CHAPTER III

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

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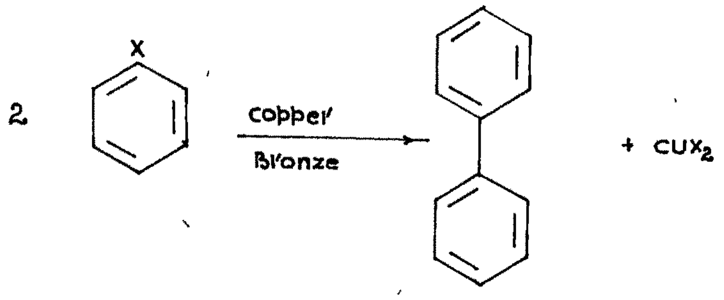
Ullmann reaction on some iodocoumarins : Synthesis of some bicoumarinyl and 8-phenylcoumarin derivatives

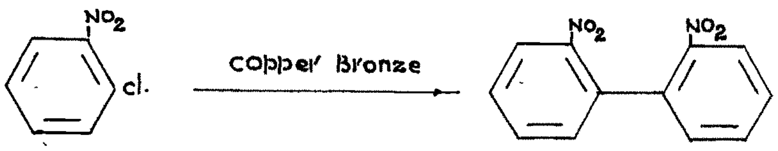
The reaction involving the removal of halogen atoms from aromatic halocompounds with the resulting union of two carbon atoms, when accomplished by the use of copper bronze has come to be known as the Ullmann reaction.

The synthesis devised by Ullmann is of general applicability and has found wide use in the preparation of many symmetrical and unsymmetrical biaryls which would otherwise be difficult to obtain. The Ullmann reaction has been reviewed by Fanta (Chem. Revs., 1946, 38, 139).

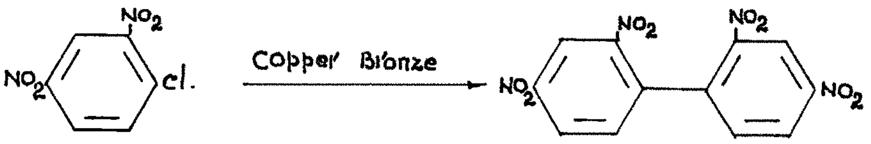


The success of the Ullmann reaction is dependent upon the nature of the aromatic halide. It has been observed that chlorine, bromine and iodine may be eliminated with biaryl formation. Aromatic fluorine atom has not been reported to be active in the Ullmann reaction. The order of reactivity of halogens is $I > Br > Cl$. In general the latter two substituents undergo reaction only when activating groups are present in the aromatic nucleus.

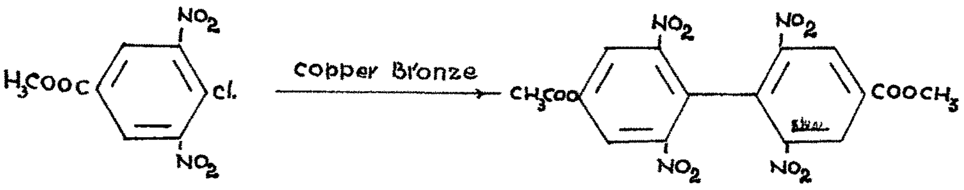
Ullmann (Ber., 1901, 34, 2174) observed that electronegative groups in the ortho and para positions with respect to the halogen atom activate the molecule. The nitro group is the most effective activator. Thus (I) gave in nitrobenzene 60 % yield of (II), (IV) was obtained in 60 % yield from (III) and (VI) was obtained in 54 % yield from (V).



I II



III IV



V VI

Ullmann (Ann., 1904, 332, 38) observed decrease in yield of biaryls when groups such as NH_2, $NHCOCH_3$, COOH, and OH are present in the aromatic nucleus, because they give rise to amination, decarboxylation, or ether formation as a side reaction. The amino groups must be protected by alkylation or 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-trichloroiodobenzene in 52 % yield but the yield of the biaryl derivative from 2,4,6-trimethyl iodobenzene was poor.

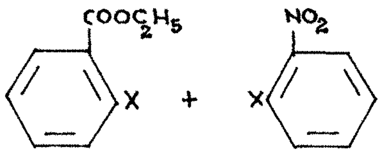
The generalizations regarding the effect of substituents on the Ullmann reaction on derivative of benzene may be applied to other aromatic compounds according to the usual concepts of aromaticity.

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

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

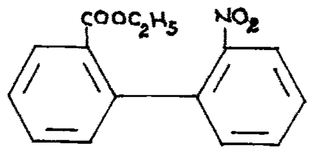
In the reaction of RX + R'X' if RX is more reactive then RX would be completely used up in the formation of RR. When the reaction is continued for a longer time or under more drastic conditions, R'X' reacts to give R'R'. The symmetrical biaryls are the only products of the reaction. In such a case the 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 and co-workers

(J. Chem. Soc., 1944, 71) obtained it in 68 % yield from (C) and (D). In the latter case both the components are of more nearly equal reactivity since the lower activity of bromine as compared to iodine is compensated by the greater activation effect of the nitro group as compared to the carbalkoxyl group.



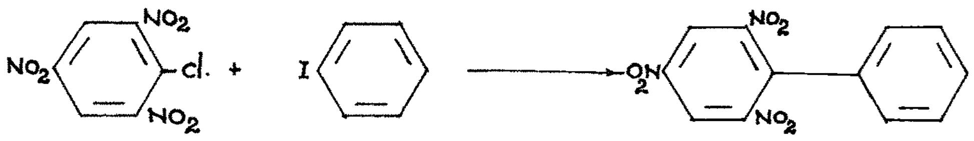
B , X = Br　　D , X = Br

C , X = I　　E , X = I

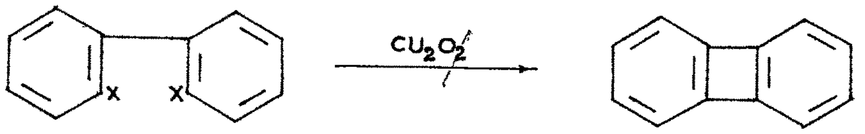


A

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 biaryls differ sufficiently. Another condition which favours the unsymmetrical biaryl formation is the presence of an excess of the less reactive component. Rule and Smith (J. Chem. Soc., 1937, 1096) studied the reaction of picryl chloride and iodobenzene and obtained 2,4,6-trinitrodiphenyl as the only detectable product.

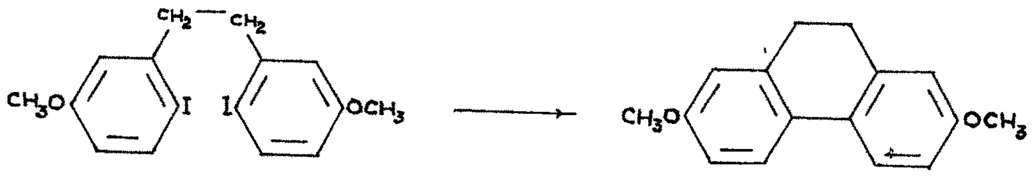


Several intramolecular Ullmann reactions have also been reported in literature. Lothrop (J. Am. Chem. Soc., 1941, 63, 1187 ; 1942, 64, 1698) reported the synthesis of biphenylene and several of its derivatives by the treatment of appropriately substituted 2,2'-dihalogen biphenyls with cuprous oxide.

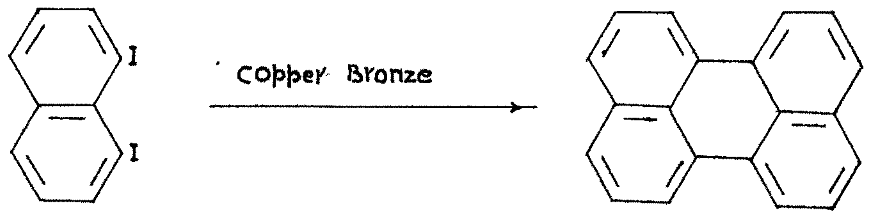


Cu_2O

Cornforth and Robinson (J. Chem. Soc., 1942,684) synthesised 2,7-dimethoxy-9,10-dihydrophenanthrene in intramolecular Ullmann reaction on appropriately substituted dibenzyl derivative.



Cyclic products may also be obtained when polyhalogenated compounds are subjected to the conditions of Ullmann reaction. Thus 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, 2047) successfully used freshly precipitated copper. This was prepared by treatment of zinc dust with copper sulphate solution followed by washing with alcohol and ether and drying. 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 and drying in a desiccator. They state that whereas ordinary copper bronze at times gives poor results in the Ullmann reaction, this simple treatment ensures more uniform results and frequently makes possible a more rapid reaction at lower temperature.

A 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 the 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. Usually the 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 diluent. Mann and co-workers (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.

Mechanism

Rapson and Shuttleworth (Nature, 1941, 147, 675) suggested the possibility of a free redical mechanism for this reaction. However, in all cases in which the Ullmann reaction has been carried out in the usual way, biaryl bond formation was observed to occur only at the carbon atom from which a reactive halogen atom had been displaced. Since the existence of the free radical intermediate would be expected often to lead to a variety of products, it cannot be considered a possible plausible mechanism for the normal reaction.

Gilman and Straley (Rec. trav. chim., 1936, 55,821) who studied the preparation and reaction 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.

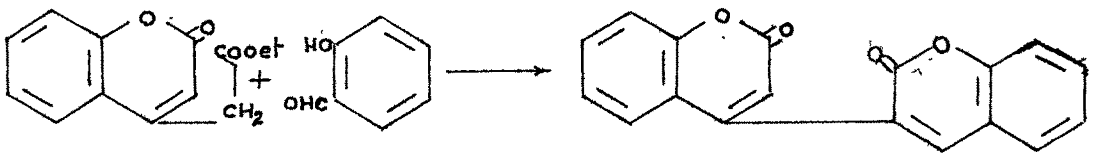
A possible mechanism of the reaction consists of two conse~~qu~~cutive steps (1) A nucleophillic reaction of copper with the aromatic halide to form an activated complex at the metal surface. The occurrence of this step is governed largely by the nature of the aromatic halide. (2) The reaction of the activated complex with a second molecule of aromatic halide to form a biaryl molecule plus copper halide. This reaction is governed to a greater extent by Steric effect.

Synthesis of bicoumarinyls and 8-phenylcoumarins

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 such as (II) 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. Huebener and Link (J. Am. Chem. Soc., 1945, 67, 99) reported the formation of the bicoumarinyl derivative from 3-bromo-4-methoxycoumarin by Ullmann reaction. Harle and 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 phenylcoumarins are known, 3-phenylcoumarins are known and have been prepared (1) by condesning o-hydroxyaldehydes with phenyl acetonitrile in presence of sodium ethoxide (Borsche and Streitberger, Ber., 1904, <u>37</u>, 3165) (2) by Meerwein reaction by the condensation of a coumarin with simple or substituted diazotised aniline. Meerwein and co-workers (J. Prakt. Chem., 1939, <u>152</u>, 237) prepared 3-phenylcoumarin by the above method.



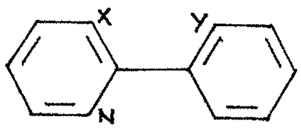
I

II

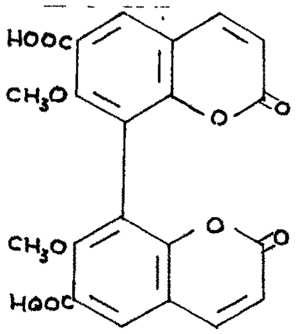
(3) By condensing o-formylacetonitrile and its derivatives with phenols such as resorcinol in presence of phosphorus oxychloride (Baker et al., J. Chem. Soc., 1931, 1541) and (4) by heating o-hydroxy acetophenone with phenyl acetate and acetic anhydride. 4-Phenylcoumarins have been obtained by Pechmann condensation of ethyl benzoylacetate with various phenols in presence of sulphuric acid (80 %) Pechmann and Duisberg Ber., 1883, <u>16</u>, 2119). Cramer and Windel (Ber., 1956, <u>89</u>, 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 benzene sulphonate by Aleykutti 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 synthesise these from the iodocoumarins described in Chapter II by the Ullmann reaction. Further, as is well known, diaryl derivatives with ~~at least~~ two or 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.



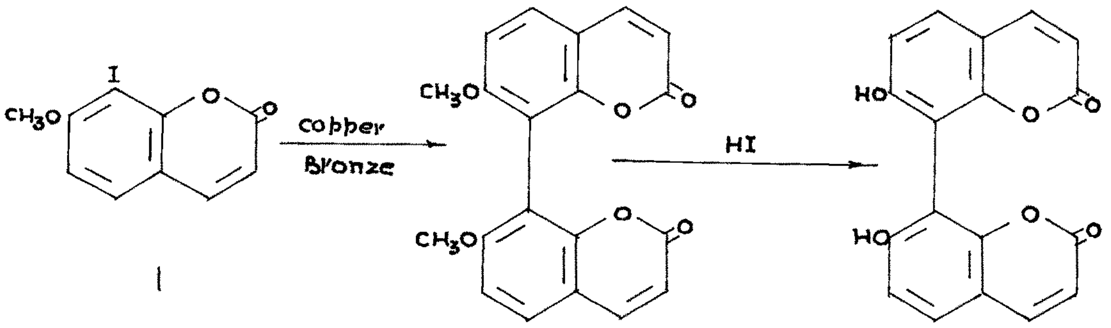
(A)



(B)

7,7'-Dimethoxy-8,8'-bicoumarinyl

7-Methoxy-8-iodocoumarin (I) when treated with copper bronze in boiling diphenyl ether gave a mixture of two products, (A) m.p. 378° and (B) m.p. 118°. The product (B) was found to be identical with 7-methoxycoumarin on direct comparison. The product (A), sparingly soluble in the common organic solvents, has been assigned the 7,7'-dimethoxy-8,8'-bicoumarinyl structure (II). On demethylation with hydriodic acid in acetic anhydride it gave 7,7'-dihydroxy-8,8'-bicoumarinyl (III). The resolution of this compound could not be attempted because of the low yield of this compound and very sparing solubility in organic solvents.



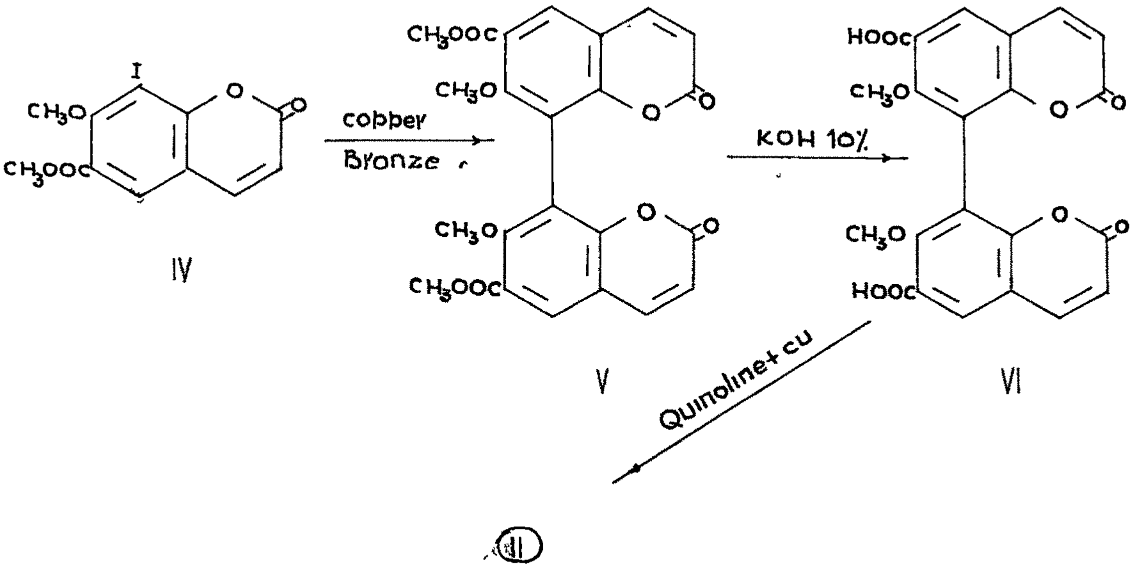
I II III

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

Methyl 7-methoxy-8-iodocoumarin-6-carboxylate (IV) in boiling diphenyl ether when treated with copper bronze gave a product having m.p. 268° which has been assigned

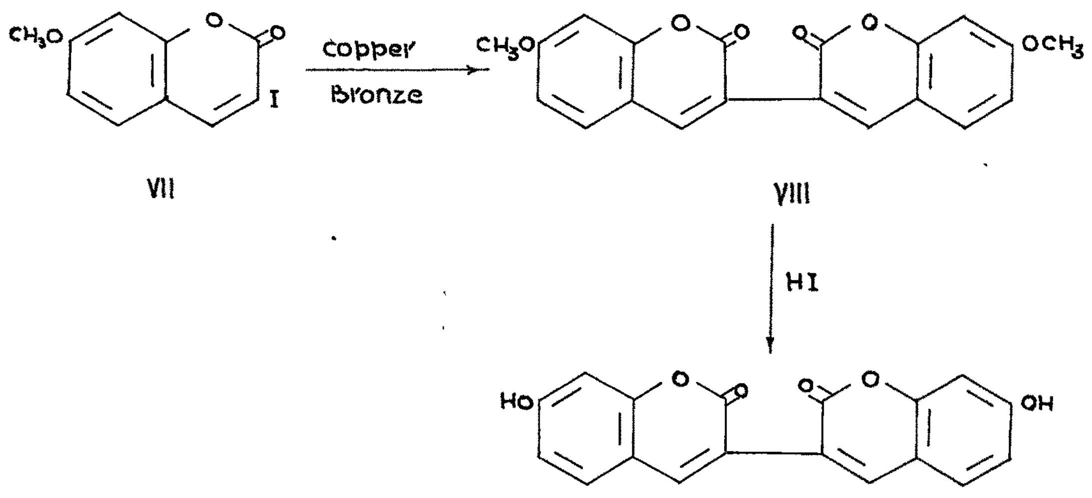
7,7'-dimethoxy-6,6'-dicarbomethoxy-8,8'-bicoumarinyl (V) structure. Methyl-7-methoxycoumarin-6-carboxylate was isolated from the mother liquor.

On hydrolysis with alcoholic potassium hydroxide solution (V) gave ~~the corresponding~~ 7,7'-dimethoxy-6,6'-dicarboxy-8,8'-bicoumarinyl (VI) which on decarboxylation yielded 7,7'-dimethoxy-8,8'-bicoumarinyl (II) described earlier. Attempts to prepare (-)brucine salt of the acid (VI) to see if this acid could be resolved into optical isomers, did not succeed on account of the sparing solubility of the acid in various organic solvents.



7,7'-Dimethoxy-3,3'-bicoumarinyl

7-Methoxy-3-iodocoumarin (VII) when heated with copper bronze in boiling diphenyl ether gave a product m.p. 295° to which the 7,7'-dimethoxy-3,3'-bicoumarinyl (VIII) structure has been assigned. 7-Methoxycoumarin was isolated from the mother liquor. On demethylation in acetic anhydride with hydriodic acid, (VIII) yielded 7,7'-dihydroxy-3,3'-bicoumarinyl (IX).



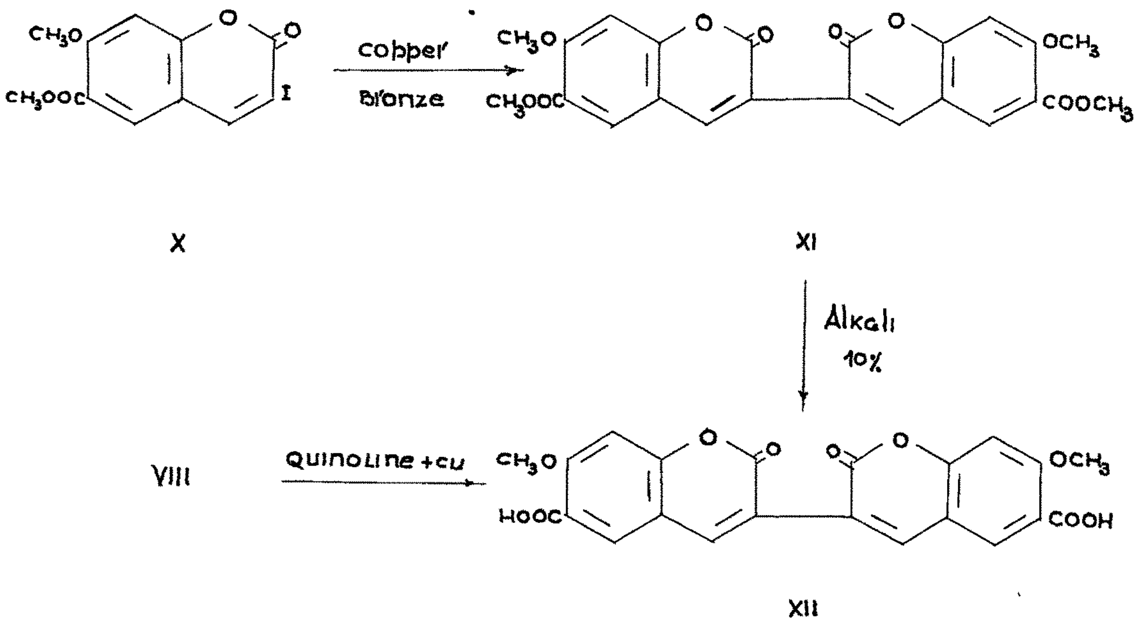
VII

VIII

IX

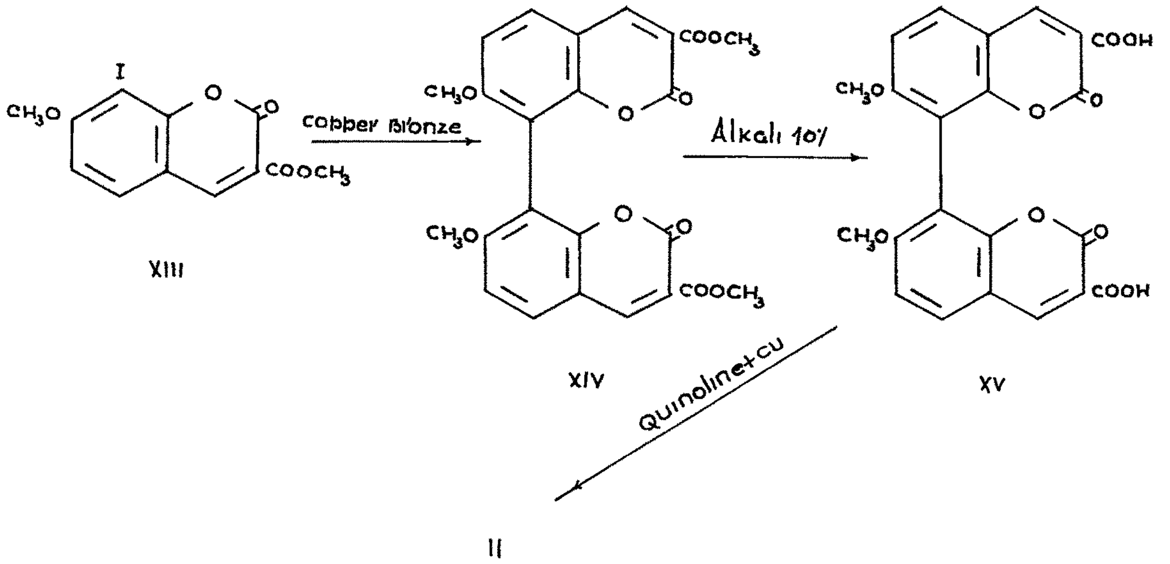
7,7'-Dimethoxy-6,6'-dicarbomethoxy-3,3'-bicoumarinyl

Methyl-7-methoxy-3-iodocoumarin-6-carboxylate (X) when treated with copper bronze in boiling diphenyl ether gave a product, m.p. 326°. 7,7'-Dimethoxy-6,6'-dicarbomethoxy-3,3'-bicoumarinyl (XI a) structure has been assigned to this product. Methyl-7-methoxycoumarin-6-carboxylate was also isolated as the only other product from the reaction mixture. On hydrolysis with alcoholic potassiun hydroxide solution (XI a) gave the corresponding acid (XI b) which on decarboxylation yielded 7,7'-dimethoxy-3,3'-bicoumarinyl (VIII) described earlier.



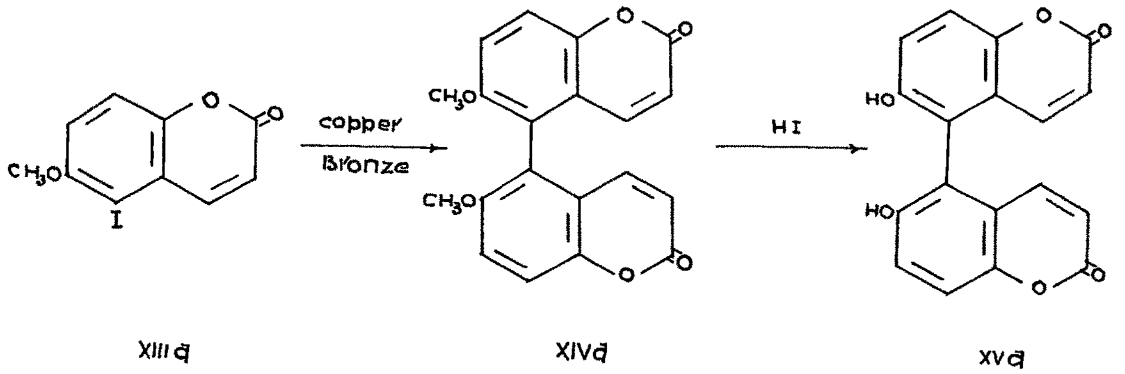
7,7'-Dimethoxy-3,3'-dicarbomethoxy-8,8'-bicoumarinyl

Methyl 7-methoxy-8-iodocoumarin-3-carboxylate (XIII) in boiling diphenyl ether when treated with copper bronze gave a product, m.p. 322° which has been assigned 7,7'-dimethoxy-3,3'-dicarbomethoxy-8,8'-bicoumarinyl (XIV) structure. Methyl 7-methoxycoumarin-3-carboxylate was isolated from the mother liquor. On hydrolysis with alcoholic potassium hydroxide solution (XIV) gave the corresponding dicarboxylic acid (XV) which on decarboxylation yielded 7,7'-dimethoxy-8,8'-bicoumarinyl (II) described earlier.



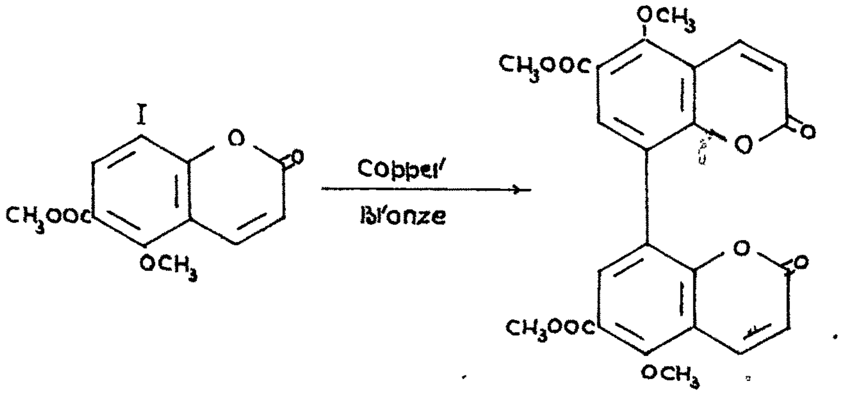
6,6'-Dimethoxy-5,5'-bicoumarinyl

6-Methoxy-5-iodocoumarin (XIII a) when treated with copper bronze in boiling diphenyl ether solution gave a product m.p. 292° which has been assigned the 6,6'-dimethoxy-5,5'-bicoumarinyl (XIV a) structure. 6-Methoxycoumarin was also isolated from the reaction mixture. On demethylation it yielded 6,6'-dihydroxy-5,5'-bicoumarinyl (XV a).



5,5'-Dimethoxy-6,6'-dicarbomethoxy-8,8'-bicoumarinyl

Methyl-5-methoxy-8-iodocoumarin-6-carboxylate (XVI) when treated with copper bronze in boiling diphenyl ether gave a product m.p. 241-242° which has been assigned the 5,5'-dimethoxy-6,6'-dicarbomethoxy-8,8'-bicoumarinyl (XVII) structure. Search for other products in the original mother liquor led to the isolation of only methyl-5-methoxycoumarin-6-carboxylate.



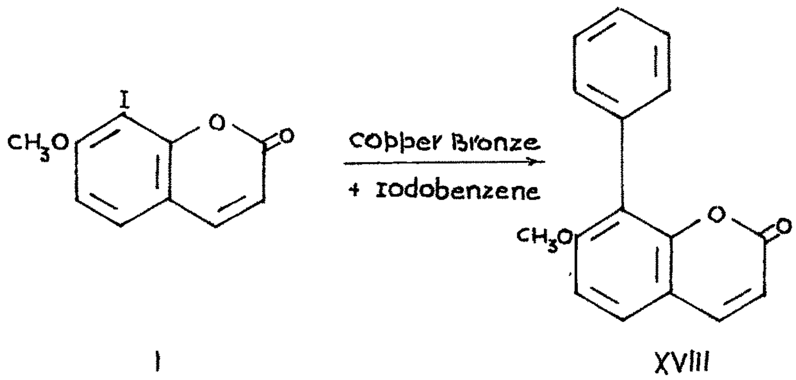
XVI

XVII

Synthesis of 8-phenylcoumarin derivatives

7-Methoxy-8-phenylcoumarin

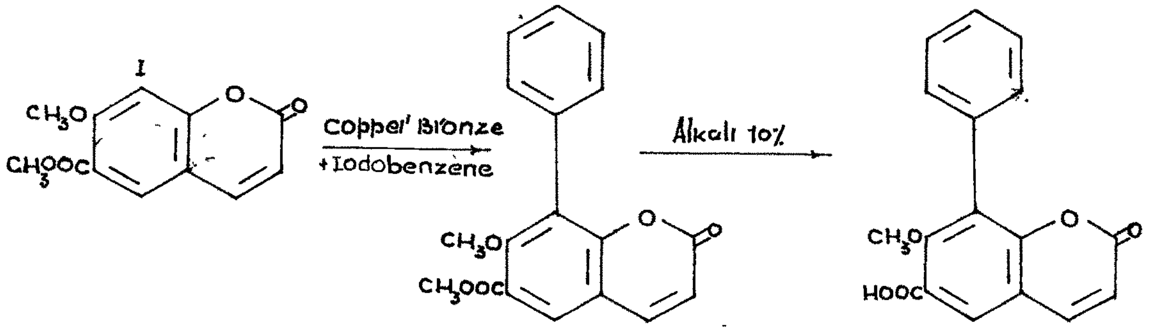
7-Methoxy-8-iodocoumarin (I) when heated with iodo-benzene and copper bronze at 220-225° gave a mixture of various products from which 7-methoxy-8-phenylcoumarin (XVIII) was isolated by fractional crystallisation. Other products isolated and identified were biphenyl and 7,7'-dimethoxy-8,8'-bicoumarinyl (II) mentioned earlier. Yield of the 8-phenyl-coumarin (XVIII) was very poor when diphenyl ether or nitrobenzene was used as solvent.



I XVIII

Methyl 7-methoxy-8-phenylcoumarin-6-carboxylate

Methyl 7-methoxy-8-iodocoumarin-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-phenylcoumarin-6-carboxylate (XIX) was isolated by fractional crystallisation. Other products isolated and identified were biphenyl and 7,7'-dimethoxy-6,6'-dicarbomethoxy-8,8'-bicoumarinyl (V) mentioned earlier. Yields of 8-phenylcoumarin ester (XIX) were poor when a solvent was not employed. On heating with alcoholic potassium hydroxide solution (XIX) gave the corresponding acid (XX) which on decarboxylation yielded 7-methoxy-8-phenylcoumarin (XVIII) described earlier.



IV XIX XX

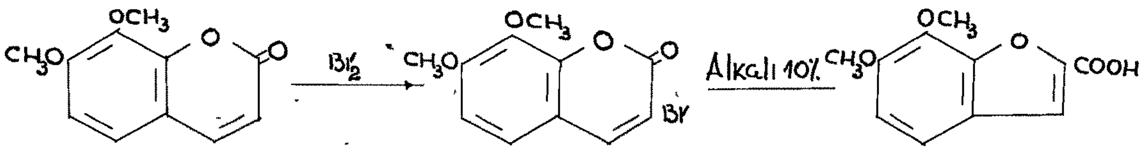
Attempted Ullmann reaction on methyl 7-methoxy-8-iodocoumarin-4-acetate

Methyl 7-methoxy-8-iodocoumarin-4-acetate was subjected to Ullmann reaction with and without solvent. In both the experiments 7-methoxy-4-methylcoumarin was recovered. No bicoumarinyl derivative was obtained.

Attempted synthesis of bicoumarinyls from the monobromo derivatives of (a) 7,8-dimethoxycoumarin and (b) naphtha-1,2-α-pyrone

As the iodination of 7,8-dihydroxycoumarin and naphtha-1,2-α-pyrone did not succeed it was thought of interest to see if the mono bromo derivatives of these compounds would undergo Ullmann reaction to yield bicoumarinyl derivatives.

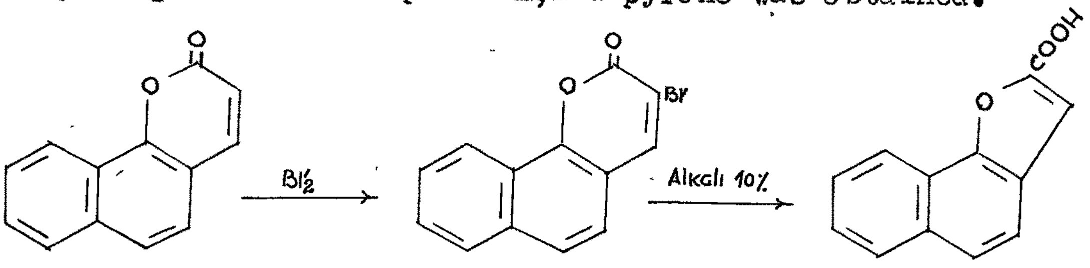
(a) Neither 7,8-dihydroxycoumarin nor 7,8-dimethoxycoumarin has been previously brominated. On bromination with one mole of bromine in acetic acid 7,8-dimethoxycoumarin gave a mono bromo derivative ~~(XXII)~~ which gave a coumarilic acid derivative on heating with alkali indicating that the bromine atom had entered the 3-position. 7,8-Dimethoxy-3-bromocoumarin (XXII) structure has therefore been assigned to this product. When this was subjected to Ullmann reaction with and without solvent no bicoumarinyl derivative was obtained. Only 7,8-dimethoxycoumarin was recovered. The bromine was eliminated in this reaction.



XXI XXII XXIII

(b) Naphtha-1,2-α-pyrone has also not been previously brominated. On bromination with one mole of bromine no pure product was obtained but with two moles of bromine a monobromo product was obtained which gave a coumarilic acid derivative with alcoholic alkali. The monobromo compound is therefore assigned the 3'-bromo structure (XXV) and the coumarilic acid has therefore structure (XXVI).

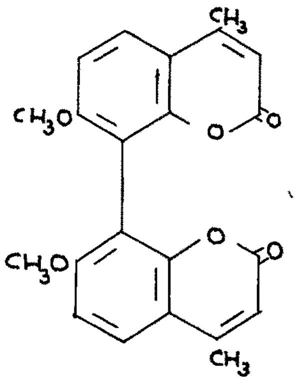
When this was subjected to Ullmann reaction with and without solvent no bicoumarinyl derivative was obtained. Only original bromo-naphtha-1,2-α-pyrone was obtained.



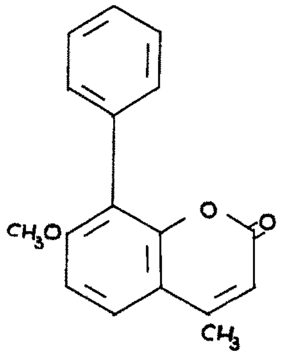
XXIV XXV XXVI

With a view to see if a bromocoumarin with bromine in the benzenoid part, would undergo this reaction or not, an attempt was made to synthesise 7-hydroxy-6-bromocoumarin by the condensation of 4-bromoresorcinol with malic acid in the presence of concentrated sulphuric acid. The condensation however did not yield a pure product. It was therefore decided to carry out the Ullmann reaction with the more easily accessible 7-methoxy-8-bromo-4-methylcoumarin which was prepared as described in chapter VI (P-190). When this was subjected to Ullmann reaction 7,7'-dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl (XXVII) was obtained as seen by direct comparison with a specimen prepared according to Lele, Patel and Sethna (J. Chem. Soc., 1961, 969-971).

The 8-bromo derivative also underwent crossed Ullmann reaction with iodobenzene to give 7-methoxy-8-phenyl-4-methylcoumarin (XXVIII) as seen by direct comparison with the product obtained by Lele et al. (loc.cit.)



XXVII



XXVIII

The molecular weights of the bicoumarinyl derivatives could not be determined by the Rast method because of the sparing solubility of the bicoumarinyl derivatives in camphor.

The yields of the bicoumarinyl derivatives ranged from 63 % for 7,7'-dimethoxy-6,6'-carbomethoxy-8,8'-bicoumarinyl to 16 % for 7,7'-dimethoxy-6,6'-dicarbomethoxy-3,3'-bicoumarinyl.

EXPERIMENTAL

Ullmann reaction on 7-methoxy-8-iodocoumarin : 7,7'-Dimethoxy-8,8'-bicoumarinyl

7-Methoxy-8-iodocoumarin (3.02 g. ; 0.01 mole) dissolved in dry diphenyl ether (40 ml.) was treated with copper bronze (1.8 g. ; 0.03 mole) and the mixture refluxed on a wire gauze for 2 hours with an air condensor. The reaction mixture was filtered while hot and the filtrate was then cooled and diluted with petroleum ether (b.p. 60-80°) with vigorous stirring. A mixture of various products was obtained. It was dissolved in large amount of acetic acid and refluxed with animal charcoal. The product which separated on cooling crystallised from the same solvent in shining thin plates, m.p. 376°. Yield 0.8 g. It was sparingly soluble in common organic solvents such as alcohol, acetone, acetic acid, benzene and ether.

Analysis :

10.12 mg. of the substance gave 25.26 mg. of carbon dioxide and 3.96 mg. of water.

Found : C = 68.10 % ; H = 4.40 %.

$C_{20}H_{14}O_6$ requires : C = 68.60 % ; H = 4.10 %.

The product obtained on diluting the acetic acid solution and also on removal of diphenyl ether from the original mother liquor by steam distillation was found on direct comparision to be 7-methoxycoumarin.

7,7'-Dihydroxy-8,8'-bicoumarinyl

The above bicoumarinyl derivative (0.5 g.) was heated in acetic anhydride (8 ml.) solution with hydriodic acid (8 ml. d. 1.7) in an oil bath at 130-140° for 2 hours. The reaction mixture was then cooled and poured in ice cold sodium bisulphite solution. The product obtained was purified through dilute sodium hydroxide solution. It came down from acetic acid as an amorphous powder, m.p. 390°.

Analysis :

10.18 mg. of the substance gave 24.94 mg. of carbon dioxide and 2.94 mg. of water.

Found : C = 66.90 % ; H = 3.20 %.

$C_{18}H_{10}O_6$ requires : C = 67.10 % ; H = 3.10 %.

The product readily dissolved in sodium hydroxide solution. Neither alkaline solution nor the sulphuric acid solution of the product showed any fluorescence. Its alcoholic solution did not give any colouration with alcoholic ferric chloride.

Ullmann reaction on methyl-7-methoxy-8-iodocoumarin-6-carboxylate : 7,7'-Dimethoxy-6,6'-dicarbomethoxy-8,8'-bicoumarinyl

Methyl-7-methoxy-8-iodocoumarin-6-carboxylate (3.6 g. ; 0.01 mole) dissolved in dry diphenyl ether (40 ml.) was treated with copper bronze (1.8 g. ; 0.03 mole) and the mixture refluxed with an air condenser on a wire gauze for 3 hours. The reaction mixture on working up as before gave a product which on repeated crystallisation from acetic acid

(charcoal) gave thin plates, m.p. 268°. Yield 1.1 g.

Analysis :

10.44 mg. of the substance gave 23.60 mg. of carbon dioxide and 3.09 mg. of water.

Found : C = 61.70 % ; H = 4.20 %.

$C_{24}H_{18}O_{10}$ requires : C = 61.80 % ; H = 3.90 %.

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-methoxycoumarin-6-carboxylate.

7,7'-Dimethoxy-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 mixture was then cooled, diluted with water and acidified with hydrochloric acid. The separated product was purified through sodium bicarbonate solution. It crystallised from acetic acid in needles, m.p. 310° (decomp.).

Analysis :

10.52 mg. of the substance gave 23.42 mg. of carbon dioxide and 3.42 mg. of water.

Found : C = 60.80 % ; H = 3.60 %.

$C_{22}H_{14}O_{10}$ requires : C = 60.30 % ; H = 3.20 %.

The above acid (0.5 g.) in quinoline (10 ml.) was refluxed on a sand bath with a small amount of copper powder for half an hour. The mixture was then filtered and poured in dilute hydrochloric acid. The separated product was washed with sodium bicarbonate solution to remove unreacted acid and then crystallised from glacial acetic acid in thin plates, m.p. 376°. Mixed m.p. with 7,7'-dimethoxy-8,8'-bicoumarinyl described earlier, was not depressed.

7,7'-Dimethoxy-3,3'-bicoumarinyl

7-Methoxy-3-iodocoumarin (3.02 g. ; 0.01 mole) dissolved in dry diphenyl ether (30 ml.) was treated with copper bronze (1.80 g. ; 0.03 mole) and the mixture refluxed with an air condenser on a wire gauze for 2 hours. The reaction mixture on working up as before gave a product which crystallised from acetic acid in thin yellow plates, m.p. 295°. Yield 0.5 g.

Analysis :

9.88 mg. of the substance gave 24.72 mg. of carbon dioxide and 3.72 mg. of water.

Found : C = 68.30 % ; H = 4.20 %.

$C_{20}H_{14}O_6$ requires : C = 68.60 % ; H = 4.10 %.

7-Methoxycoumarin was recovered on diluting the acetic acid filtrate and on steam distillation of the diphenyl ether from the original mother liquor.

7,7'-Dihydroxy-3,3'-bicoumarinyl

The above bicoumarinyl (0.5 g.) was heated with acetic anhydride (8 ml.) and hydriodic acid (8 ml. ; d. 1.7) in an oil bath at 130-140° for 2 hours. The product obtained on pouring the reaction mixture in ice cold sodium bisulphite solution was purified through sodium hydroxide solution. It crystallised from a large amount of acetic acid as yellow powder, m.p. > 400°. It was very sparingly soluble in acetic acid, alcohol and acetone.

The product freely dissolved in sodium hydroxide solution with deep yellow colour without any fluorescence. With sulphuric acid also it did not give any fluorescence.

Analysis :

8.24 mg. of the substance gave 20.32 mg. of carbon dioxide and 2.58 mg. of water.

Found : C = 67.30 % ; H = 3.50 %.

$C_{18}H_{10}O_6$ requires : C = 67.10 % ; H = 3.10 %.

Ullmann reaction on methyl-7-methoxy-3-iodocoumarin-6-carboxylate : 7,7'-Dimethoxy-6,6'-dicarbomethoxy-3,3'-bicoumarinyl

Methyl-7-methoxy-3-iodocoumarin-6-carboxylate (1.80 g. ; 0.005 mole) dissolved in diphenyl ether (20 ml.) was treated with copper bronze (0.9 g. ; 0.15 mole) and the mixture was refluxed with an air condenser on a wire gauze for 3 hours. The reaction mixture on working up as before gave a product which crystallised from acetic acid in shining needles, m.p. 326°. Yield 0.3 g.

Analysis :

10.62 mg. of the substance gave 23.84 mg. of carbon dioxide and 4.08 mg. of water.

Found : C = 61.30 % ; H = 4.30 %.

$C_{24}H_{18}O_{10}$ requires : C = 61.80 % ; H = 3.90 %.

On steam distilling the diphenyl ether from the mother liquor ~~the~~ methyl-7-methoxycoumarin-6-carboxylate was obtained.

7,7'-Dimethoxy-6,6'-dicarboxy-3,3'-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 obtained on acidification was purified through sodium bicarbonate solution. It crystallised from glacial acetic acid in shining thin plates, m.p. 365° (decomp.)

Analysis :

10.30 mg. of the substance gave 22.68 mg. of carbon dioxide and 3.24 mg. of water.

Found : C = 60.10 % ; H = 3.50 %.

$C_{22}H_{14}O_{10}$ requires : C = 60.30 % ; H = 3.20 %.

The above acid (0.5 g.) in quinoline (5 ml.) was refluxed on a sand bath for half an hour with a speck of copper powder. The product obtained on working up as before crystallised from acetic acid in thin plates, m.p. 295°. Mixed m.p. with 7,7'-dimethoxy-3,3'-bicoumarinyl described earlier was not depressed.

Attempted Ullmann reaction on methyl 7-methoxy-8-iodocoumarin-4-acetate

Methyl 7-methoxy-8-iodocoumarin-4-acetate (3.74 g. ; 0.01 mole) dissolved in dry diphenyl ether (40 ml.) and copper bronze (1.8 g. ; 0.03 mole) were refluxed on a wire gauze for 2 hours. The reaction mixture was filtered while hot and the filtrate was diluted with petroleum ether (b.p. 60-80°). The separated paste was decanted. This was non crystallisable.

The mother liquor was steam distilled and the solution was extracted with ether. On removal of ether a pasty product was ~~not~~ obtained. This paste was dissolved in benzene and chromatographed over alumina with petroleum ether (b.p. 60-80°) as eluent. The only product separated was 7-methoxy-4-methylcoumarin as seen by direct comparision with an authentic specimen.

(ii) Methyl 7-methoxy-8-iodocoumarin-4-acetate (3.74 g. ; 0.01 mole) was mixed with copper bronze (1.8 g. ; 0.03 mole) and heated at 220° for 2 hours. The reaction mixture was cooled and extracted with petroleum ether (b.p. 60-80°) and then with benzene. On removal of benzene a paste was obtained which was chromatographed over alumina. The product obtained was 7-methoxy-4-methylcoumarin as seen by direct comparis~~i~~on with an authentic specimen.

Ullmann reaction on methyl 7-methoxy-8-iodocoumarin 3-carboxylate : 7,7'-Dimethoxy-3,3'-dicarbomethoxy-8,8'-bicoumarinyl

Methyl 7-methoxy-8-iodocoumarin-3-carboxylate (1.8 g. ; 0.005 mole) in diphenyl ether (10 ml.) and copper bronze (0.9 g. ; 0.015 ml.) were refluxed for 3 hours. The product obtained on working up the reaction mixture was purified from acetic acid as yellowish white powder, m.p. 322°. Yield 0.1 g.

Analysis :

4.708 mg. of the substance gave 10.670 mg. of carbon dioxide and 1.712 mg. of water.

Found : C = 61.85 % ; H = 4.07 %.

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

The mother liquor on steam distillation left a residue which was found to be methyl 7-methoxycoumarin-3-carboxylate.

7,7'-Dimethoxy-3,3'-dicarboxy-8,8'-bicoumarinyl

The above bicoumarinyl ester (0.1 g.) was hydrolysed with alcoholic potassium hydroxide solution (10 ml.; 10 %) by refluxing on a steam bath for 2 hours. The product obtained on working up the reaction mixture as usual crystallised from acetic acid in small needles, m.p. 335°.

Analysis :

4.638 mg. of the substance gave 9.924 mg. of carbon dioxide and 1.320 mg. of water.

Found : C = 58.39 % ; H = 3.18 %.

$C_{22}H_{14}O_{10}$ H_2O requires: C = 57.89 % ; H = 3.50 %.

The above acid (0.1 g.) was refluxed with quinoline and copper powder for half an hour. The product obtained on working up as usual crystallised from acetic acid. M.P. and mixed melting point with 7,7'-dimethoxy-8,8'-bicoumarinyl was 378°.

Ullmann reaction on 6-methoxy-5-iodocoumarin : 6,6'-Dimethoxy-5,5'-bicoumarinyl

6-Methoxy-5-iodocoumarin (3.02 g. ; 0.01 mole) dissolved in dry diphenyl ether (20 ml.) was refluxed on a wire gauze with copper bronze (1.8 g. ; 0.03 mole) for 3 hours. The mixture was then filtered while hot and the filtrate diluted with petroleum ether. (b.p. 60-80°) The product which separated crystallised from acetic acid in thick needles, m.p. 292°. Yield 0.5 g.

Analysis :

10.28 mg. of the substance gave 25.70 mg. of carbon dioxide and 3.78 mg. of water.

Found : C = 68.21 % ; H = 4.11 %.

$C_{20}H_{14}O_6$ requires : C = 68.60 % ; H = 4.10 %.

6-Methoxycoumarin was isolated from the mother liquors.

6,6'-Dihydroxy-5,5'-bicoumarinyl

The above bicoumarinyl (0.5 g.) was heated with acetic anhydride (9 ml.) and hydriodic acid (9 ml. ; d. 1.7) 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 needles, m.p. 395-396°.

The product freely dissolved in sodium hydroxide solution with a yellow colour.

Analysis :

9.86 mg. of the substance gave 24.36 mg. of carbon dioxide and 3.18 mg. of water.

Found : C = 67.41 % ; H = 3.61 %.

$C_{18}H_{10}O_6$ requires : C = 67.10 % ; H = 3.10 %.

Ullmann reaction on methyl 5-methoxy-8-iodocoumarin-6-carboxylate : 5,5'-Dimethoxy-6,6'-dicarbomethoxy-8,8'-bicoumarinyl

Methyl 5-methoxy-8-iodocoumarin-6-carboxylate (1.80 g. ; 0.005 mole) dissolved in diphenyl ether (20 ml.) was ~~heated~~ refluxed 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 on repeated crystallisations from acetic acid gave colourless needles, m.p. 241-242°. Yield 0.3 g.

Analysis :

8.66 mg. of the substance gave 19.66 mg. of carbon dioxide and 3.24 mg. of water.

Found : C = 62.10 % ; H = 4.20 %.

$C_{24}H_{18}O_{10}$ requires : C = 61.80 % ; H = 3.90 %.

The mother liquors on working up as before gave methyl 5-methoxycoumarin-6-carboxylate.

Crossed Ullmann reaction between 7-methoxy-8-iodocoumarin and iodobenzene : 7-Methoxy-8-phenylcoumarin

An intimate mixture of 7-methoxy-8-iodocoumarin (3.02 g. ; 0.01 mole) iodobenzene (4.12 g. ; 0.02 mole) and copper bronze (4 g. excess) was heated in an oil bath at 220-225° under reflux for 3 hours. The mixture was then cooled and extracted with petroleum ether (60- 80°). The product obtained from petroleum ether was identified as biphenyl. The reaction mixture was then extracted several times with benzene. The product obtained on removal of benzene crystallised repeatedly from alcohol in colourless shining needles, m.p. 128-130°. Yield 0.5 g.

When the above reaction was carried out with nitrobenzene as solvent it gave an unworkable mass from which no pure product could be isolated.

Analysis :

10.32 mg. of the substance gave 28.58 mg. of carbon dioxide and 4.52 mg. of water.

Found : C = 75.60 % ; H = 4.90 %.

$C_{16}H_{12}O_3$ requires : C = 76.20 % ; H = 4.80 %.

After removal of the 8-phenylcoumarin the reaction mixture was extracted successively with acetic acid and with diphenyl ether and 7,7'-dimethoxy-8,8'-bicoumarinyl was obtained from these extracts.

(i) Attempted demethylation of 7-methoxy-8-phenylcoumarin

7-Methoxy-8-phenylcoumarin (0.3 g.) was heated with acetic anhydride (4 ml.) and hydriodic acid (4 ml. ; d. 1.7) in an oil bath at 130-140° for 2 hours. The reaction mixture was cooled and poured in sodium bisulphite solution. The separated product was treated with sodium hydroxide solution. The product obtained on acidification did not give a pure product from any solvent.

(ii) 7-Methoxy-8-phenylcoumarin (0.3 g.) was intimately mixed with powdered anhydrous aluminium chloride (0.3 g.) and the mixture heated in an oil bath at 120-130° for 2 hours. The reaction mixture was treated then with dilute hydrochloric acid (5 ml.). The separated product could not be purified. A product with considerable range in melting point was obtained.

Crossed Ullmann reaction between methyl-7-methoxy-8-iodocoumarin-6-carboxylate and iodobenzene : Methyl-7-methoxy-8-phenylcoumarin-6-carboxylate

Methyl-7-methoxy-8-iodocoumarin-6-carboxylate (3.60 g. ; 0.01 mole) in dry nitrobenzene (20 ml.) was treated with iodobenzene (4.12 g. ; 0.02 mole) and copper bronze (4 g. excess) and the reaction mixture was refluxed with an air condenser on a wire gauze for 3 hours. The reaction mixture was filtered while hot and the filtrate was diluted with petroleum ether (b.p. 60-80°). The separated product crystallised from acetic acid in needles, m.p.268°. Mixed m.p. with 7,7'-dimethoxy-6,6'-dicarbomethoxy-8,8'-bicoumarinyl was not depressed.

The 8-phenyl derivative was obtained on removal of nitrobenzene from the mother liquor by steam distillation. It crystallised from dilute alcohol in thin needles, m.p. 120-121°. Yield 0.4 g.

Analysis :

10.62 mg. of the substance gave 27.20 mg. of carbon dioxide and 4.50 mg. of water.

Found : C = 69.90 % ; H = 4.70 %.

$C_{18}H_{14}O_5$ requires : C = 69.70 % ; H = 4.50 %.

7-Methoxy-8-phenylcoumarin-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. 237-238° (decomp.).

Analysis :

10.22 mg. of the substance gave 25.66 mg. of carbon dioxide and 3.94 mg. of water.

Found : C = 68.50 % ; H = 4.30 %.

$C_{17}H_{12}O_5$ requires : C = 68.90 % ; H = 4.10 %.

The above acid (0.5 g.) in quinoline (5 ml.) was heated in an oil bath at 215° with a speck of copper powder, for half an hour. The product obtained on working up as usual crystallised from dilute alcohol in needles, m.p. 128-130°. Mixed m.p. with 7-methoxy-8-phenylcoumarin described earlier was not depressed.

Bromination of 7,8-dimethoxycoumarin : 7,8-Dimethoxy-3-bromocoumarin

7,8-Dimethoxycoumarin (2.06 g. ; 0.01 mole) in acetic acid (10 ml.) was treated with bromine in acetic acid (10 % ; 0.8 g. ; 0.01 mole) with stirring for 2 hours. The product crystallised from alcohol in needles, m.p. 152°. Yield 1.2 g.

Analysis :

12.542 mg. of the substance gave 8.308 mg. of silver bromide.

Found : Br = 28.18 %.

$C_{11}H_9O_4Br$ requires : Br = 28.0 %.

6,7-Dimethoxycoumarilic acid

The above bromocoumarin (0.3 g.) was refluxed with alcoholic potassium hydroxide solution (10 ml.) on a steam bath for 2 hours. The product obtained on acidifying the solution was purified through sodium bicarbonate solution. It crystallised from dilute alcohol in needles, m.p. 200°.

Analysis :

4.634 mg. of the substance gave 10.054 mg. of carbon dioxide and 1.874 mg. of water.

Found : C = 59.21 % ; H = 4.52 %.
$C_{11}H_{10}O_5$ requires : C = 59.46 % ; H = 4.50 %.

Attempted Ullmann reaction on 7,8-dimethoxy-3-bromocoumarin

7,8-Dimethoxy-3-bromocoumarin (2.85 g. ; 0.01 mole) was dissolved in nitrobenzene (10 ml.) and treated with copper bronze (1.89 g. ; 0.03 mole) and refluxed for 3 hours. The nitrobenzene was filtered and diluted with petroleum ether when it gave a product which was found to be 7,8-dimethoxycoumarin. The mother liquor after removal of petroleum ether was steam distilled when it yielded more 7,8-dimethoxycoumarin.

When the reaction was carried out by heating at 220° for 3 hours with the same quantities but without nitrobenzene, only 7,8-dimethoxycoumarin was the isolable product.

Bromination of naphtha-1:2-α-pyrone : 3'-Bromonaphtha-1:2-α-pyrone

Naphtha-1:2-α-pyrone (1.96 g. ; 0.01 mole)in acetic acid (8 ml.) was treated with bromine in acetic acid (1.6 g. ; 0.02 mole ; 10 %). The solution was stirred for 3 hours and then diluted with water. The separated solid crystallised from acetic acid in needles, m.p. 168-169°. Yield 0.3 g.

Analysis :

14.820 mg. of the substance gave 10.100 mg. of silver bromide.

Found : Br = 28.99 %.

$C_{13}H_7O_2Br$ requires : Br = 29.09 %.

6,7-Benzocoumarilic acid

The above bromo-naphtha-1,2-α-pyrone (0.3 g.) was refluxed with alcoholic potassium hydroxide solution (20 ml. ; 10 %) for 2 hours on a steam bath. The product obtained on working up the reaction mixture crystallised from dilute alcohol in yellow needles, m.p. 168-170°.

Analysis :

4.210 mg. of the substance gave 11.328 mg. of carbon dioxide and 1.434 mg. of water.

Found : C = 73.43 % ; H = 3.81 %.

$C_{13}H_8O_3$ requires : C = 73.48 % ; H = 3.77 %.

Attempted Ullmann reaction on 3'-bromo-naphtha-1:2-α-pyrone

3'-Bromo-naphtha-1:2-α-pyrone (1.37g. ; 0.005 mole) was dissolved in diphenyl ether (10 ml.) and treated with copper bronze (0.95 g. ; 0.015 mole) and refluxed for 6 hr. The diphenyl ether was filtered and diluted with petroleum ether. ~~When~~ It gave ~~an~~ the original 3'-bromo naphtha-1,2-α-pyrone. The mother liquor after removal of petroleum ether was steam distilled when it yielded more of the original coumarin.

When the above reaction was carried out by heating at 240° for 5 hours with the same quantities but without diphenyl ether, only the original 3'-bromo-naphtha-1,2-α-pyrone was the isolable product.

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

7-Methoxy-8-bromo-4-methylcoumarin (2.6 g. ; 0.01 mole) dissolved in dry nitrobenzene (40 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 and the filterate was diluted with petroleum ether (60-80°) when a product separated ~~and~~ which crystallised from acetic acid in needles, m.p. 358°. Yield 0.3 g. Mixed melting point with 7,7'-dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl prepared according to Lele, Patel and Sethna (J. Chem. Soc., 1961, 969-971) was not depressed.

The mother liquor when diluted with water gave 7-methoxy-4-methylcoumarin. This was also obtained when the nitrobenzene was steam distilled.

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

7-Methoxy-8-bromo-4-methylcoumarin (2.6 g. ; 0.01 mole), iodobenzene (4.12 g. ; 0.02 mole) and copper bronze (4 g excess) ~~was~~ were heated together in an oil bath at 220-230° under reflux for 3 hours. The mixture was cooled and extracted with petroleum ether (60-80°). The product obtained on removal of petroleum ether was found to be diphenyl.

The reaction mixture was then extracted with acetone. The product obtained on removal of acetone was crystallised from acetic acid and then from alcohol in needles, m.p. 158°. Yield 0.3 g. Mixed melting point with 7-methoxy-8-phenyl-4-methylcoumarin prepared according to Lele, Patel and Sethna (loc. cit.) was not depressed.

Further extraction of the reaction mixture with acetic acid gave 7,7'-dimethoxy-4,4'-dimethyl-8,8'-bicoumarinyl described above.