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CHEMICAL EXAMINATION
OF
GRINDELIA

PART II.

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[A Contribution from the Wellcome Chemical Research Laboratories, London.]

In a paper communicated to this Association at the meeting held in Atlantic City, N. J., in September, 1905 (Proc. A. Ph. A., 1905, 53, p. 193), the authors described the results of a general examination of the constituents of *Grindelia*. The material employed in that investigation consisted of an original bale of the drug obtained from California, and it was stated that it conformed most closely in its characters to the description of *Grindelia camporum*, Greene. That the drug was, in fact, *G. camporum*, has since been confirmed by Dr. Willis L. Jepson (compare P. E. F. Perrédès, Proc. A. Ph. A., 1906, 54, p. 370).

In the above-mentioned communication the isolation of the hydrocarbon hentriacontane, $C_{31}H_{64}$, and of a new phytosterol (m. p. 166° C.) were recorded, and it was also noted that the drug contained a considerable amount of *l*-glucose, together with tannin, amorphous coloring matter, and small amounts of formic acid and an essential oil. It was, however, particularly stated that the chief constituents of *Grindelia* are amorphous resins, and with the object of more completely examining the latter, especially the portion soluble in petroleum, the investigation has been continued.

The material used in the present investigation was a further portion of the identical extract of *Grindelia* which had previously been employed. During the two years which had elapsed since this extract was first examined a portion of the chlorophyll had become altered, but otherwise it appeared to be unchanged. The extract was mixed with water and subjected to steam distillation for the removal of the volatile constituents, after which the cake of resins was separated from the aqueous liquid, and thoroughly washed. These resins were mixed with purified sawdust, the mixture dried, and extracted successively in a Soxhlet apparatus with light petroleum (b. p. $33-50^{\circ}$ C.) and ether. The portion of the resins which remained undissolved by this treatment amounted to only about 8 per cent. of the whole. As stated in the previous paper (*loc. cit.*), this portion of the resin appeared to contain nothing crystalline, and being for the most part only soluble in alcohol, it has not been further examined.

Examination of the Petroleum Extract of the Resins.

The petroleum extract of the resins was, at the ordinary temperature, a soft, very sticky solid, but when warmed it rapidly melted to a thick, oily liquid, which was specifically heavier than water. It was dissolved in

ether, and the ethereal solution shaken with 10 per cent. sulphuric acid. As nothing was removed by this treatment, the ethereal liquid was repeatedly extracted with a strong solution of sodium carbonate. The alkaline liquid thus obtained possessed a dark greenish color, and had the characters of a soap solution. It was acidified with sulphuric acid, when a sticky oil was precipitated, which was extracted with ether. On evaporating the ethereal liquid a mixture of acids was obtained, which amounted to more than one-half of the original petroleum extract, and when freed from solvent, formed an extremely sticky, soft mass. It possessed a strongly acid reaction, and could be distilled under diminished pressure without suffering decomposition, but this operation was rendered extremely difficult on account of the viscous nature of the material. The crude mixture of acids was therefore dissolved in about six times its volume of warm methyl alcohol, when, on allowing the solution to stand, it deposited a small amount of a crystalline solid. This was collected on a filter, and recrystallized from ethyl acetate, when it was found to melt at $81-82^{\circ}\text{C}$. It was analyzed with the following result:

0.0993 gave 0.2871 CO_2 and 0.1176 H_2O . $\text{C} = 78.9$; $\text{H} = 13.2$.
 $\text{C}_{27}\text{H}_{54}\text{O}_2$ requires $\text{C} = 79.0$; $\text{H} = 13.2$ per cent.

This acid agrees in composition with *cerotic acid*, and is probably identical with it, although the observed melting-point ($81-82^{\circ}\text{C}$.) is somewhat higher than that recorded (79°C .) for the latter acid.

The acids contained in the methyl alcoholic filtrate from this solid acid were converted into their methyl esters by passing dry hydrogen chloride into the boiling liquid for two hours. The resulting esters were isolated in the usual manner, and repeatedly submitted to a systematic process of fractional distillation under a pressure of 20 Mm., when the following fractions were collected: (I) About $150-200^{\circ}$; (II) $200-215^{\circ}$; (III) $215-225^{\circ}$; (IV) $225-230^{\circ}$; (V) $230-235^{\circ}$; (VI) $235-240^{\circ}$; (VII) $240-245^{\circ}$; (VIII) $245-250^{\circ}$; (IX) $250-260^{\circ}$; (X) $260-270^{\circ}$; (XI) above 270°C . / 20 Mm.

All these fractions possessed a brownish-yellow color, although No. I, on standing, rapidly darkened. The lower fractions were fairly mobile liquids, but with the increase of temperature at which the fractions were collected their viscosity also became progressively greater, the last two fractions being sticky solids. The results of the examination of the various fractions indicated that they represented an extremely complex mixture, as will be seen by reference to the following table:

Fraction Number.	Boiling-point at 20 Mm.	Weight in Grams.	Density at 20° C.	Specific Rotation.	Analysis C %; H %.	Iodine Value.	Saponification Value.
I	150-200° C.	4.50	0.9826	+ 7.4°	75.8; 10.1	81.0	—
II	200-215° C.	5.25	0.9743	+ 0.5°	78.8; 10.8	104.2	—
III	215-225° C.	10.40	0.9869	— 6.9°	78.8; 10.5	103.8	7.0; 9.0 and 9.7
IV	225-230° C.	8.47	1.0037	— 8.8°	78.1; 10.5	86.4	—
V	230-235° C.	9.18	1.0147	— 9.1°	77.5; 10.3	72.4	10.0
VI	235-240° C.	9.30	1.0312	— 10.5°	76.8; 10.2	62.9	—
VII	240-245° C.	8.39	1.0432	— 8.3°	75.6; 10.6	56.2	—
VIII	245-250° C.	10.22	1.0535	— 5.8°	74.0; 9.7	48.8	11.5
IX	250-260° C.	9.05	1.0634	— 1.8°	74.9; 9.7	41.2	—
X	260-270° C.	3.92	—	+ 2.2°	74.2; 9.8	40.3	—
XI	Above 270° C.	1.70	—	—	—	—	—

For the purpose of comparison the density of a fraction (b. p. 215-225° C. / 20 Mm.) of methyl esters of fatty acids, consisting largely of methyl oleate, was determined, and found to be 0.8784 at 20° C.

Fraction I boiled over a wide range of temperature, and was obviously a mixture. The analyses of fractions II and III agree with the formula $C_{20}H_{32}O_2$, but this formula is not in harmony with the iodine value of these fractions, thus indicating them to be mixtures. The numbers obtained for the saponification value of fraction III varied considerably (7.0 to 9.7), and were all lower than the theoretical value (13.1) for an ester possessing the above formula. It was found that this was due to the fact that this fraction consisted partially of an ester which was saponified only with great difficulty. A quantity of fraction III was therefore boiled for two hours with an excess of alcoholic potash, the alcohol removed, and the unsaponified ester isolated by means of ether. This ester was distilled under diminished pressure and analyzed:

0.1260 gave 0.3813 CO_2 and 0.1170 H_2O . C = 82.5; H = 10.3.

$C_{31}H_{46}O_2$ requires C = 82.7; H = 10.2 per cent.

On acidifying the alkaline liquid from which this ester had been removed an acid was precipitated, which, when isolated by means of ether, was obtained as a very thick oil. It deposited, on standing, a trace of crystalline substance, and this, after being collected and recrystallized, was found to possess the properties of *palmitic acid*. Fraction III was, therefore, a mixture of esters.

The results obtained by the analysis of fraction V agree with the formula $C_{25}H_{40}O_3$. The saponification value (10.0) is also in harmony with this formula ($C_{25}H_{40}O_3$ requiring 10.3), whilst the iodine value (72.4) is not far removed from that required for an ester $C_{25}H_{40}O_3$ containing one double linking, namely, 65.5. It therefore appears probable that an acid possessing a formula approximating to $C_{24}H_{38}O_3$ is present in *Grindelia*,

and as this acid contains only one double linking, it may be assumed that a benzene nucleus is also present in its structure. In view of this consideration a quantity of the ester was oxidized by means of a chromic acid mixture, with the hope of isolating a known benzene derivative from the products, but only resins were obtained. The acid produced by the hydrolysis of fraction V was an extremely viscous liquid, and nothing crystalline could be obtained from it. Fraction VI was evidently similar to the preceding one, whilst the fractions of higher boiling-point, although obviously mixtures, would appear to contain esters of more highly oxygenated acids. It is evident from a consideration of the iodine values of the above fractions of esters, together with the amount of hydrogen which they respectively contain, that cyclic compounds must be present in each of them.

The original ethereal liquid, which, after extraction with sodium carbonate, still contained the non-acidic constituents of the petroleum extract, was shaken with a 10 per cent. solution of potassium hydroxide. This treatment removed nothing, but on washing the ethereal liquid with water, after separating the alkaline solution, a deep green, aqueous liquid was obtained. This evidently contained that portion of the chlorophyll which had been present in the petroleum extract. It was separated from the ethereal liquid, acidified with sulphuric acid, and extracted with ether, when, on removing the solvent, a quantity of a bright green, resinous substance was obtained. This product, which consisted of chlorophyll, evolved ammonia when boiled with alcoholic potash, and since none of the other constituents of the petroleum extract contained nitrogen, it must have been the source of the ammonia which, as noted in the previous communication (*loc. cit.*), was evolved in considerable amount on boiling the entire petroleum extract with the alcoholic alkali.

The ethereal liquid, which now no longer contained any acidic or phenolic substances, was dried, and the ether removed. The residual fatty matter was dissolved in alcohol, and boiled for two hours with an excess of an alcoholic solution of potassium hydroxide. The alcohol was then removed, water added, and the resulting liquid repeatedly extracted with ether. During the first extraction a small quantity of a flocculent precipitate accumulated in the lower portion of the ethereal layer. This solid was collected on a filter, well washed with warm ether, and dried. On examination it was found to be the potassium salt of a fatty acid, for, when treated with sulphuric acid, it afforded an acid which crystallized from ethyl acetate in leaflets melting at 84°C . This was analyzed with the following result:

0.1119 gave 0.3245 CO_2 and 0.1340 H_2O . $\text{C} = 79.1$; $\text{H} = 13.3$.
 $\text{C}_{27}\text{H}_{54}\text{O}_2$ requires $\text{C} = 79.0$; $\text{H} = 13.2$ per cent.

This substance appears to be identical with the acid melting at $81\text{--}82^{\circ}\text{C}$.,

previously obtained, and is presumably *cerotic acid*, although the possibility of its being a higher homologue of the latter is not excluded.

The product obtained on evaporation of the ethereal extracts of the alkaline liquid was shown in the previous communication to contain hentriacontane, $C_{31}H_{64}$, and a small amount of a phytosterol (m. p. 166° C.). On submitting this product to fractional distillation under diminished pressure, evidence has now been obtained that a small quantity of a hydrocarbon other than hentriacontane is also present. This second hydrocarbon melts at a temperature lower than that at which the one previously isolated fuses, but it could not be isolated in a state of purity. The alkaline liquid from which the unsaponifiable matter had been removed was acidified with sulphuric acid, and the acids which separated were extracted by means of ether. The ethereal solution of these acids was evaporated to a small bulk, and a considerable volume of light petroleum then added, which caused the separation of a small amount of a brown, resinous product. This product, from which the clear liquid was decanted, was heated with methyl alcohol and dry hydrogen chloride, when it afforded a little resin and a viscous mixture of esters resembling the higher fractions of the esters obtained from the free acids previously described. The clear petroleum liquid was evaporated, and the residual acids converted into their methyl esters in the manner above described. The product thus obtained was not nearly so large in amount as the esters prepared from the free acids, but resembled the latter esters in its general properties. It was distilled under a pressure of 20 Mm., when the following fractions were collected: (I) Below 210° ; (II) $210-230^{\circ}$; (III) $230-240^{\circ}$; (IV) $240-250^{\circ}$; (V) $250-260^{\circ}$; (VI) above 260° C./20 Mm.

Fractions II, III, and IV were the largest, the remainder being only small in amount. The specific rotations of these three principal fractions varied from $[\alpha]_D -20.0^{\circ}$ to -22.6° , and their densities from 0.9422 to 0.9844 at 20° C. All the fractions were obviously mixtures, and appeared to contain esters similar to those prepared from the free acids. On analysis, fraction II gave C = 76.3; H = 11.1 per cent., and when hydrolysed it yielded an oily acid, which, on standing, deposited a small quantity of a crystalline solid. This substance was separated and recrystallized, after which it melted at 62° C., and appeared to be identical with the solid acid obtained from fraction III of the esters of the free acids. The amount of crystalline acid isolated in this latter case was, however, rather larger than that previously obtained. It was analyzed with the following result:

0.1069 gave 0.2968 CO_2 and 0.1211 H_2O . C = 75.7; H = 12.6.

$C_{16}H_{32}O_2$ requires C = 75.0; H = 12.5 per cent.

$C_{18}H_{36}O_2$ requires C = 76.1; H = 12.7 per cent.

This crystalline solid would, therefore, appear to be a mixture of *palmitic* and *stearic acids*.

Examination of the Ether Extract of the Resins.

When the resins no longer yielded anything to petroleum they were submitted to a prolonged extraction with purified ether. The entire ethereal solution thus obtained was concentrated to the volume of about one litre, and this liquid allowed to stand over night, when it deposited a small amount of a black, tarry resin, together with a little of a *substance* in the form of crystalline plates. The dark-green liquid was then decanted from the resin, and the crystalline substance collected on a filter and washed with ether. The small amount of black resin also contained a little of this crystalline substance, but nothing else could be isolated from it. The crystalline compound was insoluble, or nearly so, in most solvents, but could be dissolved in a moderate volume of boiling glacial acetic acid, from which it separated in handsome, crystalline plates, melting at 256–257° C. On analysis it gave the following result :

0.1033 gave 0.2755 CO₂ and 0.0951 H₂O. C = 72.7; H = 10.2.

C₁₇H₂₈O₃ requires C = 72.9; H = 10.0 per cent.

C₂₃H₃₈O₄ “ C = 73.0; H = 10.1 per cent.

The amount of this substance obtained from 2500 Gm. of *Grindelia* extract (representing 7353 Gm. of the air-dried drug) was only about 0.2 Gm., and it was therefore impossible to decide which of the above two formulas should correctly be assigned to it, but apparently it is not identical with any substance hitherto described. When treated with sodium methoxide and methyl iodide, it did not undergo methylation, but on boiling with acetic anhydride it yielded an *acetyl derivative*, and was, therefore, an alcohol. This acetyl derivative, when separated from anhydrous solvents, was obtained in the form of a jelly, but, on cooling its solution in dilute alcohol or in dilute acetic acid, it formed colorless needles, which, after drying at 100° C., melted at 161° C.

The filtered ethereal solution of the readily soluble constituents of the ether extract of the resins was subsequently extracted with successive portions of a strong solution of sodium carbonate so long as anything was removed by this treatment. The first two or three shakings with alkali yielded rather thick, dark brown liquids, which, when acidified and extracted with ether, afforded a large quantity of a brown resin. This product represented by far the greater part of the ether-soluble portion of the resins, but nothing crystalline could be obtained from it. The aqueous liquids obtained by all the subsequent extractions with alkali were not mixed, but were separately examined. Each of them, on standing, separated into two layers, the lower of which was a clear, yellowish-brown liquid, whilst the upper one was rather thick, and dark greenish-brown in color. All the dark colored aqueous liquids, on acidification, afforded only resins, but the examination of the clear, yellowish liquids was at-

tended with a different result. The material obtained on acidifying the first two of these yellowish-brown liquids consisted only of a little resin, but each of the remaining seven or eight portions of alkaline liquid, when acidified, afforded a small amount of a product which, when dissolved in ethyl acetate, and the solution allowed slowly to evaporate, gave a little of a yellow, crystalline solid. This *substance* was collected on a filter, washed with ethyl acetate, and then recrystallized from this solvent, when it was obtained in tufts of yellow prisms which melted at $227-228^{\circ}\text{C}$. On analysis the following results were obtained :

0.0998 gave 0.2358 CO_2 and 0.0409 H_2O . $\text{C} = 64.4$; $\text{H} = 4.6$

0.1042 gave 0.2473 CO_2 and 0.0449 H_2O . $\text{C} = 64.7$; $\text{H} = 4.8$

$\text{C}_{14}\text{H}_{12}\text{O}_5$ requires $\text{C} = 64.6$; $\text{H} = 4.6$ per cent.

This substance appears to be of a phenolic nature, and, as far as can be ascertained, it is not identical with any compound heretofore described. A small quantity of it was boiled with acetic anhydride, when it underwent acetylation. The resulting *acetyl derivative* was crystallized twice from ethyl acetate, when it formed pale yellow, needle-shaped crystals, which melted at 154°C .

The ethereal liquid, from which the above-mentioned yellow, phenolic substance had been extracted by means of sodium carbonate, was shaken with a 10 per cent. solution of potassium hydroxide, but this yielded a dark greenish-brown liquid from which only a little resin could be obtained. The remaining ethereal liquid, after being washed with water, which removed a little chlorophyll, was dried, and the ether removed. The residue was small in amount, and consisted of a soft, bright green resin, from which nothing crystalline could be obtained.

SUMMARY AND CONCLUSIONS.

From this investigation it is seen that that portion of the *Grindelia* resins which is soluble in petroleum consists, to a large extent, of a complex mixture of liquid *acids*. These acids are, for the most part, optically active, unsaturated cyclic compounds. Some of them are oxy-acids and appear to contain benzene nuclei. A very small amount of *cerotic acid*, and apparently a trace of palmitic acid, are also present in *Grindelia*. The large amount of ammonia which, as stated in our previous communication (Proc. A. Ph. A., 1905, 53, p. 197), was evolved on boiling the petroleum extract of the resins with alcoholic potash, is now shown to have been derived from the chlorophyll present in this extract.

The non-acidic portion of the petroleum extract was previously shown to contain a new *phytosterol* (m. p. 166°C .) and the hydrocarbon *hentriacotane*, $\text{C}_{31}\text{H}_{64}$, whilst evidence has now been obtained that a small amount of another *hydrocarbon* is also present. It consists, however, for the most part, of a complex mixture of esters, presumably glycerides.

The acids obtained by the hydrolysis of these esters possessed a considerable degree of optical activity, and appeared to be similar to those which occur in a free state, but the only products that could be isolated from them were small amounts of *cerotic acid*, and a mixture of *palmitic* and *stearic acids*.

The ether extract of the resins consists, to a very large extent, of a mixture of amorphous products, but very small amounts of a *colorless crystalline alcohol* and a *yellow substance of phenolic nature*, both of which are apparently new compounds, were obtained from it. The alcoholic body possesses either the formula $C_{17}H_{28}O_3$ or $C_{23}H_{38}O_4$. It crystallizes in plates melting at $256-257^\circ C.$, and yields an acetyl derivative melting at $161^\circ C.$ The yellow phenolic substance crystallizes in prisms melting at $227-228^\circ C.$, and possesses the formula $C_{14}H_{12}O_5$. It gives an acetyl derivative melting at $154^\circ C.$

All the crystalline substances which have been isolated from the *Grindelia* resins, with the exception of the hentriacontane, occur in exceedingly small amounts, and their isolation in quantities sufficient for examination has only been rendered possible by the employment of large quantities of material.



