

PAPERS READ BEFORE THE BRANCHES OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

THE QUALITY OF SOME DRUGS AVAILABLE ON THE MARKET AND PURCHASED ON PRESCRIPTION, WITH METHODS OF ANALYSIS.*

BY L. F. KEBLER with the collaboration of W. O. EMERY, E. C. MERRILL, A. G. MURRAY,
E. K. NELSON, S. PALKIN, B. H. ST. JOHN, G. C. SPENCER AND C. D. WRIGHT.

SOAP LINIMENT.

METHODS OF ANALYSIS.

Camphor.—Make a standard soap liniment and determine the optical rotation in a 200 mm. tube at a convenient temperature. Optical rotation about $+10.7^\circ$ sugar scale in a 200 mm. tube at 25°C .

Determine the optical rotation of the sample under consideration at the same temperature. Multiply the rotation of the sample by 4.5 and divide by the rotation of the standard. The result will be grammes of camphor per 100 mils of the sample.

Alcohol.—Introduce 25 mils into a suitable distillation flask, dilute with an equal volume of water and a sufficient amount of a 10% solution of calcium chloride to disintegrate the soap, then make the volume up to about 75 mils with water, mix and distil slowly, so as to avoid loss, about 50 mils into a 200 mil separatory funnel. Saturate the distillate with common salt and shake out with two 15 mil portions of petroleum ether. The remaining portion of the operation is carried out as directed for alcohol under Paregoric.

Summary of Analysis.—Seventy-seven samples were examined, 56, or 73% came within a 20% variation. A number of the samples were woefully deficient in camphor.

Comments.—Soap Liniment contains one percent of oil of rosemary which according to 8th rev. U. S. Pharmacopocia is optically dextrogyrate up to $+15^\circ$ angular rotation in a 100 mm. tube at 25°C . In estimating camphor this point is of little practical value, excepting in doubtful cases when it should be taken into consideration.

SPIRIT OF CAMPHOR.

METHODS OF ANALYSIS.

Camphor.—Make a standard solution by dissolving 10 Gm. of dry camphor in enough U. S. P. alcohol to make 100 mils.

Determine the optical rotations of the sample and standard in a 200 mm. tube at the same temperature. Multiply the rotation of the sample by 10 and divide by the rotation of the standard. The result expresses the number of grams of camphor in 100 mils of the sample.

Alcohol.—Introduce 25 mils into a separatory funnel, add 50 mils of water, saturate with sodium chloride and extract with three successive portions of petroleum ether. Transfer the hydro-alcoholic salt solution to a distillation flask, wash the petroleum ether with successive portions—20, and 5 mils of saturated salt solution, transfer to distillation flask, and distil until 50 mils of distillate are obtained. Determine the alcohol in the usual way. The percent of alcohol contained in the distillate is one-half that present in the original material.

Summary of Analysis.—Forty-four samples were examined; 19, or 43% came within 10% of the standard; 23, or 52% came within 15%; and 27, or 61% came

* Concluded from p. 621, July issue.

within 20%. The deviations exceeding 20% were in some instances very great. One contained only about one-fourth the amount of camphor called for; one was double strength; and two exceeded even this amount.

Comments.—Spirit of camphor is an extremely simple drug, easily prepared, and it is therefore difficult to explain the divergencies referred to above.

The optical rotation of standard spirits of camphor was found to be $+24.7^\circ$ (sugar scale) in a 200 mm. tube at 25°C .

The rotation of an alcoholic solution of camphor varies somewhat with the concentration of alcohol and camphor. Landolt found the specific rotation of camphor in alcoholic solution to vary from 42.806° in 10% solution to 50.801° in 50% solution, in a 100 mm. tube at 20°C .

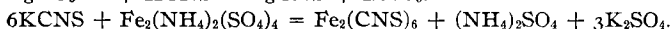
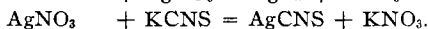
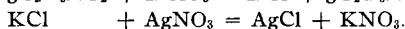
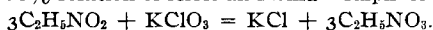
Hence the results obtained are strictly comparable only when the percentages of camphor and alcohol are approximately those of the standard solution.

SPIRIT OF NITROUS ETHER.

METHODS OF ANALYSIS.

Ethyl Nitrite.—(a) 8th Rev. U. S. P. Method.

(b) Introduce 5 Gm. of the sample into a 100 mil flask containing 25 mls of water, add 5 mls of a saturated aqueous solution of potassium chlorate and 5 mls of 10% nitric acid, stopper, mix well and allow to stand about one hour; then add an excess of $\frac{N}{10}$ silver nitrate, mix well and titrate back the excess of silver nitrate with $\frac{N}{10}$ potassium sulphocyanate, using about one mil of a 10% solution of ferric ammonium sulphate as indicator.



Each mil of $\frac{N}{10}$ silver nitrate is the equivalent of 0.0225 Gm. of ethyl nitrite.

Alcohol.—Place 25 mls into a suitable sized flask, add 25 mls of a 10% aqueous solution of sodium hydroxide, connect with a reflux condenser and heat for about an hour, cool, add 25 mls of water and submit to distillation; collect 50 mls of the distillate and ascertain the amount of alcohol in the usual way. From the result obtained deduct the amount of alcohol formed in saponifying the ethyl nitrite. Ethyl nitrite yields 61.33% of its weight in alcohol.

Summary of Analysis.—Seventy-nine samples were examined. Of these 45, or 57% failed to come within 20% of the standard; 51, or 64.5% deviated from the standard in excess of 25%. There is certainly room for improvement.

Comments.—The general experience is that there is an excessive amount of low grade spirit of nitrous ether on the market. There is no doubt but that it is one of the drugs most commonly found at variance with the standard. The reasons are undoubtedly manifold. Faulty methods of manufacture are believed to be the chief trouble. Numerous studies have been made on the keeping qualities of this drug.

J. E. Stacy,¹ Farr and Wright,² D. Gilmour,³ G. E. Shaw,⁴ L. A. Brown,⁵ J.

¹ *Proc. Mass. Pharm. Assoc.*, 54, 1899.

² *Trans. Br. Pharm. Conf.*, 447, 1901.

³ *Pharm. J.*, 66, 54, 1901.

⁴ *Ibid.*, 71, 236, 1903.

⁵ *Am. Drug.*, 59, 215, 1911.

R. Rippetoe,⁶ and F. L. Shannon.⁷ The general conclusions arrived at are that spirit of nitrous ether of good quality does not deteriorate materially within a reasonable length of time (six months) if kept in filled, small, amber-colored bottles, in diffused light, at a moderately low temperature. Brown⁵ believes that absolute alcohol as a solvent increases stability.

The 8th Dec. U. S. Pharmacopoeial method for determining the percent of ethyl nitrite in this drug is tedious and time consuming. In order to eliminate this feature in our work the initial examinations were made by the potassium chlorate method and, if a sample was found deficient by this process, it was checked by the official method. The chlorate method for estimating nitrites was first described by F. Dietze,⁸ and further studied by E. Beuttner,⁹ B. Grützner,¹⁰ F. Keppler¹¹ and C. E. Smith.¹² It is thought by some that the results by the method elaborated for spirit of nitrous ether are a trifle high in some cases due to the possible presence of associated products, such as aldehyde, ethyl acetate, etc. Smith's results indicate that the method under ordinary conditions gives data which are neither too high nor too low. O. Herting¹³ described a procedure almost identical to that of Dietze's (1897), fourteen years later (1911). Herting gave 0.0255 Gm. as the $\frac{N}{10}$ silver nitrate equivalent for ethyl nitrite which is incorrect. This incorrect figure, instead of 0.0225 is inadvertently used at times by some in making calculations.

TINCTURE OF IODINE.

METHODS OF ANALYSIS.

Iodine.—The 8th Rev. U. S. P. method.

Potassium Iodide.—(a) Five mils of the tincture are pipetted into a deep tared porcelain crucible and heated on the steam bath in a hood until the alcohol and practically all the iodine are volatilized. The crucible is then heated to a dull red for about a minute for the purpose of expelling the remaining traces of free iodine, cooled and weighed. The residue represents potassium iodide if no other non-volatile matter has been added.

(b) Dissolve the residue obtained in (a) in about 100 mils of water, transfer to a 200 mil beaker and titrate with tenth normal silver nitrate in the usual manner, using from one to two drops of a 10% solution of potassium chromate as indicator.

(c) Dissolve residue under (a) as directed under (b), acidulate with nitric acid, add an excess of $\frac{N}{10}$ silver nitrate to precipitate the iodine as silver iodide; then titrate back the excess of silver nitrate with $\frac{N}{10}$ potassium thiocyanate using about 1 mil of a 10% solution of ferric ammonium sulphate as indicator.

Summary of Analysis.—Sixty-five samples were examined. In the case of iodine, 38, or 58% came within a 10% variation; and 48, or 74% came within a

⁶ *Am. Drug.*, 59, 307, 1911.

⁷ *J. Am. Pharm. Assn.*, 2, 83, 1913.

⁸ *Süd. Apoth. Ztg.*, 37, 305, 1897.

⁹ *Schw. Woc. Pharm. and Chem.*, 35, 545 and 562, 1897.

¹⁰ *Chem. Ztg.*, 21, 308, 1897.

¹¹ *Süd. Apoth. Ztg.*, 38, 484, 1898; *Abstr. Pharm. Ztg.*, 43, 552, 1898.

¹² *Am. J. Pharm.*, 70, 273, 1898.

¹³ *Pharm. Ztg.*, 56, 423, 1911.

15% variation. In the case of potassium iodide 18, or 28% exceeded a 25% limit.

Comments.—It will be noted that a large number of the samples varied materially from the standard either in iodine or potassium iodide content or both. The amount of alcohol present usually came within the working limits.

PRESCRIPTION A.

Six drachms of potassium iodide dissolved in enough water to make two fluid ounces.

10 mils should contain 3.94 Gm. of potassium iodide.

METHODS OF ANALYSIS.

(a) This being a simple aqueous solution of potassium iodide the potassium iodide can readily be determined by evaporating the water from a given volume in a weighed dish as follows: Pipette 5 mils of the sample into a suitable tared dish and evaporate on the steam bath; finally render anhydrous by heating in the air bath at 110° C. for fifteen minutes, cool and weigh. The residue is potassium iodide if the prescription was correctly filled.

(b) Introduce ten mils, accurately measured, into a 100 mil flask, dilute with distilled water to the mark, remove an aliquot portion, 10 mils, dilute to about 50 mils, acidulate with nitric acid, add an excess of $\frac{N}{10}$ silver nitrate, mix well, and titrate back with $\frac{N}{10}$ potassium sulphocyanate, using about one mil of a 10% solution of ferric ammonium sulphate as indicator. For reactions see potassium iodide under Tincture of Iodine. Each mil of $\frac{N}{10}$ silver nitrate is equivalent to 0.0166 Gm. of potassium iodide.

(c) Determine the refractometric readings by immersing the immersion refractometer directly into the solution at a temperature of 25° C. From the reading on the scale the amount of potassium iodide can readily be found by reference to table below.

Refractometer Readings at 25° C.

Potassium Iodide in Aqueous Solution.

Scale readings.	Gms. per 100 mils.	Scale readings.	Gms. per 100 mils.	Scale readings.	Gms. per 100 mils.	Scale readings.	Gms. per 100 mils.	Scale readings.	Gms. per 100 mils.
		31	5.50	51	11.56	71	17.40	91	23.39
12.4	0.0	32	5.80	52	11.76	72	17.70	92	23.69
13	0.2	33	6.10	53	12.05	73	18.00	93	23.99
14	0.5	34	6.35	54	12.35	74	18.30	94	24.29
15	0.8	35	6.70	55	12.65	75	18.60	95	24.59
16	1.1	36	6.95	56	12.95	76	18.90	96	24.89
17	1.4	37	7.25	57	13.20	77	19.20	97	25.10
18	1.7	38	7.55	58	13.50	78	19.50	98	25.45
19	1.95	39	7.85	59	13.80	79	19.80	99	25.75
20	2.3	40	8.15	60	14.10	80	20.10	100	26.00
21	2.57	41	8.45	61	14.40	81	20.40		
22	2.85	42	8.75	62	14.70	82	20.70		
23	3.15	43	9.00	63	15.00	83	21.00		
24	3.45	44	9.4	64	15.30	84	21.29		
25	3.75	45	9.7	65	15.60	85	21.59		
26	4.05	46	10.00	66	15.90	86	21.89		
27	4.30	47	10.30	67	16.20	87	22.19		
28	4.60	48	10.60	68	16.50	88	22.49		
29	4.90	49	10.90	69	16.80	89	22.79		
30	5.20	50	11.16	70	17.10	90	23.09		

Summary of Analysis.—The prescription was filled by 57 different druggists; six, or 10¹/₂% failed to come within a 10% limitation; four contained excessive

amounts, varying from 21 to 29%; and two prescriptions were deficient, one 46%, and the other 81%.

Comments.—This being a simple aqueous solution the results obtained by the immersion refractometer are sufficiently accurate for practical purposes. If undue variation is noted, the result should be checked by method (a) or (b) outlined above, or both.

PRESCRIPTION B.

Acetphenetidin 36 grains, bismuth subnitrate 1 drachm, sodium bicarbonate 2 drachm; mix and make twelve powders.

Each powder should contain 3 grains of acetphenetidin.¹⁴ 5 grains bismuth subnitrate and 10 grains of sodium bicarbonate.

METHOD OF ANALYSIS.

Acetphenetidin.—Place from $\frac{1}{2}$ to 1 Gm. of the finely powdered well mixed material on small, counterpoised filters, one within the other, in a funnel, and treat with successive portions of chloroform until all of the acetphenetidin is removed. From 40 to 60 mils are generally sufficient. The solvent must be carefully applied, best from a pipette, not only to the powder directly, but to the sides and upper edges of the filters. Each addition should be allowed to drain before more solvent is used. When exhausted, wash the stem of the funnel with chloroform, collect the filtrate and washings in a tared Jena or non-sol beaker, evaporate carefully at a slightly elevated temperature or in a current of air until the solvent is apparently dissipated, add 5 mils of ether, evaporate, then heat for 15 minutes at about 100° C., cool in a desiccator and weigh.

Comments.—The ingredients of a mixture of this character should not vary to exceed 20% from the written order. On this basis the deviation was excessive in four instances. Attention should also be called to the fact that acetphenetidin was substituted in two instances by acetanilide, by antipyrin in another, and bismuth subcarbonate was substituted for bismuth subnitrate in one case.

PRESCRIPTION C.

Antipyrin, 24 grains, and 120 grains of sodium bicarbonate, to make one dozen powders.

Each powder should contain two grains of antipyrin and ten grains of sodium bicarbonate.

METHODS OF ANALYSIS.

Antipyrin.—Weigh out on a small (5.5 Cm.) filter an amount of the powdered sample equal to or a multiple of the average weight of one powder, wash with successive small portions of 95% alcohol, in quantity about 20 to 30 mils, sufficient at least to extract all the antipyrin present in the mixture. Collect solvent in a 100 mil Erlenmeyer, add 10 mils of an alcoholic solution of mercuric chloride (5 Gm. in 100 mils 95% alcohol), then run in a standard solution of pure iodine (1.351 Gm. resublimed iodine dissolved in 100 mils 95% alcohol, 1 mil of which is either exactly or approximately equivalent to 10 Mg. pure antipyrin) until a faint yellow coloration persists. The number of mils required to bring about this result, multiplied by the value of 1 mil in terms of antipyrin will give the quantity of this substance present in the sample under examination.

Sodium Bicarbonate.—(a) This chemical can be estimated by direct titration with a standard acid solution, using methyl red as indicator.

(b) The average weight of a powder or a multiple thereof can be incinerated and the residue titrated with normal acid solution, using methyl red as indicator. From the results obtained the amount of sodium bicarbonate can readily be calculated.

¹⁴ Complete analysis of prescriptions was not attempted. Only such ingredients considered necessary to determine whether or not the prescriptions were properly filled, in certain particulars, were estimated.

(c) Introduce into a tared platinum dish the average weight of one powder, add sufficient dilute sulphuric acid to decompose the sodium bicarbonate and submit to ignition; this will convert the sodium bicarbonate into sodium sulphate which can be weighed, and from the results the amount of sodium bicarbonate can be readily determined.

Comments.—The prescriptions examined, excepting in two cases, complied closely with the written instructions. In one instance the amount of antipyrin was considerably excessive, and in another the sodium bicarbonate present was only about one-half that called for.

PRESCRIPTION D.

Two drachms of ammonium bromide dissolved in four fluid ounces of cinnamon water.

The four fluid ounces should contain two drachms of ammonium bromide.

Comments.—With one exception the compounding was satisfactory.

PRESCRIPTION E.

Salol and quinine sulphate, of each 30 grains, put into ten capsules.

Each capsule contains 3 grains each of salol and quinine sulphate.

METHODS OF ANALYSIS.

Salol.—Introduce the average weight of one capsule, or multiple thereof into a separatory funnel containing 25 mls of water, render slightly acid and extract with several successive portions of 15 mls of chloroform; introduce the chloroformic extract into a tared beaker and evaporate with a current of warm air. After the solvent has apparently all been dissipated, the beaker should be introduced into a desiccator and allowed to remain for 24 hours before weighing. From the data obtained from the above procedure the amount of salol can readily be ascertained.

Quinine Sulphate.—Render the acid aqueous solution in the separatory funnel alkaline with either sodium bicarbonate or sodium carbonate, extract the liberated quinine with three successive portions of chloroform, transfer the chloroformic extracts to a suitable sized beaker and evaporate at a low temperature, dissolve the quinine residue in alcohol and titrate with $\frac{N}{20}$ sulphuric acid, using methyl red as indicator. From the results so obtained the amount of quinine sulphate can readily be calculated.

Comments.—Results satisfactory.

PRESCRIPTION F.

Antipyrin, 24 grains and 60 grains of sodium salicylate to be mixed and made into a dozen powders.

Each powder should contain 2 grains of antipyrin and 5 grains of sodium salicylate.

METHODS OF ANALYSIS.

Antipyrin.—Introduce the average weight of a powder, or multiple thereof, into a separatory funnel containing about 25 mls of water and a small amount of sodium bicarbonate; extract the resulting solution with four successive portions of 20 mls of chloroform, transfer the chloroformic extracts into a suitable size beaker, evaporate the chloroform in a current of warm air, dissolve the residue in from 30 to 40 mls of alcohol, then add 10 mls of an alcoholic solution of mercuric chloride (5 Gm. in 100 mls of 95% alcohol) and complete by process given under Prescription C for antipyrin.

Sodium Salicylate.—(a) Acidulate solution in separatory funnel with dilute sulphuric acid and extract the liberated salicylic acid with several successive portions of chloroform. Transfer the chloroformic extract containing the salicylic acid, into a tared beaker through a dry filter paper. Evaporate the chloroform at a low temperature in a current of air. Finally dry at 80° C., transfer to a desiccator, cool and weigh. From the results obtained the amount of sodium salicylate contained in the prescription can be calculated.

(b) Proceed as directed under (a) above until chloroform is evaporated. At this stage dissolve the residue in about 10 mls of alcohol, dilute with water to 25 mls and titrate with $\frac{N}{10}$ sodium hydroxide solution, using phenolphthalein as indicator. 1 ml of $\frac{N}{10}$ sodium hydroxide is the equivalent of 0.016 Gm. of sodium salicylate.

(c) Ignite a given weight of the material, extract the residue with water and titrate with $\frac{N}{10}$ sulphuric acid, using methyl red as indicator. 1 ml of $\frac{N}{10}$ sulphuric acid is the equivalent of 0.016 Gm. of sodium salicylate.

Comments.—Acetanilide was substituted for antipyrin in two cases.

PRESCRIPTION G.

Phenacetin and salol, each 60 grains, to be mixed and made into one dozen powders.

Each powder should contain 5 grains each of phenacetin and salol.

METHODS OF ANALYSIS.

These methods are given in an article recently published in the *J. Ind. and Eng. Chem.*, 7, 681, 1915, by W. O. Emery, G. C. Spencer and C. C. LeFevre.

Comments.—The compounding was well done.

SUMMARY.

1. The results in this article show that there is considerable room for improvement in the quality of the drugs examined.

2. An examination of the mixtures procured on prescriptions shows that carelessness in compounding obtained in some cases and actual substitution in a few others.

3. A few of the methods of analysis used are new, some an adaptation of well-known procedures and others are the common ones in use.

BUREAU OF CHEMISTRY,

UNITED STATES DEPARTMENT OF AGRICULTURE.

TUBERCULINS.*

BY L. K. DARBAKER.

Barnard and Baron claim that pronounced reactions are more easily obtained with patients in the incipient stages; moderate reactions occur with advanced lesions, and that the absence of a reaction in a clinically advanced patient heralds a speedy death.

The Ophthalmic or Calmette Reaction.—Calmette placed a drop of a 10 percent solution of tuberculin in the eye. This was claimed, in tuberculous patients, to be followed by a more or less severe conjunctivitis, while in the non-tuberculous patients a slight reddening only occurred. The reaction appears in three to ten hours and is highest in six to twelve hours, disappearing in twenty-four to

* Concluded from p. 627, July issue.