

Electro-organic Reactions. Part VII.¹ The Cathodic Reduction of Carvomenthone, Menthone, and Camphor

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The results of cathodic reduction in ethanol of some hindered cyclic ketones (carvomenthone, menthone, and camphor) have been compared with those obtained for unhindered cyclic ketones. Carvomenthone behaves similarly to the unhindered ketones giving predominantly 2e reduction to the alcohol. Menthone gives predominantly 4e reduction to menthane, and camphor can only be reduced [to borneol (84%) and isoborneol (16%)] *via* the cathodic generation in hexamethylphosphoramide of solvated electrons.

The differing results from carvomenthone and menthone are rationalised in terms of a common reaction pathway analogous to that previously proposed for Clemmensen reduction.

In the course of an investigation of the stereochemistry of cathodic hydrogenation¹ of unhindered cyclic ketones it was found that (a) high ratios of axial:equatorial alcohol were associated with good ion-pairing conditions, *e.g.* the presence in ethanol solution of zinc or magnesium ions, and (b) that small amounts of the corresponding cycloalkane were formed. A preliminary

¹ Part IV, J. P. Coleman, R. J. Holman, and J. H. P. Utley, Part VI, preceding paper.

² R. J. Holman and J. H. P. Utley, *Tetrahedron Letters*, 1974, 1553.

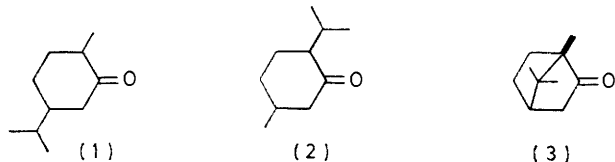
report² describes how, for more hindered cyclic ketones (*e.g.* menthone), formation of the alkane can predominate.

The electrochemical reduction of carbonyl groups to the corresponding methylene compounds is well established and in particular menthone^{3b} and steroidal ketones^{3b} have been so reduced. In each case, however, reduction to the alkane occurs only in acidic

³ (a) 'Organic Electrochemistry,' ed. M. M. Baizer, Dekker, New York, 1973, p. 371; (b) L. Throop and L. Tökés, *J. Amer. Chem. Soc.*, 1967, **89**, 4789.

solution and the method offers little advantage over conventional Clemmensen reduction.

We herein report fully on experiments concerned with the cathodic reduction in neutral solution of a series of cyclic ketones with increasing hindrance at the carbonyl function, *i.e.* carvomenthone (1), menthone (2), and camphor (3).



RESULTS

Voltammetry on Menthone.—Cyclic voltammetry on menthone (6.0–10mm) showed that in dimethylformamide (DMF) or acetonitrile containing tetra-*n*-butylammonium perchlorate (0.3M) and at a sweep rate of 0.3 V s⁻¹ no reduction of substrate was detected at a hanging mercury drop cathode. In DMF reduction would have been detected at ≥ -2.75 V (*vs.* Ag wire) and in acetonitrile at ≥ -3.0 V (*vs.* Ag wire).

Product Distribution.—Table 1 contains the results of

TABLE 1

Cathodic reduction^a of dihydroisophorone, carvomenthone, and menthone

Compound	Solvent	Supporting electrolyte	Product distribution (%)		Alkane (%)	Total current efficiency ^b (%)
			<i>ax.</i>	<i>eq.</i>		
Dihydroisophorone	EtOH	LiCl	20	80	2	42
	EtOH	MgCl ₂	54	46	2	5
	EtOH	Zn(ClO ₄) ₂	78	22	2	<i>ca.</i> 2
	EtOH	Bu ₄ N ⁺ I ⁻	3	97	Not detected	
(1)	EtOH	LiCl	12	87	<i>ca.</i> 1	
	EtOH	Zn(ClO ₄) ₂	24	75	<i>ca.</i> 1	
(2)	EtOH	Bu ₄ N ⁺ I ⁻	5	31	64	15
	EtOH	LiCl	10	29	61	57
	DMF	LiCl	6	24	70	40
	EtOH	MgCl ₂	10	0	90	27
	EtOH	Zn(ClO ₄) ₂	0	0	100	39

^a Electrolyses in a divided H cell at *ca.* 20°; mercury cathode, 2 F mol⁻¹, constant current density (62.5 mA cm⁻²), substrate 0.01M, electrolyte 0.1M, quinol 0.01M. ^b Calculated on the basis of 2e reduction to ROH and 4e reduction to RH.

amperostatic electrolyses in a divided cell and at a mercury pool cathode. The results for the reduction of dihydroisophorone give the pattern found¹ for compounds with little hindrance at the carbonyl group, *i.e.* an increase in the proportion of axial alcohol as the supporting electrolyte cation changed from Li⁺ to Zn²⁺. The total current efficiency for alcohol production is, however, low. For carvomenthone (methyl group in the 2-position), alcohol formation is still the predominant reaction and stereoselectivity in favour of the axial alcohol is influenced by the nature of the cation but to a much lesser extent than for the unhindered ketones. For the reduction of unhindered cyclic ketones it was found¹ that in the presence of Bu₄N⁺ the equilibrium mixture of epimeric alcohols was formed. On this basis it would appear that in the reduction products of carvomenthone the equatorial alcohol is, relative to the axial alcohol, more stable than is the case for the 4-*t*-butylcyclohexanols¹ (97 : 3 *vis à vis* 65 : 33).

An increase in hindrance adjacent to the carbonyl group is associated with a major change in the product distribution following cathodic reduction. Reduction of menthone (isopropyl group in the 2-position), gives menthane as the predominant product. In the presence of Bu₄N⁺ and Li⁺ the ratio alcohols : alkane is *ca.* 40 : 60 but the proportion of alcohol decreases as the cation is changed to Mg²⁺ and Zn²⁺; indeed in the latter case alkane only is formed. Where alcohol is formed the ratio of axial : equatorial alcohol is influenced as before by the cation and, for Mg²⁺, only axial alcohol is formed, albeit in low yield.

Using the conditions described in Table 1 prolonged electrolysis of the most highly hindered substrate, camphor, led to no detectable conversion of the ketone into products. Accordingly attempts were made to reduce camphor using conditions normally assumed to give electrochemically generated solvated electrons.⁴

Reductions by Solvated Electrons.—Reduction of ketones in an undivided cell at a platinum or graphite cathode in a solution of LiCl in hexamethylphosphoramide (HMPA) or ethylamine gives, in the presence of a proton donor (EtOH), efficient reduction to the alcohol. The results, summarised in Table 2, show that good yields are obtained from camphor

TABLE 2

Reduction of 4-*t*-butylcyclohexanone, dihydroisophorone, and camphor by cathodically generated solvated electrons^a

Compound	Alcohols (%)		Current yield (%) ^b	Chemical yield (%) ^c
	<i>ax.</i>	<i>eq.</i>		
4- <i>t</i> -Butylcyclohexanone	5	95	87	87
Dihydroisophorone	9	91	50	65
(3)	84 ^d	16	50–75	
	81 ^{d,e}	19	30–40	
At equilibrium ^f	84	16		

^a Electrolyses in an undivided cell at *ca.* 20°; platinum cathode, constant current density (59 mA cm⁻²), solvent HMPA (5% EtOH v/v), LiCl (0.3M), substrate 0.05–0.2M. ^b Calculated for 2 F mol⁻¹. ^c Based on starting material consumed. ^d Constant current density (63 mA cm⁻²). ^e Ethylamine as solvent. ^f Ref. 6.

and from the relatively unhindered ketones 4-*t*-butylcyclohexanone and dihydroisophorone. The proportions of the epimeric alcohols suggest that the reaction is thermodynamically controlled.

DISCUSSION

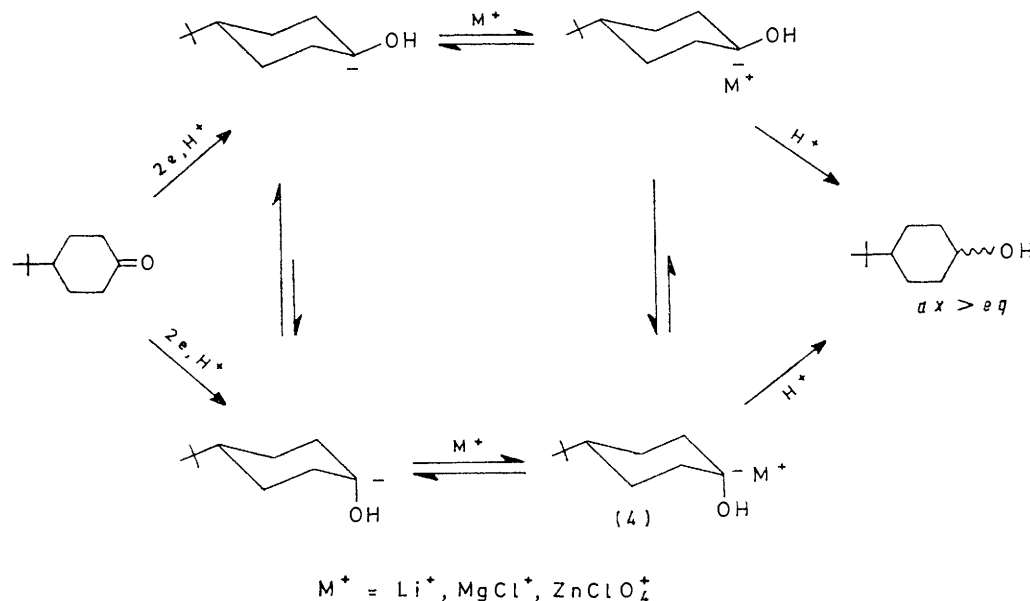
Alcohols.—The effect of added cation on the ratio of axial : equatorial alcohols has been discussed in detail and the results have been rationalised¹ in terms of ion-pairing of key carbanionic intermediates (Scheme 1). Thus small, doubly charged ions disturb the conformational equilibrium of the ion pairs (4) in favour of axial OH because the metal ion prefers to be equatorial. The decreased effectiveness of, say, Zn²⁺ in favouring axial alcohol formation from carvomenthone (1) *vis à vis* dihydroisophorone (Table 1) is consistent with this hypothesis. The possibility of non-bonded atom interactions between the metal ion (M⁺) and the adjacent

⁴ H. W. Sternberg, R. E. Markby, I. Wendler, and D. M. Mohilner, *J. Amer. Chem. Soc.*, 1969, **91**, 4191; L. A. Avaca and A. Bewick, *J. Electroanal. Chem. Interfacial Electrochem.*, 1973, **41**, 395.

methyl group means that in the relevant ion pair the C(1)-M⁺ distance is longer than for the ketones without a 2-substituent [see Newman projections (5) and (6)]. The equatorial conformational preference for M⁺, which determines the stereoselectivity, is thereby decreased. The degree of stereoselectivity must be judged against the equilibrium ratio of epimeric alcohols. For the carvomenthols this is significantly different (97% equatorial) from the unhindered alcohols (ca. 65–80%

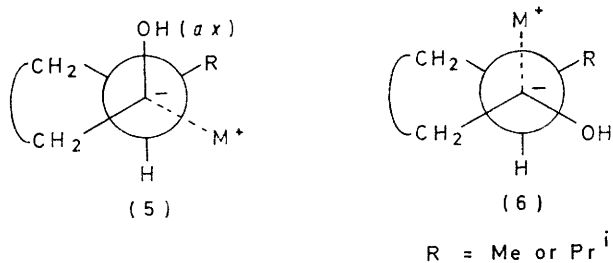
relatively inert compounds in basic solvents such as HMPA or ethylamine is believed to proceed *via* the generation of solvated electrons.⁴ In this way hindered alkenes and aromatic substrates are efficiently reduced. The mechanism of such reduction is analogous to that assumed for dissolving metal reductions.

It is not surprising therefore that highly hindered ketones such as camphor may be so reduced (Table 2). Camphor may also be reduced by dissolving metals⁵



SCHEME 1

equatorial). Consequently the considerable equatorial preference of the carvomenthol hydroxy-group will be evident in the ion-paired intermediate whereas that of M⁺ is diminished because of the long C(1)-M⁺ distance.



From menthone the epimeric menthols are obtained in low yield. The equilibrium ratio of epimers, assumed to result from reduction in the presence of Bu₄N⁺, is closer to that associated with unhindered ketones (86% equatorial). Furthermore, in the presence of Mg²⁺, axial alcohol only is formed (Table 1). An explanation of this follows if it is assumed that, even with a relatively long C(1)-M⁺ distance, the buttressing of M⁺ between the C(3) axial hydrogen and R = isopropyl is severe *vis à vis* the case for R = methyl [(5) and (6)].

Solvated Electron Reductions.—Cathodic reduction of

⁵ W. S. Murphy and D. F. Sullivan, *Tetrahedron Letters*, 1971, 3707.

and for those conditions stereochemical control may be achieved by varying the alkali metal and/or added alkali metal bromides. However, chemical reduction of camphor usually gives the less stable *exo*-alcohol (isborneol), a result which is often explained in terms of hindrance by C(7) methyl to reagent approach at the face leading to *endo*-alcohol (borneol). For dissolving metal reduction in liquid ammonia, in the absence of proton donor, the use of lithium gives⁵ borneol (20%) as the predominant isomer, isborneol (5%), and the pinacol (70%). The use of potassium gives borneol (37%), isborneol (58%), but no pinacol. Therefore, although stereoselectivity in favour of the *endo*-isomer may be achieved, the method does not constitute a convenient practical procedure. The electrochemical method, however, is convenient, efficient, reproducible, and it gives a product mixture rich in borneol (86%). It is also interesting that the product composition is that predicted⁶ for equilibrium at 240 K on the basis of Meerwein-Ponndorf-Oppenauer-Varley equilibration at higher temperatures (which produces mixtures containing ca. 65% borneol).

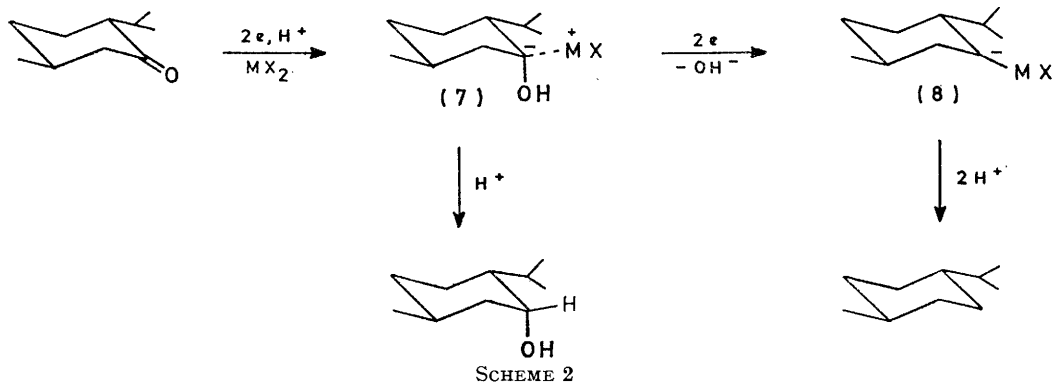
Formation of Alkanes.—The 4e electrochemical reduction of carbonyl compounds to hydrocarbons has invariably been associated with acidic conditions,³ as is

⁶ A. Coulombeau and A. Rassat, *Bull. Soc. chim. France*, 1970, 4393.

the conventional Clemmensen reduction. Indeed, because alcohols and pinacols are products of both Clemmensen and cathodic reduction it is tempting to draw mechanistic analogies between the two.

The efficient cathodic reduction of menthone to menthane is, however, carried out in ethanol in formally neutral solution whereas the cathodic reduction of steroidal ketones to hydrocarbon is typically carried out in 50% aqueous dioxan containing 5% sulphuric acid (v/v or w/v?).^{3b} For both menthone and the steroidal ketones the 4e reduction does not involve the alcohol as an intermediate because prolonged electrolysis of the alcohols does not yield hydrocarbon. Alcohols are not intermediates in conventional Clemmensen reduction either. For menthone the 4e reduction is associated with (a) the presence of Zn^{2+} or Mg^{2+} ions, and (b) hindrance at the carbonyl function which is not, however, sufficiently severe to preclude electron transfer as

(7) (alcohol formation) and further electron transfer (alkane formation) are likely to include (a) proton availability, (b) reduction potential of the ion pair (7), and (c) the relative relief of strain following either protonation or expulsion of hydroxide ion. On point (a) the results give moderate support for the hypothesis. For reduction of menthone in the presence of Li^+ slightly more alcohol (40% vs. 30%) is obtained in EtOH-quinol (0.01M) than in the more basic DMF-quinol (0.01M) solution (Table I). It is possible only to speculate about point (b) but, if hindrance at C(2) gives a relatively long C(1)-metal distance in (7) with less efficient positive charge dispersal, electron transfer *via* the metal atom might well be easier than for the corresponding ion pairs of unhindered ketones. The greater influence of the doubly charged ions Zn^{2+} and Mg^{2+} , in promoting alkane formation *vis à vis* Li^+ might also be connected with this point. Hence 4e reduction is



is the case for camphor. The potentials for electron transfer to the carbonyl function are very negative [≤ -2.5 V (vs. s.c.e.)] and it is almost certain that reduction of the metal cations competes. However, it is unlikely that reduction is proceeding *via* amalgam formation because prolonged stirring of menthone over a preformed amalgam electrode gave no detectable production of alcohols or menthane. This is entirely in line with the results of similar experiments on the unhindered ketones.¹

Comparison of the mechanism for cathodic reduction summarised in Scheme 1 and the best hypothesis for the mechanism of Clemmensen reduction⁷ allows the construction of a relatively simple explanation of the results of cathodic reduction of hindered and unhindered ketones. The hypothesis is contained in Scheme 2 and the link between conventional Clemmensen reduction and the electrochemical analogue is that intermediates such as (7) are believed to be involved for both reactions. The difference is that in chemical reduction removal of hydroxy is acid catalysed whereas at the cathode further electron transfer is possible with subsequent cleavage of hydroxide ion in neutral solution.

The hypothesis also explains why alcohols are formed from unhindered ketones and menthane from menthone. Factors influencing competition between protonation of

favoured. The likely influence of factor (c) is more clear cut. The tetrahedral ion-pair (7) is strained and expulsion of hydroxide ion, which would cause further electron transfer to be irreversible, would clearly lead to relief of strain. In the extreme the carbanion (8) could adopt anything between sp^3 and sp^2 hybridisation to minimise its conformational energy.

EXPERIMENTAL

Organic Substrates.—(–)-Menthone was prepared from the corresponding alcohol (natural menthol; B.D.H.) by Jones oxidation and purified by careful distillation under reduced pressure.

Carvomenthone. (–)-Carvone (Koch-Light; puriss grade) was reduced by catalytic hydrogenation (10% palladium on charcoal; methanol; 50°; 50 atm.). The product was taken up in ether and washed with water. An acetone solution of the crude product was titrated with Jones reagent. The ketone was taken up in ether, the solution dried ($MgSO_4$), and the solvent evaporated under reduced pressure. Carvomenthone was isolated by careful distillation under reduced pressure, b.p. 96–98° at 8 mmHg. G.l.c. analysis of the product on two polar columns gave only one peak (g.l.c. columns 15% polypropylene glycol-Chromosorb P and 15% Carbowax 1500-Chromosorb W).

⁷ T. Nakabayashi, *J. Amer. Chem. Soc.*, 1960, **82**, 3900, 3906, 3909.

D-Camphor (flowers-natural; B.D.H.) was used without further purification. Supporting electrolytes and solvents were obtained and purified as described previously.¹ Hexamethylphosphoramide (B.D.H.) was redistilled under reduced pressure. Ethylamine (anhydrous; B.D.H.) was used without further purification.

Electrochemical Experiments.—The procedure and apparatus for both voltammetric work and preparative scale electrolyses have been described previously.¹

Solvated Electron Reductions.—*Hexamethylphosphoramide as solvent.* In a typical electrolysis camphor (ca. 1.5 g) was dissolved in a solution of hexamethylphosphoramide (ca. 10 ml) containing lithium chloride (ca. 0.3M) and ethanol (up to 20% v/v). A graphite rod anode was positioned in the centre of a spiral platinum wire (0.5 mm) cathode which was wound as tightly as possible without causing a short circuit. A current density of ca. 63 mA cm⁻² was maintained during the course of the experiment. The electrolysed solution was poured into water (25 ml) and extracted with benzene (5 × 25 ml). The extract was washed with water (2 × 10 ml), brine (1 × 10 ml), dried (MgSO₄), filtered, and evaporated. Samples were taken up in ether for g.l.c. analysis.

Ethylamine as solvent. Camphor (1.46 g) was dissolved in a solution of ethylamine (15 ml) containing lithium chloride (ca. 0.1M) and ethanol (2 ml). The electrolysis was carried out at a platinum cathode and with the cell immersed in an ice-bath. After electrolysis the solvent was allowed to evaporate, the residue taken up in benzene (25 ml), washed with water (10 ml), dried (MgSO₄), and evaporated.

Analysis and Characterisation of Products.—The general procedure for the extraction and analysis of products from preparative scale electrochemical reductions of ketones has been described previously.¹

2-Isopropyl-5-methylcyclohexanols. The composition of mixtures of epimeric alcohols was measured by g.l.c. analysis and the alcohols identified by g.l.c. comparison on two columns (retentions times, equatorial OH > axial OH) using authentic samples prepared by reduction of the corresponding ketone with sodium borohydride (g.l.c.

columns 15% polypropylene glycol–Chromosorb P and 15% Carbowax 1500–Chromosorb W). Identification of menthol (equatorial OH) was confirmed by g.l.c. peak enhancement using an authentic sample.

5-Isopropyl-2-methylcyclohexanols. The composition of mixtures of epimers was obtained by g.l.c. analysis and the alcohols identified by g.l.c. comparison, on two columns, with authentic samples prepared by reduction of the corresponding ketone with sodium borohydride, and also by ¹H n.m.r., δ (100 MHz; CCl₄) 3.42br (m, 1 *ax*-H) and 4.05sh (m, 1 *eq*-H).

Borneol and isoborneol. The alcohols were analysed by g.l.c. and identified by peak enhancement using authentic samples.

trans-1-Isopropyl-4-methylcyclohexane. The hydrocarbon was identified by g.l.c. peak enhancement using an authentic sample prepared from menthone by a Clemmensen reduction.

Attempted Reduction of Menthone at a Magnesium–Mercury Amalgam.—An amalgam was prepared by dissolving clean magnesium turnings (0.3 g) in mercury (30 g) and the amalgam so produced formed the electrode pool of a standard H cell. A solution of menthone (0.74 g) and quinol (1.2 g) in dry ethanol (20 ml) was stirred above the amalgam for 18 h. The solution was worked up in the usual way to yield 1.16 g of recovered organic material which, by g.l.c. analysis, was shown to be entirely starting material.

Attempted Cathodic Reduction of Menthol.—Menthol (0.75 g) was dissolved in an ethanol (20 ml) solution of zinc perchlorate (0.1M) and quinol (ca. 0.1M). The solution was electrolysed in a divided H cell at a Hg cathode (current density 86 mA cm⁻¹; 2 F mol⁻¹). The solution was worked up in the usual way. The organic material (0.68 g) recovered was identified by g.l.c. as starting material and subsequent addition of an authentic sample of methane confirmed that it was absent in the product of electrolysis and would easily have been detected.

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