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## THE SOLUBILITY OF ACETANILIDE, PHENACETINE, CAFFEINE AND SALOL IN SEVERAL SOLVENTS.

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The experiments described in this paper were undertaken for the purpose of obtaining the necessary data upon which to base a satisfactory method for the separation of some of the constituents of headache powders. The object was to find solvents in which the solubility of one or more of the above named substances differed most from that of the others under the same conditions. The determinations were therefore not made with the care which should be devoted to results submitted primarily as solubility constants, since it was recognized that only wide differences in the actual amounts of the several substances dissolved by a single solvent, could be utilized for the quantitative separation of mixtures of these compounds.

A search of the literature indicated that comparatively few solubility results which could be used for the purpose, were available. The usual reference books upon pharmaceutical and organic chemistry give approximate determinations for each of these substances in the more common solvents such as water, alcohol, ether, chloroform, etc. In addition to data of this character there were found results upon the solubility of acetanilide in methyl alcohol, ethyl alcohol, and chloroform by Speyers<sup>1</sup> and in mixtures of ethyl alcohol and water by Holleman and Antusch.<sup>2</sup>

The material used for the determinations here recorded was in all cases that sold under the designation C. P. or U. S. P. The experiments were made at room temperature and therefore the temperatures recorded are probably accurate in most cases to within a degree or two.

The method of determination was as follows: About 30 cc. of the solvent and an excess of the solid in each case were placed in glass stoppered cylinders which were then attached to an axle which was rotated by means of a water motor. All determinations in any one solvent were made simultaneously and hence are comparable in so far as temperature, time of shaking etc. are concerned. The time of rotation was at least six hours in all cases, usually much longer. The removal of a clear portion of the solution was effected by drawing it up with the aid of suction into a pipette provided with a filter of absorbent cotton at the opening through which the liquid entered. The solution was then transferred to a pycnometer and after being weighed was washed (usually with alcohol) into a tared platinum dish. The solvent was then removed by evaporation at room temperature with the aid of an electric

<sup>1</sup> Speyers, *Am. J. Sci.* (4), 14, 294, (1902).

<sup>2</sup> Holleman and Antusch, *Rec. trav. chim.*, 13, 293, (1894).

fan. The residue remaining in the dish was alternately weighed and dried at 60° until no further loss occurred.

In the case of benzaldehyde, the benzoic acid formed during the evaporation was determined by titration with standard alkali and its amount deducted from the total weight of residue found. With salol in benzaldehyde, however, a determination could not be made since no solid separated even on continued evaporation of the solution by means of the current of air.

The first series of determinations were made in aqueous ethyl alcohol solutions and the results are presented in Table I together with those of Holleman and Antusch upon similar aqueous alcoholic solutions, determined at 25°. Eight saturated solutions were prepared and rotated at the temperature of the room which held closely at 30° for several hours previous to the withdrawal of portions for the analysis.

TABLE I.  
SOLUBILITY OF ACETANILIDE IN MIXTURES OF ETHYL ALCOHOL AND WATER.

Weight Percent Alcohol in Mixtures	Results at 25° <sup>1</sup>		Results at 30°	
	Gms. C <sub>6</sub> H <sub>5</sub> NHOC <sub>2</sub> H <sub>5</sub> per 100 gms. Sat. Solution	Sp. gr. of Solution	Gms. C <sub>6</sub> H <sub>5</sub> NHOC <sub>2</sub> H <sub>5</sub> per 100 gms. Sat. Solution	Sp. gr. of Solution
0	0.54	0.997	0.69	1.000
10	0.93	0.985	1.00	0.984
20	1.28	0.973	2.20	0.970
30	2.30	0.962	4.80	0.956
40	4.85	0.950	9.40	0.945
50	8.87	0.939	15.40	0.934
60	14.17	0.928	22.00	0.926
70	19.84	0.918	27.60	0.917
80	25.17	0.907	31.20	0.907
85	26.93	0.899	31.70	0.900
90	27.65	0.890	31.60	0.893
95	26.82	0.874	32.80	0.885
100	24.77	0.851	29.00	0.876

The weight percents of alcohol in the eight water alcohol mixtures used were calculated from their specific gravities determined by the pycnometer method. The dissolved acetanilide was determined by weighing the residue left after the evaporation of the solvent from weighed portions of the saturated solutions. The interpolated values shown in the table were read from the curve drawn through the eight points plotted on cross section paper. For this curve, the weight percents of alcohol in the alcohol-water mixtures were taken as abscissas and the grams of acetanilide per 100 grams of solution as ordinates. The curve plotted in the same manner from the 25° results of Holleman and Antusch lies somewhat below the 30° curve but in all other respects the two are entirely similar. An examination of these curves shows that the amount of dis-

<sup>1</sup>Holleman and Antusch.

solved acetanilide increases at first slowly with increase in concentration of alcohol, and then quite rapidly up to the maxima, which in the case of the 25° curve is at 90 weight percent alcohol and in the case of the 30° curve is at 85 percent alcohol. Above these concentrations of alcohol the solubility diminishes in each case. A satisfactory explanation for this increased solubility of acetanilide in alcohol containing 10 percent water (and even more at a higher temperature) is at present not apparent.

The solubility of acetanilide in methyl alcohol, ethyl alcohol and in chloroform as determined by Speyers<sup>1</sup> is reported in terms of gram molecules of acetanilide per 100 gram molecules of the solvents at irregular temperatures, and in addition the weights of the saturated solutions are given for other temperatures than those at which the solubility determinations were made. Although no new results for these solvents have been determined by the present writer it was thought of interest to recalculate those of Speyers to the basis selected for presenting all the other solubility determinations included herewith. This has been done and the results given in Table II.

TABLE II.

SOLUBILITY OF ACETANILIDE IN METHYL ALCOHOL, ETHYL ALCOHOL AND IN CHLOROFORM (SPEYERS).

Temperature.	In Methyl Alcohol		In Ethyl Alcohol		In Chloroform	
	Gms. C <sub>2</sub> H <sub>5</sub> NHOC <sub>2</sub> H <sub>5</sub> per 100 gms. Solution	Wt. of 1 cc. Solution	Gms. C <sub>2</sub> H <sub>5</sub> NHOC <sub>2</sub> H <sub>5</sub> per 100 gms. Solution	Wt. of 1 cc. Solution	Gms. C <sub>2</sub> H <sub>2</sub> NHOC <sub>2</sub> H <sub>3</sub> per 100 gms. Solution	Wt. of 1 cc. Solution
0	18.5	0.860	12.8	0.842	3.53	1.503
10	23.1	0.864	16.7	0.844	7.24	1.475
20	29.1	0.875	21.3	0.850	10.7	1.440
30	35.1	0.892	26.5	0.860	14.5	1.398
40	42.9	0.911	32.9	0.874	18.7	1.354
50	51.7	0.932	39.4	0.895	23.7	1.314
60	59.2	0.957	46.4	0.920	29.1	1.272

In Table III is shown the comparative solubilities of acetanilide, phenacetine, caffeine and salol in twelve different solvents. Although this number is not as large as would be desirable in order to fully accomplish the purpose mentioned in the first part of this paper, it is believed that a fair degree of success can be attained in the separation of mixtures of at least three of the above named substances on the basis of the results shown in the table. Thus it may be expected that with proper manipulation either toluene, benzene or xylene will remove salol when mixed with the other three compounds, and amyl alcohol or acetate will effect a separation of caffeine from a mixture of this substance with acetanilide and phenacetine. It is seen that with none of the solvents is there a wide difference between the solubility of acetanilide and phenacetine.

<sup>1</sup> loc. cit.

TABLE III.

SOLUBILITY OF ACETANILIDE, PHENACETINE, CAFFEINE AND SALOL IN ORGANIC SOLVENTS.

Solvent.	Sp. gr. of solvent. <sup>1)</sup>	Grams per 100 grams saturated solution:				
		Acetanilide.	Phenacetine.	Caffeine.	Salol.	
<sup>1)</sup> Water	0.997	25	0.56	0.11	2.14	insoluble
<sup>1)</sup> Ether	0.716	"	7.7	1.56	0.27	—
<sup>1)</sup> Chloroform	1.476	"	16.6	4.76	11.0	—
Acetone	0.827	30-31	31.15 (0.902)	10.68	2.18 (0.832)	90.99
Benzene	0.872	"	2.46 (0.875)	0.65 (0.873)	1.22 (0.875)	88.57 (1.148)
Benzaldehyde	1.055	"	18.83 (1.068)	8.44 (1.063)	11.62 (1.087)	?
Amylacetate	0.860	"	10.46 (0.882)	2.42 (0.865)	0.72 (0.862)	85.29 (1.136)
Aniline	1.02	"	19.38 (1.034)	9.46 (1.025)	22.89 (1.080)	very soluble
Amylalcohol	0.814	25	14.00	3.51 (0.819)	0.49 (0.810)	20.44 (0.869)
Acetic acid <sup>2)</sup>	1.055	21.5	33.21	13.65 (1.064)	2.44	63.24 (1.143)
Xylene	0.847	32.5	1.65 (0.847)	1.25 (0.847)	1.11 (0.847)	87.14+
Toluene	0.862	25.0	0.50 (0.862)	0.30 (0.863)	0.57 (0.861)	83.62 (1.128)

Figures in parentheses are the specific gravities of the saturated solutions.

Fairly good results have been obtained by the author in separating mixtures of different amounts of salol, caffeine, and acetanilide by digesting first in toluene for the removal of salol and then in amyl alcohol for the removal of the acetanilide.

As is shown by the table, none of the four compounds are completely insoluble in any of the solvents, and consequently it cannot be expected that a very sharp separation can be made. This is especially true for mixtures containing relatively small amounts of either of the substances. It is also to be mentioned that the influence of the presence of one substance upon the solubility of the others in the mixture has not been investigated and therefore conclusions based upon the solubility of single substances in a given solvent may be considerably in error when applied to mixtures of two or more substances acted upon by the same solvent.

The author regrets that circumstances have prevented the extension of these determinations to a larger number of solvents and the application of the results to a more accurate method of separating and determining the constituents of headache powders.

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### A RAPID METHOD FOR THE QUANTITATIVE DETERMINATION OF ACETANILIDE IN HEADACHE POWDERS.

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While continuing the investigations described in the previous paper a suggestion was obtained which has led to the following method for deter-

<sup>1</sup> Results from U. S. P., 8th Revision.

<sup>2</sup> 99.5 %