The Clemmensen Reduction of Difunctional Ketones

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The reduction of ketones to the corresponding alkanes using amalgamated zinc and hydrochloric acid has been widely employed in organic synthesis, and as a degradative step in structure elucidation, since Clemmensen first reported the reaction in 1913.[1] It is not generally appreciated, however, that the reduction of difunctional ketones under Clemmensen conditions, while often of synthetic import, rarely yields the expected alkanes in acceptable yield. Indeed, the reduction of 1,3-diketones and $\alpha\beta$-unsaturated ketones provides a useful method for the synthesis of rearranged monoketones whilst the reduction of 1,4-diketones is of considerable interest in that it leads to many unexpected and usually inaccessible compounds.

The Clemmensen reduction was reviewed by Martin[2] in 1942 and a mechanistic survey followed in 1959.[3] Apart from a brief section in the latter no summary has appeared on the reduction of difunctional ketones although considerable work has been done in this field. The present review concerns the reduction of $\alpha\beta$-unsaturated ketones, 1,3-diketones, 1,4-diketones, medium-ring ketones, 1,3-azaketones, and 1,3-thiaketones.

1 Mechanism

The studies of the Clemmensen reduction of monoketones have led to several theories concerning the reaction mechanism.[3-5] Kinetic results obtained by Nakabayashi[6] in 1960 showed that the rate depended upon both chloride ion and zinc concentration but was independent of the electrode potential of the zinc amalgam and of the hydrogen-ion concentration (thus negating earlier postulates).[4, 5] These results led to the formulation of the following scheme:

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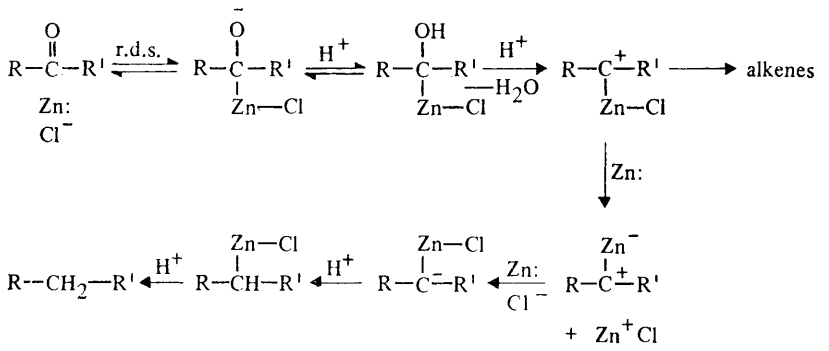
[1] E. Clemmensen, *Chem. Ber.*, (*a*) 1913, **46**, 1837; (*b*) 1914, **47**, 51; (*c*) 1914, **47**, 681.
[2] E. L. Martin, *Org. Reactions*, 1942, **1**, 155.
[3] D. Staschewski, *Angew. Chem.*, 1959, **71**, 726.
[4] W. Steinkopf and A. Wolfram, *Annalen*, 1923, **430**, 113; (*Chem. Abs.*, 1923, **17**, 1223).
[5] J. H. Brewster, *J. Amer. Chem. Soc.*, 1954, **76**, 6361, 6364, 6368.
[6] (*a*) T. Nakabayashi, *J. Amer. Chem. Soc.*, 1960, **82**, 3900, 3906, 3909; for modification of the above see 'The Chemistry of the Carbonyl Group,' ed. S. Patai, Interscience, New York, 1966, p. 518; (*b*) H. O. House, 'Modern Synthetic Reactions,' W. A. Benjamin, New York, 1965, p. 58.

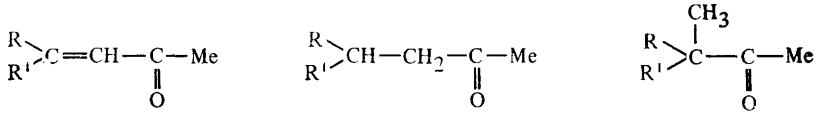


The complex formed by initial rate-determining addition of zinc to the carbonyl carbon is protonated and water is lost to give an organometallic carbonium ion. Attack by two atoms of zinc followed by protonation would give the alkane. Nakabayashi has shown that pinacol formation, frequently encountered in the Clemmensen reduction of monoketones, probably occurs by an electrochemical type (one electron) reduction as distinct from the above (two electron) reduction.

Since no definitive kinetic studies on the reduction of difunctional ketones have been carried out no detailed mechanistic evidence is available. Two sites are available for the initial metal-substrate attack, namely the carbonyl oxygen and the carbonyl carbon atoms. However, the rate of reaction of the difunctional compounds is much faster than that observed from the reduction of monoketones and hence initial zinc–oxygen attack is thought more probable (*cf.* Nakabayashi's mechanism for monoketones which postulates initial zinc–carbon attack). Some of the examples are shown in terms of the former mechanism.

2 $\alpha\beta$-Unsaturated Ketones

A. Acyclic.—Although 1-phenylbutane had previously been isolated from prolonged reduction of 4-phenylbut-3-en-2-one,[7] recent work has shown that brief treatment of acyclic enones affords products of rearrangement and partial (formally double bond) reduction.



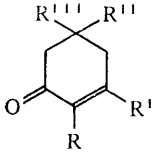
(1) (2) (3)

Thus, 4-methylpent-3-en-2-one (1, R=R′=Me) gave 4-methylpentan-2-one (2, R=R′=Me) and 3,3-dimethylbutan-2-one (3, R=R′=Me), whereas

[7] J. F. J. Dippy and R. H. Lewis, *Rec. Trav. chim.*, 1937, **56**, 1000.

3-phenylbutan-2-one (3, R=H, R′=Ph) and 4-phenylbutan-2-one (2, R=H, R′=Ph) were isolated from 4-phenylbut-3-en-2-one (1, R=H, R′=Ph).[8]

B. Cyclic.—In 1937 Auterinen[9] established that reduction of 5,5-dimethylcyclohexenone gave the saturated analogue 5,5-dimethylcyclohexanone, and a ring-contracted product 2,4,4-trimethylcyclopentanone. Subsequently it has been shown[10] that in general cyclohexenone and its methyl derivatives (4) are reduced under Clemmensen conditions to a mixture of the corresponding cyclohexanone (5) and the related 2-alkylcyclopentanone (6).



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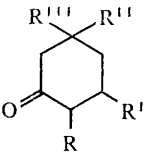

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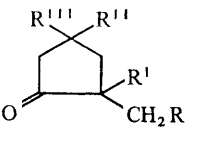

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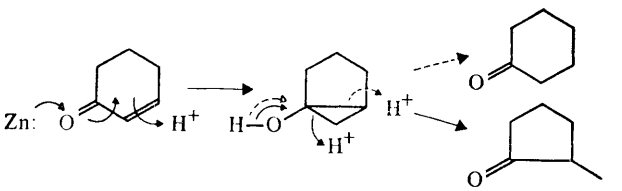
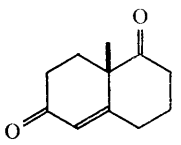
C. Mechanism.—The formation of rearranged and unrearranged monoketones can be accounted for by invoking initial intramolecular reduction and subsequent acid-catalysed cleavage of the resulting cyclopropanol, in the manner shown:



The intervention of the cyclopropanol has been confirmed by the isolation[11a] of the cyclopropylmethyl ether (8) from the bicyclic enone (7). The use of 12% hydrochloric acid in 3 : 1 methanol–water at room temperature for 90 min. gave, as major products, (8), (9), and (10), in that order, and, in addition, (11) and (12); when the reaction is run at elevated temperature (but for a shorter time), or when (8) and (9) are treated with aqueous acid, compounds (13) and (14) result from fission of the cyclopropane.

Further evidence has been derived from the acidolysis of 1,2,2-trimethylcyclo-

[8] B. R. Davis and P. D. Woodgate, *J. Chem. Soc.* (*C*), 1966, 2006.
[9] A. Auterinen, *Suomen Kem.*, 1937, **B10**, 22.
[10] B. R. Davis and P. D. Woodgate, *J. Chem. Soc.*, 1965, 5943.
[11] (*a*) E. Wenkert, J. Zylber, E. Kariv, and K. Kavkova, unpublished work; (*b*) E. Kariv, Ph.D. Dissertation, Weizmann Institute of Science, Rehovoth, 1967; (*c*) J. E. Yoder, Ph.D. Dissertation, Indiana University, 1969. The authors are indebted to Professor Wenkert for communication of these results before publication.



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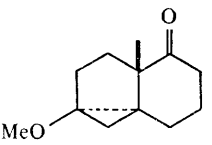

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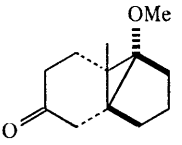

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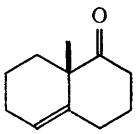

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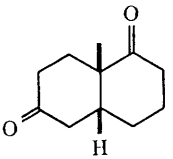

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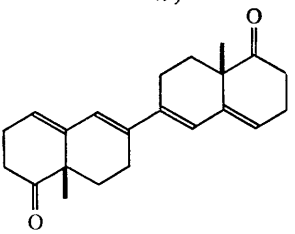

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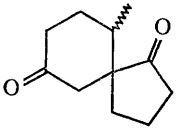

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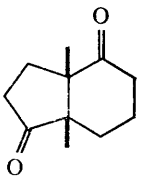


(14)

propanol (the intermediate from mesityl oxide, 1, R=R′=Me),[8] 1-methyl-2-phenylcyclopropanol (the intermediate from benzalacetone, 1, R=H, R′=Ph),[12a] and 6,6-dimethylbicyclo[3,1,0]hexan-1-ol.[8] The monocyclic cyclopropanols gave the same ketones in the same ratios as those from the Clemmensen reduction of the appropriate enone.[8, 12a] However, there is some divergence in the product ratios from 2-isopropylidenecyclopentanone and the derived bicyclic cyclopropanol,[13] possibly because of the difficulty of cyclopropanol formation when both the double bond and the carbonyl group are exocyclic, thus reducing their intramolecular bonding ability.

Acidolysis of a cyclopropanol thus affords both Clemmensen products by cleavage of the bonds α to the hydroxyl-group. The protolysis of cyclopropanols is an S_E2 reaction and occurs with retention of configuration.[12] Although the effect of structure on the relative amounts of C(1)—C(2) and C(1)—C(3) bond fission in unsymmetrical cyclopropanols is still obscure,[12] the type of substitution at both C(1) and C(2) affects the product ratio, and there is some evidence[12d] that

[12] (*a*) C. H. DePuy and F. W. Breitbeil, *J. Amer. Chem. Soc.*, 1963, **85**, 2176; (*b*) P. S. Wharton and T. I. Bair, *J. Org. Chem.*, 1966, **31**, 2480; (*c*) C. H. DePuy, F. W. Breitbeil, and K. R. De Bruin, *J. Amer. Chem. Soc.*, 1966, **88**, 3347; (*d*) C. H. DePuy, *Accounts Chem. Res.*, 1968, **1**, 33.

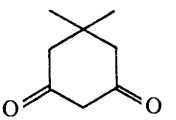
[13] F. R. S. Clark and B. R. Davis, unpublished work.

dialkyl or aralkyl substitution in these positions directs the predominant cleavage towards the least alkylated carbon atom, *i.e.* C(3). Hence, the product ratio cyclopentanone : cyclohexanone should increase in the series 2-methylcyclohexenone < cyclohexenone ≈ 5,5-dimethylcyclohexenone < 3-methylcyclohexenone, reflecting the relative amounts of C(1)—C(3) and C(1)—C(2) cleavage in the intermediate cyclopropanol, and this order ratio has been verified.[10]

Reduction of each of the 3-methylcyclohexenones (4, R=R″=R‴=H, R′=Me, and R=H, R′=R″=R‴=Me) afforded the corresponding 3-methylcyclohexene as a major product (in addition to the monoketones): none of the isomeric alkene was detected.[10] Similarly, 3-methylcyclopentenone gave 3-methylcyclopentene (cyclopentenone itself gave cyclopentene and cyclopentane),[14] while cholest-4-en-3-one afforded 5β-cholest-3-ene (48%),[8] 5α-cholest-3-ene (4%) and 5α-cholestane (1%).[15] The absence of ketonic products indicates that a cyclopropanol is not involved in the steroid system, and the preferred formation of the 5β-alkene can be rationalised by the favoured attack of the zinc on the carbonyl carbon atom (*cf.* Nakabayashi) from the less hindered α-face, subsequent proton addition yielding the 5β-epimer.

3 1,3-Diketones

Before 1935 a number of examples of normal reduction of 1,3-diketones to the corresponding alkanes were reported,[16] although the yields were low and the work-up procedures were specifically designed to prevent the isolation of any oxygen-retaining products. In 1935, however, Dey and Linstead[17] showed that the major product from 5,5-dimethylcyclohexane-1,3-dione (15) was a ring-contracted monoketone, 2,4,4-trimethylcyclopentanone (16), which was later unambiguously characterised by an independent synthesis.[18]



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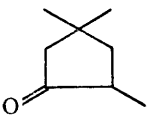

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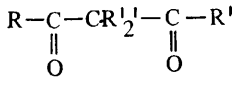
Further work by Auterinen[19] led to the identification of 1,4,4-trimethylcyclopentene and 1,3,3-trimethylcyclopentadiene as minor products.

A similar pattern of rearrangement occurs in the acyclic series. Pentane-2,4-dione (17, R=R′=Me, R″=H) gave 3-methylbutan-2-one (18, R=R′=Me,

[14] G. F. Burkinshaw, Ph.D. Thesis, University of Auckland, 1968.
[15] V. Kumar and G. D. Meakins, unpublished results.
[16] L. Ruzicka, D. R. Koolhaas, and A. H. Wind, *Helv. Chim. Acta*, 1931, **14**, 1151; J. C. Bardhan and S. C. Sengupta, *J. Chem. Soc.*, 1932, 2520; C-K. Chuang, C-M. Ma, and Y-L. Tien, *Chem. Ber.*, 1935, **68**, 1946.
[17] A. N. Dey and R. P. Linstead, *J. Chem. Soc.*, 1935, 1063.
[18] M. Qudrat-i-Khuda and A. Mukherji, *J Indian Chem. Soc.*, 1946, **23**, 465.
[19] A. Auterinen, *Suomen Kem.*, 1954, **B27**, 29.

R″=H)[20] and 3-hydroxy-3-methylbutan-2-one,[21] while 3,3-dimethylpentane-2,4-dione (17, R=R′=R″=Me) afforded 3,4-dimethylpentan-2-one (18, R=R′=R″=Me)[20] and 3,4-dimethyl-3-hydroxy-pentan-2-one.[22] No unrearranged monoketone was detected in the latter case, since dialkyl substitution at C(3) prevents dehydration of the intermediate β-ketol (see later), and an



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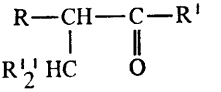

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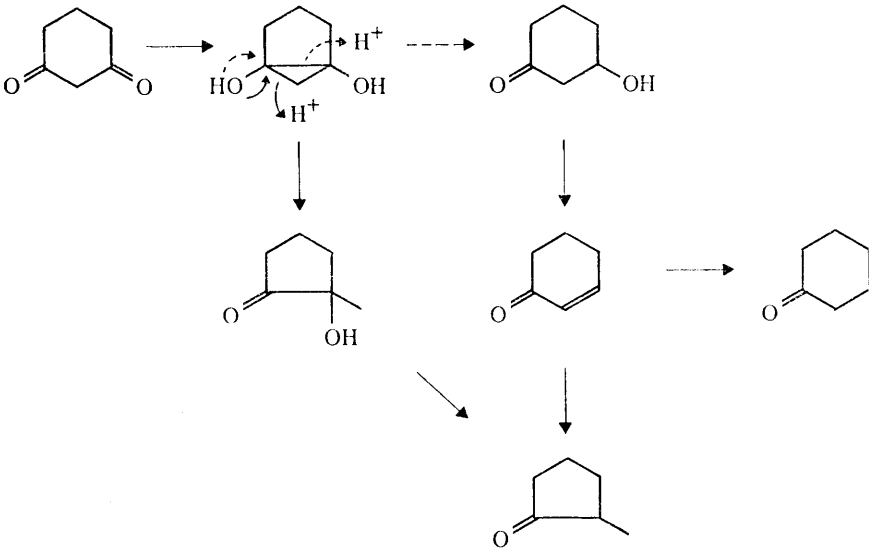
alternative carbonium ion formation at C(4) followed by methyl migration from C(3) would yield the same rearranged monoketone as before. 1-Phenylbutane-1,3-dione (17, R=Ph, R′=Me, R″=H) gave 3-phenylbutan-2-one (18, R=Ph, R′=Me, R″=H),[20] 3-hydroxy-3-phenylbutan-2-one (up to 35% of the total product),[23] together with 4-phenylbutan-2-one, 1-phenylbutan-1-one, 1-phenyl-2-methylpropan-1-one, 1-phenyl-2-methylpropane, and 2-phenylbutane.

Cyclohexane-1,3-dione reacted similarly to dimedone (15) and gave 2-methylcyclopentanone, cyclohexanone, 1-methylcyclopentene, and cyclohexene.[24] In this case the rate was such that there was little difference in product distribution from reactions of more than 10 min. duration. The presence of methyl blocking groups at C(2) in 2,2,5,5 tetramethylcyclohexane-1,3-dione permitted the isolation[11b] of an unrearranged β-ketol intermediate, 2,2,5,5-tetramethyl-3-hydroxycyclohexanone, together with 4,4-dimethyl-2-isopropylcyclopentanone and 4,4-dimethyl-2-isopropyl-2-hydroxycyclopentanone.

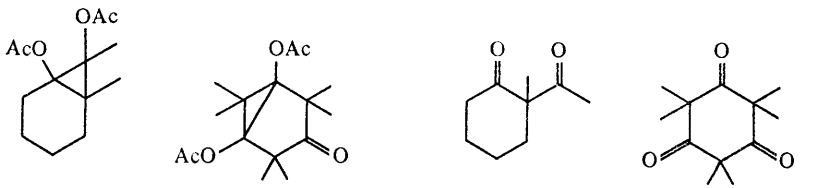
There is thus a general pattern of product distribution encompassing both rearranged and unrearranged monoketones, rearranged α-hydroxyketones, and unrearranged β-hydroxyketones. In all cases where α-ketols have been isolated, increasing the reaction time led to an increase in the yield of rearranged monoketone at the expense of the α-ketol. The formation of this range of products can be rationalised *via* internal reduction of the 1,3-diketone to a cyclopropanediol,[3] and its subsequent acidolysis, in an analogous manner to that outlined previously for the cyclopropanol intermediate in the αβ-unsaturated ketones. That is, cleavage of the cyclopropanediol can give either the rearranged α-ketol[22] or the unrearranged β-ketol. The rearranged monoketone may then arise either from further reduction of the α-ketol[25] or from dehydration of the β-ketol to the conjugated enone, and its subsequent rearrangement (see

[20] N. J. Cusack and B. R. Davis, *Chem. and Ind.*, 1964, 1426; *J. Org. Chem.*, 1965, **30**, 2062.
[21] J. G. St. C. Buchanan, (*a*) M.Sc. Thesis, University of Auckland, 1965; (*b*) Ph.D. Thesis, University of Auckland, 1967.
[22] E. Wenkert and E. Kariv, *Chem. Comm.*, 1965, 570.
[23] K. M. Baker and B. R. Davis, *Chem. and Ind.*, 1966, 768.
[24] K. M. Baker, Ph.D. Thesis, University of Auckland, 1968.
[25] W. T. Smith jun., *J. Amer. Chem. Soc.*, 1951, **73**, 1883.



section 2). In fact both routes may operate, as determined from a study[24] of the rate of formation of the rearranged monketone, compared with the rate of independent reduction of the pure α-ketol.

A recent report[26] by Curphey and his co-workers describes the isolation in high yield of the cyclopropanediol diacetates (19) and (20) from reduction of the 1,3-diketones (21) and (22) respectively, by use of zinc powder in acetic



(19) (20) (21) (22)

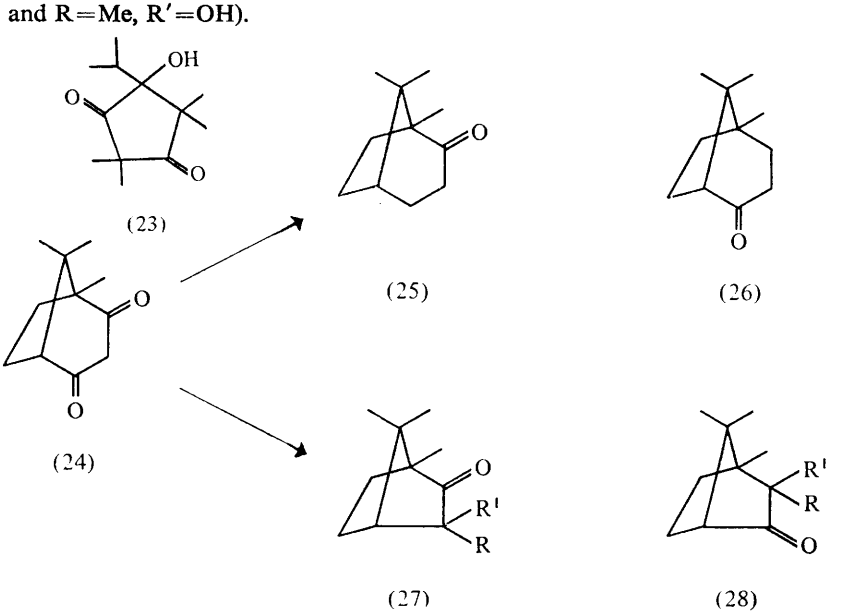
anhydride saturated with HCl gas. This reduction and the related abnormal reduction of αβ-unsaturated ketones are being investigated as general routes to cyclopropanediol and cyclopropanol derivatives. Treatment of the diacetate (20) with acid afforded the α-ketol (23), identical to the material obtained on brief Clemmensen treatment of the cyclohexanetrione (22) (*cf.* ref 27).

2-Acetylcyclopentanone and 2-acetylcyclohexanone yield products characteristic of the formation and scission of a cyclopropanediol in accord with the

[26] T. J. Curphey, C. W. Amelotti, T. P. Layloff, R. L. McCartney, and J. H. Williams, *J. Amer. Chem. Soc.*, 1969, **91**, 2817.

above scheme.[24] In particular, the isolation of 2-ethylcyclopentanone and 2-ethylcyclohexanone, respectively, is strong inferential evidence for the involvement of the β-ketol, since the alternative pathway *via* the α-ketol would not give this product. The α-ketol intermediate, 1-acetylcyclohexanol, was isolated from the cyclohexanone, and the homologue 2-acetyl-2-methylcyclohexanone similarly afforded some 1-acetyl-2-methylcyclohexanol (one diastereoisomer only).[22] The formation of only one diastereoisomer in the latter case is consonant with the retention of configuration observed on acidolysis of cyclopropanols (see above). In this case also, the possible products from the β-ketol were not detected, probably because the more highly substituted bond in the cyclopropanediol cleaves preferentially. Acidolysis of the cyclopropanediol intermediate (19) synthesised independently (as the diacetate) gave[26] 1-acetyl-2-methylcyclohexanol.

Some evidence for the intervention of two stereoisomeric cyclopropanediols as intermediates was provided by the reduction of the stereochemically rigid system homocamphorquinone (24), which gave [23] the two possible unrearranged monoketones (25) and (26), the rearranged monoketones (27, R=Me, R′=H and R=H, R′=Me; and 28, R=Me, R′=H and R=H, R′=Me), and the α-ketols (27, R=OH, R′=Me and R=Me, R′=OH; and 28, R=OH, R′=Me and R=Me, R′=OH).



Cyclopentane-1,3-diones present an unusual case since they undergo neither the characteristic reactions outlined above nor the normal reduction of one or both carbonyl functions. 2,2,4,4-Tetramethyl-5-isopropylcyclopentane-1,3-dione was recovered unchanged[27] from all attempted reductions, as was the parent

[27] M. L. Kaplan, *J. Org. Chem.*, 1967, **32**, 2346.

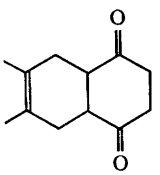
cyclopentane-1,3-dione.[14] Similarly. a cyclopentane-1,3-dione lactone derivative underwent hydrolysis of the lactone moiety, the ketone groups remaining unaffected.[28] This lack of reactivity may be due to the strain involved in the formation of an intermediate bicyclo[2,1,0]pentane-1,4-diol.

4 1,4-Diketones

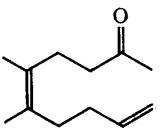
In his original work Clemmensen[1c] observed that the treatment of cyclohexane-1,4-dione with amalgamated zinc and hydrochloric acid led to the formation of volatile products, and after having washed the total product with concentrated sulphuric acid and nitric acid reported the isolation of cyclohexane in unspecified yield. A re-examination of this reaction[11c, 21, 29] showed that products of reduction, carbon–carbon cleavage, and rearrangement were formed, cyclohexane being present in only trace amount. The Clemmensen reduction of a large number of 1,4-diketones has shown that product variety and distribution depends on both the conformation and electronic environment of the carbonyl groups:

(*i*) an aromatic ring adjacent to the carbonyl group promotes normal reduction to a methylene group *e.g.* 1-phenylpentane-1,4-dione gives 5-phenylpentan-2-one in high yield, further reduction yielding 1-phenylpentane;[29]

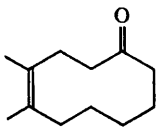
(*ii*) *syn-* or *anti*-periplanar alignment of the carbonyl groups with the C(2)—C(3) bond favours cleavage, *e.g.* cyclohexane-1,4-dione gives hexane-2,5-dione and hex-5-en-2-one whilst the products from 6,7-dimethyloctalin-1,4-dione (29) include 5,6-dimethyldeca-*cis*-5,9-dien-2-one (30) and 4,5-dimethylcyclodec-*cis*-4-en-1-one (31);[29]



(29)



(30)

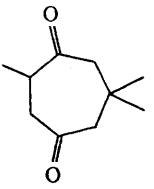


(31)

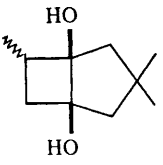
(*iii*) when interaction of the carbonyl groups is possible cyclobutanediols are formed in a reaction analogous to the production of cyclopropanediols from 1,3-diketones, *e.g.* 2,6,6-trimethylcycloheptane-1,4-dione (32) gives 3,3,6α(and β)-trimethylbicyclo[3,2,0]heptane-1β,5β-diol (33)[11c]; more mobile systems allow the formation of monoalcohols and furans (see Scheme 1);

(*iv*) non-alignment of the carbonyl groups leads to normal reduction, *e.g.* cholestan-3,6-dione yields cholestan-6-one.[29]

[28] S. Eskola, E. Keihanen, and E. Niemi, *Suomen Kem.*, 1958, **B31**, 68; (*Chem. Abs.*, 1958, **52**, 18249*c*).
[29] J. G. St. C. Buchanan and B. R. Davis, *J. Chem. Soc.* (*C*), 1967, 1340.

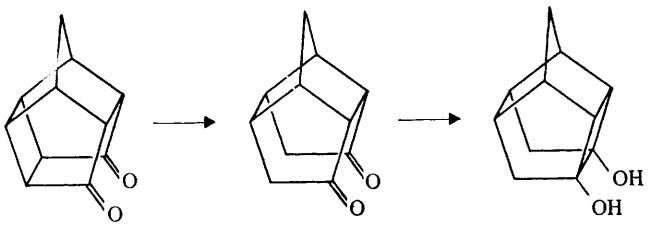


(32)



(33)

Conditions (*ii*) and (*iii*) are exemplified by the reduction of the pentacyclic diketone (34). The *syn*-periplanar conformation allows the formation of the tetracyclic diketone (35). The resulting alteration of alignment of the carbonyl groups necessary for cleavage to occur, allows another mode of reaction to predominate, namely reductive cyclisation yielding a glycol (36). In contrast to the cyclopropane-1,2-diols, the cyclobutane-1,2-diols (33) and (36) have been isolated from the reaction mixtures.[11c] Carbon–carbon bond cleavage[30] of the



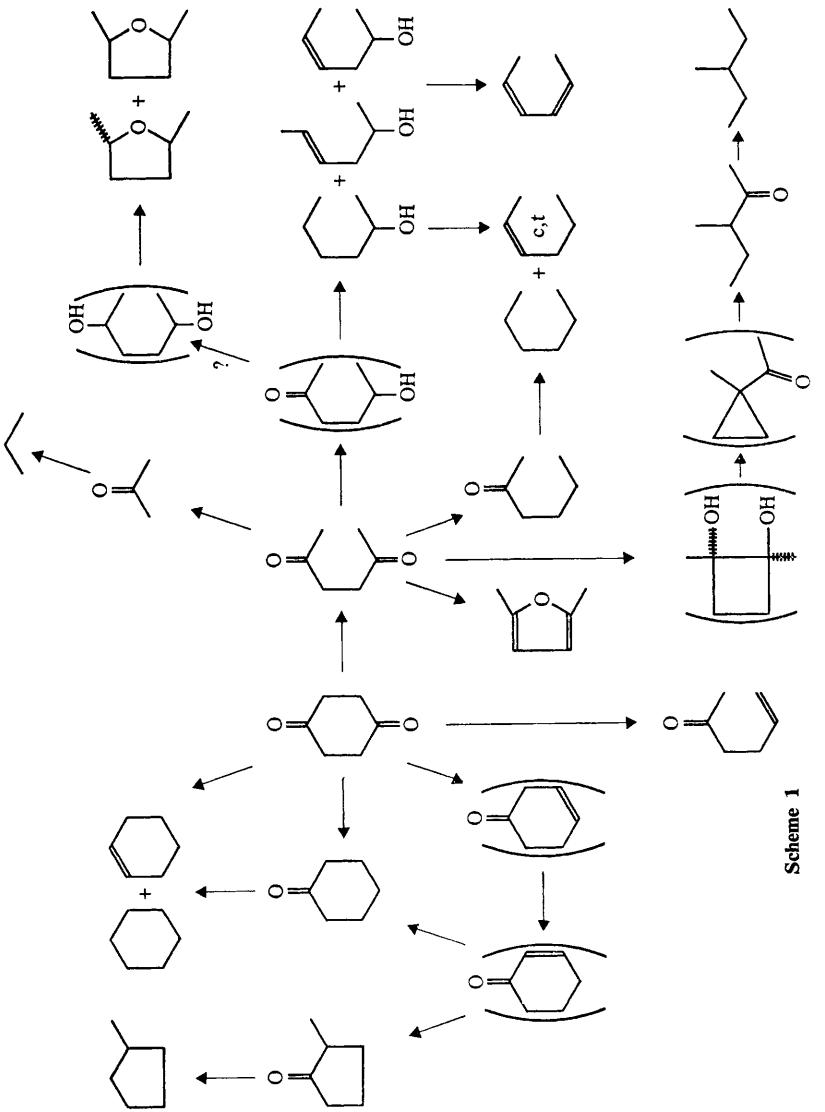
(34) (35) (36)

1,4-diketones is unique in that the carbonyl moieties may remain unaltered. When further reduction occurs these reactions are characterised by their wide product diversity. The reduction of cyclohexane-1,4-dione demonstrates the various types of products possible and is therefore discussed more fully. Twenty-six products were detected from the reduction of this diketone and twenty-two of these were identified (see Scheme 1).

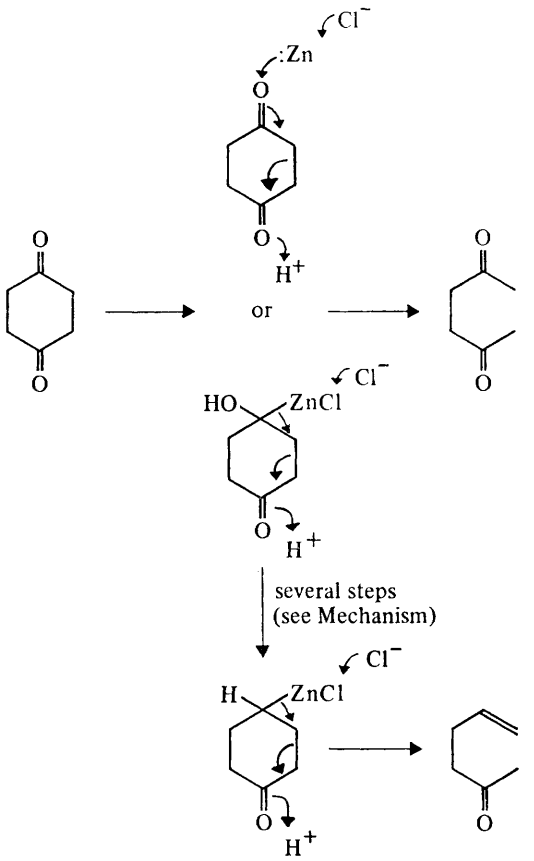
The products shown in brackets were not isolated but were synthesised and reduced independently to verify their intermediacy. More than 90% of the total product is derived from the secondary reactions of hexane-2,5-dione showing that this is the major primary product (verified by independent reduction).[21, 29] Cleavage of the conformationally-free acyclic product competes unfavourably with other reactions (normal reduction, diol and furan formation,[31] and the

[30] For a review of carbon–carbon cleavage reactions see C. A. Grob and P. W. Schiess, *Angew. Chem. Internat. Edn.*, 1967, **6**, 1.

[31] For other examples see D. J. Cram, C. S. Montgomery, and G. R. Knox, *J. Amer. Chem. Soc.*, 1966, **88**, 515; G. F. Whitfield, *J. Chem. Soc.* (*C*), 1968, 1781.



Scheme 1



Scheme 2

anomalous alcohol formation[32] which predominates). Another cleavage reaction leads to the formation of hex-5-en-2-one (Scheme 2). This compound has one of the original carbonyl groups reduced to an alkene and may be explained by the Nakabayashi mechanism although hexane-2,5-dione could result from either initial zinc–oxygen or zinc–carbon bond formation.

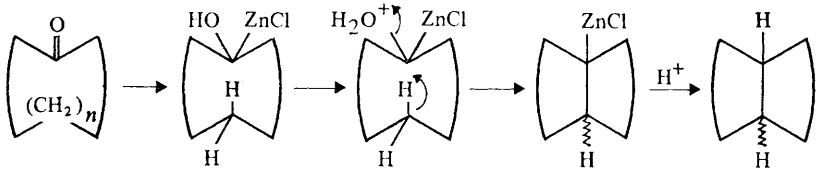
The cleavage producing a $\gamma\delta$-unsaturated ketone accounts for only a small percentage of the product in the above example, although reduction of

[32] For another example see T. Tanaka and T. Terai, Jap. P. 5263/59; (*Chem. Abs.*, 1960, **54**, 14129*g*). 9-Methyl-4,7-dioxodecanoic acid is reduced to the lactone of 4-hydroxy-9-methyldecanoic acid in high yield. The alcohols may be formed by acidolysis of an intermediate *cis*-cyclobutane-1,2-diol to give a γ-ketol (*cf.* the formation of β-ketols from cyclopropanediol). Clemmensen reduction of γ-ketols has been shown to give both saturated and unsaturated alcohols, the alchol moiety remaining intact (see ref. 18).

cyclohexane-1,4-dione with zinc metal and hydrochloric acid gives a high yield of hex-5-en-2-one. The formation of 2-methylpentanone (Scheme 1) probably arises from the reduction of cyclohexenone (see section 2) which would be formed from cyclohex-3-en-1-one, a product of partial reduction. Cyclohexanone may be formed from cyclohexenone or by direct reduction of the substrate.

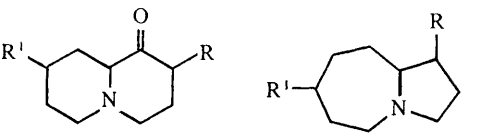
5 Medium-Ring Ketones (C_7—C_{12})

The reduction of these compounds is characterised by transannular bond formation, a methylene group acting as the other functional moiety, *e.g.* cyclodecanone is reduced to give cyclodecane and *cis*- and *trans*-decalin.[33] These reactions are envisaged as proceeding in the following manner:



6 1,3-Azaketones

The first evidence that anomalous reduction could occur in this series was obtained during degradative studies on the lupin alkaloids.[34] The product from the perhydroquinolizinone (37, R=R′=H) was shown by independent synthesis[35] to be 1-azabicyclo[5,3,0]decane (38, R=R′=H), and a number of derivatives of (37) gave analogous cleavage–condensation products.[36] Leonard and Wildman[37]



(37) (38)

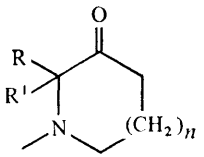
demonstrated that the ring undergoing contraction was the carbonyl-containing one so that (37, R=Me, R′=H) gave (38, R=Me, R′=H) and (37, R=H, R′=Me) gave (38, R=H, R′=Me).

In the monocyclic series *N*-methyl-2-ethylpiperidone (39, R=Et, R′=H, n=1) affords *N*-methyl-2-n-propylpyrollidine (40, R=Pr^n, R′=H, n=1),[38] and *N*-methyl-2-ethyl-1-azacycloheptan-3-one (39, R=Et, R′=H, n=2) gives

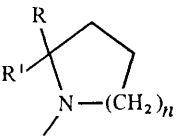
[33] E. Mueller, G. Fiedler, H. Huber, B. Narr, H. Suhr, and K. Witte, *Z. Naturforsch*, 1963, **18b**, 5; (*Chem. Abs.*, 1963, **58**, 11234).
[34] G. R. Clemo and G. R. Ramage, *J. Chem. Soc.*, 1931, 437.
[35] V. Prelog and R. Seiwerth, *Chem. Ber.*, 1939, **72**, 1638.
[36] G. R. Clemo and T. P. Metcalfe, *J. Chem. Soc.*, 1937, 1518; G. R. Clemo, J. G. Cook and R. Raper, *ibid.*, 1938, 1183, 1318.
[37] N. J. Leonard and W. C. Wildman, *J. Amer. Chem. Soc.*, 1949, **71**, 3089.
[38] N. J. Leonard and W. V. Ruyle, *J. Amer. Chem. Soc.*, 1949, **71**, 3094.

N-methyl-2-n-propylpiperidine (40, R=Pr^n, R′=H, n=2).[39] The degree of alkyl substitution in the α-position does not interfere with this rearrangement,[40] nor is it necessary for the nitrogen and carbonyl functions to be homoannular, since both 2-acetyl-*N*-methylpyrollidine (40, R=MeCO, R′=H, n=1)[41] and *N*-methyl-2-propionylpyrollidine (40, R=EtCO, R′=H, n=1)[42] suffered rearrangement, in this case by ring expansion, to *N*-methyl-2-methylpiperidine (40, R=Me, R′=H, n=2) and 2-ethyl-*N*-methylpiperidine (40, R=Et, R′=H, n=2) respectively. In contrast the product from 2-acetyl-*N*-methylpiperidine (40, R=MeCO, R′=H, n=2) was 7-(*N*-methylamino)heptan-2-one.

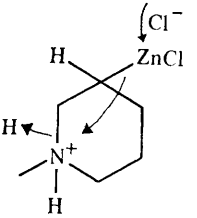
The formation of the observed products can be represented *via* rearrangement of an organozinc adduct:



(39)

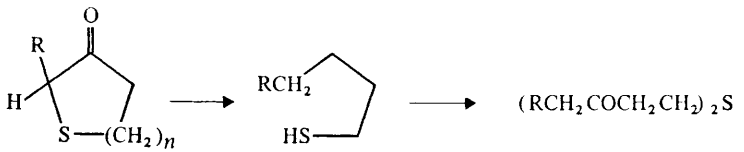


(40)



7 1,3-Thiaketones

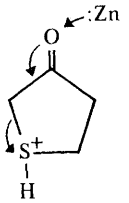
These undergo similar rearrangement reactions to those outlined for α-aminoketones. For the 4,5-dihydro-3(2*H*)-thiophenone derivatives (41, R=Me, n=1 and R=-$(CH_2)_1$OMe, n=1)[43] initial 1,2-cleavage to (42) followed

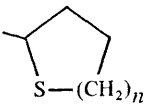


(41) (42) (43)

by dimerisation affords the corresponding sulphides (43). Again the intervention of an organozinc adduct (this time retaining the oxygen atom) can be invoked:

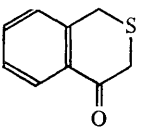
[39] N. J. Leonard and E. Barthel jun., *J. Amer. Chem. Soc.*, 1949, **71**, 3098.
[40] N. J. Leonard and E. Barthel jun., *J. Amer. Chem. Soc.*, 1950, **72**, 3632.
[41] G. R. Clemo, R. Raper, and H. J. Vipond, *J. Chem. Soc.*, 1949, 2095.
[42] G. R. Clemo and H. J. Vipond, *Chem. and Ind.*, 1949, 856.
[43] H. Schmid and E. Schnetzler, *Helv. Chim. Acta*, 1951, **34**, 894.





(44)

Dihydro-2*H*-thiapyran-3(4*H*)-one (41, R=H, n=2) and 3-thiepanone (41, R=H, n=3) yield the ring-contracted products (44, n=1) and (44, n=2) respectively.[44] Internal participation of the sulphur atom is supported by the analogous rearrangement[45] of the 4-ketoisothiachroman (45) to the thionaphthene (46), since the benzylic carbonyl should otherwise undergo rapid



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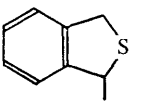

(46)

normal reduction to the expected benzothiacyclohexane. The corresponding 4-hydroxy- and 4-chloro-isothiachromans did not rearrange under the same conditions, showing that they were not intermediates.

The authors thank Professor B. R. Davis, Professor E. Wenkert, Dr. K. M. Baker, and D. R. Crump for helpful discussions.

[44] N. J. Leonard and J. Figueras jun., *J. Amer. Chem. Soc.*, 1952, **74**, 917.
[45] J. v. Braun and K. Weissbach, *Chem. Ber.*, 1929, **62**, 2416.