

# STUDIES IN SYNTHETIC DRUG ANALYSIS. VII—ESTIMATION OF MONOBROMATED CAMPHOR IN MIGRAINE TABLETS

By W. O. EMERY

Received December 24, 1918

## INTRODUCTION

The estimation of monobromated camphor *per se* by means of its bromine content may be effected with greater or less facility by any one of several procedures, notably the classic one of Carius; more speedily, however, by that of Stepanoff<sup>1</sup> which involves reduction in absolute alcohol with sodium, or by modifications thereof as reported by Bacon,<sup>2</sup> Maryott,<sup>3</sup> and Drogin and Rosanoff.<sup>4</sup> The earliest recorded experiments dealing specifically with the quantitative elimination of the halogen in monobromated camphor were undertaken by Schiff,<sup>5</sup> who, operating with sodium on a solution of the camphor derivative in toluene, showed the result of such action to be sodium bromide and sodium camphor. Taking advantage of this observation and subjecting the resulting products to titration *via* Volhard, Andre and Leulier<sup>6</sup> report satisfactory results in the examination of several commercial samples of the drug.

In medicaments like migraine tablets, however, the problem of evaluating the camphor derivative becomes more complicated. In addition to vehicular and other more or less inert materials peculiar to such products, we have here a preparation consisting essentially of acetanilide, caffeine, and monobromated camphor, with sometimes salicylates and plant extractives. From mixtures of this character monobromated camphor, on account of its physical properties, is hardly susceptible of quantitative isolation by means of immiscible solvents, although a gross separation of the drug in solution, along with acetanilide, caffeine, and other extractable material eventually present, may indeed be made by a systematic treatment of the powdered tablets with alcohol, benzene, or toluene. Such procedure, however, almost invariably gives rise to solutions of so unwieldy and varying a volume as to render any subsequent reduction, with sodium for example, quite valueless, owing to the uncertain quantity of metal required and consequent unsatisfactory results. Even when operating with like volumes of solvent, and in strict accord with the latest approved method comprehending the Stepanoff principle,<sup>7</sup> the amount of sodium required for complete reduction is generally variable and always relatively large, in fact, more than twenty times that of the bromine derivative involved. This comparatively low efficiency from the standpoint of sodium consumption arises from the phenomenon, familiar to most chemists, whereby metallic sodium when applied to heated alcohol immediately assumes the spheroidal state, moving about very actively on the surface of the

liquid, but separated therefrom by a film or cushion of hydrogen and alcohol vapor, all conditions clearly favoring incomplete reduction. Any objection to, or uncertainty attendant upon, the use of the free metal may be entirely eliminated by recourse to the procedure whereby the powdered tablet itself in alcoholic solution and suspension is subjected to the action of sodium in the form of its mercury amalgam, an effective reagent and at all times under complete control of the operator.

## EXPERIMENTAL

The tabulated data are representative of numerous results obtained with both control and commercial mixtures. The monobromated camphor required for the controls was prepared by recrystallization of a well-known foreign brand carrying a slight excess of halogen. The purified product melted sharply at 76° and had a bromine content, as determined by Carius, of 34.6 per cent. In general, the treatment consisted in subjecting the powdered sample in alcoholic solution and suspension to the action of the amalgam at about the temperature of boiling alcohol, at first over a wire gauze and with appropriate reflux, finally on the steam bath to practical exhaustion of the amalgam, and with no attempt at condensation. The amalgam was applied in a strength of about 1 per cent of sodium, although in Expts. 5 to 8, inclusive (see table), a product containing only 0.6 per cent of sodium was employed. After quantitative separation of the liquid from the mercury, the halogen is precipitated by silver nitrate in acidified solution, and the insoluble bromide determined in the usual way. In general, estimation of the bromine *via* Volhard is not advocated, on account of possible interference from accompanying organic substances.

Expt. No.	C <sub>10</sub> H <sub>15</sub> -BrO Gram	PhNHAc Gram	Caffeine Gram	Starch Gram	NaHg Gram	AgBr Gram	C <sub>10</sub> H <sub>15</sub> BrO Calcd. G.	Per cent
1	0.2000	....	....	....	25	0.1621	0.1994	99.7
2	0.1000	....	....	....	25	0.0810	0.0996	99.6
3	0.2000	....	....	....	25	0.1628	0.2002	100.1
4	0.1000	....	....	....	25	0.0809	0.0995	99.5
5	0.2000	....	....	....	25	0.1619	0.1991	99.6
6	0.2000	....	....	....	20	0.1617	0.1989	99.5
7	0.2000	....	....	....	15	0.1596	0.1963	98.2
8	0.2000	....	....	....	10	0.1526	0.1877	93.8
9	0.2000	....	....	....	15	0.1623	0.1996	99.8
10	0.2000	....	....	....	10	0.1622	0.1995	99.8
11	0.2000	0.8000	0.1000	0.1000	25	0.1627	0.2001	100.1
12	0.1000	0.4000	0.0500	0.0500	25	0.0812	0.0998	99.8
13	0.0972(?)	0.3888	0.0486	?	25	0.0762	0.0937	96.4(?)
14	0.0972(?)	0.3888	0.0486	?	25	0.0768	0.0945	97.2(?)
15	0.1000	0.4000	0.0500	0.2000	25	0.0812	0.0999	99.9
16	0.1296(?)	0.1944	0.0648	?	25	0.1052	0.1294	99.8(?)
17	0.1296(?)	0.1944	0.0648	?	25	0.1056	0.1299	100.2(?)
18	0.1300	0.2000	0.0650	0.1000	25	0.1059	0.1303	100.2
19	0.1296(?)	0.6480	....	?	25	0.1068	0.1314	101.3(?)
20	0.1296(?)	0.6480	....	?	25	0.1065	0.1310	101.1(?)
21	0.1300	0.6500	....	0.1000	25	0.1056	0.1299	99.9

In further explanation of these results, it may be stated that Expts. 1 to 10, inclusive, have to do primarily with the camphor derivative alone, 13 and 14, 16 and 17, and 19 and 20 with commercial mixtures, while 11 and 12, 15, 18, and 21 deal essentially with controls of the latter, in which the dominating ingredients were proportioned to agree with the manufacturer's label. Accordingly, any uncertainty existing relative to the quantities of such ingredients, notably monobromated camphor, actually introduced or present in the samples examined, would necessarily be re-

<sup>1</sup> Ber., 39 (1906), 4056.<sup>2</sup> J. Am. Chem. Soc., 31 (1909), 49.<sup>3</sup> Am. J. Sci., 30 (1910), 378; Chem. News, 103 (1911), 1.<sup>4</sup> J. Am. Chem. Soc., 33 (1916), 711.<sup>5</sup> Ber., 13 (1880), 1407.<sup>6</sup> J. pharm. chim., [7] 2 (1910), 64.<sup>7</sup> Loc. cit.

flected in all computations based thereon—as in the calculation of percentages—and is so indicated. With the exception of Expts. 3 and 4, the period of reduction in all the experiments was uniform, consisting of a  $\frac{1}{2}$  hr. treatment under reflux on the wire gauze and 1 hr. on the steam bath. In the exceptions noted, the reflux period was doubled, thus making the entire digestion cover 2 instead of  $1\frac{1}{2}$  hrs. While no material advantage in the longer treatment is observable there can be no objection thereto. A brief survey of the results presented will suffice to show the efficacy of the method.

#### METHOD

Ascertain the weight of 20 or more tablets, reduce to a fine powder and keep in a small tube or specimen bottle provided with a tightly fitting cork or glass stopper. On a metal or glass scoop weigh out an amount of the sample equivalent to not less than 100 or more than 200 mg. of the camphor derivative alleged to be present. Transfer quantitatively with 20 cc. of 96 per cent alcohol and 10 cc. of water, to a small (100 cc.) round-bottomed flask, containing 15 g. of 1 per cent sodium amalgam. Connect the flask, by means of a rubber stopper, with a short vertical reflux, preferably of the Allihn or of the worm type. Heat the mixture over a wire gauze just enough to cause the liquid to boil gently for a period of not less than 30 min. After cooling slightly, wash out the condenser tube first with 5 cc. of alcohol, then with 5 cc. of water, receiving the washings in the flask below. Remove the flask to the steam bath, heating for another hour, or until the evolution of hydrogen

has nearly or quite ceased. Toward the latter part of this operation, render the liquid about neutral with a few drops of acetic acid in order to further reduction. Transfer the contents of the flask to a separatory funnel, preferably of the Squibb type, withdrawing and washing the mercury in a second separatory funnel with at least two 50 cc. portions of water. Pass the several aqueous solutions quantitatively through a small filter, collecting the clear filtrate in a suitable beaker. Precipitate with silver nitrate after the addition of about 5 cc. of nitric acid, and proceed with the determination of the resulting silver bromide in the usual gravimetric way, employing, if available, a Gooch crucible in the operation of filtering. The weight of the silver bromide multiplied by the factor 1.23 will give the quantity of monobromated camphor originally present in the sample taken for analysis. A control should be run on the amalgam in order to determine whether any correction is necessary for the presence of halogen in material quantity.

#### SUMMARY

This method for the estimation of monobromated camphor in migraine tablets takes advantage of the fact that, when an aqueous-alcoholic solution of the camphor derivative, either alone or in admixture with other substances, is subjected to the action of sodium amalgam on heating, among other changes the bromine is split off quantitatively in the form of its sodium salt, which may then be determined gravimetrically in the usual way.

SYNTHETIC PRODUCTS LABORATORY  
BUREAU OF CHEMISTRY, DEPARTMENT OF AGRICULTURE  
WASHINGTON, D. C.

## LABORATORY AND PLANT

### ACID TEST ON ENAMEL WARE

By W. D. COLLINS

Received February 8, 1919

The testing of enameled steel ware and of enamels for coating sheet steel has been discussed by Orton,<sup>1</sup> J. B. Shaw,<sup>2</sup> Landrum,<sup>3</sup> Poste,<sup>4</sup> and Frost<sup>5</sup> in papers presented at meetings of the American Ceramic Society, and published in the *Transactions of the Society*. Much of the work of these authors was with special test pieces or vessels and the results of acid tests reported were largely based on loss of weight of the test pieces, or changes in appearance.

A recent article by Miller<sup>6</sup> gives the amounts of antimony dissolved from certain enameled vessels by treatment with different agents. One gray sauce pan lost 26 mg. of antimony when 1500 cc. of 4 per

cent acetic acid was boiled in the vessel for  $\frac{1}{2}$  hr. Food substances, grape juice, cider, cranberry pulp, spinach, and sweet milk, when cooked in the same vessel, dissolved proportional amounts of antimony. The results indicate that for the solution of antimony from enamel ware 4 per cent acetic acid may be considered fairly representative of a number of food products which will dissolve antimony from such vessels.

The test by boiling with 4 per cent acetic acid is comparatively old. Koerner<sup>1</sup> refers to a regulation of the German government, dated June 25, 1897, that vessels for cooking shall not give up any lead when 4 per cent acetic acid is boiled for  $\frac{1}{2}$  hr. in the vessel.

The results reported in Table I were obtained during the examination of a number of enameled dishes to learn the extent of the use of antimony oxide as a substitute for tin oxide in white enameled ware, and in connection with a few tests of different wares as to their acid resistance. Altogether, tests were made on 32 samples of white ware from 21 manufacturers, 15 samples of gray ware from 9 manufacturers, 12 samples of blue ware from 4 manufacturers, and 2

<sup>1</sup> "Testing of Enameled Sheet Steel Wares," *Trans. Am. Ceram. Soc.*, **11** (1909), 320-41.

<sup>2</sup> "Testing Sheet Steel Enamels," *Ibid.*, **12** (1910), 463-93.

<sup>3</sup> "Resistance of Sheet Steel Enamels to Acetic Acid," *Ibid.*, **13** (1911), 494-501; "Comparison of Ten White Enamels for Sheet Steel," *Ibid.*, **14** (1912), 489-509.

<sup>4</sup> "The Relative Action of Acids on Enamel," *Ibid.*, **17** (1915), 137; *Ibid.*, **18** (1916), 762.

<sup>5</sup> "The Action of Acetic Acid Solutions of Different Strengths on a Sheet Steel Enamel," *J. Am. Ceram. Soc.*, **1** (1918), 422-8.

<sup>6</sup> "Solution of Antimony from Enameled Cooking Utensils," *J. Home Econ.*, **8** (1916), 361-7.

<sup>1</sup> "Bleihaltige, im Sinne des Gesetzes ungiftige Glasuren," *Sprechsaal*, **39** (1906), 2-4.