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*Keyphrases*

Dodecatriethylammonium bromide—synthesis
Tetradecatriethylammonium bromide—synthesis
Quaternary ammonium compounds chain length—toxicity effect
Surface tension-concentration curves—purity determination
$LD_{50}$ values—quaternary ammonium compounds

# Determination of the pKa′ Value for 5,5-Diphenylhydantoin

By SURAJ P. AGARWAL and MARTIN I. BLAKE

**The pKa′ value for diphenylhydantoin was found to be 8.31 by ultraviolet spectrophotometry and 8.33 by potentiometric titration.**

A NONAQUEOUS titrimetric procedure for determining combinations of phenobarbital and sodium diphenylhydantoin was recently reported by Agarwal and Blake (1). In considering the feasibility of a differentiating titration for mixtures of phenobarbital and diphenylhydantoin, it was apparent that the pKa value for the latter component had not been reported in the literature. Preliminary studies (2) with a variety of solvents, titrants, and electrode systems indicated that a differentiating titration was not possible. It was concluded that the pKa values for the two components were probably too close together to permit an effective differentiating nonaqueous titration. This study was undertaken for the purpose of establishing the pKa′ for diphenylhydantoin. The spectrophotometric procedure described by Albert and Sergeant (3) was applied in this investigation. The pKa′ was also determined potentiometrically.

## EXPERIMENTAL

**Apparatus**—All spectrophotometric measurements were made with a Carl Zeiss model PMQII spectrophotometer, equipped with matched 1.0-cm. silica cells. Potentiometric titrations were performed with a Beckman pH meter (Expandomatic) model 76A equipped with a glass electrode (Beckman No. 41263) and a calomel electrode (Beckman No. 39170). A 5-ml. buret (Kimax) graduated in 0.01 ml. was used for delivery of the titrant.

**Reagents and Solutions**—Reference standard diphenylhydantoin and sodium diphenylhydantoin were supplied by Parke-Davis and Co. Tris-(hydroxymethyl)aminomethane (THAM), primary standard grade, was obtained from Fisher Scientific Co. Buffer solutions were prepared by combining appropriate volumes of 1.0 *N* HCl and 0.01 *M* THAM solution to give the desired pH. All other chemicals were reagent grade.

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**Spectrophotometric Procedure**—The absorption spectra of diphenylhydantoin were obtained in 0.01 *N* sodium hydroxide and in 0.01 *N* hydrochloric acid. Since the maximum difference in absorption for the ionized and unionized species occurs at 236 mμ, this was the wavelength selected for all absorbance measurements. The spectra are shown in Fig. 1.

A stock solution of diphenylhydantoin (0.01 *M*) in alcohol was prepared. One milliliter of this solution was transferred by pipet to each of seven 100-ml. volumetric flasks and the volume was brought to the mark with THAM buffer solutions having pH values of 7.7, 7.9, 8.1, 8.3, 8.5, 8.7, and 8.9, respectively. A similar series of solutions was prepared which contained 1 ml. of alcohol and the corresponding buffer solution. These served as blanks for the absorbance measurements. The average ionic strength was 0.005 (0.002–0.008).

**Potentiometric Procedure**—A series of stock solutions, 0.01 *M* in sodium diphenylhydantoin, was prepared in aqueous alcohol solution containing 20, 30, 40, and 50% alcohol by volume, respectively. Fifty milliliters of each solution was titrated potentiometrically with 1 *N* hydrochloric acid. The ionic strength was 0.01.

## DISCUSSION

The pKa′ of diphenylhydantoin was determined spectrophotometrically by the procedure described by Albert and Sergeant (3). The absorbance of the

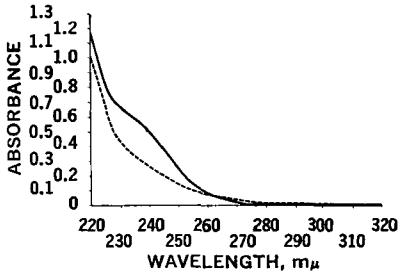


*Fig. 1—Ultraviolet absorption spectra of 5,5-diphenylhydantoin in 0.01* N *HCl, solid line; and in 0.01* N *NaOH, broken line.*

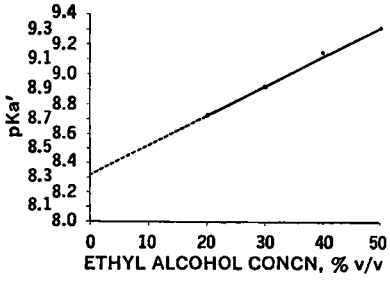


*Fig. 2—The pKa' of 5,5-diphenylhydantoin in hydroalcoholic medium plotted against the concentration of ethyl alcohol.*

ionized and unionized forms of diphenylhydantoin was determined. The absorbance values were also obtained for a series of solutions varying in pH, but still in the general region where the pH approximates the pKa' value, at which point the ionized and unionized species are equal in concentration. The pKa' was calculated by the expression,

$$pKa' = pH + \log \frac{A - B}{B - C}$$

where $A$ = absorbance of diphenylhydantoin in 0.01 $N$ NaOH, $B$ = absorbance of diphenylhydantoin in buffered solution, $C$ = absorbance of diphenylhydantoin in 0.01 $N$ HCl. For the 7 buffers used in this study an average pKa' of 8.31 ± 0.04 ($SD$) was obtained.

The pKa' was also determined potentiometrically by titrating sodium diphenylhydantoin with standard hydrochloric acid. Since diphenylhydantoin is soluble in alcohol but not in water, and the reverse is true for the sodium salt, a series of titrations was performed in solvent mixtures containing varying concentrations of alcohol in water. The average pKa' value was determined at each alcohol level from the data obtained for at least five points in each titration curve using the expression,

$$pKa' = pH - \log \frac{(salt)}{(acid)}$$

The pKa' in water (0% alcohol) was obtained by plotting the average pKa' values *versus* alcohol concentration. This procedure was first reported by Mizutani (4). Figure 2 shows a plot of pKa' *versus* alcohol concentration. Extrapolation to 0% alcohol content yields a pKa' value of 8.33 which is in good agreement with the spectrophotometric value.

The pKa' values for hydantoin and 5,5-dimethylhydantoin have been reported (5) as 9.12 and 9.19, respectively. Butler (6) reported a pKa' value of 8.5 for 5-ethyl-5-phenylhydantoin. One would expect the 5,5-diphenyl derivative to be more acidic (lower pKa) than the 5-ethyl-5-phenyl derivative. This was demonstrated in the present report by spectrophotometric and potentiometric methods.

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*Keyphrases*

5,5-Diphenylhydantoin—pKa' value determination
UV spectrophotometry—procedure
Potentiometric titration—procedure

# Chemistry and Biochemistry of Polyvalent Iodine Compounds VII. The ARP (Apparent Reduction Potential) of 1,3-Dihydro-1-hydroxo-3-oxo-1,2-benziodoxole

By A. EISENMANN* and W. WOLF

**Iodoso compounds are strong oxidizing agents. In order to define an order of magnitude for this oxidizing action, the ARP (apparent reduction potential) of 1,3-dihydro-1-hydroxy-3-oxo-1,2-benziodoxole has been measured using the method of Conant and Lutz. At pH 7.4, the ARP of benziodoxole was 0.327 ± 0.005 v., indicating that this heterocyclic iodine derivative, under the conditions used, is approximately as strong an oxidizing agent as ceric ion. The usefulness of this technique is discussed.**

THE KINETICS (1) and the mechanism (2) of the reduction of 1,3-dihydro-1-hydroxy-3-oxo-1,2-benziodoxole ($I$) to *o*-iodobenzoic acid have been studied in this laboratory. This process is irreversible, and thus, a normal oxidation-reduction potential cannot be measured. As it had been suggested that the difference between the two classes of trivalent iodine (iodoso, iodonium) is more one of degree and rate of reaction than of nature (3), it was of

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