

N-(2-Carboxyethyl)-benzoyl- α -alanine.—A mixture of 16.05 g. (0.05 mole) of ethyl N-2-carbomethoxyethyl)-benzoyl-alaninate and 4 g. of sodium hydroxide dissolved in 100 ml. of water was shaken mechanically for 2 hours at room temperature. The reaction mixture was treated in the same manner as described in the preparation of N-(2-carboxyethyl)-acetylalanine to obtain the crude product for crystallization, *i.e.*, residue from acetone distillation. This residue was crystallized twice from water to give a yield of 11.5 g. (87%) of a product melting at 126–128° (capillary) and discoloring at 170°. The solubility in g. per 100 g. of solvent at room temperature was: water, 7.2; acetone, 2.7; and ethanol, 65.

Anal. Calcd. for $C_{13}H_{15}O_5N$: N, 5.28; neut. equiv., 265. Found: N, 5.21; neut. equiv., 266.

Condensations with Diamines.—The ethyl N-(2-carbomethoxyethyl)-glycinate, alaninate, leucinate, methioninate, pyroglutamate, and the corresponding acetyl derivatives of the first four were condensed with ethylene, hexamethylene and *p*-phenylenediamine. The following example illustrates the results obtained. A mixture of 8.18 g. (0.0333 mole) of ethyl N-(2-carbomethoxyethyl)-acetyl-glycinate and 3.61 g. (0.333 mole) of *p*-phenylenediamine was placed in a

thick-walled test-tube into which a capillary tube was inserted for bubbling nitrogen through the reaction mixture. The tube was heated with a silicone-bath equipped with a thermometer. The temperature of the bath was raised to 200° over a period of 2 hours and held at 200° for 6 hours. A vacuum was applied and the temperature raised to 250° over a period of 2 hours and held at 250° for 6 hours. The brown resin weighed 7.5 g. (calcd. 8.73 g.), and contained 15.4% nitrogen (calcd. 16.1, disregarding end groups). It had a soft point of 160° and was insoluble in water, acetone and alcohol but soluble in methyl cellosolve. A film cast from solution was brittle and disintegrated when soaked in water. Similar results were obtained with ethylenediamine and hexamethylenediamine when the temperature was held at 180–200°. With prolonged heating at 250°, decomposition occurred with the formation of infusible polymers.

With the unacetylated derivatives, it was necessary to keep the temperature under 200° during the condensation reaction to avoid excessive decomposition. These polymers were water soluble, brown, brittle and had softening points from 130 to 190°.

PEORIA 5, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NORTH CAROLINA]

Preparation of Primary Amines by Reduction of Oximes with Lithium Aluminum Hydride and by the Leuckart Reaction

BY C. ROBERT WALTER, JR.*

RECEIVED MAY 12, 1952

A variety of carbonyl compounds have been converted to the corresponding primary amines by reduction of their oximes with lithium aluminum hydride. Other reducible groups in the molecule are generally not affected. The procedure is compared with an alternate one for obtaining primary amines, *viz.*, the Leuckart Reaction. Several new amines are described.

In the conversion of ketones of various types, the Leuckart reaction, while in general superior to the method involving formation and reduction of oximes by metal combinations or by catalytic means, nevertheless fails in many instances.^{1,2} Thus Ingersoll notes that the Leuckart reaction appears to be inapplicable to α,β -unsaturated ketones.² Furthermore it has been shown that compounds such as benzoin do not give the normal hydroxyamine in the Leuckart reaction.^{3,4} On the other hand, the Leuckart method has often proved to be successful with compounds in which functional groups are present that are easily reduced by many reducing agents which are ordinarily used to reduce oximes.¹

A study was therefore initiated to investigate the reduction of oximes to primary amines by means of lithium aluminum hydride, and to compare this method of amine formation with the Leuckart method. The results of this work indicate that the method of oxime formation followed by lithium aluminum hydride reduction provides in most cases a satisfactory alternate to the Leuckart procedure for the preparation of primary amines from carbonyl compounds and often supplements the Leuckart method where the latter fails.

Only few instances of reductions of oximes with $LiAlH_4$ have been reported.^{5–10} We have studied the reduction of eleven oximes using lithium aluminum hydride and compared the results to those obtained using the Leuckart method on the original carbonyl compounds. The results are given in Table I.

TABLE I
CONVERSION OF CARBONYL COMPOUNDS TO PRIMARY AMINES

Compound	Primary amine	Yield, % ^a	Yield, % ^b
		LiAlH ₄ reduction of oxime	Leuckart method
Cyclohexanone	Cyclohexylamine	42	26 ^b
2,2-Tetramethylene-cyclohexanone	2,2-Tetramethylenecyclohexylamine	65.8	44.6
2,2-Pentamethylene-cycloheptanone	2,2-Pentamethylenecycloheptylamine	40	52.5
$CH_3COC_6H_5$	$CH_3CH(NH_2)C_6H_5$	43	50–81 ^b
$(CH_3)_2CHCOCH(CH_3)_2$	$(CH_3)_2CH(NH_2)CH(CH_3)_2$	46.8	48.2
<i>p</i> - $ClC_6H_4COCH_3$	<i>p</i> - $ClC_6H_4CH(NH_2)CH_3$	56.6	65.82 ^b
<i>p</i> - $BrC_6H_4COCH_3$	<i>p</i> - $BrC_6H_4CH(NH_2)CH_3$	65.4	63.79 ^b
<i>m</i> - $NO_2C_6H_4COCH_3$	<i>m</i> - $NO_2C_6H_4CH(NH_2)CH_3$	0	56 ^b
$C_6H_5CH=CHCHO$	$C_6H_5CH=CHCH_2NH_2$	53.3	0
$C_6H_5CH=CHCOCH_3$	$C_6H_5CH=CHCH(NH_2)CH_3$	55	0 ^c
$C_6H_5CHOHCOC_6H_5$	$C_6H_5CHOHCH(NH_2)C_6H_5$	12.7	0

^a Based on oxime. ^b These figures refer to yields taken from tables, pp. 325–330 in ref. 1. ^c Ref. 2.

* Nitrogen Division, Allied Chemical & Dye Corp., Hopewell, Virginia.

(1) M. L. Moore, *Org. Reactions*, **5**, 301 (1949).

(2) A. W. Ingersoll, J. H. Brown, C. K. Kim, W. D. Beauchamp and G. Jennings, *THIS JOURNAL*, **58**, 1808 (1936).

(3) R. Leuckart, *J. prakt. Chem.*, [2] **41**, 330 (1890).

(4) D. Davidson, M. Weins and M. Jelling, *J. Org. Chem.*, **2**, 328 (1937).

(5) E. Larsson, *Svensk Kem. Tid.*, **61**, 242 (1949).

(6) E. Larsson, *Trans. Chalmers Univ. Technol.*, Gothenberg, No. 94, 15 (1950).

(7) D. R. Smith, M. Maienthal and J. Tipton, *J. Org. Chem.*, **17**, 294 (1952).

(8) A. Burger and W. B. Bennet, *THIS JOURNAL*, **72**, 5414 (1950).

(9) F. A. Hochstein, *ibid.*, **71**, 305 (1949).

(10) K. Hayes and G. Gever, *J. Org. Chem.*, **16**, 269 (1951).

The expected primary amine was obtained in all cases except one. Although the simple amine was not obtained with *m*-nitroacetophenone oxime, lithium aluminum hydride is known to convert aryl nitro groups to azo groups,¹¹ and the color of the reaction mixture indicated that such a transformation did occur, probably along with reduction of the oxime. In the case of *p*-chloro- and *p*-bromoacetophenone, the halogen atom was unaffected. In a review on reductions using lithium aluminum hydride Brown notes that the double bond is completely or partially reduced in systems containing the grouping $\text{ArC}=\text{CCO}$.¹¹ It might therefore be expected that reductions of oximes of such systems would also result in reduction of the double bond. In fact Larsson reported that the oxime of cinnamaldehyde was reduced to the fully saturated amine.⁵ We have repeated the reduction of cinnamaldehyde oxime and were able to isolate the unsaturated amine in good yield. In addition the oxime of benzalacetone was reduced to the unsaturated primary amine. These results might not be wholly unexpected even in view of Larsson's findings, for it is known that in some α,β -unsaturated carbonyl compounds, *e.g.*, cinnamaldehyde, it is possible to direct the reduction with lithium aluminum hydride to give either the saturated or unsaturated compound by appropriate choice of conditions.¹¹

The oxime of benzoin also gave the expected hydroxyamine on reduction but in quite low yield.

The ketones, 2,2-tetramethylenecyclohexanone and 2,2-pentamethylenecycloheptanone, were prepared by a pinacol reduction of cyclopentanone and cyclohexanone, respectively, followed by a pinacol rearrangement.

Experimental¹²

[Bicyclopentyl]-1,1'-diol.—This compound was prepared by a pinacol reduction of cyclopentanone according to the procedure of Zelinski and Elaginina.¹³ A mixture of 100 g. of cyclopentanone, 10 g. of mercuric chloride, 20 g. of aluminum turnings and 100 cc. of dry benzene was refluxed with stirring for three hours. To the mixture were added 100 cc. of water and 150 cc. more benzene and refluxing continued for two hours longer. After filtration the precipitate was covered three times with benzene, and the combined washings and filtrate were distilled on a steam-bath under slightly reduced pressure. The residue crystallized on standing; ligroin was added and the shining white crystals were collected on a filter. They weighed 30.9 g., m.p. 109–111°.

2,2-Tetramethylenecyclohexanone.—The [bicyclopentyl]-1,1'-diol prepared above was added to 210 cc. of 20% sulfuric acid and heated under reflux for two hours. The mixture was cooled, diluted with 50 cc. of water, and extracted with four 60-cc. portions of ether. After drying over sodium sulfate the ether was removed and the residue distilled as a greenish-yellow oil at 60–62° (2 mm.). The yield was 23.3 g.

[Bicyclohexyl]-1,1'-diol.—A modification of the directions of Qudrat-i-Khuda and Ray¹⁴ was used for the preparation of this intermediate and also for the subsequent rearrangement. A mixture of 300 g. of aluminum powder, 27 g. of mercuric chloride and 345 cc. of dry benzene was heated on a steam-bath for two hours. (The reaction first started without the application of heat.) Then 210 cc. of

water and 375 cc. of benzene were added and heating continued for three hours longer. The mixture was filtered, and the residue extracted with a hot mixture of 210 cc. of benzene and 40 cc. of water. After removal of the solvent, the residue crystallized on cooling and 200 cc. of petroleum ether was added to it. The white crystals were collected on a filter and recrystallized from ligroin (b.p. 60–90°). They melted at 124.5–126.5°. The yield was 91.1 g. (30%).

2,2-Pentamethylenecycloheptanone.—To 955 cc. of 50% sulfuric acid was added 127.3 g. of [bicyclohexyl]-1,1'-diol and the solution was heated on a steam-bath for two hours and 20 minutes. It was cooled, diluted with 500 cc. of water and extracted with four 80-cc. portions of ether. The ether extract was washed first with a 10% solution of sodium carbonate, then with water. After drying over sodium sulfate, the solution was subjected to distillation, the ether first being taken off, and the residue finally distilled as a clear liquid at 90–92° (2 mm.). The distillate weighed 87.4 g. and consisted of a mixture of the desired ketone and bicyclohexene. The ketone was purified through its semicarbazone. From 87.4 g. of the ketone-diene mixture, 18.4 g. of semicarbazone, m.p. 208.5–209.5°, was obtained after recrystallization from methanol. Hydrolysis of 19.5 g. of crude semicarbazone with 195 cc. of hot 10% hydrochloric acid for 4.5 hours gave 10.1 g. of the ketone as a clear liquid, b.p. 101–103° (2 mm.).

Preparation of Amines by the Leuckart Reaction.—All the ketones investigated were subjected to standard Leuckart reactions¹ using freshly prepared ammonium formate at 160–170°. 2,2-Tetramethylenecyclohexylamine, previously unknown, appeared as a colorless liquid boiling at 102–106° (36 mm.). The yield was 44.6%. The hydrochloride, prepared in ether solution, decomposed at 285–292°.

Anal. Calcd. for $\text{C}_{16}\text{H}_{29}\text{ClN}$: N, 7.38. Found: N, 7.02, 7.01.

2,2-Pentamethylenecycloheptylamine.—This amine, not previously known, was characterized as the hydrochloride, m.p. 285–286° (dec.).

Anal. Calcd. for $\text{C}_{17}\text{H}_{31}\text{ClN}$: N, 6.43. Found: N, 6.28.

Preparation of the Oximes.—All oximes were prepared by standard methods.¹⁵ 2,2-Pentamethylenecycloheptanone oxime, obtained in pyridine solution,¹⁶ crystallized from dilute ethanol, m.p. 108.5–109.5°.

Anal. Calcd. for $\text{C}_{17}\text{H}_{31}\text{NO}$: N, 7.17. Found: N, 7.15, 7.12.

Reduction of the Oximes.—All of the reductions were carried out in ether solution over a period of five to eight hours according to standard procedures.¹¹ The preparation of *p*-chlorophenyl- α -ethylamine exemplifies the method. A slurry of 4.5 g. (0.119 mole) of lithium aluminum hydride in 100 cc. of anhydrous ether was placed in a three-necked flask equipped with a glycerol sealed stirrer, a dropping funnel, and a reflux condenser with a calcium chloride drying tube. Five grams of *p*-chloroacetophenone oxime in 75 cc. of ether was added dropwise, and the mixture was stirred and refluxed for seven hours. The excess hydride was then hydrolyzed by the cautious addition of water and moist ether. The voluminous white precipitate was separated by filtration and the ethereal filtrate dried over sodium hydroxide. After removal of the solvent, the residue distilled as a clear liquid, b.p. 109–112° (13 mm.). The yield was 2.6 g.

The free base was converted to the hydrochloride by addition of ethereal hydrogen chloride. It was recrystallized by slow addition of ether to a hot chloroform solution, m.p. 191–192°.

Identification of the Amines.—The known amines were identified usually by boiling point and by conversion to known solid derivatives. Cinnamylamine was converted to the hydrochloride, m.p. 233°, and to the chloroplatinate, m.p. 219–221° (dec.). Both of these derivatives are known for both cinnamylamine and its saturated analog. It gave an instantaneous Baeyer test for unsaturation.

3-Amino-1-phenyl-1-butene was converted to the known *N*-benzoyl derivative by using benzoyl chloride and 10% sodium hydroxide. It was recrystallized from ethanol and melted at 133–134°. It gave a positive Baeyer test for unsaturation.

(15) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 202.

(11) W. G. Brown, *Org. Reactions*, **6**, 469 (1951).

(12) All melting points are corrected.

(13) N. D. Zelinski and N. V. Elaginina, *Compt. rend. acad. sci. U.R.S.S.*, **49**, 568 (1945) [*C. A.*, **40**, 6058^a (1946)].

(14) M. Qudrat-i-Khuda and A. K. Ray, *J. Indian Chem. Soc.*, **16**, 525 (1939).

The amines obtained by reducing the oximes of benzoin, diisopropyl ketone, *p*-bromoacetophenone and cyclohexanone were characterized by conversion to their hydrochloro-

rides. α -Phenylethylamine was characterized by conversion to the oxalate.

CHAPEL HILL, NORTH CAROLINA

[CONTRIBUTION FROM THE COLLEGE OF LIBERAL ARTS AND SCIENCES, TEMPLE UNIVERSITY]

A New Intramolecular Rearrangement¹

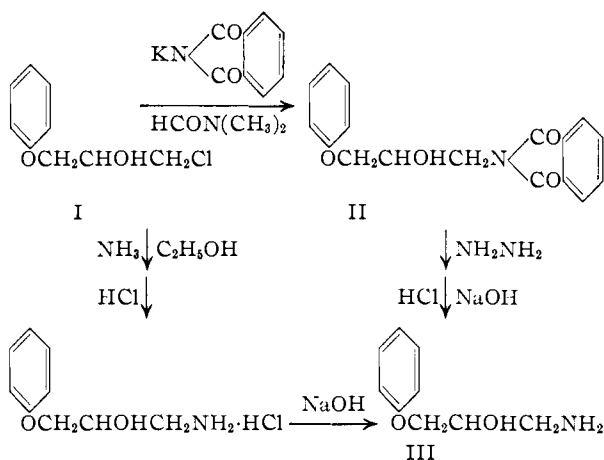
BY WILLIAM T. CALDWELL AND GEORGE C. SCHWEIKER

RECEIVED MAY 28, 1952

A new example of intramolecular rearrangement is described. It is proved that hydrolysis of 1-(*p*-nitrophenoxy)-2-acetoxy-3-phthalimidopropane (VI) and 1-(*o*-nitrophenoxy)-2-acetoxy-3-phthalimidopropane (VII) gives 1-(*p*-nitroanilino)-2,3-propanediol (VIII) and 1-(*o*-nitroanilino)-2,3-propanediol (IX).

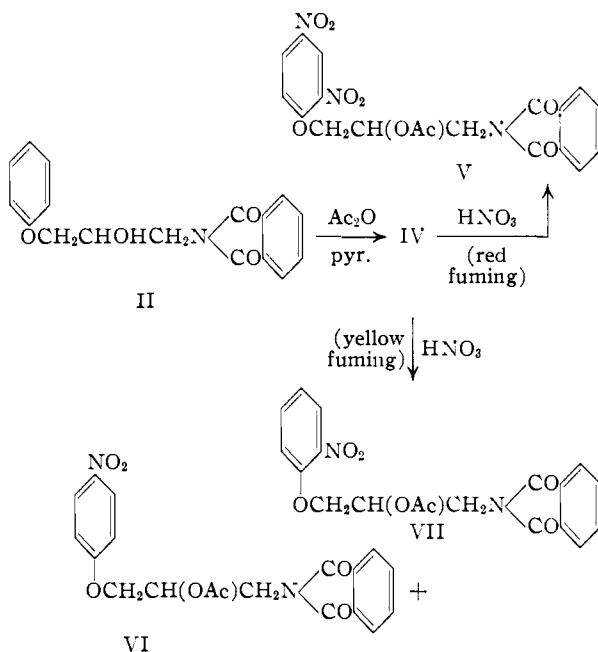
In the final step of an attempted synthesis of 1-(*p*-nitrophenoxy)-2-hydroxy-3-dichloroacetamido-propane (an isomer of Chloramphenicol) it became apparent that the expected intermediate primary amine had not been obtained in spite of excellent analyses in accord with its molecular formula.

1-Phenoxy-2-hydroxy-3-chloropropane (I) was made as described by Boyd and Knowlton² and by Levas and Lefebvre,³ and treated with potassium phthalimide using dimethylformamide as solvent⁴ to prepare 1-phenoxy-2-hydroxy-3-phthalimidopropane (II). 1-Phenoxy-2-hydroxy-3-aminopropane (III) was made from I according to Boyd's directions,⁵ and from II by treatment with hydrazine, hydrochloric acid and sodium hydroxide.⁴



All attempts to prepare a crystalline diacetyl derivative of III failed; however, it was found that acetylation of II proved an excellent way of protecting the amino and hydroxyl groups during subsequent nitration. Nitration of 1-phenoxy-2-acetoxy-3-phthalimidopropane (IV) with cold red fuming nitric acid gave 1-(2,4-dinitrophenoxy)-2-acetoxy-3-phthalimidopropane (V), but the action of yellow fuming nitric acid on IV gave a mixture of 1-(*p*-nitrophenoxy)-2-acetoxy-3-phthalimidopropane (VI) and 1-(*o*-nitrophenoxy)-2-acetoxy-3-phthalimidopropane (VII).

- (1) Taken from a thesis submitted by George C. Schweiker in partial fulfillment of the requirements for the degree of Master of Arts.
- (2) D. Boyd and H. Knowlton, *J. Chem. Soc.*, **95**, 1802 (1909).
- (3) E. Levas and H. Lefebvre, *Compt. rend.*, **222**, 555 (1946).
- (4) J. Sheehan and W. Bolhofer, *THIS JOURNAL*, **72**, 2786 (1950).
- (5) D. Boyd, *J. Chem. Soc.*, **97**, 1791 (1910).



When the mixture of VI and VII was hydrolyzed in the manner used to hydrolyze II, only a 5% yield of a mixture of 1-(*p*-nitroanilino)-2,3-propanediol (VIII) and 1-(*o*-nitroanilino)-2,3-propanediol (IX) was obtained. It was surprising to find, however, that the mixture of VI and VII gave good

