Clemmensen Reduction. Part 8.[1] Fragmentation Reactions of 1,4-Diketones

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Certain 1,4-diketones undergo fragmentation reactions on treatment with amalgamated zinc and hydrochloric acid. Where two pathways of scission are possible, the most highly substituted bond is cleaved preferentially. In particular cases other reactions, such as alcohol formation or rearrangement, compete with the fragmentation process. Further experiments to probe the mechanism are described.

IN a previous paper,[2] we reported that 1,4-diketones underwent a variety of different modes of reduction depending on their structure and stereochemistry, and Wenkert and Yoder[3] subsequently presented further results extending and confirming our own. In two papers [4,5] we focused on the production of alcohols; in this paper we examine the fragmentation reaction and its possible synthetic utility. We have proposed [4] that alcohols are formed only when the molecule has sufficient conformational mobility to allow the carbonyl groups to approach each other closely, while fragmentation reactions have demanding stereochemical requirements, the electrofuge and nucleofuge having to be *anti*-periplanar.[6] Both these features may be satisfied in one molecule and instances which illustrate this potential duality of reaction are examined.

Re-examination of the reduction of hexane-2,5-dione,[2] using cold traps to collect the more volatile components, has shown the presence of the fragmentation products, acetone and propane. Some C_6 hydrocarbons and *cis*- and *trans*-2,5-dimethyltetrahydrofuran were identified, in addition to the products reported previously.

RESULTS AND DISCUSSION

The bicyclic, unsymmetrical 1,4-diketone (1) was synthesised from the reaction of 2,3-dimethylbutadiene with *p*-benzoquinone.[7] Reaction under Clemmensen

conditions gave a large array of products; the compounds obtained in the greatest amount represented fragmentation of the central 1,6-bond; these accounted for over 50% of the starting material while the diacetyl-cyclohexene (4), the product of fragmentation of the peripheral 3,4-bond, accounted for only 5%. The major product (20%) was the dienone (6) identified by its i.r., [1]H n.m.r., and mass spectra, a positive iodoform reaction, and the formation of a monosemicarbazone. The presence of the new double bond in the thermodynamically less stable terminal position indicated that the initial fragmentation was of the 1,6-bond, followed by cleavage of the 3,4-bond. Such reasoning was confirmed when it was shown (see below) that the ketone (6) was not a product of the reduction of the diketone (4). The other products included the monoketone (7) and the corresponding dienone (8) identified by spectral methods. The latter is formed, presumably, from acid-catalysed conjugation of (3). The hydroazulene ketone (5), isolated in 10% yield, arises, presumably, from diketone (2) by acid-catalysed aldol condensation.

Cleavage in the diketone (1) suggested that reduction of the 2:1 adduct (9) might provide a route to a 14-membered ring. However, treatment of the diketone (9) in a two-phase solvent system provided only a small amount of a ketone, assigned structure (10), along with much starting material.

(1)   (2)   (3)   (4)

(5)   (6)   (7)   (8)
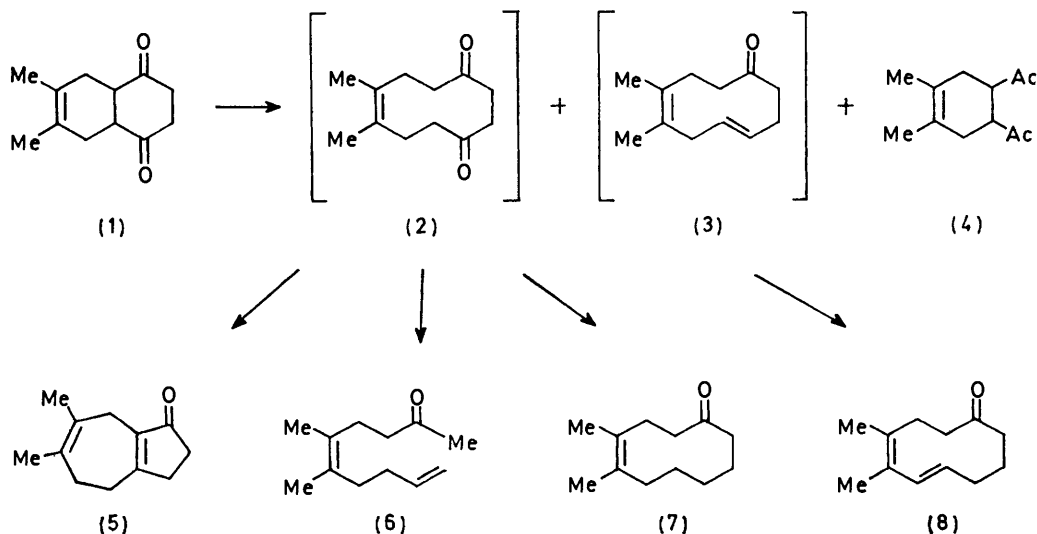
Two reactions, alcohol formation or cleavage, are possible in the Clemmensen reduction of the diketone (4). In the event, the major product was the alcohol (11) along with the oxabicyclo[3.2.1]octane (12), derived from (11) by attack of the oxygen atom on the double bond. Reduction to give (13) accounted for a lesser amount of the products, while only 10% of the product of fragmentation, (14), was obtained.

Lacking the stereochemistry required for fragmentation, bicyclo[2.2.1]heptane-2,5-dione (15) gave only the monoketones (16) and (17), while the corresponding camphor derivative did not react under similar conditions. In other work [8] we have shown that 9-bromocamphor undergoes a fragmentation reaction on treatment with zinc to give two monocyclic carvone derivatives. Replacement of the CH_2Br moiety with an aldehyde group should, likewise, produce a molecule

(9)   (10)

(4) →

(11)   +   (12)

(13)   +   (14)

(15) R = O
(16) R = H$_2$

(17)
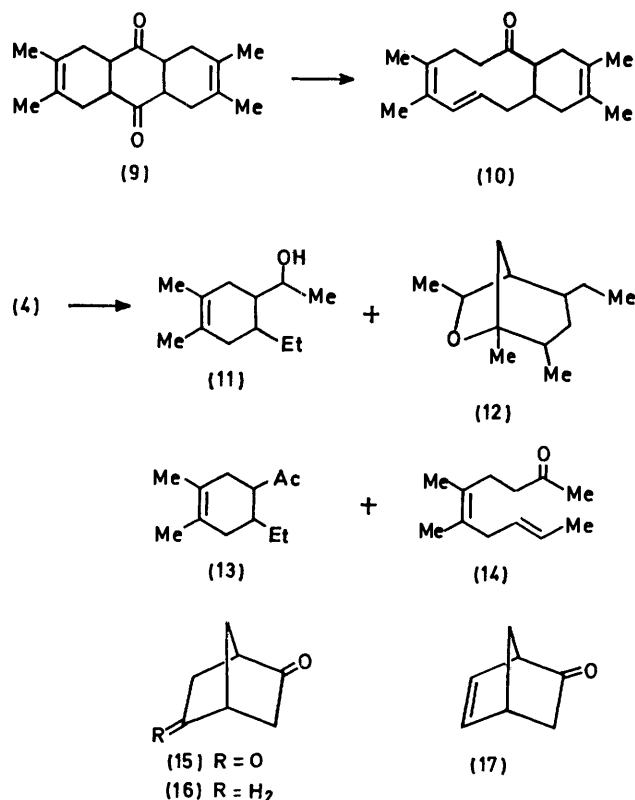
capable of undergoing fragmentation. However, the Clemmensen reduction of the keto-aldehyde (18) gave, instead, two bicyclic β-ketols, both of rearranged carbon skeleton. The ¹H n.m.r. spectrum of (19) showed one tertiary methyl group resonance (δ 1.07), one peak due to a secondary methyl group (δ 1.07, J 7 Hz) and a doublet (J 9 Hz) at δ 3.84 assigned to the carbinol proton. The epimeric ketol (20) showed a tertiary methyl group resonating at δ 1.00, a doublet due to a secondary methyl group at δ 1.18 (J 6 Hz) and a doublet, J 3 Hz, at δ 3.30. The cis arrangement of the hydroxy and methyl groups in (19) was assigned on the basis of

the larger coupling constant between the C-5 and the C-6 protons. The large chemical shift difference (0.54 p.p.m.) between the resonances of the C-6 proton in (19)

(18)   (19)

(20)
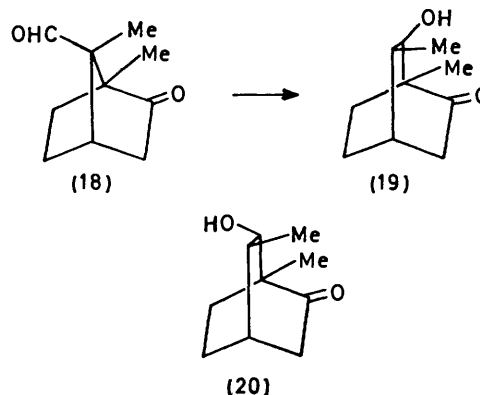
and (20) suggests that it is this proton, and not that at C-5, that is in a different configuration in the two isomers. The mass spectra of the two ketols were almost identical, the principal fragmentation being the elimination of water followed by loss of keten (Scheme 1).

[(19.)]$^{+\cdot}$ or [(20)]$^{+\cdot}$
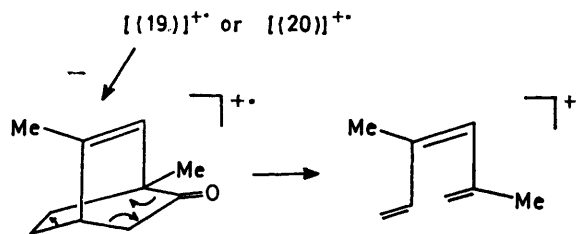
SCHEME 1

These ketols might be formed by migration of C-1 from C-8 to a protonated aldehyde group, with stabilisation of the carbonium ion so formed by the electrons of the C-2,3 enolic double bond.[9] Attack of zinc at C-8, followed by electrophilic substitution by a proton with retention of configuration, would give the observed products. The parent keto-aldehyde was unaffected by acid alone, so it is presumably reduction of the carbonium ion that provides the driving force for the reaction.

It has been proposed[2,3] that the fragmentation reaction of 1,4-diketones proceeds as shown in Scheme 2, although no evidence has been adduced to distinguish between possible heterolytic or homolytic pathways. It should be possible to substitute another electrofuge in place of the second protonated carbonyl group. To this
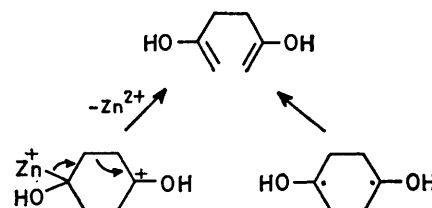
SCHEME 2

end, we prepared 4-benzoyloxy-, 4-chloro-, and 4-(*p*-tolylsulphonyloxy)-cyclohexanone and submitted them to the conditions of the Clemmensen reduction. Reaction of the former gave only cyclohexyl benzoate. While the latter two did produce a small amount (5%) of the fragmentation product hex-5-en-2-one, the main products were cyclohexane and cyclohexene, respectively along with cyclohexanone and 2-methylcyclopentanone. The two ketones were formed presumably by reduction of cyclohexenone which arose by elimination from, and isomerisation of, the starting material.

EXPERIMENTAL

M.p.s were determined with a Reichert–Kofler hot-stage apparatus. I.r. spectra were measured with a Perkin-Elmer 237 spectrometer for solutions in carbon tetrachloride or chloroform. U.v. spectra were measured on a Unicam SP 800 spectrophotometer. ^{1}H N.m.r. spectra were measured with a Varian A 60 spectrometer (solvent CCl_4 or $CDCl_3$). Mass spectra were measured by Professor R. Hodges, Massey University, Palmerston North, on an A.E.I. MS-902 spectrometer. Microanalyses were performed by Professor A. D. Campbell, University of Otago, New Zealand. Amalgamated zinc was prepared as follows: zinc wool (10 g), mercuric chloride (1 g), water (30 ml), and concentrated hydrochloric acid (2.5 ml) were shaken together, the liquid was decanted, and the metal was washed several times with water.

Reduction of Hexane-2,5-dione.—Repetition of the reduction of this diketone,[2] with collection of volatile components in traps cooled to -70 °C, gave the following products, in addition to those previously reported (analysis and identification by g.l.c.): propane; acetone [$\nu_{max.}$ 1 721 cm^{-1}, δ_H 2.07]; 3-methylpentane; hexane; hex-2-ene [$\nu_{max.}$ 1 670 (C=C), 965 (*trans* C=C), and 720 cm^{-1} (*cis* C=C); δ_H 1.71 (3 H, d, J 5.5 Hz, 1-H$_3$)]; hexa-2,4-diene; *trans*- and *cis*-2,5-dimethyltetrahydrofuran [δ_H 1.12 and 1.17 (d, J 6 Hz) respectively].

Reduction of 8,9-Dimethylbicyclo[4.4.0]dec-8-ene-2,5-dione (1).—The bicyclic diketone [7] (1) (6 g), amalgamated zinc wool (12 g), ethanol (120 ml), water (18 ml), and concentrated hydrochloric acid (21 ml) were heated under reflux for 30 min. The mixture was poured into water and yielded, to ether, an oil (5.3 g) shown by g.l.c. to contain over 30 compounds. Chromatography on alumina and preparative g.l.c. gave six compounds: (*i*) 2,3-dimethylbicyclo[4.4.0]dec-2-ene (1%), identified by g.l.c. More than 12 other hydrocarbons were observed in low yield. (*ii*) 5,6-Dimethyldeca-*cis*-5,9-dien-2-one (6) (20%), positive iodoform reaction; $\nu_{max.}$ 3 080, 3 000 (CH=CH$_2$), 1 725 (C=O), and 997 and 916 cm^{-1} (CH=CH$_2$); δ_H 1.59 (6 H, s, C-5, 6 Me), 2.04 (3 H, s, 1-H$_3$), 4.98 (2 H, m, ABX pattern, J 13, 8, and 2 Hz, 10-H$_2$), and 5.80 (1 H, m, 9-H); m/e 180 (M^+), 165 ($M^+ -$ Me), 139 ($M - C_3H_5$), and 122 ($M - C_3H_6O$). The *semicarbazone*, plates (EtOH) had m.p. 120—122 °C; M^+ 237.184 1 ($C_{13}H_{23}N_3O$ requires M, 237.184 1). (*iii*) 4,5-Dimethylcyclodec-*cis*-4-en-1-one (7) (12%); n_D^{20} 1.502 7; $\nu_{max.}$ 1 712 cm^{-1} (C=O); δ_H 1.51 (3 H, s, 4-Me) and 1.64 (3 H, s, 5-Me); m/e 180 (M^+), metastable peaks indicated the following fragmentation sequence: 180→165→137, 180→151→123, 180→137→109, 180→123→95, 180→162, and 180→121. (*iv*) 4,5-Dimethylcyclodeca-4,6-dien-1-one (8) (9%); $\nu_{max.}$ 1 705 (C=O), 967

(*trans* C=C), 907, and 694 cm^{-1} (*cis* C=C); δ_H 1.67 (6 H, s, C-4, 5 Me), 1.8—2.8 (10 H, m), and 5.57 (2 H, m, C-6, 7 H$_2$); $\lambda_{max.}$ 220 nm; M^+, 178. (*v*) 3,4-Dimethylbicyclo[5.3.0]-deca-1(7),3-dien-10-one (5) (10%), m.p. 60—62 °C; $\nu_{max.}$ 1 702 (C=O); δ_H 1.73 (6 H, s, C-4, 5 Me) and 2.3—2.9 (10 H, m); $\lambda_{max.}$ 243 nm; M^+, 176 (base peak). (*vi*) *trans*-4,5-Diacetyl-1,2-dimethylcyclohex-1-ene (4) (5%); $\nu_{max.}$ 1 715 cm^{-1} (C=O); δ_H 1.63 (6 H, s, C-4, 5 Me), 2.14 (6 H, s, COMe), 1.8—2.5 (4 H, m, 3,6-H$_2$), and 2.86 (2 H, m, C-4, 5 H); m/e 194 (M^+), 151, 109, and 107. (*vii*) Starting material (6%). Variation of acid concentration (2—12 mol l^{-1}) and reflux time (3 min—1 h) changed the extent of reduction but gave no new products, as shown by t.l.c., g.l.c., i.r., and ^{1}H n.m.r.

Clemmensen Reduction of 2,3,6,7-Tetramethyl-1,4,5,8,9,10,-11,12-octahydroanthraquinone (9).—The octahydroanthraquinone [10] (9) (5 g) in toluene (150 ml) was heated under reflux for 12 h with a mixture of amalgamated zinc wool (30 g), water (10 ml), and concentrated hydrochloric acid (10 ml). Additional acid (10 ml) was added after 6 h. Chromatography of the product on alumina gave much starting material with an orange oil (0.91 g) which on preparative t.l.c. gave 5,6,12,13-tetramethylbicyclo[8.4.0]-tetradeca-*cis*-5,7,12-trien-2-one (10) (0.20 g), needles, m.p. 76—80 °C; $\nu_{max.}$ 1 705 (C=O), 980, 965, 950, and 920 (*trans* C=C), and 855 and 690 cm^{-1} (*cis* C=C); δ_H 4.8—5.8 (2 H, m, 7,8-H); $\lambda_{max.}$ 210 nm; M^+, 258.

4,5-Diacetyl-1,2-dimethylcyclohex-1-ene.—The diketone (4) (m.p. 35—37 °C, lit.,[11] 36—37 °C) was prepared from hex-3-ene-2,5-dione and dimethylbutadiene by heating them under reflux in benzene for 9 h, and standing at 20 °C for 15 h.

Clemmensen Reduction of 4,5-Diacetyl-1,2-dimethylcyclohex-1-ene.—The diketone (4) (6 g), amalgamated zinc (12 g), ethanol (120 ml), and hydrochloric acid (5.5 mol l^{-1}, 39 ml) were heated under reflux for 1 h. Ether extraction yielded an oil (5 g) which was separated by alumina chromatography and preparative g.l.c. to give: (*i*) 4-ethyl-1,2,6-tri-methyl-7-oxabicyclo[3.2.1]octane (12) (15%) (Found: M^+, 182.167 3. $C_{12}H_{22}O$ requires M, 182.167 1); $\nu_{max.}$ 1 130, 1 115, and 1 070 cm^{-1} (cyclic ether); δ_H 1.07 (3 H, s, 1-Me), 1.17 (3 H, d, J 6 Hz, 6-Me), and 4.10 (1 H, dd, J 7, 3 Hz, 6-H): (*ii*) 5,6-dimethyldeca-5,8-dien-2-one; (14) (10%) (Found: M^+, 180.151 3. $C_{12}H_{20}O$ requires M, 180.151 4); $\nu_{max.}$ 1 725 (C=O) and 965 cm^{-1} (*trans*-disubstituted C=C); δ_H 1.60 (9 H, br s, C-5, 6 Me, 10-H$_3$), 2.03 (3 H, s, 1-H$_3$) and 5.32 (2 H, m, 8,9-H); (*iii*) 4-acetyl-1,2-dimethyl-5-ethyl-cyclohexane (13) (16%) (Found: M^+, 180.151 2. $C_{12}H_{20}O$ requires M, 180.151 4); m/e 180, 180→137, 137→95, 137→81; 180→162; 180→151, 151→109; $\nu_{max.}$ 1 715 (C=O); δ_H 1.58 (6 H, s, C-1, 2 Me) and 2.05 (3 H, s, COMe); (*iv*) 1,2-dimethyl-5-ethyl-4-(1-hydroxyethyl)cyclohexene (11) (53%) (Found: M^+, 182.167 0. $C_{12}H_{22}O$ requires M, 182.167 1); 182, 182→164, 164→135, 135→107; 164→121; 182→153; 182→109; $\nu_{max.}$ 3 580, 3 400 (OH), and 1 100 cm^{-1} (OH); δ_H 1.30 (3 H, d, J 6 Hz, ethyl Me), 1.60 (6 H, s, C-1, 2 Me), and 3.93 [1 H, m, CH$_3$C*H*(OH)]; and (*v*) starting material (2%).

Clemmensen Reduction of Bicyclo[2.2.1]heptane-2,5-dione.—The diketone (15) [12] (2.7 g), amalgamated zinc (25 g), ethanol (20 ml), and hydrochloric acid (5 mol l^{-1}, 40 ml) were heated under reflux for 1.5 h. Ether extraction gave a liquid, separated by preparative g.l.c. into: (*i*) bicyclo-[2.2.1]hept-5-en-2-one (17) (23%), i.r. and ^{1}H n.m.r. spectra identical with those of an authentic sample; and (*ii*) bi-

cyclo[2.2.1]heptan-2-one (16) (59%), i.r. and ^{1}H n.m.r. spectra identical with those of an authentic sample.

Attempted Reduction of 1,7,7-Trimethylbicyclo[2.2.1]heptane-2,5-dione.—The diketone [13] (0.5 g) and amalgamated zinc (5 g) in hydrochloric acid (10 mol l^{-1}, 15 ml) and ethanol (15 ml) were heated under reflux for 3 h. Starting material was recovered.

Reduction of 1,syn-7-Dimethyl-anti-7-formylbicyclo[2.2.1]-heptan-2-one (18).—The keto-aldehyde (18) (2 g) and amalgamated zinc (20 g) in hydrochloric acid (5 mol l^{-1}, 40 ml) and ethanol (20 ml) were heated under reflux for 15 min. Extraction with ether gave an oil, shown (g.l.c.) to consist of two compounds separated by chromatography on alumina. They were: (*i*) 6-*syn*-hydroxy-1,5-*syn*-dimethylbicyclo[2.2.2]octan-2-one (19) (40%), m.p. 94—96 °C (from ether–light petroleum); m/e 168 (M^+) ($C_{10}H_{16}O_2$), 168→150, 150→108; $\nu_{max.}$ 3 610, 3 450 (OH), 1 715 (C=O), and 1 040 cm^{-1} (OH); δ_H 1.07 (3 H, s, 1-Me), 1.07 (3 H, d, J 7 Hz, 5-Me), and 3.84 (1 H, d, J 9 Hz, 6-H): and (*ii*) 6-*anti*-hydroxy-1,5-*syn*-dimethylbicyclo[2.2.2]octan-2-one (20) (60%), m.p. 58—60 °C (from ether–light petroleum) (Found: M^+, 168.114 9. $C_{10}H_{16}O_2$ requires M, 168.115 0); m/e 168, 168→150, and 150→108; $\nu_{max.}$ 3 600 and 3 450 (OH), 1 715 (C=O), and 1 090 cm^{-1} (OH); δ_H 1.00 (3 H, s, C-1-Me), 1.18 (3 H, d, J 6 Hz, 5-Me), and 3.30 (1 H, d, J 3 Hz, 6-H). The corresponding acetate, m.p. 105—107 °C (from ether–light petroleum) had M^+ 210.125 8; $C_{12}H_{18}O_3$ requires M, 210.125 6; m/e 210, 210→168, and 168→108; $\nu_{max.}$ 1 740 (acetate C=O), 1 720 (C=O), and 1 240 cm^{-1} (acetate); δ_H 1.08 (3 H, s, 1-Me), 1.23 (3 H, d, J 6 Hz, 5-Me), 2.00 (3 H, s, COMe), and 4.57 (1 H, d, J 3 Hz, 6-H).

Clemmensen Reduction of 4-Substituted Cyclohexanones.—*4-Benzoyloxycyclohexanone.* The keto-ester (0.1 g) was unchanged after reaction with amalgamated zinc (1 g), hydrochloric acid (10 mol l^{-1}, 5 ml), and methanol (5 ml) for 30 min.

4-Chlorocyclohexanone. The chloro-ketone (4 g), amalgamated zinc (10 g), and hydrochloric acid (12 mol l^{-1},

50 ml) were heated under reflux for 15 min. Separation of the products by preparative g.l.c. gave (*i*) hex-5-en-2-one (6%), (*ii*) 2-methylcyclopentanone (16%), (*iii*) cyclohexanone (6%), and (*iv*) chlorocyclohexane (68%).

4-(p-Tolylsulphonyloxy)cyclohexanone. The keto-toluene-*p*-sulphonate (1 g), amalgamated zinc (10 g), hydrochloric acid (10 mol l^{-1}, 10 ml), and methanol (10 ml) were heated under reflux for 15 min. Separation of the products by preparative g.l.c. gave (*i*) cyclohexene (21%), (*ii*) hex-5-en-2-one (5%), (*iii*) 2-methylcyclopentanone (24%), (*iv*) cyclohexanone (18%), and (*v*) starting material (33%).

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