CHAPTER III

ULLMANN REACTION ON SOME IODOCOUMARINS : SYNTHESIS OF SOME BICOUMARINYL AND 8-PHENYLCOUMARIN DERIVATIVES.

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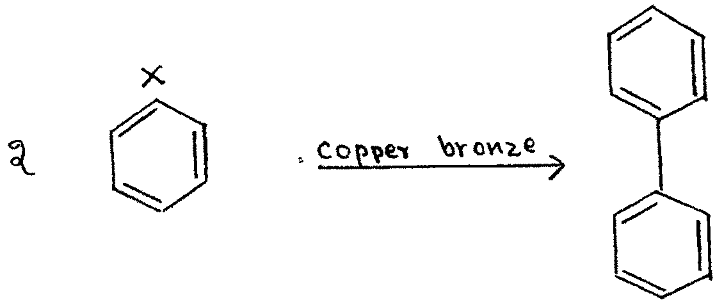
Ullmann reaction on some iodocoumarins : Synthesis of some bicoumarinyl and 8-phenylcoumarin derivatives.

The reaction, involving the removal of halogen atoms from aromatic halo compounds with the resulting union of two carbon atoms, when accomplished by the use of copper bronze, has come to be known as the Ullmann reaction. This synthesis is of general applicability and has found wide use in the preparation of many symmetrical and unsymmetrical biaryls. Ullmann reaction has been reviewed by Fanta (Chem. Revs., 1946, 38, 139).



It has been observed that chlorine, bromine and iodine may be eliminated with biaryl formation. Aromatic fluorine atom has never been reported to be active in the Ullmann reaction. The order of reactivity of the halogens is I > Br > Cl. The latter two substituents undergo reaction only when activating groups are present in the aromatic nucleus. Mascarelli (Gazz. Chim. ital., 1938, 68, 33 ; C.A., 1938, 32, 4565) studied the Ullmann reaction with a great variety of aromatic compounds and determined the amount of activation required in order that Ullmann reaction may occur.

Ullmann (Ber., 1901, 34, 2174) observed that electronegative groups in the ortho and para positions with respect to the halogen atom activate the molecule. The nitro group is the most effective activator.

Ullmann (Ann., 1904, 332, 38) observed the decrease in yield of biaryl when groups such as NH_2, $NHCOCH_3$, COOH, and OH are present in the aromatic nucleus. This is because they give rise to amination, decarboxylation or ether formation as a side reaction. Therefore amino groups must be protected by alkylation or by acylation, the carboxyl group by esterification and the hydroxyl group by etherification.

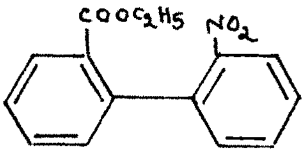
Bulky substituents in positions adjacent to the reactive halogen hinder biaryl formation. Thus Ullmann (loc. cit.) obtained the biaryl derivative from 2,4,6-trichlorobenzene in 52 % yield but the yield of the biaryl derivative from 2,4,6-trimethyliodobenzene was very poor.

The generalization regarding the effect of substituents on the Ullmann reaction on derivatives of benzene may be applied to other aromatic compounds according to the usual concepts of aromaticity.

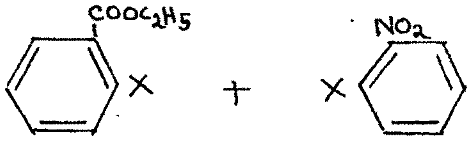
The Ullmann reaction has been applied with considerable success to the synthesis of unsymmetrical biaryls.

$$RX + R'X' \longrightarrow RR + RR' + R'R'$$

In addition to a consideration of the previously discussed conditions, the synthesis of an unsymmetrical biaryl requires the selection of an optimum ratio of the two component starting materials. If one component is more reactive th~~a~~en RX would be completely used up in the formation of RR. When the reaction is continued for a longer time or under more drastic conditions, R'X' reacts to give R'R'. The symmetrical biaryls are the only products of the reaction. In such a case the formation of RR' may be favoured by changing either X or X' in the starting materials so that aromatic halides are of more equal reactivity for example Sadler and Powell (J. Am. Chem. Soc., 1934, 56, 2650) obtained A from (B and E) in 20 % yield while Stewert et al. (J. Chem. Soc., 1944, 71) obtained it in 68 % yield from (C and D). In the latter case both the components are of equal reactivity.



A

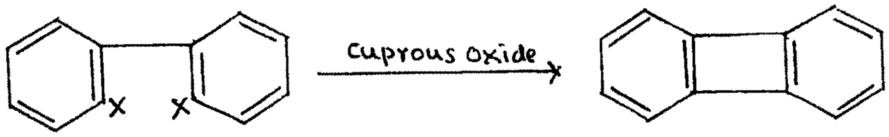


B, X= Br
C, X= I

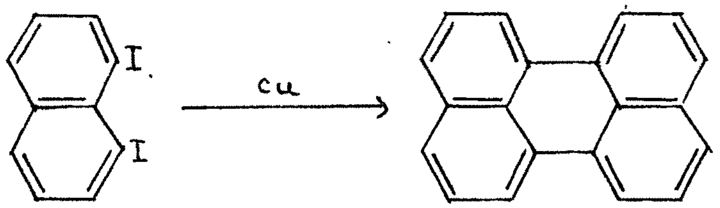
D, X=Br
E, X=I

The success of such a reaction also depends on the feasibility of separating the desired product from the symmetrical biaryls. This may be accomplished if the chemical or the physical properties of the biaryl differ sufficiently. Another condition which favours the unsymmetrical biaryl formation is the presence of an excess of the less reactive component.

Several intramolecular Ullmann reactions have also been reported in the literature. Lothrop (J. Am. Chem. Soc., 1941, 63, 1187 ; 1942, 64, 1698) reported the synthesis of biphenylene and several of its derivatives by the treatment of appropriately substituted 2,2'-dihalogen biphenyls with cuprous oxide.



Cyclic products may also be obtained when polyhalogenated aromatic compounds are subjected to the conditions of Ullmann reaction. Scholl et al. (Ber., 1910, 43, 2202) obtained perylene from 1,8-diiodonaphthalene.



Experimental conditions

Copper bronze has long been one of the most commonly employed forms of the metal. Brady and McHugh (J. Chem. Soc., 1923, 204) successfully used freshly precipitated copper. This was prepared by treatment of zinc dust with copper sulphate solution. However, Ullmann (loc.cit.) and Schreiner (J. prakt. Chem., 1910, 81, 422) observed that mechanically pulverised copper is preferable to the chemically precipitated copper. Kleiderer and Adams (J. Am. Chem. Soc., 1933, 55, 4219) recommended activation of copper bronze by treatment with iodine in acetone followed by washing with hydrochloric acid and acetone. Generous excess of copper is always used in the Ullmann reaction. Since the reaction is exothermic only a small portion of the copper is placed in the reaction mixture at the outset, the remainder of the metal is added in small portions during the course of the reaction. The temperature employed in the Ullmann reaction varies from 100° to 360° depending upon the activity of the aromatic halide. Reactions of compounds containing the nitro group must not be carried out at a temperature exceeding 240° otherwise reduction of the nitro group by the copper occurs. The usually exothermic reaction may be moderated by the use of a diluent. The organic substances used for this purpose are nitrobenzene, p-cymene, biphenyl, anthracene and diphenyl ether. Sand has also been employed as a diluent. Mann et al. (J. Chem. Soc., 1940, 1379) reported improvement in yield when the reaction was carried out in an atmosphere of nitrogen. Copper powder added to the reaction mixture rapidly settles to the bottom of the reaction vessel and must be stirred to expose the active surface of the metal.

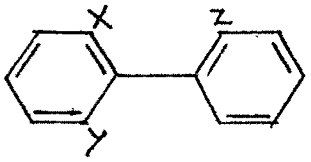
Rapson and Shattleworth (Nature, 1941, 147, 675) suggested the possibility of a free radical mechanism for this reaction. Gilman and Straley (Rec. Trav. Chim., 1936, 55, 821) who studied the preparation and reactions of organo copper compounds pointed out that although Rcu compounds are known to undergo coupling to yield RR compounds it is not known whether the organo copper compound of this type is formed as an intermediate in the Ullmann reaction. An R_2Cu compound has also been suggested as a possible intermediate in the coupling reaction but there is no experimental evidence for the existence of such a compound. A possible mechanism of the reaction envisages two steps. (1) A nucleophilic reaction of copper with the aromatic halide to form an activated complex at the metal surface. The occurence of this step is governed largely by the nature of the aromatic halide. (2) The reaction of the activated complex with a second molecule of the aromatic halide to form a biaryl molecule plus copper halide. This reaction is governed to a greater extent by steric effect.

Synthesis of bicoumarinyls.

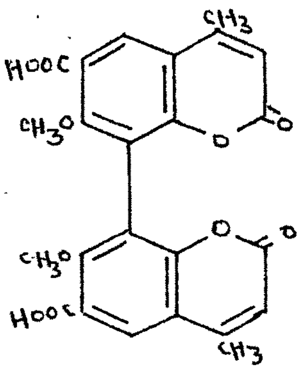
Very little work appears to have been done on the synthesis of bicoumarinyls. Dey and Row (J. Indian Chem. Soc., 1924, 1, 107) prepared 4,3'-dicoumarinyls by the condensation of various phenolic aldehydes with 4-coumarinyl acetic acids. Sen and Dutta (J. Indian Chem. Soc., 1931, 8, 223) obtained 6,6'-dicoumarinyl by the action of acetic anhydride and sodium acetate on 4,4'-dihydroxydiphenyl-3,3'-dialdehyde. Huebner and Link reported the formation of the bicoumarinyl derivative from 3-bromo-4-methoxycoumarin by the Ullmann reaction. Lyons (J. Chem. Soc., 1950, 1575) obtained tetrahydro-4,4'-dicoumarinyl as one of the products in the reduction of coumarin using zinc and acetic acid.

Several 3-phenylcoumarins are known and have been prepared : by condensing o-hydroxyaldehydes with phenyl acetonitrile in presence of sodium ethoxide (Borsche, Ber., 1904, 37, 3165) ; by Meerwein reaction (See Introduction p. 30) ; by condensing α-formylphenylacetonitrile and its derivatives with phenols such as resorcinol in presence of phosphorus oxychloride (Baker et al., J. Chem. Soc., 1931, 1541) and by heating o-hydroxyacetophenones with sodium phenylacetate and acetic anhydride. 4-Phenylcoumarins have been obtained by Pechmann condensation of ethyl benzoylacetate with various phenols in presence of sulphuric acid (80 %). Cramer and Windel (Chem. Ber., 1956, 89, 354) obtained ethyl-6-phenylcoumarin-3-carboxylate by condensation of 2-hydroxy-5-phenylbenzaldehyde with diethyl malonate in presence of piperidine. On hydrolysis and decarboxylation it yielded 6-phenylcoumarin. 8-Phenylcoumarins have hitherto been unknown except for some 8-phenylsulphonylcoumarins prepared by the Fries migration of 7-coumarinyl benzenesulphonates by Aleykutty and Baliah (J. Indian Chem. Soc., 1955, 32, 773)

As very little work has been done on the synthesis of bicoumarinyl and 8-phenylcoumarin derivatives it was thought of interest to synthesis these from the iodocoumarins described in Chapter II by the Ullmann reaction. Further, as is well known, diaryl derivatives with at least three ortho substituents of suitable size as in (A) can be resolved into optical isomers. It was therefore of interest to see if bicoumarinyl derivatives such as (B) could be resolved into optical isomers.



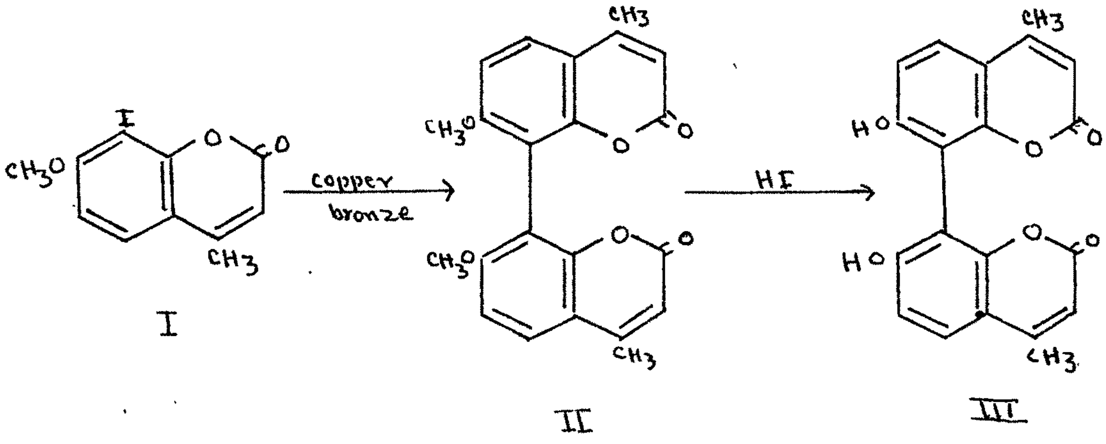
A



B

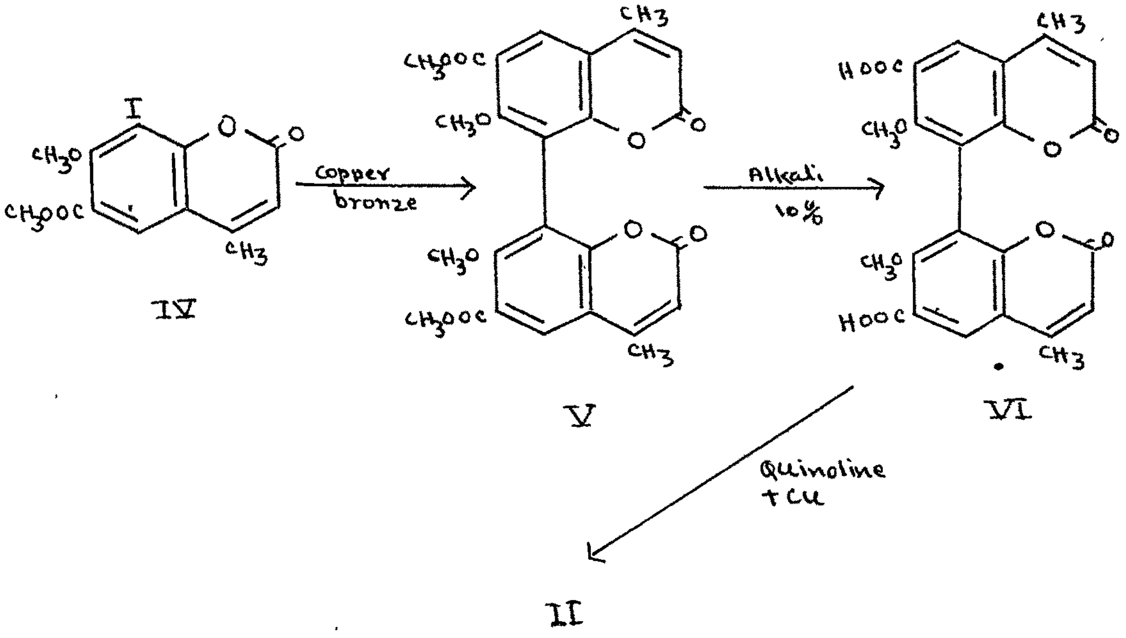
7,7'-Dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl

7-Methoxy-8-iodo-4-methylcoumarin (I) when treated with copper bronze in boiling diphenyl ether gave a mixture of two products, (A) m.p. 358° and (B) m.p. 159°. The product (B) was found to be identical with 7-methoxy-4-methylcoumarin on direct comparison. The product (A) which was found to be sparingly soluble in all the solvents, has been assigned the structure : 7,7'-dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl (II). Attempts to estimate the molecular weight of this compound by Rast's method did not succeed as the substance was not soluble in camphor. The yield of the bicoumarinyl derivative was very poor when the reaction was carried out without any solvent. Activation of copper bronze with iodine and acetone did not improve the yields. On demethylation (II) gave 7,7'-dihydroxy-4,4'-dimethyl-8,8'-bicoumarinyl.



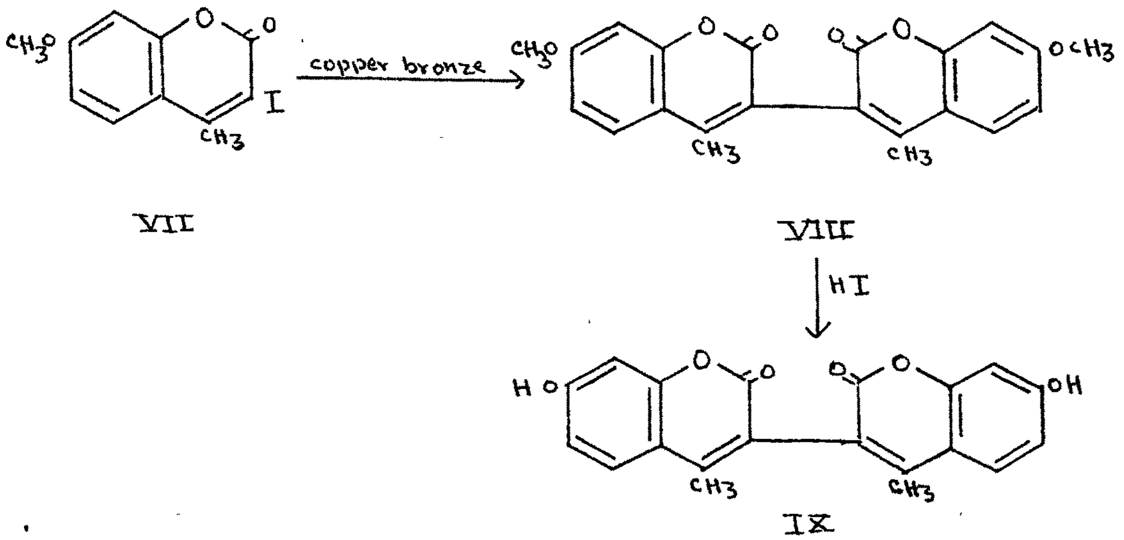
7,7'-Dimethoxy-4,4'-dimethyl-6,6'-dicarbomethoxy-8,8'-bicoumarinyl

Methyl-7-methoxy-8-iodo-4-methylcoumarin-6-carboxylate (IV) when treated with copper bronze in boiling diphenyl ether gave methyl-7-methoxy-4-methylcoumarin-6-carboxylate and a product m.p. 250° which has been assigned 7,7'-dimethoxy-4,4'-dimethyl-6,6'-dicarbomethoxy-8,8'-bicoumarinyl (V) structure. On hydrolysis with alcoholic potassium hydroxide solution (10 %) the ester (V) gave the corresponding acid : 7,7'-dimethoxy-4,4'-dimethyl-6,6'-dicarboxy-8,8'-bicoumarinyl (VI) which on decarboxylation yielded 7,7'-dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl (II) described earlier. Attempts to prepare the (-) brucine salt of the acid (VI), to see if this could be resolved into optical isomers, did not succeed on account of the sparing solubility of the acid in various solvents.



7,7'-Dimethoxy-4,4'-dimethyl-3,3'-bicoumarinyl

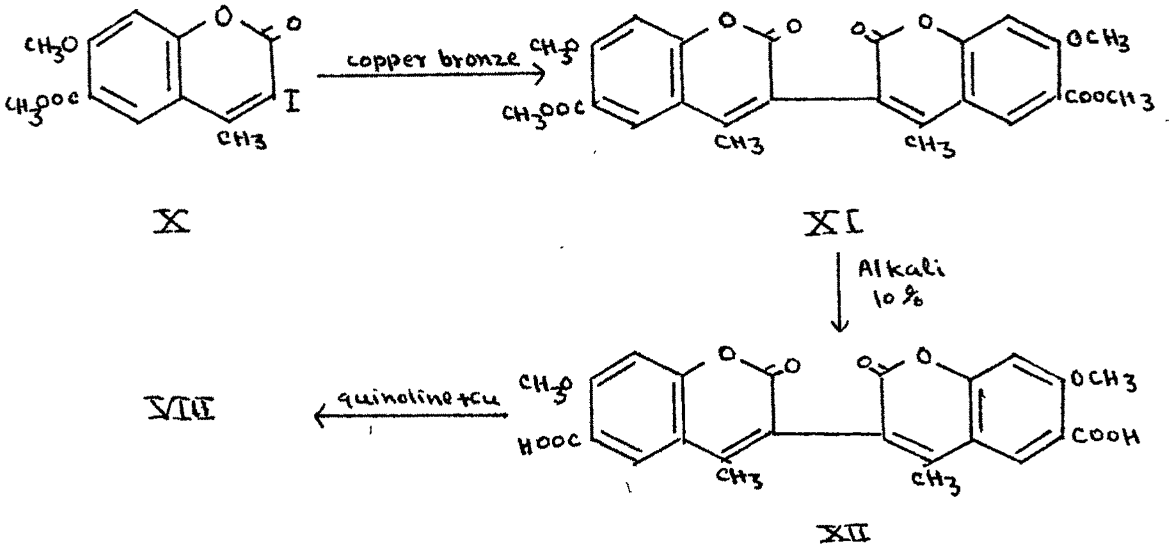
7-Methoxy-3-iodo-4-methylcoumarin (VII) when heated with copper bronze in boiling diphenyl ether gave 7-methoxy-4-methylcoumarin and a product m.p.268°. 7,7'-Dimethoxy-4,4'-dimethyl-3,3'-bicoumarinyl (VIII) structure has been assigned to this product. On demethylation it yielded 7,7'-dihydroxy-4,4'-dimethyl-3,3'-bicoumarinyl (IX).



7,7'-Dimethoxy-4,4'-dimethyl-6,6'-dicarbomethoxy-3,3'-bicoumarinyl

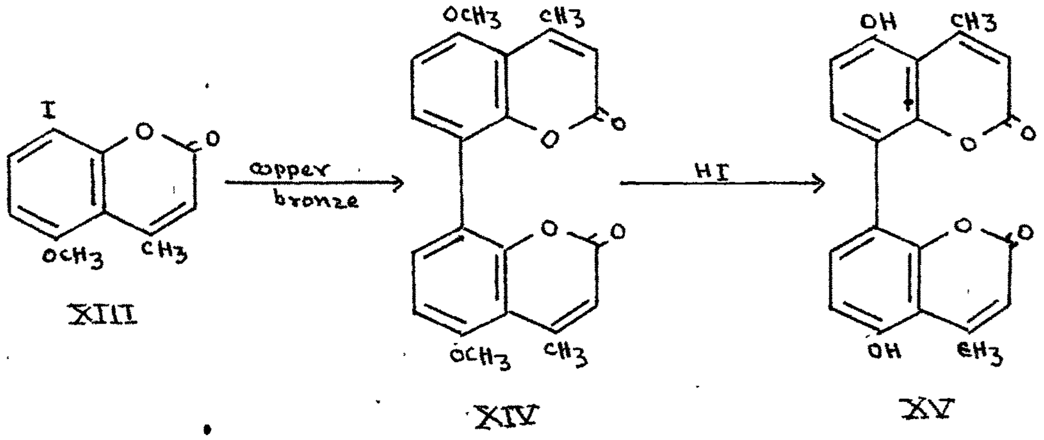
Methyl-7-methoxy-3-iodo-4-methylcoumarin-6-carboxylate (X) when treated with copper bronze in boiling diphenyl ether gave methyl-7-methoxy-4-methylcoumarin-6-carboxylate and another product m.p.292°. 7,7'-Dimethoxy-4,4'-dimethyl-6,6'-dicarbomethoxy-3,3'-bicoumarinyl (XI) structure has been assigned to this product. On hydrolysis with alcoholic potassium hydroxide solution (10 %) the bicoumarinyl derivative (XI) gave the corresponding acid

(XII) which on decarboxylation yielded 7,7'-dimethoxy-4,4'-dimethyl-3,3'-bicoumarinyl (VIII) mentioned earlier.



5,5'-Dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl

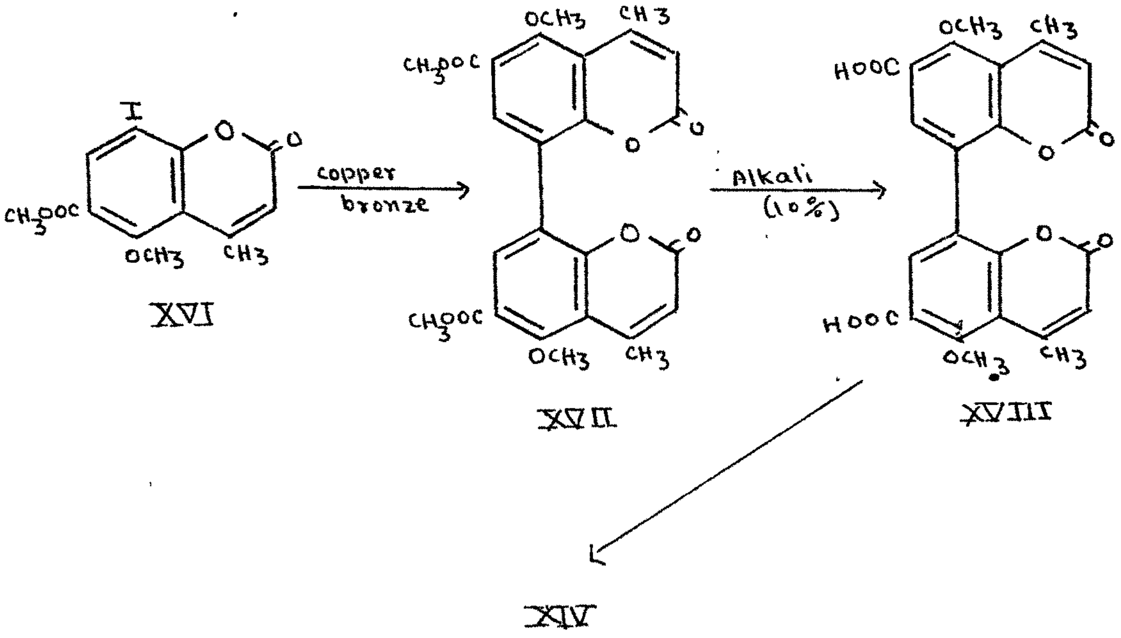
5-Methoxy-8-iodo-4-methylcoumarin (XIII) when treated with copper bronze in boiling nitrobenzene solution gave 5-methoxy-4-methylcoumarin and a product melting above 400°. 5,5'-dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl (XIV) structure has been assigned to this product. Yield of the



bicoumarinyl derivative (XIV) was very poor when diphenyl ether was used as solvent. On demethylation (XIV) yielded 5,5'-dihydroxy-4,4'-dimethyl-8,8'-bicoumarinyl (XV).

<u>5,5'-Dimethoxy-4,4'-dimethyl-6,6'-dicarbomethoxy-8,8'-bicoumarinyl</u>

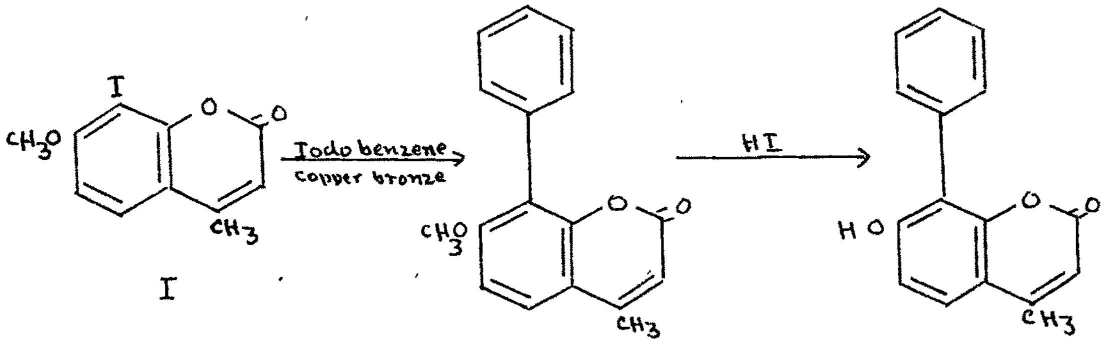
Methyl-5-methoxy-8-iodo-4-methylcoumarin-6-carboxylate (XVI) when treated with copper bronze in boiling diphenyl ether gave methyl-5-methoxy-4-methylcoumarin-6-carboxylate and a product m.p.353°. 5,5'-Dimethoxy-4,4'-dimethyl-6,6'-dicarbomethoxy-8,8'-bicoumarinyl (XVII) structure has been assigned to this product. On hydrolysis with alcoholic potassium hydroxide solution (10 %) it gave the corresponding acid (XVIII). On decarboxylation this acid yielded 5,5'-dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl (XIV) mentioned earlier.



Synthesis of 8-phenylcoumarin derivatives.

7-Methoxy-8-phenyl-4-methylcoumarin

7-Methoxy-8-iodo-4-methylcoumarin (I) when heated with iodobenzene and copper bronze at 220° gave a mixture of various products from which 7-methoxy-8-phenyl-4-methylcoumarin (XIX) was isolated by fractional crystallisations. Other products isolated were biphenyl and 7,7'-dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl (II) mentioned earlier. Yield of the 8-phenylcoumarin (XIX) was very poor when a solvent (diphenyl ether or nitrobenzene) was used. On demethylation,(XIX) gave 7-hydroxy-8-phenyl-4-methylcoumarin (XX).



I

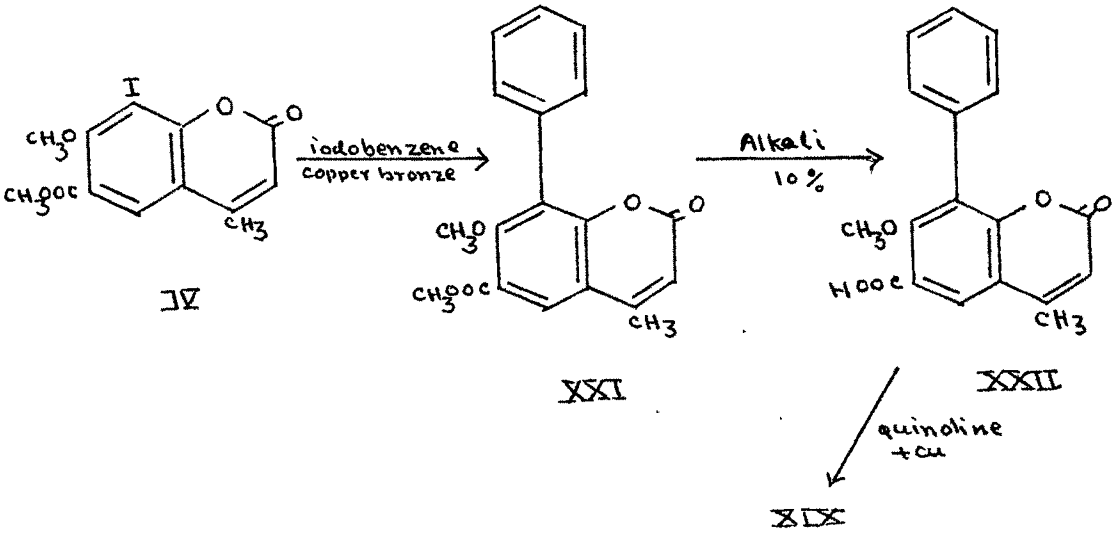
XIX

XX

Methyl-7-methoxy-8-phenyl-4-methylcoumarin-6-carboxylate

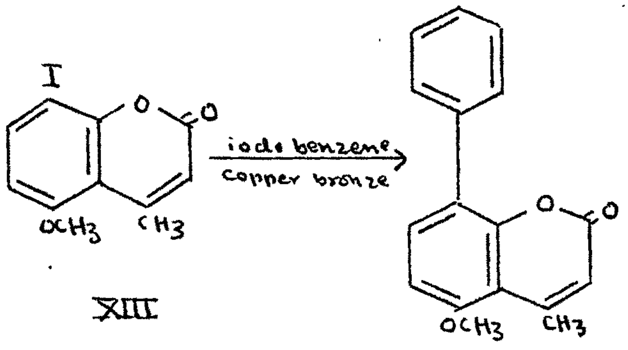
Methyl-7-methoxy-8-iodo-4-methylcoumarin-6-carboxylate (IV) and iodobenzene in boiling nitrobenzene solution when treated with copper bronze gave a mixture of various products from which methyl-7-methoxy-8-phenyl-4-

methylcoumarin-6-carboxylate (XXI) was isolated by fractional crystallisation. Other products isolated were biphenyl and 7,7'-dimethoxy-4,4'-dimethyl-6,6'-dicarbomethoxy-8,8'-bicoumarinyl (V) mentioned earlier. Unlike the previous condensation, yields of the 8-phenylcoumarin ester (XXI) were greatly reduced when no solvent was used. On heating with alcoholic potassium hydroxide solution (10 %) (XXI) gave the corresponding acid (XXII) which on decarboxylation yielded 7-methoxy-8-phenyl-4-methylcoumarin (XIX) described earlier.



<u>5-Methoxy-8-phenyl-4-methylcoumarin</u>

5-Methoxy-8-iodo-4-methylcoumarin (XIII) when heated with iodobenzene and copper bronze at 260° gave a mixture of various products from which 5-methoxy-8-phenyl-4-methylcoumarin (XXIII) was isolated by fractional crystallisation. Other products isolated were biphenyl and 5,5'-dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl (XIV) described earlier.



XIII

XXIII

EXPERIMENTAL

Ullmann reaction on 7-methoxy-8-iodo-4-methylcoumarin : 7,7'-Dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl.

7-Methoxy-8-iodo-4-methylcoumarin (3.16 g. ; 0.01 mole) dissolved in dry diphenyl ether (50 ml.) was treated with copper bronze (1.80 g. ; 0.03 mole) and the mixture refluxed on a wire gauze for 3 hours. The reaction mixture was filtered hot . The filtrate was then cooled and diluted with petroleum ether (60-80°) with stirring. The product obtained was dissolved in large amount of acetic acid and refluxed with animal charcoal. It was then filtered. The product which separated on cooling crystallised from the same solvent in thick yellowish brown needles, m.p.358°. Yield 1.3 g.

Analysis :

9.56 mg. of the substance gave 24.36 mg. of carbon dioxide and 4.20 mg. of water.

Found : C = 69.54 % ; H = 4.76 %.

$C_{22}H_{18}O_6$ requires : C = 69.84 % ; H = 4.76 %.

The product obtained on diluting the acetic acid solution and also on removal of diphenyl ether from the original mother liquor was found on direct comparison to be 7-methoxy-4-methylcoumarin.

The bicoumarinyl derivative is sparingly soluble in the common organic solvents.

7,7'-Dihydroxy-4,4'-dimethyl-8,8'-bicoumarinyl.

The above bicoumarinyl derivative (0.5 g.) was heated with acetic anhydride (8 ml.) and hydriodic acid (8 ml. ; d. 1.7) in an oil bath at 130-40° for 2 hours.

The reaction mixture was then cooled and poured in cold sodium bisulphite solution. The product, purified through dilute sodium hydroxide, crystallised from acetic acid as yellow amorphous powder, m.p. 388°.

<u>Analysis</u> :

10.54 mg. of the substance gave 26.54 mg. of carbon dioxide and 4.02 mg. of water.

Found : C = 68.71 % ; H = 4.27 %.

$C_{20}H_{14}O_6$ requires : C = 68.57 % ; H = 4.00 %.

The product freely dissolved in sodium hydroxide solution but did not show any fluorescence.

<u>Ullmann reaction on methyl-7-methoxy-8-iodo-4-methylcoumarin-6-carboxylate</u> : <u>7,7'-Dimethoxy-4,4'-dimethyl-6,6'-dicarbomethoxy-8,8'-bicoumarinyl</u>.

Methyl-7-methoxy-8-iodo-4-methylcoumarin-6-carboxylate (3.74 g. ; 0.01 mole) dissolved in dry diphenyl ether (50 ml.) was treated with copper bronze (1.8 g. ; 0.03 mole) and the mixture refluxed on a wire gauze for 3 hours. The reaction mixture was filtered hot. The filtrate on cooling was diluted with petroleum ether and the product obtained treated with acetic acid (charcoal) and finally recrystallised from the same solvent in yellow needles, m.p. 250°. Yield 1.6 g.

<u>Analysis</u> :

8.50 mg. of the substance gave 19.62 mg. of carbon dioxide and 3.44 mg. of water.

Found : C = 62.99 % ; H = 4.53 %.
$C_{26}H_{22}O_{10}$ requires : C = 63.15 % ; H = 4.45 %.

The product obtained on diluting the acetic acid mother liquor and on removal of diphenyl ether from the original mother liquor by steam distillation was found to be methyl-7-methoxy-4-methylcoumarin-6-carboxylate.

<u>7,7'-Dimethoxy-4,4'-dimethyl-6,6'-dicarboxy-8,8'-bicoumarinyl</u>.

The above ester (0.5 g.) was refluxed with alcoholic potassium hydroxide solution (10 % ; 20 ml.) on a steam bath for 2 hours. The mixture was diluted with water and acidified. The separated product was purified through sodium bicarbonate solution. It crystallised from large volumes of glacial acetic acid in needles, m.p. 306° (effer.).

<u>Analysis</u> :

10.04 mg. of the substance gave 22.68 mg. of carbon dioxide and 3.84 mg. of water.

Found : C = 61.64 % ; H = 4.28 %.
$C_{24}H_{18}O_{10}$ requires : C = 61.80 % ; H = 3.86 %.

The above acid (0.5 g.) in quinoline (10 ml.) was refluxed on a sand bath with a speck of copper powder for half an hour. The mixture was then filtered and poured in dilute hydrochloric acid solution. The separated product was washed with sodium bicarbonate solution and then crystallised from glacial acetic acid in needles, m.p.358°. Mixed melting point with 7,7'-dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl described earlier, was not depressed.

7,7'-Dimethoxy-4,4'-dimethyl-3,3'-bicoumarinyl.

7-Methoxy-3-iodo-4-methylcoumarin (3.16 g. ; 0.01 mole) dissolved in dry diphenyl ether (25 ml.) was treated with copper bronze (1.80 g. ; 0.03 mole) and the mixture refluxed on a wire gauze for 3 hours. The product obtained on working up as before crystallised from acetic acid in yellow needles, m.p. 268°. Yield 0.35 g.

Analysis :

8.98 mg. of the substance gave 22.96 mg. of carbon dioxide and 3.84 mg. of water.

Found : C = 69.77 % ; H = 4.78 %.

$C_{22}H_{18}O_6$ requires : C = 69.84 % ; H = 4.76 %.

7-Methoxy-4-methylcoumarin was obtained on diluting the acetic acid and also from the diphenyl ether mother liquor by steam distillation.

7,7'-Dihydroxy-4,4'-dimethyl-3,3'-bicoumarinyl.

The above bicoumarinyl derivative (0.5 g.) was heated with acetic anhydride (10 ml.) and hydriodic acid (d. 1.7 ; 10 ml.) in an oil bath at 130-140° for 2 hours. The product obtained on pouring the reaction mixture in cold sodium bisulphite solution was purified through dilute sodium hydroxide solution. It crystallised from acetic acid as brown amorphous powder, m.p. $>$ 400°.

The product freely dissolved in sodium hydroxide solution with a deep yellow colour but did not show any fluorescence. It is sparingly soluble in the common organic solvents.

Analysis :

10.50 mg. of the substance gave 26.42 mg. of carbon dioxide and 4.08 mg. of water.

Found : C = 68.66 % ; H = 4.35 %.

$C_{20}H_{14}O_6$ requires : C = 68.57 % ; H = 4.00 %.

7,7'-Dimethoxy-4,4'-dimethyl-6,6'-dicarbomethoxy-3,3'-bicoumarinyl.

Methyl-7-methoxy-3-iodo-4-methylcoumarin-6-carboxylate (1.87 g. ; 0.005 mole) dissolved in dry diphenyl ether (25 ml.) was treated with copper bronze (0.9 g. ; 0.015 mole) and the mixture refluxed on a wire gauze for 2 hours. The reaction mixture was then filtered hot and the filtrate on cooling was diluted with petroleum ether (60-80°). The product which separated recrystallised from acetic acid in fine yellow needles, m.p.286°. Yield 0.25 g.

Analysis :

8.70 mg. of the substance gave 20.14 mg. of carbon dioxide and 3.28 mg. of water.

Found : C = 63.17 % ; H = 4.22 %.

$C_{26}H_{22}O_{10}$ requires : C = 63.15 % ; H = 4.45 %.

Methyl-7-methoxy-4-methylcoumarin-6-carboxylate was isolated from the diphenyl ether mother liquor on working up as before.

7,7'-Dimethoxy-4,4'-dimethyl-6,6'-dicarboxy-3,3'-bicoumarinyl.

The above bicoumarinyl ester (0.5 g.) was refluxed on a steam bath for 2 hours with alcoholic potassium hydroxide solution (10 % ; 20 ml.). The product obtained on acidification was purified through sodium bicarbonate solution . It crystallised from glacial acetic acid in needles, m.p. 348° (effer.).

Analysis :

10.54 mg. of the substance gave 23.82 mg. of carbon dioxide and 3.92 mg. of water.

Found : C = 61.70 % ; H = ~~3~~4.16 %.

$C_{24}H_{18}O_{10}$ requires : C = 61.80 % ; H = 3.86 %.

The above acid (0.5 g.) in quinoline (10 ml.) was refluxed on a sand bath for half an hour with a speck of copper powder. The mixture was then filtered and poured in dilute hydrochloric acid solution. The separated product crystallised from acetic acid, m.p.268°. Mixed melting point with 7,7'-dimethoxy-4,4'-dimethyl-3,3'-bicoumarinyl described before was not depressed.

5,5'-Dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl.

5-Methoxy-8-iodo-4-methylcoumarin (1.58 g. ; 0.005 mole) dissolved in dry nitrobenzene (25 ml.) was treated with copper bronze (0.9 g. ; 0.015 mole) and the mixture refluxed on a wire gauze for 3 hours. The mixture was then filtered hot and the filtrate diluted with petroleum ether. The product which separated was refluxed with acetic acid (20 ml.) and filtered. The insoluble portion was crystallised from a large volume of acetic acid. It separated in a powder form, m.p. > 400°. Yield 0.1 g.

Analysis :

10.28 mg. of the substance gave 26.14 mg. of carbon dioxide and 4.78 mg. of water.

Found : C = 69.40 % ; H = 5.20 %.

$C_{22}H_{18}O_6$ requires : C = 69.84 % ; H = 4.76 %.

5-Methoxy-4-methylcoumarin was isolated from the mother liquors as in the previous experiments.

5,5'-Dihydroxy-4,4'-dimethyl-8,8'-bicoumarinyl.

5,5'-Dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl (0.5 g.) was heated with acetic anhydride (10 ml.) and hydriodic acid (d. 1.7 ; 10 ml.) in an oil bath at 130-140° for 2 hours. The product obtained on pouring the reaction mixture in cold sodium bisulphite solution was purified through dilute sodium hydroxide solution. It crystallised from acetic acid in small needles, m.p. > 400°. The product freely dissolved in sodium hydroxide solution with a yellow colour but was sparingly soluble in the common organic solvents.

Analysis :

8.98 mg. of the substance gave 22.42 mg. of carbon dioxide and 3.12 mg. of water.

Found : C = 68.13 % ; H = 3.89 %.

$C_{20}H_{14}O_6$ requires : C = 68.57 % ; H = 4.00 %.

5,5'-Dimethoxy-4,4'-dimethyl-6,6'-dicarbomethoxy-8,8'-bicoumarinyl.

Methyl-5-methoxy-8-iodo-4-methylcoumarin-6-carboxylate (1.87 g. ; 0.00 5 mole) dissolved in dry diphenyl ether (25 ml.) was treated with copper bronze (0.9 g. ; 0.015 mole) and the mixture refluxed on a wire gauze for 2 hours. The reaction mixture on working up as before gave a product which crystallised from acetic acid in colorless needles; m.p. 353°. Yield 0.15 g.

Analysis :

9.44 mg. of the substance gave 21.86 mg. of carbon dioxide and 3.90 mg. of water.

Found : C = 63.20 % ; H = 4.60 %.

$C_{26}H_{22}O_{10}$ requires : C = 63.15 % ; H = 4.45 %.

The motner liquors on working up as before gave methyl-5-methoxy-4-methylcoumarin-6-carboxylate.

5,5'-Dimethoxy-4,4'-dimethyl-6,6'-dicarboxy-8,8'-bicoumarinyl.

The above bicoumarinyl ester (0.5 g.) was refluxed with alcoholic potassium hydroxide solution (10 % ; 20 ml.) on a steam bath for 2 hours. The product which separated on acidification was purified through sodium bicarbonate solution. It crystallised from acetic acid in shining crystals, m.p.>400°.

Analysis :

8.12 mg. of the substance gave 18.28 mg. of carbon dioxide and 2.56 mg. of water.

Found : C = 61.44 % ; H = 3.52 %.

$C_{24}H_{18}O_{10}$ requires : C = 61.80 % ; H = 3.86 %.

The above acid (0.5 g.) in quinoline (10 ml.) was refluxed on a sand bath with a speck of copper powder for half an hour. The product which separated on working up as before and presumed to be 5,5'-dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl crystallised from glacial acetic acid, m.p. 400°.

Analysis :

5.08 mg. of the substance gave 12.960 mg. of carbon dioxide and 2.072 mg. of water.

Found : C = 69.61 % ; H = 4.56 %.

$C_{22}H_{18}O_6$ requires : C = 69.84 % ; H = 4.76 %.

Crossed Ullmann reaction between 7-methoxy-8-iodo-4-methylcoumarin and iodobenzene : 7-Methoxy-8-phenyl-4-methylcoumarin.

An intimate mixture of 7-methoxy-8-iodo-4-methylcoumarin (3.16 g. ; 0.01 mole), iodobenzene (4.12 g. ; 0.02 mole) and copper bronze (4 g., excess) was heated in an oil bath at 220-30° under reflux for 3 hours. The mixture was then cooled and extracted with petroleum ether (60-80°).

The prdouct obtained after removal of petroleum ether was found to be biphenyl. The reaction mixture was then extracted exhaustively with benzene. The product, obtained after removal of benzene was crystallised first from acetic acid and then from alcohol in colourless needles, m.p. 158°. Yield 0.35 g.

Analysis :

8.82 mg. of the substance gave 24.66 mg. of carbon dioxide and 3.88 mg. of water.

Found : C = 76.30 % ; H = 4.92 %.

$C_{17}H_{14}O_3$ requires : C = 76.68 % ; H = 5.26 %.

On further extraction of the reaction mixture successively with acetic acid and with diphenyl ether, 7,7'-dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl, described earlier was obtained.

7-Hydroxy-8-phenyl-4-methylcoumarin.

7-Methoxy-8-phenyl-4-methylcoumarin (0.3 g.) was heated with acetic anhydride (5 ml.) and hydriodic acid (5 ml. ; d. 1.7) in an oil bath at 130-40° for 2 hours. The reaction mixture on working up as before, gave a product which crystallised from dilute acetic acid in colourless needles, m.p.184°. It dissolved in sodium hydroxide solution with a bright blue fluoresence.

Analysis :

10.26 mg. of the substance gave 28.80 mg. of carbon dioxide and 4.48 mg. of water.

Found : C = 76.60 % ; H = 4.88 %.

$C_{16}H_{12}O_3$ requires : C = 76.19 % ; H = 4.76 %.

Methyl-7-methoxy-8-phenyl-4-methylcoumarin-6-carboxylate.

Methyl-7-methoxy-8-iodo-4-methylcoumarin-6-carboxylate (3.72 g. ; 0.01 mole) in dry nitrobenzene (25 ml.) was refluxed with iodobenzene (4.12 g. ; 0.02 mole) and copper bronze (4 g. ; excess) for 3 hours. The reaction mixture was then filtered hot and the filtrate dilute with petroleum ether (60-80°). The separated product crystallised from acetic acid in yellow needles, m.p. 250°. Mixed melting point with 7,7'-dimethoxy-4,4'-dimethyl-6,6'-dicarbomethoxy-8,8'-bicoumarinyl was not depressed.

The product obtained on removal of nitrobenzene from the mother liquor by steam distillation crystallised from acetic acid in needles, m.p. 168°. Yield 0.62 g.

<u>Analysis</u> :

9.14 mg. of the substance gave 23.60 mg. of carbon dioxide and 4.12 mg. of water.

Found : C = 70.46 % ; H = 5.04 %.

$C_{19}H_{16}O_5$ requires : C = 70.37 % ; H = 4.93 %.

7-Methoxy-8-phenyl-4-methylcoumarin-6-carboxylic acid.

The above coumarin ester (0.5 g.) was refluxed with alcoholic potassium hydroxide solution (10 % ; 20 ml.) on a steam bath for 2 hours. The product obtained on acidification was purified through sodium bicarbonate solution. It crystallised from acetic acid in needles, m.p. 258°.

<u>Analysis</u> :

9.54 mg. of the substance gave 24.32 mg. of carbon dioxide and 4.14 mg. of water.

Found : C = 69.57 % ; H = 4.85 %.

$C_{18}H_{14}O_5$ requires : C = 69.67 % ; H = 4.51 %.

The above acid (0.5 g.) in quinoline (5 ml.) was heated in an oil bath at 200° with a speck of copper powder for half an hour. The mixture was then filtered and poured in dilute hydrochloric acid solution. The separated product crystallised from rectified spirit in needles, m.p. 158°. Mixed melting point with 7-methoxy-8-phenyl-4-methylcoumarin described earlier was not depressed.

5-Methoxy-8-phenyl-4-methylcoumarin.

An intimate mixture of 5-methoxy-8-iodo-4-methylcoumarin (3.16 g. ; 0.01 mole), iodobenzene (4.12 g. ; 0.01 mole) and copper bronze (4 g., excess) was heated in an oil bath at 260° under reflux for 3 hours. The mixture was then cooled and extracted with petroleum ether (60-80°). The product obtained after removal of petroleum ether was found to be biphenyl. The reaction mixture was next repeatedly extracted with benzene. The product obtained after removal of benzene crystallised from rectified spirit in fine colourless needles, m.p. 156-158°. Yield 0.6 g.

Analysis :

7.96 mg. of the substance gave 22.26 mg. of carbon dioxide and 3.64 mg. of water.

Found : C = 76.32 % ; H = 5.11 %.

$C_{17}H_{14}O_3$ requires : C = 76.69 % ; H = 5.26 %.

The reaction mixture was finally extracted with diphenyl ether. 5,5'-Dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl, described earlier, was obtained on removal of the diphenyl ether by steam distillation.