77, 334 (1955).

[13] D.M.S. Wheeler and J.W. Huffman, Experentia, 16, 516 (1960).

These results, considered along with Brown's observations[7] that sodium borohydride and acetone show no reaction in 24 hours in diglyme, acetonitrile, or dimethylformamide solutions strongly suggest that previous data reported for borohydride reductions of ketones in non-hydroxylic solvents are in error. Apparently, the complication of considerable reaction during work-up is not so severe in hydroxylic solvents.[4]

Another interesting point to the data which we have obtained is found in connection with Brown's suggestion[6,7] that borohydride reductions be used as models for carbonium ion processes. Our data is particularly apropos for the comparison of the two processes for stereoisomers. Since the borohydride reductions in hydroxylic solvents involve alkoxyborohydrides for at least 75% of the reaction, the stereochemistry of the product obtained gives no information as to the stereochemistry of the attack of borohydride itself. In pyridine solution, however, the attack of borohydride on the ketone gives alcohol and pyridine borane as products. The pyridine borane does not react with the ketone. The stereochemistry of the product, therefore, is a direct indication of the relative rates of borohydride attack at the two positions.

Fischer, Grob, and Schwarz[14] have recently reported the relative rates of ethanolysis of cyclohexyl tosylate, and of cis- and trans-3,3,5-trimethylcyclohexyl tosylate. Their observation that the trans-tosylate solvolyzes thirteen times faster than does the cis-tosylate is nicely consistent with Brown's suggestion when compared to the ten times faster production of the cis-alcohol on lithium borohydride reduction of the ketone. The trans-tosylate, however, solvolyzes only four times faster than cyclohexyl tosylate, whereas our data shows cyclohexanol to be produced about three hundred times faster than the trans-alcohol.

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14. H. Fischer, C.A. Grob, and W. Schwarz, Tetrahedron Letters, 1962, 25.

Obviously, we are being somewhat naive in comparing reactions in two such different solvents. Nevertheless, we believe that the great discrepancy between the relative rates of borohydride reaction and the solvolysis reaction indicates that some factors other than simple steric effects are involved in the tosylate reactions.

The fact that the relative rates of reaction of cyclohexanone and dihydroisophorone with lithium borohydride in pyridine (28:1) are comparable to the relative stabilities of the cyanohydrins of the ketones (38:1)[15] indicates that steric effects are the major contributor to the differences in reduction rates of these compounds. In agreement with the previous discussion, this last result also indicates that the transition state for the borohydride reductions is quite similar to product.

EXPERIMENTAL

Analytical techniques and purification of reagents are discussed in a separate paper.[1]

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15. O.H. Wheeler and J.Z. Zabicky, Can. J. Chem., **36**, 656 (1958)