

EUDESMIN AND ITS DERIVATIVES, PART I.

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THE object of the present series of papers is to determine the constitution of naturally occurring substances of Australian origin, and eudesmin was chosen for the first investigation because it appeared to be a substance unlike any other which had been found in plants, and also because it may readily be prepared in considerable quantity. The compound was discovered by Maiden and Smith in 1895, (Proc. Roy. Soc. N.S.W.) during the course of an investigation on the kinos of the Eucalypts, and so far as has been determined, eudesmin occurs only in the kinos of trees belonging to the genus *Eucalyptus*. It does not, however, occur in the exudations of all the species, and certain regularities and correspondences with earlier classifications of these trees have been observed. The distribution of eudesmin in the kinos seems to follow roughly the predominant oil constituents, and, as these are connected with characteristic leaf venations, it may also be said that a connection exists between the leaf venation and the occurrence of eudesmin in the kino. The kinos of species of *Eucalyptus* which contain phellandrene as the predominant constituent in the oil, all give a violet colouration with ferric chloride in aqueous solution, and in none of them has eudesmin been detected. This group includes a large number of species growing in Eastern Australia, and may also be taken to include such species as *E. Risdoni*, in the oil of which cineol is a pronounced constituent but which

also contains abundance of phellandrene. Another group free from eudesmin comprises most of the pinene yielding species, which are, however, usually distinguished from the phellandrene group by the fact that their kinos contain aromadendrin. On the other hand eudesmin has been observed in many of the kinos of the cineol-pinene oil bearing species and probably occurs in all of them, but always in association with aromadendrin.

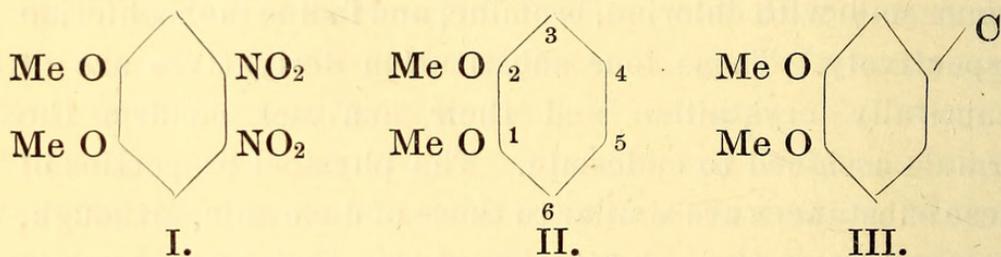
Probably not more than one-third of the known species of *Eucalyptus* growing in Eastern Australia have kinos which contain eudesmin, and in only a few of these does it occur in great amount. It is found in greatest abundance in the typical 'Boxes,' and the species employed for the preparation of the substance for the present research has been *Eucalyptus hemiphloia* which grows plentifully in the immediate neighbourhood of Sydney, and exudes a large amount of kino (sometimes in pieces the size of a hen's egg) which contains about 10 per cent. of eudesmin. The tannins of the group of kinos which contain eudesmin are catechol tannins, and eudesmin itself is a catechol derivative, whilst, on the other hand, the tannins of kinos not containing eudesmin are resorcinol or phloroglucin derivatives, and coupling together the above observations it appears that production of phellandrene in the oil is connected with production of metahydroxy phenols in the kino, whilst the cineol-pinene combination is associated with the production of catechol derivatives. On the very probable assumption that most of the constituents of plants are condensation, reduction, or oxidation products of carbohydrates, it may be stated with some confidence that the connection between the nature of the oil and the nature of the kino indicates some deep seated particular mode of condensation of the carbohydrate at an early stage, and, indeed, it is easy to see how stereochemical differences in aldohexoses could

give rise to the preferential production of either catechol or resorcin derivatives. This is an aspect of the chemistry of these trees which appeals to the authors as possessing great general significance, and we propose to follow up the investigation, and, to this end, a more detailed research into the constituents of *Eucalyptus kinos* is at present in progress.

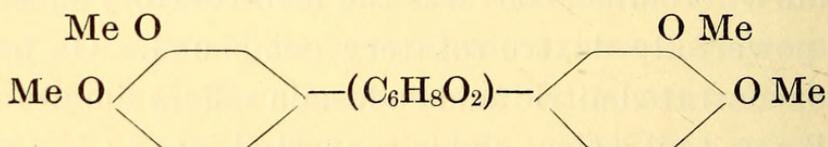
The Constitution of Eudesmin.

The analytical data recorded in the experimental portion of the paper show that the substance is $C_{22}H_{26}O_6$ and that it contains four methoxy groups. It is levo-rotatory and must, therefore, have one or more asymmetric carbon atoms. On treatment with nitric acid a dinitro-derivative is produced, and dichlor-, dibromo-, and diiodo eudesmins are as readily obtained by treating a glacial acetic acid solution of eudesmin with chlorine, bromine, and iodine monochloride respectively. These four substitution derivatives are all beautifully crystalline and their analyses confirm the formula assigned to eudesmin. The physical properties of these substances are similar to those of eudesmin, although, strange to say, the substitution of two hydrogen atoms in eudesmin by bromine, converts the levo-rotatory substance into a powerfully dextro-rotatory compound. On boiling with concentrated nitric acid eudesmin suffers simultaneous oxidation and nitration, and is converted into 4:5-dinitroveratrol (I) a substance whose constitution has been completely proved. Moreover a quantitative determination showed that the amount of dinitroveratrol that can be obtained from a given quantity of eudesmin, is very much greater than that which is theoretically possible on the assumption that the molecule contains only one veratrol nucleus. Eudesmin contains, therefore, two veratrol nuclei, and the four methoxy groups are thus accounted for. The manner of connection of the veratrol nuclei to the rest of

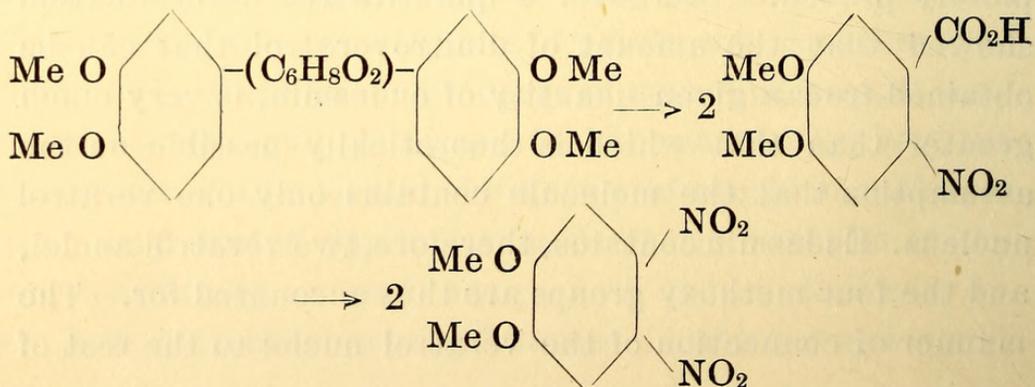
the molecule follows from the following considerations:— In the first place the connection must be with carbon and not oxygen, for, otherwise, the production of dinitroveratrol would be impossible. This connection may involve either the position 4- or 4:5- (II), but dinitroveratrol would not be produced if carbon were attached to the position 3- (or 6-) of the veratrol ring. It is evident from the ready production of disubstitution derivatives that each nucleus is attached in one position only to carbon, and confirmation of this statement may be found in the production of 6- bromo- veratric acid, unmixed with any isomeride, by the oxidation of dibromo-eudesmin by means of potassium permanganate. It may also be pointed out that the constitution of dinitro-eudesmin is proved by its subsequent conversion to 4:5- dinitroveratrol on boiling with nitric acid. The veratrol nuclei both occur, therefore, in the state of combination indicated in (III).



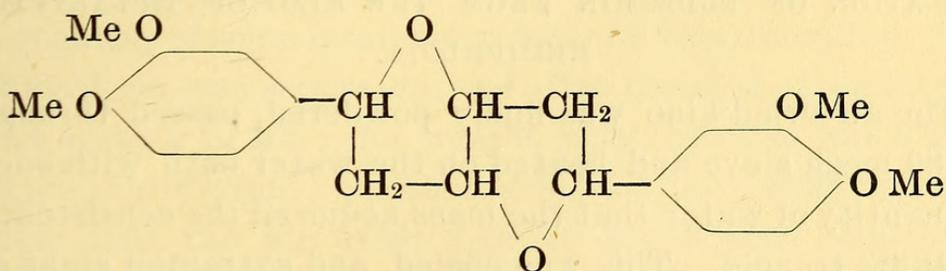
The formula of eudesmin may be written



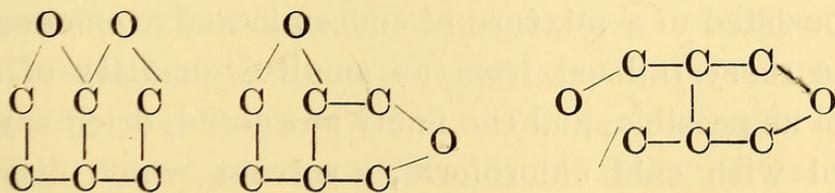
and its conversion to dinitroveratrol is represented in the scheme :



With regard to the central portion of the molecule the first point to notice is the function of the oxygen atoms. The negative experiments detailed in the experimental portion conclusively demonstrate the absence of hydroxyl or carbonyl groups. Both oxygen atoms have, therefore, ether function. The absence of ethylene linkages is also proved, and, if these conclusions be accepted as accurate, then an inspection of the above formula will show that this central portion of the molecule must contain two closed rings in order to account for the number of hydrogen atoms below the saturation capacity. Now there are six carbon atoms and two oxygen atoms, altogether eight atoms which could be members of a ring structure, and from this it follows that if the rings be separate the number of members in the two rings will be five and three or four and four—in either case a very improbable supposition. The rings are, therefore, fused as in naphthalene and the possible systems will then be seven fused with three, six with four, or five with five. The latter is clearly the most probable in view of the almost complete absence of three and four membered rings from natural products. The following formula indicates a probable constitution for eudesmin



although there is no evidence for the position of the veratryl rests, and the following ring systems are alternatives to the one figured above:—

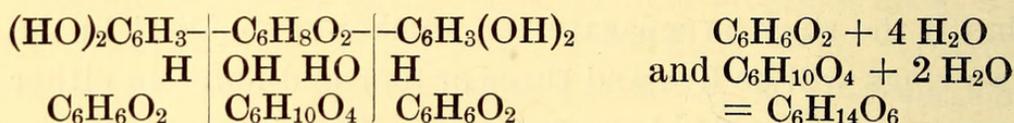


It is now proposed to make a series of oxidation and other experiments in order to advance further in our knowledge of this central portion of the molecule.

It will be admitted that methylation is an adventitious part of the synthesis of a plant product, and the formula of eudesmin stripped of its methyl groups appears as



If now a process of hydrolysis be imagined to occur, it will be seen that the nor-eudesmin splits up into three groups, each of which is in the same state of oxidation and could be regarded as a condensation product of a hexite $\text{C}_6\text{H}_{14}\text{O}_6$.



We believe therefore that when the constitution of eudesmin is completely elucidated, the central portion will be found to be readily derivable from a reduced hexose structure.

Experimental.

ISOLATION OF EUDESMIN FROM THE KINO OF EUCALYPTUS HEMIPHLOIA.

The air-dried kino was finely powdered, passed through an 80 mesh sieve and heated on the water bath with such a quantity of water that the mass acquired the consistency of thick treacle. This was cooled, and extracted eight or nine times with a considerable volume of ether, the combined yellowish extracts being then distilled. The residue, resulting from the evaporation of the ether was crystalline and consisted of a mixture of eudesmin and aromadendrin. It was recrystallised from as small a quantity of ethyl alcohol as possible, and the finely powdered, dried crystals treated with cold chloroform, a solvent which dissolves

eudesmin quite readily, but in which aromadendrin is very sparingly soluble. The filtered chloroform solution was evaporated and the residue crystallised several times from methyl or ethyl alcohols or from ethyl acetate. The above process was adopted after many comparative experiments, and it is especially important to employ a thick aqueous solution of the kino for extraction. In this way the tannins are retained by the water and the formation of a troublesome emulsion, so readily produced by more dilute solutions, is avoided.

The following method of gravimetric determination of the eudesmin in eucalyptus kinos has been devised, and is now illustrated in the case of the kino of *Eucalyptus hemiphloia* :

The finely powdered kino (1 gram) was dissolved in 50 ccm. of water by heating, and the cooled solution extracted during several hours with chloroform (10 ccm.), the process being then repeated with another equal quantity of chloroform. After remaining during twenty-four hours the mixture had resolved itself into two layers; a colourless chloroform solution containing the eudesmin, and an aqueous liquid containing the tannins. At the junction of the two, a quantity of some insoluble substance was deposited. The chloroform was separated, and after removal of the solvent and heating to 105°, the weight of the residue was 0.1 gr. Since this residue consisted of almost pure eudesmin it is clear that the air dried kino of *Eucalyptus hemiphloia* (with 9.9% H₂O) contains 10% eudesmin.

PROPERTIES OF EUDESMIN AND ANALYTICAL DATA.

Eudesmin is readily soluble in chloroform, benzene, acetic acid, and ethyl acetate, but sparingly so in cold methyl or ethyl alcohols and in ether. It also dissolves to some extent in boiling water and crystallises on cooling in slender needles. It is best crystallised from methyl alcohol and is

so obtained in colourless prismatic needles. When not quite pure, eudesmin occasionally crystallises in the form of leaflets. The melting point of pure eudesmin is 107° and although the molecule is large, small quantities of the substance may be distilled unchanged in vacuo. The substance is levo-rotatory and the following determinations have been made:—

1·3112 made up to 100 ccm. with chloroform at 21° gave

$$[a]_D = -64\cdot4^{\circ}$$

1·0022 made up to 10 ccm. with chloroform,

$$[a]_D = -64\cdot3^{\circ}$$

1·0834 made up to 10 ccm. with benzene,

$$[a]_D = -92\cdot3^{\circ}$$

1·0294 made up to 10 ccm. with acetic acid,

$$[a]_D = -73\cdot8^{\circ}$$

The first two determinations were made with distinct specimens of eudesmin and with different instruments, so that the rotation in chloroform is a physical constant, the determination of which will be of great value in proving the identity of eudesmin derived from different sources.

The following analyses of eudesmin have been performed:

0·1224 gave 0·3051 CO_2 and 0·0763 H_2O . C = 68·0; H = 6·9.

0·1206 gave 0·3018 CO_2 and 0·0718 H_2O . C = 68·2; H = 6·6.

0·1211 gave 0·3028 CO_2 and 0·0730 H_2O . C = 68·2; H = 6·7.

1·1972 dissolved in 77·504 benzene gave a solution whose freezing point was 193° lower than that of benzene. Whence M.W. = 392. $\text{C}_{22}\text{H}_{26}\text{O}_6$ requires C = 68·4, H = 6·7 per cent., and M.W. = 386.

The methoxy groups were determined by Zeisel's method:

0·1400 gave 0·3417 AgI. MeO = 32·2. $\text{C}_{22}\text{H}_{26}\text{O}_6$ containing 4 MeO requires MeO = 32·1 per cent.

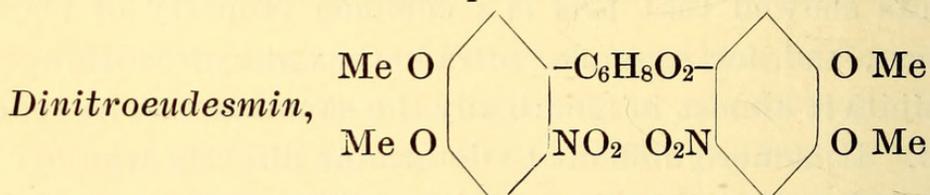
Eudesmin dissolves in sulphuric acid to a red solution which slowly becomes purple, this latter change is how-

ever prevented by the addition of veratrol and the colour obtained is then intense crimson lake. It is interesting to notice that a similar colour is produced when veratrol and glucose or cellulose are treated with concentrated sulphuric acid. With nitric acid eudesmin gives a pure yellow solution, from which, in course of time, a nitro derivative (dinitro.eudesmin, see below) separates in crystals. Since aromadendrin gives in nitric acid a fleeting green and then a red solution the progress of a separation of eudesmin and aromadendrin may be easily followed.

Eudesmin is unchanged by boiling alcoholic potash, by hydroxylamine, hydrazine and phenylhydrazine, and by semicarbazide in dilute acetic acid solution. It is also inactive towards acetylchloride, benzoyl chloride, phenyl isocyanate, and was recovered unchanged after being boiled during an hour with acetic anhydride and sodium acetate. It is clear, therefore, that it contains neither carbonyl nor hydroxyl. With an ethereal solution of magnesium methyl iodide a colourless precipitate is formed, but a few experiments showed that this is a common property of phenol ethers, and, for example, tetramethoxydihydroanthracene exhibits it almost in identically the same manner as eudesmin. It is more difficult to determine directly whether or not eudesmin contains ethylene linkages. It reduces potassium permanganate slowly in acetone solution, and is quickly attacked by bromine, but the reaction is one of substitution, and is accompanied by the production of hydrobromic acid, however little bromine is employed. The substitution derivatives described below are quite stable towards halogens, and eudesmin must, therefore, be saturated. Confirmation of this conclusion is obtained by studying the reduction of the substance since it was found that eudesmin is unchanged after treatment with a great excess of sodium amalgam in aqueous alcoholic solution, as also

by treatment with hydrogen in the presence of colloidal palladium. Eudesmin may be boiled with aniline without condensation and is recovered unchanged.

Cold aqueous hydrobromic acid dissolves it, but the solution soon clouds and an oil separates. At the same time a pink colour appears, and this is much increased if the liquid be heated. On the addition of water an almost colourless precipitate is obtained, but could not be crystallised. This substance contained bromine which was removed by means of alcoholic potash, without, however, altering the appearance of the substance. The bromine free product could also not be crystallised. When the aqueous hydrobromic acid solution was boiled and then diluted with water, the odour of guaiacol was very pronounced. On oxidation of eudesmin in the usual manner with potassium permanganate, a small quantity of veratric acid was isolated. There was also evidence of the presence of a phenyl glyoxylic acid, and when larger amounts of eudesmin are available, this oxidation will be studied in greater detail than has been possible hitherto.



This nitro derivative is obtained by the action of nitric acid on eudesmin under almost any conditions in the cold. It is produced slowly when the reagent is 30% aqueous nitric acid, and is also the product obtained when cold concentrated nitric acid is allowed to react with eudesmin. The substance is a dinitro derivative but it was not found possible to prepare a mononitro or any higher nitro eudesmins by modifications of the conditions. The following method of preparation is most convenient:—

A solution of eudesmin (5 gr.) in acetic acid (25 ccm.) was carefully cooled under the tap and a mixture of nitric

acid ($D = 1.42$, 10 ccm.) and acetic acid (15 ccm.) gradually added. When all the nitric acid had been added, the nitro derivative crystallised from the solution, and, after five minutes, the mixture was diluted with water, the precipitate collected, washed with water, dried and crystallised first from acetic acid and then from ethyl acetate. The substance is, when freshly prepared, almost colourless and crystallises from all solvents in the form of extremely slender needles, which fill the whole solution. It melts without decomposition at 214° .

0.1275 gave 0.2608 CO_2 and 0.0582 H_2O . $C = 55.8$; $H = 5.1$.

0.1242 gave 5.9 ccm. N_2 reduced to N.T.P. $N = 6.0$.

$\text{C}_{22}\text{H}_{24}\text{O}_6(\text{NO}_2)_2$ requires $C = 55.5$, $H = 5.0$, $N = 5.9$ per cent.

Dinitroeuodesmin turns yellow on exposure to light, and dissolves in sulphuric acid to a bright red solution. It is unchanged by treatment with nitric acid in the cold, and is perfectly stable to bromine in carbon disulphide solution. It is readily soluble in chloroform but sparingly so in other solvents, and remarkably sparingly soluble in alcohol. It may be easily reduced by means of tin and hydrochloric acid, but the corresponding amine is unstable and undergoes some decomposition in acid solution, which will be further investigated. The solution of the aminoeuodesmin obtained by elimination of the tin with hydrogen sulphide gives a bright blue colour with ferric chloride, and exhibits the diazo reaction. The constitution of dinitroeuodesmin as regards the position of the groups directly attached to the benzene nuclei is clearly proved by the experiment described in the next section.

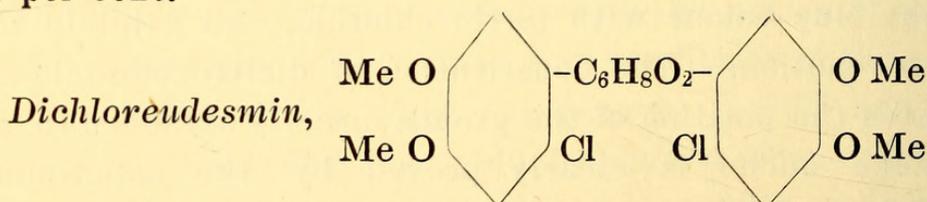
SIMULTANEOUS OXIDATION AND NITRATION OF EUDESMIN;
FORMATION OF 4:5—DINITROVERATROL.

Euodesmin (1 gr.) was boiled for ten minutes with ordinary concentrated nitric acid (10 ccm.) when the substance was oxidised and a large amount of nitrous fumes evolved. The

liquid was diluted with water and the precipitated solid crystalline substance separated and crystallised from methyl alcohol, and then again from ethyl alcohol. It was so obtained in pale yellow needles which melted at 132° , and at the same temperature when mixed with an equal quantity of 4:5-dinitroveratrol. The substance was further identified with 4:5-dinitroveratrol by a careful direct comparison, and by the preparation of a quinoxaline derivative by reduction and condensation with phenanthrenequinone in the usual manner. The nitric acid solution after separation of the dinitroveratrol was examined and found to contain oxalic acid.

This important experiment was performed quantitatively and it was found that the yield of dinitroveratrol was greater than the theoretical on the assumption that the molecule of eudesmin contains only one veratrol nucleus. It is, therefore, beyond question that eudesmin contains in its molecule two veratrol nuclei.

0.6451 gr. eudesmin gave by the above method 0.6926 gr. dinitroveratrol, perfectly dry but in the crude condition. This is a yield of 90 per cent. on the assumption that there are two veratrol nuclei. After crystallisation the amount of perfectly pure dinitroveratrol was 0.531 gr., a yield of 69 per cent.



A slow stream of chlorine was passed through a well cooled solution of eudesmin (5 gr.) in acetic acid (50 ccm.) during half an hour. Hydrochloric acid was produced and a very sparingly soluble crystalline substance precipitated. After dilution with an equal volume of water, the solid was collected and crystallised, first from acetic acid

(needles), and then again from ethyl acetate until no change in the melting point could be observed. The colourless, rectangular plates melted at 163° .

0.1302 gave 0.0840 AgCl. Cl = 15.8

$C_{22}H_{24}O_6Cl_2$ requires Cl = 15.5 per cent.

This compound is stable to bromine in carbon disulphide solution, and dissolves in sulphuric acid to a red solution which very quickly becomes dirty brown red and then slowly dark green and green blue, finally the solution becomes almost colourless and a black precipitate is produced.

DIBROMEUEDESMIN, (CONSTITUTION SIMILAR TO THAT SHOWN ABOVE FOR DICHLOREUEDESMIN).

A solution of bromine (12 gr.) in acetic acid (55 ccm.) was added in the course of five minutes to eudesmin (5 gr.) in acetic acid (25 ccm.) any rise of temperature being checked by cooling in running water. After a further five minutes a dilute solution of sodium sulphite was added and the crystalline precipitate collected and recrystallised from ethyl acetate. Although this solvent was found to be the most satisfactory for the crystallisation of large amounts of this bromo derivative, yet, when it is used a slight pink tint of the crystals cannot be removed, and, for analysis, a portion was crystallised from glacial acetic acid and so obtained in the form of colourless prismatic needles which melt at 172° .

0.1778 gave 0.1233 AgBr. Br = 29.5

$C_{22}H_{24}O_6Br_2$ requires Br = 29.4 per cent.

This compound always crystallises in needles and is very sparingly soluble in most organic solvents, readily, however, in chloroform. Its specific rotation was accordingly determined in this solvent.

0.9182 made up to 25 ccm. with chloroform gave

$[\alpha]_D^{22} = +69.4^{\circ}$

The colour reaction with concentrated sulphuric acid was almost exactly the same as that described for dichlor-eudesmin (see above). Bromine in carbon disulphide solution leaves this substance unchanged under ordinary conditions, but, if a solution containing the bromo derivative and bromine is placed in a quartz vessel in the sunlight, reaction occurs and the bromine is very slowly absorbed. Even in this case, however, hydrobromic acid is produced and the action is evidently one of further substitution.

DIIDOEUEDESMIN, (CONSTITUTION CORRESPONDING TO THAT OF DICHLOREUEDESMIN).

Iodine does not attack eudesmin, and in order to produce an iodo derivative, recourse was had to the action of iodine monochloride. The yield of this compound was, however, not so satisfactory as that of the chloro and bromo derivatives.

Eudesmin (5 gr.) dissolved in acetic acid (50 ccm.) was gradually treated with 50 ccm. of an acetic acid solution of iodine monochloride (containing 64 grs. ICl in 500 ccm. acetic acid) and the whole then heated on the steam bath during half an hour. The mixture was then treated with excess of aqueous sulphurous acid and the sticky residue dissolved in acetic acid. After standing overnight in the ice chest feathery needles were found to have separated, and these were collected and recrystallised from ethyl acetate. The colourless needles were sparingly soluble in organic solvents with the exception of chloroform and melted without decomposition at 175°.

0.1113 gave 0.0824 AgI. I = 40.0

$C_{22}H_{24}O_6I_2$ requires I = 39.8 per cent.

The substance is similar in most of its properties to the previously described bromo derivative, but, on treatment with nitric acid it loses its iodine as such. Iodine in the elementary condition is also observed as a momentarily

formed black precipitate on dissolving the diiodo derivative in concentrated sulphuric acid, when, however, a brown solution is quickly produced as the result of some further reaction.

OXIDATION OF DIBROMEUEDESMIN ; FORMATION OF 6-BROMO-
VERATRIC ACID.

Dibromeudesmin (5 gr.) was dissolved in hot acetic acid and the solution poured into a large volume of cold water. The finely divided substance was collected, washed with water, and oxidised at about 50° with three per cent. aqueous potassium permanganate with continual shaking. The oxidation was very slow at first, but soon became more rapid, and was discontinued when the amount of unchanged substance became relatively small. This point was determined by means of tests made from time to time on a portion of the well stirred liquid, which was saturated with sulphur dioxide until the manganese precipitate dissolved. The excess of permanganate was destroyed by sulphurous acid and the liquid heated, filtered, concentrated to small bulk and acidified whilst hot with hydrochloric acid. On cooling, needles separated from the solution and these were recrystallised several times from hot water, the first solution being decolourised with the aid of animal charcoal. The colourless satiny needles melted at 184° and at the same temperature when mixed with an equal quantity of 6-bromoveratric acid which had been prepared by the hydrolysis of its methyl ester obtained by the bromination of methyl veratrate in acetic acid solution.



Robinson, R and Smith, Henry George. 1914. "Eudesmin and its derivatives, Part 1." *Journal and proceedings of the Royal Society of New South Wales* 48, 449–463. <https://doi.org/10.5962/p.359667>.

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