[CONTRIBUTION FROM THE CHEMICAL LABORATORY, FACULTY OF LIBERAL ARTS AND EDUCATION, MIYAZAKI UNIVERSITY, MIYAZAKI CITY, MIYAZAKI, JAPAN]

Studies on the Mechanism of Clemmensen Reduction. III. The Relation of Clemmensen Reduction to Electrochemical Reduction

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Polarographic reduction potentials of *p*-substituted acetophenones are almost equal to or higher than the zinc amalgam potentials measured in the course of Clemmensen reduction. Electrolytic reduction of acetophenone at a mercury cathode under the same condition as that of Clemmensen reduction gives one-electron reduction products exclusively, neither ethylbenzene nor styrene being produced. The rate of pinacol formation in Clemmensen reduction increases as the potential of zinc amalgam drops. It is concluded that pinacol formation is an electrochemical reduction whose mechanism is not related to Clemmensen reduction.

In Clemmensen reduction pinacol formation is frequently observed. Steinkopf and Wolfram[1] and Bradlow[2] assumed the formation of a radical $R\dot{C}OHR'$ from the ketone RCOR′ as an essential intermediate to hydrocarbon RCH_2R' and pinacol. Brewster[3] proposed a mechanism in which pinacol and hydrocarbon are formed from carbonyl compound coördinated to the metal surface.

In considering the process of reduction employing metal as reducing agent, as in the case of Clemmensen reduction, the relation of the reaction to the electrochemical reduction must always be taken into consideration. Indeed with cadmium or lead cathode, reduction of carbonyl compound to hydrocarbon or reductive rearrangement of α-aminoketones can be effected electrochemically.[4] As described in Part I of this series, the electrode potential of the zinc amalgam during Clemmensen reduction of *p*-hydroxyacetophenone lies between −0.99 and −1.06 v. (S.C.E.). By extrapolating polarographic data,[5] electrochemical reductions of substituted acetophenones in strong acidic media at 60° are presumed to occur near −1.0 v. (S.C.E.). Since, in this study, amalgam containing no more than 2% of zinc is employed, an electrochemical reduction similar to that which occurs at the mercury cathode may also occur in the case of the Clemmensen reduction. Polarographic reductions of *p*-substituted acetophenones, electrochemical reduction of acetophenone at the mercury cathode and the effect of electrode potential of zinc amalgam on Clemmensen reduction of acetophenone and of *p*-hydroxyacetophenone were studied in order to estimate the relationship between Clemmensen reduction and electrochemical reduction.

Experimental

Polarographic Reduction of *p*-Substituted Acetophenones. a. Materials.—*p*-Substituted acetophenones were prepared by known methods[6]; *p*-methoxyacetophenone, b.p. 121–122° (8 mm.); *p*-methylacetophenone, b.p. 110.5–111° (20 mm.); *p*-chloroacetophenone, b.p. 124–126° (24 mm.). *p*-Hydroxyacetophenone, acetophenone and hydrochloric acid were prepared as described before[7]; 0.01% polyvinyl alcohol was added to the acid as a maximum suppressor.

b. Apparatus and Procedure.—A polarograph constructed with a precision potentiometer, model P-1, of Yokogawa Electric Works, was used. The characteristics of the dropping mercury electrode were: t = 3.0 sec., m = 1.58 mg./sec. Polarograms of *p*-substituted acetophenones at 60° were recorded using 0.6–2 *N* hydrochloric acid as supporting electrolyte and 13.3% aqueous ethanol as solvent; these conditions were the same as those of the Clemmensen reduction described in Part I. Concentration of acetophenones was 0.01 mole./l. Since the wave of hydrogen began to appear at −1.0–−1.05 v. (S.C.E.) and consequently the half-wave potentials of these acetophenones could not be measured, reduction potentials (the potential at which the rate of increase of the current came up to 2×10^{-7} amp./mv.) of them were recorded. Results are shown in Table I and examples of polarograms for the case of 1.81 *N* hydrochloric acid in Fig. 1.

TABLE I

THE REDUCTION POTENTIALS OF *p*-SUBSTITUTED ACETOPHENONES[a] AT 60° (S.C.E.)

Substituent	Concentration of hydrochloric acid, *N* 0.600	0.998	1.81	1.97
Cl	0.83 v.	0.82 v.	0.82 v.	0.81 v.
H	.90	.92	.87	.89
CH_3	.92	.91	.88	.89
CH_3O	.96	.96	.93	.94
OH	1.03	1.02	1.04	1.00

[a] Concentration of acetophenones 0.01 mole/l.

The Electrode Potential of the Zinc Amalgam in the Clemmensen Reduction of Acetophenone.—The electrode potential of the zinc amalgam in the reduction of acetophenone was measured as described before.[7] Initial concentrations were: acetophenone $1–2 \times 10^{-2}$ mole. l., 0.60–1.81 *N* hydrochloric acid (containing 0.01% polyvinyl alcohol), 2.03% zinc amalgam. The electrode potential of zinc amalgam referred to S.C.E. was measured at 60°. Results are shown in Fig. 2. The potential of zinc amalgam lay between −1.02 and −1.06 v. (S.C.E.) during the reaction.

Reduction of Acetophenone at the Mercury Cathode.—In a porous cylinder (inside diameter 5.2 cm. and 15 cm. high) equipped with a stirrer, a thermometer, a salt bridge of saturated potassium chloride and a reflux condenser, were placed 30 ml. of mercury (cathode), 100 ml. of 1.19 *N* hydrochloric acid (containing 0.01% polyvinyl alcohol) and 20 ml. of 0.3 *M* acetophenone solution in 95% ethanol. A platinum gauze was used as anode and 1 *N* hydrochloric acid as anolyte. The apparatus was immersed in a thermostat at 65°. When the temperature of the catholyte had reached 60°, current was applied and the cathode potential was maintained at −1.05 v. (S.C.E.) by controlling the current. The current flowed 0.25 amp. at the outset and decreased to 0.1 amp. after 30 min., when the electrolysis was stopped. The whole process was carried out under nitrogen.

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(1) W. Steinkopf and A. Wolfram, *Ann.*, **430**, 113 (1923).

(2) H. L. Bradlow and C. A. VanderWerf, THIS JOURNAL, **69**, 1254 (1947).

(3) J. H. Brewster, *ibid.*, **76**, 6364 (1954).

(4) M. J. Allen, "Organic Electrode Processes," Chapman & Hall Ltd., London, 1958, p. 58.

(5) I. M. Kolthoff and J. J. Lingane, "Polarography," Vol. II, 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1952, p. 684.

(6) H. Gilman, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1932, p. 109.

(7) T. Nakabayashi and K. Kai, *J. Chem. Soc. Japan, Pure Chem. Soc.*, **76**, 1332 (1955).

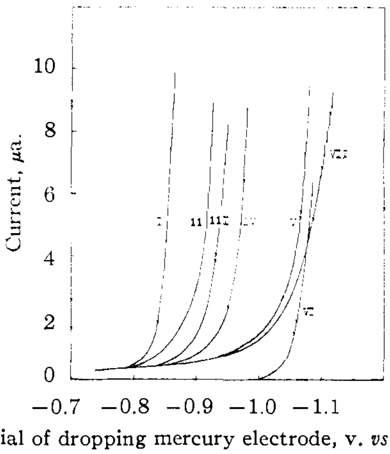

Fig. 1.—The polarograms of p-substituted acetophenones; 1.81 N HCl, 60°, 0.010 mole/l. p-XC_6H_4Ac: I, X = Cl; II, H; III, CH_3; IV, OCH_3; V, OH; VI, OH (current of H_2 is subtracted); VII, HCl.

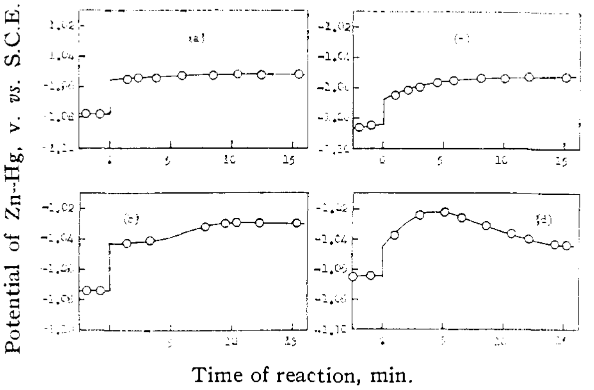

Fig. 2.—The electrode potential of Zn–Hg vs. time of reaction in the reduction of acetophenone; 2.03% Zn–Hg, 60°: (a) 0.600 N HCl, 0.010 mole/l. acetophenone; (b) 0.600 N, 0.020 mole/l.; (c) 1.81 N, 0.010 mole/l.; (d) 1.81 N, 0.020 mole/l.

The catholyte was cooled immediately and neutralized with sodium hydroxide solution. The products of the 11 experiments were combined and extracted with ether. The ethereal solution was washed with water several times, dried with anhydrous sodium sulfate and ether was removed The residue was fractionated by distillation with a 15-cm. column.

Fraction	B.p. °C.	Mm.	Yield, g.
a	Up to 92	22	3.2
b	152–189	2	2.6
c	Residue		0.8
		Total	6.6

These fractions were treated as follows: Fraction a, colorless liquid, crystallized on cooling and melted at 17–18°. The acetophenone content was found to be 99.4% by the 2,4-dinitrophenylhydrazine method.[8]

Fraction b, light yellow viscous liquid, solidified after one or two days. It was dissolved in a small amount of benzene, petroleum benzine was added to it and the mixture was cooled in ice; 1.3 g. of white crystals precipitated. They were identified with acetophenone pinacol by treating them with hydrochloric acid and converting the product into oxime. The mother liquor was analyzed after evaporation of the solvent. It had the composition 80.20% C, 7.74% H corresponding to the formula $C_{16}H_{18.4}O_{1.82}$. This formula shows that acetophenone pinacol is the main constituent.

Fraction c, reddish-brown, transparent and brittle solid, had the composition 82.8% C, 7.35% H which coincided with that of the corresponding fraction of the product of Clemmensen reduction of acetophenone described in Part II of this series.

p-Hydroxyacetophenone also gave no p-ethylphenol when reduced on a mercury cathode maintained at −1.15 v. (S.C.E.) under the same conditions.

The Effect of Zinc Amalgam Potential on Clemmensen Reduction of Acetophenone.—The apparatus was the same as that employed in the electroreduction of acetophenone: 25 ml. of hydrochloric acid, 25 ml. of 95% ethanol and 30 ml. of zinc amalgam were placed in the porous cylinder. After the temperature of the mixture had risen, reaction was started by adding 10 ml. of acetophenone solution in 95% ethanol. The potential of the zinc amalgam was kept constant during the reaction by controlling the current. Initial concentrations were: 1.00 N hydrochloric acid, 2.0×10^{-2} mole/l. acetophenone, 2.0% zinc amalgam. Other conditions were the same as those of the electroreducton of acetophenone. After 7 min., the aqueous layer was withdrawn and acetophenone, styrene, acetophenone pinacol and zinc chloride in the solution were determined. The ratio [acetophenone pinacol]/{[styrene] + [ethylbenzene]} increases as the potential of zinc amalgan drops (Fig. 3).

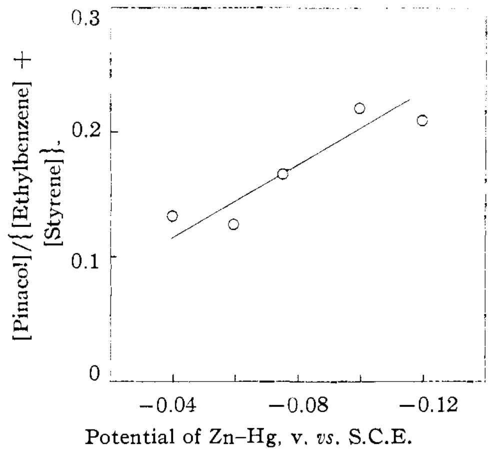

Fig. 3.—The effect of the electrode potential of Zn–Hg on the rate of pinacol formation in Clemmensen reduction of acetophenone; 1.00 N HCl, 0.020 mole/l. acetophenone, 2.00% Zn–Hg, 60°.

Analysis of the Product of Electrolysis. a. Acetophenone.—The reaction product (25 ml.) was neutralized with sodium hydroxide, steam distilled and acetophenone in the distillate was determined by the 2,4-dinitrophenylhydrazine method.[8]

b. **Zinc Chloride.**—The residual solution from the steam distillation was titrated with 0.02 mole./l. EDTA solution.[9]

c. **Styrene.**—The reaction product (25 ml.) was cooled in ice, 0.2 N $KBr-KBrO_3$ was added until the solution became yellow, an additional 1 ml. of the reagent was added and, after 30 sec., excess bromine was iodometrically determined.

d. **Acetophenone Pinacol.**—The reaction product (25 ml.) was placed in a modified Soxhlet extractor, neutralized with sodium hydroxide solution and extracted with ether for four hours. After evaporation of the ether, 25 ml. of acetic acid and 4 g. of sodium acetate were added to the extract and the mixture was steam distilled to expel styrene, ethanol and acetophenone. When the distillate amounted to 80 ml., the residual solution was cooled in an ice-bath, 10 ml. of acetic acid and 5 ml. of 0.04 N lead tetraacetate solution in acetic acid were added and the mixture was kept in an ice-bath. After 30 min., excess potassium iodide was added to the solution and the liberated iodine was titrated with 0.1 N sodium thiosulfate. The pinacol content was cal-

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(8) H. A. Iddles and other workers, *Ind. Eng. Chem., Anal. Ed.*, **11**, 102 (1939).

(9) W. Biedermann and G. Schwarzenbach, *Chimia* (*Switz.*), **2**, 56 (1948).

TABLE II

THE MATERIAL BALANCE OF THE REDUCTION OF ACETOPHENONE AT 60°

Concn. of HCl, *N*	% of Zn in Zn–Hg[a]	Time of reacn., min.	Reacn., %	Reaction products Mole % based on the reacted AcPh Styrene	Pinacol × 2	EtPh[b]	$ZnCl_2$	H_2	*n*[c]
1.02	0.486	9	42.1	32.3	38.5	29.2	125.4	. .	2.49
1.02	1.98	5	35.3	34.0	14.4	51.6	148.8	2.8	2.03
0.100	1.96	12	55.6	39.6	11.7	48.7	148.3	. .	2.10
2.00	1.98	5	38.2	32.0	13.1	54.9	172.7	15.6	2.14

[a] Zn/Hg. [b] 100 − (styrene + pinacol × 2). [c] ($ZnCl_2$ − styrene − pinacol − H_2)/(100 − styrene − pinacol × 2).

culated from the difference between blank and titrated values multiplied by the correction factor 1.03 which was determined by analysis of known amounts of pinacol.

e. Material Balance of the Reaction.—The material balance of the reaction was examined without applying current. The reaction was carried out in a 100-ml. flask under the same condition as that described above except that current was not applied. Results are shown in Table II. The figures under the heading *n* show the number of zinc atoms consumed to reduce each molecule of acetophenone which is reduced to something other than styrene and acetophenone pinacol. As *n* is close to 2, the number of zinc atoms required to reduce acetophenone to ethylbenzene, it may be concluded that the main reaction product other than styrene and pinacol is ethylbenzene. Therefore it may be reasonable to assume that the reaction product consists mainly of ethylbenzene, styrene and acetophenone pinacol; the amount of ethylbenzene was determined by subtracting those of styrene and pinacol from that of reacted acetophenone. This assumption may also be reasonable in the case where external current is applied. The ratio [acetophenone pinacol]/{[ethylbenzene] + [styrene]} shown in Fig. 3 was determined in this way.

Pinacol Formation in Clemmensen Reduction of *p*-Hydroxyacetophenone.—A mixture of 50 ml. of hydrochloric acid (containing 0.01% polyvinyl alcohol) and 10 ml. of *p*-hydroxyacetophenone solution in 95% ethanol maintained at 60° was flushed with purified nitrogen and treated with 30 ml. of zinc amalgam. The flask was mechanically shaken during the reaction. The reaction was allowed to continue for 15 min. Evolved hydrogen, dissolved zinc, produced *p*-ethylphenol and unreacted *p*-hydroxyacetophenone were determined. Initial concentrations were: 1.81 *N* hydrochloric acid, 2.05×10^{-2} mole/l. *p*-hydroxyacetophenone, 2.03% zinc amalgam. Five experiments were carried out, and the averaged result is shown in Table III.

TABLE III

THE MATERIAL BALANCE OF THE REDUCTION OF *p*-HYDROXYACETOPHENONE AT 60°

Reacn. %	Reaction products, mole % $ZnCl_2$	*p*-Ethylphenol	H_2	*n*[a]
40.4	200.0	58.0	58.6	0.61

[a] *n* = ($ZnCl_2$ − *p*-ethylphenol × 2 − H_2)/(100 − *p*-ethylphenol).

The figure under the heading *n* shows the number of zinc atoms consumed to reduce each molecule of *p*-hydroxyacetophenone which is not reduced to *p*-ethylphenol. As one-half-atom of zinc is required per molecule of ketone to produce pinacol, it may be concluded that the main components of the reaction products other than *p*-ethylphenol are the corresponding pinacol and the like.

The Effect of Zinc Amalgam Potential on the Clemmensen Reduction of *p*-Hydroxyacetophenone.—The apparatus was the same as that employed in the electroreduction of acetophenone. Hydrochloric acid (50 ml.) and 30 ml. of zinc amalgam were placed in the porous cylinder and the reaction was started by adding 10 ml. of *p*-hydroxyacetophenone solution in 95% ethanol. The potential of zinc amalgam was kept constant throughout the reaction by controlling the external current. Initial concentrations were: 2.00 *N* hydrochloric acid, 2.0×10^{-2} mole/l. *p*-hydroxyacetophenone, 2.03% zinc amalgam, temperature 60°. After 50–60% of *p*-hydroxyacetophenone had reacted, the reaction mixture was withdrawn and *p*-hydroxyacetophenone and *p*-ethylphenol determined.[7] The first-order rate constant *k* was calculated from the concentration of *p*-hydroxyacetophenone and the time of reaction. The rate constants of *p*-ethylphenol and pinacol formation (denoted by k_e and k_p, respectively) were calculated according to the equations

$$k_e = k \times \text{yield \% of } p\text{-ethylphenol}/100$$

$$k_p = k - k_e$$

The effect of zinc amalgam potential on k, k_e, k_p and k_p/k_e is shown in Figs. 4 and 5. As shown in the figures, k, k_e and k_p all increase as the potential drops; k_p increases most remarkably but k_e does less, so that the ratio k_p/k_e increases as the potential drops.

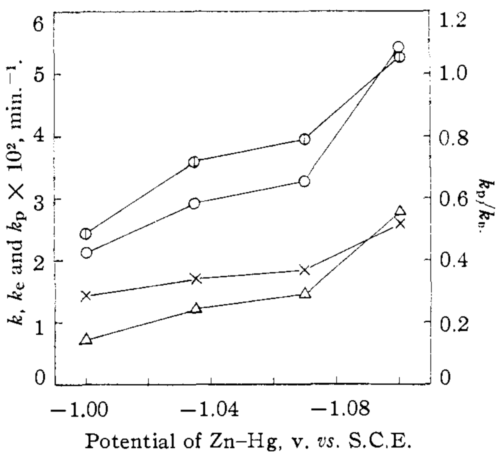

Fig. 4.—The effect of the electrode potential of Zn–Hg on Clemmensen reduction of *p*-hydroxyacetophenone; 1.81 *N* HCl, 0.008% polyvinyl alcohol, 0.020 mole/l. *p*-OHC_6H_4Ac, 2.03% Zn–Hg: ○, k; ×, k_e; △, k_p; ⦶, k_p/k_e.

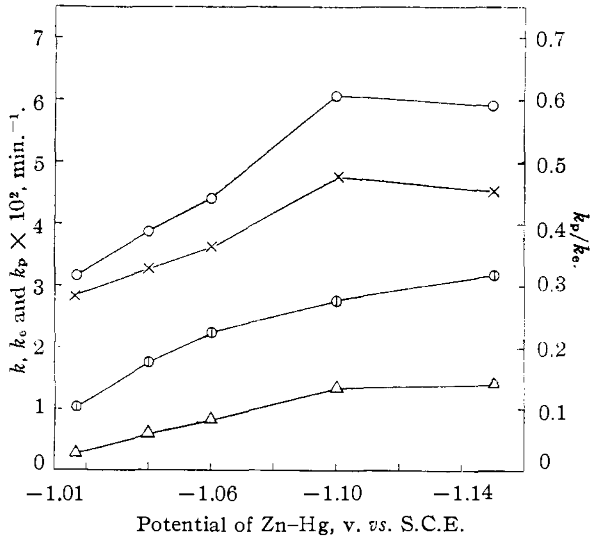

Fig. 5.—The effect of the electrode potential of Zn–Hg on Clemmensen reduction of *p*-hydroxyacetophenone; 2.00 *N* HCl, 0.020 mole/l. *p*-OHC_6H_4Ac, 2.03% Zn–Hg, 60°: ○, k; ×, k_e; △, k_p; ⦶, k_p/k_e.

Discussion

As shown in Table I, the reduction potentials of *p*-substituted acetophenones lie between −1.0 v. (*p*-hydroxyacetophenone) and −0.8 v. (*p*-chloroacetophenone) *vs.* S.C.E. under conditions similar to those of Clemmensen reduction, *i.e.*, 0.6–2 *N* hydrochloric acid, temperature 60°. While the potential of zinc amalgam lies at −0.99– −1.03 v. in the Clemmensen reduction of *p*-hydroxyacetophenone and −1.04– −1.06 v. (S.C.E.) in the case of acetophenone. These values are almost equal to or lower than the reduction potentials of the ketones; this suggests that electrochemical reduction may occur simultaneously with Clemmensen reduction, because the zinc amalgam employed in this work is so dilute (no more than 2%) that the electrode characteristics of the zinc amalgam may be regarded to be the same as that of mercury itself. Electroreduction of acetophenone on a mercury cathode under conditions similar to those of Clemmensen reduction (1.0 *N* hydrochloric acid, 60°, cathode potential −1.05 v. *vs.* S.C.E.) gives one-electron reduction products exclusively, neither styrene nor ethylbenzene being produced. Similarly, electroreduction of *p*-hydroxyacetophenone on a mercury cathode does not give *p*-ethylphenol; one-electron reduction may also occur exclusively in this case. The presence of zinc is essential to the formations of hydrocarbons or unsaturated compounds, while other conditions, *e.g.*, temperature, acidity of the reaction mixture and electrode potential, are secondary in importance in Clemmensen reduction. In contrast, pinacol and the like are formed both on the mercury cathode and on zinc amalgam; the presence of zinc is not necessarily essential to this reaction. So it is reasonable to regard the pinacol formation observed in Clemmensen reduction as a reaction similar to the electrochemical reduction which occurs on a mercury cathode.

Generally speaking, the relation between the formation of pinacol and that of hydrocarbon may be expressed by one of the two mechanisms

$$\begin{tikzcd} \mathrm{RCOR'} \arrow[r, "\mathrm{H}"] & \begin{array}{c}\text{an intermediate}\\ \mathrm{R\dot{C}OHR'}\end{array} \arrow[r, "v_1"'] \arrow[d, "v_2"', "3\mathrm{H}"] & \text{pinacol} \qquad (1) \\ & \mathrm{RCH_2R'} & \end{tikzcd}$$

$$\begin{tikzcd} \mathrm{RCH_2R'} & \mathrm{RCOR'} \arrow[l, "4\mathrm{H}"', "v_4"] \arrow[r, "\mathrm{H}", "v_3"'] & \text{pinacol} \qquad (2) \end{tikzcd}$$

In mechanism 1, carbonyl compound is reduced to an intermediate such as the radical $\mathrm{R\dot{C}OHR'}$ which produces pinacol on one hand and hydrocarbon on the other. The rate of pinacol formation, v_1, may be independent of the zinc amalgam potential because this reaction involves no process of reduction, while v_2, the rate of hydrocarbon formation, may increase with drop in zinc amalgam potential if the process involves electron transfer as the rate-determining step, or it may be independent of the potential if the process involves no electron transfer in the rate-determining step. Consequently the ratio v_1/v_2 may decrease with or may be unaffected by a drop in zinc amalgam potential; v_1/v_2 never increases with a drop in zinc amalgam potential. But this is not the case; as shown in Figs. 3–5, v_1/v_2 increases with the drop of zinc amalgam potential showing that mechanism 1 does not apply to Clemmensen reduction. In mechanism 2, hydrocarbon is produced in a process independent of pinacol formation. No intermediate common to both exists. Kinetic study of the Clemmensen reduction of *p*-hydroxyacetophenone has shown that the potential of zinc amalgam has only a slight effect on the rate. On the other hand, the rate of pinacol formation v_3 may increase with the drop of zinc amalgam potential, because this reaction is supposed to be the same as the electrochemical reduction which occurs on a mercury cathode. So the ratio v_3/v_4 must increase with a drop in zinc amalgam potential; this coincides with the experimental results. As shown in Figs. 4 and 5, the rate of pinacol formation in Clemmensen reduction of *p*-hydroxyacetophenone increases 3.2–4.7-fold as the zinc amalgam potential drops by 100 mv. This corresponds to 12–17% increase for 10 mv. drop of the potential, a reasonable percentage of increase for electrochemical reduction.[10]

It may thus be concluded that the pinacol formation observed in Clemmensen reduction is the same reaction as the electrochemical reduction which occurs on a mercury cathode. An electrochemical mechanism, say

$$\mathrm{RCOR'} + \mathrm{H_3O^+} \rightleftarrows \mathrm{RC^+OHR'} + \mathrm{H_2O}$$
$$\mathrm{RC^+OHR'} + e^- \longrightarrow \mathrm{R\dot{C}OHR'}$$
$$2\mathrm{R\dot{C}OHR'} \longrightarrow \mathrm{RR'COHCOHRR'}^{11}$$

may be given for this reaction.

In contrast, formations of saturated, unsaturated hydrocarbon and alcohol are not in accord with the electrochemical mechanism; these reactions involve the reaction of the carbonyl compound with a *zinc atom* as shown in the mechanism proposed by the author.

However, there remain the following facts unexplained in terms of this theory. First, the potential of zinc amalgam does not affect the rate of Clemmensen reduction entirely; the rate increases 3–5% with 10 mv. drop of the potential. It cannot be fully explained in terms of the author's theory, although the percentage of increase is too small to establish an electrochemical mechanism. Second, in Clemmensen reduction of *p*-hydroxyacetophenone there is considerable difference in the yield of *p*-ethylphenol between the reactions in the presence and absence of polyvinyl alcohol. Considerable hydrogen is also evolved in the presence of polyvinyl alcohol, but not in its absence. The

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(10) The effect of electrode potential on the rate of electrochemical reduction is expressed by the equation

$$k = k_0 e^{-\alpha z EF/RT}$$

(S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 576), where k is the rate constant of the reaction, k_0 a constant, E the potential of the electrode, z the valency of the ion reduced and α a constant between 0 and 1. In the reduction of a neutral molecule, z may be regarded as the number of electrons transferred from the electrode to the molecule at the rate-determining step. Assuming $\alpha = 0.5$, $z = 1$, $E_1 - E_2 = 10$ mv. and $T = 333$°K., we obtain $k_2/k_1 = 1.19$. That is, the rate of the reaction increases by 19% as the potential drops by 10 mv.

(11) I. M. Kolthoff and J. J. Lingane, "Polarography," Vol. 2, 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1952, p. 680.

difference between the two cases is too large to be ascribed to the difference in the potentials of zinc amalgam (the potentials of zinc amalgam in the presence and absence of polyvinyl alcohol are −1.04 v. and −1.01– −1.02 v. *vs.* S.C.E., respectively). It may be due to the surface activity of polyvinyl alcohol. The remarkable difference in the zinc amalgam potential–time relations between two cases supports this view, although a detailed discussion is impossible for the present.

The electrolytic reduction of carbonyl compound on cadmium or lead electrode may proceed by a mechanism similar to that of Clemmensen reduction, the low chemical activity of the metals being compensated by the voltage applied to the electrode.

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[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF OAK RIDGE NATIONAL LABORATORY]

The Effect of Changing Reagent upon Stereoselectivity[1a]

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The stereoselectivities exhibited during several reactions in which a second, adjacent asymmetric carbon atom is formed have been observed. The effect of changing the organometallic reagent from phenyllithium to phenylmagnesium iodide to phenylmagnesium bromide to phenylmagnesium chloride also has been studied in the addition of these reagents to biacetyl or to phenylacetoin. It has been shown that the product *dl*:*meso* ratio is greater than one when either phenyllithium or phenylmagnesium iodide is employed, and less than one when phenylmagnesium bromide or chloride is employed. A similar series of reactions between benzil or methylbenzoin and the corresponding methyl reagents is also reported. All results are discussed in terms of the hypothetical intermediates.

Introduction

Our interest in the stereoselectivity of reactions in which a second, adjacent asymmetric carbon atom is introduced into a molecule stemmed from our need for stereospecifically phenyl-labeled 1,1-diphenyl-2-aminopropanol, successfully prepared[2] through the action of phenylmagnesium bromide upon the stannic chloride complex salt of 2-aminopropiophenone-*phenyl*-C^{14}. During the foregoing study it was demonstrated that the action of *p*-tolylmagnesium bromide upon 2-aminopropiophenone also was highly stereoselective, such that of the two possible diastereomeric products, one predominated over the other by a factor of about 99:1. Although other authors had hinted at such a possibility,[3] we believe the two examples[2] just mentioned provide the first clear-cut evidence that stereoselectivity of such a magnitude is possible.

We have now extended these studies to an investigation of the diastereomer ratios obtained when several α-hydroxy ketones, plus biacetyl and benzil, are treated with organometallic reagents or with lithium aluminum hydride.[4] The results with one monofunctional ketone and one monofunctional aldehyde are also included.

Results

In each of the reactions studied a carbonyl group was converted to an asymmetric center by (a) reduction with lithium aluminum hydride or (b) treatment with an organometallic reagent. In two of the reactions (runs 1 and 2) the carbonyl group was adjacent to an asymmetric center containing no functional groups, whereas in all of the other reactions considered, a carbonyl was either (a) adjacent to an asymmetric center containing a functional group or (b) adjacent to another carbonyl. Each reaction yielded two diastereomeric products. The ratios of diastereomers in all of the experiments were obtained through the carbon-14 dilution method,[5] in which labeled reactants and previously synthesized, unlabeled diluents, or unlabeled reactants and labeled product-diluents were employed.

In Table I are given the results of experiments 1–11, involving primarily the reactions of aryl or aralkyl α-hydroxy ketones with Grignard reagents, or with lithium aluminum hydride. In Tables II–V we have recorded the ratios of diastereomeric (*meso* and *dl*) 2,3-diphenyl-2,3-butanediols produced when several organometallic reagents are allowed to react with (a) biacetyl or phenylacetoin and (b) benzil or methylbenzoin. In Table II results are recorded in which the organometallic reagents employed were methyllithium and phenyllithium. In Table III the data concern methylmagnesium iodide and phenylmagnesium iodide, in Table IV methylmagnesium bromide and phenylmagnesium bromide, and in Table V methylmagnesium chloride and phenylmagnesium chloride.

Finally, we carried out one experiment not given in Tables I–V, namely, the addition of carbon-14-labeled phenylacetoin to diphenylmagnesium. The results (see Experimental section) show that *meso*-2,3-diphenyl-2,3-butanediol was formed in 13.0% yield, the *dl*-isomer in 28.4% yield, and that the *meso*: *dl* ratio is thus 1:2.18.

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[1] (a) This paper is based upon work performed at Oak Ridge National Laboratory, which is operated for the Atomic Energy Commission by Union Carbide Corporation. (b) ORINS research participant from Louisiana State University in New Orleans, June–September, 1959. (c) Participant of the United Nations International Atomic Energy Agency from Bangkok, Thailand, September, 1959, to January, 1960.

[2] B. M. Benjamin, H. J. Schaeffer and C. J. Collins, THIS JOURNAL, **79**, 6160 (1957).

[3] See, for example, A. McKenzie and H. Wren, *J. Chem. Soc.*, **97**, 473 (1910).

[4] A preliminary report of these results was given at the meeting of the American Chemical Society, San Francisco, Cal., April 13, 1958. See page 11-N of the Abstracts, Division of Organic Chemistry.

[5] See, for example, R. H. Mayor and C. J. Collins, THIS JOURNAL, **73**, 471 (1951); C. J. Collins, *ibid.*, **77**, 5517 (1955); H. J. Schaeffer and C. J. Collins, *ibid.*, **78**, 124 (1956); and B. M. Benjamin and C. J. Collins, *ibid.*, **78**, 4952 (1956).