Effect of Inert Tablet Ingredients on Drug Absorption I

Effect of Polyethylene Glycol 4000 on the Intestinal Absorption of Four Barbiturates

By PARVINDER SINGH*, J. KEITH GUILLORY†, THEODORE D. SOKOLOSKI‡, LESLIE Z. BENET, and V. N. BHATIA

The effect of polyethylene glycol 4000 on dissolution and absorption rates of 4 barbiturates has been studied. It has been shown that in the case of phenobarbital, which formed a complex of reduced solubility with polyethylene glycol 4000, the dissolution and intestinal absorption rates of the drug were reduced. The other 3 barbiturates did not interact with the polyethylene glycol 4000, and its presence did not affect their dissolution and absorption rates. The reduction in the absorption rate of the phenobarbital was closely related to the reduced dissolution rate of the complex, although only the phenobarbital was shown to be absorbed through the gut. It was also shown that the absorption rate of the phenobarbital from the complex was independent of the degree of dissociation of the latter in the mucosal fluid. An hypothesis is proposed to explain that phenomenon.

IN THE PREPARATION of medicinal tablets, a number of so-called inert ingredients are used as adjuvants. These adjuvants are used as binding agents, disintegrators, lubricants, diluents, or coating materials. Since the adjuvants often constitute a considerable portion of a tablet (in some cases as much as 30% or more), there is good reason to believe that they might influence drug availability and absorption in those instances where drug–adjuvant interactions occur. This point of view has been expressed in numerous reports (1, 2). More recently, studies have been concerned specifically with quantifying the effects of selected complexations on drug absorption rates (3, 4).

The objectives of this study are to determine the influence of 8 selected adjuvants on a group of selected drugs with respect to (*a*) the occurrence of interactions between the adjuvants and the drugs, (*b*) the effect of interactions on the dissolution rates of the drugs, and (*c*) the effect of the interactions on the absorption rate of the drugs.

The adjuvants selected for this study have been picked because they are among the ones frequently used in the manufacture of tablets. They are: polyethylene glycols, sodium carboxymethylcellulose, sodium alginate, cation-exchange resins, starch, acacia, cellulose acetate phthalate, and polyvinylpyrrolidone.

Twelve drugs have been chosen for this study. These drugs have been selected because either they or closely related chemicals are frequently used in tablet form, and because, as a group, they provide a wide range of physical properties including solubility, partition coefficient, and pK useful for this study. The 12 drugs are: barbital, phenobarbital, pentobarbital, barbituric acid, salicylamide, salicylic acid, benzyl penicillin, caffeine, acetanilide, phenacetin, sulfadiazine, and sulfathiazole.

This first report deals with the descriptions of the methods and procedures as well as the study of the effect of the adjuvant, polyethylene glycol 4000 (hereafter referred to as PEG 4000), on the dissolution and absorption of 4 barbiturates: barbital, phenobarbital, pentobarbital, and barbituric acid. In general, the procedure consisted of the following steps. (*a*) Determination of any complex formation between the drugs and the adjuvant by the phase solubility method. (*b*) Determination of the dissolution rates of pure drug tablets in pH 5.3 buffer, both in the presence and in the absence of the adjuvant. (With phenobarbital where an insoluble complex could be isolated, the dissolution rate of the pure complex tablets was studied.) (*c*) Determination of the absorption rate of the drug by the "everted intestinal sac" technique, both in the presence and in the absence of the adjuvant. (In the case of phenobarbital where an insoluble complex could be isolated, the absorption rate of the complex was studied.)

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Abstracted in part from a thesis submitted by Parvinder Singh in partial fulfillment of Master of Science degree requirements.
Present address: College of Pharmacy, University of Michigan, Ann Arbor.
* Honorable Mention, Richardson-Lunsford Award, 1965.
† Present address: College of Pharmacy, University of Iowa, Iowa City.
‡ Present address: College of Pharmacy, Ohio State University, Columbus.

EXPERIMENTAL

Reagents.—Recrystallized phenobarbital U.S.P., m.p. 175–176°; recrystallized pentobarbital U.S.P. m.p., 128–129°, (prepared from sodium pentobarbital); recrystallized barbital N.F., m.p. 188–190°; recrystallized barbituric acid (Eastman Kodak); PEG 4000 (Union Carbide Chemicals Co.); isotonic phosphate buffer,[1] pH 5.3; isotonic phosphate buffer (5), pH 7.4; sodium borate buffer (0.05 *M*), pH 9.1.

Complexation.—All interaction studies between PEG 4000 and the barbiturates under consideration were carried out in a manner similar to that used by Higuchi and Lach (6). An excess of the barbiturate was placed in each of a series of 125-ml. glass-stoppered flasks and varying amounts of PEG 4000 added. Specifically, 250 mg. each of phenobarbital and pentobarbital, 500 mg. of barbital, and 1.9 Gm. of barbituric acid were used in each flask in these studies. Fifty milliliters of isotonic phosphate buffer solution (pH 5.3) was added to each flask, and the contents were equilibrated in a mechanical shaker bath at 37° for 24 hr.

Measured aliquot portions were removed and analyzed for their barbiturate content in a Beckman DB recording spectrophotometer. (The absorption maxima for phenobarbital, barbital, and pentobarbital were taken to be 240 mμ and for barbituric acid 258 mμ.) All spectrophotometric analyses were conducted in a sodium borate buffer having a pH of 9.1.

Manufacture of Tablets.—Cylindrical tablets of the pure drug were compressed in a single punch Colton machine using $^{9}/_{32}$ in. flatfaced punches. Tablet hardness ranged between 5 and 7 on the Strong-Cobb scale.

Phenobarbital tablets weighed 190 mg., pentobarbital 155 mg., barbital 180 mg., and barbituric acid 200 mg.

Dissolution.—The barbiturate tablets were firmly fixed into cylindrical Plexiglas containers with the aid of paraffin wax in such a way that only one surface of the tablet was exposed to the solution. [This is a variation of the technique first introduced by Nelson (7).] The Plexiglas disks were weighted down with a metal plate which prevented them from overturning or sliding during an experimental run (Fig. 1). The tablets were so fixed that their upper surfaces were level with those of the disks. Two such affixed tablets were placed in each of a set of 250-ml. glass-stoppered flasks. One hundred milliliters of isotonic phosphate buffer (pH 5.3) was added to each flask, and the flasks were placed in a constant-temperature (37°) shaker bath and mechanically stirred at 120 strokes/min.

Aliquot portions of the solution were removed at fixed time intervals and analyzed spectrophotometrically for their barbiturate content.

Dissolution in the Presence of PEG 4000.—The experimental procedure was similar to that used for pentobarbital, barbital, and barbituric acid (the 3 barbiturates that did not complex with PEG 4000) as described above, except that a known amount of PEG 4000 was added to the solution (0.880 Gm./100 ml. of PEG 4000 in each flask).

[1] One liter contains 0.568 Gm. of anhydrous disodium hydrogen phosphate, 13.248 Gm. of sodium phosphate, monobasic, and 3.40 Gm. of sodium chloride.

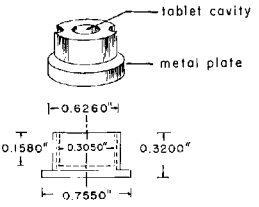

Fig. 1.—A Plexiglas disk with tablet cavity used to hold tablets for dissolution study.

With phenobarbital, which formed an insoluble complex in the presence of PEG 4000, a different procedure was adopted. To a saturated solution of phenobarbital in pH 5.3 buffer, sufficient PEG 4000 was added so that the ratio of adjuvant to drug was identical to the ratio found in the complexation studies (*vide infra*). Specifically, 77.38 mg. of PEG 4000 was added to each 100 ml. of a pH 5.3 buffered solution of phenobarbital having a concentration of 170 mg. %. The phenobarbital–*polyethylene glycol 4000 complex* (hereafter referred to as PB–PEG complex) was allowed to form over a period of 24 hr., filtered, and dried, m.p. 145–147°. The dry powder was then compressed into cylindrical tablets having the same specifications as the drug tablets and weighing 175 mg. The tablets were fixed into the Plexiglas disks, and the dissolution study was conducted. Spectrophotometric determinations were carried out by measuring the phenobarbital equivalent of the complex in solution. It should be noted that the presence of PEG 4000 had no effect on the absorption maxima of the barbitals, and that the pH of all solutions, containing either pure drug or the drug in the presence of PEG 4000, remained constant at pH 5.3.

Absorption.—The "everted intestinal sac" technique of Wilson and Wiseman (8) was adopted in all absorption studies conducted in the present series. Female Sprague-Dawley rats weighing about 250 Gm. were starved for 24 hr. prior to the experiments. The small intestine was freed of all adhering tissue, removed, and cut into 6-cm. segments. No more than 5–6 segments were used from any rat, and these segments were continually bathed in pH 5.3 buffered medium which was aerated with oxygen. Preliminary experiments showed that under our experimental conditions, there was no difference in absorption rates obtained from segments taken from different parts of the small intestine. This is corroborated by Schanker *et al.* (9) in the case of perfused rat intestines. Once cut, the segments were everted and sacs containing 0.4 ml. of isotonic 7.4 buffer were prepared by established techniques. The sacs were kept in a aerated pH 5.3 buffered medium.

One segment was introduced into each of a series of 250-ml. glass-stoppered flasks containing 100 ml. of a solution of known strength of a barbiturate drug. The flasks were placed in a shaker bath at 37°. Before starting the experiment, the air in the flasks was replaced by oxygen.

Corresponding to each sample flask containing the barbiturate solution, a control flask was also run simultaneously. The contents of the control flask were similar to the sample flask except that it did not contain the drug.

The flasks were mechanically stirred at 120 strokes/min., and 2 flasks (a sample and a control)

were removed at regular time intervals. The 2 intestinal sacs were removed from solution, wiped dry with tissue paper, punctured, and 0.16 ml. of the solution contained in each was removed and diluted to an appropriate extent with pH 9.1 buffer, so that the barbiturate content of each sample could be analyzed spectrophotometrically.

Absorption in the Presence of PEG 4000.—With pentobarbital, barbital, and barbituric acid the experiments described above were repeated except that a known weight of PEG 4000 was added to both the sample and control flasks (0.880 Gm./100 ml. of PEG 4000 in each flask).

With phenobarbital, however, the solution in the flask was prepared by placing a weighed quantity of the powdered complex described above into 100 ml. of phosphate buffer (pH 5.3). Initially an attempt was made to have the amount of phenobarbital available (170 mg. %) correspond to the amount used in the absorption studies run without PEG; therefore, 247.38 mg. of the complex (each 247.38 mg. of complex contained 170 mg. of phenobarbital and 77.38 mg. of PEG 4000) was added to 100 ml. of the 5.3 buffer. Since the complex only has a limited solubility (61.7 mg. % measured as the phenobarbital content[2]) an excess of the complex was always present as a solid in all of the sample flasks. Absorption studies were also run at lower complex concentrations (48.0 mg. % and 25.8 mg. % measured as the phenobarbital content), where, in these cases, all of the complex present was in solution.

RESULTS

Complexation.—Phenobarbital was the only one of the 4 barbiturates which complexes with PEG 4000. The complex formed in this case was an insoluble one, the ratio being 1:2.4 (*i.e.*, 1 Gm. molecular weight of phenobarbital and 2.4 Gm. equivalents of the ether linkages of PEG 4000). The data for the complexation are illustrated in Fig. 2. It should be noted that Higuchi and Lach (6) obtained a ratio of 1:2 for this complexation; however, this value was obtained at a different temperature (30°) and in a nonbuffered system at a different pH.

Dissolution.—Figure 3 shows that the dissolution rate of the PB–PEG complex differs from that of phenobarbital by a factor of about 3. (Rate for phenobarbital was 0.208 mg. %/min., and rate for PB–PEG complex was 0.07 ± 0.002 mg. %/min.) The dissolution rates of pentobarbital, barbital, and barbituric acid were not affected by the presence of PEG 4000. An example of this (barbital) is shown in Fig. 4. The dissolution rate values for all 4 drugs, as determined under the authors' experimental conditions, are given in Table I. (In each case, the method of least squares was used to calculate the rates. Each rate listed is a statistically treated average of 4–6 experiments.)

Absorption.—Figure 5 shows the absorption rates of the free phenobarbital and the PB–PEG complex (when excess complex was present). The absorption rate of the complex is about one-third that of pure phenobarbital, but these values must be

[2] All spectrophotometric measurements were made with reference to phenobarbital in solution. Therefore, the abscissas of Figs. 2 and 5 and the ordinate of Fig. 7 should be read as concentration of phenobarbital.

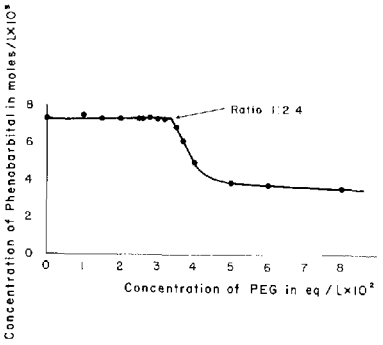

Fig. 2.—Phase diagram showing the effect of varying concentrations of PEG 4000 on the solubility of phenobarbital at 37° and at a pH of 5.3.

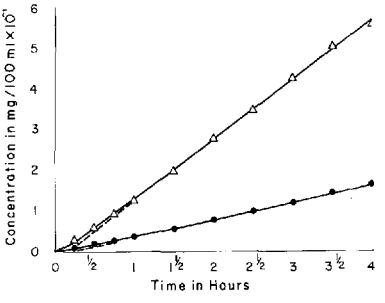

Fig. 3.—Dissolution rate of phenobarbital (△) and PB–PEG complex tablets (●). Average rate: △, 0.208 mg.%/min.; ●, 0.07 ± 0.002 mg. %/min.

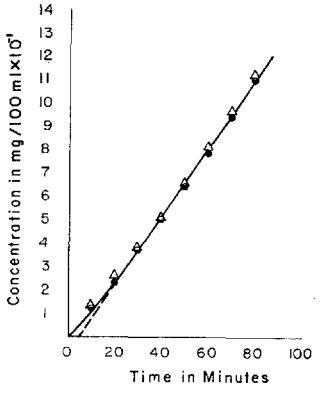

Fig. 4.—Dissolution rate of barbital tablets. Key: △, without PEG; ●, with PEG. Average rate: 1.33 mg. %/min. Range of error: △, ± 0.015 mg. %/min.; ●, ± 0.03 mg. %/min.

TABLE I.—DISSOLUTION RATES OF THE FOUR BARBITURATES

Drug	*Dissolution* Rate, mg. %/min.	Dissolution Rate in Presence of PEG 4000, mg. %/min.
Pentobarbital	0.140 ± 0.004	0.140 ± 0.005
Barbital	1.330 ± 0.015	1.330 ± 0.030
Barbituric acid	3.960 ± 0.400	3.960 ± 0.210
Phenobarbital	0.208	...
PB–PEG complex	...	0.070 ±0.002

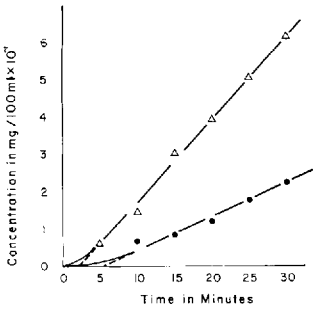

Fig. 5.—Absorption rate of phenobarbital (△) and of the PB–PEG complex (●) (when excess complex present). Average rate: △, 2.36 ± 0.17 mg. %/min.; ●, 0.81 ± 0.14 mg. %/min.

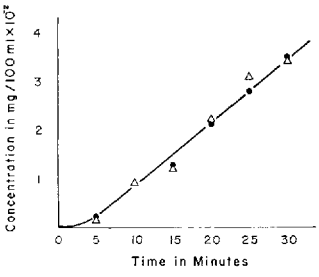

Fig. 6.—Absorption rate of barbital. Key: △, without PEG; ●, with PEG. Rate: 11.7 mg. %/min.

TABLE II.—ABSORPTION RATES OF THE FOUR BARBITURATES

Drug	Absorption Rate, mg. %/min.	Absorption Rate in Presence of PEG 4000, mg. %/min.
Pentobarbital (initial concn. = 115 mg./100 ml.)	1.91	1.90
Barbital (initial concn. = 807 mg./100 ml.)	11.7	11.7
Barbituric acid (initial concn. = 1,580 mg./100 ml.)	29.87	31.48
Phenobarbital (initial concn. = 168 mg./100 ml.) (av. of 5 expt.)	2.36 ± 0.17	...
PB–PEG complex[a] (initial concn. = 61.7 mg./100 ml.) (av. of 5 expt.)	...	0.81 ± 0.14
(initial concn. = 48.0 mg./100 ml.) (av. of 3 expt.)	...	0.52 ± 0.09
(initial concn. = 25.8 mg./100 ml.) (av. of 6 expt.)	...	0.31 ± 0.04

[a] Measured as phenobarbital equivalents.

related to the concentration of phenobarbital equivalents in the outside solution. For free phenobarbital the outside concentration was 170 mg. %, while the concentration of phenobarbital equivalents was only 61.7 mg. % when 247.38 mg. of the PB–PEG complex was added to 100 ml. of buffer. The absorption rates of the 3 other barbiturates were not affected by the presence of PEG 4000. An example of this (barbital) is shown in Fig. 6. The absorption rates of all 4 barbiturates, in addition to the absorption rates of the complex at 3 different outside concentrations, are given in Table II. In each case, the method of least squares was used to calculate the rates.

DISCUSSION

Schanker *et al.* (9) have stated that most drugs are absorbed by passive diffusion. This hypothesis applied to the drugs in this study. Figure 7 shows that in absorption studies carried out by using phenobarbital solutions of different concentrations (closed circles), the absorption rate bears a linear relationship to the initial concentration of the solutions. The open circles on this plot correspond to average absorption rates found for the 3 different concentrations of PB–PEG complex listed in Table II.

A modification of Fick's first law of diffusion has been employed by Higuchi (10) to explain the phenomenon of percutaneous absorption. The equation can also be applied to absorption through the small intestine. The rate of absorption is then given by

$$\frac{dq}{dt} = \frac{DA}{L}(\text{P.C.})\,C \qquad \text{(Eq. 1)}$$

where dq/dt is the absorption rate, D is the diffusion coefficient, A is the cross-sectional area of the gut wall exposed to the drug, L is the thickness of the gut wall, C is the concentration of the drug solution outside the everted sac, and P.C. is the partition coefficient of the barbiturate between the wall and the drug solution.

Similar equations can be written to describe both the phenobarbital absorption rate and the PB–PEG complex. The ratio of the absorption rates is given by

$$\frac{\text{absorption rate of phenobarbital}}{\text{absorption rate of the PB–PEG complex}} = \frac{D_{PB}\,A/L\,(\text{P.C.}_{PB})C_{PB}}{D_{PB-PEG}A/L\,(\text{P.C.}_{PB-PEG})\,C_{PB-PEG}} \qquad \text{(Eq. 2)}$$

Equation 2 is only applicable if the PB–PEG complex can be shown to diffuse through the gut membrane as an intact complex. This seems unlikely in light of recent work which shows that PEG 4000 does not pass through the biological membrane (11). In addition, experiments were run with uneverted whole (40 cm.) rat guts. These guts were first flushed with distilled water, and then filled with a solution of the PB–PEG complex in distilled water (60 mg. % measured as phenobarbital equivalents). The guts were continually aerated as previously described and were placed in flasks containing 25 ml. of distilled water. The flasks were shaken at 37° for 1 hr., after which the gut was discarded, and the outside solution was centrifuged and filtered so as to remove insoluble gut particles. The solution was concentrated by evaporation, and the precipitate was dried overnight at 60°. The melting point of the solid was then observed on a microscope equipped with a hot stage. Although the concentrate was not purified,

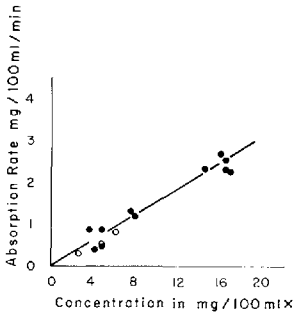

Fig. 7.—Plot showing the linear dependence of the absorption rate on the initial concentration of phenobarbital in the solution surrounding the everted sac. Key: ●, absorption runs with pure phenobarbital; O, average values obtained for absorption runs with excess complex (61.7 mg. % phenobarbital equivalent) and for a series of runs with all complex in solution (48.0 mg. % and 25.8 mg. %).

particles were seen to melt beginning at 173°.[3] Similar results were obtained when pure phenobarbital was placed in the large uneverted gut segments. Although the above experiments were not run under the same conditions as the absorption studies, it seems reasonable to conclude that only phenobarbital passes through the gut wall.

Under this assumption Eq. 2 will reduce to Eq. 3, since D, A, L, and (P.C.) are the same for both the solutions of pure phenobarbital and PB–PEG complex.

$$\frac{\text{absorption rate of phenobarbital}}{\text{absorption rate of phenobarbital from complex}} = \frac{C_{PB}}{C_{PB-PEG}\ \text{(measured as PB equiv.)}} \quad \text{(Eq. 3)}$$

If Eq. 3 is valid, the rate of absorption of phenobarbital from the complex will be a function of the concentration of phenobarbital in solution as the complex, and, therefore, the rate of absorption of the complex should follow the same linear relation with concentration as does the rate of absorption of pure phenobarbital. This relation is shown in Fig. 7, and seems to be true within the experimental error expected from biological work.

It should be pointed out that Fig. 7 implies that the rate of absorption of phenobarbital from the complex is a function of the *total* phenobarbital in solution, not just the concentration of the free phenobarbital resulting from dissociation of the complex. This was checked by running everted gut absorption studies with solutions containing PB–PEG complex (at the 3 concentrations studied) and various concentrations of excess PEG 4000 (up to 1:1 weight–weight, complex to PEG). If absorption was a function of the concentration of free phenobarbital resulting from complex dissociation, the rate of absorption should decrease as excess PEG 4000 is added. In all cases the rates of absorption of phenobarbital from the complex were similar to the rates reported in Table II when no excess PEG was present, indicating that the rate of absorption of phenobarbital from the complex is, indeed, a function of the total phenobarbital in solution, and is not dissociation related.

In light of the evidence presented it would seem that the gut is acting as a "dissociating membrane," causing the complex to dissociate and allowing the diffusible phenobarbital to be absorbed. This hypothesis has previously been proposed by Levy and Matsuzawa (4) to explain the fact that eosin-B was absorbed through the cannulated everted intestine at the same rate from solutions containing the free dye as from solutions containing the dye (at an identical concentration) complexed with atropine and pheniramine. In the previous work (4) the complexes dissociated into 2 components, both of which passively diffused through the intestine, while in the present study the complex dissociates to give 1 passively diffusible component, and 1 component which cannot pass through the intestinal membrane.

Although the above reasoning is hypothetical, it appears that complex dissociation does take place either at the gut surface or in an outer layer of the gut, since the absorption rates are related to total phenobarbital concentration. Additional tests of the above hypothesis are being carried out in this laboratory on a PEG-sulfathiazole complex which increases the total solubility of the drug.

CONCLUSIONS

This portion of the study has demonstrated that the absorption of phenobarbital in the presence of PEG is markedly decreased and that the decrease is probably a function of the decreased solubility of the PB–PEG complex. It has also been demonstrated that the dissolution rate of the complex is only about one-third the rate for pure phenobarbital. As has been pointed out in the literature (12, 13), dissolution is usually the rate-limiting step in attaining therapeutic blood levels. Thus, a PB-PEG complex would markedly decrease the therapeutic efficacy of phenobarbital at both the level of availability rate (dissolution) and at the level of maximum availability attainable (solubility). It was also observed that the dissolution and absorption rates of 3 other closely related drugs were not affected when the same adjuvant showed no interaction with them. Thus, the work so far supports the validity of the hypothesis that tablet adjuvants may not be as inert in their effect as has been traditionally assumed.

SUMMARY

1. The effect of a tablet adjuvant (polyethylene glycol 4000) on the dissolution and absorption rates of 4 barbiturates has been studied.

2. It has been shown that in the case of pentobarbital, barbital, and barbituric acid, all of which did not interact with polyethylene glycol 4000, the dissolution and absorption rates were not affected.

3. Phenobarbital formed a complex of reduced solubility with polyethylene glycol 4000. The effect of this interaction was to reduce the dissolution and absorption rates of the drug.

4. The reduction in the absorption rate of phenobarbital was found to be closely related to the reduced solubility of the complex, and although it was

[3] Phenobarbital, m.p. 174–178°; PEG 4000 congeals at 53–56°; PB–PEG complex, m.p. 145–147°.

demonstrated that only phenobarbital was absorbed through the gut, it was also shown that the rate of absorption was independent of the degree of dissociation of the complex in the mucosal fluid. It has been proposed [after Levy and Matsuzawa (4)] that the intestinal membrane has a dissociating effect on the complex, allowing the phenobarbital to be absorbed, but preventing absorption of PEG.

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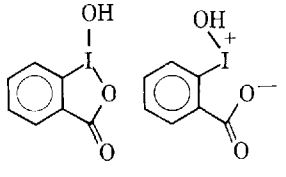
Chemistry and Biochemistry of Polyvalent Iodine Compounds V

Ionization of Heterocyclic Polyvalent Iodine Compounds

By WALTER WOLF, JAMES C. J. CHEN, and LAUREEN L. J. HSU

The ionization constants of several polyvalent compounds were determined and found to be consistent with the ionization of an hydroxyl group of polyvalent iodine. The pKa of 1,3-dihydro-1-hydroxy-3-oxo-1,2-benziodoxole is 7.35 ± 0.13, and those of its two immediate higher homologs are 7.54 ± 0.29 and 7.37 ± 0.17, respectively. The behavior of 1,3-dihydro-1-hydroxy-3-oxo-1,2-benziodoxole was studied in varying concentrations of sulfuric acid. Two protonation steps seem to occur, with apparent pKa values of −0.58 and −5.75, on the H_0 scale. The structural implications of these findings on the heterocyclic nature of the benziodoxole ring are discussed.

RECENT WORK on the structure of certain polyvalent iodine compounds (1, 2) confirms their heterocyclic nature. The structure of 1,3-dihydro-1-hydroxy-3-oxo-1,2-benziodoxole (I) has been unequivocally determined by X-ray crystallography (3). This study revealed a significant difference between the two I—O bonds; the intra-annular bond between iodine and oxygen is 2.30 Å. long, while the bond between iodine and the hydroxylic oxygen is 2.00 Å. This difference can be ascribed either to the steric strain of a 5-membered ring or to a strong ionic contribution to the iodine-oxygen (ring) bond. An alternative possibility, that a betaine type of ring (iodonium-carboxylate, I*a*) makes a significant contribution to the structure of 1,3-dihydro-1-hydroxy-3-oxo-1,2-benziodoxole had to be evaluated. The behavior of 2-carboxy-diphenyl iodonium (III), containing such a ring system, had been studied recently (4). The ionization constants of I and its homologs (II, $n = 1$ or 2) were investigated in order to provide further information on the structure of these iodine-containing heterocyclic rings, and to evaluate the possible contribution of betainic structures such as (I*a*). This study was conducted both in dilute aqueous



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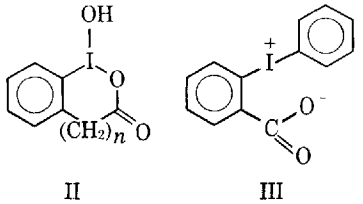

II III

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