PART III

ATTEMPTS AT THE SYNTHESIS OF PIMPINELLIN:

SYNTHESIS OF ISOBERGAPTENE
Hence the structure (III) has been assigned to pimpinellin in view of the experimental data provided above.

Isobergaptene (IV) and pimpinellin (III) are structurally related just as are bergaptene (I) and isopimpinellin (II).


Isobergaptene (IV) was first isolated from the roots of *P. saxifraga* (Wessely and Nadler, Montash, 1932, 60, 141) and its presence was reported in various species of *Heracleum* (Späth and Simson, loc. cit.; Fujita and Furuva, J. Pharm. Soc., Japan, 1954, 74, 795; 1956, 76, 535).

Its constitution was established as furo-(2'-3'-7-8)-5-methoxy coumarin (IV) by Wessely and Nadler (loc. cit.).
It was first synthesised from 3,4,6-triacetoxy coumarone (V) in a very poor yield by Späth and Kubiczek (Ber., 1937, 70B, 1253). Subsequently Rodighiero and Antonello (Il. Farmaco. (Pavia), Ed. Sci., 1955, 10, 889) obtained isobergaptene in better yields, starting from 2-O-methyl phloroglucinaldehyde (VI) through 7-hydroxy-5-methoxy coumarin (VII) and its 8-aldehyde (VIII). Finally, the furan ring was built using α-bromo-acetic ester. It is represented by the following reactions:

\[
\begin{align*}
\text{OH} & \quad \stackrel{\text{Me}_3\text{SO}_4}{\longrightarrow} \quad \text{OCH}_3 \\
\text{OH} & \quad \text{OCH}_3 \\
\text{OH} & \quad \text{OCH}_3 \\
\end{align*}
\]

(VII)
The absorption spectrum in ethanol showed a maxima at $\lambda (\log \varepsilon)$, 223 (4.2), 250 (4.18) and 308 (3.9), and a minima at 235 (4.0) and 279 (3.59).

Seshadri and Sood (Indian J. Chem., 1965, 3(8), 354) made a convenient synthesis of isobergaptene, modifying the above method. Starting with 2-O-methyl-phloroglucinaldehyde (VI), it was synthesised as follows: -
7-Hydroxy-5-methoxy coumarin (VII) was converted to its 8-allyl derivative (XII) through Claisen rearrangement of its allyl ether (XI). This was converted to isobergaptene (IV) by treatment with ozonised oxygen (3 per cent) for 5 minutes, followed by hydrogen in presence of palladium charcoal and finally with polyphosphoric acid.

Though the constitution of pimpinellin has long been
determined, no reference is available as to its synthesis. Attempts have been made here to investigate the possibilities of synthesising pimpinellin by various possible methods. This work also furnished another synthesis of isobergaptene, a valuable natural furocoumarin.

The possibility that angelicin (I) could furnish pimpinellin (V) in four stages as shown in the following scheme, has been examined. The Elbs persulphate oxidation of angelicin (I) would give 6-hydroxy-angelicin (II) (Sethna, et al., J. Ind. Chem. Soc., 1950, 27, 369; 1951, 28, 366; 1953, 30, 610) which, on hexamine reaction, would afford the corresponding 5-aldehyde (III). This, on Dakins oxidation, would furnish 5:6-dihydroxy-angelicin (IV) which on methylation would give pimpinellin (V).
For the synthesis of angelicin, the method by Späth and Pailer (Ber., 1936, 68, 941) from 7-hydroxy-coumarin (VI), was employed. 7-Hydroxy-8-formyl coumarin (VII) obtained by using hexamine, gave on reaction with ethyl bromo-acetate, in presence of anhydrous potassium carbonate-acetone a good yield of the 7-o-acetic ester (VIII), m.p. 163° C. Spath and Pailer (loc. cit.) give m.p. 157° C. However, the hydrolysis of the ester furnished the 8-formyl coumarin-7-o-acetic acid (IX) which has melting point (248-49°), much higher than what Spath and Pailer mentioned (178-81°) (cf. Naik and Thakor, J. Org. Chem., 1957, 22, 1696). This acid, on heating with fused sodium acetate and acetic anhydride, gave along with angelicin (I), a good amount of furo-2'-carboxy-7-7-(4':5')-coumarin (X) as stated by Naik and Thakor. This could be smoothly decarboxylated to angelicin (I) by means of quinoline and copper powder.

![Synthesis Diagram](attachment:chemistry_diagram.png)
The Elbs persulphate oxidation of angelicin (I) did not succeed and no oxidation product could be isolated. However, a blackish brown complex product was isolated. It did not melt on a spatula but charred and left a good amount of residue. The reaction failed under different conditions such as using pyridine as a solvent.

In view of this, it was thought that the hydroxyl group might be introduced prior to the building of the furan ring as in the following scheme:

The Elbs oxidation of 8-formyl coumarin-7-o-acetic acid (IX) as well as the corresponding ester (VIII) met with a failure, giving rise to a very small amount of a dark pasty product, which could not afford any pure product on either crystallisation from alcohol (charcoal), or treatment with
petroleum ether and benzene. However, a stable coumarinic acid was isolated in place of the unreacted compound, which regenerated the original coumarin on crystallisation from acetic acid. The failure in effecting the Elbs oxidation may be due to the presence of a free formyl group. Hence the above scheme had to be abandoned.

The above failures have been reported by Naik and Thakor (loc. cit.), but it was thought interesting to re-investigate the possibility under various conditions.

Since 5:6:7-trihydroxy-4-methyl coumarin (XIII) could be easily prepared and in good yield (Parikh and Sethna, J. Ind. Chem. Soc., 1960, 27, 369), it was thought to investigate the possibility of synthesising 4-methyl-pimpinellin (XV) according to the following scheme:

\[ (XIII) \rightarrow (XIV) \rightarrow (XV) \]
This, if successful, would furnish a similar possibility for the synthesis of pimpinellin. Hence, an attempt was made to formylate 5:6:7-trihydroxy-4-methyl coumarin with both hexamine and dimethylformamide. The hexamine formylation yielded entirely an orange red complex product and the aldehyde derivative was not isolated at all. The formylation with dimethyl formamide under the usual conditions was unsuccessful and the original product was recovered almost quantitatively, whereas under drastic conditions such as heating for a long time with a little excess of phosphorus oxychloride, the reaction deteriorated considerably. On working up the reaction mixture, a dark pasty product could be obtained. No pure product, either the unreacted coumarin or the aldehyde derivative could be isolated from the paste.

The Gattermann formylation in coumarin series has been found to be unsuccessful (Sethna and Shah, Chem. Revs., 1945, 36, 26). However, attempts were made to formylate 5:6:7-trihydroxy-4-methyl coumarin by the Gattermann reaction with modifications introduced by Adams, et al. (J. Am. Chem. Soc., 1924, 46, 1518) and Hinkel, et al. (J. Phys. Chem. Soc., 1936, 339). The reaction was carried out in ether at 0° and in o-dichlorobenzene at 30°, when the original coumarin was recovered and the aldehyde could not be isolated. When the reaction was carried out in o-dichlorobenzene at 80° with anhydrous aluminium chloride as the condensing agent (Hinkel,
et al., loc. cit.), a deep green coloured oily product was obtained. On treatment with benzene, petroleum ether or chloroform, the product could not be solidified. On refluxing with activated charcoal in alcohol, and then working up, no change was observed. The pasty product did not give a 2:4-dinitrophenyl-hydrazone, indicating that formylation had not taken place.

Thus, all the three methods of formylation failed to give 5:6:7-trihydroxy-4-methyl-3-formyl coumarin (XIV) and the above scheme had to be given up.

Baker, Nodzu and Robinson (J. Chem. Soc., 1929, 78) obtained 2:6-dibenzylcxyquinol (XVI) in good yield by oxidation of pyrogallol tribenzyl ether to 2:6-dibenzylcxy-p-quinone and subsequent reduction. Hence, it was thought that 5:7-dihydroxy-6-methoxy coumarin (XVIII) could be prepared from the quinol derivative (XVI) according to the following scheme:
Although the formylation of 5:6:7-trihydroxy-4-methyl coumarin did not succeed, the formylation of 5:7-dihydroxy-6-methoxy coumarin (XVIII) or its 4-methyl derivative with N-methyl formanilide may succeed in view of the smooth formylation of 5:7-dihydroxy-4-methyl coumarin with good yield (Naik and Thakor, J. Org. Chem., 1957, 22, 1626-29; 1630-33). Thus, the synthesis of pimpinellin could possibly be effected without ambiguity according to the following stages:
Chapman, Perkin and Robinson (J. Chem. Soc., 1927, 3019) obtained an aldehyde in extremely poor yield from 2:6-dimethoxyquinol by the Gattermann reaction. They used hydrogen cyanide gas for the reaction. But later Spath, et al. (Ber., 1937, 70Б, 698) claimed to have obtained in 70-75 per cent yield 2:6-dimethoxy quinol-3-aldehyde by the same reaction using zinc cyanide. Hence the Gattermann reaction was carried out on 2:6-dibenzylxyquinol using zinc cyanide and dry hydrogen chloride gas. On completion of the reaction, a brown thick oil separated. It was hydrolysed by heating with water when a small amount of a bright yellow product separated. This soon deteriorated to a dark brown pasty substance. On taking up in ether and treating with activated charcoal, a pale yellow product could be isolated in poor yield. It was very soluble
in the usual solvent like chloroform, benzene, ethyl acetate, ethyl alcohol, acetic acid, etc. On keeping in air, the product soon changed colour, indicating the high susceptibility to oxidation. It does not melt at a definite melting point, but turns black and then softens. Thus, it was not possible to carry further reactions with such a poor yield and an impure product.

The Pechmann condensation was carried out on 2:6-dibenzyl-
-oxy quinol with ethyl acetoacetate in presence of 80 per cent sulphuric acid, in order to obtain 6-hydroxy-5:7-dibenzyloxy-
-4-methyl coumarin. If this reaction was successful, a synthesis of 5:7-dihydroxy-6-methoxy-4-methyl coumarin can be carried out. But this condensation also met with a failure. On pouring in water, a yellow paste was obtained. After removing the unreacted ethyl acetoacetate, 2:6-dibenzyloxy-
-p-quinone was isolated. It may be mentioned here that 2:6-dibenzyloxy quinol gets converted into 2:6-dibenzyloxy-
-p-quinone in presence of water and more readily with dilute alkali (Baker, et al., loc. cit.). Hence this method had also to be abandoned.

Since the formylation of 5:7-dihydroxy-4-methyl coumarin with N-methyl formanilide gave a good yield of 8-formyl derivative (Naik and Thakor, loc. cit.), the reaction can be applied to synthesise 5:7-dihydroxy-8-formyl coumarin (XIX). Hence pimpinellin (V) could possibly be prepared according to
the following scheme by a series of reactions via isobergaptene (XXIII).

\[ \text{HOOC} \quad \text{CHO} \quad \text{O} \quad \text{CO} \quad \text{CH} \quad \text{OH} \quad \text{CH} \]

\[ \text{(XIX)} \]

\[ \xrightarrow{\text{HOOC}} \quad \text{CHO} \quad \text{O} \quad \text{CO} \quad \text{CH} \quad \text{CH} \]

\[ \text{OCH}_3 \quad \text{CH} \]

\[ \text{(XXIV)} \]

\[ \xrightarrow{\text{H}_2\text{CO}} \quad \text{CHO} \quad \text{O} \quad \text{CO} \quad \text{CH} \quad \text{CH} \]

\[ \text{OCH}_3 \quad \text{CH} \]

\[ \text{(XXV)} \]

\[ \text{CO} \]

\[ \text{OH} \quad \text{CH} \]

\[ \text{(V)} \]

The methylation of 5:7-dihydroxy-8-formyl coumarin with dimethyl sulphate gave a mixture of 5-methoxy-7-hydroxy-8-formyl coumarin and 5:7-dimethoxy-8-formyl coumarin. The 5-methoxy-7-hydroxy-8-formyl coumarin was separated by dissolving in an alkaline solution.

When 5-methoxy-7-hydroxy-8-formyl coumarin (XX) was refluxed for 16 hours with ethyl bromacetate in presence of
sodium ethoxide, the reaction met with a failure and an insoluble sodium salt precipitated quantitatively. However, 5-methoxy-7-hydroxy-8-formyl coumarin (XX), on refluxing with an excess of ethyl bromoacetate and anhydrous potassium carbonate in acetone for 72 hours, afforded ethyl-5-methoxy-8-formyl coumarin-7-O-acetic ester (XXI) in a low yield. The original compound was recovered in good quantity as the potassium salt. The original coumarin was recovered almost quantitatively, when the reaction mixture was refluxed for a short time as 24 hours.

The ester (XXI) was hydrolysed with 5 per cent methanolic potassium hydroxide to give 5-methoxy-8-formyl coumarin-7-O-acetic acid (XXII). This acid (XXII), on refluxing with fused sodium acetate and acetic anhydride afforded isobergaptene (XXIII) in a poor yield. Some other dark coloured alkali soluble substance was obtained which could not be purified to give a definite product.

Elbs persulphate oxidation was carried out on isobergaptene (XXIII) as well as on the corresponding O-acetic acid (XXII) and O-acetic ester (XXI) under different conditions. However, all the attempts met with failure.

Alternatively, demethylation of isobergaptene, introduction of a formyl or an acetyl group in the 6-position and then Dakins oxidation followed by methylation may furnish
pimpinellin (V). However, it was not possible to proceed with the above scheme on account of the very poor yield of isobergaptene.

Isobergaptene may also be prepared through the following routes (cf. Zagorevski and Zykoy, loc. cit.):

As the 8-position in coumarin nucleus u is more reactive,
the possibility of formation of coumarino-γ-pyrone on 7-8 position is greater and hence compound (IV) will be obtained.

Also pimpinellin can be prepared according to the following scheme:

![Diagram of chemical reactions]

The work for these syntheses is under progress. More yield of the isobergaptene may furnish pimpinellin according to the above proposed synthesis, or by synthesising 5:6:7-tri-hydroxy coumarin and following the reactions shown in the above scheme, pimpinellin could be prepared.
EXPERIMENTAL
EXPERIMENTAL

7-Hydroxy coumarin:

It was prepared by the method described in Part III, m.p. 227-28°C.

7-Hydroxy-8-formyl coumarin:

To 7-hydroxy coumarin (10.0 g.) dissolved in glacial acetic acid (100 ml.), hexamethylene tetramine (20.0 g.) was added and the reaction mixture heated on a steam bath for 5 hours. Hot dilute hydrochloric acid (1:1-100.0 ml.) was added and the reaction mixture further heated for an hour. It was cooled and extracted with ether. On evaporation of the ether and the residual acetic acid, a yellow product was obtained. This was triturated with a limited amount of ethanol to remove some pasty material. The granular product thus obtained was crystallised from ethanol in thin golden yellow needles, m.p. 188°C. Yield: 1.6 g. Späth and Pailer (Ber., 1935, 68, 942) give m.p. 189-91°C (in a vacuum capillary).

Ethyl 8-formyl coumarin-7-0-acetic ester:

To the pure aldehyde (2.0 g.) dissolved in dry acetone (100 ml.), anhydrous potassium carbonate (4.0 g.) and then ethyl bromoacetate (2.0 ml.) were added, and the reaction mixture refluxed on a steam-bath for 36 hours. On filtering off the potassium carbonate and evaporating the
acetone, a white crystalline product separated. It was treated with a small quantity of cold methanol to remove excess of ethyl bromoacetate, filtered and crystallised from ethanol, m.p. 163° C. Yield: 1.6 g. It does not instantaneously dissolve in dilute alkali but does so on keeping (on account of the hydrolysis of the ester). Späth and Pailer (loc. cit.) give m.p. 157° C (in a vacuum capillary). Naik and Thakor (J. Org. Chemistry, 1957, 22, 1696) give m.p. 163° C.

8-FORMYL COUMARIN-7-O-ACETIC ACID:

The above ester (0.5 g.) was kept at room temperature with sodium hydroxide (5 per cent: 4.0 ml.) for 3 hours with occasional shaking. The product slowly went into solution, the colour changing to orange red. It was then filtered and the filtrate acidified. The product, which separated, was collected and crystallised from acetic acid in thin white needles, m.p. 248-49° (decomp.). Yield: 0.3 g. Naik and Thakor (loc. cit.) give m.p. 248-49° C.

The same acid was obtained when the ester (0.2 g.) was kept with sulphuric acid (80 per cent: 4.0 ml.) for 6 hours with occasional shaking and then poured into ice when a white product separated. The same acid was also obtained when the ester (0.2 g.) was refluxed on a water-bath with
with alcoholic potassium hydroxide (5 per cent: 4.0 ml.) for an hour, acidified and alcohol removed under reduced pressure.

**Furo-2-carboxy-7;8-(4';5')-coumarin and Angelicin:**

The above acid (0.5 g.), freshly fused sodium acetate (1.5 g.) and acetic anhydride (12.0 ml.) were refluxed together in an oil-bath at 150-55°C for half an hour, when a white granular product separated out. The reaction mixture was cooled and poured into crushed ice when the substance separated. The contents were made alkaline with excess of sodium hydroxide and then extracted with excess of ether. On evaporation of ether a white flaky angelicin separated. It was crystallised from methanol in thick white needles, m.p. 138°C. Yield: 60 mg. Späth and Pailer (loc. cit.) give m.p. 138-39°C. Naik and Thakor (loc. cit.) give m.p. 138-39.5°C.

The alkaline solution after extracting with ether was acidified to give angelicin 2'-carboxylic acid (0.2 g.). It was crystallised from acetic acid in thin white prisms, m.p. > 315°C. It melts on a spatula and leaves no residue. It gives effervescence with sodium bicarbonate and dissolves in dilute alkali, giving light yellow solution. Späth and Pailer (loc. cit.) do not appear to have isolated this acid.
DECARBOXYLATION OF FURO-2-CARBOXY-7:8-(4':5') COUMARIN: ANGELICIN:

The acid (0.2 g.), copper powder (0.5 g.) and dry and distilled quinoline (5.0 ml.) were heated in an oil-bath at 235° C for half an hour. Copious evolution of carbon dioxide took place within 15 minutes of heating and soon subsided. It was filtered, washed with acetone and then dilute hydrochloric acid was added. On extracting the contents with ether, washing the ether extract with dilute alkali and evaporating ether, angelicin was obtained. Yield: 120 mg. It was crystallised from dilute methanol in thick needles, m.p. 138° C. It did not depress the melting point of the sample from the above experiment.

ATTEMPTED ELBS PERSULPHATE OXIDATION OF ANGELICIN:

Angelicin (1.86 g.) was dissolved in a mixture of pyridine (20.0 ml.) and aqueous sodium hydroxide (10 per cent: 20.0 ml.). Potassium persulphate (2.7 g.) dissolved in water (55.0 ml.) was dropwise added with mechanical stirring during the course of two hours. The reaction mixture was then left overnight, just acidified and extracted with ether to remove the unreacted angelicin (0.6 g.). More of concentrated hydrochloric acid was then added and the contents heated on a steam-bath for an hour. A blackish complex product separated and was collected. It did not melt on a spatula, left a residue after some of it burnt away with
conflagrations. No organic crystallisable product could be isolated.

ATTEMPTED ELBS PERSULPHATE OXIDATION OF

8-FORMYL COUMARIN-7-O-ACETIC ACID:

The acid (2.6 g.) was dissolved in a mixture of pyridine (20.0 ml.) and aqueous sodium hydroxide (10 per cent: 20.0 ml.). Potassium persulphate (2.7 g.) dissolved in water (55.0 ml.) was dropwise added with mechanical stirring (two hours) and the reaction mixture left overnight. Next day it was acidified and the product separated was taken up in ether and was found to be the corresponding coumarinic acid which reverted to the above coumarin-O-acetic acid on crystallisation from acetic acid. The aqueous solution was heated on a steam-bath for an hour with more of concentrated hydrochloric acid. No pure product could be isolated from the black pasty product which separated in small quantity.

ATTEMPTED ELBS PERSULPHATE OXIDATION OF

ETHYL 8-FORMYL COUMARIN-7-O-ACETIC ESTER:

The ester (1.5 g.) was dissolved in a mixture of pyridine (20.0 ml.) and aqueous sodium hydroxide (10 per cent: 20.0 ml.). Potassium persulphate (2.7 g.) dissolved in water (55.0 ml.) was dropwise added with mechanical stirring (two hours) and the reaction mixture left overnight. Next day, it was acidified and the product separated was taken up
In ether and was found to be the corresponding coumarinic acid which reverted to the above coumarin-0-acetic ester on crystallisation from acetic acid. The aqueous solution was heated on a steam-bath for an hour with more of concentrated hydrochloric acid. No pure product could be isolated from the black pasty product which separated in small quantity.

5:7-DIHYDROXY-4-METHYL COUMARIN :

It was prepared by the method described in Part III, m.p. 282-284° C.

5:7-DIMETHOXY-4-METHYL COUMARIN :

5:7-Dihydroxy-4-methyl coumarin (10.0 g.), dimethyl sulphate (10.0 ml.), anhydrous potassium carbonate (15.0 g.) and dry acetone (300 ml.) were refluxed together on a steam-bath for 12 hours. The product obtained on working up as usual, was crystallised from ethanol in colourless needles, m.p. 174° C. Yield: 10.4 g. Canter, Curd and Robertson (J. Chem. Soc., 1931, 1258) give m.p. 171° C.

6-HYDROXY-5:7-DIMETHOXY-4-METHYL COUMARIN :

The dimethoxy coumarin (10.0 g.) was dissolved in a sodium hydroxide solution (9.0 g. in 90 ml. of water) by heating on a steam-bath and oxidised with potassium persulphate (13.0 g. in 270 ml. of water) as before. The unreacted
coumarin (2.2 g.) was recovered and the product obtained on heating with excess of hydrochloric acid was crystallised from ethanol in colourless square plates, m.p. 195°C. Yield: 2.6 g. Parikh and Sethna (loc. cit.) give the same melting point.

5:6:7-TRIHYDROXY-4-METHYL COUMARIN:

The above product (0.6 g.) was heated with acetic anhydride (5.0 ml.) and hydrochloric acid (4.0 ml.) in an oil-bath at 135-40°C for 3 hours. The product obtained on pouring the reaction mixture in ice cold sodium bisulphite solution, was crystallised from ethanol, m.p. 288-89°C. Yield: 0.3 g. Parikh and Sethna (loc. cit.) give m.p. 278°C.

ATTEMPTED FORMYLATION OF 5:6:7-TRIHYDROXY-4-METHYL COUMARIN WITH HEXAMETHYLENE TETRAMINE:

5:6:7-Trihydroxy-4-methyl coumarin (1.0 g.), hexamine (2.0 g.) and acetic acid (5.0 ml.) were heated on a boiling water bath for 3 hours. After about half an hour an orange yellow flocculent complex product separated. Hot dilute hydrochloric acid (20.0 ml. 1:1) was added and the contents further heated for 2 hours. After cooling, the complex was collected by filtration, and the filtrate extracted with ether. On evaporation of ether and the residual acetic acid, no formyl derivative could be traced. It did not give
a 2:4-dinitro-phenyl hydrazone.

**ATTEMPTED FORMYLATION OF 5:6:7-TRIHYDROXY-4-METHYL COUMARIN WITH DIMETHYL FORMAMIDE:**

A mixture of 5:6:7-trihydroxy-4-methyl coumarin (2.1 g.), dimethyl formamide (1.65 g.), phosphorus oxychloride (1.2 g.) and o-dichloro benzene (12.0 ml.) was heated on a steam-bath for 2 hours. A saturated solution of sodium acetate was then added and the contents were steam distilled to remove o-dichloro benzene. The light yellow product which separated was filtered while hot. The filtrate on cooling, yielded a white product. However, both of them were found to be the unreacted coumarin. The pasty product which stuck to the container in very small quantity could not afford any definite product. However, the pasty product furnished a 2:4-dinitro-phenyl hydrazone in very minute amounts indicating the formyl derivative formed in traces.

Even when the reaction mixture was heated for 6 hours, the unreacted coumarin was recovered almost quantitatively and the formyl derivative could not be isolated at all. When the reaction mixture was heated with excess of phosphorus oxychloride, the reaction deteriorated considerably giving rise to a black pasty mass from which neither the unreacted coumarin nor the formyl derivative could be isolated.
ATTEMPTED GATTERMANN FORMYLATION OF
5:6:7-TRIHYDROXY-4-METHYL COUMARIN

In a one litre three necked flask fitted with an air tight stirrer, was taken a mixture of 5:6:7-trihydroxy-4-methyl coumarin (2.1 g.), zinc cyanide (6.0 g.) and dry ether (500 ml.). The flask was externally cooled and dry hydrochloric acid gas was passed for 5 hours, through the reaction mixture which was being stirred. Stirring was continued for an hour more after the reaction. The contents were then kept overnight in a frigidaire. No apparent change could be observed. On removing ether and heating the contents with 5 per cent sulphuric acid, the unreacted coumarin was recovered in good quantity. The formyl derivative could neither be isolated nor characterised by the formation of 2:4-dinitro phenyl hydrazone.

The above reaction was repeated using anhydrous aluminium chloride (9.0 g.) in dry ether. However, the unreacted coumarin was isolated almost quantitatively. The reaction met with a failure when carried out in o-chloro benzene at room temperature.

The Gattermann reaction was then repeated using anhydrous aluminium chloride in o-dichloro benzene at 80° (Hinkel, et al., loc. cit.) when the reaction mixture turned green. On working up the reaction mixture, a dark green pasty mass was
obtained. Neither the original coumarin nor the aldehyde derivative could be isolated from the paste.

**PYROGALLOL TRIBENZYL ETHER**

A mixture of pyrogallol (50.0 g.), anhydrous potassium carbonate (80.0 g.), dry acetone (350 ml.) and benzyl chloride (80.0 g.) was refluxed on a warm water-bath for 30 hours. More of benzyl chloride (130 g.) was added in small lots during that period, and the reaction mixture was further refluxed for 10 hours. Potassium carbonate was removed by filtration and washed with excess of acetone. After removing acetone by distillation, water was added and the contents steam-distilled when excess of benzyl chloride distilled over with steam. The residual mass was collected and crystallised from ethanol in colourless needles, m.p. 70°. Yield: 50 g. Baker, et al. (J. Chem. Soc., 1929, 78) give the same melting point.

**2:6-DIBENZYL OXY- p-QUINONE**:

Nitric acid (40 ml.: 1.2 d.) was added to a solution of pyrogallol tribenzyl ether (80 g.) in acetic acid (800 ml.) at 40° C. After the reaction mixture had been kept for 4 hours at room temperature, 5-nitro-pyrogallol tribenzyl ether (15 g. m.p. 139°) which separated was filtered. A second lot of nitric acid (40 ml.: 1.2 d.) was added to the reddish brown filtrate and the contents left overnight at room
temperature. On the following day, the quinone separated as bright yellow needles and was collected by filtration and crystallised from acetone in long bright yellow needles, m.p. 201-202°C. Yield: 30 g. Baker, et al. (loc. cit.) give the same melting point.

2:6-DIBENZYL0XY QUINOL:

Sulphuric acid (25 per cent: 60 ml.) was gradually added during 3 hours to a gently boiling well stirred mixture of 2:6-dibenzyloxy-p-quinone (40 g.), ethanol (400 ml.) and zinc dust (80 g.). When the yellow quinone disappeared the liquid was filtered hot. Addition of dilute sulphurous acid to the filtrate caused the separation of fairly pure lustrous white plates, m.p. 116°. Yield: 40 g. Barker, et al. (loc. cit.) give m.p. 116-17°.

ATTEMPTED GATTERMANN FORMYLATION OF 2:6-DIBENZYL0XY QUINOL:

A mixture of 2:6-dibenzyloxy quinol (3.2 g.), zinc cyanide (2.4 g.) and dry ether (150 ml.) was externally cooled and mechanically stirred. Dry hydrochloric acid gas was passed for 5 hours when after about half an hour heat was generated and ether started refluxing. An orange yellow thick oil separated, which did not solidify till the end. The reaction mixture was left overnight in a frigidiaire. The next day ether was decanted and the orange yellow oil was
washed with more ether. The oil was then heated with water (100 ml.) when a bright yellow product separated. This soon deteriorated to a dark brown pasty product. The contents were extracted with excess of ether and the ether extract treated with activated charcoal. On filtering and evaporating the ethereal solution, a yellow substance (0.2 g.) was isolated. This product turned brown on keeping at room temperature. It is very soluble in ethyl alcohol, methyl alcohol, acetic acid, benzene, chloroform and ethyl acetate and hence it could not be purified. It does not melt at a definite temperature, but turns black and then softens. It gives a greenish brown colouration with alcoholic ferric chloride.

**ATTEMPTED PECHMANN CONDENSATION OF**

**2:6-DIBENZYLXOXYQUINOL WITH ETHYL ACETOACETATE**

2:6-Dibenzylxyquinol (3.2 g.), ethyl acetoacetate (1.3 ml.) and sulphuric acid (10 per cent: 80 ml.) were mixed and kept overnight at room temperature. The next day water was added when a yellow pasty product was obtained. On removing the unreacted ethyl acetoacetate by treating with ethanol, a deep yellow product was obtained. It was identified to be 2:6-dibenzyloxy-p-quinone by mixed melting point.
PHLOROGLUCINALDEHYDE:

It was prepared according to the method of Malkin and Nierenstein (J. Am. Chem. Soc., 1931, 53, 239).

Into a solution of anhydrous phloroglucinol (2.0 g.) in dry ether (25 ml.) containing zinc cyanide (1.2 g.) a good stream of dry hydrogen chloride was passed until the oil formed solidified. After standing for 3 hours, the solid was collected, washed with ether, and the imide salt dissolved in water (40 ml.) and hydrolysed on a boiling water-bath. The solid (2.0 g.) obtained on cooling was collected and dissolved in ether, filtered from traces of a red coloured by-product and the ether evaporated. Phloroglucin aldehyde thus obtained crystallised from water containing a trace of sulphur dioxide in long cream coloured needles. As already recorded by Gattermann, the product has no definite melting point.

It was confirmed by preparing its acetyl derivative, crystallised from ethanol, thick colourless plates, m.p. 101°. Malkin and Nierenstein (loc. cit.) give the same melting point.

5:7-DIHYDROXY COUMARIN:

A mixture of phloroglucinaldehyde (8.0 g.), sodium acetate (8.0 g.) and acetic anhydride (40 ml.) was heated
on an oil-bath at 185-190° for 12-14 hours. On isolation, 5:7-diacetoxy coumarin separated from methyl alcohol and then ethyl alcohol (charcoal) in slender colourless prisms, m.p. 140° C. Yield: 5 g. Gattermann (Annalen 1907, 357, 345) gives m.p. 138° C.

Aqueous sodium hydroxide (10 per cent: 30.0 ml.) was added to the diacetate (5.0 g.) in warm ethanol (30.0 ml.) and the mixture heated on a steam-bath until a homogeneous solution was obtained. More aqueous sodium hydroxide (30 ml.) was then added, the mixture was kept for 15 minutes and acidified with hydrochloric acid. A greater part of the alcohol was evaporated and the dihydroxy coumarin which separated from the cooled solution was recrystallised from dilute acetic acid, forming elongated colourless prisms, m.p. 285-286° C. Yield: 4 g.

5:7-DIHYDROXY-8-FORMYL COUMARIN:

A mixture of 5:7-dihydroxy coumarin (5.0 g.), dimethyl formamide (5.0 ml.), phosphorus oxychloride (5.0 ml.) and nitrobenzene (25 ml.) was heated for 3 hours on a steam-bath with intermittent shaking. On adding saturated sodium acetate solution (100 ml.) and removing the nitrobenzene by steam distillation, a pinkish brown amorphous product separated (3.2 g.). The amorphous product was found to be very sparingly soluble in boiling alcohol, acetic acid, acetone, etc. This product was refluxed with acetone and filtered and the
product which separated the next day was collected, m.p. > 315°. Red
Yield : 3 g. It gives a deep blood colouration with alcoholic
ferric chloride and dissolves in alkali giving light yellow solution.
Analysis:

4.260 mg. of the substance gave 9.101 mg. of CO₂ and
1.116 mg. of H₂O.

Found : C, 58.2; H, 2.9 per cent.

C₁₀H₆O₅ requires : C, 58.2; H, 2.9 per cent.

5-METHOXY-7-HYDROXY-8-FORMYL COUMARIN AND
5:7-DIMETHOXY-8-FORMYL COUMARIN:

5:7-Dihydroxy-8-formyl coumarin (3.0 g.) was suspended
in dry acetone (300 ml.) and dimethyl sulphate (5.0 ml.)
and anhydrous potassium carbonate (10.0 g.) were added and
the mixture gently refluxed for 30 hours. On evaporating
acetone and neutralising the carbonate, an amorphous, dirty
product separated. It was filtered and then treated with
2 per cent sodium hydroxide. The dimethyl ether which
remained over as insoluble was contaminated with the insoluble
sodium salt of 5-methoxy-7-hydroxy-8-formyl coumarin. It
was repeatedly treated with dilute alkali and washed with
water and filtered. The filtrate on acidification gave the
5-monomethyl ether which was crystallised from acetic acid
(charcoal) in thin long white needles, m.p. 254° C.
Yield : 1.8 g. It gives a deep red colouration with alcoholic
ferric chloride and forms a sodium salt with alkali even in a dilute solution. Rodigherio and Antonello (Il. Farmaco (Pavia), Ed. Sci.) give m.p. 254° C.

The alkali insoluble dimethyl ether was crystallised from acetic acid (charcoal) in thin shining light yellow needles, m.p. 264° C. Yield: 0.4 g. It is insoluble in alkali and does not give any colouration with alcoholic ferric chloride.

Analysis:
4.623 mg. substance gave 10.431 mg. CO₂ and 1.773 mg. H₂O.

Found: C, 61.5; H, 4.1 per cent.

C₁₂H₁₀O₅ requires: C, 61.5; H, 4.2 per cent.

Ethyl 5-Methoxy-8-Formyl Coumarin-7-O-Acetic Ester:

5-Methoxy-7-hydroxy-8-formyl coumarin (5.0 g.), anhydrous potassium carbonate (15.0 g.), dry acetone (300 ml.) and excess of ethyl bromoacetate (5.0 ml.) were continuously refluxed on a steam-bath for 72 hours. It was filtered while hot and the insoluble potassium salt and potassium carbonate obtained were treated with water and acidified. The original product (about 3.0 g.) was thus recovered. On evaporation of acetone, the product was obtained along with ethyl bromoacetate. Water was added and the whole steam distilled to remove the ester. A white flocculent product which separated was collected and
crystallised from acetic acid in thin wooly needles, m.p. 156° C. Yield : 1.2 g. It is insoluble in cold alkali, but dissolves on keeping. It does not give any colouration with alcoholic ferric chloride. Rodighiero, et al. (loc. cit.) give m.p. 154° C.

Analysis:

4.785 mg. substance gave 10.318 mg. Co₂ and 1.971 mg. H₂O.

Found : C, 58.8; H, 4.6 per cent.

C₁₅H₁₄O₇ requires : C, 58.8; H, 4.6 per cent.

5-METHOXY-8-FORMYL COUMARIN-7-O-ACETIC ACID:

The above ester (1.0 g.) was refluxed on a steam-bath for half an hour with methanolic potassium hydroxide (5 per cent : 20 ml.) when the product went into solution giving a deep red solution. It was filtered and the filtrate was acidified. On stirring with a rod, greenish coloured product separated. It was immediately filtered and washed with methyl alcohol. It was crystallised from acetone, m.p. 241-242° C (decomp.). Yield : 0.5 g. It dissolves in sodium bicarbonate without visible effervescence and in dilute sodium hydroxide giving pale yellow colour. It does not give any colouration with alcoholic ferric chloride. Rodighiero, et al. (loc. cit.) give m.p. 241-242° C.
Analysis:

4.426 mg. substance gave 9.111 mg. CO₂ and 1.431 mg. H₂O.

Found: C, 56.1; H, 3.6 per cent.

C₁₃H₁₀O₇ requires: C, 56.1; H, 3.6 per cent.

ISOBERGAPTENE:

5-Methoxy-8-formyl coumarin-7-O-acetic acid (500 mg.), freshly fused sodium acetate (1.0 g.) and acetic anhydride (15 ml.) were refluxed together in an oil bath at 150-155° for 2 hours. Most of the acetic anhydride was removed by distillation, and then water and excess of sodium hydroxide added. On exhaustive extraction with ether and evaporation of ether, a pale yellow product was isolated. It was crystallised from methyl alcohol, m.p. 222-223° C.


The absorption spectrum was tallied with that obtained by Rodighiero, et al. (loc. cit.).

The absorption spectra in ethanol showed max. (m/λ) (log ε), 223 (4.2), 250 (4.18) and 308 (3.9) and min. 235 (4.0) and 279 (3.59).
ATTEMPTED PERSULPHATE OXIDATION OF ISOBERGAPTENE:

Isobergaptene (100 mg.) was dissolved in sodium hydroxide (10 per cent: 10.0 ml.) by warming on a steam bath and the solution cooled to 0°C. Potassium persulphate (1.7 g.) dissolved in water (35.0 ml.) was dropwise added with mechanical stirring during the course of two hours. The reaction mixture was then left overnight in a frigidaire, just acidified and extracted with ether to remove the unreacted isobergaptene (40.0 mg.). More of concentrated hydrochloric acid was then added and the contents heated on a steam-bath for an hour. A blackish complex product separated and was collected. It did not melt on a spatula, left a residue after some of it burnt away with conflagrations. No organic crystallisable product could be isolated.

The above persulphate oxidation was repeated with pyridine (20.0 ml.) following the procedure carried out for angelicin. No pure product could be isolated.

ATTEMPTED PERSULPHATE OXIDATION OF

ETHYL-5-METHOXY-8-FORMYL COUMARIN-7-O-ACETIC ESTER:

The ester (2.5 g.) was warmed with sodium hydroxide (10 per cent: 20.0 ml.) on a steam bath for 15 minutes, and cooled to 0°C. Potassium persulphate (2.7 g.) dissolved in water (55 ml.) was dropwise added with mechanical stirring
(two hours) and the reaction mixture left overnight in a frigidaire. Next day, it was acidified and the product separated was taken up in ether and crystallised from acetic acid when the corresponding coumarin-O-acetic acid (1.2 g.) was obtained. The aqueous solution was heated on a steam-bath for an hour with more of concentrated hydrochloric acid. No pure product could be isolated from a brown pasty product which separated in a small quantity.

The above reaction was repeated with pyridine (20.0 ml.) as solvent, as before, but no pure product could be isolated.

**ATTEMPTED PERSULPHATE OXIDATION OF 5-METHOXY-8-FORMYL COUMARIN-7-O-ACETIC ACID:**

The acid (1.5 g.) was warmed with sodium hydroxide (10 per cent: 20.0 ml.) on a steam-bath for 15 minutes and cooled to 0°C. Potassium persulphate (2.7 g.) dissolved in water (55 ml.) was dropwise added with mechanical stirring (two hours) and the reaction mixture left overnight in a frigidaire. Next day, it was acidified and the product separated was taken up in ether when the above coumarin-O-acetic acid was obtained (0.9 g.). The aqueous solution was heated on a steam-bath for an hour with more of concentrated hydrochloric acid. No pure product could be isolated from the dark brown product.

The above reaction was repeated with pyridine (20.0 ml.), but no pure product could be isolated.