CHAPTER IV

BIFLAVONYLS

CHAPTER IV

THEORETICAL

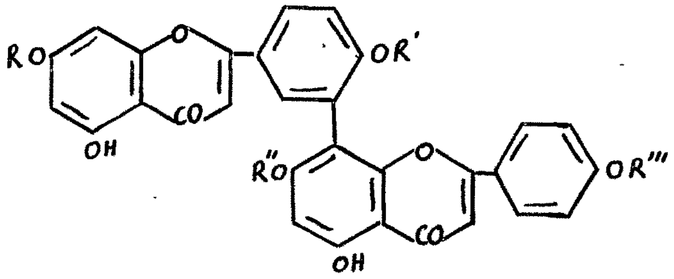
Biflavonyls

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

The story of biflavonyls begins with the isolation by Furukawa (1) of a yellow phenolic product in 1932 from the autumn leaves of the Gingko biloba or maidenhair tree. To this yellow phenolic compound he gave the 5,8-dihydroxy-4'-methoxyflavone structure but the synthesis of this compound showed that the structure was incorrect. Examination of Furukawa's evidence led Baker (2) and his co-workers 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. So they synthesised various flavanoids including furanoflavones ; but they were all 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 three had similar skeletal structures and that these were biflavonyl derivatives.

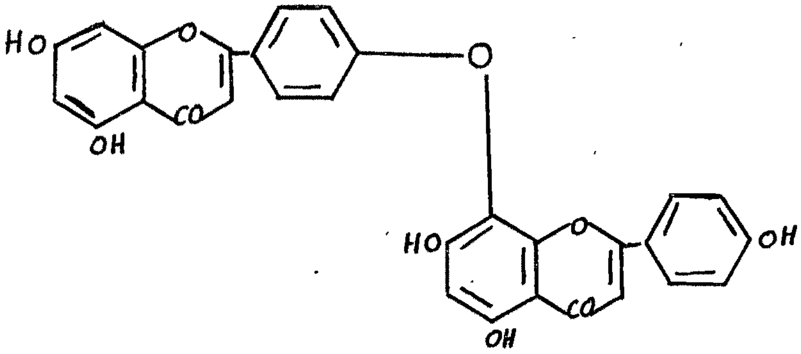
Ollis (4) has summarised the work done on biflavonyls upto 1961.

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 ultra violet and infra red spectra. Ginkgetin, isoginkgetin, sciadopitysin, kayaflavone, and sotetsuflavone are some of the important biflavonyl derivatives isolated from gingko biloba, sciadopitys verticillata (umbrella pine), gymnosperm torreyanucifera sieb et. zucc and cycad cycas revoluta thunb, respectively. The structures of the above biflavonyls have been established. The structures with the 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
Kayaflavone (6)	H	Me	Me	Me
Sotetsuflavone (7)	H	H	H	H

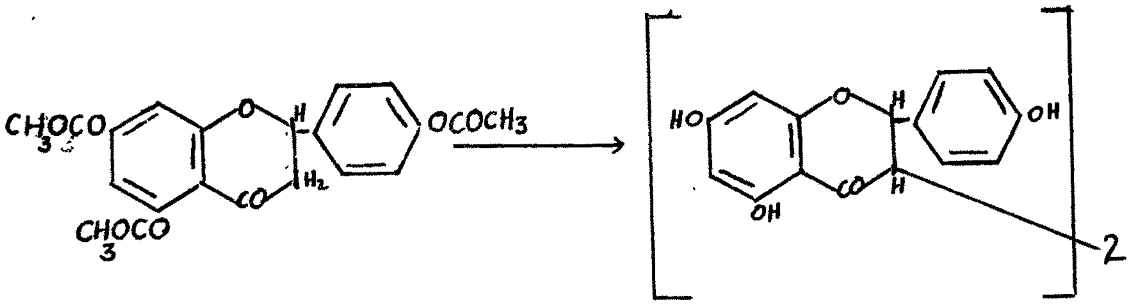
Hinokiflavone (8) isolated from the leaves of "Cryptomeria japonica" has been shown to be a biflavonyl ether.



Hinokiflavone

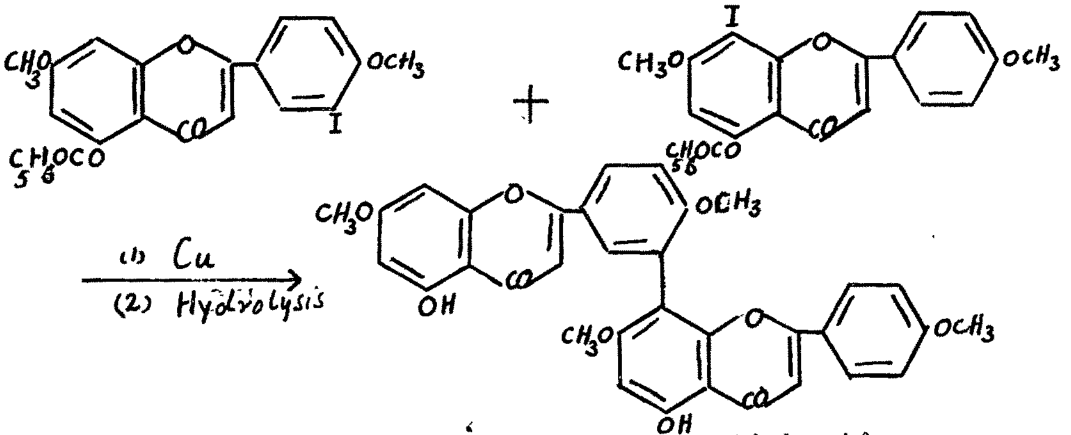
The biflavonyls are probably produced in the plant by oxidative coupling of a flavanoid precursor such as epigenin or a closely related compound. This could be followed by methylation of the di-epigeninyl in various positions and this is in agreement with the simultaneous occurrence of various biflavonyls 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. It would be of interest if it could be proved that a labelled epigenin is converted into labelled biflavonyl by feeding it to a suitable plant.

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''-biflavanonyl as a byproduct. They did not give a definite proof for this compound : but gave the bimolecular structure to this compound 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'-methoxyflavanol derivatives did not succeed.

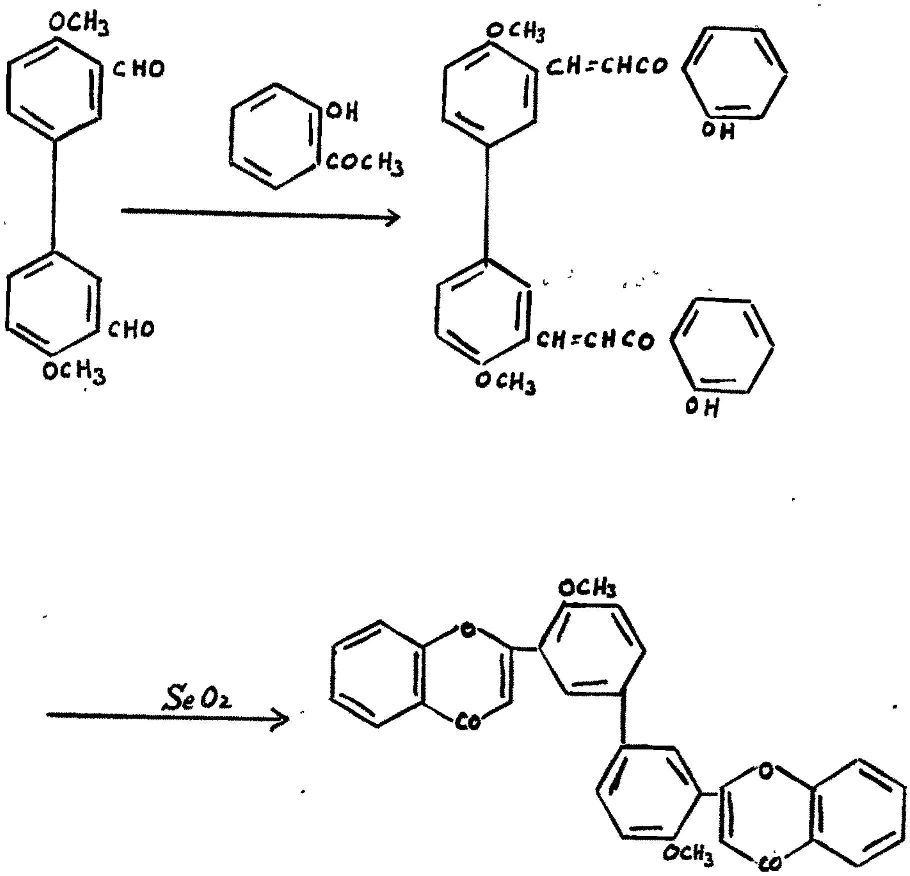
Other symmetrical biflavonyls have been synthesised through the Ullmann reaction on the appropriate halogenoflavones. Thus 3-bromo, 6-iodo, 6-iodo-4'-methoxy, 7-iodo, 7-iodo-4'-methoxy, 8-iodo, 8-bromo, 8-chloro, 3'-iodo and 4'-iodoflavone derivatives were converted into their respective biflavonyls by Chen et al. (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 methoxy biflavonyls with aluminium chloride in boiling benzene gave the corresponding hydroxy biflavonyls. In this laboratory Shah (14) has synthesised symmetrical biflavonyls by the Ullmann reaction on 7-methoxy-8-iodoflavone, and 7-methoxy-6-iodo-3-benzoylflavone. Recently, ginkgetin was synthesised by Nakazawa and Ito (15) by the crossed Ullmann reaction between 3'-iodo-5-benzoyloxy-4',7-dimethoxy flavone 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.

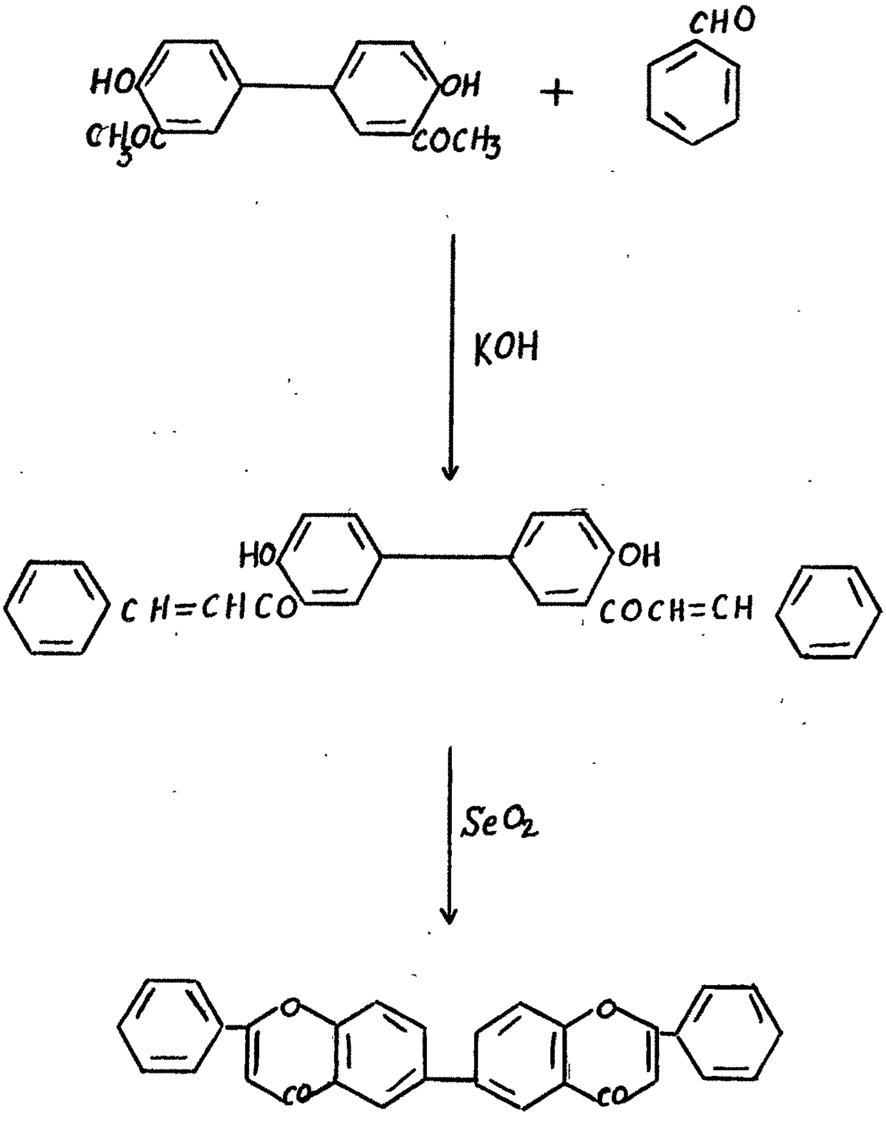


Ginkgetin

Chen (16) synthesised 7,7''-,8,8''-,3',3'''- and 4',4'''-biflavonyl derivatives by the Ullmann reaction on methoxy iodoflavone derivatives.

Mathai and Sethna (17) prepared 3',3''' - and 6,6''-biflavonyls by cyclising the bichalkoyl derivatives, obtained from the condensation of 2,2'-and 4,4'-dimethoxy 3,3'-diformyl-biphenyls with 2-hydroxyacetophenone and from the condensation of 4,4'-dihydroxy-3,3'-diacetyl-biphenyl with benzaldehyde respectively.



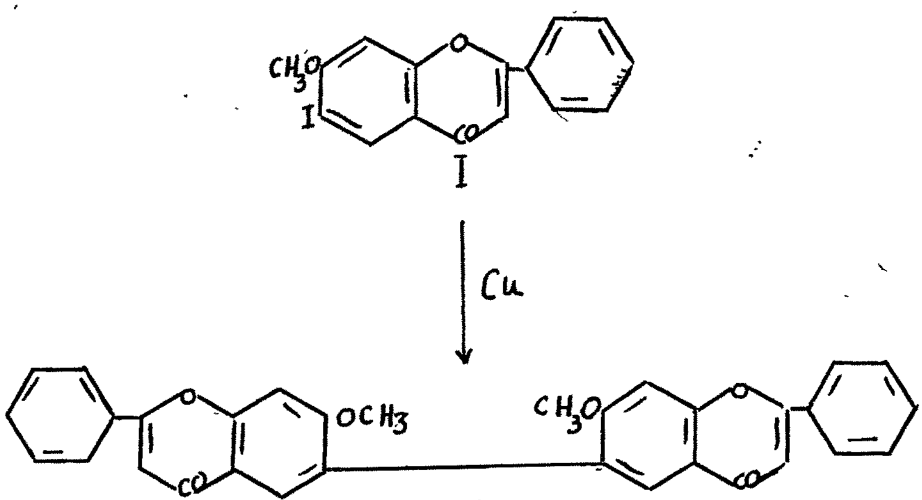


The present work deals with the synthesis of the hitherto unknown

7,7''-dimethoxy-6,6''-, 7,7'',4',4'''-tetramethoxy-6,6''-, and 6,6''-dimethoxy-5,5''-biflavonyl from the iodoflavones described in Chapter II.

Synthesis of 7,7''-dimethoxy-6,6''-biflavonyl by Ullmann reaction on 7-methoxy-6-iodoflavone :

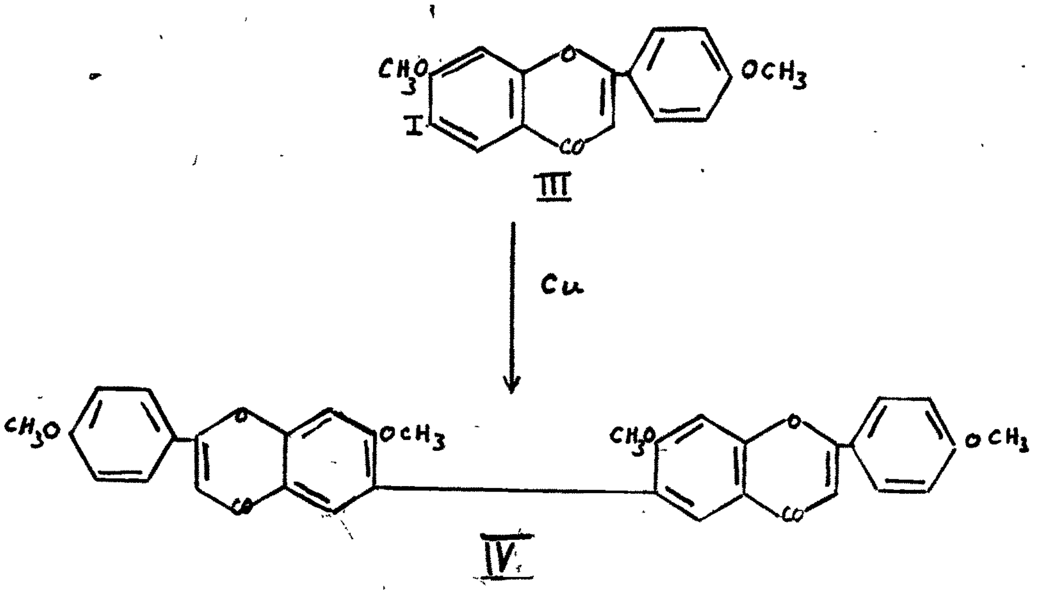
7-Methoxy-6-iodoflavone (I) when subjected to Ullmann reaction with copper bronze at 240-250° gave an iodine free product m.p. 337° which was different from 7-methoxyflavone. It has been assigned the 7,7''-dimethoxy-6,6''-biflavonyl (II) structure. It was also obtained by carrying out the reaction in diphenyl ether.



II

Synthesis of 7,7'',4',4'''-tetramethoxy-6,6''-biflavonyl by Ullmann reaction on 7,4'-dimethoxy-6-iodoflavone :

7,4'-Dimethoxy-6-iodoflavone (III) on Ullmann reaction with copper bronze at 240-250° gave an iodine free product m.p. 326° which was different from 7,4'-dimethoxyflavone. To this 7,7'',4',4'''-tetramethoxy-6,6''-biflavonyl (IV) structure has been assigned.

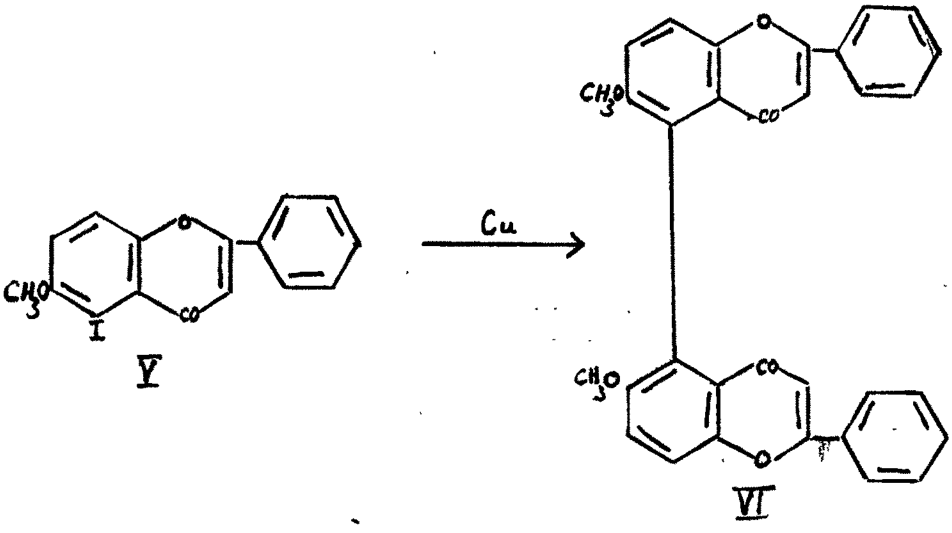


III

IV

Synthesis of 6,6''-dimethoxy-5,5''-biflavonyl by Ullmann reaction on 6-methoxy-5-iodoflavone :

6-Methoxy-5-iodoflavone (V) on Ullmann reaction with copper bronze at 240-250° gave a product which did not contain iodine and melted at 336°. This was found to be different from 6-methoxyflavone. To this 6,6''-dimethoxy-5,5''-biflavonyl (VI) structure has been assigned.



V

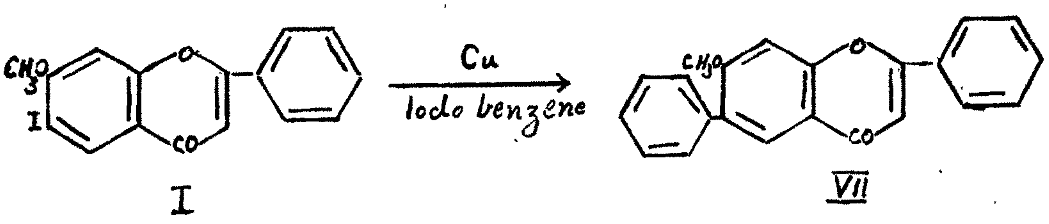
VI

With a view to synthesise unsymmetrical biflavonyls it was thought of interest to study crossed Ullmann reactions. Before proceeding with the crossed Ullmann reaction between two iodoflavones some crossed Ullmann reactions were carried out between iodoflavones and iodobenzene and 7-methoxy-6-phenyl-, 7,4'-dimethoxy-6-phenyl-, and 6-methoxy-5-phenylflavone synthesised.

<u>Synthesis of 7-methoxy-6-phenylflavone by crossed Ullmann reaction between 7-methoxy-6-iodoflavone and iodobenzene</u>

7-Methoxy-6-iodoflavone (I) on crossed Ullmann reaction with iodobenzene in the presence of copper bronze gave a mixture from which the following products were isolated by fractional crystallisation :

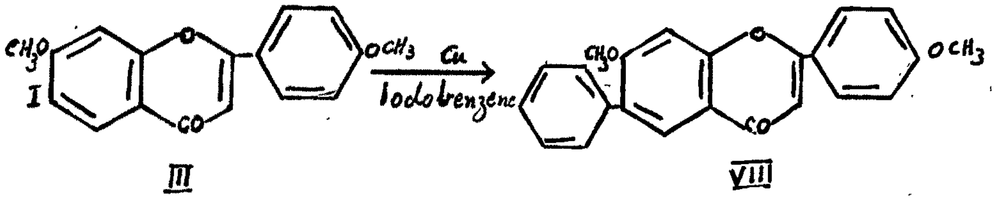
(i) 7,7''-dimethoxy-6,6''-biflavonyl (ii) 7-methoxyflavone (iii) an iodine free product m.p. 161°. To this 7-methoxy-6-phenylflavone (VII) structure has been assigned on the basis of the analysis.



Synthesis of 7,4'-dimethoxy-6-phenylflavone by crossed Ullmann reaction between 7,4'-dimethoxy-6-iodoflavone and iodobenzene

7,4'-Dimethoxy-6-iodoflavone (III) when heated with iodobenzene in the presence of copper bronze gave a mixture from which the following products were isolated by fractional crystallisation :

(I) 7,7",4',4"'-tetramethoxy-6,6"-biflavonyl (ii) 7,4'-dimethoxyflavone (iii) an iodine free product m.p. 200° to which 7,4'-dimethoxy-6-phenylflavone (VIII) structure has been assigned on the basis of the analysis.

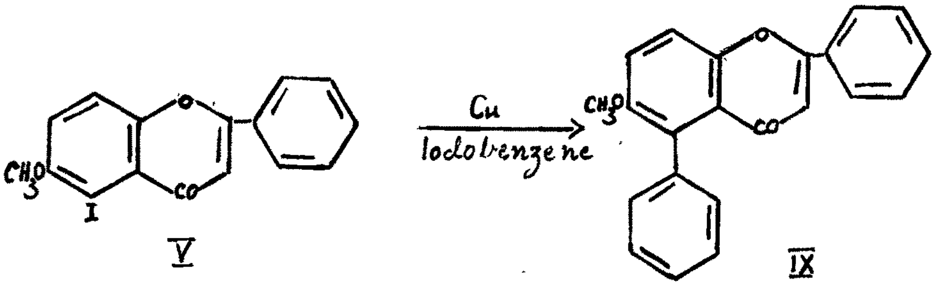


Synthesis of 6-methoxy-5-phenylflavone by crossed Ullmann reaction between 6-methoxy-5-iodoflavone and iodobenzene

6-Methoxy-5-iodoflavone (V) on crossed Ullmann reaction with iodobenzene in the presence of copper bronze gave a mixture from which the following products were isolated by fractional crystallisation :

(i) 6,6"-dimethoxy-5,5"-biflavonyl (ii) 6-methoxyflavone and (iii) an iodine free product, m.p. 223°

to which 6-methoxy-5-phenylflavone (IX) structure has been assigned on the basis of the analysis.



Attempted synthesis of 7,7''-dimethoxy-8,6''-biflavonyl by crossed Ullmann reaction between 7-methoxy-8-iodoflavone and 7-methoxy-6-iodoflavone

7-Methoxy-8-iodoflavone and 7-methoxy-6-iodoflavone on Ullmann reaction with copper bronze gave a pasty product which did not give any pure product on fractional crystallization. The same pasty product was dissolved in chloroform and chromatographed over alumina when only 7-methoxyflavone was obtained in pure form, the other elutes gave ~~the~~ pasty products which could not be purified further.

EXPERIMENTAL

Ullmann reaction on 7-methoxy-6-iodoflavone: 7,7''-Dimethoxy-6,6''-biflavonyl

7-Methoxy-6-iodoflavone (3.78 g.) dissolved in dry diphenyl ether (20 ml.) was treated with copper bronze (1.89 g.) and a trace of iodine and the reaction mixture refluxed on a wire gauze for half an hour with an air-condenser. The reaction mixture was filtered while hot and the filtrate diluted with petroleum ether (b.p. 40-60°). The solid obtained crystallised from acetic acid in white needles, m.p. 337°.

The same product was obtained by heating the iodoflavone (3.78 g.) with copper bronze (1.89 g.) without any solvent in an oil bath for 10 minutes at 240-250°.

Analysis : Found : C = 75.94 ; H = 4.84 %.
$C_{32}H_{22}O_6$ requires : C = 76.49 ; H = 4.38 %.

7-Methoxyflavone was recovered from the mother liquor.

Ullmann reaction on 7,4'-dimethoxy-6-iodoflavone : 7,7'',4',4'''-Tetramethoxy-6,6''-biflavonyl

7,4'-Dimethoxy-6-iodoflavone (3.96 g.) was thoroughly mixed with copper bronze (1.89 g.). The tube containing the reaction mixture was inserted in a previously heated oil bath at 240-250°, stirred and kept there for 10 minutes. The brown reaction mixture was powdered and extracted with acetic acid. The above extract was diluted with water when a solid separated which was crystallised from acetic acid in white needles, m.p. 326°.

The same product was also obtained when 7,4'-dimethoxy-6-iodoflavone (3.96 g.) dissolved in dry diphenyl ether (15 ml.) was treated with copper bronze (1.89 g.) and a trace of iodine. The reaction mixture was refluxed on a wire gauze for half an hour with an air condenser. The reaction mixture was filtered hot and the filtrate on cooling gave a solid product which was crystallised from acetic acid as above.

<u>Analysis</u> : Found : C = 72.53 ; H = 4.53 %.
$C_{34}H_{26}O_8$ requires : C = 72.61 ; H = 4.63 %.

<u>Ullmann reaction on 6-methoxy-5-iodoflavone : 6,6''-Dimethoxy-5,5''-biflavonyl</u>

6-Methoxy-5-iodoflavone (3.78 g.) dissolved in dry diphenyl ether (10 ml.) was treated with copper bronze and a trace of iodine and the reaction mixture refluxed on a wire gauze for one hour with an air condenser. The reaction mixture was filtered while hot. The filtrate on cooling gave a product which was filtered and washed with petroleum ether. It crystallised from acetic acid in shining square plates, m.p. 335-336°. The same product could be obtained when iodoflavone with copper bronze was heated in an oil bath at 240-250°.

Analysis : Found : C = 76.48 ; H = 4.50 %.
$C_{32}H_{22}O_6$ requires : C = 76.49 ; H = 4.38 %.

Crossed Ullmann reaction between 7-methoxy-6-iodoflavone and iodobenzene : 7-Methoxy-6-phenylflavone .

7-Methoxy-6-iodoflavone (3.16 g.) was intimately mixed with copper bronze (4.40 g.) and iodobenzene (4.14 g.) in a test tube equipped with a short air condenser. The reaction mixture was heated in an oil bath at 250° for an hour with occasional shaking. The reaction mixture was then extracted with cold petroleum ether (b.p. 40-60°) to remove the unreacted iodobenzene and biphenyl. The residue was then repeatedly extracted with hot benzene and petroleum ether mixture (1 : 1). On cooling the above extract a product was obtained which crystallised from benzene in shining needles, m.p. 161°.

Analysis : Found : C = 80.40 ; H = 4.94 %.
$C_{22}H_{16}O_3$ requires : C = 80.48 ; H = 4.88 %.

7-Methoxyflavone was recovered from the mother liquor.

The residue after extraction gave 7,7''-dimethoxy-6,6''-biflavonyl described earlier.

Crossed Ullmann reaction between 7,4'-dimethoxy-6-iodoflavone and iodobenzene : 7,4'-Dimethoxy-6-phenylflavone

7,4'-Dimethoxy-6-iodoflavone (3.20 g.) was intimately mixed with copper bronze (4.40 g.) and iodobenzene (4.14 g.) in a test tube equipped with a short air-condenser. The reaction mixture was heated in an oil bath at 250° for an hour with occasional shaking. The reaction mixture was extracted with cold petroleum ether (b.p. 40-60°) to remove the unreacted iodobenzene and biphenyl. The residue was then repeatedly extracted with hot benzene and petroleum ether mixture (1 : 1) to remove 7,4'-dimethoxyflavone. The residue was then extracted with hot benzene and the product from the benzene extract crystallised from dilute acetic acid in white needles, m.p. 200°.

Analysis : Found : C = 77.02 ; H = 5.43 %.

$C_{23}H_{18}O_4$ requires : C = 77.09 ; H = 5.03 %.

The remaining residue was 7,4'',7'',4''''-tetramethoxy-6,6''-biflavonyl described earlier.

Crossed Ullmann reaction between 6-methoxy-5-iodoflavone and iodobenzene : 6-Methoxy-5-phenylflavone

6-Methoxy-5-iodoflavone (3.16 g.) was intimately mixed with copper bronze (4.40 g.) and iodobenzene (4.14 g.)

in a test tube equipped with a short air condenser. The reaction mixture was heated in an oil bath at 250° for an hour with occasional shaking. The reaction mixture was then extracted with cold petroleum ether (b.p.40-60°) to remove unreacted iodobenzene and biphenyl. The residue was then extracted repeatedly with hot benzene and petroleum ether mixture (1 : 1) . On cooling the above extract a product was obtained which crystallised from alcohol, m.p. 223°.

<u>Analysis</u> : Found : C = 80.90 ; H = 5.08 %.

$C_{22}H_{16}O_3$ requires : C = 80.48 ; H = 4.88 %.

6-Methoxyflavone was recovered from the mother liquor.

The residue after extraction gave 6,6''-dimethoxy-5,5''-biflavonyl described earlier.

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