RESIN OF IPOMEA.*

BY L. E. WARREN.**

INTRODUCTION.

Resin of ipomea is the chief therapeutic constituent of *Ipomœa orizabensis* Ledenois. It is described in the Pharmacopœia of the United States,[1] and a method for its preparation from the crude drug is given. The resin is rarely prescribed alone but it is a constituent of Compound Extract of Colocynth U. S. P.[2] and of Compound Tincture of Jalap N. F. V.[3] Also it enters into the composition of many unofficial preparations.

Criticisms were received by the Food and Drug Administration that resin of ipomea of authentic origin did not conform in all respects to the standards of the U. S. P. X. It was claimed that the maximum moisture limit permitted by the Pharmacopœia (1%) is too low, since most specimens contained from 2% to 3% of moisture. Some analysts reported that the determination of moisture in the product gave considerable trouble because the dried product is very hygroscopic. In general it was asserted that the limits for the acid number (25–30), the saponification number (195–215) and ester number (170–185) as specified in the Pharmacopœia are much too high; it was also claimed that the U. S. P. requirements for ether solubility (from 80 to 90% ether-soluble) cannot always be met. Because of the importance of the subject from the standpoint of the administration of the Food and Drugs Act, an investigation of the properties of resin of ipomea was undertaken.

REVIEW OF LITERATURE.

Several investigators have studied resin of ipomea and much of the information in the literature concerning its constants is confusing and contradictory.

Resin of ipomea appears to have been first isolated by Planche and Ledenois.[4] Other early investigators were Mayer[5] and Spirgatis.[6] Flückiger and Hanbury[7] found 11.8% of resin in orizaba root. They stated that the resin had an optical rotatory value of —19.6° in alcohol. Under the same conditions convolvulin (from true jalap) had a value of —11.6°. They stated that the pure resin is completely soluble in ether.

Weigel[8] found 6.4 to 22.2% of resin in 14 specimens of orizaba root. About 82% of the resin obtained was soluble in ether.

Deane[9] obtained the resin from Mexican scammony root by exhausting the drug with alcohol, evaporating the solvent and pouring the residue into water. The resin was purified by washing repeatedly with hot water. A yield of 18.5%

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* Scientific Section, A. PH. A., Miami meeting, 1931.

** Food and Drug Administration, Washington, D. C.

[1] Pharmacopœia of the United States of America, 10 (1926), 319.

[2] *Ibid.*, 144.

[3] The National Formulary, 5 (1926), 254.

[4] *Jour. Chim. Med.*, 10 (1834), 1.

[5] *Ann.*, 95 (1855), 129.

[6] *Ibid.*, 116 (1860), 289; 139 (1866), 41.

[7] "Pharmacographia," 2nd Edition (1879), 446.

[8] *Pharm. Zentralhalle*, 44 (1903), 789.

[9] *Pharm. J.*, 72 (1904), 327.

was obtained. The color of the resin was pale brown. Over 98% of it was soluble in ether.

Duncan[1] reported that a sample of Mexican scammony which he assayed yielded 16.5% of resin but that a picked root from the same lot yielded 20.1%. The resin resembled that from true scammony except in respect to its melting point and saponification value. This resin melted at 110°, whereas the true scammony resin melted at 119°. The respective saponification numbers were 149.3 and 196.2.

Cowie and Brander[2] examined a specimen of resin of Mexican scammony which they had prepared from crude drug believed to be *Ipomœa orizabensis* and two specimens of the commercial resin. They found from 2 to 3.05% of moisture; from 0.16 to 0.20% of ash, and from 68.6 to 72% soluble in ether. The acid value was 8.4 and the saponification values 295 to 327. The optical rotatory values of two specimens were —18.75° and —27.0°.

Taylor[3] examined two specimens of resin of Mexican scammony believed to be pure and one which he believed to be nearly pure. He reported from 1.77 to 2.03% of moisture, 0.08 to 0.22% of ash, 14.6 to 21.5 for acid values, 186.6 to 198.4 for saponification values, from 171.1 to 183.8 for ester numbers and from 8.7 to 11.5 for iodine absorption values. In the determination of acid number and saponification number Taylor noted that the solution became so dark that it was difficult to determine the end-point. He overcame this difficulty in part by using larger amounts of phenolphthalein solution as indicator. He also observed that the resin soaps formed in the saponification were not very soluble in the alcoholic solution. They had a tendency, therefore, to settle to the bottom of the flask with resultant occlusion of alkali. He diluted the soap solution with water before titration, which overcame the difficulty to some extent. Taylor believed that the saponification values sharply distinguish the orizaba resin from resin of true scammony, the latter having a saponification value of from 230–240. He considered the acid number and the iodine absorption number of no value in distinguishing between the two resins.

Weigel[4] disagreed with Taylor[3] that the resins of scammony and ipomea may be distinguished by their saponification numbers. He reported that eight samples of resin of ipomea had saponification values of from 179.71 to 228.68. He believed that Taylor's findings for acid and saponification numbers of true scammony resin were too high. Weigel found that the saponification value of ipomea resin is lower if the back titration were conducted in the hot solution. Two specimens, back titrated hot, gave, respectively, 162.8 and 184.8 for saponification values. The same specimens, each titrated cold, gave, respectively, 182.0 and 210.6. He recommends that the back titration be made in the hot solution. He believes that the resin should be free from water-soluble material.

Engelhart and Schmidt[5] examined five specimens believed to be resin of ipomea, together with several specimens known to be true resin of scammony. For the resin of ipomea they found from 1.45 to 4.29% of moisture, from 0.07 to 0.3% of ash, acid values of from 10.2 to 14.9, saponification numbers of from 171.6

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[1] *Pharm. J.*, 80 (1908), 378.

[2] *Ibid.*, 81 (1908), 366.

[3] *Am. J. Pharm.*, 81 (1909), 105.

[4] *Pharm. Zentralhalle*, 51 (1910), 721.

[5] A. PH. A. PROCEEDINGS, 58 (1910), 1025.

to 183.8, ester numbers of from 157.6 to 170.2, iodine absorption numbers of from 11.48 to 13.93, optical rotatory values of from —31.31° to —34.27° and ether solubility of from 80.9 to 91.5%. They compared these findings with the corresponding results from true resin of scammony. Examination of their findings shows that the saponification numbers, the optical rotatory values and the solubilities in ether are the only factors of value in distinguishing between the two resins. In determining the acid number Engelhart and Schmidt used the method of Marks.[1] This consists in making the titration in a flat-bottomed porcelain dish. The solution is thus brought against a white background in a thin layer, which facilitates the determination of the end-point.

During the chemical examination of the root of Mexican scammony, Power and Rogerson[2,3] obtained 14.55% of the resin. Of this 71% was soluble in ether. After treatment with animal charcoal the resin was colorless. The decolorized resin was levorotatory; α_D – 23.0°. The resin melted at 125° to 130° C.

EXPERIMENTAL.

Twelve specimens of resin of ipomea were obtained from manufacturers or users of the drug and three laboratory specimens were prepared from the crude drug which had been authenticated by Mr. J. F. Clevenger, Administration Pharmacognosist. In preparing one of these specimens the U. S. P. X process for making resin of ipomea was followed and in the other two the resin was prepared by extracting the ground drug with alcohol in an automatic extraction apparatus, evaporating the extract to dryness, and washing the residue with successive portions of hot water.

Moisture, ash, acid number,[4] saponification value,[4] ester number and ether solubility were determined. With certain exceptions as noted later, the methods described in the U. S. P. X were employed. No attempt was made to determine the iodine absorption value, for it had been shown by previous workers* that this factor is of no value in distinguishing between resin of scammony and resin of ipomea. The optical rotatory values were not observed. Cowie[5] had shown that the optical rotatory value of pure scammony resin (scammonin) was about —25°. This value is so near that of ipomea resin that this property cannot be utilized in distinguishing between the two resins. In addition, the material insoluble in alcohol and the substances soluble in water were determined. Tests for aloin, guaiac, resin and soluble impurities were also carried out according to the U. S. P. X methods.

During the first determinations of saponification number (in which the U. S. P. X method was followed) exceedingly variable results were obtained. A series of tests was then carried out in which the time of boiling, the quantity of sample taken and the concentration of the alkali were varied. In general it was found that the saponification number increased with the time of boiling (up to 2 hours) and with the concentration of the alkali. Also that the maximum saponification values

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[1] *Chem.-Ztg.*, 34 (1910), 124.

[2] *Chem. Soc. Proc.*, 27 (1911), 304.

[3] *J. Chem. Soc.*, 101 (1911), 1.

* See [3,5], preceding page.

[4] Alkali blue was found to be a more satisfactory indicator than phenolphthalein. This will be discussed later.

[5] *Pharm. J.*, 81 (1908), 365.

were not obtained by heating for 30 minutes as prescribed by the U. S. P. X method. As a result of these preliminary trials, a period of two hours was adopted as satisfactory for boiling the solution.

The alcoholic solutions of most of the specimens of resin were quite dark. When phenolphthalein was used as indicator it was difficult to ascertain the end-points in the determination of the acid numbers and the saponification numbers. The difficulty was not remedied by using aldehyde-free alcohol to dissolve the resins before saponification. Alkali blue was tried as an indicator with somewhat better success. In preparing this solution 0.25 Gm. of alkali blue (sodium triphenylpara-rosaniline monosulphonate) was dissolved in about 5 cc. of water and the solution diluted to 25 cc. with alcohol. Most of the results for acid values and saponification values recorded in Table I were obtained by the use of alkali blue as indicator.

In the determination of saponification numbers it was observed that a portion of the resin soaps was precipitated in the saponification flask. As previously mentioned, Taylor* had noted that a similar precipitate which he had obtained occluded some of the alkali. In order to reduce the error from this phenomenon in these studies the hot, alcoholic solution of soap and alkali was poured into a 2-liter Erlenmeyer flask and the back titration conducted nearly to neutrality. The resin soap remaining in the saponification flask was dissolved in about 1 cc. of water and the solution added to the partially titrated solution. The titration was then completed. By this procedure it is believed that all of the occluded alkali in the resin soap was brought into the reaction. Owing to the small quantity of water used for the solution of the resin soaps, and the subsequent dilution of the solution with a large excess of alcohol, the hydrolysis is thought to have been reduced to a minimum.

No particular difficulty was encountered in the determination of moisture and ash. Moisture was determined by drying in a flat-bottomed silica dish at 100° in a Freas oven. Ash was then determined by heating the silica dish and contents to low redness in a muffle.

After the preliminary experimentation, as outlined in the preceding paragraphs, had been completed, the following procedures (in addition to methods for the determination of moisture and ash) were adopted:

ALCOHOL-INSOLUBLE.

Weigh 10.0 Gm. of resin of ipomea into a beaker, add 50 cc. of neutral alcohol and warm the mixture gently with stirring until the resin is dissolved. Decant the liquid through a weighed Gooch crucible and wash the container with several small portions of neutral alcohol, taking care to transfer any insoluble material to the crucible. Wash the crucible and contents with several small portions of neutral alcohol. To insure complete extraction of the resin place the partially washed crucible and contents in a Bailey extractor[1] and extract with neutral alcohol to exhaustion. Dry the crucible to constant weight at 100° C. and weigh.

ACID NUMBER.

Transfer the alcoholic solution (obtained in the determination of alcohol-insoluble material) to a 250-cc. volumetric flask, make up to the volume with neutral alcohol and mix the solution well. Place 25 cc. of the solution (equivalent to 1 Gm. of resin of ipomea) in an acetylization

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* See [3], page 218.

[1] *Ind. & Eng. Chem.*, 6 (1914), 497.

flask, add 1 cc. of alkali blue solution[1] and titrate the solution with 0.5 *N* alcoholic potassium hydroxide until a distinct, permanent, brownish red color appears.

Each cc. of 0.5 *N* KOH equals 0.02806 Gm. of KOH.

SAPONIFICATION NUMBER.

To the neutral, alcoholic solution of resin of ipomea as obtained in the preceding paragraph, add sufficient 0.5 *N* alcoholic potassium hydroxide to make a total of 15 cc. of the alkaline solution. Boil the mixture gently on the steam-bath for 2 hours with frequent agitation. Titrate the excess alkali with 0.5 *N* hydrochloric acid.

Each cc. of 0.5 *N* KOH = 0.02806 Gm. of KOH.

WATER-SOLUBLE.

Evaporate the alcohol from 25 cc. of the solution of the resin (equivalent to 1 Gm. of resin of ipomea), and dry the residue at 100° to remove the last portions of solvent. Add 15 cc. of water to the residue, bring the mixture to boiling, allow to cool about three minutes, and stir well with a flat-headed glass rod for two minutes to insure thorough washing of the resin. Cool the mixture to a temperature below 10° C. and decant the wash water into a 9-cm. filter paper. Repeat the washing of the resin with another 15-cc. portion of water, boiling and cooling the mixture, kneading the resin as before and decanting the washings onto the filter, as described previously. Repeat the washing and kneading process with hot water once more. Evaporate the aqueous filtrate and washings and dry the residue to constant weight at 100° C. Weigh the residue as "water-soluble."

The ester number is ascertained by subtracting the acid value from the saponification number. The analytical findings for the several specimens examined are given in the accompanying table.

TABLE I.—ANALYSES OF SEVERAL SPECIMENS OF RESIN OF IPOMEA.

Sample.	Moisture.	Ash.	Alcohol-Insoluble.	Acid Number.	Saponification Number.	Ester Number.	Water-Soluble.	Ether-Soluble.	Pet.-Ether-Soluble.
A	0.62	0.14	0.015	8.36	177.31	166.54	0.81	87.18	..
	0.65	0.13	...	8.36	177.31	166.81	0.80	...	..
	..	..	...	8.77	....	....	..	...	..
	..	..	...	8.50	....	....	..	...	..
B	1.39	0.19	0.051	9.06	186.04	176.98	1.19	...	..
	1.17	0.19	...	10.35	177.16	166.81	1.03	...	..
	1.38	0.18	...	10.35	182.90	172.55	..	...	..
	1.38	..	...	...	....	....	..	...	..
C	..	0.044	0.20	12.26	182.41	170.15	0.23	83.19	..
	..	..	...	12.26	182.45	170.19	0.24	82.65	..
	..	..	...	...	184.90	....	..	82.77	2.05
	..	..	...	...	181.93	....	..	...	..
D	2.42	0.07	0.24	9.01	188.67	179.66	0.22	96.26	2.05
	2.21	0.08	...	9.54	188.92	179.38	0.25	...	..
E	0.71	0.07	0.09	10.46	176.03	165.57	1.17	58.06	2.2
	0.73	0.06	0.06	11.88	172.58	160.70	1.28	58.22	..
	..	..	...	11.88	173.11	161.79	..	...	..
	..	..	...	11.32	171.31	....	..	...	..
F	1.25	0.24	0.38	14.82	190.46	175.64	3.62	81.53	..
	1.21	0.24	...	14.97	193.66	178.69	3.97	...	..
	..	..	...	13.46	195.13	181.67	..	...	..
	..	..	...	14.81	193.30	178.49	..	...	..

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[1] Dissolve 0.25 Gm. of alkali blue in 5 cc. of water and add 20 cc. of alcohol.

G	3.39	0.55	2.76	9.12	173.38	164.26	1.97	80.40	1.82
	3.37	0.56	2.75	8.34	172.86	....	1.88	...	..
	..	..	...	...	171.13	162.79	..	...	..
H	1.60	0.38	0.51	13.41	186.62	173.21	2.82	79.76	3.48
	1.62	0.29	...	12.07	185.26	173.19	2.72	80.68	..
	..	0.44	...	13.41	....	....	..	...	..
	..	0.44	...	...	....	....	..	...	..
I	3.10	0.18	0.38	17.70	185.34	167.64	2.38	74.56	2.05
	3.71	0.19	....	17.70	187.90	170.20	2.42	76.12	..
	3.71	0.19	...	17.70	185.30	167.60	..	...	..
J	2.98	0.27	0.35	9.55	175.52	165.97	2.78	85.20	2.10
	3.25	0.25	...	9.55	175.52	165.97	3.37	...	..
K	3.21	1.00	0.61	11.49	172.41	160.92	5.95	69.06	1.70
	3.25	1.00	0.73	11.49	172.41	160.92	5.98	69.68	..
L	3.36	0.83	0.59	11.48	183.82	172.34	5.78	66.44	2.10
	3.35	0.84	0.55	11.23	182.41	171.18	7.49	63.72	..
	..	..	...	10.70	....	....	6.48	...	..
M	2.14	0.20	0.13	9.92	181.06	171.14	2.40	81.10	3.06
	2.15	0.20	...	9.39	178.29	168.90	3.90	...	..
	..	..	...	9.39	....	....	2.31	...	..
N	3.19	0.55	1.17	10.53	172.23	161.70	6.38	51.46	2.88
	3.21	0.54	...	10.56	173.56	163.00	6.41	51.04	..
	..	..	...	11.05	172.24	161.19	..	...	..
O	5.23	1.03	0.97	13.43	190.45	177.02	7.45	72.08	2.3
	5.17	1.03	...	13.82	190.45	176.63	6.09	72.06	..
U. S. P. requirements	1.0	0.5	...	25–30	195–215	170–185	..	80–90	5.00

Jois, Manjunath and Rao[1] have worked out a method for determining the saponification value and the acid value of highly colored oils which they claim is much more satisfactory than the ordinary process. Their method as applied to oils is as follows:

> Heat from 1 to 1.5 Gm. of the oil with a measured excess of 0.5 *N* alcoholic potassium hydroxide for half an hour in a reflux apparatus. Add 50 cc. of toluene, 25 cc. of neutral, saturated sodium chloride solution, 5 Gm. of solid sodium chloride (to prevent dilution of the salt solution during addition of the acid) and 1 cc. of phenolphthalein T.S. Titrate the excess of alkali with 0.5 *N* hydrochloric acid, heating the mixture on the water-bath toward the end of the reaction. Conduct a blank experiment with the same quantities of reagents and apply the necessary correction.
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> Each cc. of 0.5 *N* KOH = 0.02806 Gm. of KOH.

This method was tried out on a few specimens of resin of ipomea, the saponification numbers of which had already been determined by the use of alkali blue as indicator. Some difficulty in ascertaining the end-point was encountered with the new method so that it was not considered superior to the older one. However, if the precautions be taken to prevent occlusion of alkali which were described above, the results obtained are comparable to those with alkali blue.

As long ago as 1908 Cowie[2] cautioned against establishing too rigid a standard for moisture in resin of scammony because of the readiness with which such resins

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[1] *Jour. Mysore Univ.*, 4 (1930), 241.

[2] *Pharm. J.*, 81 (1908), 365.

absorb moisture. This study shows that this criticism applies also to resin of ipomea. The moisture in the specimens examined varied from 0.65 to 5.25%. An upper limit of 4.0% would appear to be reasonable. The ester numbers ranged from 160.9 to 181.7. A range of from 160 to 185 would be reasonable. The ash ranged from 0.07% to 1.03%. Most of the specimens fell below 0.5% in ash. The upper limit of 0.5% as now required by the U. S. P. appears to be satisfactory. The acid numbers ranged from 8 to 18. A standard for acid number of from 8 to 20 is suggested. The saponification values ranged from 171 to 195. Limits of from 170 to 200 are suggested.

The U. S. P. X specifies that less than 5% of resin of ipomea shall be soluble in petroleum benzin. This test was applied to several of the specimens but, since no criticisms of this test had been received and each of the specimens tested complied with the requirements, not all of the specimens were subjected to the test. The tests for rosin, guaiac and other resins were carried out according to the U. S. P. The results were negative in each instance.

The U. S. P. X requires that from 80% to 90% resin of ipomea shall be soluble in ether. This test was applied to all of the specimens with one exception. Each of the three laboratory specimens complied with the requirements. About one-half of the others did not. It is noteworthy that some of the specimens which were prepared by manufacturers from drugs which they believed to be authentic fell below the U. S. P. X requirement. The portion of the resin which was insoluble in ether was dissolved in alcohol and the solution evaporated on lactose. Administration of these residues to cats indicated that they were physiologically inert.

Only one specimen exceeded 1% of alcohol-insoluble matter and only two contained over 0.5%. The laboratory specimens contained less than 0.1%. A limit of not to exceed 0.5% of alcohol-insoluble material would appear reasonable.

SUMMARY.

Fifteen specimens of resin of ipomea were examined. In most instances the moisture content exceeded the limit permitted by the U. S. P. X (1%). In a few cases the ash exceeded the U. S. P. X limit (0.5%). The acid number, saponification values and ester numbers were lower than are required by the U. S. P. X. In addition to the standards in the U. S. P. X, it is suggested that the alcohol-insoluble fraction and the water-soluble constituents should be determined. The iodine absorption number and the optical rotatory value are not of much value in differentiating between resin of ipomea and true resin of scammony.

ACKNOWLEDGMENTS.

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