matically than did the blood levels that absorption and excretion of phenylephrine from the hydrochloride show very wide individual variations, whereas the tannate complex sustained-release form showed an unusual degree of consistency of performance.

SUMMARY

Tritium-labeled phenylephrine hydrochloride and tannate were prepared and incorporated into ordinary and sustained-release type dosage forms, respectively.

Blood levels of tritium radioactivity in humans following oral ingestion of the ordinary hydrochloride dosage form followed a characteristic pattern of rapid rise and fall; blood levels following administration of a tannate complex dosage form rose more slowly but appeared to be more sustained.

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Electrochemical Oxidation of Chlorpromazine Hydrochloride

By F. HENRY MERKLE and CLARENCE A. DISCHER

The electrolytic oxidation of chlorpromazine hydrochloride has been studied. Controlled potential coulometry has shown the chlorpromazine undergoes a two-electron oxidation in dilute aqueous acid media. In 9 *N* sulfuric acid two successive one-electron oxidations, involving a stable semiquinone free radical intermediate, are identifiable. Polarographic studies with a rotating platinum electrode confirm the occurrence of two separate one-electron oxidation steps in 9 *N* sulfuric acid. The coulometrically determined *n* values are in agreement with these observations. Reaction mechanisms are proposed for the electrolytic oxidation of chlorpromazine under various conditions of acidity. Spectral absorbance curves are presented as supporting evidence for the indicated reaction mechanisms.

THE OXIDATION of chlorpromazine hydrochloride[1] by cerium (IV), iron (III), permanganate, and hydrogen peroxide as well as by photo-irradiation has been reported (1–3). It has also been shown that the intermediate species in the oxidation of chlorpromazine exists as a free radical (4). More recently, the existence of stable semiquinone free radicals of chlorpromazine and other *N*-substituted phenothiazine derivatives has been demonostrated (5). However, because of the inherent difficulties in the quantitative determination of the free radical species, their study has been restricted considerably.

This study was undertaken to establish an oxidation mechanism for chlorpromazine hydrochloride in aqueous media. Since chlorpromazine and its oxidation products are electrolytically active, controlled-potential coulometry offered a direct approach for this study. The oxidation at a platinum anode has proved to be an extremely useful method for the production of the intermediate free radical species. Moreover, this study indicates the possible use of controlled-potential coulometry as a quantitative analytical technique for chlorpromazine and its oxidized forms in the presence of one another.

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[1] Chlorpromazine hydrochloride and chlorpromazine 5-oxide were supplied by Smith Kline and French Laboratories, Philadelphia, Pa.

INSTRUMENTATION

An electronic controlled-potential coulometric titrator, model Q-2005 ORNL, was used to perform the electrolyses (6). Oxidations were performed in a cell designed to accept a cylindrical wire mesh rotating platinum electrode (1 in. diameter × 2 in. height) and approximately 100 ml. of solution. The reference (S.C.E.) and auxiliary (working cathode) electrodes were separated from the sample solution by agar plugs and fritted glass diaphragms. A triplet vacuum tube voltmeter, model 805, with a 7-in. scale served as the readout device.[2] Polarograms were obtained on the Sargent model XXI recording polarograph. An H-type cell was used with a rotating platinum microelectrode. A saturated calomel reference electrode was separated from the sample portion by an agar plug and fritted-glass diaphragm.

PROCEDURE AND RESULTS

Controlled Potential Data.—When chlorpromazine hydrochloride is electrolyzed at a potential of approximately +0.70 v. *versus* S.C.E. in 1 *N* sulfuric acid under an atmosphere of nitrogen, the solution gradually assumes a deep red. As the electrolysis is

[2] In the latter stages of this study readout voltages were measured with a Non-Linear Systems model 484 A digital voltmeter.

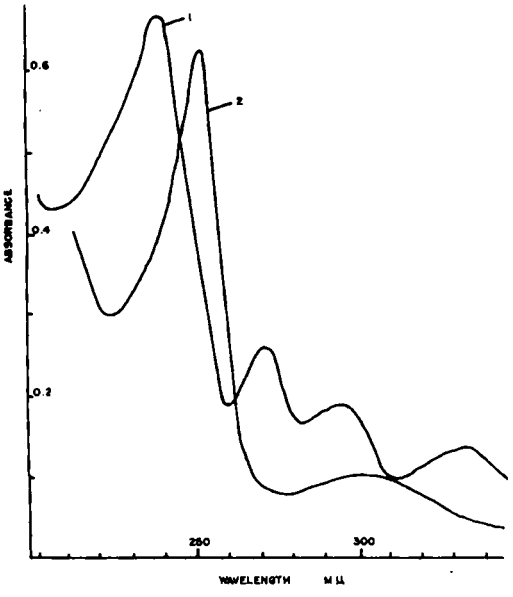

Fig. 1.—Ultraviolet spectral absorbance curves in 1 *N* sulfuric acid. Key: curve 1, chlorpromazine 5-oxide generated electrolytically from chlorpromazine; curve 2, chlorpromazine hydrochloride.

continued beyond this point, the solution becomes progressively lighter. When the oxidation is complete, as indicated by a negligible background current, the solution is again colorless. The final colorless oxidation product was shown to be chlorpromazine 5-oxide by comparison of its ultraviolet absorption spectrum with that of the pure material, Fig. 1. Equation 1 depicts a proposed oxidation of chlorpromazine to chlorpromazine 5-oxide *via* the colored free radical intermediate

$$\text{CLP} \rightarrow \text{CLP}^* \rightarrow \text{CLP-O} + 2e^- \quad \text{(Eq. 1)}$$

where CLP represents chlorpromazine, CLP-O represents chlorpromazine 5-oxide, and CLP* represents the colored free radical intermediate. The current-time integrals for a series of oxidations indicates an *n* value of 2.0, Table I.

When the electrolysis is interrupted at some point before completion and allowed to stand for 1000 to 2000 seconds under a nitrogen atmosphere, the red slowly fades. However, if the electrolysis is resumed, the red again intensifies. This process could be repeated many times during the course of a single electrolysis. The initial electrolysis current observed after standing is significantly larger than the current observed at the time when the electrolysis was interrupted.

These observations indicate that the unstable red free radical intermediate undergoes disproportionation, producing an electrolytically oxidizible species. Equation 2 is proposed for this disproportionation

$$\underset{\text{(dark red)}}{2\,\text{CLP}^*} \rightarrow \underset{\text{(colorless)}}{\text{CLP}} + \underset{\text{(colorless)}}{\text{CLP-O}} \quad \text{(Eq. 2)}$$

The changes observed in the ultraviolet spectrum of the electrolytically generated free radical support this reaction. Samples of chlorpromazine were oxidized electrolytically to maximum color (a dark red solution). The solution was then allowed to stand under nitrogen until the color faded. The ultraviolet spectrum of this solution was identical to that of an equimolar mixture of chlorpromazine and chlorpromazine 5-oxide, Fig. 2. Moreover, comparison of the ultraviolet spectra of the electrolytically generated free radical and that obtained using crystalline free radical, prepared as described in a previous report (7), indicate they are the same species.

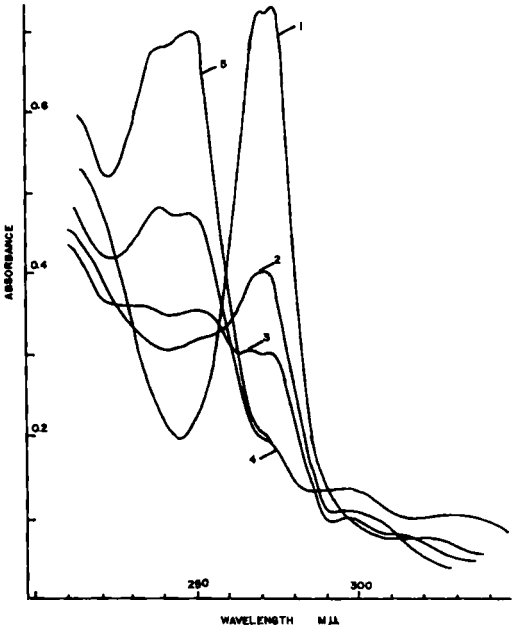

Fig. 2.—Ultraviolet spectra demonstrating the free radical disproportionation in 1 *N* sulfuric acid of the electrolytically generated product. Key: curve 1, spectrum immediately after generation; curve 2, spectrum after 15 minutes standing; curve 3, spectrum after 1 hour standing; curve 4, spectrum after 5 hours standing; curve 5, spectral curve of a synthetic equimolar mixture of chlorpromazine and chlorpromazine 5-oxide.

TABLE I.—*n* VALUES OBTAINED BY CONTROLLED-POTENTIAL ELECTROLYSES

Sample	Moles Taken, $\times 10^{-4}$	Supporting Electrolyte, H_2SO_4	Conditions	E *vs.* S.C.E.	*n* Values
CLP HCl[a]	1.407	1 *N*	Oxidation[c]	+0.7	1.96
CLP HCl[a]	1.407	9 *N*	Oxidation[c]	+0.5	0.98
CLP*	1.407	9 *N*	Oxidation[c]	+1.0	1.00
CLP HCl[a]	1.407	9 *N*	Oxidation[c]	+1.0	2.00
CLP*	1.407	9 *N*	Reduction[c]	+0.2	0.98
CLP-O HCl[b]	1.346	1 *N*	Reduction[d]	−1.0	1.92

[a] Based on a molecular weight of 355.33. [b] Based on a molecular weight of 371.33. [c] Rotating platinum gauze electrode. [d] Mercury pool electrode.

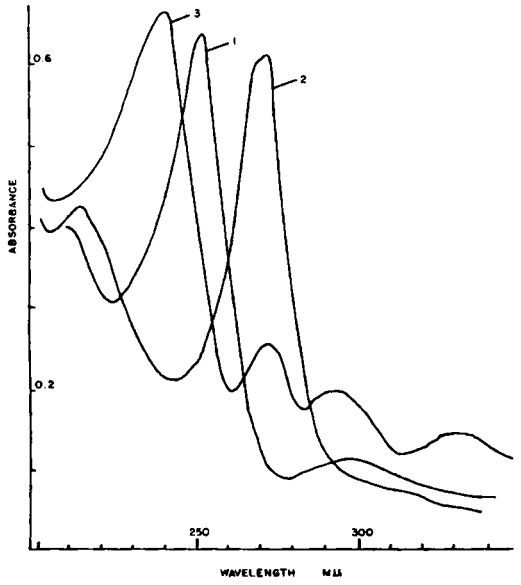

Fig. 3.—The ultraviolet spectral absorbance curves in 9 *N* sulfuric acid. Key: curve 1, chlorpromazine hydrochloride; curve 2, electrolytically produced free radical; curve 3, electrolytically produced chlorpromazine 5-oxide.

The complicating disproportionation of the free radical intermediate could be repressed by using 9 *N* sulfuric acid as the supporting electrolyte. A one-electron oxidation step could be isolated when electrolyzed at a potential of +0.50 v. *versus* S.C.E. (see Eq. 3). If after complete oxidation to the free

$$CLP \rightarrow CLP^* + e^- \qquad \text{(Eq. 3)}$$

radical, as indicated by negligible residual current, the potential of the working electrode was increased to approximately +1.0 v. *versus* S.C.E., the oxidation of the free radical species proceeds by a second one-electron step to the corresponding 5-oxide (see Eq. 4). If instead the potential of the working

$$CLP^* \rightarrow CLP\text{-}O + e^- \qquad \text{(Eq. 4)}$$

platinum electrode was lowered to approximately +0.2 v. *versus* S.C.E., the complete reduction of the free radical (CLP*) was possible (see Eq. 5).

$$CLP^* + e^- \rightarrow CLP \qquad \text{(Eq. 5)}$$

The coulometrically determined *n* values for the reactions, represented by Eqs. 3 and 4, show that each is a single-electron oxidation step, while the reaction represented by Eq. 5 indicates a one-electron reduction (Table 1). Ultraviolet spectral absorbance curves confirm the selective oxidation or reduction of the electrolytically produced free radical to chlorpromazine 5-oxide and chlorpromazine, respectively (Fig. 3).

In contrast to the two single oxidation steps occurring in 9 *N* sulfuric acid, the over-all reaction taking place in dilute aqueous acid media (1 *N* sulfuric acid) may now be represented

$$2\,CLP \xrightarrow{+0.7\text{ v.}} 2\,CLP^* + 2e^- \qquad \text{(Eq. 6)}$$

$$CLP \xleftarrow{\text{(spontaneous)}} \text{(from } 2\,CLP^*\text{)} \rightarrow CLP\text{-}O$$

The free radical, as produced by oxidation, undergoes spontaneous disproportionation to form chlorpromazine and chlorpromazine 5-oxide. This explains the *n* value of 2, observed when the electrolysis is conducted under these conditions.

Polarographic Data.—To demonstrate further the effect of the supporting electrolyte on the oxidation potentials of CLP and CLP*, polarographic studies were undertaken using a rotating platinum microelectrode. Polarograms obtained using 1 *N* sulfuric acid as the supporting electrolyte showed a single wave, with a $E_{1/2}$ of +0.6 v. *versus* S.C.E. When 9 *N* sulfuric acid was used, there appeared to be a separation of the single wave into two waves, with $E_{1/2}$ values of +0.37 and +0.95 v., respectively. The proposed reaction for the former is given by Eq. 3. That for the latter, somewhat less informative due to background current, is indicated by Eq. 4. The shift in half-wave potentials as a function of the supporting electrolyte is shown in Fig. 4.

Small additions of the crystalline free radical to solutions of chlorpromazine in 9 *N* sulfuric acid resulted in the appearance of a reduction wave with a $E_{1/2}$ of approximately +0.3 v. *versus* S.C.E. The second oxidation wave was more clearly defined as

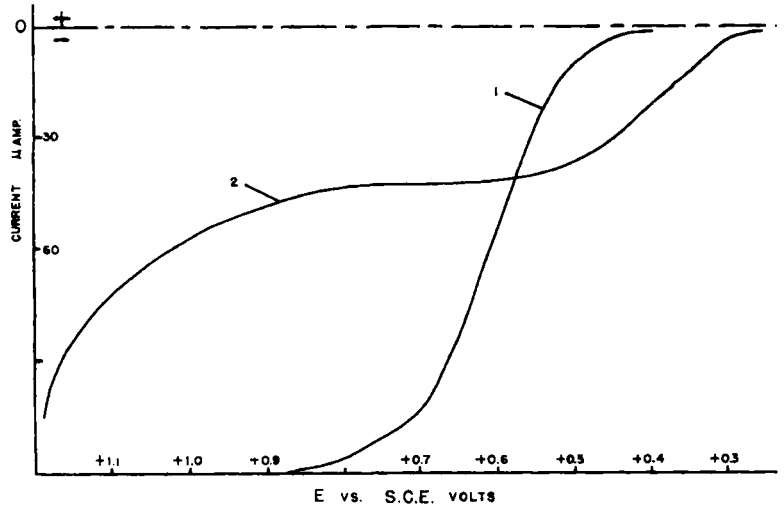

Fig. 4.—Polarograms obtained by the oxidation of chlorpromazine. Key: curve 1, 1 *N* sulfuric acid supporting electrolyte; curve 2, 9 *N* sulfuric acid supporting electrolyte.

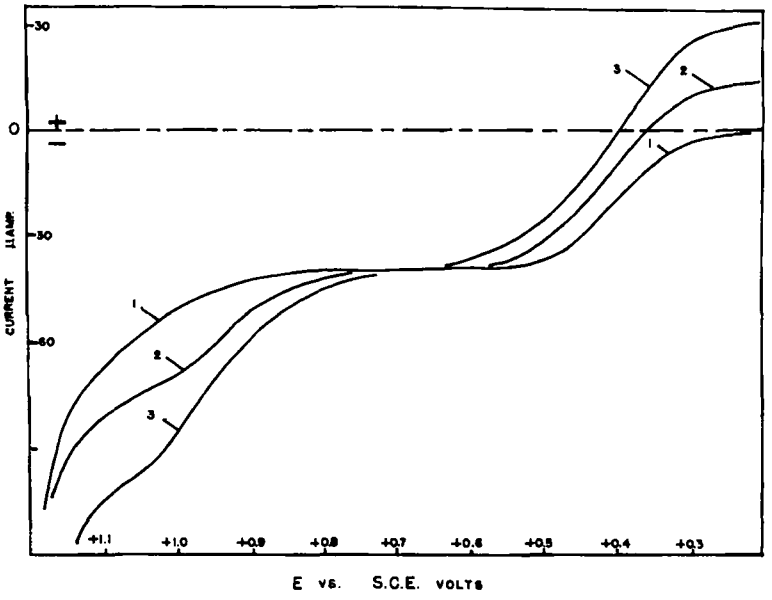

Fig. 5.—Polarograms demonstrating the effect of small additions of the solid free radical of chlorpromazine to the polarographic cell using 9 *N* sulfuric acid as the supporting electrolyte. Key: curve 1, no solid free radical added; curve 2, first addition of solid free radical; curve 3, second addition of solid free radical.

the concentration of added free radical was increased. This confirmed that the second wave was due to the oxidation of the free radical intermediate. The effect of addition of crystalline free radical is shown in Fig. 5.

SUMMARY

The coulometric oxidation of chlorpromazine in dilute aqueous acid solution was shown to proceed through a single-electron oxidation step to a colored free radical. This red free radical was shown to disproportionate rapidly to form chlorpromazine and chlorpromazine 5-oxide. This fact was verified by observing the changes in the ultraviolet absorption spectrum within a given period of time.

When chlorpromazine was electrooxidized in 9 *N* sulfuric acid, the free radical intermediate stabilized. Under these conditions it was possible to oxidize selectively chlorpromazine and chlorpromazine free radical, depending on the oxidation potentials selected. The reduction of chlorpromazine free radical was accomplished with equal facility.

Coulometrically determined *n* values are in complete agreement with the proposed oxidation-reduction reactions. Polarographic data demonstrated the effect of 9 *N* sulfuric acid in stabilizing the free radical intermediate, thereby enabling the selective oxidation or reduction of the species present.

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