CHAPTER 3

# CLEMMENSEN REDUCTION OF KETONES IN ANHYDROUS ORGANIC SOLVENTS

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CONTENTS

## INTRODUCTION

The Clemmensen reduction of ketones and aldehydes using zinc and hydrochloric acid is the simplest direct method for converting the carbonyl group into a methylene group. Procedures and results with acid-stable compounds were reviewed by Martin in *Organic Reactions* in 1942 and more recently by Staschewski.[1, 2] Typically, the carbonyl compound is

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[1] E. L. Martin, *Org. Reactions*, **1**, 155 (1942).

[2] D. Staschewski, *Angew. Chem.*, **71**, 726 (1959).

refluxed for several hours with 40% aqueous hydrochloric acid, amalgamated zinc, and a water-immiscible organic cosolvent such as toluene. Because of these harsh conditions, reports of successful Clemmensen reduction of polyfunctional ketones have been rare. However, the milder procedure described by Yamamura and his collaborators using dry hydrogen chloride in organic solvents extends the synthetic potential of Clemmensen reduction to acid- and heat-sensitive compounds; this procedure is summarized later (pp. 412–414) in this review. Other developments that define the scope of both aqueous and anhydrous reduction conditions are discussed, and an effort is made to compare the properties of possible reduction intermediates with other organozinc species.
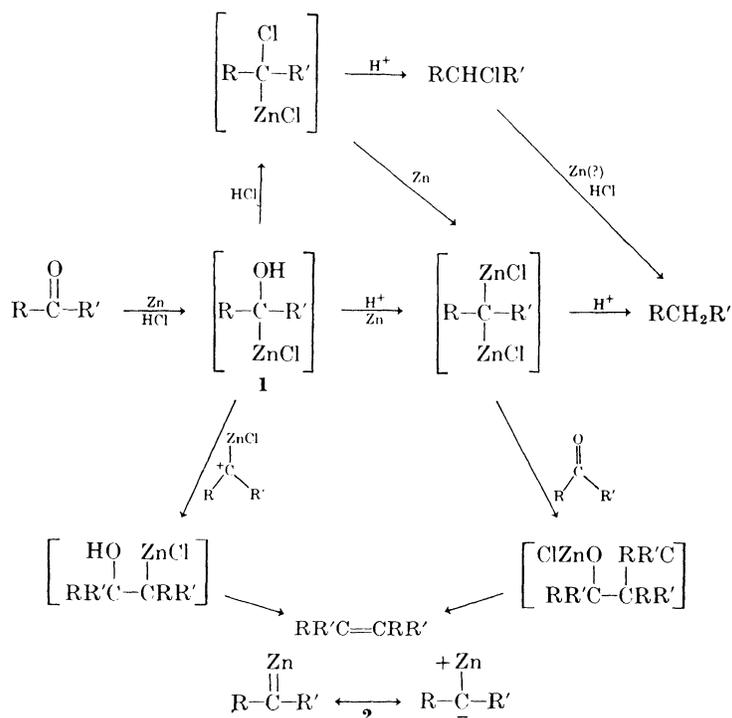
## MECHANISM

Because the mechanism of the Clemmensen reduction is poorly understood, much additional information is necessary before the effect of experimental variables on results can be rationalized. Studies by Nakabayashi,[3] Brewster,[4] and numerous earlier workers have established several general characteristics of the reaction that suggest a stepwise reduction involving organozinc intermediates. It has been shown that reduction occurs with zinc but not with other metals of comparable reduction potential. The rate-determining step does not involve an electrochemical process (i.e., two one-electron transfer steps) because the rate of reduction is not sufficiently sensitive to changes in the zinc reduction potential.[3] An electrochemical reduction (pinacol coupling) often competes with the Clemmensen reduction, but the two reactions do not have a common intermediate in the only case studied.[3] The reduction rate is relatively insensitive to acid concentration but responds sufficiently to changes in halide concentration to suggest involvement of halide in the initial step.[3] Intermediates have not been identified conclusively, but older mechanisms involving alcohols as intermediates have been ruled out because alcohols are generally not reduced under Clemmensen conditions.[2, 4]

The experimental and kinetic data are rationalized by the rate-limiting attack of zinc and chloride ion on the carbonyl group with subsequent rapid protonation to afford the α-hydroxyalkylzinc chloride 1.[3] The nature of any further intermediates is highly speculative, but a second reductive step is ultimately necessary in order to form an organozinc species capable of undergoing protolysis to the hydrocarbon product. One possibility involves acid-catalyzed reduction of the carbon-oxygen bond

[3] T. Nakabayashi, J. Amer. Chem. Soc., **82**, 3900, 3906, 3909 (1960).

[4] J. H. Brewster, J. Amer. Chem. Soc., **76**, 6364 (1954); J. H. Brewster, J. Patterson, and D. A. Fidler, ibid., **76**, 6368 (1954).

## Scheme 1

$$\begin{bmatrix} & Cl & \\ R-&C&-R' \\ & ZnCl & \end{bmatrix} \xrightarrow{\;H^+\;} RCHClR'$$

$$HCl \uparrow \qquad\qquad \searrow^{Zn} \qquad\qquad \searrow^{Zn(?)}_{HCl}$$

$$\underset{R-C-R'}{\overset{O}{\parallel}} \xrightarrow[HCl]{Zn} \begin{bmatrix} & OH & \\ R-&C&-R' \\ & ZnCl & \end{bmatrix} \xrightarrow[Zn]{H^+} \begin{bmatrix} & ZnCl & \\ R-&C&-R' \\ & ZnCl & \end{bmatrix} \xrightarrow{\;H^+\;} RCH_2R'$$

$$\mathbf{1}$$

$$\swarrow^{ZnCl}_{\overset{+}{C}} \qquad\qquad \searrow$$
$$R \quad R'$$

$$\begin{bmatrix} HO & ZnCl \\ | & | \\ RR'C-CRR' \end{bmatrix} \searrow \qquad\qquad \swarrow \begin{bmatrix} ClZnO & RR'C \\ | & | \\ RR'C-CRR' \end{bmatrix}$$

$$RR'C{=}CRR'$$

$$\underset{R-C-R'}{\overset{Zn}{\parallel}} \xleftrightarrow{\;\;\mathbf{2}\;\;} \underset{R-C-R'}{\overset{+Zn}{|}}$$

of **1** to a bis(chlorozinc)alkyl structure. An alternative reduced species **2** has been suggested,[3] but this unprecedented molecule involves either charge separation or unlikely carbon $2p$-zinc $4p\pi$-bonding.

The proposed bis(chlorozinc)alkyl also lacks precedent, although a related substance appears to be formed in the zinc-copper couple reduction of iodomethyl tosylate, as evidenced by the formation of methane upon hydrolysis and of the corresponding amount of methylene iodide upon treatment with iodine.[5] Methane is also formed in low yield upon hydrolysis of the reduction product of methylene iodide with zinc-copper couple, but Blanchard and Simmons have shown that methane results from stepwise reduction to methyl iodide and then to methylzinc iodide, and not from bis(iodozinc)methane as suggested previously.[6, 7]

The proposed reduction of **1** by zinc in the presence of an acid catalyst is an example of the high electrophilic reactivity of $\alpha$-heteroatom-substituted zinc alkyls. Thus hydrolysis of bis(chloromethyl)zinc in

[5] M. Jautelat, Ph.D. Thesis, Heidelberg, 1965.

[6] E. P. Blanchard and H. E. Simmons, *J. Amer. Chem. Soc.*, **86**, 1337 (1964).

[7] E. Emschwiller, *Compt. Rend.*, **188**, 1555 (1929).

aqueous zinc iodide affords 80 % of methyl iodide and only 1 % of methyl chloride, indicating that nucleophilic displacement of chloride by iodide is faster than protolysis of the carbon-zinc bond.[8] This observation raises the possibility that acid-catalyzed nucleophilic displacement of hydroxide by chloride may be faster than reduction under Clemmensen conditions; if it is, the result would be conversion of the α-hydroxyalkylzinc chloride 1 into an α-chloroalkylzinc chloride. Protolysis of the zinc-carbon bond of the latter would explain the occasional appearance of alkyl chlorides as side products of Clemmensen reduction. It is also conceivable that some alkyl chlorides are reduced to hydrocarbons and may serve as Clemmensen intermediates. Few experimental data about this point are available since it has been assumed that chlorides would be formed from alcohols which are definitely not reduced under Clemmensen conditions. It is reported that cyclohexyl chloride is not reduced under conditions which convert cyclohexanone into cyclohexane,[4] but reduction of the exocyclic methylene group of the gibberellin 3 to a methyl group using zinc and dry hydrogen chloride suggests that an intermediate tertiary chloride would be reduced.[9]
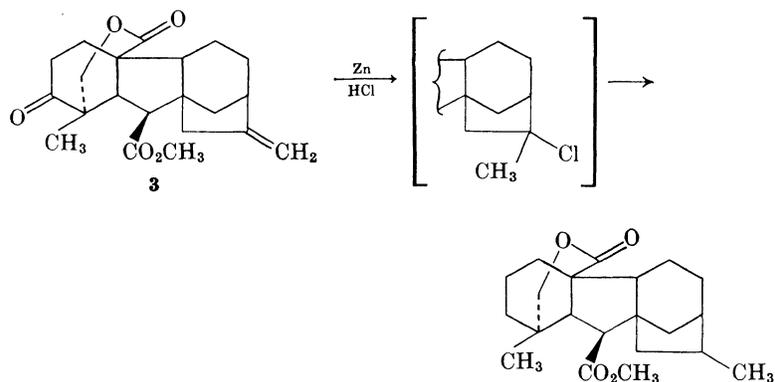


Other side reactions accompanying Clemmensen reduction can be explained on the basis of a polar carbon-heteroatom bond in intermediates at the same reduction stage as 1, represented for simplicity by chlorozinc-carbonium ions in the following discussion. Migration of an adjacent substituent (hydride, alkyl, aryl) to the positive center would afford monomeric olefin, as illustrated for the formation of cyclohexene from cyclohexanone. The relative yield of cyclohexene increases from 6 to 47 % as the concentration of hydrogen chloride in the aqueous reduction

[8]  H. Hoberg, Ann., **656**, 15 (1962); G. Wittig and F. Wingler, ibid., **656**, 18 (1962).
[9]  B. E. Cross and J. C. Stewart, J. Chem. Soc., C, **1971**, 245.
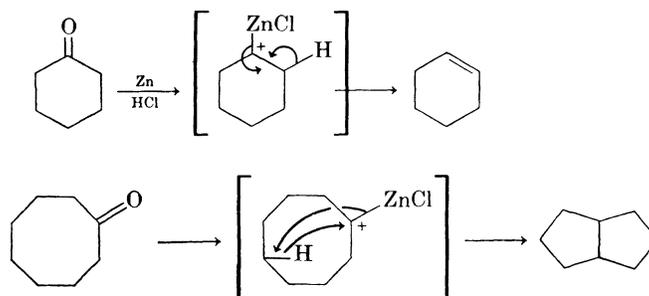
medium is decreased from 20 to 3 %.[10a] Actual yields were not reported, however, so it is unclear whether the dependence of product ratio on acid concentration has any bearing on the reduction mechanism or merely reflects selective destruction of cyclohexene under strongly acidic conditions. Synthetically useful yields of alkenes can be obtained by reduction of ketones with zinc in the presence of chlorotrimethylsilane (aprotic conditions, ether solution).[10b]

Reduction of medium-sized ring ketones affords the transannular insertion products.[11] Thus bicyclo[3.3.0]octane is formed in addition to cyclooctene and cyclooctane upon reduction of cyclooctanone. Related carbonium ion-like rearrangements are observed upon zinc reduction of α,α-diiodoalkanes, probably via α-iodoalkylzinc iodides which are closely related to the proposed Clemmensen intermediates.[12]

Dimeric olefins are often formed as side products of Clemmensen reduction, especially from aryl ketones.[2] These products may result from self-condensation of the hydroxyalkylzinc chloride 1, followed by elimination of zinc chlorohydroxide (Scheme 1, p. 403). This mechanism has a precedent in the for mation of ethylene from iodomethylzinc iodide or of stilbene from α-iodobenzylzinc iodide.[6, 12a, 13]

Alternatively, condensation of unreacted ketone with a bis(chlorozinc) species derived from the second reductive step and subsequent elimination could be invoked. Analogous reactions between aldehydes or ketones and methylene iodide in the presence of excess zinc have been reported to give methylene derivatives.[14] However, formation of the methylene derivatives

[10] (a) G. E. Risinger, E. E. Mach, and K. W. Barnett, Chem. Ind. (London), 1965, 679; (b) W. B. Motherwell, Chem. Commun., 1973, 935.

[11] E. Muller, G. Fiedler, H. Huber, B. Narr, H. Suhr, and K. Witte, Z. Naturforsch., 18B, 5 (1963).

[12] (a) H. E. Simmons, E. P. Blanchard, and R. D. Smith, J. Amer. Chem. Soc., 86, 1347 (1964); (b) R. Newman, Tetrahedron Lett., 1964, 2541.

[13] L. Y. Goh and S. H. Goh, J. Organometal. Chem., 23, 5 (1970).

[14] H. Hashimoto, M. Hida, and S. Miyano, J. Organometal. Chem., 10, 518 (1967); ibid., 12, 263 (1968); I. T. Harrison, R. J. Rawson, P. Turnbull, and J. H. Fried, J. Org. Chem., 36, 3515 (1971).

as well as the dimeric olefins from Clemmensen reduction can also be explained by condensation of an α-halozinc halide with a carbonyl group to form the zinc salt of a β-haloalcohol which would afford olefin upon further reduction.

The preceding discussion relates Clemmensen intermediates to α-haloalkylzinc halides, the carbenoid reagents of the Simmons-Smith cyclopropane synthesis.[15] Another similarity between the two types of reactions is apparent in the formation of 7-phenylnorcarane by aprotic reduction of benzaldehyde with zinc and boron trifluoride etherate in the presence of cyclohexene.[16] The scope of this reaction is not known, although it has been reported that zinc does not reduce ketones under similar conditions.

In summary, it is possible to rationalize the principal side products of Clemmensen reduction on the basis of hypothetical intermediates derived from the first reductive step. In general, the second reductive step (resulting in formation of hydrocarbon) competes effectively with protolysis, rearrangement, or intermolecular coupling of the intermediate 1. To explain the observation that protolysis after the first reductive step is a minor reaction pathway, it has been argued that both reductive steps involve species which are bound to the solid zinc surface. However, electron transfer from the metal surface to dissolved intermediates could be more efficient than various possible side reactions. Experimental support for either argument is lacking, but there is no compelling reason to assume unusual bonding properties for the great variety of zinc surfaces (liquid 2% zinc amalgam, solid zinc amalgam, ordinary zinc dust, etc.) which can be used and generally afford similar product mixtures.

## SCOPE AND LIMITATIONS

In most instances the success of the Clemmensen reduction depends on the stability of a given ketone to acid. This is not a severe limitation, especially under the conditions reported by Yamamura and co-workers (pp. 412–414).
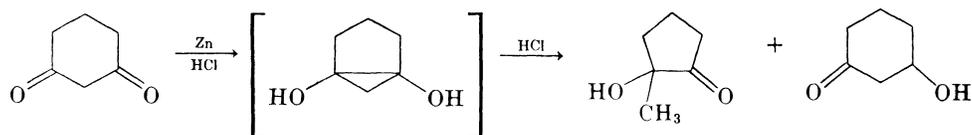
### 1,3-Diketones

1,3- and 1,4-Diketones seldom give useful yields of Clemmensen reduction products. Intramolecular pinacol coupling to cyclopropanediols is the favored initial reaction of acyclic 1,3-diones, cyclohexane-1,3-diones, and 2-acylcycloalkanones. It is possible to trap the cyclopropanediols as

[15] H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, *Org. Reactions*, **20**, 1 (1973).

[16] I. Elphimoff-Felkin and P. Sarda, *Chem. Commun.*, **1969**, 1065.

the diacetates by using acetic anhydride as the reduction medium; but, under ordinary Clemmensen conditions, cleavage of the cyclopropane ring is rapid and a mixture of $\alpha$- and $\beta$-hydroxyketones is formed. Further reduction of the hydroxyketones is then possible, and the ultimate products may include rearranged and unrearranged monoketones and hydrocarbons derived from reduction of the initial products.[17]



## 1,4-Diketones

Reduction of 1,4-diketones is complex and unpredictable. Occasionally, normal reduction is observed as in the conversion of 1-phenylpentane-1,4-dione into 5-phenylpentan-2-one or of cholestane-3,6-dione into cholestan-6-one.[18] More commonly the initial process is reductive fragmentation of the $C_2$–$C_3$ bond. Depending on conditions, cyclohexane-1,4-dione affords as many as twenty-six products, beginning with cleavage to hexane-2,5-dione followed by numerous reduction processes, rearrangements, acid-catalyzed cyclization, etc.[18, 19] Cleavage of a strained cyclobutane bond is more easily controlled, and the diketone 4 is reduced smoothly to a dihydro derivative. However, internal pinacol coupling to a cyclobutane diol occurs upon prolonged treatment with zinc.[19]
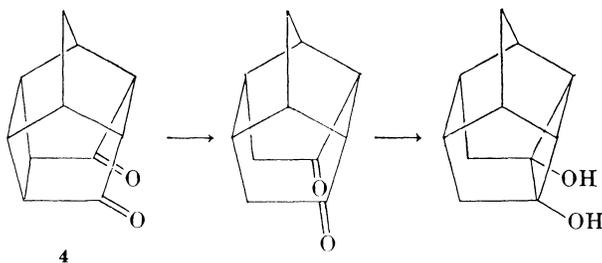


## 1,5-Diketones

Internal pinacol coupling is a general reaction of diketones such as cyclooctane-1,5-dione and bicyclo[3.3.1]nonane-3,7-dione which can

[17] J. G. St. C. Buchanan and P. D. Woodgate, *Quart. Rev.*, **23**, 522 (1969).
[18] J. G. St. C. Buchanan and B. R. Davis, *J. Chem. Soc., C*, **1967**, 1340.
[19] E. Wenkert and J. E. Yoder, *J. Org. Chem.*, **35**, 2986 (1970).

adopt conformations with the two carbonyl groups in close proximity.[20] Other intramolecular interactions are responsible for the unusual behavior of the related 1,5-diketone 1,5-dimethylbicyclo[3.3.0]octane-3,7-dione. Zinc in acetic anhydride-hydrogen chloride affords the acetate 6 in 50% yield, while reduction in aqueous hydrochloric acid results in 1,5-dimethyl-bicyclo[3.3.0]octane as the major product.[20] The solvent effect indicates that a reduction intermediate such as 5 is converted primarily into hydrocarbon in the protic solvent but, in acetic anhydride-hydrogen chloride, carbon-zinc bonds survive long enough to allow cyclization of 5 to the tricyclic product.
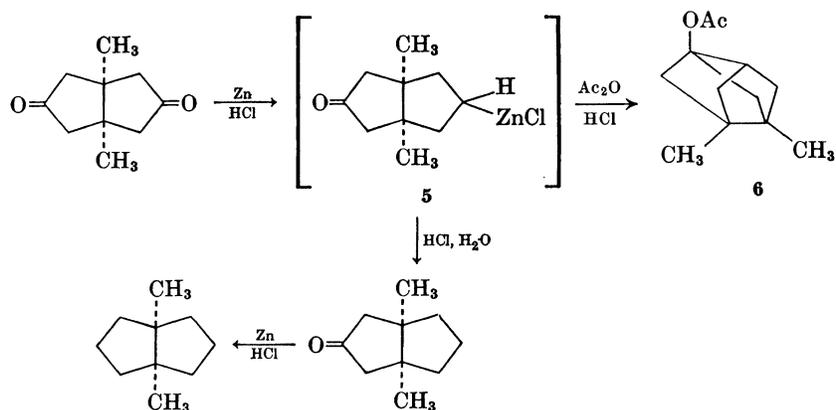


## α,β-Unsaturated Ketones

Reduction of simple α,β-unsaturated ketones affords mixtures containing the corresponding saturated ketone and derived hydrocarbons, ketonic and hydrocarbon dimers derived from radical coupling at the β position, pinacol coupling products, and skeletal rearrangement products derived from cyclopropanol intermediates.[17] The intermediacy of cyclopropanols has been established by trapping experiments with acetic anhydride, but the mechanism of cyclopropanol formation is not known.[21]

Certain steroidal enones can be reduced in acceptable yield with the result that first the enone double bond and then the carbonyl group are reduced (see Table I). Reduction of the double bond is especially facile in systems such as 8 owing to activation by a second carbonyl group, and the resulting γ-ketoacid is reduced normally.[22, 23] Analogous reduction
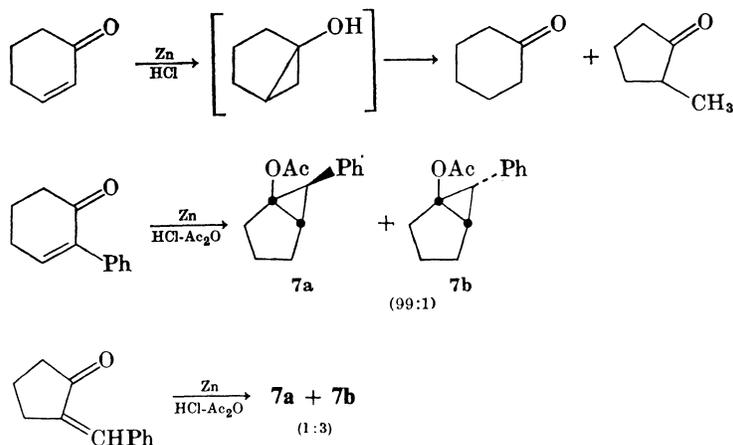
[20] W. T. Borden and T. Ravindranathan, *J. Org. Chem.*, **36**, 4125 (1971).

[21] I. Elphimoff-Felkin and P. Sarda, *Tetrahedron Lett.*, **1969**, 3045.

[22] J. A. Marshall and S. F. Brady, *J. Org. Chem.*, **35**, 4068 (1970); D. L. Dreyer, *ibid.*, **36**, 3719 (1971).

[23] K. Ohkata and T. Hanafusa, *Bull. Chem. Soc. Jap.*, **43**, 2204 (1970).

of the enedione **9** to the dihydro derivative also occurs without rearrange-
ment or fragmentation.[24]





7a        7b
(99:1)



## Ketones with α-Heteroatom Substituents

Heteroatoms attached to carbon atoms alpha to the carbonyl function
are subject to reductive elimination under Clemmensen conditions.[17]
Similar reactions occur with other reducing metals; an electrochemical
mechanism is probably involved. Transfer of two electrons from the metal
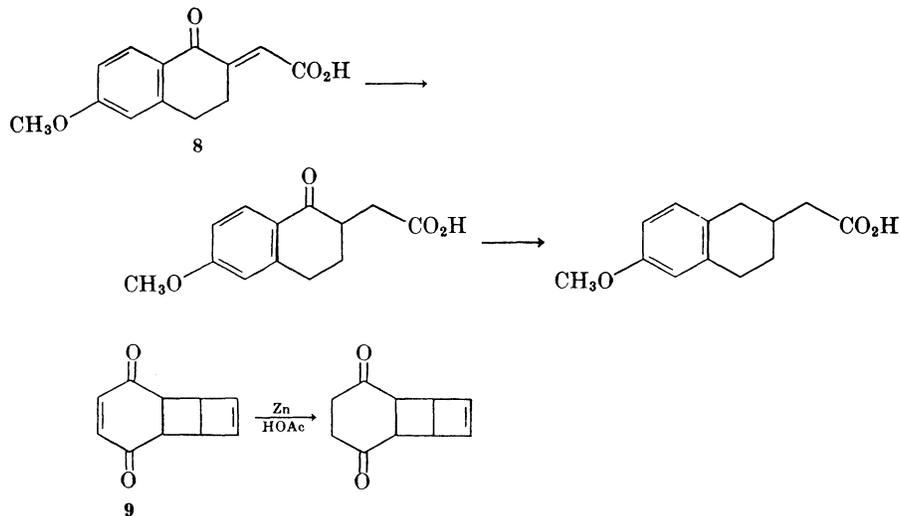




[24] E. Vedejs, unpublished results.

to the carbonyl group, followed by departure of the heteroatom as the anion affords an enolate which is converted into the corresponding ketone by acid. Clemmensen reduction of α-dicarbonyl compounds occurs by way of a related electrochemical mechanism. Thus the Diels-Alder adduct of 1,2-naphthoquinone and cyclopentadiene is reduced stepwise by zinc in acetic acid, first to an α-hydroxyketone, more slowly to a mono-ketone, and ultimately to the alkene.[24] Reduction of oxalylcyclopentanone (an α-ketoester as well as a 1,3-diketone) may also involve an electro-chemical reduction to the α-hydroxyester followed by reductive elimina-tion of hydroxide and hydrolysis to the ketoacid 10. Clemmensen reduction of the isolated cyclopentanone carbonyl group of 10 occurs only under forcing conditions.[25]
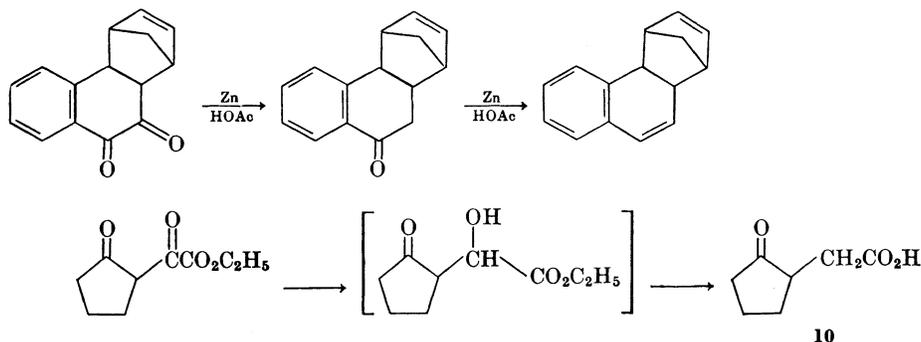


Reductive elimination of the α-chloro substituents in 1,4-dichloro-bicyclo[2.2.1]heptan-7-one does not occur because the intermediate enolate would have to violate Bredt's rule.[26]
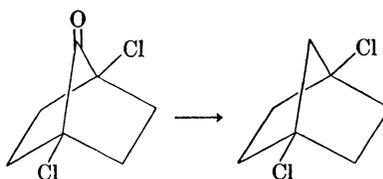


## Hindered Ketones

The rate of Clemmensen reduction is sensitive to steric hindrance, as expected for a heterogeneous reaction. Ketones having adjacent t-butyl- or neopentyl-like substituents are reduced slowly, and in extreme cases

[25] R. Mayer, H. Burger, and B. Matauschek, J. Prakt. Chem. [IV] 14, 261 (1961).
[26] A. P. Marchand and W. R. Weimar, Jr., J. Org. Chem., 34, 1109 (1969).

such as **11** and **12** reduction fails completely.[27, 28] Substantial differences in reduction rate due to steric factors permit selective reduction of the 3-keto group of androsta-3,17-dione in 67 % yield (Table I).
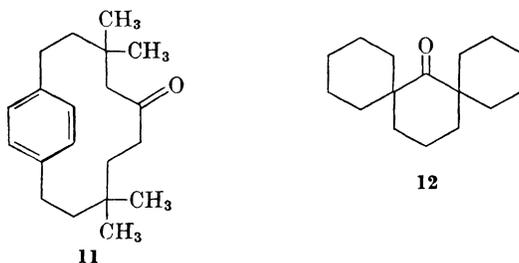


## COMPARISON WITH OTHER METHODS OF REDUCTION

In view of the limitations of the Clemmensen reduction, other reasonably general methods for conversion of carbonyl into $-CH_2-$, such as Raney nickel desulfurization of the derived thioketal, or Wolff-Kishner reduction, may be preferred.[29, 30]

Desulfurization is particularly useful for selective reduction of enones and ketones having $\alpha$-heteroatom substituents. Bisthioketals derived from 1,3- or 1,4-diketones are reduced without rearrangement, and selective reduction of one carbonyl group is possible if the corresponding monothioketal can be prepared.[27] The most common limitation of the desulfurization method is the hydrogenation of alkenes by active forms of Raney nickel.

The Wolff-Kishner reduction is a useful alternative to either the Clemmensen reduction or the desulfurization procedure, both of which employ a reducing metal capable of cleaving N–O bonds, reducing imines, hydrazines, azo compounds, and other electron-deficient functional groups. The Wolff-Kishner method is especially suited for reduction of medium-ring or strained-ring ketones to the corresponding hydrocarbons without rearrangement. There are few specific reports of the Clemmensen reduction applied to strained ketones, and the lack of positive results is discouraging.

In other respects the Wolff-Kishner reduction is more limited in scope than the Clemmensen reduction since enones, 1,3- and 1,4-dicarbonyl

[27] H. A. P. DeJongh and H. Wynberg, *Tetrahedron*, **20**, 2553 (1964).
[28] A. T. Blomquist and B. H. Smith, *J. Org. Chem.*, **32**, 1684 (1967).
[29] G. R. Pettit and E. E. van Tamelen, *Org. Reactions*, **12**, 356 (1962).
[30] H. H. Szmant, *Angew. Chem. Int., Ed. Engl.*, **7**, 120 (1968).

compounds of various kinds, and α-heteroatom-substituted ketones behave anomalously. Furthermore, the presence of base-sensitive substituents precludes use of the Wolff-Kishner reductions in which potassium hydroxide is employed in typical experiments at temperatures between 100 and 200°. The tosylhydrazone modification avoids strong base and requires temperatures no higher than 80°.[31] This technique employs sodium borohydride or sodium cyanoborohydride to convert the tosylhydrazone into a tosylhydrazine which decomposes to the hydrocarbon at 80°.

## REDUCTIONS WITH HYDROGEN CHLORIDE IN APROTIC ORGANIC SOLVENTS

Clemmensen reduction in organic solvents (alcohols, acetic acid) has been known for some time,[2] but it was generally found that a homogeneous liquid phase favored the formation of dimeric products (pinacols).[32] However, Yamamura and his associates have shown that anhydrous hydrogen chloride and zinc dust in organic solvents (ether, tetrahydrofuran, acetic anhydride, benzene) affords hydrocarbons in high yield.[33-39] Optimum results are obtained when a large excess of activated zinc dust in diethyl ether saturated with hydrogen chloride at ice-bath temperatures is used. In contrast to the original Clemmensen method, typical reductions are complete within an hour at 0° (Procedure A, p. 414). Activation of the zinc dust is recommended for hindered ketones, but commercial zinc dust may be used in most instances. A large excess of hydrogen chloride is generally used, but as little as 2 moles of acid per mole of substrate is sufficient for reduction of unhindered ketones.[40, 41] Slow addition of a small excess of deuterium chloride to the ketone and zinc dust in tetrahydrofuran (see Procedure B, p. 415) is convenient for reduction to gem-dideutero hydrocarbons, typically 75–80 % $d_2$.[40]

[31] L. Cagliotti, Tetrahedron, **22**, 487 (1966); R. O. Hutchins, B. E. Maryanoff, and C. A Milewski, J. Amer. Chem. Soc., **93**, 1793 (1971).

[32] G. E. Risinger and J. A. Thompson, J. Appl. Chem., **13**, 346 (1963).

[33] S. Yamamura, S. Ueda, and Y. Hirata, Chem. Commun., **1967**, 1049.

[34] S. Yamamura and Y. Hirata, J. Chem. Soc., C, **1968**, 2887.

[35] S. Yamamura, Chem. Commun., **1968**, 1494.

[36] S. Yamamura, H. Irikawa, and Y. Hirata, Tetrahedron Lett., **1967**, 3361.

[37] M. Toda, Y. Hirata, and S. Yamamura, Chem. Commun., **1969**, 919.

[38] M. Toda, Y. Hirata, H. Irikawa, and S. Yamamura, Nippon Kagaku Zashi, **91**, 103 (1970) [C.A., **73**, 22137j (1970)].

[39] M. Toda, M. Hayashi, Y. Hirata, and S. Yamamura, Bull. Chem. Soc. Jap., **45**, 264 (1972).

[40] R. P. Steiner, Ph.D. Thesis, University of Wisconsin, 1972 [Diss. Abstr., **33**, 3563-B (1973)].

[41] I. Felkin, personal communication.

Successful reduction of $\alpha,\beta$-unsaturated ketones may require a large excess of acid. At low acid concentration it appears that partially reduced organozinc intermediates survive long enough in solution to undergo intermolecular condensation. Thus, treatment of 4,4-diphenylcyclohex-2-en-1-one according to Procedure A (excess zinc dust in diethyl ether
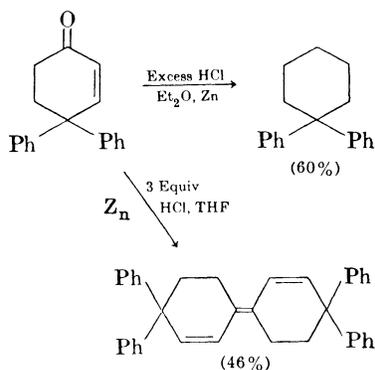


saturated with hydrogen chloride) affords 1,1-diphenylcyclohexane,[24] while Procedure B (3 equivalents of hydrogen chloride in tetrahydrofuran) results in dimeric triene, but no diphenylcyclohexane.[40] Reduction of $\alpha$-tetralone according to Procedure B also leads to dimeric hydrocarbons.[40]

Benzylidenecyclohexanone, however, affords monomeric products using 2 equivalents of hydrogen chloride in ether.[41] The benzylidenecyclohexane
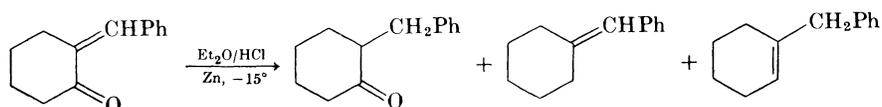


and 1-benzylcyclohexene may be formed via the allylic alcohol 13, because in control experiments the alcohol 13 furnished these two products in a
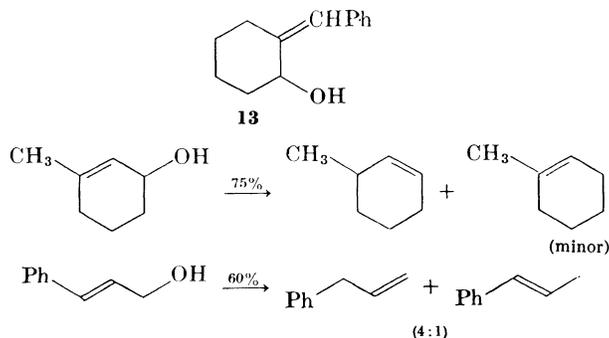
combined yield of 95 %. Other typical allylic alcohols are reduced smoothly under the same conditions, as shown for 3-methylcyclohex-2-enol and cinnamyl alcohol.[41]

From available data there is no reason to believe that reduction with zinc and dry hydrogen chloride differs mechanistically from the original method. The same side reactions are observed, including formation of monomeric and dimeric alkenes, transannular insertion products from cyclooctanone, and alkyl chlorides from certain steroidal ketones. Reduction in ether generally proceeds directly to the hydrocarbon, but alkyl chlorides become significant products when benzene is the solvent.[39] This observation again raises the possibility that alkyl chlorides are precursors of hydrocarbons under Clemmensen reduction conditions.

Yamamura and co-workers initially observed reduction with hydrogen chloride in acetic anhydride (Procedure C).[33, 34, 36] This procedure is less convenient than Procedure A or B, and it yields enol acetates and saturated acetates as side products. Other solvents such as methanol or ethyl acetate are unsatisfactory. As in aqueous Clemmensen reduction, hydrogen chloride (or hydrogen bromide) is necessary for good results. Sulfuric acid, toluenesulfonic acid, and fluoroboric acid have been tried without success.[24, 38, 39]

## EXPERIMENTAL PROCEDURES

**Activated zinc dust.** Commercial zinc dust (16 g, 325 mesh) was activated by stirring for 3–4 minutes with 100 ml of 2 % hydrochloric acid. The zinc was immediately filtered under suction, washed to neutrality with water, and then washed with 50 ml ethanol, 100 ml of acetone, and diethyl ether. The resulting powder was dried at 90° under vacuum (10 minutes) and was used within 10 hours of preparation.

**Cholestane** (*Example of Procedure A. Zinc, Diethyl Ether, Excess Hydrogen Chloride*).[39, 42] Cholestan-3-one (0.5 g, 1.30 mmol) was dissolved in 75 ml of dry ether saturated with hydrogen chloride at 0°. Activated zinc dust (5.0 g, 0.076 g-at) was slowly added to the cooled mixture with vigorous stirring at a rate such that the temperature was maintained below 5°. The reaction was exothermic and considerable hydrogen evolution occurred. The reaction mixture was stirred for 1 hour at 0° and then filtered. The filtrate was shaken with 500 ml of ice water and then washed to neutrality with aqueous sodium carbonate. The aqueous washings were extracted with additional ether, the combined ether extracts were dried over sodium sulfate and evaporated under vacuum. Chromatography of

[42] S. Yamamura, M. Toda, and Y. Hirata, *Org. Syntheses*, **53**, 86 (1973).

the residual oil over silica gel (Mallinckrodt, 100 mesh, 25 g) using benzene as eluant afforded 0.43 g (89%) of cholestane, mp 77.5–79°. A slightly modified procedure on a preparative scale gave a yield of 80%.[44]

**1,1-Diphenylcyclohexane** (*Example of Procedure B. Zinc, Tetrahydrofuran, 3 Equivalents of Hydrogen Chloride*).[40] 4,4-Diphenylcyclohexanone (0.5 g, 2 mmol) was dissolved in dry tetrahydrofuran (10 ml, distilled from lithium aluminum hydride) at 0° and was stirred vigorously with 2 g of commercial zinc dust. A previously titrated solution of dry hydrogen chloride (3 equiv, 6 mmol) in tetrahydrofuran (*ca.* 5 ml) was added dropwise over 20 minutes while the reaction temperature was maintained below 10°. The mixture was then stirred overnight at room temperature, diluted with 75 ml of ether, and worked up according to Procedure A. Chromatography of the crude product over 20 g of silica gel using 2:1 hexane-benzene as eluant afforded 0.345 g (74%) of 1,1-diphenylcyclohexane, mp 40–41°.

**4,4-Dideuterio-1,1-diphenylcyclohexane** (*Preparation of gem-Dideuterated Hydrocarbons Using Procedure B*).[40] Freshly distilled trimethylchlorosilane (1.63 g, 15 mmol) was added by syringe with gentle agitation to deuterium oxide (0.11 g, 6 mmol) in 5 ml of dry tetrahydrofuran in a dropping funnel. After 5 minutes the solution of deuterium chloride was added to 4,4-diphenylcyclohexanone (0.5 g, 2 mmol) as described under Procedure B above. 4,4-Dideuterio-1,1-diphenylcyclohexane (0.33 g, 70%) was isolated as before, mp 39–40.5°. Analysis by nmr and low-voltage mass spectroscopy indicated 81% $d_2$, 10% $d_1$, 6% $d_3$, 3% $d_4$.

**Cholestane** (*Example of Procedure C. Zinc, Acetic Anhydride, Excess Hydrogen Chloride.*)[39] Cholestan-3-one (0.25 g, 0.65 mmol) was dissolved with stirring in 10 ml of acetic anhydride saturated with hydrogen chloride at 0°. Activated zinc powder (2.5 g) was added slowly at a rate such that the temperature did not exceed 5°. After the mixture was stirred at 0° for 6 hours, it was poured with vigorous stirring into a large volume of water and made basic with sodium carbonate. After carbon dioxide evolution ceased, the product was extracted with diethyl ether and purified by the same method as described under Procedure A to yield cholestane (0.21 g, 87%), mp 77.5–79°.

## TABULAR SURVEY

Ketones that have been reduced by zinc and hydrogen chloride in aprotic organic solvents are listed in the tables. All examples which make

reference to the general reduction conditions of Yamamura and collaborators through December 1973 (*Science Citation Index*) are included. For comparison, reduction of androstane-3,17-dione with zinc amalgam in aqueous hydrochloric acid is included, but no effort has been made to survey the numerous other examples of reduction by the original method.

The reaction conditions are specified unless one of the three general procedures described under Experimental Procedures was employed. These are A (zinc dust, diethyl ether, excess hydrogen chloride, 1 hour at 0°), B (zinc dust, tetrahydrofuran, slow addition of 3 equiv of hydrogen chloride at 0°), and C (zinc dust, acetic anhydride, excess hydrogen chloride, x hours at 0°). Commercial zinc dust is used unless specified otherwise.

Many of the Clemmensen reductions using anhydrous hydrogen chloride employ ketones in the steroid series. These examples are surveyed in Tables I and II. Table III deals with α,β-unsaturated ketones and includes a number of examples in which undesirable side reactions play a major role. Table IV includes simple cyclic ketones as well as several complex natural products.