HYDROXY-CARBONYL COMPOUNDS

A Thesis presented

by

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The author is indebted to Professor A. Robertson for advice and helpful criticism during the course of these investigations.

C O N T E N T S

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SUMMARY

This thesis begins with a brief survey dealing with a large number of naturally occurring furano-benzo-pyrones, which differ from each other only in the number, relative positions of the heterocyclic oxygen ring system, or the nature of the substituent groups (hydroxyl, methoxyl, methyl, etc.). It then deals with the thermal rearrangement of allyl ethers of various phenols and hydroxy coumarins. This account has been considered necessary, since it is with the allyl migration that the preparation of certain methyldihydrofurano-coumarins and methyldihydrofurano-chromones has been achieved. An account is given of allyl migration of various allyloxy coumarins, from which a methyldihydrofurano-ring system is obtained. Mention is made of the methods for the preparation of methyldihydrofurano-chromones from 4-hydroxy-5-acetyl-2-methyldihydrobenzofurane. The latter was obtained by cyclisation of 3-allylresacetophenone. An unsuccessful attempt to obtain 4-hydroxy-2-methyldihydrobenzofurane by alkali fission of 2'-methyldihydrofurano-(4':5')-4-methyl-coumarin (8:7) is described, which is an endeavour to obtain an easily

accessible phenol for the synthesis of coumarins and chromones. The preparation of these compounds is part of a comprehensive study of the relationship between the structure of an organic compound and its physiological activity which is being conducted in these laboratories. Their physiological activity will be tested at a later date.

Next, an investigation into the constitution of euparin, the yellow bitter principle of gravel roots, is described, and an historical survey is given of the previous researches on this subject.

A new method for isolation of euparin is successfully adopted. The molecular formula $C_{13}H_{12}O_3$ for euparin is accepted beyond doubt, the recent empirical formula $C_{12}H_{11}O_3$ being rejected after consideration of certain data. Euparin contains one phenolic hydroxyl group. That euparin contains two reducible double bonds in a conjugated system is proved by quantitative hydrogenation and by an additive reaction with maleic anhydride. Oxidation and ozonolysis experiments revealed that (a) one resacetophenone nucleus is present and (b) one of the double bonds is in the β-position to the nucleus, and the other is a methylene double bond. Hydrogenation of euparin takes a normal course, on consideration of hydrogenation experiments of euparin

methyl ether. The Beckmann transformation of tetrahydro-euparin — methyl ether oxime is achieved. The formation of a 2-methylchromone from tetrahydro-euparin is outlined. These reactions indicate that tetrahydro-euparin contains a phenolic hydroxyl group in an ortho-position to an acetyl group. In an endeavour to prove the presence of a furane ring in euparin, an unsuccessful attempt to oxidise euparin with hydrogen peroxide is made. In spite of this failure, the majority of practical evidence leads to the prediction of only two alternative formulae for tetrahydro-euparin.

The next part of this thesis is devoted to the synthesis of 6-hydroxy-5-acetyl-2-isopropyl-dihydrobenzofurane, which is one of the predicted formulae for tetrahydro-euparin. The result fully justifies the prediction. The synthesis of this compound involved in the first instance a method for the synthesis of 6-hydroxy-2-isopropyl-dihydrobenzofurane, which is successfully achieved. A description is given of the application of the Hoesch reaction and of the Fries reaction to the phenol, furnishing tetrahydro-euparin and 6-hydroxy-7-acetyl-2-isopropyl-dihydrobenzofurane respectively. Though the constitution of euparin has not been confirmed by an unequivocal synthesis, it is probably 6-hydroxy-5-acetyl-2-isopropylene-benzofurane, on consideration of

tetrahydro-euparin.

The appendix describes a new method for the synthesis of 2-methoxyresacetophenone from resacetophenone itself.

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I N T R O D U C T I O N

INTRODUCTION

Heterocyclic compounds of the furano-pyrone or furano-benzopyrone type are widely found in various plants. They differ from each other only in the number, relative positions of the heterocyclic ring system, or the nature of the substituent groups (hydroxyl, methoxyl, methyl, etc.). Coumarins stand in a unique position. According to Späth in his papers of May 1937 (Ber., 1937, 70 A, 83), the coumarins isolated from plants are classified into the following distinct groups.

(1) Coumarin and its simple derivatives.

(2) Hydroxy- and methoxy-(alkoxy)-coumarins and the glycosides, and in certain cases the esters of these substances.

(a) The hydroxyl or alkoxyl radicals in the benzene nucleus.

(b) The substituents are attached to the pyrone ring.

(3) The hydroxy or methoxy-coumarins into which alkyl radicals are introduced in the benzene or pyrone nucleus.

(4) Furo-coumarins which contain a furane ring attached to a benzene ring.

(a) The furane ring is not substituted.

(b) There are substituents in the furane ring.

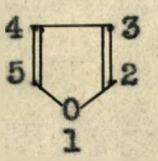
(5) The coumarins which contain 2:2-dimethyl-1:2-chromeno ring.

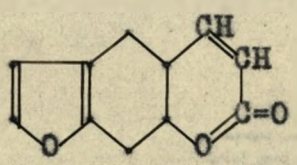
About 48 natural coumarins have been known, the constitutions of which have been fully investigated.

It is therefore of interest to make a choice of the study of furano-benzopyrones or furano-pyrones, which are related to the furo-coumarins of group (4).

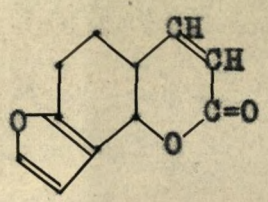
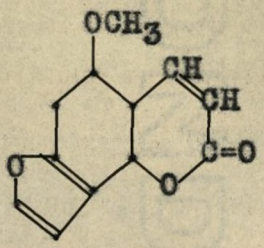
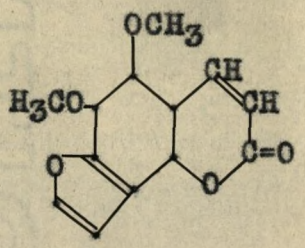
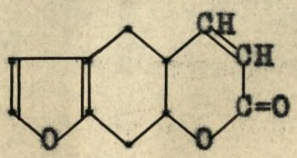
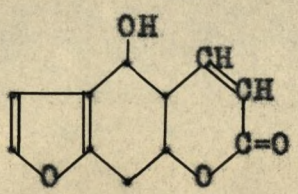
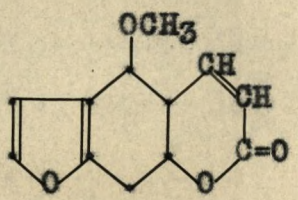
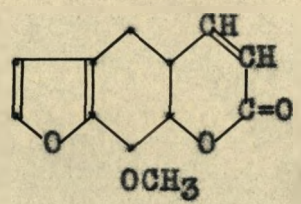
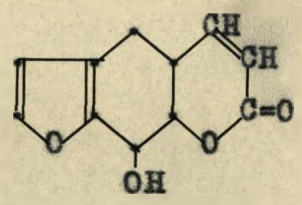
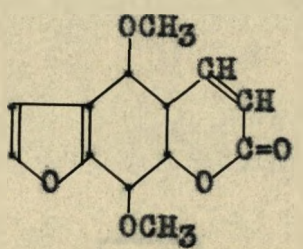
Group (4a).

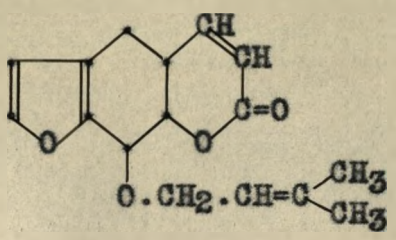
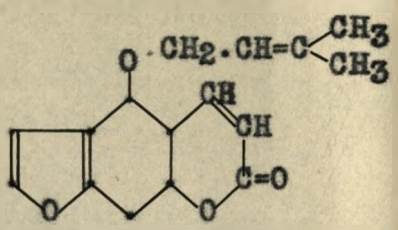
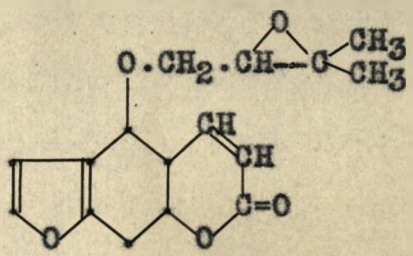
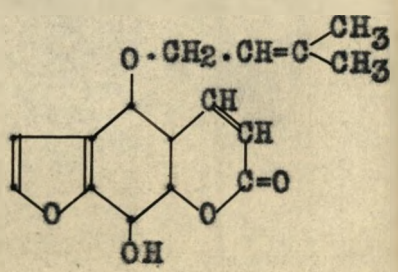
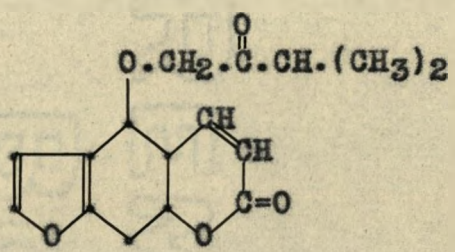
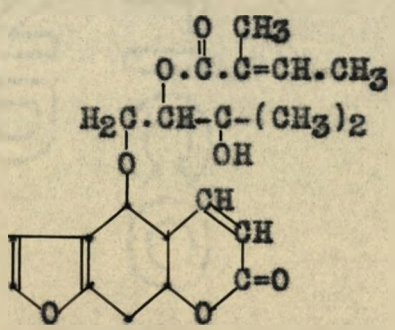
Those which belong to the furo-coumarins of group (4a) include a benzofurane type (coumarone), of which there are six possible isomers, the benzene ring being fused into the furane ring in the 2:3-positions.

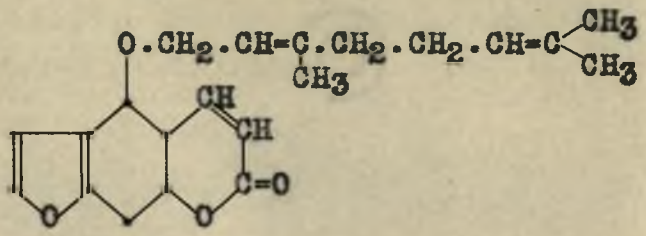




These form an interesting class of natural coumarins, of which the following members represent the typical examples:-

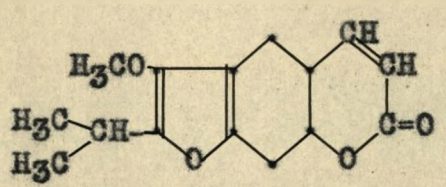
Typical member	Derivatives
 Angelicin	 Isobergapten  Pimpinellin
 Psoralene	 Bergaptol  Bergapten
	 Xanthotoxin  Xanthotoxol
	 Isopimpinellin

Typical member	Derivatives
Psoralene	 Imperatorin  Iso-imperatorin
	 Oxy-peucedanin  Allo-imperatorin
	 Iso-oxypeucedanin
	 Ostruthol

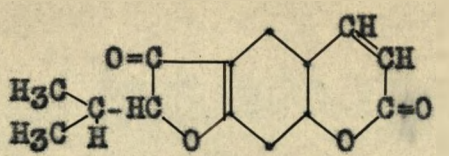
Typical member	Derivatives
Psoralene	 Bergamottin

Group (4b).

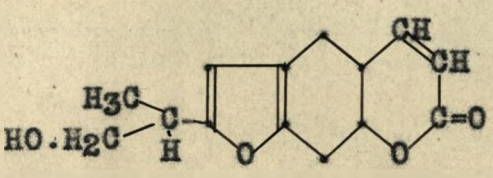
To this group belong peucedanin, oreoselone, nodakenin and nodakenetin as typical members.



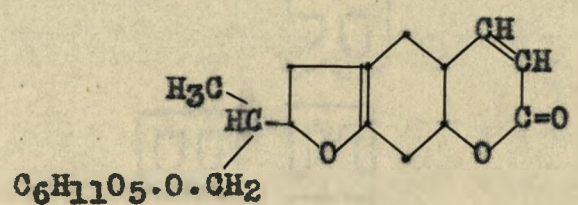
Peucedanin



Oreoselone



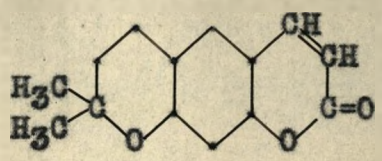
Nodakenetin



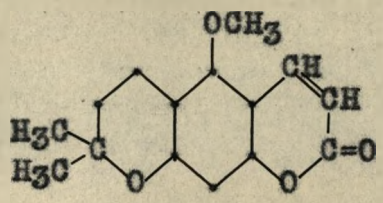
Nodakenin

Group (5).

To Group (5) belong xanthyletin and xanthoxyletin which are obtained from xanthoxylum americanum.

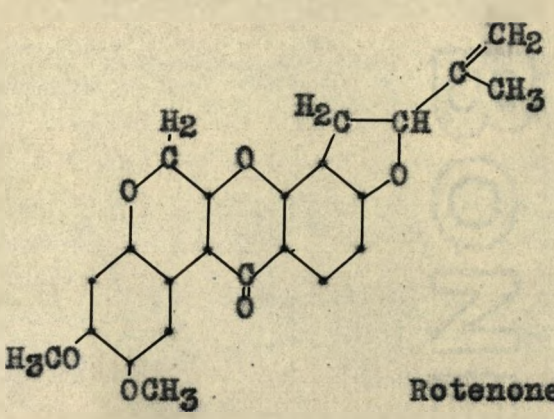


Xanthyletin



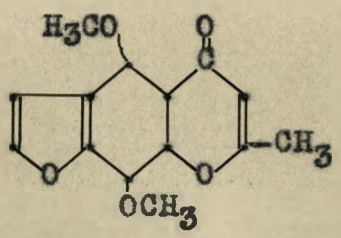
Xanthoxyletin

Further, one of the more complex natural products of the heterocyclic oxygen ring system is to be found in rotenone and the related compounds, the former containing a benzo-γ-pyrone in conjunction with chromano- and furano- rings.



Rotenone

Recently Späth (Ber., 1938, 106) isolated kellin from Ammi visnaga. It is a furo-benzo-γ-pyrone.



Kellin.

The naturally-occurring furo-coumarins in general possess toxicating properties towards fish and insects (Späth, Ber., 1937, 70 A, 115). Compounds like peucedanin, ostruthin and pimpinellin, for example, have a pronounced physiological action on mice.

Although investigations have been carried out on the comparative toxicities of certain naturally-occurring compounds towards fish and insects, no definite conclusions were drawn regarding which portions of the molecule are responsible for, or contribute to, this particular property. Among the naturally-occurring fish poisons, the members of the rotenone group showed marked physiological action. Rotenone consists of complex substances containing three heterocyclic rings, and tests have been applied to these members and some of their degradation products, but the results are in some cases conflicting. (Cf. Gersdorff, J.Amer.Chem.Soc., 1930, 52, 5051; 1933, 55, 1147; 1934, 56, 979; Danneel, Arch.Expt. Path.Pharm., 1933, 170, 59.) In addition to the rotenone group, certain furano-coumarins, e.g. bergapten, which contain more than one heterocyclic system in the molecule

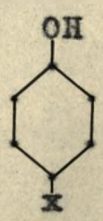
give marked evidence of insecticidal properties. It is evident that there is a relationship between the structures of these compounds and their toxicities towards fish.

Hence, the preparation of a number of compounds containing two heterocyclic systems was undertaken in an endeavour to elucidate the relationship between the structure of a compound and its physiological properties. The following pages describe the syntheses of certain methyldihydrofurano-coumarins and methyldihydrofurano-chromones, the physiological action of which will be studied at a later date. The syntheses of the latter compounds involve the application of thermal rearrangement of allyl ethers of various phenols and coumarins, which are described in the earlier pages.

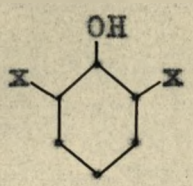
The problem regarding the constitution of euparin is therefore a matter of considerable interest in relation to the widely distributed furo-compounds in general. Its molecular formula $C_{13}H_{12}O_3$ is accepted beyond doubt. Degradation experiments lead to the prediction of a formula for tetrahydroeuparin which is proved by an unequivocal synthesis.

It was shown by Claisen (Ber., 45, 3157) that the allyl ethers of many phenols, on heating, underwent a rearrangement, furnishing allylphenols. β-Naphthol

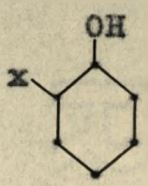
allyl ether isomerised into allyl β-naphthol. Claisen and Eisleb (Ann., 401, 26) extended the method to the substituted phenols of type (I), in which both the ortho-positions were free; of type (II), in which both the ortho-positions were substituted, leaving free para-position; and of type (III), in which the ortho- and para-positions were free.



(I)

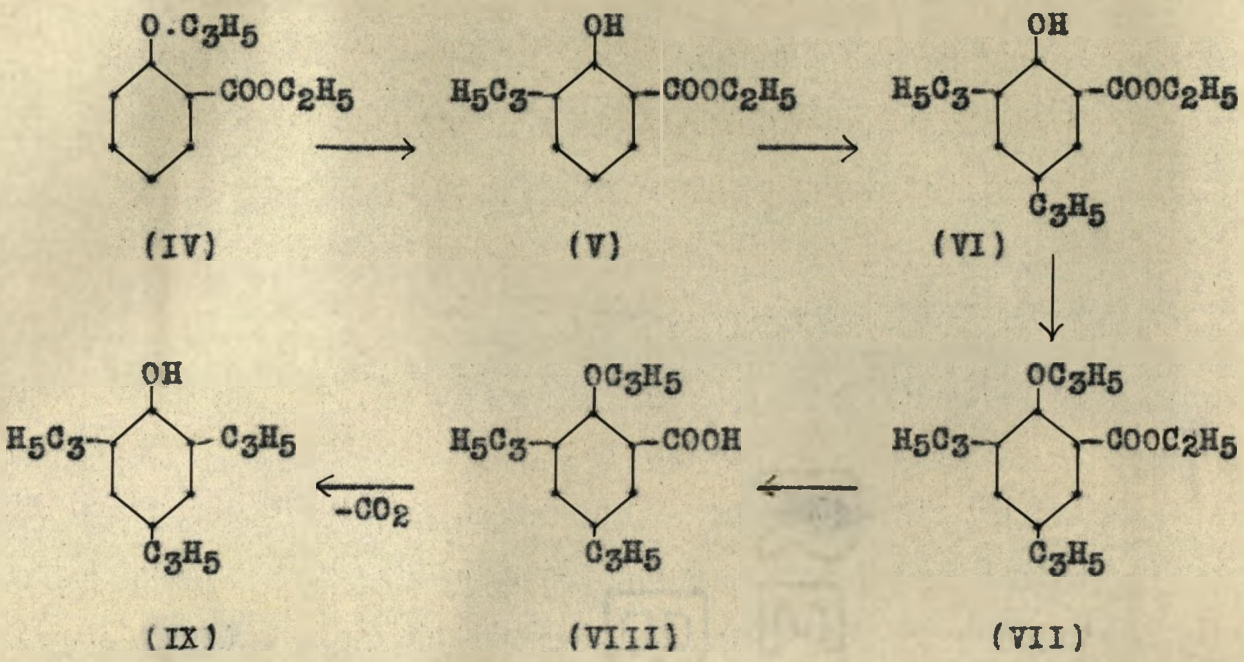


(II)

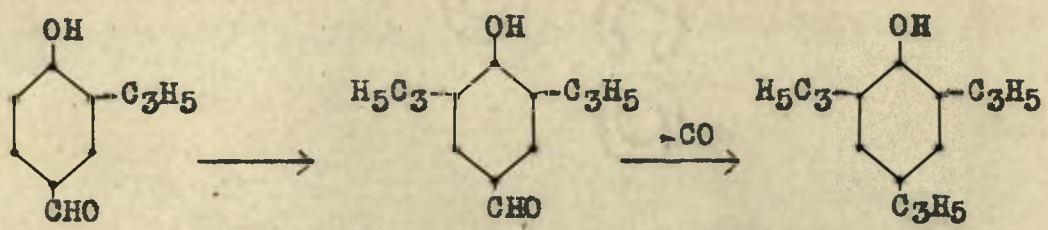


(III)

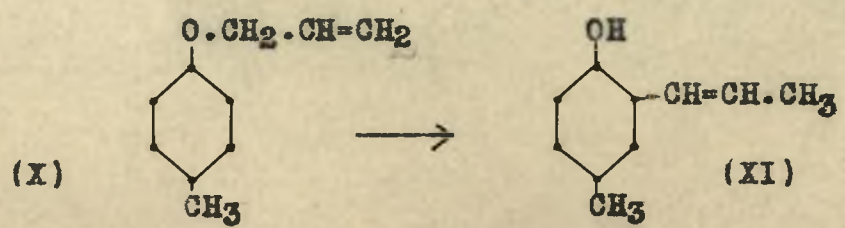
In type (I), the allyl group entered the ortho-position, in type (II), it entered the para-position, and in type (III), the ortho-position was preferential. In the case of an ortho-hydroxy carboxylic acid of salicylic acid type, an interesting isomerisation took place. The allyl group replaced the carboxylic group with the loss of carbon dioxide through the stages (IV) to (IX) summarised below.



In an analogous manner the allyl ether of para-hydroxybenzaldehyde underwent the following rearrangements.

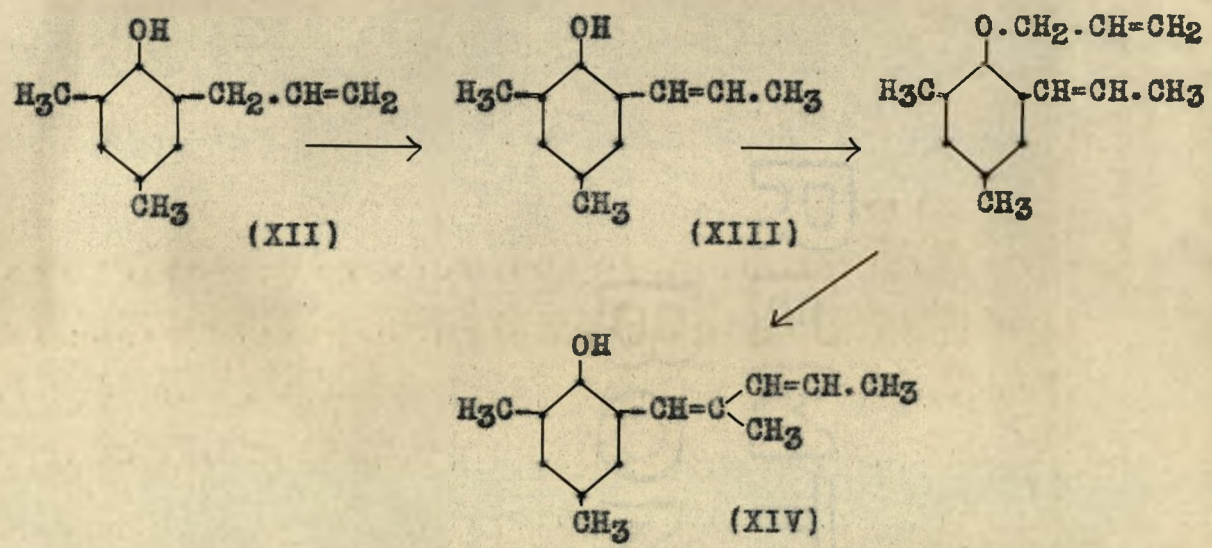


It is interesting to note that treatment of o-allyl-p-cresol (X) with strong alkali at 140°C. (Anwers, Ann., 413, 299) gave rise to the isomeric o-propenyl-p-cresol (XI).

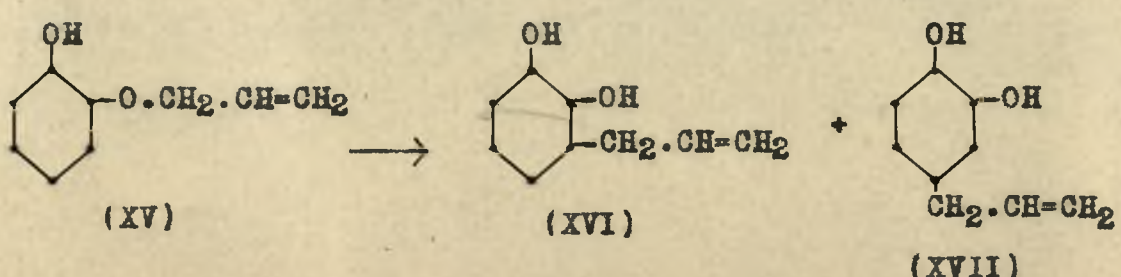


(X) (XI)

Further, according to the observation of Claisen and Tietze (Ann., 449, 88), treatment of o-p-dimethyl o-allyl phenol (XII) with 26% methyl alcoholic alkali furnished o-p-dimethyl o-propenylphenol (XIII) which, on further allylation and subsequent treatment with 26% methyl alcoholic alkali, afforded o-p-dimethyl o-(β-propenyl-propenyl) phenol (XIV).

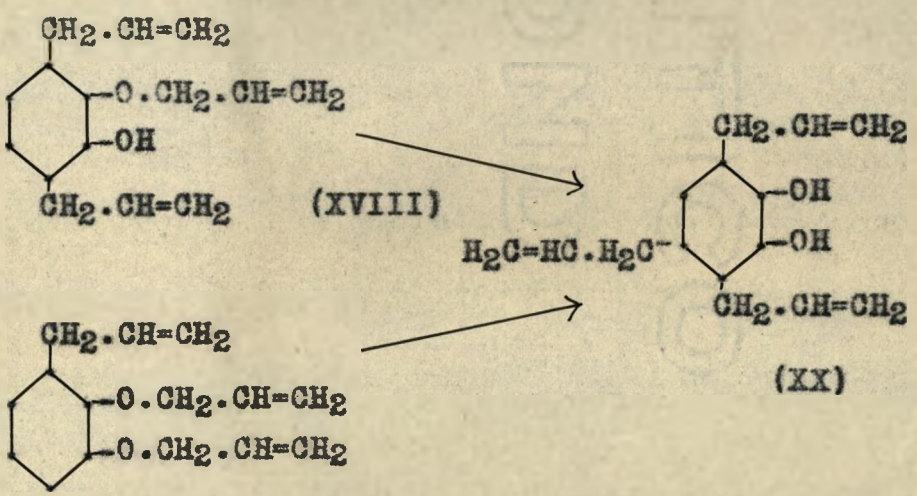


According to Kawai (Sci.Papers Inst.Phys.Chem.Res., 1926, 3, 263), Perkin Jr. and Trikojus (J.C.S., 1927, 1663), the catechol mono-allyl ether (XV) isomerised into both 3-allyl catechol (XVI) and 4-allyl catechol (XVII), the former predominating.



From catechol diallyl ether, Kawai obtained an evidence for a rearrangement into 3:5-diallyl catechol.

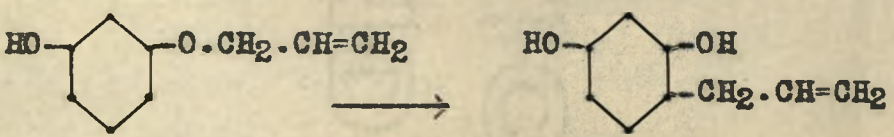
Hurd and his co-workers (J.Amer.Chem.Soc., 1930, 52, 1702) extended the study of these ethers to triallyl catechol (XX) which they obtained in two ways: firstly, from the rearrangement of mono-allyl ether of diallyl-catechol (XVIII), and secondly, from the diallyl ether of mono-allyl catechol (XIX).



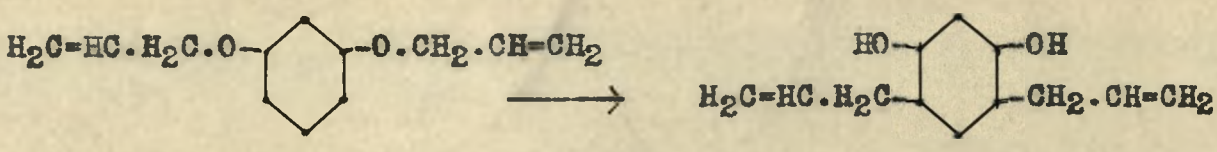
Similarly, tetra-allyl-catechol was also prepared by isomerisation of diallyl-ether of diallyl-catechol.

According to Hurd and his co-workers (loc.cit.), resorcinol mono-allyl ether (XXI) isomerised exclusively to 1-allyl-2:4-dihydroxybenzene (XXII). The diallyl ether of resorcinol (XXIII) was found to undergo a rearrangement into 1:5-diallyl-2:4-dihydroxybenzene

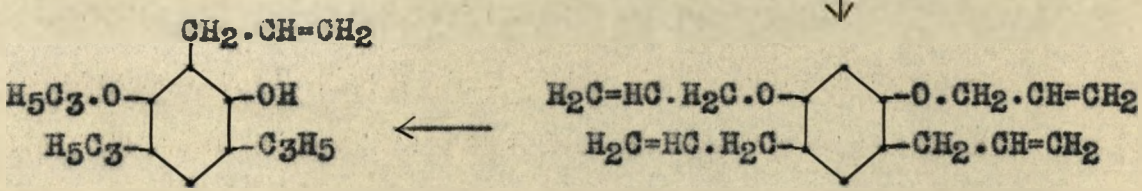
(XXIV). The diallyl ether of the latter compound still has two available nuclear carbon atoms, but one of them is meta; therefore one of the allyl groups wandered to the ortho-position, furnishing 1:3:5-triallyl-2-allyloxy-4-hydroxybenzene (XXV). It was observed that the rearrangements took place with evolution of heat and that the temperature for the allyl migration was in the region of 200°C.



(XXI) (XXII)



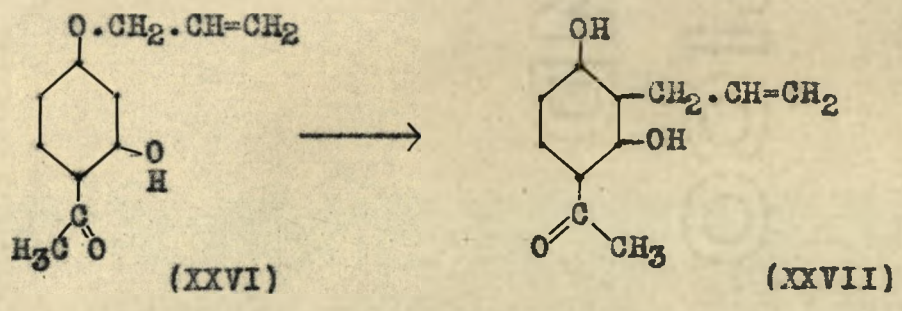
(XXIII) (XXIV)



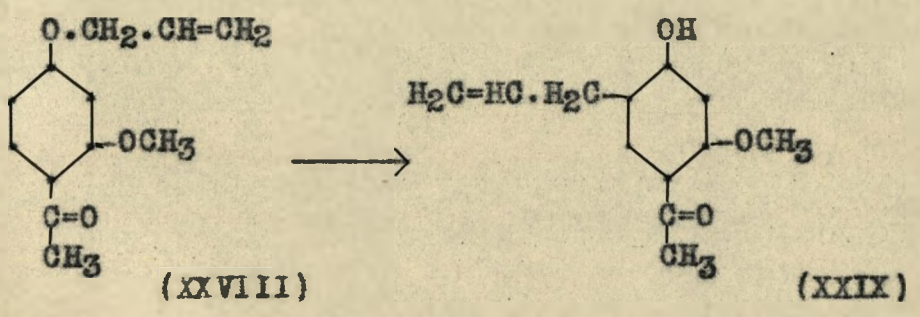
(XXV)

The allyl rearrangement in a phenol nucleus appears to afford one of the best methods of establishing

the positions of a double bond in the nucleus. It is evident that the allyl group can migrate only to that o-carbon atom which is doubly bound to the $C.O.CH_2.CH=CH_2$ group. On this basis, Baker (J.C.S., 1935, 628) showed that the thermal rearrangement of 4-o-allylresacetophenone (XXVI) gave exclusively 3-allyl-resacetophenone (XXVII) and that the rearrangement of 2-o-methyl-4-o-allyl-resacetophenone (XXVIII) gave the differently oriented 2-o-methyl-5-allyl-resacetophenone (XXIX), a symmetrical type of product, usually given by a resorcinol derivative.



(XXVI) (XXVII)

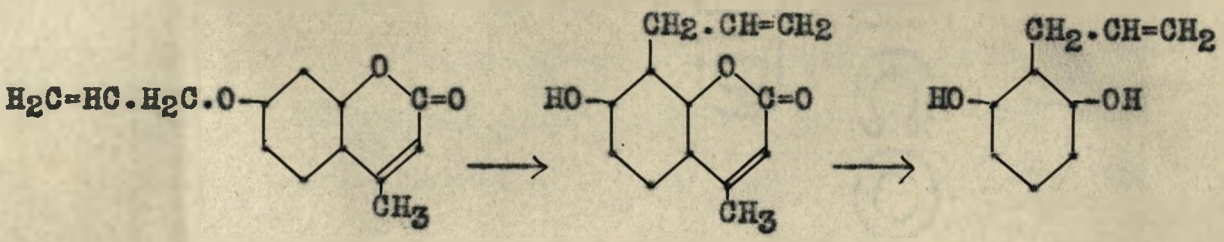


(XXVIII) (XXIX)

The same effects had been found to occur in o-hydroxy-propiophenones and o-hydroxyaldehyde (Baker,

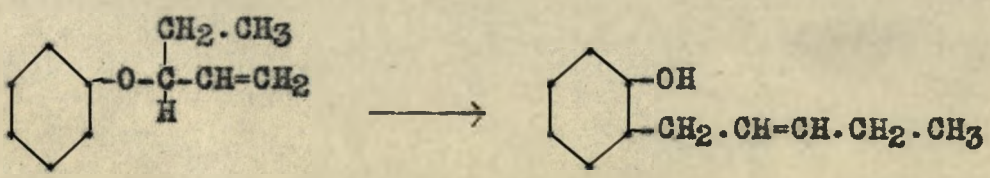
J.C.S., 1936, 274).

Evidence was brought forward by Baker (loc.cit.) that 7-allyloxy-4-methylcoumarin (XXX) underwent a thermal rearrangement, forming 7-hydroxy-4-methyl-8-allylcoumarin (XXXI), which on treatment with 20% alkali furnished 2-allylresorcinol (XXXII).

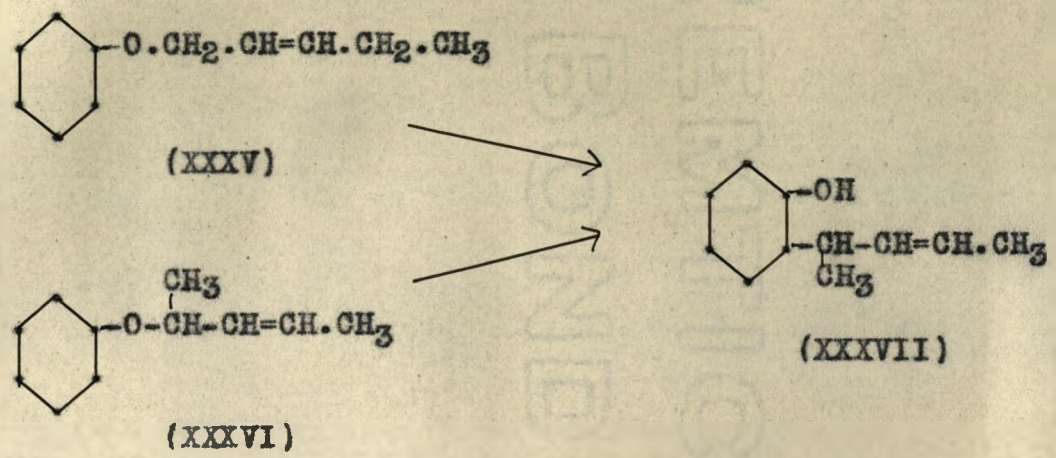


(XXX) (XXXI) (XXXII)

The rearrangement of substituted allyl ethers was examined by Lauer and Filbert (J.Amer.Chem.Soc., 1936, 1388), who found that α-ethylallylphenyl ether (XXXIII) isomerised into o-(γ-ethylallyl)-phenol (XXXIV). Isomerisation of γ-ethylallylphenyl ether (XXXV) and α:γ-dimethylallylphenyl ether (XXXVI) furnished o-(α:γ-dimethylallyl)-phenol (XXXVII).



(XXXIII) (XXXIV)

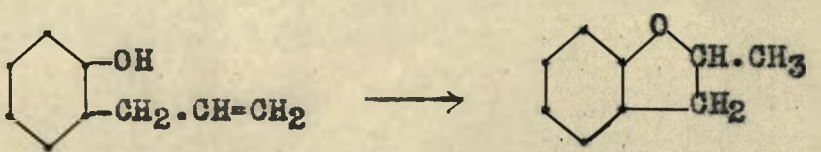


(XXXV)

(XXXVI)

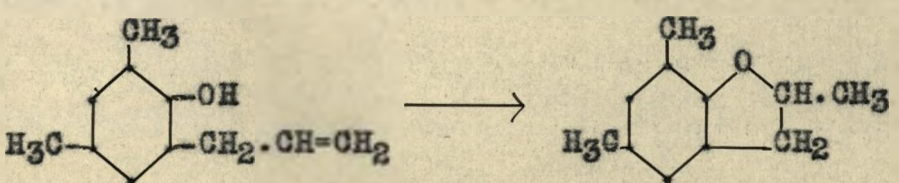
(XXXVII)

According to the observations of Claisen and his co-workers (loc.cit.), cyclisation of o-allyl phenol (XXXVIII) with pyridine hydrochloride gave rise to 2-methyl-dihydrobenzofurane (XXXIX). Similarly o-p-dimethyl-o-allyl phenol (XL) furnished 2:5:7-trimethyl-coumaran (XLI).



(XXXVIII)

(XXXIX)

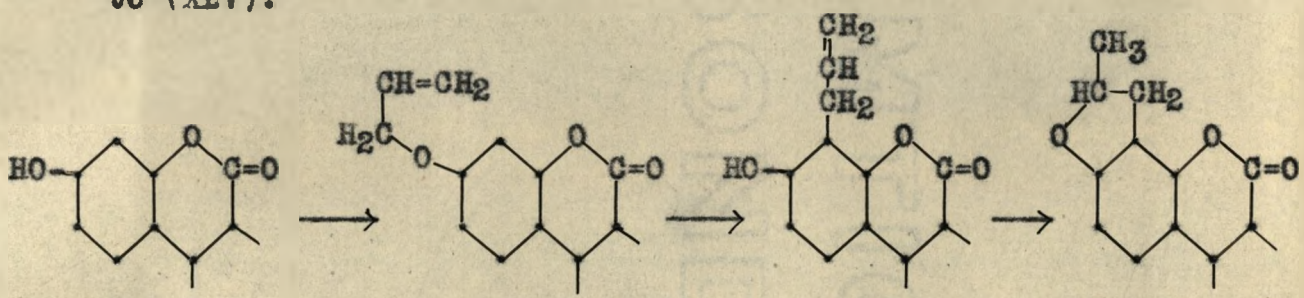


(XL)

(XLI)

On the foregoing considerations, it was thought that the application of an allyl migration to various

coumarins would, in an analogous manner to that indicated, give rise to appropriate 7-hydroxy-8-allyl-coumarins, which cyclised with pyridine hydrochloride, furnishing furano-coumarins by way of the stages (XLII) to (XLV).



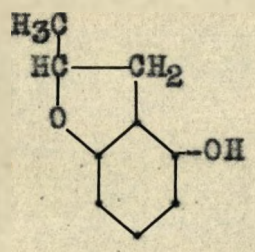
(XLII) (XLIII) (XLIV) (XLV)

The appropriate coumarins (XLII) can be readily prepared by the methods of Pechmann and Robinson, which are described in the experimental section. The allyl ethers (XLIII) are accessible by the standard method using allyl bromide and potassium carbonate in boiling acetone (Hurd and co-workers, loc.cit; Baker, loc.cit.). Rearrangement of allyl ethers took place with evolution of heat and the temperature for the allyl migration was approximately in the region of 200°C. in all cases.

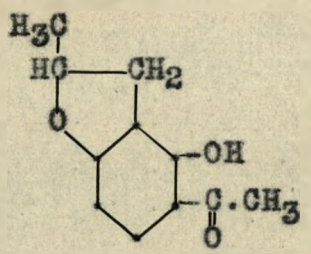
It was thought that 4-hydroxy-2-methyl-dihydrobenzofurane (XLVI) might furnish a suitable starting phenol, for the syntheses of furano-coumarins and furano-chromones. In an analogous manner to the method of Baker (loc.cit.), fission of 2'-methyl-dihydrofurano-

(4':5')4-methylcoumarin (8:7) (XLV) was expected to yield 4-hydroxy-2-methyl-dihydrobenzofurane (XLVI), but it was found that fission of the coumarin (XLV) gave rise to 4-hydroxy-5-acetyl-2-methyl-dihydrobenzofurane (XLVI) as one of the phenolic products. The phenol (XLVI) which was anticipated could not be purified by the methods adopted in the experimental section.

The method developed for the synthesis of furanochromones is discussed in detail in the experimental section. It is sufficient to state that 4-hydroxy-5-acetyl-2-methyl-dihydrobenzofurane (XLVII), which was used as a starting material, could be readily obtained by cyclisation of 3-allyl-resacetophenone (XXVII).



(XLVI)



(XLVII)

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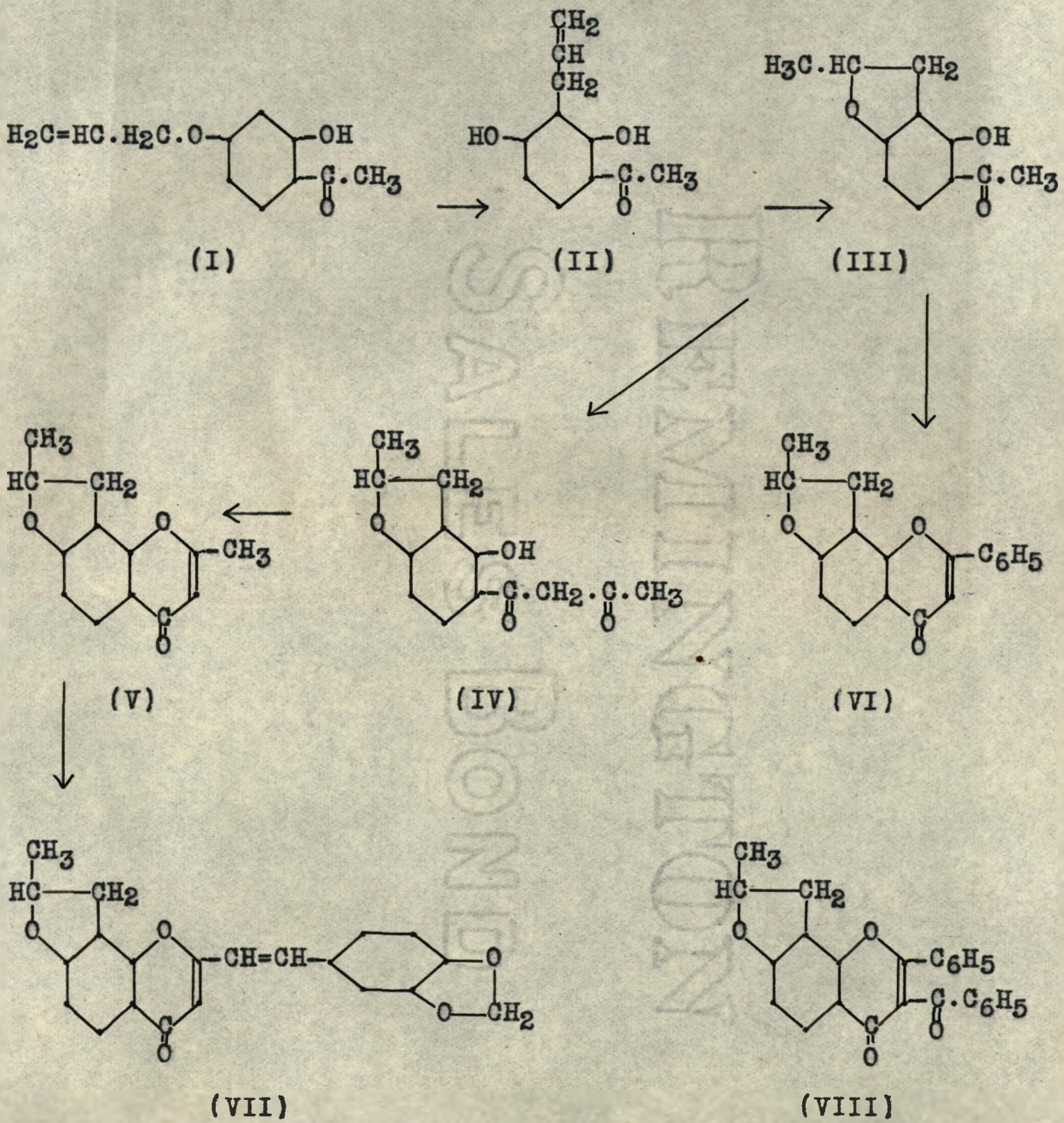
SYNTHESIS OF DIHYDROFURANO-COMPOUNDS

2'-Methyl-dihydrofurano-(4':5')-2-methyl-chromone (8:7) (V) and 2'-methyl-dihydrofurano-(4':5')-2-phenyl-chromone (8:7) (VI).



4-o-Allylresacetophenone (I) was prepared by allylation of resacetophenone with allyl bromide (Baker, J.C.S., 1935, 628). The rearrangement of the foregoing allyl ether into 3-allylresacetophenone (II) was carried out by the method of Baker (loc.cit.). When this 3-allylresacetophenone was heated at 200-210°C. with pyridine hydrochloride by the method of Claisen and Eisleb (Ann., 401, 26), and Claisen and Tietze (ibid., 449, 88), a 60% yield of 4-hydroxy-5-acetyl-2-methyldihydrobenzofurane (III) was obtained, b.p. 105-110°/2 mm. It solidified on standing and crystallised from petrol ether in colourless needles m.p. 48°C. It gave a deep red colour with ferric chloride in alcoholic solution.

Condensation of the foregoing ortho-hydroxy acetyl ketone (III) with ethyl acetate and sodium by the method of Wittig (Ann., 446, 169) gave rise to 4-hydroxy-5-aceto-acetyl-2-methyldihydrobenzofurane (IV), which crystallised from alcohol in colourless rhombic prisms. It gave a red colour with ferric chloride in alcoholic solution. Cyclisation of this diketone with acetic acid in the presence of a few drops of mineral acid (Wittig, loc.cit.) furnished 2'-methyldihydrofurano-(4':5')-2-methyl-chromone (8:7) (V) in almost quantitative yield. It crystallised from dilute alcohol in colourless needles

m.p. 150-152°C., devoid of a ferric reaction. A trace of it in concentrated sulphuric acid gives a blue fluorescence. Its alcoholic solution is devoid of any fluorescence. This chromone condensed with piperonal by the method of Heilbron and co-workers (J.C.S., 1923, 2565), giving the condensation product (VII) which crystallised from alcohol in yellowish needles, m.p. 235-6°C.

When 4-hydroxy-5-acetyl-2-methyl-dihydrobenzofurane (III) was heated with benzoic anhydride and sodium benzoate at 180-185°C. (cf. Robinson, J.C.S., 1926, 2344), and the product was boiled with 50% aqueous potassium hydroxide, 2'-methyldihydrofurano-(4':5')-2-phenylchromone (8:7) (VI) was obtained. It crystallised from alcohol in fine yellow needles m.p. 208-209°C. An attempt to isolate 2'-methyldihydrofurano-3-benzoyl-2-phenylchromone (8:7) (VIII) by treatment of the reaction product with cold 50% potassium hydroxide was unsuccessful. The product could not be induced to crystallise, but when it was boiled with 50% alkali, an approximately identical yield of 2'-methyldihydrofurano-(4':5')-2-phenylchromone (8:7) (VI) was obtained. A trace of it in concentrated sulphuric acid gave a yellowish-green fluorescence. Its alcoholic solution is devoid of any fluorescence.

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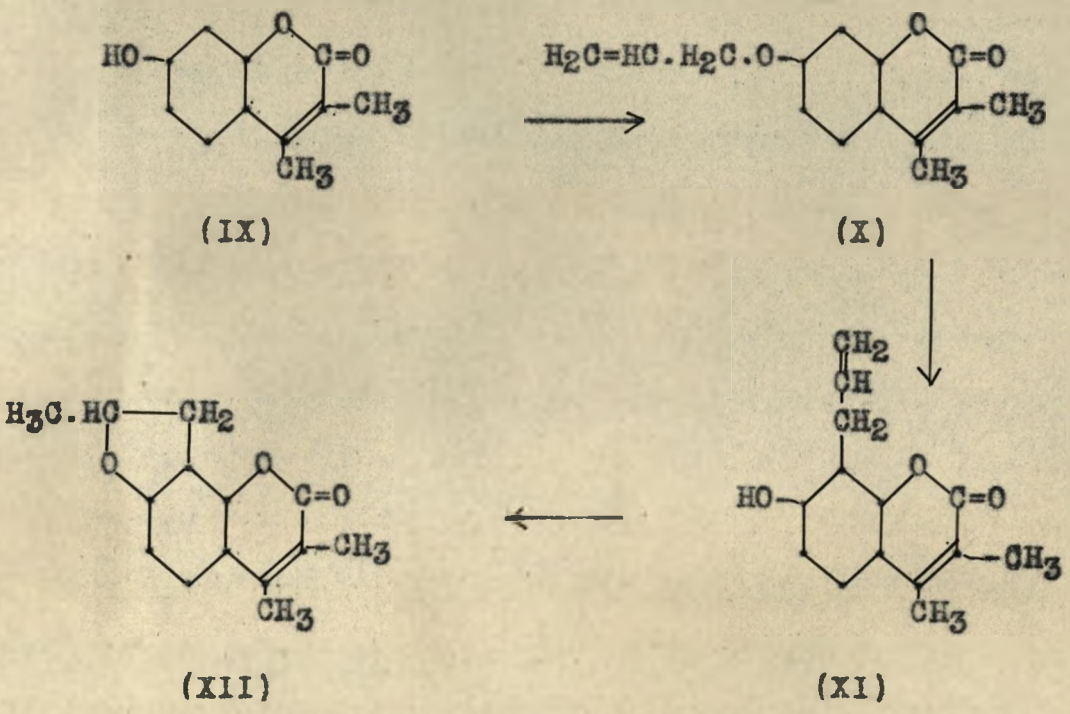
2'-Methyldihydrofurano-(4':5')-3:4-dimethyl-coumarin (8:7) (XII)



3:4-dimethyl-umbelliferone (IX) was prepared by the method of von Pechmann (Ber., 16, 2127). When this coumarin was allylated with allyl bromide by the potassium carbonate-acetone method (cf. Hurd, Greengard and Pilgrim, J.Amer.Chem.Soc., 1930, 52, 1702; Baker, loc.cit.), o-allyl-3:4-dimethyl-umbelliferone (X) was obtained, which crystallised from dilute alcohol in colourless elongated prisms, m.p. 99-100°C. This allyl ether underwent a rearrangement into 7-hydroxy-

8-allyl-3:4-dimethylcoumarin (XI), when it was heated to 210°C. The rearrangement was accompanied by an evolution of heat and it was necessary to keep the ether well stirred. Treatment of the product with 2% aqueous alkali and subsequent acidification furnished 7-hydroxy-8-allyl-3:4-dimethylcoumarin (XI) in 60% yield, which crystallised from dilute alcohol in colourless needles m.p. 196°C. A trace of it in dilute aqueous sodium hydroxide gave a yellowish solution with blue fluorescence. A small amount of this compound in concentrated sulphuric acid gives a blue fluorescence. It gives a negative ferric reaction.

Cyclisation of the foregoing phenol with pyridine-hydrochloride by the method of Claisen and his co-workers (loc.cit.) gave rise to 2'-methyldihydro-(4':5')-3:4-dimethylcoumarin (8:7) (XII) in 60% yield, which crystallised from dilute alcohol in pale yellow needles m.p. 133°C. This compound is insoluble in dilute sodium hydroxide and is devoid of a ferric reaction. A trace of it in concentrated sulphuric acid gives a blue fluorescence. Its alcoholic solution does not show any fluorescence.

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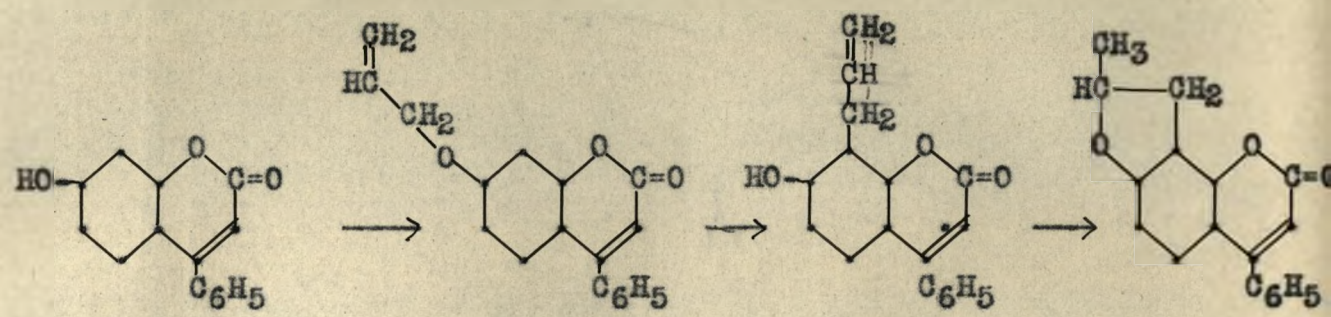
2'-Methyldihydrofurano-(4':5')-4-phenylcoumarin (8:7) (XVI)



(XIII) (XIV) (XV) (XVI)

4-Phenyl-umbelliferone (XIII) was prepared by the method of von Pechmann (Ber., 16, 2126). When this phenol was treated with allyl bromide and potassium carbonate in boiling acetone (cf. Hurd, Greengard and Pilgrim, loc.cit.; Baker, loc.cit.), 7-allyloxy-4-phenylcoumarin (XIV) was obtained which crystallised from dilute alcohol in colourless prisms m.p. 84°C. Migration of the allyl group took place at 205°C. with evolution of heat, giving 7-hydroxy-8-allyl-4-phenylcoumarin (XV), which was purified by treatment with 2% aqueous alkali and subsequent neutralisation with dilute hydrochloric acid. It crystallised from dilute alcohol in colourless needles m.p. 203°C. It shows a negative ferric reaction.

Cyclisation of the foregoing phenol with pyridine hydrochloride by the method of Claisen and his co-workers

(loc.cit.) furnished 2'-methyldihydrofurano-(4':5')-4-phenylcoumarin (8:7) in 68% yield, which crystallised from alcohol in colourless needles, m.p. 199-200°. It is insoluble in dilute sodium hydroxide. A trace of it in concentrated sulphuric acid gives a green fluorescence. Its alcoholic solution is devoid of any fluorescence.

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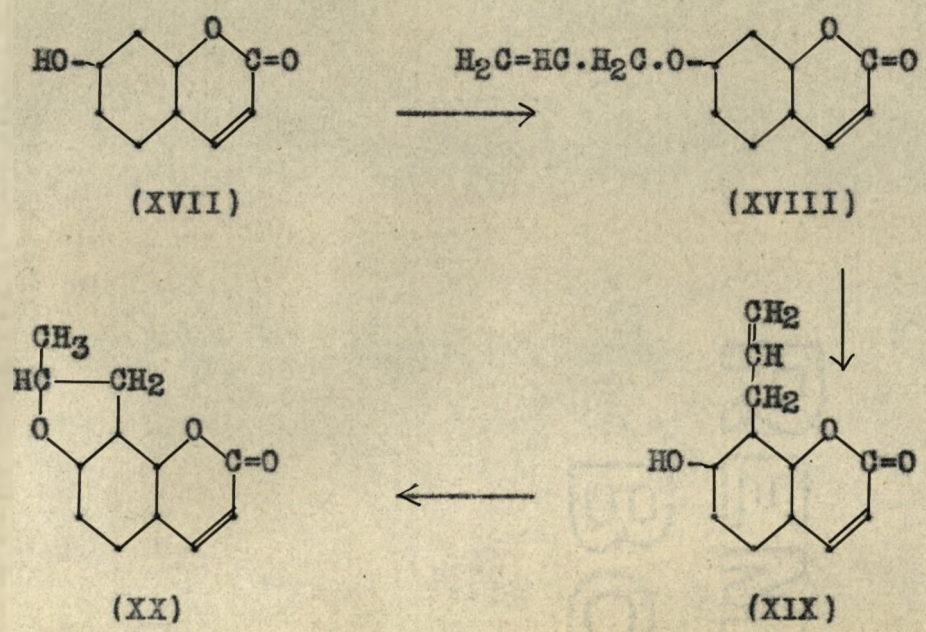
2'-Methyldihydrofurano-(4':5')-coumarin (8:7) (XX)



Umbelliferone (XVII) was prepared by the method of Von Pechmann (Ber., 17, 932). When this phenol was allylated with allyl bromide by the potassium carbonate-acetone method (cf. Hurd, Greengard and Pilgrim, loc. cit.; Baker, loc.cit.), o-allyl-umbelliferone (XVIII) was obtained, which crystallised from alcohol in colourless prisms, m.p. 81°C. Migration of the allyl group to the benzene nucleus took place at 195°C with evolution of heat, furnishing 7-hydroxy-8-allylcoumarin (XIX) in 65% yield, which was purified by treatment with 2%

aqueous sodium hydroxide and subsequent neutralisation with dilute hydrochloric acid. It crystallised from dilute alcohol in colourless needles, m.p. 164-5°C. It is devoid of a ferric reaction. A trace of it in concentrated sulphuric acid gives a green fluorescence.

Cyclisation of the foregoing phenol with pyridine hydrochloride by the method of Claisen and his co-workers (loc.cit.) furnished 2'-methyldihydrofurano-(4':5')-coumarin (8:7) (XX), which crystallised from alcohol in colourless needles, m.p. 100-101°C. It is insoluble in dilute alkali. A trace of it in concentrated sulphuric acid is devoid of any fluorescence.

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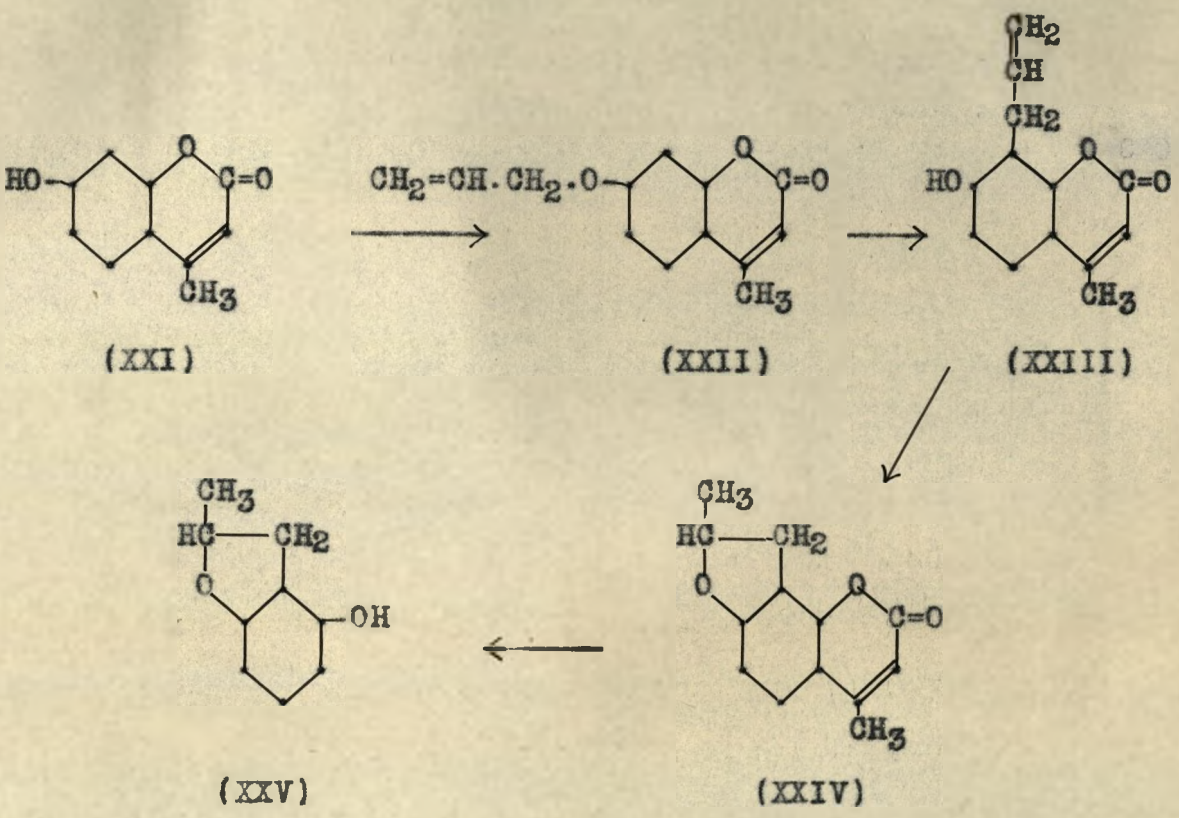
2'-Methyldihydrofurano-(4':5')-4-methylcoumarin (8:7) (XXIV) and an attempt to synthesise 4-hydroxy-2-methyldihydrobenzofurane (XXV)



The synthesis of 2'-methyldihydrofurano-(4':5')-4-methylcoumarin (8:7) (XXIV) was accomplished by Dr. W. H. Davies, formerly of this laboratory (private communication). An attempt to obtain 4-hydroxy-2-methyldihydrobenzofurane (XXV) by alkali fission of the foregoing coumarin was unsuccessful. The author, revising the work in conjunction with him, was able to confirm the results.

7-Hydroxy-4-methylcoumarin (XXI) was prepared by

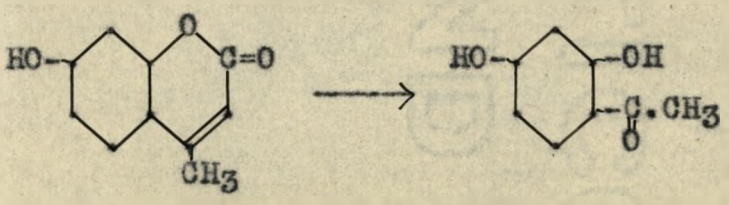
the method of von Pechmann (Ber., 17, 931). 7-Allyloxy-4-methylcoumarin (XXII) and 7-hydroxy-8-allyl-4-methylcoumarin (XXIII) were prepared by the method of Baker (J.C.S., 1935, 628). Cyclisation of the latter coumarin with pyridine hydrochloride furnished 2'-methyldihydrofurano-(4':5')-4-methylcoumarin (8:7) (XXIV), which crystallised from alcohol in colourless needles, m.p. 118-119°C. It is insoluble in dilute alkali. A trace of it in concentrated sulphuric acid gave a blue fluorescence.

Alkali fission of the foregoing coumarin (XXIV).

When the foregoing 2'-methyldihydrofurano-(4':5')-4-methylcoumarin (8:7) was heated to boiling with 30% aqueous sodium hydroxide, according to the method of Baker (loc.cit.), the starting material could be recovered unchanged. When the coumarin was heated to boiling with 40% aqueous sodium hydroxide for four hours, fission took place. The acidified solution was extracted with ether from which a phenol was isolated by a dilute alkali. Acidification of the alkali extract and extraction with ether yielded a colourless liquid, b.p. 110-120°C./2 mm., which solidified after standing. It crystallised from petrol ether in colourless needles, m.p. 70-72°C. It gave a dark brown colour in alcoholic ferric chloride.

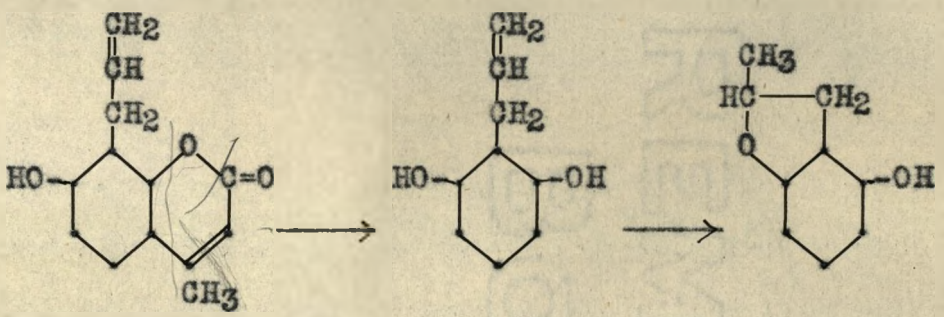
The analytical results of this phenol and its p-nitrobenzoate did not agree for 4-hydroxy-2-methyldihydrobenzofurane (XXV). The found molecular weight of 170 seems to be in agreement with $C_{10}H_9O_2$, which requires 150 for the molecular weight. This phenol gave a 2:4-dinitrophenylhydrazone which crystallised from alcohol in reddish brown needles, m.p. 252°C., and which was identical in every way with the 2:4-dinitrophenylhydrazone of 4-hydroxy-5-acetyl-2-methyldihydrobenzofurane (vide supra). Therefore fission gave rise to a mixture of phenols, one of which is 4-hydroxy-5-acetyl-2-methyldihydrobenzofurane (III). It seems that the expected phenol 4-hydroxy-2-methyldihydrobenzofurane (XXV) could not be isolated in a pure state by the methods adopted.

The production of 4-hydroxy-5-acetyl-2-methyldihydrobenzofurane (III) was also supported by the fact that alkali fission of 4-methyl-umbelliferone (Pechmann and Duisberg, Ber., 16, 2123) gave rise to resacetophenone (XXVI).



(XXVI)

On the other hand Baker (loc.cit.) obtained 2-allyl-resorcinol (XXVII) by alkali fission of 7-hydroxy-8-allyl-4-methylcoumarin with 20% aqueous sodium hydroxide.



(XXVII) (XXV)

A possible synthesis of 4-hydroxy-2-methyldihydrobenzofurane (XXV).

Cyclisation of 2-allyl-resorcinol (XXVII) with pyridine hydrochloride proceeded normally into 4-hydroxy-2-methyldihydrobenzofurane (XXV) (Dr. W. H. Davies, loc.cit.), but because the starting material was also a phenol, it was difficult to separate them from each other.

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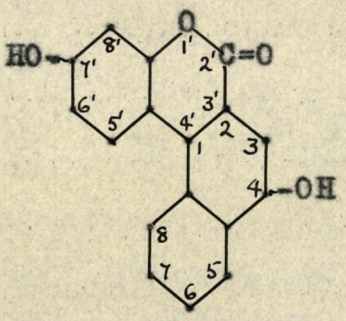
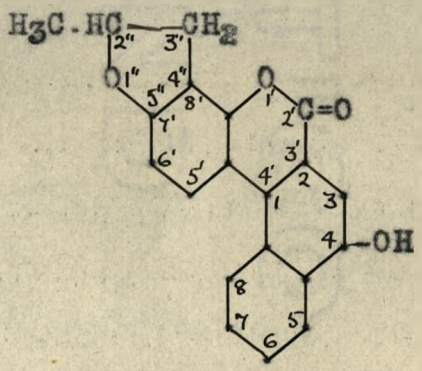
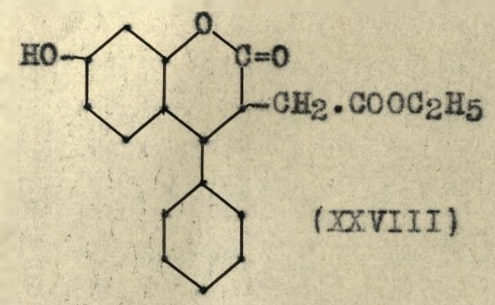
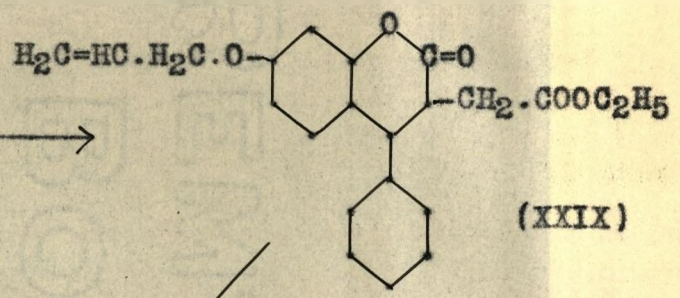
An attempt to synthesise 2"-methyldihydrofurano-(4":5":8':7')-α-naphthol-(1:2:4':3')-coumarin (XXXV)



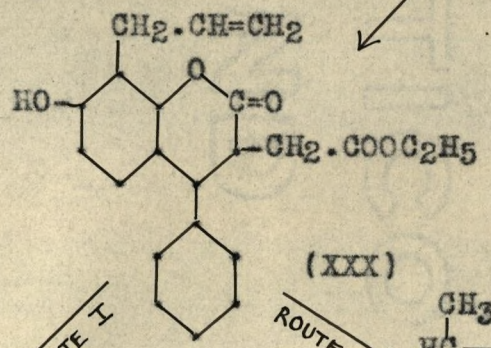




(XXVIII)



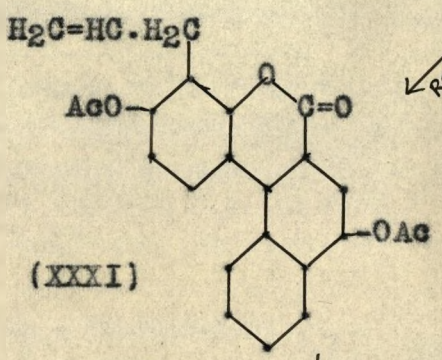
(XXIX)



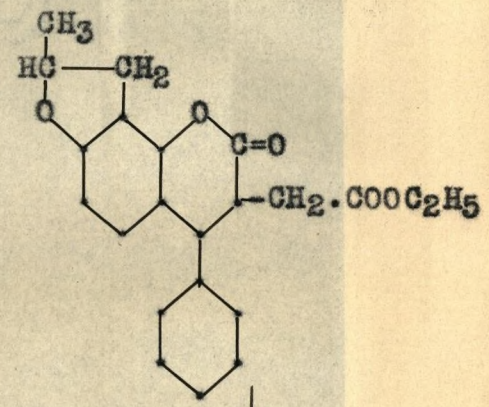
(XXX)

ROUTE I

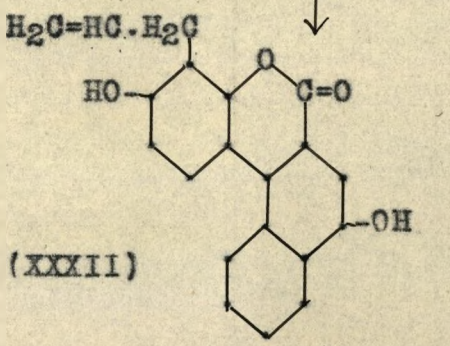
ROUTE III



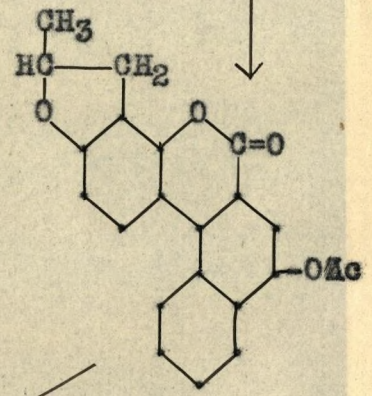
(XXXI)



(XXXIII)

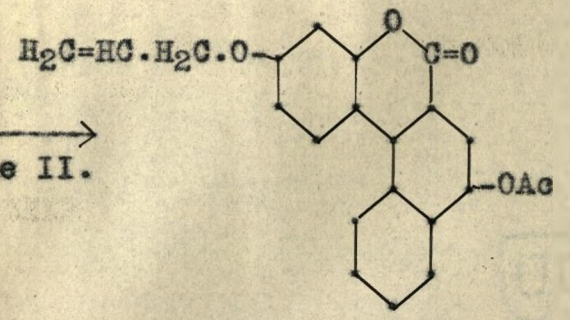


(XXXII)

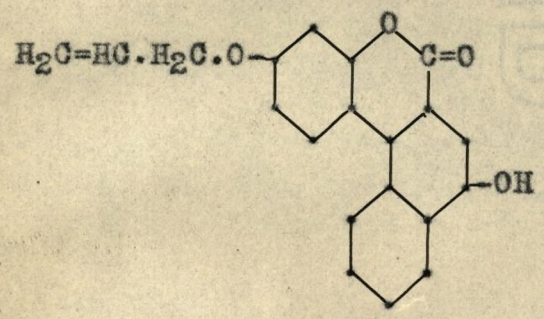


(XXXV)

Route II.



(XXXIII)



(XXXIV)

Route (I) and Route (II) were attempted.

Ethyl 7-hydroxy-4-phenylcoumarin-3-acetate (XXVIII) was prepared by Robinson's method (J.C.S., 1933, 1469).

Route I

When the foregoing coumarin was allylated by the potassium carbonate-acetone method, a brownish oil was obtained which could not be induced to crystallise. The oil was insoluble in dilute aqueous sodium hydroxide. Rearrangement of the allyl group took place when the oil was heated at 210°C., giving 7-hydroxy-8-allyl-4-phenylcoumarin-3-acetate (XXX), which crystallised from alcohol in colourless prisms, m.p. 154-157°C. It was soluble in dilute aqueous alkali. It gave a negative ferric reaction. Hydrolysis of the foregoing acetate with alcoholic sodium hydroxide gave rise to 7-hydroxy-8-allyl-4-coumarin acetic acid which crystallised from acetic acid in colourless prisms, m.p. 225°C., after darkening at 178°C. This acid seemed difficult to purify. [By a similar hydrolysis of ethyl 7-hydroxy-4-phenylcoumarin-3-acetate, Robinson (loc.cit.) could not obtain 7-hydroxy-4-phenylcoumarin-3-acetic acid in the pure state (Found C 68.1%, H 4.4%; the acid he investigated required C 68.9%, H 4.1%).

He stated also that low values for the content of carbon were obtained in many estimations, and that this was attributed to contamination with a substituted trans-o-coumaric acid.] Low values in the content of carbon appeared to confirm this view.

Treatment of the foregoing acid with acetic anhydride gave rise to 4:7'-diacetoxy-8'-allylnaphtha-coumarin-(1:2:4':3') (XXXI), which crystallised from acetic acid in colourless needles, m.p. 235-236°C. It is insoluble in sodium hydroxide.

Treatment of the foregoing acetate with alcoholic potassium hydroxide gave 4:7'-dihydroxy-8'-allylnaphtha-coumarin (1:2:4':3') (XXXII), which could not be purified. It is soluble in dilute aqueous sodium hydroxide. An attempt to cyclise it with pyridine hydrochloride gave rise to brownish needles, m.p. 195°C., which crystallised from alcohol. Analytical results showed low values in the content of carbon for 2"-methyldihydrofurano-(4":5":8':7')-α-naphthol-(1:2:4':3')-coumarin (XXXV). A further investigation was prohibited through lack of sufficient material.

Route II

Hydrolysis of ethyl 7-allyloxy-4-phenylcoumarin-3-acetate (XXIX) with sodium hydroxide gave rise to 7-allyloxy-4-phenylcoumarin-3-acetic acid, m.p. 83-85°C.,

which crystallised from alcohol. It is soluble in sodium bicarbonate solution. Treatment of the foregoing acid with acetic anhydride yielded 4-acetoxy-7'-allyloxynaphthacoumarin (1:2:4':3') (XXXIII), which crystallised from acetic acid in yellowish needles, m.p. 194°C. Deacetylation of the foregoing compound with alcoholic potassium hydroxide gave rise to 4-hydroxy-7'-allyloxynaphthacoumarin (1:2:4':3'), which crystallised from alcohol in fine needles, m.p. 232-235°C. (decomposition). An attempt to isomerise it to 4:7'-dihydroxy-8'-allylnaphthacoumarin (1:2:4':3') at 240°C. was unsuccessful, since the allyl ether decomposed at its melting point.

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The following table shows the temperatures for the allyl migration. All the allyl coumarins in the extreme right-hand column give a negative ferric reaction in alcoholic ferric chloride.

Mono-allyl ether heated	Temperature for migration	Product
Umbelliferone	195-200°C. (exothermic)	7-hydroxy-8-allyl-coumarin.
7-Hydroxy-4-methyl-coumarin.	210-240°C, (exothermic)	7-hydroxy-8-allyl-4-methylcoumarin.
7-Hydroxy-3:4-di-methylcoumarin.	210-224°C. (exothermic)	7-hydroxy-8-allyl-2:4-dimethylcoumarin.
7-Hydroxy-4-phenyl-coumarin.	205-210°C. (exothermic)	7-hydroxy-8-allyl-4-phenylcoumarin.
7-Hydroxy-4-phenyl-coumarin-3-acetate.	210°C.	7-hydroxy-8-allyl-4-phenylcoumarin-3-acetate.
4:7'-Dihydroxynaphtha-coumarin (1:2:4':3').	(Decomposed)	-------

*** *** ***

All the furano-coumarins and furano-chromones prepared do not give any fluorescence in alcohol solution. They all give a fluorescence in concentrated sulphuric acid, the colours of this fluorescence being tabulated below.

Substance	Fluorescence in concentrated H_2SO_4
2'-Methyldihydrofurano-(4':5')-coumarin (8:7)	Blue
2'-Methyldihydrofurano-(4':5')-4-methyl-coumarin (8:7)	Blue
2'-Methyldihydrofurano-(4':5')-3:4-dimethyl-coumarin (8:7)	Blue
2'-Methyldihydrofurano-(4':5')-4-phenyl-coumarin (8:7)	Green
2'-Methyldihydrofurano-(4':5')-2-methyl-chromone (8:7)	Blue
2'-Methyldihydrofurano-(4':5')-2-phenyl-chromone (8:7)	Yellowish green
4:7'-Diacetoxy-8'-allylnaphthacoumarin (1:2:4':3')	Intense green

*** *** ***

4-o-allyl resacetophenone.

(Baker, J.C.S., 1935, 628)

A mixture of resacetophenone (76 g.), anhydrous potassium carbonate (90 g.) and allyl bromide (61 g.) in acetone (180 c.c.) was refluxed and continuously stirred on the water bath for six hours. After this period most of the acetone was removed by distillation and the remaining solution was acidified with 2N

hydrochloric acid, and extracted with ether. The pure product was best obtained by isolation as its very sparingly soluble sodium salt. The ethereal layer was shaken with excess of 2N sodium hydroxide and the precipitated sodium salt was collected on a sintered glass funnel. Decomposition with dilute hydrochloric acid and extraction with ether yielded 4-o-allyl resacetophenone (59 g.) as a faint yellow liquid which was distilled at 118-119°C./2 mm. pressure. It gives an intense brownish colouration with alcoholic ferric chloride.

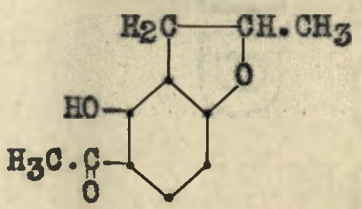
3-Allyl-resacetophenone.

(Baker, J.C.S., 1935, 628)

Pure 4-o-allyl resacetophenone (45.8 g.) was heated cautiously in an oil bath, the temperature both of the bath and of the substance being recorded. Rearrangement began at 185°C. with evolution of considerable heat and the tube was raised from the bath for a few minutes so that the temperature of the melt did not rise above 200°C. The liquid must be continuously stirred at this stage. Unless this precaution is taken, the highly exothermic rearrangement causes considerable rise of temperature, and profound decomposition of the product ensues. The temperature was then kept

at 200-210°C. for 2½ hours. On cooling, faintly coloured crystals of 3-allyl resacetophenone were obtained. It had an m.p. of 113-130°C. After crystallisation from carbon tetrachloride, 3-allyl resacetophenone (35.1 g.) was obtained. It had an m.p. of 132-133°C.

4-Hydroxy-5-acetyl-2-methyldihydrobenzofurane.



3-Allyl-resacetophenone (30 g.) was heated with pyridine hydrochloride (1.5 g.) in a tube which was placed in an oil bath at 200-210°C. It was maintained at this temperature for 1½ hours. The product after cooling was dissolved in the least possible amount of alcohol and poured into a large bulk of cold water (300 c.c.). It was extracted three times with ether, washed with small amounts of dilute hydrochloric acid, twice with a small amount of sodium bicarbonate solution and finally with water. After drying the ether extract over sodium sulphate, and removal of ether, the residual brown oil was distilled at 2 mm. pressure with

the oil bath temperature at 130°C. The liquid was collected at 105-110°C. and solidified after standing. It crystallised from petrol ether (80-100°C.) in colourless needles (15.5 g.). It had an m.p. of 48°C.

It gave a deep red colouration with alcoholic ferric chloride. It was soluble in ethyl alcohol, methyl alcohol and benzene.

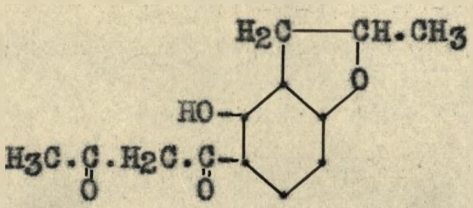
Found: C. 68.68%, H. 6.10%

$C_{11}H_{12}O_3$ requires: C. 68.76%, H. 6.25%

It gave a 2:4-dinitrophenylhydrazone which crystallised from alcohol in reddish brown needles, m.p. 252°C.

... ...

4-Hydroxy-5-acetoacetyl-2-methyl-dihydrobenzofurane.



4-Hydroxy-5-acetyl-2-methyl-dihydrobenzofurane (3 g.) was heated under reflux on the water bath with finely-cut sodium (1.5 g.) and absolute ethyl acetate (7.5 c.c.). At the end of 1½ hours a further amount of sodium (0.5 g.) and ethyl acetate (5 c.c.) was added

and the heating continued for a total time of about 4½ hours. At the end of this period, all the sodium had dissolved, the flask and contents were cooled, and water added, when the sodium salt was precipitated. The solution was cooled in ice and acidified with acetic acid, and the precipitate of the diketone was filtered off the next day, when most of the ethyl acetate had evaporated off. The yellowish solid obtained gave a permanent red colouration with ferric chloride in alcohol. The crude product melted at 87-90°. Crystallisation from dilute alcohol yielded colourless rhombic prisms of the diketone. It had a melting point of 98°C. Yield 1.9 g.

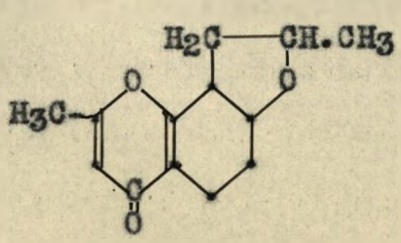
It is soluble in methyl alcohol, petrol ether and benzene.

Found: C. 66.61%, H. 6.03%

$C_{13}H_{14}O_4$ requires: C. 66.66%, H. 5.98%

... ...

2'-Methyldihydrofurano-(4':5')-2-methylchromone (8:7).



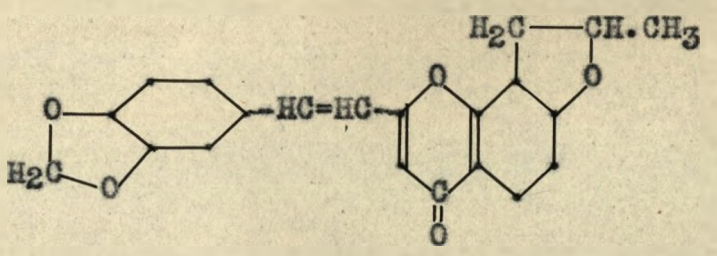
The foregoing diketone (1.2 g.) was dissolved

in glacial acetic acid (25 c.c.). A few drops of concentrated hydrochloric acid were added. After boiling for five minutes, it was poured into cold water (100 c.c.). The colourless solid which separated crystallised from dilute alcohol as colourless needles. It had a melting point of 150-2°C. Yield 0.8 g.

It is soluble in benzene, carbon tetrachloride, petrol ether and ethyl acetate.

It exhibits blue fluorescence when a trace of it is dissolved in concentrated sulphuric acid.

Condensation with piperonal



The foregoing chromone (0.8 g.) was dissolved in a small quantity of alcohol and treated with a solution of sodium ethoxide (containing 0.1 g. of sodium). The calculated amount of piperonal (0.56 g.) was added to the solution. The mixture was allowed to stand at room temperature for three days. The condensation product, a yellowish solid, was filtered and purified by crystallisation from alcohol. Yellowish needles

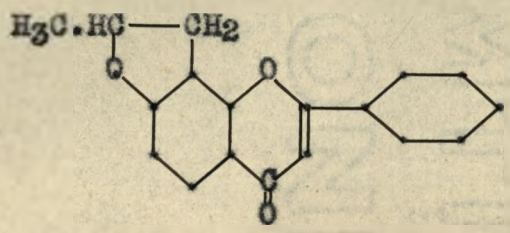
(1.1 g.) were obtained. It had a melting point of 235-236°C.

Found: C. 72.61%, H. 4.63%

$C_{21}H_{16}O_5$ requires: C. 72.41%, H. 4.59%

... ...

2'-Methyldihydrofurano-(4':5')-2-phenylchromone (8:7).



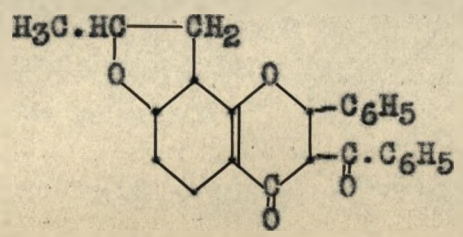
A mixture of 4-hydroxy-5-acetyl-2-methyldihydrobenzofurane (2 g.), benzoic anhydride (9.6 g.) and sodium benzoate (2 g.) was heated in an oil bath at 180-185°C. for 8 hours. After cooling, the pale brown mass was broken up and dissolved in alcohol (42 c.c.). The mixture was boiled during the gradual addition of aqueous potassium hydroxide (7.5 g. potassium hydroxide and 8 c.c. water) under reflux for 30 minutes. After removal of the greater part of the alcohol by distillation, the residue was dissolved in water (30 c.c.). The light brown solid which did not dissolve was collected and crystallised from alcohol in fine, yellow needles. Yield 1.8 g. It had a melting point of 208-9 C.

It is slightly soluble in petrol ether. It exhibits yellowish green fluorescence in concentrated sulphuric acid.

Found: C. 77.3%, H. 5.1%

$C_{18}H_{14}O_3$ requires: C. 77.7%, H. 5.0%

Attempt to isolate 2'-methyldihydrofurano-3-benzoyl-2-phenylchromone (8:7).

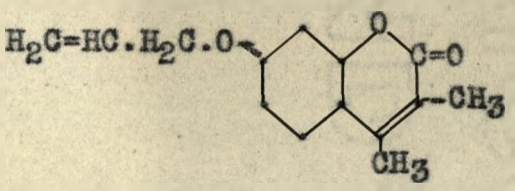


Repeat, but the molten mixture after cooling was poured into cold water and made just alkaline with dilute sodium hydroxide (2N). In this way, a brown viscous oil was obtained. The oil was extracted with ether, washed with a little sodium hydroxide and finally with water. The ether extract was dried over sodium sulphate and the ether removed. The residue did not solidify and could not be purified by crystallisation. By dissolving the residue in alcohol (42 c.c.) and adding aqueous potassium hydroxide as before, practically the same amount of the flavone was obtained.

... ...

3:4-Dimethyl-umbelliferone was prepared by the method of von Pechmann (Ber., 16, 2127) by interaction of resorcinol and α-methyl acetoacetic ester in presence of sulphuric acid.

α-Allyloxy-3:4-dimethyl-umbelliferone.



3:4-Dimethyl-umbelliferone (29 g.), anhydrous potassium carbonate (28 g.), acetone (56 c.c.) and allyl bromide (18.6 g.) were refluxed on the water bath for 12 hours. At the end of this period, acetone was removed and the residue was dissolved in water (200 c.c.). The solid which did not dissolve was collected and ground up with 2% aqueous sodium hydroxide. It crystallised from dilute alcohol in colourless elongated prisms. It had a melting point of 99-100°C. Yield 27 g.

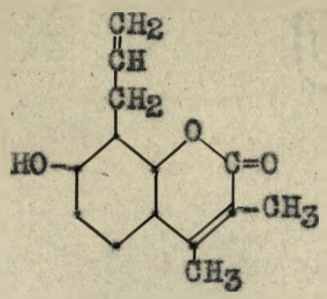
It is soluble in benzene, carbon tetrachloride and hot petrol ether.

Found: C. 72.79%, H. 6.25%

$C_{14}H_{14}O_3$ requires: C. 73.04%, H. 6.09%

... ...

7-Hydroxy-8-allyl-3:4-dimethylcoumarin.



The foregoing 7-allyloxy-3:4-dimethylcoumarin (20 g.) in a large boiling tube was placed in an oil bath at 210°C. When the ether had reached the same temperature as the bath, the oil bath temperature was slowly raised, keeping the coumarin well stirred. After the initial reaction was over at 224°C. the coumarin was maintained at 210° for two hours. After cooling the solid was dissolved in the least possible amount of alcohol, and poured into cold water (400 c.c.). The solid was filtered and ground up in 2% aqueous sodium hydroxide. It was filtered and 8-allyl-7-hydroxy-3:4-dimethylcoumarin was obtained by acidifying the filtrate with dilute hydrochloric acid. It was crystallised from dilute alcohol in colourless needles. It had a melting point of 196°C. Yield 12 g.

Found: C. 72.79%, H. 6.1%

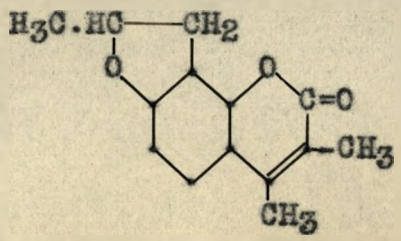
$C_{14}H_{14}O_3$ requires: C. 73.04%, H. 6.09%

8-Allyl-7-hydroxy-3:4-dimethylcoumarin is insoluble in carbon tetrachloride, sparingly soluble in hot

benzene. A trace of it in dilute aqueous sodium hydroxide shows a yellowish solution with blue fluorescence. A small amount dissolved in concentrated sulphuric acid shows blue fluorescence. Its alcoholic solution does not show fluorescence or ferric reaction.

... ...

2'-Methyldihydrofurano-(4':5')-3:4-dimethylcoumarin (8:7).



The foregoing 8-allyl-7-hydroxy-3:4-dimethylcoumarin (10 g.) was intimately mixed with pyridine hydrochloride (0.5 g.). The mixture was heated in an oil bath at 220-230° for 1½ hours. After cooling, the product was dissolved in the least possible amount of alcohol, poured into water (100 c.c.) and filtered. The solid was washed with a little dilute hydrochloric acid, then with water and finally ground up in 2% aqueous sodium hydroxide. The insoluble body was collected and crystallised from dilute alcohol in pale yellow needles. It had a melting point of 133°C. Yield 6 g.

Found: C. 73.00%, H. 6.13%

$C_{14}H_{14}O_3$ requires: C. 73.04%, H. 6.09%

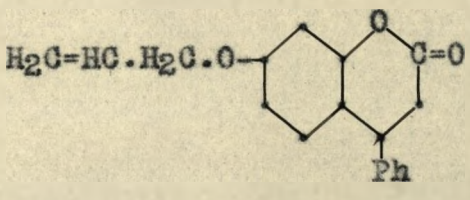
It is soluble in carbon tetrachloride and benzene, but sparingly soluble in petrol ether.

A trace of it in concentrated sulphuric acid gave blue fluorescence.

... ...

4-Phenyl-umbelliferone was prepared by the method of von Pechmann (Ber., 16, 2126) by interaction of resorcinol and benzoyl ethyl acetate in the presence of concentrated sulphuric acid.

7-Allyloxy-4-phenylcoumarin.



A mixture of 4-phenyl-umbelliferone (30 g.), allyl bromide (15.3 g.), anhydrous potassium carbonate (23 g.) and acetone (50 c.c.) was refluxed on the water bath for 12 hours. At the end of this period acetone was removed. The residue was treated with water (250 c.c.) and filtered. The solid body was ground up in

2% aqueous sodium hydroxide. The insoluble allyl ether was collected and crystallised from dilute alcohol in colourless prisms. It had a melting point of 84°C. Yield 25 g.

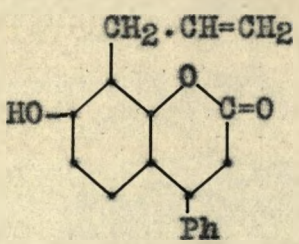
Found: C. 77.64%, H. 5.35%

$C_{18}H_{14}O_3$ requires: C. 77.69%, H. 5.04%

It is soluble in carbon tetrachloride, benzene and petrol ether.

... ...

7-Hydroxy-8-allyl-4-phenylcoumarin.



The foregoing allyl ether (10 g.) in a large boiling tube was placed in an oil bath at 190°C. When the ether had reached the same temperature as the bath, the temperature was slowly raised, keeping the ether well stirred. After the initial reaction was over at 205°C., the coumarin was maintained at 205-210°C. for 2½ hours. After cooling, the contents were dissolved in the least possible amount of alcohol, poured into cold water (300 c.c.). The solid was filtered and

ground up in 2% aqueous sodium hydroxide. The required 8-allyl-7-hydroxy-4-phenylcoumarin was obtained by acidifying the alkaline solution with dilute hydrochloric acid. The solid was crystallised from dilute alcohol in colourless needles. It had a melting point of 203°C. Yield 7.3 g.

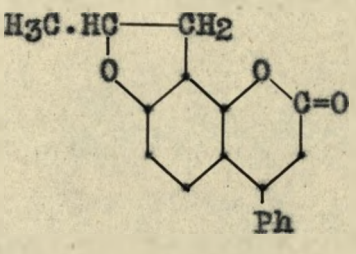
Found: C. 77.3%, H. 5.18%

$C_{18}H_{14}O_3$ requires: C. 77.69%, H. 5.04%

It is soluble in benzene, carbon tetrachloride, but is sparingly soluble in petrol ether. It showed a negative ferric reaction.

... ...

2'-Methyldihydrofurano-(4':5')-4-phenylcoumarin (8:7).



8-Allyl-7-hydroxy-4-phenylcoumarin (5 g.) was intimately mixed with pyridine hydrochloride (0.25 g.). The mixture was heated in an oil bath at 210-215° for 1½ hours. After cooling, the product was dissolved in the least possible amount of alcohol, and poured into water (100 c.c.). It was filtered and the solid

was washed with a little dilute hydrochloric acid, then with water, and finally ground up in 2% aqueous sodium hydroxide. The insoluble solid was collected and crystallised from dilute alcohol in colourless needles. It had a melting point of 199-200°C. Yield 3.4 g.

Found: C. 77.43%, H. 5.13%

$C_{18}H_{14}O_3$ requires: C. 77.69%, H. 5.04%

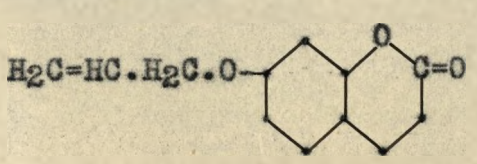
It is soluble in benzene, carbon tetrachloride, and sparingly soluble in petrol ether.

A trace of it in concentrated sulphuric acid gave green fluorescence.

... ...

Umbelliferone was prepared by the method of von Pechmann (Ber., 17, 932) by interaction of resorcinol and malic acid in presence of concentrated sulphuric acid at 120-125°C.

o-Allyloxy-umbelliferone.



A mixture of umbelliferone (15 g.), anhydrous

potassium carbonate (15 g.), allyl bromide (14.1 g.) and acetone (50 c.c.) was refluxed on the water bath for eight hours. The product was filtered hot and the inorganic salt washed with hot acetone. The solvent was removed from the filtrate and the residue was titurated with 2% aqueous sodium hydroxide. The insoluble allyl ether was collected and crystallised from alcohol in colourless prisms. It had a melting point of 81°C. Yield 12 g.

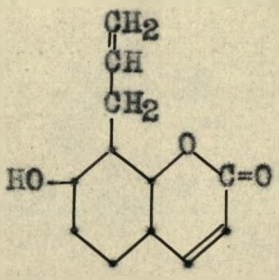
Found: C. 71.32%, H. 5.25%

$C_{12}H_{10}O_3$ requires: C. 71.28%, H. 4.95%

It is soluble in benzene, carbon tetrachloride, and hot petrol ether.

... ...

7-Hydroxy-8-allylcoumarin.



The foregoing allyl ether (10 g.) in a large boiling tube was placed in an oil bath at 185°C. When the ether had reached the same temperature as the bath, the temperature was slowly raised, keeping the ether well stirred. After the initial reaction was over,

the coumarin was maintained at 195-200°C. for 2 hours. After cooling, the solid was dissolved in the least possible amount of alcohol and poured into cold water (300 c.c.). The solid was filtered and ground up in 2% aqueous sodium hydroxide. The required 8-allyl-7-hydroxy-coumarin was obtained by acidifying the alkaline solution with dilute hydrochloric acid. The solid was collected and crystallised from alcohol in colourless needles. It had a melting point of 164-165°C. Yield 6.5 g.

Found: C. 71.21%, H. 5.16%

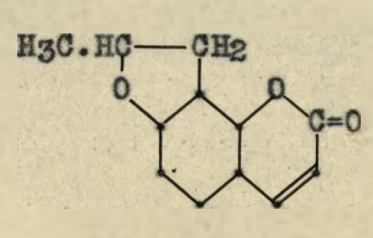
$C_{12}H_{10}O_3$ requires: C. 71.28%, H. 4.95%

It is soluble in benzene, carbon tetrachloride, and sparingly soluble in petrol ether.

It gave a negative ferric reaction in alcoholic solution. A trace of it in concentrated sulphuric acid gave a green fluorescence.

... ...

2'-Methyldihydrofurano-(4':5')-coumarin (8:7).



8-Allyl-7-hydroxycoumarin (5 g.) was intimately

mixed with pyridine hydrochloride (0.25 g.). The mixture was heated in an oil bath at 210-215° for 1½ hours. After cooling, the product was dissolved in the least possible amount of alcohol, and poured into water (100 c.c.). The solid which separated was filtered, washed with a little dilute hydrochloric acid, then with water and finally titurated with 2% aqueous sodium hydroxide. The insoluble solid was collected and crystallised from alcohol in colourless needles. It had a melting point of 100-101°C. Yield 3.1 g.

Found: C. 71.34%, H. 5.14%

$C_{12}H_{10}O_3$ requires: C. 71.28%, H. 4.95%

It is soluble in methyl alcohol, acetone and petrol ether.

A trace of it in concentrated sulphuric acid showed a blue fluorescence.

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7-Hydroxy-4-methylcoumarin was prepared by the method of von Pechmann, Ber., 17, 931.

7-Allyloxy-4-methylcoumarin.
(Baker, J.C.S., 1935, 628).

7-Hydroxy-4-methylcoumarin (92.5 g.) and allyl

bromide (60.5 g.) were refluxed for 6 hours with anhydrous potassium carbonate (100 g.) in acetone (250 c.c.). The solution was filtered hot and the inorganic residue was thoroughly washed with hot acetone. The solvent was removed and the residue ground up with a small amount of 2% aqueous sodium hydroxide. After thoroughly washing with water and drying, the allyl ether (m.p. 102-104°) was obtained. It was sufficiently pure to carry on with the migration.

... ...

7-Hydroxy-8-allyl-4-methylcoumarin.

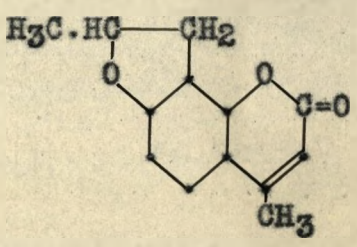
(Baker, J.C.S., 1935, 628)

The allyl ether (50 g.) in a large boiling tube was placed in an oil bath at 220°C.. When the ether had reached the same temperature as the bath, the temperature of the oil bath was slowly raised, keeping the ether well stirred. At an oil bath temperature of 228-233°C. the exothermic rearrangement began and the internal temperature rose fairly rapidly. Thorough stirring of the coumarin at this stage is essential if charring is to be avoided. The oil bath was allowed to cool slightly and the temperature of the coumarin was kept below 240°C. by raising the tube out of the oil bath if necessary. After the initial reaction was over the

coumarin was maintained at 210°C. for 1½ hours and poured into a large evaporating basin with stirring to prevent caking. The melting point of the crude material was 160-180°C. Repeated crystallisation from a large bulk of alcohol gave pure 8-allyl-7-hydroxy-4-methylcoumarin. It had a melting point of 193-194°. Yield 32.5 g.

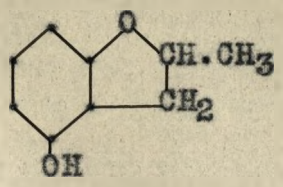
... ...

2'-Methyldihydrofurano-(4':5')-4-methylcoumarin (8:7).



8-Allyl-7-hydroxy-4-methylcoumarin (20 g.) was intimately mixed with pyridine hydrochloride (1 g.). The mixture was heated in an oil bath at 220-230° for one hour. After cooling, the product was dissolved in the least possible amount of alcohol, poured into water (200 c.c.) and filtered. The solid was thoroughly washed with water and titurated with 2% sodium hydroxide solution. After washing with water and drying, it crystallised from petrol ether (80-100°) and finally from alcohol in colourless prisms. It had a melting point of 118-119°, identical with Dr. W.H. Davies' specimen (private communication). Yield 15.5 g. It gives a blue fluorescence in concentrated sulphuric acid.

Attempt to obtain 4-hydroxy-2-methyldihydrobenzofurane.



This can be prepared via 2-allyl resorcinol (Baker, J.C.S., 1935, 631), using nitrogen as the inert gas instead of coal gas. The product can be cyclised in the usual way, but it is difficult to separate the product from the unchanged starting material.

The better method was as follows:

2'-Methyldihydrofurano-(4':5')-4-methylcoumarin (8:7) (20 g.), and 40% aqueous sodium hydroxide were refluxed on a sand bath under nitrogen, until a semi-solid separated which took 4 hours. After cooling, crushed ice was added, and the mixture was acidified with dilute hydrochloric acid. It was extracted with ether and the ether extract was washed several times with aqueous sodium hydroxide (2N). The unchanged material (7 g.) was recovered from the ether extract.

The alkali extract was made acid with dilute hydrochloric acid and extracted with ether. The ether extract was dried over sodium sulphate. Removal of ether yielded a residue which was distilled in vacuo. The viscous liquid, b.p. 110-120°/2 mm., solidified on

standing. It crystallised from petrol ether in colourless needles, m.p. 70-72°C. Yield 6.2 g.

It is soluble in ethyl alcohol and benzene. Its alcoholic solution gave a dark brown colour with ferric chloride.

Found: C. 70.17%, H. 6.5%, molecular weight 170

$C_9H_{10}O_2$ requires: C. 72.00%, H. 6.67%, molecular weight 150.

The compound is identical in every way with Dr. W. H. Davies' specimen (private communication loc.cit.).

The phenol gave 2:4-dinitrophenylhydrazone, which crystallised from alcohol in reddish brown needles, m.p. 252°C. It was identical in every way with the 2:4-dinitrophenylhydrazone of 4-hydroxy-5-acetyl-2-methyldihydrobenzofurane (vide supra). There was no depression in their mixed melting point.

The p-nitrobenzoate was prepared and crystallised from dilute alcohol as colourless needles. It had a melting point of 131°C.

Found: C. 63.14%, H. 4.49%, N. 4.68%

$C_{16}H_{13}O_3N$ requires: C. 64.21%, H. 4.35%, N. 4.68%

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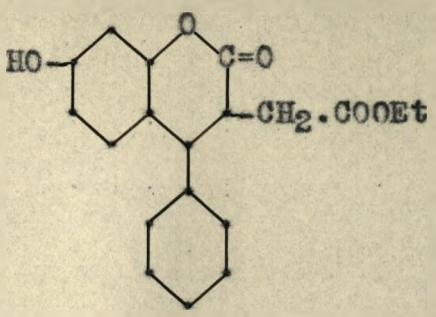
Ethyl 7-hydroxy-4-phenylcoumarin-3-acetate (XXVIII)



This was prepared by Robinson's method (J.C.S., 1933, 1469).

Route I.

4:7'-diacetoxy-8'-allylnaphthacoumarin (1:2:4':3').
(Formula XXXI)

Ethyl-7-hydroxy-4-phenyl-3-acetate (9 g.), allyl bromide (3.5 g.) and anhydrous potassium carbonate (5 g.) were refluxed on the water bath with acetone (30 c.c.) for 10 hours. After this period, most acetone was removed and water (200 c.c.) was added. A brownish oil separated. It was extracted with ether, washed three times with 1% aqueous sodium hydroxide and finally with water. After drying the ether extract over sodium sulphate, and after removal of ether, a viscous brownish oil was obtained, which could not be purified by crystallisation. Distillation under

reduced pressure may cause the isomeric changes. Yield of brown oil 8 g.

The oil (4 g.) was placed in a boiling tube in an oil bath at 200°C. During the course of 2½ hours, the temperature was gradually raised to 210°C. The solid contents were allowed to cool, dissolved in the least possible amount of alcohol and poured into water (50 c.c.). The solid was collected and ground up in 1% aqueous sodium hydroxide to isolate the allyl isomer. It was filtered and the filtrate was made acid with dilute hydrochloric acid. The solid which separated was crystallised from dilute alcohol in colourless prisms, m.p. 154-157°C. Yield 2.1 g. It is slightly soluble in benzene or petrol ether. It shows no colour reaction with alcoholic ferric chloride.

The above ester (2 g.) was refluxed with 5% aqueous sodium hydroxide (20 c.c.) for one hour. The 8-allyl-7-hydroxy-4-phenylcoumarin-3-acetic acid was precipitated by acidification with dilute hydrochloric acid and crystallised from acetic acid in colourless prisms (1.7 g.). It had a melting point of 225°C. after darkening at 178°C.

Found: C. 69.22%, H. 4.96%

$C_{20}H_{16}O_5$ requires: C. 71.43%, H. 4.76%

It is soluble in ethyl alcohol.

A mixture of the above acid (1.5 g.) and acetic anhydride (10 c.c.) was refluxed for 12 hours. On cooling colourless needles (0.95 g.) separated. A further amount (0.4 g.) was obtained by dilution of the filtrate with water. Crystallisation from acetic acid gave colourless needles, m.p. 235-236°C. It is soluble in hot alcohol. It gives an intense green fluorescence in concentrated sulphuric acid.

Found: C. 71.66%, H. 4.61%, Acetyl 24.9%

$C_{24}H_{18}O_6$ requires: C. 71.64%, H. 4.47%, Acetyl 21.4%

... ...

4:7'-Dihydroxy-8'-allylnaphthacoumarin (1:2:4':3').

(Formula XXXII)

The foregoing diacetate (0.9 g.) was refluxed for an hour with 5% alcoholic potassium hydroxide (5 c.c.) and the solution acidified hot with dilute hydrochloric acid and poured into cold water (15 c.c.). It was extracted with ether and the ether extract washed with 5% aqueous sodium hydroxide. The alkaline washings were acidified with dilute hydrochloric acid and extracted with ether. After removal of ether a brown oil (0.5 g.) was obtained, which could not be purified.

... ...

Attempt to obtain 2"-methyldihydrofurano-(4":5":8':7')-α-naphthol-(1:2:4':3')-coumarin. (Formula XXXV)

An intimate mixture of the foregoing compound (0.5 g.) and pyridine hydrochloride (0.1 g.) was maintained at 200-210°C. for 1½ hours. After cooling, it was dissolved in the least possible amount of alcohol and poured into cold water (20 c.c.). The brownish solid was filtered and crystallised from alcohol as brownish needles, m.p. 195°C. Yield 0.2 g.

Found: C. 77.39%, H. 5.30%

$C_{20}H_{14}O_4$ requires: C. 75.47%, H. 4.40%

*** *** ***

Route II.

4-Acetoxy-7'-allyloxynaphthacoumarin (1:2:4':3') (XXXIII)

7-Allyloxy-4-phenylcoumarin-3-acetate (4 g.) was refluxed with 5% aqueous sodium hydroxide (40 c.c.) for one hour. The acid (2.6 g.) was precipitated by acidifying with dilute hydrochloric acid. It was dissolved in saturated sodium bicarbonate solution and reprecipitated with dilute hydrochloric acid. It crystallised from alcohol in colourless prisms, m.p. 83-85°C. After drying the acid was refluxed with acetic anhydride

(20 c.c.) for 12 hours. On cooling, light yellow needles (1.4 g.) separated. It crystallised from acetic acid in yellowish needles, m.p. 194°C. A further amount (0.9 g.) was obtained by decomposition of the acetic anhydride liquor with water. It is soluble in alcohol and insoluble in dilute aqueous sodium hydroxide.

Found: C. 73.33%, H. 4.53%, Acetyl 16.7%

$C_{22}H_{16}O_5$ requires: C. 73.33%, H. 4.44%, Acetyl 11.94%

... ...

Attempt to isomerise the foregoing compound 4-hydroxy-7'-allyloxynaphthacoumarin (1:2:4':3') (Formula XXXIV) to 4-7'-dihydroxy-8'-allylnaphthacoumarin (1:2:4':3') (XXXII).

The foregoing acetate (1.2 g.) was refluxed with 5% alcoholic potassium hydroxide (7 c.c.) for one hour and the solution acidified hot with dilute hydrochloric acid, and added to cold water (20 c.c.). The yellow powder was collected and crystallised from alcohol in fine needles. Yield 0.8 g. It had a melting point of 232-235°C. (decomposition). It was sparingly soluble in cold alcohol but was soluble in acetic acid. An attempt to convert it to 4-7'-dihydroxy-8'-allylnaphthacoumarin (1:2:4':3') (Formula XXXII), by heating at 240°C. was unsuccessful, since the allyl ether decomposed at its melting point.

THE CONSTITUTION OF EUPARIN AND THE SYNTHESIS OF TETRAHYDROEUPARIN

HISTORICAL INTRODUCTION

Purple boneset, trumpet weed, gravel root or queen of the meadow (Eupatorium purpureum) was described by H. Rays in his private communication with Trimble (Amer.J.Pharm., 1890, 62, 73) as having some purple characteristics and these were found in its purplish coloured stem and flowers. The rhizome and rootlets were parts stated to be used medicinally but no description of the drug was given.

The plant is found growing abundantly in low places and attains a height of from three to four feet and even more. The rhizome is horizontal, one to four inches long, one half to three quarters of an inch in thickness, and with many thin, rather tough rootlets. It is brownish black externally, yellowish internally and is broken with difficulty. The medulla is darker than the other portions, the odour slight but peculiar, the taste bitter, and the bark thin.

The rootlets are lighter in colour, four to eight inches long, with a thick, easily removable bark enclosing a tough central cord.

Trimble (loc.cit.) mentioned that the bitter principle of the plant was first isolated in yellow

crystalline form by J.U. Lloyd in the latter's private communication between 1870 and 1875. The method adopted was to digest the powdered root with aqueous alcohol (3 parts of alcohol and 2 parts of water). After removal of the solvent to the consistency of thick honey, the residue was poured into water. After a day, the supernatant liquid was decanted. The precipitate was washed with water and dried. The dark coloured precipitate was crystallised from alcohol in deep yellow colour, m.p. 117.2°C. No yield of the substance was mentioned. Lloyd believed it to be identical with quercitrin and the name Eupapurin or Euparin was suggested. E. G. Eberhardt, according to Trimble (loc.cit.), obtained it from a sediment in a fluid extract of the drug. Elementary analyses of the two samples showed they were identical, having the empirical formula $C_{12}H_{11}O_3$, and the compound quercitrin or quercitin was therefore excluded. The adoption of one of the names "Euparin" proposed by Lloyd was suggested.

Charles C. Manger (Amer.J.Pharm., 1894, 66, 120) investigated Lloyd's and Eberhardt's Euparin and agreed on the same empirical formula with m.p. 116°C. after crystallisations from alcohol. By the action of chlorine in absolute ether, he obtained a thick yellow

liquid which could not be purified. The product was treated with ammonium hydroxide, and the insoluble body which had a greyish black appearance was submitted to elementary analysis. The compound $C_{24}H_{15}Cl_7O_6$ was stated to be obtained. Manger was unable to obtain a crystalline product by boiling Euparin with acetic anhydride either alone or with sodium acetate. The action of concentrated nitric acid converted euparin to a substance resembling picric acid in chemical properties. Fusion of euparin with potassium hydroxide yielded a substance resembling phloroglucinol in chemical properties. In both cases no definite crystalline compounds were isolated. Manger concluded the presence of picric acid and phloroglucinol. Manger's euparin was insoluble in water, sparingly soluble in petrol ether, readily soluble in ether, chloroform, benzene, and acetone. Ferric chloride gave a grass green colour with an alcoholic solution of euparin. It was unaffected by dilute acids or alkalies.

*** *** ***

A new method of isolation

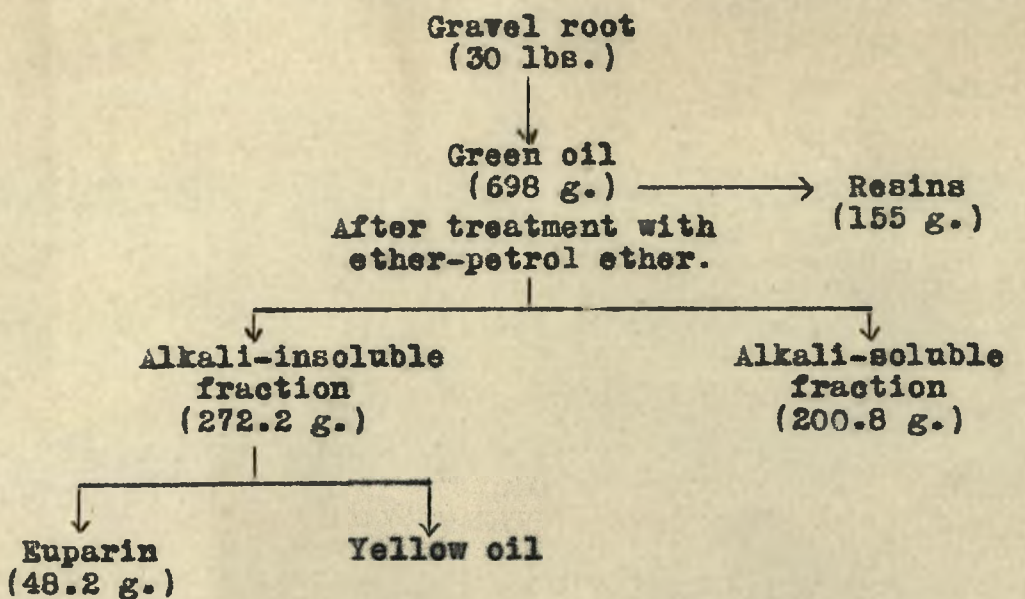
The euparin used in this investigation was obtained from commercial gravel root by extraction with ether by means of Soxhlets for three weeks. After evaporation of the ether, a green oil was obtained. Two volumes of ether were added with stirring, afterwards petrol ether (40-60°) (2½ litres) was gradually added with stirring. The turbid mixture was allowed to stand overnight. The supernatant liquid was decanted off, and the dark green resins left behind were collected aside. The solvent was removed from the ether-petrol ether mixture and two volumes of ether and petrol ether (2½ litres) were again added to the residue, allowed to stand overnight and decanted. After removal of the ether-petrol ether mixture, a green oil was obtained. The oil gave a dark brown colour with ferric chloride in alcoholic solution.

The green oil and 10% aqueous sodium hydroxide (12 c.c. to 1 gram of the oil) were shaken for five minutes. The mixture was extracted many times with ether. The ether extract was washed with water, dried over sodium sulphate and finally ether was removed. A yellow oil was obtained. Addition of petrol ether yielded yellow crystalline solid euparin, m.p. 112-117°C. The alkali-soluble fraction was made acid with dilute

hydrochloric acid and extracted with ether. After drying over sodium sulphate and removal of ether, a greenish oil was obtained which deposited a solid on keeping.

Treatment of the oil with caustic soda for a longer period (30 minutes) yielded practically the same result.

The yield of euparin was 0.88% of the green oil after preliminary treatment with ether and petrol ether, or 0.016% calculated from the weight of the gravel roots used.



The difference was separated as resins.

DISCUSSION OF EXPERIMENTAL WORK

The euparin used in this investigation was obtained from commercial gravel root by extraction with ether using a Soxhlet extractor. After removal of ether, it was treated with a mixture of ether and petrol ether. In this way, a quantity of resinous substance was removed, which would otherwise interfere with subsequent crystallisation. Removal of the ether-petrol ether extract yielded a green oil which was subsequently treated with 10% aqueous sodium hydroxide. The alkali-insoluble fraction was removed with ether, from which euparin was obtained. It crystallised from alcohol and petrol ether in yellow prisms, m.p. 118.5°C. The total yield of pure euparin was found to be 0.88% of the green oil, after preliminary treatment with a mixture of ether-petrol ether, or 0.016% of the weight of the gravel root used.

The euparin so obtained had identical properties with the euparin described by previous investigators except that it had a melting point 1.5° higher than any previously recorded specimens (cf. Trimble, loc. cit., 117.2°C.; Manger, loc.cit., 116°C.).

Analytical data for euparin agree for the molecular formulae $C_{13}H_{12}O_3$ and $C_{17}H_{16}O_4$, which require 216

and 284 for its molecular weight respectively. The found molecular weight lies between 241 and 254. Wholly consistent figures were obtained by analyses on four samples. Neither of the formulae, however, agreed for the empirical formula $C_{12}H_{11}O_3$ (Trimble and Eberhardt, loc.cit.; Manger, loc.cit.). The molecular formula $C_{13}H_{12}O_3$ of euparin is accepted by the present author on consideration of the analytical data for the derivatives of euparin. Euparin contains no methoxyl group.

Oximation was effected, using hydroxylamine hydrochloride, and sodium acetate in boiling alcohol. The product crystallised from dilute alcohol in colourless prisms, m.p. 147-148°C. The analytical data agree for a monoxime $C_{13}H_{13}O_3N$. The euparin semicarbazone $C_{14}H_{15}O_3N_3$ was prepared by interaction of alcoholic euparin with semicarbazide hydrochloride and sodium acetate. The product crystallised from a large volume of ethyl acetate in yellow prisms, m.p. 255°C. 2:4-Dinitrophenylhydrazine hydrochloride in alcoholic solution reacted with euparin to give dark brown prisms of the 2:4-dinitrophenylhydrazone of euparin, $C_{19}H_{16}O_6N_4$, m.p. 252°C., being crystallised from a large volume of ethyl acetate. The three nitrogen derivatives of euparin showed beyond doubt that there was one active

carbonyl group in the euparin molecule and that the compound having the alternative formula $C_{17}H_{16}O_4$ was excluded.

Methylation of euparin, using methyl iodide and anhydrous potassium carbonate in boiling acetone, resulted in the formation of the monomethyl ether of euparin, $C_{14}H_{14}O_3$, which crystallised from dilute alcohol in colourless prisms, m.p. 76-77°C. It gave a negative ferric reaction with ferric chloride in alcoholic solution.

Acetylation of euparin, using pyridine and acetic anhydride at room temperature during three days, gave rise to the formation of mono-acetoxy euparin, $C_{15}H_{14}O_4$, m.p. 80°C., which crystallised from petrol ether in colourless prisms. It is insoluble in alkali, and gives a negative ferric reaction.

The action of both aqueous and alcoholic sodium hydroxide of various concentrations (10%, 20%, 30%) on euparin was studied. Euparin only very slightly dissolved to give a light yellow solution in the aqueous alkali. It was heated to its boiling point for four hours. No trace of decomposition was detected. The starting material could be recovered by steam distillation or by acidification with dilute hydrochloric acid.

Quantitative hydrogenation of euparin was studied.

A solution of one gram of euparin in ethyl acetate was shaken with catalytic palladium-charcoal in the presence of hydrogen at ordinary temperature. The total volume of hydrogen taken after three hours was equivalent to 210.2 c.c. at N.T.P., after making allowances for a blank experiment under similar conditions. Theoretical absorption by two double bonds on the basis of the formula $C_{13}H_{12}O_3$ is 208 c.c. Removal of the charcoal and the solvent furnished tetrahydro-euparin, $C_{13}H_{16}O_3$, in colourless prisms, m.p. 71°C., which crystallised from petrol ether. (Found molecular weight 220.8-226.5; $C_{13}H_{16}O_3$ requires molecular weight 220.)

It gave brownish red colour with ferric chloride in alcoholic solution. It was insoluble in dilute sodium hydroxide and optically inactive. It was noted that absorption of approximately half of the total volume of hydrogen took place rapidly within five minutes. Methylation of tetrahydro-euparin, using methyl iodide and anhydrous potassium carbonate in boiling acetone, led to the formation of the monomethyl ether of tetrahydro-euparin, $C_{14}H_{18}O_3$, in almost theoretical yield. This compound crystallised from dilute alcohol in colourless prisms, m.p. 57°C. It gave a negative ferric reaction with ferric chloride in alcoholic solution.

Acetylation of tetrahydro-euparin, using pyridine and acetic anhydride at room temperature during three days, resulted in the formation of mono-acetoxytetrahydro-euparin, $C_{15}H_{18}O_4$, which crystallised from petrol ether in colourless needles, m.p. 96-97°C. Mono-acetoxytetrahydro-euparin shows a negative ferric reaction with ferric chloride in alcoholic solution. It is insoluble in dilute sodium hydroxide.

Tetrahydro-euparin furnished a 2:4-dinitrophenylhydrazone, $C_{19}H_{20}N_4O_6$, which crystallised from benzene in scarlet prisms, m.p. 240-241°C. Oximation of tetrahydro-euparin, using hydroxylamine hydrochloride and sodium acetate in boiling alcohol, yielded the mono-oxime of tetrahydro-euparin, $C_{13}H_{17}NO_3$, which crystallised from petrol ether in colourless needles, m.p. 133°C.

Hydrogenation of methoxyeuparin in the presence of catalytic palladium charcoal gave rise to the mono-methyl ether of tetrahydro-euparin, m.p. 57°C., which was identical in every respect with the compound prepared by methylation of tetrahydro-euparin (vide supra). No alkali-soluble product was obtained.

The monomethyl ether of euparin was oxidised for four hours with 4% aqueous potassium permanganate. The total volume of potassium permanganate taken was approximately equivalent to ten atoms of oxygen. The solution

was decolourised with sulphur dioxide and heated on the water bath with a few drops of dilute sulphuric acid. Extraction with ether and subsequent evaporation left a 40% yield of 4-hydroxy-2-methoxyresacetophenone-5-carboxylic acid, $C_{10}H_{10}O_5$, which crystallised from hot water in colourless needles, m.p. 215-217°C. A poor yield of the acid was obtained if a larger amount of the ether was oxidised at a time. The acid gave a reddish brown colour with ferric chloride in alcoholic solution, and was optically inactive. Its equivalent weight was determined by titrating an alcoholic solution of the acid with aqueous sodium hydroxide (0.009668 N), which had been standardised with a solution of potassium hydrogen phthalate, phenolphthalein being used as indicator (soda lime tube). The found equivalent weight was 216.9, while $C_{10}H_{10}O_5$ requires 210. The identity of this acid was established beyond doubt by various methods. Firstly, a mixture of the acid and an excess of diazomethane in absolute ether was allowed to stand overnight. An oily residue was obtained after removal of ether. The oil was insoluble in aqueous sodium bicarbonate, but its alcoholic solution still showed a brownish red colour with ferric chloride in alcoholic solution. Obviously, the acid had undergone esterification but not methylation. The

residue could not be induced to crystallise. It was further treated with an excess of methyl iodide and anhydrous potassium carbonate in boiling acetone for eight hours, when it no longer showed a ferric reaction. The solution, being freed from an inorganic salt, was evaporated and the residue taken up with hot water. In this way the ester was completely saponified to free acid, which was isolated by making the aqueous solution acid with dilute hydrochloric and by subsequent extraction with ether. Removal of ether furnished a colourless solid which crystallised from hot alcohol in colourless needles, m.p. 233-234°. The acid was identical in every respect with 2:4-dimethoxyresacetophenone-5-carboxylic acid (Lindermann-Lindenbaum, Ber., 41, 1610, m.p. 231-233°C.). Their mixed melting point was 231-233°C.

Secondly, as 2:4-dimethoxyresacetophenone-5-carboxylic acid (Lindermann-Lindenbaum, loc.cit.) was prepared by a somewhat ambiguous method, decarboxylation of the 2-methoxy-4-hydroxyacetophenone-5-carboxylic acid (vide supra) was carried out to confirm its identity. Using anhydrous quinoline and copper bronze it furnished 2-methoxyresacetophenone, which crystallised from hot water in colourless needles, m.p. 135-137°C. It gave a negative ferric reaction and formed a 2:4-

dinitrophenylhydrazone, which crystallised from alcohol in dark brown prisms, m.p. 216-217°C. The identity of the 2-methoxy-resacetophenone was established by comparison with the authentic specimen (Hoesch, Ber., 48, 1126, m.p. 136-137°) and another specimen prepared by a new method (vide infra).

Thirdly, the 2-methoxy-4-hydroxyresacetophenone-5-carboxylic acid was demethylated, using hydriodic acid. 2:4-dihydroxy-resacetophenone-5-carboxylic acid was obtained, which crystallised from alcohol in prisms, m.p. 256°C. Its identity was established by comparison with 1:2:4:5-resacetophenone carboxylic acid (Lindermann-Lindenbaum, loc.cit., m.p. 255-256°C.).

Ozonolysis of the methyl ether of euparin in absolute chloroform was studied. After 1½ hours the solvent was removed at 40°C. under reduced pressure, and the glassy residue was treated with water and allowed to stand overnight. It was heated on the steam bath for twenty minutes, and on cooling, colourless needles separated. It crystallised from water in colourless needles, m.p. 117-118°C. The yield was approximately 35%. It gave a brown colour with alcoholic ferric chloride and was aldehydic or ketonic towards ordinary ketonic reagents. Analytical data agree for the formula $C_{10}H_{10}O_4$. Although its identity had not been

definitely established, through lack of sufficient material, it was very likely 2-methoxy-4-hydroxy-acetophenone-5-aldehyde. The main filtrate was distilled on a wire gauze, keeping the volume of the solution constant. The distillate was collected in an aqueous solution of 2:4-dinitrophenylhydrazine hydrochloride in excess of 2N dilute hydrochloric acid. The precipitate crystallised from alcohol in orange yellow needles, m.p. 161-162°. It was identified as 2:4-dinitrophenylhydrazone of formaldehyde, by comparison with an authentic specimen, m.p. 163-164°C.

Diels and Alder's reaction on the methyl ether of euparin was studied. When a mixture of methyl ether of euparin, maleic anhydride and absolute benzene was refluxed on the water bath for twelve hours, an additive reaction took place. A colourless solid which separated from the hot solution was collected and crystallised from alcohol in colourless plates, m.p. 212-213°C. Analytical data agree for $C_{18}H_{16}O_6$, which requires one molecule of methyl ether of euparin and one molecule of maleic anhydride. Using toluene as a condensing medium, an identical product was obtained. On the other hand, using nitrobenzene as a condensing solvent at its boiling point, brownish prisms, m.p. 296-298°C., were obtained which were not further

investigated. This was not surprising, since nitrobenzene under the conditions might act as an oxidising agent. In the case of euparin, Diels and Alder's reaction gave rise to a condensation product having the formula $C_{17}H_{14}O_6$, which crystallised from alcohol in colourless needles, m.p. 244-245°C.

Oximation of the monomethyl ether of tetrahydroeuparin by hydroxylamine hydrochloride and sodium acetate in boiling alcohol gave rise to a monoxime, $C_{14}H_{19}O_3N$, which crystallised from alcohol in colourless prisms, m.p. 139°C. This oxime underwent a Beckmann rearrangement, using thionyl chloride (cf. Stephen, J.C.S., 1931, 886). A solution of the oxime (1 mole) in absolute ether was cooled down to -5°C. Thionyl chloride (1 mole) in absolute ether was gradually added during ten minutes. The addition of thionyl chloride produced a colourless precipitate which gradually developed a red solution. After a total time of fifteen minutes (not longer, if charring was to be avoided), the content was poured into ice water. Ether was removed at ordinary temperature. Colourless leaflets, m.p. 133-134°C., of an amide $C_{14}H_{19}O_3N$ crystallised from petrol ether. The yield was approximately 60% and no other crystalline product was obtained.

Hydrolysis of the foregoing amide with 20%

alcoholic potash gave rise to a primary amine which crystallised from dilute alcohol in colourless needles, m.p. 68-69°C. The amine was soluble in dilute mineral acids, from which it could be reprecipitated by addition of dilute alkali. It could be diazotised, and the diazo compound readily coupled with β-naphthol to give a bright scarlet dye. It does not give a carbylamine reaction, however, which is not surprising, considering the size of its molecule.

The foregoing amine was acetylated with acetic anhydride at room temperature for five minutes and the mixture was poured into hot water containing a little hydrochloric acid. The colourless leaflets, m.p. 133-134°C. after crystallisation from petrol ether were identical in every respect with the starting amide.

In order to confirm and to establish the position of the acetyl group in the tetrahydro-euparin molecule, the latter was treated with absolute ethyl acetate and finely cut sodium under reflux. Acidification of the reaction mixture furnished an ortho-hydroxy-aceto-acetyl ketone, $C_{15}H_{18}O_4$, which crystallised from petrol ether in colourless prisms, m.p. 109-110°C. The ketone gave a dark brown colour with ferric chloride in alcoholic solution. The diketone was cyclised with boiling acetic acid in presence of a few drops of hydrochloric

acid to give a-methylchromone, $C_{15}H_{16}O_3$, which crystallised from petrol ether in colourless needles, m.p. 119-120°C. The chromone gave a negative ferric reaction. A trace of it in concentrated sulphuric acid gave a faint blue fluorescence.

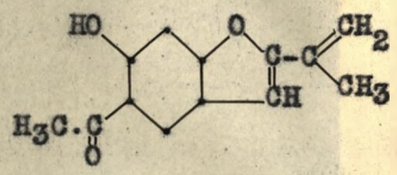
Fission of tetrahydro-euparin with potassium hydroxide gave rise to isovaleric acid and a phenol which showed a brownish red colour with alcoholic ferric chloride. The isovaleric acid was converted into its phenylhydrazide, which was compared with an authentic isovaleric phenylhydrazide. A further investigation of the phenol was prohibited through lack of the starting material. Further experiments on the fission of tetrahydro-euparin will be repeated at a later date.

Oxidation of euparin with 8% hydrogen peroxide in acetic acid was unsuccessful. No crystalline product was obtained.

The chart on page 86 has been compiled in order to indicate at a glance the chief reactions of euparin.

*** *** ***

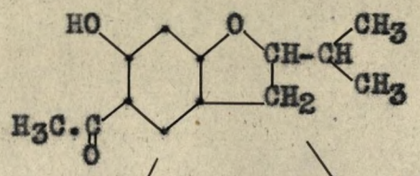
Euparin
$C_{13}H_{12}O_3$



(?)

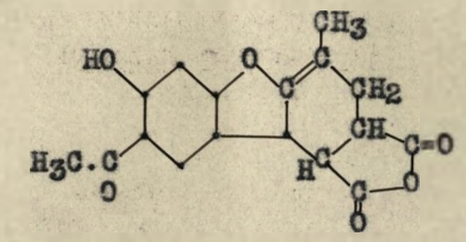
Pd/H_2

Tetrahydro-euparin
$C_{13}H_{16}O_3$



Maleic anhydride
Benzene

A condensation product
$C_{17}H_{14}O_6$



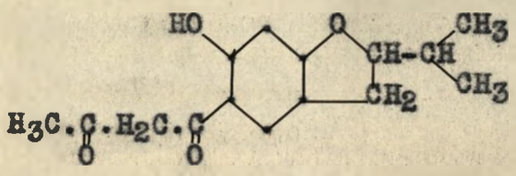
(?)

Methylation
MeI, K_2CO_3,
acetone

Monomethoxy-euparin
$C_{13}H_{11}O_2(OCH_3)$

Ethyl acetate
sodium

Hydroxy diketone
$C_{15}H_{18}O_4$



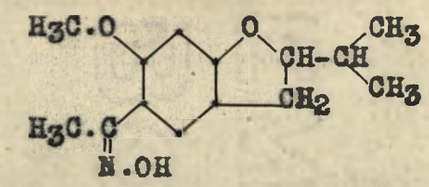
Methylate
MeI, K_2CO_3
Acetone

Pd/H_2

Monomethoxy-tetrahydro-euparin
$C_{13}H_{15}O_2(OCH_3)$

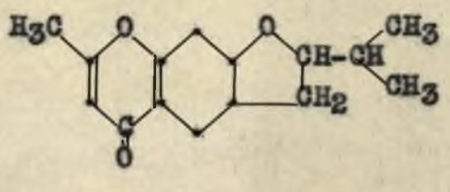
Oximation

Monomethoxy-tetrahydro-euparin oxime
$C_{14}H_{19}O_3N$



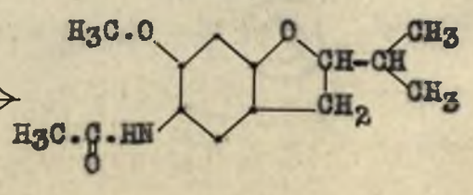
HAc HCl
(-H_2O)

α-methyl chromone
$C_{15}H_{16}O_3$



Beckmann
rearrangement
$SOCl_2$

An Amide (monomethoxy)
$C_{14}H_{19}O_3N$

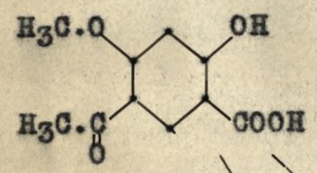


Primary Amine

Ac_2O

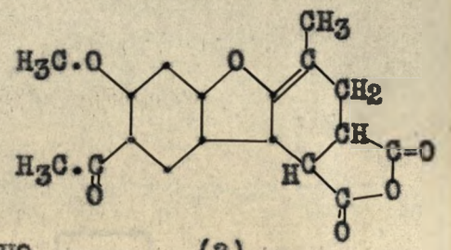
Hydrolysis
20% aq. KOH

Oxidation
$KMnO_4$



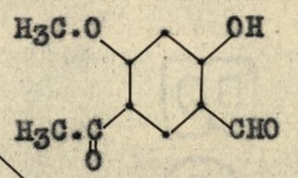
Maleic anhydride
Benzene

A condensation product
$C_{17}H_{13}O_5(OCH_3)$



Ozonolysis

$C_{10}H_{10}O_4$ + HCHO (?)

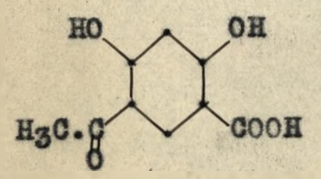


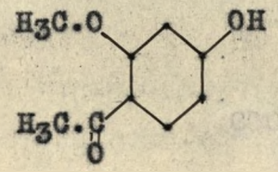
(?)

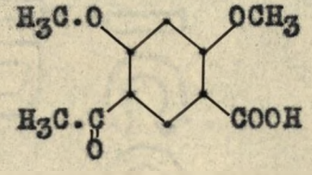
Demethyl-
ation

Decar-
boxylation

Methylation







From the historical introduction it can be seen that little has been known of the constitution of euparin. Although its empirical formula $C_{12}H_{11}O_3$ was put forward, no definite derivatives and no degradation products had been isolated.

The author has revised the problem of the constitution of euparin and has obtained a specimen having a melting point approximately 2° higher than any previously recorded. It was possible to obtain fairly consistent analyses of euparin. It is certain that it has the molecular formula $C_{13}H_{12}O_3$. The only alternative formula $C_{17}H_{16}O_4$ is excluded on consideration of its oxime, semicarbazone, 2:4-dinitrophenylhydrazone, methyl ether and acetate. Hydrogenation experiments using palladium catalyst prove that euparin contains two double bonds, and the analytical figures for tetrahydro-euparin agree accurately for $C_{13}H_{16}O_3$. Further confirmation of the molecular formula $C_{13}H_{16}O_3$ for tetrahydro-euparin is to be found in the elementary analyses of its methyl ether, 2:4-dinitrophenylhydrazone, oxime and acetate. The following tables indicate that the formula $C_{17}H_{16}O_4$ is untenable for euparin.

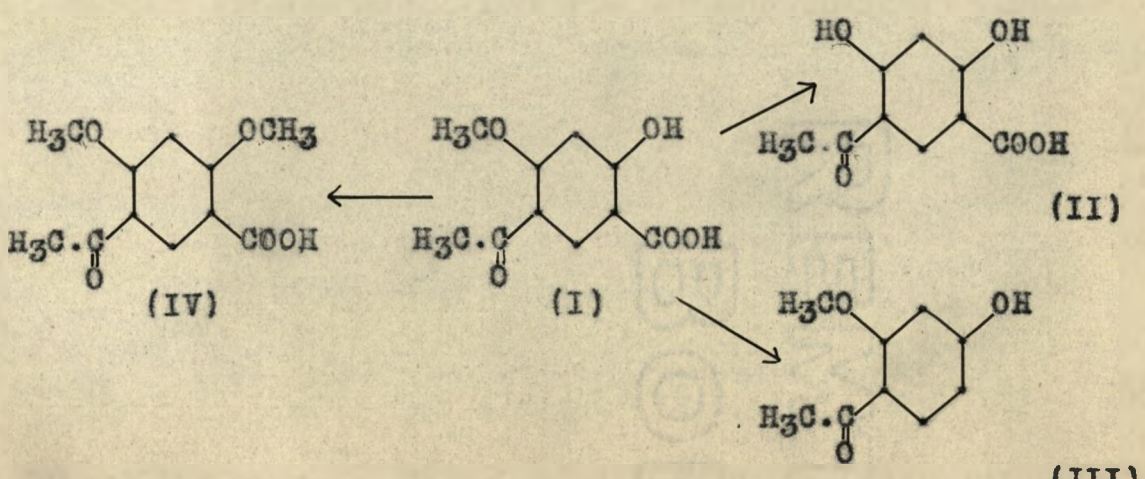
	Found	$C_{13}H_{12}O_3$	$C_{17}H_{16}O_4$
Euparin	C. 72.22%, H. 5.70% 72.18% 5.50% 72.06% 5.58% 72.40% 5.52% molecular weight 241 254	C. 72.22% H. 5.55% molecular weight 216	C. 71.89% H. 5.63% molecular weight 284
Oxime of euparin		$C_{13}H_{13}O_3N$	$C_{17}H_{17}O_4N$
	N. 6.18%	N. 6.07%	N. 4.68%
Semicarbazone of euparin		$C_{14}H_{15}O_3N_3$	$C_{17}H_{19}O_4N_3$
	N. 15.38%	N. 15.38%	N. 12.76%
2:4-Dinitrophenylhydrazone of euparin		$C_{19}H_{16}O_6N_4$	$C_{23}H_{20}O_7N_4$
	N. 14.18%	N. 14.14%	N. 12.07%
Methyl ether of euparin		$C_{13}H_{11}O_2(OMe)$	$C_{17}H_{15}O_3(OMe)$
	C. 73.26%, H. 5.98% OCH_3. 12.8%	C. 73.04% H. 6.09% OCH_3. 13.48%	C. 76.6% H. 6.38% OCH_3. 10.9%
Acetate of euparin		$C_{13}H_{11}O_2(OAc)$	$C_{17}H_{15}O_3(OAc)$
	C. 69.64%, H. 5.45%	C. 69.77% H. 5.43%	C. 69.94% H. 5.52%

	Found	$C_{13}H_{16}O_3$	$C_{17}H_{20}O_4$
Tetrahydro-euparin	C. 71.16% H. 7.40% molecular weight 220.8 226.5	C. 70.91% H. 7.27% molecular weight 220	C. 70.84% H. 6.94% molecular weight 288
Methyl ether of tetrahydro-euparin		$C_{13}H_{15}O_2(OMe)$	$C_{17}H_{19}O_3(OMe)$
	C. 72.05% H. 7.69% OCH_3. 13.4%	C. 71.8% H. 7.69% OCH_3. 13.25%	C. 71.52% H. 7.28% OCH_3. 10.26%
2:4-Dinitrophenyl-hydrazone of tetrahydro-euparin		$C_{19}H_{20}N_4O_6$	$C_{23}H_{24}N_4O_7$
	N. 13.91%	N. 14.00%	N. 11.97%
Oxime of tetra-hydro-euparin		$C_{13}H_{17}NO_3$	$C_{17}H_{21}NO_4$
	N. 5.88%	N. 5.96%	N. 4.62%
Acetate of tetra-hydro-euparin		$C_{13}H_{15}O_2(OAc)$	$C_{17}H_{19}O_3(OAc)$
	C. 68.77% H. 6.88%	C. 68.70% H. 6.87%	C. 72.61% H. 7.00%

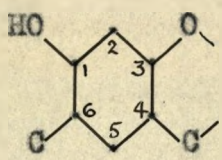
The acetylation and methylation of euparin prove the presence of one hydroxyl group in the euparin molecule. Analytical data for its oxime, semicarbazone and 2:4-dinitrophenylhydrazone show the presence of one

active carbonyl group in the euparin molecule. There remains therefore only one oxygen atom in the euparin molecule to be accounted for.

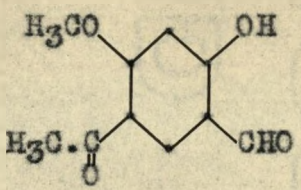
Oxidation of the methyl ether of euparin with neutral aqueous potassium permanganate gives rise to 4-hydroxy-2-methoxy-resacetophenone-5-carboxylic acid (I) which is converted into 2:4-dihydroxy-resacetophenone-5-carboxylic acid (II) by demethylation. Decarboxylation of the acid (I) gives rise to 2-methoxy-resacetophenone (III). Methylation of the acid (I) also furnishes 2:4-dimethoxy-[redacted]acetophenone-5-carboxylic acid (IV). That the acid (I) is monobasic is proved by the determination of its equivalent weight. In addition, 2:4-dihydroxy-[redacted]acetophenone-5-carboxylic acid (II), 2-methoxy-resacetophenone (III) and 2:4-dimethoxy-resacetophenone-5-carboxylic acid are identical with authentic specimens (<u>vide infra</u>).



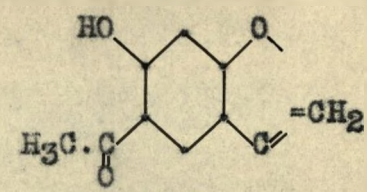
The foregoing oxidation therefore shows that (a) the molecule of euparin contains a resorcinol nucleus, (b) the methoxyl group present in the 4-hydroxy-2-methoxy-resacetophenone-5-carboxylic acid (I) must have come from the original methoxyl group in the molecule of euparin methyl ether, (c) the oxidation has involved a gain of a new hydroxyl group in an ortho-position to a carbonyl group, the fact which is compatible with its ferric reaction, and (d) euparin molecule contains a C_7 unit which is attached to the resorcinol residue in the 3:4:6 positions, according to the skeleton (V).



(V)



(VI)

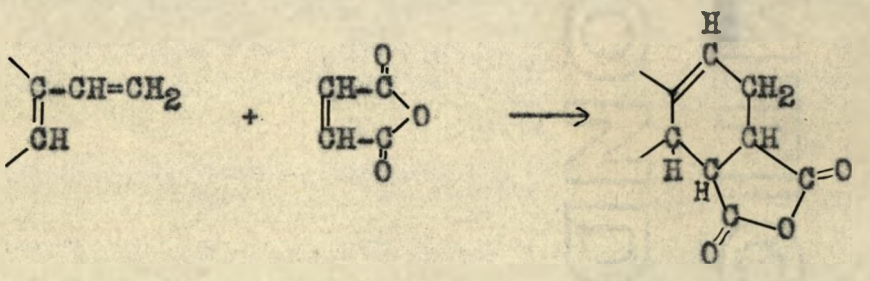


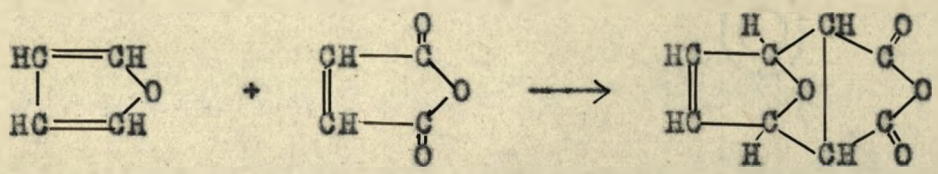
(VII)

That the fission of the two double bonds by ozone is accompanied by the loss of four carbon atoms, giving rise to an aldehyde ($C_{10}H_{10}O_4$) [which analyses for 4-hydroxy-2-methoxy-resacetophenone-5-aldehyde (VI)] and formaldehyde, is a proof that (a) euparin contains a C_5 unit which is attached to a resacetophenone residue, (b) on the assumption that they do not migrate, one of

the two double bonds is a methylene double bond and the other is in the β-position to the resorcinol residue. There is present a skeleton (VII).

The action of maleic anhydride on the methyl ether of euparin produces a condensation product. The Diels and Alder reaction (to I.G. Farbenind.A.-G., B.P. 300,130, Nov.5, 1927) (Ann., 486, 211-215; 490, 236-294) characterises a conjugated double bond system (.C-C-C-C.). In the addition product, the double bond is opened up in the 1:4 position. For example,



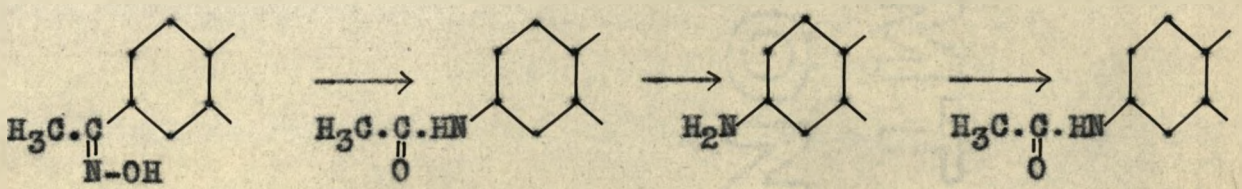


The reaction was further confirmed with the euparin itself.

When the methyl ether of euparin is hydrogenated in the presence of a palladium catalyst, the methyl ether of tetrahydro-euparin is obtained, the latter being identical with the product formed by the methyla-

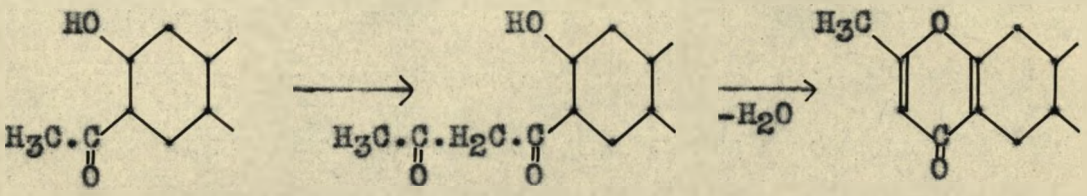
tion of tetrahydro-euparin. This is a clear proof that the hydrogenation of euparin methyl ether, and hence euparin, has taken a normal course, and no change such as fission or condensation within the molecule has taken place. A methyl group therefore resulted from the reduction of the methylene group ($=CH_2$).

The methyl ether of tetrahydro-euparin gives an oxime which readily undergoes a Beckmann rearrangement into an amide by the action of thionyl chloride. The amide is hydrolysed to a primary amine which diazotises readily, and the diazo-compound couples with β-naphthol to give a bright scarlet dye. The amine is reconverted into the starting amide by acetylation with acetic anhydride. The result of the Beckmann transformation clearly shows that the active carbonyl group in the tetrahydro-euparin and hence euparin is present in the form of an acetyl group ($\overset{O}{\overset{\|}{C}}.CH_3$). The mechanism of the reaction can be represented thus:-



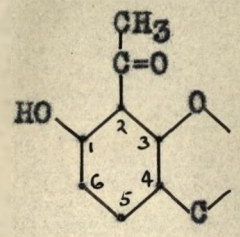
In order to confirm this view, and to establish the position of the hydroxyl group in the tetrahydro-

euparin molecule, it is further shown that the latter compound condenses with ethyl acetate, giving a hydroxyketone (A), which shows a ferric reaction. Cyclisation of the hydroxyketone (A) with boiling acetic acid in the presence of a few drops of mineral acid involves a loss of one molecule of water, forming a neutral compound (B), which is devoid of a ferric reaction and which gives a faint blue fluorescence in concentrated sulphuric acid. These reactions (cf. Wittig, Ann., 446, 169) are characteristic of the formation of an ortho-hydroxy-acetoacetylketone, and its subsequent cyclisation into a-methylchromone with the loss of one molecule of water. The mechanism of the reaction can be represented thus:-

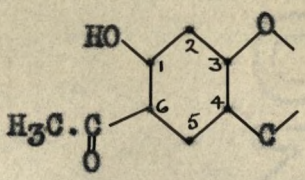


It follows therefore that the hydroxyl group in the tetrahydro-euparin must be present in an ortho-position to the acetyl group. Further, since the presence of a resorcinol residue has been established (vide supra), the hydroxyl group must be in the 1-position, and the acetyl group can occupy either the 2-

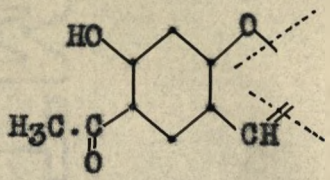
or 6-position as in the expressions (VIII) or (IX).



(VIII)

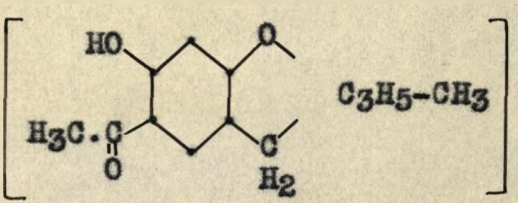


(IX)

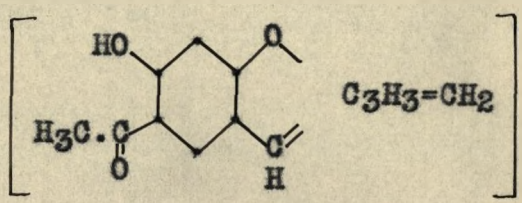


(X)

Compounds having such a structure (VIII) cannot give rise to 1:2:4:5-resacetophenone carboxylic acid (II) on oxidation. In addition, since one of the double bonds is in the β-position to the resorcinol nucleus (vide supra) (X), it is reasonable to assume that the oxidation of euparin methyl ether involves the fission at this double bond. It follows that tetrahydro-euparin has the formula of the type (XI) and euparin has the formula of the type (XII).



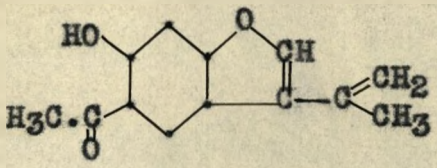
(XI)



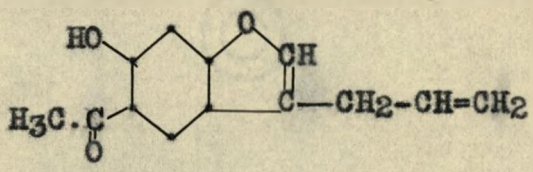
(XII)

Further, since the functions of two of the three oxygen atoms in euparin have now been defined, one in the hydroxyl group and the other in the acetyl group,

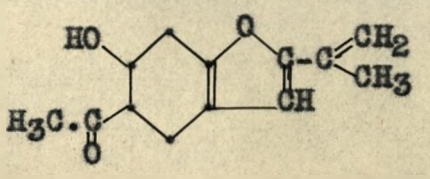
and since the absence of any methoxyl group has been shown, the third oxygen atom must form an ether system with the C_5 unit in agreement with the existence of the two double bonds in the C_5 unit. It is obvious that the C_5 unit with two double bonds cannot possibly possess a chromeno-system, otherwise it dissatisfies the total H_{12} unit. On the other hand, the C_5 unit cannot be present either as in β-isopropylenefurano-system or in the β-n-propylenefurano-system of types (XIII) and (XIV), because compounds having such a structure will not give rise to an ortho-hydroxy aldehyde. Consequently it follows that the C_5 unit must be present either as in an α-isopropylenefurano or in an α-n-propylenefurano system. Hence euparin has either the formula (XV) or (XVI), and tetrahydro-euparin has the structure (XVII) or (XVIII).



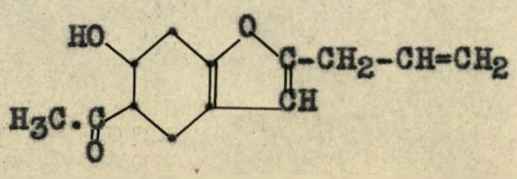
(XIII)



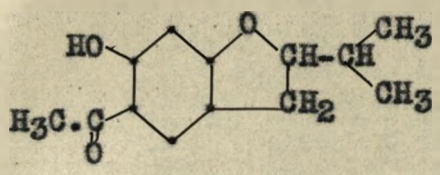
(XIV)



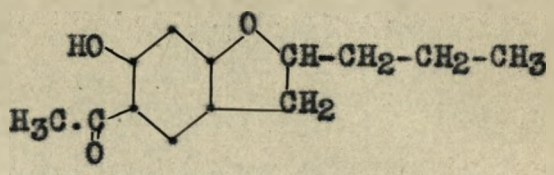
(XV)



(XVI)



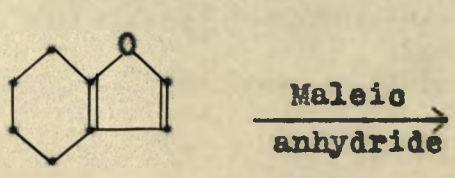
(XVII)



(XVIII)

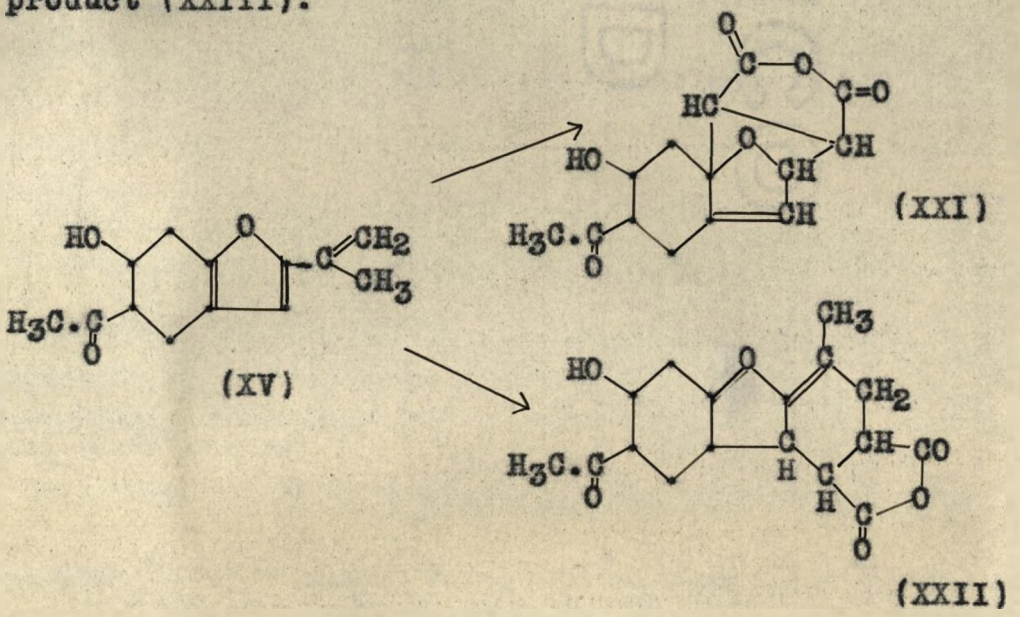
Alkali fission of tetrahydro-euparin under drastic conditions (290°C.) gives rise to isovaleric acid and a phenol, a further investigation of which was prohibited through lack of the starting material. The mechanism of the formation of isovaleric acid cannot be explained on consideration of either of the formulae (XVII) or (XVIII). Considering the conditions under which fission was carried out, one has to accept the result with reserve. Under milder conditions, however, tetrahydro-euparin is not affected.

It is definitely known that a simple furane ring forms an addition reaction with maleic anhydride (vide supra), but no reference can be found regarding whether a benzofurane ring system of type (XIX) undergoes a similar reaction. On the assumption that it does, an addition product (XX) would be produced in analogy to the case of a furane.

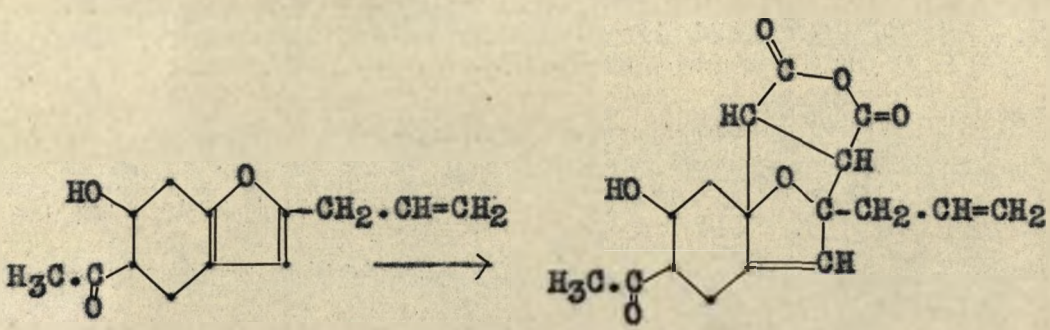


(XIX) (XX)

Similarly, on the same assumption, the expression (XV) for euparin will furnish the addition products (XXI) or (XXII), depending on the choice of a conjugated system. The expression (XVI) for euparin furnishes the product (XXIII).



(XV) (XXI) (XXII)



(XVI) (XXIII)

If that was so, the expressions (XV) and (XVI) cannot be distinguished by the Diels and Alder reaction.

Oxidation of euparin with hydrogen peroxide (cf.

Späth, Ber., 66, 1137-1145) is unsuccessful. It is possible that under the chosen conditions the furane ring is attacked.

Since the majority of practical results lead to only two alternative formulae (XVII) and (XVIII) for tetrahydro-euparin, it is proposed to synthesise both 6-hydroxy-5-acetyl-2-isopropyldihydrobenzofurane (XVII) and 6-hydroxy-5-acetyl-2-N-propyldihydrobenzofurane (XVIII) for comparison with tetrahydro-euparin. Finally, the expression (XVII) is accepted for tetrahydro-euparin by synthesis.

---------oOo---------

ANALYTICAL AND DEGRADATION

Purification of Euparin

Euparin was repeatedly crystallised, first from dilute alcohol and finally from petrol ether (80-100°C.) in yellow prisms, m.p. 118.5°C.

Found (on four separate specimens):-

C. 72.22, 72.18, 72.06, 72.40%
H. 5.70, 5.50, 5.58, 5.52%
Negative methoxyl.

Molecular weight found: 241, 254.

$C_{13}H_{12}O_3$ requires: C. 72.22%, H. 5.55%, molecular weight 216
$C_{17}H_{16}O_4$ requires: C. 71.89%, H. 5.63%, molecular weight 284.

Ferric chloride gave a grass-green colour with an alcoholic solution of euparin. Cold concentrated sulphuric acid gave a reddish brown solution of the substance which became black on heating. 10%, 20% and 30% aqueous sodium hydroxide or alcoholic sodium hydroxide had no action on euparin. Euparin was not reduced by ammonium sulphide.

Euparin is insoluble in water, sparingly soluble in petrol ether, very soluble in ether, chloroform, benzene, carbon disulphide and boiling alcohol. It is steam-volatile and can be sublimed. It is not optically active. Euparin is slightly soluble in 8% aqueous

sodium hydroxide to which it imparts a yellowish colour.

Euparin Oxime.

Euparin (1 g.) was dissolved in absolute alcohol (50 c.c.). Hydroxylamine hydrochloride (0.5 g.) and sodium acetate (1 g.) dissolved in the least possible amount of water were added. After refluxing on the water bath for 4 hours, most of the alcohol was removed in vacuum, and cold water (50 c.c.) was added to the residue. The colourless solid obtained after filtration crystallised from dilute alcohol in colourless prisms. It had a melting point of 147-148°C. and was soluble in benzene.

Found: N. 6.18%

$C_{13}H_{13}O_3N$ requires: N. 6.07%

... ...

Euparin semicarbazone.

Euparin (0.5 g.) was dissolved in alcohol (50 c.c.). Semicarbazide hydrochloride (0.3 g.) and sodium acetate (0.5 g.) dissolved in the least possible amount of water were added. The mixture was allowed to stand for 3 days, sufficient alcohol being added to maintain a clear solution at first. Yellowish crystals together with some inorganic salts were filtered and washed with water. Crystallization from a large volume of ethyl

acetate yielded yellow prisms of euparin semicarbazone. It had a melting point of 255°C.

Found: N. 15.38%

$C_{14}H_{15}O_3N_3$ requires: N. 15.38%

... ...

Euparin 2:4-dinitrophenylhydrazone.

Euparin (0.5 g.) was dissolved in hot absolute alcohol (10 c.c.). 2:4-Dinitrophenylhydrazine (0.5 g.) was dissolved in hot absolute alcohol to which a few drops of concentrated hydrochloric acid were added. The two solutions were mixed and boiled on the water bath for a few minutes, and allowed to stand. The brown crystalline solid was collected and crystallised from a large volume of ethyl acetate in dark brown prisms. It had a melting point of 252°C. Yield 0.8 g.

Found: N. 14.18%

$C_{19}H_{16}O_6N_4$ requires: N. 14.14%

... ...

Methylation of euparin.

Euparin (0.5 g.), methyl iodide (0.5 g.), anhydrous potassium carbonate (2 g.) and acetone (20 c.c.) were refluxed on the water bath for 6 hours. The mixture was filtered hot and the solvent removed from the filtrate. The residue, which consisted of a little

acetone, was poured into cold water (100 c.c.). After standing for some time, the colourless solid (0.5 g.) was collected, m.p. 74-75°C. Crystallization from dilute alcohol yielded colourless prisms of methoxy-euparin. It had a melting point of 76-77°C.

Euparin methyl ether is soluble in most organic solvents. It has a negative ferric reaction with alcoholic ferric chloride.

Found: C. 73.26%, H. 5.98%, OCH_3. 12.8%

$C_{13}H_{11}O_2(OCH_3)$ requires:

C. 73.04%, H. 6.09%, OCH_3. 13.48%

... ...

Acetylation of euparin.

Euparin (0.2 g.), anhydrous pyridine (5 g.) and acetic anhydride (10 g.) were shaken together and allowed to stand at room temperature for three days. The mixture was poured into water (100 c.c.) and allowed to stand overnight. A colourless solid (0.19 g.) which had a melting point of 79°C. was obtained. It was crystallised from petrol ether (80-100°) in colourless prisms. It had a constant melting point of 80°C.

Euparin acetate is soluble in alcohol, acetone and ether, but is sparingly soluble in petrol ether. It gives a negative ferric reaction in alcoholic ferric chloride.

Found: C. 69.64%, H. 5.45%

$C_{13}H_{11}O_2(OAc)$ requires: C. 69.77%, H. 5.43%

... ...

Action of sodium hydroxide on euparin.

A mixture of euparin (1 g.) and 10% aqueous sodium hydroxide (100 c.c.) was heated to boiling for four hours. Euparin was not dissolved and the aqueous solution was slightly yellow. Filtration of the product gave unchanged euparin. A small amount of euparin was also obtained by acidifying the filtrate.

The same result was obtained when euparin was treated in the same way with 20% and 30% aqueous sodium hydroxide.

With 10%, 20% or 30% alcoholic sodium hydroxide at its boiling point, the same result was obtained and euparin was recovered after removal of alcohol under reduced pressure.

... ...

Quantitative hydrogenation of euparin.

Euparin (1 g.), ethyl acetate (100 c.c.) and catalytic palladium charcoal (2 g. charcoal and 0.2 g. palladium chloride) were shaken in hydrogen at ordinary temperature (19°C.). 136 c.c. of hydrogen were rapidly absorbed after five minutes and a further volume of

145 c.c. was absorbed after three hours' shaking. The total volume of 281 c.c. at 19°C. and 758.8 mm. pressure or 262.2 c.c. at N.T.P. was therefore taken. Absorption by blank experiment was 52 c.c. at N.T.P. The total absorption by euparin was therefore 210.2 c.c. Theoretical absorption by two double bonds on the basis of the formula $C_{13}H_{12}O_3$ is 208 c.c.

The product was filtered from charcoal and the solvent was removed from the filtrate under reduced pressure. The colourless solid (1 g.) which was left behind was crystallised from petrol ether (80-100°) in rhombic prisms, m.p. 71°C. It is very soluble in alcohol, ethyl acetate, ether and acetone. It shows a brownish red colour with ferric chloride in alcoholic solution. It forms a 2:4-dinitrophenylhydrazone. It is more soluble in 2N sodium hydroxide than euparin. Tetrahydro-euparin is insoluble in sodium bicarbonate solution.

Found: C. 71.16%, H. 7.40%

$C_{13}H_{16}O_3$ requires: C. 70.91%, H. 7.27%

Molecular weight found: 220.8, 226.5

$C_{13}H_{16}O_3$ requires molecular weight: 220.

Tetrahydro-euparin is not optically active.

... ...

Methylation of tetrahydro-euparin.

A mixture of tetrahydro-euparin (1 g.), anhydrous potassium carbonate (5 g.), acetone (30 c.c.) and methyl iodide (1 g.) was refluxed on the water bath for 6 hours. The product showed a negative reaction with ferric chloride in alcoholic solution. It was filtered and most of the acetone was removed from the filtrate. The residue was poured into water (200 c.c.). After standing for 30 minutes, the crystalline solid (0.9 g.) was collected. It had a melting point of 55-57°C. Crystallization from petrol ether (80-100°) yielded colourless plates of methoxytetrahydro-euparin. It had a melting point of 57°C.

It is soluble in most organic solvents, especially in alcohol, ethyl acetate, acetone and ether.

Found: C. 72.05%, H. 7.69%, OCH_3. 13.4%

$C_{13}H_{15}O_2(OCH_3)$ requires:

C. 71.79%, H. 7.69%, OCH_3. 13.25%

... ...

Acetylation of tetrahydro-euparin.

A mixture of tetrahydro-euparin (0.3 g.), anhydrous pyridine (1 g.) and freshly distilled acetic anhydride (2 g.) was allowed to stand at room temperature for 3 days. The mixture was poured into cold water (100 c.c.). After standing overnight, it was

filtered. The colourless solid was collected, and had a melting point of 92-94°C. Crystallisation from petrol ether yielded colourless needles of tetrahydro-euparin acetate (0.31 g.), m.p. 96-97°C.

Tetrahydro-euparin acetate is soluble in alcohol, ether and acetone. It shows a negative ferric reaction with ferric chloride in alcoholic solution.

Found: C. 68.77%, H. 6.88%

$C_{15}H_{18}O_4$ requires: C. 68.70%, H. 6.87%

... ...

Tetrahydro-euparin 2:4-dinitrophenylhydrazone.

Tetrahydro-euparin (0.5 g.) was dissolved in hot absolute alcohol. 2:4-dinitrophenylhydrazine (0.5 g.) was dissolved in hot absolute alcohol to which a few drops of concentrated hydrochloric acid were added. The two solutions were mixed and heated on the water bath for a few minutes. Scarlet crystals immediately separated. These were filtered and crystallised from benzene as scarlet prisms (0.5 g.), m.p. 240-241°C. They were sparingly soluble in alcohol and ethyl acetate.

Found: N. 13.91%

$C_{19}H_{20}N_4O_6$ requires: N. 14.00%

... ...

Tetrahydro-euparin oxime.

Tetrahydro-euparin (1 g.) was dissolved in absolute alcohol (50 c.c.). Hydroxylamine hydrochloride (0.5 g.) and sodium acetate (1 g.) dissolved in the least possible amount of water were added. After refluxing on the water bath for four hours, most of the alcohol was removed under reduced pressure, and water (50 c.c.) was added to the residue. The colourless solid was collected. Crystallisation from petrol ether yielded colourless needles (0.9 g.), which had a melting point of 133°C.

Tetrahydro-euparin oxime is soluble in alcohol, somewhat less soluble in benzene.

Found: N. 5.88%

$C_{13}H_{17}NO_3$ requires: N. 5.96%

... ...

Hydrogenation of the monomethyl ether of euparin.

Methoxyeuparin (0.5 g.), ethyl acetate (50 c.c.) and catalytic palladium charcoal (2 g. charcoal and 0.2 g. palladium chloride) were shaken with hydrogen at ordinary temperature. After two hours' shaking, a total volume of 104 c.c. of hydrogen was absorbed. Theoretical absorption by methoxyeuparin, $C_{14}H_{14}O_3$, is 96.5 c.c. The product was filtered from charcoal and the solvent removed from the filtrate under reduced

pressure. The colourless residue was extracted with ether and the ether extract (A) was washed several times with dilute sodium hydroxide. The combined alkali extracts were made acid with dilute hydrochloric acid and extracted with ether. The ether extract was dried over sodium sulphate. After removal of ether, no residue was obtained.

The ether extract (A) was dried over sodium sulphate and evaporated. A colourless oily residue was obtained which solidified on standing. It crystallised from petrol ether in colourless plates, m.p. 57°C. It is identical in every respect with methoxytetrahydroeuparin (vide supra). The mixed melting point of both samples was 57°C.

... ...

Oxidation of methoxyeuparin by potassium permanganate.

Methoxyeuparin (1 g.) and acetone (30 c.c.) (which was distilled over potassium permanganate) were placed in a large flask fitted with a mechanical stirrer. 4% aqueous potassium permanganate was added gradually; when after 4 hours a slight excess had been added, the solution was allowed to stand for one hour. The total volume of potassium permanganate required was 110 c.c., which is approximately equivalent to 10 atoms of oxygen. Dilute sulphuric acid (5 c.c.) was added and the solution

was decolourised by passing sulphur dioxide into it. The content was warmed on the water bath for 20 minutes. After cooling, it was extracted with ten volumes of ether. The ether extract was dried over sodium sulphate. After removal of ether, a brownish solid (0.43 g.) was obtained. This was dissolved in saturated sodium bicarbonate solution, and extracted three times with ether. The aqueous residue was made acid with dilute hydrochloric acid and extracted with ten volumes of ether. The ether extract was dried over sodium sulphate. After removal of ether, the brown solid was charcoaled in hot dilute alcohol. Brownish needles separated on cooling. The needles were subsequently crystallised from a large volume of hot water. After five crystallisations the melting point rose from 211° to 214-217° and finally to 215-217° with decomposition.

Poorer yield of the acid was obtained if more than one gram of the ether was used.

The acid obtained forms colourless needles which are soluble in alcohol, slightly soluble in benzene and insoluble in petrol ether. It shows a reddish brown colour with ferric chloride in alcoholic solution. It is optically inactive. It is ketonic towards ordinary ketonic reagents.

Found: C. 56.87%, H. 4.80%, OCH_3. 14.3%

$C_9H_7O_4(OCH_3)$ requires:

C. 57.14%, H. 4.76%, OCH_3. 14.76%

... ...

The equivalent weight of the foregoing methoxy acid.

The accurately weighed acid (0.1 g.) was dissolved in absolute alcohol (15 c.c.) (which was left over caustic potash for three days and then distilled). The solution was titrated with aqueous sodium hydroxide (0.009668 N) (soda lime tube), the latter having been standardised with a solution of potassium hydrogen phthalate. Phenolphthalein (5 drops) was used as indicator. The volume required of sodium hydroxide was 51.10 c.c. A blank experiment required 0.40 c.c. Therefore the actual volume of sodium hydroxide required by the acid was 47.70 c.c. Hence the equivalent weight of the acid was

$$\frac{0.1 \times 40 \times 1000}{47.70 \times 0.009668 \times 40}$$

$$= 216.9$$

$C_9H_7O_4(OCH_3)$ requires 210

On the basis of the formula $C_9H_7O_4(OCH_3)$, the methoxy acid is monobasic.

... ...

Methylation of the foregoing methoxy acid.

The foregoing methoxy acid (0.5 g.) was suspended in absolute ether (20 c.c.). Sufficient diazomethane was added with shaking. After allowing the mixture to stand overnight, the ether and the excess of diazomethane were removed, and the oily residue which still showed a brownish red colour reaction with alcoholic ferric chloride but which was insoluble in sodium bicarbonate, could not be purified. It was refluxed with a mixture of acetone (20 c.c.), anhydrous potassium carbonate (1 g.) and methyl iodide (0.5 g.) for 8 hours. After this period the solution no longer showed any ferric reaction with alcoholic ferric chloride. Most of the acetone was removed and the residue was poured into hot water (50 c.c.). It was extracted with ether, and the ethereal extract was washed several times with saturated sodium bicarbonate solution. The combined washings were made acid with dilute hydrochloric acid, extracted with ether, and the ether extract dried over sodium sulphate. After removal of ether, colourless needles (0.4 g.) were obtained. By the above procedure, the ester was completely hydrolysed to free acid. The acid was crystallised from hot absolute alcohol in colourless needles, m.p. 233-234°C.

It is sparingly soluble in cold alcohol and

insoluble in petrol ether.

Found: C. 58.85%, H. 5.45%, OCH_3. 26.6%

$C_9H_6O_3(OCH_3)_2$ requires:

C. 58.92%, H. 5.36%, OCH_3. 27.69%

The melting point of the acid admixed with 2:4-dimethoxyresacetophenone-5-carboxylic acid (m.p. 231-233°, Lindermann-Lindenbaum, Ber., 41, 1610) was 231-233°C. They are identical in every way.

... ...

Decarboxylation of the foregoing monomethoxy acid.

The acid (0.5 g.), anhydrous quinoline (1 g.) and copper bronze (0.1 g.) in a tube were heated in an oil bath at 200-220°C. A vigorous evolution of carbon dioxide took place. When the acid was completely decarboxylated, as shown by cessation of gas evolution (after 20 minutes), the tube was raised out of the bath and allowed to cool. It was filtered and the filtrate was acidified with hydrochloric acid and extracted many times with ether. The combined ether extracts were dried over sodium sulphate. After removal of ether, a brownish viscous oil was obtained which solidified on standing. The solid was stirred with a little petrol ether and crystallised from water. Yield 0.2 g. It had a melting point of 135-137°C., and formed colourless needles. The phenol does not show any colour

reaction with ferric chloride in alcoholic solution.

Its 2:4-dinitrophenylhydrazone crystallised from alcohol in dark brown prisms, m.p. 216-217°C.

Found: N. 16.08%

$C_{15}H_{14}N_4O_6$ requires: N. 16.19%

The phenol shows no melting-point depression when mixed with the authentic specimen 2-methoxyresacetophenone (Hoesch, Ber., 48, 1126) or 2-methoxyresacetophenone which was prepared by a new method (vide infra). The three specimens are identical in every way.

... ...

Demethylation of the acid $C_9H_7O_4(OCH_3)$ which was obtained by oxidation of the methyl ether of euparin with potassium permanganate.

The acid (0.3 g.) was heated for two minutes with hydriodic acid (3 g.) (sp.gr. 1.9). The demethylated acid separated from the solution during heating. After cooling, it was filtered, washed with a little hydriodic acid and finally with water. Reddish brown crystals (0.2 g.), m.p. 248-250°C., were obtained. The acid was dissolved in hot aqueous sodium bicarbonate with charcoaling and acidified with hydrochloric acid. The solid was collected and crystallised from alcohol

in prisms, m.p. 256°C. Mixed with 2:4-dihydroxy-resacetophenone-5-carboxylic acid (Lindermann-Lindenbaum, loc.cit.) it had a melting point of 255-256°C.

... ...

Ozonolysis of methoxyeuparin.

Methoxyeuparin (1 g.) and absolute chloroform (50 c.c.) were ozonised for 1½ hours. After this period, chloroform was removed under reduced pressure at 40°C. To the brownish residue in the flask, cold water (50 c.c.) was added and the mixture was allowed to stand overnight. The next morning, it was heated on the steam bath for 20 minutes. It was allowed to cool, when colourless needles separated. The crystals were collected and recrystallised from hot water with charcoaling. It had a melting point of 117-118°C. Yield 0.35 g.

It is soluble in most organic solvents, and gave a brown colour with ferric chloride in alcoholic solution.

Found: C. 61.71%, H. 5.49%, OCH_3. 15.65%

$C_{10}H_{10}O_4$ requires:

C. 61.85%, H. 5.15%, OCH_3. 15.98%

The main filtrate was distilled on the wire gauze, keeping the volume of the content constant. The

distillate was collected in an excess of solution of 2:4-dinitrophenylhydrazine hydrochloride in excess of 2N dilute hydrochloric acid. The brown precipitate was crystallised from dilute alcohol in orange yellow needles, m.p. 161-162°. Mixed with an authentic specimen of formaldehyde 2:4-dinitrophenylhydrazone (m.p. 163-164°), the substance melted at 161-162°C.

Found: N. 26.88%

$C_7H_6O_4N_4$ requires: N. 26.67%

... ...

Action of maleic anhydride on methoxyeuparin.

A mixture of methoxyeuparin (1 g.), maleic anhydride (1 g.) and absolute benzene (50 c.c.) was refluxed on the water bath for 12 hours. Colourless crystals gradually separated from the hot solution. After cooling, it was filtered and the solid repeatedly crystallised from a large volume of absolute alcohol. Yield 0.8 g. It had a melting point of 212-213° with decomposition, and formed colourless plates insoluble in cold alcohol or petrol ether.

Found: C. 65.64%, H. 4.95%, OCH_3. 9.08%

$C_{18}H_{16}O_6$ requires:

C. 65.85%, H. 4.87%, OCH_3. 9.45%

Using absolute toluene as condensing medium, an identical product was obtained.

Using nitrobenzene as condensing medium at 210° for 1½ hours, brownish prisms, m.p. 296-298°C., were obtained and were not further investigated.

... ...

Action of maleic anhydride on euparin.

A mixture of euparin (0.5 g.), maleic anhydride (0.25 g.) and absolute benzene (25 c.c.) was refluxed on the water bath for 14 hours. The solid which separated on cooling was collected and crystallised from absolute alcohol in colourless needles (0.5 g.). It had a melting point of 244-245°C., and was insoluble in petrol ether.

Found: C. 64.67%, H. 4.56%

$C_{17}H_{14}O_6$ requires: C. 64.97%, H. 4.46%

... ...

Methoxytetrahydro-euparin oxime.

A mixture of methoxytetrahydro-euparin (1 g.), absolute alcohol (25 c.c.) and an aqueous solution containing hydroxylamine hydrochloride (0.3 g.) and sodium acetate (1 g.) in the least possible amount of water, was refluxed on the water bath for 3 hours. After this period, sufficient water was added to dissolve the inorganic salt. The colourless solid was collected, dried, and crystallised from petrol ether (60-80°) in

colourless prisms (0.8 g.). It had a melting point of 139°C.

Found: C. 67.46%, H. 8.03%, N. 5.78%, OCH_3. 12.50%

$C_{14}H_{19}O_3N$ requires:

C. 67.47%, H. 7.63%, N. 5.61%, OCH_3. 12.45%

... ...

Beckmann transformation.

The foregoing oxime (1.5 g.) was dissolved in absolute ether (100 c.c.). The mixture was cooled in a mixture of ice and salt to -5°C. Freshly distilled thionyl chloride (1 mole = 9 c.c.) in absolute ether (25 c.c.) at the same temperature was gradually added during ten minutes with shaking. The colourless precipitate gradually turned red, and after standing for 15 minutes (not longer if charring is to be avoided), the content was poured into a mixture of crushed ice and water (100 c.c.) with shaking. After allowing the ether to evaporate at room temperature by bubbling air through the solution, pale pink crystals of the amide separated. The solid was collected and crystallised from petrol ether with charcoaling as colourless leaflets. Yield 1 g. It had a melting point of 133-134°C. and was soluble in alcohol and acetic acid.

Found:: C. 67.42%, H. 7.89%, N. 5.42%, OCH_3. 12.18%

$C_{14}H_{19}O_3N$ requires:

C. 67.47%, H. 7.63%, N. 5.61%, OCH_3. 12.45%

No other crystalline product was obtained from the aqueous filtrate.

... ...

Hydrolysis of the amide.

The foregoing amide (0.6 g.) and 20% alcoholic caustic potash (10 c.c.) were refluxed on the water bath for four hours. The reaction mixture was poured into cold water (50 c.c.). Colourless needles separated, m.p. 66-68°C. Yield 0.5 g.

The amine was purified by dissolving in dilute hydrochloric acid, and filtered from insoluble material. The filtrate was made just alkaline with dilute sodium hydroxide and the precipitated amine was filtered, and washed thoroughly with water. It was finally crystallised from dilute alcohol in colourless needles. It had a melting point of 68-69°C.

The amine can be diazotised, and the diazo-compound readily coupled with β-naphthol to give a bright scarlet dye. It does not give a carbylamine reaction.

... ...

Acetylation of the foregoing amine.

The foregoing amine (0.4 g.) was acetylated by adding gradually freshly distilled acetic anhydride (0.5 g.) with shaking. After allowing the mixture to

stand for five minutes, the homogeneous solution was poured into hot water (25 c.c.) containing a few drops of dilute hydrochloric acid. After the acetic anhydride was completely hydrolysed, the solid was filtered, Yield 0.4 g. It had a melting point of 131-133°C. After three crystallisations from petrol ether (60-80°), the melting point rose to 133-134°C. and remained constant. It forms colourless leaflets, identical in every way with the starting amide. There was no depression in their mixed melting point.

Found: C. 67.39%, H. 7.73%, N. 5.65%, OCH_3. 12.58%

$C_{14}H_{19}O_3N$ requires:

C. 67.47%, H. 7.63%, N. 5.61%, OCH_3. 12.45%

... ...

Condensation of tetrahydroeuparin with ethyl acetate.

Tetrahydro-euparin (1 g.) was dissolved in absolute ethyl acetate (2 c.c.). Finely-cut sodium (0.5 g.) was gradually added with shaking and cooling. When the initial reaction was over, the mixture was refluxed on the water bath for four hours. A little more sodium (0.1 g.) and ethyl acetate (1 c.c.) was added and the mixture was refluxed for a total time of 6 hours. After cooling, a little alcohol (0.5 c.c.) was added with shaking to dissolve free sodium, if any.

A few pieces of crushed ice were added and the mixture acidified with acetic acid. It was allowed to stand overnight. The next morning, a yellowish solid (0.8 g.) was collected. It had a melting point of 98-104°C. Washing with a little ethyl acetate yielded colourless prisms, m.p. 104-108°C. Crystallisation from petrol ether (80-100°) yielded a diketone in colourless prisms, which melted at 109-110°C. It gave a dark brown colour with ferric chloride in alcoholic solution.

It is soluble in benzene, petrol ether and alcohol.

Found: C. 68.92%, H. 6.79%

$C_{15}H_{18}O_4$ requires: C. 68.70%, H. 6.87%

... ...

Cyclisation of the foregoing diketone.

The foregoing diketone (0.2 g.) was dissolved in boiling glacial acetic acid (5 c.c.). A few drops of concentrated hydrochloric acid were added and the mixture was heated to boiling on the wire gauze for 3 minutes. After cooling, it was poured into cold water (30 c.c.) and allowed to stand. The colourless solid (0.18 g.) was collected, and had a melting point of 114-118°C. Crystallisations from petrol ether (80-100°) yielded colourless needles, m.p. 119-120°C.

It is soluble in benzene and alcohol, and gives

a negative ferric reaction with ferric chloride in alcoholic solution. A trace of it in concentrated sulphuric acid gives a faint blue fluorescence.

Found: C. 73.64%, H. 6.42%

$C_{15}H_{16}O_3$ requires: C. 73.77%, H. 6.56%

... ...

Alkali fusion of tetrahydro-euparin.

A mixture of tetrahydro-euparin (1 g.) in absolute alcohol (10 c.c.) and 50% aqueous caustic potash (50 c.c.) was heated in a flask in an atmosphere of nitrogen; the temperature of the oil bath was gradually raised and maintained at 100°C. When all alcohol was completely removed, the temperature was raised to 130°C. and maintained until most of the water was removed. The temperature was gradually raised to 200-210°C. and finally to 290°C. after four hours. After cooling, ice water (100 c.c.) was added, and the solution acidified with 50% sulphuric acid (Congo red paper), and then neutralized with aqueous sodium bicarbonate. It was extracted with ether, the ether extract dried over sodium sulphate, and after the removal of ether, an oil was obtained. Distillation in high vacuum (0.2 mm.) furnished a brownish viscous oil (0.35 g.) at 110-120°C. The oil gave a brownish red colour with ferric chloride in alcoholic solution.

Its p-nitrobenzoate crystallised from alcohol in colourless prisms, m.p. 182-183°C. The yield of p-nitrobenzoate was not sufficient for further investigation.

The sodium bicarbonate extract was made just acid with dilute sulphuric acid (Congo red paper), and extracted with ether. After drying the ether extract over sodium sulphate and subsequent evaporation of ether, a brown oil (0.32 g.) with a strong odour was obtained, which was soluble in sodium bicarbonate solution. It was treated with a slight excess of ammonia and calcium chloride. The insoluble material was removed by filtration. The filtrate was made slightly acid with sulphuric acid and extracted with ether. After drying the ether extract over sodium sulphate and its subsequent removal, the oily residue was heated with freshly distilled phenylhydrazine (2 c.c.) in an oil bath at 120-130°C. for two hours. The reaction product was distilled at 2 mm., collecting the distillate at 110-130°C. Yield 0.18 g. The oily distillate crystallised from a mixture of ether and petrol ether in colourless prisms, m.p. 105-106°C., identical in every respect with the phenylhydrazide of isovaleric acid prepared by the same method.

When the fusion was carried out at 200-210°C.,

unchanged tetrahydro-euparin was recovered.

It is proposed, at the time of writing this Thesis, to repeat the fusion when more tetrahydro-euparin is available at a later date.

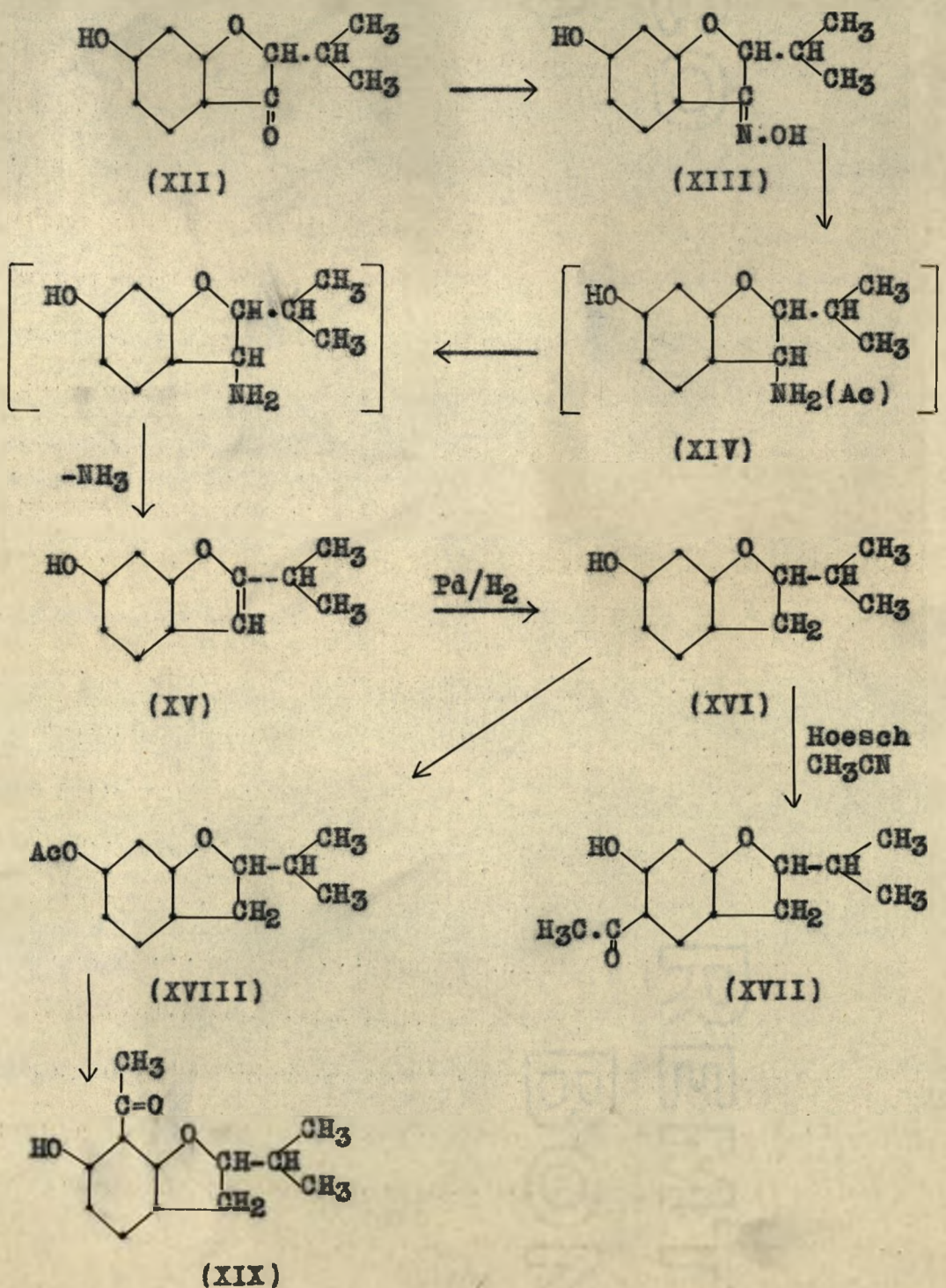
... ...

Oxidation of euparin by hydrogen peroxide.

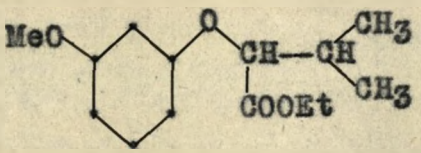
Euparin (1 g.) was dissolved in acetic acid (75 c.c.) and oxidised with hydrogen peroxide (8%) (45 c.c.) at room temperature for 15 hours. The solvent was removed under reduced pressure at 80°C.; the brown residue was taken up in water (50 c.c.) and made alkaline with ammonia. Calcium chloride solution was added, the insoluble matter was removed by filtration and the filtrate was acidified with dilute hydrochloric acid and extracted with ether. The oily extract (0.15 g.) could not be induced to crystallise or to sublime. It was methylated with an excess of diazomethane in absolute ether and distilled at 1 mm. pressure. The distillate at 120-130°C. was a colourless mobile liquid which was not further investigated.

*** *** ***

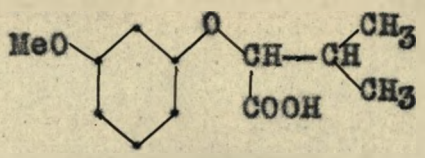
Synthesis of Tetrahydro-euparin (6-hydroxy-5-acetyl-2-isopropyldihydrobenzofurane) (XVII) and 6-hydroxy-7-acetyl-2-isopropyldihydrobenzofurane (XIX).



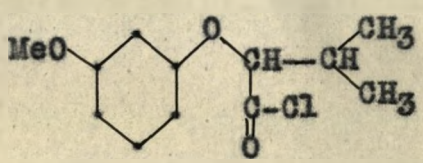
The synthesis of 6-hydroxy-5-acetyl-2-isopropyl-dihydrobenzofurane for purposes of comparison with tetrahydro-euparin involved, in the first instance, the application of a method for the synthesis of 6-hydroxy-2-isopropylcoumaranone (V). The standard method described by Stephen and co-workers (J.C.S., 1931, 896) in its simplest form is represented thus: Interaction of sodium salt of resorcinolmonomethyl ether and ethyl α-bromoisovalerate gives rise to the ester (I). After hydrolysis of this ester, the acid (II) is converted into the chloride (III), which on cyclisation with aluminium chloride and benzene gives 6-methoxy-2-isopropylcoumaranone (IV).



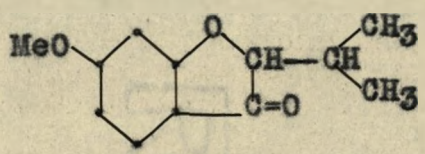
(I)



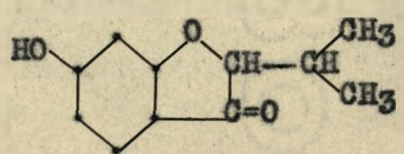
(II)



(III)

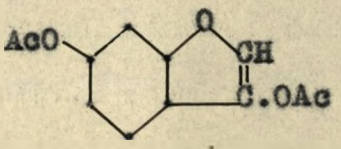


(IV)

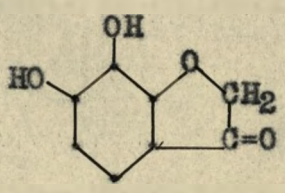


(V)

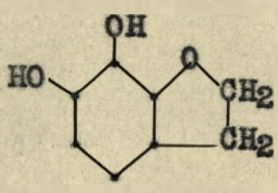
Robertson and Bridge (J.C.S., 1937, 1530-1535) showed that 6-methoxy-2-isopropylcoumaranone (IV) could be accessible by the application of a less tedious method of Arima and Okamoto (J.Chem.Soc.Japan, 1926, 50, 344). This method involves the cyclisation of resorcinol and α-bromoisovaleryl chloride with aluminium chloride in nitrobenzene. According to them, attempts to reduce the coumaranone (V) with the aid of amalgamated zinc by the method of Clemmensen gave rise to an amorphous product, whilst catalytic reduction of the diacetyl derivative (3:6-diacetoxy-2-isopropylbenzofurane) according to the procedure of Roll and Adams (J.Amer.Chem.Soc., 1931, 53, 3469) yielded a product which, after hydrolysis, was resolved into the coumaranone (V) and a pleasant smelling oil, insoluble in aqueous sodium hydroxide. Similar behaviour was observed by Sonn (Ber., 58, 98) who attempted to reduce 3:6-diacetoxy-β-benzofurane (VI) with platinum black in alcohol.



(VI)



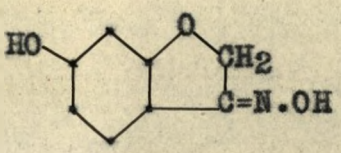
(VII)



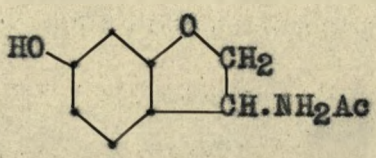
(VIII)

According to Späth (Ber., 59, 769) reduction of 6:7-dihydroxycoumaranone (VII) with the aid of catalytic palladium-charcoal in acetic acid at 40-45°C., gave rise to 6:7-dihydroxy-dihydrobenzofurane (VIII), and much of an amorphous product which was not investigated. The yield of 6:7-dihydroxy-dihydrobenzofurane was not mentioned.

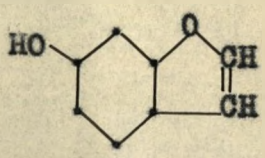
A general method of Sonn (Ber., 58, 96) for converting a coumaranone into a benzofurane now appeared to be available, and can be represented thus: Reduction of 6-hydroxycoumaranone oxime (IX) with sodium amalgam in a mixture of absolute alcohol and acetic acid furnished 6-hydroxy-dihydrobenzofurane-2-aminoacetate (X), which loses one molecule of ammonia on heating, giving rise to 6-hydroxybenzofurane (XI). The yield was not mentioned.



(IX)



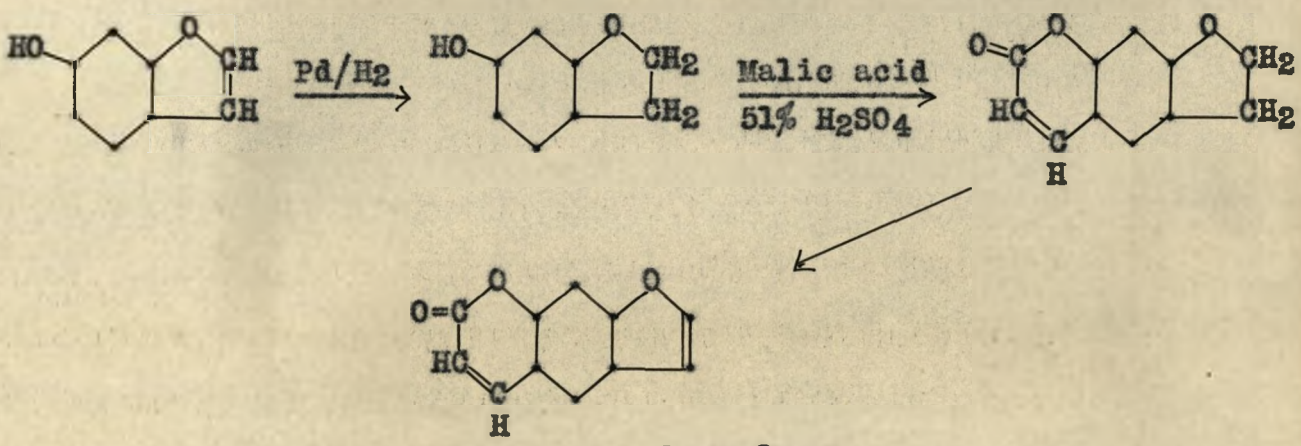
(X)



(XI)

The conversion of a coumaranone into a benzofurane by the application of Sonn's method (loc.cit.) is of great importance in the elucidation of many organic compounds by synthetic methods. As an example, Späth

(Ber., 69, 1087), in the synthesis of furano-coumarin for comparison with the natural psoralene, was able, by the application of the Sonn reduction, to obtain 6-hydroxybenzofurane as a starting material, which was finally converted to furano-coumarin, identical with psoralene according to the following scheme:-



Psoralene.

On the foregoing considerations, it was thought that the application of the Sonn reduction to 6-hydroxy-2-isopropylcoumaranone (V) would, in an analogous manner, give rise to 6-hydroxy-2-isopropylbenzofurane (XV) (*vide infra*), which furnishes 6-hydroxy-2-isopropyldihydrobenzofurane (XVI) on reduction with the aid of catalytic palladium-charcoal (cf. Späth, *loc.cit.*).

6-Hydroxy-2-isopropyl-3-coumarone (XII) (cf. Arima and Okamoto, J.Chem.Soc.Japan, 1926, 50, 344, who

used α-bromoisovalerylbromide) was prepared by interaction of resorcinol, α-bromoisovalerylchloride and aluminium chloride in nitrobenzene.

Oximation of the foregoing compound with hydroxylamine hydrochloride and sodium acetate in boiling alcohol gave rise to 6-hydroxy-2-isopropyl-3-coumaranone oxime (XIII) which crystallised from dilute alcohol in colourless needles, m.p. 165-166°C.

Reduction of the foregoing oxime with 2½% sodium amalgam in a mixture of absolute alcohol and acetic acid (cf. Sonn, Ber., 58, 96; Späth, ibid., 69, 1087) at 0°C. and evaporation of the solvent under reduced pressure gave rise to a brown residue. The latter was neutralised with sodium bicarbonate and extracted with ether. Removal of ether furnished a brown resinous semi-solid which could not be induced to crystallise. Extraction of the residue with hot petrol ether left a brown amorphous solid which yielded a small amount of 6-hydroxy-2-isopropylcoumarone (XV) on sublimation. When the petrol ether extract was diluted with ether and the solvent mixture washed with 4% aqueous sodium hydroxide, acidification of the aqueous residue with acetic acid furnished a brownish solid which could not be induced to crystallise. Sublimation of this solid at 110-120°C./2 mm. yielded colourless prisms of 6-

hydroxy-2-isopropylcoumarone which crystallised from petrol ether, m.p. 75-76°C. The yield was about 10%, and poorer yield was obtained if the reduction was carried out at 40-50°C. A trace of it in alcohol is devoid of a ferric reaction, while a concentrated solution of the substance shows a greenish colour with ferric chloride. A trace of it in concentrated sulphuric acid gave a yellowish colour which changed into reddish on warming.

Reduction of the foregoing compound with hydrogen in the presence of catalytic palladium gave rise to 6-hydroxy-2-isopropyldihydrobenzofurane (XVI) which crystallised from petrol ether in colourless prisms, m.p. 79-80°C. The absorption of hydrogen was compatible with the presence of one double bond in the 6-hydroxy-2-isopropylcoumarone (XV).

Acetylation of the foregoing compound with acetic anhydride and pyridine gave rise to 6-acetoxy-2-isopropyldihydrobenzofurane (XVIII), which formed colourless elongated prisms, m.p. 47-48°C. It was insoluble in dilute aqueous alkali and was devoid of a ferric reaction. This compound underwent a Fries reaction (cf. Rosamund and Schmurr, Ann., 460, 56), yielding 6-hydroxy-7-acetyl-2-isopropyldihydrobenzofurane (XIX) which crystallised from petrol ether in fine colourless

needles, m.p. 115-116°C. It gave a reddish brown colour with alcoholic ferric chloride. Its 2:4-dinitrophenylhydrazone crystallised from alcohol in dark orange needles, m.p. 295-297°C.

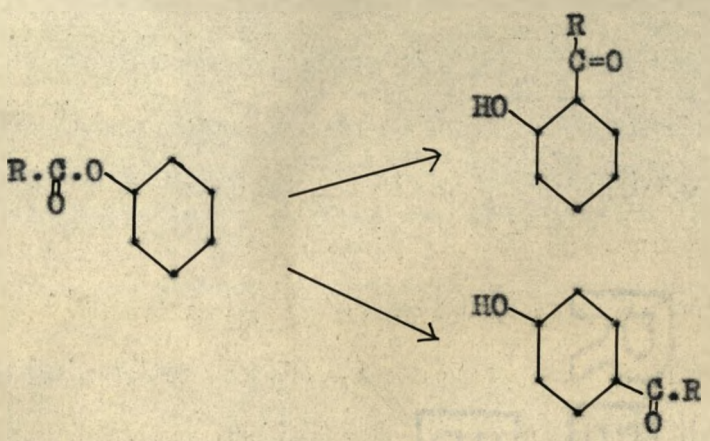
The Hoesch reaction on the 6-hydroxy-2-isopropyldihydrobenzofurane (XVI) in the presence of acetonitrile was studied. It gave rise exclusively to 6-hydroxy-5-acetyl-2-isopropyldihydrobenzofurane (XVII) which crystallised from petrol ether in colourless rhombic prisms, m.p. 70-71°C. It gave a brownish red colour with alcoholic ferric chloride and was slightly soluble in dilute aqueous sodium hydroxide. It is identical in every respect with tetrahydro-euparin (m.p. 70-71°C.). Their mixed melting point was undepressed.

It gave a 2:4-dinitrophenylhydrazone which crystallised from benzene in scarlet prisms, m.p. 240-241°C. This is identical in every respect with tetrahydro-euparin 2:4-dinitrophenylhydrazone, m.p. 240-241°C. Their mixed melting point was undepressed.

It has been stated that 6-acetoxy-2-isopropyldihydrobenzofurane (XVIII) undergoes a Fries reaction. The ketone so produced shows a ferric reaction.

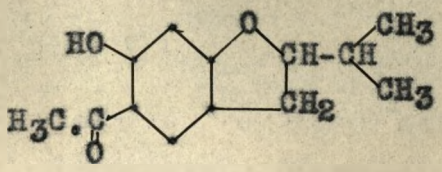
It has been shown by Rosamund and Schnurr (Ann., 1927, 460, 56) that when aluminium chloride is added to a solution of a phenolic ester in anhydrous nitrobenzene,

the proportions of the corresponding o- and p-hydroxy ketones formed are entirely dependent on the temperature at which the reaction was performed. Under normal conditions (20-30°C.) almost exclusive formation of p-hydroxyketone resulted, whilst at higher temperature (100°C.) the reverse effect obtained with almost exclusive formation of the o-hydroxyketone.

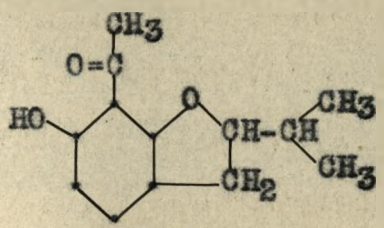


In the application of this reaction to 6-acetoxy-2-isopropyldihydrobenzofurane (XVIII) for the synthesis of the ortho-hydroxyketone, it was considered that, since the p-position in 6-acetoxy-2-isopropyldihydrobenzofurane (XVIII) already forms a part of the dihydrofurane ring system, under the normal temperature conditions favourable to p-hydroxy substitution, o-hydroxy-substitution would result. In 6-acetoxy-2-isopropyldihydrobenzofurane (XVIII), there are only two ortho-positions, namely, positions 5- and 7-, into which the acetyl group

can wander, forming 6-hydroxy-5-acetyl-2-isopropyldihydrobenzofurane (XX) or 6-hydroxy-7-acetyl-2-isopropyldihydrobenzofurane (XXI) respectively.



(XX)

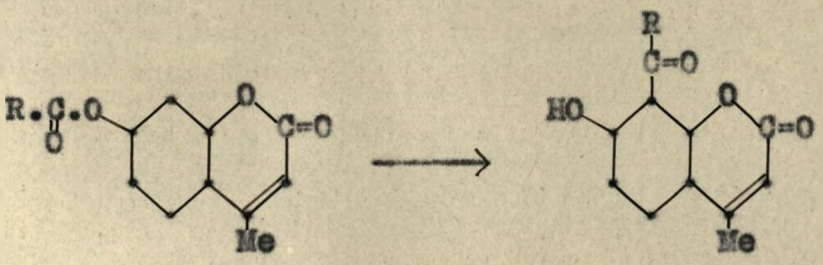


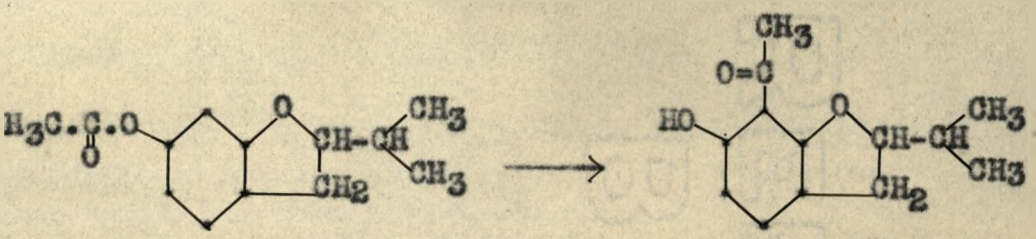
(XXI)

Since only one ketone is isolated from the Fries reaction of 6-acetoxy-2-isopropyldihydrobenzofurane (XVIII), a choice of one of these two formulae of the ketone has to be made.

The fact that the ketone in question is not identical with tetrahydro-euparin, whose expected formula would be 6-hydroxy-5-acetyl-2-isopropyldihydrobenzofurane (XX), leads at once to the choice of the alternative formula 6-hydroxy-7-acetyl-2-isopropyldihydrobenzofurane (XXI). Further evidence in support of the formula (XXI) for the ketone in question is to be found in the analogy of the application of the Fries reaction to the acetate, benzoate or isovalerate of 7-hydroxy-4-methylcoumarin which gives the isomeric 7-hydroxy-8-acetyl-4-methylcoumarin, 7-hydroxy-8-benzoyl-4-methylcoumarin and 7-hydroxy-8-isovaleryl-4-methyl-

coumarin respectively (cf. Limaye, Ber., 1934, 67, 12; Robertson and Subramaniam, J.C.S., 1937, 278).



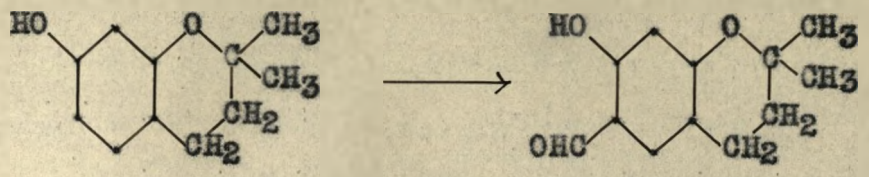


(XVIII) (XIX)

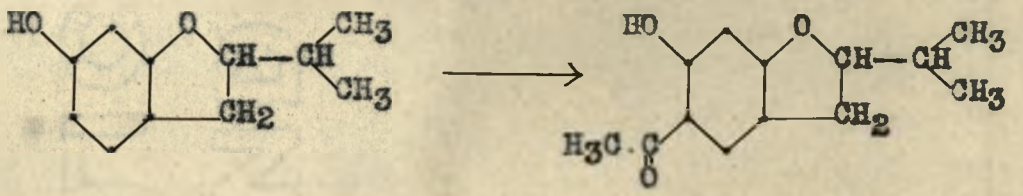
It has also been stated in the experimental section that the application of the Hoesch reaction to 6-hydroxy-2-isopropyldihydrobenzofurane (XVI), using acetonitrile, gives rise to a ketone which is identical in every way with the natural tetrahydro-euparin. Considerations of the practical evidence lead to the prediction of the structure 6-hydroxy-5-acetyl-2-isopropyldihydrobenzofurane (XVII) for tetrahydro-euparin.

Robertson, Bell and Bridge (J.C.S., 1937, 1542) showed that the application of the Gattermann reaction to 7-hydroxy-2:2-dimethylchroman (XXII) gave rise to 7-hydroxy-6-formyl-2:2-dimethylchroman (XXIII), the 6-

position being active to the reaction.



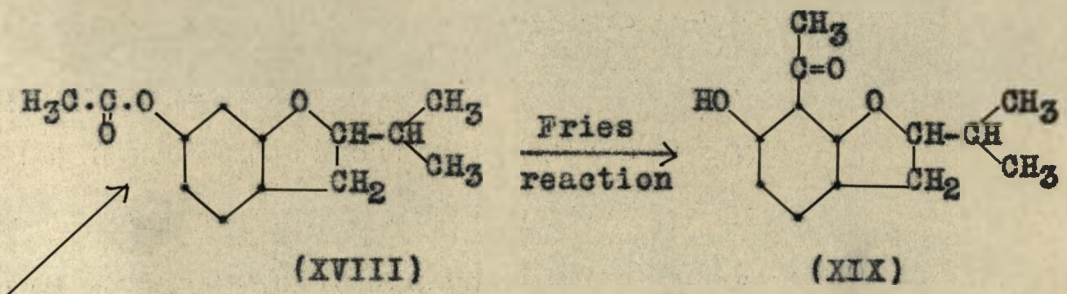
(XXII) (XXIII)



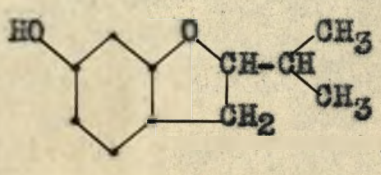
(XVI) (XVII)

Since Gattermann and Hoesch reactions are fundamentally similar in character concerning the active positions of a given phenol, and since 6-hydroxy-2-isopropyldihydrobenzofurane (XVI) is analogous to 7-hydroxy-2:2-dimethylchroman (XXII), both containing an oxygen ring system, it is reasonable to predict that, in an analogous manner, the application of the Hoesch reaction to 6-hydroxy-2-isopropyldihydrobenzofurane (XVI) leads to the acetyl substitution in the 5-position, forming 6-hydroxy-5-acetyl-2-isopropyldihydrobenzofurane (XVII). That only the latter is identical in every way with tetrahydro-euparin in agreement with their predicted

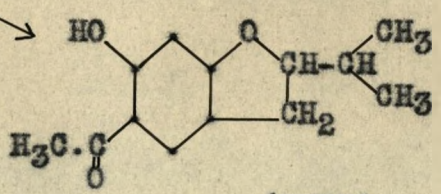
constitution, is in itself a clear proof that one of the isomeric ketones is 6-hydroxy-7-acetyl-2-isopropyldihydrobenzofurane (XIX), and the other is 6-hydroxy-5-acetyl-2-isopropyldihydrobenzofurane (XVII).



(XVIII) (XIX)

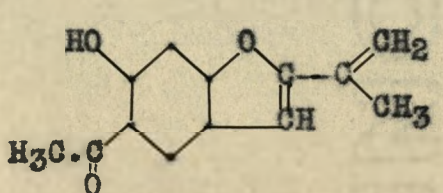


(XVI) Hoesch reaction CH_3CN



(XVII)

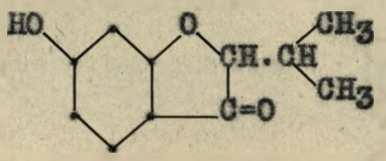
In conclusion, the constitution of tetrahydroeuparin is 6-hydroxy-5-acetyl-2-isopropyldihydrobenzofurane (XVII). Consequently it is extremely probable that euparin has the configuration (XXIV), being 6-hydroxy-5-acetyl-2-isopropylenebenzofurane.



(XXIV)

EXPERIMENTAL

6-Hydroxy-2-isopropyl-3-coumaranone.



(Cf. Arima and Okamoto, J.Chem.Soc.Japan, 1929, 50, 344, who used α-bromoisovalerylbromide)

α-Bromoisovalerylchloride (30 g.) was slowly added to a cooled solution of resorcinol (20 g.) and aluminium chloride (26 g.) in nitrobenzene (335 c.c.), and the mixture was kept for four days; more aluminium chloride (10 g.) was added after two days. The reaction mixture was very slowly heated to 60°C., maintained at this temperature for one hour, cooled and treated with excess of crushed ice and hydrochloric acid. The mixture was extracted many times with ether, the combined extracts evaporated and the nitrobenzene removed by steam. The residual aqueous liquor deposited coumaranone as colourless prisms on keeping. The dark oil was dissolved in a large volume of ether, and the ether extract was washed several times with 4% aqueous sodium hydroxide. The combined alkaline extract was made acid with acetic acid and allowed to stand. Dark

prisms of coumaranone (8.4 g.), which after one crystallisation from benzene was colourless, were obtained. Recrystallisations from dilute alcohol with charcoaling yielded colourless prisms of 6-hydroxy-2-isopropyl-3-coumaranone (4.1 g.). It had a melting point of 180°C. It does not give any ferric reaction with ferric chloride in alcoholic solution. Five lots of this experiment were carried out.

... ...

6-Hydroxy-2-isopropyl-3-coumaranone oxime.

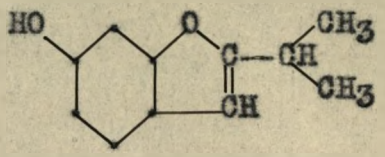
The foregoing 6-hydroxy-2-isopropyl-3-coumaranone (20 g.) was dissolved in absolute alcohol (200 c.c.). Hydroxylamine hydrochloride (9 g.) and sodium acetate (10 g.) dissolved in the least possible amount of water were added. The mixture was refluxed on the water bath for four hours. Most of the alcohol was removed under reduced pressure. Water (300 c.c.) was added to the residue. The oxime was filtered and crystallised from dilute alcohol in colourless needles, m.p. 165-166°C. Yield 19.5 g. It is insoluble in petrol ether.

Found: N. 6.89%

$C_{11}H_{13}NO_3$ requires: N. 6.76%

... ...

6-Hydroxy-2-isopropylcoumarone.



The foregoing oxime (13 g.) dissolved in a mixture of absolute alcohol (150 c.c.) and glacial acetic acid (60 c.c.) was cooled to 0°C. 2½% sodium amalgam (650 g.) was gradually added with vigorous stirring during the course of 3 hours. After another hour, the solution was made definitely acid by further addition of glacial acetic acid. The solution was filtered from mercury and most of the alcohol was removed from the filtrate. The residue was neutralised with solid sodium bicarbonate and extracted with ether. The ether extract was dried over calcium chloride and the ether removed. A brown resinous residue which could not be crystallised was obtained. It was extracted many times with petrol ether (80-100°) at its boiling point. The volume of the combined extracts (500 c.c.) was reduced to about 100 c.c. After cooling a brown semi-solid separated. It was collected, dried and sublimed in high vacuum (2 mm.) at 110-120°C. as colourless prisms of 6-hydroxy-2-isopropylcoumarone (0.2 g.), m.p. 73-75°C. The mother liquor was diluted with ether,

and the ether-petrol ether extract was shaken several times with 4% aqueous sodium hydroxide. The alkali extract was made acid with glacial acetic acid and allowed to stand overnight. The next morning, the brownish solid was collected, thoroughly washed with water and dried. An attempt to crystallise it at this stage would involve a great loss of the material, because the substance tends to precipitate in an oily state. It was therefore sublimed at 110-120°C./2 mm. in colourless prisms of 6-hydroxy-2-isopropylcoumarone (1.6 g.) which readily crystallised from petrol ether (60-80°). It had a melting point of 75-76°C. With concentrated sulphuric acid, the solution was slightly yellow and turned reddish on warming. A trace of it gave a negative ferric reaction in alcoholic ferric chloride. Its fairly concentrated solution in alcohol showed a greenish colour with ferric chloride.

Found: C. 75.28%, H. 7.16%

$C_{11}H_{12}O_2$ requires: C. 75.00%, H. 6.81%

A poorer yield was obtained if the reduction was carried out at 40-50°C.

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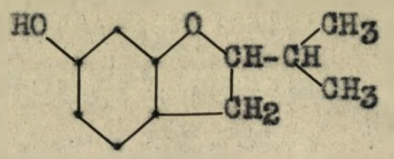
6-Hydroxy-2-isopropyldihydrobenzofurane.



6-Hydroxy-2-isopropylcoumarone (1 g.), ethyl acetate (100 c.c.) and catalytic palladium-charcoal (2 g. charcoal and 0.2 g. palladium chloride) were shaken in hydrogen at ordinary temperature (16°C.). Hydrogen (50 c.c.) was absorbed after a few minutes and a total volume of 141 c.c. was absorbed after 1½ hours. (One double bond for $C_{11}H_{12}O_2$ requires 136 c.c.) After filtering off the charcoal, the solvent was removed under reduced pressure. The colourless residue which solidified after scratching readily crystallised from petrol ether (60-80°) in colourless prisms, m.p. 79-80°C. Yield after crystallisation 0.6 g. Mixed with the parent 6-hydroxy-2-isopropylcoumarone, it had a melting point of 56-61°C.

It is soluble in ethyl alcohol, methyl alcohol and benzene.

Found: C. 73.95%, H. 7.69%

$C_{11}H_{14}O_2$ requires: C. 74.14%, H. 7.86%

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6-Hydroxy-7-acetyl-2-isopropyldihydrobenzofurane.

6-Acetoxy-2-isopropyldihydrobenzofurane.

6-Hydroxy-2-isopropyldihydrobenzofurane (0.9 g.), absolute pyridine (5 c.c.) and acetic anhydride (8 g.) were heated on the water bath for one hour. The mixture was poured into cold water (75 c.c.) and allowed to stand overnight; colourless elongated prisms, m.p. 47-48°C., were obtained.

Fries reaction on the foregoing acetate.

The foregoing acetate (dried over phosphorus pentoxide) (0.9 g.), nitrobenzene (10 c.c.) and aluminium chloride (1.4 g.) were allowed to stand for 24 hours at ordinary temperature. The next morning, the mixture was poured into crushed ice containing excess of hydrochloric acid, and extracted many times with ether. The ether-nitrobenzene mixture was removed by steam; when the volume was reduced to approximately 100 c.c., it was extracted with 5% aqueous sodium hydroxide. On acidifying the alkali extract with acetic acid, fine colourless needles of the 6-hydroxy-7-acetyl-2-isopropyldihydrobenzofurane (0.3 g.) were obtained. A further amount (0.1 g.) was also obtained in the volatile distillate, after nitrobenzene was removed by steam. It crystallised from petrol ether

in colourless needles, m.p. 115-116°C. It gave a reddish brown colour with alcoholic ferric chloride.

Its 2:4-dinitrophenylhydrazone crystallised from a large volume of alcohol in dark orange needles, m.p. 295-297°C.

Found: N. 14.30%

$C_{19}H_{20}N_4O_6$ requires: N. 14.00%

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6-Hydroxy-5-acetyl-2-isopropyldihydrobenzofurane.

A stream of dry hydrogen chloride was passed into a mixture of 6-hydroxy-2-isopropyldihydrobenzofurane (1 g.) in absolute ether (50 c.c.), zinc chloride (2 g.) and freshly distilled acetonitrile, which was cooled in ice. When it was saturated, the mixture was allowed to stand for three days at ordinary temperature. A brownish oil separated and formed the lower layer in the flask. Absolute ether (200 c.c.) was added with shaking. When the solution had settled, ether was decanted off and the oily residue was heated with water (50 c.c.) on the water bath for twenty minutes. In this way an at first clear solution gradually turned turbid with separation of a colourless oil which solidified on cooling. The solid was collected and crystallised from petrol ether (60-80°)

in rhombic prisms, m.p. 70-71°C. Yield 0.9 g. Mixed with tetrahydro-euparin, m.p. 70-71°C. the melting point was undepressed. It gives a brownish red colour with ferric chloride in alcoholic solution and is slightly soluble in aqueous sodium hydroxide. It is soluble in most organic solvents.

Found: C. 70.99%, H. 7.25%

$C_{13}H_{16}O_3$ requires: C. 70.91%, H. 7.27%

Its 2:4-dinitrophenylhydrazone crystallised from benzene in bright scarlet prisms, m.p. 240-241°C. This is identical in every respect with tetrahydro-euparin 2:4-dinitrophenylhydrazone. There was no depression in their mixed melting point.

Found: N. 14.25%

$C_{19}H_{20}N_4O_6$ requires: N. 14.00%

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A P P E N D I X

A NEW SYNTHESIS OF 2-METHOXY-RESACETOPHENONE

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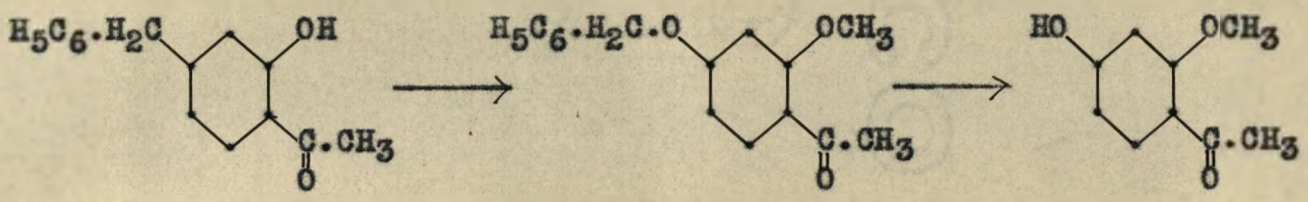

2-Hydroxy-4-benzyloxyacetophenone, m.p. 106°C., was prepared by the method of Gulati, Seth and Venkataraman (J.C.S., 1934, 1765, m.p. 111°C.); (Centr., 1932, 2, 2485, m.p. 105-106°C.); (Robertson and Bridge, J.C.S., 1937, 1535, m.p. 105°C.).

When the foregoing compound was methylated with methyl iodide by the potassium carbonate-acetone method, 2-methoxy-4-benzyloxyacetophenone was obtained, which crystallised from alcohol in colourless prisms, m.p. 69°C., devoid of any ferric reaction. Debenzylation of the foregoing compound with acetic acid and concentrated hydrochloric acid (cf. Sugasawa, J.C.S., 1933, 1621; Mahal, Rai and Venkataraman, ibid., 1934, 1121) furnished 4-hydroxy-2-methoxyacetophenone which crystallised from hot water in colourless needles, m.p. 136-137°C. It is identical in every respect with 2-methoxyresacetophenone (Hoesch, Ber., 48, 1128). The

method had the advantage over that of Hoesch in the fact that it was simpler and a good yield of 2-methoxy-resacetophenone was obtained.

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2-Hydroxy-4-benzyloxyacetophenone was prepared by the method of Gulati, Seth and Venkataraman (J.C.S., 1934, 1765, m.p. 111°C.) cf. (Centr., 1932, 2, 2485, m.p. 105-106°C.; Robertson and Bridge, J.C.S., 1937, 1535, m.p. 105°C.). In the present case it has a melting point of 105-106°C.

2-Methoxy-4-benzyloxyacetophenone.

2-Hydroxy-4-benzyloxy-acetophenone (5 g.), acetone (20 c.c.), anhydrous potassium carbonate (8 g.) and methyl iodide (3 g.) were refluxed on the water bath for 14 hours. After the end of 8 hours a little more methyl iodide (3 g.) and potassium carbonate (5 g.) was added. When the reaction was complete, i.e. when it no longer showed any ferric reaction with alcoholic ferric chloride, the reaction mixture was filtered and most of the acetone was removed by evaporation. The residue was taken up with cold water (200 c.c.). The solid was collected and crystallised from hot alcohol as prisms (4.5 g.).

It had a melting point of 69°C. and was soluble in most organic solvents.

Found: OCH_3. 11.91%

$C_{15}H_{13}O_2(OCH_3)$ requires: OCH_3. 12.11%

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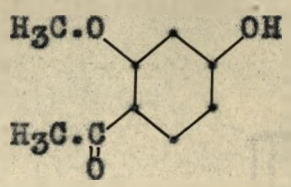
4-Hydroxy-2-methoxyacetophenone.



The foregoing 4-benzyloxy-2-methoxyacetophenone (1 g.) and glacial acetic acid (25 c.c.) were warmed on the water bath. Concentrated hydrochloric acid (15 c.c.) was gradually added in portions during one hour. After this period, the solution was finally heated on the wire gauze for five minutes. After cooling, it was poured into cold water (100 c.c.) and extracted with ether. The dark oil obtained after removal of ether was treated with 2% aqueous sodium hydroxide (20 c.c.) and extracted with ether. The aqueous residue was made acid with dilute hydrochloric acid and extracted with ether. The ether extract was dried over sodium sulphate and after removal of ether, the residual solid was dissolved in hot water with

charcoaling. Colourless needles of 4-hydroxy-2-methoxy-acetophenone separated, m.p. 136-137°C. Mixed with the natural product (vide supra) or with 2-methoxy-resacetophenone (Hoesch, Ber., 48, 1126), it had a melting point of 136-137°C.

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