Tetrahedron Vol. 42, No 24, pp. 6615 to 6620, 1986
Printed in Great Britain

0040-4020/86 $3.00+.00
Pergamon Journals Ltd

THE CLEMMENSEN REDUCTION OF α,β-UNSATURATED KETONES

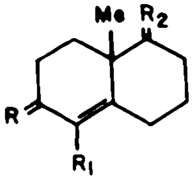
Ajoy K. Banerjee*, Jaime Alvárez G., Magaly Santana
and María C. Carrasco

Contribution from the Centro de Química, Instituto
Venezolano de Investigaciones Científicas, IVIC,
Apartado 21827, Caracas 1020-A, San Martín, Venezuela

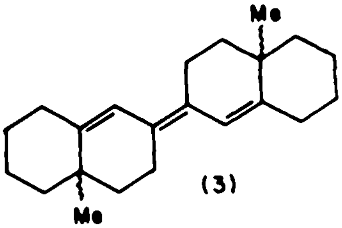
(*Received in USA* 25 *June* 1986)

Abstract - The deoxygenation of the α,β-unsaturated ketones (1) and (5) under the Clemmensen condition yielded the olefins (2) and (6) along with their respective dimers (3+4) and (8+9). The α,β-unsaturated ketone (13) under similar treatment yielded the olefin (14) in satisfactory yield but the dimer could not be characterized. The deoxygenation of the α,β-unsaturated ketones (10) and (16) under similar conditions afforded the olefins (12) and (15) respectively in satisfactory yield along with the rearranged olefins (11) and (17) respectively. Epoxidation of the olefin (17) followed by heating with p-toluenesulfonic acid yielded the ketone (18).

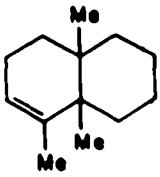
The deoxygenation of α,β-unsaturated ketones by the method of Clemmensen[1-3] has been reported[4,5] to yield corresponding saturated ketones, both rearranged and unrearranged (eg: cyclohex-2-enone→cyclohexanone and 2-methylcyclopentanone). In some cases the expected alkene was obtained without rearrangement of the double bond (eg: 3-methylcyclohex-2-enones→3-methylcyclohexene) while in certain cases the formation of rearranged alkene (eg: cholest-4-en-one→cholest-4-en-3-one) was observed. The results of these investigations prompted us in examining the behavior of some undermentioned α,β-unsaturated ketones under Clemmensen reduction. This paper summarizes the results of our investigations.



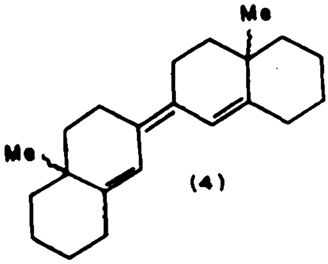
(1) $R=O, R_1=H, R_2=H,H$
(2) $R=H,H, R_1=H, R_2=H,H$
(10) $R=R_2=O, R_1=Me$
(12) $R=H,H\ R_1=Me, R_2=O$



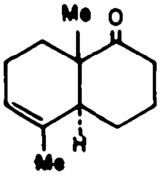
(3)



(7)



(4)



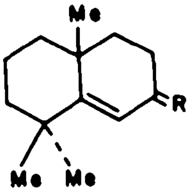
(11)

Our investigation began with the ketone[6] (1) which was reduced under Clemmensen reduction[1] using amalgamated zinc and hydrochloric acid. No co-solvent was employed. This operation yielded the octalin (2) in 60% yield whose spectral data (see Experimental) closely resemble the published data.[7,8] It is worthwhile to mention that we accidentally developed a simple synthesis of the octalin (2).

The reduction of (1) also yielded a solid material (30-40%) which was shown to be a dimer $C_{22}H_{32}$ by mass spectrometry and combustion analysis. The ^{1}H NMR spectrum which exhibited signals at δ 1.02 (6H) and 6.05 (2H) due to two methyl groups and two vinyl protons respectively supported the formation of the dimer. These spectroscopic data led us to propose either the structure (3) (E form) or (4) (Z form) for the dimer whose formation must have followed the scheme outlined by Vedej's.[2] In order to determine if the dimer was only one diastereoisomer or a mixture, its ^{13}C NMR spectrum was studied. To our surprise the spectrum presented more than twenty lines and therefore we concluded that the dimer was a mixture of diastereisomer (3 and 4). However no attempt was made to separate the diastereoisomers.

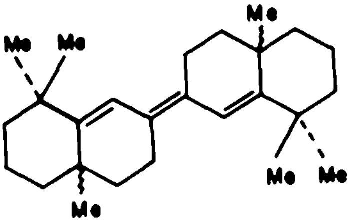
The above findings led us to examine the behavior of the α,β-unsaturated ketone[9] (5) under Clemmensen reduction. The major product obtained in 80% yield was identified as the octalin (6) on the basis of ^{1}H NMR, IR and TLC comparisons with an authentic specimen.[10] It has been reported[11] that the octalin (6), on treatment with 5%-sulfuric acid-acetic acid, afforded an equilibrium mixture containing 94% of the octalin (7) but such rearrangement was not observed during the Clemmensen reduction of the unsaturated ketone (5).

The minor product obtained (1-1.8%) was shown to be a dimer $C_{26}H_{40}$ by mass spectrometry and combustion analysis. Its ^{1}H NMR spectrum exhibited the signals at δ 1.18 (18H) and 6.25 (2H) due to six methyl groups and two vinyl protons respectively. Owing to insufficient material its ^{13}C NMR spectrum could not be studied. On the basis of these spectroscopic data (^{1}H NMR and MS) and by analogy with the reduction of related ketone (1), the dimer was assumed to be a mixture of diastereoisomers (8) (E form) and (9) (Z form). It is worthwhile to mention that the ketones (1) and (5) did not undergo any molecular rearrangement when heated with dilute hydrochloric acid or with zinc chloride and hydrochloric acid.

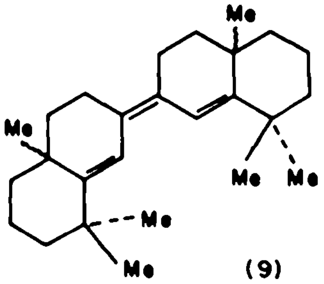


(5) R = O

(6) R = H,H



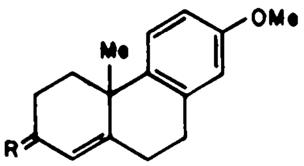
(8)



(9)

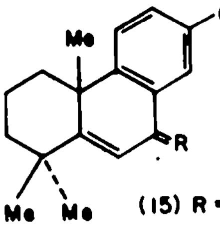
Our next experiment involved the reduction of α-substituted enone[12] (10) which under Clemmensen reduction yielded principally two products. The major product (50%) was identified as octalone (11) by comparing its spectral data with the one reported.[13] It is worthwhile to mention that the Clemmensen reduction of the enone (10) constitutes an alternative method for the preparation of the octalone (11) which has been utilized for the synthesis of triptolide, an antitumoral diterpene. The second major product (20%) was characterized on the basis of spectroscopic data as octalone (12) whose alternative synthesis[14] was already reported. The repeated purification of the octalone (12) failed to provide a pure sample for analytical purposes. The identity of the octalone (12) was confirmed by preparing its semicarbazone derivative whose melting point was almost identical with the one reported.[14]

The next phase of our studies involved the reduction of the α,β-unsaturated tricyclic ketones. It has already been reported[15] that the reduction of the tricyclic ketone (13) under Clemmensen condition produce the olefin (14) in 83% yield. The reduction experiment also afforded an amorphous solid in very poor yield and this was found very susceptible to aerial oxidation as evidenced by its change of color within a day from deep yellow to reddish brown. It has a molecular ion m/z 452 (M^+) in the mass spectrum and exhibited the presence of methyl, vinyl and methoxy groups in the ^1H NMR spectrum. Its ^{13}C NMR spectrum, though not well-defined owing to insufficient amount, exhibited 28 lines. These spectroscopic data indicated the formation of a dimer but owing to our inability to obtain an analytically pure sample, the structural assignment of the dimer was omitted.



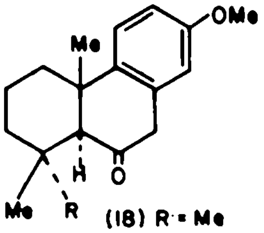
(13) R=O

(14) R=H,H



(15) R = H,H

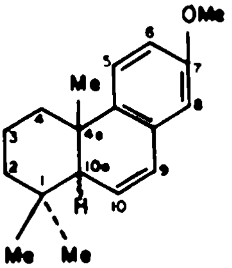
(16) R = O



(18) R = Me

(19) R = COOH

Our last example in this series involved the reduction of the ketone (16) which was prepared by the oxidation of the olefin[16] (15) with chromium trioxide and pyridine. The major product (60%) was identified as olefin (15) on the basis of its spectral data with that of reported.[16] The minor product (30%) was shown to be the olefin (17) on the basis of its spectral data. The mass spectrum displayed parent peak at m/z 256 (M^+) and the UV spectrum exhibited the characteristic absorption[17] for the styrene band. The signals between δ 0.91-1.07 indicated the presence of 18 protons (six methyl groups). Two one-proton doublet at δ 2.14 (J=3 Hz) and δ 1.86 (J=6 Hz) were assignable to the C-10a protons of trans and cis isomer of olefin (17) respectively.[18,19] The dihedral angle between C-10 and C-10a hydrogens for trans isomer is about 90°(Fig A) where as for cis isomer the dihedral angle is very small (Fig B) and thus the coupling constant in trans isomer will be much smaller[20] than cis isomer of the olefin (17). Another signal due to C-10 proton which appeared at δ 6.15 showed coupling constants (J=3 Hz, J=10 Hz) and (J=6 Hz, J=10 Hz) due to the trans and cis isomer of olefin (17) respectively. As the isomers were not easily separable, the olefin (17) was oxidized with m-chloroperbenzoic acid in chloroform and the resulting crude epoxide on heating with p-toluenesulfonic acid in chloroform afforded in major proportion the ketone (18) whose spectral data (IR and ^1H NMR) were found to be in perfect agreement with those of the reported.[16] This experiment led us to the conclusion that the olefin (17) contained the major proportion of the trans isomer. The conversion of the ketone (18) to the ketoacid (19), a potential intermediate for the synthesis of pimarane diterpenes and tetracyclic diterpenes,



(17)

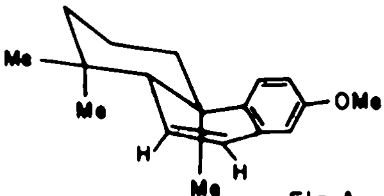


Fig.A

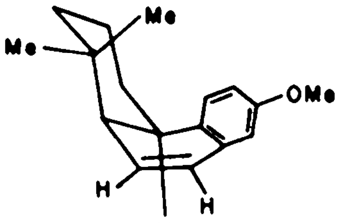


Fig. B

has already been reported.[16]

In conclusion, we have shown that the Clemmensen reduction of the α,β-unsaturated ketones (1),(5),(13) and (16) led to the formation of olefins (2),(6),(14) and (15) respectively in major proportions. Neither the reduction of the double bond nor ring rearrangement was observed during the reduction. It is very interesting to note also that the ketones (1),(5),(13) and (16) behaved very differently in the formation of dimeric products. This can only be accounted by assuming a continuous increment in the rigidity of ketones (1)→(5)→(13)→(16) owing to the introduction of additional functional groups and increasing the ring number of cyclic systems. An alternative synthesis of olefin (2) and octalone (11) has been developed during Clemmensen reduction.

EXPERIMENTAL

Mps were determined on a Kofler hot stage apparatus and are uncorrected unless otherwise stated. IR spectra were taken on a Perkin-Elmer spectrometer for KBr or liquid films and UV spectra were measured with a Cary model 15 spectrometer for methanol solution. ^{1}H NMR spectra were obtained for solution in $CDCl_3$ and CCl_4 with a Varian A-90 spectrometer. Chemical shifts are reported as units using TMS as internal standard. The form of signals is expressed as s:singlet, d:doublet, t:triplet and m:multiplet. The ^{13}C NMR spectra were taken in chloroform and in Bruker PW 60. Mass spectra were recorded on Du Pont 21-492B and Hitachi Perkin Elmer RMU-6H at 70 ev using a direct inlet system. Column chromatography was carried out with Neutral Brockman alumina and silica gel (BDH). TLC plates were coated with silica gel having a thickness of ca 0.2 mm and the spots were located by exposing the dried plates to iodine vapor. DC-plates precoated SIF (20 x 20 cm^{-1}) layer thickness (1 mm) were used for preparative thin layer chromatography. Unless otherwise stated all organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and evaporated under reduced oressure. Microanalyses were carried out in Franz Pascher Microanalisches Laboratorium at Bonn, Germany. All compounds described here are racemic although the prefix (±)- is omitted and only one enantiomer is depicted in the structural formula.

Octalin (2) and the dimer (3+4)

The ketone (1) (584 mg) was heated under reflux for 3 h with amalgamated zinc (5.8g), water (6 ml), and concentrated hydrochloric acid (18 ml). The reaction mixture was diluted with water and extracted with ether. The ethereal extract was washed, dried, evaporated and subjected to silica gel chromatography. Evaporation of hexane elute yielded the octalin (2) as oil 320 mg, 60%), NMR: δ 0.95 (3H, s, 10-Me) and 5.42 (1H, m, 4-H), MS: m/z 150 (M+). (Found: C, 87.84; H, 12.04. Calc. for $C_{11}H_{18}$: C, 87.92; H, 12.08%).

The portion eluted with benzene afforded the dimer (3+4) (421 mg, 40%), m.p. 160-162°C (from ether), IR: 1615 cm^{-1}, NMR: δ 1.02 (6H, s, 2 Me) and 6.05 (2H, s, vinyl protons), ^{13}C NMR: δ 146.398, 146.216, 127.171, 124.613, 124.311, 119.686, 118.226, 76.162, 77.032, 74.903, 41.923, 39.489, 37.786, 37.360, 35.656, 35.238, 33.232, 28.294, 26.251, 26.103, 23.304, 22.452 and 21.905, MS: m/z 296 (M+). (Found: C, 89.07; H, 1069. Calc. for $C_{22}H_{32}$: C, 89.12; H, 10.88%).

Octalin (6) and the dimer (8+9)

The ketone (5) (1 g) was heated under reflux for 4 h with amalgamated zinc (7.5 g), water (8 ml), and concentrated hydrochloric acid (15 ml). The reaction mixture was diluted with water and extracted with ether. The ethereal extract was washed, dried, evaporated to yield an oil which was chromatographed on silica gel (8:2 hexane-benzene) to yield the oily olefin (6) (740 mg, 80%) as a clear oil, IR: 1642, 998, 976 and 797 cm^{-1}, NMR: δ 1.04. 1.08 and 1.16 (4, 10-Me) and 5.62 (6-H, t, J=4 Hz), MS: m/z 178 (M$^+$). These spectroscopic properties were identical with one reported.[10,11]

Evaporation of the elute (4:6 hexane-benzene) yielded the dimer (8+9), (32 mg, 1.8%), m.p. 150-152°C (from chloroform), UV (methanol): 304 mμ (ε 10.000), NMR: δ 1.18 (18H, s, 6-Me), 1.42-2.52 (20H, m, 10 CH_2), 6.25 (2H, s, vinyl protons), MS: m/z 352 (M+). (Found: C, 88.17; H, 11.32. Calc. for $C_{26}H_{40}$: C, 88.56; H, 11.44%).

Octalone (11) and octalone (12)

The enone (10) (2 g) was heated under reflux for 3 h with amalgamated zinc (5.8 g), water (6 ml), and concentrated hydrochloric acid (20 ml). The reaction mixture was diluted with water and extracted with ether. The ethereal extract was washed, dried, and evaporated to obtain an oily material which was subjected to thin layer chromatography on silica gel impregnated silver nitrate (8:2 hexane benzene). The octalone (11) (840 mg, 50%) was obtained as colorless oil, b.p. 82-85°C (0.05 bath), IR: 1720 cm^{-1}, NMR: δ 1,08 (3H, s, 10-Me), 1.65 (3H, s, 4-Me) and 5.68 (1H, m, vinyl proton), MS: 178 (M+). (Found: C, 80.81; H, 10.15. Calc. for $C_{12}H_{18}O$: C, 80.85; H, 10.18%).

The octalone (12) (336 mg, 20%) was obtained as pale yellow liquid, IR: 1710 cm^{-1}, NMR: δ 1.16 (3H, s, 10-Me) and 1.64 (3H, s, 4-Me), MS: 178 (M+), semicarbazone, m.p. 218-220°C (from ethanol), lit.[14] 221-222°C. (Found: C, 66.31; H, 8.96; N, 17.82. Calc. for $C_{13}H_{21}N_3O$: C, 66.35; H, 9.00 and N, 17.86%).

Olefin (14) and dimer

The ketone (13) (1.22 g) subjected to Clemmensen reduction following the published procedure[15] to obtain the olefin (14) (946 mg, 83%) whose spectral and physical properties were identical with the published data.[15]

The residue left after the distillation of the olefin (14) on trituration with ether yielded a solid (22 mg), m.p. 180-184°C (from chloroform), IR: 1610 cm^{-1}, NMR: δ 1.38 (6H, s, 2-Me), 3.78 (6H, s, 2 OCH_3)5.45 (2H, s, vinyl protons) and 6.78-7.24 (6H, aromatic protons), MS: m/z 452 (M+).

Ketone (16)

To an ice-cold solution of dry pyridine (9 ml) in methylene chloride (40 ml) was added chromium trioxide (4 g), stirred for 5 min and then added the olefin (15) (768 mg) in methylene chloride (3 ml). After stirring for 24 h at room temperature the reaction mixture was filtered and the filtrate was concentrated to yield tarry material which was taken in ether. The ethereal solution was washed with dilute hydrochloric acid, brine, dried and evaporated to obtain an oily material which was subjected to silica gel chromatography. Evaporation of elute (1:1 hexane:benzene) yielded the ketone (16) (388 mg, 48%), m.p. 78-80°C (from ether), IR: 1660, 1610 cm^{-1}, NMR: δ 1.29 (3H, s), 1.37 (3H, s) and 1.52 (3H, s) (1, 4a-Me), 3.89 (3H, s, 7-OMe), 6.52 (1H, s, 10-H) and 7.16-7.68 (3H, m, aromatic protons), MS: m/z 270 (M+). (Found: C, 79.93; H, 8.18. Calc. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20%).

Olefins (15) and (17)

The ketone (16) (920 mg) was refluxed for 6 h with amalgamated zinc (6.8 g), water (8 ml), and hydrochloric acid (18 ml). The reaction mixture was diluted with water and extracted with ether. The ethereal extracted was washed, dried and evaporated to obtain an oily material which was chromatographed over silica gel. Elution with hexane (the first 32 fractions, each 10 ml) afforded the olefin (15) (522 mg, 60%) whose spectral properties were identical with that of reported.[16]

Further elution with hexane (the fractions 42-58, each 10 ml) yielded the olefin (260 mg, 30%), IR: 1615 cm^{-1}, UV (methanol): 200 mμ (ε 14125), 275 mμ (ε 9120) and 315 mμ (ε 1585), NMR: (cis and trans isomers): δ 0.91-1.07 (18H, 1-Me and 4a-Me), 1.86 (1H, d, J=6 Hz, 10a-H), 2.14 (1H, d, J=3 Hz, 10a-H), 3.84 (6H, s, 7-OMe), 6.15 (1H, m, J=10 Hz, J=3 Hz, 10-H), 6.56-7.42 (m, aromatic protons, 9-H), MS: m/z 256 (M⁺). (Found: C, 83.98; H, 9.12. Calc. for $C_{18}H_{24}O$: C, 84.32; H, 9.44%).

Ketone (18)

To a solution of the olefin (17) (200 mg) in dry chloroform (10 ml), cooled to 0°C was added m-chloroperbenzoic acid (100 mg) and the resulting solution after stirring at room temperature for 40 min was treated with sodium sulfite (10%, 5 ml). The reaction mixture was then successively washed with aqueous sodium carbonate solution (5%), brine, dried and evaporated at room temperature. The crude epoxide (230 mg) dissolved in chloroform (15 ml) was heated for 5 h with p-toluenesulfonic acid (80 mg). The reaction mixture was neutralized with aqueous sodium carbonate solution (5%, 4 ml) and the chloroform layer was washed, dried and evaporated to yield an oily material which was subjected to silica gel chromatography. Evaporation of the elute (6:4 hexane:ether) afforded the ketone (18) (273 mg, 72%) whose spectral properties were identical with that of authentic specimen.[16]

ACKNOWLEDGEMENTS

We are most grateful to Prof. Kakiuchi, Faculty of Engineering, Osaka University, for helpful discussions.

REFERENCES

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

[2] E. Vedejs, Org. Reactions, 22, 401 (1975).

[3] J.G.St.C. Buchanan and P.D. Woodgate, Quart. Rev., 23, 522 (1969).

[4] B.R. Davis and P.D. Woodgate, J. Chem. Soc. (C), 2006 (1966).

[5] A. Auterinen, Suomen Kem., B10, 22 (1937).

[6] N.C. Ross and A.C. Ashcraft, J. Org. Chem., 29, 2341 (1964).

7 R.K. Boeckman, Jr. and S.M. Silver, J. Org. Chem., 40, 1755 (1975).

8 J.A. Marshall and A.R. Hochstetler, J. Org. Chem., 31, 1020 (1966).

9 W.G. Dauben and A.C. Ashcraft, J. Am. Chem. Soc., 85, 3673 (1963).

10 A.K. Banerjee, P.C. Caraballo, H.E. Hurtado, M.C. Carrasco and C. Rivas, Tetrahedron, 37, 2749 (1981).

11 J.A. Marshall and A.R. Hochstetler, J. Am. Chem. Soc., 91, 648 (1969).

12 A.K. Banerjee and M.I. Pita-Boente, Heterocycles, 5, 5 (1985)

13 L.C. Graver and E.E. van Tamelen, J. Am. Chem. Soc., 104, 867 (1982).

14 S.L. Mukerjee, J. Ind. Chem. Soc., 39, 347 (1962) (Chem. Abs., 57, 9688, 1962).

15 A.K. Banerjee and H.E. Hurtado, Heterocyles, 16, 613 (1981).

16 A.K. Banerjee, C.D. Ceballo, M.N. Vallejo and E.H. Bolivar, Bull. Chem. Soc. Japan, 52, 608 (1979).

17 A.I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products", Pergamon Press, London, p. 97, 1964.

18 T. Matsumoto, Y. Oshuga and K. Fukui, Chemistry Lett., 297 (1976).

19 T. Matsumoto, S. Imai and S. Yuki, Bull. Chem. Soc. Japan, 55, 3836 (1982).

20 L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance in Organic Chemistry", 2nd ed., Pergamon Press, Oxford, p. 316, 1969.