ranging between 5.0 and 7.5, and its migration velocity is much slower than that of the pressor factors.

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The Determination of Theobromine in Tablet Mixtures*

By A. G. Richardson and Y. C. Campbell

In an effort to find a suitable rapid method for the determination of the alkaloid theobromine in tablet mixtures containing other nitrogenous organic compounds it became plainly evident that the ordinary shake-out methods using two immiscible solvents were unsatisfactory. This was confirmed by E. C. Deal (1) who recommended the Emery-Spencer (2) method wherein the theobromine in a tablet mixture is precipitated with iodine; phenobarbital or other barbiturates being uneffected. He pointed out, however, that starch, which is present in most tablet mixtures, would interfere and produce inaccurate results.

The A. O. A. C. volumetric method (3), in which the silver salt of theobromine is precipitated and the nitric acid formed from a known amount of standard silver nitrate

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thereby is titrated, does not proceed satisfactorily in the presence of other nitrogenous compounds which form silver salts easily.

Taking advantage of the alkaloidal precipitant phosphotungstic acid, preliminary test-tube experiments revealed that a copious yellow-orange precipitate could be obtained with this reagent. Roughly, quantitative experiments showed that the precipitate did not form with phenobarbital.

This led to the method used in this work. The method used is, briefly, the gravimetric precipitation of the insoluble compound formed by the action of phosphatododecatungstic acid (4) on hot strongly acidified (5) solutions of the tablet mixtures containing theobromine or its salts. The precipitate is filtered while hot, washed, dried and weighed.

The reaction for this precipitation is probably as follows:

$$P_2O_5.24WO_3 + 7H_2O + 6C_7H_8O_2N_4 \longrightarrow 2H_7P(W_2O_7)_6.(C_7H_8O_2N_4)_3$$

The precipitate obtained from a typical assay was analyzed to determine its composition. *Analysis.*—Calcd. for $C_{21}H_{31}O_{48}N_{12}W_{12}P$: N, 4.86; W, 63.83. Found: N, 4.85, 4.84, W, 63.48, 63.37. These data and the findings of Heiduschka and Wolf (6), who have found that one mol of the acid combines with 3 mols of most alkaloids, indicate that the precipitate is $P(W_2O_7)_6H_7.(C_7H_8O_2N_4)_3$.

EXPERIMENTAL

Reagent.—Phosphatododecatungstic acid or simple phosphotungstic acid is prepared by dissolving 103.6 Gm. of sodium tungstate $Na_2WO_4.2H_2O$ with 13.75 Gm. 85% H_3PO_4 and a sufficient volume of distilled water to make 500 cc. of reagent.

Technique.—Twenty or more tablets were reduced to a fine powder and dried to constant weight. A quantity of the dried material equivalent to approximately 0.2 Gm. of theobromine alkaloid was accurately weighed and transferred to a 250-cc. beaker. To this 100 cc. of distilled water were added followed by 5 cc. of concentrated H_2SO_4. This mixture was heated to boiling to dissolve the theobromine. (The usual tablet mixtures will dissolve completely in this hot acid solution with perhaps a slight opalescence. If at this stage any insoluble matter is present, filter the hot solution through a Gooch crucible and wash the residue thoroughly with boiling water uniting the filtrate and washings.) To the boiling hot solution was added reagent phosphotungstic acid drop by drop until precipitation was complete, then 10 per cent excess of reagent was added (usually a total of approximately 8 cc.). The mixture thus produced was digested four hours on the steam bath, then filtered while hot through a tared Gooch crucible having a thick asbestos mat. The precipitate was transferred quantitatively to the Gooch crucible and washed with a total of not more than 15 cc. of approximately $N/10$ H_2SO_4 followed by 4 1-cc. portions of cold distilled water, dried to constant weight at 110° C., cooled and weighed. The weight of the dried precipitate multiplied by 0.15627 equaled the weight of theobromine in the original sample.

The following table shows the results obtained when the various tablet mixtures were assayed for theobromine using the above technique. A total of 25 Gm. of each mixture was prepared by weighing the U. S. P. or C.P. ingredients accurately on the analytical balance. Each mixture was triturated thoroughly.

Table I.—Results of Assays for Theobromine on Known Mixtures

Tablet Mixtures		Assays for Theobromine
No. 1		
Theobromine salicylate	68.74%	100.23
Calcium salicylate	11.46%	100.17
Phenobarbital	2.86%	99.67
Lactose	9.55%	99.83
Starch	6.44%	100.30
Calcium stearate	0.96%	
No. 2		
Theobromine salicylate	42.96%	100.50
Calcium salicylate	11.46%	99.52
Phenobarbital	28.64%	100.42
Lactose	10.02%	100.71
Starch	6.44%	
Calcium stearate	0.48%	
No. 3		
Theobromine alkaloid	41.44%	96.79
Potassium iodide	41.44%	95.75
Phenobarbital	4.13%	99.74
Starch	4.94%	99.76
Lactose	7.31%	105.09
Calcium stearate	0.74%	102.50
No. 4		
Theobromine alkaloid	41.44%	100.74
Acetophenetidin	41.44%	100.45
Phenobarbital	4.13%	101.13
Starch	4.94%	100.05
Lactose	7.31%	
Calcium stearate	0.74%	
No. 5		
Theobromine with sodium salicylate	83.68%	100.52
Phenobarbital	2.86%	100.92
Starch	6.44%	100.70
Lactose	6.54%	100.10
Calcium stearate	0.48%	100.60
No. 6		
Theobromine salicylate	68.74%	
Calcium salicylate	11.46%	
Barbital	2.86%	100.41
Lactose	10.02%	100.61
Starch	6.44%	
Calcium stearate	0.48%	

The table given below shows the results of the assays made on tablets that can be purchased on the open market. These assays, of course, show quite a variation on account of the variations of manufacturing technique.

Table II.—Results of Assays for Theobromine on Manufactured Tablets Purchasable on the Open Market

Tablet Mixtures		Assays for Theobromine
No. 1		
Theobromine salicylate	68.74%	99.71
Calcium salicylate	11.46%	99.69
Phenobarbital	2.86%	99.20
Tablet excipients	16.94%	99.85
		98.62
		99.13
No. 2		
Theobromine with calcium salicylate	85.20%	99.55
Phenobarbital	2.84%	100.49
Tablet excipients	11.96%	100.83
No. 3		
Theobromine	69.66%	100.44
Phenobarbital	3.48%	99.83
Tablet excipients	26.86%	100.42
		99.78

Discussion of Results.—It is obvious that phenobarbital and other nitrogenous, non-alkaloidal substances have practically no effect upon this gravimetric precipitation. Iodides cause a marked interference. The method is applicable to mixtures containing theobromine alkaloid, theobromine salicylate, theobromine with sodium salicylate and theobromine calcium salicylate.

It was noticed that mixtures containing the free alkaloid had a tendency to form finer precipitates. The effect of this tendency may be overcome somewhat by longer digestion and by the use of sintered glass crucibles in place of Gooch crucibles with asbestos mats.

The precipitate on the filter in one determination was dried and weighed, then washed with cold $N/10$, H_2SO_4 a few cubic centimeters at a time until 100 cc. had been passed through, then re-weighed after drying to constant weight again. By this procedure, which resembles the usual washing technique, it was found that approximately 5 mg. of the precipitate on the filter were dissolved. The precipitates usually weigh approximately 1.2400 Gm. Therefore, the loss in weight from careful washing is quite low.

It is to be remembered that phosphatododecatungstic acid is an alkaloidal precipitant, and that if other alkaloids are present in the tablet mixtures they will be precipitated along with the theobromine.

SUMMARY

1. A method is proposed for the assay of theobromine and its salts in tablet mixtures.

2. The method is rapid and reasonably accurate.

3. The assay is satisfactory even though theobromine may be present with other nitrogenous substances such as the barbiturates.

4. The common tablet diluents, excipients and lubricants do not interfere with the assays.

5. Tablet mixtures containing iodides cannot be assayed satisfactorily by this method.

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Book Reviews

Food Analysis, by A. G. WOODMAN, Associate Professor of Analytical Chemistry, Emeritus, Massachusetts Institute of Technology. 4th Edition. 607 pages. 1941. McGraw-Hill Book Company, Inc. Price $4.00

The scope of the book remains the same as that of the third edition. The new edition has been enlarged by 50 pages. The first three chapters are devoted to the consideration of general methods; the microscopical examination of foods; and food colors and preservatives. The remaining eight chapters consider the methods of analysis and the interpretation of the analytical results obtained for milk, cream and ice cream; edible oils and fats; carbohydrate foods; cocoa and chocolate; spices; cider vinegar; flavoring extracts; and alcoholic foods.

Since no new chapters were added the slight enlargement is distributed throughout the contents. Fourteen pages were added to the chapter on alcoholic foods, the section on whiskey undergoing the major change. Other additions include a discussion of photometers; a brief section on ice cream; a re-