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THE SOLUBILITIES OF THE PHARMACOPŒIAL ORGANIC ACIDS AND THEIR SALTS

BY

ATHERTON SEIDELL

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THE SOLUBILITIES OF THE PHARMACOPŒIAL ORGANIC ACIDS AND THEIR SALTS.[a]

By ATHERTON SEIDELL,

Chemist, Division of Pharmacology, Hygienic Laboratory, U. S. Public Health and Marine-Hospital Service.

INTRODUCTION.

Among the physical properties of the chemical compounds of the Pharmacopœia none have apparently received more attention at the hands of the compilers of the book than the solubilities. The reasons for this are no doubt due to the fact that such data are known to be of practical value to the pharmacist on the one hand and to the physician on the other. The former uses the figures as a guide in compounding every mixture he is called upon to make; the latter must take this property into consideration in the selection of many substances he prescribes for particular purposes. It is to the chemist, however, who is concerned with the preparation, purification, and accurate determination of chemical compounds, that solubility data are of greatest importance. Most analytical methods are more or less directly dependent upon some solubility relation; furthermore, the technical production of a large proportion of the chemicals and drugs now in use is made possible only by means of known solubility characteristics.

The very fact of the diversified uses which solubility data fulfill accounts for the great variation in the accuracy of the results reported in the literature. One investigator may have desired a solvent for a new compound, while another may have been concerned with the solubility of a precipitate obtained in making a molecular weight determination. Probably very few have worked under identical conditions, either of purity of the substance or of the solvent, of equally exact temperature regulation or care in securing the saturation of the solution. It is easy, then, to understand why equally creditable reference books may differ so widely in the values, gathered from the literature, for the solubility of the same compound.

[a] Manuscript submitted for publication May 18, 1910.

Of reference books for this class of data, the pharmacopœias of the various countries are particularly subject to differences in the values quoted. This fact was very forcibly demonstrated by a compilation made by me [a] some two years ago of the solubilities and other physical constants reported by the latest pharmacopœias and pharmaceutical reference books. The extent of the variations for some of the compounds, especially the inorganic salts, was not very great; for many others, however, there was no way of deciding which of the reported values were nearest the truth. This was especially the case with the alkaloids, and to a large extent with the other organic compounds of the pharmacopœias. The matter was still further complicated by the fact that very concordant results were sometimes reported, although the standards of temperature, purity, etc., indicated that such good agreement was not justified, thus showing that the compilers of these works of reference frequently borrow from one another without giving the information which would enable the reader to consult the original source of the data. These difficulties and many others made it impossible to gather from the compiled solubility values the particular ones which might be considered the most reliable; in fact, the great number of different figures only added to the uncertainty and made it apparent that the publication of the compilation could serve no other purpose than to call attention to the need for renewed investigations of the solubilities of the pharmacopœial compounds. The original intention of publishing this compilation as a bulletin from this laboratory was therefore abandoned in favor of publishing only such values as we might be able to determine with accuracy or select from the chemical literature as of undoubted reliability.

Although, as has been pointed out above, the solubility data for alkaloids and their salts are perhaps most in need of careful revision, the lack of a sufficient amount of material and of satisfactory methods for their accurate determination made it advisable to leave this class of substances for a later study and take up first a group which offered less difficulties and for which, after the alkaloids, there appeared most need for careful investigation. This group is that of the organic acids and their salts, and is composed of about 40 compounds, the solubilities of very few of which, in the solvents prescribed by the Pharmacopœia, have been reported in recent chemical literature. For this group of compounds, therefore, original determinations were required for practically every member.

In the present bulletin the arrangement is alphabetical according to the names of the acids, with the salts of each immediately follow-

[a] For a more complete description of this compilation, with comments, see Proc. Am. Pharm. Assoc., **55**, 473–479, 1907.

ing. The solubility of each acid has been determined in water and aqueous alcohol solutions of varying concentrations and in a large number of the common organic solvents. For the salts, determinations only in the water and aqueous alcohol solutions are given. Although the strength of the alcohol used as the solvent when the solubility in this substance is mentioned in the Pharmacopœia is generally understood to be that of the official strength, viz, 92.3 per cent by weight, it is evident that from a practical standpoint the solubility of substances in alcohol of slightly and also widely different strengths would be useful in many cases. Furthermore, the determination of the solubility in alcohols of different strengths does not require a very much greater amount of work than the determination in only one strength, since in the former case the result in each solvent is as satisfactory a check upon the results found for the other strengths of alcohol, when all are plotted on cross-section paper, as would be an equal number of duplicate determinations in alcoholic solutions of the same concentration. The results for the whole series of alcoholic concentrations give curves which, by their direction, whether horizontal or greatly inclined, show the extent of the influence of small differences in alcoholic concentration upon the solubility at any given point. The added value of the results over the determination in alcohol of official strength only, seems therefore, sufficient to warrant the expenditure of the additional time required. There is still another point worthy of consideration, and that is the possibility of learning more in regard to the nature of solution in mixed solvents—whether it is a mechanical relation proportional to the amounts of the two liquids present or controlled by some other factor not as yet known.

The results are given in the tables in all cases in the terms in which solubility data are usually expressed in the chemical literature, and in addition the equivalent values are expressed as customarily found in the pharmaceutical literature, viz, the amount of solvent required to dissolve a unit amount of the dissolved substance. Although this latter mode of expressing solubility results has been used for many years by pharmacists, it is unscientific and not even as useful for practical purposes as the percentage basis adopted by chemists. As an illustration, pharmacists are usually called upon to compound their mixtures in certain definite amounts, and therefore the quantity of the dissolved substance which will be contained by the given volume of the solution is certainly of more practical interest to them than the knowledge of the amount of the solvent required for one part of the given substance. It would therefore appear of considerable advantage to pharmacists to abandon their antiquated mode of expressing solubility results and adopt the more rational percentage or unit of solvent basis in their pharmacopœias and pharmaceutical reference books.

EXPERIMENTAL METHODS.

In all cases attempts were made to purify the material used for the solubility determinations at least to the extent required by the purity rubric of the Pharmacopœia. In a very few cases this could not be done with certainty, but in the others was accomplished successfully. The samples were analyzed quantitatively and the results reported in connection with the solubility determinations in most cases. It is believed that in those cases where the presence of certain very small amounts of unknown impurities were indicated by the analyses they were not sufficient to exert an appreciable effect upon the solubility values reported. This is concluded from the observation that in several instances determinations made upon samples containing considerable more impurity than shown by the analyses of the majority of the following compounds did not differ appreciably from the results obtained with the material of the highest purity.

All of the solubility determinations, except those for the liquid compounds, ethyl acetate, methyl salicylate, and oleic acid, were made under strictly identical conditions. A constant temperature water bath, regulated to within + 0.05° of 25° C., was used. The saturated solutions were prepared by mixing the solvent and the salt in thick-walled test tubes of about 15 to 20 cubic centimeters capacity, closed with well-washed rubber stoppers. Glass-stoppered cylinders were used for the determinations made in organic solvents. The test tubes or cylinders, as the case might be, were attached to a rotating frame immersed in the water bath and revolved upon the axis parallel to the diameter of the test tube at a rate of about six revolutions per minute. Equilibrium was assured in most cases by analyzing solutions which had been agitated for different lengths of time. In those cases where only one series of determinations was made the time of shaking was continued long enough to insure complete saturation. Care was taken that a sufficient excess of salt was in contact with every solution at the saturation point.

The time allowed in the present experiments for obtaining saturated solutions is not necessarily an indication of the time that is actually necessary. It is very probable that the saturation point could be reached in very much shorter time than indicated in most of the following experiments, but since the object was to ascertain the true solubility in the several cases care was taken that sufficient time for obtaining the maximum solubility should be allowed in every case.

A sufficient quantity of each of the aqueous alcoholic solutions for all of the experiments was prepared at the beginning and the specific gravities of these solutions carefully determined by the pycnometer

method. These determinations were made upon the solutions cooled to 15°, and the weight per cents of absolute alcohol (C_2H_5OH) corresponding to each was read from the U. S. Pharmacopœia alcohol table.

The general plan of analyzing the saturated solutions was as follows: At the end of the period of rotation the tubes were placed in an upright position in the bath until the undissolved salt had settled to the bottom. Each tube was then removed to the laboratory table in a beaker filled with the water of the constant temperature bath, and immediately thereafter the supernatant clear liquid was siphoned directly into a 10-cubic centimeter pycnometer with the aid of a suction pump. The suction siphon used for this purpose consisted of a closed glass cylinder just large enough to contain the pycnometer. The siphon tube passed through the stopper of this cylinder directly into the mouth of the pycnometer. Another glass tube through the stopper served to connect the apparatus with the suction pump. In those cases where there was suspended matter remaining in the saturated solution a small tube containing a plug of cotton or of glass wool in the case of organic solvents was attached to the end of the siphon which was introduced into the saturated solution. After filling, the pycnometer was weighed and, in the case of salts which could be dried without decomposition, the saturated solution was transferred to a weighing bottle, evaporated to dryness, and the residue weighed. With the organic acids which could be titrated, or with the salts which decomposed on drying, the saturated solutions were transferred to graduated flasks and aliquot portions analyzed in the most convenient manner.

The results in all cases were calculated to the grams of salt dissolved in 100 grams of the saturated solution. The figures were plotted as the abscissæ and the weight per cents of alcohol in the several solvents as the ordinates on cross-section paper. The curve drawn through the several points represents the solubility of the particular salt in the aqueous alcoholic solutions of increasing content of alcohol. From this curve the figures corresponding to regular intervals of alcoholic strength of the solvent were read.

The specific gravities are in all cases the weight of a given volume of the saturated solution or of the alcoholic solvent divided by the weight of an equal volume of water at the same temperature, i. e., $d_{\frac{5}{5}}^{\frac{5}{5}}$, or for the alcoholic solvents, $d_{1\frac{5}{5}}$.

ACETIC ACID AND THE ACETATES.

The solubility of acetic acid.—Although this acid mixes with water, alcohol, and the ordinary organic solvents in all proportions, numerous experiments have shown that when a given quantity is added to a mixture of equal volumes of water and an immiscible solvent

there is a distribution between the two layers which varies considerably with the nature of the immiscible solvent. To illustrate the differences more clearly, the following table (No. I) has been compiled from the available results. In this table the organic solvents have been arranged in the descending order of their power of withdrawing acetic acid from its aqueous solution. It will be seen that amyl alcohol exerts by far the strongest solvent action, chloroform comes next, with less than one-sixth the strength, and then follow bromoform, benzene, toluene, the xylenes, carbon tetrachloride, and carbon bisulphide in a gradually descending scale of efficiency as solvents for acetic acid. A comparison of these results with those for the other pharmacopœial acids in some of the above solvents show that the general order of their solvent action is nearly the same for the whole series of acids.

TABLE NO. I.—*Distribution of acetic acid between water and several immiscible organic solvents at 25°.*

[Compiled from the results of Herz and Fischer, Ber. **37**, 4747, 1904; **38**, 1140, 1905; Herz and Lewey, Z. electro. Chem., **11**, 818, 1905, and Rothmund and Wilsmore, Z. physik. Chem., **40**, 623, 1902.]

CH_3COOH per 100 c. c. H_2O layer.	CH_3COOH per 100 c. c. of the immiscible layer.								
	Amyl alcohol.	$CHCl_3$.	$CHBr_3$.	C_6H_6.	$C_6H_5CH_3$.	$C_6H_4(CH_3)_2$ (o) or (p).	$C_6H_4(CH_3)_2$ (m).	CCl_4.	CS_2.
Grams.	*Grams.*	*Grams.*	*Grams.*	*Grams.*	*Grams.*	*Grams.*	*Grams.*	*Grams.*	*Grams.*
2	1.847	0.089	.....	.....	.....	.....	.....	.....	.....
5	4.587	0.450	.....	0.13	0.12	0.24	0.06	.....	.....
10	[a] 9.100	1.430	.....	0.42	0.33	0.48	0.30	.....	.....
20	.....	5.100	1.5	1.55	1.13	1.13	0.95	.....	.....
30	.....	10.200	3.0	3.03	2.26	2.15	1.91	1.8	.....
40	.....	15.300	4.8	4.95	3.73	3.40	3.04	3.0	.....
50	.....	21.900	7.8	.....	5.84	5.10	4.65	4.8	.....
60	.....	.....	12.0	.....	8.34	7.27	6.65	5.8	2.3
70	.....	.....	27.0	.....	.....	12.52	.....	12.0	3.0
80	.....	.....	.....	.....	.....	.....	.....	.....	5.4

[a] Estimated.

The solubility of ethyl acetate in aqueous alcohol solutions.—The U. S. Pharmacopœia description of this product specifies that it consist of about 90 per cent by weight of ethyl acetate and 10 per cent of alcohol containing a little water. Since, however, the alcohol which a given sample of the compound may contain is wholly soluble in water, it follows that the saturation of the solution is due only to the ethyl acetate present. For the purpose of the determination of the solubility of the pharmacopœial acetate it is therefore evident that the object will be more satisfactorily attained by the investigation of the solubility of the pure compound in aqueous alcohol solutions of increasing concentration. Studies of this character were made some years ago by Bancroft [a] in the manner that ethyl acetate was grad-

[a] Phys. Review, **3**, 122, 131, 1895–96.

ually added to mixtures of known volumes of alcohol and water until an opalescence was observed. The experiments were made at 20°. Furthermore, the water and ethyl acetate used were each previously saturated with the other. It would therefore be necessary to apply a calculated correction factor to the results in order to bring them to the terms desired for the present purposes. In view of the possible uncertainty which might arise through such calculations it appeared more desirable to make new determinations upon materials of highest purity.

The ethyl acetate used was prepared from the Kahlbaum product by allowing it to stand over calcium chloride for a day, filtering, and distilling. That part of the liquid, amounting to nearly one-half of the whole, which distilled between 75° and 76° (corrected) was reserved for the solubility determinations. The specific gravity of this fraction was 0.8984 at 15°, 0.8948 at 20°, and 0.8915 at 25°. The aqueous alcohol solutions were those prepared, as already mentioned (p. 10), for the solubility determinations of all the compounds described in this bulletin. The method used in the present case was as follows: The accurately measured portions of the aqueous alcohol solutions were placed in small Erlenmeyer flasks and brought to as near 25° as possible; a burette was filled with the purified ethyl acetate, which had been allowed to remain in the constant temperature bath at 25° for an hour or longer. The temperature of the room at the time the determinations were made was 22° to 24°. The ethyl acetate was added very gradually to the aqueous alcohol and the solution shaken between each addition. The saturation point was indicated by the appearance of a distinct opalescence, less than 0.05 cubic centimeter being sufficient to cause the change from clear to cloudy condition in most cases. Satisfactory concordance in duplicate determinations was obtained. The flasks containing the slightly opalescent saturated solutions were suspended in the constant temperature bath for an hour or longer, after which time the specific gravities of the solutions were determined by the pycnometer method. The results of the determinations are given in Table No. II and show that ethyl acetate is completely miscible with aqueous alcohol solutions of about 40 weight per cent or more concentration. The curve for this compound in Plate No. I shows that the solubility increases gradually at first and then very rapidly, with increase of alcoholic strength of the solvent.

TABLE NO. II.—*The solubility of ethyl acetate in aqueous alcohol solutions at 25° C.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$CH_3COOC_2H_5$ per 100 c. c. solvent.	$CH_3COOC_2H_5$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.			
			c. c.	*Grams.*
Dist. H_2O	0.0	0.9993	9.6	7.90
0.9856	8.9	0.9897	11.8	9.64
0.9752	17.0	0.9690	17.0	13.45
0.9628	26.4	0.9414	49.0	31.19
0.9545	32.0	0.9268	86.1	44.58
0.9359	41.7	.....	∞	∞

CALCULATED RESULTS.

The above results plotted on cross-section paper gave a curve from which the following figures were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$CH_3COOC_2H_5$ per 100 c. c. solvent.	$CH_3COOC_2H_5$ per 100 grams.		Solvent to dissolve 1 gram $CH_3COOC_2H_5$.
			Saturated solution.	Solvent.	
		c. c.	*Grams.*	*Grams.*	*Grams.*
0	0.999	10.0	7.9	8.6	11.10
5	0.993	10.5	8.7	9.5	10.50
10	0.986	12.0	9.8	10.9	9.20
15	0.974	15.0	11.7	13.3	7.50
20	0.960	27.0	16.4	19.6	5.10
25	0.945	44.0	27.0	37.0	2.70
30	0.931	70.0	40.0	66.7	1.50
35	0.918	125.0	57.0	132.5	0.75
40	.....	∞	∞	∞	.....

Since the effect of the alcohol upon the solubility of the acetate is gradual at first, it follows that the solubility of the pharmacopœial product containing approximately 10 per cent alcohol is not very different from the value shown above for the pure compound. Thus if pharmacopœial ethyl acetate containing 10 per cent alcohol be added to 100 grams of pure water the necessary amount to form a saturated solution would carry with it only enough alcohol to make an approximately 1 per cent aqueous alcoholic solvent; therefore the amount of the pharmacopœial acetate required would be only about one-tenth more than the quantity of the pure compound indicated in the above table—i. e., 8.6 +0.86 grams=9.66 per 100 grams water or 10.3 weight parts of water per 1 part of pharmacopœial ethyl acetate. This figure is somewhat higher than that quoted by the present Pharmacopœia, viz, 9.0 parts water per 1 part acetate.

The solubility of ethyl acetate in water at different temperatures.—Two determinations of the solubility of ethyl acetate in water at 20° and 28° are reported in the literature respectively by Bancroft[a] and

[a] Loc. cit.

Euler.[a] The results in terms of grams of ethyl acetate per 100 cubic centimeters of water are, at 20°, 8.25 grams, and at 28°, 7.26 grams. Since these figures indicate that this compound shows the rather unusual property of a decreasing solubility with increase of temperature, and also since my value for 25° did not fall between these two for a higher and lower temperature, it appeared desirable to investigate the solubility of this compound in water over a range of temperature.

The determinations were made by titrating to appearance of opalescence 50 cubic centimeter portions of distilled water, of approximately the desired temperature, with the purified ethyl acetate described above and noting the exact temperature of the mixture immediately after the saturation point was reached. The actual readings were made between 10° and 40°, but the regularity of the curve permitted the extention of the values beyond this range as shown in the accompanying table, No. III.

TABLE No. III.—*The solubility of ethyl acetate in water at temperatures between 0° and 55° C.*

Temperature.	$CH_3COOC_2H_5$ per 100 c. c. H_2O.	$CH_3COOC_2H_5$ per 100 grams H_2O.	$CH_3COOC_2H_5$ per 100 grams saturated solution.
°C.	c. c.	*Grams.*	*Grams.*
0	13.20	11.8	10.53
5	12.10	10.8	9.74
10	11.30	10.1	9.15
15	10.70	9.5	8.71
20	10.10	9.0	8.27
25	9.60	8.6	7.90
30	9.20	8.2	7.61
35	8.90	7.9	7.39
40	8.60	7.7	7.17
45	8.35	7.4	7.00
50	8.10	7.2	6.81
55	7.94	7.1	6.70

In addition to the above determinations of the solubility of ethyl acetate in water and alcohol solutions, one determination was made of the solubility of water in ethyl acetate giving the following results:

Cubic centimeters of H_2O per 100 cubic centimeters $CH_3COOC_2H_5$ at 25°=4.8.
Grams of H_2O per 100 grams $CH_3COOC_2H_5$ at 25°=5.38.
Specific gravity of saturated solution at 25°=0.9059.

The solubility of lead acetate in aqueous alcohol solutions.—Since no quantitative method is prescribed by the pharmacopœia for the determination of the purity of lead acetate, the following plan, based upon the insolubility of lead sulphate, was used. A weighed amount of 0.5 to 1.0 gram of the sample is dissolved in about 50 cubic centimeters of distilled water and dilute H_2SO_4 added to the cloudy solution until no further precipitation occurs. The flocculent white precipitate is filtered on a weighed Gooch crucible, washed with a little water, and finally with a few cubic centimeters of alcohol, dried

[a] Z. physik. Chem., **31**, 360, 1899.

in an oven at about 150°, and weighed as $PbSO_4$. The solubility of lead sulphate in water is stated to be 0.041 gram per liter, and therefore in case the filtrate and washings in the determination as above outlined amount to 100 cubic centimeters the error, when a 0.5 gram sample is employed, may amount to 1 per cent. It is probable, however, that the excess of sulphuric acid used for the precipitation would lower this error somewhat.

A number of commercial samples of lead acetate examined in this laboratory by the above method gave results showing, when calculated to $Pb(C_2H_3O_2)_2+3H_2O$, a variation between 101.6 and 106.1 per cent. The pharmacopœial requirement of 99.5 per cent $Pb(C_2H_3O_2)_2+3H_2O$ appears, therefore, to be practically unattainable. None of the samples gave a clear solution with recently boiled distilled water, as required by the pharmacopœia. Each of them smelled strongly of acetic acid, and as far as could be judged differed only in the extent to which the volatilization of this constituent had proceeded. It would be interesting to determine the vapor pressure conditions under which a compound of the theoretical composition exists, but for the purpose of the present solubility determinations such a study does not appear of particular importance.

The sample of lead acetate used for the following experiments was the one which contained upon analysis the amount of lead (57.9 per cent) corresponding to 106.1 per cent $Pb(C_2H_3O_2)_2+3H_2O$. In appearance it differed from the one containing 101.6 per cent of the salt only in being less moist, and would probably be selected by most persons as the better sample. Although it might be possible to prepare a quantity of lead acetate of the theoretical composition, calculated from the determination of the lead, it is doubtful whether such a sample would really be of 100 per cent purity, since adhering moisture and acetic acid would probably be present, and the true composition of the salt in hand might vary as far in the opposite direction as the present sample goes toward the basic salt. The question would then resolve itself into what effect the difference in amounts of acetic acid might have upon the solubility in the aqueous alcohol solutions and would require solubility determinations in solutions containing varying amounts of free acetic acid. The following results show the position of the curve for a sample of lead acetate containing a certain amount of the basic salt. Another sample would no doubt give slightly different results, but, as pointed out above, the same uncertainty would be present in both cases.

Two series of determinations were made in the present case. The second was for the particular purpose of establishing the point of change of solid phase from the hydrated to the anhydrous salt. The lengths of time of the shaking for reaching the saturation point were respectively two and four days. The saturated solutions were perfectly clear in all cases, but upon dilution, preparatory to making

the lead sulphate determination, each became cloudy. The solid phase in the solutions of lower alcoholic content consisted of clear crystals, and in the solutions of 81.5 per cent or more alcohol it was of a very fine, silky, fibrous appearance. The line of demarcation between the two forms was very sharp. An analysis made of the undissolved residue remaining in the tube of 81.5 per cent by weight alcohol showed it to consist of the anhydrous salt, thus confirming the conclusion based upon the difference in appearance of the solid phase in the tubes of the higher alcoholic concentrations.

The saturated solutions were analyzed by precipitation with dilute H_2SO_4 and weighing the lead sulphate, as already described. The results are shown in Table No. IV and the solubility curve in figure 1.

TABLE No. IV.—*Solubility of lead acetate in aqueous alcohol solutions at 25° C.*

EXPERIMENTAL RESULTS.

Solvent.		Specific gravity of saturated solution at 25°.	Salt per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.343	42.61
0.9856	8.9	1.285	38.41
0.9545	32.0	1.150	28.45 [a]
0.9164	51.0	1.052	21.49
0.8718	70.2	0.952	14.42
0.8441	81.5	0.902	9.42
0.8234	89.6	0.827	1.80
0.8190	91.4	0.821	1.27 [b]
0.8048	96.2	0.802	0.46
0.7941	99.9	0.791	0.40

[a] Figures show grams of $(CH_3COO)_2Pb+3H_2O$.
[b] Figures show grams of $(CH_3COO)_2Pb$.

CALCULATED RESULTS.

The above results yielded a curve from which the following figures were read or calculated:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	Salt per 100 grams.		Solvent to dissolve 1 gram salt.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.343	42.6	72.5	1.38
10.0	1.275	37.7	60.5	1.65
20.0	1.215	33.3	50.0	2.00
30.0	1.157	29.2	41.3	2.42
40.0	1.105	25.5 [a]	34.2 [a]	2.92
50.0	1.055	21.8	27.9	3.59
60.0	1.002	18.2	22.3	4.49
70.0	0.955	14.5	17.0	5.90
80.0	0.907	11.0	12.4	8.09
81.0	0.905	10.5	11.7	8.52
85.0	0.855	4.0	4.2	24.00
90.0	0.826	1.6 [b]	1.6 [b]	61.50
[c] 92.3	0.817	1.1	1.1	89.90
95.0	0.806	0.6	0.6	131.60
100.0	0.790	0.4	0.4	249.00

[a] Figures show grams of $(CH_3COO)_2Pb+3H_2O$.
[b] Figures show grams of $(CH_3COO)_2Pb$.
[c] U. S. Pharmacopœia strength.

The solubility of potassium acetate in aqueous alcohol solutions.—The pharmacopœial method of analysis of the sodium and potassium salts of organic acids consists in incinerating the sample, extracting the charred residue, with water, and titrating the filtered solution with 0.5 N HCl, using methyl orange as the indicator. This procedure, although perhaps satisfactory for some of the salts to which it is applied, requires a modification for the attainment of accurate results in the case of certain of the others, notably sodium benzoate. A number of experiments with this salt (for details see p. 28) showed that a part of the alkali can not be successfully extracted from the charred residue, and therefore low results are obtained unless the unburned carbon is subsequently ignited and the residue dissolved in water and mixed with the main extract of the ignited sample. Although no experiments have been made with other salts than sodium benzoate to ascertain the extent of the error due to the neglect of this modification, qualitative observations indicate that it may arise with practically all of these salts. This procedure was therefore followed in all the analyses of these compounds reported in the following pages.

Two samples of potassium acetate from different sources contained, respectively, 96.4 and 96.7 per cent CH_3COOK. Since this compound absorbs moisture very rapidly, it appears that this low result might be due to adhering water. That this was not the case, however, was shown by analyzing one of the samples after drying in an air bath at 160° for six hours and overnight in a vacuum desiccator containing concentrated H_2SO_4. The second analysis showed a purity of only 97.6 per cent.

In order to obtain a product of greater purity than the purchased samples, a portion of one of them was recrystallized from hot 95 per cent alcohol, washed with a little alcohol, and dried in a hot air bath at 135° to 140° for fifteen hours. Duplicate determinations showed the material to contain 99 per cent CH_3COOK. The free acid present corresponded to less than 0.2 per cent CH_3COOH. The recrystallized sample was used for the solubility determinations contained in the accompanying table, No. V.

Two series of determinations were made. In the one the period of shaking was two and in the other four days. Some difficulty was experienced in withdrawing sufficient amounts of the clear saturated solution for analysis, since the undissolved excess of salt settled imperfectly. The weighed saturated solutions were transferred to weighing bottles, evaporated to dryness in an air bath, and dried to nearly constant weight at a temperature of 120° to 140°. Portions of each of the residues were analyzed, as above described, for the original samples and the amount of anhydrous CH_3COOK present in each

calculated. The proportion of the anhydrous salt in the several residues varied from 94.3 per cent in the case of solution in water alone to 99.1 per cent in the absolute alcohol solution.

TABLE NO. V.—*The solubility of potassium acetate in aqueous solutions of ethyl alcohol at 25° C.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	CH_3COOK per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.417	68.73
0.9545	32.0	1.336	67.74
0.9164	51.0	1.255	62.50
0.8718	70.2	1.154	55.30
0.8234	89.6	0.997	35.70
0.8048	96.2	0.909	22.90
0.7941	99.9	0.857	14.50

CALCULATED RESULTS.

The above determinations plotted on cross-section paper gave a curve from which the following figures were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	CH_3COOK per 100 grams.		Solvent to dissolve 1 gram CH_3COOK.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.417	68.7	219.6	0.455
20.0	1.363	68.7	219.6	0.455
40.0	1.302	65.8	192.4	0.520
50.0	1.260	63.2	171.8	0.582
60.0	1.210	59.6	147.5	0.678
70.0	1.156	54.2	118.3	0.855
80.0	1.085	46.7	87.6	1.140
90.0	0.990	34.6	52.9	1.890
92.3	0.957	30.5	43.9	2.280
95.0	0.922	25.5	34.2	2.920
100.0	0.850	14.0	16.3	6.140

The solubility of sodium acetate in aqueous alcohol solutions.—The analyses of the salt and of the residues obtained from the saturated solutions were made by the pharmacopœial method, modified as described under potassium acetate. It should be mentioned, however, that with this salt all of the carbon in the residue could be burned, if enough heat were applied, and the white residue dissolved in water and titrated directly. The sample used for the solubility determinations was in the form of moderately sized clear crystals and contained 99.0 per cent $CH_3COONa + 3H_2O$. The impurity was evidently adhering moisture, since the analyses of the dried residues from the saturated solutions showed them to contain 99.5 or more

per cent CH_3COONa. The sample was neutral to litmus and practically so toward phenolphthaleine, since about 3.0 grams dissolved in 20 cubic centimeters water required only 3 drops of 0.1 N NaOH to give the strong pink color of phenolphthaleine.

Two series of determinations were made, the time of shaking being respectively two and four days. No change in the solid phase was apparent in any of the tubes. The weighed saturated solutions were transferred to weighing bottles, evaporated to dryness in an air bath at about 120°, and dried for three to five hours at 150°. Portions of the resulting residues of anhydrous sodium acetate were analyzed and shown to contain approximately 99.5 per cent CH_3COONa. The weights of the anhydrous salt were calculated to the hydrated compound, since it was evident that the salt had dissolved as such without change. The results are given in Table No. VI and the curve in figure 1.

The solubility of sodium acetate in water and in alcohol solutions of several concentrations has been determined by G. Schiavon (Gazz. chim. ital. (Roma), 1902, *32* II, p. 532), but the solutions were agitated only at intervals and the temperature maintained constant for comparatively short periods of time. The results are somewhat higher than those here shown, due probably to the fact that the saturation point was approached from above and equilibrium had not been reached. One determination in water at 31.5°, reported by Köhler (Z. Ver. Zuckerind, 1897, *44*, 447), is evidently much too low as compared with the results of Schiavon and the present value for 25°.

TABLE No. VI.—*The solubility of sodium acetate in aqueous solutions of ethyl alcohol at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$CH_3COONa+3H_2O$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.209	55.75
0.9856	8.9	1.162	53.22
0.9545	32.0	1.104	45.59
0.9164	51.0	1.034	36.44
0.8718	70.2	0.941	22.18
0.8441	81.4	0.876	11.74
0.8190	91.4	0.834	6.28
0.7941	99.9	0.823	7.31

TABLE NO. VI.—*The solubility of sodium acetate in aqueous solutions of ethyl alcohol at 25°*—Continued.

CALCULATED RESULTS.

The above results plotted on cross-section paper gave a curve from which the following figures were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$CH_3COONa+3H_2O$ per 100 grams.		Solvent to dissolve 1 gram $CH_3COONa+3H_2O$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.209	55.7	125.7	0.795
10.0	1.160	53.0	112.8	0.887
20.0	1.135	49.8	99.2	1.008
30.0	1.108	46.5	86.9	1.150
40.0	1.072	42.0	72.4	1.380
50.0	1.038	37.0	58.7	1.700
60.0	0.990	30.4	43.7	2.290
70.0	0.942	22.8	29.5	3.390
80.0	0.882	13.0	14.9	6.690
90.0	0.838	6.7	7.2	13.93
92.3	0.833	6.2	6.6	15.13
95.0	0.828	6.1	6.5	15.39
100.0	0.823	7.3	7.9	12.70

Solubility of zinc acetate in aqueous alcohol solutions.—As in the case of lead acetate, there is no method given in the Pharmacopœia for the quantitative analysis of this salt. The following method, based upon the determination of the zinc as oxide, was therefore used: A weighed sample of about 0.5 gram of the salt is dissolved in about 100 cubic centimeters of water and heated to the boiling point; dilute sodium carbonate solution (10 per cent) is then gradually added until the precipitation is complete. The heating continued for about one-half hour and the precipitate then filtered on a Gooch crucible, converted to oxide by igniting to bright redness, and weighed. The principal difficulty with the method is the tendency of the precipitate to adhere to the sides of the beaker and the almost unavoidable slight loss due to this cause. By great care, however, this source of error may be rendered practically negligible.

The sample of zinc acetate used for the following solubility determinations when analyzed by the above method gave an amount of zinc oxide corresponding to 102.4 per cent $Zn(C_2H_3O_2)_2+2H_2O$. This variation from the theoretical composition was no doubt due to loss of acetic acid, as has already been mentioned in connection with lead acetate. The odor of acetic acid was distinctly perceptible on opening the bottle containing the sample. It is possible that a sample of more nearly 100 per cent purity could have been prepared, but it is questionable whether the solubility results which it might have yielded would be of more interest than those here shown. The pharmacopœial purity rubric of 99.5 per cent for this salt is clearly unjustifiable, in view of the unstable character of the compound. It is

quite probable that the sample used for the present investigation represents as good quality as the market may be expected to afford.

Only one series of determinations was made, but the time allowed for the attainment of saturation was five days. The saturated solutions were analyzed by precipitating the whole amount or an aliquot part by means of dilute sodium carbonate solution, as described above. The zinc oxide residues were analyzed in several cases by titration with standard acid and shown to be of the theoretical purity. The solid phase in contact with the alcoholic solutions of 96.3 and 99.9 weight per cent alcohol after the period of shaking was changed from its original crystalline character to the amorphous condition. Although the amount in either case was not sufficient for an analysis, there is little doubt that it consisted of the anhydrous salt, as was demonstrated for the amorphous lead acetate in contact with the strong alcohol solutions.

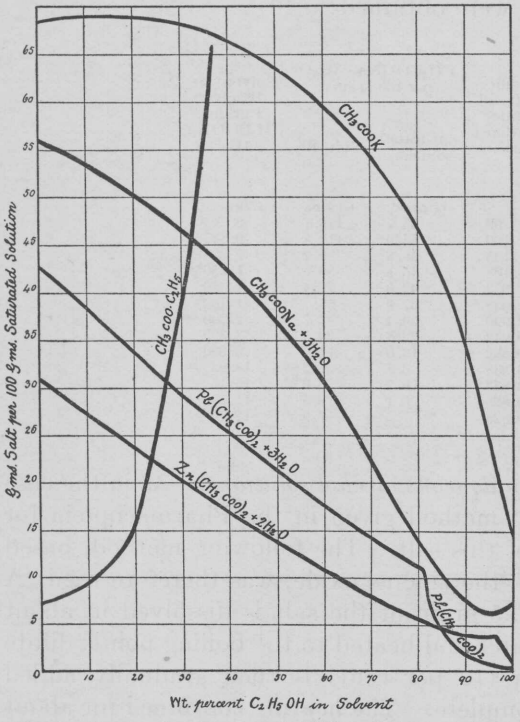

FIG. 1.—Curves showing the solubilities of the acetates in aqueous alcohol solutions at 25°.

TABLE NO. VII.—*The solubility of zinc acetate in aqueous solutions of ethyl alcohol at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	Acetate per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.168	30.78 $(C_2H_3O_2)_2Zn+2H_2O$
0.9856	8.9	1.132	27.64 $(C_2H_3O_2)_2Zn+2H_2O$
0.9545	32.0	1.048	19.78 $(C_2H_3O_2)_2Zn+2H_2O$
0.8718	70.2	0.878	7.90 $(C_2H_3O_2)_2Zn+2H_2O$
0.8190	91.4	0.832	4.16 $(C_2H_3O_2)_2Zn+2H_2O$
0.8048	96.3	0.822	3.87 $(C_2H_3O_2)_2Zn$
0.7941	99.9	0.796	1.18 $(C_2H_3O_2)_2Zn$

TABLE NO. VII.—*The solubility of zinc acetate in aqueous solutions of ethyl alcohol at 25°*—Continued.

CALCULATED RESULTS.

The above figures plotted on cross-section paper gave a curve from which the following results were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$(C_2H_3O_2)_2Zn+2H_2O$ per 100 grams.		Solvent to dissolve 1 gram $(C_2H_3O_2)_2Zn+2H_2O$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.168	30.80	44.5	2.25
10.0	1.127	27.20	37.4	2.67
20.0	1.090	23.70	31.1	3.22
30.0	1.055	20.40	25.6	3.90
40.0	1.015	17.00	20.5	4.88
50.0	0.970	13.80	16.0	6.25
60.0	0.920	10.60	11.9	8.42
70.0	0.880	7.80	8.5	11.80
80.0	0.850	5.50	5.8	17.20
90.0	0.830	4.20	4.4	22.80
92 3	0.827	4.10	4.3	23.40
95.0	0.825	4.00	4.2	24.60
100.0	0.796	[a] 1.18	[a] 1.2	[a] 83.75

[a] Solubility of the anhydrous salt.

BENZOIC ACID AND THE BENZOATES.

The solubility of benzoic acid in alcohol solutions.—The sample of benzoic acid used for the solubility determinations was analyzed by titration with standard alkali, using phenolphthaleine as indicator. Since the acid is only sparingly soluble in water, it is advisable to add enough alcohol to dissolve all of the sample previous to making the titration. It is to be noted, however, that since the ordinary alcohol is usually acid itself, it is necessary to previously neutralize that used for dissolving the benzoic acid. The titration gave average results showing a purity of practically 100 per cent. The melting-point determinations were within the limits quoted by the pharmacopœia.

The saturated solutions were analyzed by titrating aliquot portions after dilution, with 0.1 N NaOH. The results which were obtained are given in Table No. VIII and the solubility curve in Plate No. II.

TABLE NO. VIII.—*Solubility of benzoic acid in aqueous ethyl alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	C_6H_5COOH per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.000	0.367
0.9856	8.9	0.9865	0.581
0.9545	32.0	0.9574	4.677
0.9164	51.0	0.9464	17.800
0.8718	70.2	0.9404	30.070
0.8401	83.0	0.9311	35.050
0.8048	96.3	0.9128	36.510
0.7941	99.8	0.9093	36.910

TABLE NO. VIII.—*Solubility of benzoic acid in aqueous ethyl alcohol solutions at 25°*—Continued.

CALCULATED RESULTS.

The above results plotted on cross-section paper gave a curve from which the following figures were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	C_6H_5COOH per 100 grams.		Solvent to dissolve 1 gram C_6H_5-COOH.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.00	0.367	0.368	271.40
10.0	0.985	0.600	0.604	165.30
20.0	0.970	1.700	1.730	57.80
30.0	0.959	3.900	4.060	24.60
40.0	0.951	9.100	10.010	9.99
50.0	0.946	17.000	20.470	4.88
60.0	0.943	23.800	31.230	3.20
70.0	0.940	29.700	42.250	2.37
80.0	0.934	34.000	51.520	1.94
90.0	0.922	36.000	56.240	1.78
[a] 92.3	0.919	36.200	56.740	1.76
100.0	0.908	36.900	58.480	1.71

[a] U. S. Pharmacopœia strength.

The solubility of benzoic acid in organic solvents.—The solvents used for the determinations were obtained from different sources; the amyl alcohol, chloroform, ligroin, nitrobenzene, and toluene were the Kahlbaum products, the amyl acetate, benzene, cumene, and turpentine (double distilled) bore the Eimer and Amend label. A 5 cubic centimeter portion of each solvent was shaken with water and the acidity toward phenolphthaleine determined by titration with 0.1 N NaOH. Only the samples of naphtha and turpentine showed enough acidity to require a correction in the amount of alkali necessary for the saturated solution of the benzoic acid in these two solvents. No other quantitative tests were made of the purity of the solvents. The densities quoted in the table (No. IX) were taken for the most part from the second issue of Olsen's Chemical Annual and were used in the calculation of the grams of benzoic acid dissolved per 100 cubic centimeters of the several solvents.

The solubility determinations were made by rotating the glass-stoppered cylinders containing the solvents and an excess of the benzoic acid for four days at 25°. The clear saturated solutions were then weighed in a pycnometer, transferred to a glass-stoppered bottle with water, a few drops of phenolphthaleine added and the mixture titrated with 0.1 N NaOH solution.

TABLE NO. IX.—*Solubility of benzoic acid in organic solvents at 25°.*

Solvent.	Specific gravity of solvent.	d_{25} of saturated solution.	C_6H_5COOH dissolved per—			Solvent to dissolve 1 gram C_6H_5COOH.
			100 grams saturated solution.	100 grams solvent.	100 c. c. solvent.	
			Grams.	*Grams.*	*Grams.*	*Grams.*
Amyl alcohol (iso)	d_{20}=0.817	0.875	24.45	32.37	26.44	3.09
Amyl acetate	d_{20}=0.875	0.912	18.24	22.00	19.26	4.54
Alcohol (abs.)	d_{25}=0.785	0.908	36.90	58.40	45.92	1.71
Benzene	d_{25}=0.873	0.897	10.90	12.23	10.76	8.17
Chloroform	d_{22}=1.476	1.456	13.15	15.14	22.35	6.61
Carbon tetrachloride	d_{25}=1.591	1.564	4.01	4.18	6.65	23.94
Carbon bisulphide	d_{25}=1.258	1.282	4.60	4.82	6.06	20.73
Cumene	d_{20}=0.862	0.906	7.91	8.59	7.41	11.04
Ether (abs.)	d_{22}=0.711	.....	31.85	46.74	33.24	2.14
Ligroin	d_{25}=0.714	0.720	1.72	1.75	1.26	57.15
Naphtha	ca=0.720	0.730	2.48	2.65	1.91	37.70
Nitrobenzene	d_{25}=1.204	1.225	9.13	10.05	12.13	9.95
Toluene	d_{15}=0.872	0.884	9.46	10.69	9.33	9.57
Spirits of turpentine	d_{20}=0.865	0.859	4.84	5.09	4.40	19.66
Water	d_4=1.000	1.000	0.367	0.368	0.368	271.40
Xylene	d_{25}=0.861	0.877	8.85	9.71	8.52	9.71

The solubility of ammonium benzoate in aqueous alcohol solutions.—The sample of ammonium benzoate used for the solubility determinations was recrystallized from warm alcohol and washed with ether. Analyses showed it to contain 99.8 per cent $C_6H_5COONH_4$. In some cases unrecrystallized material of approximately 98.8 per cent purity was used. The analytical details involved in the determination of the purity of samples of ammonium benzoate have already been described in a paper from this laboratory entitled "Pharmacopœial Tests for Ammonium Benzoate."[a] It was shown that the most satisfactory method of analysis is the determination of the ammonia liberated by caustic alkali. The melting or decomposition point is of no value whatever in judging the purity of a sample of the salt. Furthermore, the litmus paper test is inadequate for showing the presence of less than 10 per cent of benzoic acid.

The analysis of the salt and of the saturated solution was made by distillation of the ammonia after adding an excess of caustic alkali. The distilled ammonia was titrated in the usual way, and in addition the amount of alkali required to liberate the ammonia was determined by titrating the portion of the liquid remaining in the distilling flask. The benzoate calculated from the two titrations agreed only fairly well, therefore the values obtained from the ammonia titrations were used for the solubility determinations reported in the accompanying table, since the results calculated from the alkali neutralized in the distilling flask are subject to the error arising from the solubility of the glass and from inaccuracies of the indicator.

The periods of shaking the tubes were from one to three days. The curve is interesting in that it is almost horizontal in the region

[a] Seidell and Menge, Am. Journ. of Pharmacy, **82**, 12–30, 1910.

of dilute alcoholic solvents. Thus alcohol solutions between 5 and 40 per cent strength dissolve practically the same amount of ammonium benzoate. The figure for the solubility in water, as given by the Pharmacopœia, is evidently incorrect, the actual solubility being more than twice as great as stated. The result given for U. S. P. alcohol, on the other hand, is very near the figure found in the present investigation.

TABLE NO. X.—*Solubility of ammonium benzoate in aqueous alcohol solutions at 25° C.*

EXPERIMENTAL RESULTS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_6H_5COONH_4$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.043	18.6
0.9856	8.9	1.029	18.0
0.9545	32.0	0.993	18.1
0.9164	51.0	0.954	16.9
0.8718	70.2	0.900	12.1
0.8190	91.4	0.825	3.8
0.8048	96.3	0.808	2.5
0.7941	99.9	0.796	1.6

CALCULATED RESULTS.

The above results, plotted on cross-section paper, gave a curve from which the following figures were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$C_6H_5COONH_4$ per 100 grams.		Solvent to dissolve 1 gram $C_6H_5COONH_4$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.043	18.6	22.8	4.38
10.0	1.027	18.0	22.0	4.55
20.0	1.012	18.0	22.0	4.55
30.0	0.997	18.1	22.1	4.53
40.0	0.979	18.0	22.0	4.55
50.0	0.956	17.0	20.5	4.88
60.0	0.930	15.0	17.6	5.67
70.0	0.901	12.2	13.9	7.20
80.0	0.864	8.3	9.1	11.05
90.0	0.828	4.2	4.4	22.81
[a] 92.3	0.819	3.4	3.5	28.41
95.0	0.810	2.7	2.8	36.03
100.0	0.796	1.6	1.6	61.15

[a] U. S. Pharmacopœia strength.

The solubility of lithium benzoate in aqueous alcohol solutions.—The sample of lithium benzoate was in the form of a very fine white powder. The aqueous solution did not react alkaline to litmus paper, but was, on the other hand, acid towards phenolphthaleine. Two grams of the sample dissolved in about 50 cubic centimeters of water required 1.4 cubic centimeters 0.1 N NaOH for neutralization, indicator phenolphthaleine. Therefore indicating the presence of 0.85

per cent free benzoic acid. A determination of the lithium by the pharmacopœial method gave an average amount corresponding to 99.2 per cent lithium benzoate. The sample was therefore well within the limit of purity required by the Pharmacopœia, viz., 98.5 per cent. It appears that the pharmacopœial statement regarding the reaction of lithium benzoate to indicators should be changed to prescribe neutrality toward litmus (or better the omission of reference to litmus) and not exceeding a definite acidity toward phenolphthaleine. The additional pharmacopœial tests applied to the present sample gave further evidence of its satisfactory quality. The benzoic acid obtained from it gave a melting point of 121° (cor.) and the lithium chloride dissolved practically completely in amyl alcohol and contained Cl corresponding to a purity of 99.7 per cent. Although for some reasons it might have been better to have used a sample of more nearly 100 per cent purity than the present one, it is probable that the small percentage of free benzoic acid could not appreciably affect the solubility values obtained. In preparing the saturated solutions, an excess of salt was added to each solvent in the usual way and the tubes rotated at 25° for two days. The weighed portions of the saturated solutions were transferred to weighing bottles and evaporated in a vacuum desiccator containing concentrated sulphuric acid. No especial attempt was made to carry the desiccation to the end, but only until the residues were sensibly dry. Portions of each were then removed and the lithium determined as sulphate by fusion with ammonium sulphate according to the method of the pharmacopœia. The weight of anhydrous benzoate in each residue was then calculated from the lithium sulphate found. The curve which was obtained (see Plate No. II) is perfectly regular, and only one series of determinations made after a two-day period of shaking was deemed necessary. It will be noted that a maximum solubility occurs at about 15 per cent alcohol. In the case of the ammonium benzoate curve a slight minimum exists at about this concentration of solvent.

TABLE No. XI.—*Solubility of lithium benzoate in aqueous alcohol solutions at 25° C.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	C_6H_5COOLi per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O.	0.0	1.103	27.64
0.9856	8.9	1.090	28.52
0.9545	32.0	1.047	27.79
0.9164	51.0	0.999	23.46
0.8718	70.2	0.931	15.23
0.8190	91.4	0.838	5.98
0.8048	96.2	0.815	4.02
0.7941	99.9	0.799	2.61

TABLE No. XI.—*Solubility of lithium benzoate in aqueous alcohol solutions at 25° C.*—Continued.

CALCULATED RESULTS.

The above results plotted on cross section paper gave a curve from which the following figures were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	C_6H_5COOLi per 100 grams.		Solvent to dissolve 1 gram C_6H_5COOLi.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.103	27.64	38.2	2.62
10.0	1.088	28.60	40.1	2.50
20.0	1.072	28.50	39.9	2.51
30.0	1.052	27.80	38.5	2.60
40.0	1.030	26.20	35.5	2.82
50.0	1.003	23.60	30.9	3.24
60.0	0.970	19.80	24.7	4.05
70.0	0.932	15.40	18.2	5.49
80.0	0.890	10.70	11.9	8.35
90.0	0.847	6.40	6.8	14.62
[a]92.3	0.835	5.50	5.8	17.18
95.0	0.823	4.50	4.7	21.22
100.0	0.799	2.60	2.7	37.46

[a] U. S. Pharmacopœia strength.

Solubility of sodium benzoate in aqueous alcohol solutions.—Several difficulties were encountered while investigating the solubility of this salt. In the first place, the purification of the material by recrystallization could not be accomplished by any means at command. The solubility of the salt in water is so great that the saturated solution is rather viscous, and on standing shows no tendency towards crystallization. The liquid climbs up the sides of the vessel and deposits a crust as the solvent evaporates. A hot saturated aqueous solution yields a crust on the surface, or if sufficiently concentrated will form a solid mass upon cooling. Alcohol, ether, and various mixtures of these with water were tried without success. In all cases the salt deposited at the surface as the solvent evaporated and no crystals appeared in the solution.

In analyzing the salt by the pharmacopœial method, which requires that the sample be ignited and the solution of the residue titrated with standard acid, using methyl orange as the indicator, it was found that concordant results could not be obtained unless the charred residue remaining after the incineration and extraction with hot water be ignited and the second residue dissolved in water and added to the first extract. The several determinations showing the additional amounts of the salt recovered by the second ignition are as follows:

Weight of sample.	0.5 N HCl required—		Calc. per cent C_6H_5COONa.	
	After first incineration.	After second incineration.	U. S. P.	Modified.
Gram.	*c. c.*	*c. c.*		
1.0	13.15	13.50	94.7	97.4
1.0	12.70	13.55	91.45	97.6
1.0	12.90	13.40	92.9	96.5
1.0	12.60	13.40	90.7	96.5

The method as modified was therefore used in all cases for the analysis of the samples and of the residues remaining after evaporation of the saturated solutions obtained in the solubility determinations. An attempt was made to prepare a pure sample of sodium benzoate by fractionating a hot aqueous solution of the salt as follows: The solution was evaporated over a flame until a crust just began to form; it was then cooled somewhat and the separated salt removed, dried on filter paper, and finally in a vacuum desiccator containing concentrated H_2SO_4. The liquor from this fraction was then evaporated until a second crust was formed and then cooled as before and the new fraction removed and dried. The final liquor was evaporated far enough so that it solidified on cooling. The original material and the three products were thoroughly dried in a vacuum desiccator containing conc. H_2SO_4 and analyzed. The results were, respectively, 97.5, 98.1, 98.4, and 98.4 per cent, showing the process to be only partially successful. It seems probable that the differences between the results found and 100 per cent are due to adhering water which can not be removed by vacuum desiccation. It is questionable whether the pharmacopœial requirement of 99 per cent C_6H_5COONa is a reasonable limit. Of two purchased samples, claimed to be of U.S.P. purity, one gave 97.5 and the other 96.5 per cent C_6H_5COONa upon analysis. The efforts made in the laboratory to prepare a product of the pharmacopœial purity from one of these samples was unsuccessful.

The material used for the solubility determinations was the product containing by analysis 97.5 per cent C_6H_5COONa. The determination of the free benzoic acid in this sample by titration with standard alkali showed 0.36 per cent. It was found that in preparing the saturated solutions for the solubility determinations it was advisable to have only a very small excess of the solid, since the undissolved salt becomes apparently gelatinous, and may form an almost solid mass from which it is impossible to remove enough clear saturated solution for analysis. Even with only a slight excess of the salt considerable time is required for the suspended solid to subside. This happens in both the aqueous and alcoholic solutions. After considerable difficulty the tubes were prepared with a satisfactory excess of the solid in each and rotated at 25° two days; in the case of one

duplicate determination the time of rotation was extended to three days without changing the figure obtained in the two-day period.

The saturated solutions were weighed in the pycnometer as usual and transferred to weighed weighing bottles and evaporated in a vacuum desiccator containing conc. H_2SO_4 until no further loss in weight occurred. The residues were then dissolved in water and the whole, or an aliquot portion of each solution, evaporated to dryness in a platinum dish and incinerated, the alkali being determined by titration, as already described. The values calculated from the analysis were in all cases, except with the solvents of highest alcoholic content, 97 to 98 per cent of the weight of dried residue obtained after the desiccation, thus lending weight to the view that the original impurity in the sample was nothing else than adhering water and a slight amount of free benzoic acid. Otherwise it would be expected that the residues from the solubility determinations would show a different degree of purity than the original material. The results of the determinations are shown in Table No. XII and the curve of the solubility in figure 2.

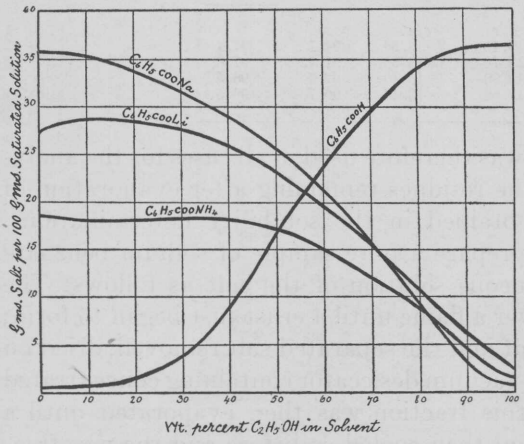

FIG. 2.—Curves showing the solubilities of benzoic acid and the benzoates in aqueous alcohol solutions at 25°.

TABLE No. XII.—*Solubility of sodium benzoate in aqueous alcohol solutions at 25° C.*

EXPERIMENTAL RESULTS.

Solvent.		Specific gravity of saturated solution at 25°.	C_6H_5COONa per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O.	0.0	1.155	35.99
0.9856	8.9	1.137	35.53
0.9545	32.0	1.082	31.74
0.9164	51.0	1.016	25.43
0.8718	70.2	0.927	15.25
0.8190	91.4	0.825	2.25
0.8048	96.3	0.807	1.05
0.7941	99.9	0.795	0.58

TABLE No. XII.—*Solubility of sodium benzoate in aqueous alcohol solutions at 25°*—Continued.

CALCULATED RESULTS.

The above results plotted on cross-section paper gave a curve from which the following figures were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	C_6H_5COONa per 100 grams.		Solvent to dissolve 1 gram C_6H_5COONa.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.155	36.0	56.24	1.78
10.0	1.132	35.3	54.39	1.88
20.0	1.110	33.7	50.83	1.97
30.0	1.086	31.5	45.98	2.18
40.0	1.055	28.9	40.64	2.46
50.0	1.020	25.6	34.41	2.91
60.0	0.975	21.3	27.07	3.69
70.0	0.927	15.4	18.20	5.49
80.0	0.877	8.8	9.65	10.36
90.0	0.831	2.8	2.88	34.71
[a]92.3	0.822	2.0	2.04	49.00
95.0	0.812	1.3	1.32	75.93
100.0	0.795	0.6	0.60	165.70

[a] U. S. Pharmacopœia strength.

CAMPHORIC ACID.

The solubility of camphoric acid in aqueous alcohol solutions at 25°.—The material used for the solubility determinations was pure white crystalline powder, and when analyzed by titrating weighed portions with standard alkali, using phenolphthalein as indicator, gave results indicating a purity of practically 100 per cent. The sample was dextro rotatory. The melting point was found to be 184° to 187° (cor). Two series of solubility determinations were made; the time allowed for the attainment of saturation was four days in one case and six in the other. The saturated solutions were analyzed by evaporating and drying the residue to constant weight at 100°. A blank test made at the same time showed that the original sample lost practically nothing when dried under the same conditions.

The curve drawn from the results obtained is interesting in that a maximum point occurs at about 85 weight per cent alcohol. It is therefore seen that although the solubility of camphoric acid increases very rapidly with increase of alcoholic strength through the greater part of its length, beyond a concentration of about 85 weight per cent alcohol a diminution of solubility occurs and less camphoric acid is dissolved by absolute than by alcohol of the U. S. Pharmacopœia strength.

TABLE NO. XIII.—*Solubility of camphoric acid in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_8H_{14}(COOH)_2$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
1.000	0.0	1.000	0.754
0.9856	8.9	1.000	1.239
0.9545	32.0	1.000	16.29
0.9164	51.0	1.000	38.61
0.8718	70.2	1.000	48.95
0.8401	83.0	0.985	51.46
0.8189	91.4	0.980	51.13
0.8048	96.3	0.970	50.37
0.7941	99.8	0.960	50.13

CALCULATED DETERMINATIONS.

The above results plotted on cross section paper gave a curve from which the following figures were read or calculated.

Per cent by weight of alcohol in solvent.	Specific gravity of saturated solution at 25°.	$C_8H_{14}(COOH)_2$ per 100 grams.		Solvent to dissolve 1 gram $C_8H_{14}(COOH)_2$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.000	0.754	0.76	131.60
10.0	1.000	1.6	1.63	61.50
20.0	1.000	6.3	6.72	14.87
30.0	1.000	14.0	16.28	6.14
40.0	1.000	26.0	35.14	2.84
50.0	1.000	38.0	61.30	1.63
60.0	1.000	45.0	81.81	1.22
70.0	1.000	49.0	96.12	1.04
80.0	0.995	51.2	104.9	0.95
85.0	0.987	51.6	106.6	0.94
90.0	0.980	51.4	105.8	0.945
[a] 92.3	0.977	51.1	104.5	0.957
95.0	0.974	50.8	103.2	0.968
100.0	0.960	50.1	100.4	0.996

[a] U. S. Pharmacopœia strength.

The statements of the solubility of camphoric acid as quoted in the literature are very variable. For water they range between 1 part acid per 160 parts water at 12° (Beilstein) to 1 part in 125 water at 25° (U. S. P.). The present results indicate that the correct figure is 1 part in 131.6 parts water at 25°. For alcohol even wider variations are to be found. Thus, Beilstein gives 1 part in 0.89 parts alcohol at 15.5° and Hager[a] quotes 1 part in 1.3 parts alcohol. This divergence probably accounts for the fact that no figure is quoted by the U. S. Pharmacopœia and only the description "readily soluble in alcohol" is given. The present results show that 1 part camphoric

[a] Handbuch der Pharmaceutischen Praxis. (1903.)

acid requires 0.957 grams of U. S. Pharmacopœia alcohol (of 92.3 weight per cent) for solution.

The complete results which were obtained are given in Table No. XIII, and the curve shown in figure 4.

Solubility of camphoric acid in organic solvents.—In addition to the solubility determinations in aqueous alcohol solutions a series was made in a large number of organic solvents. The solvents were described in connection with benzoic acid (p. 24). The time of rotation was two days; the dissolved acid was determined by titration with 0.1 N NaOH or N NaOH in the cases where much acid was present. The results are given in Table No. XIV. It will be noted that with the exception of absolute alcohol, ether and amyl alcohol are the only solvents which dissolve large amounts of camphoric acid. The result for ether is almost twice that quoted by Hager,[a] viz, 1 part in 1.8 parts; that is, 55 grams per 100 grams ether, and likewise the present figure for chloroform is higher than the quoted value of 1 part per 1,000. The present result for carbon bisulphide confirms the statement given in Beilstein in regard to the practical insolubility of camphoric acid in this solvent.

TABLE NO. XIV.—*Solubility of camphoric acid in organic solvents at 25°.*

Solvent.	Specific gravity of solvent.	Specific gravity of saturated solution at 25°.	$C_8H_{14}(COOH)_2$ dissolved per—			Solvent to dissolve 1 gram $C_8H_{14}(COOH)_2$.
			100 grams saturated solution.	100 grams solvent.	100 c. c. solvent.	
			Grams.	*Grams.*	*Grams.*	*Grams.*
Amyl alcohol (Iso)	$d_{20}=0.817$	0.907	33.320	50.000	40.800	2.0
Alcohol (abs.)	$d_{25}=0.785$	0.960	50.100	100.400	78.800	0.996
Benzene	$d_{25}=0.873$	0.873	0.008	0.008	0.007	12,500.0
Carbon bisulphide	$d_{25}=1.258$	1.258	0.020	0.020	0.025	5,000.0
Chloroform	$d_{22}=1.476$	.....	0.153	0.153	0.230	652.5
Cumene	$d_{20}=0.863$	0.890	0.197	0.197	0.170	506.5
Ether (abs.)	$d_{22}=0.711$	0.922	47.750	91.400	65.000	1.094
Ligroin	$d_{25}=0.714$	0.714	0.007	0.007	0.005	14,290.0
Nitro benzene	$d_{25}=1.205$	1.198(?)	0.500	0.500	0.600	199.0
Spirits of turpentine	$d_{20}=0.865$	0.852	1.710	1.740	1.500	57.6
Toluene	$d_{25}=0.864$	0.862	0.151	0.150	0.130	661.2
Water	$d_{4}=1.000$	1.000	0.754	0.760	0.760	131.6
Xylene	$d_{25}=0.861$	0.859	0.233	0.230	0.200	427.9

CITRIC ACID AND THE CITRATES.

Solubility of citric acid in aqueous alcohol solutions.—The material used for the following solubility determinations was in the form of rather large clear crystals. The analysis by titration with normal alkali using phenolphthaleine as indicator gave an average of 100.1 per cent $(CH_2)_2C(OH)(COOH)_3 + H_2O$. For the first series of solubility determinations an excess of the original sample of citric acid

[a] Handbuch der Pharmaceutischen Praxis. (1903.)

was added to each of the alcoholic solvents and the tubes rotated three days. After this time it was observed that the solid phase in the tubes of higher alcoholic concentration had changed from its original crystalline form to a more or less opaque powder, indicating that dehydration had occurred at about 70 to 80 weight per cent alcohol. The clear saturated solutions were withdrawn as usual and the dissolved citric acid determined by titration with normal alkali. The results calculated to the hydrated citric acid gave a curve with a slight but unmistakable irregularity at the alcoholic concentration corresponding to the change of solid phase. When the figures for the alcoholic solutions containing the opaque solid phase were calculated to the anhydrous acid the curve then lay below and almost parallel to the curve for the hydrated acid and gave no indication of there being a point of intersection of the two, as would be expected if the solid phase had changed completely. The dehydration by the stronger alcoholic solvents therefore appeared incomplete, and it was decided to prepare a quantity of the anhydrous acid by drying and use it as the solid phase for a series of determinations. The dehydration of the sample was effected by drying in an oven at approximately 85° for about twenty-four hours. The analysis showed the material thus dried to contain 98.9 per cent anhydrous citric acid. All of the determinations made with the dehydrated acid as solid phase except the two in which water alone and 8.9 per cent alcohol were the solvents gave a perfectly regular curve lying some distance below the values for the anhydrous acid calculated from the determinations made by starting with the hydrated acid. In the case of the water and 8.9 per cent alcohol the anhydrous acid was converted to the crystalline compound and the results agreed exactly with the determinations made with hydrated citric acid as the solid phase. By calculating all of the results obtained with the hydrated citric acid to anhydrous acid a curve was obtained which lay below the curve for the anhydrous acid in the dilute alcohol solutions, and above the latter in the more concentrated alcohol solutions. It may be concluded, therefore, that the tendency for the hydrated form of citric acid to be converted to the anhydrous or vice versa in aqueous alcohol solutions is very slight, and that whatever form of the acid is used as the solid phase, the change to the other form takes place very gradually. The peculiarity in connection with the curves showing the solubility of the hydrated and anhydrous forms of citric acid is that they lie so nearly parallel that there is no intersection corresponding to a true transition point as has been shown in the case of the zinc and lead acetate curves.

TABLE No. XV.— *The solubility of citric acid in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$(CH_2)_2COH(COOH)_3$+ H_2O per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist H_2O	0.0	1.311	67.5
0.9854	8.9	1.302	66.9
0.9545	32.0	1.270	65.3
0.9164	51.0	1.236	63.2
0.8718	70.2	1.193	[a] 60.7
0.8441	81.5	1.156	[a] 57.6
0.8190	91.4	1.121	[a] 54.1
0.7941	99.9	1.069	[a] 49.9

[a] Solid phase changed more or less completely during the period of saturation from crystalline to opaque appearance.

CALCULATED RESULTS.

The above results plotted on cross-section paper gave a curve from which the following figures were obtained:

Per cent by Weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$(CH_2)_2COH(COOH)_3$ $+H_2O$ per 100 grams.		Solvent to dissolve 1 gram $(CH_2)_2$ COH $(COOH)_3$ $+H_2O$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.311	67.5	207.7	0.481
10.0	1.300	66.8	201.2	0.497
20.0	1.286	66.0	194.1	0.515
30.0	1.272	65.3	188.2	0.531
40.0	1.257	64.3	180.1	0.555
50.0	1.237	63.3	172.5	0.580
60.0	1.216	62.0	163.1	0.613
70.0	1.192	60.8	155.1	0.645
80.0	1.163	58.1	138.7	0.721
90.0	1.125	54.7	120.8	0.828
92.3	1.114	53.7	116.0	0.862
95.0	1.100	52.4	110.1	0.908
100.0	1.068	49.8	99.2	1.008

TABLE No. XVI.—*Solubility of anhydrous citric acid in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

[Solid phase—Anhydrous salt.]

Solvent.		Specific gravity of saturated solution at 25°.	$(CH_2)_2COH(COOH)_3$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
0.9545	32.0	1.268	60.6
0.9164	51.0	1.216	57.1
0.8718	70.2	1.160	51.9
0.8441	81.5	1.115	47.9
0.8190	91.4	1.057	43.0
0.7941	99.9	1.010	38.4

TABLE No. XVI.—*Solubility of anhydrous citric acid in aqueous alcohol solutions at 25°*—Continued.

CALCULATED RESULTS.

Per cent by Weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$(CH_2)_2COH(COOH)_3$ per 100 grams saturated solution.
		Grams.
20	1.297	62.3
40	1.246	59.0
60	1.190	54.8
70	1.160	52.2
80	1.120	48.5
90	1.065	43.7
100	1.010	38.3

The analytical results upon the ordinary and anhydrous forms of citric acid are given in Tables Nos. XV and XVI and the curves shown in figure 3. It will be seen that the present values differ considerably from those quoted by the U. S. Pharmacopœia, which in terms of grams of citric acid per 100 grams of water and of alcohol would be 185 and 64.5, respectively, instead of 207.7 and 116.0 as given in Table No. XV. The values quoted by other reference books also differ considerably from those here shown, but since they probably refer to a temperature of 15° a strict comparison can not be made. It should be mentioned, however, that the differences can not be accounted for entirely on the basis of temperature, since a few results seem to show that the solubility of citric acid increases comparatively little with temperature, while most of the values to be found for the solubility in cold water and alcohol are only a little more than one-half the quantities indicated by the present determinations, which were made at 25° C.

Solubility of citric acid in organic solvents.—The determinations were made, as already described, with the same organic solvents used for benzoic and camphoric acids. Both the hydrated and anhydrous citric acid were used, and it is seen that the latter is the less soluble of the two in all cases. The results are given in Table XVII. An examination of the literature shows that in addition to water and alcohol, results are given for none of the solvents included in the table, except ether. The results quoted for ether are quite variable; thus 100 parts of ether dissolve, according to the U. S. Pharmacopœia, 5.5 parts of citric acid, 2 parts according to Hager, and 9.1 parts are reported by Beilstein. These variations are easily explained by the fact that the solubility of citric acid is very great in water and in alcohol, and therefore the presence of either of these solvents in the ether used for the determinations would account for the different values reported. A few results obtained by me with ether from a can which had been opened for some time illustrated this point very forcibly. The values were from about 30 to 80 per cent higher than

those given in the tables for absolute ether. The figures are not given herewith, however, since the actual composition of the ether was not known, and they therefore have no especial interest.

TABLE NO. XVII.—*Solubility of citric acid in several organic solvents at 25°.*

SOLUBILITY OF HYDRATED CITRIC ACID.

Solvent.	Specific gravity of solvent.	d_{25} of saturated solution.	$(CH_2)_2C(OH)(COOH)_3+H_2O$ dissolved per—			Solvent to dissolve 1 gram $(CH_2)_2C(OH)(COOH)_3+H_2O$.
			100 grams solution.	100 grams solvent.	100 c. c. solvent.	
			Grams.	*Grams.*	*Grams.*	*Grams.*
Amyl acetate	$d_{20}=0.8750$	0.8917	5.980	6.360	5.67	15.690
Amyl alcohol (iso)	$d_{20}=0.8170$	0.8774	15.430	18.240	16.01	5.480
Ethyl alcohol (abs.)	$d_{15}=0.7940$	1.0690	49.800	99.200	78.75	1.008
Ethyl acetate	$d_{25}=0.8915$	0.9175	5.276	5.570	5.11	17.950
Ether (abs.)	$d_{22}=0.7110$	0.7228	2.174	2.223	1.60	45.000
Chloroform	$d_{22}=1.4760$	1.4850	0.007	0.007	0.01	14,290.0

The amounts of citric acid dissolved by the following solvents were too small for estimation:

Benzene, carbon bisulphide, carbon tetrachloride, toluene.

SOLUBILITY OF ANHYDROUS CITRIC ACID.

Solvent.	Specific gravity of solvent.	d_{25} of saturated solution.	$(CH_2)_2C(OH)(COOH)_3$ dissolved per—			Solvent to dissolve 1 gram $(CH_2)_2C(OH)(COOH)_3$.
			100 grams solution.	100 grams solvent.	100 c. c. solvent.	
			Grams.	*Grams.*	*Grams.*	*Grams.*
Amyl acetate	$d_{20}=0.875$	0.8861	4.22	4.41	3.900	22.70
Ethyl alcohol (abs.)	$d_{15}=0.794$	1.0100	38.40	62.20	49.400	1.61
Ether (abs.)	$d_{22}=0.711$	0.7160	1.05	1.06	0.757	94.50
Chloroform	$d_{22}=1.476$	1.4880	None.	None.	None.	.....

Solubility of bismuth citrate in aqueous alcohol solutions.—Although the U. S. Pharmacopœia gives the ordinary formula for neutral bismuth citrate, the purity rubric requires simply that the preparation contain 56 to 58 per cent bismuth oxide. The theoretical percentage of bismuth oxide according to the formula is 58.43, and therefore the variation allowed by the pharmacopœia corresponds to a range of purity from 95.94 to 99.24 per cent. The determination of the bismuth oxide according to the pharmacopœial method offers considerable difficulties. The original ignition of the sample is easily accomplished, but the subsequent evaporation of the excess of nitric acid which must be added is attended by creeping of the liquid over the edge of the crucible; furthermore, just as the last of the excess of nitric acid is being driven off a slight explosion of the nitrate usually occurs, due to the presence of undecomposed carbon, and therefore leads to a probable loss of a portion of the residue. A determination of the bismuth in the sample used for the solubility experiments gave 0.553

gram Bi_2O_3 per 1.0 gram of sample, which is slightly below the pharmacopœial requirement, and corresponds to a purity of 94.62 per cent. This result may, however, be low, since it is not certain that no loss occurred during the determination. With a compound having the more or less uncertain composition of the present one, no very precise solubility results could be expected. The following determinations therefore represent only approximate values. The time of shaking was four days at 25° C. Three tubes were prepared, the solvents being water, 51 and 91.4 weight per cents alcohol. The saturated solutions were evaporated to dryness in weighing bottles and the residues weighed. The following results were obtained:

Per cent by weight of C_2H_5OH in solvent.	$BiC_6H_5O_7$ per 100 grams saturated solution.
	Grams.
0.0	0.011
51.0	0.041
91.4	0.065

Solubility of bismuth and ammonium citrate in aqueous alcohol.—A formula is not given by the pharmacopœia for this compound, and the requirements of bismuth content covers a wider range than in the case of bismuth citrate. The allowable content according to the pharmacopœial purity rubric is 46 to 50 per cent bismuth oxide. The same sources of error are present in the quantitative method of determination of the bismuth as have already been pointed out for the bismuth citrate with the further difficulty due to decrepitation during the initial ignition. The content of bismuth oxide in the sample used for the solubility determinations was found to be 0.475 gram, Bi_2O_3 per 1.0 gram, thus well within the limit given by the pharmacopœia. The following solubility results are therefore probably fairly representative of the product as described by the pharmacopœia. For these determinations the tubes were rotated at 25° four days; the weighed saturated solutions were transferred to porcelain crucibles, evaporated to dryness, and the residue converted to bismuth oxide and weighed. The weight of the original material was calculated by dividing by the percentage of Bi_2O_3 found in the sample used for the determinations. The results were as follows:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	Bi and NH_4 citrate per 100 grams saturated solution.
		Grams.
0.0	1.25	22.25
51.0	0.92	1.34
91.4	0.81	None.

The only statement in regard to the solubility of bismuth and ammonium citrate given in the pharmacopœia is to the effect that it is very soluble in water and sparingly soluble in alcohol. The present results therefore will serve to give a somewhat better idea in regard to solubility of this substance in these two solvents than could have previously been obtained.

Solubility of lithium citrate in aqueous alcohol solutions.—The pharmacopœial quantitative method of analysis of this compound requires that the weighed sample be dried at 150° and then cautiously ignited, after which the charred residue is converted to lithium sulphate by repeated additions of concentrated sulphuric acid and careful ignitions. The drying at 150° appears to be unnecessary, since the water of crystallization can be satisfactorily removed by heating with care over the free flame. There appears some advantage in adding anhydrous ammonium sulphate and mixing after the dehydration and before proceeding to the ignition. The use of ammonium sulphate does not, however, obviate the necessity for adding concentrated sulphuric acid repeatedly to obtain the required white residue. In attempting to determine the water of crystallization of a sample by drying at 150° it was found that the loss of weight was very gradual, so that even after a total of about fifteen hours' drying with the temperature as high as 175° constant weight had not been obtained. The loss of moisture corresponded to 23.4 per cent instead of the theoretical 25.0 per cent for 4 molecules of water of crystallization. The determination of the lithium in this sample as above outlined gave results corresponding to 98.4 per cent $(CH_2)_2COH(COOLi)_3+4H_2O$. The acidity calculated as citric acid corresponded to 0.35 per cent. Although this result shows that the sample is practically up to the pharmacopœial requirement of 98.5 per cent, it was thought desirable to prepare material of better quality if possible. This was done by recrystallization from alcohol of about 50 per cent strength. The hot saturated alcoholic solution showed some tendency to separate into two layers, but on standing crystals began to separate from the lower portion of the solution, and on stirring the mixture was apparently uniform. Upon a further cooling a good crop of crystals was obtained. They were washed once with strong alcohol, dried in an ordinary desiccator over night, and for a few minutes at 40° to 50°. The analysis gave results corresponding to a purity of 99.3 per cent $(CH_2)_2COH(COOLi)_3+4H_2O$.

The solubility determinations were made with both the original and recrystallized samples, but no differences in the values obtained could be definitely ascribed to a difference of purity of the two samples. Three series of determinations were made and the time of shaking varied from two to three days. All of the points except

one, viz, that for 17.0 weight per cent alcohol fell on the very regular curve (see fig. 3) drawn through them. It is probable that in this one case the discrepancy was due to some error for which I am unable to account. The value is given in Table No. XVIII, however, for the sake of completeness, but it is not used in obtaining the interpolated results for regular intervals of alcoholic strengths.

The analyses of the saturated solutions were made by evaporating in weighing bottles and drying the residues to practically constant weight at 170° to 180°. Portions of the residues were then used for lithium determinations by igniting and converting to lithium sulphate, and these results served as checks upon the thoroughness of the drying process.

In comparison with the present results it will be seen that the figures quoted by the pharmacopœia are very much too low.

TABLE No. XVIII.—*Solubility of lithium citrate in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$(CH_2)_2COH(COOLi)_3+4H_2O$ per 100 grams saturated solution.
d_{15}.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.2160	42.70
0.9856	8.9	1.1570	33.50
[a] (0.9752	17.0	1.1150	29.00)
0.9628	26.4	1.0430	18.50
0.9359	41.7	0.9692	7.90
0.9164	51.0	0.9296	4.40
0.8718	70.2	0.8674	0.54
0.8234	89.6	0.8166	0.06
0.7941	99.9	0.7883	0.02

[a] This determination not used in plotting the curve.

CALCULATED RESULTS.

The above figures plotted on cross-section paper gave a curve from which the following results were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$(CH_2)_2COH(COOLi)_3+4H_2O$ per 100 grams.		Solvent to dissolve 1 gram $(CH_2)_2COH(COOLi)_3+4H_2O$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0	1.216	42.70	74.50	1.34
10	1.150	33.00	49.30	2.03
20	1.083	24.30	32.10	3.12
30	1.025	15.80	18.80	5.33
40	0.976	8.80	9.65	10.36
50	0.933	4.70	4.93	20.30
60	0.897	2.20	2.25	44.50
70	0.867	0.60	0.60	165.80
80	0.838	0.30	0.30	332.40
100	0.788	0.02	0.02	4,999.00

Solubility of potassium citrate in aqueous alcohol.—This salt belongs to that group of compounds which has the power of separating mixtures of alcohol and water into layers consisting of more or less pure alcohol as the upper and the aqueous salt solution as the lower. A systematic search for the members of this group of compounds was made some years ago by Linebarger,[a] and although a number were found no experiments were made with citrates, and therefore the fact that postassium citrate possesses this power of forming layers with aqueous alcohol solutions was overlooked.

The sample of potassium citrate used for the solubility determinations described in the following pages was purified by recrystallization from the hot aqueous solution, washing with absolute alcohol and ether and drying in an air bath at 130°–150° for five hours. The statement of the pharmacopœia that the salt begins to lose water at as low as 100° is evidently incorrect, since the present sample retained its water of crystallization even when heated to 150°. The analysis by igniting and titrating the residue, as described under sodium benzoate (p. —), gave 98.6 per cent $(CH_2)_2COH(COOK)_3 + H_2O$. The acidity calculated as citric acid corresponded to 0.94 per cent.

The solubility determinations were made by adding an excess of the salt to about 10 to 15 cubic-centimeter portions of the several alcohol solutions of known strengths and rotating the tubes for five days at 25°. After this time they were each removed in a beaker filled with the water of the constant temperature bath and as much as possible of each layer drawn into a pycnometer by means of the suction siphon described in the first part of this bulletin (p. 11). In the case of several of the solutions enough of both layers to fill the pycnometer could not be obtained, and therefore the specific gravity could not be calculated. A dotted line in the Table No. XIX indicates that the determination could not be made on account of there being too little of the solution. After weighing the saturated solution in those cases where two layers were present it was transferred to a distilling bulb, diluted with several times its volume of water, the alcohol distilled and its amount determined by the pycnometer method. The aqueous solution remaining after the distillation was transferred to a weighing bottle, evaporated to dryness, and the residue weighed after being dried to constant weight at 150°. The composition of the residues was ascertained in most cases by a determination of the potassium in the manner mentioned for the original material used for the solubility experiments. In those cases where the residues came from the strong alcoholic solutions or upper layers, that is, with relatively very little of the salt present, the correction for impurity on the basis of the potassium determinations was very great.

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[a] Am. Chem. Jour., **14**, 380, 1892.

TABLE No. XIX.—*Solubility of potassium citrate in aqueous alcohol solutions at 25° C.*

No.	Per cent by weight of C_2H_5OH in original solvent.	Specific gravity of saturated solution at 25°.	Per cent by weight of C_2H_5OH in saturated solution.	$(CH_2)_2COH(COOK)_3 + H_2O$ per 100 grams saturated solution.
				Grams.
1	0.0	1.5180	0.0	64.50
2	8.9	[a]	....	.....
		[b] 1.4920	0.0	60.00
3	32.0	[a]	....	0.2
		[b] 1.4930	0.0	61.60
4	51.0	[a]	65.1	0.38
		[b]	....	62.50
5	70.2	[a] 0.8366	81.0	0.10
		[b]	....	62.30
6	81.4	0.8356	81.4	0.038
7	91.6	0.8139	91.6	0.016
8	99.9	0.7896	99.9	0.014

[a] Upper layer. [b] Lower layer.

One hundred grams H_2O dissolve 181.8 grams $(CH_2)_2COH(COOK) + H_2O$ or 1 gram of the salt requires 0.55 grams H_2O for solution at 25°.

The results which were obtained are given in Table No. XIX and show that two layers are formed in alcoholic solutions of less than 80 weight per cent alcohol. An interesting point is that in the lower layers of Nos. 2 and 3 although no alcohol could be found, the amounts of citrate dissolved were considerably less than in tube No. 1 in which the solvent was water. In the case of the solutions of high alcoholic content the solubility, as might be expected, diminishes with increase of alcohol. In those cases, however, where the alcoholic solution was in contact with the aqueous layer this relation is apparently not so rigid, as will be seen by comparing the figure for tube No. 6 with that for the upper layer of tube No. 5 and also the case of the upper layer of tube No. 3, which can only be explained on the assumption that the alcoholic concentration is greater than in the upper layer of tube No. 4.

A comparison of the results here shown with those quoted by the U. S. Pharmacopœia shows that the present figure for water is considerably lower than that quoted, which is 1 part of salt in 0.5 parts of water at 25°, or 200 grams of salt per 100 grams of water. Of the other results found in the literature for the solubility in water that of Greenish and Smith [a] for 15.5° is given as 1 part in 0.65 parts of water, the d_{15} of the saturated solution being 1.519. If this result

[a] Pharmaceutical Journal. (Lond.). June 22, 1901.

is calculated to the basis selected for stating the present results it is seen that their value becomes 162.9 grams $(CH_2)_2COH(COOK)_3+H_2O$ per 100 grams of H_2O. Another figure for the solubility of potassium citrate in water is given by Köhler,[a] who finds that 100 grams H_2O dissolves 169.7 grams anhydrous potassium citrate at 31.25°. This result calculated to the hydrated salt becomes 199.9 grams $(CH_2)_2COH(COOK)_3+H_2O$ per 100 grams of H_2O at 31.25°. Considering, therefore, the three available determinations, we have for

15.5°, 162.9 grams $(CH_2)_2COH(COOK)_3+H_2O$ per 100 grams H_2O
25.0°, 181.9 grams $(CH_2)_2COH(COOK)_3+H_2O$ per 100 grams H_2O
31.25°, 199.9 grams $(CH_2)_2COH(COOK)_3+H_2O$ per 100 grams H_2O

from which the following interpolated values are obtained:

t°	$(CH_2)_2COH(COOK)_3+H_2O$ per 100 grams.	
	Saturated solution.	Water.
	Grams.	*Grams.*
15	61.8	162.0
20	63.2	172.0
25	64.5	182.0
30	66.0	194.0

As regards the solubility of potassium citrate in alcoholic solutions, most of the reference books give only a qualitative statement that it is sparingly soluble. In Squire's Companion to the British Pharmacopœia, however, it is stated that 1 part of the salt dissolves in 9 parts of 60 per cent alcohol "but if more of the salt is added the alcohol separates from the watery solution," thus recognizing the power of potassium citrate to salt alcohol out of its aqueous solution.

In order to obtain exact figures upon this particular action of potassium citrate a series of determinations was made with alcoholic solutions of known concentrations and weighed amounts of the recrystallized potassium citrate. The method employed was as follows: To a measured volume of the alcoholic solution contained in a glass-stoppered bottle there was added enough potassium citrate from a weighing bottle to cause a distinct cloudiness upon shaking. The amount of the citrate which had been added was determined by noting the difference in weight of the weighing bottle after the addition of the citrate. The temperature of the cloudy solution was then brought to as near 25° as possible and successive amounts of the same alcoholic solvent added from a burette until the cloudiness just disappeared upon shaking thoroughly. The specific gravity of the clear solution was then determined by the pycnometer method. The weight of the potassium citrate divided by the total volume of

[a] Z. Ver. Zuckerind, **47**, 447, 1897.

the alcohol employed gave the grams of citrate per unit volume of alcohol. The results which were obtained are given in Table No. XX and the curve in figure 3. They yielded a very smooth curve when plotted on cross-section paper and from this curve the interpolated values shown in the lower part of the table were obtained. Although these results indicate that the value quoted in Squire's Companion to the British Pharmacopœia is much too high, an exact comparison can not be made on account of the difference in temperature in the two cases. An experiment was therefore made at 15°, using alcohol of approximately 59 volume per cent strength. It was found that 100 cubic centimeters of this alcohol just remained clear upon the addition of 4.51 grams $(CH_2)_2COH(COOK)_3+H_2O$, which corresponds to about 22 parts of alcohol per 1 of citrate instead of 9 parts per 1 of citrate as quoted by Squire's Companion.

TABLE No. XX.—*Showing the amounts of potassium citrate necessary to cause the separation of a second liquid phase in aqueous alcohol solutions of different concentrations at 25° C.*

EXPERIMENTAL DETERMINATIONS.

Aqueous alcoholic solvent.		Specific gravity of saturated solution at 25°.	$(CH_2)_2COH(COOK)_3+H_2O$ per—	
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		100 c. c. solvent.	100 grams saturated solution.
			Grams.	*Grams.*
Dist. H_2O	0.0	1.5180	181.80	64.50
0.9854	8.9	1.3250	84.70	46.20
0.9545	32.0	1.0710	23.50	19.60
0.9359	41.7	0.9945	11.40	10.90
0.9164	51.0	0.9361	4.73	4.90
0.8718	70.2	0.8678	0.38	0.43

CALCULATED RESULTS.

The above values plotted on cross-section paper yielded a curve from which the following figures were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$(CH_2)_2COH(COOK)_3+H_2O$ per—	
		100 c. c. solvent.	100 grams saturated solution.
		Grams.	*Grams.*
0.0	1.518	181.80	64.50
5.0	1.400	111.00	52.50
10.0	1.310	80.00	45.50
20.0	1.177	47.00	31.50
30.0	1.085	26.50	21.50
40.0	1.005	13.20	12.40
50.0	0.943	5.50	5.60
60.0	0.900	1.50	1.60
70.0	0.868	0.40	0.40
80.0	0.838	0.04	0.04

Solubility of sodium citrate in aqueous alcohol solutions.—A sample of this salt purchased for solubility determinations was analyzed by incineration and titrating, as usual, but the results when calculated to $(CH_2)_2COH(COONa)_3+5\frac{1}{2}H_2O$ corresponded to 119.6 per cent. It was therefore evident that considerable dehydration had taken place, and in order to obtain a sample containing the desired amount of water of crystallization it would be necessary to recrystallize under proper conditions. According to a statement in Beilstein the salt crystallizes above 60° with $2H_2O$; therefore the following precautions were taken: About 100 to 150 grams of the salt were dissolved in just enough water to yield an almost saturated solution at 50°. The beaker was then placed outside the window, where the temperature remained below about 5° for several days. The mother liquor was drained off and the crystals powdered, placed in a bottle, and allowed to stand in a vacuum desiccator containing a few lumps of $CaCl_2$ for about a week. The analysis showed a composition of 98.7 per cent $(CH_2)_2COH)COONa)_3+5\frac{1}{2}H_2O$, which is considerably above the pharmacopœial requirement of 97 per cent. A calculation to salt of $6H_2O$ corresponded to 102.0 per cent, showing that the impurity was most probably adhering moisture. The mother liquor from the above crystallization was boiled until a scum appeared, cooled slightly, and the crystals which separated filtered on a Buchner funnel, dried in a desiccator for about a week, and analyzed. The results corresponded to 95.4 per cent $(CH_2)_2COH(COONa)_3+2H_2O$. This product was then dried at 150° for about five hours and gave results upon analysis corresponding to 98.5 per cent anhydrous salt. The acidity of the sample corresponded to 0.34 per cent anhydrous citric acid.

The solubility determinations were made with both the salt containing $5\frac{1}{2}$ H_2O and the anhydrous material. A smooth curve was obtained, and the only difference in the two sets of results was that the determinations made with the anhydrous salt were slightly below those made with the hydrated salt, due, no doubt, to the tendency of the dehydrated salt to take water from the solvent, and thereby increase the alcoholic concentration with resulting apparent lowering of the solubility in the particular solvent. Two series of determinations were made with the crystallized salt, the periods of shaking being two and three days, respectively. The weighed saturated solutions were transferred to weighing bottles, evaporated to dryness, and the residues dried to constant weight at 150° to 180°. Certain of the residues were analyzed by determination of the sodium in order to check the completeness of the dehydra-

tion. The weights of the hydrated salt were calculated from the anhydrous residues obtained. The results are given in Table No. XXI, and the curve shown in figure 3.

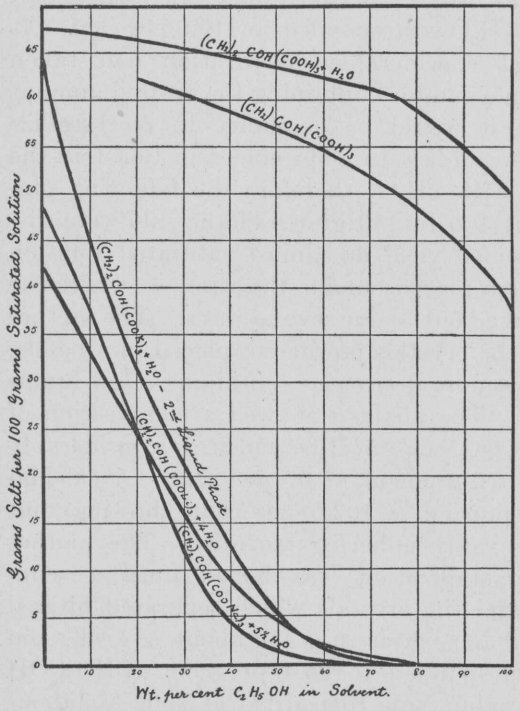

FIG. 3.—Curves showing the solubilities of citric acid and the citrates in aqueous alcohol solutions at 25°.

The present figure for the solubility of sodium citrate in water agrees fairly well with the value quoted by the U. S. Pharmacopœia, which is 1 part in 1.1 parts H_2O, or 90.9 grams salt per 100 grams H_2O. The statement regarding the solubility in alcohol should, however, be modified since the salt is evidently practically insoluble in pharmacopœial alcohol instead of slightly soluble, as reported. There are apparently no other results upon the solubility of this salt to be found in the literature.

TABLE NO. XXI.—*Solubility of sodium citrate in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$(CH_2)_2COH(COONa)_3 5\frac{1}{2} H_2O$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.2760	48.10
0.9856	8.9	.....	38.90
0.9752	17.0	1.1290	29.30
0.9628	26.4	1.0370	15.70
0.9359	41.7	0.9473	3.70
0.9164	51.0	0.9166	1.35
0.8718	70.2	0.8654	0.09
0.7941	99.9	0.7894	.....

TABLE XXI.—*Solubility of sodium citrate in aqueous alcohol solutions at 25°*—Cont'd.

CALCULATED RESULTS.

The above figures plotted on cross-section paper gave a curve from which the following results were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$(CH_2)_2COH(COONa)_3 + 5\frac{1}{2}H_2O$ per 100 grams.		Solvent to dissolve 1 gram $(CH_2)_2COH(COONa)_3 + 5\frac{1}{2}H_2O$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0	1.276	48.1	92.7	1.08
10	1.190	37.4	59.7	1.67
20	1.100	25.0	33.3	3.00
30	1.006	11.8	13.4	7.57
40	0.953	4.5	4.7	21.22
50	0.918	1.4	1.4	70.40
60	0.892	0.3	0.3	332.40
100	0.789	.....	.....	.....

GALLIC ACID.

Solubility of gallic acid in aqueous alcohol solutions at 25°.—There is no satisfactory method by which gallic acid can be quantitatively determined, and therefore an analysis of a given sample can not be made. Certain qualitative tests are prescribed by the Pharmacopœia but probably would not indicate the presence of as small amounts of impurities as would be considered undesirable in a sample to be used for accurate solubility determinations. In order, therefore, to obtain material which might be considered of satisfactory quality for the solubility determinations desired for the present bulletin, a sample of apparent good quality was subjected to recrystallization from hot water, dried in a vacuum desiccator, and the water of crystallization determined by loss of weight on drying at 100°. The result obtained was 9.57 per cent, instead of the theoretical 9.58 per cent, therefore indicating a high degree of purity.

The solubility determinations were made with the recrystallized product in the usual manner, the time allowed for solution being two days. The weighed saturated solutions were evaporated to dryness in weighing bottles and the residues rendered anhydrous by drying at 100° and subsequently at 125° to 140° without further loss of weight. The weight of dissolved hydrated gallic acid was calculated from the anhydrous residues. The values yielded a perfectly smooth curve from which the interpolated results were obtained. The figures are given in Table No. XXII, and the curve shown in figure 4.

It will be noted that the values for water and alcohol of pharmacopœial strength are in fair agreement with those quoted by the U. S.

Pharmacopœia which are 1 part of acid in 83 to 86 parts of water and in 4.14 parts of alcohol.

TABLE No. XXII.—*Solubility of gallic acid in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_6H_2(OH)_3COOH+H_2O$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.002	1.15
0.9752	17.0	0.985	3.31
0.9359	41.7	0.974	11.16
0.8718	70.2	0.946	18.01
0.8234	89.6	0.919	21.17
0.7941	99.9	0.902	22.14

CALCULATED RESULTS.

The above determinations plotted on cross-section paper yielded a curve from which the following results were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$C_6H_2(OH)_3COOH+H_2O$ per 100 grams.		Solvent to dissolve 1 gram of $C_6H_2(OH)_3COOH+H_2O$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.002	1.15	1.16	86.00
10.0	0.992	2.0	2.04	49.00
20.0	0.983	4.2	4.38	22.80
30.0	0.977	7.5	8.11	12.30
40.0	0.972	10.6	11.86	8.60
50.0	0.965	13.4	15.47	6.46
60.0	0.957	16.0	19.04	5.25
70.0	0.946	18.0	21.96	4.55
80.0	0.933	19.9	24.85	4.02
90.0	0.919	21.2	26.90	3.72
[a] 92.3	0.915	21.4	27.23	3.67
95.0	0.911	21.6	27.55	3.63
100.0	0.902	22.2	28.54	3.50

[a] U. S. Pharmacopœia strength.

The solubility of gallic acid in several solvents has been determined by Rosenheim and Schidrowitz[a] and their results published in a paper with the title "The Optical Activity of Gallotannic Acid." The form in which the results are given is misleading since it is impossible to know whether the figures represent grams of hydrated or anhydrous acid dissolved in the given weight of solvent or of the saturated solution. If we assume, however, that the basis intended is the grams per 100 grams of solvent, their results are, respectively, for water 0.76 gram gallic acid per 100 grams at 12.5°, for 90 per cent alcohol (weight or volume?) 18.9 grams per 100 grams

[a] J. Chem. Soc., (Lond.), **73**, 882, 1898.

alcohol, and for absolute alcohol 22.2 grams acid per 100 grams alcohol at 15°.

A figure which is very much at variance with the present results and all others reported in the literature is quoted by Squire's Companion to the British Pharmacopœia as 1 part of gallic acid in 8 parts of 90 per cent alcohol. This is evidently an error, possibly typographical.

Solubility of gallic acid in several organic solvents.—The same recrystallized material was used for these determinations and the solvents which have already been described. The saturated solutions were transferred to weighing bottles and evaporated to dryness and the residues dried to constant weight at a little over 100°. It will be seen that with the exception of acetone and alcohol none of the solvents dissolved very large amounts of the acid. Some of the present results differ considerably from those of Rosenheim and Schidrowitz,[a] made at 15°. These authors do not describe the method by which their determinations were made and a correct opinion of their accuracy can not be formed.

The comparative results are as follows:

Solvent.	R. and S., 15°.	Present results, 25°.
Acetone	29.4	26.0
Alcohol (abs.)	22.2	22.1
Ethyl acetate	8.4	3.6
Benzene	.....	0.02
Chloroform	.....	.....
Ether (abs.)	2.5	1.37

TABLE No. XXIII.—*Solubility of gallic acid in organic solvents at 25°.*

Solvent.	Specific gravity of solvent.	d_{25} of saturated solution.	$C_6H_2(OH)_3COOH+H_2O$ per 100.			Solvent to dissolve 1 gram $C_6H_2(OH)_3COOH+H_2O$.
			Grams saturated solution.	Grams solvent.	C. c. Solvent.	
			Grams.	*Grams.*	*Grams.*	*Grams.*
Acetone	$d_{15}=0.797$	0.941	25.990	35.120	27.99	2.85
Amyl alcohol (iso)	$d_{20}=0.817$	0.834	5.390	5.700	4.65	17.55
Amylacetate	$d_{20}=0.875$	0.878	2.720	2.800	2.45	35.77
Benzene	$d_{25}=0.873$	0.875	0.022	0.022	0.02	4544.00
Carbon bisulphide	$d_{25}=1.258$	1.262	0.042	0.042	0.05	2381.00
Ether (abs.)	$d_{22}=0.711$	0.718	1.370	1.390	0.99	72.00
Ethyl acetate	$d_{25}=0.892$	0.911	3.610	3.750	3.34	26.70

The amounts of gallic acid dissolved by the following solvents were too small for estimation: Carbon tetrachloride, chloroform, and toluene.

[a] Loc. cit.

LACTIC ACID.

Lactic acid in its usual form is a very hygroscopic syrupy liquid composed, according to the requirements of the Pharmacopœia, of not less than 75 per cent by weight of absolute lactic acid ($CH_3CHOH{\cdot}COOH$) and about 25 per cent of water. It is freely miscible with water, alcohol, and ether. A sample analyzed by titration with normal alkali using phenolphthaleine as indicator was found to contain 72.8 per cent $CH_3CHOH{\cdot}COOH$. It has been shown by Krafft and Dyes[a] that the ordinary commercial lactic acid can be purified by distillation under diminished pressure (about 1 mm.) and the distillate so obtained is of 98.99 per cent purity and solidifies to a crystalline mass when cooled in an ice mixture. The crystals are very hygroscopic and the melting point is approximately 18°. A product of this character is no doubt the kind which should be used for quantitative solubility determinations but the results would probably be of little interest from the standpoint of the pharmacopœia at present. On this account it was not considered necessary to undertake other than approximate determinations with the pharmacopœial lactic acid.

A few experiments were therefore made with the lactic acid of 72.8 per cent referred to above and a number of the organic solvents used for the determinations, with other acids as described in the preceding pages of this bulletin. The plan of the experiments was simply to add the lactic acid from a burette to the measured quantities of organic solvent contained in a glass stoppered bottle and note the point where opalescence occurred on shaking. It was found that 20 cubic centimeter portions of benzene, carbon tetrachloride, chloroform, carbon bisulphide, nitro benzene, and toluene each required less than 0.1 cubic centimeter of the lactic acid to give the opalescence on shaking. The solubility in these solvents is therefore not greater than one part in 200, and is probably even very much less than this figure. In the cases of amyl alcohol, amyl acetate, acetone, ethyl acetate, and ether, the addition of equal volumes of the lactic acid did not produce opalescence. On adding water, however, to the mixture a second layer separated in all cases except with acetone. In the cases of amyl alcohol and acetate the volumes of the upper or organic solvent layer appeared about equal to the volume originally used; in the case of ethyl acetate and ether the upper layers appeared considerably smaller than the volume of each used in the beginning.

[a] Ber. 28, 2589, 1895.

OLEIC ACID.

Solubility of oleic acid in aqueous alcohol solutions.—The sample used for the following experiments was pale amber colored and had specific gravity of 0.8969 at 20° and 0.8935 at 25°. A quantitative determination made by dissolving 10.1089 grams in enough alcohol to make 100 cubic centimeter of solution and titrating 10 cubic centimeter portions of this with standard 0.1 normal alcoholic potassium hydroxide, phenolphthaleine being used as indicator, gave results indicating a purity of 99.5 per cent $C_8H_{17}CH : CH(CH_2)_7COOH$. The preliminary solubility determinations were made by titrating aqueous alcohol solutions of increasing alcoholic content with the above oleic acid. In the case of all solutions below 50 weight per cent alcohol, the first drop of acid caused an opalescence on shaking, therefore indicating a solubility of less than about 0.05 grams acid per 100 cubic centimeters of alcohol. With solutions containing more than 50 per cent alcohol the following results were obtained:

Per cent by weight of C_2H_5OH.	Oleic acid per 100 c. c. alcohol to produce cloudiness.	Remarks.
	C. c.	
51.0	0.08–0.2	Cloudiness increased with continued addition of acid.
58.2	0.2 –0.4	Do.
65.5	0.3 –0.6	Cloudiness increased until about 5.5 c. c. had been added and then solution cleared.
70.2	0.6 –1.0	Cloudiness disappeared when about 4.5 c. c. acid had been added.
81.4	∞	No cloudiness appeared at all.

From these results it appears that below about 50 weight per cent alcohol the oleic acid is practically insoluble, between about 50 and 70 weight per cent the solubility apparently increases very gradually and then at about 75 per cent alcohol it goes up very abruptly to probable complete miscibility.

It should be mentioned that the point of the appearance of opalescence caused by adding the oleic acid to the alcohol is very uncertain. The cloudiness is at first very faint and increases gradually, so that no definite end point can be selected. Since it was observed that by continued addition of the oleic acid to the alcoholic solution of 70.2 weight per cent a point was reached at which the amount of opalescence began to diminish and finally disappeared entirely, it was decided to attempt to find the exact end points by titrating backwards; that is, by dissolving an excess of the oleic acid in the aqueous alcohol and then adding water until opalescence reappeared. Working in this way it was found that a very sharp end point could be obtained, one drop of water in excess being sufficient to cause the perfectly

clear solution to become distinctly cloudy on shaking. The values obtained by these two methods were widely different, however, evidently corresponding to two sets of conditions. In the one case the end point was marked only by an increasing cloudiness, while in the other the perfectly clear solution was transformed by one drop of the added solvent to an opalescent mixture, which after a few minutes' standing separated into two liquid layers, the volume of neither of which corresponded to the one drop of water which caused the separation. A series of experiments made according to the last-mentioned method of determination was made as follows:

Amounts of oleic acid varying between 2 and 25 cubic centimeters were added to definite volumes of 70.2 weight per cent alcohol (65.5 weight per cent was used, however, in one case and 81.4 per cent in another), and the mixtures were then titrated to appearance of opalescence with water, care being taken to bring the temperature just to 25° before reaching the end point. One determination (No. 7) was made by continuing the titration with the oleic acid until opalescence appeared, thus making the determination direct and not by back titration. The result obtained in this case was in satisfactory agreement with the others, showing that it is immaterial whether the end point with these concentrations of oleic acid be approached from one or the other direction. The quantities used in the titration were as follows:

Determination No.	C_2H_5OH in solvent, per cent by weight.	Amount of alcoholic solvent.	Oleic acid added.	H_2O for back titration.
		c. c.	c. c.	c. c.
1	70.2	25.0	2.0	3.90
2	70.2	25.0	4.0	3.70
3	[a] 65.5	26.5	5.0	1.75
4	70.2	25.0	8.0	2.75
5	70.2	25.0	12.5	1.55
6	70.2	35.0	25.0	1.00
7	70.2	25.0	23.2	....
8	81.5	1.5	10.0	0.05

[a] Made from 70.2 weight per cent alcohol by adding 1.55 c. c. H_2O to 25 c. c. of the alcohol.

From the above results it is possible to calculate the amounts of the three components, water, alcohol, and oleic acid which are present in each case and from these values the percentage of alcohol in each solvent (water + alcohol) at the end of the titration and also the weight of oleic ocid present per 100 grams of the saturated solution. This has been done and the results which were obtained are given in the accompanying Table No. XXIV.

TABLE NO. XXIV.—*Showing the amounts of oleic acid necessary to cause the separation of a second liquid phase in aqueous alcohol solutions of different concentrations at 25°.*

CALCULATED VALUES.

[From experimental determinations shown on p. 52.]

Determination No.	Composition of saturated solution.			Calculated per cent by weight of C_2H_5OH finally in solvent.	Oleic acid per 100 c. c. of alcoholic solvent.	Oleic acid per 100 grams saturated solution.
	C_2H_5OH.	H_2O.	Oleic acid.			
	Grams.	*Grams.*	*Grams.*		*c. c.*	*Grams.*
1	15.300	10.400	1.794	59.50	6.92	6.53
2	15.300	10.200	3.588	60.00	13.93	12.34
3	15.300	9.800	4.485	60.95	17.70	15.16
4	15.300	9.250	7.175	62.30	28.83	22.60
5	15.300	8.050	11.210	65.50	47.09	32.40
6	24.420	10.100	22.420	67.95	69.44	41.57
7	15.300	6.500	20.810	70.20	92.81	51.57
8	1.195	0.321	8.969	78.80	645.20	85.10

INTERPOLATED RESULTS.

These values plotted on cross-section paper give practically straight lines, from which the following results were obtained.

Per cent by weight of C_2H_5OH in solvent.	Oleic acid per 100 c. c. solvent.	Oleic acid per 100 grams saturated solution.
	c. c.	*Grams.*
57.0	....	0.0
58.5	0.0	5.0
60.0	11.0	12.3
62.5	30.0	20.0
65.0	49.0	30.5
67.5	69.0	40.0
70.0	91.0	50.0
75.5	....	68.5
80.0	....	88.0

From these results it is seen that the amount of oleic acid which will remain in a homogeneous mixture with alcohol and water increases very rapidly with relatively slight increases of alcoholic content beginning in solutions containing about 57 weight per cent alcohol. That part of the curve (or rather straight line, see figure 4) between 0 and about 5.0 grams of oleic acid per 100 grams of the saturated solution can not be determined directly since this quantity of oleic acid is not sufficient to yield a clear solution before the back titration with the water. In regard to the upper limit of the amount of oleic acid in the alcoholic solutions of higher concentrations it appears that the point of complete miscibility is reached at about 80 to 85 weight per cent alcohol, and therefore no second liquid layer can be made to separate in alcohol-water mixtures containing more than this per cent of alcohol.

As has already been mentioned, the opalescent solutions which are produced by the addition of the last drop of water in the back

titration, separate into two layers when allowed to stand. These solutions which resulted in the titration numbers 1 to 6 (see p. 52), were transferred to graduated cylinders and allowed to stand 24 hours and the volumes of the upper and lower layers then read. The perfectly clear layers of which the upper was yellowish and the lower nearly white or pale straw colored in each case were then analyzed by withdrawing enough to fill a pycnometer, weighing and titrating the dissolved oleic acid with alcoholic sodium hydroxide solution. An unsuccessful attempt was made in one case to determine the alcohol present by neutralizing the oleic acid with aqueous alkali and distilling. The excessive foaming, however, prevented a successful distillation of the alcohol and the procedure was abandoned. The results which were obtained are as follows. The figures in parentheses indicate estimated values. Some loss occurred in transferring the solutions from the titration flasks to the graduated cylinders, and therefore the sum of the volumes of the upper and lower layers are less than that of the solutions mixed as given for the titration results on page 52. This loss also accounts for the differences in the amounts of oleic acid found and those originally added.

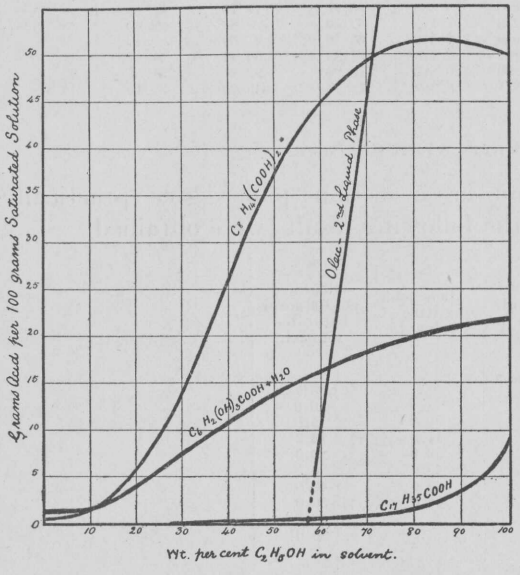

FIG. 4.—Curves showing the solubilities of camphoric, gallic, oleic, and stearic acids in aqueous alcohol solutions at 25°.

Determination No.	Lower layer.				Upper layer.			
	Volume of lower layer.	Specific gravity.	Oleic acid per 100 grams solution.	Oleic acid in lower layer.	Volume of upper layer.	Specific gravity.	Oleic acid per 100 grams solution.	Oleic acid in upper layer.
	c.c.		*Grams.*	*c.c.*	*c.c.*		*Grams.*	*c.c.*
1	29.0	0.893	5.123	1.48	1.0	.....	.....	(0.35)
2	26.0	0.890	7.347	1.89	6.0	(0.875)	33.83	1.98
3	22.7	0.891	8.572	1.93	9.3	(0.875)	31.39	2.78
4	16.0	0.893	6.139	0.98	19.0	0.876	35.54	6.59
5	6.0	(0.890)	6.259	0.37	33.2	0.878	36.61	11.87
6	4.5	.....	.....	(0.28)	55.5	0.877	44.59	24.14

From these results it appears that the composition of each of the upper layers and of each of the lower layers is nearly the same in all cases. The percentage of oleic acid in the upper averages about 36, and in the lower about 7.

The statements in the literature in regard to the solubility of oleic acid are mostly to the effect that it is insoluble in water and soluble in alcohol. The present results verify this statement as far as the water is concerned, but show that with alcohol of less than 80 weight per cent the insolubility may vary over a very considerable range, depending upon slight changes in the alcoholic concentration.

PHENOLSULPHONATES.

Solubility of sodium phenolsulphonate in aqueous alcohol solutions.— In igniting this compound, as mentioned in the Pharmacopœia, the residue at first contains unburned carbon which on heating to a higher temperature reduces a part at least of the sulphate to sulphide, thus not yielding a white residue of sodium sulphate amounting to 30.6 per cent of the original weight as stated. It was found that a fairly good determination could be made by first drying the weighed samples in the air bath at 120° to 140°, and after having cooled and weighed the residue to determine the loss of water of crystallization, igniting it very carefully so that no flaming occurs. The charred residue is then treated with a few drops of concentrated nitric acid and heated to redness. This procedure is repeated until a perfectly white residue is obtained. Determinations made in this way upon the sample to be used for the solubility experiments showed the presence of 15.44 per cent of water of crystallization instead of the theoretical 15.52 per cent, and gave sodium sulphate corresponding to 98.9 per cent $C_6H_4(OH)SO_3Na + 2H_2O$.

One series of solubility determinations was made, the time of shaking being two days. The weighed saturated solutions were transferred to weighing bottles and evaporated to dryness, the residues were dried to constant weight at 140°, and in addition some were analyzed as mentioned above for the sodium, and in this way the completeness of the drying was verified. The results which were obtained are given in Table No. XXV, and the curve from them in figure 5. The figures for water and pharmacopœial alcohol are in fair accord with those reported by the pharmacopœia which are respectively 1 part in 4.8 water and 1 part in 130 parts alcohol. A determination made by Greenish and Smith[a] at 15° gave 1 part of $C_6H_4(OH)SO_3Na + 2H_2O$ per 5.48 parts of water, the specific gravity of the saturated solution being 1.0675.

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[a] Pharm. Jour., (Lond.) June 22, 1901.

TABLE NO. XXV—*Solubility of Sodium Phenolsulphonate (para) in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_6H_4(OH)SO_3Na+2H_2O$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist H_2O	0.0	1.079	19.38
0.9856	8.9	1.057	17.46
0.9752	17.0	1.038	15.98
0.9628	26.4	1.016	14.47
0.9164	51.0	0.952	[a] 10.23
0.8718	70.2	0.886	5.03
0.8234	89.6	0.821	1.16
0.7941	99.9	.....	[b] 1.49

[a] This result unaccountably about 0.7 per cent high.
[b] Solid phase became opaque.

CALCULATED RESULTS.

The above figures plotted on cross section paper gave a curve from which the following results were obtained.

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$C_6H_4(OH)SO_3Na+2H_2O$ per 100 grams.		Solvent to dissolve 1 gram $C_6H_4(OH)SO_3Na+2H_2O$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.079	19.4	24.1	4.16
10.0	1.054	17.4	21.2	4.71
20.0	1.030	15.5	18.3	5.45
30.0	1.004	13.6	15.7	6.35
40.0	0.977	11.7	13.3	7.55
50.0	0.950	9.7	10.7	9.31
60.0	0.919	7.5	8.1	12.30
70.0	0.886	5.1	5.4	18.60
80.0	0.852	2.9	3.0	33.50
90.0	0.820	1.1	1.1	89.90
92.3	0.815	0.9	0.9	110.10
95.0	0.810	0.8	0.8	124.00
100.0	0.800	1.5	1.5	65.70

Solubility of zinc phenolsulphonate in aqueous alcohol solutions.—The sample used for the following solubility experiments was analyzed by determining the water of crystalization and by precipitating the zinc as carbonate from the hot solution by means of sodium carbonate, washing, igniting, and weighing as zinc oxide. The results were 25.85 per cent water of crystallization instead of the theoretical 25.93 per cent, and the zinc oxide corresponded to 100.7 per cent $Zn(C_6H_4(OH)SO_3)_2+8H_2O$. One series of determinations was made, the time of shaking being two days for some of the tubes and four for others. The weighed saturated solutions were evaporated in weighing bottles and the residues dried to constant weight at 130 to 140°.

The weights of anhydrous salt were calculated to the hydrated compound and these values converted to the quantities per 100 grams of the saturated solutions. The results are given in Table No. XXVI, and the curve in figure 5.

TABLE No. XXVI—*Solubility of zinc phenolsulphonate (para) in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$(C_6H_4(OH)SO_3)_2Zn+8H_2O$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist H_2O	0.0	1.185	39.81
0.9856	8.9	1.174	40.11
0.9752	17.0	1.165	40.53
0.9628	26.4	1.155	41.24
0.9164	51.0	1.124	42.12
0.8718	70.2	1.080	40.85
0.8234	89.6	1.047	41.34
0.7941	99.9	1.075	48.77

CALCULATED RESULTS.

The above figures plotted on cross section paper gave a curve from which the following values were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$(C_6H_4(OH)SO_3)_2Zn+8H_2O$ per 100 grams.		Solvent to dissolve 1 gram $(C_6H_4(OH)SO_3)_2Zn+8H_2O$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.185	39.8	66.1	1.512
20.0	1.161	40.7	68.6	1.457
40.0	1.139	42.1	72.7	1.375
60.0	1.106	41.6	71.2	1.404
80.0	1.057	40.7	68.6	1.457
90.0	1.047	41.4	70.6	1.416
92.3	1.048	41.9	72.1	1.387
95.0	1.052	42.9	75.1	1.330
100.0	1.075	48.8	95.3	1.049

Maximum at 47 weight per cent C_2H_5OH, 42.2 grams $(C_6H_4(OH)SO_3)_2Zn+8H_2O$ per 100 grams saturated solution.
Minimum at 78 weight per cent C_2H_5OH, 40.7 grams $(C_6H_4(OH)SO_3)_2Zn+8H_2O$ per 100 grams saturated solution.

The figures quoted by the U. S. Pharmacopœia are somewhat below the present results. Some results by Greenish and Smith [a] and Squire [b] for 15° C. are even below those reported by the U. S. Pharmacopœia.

[a] Pharm. Jour., (Lond.), i, 552, 1902; ibid., ii, 947, 1903.
[b] Companion to the British Pharmacopœia, 18th Ed.

The solubility curve for this salt is very striking in that it shows both a maximum and minimum point.

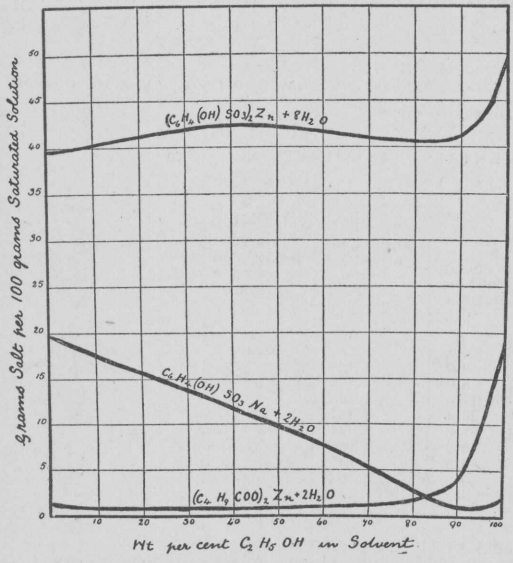

FIG. 5.—Curves showing the solubilities of sodium and zinc phenolsulphonate and of zinc valerate in aqueous alcohol solutions at 25°.

SALICYLIC ACID AND THE SALICYLATES.

Solubility of salicylic acid in aqueous alcohol solutions at 25°.—The samples of salicylic acid used for the solubility determinations were analyzed by dissolving weighed samples in neutralized alcohol and titrating with standard alkali using phenolphthaleine as indicator. The results indicated a purity in all cases of at least 99.8 per cent. The melting point was found to be 158.2° to 159° (Cor.) [a]. One series of determinations was made, the time allowed for saturation being three days. The weighed saturated solutions were transferred to measuring flasks, diluted to the mark with neutralized alcohol and aliquot portions titrated with standard alkali. The results are given in Table No. XXVII and the curve shown in figure 6.

The curve rises at first very slowly and then at about 25 weight per cent alcohol goes up very rapidly to the solvent of 100 per cent alcoholic strength in which the solubility is 33.2 grams salicylic acid per 100 grams of the saturated solution.

TABLE XXVII.—*Solubility of salicylic acid in aqueous ethyl alcohol solutions at 25°.*

EXPERIMENTAL RESULTS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_6H_4OHCOOH$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.00	1.001	0.22
0.9856	8.90	0.986	0.336
0.9545	32.00	0.957	2.68
0.9164	51.00	0.945	12.82
0.8718	70.20	0.941	24.01
0.8279	88.00	0.932	31.03
0.8048	96.30	0.923	32.45
0.7941	99.80	0.919	33.20

[a] In a previous report of these results upon salicylic acid (cf. Proc. Am. Electro-chem. Soc., Albany Meeting, 1908) the m. pt. was given as 156°, but this figure refers to the uncorrected value.

TABLE No. XXVII.—*Solubility of salicylic acid in aqueous ethyl alcohol solutions at 25°*—Continued.

CALCULATED RESULTS.

The above experimental determinations plotted on cross-section paper gave a curve, from which the following figures were read or calculated:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$C_6H_4OHCOOH$ per 100 grams.		Solvent to dissolve 1 gram $C_6H_4OHCOOH$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.001	0.22	0.22	453.50
10.0	0.984	0.38	0.38	262.00
20.0	0.970	0.80	0.81	124.00
30.0	0.959	2.20	2.25	44.45
40.0	0.951	5.90	6.27	15.95
50.0	0.945	12.20	13.90	7.20
60.0	0.943	18.30	22.41	4.46
70.0	0.941	24.00	31.58	3.17
80.0	0.937	28.30	39.48	2.93
90.0	0.930	31.40	45.77	2.19
[a] 92.3	0.928	31.90	46.85	2.13
100.0	0.919	33.20	47.50	2.11

[a] U. S. Pharmacopœia strength.

The solubility values for salicylic acid in water to be found in pharmaceutical literature vary considerably. Thus it is given as 1 part in 308 by the U. S. Pharmacopœia and from 1 part in 444 to 1 part in 550 by other reference books. The present value agrees closely with the average of the determinations compiled from the chemical literature, which are as follows:[a]

Temperature °C	0	10	20	25	30	40	60	80
Grams $C_6H_4OHCOOH$ per 100 c. c. solution	0.08	0.12	0.18	0.22	0.27	0.37	0.82	2.05

As for the solubility in alcohol, the values from the pharmaceutical reference books vary from 1 part in 2 to 1 part in 3.5 parts. The result for alcohol of U. S. Pharmacopœial strength, viz, 92.3 weight per cent, according to the present results for 25° is seen to be 1 part in 2.13 parts by weight.

Solubility of salicylic acid in organic solvents at 25°.—In these determinations the excess of acid was shaken with the solvent in each case for two days at 25° and the clear saturated solution weighed in a pycnometer, transferred to a glass-stoppered bottle, and titrated with standard alkali, using phenolphthaleine as indicator. The results are given in Table No. XXVIII. Only a few determinations are to be found in the literature with which to compare the present results, and for most of these the different temperature standards make an accurate comparison impossible. In the case of benzene

[a] Cf. Seidell's Solubilities of Inorganic and Organic Substances (1907), p. 274. (D. Van Nostrand Co.)

the value obtained by Walker and Wood[a] is 0.78 grams, $C_6H_4(OH)COOH$ per 100 grams, C_6H_6 at 25°, instead of 0.86 grams per 100 grams of benzene as reported in the accompanying table. These same authors also give the following figures for the solubility in acetone and in ether. One hundred cubic centimeters of acetone solution at 23° contained 31.3 grams of the acid and 100 cubic centimeters of the ethereal solution at 17° contained 23.4 grams. The weight of salicylic acid per 100 cubic centimeters of saturated ethereal solution as calculated from the accompanying results at 25° is 27.68 grams. According to several of the pharmaceutical reference books, the solubility of salicylic acid in chloroform is given at 1.25 grams per 100 grams $CHCl_3$ at about 15°, which is, as would be expected, somewhat below the value 1.67 grams shown below. A value for amyl alcohol is given by Hager as 1 part in 3.5 parts, which is somewhat above the present figure of 1 part per 4.89 parts at 25°.

TABLE NO. XXVIII.—*Solubility of salicylic acid in organic solvents at 25°.*

Solvent.	d of solvent.	d_{25} of saturated solution.	$C_6H_4OHCOOH$ dissolved per 100.			Solvent to dissolve 1 gram $C_6H_4OHCOOH$.
			Grams saturated solution.	Grams solvent.	cc. solvent.	
			Grams.	*Grams.*	*Grams.*	*Grams.*
Amyl alcohol (iso.)	d_{20}=0.817	0.878	20.47	25.73	21.02	4.89
Amyl acetate	d_{20}=0.875	0.917	16.67	20.00	17.50	5.00
Benzene	d_{25}=0.873	0.875	0.85	0.86	0.75	116.60
Carbon bisulphide	d_{25}=1.259	1.259	0.23	0.23	0.29	434.00
Carbon tetrachloride	d_{25}=1.587	1.587	0.25	0.25	0.40	399.00
Chloroform	d_{23}=1.476	1.477	1.64	1.67	2.46	60.00
Cumene	d_{20}=0.863	0.889	0.86	0.87	0.75	115.00
Ether (abs.)	d_{22}=0.711	0.857	32.29	47.68	33.90	2.10
Ligroin	d_{25}=0.714	0.714	0.13	0.13	0.09	768.00
Nitrobenzene	d_{25}=1.205	1.200	2.18	2.23	2.68	44.90
Spirits of turpentine	d_{20}=0.865	0.854	2.22	2.27	1.96	44.10
Toluene	d_{15}=0.872	0.863	0.84	0.85	0.74	118.00
Xylene	d_{25}=0.861	0.860	0.90	0.91	0.78	110.00

Methods for the determination of salicylates.—In beginning the work upon the solubilities of the salicylates it appeared desirable to find a method for the accurate analysis of the various samples required and for determining the quantities of the several salts dissolved. The experiments were directed in the first place toward those methods by which the salicylic radicle could be estimated. Of these, two are described in the literature as the Freyer bromate method and the Messinger and Vortmann iodine method, respectively. Attempts were therefore made to apply each of these methods to the salicylates described in the following pages, but the results were uncertain, and

[a] J. Chem. Soc., Lond., **73**, 620, 1898.

it was found that with both methods the limits of the conditions within which the reactions proceed according to the accepted equations are so narrow that the results obtained under ordinary conditions were of uncertain reliability. The details of the experiments which led to this conclusion have been published elsewhere [a] and therefore need not be given here.

In regard to the methods for the determination of the inorganic constituent of the salts it will be noted that the procedures recommended by the pharmacopœia vary for each of the three different basic constituents present, viz, for the sodium, lithium, and strontium salts. In the first case the sample is ignited and the ash titrated with standard acid; in the second it is mixed with ammonium sulphate and ignited in order to convert the lithium to lithium sulphate; with the last, concentrated sulphuric acid is prescribed as the agent for converting the residue to strontium sulphate. As has been shown in the case of sodium benzoate (p. 28), so also with sodium salicylate has it been found necessary to extract the first ignited residue of the sample with water and ignite the unburned carbon, adding the solution of this second ash to the first in order to have all the sodium in available form for the titration with standard acid. With this precaution the pharmacopœial method for sodium salicylate is entirely satisfactory.

Some years ago a method for the determination of salicylates was proposed by Barthe,[b] according to which an excess of hydrochloric acid was added to the aqueous solution of the sample of salicylate and the mixture evaporated to dryness at not over 50°. The residue, consisting of free salicylic acid and the chloride of the base, was then titrated with standard alkali, using phenolphthaleine as indicator, and subsequently the chloride was titrated with standard silver nitrate solution. In view of the experiments of Fresenius and Grünhut,[c] who found that satisfactory results for salicylic acid could not be obtained by any method of liberating salicylic acid, shaking out with volatile solvents and evaporating at a very low temperature, it did appear advisable to attempt the determination of salicylic acid as suggested by Barthe, but it was believed that the determination of the base by titration of the chloride might yield good results. Experiments along this line were therefore made, including, however, a modification for removing as much as possible of the free salicylic acid before titrating the chloride. The following results were obtained upon a sample of sodium salicylate which contained 100.2 per cent $C_6H_4OHCOONa$ on the basis of the determination made by the pharmacopœial method modified as above mentioned. 50 grams were dissolved in water and

[a] Seidell, J. Am. Chem. Soc., **31**, 1168–77, 1909.
[b] Bull. soc. chim., (3) **11**, 517, 1894.
[c] Z. anal. Chem., **38**, 292, 1899.

diluted to 500 cubic centimeters. An excess of HCl was added to aliquot portions of this solution, which were then evaporated to dryness on the steam bath and either filtered and just neutralized with alkali before the titration with standard silver nitrate, or the residue (determination No. 2) was gently ignited to remove the free salicylic acid before the titration for chlorides.

Determination No.	Salicylate solution.	$C_6H_4OHCOONa$.	0.1 N $AgNO_3$ required.	Calc. $C_6H_4OHCOONa$.
	C. c.	*Grams.*	*C. c.*	*Per cent.*
1	25	0.250	15.6	99.9
2	50	0.500	31.3	100.2
3	75	0.750	47.0	100.3

These results show that in the case of sodium salicylate this method is as reliable as that of the pharmacopœia; that it will prove equally so in the case of the other salicylates is hardly to be doubted. If further experiments should confirm this expectation we would then have a single procedure for these salts instead of three as is now the case.

Solubility of ammonium salicylate in aqueous alcohol solutions.—In the case of this compound two series of determinations were made with two samples of the salt. In one case the solutions were allowed two days for reaching equilibrium and in the other something over a week. It was evident that the shorter time was ample; in fact, it seems probable that even ten hours would have been sufficient. The two samples of material were each analyzed as follows: A weighed quantity of the salt was transferred to a 200 cubic centimeter flask, dissolved in water and diluted to the mark. Aliquot portions of the solution containing 1 to 2 grams ammonium salicylate were placed in a Kjeldahl distilling flask with 25 cubic centimeters of normal alkali. The liberated ammonia was distilled into 25 cubic centimeters of normal acid, and the excess of acid in the receiver titrated back with standard alkali and the excess of alkali in the distillation flask titrated back with standard acid. The amount of alkali equivalent to the ammonia in both cases agreed fairly satisfactorily. From these readings the amount of ammonia and thus of the ammonium salicylate in the aliquot portion of the solution was easily calculated. According to this method the two samples gave the following results expressed in the percentage of $C_6H_4OH.COONH_4$ present. Sample (a), 96.8 per cent; sample (b), 98.7 per cent. Although one of these samples was below the United States Pharmacopœia requirement and the other above, the solubility determinations made with them gave a curve in which no irregularities could be traced definitely to either sample. It may be mentioned that of the results shown in Table No. XXIX, the second, third, and sixth

were made with sample (a), and the others with sample (b). The impurity in the two samples was apparently principally moisture, and it might therefore be expected that in the solvents of higher alcoholic content the presence of this water would impair the results. That it did not do so to an appreciable extent is probably due to the lack of greater exactitude in the method by which the determinations were made.

TABLE No. XXIX.—*Solubility of ammonium salicylate in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_6H_4OHCOONH_4$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
1.00	0.00	1.148	50.8
0.986	8.9	1.137	50.8
0.955	32.0	1.104	49.3
0.872	70.2	1.014	42.0
0.828	88.0	0.946	33.1
0.819	91.4	0.932	30.5
0.805	96.3	0.901	26.5
0.794	99.8	0.875	22.3

CALCULATED DETERMINATIONS.

These results plotted on cross-section paper gave a curve from which the following figures were read or calculated:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$C_6H_4OHCOONH_4$ per 100 grams.		Solvent to dissolve 1 gram $C_6H_4OHCOONH_4$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.148	50.8	103.2	0.969
20.0	1.122	50.3	101.2	0.988
40.0	1.088	48.3	93.4	1.070
50.0	1.067	46.7	87.6	1.141
60.0	1.042	44.7	80.8	1.237
70.0	1.015	42.0	72.4	1.381
80.0	0.979	38.0	61.3	1.631
85.0	0.958	35.0	53.9	1.857
90.0	0.936	31.6	46.2	2.165
[a] 92.3	0.925	30.0	42.86	2.333
95.0	0.907	27.8	38.5	2.596
100.0	0.875	22.3	28.7	3.484

[a] U. S. Pharmacopœia strength.

Attention should be called here to the observation that on diluting to 200 cubic centimeters the weighed portions of each of the saturated solutions, except the one in water alone, considerable opalescence resulted. This opalescence increased with increasing alcohol content of the solvent. The cause of this separation of a portion of the constituents of the compound may possibly have been due to a

certain amount of dissociation of the ammonium salicylate by the alcohol, yielding some salicylic acid which remained dissolved in the alcohol but separated upon the addition of water. In withdrawing the aliquot portions from each of the 200 cubic centimeters dilutions for the determination of ammonia, the solutions were well shaken and no attempt made to use only the clear portion. The ammonia determinations were made by distilling as described for the analyses of the sample of salt employed. A comparison of the standard alkali neutralized in the distillation flask and of the amount equivalent to the liberated ammonia showed no regular differences with increase of alcoholic content, indicating that even if a portion of the salicylic acid of the compound was set free by the alcohol, the ammonia simultaneously liberated was not lost in the subsequent treatment of the solution.

The curve (see fig. 6) plotted from the determined results is found to descend regularly with increase of the strength of the alcohol. It bows upward as a result of the fact that the increase in the solubility of the ammonium salicylate proceeds slowly at first, but with increasing concentration of alcohol in the solvent its decrease is much more rapid. This bowing of the curve from a straight line shows that the water and alcohol in the several solvents do not act independently in their solvent action upon the ammonium salicylate; that is, the amount dissolved by any mixture of water and alcohol is more than the amount dissolved by the quantity of water present plus the amount dissolved by the quantity of alcohol present.

A comparison of the results of the present determinations with those quoted in the U. S. Pharmacopœia shows that the latter are somewhat higher. According to the U. S. Pharmacopœia, 1 gram of ammonium salicylate is dissolved by 0.9 grams H_2O and by 2.3 grams of official alcohol at 25° or 100 grams of water dissolve 111 gram ammonium salicylate and 100 grams official alcohol 46 grams of the salt. The present results are 103.2 and 42.9 grams, respectively, for the amounts dissolved by 100 grams of each by the two pure solvents.

Solubility of bismuth subsalicylate in aqueous alcohol solutions.—Solubility determinations were made upon a sample of "Bismuth Salicylate, Merck—basic 64 per cent Bi_2O_3" by the same procedure followed for the determinations already described. The amounts dissolved were determined in the usual way by evaporation and drying in a vacuum desiccator, but the quantities of the residues were so small that the results are not entirely free from criticism. When, however, the values were plotted on cross-section paper, the average curve drawn through them was no doubt very close to the true results for the particular sample employed. The figures read from this curve are as follows:

Per cent by weight of C_2H_5OH in solvent.	$C_6H_4OH \cdot COO \cdot OBi$ per 100 grams saturated solution at 25°.
	Grams.
0.0	0.010
20.0	0.015
40.0	0.022
60.0	0.036
80.0	0.065
90.0	0.095
[a] 92.3	0.105
100.0	0.160

[a] U. S. Pharmacopœia strength.

The statement in most of the pharmaceutical reference books is that bismuth subsalicylate is almost insoluble in water. The above figures will serve only to show about how insoluble the salt is, for it is evident that different samples will give different results, depending upon their actual composition.

Solubility of lithium salicylate in aqueous alcohol solutions.—The sample used for these solubility determinations was analyzed by the method given in the U. S. Pharmacopœia. According to this method, the weighed portion of the material is intimately mixed with anhydrous ammonium sulphate and the mixture fused, the amount of lithium sulphate obtained being calculated to salicylate. The original sample as received from the manufacturer, as well as a recrystallized portion of the same, yielded practically identical results by this method as did also the residues which were obtained from the solubility determinations after drying to constant weight in a vacuum desiccator. The average of these determinations was 95.5 per cent of anhydrous lithium salicylate, or 101.5 per cent of $C_6H_4OHCOOLi + \frac{1}{2}H_2O$. The lithium sulphate residues that were obtained were powdered and mixed and analyzed by means of a determination of SO_4. The calculated Li_2SO_4 was found in this way to be approximately 1 per cent too high, showing that the lithium salicylate itself was probably contaminated with some other alkali. Assuming this to be the case, the calculated 101.5 per cent of $C_6H_4OHCOOLi + \frac{1}{2}H_2O$ instead of an even 100 per cent would be easily explained by assuming the presence of admixed sodium or potassium salicylate. Since the process of recrystallization of the original material from strong alcohol had not yielded a better product, other attempts to effect an improvement were not made. The accompanying solubility determinations are therefore open to the criticism that more or less impure material was used. It is probable, however, that the errors due to the possible impurities of the sample are comparatively small and the results as given in the

accompanying table No. XXX are of sufficient reliability for all practical purposes.

TABLE No. XXX.—*Solubility of lithium salicylate in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_6H_4OHCOOLi+\frac{1}{2}H_2O$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.209	56.0
0.986	8.9	Not det.	55.9
0.954	32.4	1.159	54.2
0.915	51.6	1.120	52.0
0.869	71.5	1.080	49.2
0.815	92.6	1.021	45.4
0.804	96.6	1.018	45.6
0.794	99.9	1.027	48.2

CALCULATED DETERMINATIONS.

The above results plotted on cross section paper yielded a curve from which the following results were obtained:

Weight per cent of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$C_6H_4OHCOOLi+\frac{1}{2}H_2O$ per 100 grams.		Solvent to dissolve 1 gram of $C_6H_4OHCOOLi+\frac{1}{2}H_2O$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0	1.209	56.0	127.3	0.786
10	1.195	55.9	126.8	0.789
20	1.180	55.4	124.3	0.805
30	1.163	54.7	120.8	0.828
40	1.144	53.7	116.0	0.862
50	1.124	52.5	110.5	0.905
60	1.104	51.1	104.5	0.957
70	1.083	49.5	98.0	1.021
80	1.056	47.5	90.5	1.105
90	1.026	45.8	84.5	1.183
[a]92.3	1.020	45.6	83.8	1.193
100	1.027	48.2	93.1	1.075

[a] U. S. Pharmacopœia strength.

The amounts of lithium salicylate dissolved were determined by evaporating the solvents and drying the residues in a vacuum desiccator containing concentrated sulphuric acid at room temperature. In the case of a duplicate determination of the solubility in water, however, the solvent was evaporated in a drying oven at about 60°, and in this case the residue which was obtained was found upon analysis to be almost anhydrous lithium salicylate. It differed considerably in physical appearance from the crystalline residues obtained in the other cases and therefore lends further evidence to the conclusion that the ordinary crystalline lithium salicylate contains one-half molecule of water of crystallization instead of being anhydrous, as described in the U. S. Pharmacopœia.

The solubility curve (see fig. 6) presents one unexpected peculiarity in that a minimum point is reached at a concentration of about 95 weight per cent alcohol.

Very few results are given in the literature with which the present values can be compared. The only statement in the U. S. Pharmacopœia is to the effect that lithium salicylate is very soluble in water and alcohol. Results from other sources vary from 1 part in 0.75 to 1 part in 1.0 part of water and from 1 part in 2.0 parts to 1 part in 1 part of alcohol. These figures are uncertain, however, since they may refer to the anhydrous salt, or, as is more likely, to a temperature different from that at which the present values were determined.

Solubility of methyl salicylate in aqueous alcohol solutions at 25°.— This compound, being a liquid at ordinary temperatures, does not require the usual procedure for determination of its solubility in alcohol solutions that has been adopted for the solid compounds. The titration method described under ethyl acetate (p. 13) may be used with satisfactory results. The method there described was modified, however, to some extent in the present case in order to insure a more accurate control of the temperature, since the change of solubility with temperature is very great with this compound. The details of the determinations are as follows: The measured volume of the aqueous alcoholic solvent of determined strength is brought to nearly 25° in a 100 cubic centimeters Erlenmeyer flask; the methyl salicylate is added slowly from a burette until a permanent clouding is observed. A thermometer is kept in the flask and the temperature noted during the addition of the salicylate. The temperature of the flask can be controlled by warming with the hands or cooling under the cold-water faucet. The last few drops of methyl salicylate must be added just as the temperature stands at 25°. The burette is read and the specific gravity of the saturated solution is immediately determined by the pycnometer method. For the determinations of the solubility made at various temperatures (Table No. XXXII) the solvent was cooled to the lowest temperature desired, viz, 15°, and the reading of the methyl salicylate taken just on appearance of opalescence at this point; the temperature was then allowed to rise to 20° and the addition of methyl salicylate continued until the end point at this temperature was observed, and so on with the 25° and 30° determinations.

The sample of methyl salicylate (artificial oil of wintergreen) was purified by distillation and the fraction obtained at 220° to 221° (cor.) used for the solubility determinations. The specific gravity of both the original and the distilled portion of the sample was found to be 1.182 at 25°.

TABLE No. XXXI.—*Solubility of methyl salicylate in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_6H_4OHCOOCH_3$ per 100 c. c. aq. alcohol.	$C_6H_4OHCOOCH_3$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.			
			Cubic centimeters.	*Grams.*
Dist H_2O	0.0	1.000	(Ca.) 0.1	0.12
0.955	32.0	0.955	0.5	0.61
0.9164	51.0	0.924	5.3	6.40
0.8718	70.2	0.944	34.0	31.56
0.8441	81.4	1.090	270.0	79.09
0.8234	89.6	.....	∞	.....

CALCULATED RESULTS.

The above determinations plotted on cross-section paper yielded a curve from which the following results were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$C_6H_4OHCOOCH_3$ per 100 grams.		Solvent to dissolve 1 gram C_6H_4OH $COOCH_3$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0	1.000	0.12	0.12	832.00
30	0.958	0.60	0.61	166.00
40	0.940	2.30	2.35	42.50
50	0.925	6.20	6.61	15.10
55	0.922	10.00	11.10	9.00
60	0.923	18.60	22.87	4.37
65	0.929	30.50	43.88	2.28
70	0.943	39.40	65.01	1.54
75	0.974	58.50	141.00	0.71
80	1.050	72.00	275.10	0.39

The results obtained for 25° have been calculated to the usual terms adopted for the other compounds and are given in Table No. XXXI. The value for the solubility in water alone is more or less uncertain since the first few drops of the salicylate added to 50 c. c. of water apparently remained undissolved. The opalescence which is produced in the solutions of higher alcoholic concentration by an excess of salicylate is not observed in water alone, and the detection of the end point is therefore uncertain. Determinations of the solubility in water, which are no doubt very accurate, have recently been reported by Gibbs.[a] They were made by agitating an excess of the salicylate with pure water for eighteen hours or longer and analyzing the clear solution by a colorimetric method. The result for 30° was 0.074 grams $C_6H_4OHCOOCH_3$ per 100 cubic centimeters H_2O. From the present results it is seen that very little increase of solubility of methyl salicylate occurs even up to approximately 30 per cent alcohol. Beyond this point the increase is more rapid, and between 60 and 80 per cent alcohol the curve (see figure 6) turns up very abruptly, evidently reaching the point corresponding to complete

[a] Philippine Jour. of Sci. (A), **3**, 359, 1908.

miscibility of the methyl salicylate at about 85 weight per cent alcohol. There are no quantitative figures for the solubility of methyl salicylate in alcohol to be found in the U. S. Pharmacopœia or indeed in the chemical literature. The available statements are, to the effect that it is slightly soluble in water and in all proportions in alcohol. The results show that the first part of this statement is true not only for water but even for alcoholic solutions up to about 40 per cent strength. The complete miscibility, on the other hand, applies for alcoholic solvents of only about 85 weight per cent or more, and below this strength the amount dissolved diminishes very rapidly, with lowering of alcoholic strength.

TABLE No. XXXII.—*Solubility of methyl salicylate in aqueous alcohol solutions at different temperatures.*

EXPERIMENTAL DETERMINATIONS.

Per cent by weight of C_2H_5OH in solvent.	$C_6H_4OHCOOCH_3$ per 100 c. c. alcoholic solvent at—			
	15°.	20°.	25°.	30°.
	c. c.	c. c.	c. c.	c. c.
0.0	(Ca.) 0.1	0.1	0.1	0.1
32.0	0.3	0.4	0.5	0.6
51.0	3.4	4.1	5.3	6.2
70.2	22.8	27.4	34.0	43.2
81.4	160.0	214.0	270.0	335.0

INTERPOLATED RESULTS.

The above determinations plotted on cross-section paper yielded curves from which the following values were obtained:

Per cent by weight of C_2H_5OH in solvent.	$C_6H_4OHCOOCH_3$ per 100 c. c. alcoholic solvent at—			
	15°.	20°.	25°.	30°.
	c. c.	c. c.	c. c.	c. c.
0	(Ca.) 0.1	0.1	0.1	0.1
30	0.3	0.4	0.5	0.6
40	0.8	1.1	1.4	1.8
50	2.4	3.5	5.0	6.0
55	4.2	6.0	7.8	9.5
60	7.7	10.0	12.5	15.5
65	13.0	16.5	20.2	24.5
70	22.0	28.0	33.0	40.0
75	43.0	52.0	62.0	72.0
80	92.0	135.0	180.0	230.0

Another point of much importance in connection with this compound is the great effect of temperature upon the solubility. The variations between 15° and 30° are shown very strikingly by the results contained in Table No. XXXII. It will be noticed that at nearly every concentration of alcohol the amount of methyl salicylate dissolved is more than doubled through the range of 15° of temperature.

The solubility of phenyl salicylate in aqueous alcohol solutions.—The sample used for the solubility determinations was analyzed by

saponifying in a closed flask and titrating the excess of alkali used. The results showed the material to be of practically 100 per cent purity.

Only one series of solubility determinations was made, the time of shaking being two days. The amount of phenyl salicylate was determined by evaporation of the solvents at 55–60° and drying the residues to constant weight in a vacuum desiccator. The results are given in Table No. XXXIII and the curve in figure 6.

The amount dissolved by water according to the present determination is only about one-third that reported by the pharmacopœia. The actual amount, however, in both cases is very small and the statement of most of the other reference books that salol is almost insoluble in water is perhaps sufficient for all practical purposes. In regard to the figures quoted for alcohol very great variations exist in the literature. Thus it is given as 1 part in 5 by the U. S. Pharmacopœia, as 1 part in 10 by most of the German authorities, and as 1 part in 20 by Squire's Companion to the British Pharmacopœia. The present results show that the value quoted by the U. S. Pharmacopœia is very near the correct figure.

TABLE No. XXXIII.—*Solubility of phenyl salicylate in aqueous alcohol at 25° C.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25° C.	C_6H_4OH-$COOC_6H_5$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	0.999	0.015
0.986	8.9	0.985	0.018
0.954	32.0	0.950	0.067
0.916	51.0	0.912	0.861
0.872	70.2	0.877	4.44
0.828	88.0	0.863	11.91
0.805	96.3	0.878	26.68
0.794	99.8	0.897	34.73

CALCULATED DETERMINATIONS.

The above results plotted on cross-section paper yielded a curve from which the following results were read:

Per cent by weight of C_6H_5OH in solvent.	Specific gravity saturated solution at 25° C.	$C_6H_4OHCOOC_6H_5$ per 100 grams.		Solvent to dissolve 1 gram $C_6H_4OHCOOC_6H_5$.
		Saturated solution.	Solvent.	
Per cent.		*Grams.*	*Grams.*	*Grams.*
0	0.999	0.015	0.015	6665.00
20	0.967	0.020	0.020	5000.00
40	0.934	0.220	0.220	453.50
50	0.914	0.760	0.770	130.60
60	0.895	2.100	2.150	46.62
70	0.877	4.400	4.600	21.73
80	0.863	7.700	8.340	11.99
90	0.865	14.000	16.280	6.14
[a] 92.3	0.868	17.700	21.510	4.65
100	0.898	35.000	53.860	1.86

[a] U. S. Pharmacopœia strength.

The solubility of quinine salicylate in aqueous alcohol solutions.—The material used for these solubility determinations bore the label "Quinine salicylate, Merck," and consisted of very light fibrous white crystals which melted at approximately 195°. The U. S. Pharmacopœia gives the melting point as 183° to 187° with decomposition. No other tests for the identification or purity of the product were made. The solubility determinations were carried out in the usual manner, the solvents being evaporated and the residues dried in a vacuum desiccator at room temperature. The results are given in Table No. XXXIV and the curve in figure 6.

The curve shows a maximum point at about 90 weight per cent alcohol. The values for the solubility in water and in alcohol of U. S. Pharmacopœia strength differ considerably from those quoted in the U. S. Pharmacopœia; the present results being 1 part in 1,538 and 20.65, respectively, for water and alcohol, and those of the Pharmacopœia being 1 part in 77 and 1 part in 11.

As is generally the case with the solubilities of alkaloids and their salts, the values quoted in the literature for quinine salicylate are very variable. Thus, for the solubility in water, figures are given all the way from 1 part in 77 parts to 1 part in 630 parts of water, and for alcohol from 1 part in 11 to 1 part in 25. Such great differences can not be satisfactorily explained, and, as has been mentioned in the first part of this bulletin, the subject of the solubilities of the alkaloids is one upon which there is the most pressing need for investigation.

TABLE NO. XXXIV.—*Solubility of quinine salicylate in aqueous alcohol solutions at 25° C.*

EXPERIMENTAL RESULTS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_6H_4OHCOOH.C_{20}H_{24}N_2O_2+\frac{1}{2}H_2O$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.00	0.999	0.065
0.954	32.40	0.950	0.571
0.915	51.60	0.914	1.839
0.869	71.50	0.873	3.390
0.815	92.60	0.825	4.609
0.804	96.60	0.811	4.066
0.794	99.90	0.797	3.152

TABLE No. XXXIV.—*Solubility of quinine salicylate in aqueous alcohol solutions at 25° C.*—Continued.

CALCULATED RESULTS.

The above results plotted on cross-section paper yielded a curve from which the following figures were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	Quinine salicylate per 100 grams.		Solvent to dissolve 1 gram quinine salicylate.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	0.999	0.065	0.065	1,538.00
10.0	0.982	0.080	0.080	1,250.00
20.0	0.966	0.200	0.200	500.00
30.0	0.952	0.480	0.480	207.00
40.0	0.935	1.000	1.010	99.00
50.0	0.916	1.700	1.730	57.80
60.0	0.896	2.450	2.510	39.80
70.0	0.876	3.270	3.380	29.60
80.0	0.854	4.200	4.380	22.80
90.0	0.832	4.710	4.940	20.20
[a] 92.3	0.826	4.620	4.840	20.65
100.0	0.797	3.150	3.250	30.75

[a] U. S. Pharmacopœia strength.

Solubility of sodium salicylate in aqueous alcohol solutions.—The sodium salicylate which was used for the solubility determinations given herewith was carefully recrystallized from hot 95 per cent alcohol and dried for about a week in a vacuum desiccator containing concentrated H_2SO_4. The scaly crystals were almost white, and an analysis by the pharmacopœial method, modified as already described under sodium benzoate, gave results indicating a purity of 100.2 per cent. Two closely agreeing series of solubility determinations were made; in the first the time of shaking was two days and in the second five days. The weighed portions of the saturated solutions were transferred to weighing bottles and the solvents evaporated at not over 60° C. The residues were dried to constant weight in a vacuum desiccator containing concentrated sulphuric acid. The results are given in Table No. XXXV and the curve is shown in figure 6.

It will be noted, as might be expected, that alcohol decreases regularly the solubility of sodium salicylate. The decrease is at first very gradual and then more rapid, giving a curve which bows upward and shows that the solubility in mixtures of alcohol and water is greater than corresponds to a simple additive function of the amount dissolved in each solvent separately.

The values in the literature for water and pharmacopœial alcohol agree on the whole fairly well with the results here shown.

TABLE No. XXXV.—*Solubility of sodium salicylate in aqueous alcohol solutions at 25° C.*

EXPERIMENTAL RESULTS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_6H_4OHCOONa$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.252	53.56
0.986	8.9	Not det.	52.10
0.954	32.4	1.169	47.40
0.915	51.6	1.102	41.93
0.869	71.5	1.010	32.10
0.815	92.6	0.864	11.75
0.804	96.6	0.828	6.56
0.794	99.9	0.805	3.82

CALCULATED DETERMINATIONS.

The above results plotted on cross-section paper gave a curve from which the following figures were read or calculated:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$C_6H_4OHCOONa$ per 100 grams.		Solvent to dissolve 1 gram $C_6H_4OHCOONa$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.256	53.56	115.30	0.867
10.0	1.235	52.10	108.70	0.919
20.0	1.205	50.20	100.80	0.992
30.0	1.176	48.00	92.30	1.083
40.0	1.142	45.50	83.50	1.198
50.0	1.106	42.20	73.00	1.370
60.0	1.060	38.40	62.30	1.604
70.0	1.016	33.00	49.20	2.031
80.0	0.957	25.00	33.30	3.000
90.0	0.885	15.00	17.60	5.666
[a] 92.3	0.864	12.00	13.60	7.333
100.0	0.805	3.82	3.98	25.160

[a] U. S. Pharmacopœia strength.

Solubility of strontium salicylate in aqueous alcohol solutions.—The averages of the results obtained from two samples of strontium salicylate purchased for the following solubility determinations were, respectively, 99.04 and 99.55 per cent $(C_6H_4OHCOO)_2Sr+2H_2O$; the analyses being made according to the U. S. Pharmacopœia method, which involves incineration of the sample after mixing with concentrated sulphuric acid and repeating this procedure until a residue of strontium sulphate uncontaminated with unburned carbon is obtained. The method yields satisfactory results, but great care is required to prevent loss by spattering and to insure the complete removal of all carbon. The former source of error may be satisfactorily overcome by placing the crucible in a hole in an asbestos board and covering with a piece of ashless filter paper during the evapora-

tion of the excess of sulphuric acid, the filter paper being allowed to drop into the crucible when the temperature is raised to redness.

The better of the above-mentioned samples of strontium salicylate was recrystallized from hot 80 to 90 per cent alcohol and the crystals dried in a vacuum desiccator over concentrated sulphuric acid for about a week. The product analyzed practically 100 per cent $(C_6H_4OHCOO)_2Sr+2H_2O$, showing that no loss of water of crystallization had occurred in drying the material as described.

The tubes for the solubility determinations were prepared as has already been described, but after the period of rotation it was noticed that the solid phase in the tube containing the solvent of 99.9 per cent alcoholic strength had been converted into an amorphous bulky white powder. It therefore appeared that absolute alcohol is able to remove some or all of the water of crystallization of strontium salicylate. This point was tested by preparing a quantity of the dehydrated salt by allowing some of the crystallized material to stand in contact with absolute alcohol until it had practically all been converted to the powder form and then filtering, washing, and drying. Solubility determinations made with this product did not differ appreciably from those obtained for the crystalline dihydrate. Analyses of it gave an amount of strontium sulphate which corresponded to 93.87 per cent $(C_6H_4OHCOO)_2Sr$, 99.49 per cent of monohydrate or 100.85 per cent of $(C_6H_4OHCOO)_2Sr+1\frac{1}{2}H_2O$. These results show that although absolute alcohol changes the appearance of the ordinary strontium salicylate very materially the amount of dehydration which it effects is comparatively small. Under the high power microscope the salicylate powder shows minute irregular crystals and no appreciable amount of amorphous material.

Four series of solubility determinations were made, in three of which the crystalline salicylate was used, and in the other the powder obtained by treating the crystals with absolute alcohol. The results in all cases were in satisfactory agreement.

TABLE NO. XXXVI.—*Solubility of strontium salicylate in aqueous ethyl alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$(C_6H_4OHCOO)_2Sr+2H_2O$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.022	5.04
0.986	8.9	1.007	4.91
0.954	32.4	0.979	6.55
0.915	51.6	0.945	8.02
0.869	71.5	0.891	5.80
0.804	96.6	0.804	1.24
0.794	99.9	0.790	0.44

TABLE NO. XXXVI.—*Solubility of strontium salicylate in aqueous ethyl alcohol solutions at 25°.*—Continued.

CALCULATED DETERMINATIONS.

These results plotted on cross-section paper gave a curve from which the following figures were read or calculated:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$(C_6H_4OHCOO)_2Sr+2H_2O$ per 100 grams.		Solvent to dissolve 1 gram of $(C_6H_4OHCOO)_2Sr+2H_2O$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.022	5.04	5.31	18.85
10.0	1.006	4.88	5.13	19.49
20.0	0.993	5.22	5.51	18.16
30.0	0.982	6.20	6.61	15.13
40.0	0.966	7.70	8.34	11.99
50.0	0.948	8.08	8.79	11.38
60.0	0.923	7.15	7.70	12.98
70.0	0.893	5.90	6.27	15.95
80.0	0.859	4.40	4.60	21.73
90.0	0.824	2.56	2.63	38.07
[a] 92.3	0.815	2.02	2.06	48.51
100.0	0.790	0.44	0.44	226.20

[a] U. S. Pharmacopœia strength.

Although in the present case we are dealing with a salt containing water of crystallization and naturally expect that in so far as the salt dissolves, this water will change the concentration of the alcoholic solvent, it happens that this error is really not large enough to materially affect the results. If we consider the solution in which the maximum amount of salt is dissolved it is found that the amount of water arising from this salt is less than 1 per cent of the weight of the solvent required to dissolve this quantity of the salt. This solvent is the one containing approximately 50 weight per cent of alcohol, hence it is evident that the maximum error produced is less than one-half of 1 per cent and in the present case this amount would not affect the position of the solubility curve obtained.

The analyses of the saturated solutions were made both by weighing the evaporated residues which were dried to constant weight in a vacuum desiccator containing concentrated sulphuric acid and also by determination of the strontium in these residues by incineration as already described. The two methods gave satisfactory agreement. The results which were obtained have been compiled in the first part of Table No. XXXVI. The curve drawn through the plotted results gave the figures shown in the lower part of the table.

The solubility curve for this salt which is shown in figure 6 is quite remarkable, and the cause for its irregularities can not be readily explained. The solubility at first decreases slightly and then rises very rapidly to a sharp maximum of 8.1 grams in 100 grams of 48

weight per cent alcohol. After which with increasing alcoholic strength the solubility falls steadily to 0.44 gram of salicylate in 100 grams of absolute alcohol.

The results for the solubility of strontium salicylate quoted by the U. S. Pharmacopœia are respectively 1 part in 18 parts of water

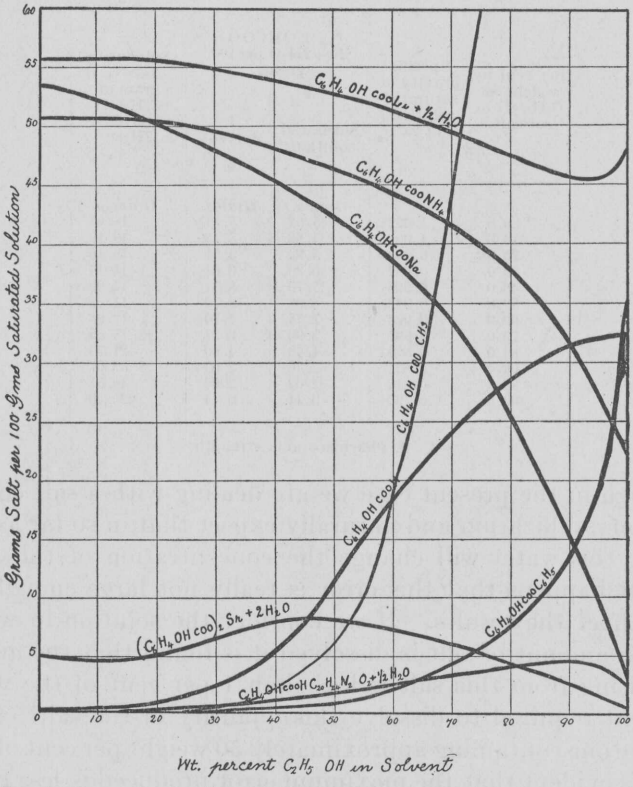

FIG. 6.—Curves showing the solubilities of salicylic acid and the salicylates in aqueous alcohol solutions at 25°.

and 1 part in 66 parts of alcohol. The present results are, however, 1 part in 18.85 and 1 part in 48.51.

STEARIC ACID.

Solubility of stearic acid in aqueous alcohol solutions.—No definite requirements of purity of this acid are prescribed by the Pharmacopœia and likewise no quantitative methods for its analysis. It would really appear that commercial more or less impure material obtained from the more solid fats, chiefly tallow, is all that the Pharmacopœia demands. It is clear therefore that only approximate solubility values are necessary for such a product. The material used for the present solubility determinations was purchased as C. P. and is presumably the best that the market affords. A quantitative

determination made by dissolving the weighed sample in neutralized alcohol and titrating aliquot portions of the solution with standard alcoholic potassium hydroxide, using phenolphthaleine as indicator, gave results corresponding to 102.3 per cent $C_{17}H_{35}COOH$ in the case of a sample from one source and 101.7 per cent with a different sample of the acid. It was noticed that in making these titrations the presence of water increased the amount of alkali required and therefore led to high results. Thus titrations made in alcoholic solutions containing about 50 per cent alcohol might give results 1 per cent or more above that found with solutions in which only relatively very little water was present.

The analytical results upon these two samples indicate that they were really not pure stearic acid, but they are no doubt much within the very loose requirements of the pharmacopœia, and the accompanying solubility results will show the general direction and approximate solubility values, but not the absolute figures for the purest stearic acid.

TABLE No. XXXVII.—*Solubility of stearic acid in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_{17}H_{35}COOH$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	0.999	0.034
0.9752	17.0	0.972	0.035
0.9359	41.7	0.929	0.121
0.8718	70.2	0.864	0.813
0.8234	89.6	0.817	3.163
0.8048	96.4	0.803	6.442
0.7941	99.9	0.795	8.277

CALCULATED RESULTS.

The above figures plotted on cross-section paper gave a curve from which the following values were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$C_{17}H_{35}COOH$ per 100 grams.		Solvent to dissolve 1 gram $C_{17}H_{35}COOH$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	0.999	0.034	0.035	2,809.0
20.0	0.967	0.04	0.04	2,500.0
40.0	0.932	0.10	0.10	999.0
50.0	0.911	0.18	0.18	555.0
60.0	0.888	0.40	0.40	249.0
70.0	0.865	0.80	0.81	124.0
80.0	0.841	1.63	1.66	60.4
90.0	0.818	3.30	3.41	29.3
92.3	0.813	4.15	4.33	23.1
95.0	0.807	5.55	5.88	17.0
100.0	0.795	8.30	9.05	11.1

Only one series of determinations was made and the time allowed for saturation was three days. The weighed saturated solutions were transferred to Erlenmeyer flasks with the aid of (neutral) absolute alcohol and titrated with standard alcoholic alkali. It was noticed that if, after the titration, water be added to the solutions, the faint excess of pink color was at first discharged and then with more water it reappeared and became deeper red with continued dilution. The titration results were calculated without making a correction for the impurity indicated by the analysis of the samples. The results are given in Table No. XXXVII and the solubility curve shown in figure 4.

An examination of the literature shows the most divergent values for the solubility of stearic acid in alcohol. This is probably due to a number of causes. The variation in the purity of the samples is to be considered first, but perhaps the most serious difficulty is the very steep character of the curve in the vicinity of the very strong alcohol solutions. It will be noticed that for a change of alcoholic strength of from only 90 to 95 per cent the amount of acid dissolved is increased more than 1.7 times; therefore small differences in the concentration of the alcohol used by different investigators make large differences in the results found. Although there are no available results showing the effect of temperature on the solubility of stearic acid, it is probable that this is also a source of some of the differences in the reported values.

Solubility of stearic acid in organic solvents.—These determinations were made by agitating an excess of the acid with the several solvents for two days. The saturated solutions were titrated with standard alcoholic alkali as already mentioned for the solubility determinations in aqueous alcohol. The results are given in Table No. XXXVIII. It will be noticed that stearic acid is fairly soluble in all of the ten organic solvents. The solubility is greatest in ether and least in nitrobenzene.

TABLE No. XXXVIII.—*Solubility of stearic acid in organic solvents at 25°.*

Solvent.	d of solvent.	d_{25} of saturated solution.	$C_{17}H_{35}COOH$ dissolved per 100.			Solvent to dissolve 1 gram $C_{17}H_{35}COOH$.
			Grams saturated solution.	Grams solvent.	C. C. solvent.	
			Grams.	*Grams.*	*Grams.*	*Grams.*
Acetone	$d_{15}=0.797$	0.815	4.73	4.97	3.96	20.14
Amyl alcohol (iso)	$d_{20}=0.817$	0.815	9.43	10.41	8.51	9.60
Amyl acetate	$d_{20}=0.875$	0.867	11.19	12.60	11.03	7.94
Carbon bisulphide	$d_{25}=1.259$	1.163	19.20	23.76	29.91	4.21
Carbon tetrachloride	$d_{25}=1.587$	1.465	10.25	11.42	18.13	8.76
Chloroform	$d_{22}=1.476$	1.332	15.54	18.40	27.16	5.44
Ether (abs.)	$d_{22}=0.711$	0.744	20.04	25.06	17.82	3.99
Ethyl acetate	$d_{25}=0.892$	0.895	7.36	7.95	7.09	12.59
Nitrobenzene	$d_{25}=1.205$	1.199	1.24	1.26	1.52	79.66
Toluene	$d_{15}=0.872$	0.865	13.61	15.75	13.74	6.35

TANNIC ACID.

Attempts to determine the solubility in aqueous alcohol solutions of a sample of tannic acid [a] of apparently very good quality were unsuccessful on account of the impossibility of saturating the solution with the acid. So much of the sample dissolved in water and also in absolute alcohol that before an excess of it remained undissolved the solution had become so viscous that it flowed from one end of the tube to the other only with extreme slowness. It appeared doubtful whether it would have been possible to separate the saturated solution from the undissolved material even if the saturation point could have been reached. Furthermore, there was apparently no satisfactory method available for analyzing the saturated solution even if it could have been obtained. It was therefore necessary to abandon attempts to determine the solubility of this acid in the manner followed for the remaining members of the series of pharmacopœial compounds.

According to the literature the solubility in water is given all the way from 1 part in 0.35 parts of water to 1 part in 5.0 parts, and the solubility in alcohol from 1 part in 0.23 to 1 part in 2.0. The statement that it is almost insoluble in absolute alcohol occurring in several reference books is, according to the experiment mentioned above, certainly open to question.

TARTARIC ACID AND THE TARTRATES.

Solubility of tartaric acid in aqueous alcohol solutions.—The sample used for the solubility determination was analyzed by titration with normal alkali, using phenolphthaleine as indicator. The results corresponded to a purity of 99.3 per cent $C_2H_2(OH)_2(COOH)_2$. The melting point was found to be 166.1° to 167.3° (cor.).

One series of determinations was made and the time allowed for saturation, with constant shaking, was two days. The saturated solutions were weighed and, after dilution, aliquot portions were titrated with normal alkali. The results are given in Table No. XXXIX and the curve shown in figure 7. The decrease in solubility with increase of alcoholic content of the solution is perfectly regular, but at no point is the sum of the amounts which the alcohol and water in each solvent would dissolve independently as great as actually found. The figure for water agrees fairly well with that quoted by the pharmacopœia, but with alcohol of U. S. Pharmacopœia strength the difference is much greater.

A series of determinations of the solubility of tartaric acid in water at different temperatures published by Leidie [b] contains a value for

[a] Kindly furnished by Dr. Geo. W. Hoover, of the Drug Laboratory, Bureau of Chemistry, U. S. Department of Agriculture.

[b] Compt. rend., **95**, 87, 1882.

25°, which is considerably above the present results, viz, 147.44 grams acid per 100 grams water instead of 137.5. Other values from the principal pharmaceutical reference books for the temperature 15° also indicate that Leidie's results are too high for this temperature. Since he gives no details concerning the purity of the samples employed or of the method by which his determinations were made, satisfactory conclusions in regard to the accuracy of his results can not be drawn. It is probable, however, that the material at hand and the facilities for accurate determinations available nearly thirty years ago were not as satisfactory as we have at present, and therefore his results should not be accepted with the same confidence that is to be placed in the more recent determinations.

TABLE No. XXXIX.[a]—*Solubility of tartaric acid in aqueous alcohol solutions at 25° C.*

EXPERIMENTAL RESULTS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_2H_2(OH)_2(COOH)_2$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.321	57.93
0.9856	8.9	1.304	56.10
0.9545	32.0	1.246	51.40
0.9164	51.0	1.181	46.76
0.8718	70.2	1.091	39.95
0.8190	91.4	0.963	27.83
0.8048	96.3	0.929	24.22
0.7941	99.9	0.906	21.67

CALCULATED RESULTS.

The above figures plotted on cross-section paper gave a curve from which the following values were read and calculated:

Per cent by weight of C_2H_5OH in solvent.	d_{25} of saturated solution.	$C_2H_2(OH)_2(COOH)_2$ per 100 grams.		Solvent to dissolve 1 gram $C_2H_2(OH)_2(COOH)_2$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.321	57.9	137.5	0.727
10.0	1.300	56.0	127.3	0.786
20.0	1.276	54.1	117.9	0.848
30.0	1.251	52.0	108.3	0.923
40.0	1.220	49.6	98.4	1.016
50.0	1.184	47.0	88.6	1.128
60.0	1.142	43.9	78.3	1.277
70.0	1.095	40.2	66.9	1.495
80.0	1.040	35.3	54.6	1.832
90.0	0.973	29.0	40.8	2.448
[a] 92.3	0.955	27.2	37.4	2.676
95.0	0.937	25.4	34.1	2.937
100.0	0.905	21.6	27.6	3.629

[a] U. S. Pharmacopœia strength.

Solubility of tartaric acid in organic solvents at 25°.—The solubility in the several solvents was determined in the manner already described, the dissolved acid being estimated by the titration method. The results are given in Table No. XL, and show that, aside from amyl alcohol and ether, none of the six solvents dissolve much more than traces of the acid. Of these solvents quantitative results for ether alone are to be found in the literature. Bourgoin[a] found that 100 grams of absolute ether dissolved 0.40 grams of tartaric acid at 15°. As compared with the present value for 25°, it appears as though Bourgoin's figure is somewhat too low; but this can not be stated positively.

TABLE No. XL.—*Solubility of tartaric acid in organic solvents at 25°.*

Solvent.	d of solvent.	d_{25} of saturated solution.	$C_2H_2(OH)_2(COOH)_2$ per 100.			Solvent to dissolve 1 gram $C_2H_2(OH)_2(COOH)_2$.
			Grams saturated solution.	Grams solvent.	C. C. solvent.	
			Grams.	*Grams.*	*Grams.*	*Grams.*
Amyl alcohol (iso)	d_{20}=0.817	0.824	3.383	3.50	2.86	28.6
Benzene	d_{25}=0.873	0.875	0.0086	0.0086	0.0075	11620.0
Carbon tetra-chloride	d_{25}=1.587	1.589	0.0189	0.0189	0.030	5289.0
Chloroform	d_{22}=1.476	.....	Trace.	Trace.	Trace.	∞
Ether	d_{22}=0.711	0.715	0.6096	0.6134	0.4361	163.0
Toluene	d_{15}=0.872	0.865	Trace.	Trace.	Trace.	∞

Solubility of antimony potassium tartrate in aqueous alcohol solutions.—The sample used for the following solubility determinations was analyzed by the iodometric method recommended by the pharmacopœia. Two grams of the sample were dissolved in water and diluted to 200 cubic centimeters, 50 cubic centimeter portions of the solution to which 25 cubic centimeters of saturated sodium bicarbonate solution were added required 30.3 cubic centimeters 0.1 N iodine, therefore indicating a purity of 100.6 per cent $C_2H_2(OH)_2(COOK)(COOSbO) + \frac{1}{2}H_2O$. The addition of alcohol to the solution before titration with the iodine did not affect the results, showing that the method is applicable to the determination of the tartrate dissolved in the alcohol solutions used for the solubility determinations.

One series of determinations was made, the time allowed for the saturation being two days. The titrations of the dissolved tartrate being made, as above mentioned, for the sample. The results are given in Table No. XLI and the curve shown in figure 7.

[a] Ann. chim. phys. (5), **13**, 405, 1878.

TABLE No. XLI.—*Solubility of antimony potassium tartrate in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_2H_2(OH)_2(COOK)(COOSbO)+\frac{1}{2}H_2O$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.052	7.85
0.9856	8.9	1.011	4.20
0.9752	17.0	0.988	2.49
0.9628	26.4	0.966	1.16
0.9164	51.0	0.911	0.22
0.8718	70.2	0.865	0.06
0.8234	89.6	0.816	Trace.
0.7941	99.9	0.788	Trace.

CALCULATED RESULTS.

The above figures plotted on cross-section paper gave a curve from which the following results were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$C_2H_2(OH)_2(COOK)(COOSbO)+\frac{1}{2}H_2O$ per 100 grams.		Solvent to dissolve 1 gram $C_2H_2(OH)_2(COOK)(COOSbO)+\frac{1}{2}H_2O$.
		Saturated solution.	Solvent.	
		Grams.		*Grams.*
0	1.052	7.85	8.52	11.74
5	1.025	5.50	5.82	17.18
10	1.007	3.92	4.08	24.51
20	0.980	1.92	1.96	51.09
30	0.958	0.84	0.85	118.0
40	0.935	0.38	0.38	262.2
50	0.913	0.23	0.23	433.8
60	0.890	0.12	0.12	832.2
70	0.866	0.06	0.06	1665.0
100	0.788	Trace.	Trace.	∞

The above results show a somewhat greater solubility of the tartrate in water than is quoted by the U. S. Pharmacopœia, the respective values per 100 grams of water being 6.45 and 8.52. Since the solubility quoted by most of the pharmaceutical reference books in which the temperature standard is 15° agrees so closely with the value quoted by the U. S. Pharmacopœia, it would appear that the figure in the latter book was taken directly from the others without regard to the difference in temperature standards.

Solubility of potassium bitartrate in aqueous alcohol solutions.—The pharmacopœia recommends a quantitative method based upon the ignition of the sample and titrating the residue with standard acid using methyl orange as indicator. Since, however, the compound contains an available hydrogen ion which can be titrated directly with standard alkali, an ignition as recommended by the pharmacopœia appears altogether unnecessary. Furthermore, experiments showed that decrepitation occurred during the ignition and low results

were apt to be obtained. An analysis of the sample used for the following solubility determinations showed a purity of 99.3 per cent $C_2H_2(OH)_2(COOH)(COOK)$ by direct titration with standard alkali using phenolphthaleine as indicator, but only 97.2 per cent was found by the ignition method; since, however, decrepitation occurred, it is easy to explain the low result by the latter method.

One series of solubility determinations was made, the time of agitation being two days. The weighed saturated solutions were titrated with 0.1 N sodium hydroxide, using phenolphthaleine as indicator. On account of the comparatively small amounts of dissolved tartrate it was necessary to apply corrections to the titrations for the acidity of the alcoholic solvents. The actual amount of the correction was of course very small and would be entirely negligible in such a case as tartaric acid, for instance, where very large amounts are dissolved, but with potassium bitartrate in the stronger alcoholic solvents the correction may amount to one-third of the total amount of the alkali required. The results are given in Table No. XLII and the curve in figure 7.

TABLE No. XLII.—*Solubility of potassium bitartrate in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_2H_2(OH)_2(COOH)(COOK)$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.002	0.649
0.9856	8.9	0.986	0.382
0.9752	17.0	0.975	0.242
0.9628	26.4	0.961	0.157
0.9164	51.0	0.911	0.062
0.8234	89.6	0.816	0.018
0.7941	99.9	0.789	0.010

CALCULATED RESULTS.

The above figures plotted on cross-section paper gave a curve from which the following results were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$C_2H_2(OH)_2(COOH)(COOK)$ per 100 grams.		Solvent to dissolve 1 gram $C_2H_2(OH)_2(COOH)(COOK)$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.002	0.649	0.654	153.1
10.0	0.985	0.358	0.359	278.4
20.0	0.970	0.210	0.210	475.2
30.0	0.953	0.131	0.131	762.3
40.0	0.933	0.087	0.087	1,148.0
50.0	0.912	0.064	0.064	1,562.0
60.0	0.890	0.043	0.043	2,323.0
80.0	0.842	0.023	0.023	4,347.0
92.3	0.807	0.014	0.014	7,144.0
100.0	0.789	0.010	0.010	10,000.0

The present value for the solubility in water is in close agreement with the results of Noyes and Clement,[a] which is 0.654 gram per 100 grams saturated solution, lending weight, therefore, to the correctness of this figure and indicating the probable inaccuracy of the results of Roelofsen[b] and Blarez.[c] The solubility of potassium bitartrate in aqueous alcohol solutions was also determined by Roelofsen at several temperatures. The results were more or less irregular, however, and are evidently only approximately correct. The method he used for obtaining saturation is certainly of doubtful efficacy. Various amounts of 93 weight per cent alcohol were added to the saturated aqueous solution of the salt and the solutions shaken at intervals during about six hours while kept at the desired temperature. Some experiments made by me with ammonium iodide by a similar procedure involving shaking at intervals daily for several weeks did not give saturated solutions in the several cases.

The figure quoted by the pharmacopœia for the solubility in water is 1 part in 200, which is evidently too low and was probably taken from some other pharmaceutical reference book in which the temperature standard was 15° instead of 25°.

Solubility of potassium sodium tartrate in aqueous alcohol solutions.—The method given by the pharmacopœia for analyzing this salt depends upon the incineration and subsequent titration of the ash with standard hydrochloric acid, using methyl orange as indicator. This method applied to the sample used for the following solubility determinations gave an average of 99.3 per cent $C_2H_2(OH)_2(COONa)(COOK)+4H_2O$. By evaporating the titrated solution to dryness and determining the potassium as the platinic chloride, 14.15 per cent was found instead of the theoretical 13.86 per cent; the molecular ratio of sodium to potassium as calculated from this determination gave Na:K=1:1.02. Several determinations of the molecular ratio by calculation from the weight of sodium and potassium chloride obtained by evaporation and of the total chlorine in the mixed chlorides by titration with standard silver nitrate, using the usual algebraic formula, gave fairly satisfactory results. In this determination, as well as by the direct estimation of the potassium, very small differences in the analytical results make quite large errors in the molecular ratio, consequently this determination is not of very great value in judging the quality of samples of this salt.

One series of solubility determinations was made and the time allowed for saturation was five days. The saturated solutions were weighed and transferred to weighing bottles, but satisfactory residues

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[a] Z. physik. Chem., **13,** 413, 1894.
[b] Am. Chem. Jour., **16,** 466, 1894.
[c] Compt. rend., **112,** 434, 1891.

for weighing could not be obtained upon evaporation, and it was therefore necessary to redissolve, ignite in platinum dishes, and titrate the ash with standard acid. The usual precautions for obtaining all of the alkali in solution for titration as described under sodium benzoate (p. 28) were of course observed. The results were all calculated to the hydrated salt, since no change in the solid phase was observed in any of the solutions except those with 81.5 and 99.9 weight per cent alcohol, in which almost inappreciable amounts of the salt were dissolved. The results are given in Table No. XLIII and the curve shown in figure 7.

TABLE NO. XLIII.—*Solubility of potassium sodium tartrate in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$C_2H_2(OH)_2(COONa)(COOK)+4H_2O$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O	0.0	1.310	53.33
0.9856	8.9	1.229	43.26
0.9752	17.0	1.152	31.49
0.9628	26.4	1.065	17.63
0.9359	41.7	0.955	5.09
0.9164	51.0	0.922	2.20
0.8441	81.5	0.838	0.04
0.7941	99.9	0.789	Trace.

CALCULATED RESULTS.

The above figures plotted on cross-section paper gave a curve from which the following results were obtained:

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$C_2H_2(OH)_2(COONa)(COOK)+4H_2O$ per 100 grams.		Solvent to dissolve 1 gram, $C_2H_2(OH)_2(COONa)(COOK)+4H_2O$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0	1.310	53.33	114.20	0.875
10	1.216	41.60	71.20	1.404
20	1.124	26.20	35.50	2.820
30	1.034	13.80	16.00	6.250
40	0.961	6.00	6.40	15.660
50	0.908	2.40	2.50	40.700
60	0.878	0.90	0.90	110.100
70	0.857	0.30	0.30	332.400
80	0.840	0.06	0.06	1,665.000
100	0.789	Trace.	Trace.	∞

It will be noticed that the U. S. Pharmacopœia figure for the solubility in water is much too low, evidently having been taken from some other reference book in which the temperature standard is 15°

instead of 25°. A determination at 15° made by Greenish and Smith[a] is 1 gram $C_2H_2(OH)_2(COONa)(COOK)+4H_2O$ in 1.392 cubic centimeters H_2O or 71.84 grams of the salt per 100 grams H_2O.

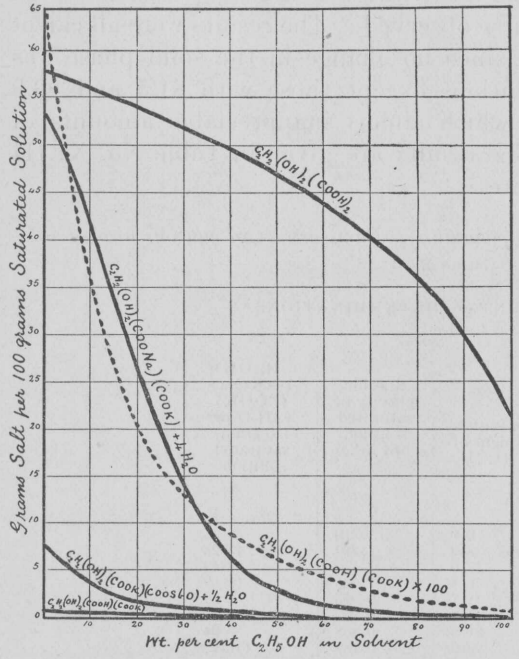

FIG. 7.—Curves showing the solubilities of tartaric acid and the tartrates in aqueous alcohol solutions at 25°.

TRICHLORACETIC ACID.

No quantitative figures for the solubility of this acid are to be found in the literature. The general statement that it is very soluble in water and alcohol is widely quoted. The compound is in fact very deliquescent; a crystal exposed in the air quickly absorbs enough moisture to cause it to liquify. It would probably be found one of the most efficient dehydrating agents.

Two samples which were analyzed by titrating aliquot portions of the aqueous solutions of weighed amounts were found to contain, respectively, 97.7 and 98.6 per cent CCl_3COOH. Standard 0.1 N NaOH was used and phenolphthaleine employed as indicator. The end point was very sharp, but the pink color was inclined to fade on standing. The sample which gave the 98.6 per cent results was from a fresh bottle just opened; the other had been previously opened and partially used.

In making the solubility determinations 25 cubic centimeter glass stoppered cylinders were about half filled as quickly as possible with the acid and 2 to 3 cubic centimeter portions of the solvents which were water, 32, 70.2, and 99.9 weight per cent alcohol, added. After a short period of rotation the excess of solid phase had disappeared in the cylinders to which the alcoholic solvents had been added, more of the acid was therefore introduced into these and this addition of acid repeated from time to time without yielding a saturated solution in any case except the cylinder in which water alone was the solvent. After about 15 hours constant agitation at 25°, the saturated solution in water was removed and after weighing in the pycnometer the

[a] Pharm. Jour. (Lond.), June 22, 1901.

amount of the trichloracetic acid determined by titration. The following results were obtained:

Solubility of trichloracetic acid in water at 25°.

Specific gravity of saturated solution at 25°	1.615
Grams CCl_3COOH per 100 grams saturated solution	92.32
Grams CCl_3COOH per 100 grams water	1,201.00
Grams H_2O to dissolve 1 gram CCl_3COOH	0.0832

Since my supply of trichloracetic acid was nearly exhausted before either of the alcoholic solutions was saturated at 25°, I lowered the temperature of the bath to 15° and hoped that an additional crystal of trichloracetic acid in each cylinder would cause the separation of the excess of acid which might possibly be present at the lower temperature. The added crystals dissolved, however, as quickly as before and there was no further possibility of obtaining saturated solutions. Even the aqueous solution to which a little more water had been added contained none of the undissolved acid. Although none of the four solutions were saturated at 15°, I thought it would nevertheless be of interest to determine the quantity of acid present in each and thus have figures which would show that the actual solubility was not below the amounts found. In the case of the aqueous solution the following results were obtained:

Specific gravity of solution (not quite saturated) at 15°	1.593
Grams CCl_3COOH per 100 grams of the solution	87.22

Thus it is certain that the solubility of trichloracetic acid in water at 15° is *not less* than 87.22 grams per 100 grams of the saturated solution.

Now, in the case of the solution made with trichloracetic acid and alcohol of 99.9 weight per cent the specific gravity was found to be 1.508. On diluting 10 cubic centimeters of this solution with water in order to determine the dissolved acid by titration of an aliquot part, a second liquid layer amounting to about 4 cubic centimeters separated. The aqueous part having been diluted to 500 cubic centimeters was found by titration to contain 8.9475 grams CCl_3COOH. It gave no opalescence with silver nitrate, showing that by whatever reaction the second compound had been formed no free hydrochloric acid had been liberated. It appeared most probable that the ethyl ester of the trichloracetic acid had been formed, no doubt under the influence of the very great dehydrating power of the acid. That the second liquid phase was really the trichloracetic acid ester was proved by separating and determining its boiling point which was found to be 162° to 165°. The boiling point as given by Beilstein is 164°. The liquid obtained therefore by attempting to prepare a saturated solution of trichloracetic acid in absolute alcohol was really a mixture of the trichloracetic acid ethyl ester and trichlor-

acetic acid containing a little water. In adding water to this mixture a separation occurred at a certain point and it therefore appeared of interest to determine the amount of water necessary to just cause this separation and also the amount required to dissolve all of the acid out of the ester solution. The experiment was made as follows: Ten cubic centimeters of the solution was transferred to a graduated cylinder and water added slowly from a burette. It was found that 5.9 cubic centimeters of H_2O just produced a faint opalescence at 15°, 6.05 cubic centimeters gave a milky solution which showed no tendency to separate into two layers until 7.1 cubic centimeters of H_2O had been added and then on standing the two layers measured respectively 9.2 cubic centimeters for the lower and 7.6 cubic centimeters for the upper. Now, by adding more water and shaking, the volume of the lower layer gradually diminished, so that with a total of 8.0 cubic centimeters of water the lower layer measured 8.3 cubic centimeters and with 10 cubic centimeters of water it became 7.2 cubic centimeters in volume. At this point an aliquot portion of the upper layer was removed and on titration it was found that 5.104 grams of CCl_3COOH were present in the whole of the upper layer. According to the previous analysis (p. 87) in which an equal volume of the solution had been diluted to 500 cubic centimeters the amount of acid found was 8.9475 grams, therefore in adding 10 cubic centimeters instead of 500 cubic centimeters of water the removal of the trichloracetic acid from the ester was not complete. In order to ascertain how much additional water would be necessary to dissolve out the remaining (8.9475 − 5.104 =) 3.8435 grams of acid, the upper layer was siphoned off as completely as possible from the 7.1 cubic centimeters of lower layer and successive amounts of water were added and the mixture shaken after each addition. It was found that with 3 cubic centimeters of H_2O the lower layer was reduced in volume to 5.4 cubic centimeters, with 8 cubic centimeters it became 4.6 cubic centimeters, and with 18 cubic centimeters it had become 4.0 cubic centimeters. The aqueous layer was then found to contain a total of 3.226 grams of CCl_3COOH, or nearly the calculate amount which should have been recovered.

The two solutions which had been prepared with 70.2 and 32 weight per cent alcohol respectively were also titrated with water as just described for the solution in which 99.9 weight per cent alcohol had been used. The results were as follows:

Five cubic centimeters of the first (the 70.2 per cent alcoholic solution, required 7.3 cubic centimeters of H_2O to produce opalescence; when 9.0 cubic centimeters of H_2O had been added the layers separated within about one-half hour into 1.4 cubic centimeters of lower and 12.1 cubic centimeters of upper layer. With 15 cubic

centimeters of H_2O the volume of the lower layer had been reduced to 1.3 cubic centimeters and with 25 cubic centimeters of water it became 1.1 cubic centimeters.

Five cubic centimeters of the second (the 32 per cent alcoholic solution) required 11.3 cubic centimeters of H_2O to become opalescent, and when a total of 20 cubic centimeters H_2O had been added the lower layer measured only about 0.5 cubic centimeter.

These results show that the solubility of trichloracetic acid can not be determined in solutions containing any appreciable amount of alcohol since the ester of the acid will be formed and therefore alter the equilibrium of the system.

It would no doubt be of much interest to determine the limits within which the ester may form and also the extent to which the alcohol is consumed in the reaction but such experiments are hardly within the scope of the present bulletin.

VALERATES.

The solubility of ammonium valerate.—No requirements are made for this salt by the pharmacopœia other than it be kept in well-stoppered bottles. A sample purchased for solubility determinations was in the form of almost colorless, apparently hygroscopic crystals which when analyzed by distillation of the ammonia gave results indicating a composition of $C_4H_9COONH_4 \cdot 2C_4H_9COOH$. Attempts to saturate a series of alcoholic solvents with this salt were unsuccessful. Since no particular composition is required by the pharmacopœia for this compound it appeared useless to prepare samples and make solubility determinations until some definite requirements are made for this salt.

Solubility of zinc valerate in aqueous alcohol solutions.—No method is prescribed by the pharmacopœia for the analysis of this salt, the determination of the zinc was therefore made as follows. An aliquot portion of the solution of the weighed sample was heated to the boiling point and sodium carbonate solution added until the precipitation of the zinc as carbonate was complete. After digestion on the steam bath for about an hour the precipitate was filtered on a Gooch crucible, ignited, and weighed as zinc oxide; the results indicated a purity of 97.8 per cent $Zn(C_4H_9COO)_2 + 2H_2O$. Attempts to ignite the sample directly and determine the zinc by weighing the ignited residue gave low results, indicating that loss by volatilization had occurred.

Two series of solubility determinations were made, the period of constant agitation being three days in each case. The saturated solutions were analyzed by precipitation of the zinc as carbonate as above mentioned, and weighing as zinc oxide. The results are given in Table No. XLIV and the curve shown in figure 5. The phar-

macopœial values for water and alcohol are quite different from the above results. The difference for alcohol is considerable, the figure being less than half as great as that shown in the table. Only a few results are quoted in the pharmaceutical reference books and none in the chemical literature. Of the available ones the variation is from 1 part in 40 to 1 part in 120 parts of water and from 1 part in 40 to 1 part in 60 of alcohol.

TABLE No. XLIV.—*Solubility of zinc valerate in aqueous alcohol solutions at 25°.*

EXPERIMENTAL DETERMINATIONS.

Solvent.		Specific gravity of saturated solution at 25°.	$Zn(C_4H_9COO)_2+2H_2O$ per 100 grams saturated solution.
Specific gravity at 15°.	Per cent by weight of C_2H_5OH.		
			Grams.
Dist. H_2O.	0.0	1.004	1.437
0.9752	17.0	0.976	0.900
0.9628	26.4	0.961	0.723
0.9359	41.7	0.933	0.809
0.9164	51.0	0.914	0.998
0.8441	81.5	0.844	1.841
0.8234	89.6	0.827	3.143
0.8190	91.4	0.826	4.397
0.8125	93.6	0.830	7.148
0.8048	96.3	0.835	10.53
0.7941	99.9	0.844	15.61

The above figures plotted on cross-section paper gave a curve from which the following results were obtained:

CALCULATED RESULTS.

Per cent by weight of C_2H_5OH in solvent.	Specific gravity of saturated solution at 25°.	$Zn(C_4H_9COO)_2+2H_2O$ per 100 grams.		Solvent to dissolve 1 gram, $Zn(C_4H_9COO)_2+2H_2O$.
		Saturated solution.	Solvent.	
		Grams.	*Grams.*	*Grams.*
0.0	1.004	1.44	1.46	68.40
20.0	0.972	0.75	0.75	132.30
40.0	0.936	0.76	0.76	130.60
60.0	0.894	1.15	1.16	86.00
80.0	0.848	1.70	1.73	57.80
85.0	0.836	2.15	2.20	45.50
90.0	0.827	3.20	3.31	30.30
92.3	0.828	5.50	5.82	17.20
95.0	0.832	8.80	9.65	10.36
100.0	0.844	15.60	18.48	5.41

Minimum point at about 30 weight per cent C_2H_5OH; 0.7 grams Zn $(C_4H_9COO)_2+2H_2O$ per 100 grams saturated solution.

The curve is interesting in that it shows a well-marked minimum point at about 30 weight per cent alcohol and also that it changes its direction so abruptly between 85 and 90 weight per cent alcohol. It is possible that a transition of the solid phase occurs at this point and there is really an intersection of two curves, but it did not appear advisable to pursue this point further at the present time.

TABLE No. XLV.—*Showing the solubilities of the pharmacopœial organic acids and their salts in water and official (92.3 weight per cent) alcohol at 25° as compared with the values quoted by the eighth revision of the U. S. Pharmacopœia.*

Compound.	Formula.	Compound per 100 grams solvent at 25°.			
		In water.		In 92.3 weight per cent alcohol.	
		Present result.	U. S. P. value.	Present result.	U. S. P. value.
		Grams.	*Grams.*	*Grams.*	*Grams.*
Ethyl acetate	$CH_3COOC_2H_5$	8.6	11.1	∞	∞
Lead acetate	$(CH_3COO)_2Pb+3H_2O$	72.5	50.0	[a] 1.1	3.33
Potassium acetate	CH_3COOK	219.6	250.0	43.9	50.00
Sodium acetate	$CH_3COONa+3H_2O$	125.7	100.0	6.6	4.30
Zinc acetate	$(CH_3COO)_2Zn+2H_2O$	44.5	40.0	4.3	2.77
Benzoic acid	C_6H_5COOH	0.37	0.35	56.74	55.50
Ammonium benzoate	$C_6H_5COONH_4$	22.8	9.5	3.5	3.50
Lithium benzoate	C_6H_5COOLi	38.2	33.3	5.8	7.7
Sodium benzoate	C_6H_5COONa	56.24	62.5	2.04	2.3
Camphoric acid	$C_8H_4(COOH)_2$	0.76	0.8	104.5	[b]
Citric acid	$(CH_2)_2COH(COOH)_3+H_2O$	207.70	185.2	116.0	64.5
Bismuth citrate	$(CH_2)_2COH(COO)_3Bi$	0.011	[c]	0.07	[c]
Bismuth subsalicylate	Variable composition	22.25	[d]	0.0	[e]
Lithium citrate	$(CH_2)_2COH(COOLi)_3+4H_2O$	74.5	50.0	0.04	[f]
Potassium citrate	$(CH_2)_2COH(COOK)$	181.8	200.0	0.01+	[e]
Sodium citrate	$(CH_2)_2COH(COONa)+5\frac{1}{2}H_2O$	92.7	90.9	0.0	[g]
Gallic acid	$C_6H_2(OH)_3COOH+H_2O$	1.16	1.18	27.23	24.1
Sodium phenolsulphonate	$C_6H_4(OH)SO_3Na+2H_2O$	24.1	20.8	0.9	0.77
Zinc phenolsulphonate	$(C_6H_4(OH)SO_3)_2Zn+8H_2O$	66.1	59.0	72.1	59.0
Salicylic acid	$C_6H_4OHCOOH$	0.22	0.32	46.85	50.0
Ammonium salicylate	$C_6H_4OHCOONH_4$	103.2	111.0	42.86	43.4
Bismuth subsalicylate	$C_6H_4OHCOO\cdot OBi$	0.01	[f]	0.105	.....
Lithium salicylate	$C_6H_4OHCOOLi+\frac{1}{2}H_2O$	127.3	[d]	83.8	[d]
Methyl salicylate	$C_6H_4OHCOOCH_3$	0.1	[e]	∞	∞
Phenyl salicylate	$C_6H_4OHCOOC_6H_5$	0.01+	0.043	21.51	20.0
Quinine salicylate	$C_6H_4OHCOOHC_{20}H_{24}N_2O_2+\frac{1}{2}H_2O$	0.06+	1.3	4.84	9.0
Sodium salicylate	$C_6H_4OHCOONa$	115.3	125.0	13.6	18.2
Strontium salicylate	$(C_6H_4OHCOO)_2Sr+2H_2O$	5.31	5.5	2.06	1.5
Stearic acid	$C_{17}H_{35}COOH$	0.03+	[c]	4.33	6.0
Tartaric acid	$C_2H_2(OH)_2(COOH)_2$	137.5	140.8	37.4	60.0
Antimony potassium tartrate	$C_2H_2(OH)_2(COOK)(COOSbO)+\frac{1}{2}H_2O$	8.52	6.45	Trace.	[c]
Potassium bitartrate	$C_2H_2(OH)_2(COOH)(COOK)$	0.654	0.5	0.014	[h]
Potassium sodium tartrate	$C_2H_2(OH)_2(COONa)(COOK)+4H_2O$	114.2	83.3	Trace.	[f]
Trichloracetic acid	CCl_3COOH	1,201.0	[d]	Decomp.	[d]
Zinc valerate	$(C_4H_9COO)_2Zn+2H_2O$	1.46	2.0	5.82	2.8

[a] Solid phase anhydrous.
[b] Readily soluble.
[c] Insoluble.
[d] Very soluble.
[e] Sparingly soluble.
[f] Almost insoluble.
[g] Slightly soluble.
[h] Very sparingly.

GENERAL CONCLUSIONS.

During the course of the preceding investigations many points of especial interest have arisen, and since it appears desirable to emphasize some of them more particularly they are briefly summarized here at the end of the bulletin.

1. In order to show the differences between the solubility values as found in the present investigations and those quoted by the pharmacopœia, a comparative table, No. XLV, has been made. The pharmacopœial values in the table are in all cases the reciprocals of the

figures quoted by the U. S. Pharmacopœia in terms of parts of solvent to dissolve one part of the compound. It is of course not certain just what is meant by "part" in the Pharmacopœia, whether weight or volume, and therefore the figures can not be accurately interpreted. An examination of the table shows that of the 35 compounds included satisfactory agreement exists only in the cases of benzoic, camphoric, gallic, and tartaric acids in the aqueous solutions, and of benzoic acid, ammonium benzoate, ammonium salicylate, salicylic acid, and phenol salicylate in the alcohol solutions. Of the remaining results the differences vary from about 5 to 100 per cent.

2. A number of experiments have shown that with the class of compounds dealt with in the present bulletin an apparent impurity which in some cases may be comparatively large does not materially affect the solubility results obtained. It would therefore appear that in many cases solubility determinations are ineffectual as tests for purity. In view of the far more expedient and trustworthy chemical tests, their value as tests for identity is of importance only in certain exceptional cases, consequently the suggestion that has frequently been made that a standard method for solubility determinations be included in the U. S. Pharmacopœia does not deserve much consideration. A brief statement embodying the essential requirements of accurate solubility determinations (intended as physical constants), such as proper temperature regulation, agitation to complete saturation, purity of materials employed, and methods of analysis of solutions, would no doubt be sufficient for all the needs of the pharmacopœia.

3. The solubility curves shown in the accompanying plates present almost every variety of form, some descend or ascend regularly with increase of alcohol, others show maximum or minimum points, while in one or two cases both a maximum and minimum point are present. It would therefore appear that in no case is it possible to predict from the solubility of the substance in alcohol and water separately what it will be in any mixture of these two solvents.

4. It is pointed out that certain advantages are to be gained by pharmacists in adopting the percentage or unit of solvent basis for stating solubility results in place of the antiquated method according to which the amount of solvent required per unit of dissolved substance is given.

5. Attention is called to the fact that the present pharmacopœial purity requirement for certain of the compounds, viz, lead acetate, zinc acetate, sodium benzoate, and lithium salicylate ($? \frac{1}{2}$ Mol. H_2O) is too rigid in view of their unstable character or of difficulty in their purification; whereas in other cases, viz, ammonium benzoate, phenyl salicylate, strontium salicylate, and trichloracetic acid, the

present requirements for purity might be raised without either working an undue hardship upon the producer or increasing the cost to the consumer.

6. The pharmacopœial method for the assay of many of the salts of the organic acids depending upon their incineration and titration of the resulting alkaline residue requires a modification for accurate results. This consists simply in leaching the residue after the first ignition, igniting the unburned carbon and adding the solution of this to the first leachings before making the titration.

7. Quantitative methods of analysis or improvements upon the pharmacopœial processes are suggested for the following salts: Ammonium benzoate, salicylate and valerate, lead acetate, zinc acetate, phenolsulphonate and valerate, sodium phenolsulphonate, phenyl salicylate, potassium bitartrate, and potassium and sodium tartrate.

8. The pharmacopœial statements in regard to the reaction of a number of the salts of the present series toward indicators should be revised.

9. Certain peculiarities in the solubility behavior were noted (*a*) with citric acid which shows two nearly parallel curves for the hydrated and anhydrous forms, (*b*) with potassium citrate, which belongs to that class of compounds which have the power of dividing aqueous alcohol solutions into layers, (*c*) with oleic acid, which presents a striking case of apparently unstable solubility equilibrium at certain concentrations, and finally (*d*) of trichloracetic acid, which unites with alcohol to form the ester in alcoholic solutions of various concentrations.

LIST OF HYGIENIC LABORATORY BULLETINS OF THE PUBLIC HEALTH AND MARINE-HOSPITAL SERVICE.

The Hygienic Laboratory was established in New York, at the Marine Hospital on Staten Island, August, 1887. It was transferred to Washington, with quarters in the Butler Building, June 11, 1891, and a new laboratory building, located in Washington, was authorized by act of Congress, March 3, 1901.

The following *bulletins* [Bulls. Nos. 1–7, 1900 to 1902, Hyg. Lab., U. S. Mar.-Hosp. Serv., Wash.] have been issued:

*No. 1.—Preliminary note on the viability of the *Bacillus pestis*. By M. J. Rosenau.

No. 2.—Formalin disinfection of baggage without apparatus. By M. J. Rosenau.

*No. 3.—Sulphur dioxid as a germicidal agent. By H. D. Geddings.

*No. 4.—Viability of the *Bacillus pestis*. By M. J. Rosenau.

No. 5.—An investigation of a pathogenic microbe (*B. typhi murium* Danyz) applied to the destruction of rats. By M. J. Rosenau.

*No. 6.—Disinfection against mosquitoes with formaldehyde and sulphur dioxid. By M. J. Rosenau.

No. 7.—Laboratory technique: Ring test for indol, by S. B. Grubbs and Edward Francis; Collodium sacs, by S. B. Grubbs and Edward Francis; Microphotography with simple apparatus, by H. B. Parker.

By act of Congress approved July 1, 1902, the name of the "United States Marine-Hospital Service" was changed to the "Public Health and Marine-Hospital Service of the United States," and three new divisions were added to the Hygienic Laboratory.

Since the change of name of the service the bulletins of the Hygienic Laboratory have been continued in the same numerical order, as follows:

*No. 8.—Laboratory course in pathology and bacteriology. By M. J. Rosenau. (Revised edition, March, 1904.)

*No. 9.—Presence of tetanus in commercial gelatin. By John F. Anderson.

No. 10.—Report upon the prevalence and geographic distribution of hookworm disease (uncinariasis or anchylostomiasis) in the United States. By Ch. Wardell Stiles.

*No. 11.—An experimental investigation of *Trypanosoma lewisi*. By Edward Francis.

*No. 12.—The bacteriological impurities of vaccine virus; an experimental study. By M. J. Rosenau.

*No. 13.—A statistical study of the intestinal parasites of 500 white male patients at the United States Government Hospital for the Insane; by Philip E. Garrison, Brayton H. Ransom, and Earle C. Stevenson. A parasitic roundworm (*Agamomermis culicis* n. g., n. sp.) in American mosquitoes (*Culex sollicitans*); by Ch. Wardell Stiles. The type species of the cestode genus *Hymenolepis;* by Ch. Wardell Stiles.

No. 14.—Spotted fever (tick fever) of the Rocky Mountains; a new disease. By John F. Anderson.

No. 15.—Inefficiency of ferrous sulphate as an antiseptic and germicide. By Allan J. McLaughlin.

*No. 16.—The antiseptic and germicidal properties of glycerin. By M. J. Rosenau.

*No. 17.—Illustrated key to the trematode parasites of man. By Ch. Wardell Stiles.

*No. 18.—An account of the tapeworms of the genus *Hymenolepis* parasitic in man, including reports of several new cases of the dwarf tapeworm (*H. nana*) in the United States. By Brayton H. Ransom.

*No. 19.—A method for inoculating animals with precise amounts. By M. J. Rosenau.

*No. 20.—A zoological investigation into the cause, transmission, and source of Rocky Mountain "spotted fever." By Ch. Wardell Stiles.

No. 21.—The immunity unit for standardizing diphtheria antitoxin (based on Ehrlich's normal serum). Official standard prepared under the act approved July 1, 1902. By M. J. Roseneau.

*No. 22.—Chloride of zinc as a deodorant, antiseptic, and germicide. By T. B. McClintic.

*No. 23.—Changes in the Pharmacopœia of the United States of America. Eighth decennial revision. By Reid Hunt and Murray Galt Motter.

No. 24.—The International Code of Zoological Nomenclature as applied to medicine. By Ch. Wardell Stiles.

No. 25.—Illustrated key to the cestode parasites of man. By Ch. Wardell Stiles.

No. 26.—On the stability of the oxidases and their conduct toward various reagents. The conduct of phenolphthalein in the animal organism. A test for saccharin, and a simple method of distinguishing between cumarin and vanillin. The toxicity of ozone and other oxidizing agents to lipase. The influence of chemical constitution on the lipolytic hydrolysis of etheral salts. By J. H. Kastle.

No. 27.—The limitations of formaldehyde gas as a disinfectant with special reference to car sanitation. By Thomas B. McClintic.

*No. 28.—A statistical study of the prevalence of intestinal worms in man. By Ch. Wardell Stiles and Philip E. Garrison.

*No. 29.—A study of the cause of sudden death following the injection of horse serum. By M. J. Rosenau and John F. Anderson.

No. 30.—I. Maternal transmission of immunity to diphtheria toxine. II. Maternal transmission of immunity to diphtheria toxine and hypersusceptibility to horse serum in the same animal. By John F. Anderson.

No. 31.—Variations in the peroxidase activity of the blood in health and disease. By Joseph H. Kastle and Harold L. Amoss.

No. 32.—A stomach lesion in guinea pigs caused by diphtheria toxine and its bearing upon experimental gastric ulcer. By M. J. Rosenau and John F. Anderson.

No. 33.—Studies in experimental alcoholism. By Reid Hunt.

No. 34.—I. *Agamofilaria georgiana* n. sp., an apparently new roundworm parasite from the ankle of a negress. II. The zoological characters of the roundworm genus *Filaria* Mueller, 1787. III. Three new American cases of infection of man with horsehair worms (species *Paragordius varius*), with summary of all cases reported to date. By Ch. Wardell Stiles.

*No. 35.—Report on the origin and prevalence of typhoid fever in the District of Columbia. By M. J. Rosenau, L. L. Lumsden, and Joseph H. Kastle. (Including articles contributed by Ch. Wardell Stiles, Joseph Goldberger, and A. M. Stimson.)

No. 36.—Further studies upon hypersusceptibility and immunity. By M. J. Rosenau and John F. Anderson.

No. 37.—Index-catalogue of medical and veterinary zoology. Subjects: Trematoda and trematode diseases. By Ch. Wardell Stiles and Albert Hassall.

No. 38.—The influence of antitoxin upon post-diphtheritic paralysis. By M. J. Rosenau and John F. Anderson.

No. 39.—The antiseptic and germicidal properties of solutions of formaldehyde and their action upon toxines. By John F. Anderson.

No. 40.—1. The occurrence of a proliferating cestode larva (*Sparganum prolifcrum*) in man in Florida, by Ch. Wardell Stiles. 2. A reexamination of the type specimen of *Filaria restiformis* Leidy, 1880=*Agamomermis restiformis*, by Ch. Wardell Stiles. 3. Observations on two new parasitic trematode worms: *Homalogaster philippinensis* n. sp., *Agamodistomum nanus* n. sp., by Ch. Wardell Stiles and Joseph Goldberger. 4. A reexamination of the original specimen of *Tænia saginata abietina* (Weinland, 1858), by Ch. Wardell Stiles and Joseph Goldberger.

*No. 41.—Milk and its relation to the public health. By various authors.

No. 42.—The thermal death points of pathogenic micro-organisms in milk. By M. J. Rosenau.

No. 43.—The standardization of tetanus antitoxin (an American unit established under authority of the act of July 1, 1902). By M. J. Rosenau and John F. Anderson.

No. 44.—Report No. 2 on the origin and prevalence of typhoid fever in the District of Columbia, 1907. By M. J. Rosenau, L. L. Lumsden, and Joseph H. Kastle.

No. 45.—Further studies upon anaphylaxis. By M. J. Rosenau and John F. Anderson.

No. 46.—*Hepatozoon perniciosum* (n. g., n. sp.); a hæmogregarine pathogenic for white rats; with a description of the sexual cycle in the intermediate host, a mite (*Lelaps echidninus*). By W. W. Miller.

No. 47.—Studies on Thyroid: I. The relation of iodine to the physiological activity of thyroid preparations. By Reid Hunt and Atherton Seidell.

No. 48.—The physiological standardization of digitalis. By Charles Wallis Edmunds and Worth Hale.

No. 49.—Digest of comments on the United States Pharmacopœia. Eighth decennial revision for the period ending December 31, 1905. By Murray Galt Motter and Martin I. Wilbert.

No. 50.—Further studies upon the phenomenon of anaphylaxis. By M. J. Rosenau and John F. Anderson.

No. 51.—Chemical tests for blood. By Joseph H. Kastle.

No. 52.—Report No. 3 on the origin and prevalence of typhoid fever in the District of Columbia. By M. J. Rosenau, L. L. Lumsden, and J. H. Kastle.

No. 53.—The influence of certain drugs upon the toxicity of acetanilide and antipyrine. By Worth Hale.

No. 54.—The fixing power of alkaloids on volatile acids and its application to the estimation of alkaloids with the aid of phenolphthalein or by the Volhard method. By Elias Elvove.

No. 55.—Quantitative pharmacological studies: Adrenalin and adrenalin-like bodies. By W. H. Schultz.

No. 56.—Milk and its relation to the public health. By various authors.

No. 57.—I. The presence of tubercle bacilli in the circulating blood in clinical and experimental tuberculosis. By John F. Anderson. II. The viability of the tubercle bacillus. By M. J. Rosenau.

No. 58.—Digest of comments on the Pharmacopœia of the United States of America (eighth decennial revision) and the National Formulary for the period ending December 31, 1906. By Murray Galt Motter and Martin I. Wilbert.

No. 59.—The oxidases and other oxygen catalysts concerned in biological oxidation. By Joseph Hoeing Kastle.

No. 60.—A study of the anatomy of Watsonius (n. g.) Watsoni of man, and of 19 allied species of mammalian trematode worms of the superfamily Paramphistomoidea. By Ch. Wardell Stiles and Joseph Goldberger.

No. 61.—Quantitative pharmacological studies: Relative physiological activity of some commercial solutions of epinephrin. By W. H. Schultz.

No. 62.—The taxonomic value of the microscopic structures of the stigmal plates in the tick, genus Dermacentor. By Ch. Wardell Stiles.

No. 63.—Digest of comments on the Pharmacopœia of the United States of America (eighth decennial revision) and the National Formulary (third edition) for the calendar year ending December 31, 1907. By Murray Galt Motter and Martin I. Wilbert.

No. 64.—Studies upon anaphylaxis with special reference to the antibodies concerned. By John F. Anderson and W. H. Frost.

No. 65.—Facts and problems of rabies. By A. M. Stimson.

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No. 67. The solubilities of the pharmacopœial organic acids and their salts. By Athreton Seidell.

In citing these bulletins, beginning with No. 8, bibliographers and authors are requested to adopt the following abbreviations: Bull. No. ——, Hyg. Lab., U. S. Pub. Health & Mar. Hosp. Serv., Wash., pp. ——.

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