[Contribution from the Department of Chemistry, James Millikin University]

REDUCTION OF OXIMES WITH LITHIUM ALUMINUM HYDRIDE

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Lithium aluminum hydride has been used with success in reducing a number of types of organic compounds. A review on reductions by this reagent was recently written by Brown (1). The chemical literature contains only a few instances where this reducing agent has been used to reduce oximes. Larsson (2, 3) obtained the expected amines from the oximes of enanthaldehyde, benzaldehyde, butanone, cyclohexanone, and $PhCH_2COMe$ in yields of 50–75%. He reported that the oxime of cinnamaldehyde was reduced to the fully saturated aromatic amine. In the case of acetophenone oxime a rearrangement occurred and in addition to the expected amine there was also formed some N-ethylaniline. Burger and Bennet (4) reduced the oxime of 2,2-diphenylcyclohexanone to the corresponding amine in 80% yield.

We have reduced the oximes of enanthaldehyde, butanone, heptanone-2, butyraldehyde, cyclohexanone, and cyclopentanone to the corresponding amines in yields of 30–80%.

We have repeated the reduction of acetophenone oxime as reported by Larsson (2) and have obtained the products previously reported. To see how general the rearrangement may be in this homologous series the oxime of propiophenone was reduced in the same manner. In addition to the normal product there was obtained the secondary amine PhNHPr. The identity of the secondary amine was established by a mixed melting point of its phenylthiourethan.

No reduction of benzophenone oxime was found when the reaction took place at the reflux temperature of ether. However, Hochstein (5) reduced this oxime with $LiAlH_4$ by using the higher-boiling solvent tetrahydrofuran.

A study was made of the effect of varying the ratio of lithium aluminum hydride to oxime. Attempts to apply the Gilman and Schulze (6) color test to these reactions were not successful. Amundsen and Nelson (7) have also found that this color test is not applicable to the reduction of nitriles with lithium aluminum hydride. The results of varying the ratio of oxime to hydride are condensed in Table II. Also included in this table are several reductions using tetrahydrofuran as the solvent. When tetrahydrofuran was used as the solvent for the hydride and oxime, the same procedure was used as for the other reductions and the hydrolyzed mixture was extracted with ether. Since tetrahydrofuran is soluble in water it was necessary to extract for a few hours longer to remove the amine from the tetrahydrofuran and water layer.

Noyce and Denney (8) reduced the three isomeric methylcyclohexanones with $LiAlH_4$ and obtained the *trans* forms of the alcohols as the principal products of the reactions. We have reduced the oximes of the three methylcyclohexanones with $LiAlH_4$ and have found the principal product in each case to be the *trans* form of the amine. The constancy of the boiling points and indices of refraction

TABLE I

REDUCTION OF OXIMES WITH LITHIUM ALUMINUM HYDRIDE

OXIME	MOLES REACTED		SOLVENT	PRODUCT[a]	YIELD, %
	Oxime	$LiAlH_4$			
Enanthaldehyde	0.1	0.22	Ether	*n*-Heptylamine	79
Butanone	.1	.22	Ether	*sec*-Butylamine	32
Heptanone-2	.1	.22	Ether	α-Methylhexylamine	40
Butyraldehyde	.1	.22	Ether	*n*-Butylamine	47
Cyclohexanone	.1	.22	T.H.F.[b]	Cyclohexylamine	71
Benzophenone	.1	.22	Ether	No product	
Cyclopentanone	.1	.22	Ether	Cyclopentylamine	33
Acetophenone	.1	.22	Ether	α-Phenylethylamine	56
				N-Ethylaniline	16
Propiophenone	.1	.15	T.H.F.	α-Phenylpropylamine[c]	48
				N-Propylaniline[d]	14

[a] Products were identified by their physical properties and derivatives. [b] Tetrahydrofuran. [c] B.p. 112° (45 mm.); n_D^{18} 1.5212; Benzoyl deriv., m.p. 114–115°. Heilbron, *Dictionary of Organic Compounds*, Oxford Press, 1943, gives n_D^{25} 1.5173; benzoyl deriv., m.p. 115–116°. [d] B.p. 114° (20 mm.); Phenylthiourethan, m.p. 103–104°. Phenylthiourethan of an authentic sample of N-propylaniline, m.p. 104–105°. Mixture melting point of derivs., 104°.

TABLE II

EFFECT OF CHANGING SOLVENT AND VARYING THE RATIO OF OXIME TO LITHIUM ALUMINUM HYDRIDE

OXIME	MOLES OF OXIME	MOLES OF $LiAlH_4$	SOLVENT	YIELD, %
Enanthaldehyde	0.1	0.11	Ether	65
	.1	.22	Ether	79
	.1	.33	Ether	78
	.1	.22	Tetrahydrofuran	75
Cyclohexanone	.1	.22	Ether	61
	.1	.22	Tetrahydrofuran	71

TABLE III

REDUCTION OF THE METHYLCYCLOHEXANONE OXIMES WITH $LiAlH_4$

OXIME	MOLES REACTED		SOLVENT	PRODUCT	YIELD, %
	Oxime	$LiAlH_4$			
2-Methylcyclohexanone	0.2	0.33	Ether	*trans*-2-Methylcyclohexylamine	53
3-Methylcyclohexanone	.2	.33	Ether	*trans*-3-Methylcyclohexylamine	43
4-Methylcyclohexanone	.2	.33	Ether	*trans*-4-Methylcyclohexylamine	81

of the fractionated amines indicated that very little, if any, of the *cis* forms of any of the amines were produced.

EXPERIMENTAL

2-Methylcyclohexanone. This ketone was prepared by oxidizing 2-methylcyclohexanol with potassium dichromate and sulfuric acid according to the procedure of Sandborn (9).

Preparation of the oximes. The oximes of enanthaldehyde, cyclohexanone, cyclopentanone, butanone, *n*-butyraldehyde, and heptanone-2 were prepared using hydroxylamine hydrochloride and sodium carbonate (10). Benzophenone oxime was prepared using sodium hydroxide to neutralize excess acid (11). Acetophenone oxime and propiophenone oxime were prepared using potassium hydroxide as the neutralizing agent (12). Acetophenone oxime was purified by recrystallization from hot water, and propiophenone oxime was purified by redistillation followed by recrystallization from alcohol and water. The three methylcyclohexanone oximes were prepared by adding 50 ml. (0.45 mole) of ketone, 35 g. (0.5 mole) of hydroxylamine hydrochloride, and 75 g. (0.9 mole) of sodium acetate to 250 ml. of water and then adding enough alcohol to form a clear solution. The solution was allowed to stand overnight at room temperature and then the alcohol was distilled off until the solution started to become cloudy and to separate into layers. The remaining solution was then extracted with ether and the oxime obtained from the ether extract by distillation.

Reduction of aliphatic and alicyclic oximes. Into a liter three-necked flask equipped with a separatory-funnel, reflux condenser, and mechanical stirrer was placed 150 ml. of dry reagent grade ether. There was added 8.4 g. (0.22 mole) of lithium aluminum hydride and the mixture was stirred until the hydride had dissolved. A solution of 0.1 mole of the oxime in 50 ml. of reagent grade ether was added dropwise with stirring into the hydride solution at a rate to maintain gentle refluxing. After all of the oxime had been added the mixture was refluxed for 30 minutes. The reaction mixture was then allowed to cool and the excess hydride decomposed by slowly adding water with stirring until further addition of water did not cause the evolution of hydrogen. It was found advisable during this step to add enough dry ether to the flask at intervals to compensate for the ether which was being carried out through the top of the condenser by the evolved hydrogen. The complex was then hydrolyzed by the addition of 250 ml. of 20% Rochelle's salt solution and 50 ml. of 10% sodium hydroxide. The hydrolyzing mixture was stirred 30 minutes at room temperature. The thick slurry was transferred to a liter round-bottom flask fitted with a condenser for continuous extraction, and extracted for ten hours with ether into a 500-ml. flask. The ether extract was dried over potassium carbonate and the ether removed by distillation. After removal of the ether the amine was distilled.

Reduction of propiophenone oxime. This was performed by the same procedure as outlined above using 0.1 mole of oxime. The final ether extract contained a mixture of two amines and was shaken with 150 ml. of 0.5 *N* HCl to bring both amines into aqueous solution. The water solution was made neutral to Methyl Red with 20% sodium hydroxide and this aqueous solution was extracted with ether. The ether extract thus obtained contained the N-propylaniline. The remaining water layer was made basic to litmus with sodium hydroxide and extracted with ether to obtain the α-phenylpropylamine.

In order to establish the identity of the N-propylaniline a mixture melting point of the phenylthiourethan was taken. The authentic sample of N-propylaniline was prepared from aniline and propyl bromide in the manner described by Hickinbottom (13). The N-propylaniline thus prepared was purified by redistillation through a column, and physical constants taken from a center cut were: b.p. 93° (7 mm.); n_D^{23} 1.5418.

Reduction of the methylcyclohexanone oximes. The same general procedure was used except that 0.33 mole of hydride was used for the reduction of 0.2 mole of the oxime in each run. The yields given in Table III are based on the crude amine obtained from individual runs.

The products from several individual reductions were combined and fractionated through a column under reduced pressure. The amines distilled at a constant temperature and the indices of refraction of successive fractions were identical. They were identified as the *trans* forms by their indices of refraction and the melting points of their benzoyl derivatives. The 2-methylcyclohexylamine had the following properties: b.p. 71–72° (50 mm.); $n_D^{20.5}$ 1.4590; benzoyl deriv., m.p. 148–149° (Skita reported for *trans*-2-methylcyclohexylamine and its benzoyl derivative n_D^{20} 1.4650; m.p. 146°) (14). Physical properties and melting point of the benzoyl derivative for the 3-methylcyclohexylamine were as follows: b.p. 72–73° (50 mm.); $n_D^{21.5}$ 1.4550; m.p. 125–126° (reported for *trans*-3-methylcyclohexylamine n_D^{20} 1.4547; m.p. 127°) (14). Physical properties for the 4-methylcyclohexylamine and derivative were as follows: b.p. 72–73° (50 mm.); n_D^{20} 1.4550; m.p. 179–180° (reported for *trans*-4-methylcyclohexylamine n_D^{20} 1.4550; m.p. 180°) (14).

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SUMMARY

1. The oximes of enanthaldehyde, butanone, heptanone-2, butyraldehyde, cyclohexanone, and cyclopentanone were reduced with lithium aluminum hydride to the corresponding amines.

2. The oximes of acetophenone and propiophenone were reduced to the corresponding amines and N-alkylanilines.

3. The best ratio of oxime to $LiAlH_4$ was found to be 1 to 1.5 moles.

4. The oximes of three methylcyclohexanones were reduced to their *trans* amines.

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