

SUMMARY

Phenols are compounds of great importance both from the synthetical and from the commercial view point and a large amount of work has been done. Biphenols have been studied to a comparatively lesser extent. It was therefore thought of interest to study in our laboratories some of the substitution and rearrangement reactions on the hydroxy and methoxy biphenyls and also to synthesise oxygen and other heterocyclics from the biphenyl derivatives. The present work is a part of that study and deals with: (1) chloromethylation of some biphenyl derivatives, (2) synthesis of biflavoryls from biphenyl derivatives, (3) synthesis of some C-acyl derivatives of biphenyl through the application of the Fries and Friedel-Crafts reactions, (4) the Beckmann rearrangement of the di-oximes of some C-acyl biphenyls and (5) the preparation of a few biquinolyls.

In chapter I. (general introduction) some aspects of the chemistry of biphenyl derivatives such as the therapeutic and commercial uses, methods of synthesis, stereochemistry and substitution reactions have been briefly reviewed.

In chapter II, the chloromethylation of some biphenyl derivatives is described. Chloromethylation is an excellent tool in synthetic work as the chloromethyl group undergoes a variety of reactions.

The present work deals with the chloromethylation

of 2,2',4,4'-tetramethoxy-, 2,2',5,5'-tetramethoxy- and 2,2',6,6'-tetramethoxybiphenyl derivatives.

2,2',4,4'-Tetramethoxybiphenyl on chloromethylation with excess of paraformaldehyde in dioxan gave the 5,5'-di-(chloromethyl) derivative which on oxidation with alkaline potassium permanganate gave 2,2',4,4'-tetramethoxy-5,5'-dicarboxylic acid identical with the acid synthesised for comparison as follows : 2,4-Dimethoxy-5-iodo-acetophenone, prepared according to Shah and Sethna, was oxidised with alkaline potassium permanganate to 2,4-dimethoxy-5-iodobenzoic acid. This was esterified and subjected to Ullmann reaction. Dimethyl 2,2',4,4'-tetramethoxybiphenyl-5,5'-dicarboxylate obtained was hydrolysed to the above acid with alkali.

2,2',5,5'-Tetramethoxybiphenyl on chloromethylation in acetic acid furnished the 4,4'-di-(chloromethyl) derivative which on oxidation with alkaline potassium permanganate provided the known 2,2',5,5'-tetramethoxybiphenyl-4,4'-dicarboxylic acid. The di-(chloromethyl) derivative, when subjected to reduction in dioxan with zinc and hydrochloric acid afforded 2,2',5,5'-tetramethoxy-4,4'-dimethylbiphenyl.

2,2',6,6'-Tetramethoxybiphenyl on chloromethylation in acetic acid provided the 3,3'-dichloromethyl derivative which on reduction with zinc and hydrochloric acid in dioxan yielded the 3,3'-dimethylbiphenyl derivative. The structure was confirmed by direct comparison with the

product obtained by the Ullmann reaction on 2,4-dimethoxy-3-iodotoluene which in turn was prepared from 2,4-dimethoxy-3-methyl aniline. Another product was isolated from the reaction mixture, ^{the} analysis of which agreed with a tetra-(chloromethyl) derivative. 3,3',5,5'-Tetra-(chloromethyl) structure has been tentatively assigned to the product as this appears to be the only possible structure.

The di-(chloromethyl) derivatives have been converted into the corresponding diformyl derivatives by the Sommelet reaction and into the di-(acetoxymethyl) derivatives by sodium acetate and acetic anhydride.

Chapter III deals with the synthesis of some biflavonyls starting with biphenyl derivatives. It is only in recent years that the presence in nature of a new class of flavanoids in which two flavone nuclei are joined together and which are therefore designated as biflavonyls has been discovered. Several natural biflavonyls have been isolated during the past few years and their structures have been established by degradation and by physical methods. Ginkgetin, isoginkgetin, sciadopitysin, kayaflavone and sotetsuflavone are some of the important biflavonyl derivatives isolated from plants.

The present work deals with the synthesis of several 3',3''' and 4',4'''-biflavonyls starting with appropriate biphenyl derivatives.

2,2',6,6'-Tetramethoxy-3,3'-diformyl biphenyl on

condensation with 2-hydroxy acetophenone in the presence of alcoholic potassium hydroxide gave 2',2''' -dihydroxy-2,2'',4,4'' -tetramethoxy-3,3'' -bichalconyl which on refluxing with selenium dioxide in iso-amyl alcohol gave 2',2''',4',4'' -tetramethoxy-3',3''' -biflavoryl. An attempt was made to synthesise the same biflavoryl derivative for comparison by an alternate route as follows : 2,4-Dimethoxy-3-nitro benzaldehyde on condensation with 2-hydroxyacetophenone in the presence of alcoholic potassium hydroxide gave 2'-hydroxy-2,4-dimethoxy-3-nitrochalcone which on refluxing with selenium dioxide in isoamyl alcohol gave 2',4'-dimethoxy-3'-nitroflavone. The nitroflavone was reduced to the aminoflavone with stannous chloride and hydrochloric acid. The aminoflavone on diazotisation and Sandmeyer reaction gave the iodoflavone. This on Ullmann reaction either with diphenyl ether as solvent or without any solvent gave a deiodinated but impure compound which could not be purified.

Similarly 2',2'''-dihydroxy-2,2'',4,4',4'',4''' - hexamethoxy bichalconyl was prepared by the condensation of 2,2',6,6'-tetramethoxy-3,3'-diformyl biphenyl with 2-hydroxy-4-methoxy acetophenone. This gave 2',2''',4',4'',7,7'' - hexamethoxy-3',3''' -biflavoryl when refluxed with selenium dioxide in isoamyl alcohol.

2,2',5,5'-Tetramethoxy-4,4'-diformyl biphenyl gave 2',2''' -dihydroxy-2,2'',5,5''-tetramethoxy-4,4'' -bichalconyl on condensation with 2-hydroxy acetophenone. This gave 2',2''',5',5''' -tetramethoxy-4',4'' -biflavoryl on cyclisation with

selenium dioxide in isoamyl alcohol.

2',2'''-Dihydroxy-2,2'',4',4'',5,5''-hexamethoxy-4,4''-bichalconyl obtained from 2,2',5,5'-tetramethoxy-4,4'-diformyl biphenyl and 2-hydroxy-4-methoxyacetophenone gave 2',2''',5',5''',7,7''-hexamethoxy-4',4''-biflavonyl on cyclisation with selenium dioxide in isoamyl alcohol.

2',2'''-Dihydroxy-4,4'',6,6''-tetramethoxy-3,3''-bichalconyl was prepared from 2,2',4,4'-tetramethoxy-5,5'-diformylbiphenyl by condensing with 2-hydroxyacetophenone and then converted into 4',4'',6',6''-tetramethoxy-3',3''-biflavonyl as before.

2,2',4,4'-Tetramethoxy-5,5'-diformylbiphenyl on condensation with 2-hydroxy-4-methoxyacetophenone gave 2',2'''-dihydroxy-4,4',4'',4'''',6,6''-hexamethoxy-3,3''-bichalconyl which did not give the biflavonyl on cyclisation with selenium dioxide in isoamyl alcohol.

4,4'-Dibenzoyloxy-3,3'-diacetylbiphenyl when kept with powdered caustic potash and pyridine for 4 hours at room temperature gave the 4,4'-dihydroxy-3,3'-di(ω -benzoyl acetyl) biphenyl. This on cyclisation by keeping in contact with cold conc. sulphuric acid or on boiling with glacial acetic acid gave a product which was found to be identical on direct comparison with 6,6''-biflavonyl prepared by Mathai and Sethna by other methods.

Chapter IV deals with the Fries and Friedel-Crafts studies in biphenyl derivatives.

2,2'-Diacetoxybiphenyl on Fries migration with anhydrous aluminium chloride at 110-20° gave

2,2'-dihydroxy-5,5'-diacetylbiphenyl. On methylation it gave the dimethyl ether which on oxidation with alkaline potassium permanganate gave 2,2'-dimethoxy-5,5'-dicarboxylic acid which was identical with the acid obtained on the oxidation of 2,2'-dimethoxy-5,5'-di-(chloromethyl)biphenyl. 2,2'-Dihydroxybiphenyl on Friedel-Crafts acetylation with acetyl chloride at 120° gave the same 5,5'-diacetylbiphenyl as seen by direct comparison. 2,2'-Diacetoxy-5,5'-diacetylbiphenyl also was isolated from the reaction mixture.

2,2'-Dimethoxybiphenyl on Friedel-Crafts acetylation with acetyl chloride in the presence of aluminium chloride gave 2,2'-dimethoxy-5,5'-diacetylbiphenyl which was identical with the product obtained on methylation of 2,2'-dihydroxy-5,5'-diacetylbiphenyl as seen by direct comparison.

2,2',4,4'-Tetraacetoxybiphenyl on Fries migration with anhydrous aluminium chloride at 130-40° afforded 2,2',4,4'-tetrahydroxy-5,5'-diacetylbiphenyl which on methylation gave the tetramethyl ether. This on oxidation with alkaline potassium permanganate afforded 2,2',4,4'-tetramethoxybiphenyl-5,5'-dicarboxylic acid as seen by direct comparison with the product obtained on oxidation of 2,2',4,4'-tetramethoxy-5,5'-di-(chloromethyl)biphenyl. An isomeric product isolated from the reaction mixture has been tentatively assigned the 3,3'-diacetyl structure as its m.p. is in close agreement with the same product prepared by Apsimon et al by another method. 2,2',4,4'-Tetrahydroxy-3,3',5,5'-tetraacetylbiphenyl also was isolated from the

reaction mixture. Fries migration of 2,2',4,4'-tetraacetoxy-biphenyl at room temperature with aluminium chloride in nitrobenzene gave similar results.

2,2',4,4'-Tetrahydroxybiphenyl on Friedel-Crafts acetylation with acetyl chloride at 110-20° in the presence of anhydrous aluminium chloride gave a tetraacetyl derivative to which 2,2',4,4'-tetrahydroxy-3,3',5,5'-tetraacetylbiphenyl structure has been tentatively assigned.

2,2',4,4'-Tetramethoxybiphenyl on Friedel-Crafts acetylation with acetyl chloride at 10° in ^{the} presence of anhydrous aluminium chloride gave 2,2',4,4'-tetramethoxy-5,5'-diacetylbiphenyl as seen by direct comparison with the product obtained on methylation of 2,2',4,4'-tetrahydroxy-5,5'-diacetylbiphenyl described before.

4,4'-Dimethoxybiphenyl on Friedel-Crafts acetylation afforded the 3,3'-diacetyl derivative which was identical with the product obtained on methylation of the known 3,3'-diacetyl-4,4'-dihydroxybiphenyl as seen by direct comparison.

2,2',5,5'-Tetramethoxybiphenyl on Friedel-Crafts acetylation gave 2,2',5,5'-tetramethoxy-4,4'-diacetylbiphenyl which on oxidation with alkaline potassium permanganate furnished 2,2',5,5'-tetramethoxybiphenyl-4,4'-dicarboxylic acid as seen by direct comparison with the product obtained on oxidation of 2,2',5,5'-tetramethoxy-4,4'-di(chloromethyl)biphenyl.

The above diacetyl derivatives were characterised by the preparation of their di-(2,4-dinitrophenylhydrazones).

Chapter V deals with the Beckmann rearrangement of the oximes of some C-acyl derivatives of biphenyls.

The di-oxime of 2,2'-dimethoxy-5,5'-diacetyl-biphenyl on heating with polyphosphoric acid gave 2,2'-dimethoxy-5,5'-diacetamidobiphenyl. This on hydrolysis with hydrochloric acid furnished 2,2'-dimethoxy-5,5'-diaminobiphenyl as seen by direct comparison with the product obtained on reduction of the known 2,2'-dimethoxy-5,5'-dinitrobiphenyl with stannous chloride and hydrochloric acid.

The di-oxime of 4,4'-dimethoxy-3,3'-diacetylbiphenyl when subjected to Beckmann rearrangement with polyphosphoric acid gave 4,4'-dimethoxy-3,3'-diacetamidobiphenyl which on hydrolysis with conc. hydrochloric acid gave the known 4,4'-dimethoxy-3,3'-diaminobiphenyl as seen by direct comparison.

The dioxime of 2,2',4,4'-tetramethoxy-5,5'-diacetylbiphenyl on Beckmann rearrangement with polyphosphoric acid gave 2,2',4,4'-tetramethoxy-5,5'-diacetamidobiphenyl which on hydrolysis with conc. hydrochloric acid gave 2,2',4,4'-tetramethoxy-5,5'-diaminobiphenyl. This amino derivative was also prepared by the nitration of 2,2',4,4'-tetramethoxybiphenyl and subsequent reduction of the 5,5'-dinitro derivative formed.

The di-oxime of 2,2',5,5'-tetramethoxy-4,4'-diacetylbiphenyl when subjected to Beckmann rearrangement afforded 2,2',5,5'-tetramethoxy-4,4'-diacetamidobiphenyl which on hydrolysis with conc. hydrochloric acid gave

2,2',5,5'-tetramethoxy-4,4'-diaminobiphenyl. This diamino derivative was also prepared by the nitration of 2,2',5,5'-tetramethoxybiphenyl with conc. nitric acid and subsequent reduction of the dinitro derivative formed. When fuming nitric acid was used instead of conc. nitric acid, a tetranitro derivative was obtained which is tentatively assigned the 4,4',6,6'-tetranitro structure.

The di-oxime of 2,2',6,6'-tetramethoxy-3,3'-diacetyl-biphenyl on Beckmann rearrangement did not give a pure product.

Some of the di-amino derivatives described in chapter V have been converted into biquinolyl derivatives and this work is described in the appendix.

2,2',4,4'-Tetramethoxy-5,5'-diaminobiphenyl on Skraup synthesis with anhydrous glycerol in presence of conc. sulphuric acid, nitrobenzene and ferrous sulphate gave 6,6',8,8'-tetramethoxy-5,5'-biquinolyl.

5,5',8,8'-Tetramethoxy-6,6'-biquinolyl was obtained when 2,2',5,5'-tetramethoxy-4,4'-diaminobiphenyl was subjected to Skraup synthesis with anhydrous glycerol in ^{the} presence of conc. sulphuric acid, nitrobenzene and ferrous sulphate.

2,2',5,5'-Tetramethoxy-3,3'-diaminobiphenyl on Skraup synthesis as before gave 6,6',8,8'-tetramethoxy-7,7'-biquinolyl.