

Chemical examination of grindelia. [Pt. I] / by Frederick B. Power and Frank Tutin.

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Publication/Creation

London : Wellcome Chemical Research Laboratories, [1905]

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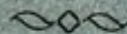
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No. 57

(25)

CHEMICAL EXAMINATION
OF
GRINDELIA

BY
FREDERICK B. POWER, PH.D.
AND
FRANK TUTIN

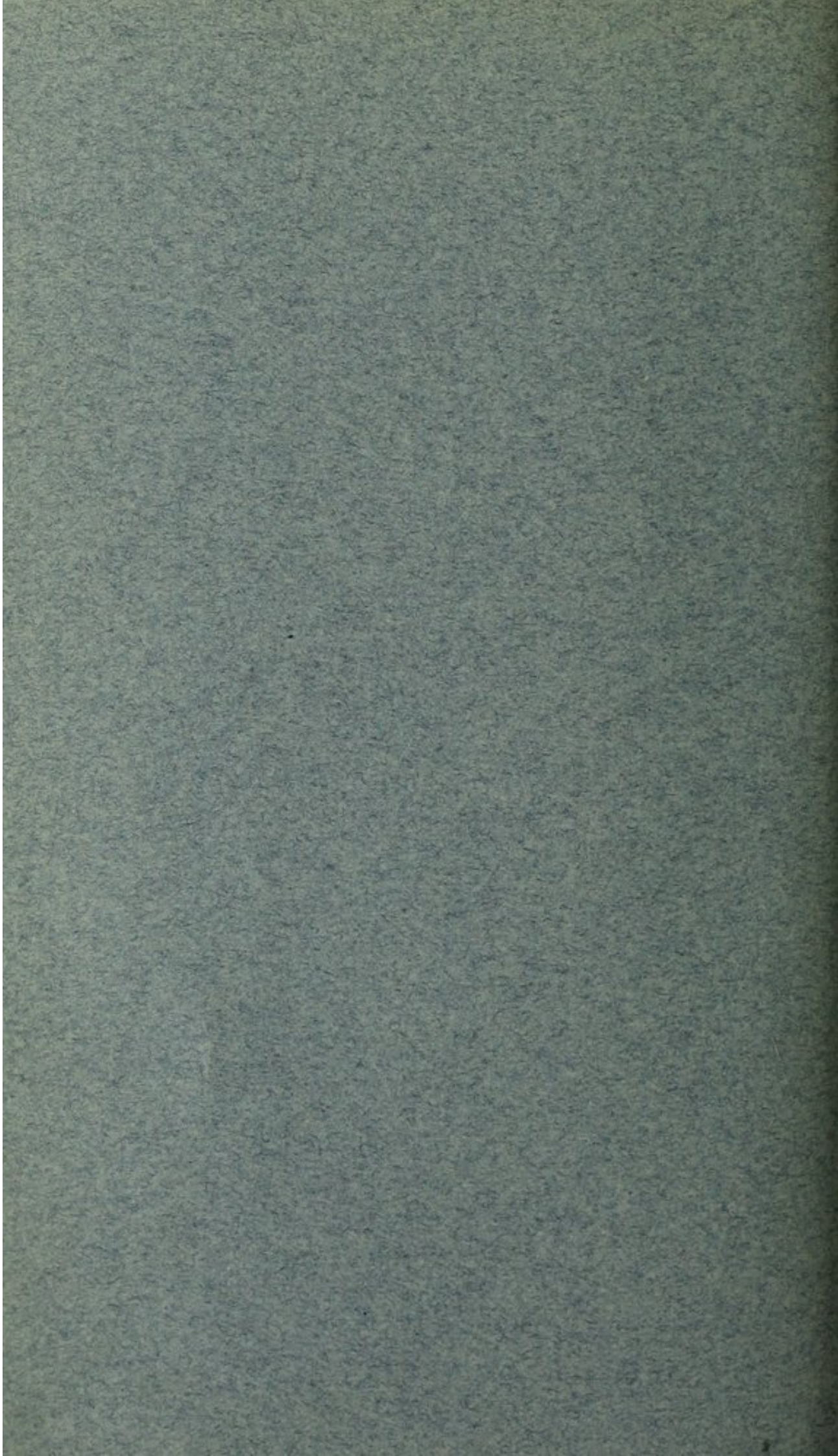


THE WELLCOME CHEMICAL RESEARCH LABORATORIES

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CHEMICAL EXAMINATION OF GRINDELIA.

BY FREDERICK B. POWER, PH. D.,
Director of the Wellcome Chemical Research Laboratories, London,
and
FRANK TUTIN.

Under the title of *Grindelia* the Pharmacopœia of the United States recognizes "the dried leaves and flowering tops of *Grindelia robusta*, Nuttall, or of *Grindelia squarrosa* (Pursh) Dunal." It is also officially recognized under the same designation in the Indian and Colonial Addendum to the British Pharmacopœia.

A description of *Grindelia robusta*, with information concerning its therapeutic uses and the recommendation of suitable pharmaceutical preparations, was given by James G. Steele in a paper communicated to the American Pharmaceutical Association in 1875.*

Although the drug has been used medicinally for a number of years, the chemical examinations which have hitherto been made of it are somewhat incomplete. Moreover, a number of statements respecting substances which have been supposed to be contained in the drug are either of a contradictory nature or, not being accompanied by any analytical data, are exceedingly indefinite and of doubtful accuracy.† For these reasons it does not seem expedient to enter in detail upon a critical review of the existing literature, although consideration may be given to some of the recorded observations pertaining to special substances. Clark, for example (*loc. cit.*), was unable to confirm a statement by Rademaker respecting the occurrence of an alkaloid in the drug, but inferred that it contained "saponin or an allied body," for which the name of *grindelin* was suggested. He, furthermore, considered it probable that the medicinal properties of the Grindelias are due to this substance, and advanced the theory that "the resin found in the drug is wholly a decomposition product of grindelin." Fischer (*loc. cit.*) has indicated that the most important constituents found by him were a crystallizable acid, soluble in water, alcohol, and ether, which he termed "robustic acid," and an alkaloid which was designated as "grindeline," but neither of these substances appear to have been sufficiently characterized. Schneegans (*loc. cit.*) stated that he obtained two glucosides having the characters of saponin, one of which was precipitated by the normal acetate and the other by the

* Proc. A. Ph. A., 1875, 23, p. 637. Compare also *Ibid.*, 1879, 27, p. 609.

† Clark, Amer. Journ. Pharm., 1880, 60, p. 433; Schneegans, *Ibid.*, 1892, 64, p. 369; Fischer, Proc. A. Ph. A., 1888, 36, p. 342; Libby, *Ibid.*, p. 343.

basic acetate of lead. On the other hand, the evidence for an alkaloid was so slight as to lead him to doubt the presence of such a substance.

It is apparent from this brief survey that our knowledge of the constituents of *Grindelia* could not be regarded as satisfactory, and it was, therefore, with the hope of somewhat further elucidating the subject that the present investigation was undertaken.

EXPERIMENTAL.

The material employed for this investigation consisted of an original bale of the drug procured directly from California. Having been obtained from this region, it was evidently *Grindelia robusta*, one of the varieties of the latter, or a closely related species. The material in question was, in fact, found to conform most closely in its characters to the description of *Grindelia camporum*, Greene. There is, however, according to Jepson,* a complete chain from *G. robusta*, Nuttall, var. *Davyi* to *G. camporum*, in which every gradation occurs. The same botanist remarks that "*G. robusta* and its varieties in their extreme forms are more unlike each other than are the species *G. camporum* and *G. rubricaulis*, thus affording an excellent illustration of the principle that, in a highly variable group, varieties of a species may be more unlike than a species is unlike another species."

The drug was of good quality, and in every respect met the requirements of the United States Pharmacopœia.

In order to ascertain the general character of the constituents of the drug, 50 Gm. of it, in moderately fine powder, were extracted successively in a Soxhlet apparatus with the following liquids. After removing the solvents, the residual extracts were dried at 100° C. until of constant weight.

Petroleum (b. p. 40-50° C.) yielded.....	3.63 Gm.=	7.26 per cent.
Ether	"	2.56 " = 5.12 "
Chloroform	"	0.66 " = 1.32 "
Alcohol	"	3.95 " = 7.90 "
Water	"	5.35 " = 10.70 "
	Total	= 32.30 "

The petroleum extract was a light yellowish-brown, viscid substance, which, when heated in the water-oven, formed a thick, oily liquid. The ether and chloroform extracts were dark greenish-brown resins. These three extracts were treated with acidulated water and tested for an alkaloid, but with a negative result. The alcoholic extract was a dark-brown, sticky mass. When treated with acidulated water, the filtered liquid gave a very slight reaction with alkaloid reagents and frothed somewhat on

* Jepson, "Flora of Western Middle California," p. 554.

shaking, but both of these characters were apparently due to proteid substances. The liquid also reduced Fehling's solution, gave a black coloration with ferric chloride, and a very voluminous precipitate with basic lead acetate. The final aqueous extract was of a dark-brown color, and consisted chiefly of gummy substances.

For the more complete examination of the constituents of the drug, 207 pounds of it were finely ground and extracted in a suitable apparatus with hot alcohol. After the removal of the greater portion of the solvent, a soft, dark-brown extract was obtained which weighed 70½ pounds, thus representing 34 per cent. of the weight of the drug. 100 Gm. of this extract, after heating in a water-oven, weighed 87 Gm. The yield of dry extract from the drug was therefore 29.6 per cent. A portion of this was successively extracted in a Soxhlet apparatus with light petroleum, ether and alcohol.

Petroleum (b. p. 40-50° C.) extracted.	46.4 per cent.
Ether.....	38.0 “
Alcohol.	15.6 “
	100.0 per cent.

The petroleum extract was a soft, sticky solid, having a bright green color and the characteristic odor of the drug. It was heavier than water, and did not consist of fatty oil, but, as will be shown later, was of a resinous nature. The ether extract was a dark-green, rather soft resin. The alcoholic extract formed a dark-brown, sticky mass.

Constituents of the Alcoholic Extract of the Drug.

1000 Gm. of the original alcoholic extract were brought into a flask with water, and steam passed through the mixture until oily drops were no longer visible in the condenser. The contents of the flask, when cold, consisted of a dark-brown aqueous liquid (*A*) and a solid cake of resin (*B*). The latter was separated, extracted with a further quantity of hot water to remove any soluble matter, and these washings added to the decanted aqueous liquid.

Examination of the Steam Distillate.

The aqueous distillate had an acid reaction, and contained a small quantity of a *volatile oil* floating on the surface. It was shaken out with pure ether, the ethereal liquid dried with anhydrous sodium sulphate, and the ether removed, when two grams of a bright yellow oil were obtained, corresponding to 0.068 per cent. of the original drug.* The volatile oil possessed in a high degree the characteristic odor of the drug, but the amount was too small for its further examination. The acids contained

* Compare Haensel, Pharm. Zeitung, 1903, No. 57, p. 574, and *Proc. A. Ph. A.* 1904, 52, p. 865.

in the aqueous liquid from which the oil had been removed were converted into their barium salts. The latter rapidly reduced silver nitrate and mercuric chloride, and when warmed with a little ethyl alcohol and sulphuric acid developed the odor of a butyric ester. The volatile acids, therefore, consisted chiefly of *formic acid*, with apparently a little *butyric acid*.

Examination of the Aqueous Liquid (A).

The aqueous liquid from which the resinous substances had been removed, as described in the preceding operation, and which, therefore, contained those constituents of the original alcoholic extract which are soluble in water, had a very dark brown color. It afforded no reaction for an alkaloid, but was abundantly precipitated by both neutral and basic lead acetates. It was, therefore, first completely precipitated by neutral lead acetate, the yellowish-brown precipitate collected, and washed with a little water. To the filtrate from this precipitate a solution of basic lead acetate was added until no further precipitate was produced. This precipitate, which was much more voluminous than the preceding one and had a bright lemon-yellow color, was also collected, and washed with a little water. The filtrate from the latter precipitate was finally deprived of lead by means of hydrogen sulphide, and filtered.

Precipitate produced by Neutral Lead Acetate.—This was suspended in water and treated with hydrogen sulphide until the lead had become completely converted into sulphide, the liquid then heated to the boiling-point, and filtered. On cooling, a quantity of tarry matter separated, which was removed by filtration, and the liquid was then concentrated under diminished pressure, when a further quantity of a dark reddish-brown tarry substance was deposited. The filtrate from the latter, when further concentrated, formed a thick, dark-brown syrup, from which nothing crystalline could be obtained.

Precipitate produced by Basic Lead Acetate.—This was treated in precisely the same manner as the preceding precipitate, and yielded ultimately only a small amount of tarry and resinous substances.

Neither of the liquids obtained from the above-mentioned lead precipitates produced any characteristic froth when vigorously shaken, and there was, therefore, no evidence of the presence in *Grindelia* of substances belonging to the class of saponins, as had been assumed by Clark and by Schneegans (*loc. cit.*).

Filtrate from the Precipitate produced by Basic Lead Acetate.—This liquid, as previously stated, was deprived of lead by means of hydrogen sulphide, and filtered. It was then of a light brownish-yellow color, and, when concentrated under diminished pressure, formed a thick, brownish syrup. It gave no reaction for alkaloids, but when warmed with a solution of potassium hydroxide evolved an abundance of ammonia, thus indicating the presence of *proteid substances* or their degradation products. A

portion of the liquid was decolorized by means of animal charcoal, and then allowed to remain for some time in a vacuum over sulphuric acid, but no crystalline substance separated. The syrupy liquid was lævoptatory, and readily afforded a crystalline osazone, which melted at 205–206° C. The sugar present in the liquid was, therefore, apparently *l*-glucose.

Examination of the Resins (B).

The mixture of resinous substances obtained by the treatment of 1000 Gm. of the original alcoholic extract of the drug with water, as previously described, was dried in a water-oven, and then weighed 637 Gm. For the further examination of this product it was mixed with purified sawdust, the mixture dried as completely as possible, and then extracted successively in a Soxhlet apparatus with light petroleum, ether and alcohol. After the removal of the respective solvents, the residual extracts were dried in a water-oven.

Petroleum (b. p. 40–50° C.) extracted	40.2	per cent.
Ether "	49.8	"
Alcohol "	8.2	"
Loss.....	1.8	"
	100.0	

I. Petroleum Extract of the Resins.

This extract consisted of a soft, sticky solid, having a dark greenish color. 228 Gm. of it were mixed with an alcoholic solution of 60 Gm. of potassium hydroxide, this amount of alkali being about 1½ times that required to hydrolyze an equal weight of tri-stearin. On heating, the liquid rapidly became black and a very large amount of ammonia was evolved. After boiling the mixture for half an hour the evolution of ammonia ceased, but as the addition of another 10 Gm. of caustic potash caused the further development of ammonia, 30 Gm. more of alkali were added in order to ensure complete hydrolysis, and the boiling was then continued for 1½ hours. The alcohol having been removed by distillation, the residual alkaline mixture was diluted with water, and shaken out with six successive portions of ether. The ethereal liquid was washed with water, dried with calcium chloride, and the ether removed, when an orange-colored crystalline residue was obtained. This was purified by dissolving it in warm alcohol and treatment with animal charcoal, when, on cooling, about 5 Gm. of a crystalline substance separated. After recrystallization from ethyl acetate, it was obtained in the form of glistening, pearly plates, melting at 68° C. It was analyzed with the following result: 0.1344 gave 0.4176 CO₂ and 0.1760 H₂O. C = 84.7; H = 14.5. C₃₁H₆₄ requires C = 85.3; H = 14.7 per cent.

The substance was thus identified as *hentriacontane*, a hydrocarbon

which has recently been found by us in *Gymnema* leaves,* and has also been isolated from Kô-sam seeds † and from the leaf of tobacco. ‡

The alcoholic mother-liquors from the hentriacontane, when concentrated and allowed to stand for some time, afforded a small amount of another substance in the form of glistening plates. These were separated from the syrupy liquid and recrystallized from alcohol, when, after drying at 100° C., they melted at 164° C. The air-dried substance was analyzed :

0.0621 gave 0.1821 CO₂ and 0.0651 H₂O. C=80.0 ; H=11.6.

C₂₆H₄₄O, H₂O requires C=80.0 ; H=11.8 per cent.

C₂₄H₄₀O, H₂O requires C=79.6 ; H=11.6 per cent.

In order to obtain a further quantity of this substance, 3000 grams of the original alcoholic extract were boiled with an excess of an alcoholic solution of potassium hydroxide, the liquid then diluted with water, and shaken out several times with ether. The ethereal liquid afforded a residue which was fractionally crystallized from alcohol in order to remove the hentriacontane, and the substance obtained from the mother-liquors, after being recrystallized several times from a mixture of ethyl acetate and alcohol, was finally crystallized from alcohol. It then melted at 166° C., and this melting-point was not altered by further crystallization.

0.1097 on drying at 110° C. lost 0.0051 H₂O. H₂O=4.6.

C₂₆H₄₄O, H₂O requires H₂O=4.6 per cent.

C₂₄H₄₀O, H₂O requires H₂O=5.0 per cent.

0.1046 of anhydrous substance gave 0.3185 CO₂ and 0.1092 H₂O.

C=83.0 ; H=11.6 per cent.

C₂₆H₄₄O requires C=83.9 ; H=11.8 per cent.

C₂₄H₄₀O requires C=83.7 ; H=11.6 per cent.

When a small quantity of this substance was dissolved in chloroform, a little acetic anhydride added, and then a drop of concentrated sulphuric acid, a rose color was at once produced which rapidly changed to violet, then to an intense blue, and, on long standing, became dark-green and finally brown. It is evident from these characters that the substance is either an isomeride of phytosterol or a lower homologue.

The strongly alkaline solution of the petroleum extract from which the hentriacontane and phytosterol had been obtained was acidified with sulphuric acid, when a considerable quantity of dark-brown, tarry matter separated. It was then distilled in steam, when an acid distillate was obtained which contained a small amount of oily substance. The distillate was therefore extracted with ether, and from the acid removed by the latter a barium salt was prepared, which was subsequently converted into a silver salt. This was dried in a vacuum over sulphuric acid and analyzed.

* Year-Book of Pharmacy, 1904, p. 531.

† Power and Lees, *Ibid.*, 1903, p. 512.

‡ Thorpe, Journ. Chem. Soc., 1901, 79, p. 985.

0.2337 gave on ignition 0.1162 Ag. Ag = 49.7 per cent.

As silver valerate and silver caproate require respectively 51.7 and 48.4 per cent. of silver, the oily acid was apparently a mixture. In the distillate, after extraction with ether, *formic acid* was identified.

The liquid remaining in the distillation flask was extracted with ether, which removed a quantity of a dark-brown, tarry substance of disagreeable odor. This was soluble in all the ordinary organic solvents, and nothing crystalline could be obtained from it. 20 Gm. of this tarry substance were fused with 100 Gm. of potassium hydroxide. The temperature of the melted mass, which was at first about 130° C., was gradually increased to 280° C., and maintained at that point for some time, but a portion of the substance still remained undissolved and formed an oily layer on the surface. After being allowed to cool, the mass was dissolved in hot water and the liquid acidified with sulphuric acid, when a quantity of a black resin separated. The mixture was then distilled in steam, and yielded an acid distillate which contained a few oily drops having an odor of valeric acid. It was extracted with ether, but the amount of acid removed by the latter was too small for analysis. The acids remaining in the distillate were converted into barium salts, and from the concentrated solution of the latter a crystalline salt separated, which was dried at 110° C., and analyzed.

0.3026 of the salt gave 0.2768 BaSO₄. Ba = 53.8 per cent.

Ba (C₂H₃O₂)₂ requires Ba = 53.8 per cent.

The mother-liquors from this salt contained an abundance of barium formate.

The volatile acids formed by the fusion of the above-mentioned tarry substance with alkali therefore consisted chiefly of *acetic* and *formic acids*.

The liquid remaining in the distillation flask, after the removal of the resin, was extracted with ether, but this afforded only a very small amount of an oily substance of indefinite character.

The results of our examination of the portion of *Grindelia* resin which is soluble in light petroleum, do not enable us to confirm the observation of Clark * respecting the presence of a fatty oil. The latter investigator although apparently having used but 100 Gm. of the crude drug for extraction with petroleum, states that he obtained "a fixed oil which was solid at ordinary temperatures, melting at 37° C." It was furthermore stated that, after saponification of the oil, "non-volatile fatty acids were obtained, which were separated by fractional precipitation with magnesium acetate, and found to consist of palmitic, stearic, and oleic acids. He has, however, recorded no analyses, nor given any other evidence of the identity of these substances.

* Amer. Journ. Pharm., 1888, 60, p. 435.

II. Ether Extract of the Resins.

This was a very dark-colored solid, and, as it appeared to contain no crystalline substance, it was thought of some interest to ascertain the character of the products afforded by its fusion with caustic alkali. 48 Gm. of the resin were therefore added to 250 Gm. of potassium hydroxide, previously dissolved in a little water and heated to about 100° C. The heating was then continued until a temperature of 250° C. was gradually attained, when the resin formed a slimy black mass on the surface of the fused alkali. After being allowed to cool, the mass was boiled with water, when it entirely dissolved, forming a dark reddish-brown liquid. This was acidified with sulphuric acid, which caused the separation of a considerable quantity of black resin, and then distilled in steam. The acid distillate, which contained some oily drops having the odor of valeric acid, was extracted with ether. After the removal of the ether, the acid was converted into a barium salt, from which, by fractional precipitation with silver nitrate, three silver salts were subsequently obtained.

First Fraction.—This became decomposed, owing to the presence of a little formic acid.

Second Fraction.—This was washed with water, dried on a tile, and finally in a vacuum.

0.0724 gave on ignition 0.0348 Ag. Ag = 48.1 per cent.

Ag C₆H₁₁O₂ requires Ag = 48.4 per cent.

Third Fraction.—This was much more readily soluble in water than the preceding fraction.

0.1812 gave on ignition 0.1096 Ag. Ag = 60.4 per cent.

Ag C₃H₅O₂ requires Ag = 59.7 per cent.

Ag C₂H₃O₂ requires Ag = 64.7 per cent.

The acids remaining in the distillate after extraction with ether were converted into barium salts. The solution of the latter was found to contain a considerable amount of formate, and when concentrated a crystalline salt separated. This was recrystallized from water, dried at 110° C., and analyzed.

0.3334 gave 0.3049 BaSO₄. Ba = 53.8 per cent.

Ba (C₂H₃O₂)₂ requires Ba = 53.8 per cent.

The volatile acids formed by the fusion of the ether-soluble resin with caustic alkali were therefore chiefly *formic* and *acetic*, with small amounts of some higher acids of the same series.

The liquid remaining in the distillation flask was allowed to cool, decanted from a large amount of resinous matter, and repeatedly extracted with ether. The ethereal liquid yielded a residue which, after solution in water and treatment with animal charcoal, separated in a crystalline form. It was further purified by recrystallization from water, when 0.46 Gm. of a colorless substance was obtained, which melted at 194° C. and gave the color-reactions characteristic of protocatechuic acid. The substance was dried at 110° C. and analyzed.

0.1411 gave 0.2973 CO₂ and 0.0536 H₂O. C = 57.4; H = 4.2.

C₇H₆O₄ + C₇H₆O₃ requires C = 57.5; H = 4.1 per cent.

This substance evidently represents the *molecular compound of protocatechuic and para-oxybenzoic acids*, which is produced by the fusion of certain resins with caustic alkali, and was recently obtained by us by this means from the so-called gymnemic acid of gymnema leaves.*

III. Alcohol Extract of the Resins.

This was a firm, black, amorphous solid. As previously indicated, it represented but a relatively small proportion of the total resin, and, as it apparently contained no crystalline substance, it was subjected to no further treatment.

SUMMARY.

The result of this investigation may be briefly summarized as follows:

The chief constituents of *Grindelia* are amorphous resins, to which its medicinal value is probably to be attributed.

The total amount of resinous substances contained in the official drug, as determined by extracting it with hot alcohol and treating this extract with water, was found to be 21.6 per cent. These resins represent a complex mixture, which, by successive extraction with light petroleum, ether, and alcohol, was resolved into the following products:

I. *Petroleum Extract of the Resins*.—This was a soft, sticky solid, of a greenish color. It was of a resinous nature, and did not consist of fatty oil, which a previous investigator stated to have obtained from the drug by extraction with petroleum. When heated with an alcoholic solution of potassium hydroxide, it evolved a large amount of ammonia. From this alkaline liquid ether extracted a crystalline hydrocarbon, *hentriacontane*, C₃₁H₆₄, and another crystalline substance, melting at 166° C., which is either an isomeride of *phytosterol*, C₂₆H₄₄O, or a lower homologue. On subsequently acidifying the alkaline liquid with sulphuric acid, a quantity of dark-brown, tarry matter separated, and this mixture, when distilled, yielded *formic acid*, with a very small amount of a mixture of higher fatty acids. The liquid containing the tarry matter was extracted with ether, which removed a quantity of a dark-colored, amorphous product. This when fused with caustic potash yielded chiefly *formic* and *acetic acids*.

II. *Ether Extract of the Resins*.—This was a dark-colored resin, from which no crystalline substance could be separated. When fused with caustic potash, it yielded *formic*, *acetic*, and *some higher acids* of the same series, together with a crystalline substance, melting at 194° C., corresponding to the *molecular compound of protocatechuic and para-oxybenzoic acids*.

* Year-Book of Pharmacy, 1904, p. 537, and Beilstein's Handbuch der organischen Chemie, Bd II, p. 1740.

III. *Alcohol Extract of the Resins.*—This was a very dark-colored, amorphous substance. It represented but a relatively small proportion of the total resin, and did not admit of further examination.

In addition to the above-mentioned resinous substances, *Grindelia* contains a considerable amount of a lævo-rotatory sugar, which afforded an osazone melting at 205–206° C., and is apparently *l-glucose*. It also contains *proteid substances*, amorphous *coloring matter* and *tannin*, and an exceedingly small amount of an *essential oil*, possessing the characteristic odor of the drug.

We are unable to confirm the observations of previous investigators respecting the presence of a saponin or an alkaloid.

