

LXXXII.—*The Constitution of Homoeriodictyol.—A Crystalline Substance from Eriodictyon Leaves.*

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At the meeting of the American Pharmaceutical Association held at Indianapolis, Ind., in September, 1906, a paper was communicated by the authors, entitled "Chemical Examination of Eriodictyon" (com-

pare *Pharm. J.*, 1906, **77**, 381, and *Abstr.*, 1906, **90**, ii, 885). The material used for this investigation consisted of the leaves of *Eriodictyon californicum* (Hooker and Arnott), Greene (syn. *E. glutinosum*, Benth.), which had been specially collected for us in California.

In the above-mentioned communication it was shown that the leaves of eriodictyon contain, besides a small amount of essential oil, a considerable amount of glucose, resins, and other amorphous substances, the hydrocarbons triacontane (m. p.  $65\cdot2^\circ$ ) and pentatriacontane (m. p.  $74\cdot5-75^\circ$ ), together with formic, acetic, butyric, cerotic, and other acids, both in the free state and as glycerides, and a very small amount of a phytosterol (m. p.  $136-137^\circ$ ). In addition to these, three new crystalline substances of a phenolic nature were isolated and described, namely :

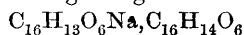
1. A substance crystallising in fawn-coloured plates, melting at  $267^\circ$ , and possessing the formula  $C_{15}H_{12}O_6$ , which was designated *eriodictyol*.

2. A substance crystallising in pale yellow plates, melting at  $223^\circ$ , and possessing the formula  $C_{16}H_{14}O_6$ . As this substance was apparently a homologue of the preceding one, differing by the increment of  $CH_2$ , it was designated *homoeriodictyol*.

3. A very small quantity of a substance crystallising in minute, bright yellow spangles, and possessing the formula  $C_{16}H_{12}O_6$ .\*

The amount of this last-mentioned substance present in the leaves (0.014 per cent.) was too small to permit of its further examination, and hence no name was given to it. Homoeriodictyol and eriodictyol, however, which occur to the extent of about 3 and 0.23 per cent. respectively of the weight of dried leaves, have now been further investigated, and the results obtained are embodied in the present communication.

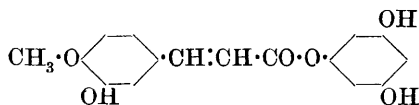
Homoeriodictyol is isomeric with hesperitin, and its melting point ( $223^\circ$ ) is but three degrees lower than that recorded for the latter compound. It is also similar to hesperitin in most of its properties, and gives the same reaction as the latter compound when treated with sodium amalgam (Beilstein's *Handbuch*, Bd. III., 594). It was shown, however, not to be identical with hesperitin by the fact that its sodium derivative possesses the normal formula  $C_{16}H_{13}O_6Na$ , whereas sodium hesperitin has a composition agreeing with the formula



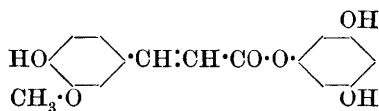
(Perkin, *Trans.*, 1898, **73**, 1037). It was therefore concluded that homoeriodictyol possessed a constitution analogous to that of hesperitin

\* In *Abstr.*, 1906, **90**, ii, 885, the formula of this substance is incorrectly given as " $C_{16}H_{14}O_6(C_{16}H_{14}O_6?)$ ."

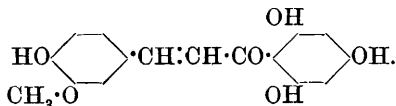
to which Tiemann and Will (*Ber.*, 1881, 14, 970) assigned the following formula :



In view of this conclusion, homoeriodictyol has been submitted to the action of aqueous potassium hydroxide under the same conditions as were employed by Tiemann and Will (*loc. cit.*) for the hydrolysis of hesperitin, and it has been found that it undergoes hydrolysis in a manner analogous to that exhibited by the latter compound. The products yielded by the hydrolysis of homoeriodictyol are phloroglucinol and ferulic acid (4-hydroxy-3-methoxycinnamic acid), whilst hesperitin gives the same phenol together with *isoferulic* acid (3-hydroxy-4-methoxycinnamic acid). On fusion with potash, homoeriodictyol, like hesperitin, readily gives protocatechuic acid. It would appear from these results that homoeriodictyol differs from hesperitin only in the position of the methylated hydroxyl group and that it possesses a constitution represented by the following formula :

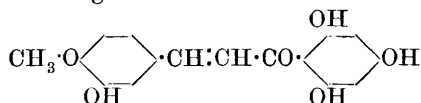


If this were the case, homoeriodictyol would contain three hydroxyl groups and should give a triacetyl derivative. Acetylhomoeriodictyol (m. p. 154°) was therefore prepared, but on examining this compound it was found to contain four acetyl groups. Homoeriodictyol cannot therefore be represented by the above formula. The only alternative is that it possesses a ketone structure, analogous to that of phloretin (*Ber.*, 1895, 28, 1393), and consequently must possess the following constitution :



From a consideration of these facts it would appear that homoeriodictyol is not so closely related to hesperitin as was at first supposed, provided that the latter compound is correctly represented by the ester structure assigned to it by Tiemann and Will. The chief evidence in support of this ester structure for hesperitin appears to be that deduced by A. G. Perkin (*loc. cit.*), who obtained from the latter a triacetyl derivative. On the other hand, if hesperitin is a true ester it is difficult to see why it should yield phloroglucinol and *isoferulic* acid when hydrolysed by boiling with concentrated alkalis,

and that when heated with more dilute alkali only amorphous colouring matters should be produced (compare Tiemann and Will, *loc. cit.*, p. 953). It was, moreover, shown by Perkin that when acetylhesperitin is hydrolysed by means of sulphuric acid it gives a quantitative yield of hesperitin, none of the latter undergoing hydrolysis, and this behaviour would not be expected were hesperitin itself an ester. In view of these considerations it is most probable that hesperitin also possesses the ketonic structure, notwithstanding the fact that no tetra-acetyl derivative appears as yet to have been obtained from it. If this should prove to be the case, hesperitin would have the following constitution :



It will be seen that this formula for hesperitin differs from that assigned to homoeriodictyol only in the position of the methoxy-group.

The fact that the empirical formula of eriodictyol ( $\text{C}_{15}\text{H}_{12}\text{O}_6$ ) differs from that of homoeriodictyol ( $\text{C}_{16}\text{H}_{14}\text{O}_6$ ) by the elements  $\text{CH}_2$ , and that these two substances occur together in the plant, led to the conclusion that the latter compound might be a monomethyl ether of the former. This view receives support from a comparison of their properties and also from the fact that eriodictyol contains no methoxyl group, whilst it has been shown that homoeriodictyol contains one such group.

By the action of acetic anhydride on eriodictyol two compounds have been obtained. One of these melts at  $137^\circ$  and yielded results on analysis which indicate that it contains either four or five acetyl groups, whilst the other melts at  $195\text{--}196^\circ$ . The latter compound is obtained by the more prolonged action of the anhydride, and is possibly formed by the elimination of a molecule of water from the acetyl derivative melting at  $137^\circ$  (compare Ciamician and Silber, *Ber.*, 1895, 28, 1395). The amount of eriodictyol at our disposal was insufficient to permit of its constitution being definitely ascertained.

Since the publication of abstracts of our paper (*loc. cit.*) on the "Chemical Examination of Eriodictyon" \* a communication by Mossler has appeared, entitled: "*Ueber die chemische Untersuchung von Eriodictyon glutinosum*" (*Annalen*, 1907, 351, 233). The author of this paper has isolated from eriodictyon leaves a substance of the formula  $\text{C}_{16}\text{H}_{14}\text{O}_6$  (m. p.  $214\text{--}215^\circ$ ) and proposes to designate it "eriodictionon." This substance is evidently identical with the com-

\* The full paper will appear in the *Proceedings of the American Pharmaceutical Association*, 1906.

pound which the present authors had previously described and designated *homoeriodictyol*, although it is stated to have a melting point eight degrees lower than that of homoeriodictyol. The observations of Mossler respecting the presence in homoeriodictyol of one methoxyl and four hydroxyl groups are in agreement with the results recorded in the present paper, but we are unable to confirm his statement regarding the formation of an oxime from homoeriodictyol and its acetyl derivative respectively. On treating acetylhomoeriodictyol with hydroxylamine or with semicarbazide, hydrolysis resulted, the product in both cases being readily soluble in a cold dilute solution of sodium carbonate. Homoeriodictyol, after treatment with hydroxylamine, was recovered unchanged.

It was finally stated by Mossler (*loc. cit.*, p. 253) that the results obtained by him did not permit of forming a conclusive opinion respecting the substance of the composition  $C_{16}H_{14}O_6$ , which he had isolated from eriodictyon leaves.

#### EXPERIMENTAL.

The method by which eriodictyol and homoeriodictyol were isolated from the leaves of *Eriodictyon californicum* was described in detail in the previous communication (*loc. cit.*), and was briefly as follows. The concentrated alcoholic extract of the leaves was distilled in steam for the removal of the volatile constituents, after which the aqueous liquid in the distillation flask was separated from the large cake of resins, and extracted with ether. On shaking this ethereal extract with a solution of sodium carbonate an alkaline aqueous liquid was obtained, which contained a crystalline precipitate of sodium homoeriodictyol. This substance was collected, purified by recrystallisation from hot water, decomposed by acetic acid, and the homoeriodictyol thus obtained recrystallised from 70 per cent. acetic acid. The original filtrate from the sodium homoeriodictyol, when acidified and extracted with ether, yielded eriodictyol, which was obtained pure by recrystallisation from alcohol, and subsequently from 70 per cent. acetic acid.

The resins which remained in the distilling flask were extracted with light petroleum and subsequently with ether, and on shaking the ethereal liquid thus obtained with a solution of sodium carbonate a further and larger quantity of sodium homoeriodictyol separated.

Homoeriodictyol,  $C_{16}H_{14}O_6$ , is moderately soluble in alcohol and in acetic acid, sparingly so in ethyl acetate, and nearly insoluble in water; it does not dissolve in either chloroform or benzene. When crystallised from 70 per cent. acetic acid it is obtained in handsome, pale yellow plates, which melt at  $223^\circ$ , and possess a slightly sweetish taste. If to a dilute alcoholic solution of homoeriodictyol a drop of

ferric chloride solution is added, an intense reddish-brown colour is produced.

An estimation of the methoxyl groups present in homoeriodictyol by means of Perkin's modification of Zeisel's method gave the following result :

0.2656 gave 0.2032 AgI. MeO = 10.1.

$C_{15}H_{11}O_5 \cdot OMe$  requires MeO = 10.3 per cent.

It is thus evident that homoeriodictyol contains one methoxyl group.

*Hydrolysis of Homoeriodictyol. Formation of Phloroglucinol and Ferulic Acid.*

Six grams of homoeriodictyol were dissolved in a solution of 18 grams of potassium hydroxide in 60 c.c. of water, and the mixture, which rapidly became very dark in colour, boiled for three hours in a flask attached to a reflux condenser. The liquid was allowed to cool, and then acidified with hydrochloric acid, when a quantity of tarry matter separated. As it was probable that this precipitate contained unchanged homoeriodictyol, an excess of calcium carbonate was added, the mixture heated for half an hour, and then filtered. The filtrate, which was very brown in colour, did not become decolorised when boiled with animal charcoal. Sodium carbonate solution was therefore gradually added to the hot liquid, when the precipitate of calcium carbonate which was formed carried down with it the greater part of the colouring matter, and was removed by filtration. The filtrate was concentrated somewhat under diminished pressure, then repeatedly extracted with ether, and the ethereal liquid, after being washed with water and dried with calcium chloride, yielded on evaporation a syrupy residue, which, on the addition of a little water, instantly became crystalline. This crystalline substance possessed a strong vanilla-like odour, and its aqueous solution gave a dark violet colour on the addition of a drop of a solution of ferric chloride. It was recrystallised from water, when it separated in plates which possessed a somewhat brown colour, and were associated with a small amount of a viscid substance, but was obtained pure by crystallisation from a little anhydrous ethyl acetate. This substance, when separated from its aqueous solution, evidently contained water of crystallisation, but, when crystallised from dry ethyl acetate, was obtained in the anhydrous state. When rapidly heated it melted at about  $218^{\circ}$  :

0.0778 gave 0.1622  $CO_2$  and 0.0344  $H_2O$ . C = 56.9 ; H = 4.9.

$C_6H_6O_3$  requires C = 57.1 ; H = 4.8 per cent.

This product of the hydrolysis of homoeriodictyol was thus identified as phloroglucinol, and the viscid substance originally associated with it,

which possessed the vanilla-like odour, doubtless contained vanillin, as this compound would be produced by the oxidation of the ferulic acid which was subsequently isolated.

The aqueous liquid, from which the phloroglucinol had been removed by means of ether, was acidified with hydrochloric acid, when an acid of a tarry nature separated. This mixture was then shaken with a considerable volume of ether, when a quantity of a liquid tarry substance did not dissolve, but remained mixed with the ethereal liquid. The aqueous liquid was therefore separated, and the ethereal solution shaken with animal charcoal and filtered. On evaporating the filtrate, a crystalline residue was obtained, which was dissolved in hot ethyl acetate, when, on cooling, it separated in almost colourless needles which melted at  $170^{\circ}$ . A dilute aqueous solution of this acid gave with ferric chloride a dark red precipitate. The acid was analysed with the following result :

0.1103 gave 0.2508  $\text{CO}_2$  and 0.0517  $\text{H}_2\text{O}$ . C = 62.0 ; H = 5.2.

$\text{C}_{10}\text{H}_{10}\text{O}_4$  requires C = 61.9 ; H = 5.2 per cent.

The properties of this substance agree with those of ferulic acid (4-hydroxy-3-methoxycinnamic acid), but for the purpose of confirming its identity with the latter a portion of it was methylated by means of sodium and methyl iodide, when 3 : 4-dimethoxycinnamic acid (m. p.  $180^{\circ}$ ) and its methyl ester (m. p.  $64^{\circ}$ ) were obtained.

*Fusion of Homoeriodictyol with Potassium Hydroxide.*—Two grams of homoeriodictyol were gradually added to a fused mixture of 20 grams of potassium hydroxide and a little water, the temperature of which was about  $120^{\circ}$ . A considerable amount of gas was evolved and the melt at first assumed a red colour, but when the temperature reached  $190^{\circ}$  the mass became colourless and tranquil. It was then dissolved in water, acidified with sulphuric acid, and extracted with ether, when an acid was obtained which crystallised from water in needles melting at  $192^{\circ}$ . This substance was evidently protocatechuic acid, as it gave with ferric chloride the colour reaction characteristic of this compound.

*Tetra-acetylhomoeriodictyol*,  $\text{C}_{16}\text{H}_{10}\text{O}_6(\text{CO}\cdot\text{CH}_3)_4$ .

Two grams of homoeriodictyol were dissolved in 10 grams of acetic anhydride and 1 gram of fused sodium acetate added. After boiling the mixture for four hours it was shaken with water until the greater part of the anhydride was decomposed. Ether was then added, and the mixture again shaken vigorously, when the acetylated product, which had not become solid, was dissolved by the ether, from which it separated almost immediately in a crystalline state. The crystalline acetyl derivative was collected on a filter, washed, dried, and

recrystallised from ethyl acetate, when it readily separated in slightly yellow needles which melted at  $154^{\circ}$ . On concentrating the mother liquors from this acetyl derivative, a substance separated which appeared to be not quite homogeneous, but no compound other than the acetylhomoeriodictyol melting at  $154^{\circ}$  could be isolated, nor was the melting point of this acetyl derivative altered by further crystallisation:

0.1239 gave 0.2794  $\text{CO}_2$  and 0.0524  $\text{H}_2\text{O}$ . C = 61.5; H = 4.7.

$\text{C}_{16}\text{H}_{11}\text{O}_6(\text{CO}\cdot\text{CH}_3)_3$  requires C = 61.7; H = 4.7 per cent.

$\text{C}_{16}\text{H}_{10}\text{O}_6(\text{CO}\cdot\text{CH}_3)_4$  ,, C = 61.3; H = 4.7 ,,

The acetyl groups present in acetylhomoeriodictyol were estimated as follows. A weighed quantity of the substance was hydrolysed by heating with a solution of potassium hydroxide, after which the liquid was acidified with sulphuric acid, and distilled from a double-necked flask until acid ceased to pass over:

0.3180 gave an amount of acetic acid equivalent to 0.1072 NaOH.

$\text{CH}_3\cdot\text{CO} = 36.2$ .

0.2964 gave an amount of acetic acid equivalent to 0.1016 NaOH.

$\text{CH}_3\cdot\text{CO} = 36.8$ .

$\text{C}_{16}\text{H}_{11}\text{O}_6(\text{CO}\cdot\text{CH}_3)_3$  requires  $\text{CH}_3\cdot\text{CO} = 30.1$  per cent.

$\text{C}_{16}\text{H}_{10}\text{O}_6(\text{CO}\cdot\text{CH}_3)_4$  ,,  $\text{CH}_3\cdot\text{CO} = 36.6$  ,,

In view of the statement of Mossler (*loc. cit.*) that acetylhomoeriodictyol affords an oxime, the following experiments were conducted. Half a gram of acetylhomoeriodictyol was dissolved in alcohol, and an aqueous solution of 0.5 gram of hydroxylamine hydrochloride and 0.9 gram of sodium acetate added. The mixture, which rapidly became bright yellow, was allowed to stand overnight, when, on the addition of water, a yellow, viscid product separated. This contained no nitrogen, and was completely soluble in a dilute solution of sodium carbonate. An analogous experiment was conducted with the use of semicarbazide hydrochloride, and a similar result was obtained. In order to ascertain whether hydroxylamine would react with homoeriodictyol itself, 1 gram of the latter substance was dissolved in alcohol and a concentrated aqueous solution of 0.47 gram of hydroxylamine hydrochloride added. To this a solution of 0.15 gram of sodium in ethyl alcohol was then added, the mixture warmed, and allowed to stand overnight, after which it was mixed with a large volume of water. A substance was thus precipitated, which was collected on a filter and crystallised from ethyl acetate, in which it dissolved only sparingly. It was then found to melt at  $223^{\circ}$ , and evidently consisted of unchanged homoeriodictyol.

Several experiments were made with the object of ascertaining whether a completely methylated homoeriodictyol could be obtained,



but it was found that the desired product was not readily formed. A *monomethylhomoeriodictyol* was, however, prepared in the following manner. A quantity of sodium homoeriodictyol was heated in a water-bath with an excess of methyl alcohol and methyl iodide, when the solid gradually passed into solution. After the heating had been continued for about three hours, water was added to the mixture, when a yellow substance was precipitated. This substance would not crystallise from anhydrous solvents, but when dissolved in a mixture of ether and 90 per cent. alcohol, and the solution allowed to evaporate spontaneously, it separated in aggregates of pale yellow leaflets which melted at about 80°. As thus obtained it evidently contained water of crystallisation, for, when heated at 100°, the fused substance gradually solidified, and was then found to melt at 138—139°:

0·1146, on heating at 105°, lost 0·0062 H<sub>2</sub>O. H<sub>2</sub>O = 5·4.

0·1084, dried at 105°, gave 0·2569 CO<sub>2</sub> and 0·0503 H<sub>2</sub>O. C = 64·6 ;  
H = 5·2.

C<sub>17</sub>H<sub>16</sub>O<sub>6</sub>, H<sub>2</sub>O requires H<sub>2</sub>O = 5·4 per cent.

C<sub>17</sub>H<sub>10</sub>O<sub>6</sub> requires C = 64·6 ; H = 5·1 ..

*Eriodictyol*, C<sub>15</sub>H<sub>12</sub>O<sub>6</sub>.

*Eriodictyol* crystallises in fawn-coloured plates which melt at 267°. It is moderately soluble in hot alcohol and in acetic acid, very sparingly so in boiling water, and insoluble, or very sparingly soluble, in the other usual organic solvents. The fixed alkalis and alkaline carbonates readily dissolve it, yielding at first almost colourless solutions, which, however, rapidly absorb oxygen and assume a deep brown colour. It was ascertained, by means of Perkin's modification of Zeisel's method, that *eriodictyol* contains no methoxyl group.

*Action of Acetic Anhydride on Eriodictyol.*—A small quantity of *eriodictyol* was dissolved in a large 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, and crystallised from ethyl acetate, when it was obtained in small tufts of minute, nearly colourless needles which melted at 195—196°. In another experiment 1 gram of *eriodictyol* was boiled for two hours with ten times its weight of acetic anhydride and 1 gram of anhydrous sodium acetate, at the end of which time water was added and the mixture shaken until the anhydride was decomposed. The product, which had not solidified, was then extracted with ether, the ethereal liquid being washed with a solution of sodium carbonate and subsequently with water. On removing the greater portion of the ether, a solid substance separated in the form of

almost colourless prisms. This substance was collected on a filter and recrystallised from ethyl acetate, when it was observed to be not quite homogeneous. After two recrystallisations, however, it was obtained pure, and was then found to melt at  $137^{\circ}$ :

0.0970 gave 0.2146  $\text{CO}_2$  and 0.0405  $\text{H}_2\text{O}$ . C = 60.3; H = 4.6.

$\text{C}_{15}\text{H}_8\text{O}_6(\text{CO}\cdot\text{CH}_3)_4$  requires C = 60.5; H = 4.4 per cent.

$\text{C}_{15}\text{H}_7\text{O}_6(\text{CO}\cdot\text{CH}_3)_5$  „ C = 60.2; H = 4.4 „

The mother liquors from this acetyl derivative yielded a small quantity of a substance which crystallised in tufts of white needles melting at  $195$ — $196^{\circ}$ , and was identical with the compound melting at this temperature which had previously been obtained by the more prolonged action of acetic anhydride on eriodictyol. The amount of eriodictyol available did not permit of the further examination of these acetyl derivatives.

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