Disappearance of I after Incubation with Rat Liver Microsomes—Rat liver microsomes were prepared according to the standardized technique described previously (11). The incubation medium contained 0.93 μmole of I, 1.5 μmoles of NADP, 50 μmoles of glucose 6-phosphate, 0.7 international unit of glucose 6-phosphate dehydrogenase, 25 μmoles of magnesium chloride, 0.08 *M* phosphate buffer (pH 7.0), and 30 mg of microsomes in a total volume of 5 ml. Samples (1.0 ml) of the incubation medium were taken at different time intervals, acidified with citric acid (0.1 ml of 1 *M* solution), and immediately extracted with 5 ml of *n*-pentane for 10 min at room temperature. The results are reported in Tables II and III.

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Automated Potentiometric Procedure for Studying Dissolution Kinetics of Acidic Drugs under Sink Conditions

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Abstract □ An automated potentiometric procedure was used for studying *in vitro* dissolution kinetics of acidic drugs. Theoretical considerations indicated that the pH-stat method could be used to establish approximate sink conditions or, possibly, a perfect sink. Data obtained from dissolution studies using the pH-stat method were compared with data obtained from known sink and nonsink conditions. These comparisons indicated that the pH-stat method can be used to establish a sink condition for dissolution studies. The effective diffusion layer thicknesses for benzoic and salicylic acids dissolving in water were determined, and a theoretical dissolution rate was calculated utilizing these values. The close agreement between the experimental dissolution rates obtained under pH-stat conditions and the theoretical dissolution rates indicated that perfect sink conditions were established under the experimental conditions used.

Keyphrases □ Dissolution kinetics, *in vitro*—acidic drugs, automated potentiometric study, pH-stat method used to establish sink conditions □ Potentiometry, automated—study of *in vitro* dissolution kinetics of acidic drugs, pH-stat method used to establish sink conditions □ pH-stat method—used to establish sink conditions for *in vitro* automated potentiometric study of dissolution kinetics of acidic drugs

Recognition that the availability for GI absorption of drugs in oral solid dosage forms is often reflected by *in vitro* dissolution rates has stimulated the development and use of numerous dissolution rate tests for tablets and capsules. Various types of apparatus have been used to determine dissolution rates of drugs, most of which have been critically reviewed (1–3).

Emphasis has been placed on the need for dissolution systems to be operated under sink conditions, where there is no effective buildup of drug concentration (4, 5). It was suggested that unless sink conditions are embodied in the design of *in vitro* dissolution rate methods, the *in vitro* results may bear little relationship to *in vivo* observations (6). It was also suggested that all dissolution systems should be operated under sink conditions and that systems that do not meet this requirement should either be modified accordingly or discarded (7).

The utility of automatic titration at a stat-pH for studying *in vitro* dissolution rates of acidic and basic drugs was demonstrated previously (8, 9). A pH-stat procedure was used in evaluating antacid products (10, 11). It was thought that the pH-stat method might be used to establish approximate sink conditions or, possibly, a perfect sink during dissolution rate testing.

THEORY

The Noyes–Whitney (12) equation describes the dissolution process:

$$\frac{dW}{dt} = kS(C_{sat} - C_{soln}) \qquad \text{(Eq. 1)}$$

where dW/dt is the dissolution rate, k is a constant, S is the surface area of the dissolving solid, C_{sat} is the concentration of a saturated solution, and C_{soln} is the drug concentration in the solvent at time t. As the C_{soln} increases, the equation predicts that dW/dt decreases. When $C_{sat} \gg C_{soln}$, a sink condition exists; if a buildup of C_{soln} can be prevented, then a sink condition will be maintained.

The total solubility of a weak acid, HA, is the sum of the concentration of the unionized [HA] and the ionized acid [A^-]:

$$C_{sat} = [HA] + [A^-] \qquad \text{(Eq. 2)}$$

and the concentration, C_t(soln), at any time before saturation is:

$$C_t(\text{soln}) = [HA]_t + [A^-]_t \qquad \text{(Eq. 3)}$$

The solubility of the ionized species, A^-, in water is generally much greater than that of the unionized acid, HA. Therefore, for dissolution phenomena involving relatively small quantities of acidic drugs in solution, the concentration of the unionized acid determines the concentration buildup. For example, the solubility of salicylic acid is 1.0 g in 460 ml of water while the solubility of sodium salicylate is 1.0 g in 0.9 ml of water (13).

In dissolution, the sequence of events in Schemes I and II occurs for

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an acid.

$$HA_{solid} \rightleftharpoons HA_{soln}$$

Scheme I

$$HA_{soln} \rightleftharpoons H_3O^+ + A^-$$

Scheme II

The equilibrium of Scheme II is shifted to the right by the automatic titration as shown in Scheme III.

$$H_3O + A^- + NaOH \rightleftharpoons Na^+ + A^- + 2H_2O$$

Scheme III

Therefore, the pH-stat method, operated at 1.5 pH units or more above the pKa of the acid, would keep the dissolving acid in the ionized form (salt). The salt would be much more water soluble than the acid, and this condition would have the same effect as removing the acid as it dissolves, keeping $C_{sat} \ggg C_{soln}$ and thus maintaining a sink condition.

The pH-stat method should not appreciably affect the dissolution rate since the titrant is reacting with the acid dissolved and does not influence the saturated solution layer (diffusion layer) as would a buffer solution. The effect of bases and buffers on the dissolution rate of acidic solids has been studied, and the double film concept of diffusion-controlled dissolution was used to explain the data (14–16). The solid acid dissolves and diffuses toward the bulk solution; simultaneously the base diffuses from the bulk solution toward the solid surface. Neutralization and formation of a salt occur somewhere in the diffusion layers.

The dissolution rate of the acid depends on the diffusion rate of the dissolved acid through the diffusion layer. The buffer has the effect of reducing the distance the acid must diffuse by diffusing toward the acid, thus increasing the dissolution rate. In the pH-stat method, the base is not added until the dissolved acid has diffused through the diffusion layer to the bulk solution. Therefore, in the pH-stat method, the effective film thickness, h, of the diffusion layer should be essentially the same as in the pure water and the dissolution rate should not be affected.

Higuchi *et al.* (16) derived an equation for calculating the thickness:

$$C_1 = \frac{D_{HA}[HA]_o - D_{HA}[HA]_h}{h} \quad \text{(Eq. 4)}$$

where C_1 is the dissolution rate of HA per unit area of the film, D_{HA} is the diffusion coefficient of the acid in pure water, $[HA]_o$ is the concentration of the acid at the solid–liquid interface, $[HA]_h$ is the concentration of the acid in the bulk dissolution medium, and h is the film thickness. Whenever the pH of the dissolution medium is 2 pH units above the pKa of the acid, $[HA] \cong 0$ and Eq. 4 becomes:

$$C_1 = \frac{D_{HA}[HA]_o}{h} \quad \text{(Eq. 5)}$$

The same equation can be derived from the Noyes–Whitney equation as derived from Fick's law of diffusion:

$$\frac{dW}{dt} = \frac{D_{HA}S}{h}(C_s - C) \quad \text{(Eq. 6)}$$

where dW/dt is the dissolution rate, D_{HA} is the diffusion coefficient of the acid HA, $(C_s - C)$ is the concentration difference, S is the surface area, and h is the film thickness. Under sink conditions, $(C_s - C) = C_s$ (saturated concentration of HA) or $[HA]_o$. If $(dW/dt)/S$ = rate per unit area = C_1, then:

$$C_1 = \frac{D_{HA}[HA]_o}{h} \quad \text{(Eq. 7)}$$

During dissolution studies using a pH-stat method, the diffusion layer, h, of the dissolving substance should not be affected if sink conditions exist. If this is true, then the same diffusion layer thickness, h, should be obtained from pH-stat dissolution data as from data obtained using previously reported methods (14–16).

EXPERIMENTAL

Materials—Benzoic acid USP and salicylic acid USP were the acidic drugs studied. Ceresin wax (technical), cyclohexane, octyl alcohol, potassium phosphate (certified), sodium hydroxide, and hydrochloric acid also were used.

Equipment—A pH-stat instrumental setup similar to that of Shah (8) and a dissolution assembly with a 100-mm o.d. round-bottom dissolution vessel covered with a four-neck flask cover, described previously (17), were used. The propeller was centered in the dissolution medium and immersed 2.2 cm below the solvent surface.

Table I—Dissolution of Benzoic and Salicylic Acids (Milligrams) from Nondisintegrating Disks in Sodium Hydroxide Solutions [a]

Dissolution Time, min	Sodium Hydroxide 0.005 N	0.01 N	0.02 N	0.03 N
		Benzoic Acid		
10	64.5	69.0	96.9	110.5
20	126.0	132.5	185.0	218.0
30	180.0	200.4	264.0	324.0
40	246.0	269.4	353.0	430.0
50	302.0	335.5	444.0	541.0
		Salicylic Acid		
10	53.8	59.9	84.8	120.0
20	103.0	112.0	168.0	228.0
30	149.5	168.5	246.5	341.0
40	195.0	225.0	329.0	449.0
50	243.0	278.0	405.0	555.0

[a] All experiments were run at 37° and 100 rpm. Each value is an average of two experiments.

Preparation of Nondisintegrating Disks—Nondisintegrating disks of benzoic acid and salicylic acid were prepared with a hydraulic press[1] by slugging 3.0 g of the compound in a 2.85-cm diameter punch and die set at 1425 kg/cm^2. These disks were mounted on the tapered end of a rubber stopper (3 cm diameter) with ceresin wax. The disks were affixed to the stopper by pouring a small quantity of melted ceresin wax (mp 70–75°) onto the face of the stopper and pressing the disk on the stopper before the wax solidified. The sides of the disks were coated with melted wax using a cotton-tipped applicator; one surface was left exposed. Any wax on the surface of the tablet to be exposed was removed carefully with a knife blade.

Nondisintegrating Disks in Buffer—The dissolution medium used was 400 ml of a pH 6.2 phosphate buffer (buffer capacity of 0.045) at 37°. Two-milliliter samples were taken at appropriate intervals, and the volume of sample was replaced immediately with an equal volume of the buffer. The samples were diluted with buffer, and the absorbance was read on a spectrophotometer[2] at 230 nm. The amount of benzoic acid in solution as a function of time was calculated from a standard Beer's curve of benzoic acid in the buffer. The buffer was used in the reference cell.

Nondisintegrating Disks in Distilled Water with Organic Reservoir—The dissolution medium used was 400 ml of distilled water at 37° overlayed with 350 ml of 1-octanol–cyclohexane (1:1), previously brought to 37° in a constant-temperature water bath. A nonflexible plastic tube (14 cm long × 1.2 cm i.d.) was inserted through a stopper and fitted in one neck of the flask cover. The tube extended through the organic layer into the aqueous phase. Samples of the aqueous layer were taken through this tube with a pipet, and the volume of solvent removed was replaced immediately through the tube, avoiding contact with the organic phase. The organic phase was sampled through one of the other openings in the flask cover, and the volume of liquid removed was replaced immediately.

The stirring blade and shaft from the stirring motor were inserted in the center neck of the flask cover. An additional marine-type propeller, having a stirring diameter of 44 mm, was placed on the shaft and centered in the organic phase. The propeller consisted of three blades, 18 mm in diameter, set at 45° angles to the shaft.

Two-milliliter samples of each phase were taken at appropriate intervals and assayed spectrophotometrically. The samples from the organic phase were diluted with methanol, and the absorbance was measured at 230 nm with methanol as the reference. The aqueous samples were diluted with 0.1 N HCl, and the absorbance was measured at 273 nm using 0.1 N HCl as the reference. The amount of benzoic acid in each layer as a function of time was determined by appropriate calculations from standard curves.

Nondisintegrating Disks in pH-Stat System—A volume of 400 ml of distilled water was placed in the dissolution vessel and brought to 37 ± 0.1° in the constant-temperature bath. The dissolution medium was adjusted to the predetermined experimental stat-pH by the addition of hydrochloric acid or sodium hydroxide. Two-milliliter samples were taken at appropriate intervals, and the volume of sample was replaced immediately with an equal volume of dissolution medium. The benzoic and

[1] Carver model B.
[2] Beckman DU-2.

Table II—Dissolution Rates in Various Sodium Hydroxide Solutions and Effective Film Thicknesses (h) of Benzoic and Salicylic Acids [a]

Sodium Hydroxide, N	Rate, mg/min/cm^2	h, cm × 10^{-3}
	Benzoic Acid	
0.005	0.9399	3.83
0.010	1.0580	3.40
0.020	1.3620	2.64
0.030	1.6951	2.12
	Salicylic Acid	
0.005	0.7431	3.25
0.010	0.8676	2.78
0.020	1.2660	1.91
0.030	1.7235	1.40

[a] Calculated from data presented in Table I.

salicylic acid samples were diluted with 0.1 N HCl, and the absorbances were measured at 273 and 297 nm, respectively, with 0.1 N HCl as the reference. The amount of benzoic or salicylic acid in solution as a function of time was determined by appropriate calculations from standard curves.

Effective Film Thickness of Diffusion Layer in pH-Stat System—Nondisintegrating disks of benzoic and salicylic acids were placed in 400 ml of various concentrations of sodium hydroxide, which were held constant using pH-stat automatic titration. Samples were taken periodically and assayed spectrophotometrically. Dissolution profiles (amount dissolved *versus* time) were prepared for each sodium hydroxide concentration, and the dissolution rates were calculated from the slopes of the line (Table I). The effective film thicknesses were calculated utilizing Eq. 5 (Table II). Diffusion coefficients of 1.2×10^{-5} and 1.13×10^{-5} cm^2/sec for salicylic and benzoic acids, respectively (18), were used in the calculations.

RESULTS AND DISCUSSION

The dissolution rate of a drug from a constant surface area under sink conditions should follow zero-order kinetics as described by Gibaldi and Feldman (6). This relationship can also be derived from the Noyes–Whitney equation, $dW/dt = kS(C_s - C)$, which describes the dissolution process quantitatively. Under sink conditions, the concentration difference, $(C_s - C)$, remain constant, and when a constant surface area is maintained, the equation becomes dW/dt = constant, the equation for a zero-order process.

The dissolution profile for benzoic acid disks at a pH-stat of 6.2 is shown in Fig. 1. The straight-line curve is characteristic of zero-order kinetics and indicative of a sink condition. Straight-line curves were obtained for pH-stats 4.2, 5.2, 7.2, and 8.2 almost identical to the curve

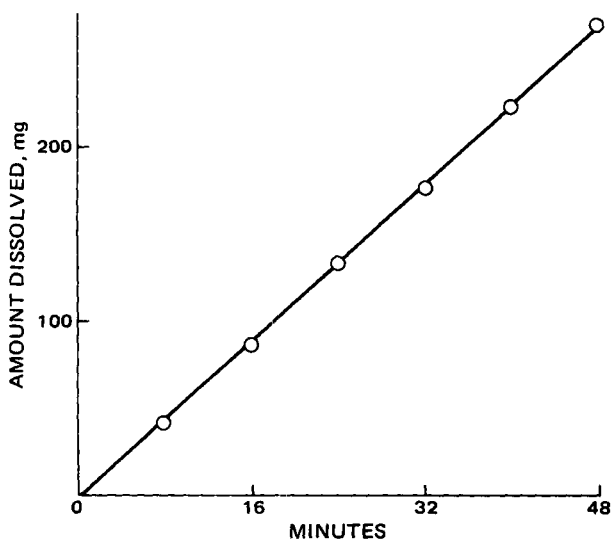

Figure 1—*Dissolution of benzoic acid from a nondisintegrating disk in distilled water (pH-stat 6.2) at 37° and 100 rpm.*

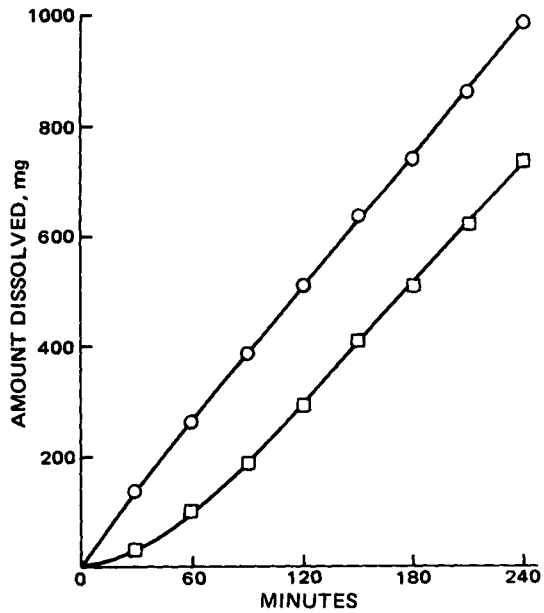

Figure 2—*Dissolution of benzoic acid from a nondisintegrating disk in distilled water having an organic reservoir at 37° and 100 rpm. Key: ○, aqueous plus organic; and □, organic.*

for pH-stat 6.2, which indicated that the dissolution rate was not affected by different pH conditions. Collett *et al.* (9) found that the dissolution of salicylic acid increased in a pH-stat experiment (absence of buffer salts) up to a maximum of pH 3–4. There was no significant difference in dissolution rate from pH 4 to 7.

Further evidence to prove that the pH-stat method actually established sink conditions during dissolution is obtained by comparing the pH-stat method data to data obtained from known sink and nonsink conditions. For this purpose, the dissolution of benzoic acid disks in distilled water at pH-stat 6.2 conditions (Fig. 1) was compared to the dissolution of: (*a*) benzoic acid disks in distilled water overlayed with an organic layer [cyclohexane–1-octanol (1:1)] as a sink (Fig. 2), (*b*) benzoic acid disks in pH 6.2 buffer (Fig. 3), and (*c*) benzoic acid disks in distilled water (Fig. 4).

The dissolution curves obtained using an organic reservoir as a sink (Fig. 2) were the same type as those obtained by Gibaldi and Feldman (6). There was an initial lag period for partitioning of the drug in the organic sink; then the dissolution process followed zero-order kinetics in

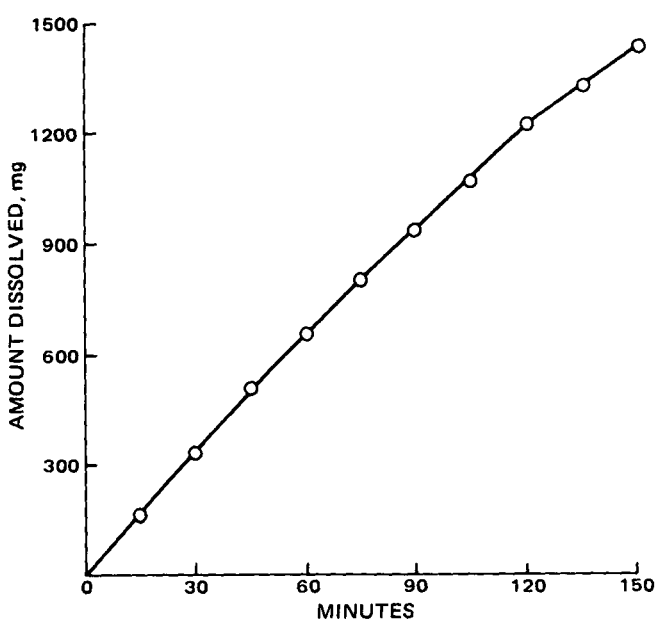

Figure 3—*Dissolution of benzoic acid from a nondisintegrating disk in buffer (pH 6.2) at 37° and 100 rpm.*

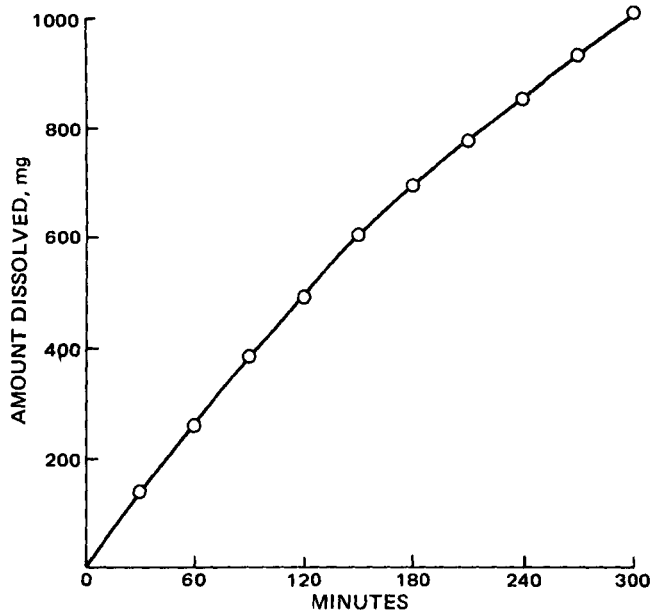

Figure 4—*Dissolution of benzoic acid from a nondisintegrating disk in distilled water at 37° and 100 rpm.*

the sink. The curve for the total amount of drug dissolving followed zero-order kinetics without a lag time (Fig. 2). In the pH-stat method, the straight-line curve was obtained (Fig. 1) without an initial lag period and without the need to analyze two phases.

The dissolution rate in the pH 6.2 buffer (Fig. 3) was much faster than the dissolution rate of a pH-stat of 6.2 (Fig. 1). Bases and buffers increase the dissolution rate of acidic drugs, and this effect was explained by use of the double film concept of diffusion-controlled dissolution (11–13). In this concept, the base diffuses toward the acid at the same time as the acid diffuses toward the bulk medium, having the effect of reducing the diffusion film thickness. This situation would not have been the case in the pH-stat experiment (Fig. 1) since there was essentially no buffer system present in solution.

The dissolution rate also decreased slightly with time in the buffer (Fig. 3) whereas it remained constant for the period studied at pH-stat 6.2 (Fig. 1). A possible reason for this decrease is that the concentration of the buffering compounds in the dissolution medium could retard the dissolution of benzoic acid. As the concentration of benzoic acid in solution increases, there is competition for solvent. Also, the buffer pH decreased slightly as the benzoic acid dissolved, which could have decreased the pH of the diffusion layer next to the benzoic acid and caused a decrease in the dissolution rate. In the pH-stat method, the dissolution medium pH is held constant throughout the experiment.

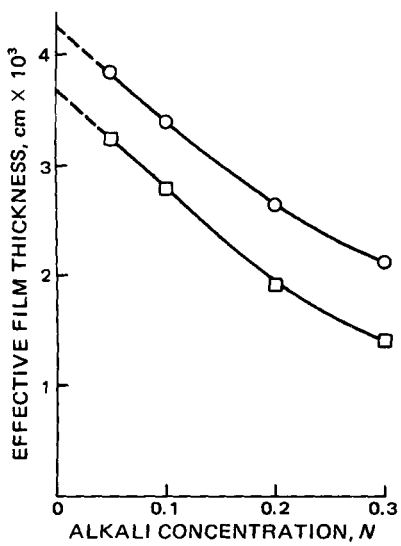

Figure 5—*Effective film thicknesses for dissolution of benzoic acid (○) and salicylic acid (□) in sodium hydroxide solutions.*

Table III—Theoretical and Experimental Dissolution Rates for Benzoic and Salicylic Acids

Compound	h^a, cm × 10^{-3}	Theoretical[b] Dissolution Rate, mg/min/cm²	Experimental[c] Dissolution Rate, mg/min/cm²
Benzoic acid	4.20	0.857	0.845
Salicylic acid	3.68	0.656	0.640

[a] Data obtained from Fig. 5; extrapolated value at zero alkali concentration. [b] Calculated using Eq. 5. [c] Determined at pH-stat 6.2 for benzoic acid and at pH-stat 5.0 for salicylic acid. The rate is the slope of the dissolution curve divided by the surface area of the disk.

When a benzoic acid disk was dissolved in distilled water under the same hydrodynamic conditions, there was a decrease in the dissolution rate with time (Fig. 4). This result is expected for nonsink conditions since the concentration difference is not constant and is decreasing as the benzoic acid dissolves. There is a buildup of benzoic acid in the solution during dissolution, which slows dissolution.

Experimental results indicate that the pH-stat method approximates sink conditions. Since no lag time was involved in establishing the sink, there was at no time a buildup of unionized drug concentration in the dissolution medium. The dissolution rate did not appear to be appreciably affected using the pH-stat method, as was the case when a buffer was used. It appears from these findings that the pH-stat method can be used to establish a perfect sink condition for dissolution studies in distilled water.

If a perfect sink is established in the pH-stat method, the intrinsic dissolution rate should not be affected by the conditions of a pH-stat method and the diffusion layer thickness, h, should remain virtually the same as in distilled water.

Hixson and Baum (15) used various concentrations of sodium hydroxide as the dissolution medium for benzoic acid and calculated the effective film thickness at each concentration. A plot of effective film thickness *versus* initial alkali concentration was extrapolated to zero alkali concentration, and this value was considered as the effective film thickness of the diffusion layer for benzoic acid pellets dissolving in pure water. This general procedure was used in the pH-stat apparatus for benzoic and salicylic acid disks.

A plot of the film thickness *versus* the initial alkali concentration (Fig. 5) extrapolated to a thickness of 3.68 ± 10^{-3} cm for salicylic acid and of 4.2×10^{-3} cm for benzoic acid at zero concentration. This extrapolation should be the diffusion layer thickness of compounds in distilled water according to the concept of Hixson and Baum (15) and should essentially be the thickness of the diffusion layer in the pH-stat method based on the theory that the thickness of the diffusion layer is virtually unaffected by this method.

To test this theory, the extrapolated diffusion layer thicknesses were used to calculate the theoretical dissolution rates of benzoic and salicylic acids and were compared to experimentally determined dissolution rates under the same experimental conditions at pH-stat 6.2 for benzoic acid and at pH-stat 5.0 for salicylic acid (Table III). The theoretical dissolution rates for benzoic acid (0.857 mg/min/cm²) and salicylic acid (0.656 mg/min/cm²) are in close agreement with the experimental rates of 0.845 and 0.640 mg/min/cm², respectively.

These results apparently substantiate the theory that the pH-stat method can be used to establish sink conditions for dissolution studies. Moreover, perfect sink conditions apparently were established under the experimental conditions used.

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NOTES

Synthesis of Dextroamphetamine Sulfate and Methamphetamine Hydrochloride from D-Phenylalanine

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Abstract □ Starting from D-phenylalanine, dextroamphetamine sulfate and methamphetamine hydrochloride were synthesized. The reaction sequence proceeds through three intermediates, in which the absolute configuration of the asymmetric carbon atom is changed but the relative configuration remains the same. Either product can be obtained from a common intermediate by altering the reductive conditions employed for the removal of a carbamate protecting group.

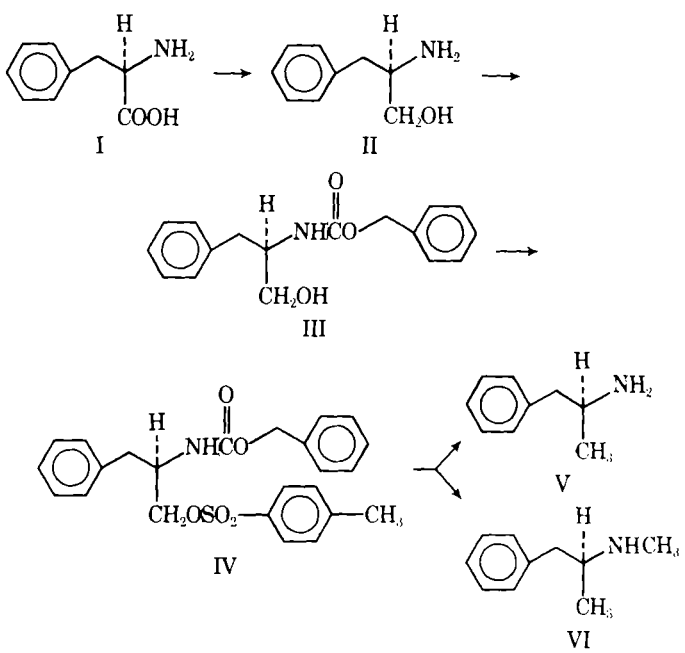
Keyphrases □ Dextroamphetamine sulfate—synthesized from D-phenylalanine □ Methamphetamine hydrochloride—synthesized from D-phenylalanine □ D-Phenylalanine—starting material for synthesis of dextroamphetamine sulfate and methamphetamine hydrochloride □ Stimulants, central—dextroamphetamine sulfate and methamphetamine hydrochloride, synthesized from D-phenylalanine

Following initial observations on the sympathomimetic properties of amphetamine and related compounds (1–4), the racemate of amphetamine was introduced into clinical medicine for the relief of nasal congestion (5). The (*S*)-(+)-isomers of amphetamine [dextroamphetamine (V)] and methamphetamine (VI) (Scheme I) have been used in the therapy of obesity, narcolepsy, parkinsonism, and certain behavioral disorders (6). Considerable interest also has been generated in the central stimulant properties of these compounds (7).

dl-α-Methylphenethylamine and D-α,*N*-dimethylphenethylamine have been prepared by several routes (4, 8–12). The deuterium-labeled analogs of these compounds also have been synthesized (13, 14). Karrer and Ehrhardt (15) originally prepared V from D-phenylalanine *via* the *N,O*-di-*p*-toluenesulfonate derivative of II. Using a modification of that procedure, Gal (16) recently synthesized the deuterium analog of V and the corresponding (*R*)-(−)-isomer for use as internal standards in GLC–mass spectral studies. An asymmetric synthesis of V also was described (17).

An earlier report (18) presented the synthesis of (*R*)-(−)- and (*S*)-(+)-α-methyltryptamine from the corresponding tryptophan isomers. The present work outlines the application of this method to another aromatic α-amino acid, phenylalanine.

The reaction sequence (Scheme I) is essentially the same



Scheme I