coöperative studies now in progress. The pharmacological action of azulene is being investigated by Dr. A. S. Loevenhart and his students.[1] In conjunction with Dr. G. L. Clark the study of the surface energy relations has been begun. This research will include a general survey of all of the types of compounds occurring in the volatile oils. Thus does the rational chemical study of a single drug plant lead on and on. What the future will reveal is but speculation to-day. Yet as Dr. F. B. Power[2] has remarked, "it may be noted that one of the largest and most attractive fields of chemical investigation still remains practically unexplored, for comparatively little is yet known respecting the constituents of the plants which inhabit North America."

NOTES ON EMETINE BISMUTH IODIDE.

BY GEO. E. ÉWE.

Emetine bismuth iodide was brought to the attention of the medical profession for the treatment of entamoebiasis by A. G. DuMez, formerly of School of Pharmacy, College of Medicine and Surgery, University of the Philippines, in an article entitled "Two Compounds of Emetine Which May Be of Service in the Treatment of Entamoebiasis," published in the *Philippine Journal of Science*, Vol. X, No. 1, Section V, Tropical Medicine, January 1915, pages 75–79.

The second compound mentioned in the publication was emetine mercuric iodide which, however, has not found any extensive use.

Notes on Preparation.—The method outlined by DuMez consisted of precipitating an acidified aqueous solution of emetine hydrochloride with Dragendorff's reagent, collecting and washing the precipitate with water and drying it in the air at a temperature below 50° C. When so prepared, the compound has an ugly brick-red color. But if the product is made by precipitating an acidified aqueous solution of emetine hydrochloride with Dragendorff's reagent, then warming the mixture slightly until the maximum bright red color, consistent with no alteration of the emetine alkaloid, is attained, a more beautiful and more thoroughly combined product is obtained. The amount of heat required to effect the combination must be carefully controlled by experiment in order to prevent alteration of the emetine alkaloid, which is sensitive to heat under the conditions of manufacture of this compound. The difference in results of alkaloidal assays of this compound by gravimetric and volumetric methods is a measure of the heat control; the volumetric method giving results only for unaltered alkaloid, whereas the gravimetric method includes both altered and unaltered alkaloid. Therefore, a properly made compound should give results by both methods which fairly closely check each other.

The following table shows the results of assays, of a number of samples of emetine bismuth iodide from various sources, by both volumetric and gravimetric assay methods:

[1] A paper on the toxicity of azulene by Dr. Loevenhart, Miss Whelan and Dr. Leonard, was read by the first-mentioned investigator at the Chicago (1919) meeting of the A. A. A. S. before the Pharmacological Society.

[2] "The Aims and Development of Phytochemical Research," *American Journal Pharmacy*, March 1917, p. 97.

Sample No.	Percent of anhydrous emetine alkaloid. Gravimetric method.	Volumetric method.	Sample No.	Percent of anhydrous emetine alkaloid. Gravimetric method.	Volumetric method.
1	26.99	21.3	10	29.8	23.4
2	22.85	17.94	11	24.82	24.6
3	27.75	19.84	12	19.84	19.3
4	27.4	14.63	13	27.0	21.5
5	28.2	28.2	14	22.5	14.1
6	24.8	24.8	15	22.8	17.6
7	27.2	25.13	16	32.7	31.5
8	26.0	23.15	17	22.5	22.1
9	25.02	23.35	18	28.2	28.2

It is the opinion of the writer that samples numbers 1, 2, 3, 4, 10, 13, 14 and 15 contain too much altered alkaloid to be considered as having been properly made.

The nature of the alteration products of the alkaloid was not determined, but since they fail to neutralize acid they are not alkaloidal in nature and therefore should not be credited in the evaluation of this compound. Furthermore, since the identity and action of these alteration products are unknown at present only a compound which is practically free from them can be considered perfectly satisfactory for use in the treatment of entamoebiasis.

State of Combination of the Emetine Alkaloid.—As pointed out by Rabak,[1] this compound is "slightly soluble" in water and in very dilute hydrochloric acid and "emetine is split off by the action of the solvent." I have confirmed Rabak's conclusions by washing 5 grammes of emetine bismuth iodide with distilled water continuously during three working days, under which treatment the alkaloidal content was reduced from 23.4 to 9.08 percent. For this reason, washing of this compound during manufacture must be discontinued as soon as the excess of Dragendorff's reagent is eliminated and the emetine content of the washings is approximately constant. A large number of experiments in which the proportions of emetine hydrochloride, reagent, and solvents and manufacturing conditions were investigated, failed to produce a compound which would not yield alkaloid upon washing with water.

Therefore it is evident that the emetine in this compound is rather loosely combined. It probably exists as an adsorptive compound and not as a true chemical compound. However, the rate of liberation of the alkaloid is so slow as to make this compound infinitely superior to emetine hypochloride and ipecac preparations for oral administration.

The possibility that emetine bismuth iodide is an adsorptive compound is further strengthened by the fact that the composition of the compound varies with the conditions existing during manufacture. This is illustrated by the varying emetine content of the different samples listed in the above table.

Martindale and Westcott, in the 17th Edition of the Extra Pharmacopoeia, also report a similar experience: "Elutriated with successive quantities of 0.2 percent hydrochloric acid—all of the emetine could be extracted" and "unless properly protected with Stearette or salol coating is liable to be dissolved to a great extent in the stomach."

[1] William Rabak, Ph.G., B.S., in "Annual Reports of the Chemical Laboratory of the A. M. A.," Vol. XI, January to December 1918, pages 66 to 73.

Influence of Altered Emetine upon Emetic Effect.—As pointed out by DuMez, this compound, as prepared by him, can be given in doses representing 0.03 Gm. of emetine hydroiodide without causing vomiting and without any apparent nausea; whereas vomiting does occur when given in very large doses.

Physiologic experiments made on dogs to which doses of emetine bismuth iodide containing 7.91 percent, 2.85 percent and 1.67 percent of altered emetine, respectively, were administered, indicated that the altered alkaloid exerted no influence on the tendency of this compound to cause vomiting, since the vomiting dosage per kilogramme of dog, of the three compounds, was fairly constant, within the limits of the experimental error due to varying sensitiveness of the subjects.

The Pharmacy of Emetine Bismuth Iodide.—By far, the most favored method of administering this compound, at present, is in the form of the powder enclosed in cachets or capsules. However, the moulded tablet readily disintegrates and is quite practical. This was determined by administering progressively increasing doses of moulded tablets to dogs until the smallest amount which would produce nausea was determined. Then some of the tablets were powdered; the powder was enclosed in cachets and administered to dogs in increasing doses until the smallest amount which would produce nausea was determined. The vomiting dosage per kilogramme of dog was found to be fairly constant, when based on the average of results on 25 dogs.

A properly made, readily disintegrating compressed tablet should also prove satisfactory. This compound should never be dispensed as an ingredient of a liquid preparation since it would be partially decomposed with the liberation of soluble emetine salt and therefore more readily cause nausea. Success has been attained in administering this substance in salol or stearic acid coated pills (The Extra Pharmacopoeia, 17th Edition).

I am indebted to Dr. Paul S. Pittenger for conducting the careful physiologic tests mentioned in these notes.

PHARMACEUTICAL RESEARCH LABORATORIES,
H. K. MULFORD COMPANY,
PHILADELPHIA, PA.

IODIDE AND BROMIDE PASTES AS USED IN ROENTGENOGRAPHY.*

Since Cameron[1] found that watery solutions of the iodides of sodium and potassium could be successfully used as opaque mediums in roentgenography, it has also been found at the Mayo Clinic that the bromides can be used to the same advantage. At present from 12 to 25 percent solutions of these salts are being used for cystograms and pyelograms. Similar solutions can also be used to great advantage for the injection of chronic tracts, sinuses, cavities and fistulas. A thin, watery solution, however, is difficult to retain long enough to obtain good roentgenograms.

With the idea of finding a suitable medium for injection purposes, I undertook a systematic study of various pastes for the incorporation of iodine and bromine

* From a preliminary report by Robert F. Schanz, M.D., Fort Wayne, Ind., in the *Journal A. M. A.*, January 31, p. 316, 1920.

[1] D. F. Cameron, "Aqueous Solutions of Potassium and Sodium Iodides as Opaque Mediums in Roentgenography," preliminary report, *J. A. M. A.*, 70, 754 (March 16), 1918.