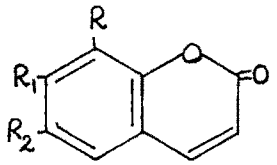
CHAPTER II

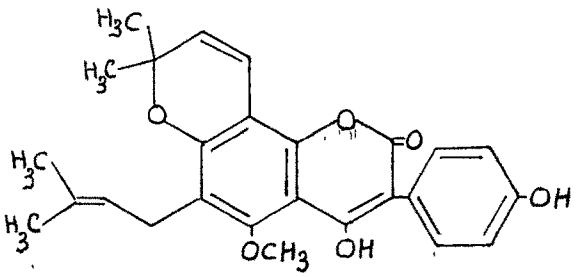
Synthesis of some α- and γ-pyrone derivatives from dihydroxy derivatives of diphenyl methane and diphenyl sulfone :

Benzo-α-pyrones known as coumarins and benzo-γ-pyrone derivatives such as chromones, flavones, isoflavones and xanthones are found to be widely distributed in the plant kingdom either in the free state or in the combined state. Umbelliferon (I), aesculetin (II), scopoletin (III), daphnetin (IV) and fraxetin (V) are a few of the simple coumarins occurring in nature[1].

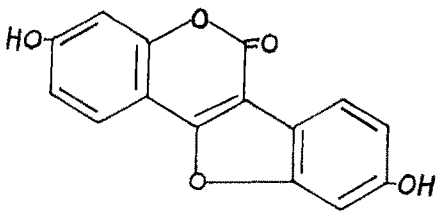


		R	R_1	R_2
Umbelliferon	(I)	H	OH	H
Aesculetin	(II)	H	OH	OH
Scopoletin	(III)	H	OH	OCH_3
Daphnetin	(IV)	OH	OH	H
Fraxetin	(V)	OH	OH	OCH_3

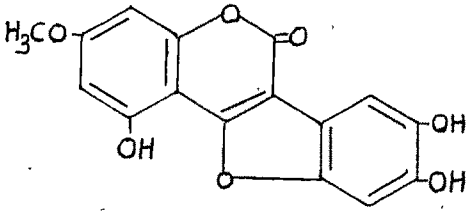
Many complex compounds having the coumarin ring system, have also been isolated from plants, such as scandenin (VI), coumestrol (VII), wedelolactove (VIII), robustic acid (IX) and ferruol-A[2] (X).



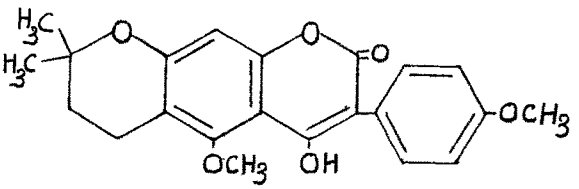
VI



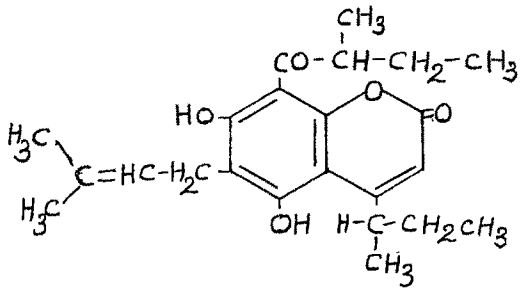
VII



VIII



IX



X

Flavones and isoflavones are 2-phenyl and 3-phenyl chromones respectively. Both classes of compounds occur in a a variety of plants either in combination with rhamnose and glucose or associated with tannins or in the uncombined state. Chrysin (XI), luteolin (XII), quercetin (XIII), calycopterin

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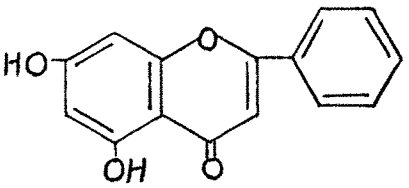
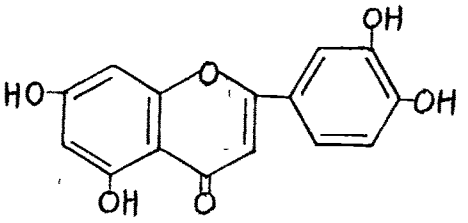
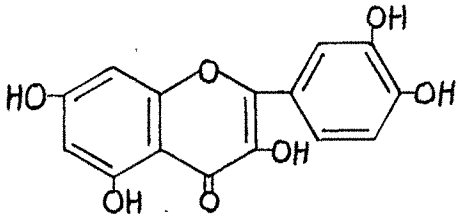
(XIV), daidzein (XV) and tectorigenin (XVI) are some of the simple members of these groups found in nature.



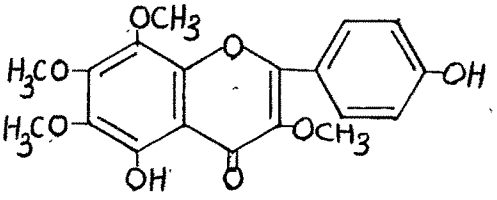
XI



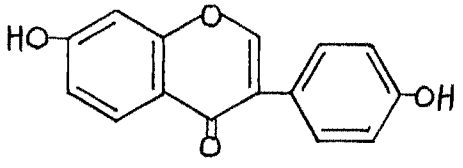
XII



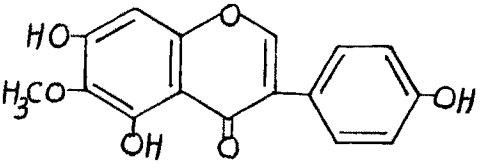
XIII



XIV

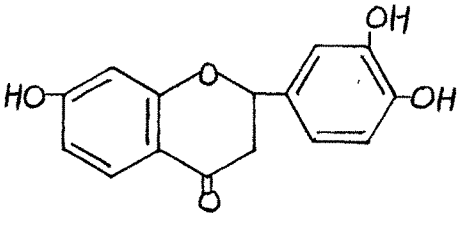


XV

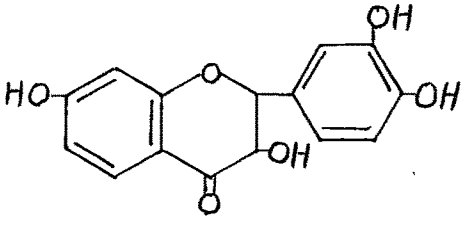


XVI

2,3-Dihydroflavones are known as flavanones and the 3-hydroxy derivatives of flavanones are called flavanolones. Butin (XVII) and fustin (XVIII) respectively are the members of these groups.



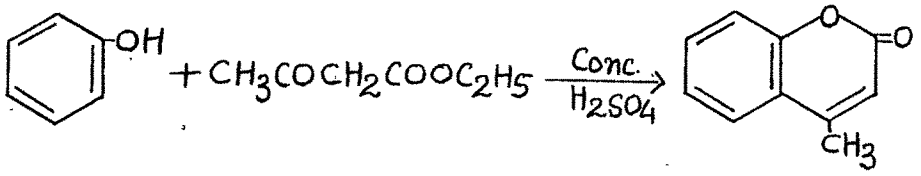
XVII



XVIII

As the present chapter deals with the synthesis of α-pyrone and γ-pyrone derivatives from diaryl derivatives, a few important methods for their synthesis which have been used in the present work may be briefly mentioned here.

(i) The Pechmann condensation[3] is an important method for preparing coumarins, since it proceeds from very simple starting materials and gives good yields of coumarins. It consists in the condensation of phenols with β-ketonic esters in the presence of condensing agents such as sulfuric acid, phosphorus pentoxide, anhydrous aluminium chloride, polyphosphoric acid, phosphoryl chloride, hydrogen fluoride and zinc chloride.

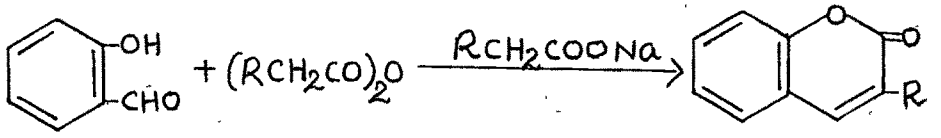


Coumarins without substituents in the pyrone ring can be synthesised by condensing phenols with malic acid in the presence of conc. sulfuric acid[4]. Various aspects of this reaction have been reviewed by Sethna and Phadke[5].

The use of sulfuric acid as the condensing agent leads to the formation of coumarins except in a very few cases where chromones are also formed[5]. Those phenols which

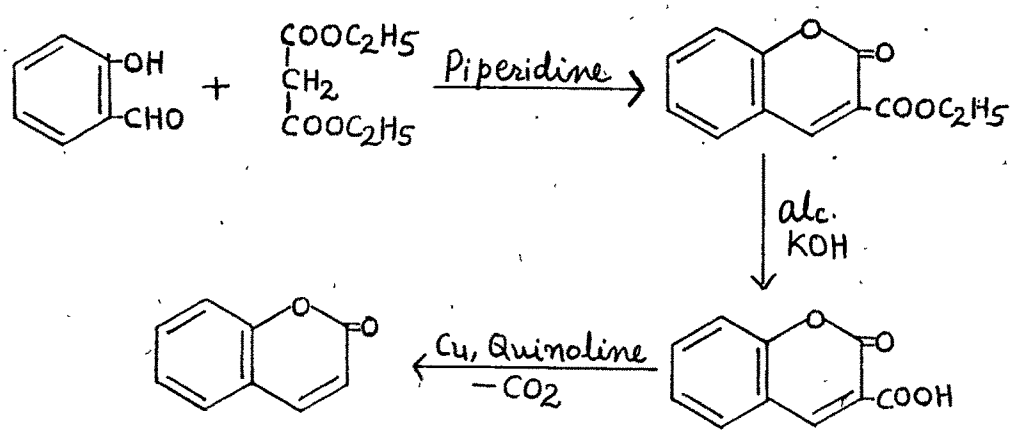
do not condense in the presence of sulfuric acid or form coumarins in low yield give chromones when phosphorus pentoxide is employed as the condensing agent. Mentzer et al.[6] found that if a phenol was heated with α,β-ketonic ester at a high temperature without any condensing agent chromones are formed instead of coumarins. Later, Desai, Trivedi and Sethna[7] found that the reaction is more rapid and better products are obtained if diphenyl ether is used as a solvent and the reaction mixture refluxed with a short condenser to remove the water formed.

(ii) The Perkin reaction[8,9] has proved successful in the synthesis of coumarins from salicylaldehyde derivatives. It involves the condensation of an o-hydroxyaldehyde with acetic anhydride in the presence of sodium acetate.

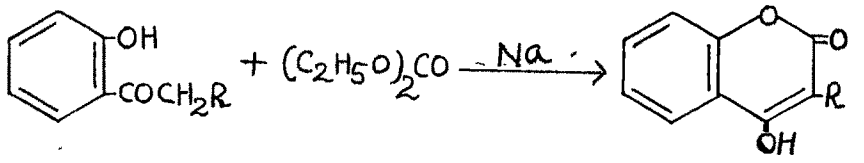


Iodine has been used as a catalyst and is reported to increase the yield of coumarin[10]. Other higher aliphatic acid anhydrides and salts when substituted for the acetic acid derivatives give 3-substituted coumarins[11,12].

The Knoevenagel reaction[13] is another reaction which gives coumarins from aromatic o-hydroxyaldehydes when they are condensed with substances containing an active methylene group such as malonic ester, acetoacetic ester and cyanoacetic ester, in the presence of organic bases such as piperidine.



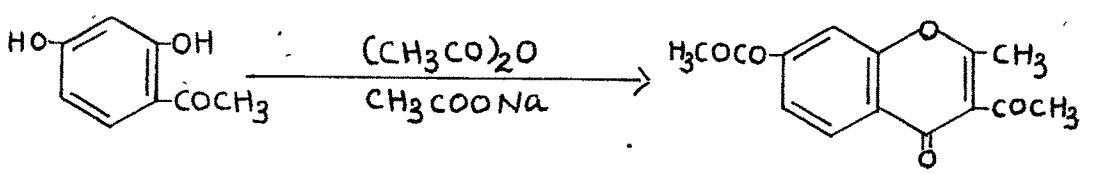
4-Hydroxycoumarins are formed in good yields by the condensation of o-hydroxyphenyl ketones with diethyl carbonate in presence of pulverised sodium[14].



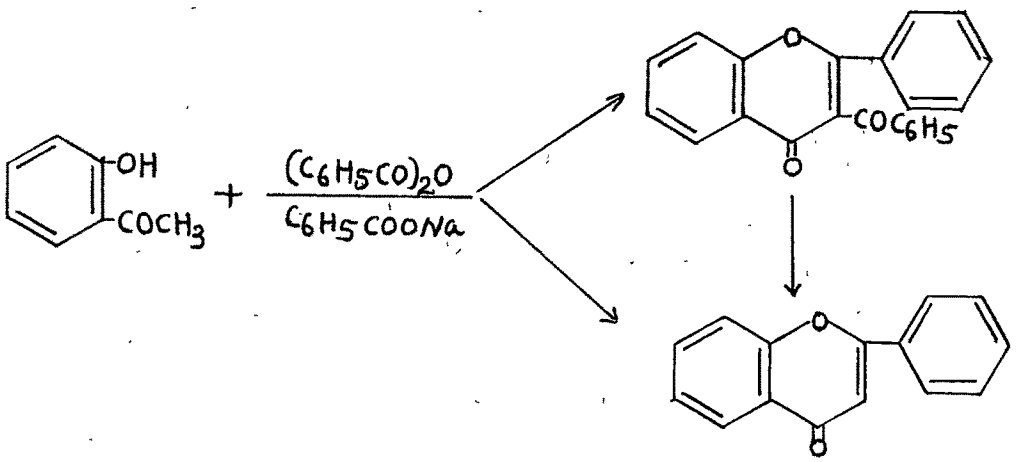
Several other methods[15,16,17,18,19] have also been developed for the synthesis of 4-hydroxycoumarins.

Synthesis of chromone derivatives :

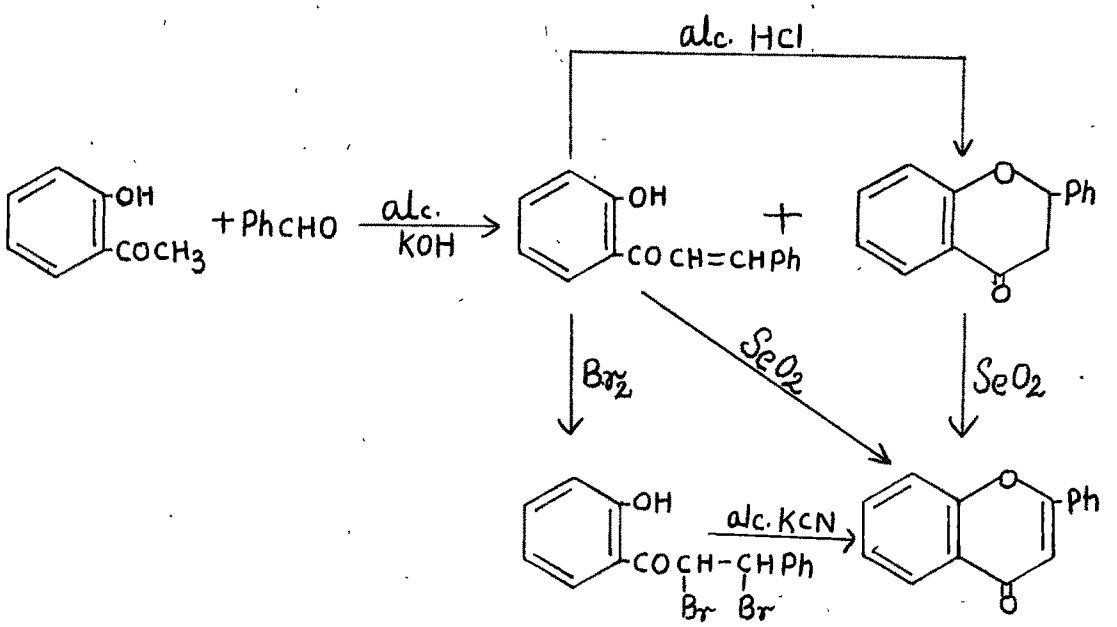
Kostanecki and Rozycki[20] showed that a chromone derivative was formed when resacetophenone was heated with sodium acetate and acetic anhydride.



Allan and Robinson[21] found that when o-hydroxy acetophenones were heated with the sodium salt and the anhydride of an aromatic acid, a flavone derivative was obtained. This method now known as the Kostanecki-Robinson reaction has been extensively used for the synthesis of chromone and flavone derivatives.

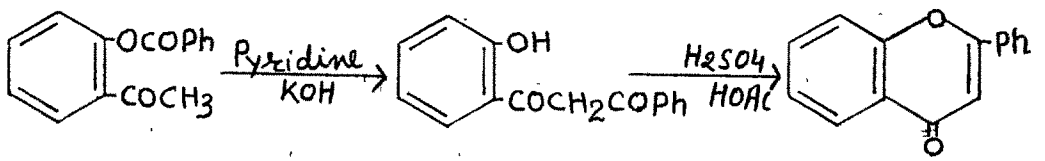


Another method also due to Kostanecki[22] consists in the condensation of o-hydroxy acetophenones with aromatic aldehydes. This gives chalcones which can be cyclised to flavanones by heating with a mineral acid[23,24]. The chalcone can be treated with bromine to give chalcone dibromide which when heated with alcoholic potassium cyanide or heated above the m.p. under reduced pressure gives flavone[25]. o-Hydroxy chalcones[26] and flavanones[27] may be converted into flavones by heating with selenium dioxide in iso-amyl alcohol.



Baker[28] and Venkataraman[29] developed a method for the synthesis of γ-pyrones which consists in the rearrangement of an o-aryloxy acetophenone in the presence of sodamide, potassium carbonate or according to a modification of Looker et al.[30] with pyridine and potassium hydroxide.

The β-diketone is then cyclised with a mineral acid.

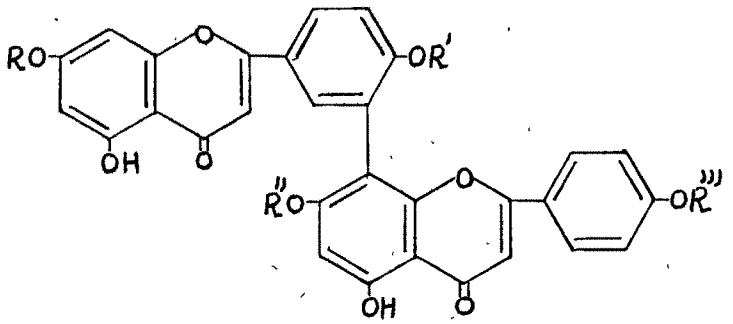


The presence of flavones in plants has been known since many years but it is only in recent years that the

presence of biflavonyls has been noticed. As stated in the general introduction our interest in studies in diaryl derivatives arose from the possibility of synthesis of biflavonyl, bichromonyl and bicoumarinyl derivatives from diaryl derivatives.

Naturally occurring biflavonyls :

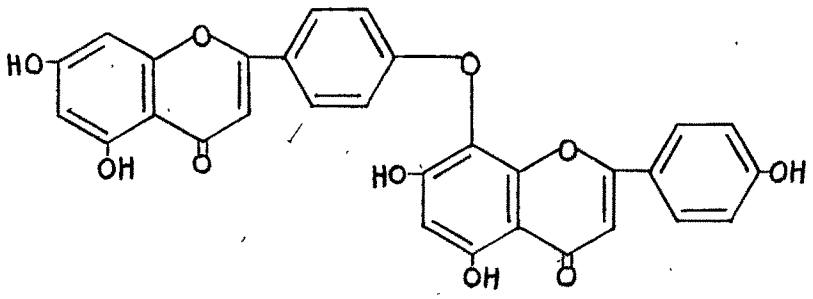
Several natural biflavonyls have been isolated during the past few years and their structures have been established by degradation methods and spectral data such as ultra-violet and infra-red spectra. Sotetsuflavone[31] (XIX), kayaflavone[32] (XX), ginkgetin[33,34] (XXI), isoginkgetin[35] (XXII), sciadopitysin[36] (XXIII) are some of the important biflavonyl



		R	R'	R''	R'''
Sotetsuflavone	(XIX)	H	H	H	H
Kayaflavone	(XX)	H	CH_3	CH_3	CH_3
Ginkgetin	(XXI)	CH_3	CH_3	H	H
Isoginkgetin	(XXII)	H	CH_3	H	CH_3
Sciadopitysin	(XXIII)	CH_3	CH_3	H	CH_3

derivatives isolated from cycas revoluta, torreya nucifera, ginkgo biloba and sciadopitys verticillata Sieb. et Zucc. (umbrella pine), respectively. The structures of the above biflavonyls have been established.

Hinokiflavone[37] (XXIV) isolated from the leaves of Cryptomeria japonica" has been shown to be a biflavonyl ether.

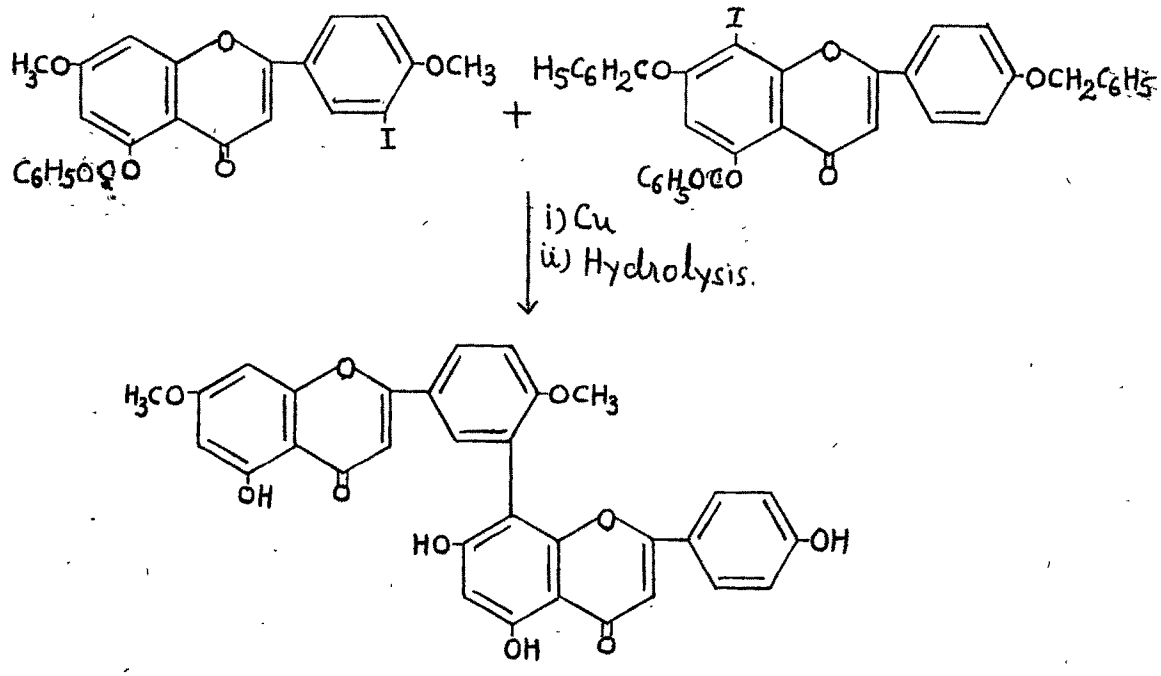


XXXIV

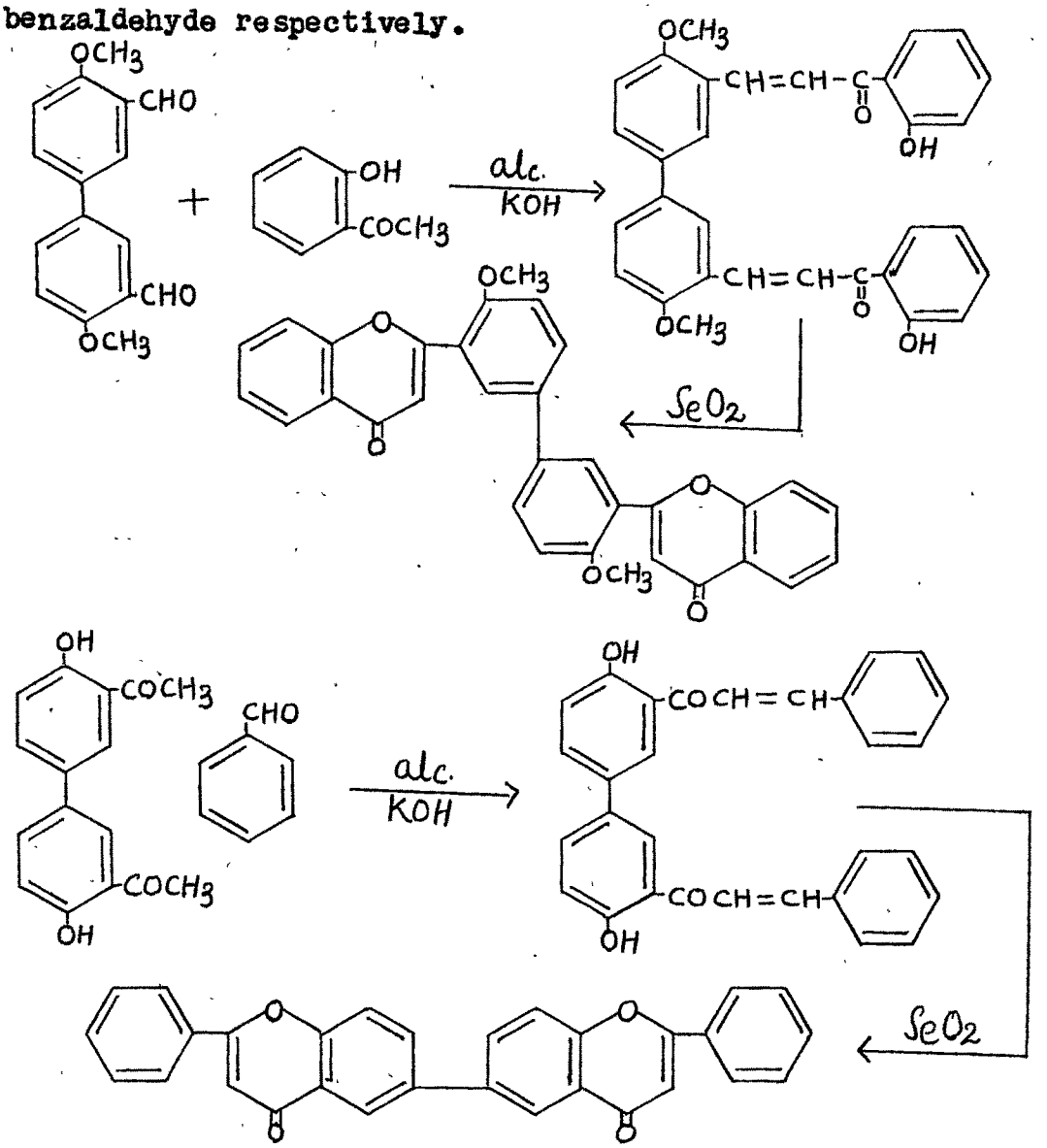
Synthetic biflavonyls :

Several symmetrical biflavonyls have been synthesised by the Ullmann reaction on bromo or iodo-flavones. Thus, Chen and Liu[38] synthesised 3,3'-biflavonyl by the Ullmann reaction on 3-bromoflavone. They further reported that the Ullmann reaction on 6-bromo, 7-bromo, 4'-iodo and 6-bromo-4'-methoxy flavanol derivatives did not succeed. Other symmetrical biflavonyls have also been synthesised through the Ullmann reaction on the appropriate halogenoflavones, Thus, 3-bromo, 6-iodo, 6-iodo-4'-methoxy, 7-iodo, 7-iodo-4'-methoxy, 8-iodo, 8-bromo, 8-chloro,3'-iodo and 4'-iodoflavone derivatives were converted into their respective biflavonyls by Chen et al.[39,40]. Chen[40] synthesised

7,7''-8,8''-3,3''- and 4',4'''-biflavonyl derivatives by the Ullmann reaction on methoxy iodoflavone derivatives. Jurd[41] synthesised 7,7''-dimethoxy-8,8''-biflavonyl and 7,7'', 4',4'''-tetramethoxy-8,8''-biflavonyl from the corresponding 8-iodoflavones by the Ullmann reaction. Demethylation of the above methoxy biflavonyls with aluminium chloride in boiling benzene gave the corresponding hydroxy biflavonyls. In this laboratory Shah[42] has synthesised symmetrical biflavonyls by the Ullmann reaction on 7-methoxy-8-iodo-flavone, and 7-methoxy-6-iodo-3-benzoylflavone. Ginkgetin has been synthesised by Nakazawa and Ito[43] by the crossed Ullmann reaction between 3'-iodo-5-benzoyloxy-4',7-dimethoxy flavone and 5-benzoyloxy-8-iodo-4',7-dibenzyloxyflavone in the presence of activated copper powder and subsequent hydrolysis with 10 % sulfuric acid in acetic acid.



Mathai and Sethna[44] used a different appreach for the synthesis of symmetrical biflavonyls. They prepared 3',3'''-and 6,6'''-biflavonyls by simultaneous cyclisation and dehydrogenation of the bichalkonyl derivatives obtained from the condensation of 2,2'- and 4,4'-dimethoxy-3,3'-diformyl diphenyls with 2-hydroxy acetophenone and from the condensation of 4,4'-dihydroxy-3,3'-diacetyl diphenyl with benzaldehyde respectively.



This work was further extended by Sethna and his co-workers[45,46]. Balani and Sethna[47] prepared bi-(6-flavonyl) ketone and bi-(6'-methoxy-3'-flavonyl)ketone by cyclising the corresponding bichalconyl derivatives obtained from the condensation of 3,3'-diacetyl-4,4'-dihydroxybenzophenone with benzaldehyde and from the condensation of 3,3'-diformyl-4,4'-dimethoxybenzophenone with 2-hydroxyacetophenone respectively.

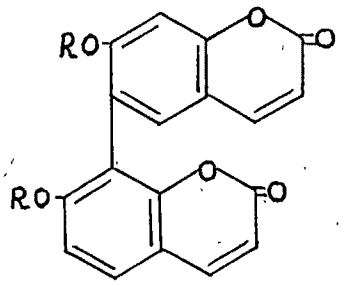
Bicoumarinyls :

Several symmetrical bicoumarinyls have also been synthesised. Dyson[48] synthesised 3,3'-bicoumarinyl by heating salicylaldehyde with sodium succinate and acetic anhydride in a sealed tube at 140° for 40 hr. Huebner and Link[49] reported the formation of 3,3'-bicoumarinyl derivative from 3-bromo-4-methoxycoumarin. Lele et al.[50] have synthesised 8,8' - and 3,3'-bicoumarinyl derivatives by the Ullmann reaction on iodocoumarins.

Sen and Dutt[51] obtained 6,6'-bicoumarinyl by the action of acetic anhydride and sodium acetate on 4,4'-dihydroxy-diphenyl-3,3'-dialdehyde. Harle and Lyons[52] obtained tetrahydro-4,4'-bicoumarinyl as one of the products in the reduction of coumarin using zinc and acetic acid.

Recently some unsymmetrical bicoumarinyls have been isolated from plants. Thus Mihashi et al.[53,54] have isolated 6,8'-bicoumarinyl and named it Matsukaze Lactone

(XXIVAa). Spencer et al.[55] have isolated 7,7'-dihydroxy-6,8'-bicoumarinyl(bicoumol) (XXIVAb) from ladino clover.



(a) R = CH_3

(b) R = H

XXVA

Dey and Row[56] synthesised several 4,3'-bicoumarinyls through the condensation of coumarin 4-acetic ester with various salicyl aldehydes under the conditions of Perkin reaction or Knoevenagel reaction.

7-Chloro-4,3'-bicoumarinyl has been synthesised by Thakar[57] by the condensation of 7-chlorocoumarin-4-acetic acid with salicylaldehyde in the presence of piperidine. Jainamma and Sethna[58] synthesised 3,6'-bicoumarinyl by Perkin acetylation of 3-(4'-hydroxy-3'-formylphenyl)-coumarin.

Present work :

No work appears to have been done on building up of α- and γ-pyrone rings on suitable diphenylmethane and diphenyl sulfone derivatives. The present work deals with the synthesis of some bicoumarinyl- and biflavonyl-methane derivatives from 2,2'- and 4,4'-dihydroxydiphenyl methane and the synthesis of a biflavonyl sulfone from 4,4'-dihydroxydiphenyl sulfone.

Pechmann condensation of 4,4'-dihydroxydiphenyl methane with ethyl acetoacetate : Synthesis of bi(4-methyl-6-coumarinyl)methane :

4,4'-Dihydroxydiphenyl methane on Pechmann condensation with ethyl acetoacetate in the presence of sulfuric acid (80 %) gave a product which was insoluble in dilute alkali. On heating with alkali and dimethyl sulfate in acetone solution on a steam bath it gave an unsaturated acid as seen by decolourisation of bromine water and potassium permanganate solution. The formation of such an unsaturated acid is a diagnostic test for a coumarin derivative[59]. Bi(4-methyl-6-coumarinyl)methane structure (XXVI) has, therefore, been assigned to the condensation product and the unsaturated acid has been assigned structure (XXVII). Spectral data for (XXVI): I.R. 1680 $cm.^{-1}$ U.V. λ max (chloroform) 274, 322 nm. Coumarins absorb infra-red radiation at 1720 $cm.^{-1}$ and U.V. light at 300 nm.[59A]

Synthesis of bi(6-coumarinyl)methane : Perkin reaction on 3,3'-diformyl-4,4'-dihydroxydiphenyl methane :

3,3'-Diformyl-4,4'-dihydroxydiphenyl methane was prepared earlier by Marvel and Tarkoy[60] by the condensation of salicylaldehyde with trioxan. Attempt to prepare it by heating 4,4'-dihydroxydiphenyl methane with hexamine in acetic acid resulted in a non-melting unworkable product. It was therefore prepared by Sommelet reaction on 3,3'-di-(chloromethyl)4,4'-dimethoxydiphenyl methane as given on page 137 . On heating with acetic anhydride and sodium acetate it gave a compound which was insoluble in alkali and did not

give the test for an aldehyde group. Bi(6-coumarinyl) methane structure (XXVIII) is assigned to this compound.

The same product was also obtained through the following route :

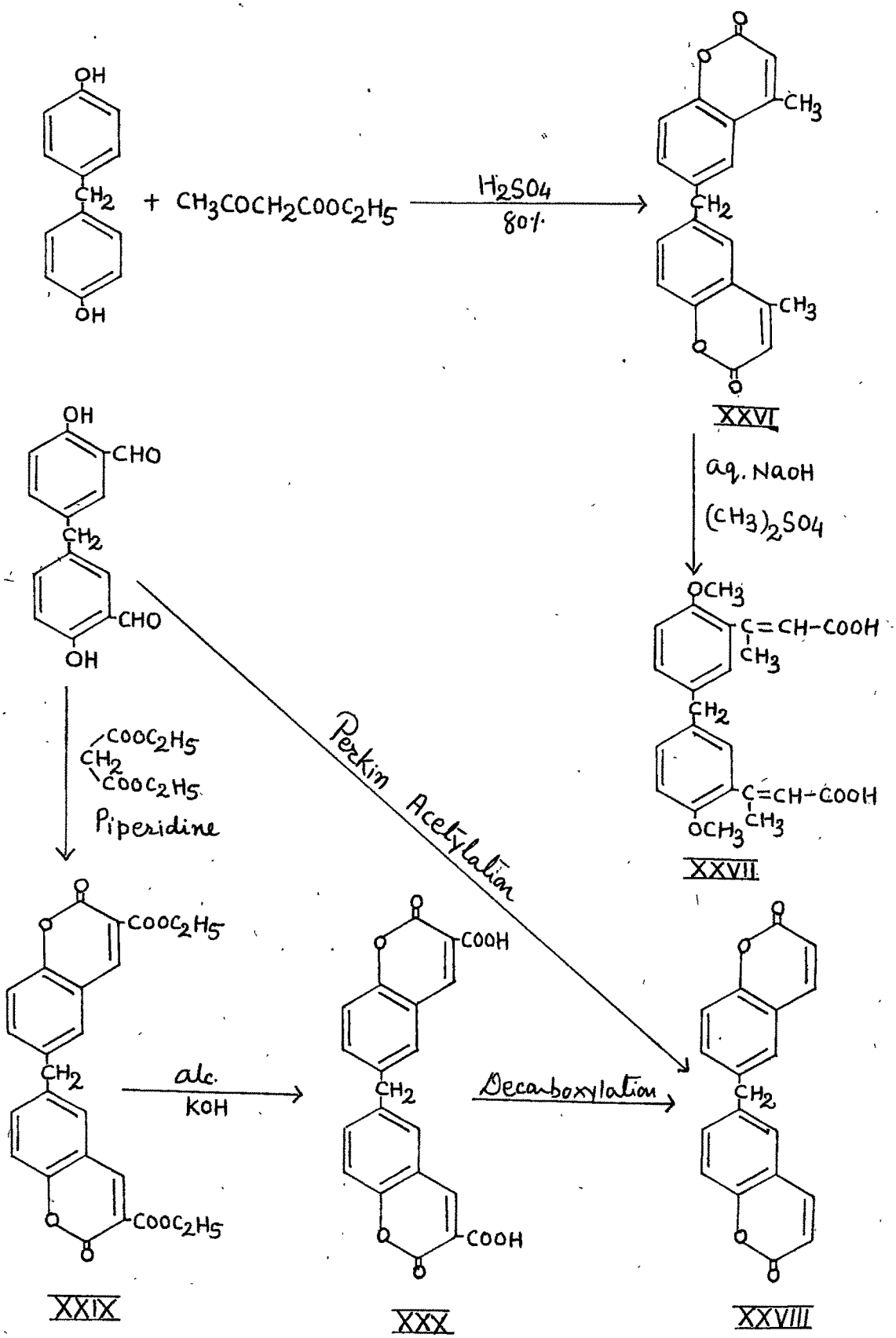
Knoevenagel condensation of 3,3'-diformyl-4,4'-dihydroxy-diphenyl methane with diethyl malonate :

3,3'-Diformyl-4,4'-dihydroxydiphenyl methane on condensation with diethyl malonate in the presence of a few drops of piperidine furnished a product which was insoluble in cold dilute alkali and did not give any colouration with alcoholic ferric chloride. Bi(3-carbethoxy-6-coumarinyl)methane structure (XXIX) was assigned to this product. On hydrolysis with alcoholic potassium hydroxide it gave the corresponding dicarboxylic acid (XXX) which on decarboxylation by heating in quinoline with copper powder gave bi(6-coumarinyl)methane (XXVIII) described above. I.R. 1675 cm^{-1} (δ lactone). U.V. λ max. (Chloroform) 276, 324 nm.

Synthesis of bi(4-hydroxy-6-coumarinyl)methane :

The blood anticoagulating agent dicoumarol[61] which is 3,3'-methylene-bis(4-hydroxycoumarin) is prepared by heating 4-hydroxycoumarin with formalin.

This method is not applicable for the synthesis of bis(4-hydroxycoumarin) derivatives with the methylene bridge in any other position. It was, therefore, thought of interest to see if such compounds could be prepared from suitable diphenyl methane derivatives.

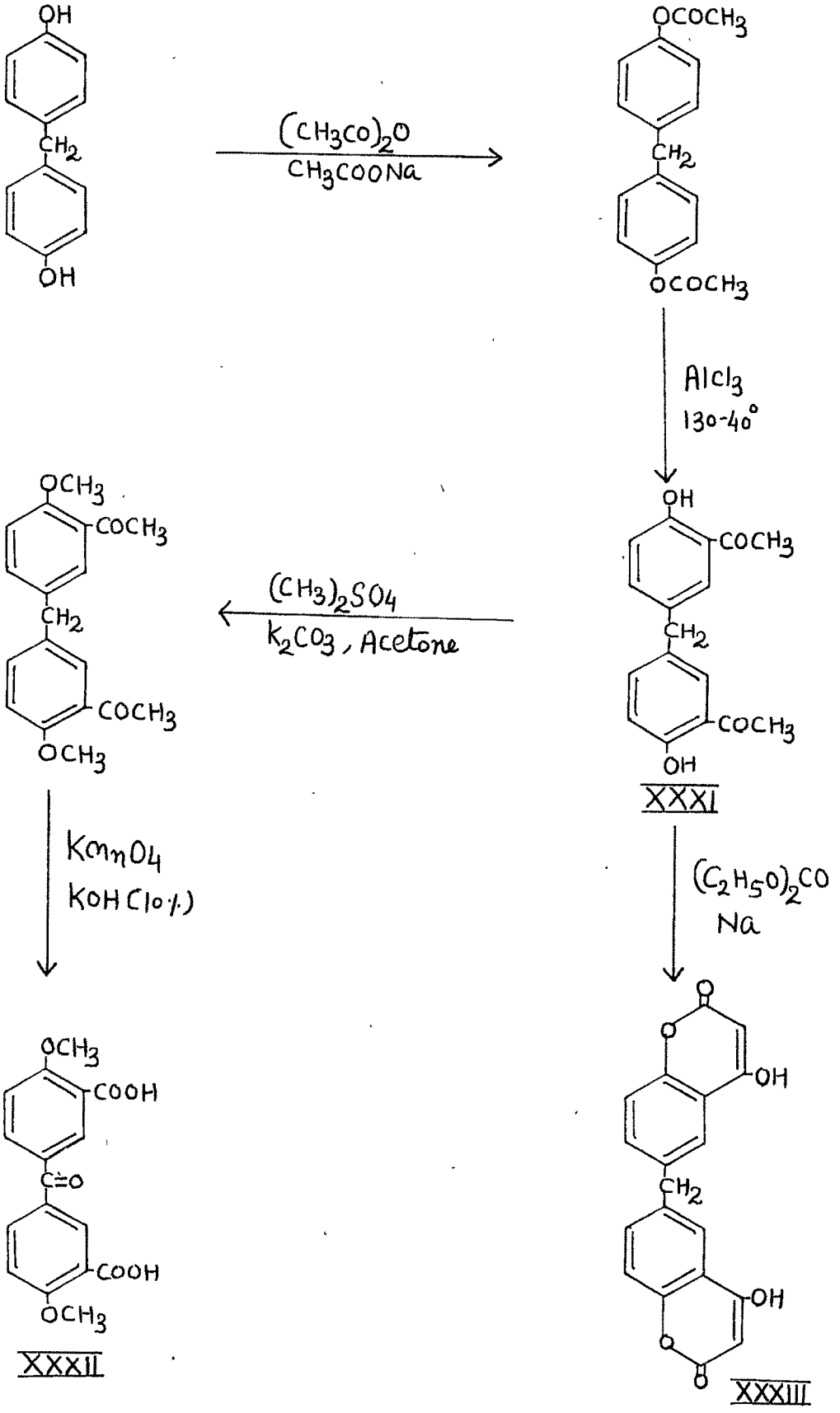

OH
CH2
OH
+ CH3COCH2COOC2H5
H2SO4
80%
CH3
CH2
CH3
O
O
XXVI
aq. NaOH
(CH3)2SO4
OCH3
C=CH-COOH
CH3
CH2
C=CH-COOH
CH3
OCH3
XXVII
OH
CHO
CH2
CHO
OH
COOC2H5
CH2
COOC2H5
Piperidine
Perkin Acetylation
COOC2H5
CH2
COOC2H5
alc. KOH
COOH
CH2
COOH
Decarboxylation
CH2
XXIX
XXX
XXVIII

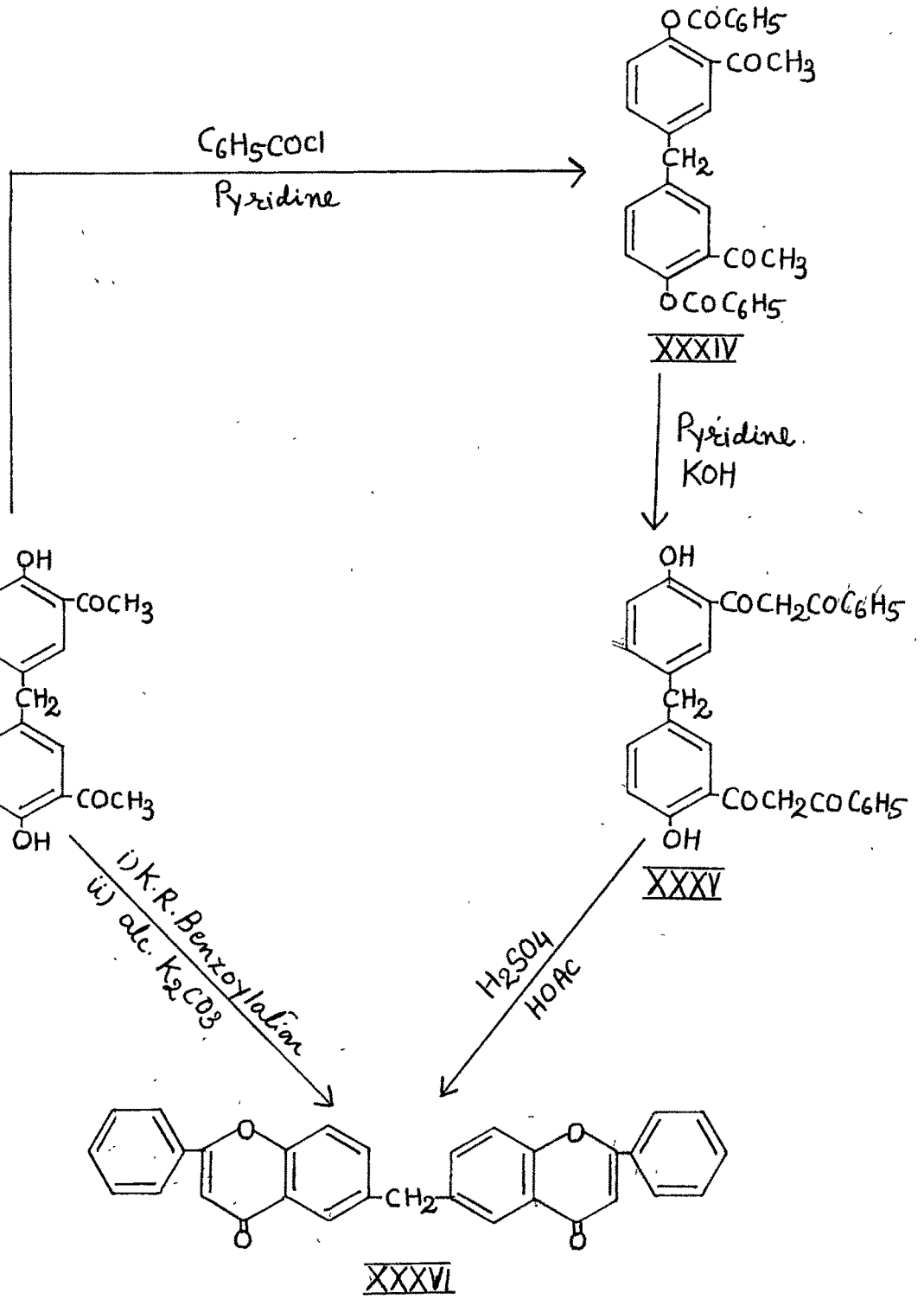
3,3'-Diacetyl-4,4'-dihydroxydiphenyl methane was required as an intermediate for the synthesis of the above compound. It was prepared by the Fries migration of 4,4'-diacetoxydiphenyl methane with anhydrous aluminium chloride at 130-40°. The 3,3'-diacetyl-4,4'-dihydroxydiphenyl methane structure (XXXI) was assigned to the Fries migration product as it gave a greenish-brown colouration with alcoholic ferric chloride and its dimethyl ether on oxidation with alkaline potassium permanganate gave the known 4,4'-dimethoxy-benzophenone-3,3'-dicarboxylic acid (XXXII) as seen by direct comparison with an authentic specimen prepared according to Balani and Sethna[47].

3,3'-Diacetyl-4,4'-dihydroxydiphenyl methane when heated with diethyl carbonate in the presence of pulverised sodium gave a product which analysed for $C_{19}H_{12}O_6$ and was soluble in sodium bicarbonate solution. It gave a dimethyl ether $C_{21}H_{16}O_6$ with dimethyl sulfate. However, it did not give any colouration with alcoholic ferric chloride probably due to its very low solubility in alcohol. The bi(4-hydroxy-6-coumarinyl)methane structure (XXXIII) is assigned to the product. I.R. 1670 cm^{-1} (δ lactone), 3450 cm^{-1} (b. free -OH).

Synthesis of bi(6-flavonyl)methane :

3,3'-Diacetyl-4,4'-dihydroxydiphenyl methane was converted into its dibenzoyloxy derivative (XXXIV) by treating it with benzoyl chloride in presence of pyridine. The


OH
CH2
OH
(CH3CO)2O
CH3COONa
OCOCH3
CH2
OCOCH3
AlCl3
130-40°
OH
COCH3
CH2
COCH3
OH
XXXI
(CH3)2SO4
K2CO3, Acetone
OCH3
COCH3
CH2
COCH3
OCH3
KMnO4
KOH (10%)
OCH3
COOH
C=O
COOH
OCH3
XXXII
(C2H5O)2CO
Na
OH
CH2
OH
XXXIII


C6H5COCl
Pyridine
XXXIV
Pyridine
KOH
XXXV
i) K.R. Benzoylation
ii) alc. K2CO3
H2SO4
HOAc
XXXVI

dibenzoyloxy derivative was then subjected to Baker-Venkataraman transformation according to the modified method of Looker et al.[30] in the presence of pyridine and potassium hydroxide. The rearranged product was soluble in dilute sodium hydroxide solution and gave greenish-brown colouration with alcoholic ferric chloride. 3,3'-Di(benzoylacetyl)-4,4'-dihydroxydiphenyl methane structure (XXXV) was assigned to the product. It was cyclised by heating it in glacial acetic acid with a few drops of conc. sulfuric acid when the desired bi(6-flavonyl) methane (XXXVI) was obtained. The same bi(6-flavonyl)methane was obtained when 3,3'-diacetyl-4,4'-dihydroxydiphenyl methane was subjected to Kostanecki-Robinson benzoylation by heating with sodium benzoate and benzoic anhydride at 190-200°. U.V. λ max. (chloroform) 264, 298 nm. I.R. 1635 $cm.^{-1}$ (C=O).

Synthesis of bi(4'-methoxy-6-flavonyl)methane :

3,3'-Diacetyl-4,4'-dihydroxydiphenyl methane was condensed with anisaldehyde in the presence of alcoholic potassium hydroxide. The bi(4-methoxy-6'-hydroxy-3'-chalconyl) methane structure (XXXVII) was assigned to the bichalconyl derivative as it gave a positive Wilson test, a deep red colouration with conc. sulfuric acid and brown colouration with alcoholic ferric chloride. It gave a single spot in TLC. The above bichalconyl derivative when refluxed with selenium dioxide in iso-amyl alcohol gave a product which was insoluble

in alkali and gave light blue fluorescence with conc. sulfuric acid. Bi(4'-methoxy-6-flavonyl)methane structure (XXXVIII) has been assigned to the product. U.V. λ max. (Chloroform) 262, 318 nm. I.R. 1635 cm^{-1} (C=O).

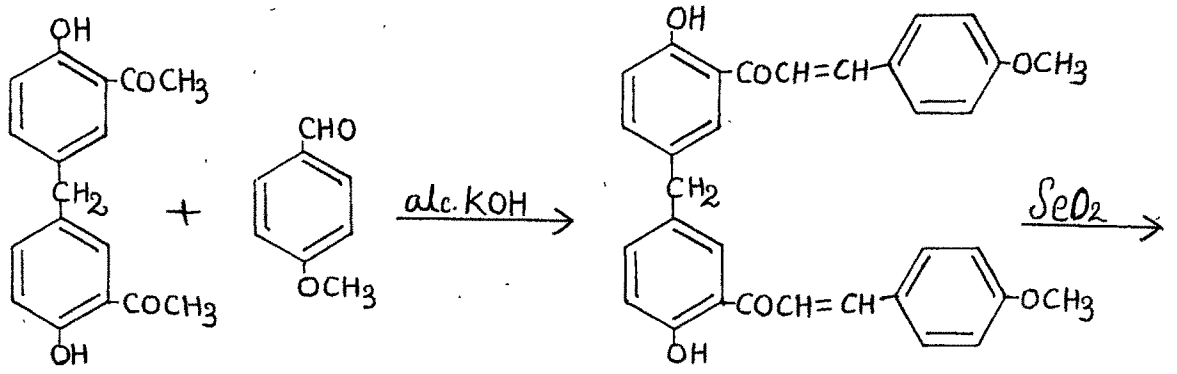
Synthesis of bi(6'-methoxy-3'-flavonyl)methane :

3,3'-Diformyl-4,4'-dimethoxydiphenyl methane prepared as described on page 137, was condensed with 2-hydroxy acetophenone in the presence of alcoholic potassium hydroxide. The bi(2'-hydroxy-6-methoxy-3-chalconyl)methane structure (XXXIX) was assigned to the bichalconyl derivative as it gave a positive Wilson test, a deep red colouration with conc. sulfuric acid and brown colouration with alcoholic ferric chloride. It gave a single spot in TLC. The above bichalconyl derivative when refluxed with selenium dioxide in iso-amyl alcohol gave a product which was insoluble in alkali and gave a single spot in TLC. Bi(6'-methoxy-3'-flavonyl) structure (XL) has been assigned to the product. U.V. λ max. (chloroform) 288, 308 nm. I.R. 1630 cm^{-1} (C=O).

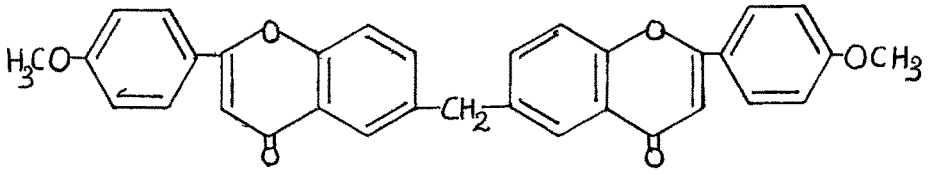
Synthesis of bi(6-flavonyl)sulfone :

3,3'-Diacetyl-4,4'-dihydroxydiphenyl sulfone required as an intermediate for the synthesis of the title compound was prepared as follows :-

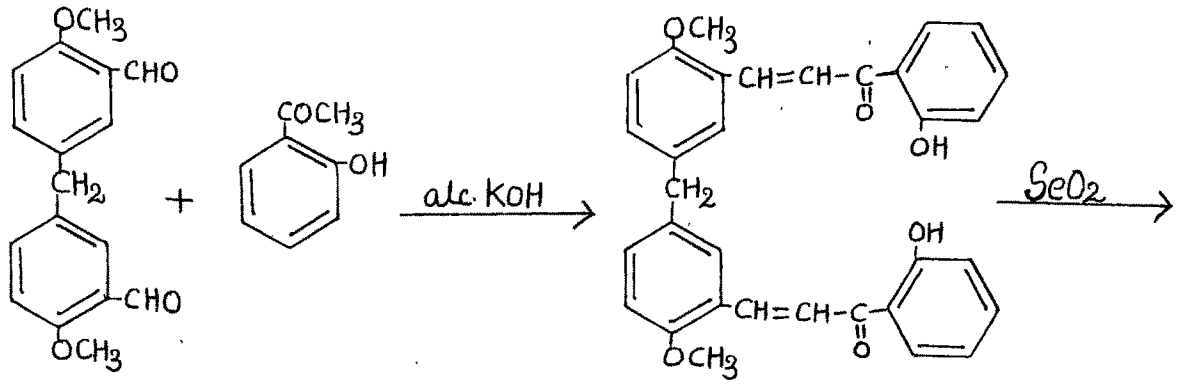
4,4'-Dihydroxydiphenyl sulfone[62] on acetylation with acetic anhydride gave 4,4'-diacetoxydiphenyl sulfone which on Fries migration with anhydrous aluminium chloride at 140-50° gave the 3,3'-diacetyl-4,4'-dihydroxydiphenyl sulfone(XLI).



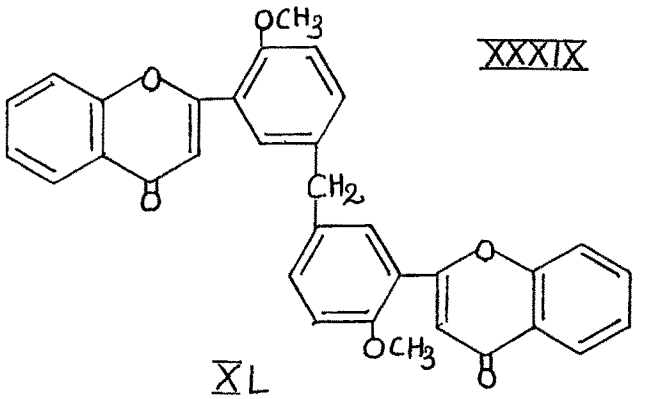
XXXVII



XXXVIII



XXXIX



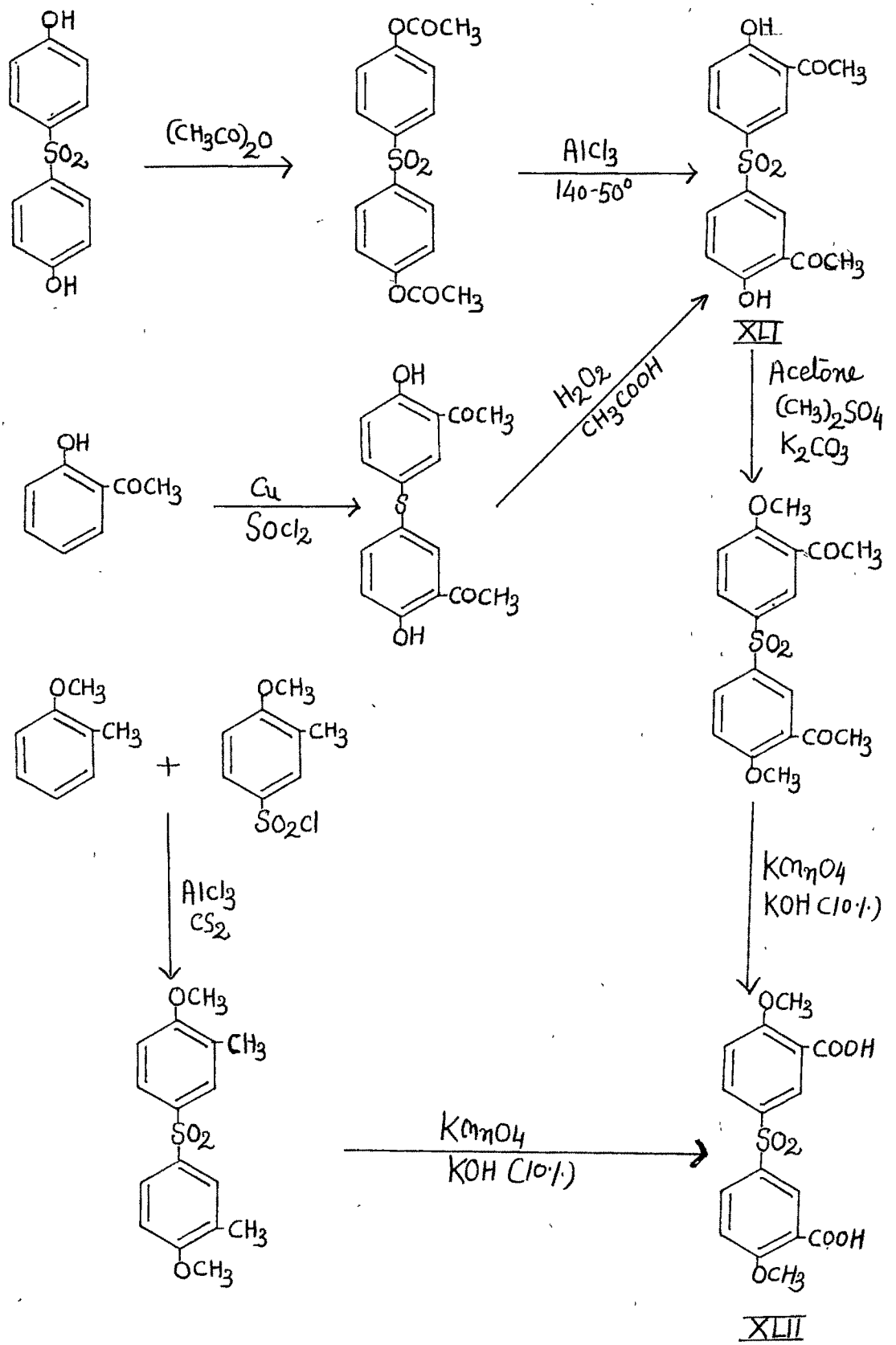
XL

It was soluble in alkali and gave a deep red colouration with alcoholic ferric chloride. The same diacetyl derivative was obtained according to Kulkarni[63] as follows :-

o-Hydroxy acetophenone was condensed with thionyl chloride in presence of copper powder when 3,3'-diacetyl-4,4'-dihydroxydiphenyl sulfide was obtained. The above sulfide was oxidised to the corresponding sulfone with hydrogen peroxide in glacial acetic acid solution. M.p. and mixed m.p. with the product obtained above was found to be 188°.

For the further confirmation of the structure of the Fries migration product, it was converted into its dimethoxy derivative by refluxing with dimethyl sulfate in acetone solution and the dimethyl ether was oxidised by heating with alkaline potassium permanganate to the known 4,4'-dimethoxydiphenyl sulfone-3,3'-dicarboxylic acid (XLII) m.p. 252°. Mixed m.p. with an authentic sample prepared according to Kulhatkar and Bokil[64] was not depressed. These authors prepared this dicarboxylic acid by condensing 3-methyl-4-methoxybenzenesulfonyl chloride with 2-methylanisole in the presence of anhydrous aluminium chloride to get 3,3'-dimethyl-4,4'-dimethoxydiphenyl sulfone and then oxidising it with alkaline potassium permanganate to the dicarboxylic acid. They reported m.p. 250°.

3,3'-Diacetyl-4,4'-dihydroxydiphenyl sulfone on condensation with benzaldehyde in the presence of alcoholic potassium hydroxide gave bi(6'-hydroxy-3'-chalconyl) sulfone

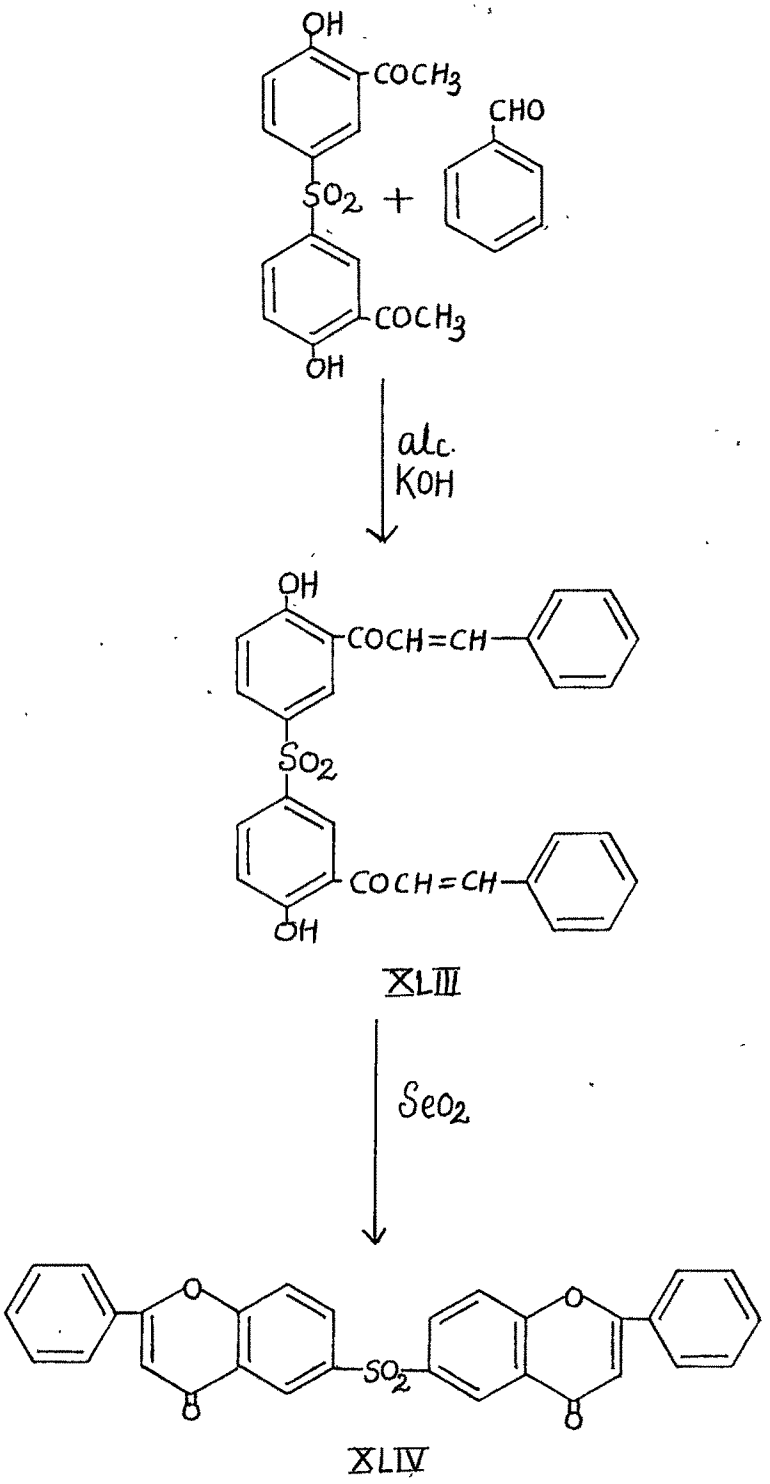

OH
SO2
OH
(CH3CO)2O
OCOCH3
SO2
OCOCH3
AlCl3
140-50°
OH
COCH3
SO2
COCH3
OH
XLI
Acetone
(CH3)2SO4
K2CO3
OH
COCH3
Cu
SOCl2
S
COCH3
OH
H2O2
CH3COOH
OCH3
COCH3
SO2
COCH3
OCH3
OCH3
CH3
+
OCH3
CH3
SO2Cl
AlCl3
CS2
KMnO4
KOH (10%)
OCH3
CH3
SO2
CH3
OCH3
KMnO4
KOH (10%)
OCH3
COOH
SO2
COOH
OCH3
XLII

(XLIII). It gave a dimethoxy derivative, red colour with conc. sulfuric acid and a positive Wilson test. It also gave a single spot in TLC. The above bichalconyl derivative when refluxed with selenium dioxide in iso-amyl alcohol gave a product which was insoluble in alkali and gave light blue fluorescencewith conc. sulfuric acid. The bi(6-flavonyl) sulfone structure (XLIV) is assigned to the product. U.V. λ max. (chloroform) 268, 296 nm . I.R. 1645 $cm.^{-1}$ (C=O).

Attempted Pechmann condensation of 2,2'-dihydroxydiphenyl methane with ethyl acetoacetate :

2,2'-Dihydroxydiphenyl methane on keeping with ethyl acetoacetate in the presence of sulfuric acid did not undergo any reaction and the unreacted original compound was recovered. The condensation did not take place even with other condensing agents like phosphorus pentoxide, anhydrous aluminium chloride or polyphosphoric acid. The original compound was also recovered unchanged when 2,2'-dihydroxidiphenyl methane was refluxed with ethyl acetoacetate in diphenyl ether.

It may be mentioned here that o-cresol also does not condense with ethyl acetoacetate in the presence of sulfuric acid. It is however reported that it gives a 8 % yield of 2,8-dimethylchromone on condensation with ethyl acetoacetate in the presence of phosphorus pentoxide.


OH
COCH3
CHO
SO2
+
COCH3
OH
alc.
KOH
OH
COCH=CH
SO2
COCH=CH
OH
SeO2
O
SO2
O
O
O

XLIII

XLIV

Attempted Pechmann condensation of 4,4'-dihydroxydiphenyl sulfone with ethyl acetoacetate :

4,4'-Dihydroxidiphenyl sulfone did not condense with ethyl acetoacetate in the presence of sulfuric acid. The original product was recovered unchanged when it was condensed with ethyl acetoacetate either in the presence of phosphorus pentoxide or anhydrous aluminium chloride in nitrobenzene at 120-30°. It also did not undergo any condensation when refluxed with ethyl acetoacetate in diphenyl ether.

Attempted condensation of 3,3'-diacetyl-4,4'-dihydroxydiphenyl sulfone with diethyl carbonate :

3,3'-Diacetyl-4,4'-dihydroxidiphenyl sulfone did not undergo condensation when refluxed with diethyl carbonate in the presence of pulverised sodium.

EXPERIMENTAL.

Pechmann condensation of 4,4'-dihydroxydiphenyl methane with ethyl acetoacetate : Bi-(4-methyl-6-coumarinyl)-methane :

4,4'-Dihydroxydiphenyl methane (2 g.) and ethyl acetoacetate (4 ml.) were mixed together and sulfuric acid (15 ml.; 80 %) was added with external cooling and stirring. The reaction mixture was kept for 24 hr. and was then poured on crushed ice. The solid obtained was filtered and washed with dilute sodium hydroxide and then with water. It crystallised from glacial acetic acid. M.P. 282-84°. Yield 0.5 g.

Analysis : Found : C, 75.71 ; H, 4.64 %.

$C_{21}H_{16}O_4$ requires : C, 75.89 ; H, 4.85 %.

Bi(α-methyl-β-carboxy-2-methoxy-5-styryl)methane :

The above bicoumarinyl derivative (0.2 g.) was dissolved in hot acetone (20 ml.). Sodium hydroxide solution (5 ml.; 20 %) was added followed by dimethyl sulfate (0.5 ml.). The reaction mixture was refluxed on a steam bath for 4 hr. after making the solution distinctly alkaline. The product obtained on acidification was filtered and purified by extraction with sodium bicarbonate solution. The dicarboxylic acid crystallised from dilute alcohol in white needles, m.p. 178-79°. It decolourised bromine water and potassium permanganate solution.

Analysis : Found : C, 69.95 ; H, 5.97 %.

$C_{23}H_{24}O_6$ requires : C, 69.70 ; H, 6.06 %.

Perkin acetylation of 3,3'-diformyl-4,4'-dihydroxydiphenyl methane : Bi-(6-coumarinyl)methane :

A mixture of 3,3'-diformyl-4,4'-dihydroxydiphenyl methane (0.5 g.), fused sodium acetate (2 g.) and acetic anhydride (5 ml.) was refluxed in an oil bath at 180-90° for 12 hr. The reaction mixture was then poured on ice and the separated solid was filtered and washed with dilute sodium hydroxide solution. The alkali insoluble product crystallised from dilute alcohol. M.p. 203°. Yield 0.1 g.

Analysis : Found : C, 75.36 ; H, 4.42 %.

$C_{29}H_{12}O_4$ requires : C, 74.98 ; H, 3.95 %.

Knoevenagel condensation of 3,3'-diformyl-4,4'-dihydroxy-diphenyl methane with diethyl malonate : Bi-(3-carbethoxy--6-coumarinyl)methane :

A mixture of 3,3'-diformyl-4,4'-dihydroxydiphenyl-methane (0.5 g.), diethyl malonate (1 ml.) and a few drops of piperidine was kept at room temperature for 48 hr. The reaction mixture was then washed with alcohol and dilute hydrochloric acid. The product crystallised from alcohol in pale yellow needles. (0.2 g.), m.p. 178°.

Analysis : Found :C, 66.77 ; H, 4.48 %.

$C_{25}H_{20}O_8$ requires:C, 66.96 ; H, 4.46 %.

Bi-(3-carboxy-6-coumarinyl)methane :

The above ester (0.5 g.) was refluxed with alcoholic potassium hydroxide solution (20 ml.; 20 %) for 5 hr. The product obtained on acidification of the clear alkaline solution crystallised from nitrobenzene. M.p. 306°. Yield 0.3 g.

Analysis : Found : C, 64.04 ; H, 3.13 %.

$C_{21}H_{12}O_8$ requires : C, 64.29 ; H, 3.06 %.

Decarboxylation :

The above dicarboxylic acid (0.5 g.) was dissolved in quinoline (10 ml.) and a pinch of copper powder was added. The mixture was refluxed gently for half an hour and then filtered. The filtrate was poured in 1 : 1 hydrochloric acid. The separated product crystallised from dilute alcohol. M.p. 203°. Yield 0.2 g.

The mixed m.p. of the compound with bi-(6-coumarinyl) methane obtained through the Perkin acetylation described before was not depressed.

3,3'-Diacetyl-4,4'-dihydroxydiphenyl methane :

A mixture of 4,4'-diacetoxydiphenyl methane (1 g.) and anhydrous aluminium chloride (2 g.) was heated in an oil bath at 130-40° for 1 hr. The reaction mixture was decomposed with ice-cold hydrochloric acid and the product was taken up in sodium hydroxide solution. The product obtained on acidification crystallised from alcohol in brown needles (0.5 g.), m.p. 155°. It gave a brownish green

colouration with alcoholic ferric chloride.

Analysis : Found : C, 71.83 ; H, 5.55 %.

$C_{17}H_{16}O_4$ requires : C, 71.82 ; H, 5.63 %.

Di-(2,4-dinitrophenylhydrazone) :

The above ketone was dissolved in alcohol and a solution of 2,4-dinitrophenylhydrazine in alcohol was added. The separated solid crystallised from diphenyl ether in orange shining needles, m.p. 291° (decomp.).

Analysis : Found : N, 17.66 %.

$C_{29}H_{24}N_8O_{10}$ requires : N, 17.40 %.

The dimethyl ether :

A mixture of 3,3'-diacetyl-4,4'-dihydroxydiphenyl methane (1 g.), dimethyl sulfate (1.5 ml.) and anhydrous potassium carbonate (2 g.) in dry acetone was refluxed for 16 hr. The product obtained on removal of acetone and adding water crystallised from benzene-petroleum ether mixture in white shining plates (0.8 g.), m.p. 71-72°.

Analysis : Found : C, 73.14 ; H, 6.13 %.

$C_{19}H_{20}O_4$ requires : C, 73.06 ; H, 6.41 %.

Oxidation : 4,4'-Dimethoxybenzophenone-3,3'-dicarboxylic adid :

A mixture of the above dimethyl ether (0.5 g.), potassium permanganate (2 g.) and potassium hydroxide solution (15 ml. ; 10 %) was refluxed for 8 hr. More of potassium permanganate (1 g.) was added in small quantity at regular intervals. The reaction mixture was filtered and

the filtrate was decolourised by adding sodium sulfite solution. The clear alkaline solution was acidified with hydrochloric acid. The separated product was purified by bicarbonate treatment and crystallised from alcohol in white needles (0.2 g.), m.p. 244°. Ishiwata and Takada[65] reported m.p. 242-43°. Balani and Sethna[47] reported m.p. 242°.

Bi-(4-hydroxy-6-coumarinyl)methane :

A mixture of 3,3'-diacetyl-4,4'-dihydroxydiphenylmethane (1 g.), diethyl carbonate (25 ml.) and pulverised sodium (3 g.) was refluxed on a steam bath for 6 hr. The reaction mixture was poured in cold water and the excess diethyl carbonate was removed by extraction with ether. The product obtained on acidification of the clear alkaline solution crystallised from nitrobenzene. M.p. 296°. Yield 0.5 g. It was soluble in sodium bicarbonate solution.

Analysis : Found : C, 67.45 ; H, 3.44 %.

$C_{19}H_{12}O_6$ requires : C, 67.86 ; H, 3.57 %.

The dimethyl ether :

A mixture of bi-(4-hydroxy-6-coumarinyl)methane (0.2 g.), dimethyl sulfate (0.5 ml.) and anhydrous potassium carbonate (1 g.) in dry acetone was refluxed for 15 hr. The product obtained on removal of acetone and adding water crystallised from glacial acetic acid, M.p. 310°. Yield 0.1 g.

Analysis : Found : C, 69.16 ; H, 4.40 %.

$C_{21}H_{16}O_6$ requires : C, 69.23 ; H, 4.39 %.

3,3'-Diacetyl-4,4'-dibenzoyloxydiphenyl methane :

A mixture of 3,3'-diacetyl-4,4'-dihydroxydiphenyl methane (0.5 g.), pyridine (1 ml.) and benzoyl chloride (0.5 ml.) was stirred for 15 minutes. The reaction mixture was then treated with cold hydrochloric acid. The separated product crystallised from alcohol in white shining needles (0.4 g.), m.p. 123-24°.

Analysis : Found : C, 75.82 ; H, 4.83 %.

$C_{31}H_{24}O_6$ requires : C, 75.60 ; H, 4.88 %.

3,3'-Di(benzoylacetyl)-4,4'-dihydroxydiphenyl methane :

A mixture of 3,3'-diacetyl-4,4'-dibenzoyloxy-diphenyl methane (0.5 g.), crushed potassium hydroxide (3 g.) and pyridine (5 ml.) was kept for 4 hr. at room temperature. Ice-cold hydrochloric acid was then added to the above reaction mixture. The separated product was purified by extraction with sodium hydroxide solution and crystallised from acetic acid. M.p. 182-83°. Yield 0.2 g. It gave brownish green colouration with alcoholic ferric chloride solution.

Analysis : Found : C, 75.53 ; H, 4.97 %.

$C_{31}H_{24}O_6$ requires : C, 75.60 ; H, 4.88 %.

Bi-(6-flavonyl)methane :

The above β-diketone (0.5 g.) was refluxed with glacial acetic acid (10 ml.) and conc. sulfuric acid (2 drops)

for 4 hr. The separated product crystallised from glacial acetic acid in white shining plates (0.4 g.), m.p. 253-54°. It was insoluble in sodium hydroxide solution and gave light violet fluorescence with conc. sulfuric acid.

Analysis : Found : C, 81.51 ; H, 4.34 %.

$C_{31}H_{20}O_4$ requires : C, 81.55 ; H, 4.39 %.

Kostanecki-Robinson benzoylation of 3,3'-diacetyl-4,4'-dihydroxydiphenyl methane :

3,3'-Diacetyl-4,4'-dihydroxydiphenyl methane (0.5 g.) was mixed with sodium benzoate (1 g.) and benzoic anhydride (1 g.) and heated in an oil bath at 190-200° for 12 hr. The mixture was treated with water and kept overnight. The pasty mass obtained was repeatedly boiled with water to remove the sodium benzoate and unreacted benzoic anhydride. The solid remaining undissolved on treatment with dilute sodium hydroxide solution was filtered, washed with water and refluxed in alcohol with anhydrous potassium carbonate (1 g.) on a steam bath for 5 hr. The product obtained on removal of alcohol was washed with water and then with dilute sodium hydroxide. The alkali insoluble product crystallised from acetic acid. M.p. 253°. Yield 50 mg.

The mixed m.p. of the compound with bi-(6-flavonyl) methane obtained through the Baker-Venkataraman transformation described above was not depressed.

Condensation of 3,3'-diacetyl-4,4'-dihydroxydiphenyl methane with anisaldehyde : Bi-(4-methoxy-6'-hydroxy-3'-chalconyl)-methane :

A mixture of 3,3'-diacetyl-4,4'-dihydroxydiphenyl methane (1 g.), anisaldehyde (2 ml.) and potassium hydroxide (5 g. in 5 ml. water) in alcohol (30 ml.) was kept at room temperature for 24 hr. The solution turned dark-red in colour. Crushed ice was added to the reaction mixture and it was acidified with hydrochloric acid. The separated product was filtered and washed several times with sodium bicarbonate solution. The residue crystallised from glacial acetic acid. M.p. 198-200°. Yield 0.8 g.

Analysis : Found : C, 75.68 ; H, 5.36 %.

$C_{33}H_{24}O_6$ requires : C, 76.15 ; H, 5.38 %.

It gave a positive Wilson test and a deep red colour with conc. sulfuric acid. It gave browm colouration with alcoholic ferric chloride and showed a single spot in TLC.

Bi-(4'-methoxy-6-flavonyl)methane :

Bi-(4-methoxy-6'-hydroxy-3'-chalconyl)methane (0.5 g.) was refluxed with selenium dioxide (4 g.) in iso-amyl alcohol (30 ml.) for 35 hr. and filtered hot. Iso-amyl alcohol was removed by steam distillation and the alkali insoluble product crystallised from glacial acetic acid in pale yellow needles (0.2 g.), m.p. 254-55°. It gave a light blue fluorescence with conc. sulfuric acid.

Analysis : Found : C, 76.83 ; H, 4.52 %.

$C_{33}H_{24}O_6$ requires : C, 76.75 ; H, 4.65 %.

It showed a single spot in TLC.

Condensation of 3,3'-diformyl-4,4'-dimethoxydiphenyl methane with o-hydroxy acetophenone : Bi-(2'-hydroxy-6-methoxy-3-chalconyl)methane :

A mixture of 3,3'-diformyl-4,4'-dihydroxydiphenyl methane (1 g.), o-hydroxy acetophenone (2 ml.) and potassium hydroxide (5 g.) in alcohol (100 ml.) was kept at room temperature for 24 hr. The solution turned dark-red in colour. Crushed ice was added to the reaction mixture and it was acidified with hydrochloric acid. The separated product was filtered and crystallised from glacial acetic acid. M.p. 170-72°. Yield 0.7 g.

Analysis : Found : C, 76.26 ; H, 5.33 %.

$C_{33}H_{28}O_6$ requires : C, 76.15 ; H, 5.38 %.

It gave a positive Wilson test, a deep red colour with conc. sulfuric acid and brown colour with alcoholic ferric chloride solution. It also showed a single spot in TLC.

Bi-(6'-methoxy-3'-flavonyl)methane :

Bi-(2'-hydroxy-6-methoxy-3-chalconyl)methane (0.7 g.) was refluxed with selenium dioxide (7 g.) in iso-amyl alcohol (100 ml.) for 35 hr. and filtered hot. Iso-amyl alcohol was removed by steam distillation. Pasty product obtained was dissolved in chloroform

and passed over alumina. The solid product obtained on removal of the solvent crystallised from xylene in yellow cluster of needles (0.2 g.), m.p. 209-10°.

Analysis :Found : C, 76.45 ; H, 4.84 %.

$C_{33}H_{24}O_6$ requires : C, 76.75 ; H, 4.85 %.

It showed a single spot in TLC.

3,3'-Diacetyl-4,4'-dihydroxydiphenyl sulfone :

A mixture of 4,4'-diacetoxydiphenyl sulfone (5 g.) and anhydrous aluminium chloride (10 g.) was heated in an oil bath at 140-50° for 5 hr. The reaction mixture was decomposed with ice-cold hydrochloric acid and the product was taken up in sodium hydroxide solution. The product obtained on acidification crystallised from acetic acid in brown needles (1.5 g.), m.p. 189-90°. Kulkarni[60] who prepared it by a different method reported m.p. 189°. It gave red colouration with alcoholic ferric chloride solution.

Analysis : Found : C, 57.59 ; H, 4.06 %.

$C_{16}H_{14}O_6S$ requires : C, 57.50 ; H, 4.19 %.

Di-(2,4-dinitrophenylhydrazone) :

The above ketone was dissolved in alcohol and a solution of 2,4-dinitrophenylhydrazine in alcohol was added. The separated product was filtered and crystallised from diphenyl ether in orange needles, m.p. 306-07°.

Analysis : Found : N, 16.00 %.

$C_{28}H_{22}N_8O_{12}S$ requires : N, 16.14 %.

The dimethyl ether :

A mixture of 3,3'-diacetyl-4,4'-dihydroxydiphenyl sulfone (1 g.), dimethyl sulfate (2 ml.) and anhydrous potassium carbonate (5 g.) in dry acetone was refluxed for 12 hr. The solid obtained on removal of acetone and adding water crystallised from alcohol in white shining plates (0.8 g.), m.p. 179°.

Analysis : Found : C, 59.87 ; H, 4.89 %.

$C_{18}H_{18}O_6S$ requires : C, 59.68 ; H, 4.97 %.

3,3'-Dicarboxy-4,4'-dimethoxydiphenyl sulfone :

A mixture of the above dimethyl ether (0.5 g.), potassium permanganate (2 g.) and potassium hydroxide solution (20 ml. ; 10 %) was refluxed for 6 hr. More of potassium permanganate (1 g.) was added in small quantity at regular intervals. The reaction mixture was filtered and the filtrate was decolourised by adding sodium sulfite solution. The clear alkaline solution was acidified with hydrochloric acid. The separated product was purified by extraction with sodium bicarbonate and crystallised from alcohol. M.p. 252°. (decomp.). Yield 0.2 g. Mixed m.p. with a sample prepared according to Kolhatkar and Bokil[61] was not depressed.

Condensation of 3,3'-diacetyl-4,4'-dihydroxydiphenyl sulfone with benzaldehyde : Bi-(6'-hydroxy-3'-chalconyl)sulfone :

A mixture of 3,3'-diacetyl-4,4'-dihydroxydiphenyl sulfone (1 g.), benzaldehyde (2.5 g.) and potassium hydroxide (5 g. in 5 ml. water) in alcohol (30 ml.) was kept at room

temperature for 24 hr. The solution turned dark red in colour. Some ice-cold water was added and the solution was acidified with hydrochloric acid. The separated solid was filtered and washed with sodium bicarbonate solution. The residue crystallised from acetic acid. M.p. 208-10°.
Yield 0.5 g.

Analysis : Found : C, 70.53 ; H, 4.34 %.
$C_{30}H_{22}O_6S$ requires : C, 70.60 ; H, 4.31 %.

It did not give any colouration with alcoholic ferric chloride (probably due to very low solubility in alcohol. It gave a positive Wilson test and a deep red colouration with conc. sulfuric acid. It showed a single spot in TLC.

Bi-(6'-methoxy-3'-chalconyl)sulfone :

The above chalcone (0.5 g.) was refluxed with anhydrous potassium carbonate (2 g.) and dimethyl sulfate (1 ml.) in dry acetone solution on a steam bath for 15 hr. The solvent was removed and the reaction mixture was treated with water. The solid obtained crystallised from acetic acid in pale yellow shining plates (0.3 g.), m.p. 175-77°.

Analysis : Found : C, 71.03 ; H, 4.75 %.
$C_{32}H_{26}O_6S$ requires : C, 71.36 ; H, 4.83 %.

Bi-(6-flavonyl)sulfone :

Bi-(6'-hydroxy-3'-chalconyl)sulfone (0.5 g.) was refluxed with selenium dioxide (3 g.) in iso-amyl alcohol (50 ml.) in an oil bath for 25 hr. It was filtered hot and cooled. Excess petroleum ether was added to the filtrate

and the separated product was washed with sodium hydroxide solution. Alkali-insoluble product crystallised from acetic acid. M.p. 324-26°. Yield 0.1 g. It gave a light blue fluorescence with conc. sulfuric acid.

Analysis : Found : C, 71.53 ; H, 3.40 %.

$C_{30}H_{18}O_6S$ requires : C, 71.13 ; H, 3.56 %.

Attempted Pechmann condensation of 4,4'-dihydroxydiphenyl sulfone with ethyl acetoacetate :

A mixture of 4,4'-dihydroxydiphenyl sulfone (1 g.), ethyl acetoacetate (2 ml.) and sulfuric acid (10 ml. ; 80 %) was kept at room temperature for 48 hr. It was then poured on ice and the separated paste was treated with sodium hydroxide solution. It was completely soluble. The product obtained on acidification of the clear alkaline solution was found to be the original 4,4'-dihydroxydiphenyl sulfone.

4,4'-Dihydroxydiphenyl sulfone was recovered unchanged when phosphorus pentoxide or aluminium chloride was used as the condensing agent at steambath temperature.

Attempted condensation of 3,3'-diacetyl-4,4'-dihydroxydiphenyl sulfone with diethyl carbonate :

A mixture of 3,3'-diacetyl-4,4'-dihydroxydiphenyl sulfone (1 g.), diethyl carbonate (15 ml.) and pulverised sodium (2 g.) was heated in an oil bath at 140° for 15 hr. The reaction mixture was then poured over crushed ice. Excess

diethyl carbonate was removed by ether extraction. The product obtained on acidification of the clear alkaline solution was crystallised from acetic acid. The mixed m.p. with 3,3'-diacetyl-4,4'-dihydroxydiphenyl sulfone was not depressed.

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