

Organic Reactions
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CHAPTER 7

THE CLEMMENSEN REDUCTION

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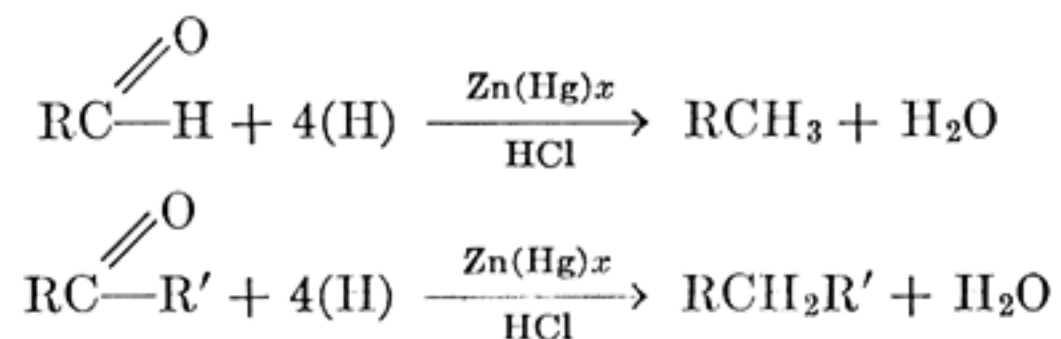
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INTRODUCTION

The replacement of the oxygen atom of the carbonyl group in an aldehyde or ketone by two hydrogen atoms through the use of amalgamated zinc and hydrochloric acid was first employed in 1913 by Clemmensen¹ and is known as the Clemmensen method of reduction. The process has been applied to a large number of aldehydes and ketones as a step in the synthesis of polynuclear hydrocarbons and alkylated aromatic compounds, including those containing one or more phenolic hydroxyl groups. It has also played an important role in the elucidation of the structures of highly complex natural products.

The formation of hydrocarbons from aldehydes and ketones by the Clemmensen reaction can be illustrated by the following equations:



The method is of peculiar value because nearly all other reducing agents which have been employed convert aldehydes and ketones to the corresponding carbinols or pinacols, rather than to the hydrocarbons. The chief alternative methods of accomplishing the same transformation are catalytic hydrogenation and reduction with hydrazine and alkali (Wolff-Kishner method).

The mechanism of the reduction by amalgamated zinc and hydrochloric acid is not clearly understood. If the carbinol is assumed to be the intermediate, then these same reagents should be suitable for the replacement of an alcoholic hydroxyl group by a hydrogen atom. However, with few exceptions, alcohols are not affected by zinc amalgam and hydrochloric acid. Only activated alcoholic hydroxyl groups, such as those in β -hydroxy acids and benzyl alcohols, are removed by the Clemmensen reagents.

The wide use of this method of reduction has resulted in the development of several modifications of the original procedure. These consist

¹ Clemmensen: (a) *Ber.*, **46**, 1838 (1913); (b) *Ber.*, **47**, 51 (1914); (c) *Ber.*, **47**, 681 (1914).

primarily in the addition of solvents, in some cases miscible and in other cases immiscible with the aqueous hydrochloric acid, and in methods of treating and amalgamating the zinc.

TYPES OF COMPOUNDS REDUCED BY THE CLEMMENSEN METHOD

Aldehydes

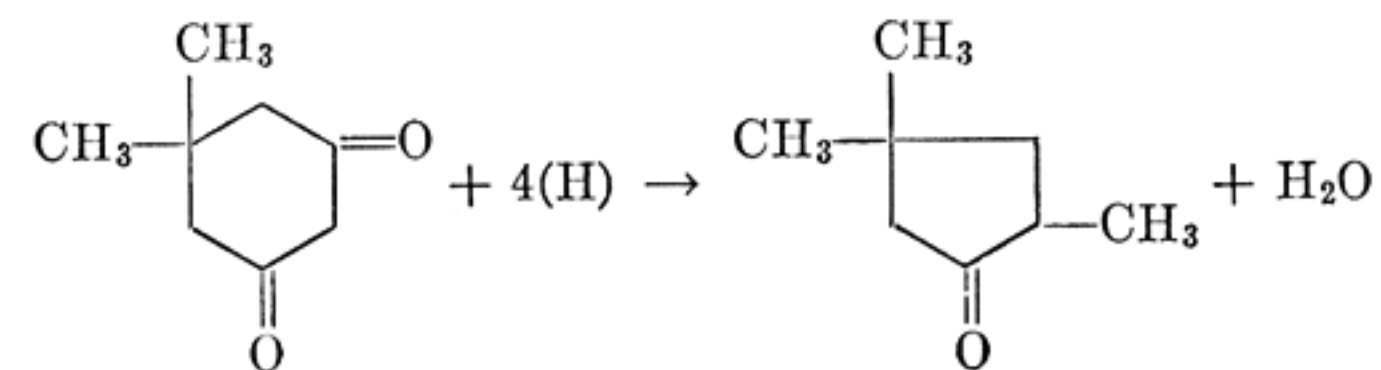
Aliphatic Aldehydes. The conversion of heptaldehyde to *n*-heptane^{1a} in 72% yield appears to be the only recorded instance of a Clemmensen reduction of an aliphatic aldehyde.

Aromatic Aldehydes. The number of aromatic aldehydes which have been subjected to the action of zinc amalgam and hydrochloric acid is not large. The original procedure of Clemmensen gives excellent results with certain phenolic aldehydes but is less satisfactory for the reduction of benzaldehyde. Robinson and Shah² obtained good yields from aromatic aldehydes by carrying out the reaction in the presence of dilute ethanol with a specially prepared zinc amalgam.

Ketones

Aliphatic and Alicyclic Ketones. Aliphatic and alicyclic ketones of low molecular weight are reduced smoothly, but those of higher molecular weight are attacked only slowly. Apparently small amounts of unsaturated compounds are formed as by-products from some ketones. Both propylene and pinacol are reported to be present in the products of the Clemmensen reduction of acetone.³ With ketones of the sterol series it is necessary to employ a solvent miscible with the hydrochloric acid to increase the solubility of the carbonyl compound in the reaction mixture. This modification of procedure is not desirable with the simple aliphatic ketones, since with such compounds it favors the formation of resinous by-products.

No reduction of an aliphatic or alicyclic α -diketone has been described. The cyclic β -diketone, 5,5-dimethylcyclohexadione-1,3, undergoes reduction and rearrangement to 2,4,4-trimethylcyclopentanone-1.⁴



² Robinson and Shah, *J. Chem. Soc.*, 1491 (1934).

³ Muller, *Z. Electrochem.*, **33**, 255 (1927).

⁴ Dey and Linstead, *J. Chem. Soc.*, 1063 (1935).

Several other β -diketones have been reduced without rearrangement; some of the reactions have been interrupted to produce monoketones.⁵

Aliphatic ketones containing primary,^{1c} secondary,⁶ or tertiary⁷ hydroxyl groups undergo reduction of the carbonyl group without change of the alcohol function. These observations, together with the fact that alcohols have been used satisfactorily as solvents, indicate that alcoholic hydroxyl groups are not ordinarily reduced by amalgamated zinc and hydrochloric acid. However, the direct replacement of an unactivated hydroxyl group has been observed in one case; 3-hydroxy-7,12-diketocholanic acid is reduced to cholanic acid.⁸ The reduction of 1,2-glycols, which has been observed with certain sterol derivatives,⁹ may depend on preliminary dehydration to ketones which then react in the usual way.

Aliphatic-Aromatic Ketones. Most aliphatic-aromatic ketones react normally, and numerous carbonyl compounds of this type, particularly phenolic ketones, have been reduced by the Clemmensen method. Cyclic ketones obtained by ring closure of γ -arylbutyric acids are also readily converted to hydrocarbons. Ketones of very slight water solubility are best reduced by employing a hydrocarbon solvent and operating in such a way that the amalgamated zinc is in contact with both the aqueous acid and the hydrocarbon solution¹⁰ (see p. 167).

The presence of a carboxyl group attached to the aromatic nucleus frequently causes the reaction to proceed more rapidly and in excellent yields.¹¹ It is probable that the carboxyl group assists in maintaining the required concentration in the acid mixture by increasing the solubility of the carbonyl compound.

The reduction of aliphatic-aromatic ketones containing one, two, or three hydroxyl or methoxyl groups on the aromatic ring proceeds exceptionally well. Quantitative yields are obtained with the lower members, and even with the higher homologs the yields are very good. The reaction proceeds rapidly, and in some cases it is possible to employ the color produced with ferric chloride as a control test.¹²

⁵ (a) Wieland and Martz, *Ber.*, **59**, 2352 (1926); (b) Qudrat-i-Khuda, *J. Chem. Soc.*, 206 (1930); (c) Ruzicka, Koolhaas, and Wind, *Helv. Chim. Acta*, **14**, 1151 (1931); (d) Chuang, Ma, and Tien, *Ber.*, **68**, 1946 (1935); (e) Friedmann, *J. prakt. Chem.*, **146**, 65 (1936); (f) Bardhan and Sengupta, *J. Chem. Soc.*, 2520 (1932).

⁶ Marker and Lawson, *J. Am. Chem. Soc.*, **61**, 852 (1939).

⁷ Lutz and Small, *J. Org. Chem.*, **4**, 220 (1939).

⁸ Borsche and Hallwass, *Ber.*, **55**, 3325 (1922).

⁹ Marker, Kamm, Oakwood, Wittle, and Lawson, *J. Am. Chem. Soc.*, **60**, 1067 (1938).

¹⁰ Mikeska, Smith, and Lieber, *J. Org. Chem.*, **2**, 499 (1938).

¹¹ Cox, *J. Am. Chem. Soc.*, **52**, 352 (1930).

¹² (a) Dohme, Cox, and Miller, *J. Am. Chem. Soc.*, **48**, 1688 (1926); (b) Cox, *J. Am. Chem. Soc.*, **52**, 352 (1930).

Side reactions accompany the reduction of many aliphatic-aromatic ketones, and in a few cases resinous products are formed in considerable quantities. Styrene, styrene polymers, and the pinacolone of acetophenone (formed by rearrangement of the pinacol) have been isolated as by-products in the preparation of ethylbenzene from acetophenone.¹³ In the reaction of 2,6-dihydroxyvalerophenone with amalgamated zinc and aqueous hydrochloric acid, cleavage of the ketone has been observed, but in ethanolic solution the reduction is satisfactory.¹⁴ Although most indandiones which have been studied react normally,¹⁵ the indan produced from 2,2-diethyl-6,7,8,9-tetrahydro-1,3- α -naphthindandione by the ordinary procedure is not completely free of oxygen compounds, and reaction over an extended period yields the 2-alkyl-5,6,7,8-tetrahydronaphthalene, formed by reductive opening of the indan ring.^{15a}

Aromatic Ketones. The reduction of benzophenone and its homologs by the original Clemmensen procedure is reported to be unsatisfactory because of the formation of resinous materials. On the other hand, *p*-hydroxybenzophenone^{1c} is transformed to *p*-hydroxydiphenylmethane in quantitative yield. 2,4-Dihydroxy^{16a} and 2,4,6-trihydroxybenzophenones^{16b} give the expected products in somewhat less satisfactory yields. *o*-Benzoylbenzoic acid is converted to *o*-benzylbenzoic acid, but reduction with zinc dust and alkali is more convenient and gives better yields.¹⁷ Either benzil or benzoin is transformed to diphenylethane in good yields by the action of amalgamated zinc and aqueous hydrochloric acid,^{1c} but the reduction of benzoin in the presence of ethanol affords stilbene in good yield.¹⁸ 2,4,6,2',4',6'-Hexamethylbenzil is unaffected by zinc amalgam and concentrated hydrochloric acid. Anthraquinone^{1a} and certain of its derivatives¹⁹ are reduced to dihydroanthracenes.

Keto Acids

α -Keto Acids. The carbonyl group of α -keto acids is attacked under the conditions of the Clemmensen reduction, but the products are the α -hydroxy derivatives rather than the completely reduced acids. For example, phenylglyoxylic acid and its ethyl ester give mandelic acid and

¹³ Steinkopf and Wolfram, *Ann.*, **430**, 113 (1923).

¹⁴ Adams, Cain, and Baker, *J. Am. Chem. Soc.*, **62**, 2201 (1940).

¹⁵ (a) v. Braun, Kirschbaum, and Schuhmann, *Ber.*, **53**, 1155 (1920); (b) Fleischer and co-workers, *Ber.*, **53**, 1255 (1920); **56**, 228 (1923); *Ann.*, **422**, 231, 272 (1921).

¹⁶ (a) Klarmann, *J. Am. Chem. Soc.*, **48**, 791 (1926); (b) Klarmann and Figdor, *ibid.*, **48**, 803 (1926).

¹⁷ Martin, *J. Am. Chem. Soc.*, **58**, 1438 (1936).

¹⁸ Ballard and Dehn, *J. Am. Chem. Soc.*, **54**, 3969 (1932).

¹⁹ Backer, Strating, and Huisman, *Rec. trav. chim.*, **58**, 761 (1939).

ethyl mandelate, respectively,¹³ and ethyl 9-fluoreneglyoxylate yields the corresponding hydroxy ester.²⁰

β -Keto Acids. The reduction of a few esters of β -keto acids has been investigated. Ethyl acetoacetate is transformed to ethyl butyrate in 30% yield, and ethyl benzoylacetate to ethyl hydrocinnamate in 59% yield.¹³ The reduction of a β -keto ester of the bile acid series, the methyl ester of 6-ketolithobilianic acid,²¹ and of two bicyclic di-(β -keto) esters²² is recorded.

γ -Keto Acids. The most important acids of this type are those obtainable by the Friedel and Crafts reaction of succinic anhydride or its substitution products with aromatic compounds or by the action of an aryl Grignard reagent with such an anhydride. The reduction of these keto acids by one of the Clemmensen procedures is satisfactory, although in certain cases some resinification occurs. A bimolecular by-product, the dilactone of γ,γ' -diphenyl- γ,γ' -dihydroxysuberic acid, has been isolated from β -benzoylpropionic acid.²³

β -Aroylpropionic acids with methoxyl groups attached to the aromatic ring are best reduced in the presence of a solvent (toluene) immiscible with the hydrochloric acid.¹⁷ β -(4,8-Dimethoxy-1-naphthoyl)-propionic acid yields γ -(4,8-dimethoxy-1-naphthyl)-butyric acid and an abnormal product, γ -(4-methoxy-5-tetra-1-yl)-butyric acid.²⁴ The formation of the latter compound involves the reduction of the ring carrying the carbonyl group and the elimination of the methoxyl group from that ring. A side reaction in the reduction of β -(*p*-bromobenzoyl)-propionic acid results in the replacement of the bromine atom by a hydrogen atom.²⁵ Esters of β -aroylpropionic acids undergo simultaneous reduction and hydrolysis to give γ -arylbutyric acids.²⁶

The Clemmensen reduction of purely aliphatic γ -keto acids and their esters has not been studied extensively. Ethyl levulinate¹³ yields ethyl valerate, but neither γ -ketopimelic acid nor its dimethyl ester²⁷ is reduced.

Other Keto Acids. δ -Keto acids and molecules in which the keto group is still further removed from the carboxyl group react normally in both aliphatic and aliphatic-aromatic series. Thus, the reductions

²⁰ Wislicenus and Weitemeyer, *Ann.*, **436**, 1 (1924).

²¹ Windaus, *Ann.*, **447**, 233 (1926).

²² Guha, *Ber.*, **72**, 1359 (1939).

²³ Overbaugh, Allen, Martin, and Fieser, *Org. Syntheses*, **15**, 64 (1935).

²⁴ Fieser and Hershberg, *J. Am. Chem. Soc.*, **58**, 2382 (1936).

²⁵ Fieser and Seligman, *J. Am. Chem. Soc.*, **60**, 170 (1938).

²⁶ (a) Fieser and Peters, *J. Am. Chem. Soc.*, **54**, 4373 (1932); (b) Haworth and Mavin, *J. Chem. Soc.*, 2720 (1932).

²⁷ Komppa, *Ann. Acad. Sci. Fennicae*, **A51**, No. 3 (1938) [*C. A.*, **34**, 2335 (1940)].

of γ -(*p*-anisoyl)-butyric acid,²⁸ of octacosan-14-one-1,28-dioic acid²⁹ [HO₂C(CH₂)₁₂CO(CH₂)₁₃CO₂H], and of 22-phenyldocosan-13-one-1-oic acid³⁰ [C₆H₅(CH₂)₉CO(CH₂)₁₁CO₂H] have been reported. With the last two compounds extended periods are required for the completion of the reaction.

α,β -Unsaturated Carbonyl Compounds

Little information is available concerning the Clemmensen reduction of α,β -unsaturated compounds. Both the carbonyl group and the ethylenic linkage of unsaturated acids of the β -aroylacrylic acid type³¹ are reduced. Similarly, 2,3-diphenylcyclopentene-2-one-1 is converted to 2,3-diphenylcyclopentane.³² *n*-Butylbenzene is obtained in 50% yield from benzalacetone, but the major product from benzalacetophenone is a bimolecular one, 1,3,4,6-tetraphenylhexane-1,6-dione.³³ Isolated double bonds apparently are not affected by amalgamated zinc and hydrochloric acid.

Chromanones are converted to chromans by means of amalgamated zinc and hydrochloric acid;³⁴ e.g., 7-hydroxy-2,2-dimethylchromanone is reduced to 7-hydroxy-2,2-dimethylchroman.^{34a} Acylated coumarins are reduced to alkyl coumarins by the method of Clemmensen,³⁵ and it is reported that 6,8-diethyl-5-hydroxy-4-methylcoumarin is obtained by the reduction of 6-acetyl-8-ethyl-5-hydroxy-4-methylcoumarin.^{35c}

The Reduction of Other Functional Groups by Amalgamated Zinc and Hydrochloric Acid

Compounds containing sensitive groups in addition to carbonyl sometimes undergo reductions of more than one type. It was mentioned above that an ethylenic link is reduced when it is conjugated with a carbonyl group. The double bond of α,β -unsaturated acids, such as cinnamic acid,¹³ is also saturated by zinc amalgam and acid. Pyrroles³⁶ and

²⁸ Plant and Tomlinson, *J. Chem. Soc.*, 1092 (1935).

²⁹ Ruzicka, Brugger, Seidel, and Shinz, *Helv. Chim. Acta*, **11**, 496 (1928).

³⁰ Hills and Robinson, *J. Chem. Soc.*, 281 (1936).

³¹ Sengupta, *J. Indian Chem. Soc.*, **17**, 183 (1940).

³² Burton and Shoppee, *J. Chem. Soc.*, 567 (1939).

³³ Dippy and Lewis, *Rec. trav. chim.*, **56**, 1000 (1937).

³⁴ (a) Bridge, Crocker, Cubin, and Robertson, *J. Chem. Soc.*, 1530 (1937); (b) George and Robertson, *J. Chem. Soc.*, 1535 (1937); (c) Anderson and Marrian, *J. Biol. Chem.*, **127**, 647 (1939).

³⁵ (a) Chowdhry and Desai, *Proc. Indian Acad. Sci.*, **8A**, 1 (1938) [*C. A.*, **32**, 9065 (1938)]; (b) Linaye and Limaye, *Rasayanam (Suppl.)* (1938) [*C. A.*, **33**, 1698 (1939)]; (c) Desai and Ekhlal, *Proc. Indian Acad. Sci.*, **8A**, 567 (1938) [*C. A.*, **33**, 3356 (1939)].

³⁶ (a) Wibaut and Hackmann, *Rec. trav. chim.*, **51**, 1157 (1932); (b) Wibaut and Oosterhuis, *ibid.*, **52**, 941 (1933).

isoquinolines³⁷ appear to be easily reduced to pyrrolines and tetrahydroisoquinolines, and in one instance (p. 160) the reduction of a naphthalene to a tetralin has been observed. The hydroxyl group of β -hydroxy acids³⁸ and of benzyl alcohol¹³ is replaced by hydrogen upon treatment with amalgamated zinc and hydrochloric acid. The same reagent reduces γ -aryl- γ -lactones to γ -aryl butyric acids.³⁹ The halogen of α -halo acids⁴⁰ and α -haloketones⁴¹ is substituted by hydrogen under the conditions of the Clemmensen reduction. With a few compounds the removal of a halogen atom attached to a benzene ring has been observed.²⁵ When ω -dimethylaminoacetophenone is reduced by the Clemmensen method the dimethylamino group is removed and ethylbenzene is produced.⁴² Somewhat similar is the formation of ethylresorcinol from 2,4-dihydroxy- ω -butoxyacetophenone.⁴³ Under certain conditions, highly reactive ketones such as 2,6-dihydroxyvalerophenone (p. 159) and 2,2-diethyl-6,7,8,9-tetrahydro-1,3-naphthindandione^{15a} undergo cleavage of carbon chains.

EXPERIMENTAL PROCEDURES

General Discussion

The procedure originally used by Clemmensen is satisfactory for the reduction of many carbonyl compounds which are appreciably soluble in the acid mixture or which melt below the boiling point of the reaction mixture. The exact proportions of zinc and hydrochloric acid employed are not of great importance provided that both are present in large excess. Although most reductions reported in the literature have made use of 20–40% hydrochloric acid, many have been successful with acid as dilute as 5%. It has been shown²³ that the product obtained from β -benzoylpropionic acid in the presence of constant-boiling hydrochloric acid is not as pure as that obtained when concentrated hydrochloric acid is used.

The reduction is carried out generally by heating the mixture under reflux for a period of four to ten hours. Longer reaction periods are required in some instances. Occasionally it is desirable to carry out the

³⁷ (a) Awe, *Ber.*, **67**, 836 (1934); (b) Awe and Unger, *Ber.*, **70**, 472 (1937).

³⁸ Cook and Lawson, *J. Chem. Soc.*, 827 (1933).

³⁹ (a) Martin, *J. Am. Chem. Soc.*, **58**, 1438 (1936); (b) Fieser and co-workers, *ibid.*, **58**, 2382 (1936); **60**, 170, 1940 (1938); **61**, 862 (1939); (c) Newman and Orchin, *ibid.*, **60**, 586 (1938); (d) Hewett, *J. Chem. Soc.*, 293 (1940).

⁴⁰ Clemo, Haworth, and Walton, *J. Chem. Soc.*, 2368 (1929).

⁴¹ (a) Johnson and Hodge, *J. Am. Chem. Soc.*, **35**, 1014 (1913); (b) Funke and Ristic, *J. prakt. Chem.*, **146**, 151 (1936).

⁴² v. Braun and Weissbach, *Ber.*, **62**, 2416 (1929).

⁴³ Hurd and Fowler, *J. Am. Chem. Soc.*, **61**, 249 (1939).

reaction at room temperature, particularly when the carbonyl compound is sensitive to the strong acid mixture. In such cases the reactants are allowed to stand at room temperature for one to two days and the reduction is then completed by heating to reflux for a period ranging from fifteen minutes to two hours. By this method 3,4-dihydroxytoluene has been obtained from 3,4-dihydroxybenzaldehyde,⁴⁴ and γ -(α -thienyl)-butyric acid is produced in excellent yield from β -(α -thenoyl)-propionic acid.⁴⁵

An improvement in yield frequently results if the substance to be reduced is first converted to a derivative which has a lower melting point and a greater solubility in the reaction mixture. Although β -3-acenaphthoylpropionic acid^{26a} and β -(1-methyl-4-naphthoyl)-propionic acid^{26b} are not attacked by amalgamated zinc and hydrochloric acid, their ethyl esters are reduced in yields of about 40%.

The use of mechanical stirring has been reported in the conversion of 4-acylresorcinols^{12a} to alkylresorcinols, but in most cases sufficient agitation is provided by the ebullition of the hot acid.

The physical form of the zinc appears not to be critical, since zinc turnings, zinc wool, granulated zinc, zinc powder, and mossy zinc have given good results. Mossy zinc has been most commonly used. It has been reported² that a very satisfactory zinc dust can be prepared by pulverizing pure zinc.

The zinc is ordinarily amalgamated by treatment with 5 to 10% of its weight of mercuric chloride in the form of a 5 to 10% aqueous solution. The time required for amalgamation can be diminished by employing a solution of mercuric chloride in very dilute hydrochloric acid.¹⁷ In order to obtain a homogeneous amalgam, it is advisable to shake or stir the mixture during the amalgamation. The quality of the amalgam is said to be improved by three washings of the zinc with hot hydrochloric acid² before amalgamation.

Preparation of Zinc Amalgam

A mixture of 100 g. of mossy zinc, 5 to 10 g. of mercuric chloride, 5 cc. of concentrated hydrochloric acid, and 100 to 150 cc. of water is stirred or shaken for five minutes. The aqueous solution is decanted, and the amalgamated zinc is covered with 75 cc. of water and 100 cc. of concentrated hydrochloric acid. The material to be reduced, usually 40 to 50 g., is then added immediately and the reaction is started.

⁴⁴ Anshultz and Wenger, *Ann.*, **482**, 25 (1930).

⁴⁵ Fieser and Kennelly, *J. Am. Chem. Soc.*, **57**, 1611 (1935).

The Clemmensen Reduction in the Absence of an Organic Solvent (Method I)

Reduction of β -(*p*-Toluyyl)-propionic acid.¹⁷ A mixture of amalgamated zinc (prepared from 100 g. of mossy zinc and 5 g. of mercuric chloride as described above), 75 cc. of water, 175 cc. of concentrated hydrochloric acid, and 50 g. of β -(*p*-toluyyl)-propionic acid is refluxed vigorously for ten hours in a 1-l. round-bottomed flask. A 50-cc. portion of concentrated hydrochloric acid is added every three hours during the heating period. After the reaction mixture has been cooled to room temperature, the solid γ -(*p*-tolyl)-butyric acid is collected and washed with small amounts of cold water. The filtrate and washings are combined and extracted with three 75-cc. portions of ether. The solid product is dissolved in the combined extracts and, after filtration from a small amount of insoluble material, the solution is dried over calcium chloride. The solvent is then removed and the residue is distilled under diminished pressure. The product, a colorless oil, crystallizes to a white solid melting at 61–62°. The yield is 41 g. (88%).

Reduction of 2,4-Dihydroxyacetophenone.^{1b, 41a, 46} A mixture of amalgamated zinc (prepared from 200 g. of mossy zinc and 10 g. of mercuric chloride as described on p. 163), 150 cc. of water, 150 cc. of concentrated hydrochloric acid, and 50 g. of 2,4-dihydroxyacetophenone (resacetophenone) is refluxed in a 1-l. round-bottomed flask until a drop of the liquid in ethanol gives no color with aqueous ferric chloride. A portion of about 10–15 cc. of concentrated hydrochloric acid is added hourly. When the color test indicates the reaction to be complete (three to four hours) the mixture is cooled and the solution is decanted from any unchanged zinc amalgam. The solution is saturated with sodium chloride and extracted with ether to remove the reaction product. Removal of the solvent yields a light yellow solid which crystallizes from benzene or chloroform as thick white prisms, m.p. 97°. The yield is 44 g. (97%).

The Clemmensen Reduction in the Presence of a Solvent Miscible with Aqueous Hydrochloric Acid (Method II)

Certain carbonyl compounds which are not appreciably soluble in the acid mixture are reduced with difficulty by Method I. In such cases the reaction is often facilitated by the addition of a solvent, such as ethanol, acetic acid, or dioxane, which is miscible with the aqueous hydrochloric acid. For example, bilianic acid is reduced by means of a

mixture of acetic and hydrochloric acids,⁴⁷ and γ -(3-phenanthryl)-butyric acid is obtained in 50% yield by the gradual addition of concentrated hydrochloric acid to a boiling mixture of β -(3-phenanthroyl)-propionic acid, acetic acid, and amalgamated zinc.⁴⁸ The use of acetic acid as a solvent in the reduction of a number of natural products has become standard practice (see p. 197). In some cases it is used without the addition of hydrochloric acid.

Ethanol is employed to increase the solubility of α -, β -, and γ -keto esters.¹³ It has been reported that γ -keto- γ -(2-fluorene)-butyric acid is unaffected by the Clemmensen reduction according to Method I, but that it is reduced almost quantitatively in the presence of aqueous ethanol.⁴⁹ The cleavage of 2,6-dihydroxyvalerophenone is avoided by carrying out the reaction in aqueous ethanol,¹⁴ and the reduction of other hydroxyphenyl alkyl ketones is assisted by the same solvent.⁵⁰ The gradual addition of an ethanolic solution of the ketone or aldehyde to a refluxing mixture of aqueous hydrochloric acid and zinc has given excellent yields of reduction products from various indanones⁵¹ and aromatic aldehydes.² The preparation of 4-chloro-7-methylindan illustrates this procedure.

Preparation of 4-Chloro-7-methylindan.⁵² A solution of 100 g. of a mixture of 4-chloro-7-methyl-1-indanone and 7-chloro-4-methyl-1-indanone⁵² in 500 cc. of ethanol is added in portions, over a period of four to five hours, to a refluxing mixture of 100 cc. of water, 40 cc. of ethanol, 250 cc. of concentrated hydrochloric acid, and the amalgamated zinc prepared from 350 g. of granulated zinc and 17.5 g. of mercuric chloride (see p. 163). After the addition is complete the mixture is refluxed for ten hours, during which time 200 cc. of concentrated hydrochloric acid is added in portions. The mixture is cooled; the aqueous layer is decanted and, after dilution with an equal volume of water, is extracted twice with ether. The greater portion of the product is recovered by extraction of the zinc residues with ether. Any lumps of material must be broken up to facilitate the extraction. The ether extracts are combined, and, after removal of the solvent, the residual oil is steam-distilled from an aqueous solution of sodium hydroxide. The colorless oil is separated from the distillate, and the aqueous layer is extracted with ether. The oil is combined with the ether solution and, after drying and removal of the solvent, is distilled under diminished pressure. The

⁴⁷ Borsche and Rosenkranz, *Ber.*, **52**, 342 (1919).

⁴⁸ Haworth and Mavin, *J. Chem. Soc.*, 1012 (1933).

⁴⁹ Koelsch, *J. Am. Chem. Soc.*, **55**, 3885 (1933).

⁵⁰ Coulthard, Marshall, and Pyman, *J. Chem. Soc.*, 280 (1930).

⁵¹ Fieser and Seligman, *J. Am. Chem. Soc.*, **57**, 942 (1935).

⁵² Fieser and Seligman, *J. Am. Chem. Soc.*, **58**, 2482 (1936).

⁴⁶ Brewster and Harris, *J. Am. Chem. Soc.*, **52**, 4866 (1930).

product is a colorless liquid b.p. 132–133°/25 mm. The yield is 88.5 g. (95%).

Reduction of γ -Keto- γ -(2-fluorene)-butyric Acid.⁴⁹ A mixture of 90 g. of γ -keto- γ -(2-fluorene)-butyric acid, 450 cc. of ethanol, 450 cc. of concentrated hydrochloric acid, and 180 g. of amalgamated zinc is refluxed for one hour. A second 450-cc. portion of concentrated hydrochloric acid is then added, and refluxing is continued for eight hours. The mixture is cooled, and the solid is collected and dissolved by boiling with 1000 cc. of 5% aqueous sodium hydroxide. After filtration and acidification the γ -(2-fluorene)-butyric acid separates. The yield of crude product is 85 g. It is readily purified by recrystallization from acetic acid followed by recrystallization from benzene-petroleum ether, yielding white plates, m.p. 151–151.5°.

The Clemmensen Reduction in the Presence of a Solvent Immiscible with the Hydrochloric Acid (Method III)

A large number of carbonyl compounds have been reduced in poor yields by Methods I and II, and, especially in the cases of certain keto acids, the difficulty has been ascribed to the formation of insoluble polymolecular reduction products which coat the surface of the zinc.¹⁷ The addition of a hydrocarbon solvent, such as toluene, which is immiscible with the hydrochloric acid is beneficial in those cases because it keeps most of the material out of contact with the zinc, and in the aqueous layer the reduction occurs at such a high dilution that polymolecular reactions are largely inhibited.

The modification is particularly advantageous with keto acids which contain methoxyl groups. Such compounds may suffer hydrolysis of methoxyl groups during the reduction; consequently it is desirable to treat an alkaline solution of the crude reaction product with methyl sulfate, in the presence of a trace of sodium hydrosulfite if darkening occurs during methylation, to recover any demethylated material.

Certain extremely insoluble compounds cannot be reduced by this method unless both the aqueous layer and the hydrocarbon layer are in contact with the zinc.

Reduction of β -Benzoylpropionic Acid.¹⁷ To 120 g. of mossy zinc, amalgamated as described on p. 163, 75 cc. of water, 175 cc. of concentrated hydrochloric acid, and 100 cc. of toluene is added 50 g. of β -benzoylpropionic acid. The mixture is refluxed briskly for twenty-four to thirty hours, during which time a 50-cc. portion of concentrated hydrochloric acid is added every six hours. The solution is cooled to room temperature, the aqueous layer is separated and, after dilution with 200

cc. of water, is extracted with three 75-cc. portions of ether. The combined ether and toluene solutions are washed with a little water and dried over calcium chloride. The solvents are removed by distillation under diminished pressure, and the residue is distilled. γ -Phenylbutyric acid, b.p. 178–181°/19 mm., is obtained as a colorless oil which solidifies to white crystals, m.p. 46–48°. The yield is 41 g. (90%).

Reduction of β -(*p*-Anisoyl)-propionic Acid.¹⁷ To 120 g. of mossy zinc amalgamated as described on p. 163 are added, in the order given, the following: 75 cc. of water, 175 cc. of concentrated hydrochloric acid, 100 cc. of toluene, and 50 g. of β -(*p*-anisoyl)-propionic acid. The mixture is refluxed briskly for forty-eight hours, during which time a 25-cc. portion of concentrated hydrochloric acid is added every six hours. The solution is cooled to room temperature; the aqueous layer is separated and, after dilution with 200 cc. of water, is extracted with three 75-cc. portions of ether. The toluene and ether extracts are added to 300 cc. of 5% aqueous sodium hydroxide, and the solvents are removed by steam distillation.

The residual alkaline solution is cooled to 80°, and 5 to 10 cc. of methyl sulfate is added. If necessary, aqueous sodium hydroxide is introduced to keep the solution alkaline. After the mixture has been shaken or stirred for thirty to forty-five minutes, the excess alkali is neutralized and the solution is treated with charcoal. The colorless or yellow filtrate is cooled to 10° and acidified by the slow addition of hydrochloric acid. The mixture is kept in an ice bath until the precipitation of the product is complete. It is then filtered and the solid is washed with a little cold water. The crude material, obtained in quantitative yield, is sufficiently pure for most purposes. For purification it is dissolved in ether and the solution is filtered from any insoluble material. The solvent is removed and the residue is distilled under diminished pressure. The yield of γ -(*p*-anisyl)-butyric acid, b.p. 182–186°/4 mm., m.p. 61–62°, is 43 g. (94%). For further purification the acid may be recrystallized from petroleum ether (b.p. 30–60°).

Reduction of Stearophenone.¹⁰ Mossy zinc is added to a weighed 2-l. Erlenmeyer flask until a layer about 8 cm. deep is formed. The weight of the zinc is determined, and the metal is amalgamated by treatment with the appropriate amounts of mercuric chloride, water, and hydrochloric acid (p. 163). To the zinc amalgam is added sufficient concentrated hydrochloric acid to cover about one half of it, followed by a solution of 250 g. of stearophenone in 750 cc. of xylene. The mixture is heated under reflux for seven hours, during which time gaseous hydrogen chloride is passed into the bottom of the flask to replace losses. The xylene layer is separated, the solvent removed, and the product distilled, b.p.

220–235°/5 mm. A residue of about 30 g. of a heavy oil is discarded. The distillate is dissolved in 750 cc. of xylene and treated with another portion of zinc amalgam and hydrochloric acid as described above. The product isolated, b.p. 195–205°/4 mm., m.p. 33°, weighs 190 g. (77%). Crystallization of the *n*-octadecylbenzene from ether yields a product of m.p. 35–36°.

The Clemmensen Reduction in the Presence of Solvents of Both Types (Method IV)

Certain carbonyl compounds of very slight solubility are reduced in the presence of toluene only when a small amount of a solvent such as acetic acid, ethanol, or dioxane is added to the reaction mixture. The water-soluble solvent effects a satisfactory distribution of the compound between the two layers, permitting a low concentration of the material in the aqueous layer. 4-Hydroxy-3-phenylpropiophenone,⁵³ and 4-methyl-1-keto-1,2,3,4-tetrahydrophenanthrene⁵⁴ have been reduced by this modification in yields of 74 and 94%, respectively. The experimental procedure is essentially the same as that of Method III.

The Clemmensen Reduction with Unamalgamated Zinc (Method V)

Unamalgamated zinc has been employed successfully with chlorogestone, cholestanedione-3,6, cholestanone-7, and other ketones of the sterol family.⁵⁵ The compound to be reduced is dissolved in 95% ethanol, and 20-mesh granulated zinc is added. To the boiling mixture small amounts of concentrated hydrochloric acid are added over a period of several hours. Apparently this procedure represents another modification suitable for ketones of very low water solubility.

⁵³ Harris and Pierce, *J. Am. Chem. Soc.*, **62**, 2223 (1940).

⁵⁴ Bachmann and Edgerton, *J. Am. Chem. Soc.*, **62**, 2219 (1940).

⁵⁵ Marker and Rohrmann, *J. Am. Chem. Soc.*, **61**, 846, 946, 1284, 2719, 3314, 3479 (1939).