CHAPTER III

SYNTHESIS OF SOME BIFLAVONYLS FROM BIPHENYL DERIVATIVES

CHAPTER III

Synthesis of some Biflavonyls from biphenyl derivatives :

The presence of flavones in plants has been known since long. The structure of many of them have been established and a large number of them have been synthesised. It is only in recent years that a new class of flavanoids where two flavone nuclei are joined together and which are therefore designated as biflavonyls have been found in nature.

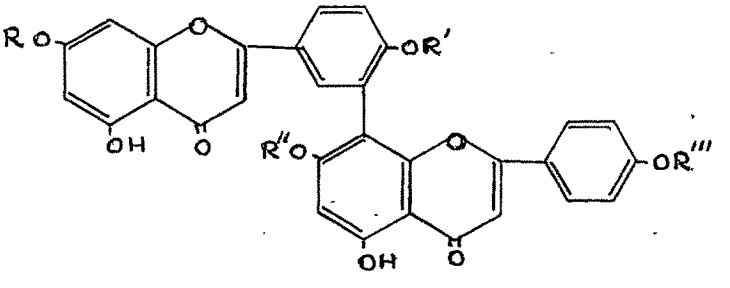
The story of the biflavonyls begins with the isolation by Furukawa[1] of a yellow phenolic product in 1932 from the autumn leaves of the Ginkobiloba or maidenhair tree. To this yellow phenolic compound he gave the 5,8-dihydroxy-4'-methoxyflavone structure but the synthesis of this flavone showed that the structure assigned to the natural product was incorrect. Examination of Furukawa's evidence led Baker and his co-workers[2] to suggest that the yellow product of Furukawa which they named "Ginkgetin", probably had a higher molecular weight than that corresponding to a normal flavanoid structure. They synthesised various flavanoids including furano-flavones, but all these were found to be different from ginkgetin. Later, Nakazawa[3] showed that ginkgetin has a formula $C_{32}H_{22}O_{10}$ but the formula suggested by him on the basis of degradation products was later found to be incorrect. The discovery of other natural products like

Kayaflavone and Sotetsuflavone and their study led to the conclusion that all these had similar skeletal structure and that these were biflavonyl derivatives.

Ollis[4] has summarised the work done on biflavonyls upto 1961.

Naturally occurring biflavonyls :

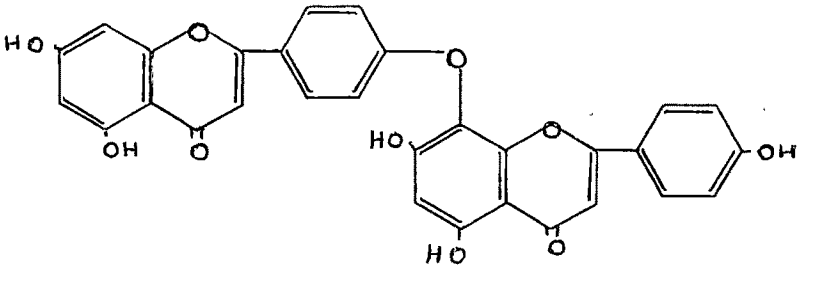
Several natural biflavonyls have been isolated during the past few years and their structures have been established by degradation methods and by physical methods such as ultraviolet and infra-red spectra. Ginkgetin, isoginkgetin, sciadopitysin, kayaflavone, sotetsuflavone are some of the biflavonyl derivatives isolated from various plants. The structures of the above biflavonyls have been established. The structures, with references to publications of the principal investigators, are given below :



	R	R′	R″	R‴
Ginkgetin[1,3]	Me	Me	H	H
Isoginkgetin[2]	H	Me	H	Me
Sciadopitysin[5]	Me	Me	H	Me

	R	R′	R″	R‴
Kayaflavone[6]	H	Me	Me	Me
Sotetsuflavone[7]	H	H	H	H

Hinokiflavone, isolated from the leaves of Cryptomeria Japonica has been shown to be a biflavonyl ether[8].

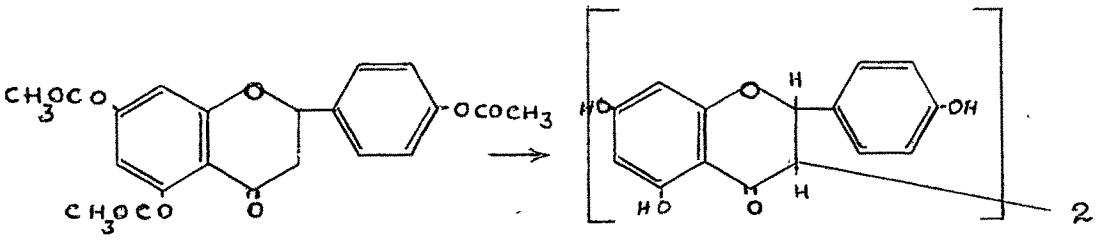


Hinokiflavone

The biflavonyls are probably produced in the plants by oxidative coupling of a flavanoid precursor such as epigenin or a closely related compound. This could be followed by methylation of the diepigeninyl in various positions and this is in aggrement with the simultaneous occurrence of various biflavonyls in the same plant. It is also supported by the biflavonyl ether structure of hinokiflavone since it is recognised that oxidative coupling of phenols can lead either to diaryls or diaryl ethers.

Synthetic biflavonyls :

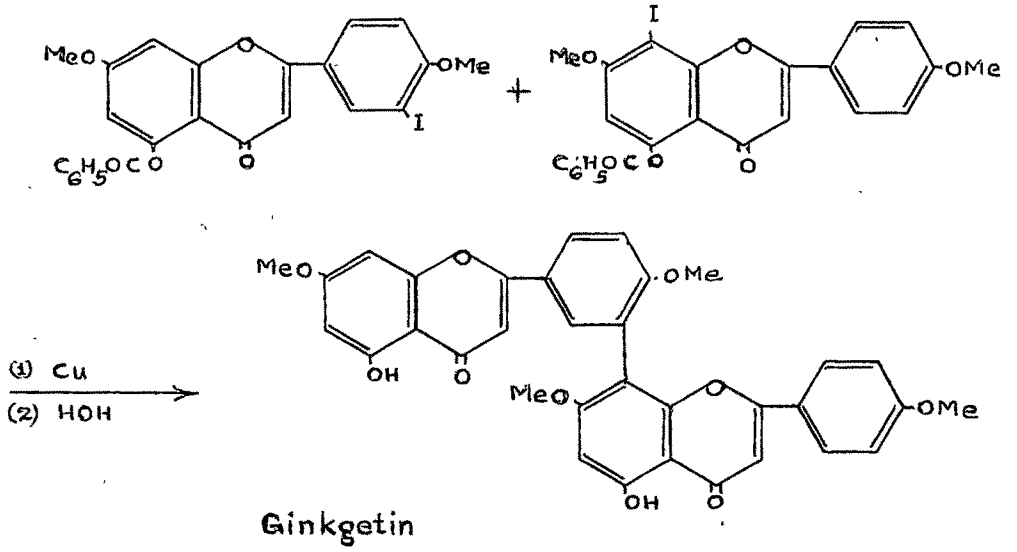
Mahesh and Seshadri[9] in their attempt to oxidise narigenin triacetate with Fenton's reagent[10] obtained 4′,4‴,5,7,5″,7″-hexahydroxy-3,3″-biflavonyl as a byproduct. They did not give a definite proof for this compound but gave the bimolecular structure because of the availability of a number of organic bimolecular compounds when the simple ones are oxidised with Fenton's reagent.



Chen and Liu[11] 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 did not succeed.

Other symmetrical biflavonyls have been synthesised through the Ullmann reaction on the appropriate halogenoflavones. Thus 3-bromo-,6-iodo-,6-iodo-4′-methoxy-, 7-iodo-4′-methoxy-,8-iodo-, 8-bromo-, 8-chloro-, 3-iodo- and 4-iodo-flavone derivatives were converted into their respective biflavonyls by Chen et al.[12]. Jurd[13] synthesised 7,7″-dimethoxy-8,8″-biflavonyl and 7,7′,4,4′-tetramethoxy-8,8′-biflavonyl from the corresponding 8-iodoflavone derivatives by the Ullmann reaction. Demethylation of the above

methoxybiflavonyls with aluminium chloride in boiling benzene gave the corresponding hydroxybiflavonyls. Ginkgetin has been synthesised by Nakazawa and Ito[14] by the cross Ullmann reaction between 3′-iodo-5-benzoyloxy-4′,7-dimethoxyflavone and 5-benzoyloxy-8-iodo-4′,7-dimethoxyflavone in the presence of activated copper powder and subsequent hydrolysis with 10 % sulphuric acid in acetic acid.



Ginkgetin

In this laboratory Shah[15] synthesised symmetrical biflavonyls by the Ullmann reaction on 7-methoxy-8-iodoflavone and 7-methoxy-6-iodo-3-benzoylflavone.

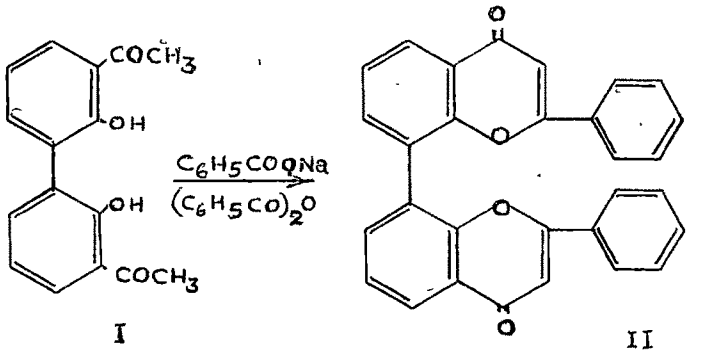
Other possible routes to symmetrical biflavonyls :

Other approaches to the synthesis of symmetrical biflavonyls are possible and it was thought of interest to investigate some of them. One approach is to start with a suitable biphenyl derivative and to build up the heterocyclic ring on each of the phenyl rings. This can be

done by various methods available for the synthesis of flavones. Some of these are given below.

(a) Kostanecki-Robinson acylation[16] :

A ketone of the type (1) can be subjected to Kostanecki-Robinson acylation by heating with the sodium salt of an aromatic acid and its anhydride and the biflavonyl (II) can be synthesised.



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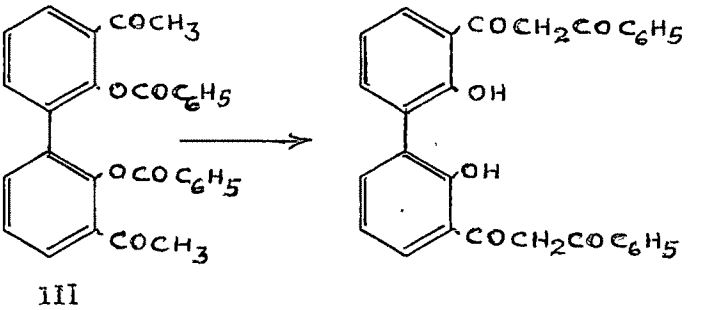
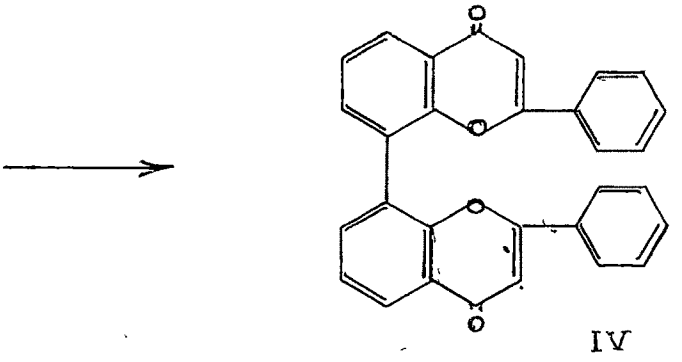
(b) A biphenyl derivative such as (III) can be subjected to Baker-Venkataraman[17] transformation and a biflavonyl such as (IV) can be synthesised.



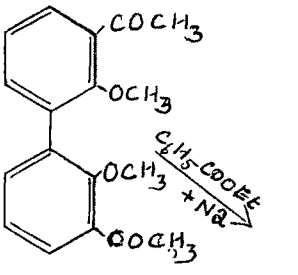
III



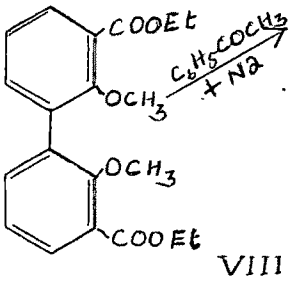
IV

(c) Cyclisation of β-diketones[18,19] :

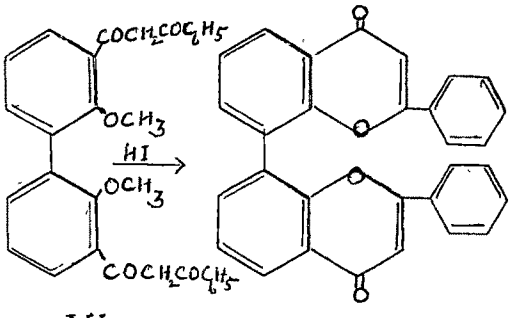
A biphenyl derivative such as (V) can be condensed with the ester of an aromatic acid and the β-diketone (VI) obtained subjected to cyclisation in the presence of hydriodic acid to (VII).



V



VIII

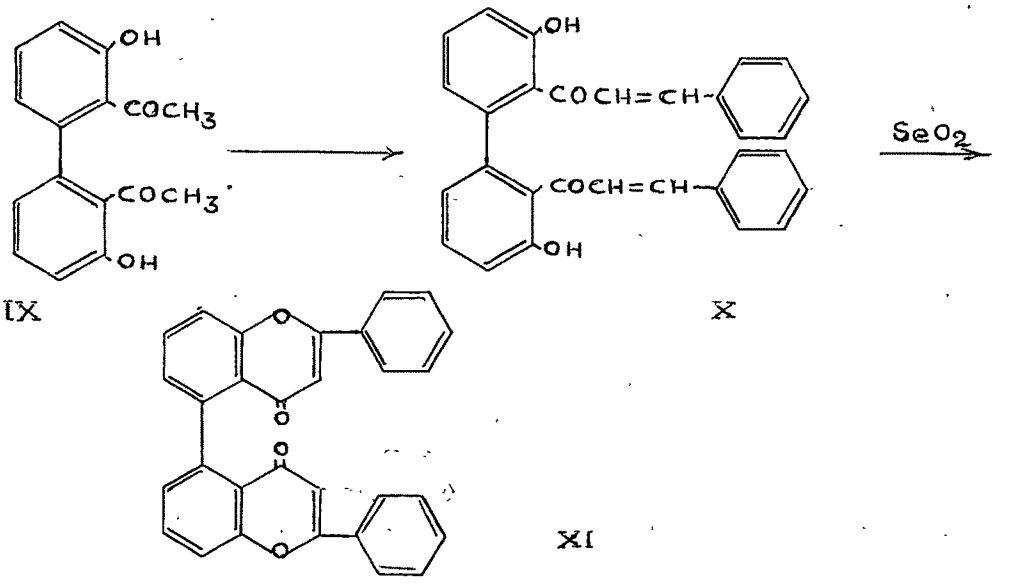


VI VII

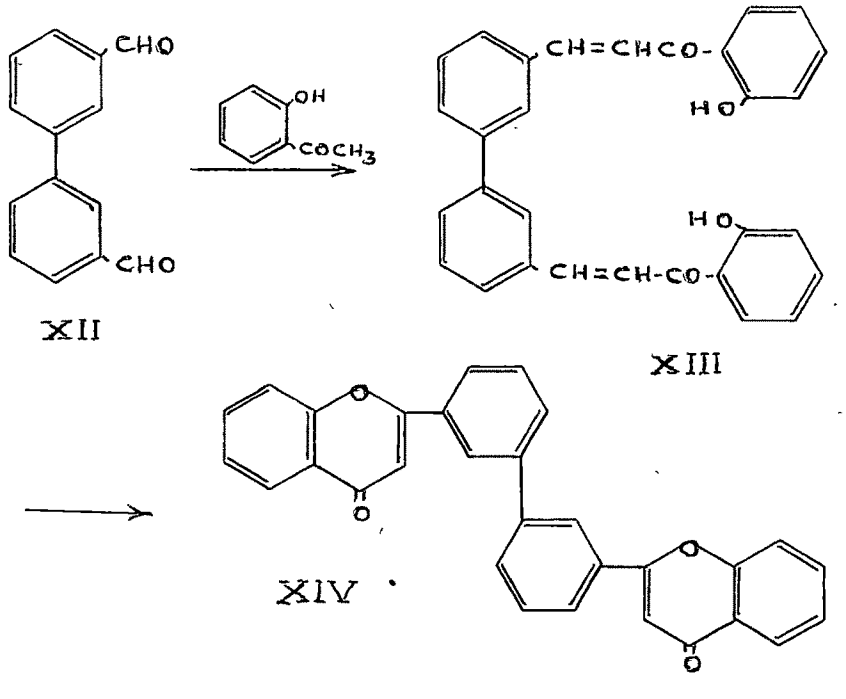
Alternately, an ester such as (VIII) can be condensed with an aromatic ketone and the β-diketone formed cyclized with hydriodic acid to the corresponding biflavonyl.

(d) Kostanecki & chalcone method[20] :

A ketone from a biphenyl such as (IX) can be condensed with an aromatic aldehyde and the bichalconyl derivative (X) formed can be cyclised and dehydrogenated with selenium dioxide[21] to get the biflavonyl derivative (XI).



Alternately, one could start with a diformyl derivative of a biphenyl such as (XII) and condense it with an o-hydroxy acetophenone to get a bichalconyl derivative (XIII) which can then be cyclised and dehydrogenated to a biflavonyl derivative (XIV).



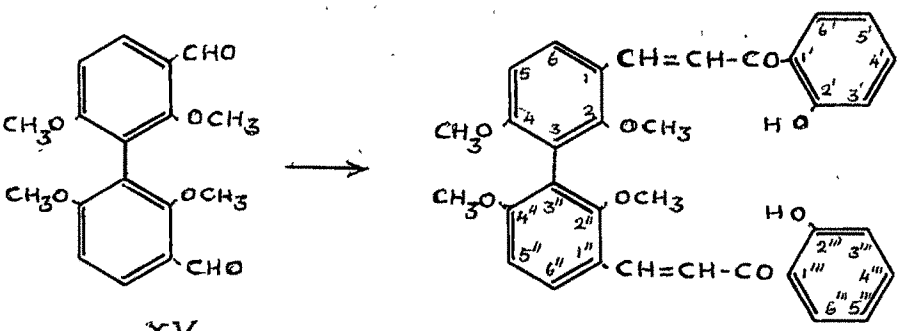
It will be seen from the above that by starting with a diacetyl derivative of a biphenyl one can obtain a biflavonyl with a linkage between the two flavone nuclei in the benzenoid part of the molecule and by starting with a diformyl derivative of a biphenyl one can synthesise a biflavonyl where the two flavonyl nuclei are linked through the side phenyl nuclei.

In this laboratory Mathai and Sethna[22] have synthesised some symmetrical biflavonyls such as (1) 6′,6‴-dimethoxy-3′,3‴-biflavonyl (2) 6′,6‴,7″,7‴-tetramethoxy-3′,3‴-biflavonyl (3) 4′,4‴-dimethoxy-3′,3‴-biflavonyl (4) 4′,4‴,7″,7‴-tetramethoxy-3′,3‴-biflavonyl (5) 6,6″-biflavonyl (6) 4′,4‴-dimethoxy-6,6″-biflavonyl by starting with an appropriate biphenyl derivatives and using the above mentioned approaches. They also synthesised the biflavonyls Nos. 1-5 by the Ullmann reaction on the appropriate iodo-flavone derivatives to confirm the structures.

The present work which was started simultaneously deals with the synthesis of several new symmetrical biflavonyls starting with suitable biphenyl derivatives.

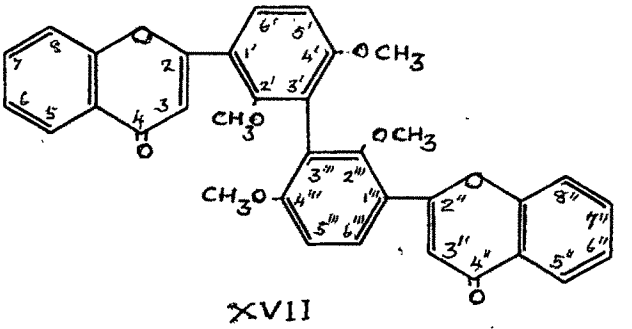
Synthesis of 2′,2‴,4′,4‴-tetramethoxy-3′,3‴-biflavonyl (XVII):

2,2′,6,6′-Tetramethoxy-3,3′-diformylbiphenyl (XV) prepared by the chloromethylation of 2,2′,6,6′-tetramethoxy biphenyl and subsequent Sommelet reaction on the resulting 2,2′,6,6′-tetramethoxy-3,3′-dichloromethylbiphenyl as described in Chapter II was condensed with 2-hydroxy acetophenone in the presence of alcoholic potassium hydroxide.

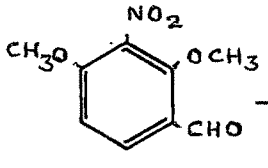


XV

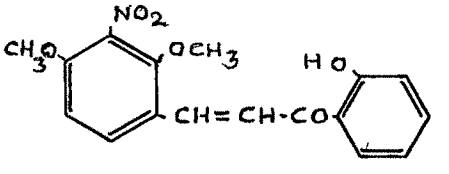
XVI



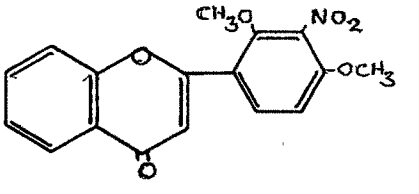
XVII



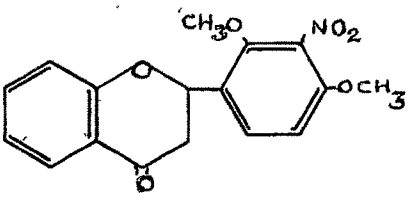
XVIII



XIX



XXI



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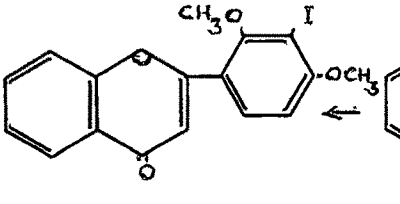
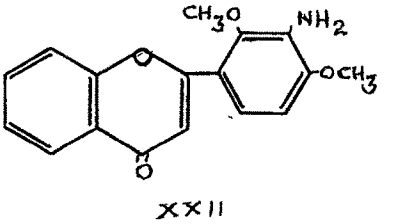


XXIII



XXII

The orange red product obtained on acidification gave tests for a chalcone such as (1) red colouration with conc. sulphuric acid, (2) yellow colouration with acetone (dry) solution of citric acid-boric acid mixture (Wilson Test[23]) and (3) a faint colouration with alcoholic ferric chloride[÷]. Moreover it gave a diacetoxy derivative when refluxed with acetic anhydride and fused sodium acetate. 2′,2‴-Dihydroxy-2,2″,4,4″-tetramethoxy-3,3″-bichalconyl (XVI) structure has therefore been assigned to this product. The above bichalconyl derivative on refluxing with selenium dioxide in iso-amyl alcohol gave a light yellow compound which gave a yellow colouration with sulphuric acid. The Wilson test was negative. 2′,2‴,4′,4‴-Tetramethoxy-3′,3‴-biflavonyl (XVII) structure was assigned to this compound.

An attempt was made to synthesise the same biflavonyl derivative for comparison by an alternate route as follows :-

2,4-Dimethoxy-3-nitro benzaldehyde[24] (XVIII) on condensation with 2-hydroxy acetophenone in the presence of alcoholic potassium hydroxide gave 2′-hydroxy-2,4-dimethoxy-3-nitro chalcone (XIX). The chalcone structure was established by the formation of a mono acetyl derivative,

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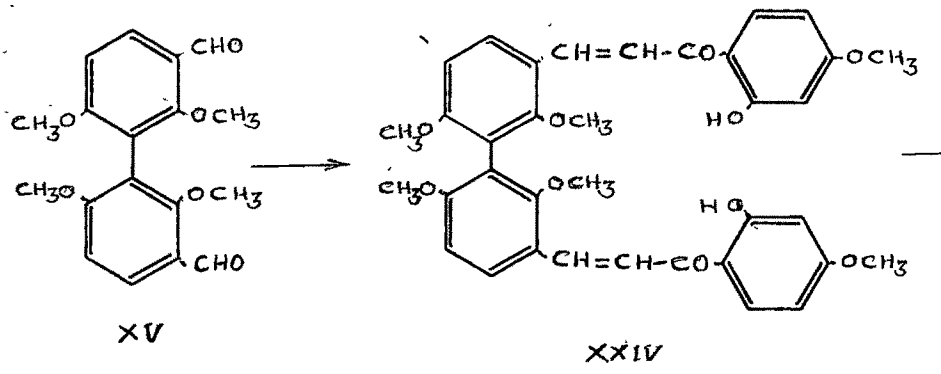
÷ Faint colouration may be due to the very sparing solubility of the bichalconyl derivative in alcohol.

positive ferric chloride and Wilson tests and deep red colouration with sulphuric acid. On refluxing with alcoholic hydrochloric acid a colourless compound, isomeric with the chalcone, was obtained to which 2',4'-dimethoxy-3'-nitroflavanone (XX) structure has been assigned. The above nitro chalcone on heating with selenium dioxide in amyl alcohol gave 2',4'-dimethoxy-3'-nitroflavone (XXI) which was reduced to the aminoflavone (XXII) by stannous chloride and hydrochloric acid. The aminoflavone on diazotisation and Sandmeyer's reaction gave the iodoflavone (XXIII). This on Ullmann reaction using diphenyl ether as solvent or without any solvent gave a deiodinated but impure compound which could not be purified.

2',2''',4',4''',7,7''-Hexamethoxy-3',3'''-biflavonyl (XXV) :

2,2',6,6'-Tetramethoxy-3,3'-diformylbiphenyl (XV) on condensation with 2-hydroxy-4-methoxy acetophenone in the presence of alcoholic potassium hydroxide gave an orange red product which gave tests for a chalcone and also gave a pale yellow diacetyl derivative. 2',2'''-Dihydroxy-2,2'',4,4',4'',4'''-Hexamethoxy-3,3''-bichalconyl (XXIV) structure has been assigned to the product. On refluxing with selenium dioxide in amyl alcohol it afforded a pale yellow product which gave yellow colouration with sulphuric acid and Wilson test was negative. To this product 2',2''',4',4''',7,7''-hexamethoxy-3',3'''-biflavonyl (XXV) structure has been assigned.



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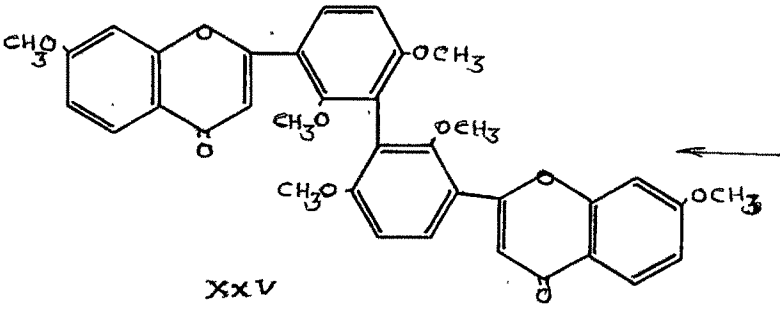
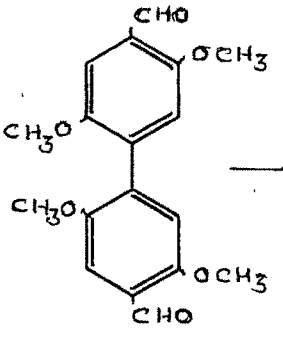
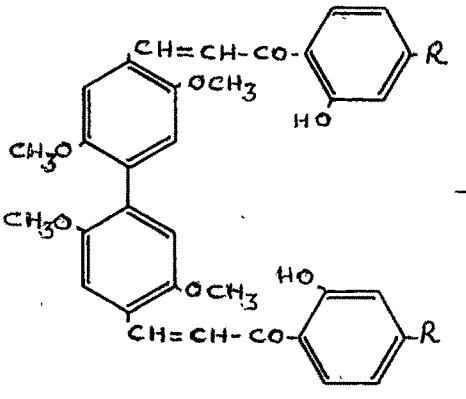
XXIV



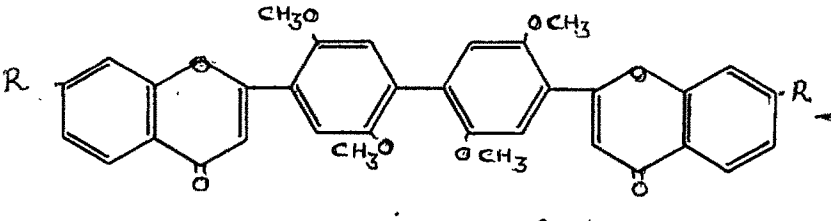
XXV



XXVI



XXVII a, R = H
XXVII b, R = OCH_3



XXVIII a, R = H
XXVIII b, R = OCH_3

Synthesis of 2′,2‴,5′,5‴-tetramethoxy-4′,4‴-biflavonyl (XXVIIIa) :

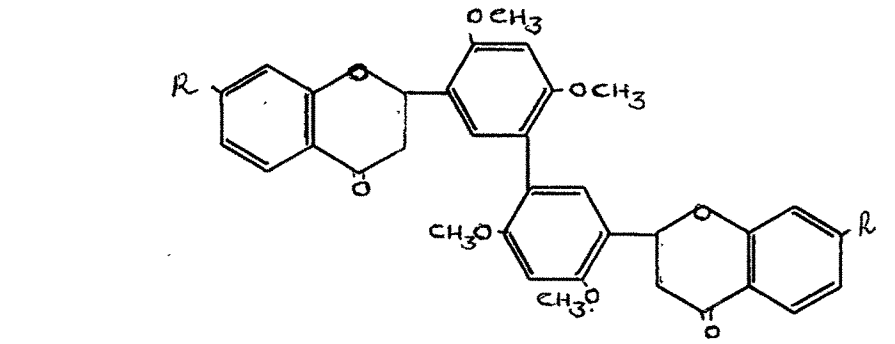
2,2′,5,5′-Tetramethoxy-4,4′-diformylbiphenyl (XXVI) prepared by the chloromethylation of 2,2′,5,5′-tetramethoxybiphenyl and subsequent Sommelet reaction as described in Chapter II, on condensation with 2-hydroxy acetophenone in the presence of alcoholic potassium hydroxide gave an orange red product which gave tests for a chalcone and also gave a pale yellow diacetyl derivative. 2′,2‴-Dihydroxy-2,2″,5,5″-tetramethoxy-4,4″-bichalconyl (XXVIIa) structure has therefore been assigned to the product. The above bichalconyl derivative on refluxing with selenium dioxide in amyl alcohol gave 2′,2‴,5′,5‴-tetramethoxy-4′,4‴-biflavonyl (XXVIIIa).

Synthesis of 2′,2‴,5′,5‴,7,7″-hexamethoxy-4′,4‴-biflavonyl (XXVIII b) :

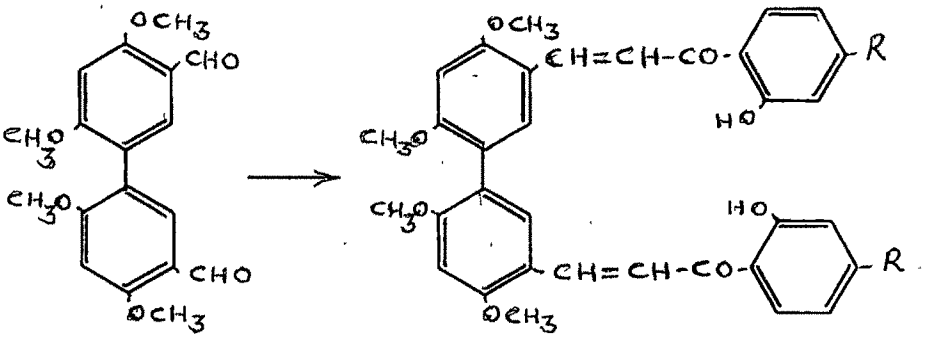
2,2′,5,5′-Tetramethoxy-4,4′-diformylbiphenyl (XXVI) on condensation with 2-hydroxy-4-methoxy acetophenone in the presence of alcoholic potassium hydroxide gave 2′,2‴-dihydroxy-2,2″,4′,4‴,5,5″-hexamethoxy-4,4″-bichalconyl (XXVII b). It gave a diacetyl derivative and tests for a chalcone. When refluxed with selenium dioxide in iso amyl alcohol it afforded the 2′,2‴,5′,5‴,7,7″-hexamethoxy-4′,4‴-biflavonyl (XXVIII b) which gave tests for a flavone.

Synthesis of 4′,4‴,6′,6‴-tetramethoxy-3′,3‴-biflavonyl (XXXII a) :

2,2′,4,4′-Tetramethoxy-5,5′-diformyl biphenyl(XXIX)

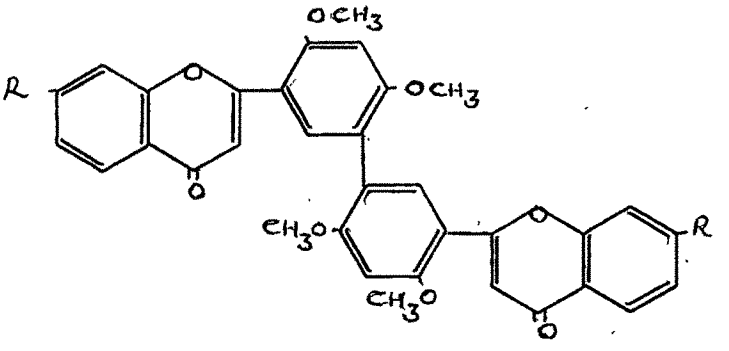


xxxi , R = H



xxix

xxx a, R = H
xxx b, R = OCH3



xxxii a, R = H

prepared by the chloromethylation of 2,2′,4,4′-tetramethoxy-biphenyl and subseugent Sommelet reaction on the 5,5′-dichloromethyl derivative as described in Chapter II on condensation with o-hydroxyacetophenone in the presence of alcoholic potassium hydroxide gave an orange product which gave a diacetyl derivative and gave positive tests for a chalcone. 2′,2‴-Dihydroxy-4,4″,6,6″-tetramethoxy-3,3″-bichalconyl (XXX a) structure has therefore been assigned to the product. On refluxing with alcoholic hydrochloric acid it gave the pale yellow isomeric 3′,3‴-biflavanonyl (XXXI). 2′,2‴-Dihydroxy-4,4″,6,6″-tetramethoxy-3,3″-bichalconyl when refluxed with selenium dioxide in isoamyl alcohol furnished the 3′,3‴-biflavonyl (XXXII a) which gave tests for a flavone.

Attempted synthesis of 4′,4‴,6′,6‴,7,7″-hexamethoxy-3′,3‴-biflavonyl :

2,2′,4,4′-Tetramethoxy-5,5′-diformyl biphenyl (XXIX) on condensation with 2-hydroxy-4-methoxy acetophenone in the presence of alcoholic potassium hydroxide gave a yellow coloured product to which 2′,2‴-dihydroxy-4,4′,4″,4‴,6,6″-hexamethoxy-3,3″-bichalconyl (XXX b) structure has been assigned as it gave a diacetyl derivative and colour reactions of a chalkone derivative. It gave the original bichalconyl (XXX b) on refluxing with selenium dioxide in isoamyl alcohol.

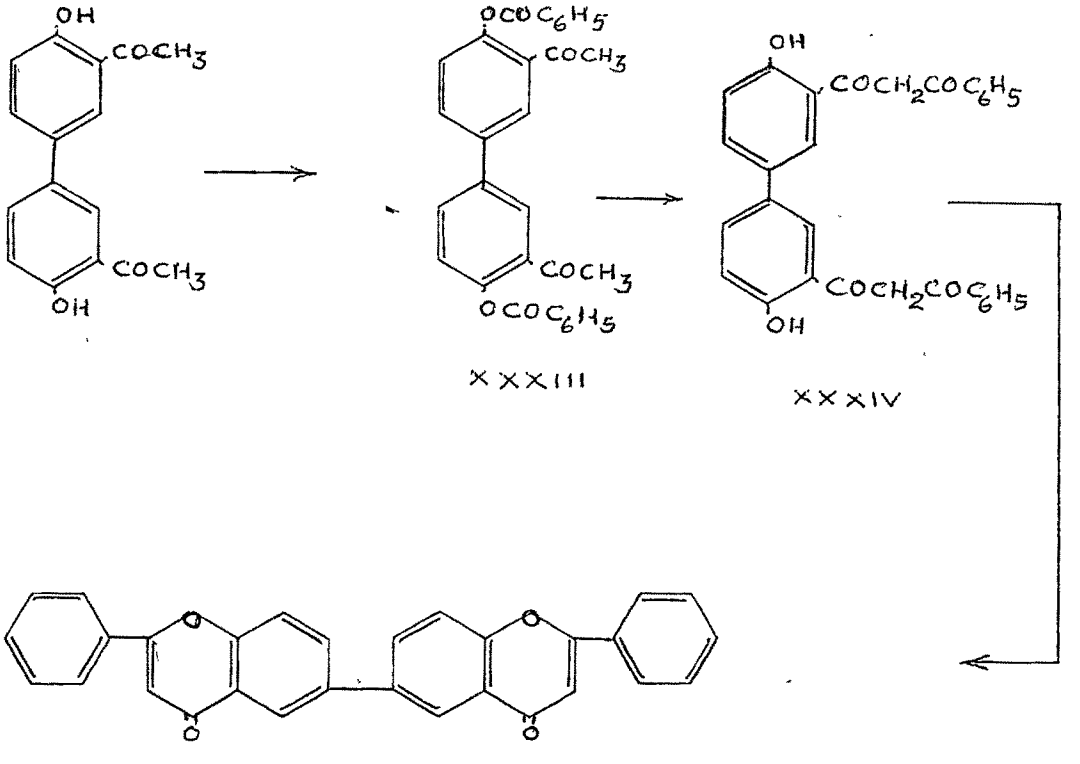
Synthesis of 6,6″-biflavonyl

With a view to explore other approaches to the synthesis of biflavonyl, 4,4′-dibenzoyloxy-3,3′-diacetyl-

b

biphenyl (XXXIII) was subjected to Baker-Vankataraman rearrangement as modified by Looker et al[25] which consists in treating the o-benzoyl derivative with powdered caustic alkali and pyridine.

4,4'-Dibenzoyloxy-3,3'-diacetylbiphenyl (XXXIII) when kept with powdered caustic potash and pyridine for 4 hours at room temperature gave the β-diketone (XXXIV). This on cyclisation by keeping in contact with cold conc. sulphuric acid for 4 hours or on boiling with glacial acetic acid for 8 hours gave a product which was found to be identical on direct comparison with 6,6-biflavonyl (XXXV) prepared by Mathai and Sethna[22] by other methods.



XXXIII XXXIV XXXV

EXPERIMENTAL

2′,2‴-Dihydroxy-2,2″,4,4″-tetramethoxy-3,3″-bichalconyl :

A mixture of 2,2′,6,6′-tetramethoxy-3,3′-diformyl biphenyl (3.3 g. ; 0.01 M) and 2-hydroxy acetophenone (5.5 g. ; 0.04 M), alcohol (100 ml.) and potassium hydroxide (30 g. ; 30 ml. water) was refluxed on a steam bath till the mixture became clear. It was kept overnight. It was acidified with conc.hydrochloric acid, and the precipitated orange product crystallised from xylene in orange cubes, m.p. 235°. Yield 3 g. It gave a positive Wilson test and a deep red colouration with conc. sulphuric acid. With alcoholic ferric chloride it gave only a faint colouration.

Analysis : Found : C, 72.0 % ; H, 5.1 %.

$C_{34}H_{30}O_8$ requires : C, 72.1 % ; H, 5.3 %.

The diacetyl derivative of the above bichalconyl (0.5 g.) was prepared by heating with acetic anhydride (5 g.) and fused sodium acetate (2 g.) on a steam bath for 2 hours. it crystallised from benzene-petroleum ether, m.p. 155°.

Analysis : Found : C, 70.3 % ; H, 5.3 %.

$C_{38}H_{34}O_{10}$ requires : C, 70.1 % ; H, 5.2 %.

2′,2‴,4,4‴-Tetramethoxy-3′,3‴-biflavonyl :

A mixture of 2′,2‴dihydroxy-2,2″,4,4″-tetramethoxy-3,3″-bichalconyl (1 g.), selenium dioxide (6 g.) and dry isoamyl alcohol (40 ml.) was refluxed in an oil bath

at 140-50° for 18 hours. It was filtered hot. The residue after removing the isoamyl alcohol by steam distillation crystallised from benzene-petroleum ether in pale yellow needles, m.p. 215°. It gave a pale yellow colouration with conc. sulphuric acid and the Wilson test was negative.

Analysis : Found : C, 72.8 % ; H, 4.6 %.

$C_{34}H_{26}O_8$ requires : C, 72.6 % ; H, 4.6 %.

2'-Hydroxy-2,4-dimethoxy-3-nitrochalcone :

To a mixture of 2,4-dimethoxy-3-nitro benzaldehyde[24] (2.1 g. ; 0.01 M) and 2-hydroxy acetophenone (2.7 g.; 0.02 M) in alcohol (25 ml.), potassium hydroxide (5 g. in 5 ml. water) was added and the mixture kept overnight in a well stoppered flask. The mixture after dilution with water and acidification gave an orange red precipitate which crystallised from benzene in orange needles, m.p. 163°. Yield 3.1 g. It gave the following tests (1) orange colour with conc. sulphuric acid (2) brown colour with ferric chloride (3) positive Wilson test.

Analysis : Found : C, 62.3 % ; H, 4.2 % ; N, 4.5 %.

$C_{17}H_{15}NO_6$ requires : C, 62.0 % ; H, 4.6 % ; N, 4.3 %.

The acetyl derivative : Prepared from the above chalcone (0.5 g.) by heating with acetic anhydride (3 g.) and fused sodium acetate (2 g.) on a steam bath for 2 hours. It crystallised from benzene, m.p. 114°.

Analysis : Found : C, 59.7 %; H, 4.7 %; N, 4.2 %.

$C_{19}H_{27}NO_7$ requires : C, 60.0 % ; H, 4.7%; N, 3.9 %.

2',4'-Dimethoxy-3'-nitroflavanone :

2'-Hydroxy-2,4-dimethoxy-3-nitrochalcone (0.5 g.) was refluxed with alcohol (50 ml.) containing hydrochloric acid (5 ml.) for 24 hours over a steam bath. It was filtered hot and on cooling, the colourless crystals of nitroflavanone separated which crystallised from benzene in colourless needles, m.p. 164°. Mixed m.p. with the isomeric nitrochalcone was depressed by 10°.

Analysis : Found : C,61.7 % ; H,4.2 % ; N,4.2 %.

$C_{17}H_{15}NO_6$ requires : C,62.0 % ; H,4.6 % ; N,4.3 %.

2',4'-Dimethoxy-3'-nitroflavone :

2'-Hydroxy-2,4-dimethoxy-3-nitrochalcone (0.5 g.) was dissolved in dry isoamyl alcohol (15 ml.) and the solution refluxed with selenium dioxide (2 g.) in an oil bath at 140-50° for 10 hours. It was filtered hot and the filtrate on cooling gave crystals of the flavone. It crystallised from benzene in yellow needles, m.p.166°. Mixed m.p. with the nitrochalcone was depressed by more than 10°. The mother liquor on removal of the solvent by steam distillation gave a further crop of nitroflavone.

Analysis : Found : C,62.1 % ; H,4.4 % ; N,4.4 %.

$C_{17}H_{13}NO_6$ requires : C,62.1 % ; H,4.0 % ; N,4.3 %.

2',4'-Dimethoxy-3'-aminoflavone :

Stannous chloride (2 g.) was dissolved in glacial acetic acid (4 ml.) and 2 drops of conc.hydrochloric acid

were added. 2',4'-Dimethoxy-3'-nitroflavone (0.5 g.) was added to the above mixture and hydrogen chloride was passed through the reaction mixture. The precipitated amine hydrochloride was filtered, dissolved in water and neutrallised with sodium hydroxide. The aminoflavone obtained crystallised from acetic acid, m.p. 152°.

Analysis : Found : C,68.2 % ; H,4.7 %; N,4.7 %.

$C_{17}H_{15}NO_4$ requires : C,68.7 % ; H,5.1 %; N,4.7 %.

2',4'-Dimethoxy-3'-iodoflavone :

2',4'-Dimethoxy-3'-aminoflavone (1 g.) was dissolved in hydrochloric acid (1 : 1 ; 10 ml.) and the solution cooled below 5°. Sodium nitrite solution (0.5 g. in 2 ml. water) was then added portionwise. The reaction mixture was kept for 30 minutes below 5°. Potassium iodide (2 g. in 5 ml. water) was added to it and the mixture was kept for one hour at room temperature. It was heated on a steam bath for 1 hour and the product which separated was filtered and crystallised from acetic acid, m.p. 183°.

Analysis : Found : C, 49.8 % ; H, 3.0 % ; I, 31.0 %.

$C_{17}H_{13}IO_4$ requires : C, 50.0 % ; H, 3.2 % ; I, 31.1 %.

Attempted Ullmann reaction on 2',4'-dimethoxy-3'-iodoflavone :

A mixture of 2',4'-dimethoxy-3'-iodoflavone (1 g.) and copper bronze (3 g.) was refluxed in diphenyl ether (20 ml.) over a wire gauze for 5 hours. It was filtered

hot and the filtrate was steam distilled to remove the diphenyl ether. The residue on crystallisation did not give the expected biflavonyl, instead of that an impure product which did not contain iodine was obtained.

The Ullmann reaction was carried out by heating the above mixture without any solvent in an oil bath at 190°. On working up the reaction mixture as before a product similar to the above was obtained.

2′,2‴-Dihydroxy-2,2″,4,4′,4″,4‴-hexamethoxy-3,3″-bichalconyl :

A mixture of 2,2′,6,6′-tetramethoxy-3,3′-diformyl-biphenyl (3.3 g. ; 0.01 M), prepared as described in Chapter II, and 2-hydroxy-4-methoxy acetophenone (6 g. ; 0.04 M) , alcohol (60 ml.) and potassium hydroxide (10 g. in 10 ml. water) was refluxed on a steam bath till the mixture became clear. It was kept overnight. On working up as usual, the yellow coloured chalcone was obtained which crystallised from benzene in orange coloured needles, m.p. 215°. Yield 3.5 g.

Analysis : Found : C, 69.2 % ; H, 5.6 %.

$C_{36}H_{34}O_{10}$ requires : C, 69.0 % ; H, 5.3 %.

The diacetyl derivative : Prepared as usual by refluxing the above bichalconyl derivative (1 g.) with acetic anhydride (10 ml.) and fused sodium acetate (3 g.). It crystallised from benzene in yellow coloured plates, m.p. 165-66°

Analysis : Found : C, 67.1 % ; H, 5.3 %.
$C_{40}H_{38}O_{12}$ requires : C, 67.4 % ; H, 5.6 %.

2',2''',4,4''',7,7''-Hexamethoxy-3',3'''-biflavonyl :

2',2'''-Dihydroxy-2,2'',4,4,4'',4'''-hexamethoxy-3,3''-bichalconyl (1 g.) was mixed with selenium dioxide (6 g.) and isoamyl alcohol (40 ml.) and refluxed in an oil bath at 140-50° for 17 hours. It was filtered hot. On cooling, light yellow biflavonyl derivative precipitated out which crystallised from xylene in pale yellow cubes, m.p. 255°. On removal of isoamyl alcohol from the filtrate by steam distillation a further crop of the biflavonyl was obtained.

Analysis : Found : C, 69.5 % ; H, 4.6 %.
$C_{36}H_{30}O_{10}$ requires : C, 69.5 % ; H, 4.8 %.

2',2'''-Dihydroxy-2,2'',5,5''-tetramethoxy-4,4''-bichalconyl :

A mixture of 2-hydroxy acetophenone (5.5 g. ; 0.04 M) and 2,2',5,5'-tetramethoxy-4,4'-diformylbiphenyl (3.3 g. ; 0.01 prepared as described in Chapter II, in alcohol (50 ml.) and potassium hydroxide (10 g. in 10 ml. of water) was refluxed on a steam bath till the solution became clear and then kept for 4 hours. It was acidified with conc. hydrochloric acid and the precipitated bichalconyl derivative crystallised from nitrobenzene in orange needles, m.p. 267°. Yield 3.4 g. It gave a red colouration with conc. sulphuric acid, a faint colouration with alcoholic ferric chloride and a positive Wilson test.

Analysis : Found : C, 72.0 % ; H, 5.2 %.

$C_{34}H_{30}O_8$ requires : C, 72.1 % ; H, 5.3 %.

The diacetyl derivative : Prepared as usual and crystallised from benzene-petroleum ether in yellow needles gave m.p. 143°.

Analysis : Found : C, 69.9 % ; H, 5.4 %.

$C_{38}H_{34}O_{10}$ requires : C, 70.1 % ; H, 5.4 %.

2′,2‴,5′,5‴-Tetramethoxy-4′,4‴-biflavonyl :

2′,2‴-Dihydroxy-2,2″,5,5″-tetramethoxy-4,4″,-bichalconyl mixed with selenium dioxide (6 g.) was refluxed in isoamyl alcohol (50 ml.) in an oil bath at 140-50° for 16 hours. The product obtained on working up as before crystallised from diphenyl ether, m.p.288°. It gave a yellow colouration with sulphuric acid and the Wilson test was negative.

Analysis : Found : C, 73.0 % ; H, 4.4 %.

$C_{34}H_{26}O_8$ requires : C, 72.6 % ; H, 4.6 %.

2′,2‴-Dihydroxy-2,2″,4,4‴,5,5″-hexamethoxy-4,4″-bichalconyl :

A solution of 2,2′,5,5′-tetramethoxy-4,4′-diformyl-biphenyl (3.3 g. ; 0.01 M) and 2-hydroxy-4-methoxy acetophenone (6 g. ; 0.04 M) in alcohol and potassium hydroxide (15 g. in 15 ml. water) were heated on a steam bath till the solution became clear. The reaction mixture was kept overnight. The product obtained on

acidification crystallised from xylene in orange needles, m.p. 235°. It gave a positive Wilson test and a deep red colouration with conc.sulphuric acid. With alcoholic ferric chloride it gave only a faint colouration.

Analysis : Found : C, 69.0 % ; H, 5.5 %.

$C_{36}H_{34}O_{10}$ requires : C, 69.0 % ; H, 5.4 %.

The diacetyl derivative : Prepared by refluxing the above bichalconyl derivative with acetic anhydride and sodium acetate for 1 hour was crystallised from benzene-petroleum ether in pale yellow plates, m.p. 150°.

Analysis : Found : C, 67.5 % ; H, 5.8 %.

$C_{40}H_{38}O_{12}$ requires : C, 67.4 % ; H, 5.6 %.

2',2''',5',5''',7,7''-Hexamethoxy-4,4'''-biflavonyl :

A mixture of 2',2'''-dihydroxy-2,2'',4,4''',5,5''-hexamethoxy-4,4''-bichalconyl (0.5 g.), selenium dioxide (3 g.) and dry isoamyl alcohol (20 ml.) was refluxed in an oil bath at 140-50° for 18 hours. It was filtered hot. On cooling, the biflavonyl separated which was crystallised from xylene. M.P. 291°. On removing the isoamyl alcohol by steam distillation a further crop of biflavonyl was obtained. It gave a pale yellow colouration with conc. sulphuric acid and Wilson test was negative.

Analysis : Found : C, 69.7 % ; H, 5.1 %.

$C_{36}H_{30}O_{10}$ requires : C, 69.5 % ; H, 4.8 %.

2′,2‴-Dihydroxy-4,4″,6,6″-tetramethoxy-3,3″-bichalconyl :

A mixture of 2,2′,4,4′-tetramethoxy-5,5′-diformyl-biphenyl (3.3 g. ; 0.01 M), prepared as described in Chapter II, and 2-hydroxy acetophenone (5.5 g. ; 0.04 M) in alcohol (150 ml.) and potassium hydroxide (30 g. in 30 ml. water) was refluxed on a steam bath till the mixture became clear. It was kept for 2 days. The orange coloured product obtained on acidification crystallised from xylene in orange cubes, m.p. 255°. It gave a positive Wilson test and a deep red colouration with conc. sulphuric acid. With alcoholic ferric chloride it gave only a faint colouration.

Analysis : Found : C, 72.4 % ; H, 5.0 %.

$C_{34}H_{30}O_8$ requires : C, 72.1 % ; H, 5.3 %.

The diacetyl derivative : Prepared as before and crystallised from benzene in pale yellow needles gave m.p. 212°.

Analysis : Found : C, 70.41 % ; H, 5.1 %.

$C_{38}H_{34}O_{10}$ requires : C, 70.10 % ; H, 5.2 %.

4′,4‴,6′,6‴-Tetramethoxy-3′,3‴-biflavanonyl :

2′,2‴-Dihydroxy-4,4″,6,6″-tetramethoxy-3,3″-bichalconyl (1 g.) was refluxed with alcoholic hydrochloric acid on a steam bath for 30 hours. The product obtained after removal of alcohol crystallised from xylene in pale yellow needles, m.p. 270°.

Analysis : Found : C, 72.2 % ; H, 5.3 %.

$C_{34}H_{30}O_8$ requires : C, 72.1 % ; H, 5.3 %.

4',4''',6',6'''-Tetramethoxy-3',3'''-biflavonyl :

A mixture of 2',2'''-dihydroxy-4,4'',6,6''-tetramethoxy-3,3'',-bichalconyl (1 g.), selenium dioxide (5 g.) and isoamyl alcohol (30 ml.) was refluxed in an oil bath at 140-50° for 16 hours. It was filtered hot and the product obtained on cooling crystallised from nitrobenzene in yellow plates, m.p. 328°. It gave a pale yellow colouration with conc. sulphuric acid and the Wilson test was negative.

Analysis : Found : C, 72.1 % ; H, 4.5 %.

$C_{34}H_{26}O_8$ reqiures : C, 72.6 % ; H, 4.6 %.

2',2'''-Dihydroxy-4,4',4'',4''',6,6''-hexamethoxy-3,3''-bichalconyl :

A mixture of 2,2',4,4'-tetramethoxy-5,5'-diformyl biphenyl (3.3 g. ; 0.01 M) and 2-hydroxy-4-methoxy acetophenone (6 g. ; 0.04 M) in alcohol (60 ml.) and potassium hydroxide (15 g. in 15 ml. water) was refluxed on a steam bath till the mixture became clear. It was kept overnight. The product obtained on acidification crystallised from nitrobenzene, m.p. 320°. It gave red colouration with conc. sulphuric acid, pale yellow colouration with alcoholic ferric chloride and positive Wilson test.

Analysis : Found : C, 68.7 % ; H, 5.4 %.
$C_{36}H_{34}O_{10}$ requires : C, 69.0 % ; H, 5.4 %.

The diacetyl derivative : Prepared as before and crystallised from benzene-petroleum ether in pale yellow needles gave m.p. 191°.

Analysis : Found : C, 67.1 % ; H, 5.3 %.
$C_{40}H_{38}O_{12}$ requires : C, 67.4 % ; H, 5.6 %.

Attempted cyclization of 2',2'''-dimethoxy-4,4',4'',4''',6,6''-hexamethoxy-3,3''-bichalcoryl :

A mixture of 2',2'''-dihydroxy-4,4',4'',4''',6,6''-hexamethoxy-3,3''-bichalcoryl (1 g.), selenium dioxide (5 g.) and iso-amyl alcohol (150 ml.) was refluxed in an oil bath at 140-50° for 24 hours. The reaction mixture on working up as usual gave the original bichalcoryl instead of the biflavoryl.

4,4'-Dibenzoyloxy-3,3'-diacetylbiphenyl :

4,4'-Dihydroxy-3,3'-diacetylbiphenyl (1 g.) was dissolved in acetone and benzoyl chloride (3 ml.) and anhydrous potassium carbonate (8 g.) was added. The reaction mixture was refluxed on a steam bath for 8 hours. Most of the acetone was removed and the product obtained on pouring the reaction mixture into water crystallised from acetic acid, m.p. 175°.

Analysis : Found : C, 75.6 % ; H, 4.6 %.
$C_{30}H_{22}O_6$ requires : C, 75.3 % ; H, 4.6 %.

4,4′-Dihydroxy-3,3′-di(ω-benzoyl acetyl) bipheryl :

The 4,4′-dibenzoyloxy-3,3′-diacetylbipheryl (0.5 g.) was dissolved in minimum quantity of pyridine and powdered potassium hydroxide (3 g.) was added with stirring. The reaction mixture was kept for 4 hours at room temperature, and then poured in ice cold hydrochloric acid. The product obtained crystallised from xylene, m.p. 253°. It was soluble in alkali.

Analysis : Found : C, 75.7 % ; H, 4.4 %.

$C_{30}H_{22}O_6$ requires : C, 75.3 % ; H, 4.6 %.

6,6″-Biflavonyl :

The above β-diketone (0.5 g.) was mixed with conc. sulphuric acid (5 ml.) and kept at room temperature for 4 hours. The product obtained on pouring the reaction mixture in ice cold water crystallised from glacial acetic acid, m.p. 312°.

The cyclisation was also carried out by refluxing the β-diketone (0.5 g.) with glacial acetic acid (10 ml.) for 8 hours. The product obtained on cooling crystallised from glacial acetic acid.

Mathai and Sethna[22] prepared the same compound by other methods. Mixed m.p. with their sample was not depressed.

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