The Extraction of Caffeine from Pharmaceutical Preparations*

By KENNETH E. HOLT

Advantage is taken of the relatively low solubility of caffeine in ether to separate it from other drugs with which it is frequently combined in tablets and capsules. The method was developed previously by the author for caffeine, aspirin, and acetophenetidin in simple admixture and is applied here to mixtures containing in addition to caffeine one or more of the following: ephedrine, acetanilid, camphor, monobromated camphor, phenobarbital, and aspirin. The principle may be extended to preparations containing other alkaloids as well.

CAFFEINE is one of the more common ingredients found in pharmaceutical preparations usually in combination with such compounds as acetylsalicylic acid, acetanilid, phenobarbital, camphor, etc. Because of the similarity in physical properties the separation of caffeine from these compounds is often a laborious and time-consuming procedure.

In a recent article (1, 2) a method of separation of caffeine, acetylsalicylic acid, and acetophenetidin was proposed which decreased the time of separation of these compounds by several hours over that required by the A. O. A. C. method (3) without loss in accuracy. The proposed method utilizes the relative solubility of caffeine in ether, chloroform, and water. The approximate solubility of caffeine in the above solvents in terms of cc. of solvent per gram of caffeine is: chloroform 6 cc., water 50 cc., and ether 550 cc. (4). This gives a ratio of approximately 1 to 10 between the water-ether phase and also the water-chloroform phase. The solubility of caffeine in water is increased by acids and decreased by alkalies, thereby increasing the above ratios.

The method used for the separation of caffeine from acetylsalicylic acid and acetophenetidin has been successfully applied to other pharmaceuticals containing caffeine. The results of some of these experiments are given in the accompanying tables. The procedure used in these experiments is essentially the same as previously reported (1, 2) with minor changes in sample sizes and volumes of solvents depending upon the solubility ratios of the ingredients present. Because of the small amount of caffeine usually found in pharmaceuticals, the minute quantities of caffeine retained by the ether extracts will result in a high percentage error if the size of sample and volumes of solvents used are not held rather closely to those used in the following procedures.

The ingredients used in these experiments were desiccated U. S. P. grade chemicals and were mixed in the approximate proportions usually found in preparations of this type. Purified (fat extraction) ether and U. S. P. grade chloroform were used, both were redistilled before using and the ether was washed with water to remove any alcohol present.

EXPERIMENTAL

Separation of Caffeine, Acetanilid, and Ephedrine

Acetanilid.—Accurately weigh a sample containing 0.3–0.5 Gm. of acetanilid and transfer to a separatory funnel. Add 25 cc. of HCl (1 + 10) and extract with purified ether using one 40-cc. portion and five 20-cc. portions. Combine ether extracts in another separatory funnel and wash with one 10-cc. portion HCl (1 + 10) and one 10-cc. portion of water, washing these in turn through two 25-cc. portions of ether and adding to the original acid solution. (Save the acid solution for caffeine and ephedrine.) Filter all ether extracts through a cotton pledget into a tared flask. Evaporate ether, dry at 100°, cool, and weigh as acetanilid.

Caffeine.—Extract the original acid solution with four 30-cc. portions of chloroform, washing each in turn through 10 cc. water. Filter the chloroform extracts through a cotton pledget into a tared flask. Evaporate the chloroform, dry at 100°, cool, and weigh as anhydrous caffeine.

Ephedrine.—Transfer the original acid solution containing the ephedrine to a 300-cc. Kjeldahl flask, dilute to about 100 cc., and add 15 cc. 50%

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NaOH. Steam distill the ephedrine collecting in an excess of standard acid solution according to the method by Schoen (5).

The results of experiments with caffeine and acetanilid and with caffeine, acetanilid, and ephedrine are given in Table I.

Filter all ether extracts through a cotton pledget into a tared flask. Evaporate ether, dry at 100°, cool, and weigh as phenobarbital.

Caffeine.—Extract the original acid solution with four 30-cc. portions of chloroform, washing each in turn through 5 cc. 2% NaOH and 5 cc. water.

TABLE I.—SEPARATION OF CAFFEINE, ACETANILID AND EPHEDRINE MIXTURES

Caffeine			Acetanilid			Ephedrine HCl		
Gm. Present	Gm. Found	%	Gm. Present	Gm. Found	%	Gm. Present	Gm. Found	%
0.1007	0.1008	100.1	0.6077	0.6069	99.9	...	...	...
0.0478	0.0488	102.1	0.5216	0.5220	100.1	...	...	...
0.0304	0.0305	100.3	0.5231	0.5238	100.1	...	...	...
0.0540	0.0528	97.8	0.5105	0.5077	99.5	0.2005	0.1990	99.2
0.0371	0.0376	101.3	0.2600	0.2636	101.4	0.2227	0.2214	99.4

Many preparations containing acetanilid and caffeine also contain camphor or monobromocamphor which would be extracted by the ether along with the acetanilid. These may be removed first by boiling the acid solution of the sample gently until the odor of camphor is absent, cooling and extracting as described above.

Any alkaloid which gives an acid salt, such as morphine, codeine, etc., may be substituted for the ephedrine in the above preparation. These will be retained in the acid solution and are readily extracted after the removal of the caffeine by rendering the solution alkaline.

Filter the chloroform extracts through a cotton pledget into a tared flask. Evaporate the chloroform, dry at 100°, cool, and weigh as anhydrous caffeine.

Acetylsalicylic Acid.—Dilute the $NaHCO_3$ solution to 100 cc., add 20 cc. of 5% NaOH, and boil fifteen minutes. Cool and dilute in a volumetric flask. Transfer an aliquot containing about 65 mg. acetylsalicylic acid to an iodine flask and proceed using the bromate method (6).

The results of experiments with caffeine and phenobarbital and with caffeine, phenobarbital, and acetylsalicylic acid are given in Table II.

TABLE II.—SEPARATION OF CAFFEINE, PHENOBARBITAL, AND ACETYLSALICYLIC ACID MIXTURES

Caffeine			Phenobarbital			Acetylsalicylic Acid		
Gm. Present	Gm. Found	%	Gm. Present	Gm. Found	%	Gm. Present	Gm. Found	%
0.0235	0.0229	97.5	0.0541	0.0544	100.6	...	...	...
0.0288	0.0284	98.6	0.0592	0.0604	102.0	...	...	...
0.0234	0.0229	97.9	0.1014	0.1039	102.4	...	...	...
0.0280	0.0278	99.3	0.1018	0.1032	101.4	...	...	...
0.0356	0.0351	98.6	0.1050	0.1062	101.1	...	...	...
0.0491	0.0485	98.8	0.1120	0.1129	100.8	0.4974	0.5022	101.0
0.0238	0.0234	98.3	0.0579	0.0596	102.9	0.4895	0.4860	99.3
0.0552	0.0538	97.5	0.0448	0.0439	98.0	0.2015	0.2012	99.9

Separation of Caffeine, Phenobarbital, and Acetylsalicylic Acid

Phenobarbital.—Accurately weigh a sample containing 0.05 Gm. to 0.10 Gm. of phenobarbital and transfer to a separatory funnel. Add 25 cc. of HCl (1 + 10) and extract with purified ether using four 25-cc. portions. Combine ether extracts in another separatory funnel and wash with one 10-cc. portion HCl (1 + 10) and one 10-cc. portion of water, washing these in turn through one 25-cc. portion of ether and adding to the original acid solution. (Save the acid solution for caffeine.) Combine the ether solutions and extract the acetylsalicylic acid with one 25-cc. and one 15-cc. portion of 5% $NaHCO_3$ and one 10-cc. portion of water, washing each through two 25-cc. portions of ether and combining in a 300-cc. Erlenmeyer flask. (Save the $NaHCO_3$ solution for acetylsalicylic acid.)

Acetylsalicylic acid when present in a pharmaceutical usually represents the major portion of the preparation and traces of it will remain in the acid solution after extraction with ether. These traces, while negligible in the acetylsalicylic acid analysis, will introduce a large percentage error in the caffeine analysis unless removed from the chloroform extracts by the 2% NaOH wash solution.

The solubility ratio of phenobarbital in water-ether is considerably greater than acetophenetidin or acetanilid; therefore, the smaller volume of ether used above will completely extract the phenobarbital, while the amount of caffeine extracted will be reduced to a fraction of a milligram.

Ephedrine or any acid-soluble alkaloid added to the above combination will be retained in the original acid solution and can be analyzed as indicated previously.

SUMMARY

A previously published method on the separation of acetylsalicylic acid, acetophenetidin, and caffeine has been adapted to other pharmaceuticals in which caffeine is an ingredient.

The pharmaceutical mixture is dissolved in an acid solution and ingredients such as acetanilid, phenobarbital, and acetylsalicylic acid are extracted with ether. The caffeine is then removed from the acid solution with chloroform, the acid solution retaining any ephedrine or other alkaloids present.

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The Identification of an Acid in the Root Bark of *Viburnum Prunifolium**

By JAMES M. HOLBERT

The major portion of the acid from *Viburnum prunifolium* root bark has been identified as isovaleric acid. The identification was made by the method of mixed melting points in which the anilide of the acid from *Viburnum prunifolium* root bark was compared to the anilides of known acids. The melting points of the anilides of the valeric and caproic acids are given.

IN A PARTIAL investigation of the contents of the root bark of *Viburnum prunifolium* Heyl and Barkenbus (1) reported the isolation of a valeric acid as the major portion of the total acid content. Since the identification of the acid was based on the analysis of its silver salt and since other work (2) suggested a caproic rather than a valeric acid, it was decided to reinvestigate the problem in order definitely to classify the acid as to kind and isomeric form.

The obvious approach to the problem was to convert the unknown acid to a derivative which in turn could be compared by the method of mixed melting point to the same derivative of known acids. Since only valeric and caproic acids were to be considered, the problem was resolved into the following steps: first, obtaining all isomers of valeric and caproic acid; second, converting these acids to a suitable derivative; third, isolating the major acid portion from the root bark of *Viburnum prunifolium* and subsequently converting it to the same derivative as the known acids; and fourth, identifying the unknown derivative by the method of mixed melting point.

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EXPERIMENTAL

Preparation of the Acids.—All of the valeric acids, *n*-valeric, isovaleric, methylethylacetic, and trimethylacetic, and three of the caproic acids, *n*-caproic, isocaproic, and diethylacetic, are available from Eastman. The remaining five caproic acids were prepared by the following methods.

Methyl-*n*-propylacetic Acid.—This acid was prepared by the oxidation of 2-methylpentanol-1 with boiling 50% nitric acid.

sec-Butylacetic Acid.—This acid was prepared in fair yields by means of the malonic ester synthesis from *sec*-butyl alcohol (3).

Dimethylethylacetic Acid.—The preparation of this acid was accomplished by means of the Grignard synthesis according to the method of Putambeker and Zoellner (4, 5).