CHAPTER IV

SOME STUDIES ON 4,4'-DIHYDROXY DIPHENYL ETHER

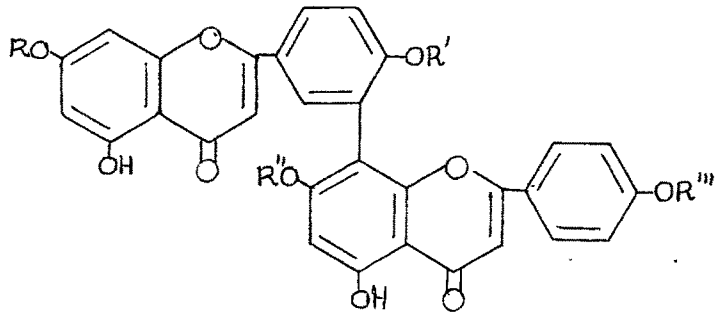
Some studies on 4,4'-dihydroxy diphenyl ether :

Phenols are very reactive substances and they undergo a large number of reactions to give products of industrial, agricultural, medicinal and other importance. They are also the starting materials for the synthesis of different types of oxygen heterocycles. Extensive studies have therefore been made on these substances. The studies on biphenols, dihydroxy derivatives of diphenyl methane, diphenyl sulphone and diphenyl ether are meagre. Biflavonyls and bicoumarinyls have been found in nature in recent years and this has also increased our interest in the studies on diphenyl derivatives.

Some work has been done in our laboratories on the electrophilic substitution in noncondensed rings. A few syntheses of oxygen heterocycles from hydroxy derivatives of diphenyl, benzophenone, diphenylmethane and diphenyl sulphone have also been carried out. No work has, however, been done on building up of α-and γ-pyrone or furan rings on suitable hydroxy derivatives of diphenyl ether. In the present work bichromonyl, bicoumarinyl and bifuranyl ethers have been synthesised.

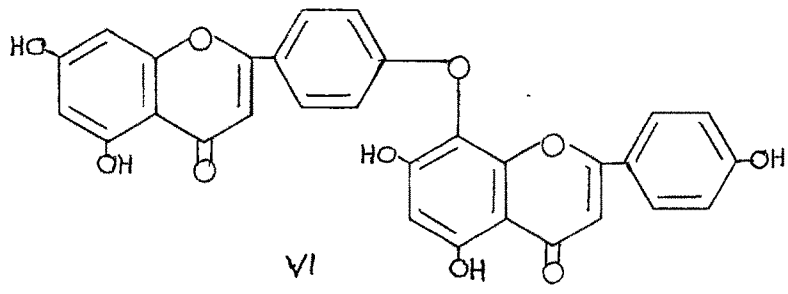
Biflavonyls : The only bichromonyls found in nature so far are the biflavonyls. Several natural biflavonyls have been isolated during the past few years and their structures have been established by degradation methods and spectral data such as ultra-violet and infra-red spectra. Sotetsuflavone[1] (I), Kayaflavone[2] (II), Ginkgetin[3,4] (III), isoginkgetin[5] (IV) and

Sciadopitysin[6] (V) are some of the important biflavonyl derivatives, isolated from plants.



		R	R'	R''	R'''
Sotetsuflavone	I	H	H	H	H
Kayaflawone	II	H	CH_3	CH_3	CH_3
Ginkgetin	III	CH_3	CH_3	H	H
Isoginkgetin	IV	H	CH_3	H	CH_3
Sciadopitysin	V	CH_3	CH_3	H	CH_3

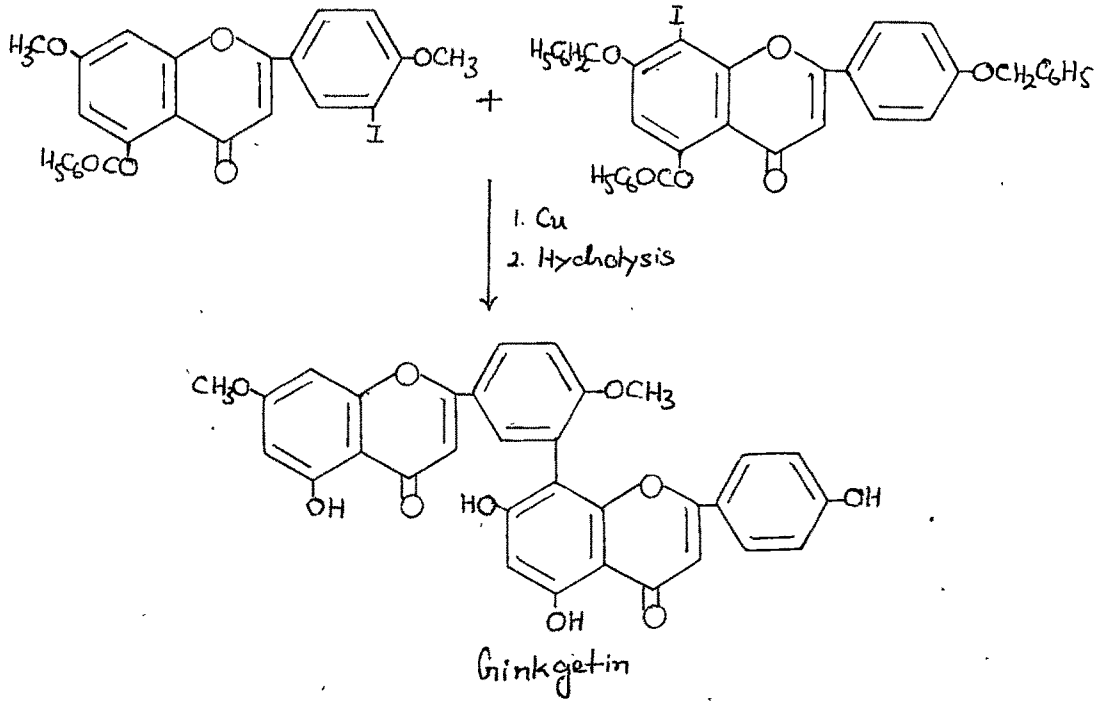
Hinokiflavone[7] (VI) isolated from the leaves of Cryptomeria japonica has been shown to be a biflavonyl ether.



VI

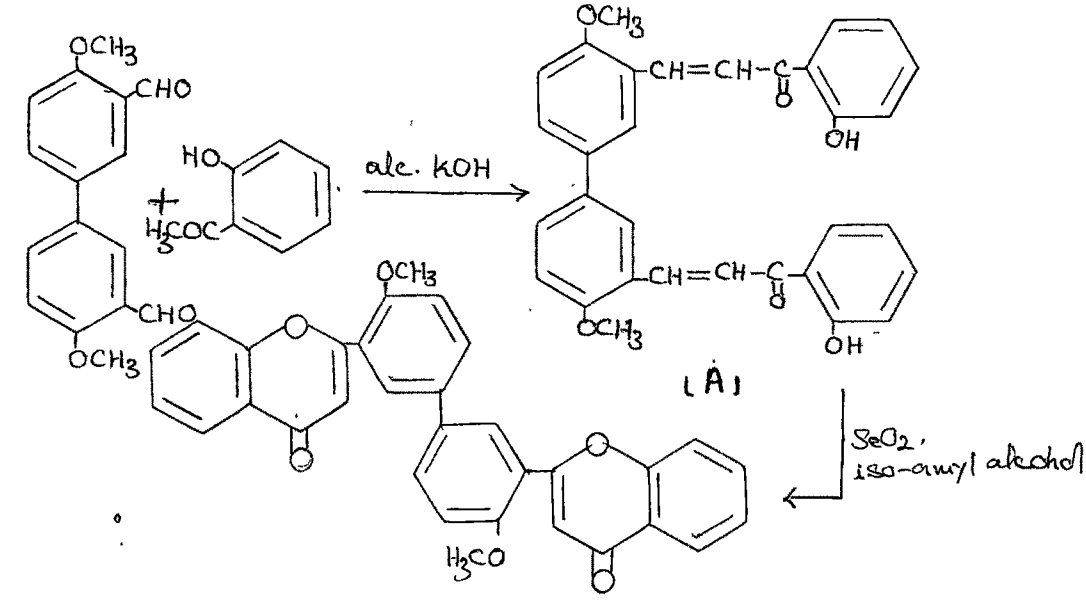
Several symmetrical biflavonyls have been synthesised by the Ullmann reaction on bromo or iodo flavones. Thus, Chen and Liu[8] synthesised 3,3'-biflavonyl

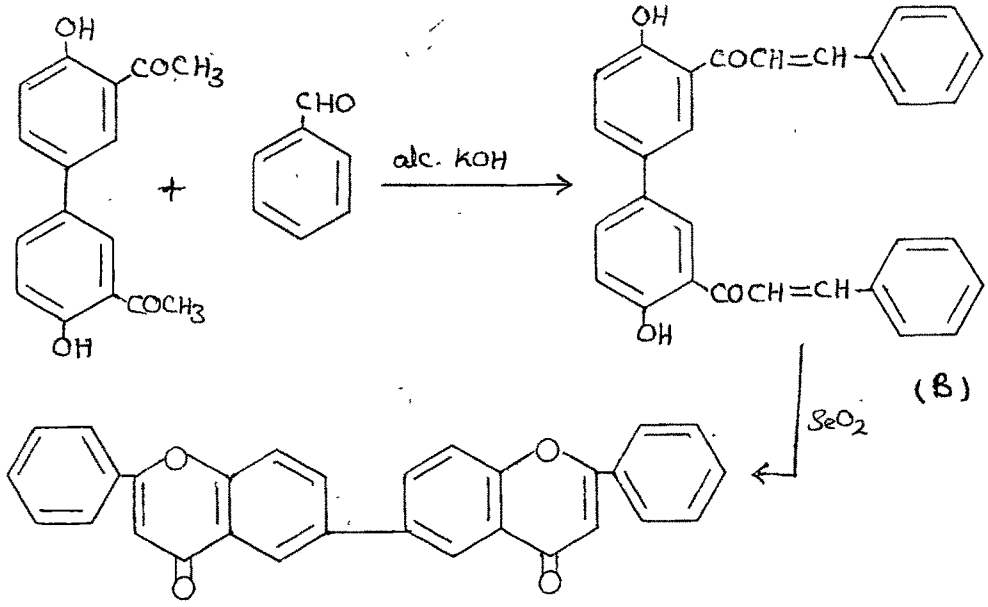
by the Ullmann reaction on 3-bromoflavone. Other symmetrical biflavonyls have also been synthesised through the Ullmann reaction on the appropriate halogenoflavones and on methoxy iodoflavones by Chen et al[9,10]. Jurd[11] synthesised 7,7''-dimethoxy-8,8''-biflavonyl and 7,7'':4',4''' tetramethoxy-8,8''-biflavonyl from the corresponding 8-iodoflavones by Ullmann reaction. Demethylation of the above methoxy biflavonyls with aluminium chloride in boiling benzene gave the corresponding hydroxy biflavonyls. Symmetrical biflavonyls have also been synthesised from 7-methoxy-8-iodoflavone and 7-methoxy-6-iodo-3-benzoyl flavone by Shah[12] in this laboratory. Ginkgetin has been synthesised by Nakazawa and Ito[13] by the crossed Ullmann reaction between 3'-iodo-5-benzoyloxy-4',7-dimethoxyflavone and 5-benzoyloxy-8-iodo-4',7-dibenzyloxyflavone in the presence of activated copper powder and subsequent hydrolysis with 10 % sulphuric acid in acetic acid.



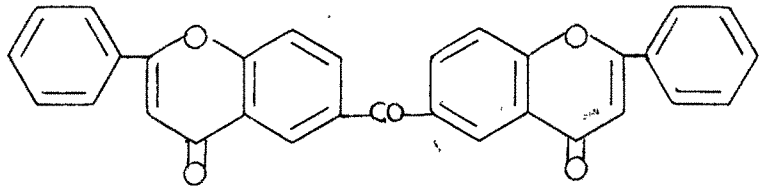
Ginkgetin

Mathai and Sethna[14] used a different approach for the synthesis of symmetrical biflavonyls. They prepared 3,3'''-and 6,6''-biflavonyls by the simultaneous cyclisation and dehydrogenation of the bichalkonyl derivatives (A) and (B) prepared 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.

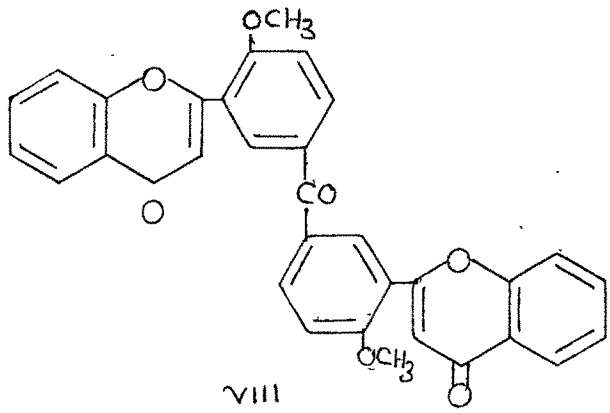




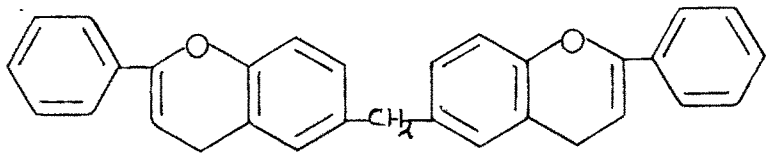
Sethna and his coworkers[15,16] extended this work. Balani and Sethna[17] prepared bi-(6-flavonyl)ketone(VII) and bi-(6'methoxy-3'-flavonyl) ketone(VIII) by cyclising the corresponding bichalkonyl derivatives. Prajapati and Sethna[18] prepared bi(6-flavonyl)methane (IX) from 3,3'-diacetyl-4,4'-dihydroxy diphenyl methane.



VII



VIII

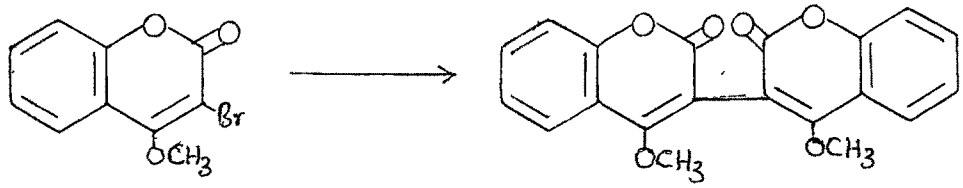


IX

Bicoumarinyls : Several symmetrical bicoumarinyls have also been synthesised. Dyson[19] synthesised 3,3'-bicoumarinyl by heating salicylaldehyde with sodium succinate and acetic anhydride.

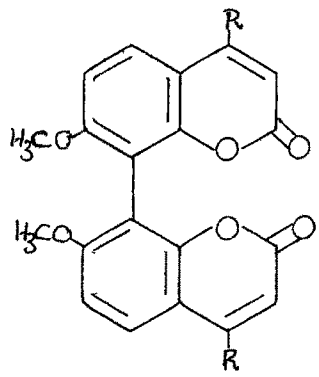
Huebner and Link[20] reported the formation of

3,3'-bicoumarinyl derivative (X) from 3-bromo-4-methoxy-coumarin.



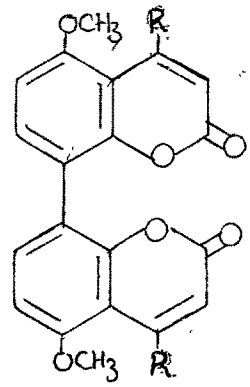
X

Lele et al.[21] have synthesised 8,8'-bicoumarinyl derivatives (XI a, XI b and XII a and XII b) and 3,3'-bicoumarinyl derivatives (XIII a and XIII b) by the Ullmann reaction on iodocoumarins.

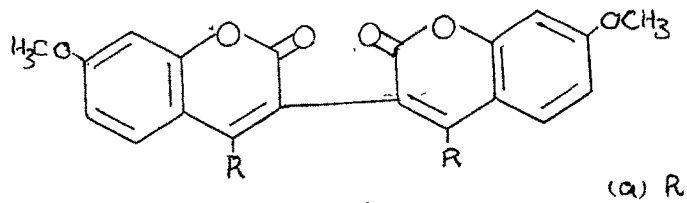


XI

(a) R = H
(b) R = CH3



XII

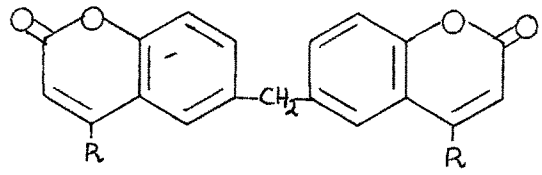


XIII

(a) R = H
(b) R = CH3

Sen and Dutt[22] obtained 6,6'-bicoumarinyl by the action of acetic anhydride and sodium acetate on 4,4'-dihydroxy-diphenyl-3,3'-dialdehyde. Harle and Lyons[23] obtained tetra-hydro-4,4'-bicoumarinyl as one of the products in the reduction of coumarin using zinc and acetic acid.

Prajapati and Sethna[18] synthesised bi(4-methyl-6-coumarinyl)methane (XIVa) by the condensation of 4,4'-dihydroxy diphenylmethane with ethyl acetoacetate and bi(6-coumarinyl) methane (XIV b) by Perkin acetylation of 3,3'-diformyl-4.4'-dihydroxydiphenylmethane. They also prepared bi(4-hydroxy-6-coumarinyl)methane (XIVc) by condensing 3,3'-diacetyl-4,4'-dihydroxy diphenyl methane with ethyl carbonate and pulverised sodium.

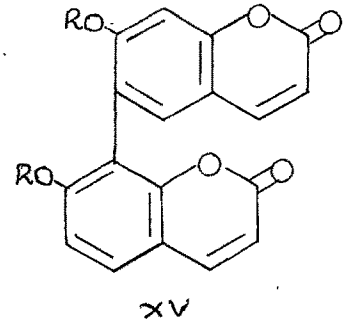


XIVa R = CH_3

XIVb R = H

XIVc R = OH

Recently some unsymmetrical bicoumarinyls have been isolated from plants. Thus Mihashi et al,[24,25] have isolated 6,8'-bicoumarinyl derivative and named it Matsukaze lactone (XVa). Spencer et al.[26] have isolated 7,7'-dihydroxy-6,8'-bicoumarinyl(bicoumol) (XVb) from ladino clover.



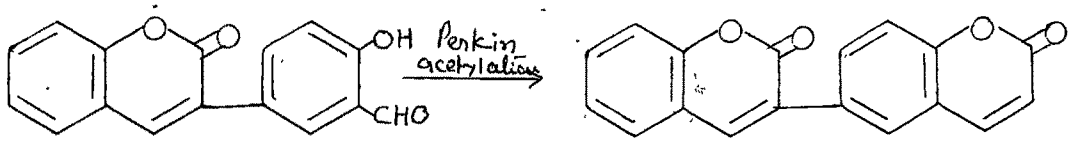
XV

(a) R = CH_3

(b) R = H

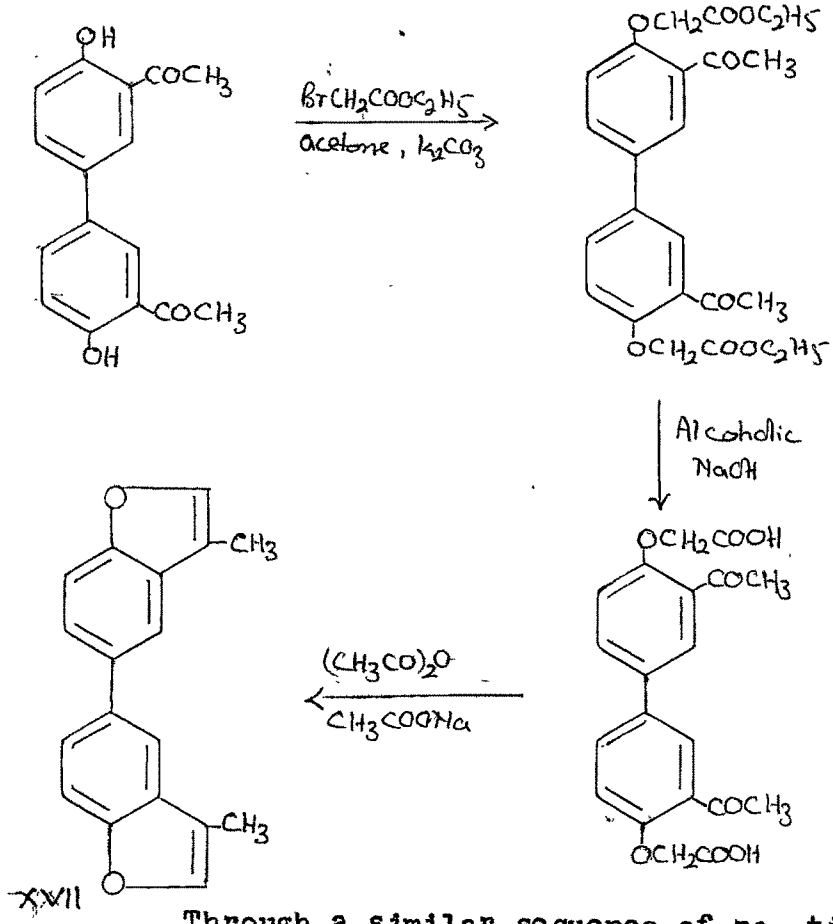
Dey and Row[27] synthesised several 4,3'-bicoumarinyls through the condensation of coumarin-4-acetic ester with various salicylaldehydes under the conditions of Perkin and Knoevenagel reactions. 7-Chloro-4,3'-bicoumarinyl has been synthesised by Thakar[28] by the condensation of 7-chlorocoumarin-4-acetic acid with salicylaldehyde in the presence of piperidine.

Jainamma and Sethna[29] synthesised 3,6'-bicoumarinyl (XVI) by Perkin acetylation of 3-(4'-hydroxy-3'-formylphenyl) coumarin.



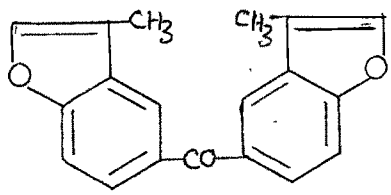
XVI

Dibenzofuranyls : There are very few references in the literature on the synthesis of dibenzofuranyls. Mathai and Sethna[30] synthesised 3,3'-dimethyl-5,5'-bibenzofuranyl (XVII) by the condensation of 3,3'-diacetyl-4,4'-dihydroxy diphenyl with ethyl bromoacetate in the presence of anhydrous potassium carbonate in dry acetone. 3,3'-Diacetyl-4,4'-di(O-ethylacetate) diphenyl obtained on hydrolysis with alcoholic sodium hydroxide yielded the corresponding acid which on refluxing with fused sodium acetate and acetic anhydride provided the 3,3'-dimethyl-5,5'-bibenzofuranyl.

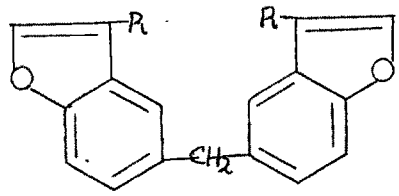


XVII

Through a similar sequence of reactions 5,5'-di(3-methyl benzofuranyl)ketone (XVIII) was synthesised from 3,3'-diacetyl-4,4'-dihydroxy benzophenone by Balani and Sethna[31]. Similarly bi(3-methyl-5-benzofuranyl)methane and bi(5-benzofuranyl)methane (XIXa and XIXb) were synthesised from 3,3'-diacetyl-4,4'-dihydroxy diphenyl methane and 3,3'-diformyl-4,4'-dihydroxy diphenyl methane by Prajapati and Sethna[18].



XVIII



XIX

(a) R = CH_3
(b) R = H

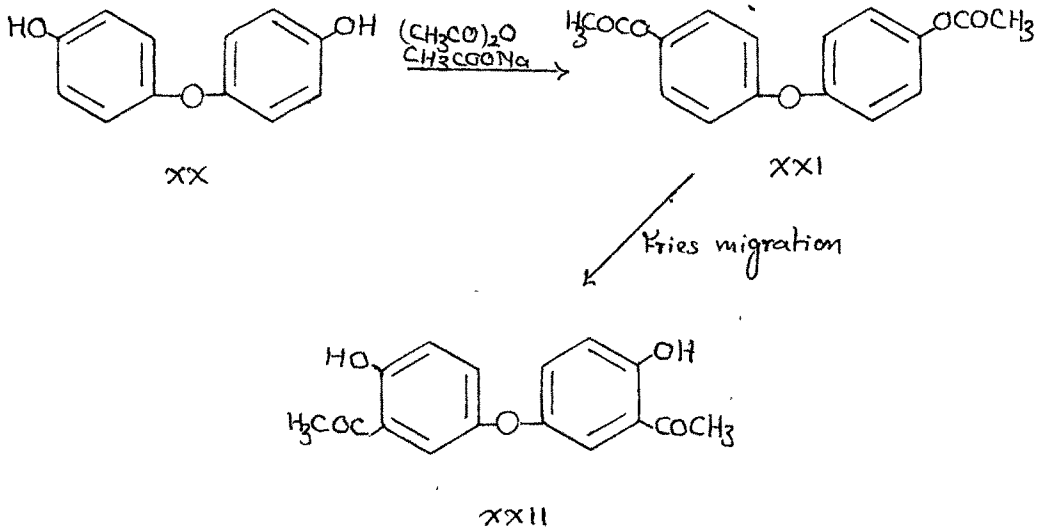
Present work :

In continuation of the work going on in these laboratories on noncondensed rings, some studies have been made on 4,4'-dihydroxy diphenyl ether.

4,4'-Dihydroxy diphenyl ether has been prepared in the present work by the condensation of p-bromoanisole[32] with p-methoxy phenol[33] in the presence of copper bronze and potassium hydroxide (80 %) and subsequent demethylation of the product obtained.

3,3'-Diacetyl-4,4'-dihydroxy diphenyl ether required as an intermediate for the synthesis of various oxygen heterocycles was prepared as follows :

4,4'-Dihydroxy diphenyl ether (XX) was acetylated with acetic anhydride and fused sodium acetate. The diacetoxy derivative (XXI) when subjected to Fries rearrangement with anhydrous aluminium chloride gave the 3,3'-diacetyl-4,4'-dihydroxy diphenyl ether (XXII). It was soluble in alkali and gave a violet colour with alcoholic ferric chloride.

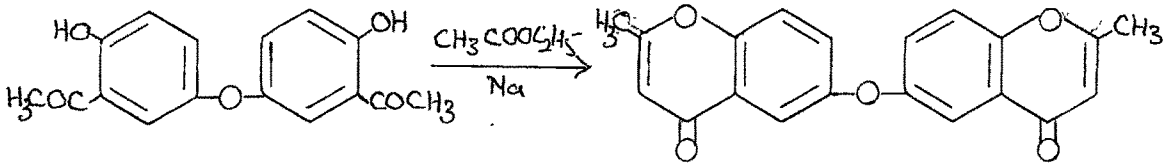


XX XXI XXII

Synthesis of Bi(2-methyl-6-chromonyl)ether :

3,3'-Diacetyl-4,4'-dihydroxy diphenyl ether was condensed with ethyl acetate in the presence of pulverised sodium. On working up the reaction, the product obtained was found to be insoluble in alkali and did not give any colouration with alcoholic ferric chloride. It analysed for $C_{20}H_{14}O_5$. Bi(2-methyl-6-chromonyl)ether (XXIII) structure has been assigned to this product. It had undergone simultaneous condensation and cyclisation.

I.R.spectrum showed a band at 1650 cm^{-1} (γ-pyronyl >C=O group)



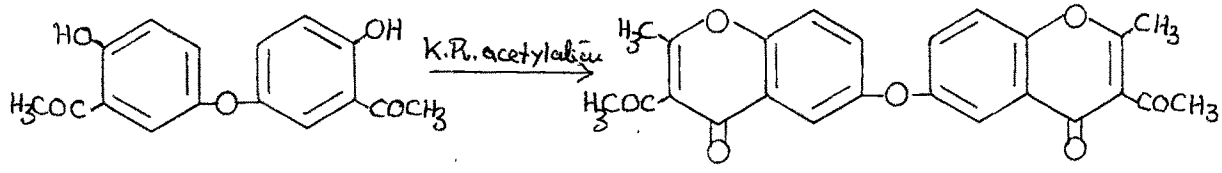
XXIII

Kostanecki-Robinson acetylation of 3,3'-diacetyl-4,4'-dihydroxy diphenyl ether : Bi(2-methyl-3-acetyl-6-chromonyl) ether :

3,3'-Diacetyl-4,4'-dihydroxy diphenyl ether when refluxed with acetic anhydride and fused sodium acetate at 170-80° in an oil bath for 10 hr. gave a product which was insoluble in alkali and it did not give any colouration with alcoholic ferric chloride. It analysed for $C_{24}H_{18}O_7$.

Bi(2-methyl-3-acetyl-6-chromonyl) ether (XXIV) structure has been assigned to this product. The deacetylation with alcoholic potassium hydroxide did not succeed.

I.R.spectrum showed two bands in the carbonyl region viz. 1650 cm^{-1}(γ-pyronyl >C=0 group) and 1680 cm^{-1}(acetyl group at 3-position).



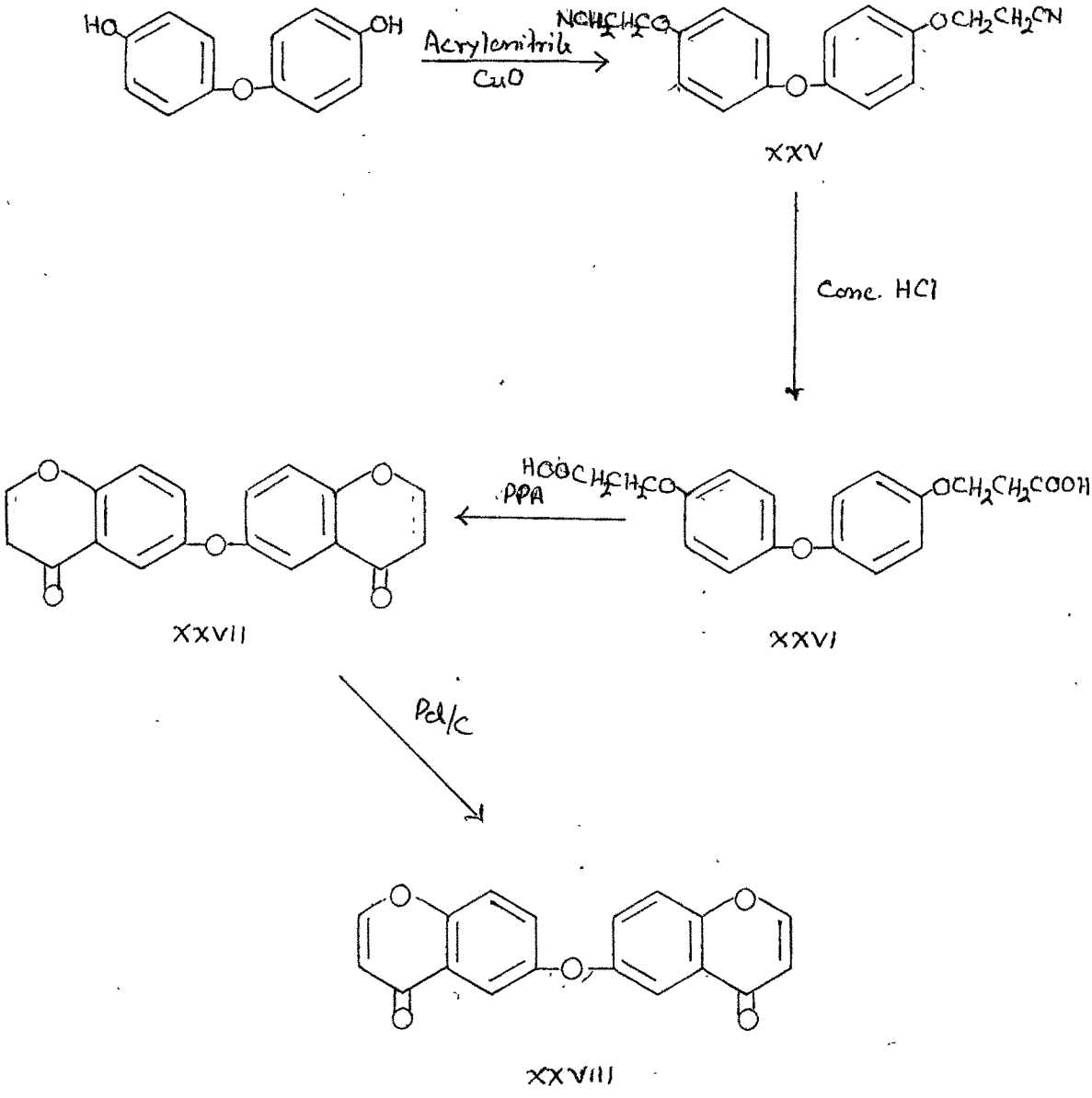
XXIV

Synthesis of bi(6-chromonyl) ether :

Cyanoethylation of phenols provides a good method for the preparation of chromone derivatives, unsubstituted in the heterocyclic ring. The intermediate β-phenoxy propionitrile after hydrolysis can be cyclised to chromanones using a suitable cyclising agent such as anhydrous hydrofluoric acid, conc.sulphuric acid or polyphosphoric acid.

4,4'-Dihydroxy diphenyl ether was condensed with acrylonitrile in the presence of cupric oxide. 4,4'-Dicyanoethoxy diphenyl ether (XXV) obtained on acid hydrolysis gave the corresponding acid (XXVI). The acid cyclised with polyphosphoric acid to bi(6-chromanonyl) ether (XXVII) which on dehydrogenation with palladised charcoal in diphenyl ether resulted in bi(6-chromonyl)ether (XXVIII).

I.R.showed a band at 1640 cm^{-1}(γ-pyronyl >C =0 group).



Attempted Pechmann condensation of 4,4'-dihydroxy diphenyl ether with malic acid and ethyl acetoacetate :

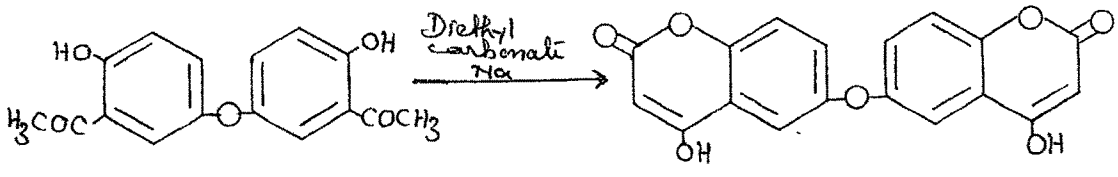
The condensation of 4,4'-dihydroxy diphenyl ether with malic acid in the presence of conc.sulphuric acid was

tried but the original hydroxy diphenyl ether was obtained back. Attempt to condense 4,4'-dihydroxy diphenyl ether with ethyl acetoacetate in the presence of either conc. or 80 % sulphuric acid did not succeed. It was also recovered unchanged when the condensation was tried in the presence of aluminium chloride in nitrobenzene at 130°.

4,4'-Dihydroxy diphenyl ether also did not condense with ethyl acetoacetate in boiling diphenyl ether.

Synthesis of bi(4'-hydroxy-6-coumarinyl) ether :

4,4'-Dihydroxy-3,3'-diacetyl diphenyl ether was condensed with diethyl carbonate in the presence of pulverised sodium according to the method of Boyd and Robertson. The reaction mixture was heated for 8 hr. on a steam bath. The product obtained gave the tests for a 4-hydroxycoumarin derivative such as solubility in sodium bicarbonate solution and ferric chloride colouration. Bi(4'-hydroxy-6-coumarinyl)ether structure (XXIX) has been assigned to this compound.

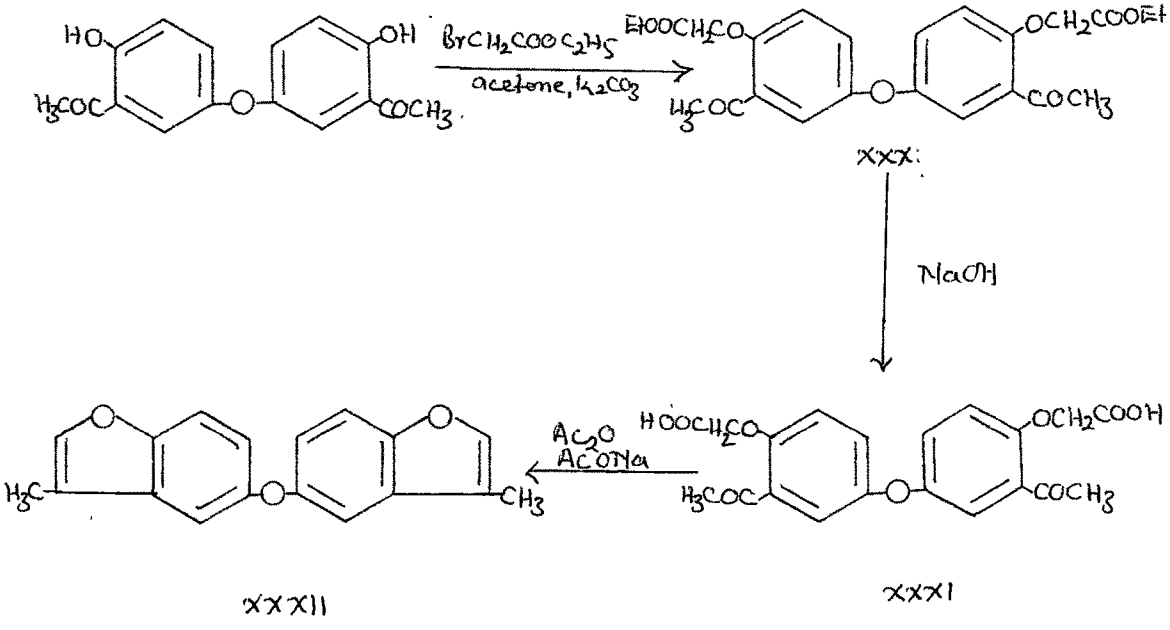


XXIX

Synthesis of Bi(3-methyl-5-benzofuranyl)ether :

4,4'-Dihydroxy-3,3'-diacetyl diphenyl ether was condensed with ethyl bromoacetate in dry acetone in the presence of anhydrous potassium carbonate. Removal of acetone afforded a product which was insoluble in alkali. 4,4'-Dicarbethoxymethoxy-3,3'-diacetyl diphenyl ether (XXX) thus obtained was hydrolysed by keeping it with 10 % sodium hydroxide for 24 hr. to 4,4'-dicarboxymethoxy-3,3'-diacetyl diphenyl ether (XXXI). This acid on heating with sodium acetate and acetic anhydride underwent cyclisation with simultaneous decarboxylation which resulted in bi(3-methyl-5-benzofuranyl) ether (XXXII).

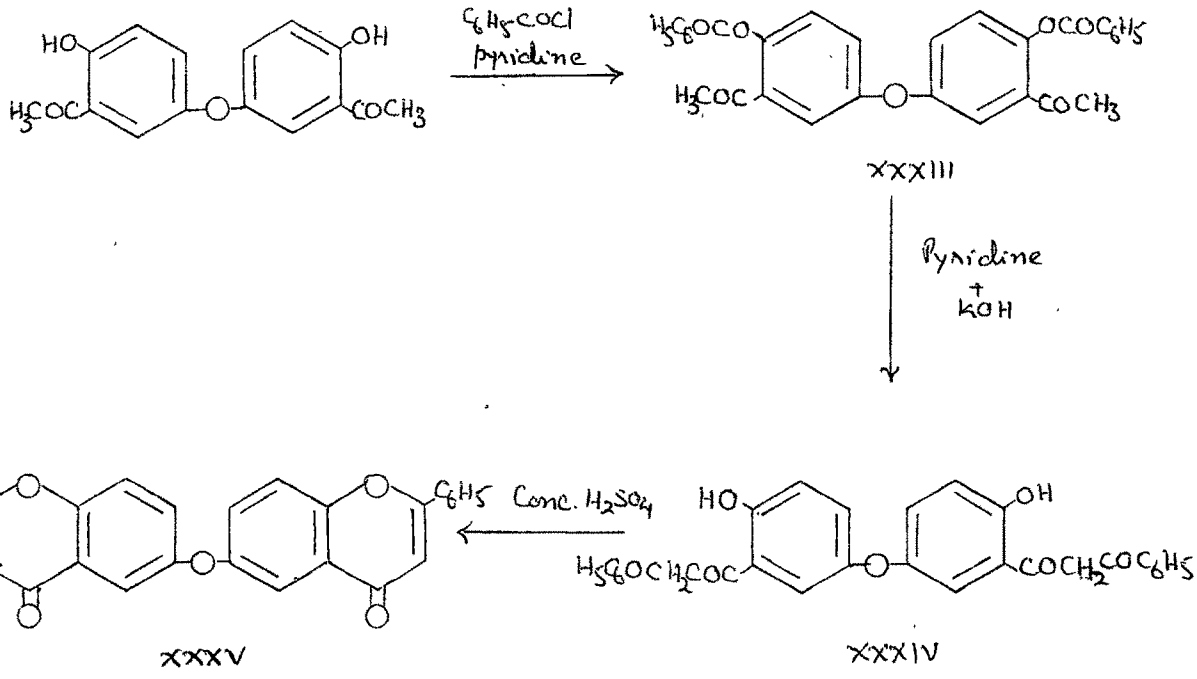
I.R. showed a band at 885 cm^{-1} (furan ring breathing) UV λmax (in chloroform) 258,290 nm.



Synthesis of bi(6-flavonyl)ether :

To the solution of 4,4'-dihydroxy-3,3'-diacetyl diphenyl ether in pyridine was added benzoyl chloride. The resulting benzoyloxy derivative (XXXIII) was rearranged to 4,4'-dihydroxy-3,3'-di(benzoylacetyl) diphenyl ether (XXXIV) with pyridine and powdered potassium hydroxide. The cyclisation of this diketone ether with conc.sulphuric acid gave the bi(6-flavonyl)ether(XXXV).

I.R.spectrum showed a band at 1645 cm^{-1} (γ-pyronyl >C = O group).

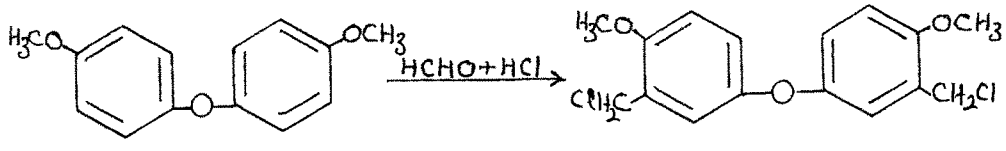


In order to obtain 4,4'-dihydroxy-3,3'-diformyl diphenyl ether for the synthesis of other oxygen heterocycles formylation of 4,4'-dihydroxy diphenyl ether was attempted.

Chloromethylation of 4,4'-dimethoxy diphenyl ether :

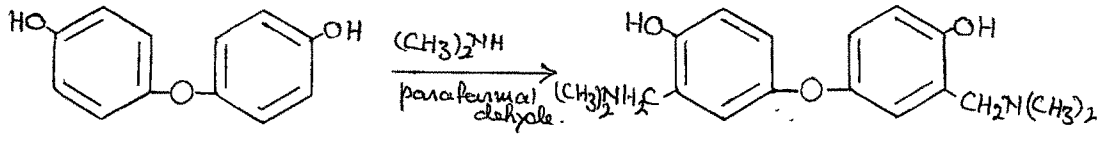
As direct formylation met with failure, it was thought of interest to see whether the diformyl derivative would be available from the chloromethyl derivative or from a Mannich base prepared from dihydroxy diphenyl ether by reacting it with hexamine.

Chloromethylation of 4,4'-dihydroxy diphenyl ether was attempted under different conditions using zinc chloride as a catalyst, but no pure chloromethyl derivative could be isolated from the reaction mixture. However, when 4,4'-dimethoxy diphenyl ether (XXV) was subjected to chloromethylation in acetic acid, paraformaldehyde and zinc chloride, an oily product was obtained from which the dichloromethyl derivative (XXXVI) could be obtained in a poor yield. 3,3'-Dichloromethyl-4,4'-dimethoxy diphenyl ether structure has been assigned to this product. Because of the poor yield its reaction with hexamine could not be studied.



XXXVI

Mannich reaction was tried with dimethyl amine and paraformaldehyde, this resulted in the product which was soluble both in acid and in alkali. On the bases of this and the analysis the product was assigned 4,4'-dihydroxy-3,3'-dimethylaminomethyl diphenyl ether (XXXVII) structure. The yield in this case was also poor so no further work could be done.



XXXVII

EXPERIMENTAL

Preparation of 4,4'-dihydroxy diphenyl ether :

4,4'-Dihydroxy diphenyl ether was prepared by the Ullmann reaction between p-bromoanisol[32] and p-methoxy phenol[33].

p-Bromoanisol was prepared by refluxing anisol (15 ml.) with N-bromo succinimide (9 g.) without any solvent for 16 hr. p-bromo anisol (3 ml.) b.p.220-22° was obtained.

p-Methoxyphenol was prepared by partial methylation of hydroquinone (50 g.) in 20 % sodium hydroxide (4 g.) in 200 ml. of water) and dimethyl sulphate (20 ml.). The reaction mixture was shaken for 30 minutes. After cooling, sodium hydroxide (5 g.) was added and the mixture heated for 3/4 hr. 50 ml. of 10 % sodium hydroxide was added. Solid dimethoxy derivative separated. It was filtered out and the reaction mixture extracted with ether which gave further dimethoxy derivative. Aqueous layer on acidification gave p-methoxyphenol which was extracted with benzene. M.P 53°. Yield 2.8 g.

A mixture of p-methoxyphenol (9 g.), p-bromo anisol (10 ml.), potassium hydroxide (9 ml. 80 %) and a little copper powder was heated at 200-10° for 6 hr. The reaction mixture was extracted with hot benzene. Removal of benzene gave 4,4'-dimethoxy diphenyl ether[34] which crystallised from alcohol in fine plates, m.p.100-2°. Yield 4 g.

Demethylation : The above dimethoxy derivative (5 g.)

dissolved in benzene was heated in an oil bath at 180-90° for 2 hr. with anhydrous aluminium chloride (5 g.). Decomposition with dilute hydrochloric acid resulted in dihydroxy diphenyl ether. It crystallised from toluene, m.p.160-61°. This was used for further work. Yield 2 g.

Synthesis of 4,4'-diacetoxy diphenyl ether :

A mixture of 4,4'-dihydroxy diphenyl ether (3 g.) acetic anhydride (15 ml.) and sodium acetate (5 g.) was refluxed for 2 hr. The product obtained on pouring the reaction mixture in cold water crystallised from alcohol in needles (1.8 g.), m.p.112°.

Analysis : Found : C, 67.03 ; H, 4.83 %.

$C_{16}H_{14}O_5$ requires : C, 67.18 ; H, 4.89 %.

Fries rearrangement of 4,4'-diacetoxy diphenyl ether :

An intimate mixture of 4,4'-diacetoxy diphenyl ether (2 g.) and anhydrous aluminium chloride (5 g.) was heated in an oil bath at 140° for 3 hr. The reaction mixture was decomposed with ice cold hydrochloric acid(1:1). The separated product was taken in sodium hydroxide solution. Acidification of the alkaline extract gave a yellow product, which crystallised from benzene, m.p.185°. Yield 0.8 g. It gave a violet colour with alcoholic ferric chloride.

Analysis : Found : C, 66.70 ; H, 4.66 %.

$C_{16}H_{14}O_5$ requires : C, 67.13 ; H, 4.89 %.

Claisen condensation of 4,4'-dihydroxy-3,3'-diacetyl diphenyl ether with ethyl acetate : Bi(2-methyl-6-chromonyl)ether :

A mixture of 4,4'-dihydroxy-3,3'-diacetyl diphenyl ether (1.5 g.), ethyl acetate (15 ml.) and pulverised sodium (2 g.) was refluxed on a steam bath for 8 hr. The reaction mixture was cooled and a little alcohol was added to decompose unreacted sodium. It was then diluted with water and extracted with ether, to remove unreacted ketone. Acidification of the alkaline solution resulted in a pasty mass, which was obtained in a solid form by treating repeatedly with ether petroleum and crystallisstion from benzene-petrol ether mixture. This was found to be insoluble in alkali and did not give any colouration with alcoholic ferric chloride, m.p.213°. Yield 0.2 g.

Analysis : Found : C, 71.97 ; H, 3.86 %.

$C_{20}H_{14}O_5$ requires : C, 71.86 ; H, 4.19 %.

Kostanecki-Robinson acetylation of 4,4'-dihydroxy-3,3'-diacetyl diphenyl ether : Bi(2-methyl-3-acetyl-6-chromonyl) ether :

A mixture of 4,4'-dihydroxy-3,3'-diacetyl diphenyl ether (1.5 g.), acetic anhydride (15 ml.) and fused sodium acetate (6 g.) was refluxed in an oil bath for 10 hr. at 180-90°. The reaction mixture was poured in ice cold water. The separated solid was filtered and washed with dilute alkali. It crystallised from alcohol, m.p.212°. Yield 0.6 g. The product did not give any colouration with alcoholic ferric chloride.

Analysis : Found : C, 68.84 ; H, 4.70 %.

$C_{24}H_{18}O_7$ requires : C, 68.90 ; H, 4.30 %.

Attempted deacetylation :

The above 3'-acetyl derivative (0.25 g.) was refluxed with alcoholic potassium hydroxide (10 % ;10 ml.) for 2 hr. The product obtained on dilution of the reaction mixture was crystallised from alcohol. M.P.210°. Mixed m.p. with the original 3'-acetyl derivative was not depressed.

Cyanoethylation of 4,4'-dihydroxy diphenyl ether :

4,4'-Di(β-cyanoethoxy)diphenyl ether :

A mixture of 4,4'-dihydroxy diphenyl ether (2 g.) acrylonitrile (5 ml.) and cupric oxide (0.2 g.) was refluxed on a sand bath for 25 hr. The reaction mixture was then treated with chloroform and sodium hydroxide. After filtering, the chloroform layer was separated and washed with water. The solvent was evaporated and the product obtained was crystallised from alcohol, m.p.102°. Yield 0.6 g.

Analysis : Found : C, 70.31 ; H, 5.25 ; N, 9.01 %.

$C_{18}H_{16}O_3N_2$ requires : C, 70.03 ; H, 5.19 ; N, 9.08 %.

Hydrolysis :

A mixture of 4,4'-di(β-cyanoethoxy)diphenyl ether (1 g.) was refluxed with conc.hydrochloric acid(20 ml.) for 4 hr. After 1 hr. the product started separating. The reaction mixture was poured into water. The product obtained was purified by sodium bicarbonate treatment. The pure acid obtained on acidification of the bicarbonate extract was crystallised from alcohol. M.P.198°.

Analysis : Found : C, 62.63 ; H, 4.83 %.

$C_{18}H_{18}O_7$ requires : C, 62.79 ; H, 5.23 %.

Cyclisation : Bi(6-chromanonyl)ether :

The above dicarboxylic acid (0.5 g.) was heated with polyphosphoric acid (20 g. P_2O_5 ; 10 ml. o-phosphoric acid) in an oil bath for 3 hr. at 120°. The reaction mixture was then poured into cold water. The product separated was washed with bicarbonate solution and water. It crystallised from alcohol in yellow needles (0.2 g.), m.p.175°.

Analysis : Found : C, 69.47 ; H, 4.77 %.

$C_{18}H_{14}O_5$ requires : C, 69.68 ; H, 4.41 %.

Dehydrogenation: Bi(6-chromonyl) ether :

A mixture of Bi(6-chromanonyl)ether (0.25 g.) in diphenyl ether and palladised charcoal (10 % 0.2 g.) was refluxed for 6 hr. The mixture was filtered hot. The product obtained on cooling was filtered and washed with petroleum ether and crystallised from alcohol. M.P.218°. Yield 0.1 g.

Analysis : Found : C, 70.66 ; H, 3.48 %.

$C_{18}H_{10}O_5$ requires : C, 70.60 ; H, 3.26 %.

Attempted condensation of 4,4'-dihydroxy diphenyl ether with (i) malic acid in the presence of sulphuric acid (ii) ethyl acetoacetate in the presence of (a) sulphuric acid (b) anhydrous aluminium chloride (c) phosphorus pentoxide and (d) in boiling diphenyl ether without any condensing agent :

(i) Condensation with malic acid in the presence of sulphuric acid :

A mixture of 4,4'-dihydroxy diphenyl ether (1 g.)

malic acid (1 g.) and concentrated sulphuric acid (3 ml.) was heated at 120-30° until the effervescence ceased. The solid separating on adding the reaction mixture to water was found to be indentical with the original dihydroxy derivative on direct comparison. It was soluble in dilute alkali.

(ii) (a) Condensation with ethyl acetoacetate in the presence of sulphuric acid :

To a mixture of 4,4'-dihydroxy diphenyl ether (1.5 g.) and ethyl acetoacetate (20 ml.), sulphuric acid (6 ml. ; 80 %) was added slowly. The reaction mixture was left overnight and then poured in ice cold water. The product obtained was found to be the original compound.

(ii) (b) Condensation with ethyl acetoacetate in the presence of anhydrous aluminium chloride :

The 4,4'-dihydroxy diphenyl ether was recovered unchanged when a mixture of 4,4'-dihydroxy diphenyl ether (1 g.) and ethyl acetoacetate (2 ml.) was heated at in nitrobenzene with anhydrous aluminium chloride (2 g.) for 3 hr. The reaction mixture was added to ice cold hydrochloric acid and nitrobenzene was removed by steam distillation. The product obtained was found to be the original 4,4'-dihydroxy diphenyl ether.

(ii) (c) Condensation with ethyl acetoacetate in the presence of phosphorus pentoxide :

A mixture of 4,4'-dihydroxy diphenyl ether (1 g.) and ethyl acetoacetate (2 ml.) in absolute alcohol(30 ml.)

and phosphorus pentoxide (3 g.) was heated on a steam bath for 2 hr. The product obtained was found to be the original dihydroxy diphenyl ether.

(ii) (d) Condensation with ethyl acetoacetate in boiling diphenyl ether :

A solution of 4,4'-dihydroxy diphenyl ether(1 g.) in diphenyl ether (5 ml.) was refluxed with ethyl acetoacetate (2 ml.) for 3 hr. The product obtained on removal of diphenyl ether was found to be an unworkable product from which no pure product could be isolated.

Condensation of 4,4'-dihydroxy-3,3'-diacetyl diphenyl ether with diethyl carbonate : Bi(4'-hydroxy-6-coumarinyl) ether :

A mixture of 4,4'-dihydroxy-3,3'-diacetyl diphenyl ether (1.5 g.), ethyl carbonate (20 ml.) and pulverised sodium (2 g.) was heated on a steam bath for 10 hr. A little alcohol was added to decompose the unreacted sodium followed by cold water. It was extracted with ether. The aqueous layer was acidified. The product obtained was taken in sodium bicarbonate. The alkaline filtrate was acidified and the product thus obtained was crystallised from alcohol, m.p. 302°(decomp.)

Analysis : Found :C, 63.52 ; H, 2.88 %.

$C_{18}H_{10}O_7$ requires :C, 63.92 ; H, 2.95 %.

Condensation of 4,4'-dihydroxy-3,3'-diacetyl diphenyl ether with ethyl bromoacetate : 4,4'-di(carbethoxy-methoxy)-3,3'-diacetyl diphenyl ether :

4,4'-Dihydroxy-3,3'-diacetyl diphenyl ether (1 g.) was refluxed on a steam bath with ethyl bromoacetate(0.7 ml.) in the presence of anhydrous potassium carbonate(5 g.) in dry acetone for 5 hr. The acetone was then removed and water was added. The product obtained was washed with dilute alkali and crystallised from alcohol in thin shining plates (0.6 g.). M.P.117°.

Analysis : Found : C, 62.82 ; H, 5.69 %.

$C_{24}H_{26}O_9$ requires : C, 62.88 ; H, 5.67 %.

4,4'-Di(carboxymethoxy)-3,3'-diacetyl diphenyl ether :

The above ester (1 g.) was kept overnight in sodium hydroxide solution (20 ml. ; 10 %). The clear liquid on acidification gave a product which was extracted with sodium bicarbonate solution. The bicarbonate filtrate on acidification gave the acid which crystallised from alcohol, m.p.176°. Yield 0.6 g.

Analysis : Found : C, 59.36 ; H, 4.86 %.

$C_{20}H_{18}O_9$ requires : C, 59.70 ; H, 4.47 %.

Bi(3-methyl-5-benzofuranyl)ether :

The above acid (0.5 g.) was refluxed with freshly fused sodium acetate (1 g.) and acetic anhydride (5 ml.) on a wire gauze for 1 hr. The reaction mixture was then poured in water. The separated solid was washed with sodium

bicarbonate and crystallised from alcohol in thick needles (0.2 g.). M.P.78°.

Analysis : Found : C, 77.80 ; H, 5.32 %.

$C_{18}H_{14}O_8$ requires : C, 77.71 ; H, 5.03 %.

4,4'-Dibenzoyloxy-3,3'-diacetyl diphenyl ether :

3,3'-Diacetyl-4,4'-dihydroxy diphenyl ether(1.5 g.) in pyridine and benzoyl chloride (2 ml.) mixture was kept at room temperature for 1 1/2 hr. The reaction mixture was treated with ice cold hydrochloric acid (1:1). The pasty product obtained was treated with sodium bicarbonate solution and boiling water. It was crystallised from acetic acid. M.P. 127°.

Analysis : Found : C, 73.36 ; H, 4.66 %.

$C_{30}H_{22}O_7$ requires : C, 72.88 ; H, 4.45 %.

4,4'-Dihydroxy-3,3'-di(benzoylacetyl)diphenyl ether :

A solution of the above benzoyloxy derivative (1.5 g.) in pyridine was mixed with powdered potassium hydroxide (9 g.). After keeping the reaction mixture t at room temperature for 4 hr. ice cold dilute hydrochloric acid was added. The product obtained was purified by taking in sodium hydroxide solution. Acidification gave a yellow product. It crystallised from benzene. M.P.163°. Yield 0.8 g.

Analysis : Found : C, 72.49 ; H, 4.35 %.

$C_{30}H_{22}O_7$ requires : C, 72.88 ; H, 4.45 %.

Cyclisation : Bi(6-flavonyl)ether :

The above β-diketone derivative (0.5 g.) was mixed with conc.sulphuric acid and the reaction mixture was kept overnight. The product separating on pouring the reaction mixture in water was insoluble in dilute alkali and did not give any colour with alcoholic ferric chloride. It crystallised from acetic acid, m.p.257°.

Analysis : Found : C, 73.13 ; H, 4.29 %.

$C_{30}H_{18}O_5.2H_2O$ requires : C, 72.88 ; H, 4.45 %.

Attempted formylation of 4,4'-dihydroxy diphenyl ether :

(i) Through a mixture of 4,4'-dihydroxy diphenyl ether (2 g.) in dry ether (100 ml.), zinc cyanide (5 g.) and aluminium chloride (1 g.),dry hydrogen chloride gas was passed for 3 hr. On working up the reaction mixture after keeping overnight, the product obtained was the original dihydroxy diphenyl ether.

(ii) A mixture of 4,4'-dihydroxy diphenyl ether (1 g.) dissolved in acetic acid and hexamine(3 g.) was refluxed for 1/2 hr. and the heating was continued for further 15 minutes after adding hydrochloric acid(1:1) (10 ml.). The product obtained on dilution was an unworkable one and no pure product could be obtained from it.

4,4'-Dimethoxy-3,3'-dichloromethyl diphenyl ether :

Paraformaldehyde (0.3 g.) was treated in acetic acid(5 ml.)with dry hydrogen chloride gas at room temperature

until the solution became clear. 4,4'-Dihydroxy diphenyl ether (0.8 g.) was then added and hydrogen chloride gas was passed for further 1hr. Only polymeric product separated out from the reaction mixture from which no pure chloromethyl derivative could be isolated.

When instead of 4,4'-dihydroxy diphenyl ether, 4,4'-dimethoxy diphenyl ether was added in the presence of zinc chloride as a catalyst a pasty mass was obtained which on warming with petroleum ether repeatedly gave a white product but the yield was very poor. It crystallised from ether petroleum. M.P.85°.

Analysis : Found : C, 58.65 ; H, 4.54 ; Cl, 21.55 %.

$C_{16}H_{16}O_3Cl_2$ requires : C, 58.72 ;, H, 4.89 ; Cl, 21.72 %.

Mannich reaction on 4,4'-dihydroxy diphenyl ether with dimethyl amine : 4,4'-Dihydroxy-3,3'-dimethylaminomethyl diphenyl ether :

Paraformaldehyde (0.2 g.) was dissolved in alcohol (5 ml.) containing potassium hydroxide (0.1 g.) by gentle warming . Dimethylamine (0.4 g.) and 4,4'-dihydroxy diphenyl ether (1 g.) dissolved in alcohol were added to the reaction mixture which was refluxed for 1 hr. on a steam bath. The product separated was found to be soluble both in dilute alkali and acid. It crystallised from benzene-petroleum ether mixture. M.P.166°. The yield was poor.

Analysis : Found : C, 72.76 ; H, 8.10 ; N, 6.98 %.

$C_{24}H_{32}O_3N_2$ requires : C, 72.73 ; H, 8.08 ; N, 7.07 %.

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