Model Reactions for the Metabolism of Thyroxine. II. Reaction of Thyropropionic Acid with Hydroxyl Radical[1]

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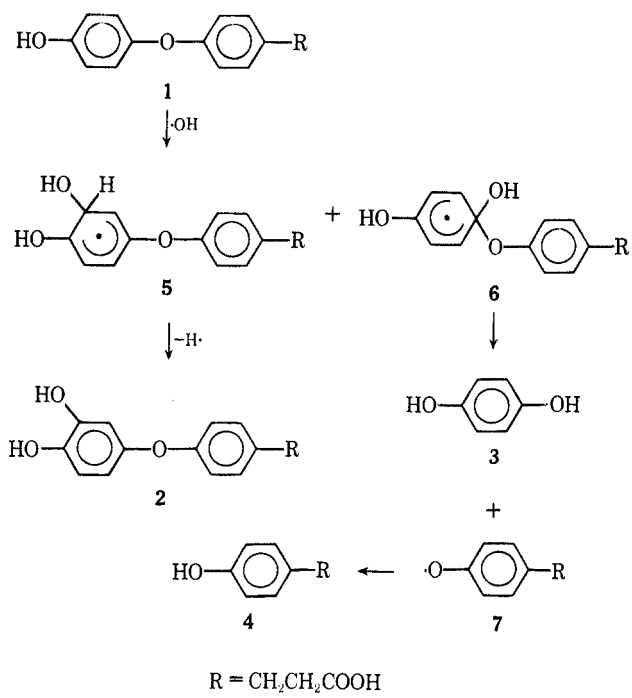
The rupture of the diphenyl ether linkage in thyronines has been considered to be one of the possible metabolic pathways of thyronines,[2] although Pittman and Chambers[3] reported that in the rat the major excretion products arising from administrated thyroxine still had an intact diphenyl ether structure. It has been shown in the previous papers that the rupture of the diphenyl ether linkage takes place easily by autoxidation of 3′-hydroxythyropropionic acid[4] and by autoxidation of 3′,5′-unsubstituted thyronines and their analogs in the presence of *tert*-butoxide in dimethyl sulfoxide.[5] In the course of studies on the hydroxylation of thyropropionic acid (**1**) for the preparation of 3′-hydroxythyropropionic acid (**2**), we found a direct cleavage of the diphenyl ether linkage of **1**.



R = CH_2CH_2COOH

thyropropionic acid (**2**) and the rupture of the diphenyl ether linkage giving hydroquinone (**3**) and phloretic acid (**4**) occur simultaneously. While the total yield of **3** and **4** increased with increasing amount of hydrogen peroxide, the optimum yield of **2** was obtained at limited concentrations of hydrogen peroxide. Photolysis without hydrogen peroxide at 0° led to the recovery of the starting material, but at room temperature a complex mixture was obtained.

TABLE I

PHOTOLYSIS OF THYROPROPIONIC ACID AND HYDROGEN PEROXIDE[a]

Run	1, mmol	H_2O_2, mmol	Initial pH	Final pH	Decomposed H_2O_2, mmol	Recovered 1, %	Yields of products, %[b] 2	3	4
1	2	50.5	8.8	6.5	2.6	20	33	15	6
2	2	33.6	9.0	7.5	1.9	28	38	11	4
3	2	16.8	9.2	8.5	1.8	31	44	12	1.5
4	2	5.05	9.1	9.1	0.4	51	20	7	0
5	2	0	9.2	9.2		98	0	0	0

[a] See Experimental Section. [b] Yields were based on the amount of 1 consumed.

Omura and Matsuura have reported the hydroxylation of phenols with the hydroxyl radical generated by the photodecomposition of hydrogen peroxide in aqueous media and also in acetonitrile.[6] They have shown that the hydroxylation occurs at the ortho and para positions but not at the meta position and that a methoxy group at the para position with respect to the phenolic hydroxyl is replaced by a hydroxy group in addition to simultaneous ortho hydroxylation.

This method was applied to thyropropionic acid (**1**). A solution of **1** and various amounts of hydrogen peroxide in aqueous sodium hydroxide was irradiated with a low-pressure mercury lamp of Vycor housing under bubbling nitrogen at 0°. The products were analyzed by vpc. The results summarized in Table I showed that hydroxylation at the 3′ position giving 3′-hydroxy-

The formation of **2**, **3**, and **4** can be rationalized by a scheme similar to that proposed earlier.[6] Of two cyclohexadienyl radicals **5** and **6**, which are formed by the addition of hydroxyl radicals to **1**, **5** loses a hydrogen atom to give **2**, and **6** cleaves to **3** and a phenoxy radical **7** which then abstracts hydrogen to give **4**.

The present reaction provides nonenzymic models for the direct cleavage of the diphenyl ether linkage of thyronines without 3′ hydroxylation in their metabolic pathways and also for the hydroxylation of thyronines to 3′-hydroxythyronines, in addition to the previous model in which the hydroxylation of thyronine at the 3′ position was carried out with the ferrous ion–ascorbic acid–oxygen system.[7]

Experimental Section

General Procedure.—To a solution of 516 mg (2 mmol) of thyropropionic acid[4] in 25 ml of 0.1 *N* sodium hydroxide was added the given amount of 30% hydrogen peroxide, and the

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mixture was diluted with water to a total volume of 100 ml. The solution was internally irradiated with a low-pressure mercury lamp (*ca.* 10 W) of Vycor housing, under bubbling nitrogen, at 0° for 5 hr. An aliquot (10 ml) was subjected to analysis for hydrogen peroxide and the remaining portion was treated with 6 g of sodium bisulfite under ice cooling. The reduced mixture was extracted with ether (total volume, 350 ml). The ethereal layer was washed with a small volume of water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was analyzed by vpc. The products were identified by a comparison with authentic samples.

Analysis.—Hydrogen peroxide was analyzed by iodometry. For vpc analysis, the residue from the above ether extract was mixed with 50 mg of diphenyl (internal standard) and then the mixture was treated with an excess of *N,O*-bis(trimethylsilyl)-acetamide in a small volume of absolute benzene. The silylated mixture was analyzed by vpc using a 25% silicone DC 550-on-celite column (1100 × 3 mm).

Registry No.—1, 500-81-2; hydroxyl radical, 3352-57-6.

Electrochemical Preparation of Highly Strained Hydrocarbons. IV. Controlled Potential Electrolysis

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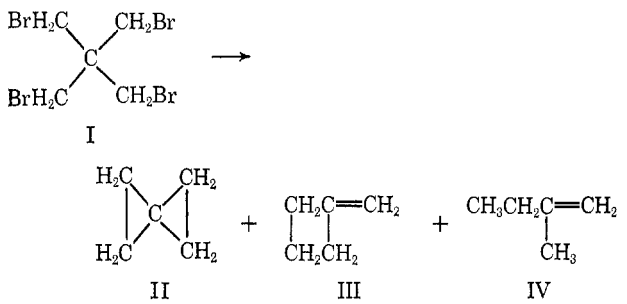
Previous papers in this series[1-3] reported the use of electrolysis as a tool for the preparation of small-ring compounds such as cyclopropane, cyclobutane, bicyclobutane, and spiropentane from the reduction of appropriate α,ω-dihalides. We would now like to describe an important advantage that this technique has, particularly under controlled potential electrolysis (CPE), over conventional reducing agents in organic synthesis.

The reduction of 1,3-dibromobis(bromomethyl)propane (I) by conventional reducing agents has been described[4-6] as forming a variety of products which included the compounds shown below. Under uncon-



I II III IV

trolled potential electrolysis, however, compound I was reduced to give spiropentane in high yield.[7]

The formation of compounds II–IV from I under uncontrolled potential electrolysis or by conventional reducing agents presumably takes place through a common intermediate, namely 1,1-bromomethylcyclopropane (V). Subsequent reduction of this intermediate under the above reaction conditions has not allowed its isolation. Thus, the electrolysis of I under controlled potential was investigated to isolate the presumed intermediate V and to compare the utility of CPE with conventional reduction methods in organic synthesis.

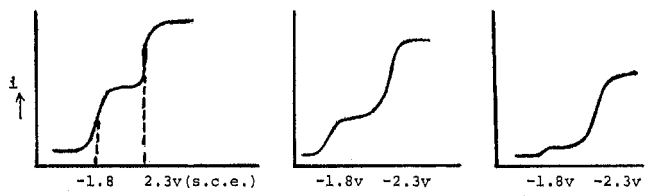
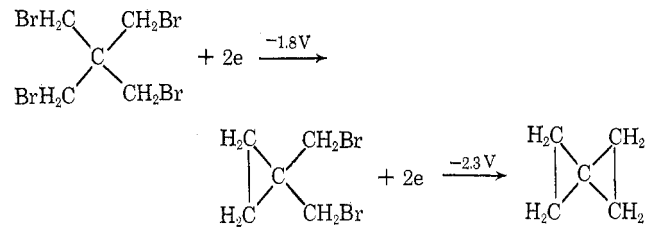


Figure 1.—Polarographic behavior of the cathode solution during electrolysis at a cathode potential of −1.2 to −1.4 V (sce).

It was the polarographic behavior of the tetrabromide I (two 2-electron waves at −1.8 and −2.3 V) which led us to believe that its reduction proceeds in a stepwise manner to yield spiropentane through the intermediate V. It was thus concluded that if



the reduction of I is carried out at a controlled potential the isolation of V would be possible. This was indeed verified experimentally as the reduction of I at a cathode potential of −1.2 to −1.4 V (sce) yielded compound V and the reduction of V at a potential of −2.2 V (sce) yielded spiropentane. Furthermore, the course of the reduction was easily followed by examining the polarographic behavior of the cathode solution in the macroscale reduction. Thus, in the formation of compound V, the intensity of the polarographic wave with $E_{1/2}$ = −1.8 V (sce) decreased with time while that of the wave with $E_{1/2}$ = −2.3 V did not change (Figure 1). Compound V exhibits one 2-electron polarographic wave with $E_{1/2}$ at −1.8 V (sce). Thus, its reduction was easily followed by observing the decrease of the intensity of this wave with time.

The isolation of the previously undetected intermediate V from the reduction of I demonstrates the merit of CPE in conjunction with polarography. It is believed that CPE represents a powerful tool for the elucidation of certain organic reactions as well as the synthesis of organic compounds. The synthesis of V by conventional methods[8] involves four steps while the current method requires only one.

Experimental Section

Polarographic Studies.—All polarograms were measured on a Beckman electroscan-30. A saturated calomel electrode (sce) was used as the reference. A solution of 0.05 *N* n-Bu_4NClO_4

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