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Contributors

Power, Frederick B. 1853-1927.
Tutin, Frank.
Royal College of Surgeons of England

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FREDERICK B. POWER, PH.D.

AND

FRANK TUTIN

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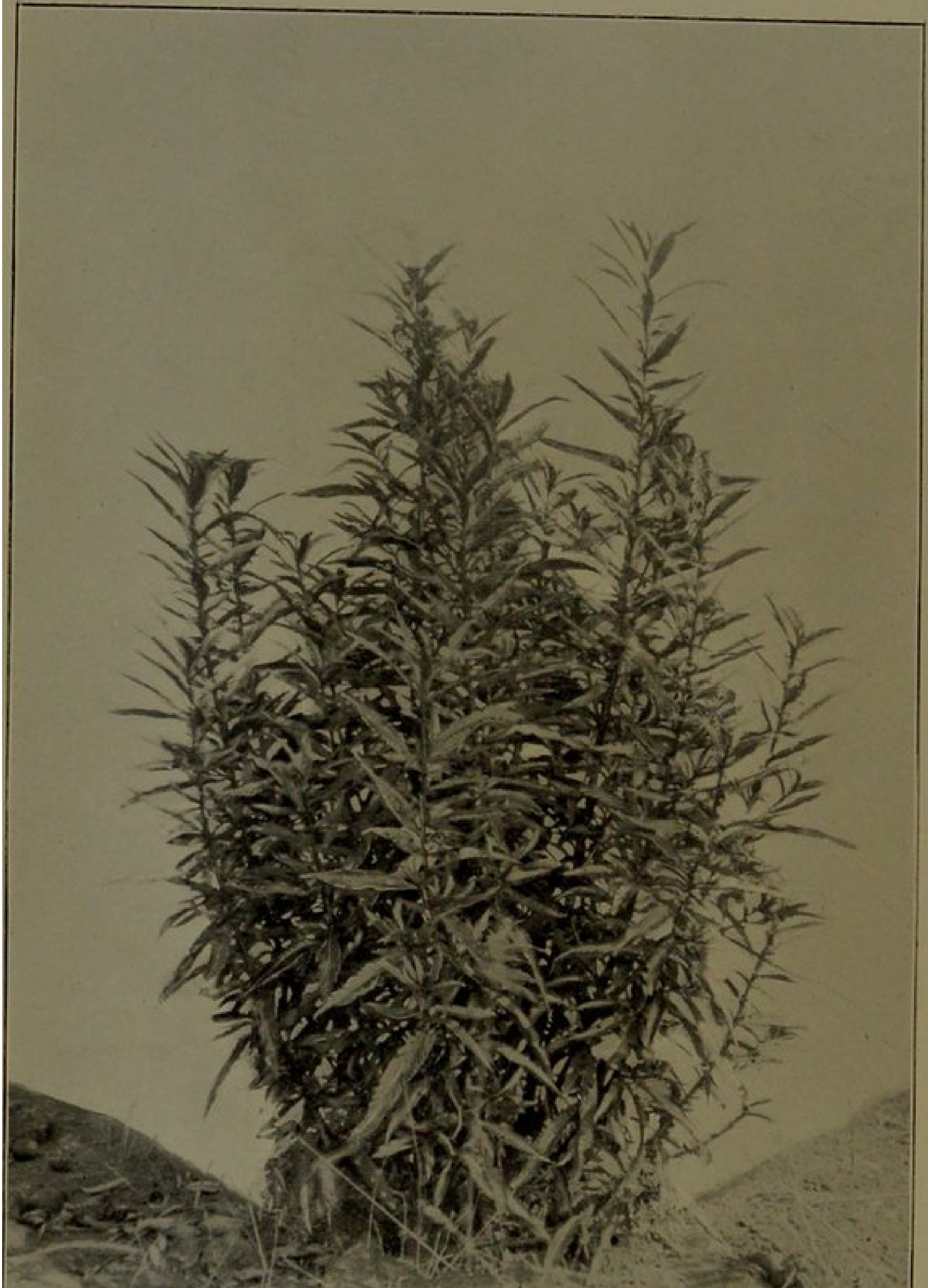
THE WELLCOME CHEMICAL RESEARCH LABORATORIES
FREDERICK B. POWER, PH.D., *Director*
6, King Street, Snow Hill
LONDON, E.C.



ERIODICTYON CALIFORNICUM (HOOKER ET ARNOTT), GREENE.
[*Eriodictyon glutinosum*, Bentham.]
Growing on Table Mountain, near Middletown, Lake Co., California

Presented to the Scientific Section of the American Pharmaceutical Association, at the Fifty-fourth Annual Meeting held at Indianapolis, Ind., September, 1906.

CHEMICAL EXAMINATION OF ERIODICTYON.

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

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

Eriodictyon was first officially recognized by the United States Pharmacopœia in the edition of 1890, and was retained in the eighth decennial revision (1905) of that work, where it is defined as "the dried leaves of *Eriodictyon californicum* (Hooker and Arnott), Greene." It does not appear to have been included in any other national pharmacopœia.

A systematic description of the plant, under the title of *Eriodictyon glutinosum*, Benth., is given in the "Synoptical Flora of North America," by Asa Gray, Vol. II., Part I., p. 176, New York, 1878. It is also described in Jepson's "Flora of Western Middle California," p. 440, where it is stated that the generic name is derived from the Greek words *erion*, wool, and *diktuon*, a net, by reason of the netted, woolly undersurface of the leaves. Various popular names have been given to the plant, such as "Yerba Santa," "Mountain Balm," "Consumptives' Weed," "Bears' Weed," and "Gum Bush."

One of the earliest notices in pharmaceutical literature of *Eriodictyon californicum* was a paper by Henry S. Wellcome,* which was illustrated by some excellent drawings. In that paper a description was given of the plant, together with indications of its medicinal uses, and the preparations adapted for its administration. It was also noted that the leaves yield from 20 to 30 per cent. of resin, which appeared to consist of several distinct substances, but these were not further examined chemically.

Charles Mohr,† in 1879, published a paper entitled "Analysis of *Eriodictyon californicum*," but this examination appears to have been conducted for the most part with only ten grams of the air-dried herb, and the results were therefore of correspondingly limited value. He states to have ascertained the presence of a little volatile oil; a bitter, acrid resin, soluble in ether; an inert resin, which was extracted by alcohol; tannic acid and coloring matter; a peculiar glucoside of the tannic acid series, but not more definitely characterized; gum, etc. The therapeutic value of the drug was attributed by him to the acrid resin which is soluble in ether.

J. Moeller ‡ has given a description of the anatomy of eriodictyon leaves, in which he notes that the parenchyma is free from tannin, and that strong alcohol extracts from 30 to 40 per cent. of resin of a tolu-like odor.

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* "The Pharmacist," Chicago, Feb., 1876, p. 33, and Proc. A. Ph. A., 1876, *24*, p. 134.

† Proc. A. Ph. A., 1879, *27*, p. 736.

‡ *Ibid.*, 1884, *32*, p. 141.

R. Thal,* in 1883, published a series of papers relating to the composition and distribution of "ericolin," in which he states that he has not only found this substance in a large number of plants belonging to the *Ericaceæ*, but also in *Eriodictyon glutinosum*, Benth.=*E. californicum* (H. and A.), Greene, and indicates it to be present in the leaves of this plant in considerable amount. The name "ericolin," it may be noted, appears to have been first given by Rochleder and Schwarz † to a substance obtained from *Ledum palustre*, Linn. and several other plants belonging to the *Ericaceæ*. It was described by them as a brownish-yellow, amorphous powder, possessing a very bitter taste, and having the property, when boiled with dilute sulphuric acid, of becoming resolved into sugar and "ericinol." The latter substance was stated to be a colorless oil, which on exposure to the air rapidly becomes dark brown, and possesses a peculiar not unpleasant odor.

The "ericolin" obtained by Thal (*loc. cit.*) from *Ledum palustre* was described as an odorless, brownish-yellow, sticky, hygroscopic substance, which is readily soluble in alcohol and ether-alcohol, but not soluble in water without decomposition. The last-mentioned character of the substance appears, however, quite inconsistent with the method adopted for its extraction, the first stage of which consisted in boiling the herb with water for several hours. According to Thal, the products formed by heating ericolin with dilute mineral acids are a brown-black, resinous substance, sugar, and ericinol, but he assumed that the latter, through absorption of the elements of water, becomes converted into a so-called "hydro-ericinol," which was described as a viscid, brownish-yellow mass, having a peculiar, strong, somewhat narcotic odor. In connection with this description which Thal has given of ericolin and its hydrolytic products, it is of particular interest to note his concluding remark on the subject, namely, that "as he could not find a characteristic chemical reaction for 'hydro-ericinol,' he was obliged to depend upon its peculiar odor for ascertaining the distribution of ericolin in the *Ericaceæ*."

It is apparent from the preceding statement that the only evidence adduced by Thal for the existence of "ericolin" in the large number of plants examined by him, including eriodictyon, was the odor developed on heating specially prepared extracts of the respective plants with dilute sulphuric acid. Our own observations concerning the character of the above-described compounds, insofar as they pertain to the constituents of eriodictyon leaves, are recorded in the experimental part of this paper.

R. Rother,‡ in a paper entitled "Some Constituents of Yerba Santa,"

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* Pharm. Zeit. f. Russland, 1883, xxii, pp. 209–219, 233–237, 249–259. Abstracted in Proc. A. Ph. A., 1884, *32*, p. 146.

† Wien. Akad. Ber., *9*, 308; *11*, 371.

‡ Amer. Journ. Pharm., 1887, *59*, p. 225.

has considered the use of preparations of eriodictyon for disguising the bitter taste of quinine. He attributed this effect to "a certain resinous component of the leaves, which is characterized by the property of forming in contact with some bases very soluble compounds," and assumed that these, "when mixed with quinine salts, generate by double decomposition an ordinarily insoluble quinine-resin salt." No definite constituent of the leaves, however, was isolated by him.

A. Quirini,* in 1887–88, described the isolation of a substance from the leaves of eriodictyon, which he regarded as a peculiar acid, and to which he gave the name of "eriodictyonic acid." This was obtained by treating an alcoholic extract of the plant with boiling water, when it was observed that, on cooling, a green resinous substance separated, together with a light-yellow, crystalline precipitate which was soluble in a dilute solution of potassium hydroxide with a red-brown color. This latter substance, the so-called eriodictyonic acid, is said to be contained in the plant to the extent of 2.4 per cent., and has been described as forming delicate yellow plates, with a dull lustre, which melt at 86–88° C., readily attract moisture from the air, are neutral, and possess a sweet acidulous taste. On exposure to the air it gradually becomes colored red. No analyses of this substance are recorded in the paper (*loc. cit.*), but it was stated to possess the formula $C_{14}H_{18}O_5$, and considered probable that it could be regarded as a substituted phloroglucin, of the composition $C_6H_3(OC_4H_7O)_2OH$. Its characters were further described by Quirini as follows: "With concentrated sulphuric acid it gave a slight reddish-yellow color, which soon disappeared. The yellowish alcoholic solution was readily decolorized by stannous chloride, and the hydrophloroglucin thus produced, when extracted with ether, was obtained on evaporation of the solution as a colorless mass, which was insoluble in water. By treatment with ferric chloride this could again be readily oxidized to phloroglucin. In alcoholic solution the so-called eriodictyonic acid gave with aniline a handsome emerald-green compound, which dissolved in concentrated sulphuric acid with a blue color."

The foregoing extracts from the existing literature are believed to afford a comprehensive survey of all the information which has hitherto been recorded respecting the constituents of eriodictyon leaves. The statements concerning the character of these constituents have been duly considered in connection with the results of the present investigation, and it is obvious that many of them require considerable modification. On the other hand, our more extended study of the subject has revealed a number of new substances of chemical interest, which have been definitely characterized.

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* Zeit. d. Oest. Apoth. Ver., 1887, p. 404, and 1888, p. 159. Abstracted in Proc. A Ph. A., 1888, *36*, p. 539

EXPERIMENTAL.

For the purpose of this investigation a quantity of the leaves of *Eriodictyon californicum* was specially collected for us in September, 1902. The locality from which the plant was obtained was Table Mountain, near Middletown, Lake Co., California, where it occurs in great abundance. This locality is in the inner coast range of Western Middle California, and has an altitude of about 1400 feet above the sea.

Test for Alkaloid.—As a preliminary test, 10 Gm. of the finely-ground leaves were extracted with Prollius' fluid, the resulting liquid evaporated, and the residue treated with acidulated water. The filtered, aqueous liquid was then tested with the usual alkaloidal reagents, but with a perfectly negative result.

Preliminary Extraction with Different Solvents.—In order to ascertain the general character of the constituents of the drug, 50 Gm. of the ground, air-dry leaves were successively extracted in a Soxhlet apparatus with the following solvents, and the resulting extracts dried at 100° C. until of constant weight.

Petroleum (b. p. 35—45° C.)	extracted	2.02	per cent.
Ether	"	18.26	"
Chloroform	"	1.38	"
Ethyl Acetate	"	2.04	"
Alcohol	"	3.72	"
	Total	27.42	"

The petroleum extract was a dark-green, fatty solid; the ether and chloroform extracts were of a resinous character, and also possessed a dark-green color; the portion removed by ethyl acetate was similar to the two preceding extracts, but of a somewhat lighter color; the alcohol extract was a dark-brown, syrupy mass. No crystals could be observed in any of these products. The dried marc was subsequently extracted with boiling water, and the liquid thus obtained, which possessed a slightly bitter taste, was found to give a dark-green coloration with ferric chloride and a dense yellow precipitate with basic lead acetate; it apparently contained a little tannin, together with gum and coloring matter.

For the purpose of a complete examination, 96 pounds (43545 Gm.) of the air-dried eriodictyon leaves were thoroughly extracted by continuous percolation with hot alcohol. After the removal of the greater portion of the alcohol, 44¾ pounds (20298 Gm.) of a thick, dark-green extract were obtained, corresponding to 46.6 per cent. of the weight of the leaves.

1000 Gm. of the alcoholic extract just mentioned were brought into a large flask, some water added, and steam then passed through the mixture until the entire amount of volatile substances present had been removed.

Examination of the Steam Distillate.

This liquid had an acid reaction, and contained a small amount of an *essential oil.* It was extracted three times with ether, the ethereal liquid washed, dried with anhydrous sodium sulphate, and the ether removed. The residue was a mobile, yellow oil, which possessed the characteristic odor of the drug. The amount obtained was 2.25 Gm., corresponding to 0.1 per cent. of the weight of air-dried leaves. It was distilled under atmospheric pressure, when it boiled between about 150 and 245° C., the greater portion, however, passing over below 190° C. This essential oil was readily soluble in 70 per cent. alcohol, and had the following constants: $d=0.9372$ at $15°/15°$ C. and $\alpha_{D} = -0°.24'$ in a 25 Mm. tube.

The acids contained in the aqueous distillate from which the essential oil had been removed were converted into their barium salts for the purpose of identification. They were thus found to consist of *formic* and *acetic acids*, the former preponderating.

Non-volatile Constituents of the Alcoholic Extract.

After the removal of the volatile constituents, by distillation in steam, as above described, the contents of the distilling flask consisted of a brown, aqueous liquid and a large cake of soft, green resin, which had separated at the bottom. The aqueous liquid was decanted while hot, and, after adding a further quantity of water to the residual resin, steam was again passed into the mixture until it became heated to the boiling-point. The flask was then placed in a bath of boiling water, and, after the green resin had been allowed to settle, the supernatant, aqueous liquid was decanted as before. This contained a small quantity of a semi-solid, bright yellow substance in a state of fine division, together with a small amount of the green resin. A further quantity of water was subsequently added to the resin, and the preceding oparation repeated.

The first aqueous liquid which had been decanted from the resin, as above described, was allowed to cool, when it deposited a quantity of the same semi-solid, bright yellow substance as was contained in the liquids from the subsequent washings of the resin. All these aqueous liquids were allowed to stand for some time, when the substance in suspension gradually subsided to the bottom of the vessel. The clear portion of the liquid was then decanted, and the remainder separated as completely as possible from the precipitate by filtration. In this manner the following products were obtained: A clear, brown, aqueous liquid (A); a quantity of a slimy, semi-solid, bright yellow substance (B), which contained a few particles of green resin, and the previously mentioned large cake of green resinous matter (C).

Examination of the Aqueous Liquid (A).

This clear, aqueous liquid was concentrated to a small bulk on a water-bath, but, on cooling, nothing further separated. It was then repeatedly extracted with ether until nothing more was removed, and the ethereal liquid, after being washed with a little water, shaken with successive portions of a saturated solution of sodium carbonate. The alkaline liquid obtained by treatment with the first portion of carbonate solution (about 30 Cc.) was clear and of a brown color. This was acidified with sulphuric acid, and extracted with ether, the ethereal liquid being subsequently washed, dried, and the ether removed. Several grams of a deep yellow, sticky, varnish-like substance, possessing a strong sour smell, were thus obtained, but nothing of a crystalline character could be separated from it. The second and third extractions of the original ethereal liquid with sodium carbonate solution afforded intensely yellow liquids, containing a considerable quantity of a crystalline substance in suspension, which will subsequently be described. As these two aqueous, alkaline liquids appeared to be similar in character, they were mixed and filtered for the purpose of further examination.

Isolation of a New Phenolic Substance, Eriodictyol, $C_{15}H_{12}O_6$.

The clear alkaline filtrate from the above-mentioned crystalline substance was at first of a deep yellow color, but rapidly became brown, which was apparently due to the absorption of atmospheric oxygen. It was at once acidified with sulphuric acid, extracted several times with ether, and the ethereal liquid washed, dried, and evaporated. Before all the ether had been removed, the contents of the flask became for the most part solid, and apparently crystalline. The solid thus obtained was first drained on a porous tile, and, after having been freed from a small amount of a bright yellow, varnish-like substance by washing with warm ether, it was obtained in the form of a brown powder. This substance was dissolved in hot alcohol, the solution boiled with animal charcoal, filtered, and concentrated on a water-bath, when the greater portion separated in small, glistening spangles of a light fawn color. After being collected on a filter, and dried, it was found to melt, with decomposition, between 260 and 270° C. When crystallized from glacial acetic acid, it was obtained in the form of small, fawn-colored plates, which darkened and melted to a red liquid at 267° C.

0.1100 gave 0.2529 CO_2 and 0.0422 H_2O. $C = 62.7$; $H = 4.3$.

0.1170 gave 0.2672 CO_2 and 0.0456 H_2O. $C = 62.3$; $H = 4.3$.

A portion of the substance was then recrystallized from boiling alcohol, when the melting-point remained unaltered. It was again analyzed with the following result:

0.0974 gave 0.2231 CO_2 and 0.0385 H_2O. $C = 62.5$; $H = 4.4$.

$C_{15}H_{12}O_6$ requires $C = 62.5$; $H = 4.2$ per cent.

This substance is not identical with any compound hitherto described, and as its properties indicate that it is of a phenolic nature, and not a true acid, it is proposed to designate it *eriodictyol*.

Eriodictyol is moderately soluble in hot alcohol and in acetic acid, very sparingly soluble in boiling water, and insoluble, or very sparingly soluble, in the other organic solvents. It dissolves readily in the fixed alkalies and alkali carbonates, affording at first almost colorless solutions, but which rapidly absorb oxygen and assume a deep brown color. When to a dilute solution of eriodictyol in water or in dilute alcohol a drop of ferric chloride solution is added, a deep greenish-brown color is produced, which rapidly changes to a pure brown. A saturated aqueous solution of eriodictyol does not reduce Fehling's solution, and is not appreciably precipitated by a solution of normal lead acetate, but with basic lead acetate it affords a bulky, yellow precipitate.

Acetyl Eriodictyol.—A small quantity of eriodictyol was dissolved in an excess of hot acetic anhydride, and the mixture boiled for six hours. The greater part of the anhydride was then removed by distillation, and a small quantity of alcohol added, when, after standing for some time, a solid substance separated. This was collected on a filter, and recrystallized from ethyl acetate, when it was obtained in small tufts of minute, nearly colorless needles, which melted at 195–196° C.

The amount of eriodictyol obtained from 1000 Gm. of the alcoholic extract of the drug was about 5 Gm., which corresponds to 0.23 per cent. of the weight of air-dried leaves.

Isolation of Homo-Eriodictyol, $C_{16}H_{14}O_6$.

The crystalline substance separated by filtration from the aqueous alkaline liquid which afforded the eriodictyol, as previously described, was spread on a porous plate and allowed to dry. As thus obtained, it dissolved with moderate facility in boiling water, and, on cooling the solution, it separated in glistening, leaf-like crystals, possessing a beautiful silky lustre. After several recrystallizations from water, it was obtained perfectly white, and was evidently the sodium derivative of some organic substance of an acidic nature. The aqueous solution of this compound had a faintly alkaline reaction and a slightly yellow color, which was much intensified on the addition of an excess of alkali.

A quantity of the above-mentioned sodium derivative was dissolved in hot water, dilute acetic acid added so long as a precipitate was produced, and the liquid allowed to cool. The pale-yellow, crystalline substance which separated was collected on a filter, washed with water, and dried, when it melted at 223° C. This substance was subsequently dissolved in boiling 70 per cent. acetic acid, when, on cooling, it separated from the solution in handsome, lemon-yellow plates, which were likewise collected on a filter, washed with water, and dried. As its melting-point remained unchanged after this treatment, it apparently represented a pure substance. It was analyzed with the following result:

0.0977 gave 0.2267 CO_2 and 0.0424 H_2O. C=63.3; H=4.8.
0.1156 gave 0.2686 CO_2 and 0.0493 H_2O. C=63.4; H=4.7.
$C_{16}H_{14}O_6$ requires C=63.5; H=4.6 per cent.

A portion of this substance was dissolved by boiling with water and sodium bicarbonate, and the solution cooled. The crystalline sodium derivative which separated was collected on a filter, washed with water, and allowed to dry in the air.

0.1794 of the air-dried sodium derivative, when heated at 115° C. until of constant weight, lost 0.0361 or 20.1 per cent.

$C_{16}H_{13}O_6\,Na,5H_2O$ requires H_2O=21.7 per cent.

0.1433 of the anhydrous compound gave on ignition 0.0238 Na_2CO_3. Na=7.2.

$C_{16}H_{13}O_6\,Na$ requires Na=7.1 per cent.

The fact that the sodium compound effloresces slightly on exposure to the air, would account for the somewhat low percentage of water found.

From the above analytical results it is evident that the substance melting at 223° C. is correctly represented by the formula $C_{16}H_{14}O_6$. The only known substance of this formula which has properties at all agreeing with those of the substance just described is hesperitin, which melts at 226° C. Although the melting-points of these two compounds are almost identical, there are other important differences which lead to the conclusion that the substance which we have isolated from eriodictyon, having the melting-point of 223° C., is not hesperitin, but an isomeric compound of a similar type. The differences referred to may be summarized as follows: Hesperitin has been described as crystallizing in almost colorless needles, which possess an intensely sweet taste, and dissolve in alkalies with, at the most, a faintly yellow color.* The compound from eriodictyon, on the other hand, crystallizes in pale yellow plates, which have only a slightly sweetish taste, and dissolve in alkalies with a bright yellow color. Furthermore, hesperitin affords a sodium derivative of the formula $C_{16}H_{13}O_6Na.C_{16}H_{14}O_6$,† whereas the sodium derivative of the compound from eriodictyon, when prepared under the same conditions, has been shown to have the normal formula $C_{16}H_{13}O_6Na$. As the formula of the compound melting at 223° C. differs by the increment of CH_2 from that of the other newly isolated substance, eriodictyol, it is proposed to designate it *homo-eriodictyol*.

Homo-eriodictyol resembles eriodictyol in solubility, but it is even more sparingly soluble in water than the latter, and apparently more readily soluble in alcohol and in acetic acid.

When to a dilute alcoholic solution of homo-eriodictyol a drop of ferric chloride solution is added, an intense red-brown color is produced. An aqueous solution of homo-eriodictyol is not appreciably precipitated by either normal or basic lead acetate solution. Acetyl and benzoyl homo-

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* Journ. Chem. Soc., 1898, *73*, p. 1032.

† *Ibid*, 1898, *73*, p. 1037.

eriodictyol were prepared, but all the attempts to obtain these compounds in a crystalline condition were unsuccessful.

A considerable amount of homo-eriodictyol was also obtained from other products of the drug, as will subsequently be noted. The total yield of this substance from 1000 Gm. of the original alcoholic extract was about 65 Gm., which corresponds to 3 per cent. of the weight of air-dried leaves.

The ethereal liquid from which the eriodictyol and homo-eriodictyol had been extracted by sodium carbonate solution was subsequently shaken with further quantities of the alkali until nothing more was removed, and it was then found that practically nothing remained dissolved in the ether. The alkaline liquids from these final extractions with sodium carbonate solution were acidified, and shaken out with ether in the usual manner, but they only afforded a small amount of uncrystallizable resinous matter.

The aqueous liquid (A), from which the mixture of the above-described products had been removed by shaking with ether, had a brown color, and afforded a voluminous precipitate of a bright yellow color on the addition of a solution of basic lead acetate. A slight excess of the latter was therefore added, the resulting precipitate collected by filtration under pressure, washed with a little water, then suspended in water, and completely decomposed by hydrogen sulphide. The liquid containing lead sulphide was then heated to the boiling-point, filtered, and the filtrate concentrated on a water-bath to a small bulk, when a very dark brown, thick liquid was obtained. This liquid readily reduced Fehling's solution, gave an abundant green-black precipitate with ferric chloride, and an intense yellowish-brown color with alkalies. It apparently contained a considerable amount of tannin, but nothing crystalline.

The filtrate from the precipitate produced by basic lead acetate was deprived of lead by hydrogen sulphide, filtered, and the filtrate concentrated on a water-bath to a small bulk. The clear syrupy liquid thus obtained had a yellowish-brown color, and contained a large amount of *glucose*, for a portion of it when treated with a solution of phenylhydrazine acetate readily yielded a crystalline osazone melting at 205° C. Nothing crystalline separated from this liquid, even after standing for several weeks.

It has been stated by Thal * that eriodictyon contains the glucoside "ericolin," and indeed in such an amount that an extract from five small leaves of the plant, when heated with a few drops of dilute sulphuric acid, not only developed an exceptionally strong odor of its hydrolytic product "ericinol," but that "an oily layer of ericinol appeared on the surface of the liquid, which could be detected even with the naked eye." This, however, is followed by the significant remark that "as he experienced much difficulty in his investigations on account of the readiness with which

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* Pharm. Zeit. für Russland, 1883, xxii, p. 257.

the ericolin became decomposed, he cannot regard them as exhaustive, and must admit that they are possibly not free from errors."

Notwithstanding the extremely unsatisfactory character of the evidence which has been adduced for the existence of the so-called "ericolin" in eriodictyon, and the equally indefinite chemical character of ericolin itself, it was considered of interest to ascertain whether the above-mentioned aqueous liquid, when heated with dilute sulphuric acid, was capable of yielding anything corresponding to the hydrolytic product of ericolin, which, under the name of "ericinol," has been described as a volatile, colorless, oily liquid, possessing a peculiar not unpleasant odor, and becoming dark brown on exposure to the air. Accordingly, about one-third of the purified, concentrated aqueous liquid, obtained as above described, was diluted with water, and such an amount of sulphuric acid added as to correspond to about 5 per cent. of the weight of liquid employed. This mixture was first boiled for 5 hours in a flask provided with a reflux condenser, when a quantity of black, resinous matter separated. Steam was then passed through the liquid until all volatile substances were completely removed, when a clear distillate, having an acid reaction and an odor recalling that of furfural, was obtained. The distillate was repeatedly extracted with ether, the ethereal liquid washed, dried, and the ether removed. The residue consisted of a few drops of a clear liquid, which contained a little acetic acid, and had an odor suggestive of furfural. With aniline it instantly afforded the intense carmine-red color which is characteristic of furfural when brought in contact with this base.* It also afforded an immediate precipitate with phenylhydrazine acetate. This odorous volatile substance therefore appeared to consist essentially of *furfural*, which was doubtless produced by the action of the sulphuric acid on the carbohydrates contained in the liquid.

From the results of the preceding experiment it appears highly probable that the peculiar odor observed by Thal, and attributed by him, as well as by previous investigators, to the so-called "ericinol," was really due to furfural, which would obviously be produced from a great variety of plant extracts when heated with a dilute mineral acid. The fact that "ericolin" has never been obtained in any other form than an amorphous, brown powder or a sticky extract, in which even the complete absence of sugar does not seem to have been proved, and that its assumed product of hydrolysis, "ericinol," has apparently never been chemically characterized or submitted to analysis, lends further support to the view that no definite glucoside is known to exist which is entitled to the specific designation of ericolin. It is certain that there is at present no known constituent of eriodictyon leaves to which this name should be applied.

The liquid from which the furfural had been removed by distillation was

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* Ber. d. deutsch. chem. Ges., 1887, *20*, p. 541.

of a brown color, and contained about 20 Gm. of a hard, black resin. This was found to be insoluble in the usual organic solvents, but dissolved slowly in alkalis, and appeared to contain nothing crystalline. The clear aqueous liquid from which the resin had been separated was repeatedly extracted with ether, but this removed only a trace of a brown-colored syrup. The sulphuric acid contained in the aqueous liquid was then removed by means of barium hydroxide and filtering, and from the sugar contained in the filtrate an osazone was prepared. As the latter melted at 206° C., it was evidently glucosazone, and indicated that by the treatment with sulphuric acid no appreciable amount of a sugar had been formed which differed from that contained in the original aqueous liquid.

Examination of the Yellow Substance (B).

This substance consisted of a slimy mass of apparently semi-solid particles possessing a bright yellow color, together with a little green resinous matter, and amounted to about 10–15 Gm. It was very sparingly soluble in hot, and insoluble in cold water, and could not be crystallized from any solvent. As it evidently represented a mixture of substances it was dissolved in ether, and the ethereal solution, after being washed with water, extracted with successive portions of sodium carbonate solution, in the same manner as described in the treatment of the ethereal extract of the aqueous liquid (*A*). By this means the substance was found to consist, to a large extent, of homo-eriodictyol, which separated in the form of its mono-sodium compound, together with a trace of eriodictyol, a small amount of a brown and a green resinous substance, both of an acidic nature, and several grams of a green resin, which was insoluble in sodium carbonate solution.

It has already been noted that some years ago Quirini (*loc. cit.*) obtained from eriodictyon a substance to which he gave the name of "eriodictyonic acid." Although this was described as forming yellow plates, which melt at 86–88° C., it was evidently a mixture, as from its method of preparation it must have consisted to a large extent of homo-eriodictyol, which melts at 223° C.

Examination of the Resins (C).

The cake of soft, dark-green, resinous matter, which had been separated from the aqueous liquid subsequent to the steam distillation, as previously described, was heated on a water-bath until dry, when it weighed 627 Gm., corresponding to 29.2 per cent. of the weight of air-dried leaves. It was then intimately mixed with prepared sawdust, and successively extracted in a Soxhlet apparatus with the following solvents. The extracts thus obtained were dried at 100° C., until of constant weight.

I. Petroleum (b. p. 35–45° C.)	extracted	5.54	per cent.
II. Ether	"	75.24	"
III. Chloroform	"	6.16	"
IV. Ethyl Acetate	"	7.82	"
V. Alcohol	"	3.90	"
	Total	98.66	"

I. *Petroleum Extract of the Resins.*

This was a soft, fatty solid, of a dark greenish color, and amounted to 34.7 Gm. When heated, it melted to a clear, dark green oil. It was dissolved in about 500 cc. of boiling ether, and the solution cooled by immersing the flask in cold water. Several grams of a solid substance then separated, which was removed by filtration, washed with cold ether, and allowed to dry, when it was obtained as a pale greenish, amorphous powder. When heated, it melted at 70–75° C., and, on re-solidifying formed a mass resembling paraffin and having the properties of a hydrocarbon. The whole of the substance was then brought into a distilling flask, and distilled under a pressure of 8 Mm., when a clear distillate was obtained, which, on cooling, solidified to a crystalline mass. It was subsequently crystallized from ethyl acetate, when it was obtained in small, colorless plates, which, after drying, melted at 74.5–75° C. On analysis it gave the following result:

0.1564 gave 0.4858 CO_2 and 0.2071 H_2O. $C = 84.7$; $H = 14.7$.

$C_{35}H_{72}$ requires $C = 85.4$; $H = 14.6$ per cent.

The substance was thus identified as *pentatriacontane*, which had previously been isolated by the authors from *Aethusa Cynapium*, Linn.*

The ethereal solution of the petroleum extract, from which the pentatriacontane had been separated by filtration, was then shaken with sodium carbonate solution. This caused the precipitation of an amorphous, pale green substance, which was separated from the ethereal solution, together with the alkaline, aqueous liquid. It was removed from the alkaline liquid by filtration, washed first with ether, then with water, and dried on a tile. As thus obtained, it had the appearance of a dried soap, contaminated with a little resinous matter. It was then dissolved in hot, dilute alcohol, the solution acidified with sulphuric acid, and the mixture cooled and extracted with ether. The ethereal liquid, which had a green color, was washed with water, dried, and the ether removed. The residue thus obtained was dissolved in hot ethyl acetate, and the solution allowed to cool, when a substance of a pale green color separated in the form of nodules, which possessed no definite crystalline form. This solid was collected on a filter, washed with ethyl acetate, and dried, when it melted at 78° C. Although its sharp melting-point indicated that it was a fairly pure substance, it would not separate in a crystalline condition from any

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* Journ. Amer. Chem. Soc. 1905. *27*, p. 1468.

solvent, and it was therefore distilled under diminished pressure. A distillate was thus obtained which, after dissolving in hot ethyl acetate, and allowing the solution to cool, yielded the substance in the form of glistening plates. These were removed by filtration, and dried, when they melted at 79° C.

0.0749 gave 0.2167 CO_2 and 0.0923 H_2O. $C = 78.9$; $H = 13.6$.

$C_{27}H_{54}O_2$ requires $C = 79.0$; $H = 13.2$ per cent.

The properties and analysis of this substance confirmed its identity with *cerotic acid*, which existed in the leaves in a free state.

The substance contained in the original ethyl acetate mother liquors from this cerotic acid was distilled under diminished pressure, when it afforded a distillate which, after several recrystallizations from ethyl acetate, melted between 71 and 74° C., and was apparently a mixture of acids. The alkaline aqueous liquid from which the sodium salts of the above-mentioned acids had been separated by filtration was found to contain no fatty acids.

The ethereal solution of the petroleum extract, from which the pentatriacontane had been obtained, and which had been freed from acids by shaking with sodium carbonate solution, was found to contain nothing soluble in dilute mineral acids. The ether was therefore removed, and the residue hydrolysed by boiling it for 3 hours with an alcoholic solution of 20 Gm. of potassium hydroxide, when it was observed that a small amount of ammonia was evolved. The alcohol was then removed, the residue poured into water, and the mixture repeatedly extracted with ether. The ethereal liquid, after being washed and dried, was concentrated to about 100 Cc., and allowed to cool, when a considerable quantity of a crystalline substance separated. This was collected on a filter, then distilled under a pressure of 10 Mm., and the distilled product crystallized from ethyl acetate, when it was obtained in the form of extremely handsome, colorless plates. These crystals, after being dried on a tile, melted sharply at 65.2° C., and this melting point was not altered by further recrystallization.

0.0998 gave 0.3110 CO_2 and 0.1311 H_2O. $C=85.0$; $H=14.6$.

$C_{30}H_{62}$ requires $C=85.3$: $H=14.7$ per cent.

This substance is obviously a hydrocarbon. As its melting-point lies between that of nonacosane, $C_{29}H_{60}$ (m. p. 63.5—64° C.), and hentriacontane, $C_{31}H_{64}$ (m. p. 68.1° C.), and as it also differs in appearance from the latter, it is probable that it is *triacontane*, $C_{30}H_{62}$. If this supposition be correct, it is apparently the first time that this hydrocarbon has been obtained from any source.

The substance contained in the ethereal mother-liquors from this hydrocarbon was fractionally distilled under 10 Mm. pressure, when the lower boiling portion, on fractional crystallization, yielded a further quantity of triacontane, together with a very small amount of a substance melting at

136–137° C., which afforded the color reaction characteristic of the *phytosterols*. The fraction of higher boiling-point yielded a substance which melted between 66 and 68° C., and was apparently a mixture of triacontane and pentatriacontane. The total amount obtained of these hydrocarbons was about 15 Gm., which corresponds to 0.7 per cent. of the weight of air-dried leaves.

The alkaline, aqueous liquid from which these neutral substances had been removed by means of ether contained a small amount of a sparingly soluble potassium salt in the form of a flocculent precipitate. This was removed by filtration and decomposed by sulphuric acid. The liberated acid was first distilled under diminished pressure, and then crystallized from ethyl acetate, when it was found to be identical with the cerotic acid previously obtained. The filtrate from this potassium cerotate was acidified with sulphuric acid and distilled in steam. The distillate contained no oily drops, but had an acid reaction, and was found to contain both *formic* and *butyric acids*, which were identified by means of their barium salts. The non-volatile acids contained in the steam distillation flask were extracted by ether. On evaporating the ethereal solution a dark green, sticky residue was obtained, which was redissolved in a small quantity of warm ether, a large volume of warm, light petroleum added, the mixture well stirred, and the clear liquid decanted from a soft, dark green resin which was only sparingly soluble in light petroleum. The petroleum was removed from this liquid, the residue distilled under diminished pressure, and the distillate fractionally crystallized from ethyl acetate, when it yielded cerotic acid, a mixture of acids melting between 62 and 66° C., and a small amount of an unsaturated oily acid, which was apparently oleic acid. The total amount of fatty acids obtained from the original petroleum extract was about 10 Gm.

II. *Ether Extract of the Resins.*

This was a nearly hard, dark green resin, and amounted to 472 Gm. It was dissolved in about 2 liters of ether, and the solution extracted with several successive portions of a solution of sodium carbonate, followed by a 10 per cent. solution of potassium hydroxide, when the following products were obtained.

The first few extractions with sodium carbonate afforded a rather thick, dark green liquid (*a*), containing a large amount of a crystalline substance in suspension, which proved to be mono-sodium homo-eriodictyol. The next portions of sodium carbonate afforded a further quantity of mono-sodium homo-eriodictyol, together with an intensely yellow liquid (*b*). The treatment with sodium carbonate was then continued until nothing further was removed from the liquids, when no more mono-sodium homo-eriodictyol separated, but a clear, greenish-brown liquid (*c*) was obtained. The ethereal liquid was then washed with water, which removed a further quantity of a substance that imparted a dark greenish-brown color to the aqueous liquid (*d*). As the ethereal liquid still possessed a very dark green color, although now free from substances of an acidic nature, it was extracted with a 10 per cent. aqueous solution of potassium hydroxide, which afforded a deep green, alkaline liquid (*e*). After washing the ethereal liquid, which was still colored, and which contained nothing soluble in 20 per cent. sulphuric acid, it was dried, and the ether removed. It then finally yielded a quantity of a soft, green solid (*f*).

The above-described treatment of the ether extract of the resins showed it to be an extremely complex mixture, and as all the products thus obtained evidently differed in character, they were separately examined.

(*a*) This liquid, from which the crystalline mono-sodium homo-eriodictyol held in suspension had been removed by filtration, was acidified with sulphuric acid, and extracted with ether in the usual manner. By this means the following products were obtained: (1) A small amount of a black resin, insoluble in ether; and (2) a large amount of a soft, green, resin, readily soluble in ether, which evidently represented the principal constituent of the ether extract of the resins (*C*). As there was no evidence of any crystalline substance in this soft, green resin, it seemed of interest to ascertain whether it was of a glucosidal nature. A portion of it was accordingly dissolved in alcohol, a little of water added, and subsequently an amount of sulphuric acid corresponding to about 5 per cent. of the weight of liquid employed. This mixture was boiled for five hours, after which the alcohol was removed, and the residue submitted to steam distillation, but no volatile products were obtained. The liquid contained in the steam distillation flask was then filtered from the apparantly unchanged resin, and extracted with ether, but this removed only a trace of substance. The aqueous liquid was finally freed from sulphuric acid by means of barium hydroxide, filtered and concentrated, when it yielded nothing but a small amount of crystalline barium ethyl sulphate, which was doubtless produced by the action of the sulphuric acid on the alcohol employed. The chief constituent of the ether extract of the resins was therefore not a glucoside.

Isolation of a new yellow, crystalline substance, $C_{16}H_{12}O_6$.

(*b*). This intensely yellow liquid was acidified with sulphuric acid, and extracted with ether in the manner previously described. The ethereal liquid afforded a small amount of a yellow varnish, which was dissolved in ethyl acetate and allowed to stand. In the course of a few days, bright yellow, crystalline crusts were deposited, which were removed by filtration, and washed with ethyl acetate. The substance thus obtained was dissolved in a large quantity of boiling alcohol, the solution filtered, and concentrated to a small bulk, when minute, glistening spangles of a deep golden-yellow color separated from the boiling liquid. This substance, which appeared to be homogeneous, was collected on a filter, washed with alcohol, dried, and analyzed.

0.0895 gave 0.2092 CO_2 and 0.0330 H_2O. $C = 63.75$; $H = 4.08$.

The remainder of the compound was then recrystallized from alcohol, and again analyzed.

0.0873 gave 0.2050 CO_2 and 0.0328 H_2O. $C = 64.04$; $H = 4.17$.

$C_{16}H_{12}O_6$ requires $C = 64.00$; $H = 4.00$ per cent.

This substance did not melt when heated to 337° C., but from its appearance and the analytical results it was evidently pure. As it is not identical with any compound hitherto described, it must be regarded as a new substance. It was very sparingly soluble in alcohol and in ethyl acetate, and apparently insoluble in the other ordinary solvents, but it dissolved in alkalies and in concentrated sulphuric acid, yielding solutions of a bright yellow color.

Acetyl Derivative of the Yellow Substance.—A small quantity of the yellow, crystalline substance was dissolved in hot acetic anhydride, and the solution boiled for one hour. After cooling, a considerable volume of water was added, and the mixture allowed to stand for several hours, when a colorless, crystalline substance separated in tufts of needles. This was collected on a filter, and, after recrystallization from a mixture of ethyl acetate and alcohol, it melted at 213–215° C. As the total amount of the yellow substance obtained was only about 0.3 Gm., it could not be subjected to further study.

It has already been noted that a considerable amount of mono-sodium homo-eriodictyol separated from the liquids (*a*) and (*b*), and it was from this source that the greater portion of the homo-eriodictyol was obtained.

(*c*), (*d*), and (*e*). These liquids were acidified with sulphuric acid and extracted with ether, as before described. (*c*) and (*d*) each afforded about 10 Gm. of a greenish-brown resin, while (*e*) yielded about 20 Gm. of a bright green resin, but from none of these products could anything crystalline be obtained.

(*f*). This substance, as previously indicated, represented that portion of the ether extract of the resins which was not dissolved by shaking the ethereal solution successively with solutions of sodium carbonate and potassium hydroxide. In appearance it resembled the petroleum extract of the resins, and was found to contain some of the hydrocarbons and other constituents of that extract which had not been completely removed by the treatment with petroleum, but no other crystalline substance could be isolated from it.

III. *Chloroform Extract of the Resins.*

This was a hard, greenish resin, and amounted to about 39 Gm. A portion of it was dissolved in amyl alcohol, and the liquid extracted with sodium carbonate solution, when the greater part of the resin was taken up by the alkali, yielding a solution of a bright yellow color and a small amount of a brown, sparingly soluble sodium compound. Nothing crystalline could be obtained from these products.

IV. *Ethyl Acetate Extract of the Resins.*

This was a very soft, dark brown resin, and amounted to about 49 Gm. It was not entirely soluble in sodium carbonate solution, and was evidently a complex mixture of substances. The only crystalline product that could be obtained from it was a small amount of homo-eriodictyol.

V. *Alcohol Extract of the Resins.*

This was a thick, dark brown, tarry liquid, and amounted to about 24 Gm. It was entirely soluble in sodium carbonate solution, but was evidently a mixture of substances, and contained nothing crystalline.

Summary and Conclusions.

The results of this investigation have shown the leaves of *Eriodictyon californicum* to contain, in addition to some essential oil, resins, and other amorphous bodies, the following substances, in the amounts approximately indicated:

Triacontane, $C_{30}H_{62}$ (m. p. 65.2° C.)
Pentatriacontane, $C_{35}H_{72}$ (m. p. 74.5–75° C.)] about 0.7 per cent.

Formic, acetic, cerotic, and other acids, in a free state.

Glycerides of formic, butyric, cerotic, and other acids.

The total amount of acids, free and combined, amounted to about 0.5 per cent.

A Phytosterol (m. p. 136–137° C.), in very small amount.

Eriodictyol, $C_{15}H_{12}O_6$ (m. p. 267° C.), a new, crystalline substance of phenolic nature, about 0.23 per cent.

Homo-eriodictyol, $C_{16}H_{14}O_6$ (m. p. 223° C.), another new, crystalline substance of phenolic nature, about 3 per cent.

A new, yellow, crystalline substance, $C_{16}H_{12}O_6$, also of a phenolic nature, about 0.014 per cent.

Glucose (phenylglucosazone, m. p. 205° C.), a considerable amount.

The amount of essential oil obtained corresponded to about 0.1 per per cent. of the weight of the leaves. It was a yellow liquid, which possessed the characteristic odor of the drug, and had the following constants: $d=0.9372$ at 15°/15° C.; α_D—0° 24′ in a 25 Mm. tube. It was readily soluble in 70 per cent. alcohol.

The total amount of crude resinous substances was 29.2 per cent. of the weight of the leaves, and about 75 per cent. of these resins was soluble in ether. They represented an exceedingly complex mixture, from which some of the above-mentioned crystalline substances were isolated.

The statememt of Thal (*loc. cit.*) that Eriodictyon leaves contain the so-called "ericolin," we are not able to confirm. The peculiar odor which he observed on heating an extract of the leaves with dilute sulphuric acid, and which he regarded as characteristic of "ericinol"—the assumed hydrolytic product of ericolin—we believe to have been due to the formation of a small amount of *furfural*. The latter compound has now been definitely identified as the chief volatile product resulting from the action of a dilute mineral acid on a purified extract of Eriodictyon leaves, and is doubtless produced from the carbohydrates contained therein.

The so-called eriodictyonic acid, which was described some years ago by Quirini (*loc. cit.*), was evidently not a pure substance. The method by which it was obtained indicates that it must have consisted, to a large extent, of the new crystalline substance of a phenolic nature which we have designated *homo-eriodictyol*.

In conclusion it may be noted that our investigation of Eriodictyon leaves has disclosed the occurrence, among other compounds, of four substances which have not hitherto been known. It is our intention to continue the chemical study of two of these newly isolated substances, namely, eriodictyol and homo-eriodictyol.