

1113. *The Clemmensen Reduction. Part II.*¹ *Cyclohexenones*

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Cyclohex-2-enone and its methyl derivatives are reduced on comparatively brief treatment under Clemmensen conditions to give a mixture of the corresponding cyclohexanone and the related 2-methylcyclopentanone. Alkenes and dimers are produced in some cases.

In Part I of this Series¹ we demonstrated that several 1,3-diketones on reduction with amalgamated zinc and concentrated hydrochloric acid underwent both reduction and rearrangement to give a monoketone. This supported the hypothesis² that an intramolecular pinacol reduction is the step in which a new carbon-carbon bond is formed. To extend this work we have studied the Clemmensen reduction of some cyclohex-2-enones.

Auterinen, in 1937,³ noted that 5,5-dimethylcyclohex-2-enone was reduced by amalgamated zinc and hydrochloric acid to a mixture of 2,4,4-trimethylcyclopentanone and 3,3-dimethylcyclohexanone, isolated and identified as their semicarbazones. Reduction of acyclic $\alpha\beta$ -unsaturated ketones has not been reported to yield any rearranged products.⁴

Authentic samples of the cyclohex-2-enones used in this study were prepared by published methods⁵⁻⁹ and reduced under normal Clemmensen conditions¹⁰ using

¹ Part I, N. J. Cusack and B. R. Davis, *Chem. and Ind.*, 1964, 1426.

² D. Staschewski, *Angew. Chem.*, 1959, **71**, 726.

³ A. Auterinen, *Suomen Kem.*, 1937, **B10**, 22.

⁴ E.g., H. Burton and C. W. Shoppee, *J.*, 1939, 567; J. F. J. Dippy and R. H. Lewis, *Rec. Trav. chim.*, 1937, **56**, 1000.

⁵ A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5360.

⁶ E. W. Warnhoff and W. S. Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 494.

⁷ M. W. Cronyn and G. H. Reisser, *J. Amer. Chem. Soc.*, 1953, **75**, 1664.

⁸ R. L. Frank and H. K. Hall, *J. Amer. Chem. Soc.*, 1950, **72**, 1645.

⁹ A. W. Allan, R. P. A. Sneed, and J. M. Wilson, *J.*, 1959, 2186.

¹⁰ E. L. Martin, *Org. Reactions*, 1942, **1**, 155.

amalgamated zinc wool and approximately 6*M*-hydrochloric acid. No co-solvent was employed. Infrared spectra showed that all the cyclohexenone had reacted after 30 min., when ether extraction yielded a liquid product. Distillation of this total product yielded a fraction of b. p. about 60—190° representing 30—40% of the weight of the starting ketone. This distillate was then examined by analytical and preparative gas-liquid chromatography (g.l.c.). In all cases except that of isophorone, the product contained a few percent of low-boiling compounds, presumably including the saturated hydrocarbon, together with, as major products, a cyclopentanone and a cyclohexanone. The ketones were normally identified with authentic samples by their infrared (i.r.) and nuclear magnetic resonance (n.m.r.) spectra, by their refractive indices, and by the m. p. and mixed m. p. of their semicarbazones.

Thus, cyclohex-2-enone gave 2-methylcyclopentanone¹¹ and cyclohexanone in the ratio 5 : 2, while 2-methylcyclohex-2-enone gave 2-ethylcyclopentanone¹² and 2-methylcyclohexanone in approximately equal amounts. The total product from 3-methylcyclohex-2-enone showed the presence of 5- and 6-membered ring ketones, but the fraction b. p. <200° contained only a 5-membered ring ketone. Presumably the cyclohexanone was present in a dimeric product. The i.r. spectrum of the distillate suggested the presence of an alkene, and preparative g.l.c. gave two major fractions in the ratio 2 : 3. The first was an unsaturated hydrocarbon identified as 3-methylcyclohexene by comparison of its i.r. absorption with a published spectrum and by its n.m.r. spectrum and refractive index. The second product of the reaction was shown to be 2,2-dimethylcyclopentanone.¹³

5,5-Dimethylcyclohex-2-enone behaved like the unsubstituted compound and gave both 2,4,4-trimethylcyclopentanone and 3,3-dimethylcyclohexanone in the ratio 4 : 3. In the course of the preparation of authentic 3,3-dimethylcyclohexanone by the method of Crossley and Renouf,¹⁴ 3-chloro-5,5-dimethylcyclohex-2-enone was reduced with zinc and acetic acid. The total product showed the presence of both 5- and 6-membered ring ketones and preparative g.l.c. yielded both 2,4,4-trimethylcyclopentanone and 3,3-dimethylcyclohexanone, with the latter predominating slightly.

3,5,5-Trimethylcyclohex-2-enone (isophorone) gave both 2,2,4,4-tetramethylcyclopentanone and 3,5,5-trimethylcyclohexanone in small and approximately equal amounts together with, as major product, an unsaturated hydrocarbon which analysed for C₉H₁₆ and the i.r. and n.m.r. spectra of which were completely in accord with the structure proposed, 3,5,5-trimethylcyclohexene. The refractive index was virtually identical with the published value for this hydrocarbon. In addition, the total product of Clemmensen reduction deposited crystals of a compound identified by its m. p. and n.m.r. spectrum as the dimeric 1,1',5,5',5'-hexamethylbicyclohexyl-3,3'-dione, m. p. 162—163°. Chromatography of the total product yielded a small amount of the isomeric diketone, m. p. 120°, the n.m.r. spectrum of which was almost identical with that of the higher-melting isomer. These ketones have previously been isolated in reactions involving reduction, presumably through radical intermediates, of isophorone.¹⁵ The higher-melting isomer is probably the centrosymmetric *meso*-compound.

The results obtained clearly establish that the conversion of a cyclohex-2-enone to a methylcyclopentanone under Clemmensen conditions is a general one. To demonstrate that this reaction requires an electron source, as well as a proton source, 3-methylcyclohex-2-enone was treated with boiling hydrochloric acid for 30 min. No cyclopentanone was detected in the product, which appeared to be a mixture of starting material and polymeric products.

¹¹ L. Nicole and L. Berlinguet, *Canad. J. Chem.*, 1962, **40**, 353.

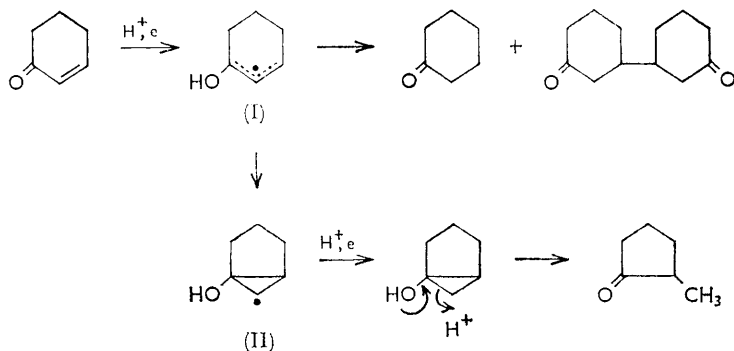
¹² S. V. Kessar and K. P. Mahajan, *J. Indian Chem. Soc.*, 1962, **39**, 147.

¹³ A. N. Dey and R. P. Linstead, *J.*, 1935, 1063; M. Qudrat-i-Khuda and A. Mukherji, *J. Indian Chem. Soc.*, 1946, **23**, 465.

¹⁴ A. W. Crossley and N. Renouf, *J.*, 1907, **91**, 63.

¹⁵ (a) J. W. Baker, *J.*, 1926, 669; (b) M. S. Kharasch, J. W. Hancock, N. Nudenberg, and P. O. Tawney, *J. Org. Chem.*, 1956, **21**, 322; (c) S. Cabani and G. Conti, *Ann. Chim. (Italy)*, 1962, **52**, 409.

For this reaction we propose the following mechanism:



Addition of a proton and an electron to the carbonyl group could give the allylic radical (I). This may then react by intramolecular attack to give the bicyclic radical (II), it may dimerise at C-3, or by further addition of a proton and an electron it may yield the cyclohexanone. The formation of a single alkene in the reduction of 3-methylcyclohex-2-enone under conditions where g.l.c. would detect the other isomers is surprising, and seems to exclude a simple carbonium ion intermediate. That reasonable amounts of dimer are

TABLE 1

	Vinyl protons, (δ)		Coupling constants, (c./sec.)			Methyl groups, (δ)		
	C-2	C-3	$J_{2,3}$	$J_{3,4}$	$J_{2,4}$	C-2	C-3	C-5
Cyclohex-2-enone	5.93	6.88	10	4	1	—	—	—
„, 2-methyl	—	6.66	—	—	—	1.73	—	—
„, 3-methyl	5.79	—	—	—	1	—	1.96	—
„, 5,5-dimethyl	5.94	6.78	10	4	2	—	—	1.06
„, 3,5,5-trimethyl	5.74	—	—	—	<1	—	1.91	1.02

TABLE 2

	Ring CH_2, CH	Methyl groups	
		C-2	C-4
Cyclopentanone, 2-methyl	1.33—2.50	1.06	—
„, 2,2-dimethyl	1.74—2.42	0.99	—
„, 2,4,4-trimethyl	1.33—2.50	1.05	1.18
„, 2,2,4,4-tetramethyl	1.76 (C-3); 2.14 (C-5)	1.08	1.14

formed only where the 3-methyl group is present is probably due to the fact that this group stabilises the initial radical sufficiently to allow dimerisation to occur.

The n.m.r. spectra of the cyclohex-2-enones showed the expected features and are summarised in Table 1. The methylcyclopentanones provide an interesting comparison with the parent ketone and the chief spectral features are reported in Table 2.

Wiberg and Nist¹⁶ found that the eight protons in cyclopentanone all had very similar chemical shifts; the spectrum appeared as an approximate doublet with signals at 2.06 and 2.02 δ . Anet¹⁷ reported a similar spectrum with some additional weak signals, indicating some quite large coupling constants. He observed that the chemical shift between the α and β protons was increased, in benzene, to over 0.3 p.p.m.

EXPERIMENTAL

Analyses were by Dr. A. D. Campbell and his associates, University of Otago, New Zealand. Infrared spectra were measured for carbon tetrachloride solutions on a Perkin-Elmer model 137

¹⁶ K. B. Wiberg and B. J. Nist, *J. Amer. Chem. Soc.*, 1961, **83**, 1226.

¹⁷ F. A. L. Anet, *Canad. J. Chem.*, 1961, **39**, 2316.

"Infracord." Proton magnetic resonance spectra were measured for carbon tetrachloride solutions with a Varian Associates A60 spectrometer using tetramethylsilane as internal reference. Preparative gas-liquid chromatography was carried out using a Wilkens "Aerograph A-700" on 20 ft. columns of 30% S.E. 40 (silicone) on Chromosorb P using helium as carrier gas.

Preparation of Cyclohex-2-enones.—(a) Anisole in liquid ammonia was reduced with lithium and the derived enol ether hydrolysed with aqueous methanolic hydrochloric acid to give cyclohex-2-enone, b. p. 166—176°/760 mm., n_D^{16} 1.4883 (lit.,¹⁸ b. p. 166°/734 mm., n_D^{20} 1.4879).

(b) 2-Methylcyclohexanone with sulphuryl chloride gave 2-chloro-2-methylcyclohexanone which was dehydrochlorinated directly with collidine at 160° to give 2-methylcyclohex-2-enone, b. p. 66.5—68°/19 mm., n_D^{16} 1.4918 (lit.,⁶ b. p. 98—101°/77 mm., n_D^{25} 1.4836).

(c) Ethyl acetoacetate and paraformaldehyde were condensed together using piperidine as catalyst to give, after hydrolysis and decarboxylation, 3-methylcyclohex-2-enone, b. p. 90—92°/22 mm., n_D^{16} 1.4908 (lit.,¹⁹ b. p. 90.5—91.5°/23 mm., n_D^{26} 1.4921).

(d) (i) 5,5-Dimethylcyclohexane-1,3-dione was treated with isobutyl alcohol and toluene-*p*-sulphonic acid in benzene to give the mono-enol ether which was reduced with lithium aluminium hydride and acidified to yield 5,5-dimethylcyclohex-2-enone, b. p. 81.5—82°/20 mm. (lit.,⁹ b. p. 76°/16 mm.). (ii) 5,5-Dimethylcyclohexane-1,3-dione was reacted with phosphorus trichloride in dry chloroform to give 3-chloro-5,5-dimethylcyclohex-2-enone, b. p. 116°/34 mm. (lit.,⁸ 105°/20 mm.). This chloro-ketone was reduced with zinc dust and potassium iodide in methanol to give 5,5-dimethylcyclohex-2-enone, b. p. 76°/17 mm.

Preparation of Cyclopentanones.—(a) Diethyl adipate was cyclised, using sodium metal, to 2-ethoxycarbonylcyclopentanone. Reaction of this β -keto-ester with methyl iodide and hydrolysis and decarboxylation with dilute hydrochloric acid gave 2-methylcyclopentanone, b. p. 139—142°/762 mm., n_D^{16} 1.4383, semicarbazone, m. p. 175.5—176° (lit.,¹¹ b. p. 138—140°/760 mm., n_D^{20} 1.4330, semicarbazone,²⁰ m. p. 175.4—176.2°).

(b) In a similar manner was prepared 2-ethylcyclopentanone, b. p. 162—167°/760 mm., n_D^{25} 1.4375, semicarbazone, m. p. 182.5—183.5° (lit.,²¹ b. p. 160.5°/760 mm., n_D^{20} 1.4399, semicarbazone, m. p. 188—189°).

(c) 2-Methylcyclohexanone was methylated with methyl iodide and the crude 2,2-dimethyl derivative purified through the 6-hydroxymethylene compound. Pure 2,2-dimethylcyclohexanone was oxidised with boiling concentrated nitric acid to give 2,2-dimethyladipic acid, which was heated with barium hydroxide at 285° to yield 2,2-dimethylcyclopentanone, b. p. 142—144°/760 mm., n_D^{25} 1.4308, semicarbazone, m. p. 188.5—189.5° (lit.,¹² b. p. 142—144°/760 mm., n_D^{19} 1.4314, semicarbazone, m. p. 190—191°).

(d) Clemmensen reduction of 5,5-dimethylcyclohexane-1,3-dione gave 2,4,4-trimethylcyclopentanone, b. p. 158—162°/764 mm., semicarbazone, m. p. 165.5—167° (lit.,²² b. p. 160—164°/760 mm., semicarbazone, m. p. 168—169°).

Preparation of Methylcyclohexenes.—(a) 2-Methylcyclohexanol was heated with orthophosphoric acid at 160—200° and the alkene removed by distillation. Drying and distillation gave a mixture of 1- and 3-methylcyclohexenes (67%), b. p. 109—111°/760 mm. Preparative g.l.c. gave 3-methylcyclohexene, n_D^{23} 1.4402 (lit.,²³ n_D^{25} 1.4400), i.r. spectrum identical with a published spectrum^{24a} and 1-methylcyclohexene, n_D^{24} 1.4482 (lit.,²³ n_D^{25} 1.4480), i.r. spectrum identical with a published spectrum.^{24b}

(b) The procedure described was repeated using 3-methylcyclohexanol. Preparative g.l.c. gave 3-methylcyclohexene, the refractive index and infrared spectrum of which were identical with those of material prepared as described in (a), and 4-methylcyclohexene, the infrared spectrum of which was identical with a published spectrum.^{24c}

Clemmensen Reductions.—*General procedure.* Zinc wool (1 g., 0.015 mole) was amalgamated with mercuric chloride (0.2 g., 0.7 mmole) by shaking with concentrated hydrochloric acid

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¹⁹ G. Buchi, J. H. Hansen, D. Knutson, and E. Koller, *J. Amer. Chem. Soc.*, 1958, **80**, 5517.

²⁰ J. B. Umland and M. I. Jefraim, *J. Amer. Chem. Soc.*, 1956, **78**, 2788.

²¹ A. F. Plate and A. A. Mel'nikov, *Zhur. obshchei Khim.*, 1960, **30**, 935.

²² R. Swaminathan, D. Mukherji, and J. C. Bardhan, *J.*, 1949, 192.

²³ H. Adkins and A. K. Roebuck, *J. Amer. Chem. Soc.*, 1948, **70**, 4041.

²⁴ Documentation of Molecular Spectroscopy. Infra-red spectra. (a) Spectrum No. 4708; (b) Spectrum No. 4218; (c) Spectrum No. 4709.

(0.05 ml.) and water (1.5 ml.) for 5 min. The liquid was then decanted and concentrated hydrochloric acid (1 ml., 0.013 mole) and water (0.75 ml.) were added. The ketone (0.005 mole) was added and the mixture heated under reflux. After 30 min. the products were extracted with ether.

Cyclohex-2-enone. Cyclohex-2-enone (5 g.) gave a yellow oil (3.8 g.) which on distillation gave a liquid, b. p. 60—160° (2.02 g.). G.l.c. showed the presence of four compounds; the two major components were isolated by preparative g.l.c. and identified as 2-methylcyclopentanone and cyclohexanone by comparison with authentic samples using i.r. and n.m.r. spectra and the m. p. and mixed m. p. of the derived semicarbazones. A minor product was identified as cyclohexane by its retention volume on g.l.c.

2-Methylcyclohex-2-enone. 2-Methylcyclohex-2-enone (5 g.) gave a yellow oil (3.15 g.) which was submitted to preparative g.l.c. to yield 2-ethylcyclopentanone and 2-methylcyclohexanone, both identified with authentic samples by their i.r. and n.m.r. spectra and the m. p. and mixed m. p. of their semicarbazones.

3-Methylcyclohex-2-enone. 3-Methylcyclohex-2-enone (15 g.) was reduced to give a yellow oil (9.3 g.) which was distilled to yield a liquid, b. p. 110—190° (5.8 g.). Preparative g.l.c. yielded 3-methylcyclohexene, n_D^{20} 1.4437, the i.r. spectrum of which was identical with that of authentic material, and 2,2-dimethylcyclopentanone identified with an authentic sample by its i.r. and n.m.r. spectra and the m. p. and mixed m. p. of its semicarbazone.

5,5-Dimethylcyclohex-2-enone. 5,5-Dimethylcyclohex-2-enone (5 g.) was reduced to yield a yellow oil (4.06 g.) which on distillation gave a liquid, b. p. 60—180° (3.16 g.). Preparative g.l.c. yielded 2,4,4-trimethylcyclopentanone and 3,3-dimethylcyclohexanone, identified with authentic samples by their i.r. and n.m.r. spectra and the m. p. and mixed m. p. of their semicarbazones.

3,5,5-Trimethylcyclohex-2-enone. 3,5,5-Trimethylcyclohex-2-enone (15 g.) was reduced to yield a dark yellow oil (11.22 g.) which on standing deposited crystals. Recrystallisation from ethanol gave *meso*(?)-1,1',5,5,5',5'-hexamethylbicyclohexyl-3,3'-dione, m. p. 162.5—163° (lit.,^{15a,b} 162°), δ 1.05 and 1.09 (6 quaternary methyl groups) and 1.27, 1.49, 1.71, 1.93, 2.18, 2.30, and 2.53 (CH₂ protons). Chromatography of the oil gave, on elution with acetone, a compound, m. p. 118.5—120°, the n.m.r. spectrum of which was almost identical with that of the higher-melting dimer, assumed to be the DL-isomer of the diketone (lit.,^{15a} m. p. 126°).

The remaining Clemmensen reduction product was distilled to yield a liquid, b. p. 120—190° (3.81 g.) which on preparative g.l.c. gave 3 fractions in the ratio 14 : 1 : 1. (i) 3,5,5-Trimethylcyclohexene, n_D^{25} 1.4380 (lit.,²⁵ n_D^{20} 1.4400) (Found: C, 86.7; H, 12.75. Calc. for C₉H₁₆: C, 87.0; H, 13.0%), the i.r. and n.m.r. spectra of which were entirely consistent with the proposed structure, δ 0.92 and 1.03 (CH₃ on C-3, $J = 7$ c./sec.), 0.95 (*gem*-CH₃ on C-5), 1.14—1.77 (5 methylene and methine protons), 5.49 (2 vinyl protons). (ii) 2,2,4,4-Tetramethylcyclopentanone, n_D^{23} 1.4309 (lit.,²⁶ n_D^{20} 1.4305), i.r. spectrum consistent with this structure, n.m.r. spectrum δ 1.08 and 1.14 (2 *gem*-dimethyl groups), 1.76 (2 protons on C-3), and 2.14 (2 protons on C-5). The semicarbazone crystallised from methanol as flakes, m. p. 187.5—189.5° (lit.,²⁶: 189—189.5°). (iii) 3,5,5-Trimethylcyclohexanone, n_D^{24} 1.4445 (lit.,²⁷ n_D^{15} 1.4454) identified with an authentic sample by its i.r. and n.m.r. spectra and the m. p. and mixed m. p. of its semicarbazone, 199.5—200.5° (lit.,²⁷ 202°).

Action of Hydrochloric Acid on 3-Methylcyclohex-2-enone.—3-Methylcyclohex-2-enone (1.0 g.) was heated under reflux with concentrated hydrochloric acid (2.4 ml.) and water (1.5 ml.) for 30 min. Ether extraction yielded a golden oil (0.3 g.) the i.r. spectrum of which indicated that it was mainly starting material. No five-membered ring ketone was apparent.

Zinc-Acetic Acid Reduction of 3-Chloro-5,5-dimethylcyclohex-2-enone.—Zinc dust (9.75 g.) was slowly added to a boiling solution of 3-chloro-5,5-dimethylcyclohex-2-enone (5.9 g.) in acetic acid (23.6 g.). Heating and stirring were continued for 12 hr. Neutralisation and steam distillation yielded, to ether, an oil which on distillation gave a liquid of minty odour (1.6 g., 35%) b. p. 55—60°/35 mm., ν_{\max} . 1740 and 1715 cm⁻¹. Preparative g.l.c. gave two fractions in the ratio 2 : 3 which were identified by i.r. and n.m.r. spectra as 2,4,4-trimethylcyclo-

²⁵ H. Eliel and R. P. Gerber, *Tetrahedron Letters*, 1961, 473.

²⁶ G. Slomp, M. Inatome, C. W. Bowers, J. M. Derfer, K. W. Greenlee, and C. E. Boord, *J. Org. Chem.*, 1960, **25**, 514.

²⁷ M. Pringsheim and J. Bondi, *Ber.*, 1925, **58**, 1409.

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pentanone, semicarbazone, m. p. 165—166.5° (lit.,²² 168—169°) and 3,3-dimethylcyclohexanone, semicarbazone, m. p. 189—190° (lit.,¹¹ 195°).

We are grateful to the New Zealand Universities Research Grants Committee for continued assistance.

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[Received, April 15th, 1965.]
