Synthetic Organic Electrochemistry. Application to Perhydrophenanthrene Syntheses

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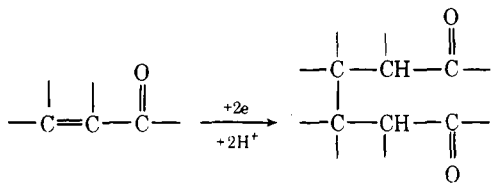
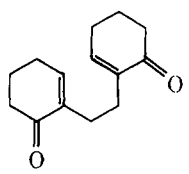
Compound **2** was synthesized and subjected to controlled potential reduction. The product was shown to be **3a** indicating the process to be both regio- and stereospecific.

The electrochemical reduction of α,β-unsaturated ketones has been well studied.[2] It has been shown that the process can be carried out in a way to produce β–β coupling products as the primary product though the precise mechanism of the dimerization is still in question. It is apparent that



this process could have interesting applications to synthetic organic chemistry as it represents the formation of a carbon to carbon bond between two electron-deficient centers. We wished to establish the potential utility of this reaction for perhydrophenanthrene syntheses by applying it to compounds of type **1**.



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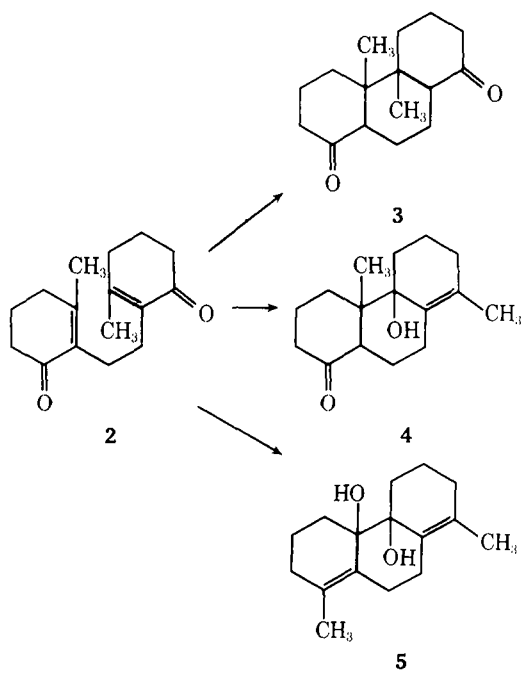
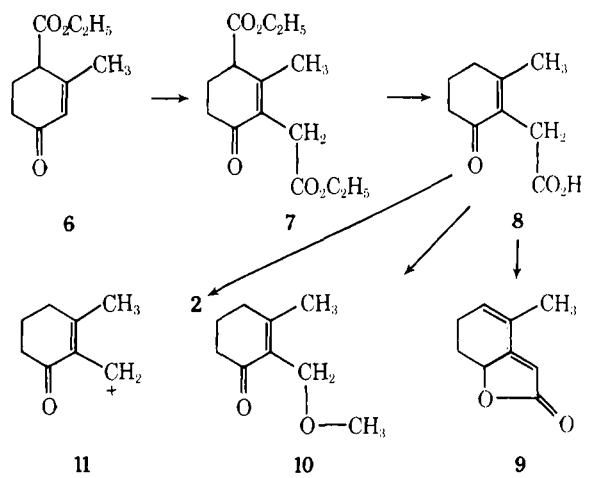
Two questions arise in considering the applicability of electrochemical predictions of this type; namely, the regiospecificity and stereospecificity of the process. Consider, for example, the reduction of compound **2**. Three cyclization products are possible, **3**, **4**, and **5**, depending on whether the normal β–β mode of coupling (leading to **3**), or "head to tail" coupling (leading to **4**), or "head to head" coupling (leading to **5**) would be realized.[6] Further, the stereochemistry of the coupling products at the nonepimerizable centers (those asymmetric centers not adjacent to carbonyl groups) must also be established. The dienedione **2** is an ideal substrate to answer these questions for the structures of the products should be easily established by nuclear magnetic resonance spectroscopy using the methyls as "tagging" substituents.



2 **3** **4** **5**

The synthesis of compound **2** is given in Scheme I. Hagemann's ester, **6**, was alkylated with ethyl chloroacetate to yield **7**, which could be smoothly hydrolyzed and decarboxylated with barium hydroxide to **8**. Electrolysis of **8** as its carboxylate anion in methanol (the usual Kolbe oxidative dimerization[7] conditions) afforded **10**, apparently by oxidation of the intermediate radical to carbonium ion **11** and thence solvation by methanol to the ether **10**. In one oxidation attempt, where only 20% of the acid was present as its sodium salt, lactone **9** was isolated rather than the usual Kolbe product. This transformation required the presence of an electrode, apparently to function as a Lewis acid. The conversion of **8** to **9** also occurred by treatment of **8** with sulfuric acid in acetic acid. Structural assignment to **9** was made on the basis of ^{1}H NMR, ^{13}C NMR, ir, uv, and mass spectral analysis. The desired dimerization of **8** to **2** could be realized, albeit in poor yield (11%), by doing the reaction in dimethylformamide solution.

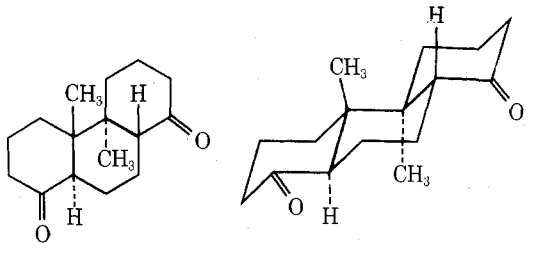
Scheme I



6 **7** **8** **2** **11** **10** **9**

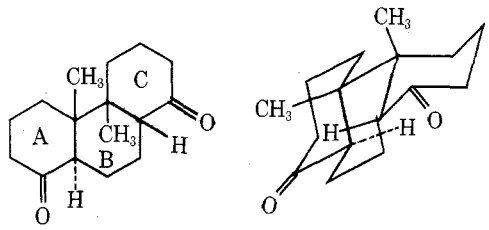
The conditions for the controlled potential reduction of **2** were determined from the polarography of **2** in acetonitrile–water (20% water). A 90% material recovery was obtained from the electrolysis. The reduced material was separated by chromatography into two fractions which proved to be the coupled product **3** (80%) and starting material (20%). The structure of **3** was clearly indicated by its NMR spectrum which exhibited uncoupled angular methyl protons at 0.93 ppm and no methyls on olefinic carbons.

It is possible to assign stereochemistry to **3** by considering the two possible dispositions of the angular methyls, namely, either trans or cis. If they are trans, then the product would have the stereochemistry shown in **3a** since during the coupling process the more stable configuration may obtain at the epimerizable centers adjacent to the carbonyl groups. In this configuration, the ring system is in the most stable trans-anti-trans arrangement.



3a

If the two angular methyls are cis, the configuration of the product would be as shown in **3b.** The cis (rather than trans) B/C ring fusion would be expected since this allows ring B to exist in a chair conformation.[3] In **3a** the angular methyls are in chemically shift equivalent positions and in axial conformations. In **3b,** the angular methyl at the trans ring fusion is axial while the angular methyl at the cis ring fusion is equatorially disposed to the B ring. One would therefore expect two NMR resonances for the angular methyl groups of **3b** whereas **3a** should show only one angular methyl resonance. The NMR spectra of the coupling product in $CHCl_3$, pyridine, and at −40 °C in chloroform shows only one angular methyl resonance and hence the product may be assigned structure **3a.**



3b

This assignment was further confirmed by the ^{13}C NMR spectrum, which had only eight peaks. The symmetry of **3a** is in accord with eight chemical shift nonequivalent carbons, whereas one would have expected **3b** to have more than eight resonances.

These results indicate that this route to the perhydrophenanthrene ring system is attended by both regio- and stereospecificity.

Experimental Section

All solvents are distilled. Where specified as dry, they were distilled from calcium hydride and stored over molecular sieves. Reagents were used without further purification, except for Hagemann's ester, which was distilled. Analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga.

Infrared spectra were recorded on either a Perkin-Elmer Model 257 or Model 467 spectrometer. Ultraviolet spectra were determined on a Cary Model 14. Nuclear magnetic resonance spectra (60 MHz) were obtained on a Varian Model T-60 or EM-360, while 100-MHz spectra were obtained on a JEOL MH-100 spectrometer. Carbon-13 magnetic resonance spectra were run on a Varian CFT-20 spectrometer. Mass spectra were obtained on a Varian M-66 spectrometer. The reductive coupling reaction was done using a Princeton Applied Research Model 170 electrochemistry system.

Synthesis of Diester 7. Sodium metal (3.5 g, 0.15 mol) was added to 150 ml of anhydrous ethanol. The resulting solution was cooled to 0 °C. Then 27 g (0.15 mol) of Hagemann's ester, **6,** was added dropwise to the solution. After stirring for 30 min under a N_2 atmosphere, the reaction mixture was warmed to 40 °C and 18.2 g (0.16 mol) of α-chloroethyl acetate was added dropwise. The temperature was raised to 60 °C and the reaction mixture was stirred further for 2.5 h. The ethanol was evaporated under reduced pressure and the residue was taken up in water. This was extracted with 3 × 150 ml of ether. After workup the residue was distilled at 132–133 °C (0.27 mm). This gave 24.8 g (62%) of diester **7.**

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.59; H, 7.54.

Hydrolysis of the Diester 7. To a solution of 5 g of NaOH in 25 ml of water was added 5 g of diester **7.** Enough ethanol was added (about 15 ml) to bring the ester into solution. This solution was stirred at 50–60 °C for 1.5 h and then poured into about 50 ml of water. The reaction mixture was acidified with 40% H_2SO_4 and extracte with 3 × 50 ml of methyl ethyl ketone (MEK), and the extract washed with saturated NaCl. Evaporation of the solvent afforded a solid which was crystallized from MEK. This gave 1.95 g (49%) of diacid, mp 148–148.5 °C with gas evolution.

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.83; H, 5.78.

3-Methyl-2-cyclohexen-1-one-2-acetic Acid (8). Procedure A. Into the distilling flask of a Kugelrohr apparatus was placed 9.42 g (0.045 mol) of the above solid diacid. This was heated under a vacuum with the temperature slowly increased to 175 °C when a semisolid material began to distill. This distillation began with much foaming. The temperature was maintained at 175 °C until distillation stopped; 7.4 g of distillate was obtained. Recrystallization from a 3:1 mixture of benzene and petroleum ether (bp 30–60 °C) yielded 4.5 g (61%) of crystalline **8,** mp 113–114 °C.

Procedure B. To a mixture of 263 g (0.72 mol) of $Ba(OH)_2$ decahydrate, 750 ml of water, and 250 ml of ethanol was added 89 g (0.30 mol) of diester **7.** The reaction mixture was refluxed for 24 h, cooled, and cautiously acidified with 10% HCl. Enough acid was added to dissolve all the precipitate from the reaction. The resultant solution was extracted with 3 × 150 ml of MEK. The combined extracts were washed with saturated NaCl solution. Evaporation of the solvent left a solid residue which was recrystallized from a benzene and petroleum ether mixture to afford 35.5 g (64%) of acid **8,** mp 113–114 °C.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.16; H, 7.22.

Kolbe Electrolysis[7] of 8. To 75 ml of dry methanol was added 2.1 g (0.012 mol) of keto acid **8** and 25 ml of 0.1 M sodium methoxide in methanol. This solution was placed into a 200-ml three-neck round-bottom flask equipped with a magnetic stirring bar, condenser in the center neck, and a pair of 1-cm^2 platinum sheet electrodes about 2 in. apart. Fifty-five volts at 0.5 A was applied to the solution. The solution was stirred until the pH reached about 8 to pH paper or about 2 h. The methanol was distilled and the residue extracted with benzene. The benzene was removed under vacuum and the resultant oil distilled at 100–102 °C (0.35 mm). The solid distillate was recrystallized from petroleum ether to give 1.35 g (72%) of white needles: mp 63–63.5 °C; infrared 1739 cm^{-1}; ^1H NMR 6.03 ppm broad, 1 H; 5.72 ppm, s, 1 H; 4.93 ppm, 8-line multiplet, 1 H, J_{vic} = 12, J_{vic} = 7 Hz, $J_{allylic}$ = 2 Hz; 2.47 ppm, m, 4 H; 1.96 ppm, s, 3 H. The decoupled ^{13}C NMR: 173.5, 166.8, 135.3, 127.8, 108.9, 79.8, 29.3, 24.9, 17.9 ppm. The ^{13}C NMR in which carbon–hydrogen coupling was allowed showed the resonances at 173.5, 166.8, and 127.8 ppm as singlets, the resonances at 135.3, 108.9, and 79.8 ppm as doublets, the resonances at 29.3 and 24.9 ppm as triplets, and the resonance at 17.9 ppm as quartet. Mass spectrum: parent ion and base peak *m/e* 150. Ultraviolet λ_{max} 261 nm (ϵ 2.64 × 10^4). These spectra are consistent with the unsaturated lactone **9.**

Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.88, 71.85; H, 6.70, 6.69.

Synthesis of Lactone 9. To 15 ml of a 1 M solution of H_2SO_4 in acetic acid was added 250 mg of the keto acid **8.** This solution was stirred at room temperature for 6 h. The solution was then poured into 100 ml of 5% NaCl solution and extracted with MEK. The solvent was removed and the residue distilled to give 190 mg (85%) of lactone **9.**

Kolbe Electrolysis[7] of the Salt of 8. To 75 ml of dry methanol were added 2.0 g (0.0118 mol) of the acid **8** and 5.9 ml of 2 M sodium methoxide in methanol. This solution was placed in the cell described above. Fifty-five volts at 1.5 A was applied to the reaction mixture for 2 h. The workup was as described above. Distillation of the resultant product at 85.8 °C (0.28 mm) gave 1.55 g of a colorless oil: infrared 1652, 1637 cm^{-1}; ^1H NMR 4.18 ppm, s, 2 H; 3.32 ppm, s, 3 H; 2.40 ppm, m, 6 H; 2.08 ppm, s, 3 H. Mass spectrum: parent ion *m/e* 154, base peak *m/e* 139. These spectra are consistent with the methyl ether **10.**

Electrolysis of 8 in Dimethylformamide.[5] To 70 ml of dry DMF were added 2.52 g (0.015 mol) of keto acid **8** and 0.25 g (0.0022 mol)

of triethylamine. The solution was placed in the cell described above and electrolyzed at 0 °C and 105–170 V with the current maintained at 0.25 A for 9 h. The reaction mixture was poured into 350 ml of saturated NaCl solution and extracted with 4 × 100 ml of ether. The solvent was removed and the resultant oil distilled at 120–130 °C (0.15 mm) to produce a solid distillate. Chromatography on neutral alumina with a 1:1 mixture of ether to petroleum ether gave 210 mg of a white, crystalline solid: mp 121–121.5 °C; infrared 1655 cm^{-1}; mass spectrum parent ion *m/e* 246; ultraviolet λ_{max} 241 nm (ϵ 2.14 × 10^4). These data are consistent with the structure of compound **2**. The yield was 11.4%.

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.92; H, 9.04.

Reductive Coupling of 2. To 50 ml of acetonitrile were added 200 mg (0.81 mmol) of **2**, a solution of 5 g of tetraethylammonium chloride in 50 ml of acetonitrile, and 13 ml of distilled water. The solution was placed in the electrolysis cell and degassed by bubbling nitrogen through the stirred solution for 45 min. The half-wave reduction potential was determined by polarography to be at −1.7 V (vs. SCE). The preparative reaction was run at −1.80 V (vs. SCE) for 7 h. The acetonitrile was distilled and the residue taken up in 200 ml of 5% NaCl solution and extracted with 3 × 50 ml of ether. The ether was dried and removed under vacuum and the oily residue was placed on a neutral alumina column and eluted with 15% ether in petroleum ether. This yielded 130 mg of a slightly yellowish, crystalline solid: mp 180–181 °C; infrared 1707 cm^{-1}; ^1H NMR 0.93 ppm, s, in $CHCl_3$; 0.97 ppm, s, in C_5H_5N. The NMR spectrum in $CHCl_3$ at −40 °C was essentially unchanged. The ^{13}C NMR in $CDCl_3$ exhibited eight resonances at 213.0, 52.3, 44.7, 41.0, 31.2, 22.1, 19.6, and 15.5 ppm. Mass spectrum: parent ion *m/e* 248. These data identified the product as **3a**. The yield was 81% taking into account recovered starting material (see below).

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.95; H, 9.03.

Elution of the alumina with 50% ether–petroleum ether afforded 40 mg of the starting diketone **2**.

Registry No.—**2**, 60410-71-1; **3a**, 60410-72-2; **6**, 487-51-4; **7**, 20653-49-0; **7** diacid, 60410-73-3; **8**, 60410-74-4; **9**, 60410-75-5; **10**, 60410-76-6; ethyl chloroacetate, 105-39-5.

References and Notes

(1) Abstracted from the Ph.D. Dissertation of Richard F. Daley, Emory University, 1976.
(2) J. P. Zimmer, J. A. Richards, J. C. Turner, and D. H. Evans, *Anal. Chem.*, **43**, 1000 (1971), and references cited therein; N. L. Weinberg "Technique of Electro-organic Synthesis", in two parts, "Techniques of Chemistry", Vol. V, A. Weissberger, Ed., Wiley, New York, N.Y., 1975.
(3) W. S. Johnson, *J. Am. Chem. Soc.*, **75**, 1498 (1953).
(4) S. Swann, Jr., and W. E. Garrison, Jr., "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 463.
(5) M. Finkelstein and R. C. Peterson, *J. Org. Chem.*, **25**, 136 (1960).
(6) For example Δ^4-3 keto steroids seem to couple to afford pinacols similar to **5** [P. Kabasakalian and J. McGlotten, *J. Am. Chem. Soc.*, **78**, 5032 (1956)] and even cyclohexenone gives a mixture of β–β coupling and "head to tail" coupling (similar to 4) [E. Touboul, F. Weisbuck, and J. Wiemann, *C. R. Acad. Sci.*, **268**, 1170 (1969).
(7) J. H. P. Utley in the text cited in ref 2, p 793.

Cis Reduction of Acetylenes by Organocopper Reagents[1a]

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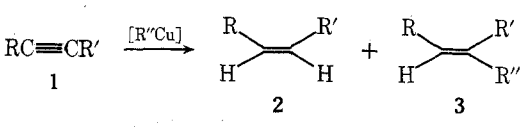
The stereoselective reduction of several disubstituted acetylenes to the corresponding cis olefins has been effected by an organocopper reagent prepared from CuI and 2 equiv of a primary Grignard reagent. A mechanistic pathway is proposed which involves the generation of a copper hydride species and subsequent cis addition of this intermediate to the acetylene function. Evidence for a vinylcopper intermediate of type **13** was obtained by trapping experiments with D_2O and allyl bromide. Phenyl-substituted acetylenes also undergo competitive addition of the alkylcopper reagent when THF is employed as the solvent (but not in ether solution). On the other hand, 3-phenyl-2-propyn-1-ol (**11**) shows only a regioselective trans addition of alkylcopper reagents leading to allylic alcohols of type **10**.

Organocopper reagents are known to add to terminal[2] and certain functionalized acetylenes[3] in synthetically useful reactions usually with high regio- and stereoselectivity. In connection with a study of related intramolecular analogues,[4] we have found that organocopper reagents also react with simple disubstituted acetylenes under some conditions. The predominant reaction in this case is reduction of the acetylene to the corresponding cis olefin, a highly stereoselective transformation of some synthetic potential. In several instances, addition of the organometallic species also takes place in the same fashion as with terminal acetylenes.[2]

Results

The organocopper reagent obtained by mixing *n*-BuMgBr and CuI in a 2:1 ratio at −35 °C in THF solution undergoes obvious decomposition upon warming to room temperature. The inclusion of 1-phenylpropyne (**1a**) in a fivefold excess of this reagent during the warming process resulted in 98% conversion of **1a** to a 68:30 mixture of (*Z*)-phenylpropene (**2a**) and (*E*)-2-methyl-1-phenyl-1-hexene (**3a**) after hydrolysis at the end of a 1-h reaction period. Under these conditions the cis reduction product **2a** was formed with a minimum of 99%



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stereoselectivity, although allowing the reaction mixture to stand for 24 h before hydrolysis resulted in contamination of the **2a** with 6% of **4a**, its *E* isomer. Quenching a similar reaction with D_2O gave **2a** with the incorporation of 41% deuterium, exclusively at C-1 as determined by NMR analysis. The addition product **3a** incorporated 86% deuterium in this experiment.

The structure of **3a** was established by comparison with an authentic sample obtained from the Wittig reaction[5] of the ylide derived from benzyltriphenylphosphonium chloride with 2-hexanone. The isomeric olefins produced in this fashion were separated by GLC and examined by ^{13}C NMR in order to secure stereochemical assignments. Thus, *E* isomer **3a** displays its allylic methyl at higher field (17.5 ppm) than that of the *Z* isomer **5** (23.8 ppm), whereas the allylic methylene carbon appears at higher field for **5** (32.0 ppm) than it does for **3a** (40.2 ppm). These assignments are based on the expecta-