30. Heinrich Will, "Zusammensetzung des Chelidonin's und Jervin's." *Annalen der Chemie*, 35, 116, 1840.

31. G. B. Wood, In an article by Wormley, *Am. J. Pharm.*, 48, 1, 1876.

32. T. G. Wormley, "The Alkaloids of *Veratrum viride* and *album*—History, Preparation and Recovery from Complex Mixtures and the Blood," *Am. J. Pharm.*, 48, 1–10, 1876.

33. Henry W. Worthington, "On *Veratrum viride*, with Experimental Facts, to Serve as a Chemical History of the Root of This Plant." Inaugural Essay, *Am. J. Pharm.*, 10, No. 2, 89–97, 1838.

34. C. R. Wright and A. P. Luff, "The Alkaloids of the Veratrums, Part II," *J. Chem. Soc.*, 35, 405–420, 1879.

35. C R. A. Wright, "The Alkaloids of the Veratrums, Part III. The Alkaloids of *Veratrum viride*," *J. Am. Chem. Soc.*, 35, 421–426, 1879.

PHYSIOLOGICAL.

36. Frank F. Casseday, "*Veratrum album* and *Veratrum viride*—A Comparison," *J. Amer. Institute of Homoeopathy*, 9, 281–2, 1916.

37. Russell J. Collins, "The Clinical Actions of Veratrum," *Arch. Int. Med.*, 16, 54–58, 1915.

38. Russell J. Collins and Paul Hanzlik, "Further Observations of the Clinical Actions of Veratrum," *J. Pharmacology and Experimental Therapeutics*, 11, 90, 1918.

39. William Cramer, "On the Action of *Veratrum viride*," *J. Pharmacology and Experimental Therapeutics*, 7, 63–6, 1915.

40. Albion Walter Hewlett, "The Pulse Flow in the Brachial Artery," *Archives of Internal Medicine*, XX, 6, 1917.

41. J. D. Pilcher, "The Bio-Assay of *Veratrum viride*," *Amer. J. of Physiology*, 44, 12, 1917.

42. Horatio C. Wood, "Pharmacology of Veratrum," *J. Amer. Medical Assoc.*, 47, No. 25, 2061–65 (1906).

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DISTRIBUTION OF CERTAIN DRUGS BETWEEN IMMISCIBLE SOLVENTS.*

BY W. O. EMERY AND C. D. WRIGHT.

Of the many medicinal preparations examined by this laboratory, those containing analgesic and antipyretic agents have been fruitful fields for various lines of investigation. In the isolation of these substances preliminary to their quantitative determination, recourse was frequently had to the use of immiscible solvents such as aqueous solutions and chloroform, the latter preferably on account of its physical properties and consequent ease of separation and recovery. During the earlier stages of the work, the relative volumes of the solvents, as well as the number of extractions deemed necessary or expedient for complete isolation of the substance sought, were governed largely by empirical considerations, care being taken, however, that any error of commission should involve an excess rather than a deficiency in organic solvent. In operations with caffeine and antipyrine, for example, substances possessing about equal solubility in chloroform but differing widely in this respect toward water (1 Gm. of caffeine is soluble in 46 cc, 1 Gm. of antipyrine, on the other hand, in less than 1 cc of water), it was assumed that, given like volumes, antipyrine would require a greater number of extractions than caffeine. From preliminary experiments on controls, carried out in the usual way with the

* Contribution from the Synthetic Products Laboratory, Drug Division, Bureau of Chemistry, U. S. Department of Agriculture, to the *Journal of the American Chemical Society*, from which the article is reprinted by permission.

Squibb type of separatory funnel at the room temperature, results were obtained quite different from those anticipated. Thus, in "shaking out" caffeine and antipyrine with chloroform, one such treatment effected the following recoveries from aqueous solutions.

TABLE I.—RECOVERY OF CAFFEINE AND ANTIPYRINE WITH CHLOROFORM.

Subs. in Aq. Soln. Gm.	$CHCl_3$ Cc.	H_2O Cc.	Caffeine %.	Antipyrine Recovery.
0.1000	50	20	98.2	98.0
0.1000	50	20	98.1	...
0.1000	50	20[a]	97.5	96.0
0.1000	50	20[b]	97.6	..
0.1000	20	20	94.3	94.0
0.1000	20	50	88.1	88.0
0.2000	50	20	..	97.0
0.5000	50	20	..	97.5
1.0000	50	20	..	96.0

[a] Acidified with H_2SO_4.

[b] Made alkaline with NaOH.

These findings seemed to indicate that under more nearly ideal conditions involving moderate to low concentrations the distribution ratios of caffeine and antipyrine between aqueous solutions and chloroform might be almost, if not quite, identical. The results as above tabulated formed the material for a preliminary communication to the Society at its 49th (Spring) meeting in Cincinnati, and in effect constituted the main incentive to the present study. Owing to the intervening war, however, and the consequent interruption to the normal activities of the Bureau, the final solution of the problem has involved a period of time far in excess of that originally contemplated.

CAFFEINE.

In order to gather more precise information relative to some of the factors influencing distribution, such as temperature, concentration, alcohol, acid, alkali and other solutes, several series of experiments were carried out, at first in a so-called constant temperature room at about 19.5°, later in a water-bath maintained at different temperatures, but accurate to within 1°. The pipet employed in this work for withdrawing the chloroform was specially prepared by drawing out the tip of an ordinary 25-cc instrument to a capillary about 10 cm. in length, and adjusting the volume by blowing a small bulb in the stem to 25.00 ± 0.02 cc as determined by the weight of water delivered.

Effect of Temperature.—In these and the following experiments, portions of anhydrous caffeine[1] were weighed out in small glass capsules and placed in glass-stoppered bottles of about 150-cc capacity, and then by means of a pipet prepared as above 50 cc of water and 50 cc of chloroform were added, the bottles were tightly stoppered and placed in a water-bath at the desired temperature, shaken vigorously at intervals and finally allowed to stand until the water and chloroform layers had become clear. Meanwhile, and in order to forestall any possible intake of the aqueous layer preparatory to withdrawal of the chloroform aliquot a minute bulb was blown at the extreme tip of the pipet, sufficiently thin to be easily crushed

[1] The caffeine used was a well-known commercial brand, recrystallized from water and dried at 100°.

by gentle pressure against the bottom of the container, 25 cc of the chloroform was withdrawn and run into a tared beaker. The solvent was then evaporated by an air blast and gentle heat, and the beaker and contents were weighed. The difference in weight multiplied by two[1] represents the amount of caffeine in the chloroform layer. The results obtained in the first extractions are given below.

TABLE II.—EFFECT OF TEMPERATURE UPON EXTRACTION WITH CHLOROFORM.

Total Caffeine Gm.	Temp. °C.	Caffeine in 25 cc of $CHCl_3$ Gm.	Recovery %.
0.5000	12	0.2407	96.3
0.5000	21	0.2383	95.3
0.5000	30	0.2357	94.3
0.5000	40	0.2330	93.2

It is evident that a low temperature is favorable to the extraction of caffeine from water by means of chloroform.

Effect of Concentration.—A series of experiments similar to the above was carried out in the constant-temperature room at about 19.5° but with varying concentration of caffeine, with the following results.

TABLE III.—EFFECT OF CONCENTRATION OF CAFFEINE UPON EXTRACTION.

Total Caffeine Gm.	Caffeine in 25 Cc of $CHCl_3$ Gm.	Recovery %.
0.1000	0.0480	96.0
0.2000	0.0958	95.8
0.5000	0.2376	95.0
1.0000	0.4702	94.0
2.0000	0.9240	92.4
2.5000	1.1400	91.2
5.0000	2.1710	86.8

The above findings show that the distribution is more favorable to the chloroform in dilute solution, *i. e.*, that the recovery of caffeine decreases with increase in concentration in water.

Effect of Alcohol.—Since U. S. P. chloroform contains 0.6 to 1.0% of alcohol, it was of interest to determine how much, if at all, distribution would be influenced by its presence. A similar series of experiments was therefore carried out, using instead of pure chloroform a mixture containing 1% of alcohol, prepared by diluting 5 cc of absolute alcohol to 500 cc with chloroform. These experiments were likewise conducted at the uniform temperature of 19.5°.

TABLE IV.—EFFECT OF ALCOHOL IN CHLOROFORM UPON EXTRACTION OF CAFFEINE.

Total Caffeine Gm.	Caffeine in 25 Cc of $CHCl_3$ Gm.	Recovery %.
0.1000	0.0483	96.6
0.2000	0.0964	96.4
0.5000	0.2403	96.1
1.0000	0.4752	95.0
2.5000	1.1500	92.0
5.0000	2.1810	87.2

[1] On the assumption that the volume of the chloroform layer is the same as that introduced. This is of course not strictly true, since the caffeine increases the volume slightly. Another conceivable source of error would be in a change in the volumes of water and chloroform on shaking, owing to mutual solubility, but tests indicated that this is inappreciable.

These percentages are in all probability somewhat too high, due to the fact that most of the alcohol passes into the water on shaking, with consequent diminution of the chloroform layer, the 25-cc portion removed representing slightly more than $^1/_2$ of the total volume. A more accurate method would undoubtedly be to use a 1% solution of alcohol in water, and alcohol-free chloroform.

Effect of Acid.—The feebly basic character of caffeine makes the study of its extraction from acid solutions of considerable interest. Accordingly experiments were undertaken to determine its distribution between pure chloroform and N sulphuric acid, 50 cc of each reagent being taken. The temperature in this series was maintained at 20.4°.

TABLE V.—EFFECT OF ACID SOLUTIONS UPON EXTRACTION OF CAFFEINE.

Total Caffeine Gm.	Caffeine in 25 Cc of $CHCl_3$ Gm.	Recovery %.
0.1000	0.0455	91.0
0.2000	0.0908	90.8
0.5000	0.2255	90.2
1.0000	0.4463	89.3
2.5000	1.0795	86.4
5.0000	2.0410	81.6

These results are what might be reasonably expected, showing as they do a somewhat less efficient extraction from an acid solution. Beal and Lewis,[1] on the other hand, operating on 0.2-Gm. samples of caffeine in 25-cc portions of 0.5 N, 0.25 N and 0.125 N sulphuric acid with 20-cc portions of chloroform, report higher recoveries for caffeine than were obtained from a similar operation on a neutral aqueous solution. The accompanying Fig. 1 affords a graphical representation of results obtained in the above three series.

Effect of Other Solutes.—The influence of various solutes, as ammonium hydroxide, sodium hydroxide, sodium acetate, sodium salicylate, sucrose and citric acid, was observed in a few preliminary experiments with the Squibb type of separatory funnel at a temperature of about 25°.

TABLE VI.—EFFECT OF OTHER SOLUTES UPON EXTRACTION OF CAFFEINE.

Total Caffeine Gm.	$CHCl_3$ Cc.	% Cc.	Aqueous Solvent.	Recovery %.
0.5000	25	20	H_2O + 5 cc of 28% NH_4OH	94.1
0.5000	25	20	H_2O + 5 cc of 5% NaOH	95.5
0.5000	50	50	Mol. Na acetate sol.	96.6
0.5000	25	25	Mol. Na salicylate sol.	20.7
0.5000	25	25	0.1 mol. Na salicylate sol.	82.0
0.2000	50	50	Mol. sucrose sol.	96.4
0.5000	25	25	Mol. citric acid sol.	85.2

Of these and other solutes examined in this manner, sodium salicylate appears to have by far the greatest effect on the distribution ratio, due apparently to the formation of some molecular compound not readily yielding its caffeine component to the chloroform.

Constant Temperature Bath.—In order to control temperature conditions more accurately, a tank was constructed of sheet copper, elliptical in form, with double walls inclosing an insulating space 25 mm. thick, packed with "mineral wool." The inside dimensions were length 70 cm., width 50 cm., and depth 45 cm., thus affording a capacity of about 150 liters. A tubular vertical shaft at the lower end carried, in addition to a set of stirring blades, a curved cross tube (hydraulic tourniquet

[1] Beal and Lewis, JOUR. A. PH. A., 5, 824, 1916.

or Barker's mill type), and a glass mercury-cup seal at the top similar to that illustrated by Hudson,[1] which, being connected by rubber tubing with a jacket of glass tubing 38 mm. in diameter containing either a pipet or buret as the experiment required, served as a pump for drawing water from the bath, and thus gave vigorous circulation and maintained the pipet (or buret) with its contents at the same temperature. A temperature control within 0.01° was secured by means of a hydrogen-sealed mercury thermo-regulator of the general type described by Clark,[2] heat being supplied by two 100-watt carbon lamps submerged in the water and controlled by a relay in the usual manner, which served to maintain the bath at 25° when the room was not below 20°, and also to illuminate the interior. In the event of temperatures lower than 20°, additional heat could be supplied by means of an auxiliary resistance coil. The temperature of 25° was selected because of its convenience and close approximation to ordinary laboratory conditions, also because it is the standard of the U. S. Pharmacopoeia. For convenient observation of the temperature, a Beckmann thermometer was used, the reading corresponding to 25.00° being determined by comparison with two calibrated (Bureau of Standards) thermometers reading to 0.01°. Midway of the tank was a submerged horizontal shaft so geared as to rotate about 20 times per minute, carrying spring clamps suitable for holding bottles. These were of the type known as "German tinctures," having flat-topped glass stoppers. They were very carefully tested for leakage before use. A basket at the side of the tank was provided for allowing the bottles to stand submerged to the necks for any period of time desired.

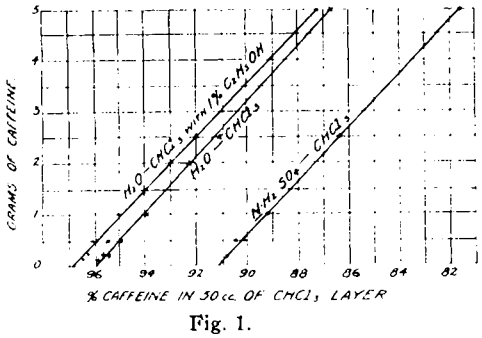

Fig. 1.

TABLE VII.—SOLUBILITIES OF CAFFEINE IN VARIOUS AQUEOUS SOLUTIONS.

Solvent.	Caffeine in 10 Cc. Gm.[a]	Gm.
Water	0.2133	0.2072
	0.2199	0.2063
	0.2183	0.2074
	0.2316	0.2076
		Mean, 0.2071
N sulphuric acid	0.3495	0.3361
	0.3526	0.3351
N citric acid		0.6406
		0.6417
N potassium bromide		0.2135
		0.2137
2.5 *N* potassium bromide		0.2031
		0.2041
N sodium salicylate	2.282	2.221
	2.278	2.222
	2.274	2.222
0.1 *N* sodium salicylate		0.4930
		0.4913
N sodium benzoate		1.545
		1.527
		1.511
0.1 *N* sodium benzoate		0.3431
		0.3414

[a] These values are unquestionably too high, being the result of earlier operations not strictly in accord with the above method.

[1] Hudson, *Jour. Am. Chem. Soc.*, 30, 1572, 1908.

[2] Clark, *Ibid.*, 35, 1889, 1913.

SOLUBILITY OF CAFFEINE.

In connection with the work on distribution, it was deemed advisable to acquire additional information on the solubility of caffeine in both water and certain aqueous solutions, the more so since the values obtained in some of the earlier experiments were unquestionably too high, due to supersaturation. Considerable difficulty was experienced in overcoming this condition. Starting with anhydrous caffeine, a much larger apparent solubility is obtained, hence it is necessary to convert the substance into its hydrated form by solution and redeposition before a true equilibrium is established. If sufficient caffeine is originally taken such supersaturated solutions yield a dense mass of hydrated crystals from which no solution can be separated conveniently. The anhydrous form, therefore, has a much greater solubility, but is unstable under these conditions. The method as finally developed for caffeine is essentially that outlined above.

Method.—Bottles containing the solvent and an excess of caffeine were allowed to stand for 3 days (or until the separation of crystals appeared to be complete), then rotated for 2 hours, and allowed to stand for another 2 hours in the bath. Portions of the clear solution were thereupon withdrawn by means of the water-jacketed pipet referred to above, and, in the case of water, run directly into tared beakers for evaporation, or into separatory funnels for extraction of the caffeine with chloroform from the other aqueous media employed.

The relatively high values obtained in certain of these experiments, notably in the case of sodium salicylate and benzoate, point to the existence of molecular compounds having a higher solubility than caffeine itself. The existence of such compounds has already been assumed by Daudt,[1] but so far as known no satisfactory proof has as yet been adduced.

Cryoscopic Experiments.—In order to obtain further information on the increased solubility of caffeine in salicylate and benzoate solutions, and on the nature of the combinations existing therein, experiments were undertaken with solutions containing these solutes singly and in admixture, using the ordinary Beckmann freezing-point apparatus. The results obtained are given below, being averages of several determinations.

TABLE VIII.—FREEZING-POINT DEPRESSIONS.

Solute in 100 cc.	Depression ° C.	
Caffeine, 1 Gm.	0.08	
Sodium salicylate, 1 Gm.	0.23	
Caffeine + sod. salicylate, each 1 Gm.	0.233	(0.31°)[a]
Sodium salicylate, 0.824 Gm.[b]	0.20	
Caff. 1 Gm. + sod. salicylate 0.824 Gm.	0.20	(0.28°)[a]
Sodium benzoate, 0.742 Gm.[b]	0.22	
Caff. 1 Gm. + sod. benzoate 0.742 Gm.	0.26	(0.30°)[a]

[a] Sums of the depressions of single solutes.

[b] These amounts represent the molecular equivalent of 1 gram of caffeine.

The above values clearly show that, in the case of sodium salicylate solutions, the addition of a molecular equivalent of caffeine produces no further depression of the freezing point; and, in the case of sodium benzoate solutions, the addition of a molecular equivalent of caffeine produces only about $^1/_2$ the depression to be expected. These results are in apparent harmony with those obtained in the solubility tests, and, as will later appear, in the distribution studies.

Distribution.—In the experiments on caffeine enumerated below, the chloroform and aqueous solutions were brought to 25° by standing in the constant-temperature bath; then, by means of the jacketed pipets referred to previously, were measured into bottles containing weighed amounts of caffeine, the aqueous layer being introduced first in order to minimize loss by evaporation. The bottles were tightly stoppered and, to insure that they remained so, cork discs were laid over the stoppers and spring clamps applied to hold them firmly in place. After rotating for two hours, and standing for about the same period in the bath as in the case of the solubility experiments, half aliquot portions of the chloroform layer were with-

[1] Daudt, *Pharm. Ztg.*, 32, 376, 1887.

drawn by jacketed capillary-tipped pipets and run into tared beakers for evaporation. In the cases where salts were present an additional precaution was taken of washing with a small portion of water in a separatory funnel, the chloroform aliquot removed, the water then being exhausted of any dissolved caffeine by two small portions of chloroform, and all of the latter solvent evaporated in a tared beaker. The results obtained in the several series are as follows.

TABLE IX.—DISTRIBUTION EXPERIMENTS WITH CAFFEINE.

Total Caffeine Gm.	Aqueous Solvent Cc.	Chloroform Cc.	Caffeine Gm.	Recovery %.
I. Water and absolute chloroform.				
0.1000	50	50	0.0479	95.8
0.2000	50	50	0.0957	95.7
0.5000	50	50	0.2368	94.7
1.0000	50	50	0.4685	93.7
1.0000	20	20	0.4575	91.5
2.0000	20	20	0.866	86.6
1.0000	20	20	0.455	91.0
2.0000	20	20	0.864	86.4
1.0000	20	20	0.457	91.4
2.0000	20	20	0.865	86.5
II. *N* sulph. acid and abs. chlorof.				
0.1000	50	50	0.0455	91.0
0.5000	50	50	0.2232	89.3
1.0000	50	50	0.4434	88.7
0.1000	50	50	0.0456	91.2
0.1000	50	50	0.0450	90.0
0.1000	50	50	0.0453	90.6
0.2000	50	50	0.0904	90.4
0.2000	50	50	0.0898	89.8
0.2000	50	50	0.0911	91.1
0.5000	50	50	0.2238	89.5
1.0000	20	20	0.4307	86.1
2.0000	20	20	0.8166	81.7
III. *N* potass. brom. and abs. chlorof.				
0.1000	50	50	0.0482	96.4
0.1000	50	50	0.0485	97.0
0.1000	50	50	0.0483	96.6
0.2000	50	50	0.0958	95.8
0.2000	50	50	0.0964	96.4
0.2000	50	50	0.0957	95.7
0.2000	50	50	0.0957	95.7
0.5000	50	50	0.2373	94.9
0.5000	50	50	0.2379	95.2
1.0000	50	50	0.4702	94.0
1.0000	50	50	0.4709	94.2
1.0000	20	20	0.4567	91.3
2.0000	20	20	0.8671	86.7
IV. 0.1 *N* sod. salicyl. and abs. chlorof.				
0.1000	50	50	0.0427	85.4
0.2000	50	50	0.0848	84.8
0.5000	50	50	0.2094	83.8
1.0000	50	50	0.4147	82.9
0.1000	50	50	0.0426	85.2
1.0000	20	20	0.4021	80.4
2.0000	20	20	0.7641	76.4
1.0000	20	20	0.4012	80.2
2.0000	20	20	0.7615	76.2
2.0000	20	20	0.7644	76.4
V. 0.1 *N* sod. benz. and abs. chlorof.				
0.1000	50	50	0.0466	93.2
0.2000	50	50	0.0922	92.2
0.5000	50	50	0.2288	91.5
1.0000	50	50	0.4532	90.6
1.0000	20	20	0.4375	87.5
2.0000	20	20	0.8249	82.5
0.1000	50	50	0.0466	93.2
0.1000	50	50	0.0459	91.8
0.2000	50	50	0.0926	92.6

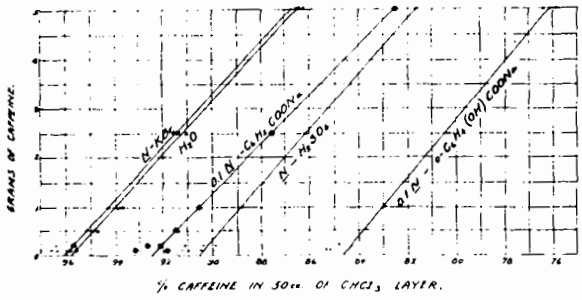

Fig. 2.

A graphical representation of these data is given in Fig. 2, from which the relatively slight effect of potassium bromide, as contrasted with that of the other solutes, is immediately apparent. Since the percentage error in the case of small amounts of caffeine is naturally much greater than when larger quantities are em-

ployed, the exact course of the line at such low concentrations becomes difficult of determination.

ANTIPYRINE.

The procedure followed in studying the distribution of antipyrine between absolute chloroform and aqueous solutions was in the main quite similar to that described for caffeine, with this difference, however, that instead of weighing the recovered product directly the residues obtained on evaporation of the chloroform half-aliquots, which are withdrawn after rotation in the constant-temperature bath, were titrated either as a whole (in alcoholic solution with iodine in the presence of mercuric chloride), or as aliquots, according to the method of Bougault.[1] As a preliminary thereto, a few tests were carried out in Squibb separatory funnels at 25° with U. S. P. chloroform and aqueous solutions of sodium acetate, potassium bromide, sucrose and sulphuric acid. The results obtained in these operations are indicated below.

TABLE X.—CHLOROFORM EXTRACTION OF ANTIPYRINE.

50 cc of chloroform used in each experiment.

Total antipyrine Gm.	Aqueous Solvent.	Recovery %.
0.1000	50 cc mol. Na acetate	95.6
0.1000	50 cc mol. K bromide	95.9
0.2000	50 cc mol. sucrose	95.8
0.1000	50 cc *N* H_2SO_4	54.2

The values yielded by the use of bottle containers in connection with the constant-temperature bath are given in the following series.

TABLE XI.—DISTRIBUTION EXPERIMENTS WITH ANTIPYRINE.

Total Antipyrine Gm.	Aqueous Solvent Cc.	Chloroform Cc.	Antipyrine by Titration Gm.	%
VI. Water and absolute chloroform.				
0.1000	50	50	0.0481	96.2
0.2000	50	50	0.0959	95.9
0.5000	50	50	0.2368	94.7
1.0000	50	50	0.4698	94.0
1.0000	20	20	0.4605	92.1
2.0000	20	20	0.884	88.4
VII. *N* sulphuric acid and absolute chloroform.				
0.1000	50	50	0.0273	54.6
0.2000	50	50	0.0529	52.9
0.5000	50	50	0.1339	53.6
1.0000	50	50	0.2662	53.2
1.0000	20	20	0.2685	53.7
2.0000	20	20	0.5432	54.3
2.0000	20	20	0.5426	54.3
0.5000	50	50	0.1341	53.6
VIII. 0.1 *N* sodium salicylate and absolute chloroform.				
0.1000	50	50	0.0477	95.4
0.2000	50	50	0.0947	94.7
2.0000	20	20	0.8750	87.5
0.5000	50	50	0.2354	94.2
1.0000	20	20	0.4584	91.7
1.0000	20	20	0.4576	91.5
0.1000	50	50	0.0477	95.4
1.0000	50	50	0.4672	93.4

[1] Bougault, *J. pharm. chim.*, 1, 858, 1898.

Fig. 3 is a graphical representation of the results shown in the last three series.

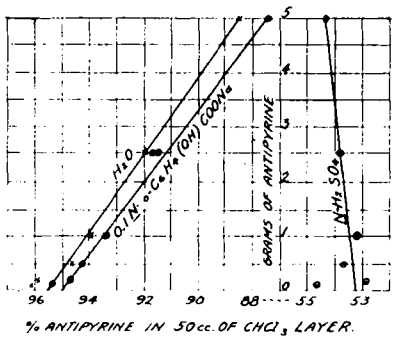

Fig. 3.

A study of these data shows that there is no such tendency to the formation of double salts as obtains in the case of caffeine (cf. Series IV and VIII). There is, on the other hand, a far greater depression in the percentage of antipyrine extracted from N sulphuric acid, when compared with that from purely aqueous solution, due presumably to difference in basicity.

p-ACETOXY-ACETANILIDE.

As a preliminary to more refined work on the behavior of this substance when agitated with water and U. S. P. chloroform, a few experiments were carried out in the usual way with separatory funnels at a temperature of about 20°. The material employed in this and all subsequent work was a carefully recrystallized product melting at 150–151°. The results obtained, as also the quantities of solute and solvents involved, are indicated below.

TABLE XII.—RECOVERY OF *p*-ACETOXY-ACETANILIDE.

Total Solute Gm.	Water Cc.	Chloroform Cc.	Recovery in 1st Extn. Gm.	Recovery in 1st Extn. %
0.1000	25	25	0.0891	89.1
0.1000	25	25	0.0891	89.1
0.1000	10	25	0.0953	95.3
0.1000	25	10	0.0776	77.6

These results reflect a somewhat lower distribution ratio than obtains for either caffeine or antipyrine under like treatment.

Solubility.—Preparatory to a more exact study on distribution, some information was deemed essential with respect to the solubility of *p*-acetoxy-acetanilide, notably in water and absolute chloroform. The method followed in this case was quite similar to that described under caffeine, with the exception that the bottles containing the solvent and excess of solute were rotated immediately upon receipt of their respective charges at 25° in the constant-temperature bath. The amounts of solute found in these experiments were as follows.

SOLUBILITY OF *p*-ACETOXY-ACETANILIDE.

Solvent.	Solute in 10 cc. Gm.
Water	0.0237
	0.0238
	0.0240
	Mean, 0.0239
Chloroform	0.3250
	0.3251
	0.3248
	Mean, 0.3250

Distribution.—The procedure followed in arriving at the results tabulated below, especially as regards the temperature (25°) and manipulation of aliquots, is entirely comparable with that previously described for caffeine.

TABLE XIII.—DISTRIBUTION EXPERIMENTS WITH *p*-ACETOXY-ACETANILIDE.

Total Solute Gm.	Chloroform Cc.	Water Cc.	Solute in 10 Cc. $CHCl_3$. Gm.	%.	H_2O. Gm.	%.	Total Recovery %.
1.2000[a]	25	25	0.3547	..	0.0254	..	..
0.8000			0.2964	92.6	0.0205	6.4	99.0
0.8000			0.2964	92.6	0.0200	6.3	98.9
0.4000			0.1469	91.8	0.0123	7.7	99.5
0.2000			0.0726	90.7	0.0069	8.6	99.3
0.1000			0.0364	91.0	0.0040	10.0	101.0
0.8000	25	50	0.2807	87.7	0.0196	12.3	100.0
0.4000			0.1373	85.8	0.0120	15.0	100.8
0.2000			0.0672	84.0	0.0071	17.8	101.8
0.1000			0.0334	83.5	0.0037	18.5	102.0
0.8000	25	35	0.2897	90.6	0.0197	8.6	99.2
0.4000			0.1421	88.8	0.0123	10.8	99.6
0.2000			0.0700	87.5	0.0072	12.6	100.1
0.1000			0.0348	87.0	0.0043	15.0	102.0
0.8000	50	25	0.1527	95.4	0.0123	3.8	99.2
0.4000			0.0761	95.1	0.0065	4.1	99.2
0.2000			0.0380	95.0	0.0034	4.3	99.3
0.1000			0.0190	95.0	0.0024	6.0	101.0

[a] An amount of solute in excess of that soluble in both solvents combined.

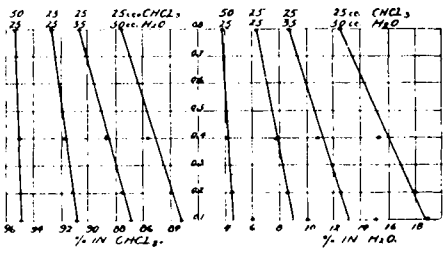

Fig. 4.

The high totals obtained in cases of small amounts of solute taken are not excessive, perhaps, in view of the factors employed in their calculation from the quantities actually weighed. The low totals, on the other hand, in cases of large amounts of solute are apparently due to the error necessarily involved in the assumption that the volumes of the solvents are unchanged by the substance dissolved. A graphical representation of the above findings is shown in Fig. 4.

It has been suggested by Marden,[1] and Marden and Elliott,[2] that the distribution ratio of a substance between two immiscible solvents be used in determining the number of extractions necessary to recover all but a negligible amount of the solute in question, as also in calculating the percentage of substance originally present in solution from data yielded by the first extraction. However attractive in principle these procedures may appear, it must be equally apparent to anyone skilled in the art that their general adoption could yield satisfactory results only under the most ideal conditions. In their practical application to many of the problems peculiar to drug analysis, one would certainly encounter grave difficulties, as in the formation of emulsions of greater or less persistence, which prevent any sharp separation of the two liquid media, more particularly, however, in cases involving two or more solutes and the possible existence of molecular compounds which, as has been noted in the work above described, markedly affect the distribution.

[1] Marden, *J. Ind. Eng. Chem.*, 6, 315, 1914.

[2] Marden and Elliott, *Ibid.*, 6, 928, 1914.

SUMMARY.

1. Studies have been made of the effect of temperature and concentration on the distribution of caffeine between water and chloroform.

2. The effect of the presence of other solutes in the aqueous layer on distribution has been determined at 25°.

3. The solubility of caffeine in water and certain aqueous solutions has been measured at 25°.

4. Further proof of the existence of molecular compounds of caffeine with sodium salicylate and sodium benzoate in aqueous solution has been obtained by cryoscopic measurements.

5. The distribution of antipyrine has been determined under similar conditions.

6. The solubility of *p*-acetoxy-acetanilide in water and chloroform has been measured at 25°. Its distribution between water and chloroform has likewise been determined.

7. Comparison of the distribution curves for caffeine and antipyrine between water and chloroform confirms the earlier assumption that the distribution ratios of these substances are nearly if not quite identical.

WASHINGTON, D. C.

HOLLYHOCK ROOT (?) FOR ALTHAEA.

BY OLIVER A. FARWELL.

There has come upon the markets of this country what purports to be althaea or marshmallow root. Superficially it bears a strong resemblance to the official drug and is of about the same size and is covered with loosened bast fibers; it is lighter colored, the longitudinal ridges are not so prominent, the grooves broader and shallower or these entirely absent; the cambium zone is circular while in Althaea it is usually angular, but in undoubted Althaea, the root often is not grooved and the cambium zone not angled; in testing for lignified tissues, we find that in the official drug the wood groups are separated, very minute and evenly distributed throughout the central cylinder; in the substitute they are less numerous, but larger, the largest forming concentric circles. It is unquestionably the root of some malvaceous plant closely related to Althaea and may be that of *Althaea rosea*, the Hollyhock, which is often used in place of Althaea.

SOURCE OF BALSAM POPLAR BUDS.

BY OLIVER A. FARWELL.

The present edition of the National Formulary allows this product to be derived from *Populus nigra* Linn or from *Populus balsamifera* Linn, the latter name interpreted as currently but wrongly applied to the northern Balsam Poplar, the proper name for which is *Populus Tacamahacca* Mill. As a question concerning the accuracy of this source arose, I determined, if possible, to verify the botanical source. While on my vacation in August, I collected branches of *P. candicans* with well-developed buds and I have seen commercial samples exactly similar; also I have seen commercial samples that agree in every particular with the buds of *P. Tacamahacca* Mill. A third sort was found upon the market that was much larger and more angled than the above mentioned.