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Certain Salts of Atropine, Ephedrine, Epinephrine and Procaine*

By Frank M. Goyan and T. C. Daniels

It is often desirable to reduce the acidity of solutions of the hydrochlorides, hydrobromides and sulfates of physiologically active bases. In many cases this adjustment might be avoided if salts of weak acids were available to replace the salts of highly ionized acids now in use.

A recommendation that any particular salt is suitable cannot be made on the basis of the p_H of the solution alone but must, of course, await careful pharmacologic and clinical evaluation. This is shown by the work of Régnier and co-workers (1, 2, 3) who report different physiologic activity for various salts of the same base, and by Tainter, Throndson and Moose (4) who have made a careful clinical investigation of the relative merits of procaine borate as compared with procaine hydrochloride.

The report of Stover and Brigham (5) on oil-soluble procaine salts supports the conclusion that significant advances may be made by investigating different salts of the same base. This point is further emphasized by the work of Abderhalden and Vlassopoulos (6) who have shown that the presence of amino acids and polypeptides increases the physiologic activity of ephedrine and epinephrine, thus indicating the possible usefulness of salts prepared by neutralizing these bases with suitable amino acids.

A useful salt of any physiologically active base must also satisfy the requirement of stability, either in the solid state or in aqueous solution or, preferably, both. Aqueous solutions of ester-type compounds, unless stabilized, may be expected to undergo decomposition in neutral or alkaline solu-

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tions. This fact is established for procaine hydrochloride by Bullock (7) who recommends that the usual procaine hydrochloride-epinephrine mixtures be dispensed in "dry ampoules" containing the quantity of dry sterile powder necessary to yield a buffered isotonic solution when a stated amount of sterile distilled water is added. The justification for this technique is to be found in the fact that a solution having the optimum p_H for use is unstable with respect to the hydrolysis of procaine and oxidation of epinephrine. The same general difficulty is encountered in the case of atropine. Vincke and Oelkers (8) recommend that atropine be dispensed in solutions having a p_H between 4 and 5 although the best p_H for use has been reported by Gifford and Smith (9) to be approximately 7.6.

THEORETICAL DISCUSSION

A systematic study of the best procedure to be followed in preparing solutions of salts of physiologically active bases must involve considerations of the osmotic effect and p_H of the solutions as well as the stability of the preparation and the equilibrium concentration of the free base. The following equations show the type of equilibria involved in a solution of procaine salt represented by the symbol, PrHX.

$$PrHX = PrH^+ + X^- \quad (1)$$
$$PrH^+ + HOH = PrHOH + H^+ \quad (2)$$
$$PrHOH = Pr + HOH \quad (3)$$

It will be noted that the equilibria represented above may be applied generally. The formula, PrHX, would be replaced by $(NH_3)HCl$ or NH_4Cl when describing a solution of ammonium chloride. With most salts reaction (1) is complete in dilute solutions but if the salt happens to be a weak electrolyte this is not the case. Equation (2) shows that the presence of a substance capable of combining with hydrogen ion (*i. e.*, HPO_4^{--}) will markedly increase the equilibrium concentration of the free base. Bullock (7) has established this point for procaine. If the anion of the salt in question is capable of combining with hydrogen ion to form a weak acid this anion will likewise increase the p_H of the solution and the equilibrium concentration of the free base.

It is reported that solutions to be used parenterally (except intravenous) or to be applied on mucous surfaces should have a p_H equal to or slightly greater than the tissues on which they are employed. This general rule may require slight modification, however, if the equilibrium concentration of the free base becomes the deciding factor, as may be the case where too rapid absorption produces irritation. A slight modification of the p_H, not sufficient to be significant in itself, may be very important in adjusting the equilibrium concentration of the free base as indicated by equation (2). A consideration of these factors indicates that salts may be found whose simple water solution, rendered isotonic when necessary, may prove to be very useful. With this thought in mind the authors have prepared the aspartates, glutamates, levulinates and secondary phosphates of atropine, ephedrine, epinephrine and procaine. Ephedrine nicotinate was also included in the series. Preliminary attempts to produce pure salts by recrystallization from water solution failed to yield satisfactory products.

EXPERIMENTAL

Materials.—The chemicals used were obtained from commercial sources. Ephedrine hemihydrate, atropine base and epinephrine were used without further purification. Procaine was recrystallized, first from ligroin and then from a 50% alcohol-water solution. The equivalent weight of each of the bases was calculated from the results of titration with hydrochloric acid as follows: atropine base 293.2, ephedrine hemihydrate 175.2, epinephrine 188.8 and procaine 237.8. The solutions of acids were titrated against sodium hydroxide. The *l*-aspartic acid was a Pfanstiel product and the *d*-glutamic and levulinic acids were obtained from the Eastman Kodak Company. These acids were used without further purification but the primary sodium phosphate was recrystallized from water and dried to the anhydrous form. The measured concentration of the amino acid solutions was less than two per cent below the concentration calculated from the weight of the solid taken; the levulinic acid was determined to be chloride free and the primary sodium phosphate was analyzed by ignition.

Experimental Procedure.—In order to determine the exact amount of acid required for neutralization of the base for normal salt formation the authors have not relied entirely upon the weights of chemical added but have titrated the bases with different acids using a glass electrode in conjunction with the

p_H meter described by Goyan, Barnes and Hind (10). The work was done at room temperature (18–26° C.), the electrode and bridge being checked from time to time by immersion in 0.05*M* potassium acid phthalate solution the p_H of which was taken to be 4.01.

Weighed samples of the base were added to large test-tubes having a total volume of 200 cc. and oxygen-free nitrogen (pyrogallol treatment) was introduced through glass capillaries reaching to the bottom of the tubes. The nitrogen served to displace air and also for the subsequent stirring of the solutions. Dilute solutions (0.05–0.1*M*) of the different acids were prepared and titrated with a standardized solution of sodium hydroxide. Each sample of base was treated with a sufficient measured volume of one of the acid solutions to give wetting and partial solution. This was followed by the addition of water introduced in such a way as to wash the sides of the tube. Additional measured quantities of acid were then added to the tubes from time to time until complete solution was attained without complete neutralization.

A battery of four tubes was often employed and the glass electrode and agar bridge introduced into them, one at a time. The addition of acid was continued until the end-point was passed as determined potentiometrically. An additional quantity of the base was then added and, when solution was complete, enough acid was added to bring the p_H of the solution to the previously determined potentiometric end-point. This process was repeated for each acid, the resulting solutions being evaporated to dryness under partial vacuum in the tubes in which the titrations were performed. During the evaporation the tubes were held under warm water (40–55° C.) and a steady stream of tank nitrogen bubbled through the solutions. The design of the still-head used for each of the tubes was such that the evaporation could be completed in about two hours. The resulting salts were transferred to vacuum desiccators and dried over magnesium perchlorate or phosphorous pentoxide.

Results.—The results of this investigation may be divided into two sections, the first dealing with the titrations themselves and the second dealing with the properties of the resulting salts. Figure 1 shows the neutralization of ephedrine with the different acids studied, the hydrochloric acid curve being included for comparison only. For the week acids the moles of acid per mole of ephedrine were calculated from the equivalent weight of the ephedrine hemihydrate as determined by titration with hydrochloric acid, the volumes of the acid solutions and their concentrations. The hydrochloric acid curve was calculated more simply by assuming the potentiometric end-point and the stoichiometric equivalent point to be the same within the limit of experimental error.

Figures 2 and 3 refer to similar work with atro-

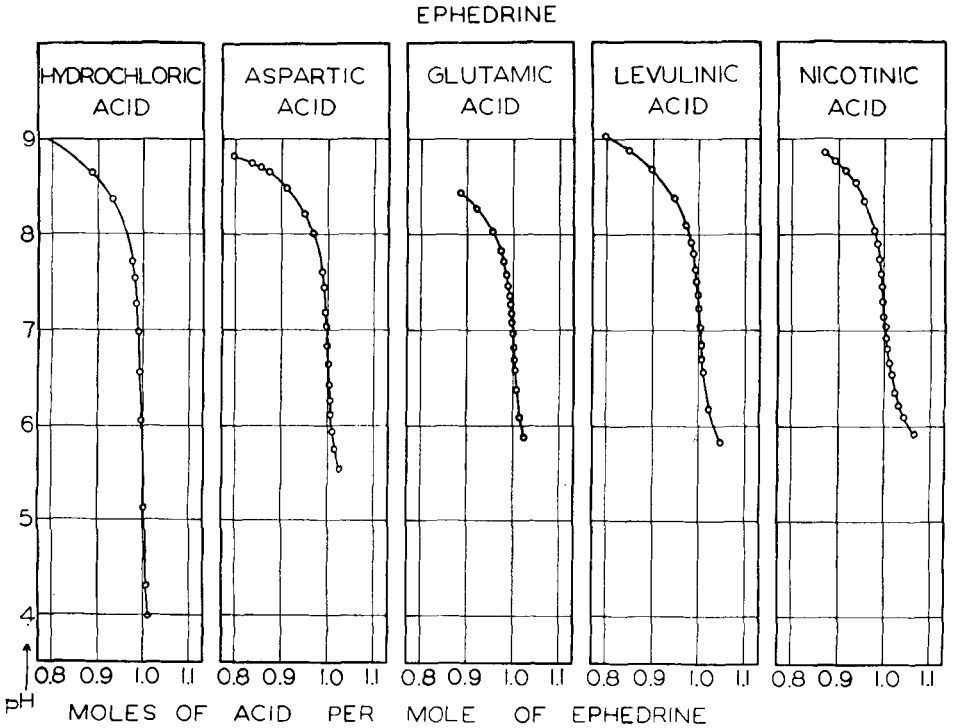

Fig. 1.—Moles of Acid per Mole of Ephedrine Calculated for the Weak Acids from the Equivalent Weight of Ephedrine Hemihydrate (175.2) Obtained from Titration with Hydrochloric Acid. The Curve for Hydrochloric Acid Was Plotted by Assuming the Stoichiometric and Potentiometric End-points to Be the Same within the Limits of Accuracy of the Work.

pine and procaine, respectively. The stoichiometric end-point for each titration of procaine and atropine with each of the weak acids was calculated from the equivalent weight determined by titrating with hydrochloric acid. This value deviated by one or two per cent from the observed potentiometric end-point. No such deviation was observed for ephedrine although the three dissociation constants do not differ by enough to account for this error. This led to the conclusion that the slight deviation was due to hydrolysis of the ester-type bases. Since the direction of the deviation confirmed this conclusion it was decided to correct the individual curves before plotting. This was accomplished by calculating the equivalent weight of each base from the titration with each of the weak acids employed and using for each base the respective average of these values. though the technique used effectively prevented oxidation. Figure 5 shows the results obtained for the phosphates which were placed on a separate graph because a comparison of all of the phosphate curves seemed to be of some interest. The weakness of the acid produces curves of characteristic shape.

Calculations.—Equivalent weights of the bases recorded under the section on materials were used except as noted below the figures. *l*-Aspartic acid solutions of 0.0490*M* to 0.0492*M* were employed. The concentration of *d*-glutamic acid was 0.0497*M* and that of levulinic acid was 0.1222*M*. However, atropine and epinephrine were titrated with 0.0566*M* levulinic acid. The primary sodium phosphate was used at a concentration of 0.1005*M* and the hydrochloric acid was always 0.1000*M*. Samples of base were weighed by difference to within 0.2 mg. using

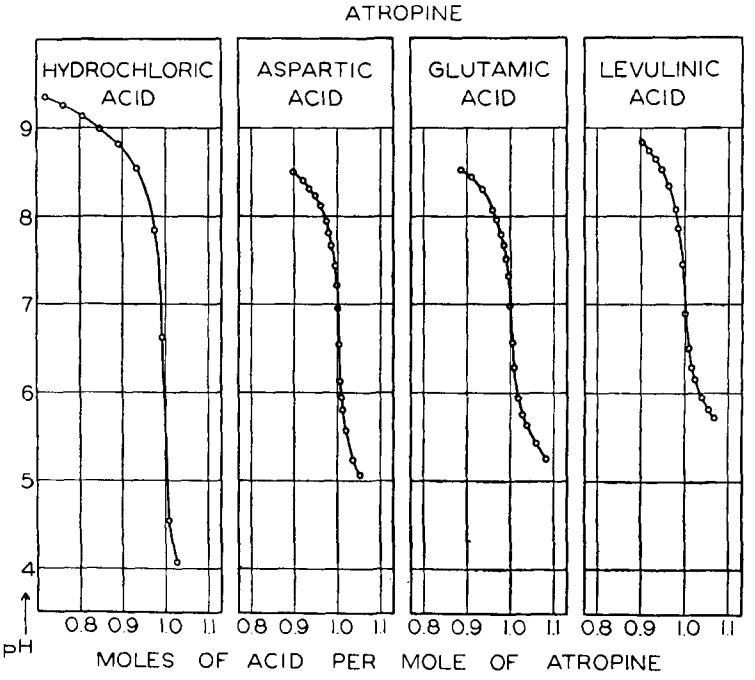

Fig. 2.—Moles of Acid per Mole of Atropine Calculated for the Weak Acids by Using the Average Equivalent Weight (295.6) Obtained by Assuming That Each Potentiometric End-point with the Weak Acids Corresponded to the Stoichiometric End-point. This Treatment Was Introduced to Correct for a Small Error Due to Hydrolysis. Otherwise the Method of Calculation Described for Ephedrine Was Followed.

This arbitrary procedure is justified because it is desirable to make the curves correspond to results obtained in the absence of hydrolysis. The equivalent weight employed in each case is recorded below the figures. Variations in the time required for the completion of the titrations and the relative alkalinity of the solutions can well account for the observed differences. Figure 4, for epinephrine, was plotted in the same manner using the equivalent weight obtained in the titration with hydrochloric acid. The technical difficulties involved in dissolving the epinephrine are apparent in the curves, al-

calibrated weights. The final volume of the solutions titrated averaged approximately 100 cc. except in the case of epinephrine where the volume was about 150 cc. On this basis the final molal concentration of the salt solutions are recorded in the order, aspartate, glutamate, levulinate, phosphate, nicotinate as follows: ephedrine 0.013, 0.015, 0.025, 0.027, 0.022; atropine 0.0075, 0.0051, 0.0038, 0.0084; procaine 0.011, 0.013, 0.010, 0.012; epinephrine 0.0075, 0.0062, 0.0029. Only approximate values are given because the concentration of the salt does not enter into the calculations.

It will be noted that the p_H at the equivalent point (corresponding to 1.0 on each abscissa) is in good agreement with the p_H calculated by using the well-known approximate equation for obtaining the p_H of solutions of salts of weak acids neutralized by weak bases.

$$p_H = {}^1/_2pK_a + {}^1/_2pK_w - {}^1/_2pK_b \qquad (4)$$

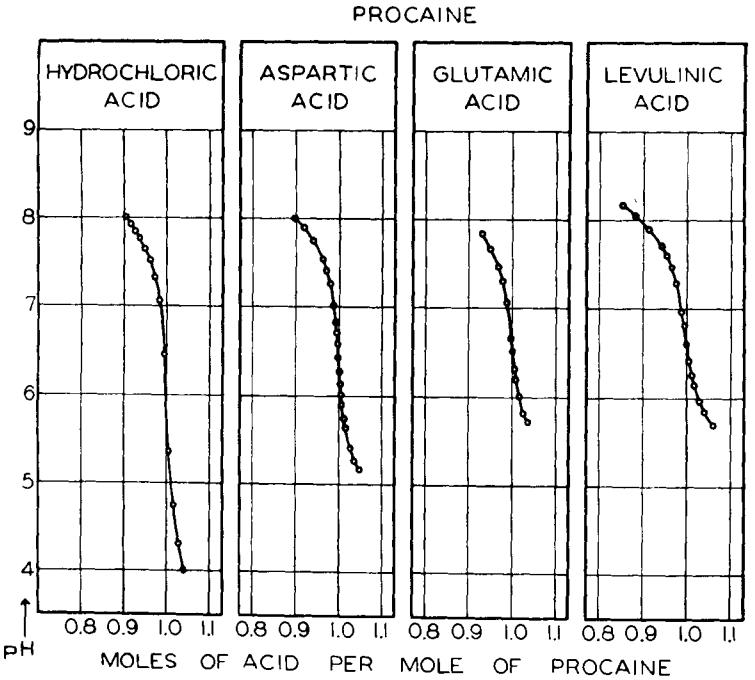

Fig. 3.—Moles of Acid per Mole of Procaine Were Calculated by the Method Described for Atropine. The Average Equivalent Weight of 241.1 Was Used for Procaine.

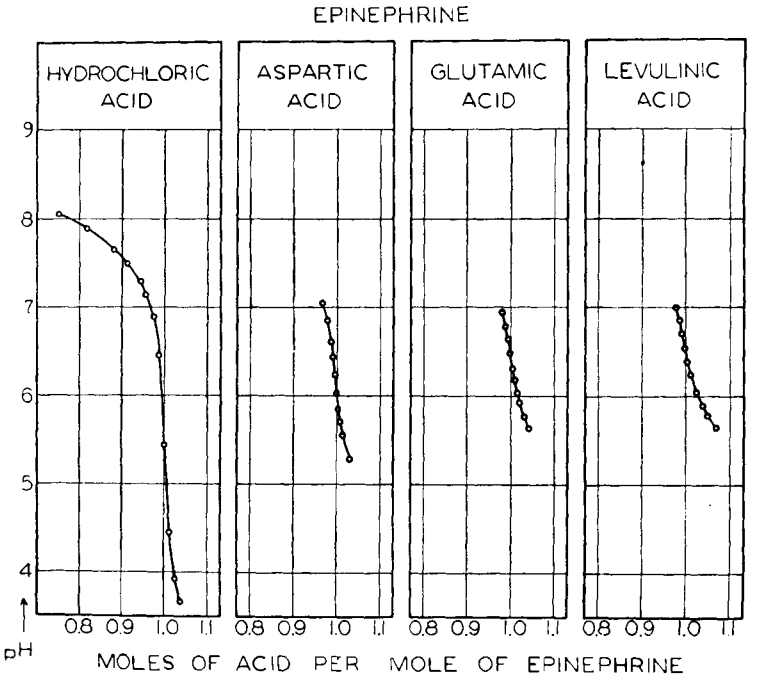

Fig. 4.—Moles of Acid per Mole of Epinephrine Were Calculated by the Method Described for Ephedrine.

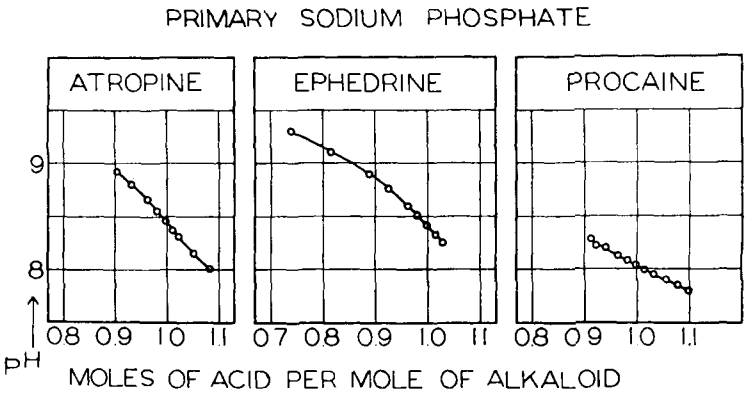

Fig. 5.—Calculations of These Curves Were Carried Out as Described for the Other Weak Acids of Figs. 1, 2 and 3.

pK_a, pK_w and pK_b refer to the negative of the logarithm of the dissociation constants of acid, water and base, respectively. Since the calculations were not intended to give results of the highest accuracy, the value of 14 was chosen for pK_w and the dissociation constants of acids and bases were chosen from the literature from the best available sources, employing values given for room temperatures. The comparison of the calculated p_H of the salts represented by the equivalent point on the curves is shown in Table I.

Solubility of Salts.—After the resulting products had been dried for several days in vacuum desiccators the approximate solubilities were determined by finding the least amount of water required to dissolve a weighed quantity of the salt. This work was done at room temperatures with constant stirring by hand. All of the salts were extremely soluble, most of them dissolving in an equal weight, or less, of water The phosphate of ephedrine deviated from this rule, 1.0 cc. of water being required to dissolve 0.164 Gm. Procaine phosphate was soluble to the extent of 0.086 Gm. in 0.12 cc. and the epinephrine salts showed slight turbidity, the glutamate in twice its weight of water, the levulinate in five times its weight and the phosphate in 100 times its weight of water. Procaine levulinate and epinephrine aspartate were viscous liquids even after standing in the desiccator for several weeks.

p_H of Salt Solutions.—At the time the solubility studies were made a portion of each salt solution was introduced into the glass electrode chamber and nitrogen was bubbled through the solution. Readings were made every few minutes and the p_H of each solution was recorded when the last two readings were the same within 0.02 of a p_H unit. The p_H values are compared with the p_H of the solutions at the end of the titrations and before evaporation. The results are given in Table II.

Discussion.—It will be noted from an examination

Table I.—A Comparison of Calculated and Observed p_H of Salt Solutions

	Atropine pK_b = 4.35 (11)		Ephedrine pK_b = 4.64 (12)		Epinephrine pK_b = 5.6 (13)		Procaine pK_b = 5.15 (11)	
	p_H		p_H		p_H		p_H	
	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
Aspartic acid, pK_a = 3.87 (14)	6.9	6.8	6.7	6.6	6.0	6.1	6.3	6.4
Glutamic acid, pK_a = 4.28 (14)	7.0	7.0	6.9	6.8	6.4	6.3	6.5	6.6
Levulinic acid, pK_a = 4.59 (15)	7.1	7.1	7.2	7.0	6.5	6.5	6.6	6.7
Nicotinic acid, pK_a = 4.80 (16)	...	...	7.1	7.1	...	...	...	...
Primary phosphate, pK_a = 7.16 (17)	8.4	8.4	8.4	8.3	...	...	8.0	8.0

Table II.—Comparison of the p_H before and after Evaporation

	Atropine		Ephedrine		Epinephrine		Procaine	
	Before	After[a]	Before	After[a]	Before	After[a]	Before	After[a]
Aspartic acid	6.75	6.53	6.52	6.16	6.14	6.15	6.38	5.98
Glutamic acid	6.95	6.82	6.86	6.34	6.32	6.30	6.43	6.37
Levulinic acid	7.03	7.03	7.00	6.58	6.52	5.94	6.67	6.70
Primary sodium phosphate	8.38	8.18	8.36	8.28	7.76	7.52	8.11	8.03

[a] These deviations may be attributed to relatively slow changes such as the hydrolysis of ester-type bases or the possible loss of volatile constituents during evaporation. The decrease in p_H of the epinephrine levulinate and epinephrine sodium phosphate may be correlated with the turbidity described under the section on solubility.

Table III.—Physical Properties of Salts Obtained by Evaporation[a]

	Atropine	Ephedrine	Epinephrine	Procaine
Aspartic acid	Deliq. white cry.	White cry., m. dec. 207° C.	Brown viscid liquid	Deliq. white cry.
Glutamic acid	Deliq. white cry.	White cry., m. 145–146° C., slow dec.	Brown cry.	Deliq. off color cry.
Levulinic acid	Deliq. paste	White needles, m. 88° C., sublimes[b]	Brown cast solid	Brown liquid
Nicotinic acid	.....	White cry., m. 118° C.	.....	.....
Primary sodium phosphate	Sinters at 100° C., white cry.	White cry., sinters 170° C., dec. 209° C.	Brown granular solid	Deliq. white cry.

[a] Abbreviations: deliq.—deliquescent; dec.—decomposes; cry.—crystals.
[b] Ephedrine levulinate may be purified by sublimation at 75° C. The purified product is a mass of loosely packed fiber-like birefringent crystals which melt at 88° C.

of the data given in Tables II and III that the technique of evaporation under a vacuum, while serving to reduce the amount of hydrolysis in procaine and atropine, does not accomplish this purpose entirely and tends to promote other changes. These factors are apparent in the data of Table II. The additional observation that the salts of procaine and atropine are deliquescent supports the conclusion that preparation of aqueous solutions of these substances is best accomplished by neutralizing the base with the appropriate acid at the time of use instead of preparing the solid salt. Vincke and Oelkers (8) have shown that buffered atropine preparations decompose in the solid state if they become slightly moist, thus indicating that hygroscopic ester-type salts may be expected to undergo hydrolysis unless kept under completely anhydrous conditions. The salts of ephedrine may be prepared and stored for use and for this reason a further study of the properties of these salts and their solutions is being undertaken together with a study of the rate of hydrolysis of the ester-type bases.

ACKNOWLEDGMENT

The authors are indebted to Dr. C. L. A. Schmidt for supplying the *l*-aspartic acid used in this work and also for his suggestion that a study of the amino acid salts of physiologically active bases should be of interest.

SUMMARY

Solutions of salts of four physiologically active bases were prepared by exact neutralization with weak acids after it was shown that recrystallization from water solution failed to yield satisfactory salts. Potentiometric titration curves are shown for the formation of aspartates, glutamates and levulinates of atropine, ephedrine, epinephrine and procaine. Similar curves are shown for the neutralization of atropine, ephedrine and procaine with primary sodium phosphate and for the neutralization of ephedrine with nicotinic acid.

The calculated p_H values for the equivalent point of each titration are in good agreement with the values read from the curves. The products prepared by evaporating the salt solutions to dryness did not in all cases redissolve in distilled water to give solutions having the original p_H. The possible significance of some of these changes are discussed.

The approximate solubilities and certain general properties of these products are given. Atropine and procaine salts of the weak acids studied are deliquescent but those of ephedrine appear to possess desirable properties. Melting points of the ephedrine salts are recorded and pure ephedrine levulinate, prepared by sublimation, is described.

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A Study of Intermolecular Compounds*

By Helmut M. Haendler with L. Wait Rising†

The residual affinity possessed by various organic compounds, whatever its origin, is a property somewhat difficult, if not impossible, to measure quantitatively. To attempt the prediction of the possibility of formation of an intermolecular compound on the basis of present evidence is useless. In most cases the procedure is somewhat empirical; solutions of the compounds are mixed and an effort made to isolate any crystalline products. The application of melting point curves, however, simplifies the method considerably, and with the collection of sufficient data the prediction as to the possibility of forming intermolecular compounds can be expected to become more definitive.

Knowledge of this sort would be particularly helpful in the field of pharmaceutical chemistry, where the preparation and chemotherapy of new compounds is of great value. Consequently, it was decided to study certain pharmaceutical combinations to determine, if possible, what compounds in particular exhibit a tendency to combine in this fashion.

The "thaw-melting point" curve (1) offers the quickest and most reliable method for this type of study. It is possible to tell directly whether a compound is formed or whether the two components merely formed a eutectic mixture. As the temperature of a mechanical mixture of the two components is raised, a point is reached where the material appears to soften or "thaw." Further heating causes complete melting, and the temperatures at which these two phenomena occur are plotted against mol percentages of various mixtures of the two substances.

EXPERIMENTAL

The combinations of acetanilid, in particular, and of several other pharmaceuticals were studied. Varying amounts of the two U. S. P. chemicals of each system, dried in a vacuum desiccator, were weighed into small test-tubes, melted in an oil bath, allowed to solidify, pulverized and the melting points taken. An aluminum block, drilled for a thermometer and a capillary tube, heated by a micro burner, and equipped with a viewing microscope, was used for the measurements.

In general, one of two types of curves is obtained. In the case of a eutectic mixture, the curve is represented as in (*a*) of Fig. 1; in the event that a compound is formed, the shape assumed is that of (*b*). The point at which the thawing curve, which is the lower of the two, intersects the melting curve represents the eutectic point in the first case (*a*); the three intersections represent the two eutectics and the melting point of the compound formed, if such is the case, as in (*b*).

None of the systems observed have given evidence of compound formation. The observational data for each system studied are given in Tables I to XII. In these tables, the mol percentage of one component is given, followed by the observed thawing temperature and the final observed melting point. From graphical consideration of these data, the

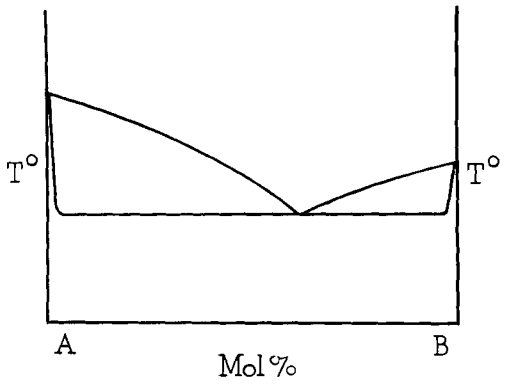

Fig. 1 (*a*).—Thaw-Melting Point Curve for a Eutectic.

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